Mixing and Modes of Mass Transfer in the Third Cerebral Ventricle: A Computational Analysis

Anatomic, velocimetric, and brain motion MRI scans were combined with a computational fluid dynamics model to investigate cerebrospinal fluid (CSF) mixing in the third cerebral ventricle of a healthy male adult. It was found that advection dominates over diffusion in most of the third ventricle. Three zones where diffusion plays an important role in the mixing process were identified. One of these zones, consisting of recessus infundibulus, recessus opticus and the adjacent regions up to commissura anterior, is likely to exist in the general population. We hypothesize that this zone may act as a buffer to flatten concentration peaks of pituitary gland hormones released into the CSF of the third ventricle. We further hypothesize that this zone may facilitate the communication between hypothalamus and the pituitary gland through the third ventricle cerebrospinal fluid by prolonging residence times of the communicated hormones.

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throughout the cardiac cycle by acquiring a time series of images. Cranio-caudal brain tissue displacement was quantified using harmonic phase (HARP) post-processing [12,13]. We were not able to measure displacements in the remaining directions, which portray much smaller amplitudes, with sufficient accuracy. A fourth order Fourier series was fit to the transient data of each measured brain location using least-squares error minimization. This approach allowed us to access displacement values at any point in time. The spatial distribution of displacement was approximated by fitting thin-plate smoothing splines through the measured locations [1].

A standard phase contrast velocity mapping sequence [14] was used to acquire CSF velocity data at the inferior end of the aqueduct of Sylvius. The velocity profile was integrated to give the volume flux through the aqueduct at each measured point in time. A Fourier series was fit through these points by estimating the Fourier coefficients using the theory of pulsatile flow in pipes [15]. The same coefficients were used to reconstruct the velocity profile. Details on the flow velocity acquisition can be found in [1].

**CFD Calculations.** In order to observe mixing, the cerebrospinal fluid present in the third ventricle at the beginning of the simulation was regarded as a different fluid than the CSF entering the third ventricle through the foramina of Monro. Both fluids were modeled as Newtonian, incompressible, and with the same material properties as water at 37°C [16]. A homogeneous mixture model, which is based on continuity and momentum equations for the mixture and on volume fraction equations for the second fluid, was solved using the finite-volume CFD package FLUENT 6.1.22 (Fluent Inc., Lebanon, NH).

The continuity equation for the mixture reads, in Einstein’s summation notation, as

\[
\frac{\partial \rho u_i}{\partial t} + \frac{\partial (\rho u_i x_j)}{\partial x_j} = 0
\]

where \( u \) is the velocity of the mixture and \( x \) is spatial location. The momentum equation can be written as

\[
\frac{d \rho u_i}{dt} = \frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} (\mu \frac{\partial u_i}{\partial x_j})
\]

where \( \rho \) is the density of the mixture, \( t \) is time, \( p \) is pressure, and \( \mu \) is dynamic viscosity. Finally, the equations
govern the volume fractions \( \alpha \) of the two involved fluids, where subscript “2” designates CSF entering from the lateral ventricles and subscript “1” refers to the CSF initially located within the third ventricle. Equations (3) and (4) can also be seen as a scalar advection model with inhibition of scalar accumulation through Eq. (4). Diffusion is not taken into account. This has a limited effect on the accuracy of the calculations, as we will show in the Results section.

We used an algebraic multigrid scheme in conjunction with PISO (pressure-implicit with splitting of operators) pressure correction [17] to solve the above equations with second order of accuracy in space and first order of accuracy in time. The computational grid consisted of approximately 558,000 tetrahedral elements. A time step size of 1/1000 \( T \) was used, where \( T \) is the length of the cardiac cycle. No-slip boundary conditions (BC) were specified at the third ventricle and aqueduct walls. A zero pressure BC was specified for the mixture at the foramina of Monro, whose twisted shape renders the accurate acquisition of velocimetric MRI data difficult. By using a constant pressure boundary condition instead, the introduction of virtual flow features due to MRI noise is avoided. At the same location, the volume fraction for CSF from the lateral ventricles (lv-CSF) was set to 1. A transient velocity BC for the mixture at the inferior end of the aqueduct of Sylvius was assigned as described above along with a zero-flux boundary condition for lv-CSF volume fraction with backflow value of zero. The fourth ventricle, to which the near cylindrical aqueduct of Sylvius is connected, features a rather complex geometry and CSF flow pattern which, principally, does not warrant the use of a Neumann BC. If, however, the actual

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**Fig. 1** Rendering of the computational domain: Third ventricle and aqueduct of Sylvius. Left: coronal view with positions of section planes A to C at the ECG R-peak as referred to in the Results section. The section planes are stationary and do not follow the feet-head motion of the computation domain with maximum amplitude of 0.25 mm. Right: Sagittal view with positions of section planes D to H as referred to in the Results section.

**Fig. 2** MRI tagging image of the midsagittal plane of a healthy volunteer’s brain acquired 50 ms after the ECG R-peak. The characteristic checker board structure consists of saturation lines of magnetization that are tracked throughout the cardiac cycle to obtain brain motion.
lv-CSF volume fraction is the same immediately upstream and downstream of the boundary, a Neumann BC can be used without introducing any errors. This is the case from the beginning of the simulation, where lv-CSF volume fraction is zero in the entire domain, to when lv-CSF reaches the fourth ventricle. Hence, the simulation was carried out only to the point in time where the volume fraction of lv-CSF reaches 0.1 at the inferior boundary of the aqueduct and results are only reported for the third ventricle.

This approach limits the errors caused by the boundary condition.

We took the feet-head motion of the third ventricle and aqueduct walls into account by specifying the position of each boundary grid node at each time step based on the brain motion MRI scans. The velocity field in the entire domain was initialized to 0 and then calculated for six periods without solving Eqs. (3) and (4) in order to obtain period-independent flow. The lv-CSF volume fraction was then initialized to 0 and the calculations were resumed, this time only solving the volume fraction equations based on previously stored velocity values. Grid independence, time-step independence, and period independence studies (for the

Fig. 3 Visualization of the two main recirculation zones in the third ventricle using stream ribbons at $t=0.25T$, where $T$ is the length of the cardiac cycle. The remainder of the jet emerging from the aqueduct of Sylvius can be seen at the center of the ventricle in between the recirculation zones.

Fig. 4 Median sagittal cut through the third ventricle. I: Areas portraying fast mixing. II: Areas with slow mixing. Ila: Region of anterior recessi including Ro, recessus opticus, and Ri, recessus infundibuli. IIB: Region above adhesio interthalamica. IIC: Region of posterior recessi, including Rsp, recessus suprapinealis, and part of Rp, recessus pinealis. Pt: Pituitary gland (hypophysis), Pn: pineal gland (epiphysis), Co: commissura anterior.

Fig. 5 Contours of volume fraction of CSF entering from the lateral ventricles (lv-CSF) in the midsagittal plane of the third ventricle at the ECG R-peak of several cardiac cycles. a: Anterior, p: Posterior, h: Head and f: Feet. Note the exponential scaling of the legend.
initial six periods) were carried out successfully [1]. The relative error $e$ due to both spatial and temporal discretization is less than 5%, where $e$ is defined as

$$\frac{p_{\text{fine}}(t,x) - p_{\text{medium}}(t,x)}{p_{\text{fine}}(t,x)} \leq 5\%$$

with $p$ being pressure, $t$ time within the cardiac cycle, and $x$ spatial position within the calculated domain. The subscripts “fine” and “medium” refer to calculations carried out with the fine and medium grid, respectively, for the grid independence study. For the remaining independence studies, they refer to the corresponding time-step size and number of calculated periods. The period independence study revealed a relative error of less than 1%.

Results

The main features of the cerebrospinal fluid flow in the third ventricle are two mobile recirculation zones (Fig. 3) produced by a jet emerging from the aqueduct of Sylvius [1]. The first recirculation zone is located superior of the jet. It governs the flow in the area between recessus pinealis, adhesio interthalamica, and the superior ventricle wall (Fig. 4). The second recirculation is located inferior of the jet, influencing the CSF flow between commissura anterior and the inferior wall of the third ventricle. Figure 5 shows volume fractions of lv-CSF in a sagittal plane of the third ventricle for different points in time. The position of the plane corresponds to section plane A in Fig. 1. Figure 6 shows volume fraction data in the axial planes B and C, both of which are also referenced in Fig. 1.

The starting point of the simulation ($t=0$) is chosen to coincide with the $R$-peak of the electrocardiogram (ECG) used for the gated MRI scans. At $t=0$, the lv-CSF volume fraction is zero in the entire domain. At the beginning of the second cardiac cycle, lv-CSF has reached the midsagittal plane of the third ventricle through the foramina of Monro. While the second recirculation zone, centered inferior of the aqueduct-foramen axis, has only a weak influence on the area anterior of commissura anterior, it is responsible for the rapid mixing at the center of the third ventricle that can be seen after four cardiac cycles. The first recirculation is centered at approximately the level of the pineal gland on the longitudinal axis and half-way between adhesio interthalamica and recessus suprapinealis on the sagittal axis. There is a net mass transport from the second recirculation zone to the first along the superior wall of the ventricle, passing inferior of adhesio interthalamica. The center of the third ventricle is filled rather quickly.

![Fig. 6](image_url)

**Fig. 6** Contours of lv-CSF volume fraction at the ECG R-peak of several cardiac cycles. Top row: Axial slice through the third ventricle in position C as outlined in Fig. 3. Bottom row: Axial slice in position B. a: Anterior, p: Posterior, l: Left and r: Right. Note the exponential scaling of the legend.

![Fig. 7](image_url)

**Fig. 7** Left axis, solid curve: average lv-CSF volume fraction in zone I as defined in Fig. 1. Right axis: Portion of zone I with lv-CSF volume fraction greater than c, where $c=0.05$ (short-dashed curve), $c=0.1$ (long-dashed curve) and $c=0.25$ (dotted curve).
with lv-CSF: Within 15 cardiac cycles, 60% of zone I as defined in Fig. 4 show a lv-CSF volume fraction of $>0.1$, and the average volume fraction is about 0.25 (Fig. 7). At the same time, the remaining regions of the third ventricle, referred to as zones IIa, b, and c in Fig. 4, portray clearly slower mixing. Zone IIa consists of recessus infundibuli, recessus opticus, and the adjacent regions up to commissura anterior. The flow velocities in the recessi are close to zero and mass transfer is, consequently, dominated by diffusion. Closer to commissura anterior, e.g., in plane D shown in Fig. 1, advection increases in importance with maximum Péclet numbers on the order of $10^2$. Considering a time scale of 15 s, which corresponds roughly to the duration simulated herein, we obtain a characteristic diffusion length of approximately 0.4 mm (see Appendix for details). This is one order of magnitude smaller than the distance from the interface between zones I and IIa to the posterior section of the recessi. Therefore, diffusion can be neglected for short simulation times as is the case here, provided that mass transfer across the ventricle walls is not the objective of the study. Maximum Péclet numbers of up to 77,562 in the influence

<table>
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<th>Re</th>
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<th>$D_b$</th>
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*Within influence region of jet from aqueduct.
Outside jet influence region.

Table 1 Maximum Reynolds numbers (Re), Schmidt numbers (Sc), and Péclet numbers (Pe) within section planes shown in Fig. 1. Sc are calculated with the self-diffusion coefficient of water ($D_s$) and with the binary diffusion coefficient between water and serotonin ($D_b$), both at 37 °C.

Fig. 8 Contours of lv-CSF volume fraction in the midsagittal plane of the third ventricle during one cardiac cycle after 15 periods. $t$: Time, where $t=0$ T corresponds to the ECG R-peak, T: Length of the cardiac cycle, a: Anterior, p: Posterior, h: Head and f: Feet.
region of the CSF jet emerging from the aqueduct and 6672 outside the influence region are found in plane G (Fig. 1), calculated with the diffusion coefficient of serotonin in water at 37°C. Other pineal and pituitary hormones have similar diffusivities [18–20]. Further Pécelt numbers are given in Table 1.

Figures 8 and 9 show the volume fraction distribution within one cardiac cycle after 15 calculated periods. The jet emerging from the aqueduct of Sylvius and feeding the third ventricle with fluid low in lv-CSF content can be seen well after \( t = 0 \). At around \( t = 0.4 \), the top section of the jet is shed and incorporated into the second recirculation. At the same time, fluid rich in lv-CSF is transported from the second to the first recirculation zone. Both of these events promote the mixing process.

**Discussion**

The third cerebral ventricle is a rather challenging environment for numerical simulations. Most of the preparations, such as the segmentation of the anatomic MRI scans and the conversion to NURBS surfaces, have to be carried out semimanually, as there are currently no tools available that perform these tasks automatically with sufficient accuracy. Consequently, the cost of studies from which statistically significant results with regard to the general population could be drawn, is at the moment prohibitively high. Studies on a single individual, as carried out in this work, will help identify areas where high accuracy is required (e.g., detailed geometry, fine grid) and where simplifications can be made to increase throughput. Furthermore, certain assumptions can be made regarding the general population if one proceeds carefully and always bears in mind that these assumptions have to be confirmed.

The three zones portraying slow mixing identified in this work differ in location, size, and form. The size of zone IIb depends on the location and size of adhesio interthalamica. Since there are significant intersubject variations of these parameters to the point where in part of the population adhesio interthalamica is absent [21], zone IIb must be viewed as a possibly unique feature of the individual studied here.

The pineal gland is situated between recessus pinealis and recessus suprapinealis, both of which are part of zone IIc. The cerebrospinal fluid has been shown to be the main distribution channel of pineal melatonin in sheep by way of recessus pinealis [6,7]. The anatomical organization of the human pineal gland is similar to that of sheep, suggesting that a comparable mechanism is likely to apply in humans as well [7]. Consequently, the speed of melatonin transport will depend on the dominating mode of mass transport in recessus pinealis. Intersubject variations of the third ventricle anatomy do not allow for generalized quantitative statements on flow and transport properties in the recess based on a single individual. However, it is conceivable that in the general population, as observed in the volunteer here, diffusion is likely to be of greater importance in recessus pinealis than in the center of the third ventricle.

The general anatomy of the aqueduct of Sylvius, the third ventricle, and the foramina of Monro, along with the pulsatile nature of cerebrospinal fluid flow, necessitate the existence of a CSF jet...
and of the thereby created recirculation zones. The recirculation located inferior of the jet transfers momentum to the anterior section of the third ventricle and thereby promotes advection. At the same time, it demotes advection by shielding the anterior section from smaller flow structures that might otherwise penetrate it. Anatomic and morphologic details determine the size of the shielded section, but its existence is likely to be a fundamental feature of the ventricular anatomy. In the individual observed here, zone IIA corresponds to this shielded section.

Three main functions are attributed to the cerebrospinal fluid: Mechanical protection of brain and spinal cord, removal of waste products, and transport of endocrine substances [22,23]. For the first function, hydrostatics plays the most important role. The latter two functions are governed by advection, diffusion, and other transport phenomena. If the third ventricle were designed with the sole purpose of waste removal, areas of slow transport like zone IIA would not exist. Consequently, the purpose of zone IIA is likely to be linked to the neuroendocrine system. The third ventricle cerebrospinal fluid acts as a communication pathway between the hypothalamus and the pituitary gland [8]. As the hypothalamus is located adjacent to the anterior section of the third ventricle, this pathway consists mainly of zone IIA. The slow mass transport therein may increase the residence time of the communicated substances in the vicinity of their respective receptors compared to a region with faster transport. This may facilitate the communication by requiring lower concentrations of the communicated substance.

Only a fraction of the pituitary gland’s hormone production is released into the cerebrospinal fluid. The other part reaches its peripheral targets directly through the vascular system (i.e., without passing through the CSF). While this pathway is well suited for fast transport, it may not be ideal for a continuous supply of hormones, as the pituitary gland releases its products in bursts [24,25]. By releasing the hormone into zone IIA, from where it can slowly diffuse to zone I, a time-release effect may be achieved.

In order to fully simulate transport of endocrine substances in the third ventricle, the computational domain will have to be extended to include the lateral ventricles and the fourth ventricle. This is due to the fact that the boundary conditions at the interface between the third ventricle and the other ventricles as used in this study do not allow for more than 15 seconds of simulated time without sacrificing accuracy. However, longer simulations are necessary for thorough slow mass transport processes. Since the lateral ventricles feature no CSF outlets and the fourth ventricle is connected to the comparatively large cerebellomedullary cistern, boundary conditions for this extended domain are less likely to negatively influence the accuracy of the simulation.

Conclusions

In our previous study [1], we presented methods to calculate the CSF flow in the third ventricle based on boundary conditions derived from MRI. In the work at hand, we have extended those methods to include the computation of scalar advection in order to investigate mixing and mass transfer. We have identified regions in the third ventricle of a healthy male volunteer that portray different speeds of CSF mixing. One of the three areas with slow mixing, consisting of recessus infundibuli, recessus opticus, and the adjacent regions up to commissura anterior, is likely to exist not only in the individual discussed here, but may also be present in the general population. The reason for its existence could be of significance via either or both of the two hypotheses that: (a) This zone facilitates communications between the hypothalamus and the pituitary through its slow mass transport. (b) This zone acts as a buffer that flattens concentration peaks caused by the pulsatile release of pituitary gland hormones.

Acknowledgment

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Appendix

The characteristic diffusion length can be approximated by considering the one dimensional diffusion equation, i.e.,

$$\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2}$$  \hspace{1cm} (A1)

where $c$ is concentration, $t$ is time, $D$ is diffusion coefficient, and $x$ is spatial location

$$t = 0 \quad 0 < x < \infty: \quad c = 0$$  \hspace{1cm} (A2)

$$t > 0 \quad x = 0: \quad c = c_i$$  \hspace{1cm} (A3)

$$t > 0 \quad x \to \infty: \quad c = 0$$  \hspace{1cm} (A4)

the concentration $c_i$ can be viewed as the average concentration in zone I at the interface to zone IIA. The solution of Eqs. (A1)–(A4) is given by

$$c(x,t) = c_i \left[ 1 - \text{erf} \left( \frac{x}{{2 \sqrt{Dt}}} \right) \right]$$  \hspace{1cm} (A5)

where erf is the error function. We now define the characteristic diffusion length $x_c$ as the location where $c=0.01c_i$ after $t_c$, the characteristic time:

$$x_c = 3.6 \sqrt{D t_c}$$  \hspace{1cm} (A6)

References


