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2 **CNS wide simulation of flow resistance and drug transport**
3 **due to spinal microanatomy**
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20 **Abbreviated Title: Spinal Microanatomy Effect on Cerebrospinal Fluid Flow**
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Abstract

Spinal microstructures are known to substantially affect cerebrospinal fluid patterns, yet their actual impact on flow resistance has not been quantified. Because the length scale of microanatomical aspects is below medical image resolution, their effect on flow is difficult to observe experimentally. Using a computational fluid mechanics approach, we were able to quantify the contribution of micro-anatomical aspects on cerebrospinal fluid (CSF) flow patterns and flow resistance within the entire central nervous system (CNS). Cranial and spinal CSF filled compartments were reconstructed from human imaging data; microscopic trabeculae below the image detection threshold were added artificially. Nerve roots and trabeculae were found to induce regions of microcirculation, whose location, size and vorticity along the spine were characterized. Our CFD simulations based on volumetric flow rates acquired with Cine Phase Contrast MRI in a normal human subject suggest a 2-2.5 fold increase in pressure drop mainly due to arachnoid trabeculae. The timing and phase lag of the CSF pressure and velocity waves along the spinal canal were also computed, and a complete spatio-temporal map encoding CSF volumetric flow rates and pressure was created.

Micro-anatomy induced fluid patterns were found responsible for the rapid caudo-cranial spread of an intrathecally administered drug. The speed of rostral drug dispersion is drastically accelerated through pulsatile flow around microanatomy induced vortices. Exploring massive parallelization on a supercomputer, the feasibility of computational drug transport studies was demonstrated. CNS-wide simulations of intrathecal drugs administration can become a practical tool for *in silico* design, interspecies scaling and optimization of experimental drug trials.

Keywords: Cerebrospinal Fluid Dynamics, Computational Fluid Dynamics, CNS microanatomy, MR image reconstruction, Drug dispersion, intrathecal drug delivery

1. Introduction

Despite precise MR observations of cerebrospinal fluid (CSF) velocities¹⁸, brain motion⁴⁶ and ventricular wall dilatations⁶, critical questions remain about CSF dynamics in the CNS: What is the exact nature of the force coupling between the pulsatile blood circulation and CSF displacements?^{24,25} How is the pulsatile expansion and contraction of the cerebrovascular bed transmitted to the CSF and the brain? The source of the volumetric dilations that actually induce CSF motion remain uncertain, even though major cerebral arteries, the oscillatory displacement by the parenchyma or choroid plexus expansion are likely involved. Moreover, the caudal decrease in CSF flow amplitude along the spinal canal^{2,40} supports the notion of compliant leptomeningeal boundaries lining the fluid-filled spinal subarachnoid space (SAS). Hence, the observed CNS compliance could result from cyclic displacement of blood inside large spinal veins, or the expansion of CSF-filled spaces against elastically deformable epidural tissues. Nevertheless, the biomechanics of deformations of the entire spinal compartment remain unclear.

Subject-specific CSF flow measurements may be significant for improving noninvasive diagnostics of pathological conditions. For example, the amplitude ratio between the aqueduct and prepontine CSF flows were found elevated in hydrocephalus patients compared to normal subjects.⁴⁶ Because *in vivo* MR measurements have limited image resolution and practical scan durations restrict the number of observed regions of interest, many researchers have attempted to address fundamental questions regarding CNS with computational fluid dynamics (CFD) techniques dynamics especially under pathological conditions.

Early CFD models used small sections of the CNS with idealized geometries.^{7,16,17,19,22} Other approaches used medical image reconstruction to represent subjects-specific anatomical spaces to enhance the model fidelity.^{9,21,31,32,34,38,39} Haller et al. showed that spinal microanatomy

induces complex mixing eddies.¹⁰ Stockman studied the impact of nerve roots and trabeculae on convective flow with Lattice Boltzman simulations in idealized cylindrical spine models.^{35,36} Gupta presented an analytical solution to oscillating fluid in a representative elliptical annulus representing a spinal segment directly inferior to the cisterna magna.⁸ Based on a simulated porous model of the cerebromedullary cistern and spinal SAS, they conclude that subresolution microstructure density and radius can triple the pressure drop in CSF flow.^{8,9}

Several groups investigated CSF flow patterns in Chiari patients relative to normal subjects.^{26,31,32} Yiallourou⁴⁵ et al. compared flow measurements in normal subjects and patients suffering from Chiari malformation with a CFD model of a cervical segment of the spine. During the review process of this paper, an updated report to the earlier CFD simulation paper of the same group including artificial nerve roots appeared.¹¹ Yet none of these studies performed CFD simulations on the entire CNS and included microanatomical trabeculae in the spinal SAS.

The goal of this paper is to address several critical questions regarding the spatiotemporal coupling of the cranio-spinal CSF compartments by performing CFD simulation on an entire CNS model of a normal subject. This study tests the hypothesis that microanatomical structures generate significant vortex phenomena in spinal CSF flow which *increase flow resistance, raise pressure drop*, and induce *complex mixing patterns responsible for the rapid biodispersion* of moieties administered to the spinal SAS. To account for the influence of detailed spinal anatomical structures, nerve roots were reconstructed from medical images; arachnoid trabeculae below the imaging threshold were artificially incorporated to the subject-specific computational mesh. This paper constitutes a first step towards a complete *in silico* model of CNS dynamics with full coupling between CSF, blood and brain. To augment the limited scope of previous studies, it is critical to account for the entire CNS including the cranial and spinal SAS with their

microscopic aspects. Modeling the complete CNS eliminates the burden of introducing uncertain assumptions about internal boundary conditions. Therefore, a parametric study to quantify the influence of microanatomical aspects on CSF dynamics and flow resistance and drug transport was conducted.

2. Methods

CSF spaces, in vivo velocity measurements and CFD simulations. Methods used are summarized here in brief, while details are presented in the Supplementary Material. A subject-specific computational model of the cranial and spinal CSF-filled spaces including nerve roots was reconstructed from medical images, up to detail limited by resolution of the dataset using MIMICS image processing software (Appendix 1.1). CSF flow measurements were acquired from the 29 year old volunteer with CINE MRI at three planes in the spinal SAS (Appendix 1.2).

The cranial pial surface and the epithelial surfaces of the choroid plexi in the lateral ventricles were periodically displaced to account for pulsatile expansion and contraction of the cerebral vasculature. Explicit deformable boundaries were also applied at the thoracic and lumbar spine (Appendix 1.3). To assess the impact of microanatomical features below the imaging resolution, arachnoid trabeculae were artificially added to a 3 cm long cervical spine segment, visualized in Fig. 1 and discussed in Appendix 1.4. Fluid flow was solved with ANSYS 14.0 Fluent on Blacklight at the Pittsburgh Supercomputing Center (Appendix 1.5). Fluid flow parameters such as volumetric flow rate, stroke volume, Womersley, and Reynolds number are calculated at each plane to characterize flow profiles and compare with MRI measurements (Appendix 1.6). Upon close inspection of the original MR images and the reconstructed subject-specific models the authors determined that the geometry was reasonably symmetrical along the

mid-sagittal plane and utilized a symmetry boundary condition to reduce mesh size and computation time.

Drug transport simulations. To assess the impact of nerve root induced CSF mixing patterns, intrathecal (IT) drug infusion in the lumbar region was simulated in multiple scenarios; more details on the IT drug delivery protocol can be found in prior work.¹⁴ The advection-diffusion of bupivacaine in eq 1 was solved for a period of 12 hours post injection. Here, the drug concentration is $C(x,t)$, and the diffusivity is $D=2.1*10^{-10} \text{ m}^2 \text{ s}^{-1}$. The pulsating convective CSF flow field, $u(x,t)$, was computed as described above. Drug metabolism and uptake were considered negligible

$$\text{Species Transport} \quad \frac{\partial C}{\partial t} + \nabla \cdot u C = \nabla \cdot D \nabla C \quad (1)$$

3. Results

3.1 Analysis of CSF flow fields in the full SAS model

The simulated CSF flow velocities are visualized as contour plots on axial planes of interest for a full cardiac cycle, in Fig. 2. Systole lasts about 25-35% of the cardiac cycle with a sharp forceful peak in the craniocaudal direction, this phase is color coded in red. Diastole covers the remainder of the cardiac cycle with a slower, more even flow in the caudocranial direction, color coded in blue. Regions of low velocities, $\|v\| < 0.1 \text{ cm s}^{-1}$, are coded in green to highlight temporary stagnation and transition of flow direction. Simulated peak plane-averaged velocities for systole and diastole are presented in Table 1.

The pressure wave depicted in Fig. 3 shows a short forceful peak during systole followed by reversal during the slower diastolic phase. A fast traveling wave enters the spinal cord cranially and can be traced caudally. The timing of the pressure in the spinal SAS follows the

pulsatile dynamics of cerebro-arterial expansion. MR imaging has shown that during systolic vessel expansion, fast craniocaudal CSF displacements can be observed in the aqueduct, the cisterna magna and the cervical SAS, while during diastole there is flow reversal due to the rostral recoil of the spinal CSF.¹⁵ Also, peak pulse amplitude becomes gradually smaller in the caudal direction. In the cervical region, amplitudes are 223/99 Pa (sys/diast), reduce to 129/52 in the thoracic, and drop to 45/18 in the lumbar region. Pressure predictions for all axial planes are listed in Table 1.

Volumetric flow profiles and stroke volume ratios are visualized in Fig. 3. Peak volumetric flow rates and stroke volume decrease caudally along the spine. The simulated volumetric flow rate lags behind the pressure wave across the entire spine with the least at CM, phase angle 7.2° , and greatest at S3 with phase angle of 64.8° ; phase angles for all regions are reported in Table 1. Phase angle at each plane is calculated as the peak-to-peak difference between pressure and velocity waves. CSF phase lag is not well characterized; Wagshul et al. reported values at the C2 level, $+10.8 \pm 11.2^\circ$ (posterior) and $-0.5 \pm 10.8^\circ$ (anterior). Our C4 phase lag is 10.8° , comparable to their reported range.⁴² Womersley numbers were calculated using eq. 11 (Appendix 1.6) to characterize flow conditions due to a pulsatile pressure gradient.

Fig. 4 plots trajectories of volumetric flow rates for one cardiac cycle acquired in the volunteer (thick lines). For comparison, simulation results are displayed as filled curves. Flow profiles of our MRI data and CFD simulations depict caudal flow as red and cranial flow as blue. At the C4 level, both measured and simulated profiles have a rapid increase in caudal flow, which tapers off over 25-35% of the cardiac cycle. Cranial flow for MR data and predicted values is gradual with lower peak amplitudes than systole. MRI stroke volume and predicted values match well for all planes. The difference in the stroke volume between simulated

magnitudes and MRI data is less than 0.004 mL for all planes, yielding a percent difference of 0.9% at C4, 1.6% at T6, and 1.5% at the L4 level. Table 1 offers a comparison of predicted CSF flow parameters with our MR measurements.

The pressure and volumetric flow results of the massive supercomputing simulations were fitted into a comprehensive *CSF pressure and volumetric flow map* condensing all computational results into an easy-to-use Fourier-approximation formula. The approximations formulae in eqs 5-8, with coefficients given in electronic supplemental material Supplemental Table 2, permit the calculation of the pressure and flow waveforms for the specific subject for any point in the spine and time point in the cardiac cycle. Approximations for location, $l \in \{\text{CM, C4, T1, T6, T11, L4, S3}\}$ along the spine are linearly interpolated between two bounding levels (l_i, l_{i+1}) using a weighting factor, ω . Fig. 5 shows a two-dimensional *map of volumetric flow rate*, $V(l,t)$, and *pressure*, $P(l,t)$, dynamics as function of spinal location, l , and time, t . These maps approximate the experimental and computational results with continuous functions, and can be used to calculate the precise timing, phase lags, and amplitudes of the pressure and fluid flow pulsations in the spinal CSF.

$$V_{l,t} = \omega l_{i+1} f_{l_{i+1}} + (1-\omega) l_i f_{l_i} + t \quad (2)$$

$$P_{l,t} = \omega l_{i+1} f_{l_{i+1}} + (1-\omega) l_i f_{l_i} + t \quad (3)$$

$$\omega = \frac{l - l_i}{l_{i+1} - l_i} \quad \text{if } l_i < l < l_{i+1} \quad \text{else } 0$$

$$(4)$$

$$f_{l,t} = a_l \sin n t + b_l \cos n t \quad (5)$$

The root mean squared deviation, NRMSD, calculated by eq. 13 (Appendix 2) for the *volumetric flow rate map* is 0.84% and for the *pressure map* is 0.66%. These results show that

the maps perfectly reproduce the expensive simulation results. Fig. 6 offers a detailed comparison of peak pressure magnitudes in systole and diastole for three data sets: (i) MRI data, (ii) CFD simulated values, and (iii) Fourier approximation at each plane of interest. Again the easy-to-use Fourier map encodes the MRI measurement and simulations with high fidelity.

3.2 Nerve root influence on micro-flow patterns in the full SAS model

Next, microcirculatory flow patterns of the full CNS model were characterized. Previous CFD simulations in an idealized spinal SAS without nerve roots already showed that pulsations break laminar fluid layers.¹⁴ Here, CNS wide simulations with all 31 nerve root pairs induced even more vigorous mixing in the spinal CSF and introduced eddies with recirculation zones. Typical micromixing patterns generated by nerve roots are depicted in Fig. 7. At peak systole frames A,C,E visualize regions of recirculation against laminar bulk flow around the base of nerve roots at C4, T6, and L4, respectively. These micromixing patterns and recirculation zones are driven by the pulsating CSF flow around the nerve roots which act as baffles.²³ Complex flow profiles in the cranial SAS are visualized in Appendix 3. To characterize the rotational component of the fluid flow, the *vorticity* defined as the magnitude of the curl of the velocity vector flow field in eq 6 was computed.

$$Vorticity = \nabla \times v \quad (6)$$

Streamlines and vorticity isosurfaces illustrate regions of high vorticity adjacent to nerve roots in the spinal SAS in Fig. 7. Frames B,D,F characterize the location and size of the recirculation zones. Around the C4 nerve root, a vortex forms with core diameter, $d=0.33$ cm, and spatial extension of 0.036 cm³. The vortex at T6 region is the largest with $d=0.56$ cm with a volume of 0.176 m³. For the L4 region, the vortex is $d=0.13$ cm its volume is 0.0022 cm³. Local macroscopic Reynolds numbers were computed at each plane with eq. 12 (Appendix 1.6),

Re=112 at C4, <86 at T6, <67 at L4. It is remarkable that vortices occur, despite the low Reynolds number. These patterns are known as geometry-induced flow.³⁰

3.3 Effect of trabeculae on flow resistance and micromixing profiles

The impact of trabeculae on CSF flow resistance was estimated with the help of detailed CFD simulations. The density of arachnoid trabeculae throughout the spinal SAS is not well characterized. Based on canine data,^{4,35} Stockman arrives at a conservative estimate of 24 trabeculae in the dorsal and ventral regions of an idealized spinal model; this equals about 85 trabeculae per cm³ (Tr cm⁻³). To cover a broad spectrum of physiologically relevant trabeculae densities, we artificially introduced between 40-200 Tr cm⁻³ of CSF into the computational mesh of spinal segments. To demonstrate mesh independence, pressure and velocity magnitude along a ray through the spinal segment mesh are plotted in Fig. 8D for different mesh densities of 12 m, 22 m, and 54 m. Mesh independence for pressure and velocity was studied with no trabeculae (data not shown) and with 100 Tr cm⁻³ meshes. For the 54 m mesh with 40 Tr cm⁻³, the pressure increases from 58 to 86 Pa; 100 Tr cm⁻³ trabeculae 58 to 109 Pa; 200 Tr cm⁻³ 58 to 145 Pa. The average pressure drop that develops across the spinal mesh segments is graphically represented in Fig. 8B, as a function of number of trabeculae per cm⁻³ (N) given by the following formula:

$$\Delta P = 0.5064 * N + 64.64 \quad (7)$$

Pressure contours across the segment are given in Fig. 8A. The fine trabeculae simulations with a 54 m mesh typically converged in one to two days of using 128 parallel processors and consuming a total of 1400 CPU hours on the Blacklight Supercomputing Facility.

In summary, the pressure drop simulation results suggest that trabeculae significantly increase the CSF resistance, almost double compared to idealized CSF compartments without

trabeculae for a physiologically consistent estimate of 100 trabeculae cm^{-3} . For the 200 trabeculae cm^{-3} mesh, the resistance would increase by a factor as great as 2.5.

In addition to elevating flow resistance, arachnoid trabeculae further enhance flow recirculation. Isosurfaces using the vorticity threshold $<6 \text{ s}^{-1}$ are generated to visualize vortex phenomena in Fig. 8C. With microanatomy, there is strong recirculation around trabeculae. In the model lacking microanatomy, vorticity is minimal.

3.4 The effect of CSF dynamics on intrathecally administered drug transport.

The flow simulations already demonstrated geometry-induced micromixing with vortex generation. These counter-currents in the spinal CSF flow are a significant finding clinically, because they drastically impact drug biodistribution in the CNS. Fig. 9A visualizes drug distribution contours in the full spinal SAS for the first 30 minutes. Drug concentration is plotted over time at spinal regions (C4, T6, L4) in Fig. 9B-D for the first 300 minutes. Peak drug concentration in the CSF occurs at 31 min for L4, 64 min for T6, and 237 min at C4. To test the role of CSF bulk flow on drug dispersion, we also performed simulations without bulk flow. The casual motion of the drug was almost as fast as in the presence of bulk flow, indicating that CSF bulk flow does not affect the cranial upward motion of IT delivered drugs. These results allow the important conclusion that the open question regarding the classical or more recent CSF reabsorption theories^{15,28} would not critically affect the dispersion speed of CSF administered drugs. The simulations confirm our prior predictions implicating CSF pulse and frequency as the main driving forces of solute dispersion in slow continuous CSF drug administration.^{12,14} Additionally drug motion is simulated on a spinal SAS without nerve roots and peak drug concentrations occur at 62 min for L4, 89 min for T6, and 285 min for C4. Drug motion in the

caudocranial direction has a slower distribution in the absence of nerve roots. These three comparative simulations of drug dispersion indicate that nerve roots facilitate CSF mixing.

We also studied the effect of molecular diffusivity on the speed of caudal drug motion. Simulations with different molecular diffusivities to mimic different solutes showed that drug dispersion speed was almost the same in all runs (computations not shown). The speed of the cranial motion for a CSF stroke volume of 0.76mL and a pulse frequency of 1 Hz was about 0.21 cm min⁻¹, irrespective of the Diffusion coefficient. The computational results confirm that drug biodistribution depends strongly on CSF pulsatility, but only weakly on drug diffusivity. The reported cranial advance of the drug front agrees with clinical studies of lumbar drug infusion, which observed the drug front advancing at a rate of 0.16-0.31 cm min⁻¹.^{27,33}

Discussion

This computational study aimed at predicting the CSF dynamics in a subject-specific model of the entire CNS including microanatomical aspects. The massive CFD computations assessed the effect of microanatomy on CSF flow and flow resistance. Simulations found the caudal flow phase to last 20-30% of the cardiac cycle, which agreed with MRI measurements. The cisterna magna had a stroke volume of 0.76 mL with caudal decrease in amplitudes.

Pressure pulsatility along the spinal canal was characterized. The craniocaudal pressure wave was sharp and short in systole, followed by a reversal in the slower diastolic phase. Substantial phase lags between pressure and velocity waves along the spinal column were predicted consistent with the spinal Womersley numbers range, $8 < \alpha < 16$. Spectral fitting of the simulated pressure and flow signals at different vertebral levels yields a closed formula for the *pressure* and *mean volumetric flow* waves for any point in the spinal SAS or time point in the cardiac cycle. The *volumetric flow* and the *pressure maps* are easy to use and encode

experiments and CFD simulations with high fidelity. The approximation formulae also enable easy computation of the amplitude attenuation, as well as phase lags between the pressure and velocity wave peaks.

Nerve roots were found to create substantial obstacles to the pulsating CSF flow that break the laminar fluid layers and generate geometry-induced flow profiles despite the relatively low Reynolds numbers, $Re < 179$. The mixing effects in the spine are similar to the mixing effects observed in pulsatile flows in baffled cylinders as described elsewhere.²³ The extent and intensity of vortex formation was visualized adjacent to nerve roots and the cerebral aqueduct for all phases of the cardiac cycle.

Our simulation results permit the estimation of flow resistance attributable to microanatomy. In the densest case, 200 Tr cm^{-3} the pressure drop experienced a 2.5-fold increase. For the physiologically more likely range of 100 Tr cm^{-3} , the flow resistance almost doubled. Our results and Gupta's work⁹ agree in identifying trabeculae as major sources of flow resistance. Computations of expected pressure ranges are useful to guide experiments to validate the predicted impact of microanatomical aspects.

Significance of CNS-wide CSF simulations. In this report, we addressed the lack of microanatomical detail in prior CFD models by artificially augmenting a subject-specific mesh with the computer-generated microanatomical aspects. Clearly, the statistical, coarse representation of the microstructures suggested here does not necessarily match subject-specific properties, but yields quantitative results on the sensitivity of pulsatile flow patterns and geometry-induced flow resistance due to presence of microscopic obstacles. Although we could at this point not ascertain experimentally the exact micro-geometry of the spinal SAS, the computational results support findings by prior authors for the need to include these structures in

future spinal CFD simulation studies to achieve more realistic approximations of pressure drops and subject-specific flow measurements. The more than two-fold increase in flow resistance over an ideal spinal SAS model without microanatomy predicted in this study may also explain the substantial discrepancies between models and experiments in earlier studies.

A second perspective underscoring the significance of CNS-wide simulation is related to the open question regarding the motor of CSF motion. The exact source location and type of force coupling between the expanding and contracting vasculature, brain movement and induced CSF dynamics are uncertain. The present model of the entire CNS system completely enclosing all CSF-filled spaces for a specific subject is a first step in the direction of linking vascular pulsations to CSF dynamics. Results such as the phase lags which can easily be computed from the *volumetric flow* and *pressure maps* for any point in time or location along the spinal cord will be needed to trace the CSF pulse waves back to the main arteries or volumetric dilatations of the microcirculatory bed that causes them.

Finally, the CNS wide model enabled us to shed light on the role of CSF bulk flow in drug transport. Recently, the classical hypothesis of CSF production in the choroid causing a net bulk CSF flow followed by reabsorption to the veins of the superior sagittal sinuses through the arachnoid villi has been questioned.²⁸ An argument in support of the classical CSF production and reabsorption hypothesis held that the caudocranial transport of intrathecally administered drugs as observed in the spinal anesthesia or the treatment of spasticity was evidence for CSF bulk flow. MR flow measurements are too inaccurate to ascertain the extent of CSF bulk flow, yet comparative simulations with and without the assumption of bulk flow, reveal that cranial drug transport does occur rapidly due to CSF pulsations even without net CSF bulk flow. Also solute diffusivity is a minor factor for the speed of solute dispersion. We demonstrated that the

pulse frequency and CSF flow amplitude transmitted from the blood to the CSF is a significant factor determining the speed of drug dispersion.

Conclusions and Limitations

The dynamic 3D model presented above is a first attempt to predict CSF circulation in the entire CNS of an individual subject. The timing of the pressure and fluid velocity fields was carefully quantified and encoded in a comprehensive *Fourier Map*. The microcirculatory flow pattern introduced by nerve roots and arachnoid trabeculae were characterized with the use of massively parallel supercomputer simulations.

The actual functional role of trabeculae has not been established, but our results seem to support their role as enhancers of micromixing, despite the low Reynolds numbers of the CSF dynamics. It is reasonable to conjecture that trabeculae in pulsatile CSF flow prevent bioaccumulation of debris and metabolites, thus protecting sensitive nerve roots and neurons. The proposed methods were shown to predict biodistribution of drugs after intrathecal infusion; rapid drug dispersion was linked to convection facilitated by eddies and vortices induced into the pulsatile CSF flow by spinal microanatomical aspects.

Limitations. Since the actual source locations of the vascular-parenchyma-CSF interaction are not yet known, the cerebro-vascular bed was not explicitly modeled in this study. Due to the uncertainty pertaining to the biomechanical properties of the CNS, especially the deformability of dura and epidural spaces, we implemented explicit boundary motion instead of attempting to predict wall deformation, although methods described previously by Sweetman for full two-way implicit fluid structure interaction could be adopted.³⁷ A future, more complete, model of CSF dynamics could incorporate organ-wide reconstruction of the vasculature²⁰ in

contact with the CSF and brain parenchyma. In the drug transport simulations, the injection impulse was neglected due to the slow micro-infusion volumes used.

In this first full model of the full CNS, we also did not perform multi-subject validation of the CSF flow field, because the emphasis lay on the characterization of parameter sensitivity as a function of trabecular density. A multi-individual study would require computational meshes for each subject; and IT drug infusions cannot be performed on healthy volunteers. Therefore we limited the scope to a detailed analysis of one subject, but with parametric variation of trabecular density and random orientation compared to flows in spinal SAS without microanatomy. Multiple subject validation and inclusion of patients suffering from a disease exceeded the scope and focus of our computational study here, but should be considered in a future study.

Velocity measurements were acquired using conventional MRI scans conducted on a volunteer in the supine position, therefore variations of body position are not accounted for in this comprehensive simulation of the entire CSF space, although it is known that posture influences intracranial compliance ¹.

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Figure 1: Presentation of the microanatomical structures present in the spinal mesh models. (A) An electron microscope image and a schematic, adapted from Weller,⁴² captures trabeculae (Tr) bridging the arachnoid (Ar) and pia (P) mater and illustrated the uniform distribution of trabeculae throughout the SAS. B-D) Overview of the process for artificially generating arachnoid trabeculae within a short cervical spinal segment. (B) A short spinal segment is cropped and tubes are projected through the volume mesh at random levels along the Y-axis and angles in the XZ-plane. (C) Volume elements intersected by the analytical tubes are deleted from the mesh and neighboring faces grouped together as a boundary. (D) The final volume mesh with 100 trabeculae and two pairs of nerve roots has 54 m elements. E-G. Details of the microanatomical aspects in the subject-specific computational mesh. (E) An axial cross section of the SAS at the level of a nerve root. (F) A thoracolumbar segment shows five nerve root pairs branching off the spinal cord and extending through the SAS to the dura membrane. (G) A magnified visualization of the subject-specific geometry of the nerve pairs.

Table 1: Summary of Simulated and MR measured Flow Parameters

Figure 2: Velocity profiles computed for axial plane in regions of interest (CM, C1, C4, C7, T1, T4, T6, T9, T11, L2, L4, and S1) in different phases of the cardiac cycle (CC). Velocity scale is identical for all planes and time points of the CC. Red encodes the craniocaudal flow direction, blue represents caudocranial flow, and green signals almost stagnant flow ($\|v\| < 0.1 \text{ cm s}^{-1}$). The spinal cord terminates at the L2 level; below this level the peripheral nerves occupy the lower spinal subarachnoidal space.

Figure 3: Relationship of pressure and volumetric flow waves. The systole (red) has a high amplitude downward flow, the caudocranial recoil in the diastole (blue) is longer with slower flow. The amplitude of both pressure and volumetric flow rate gradually decrease from the Cisterna to the Sacral region. Also the phase lag increases in the craniocaudal direction.

Figure 4: Comparison of CSF flow between simulated and MRI measured data in the human spinal canal. An axial CINE-MRI contour of the CSF space identifies the imaging plane for the volumetric flow comparison. CSF flow is simulated on a subject-specific full CNS model reconstructed from T2 MRI data. Simulated volumetric flow profiles (solid curve) are overlaid with MRI derived volumetric flow profiles (solid line). Negative velocity (red) values signify craniocaudal flow during systole, positive (blue) values are the opposite direction.

Figure 5: *Volumetric flow map and pressure map* across the length of the spinal canal over the full cardiac cycle (CC) from Fourier approximations. Craniocaudal flow during systole is represented as negative velocities (red), while caudocranial flow during diastole is positive (blue), and green encodes stagnation ($\|v\| < 0.1 \text{ cm s}^{-1}$; $P < 1 \text{ Pa}$). The amplitudes of both flow and pressure decrease along the spinal SAS with the greatest magnitudes being superior at the cisterna magna (CM). Formulas for the Fourier approximations with the coefficients are given in Supplementary Table 1 in the appendix.

Figure 6: Peak pressure and stroke volume from the MR measurements, the CFD simulation, and the Fourier approximations show close agreement in timing and magnitude. Hence, the Fourier approximation is an excellent fit for the experimental and simulated data.

Figure 7: Visualization of complex micro-flow induced patterns in the spinal SAS. Velocity streamlines with magnifications show vortices at the C4, T6, and L4 regions. Streamline are color coded from 0 (blue) to 0.04 m s^{-1} (red). Vortex sizes are delineated by isosurfaces. Despite the low Re number, geometry induced flow patterns are not laminar. Magnified vortex views show microcirculatory eddies forming close to the nerve roots.

Figure 8: Pressure drop and vorticity due to trabeculae. (A) Pressure contours for spinal SAS segment models with $40\text{-}200 \text{ Tr cm}^{-3}$. (B) The pressure drop increases with increasing number of trabeculae. Also

simulations with different mesh density demonstrate mesh independence of pressure computations. (C) The vorticity is high around trabeculae, but almost absent in a computational mesh with no trabeculae (vorticity threshold= 6 s^{-1}) (D) Mesh independence is demonstrated along a ray for different mesh densities. For the meshes with 22m and 54m elements, the computed pressure and velocity magnitudes are virtually identical.

Figure 9: Predicted drug distribution profiles over time for an IT injection in the CNS. (A) The timely evolution of the drug concentration profile shows a caudocranial rise of the injected drug. CSF Bulk flow due to arachnoid absorption did not significantly alter the speed of rostral drug motion. A one minute bolus injection is applied in a model with nerves (B) and without bulk flow (C) and an idealized annular model (D). Simulations in idealized annular models without micro-anatomy showed a significantly slower drug rise towards the cranial compartment.

Figure 1

Figure 2

Figure 3

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Figure 5

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Figure 7

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Figure 9

Table 1

Table 1: Summary of Simulated and MR measured Flow Parameters													
		Cross section A (cm ²)	Diam. D _h (cm)	Peak Pressure P _{max} (Pa)		Peak velocity V _{max} (cm s ⁻¹)		Peak vol. flow rate Q _{max} (mL s ⁻¹)		Stroke volume (mL)	Re	Wo	Phase lag ϕ (deg)
				Systole	Diastole	Systole	Diastole	Systole	Diastole				
Simulated	Cisterna	4.21	1.83	223.08	-90.99	0.98	0.51	4.13	2.17	0.763	179	22.84	7.2
	C4	1.98	0.91	200.77	-81.89	1.23	0.64	2.45	1.26	0.443	112	11.42	10.8
	T1	3.49	1.26	167.31	-68.24	0.51	0.26	1.77	0.91	0.322	64	15.78	25.2
	T6	1.27	0.80	129.39	-51.64	1.07	0.56	1.36	0.71	0.248	86	10.54	32.4
	T11	0.84	0.66	82.54	-33.67	1.49	0.77	1.25	0.64	0.228	98	8.29	43.2
	L4	1.50	0.96	44.62	-18.2	0.69	0.34	1.04	0.50	0.202	67	12.07	61.2
	S3	2.08	1.08	17.85	-7.28	0.15	0.07	0.35	0.17	0.067	16	13.47	64.8
MRI	C4	1.92	0.89	-	-	1.14	0.73	2.19	1.43	0.439	102	11.19	-
	T6	1.44	0.83	-	-	0.83	0.60	1.17	0.83	0.244	69	10.36	-
	L4	2.19	1.04	-	-	0.47	0.29	1.04	0.68	0.199	49	13.04	-

Re – Reynolds number at peak systole; Wo – Womersley number at peak systole; ϕ Phase lag between P_{max} and V_{max} at systole.