# EXCHANGE OF FLUID BETWEEN A SYRINX AND THE STENOSED SPINAL SUBARACHNOID SPACE (WITH IMPLICATIONS BEYOND SYRINGOMYELIA)

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***Abstract.*** Simplifying the geometry but retaining the true dimensions, we constructed in open-source software [1] an axi-symmetric poroelastic fluid/structure-interaction model [2,3] of the spinal cord and filum terminale, the pia mater, the spinal subarachnoid space (SSS) and the dura mater. A substantial fluid-filled syrinx took up part of the thoracic cord. The subarachnoid space was mostly occluded opposite the syrinx by a blockage of trapezoidal cross-section adhering to the dura. The model was excited by sinusoidal pressure applied to the fluid at the cranial end of the SSS, evoking the cyclic displacement of cerebrospinal fluid (CSF) caused by the pulsation of arteries in the head.

Because the SSS stenosis flexed, the remaining gap was slightly greater when pressure was high, and caudally-directed flow through the gap was greater than cranial. This caused greater mean SSS pressure caudal to the stenosis, and a steady streaming flow in a circuit past the gap and back via the syrinx, passing through the porous overlying tissue. Depending on details of the geometry, mean syrinx volume varied slightly from its initial value; see Figure 1. The model does not include representation of growth and remodeling, but such effects might amplify the small syrinx volume changes found.

The SSS pulsation caused fluid to be cyclically taken up by and given up from the adjacent poroelastic tissues in a periodic swelling that was confined to a tissue boundary layer next to the SSS. The effect was particularly marked for the tissue over the syrinx, but occurred to a lesser extent everywhere along the cord, showing that there is continuous mixing of CSF and interstitial fluid in this region. The extent of the cord swelling depended on its cyclic strain, and was therefore limited by the stiff containing pia. To the extent that there is pulsatile strain of brain tissue near the subarachnoid space, the effect can be expected in the head also.

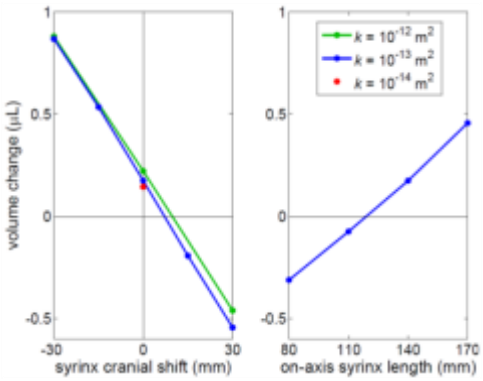


**Fig. 1.** Difference between initial syrinx volume and its final cycle-average value after the evolution of conditions over enough cycles to find a steady state. Left: variation with syrinx position relative to the SSS stenosis. Right: variation with the length (and therefore volume) of the syrinx. The findings vary only slightly with the value of poroelastic permeability, shown in the legend.

We thus describe a means of fluid ingress into a syrinx, and cord tissue in general, from the SSS that does not involve perivascular (Virchow-Robin) conduits [4,5], and a means of fluid egress from the cord that does not depend on the existence of suggested paravascular channels along basement membranes [6].

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**Chris Bertram**

***About the Presenter:*** Chris Bertram graduated in 1971 (Engineering Science) and gained his DPhil in 1975 (ultrasonic measurement of arterial mechanical properties). He then worked on hemodynamics at Johns Hopkins University's Dept of Physiology. From 1977 he experimented on unsteady flow separation at DAMTP (Cambridge, UK). In 1980 he was appointed to the then Centre for Biomedical Engineering of University of New South Wales. He moved to University of Sydney in 2010. For many years he conducted experiments on self-excited oscillations of collapsed-tube flows, and these still form the most comprehensive investigation of this dynamical system. Beyond CSF, his current research is on pumping in the lymphatic system. He has been a member of the World Council of Biomechanics, and an Associate Editor of *J. Fluids & Structures*, and is on the Editorial Board of *Med. & Biol. Eng. & Comput*.

# MATHEMATICAL MODELLING OF SPINAL CSF DYNAMICS: HUMAN AND ANIMAL MODELS OF SYRINGOMYELIA

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***Abstract.*** Syringomyelia is a severe progressive pathological condition in which fluid-filled cavities (syrinxes) form and grow in the spinal cord. There is strong evidence that syringomyelia is linked to obstructions to the movement of cerebrospinal fluid (CSF). However, the exact mechanism of cyst formation and growth has defied explanation for decades. The lack of understanding of the origins of the condition limits the success of currently available medical treatments. Syringomyelia is often linked with Chiari malformation, a congenital condition in which underdevelopment of the skull causes the lower portion of the brain to protrude into the spinal cavity and obstruct the normal communication between the cranial and spinal CSF spaces. Syringomyelia and Chiari affect, and have the same manifestation in, both humans and animals. Some breeds of dogs are particularly predisposed; in King Charles spaniels, almost all dogs suffer from Chiari and many develop syringomyelia [1]. Consequently, this breed is an excellent model for studying the causes of syringomyelia. With the lack of clinical explanation, engineers and mathematicians have resorted to computer models to identify possible physical mechanisms that can lead to syrinx formation and growth [2]. We developed one-dimensional and semi-idealized three-dimensional models of the spinal cavity of a King Charles spaniel with a large syrinx spanning almost the entire length of the cord. The models included the spinal cord (with and without the syrinx), CSF in the subarachnoid space, dura, and the epidural space. A velocity input was prescribed at the cranial end to simulate the movement of the CSF or cord due to the communication between the cranial and spinal CSF spaces related to the cardiac cycle. To simulate the normal condition, the movement was prescribed to the CSF, and the cord was free of syrinx. To simulate the pathological condition the movement was prescribed to the cord, which was either free of a syrinx (onset of the pathology) or it had a fully developed syrinx. The results suggest that there is a mild increase in the stress experienced by the spinal cord when the blockage between the cranial and spinal CSF spaces forces the cord to move with the cardiac cycle. While the 1D model predicts an axially uniform distribution of stress, the 3D model suggests that there are regional differences due to the curvature of the spine. The syrinx seems to ultimately relax the stress in the spinal cord tissue which points to the possibility of a "homeostatic" mechanism for cavity dynamics.

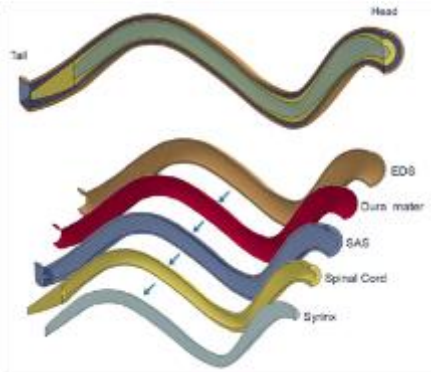


**Fig. 1.** Three-dimensional, semi-idealized model of the spinal cavity of a dog. The geometry was reconstructed from MR images of the spine of a King Charles spaniel suffering from a large syrinx. The model consists of the following layers: spinal cord, syrinx, subarachnoid space, dura, and epidural space. Each layer in the model was approximated to be of a circular cross-section with the radius varying axially. CSF was represented as a fluid and all other structures as (linear) elastic solids.

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**Serge Cirovic**

***About the Presenter:*** Serge Cirovic obtained his PhD in Aerospace Engineering at the University of Toronto, Canada in 2001. He worked as a research consultant at DRDC-Toronto and as a research associate at the University of Sheffield before assuming a lectureship position at the University of Surrey in 2006. Dr. Cirovic is the Programme Director of the MSc in Biomedical Engineering at the University of Surrey where he teaches biomechanics to undergraduate and MSc students. His research interest is in using computer models to understand the role of mechanical stimuli in the etiology of pathological conditions. He is also interested in the therapeutic effect of high-amplitude pressure waves.

# INTERACTING FLUID COMPARTMENTS OF THE CENTRAL NERVOUS SYSTEM: A HOLISTIC MATHEMATICAL MODELLING APPROACH

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***Abstract.*** Fluid compartments that are relevant to the understanding of the physiology of the central nervous system (CNS) are briefly reviewed [1], emphasizing some very recent findings that include the discovery of a meningeal lymphatic system [2], [3]. We then describe a global, closed loop mathematical model for the entire human circulation [5], [6], [7] coupled to the dynamics of cerebrospinal fluid (CSF) and brain dynamics [8]. Sample computations on the effect of extracranial venous strictures on CNS haemodynamics and CSF dynamics are presented. Intracranial venous hypertension and disturbed CSF dynamics are predicted. To conclude we point out some of the limitations of our present mathematical model and describe current work aimed at enhancing it, to include the peripheral as well as the newly discovered brain lymphatic system.

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***About the Presenter:*** Eleuterio F. Toro is currently an emeritus professor of mathematics at the University of Trento, Italy. His research interests include numerical analysis of evolutionary nonlinear systems of partial differential equations and applications to aerospace, industrial and environmental problems. For the last six years Prof. Toro's research has primarily focused on mathematical modeling of the bio-physics associated to a class of neurological disorders, such as Multiple Sclerosis, Meniere's Disease and Idiopathic Intracranial Hypertension.

# ARE MONKEYS LIKE HUMANS? COMPARISON OF INTRATHECAL CSF DYNAMICS ACROSS MAMMALIAN SPECIES

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***Problem.*** While intrathecal delivery of drugs or biologics to the CNS is promising, we have very little information about intrathecal CSF dynamics in humans in heath and disease and for animal models. This lack of knowledge has slowed therapeutic development and confounded analysis of therapeutic effectiveness. At present, targeting and optimizing the delivery of these therapies is problematic because little is known about CSF dynamics in human disease or in animal models that should, in principle, represent humans.

***Aim.*** The aim of the present study was to a) develop a non-invasive MRI method to quantify intrathecal CSF dynamics in large mammalian species and b) quantify CSF dynamics in a healthy adult human (N=1), rhesus monkeys (N=2), cynomolgus monkeys (N=8), and Göttingen minipigs (N=2)

***Methods.*** To quantify CSF space geometry, high-resolution sagittal T2-weighted MRI measurements were collected for each subject with full spine coverage. Intrathecal geometry was segmented manually and quantified in terms of axial distribution of hydraulic diameter, wetted perimeter, cross-sectional area and total volume. CSF dynamics were quantified at 6-axial levels along the spine (foramen magnum, C2/3, C5/6, T4/5, T11/12, L3/4) using phase-contrast MRI measurements with retrospective cardiac gating. Axial distribution of CSF dynamics was quantified in terms of Reynolds and Womersley number, peak value of the mean CSF velocity (based on CSF flow and area), peak flow rate and stroke volume.

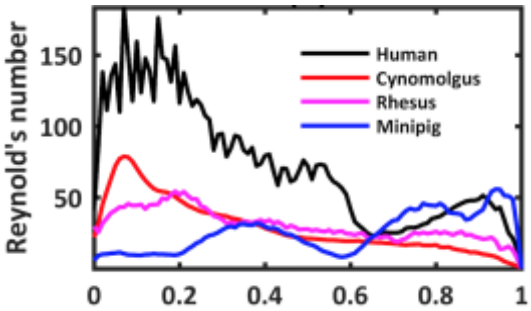


**Fig 1.** Quantification of intrathecal CSF dynamics along the spine in large mammalian species in terms of Reynolds number. Normalized values show that cynomolgus and rhesus monkeys show similar trend as humans (albeit ~2X smaller in value); results for the minipig bear no relationship to human.

***Results.*** Overall, minipig CSF dynamics were found to bear no relationship with humans. The axial trend of Reynolds number in cynomolgus and rhesus monkeys showed some degree of similarity with humans; albeit, with ~2X smaller values (**Fig 1**). Trend in peak value of mean CSF velocity compared favorably for monkeys, but not in the minipigs (**Fig 2**). Average value for intrathecal CSF volume (in ml) below the foramen magnum was: 97 ml in humans, 12 ml in rhesus, 11 ml in cynomolgus and 26 ml in minipigs.

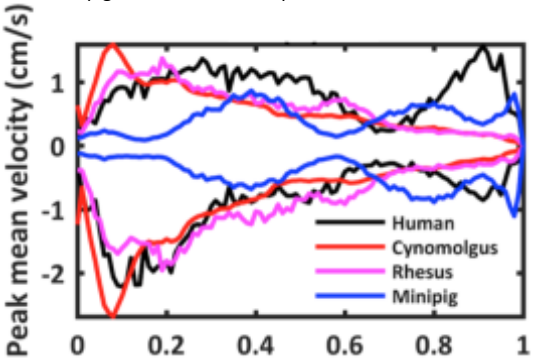


**Fig 2.** Peak value of mean CSF velocity at diastole (- values) and systole (+ values). Peak mean velocity results for monkeys show a more favorable comparison to humans. Minipigs show a poor correspondence with humans or primates.

***Conclusion.*** A reliable non-invasive MRI method was developed to quantify CSF dynamics and geometry in large mammalian species. Results indicated that the minipig had poor correspondence to human intrathecal CSF dynamics and that non-human primates compared more favorably. Further study is needed to confirm these findings in a larger population including humans with CNS disease, understand the impact of respiration on CSF dynamics in these species and assess what degree of alterations would result in a notable impact on intrathecal solute distribution.

**Bryn A. Martin**

***About the Presenter.*** Bryn Martin, PhD, is an Assistant Professor of Biological Engineering at the University of Idaho (2015-present), Joint Faculty in Neurosurgery at the University of Washington and Instructor in the University of Washington WWAMI medical school. Martin earned a PhD in Mechanical Engineering at the University of Illinois at Chicago (2008) and completed post-doctoral studies at the Swiss Federal Institute of Technology, EPFL (2009-2012). Martin served as director of the Conquer Chiari Research Center at the University of Akron (2012-2015). His research mission is to investigate CSF system physiology in CNS disorders and advance related technologies to the clinic and medical technology sector. More information can be found at the Neurophysiological Imaging and Modeling Laboratory webpage, http://www.niml.org.

# COMPUTATIONAL MODELLING OF SPINAL PERIVASCULAR FLOW: RELATIONSHIPS BETWEEN PERIVASCULAR TRANSPORT AND SUBARACHNOID SPACE PRESSURE, PULSE TIMING AND PULSE SHAPE.

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***Abstract.*** A substantial proportion of Chiari Malformation Type I patients also develop syringomyelia, a condition where a fluid-filled cavity forms in the spinal cord, causing additional, often severe, neurological dysfunction. Syringomyelia is difficult to treat, and the mechanisms are poorly understood. It is also difficult to predict which Chiari patients will develop syringomyelia.

It has been shown that the perivascular spaces around the penetrating arteries of the spinal cord are a major route by which CSF can flow from the spinal subarachnoid space (SAS) into the spinal cord, driven by arterial pulsation [1]. There is a hypothesis that these peri-arterial spaces act as a 'leaky valve' [2], with flow resistance varying with the cardiac cycle. This would mean that peri-arterial flow depends on the relative timing of the SAS pressures and arterial pulsations in the penetrating arteries [3]. This has previously only been investigated in case studies [3].

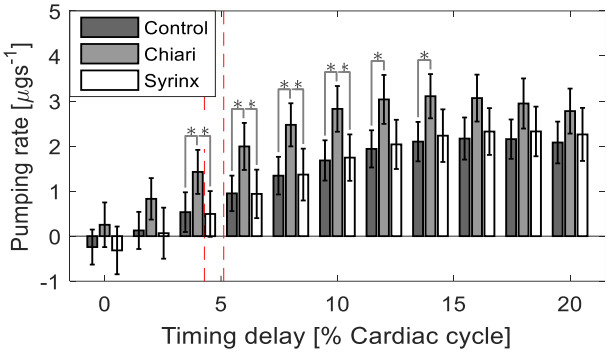


**Fig. 1.** Group mean net pumping rate per cardiac cycle with 95% CI (y-axis) against the temporal delay between the SAS pressure and arterial pulse wave (x-axis). Significant comparisons indicated by an asterisk (* = $p < 0.05$). Dashed lines indicated the 95% CI of the measured time delay between SAS and arterial pulse waves in the C5 vertebral artery.

A series (N = 24) of SAS pressures calculated from subject specific CFD models (9 controls, 7 Chiari patients with and 8 without a syrinx), were linked with a previous model of the perivascular space [2], to determine where the difference in CSF dynamics would lead to greater fluid flow into the spinal cord in the patient groups. The onset of systolic uptake (relative to the R wave) in the C5 vertebral artery was taken as estimation for the expected phase difference between the SAS and arterial pulse waves.

The model showed that on average the patients without a syrinx had greater net flow into the spinal cord than controls and syrinx patients (Fig 1.). Flow measurements found the arterial pulse to occur 4.7±0.2% later than the SAS pressure wave. A stepwise regression analysis showed that earlier arrival of peak pressures in combination with a larger peak pressure and a positive net area under the curve, would lead to increased CSF flow into the spinal cord.

These results indicate that the changes in CSF dynamics introduced by Chiari could significantly increase the fluid flowing into the spinal cord via the perivascular spaces, and the temporal offsets between cardiac and SAS pressures required for this mechanism to occur are physiologically feasible. They also suggest that the presence of a syrinx may normalize SAS pressure profiles and this could hinder further growth of the syrinx. Further analysis of how patient pressure profiles change over time, with the development of a syrinx and in response to treatment, are important to identify characteristics which lead to syrinx formation and continued growth.

**Lynne E Bilston**

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***About the Presenter:*** Professor Lynne Bilston, BE, MSE, PhD, is a biomechanical engineer with research expertise in neural tissue mechanics. She is an NHMRC senior research fellow, based at Neuroscience Research Australia and the University of New South Wales. She develops and uses novel methods for quantifying neural tissue biomechanics, including applications to cerebrospinal fluid flow disorders, including syringomyelia and hydrocephalus.

# POSTURE EFFETS ON CEREBROSPINAL FLUID PRESSURE GRADIENT AND DYNAMICS: DOES NORMAL INTRACRANIAL PRESSURE HAS SUBATMOSPHERIC (NEGATIVE) VALUE?

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**Abstract**. It is generally believed that cerebrospinal fluid (CSF) pressure (CSFP) is regulated by rate of CSF secretion and resistance to circulation and absorption of CSF. However, it is not known which factors determine CSF pressure inside craniospinal system during body position changes. Body verticalization is followed by momentary decrease of hydrostatic CSF pressure inside cranium. This decrease is shown as transient, and is explained by sudden cranial fluids exchange. We hypothesized that these effects are not related to the cranial fluid volume changes, but depend on biophysical characteristics of cranial and spinal intradural space, as well as laws of fluid mechanics. Mentioned hypothesis was tested on cats and new artificial model of cranio-spinal space. CSF pressure changes in anaesthetized cats, with or without cervical stenosis, were compared with those in artificial model of CSF consisting of non-distensible „cranial" and distensible „spinal" part at the same recording points. Measuring cannulas were introduced into lateral ventricle (LV), cortical subarachnoid space (CSS) (4 cm from foramen magnum) and lumbar subarachnoid space (LSS) in cats fixed on a board in a prone position. Recording instruments were fixed on the board at the same hydrostatic level as the corresponding measuring cannula. In horizontal position the pressures were similar in cranial and lumbar regions in both animal and artificial model. In vertical position, CSFPs (cm $H_2O$) of control animals in LV and CSS were similar (about -4), and in lumbar region it was about +32. Negative intracranial pressure was stable during recording in an upright position in cat as well as in artificial model. During postural changes, intracranial subatmospheric CSFP was not observed in animals with cervical stenosis. Results implicate that CSF pressure in cranium in upright position is determined by laws of fluid mechanics but not by changes of CSF and blood volume inside the cranium (Fig.1) [1,2,3]. Our results suggest that the cranial volume of blood and CSF remains constant in all body positions, which enables a good blood brain perfusion during everyday life activities. Hydrostatic CSFP gradient inside the cranium and LSS observed during changes of body position is not in accordance with the classical hypothesis of CSF physiology and unidirectional circulation [1,2]. It seems that normal intracranial pressure in upright position in control animals has subatmospheric value (Fig.1) [3].

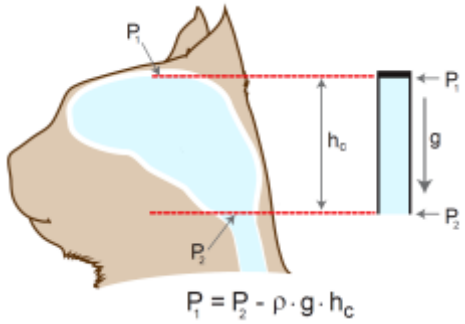


**Fig. 1.** Schematic presentation of our hypothesis. On the right side of the scheme a plastic tube is shown, filled with fluid and open at the lower end. Fluid pressure at the top of the tube ($P_1$) is lower than the atmospheric pressure ($P_2$), and it's value corresponds with the hydrostatic fluid column inside the tube ($P_1 = P_2 - \rho \times g \times h_c$). According to the law of fluid mechanics, inside tube negative (subatmospheric) pressure appears without the changes of the fluid volume. CSF inside the cranium should undergo the same fate. Thus, negative value of CSFP inside the cranium depends on the distance between the point of measurement and foramen magnum ($h_c$).

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**Klarica Marijan**

***About the Presenter.*** Klarica Marijan MD, PhD, Professor of Pharmacology. **Main research interests**: pathophysiology and pharmacology of the cerebrospinal fluid disorders and intracranial pressure. Dean, Head of the Department of Pharmacology and Department of Neurophysiology, Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia.

# MEASURING BRAIN BIOMECHANICS IN CHRONICALLY SHUNTED HYDROCEPHALUS WITH MR ELASTOGRAPHY

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***Abstract.*** While cerebrospinal fluid (CSF) shunting is a life-saving procedure in pediatric hydrocephalus, even patients who are "successfully" shunted will often suffer developmental delays, cognitive deficits, and other medical issues. In particular, headache, often severe and debilitating, occurs in as much as 40% of patients. Under the hypothesis that biomechanical changes in the brain may be in part responsible for the poor clinical outcomes, we sought to investigate the changes in brain stiffness in the hydrocephalic brain, in patients who have been shunted for many years, and to explore its associations with outcome in terms of headache and quality of life. Twenty five patients, all shunted before two years of age, were recruited for the study and compared to 12 healthy controls. MR Elastography (MRE)[3], a noninvasive MRI-based imaging technique, was used to extract measures of brain stiffness. . MRE was performed by inducing a mechanical vibration at 30Hz, transmitted through air-activated pistons at the zygomatic arches. MRE images were processed using Algebraic Helmholtz Inversion[5]. Masking of stiffness maps was used to eliminate areas of low stiffness, such as near the ventricles, and low vibration amplitude, and mean white matter brain stiffness (G* in Pascal) was extracted as the primary imaging measure. The Headache Disability Index (HDI)[2] and Hydrocephalus Outcome Questionnaire (HOQ)[4] were collected in all patients, as well as other clinical and shunt-related information. Brain stiffness in patients, averaged across the white matter, was compared to healthy controls, and linear associations between average brain stiffness were investigated as a function of total headache index, and quality of life indices.

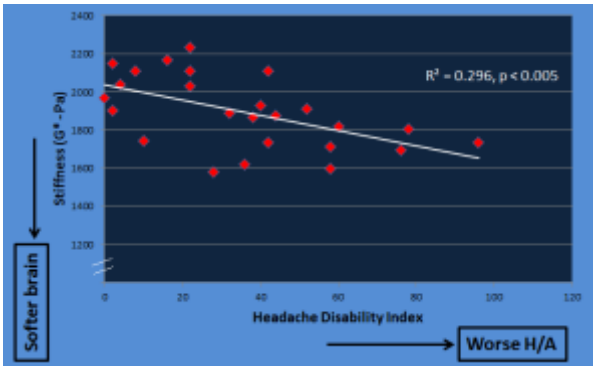


**Fig. 1.** Plot of WM brain stiffness in chronically shunted hydrocephalus patients as a function of headache severity index. The softening of the brain with increasing symptoms was consistent with the findings of softer brain tissue in shunted patients compared to healthy controls.

Overall, brain stiffness was *reduced* in patients compared to controls (G* = 1.92 ± 0.20 kPa vs. 2.10 ± 0.13 kPa, $p < 0.005$). There was a significant linear association between mean stiffness and headache index ($r^2 = 0.3$, $p < 0.005$) and QoL ($r^2 = 0.20$, $p < 0.05$), with brain stiffness decreasing with increasing headache severity and with reduced QoL (see Figure 1). The reduction in brain stiffness in patients may be an indication of a degradation of the biomechanical integrity of the brain tissue – a similar effect has been reported in the aging brain[1]. This could be the result of the hydrocephalus pathology, the ventricular distortion of the tissue at onset or over time from overdrainage, or from the repeated injury during shunt failures. MR Elastography thus may serve as a potential noninvasive tool for assessing the effect of ventricular dilation and shunting on brain tissue, and could be used to better tailor shunting strategies for minimizing these long-term effects on brain tissue and provide better clinical outcomes.

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**Mark Wagshul, PhD**

***About the Presenter:*** Mark Wagshul, PhD, is an Associate Professor of Radiology at the Albert Einstein College of Medicine. Dr. Wagshul received his PhD in physics from Harvard University in 1992. His current research interests include the development of MRI-based imaging tools for studying CSF dynamics and brain biomechanics in hydrocephalus, translational animal models of hydrocephalus, and general acquisition technique development in MRI.

**SESSION C, MON, 19JUN17, 2:20PM**

# COMPOUND CSF DISORDERS: HYPERTENSION, HYPOTENSION AND ICP MONITORING

Mark Luciano, Johns Hopkins University, Baltimore, MD, United States
Lacie Manthripragada, Johns Hopkins University, Baltimore, MD, United States
Aruna Rao, Johns Hopkins University, Baltimore, MD, United States
Abhay Moghekar, Johns Hopkins University, Baltimore, MD, United States
David Solomon, Johns Hopkins University, Baltimore, MD, United States

CSF disorders include hydrocephalus, intracranial hyper- and hypo- tension, cerebral cysts as well as Chiari anomaly-associated obstruction and compression. We have had numerous complex patients with multiple CSF disorders occurring at a given point in time. All of these anomalies can occur in a single patient at different points in time making differentiation and appropriate treatment challenging. Cases of interaction of these disorders will be presented along with diagnostic and treatment challenges. In the case of intracranial hypotension, low sensitivity of imaging diagnosis and localization of CSF leaks can be due to very slow, too fast or episodic leakage. This can present challenges as adequate treatment of intracranial hypotension rests on localization of a specific site of CSF leak as well as access. Improper treatment by subdural fluid drainage or Chiari decompression can lead to worsening patient conditions. Multiple failed epidural patches for intracranial hypotension in the context of a background of increased cranial pressure are not uncommon occurrences. As a result of these difficulties, we have collected continuous intracranial pressure monitoring data in over 20 complex patients suspected of pseudotumor cerebri, CSF leak, or both for a 2-3 day period of time. These measurements were taken in multiple positions including horizontal, sitting, standing and after ambulation. Current definitions of normal range and pressure waves appear of limited value in the assessment of these complex patients. The use of these findings in diagnosis and treatment will be analyzed and the need for new methods discussed.

***About the Presenter:*** Dr. Luciano is the Henry Brem Professor of Neurosurgery at Johns Hopkins School of Medicine where he directs the Cerebral Fluid Center. He received his medical degree from the University of Chicago and trained in General and Pediatric Neurosurgery at the University of Pennsylvania and Harvard's Boston Children's Hospital, respectively. He also earned a Ph.D. in from Tulane University and performed a research fellowship at the NIH.

# IN VITRO MODELING OF THE CSF DYNAMICS TO INVESTIGATE THE ETIOLOGY OF NPH

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***Abstract.*** The hydrodynamics of the cerebrospinal fluid (CSF) system is highly complex especially when it comes to pathological conditions. Normal Pressure Hydrocephalus (NPH) is characterized by ventricle enlargement without an attendant rise of intracranial pressure (ICP). In addition to the clinical symptoms of the Hakim Trias – dementia, gait ataxia and urinary incontinence – elevated pulse pressure amplitude [1], reduced regional blood flow [2, 3], modified reabsorption sites and resistances [2] as well as an overall reduced compliance [4] are reported for NPH patients. However the onset of NPH is still not understood. Therefore our aim is to design a concept of an in vitro model which includes all the relevant mechanisms that influence the CSF dynamics for the execution of sensitivity analyses. Furthermore we want to focus on alterations due to aging.

Based on an in-depth literature review and a requirements analysis influencing parameters were defined. A concept for an anatomical in-vitro model of the craniospinal hydrodynamics was developed separating cranial and spinal subarachnoid space (SAS) to investigate their influence. The model includes the brain parenchyma, SAS and compliances (Fig. 1).

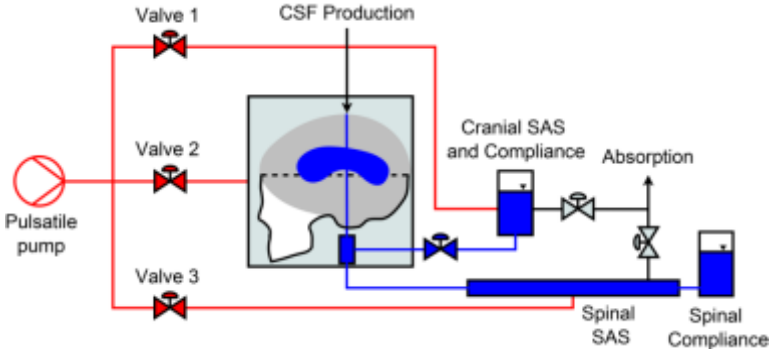


**Fig. 1.** Schematic concept of the phantom model including brain parenchyma, cranial and spinal compartment, CSF production and absorption, a pulsatile pump to reproduce the movements of the blood vessels and compliance units [5].

To simulate the pulse transmission via blood vessels a pump is connected to the rigid water filled PMMA box as well as the cranial and spinal SAS. The pump shifts fluid according to the arterial input and venous output measured by El Sankari et al. [6]. Valves are used to control the output into the different compartments. A continous pump simulates the CSF production in the ventricles with a rate of 0.35 ml/min. This flow is reabsorbed in the SAS during physiological testing but can be adapted for pathological behaviour. To investigate the influence of hydrostatics when changing the patient position the spinal canal can be connected horizontally or upright. All components of the model are designed to be adjustable enabling a variety of sensitivity analyses.

All in all the model offers a novel concept for NPH research with special consideration of the spinal compartment. Testing and validation of the experimental simulator and a corresponding simulation model as well as the integration of dynamic compliances are major objectives of our ongoing research.

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**Anne Benninghaus**

***About the Presenter:*** Anne Benninghaus received her M.Sc. degree in mechanical engineering with specialization in medical engineering from RWTH Aachen University, Germany in 2015. She is currently a PhD candidate at the Chair of Medical Engineering, RWTH Aachen University. Her research focuses on in vitro and in silico modelling of the cerebrospinal fluid dynamics in order to investigate and understand the etiology of Normal Pressure Hydrocephalus.

# INTRATHECAL BOLUS: THE INITIAL DYNAMICS AND SOLUTE ENTRANCE INTO THE PERIVASCULAR SPACES

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[2]Harvard Medical School, Boston, MA;
[3]Shriners Hospitals for Children, Boston, MA

***Abstract.*** The goal of our studies was to investigate the dynamics of in vivo transport of solutes administered to the cerebrospinal fluid (CSF) and evaluate the potential routes of non-diffusional drug entrance from the CSF to the CNS.

To observe solute transport by PET, experimental large and small molecules were labeled with $^{124}$I or $^{89}$Zr and administered intrathecally (IT) to rats and cynomolgus monkeys. Dynamic imaging data and multiple whole-body images were acquired using Siemens MicroPET focus 220 imager; CT images were acquired using CereTom NL 3000 CT scanner (Neurologica, USA). Images were analyzed to determine the rates and patterns of the label spread within the CSF from the injection site and farther into the CNS. To evaluate the potential routes of non-diffusional drug entrance from the CSF to the CNS, a model fluorescent macromolecule capable of labeling multiple cell types was administered intrathecally in rats; the microdistribution of the label was studied by fluorescence photoimaging in unstained cryosections.

The initial solute distribution in the CSF greatly depended on the injected volume. Solutes injected at a low volume initially localized near the opening of the catheter. Solutes injected at a high volume immediately translocated to the cervical/basal cerebral area (up to >90% of the injected dose). The subsequent solute spread was slow in the spinal CSF (millimeters per hour) but fast in the cerebral CSF (complete equilibration within 30 min). No evidence of directional solute flows anywhere in the CSF was found. In rats lymphatic drainage from the CSF was detected in the deep anterior cervical area (ca. 3% of the ID). In monkeys, no evidence of significant lymphatic drainage from the CSF was found in any region (<0.3% ID in total).

Solute translocation into the brain and cerebellum from the CSF was observed by PET during the first 3-5 hours after the injection, with subsequent biphasic clearance. The routes of translocation were further investigated with fluorophores labeling multiple cell types. Massive labeling of the perivascular channels entering the CNS from the outer as well as the inner boundaries was observed throughout the CNS with indications of probe exit to the parenchyma (Figure 1). The coverage of the parenchyma by large and small transporting channels was found to be very significant with highest densities at the internal boundaries.

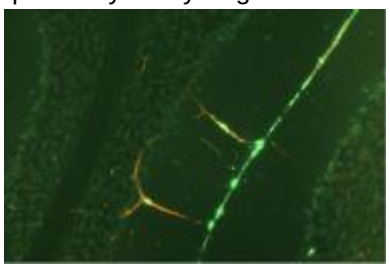

Figure 1. Perivascular channels (bright green labeling) in the cerebellum of rat along arteries (red labeling) branching from the cerebellar fissure into the granular layer (green patterned).

The overall mechanistic landscape of the cerebrospinal solute transport significantly differs from the paradigm suggesting that CSF bulk flows prevail outside the CNS, whereas interstitial flows prevail within. The major factor of the initial distribution of the administered drug is the hydrostatic compliance of the compartment. The secondary drug distribution in the CSF is an interplay of hydrostatic factors, molecular recognition and (for small molecules) diffusion. The subsequent phase of drug entrance into the CSF is an interplay of active perivascular transport, molecular recognition and diffusion.

The observed transport phenomena can explain most, if not all, known but insufficiently understood effects of IT administered drugs. The observed transport timeframes suggest a possibility for optimizing IT schedules of existing drugs, as well as a strong potential for developing highly effective, targeted novel intrathecal therapies in the near future.

***About the Presenter:*** Mikhail ("Misha") Papisov, PhD, Associate Professor of Radiology (Harvard Medical School), Investigator (Massachusetts General Hospital and Shriners Hospitals for Children – Boston). Head of Molecular Pharmacology and Pharmacological Imaging laboratory. Scientific Founder of Mersana Therapeutics. Received his M.S. in Chemistry from Moscow State University in 1982 and Ph.D. in Biology from the National Cardiology Research Center of the Academy of Medical Sciences in Moscow in 1988. Research focus: development of macromolecular and nano-therapeutics with emphasis on novel physiological aspects of macromolecule transport in vivo; structure-pharmacokinetics relationships of macromolecular therapeutics; and quantitative preclinical imaging.

# DARCY-BRINKMAN MODEL OF SHEAR-AUGMENTED DISPERSION IN CEREBRO-VASCULAR BASEMENT MEMBRANES AND THE SPINAL SUBARACHNOID SPACE

M. Keith Sharp[1], Bryn Martin[2], Roxana O. Carare [3]

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[2] Neurophysiological Imaging and Modeling Laboratory, University of Idaho, Moscow, ID, USA
[3] Institute for Life Sciences, Southampton General Hospital, University of Southampton, Southampton, UK

***Abstract.*** Diminished transport of amyloid-β in cerebrovascular basement membranes may contribute to Alzheimer's disease, and the spinal subarachnoid space (SSS) is a route for intrathecal delivery of medications to the central nervous system. These spaces differ greatly in terms of size, but both are filled with structures that can be modeled as porous media. In the SSS, the CSF moves in an oscillatory manner within a space filled with ~15 μm diameter web-like fibers called arachnoid trabeculae. Tracers move within the 100 nm wide basement membranes of intracranial arteries, which are filled with a variety of proteins. Measurement of flow in basement membranes is challenging due to the small size of the channels, but it seems reasonable to hypothesize that oscillatory flow is driven by pulsatile pressure within the blood vessels. Recognizing these commonalities, transport in both spaces was investigated with a model involving oscillatory flow in a 2D channel containing Darcy-Brinkman porous media. Dispersion was modeled by the passive transport equation.

Analytical solutions were obtained for parameters representing quasi-steady, Darcy and unsteady regimes of flow, and quasi-steady and unsteady regimes of dispersion. These parameters include the Schmidt number *Sc*, the oscillatory Peclet number β and the Darcy number *Da*. The Darcy-Brinkman model adds to the equation of motion a uniform flow resistance across the channel, while maintaining no-slip at the walls. The Darcy term flattens the velocity profile except when the flow is unsteady, and reduces transport compared to the case without porous media, except when flow and dispersion are unsteady.

Results predict that shear-augmented dispersion in the basement membranes is insignificant because both flow and dispersion are quasi-steady. In the SSS, the flow is transitional between Darcy and unsteady, and the dispersion is unsteady. As a result, the enhancement *R* of transport relative to molecular diffusion is by 1 - 2 orders of magnitude, depending on the permeability input into the model (Fig. 1).

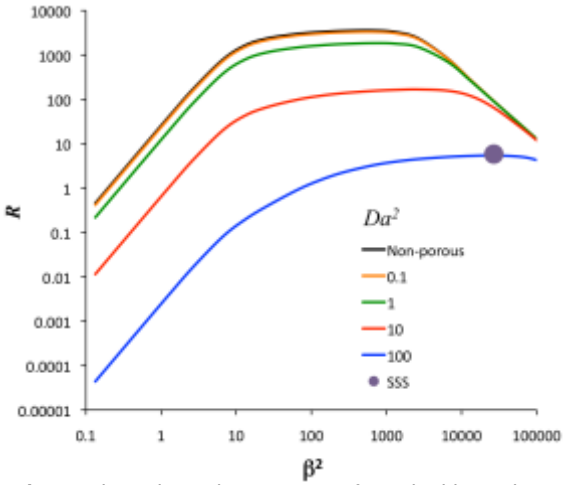


**Fig. 1.** Dispersion enhancement *R* for Schmidt number *Sc* = 1330 and nondimensional pressure gradient amplitude *P* = 156. The purple point shows estimated conditions for transport of Methotrexate in the SSS ($\beta^2$ = 26900 and $Da^2$ = 95.3)

Several simplifications inherent in the model limit the predicted enhancement, including the idealized geometry and the continuum approximation of the porous media, with its lack of cross-stream convective mixing. However, the transport enhancement in the modeled basement membranes is so small that it seems unlikely that improvements in the model would lead to significant enhancement. This means that, under the applied assumptions, shear-augmented dispersion does not help carry amyloid-β or other tracers along these channels, and observed transport likely occurs primarily by advection. In the SSS, cross-stream mixing and other improvements could lead to even greater dispersion, making the exploitation of this effect for intrathecal transport of drugs to the brain an attractive topic of further research.

**M. Keith Sharp**

***About the Presenter:*** Keith Sharp is the Director of the Biofluid Mechanics Laboratory in the Department of Mechanical Engineering at the University of Louisville. He received Bachelors, Masters and Doctor of Science degrees from the University of Cincinnati, Colorado State University and the Massachusetts Institute of Technology, respectively. His research interests span flow and transport in biological systems, including cardovascular devices, blood rheology and hemolysis, cardiovascular system modeling, and cerebrospinal and interstitial fluid in the brain.

# PRESSURE GRADIENT ESTIMATION IN THE SPINAL CANAL BASED ON IN VIVO MR MEASUREMENTS

Francis Loth[1,2,4], Soroush H. Pahlavian[1,2], John Oshinski[3]

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[2] Conquer Chiari Research Center, The University of Akron, Akron, Ohio, USA
[3] Radiology & Imaging Sciences and Biomedical Engineering, Emory University School of Medicine, Atlanta, Georgia, USA
[4] Department of Biomedical Engineering, The University of Akron, Akron, Ohio, USA

***Abstract.*** A computational tool was developed to estimate the *in vivo* unsteady pressure field within the spinal canal from pcMRI. Previous researchers [1] have shown that 4D MR measurements of velocity can be used to obtain a noninvasive estimate of the pressure gradient across a renal artery stenosis. Furthermore, they demonstrated that this estimate is well correlated with invasive measurements using a pressure catheters. The goal of the present study is to examine the applicability of this method to the spinal canal. A noninvasive measurement of pressure gradient in the spinal canal may help physicians to better understand the importance of the blockage at the foreman magnum in Chiari malformation subjects. The calculation of relative pressure from a known measured velocity field was achieved by solving the pressure Poisson equation (PPE) from the Navier-Stokes equation based on the approach proposed by Song et al. [2]. The performance of the pressure calculation technique was tested on a numerical phantom generated based on a patient-specific CFD model of CSF motion in the upper cervical SAS. The reference velocity and pressure solutions were obtained using CFD. In order to mimic the voxel-based structure of pcMRI data, CFD velocities were averaged into structured grids of various voxel sizes and used as input data. The resulting relative pressure distribution was used to calculate pressure difference between the two ends of the model. The accuracy of these pressure-based parameters was assessed by comparing them against the value obtained directly from the CFD. Figure 1 compares the cranio-caudal pressure difference waveforms and the mid-sagittal relative pressure distributions between the PPE-based estimation and the reference CFD solution of the subject-specific numerical phantom. Good agreement was observed between the reference and the estimated pressure distributions and pressure difference waveforms with the maximum of 6.4% difference between the two for the voxel size of 0.25 mm. Increasing the voxel size to a more realistically achievable value in 4D PCMRI (1.0 mm) decreased the accuracy of the method to a great degree, as the maximum error between the reference CFD and the estimated pressure difference waveforms was increased to 28.2%.

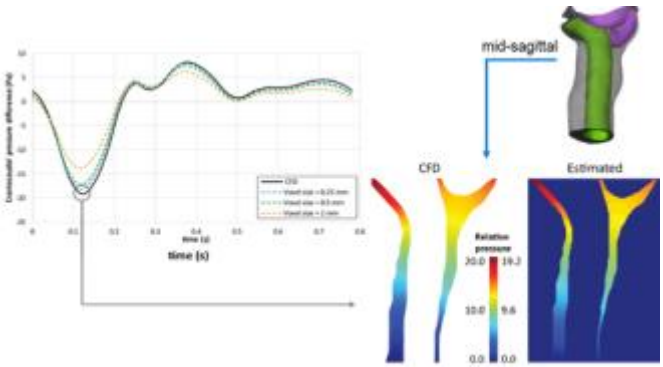


**Fig. 1.** Comparison of the craniocaudal pressure difference waveforms and the mid-sagittal relative pressure distributions obtained from the reference CFD and estimated using the PPE-based technique in the subject-specific numerical phantom.

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3. Golub, G., A. Greenbaum, and M. Luskin, Recent Advances in Iterative Methods. 1994: Springer New York.

***About the Presenter:*** Francis Loth received his Ph.D. degree in Mechanical Engineering in the area of *biofluids* at the Georgia Institute of Technology in 1993. He began his career as a faculty member of the Mechanical Engineering Department at the University of Illinois at Chicago in 1996. In 2008, he moved to The University of Akron in the Department of Mechanical Engineering. He created the Conquer Chiari Research Center in 2012. His research area is in the simulation and measurement of blood and cerebrospinal fluid dynamics. He employs both experimental and numerical techniques to better understand the mechanical forces involved in bypass graft failure as well as in diseases such as atherosclerosis, Chiari malformation, and syringomyelia. He has co-organized workshops in the area of hemodynamics (2001) and Chiari malformation and CSF (2007, 2008, 2010, 2011 and 2014). Currently, he is Professor and the F. Theodore Harrington Endowed Chair in the Department of Mechanical Engineering at The University of Akron.

**Francis Loth**

# AUTODIGESTION AND PROTEOLYTIC RECEPTOR CLEAVAGE: DIGESTIVE ENZYMES ON THE PROWL

Geert W. Schmid-Schönbein[1], Angelina E. Altshuler[1], Frank A. DeLano[1], Erik B. Kistler[2]

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[2] Department of Anesthesiology and Critical Care Medicine, University of California, San Diego and San Diego VASDHS, La Jolla, CA, USA

***Abstract.***

*How does one digest biological molecules in food but not digest one's own intestine?*

The answer to this question raises a fundamental issue that could be a key to understand many non-infectious diseases, inflammation and even death. During every meal the pancreas releases a set of digestive enzymes into the small intestine where they degrade biopolymers of diverse food sources as part of normal digestion. An important mechanism that prevents autodigestion of one's own intestine by the digestive enzymes is their containment in the lumen of the small intestine by the mucosal epithelial barrier. This barrier blocks entry of pancreatic enzymes from the lumen into the wall of the small intestine to allow digestion (of food) but not autodigestion (of autologous tissue). But our evidence suggests, that the protection by the mucosal barrier against autodigestion may fail and thereby allow escape of digestive enzymes into the systemic circulation[1]. Disruption of blood flow to the intestine, bacterial products, or high fat diet is each able to open the mucosal epithelial barrier and allow transport of digestive enzymes into the wall of the intestine. The digestive enzymes cause severe destruction of autologous tissue starting with the intestinal villi and mucosa layer. Digestive enzymes are carried into the systemic circulation together with tissue breakdown products they generate and appear the lung, heart and other organs. Digestive proteases (e.g. trypsin) activate other proenzymes (e.g. matrix metalloproteinases) and together they cause organ dysfunction by cleaving membrane proteins. For example, extracellular cleavage of the insulin receptor leads to reduction of insulin signaling and suppression of glucose transport, i.e. insulin resistance. Our evidence in experimental animals shows that inhibition of digestive enzymes inside the lumen of the small intestine, e.g. during reduction of intestinal perfusion, minimizes autodigestion and reduces organ dysfunction and mortality[2]. This unique approach may be tested in patients subject to acute organ dysfunction.

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2. DeLano, F.A., Hoyt, D.B., Schmid-Schönbein, G.W.: Digestive enzyme blockade in the lumen of the intestine increases long-term survival rate after shock. Science Translational Medicine, 5(169):169ra11, 2013.

***About the Presenter:*** Geert W. Schmid-Schönbein is Distinguished Professor and Chair of the Department of Bioengineering at UC San Diego. He teaches bioengineering of living tissues and cell and molecular mechanics. He is Founding Member of AIMBE, former President of BMES, Fellow of the American Heart Association, BMES, the Physiological Society, and the International Federation for Medical and Biological Engineering. He is Past Chair of the US National Committee on Biomechanics and Past Chair of the World Council for Biomechanics and Member of the US National Academy of Engineering. Recently his group discovered a fundamental mechanism for cell dysfunctions and organ failure due to "Auto-digestion".

# THE ROLE OF FLUID TRANSPORT IN REPERFUSION INJURY POST ISCHAEMIC STROKE

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***Abstract.*** It is well known that following ischaemia, perfusion patterns can be permanently altered, with a restoration of global blood flow not leading to reperfusion in all regions affected by hypoxia-ischaemia. There are a number of reasons that have been suggested for this, including the permanent occlusion of capillary vessels and the effect of parasite death. In ischaemic stroke, the role of fluid transport can also be important, with regions of oligaemia being of clinical significance: identifying the different types of cell swelling can assist in clinical decision making.

There is also often substantial movement of brain tissue with the dividing line between ipsilateral and contralateral hemispheres exhibiting significant displacement. This is caused by a rise in interstitial pressure, indicating potentially substantial movement of fluid between the bloodstream and the tissue. This transport and rise in pressure also has the potential to affect the behaviour of the microvasculature, potentially playing a role in reperfusion injury.

We thus investigated this transport using a model of fluid transport between three phases: blood, the interstitial space and the tissue. Using multiple compartment theory and a model of the collapsible capillary wall, we determined the threshold at which vessel collapse can occur and mimicked the behaviour post-reperfusion, showing that under certain conditions vessel collapse can play a significant part in the response. We then extended the model to examine the transport between both astrocytes and neurons and to quantify the effects of the presence of aquaporins.

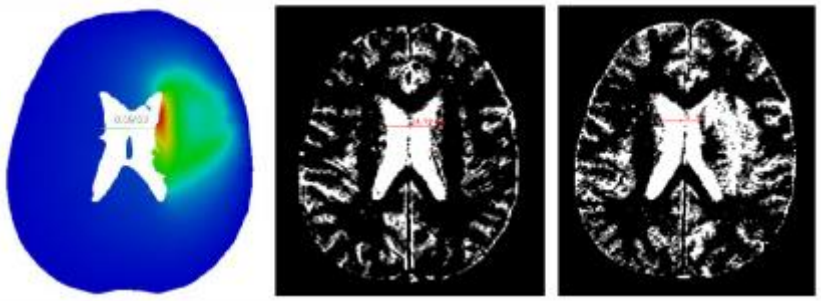

**Fig. 1.** Example simulation of ventricle compression and comparison with patient MRI data following ischaemic stroke.

Finally, we used this model to simulate the response of reperfusion in two human subjects, based on imaging data acquired post-ischaemic stroke and examined the movement of the centre line in terms of the stiffness of the brain tissue, as shown in Figure 1. The simulations indicate a good preliminary agreement with clinical imaging data, with the tissue stiffness (a parameter not well parameterised in the literature) appearing to lie consistently within a physiologically reasonable range. Future work will involve extending this to more patient data and performing a rigorous sensitivity analysis of the model to identify the most important parameters.

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2. Mokhtarudin, M.J.M. and Payne, S.J. The study of the function of AQP4 in cerebral ischemia-reperfusion injury using poroelastic theory. International Journal for Numerical Methods in Biomedical Engineering, 33: e02784, 2017.

***About the Presenter:*** Stephen Payne has been an Associate Professor in Biomedical Engineering at the University of Oxford and Fellow and Tutor at Keble College, Oxford, since 2006. His research interests primarily lie in the mathematical modelling of cerebral blood flow and metabolism, with a strong focus on autoregulation. His group have authored over 80 journal papers and he is the author of 'Cerebral Autoregulation' (Springer, 2016) and 'Cerebral Blood Flow and Metabolism (World Scientific Publishing, 2017).

**Stephen Payne**

# SUBJECT-SPECIFIC MULTIPOROELASTIC MODEL FOR EXPLORING THE RISK FACTORS ASSOCIATED WITH DEMENTIA

Liwei Guo[1], John C. Vardakis[1], Toni Lassila[2], Micaela Mitolo[3], Nishant Ravikumar[4], Dean Chou[5], Matthias Lange[2], Ali Sarrami Foroushani[2], Brett J. Tully[6], Zeike A. Taylor[4], Susheel Varma[2], Annalena Venneri[3,7], Alejandro F. Frangi[2], Yiannis Ventikos[1]

[1]Department of Mechanical Engineering, University College London, UK,

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[5]Institute of Biomedical Engineering & Department of Engineering Science, University of Oxford, UK

[6]Children's Medical Research Institute and School of Medical Sciences, Sydney Medical School, The University of Sydney, Westmead, Australia

[7]Department of Neuroscience, Medical School, University of Sheffield, UK

***Abstract.*** Alzheimer's disease (AD) is the most common form of dementia, a clinical syndrome of progressive deterioration of cognitive abilities and ordinary daily functioning. In its early stage, AD may present itself as mild cognitive impairment (MCI), a state between normal aging and dementia. MCI is characterized by objective cognitive impairment relative to the person's age, with concern about the cognitive symptoms in a person with essentially normal functional activities who does not have dementia. Evidence suggests that in many cases, AD has a vascular component, caused by impaired cerebral perfusion, which may be promoted by cardiovascular risk factors (CRF). CRFs are known to be strongly influenced by lifestyle. In order to develop an understanding of the exact nature of such a hypothesis, a biomechanical understanding of the influence of lifestyle factors is pursued. We introduce a novel consolidated pipeline within the European *VPH-DARE@IT* project that integrates three key components: a 3D multiporoelastic-based model of cerebral parenchyma; an accurate, fully automated image-based model personalization workflow (subject-specific meshes, permeability tensor maps); and a subject-specific boundary condition model (blood flow variability). The subject-specific datasets used in the modelling were collected as part of prospective data collection. The size of this database is 104 participants (52 controls and 52 MCI cases). Subject-specific characterization of 24-hour blood flow variability was obtained through a combination of ambulatory blood pressure measurements, clinical ultrasound flow measurements, and mathematical modelling. For the latter, a lumped parameter circulation model is used to simulate continuous arterial blood flow and translate spot measurements collected at finite intervals to continuous waveforms of arterial blood flow. The preliminary cases simulated involved both male and female control and MCI cases. Smokers and non-smokers during two states of activity (high and low) were investigated within this cohort. Results showed variations in clearance of CSF/ISF, elevated parenchymal tissue displacement and CSF/ISF accumulation and drainage in the MCI cases.

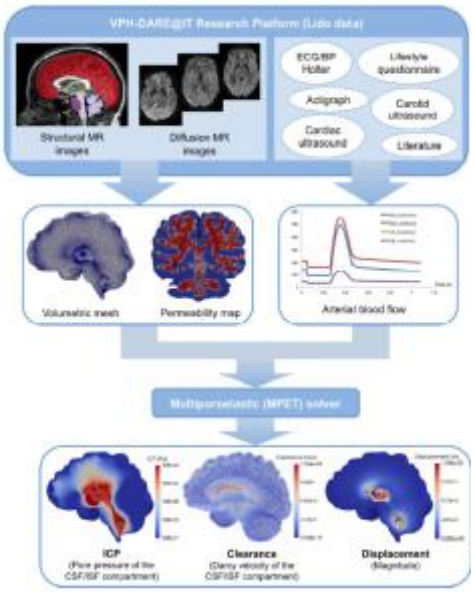
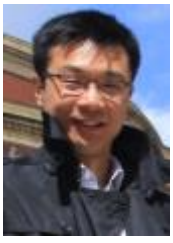



**Fig. 1.** The consolidated pipeline that incorporates the 3D MPET solver itself, with image- and non-image based model personalization modules.



**Liwei Guo**

***About the Presenter:*** Dr Liwei Guo is a Research Associate working with Prof. Yiannis Ventikos in the Department of Mechanical Engineering at University College London. Currently he works on the European VPH-DARE@IT (Virtual Physiological Human: DementiA Research Enabled by IT) project. The objective is to develop a finite element computational platform of three-dimensional multicompartmental poroelasticity model to simulate fluid transport phenomena in the brain, and use mechanistic modelling to understand dementia onset and progression and help early and individualised diagnosis. Prior to joining UCL, Dr Guo was a PhD student at Imperial College London and his main research was developing a fracture model for three-dimensional fracture and fragmentation simulations using the finite element and the discrete element methods.

# SIMULATING THE FLUID FLOW OF THE GLYMPHATIC SYSTEM - EXCTRACELLULAR FLUID FLOW

Kent-Andre Mardal[1,2], Karl Erik Holter[2,3], Klas H. Pettersen[4]

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[3] Department of Informatics, University of Oslo, Oslo, Norway
[4] Letten Centre, Institute of Basic Medical Sciences, University of Oslo, 0317 Oslo, Norway

Fig. 1 Mesh of 5 micron cube the extracellular space of the neuropil of a rodent

***Abstract.*** The recently proposed glymphatic system[1] describes a clearance mechanism where water flows through the paravascular and extracellular spaces of the brain, driven by pressure gradients between the arterial and venous parts of the vasculature. The glymphatic system has been related to the need for sleep and to the development of Alzheimer´s disease.

We have simulated pressure-mediated bulk flow through 3D electron microscope-based (EM) reconstructions of brain extracellular space[2]. Because electron microscopy is known to affect the morphology of the extracellular space, we compute flow in several reconstructions with the same extracellular volume fraction, but different shapes.

Using Darcy's law, we obtain estimates of the permeability in all reconstructions. We find that while the extracellular volume fraction is the main determinant of ECS permeability, the shape of the ECS also has a significant effect on ECS permeability. Our estimates of permeability can then be used to obtain a relationship between the hydrostatic pressure gradient and the rate at which it clears waste.

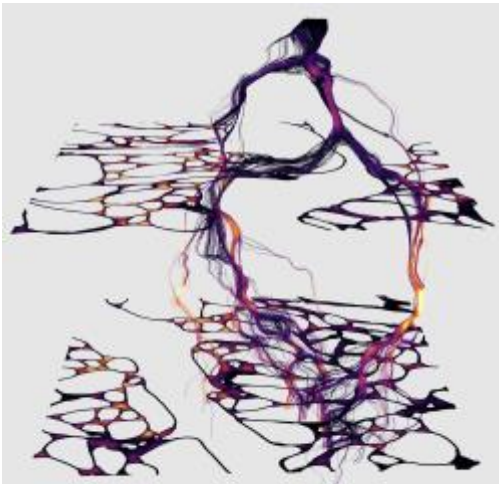

Fig. 2 Streamlines illustrating the computed flow

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***About the Presenter:*** Kent-Andre Mardal is a Professor at the University of Oslo and Adjunct Scientist at Simula Research Laboratory. His scientific interests include finite element methods, efficient solution algorithms, programming techniques for scientific computing, computational mechanics, interstitial and cerebrospinal fluid flow in association with the Chiari I malformation, syringomyelia, and hydrocephalus, Alzheimer´s disease and sleep.

# A BIOENGINEERING PERSPECTIVE ON THE HUMAN BRAIN CELLULAR STRUCTURE: WHAT DO WE KNOW AND WHAT WOULD WE NEED TO KNOW?

Diane de Zélicourt[1], Michael Schmid[1], Virginia Meskenaite[1] and Vartan Kurtcuoglu[1,2,3]

[1] The Interface Group, Institute of Physiology, University of Zurich, Switzerland
[2] Neuroscience Center Zurich, University of Zurich, Switzerland
[3] Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland

***Abstract.*** Different length scales ranging from micrometers to decimeters play an important role in physiological and pathophysiological brain mechanics and cerebral fluid dynamics. Changes in macroscopic loads induce responses or injuries at the cellular level, while cellular composition and axonal orientation impact the load bearing capacities of different brain regions. Fluid exchanges between brain interstitial fluid and surrounding cerebrospinal fluid are similarly related to the underlying tissue organization. Accordingly, multiscale frameworks have emerged as promising tools to bridge the gap between macro- and microcellular scales, reconstructing the global brain behavior from that of its individual constituents. As these frameworks rely on microscale structural information, their performance is dependent on the availability and accuracy of the corresponding data. Obtaining these from the existing literature is a tedious and time consuming undertaking. Herein we provide a global literature review on the cellular structure of the human brain, differentiating between main anatomical sub-regions and between white and gray matter. We further discuss the axonal density of selected white matter tracts and strategies to overcome the obstacle of missing data. In combination with multiscale modeling frameworks, the data contained herein provide a basis for advancing our understanding of brain mechanics and cerebral fluid dynamics.

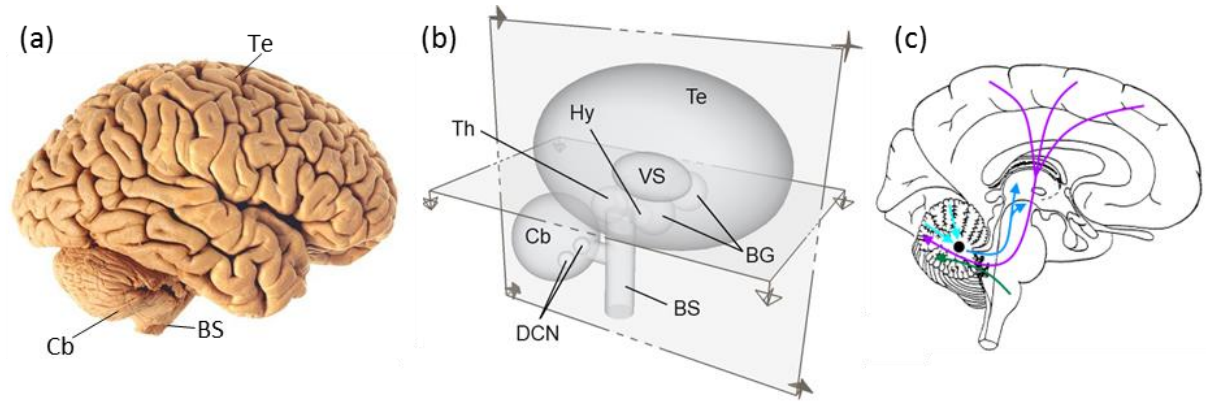


Fig. 1: (a) Lateral aspect of the human brain [1]. (b) Idealized regional representation retained for our regional analysis of the tissue composition and organization. (c) The main white matter tracts are simplified as well, and regrouped into the main paths and directions. We here illustrate the cerebellar white matter tracts, including the cerebellar corticonuclear tract (light blue), cerebellofugal tracts (dark blue), cerebellar mossy fiber system (violet) and cerebellar climbing fiber system (dark green).
*BG, basal ganglia; BS, brain stem; Cb, cerebellum; DCN, deep cerebellar nuclei; Hy, hypothalamus; Te, telencephalon (cerebrum); Th, thalamus; VS, ventricular system.*

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**Diane de Zélicourt**

***About the Presenter.*** Diane de Zélicourt studied engineering at the Ecole Polytechnique (France) followed by a Ph.D. in biomedical engineering at the Georgia Institute of Technology (USA). She is now a junior group leader within the Interface Group at the University of Zürich (Switzerland). Her primary research focus is computational methods in biomechanics, in both cardiovascular and intra-cranial arenas. Her current research seeks to provide the tools to understand normal and diseased intra-cranial mechanics, in particular normal pressure hydrocephalus.

# MR IMAGING AND MODELING OF CONNECTED PERIVASCULAR SPACES IN RODENTS

Malisa Sarntinoranont[1], Magdoom Kulam[1], Michael A. King[2], Thomas H. Mareci[3]

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***Abstract.*** Perivascular spaces (PVS) are annular gaps that exist between cerebral blood vessels and brain parenchyma[1]. In the absence of lymphatic vessels in the brain, several studies have proposed that metabolic wastes in the brain extracellular space are transported along these spaces[2-5]. Abnormalities in the perivascular pathway have been implicated in neurodegenerative disorders such as Alzheimer's[2] and syringomyelia[6]. In this study, we were interested in obtaining high-resolution, 3D reconstructions of the perivascular network in the rat brain. There is a need to know the distribution of perivascular channels in the whole brain to understand normal physiology and study the effects of abnormalities in the network such as obstruction or dilation observed in diseased brains.

Perivascular spaces were labeled using gadolinium-DTPA as a contract agent bound to albumin that was infused into the lateral ventricle of Sprague-Dawley rats. Vasculature was identified using a vascular casting technique wherein a magnetic-susceptibility-matched polymer was injected trans-cardially. MR imaging of the rodent brain was performed at 17.6 T and $T_1$ and $T_2$ weighted images were acquired. Perivascular labeling was visible in 30 μm isotropic $T_1$ weighted gradient echo images as hyperintense regions. Vasculature was identified as dark regions owing to the short $T_2$ of the solid polymer (Fig. 1).

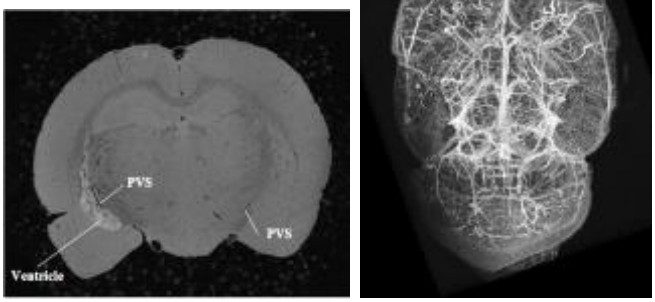


**Fig. 1.** (Left) 2D MR image showing gadolinium-labeled albumin tracer in the ventricle and PVS. (Right) 3D reconstruction of the vasculature. Vessels were then segmented and reconstructed in 3D using maximum intensity projection.

High-resolution PVS networks can be used in computational models to simulate flow and mass transport between subarachnoid, interstitial and perivascular spaces. Our lab has previously developed brain models of interstitial flow that account for specific anatomical boundaries and underlying tissue alignment[7]. PVS networks can be incorporated in this modeling framework to better understand the role of PVS connectivity on whole brain uptake and clearance.

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**Malisa Sarntinoranont**

***About the Presenter.*** Dr. Sarntinoranont is an Associate Professor in the Department of Mechanical & Aerospace Engineering at the University of Florida. For most of her career, she has been interested in understanding effects of increased and abnormal tissue flows on disease and therapy. Current research projects include: computational drug delivery models for the CNS and solid tumors, experimental tissue transport studies, traumatic brain injury, biphasic tissue modeling, and mechanical testing. Dr. Sarntinoranont received her undergraduate degree from Georgia Tech. She completed her M.S. and Ph.D. degrees in mechanical engineering at U.C. Berkeley. Her post-doctoral training was at the National Institutes of Health (NIH) in Bethesda, MD.

# Respiratory Driven CSF, Arterial and Venous Flow Oscillations Measured with Real-Time Velocity Phase Imaging

David A. Feinberg[1.2], Alexander Beckett[1], Liyong Chen[2]

[1] University of California, Berkeley

[2] Advanced MRI Technologies, Sebastopol, CA

***Abstract.*** Cardiac pulsations are known to drive CSF oscillations and brain pulsation (1), however, recently it has been shown with real-time (RT) phase contrast (PC) MRI that respiration drives bidirectional CSF motion in the cerebral ventricular system and subarachnoid spaces (2). The motion of CSF during respiration has been attributed to transient changes in intracranial venous pressure due to decrease intrathoracic pressure during breathing. Previously we measured large respiratory driven CSF movement with deep breathing through the foramen Magnum (FM) as CSF moves between the spinal canal and the cranial cavity, as also found in independent studies (3). Here venous and CSF oscillations are studied, in addition to measurement of spinal CSF motion. *Methods:* Studies of 4 subjects on a 3T scanner using RT PC SMS-EPI parameters for CSF: TR = 78–82 ms, TE = 30–32 ms; in-plane IPAT factor = 2; spatial resolution = 1.5 × 1.5 mm$^2$; slice thickness = 3–5 mm; matrix = 128 × 128; simultaneous multi-slice (SMS EPI) excited by SMS= 2-3, VENC = 5–10 cm/s, phase subtraction sliding between TRs in which the bipolar pulse had alternating polarity (2). The 30s real-time scan was performed for each RT PC time series acquisition of z-axis velocity direction. For shorter TE in blood velocity measurements, segmented two shot centric order EPI sequence for TE=6-10ms was used. Respiratory belt identified respiratory phase in 30 second RT measurements.

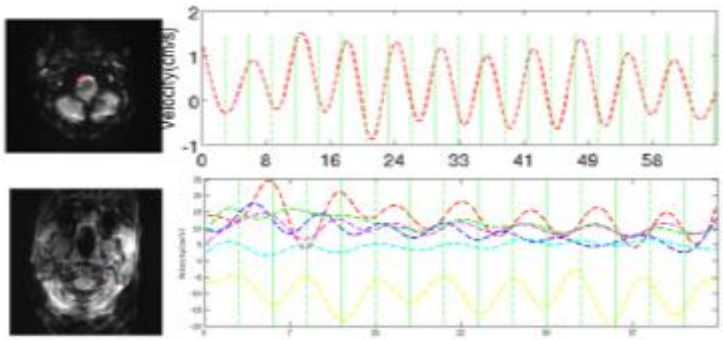


Figure 1. CSF, venous and arterial oscillations occurring with deep breathing (top) CSF at level of foramen Magnum (FM) (bottom) arteries and veins. Inspiration (hatched green line) expiration (solid green line) measured with respiration belt.

*Results* : Exemplified in one subject in Figure 1, deep breathing, respiratory variation in arterial and venous velocity were identified synchronous with CSF oscillations in FM. A higher magnitude of CSF velocity occurred with deep breathing than with restful breathing. The spinal CSF movement was simultaneous and in opposite direction of abdominal organ displacement, Figure 2, caused by downward movement of the diaphragm. *Discussion* : CSF movement with inhalation is likely driven by two opposite changes in pressure; 1) decreased thoracic pressure effecting vascular velocity and volume shifts in the cranium and 2) increased abdominal pressure from diaphragm displacement transmitted to spinal nerve root sleeves and paraspinal spaces which displace CSF in the spinal canal towards the head. *Conclusion*: Deep breathing induced by physical exercise may contribute to brain health by increasing CSF circulation to facilitate the mixing, dilution and clearance of solutes and metabolites in CSF surrounding the brain. Respiration driven motion of CSF may also be a driving force in interstitial CSF clearance mechanisms within the brain parenchyma.

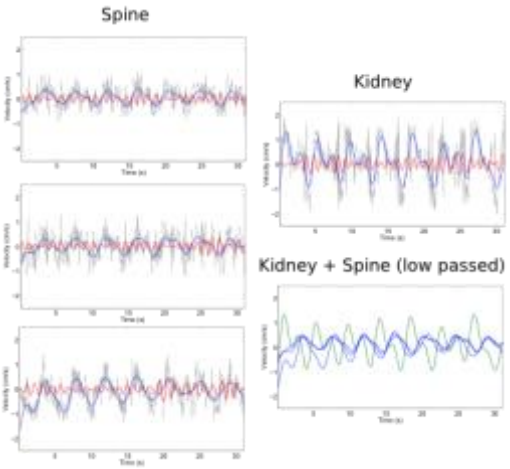


Figure 2. CSF velocity at three levels in thoracic spine and Left kidney with its displacement by diaphragm

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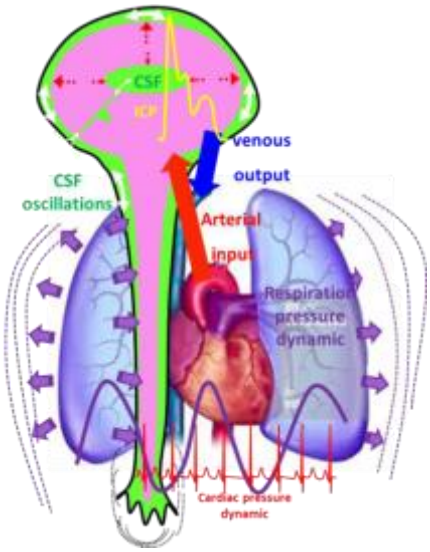
***About the Presenter:*** *David Feinberg works in the field of MRI designing novel pulse sequences for fast imaging, velocity and diffusion. He led the MRI development phase of the Human Connectome Project. He is a principle investigator in the BRAIN Initiative. Pulse sequences he innovated include; inner volume (zoomed imaging), partial Fourier imaging, Twice refocused SE (TRSE) diffusion, gradient and spin echo (GRASE) and EPI variants of fly-back EPI, multiplexed EPI, simultaneous multi-slice (SMS) techniques, gradient-and-spin echo (GRASE). At the start of his career, Dr. Feinberg published the earliest MR phase images of blood and CSF velocity and brain motion in humans and was elected first chairperson of the ISMRM Study Group on Flow and Motion Quantitation. He is a Fellow of ISMRM, president of Advanced MRI Technologies, and a professor at U.C. Berkeley.*

# CSF AND CEREBRAL BLOOD FLOWS: WHAT IS A NORMAL FLOW?

O. Balédent

University hospital of Picardie Jules Verne, BioFlowImage, Amiens, France

***Abstract.*** The large and rapid amplitude change of cerebral arterial input flow increases the brain volume over the intracranial subarachnoid spaces (large red arrows). In these areas, resistance to flow is low and as CSF viscosity is low, CSF is quickly displaced out of the cranium toward the compliant spinal canal; ICP increase is therefore limited. Nevertheless, this first CSF response is scanty and has to be supplemented with the cerebral blood venous outflow. Due to blood viscosity, this venous contribution is slower but brings a greater volume displaced. Finally, the decrease in pressure at the brain periphery induces a CSF ventricular flow, out of the fourth ventricle and through the aqueduct of Sylvius, resulting in a small inner displacement of the brain directed toward the ventricles (small red arrows). After this series of flow events during the systolic phase of cardiac cycle, arterial inflow equals venous outflow and cervical CSF flush stops. After this brief equilibrium pressure moment, venous heart aspiration increase the cerebral venous outflow, decrease ICP and reverse the cervical CSF flow to fill the cranium and prepare the next cycle. Cerebral hydrodynamic's knowledge has benefited considerably from the introduction of phase-contrast magnetic resonance imaging (PCMRI). In ten minutes CSF flow is quantified in the spinal subarachnoid spaces, the pontine cistern, the foramen of Magendi and the aqueduct of Sylvius. Blood flow is quantified in the internal carotid and the vertebral arteries, straight and sagital sinus, jugular and epidural veins. The objective of this presentation is to describe the power and the limit of such clinical 2D PCMRI and to present CSF and blood flows measurements obtain in physiological normal condition (1-8).

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***About the Presenter:*** Olivier Balédent, PhD in the area of biophysics & radiology is currently assistant professor in Amiens 'University Hospital in France. He's heading the medical image processing department and BioFlowImage research team. After a Master's degree in Informatics in Amiens, he passed a postgraduate diploma in the field of image processing in Lyon. He passed his Phd in 2001 at Jules Verne University. The thesis subject was already about CSF flow imaging using MRI technique. Now inside Amiens 'University Hospital, with clinicians he continues to develop CSF research and applies non-invasive hydrodynamic approach in clinical practice. He is also Biophysics' teacher at the medical school of Ami

**Olivier Balédent**

# CONTROL OF ACTIVE CSF SHUNTS - IS THE ICP PULSE PRESSURE AMPLITUDE A SUITABLE CONTROL VARIABLE?

Marianne Schmid Daners[1], Manuel Gehlen[2,3], Afrodite-Despina Lalou[4], Marek Czosnyka[4], Zofia Czosnyka[4], Vartan Kurtcuoglu[3,5]

[1] Product Development Group Zurich, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland
[2] Dynamic Systems and Control, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland
[3] Institute of Physiology, University of Zurich, Zurich, Switzerland
[4] Brain Physics Laboratory, University of Cambridge Academic Neurosurgery, Cambridge, UK
[5] Neuroscience Center Zurich, and the Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

***Abstract.*** With the idea of active, potentially feed-back controlled cerebrospinal fluid (CSF) shunts, slowly reaching the implementation state, the question of the optimal control variable has become critically important. Current shunts regulate CSF drainage based on the pressure gradient between the CSF space and the location of the distal catheter tip. While, arguably, the ideal controller input is the overall CSF volume, this metric cannot be determined continuously. Consequently, surrogate or other suitable variables must be used to ensure physiologic drainage control. The vascular component of the intracranial pressure (ICP) represented by the pulsation amplitude (AMP) of ICP has been used as an indirect indicator of intracranial compliance.

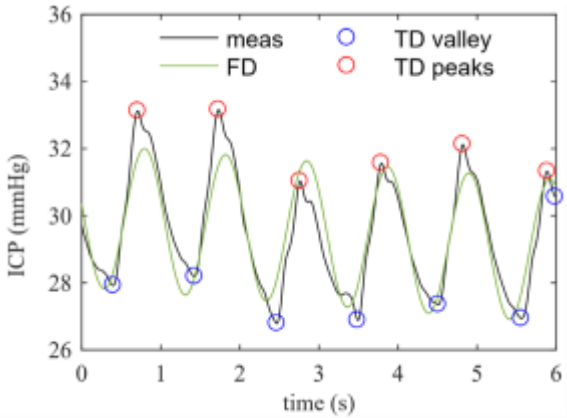


**Fig. 1.** Comparison of AMP extraction from frequency domain (FD) and time domain (TD) method. Based on the first harmonic of the discrete Fourier transform the AMP is slightly underestimated compared to the TD method.

Our goal in this study was to investigate the suitability of AMP as the control variable for an active CSF shunt by quantifying its sensitivity to postural changes. The investigations were performed in three steps: 1) The theoretical sensitivity of AMP was calculated in response to changes in CSF volume, 2) two AMP estimation methods (time and frequency domain) that identify the peak-to-peak amplitude of the ICP pulsation were evaluated and compared (Fig. 1), and 3) the posture dependence of AMP was assessed based on ICP data from infusion tests.

Our results suggest that AMP can be estimated reliably from ICP measurements using discrete Fourier transform. While AMP has been postulated to be posture independent [1], there are indications that this cannot be generalized to all situations. Therefore, further studies are needed to assess the suitability of AMP as a control input for active CSF shunts.

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**M. Schmid Daners**

***About the Presenter:*** Marianne Schmid Daners graduated in 2006 as a mechanical engineer at ETH Zurich, Switzerland (Dipl. Masch.-Ing. ETH). Under the supervision of Prof. Lino Guzzella, she received her PhD in 2012 at the Institute for Dynamic Systems and Control at ETH Zurich on the topic “Adaptive Shunts for Cerebrospinal Fluid Control”. Currently, Marianne Schmid Daners leads the Biomedical Systems group of the Product Development Group Zurich and is involved in the coordination of the Zurich Heart project. Her research interests are the modeling and control of biological systems and the development and control of biomedical devices.

# DISPLACEMENT ENCODING WITH STIMULATED ECHOES (DENSE) MRI FOR NONINVASIVE ASSESSMENT OF INTRACRANIAL PRESSURE STATUS

Amit M. Saindane[1], Deqiang Qiu[1], John N. Oshinski[1,2], Beau B. Bruce[3], Nancy J. Newman[3], Valerie Biousse[3], Xiaodong Zhong[4]

[1] Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA, United States

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[3] Department of Ophthalmology, Emory University, Atlanta, GA, United States

[4] MR R&D Collaborations, Siemens Healthcare, Atlanta, GA, United States

***Abstract.*** Intracranial pressure (ICP) is estimated invasively using lumbar puncture (LP) with cerebrospinal fluid (CSF) opening pressure (OP) measurement. Displacement encoding with stimulated echoes (DENSE) is a MRI technique sensitive to brain motion as low as 0.01 mm. This study utilized DENSE to measure brain displacements in patients with high OP before LP (Pre-LP), after a reduced closing pressure (CP) following LP and CSF removal (Post-LP), and in healthy controls.

Nine patients with suspected elevated ICP and nine healthy controls were included in this IRB-approved study. Patients and controls underwent 3T MRI (Tim Trio, Siemens, Erlangen, Germany) in the supine position with peripheral pulse unit gated segmented EPI cine DENSE sequence through the mid-sagittal brain with the following image parameters: displacement encoding frequency $k_e$=1.0-1.5 cycle/mm, through-plane dephasing frequency $k_d$=0.08 cycle/mm, TE=8.9-10.4 ms, TR=55-59 ms, EPI factor=8, segments=16, pixel size=1.2×1.2 mm$^2$, slice thickness=7 mm, averages=4, frames=10-20. Motion was measured in the foot-to-head direction. Patients with suspected elevated ICP underwent a standardized protocol of DENSE, LP with OP, post-CSF removal CP measurement, then repeat DENSE in the same session. Phase-reconstructed images were processed offline and a region of interest was placed in the central pons on the phase images for the phase-encode (foot-head) direction. Maximum change in displacement was calculated and compared between Pre-LP, Post-LP, and control groups. Displacements measured using DENSE were correlated with measured pressure by LP.

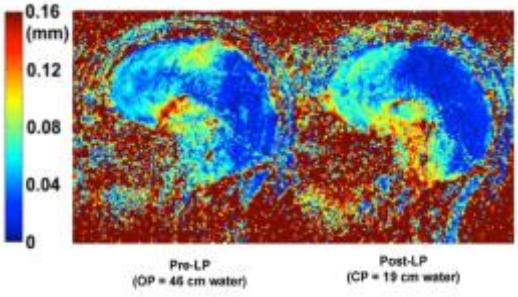


**Fig. 1.** Representative patient images from phase-encoded direction of DENSE phase data. The left image shows reduced motion of the brainstem. The patient's CSF OP obtained within 30 minutes after the first DENSE imaging was markedly elevated at 46 cm water. The right image shows increased displacement of the brainstem by DENSE in the same patient less than 30 minutes after the pressure was reduced to 19 cm water by CSF removal.

All nine patients with suspected elevated ICP had elevated OP (mean 37.6 cm water) that was decreased by removal of CSF to mean CP of 17.9 cm water. Patients and controls demonstrated no intracranial abnormalities on MRI. For brain displacement in patients, measured pressure had a significant (p=0.039) effect on brain displacement. For collective control and patient data, patients had significantly smaller Pre-LP brain displacement than Post-LP (p=0.001) and in comparison to controls (p=0.010). There was no significant difference between Post-LP patients and controls (p=0.098). This study establishes a relationship between brain displacement from DENSE MRI and measured pressure obtained contemporaneously by LP, providing a potential method for noninvasively assessing ICP status.

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**Amit M. Saindane, M.D.**

***About the Presenter:*** **Amit M. Saindane, M.D.** is an Associate Professor of Radiology and Imaging Sciences, Director of Neuroradiology, and Vice Chair of Clinical Affairs at the Emory University School of Medicine in Atlanta, GA. He has an active research interest in the imaging of intracranial pressure disorders including idiopathic intracranial hypertension, specifically surrounding noninvasive methods of assessing intracranial pressure using magnetic resonance imaging.

# BARRIER DYSFUNCTION OR DRAINAGE REDUCTION: DIFFERENTIATING CAUSES OF CSF PROTEIN INCREASE

Mahdi Asgari[1], Diane de Zélicourt[1], Vartan Kurtcuoglu[1,2,3]

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[2] Neuroscience Center Zurich, University of Zurich, Switzerland
[3] Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland

***Abstract.*** Cerebrospinal fluid (CSF) protein analysis is an important element in the diagnostic chain for various central nervous system (CNS) pathologies. Among multiple existing approaches to interpreting measured protein levels, the Reiber diagram [1] is particularly robust with respect to physiological inter-individual variability, as it uses multiple subject-specific anchoring values. Beyond the reliable identification of abnormal protein levels, the Reiber diagram has the potential to elucidate their pathophysiologic origin. In particular, both reduction of CSF drainage from the craniospinal space as well as dysfunction of blood-CNS barriers have been hypothesized as possible causes of increased concentration of blood-derived proteins [2, 3]. However, there is disagreement on which of the two is the true cause.

To test these competing hypotheses, we designed two computational models (Fig. 1) to investigate the mechanisms governing protein distribution in the spinal CSF and underlying reasons for pathological changes in protein levels. With a one-dimensional (1D) model, we evaluated the distribution of albumin and immunoglobulin G (IgG) in the spinal CSF, accounting for the protein transport rate across blood-CNS barriers, CSF dynamics (including both dispersion induced by CSF pulsation and advection by mean CSF flow) and CSF drainage from the craniospinal space. We also studied the impact of pathologic changes in barrier permeability, CSF dynamics and drainage on these distributions. The dispersion coefficients used in the 1D model to account for CSF pulsation were determined a priori by computing the axisymmetric 3D CSF dynamics and solute transport in a representative segment of the spinal canal.

Our models reproduce the empirical mathematical relationship between albumin and IgG given by Reiber, quantify the effect of CSF pulsation on protein distribution and show that barrier dysfunction rather than decreased cerebrospinal fluid drainage is the likely cause of abnormally high albumin values in the Reiber diagram. Our results further emphasize the pathophysiologic importance of dispersion, CSF drainage and blood-CNS barrier permeability for the transport of large molecules in the spinal subarachnoid space.

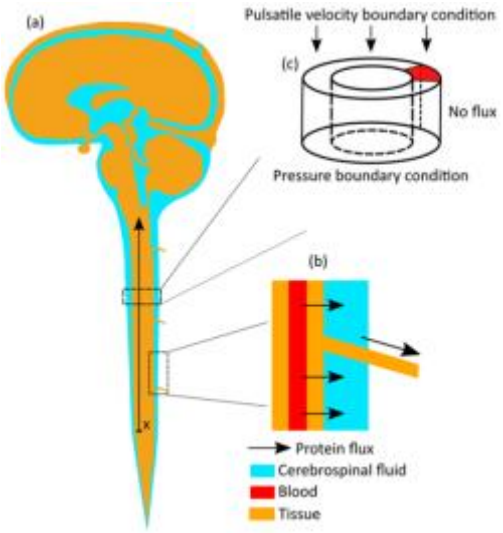


**Fig. 1.** Panel (a) shows a representative depiction of the cerebrospinal fluid compartments. The x and arrow parallel to the spinal cord indicate the anatomic correspondence and orientation of the one-dimensional model. Panel (b) shows protein efflux locations in the spine. Blood-derived proteins pass from blood by diffusion into the CSF space and exit it along nerve roots. Panel (c) shows a representation of the three-dimensional model domain as an annular channel. The boundary conditions for this model are shown on the domain surfaces.

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**Vartan Kurtcuoglu**

***About the Presenter.*** Vartan Kurtcuoglu received his mechanical engineering diploma from ETH Zurich upon completing his thesis at the French National Center of Scientific Research, CNRS PROMES. The subject of his doctoral dissertation at ETH was computational modeling of CSF flow in the human ventricular system. He is currently an assistant professor of computational and experimental physiology at the University of Zurich, and chairman of the International Cerebrospinal Fluid Dynamics Society.

**POSTER**

# A GLOBAL, MULTI-SCALE MATHEMATICAL MODEL OF THE MURINE FLUID SYSTEMS, INCLUDING MENINGEAL LYMPHATICS

C. Contarino[1,3], E. F. Toro[2], S. Da Mesquita[3], A. Louveau[3], D. Rapel[3,4], J. Kipnis[4]

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[2] Laboratory of Applied Mathematics, DICAM, University of Trento, Trento, Italy
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[4] Department of Neurosurgery, University of Virginia Healthy System, Charlottesville, USA

***Abstract.*** Building upon the recent discovery of a meningeal lymphatics system for the mouse [1] and mathematical modelling capabilities developed for extracellular fluids in humans [2-4], here we propose a holistic, multi-scale and closed-loop mathematical model for the murine circulatory system coupled to the cerebrospinal fluid (CSF), the peripheral lymphatics and the newly discovered meningeal lymphatics systems. A validation of the mathematical model for the circulatory system is provided by comparing the theoretical model results with in-vivo MRI measurements. The mathematical model shows how the intracranial venous and CSF fluid compartments respond to the high pressure arterial cerebral blood inflow, in particular, by displacing CSF into the spinal subarachnoid space [5]. We will also show pathological cases and study their effects on intracranial lymphatics and on CSF reabsorption. The pathologies include, but are not limited to, bilateral ligation of posterior facial veins. Preliminary theoretical results show that under ligation the intracranial pressure increases by more than 100%, and this is broadly in agreement with experimental measurements.

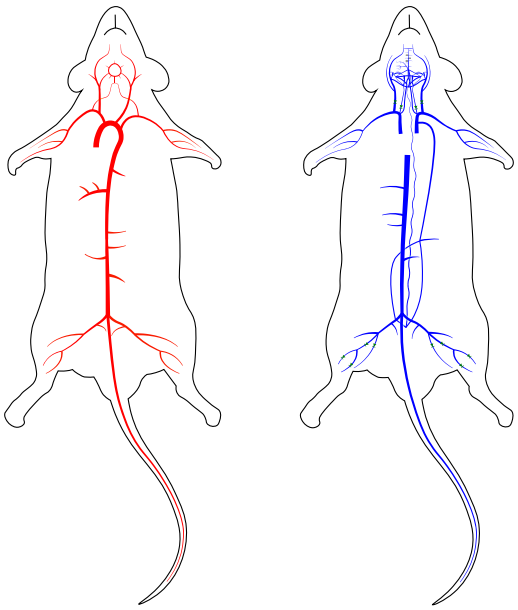

**Fig. 1.** Illustration of major modelled arteries and veins of the murine cardiovascular system

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**Christian Contarino**

***About the Presenter:*** Christian Contarino obtained the Bachelor's degree in Mathematics at the University of Genoa in 2012 and the Master of Music in piano at the Conservatory of Genoa "Niccolò Paganini" in 2012. He then received the Master of Science in Mathematics at the University of Trento and he now is a PhD student in Mathematics at the University of Trento, under the supervision of Prof. Eleuterio F. Toro. His research is mainly focused on studying the physics of neurodegenerative diseases using multi-scale mathematical models of the fluid compartments in the animal body, including the lymphatic circulation. He has already presented his work at various national and international scientific events, receiving the Young Investigator Award at the 2016 edition of the International Society of NeuroVascular Disease conference (ISNVD), Academy of Science New York, and the Lymphatic Education & Research Network Travel Award (LE&RN) at the 2017 edition of Lymphatic Forum, Chicago.

**POSTER**

# FLOW RESISTANCE ALONG BASEMENT MEMBRANES IN THE PERIVASCULAR SPACE OF CEREBRAL ARTERIES

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***Abstract.*** It has been proposed that transport of amyloid-β in perivascular channels of cerebral arteries may contribute to Alzheimer's disease. However, the exact route by which amyloid-β ends up in the lymphatic system is still an open question. One hypothesis states that amyloid-β is advected with flow of interstitial fluid in channels comprised of the basement membranes between smooth muscle cells surrounding cerebral arteries. This flow is in the direction opposite that of the blood flow, and may start from the pre-capillaries and discharge to the cervical lymphatics near the main cerebral arteries. The basement membranes are only about 100 nm thick. Depending on size of the artery, there may be from one to more than 20 layers of smooth muscle cells, each forming 100 nm wide pathways between adjacent layers. To test whether intracranial pressure may drive flow within these channels, flow resistance was calculated through the annular cross section of these perivascular spaces, establishing a relationship between the pressure drop and the flow rate of interstitial fluid.

An analytical solution was obtained for steady-state, laminar, fully developed and non-pulsatile Poiseuille flow through annular channels with rigid walls. The effect of the porous media filling the channels was neglected, as was resistance in the bifurcations. The flow channel model consisted a symmetrical arterial tree, starting from pre-capillaries of diameter 15 μm (zeroth order) and ending at the main cerebral arteries (largest order, i.e. order 23), namely the vertebral and internal carotid arteries. It was assumed that at least one annular channel exists (corresponding to the size of the basement membrane between two smooth muscle cell layers) even in the pre-capillaries, which have only one smooth muscle cell layer. One smooth muscle cell layer was added with each bifurcation order.

The resulting relationship between pressure drop and the flow rate of interstitial fluid in the perivascular space is shown in Fig.1. Results for blood flow in the vascular lumen of the same arterial network is also plotted for comparison. The resistance of the perivascular tree is $5.4\times10^{15}\mathrm{Pa.s/m^3}$, while the resistance of the luminal tree is $1.5\times10^{8}\mathrm{Pa.s/m^3}$. Assuming the difference between the intracranial pressure and that of the lymphatic duct to be 14 mmHg, the predicted interstitial flow rate is $2\times10^{-5}\mathrm{ml/min}$, shown by a red triangle. In comparison, cerebral blood flow, denoted by a black square in the corresponding curve, is $1.3\times10^{3}\mathrm{ml/min}$.

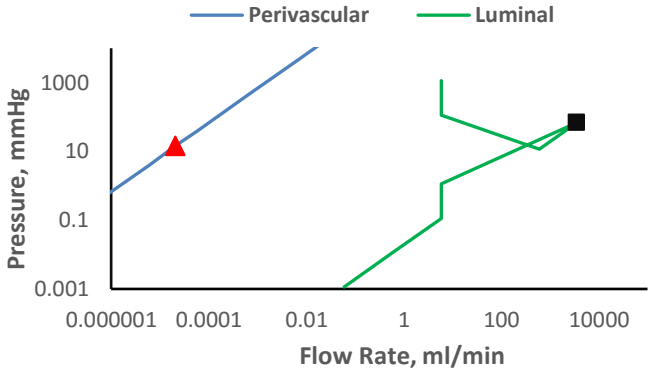


**Fig. 1.** Plot of pressure drop vs. flow rate for flow of interstitial fluid in annular perivascular space (Blue) and for blood flow within the arteries lumen (Green).

Interstitial fluid production in the rat brain is 0.1 – 0.3 μl/min/g.[1] In the absence of measurements, this range extrapolates to 0.13 – 0.39 ml/min in the human brain (assuming a mass of 1.3 kg). This range is 1.6 – 4.8 million times larger than that calculated above. It appears then that pressure-driven flow in the perivascular tree represents a very small component of the overall clearance of fluid and solutes from the brain.

**M. M. Faghih**

***About the Presenter:*** Mohammad M. Faghih is currently working as a PhD student in the Biofluid Mechanics Laboratory in the Department of Mechanical Engineering at the University of Louisville. He received Bachelors and Masters from the Iran University of Science and Technology, respectively. His research interests include flow and transport in biological systems, including cardiovascular devices, blood rheology and hemolysis, cardiovascular system modeling, and cerebrospinal and interstitial fluid in the brain.

**POSTER**

# *THE EFFECTS OF CHIARI MALFORMATION AND SYRINGOMYELIA ON CSF FLOW: CFD SUBJECT-SPECIFIC MODELS FOR A COHORT OF CHIARI PATIENTS AND CONTROLS*

Robert Lloyd[1], David F. Fletcher[2], Lynne E. Bilston[1]

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[2] School of Chemical and Biomolecular Engineering, University of Sydney, Sydney, NSW, Australia

***Abstract.*** Chiari malformation Type I is a disorder in which the cerebellar tonsils herniate through the foramen magnum. Many patients with this condition also develop a fluid filled cavity (syrinx) in the spinal cord. Syrinxes are associated with both sensory and motor disturbances, and autonomic dysfunction in rare cases. The mechanisms that lead to the accumulation of fluid in only some of the Chiari I patient population remains unknown.

Previous experimental studies showed that CSF can flow from the spinal subarachnoid space into the spinal cord via the perivascular spaces, and that this flow is dependent on arterial pulsation [1]. Computational modelling studies have shown that the arteries in the perivascular spaces could act as a 'leaky valve' [2], making the fluid content of the spinal cord dependent on the timing of the subarachnoid pressures [3].

To determine how Chiari I and syringomyelia affect the subarachnoid pressure-time profiles, a series of 24 subject-specific computational models were used to simulate the flow. The cohort included; healthy controls (N = 9) and symptomatic Chiari I patients both with (N = 7) and without (N = 8) a syrinx. Additionally, the volumes of the cerebellar tonsils and subarachnoid space in the craniocervical junction (C2 to the foramen magnum) and posterior fossa (foramen magnum to 5 mm above) were measured.

Peak pressures were found to arrive earlier in the cardiac cycle in Chiari patients without a syrinx (11.7±0.6%) compared with controls (14.3±0.8%; p = 0.045) and those with a syrinx (14.6±0.6%; p = 0.037). The peak amplitudes were measured to be 42±4, 45±4 and 61±6 Pa, for the controls, patients with and without a syrinx respectively (patents without a syrinx significantly greater than controls; p = 0.029). A regression analysis (Fig 1.) showed that the timing of the peak subarachnoid pressures were weakly correlated with the volume below the foramen magnum occupied by the cerebellar tonsils. Extending the volume to include a region of the posterior fossa 5 mm above the foramen magnum showed an increased correlation.

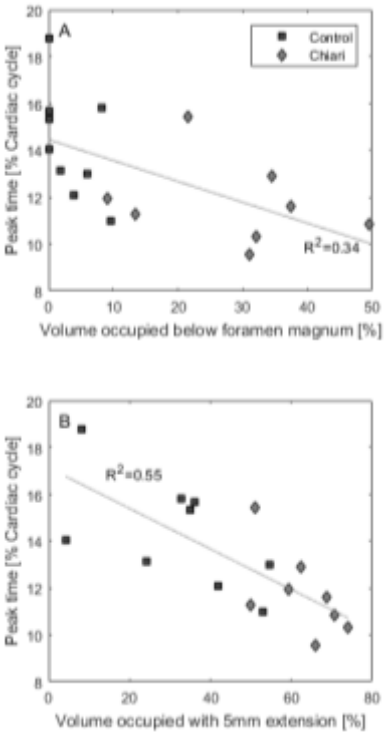


**Fig. 1.** Relationships between time of peak pressure and the percentage of the subarachnoid space occupied by the cerebellar tonsils, for healthy controls (black) and Chiari patients without a syrinx (grey). A) Shows the volume occupied by the tonsils below the foramen magnum to C2. B) Shows the volume occupied by the tonsils from 5 mm above the foramen magnum to C2.

The results show that Chiari I malformation significantly alters the timing and magnitude of the subarachnoid pressures. These changes, in conjunction with the 'Leaky valve' of the perivascular space [2], could play a role in syrinx development. Additionally, the results suggest that changes in the morphology above the foramen magnum have a significant influence on the CSF dynamics. Further experimental and modelling studies are required to better understand the mechanisms that give this effect, and how it may relate to the pathogenesis of syringomyelia.

**Robert Lloyd**

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***About the Presenter:*** Mr Robert Lloyd, MEng, is a biomechanical engineer with a research focus in experimental and computational modelling. He is a PhD student, based at Neuroscience Research Australia and the University of New South Wales. He is currently developing models of the human skull and spine to investigate cerebrospinal fluid flow disorders such as Chiari malformation and syringomyelia.

**POSTER**

## INTEREST OF MRI IN THE INVESTIGATION OF THE CSF WITH THE BLOOD FLOWS INTERACTIONS

A. Lokossou [1], S. Garnotel [1], G. Page [1] , L. Balardy [2], Z. Czosnyka [3], P . Payoux [4], O. Balédent [1] and E.A. Schmidt [5,6]

1 –University Hospital of Picardie Jules Verne, Medical Image Processing departments - BioFlowImage Laboratory, Amiens, France; 2- Departments of Geriatry, University Hospital Toulouse, France; 3 – Neurosciences department, University of Cambridge, UK; 4- Departments of Nuclear Medicine, University Hospital Toulouse, France; 5-UMR 1214 - INSERM/UPS – TONIC Toulouse Neuro-Imaging Center, Toulouse, France; 6- Departments of Neurosurgery, University Hospital Toulouse, France

***Abstract***: Last two centuries, according to Monroe-Kellie doctrine, the influx of arterial blood flow is compensated by an equivalent outflow of venous and cerebrospinal fluid (CSF) flows. Recent studies demonstrated that during the cardiac cycle, arterial blood flow energy is transferred to CSF, brain parenchyma and cerebral vessels as **a**rterial **b**lood **f**low (ABF) leading to **v**enous **b**lood **f**low (VBF) drainage and CSF oscillations[1]. However, little is known about how this energy is dissipated between intracranial and extracranial blood compartments. Adult hydrocephalus is a medical condition related to an imbalance between the absorption and the secretion of CSF. The resistance to CSF outflow (Ro) obtained during intracranial pressure (ICP) monitoring and infusion tests is an important parameter used to diagnose patients with CSF dynamic alterations[2]. Phase contrast magnetic resonance imaging (PC-MRI) is a non-invasive technique able to quantify blood and CSF oscillations and their stroke volumes (SV) over the cardiac cycle[3]. Nevertheless, the use of SV to diagnose CSF dynamic alterations remains debated. **Here we proposed to use PC-MRI to determine how arterial and venous pulsatilities were transferred between extracranial and intracranial compartments in hydrocephalus patients.**

Fifty four hydrocephalus patients underwent PC-MRI to quantify intracranial and extracranial arterial and venous blood flows. The following day, they had intracranial pressure monitoring with infusion tests to assess resistance to CSF outflow (Ro) using ICM+ [4]. A Ro of 12mmHg/ml/min [5] was used to classify in two groups patients in potential non responders (**PNR**, n=22) and potential responders (**PR**, n=32) to shunt surgery. PC-MRI data were analysed with *Flow* software [1] to extract the **max**imal, **min**imal and **mean** values of **the intracranial** ABF (internal carotid arteries [ICAs] + basilar artery) and VBF (straight + sagittal sinuses) and also **extracranial** ABF (ICAs + both vertebral arteries) and VBF (both jugular veins). A pulsatility index (**PI= (max-min)/mean)** was calculated for the arterial and venous flows for each intracranial and extracranial level.

The intracranial and extracranial arterial pulsatilities were not different between the two groups of patients. In the two groups the Arterial pulsatility was smaller at the intracranial level than in the extracranial level. The intracranial venous pulsatility was not different between the two groups. The venous pulsatility was increased at the extracranial level for the two groups and was significantly higher in the PR group than in the PNR group (Table 1).

Extracranial venous pulsatility was impaired in PR group and proved to be an interesting non-invasive biomarker to diagnose patients with high Ro. Using a threshold of 1.7 for the extracranial Venous PI, this MRI parameter presented a good sensitivity (81%) and specificity (91%) to find patients with elevated Ro.

Extracranial Venous PI seems to highlight hydrocephalus patients with CSF dynamic alterations and potentially helpful to predict candidates for shunt.

***Table 1*: Intra and extracranial blood Pulsatility Index in hydrocephalus patients PNR and PR**

| | Arterial Pulsatility Index | | | Venous Pulsatility Index | | |
|---|---|---|---|---|---|---|
| | **Intracranial** | **Extracranial** | **P** | **Intracranial** | **Extracranial** | **P** |
| **PNR** | **1,3±0,3** | **1,6±0,4** | **P < 0,0001** | **0,6±0,2** | **1,1±0,4** | **P <0,0001** |
| **PR** | **1,2±0,2** | **1,5±0,4** | **P < 0,0001** | **0, 6±0,2** | **2,5±1,1** | **P <0,0001** |
| **P** | **P > 0,05** | **P > 0,05** | **-** | **P > 0,05** | **P < 0,00001** | **-** |

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5. Kim *et al.,* Thresholds of resistance to CSF outflow in predicting shunt responsiveness. (2015).

***About the presenter*:** Armelle Lokossou is currently a PhD student in the area of Medical Imaging in BioFlowImage laboratory, University of Picardie Jules Verne. After her Master of Science diploma in human physiopathology, functional explorations and imaging, she started a PhD in October 2016. The thesis subject is "Imaging and modeling of blood and cerebrospinal fluid dynamics in craniospinal system".

**POSTER**

# RESISTANCE NETWORK MODEL OF PULSATILE FLOW DRIVERS IN RAT PARENCHYMA AND PVS

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***Abstract.*** In animal models, dissolved compounds in the subarachnoid space (SAS) have been found to preferentially transport through the perivascular spaces (PVS) of vessels in the cortex at rates faster than would be expected from diffusion alone [1]. Compounds injected into the parenchyma (PCY) also move into the PVS improving clearance [2]. Tracer transport rates have been positively correlated with arterial pulstatility, cyclic variation of blood vessel volume [3]. Though the PVS may play an important role in solute movement through the brain, the hydrodynamics and transport phenomena involved are unclear.

In this study a hydraulic network was used to model fluid flow produced by vascular pulsatility and estimate the contribution this flow makes to solute transport in the PVS and parenchyma. The network represented the PVS of a surface arteriole and vein, as well as the local SAS and parenchyma. Pulsatility derived flow drivers included (i) differences in pulse amplitude between intracortical arterioles and veins, (ii) differences in pulse timing between intracortical arterioles and veins, and (iii) vessel wall peristalsis.

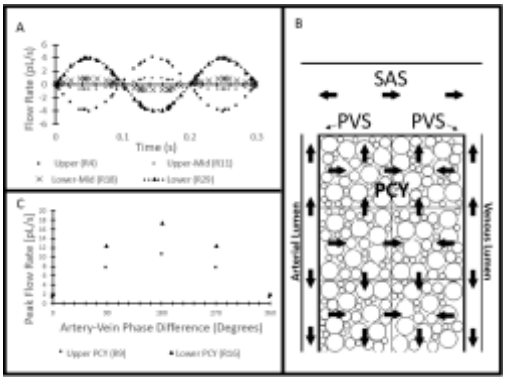


**Fig. 1.** A) *Case (i)* Plot of flow rate versus time for the arterial perivascular resistances. Positive and negative flow rate values indicate flow away and toward the SAS, respectively. B) *Case (i)* Arrow diagram depicting flow direction in the representative tissue slice during in-phase vessel expansion. C) *Case (ii)* Peak flow rate in horizontal parenchyma resistances versus phase difference in degrees. Peak flow rate was maximized when the arterial and venous flow source sources were 180 degrees out of phase.

A difference in pulse amplitude, case (i), produced fluctuating flow throughout the network but no net flow over time. Flow rates at all resistances oscillated as a sinusoid centered at zero (Fig1A). A difference in pulse timing, case (ii), also produced sinusoidal flow rates within the network, but no net flow. Flow rate magnitude depended on the time delay between arterial and venous pulses with maximum horizontal parenchyma flow observed when arterial expansion coincided with venous retraction (Fig1B). The resulting Peclet number for ovalbumin in both case (i) and case (ii) was of order ~1 in the PVS spaces and order ~$10^{-3}$ in the parenchyma ~150 μm away from the PVS. The flow rates produced by vessel peristalsis, case (iii), depended on the source parameter in the model. For a range of source inputs net flow was produced in the network but Peclet numbers varied greatly. The Peclet numbers in case (i) and case (ii) suggest that while net flow was not observed, solute transport in PVS may be enhanced by dispersion, but transport in the parenchyma is predicted to be diffusion dominated with the assumptions of this model. Case (iii) results, though varying greatly in magnitude suggest that peristaltic flow within the PVS has the potential to induce net flow within the parenchyma. Both oscillatory and net flow may contribute to tracer transport within and in the vicinity of PVS spaces in-vivo.

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3. Iliff J, Nedergaard M, et. al. (2013). Cerebral arterial pulsation drives paravascular CSF-Interstitial fluid exchange in the murine brain. Jrnl Neurosci 33 (46):18190-18199

**JULIAN REY**

***About the Presenter:*** Julian Rey is a first-year mechanical engineering PhD student in the Sarntinoranont lab at the University of Florida. He completed a combined Bachelor's/Master's degree in Biomedical Engineering at the University of Florida in 2016. His interests include numerical simulations of biofluid dynamics and tissue transport, as well as in-vivo MRI imaging of tracer transport in brain tissue. A Cuban-American raised in Miami, FL, Julian enjoys listening to Cuban son and walking on the beach.