3RD CSF DYNAMICS SYMPOSIUM

Université de Picardie Jules Verne, Amiens, France

July 9 & 10, 2015

CSF
Chiari & Syringomyelia Foundation

THE MONKTON INSTITUTE

University of Zurich[UZH]

UNIVERSITÉ de Picardie Jules Verne

CHU AMIENS PICARDIE

ORGANIZED BY DIANE DE ZÉLICOURT & OLIVIER BALÉDENT

CSF

Chiari & Syringomyelia Foundation

OUR MISSION

To advance knowledge through research and to educate the medical, allied sciences, and lay community about Chiari malformation, syringomyelia and related disorders.

ABOUT US

The Chiari & Syringomyelia Foundation is a national 501(c)(3) organization committed to disseminating accurate and current information about the diagnosis, management, and treatment of Chiari malformation (CM), syringomyelia (SM), and related disorders.

Our superior Scientific Education & Advisory (SEA) Board is made up of world-class scientists and physicians, and the trustworthy and dedicated members of our Board of Directors and Board of Trustees include community leaders, successful business people, families and patients.

FOR MORE INFORMATION

Please visit www.CSFinfo.org

WELCOME TO THE CSF SYMPOSIUM

On behalf of the Chiari & Syringomyelia Foundation and the organizing team, we welcome you to the 3rd International CSF Dynamics Symposium in Amiens, France. This year we have a diverse group of researchers with expertise in all aspects of CSF dynamics. Our aim is to provide a stimulating symposium that will showcase excellent researchers, increase collaboration between members of the group, and to help raise the field of CSF dynamics to greater notoriety.

Thank you for making the effort to be here and for making this symposium a success!

Diane de Zélicourt and Olivier Balédent

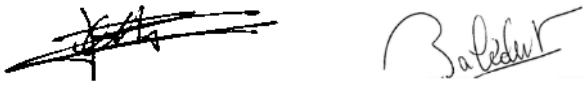


TABLE OF CONTENT

Cover photos: Top photo, original picture by Olivier Balédent entitled The Cathedral of Amiens, France. Bottom Photo, image credits to the University of Picardie Jules Verne https://www.u-picardie.fr

SPONSORSHIP

The 3rd CSF Dynamics Symposium is sponsored by the Chiari & Syringomyelia Foundation made possible through generous support of The Monkton Institute.

The Monkton Institute, Inc., founded in 2002, is a private foundation that funds research and educational initiatives to better understand, diagnose and treat Arnold-Chiari Malformation and associated problems of the brain stem.

The Chiari & Syringomyelia Foundation's mission is to advance knowledge through research and to educate the medical, allied sciences, and lay community about Chiari malformation, syringomyelia and related disorders. Please visit the foundation's website at www.CSFinfo.org.

The 3rd CSF Dynamics Symposium is hosted by the University of Picardie Jules Vernes and University Hospital of Amiens, which have generously provided the conference venue, as well as technical and communication support, and is further supported by the Picardie region.

FRAMEWORK OF THE 3RD CSF DYNAMICS SYMPOSIUM

The cerebrospinal fluid (CSF) has multiple roles in both normal brain function and neurological and neurodevelopmental disorders. The barriers and interfaces of the tissues and different fluid compartments (CSF, blood and interstitial fluid) of the central nervous system (CNS) have a key role to play in the maintenance of CNS homeostasis, including fluid secretion and absorption, specialized directional transport, mechanical and chemical buffering. Given the complexity of the system at stake, the objective of the symposium is to offer a platform for the exchange of ideas and establishment of collaborations towards the modelling of the CSF and cerebrospinal fluid dynamics.

Twenty-five invited speakers from around the world will present their research highlighting clinical, experimental or computational methods to better understand normal physiology and diseases related to CSF motion such as Chiari malformation, syringomyelia and hydrocephalus. The focus of this symposium is on modelling rather than on clinical solutions. Neurosurgeons and neuroscientists are present to lead a discussion on the challenges of translating engineering and physics analyses into clinically relevant results.

Invited speakers incur no fees to attend this two-day event. Breakfast, lunch and dinner are provided thanks to a generous sponsorship from the Chiari & Syringomyelia Foundation, which was made possible by the support of The Monkton Institute. The symposium will be held in Amiens, France, right in the historic city center, within the campus of The Université de Picardie Jules Vernes. All presentations will be video recorded and posted, with free access, on the web sites of the Chiari & Syringomyelia Foundation and the International Cerebrospinal Fluid Dynamics Society to maximize exposure of the symposium research ideas.

The symposium is organized by Diane de Zélicourt and Olivier Balédent. Dr. de Zélicourt is currently a senior researcher and lecturer within the Interface group at the University of Zürich (Switzerland). Her research thrust lies at the convergence of engineering and medicine, with a focus on multi-scale numerical modelling of the CSF and brain mechanics to understand the pathophysiology of hydrocephalus. Dr. Balédent's interest lies in Biophysics and the development and application of MRI for the non-invasive characterization of CSF hydrodynamics. He is an assistant professor at Amiens' University Hospital (France), and head of the medical image processing department and BioFlowImage (www.tidam.fr) research team.

ABOUT THE UNIVERSITY OF PICARDIE JULES VERNE

In the early 1960's, Amiens featured four pre-university level establishments: a national school of medicine and pharmacy, a law school, a college of science and an arts school. However none of these structures offered a complete education cycle, forcing the students of Amiens to continue their studies elsewhere. The University of Picardie was thus founded in 1969 and later renamed University of Picardie Jules Verne (UPJV) in honor of the French poet and novelist (Journey to the center of the Earth, Twenty thousand leagues under the sea, and Around the world in eighty days) who spent numerous years in Amiens.

Today the UPJV enrolls approximately 26'000 students, including 3'400 international students. Through its 6 campus in Picardie, UPJV provides more than 200 specialized and innovative training courses in the fields of sciences, health, humanities and social sciences, in relation with the activities of the leading laboratories and industries.

The UPJV hosts 33 research teams and internationally recognized laboratories, participating and/or leading large-scale international research programs, 9 of which are associated with national institutes CNRS, INSERM or INERIS. To foster scientific excellence and innovation, the UPJV has developed 10 shared research and industrial technology platforms allowing research units and industrial partners to carry out their innovative projects under the best conditions, and is a stakeholder in 2 international research and innovation clusters (IAR and i-Trans).

SCHEDULE

DAY 1 – THURSDAY, JULY 9TH, 2015

WELCOME COFFEE & CROISSANTS		8:00
Opening Notes Diane de Zélicourt, Olivier Balédent		8:30
PLENARY LECTURE Chair: O. Balédent	**Complex CSF disorders: old questions, new technologies and translation in to patient care.** *John D. Pickard*	8:45
SESSION A Chair: Y. Ventikos	**Quantitative Assessment of the Differences in the Resistance to Spinal CSF Motion in Chiari Malformation** *Francis Loth*	9:45
	CSF flow into the spinal cord in Chiari Malformation: Linking patient subarachnoid space CSF dynamics to perivascular flow *Lynne Bilston*	10:10
MORNING COFFEE BREAK		10:35
SESSION B Chair: A. Eklund	**Phase-Contrast Magnetic Resonance Measurements of CSF Velocity in Pediatric Subjects: Comparison of Control Subjects and Patients with Chiari Malformation** *John Oshinski*	11:00
	Origin and Clinical Relevance of the Cranio-Spinal CSF pulsation *Noam Alperin*	11:25
	Analyses of brain hydrodynamics and biomechanics using MRI: from intracranial compliance analysis to fluctuation MRI *Tosiaki Miyati*	11:50
	Impact of respiration on CSF dynamics *Olivier Balédent*	12:15
LUNCH AND POSTERS		12:40
SESSION C Chair: V. Kurtcuoglu	**A multiscale poroelastic framework for large deformations of the brain** *Diane de Zèlicourt*	14:00
	Investigating Cerebral Oedema using Poroelasticity *Yiannis Ventikos*	14:25
	Solvent flow and solute transport in perivascular channels in the brain *Keith Sharp*	14:50
AFTERNOON COFFEE BREAK		15:15
SESSION D Chair: T. Brinker	**MR-based Computational Models for Predicting Extracellular Flow and Transport in the Brain** *Malisa Sarntinoranont*	15:40
	CSF Movement and Distribution of Different Substances Inside the CSF and Interstitial Fluid Compartments in Large Animal Models *Marijan Klarica*	16:05
	The dynamics of intrathecal bolus and cerebrospinal solute transport *Mikhail Papisov*	16:30
DISCRETIONARY VISIT OF THE "HORTILLONAGES", FLOATING GARDENS		18:00
SYMPOSIUM DINNER AT "LES MARISSONS"		19:30

DAY 2 – FRIDAY, JULY 10TH, 2015

WELCOME COFFEE & CROISSANTS		8:00
PLENARY LECTURE Chair: D. de Zélicourt	**The novel understanding of CSF physiology: emerging research and clinical implications.** *Thomas Brinker*	8:30
SESSION E Chair: L. Bilston	**Posture dependencies of the venous system and implications for ICP** *Anders Eklund*	9:30
	Hardware-in-the-Loop Testing of Cerebrospinal Fluid Shunt Systems *Marianne Schmid Daners*	9:55
MORNING COFFEE BREAK		10:20
SESSION F Chair: F. Loth	**CSF Dynamics and the Effect of Starling Forces on Intracranial Water Exchange** *Andreas Linninger*	10:50
	Effects of Adding Poroelasticity to an Existing FSI Model of Spinal CSF Dynamics in Syringomyelia with Adjacent Subarachnoid Space Stenosis *Chris Bertram*	11:15
	A One-Dimensional Model of Wave Propagation within the Co-Axial Viscous Fluid Filled Spinal Cavity. *Mokhtar Zagzoule*	11:40
	On the complexity of the Cerebrospinal fluid flow in the upper spinal column – is the assumption of laminar flow appropriate? *Kent-Andre Mardal*	12:05
LUNCH & POSTER TOUR		12:30
SESSION G Chair: A. Linninger	**Translational biomechanics in neurodegenerative diseases** *Eric Schmidt*	14:00
	Towards the Mathematical Modelling of Brain Edema and Cell Death during Ischemia or Inflammation *Piotr Orlowski*	14:25
	Contribution of astrocyte networks to cerebral water flow *Vartan Kurtcuoglu*	14:50
AFTERNOON COFFEE BREAK		15:15
WORKSHOPS		15:30
Closing Remarks *Vartan Kurtcuoglu, Diane de Zélicourt, Olivier Balédent*		16:15
DISCRETIONARY PLENARY DISCUSSION AND CLOSING COFFEE		16:30

KEYNOTE LECTURE

THURSDAY, JULY 9TH 2015 – 8:45 TO 9:45

Session Chair:
Olivier Balédent, *University Hospital of Picardie Jules Verne, BioFlowImage, Amiens, France*

John D. Pickard **8^{45} - 9^{45}**

Academic Neurosurgery Unit, NIHR Brain Injury HTC and Department of Psychiatry, University of Cambridge, UK

Complex CSF Disorders: Old Questions, New Technologies and Translation to Patient Care

SESSION A

THURSDAY, JULY 9TH 2015 – 9:45 TO 10:35

Session Chair:
Yiannis Ventikos, *Department of Mechanical Engineering, University College London (UCL), London, UK*

Francis Loth **9^{45} – 10^{10}**

Department of Mechanical Engineering, University of Akron, USA; Conquer Chiari Research Center, University of Akron, USA

Quantitative Assessment of the Differences in the Resistance to Spinal CSF Motion in Chiari Malformation

Lynne Bilston **10^{10} – 10^{35}**

Neuroscience Research Australia, University of New South Wales, Sydney, NSW, Australia

CSF flow into the spinal cord in Chiari Malformation: Linking patient subarachnoid space CSF dynamics to perivascular flow

MORNING COFFEE BREAK – SESSION RESUMES AT 11^{00}

COMPLEX CSF DISORDERS: OLD QUESTIONS, NEW TECHNOLOGIES AND TRANSLATION TO PATIENT CARE

Pickard JD, Pena A, Keong NK, Czosnyka Z, Higgins N, Garnett M, Peterson K, Sahakian B, Czosnyka M.

Academic Neurosurgery Unit, NIHR Brain Injury HTC and Department of Psychiatry, University of Cambridge, Addenbrookes Hospital, Cambridge CB2 0QQ

Abstract. Hydrocephalus is not simply a balloon in need of mechanical drainage. Disorders of CSF production (choroidal and extrachoroidal), circulation and absorption may be compounded by changes in the cerebral mantle. Slit ventricles, unresponsive ventricles, arrested hydrocephalus, the pseudotumor cerebri syndrome, low pressure hydrocephalus, brain slump, intracranial hypotension and the search for a remediable hydrocephalic component in elderly patients with gait problems and cognitive decline are just some of the clinical challenges posed. However, as new technologies have been introduced, some of the old concepts have been lost such as the 'stiff ventricle', 'convexity block and ventricular reflux' and venous abnormalities. This overview will highlight some of the advances made through computerized CSF infusion studies & bench testing (UK shunt evaluation laboratory), MRI (DTI, elastography, cisternography and phase contrast), venography, neuropsychology profiling and modelling of the brain as a poroelastic medium. Translation of such advances in to patient care requires insight in to the limitations of existing treatments and an understanding of the feasibility of clinical trials in subsets of patients through long term systematic data collection mechanisms such as the UK shunt registry.

John D. Pickard

About the Presenter. Prof. Pickard is Emeritus Professor of Neurosurgery and Voluntary Director of Research at the University of Cambridge; Director: NIHR Healthcare Technology Cooperative for Brain Injury; NIHR Senior Investigator (2009-2014); formerly Professor of Neurosurgery/ Hon. Cons. Neurosurgeon, University of Cambridge (January 1991 – December 2013) and Chairman and Clinical Director, Wolfson Brain Imaging Centre; Consultant Neurosurgeon, Senior Lecturer, Reader and Professor of Clinical Neurological Sciences, Wessex Neurological Centre, Southampton (1979-1991). Prof. Pickard's research focuses on advancing the care of patients with acute brain injury, hydrocephalus and prolonged disorders of consciousness through functional brain imaging, studies of pathophysiology and new treatments as well as focusing on health, economic and ethical aspects.

QUANTITATIVE ASSESSMENT OF THE DIFFERENCES IN THE RESISTANCE TO SPINAL CSF MOTION IN CHIARI MALFORMATION

Francis Loth[1,2], Nicholas Shaffer[1,2], Soroush Pahlavian[1,2], Bryn Martin[2], Stephen Dombrowski[3], Mark Luciano[3], John Tew[4], John Oshinski[5],

[1] Department of Mechanical Engineering, University of Akron, Akron, Ohio, USA
[2] Conquer Chiari Research Center, University of Akron, Akron, Ohio, USA
[3] Department of Neurological Surgery, Cleveland Clinic Foundation, Cleveland, Ohio, USA
[4] Mayfield Chiari Center, Mayfield Clinic, Cincinnati, Ohio, USA
[5] Department of Radiology, Emory University School of Medicine, Atlanta, Georgia, USA

Abstract. Type I Chiari malformation (CM) is classically characterized by cerebellar tonsil herniation (CTH) ≥5 mm below the foramen magnum. However, it is well-documented that CTH does not necessarily correlate with neurological symptom severity or surgical outcome. Because CTH creates a partial blockage of fluid movement between the cranial and spinal subarachnoid space (SAS), it is thought that the resulting changes to the hydrodynamic environment, specifically increased pressure on neural tissue, may contribute to the symptomatology of CM. Hence, quantification of hydrodynamic differences in the CM-affected cervical SAS may be useful to the diagnostic process.

We investigated the hydrodynamic environment in the cervical spinal SAS of CM patients pre- and post-surgery (n=19) in terms of SAS geometry (hydraulic radius), impedance to flow (longitudinal impedance), and compliance (stroke volume, volumetric expansion, pulse wave velocity) and compared the results to values observed in healthy volunteers (n=15). Subject-specific cervical SAS geometries were modeled from high-resolution T2-weighted anatomic MR images. CSF flow waveforms were obtained from PCMR images taken in the transverse plane at the C2, C6, and T2 levels of the spine. Geometries and C2 flow waveforms were combined to create subject-specific computational fluid dynamics models from which longitudinal impedance (LI) was calculated.

Mean cerebellar tonsil descent (CTD) was measured to be 9.5±1.2, 6.9±1.0, and -1.7±1.0 mm for the presurgery, post-surgery, and healthy volunteer groups respectively. Using the FM and 25 mm caudal to the FM as common reference planes, mean values of LI in dyn/cm^5 were 458 ± 62, 376 ± 56, and 237 ± 11 for the pre-surgery, post-surgery, and healthy volunteer groups, respectively. Statistical analysis showed a significant difference in LI between CMI patients pre-surgery and post-surgery (65.1 dyn/cm^5 average decrease, $p = 0.016$). Mean LI in pre-surgery CMI patients was significantly higher than in healthy volunteers ($p = 0.002$). Using the FM and 25 mm caudal to the FM as common reference planes, mean cross sectional area (ACS) for the pre-surgery, post-surgery, and healthy volunteer groups was 2.08±0.11, 2.22±0.10, 2.77±0.14 cm^2, respectively. Statistical analysis showed that mean ACS increased significantly postsurgery for CMI patients (0.1 cm^2 average increase, $p = 0.009$), but was still significantly smaller than the mean ACS measured in healthy volunteers ($p = 0.008$).

Mean values of LI has been demonstrated to follow a similar trend to CTD in CM patients before and after surgery. However, values of LI can different greatly from that of CTD in specific cases where CSF space was small indicating LI may be a better indicated of CSF flow blockage than CTD. LI was well approximated by ACS. In addition, CFD studies imposing small brain motion (150 micron) show LI to increase 20%.

Francis Loth

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.

CSF FLOW INTO THE SPINAL CORD IN CHIARI MALFORMATION: LINKING PATIENT SUBARACHNOID SPACE CSF DYNAMICS TO PERIVASCULAR FLOW

Elizabeth C. Clarke[1], David F. Fletcher[1,2], Lynne E. Bilston[3]

[1] Kolling Institute, University of Sydney, Sydney, NSW, Australia
[2] School of Chemical & Biomolecular Engineering, University of Sydney, Sydney, NSW, Australia
[3] Neuroscience Research Australia, University of New South Wales, Sydney, NSW, Australia

Abstract. Syringomyelia is an enigmatic condition resulting in the formation and enlargement of fluid-filled cysts in the spinal cord. It is associated with conditions that result in obstruction to CSF flow in the subarachnoid space, such as Chiari I malformation, arachnoiditis, and spinal cord injury. These fluid-filled cysts are thought to cause neurological deficits by compressing the spinal cord as they enlarge. The mechanisms by which CSF flow obstructions in the subarachnoid space (SAS) result in the formation and enlargement of syrinxes remain unclear.

Animal studies have established that fluid flows from the SAS into the spinal cord via perivascular spaces [1], and that this flow is enhanced in models of SAS obstruction that give rise to syrinx formation [2]. This flow is dependent on the arterial pulsations [3]. Previous computational modelling studies have suggested that the arterial pulse wave may act as a 'leaky valve' in the peri-arterial spaces [4], but how this is influenced by bulk SAS flow is not known.

In these simulations, we linked the subarachnoid space pressures derived from patient-specific CFD models of 2 typical Chiari I patients, one with a syrinx, and one without, and a healthy volunteer [5], to a previous simulation of perivascular flow [4].

The perivascular flow model suggested that in the patient with a syrinx, there was greater net fluid flow into the spinal cord compared with the two non-syrinx cases (Fig 1). The effect of cardiac cycle length (heart rate) on the fluid inflow through the model perivascular space was small.

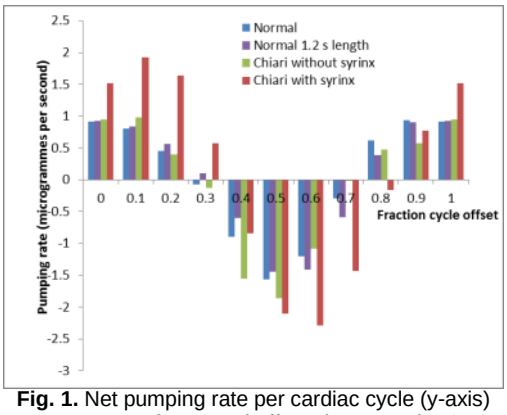


Fig. 1. Net pumping rate per cardiac cycle (y-axis) over a range of temporal offsets between the SAS pressure and the arterial pulse wave (x-axis) for a normal volunteer (blue), a Chiari patient without a syrinx (green) and Chiari patient with a syrinx (red). The effect of the cardiac cycle length (i.e. heart rate) was also tested, by varying the cycle length, and found to make minimal difference (blue).

These results suggest that the nature of the flow profile in the spinal SAS can substantially influence fluid inflow into the spinal cord through the perivascular space. Further experimental and modelling studies are needed to understand the precise features of the CSF flow that gives rise to this effect and also to better understand the in vivo temporal offsets between CSF flow in the SAS and the spinal cord arterial pulse waves, and trans-parenchymal pressure gradients that influence this flow.

1. Stoodley MA, Jones NR, Brown CJ (2006). Evidence for rapid fluid flow from the subarachnoid space into the spinal cord central canal in the rat. Brain Res 707:155-164
2. Brodbelt AR, Stoodley MA, Watling AM, Tu J, Jones NR (2003) Fluid flow in an animal model of post-traumatic syringomyelia. Eur Spine J 12:300-306.
3. Stoodley MA, Brown SA, Brown CJ, Jones NR (1997) Arterial pulsation-dependent perivascular cerebrospinal fluid flow into the central canal in the sheep spinal cord. J Neurosurg 86:686-693.
4. L.E. Bilston, M.A. Stoodley and D.F. Fletcher (2010), Relative timing of arterial and sub-arachnoid space pulse waves influences spinal perivascular CSF flow - a possible factor in syrinx development?, J Neurosurg 112(4):808-813.
5. E.C. Clarke, D.F. Fletcher, M.A. Stoodley, L.E. Bilston (2013) "Computational fluid dynamics modelling of CSF pressure in Chiari malformation and syringomyelia", J Biomechanics, 46(11): 1801-1809.

Lynne E Bilston

About the Presenter. Professor Lynne Bilston is a biomechanical engineer whose research interests focus on how soft tissues are affected by mechanical loads. She completed her undergraduate engineering degree at the University of Sydney and masters and PhD at the University of Pennsylvania in spinal cord injury biomechanics. She is a Senior Principal Research Fellow at Neuroscience Research Australia, and a Professor in the Faculty of Medicine at the University of New South Wales.

SESSION B

THURSDAY, JULY 9TH 2015 – 11:00 TO 12:40

Session Chair:
Anders Eklund, *Department of Radiation Sciences, Umeå University, Umeå, Sweden*

John Oshinski **$11^{00} – 11^{25}$**

Department of Radiology, Emory University School of Medicine, Atlanta, USA

Phase-Contrast Magnetic Resonance Measurements of CSF Velocity in Pediatric Subjects: Comparison of Control Subjects and Patients with Chiari Malformation

Noam Alperin **$11^{25} – 11^{50}$**

Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL, USA

Origin and Clinical Relevance of the Cranio-Spinal CSF pulsation

Tosiaki Miyati **$11^{50} – 12^{15}$**

Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan

Analyses of brain hydrodynamics and biomechanics using MRI: from intracranial compliance analysis to fluctuation MRI

Olivier Balédent **$12^{15} – 12^{40}$**

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

Impact of respiration on CSF dynamics: A Real-Time MRI Investigation

LUNCH AND POSTERS – SESSION RESUMES AT 14^{00}

PHASE-CONTRAST MAGNETIC RESONANCE MEASUREMENTS OF CSF VELOCITY IN PEDIATRIC SUBJECTS: COMPARISON OF CONTROL SUBJECTS AND PATIENTS WITH CHIARI MALFORMATION

John N. Oshinski[1] Samir Sarda[1,2], Nilesh K. Desai[1], Joshua Chern[2],
[1] Department of Radiology, Emory University School of Medicine, Atlanta, GA USA
[2] Department of Neurosurgery, Children's Healthcare of Atlanta, Atlanta, GA USA

Introduction. Phase-contrast magnetic resonance (PCMR) studies of cerebrospinal fluid (CSF) dynamics have shown that CSF velocities are elevated in subjects with Chiari I compared to normal subjects (1). These studies have either been in adult populations or mixed adult and pediatric subjects in the results. We have undertaken a program to use MRI to study subarachnoid space (SAS) geometry, CSF flow dynamics, and tonsilar motion in a series of pediatric subjects with Chiari malformation. The long term goal of the study is to longitudinally evaluate pediatric patients with Chiari having various degrees of tonsilar descent, both with and without syringomeylia. In this abstract, we compare average peak CSF velocities in pediatric Chiari patients to age-matched control subjects and adults.

Methods. The MRI protocol included: 1) T1/T2 sagital scans through the brain/C-spine and a high-resolution 3D axial T2-SPACE scan through the brain and C-spine to assess geometry, 2) transverse ECG-gated PCMR cine scans at the foramen magnum (FM) and C6 to measure velocity and flow, and a sagital PCMR scan through the midline of the C-spine to assess velocity. Analysis of PCMR data was done in the program FLOW (AZL Lieden, NL).

Results. Forty subjects with Chiari malformation (n=40) have been studied (ages 9.6 ± 4.3 years), and 42% (17/40) of subjects had syringomyelia at the time of the scan. In eight (8) healthy control subjects (ages 6.6 ± 4.3 years) with no evidence of any neurologic diease, CSF flow measurements were made at the FM, C6, and in the mid-sagittal plane. Analysis of PCMR data indicated that subjects with Chiari malformation had higher average peak velocities at the FM compared to controls (6.8 ± 3.4 vs 5.2 ± 1.2, p=0.037), Figure 1. There was no significant difference in CSF velocities between Chiari patients with or without a syrinx at the FM or C6. The finding of increased CSF velocity in Chiari patients over normal subjects is similar to findings in adults. However, velocities in pediatric subjects (both Chiari patients and controls) are 1.4 times as great as velocities reported for adult (1).

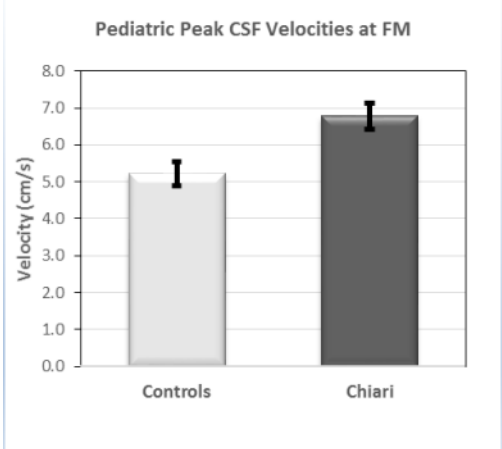


Fig. 1. Comparison of peak velocity at the foreman magnum in pediatric patient and normal age-matched subjects. The difference as significant with p<0.05

Discussion/Conclusion. Our ongoing MRI study is a focused longitudinal evaluation of a pediatric population with Chiari I, with and without syringomeylia. Results show that there are significant differences in CSF velocity between subjects with Chiari malformation and age-matched control subjects. The longitudinal nature of the study will allow us to quantitatively study the development of syringmeylia and to assess the effect of conservative treatment and surgery on SAS geometry and CSF dynamics.

1. Haughton VM, Korosec FR, Medow JE, et al. AJNR American journal of neuroradiology 2003;24:169-176

John N. Oshinski

About the Presenter. *John Oshinski is Associate Professor of Radiology & Imaging Science and Biomedical Engineering at the Emory University School of Medicine and the Georgia Institute of Technology in Atlanta. He is currently Director of Magnetic Resonance Research at Emory University. He is broadly interested in applying engineering principles to current clinical problems by using imaging to improve disease diagnosis and to evaluate the treatment of disease. He is particularly interested in diseases involving CSF and blood flow dynamics.*

ORIGIN AND CLINICAL RELEVANCE OF THE CRANIO-SPINAL CSF PULSATION

Noam Alperin, PhD

Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL, USA

Abstract. MR imaging of the CSF flow dynamics is becoming an integral part of many clinical exams. Therefore, understanding the CSF flow dynamic is critical for successful utilization of CSF flow studies for diagnosis of related brain disorders. This presentation reviews progress made over the years in identifying the driving force and the modulators of CSF pulsation and the means by which these modulators can be used for improved diagnosis and understanding of CSF related neurological problems.

The Cerebrospinal Fluid (CSF) flow is influenced by two separate processes; the circulation of the CSF from its formation sites to its absorption sites (i.e., bulk flow), and an oscillatory (back and forth) flow during the cardiac cycle (pulsatile flow). The first process governs the overall volume of CSF in the craniospinal space and thereby influences intracranial pressure (ICP). The second process, the oscillatory movement of the CSF within the craniospinal compartments, is caused by the pulsatile blood flow entering and leaving the intracranial compartment during the cardiac cycle. These two processes occur over different time scales. The circulation and replenishing of CSF in the craniospinal system occurs over minutes while the time scale of the pulsatile CSF flow is milliseconds.

A system model approach and accounting for volumetric flow rates to and from the cranium provided the first evidence that cranio-spinal CSF pulsation is driven by the net trans-cranial blood flow, i.e., arterial inflow minus venous outflow, and is modulated by the cranio-spinal intracranial compliance [1]. This has been further confirmed by direct estimation of the intracranial compliance from the ratio of the volume and pressure changes that occur with every heart beat [2, 3].

Early experience of MR measurements of intracranial compliance and pressure (MRICP) from several centers and the added value for basic research and clinical applications will be reported.

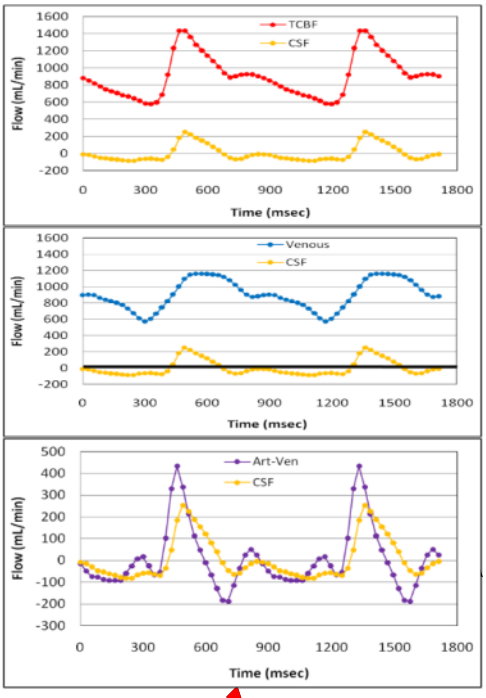


Fig. 1. MRI derived Flow Rate waveforms of arterial inflow (red), venous outflow (blue) and cranio-spinal CSF flow (yellow). Lower trace show CSF flow relative to the difference between arterial inflow and venous outflow. This demonstrates that net trans-cranial blood flow is the driving force of the cranio-spinal CSF pulsation. The CSF pulsation is modulated by the cranio-spinal compliance.

1. Alperin N, Vikingstad EM, Gomez-Anson B, Levin D.N (1996). Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. Magnetic Resonance in Medicine 35: 741-754.
2. Alperin N, Lichtor T, Mazda M, Lee SH (2006), From Cerebrospinal Fluid Pulsation to Noninvasive Intracranial Compliance and Pressure Measured by MRI Flow Studies. *Current Medical Imaging Reviews 2,* 117-129.
3. Tain and RW, Alperin N (*2009*) Noninvasive Intracranial Compliance From MRI-Based Measurements of Transcranial Blood and CSF Flows: Indirect vs. Direct Approach. IEEE Trans Biomed Eng. 56(3):544-51

Noam Alperin

About the Presenter. Noam Alperin is a professor of Radiology and Biomedical Engineering at the University of Miami, where he is heading the Physiologic Imaging and Modeling lab (PIML). Research areas include brain biomechanics, cerebral blood and CSF flow dynamics, and quantitative morphology.

ANALYSES OF BRAIN HYDRODYNAMICS AND BIOMECHANICS USING MRI: FROM INTRACRANIAL COMPLIANCE ANALYSIS TO FLUCTUATION MRI

Tosiaki Miyati[1], Naoki Ohno[1], Mitsuhito Mase[2], Noam Alperin[3],

[1] Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan
[2] Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan
[3] Department of Radiology, University of Miami, Miami, Fla, USA.

Abstract. We are working on a new project to construct an Integrative Intracranial-Condition Analysis System to noninvasively obtain the hydrodynamic and biomechanical properties of the brain using magnetic resonance imaging (MRI), and to apply them clinically (Fig. 1). In this Symposium, we first describe an analytical method for intracranial compliance (Fig. 1a) using phase-contrast cine-MRI to assess the intracranial condition and hydrodynamics, and to assist in the diagnosis of idiopathic normal pressure hydrocephalus (iNPH) [1]. Next, we show a novel method called "fluctuation MRI" (Fig. 1b) for evaluating hydrodynamic and biomechanical properties of the brain obtained with the regional water-molecular diffusion change during the cardiac cycle [2]. We describe the basis of this method, and its clinical applications, and also briefly introduce the other analytical methods (Fig. 1c and d).

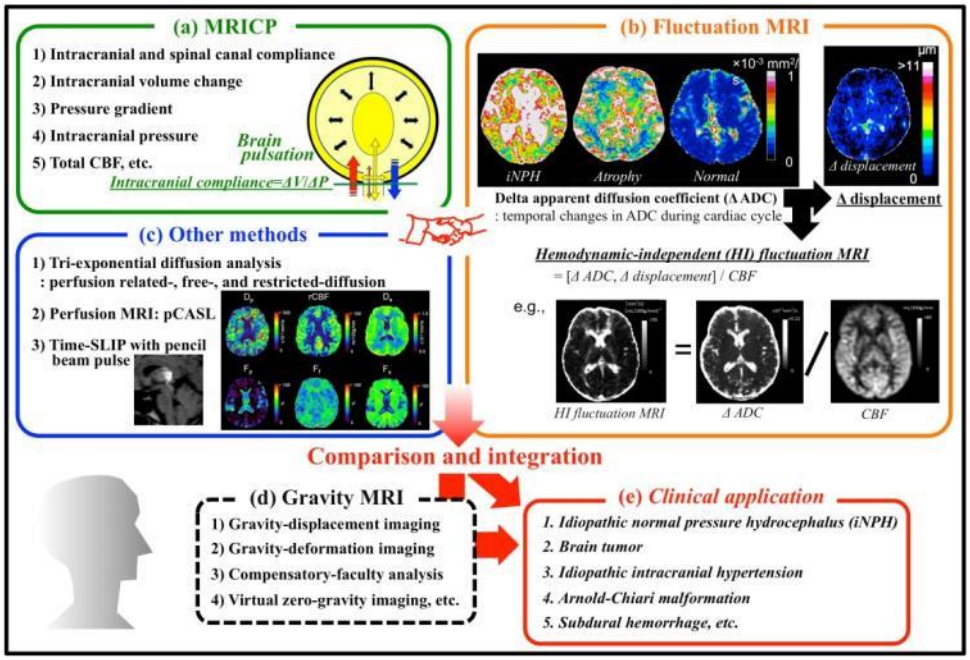


Fig. 1. Integrative Intracranial-Condition Analysis System. (a) MR–Intracranial Pressure (MRICP), (b) fluctuation MRI, and (c and d) the other analytical methods are compared and integrated to make the best use (e) in clinical.

1. Miyati T, Mase M, et al (2007). Noninvasive MRI assessment of intracranial compliance in idiopathic normal pressure hydrocephalus. J Magn Reson Imaging 26 (2):274-278.
2. Ohno N, Miyati T, et al (2011). Idiopathic normal-pressure hydrocephalus: temporal changes in ADC during cardiac cycle. Radiology 261 (2):560-565.

Tosiaki Miyati

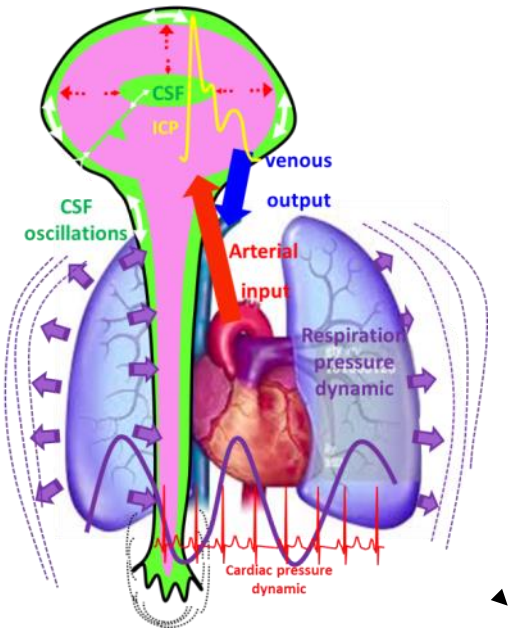
About the Presenter. **Tosiaki Miyati** completed his doctorate (Doctor of Engineering) at Gifu University in 2002. Moreover, he earned another degree (Doctor of Medical Science) at Nagoya City University in 2007. He has been working as an assistant professor (2000-2004), an associate professor (2004-2007), a full professor (2007-present), and a deputy director (2014-present) at Kanazawa University. During this period, he has been developing and evaluating noninvasive bio-functional imaging and analytical methods in MRI such as brain hemodynamics, hydrodynamics, and biomechanics. He is also a manager of Wellness Promotion Science Center, Kanazawa University (2008-present), and investigating applications of neuro-MRI to health sciences. He is a member of several academic societies (ISMRM, AAPM, JSMRM, etc.), in which he has held important positions. He has published 26 books and more than 330 journal articles, and received 23 scientific awards.

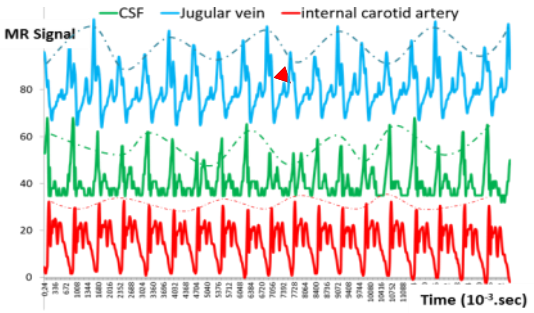
IMPACT OF RESPIRATION ON CSF DYNAMICS: A REAL-TIME MRI INVESTIGATION

O. Balédent, J Daouk, A Heintz, A Akouala, G Page, S Garnotel, C Capel, J Zmudka, C Gondry-Jouet, R Bouzerar

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

Abstract. Phase-contrast magnetic resonance imaging (PCMRI) (1-2) are used in medicine to evaluate patients presenting potential CSF flow alterations from different pathologies: Hydrocephalus, chiari malformation, syringomyela, intracranial hypertension, and multiple sclerosis or neurodegenerative diseases as Alzheimer disease. (3,4).Today lot of energy is put in 4D PCMRI (5), the last MRI flow sequence, which allows, in few minutes, to study CSF dynamics in all the spatial directions, in the entire cranio-spinal's volume. Nevertheless the PCMRI sequence is synchronized on the cardiac frequency and doesn't take in account the impact of the respiration pressure's dynamic, which is most often considered as a non-important effect in the CSF dynamics. Long times ago, authors (6) have already shown the existence of a respiration impact in the CSF flows. Recently using a time-spatial labeling MR sequence authors have visualized a CSF movement induced by respiratory motion (7) and few month ago, authors have published that inspiration is the major regulator of human CSF flow (8). As it is well known in MRI, protons moving through an MRI slice during an MR acquisition, alter the MR signal, function of their velocities. Based on this artifact we have constructed a rapid MR Echo Planar Imaging protocol, which can produce an image every 0.02 seconds during few minutes (9). This real-time protocol applied at the cervical level and in the cranium, trough arterial, veins and CSF spaces has shown in healthy subjects, the influence of respiration in the blood and CSF flows. The objective of this presentation is to describe the power and the limit of a usually PCMRI protocol and present our first results obtained with a real-time MRI showing how respiration influences the CSF and blood's flow.





1. Feinberg A, Mark S. Human brain motion and cerebrospinal fluid circulation demonstrated with MR velocity imaging. Radiology 1987
2. Balédent O, et al. Cerebrospinal fluid dynamics and relation with blood flow. Invest Radiol 2001.
3. El Sankari S, CSF and blood flow in MCI and Alzheimer's disease: a differential diagnosis from idiopathic NPH. Fluids Barriers CNS. 2011
4. Brugieres P, et al. CSF flow measurement in syringomyelia. AJNR Am J Neuroradiol. 2000
5. Yiallourou TI, et al. Comparison of 4D Phase-Contrast MRI Flow Measurements to CFD Simulations of CSF Motion in the Cervical Spine. PLoS ONE 2012
6. Schroth G1, Klose U Cerebrospinal fluid flow. II. Physiology of respiration-related pulsations. Neuroradiology. 1992
7. Yamada S, et al. Influence of respiration on cerebrospinal fluid movement using magnetic resonance spin labeling. Fluids Barriers CNS. 2013
8. Dreha-Kulaczewski S, et al. Inspiration is the major regulator of human CSF flow. J Neurosci. 2015
9. Daouk J, et al Simultaneous assessment of respiration and heart beat on CSF and blood oscillations in near real-time imaging, ISMRM 2015.

Olivier Balédent

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

SESSION C

THURSDAY, JULY 9TH 2015 – 14:00 TO 15:15

Session Chair:

Vartan Kurtcuoglu, *The Interface Group, Institute of Physiology, University of Zurich, Switzerland; Neuroscience Center Zurich and the Zurich Center for Integrative Human Physiology*

Diane de Zélicourt **$14^{00} – 14^{25}$**

The Interface Group, Institute of Physiology, University of Zurich, Zurich, Switzerland

A multiscale poroelastic framework for large deformations of the brain

Yiannis Ventikos **$14^{25} – 14^{50}$**

Department of Mechanical Engineering, University College London (UCL), London, UK

Investigating Cerebral Oedema using Poroelasticity

Keith Sharp **$14^{50} – 15^{15}$**

University of Louisville, Louisville, KY, USA

Solvent flow and solute transport in perivascular channels in the brain

AFTERNOON COFFEE BREAK – SESSION RESUMES AT 15^{40}

A MULTISCALE POROELASTIC FRAMEWORK FOR LARGE DEFORMATIONS OF THE BRAIN

Diane de Zélicourt[1], Vartan Kurtcuoglu[1]

[1] The Interface Group, Institute of Physiology, University of Zurich, Zurich, Switzerland

Abstract. While the brain and surrounding cerebrospinal fluid were classically believed to act as two separate compartments, there is now increasing evidence that they are in constant communication [1], impacting the intra-cranial dynamics across all scales, with potential relevance to our understanding of quasi-static pathological deformations such as in hydrocephalus. This work details a multi-scale poroelastic model of the brain, building on the mesoscale structure and properties of the tissue to derive the macroscale brain properties. The mesoscale model includes both the global cellular structure and the interstitial fluid. We explicitly model the mesoscale mechanics and apply the homogenization theory to derive the mean macroscale material properties and mechanical behavior. This formulation allows for the dynamic adjustment of the local properties: Deformations at the macroscale impact the mesoscale structure, which in turn affects the average macroscale properties.

Our results under quasi-static load demonstrate that seepage of fluid out of the parenchyma extends over long periods of time (Fig 1). Loads that may not suffice to yield a significant instantaneous deformation may thus have visible effects over time, shedding light onto the possible mechanisms behind large brain deformation in hydrocephalus. This framework also captures quite a few remarkable features of the brain tissue, notably hysteresis, cycle dependent behavior, consolidation and large deformations. On the other hand, as highlighted in the cyclic test experiments, the extent of the tissue non-linearities as predicted by our model underestimate those observed experimentally. This may be due to the simplifications made on the mesoscale. Future work should thus focus on refining 1) the underlying structural geometry, and 2) the underlying constitutive equation for the solid phase. More detailed modeling could also couple the homogenized tissue formulation with a more macroscopic domain, including perivascular spaces, which may yield a faster and more dynamic drainage pathway for the interstitial fluid, as well as the cerebral vasculature, which contributes to the pressure dynamics and provides a compliance chamber for the brain.

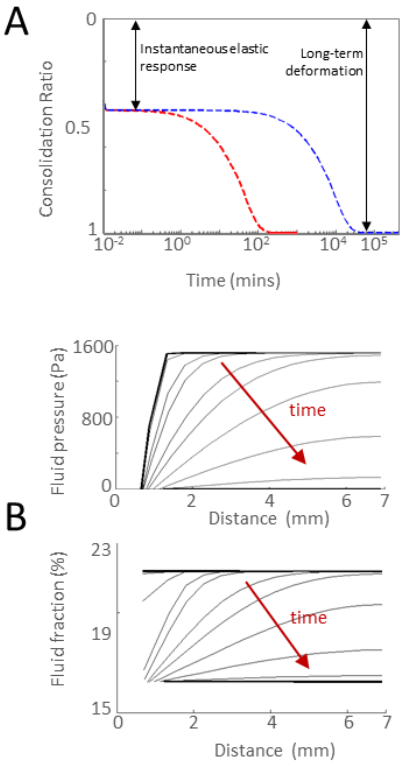


Fig. 1. (A) Consolidation of a brain sample after an initial loading of 10mmHg for sample heights of 6.9mm (as used by [2], red) and 10cm (blue). (B) Temporal evolution of the fluid fraction and fluid pressure profiles in the 6.9mm sample. Profile shortening illustrates the deformation of the sample.

1. Iliff (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med 4(147):147ra11
2. Franceschini (2006). Brain tissue deforms similarly to filled elastomers and follows consolidation theory. J Mech Phys Solids 54(12):2592-620

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 working as a post-doctoral fellow 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.

INVESTIGATING CEREBRAL OEDEMA USING POROELASTICITY

John C Vardakis[1], Dean Chou[2], Liwei Guo[1] and Brett J. Tully[3] & Yiannis Ventikos[1]

[1] Department of Mechanical Engineering, University College London (UCL), London, UK
[2] University of Oxford, Oxfordshire, UK
[3] First Light Fusion Ltd, Begbroke Science Park, Begbroke, Oxfordshire, UK

Abstract. Cerebral oedema can be classified as the tangible swelling produced by expansion of the interstitial fluid volume. Hydrocephalus can be succinctly described as the abnormal accumulation (imbalance between production and circulation) of CSF within the brain. Normal Pressure Hydrocephalus, a disorder within the realm of dementia, constitutes a further paradoxical complication in this class of conditions. Using hydrocephalus as a test bed, one is able to account for the necessary mechanisms involved in the interaction between cerebral fluid production, transport and drainage. The current state of knowledge about hydrocephalus, and more broadly integrative cerebral dynamics and its associated constitutive requirements, advocates that poroelastic theory provides a suitable framework to better understand the disease.

Multiple-network Poroelastic Theory (MPET) is used to develop a novel spatio-temporal model of fluid regulation and tissue displacement in various scales within the cerebral environment. The model is discretized in a variety of formats, through the established finite difference method, finite difference – finite volume coupling and also the finite element method (cG and dG methods). Both chronic and acute hydrocephalus was investigated in a variety of settings, and accompanied by emerging surgical techniques.

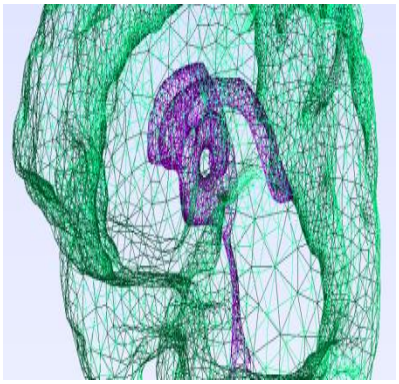


Fig. 1. Surface discretization of the cortex and ventricular system, the basis for the construction of a 3D volume FEM mesh.

To our knowledge, this is the first time such a multi-scale, multi-factorial and multi-paradigm modelling framework is tested on such a broad setting. We discuss novel results in surgical applications, oedema alleviation and the robust capabilities of this model to incorporate the glymphatic pathway.

Yiannis Ventikos

About the Presenter. Yiannis Ventikos is the Kennedy Professor of Mechanical Engineering and the Head of the Mechanical Engineering Department at University College London. He has worked or studied in Greece, France, the USA and Switzerland. Prof Ventikos has established the Fluidics and Biocomplexity Group that currently involves more than twenty researchers, mostly at the doctoral and postdoctoral level. He has published about 100 papers in peer-reviewed scientific journals, has contributed chapters in 5 books, has presented more than 200 papers in international conferences and workshops and has filed six international patents to date. He is the senior academic founder of a spin-out company and consults internationally in topics of his expertise. He has served as a reviewer for more than 50 academic journals as well as for textbook and monograph publishers. He is on the editorial board of four journals, and on the scientific and/or organising committee of numerous international conferences and workshops.

SOLVENT FLOW AND SOLUTE TRANSPORT IN PERIVASCULAR CHANNELS IN THE BRAIN

M. Keith Sharp[1], AK Diem[2], Roy O. Weller[2], Roxana O. Carare[2]

[1] University of Louisville, Louisville, KY, USA
[2] University of Southampton, UK

Abstract. Fluid flow and solute transport is fundamental to a number of disorders of the brain. For instance, intracranial interstitial fluid (ISF) and cerebrospinal fluid (CSF) balance is obviously important for hydrocephalus and flow of these fluids may impact Chiari and syringomyelia, as well as vision impairment in astronauts. Solute advection in these solvents may be central to dementia, including Alzheimer's and cerebral amyloid angiopathy. Imbalances can be created by abnormal production or clearance. Here, we investigate the mechanisms of flow of CSF/ISF in channels surrounding cerebral arteries and veins, a phenomenon that has received recent attention, but about which fundamental questions remain. Emblematic of the mystery of perivascular flow is that there is not even a consensus on the direction of flow or on the specific structures within the cross section of the vessels that carry it. While tracers injected into the parenchyma drain within minutes along periarterial (and not perivenous) basement membranes and enter cervical lymph nodes [1], tracers injected into the CSF flow along the perivascular spaces of cerebral arteries to enter the parenchyma as a slower equilibration process [2]. This presentation will explore the mechanisms of fluid flow and associated transport of tracers in peristaltic channels with a mathematical model.

The flow geometry is simplified to an annular channel with small height compared to vessel radius and with walls that oscillate in the radial direction with the blood pressure pulse, as well as perhaps with smooth muscle contraction [3]. Added to this classic peristaltic flow solution for low Reynolds number and long wavelength compared to channel height is flexible porous media within the channel that is oriented such that it favors flow in one direction. Specifically, the time-dependent flow resistance of the Darcy-Brinkman medium is modeled by cylinders that are perpendicular to flow in the direction of the blood pressure pulse (the direction of blood flow), and parallel to retrograde flow. Results show that retrograde flow is promoted by high cylinder volume fraction and by low peristaltic amplitude compared to the channel height. A decrease in cylinder concentration or an increase in amplitude reduces retrograde flow or even causes a transition to forward flow. As peristaltic amplitude increases so that the flow channel is occluded during maximum contraction, the channel behaves like a positive displacement pump, forcing forward flow. Porous media with constant orientation does not produce retrograde flow.

Because basement membranes are thin (~150 nm in height), real-time experimental observations of flow are difficult. However, extensive and specialized structure within basement membranes has been documented, making the existence of flexing flow resistors not implausible. Further, morphological and biochemical changes of the cerebrovascular basement membranes progress with ageing, affecting the dynamics of amyloid beta clearance in Alzheimer's disease. This new mechanism provides potential explanations for several fluid and solute advection-related dysfunctions of the brain. Abnormal protein orientation in inflow versus outflow channels could alter ventricular and parenchymal fluid balance. In addition, differences in protein concentration and in peristaltic amplitude could produce similar effects.

1. Carare, R.O., M. Bernardes-Silva, T.A. Newman, A.M. Page, J.A. Nicoll, V.H. Perry, et al. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol Appl Neurobiol 34(2):131-44, 2008.
2. Iliff, J.J., M. Wang, Y. Liao, B.A. Plogg, W. Peng, G.A. Gundersen, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Science Translational Medicine 4(147):147ra11, 2012. Epub 2012/08/17.
3. Jaffrin, M.Y., and A.H. Shapiro. Peristaltic pumping. Ann Rev Fluid Mech 3:13-36, 1971.

Keith Sharp

About the Presenter. M. Keith Sharp, Professor, Department of Mechanical Engineering, University of Louisville, received his BS degree from the University of Cincinnati in 1976, MS from Colorado State University in 1978 and ScD from MIT in 1987, all in Mechanical Engineering. He is Director of both the Biofluid Mechanics Laboratory and the Renewable Energy Applications Laboratory at the University of Louisville. His research interests include flow and transport in the brain, shear-induced hemolysis, blood rheology, and cardiovascular and ocular responses to microgravity in astronauts.

SESSION D

THURSDAY, JULY 9TH 2015 – 15:40 TO 16:55

Session Chair:

Thomas Brinker, *Department of Neurosurgery, Rhode Island Hospital, Providence RI USA*

Malisa Sarntinoranont **$15^{40} – 16^{05}$**

Department of Mechanical & Aerospace Engineering, University of Florida, Gainesville, FL, USA

MR-based Computational Models for Predicting Extracellular Flow and Transport in the Brain

Marijan Klarica **$16^{05} – 16^{30}$**

School of Medicine and Croatian Institute for Brain Research, University of Zagreb, Zagreb, Croatia

CSF Movement and Distribution of Different Substances Inside the CSF and Interstitial Fluid Compartments in Large Animal Models

Mikhail Papisov **$16^{30} – 16^{55}$**

Massachusetts General Hospital, Harvard Medical School, and Shriners Hospitals for Children, Boston, MA

The dynamics of intrathecal bolus and cerebrospinal solute transport

DISCRETIONARY BOAT-TOUR OF THE "HORTILLONAGES" $18^{00} – 19^{00}$

SYMPOSIUM DINNER AT 19^{30} AT "LES MARISSONS"

MR-BASED COMPUTATIONAL MODELS FOR PREDICTING EXTRACELLULAR FLOW AND TRANSPORT IN THE BRAIN

Malisa Sarntinoranont[1], Wei Dai[1], Paul R. Carney[2], and Thomas H. Mareci[3]

[1] Department of Mechanical & Aerospace Engineering, University of Florida, Gainesville, FL, USA
[2] Division of Pediatric Neurology, University of Florida, Gainesville, FL, USA
[3] Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, FL, USA

Abstract. Extracellular flows are of increasing interest in the brain since they contribute to drug transport and clearance. For example, local drug delivery methods such as convection-enhanced delivery (CED) are being used to improve targeting and increase uptake of drugs for neurological disorders such as tumors and epilepsy [1,2]. CED uses direct infusion into the interstitium to bypass the blood brain barrier and provide large volumes of tissue coverage. Our lab has been developing computational tools that solve for CED-induced extracellular flows by incorporating MR imaging data to account for specific anatomical boundaries and underlying tissue alignment [2,3]. In this study, high resolution images were used to generate 3D computational models of the rat brain that account for extracellular space as porous media. Transport models incorporate diffusion weighted imaging (DWI) data and uniquely account for the effects of crossing white matter fibers on transport. We use the model to simulate the effect of pathological changes on CED. We show that in a model of temporal lobe epilepsy (TLE), structural changes in the hippocampus and white matter connectivity result in distinct changes in CED coverage, see Fig. 1.

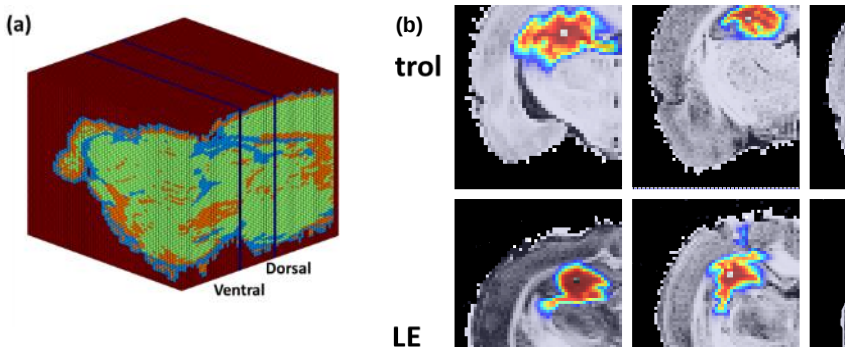


Fig. 1. MR-based computational model of CED. (a) 3D voxelized model of rat brain segmented for white matter (orange), gray matter (green), and CSF (blue). (b) Predicted coverage in normal and TLE brain for CED in the dorsal hippocampus (~ 7 uL of albumin). Normalized concentration is overlaid on generalized anistotropy images in the coronal plane.

Flow mechanics of underlying endogenous flows and effects on clearance are also investigated. Such computational transport models will aid researchers in determining the potential of new drug compounds and designing effective treatment regimes. Research in extracellular transport is emerging as an increasingly important area of research in drug delivery, since the vast majority of therapeutic agents must traverse this space to be effective. The need for this research has only increased with improved engineering and functionalization of large therapeutic agents such as viral vectors and nanoparticles.

1. Rogawski, M.A. (2009). Convection-enhanced delivery in the treatment of epilepsy. Neurotherapeutics 6(2): 344-51.
2. Lonser, R.R., Sarntinoranont, M., Morrison, P.F., Oldfield, E.H. (2014). Convection-enhanced delivery to the central nervous system. J Neurosurgery 122(3): 697-706.
3. Kim, J.H., Astary, G.W., Kantorovich, S., Mareci, T.H., Carney, P.R., Sarntinoranont, M. (2012). Voxelized computational model for convection enhanced delivery in the rat ventral hippocampus: Comparison with in vivo MR experimental studies. Annals of Biomedical Engineering 40(9):2043-58.
4. Kim, J.H., T.H. Mareci, and M. Sarntinoranont (2010). A voxelized model of direct infusion into the corpus callosum and hippocampus of the rat brain: Model development and parameter analysis. Medical & Biological Engineering & Computing 48(3): 203-214.

M. Sarntinoranont

About the Presenter. Dr. Sarntinoranont is an Associate Professor in the Department of Mechanical and Aerospace Engineering at the University of Florida. Her research expertise is in the areas of soft tissue biomechanics and regional drug delivery. Current research projects include: computational drug delivery models for the CNS and solid tumors, experimental tissue transport studies, TBI, biphasic tissue modeling, and mechanical testing. Dr. Sarntinoranont received her undergraduate degree from the Georgia Institute of Technology (1994). She completed her M.S. (1996) and Ph.D. degrees (1999) in mechanical engineering at the University of California, Berkeley. Her post-doctoral training was at the National Institutes of Health (NIH) in Bethesda, MD.

CSF MOVEMENT AND DISTRIBUTION OF DIFFERENT SUBSTANCES INSIDE THE CSF AND INTERSTITIAL FLUID COMPARTMENTS IN LARGE ANIMAL MODELS

Klarica Marijan[1], Orešković Darko[2]

[1] School of Medicine and Croatian Institute for Brain Research, University of Zagreb, Zagreb, Croatia
[2] Ruđer Bošković Institute, Zagreb, Croatia

Abstract. Over more than 30 years of work in our laboratory, we have done extensive research in the field of CSF hydrodynamics on anaesthetized and freely moving cats and dogs, observing the fate of molecules of various sizes inside the tissue and the CSF after their application into different parts of the CSF system [1,2,3,4]. We noticed that radioactive water, after its application into different CSF compartments, is locally being rapidly absorbed, and is not moving along the CSF space even in anaesthetized animals [2]. After the application of large molecules (for example, inulin, dextran blue) into the lateral ventricles, their distribution occured from the ventricles toward the subarachnoid space, which was in accordance with the classical concept of unidirectional CSF circulation from the site of hypothetical formation to the site of hypothetical apsorption. However, after the application of the same molecules into CSF somewhere outside the lateral ventricles, their distribution in all directions occured, even toward the lateral ventricles [2,4]. In addition, the velocity of the distribution of mentioned substances was several times greater along the spinal than the cranial subarachnoid space, which also doesn't fit into the classical concept of CSF movement dominantly from the ventricles toward the cortical subarachnoid space. It was noticed that molecules (benzylpenicilin, phenolsulfonphthalein etc.) which have the same physical and chemical characteristics as do acidic brain metabolits display a limited distribution along the CSF system. An active transport blockade with probenecid prolongs their residence time inside the CSF, and thus enables the distribution similar to that of large molecules [2,3,4]. Our results imply that molecules inside the CSF move in all directions, and that their distribution inside the spinal part is significantly different than it is inside the cranial part of the CSF, especially in free moving animals. Furthermore, distribution into the cortical subarachnoid space is significant in the vicinity of the interhemispheric space, and very poor along the temporal and parietal subarachnoid space. It appears that brain metabolites are predominantly being removed from the interstitium and the CSF by means of active transport at the capillary level, and not, as it is generally believed, by means of unidirectional circulation into dural sinuses of the brain convexity.

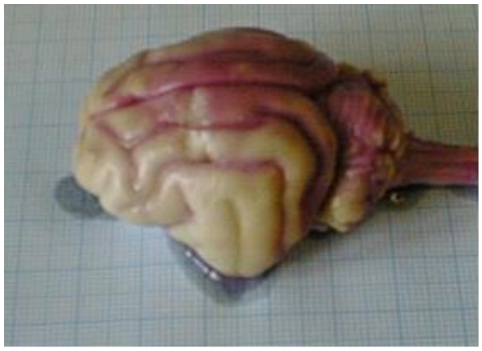


Fig. 1. Dye distribution 1 hour after its application into the cisterna magna (CM) of free moving cat implies that it is predominantly moving toward the spinal and infratentorial space, as well as toward supratentorial basal and interhemispheric space, while it cannot be seen inside the frontotemporoparietal subarachnoid space. Medulla spinalis is dyed evenly from all sides, and the depth of dye penetration into the tissue was progressively decreasing from CM to the lumbar parts. This kind of distribution is not in accordance with the classical concept of unidirectional CSF circulation.

1. Orešković D, Klarica M (2010). Formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations. Brain Res Rev 64: 241-262
2. Bulat M, Klarica M (2011). Recent insights into a new hydrodynamics of the cerebrospinal fluid. Brain Res Rev 65: 99-112
3. Zmajević M, Klarica M, Varda R, Kudelić N, Bulat M (2002). Elimination of phenolsulfonphthalein from the cerebrospinal fluid via capillaries in central nervous system by active transport. Neuroscience Letters 321: 123-125
4. Vladić A, Klarica M, Bulat M (2009). Dynamics of distribution of 3H-inulin between the cerebrospinal fluid compartments. Brain Res 1248: 127-135

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. Vice-dean, Head of the Department of Pharmacology and Department of Neurophysiology, Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia.

THE DYNAMICS OF INTRATHECAL BOLUS AND CEREBROSPINAL SOLUTE TRANSPORT

Mikhail Papisov[1-3], Vasily Belov[1-3], Alan J. Fischman[3], Ali Bonab[1-3], D. Levine[1]

[1]Massachusetts General Hospital, Boston, MA
[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 CSF. The studies were also intended to evaluate the relevance of rodent models for intrathecal drug transport studies and to develop methodologies for fully quantitative non-invasive studies of solute dynamics in CSF by PET.

To observe solute transport by PET, recombinant human enzymes, soluble polymers and nanoparticles were labeled with ^{124}I or ^{89}Zr and administered IT to rats and cynomolgus monkeys. Dynamic imaging data (0-30 min post injection) and multiple whole-body images (over at least 48 hours) were acquired using Siemens MicroPET focus 220 imager and CT images were acquired for each PET imaging session using CereTom NL 3000 CT scanner (Neurologica, USA). Images were analyzed to determine the rates and patterns of the label spread in the CSF from the injection site and farther into CNS and to the systemic circulation.

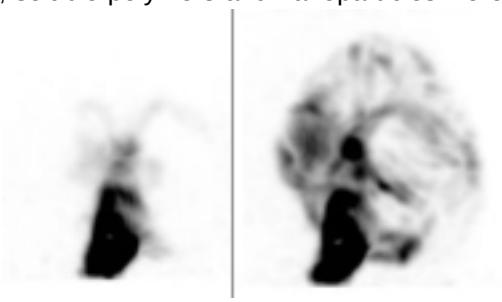


Fig. 1. The initial solute disposition after a high volume bolus (left) and the subsequent solute spread 20 minutes after the bolus (right). Cynomolgus monkey. PET, projection images.

The data showed that the initial solute distribution in the CSF greatly depended on the injected volume. Solutes injected in a high volume translocated to cervical/basal cerebral area (Figure 1, left image). In non-human primates, lumbar administration at 0.5 ml/kg resulted in the immediate delivery of >50% of the injected volume to the cerebral CSF.

The subsequent solute spread from the initial location was fast in the cerebral CSF (Figure 1, right image) and slow in the spinal CSF. No evidence of directional solute flows anywhere in the CSF was found. The general patterns of solute transport in the CSF of rodents and monkeys were similar.

Solute penetration into both white and gray matter from the CSF was found by 5 hours after the injection and confirmed by microscopy data.

Systemic presence of the solutes was detected early after the injection. The data suggests size-dependent direct drainage from the CSF to the blood through the arachnoid granulations.

No evidence of lymphatic drainage of CSF was found in monkeys in any region; in rats drainage was detected in deep anterior cervical area.

Conclusions. Hydrostatic compliance is the major factor of the initial distribution of the administered solute in the CSF compartment. CSF hydrodynamics plays the major role in the subsequent fast (head) and slow (spine) solute redistribution in the CSF. Rodent models are relevant and potentially scalable.

Mikhail Papisov

About the Presenter. Mikhail ("Misha") Papisov, PhD, Associate Chemist (Massachusetts General Hospital), Assistant Professor of Radiology (Harvard Medical School) and Associate Investigator (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.

KEYNOTE LECTURE

FRIDAY, JULY 10TH 2015 – 8:30 TO 9:30

Session Chair:
Diane de Zélicourt, *The Interface Group, Institute of Physiology, University of Zurich, Zurich, Switzerland*

Thomas Brinker **$8^{30} – 9^{30}$**

Department of Neurosurgery, Rhode Island Hospital, Providence RI USA

The novel understanding of CSF physiology: emerging research and clinical implications.

SESSION E

FRIDAY, JULY 10TH 2015 – 9:30 TO 10:20

Session Chair:
Lynne Bilston, *Neuroscience Research Australia, University of New South Wales, Sydney, NSW, Australia*

Anders Eklund **$9^{30} – 9^{55}$**

Department of Radiation Sciences, Umeå University, Umeå, Sweden

Posture dependencies of the venous system and implications for ICP

Marianne Schmid Daners **$9^{55} – 10^{20}$**

Product Development Group, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland

Hardware-in-the-Loop Testing of Cerebrospinal Fluid Shunt Systems

MORNING COFFEE BREAK – SESSION RESUMES AT 10^{50}

THE NOVEL UNDERSTANDING OF CSF PHYSIOLOGY: EMERGING RESEARCH AND CLINICAL IMPLICATIONS.

Thomas Brinker and Petra Klinge

Department of Neurosurgery, Rhode Island Hospital, Providence RI USA

Abstract

New findings indicate that both the choroid plexus formation and directional flow of CSF towards the arachnoid villi are only part of a much more complicated dynamic fluid system. Actually, CSF production and absorption at the blood brain barrier, cardiac and respiratory pulsations, and ebb and flood like fluid shifts between the intracranial and spinal CSF compartment are the factors modulating CSF movement. Indirect evidence suggests that the venous absorption of CSF at the blood brain barrier is more important than the absorption across the arachnoid villi. This presentation will summarize the new findings. Also, from a clinical point of view, the implications for the understanding of common CSF disorders will be discussed.

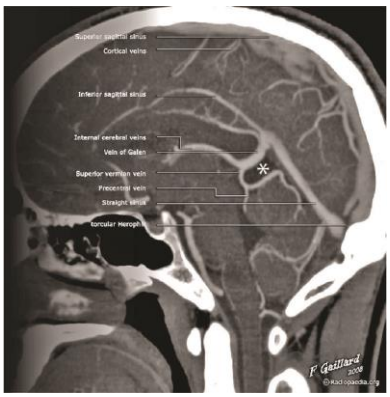


Figure: **How to explain acute obstructive hydrocephalus w/o assuming a physiological role of aqueductal flow of CSF ?** Current understanding presumes the interruption of CSF flow from ventricles across the compressed cerebral aqueduct as the cause of possibly fatal acute ventriculomegaly. Novel findings indicate that the obstruction of the aqueduct does not cause acute hydrocephalus. It is suggested that not the interruption of aqueductal CSF flow but the compression of the veins crossing the ambient cistern (*) causes the acute failure of periventricular CSF absorption and subsequent acute ventriculomegaly.

Thomas Brinker

About the Presenter

Being a fully trained neurosurgeon and Professor of Neurosurgery, I focused since 2005 on laboratory and clinical research. One of my major interest is the pathophysiology of cerebrospinal fluid absorption. In addition, since 2003 I evaluated the potential of cell based cell therapies for neurological disorders. Funded by the German Federal Ministry of Education and Research, I was PI of the first-in-man trial on the safety of encapsulated mesenchymal stem cell therapy for intracerebral hemorrhage.

POSTURE DEPENDENCIES OF THE VENOUS SYSTEM AND IMPLICATIONS FOR ICP

Anders Eklund[1], Petter Holmlund[1] Elias Johansson[2], Sara Qvarlander[1], Anders Wåhlin[1], Lars Owe Koskinen[2], Khalid Ambarki[1] and Jan Malm[2]

[1] Department of Radiation Sciences, Umeå University, Umeå, Sweden

[2] Department of Clinical Neuroscience, Umeå University, Umeå, Sweden

Abstract.

Disturbed CSF dynamics is suspected in diseases ranging from hydrocephalus to the visual impairment intracranial pressure (VIIP) syndrome identified in astronauts who have had long duration mission on the space station. An interesting feature linking these together is that the control of intracranial pressure with change in posture is linked to the gravitational hydrostatic pressure in the jugular venous system. When this component disappears in space-microgravity it affects the ICP and could thus be one important factors leading to the suspected increase in ICP and visual symptoms. For hydrocephalus, the primary symptoms are gait and balance disturbance which are naturally revealed in the up-right posture. In spite of this is CSF dynamics almost exclusively been performed with patient in the horizontal position, both when assessed with infusion technique and with MRI. By describing the CSF system and the venous system together, in a single model, we believe that we can produce a description of what controls ICP, and which components in that control that link to gravitational phenomena. A recent publication[1] imply that a model based on Davson´s equation and collapsible veins can predict ICP at different body positions, and thus at different hydrostatic loads.

We have performed a study on healthy volunteers with ultrasound imaging assessment of venous collapse with respect to upper body tilt angles. This was to understand the venous outflow pathways and how they can differ between individuals. We further evaluated suggested models of ICP and venous collapse by performing combined infusion and tilt studies in healthy volunteers, using an extensive protocol that included assessment of ICP and ultrasound. Preliminary data from this project will be presented. As a goal for the project we aim to use the developed model for how these systems interact, and identify combination of properties that is likely to produce harm to brain and eye in microgravity. We also want to understand the how the characteristics of venous drainage interacts and regulates ICP in upright which can produce new hypothesis related to hydrocephalus and other diseases that are characterised by a disturbed CSF dynamics. The NASA has declared VIIP as the largest medical obstacle for long-time stay on the Moon or for trips to Mars. The counterpart of VIIP on earth is a disease called idiopathic intracranial hypertension (IIH). Research on IIH is neglected, and our research will provide spin-off effects that may help young and obese women with IIH, to avoid the development of blindness.

1. Qvarlander et al “Postural effects on intracranial pressure: modeling and clinical evaluation.” J Appl Physiol. 2013 Sep 19

Anders Eklund

About the Presenter: Anders Eklund is Professor in Biomedical engineering at Umeå University at the Department of Radiation Sciences, Umeå University. His research field is models and measurement techniques concerning physiological fluid dynamics. Together with neurology professor Malm Eklund has published more than forty journal papers within the field of hydrocephalus.

HARDWARE-IN-THE-LOOP TESTING OF CEREBROSPINAL FLUID SHUNT SYSTEMS

Manuel Gehlen[1,2], Vartan Kurtcuoglu[2,3], Marianne Schmid Daners[4]

[1] Dynamic Systems and Control, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland
[2] Institute of Physiology, University of Zurich, Zurich, Switzerland
[3] Neuroscience Center Zurich, and the Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland
[4] Product Development Group, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland

Abstract. With a hardware-in-the-loop test bed, cerebrospinal fluid (CSF) shunt systems can be analyzed and tested under reproducible physiologic and pathologic conditions. The shunt system is positioned on moving parts of the test bed that mimic posture changes with two degrees of freedom (Fig. 1). The shunt's proximal end is placed in the intracranial pressure (ICP) tank and its distal end in the intraperitoneal pressure (IPP) tank, which interface to the mathematical model. The tanks' pressure levels are computed in real-time by a mathematical model of the patient's relevant physiology. Recordings of the CSF flow are an input to this model.

The implemented patient model comprises the exponential pressure-volume relationship of the CSF system [1], visco-elastic effects [2], posture-related pressure fluctuations [3] and vascular pulsations [4]. The model parameters were identified with results of clinical data.

Simulations of infusion tests as well as influences of different shunt systems, such as passive CSF shunts with or without gravitational shunt extensions showed comparable results to published data. Overdrainage and characteristic shunt system behavior could be imitated accurately. Therefore, realistic test cycles considering regular daily activities can now be planned, which allow to compare existing as well as new designed shunt systems.

Shunt system's performances and intracranial dynamics can be accurately reproduced. The understanding of the interaction between patient and shunt system promote the development of new concepts for active shunt systems and control strategies.

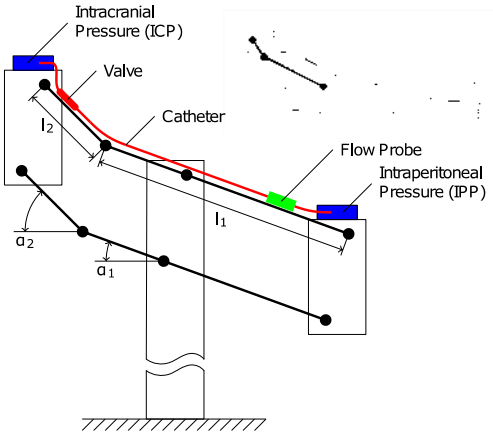


Fig. 1. Overview of the test bed and the corresponding patient position. The shunt system (red) is positioned on the moving parts that allow to mimic posture changes, such as head and body movements. Pressure tanks imitate intracranial (ICP) and intraperitoneal pressures (IPP). The expected pressure levels are computed in real-time and are influenced by the

1. Marmarou, A., et al., A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. J Neurosurg, 1978. 48(3): p. 332-344.
2. Bottan, S., et al., Assessment of intracranial dynamics in hydrocephalus: effects of viscoelasticity on the outcome of infusion tests. J Neurosurg, 2013. 119: p. 1511-1519.
3. Qvarlander, S., et al., Postural effects on intracranial pressure: modeling and clinical evaluation. Journal of Applied Physiology, 2013. 115(10): p. 1474-1480.
4. Avezaat, C.J. and J.H. van Eijndhoven, The role of the pulsatile pressure variations in intracranial pressure monitoring. Neurosurg Rev, 1986. 9(1-2): p. 113-20.

Marianne 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 responsible for the project coordination of the Zurich Heart. Her research interests are the modeling and control of biological systems and the development and control of biomedical devices.

SESSION F

FRIDAY, JULY 10TH 2015 – 10:50 TO 12:30

Session Chair:

Francis Loth, *Department of Mechanical Engineering, University of Akron, USA; Conquer Chiari Research Center, University of Akron, USA*

Andreas Linninger **$10^{50} – 11^{15}$**

Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois, U.S.A

CSF Dynamics and the Effect of Starling Forces on Intracranial Water Exchange

Chris Bertram **$11^{15} – 11^{40}$**

School of Mathematics & Statistics, University of Sydney, New South Wales, Australia

Effects of Adding Poroelasticity to an Existing FSI Model of Spinal CSF Dynamics in Syringomyelia with Adjacent Subarachnoid Space Stenosis

Mokhtar Zagzoule **$11^{40} – 12^{05}$**

IMFT, Toulouse, University Toulouse III, Toulouse, France

A One-Dimensional Model of Wave Propagation within the Co-Axial Viscous Fluid Filled Spinal Cavity

Kent-Andre Mardal **$12^{05} – 12^{30}$**

Institute of Mathematics, University of Oslo, Norway. Simula Research Laboratory, Fornebu, Norway

On the complexity of the Cerebrospinal fluid flow in the upper spinal column – is the assumption of laminar flow appropriate?

LUNCH AND POSTERS – SESSION RESUMES AT 13^{30}

CSF DYNAMICS AND THE EFFECT OF STARLING FORCES ON INTRACRANIAL WATER EXCHANGE

Andreas A. Linninger[1], Joel Buishas[1], and Kevin Tangen[1]
[1]Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois, U.S.A.

Abstract. Diseases of the central nervous system (CNS), such as hydrocephalus, idiopathic intracranial hypertension, Chiari or tumors may alter cerebrospinal fluid (CSF) flow patterns. The characterization of CSF flow and intracranial pressure (ICP) has made progress due to advances in medical imaging and in-vivo pressure measurements. Yet, conditions leading to dangerous ICP rise, ventricular enlargement, tonsil extension or syrinx formation are still poorly understood. Recently, our lab has assembled a computational model of the entire spinal and cranial CSF spaces from subject-specific medical images. This mechanistic model causally links CSF flow, spinal and cranial compliance with intracranial pressures. We also quantified the effect of spinal microanatomical aspects on CSF flow and resistance. The validation of the CSF flow with subject-specific anatomy and volumetric flow rates enabled the creation of a CNS wide flow-ICP map that encodes the CSF flow and pressure relation in normal subjects for all locations along the spinal canal and as functions of time, see Fig 1A. This work also provides quantitative evidence in support of the significant role that microanatomical aspects exert on CSF flow and flow resistance. The complex mixing patterns induced by microanatomical aspects were shown as significant drivers of intrathecally administered drugs.

Despite the wealth of clinical measurements, mathematical models cannot yet quantify the experimentally observed water exchange between intracranial compartments due to osmotic pressure gradients, see Fig 1B. A mathematical framework to elucidate the biochemical and transport mechanisms that control the dynamic balance of ICP, ventricular volume, and osmolites in the microcirculation, extracellular and ventricular spaces is lacking. This work seeks to integrate available clinical and experimental data into a comprehensive computational model that predicts momentum and mass exchange between the cerebral vasculature, the brain parenchyma, the cranial and spinal CSF. This presentation is a first step towards quantifying the effect of Starling forces on water exchange in the brain. Our research also reinforces the notion that both hydrostatic and osmotic pressure gradients are significant for CSF production and reabsorption.

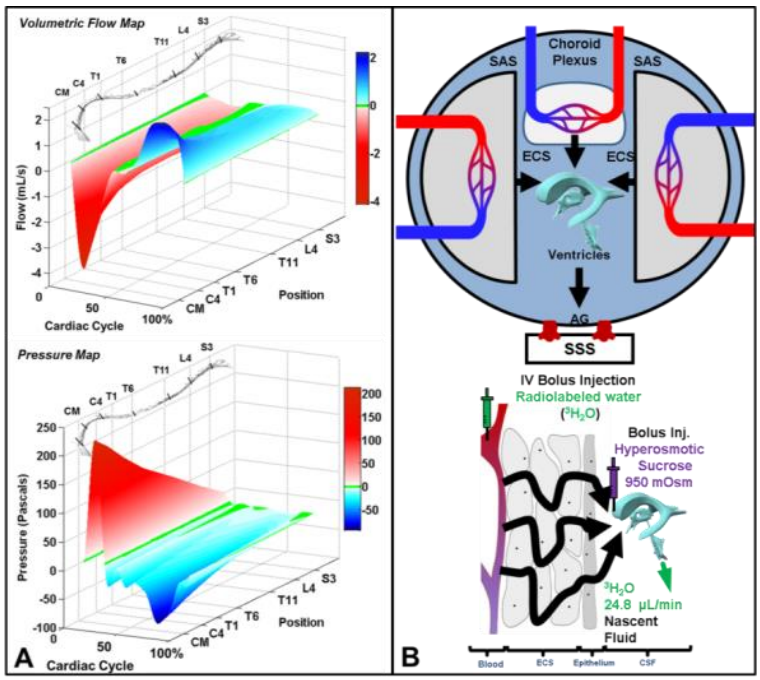


Fig. 1. (A) CSF flow and pressure maps for a normal subject for all positions along the spine as functions of time. (B) The conceptual network shows the principal CNS compartments between which water and solute exchange occurs. A ventriculo-cisternal perfusion experiment that measures the effect of nascent fluid generation in response to osmotic loading.

Finally, the model seeks to explore the relationship between ventricular enlargement and ICP and locate the source of cranial and spinal compliance. When completed, models such as the one presented here may yield clinically significant insights for the treatment of diseases associated with abnormal intracranial dynamics including hydrocephalus, edema, and intracranial hypertension.

Andreas A. Linninger

About the Presenter. Dr. Linninger is a Professor of Bioengineering at the University of Illinois at Chicago. His research interests include hydrocephalus, synthesis of magnetically guided nanoparticle platforms, intrathecal drug delivery, and hemodynamics.

EFFECTS OF ADDING POROELASTICITY TO AN EXISTING FSI MODEL OF SPINAL CSF DYNAMICS IN SYRINGOMYELIA WITH ADJACENT SUBARACHNOID SPACE STENOSIS

Christopher D. Bertram[1], Matthias Heil[2]

[1] School of Mathematics & Statistics, University of Sydney, New South Wales, Australia
[2] School of Mathematics, University of Manchester, Manchester, United Kingdom

Abstract. A pre-existing axi-symmetric FSI model [1] of the spinal cord, CSF and surrounding structures had revealed important aspects of syringogenesis mechanics, including the wave propagation, the protective role of the pia, the cord tearing stress concentration at the ends of a syrinx due to fluid slop within, and a valving effect raising SAS pressure caudal to the stenosis. However, in this model the elastic solids were impermeable, so syrinx volume was fixed. We set out to test a hypothesis generated from this model, whereby the mean pressure gradients between SAS and syrinx seemed to favour syrinx filling if the cord and pia were permeable.

The model implements the Navier-Stokes equations for the CSF and syrinx fluid, and equations of mass and momentum conservation, and a constitutive relation, for both the poroelastic media and the pore fluid in those media. FSI boundary conditions match stresses and velocities at the interfaces between bulk fluids and poroelastic media. The model is realized in open-source finite-element software (www.oomph-lib.org) [2].

Deformations, flows and pressures were grossly unchanged by poroelasticity; thus the previously observed valve effect was preserved. Despite 90% SAS stenosis by area, pulsatile axial CSF flow through the remaining gap greatly exceeded the parallel shunt flow passing through the thinned cord into the syrinx and back out again once past the stenosis. Changes in final mean syrinx volume were always small (of order 0.1%). Slow steady streaming circulated fluid under the stenosis, through the pia and cord, back via the syrinx and out through the cord and pia. Most of the pulsatile flow into the pia and cord overlying the syrinx did not reach the syrinx, but was absorbed in cyclic swelling of these media. The cyclic fluid absorption (Fig. 1) was confined to tissue boundary layers whose thickness depended on permeability and inversely on excitation frequency. Such cyclic absorption happened at the SAS interface with the solid cord as well, but to a lesser degree, dependent on the local cyclic strain. The pial stiffness acted to attenuate the extent of cyclic absorption by limiting deformation.

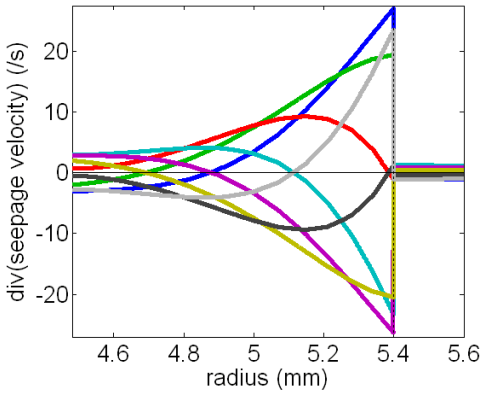


Fig. 1. Cyclic absorption rate vs. radial position in the cord and pia overlying the syrinx, at eight equi-spaced times during a 0.4s sine cycle of excitation pressure applied at the cranial end of the SAS, for an axial location ~1/4 of the way along the syrinx. The abscissa shows the entire thickness of the cord and pia at this location; to the left is the syrinx, and to the right is the SAS. The pia extends from 5.4 to 5.6mm, and is 250× stiffer than the cord. The permeability of both cord and pia is here 10^{-13} m^2.

In the absence of defined perivascular channels, we have shown that there exist mechanisms for the mixing and exchange of CSF with syrinx fluid and with ISF. This may explain apparently contradictory results from tracer studies variously supporting CSF inflow to the cord and cord ISF outflow to the SAS.

1. Bertram CD (2010). Evaluation by FSI spinal-cord simulation of effects of subarachnoid-space stenosis on an adjacent syrinx. J Biomech Eng 132:061009.
2. Heil M, Hazel AL (2006). An object-oriented multi-physics finite-element library. Fluid-Structure Interaction, eds. Schafer & Bungartz, pp. 19-49, Springer.

C.D. Bertram

About the Presenter. Beyond CSF, Chris Bertram's current research is on pumping in the lymphatic system. For many years he conducted experiments on self-excited oscillations of collapsed-tube flows, and these investigations still form the most comprehensive investigation of this dynamical system. He graduated from Oxford, with his first degree in Engineering Science, and a doctorate on ultrasonic measurement of arterial mechanical properties. He was later an associate of Tim Pedley at DAMTP in Cambridge, experimenting on unsteady flow separation and simulating collapsible tubes. He has published 90 full journal papers, and has been a member of the World Council of Biomechanics.

A ONE-DIMENSIONAL MODEL OF WAVE PROPAGATION WITHIN THE CO-AXIAL VISCOUS FLUID FILLED SPINAL CAVITY.

P. Cathalifaud[1], M. Maher[1], M. Zagzoule[1]

[1] IMFT, Toulouse, University Toulouse III, Toulouse, France

Abstract. One–Dimensional models have been used to simulate pulse waves propagation in the spinal cavity and the interactions between CSF, blood and the spinal cord. Some adopted compliant coaxial configurations but neglected the fluid's viscosity [1, 2] while others took into account CSF viscosity but simplified the cavity as one equivalent distensible tube [3]. Previous studies in the inviscid coaxial configuration have shown that the confinement reduces the wave propagation speed of the compliant part by a factor equal to the square root of the area parameter, i.e. the ratio of the tubes cross-sectional areas, when the dura is considered rigid. Here we use one-dimensional modeling of the spinal compartment in the coaxial configuration while considering CSF and blood as viscous fluids and the spinal cord as a poroelastic media. Different boundary conditions and their impact on the wave propagation are addressed. Concomitant to the area parameter, the viscous shear stresses developed at the different walls are involved in the dynamics of the system. They impact the coupled wave velocity and therefore the coupled distensibility as well as the wave attenuation due to the interaction between the contents of the spinal cavity. The addition of the viscous nature of the fluids induces a viscous attenuation whose effect depends also on the area parameter and the Womersley number. Although our modeling is non linear and the coupled system of equations is solved numerically we also consider the linear case and obtain a pressure damped wave equation similar to the so called telegrapher's equation. The pressure damping coefficient expression shows analytically how the area ratio and the shear stresses developed at the different walls are coupled.

The talk will present simplified configurations, to highlight the main physical phenomenons involved, and a more realistic configuration using the data of the Visible Human Man given in [4]. This spinal model will be integrated to the global mathematical model of the cerebral circulation in Man [5] to investigate the cranial spinal coupling and the autoregulation. This research is a part of a multi lab project called ROMBA (Retroactive Optimal Modelling of Brain Autoregulation) which aims to simulate autoregulation in the coupled cranial and spinal system, using modern fluid retroactive control optimal approach.

1. Berkouk K, Carpenter P W, Lucey A D (2003). Pressure wave propagation in fluid-filled co-axial elastic tubes Part one: Basic Theory. J Biomech Eng 125: 852-856.
2. Cirovic S, Kim M (2012) A one- dimensional model of the spinal cerebrospinal-fluid compartment. J Biomech Eng 134 (2):021005.
3. Martin B A, Reymond P, Novy J, Balédent O, Stergiopulos N (2012). A coupled hydrodynamic model of the cardiovascular and cerebrospinal fluid system. Am J Physiol Heart Circ Physiol 302: H1492-1509.
4. Loth F, Yardimci M, Alperin N (2001) Hydrodynamic modeling of cerebrospinal motion within the spinal cavity. J. Biomech. Eng. 123: 71-79.
5. Zagzoule M, Marc-Vergnes JP (1986). A global mathematical model of the circulation in man. J. of Biomechanics, 19 (12), 1015-1022.

M. Zagzoule

About the Presenter. M. Zagzoule is Professor at the university Toulouse III where he teaches continuum mechanics and biofluid mechanics. His research at the IMFT (Institut de Mécanique des Fluides de Toulouse) concerned Boundary Layers of High Dean number flows and Cerebral Circulation. He is currently working on the coupling the craniospinal flows and the cerebral autoregulation in the multi lab project ROMBA

ON THE COMPLEXITY OF THE CEREBROSPINAL FLUID FLOW IN THE UPPER SPINAL COLUMN – IS THE ASSUMPTION OF LAMINAR FLOW APPROPRIATE?

Kent-Andre Mardal[1,2], Kartik Jain[3] , Karen Helene Støverud[2], Geir Ringstad[4] and Per Kristian Eide[5]

[1] Institute of Mathematics, University of Oslo, Norway
[2] Simula Research Laboratory, Fornebu, Norway
[3] University of Siegen, Germany
[4] Department of Radiology and Nuclear Medicine, Oslo University Hospital- Rikshospitalet, Norway
[5] Department of Neurosurgery, Oslo University Hospital- Rikshospitalet, Norway

Abstract. CSF flow in the spinal canal is usually assumed to be laminar due to the relatively low Reynolds number, which is in the range 100-1000. However, the pulsatile nature of the flow as well as the complex anatomy of the subarachnoid space in the spinal canal have made us look critically at this assumption. The results are presented in this talk.

Previous computational fluid dynamics studies have demonstrated that the Chiari malformation is associated with abnormal CSF flow. Recent studies show significant differences between simulations and PC-MR velocity measurement. Therefore, we extend previous models by, in addition to the cervical subarachnoid space, including the cerebellomedullary cistern, pontine cistern, 4th ventricle, and patient-specific flow conditions in the aqueduct and cervical subarachnoid**.** The study included one healthy control and two patients with Chiari I malformation. The results demonstrated increased flow velocities in the Chiari patients, ranging from factor 5 to 15 when compared to the control. The flow was more complex in the Chiari patients, with jets and vortices forming at FM and high resolution simulations revealed transition to turbulence in parts of the domain and cycle in one of the Chiari patients.

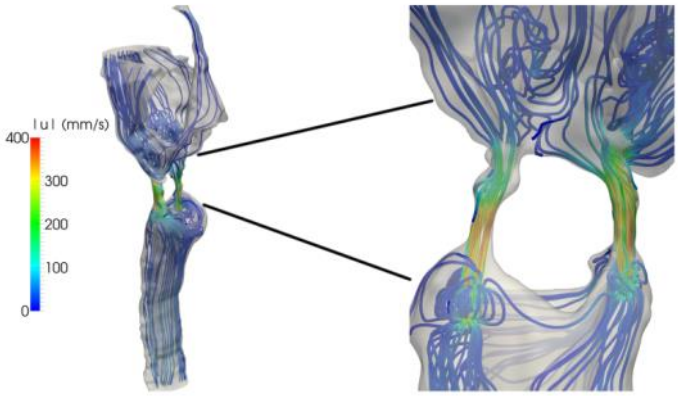


Fig. 1 Streamlines of CSF velocities in the craniovertebral junction in a patient with a Chiari I malformation. Velocities reaches 40 cm /s and the flow demonstrate complex features like vortices just below Foramen Magnum and tends to transition in parts of the cycle.

Kent-Andre Mardal

About the Presenter. Kent-Andre Mardal is an Associate 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, blood flow in cerebral aneurysms, and cerebrospinal fluid flow in association with the Chiari I malformation, syringomyelia, and hydrocephalus.

SESSION G

FRIDAY, JULY 10TH 2015 – 13:30 TO 14:45

Session Chair:

Andreas Linninger, *Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois, U.S.A*

Eric Schmidt **$14^{00} – 14^{25}$**

Department of Neurosurgery and Neurosciences Institute, University Hospital, Toulouse, France

Translational biomechanics in neurodegenerative diseases

Piotr Orlowski **$14^{25} – 14^{50}$**

Department of Engineering Science, University of Oxford, Oxford, United Kingdom

Towards the Mathematical Modelling of Brain Edema and Cell Death during Ischemia or Inflammation

Vartan Kurtcuoglu **$14^{50} – 15^{15}$**

The Interface Group, Institute of Physiology, University of Zurich, Switzerland; Neuroscience Center Zurich and the Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland

Contribution of astrocyte networks to cerebral water flow

AFTERNOON COFFEE BREAK – SESSION RESUMES AT 15^{30}

WORKSHOPS **15^{30} - 16^{15}**

CLOSING REMARKS FOLLOWED BY DISCRETIONARY PLENARY DISCUSSION AND CLOSING COFFEE

TRANSLATIONAL BIOMECHANICS IN NEURODEGENERATIVE DISEASES

Eric Schmidt

Department of Neurosurgery and Neurosciences Institute, University Hospital, Toulouse, France

To understand human biology at the system level, one must examine the structure and dynamics of cellular and organismal function, rather than the characteristics of isolated parts of a cell or organism. Properties of systems and biological networks are better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models.

Brain is a coordinating center composed of interconnected neurons and glial cells; but it can be likewise considered as a fluid-bathed densely vascularized multiphase material. Brain's mechanical behavior arises from the inherent viscoelastic neuro-glial components, but also from their interaction with the vasculature and interstitial fluid. In the context of ageing population, the prevalence of dementia is increasing. Neurodegenerative diseases refers to functional, biochemical but also structural alteration of the brain.

Alzheimer's disease (AD) and vascular dementia (VaD) are the two most common forms of dementia. Normal pressure hydrocephalus (NPH) is a less frequent but partially treatable disease, related to alteration of CSF dynamic. Although AD, VaD and NPH are distinct clinical entities, there is an overlap in both nosology and pathophysiology (cf. fig 1). A patient with gait disturbance, cognitive deterioration, urinary incontinence and enlarged ventricular system can be a combination of NPH, VaD and AD at various degrees. AD is barely remediable, VaD is mainly preventable but NPH is one of the few neurodegenerative disorders considered treatable and reversible after ventricular shunt insertion.

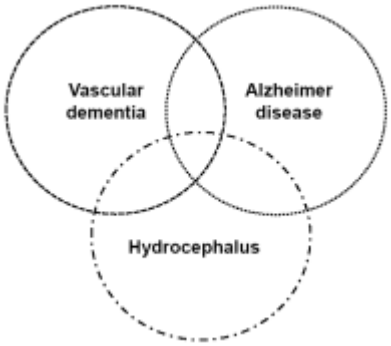


Fig. 1. Modern approach neurodegeneratve disease nosography

In a systemic perspective, our research project focuses on developing translational approaches for the analysis of high dimensional biomechanical, clinical and proteomic datasets. Thanks to a multi-disciplinary approach of brain fluid-structure interaction, this translational study aims at identifying novel noninvasive early biomechanical markers that might help evaluate/prevent risk of neurodegenerative disease and evaluate/intervene in frail elderly patients.

The objective of our project is to study brain fluid-structure interaction in aging brains and neurodegenerative diseases through an integrated and translational approach combining clinical and proteomic approaches with MRI-based biomechanical characterization. Our project includes a wide range of disciplines: clinical neurosciences, geriatrics, MR imaging, biomechanics and mathematics, embedded in complementary academic and clinical environments. We test the hypothesis that specific fluid-structure interaction profiles with abnormal biomechanical stresses on brain parenchyma, blood and CSF flow, can be helpful in differentiating patterns of AD, VaD and NPH. The project aims at implementing quantitative MRI data in the proteomic study. Through clinical research and biomechanical modeling, we plan to detail brain structure (CSF volume, atrophy, cortical thickness), flow dynamics (arterial & venous blood, CSF) and extract clinically-relevant profiles.

Eric Schmidt

Eric Schmidt graduated in neurosurgery in France and did his PhD in Cambridge (UK) under the supervision of Profs John D Pickard and Marek Czosnyka. His clinical expertise focuses on hydrocephalus & CSF disorders: clinical evaluation, CSF infusion tests, translational research. His is principal investigator of research programs: proteomic approach of neurodegenerative diseases (hydrocephalus, vascular dementia, Alzheimer), neuro/cardiac regulation (influence of ICP on autonomic system and heart/brain homeostasis) and brain biomechanics in normal and ageing brains (cerebral fluid/structure interactions).

TOWARDS THE MATHEMATICAL MODELLING OF BRAIN EDEMA AND CELL DEATH DURING ISCHEMIA OR INFLAMMATION

Piotr Orlowski[1], Simao Laranjeira[1], Stephen Payne[1], Mkael Symmonds[2], Jacqueline Palace[2]

[1] Department of Engineering Science, University of Oxford, Oxford, United Kingdom
[2] John Radcliffe Hospital, Division of Clinical Neurology, University of Oxford, Oxford, United Kingdom

Abstract. A number of vascular and inflammatory conditions of the brain such as stroke, or Neuromyelitis Optica (NMO) may lead to edema and brain tissue injury. This talk will present our progress on the mathematical modelling of ischemia and edema in view of responding to some clinical needs for these conditions that can be divided in four categories: 1) testing of hypotheses about the pathophysiology of the diseases, 2) supporting the design of new imaging modalities, 3) testing, optimizing and designing of drug-based and device-based therapies and 4) Image-based personalization of treatment planning.

Our modelling approach consists in representing brain tissue by dividing its space into four compartments: neurons, astrocytes, capillaries and the extracellular space. Furthermore, metabolism, cell membrane potential regulation and volume regulation is incorporated for the two cellular compartments [1,2]. More specifically, cell swelling is modelled by considering osmotic and hydrostatic pressures on the cell membrane and allowing water transport to occur mainly through Aquaporin 4 (AQP4) channels. Alterations to this core model are then made to simulate specific disease progress or simulate a therapeutic intervention.

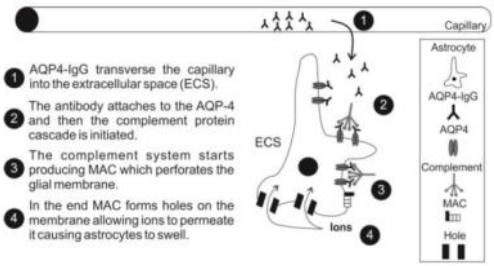


Fig. 1. Description of pathophysiology steps leading to cell swelling in Neuromyelitis Optica. The model is used to simulate the inhibitory effect of the CD59 protein on cell membrane lysis.

The talk will summarize the steps of designing the core model and of inferring tissue death from its simulation results. Recent inclusion of the glutamate neurotoxicity death model will be reported at this stage. The use of the model will be briefly illustrated with its application to stroke treatment planning [3].

The talk will then report results and challenges of ongoing research on the simulation of cell death in NMO. The model is used to discard the hypothesis that in NMO cells die due to damage to AQP-4 channels and to support the hypothesis that death occurs due to cell membrane lysis and resulting cell swelling. The pathophysiology steps considered in this analysis are summarized in Figure 1 and include: 1) transport of the NMO AQP4-IgG antibody from the capillary to the extracellular space (ECS), 2) attachment of the antibody to AQP4 channels, 3) production of the Membrane Attack Complex (MAC) which perforates the membrane and 4) transport of ions through the created holes causing the cell to swell. The model is also used to simulate swelling reduction by using the CD59 protein for inhibiting MAC.

1. Orlowski P, Chappell M, Park C, Grau V and Payne S (2011). Modelling of pH dynamics in brain cells after stroke. *Interface Focus* 1: 408-41610.1098/rsfs.2010.0025.
2. Orlowski P, O'Neill D, Grau V, Ventikos Y and Payne S (2013). Modelling of the physiological response of the brain to ischaemic stroke. Interface Focus 3 (2):20120079.
3. Orlowski P, McConnell F K, Payne S (2014). A mathematical model of cellular metabolism during ischemic stroke and hypothermia. IEEE Trans. Biomed. Eng. 61 (2): 484-490.

Piotr Orlowski

About the Presenter. Piotr Orlowski received MSc degrees in Engineering from the Warsaw University of Technology (2006) and the National Institute of Applied Sciences of Lyon (2006) with majors in Biomedical Electronics; and Instrumentation, Systems, Signal and Images respectively. He received the DPhil degree in Engineering Science from the University of Oxford (2010). He was a Postdoctoral Research Assistant and Research Fellow and Tutor at the Department of Engineering Science and Keble College at the University of Oxford. He is currently the E.P. Abraham Career Development Fellow in Imaging at Keble College. His interests include Mathematical Physiology, Bio-Fluid Dynamics and Image Processing.

CONTRIBUTION OF ASTROCYTE NETWORKS TO CEREBRAL WATER FLOW

Mahdi Asgari[1], Diane de Zélicourt[1], 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. Recent *in vivo* microscopy studies have addressed the role of aquaporin-4 (AQP4) water channels in the transport of fluorescent tracers in the brain. In AQP4 knock-out mice, the time for tracers to reach the interstitial fluid (ISF) from the cerebrospinal fluid via paravascular spaces (PVS) was increased, which was interpreted as a consequence of reduced CSF influx into the PVS [1]. This interpretation is not obvious: Both fluid and tracers pass from the PVS to the ISF via inter-endfeet gaps (IEG), but only fluid leaves the PVS additionally through AQP4. One could expect that the removal of this second pathway would lead to increased fluid flow through the first, and that the time for tracers to reach the ISF would decrease rather than increase. In this computational study we show how parallel but interconnected extra- and intracellular pathways can explain the experimentally observed behavior.

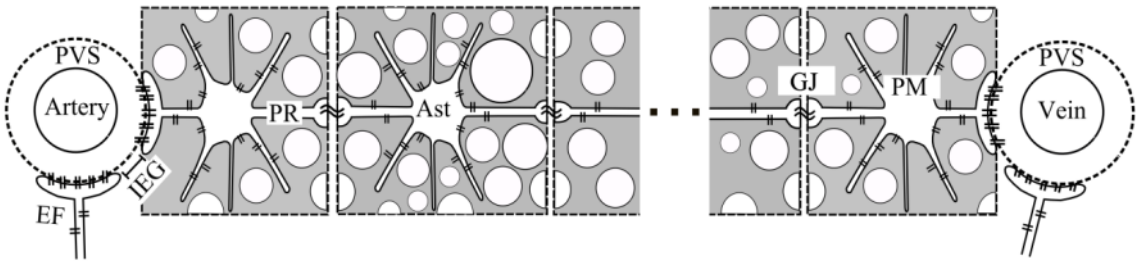


Fig. 1. Sketch of the model domain consisting of an astrocyte network between arterial and venous paravascular spaces (PVS). The perivascular astrocytes are in direct contact with their neighboring PVS via the respective astrocyte's endfoot (EF). The intra-astrocyte and extracellular spaces are in constant exchange of water through AQP4 channels expressed in the astrocyte plasma membrane (PM). Gap junctions (GJ) connect the intracellular spaces of two adjacent astrocytes. PR: Astrocyte process. IEG: Inter-endfeet-gap.

The underlying mathematical model considers flow between a pair of arterial and venous PVS driven by a hydrostatic pressure gradient. The computational implementation is based on electrical analogy to fluid flow. A sketch of the model domain is shown in Fig. 1. Our calculations show that networks of astrocytes may contribute to the passage of tracers between tissue and PVS by serving as low resistance pathways to bulk water flow. These networks are connected through AQP4 with a parallel, extracellular route taken by the tracers. Inhibition of this interconnection by knock-out of AQP4 causes a reduction of bulk flow between tissue and PVS, leading to a reduction of tracer influx from arterial PVS into the brain tissue.

More relevant than artificial tracers are metabolites in the ISF that are thought to be cleared through the venous PVS. Under normal conditions, the solute transport capacity of the tissue, which is dominated by diffusion, is higher than that of the PVS (dominated by convection). The limiting mechanism for solute transport is therefore the fluid flow rate in the PVS. Consequently, even though metabolites are transported largely by diffusion in the brain tissue, their removal is nevertheless dependent on bulk flow through the PVS, and in turn on the net flow of water through both intra- and extracellular routes in the tissue.

1. Iliff J et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma. Sci Transl Med 4:147ra111

Vartan Kurtcuoglu

About the Presenter. Vartan Kurtcuoglu received his degree in mecha-nical engineering from ETH Zurich after completing his diploma 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.

POSTERS

The role of astrocytes networks in cerebral interstitial fluid ad metabolites clearance – a computational study

Mahdi Asgari, *The Interface Group, Institute of Physiology, University of Zurich, Switzerland*

Impact of shunt placement on CSF dynamics

Cyrille Capel, *University hospital of Picardie Jules Verne, BioFlowImage, Amiens, France; University hospital of Picardie Jules Verne, Neurosurgery department, Amiens, France*

Non-invasive assessment of ICP during infusion test using Transcranial Doppler Ultrasonography

Danilo Cardim, *Division of Neurosurgery, Department of Clinical Neurosciences, Cambridge University Hospitals, UK*

Intracranial Compliance Changes During Cardiac Cycle in Hydrocephalus Patients

Simon Garnotel, *University of Picardie Jules Verne, BioFlowImage, Amiens, France; University of Reims Champagne-Ardenne, Mathematics Laboratory of Reims, Reims, France*

Hardware-in-the-loop testing of gravitational cerebrospinal fluid shunts

Manuel Gehlen, *Institute for Dynamic Systems and Control, ETH Zurich, Switzerland; The Interface Group, Institute of Physiology, University of Zurich, Switzerland*

Model of the internal jugular vein during head-up tilt

Petter Holmlund, Department of Radiation Sciences, Umeå University, Umeå, Sweden

2D and 4D PC-MRI flow software

Gwenaël Pagé, *University hospital of Picardie Jules Verne, BioFlowImage, Amiens, France*

CSF protein variations correlates with CSF oscillations in hydrocephalus patients

Vincent Puy, *University hospital of Picardy Jules Verne, Amiens, France;*

THE ROLE OF ASTROCYTES NETWORK IN CEREBRAL INTERSTITIAL FLUID AND METABOLITES CLEARANCE – A COMPUTATIONAL STUDY

Mahdi Asgari[1], Diane de Zélicourt[1], 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. Blood, cerebrospinal, paravascular (PVS) and interstitial (ISF) fluids are in constant communication through intricate networks of interconnected fluid pathways. They are vital to the brain's control of water and metabolite homeostasis, but their interaction remains poorly understood. In this computational study, we focus on the PVS to ISF interface and the role played by Aquaporin-4 (AQP4) water channels. The underlying mathematical model considers both intra- and extracellular water pathways in a network of astrocytes between two neighbouring arterial and venous PVS.

We show that networks of AQP4 expressing astrocytes may contribute to bulk water flow by providing a low resistance intracellular pathway with constant water exchange with ISF through AQP4. Inhibition of the intracellular route by deletion of AQP4 causes a reduction of bulk flow between tissue and PVS (Fig 1), leading to reduced metabolite clearance into the venous PVS or, as observed in animal studies, a reduction of tracer influx from arterial PVS into the brain tissue. Sensitivity analysis demonstrates the robustness of our findings to parameter variations within realistic bounds.

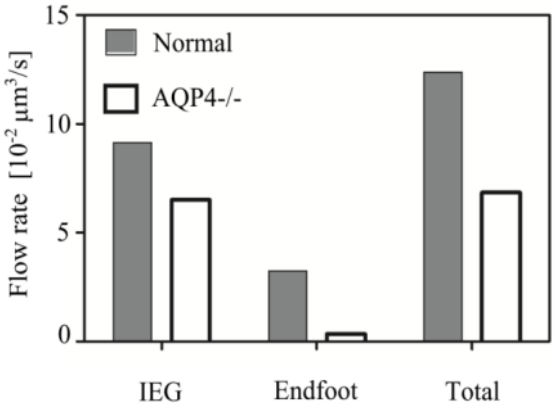


Fig. 1. Effect of AQP4 deletion on water flow rate from PVS to the parenchyma through endfoot AQP4 channels, inter-endfeet-gaps (IEG) and in total

About the Presenter. Mahdi Asgari joined The Interface Group of Prof Kurtcuoglu at the University of Zürich in September 2013 for his doctoral studies on water and solute dynamics in the brain. He obtained his Bachelor and Master degrees in mechanical engineering from Sharif University of Technology, Iran. His study focus was computational fluid dynamics. For his Master thesis carried out under Prof. Ali Moosavi, he employed nanoscale multiphase modeling of surface flows to investigate nanodroplet interaction with solid substrates.

Mahdi Asgari

IMPACT OF SHUNT PLACEMENT ON CSF DYNAMICS

C. Capel[1,2], M. Baroncini[3], J. Hodel[4], F. Dallery[1], A. Fichten[1,2], O. Balédent[1]

1 – University hospital of Picardie Jules Verne, BioFlowImage, Amiens, France
2 – University hospital of Picardie Jules Verne, Neurosurgery department, Amiens, France
3 – University hospital of Lille, Neurosurgery department, Lille, France
4 – University hospital of Lille, Radiology department, Lille France

INTRODUCTION: Normal pressure hydrocephalus (NPH) is related to cerebrospinal fluid (CSF) circulation disorders. Shunt placement is the treatment of choice for NPH. Phase-contrast MRI (PCMRI) allows a dynamic analysis of CSF flows during the cardiac cycle[3,4]. Preoperative analysis of NPH CSF dynamics by IRMCP retrieves a hyperpulsatility of intraventricular CSF measured at the aqueductal level[1–3]. The cervical CSF flows is not affected in NPH1. Global hemodynamic parameters were not altered in NPH patients1 but venous flows repartition was altered[1,2]. The objective of our study is to show the influence of shunt placement on CSF dynamics.

MATERIALS AND METHODS: 22 patients underwent preoperative (T1), 6 months (T2) and 1 year (T3) postoperative PCMRI. We calculated the intraventricular CSF dynamics by calculating the CSF stroke volume at the aqueduct level (SVaqu), CSF dynamics at subarachnoid cervical level by the CSF stroke volume at C2C3 level. We calculated a ratio between these two parameters (CSF_{RATIO}). We evaluated craniospinal system hemodynamics by cerebral blood flow, venous amplitude flow and vascular stroke volume measurements at cervical level.

RESULTS: SVaqu decreased significantly between T1 and T2 (p=0.002). SVcerv decreased significantly between T1 and T2 (p=0.01) and between T2 and T3 (p=0.002). The CSFRATIO was not modified by shunt placement. Hemodynamics parameters were not modified after shunt placement.

CONCLUSION: Shunt placement influence significantly intraventricular and subarachnoidal CSF flows. Shunt placement give an additional compliance to craniospinal system. No change was found on hemodynamics.

1. Balédent O, Gondry-Jouet C, Meyer M-E, De Marco G, Le Gars D, Henry-Feugeas M-C, et al.: Relationship between cerebrospinal fluid and blood dynamics in healthy volunteers and patients with communicating hydrocephalus. Invest Radiol 39:45–55, 2004
2. Bateman GA: The pathophysiology of idiopathic normal pressure hydrocephalus: cerebral ischemia or altered venous hemodynamics? AJNR Am J Neuroradiol 29:198–203, 2008
3. Bradley WG Jr, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P: Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. Radiology 198:523–529, 1996
4. Greitz D, Wirestam R, Franck A, Nordell B, Thomsen C, Ståhlberg F: Pulsatile brain movement and associated hydrodynamics studied by magnetic resonance phase imaging. The Monro-Kellie doctrine revisited. Neuroradiology 34:370–380, 1992

Cyrille Capel

About the presenter, Cyrille Capel is resident in neurosurgery department of Hospital University Center of Amiens and PhD Student in the medical image processing department and BioFlowImage research team. His thesis focuses on the field of hydrodynamics and hemodynamics in hydrocepalus studied by phase-contrast MRI. His thesis supervisors are on two sites, Amiens (Olivier Balédent (PhD), director of the medical image processing department and BioFlowImage research team) and Lille (Dr Marc Baroncini (MD PhD), neurosurgeon in neurosurgery department of the hospital university center of Lille)).

NON-INVASIVE ASSESSMENT OF ICP DURING INFUSION TEST USING TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Danilo Cardim, Brenno Cabella, Joseph Donelly, Chiara Robba, Marek Czosnyka, Matthew Garnett, John D Pickard, Zofia H. Czosnyka

Background. Transcranial Doppler (TCD) based methods have been used to estimate ICP noninvasively (nICP), however their relative accuracy varies between different types of intracranial hypertension: vasogenic, CSF circulatory or secondary to brain volumetric changes (oedema, contusion, hematoma, etc). This study aimed to compare four nICP methods in a prospective cohort of hydrocephalus patients whose CSF dynamics was investigated using infusion tests involving controllable test-rise of ICP.

Methods. FV, ICP and non-invasive ABP were recorded in 53 patients diagnosed for hydrocephalus. nICP methods were based on: I) interaction between FV and ABP using black-box model (nICP_BB); II) diastolic FV (nICP_FVd); III) critical closing pressure (nICP_CrCP) and IV) TCD-derived pulsatility index (nICP_PI). Correlation between rise in ICP (ΔICP) and ΔnICP and averaged correlations for changes in time between ICP and nICP during infusion test were investigated.

Results. All nICP formulas overestimated ICP at baseline ($p<0.005$): nICP_BB 10.76 (15.08-7.30); nICP_FVd 16.97 (22.56-11.64); nICP_CrCP 18.34 (20.38-14.89); nICP_PI 16.57 (17.46-16.06); and ICP 7.74 (11.06-2.95). At plateau of ICP during infusion test, only nICP_BB and nICP_PI presented significant difference from ICP. From baseline to plateau, all nICPs estimators increased significantly (paired t-test, $p<0.05$). Correlations between ΔICP and ΔnICP were better represented by ICPn_PI and ICPn_BB: 0.45 and 0.30 ($p<0.05$). nICP_FVd and nICP_CrCP presented non-significant correlations: -0.17 ($p=0.21$), 0.21 ($p=0.13$). For changes in ICP during individual infusion test ICPn_PI, ICPn_BB and ICPn_FVd presented similar correlations with ICP: 0.39±0.40, 0.39±0.43 and 0.35±0.41 respectively. ICPn_CrCP presented a weaker correlation ($R=0.29\pm0.24$). In those cases where changes of ICP related to vasogenic fluctuations (plateau waves, B waves) overlapped rise related to CSF infusion, time-correlation between real and estimated ICP seemed to be remarkably better.

Conclusions. Out of the 4 methods, nICP_PI was the one with best performance for predicting changes in ΔICP during infusion test, followed by nICP_BB. nICP_FVd and nICP_CrCP showed unreliable correlations. Changes of ICP observed during the test were expressed by nICP values with only moderate correlations. Vasogenic components of ICP seemed to be easier to estimate with TCD, than component related to increased CSF circulation.

Danilo Cardim

About the presenter, Danilo Cardim is an M.Sc Biologist, Master in Physiology. He is currently a PhD student in Clinical Neurosciences at the University of Cambridge, under supervision of Professor Marek Czosnyka. He has experience in Experimental and Clinical Neurophysiology and Brain Physics, specifically on the field of non-invasive monitoring of intracranial pressure.

INTRACRANIAL COMPLIANCE CHANGES DURING CARDIAC CYCLE IN HYDROCEPHALUS PATIENTS

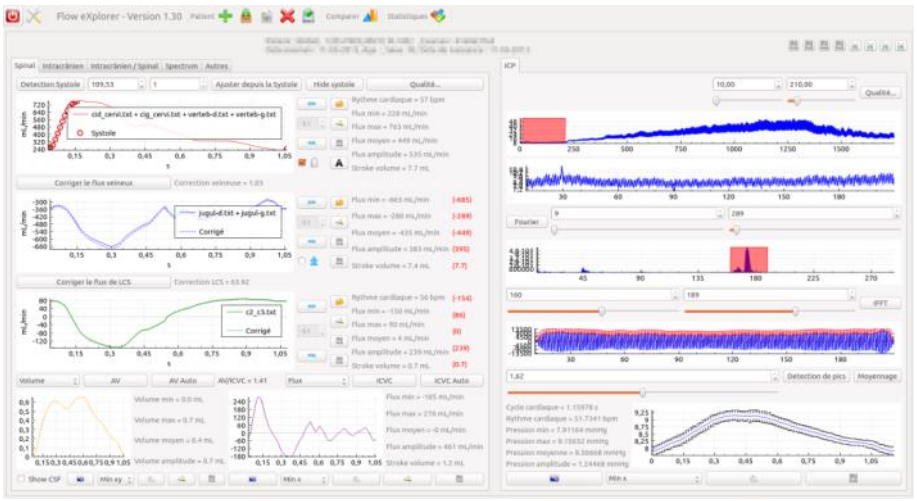
S. Garnotel[1,2], S. Salmon[2], E. Schmidt[3], Z. Czosnyka[4], Marc Baroncini[5], G. Pagé[1] and O. Balédent[1]

1 University of Picardie Jules Verne, BioFlowImage, Amiens, France
2 University of Reims Champagne-Ardenne, Mathematics Laboratory of Reims, Reims, France
3 University hospital of Toulouse, Neurosciences Department, Toulouse, France
4 University of Cambridge, Department of Clinical Neurosciences, Cambridge, United Kingdom
5 University hospital of Lille, INSERM U837, Jen-Pierre Aubert Research Center, Lille, France

Abstract. Intracranial pressure (ICP) monitoring and infusion test are widely used in the diagnosis and management of hydrocephalus. MR neuroimaging allows the quantification of cerebrospinal fluid (CSF) and blood flow dynamics that can be used to calculate intracranial volume change (IVC) during cardiac cycle. These techniques help to diagnose active hydrocephalus which need the placement of a shunt. Since compliance is a function of ICP and IVC changes, the aim of this work is to combine these two techniques to calculate the cerebrospinal compliance along the cardiac cycle with a semi-automated software.

36 patients [1] with suspected hydrocephalus underwent a spinal infusion test and a flow MRI (PC-MRI). ICP sensor data has been extracted with ICM+ [2] and CSF, arterial and venous flows have been extracted from PC-MRI with Flow Analysis [3]. ICP and flow curves have been loaded and analyzed in the new "ICP/flow analysis" software that we design.

Mean ICP was calculated in different periods of the infusion test: basal, up, plateau, down, and compared with the IVC, calculated from flow MRI, to determine the cerebrospinal system compliance. Results show significant compliance variability over the cardiac cycle, with a decrease in the middle of the cycle, when volume and pressure are increased, as well as a significant variability over all the patients.



A multi-platform ICP/flow analysis software was performed to combine ICP, CSF and cerebral blood flow changes during a short time of a cardiac cycle to calculate the cerebospinal system compliance. The results of this study provide a new point of view on the cerebrospinal system compliance, showing that it is not constant during the cardiac cycle and that significant variability exists in patients suffering from normal pressure hydrocephalus.

1. E. Schmidt. PROLIPHYC – Cerebrospinal fluid proteome in hydrocephalus – Trial details
2. Zablotny, W and Czosnyka, M and Smielewski, P. Portable software for intracranial pressure recording and waveform analysis. Intracranial Pressure IX. Springer, Tokyo. 439-440, 1994
3. Balédent, O and Henry-Feugeas, MC and Idy-Peretti, I. Cerebrospinal fluid dynamics and relation with blood flow: a magnetic resonance study with semiautomated cerebrospinal fluid segmentation. Investigative radiology. 36(7):368, 2001

Simon Garnotel

About the presenter. Simon Garnotel is currently a PhD student in the area of mathematics in BioFlowImage, University of Picardie Jules Verne. After a postgraduate diploma in applied mathematics, he started a PhD in 2013. The thesis subject is "Numerical Modeling of the Intracranial Pressure via CSF and blood flow measurements by flow MRI".

HARDWARE-IN-THE-LOOP TESTING OF GRAVITATIONAL CEREBROSPINAL FLUID SHUNTS

Manuel Gehlen[1,2], Vartan Kurtcuoglu[2,3], Marianne Schmid Daners[4]

[1] Institute for Dynamic Systems and Control, ETH Zurich, Switzerland
[2] The Interface Group, Institute of Physiology, University of Zurich, Switzerland
[3] Neuroscience Center Zurich, and Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland
[4] Product Development Group, ETH Zurich, Switzerland

Abstract. Overdrainage of cerebrospinal fluid (CSF) in upright posture through shunts has led to the development of a multitude of anti-siphon devices. It further led to the vision of actively controlled shunts that adapt to the needs of the patient. This evolution towards increasingly complex devices calls for testing methods that provide information on the interaction of shunt and patient.

To study this interaction, we built an in vitro test bed based on the hardware-in-the-loop (HIL) principle. It allows shunt testing in a dynamic environment that adapts based on a model of the simulated patients pathophysiology, a predefined profile of his or her activities, and the actual measured drainage through the tested shunt. The lumped parameter model used to simulate the patient‘s relevant pathophysiology includes the influences of the measured drainage rate, posture, cardiac-induced pulsations, and viscoelastic effects.

Using this HIL test bed, we were able to replicate overdrainage in upright posture when testing standard differential pressure valves and its avoidance through the addition of a gravitational unit. These experiments also proved that the pulsatile intracranial pressure (ICP) signal could be applied with less than 0.1 mmHg mean absolute error, allowing the application and analysis of any pathophysiological ICP waveform. Using a 24-hour test cycle derived from measured patient data allowed us to compare shunts during typical daily activities.

This pilot study revealed that our HIL testing can be used to accurately analyze and quantify the dynamic interaction between shunt and patient, which is of paramount importance for shunts with integrated anti-siphon devices. We further envision HIL testing as a foundation for the development of future shunt systems by enabling fast and cost-effective testing of new ideas and concepts in a realistic environment, while reducing in vivo experiments.

Manuel Gehlen

About the Presenter. Manuel Gehlen is working towards his PhD at The Interface Group, Institute of Physiology, University of Zurich, Switzerland and at the Institute for Dynamic Systems and Control, ETH Zurich, Switzerland. He received his degree in Mechanical Engineering from ETH Zurich, Switzerland (2013). His research focuses on the development of actively controlled cerebrospinal fluid shunts for the treatment of hydrocephalus.

MODEL OF THE INTERNAL JUGULAR VEIN DYNAMICS DURING HEAD-UP TILT

Petter Holmlund[1], Elias Johansson[2], Sara Qvarlander[1], Anders Wåhlin[1], Khalid Ambarki[1], Lars-Owe Koskinen[2], Jan Malm[2] and Anders Eklund[1]

[1] Department of Radiation Sciences, Umeå University, Umeå, Sweden
[2] Department of Clinical Neuroscience, Umeå University, Umeå, Sweden

Abstract. The regulation of ICP with changing posture has been linked to gravitational hydrostatic effects in the jugular venous system. It has been suggested that with the collapse of the internal jugular veins (IJVs) in upright the venous pressure reference point moves from the right atrium to the top of the collapsed IJVs. Given this hypothesis, this study aims to describe the dynamics of the collapsing IJVs using IJV area and flow measurements combined with mathematical descriptions of collapsible tubes.

Measurements were performed on 17 healthy subjects using ultrasound and 4D flow MRI, for assessing jugular area and flow respectively. Ultrasound imaging was used for measurement of the jugular area at the level of the neck, bilaterally for seven different tilt angles (0-71 deg). Pulsatile variations were studied by looking at differences in maximum and minimum area (A_{DIFF}) for each level. Flow measurements at the cervical level were done using 4D flow MRI in two positions: supine and at 16-degree tilt angle. The MRI investigation also included arterial cerebral inflow measurements, i.e. the internal carotid and vertebral arteries.

Description of model: In the phase with positive jugular pressure, the area is expected to vary with flow pulsations since the jugular walls are highly elastic. When the hydrostatic pressure decreases with tilt, and transmural pressure reaches zero the jugulars should enter a collapsed phase. For a collapsing tube inclined to some angle, the area of the entire collapsible segment is adjusted to create a balance between viscous losses and the hydrostatic pressure gradient, resulting in a zero transmural pressure gradient. This indicates that pressure at the top of the collapsed jugulars should be equal to atmospheric pressure. Given our hypothesis, essentially assuming atmospheric pressure on the outside along the entire IJVs, we should be able to predict the area of the collapsed IJVs as a function of tilt angle and flow rate.

The 4D flow MRI results showed a significant difference in both jugular blood flow and total cerebral inflow going from supine to 16-degree tilt ($P<0.05$). The ultrasound results for the jugular area showed a steady decrease up to 24-32 deg where it stagnated rapidly, although a small decrease was still observed between the last two tilt angles (32 to 71 deg). Similarly, the A_{DIFF} was relatively unchanged up to 24-32 deg where it started to decrease, and continued to do so up to 71 deg. On average, the minimum area had decreased with more than 50% at 16 degrees, and at 71 deg it was less than 7 % of the area in supine. The pattern corresponded reasonably well with the expected response according to the model.

In conclusion, while flow is redistributed already at lower tilt angles, and the flow area decreases substantially, the collapsing phase seems to occur later in the process, and continues all the way up to sitting position. The results support further work with the proposed two-phase model describing the IJV characteristics during tilt.

Petter Holmlund

About the Writer: Petter Holmlund is a PhD student in Biomedical engineering at Umeå University at the department of Radiation sciences. His research involves studies of the fluid dynamics of the venous drainage, mainly the internal jugular veins, and the CSF, using experimental methods and computational fluid dynamics.

2D AND 4D PC-MRI FLOW SOFTWARE

G. Pagé, J. Bettoni, R. Bouzerar, A. V. Salsac, O. Balédent

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

Introduction Phase-Contrast (PC) MRI is a non-invasive technique used for quantification and characterization of blood and CSF flow. 4D PC-MRI method allows acquiring a volume with its flow velocities in the 3 spatial directions during phases of the cardiac cycle (1). The aim of this study is to present an homemade software able to analyze 2D and 4D PC-MRI acquisitions with automatic flow segmentation, in order to reconstruct flow curve along the vessel selected.

Subjects and Methods Steps of the software:

1. Initially DICOM data is loaded and the Vx, Vy, Vz velocities volume and amplitude volume as function of time are organized.
2. A new volume in function of amplitude velocities is constructed and the value of each voxel is obtained by $\|V_{4D}\| = \sqrt{V_x^2 + V_y^2 + V_z^2}$.
3. Venous and arterial blood and CSF flow are synchronized with the cardiac cycle. Based on that physiological property of a semi-automated segmentation is developed using the Fast Fourier Transform (FFT) of the evolution of the velocity in each voxel (2).
4. From the amplitude spectrum it is possible to differentiate pulsatile flow from noise; and with the phase information, venous and arterial blood flow can be classified.
5. Then, a new volume is reconstructed and is merged with a morphological angiography.
6. A cursor allows to place a perpendicular plan to the selected vessel and then the flow curve of that vessel can be reconstructed along the cardiac cycle.

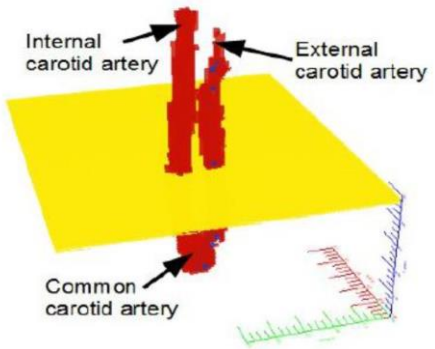


Figure 1 : 3D reconstruction of carotid bifurcation from 4D PC-MRI sequence

To evaluate the software it is used a specific flow phantom with different diameters supplied by a pulsatile control curve, and in which the 4D PC-MRI sequence is applied. In addition, in-vivo cerebral arteries of 3 healthy volunteers are studied with 2D and 4D PC-MRI.

Results The software provides an image of the surface of the ROI with an error less than 16% and reconstructs the flow curves associated with an error less than 10%. Regarding to the healthy volunteers, the 4D PC-MRI acquisitions segmented by the software provides flow along the cardiac cycle with an error less than 8% in comparison to the 2D PCMRI references values.

Discussion/Conclusion In conclusion, in less than 1min this software allows to segment and to classify venous and arterial blood and CSF flow. That it is also possible to reconstruct a morphological volume providing flow curves of the segmented vessels.

1. Markl et al. Time-Resolved Three Dimensional Phase-Contrast MRI. JMRM 1987
2. Balédent O, et al. Cerebrospinal fluid dynamics and relation with blood flow. IR 2001.

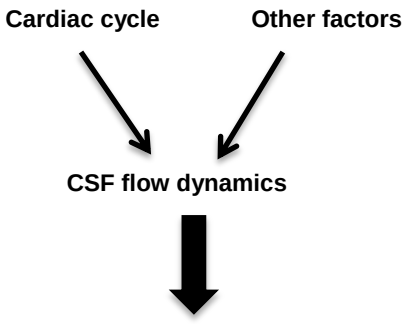
Gwenaël Pagé

About the Presenter. Gwenaël Pagé is currently a PhD student in the area of Physics in BioFlowImage, University of Picardie Jules Verne. After a postgraduate diploma in Physics, he started a PhD in 2013. The thesis subject is “Numerisation and quantification of the flow in head and neck area”.

CSF PROTEIN VARIATIONS CORRELATES WITH CSF OSCILLATIONS IN HYDROCEPHALUS PATIENTS

Puy Vincent (1); Zmudka Jadwiga (2,3); Capel Cyrille (1,2); Bouzerar Roger (1,2); Ausseil Jérome (1,4) ; Balédent Olivier (1,2)

Organization(s): 1: University hospital of Picardy Jules Verne, Amiens, France; 2: BioFlowImage, University of Picardy Jules Verne, Amiens,France; 3: General Hospital, Saint Quentin, France; 4: Inserm U1088



Introduction: No study has reported a comparative analysis of the CSF between its biochemistry and its flow dynamic. As suggested by Milhorat, the highly complex ventricular anatomy combined with an equally complex system of CSF circulation of the brain may contribute to maintain a balance between each compartment both in flow rate and in the CSF biochemical composition. This equilibrium could be disturbed in the hydrocephalus patients,so by using flow-MRI and CSF biological assessment, we aimed to determine if the alterations of the CSF flow dynamics found in hydrocephalus patients act in the CSF biochemistry of the hydrocephalus patients?

Methods: 9 elderly hydrocephalus patients, 73 ± 8 years old, underwent a morphological MRI in which two CSF flow acquisitions were added to quantify CSF stroke volume in the aqueduct and in the spinal canal. A dynamic CSF index (Dynindex) was calculated equal to the product of the two CSF stroke volumes and to the cardiac cycle duration. All patients had a CSF tap test and finally had a brain surgery, for install their shunt. During these operations, CSF was collected for both the ventricular and spinal compartments. From these CSF' prelevments, standard biochemical measurements were performed including chlorine, glucose and protein rate. For each CSF component analysis, a biochemical ratio (Biochratio) was defined by divided the ventricular concentration by the spinal concentration.

Results: The ventricilar and spinal CSF stroke volumes presented an heterogeneous behaviour among the 9 patients. In comparison with previous normal aging investigations, stroke volumes were respectively in the aqueduct and the spinal compartments: diminished (n= 1, n = 1) ; normal (n=3, n=4) and increased (n=5, n=4) . The dynindex varies from 0 to 100 with a mean value equal to 35. No difference between the ventricles and the spinal compartment was found for the concentrations of Chlorine and Glucose, their biochratio were respectively :0,99±0.01 and 0,91±0.10 , whereas the biochratio of the protein presented very different values among the population (from 1.21 and 5.58) and for each patients, their biochratios were strongly correlated (R=0.98, P<5.10-5) with its coresponding dynindex

Conclusion: In the hydrocephalus population explored in this work, the CSF flows presented important and variable alterations in the ventricles and or in the spinal compartments; nevertheless whereas Chlorine and Glucose concentrations were equivalents in the ventricles and the spine, surprisingly the protein concentration differs a lot between the ventricles and the spinal levels but was highly correlated with the CSF flow oscillations.

1. Capel C, Makki M, Gondry-Jouet C, Bouzerar R, Courtois V, Krejpowicz B, Balédent O.Insights into cerebrospinal fluid and cerebral blood flows in infants and young children. J Child Neurol. 2014
2. Chaarani B, et al. Estimation of the lateral ventricles volumes from a 2D image and its relationship with cerebrospinal fluid flow. Biomed Res Int. 2013
3. Bouzerar R, et al. Measurement of choroid plexus perfusion using dynamic susceptibility MR imaging: capillary permeability and age-related changes. Neuroradiology. 2013
4. Daouk J, et al. Acta Radiol. 2014 Relationship between cerebrospinal fluid flow, ventricles morphology, and DTI properties in internal capsules: differences between Alzheimer's disease and normal-pressure hydrocephalus.
5. Bouzerar R, Tekaya I, Bouzerar R, Balédent O.Dynamics of hydrocephalus: a physical approach. J Biol Phys. 2012

Vincent Puy

About the Presenter. Vincent Puy is currently medical resident specialized in biology. His master of Science dealt with biomarkers in neurodegenerative diseases.

GENERAL INFORMATION

VENUE: SCIENTIFIC SESSIONS, BREAKFAST & LUNCH

The symposium will be held at the Logis du Roy in Amiens (France). This very pleasant venue belongs to the University of Picardie Jules Vernes and is located right in the historic center of Amiens. It faces Amiens' courthouse ("Palais de Justice") and is a stone's throw from Amiens' cathedral (XIIIth century, UNESCO World Heritage Site). The Logis du Roy can be reached by foot from the train station and Hotel Mercure in about 10mins (see Map 1 below).

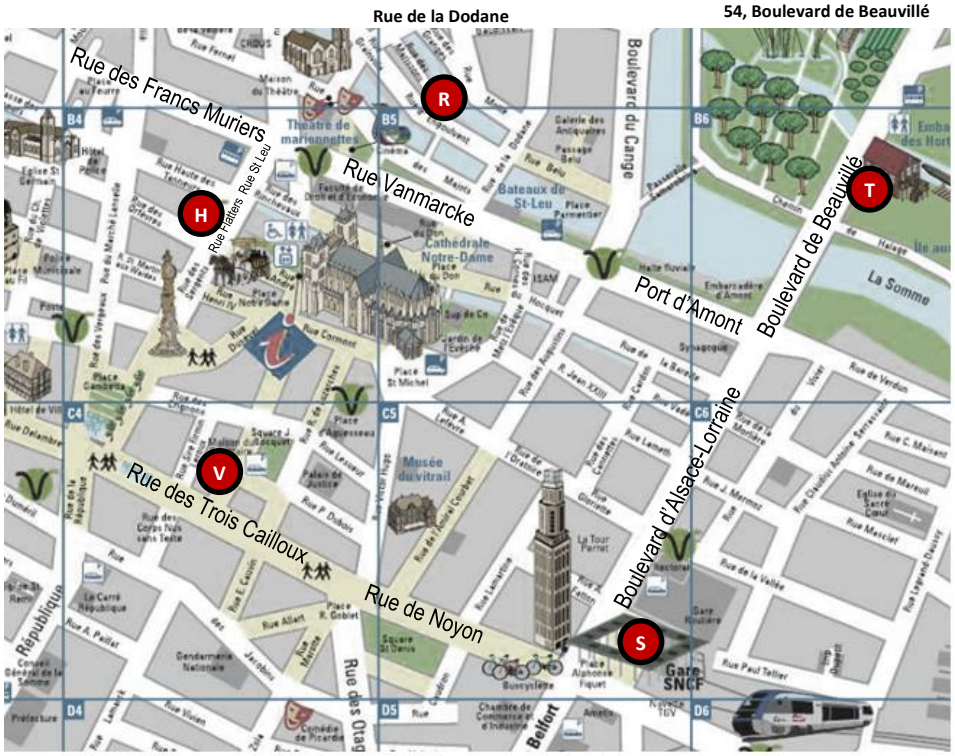
For attendees staying at the Hotel Mercure, breakfast is included in the price of the room. Coffee and croissants will be available at the conference venue as well.

Hotel Mercure, Amiens Cathedrale
21/23 rue Flatters

Conference venue:
«Le logis du Roy»

Symposium dinner at
«Les Marissons»
Rue de la Dodane

Boat tour of the «Hortillonages»
Maison des Hortillonages
54, Boulevard de Beauvillé



Train Station
Gare SNCF, Amiens

Map 1: Amiens city center and relevant symposium locations.

SYMPOSIUM DINNER

The symposium dinner will take place on Thursday, July 9th at 19h30 in the historic city center of Amiens at the restaurant "les Marissons", rue de la Dodane in the Quartier St Leu (see Map 1, location R). The location can be reached by foot from the conference venue (650m) and hotel (450m).

BOAT TOUR THROUGH THE "HORTILLONAGES" FLOATING GARDENS

For those interested and if the weather allows, a boat tour through the "Hortillonnages" will take place before the dinner (see Map 1, location T). Walking from the conference venue to the Hortillonages (about 20mins), you will see the Cathedral and city center. The "Hortillonages" or floating gardens are emblematic of Amiens. They have been cultivated since the Middle Ages covering 300 hectares interlaced with small canals. The suggested visit will take you for a peaceful ride in one of the local boats known as "barques à cornet", which are non-motorized 12-seater boats.

Image credits: http://www.hortillonnages-amiens.fr

TRANSPORTATION

Walking might be the easiest means of transportation through Amiens' city center, and an enjoyable one as well if you go through the pedestrian streets or along the canals. It might especially be true on the evening before the symposium (July 8th) as quite a few streets will be closed to traffic due to the Tour de France. However, would a vehicle be better suited, please contact the organizers and we will gladly organize it for you.

INTERNET CONNECTION

Individual login and password will be provided upon registration.

INFORMATION FOR SPEAKERS & POSTERS

Speakers are given 15 minutes for their presentation plus 10 minutes for discussion and transition to the next speaker. If a speaker exceeds the allotted presentation time, the discussion will be shortened accordingly. The respective session chair will stop presentations after a maximum of 20 minutes. Keynotes presentations will be 60 minutes including time for discussion and transition.

Accompanying doctoral students have the opportunity to present a poster, which will be displayed in the dining area during the two lunch breaks. Poster format guidelines: maximum size A0, portrait orientation.

PLACES TO EAT AND DRINK

Les Bouchées Doubles

Classic French food, centrally located. Highly recommended for its meat. Around 40 euros for a meal.
11 Bis Rue Gresset, 80000 Amiens
+33 3 22 91 00 85

La Coupole

Simple but tasty bistro. Located within the Winter Circus. Budget about 20 euros.
Place Longueville, 80000 Amiens
+33 3 22 45 50 10

Le Buzz

Classic French food again, within a simple Café and friendly athmosphere. Centrally located. Open for breakfast or a drink at any time of the day. Apero offered for the guests of the symposium. Budget 20 euros.
3 Rue des Sergents, 80000 Amiens
+33 3 22 80 76 21

Evening drink on the Quai Bélu

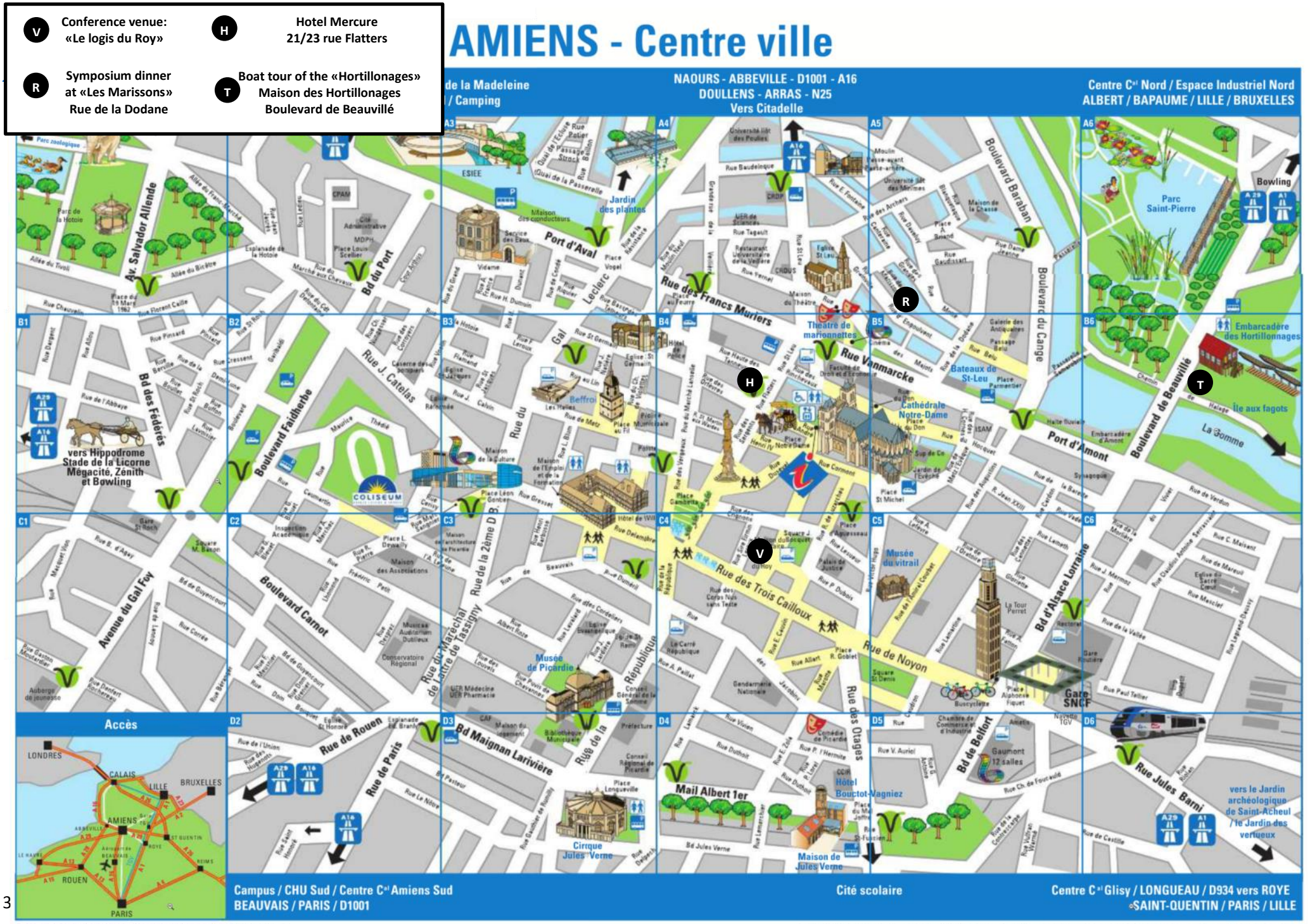
For a drink, there are countless options along the canal and Quai Bélu (in the same area as the conference dinner). Nice terraces. A possible recommendation among these:

Couleur Café

Well known for its rums, it is a nice place to enjoy a drink and little snack on a summer evening.
8 Rue des Bondes, 80000 Amiens
+33 3 22 91 40 14

Le Vert Galant

If the weather is nice, an original and quiet address away from the excitation of the Quai Bélu. You may rent a small bark to wander around the Hortillonages and then chill with a beer sitting at the restaurant's terrace. Meals are a bit pricy for the quality.
57 Chemin de Halage, 80000 Amiens
+33 3 22 92 04 27



Ce plan vous est offert par l'Office de Tourisme d'Amiens Métropole www.amiens-tourisme.com

CONDENSED SCHEDULE

DAY 1 – THURSDAY, JULY 9TH, 2015

8:00	**WELCOME COFFEE & CROISSANTS**
8:30 – 8:45	**Opening Notes**
8:45 – 9:45	**PLENARY LECTURE**
9:45 – 10:35	**SESSION A – MODELING**
10:35 – 11:00	**MORNING COFFEE BREAK**
11:00 – 12:40	**SESSION B – IMAGING**
12:40 – 14:00	**LUNCH AND POSTERS**
14:00 – 15:15	**SESSION C – POROUS MODELING**
15:15 – 15:40	**AFTERNOON COFFEE BREAK**
15:40 – 16:55	**SESSION D – TRANSPORT**
18:00 – 19:00	**VISIT OF THE HORTILLONAGES (discretionary)**
19:30	**SYMPOSIUM DINNER AT "LES MARISSONS"**

DAY 2 – FRIDAY, JULY 10TH, 2015

8:00	**WELCOME COFFEE & CROISSANTS**
8:30 – 9:30	**PLENARY LECTURE**
9:30 – 10:20	**SESSION E - ICP**
10:20 – 10:50	**MORNING COFFEE BREAK**
10:50 – 12:30	**SESSION F - MODELING**
12:30 – 14:00	**LUNCH AND POSTERS**
14:00 – 15:15	**SESSION G – JOINT SESSION**
15:15 – 15:30	**AFTERNOON COFFEE BREAK**
15:30 – 16:15	**WORKSHOPS**
16:15 – 16:30	**Closing Remarks**
16:30	**DISCRETIONARY PLENARY DISCUSSION AND CLOSING COFFEE**