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Cerebrospinal Fluid Flow Dynamics in the Central Nervous System

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Abstract—Cine-phase-contrast-MRI was used to measure the three-dimensional cerebrospinal fluid (CSF) flow field inside the central nervous system (CNS) of a healthy subject. Image reconstruction and grid generation tools were then used to develop a three-dimensional fluid–structure interaction model of the CSF flow inside the CNS. The CSF spaces were discretized using the finite-element method and the constitutive equations for fluid and solid motion solved in ADINA-FSI 8.6. Model predictions of CSF velocity magnitude and stroke volume were found to be in excellent agreement with the experimental data. CSF pressure gradients and amplitudes were computed in all regions of the CNS. The computed pressure gradients and amplitudes closely match values obtained clinically. The highest pressure amplitude of 77 Pa was predicted to occur in the lateral ventricles. The pressure gradient between the lateral ventricles and the lumbar region of the spinal canal did not exceed 132 Pa (~1 mmHg) at any time during the cardiac cycle. The pressure wave speed in the spinal canal was predicted and found to agree closely with values previously reported in the literature. Finally, the forward and backward motion of the CSF in the ventricles was visualized, revealing the complex mixing patterns in the CSF spaces. The mathematical model presented in this article is a prerequisite for developing a mechanistic understanding of the relationships among vasculature pulsations, CSF flow, and CSF pressure waves in the CNS.

Keywords—Three-dimensional modeling, Central nervous system, Cerebrospinal fluid, Intracranial dynamics, Pressure wave speed, Computational fluid dynamics.

INTRODUCTION

Cine-phase-contrast-MRI (CINE-MRI) has been used to quantify cerebrospinal fluid (CSF) flow in humans.[14,19,52] Computational fluid dynamics has been used to complement CINE-MRI measurements by calculating the CSF pressure and velocity fields in the cranial subarachnoid space and cerebral ventricles.[10,15,21,24,30] These computational studies predict and explain complex fluid flow patterns in the CSF spaces, an outcome difficult to establish with CINE-MRI alone. As a measuring device for some regions of interest in the CSF space, CINE-MRI is not apt to explain the complex dynamics inside the central nervous system (CNS). However, CINE-MRI is the basis for developing computational fluid dynamic models that help quantify intracranial dynamics of the human brain. Using CINE-MRI and image processing tools, CSF velocities can be calculated in several areas of interest in the cranial space. These experimental measurements may then be used to develop and validate computational models.

The advantage of developing a computational model from CINE-MRI is that the computational model reproduces the three-dimensional flow field in all regions of interest in the entire CSF-filled spaces of the CNS. Moreover, once the model is validated, studies can be conducted on a computer to assess whether particular deviations from normal physiology may be responsible for significant changes in flow patterns.[28,37] Conclusions may then be drawn or clinical experiments devised to improve clinicians' understanding of disease onset or progression. In effect, computational CSF flow studies are a valuable tool for developing a mechanistic understanding of normal and pathological CNS dynamics.

Previous computational studies deployed simplified models of the CSF spaces. These studies focused on two-dimensional cross sections or partial aspects of the CSF space.[15,21,30,31,36] To date, there are no three-dimensional fluid–structure interaction models of CSF motion inside the entire CNS. A physiological CSF model should account for the cranial CSF space as well as the spinal canal. Computer models that include the

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spinal canal are needed for improving our understanding of many diseases of the CNS including hydrocephalus, Chiari malformation, or benign intracranial hypertension.[11] Furthermore, a craniospinal model of the CNS may help evaluate modern drug delivery methods like intrathecal drug administration by accurately predicting therapeutic drug distribution in the CSF spaces and brain tissue.[27,39] Predicting drug distribution with computer models is possible by numerically solving the governing equations for drug diffusion coupled with convective species transport through the CSF.[29] This article presents a three-dimensional fluid dynamics model of the CNS which accurately resolves the geometry of the fluid-filled spaces in the cranium and spinal canal. The objective is to develop a computational model that quantifies the interactions among pulsating vasculature, CSF flow, and deformable brain tissue. By doing so, we hope to render a more detailed picture of CSF dynamics in the human CNS.

The rest of this article is organized as follows: In the next section we describe methods. The results section compares *in vivo* data with computer simulations and provides a detailed analysis of CSF flow and pressure dynamics in the cranium and spinal canal. The article ends with a discussion and suggestions for future advancements in computational fluid mechanics of the CNS.

METHODS

Process Overview: From Measurement to Computation

The modeling approach described here proceeds in four phases illustrated in Fig. 1. First, CINE-MRI imaging (3 T GE Signa; GE Medical Systems, Milwaukee, WI, USA) is used to extract actual patient's brain geometry and to measure CSF flow velocities *in vivo*. Second, image reconstruction software (Materialise, Belgium) is used to create accurate geometrical representations of the human ventricular system, subarachnoid spaces, and brain parenchyma. The image reconstruction process delineates the boundaries between CSF spaces and soft brain tissue. By connecting the pixel information from each MRI slice with adjacent slices, a three-dimensional representation of the individual's brain geometry is generated. In the third phase, the fluid-filled spaces bounded by the reconstructed surfaces are divided into small tetrahedral balance envelopes via grid generation software (Gambit 2.4). Finally, in phase four, physiological boundary conditions are assigned to the model, and governing equations for fluid flow and solid motion are solved numerically using finite-element methods. Computational predictions are then compared to the *in vivo* measurements.

Details related to CSF flow measurements have been discussed in our prior publications,[31,52] but for completeness will be repeated in brief. The CINE-MRI technique was used to collect CSF flow data from eight healthy subjects and three patients with hydrocephalus. The scans were performed in a 3-T GE Signa system (GE Medical Systems) equipped with a standard quadrature birdcage head coil. Study participants signed the consent forms approved by the Institutional Review Board at the University of Chicago and the University of Illinois at Chicago. Images at 16 equidistant time frames were collected at a mid-sagittal cross section and an axial slice across the middle of the lateral ventricle. Images at 32 equidistant time frames were collected at: (1) an axial slice across the junction between the aqueduct of Sylvius and the fourth ventricle to measure CSF flow rate; (2) a mid-coronal slice at the third ventricle to measure CSF flow rate; and (3) an axial slice perpendicular to the basilar artery in the prepontine region to measure blood flow rate. For CSF flow measurement, a velocity encoding value (V_{ENC}) of 5 cm/s was chosen; for blood flow measurement in the basilar artery, V_{ENC} was set to 100 cm/s. Additional acquisition parameters were echo

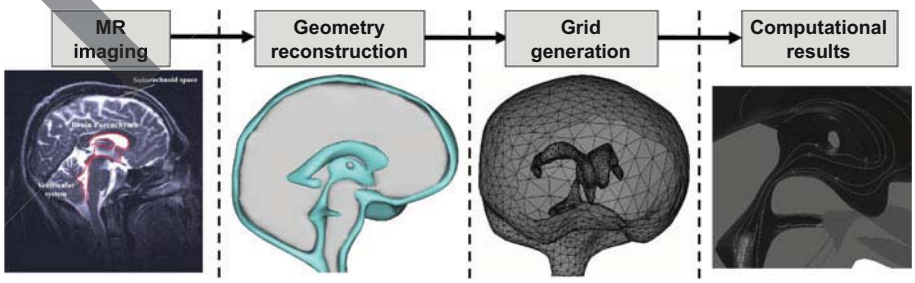

FIGURE 1. Workflow for developing a computational model of the CNS. The first step is the collection of medical images from MRI. Then, geometry reconstruction is used to detect sharp boundaries of functional regions inside the brain to generate three-dimensional surfaces. Third, grid generation partitions the surfaces into tetrahedral elements for the solution of transport equations. Finally, computational analysis solves transport equations to predict fluid velocities and pressures as well as solid strains and stresses.

time = 8.4 ms; repetition time = 18 ms; flip angle = 20°; field of view = 24 cm; slice thickness = 5 mm; matrix size = 256 × 192, 75% phase field of view to achieve an effective matrix resolution of 256 × 256. Total acquisition time was about 1 h. The measured velocity at a particular point of interest on the MR image is averaged over 180 cardiac cycles. The comparison between simulated results and experimental measurements is made point-to-point; averaged velocities from CINE-MRI are compared with simulated velocities from our computational model. The computational results provide velocity data at mesh nodes, the location of which is matched with the pixel location of the CINE-MRI CSF velocity measurement. To compute flow rates, the velocity vector field is integrated over a cross-sectional area in the model corresponding to the area of interest used in the CINE-MRI measurements.

Model Boundary Conditions and Governing Equations

Meaningful CSF flow and pressure predictions require physiologically consistent boundary conditions. CSF production, CSF reabsorption, and effects of pulsatile vasculature expansion were incorporated into the computer model. Constant CSF production is due to active secretion from the choroid plexus as well as diffuse production in the brain parenchyma. In the model, CSF is constantly produced from the lateral ventricles at a rate of 0.4 mL/min. This value is in the range of several clinical studies.[23,32,40,43] The constant production of CSF is governed by Eq. (1) which assumes fluid incompressibility and Newtonian rheological behavior. The fluid velocity vector is $\vec{u}$, and constant CSF production is represented as S_f.

$$\nabla \cdot \vec{u} = S_f \tag{1}$$

There are many clinical studies supporting the thesis that CSF is mainly reabsorbed into the circulatory system through the arachnoid villi.[12,13,46] To mimic the actual CSF uptake through the arachnoid villi, in the model CSF reabsorption occurs via a porous region superior to the upper convexity of the subarachnoid space.[30] Although some researchers believe a small amount of CSF is reabsorbed in the spinal canal, we choose to neglect spinal CSF reabsorption in this study. The assumption of negligible reabsorption in the spinal cavity is also supported by CINE-MRI measurements showing undetectable levels of CSF elimination in the spinal canal.[1,33]

Transient changes in vasculature lumen throughout the cardiac cycle cause local deformation of brain tissue. Tissue deformation, in turn, compresses the fluid-filled extracellular space in the parenchyma and causes compression of the lateral ventricles. The subsequent change in lateral ventricular volume results in CSF flow out of the ventricles.[48] This chain of events leads to the hypothesis that CSF motion in the CNS is mainly caused by vasculature expansion in the cranium.[2,8,17] To mimic the effects of vascular pulsations and tissue boundary motion near the lateral ventricles, we have imposed moving parenchyma boundaries in the model that pulsate in accordance with the physiological blood flow waveform measured *in vivo*. The measured blood flow waveform was reconstructed with a Fourier series, $f(t)$, with 17 coefficients as shown in Eq. (2).

$$f(t) = \sum_{k=-8}^{8} c_k e^{2ik\pi t} \tag{2}$$

where $i = \sqrt{-1}$, $c_k = (a_k \pm ib_k)/2$. The sign of the complex part, ib_k, is taken as plus when k is positive, and negative when k is negative. The value index zero, c_0, and coefficients a_k, b_k are listed in Table 1. The signal was further normalized and then scaled in order to apply an explicit displacement boundary condition along the upper walls of the lateral ventricles. This boundary condition mimics the effects of the tissue deformation that is transmitted to the moving lateral ventricle walls. Pulsatile volume changes in the subarachnoid space near the basilar artery and Circle of Willis are also accounted for in the model. These displacements are also due to expanding vasculature. Overall, the expansion of the intracranial vasculature decreases the space available to the cranial CSF by about 1.5 mL.[17] Because the skull is rigid and all fluids are incompressible, CSF is necessarily pushed into the spinal canal due to mass conservation. In our model,

TABLE 1. Mean value, c_0, and coefficients a_k, b_k, $k = 1, 2, \ldots, 8$ of the Fourier series in Eq. (2) used to reconstruct the measured blood flow waveform at the basilar artery.

Coefficient	Value (mL/min)
c_0	169.7760
a_1	27.9791
a_2	12.3427
a_3	14.9403
a_4	−5.3310
a_5	−5.4838
a_6	−1.6638
a_7	2.2920
a_8	4.5670
b_1	9.5584
b_2	−6.9098
b_3	−6.8080
b_4	−0.6282
b_5	3.7181
b_6	4.2953
b_7	1.6978
b_8	−0.1358