

1ST CSF HYDRODYNAMICS SYMPOSIUM

July 8th and 9th, 2011

ETH Zurich, Switzerland

Vartan Kurtcuoglu (ETH Zurich)

Dimos Poulikakos (ETH Zurich)

Francis Loth (The University of Akron)

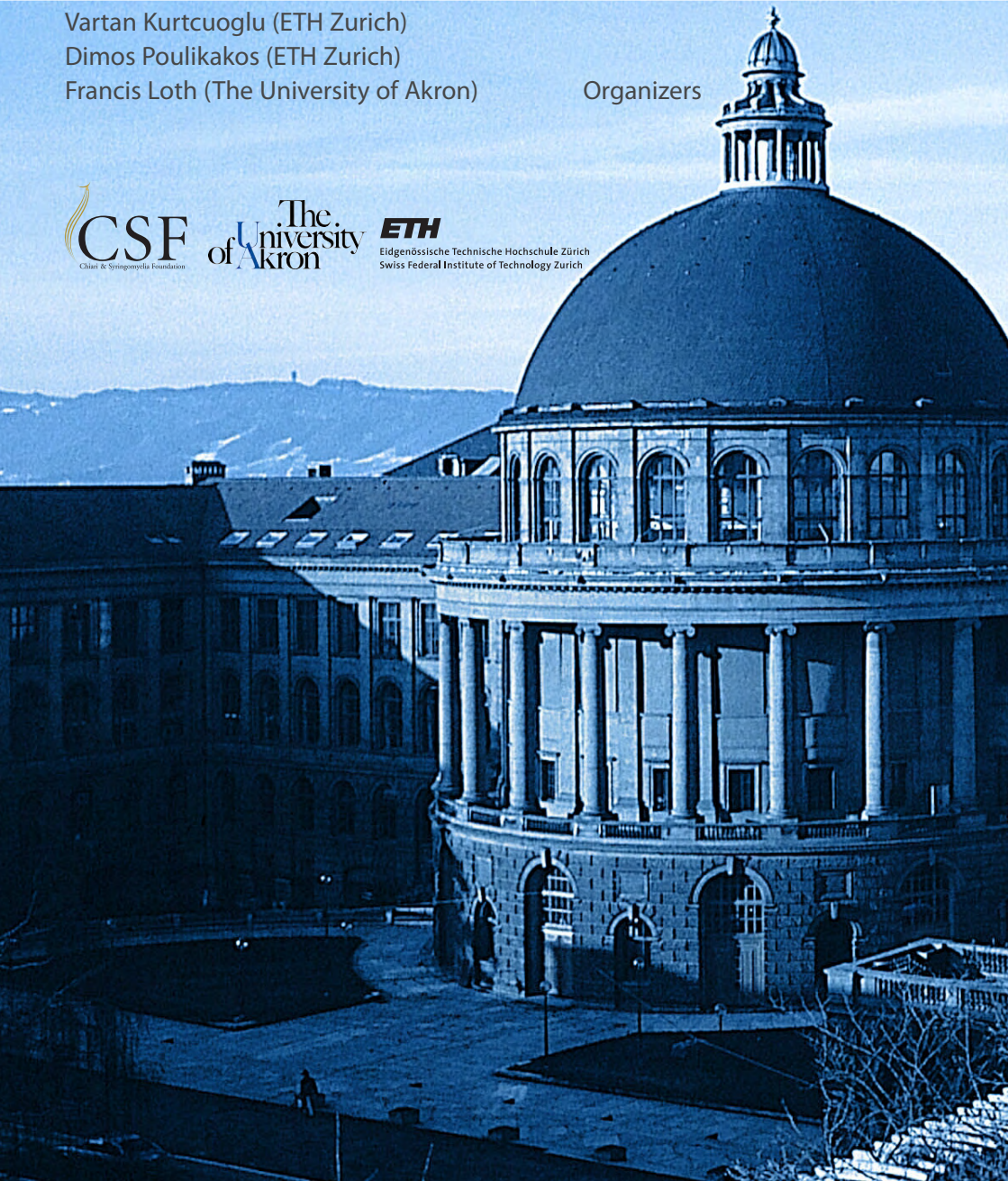
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Swiss Federal Institute of Technology Zurich



CSF HYDRODYNAMICS SYMPOSIUM SPONSORED BY



Our Mission

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

About Us

The Chiari & Syringomyelia Foundation, Inc., a 501(c)(3) organization built on leadership, vision and commitment to find a cure for Chiari malformation (CM), syringomyelia (SM) and related CSF (cerebrospinal fluid) disorders, was founded in October 2007.

Many recognized world-class physicians, scientists and professionals agreed to collaborate and form a superior Scientific, Educational & Advisory Board. The trusted and dedicated members of our Board of Directors and Board of Trustees include community and business leaders, educators, legal experts, families, and patients, who have been advocates in the CM/SM community for years. They have the skills and passion to create, fund, and direct programs and research that will change the lives of the more than 300,000 people estimated to be affected by CM and/or SM in the United States alone.



For More Information

PLEASE VISIT WWW.CSFINFO.ORG

Sponsorship

The 1st CSF Hydrodynamics 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 Malformations 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 cerebrospinal fluid disorders. Please visit the foundation's website at www.CSFinfo.org.

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Framework of the 1st Cerebrospinal Fluid Hydrodynamics Symposium

The number of investigators conducting numerical and experimental simulations to better understand the hydrodynamics of cerebrospinal fluid (CSF) has increased greatly over the past few years. The 1st Cerebrospinal Fluid Hydrodynamics Symposium aims at maintaining the momentum of CSF simulation research through the exchange of ideas toward the modeling of CSF flow.

Twenty-five invited speakers from around the world are presenting their research that involves either experiments 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 modeling rather than on clinical solutions. However, neurosurgeons 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 is held in beautiful Zurich on the campus of ETH Zurich, the Swiss Federal Institute of Technology. All presentations will be video recorded and posted, with free access, on the web sites of the Chiari & Syringomyelia Foundation and ETH Zurich to maximize exposure of the symposium research ideas (www.CSFinfo.org and <http://www.multimedia.ethz.ch/conferences/2011/csf>).

The symposium is organized by Vartan Kurtcuoglu, Dimos Poulikakos and Francis Loth. In his research, Dr. Loth employs both experimental and numerical techniques to better understand the mechanical forces involved in conditions such as Chiari malformation and syringomyelia. He is an associate professor and the F. Theodore Harrington Endowed Chair in the Department of Mechanical Engineering at The University of Akron, Ohio. Dr. Poulikakos' research focuses on interfacial transport phenomena and thermodynamics in emerging technologies, including biological systems, as well as biomedical thermofluidics. He is a full professor of thermodynamics at ETH Zurich, and head of the Laboratory of Thermodynamics in Emerging Technologies. Dr. Kurtcuoglu is a group leader in biofluidics and lecturer in biothermofluidics at ETH Zurich. He is the PI of the international SmartShunt project funded by the Swiss National Science Foundation that aims at conducting research for the subsequent development of a smart CSF shunt for normal pressure hydrocephalus.

About ETH Zurich

Founded in 1855, ETH Zurich is one of the leading international universities for technology and the natural sciences. It offers scientists an inspiring research environment and students a comprehensive education.

More than 16,000 students from approximately 80 countries, 3,500 of whom are doctoral candidates, attend ETH Zurich. More than 400 professors teach and conduct research in the areas of engineering, architecture, mathematics, natural sciences, system-oriented sciences, and management and social sciences.

ETH Zurich regularly appears at the top of international rankings as one of the best universities in the world. 21 Nobel Laureates have studied, taught or conducted research at ETH Zurich, underlining the excellent reputation of the institution.

Schedule

Day 1 – Friday, July 8, 2011

7 ⁰⁰	Breakfast	8 ¹⁵
8 ¹⁵	Introduction	9 ³⁰
8 ¹⁵ – 8 ³⁰ :	Opening Note <i>Roland Siegwart, Vice President Research and Corporate Relations, ETH Zurich</i> <i>Vartan Kurtcuoglu and Dimos Poulikakos, ETH Zurich</i>	
8 ³⁰ – 9 ³⁰ :	Keynote: Applying engineering principles to clinical problems of CSF dynamics <i>Harold Rekate, The Chiari Insititute</i>	
9 ³⁰	Session A	10 ³⁰
9 ³⁰ – 10 ⁰⁰ :	CBF-CSF circulation coupling: Clinical neurosciences perspective <i>Marek Czosnyka, University of Cambridge</i>	
10 ⁰⁰ – 10 ³⁰ :	CSF flows: From origins to alterations <i>Olivier Balédent, University Hospital of Picardie Jules Verne</i>	
10 ³⁰	Morning Coffee Break	11 ⁰⁰
11 ⁰⁰	Session B	13 ⁰⁰
11 ⁰⁰ – 11 ³⁰ :	The dynamics of spinal CSF motions, studied in a two-dimensional model <i>Christopher Bertram, University of Sydney</i>	
11 ³⁰ – 12 ⁰⁰ :	Wave propagation in a poroelastic model of the spinal canal <i>Novak Elliott, Curtin University</i>	
12 ⁰⁰ – 12 ³⁰ :	Biomechanics of syringomyelia <i>Shaokoon Cheng, Neuroscience Research Australia</i>	
12 ³⁰ – 13 ⁰⁰ :	Perivascular CSF Flow: A major route of fluid entry into the spinal cord <i>Lynne Bilston, Neuroscience Research Australia</i>	
13 ⁰⁰	Lunch Break	14 ⁰⁰
14 ⁰⁰	Session C	16 ⁰⁰
14 ⁰⁰ – 14 ³⁰ :	Computational models and results for the flow of cerebrospinal fluid in the upper cervical canal in patients with the Chiari I malformation <i>Kent-Andre Mardal, Simula Research Laboratory</i>	
14 ³⁰ – 15 ⁰⁰ :	Clinical Utility of Hydrodynamic Parameters in Chiari Malformation <i>Francis Loth, University of Akron</i>	
15 ⁰⁰ – 15 ³⁰ :	A 3D computational fluid dynamics model for prediction of molecule transport in the CSF space and its application in the pharmaceutical industry <i>Andreas Kuttler, Novartis Pharma AG</i>	
15 ³⁰ – 16 ⁰⁰ :	Convection-enhanced delivery for the treatment of epilepsy <i>Malisa Sarntinoranont, University of Florida</i>	
16 ⁰⁰	Afternoon Coffee Break	16 ³⁰
16 ³⁰	Session D	17 ³⁰
16 ³⁰ – 17 ⁰⁰ :	Non-invasive Measurement of CSF Hydrodynamics: Latest Research using the TMD Technique <i>Robert Marchbanks, Southampton University Hospitals NHS Trust</i>	
17 ⁰⁰ – 17 ³⁰ :	Cadence device and method: Novel way to directly control CSF pulsations <i>Stephen Dombrowski, Cleveland Clinic</i>	
19 ⁰⁰	Symposium Dinner	21 ⁰⁰

Schedule

Day 2 – Saturday, July 9, 2011

7 ⁰⁰	Breakfast	8 ⁰⁰
8 ⁰⁰	Introduction	9 ⁰⁰
8 ⁰⁰ – 9 ⁰⁰ :	Keynote: The ventricular system: The primary organ of cranial accommodation <i>Mark Luciano, Cleveland Clinic</i>	
9 ⁰⁰	Session E	10 ⁰⁰
9 ⁰⁰ – 9 ³⁰ :	The origin of the cranio-spinal CSF pulsation and its clinical relevance <i>Noam Alperin, University of Miami</i>	
9 ³⁰ – 10 ⁰⁰ :	MR based CSF flow measurements: current approaches, accuracy and precision, and future directions <i>Oliver Wieben, University of Wisconsin</i>	
10 ³⁰	Morning Coffee Break	10 ⁴⁵
10 ⁴⁵	Session F	12 ⁴⁵
10 ⁴⁵ – 11 ¹⁵ :	Simulation of ICP oscillations in a poroelastic model and a one-compartment model of CSF flow with application to infusion tests <i>Ian Sobey, University of Oxford</i>	
11 ¹⁵ – 11 ⁴⁵ :	Fluid-structure interaction models of pulsatile CSF flow in normal and hydrocephalic brains <i>Andreas Linninger, University of Illinois at Chicago</i>	
11 ⁴⁵ – 12 ¹⁵ :	Multicompartmental poroelasticity for the Integrative modeling of water transport in the brain <i>Yiannis Ventikos, University of Oxford</i>	
12 ¹⁵ – 12 ⁴⁵ :	On appropriateness of brain parenchyma modeling as biphasic continuum <i>Karol Miller, The University of Western Australia</i>	
12 ⁴⁵	Lunch Break	13 ⁴⁵
13 ⁴⁵	Session G	16 ¹⁵
13 ⁴⁵ – 14 ¹⁵ :	CSF hydrodynamics: Models and measurements <i>Anders Eklund, Umeå University</i>	
14 ¹⁵ – 14 ⁴⁵ :	Coupled simulation of the cardiovascular and cerebrospinal fluid system <i>Bryn Martin, EPFL</i>	
14 ⁴⁵ – 15 ¹⁵ :	Retinoid signaling pathway proteins in human arachnoid membrane: Role in regulating intracranial pressure <i>Deborah Grzybowski, The Ohio State University</i>	
15 ¹⁵ – 15 ⁴⁵ :	CSF space phantom and coupling of cerebral arterial inflow with cerebrospinal fluid dynamics: Highlights from the SmartShunt project <i>Vartan Kurtcuoglu, ETH Zurich</i>	
15 ⁴⁵ – 16 ¹⁵ :	How the EC Marie Curie Actions could contribute to the cerebrospinal fluid scientific community <i>Karim Berkouk, European Commission</i>	
16 ¹⁵	Conclusion	16 ³⁰
16 ¹⁵ – 16 ³⁰ :	Closing note <i>Francis Loth, University of Akron</i>	
16 ³⁰	Discretionary Plenary Discussion and Closing Coffee	18 ⁰⁰

Keynote and Session A

Friday, July 8, 2011 – 8³⁰ to 10³⁰

Session Chairs: Francis Loth, The University of Akron
Yiannis Ventikos, University of Oxford



H. Rekate

8³⁰ – 9³⁰

Keynote Lecture

Applying engineering principles to clinical problems of cerebrospinal fluid dynamics

Harold L. Rekate^{1, 2}

¹ The Chiari Institute, Great Neck, NY, USA

² Hofstra Northshore-LIJ College of Medicine, Hempstead, NY, USA



M. Czosnyka

9³⁰ – 10⁰⁰

CBF-CSF circulation coupling: Clinical neurosciences perspective

Marek Czosnyka, Zofia Czosnyka, John D Pickard

Academic Neurosurgical Unit, University of Cambridge, UK



O. Balédent

10⁰⁰ – 10³⁰

CSF flows: From origins to alterations

O. Balédent, C. Gondry-Jouet, A. Fichten, S. Elsankari, R. Bouzerar

University hospital of Picardie Jules Verne, Amiens, France

Applying engineering principles to clinical problems of cerebrospinal fluid dynamics

Harold L. Rekate^{1, 2}

¹ The Chiari Institute, Great Neck, NY, U.S.A.

² Hofstra Northshore-LIJ College of Medicine, Hempstead, NY, U.S.A.

Purpose. This review will utilize a hydraulic circuit concept to explain the pathophysiology of hydrocephalus and a variety of other abnormalities of intracranial pressure and ventricular volume regulation.

Methodology. The concepts presented here are based on a hydraulic circuit with the heart acting as a pumping mechanism. The volumetric regulation of the volume of the compartments containing cerebrospinal fluid (CSF) is a function of the rate of production or flow into those chambers and pressure differential across a series of real or potential resistance elements. The model was tested using an animal model of hydrocephalus.

Results. Animal studies and subsequent clinical studies utilizing the hydraulic circuit model have led to improved ability of clinicians to select among treatment options and understand enigmatic conditions related to CSF dynamics. Syringomyelia can be seen as part of the process with the central canal of the spinal cord being a fifth ventricle subject to the same processes that lead in the brain to hydrocephalus.

Conclusion. Defining the point of obstruction to the flow of CSF leads to both an understanding of the pathogenesis of individual cases of hydrocephalus and syringomyelia. Treatment then relates to the removal of the point of obstruction or its bypass.



Harold L. Rekate

About the Presenter. Dr. Harold Rekate is the director of The Chiari Institute at the North Shore University Hospital and Long Island Jewish (LIJ) Medical Center, New York. Prior to joining North Shore-LIJ, Dr. Rekate served as chairman of pediatric neurosciences and chief of pediatric neurosurgery for more than 25 years at the Barrow Neurological Institute (BNI), Arizona. While at BNI, Dr. Rekate was a clinical professor of neurosurgery at the University of Arizona College of Medicine. A widely published author of more than 200 publications, most of which are related to cerebrospinal fluid difficulties, including Chiari malformations, syringomyelia and hydrocephalus, Dr. Rekate also served as editor for a number of prestigious medical journals and was chairman of the editorial board of the Journal of Neurosurgery Pediatrics. Over the course of his career, Dr. Rekate has done extensive research regarding spinal fluid flow, receiving funding from the National Institutes of Health and the National Aeronautics and Space Administration. He also has held many local, national and international positions, including chairman of the Joint Section on Pediatric Neurological Surgery of the American Association of Neurological Surgery and the Congress of Neurological Surgery, and president of the American Society of Pediatric Neurological Surgeons and the International Society of Pediatric Neurosurgery. Dr. Rekate has received numerous awards and honors, including the prestigious Pudenz Award of Excellence in Research in Cerebrospinal Fluid Physiology.

CBF-CSF circulation coupling: Clinical neurosciences perspective

Marek Czosnyka, Zofia Czosnyka, John D Pickard

Academic Neurosurgical Unit, University of Cambridge, UK

Background: Starting from mid-eighties of previous century many brain imaging works paid attention to altered cerebral blood flow and its distribution in patients suffering from various CSF circulatory disorders, including normal pressure hydrocephalus (NPH).

Method: We interrogated local database of nearly 4000 constant rate infusion tests and 200 overnight ICP monitoring (intraparenchymal bolt). Various configurations, useful for assessment vascular components of CSF circulation were studied: ICP and arterial pressure (analysis of Pressure Reactivity Index); ICP, ABP and Transcranial Doppler (TCD) blood flow velocity (for assessment of cerebral autoregulation); ICP, ABP and Near-Infrared Spectroscopy (for analysis of fluctuation of Cerebral Blood Volume); ICP plus sagittal sinus pressure and jugular vein pressure (in patients with idiopathic intracranial hypertension to assess a hydrodynamic consequences of venous sinus stenosis). Finally, to assess vascular factors of idiopathic NPH a combination of CSF infusion study with PET-CBF studies were performed.

Results. Most important results summarizing CSF-CBF circulatory coupling are listed below:

- B waves of ICP (helpful in diagnostic of NPH), are probably forced by similar fluctuations in cerebral blood flow detectable by TCD. Waves of the same frequency as ICP B waves can be also seen in cerebral blood oxygenation monitored with near infrared spectroscopy (Figure).
- In normal volunteers distribution of PET- CBF across delineated white matter is flat. Autoregulation is worse closer to surface of ventricles than further away from ventricles. CBF in white matter in NPH decreases as a function of distance from the surface of ventricles.
- Pressure reactivity, calculated from variations between arterial pressure and ICP is correlates positively with resistance to CSF outflow. Surprisingly, character of this relationship reverses after shunting.
- TCD-assessed autoregulation is similarly negatively correlated with the resistance to CSF outflow. Those patients showing no deficit in CSF circulation have more often disturbed autoregulation, being most probably the consequence of overlapping cerebrovascular disease.
- In idiopathic intracranial hypertension there is a strong link between ICP and sagittal sinus pressure. Rise in ICP provoked by lumbar infusion produces equivalent rise in sagittal sinus pressure. This is, probably due to squeezing dural sinuses by rising ICP and obstructing venous blood outflow.

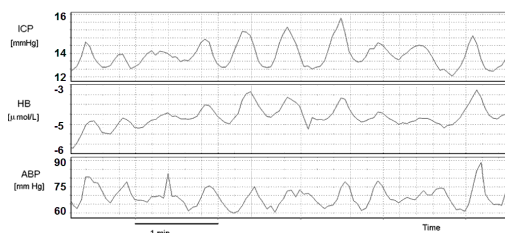


Figure. Slow waves of ICP coinciding with NIRS-Hb and ABP. Strong vasogenic fluctuations in ICP (0.5-1.3 minutes in wavelength) coincided with fluctuations of ABP and Hb of the same period. ABP, arterial blood pressure; Hb, NIRS-derived index of deoxygenated Haemoglobin concentration (a marker of cerebral blood volume).

Conclusion: CSF dynamics and CBF regulation are strongly coupled. The trouble is, that in pathophysiology of hydrocephalus we still do not know what is a chicken and what is an egg. Nevertheless, there is enough evidence that testing of CSF dynamics should be supplemented by testing of cerebrovascular reserve- using for example non-invasive CO₂ reactivity or with modern brain imaging studies. If cerebrovascular defects are severe, no matter how disturbed CSF circulation is, the shunt is unlikely to help.



Marek Czosnyka

About the Presenter. Belvedere Professor of Technical Sciences, PhD (Warsaw), DSc (Warsaw) in Biomedical Engineering. He works as Reader in Brain in Neurosurgical Unit, University of Cambridge, UK. Research: Cerebrospinal Fluid dynamics (hydrocephalus, IIH, syringomyelia), Cerebral Blood Flow and its regulation (head trauma, stroke, hydrocephalus, subarachnoid hemorrhage), Multi-modal bedside monitoring in neuro-intensive care (head trauma, poor grade SAH, stroke) & Mathematical modeling of cerebrospinal dynamics. Publications: 260 entries on Pubmed, h-index 37

CSF flows: From origins to alterations

O. Balédent, C. Gondry-Jouet, A. Fichten, S. Elsankari, R. Bouzerar

University hospital of Picardie Jules Verne, Amiens, France

Abstract. For a long time, CSF flows was mainly associated with continuous secretion and resorption flows. Knowledge of neuro-hydrodynamics has benefited considerably from the introduction of phase-contrast magnetic resonance imaging (PC-MRI), which can provide CSF and blood flow measurements throughout the cardiac cycle (CC). Using a segmentation software (1) (free access www.tidam.fr), key temporal and amplitude parameters can be calculated at different levels to investigate the role of CSF and blood compartments in response to vascular brain expansion during CC (1). CSF, blood, and tissues interact in compartments with different shapes (large, narrow, rigid, compliant) associated with different pressures (high pressure arterial, low venous or CSF) inside the compliant cranio-spinal system. All these interactions generate the variations of intracranial pressure during CC. Normal values (1-3) have been set in newborn, children, adults and aging populations. Physiological normal ranges have been determined. CSF motions result from cranio-spinal

compliance and arterio-venous oscillations in the central nervous system. This means that CSF oscillations could depict a biomechanical state of the central nervous system. For many years, in collaboration with clinicians, we have added PC-MRI sequences to standard MRI protocols to bring complementary information about neuro-hydrodynamics' diseases. Hydrocephalus (Fig 1) is the first pathology pointing CSF flow alterations: it is easy to identify a ventricular dilation in the brain ! Hyperdynamic aqueductal CSF flow was used to differentiate active hydrocephalus from atrophic brain in patients with normal CSF oscillations (2). Syringomyelia is also an interesting model where spine stresses are redistributed from outer to inner side. In patients with acute subarachnoid hemorrhage related to aneurysm rupture, significant flow perturbations could occur inside the ventricular or subarachnoid space compartments. Interestingly, we also noticed an impact of cerebral venous thrombosis on CSF oscillations as well as in patients with jugular stenosis. In conclusion, CSF is a wide field of research, which could help to understand and treat patients with hydrodynamic diseases. This presentation aims to present a PC-MRI overview of our experience concerning normal and pathologic CSF flow behaviors.

Using imaging techniques, we have been able to visualize CSF, now we can see CSF flows; soon we will see CSF flow pressure, as well as secretion and resorption of CSF.

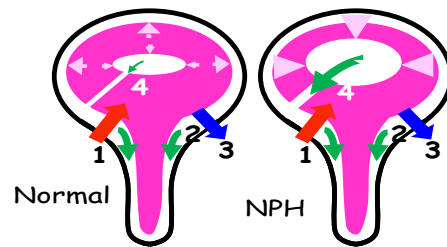


Fig. 1. Arterial flow increases cerebral blood volume (1). Extracerebral CSF is the first to respond by flushing into subarachnoid spinal spaces (2). The elasticity of the dural sac allows the brain CSF flush to be accommodated. Jugular blood flow occurs (3). Aqueduct flush flows appears much later (4). In healthy subjects, the intracranial mobile compliance predominantly depends on the intracranial subarachnoid CSF pulsation; ventricular CSF pulsations represent only around 10% of the cervical CSF oscillations. Conversely, in NPH, ventricular CSF pulsations are largely increased. NPH may redistribute the pressure stresses in the brain and increase the stress in the white matter fibers close to the ventricular system, which may lead to more dilation.

Balédent O, Henry-Feugeas MC, Idy-Peretti I. Cerebrospinal fluid dynamics and relation with blood flow. *Invest Radiol*. 2001

Balédent O, Gondry-Jouet C, et al Relationship between cerebrospinal fluid and blood dynamics in healthy volunteers and patients with communicating hydrocephalus. *Invest Radiol*. 2004.

El Sankari S, Gondry-Jouet C, Fichten A, et al. Cerebrospinal fluid and blood flow in mild cognitive impairment and Alzheimer's disease: a differential diagnosis from idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS*. 2011. Free PMC Article.



Olivier Balédent

About the Presenter. Olivier Balédent, PhD in the area of biophysics & radiology is currently assistant professor in Amiens 'University Hospital. He's also the head of the medical image processing department in this hospital. After a Master's degree in Informatics (1995, Amiens), he passed a postgraduate diploma in the field of image processing in Lyon. He passed his Phd in 2001 at Jules Verne University. The thesis subject was already about CSF flow imaging using MRI technique. Now inside Amiens 'University Hospital, he continues to develop CSF research and applies his non invasive hydrodynamic approach in clinical practice. He is also Biophysics' teacher at the medical school.

Session B

Friday, July 8, 2011 – 11⁰⁰ to 13⁰⁰

Session Chair: Francis Loth, The University of Akron



C. Bertram

11⁰⁰ – 11³⁰

The dynamics of spinal CSF motions, studied in a two-dimensional model

Christopher D. Bertram

School of Mathematics and Statistics, University of Sydney, Sydney, Australia

Currently at: Laboratoire d'Hydrodynamique, Ecole Polytechnique, Palaiseau, France



N. Elliott

11³⁰ – 12⁰⁰

Wave propagation in a poroelastic model of the spinal canal

Novak S. J. Elliott¹, Anthony D. Lucey¹, Duncan A. Lockerby², Andrew R. Brodbelt³

1 Fluid Dynamics Research Group, Department of Mechanical Engineering, Curtin University, Perth, WA, Australia

2 Fluid Dynamics Research Centre, School of Engineering, University of Warwick, Coventry, Warwickshire, UK

3 The Walton Centre NHS Foundation Trust, Liverpool, Merseyside, UK



S. Cheng

12⁰⁰ – 12³⁰

Biomechanics of syringomyelia

Shaokoon Cheng¹, Marcus Stoodley², Lynne Bilston¹

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L. Bilston

12³⁰ – 13⁰⁰

Perivascular CSF Flow: A major route of fluid entry into the spinal cord

Lynne E Bilston¹, David F. Fletcher², Marcus A Stoodley³

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

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

3 Australian School of Advanced Medicine, Macquarie University, Sydney, NSW, Australia

The dynamics of spinal CSF motions, studied in a two-dimensional model

Christopher D. Bertram

School of Mathematics and Statistics, University of Sydney, Sydney, Australia 2006

(currently at Laboratoire d'Hydrodynamique, Ecole Polytechnique, 91128 Palaiseau cedex, France)

Abstract. The neurological literature abounds with hypotheses for the aetiology of both Chiari-linked and post-traumatic syringomyelia (PTS). Typically these posit hydrodynamic and mechanical interactions purely qualitatively, and on the basis of inadequate understanding of all the possible physics. To assess such clinical hypotheses under rigorously controlled circumstances, a numerical model was constructed of the spinal subarachnoid space (SSS), the spinal cord and the dura, using dimensions from the Visible Human Project® [1] which were reduced to the corresponding axi-symmetric values for 2D modelling. Later versions of the model incorporate both the filum terminale and the pia mater. An early version incorporated the central canal of the cord, but this was shown to be unimportant. The solids are viscoelastic; the cerebrospinal fluid (CSF) has water viscosity. The fluid-structure interactions after transient or periodic excitation are solved in finite-element code (ADINA R&D Inc., Watertown MA, USA).

The model shows a distinction between the response to very quick excitations, characteristic of the leading edge of the most percussive coughing, and the response to slower smoother excitations, such as is provided by the displacement of CSF from the head with each heartbeat. Fast transients cause the propagation of three different types of waves in the elastically bounded annular fluid conduit, roughly corresponding to a pressure pulse wave, plus axial stress waves in the cord and in the dura. Where a syrinx is present, the system supports four waves, and the pulse wave is slowed down. Slower transients cause rather the slopping of fluid to and fro along the SSS, so that the system behaves more as though lumped. However there can be resonant interactions between the excitation and the characteristic frequencies of the system provided by the elastic compliance in conjunction with the fluid inertia. The presence of a syrinx provides more complex opportunities for such interaction, as does SSS stenosis, often a feature of PTS.

The model has been used to examine several different mechanical aspects of old spinal trauma in the context of adjacent syringomyelia. The past injury is often associated with arachnoiditis, which provides a variety of possibly important aspects: porous SSS plugging, cord tethering, inelastic dura/cord connection, SSS stenosis, calcification, etc. It also sheds light on the extent to which SSS wave propagation drives syrinx fluid motions, concomitant pressure differences favourable to the uptake of CSF into the cord tissue (a possible mechanism for initiating syrinx growth), and tearing stresses on cord tissue (a possible mechanism for syrinx elongation).

Contrary to what has been supposed previously, the increased SSS pressure differences across a localised SSS stenosis do not lead to increased syrinx fluid motions in an adjacent syrinx. The predominant influence of a stenosis is to damp CSF surging along the SSS. When the SSS is excited periodically with waves from the head, the system acts as a one-way valve, so that mean SSS pressure is significantly higher on the caudal side of the stenosis than in the syrinx. Although mean SSS pressure is slightly lower than syrinx pressure on the cranial side, overall these pressure differences would favour the take-up of CSF into the syrinx.

1. The Visible Human Project®. US National Library of Medicine. www.nlm.nih.gov/research/visible/visible_human.html



Chris Bertram

About the Presenter. Associate Professor Christopher Bertram, MA DPhil (Oxon.), FIEAust, graduated in Engineering Science in 1971 and gained his doctorate in 1975 on ultrasonic measurement of arterial mechanics. He then worked in haemodynamics at Johns Hopkins University's Dept of Physiology. From 1977 he experimented on unsteady flow separation at DAMTP, Cambridge University. In 1980 he was appointed to University of New South Wales, moving to University of Sydney in 2010. He has published 84 peer-reviewed journal papers, 109 conference contributions, and 5 book chapters (2 are on muscle-powered pumping for cardiac assist). He led a long-running series of experiments on collapsed-tube flows, and has explored many applications of flow-induced oscillation. He is a past member of the World Council for Biomechanics, and is on the Editorial Board of *Med. & Biol. Eng. & Comput.* and *J. of Fluids & Structures*.

Wave propagation in a poroelastic model of the spinal canal

Novak S. J. Elliott¹, Anthony D. Lucey¹, Duncan A. Lockerby², Andrew R. Brodbelt³

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² Fluid Dynamics Research Centre, School of Engineering, University of Warwick, Coventry, Warwickshire, U.K.

³ The Walton Centre NHS Foundation Trust, Liverpool, Merseyside, U.K.

Abstract. Fluid-filled cavities in the spinal cord, called syrinxes, are characteristic of syringomyelia, a debilitating spinal disease. Although the syrinx fluid source is still debated tracer studies have shown that syrinxes may communicate with the surrounding cord tissue interstitium and with the cerebrospinal fluid (CSF) in the spinal subarachnoid space (SSS) via leaky junctions in the pia mater [1]. As pressure disturbances, either cardiac or percussive, lead to wave propagation in the spinal canal, many previous studies have sought to characterise its wave-bearing properties in order to provide a rigorous mechanical foundation upon which to study the pathogenesis of syringomyelia [e.g., 2, 3]. For this purpose investigators have represented the spinal tissues as a series of two or more axisymmetric coaxial tubes (e.g., cord parenchyma, pia mater, dura mater) and the CSF represented by interposing fluid. However, in these models fluid movement within the spinal cord was limited to the central canal, which is usually abolished by adulthood, or to an established central syrinx. Therefore no provision was made for fluid to move within the cord tissue itself nor for fluid to enter or leave the cord, precluding a possible source of syrinx fluid. The aim of the present work is to address these concerns by incorporating poroelasticity into the tissue model thereby extending the wave analysis to conditions amenable to syrinx genesis.

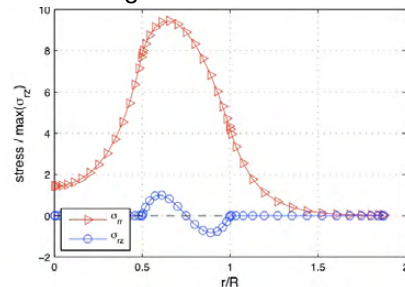


Fig. 1. First radial and shear stress eigenmode radial (r) profiles at moderate wavelength ($8R$), where R is spinal cord radius; syrinx: $r/R < 0.5$, cord: $0.5 < r/R < 1$, SSS: $1 < r/R < 2$.

The model is formulated as a system of Helmholtz equations which describe axisymmetric harmonic motion of the cylindrical layers. The eigenvalue problem is solved yielding the dispersion relation and associated displacement and stress modes [4]. This approach also has the ability to handle inhomogeneous and anisotropic media.

The computed wave speeds match other syringomyelia models and the dispersion diagrams are qualitatively similar to other acoustic models with like topologies. This demonstrates the applicability of the numerical method to the biological problem. Peak radial stress occurs in the syrinx wall and radial stress gradients are higher when a syrinx is present, which may implicate tissue fatigue. At longer wavelengths the inclusion of tissue poroelasticity slows the pulse wave. Results showing the conditions under which poroelasticity affects the movement of CSF will be presented with reference to the more familiar case of impermeable elastic tissues (Fig. 1).

1. Stoodley MA, Jones NR, Brown CJ (1996). Evidence for rapid fluid flow from the subarachnoid space into the spinal cord central canal in the rat. *Brain Res* 707:155-164

2. Cirovic S (2009). A coaxial tube model of the cerebrospinal fluid pulse propagation in the spinal column. *J Biomech Eng* 131 (2):021008.

3. Bertram CD (2009). A numerical investigation of waves propagating in the spinal cord and subarachnoid space in the presence of a syrinx. *J Fluid Struct* 25:1189-1205.

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Novak Elliott

About the Presenter. Dr Novak Elliott received a BSc (Hons) in Information Technology from the University of Western Australia in 2000, a BE (Hons) in Mechanical Engineering and MBiomedE in Biomedical Engineering from the University of New South Wales, Australia, in 2004, and a PhD in Mechanical Engineering from University of Warwick, U.K., in 2009. He has worked in the software, mechanical and biomedical engineering industries and is presently a Postdoctoral Research Fellow at the Department of Mechanical Engineering, Curtin University, Australia, and a long-term Honorary Visitor at the School of Mathematics, University of Manchester, U.K. His research interests are in the fluid and solid mechanics, and their interaction in particular, of biological phenomena. Current projects include investigating the pathogeneses of syringomyelia and sleep apnoea.

Biomechanics of syringomyelia

Shaokoon Cheng¹, Marcus Stoodley², Lynne Bilston¹

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² Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

Abstract. Syringomyelia is a serious neurological condition where high-pressure fluid-filled cysts (syrinxes) form within the spinal cord. As these cysts enlarge, they damage the spinal cord tissue and result in neurological symptoms and deficits, such as pain, weakness and loss of sensation. Neurological deficits due to syringomyelia are particularly devastating in patients with spinal cord injury, and can transform them from disabled but independent people into patients requiring assistance with basic daily tasks. As ~ 28% of patients with spinal cord injury develop syringomyelia months to years after the original injury, this suggests that fibrous scarring (arachnoiditis) from the injury is likely to play an important role in syrinx pathogenesis. Interestingly, syrinx forms above or below the location of arachnoiditis and the mechanics of syrinx formation is likely related to the change in cerebrospinal fluid (CSF) dynamics around the arachnoiditis and how this occur is unclear.

By using three-dimensional fluid flow structure interaction models of the spinal cord and CSF spinal subarachnoid space (Fig 1), this study investigate how arachnoiditis changes CSF flow dynamics and when permeability of the arachnoiditis increases. A three-dimensional model of the SAS and spinal cord was first constructed based on the axial images of a healthy human acquired from a 3-T MRI scanner (Philips Medical Systems, Best, The Netherlands). CFD studies were performed in 2 models with and without arachnoiditis). Geometry of arachnoiditis was modelled by filling the posterior half of the SAS from the level of C4 to C5 with a permeable solid. Dynamic viscosity of cerebrospinal fluid was taken as 0.007 Kg/m [1] and CSF flow was assumed laminar. Young Modulus and Poisson's ratio of the spinal cord was taken as 500 kPa and 0.45 respectively. Verification studies were performed to ensure grid and time independence of the solution.

Compared to the existing two dimensional models in the literature, peak pressure at the level of C3 and C5 in the three dimensional model (without arachnoiditis) is 2 to 3 fold higher. Arachnoiditis changes the temporal dynamics of the CSF flow and pressure dynamics. In the normal model, flow reversal at the level of C3 and C5 occurs at the same time in the cardiac cycle. However, in the model with arachnoiditis, flow reversal at the level of C3 and C5 occur at 30 % and 35% of the cardiac cycle respectively. Therefore, for approximately 5% of the cardiac cycle, CSF is flowing in opposite directions at C3 and C5 and into the arachnoiditis. As permeability of the arachnoiditis increases, the time period for this flow path increases. This study shows that using a realistic CFD model of the spinal subarachnoid space is likely important to improve our understanding on the biomechanics of syringomyelia.

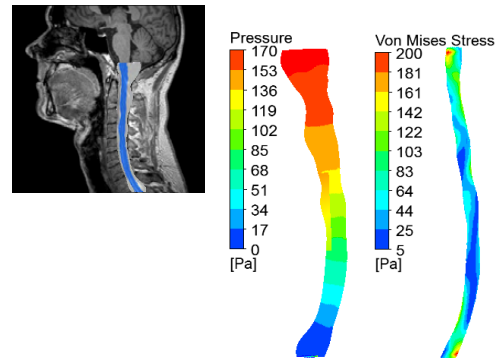


Fig. 1. Figure (left) shows a three dimensional model of the spinal subarachnoid space and spinal cord superimposed on a MRI image of the subject. Figure (right) shows the pressure in the subarachnoid space and von-mises stress of the spinal cord.

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Shaokoon Cheng

About the Presenter. Dr Shaokoon Cheng's research interest is in the area of intracranial biomechanics. He is a senior research officer at Neuroscience Research Australia based in Sydney and holds a conjoint lecturer appointment in the University of New South Wales.

Perivascular CSF Flow: A major route of fluid entry into the spinal cord

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Abstract. Syringomyelia is a condition where fluid-filled cysts form in the spinal cord. These enlarge and apply pressure to the surrounding spinal cord tissues, resulting in neurological deficits. It is associated with alterations in cerebrospinal fluid flow in the spinal subarachnoid space, which can occur in congenital conditions, such as Chiari Malformation, and due to arachnoiditis, such as after spinal cord injury.

The mechanisms by which syrinxes form and enlarge are an enduring enigma. In particular, the mechanics of how fluid flows into the spinal cord, coalesces into a syrinx, and proceeds to build up high pressures are unknown. There have been many competing theories and models aiming to explain syrinx formation, but key questions, such as the source and driving forces for fluid inflow, have yet to be definitively answered. Our research group has used a combination of animal experiments and computational modelling studies to examine the mechanics of such flow. Animal studies showed that: CSF flows into the spinal cord from the spinal subarachnoid space through the perivascular spaces [1]; this flow is dependent on the presence of cardiac pulsations [2]; and is enhanced in the presence of arachnoiditis [15]; and that this fluid ends up in the syrinx. Computational studies have shown that: CSF can be propelled along the perivascular space by the travelling cardiac pulse [4] and by temporal differences in the timing of the cardiac pulsations and the spinal subarachnoid space pressure [5], and that obstructions in the subarachnoid space increase the pressure locally [6], which may enhance this flow. This presentation will describe the current state of our understanding of spinal perivascular flow and its contribution to syringomyelia.

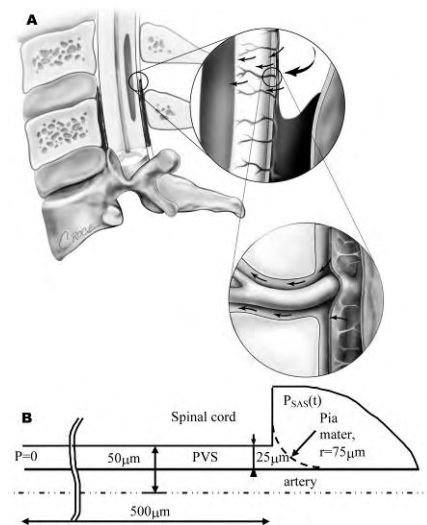


Fig. 1. Perivascular flow into the spinal cord, and schematic of computational flow model [5]

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Lynne E Bilston

About the Presenter. Professor Lynne Bilston is a biomechanical engineer, whose research interests focus on how neural tissues are affected by mechanical loads of all types and rates. She completed her undergraduate engineering degree at the University of Sydney and masters and PhD at the University of Pennsylvania. 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 C

Friday, July 8, 2011 – 14⁰⁰ to 16⁰⁰

Session Chair: Lynne Bilston, Neuroscience Research Australia



K.-A. Mardal

14⁰⁰ – 14³⁰

Computational models and results for the flow of cerebrospinal fluid in the upper cervical canal in patients with the Chiari I malformation

Kent-Andre Mardal^{1,2}, Karen Helene Støverud^{1,2}, Svein Linge^{1,3}, Hans Petter Langtangen^{1,2}, Victor Haughton^{1,4}

1 Center for Biomedical Computing, Simula Research Laboratory, Oslo, Norway

2 Institute of Informatics, University of Oslo, Oslo, Norway

3 Telemark University College, Porsgrunn, Norway

4 Department of Radiology, University of Wisconsin Hospitals and Clinics, Madison, WI, USA



F. Loth

14³⁰ – 15⁰⁰

Clinical utility of hydrodynamic parameters in Chiari malformation

Francis Loth¹, Nicholas M. Shaffer¹, John N. Oshinski², Oliver Wieben³, Bermans J. Iskandar⁴, Brandon G. Rocque⁴, Stephen M. Dombrowski⁵, Mark G. Luciano⁵

1 Departments of Mechanical & Biomedical Engineering, University of Akron, Akron, OH, USA

2 Radiology and Biomedical Engineering, Emory University, Atlanta, GA, USA

3 Medical Physics & Radiology, University of Wisconsin School of Medicine & Public Health, Madison, WI, USA

4 Neurosurgery & Pediatrics, University of Wisconsin Hospital & Clinics, Madison, WI, USA

5 Neurological Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA

15⁰⁰ – 15³⁰

A 3D computational fluid dynamics model for prediction of molecule transport in the CSF space and its application in the pharmaceutical industry

Andreas Kuttler, Thomas Dimke, Luca A. Finelli

Modeling & Simulation, Novartis Pharma AG, Basel, Switzerland



M. Sarntinoranont

15³⁰ – 16⁰⁰

Convection-enhanced delivery for the treatment of epilepsy

Malisa Sarntinoranont¹, Paul R. Carney², and Thomas H. Mareci³

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2 Division of Pediatric Neurology, University of Florida, Gainesville, FL, USA

3 Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, FL, USA

Computational models and results for the flow of cerebrospinal fluid in the upper cervical canal in patients with the Chiari I malformation

Kent-Andre Mardal^{1,2}, Karen Helene Støverud^{1,2}, Svein Linge^{1,3}, Hans Petter Langtangen^{1,2}, Victor Haughton^{1,4}

¹ Center for Biomedical Computing, Simula Research Laboratory, Oslo, Norway

² Institute of Informatics, University of Oslo, Oslo, Norway

³ Telemark University College, Porsgrunn, Norway

⁴ Department of Radiology, University of Wisconsin Hospitals and Clinics, Madison, Wisconsin, US

Abstract. In this talk we will discuss the flow of cerebrospinal fluid (CSF) in the upper cervical spinal canal with particular focus on the abnormal flow associated with the Chiari I malformation. Both idealized and patient-specific models are used to analyze the characteristic flow and pressure fields. Further, we will discuss some appropriate models for the spinal cord, where we include the elasticity and porous properties of the cord. The spinal cord is modeled as a porous medium, which is coupled with viscous flow in the subarachnoid space. We also consider the cord as a porous and elastic media, which leads to the Biot equations of poroelasticity. Furthermore, we discuss the consequences of an open or occluded central canal and cysts within the spinal cord.



Kent-Andre Mardal

About the Presenter. Kent-Andre Mardal is a Scientific Researcher at Simula Research Laboratory and an associate professor (20%) at the University of Oslo. His scientific interest 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.

Clinical utility of hydrodynamic parameters in Chiari malformation

Francis Loth¹, Nicholas M. Shaffer¹, John N. Oshinski², Oliver Wieben³,
Bermans J. Iskandar⁴, Brandon G. Rocque⁴, Stephen M. Dombrowski⁵, Mark G. Luciano⁵

¹ Departments of Mechanical & Biomedical Engineering, University of Akron, Akron, OH, USA

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⁴ Neurosurgery & Pediatrics, University of Wisconsin Hospital & Clinics, Madison, WI, USA

⁵ Neurological Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA

Abstract. Diagnosis of Chiari malformation (CM) is difficult and often takes years as the symptoms vary widely and overlap with many other conditions and diseases. Anatomically, CM is characterized by a partial blockage of the passage of cerebrospinal fluid (CSF) from the cranium to the spinal canal due to hindbrain herniation at the level of the foramen magnum. This blockage is thought to cause symptoms through direct compression of neural tissue as well as altered CSF flow and pressure. The current diagnostic definition is a tonsillar decent at least 3-5mm as measured by static MRI and the presence of symptoms. However, structural abnormalities (i.e., tonsillar ectopia) are not always predictive of symptoms or surgical outcomes, and a better method of predicting which patients might benefit from surgery is necessary.

We hypothesize that hydrodynamic changes to the CSF system may reflect the underlying pathophysiology associated with CM, and may serve as a better prognostic indicator than standard static methods. Furthermore, non-invasive measurement of these hydrodynamic changes could provide clinically relevant data beyond that obtained in static radiological findings. We have investigated the following hydrodynamic parameters in patients and healthy volunteers: longitudinal impedance, pulse wave velocity, and volumetric expansion. Longitudinal impedance, a measure of resistance to pulsatile flow, was quantified using computational fluid dynamics with a patient specific geometry. Pulse wave velocity was measured using high temporal resolution phase contrast MRI in the sagittal plane and is related to spinal canal compliance. CSF flow rate was obtained by the integration of CSF velocity measured by phase contrast MRI in the transverse plane. The difference between measurements of CSF flow rate at two different axial locations along the spinal canal was computed to assess the degree of volumetric expansion, which is also related to the spinal canal compliance. Preliminary results show CM patients have increased resistance and decreased compliance compared with healthy volunteers. Longitudinal impedance to CSF flow in the cervical spinal canal appears to be independent of the shape, amplitude, and frequency of the CSF flow waveform; it is predominantly a function of the geometric complexity of the cervical spinal canal. Median values of longitudinal impedance for volunteers (n=4), asymptomatic CM patients (n=12), symptomatic CM patients (n=2), and equivocal patients (n=2) were 205, 388, 830, and 395 dynes/cm⁵, respectively. Thus, longitudinal impedance is different between healthy and CM-affected spinal canals. However, the number of subjects in each group was too low to give the comparison sufficient statistical power.



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 joined the Mechanical Engineering Department at the University of Illinois at Chicago as Assistant Professor in 1996. 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 (2007, 2008, and 2010). Currently, he is an Associate Professor and the F. Theodore Harrington Endowed Chair in the Department of Mechanical Engineering at The University of Akron.

A 3D computational fluid dynamics model for prediction of molecule transport in the CSF space and its application in the pharmaceutical industry

Andreas Kuttler, Thomas Dimke, Luca A. Finelli

Modeling & Simulation, Novartis Pharma AG, Basel, Switzerland

Abstract. Worldwide approximately 2.5 million people live with spinal cord injury (SCI) a disease for which no fully restorative treatment exists today [1]. Development of a new regenerative therapy with an endogenous major neurite growth inhibitor, namely anti-Nogo-A [2], has been the motivation for creating a 3D computation fluid dynamics model to understand the pharmacokinetics of the delivery. The drug is administered into the cerebrospinal fluid (CSF) by lumbar intrathecal injection or infusion. The objective of the modeling approach was to gain a precise understanding of the transport mechanisms and the relevant driving forces to optimize the drug delivery to the target site.

A 3D computational fluid dynamics model of the spinal canal was developed based on actual geometry reconstructed from magnetic resonance imaging (MRI) data, and dynamics determined by the transient Navier-Stokes equations. The driving forces for fluid transport (pulsating blood flow in the cranium and breathing) are modeled based on literature data [3, 4] and additional double-gated MRI scans, allowing the separation of both effects. Simulated velocities are in good agreement with the velocities measured by phase contrast magnetic resonance imaging at five transversal cross-sections [5]. The determined local transport velocities are in the same range as those measured by CSF radionuclide scintiphotography using radiolabeled human serum albumin [6, 7].

The pulsating nature of the fluid flow together with the specific geometry of the spinal canal results in convective transport of injected drug molecules. Because of these effects, even large molecules such as monoclonal antibodies, with a low molecular diffusion rate, get distributed, though not in a spatially homogenous manner. The underlying biophysical model relied on multiple sources of experimental data and knowledge from scientific literature. The results have provided insights into the primary factors that can influence the intrathecal distribution of drug after lumbar administration. The presented approach connects the causal chain underlying drug distribution, starting with the technical aspect of drug delivery systems, through physiology driven drug transport, then eventually linking to tissue penetration, binding, residence, and ultimately clearance. By providing a framework for appropriate integration of population clinical data into a dynamic system physiology platform, this technology allows for the simulation of different clinical scenarios to support decision making, turning model based-drug development to reality.

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7. Di Chiro, G.; Hammock, M.K.; Bleyer, W.A.: Spinal Descent Of Cerebrospinal Fluid In Man, *Neurology* 26: 1-8, January 1976

About the Presenter. Andreas Kuttler graduated from the University Karlsruhe (TH) and DLR Göttingen in the field of Mechanical Engineering with specialization in physics and numerical simulation of fluid dynamics. He worked at Ciba (later Novartis) AG Basel as a Project Manager and Head of Computational Physics in computer science and simulation projects from 1985 to 2000. In 1999 he founded his own engineering-consultant company GiMS GmbH supporting BMW, Siemens, Roche, Novartis & other companies with multiphysics simulations. In 2009 he joined Novartis Pharma AG working as a member of the management team of the Modeling & Simulation Department on 3D biophysical drug delivery and disease modeling in pulmonary, ophthalmics and neuroscience projects.

Convection-enhanced delivery for the treatment of epilepsy

Malisa Sarntinoranont¹, Paul R. Carney², and Thomas H. Mareci³

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. Local drug delivery methods such as direct infusion are being used to improve targeting and increase uptake of drugs in the brain for neurological disorders such as epilepsy [1]. Rational design of such regional therapy requires new tools to evaluate drug transport issues specific to nervous tissue physiology. In addition to anatomical boundaries, drug distributions are influenced by infusion parameters as well as underlying tissue microstructure. In this study, high-resolution magnetic resonance imaging was used to visualize *in vivo* transport of contrast agents as surrogates for therapeutic agents within the rat dorsal and ventral hippocampus [2]. For these hippocampal infusions, CSF spaces were found to be a significant factor affecting infusate distribution, with considerable tracer leakage from tissues into adjacent CSF. In addition, high resolution images were used to generate 3D computational models of the rat hippocampus with care taken to segment realistic CSF and subarachnoid spaces [3]. These porous media transport models incorporate diffusion weighted imaging (DWI) data and uniquely account for the effects of embedded white matter fibers on transport. Predicted tracer distributions from computational models showed similar distribution patterns to those seen in MR experiments, see Fig. 1.

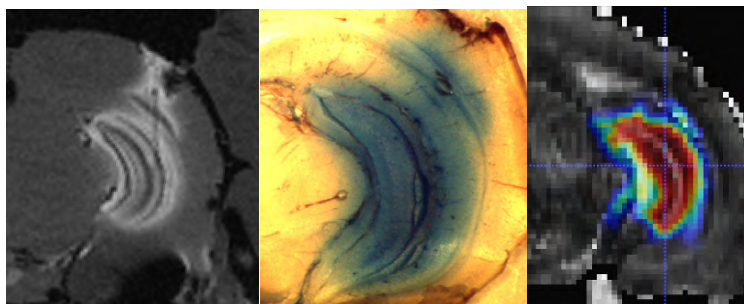


Fig. 1. (A) Magnetic resonance image of macromolecular tracer distribution in the ventral hippocampus following CED. Coronal images of (B) Evans blue-albumin tracer distribution and (C) predicted albumin tracer distribution using a 3D computational transport model. Preferential transport along the molecular layer of the dentate gyrus and CA1 in the ventral hippocampus was observed.

Mechanics of soft tissue infusion have also been investigated. Biphasic finite element models have been developed to model deformation and swelling of tissues during infusions. Validated computational transport models will aid researchers in determining the potential of new drug compounds and designing effective treatment regimes. Research in extracellular mechanics and transport is emerging as an increasingly important area of research in drug delivery, since the vast majority of therapeutic agents must traverse this space before reaching their targets. The need for this research has only increased with improved engineering and functionalization of therapeutic agents such as viral vectors and nanoparticles.

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Malisa 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: developing computational drug delivery models for the CNS and solid tumors based on medical imaging data, experimental tissue transport studies, biphasic tissue modeling, and microindentation testing. Dr. Sarntinoranont received her undergraduate degree in mechanical engineering 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).

Session D

Friday, July 8, 2011 – 16³⁰ to 17³⁰

Session Chair: Bryn Martin, EPFL



R. Marchbanks

16³⁰ – 17⁰⁰

Non-invasive Measurement of CSF Hydrodynamics: Latest Research using the TMD Technique

Robert J. Marchbanks, Anthony A. Birch

Neurological Physics Group, Medical Physics, Southampton University Hospitals NHS Trust, Southampton, Hampshire, England



S. Dombrowski

17⁰⁰ – 17³⁰

Evidence for direct CSF-CBF relationship: Findings using a novel method and device to control CSF pulsatility

Stephen Dombrowski¹, Jun Yang¹, Serge El Khoury², Deepti Guruprakash¹, Francis Loth³, Mark G. Luciano¹

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³ Department of Mechanical Engineering, University of Akron, Akron, OH, USA

Non-invasive measurement of CSF hydrodynamics: Latest research using the TMD technique

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Neurological Physics Group, Medical Physics, Southampton University Hospitals NHS Trust, Southampton, Hampshire, England SO16 6YD

Abstract. Non-invasive measurement of intracranial pressure (ICP) and CSF hydrodynamics is a major area of research. The lack of non-invasive measurements is a significant problem for both modeling and clinical diagnostic purposes. However, due to the cochlear aqueduct that connects the inner ear and the subarachnoid space, ICP pressure signals can be obtained using a technique which measures tympanic membrane displacement (TMD). The TMD technique provides a measure of baseline ICP and also shows pressure waves arising from respiration and the cardiac pulse. The amplitude, morphology and interactions of ICP waves can tell us much about the CSF hydrodynamics. For example, dependencies exist with baseline ICP, CSF compliance and flow. If the TMD technique provides a 'window' for viewing real-time ICP waveforms it could greatly expand the utility of CSF hydrodynamics in clinical practice^{1,2}.

The background to the TMD technique and the latest findings will be discussed. The technique is in clinical use and is included by the UK Department of Health in their care pathways as a screen for intracranial hypertension. Case examples will be given, including idiopathic intracranial hypertension, Arnold Chiari malformation and venous sinus thrombosis. The CSF hydrodynamics implications of each will be considered. A problem that exists in interpretation of clinical findings is a lack of data on normal CSF hydrodynamics and a lack of understanding of the pathophysiology. In addition the characteristics of the TMD technique need to be further researched, in particularly the hydrodynamics of the cochlear.

Current TMD research includes mathematical modeling of the cochlear aqueduct, investigations of cerebral cardiovascular and respiratory pressure waves and their interactions. Methods being used include a computerized tilt-table, controlled breathing and comparisons of TMD with direct intracranial, arterial and ventilation pressures in neuro-intensive care settings.

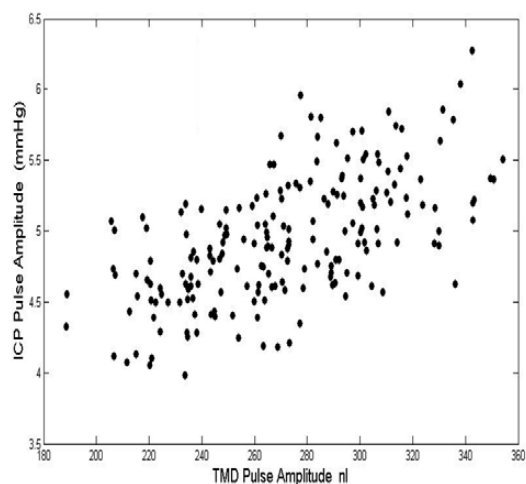


Fig. 1. Example scatter plot of TMD pulse amplitude vs. ICP pulse amplitude. 200 heart beats from same ear of patient in Southampton neuro intensive care, Pearson correlation coefficient of 0.61

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Robert Marchbanks

About the Presenter. Consultant Clinical Scientist and Director of the Non-invasive Intracranial Pressure Assessment (NIPA) Unit, Southampton. Past Clinical Director of Audiological Science, Royal National Throat, Nose and Ear Hospital, London. Honorary Senior Research Fellow Southampton University and Research Professor University of Houston, Texas, USA. Actively involved in the NASA Visual Impairment – Intracranial Pressure Project, Johnson Space Center.

Evidence for direct CSF-CBF relationship: Findings using a novel method and device to control CSF pulsatility

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² Department of Chemical and Biomedical Engineering, Cleveland State University, Cleveland, OH USA

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Abstract. Within the rigid, closed cranium, the relationship between cardiac-driven cerebrospinal fluid (CSF) oscillations and cerebral blood flow (CBF) may be more than coincidental. Specifically, it is not known whether CSF pulsatility is simply passive epiphenomena or plays a more physiologically significant role in cerebral compliance and blood flow. To study the relationship between cardiac-driven blood forces, CSF pulsatility and CBF, we developed a novel method and device for directly controlling CSF pulsatility, by either reducing or augmenting pulse pressure. Using canine subjects, we have implanted a small (0.3-3.0cc), custom-made polyurethane bladder into either the cranial or spinal epidural space. We then controlled CSF pulsatility via an oscillating, closed-air pump system gated to the cardiac cycle. The pump cycle was then timed to deflate (synergistically) or inflate (antagonistically) with incoming systolic blood flow. The resultant ICP pulse pressure can then be directly controlled: reduced, augmented or inverted with pump activation. Intra-operative measures for ICP and CBF and velocity were obtained real-time, online during pump activation and under different acute and chronic conditions. CSF pulse pressure changes (i.e., reduction, inversion, augmentation) were successfully achieved via cardiac-gated oscillation and observed globally and remotely in the cranium and spinal spaces. Under specific inflation cycles and physiological conditions, operation of the system increased CBF up to 15 mL/min*100gm, or by as much as 40% in some cases. Using TCD, CBF velocity increased in the L/R siphon and basilar arteries in both normal (9-39%) and hydrocephalus animals (7-19%). Overall, data support the hypothesis that synergistic activation may be more effective than antagonistic ICP manipulation on improving CBF globally. Mean systemic pressure and cardiac output did not significantly change with system activation. In conclusion, we have devised a method of altering CSF pulse pressure using cardiac-gated oscillating system which dynamically alters CSF space volume. The ability of the system to synergistically increase CBF without significantly affecting cerebral perfusion pressure (MAP or ICP) suggests it may work through alteration of cerebrovascular compliance and impedance. Understanding the effect of CSF pulsatility on cranial compliance may lead to the development of new therapies for increasing CBF in acute and chronic neurological conditions, including stroke, dementia, and hydrocephalus, where CSF pulsatility and CBF are abnormal.



Stephen Dombrowski

About the Presenter. Stephen Dombrowski received his Ph.D. degree in Neuroscience in the area of *neuroanatomy* at Boston University School of Medicine in 1999. He completed his post-doctoral training in cerebrovascular research in the Department of Neurosurgery, Cleveland Clinic. Currently, Dr. Dombrowski is Project Staff and Co-Director of Clinical and Experimental Studies, CSF Physiology Lab in the Section of Pediatric and Congenital Neurosurgery, Cleveland Clinic. His research interests include both clinical and experimental Hydrocephalus, Chiari Malformation, CSF hydrodynamics, and cerebral blood flow. Drs. Luciano and Dombrowski are co-inventors of the Oscillating Compliance Device, “Cadence” (WO/2007/014028; WO/2009/058353) and co-founders of *CSF Therapeutics, Inc.*

Second Keynote Lecture and Session E

Saturday, July 9, 2011 – 8⁰⁰ to 10⁰⁰

Session Chair: Vartan Kurtcuoglu, ETH Zurich



M. Luciano

8⁰⁰ – 9⁰⁰

Keynote Lecture

The ventricular system: The primary organ of cranial accommodation

Mark G. Luciano

Cleveland Clinic, Neurological Institute, Cleveland, OH, USA



N. Alperin

9⁰⁰ – 9³⁰

The origin of the cranio-spinal CSF pulsation and its clinical relevance

Noam Alperin¹, Birgit Ertl-Wagner², Tosiaki Miyati³

¹ Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL, USA

² University of Munich, Munich, Germany

³ University of Kanazawa, Kanazawa, Japan



O. Wieben

9³⁰ – 10⁰⁰

MR based CSF flow measurements: Current approaches, accuracy and precision, and future directions

Oliver Wieben, Ashley Anderson

Departments of Medical Physics & Radiology, University of Wisconsin, Madison, WI, USA

The ventricular system: The primary organ of cranial accommodation

Mark G. Luciano

Cleveland Clinic, Neurological Institute, Cleveland, OH, U.S.A.

Abstract. The primary function of the CSF ventricular system is to allow brain and vascular volume changes within a rigid cranium. It does this by the accommodating movement of CSF fluid during the cardiac cycle as well as a more extended time scale. The cardiac cycle drives an oscillation in cerebrovascular volume and pressure that induces oscillating CSF motion within the ventricles and cisterns. Failure of the ventricles and basilar cisterns to allow oscillatory fluid flow may result in: 1) suboptimal cerebral blood flow, 2) compression or stretch of brain tissue, and 3) microvessel injury. Disorders such as hydrocephalus, intracranial hypertension, slit-ventricle syndrome, cerebral cysts, Chiari malformation, and vascular dementia may be better characterized as a failure of this dynamic system. Based on this view of the ventricular system, new strategies for diagnosis, evaluation treatment and prevention of these various disorders are suggested.



Mark G. Luciano

About the Presenter. Mark G. Luciano, MD, PhD, FACS, came to the Cleveland Clinic Department of Neurosurgery in 1993 after training in general neurosurgery at the University of Pennsylvania and in pediatric neurosurgery at Harvard's Boston Children's Hospital. He received additional training in research through a PhD from Tulane University and a research fellowship at the National Institutes of Health. Currently, he is Head of Congenital and Pediatric Neurosurgery, Co-Director of Pediatric Neuroscience and adjunct staff in Neuroscience Research and Biomedical Engineering. Dr. Luciano treats both children and adults with neurological congenital anomalies, hydrocephalus, cerebral cysts, tumors, craniofacial anomalies, tethered cord, Chiari malformation and

cerebral palsy. Dr. Luciano directs the Neuroendoscopy program and also initiated the first multidisciplinary clinic in the USA to diagnose and treat normal pressure hydrocephalus. His NIH-funded experimental research has centered on the brain's adaptation to the chronic compression and hypoxia of hydrocephalus and on the dynamic relationship between the CSF and vascular systems. He has mentored PhD graduate students in both engineering and neuroscience and his experimental work also has resulted in invention and development of a novel device intended to increase cerebral blood flow.

The origin of the cranio-spinal CSF pulsation and its clinical relevance

Noam Alperin¹, Birgit Ertl-Wagner², Tosiaki Miyati³

¹ Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL, USA

² University of Munich, Munich, Germany

³ University of Kanazawa, Kanazawa, Japan

Abstract. MR imaging of the CSF flow dynamics is becoming an integral part of many clinical exams. Therefore, the understanding of CSF flow dynamic is critical for successful utilization of CSF flow studies for diagnosis of related brain disorders. This presentation reviews progress our group has made over the last 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 the underlying pathophysiology. Implementation of MR derived morphologic and CSF dynamics markers in NPH, Chiari Malformations and in Idiopathic intracranial hypertension will be presented.

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 results from multi center evaluation of the added value for differential diagnosis of MR based measurements of intracranial compliance and pressure (MRICP) will be reported.

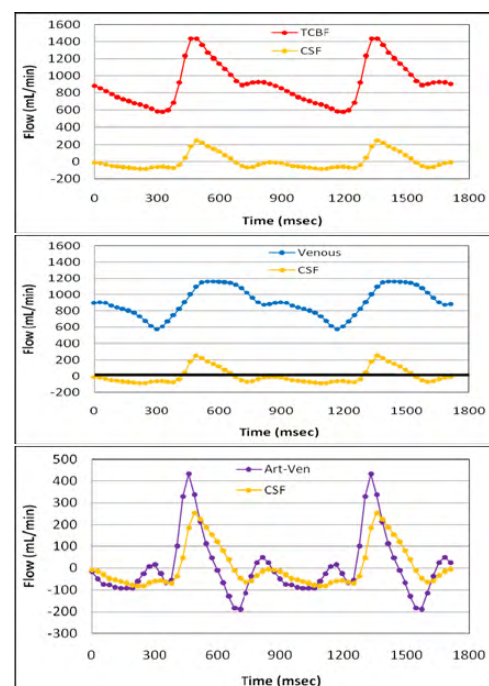


Fig. 1. MRI derived Volumetric Flow Rate waveforms of arterial inflow (red), venous outflow (blue) and cranio-spinal CSF flow (yellow). Lower trace show CSF flow relative to the difference between arterial inflow and venous outflow. This demonstrates that net trans-cranial volumetric blood flow is the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

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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 utilization of dynamic MRI techniques to study the coupling between blood and CSF flow and association between brain morphology and function in related brain disorders and in microgravity.

MR based CSF flow measurements: Current approaches, accuracy and precision, and future directions

Oliver Wieben, Ashley Anderson

Depts. of Medical Physics & Radiology, University of Wisconsin, Madison, WI, USA

Abstract. The noninvasive assessment of cerebrospinal fluid (CSF) flow and hemodynamics is desirable for several clinical applications, yet it is fairly challenging [1]. In clinical practice, this is usually accomplished with velocity sensitive magnetic resonance imaging (MRI), also referred to as phase contrast (PC) MRI. It is important to note that PC MRI has been optimized for velocity mapping of arterial blood flow where it has become part of routine cardiovascular MR exams.

Meanwhile, MR measurements of CSF flow have unique challenges, in particular slower velocity fields and the signals characteristics of the CSF fluid. The velocity ranges expected in CSF flow are much lower (<10 cm/s in the superior-inferior direction and even smaller in the AP-P and L-R directions) compared to arterial blood flow (>100 cm/s). The necessary adjustments in the MR acquisition in form of stronger bipolar gradients result in larger measurements errors from uncompensated eddy currents. The significantly longer T1 in CSF (approx. 4200 ms at 3T) vs blood (approx. 1600 ms at 3T) causes a lower signal-to-noise ratio (SNR) in the T1-weighted spoiled gradient echo sequences.

Recent advances in MR hardware design, specifically in gradient performance, have facilitated faster imaging with some improvements for PC MRI. These benefits include breath-held acquisitions, e.g. for valsalva maneuvers in CSF imaging, as well as shorter echo times to reduce the effects of intravoxel dephasing and the associated measurements errors. However, these advances have also been associated with significant measurement errors in recent multi-center studies for cardiovascular protocols. Such studies are currently lacking for CSF imaging protocols and should be strongly considered. Actually, the differences in vendor-specific implementations of the PC MR sequences make it difficult to compare results from multiple sites. These variations include, for example, the acquisition of the velocity encoded data and reference data over one single or consecutive cardiac cycles, the velocity encoding scheme, the type of temporal view sharing, voluntary derating of gradients, and the type of built-in error correction algorithms in the reconstruction and post-processing software.

Several novel approaches have been proposed to improve MR based CSF flow measurements. These include new acquisition schemes from improved SNR based on balanced SSFP [2] and spin echos [3] as well as volumetric acquisitions with 3-directional velocity encoding throughout the cardiac cycle [4]. In addition, efforts are underway for CSF flow post-processing analysis software that is freely distributed and works with flow data from various vendors [5].

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2. Markl M, Alley MT, Pelc NJ (2003). Balanced phase-contrast steady-state free precession (PC-SSFP): a novel technique for velocity encoding by gradient inversion. Magn Reson Med 49(5):945-952.
3. Spottiswoode BS, Markl M (2011). Imaging CSF Flow using Spin Echo Phase Contrast Velocity Encoded MRI at 3T. Proc ISMRM 2011, Montreal, p. 1208
4. Santini F, Wetzel SG, Bock J, Markl M, Scheffler K (2009). Time-resolved three-dimensional (3D) phase-contrast (PC) balanced steady-state free precession (bSSFP). Magn Reson Med 62(4): 966-74.
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Oliver Wieben

About the Presenter. Oliver Wieben received his Ph.D. in Electrical Engineering in the area of magnetic resonance imaging and is currently an Assistant Professor in the University of Wisconsin-Madison Depts. of Medical Physics & Radiology. His primary research interest is the development of rapid cardiovascular MR imaging methods and their application to improve clinically relevant diagnosis. He is investigating methods to improve the data acquisition and image reconstruction for accelerated imaging as well as post-processing methods to facilitate comprehensive, non-invasive hemodynamic assessment of the vascular and CSF system. His work is directed at identifying biomarkers in a variety of diseases including aneurysms, stenoses, arterio-venous malformations, dissections, CCSVI, Chiari malformation, and others in the cranium, chest, and abdomen.

Session F

Saturday, July 9, 2011 – 10⁴⁵ to 12⁴⁵

Session Chair: Adam Wittek, The University of Western Australia



I. Sobey

10⁴⁵ – 11¹⁵

Simulation of ICP oscillations in a poroelastic model and a one-compartment model of CSF flow with application to infusion tests

Ian Sobey¹, Almut Eisenträger¹, Benedikt Wirth², Marek Czosnyka³

1 Mathematical Institute, Oxford, England

2 Institute for Numerical Simulation, Bonn, Germany

3 Department of Clinical Neuroscience, Cambridge, England



A. Linninger

11¹⁵ – 11⁴⁵

Fluid-Structure Interaction Models of Pulsatile CSF Flow in Normal and Hydrocephalic Brains

Andreas A. Linninger, Brian J. Sweetman

Department of Bioengineering, University of Illinois at Chicago, Chicago, IL, USA



Y. Ventikos

11⁴⁵ – 12¹⁵

Multicompartmental poroelasticity for the integrative modelling of water transport in the brain

John C. Vardakis, Brett Tully, Yiannis Ventikos

Institute of Biomedical Engineering & Department of Engineering Science, University of Oxford, UK



K. Miller

12¹⁵ – 12⁴⁵

On Appropriateness of brain parenchyma modelling as biphasic continuum

Karol Miller, Tonmoy Dutta Roy, Adam Wittek

Intelligent Systems for Medicine Laboratory, School of Mechanical and Chemical Engineering,

Simulation of ICP oscillations for a poroelastic model and a one-compartment model of CSF flow with application to infusion tests

Ian Sobey¹, Almut Eisenträger¹, Benedikt Wirth², Marek Czosnyka³

¹ Mathematical Institute, Oxford, England

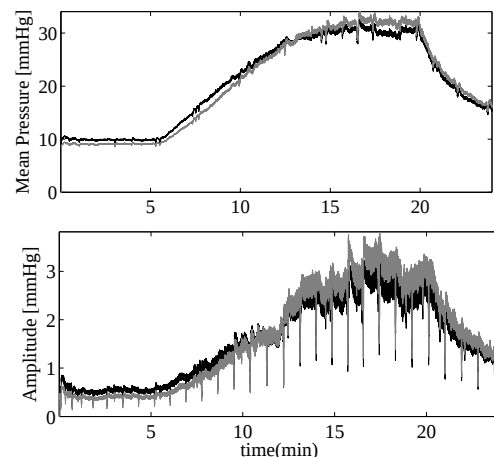
² Institute for Numerical Simulation, Bonn, Germany

³ Department of Clinical Neuroscience, Cambridge, England

Abstract. In this talk we outline our most recent developments in modeling CSF movement between production in the choroid plexus to absorption in the arachnoid villi. We model the brain parenchyma as a poro-elastic material and will describe two models. Both models take account of variation in arterial pressure. The first is a spherically symmetric model which allows both spatial and temporal variation of intracranial pressure (ICP) but has corresponding computational complexity. The second is a spatially integrated model that effectively reduces to a one-compartment model but with arterial blood pressure variation built into the model's framework. Both models are applied to compute ICP response in infusion tests and are compared to clinical observations of ICP.

In a spherically symmetric model, the stress in the parenchyma is related to the strain and ICP using poroelastic theory. In an infusion test, strain and corresponding tissue displacement are very small. We have extended the usual poroelastic formulation to allow an elastic matrix to have multiple fluid compartments that do not exchange fluid but which do communicate through stress changes in the solid matrix [1]. This extended multi-fluid poroelastic theory allows for a CSF and a single blood compartment or CSF and arterial and venous compartments. Through this multi-fluid poroelastic model, pressure variations in ICP can be taken into account.

The spherically symmetric model can be integrated over the parenchyma to eliminate spatial dependence and assuming that ICP is only weakly dependent on space variables, a model that is equivalent to a one compartment, time dependent ICP model emerges but retains dependence on blood pressure fluctuations. This model has been applied to clinical data from infusion tests where the input is only the arterial pressure fluctuation and the infusion schedule. In the diagrams on the right, the results for one test are shown. The upper diagram gives a running average ICP, clinical data in grey, results from model in black; the lower diagram shows a running average of the time dependence for the amplitude of pressure fluctuations, again clinical data in grey and predicted results in black. We will discuss that development of these models, their application and our plans to take this work forward.



1. Wirth, B. & Sobey, I. 2009 Analytic solution during an infusion test of the linear unsteady poroelastic equations in a spherically symmetric model of the brain, *Math Medicine & Biology* **26**, 25-61.



Ian Sobey

About the Presenter. Ian Sobey was born in Australia, graduated in Mathematics at Adelaide University before completing his Ph.D. in Applied Mathematics at Cambridge, UK, in 1976. He spent 5 years as a post-doc in Engineering at Oxford before taking a Lectureship in Applied Mathematics at Bristol in 1981 and moving in 1984 to work on oilfield problems at Schlumberger Cambridge Research. Since 1987 he has been a Fellow in Engineering at St John's College Oxford and a Lecturer in Numerical Analysis, presently in the Mathematical Institute, Oxford. His research interests are in unsteady laminar fluid flow with particular application to mass transfer devices involving blood and most recently, modeling CSF flow.

Fluid-Structure Interaction Models of Pulsatile CSF Flow in Normal and Hydrocephalic Brains

Andreas A. Linninger and Brian J. Sweetman

Department of Bioengineering, University of Illinois at Chicago, Chicago, IL, USA

Abstract. The flow rates and velocities of cerebrospinal fluid (CSF) in the central nervous system can be measured using advanced imaging modalities such as cine-phase-contrast MRI, yet the driving forces behind CSF motion are not fully understood. Recent clinical measurements supply in-vivo observations necessary for establishing the causal relationship between cerebral blood flow and pulsatile CSF motion. However, fundamental mathematical models for describing the dynamic force interaction between expanding cerebral vasculature, deformable brain tissue, and displaceable CSF do not exist. To close the gap between blood and CSF flow observations and models to explain mechanisms that occur in vivo, this paper proposes a multi-scale brain model for elucidating the interactions between expanding vasculature, brain tissue, and CSF.

Our hypothesis about intracranial dynamics suggests the oscillatory CSF flow is due to pulsating cerebral vasculature expansion. To test this hypothesis, a mathematical model integrating cerebral vasculature, brain tissue, and CSF has been created. Computer representations of brain tissue and CSF spaces were generated from medical images and spatially discretized using the finite volume method. Large arteries of the vasculature network were reconstructed from angiography data; an automatic vessel growth algorithm was used to generate microvasculature. The cerebral vasculature was represented as a connected network of cylindrical tubes. In the model, cerebral blood flow, pressures, and vessel expansion are solved for the entire vascular network. Changes in vessel caliber are transmitted to the brain as a volumetric strain inducing tissue displacement. The deforming brain, in turn, accelerates the CSF throughout the cranial fluid space. In this first approach, the brain tissue displacement is governed by a linear momentum balance for a linear-elastic body. CSF flow induced by pulsatile expansions is predicted by solving mass and momentum balances using the SIMPLE method for incompressible fluids. Because subarachnoid spaces are deformed along the CSF-brain tissue interface, the fluid equations are written in an Arbitrary-Lagrangian-Eulerian framework for a moving fluid mesh. A mesh displacement scheme was implemented to maintain grid integrity of the CSF flowing in a deformable domain.

The model predicts a pulsatile CSF flow pattern matching in magnitude and timing in vivo measurements of normal and hydrocephalic patients. Although the agreement between model and in-vivo measurements does not prove our hypothesis, it does provide a rational explanation for the driving forces of intracranial dynamics of the CNS. This project introduces the first fully integrated model of vasculature, brain, and CSF; it is an important step toward quantifying the complex biomechanical interactions of the physical brain.

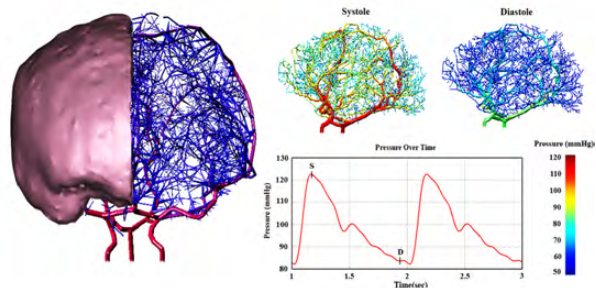


Fig. 1. Partial view of cerebral vasculature network embedded in the brain parenchyma surrounded by CSF. Large arteries were reconstructed from patient-specific angiography data, microvessels were generated artificially by an automatic vessel growth algorithm. Blood pressure simulations of the vasculature network in the model brain are shown for systole and diastole. Systolic input (S) and diastolic input (D) are indicated on the pressure waveform.



Andreas Linninger

About the Presenter. Andreas Linninger received his doctoral degree from the Vienna University of Technology and enjoyed postgraduate education at the University of California at Berkeley and the Massachusetts Institute of Technology. Currently, he is professor in the Departments of Bioengineering, Chemical Engineering and Computer Science at the University of Illinois at Chicago. His research interests include hydrocephalus, computational models for intracranial dynamics and drug delivery to the human.

Multicompartmental poroelasticity for the integrative modelling of water transport in the brain

John C. Vardakis, Brett Tully, Yiannis Ventikos

Institute of Biomedical Engineering & Department of Engineering Science, University of Oxford, Oxford, UK

Abstract. Hydrocephalus is a neurological disorder connected with abnormal flow of the cerebrospinal fluid (CSF) and is characterised by an active distension of the cerebral ventricles. It has no known cure and current treatment techniques exhibit an unacceptably high failure rate [1, 2].

A key complication associated with studying the transport of CSF, for this condition and others, stems from the fact that this water-like fluid does not act in isolation: exchange of water and ions between CFS spaces and the vasculature is continuous and apparently coupled with arteriole/capillary fluxes and possibly with cell channel fluxes.

A detailed investigation of multiscale, spatio-temporal transport of fluid between the cerebral blood, CSF and brain parenchyma is conducted.

Specifically, the MPET model of the cerebral tissue is coupled with a three-dimensional representation of the CSF flow patterns within a patient-specific cerebroventricular system. Anatomically accurate Choroid Plexuses are also investigated as there is little doubt that CSF is primarily produced here [3].

Currently, an accepted depiction of a choroid plexus can be loosely defined as a highly vascularized entity, consisting of 'leaky' plexus capillaries [4]. An ensuing investigation into these plexuses will be established, owing to their presence at different sites within the cerebral ventricles. Finally, select surgical interventions, like Third Ventriculostomy, will be applied to this ventricular model.

The novelty and most appealing feature of this modelling platform is that it allows for a natural incorporation of all transport processes – from the microscopic scale all the way to large ventricular or arterial spaces. This is accomplished by allowing for the assigning of different properties to specific discretised computational cells, but also for providing the facility to capture exchange processes, at all scales, either using resistance/transport constants, or, where the information is available, by using process-specific sub-models that are naturally embedded in the MPET framework (Figure 1).

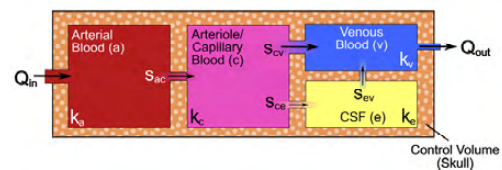


Fig. 1. A four-network MPET representation of the brain with the associated fluid transfer between select compartments. The constrictions placed in this model prohibit unwanted fluid transfer, like that between the CSF and arterial networks. In addition, choice of transfer directionality is also catered for.

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3. Oreskovic D., Klarica M. (2010). The formation of Cerebrospinal Fluid: Nearly a hundred years of interpretations and misinterpretations. *Brain Research Reviews*. 64, 241-262
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Yiannis Ventikos

About the Presenter. Yiannis formed the Fluidics and Biocomplexity Group when he joined the University of Oxford, in 2003. He is a member of the Institute of Biomedical Engineering and a Fellow and Tutor in Engineering at Wadham College. Yiannis has studied and worked in Switzerland, Greece, France and the USA, before joining the Department. His interests and specialization focus on computational simulation methods for complex phenomena, with an emphasis on multiscale/multiphysics modelling, biological/clinical transport phenomena, fluid mechanics, energy, micro- & nano-technologies, sustainability & the environment and innovative manufacturing and processing techniques.

On Appropriateness of brain parenchyma modelling as biphasic continuum

Karol Miller, Tonmoy Dutta Roy, Adam Wittek

Intelligent Systems for Medicine Laboratory, School of Mechanical and Chemical Engineering,
The University of Western Australia, Crawley-Perth, Western Australia, Australia

Abstract. Biphasic continuum theory was used as a mathematical framework for the brain parenchyma modelling in numerous studies that apply computational biomechanics in investigation of the mechanics of hydrocephalus development. In the current work, we conduct simple experiments using samples of lamb brain tissue to verify as to what extent the brain parenchyma responses are consistent with the models using biphasic continuum theory.

Approximately cylindrical samples were obtained from a lamb brain. Prior to acquiring the samples from the brain parenchyma, the pia mater was carefully teased out from the sulci features and was torn from the brain surface with gentle manipulations. The experimental set-up consisted of a cylindrical die and transparent plastic tube of length of 85 cm (Fig. 1). The cylindrical brain sample was inserted into the die and the transparent plastic tube was snapped fixed to the die. Artificial cerebrospinal fluid (CSF) solution was poured into the transparent plastic tube. As a result, the brain sample in the die was subjected to pressure from a CSF column solution. Three separate heights of CSF solution column (10 cm, 20 cm and 85 cm) were applied. No CSF solution leakage through the brain tissue was observed for all three load cases. Hydraulic conductivity as given in the literature (between 1.59×10^{-7} and 2.42×10^{-10} m/s) was used in the Darcy's Law to calculate the volume of CSF solution flow through the cylindrical samples after 120 minutes.

Table 1 Calculated total volume flow of CSF solution through the cylindrical brain parenchyma sample for the CSF solution column height of 85 cm (pressure of 8338.5 Pa). The values of hydraulic conductivity of the brain parenchyma were taken from the literature. No CSF flow through the brain sample was observed in the experiments conducted using the set-up shown in Fig. 1.

Hydraulic Conductivity [m/s]	Calculated total CSF volume flow in 120 minutes [ml]	Experimental results
1.59×10^{-7}	34.00	No CSF flow through the brain sample
1.37×10^{-7}	30.00	
8.11×10^{-8}	17.50	
2.42×10^{-10}	0.05	



Fig. 1 Experimental set-up with 85 cm CSF column applying pressure on the cylindrical brain sample inserted into the die.

Our experimental observations (no flow of CSF through the cylindrical brain sample) are in direct opposition to the total volumetric flow of CSF solution as predicted by Darcy's Law (Table 1). Therefore, it can be argued that soil consolidation theory is not in agreement with lamb brain tissue behaviour. Alternative mathematical formulations (e.g. transport theory) may be used to model the flow of fluid through the brain parenchyma. Our experimental observations also show that the hydraulic conductivity of the brain parenchyma is 0 m/s



Karol Miller

About the Presenter. Karol Miller received his PhD degree in mechanical engineering from Warsaw University of Technology, Poland in 1995 and DSc degree in biomechanics from Polish Academy of Sciences in 2001. He is a Winthrop Professor of Applied Mechanics and Director of Intelligent Systems for Medicine Laboratory at the University of Western Australia. He is internationally recognised for his research in biomechanics of the brain and modelling and computer simulation in biomechanics. Prof. Miller is a recipient of numerous awards and grants, which includes Leverhulme Visiting Professorship (UK) in 2010.

Session G

Saturday, July 9, 2011 – 13⁴⁵ to 16¹⁵

Session Chair: Dimos Poulikakos, ETH Zurich



A. Eklund

13⁴⁵ – 14¹⁵

CSF hydrodynamics: Models and measurements

Anders Eklund¹, Jan Malm²

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B. Martin

14¹⁵ – 14⁴⁵

Coupled simulation of the cardiovascular and cerebrospinal fluid system

Bryn A. Martin¹, Philippe Reymond¹, Jan Novy², Olivier Balédent³, Nikolaos Stergiopoulos¹

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2 Department of Neurology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

3 Department of Magnetic Resonance Image Processing in University Hospital of Amiens, France



D. Grzybowski

14⁴⁵ – 15¹⁵

Retinoid signaling pathway proteins in human arachnoid membrane: Role in regulating intracranial pressure

Deborah M. Grzybowski^{1,2}, Soojie B. Yu³, Ouliana Ziouzenkova⁴

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2 Biomedical Engineering, The Ohio State University, Columbus, Ohio, USA

3 College of Medicine, The Ohio State University, Columbus, Ohio, USA

4 Human Nutrition, The Ohio State University, Columbus, Ohio, USA



V. Kurtcuoglu

15¹⁵ – 15⁴⁵

CSF space phantom and coupling of cerebral arterial inflow with cerebrospinal fluid dynamics: Highlights from the SmartShunt project

Vartan Kurtcuoglu^{1,2}, Simone Bottan¹, Marianne Schmid Daners³, Verena Knobloch⁴, Dimos Poulikakos¹, Michaela Soellinger⁵, Lino Guzzella³, Peter Boesiger⁴, Burkhardt Seifert⁶

1 Laboratory of Thermodynamics in Emerging Technologies, ETH Zurich, Zurich, Switzerland

2 Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

3 Institute for Dynamic Systems and Control, ETH Zurich, Zurich, Switzerland

4 Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland

5 Neuroimaging Research Unit, Department of Neurology, Medical University Graz, Graz, Austria

6 Biostatistics Unit, Institute of Social and Preventive Medicine, University of Zurich, Switzerland



K. Berkouk

15⁴⁵ – 16¹⁵

How the EC Marie Curie Actions could contribute to the cerebrospinal fluid scientific community

Karim Berkouk

European Commission, DG for Research and Innovation, Marie Curie Actions, Brussels, Belgium

CSF hydrodynamics: Models and measurements

Anders Eklund¹, Jan Malm²

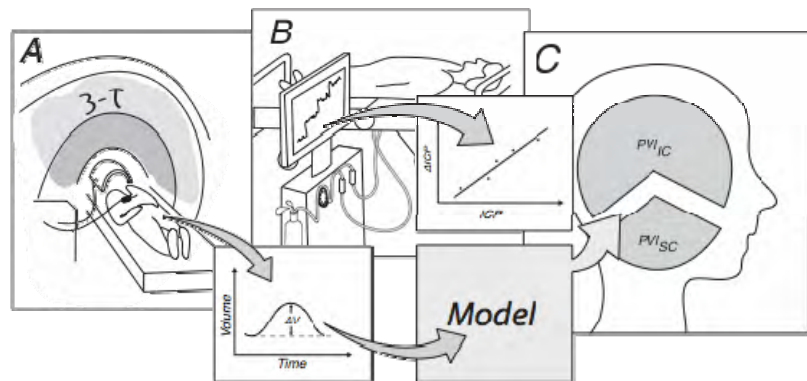
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Abstract. Modeling and analysis of CSF Hydrodynamics have two different main approaches. One has focus on slow dynamics and estimation of outflow resistance and the other on the fast dynamics and understanding of pulsatile flows in the craniospinal system.

If the researcher originates from the field of clinical infusion tests it is natural to view the system from that perspective with an infusion signal, a lumped model consisting of outflow resistance, a pressure dependent compliance and constant formation rate, and an space invariant intracranial pressure response as the measured output from the system. The system is typically analyzed with slow changes and with the pressure averaged over seconds or longer periods. The time scale of measurement is often between 20 to 40 minutes of infusion¹. With a time constant of the system that is about 5 to 15 minutes, it is then possible to estimate both the resistance parameter and the compliance parameter.

Groups that have their primary interest in Phase Contrast-MRI have their first focus on a shorter time scale, related to what happens during a heartbeat. They measure and analyze the pulsatile arterial and venous flows in vessels and the redistribution of CSF within each cardiac cycle. The time



scale of measurement being one heartbeat makes resistance analysis difficult, instead it is well suited for compliance estimations. This approach can differentiate between cranial and spinal compliance² and model pressure gradients in the intracranial system, which can give understanding to why the ventricles enlarge in hydrocephalus. Through the structural images of the MRI also give the geometries of the CSF system. An excellent complement to the MRI is therefore the approach with computational fluid dynamics. Here the flows and pressures can be modeled and simulated in order to understand the pressure gradients in the system.

This talk will discuss the assumptions behind the lumped model for the CSF hydrodynamic system and show an example of how infusion tests and PC-MRI investigation can be combined to estimate CSF- Dynamic parameters of the system.^{1,2}

1. Sundström N, Andersson K, Marmarou A, Malm J, Eklund A. Comparison between 3 infusion methods to measure cerebrospinal fluid outflow conductance. J Neurosurg. 2010 Dec;113(6):1294-303.

2. Wåhlin A, Ambarki K, Birgander R, Alperin N, Malm J, Eklund A. Assessment of craniospinal pressure-volume indices. AJNR Am J Neuroradiol. 2010 Oct;31(9):1645-50



Anders Eklund

About the Presenter. Anders Eklund has a position at the R&D-department of Biomedical Engineering at Umeå University Hospital, and since 2005 he holds an Associate Professorship in Biomedical Engineering at the Department of Radiation Sciences, Umeå University. His research field is models and measurement techniques concerning the physiological fluid dynamics. Together with neurology professor Malm Eklund has published more than thirty journal papers within the field of hydrocephalus. He is currently the Secretary/Treasurer for the International Society of Hydrocephalus and CSF disorders.

Coupled Simulation of the Cardiovascular and Cerebrospinal Fluid System

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³ Department of Magnetic Resonance Image Processing in University Hospital of Amiens, France

Abstract. Research and clinical evidence have demonstrated a coupling between the cardiovascular and CSF system. The coupling between these two systems is considered to be important to understand the pathophysiology of cerebrovascular and craniospinal disease. The goal of the present work is to expand the 1D cardiovascular model, previously developed in our laboratory (1), to encompass the spinal cord arterial network and couple it to a simplified CSF system model to examine the relation of spinal cord blood flow (SCBF) and CSF pulsations along the spinal subarachnoid space (SSS).

Methods. Coupling of the cardiovascular and CSF system was accomplished by a transfer function, based on measurements from 17 healthy subjects, relating total cerebral blood flow and CSF pulsations at the craniospinal junction. A 1D tube model of the SSS was constructed based on *in vivo* measurements.

Results. The properties and anatomy of the spinal cord arterial network and SSS were found to have an impact on pressure and flow in the blood and CSF. Fig. 1 shows the results for spinal cord blood (a[†]) and SSS CSF pressure (b) at different locations along the spine (0 cm is at the craniospinal junction). Delay between the SCBF and CSF pulsation (c) was found to vary depending on location along the spine and CSF system elasticity coefficient (k_e in Fig 1c). Overall, the CSF wave propagation results supported that the 1D tube model resulted in *in vivo* like wave phenomena in terms of pressure, flow, and wave speed.

SCBF results indicated that the cervical, thoracic and lumbar spinal cord each had a signature pressure and flow waveform shape. The spinal cord vascular anatomy (e.g. connectivity and dimensions) was found to have an impact on pressure and flow. For modeling the connection of cerebral blood and CSF flow the transfer function approach served to reproduce an *in vivo* like CSF flow waveform.

Conclusion. The coupled cardiovascular and CSF system model provides predictions about the flow and pressure environment present in the spinal cord and SSS. More detailed measurements about the CSF system are needed to improve and validate the model. A validated model could improve understanding of healthy physiological conditions and of vascular and craniospinal pathologies.

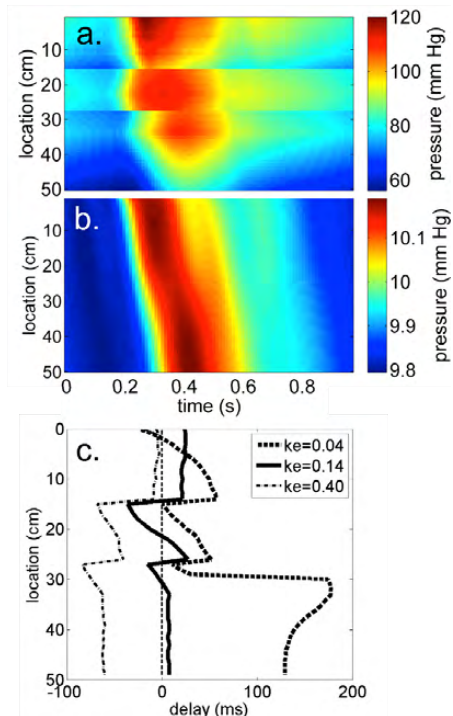


Fig. 1. a) Simulated distribution of blood pressure in the spinal cord arterial network as a function of time and distance from the craniospinal junction (junction is at 0 cm). b) Axial distribution of CSF pressure in the SSS. c) Axial distribution of delay between arrival of spinal cord and CSF pressure pulsations in the SSS (delay based on peak pressure gradient of pressure waveform).

1. Reymond P, et al. Validation of a one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol 297: H208-222, 2009.

[†] Note, the horizontal color breaks in Fig. 1a are a result of the spinal cord blood flow being considered to be supplied segmentally within the spinal cord tissue.



Bryn Martin

About the Presenter. Bryn Martin is a post-doctoral fellow at the EPFL Laboratory of Hemodynamics and Cardiovascular Technology. He completed a Ph.D. in Mechanical Engineering at the University of Illinois at Chicago on the biofluid mechanics of syringomyelia and Chiari malformation and served his first post-doctoral fellowship at the University of Akron. Bryn's research interests include cerebrospinal and cardiovascular fluid mechanics with experience in MRI, cerebrovascular ultrasound, medical instrumentation and sleep disorders.

Retinoid signaling pathway proteins in human arachnoid membrane: Role in regulating intracranial pressure

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² Biomedical Engineering, The Ohio State University, Columbus, Ohio, USA

³ College of Medicine, The Ohio State University, Columbus, Ohio, USA

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Abstract. Normal cerebrospinal fluid (CSF) homeostasis relies on a careful balance between CSF production and absorption. Alterations in the rate of CSF formation, absorption, or outflow resistance can lead to an increase in intracranial pressure (ICP), causing multiple neurological disorders. The arachnoid membrane (AM) is a major route for CSF outflow and subsequent regulation of intracranial pressure. The subarachnoid space (SAS) acts like a variable fluid capacitor, taking up excess CSF when needed or giving it up if necessary. The ability of the SAS to do so is affected by age and other factors that stiffen the arachnoid trabeculae.

Retinoids have been shown to affect ICP in both animal models and manifested in humans as secondary pseudotumor cerebri after administration of all-trans retinoic acid. Vitamin A is stored in an inactive esterified form mainly in liver and adipose tissue. Retinol is metabolized to retinaldehyde (Rald) and then to retinoic acid (RA), long believed to be the only systemically active form of vitamin A. Rald is generated by the action of alcohol dehydrogenase-1 (Adh1) on retinol, and Rald is metabolized by retinaldehyde dehydrogenase-1 (Aldh1). Although nuclear receptors, retinoic acid receptor (RAR), retinoid X receptor (RXR), and membrane retinol binding protein receptors (STRA6) have been localized in other areas of the brain, the presence of these receptors in the AM and granulations is unknown.

We investigated the presence of cellular retinoic acid binding protein II (CRABP II), transthyretin (TTR), and retinol binding protein4 (RBP4), the nuclear receptors, RAR alpha and beta, and RXR alpha by immunoblot and immunohistochemical techniques in human AM, cultured arachnoidal cells and AM tissue lysates. ELISA was used to quantify the presence of the enzymes Adh1 and Aldh1.

Expression of CRABP II was increased in the cytosolic fraction as compared to the nuclear fraction by approximately 230% in arachnoidal cells suggesting the ligand, retinoic acid, was minimally present. RBP4 was found to be localized primarily to the choroid plexus (CP) while TTR expression was primarily localized in the CP, with lesser amounts in the AM and granulations, suggesting paracrine activity between the CP and AM. In arachnoidal cells, RXR alpha, RAR alpha and RAR beta receptor protein levels were increased in the nuclear fraction as compared to the cytosolic fraction by 145%, 160% and 198%, ($p < 0.01$), respectively. Both Adh1 and 3 isoforms of Aldh1 were found in arachnoid membrane and cells. The predominant form of Aldh1 in arachnoid membrane is Aldh1a3.

The presence of Adh1 and Aldh1 prove that arachnoidal cells can produce retinoic acid, and that the retinoic acid production depends on Aldh1a3 enzyme, while in other tissues Aldh1a1 is the most abundant form. The presence of these receptors and binding proteins in the human AM provides further evidence of a role for vitamin A and its metabolites in the regulation of intracranial pressure, perhaps directly via altered metabolism and transcriptional regulatory changes in the arachnoid cells.



Deborah Grzybowski

About the Presenter. Deborah Grzybowski received the B.S. and M.S. degrees in chemical engineering in 1979 and 1980 respectively, and the Ph.D. degree in biomedical engineering in 2000 from The Ohio State University. She worked at Battelle Memorial Institute for 12 years and is currently a Research Assistant Professor in Ophthalmology at The Ohio State University where she also teaches courses in Engineering Education Innovation Center. Dr. Grzybowski's research focuses on understanding CSF outflow using in vitro and ex vivo models.

CSF space phantom and coupling of cerebral arterial inflow with cerebrospinal fluid dynamics: Highlights from the SmartShunt project

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³ Institute for Dynamic Systems and Control, ETH Zurich, Zurich, Switzerland

⁴ Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland

⁵ Neuroimaging Research Unit, Department of Neurology, Medical University Graz, Graz, Austria

⁶ Biostatistics Unit, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland

Abstract. We will present two highlights from the *SmartShunt* project funded by the Swiss National Science Foundation. *SmartShunt* aims at conducting the basic research necessary for the subsequent development of a smart cerebrospinal fluid (CSF) shunt for normal pressure hydrocephalus that addresses the key shortcomings of current shunt technology: infections, poor CSF flow control and mechanical failure. The envisioned shunt design will rely on a model of the interaction between cerebral blood flow and CSF dynamics, recognizing pathologic changes in this relation and adjusting the drainage rate accordingly. In order to establish a baseline for the interaction between blood and CSF, we have studied a set of healthy age and sex matched young and elderly volunteers using phase contrast MRI. We have further developed a dynamic CSF space phantom to be used as a test bed for the shunt (Fig. 1, left).

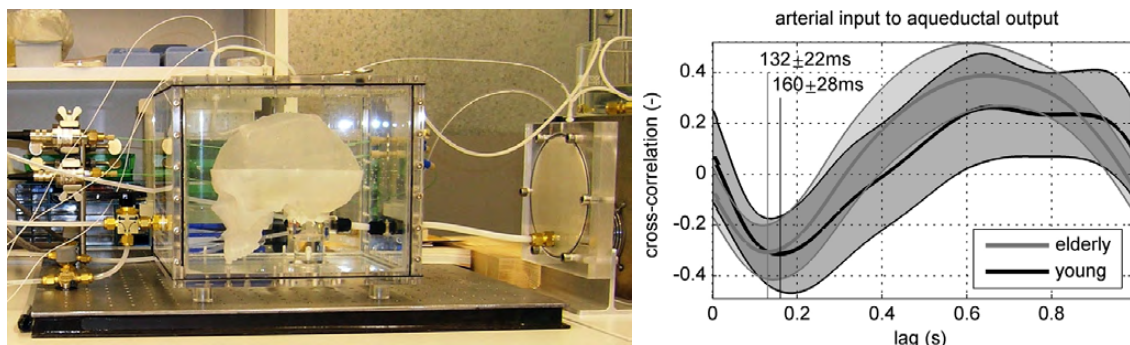


Fig. 1. *Left:* CSF space phantom setup with a silicone brain representation at the center. Tubing at the left connects to piston and syringe pumps for the generation of both pulsatile and steady flow patterns. *Right:* Cross-correlation of arterial blood inflow into the cranial space to aqueductal cerebrospinal fluid flow, depicting mean (bold line) and standard deviation (gray shading) of elderly (gray line) and young (black line) groups' results. The vertical lines indicate the mean delays from the maximum systolic peak blood flow to the maximum caudal aqueductal flows.

The phantom incorporates representations of the ventricular, as well as spinal and cranial subarachnoid spaces (SAS). CSF flow rates, e.g. through the aqueduct of Sylvius, production rates, pressure and origin of pulsation can be measured and controlled. SAS permeability can be adjusted. Access ports allow for CSF drainage through external shunts.

The MRI study showed significant differences between the young (24 ± 3 years) and elderly (70 ± 5 years) groups in the magnitudes of the frequency components of CSF flow in the aqueduct and spinal canal, as well as the combined carotid and vertebral arterial flows. The males' aqueductal CSF stroke volumes and average flow rates are significantly higher than those of the females. Cross-correlations between arterial blood and CSF flow reveal significant age-dependence of phase-shift between these (Fig. 1, right).



Vartan Kurtcuoglu

About the Presenter. Vartan Kurtcuoglu received his M.E. degree from ETH Zurich after completing his diploma thesis at the French National Center of Scientific Research, CNRS PROMES. During his PhD studies at ETH he studied CSF flow in the ventricular space. He currently holds a group leader and lecturer position at ETH Zurich, and is a visiting scientist at Brigham and Women's Hospital and Harvard Medical School, Boston. He is PI of several national and international research projects in the areas of hemodynamics and CSF flow, including the *SmartShunt* project.

How the EC Marie Curie Actions could contribute to the cerebro-spinal fluid scientific community

Karim Berkouk

European Commission, DG for Research and Innovation, Marie Curie Actions, Brussels, Belgium

Abstract. The aim of this talk is to inform CSF scientific community of the funding opportunities open within the 7th EU Framework programme for Research and Development (FP7). The talks will provide information (aim, description, rules) on the three main EU funding instruments of interest to the scientific community: collaborative grants, Marie Curie Actions and ERC grants, with a strong emphasis on the Marie Curie Actions. The presentation will be tailored specifically to the needs of the Cerebro-Spinal fluid scientific community.



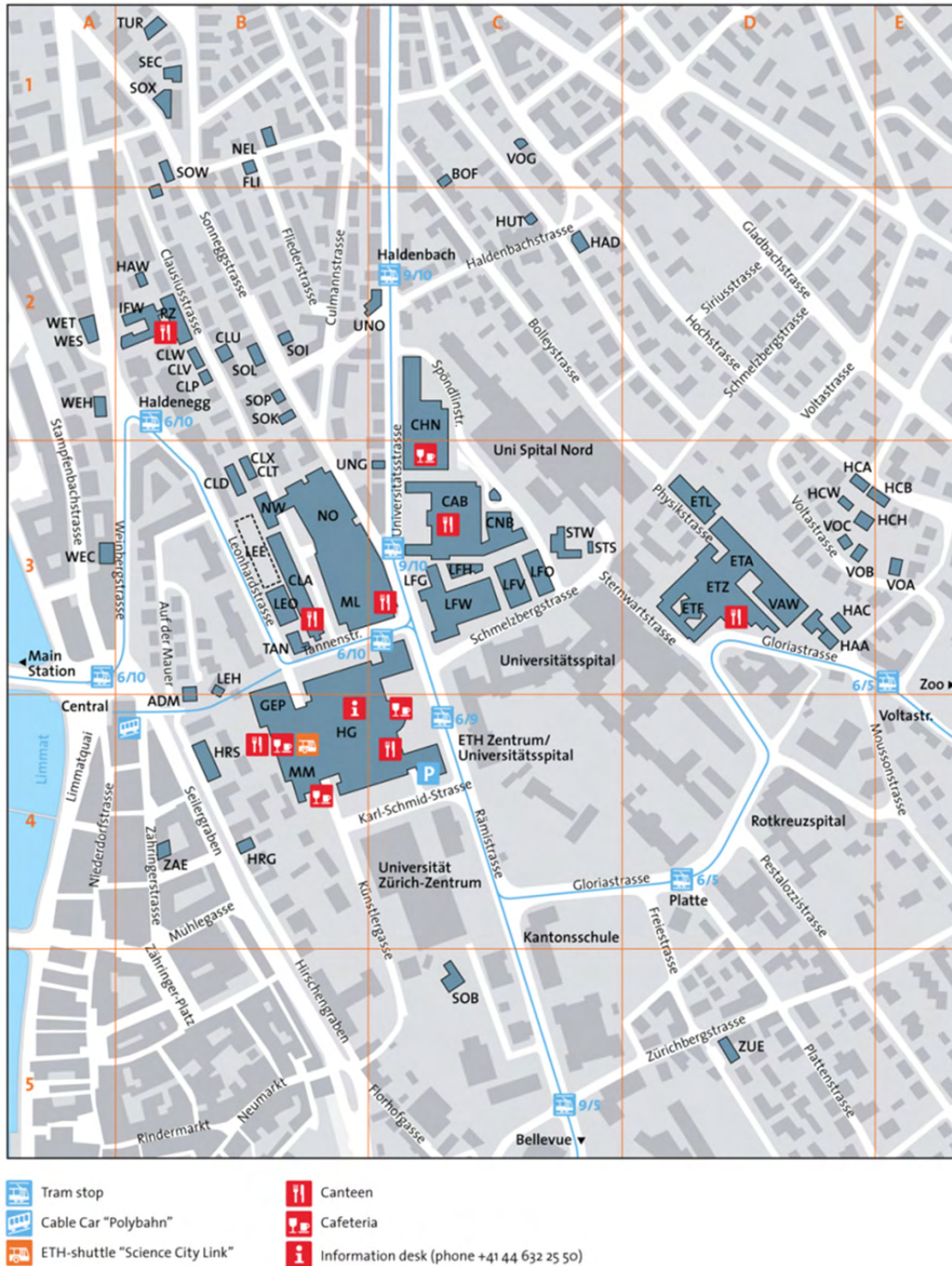
Karim Berkouk

About the Presenter. Karim Berkouk. Karim Berkouk was born in 1970 close to Toulouse in France. He studied Fluid Mechanics at the University of Paul Sabatier (Toulouse) before completing his PhD at the University of Warwick (UK) on Syringomyelia (1999). He then held various research positions in Exeter (UK), INSERM (France) and the University of Cambridge (UK), where he mainly focused on brain medical images. Since 2004, he joined the European Commission in the Directorate General for Research and Innovation. He is now the Head of Sector for Individual and Excellence grants in the Marie Curie Unit.

General Information

Venue: Scientific Sessions, Breakfast and Lunch

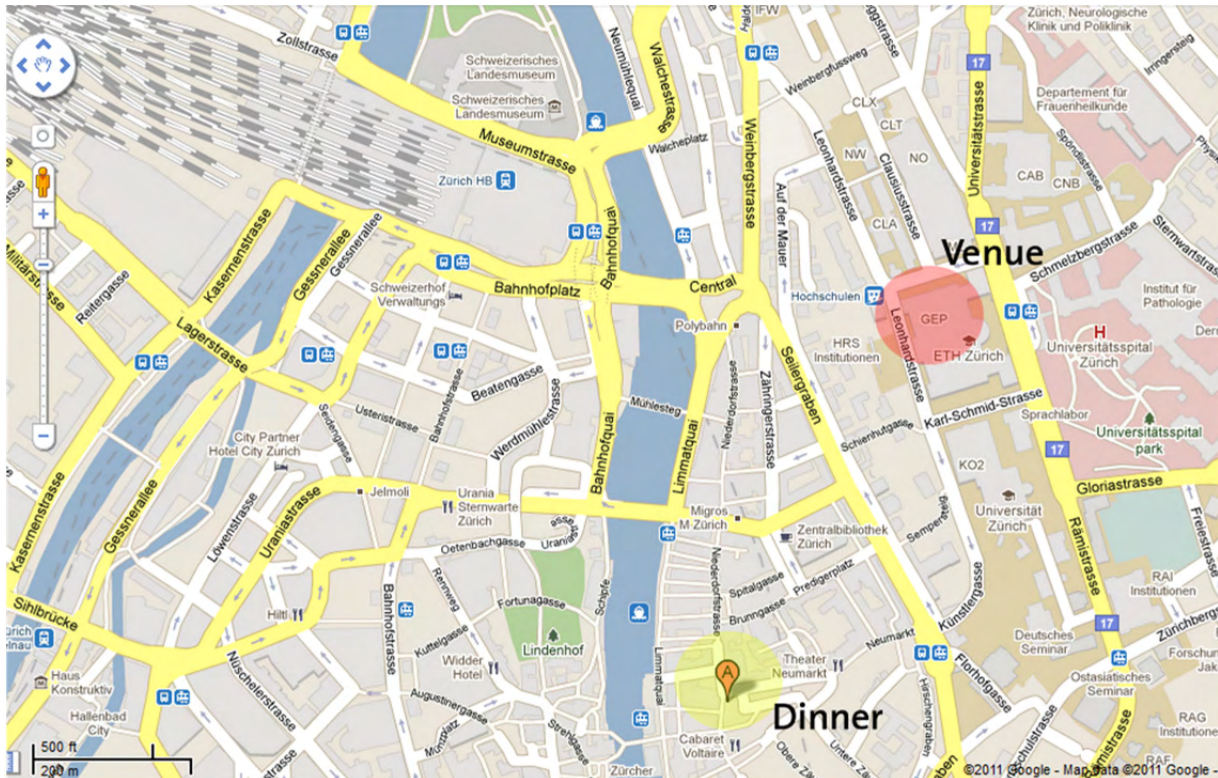
The symposium is held at the city center campus of ETH Zurich, Switzerland, in the GEP Pavillon (see Map 1 below, top of square B4). The campus can be reached by foot or with trams 6 and 10 from Zurich main train station. It can also be reached by the Polybahn cable car (not wheel chair accessible) from Central square (Map 3).



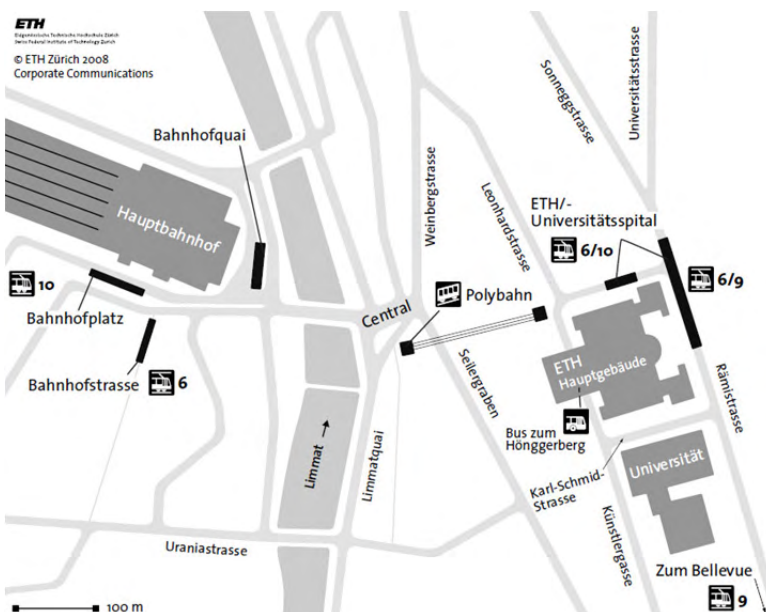
Map 1. ETH Zurich city center campus.

Venue: Symposium Dinner

The symposium dinner will take place on Friday, July 8 at 19h in the old town of Zurich at Zunfthaus zur Schmieden, Marktgasse 20 (Map 2). The location can be reached from the main train station either by foot (700m) or by tram 4, stop Rathaus, plus a short walk (150m).



Map 2. Dinner location.



Map 3. Zurich main train station and surroundings.

Connectivity

Power outlets (230V, Type J SEV 1011 socket) and internet access are provided for the participants' convenience. The WLAN connection parameters are as follows:

SSID: public
Username: csfzurich
Password: flow2011

Information for Speakers

Plenary speakers are given 20 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 25min. Keynotes will be 60 minutes including time for discussion and transition.

Both Windows 7 and Mac OS X presentation computers with the latest versions of PowerPoint, Keynote, OpenOffice Impress, Adobe Acrobat and Matlab are provided. Additional software will be installed upon the speakers' requests. The use of separate laptops is discouraged: The speakers are requested to upload their talks to the symposium server by July 6. The corresponding link has been provided by e-mail.

25 Zürich tips

- 1 Augustinergasse**
Narrow street with attractive oriel windows and small shops, restaurants and cafés
- 2 Bahnhofstrasse**
Zürich's shopping mile with international fashion labels, jewelry, watches and department stores
- 3 Chinese Garden**
One of the most beautiful Chinese gardens outside China with restaurants on the lake within walking distance
- 4 Fraumünster Church**
Former convent housing female members of the aristocracy, with famous windows by Marc Chagall
- 5 Grossmünster Church**
Church associated with many legends and the starting point of the Reformation in German-speaking Switzerland with the Kalisurm, which is open to the public and offers breathtaking views of the city
- 6 Kunsthaus Zürich**
Museum of Fine Arts, with important collection of portraits, sculptures, photos, and videos
- 7 Limmatquai**
Pedestrian precinct with shops, restaurants and cafés along the River Limmat
- 8 Lindenhof**
Former Roman customs station and modern-day viewpoint for the Old Town
- 9 Museum of Design**
Changing program of exhibitions on design, visual communication, architecture and media
- 10 Museum Rietberg**
One of the leading centers for non-European art
- 11 Nieder- and Oberdorf**
Multicultural pedestrian precinct in the Old Town with over 2,000 years of history, and bars, shops, restaurants
- 12 Oberer Letten**
Riverbank path and riverside pool with bar, beach volleyball courts and parties
- 13 Opera House**
Presents Europe's most numerous opera premieres and Heinz Spoerli's Zürich Ballet
- 14 Paradeplatz**
Zürich's most expensive square with galleries, banks, and luxury shops
- 15 Schanzengraben**
Former ski-jumping installation, now a promenade right by the river, with men's pool and open-air bar
- 16 Schauspielhaus theater**
Largest theater in Switzerland
- 17 Schiffbau**
Old shipbuilding hall with branch of the Schauspielhaus theater, jazz club, bar and restaurant
- 18 Schipfe**
Narrow artisan street in one of the oldest quarters of the city right by the River Limmat
- 19 Sihcity**
New district of the city with restaurants, cinema, and wellness centers
- 20 St. Peter's Church**
Zürich's oldest parish church with the largest clock face (8.7 m/ 28.5 ft)
- 21 Swiss National Museum**
Over 100-year-old 'fairytale castle' with the country's largest collection of Swiss cultural history
- 22 Tonhalle concert hall**
Concert hall with world-class acoustics
- 23 Viaduct Arches**
Market hall under a former railway viaduct with shops, restaurants and galleries under old viaduct arches
- 24 Zurichhorn**
Viewpoint with specialty restaurants and open-air cinema
- 25 Zürich-West & Ausserrohrli**
Former industrial district where nightlife, gastronomy, and the creative scene now thrive

More Zürich tips

zuerich.com/gastronomy
zuerich.com/culture
zuerich.com/nightlife
zuerich.com/gosopping
zuerich.com/nature





16 Zürich region excursion tips

- 1 Atzmännig – fun for all the family**
With its toboggan run, leisure park and rope park, Atzmännig offers thrills and a fun day out for all the family. Let the charliff take the strain on the way up – a mountain restaurant, hiking routes and sensational views await you.
- 2 Rapperswil – enjoy the Mediterranean lakeside promenade**
The lovely Old Town invites guests to take a stroll. Rapperswil is a popular destination for boat trips from Zurich, not only because of Rapperswil castle, the rose garden, and Switzerland's longest wooden bridge, but also because of the wonderful Alpine panorama.
- 3 Alpnahor – action, 365 days a year**
At Alpnahor, three adrenaline-producing slides totaling 1,500 meters in length provide plenty of thrills. Those in search of relaxation are also sure to get their money's worth in the Alpa thermal baths and the 36°C/96.8°F iodine saline thermal spa.
- 4 Einsiedeln – culture, sport, nature**
The beautiful countryside around Einsiedeln lends itself to a wide range of sports and exercise. The world-famous Benedictine monastery in the town of Einsiedeln itself forms an imposing focal point. Find out more about it on a guided tour of the monastery including a viewing of the unique library.
- 5 Hölzgrotten, Baar – a magical underground kingdom**
Immerse yourself in the fairytale underground world of Hölzgrotten caves. Located in the wildy romantic Lörz ravine, rock formations in multiple color shades and mystical small lakes entrance adults and children alike.
- 6 Zug – a combination of town and countryside**
Historic city walls and towers, modern shopping streets and delicious cherry gateaux, always accompanied by relaxing views of the lake and the foothills of the Alps. A small canyon, a great experience.
- 7 Zürich Wildlife Park – the rhythm of nature**
Experience wildlife right outside the city of Zurich at Langenberg in Langnau am Albis, you can watch numerous wild animals in the wild. Fascinating exhibitions also await you at the Sihlwald visitor center.
- 8 Uetliberg – stunning views**
From the Uetliberg, Zurich's local mountain, you can enjoy magnificent views of the city, the lake, and the Alps. There's plenty to discover along the marked hiking trails, the mountain bike route, and the Planet Path.
- 9 Boat trips – a delightful experience**
Enjoy a relaxed boat trip on Lake Zurich in summer or winter. Trips include everything from short and long circular tours to various themed trips. Immerse yourself in the world of dreamboats and take a trip on the BBQ, Sals, Fondue, DolceVita or Oldies' Boat.
- 10 Lake Zurich Trail – an all-round experience**
The 124-kilometer/77 miles circular trail around Lake Zurich, which is divided into ten stages, shows the diversity of the region from its best side. Along the route, there are historic towns, villages and castle parks, as well as untouched lakeside landscapes and extensive woodland.
- 11 Zürich Zoo – for pure adventure**
Take a journey of discovery through three continents. Get active as a researcher yourself and experience the animals close up in their natural habitats, including the Masoala rainforest.
- 12 Castle Kyburg**
Circular walls, towers, and stately residential quarters are symbols of the power of the former regional dynasties (Kyburg, Habsburg, Zurich) on a hill visible from afar. In the interior, an internationally recognized exhibition tells the tale of castle life over the past 800 years.
- 13 Technorama – Switzerland's science center**
At Technorama Winterthur, you can test your skill at over 500 science and technology experimentation points. Visitors of all ages can learn lots of interesting facts about phenomena of the world of science and technology.
- 14 Winterthur – photographic capital**
Be entranced by the sounds of the music college, laugh heartily at the Casino Theater, admire the world-class art treasures, and visit Europe's most innovative photographic center.
- 15 The Rhine Falls – guaranteed water spectacle**
The Rhine Falls near Schaffhausen provide the grandiose spectacle of Europe's largest waterfall. It's worth taking a boat trip and visiting the Adventure Park. There, children over four and those in search of adventure can go from tree to tree, while enjoying breathtaking views of the Rhine Falls.
- 16 Baden – city of diversity**
The spa town of Baden offers surprising diversity: restaurants and bars, music venues, the Grand Casino, museums and theater, the unique thermal springs – all an expression of the famous Baden spirit.

First CSF Hydrodynamics Symposium – Schedule

Day 1 – Friday, July 8, 2011

7 ⁰⁰	Breakfast	8 ¹⁵
8 ¹⁵	Introduction	9 ³⁰
9 ³⁰	Session A	10 ³⁰
10 ³⁰	Morning Coffee Break	11 ⁰⁰
11 ⁰⁰	Session B	13 ⁰⁰
13 ⁰⁰	Lunch Break	14 ⁰⁰
14 ⁰⁰	Session C	16 ⁰⁰
16 ⁰⁰	Afternoon Coffee Break	16 ³⁰
16 ³⁰	Session D	17 ³⁰
19 ⁰⁰	Symposium Dinner	21 ⁰⁰

Day 2 – Saturday, July 9, 2011

7 ⁰⁰	Breakfast	8 ⁰⁰
8 ⁰⁰	Introduction	9 ⁰⁰
9 ⁰⁰	Session E	10 ⁰⁰
10 ³⁰	Morning Coffee Break	10 ⁴⁵
10 ⁴⁵	Session F	12 ⁴⁵
12 ⁴⁵	Lunch Break	13 ⁴⁵
13 ⁴⁵	Session G	16 ¹⁵
16 ¹⁵	Conclusion	16 ³⁰
16 ³⁰	Discretionary Plenary Discussion and Closing Coffee	18 ⁰⁰