2ND CSF DYNAMICS SYMPOSIUM

Feinstein Institute For Medical Research, Manhasset, New York

June 24 & 25, 2013

CSF
Chiari & Syringomyelia Foundation

THE MONKTON INSTITUTE

Neuroscience Research Australia
Discover. Conquer. Cure.

The University of Akron

ORGANIZED BY BRYN MARTIN, LYNNE BILSTON, & SHAOKOON CHENG

CSF HYDRODYNAMICS SYMPOSIUM SPONSORED BY

CSF
Chiari & Syringomyelia Foundation

Our Mission

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

About Us

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

Many recognized world-class physicians, scientists and professionals agreed to collaborate and form a superior Scientific Education & 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 over one million families affected by CM, SM, and related disorders.

For More Information

WWW.CSFINFO.ORG

WELCOME TO THE CSF SYMPOSIUM

On behalf of the Chiari & Syringomyelia Foundation and the organizing team, we welcome you to the 2nd International CSF Dynamics Symposium in Manhasset, New York. This year we have a diverse group of researchers with expertise in all aspects of CSF dynamics. Our aim is to provide a stimulating symposium that will showcase excellent researchers, increase collaboration between members of the group, and to help raise the field of CSF dynamics to greater notoriety.

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

Bryn Martin, Lynne Bilston, Shaokoon Cheng

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Cover photos: Top photo, CC image by Erika39 via Flickr entitled *Empire State Building, Manhattan*. Bottom Photo: CC image by Simone Roda entitled *Brooklyn Bridge - New York City.*

SPONSORSHIP

The 2nd CSF Dynamics Symposium is sponsored by the Chiari & Syringomyelia Foundation made possible through generous support of The Monkton Institute.

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

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

FRAMEWORK OF THE 2ND CSF DYNAMICS SYMPOSIUM

The number of investigators conducting numerical and experimental simulations to better understand the dynamics of cerebrospinal fluid (CSF) has continued to increase since the 1st International CSF Dynamics Symposium held in Zurich, Switzerland. Building on this momentum, we have planned the 2nd International CSF Dynamics Symposium to continue exchange of ideas toward modeling of CSF.

Twenty-two invited speakers from around the world will present their research highlighting 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. Neurosurgeons and neuroscientists are present to lead a discussion on the challenges of translating engineering and physics analyses into clinically relevant results.

Invited speakers incur no fees to attend this two-day event. Breakfast, lunch and dinner are provided thanks to a generous sponsorship from the Chiari & Syringomyelia Foundation, which was made possible by the support of The Monkton Institute. The symposium is held in beautiful Manhasset, New York on the campus of The Feinstein Institute For Medical Research. All presentations will be video recorded and posted, with free access, on the web sites of the Chiari & Syringomyelia Foundation and the CSF Dynamics Society to maximize exposure of the symposium research ideas (www.CSFinfo.org and www.csfdynamics.org).

The symposium is organized by Bryn Martin, Lynne Bilston and Shaokoon Cheng. In his research, Dr. Martin uses experimental and numerical methods to understand the underlying mechanical forces involved in the pathophysiology of Chiari malformation, syringomyelia and hydrocephalus. Dr. Martin is the director of the newly established Conquer Chiari Research Center (chiari-research.org) and a Research Assistant Professor at the Department of Mechanical Engineering at The University of Akron, Ohio. Professor Bilston is a Senior Principal Research Fellow at Neuroscience Research Australia and Conjoint Professor in Medicine at the University of New South Wales. Dr Shaokoon Cheng is a Senior Research Associate at Neuroscience Research Australia and a Senior Lecturer in the Department of Engineering at Macquarie University.

ABOUT THE FEINSTEIN INSTITUTE

The Feinstein Institute for Medical Research comprises more than 1,500 clinicians, scientists and staff throughout the North Shore-LIJ Health System. Working in their labs and on clinical research programs, these researchers strive for medical breakthroughs that will lead to the development of new therapies and diagnostic tools. The Feinstein Institute puts effort into educating the next generation of scientists, including students from the Elmezzi Graduate School of Molecular Medicine and the Hofstra North Shore-LIJ School of Medicine.

The Feinstein Institute publishes the international peer reviewed journal, Molecular Medicine and all Molecular Medicine articles, starting with its first issue in 1994, are freely available on MolMed.org and in the US National Library of Medicine (NLM) at the National Institutes of Health. The Feinstein Institute hosts several prestigious academic events throughout the year:

- **The Centricity Series**: The Centricity Series is a full-day symposium that addresses a particular disease or disorder. Professionals and the public are invited to attend the seminar. Each Centricity Series is filmed and available on CentricitySeries.org, where viewers can earn continuing medical education (CME) credits.

- **The Merinoff Symposia**: The Merinoff Symposia provide a forum for thought leaders in patient care to gather for two days and discuss a disease state with the intention of discovering innovations that promise immediate improvement in patient care.

- **The Marsh and Match Lectures**: Scientists from around the world are invited to speak to the Feinstein Institute staff. The Match Lecture is given by Nobel Laureates. The Marsh Lecture is given by other renowned scientists who share their expertise and establish collaborations with Feinstein Institute investigators. During these events, knowledge is shared to create new discoveries so that improvements in patient care can be achieved.

SCHEDULE OF EVENTS

DAY 1 – MONDAY, JUNE 24, 2013

7:00	**BREAKFAST**
8:30	**Opening Remarks** *Bryn Martin, Lynne Bilston, Shaokoon Cheng*
	PLENARY TALK Chair: Lynne Bilston
8:45	**Fine Structure Of CSF And Interstitial Fluid Spaces And Their Drainage Pathways From The Human Central Nervous System** *Roy Weller*
	SESSION A: EFFECT OF MICROANATOMY ON CSF Chair: Lynne Bilston
9:45	**Spinal Cord Nerve Roots And Denticulate Ligaments Alter CSF Dynamics In The Upper Cervical Spine** *Bryn Martin*
10:15	**Effect Of Spinal Micro-anatomy On CSF Flow Patterns** *Andreas Linninger*
10:45	**MORNING COFFEE BREAK**
	SESSION B: MODELING Chair: Shaokoon Cheng
11:15	**CSF Dynamics Society** *Vartan Kurtcuoglu*
11:30	**Quantitative Assessment Of The Differences In Spinal CSF Dynamics In Chiari Malformation** *Frank Loth*
12:00	**The Spinal Cord And Meninges As A Fluid-filled Elastic Waveguide In Syringomyelia** *A. (Tony) Lucey*
12:30	**LUNCH**
	SESSION C: IMAGING Chair: Mark Wagshul
13:30	**4D MR Flow Imaging: Experiences In Hemodynamics And Potentials In CSF Hydrodynamics** *Oliver Wieben*
14:00	**Blood And CSF Flow: What We Can See And What We Would Like To See Soon!** *Olivier Balédent*

14:30	**Novel MRI-based Measurements Of CSF Flow Dynamics In Pediatric Patients With Chiari Malformation** *John Oshinki*
15:00	AFTERNOON COFFEE BREAK
	SESSION D: CLINICAL Chair: Frank Loth
15:30	**What Role Does CSF Play In Vision Impairment In Astronauts** *Michael Keith Sharp*
16:00	**Mathematical Models Of CSF Dynamics: Uses And Challenges** *Harold Rekate*
16:30	**Dynamics And Solute Transport In CSF In Non-human Primates As Seen By Positron Emission Tomography** *Mikhail Papisov*
19:00	SYMPOSIUM DINNER AT 7PM AT LIMANI

DAY 2 – TUESDAY, JUNE 25, 2013

7:30	BREAKFAST
	2ND PLENARY TALK Chair: Vartan Kurtcuoglu
8:30	**Pathogenesis And Pathology Of Hydrocephalus** *Marc Del Bigio*
	SESSION E: IMAGING 2
9:30	**What Can Animal Models Teach Us About CSF Flow Dynamics?** *Mark Wagshul*
10:00	**Biomechanics Of Demyelination Processes: How Shear Wave Propagation Can Reveal Microarchitectural Changes** *Ralph Sinkus*
10:30	MORNING COFFEE BREAK
	SESSION F: MODELING 2 Chair: Shaokoon Cheng
11:00	**How To Use Experimental Data Effectively In Modeling** *Lynne Bilston*

CONTINUED ON NEXT PAGE →

SCHEDULE CONTINUED...

DAY 2 – TUESDAY, JUNE 25, 2013

11:30	**Near-Wall Ventricular Cerebrospinal Fluid Dynamics** *Vartan Kurtcuoglu*
12:00	**On The Assumption Of Laminar CSF Flow In The Spinal Canal** *Kent-Andre Mardal*
12:30	LUNCH
	SESSION G: SPINAL CORD Chair: Bryn Martin
13:30	**Potential Cerebrospinal Fluid Flow Pathways In The Development Of Syringomyelia** *Shaokoon Cheng*
14:00	**Cerebrospinal Fluid And Spinal Cord Morphology Changes In The Hours After Spinal Cord Injury: Results From Novel Porcine Model** *Peter Cripton*
14:30	**Dynamic Cerebrospinal Fluid Pressure During Experimental Contusion Spinal Cord Injury: Results From Novel Porcine And Synthetic SCI Models** *Claire Jones*
15:00	AFTERNOON COFFEE BREAK
	SESSION H: MODELING 3 Chair: Lynne Bilston
15:30	**A Fractional Pressure-Volume Model Of Cerebrospinal Fluid Dynamics: Marmarou's Model Revisited** *Corina S Drapaka*
16:00	**A Pilot, Multi-scale Numerical Framework For Brain Mechanics** *Diane Dezelicourt*
16:30	**Closing Remarks** *Bryn Martin & Lynne Bilston*
17:00	DISCRETIONARY PLENARY DISCUSSION AND CLOSING COFFEE

KEYNOTE LECTURE

MONDAY, JUNE 24, 2013 – 8:45 TO 9:45

Session Chair: Lynne Bilston, *Neuroscience Research Australia, Randwick, NSW, Australia*

Roy Weller $8^{45} – 9^{45}$

Clinical Neurosciences, Faculty of Medicine, University of Southampton, UK

Keynote Lecture

Fine Structure Of CSF And Interstitial Fluid Spaces And Their Drainage Pathways From The Human Central Nervous System

SESSION A: MICROANATOMY & CSF

MONDAY, JUNE 24, 2013 – 9:45 TO 10:45

Session Chair: Lynne Bilston, Neuroscience Research Australia, Randwick, NSW, Australia

Bryn Martin 9 $^{45} – 10^{15}$

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

Spinal Cord Nerve Roots And Denticulate Ligaments Alter CSF Dynamics In The Upper Cervical Spine

Andreas Linninger 10 $^{15} – 10^{45}$

Laboratory for Product and Process Design, Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois, U.S.A.

Effect Of Spinal Micro-anatomy On CSF Flow Patterns

MORNING BREAK, SESSIONS RESUME AT 11:15 AM

FINE STRUCTURE OF CSF AND INTERSTITIAL FLUID SPACES AND THEIR DRAINAGE PATHWAYS FROM THE HUMAN CENTRAL NERVOUS SYSTEM

Roy O, Weller[1], Cheryl A. Hawkes[1], Roxana O. Carare[1].

[1]Clinical Neurosciences, Faculty of Medicine, University of Southampton, UK row@soton.ac.uk

Abstract

Two extracellular fluids of the brain and spinal cord are cerebrospinal fluid (***CSF***) volume 140 ml and interstitial fluid (***ISF***) volume 280 ml.

CSF spaces: complex compartmentalisation of cerebral and spinal subarachnoid spaces by arachnoid mater [1].

Drainage of CSF: (a) via arachnoid granulations and villi

(b) lymphatic drainage of CSF via nasal lymphatics

Pathology of CSF**:** (a) hydrocephalus, (b) meningitis,

(c) subarachnoid haemorrhage (d) ? Syringomyelia

ISF: derived from the blood and occupies narrow extracellular spaces in brain and spinal cord

Drainage of ISF: (a) diffusion through the extracellular spaces (b) bulk flow along 100-150nm wide basement membranes in walls of capillaries and arteries to regional lymph nodes [2, 3] (c) motive force for perivascular drainage of ISF may be contrary waves that follow vascular pulsations.

Pathology of ISF: (a) drainage of ISF appears to reduce with ageing of arteries and in Alzheimer's disease [4] (b) lymphatic drainage of ISF has immunological significance.

Unsolved problems - CSF: (a) effects of compartmentalisation of subarachnoid spaces on CSF flow

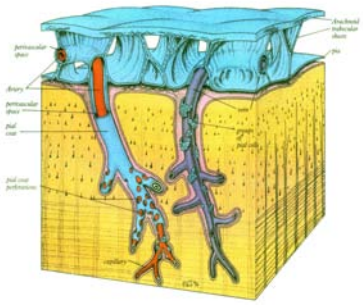
(b) relationships of CSF to brain and spinal cord tissue

(c) immunological significance of lymphatic drainage of CSF

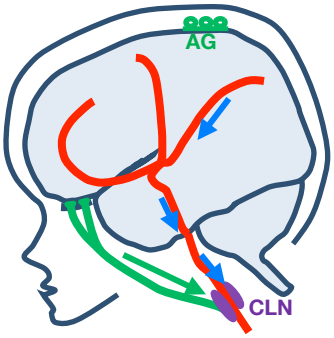
Unsolved problems - ISF: (a) motive force for perivascular drainage of ISF: possibly generated by pulse waves (b) porosity, compliance and connectivity of perivascular drainage pathways (c) interrelationships between ISF and CSF and their drainage pathways (d) deleterious effects of ageing and arteriosclerosis (stiffening of artery walls) on ISF drainage

(e) failure of ISF drainage in Alzheimer's disease and its effect on immunotherapy.

(f) immunological significance of lymphatic drainage of ISF.



Surface of the brain: Arachnoid - blue. Brain - yellow



CSF drains into blood through arachnoid granulations **(AG)** and to lymph nodes **(CLN)** **(green line)**. Perivascular drainage of ISF (**blue arrows**) to cervical lymph nodes **(CLN)**

1. Weller RO (2005) Microscopic morphology and histology of the human meninges. Morphologie 89:22-34

2. Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JAR, Perry VH, Weller RO (2008) Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries. Significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathology and Applied Neurobiology 34:131-144

3. Weller RO, Djuanda E, Yow HY, Carare RO (2009) Lymphatic drainage of the brain and the pathophysiology of neurological disease. Acta neuropathologica 117:1-14

4. Hawkes CA, Gatherer M, Sharp MM, Dorr A, Yuen HM, Kalaria R, Weller RO, Carare RO (2013) Regional differences in the morphological and functional effects of aging on cerebral basement membranes and perivascular drainage of amyloid-beta from the mouse brain. Aging cell 12 :224-236.

About the presenter. Studied medicine at Guy's Hospital in London (MD, PhD) and following a Fellowship in New York and clinical posts in London, moved to University of Southampton: Professor of Neuropathology responsible for the clinical diagnostic service, teaching and research. Major research has been: Effects of Hydrocephalus on the brain in humans and experimental models: Structural aspects of cerebral and spinal leptomeninges: Structural, Functional and Pathological aspects of Perivascular Drainage of Interstitial Fluid from the brain especially in relation to Alzheimer's disease and Multiple Sclerosis.

SPINAL CORD NERVE ROOTS AND DENTICULATE LIGAMENTS ALTER CSF DYNAMICS IN THE UPPER CERVICAL SPINE

Soroush Heidari Pahlavian[1], Theresia Yiallourou[2], R. Shane Tubbs[3], Alexander Bunck[4], Francis Loth[5,6], Mark Goodin[7], Mehrdad Raisee Dehkordi[1,8], Bryn A. Martin[5,6]

[1]Department of Mechanical Engineering, University of Tehran, Tehran, Iran.
[2]Laboratory of Hemodynamics and Cardiovascular Technology, EPFL, Lausanne, Switzerland.
[3]Children's of Alabama, Department of Neurosurgery, University of Alabama, Birmingham, U.S.A. [4]Department of Radiology, [4]University of Muenster, Muenster, Germany.
[5]Conquer Chiari Research Center, University of Akron, Akron, OH, U.S.A.
[6]Department of Mechanical Engineering, University of Akron, Akron, OH, U.S.A.
[7]SimuTech Group, Hudson, OH, U.S.A.
[8]Hydraulic machinery institute, Department of Mechanical Engineering, University of Tehran, Tehran, Iran.

Abstract. Cerebrospinal fluid (CSF) dynamics in the spinal subarachnoid space (SAS) have been thought to play a pathophysiological role in syringomyelia, Chiari malformation, and a role in intrathecal drug delivery. Yet, the impact that fine anatomical structures, including nerve roots and denticulate ligaments (NRDL), have on SAS CSF dynamics is not clear. The NRDL been difficult to quantify with *in vivo* 3T anatomy and phase-contrast MRI. The aim of the present study was to determine the impact of NRDL on CSF dynamics in the cervical SAS.

Fig.1 Streamlines plots for models with NRDL (left) and without NRDL (right)

3D geometry of the cervical SAS was reconstructed based on manual segmentation of MRI images of a healthy volunteer and Chiari malformation patient. Idealized NRDL were designed and added to each of the geometries based on in-vivo measurments in literature[1] and confirmation by a neuroanatomist. CFD simulations were performed using ANSYS software (Ansys Inc., Canonsburg, USA) for the healthy and patient case with and without NRDL included. The following parameters were quantified within each model at nine axial segments: a) hydraulic diameter, b) peak velocity, c) bidirectional flow, d) Reynolds number based on hydraulic diameter, e) local Reynolds number based on external flow over the dorsal and ventral NR and DL, f) secondary flow parameter, g) peak magnitude of wall shear stress, h) integrated longitudinal impedance, and i) frequency of velocity perturbations caudal to NRDL.

Our results showed that NRDL had an important impact on CSF dynamics in terms of velocity field, flow patterns, pressure drop and longitudinal impedance. Overall, the NRDL increased fluid mixing phenomena and resulted in a more complex flow field. NRDL had little impact on CSF dynamics near the foramen magnum because NRDL are not present in this region. Comparison of the streamlines of CSF flow (Fig. 1) revealed that the presence of NRDL lead to the formation of vortical structures and remarkably increased the local mixing of the CSF throughout SSS.

1. Alleyne, C.H., Jr., et al., Microsurgical anatomy of the dorsal cervical nerve roots and the cervical dorsal root ganglion/ventral root complexes. Surg Neurol, 1998. 50(3): p. 213-8.

About the Presenter. Dr. Bryn Martin is an Assistant Research Professor in the Department of Mechanical Engineering at the University of Akron and the director of the Conquer Chiari Research Center. He completed his post-doctoral training at the Swiss Federal Institute of Technology in Lausanne, Switzerland under Prof. Nikolaos Stergiopulos. Dr. Martin earned a Ph.D. in Mechanical Engineering from the University of Illinois at Chicago in 2008 under Prof. Francis Loth. His research interest is in pathophysiology of the CSF system disorders with focus on Chiari malformation, syringomyelia and hydrocephalus.

EFFECT OF SPINAL MICRO-ANATOMY ON CSF FLOW PATTERNS

Andreas A. Linninger[1], Kevin Tangen[1], and Ying Hsu[1]

[1]Laboratory for Product and Process Design, Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois, U.S.A.

Abstract. Multiple neuropathologies such as hydrocephalus, Chiari malformation and syringomyelia exhibit significant changes in the cerebrospinal spinal fluid (CSF) flow pattern and dynamics of the cerebral and spinal subarachnoid spaces (SAS). Patient-specific CSF flow measurements using phase contrast magnetic resonance imaging (PC-MRI) in combination with computational fluid mechanics are beginning to provide a complete picture of CSF flow fields in normal subjects. Recently, a growing number of publications reflects the research interest in using PC-MRI with CFD to elucidate flow patterns also in neuropathologies. Especially, the role of the micro-anatomy including nerve roots and trabeculae in the spinal CSF flow has attracted the attention of several research groups. Our lab showed recently that CSF pulsatility and nerve roots play a significant role in the bio-distribution of anesthetics during intrathecal drug delivery. Our work also illustrates the formation of complex micro-mixing pattern which are attributable to nerve roots and trabeculae. Computational studies based on anatomical detail as well as fluid mechanical principles support the notion of micro-anatomical structures as inducers of mixing patters despite the low Reynolds numbers in spinal CSF flow. It is plausible that *pulsations* and *micro-anatomy* are important for preventing the formation of dead zones in the spinal SAS in which cell debris or metabolites might otherwise stagnate or even accumulate.

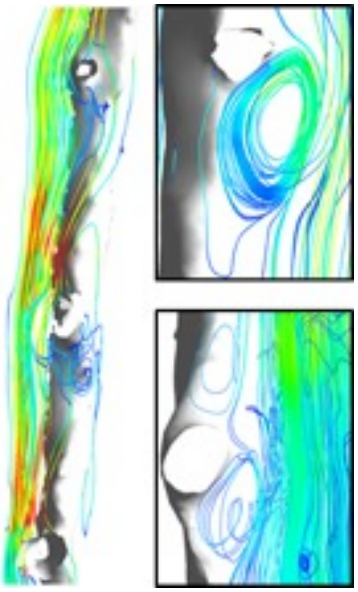


Fig. 1. Fluid flow patterns in the spinal SAS at nerve roots. Nerves with mixing patterns are displayed to the left. Magnified regions at right are of C4 and T7 nerves with eddies.

To quantify impact of micro-anatomy on CSF dynamics, we constructed a patient-specific model of the fluid filled spaces inside the CNS validated based on PC-MRI data. Nerve roots are reconstructed from patient-specific image data and incorporated into the full SAS model. We artificially added micro-anatomical detail below the image resolution threshold to quantify the effect of trabeculae on CSF flow. We systematically studied the effect of micro-anatomy in detailed spinal segments with nerves and varying density of arachnoid trabeculae. We compared complex flow profiles to simulations in structures lacking the anatomical detail. The effect on spinal flow resistance and their impact on complex flow profiles as a function of varying trabeculae density will be presented. The full spinal SAS model visualizes flow profiles at 31 nerve pairs over a complete cardiac cycle predicting the effect of successive nerve roots. Velocity and CSF pressure were predicted and compared to measurements Complex flow profiles were visualized with streamlines.

About the Presenter. Dr. Linninger's is a Professor of Bioengineering and at the University of Illinois at Chicago. His research areas focus on advancing the understanding of intracranial dynamics as it relates to hydrocephalus, drug delivery techniques targeting the central nervous system, and exploring the hemodynamics of cerebral blood flow. One objective aimed at generating a complete model of the central nervous system to better elucidate the interaction between hemodynamics and cerebrospinal fluid dynamics. Previous work examined healthy and hydrocephalic CSF flow patterns, pulsatile CSF flow in fluid structure interaction model, and three-dimensional prediction of CSF flow in the brain.

SESSION B: MODELING 1

MONDAY, JUNE 24, 2013 – 11:15 TO 12:30

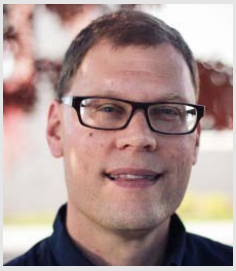
Session Chair: Shaokoon Cheng, *Neuroscience Research Australia, Randwick, NSW, Australia*

Vartan Kurtcuoglu

11^{15} – 11^{30}

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

CSF Dynamics Society



Frank Loth 11

^{30} – 12^{00}

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

Quantitative Assessment Of The Differences In Spinal CSF Dynamics In Chiari Malformation

A. (Tony) Lucey 12

^{00} – 12^{30}

Fluid Dynamics Research Group, Curtin University of Technology, Perth, Australia

The Spinal Cord And Meninges As A Fluid-filled Elastic Waveguide In Syringomyelia

BREAK FOR LUNCH, SESSIONS RESUME AT 1:30 PM

QUANTITATIVE ASSESSMENT OF THE DIFFERENCES IN SPINAL CSF DYNAMICS IN CHIARI MALFORMATION

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

[1] Department of Mechanical Engineering, University of Akron, Akron, Ohio, USA

[2] Conquer Chiari Research Center, University of Akron, Akron, Ohio, USA

[3] Department of Neurological Surgery, Cleveland Clinic Foundation, Cleveland, Ohio, USA

[4] Mayfield Chiari Center, Mayfield Clinic, Cincinnati, Ohio, USA

[5] Department of Radiology, Emory University School of Medicine, Atlanta, Georgia, USA

Abstract. A better understanding of CSF dynamics in Type I Chiari malformation (CM) may lead to clinically relevant parameters. CM classically characterized by cerebellar tonsil herniation (CTH) ≥ 5 mm below the foramen magnum. However, it is well-documented that CTH does not necessarily correlate with neurological symptom severity or surgical outcome. Because CTH creates a partial blockage of fluid movement between the cranial and spinal subarachnoid space (SAS), it is believed that the resulting changes to the hydrodynamic environment, specifically increased pressure on neural tissue, may contribute to the symptomatology of CM. Hence, quantification of hydrodynamic differences in the CM-affected cervical SAS may be useful to the diagnostic process. To this end, we investigated the hydrodynamic environment in the cervical spinal SAS of CM patients pre- and post-surgery in terms of SAS geometry (hydraulic radius), impedance to flow (longitudinal impedance), and compliance (CSF stroke volume, volumetric expansion, pulse wave velocity) and compared the results to values observed in healthy volunteers.

Subject-specific cervical SAS geometries were modeled from high-resolution T2-weighted anatomic MR images. CSF flow waveforms were obtained from pcMR images taken in the transverse plane at the C2, C6, and T2 levels of the spine. Stroke volume and volumetric expansion were computed from the resulting volume flow waveforms. Pulse wave velocity (PWV) was computed from time shifts in CSF velocity profiles obtained from high-temporal resolution pcMR scans in the midsagittal plane. Geometries and C2 flow waveforms were combined to create subject-specific computational fluid dynamics models from which longitudinal impedance was computed. Imaging has been completed for sixteen pre- and six post-surgery CM patients and six healthy volunteers. Group-wise distributions of all hydrodynamic parameters were compared using the Kruskal-Wallis test.

Results tabulated to date showed that pre-surgery CM patients had higher longitudinal impedance (median 436 vs. 243 dynes•s/cm5, $p<0.001$), smaller mean hydraulic radius of the SAS (median 0.67 vs. 0.93 cm, $p=.03$), and lower CSF stroke volume at C2 (median 0.46 vs. 0.71 cm3, $p<.01$) and C6 (median 0.37 vs. 0.58 cm3, $p=.04$) compared to healthy volunteers. Similar statistical differences were found between post-surgery CM patients and volunteers, but not between pre- and post-surgery CM patients. PWV was consistently measurable in healthy volunteers (median 4.2 m/s), but not in CM patients using the methods described. Hence, further development of our analysis methodology is necessary.

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 and CSF (2007, 2008, 2010 and 2011). Currently, he is Professor and the F. Theodore Harrington Endowed Chair in the Department of Mechanical Engineering at The University of Akron.

THE SPINAL CORD AND MENINGES AS A FLUID-FILLED ELASTIC WAVEGUIDE IN SYRINGOMYELIA

Novak S.J. Elliott[1], A.(Tony) D. Lucey[1], Duncan A. Lockerby[2], Andrew R. Brodbelt[3]

[1] Fluid Dynamics Research Group, Curtin University of Technology, Perth, Australia
[2] Fluid Dynamics Research Centre, University of Warwick, Coventry, U.K.
[3] The Walton Centre NHS Foundation Trust, Liverpool, U.K.

Abstract. We conduct an investigation of the wave-propagation characteristics of the spinal system in healthy and diseased configurations principally to serve as a reference for more anatomically-detailed models. We use the standard biomechanical analogue of cylindrical, axisymmetric solid and fluid layers. The spinal cord is represented as an elastic cylinder, which becomes an annulus containing inviscid fluid when a syrinx is included, and this is surrounded by inviscid fluid representing the cerebrospinal fluid (CSF) occupying the subarachnoid space, bound by a rigid dura. The two geometric configurations are schematically represented in the inserts of the upper (healthy) and lower (diseased) panels of Figure 1.

Axisymmetric harmonic motion of the cylindrical layers is described by a system of Helmholtz equations that is solved, using Chebyshev polynomials, as an eigenvalue problem. The formulation and its implementation are validated against published results for the asymptotic limit of infinite disturbance wavelength (e.g. [1]). We then present the dispersion diagrams that govern the wave mechanics for the full range of disturbance wavelengths and associated frequencies. Figure 1 shows the variation of disturbance wave speed with the inverse of its wavelength; the introduction of a syrinx sees the presence of two additional types of wave as compared with the healthy case.

We also present the eigenvectors corresponding to selected eigensolutions from Figure 1 for each of the wave types to illustrate the radial and axial motions of cord and fluid and the associated stress fields. We thereby identify which modes contribute to syrinx fluid sloshing and those that contribute to normal stress concentrations in the spinal-cord tissue adjacent to the syrinx. A parametric investigation of wave dependence upon variations of syrinx radius and the compressibility of the cord material is presented. Finally, we illustrate how the present results can be used to hypothesise mechanisms for the progressive growth of a syrinx.

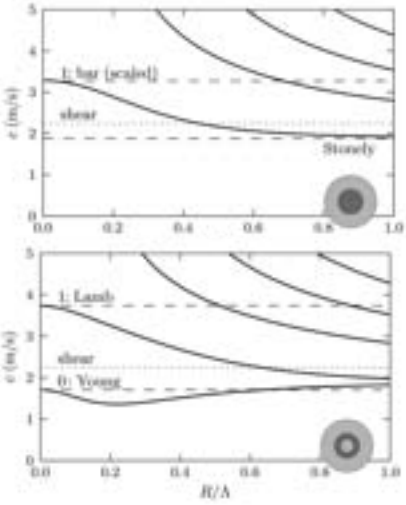


Fig. 1. Dispersion diagrams showing the variation of wave speed with the inverse of disturbance wavelength for healthy geometry (upper panel) and when a syrinx is present (lower panel); for the latter, there exist an additonal low-speed Mode 0 and a further high-speed Mode 2 (not shown) figure).

1. Cirovic, S (2009). A coaxial tube model of the cerebrospinal fluid pulse propagation in the spinal column. J. Biomechanical Engg. 131(2): 021,008.

A.(Tony) D. Lucey

About the Presenter. Tony Lucey is professor of Mechanical Engineering, former Dean of Engineering, and currently head of the School of Civil and Mechanical Engineering at Curtin University. He took his Bachelor and PhD degrees at the Universities of Cambridge and Exeter in the UK. He has held academic positions at the Universities of Exeter and Warwick in the UK and the Asian University of Science and Technology in Thailand, and industry experience as an aerodynamicist at British Aerospace PLC in the UK. He is recognized for his fundamental work in fluid-structure interaction and its applications in both engineered and biomechanical systems.

SESSION C: IMAGING 1

MONDAY, JUNE 24, 2013 – 13:30 TO 15:00

Session Chair: Mark Wagshul, *Albert Einstein College of Medicine, Bronx, NY, USA*
University of Utah, Salt Lake City, UT

Oliver Wieben

13^{30} – 14^{00}

Departments Of Medical Physics, Radiology, and Biomedical Engineering, University of Wisconsin-Madison, WI, USA

4D MR Flow Imaging: Experiences In Hemodynamics And Potentials In CSF Hydrodynamics

Olivier Balédent 14

^{00} – 14^{30}

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

Blood And CSF Flow: What We Can See And What We Would Like To See Soon!

John Oshinki 14

^{30} – 15^{00}

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

Novel MRI-based Measurements Of CSF Flow Dynamics In Pediatric Patients With Chiari Malformation

AFTERNOON BREAK, SESSIONS RESUME AT 3:30 PM

4D MR FLOW IMAGING: EXPERIENCES IN HEMODYNAMICS AND POTENTIALS IN CSF HYDRODYNAMICS

Oliver Wieben[1]

[1] Depts. Of Medical Physics, Radiology, and Biomedical Engineering, University of Wisconsin-Madison, WI, USA

Abstract. Recent developments in magnetic resonance imaging provide new insights into in vivo flow conditions. With 4D MR flow imaging, the velocity vector field over a large imaging volume can be recorded throughout the cardiac cycle and simultaneous with a high quality angiogram [1]. Most of the current research work on 4D MR Flow has focused on the imaging of the aorta, the heart, and cranial arterial vasculature. This presentation will review the methodology and limitations to derive hemodynamic parameters from the measured dynamic flow fields and provide clinical examples in the context of vascular diagnosis and discuss potential applications to CSF flow assessment.

The inherently co-registered data sets can be used to conduct velocity and flow measurements retrospectively at any desired location and plane orientation in the imaged volume. In regions of complex flow, advanced visualization techniques such as dynamic particle traces, streamlines, and vector plots can be generated to assist the clinician in identifying feeding and draining vessels, areas of retrograde flow, and mixing of blood from different contributing arteries. Moreover, additional hemodynamic parameters can be derived from the measured velocity fields including pressure gradients, wall shear stress and oscillatory shear index, transit times, kinetic energy, pulse wave velocity, and more [1]. Some of these parameters are thought to play a significant role in the development of cardiovascular disease and conceivably of CSF hydrodynamics and could possibly improve early diagnosis and treatment response.

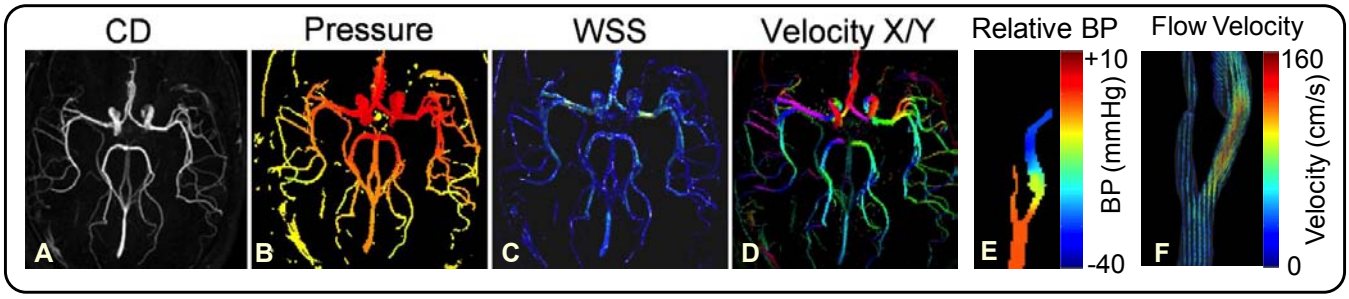


Fig. 1. Physiologic, Hemodynamic *Color Mapping* of the Cerebral Circulation from two representative 4D MR flow data sets. Panels A-D represent results from a cranial scan, displayed as a limited volume in an axial view. Panels E and F show results from a neck scan, here selectively visualizing one of the carotid bifurcations. *Panel A*: 3D mapping of cerebral arteries generated from the angiogram (complex difference – CD). *Panel B*: Blood pressure (BP) changes across the brain coded in color. *Panel C*: Wall shear stress (WSS) estimates from the measured velocity data. *Panels E & F*: Zoomed-in BP profile and CBF profile of the common carotid artery at bifurcation.

1. Markl M, Frydrychowicz A, Kozerke S, Hope M, Wieben O (2012). 4D flow MRI. J Magn Reson Imaging 36 (5):1015-36

Oliver Wieben

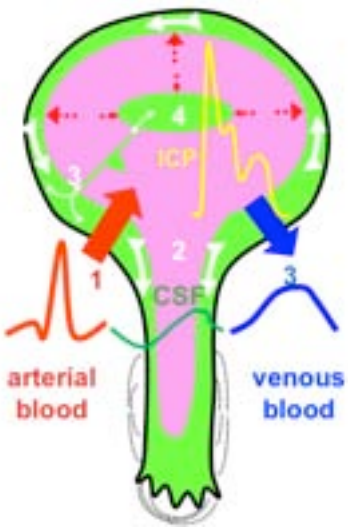
About the Presenter. Oliver Wieben is an Assistant Professor at the University of Wisconsin-Madison, where he is leading the Magnetic Resonance Flow Imaging group and co-directs the International Center of Accelerated Medical Imaging. He trained at the Universities of Karlsruhe and Freiburg in Germany, and the University of Wisconsin, USA. His primary research interest is the development of rapid cardiovascular MR imaging methods and their application to improve clinically relevant diagnosis. He currently focuses on data acquisition and image reconstruction for accelerated imaging as well as post-processing methods to facilitate comprehensive, non-invasive hemodynamic assessment of the vascular system.

BLOOD AND CSF CIRCULATION: WHAT WE CAN SEE AND WHAT WE WOULD LIKE TO SEE SOON

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

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

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



1. Marmarou, A., K. Shulman, et al. (1978). "A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics." J Neurosurg 48(3): 332-44.

2. Enzmann, D. R. and N. J. Pelc (1991). "Normal flow patterns of intracranial and spinal cerebrospinal fluid defined with phase-contrast cine MR imaging." Radiology 178(2): 467-74.

3. Baledent, O., M. C. Henry-Feugeas, et al. (2001). "Cerebrospinal fluid dynamics and relation with blood flow: a magnetic resonance study with semiautomated cerebrospinal fluid segmentation." Invest Radiol 36(7): 368-77.

4. Yamada, S., M. Miyazaki, et al. (2008). "Visualization of cerebrospinal fluid movement with spin labeling at MR imaging: preliminary results in normal and pathophysiologic conditions." Radiology 249(2): 644-52.

5. Miller, K., Ed. (2011). Biomechanics of the brain. Biological and Medical Physics, Biomedical Engineering. New-york, Dordrecht, Heidelberg, London, Springer Science+Business Media.

6. Stadlbauer A, Salomonowitz E, van der Riet W, Buchfelder M, Ganslandt O. (2010) Insight into the patterns of cerebrospinal fluid flow in the human ventricular system using MR velocity mapping. Neuroimage. 15;51(1):42-52.

7. Yiallourou TI, Kröger JR, Stergiopulos N, Maintz D, Martin BA, et al. (2012) Comparison of 4D Phase-Contrast MRI Flow Measurements to Computational Fluid Dynamics Simulations of Cerebrospinal Fluid Motion in the Cervical Spine. PLoS ONE 7(12)

8. Summers P, Staempfli P, Jaermann T, Kwiecinski S, Kollias S. (2006) A preliminary study of the effects of trigger timing on diffusion tensor imaging of the human spinal cord. AJNR Am J Neuroradiol.;27(9):1952-61

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

NOVEL MRI-BASED MEASUREMENTS OF CSF FLOW DYNAMICS IN PEDIATRIC PATIENTS WITH CHIARI MALFORMATION

John N. Oshinski[1], Kyle Pate[1,2], Kelsie Riemenschneider[2], Nilesh K. Desai[1], Joshua Chern[2],

[1] Department of Radiology, Emory University School of Medicine, Atlanta, GA USA

[2] Children's Healthcare of Atlanta, Atlanta, GA USA

Introduction. Phase-contrast magnetic resonance (PCMR) studies of cerebral spinal fluid (CSF) dynamics in pediatric subjects have shown that CSF velocities are higher in children than adults, CSF velocities are elevated in subjects with Chiari I compared to normal children, and CSF velocities are reduced after decompression surgery (1-5). However, the majority of these studies have been small, or the studies have mixed adult and pediatric subjects in the results. We have undertaken a study to use MRI to study subarachnoid space (SAS) geometry, CSF flow dynamics, and tonsilar motion in a series of pediatric subjects with Chiari malformation. The overall goal of the study is to longitudinally evaluate a series of pediatric patients with various degrees tonsilar descent, both with and without syringomeylia. In this abstract, we will discuss the findings on: 1) differences in CSF flow dynamics in Chiari patients with and without syringmeylia, and 2) differences in tonsilar motion between symptomatic and non-symptomatic patients.

Methods. Nineteen (19) subjects have been studied (age 9.6 ± 4.3 years), nine (9) subjects had syringomyelia at the time of the scan. An MRI protocol was followed which included: 1) T1 and T2 sagital scan through the brain/c-spine and a high-resolution 3D axial T2-SPACE scan through the brain and c-spine to assess geometry, 2) transverse ECG-gated PCMR cine scans at the foramen magnum (FM) and C6 and a sagital PCMR scan through the midline of the c-spine to assess velocity and flow, 3) sagital ECG-gated cine balanced steady-state free procession (SSFP) scan through the midline of the c-spine to measure spinal cord motion. Analysis of PCMR data and tonsil motion was done in the program FLOW (AZL Lieden, NL)

Results. The study subjects were divided into groups based on the presence or absence of a syrinx at the time of the scan. Analysis of PCMR data indicated that subjects with a syrinx at the time of the MRI scan had shorter duration of CSF flow in the caudal direction (during systole) compared to subjects without a syrinx ($p<0.05$). Subjects with a syrinx had a less rapid transition from sytolic to diastolic flow direction ($p<0.05$). Study subjects were also divided into groups based on reporting having a cough-associated headache at the clinic visit closest to the time of the MRI. Subjects who reported a symptomatic headache had significantly more tonsil motion than subjects not reporting this symptomatic headache (0.65 ± 0.58 vs. 2.1 ± 0.25 mm, $p<0.05$).

Discussion/Conclusion. We are undertaking a MRI study focused on focused a pediatric population with Chiari I, with and without syringomeylia. Early results show that there are significant flow differences between subjects with and without syringomeylia, and that tonsilar motion may be related reported headache symptoms. The longitudinal nature of the study will allow us to quantitatively study the development of syringmeylia and to assess the effect of surgery on SAS geometry, CSF dynamics, and tonsilar motion.

1. Armonda, et al. Neurosurgery,1994.
2. Bhadelia RA, et al. AJNR, 2011.
3. Mauer UM, et al. JNS 2011.
4. Iskandar BJ, et al. Neurosurgery Pediatrics, 2005 .
5. McGirt, MJ, et al. Neurosurgery, 2005.

John N. Oshinski

About the Presenter. John Oshinski is Associate Professor of Radiology and Biomedical Engineering at the Emory University School of Medicine and the Georgia institute of Technology in Atlanta. He is currently Director of Magnetic Resonance Research at Emory University. H is broad interest is in applying engineering principles to current clinical problems in the imaging, diagnosis, and treatment of disease. He is particularly interested in diseases involving CSF and blood flow dynamics.

SESSION D: CLINICAL

MONDAY, JUNE 24, 2013 – 15:30 TO 17:00

Session Chair: Francis Loth, *Conquer Chiari Research Center, Akron, Ohio, USA*
Department of Mechanical Engineering, University of Akron, Akron, Ohio, USA

Michael Keith Sharp

15^{30} – 16^{00}

Department of Mechanical Engineering, University of Louisville, Kentucky, USA

What Role Does CSF Play In Vision Impairment In Astronauts

Harold Rekate 16

^{00} – 16^{30}

Hofstra Northshore LIJ School of Medicine
The Chiari Institute, Great Neck, New York

Mathematical Models Of CSF Dynamics: Uses And Challenges

Mikhail Papisov 16

^{30} – 17^{00}

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

Dynamics And Solute Transport In CSF In Non-human Primates As Seen By Positron Emission Tomography

SYMPOSIUM DINNER AT 7:00 PM AT LIMANI

WHAT ROLE DOES CSF PLAY IN VISION IMPAIRMENT IN ASTRONAUTS?

Sharp MK, Pantalos GM, Tezel T, Cooper NG (U of Louisville); Loth F (U of Akron)

Astronauts experience altered vision, most commonly hyperopia, during and after spaceflight more prevalently for longer space flights. Vision impairment remains in some subjects years postflight, indicating a significant health issue that could seriously compromise future manned space exploration. The weak correlation of visual problems with marginally elevated intracranial pressure (ICP) post-flight suggests that a more complex interaction is responsible that alters pressures and thus fluid dynamics in multiple ocular compartments. For example, attributing papilledema to increased cerebrospinal fluid (CSF) pressure fails to explain the lack of increased ICP symptoms, such as chronic headaches, diplopia, transient visual obscurations and pulse-synchronous tinnitus in astronauts.

A survey of 300 astronauts found that 29% on short-duration and 60% on long-duration missions experienced altered visual acuity [Mader, et al. 2011]. Fifteen long-duration crewmembers experienced combinations of in-flight and postflight optic sheath distension, optic disc protrusion into the globe, optic disc edema, globe flattening, cotton-wool spots and choroidal folds [Alexander, et al. 2012]. Except for hyperopia, none of these symptoms were investigated preflight. Of seven astronauts on International Space Station missions of 5-6 month duration [Mader, et al. 2011], all exhibited hyperopic shifts postflight compared to preflight. Five exhibited optic nerve distension and globe flattening, while one did not, and one was not assessed. Nerve fiber layer (NFL) thickening was found in six, disc edema in five, choroidal folds in five and cotton-wool spots in three. Postflight ICP was elevated in all four astronauts in which ICP was measured. Preflight ICP was not measured. Intraocular pressure (IOP) was normal both preflight and postflight.

This complex and puzzling problem will be studied with a computational model of the interrelated fluid and tissue compartments of the cardiovascular system, spine, cranium and eye, and the gravity-dependent cephalad intravascular and extravascular fluid shifts known to occur during spaceflight that may initiate the pathophysiology of visual impairment. Mechanisms to be tested include ICP increase due to 1. venous, arterial, CSF and lymphatic fluid shifts in response to microgravity, 2. increased venous outflow resistance, 3. increased CSF production, 4. decreased CSF resorption, 5. increased capillary transport 6. decreased lymph drainage and 7. increased cabin CO_2 level, and vision impairment due to 8. decreased choroidal venous drainage, 9. altered aqueous production and 10. altered intraocular pressure. Lumped parameter models will be developed for the entire system, and finite element models will also be used to study fluid and tissue responses in the optic nerve and eye. While the importance of CSF fluid dynamics is unclear, we consider the possibility that the cardiac pulsations that create pulsatile flow and pressure in the cranium may alter the steady state conditions that could affect diffusion rates of CSF across membranes and blood vessels that may lead to altered drainage, resorption, transport and production. Key to validation of the model will be the simulated occurrence of specific indicators of impairment, including optic bulb and globe deformation, NFL edema and choroidal hypoperfusion.

Alexander DJ, et al. Risk of Spaceflight-Induced Intracranial Hypertension and Vision Alterations. Evidence Report, Human Research Program, Human Health Countermeasures Element, version 1.0, 12 July 2012.

Mader TH, et al. Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in Astronauts after long-duration space flight. *Ophthalmol* 118:10:2058-69, 2011.

MATHEMATICAL MODELS OF CSF DYNAMICS: USES AND CHALLENGES

Harold L. Rekate MD[1,2]

[1]Professor of Neurosurgery, Hofstra Northshore LIJ School of Medicine

[2]Director, The Chiari Institute, Great Neck, New York

Purpose. The purpose of this presentation will be to use the author's personal experiences with the use of a mathematical model of CSF dynamics to demonstrate the usefulness of the technique in directing physiology research. These experiences also point up the challenges in converting the mathematics and processes into clearer understanding of pathophysiology and management of disorders of CSF dynamics.

Methods. This is an autobiography of a 30 year experience related to understanding biomechanics of the brain and CSF directed by engineering principles. As part of a very large program project grant application to NIH engineers from Case Institute sought imput from the department of Neurosurgery at CWRU in Cleveland. Engineers from the Electronics Design Center and the Department of Systems and Controls met with neurosurgeons weekly for two years while at the same time worked toward developing a system of telemetry for intracranial pressure monitoring. Meetings were held for half a day a week to prepare for scientific studies to improve the treatment of hydrocephalus.

Challenges:

Finding the time

Finding a common language

Believing that eventually you will understand each other

Using models to support rather than challenging

Failure to push back when understanding is imperfect

Results. As a result of this process a mathematical model of CSF dynamics has been developed that is based on potential points of obstruction to flow. This model has been tested by observations on patients with complex hydrocephalus as well as using animal models to test hypotheses. As a result of this research a new classification of hydrocephalus has been developed. It has been accepted by the leaders in the field of hydrocephalus research as a consensus.

Conclusion. Mathematical modeling can be used as a powerful tool of inductive reasoning. It should not be seen as an end unto itself and is only useful if it can shed light on pathophysiology.

About the Presenter. Harold (Hal) Rekate is Director of the Chiari Institute and Professor of Neurosurgery at Hofstra Northshore LIJ School of medicine. His previous appointments have included Chairman of Pediatric Neurosurgery at Barrow Neurologic Institute, Professor of Neurosurgery at the University of Arizona Phoenix School of medicine, and Adjunct Professor of Systems and Design Engineering at Case Institute of Technology of Cleveland, Ohio. Dr. Rekate has also been president of both the American and International Societies of Pediatric neurosurgery. He has pursued research in hydrocephalus and intracranial pressure for over 30 years and has over 200 peer reviewed publications.

DYNAMICS AND SOLUTE TRANSPORT IN CSF IN NON-HUMAN PRIMATES AS SEEN BY POSITRON EMISSION TOMOGRAPHY

Mikhail I. Papisov[1]

[1]Massachusetts General Hospital, Harvard Medical School and Shriners Hospitals for Children.

Abstract. The overall goal of our studies was to investigate the in vivo transport of enzyme replacement therapeutics and other macromolecules and particles administered to the CSF. In particular, the studies were intended to evaluate the role of CSF flows in the drug transport from the cerebroventricular and lumbar CSF sub-compartments. The studies were also intended to evaluate the relevance of rodent models, as compared with primate models, and to develop methodology for fully quantitative non-invasive studies of solute dynamics in CSF by Positron Emission Tomography (PET).

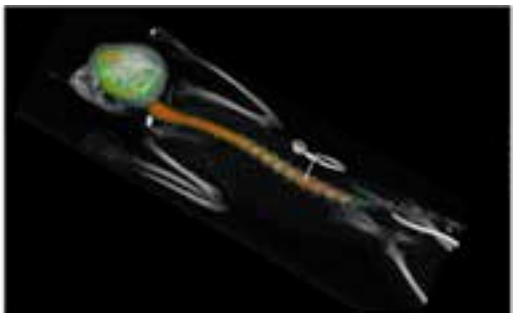


Figure 1. Scheme of the non-human primate experiment (PET/CT image). Radiolabeled proteins and particles were administered through a subcutaneous port (center) connected through a subcutaneous catheter with the leptomeningeal space. Color represents 3-dimensional map of the protein concentration as measured by PET (shown: 3 hours after the injection).

Presently, there are no effective treatments to alleviate several conditions involving CNS, such as neurodegenerative disorders, genetic diseases and cancer. With the growing number of biopharmaceuticals and drug-carrying nanoconstructs entering preclinical and clinical studies, quantitative investigation of their behavior in vivo is playing an increasingly important role in view of the well-known problems with the large molecule and particle transport through tissue barriers, especially the blood-brain barrier. Several recent reports have shown significant biological effects of the intrathecal administration of macromolecules and gene vectors. Therefore, a "back door" through the CSF to the CNS may be available for such drugs. However, the intrathecal route to the CNS relies on processes that depend on insufficiently studied factors, such as remixing of CSF by the pulsatile movement of the CNS tissues, drainage of CSF to the blood through mesothelial pores, and intraparenchymal interstitial and non-interstitial transfer. Several contradictory conclusions have been made regarding the role of the CSF dynamics in the outcome of the process. Investigation of complex combinations of transfer processes benefits from methods enabling: (i) whole-body quantitative registration of all transfer processes on all time frames, and (ii) real-time data acquisition in the same animal and using any animal as its own control, which removes the individual variances from the kinetic data. PET, as a powerful tool for quantitative in-vivo imaging of the transport of pharmaceuticals labeled with positron-emitting radionuclides, meets the above requirements. The studies were carried out using 124I as a radiolabel; among all currently available positron emitters suitable for PET, 124I has the longest physical half-life (4.2 d) and a well established catabolism.

The results of the studies have demonstrated that CSF dynamics (i) is the major factor of the initial distribution of the administered solute in the CSF compartment, and (ii) plays a significant role in the subsequent solute redistribution concurrent with entrance to the CNS and drainage to the systemic circulation. Rodent model was shown to be relevant and potentially scalable.

About the Presenter. Mikhail ("Misha") Papisov, PhD, Associate Chemist (Massachusetts General Hospital), Assistant Professor of Radiology (Harvard Medical School). Head of Molecular Pharmacology and Pharmacological Imaging laboratory. Received his M.S. in Chemistry from Moscow State University in 1982 and Ph.D. in Biology from the National Cardiology Research Center of the Academy of Medical Sciences in Moscow in 1988. Research focus: development of macromolecular and nano-therapeutics with emphasis on novel physiological aspects of macromolecule transport in vivo, structure-function relationships and quantitative preclinical PET imaging; PET studies of macromolecule and particle transport in the CSF.

KEYNOTE LECTURE

TUESDAY, JUNE 25, 2013 – 8:30 TO 9:30

Session Chair: Vartan Kurtcuoglu, *Institute of Physiology, University of Zurich, Switzerland*

Marc Del Bigio **$8^{30} – 9^{30}$**

Department of Pathology, University of Manitoba, Winnipeg MB, Canada

Keynote Lecture

Pathogenesis And Pathology Of Hydrocephalus

SESSION E: IMAGING 2

TUESDAY, JUNE 25, 2013 – 9:30 TO 10:30

Session Chair: Vartan Kurtcuoglu, *Institute of Physiology, University of Zurich, Switzerland*

Mark Wagshul 9 **$^{30} – 10^{00}$**

Albert Einstein College of Medicine, Bronx, NY, USA
University of Utah, Salt Lake City, UT

What Can Animal Models Teach Us About CSF Flow Dynamics?

Ralph Sinkus 10 **$^{00} – 10^{30}$**

Department of Biomedical Engineering, Kings College London, UK

Biomechanics Of Demyelination Processes: How Shear Wave Propagation Can Reveal Microarchitectural Changes

MORNING BREAK, SESSIONS RESUME AT 11:00 AM

PATHOGENESIS AND PATHOLOGY OF HYDROCEPHALUS

Marc R. Del Bigio[1]

[1] Department of Pathology, University of Manitoba, Winnipeg MB, Canada

Abstract. Hydrocephalus is a brain disorder in which the cerebrospinal fluid (CSF) containing cerebral ventricles enlarge as a consequence of impaired CSF flow. Abnormal pulsatility appears to play a role. Mechanical studies indicate that extremely small forces applied repeatedly can gradually deform the brain, suggesting that the poroviscoelastic concepts described by Hakim in 1971 and the importance of CSF pulsation described by di Rocco and coworkers in 1978 are correct. If ventricular enlargement is rapid (e.g. following hemorrhage in the cerebellum), increased intracranial pressure compromises cerebral blood flow and brain ischemia ensues. However, if the enlargement occurs over weeks to years (e.g. because of fibrosis in the CSF pathways) brain is distorted, and may be dysfunctional, but tissue is likely not destroyed. Beyond a certain threshold though, white matter distortion combined with local changes in blood flow, hypoxic changes, and oxidative reactions leads to irreversible axon and oligodendrocyte damage. This results in a subcortical disconnection syndrome wherein communication with the cerebral cortex and between the cerebral cortex and lower parts of the brain or spinal cord are impaired. Owing to physical proximity to the ventricles and the configuration of the brain, the corpus callosum and fornix-fimbria are particularly vulnerable. In addition to the rate of ventricular enlargement, the state of brain development is a critical variable. Hydrocephalus that begins when brain cells are proliferating (e.g. in the human fetus) can disturb production of progenitor cells and cause altered brain development. During the critical stages of rapid cerebral myelination (e.g. in the human infant), hydrocephalus can retard myelin production; if ventriculomegaly is not too severe and axons are not damaged this might be reversible after shunting. In the elderly brain, chronic cerebral vascular disease might make the white matter ischemic changes in hydrocephalus more severe. Also, degenerative disorders (e.g. Alzheimer disease) frequently coexist in the elderly and can combine with hydrocephalus to create a complex clinical dysfunction syndrome. At all ages, reactive astroglial and microglial changes occur in the white matter; these might further contribute to dysfunction. CSF shunting diverts flow around the sites of impaired flow and can correct the abnormal pulsatility, but cannot restore damaged axons. Surgical complications are possible, especially at the two extremes of the age spectrum. Therefore, pharmacologic interventions might have a role in the management of hydrocephalus. Experimental animal work suggests that reduction of calcium-mediated mechanisms, suppression of microglial reactions, or suppression of oxidative changes might be beneficial. Enzymatic restoration of CSF pathways or trophic supplementation of the shunted brain have been considered but there is currently no evidence for value in these approaches.

1. Del Bigio MR, Khan OH, da Silva Lopes L, Juliet PA (2012) Cerebral white matter oxidation and nitrosylation in young rodents with kaolin-induced hydrocephalus. J Neuropathol Exp Neurol. 71(4):274-88

2. Shulyakov AV, Buist RJ, Del Bigio MR (2012) Intracranial biomechanics of acute experimental hydrocephalus in live rats. Neurosurgery 71(5):1032-40

3. Del Bigio MR (2010) Neuropathology and structural changes in hydrocephalus. Dev Disabil Res Rev. 16(1):16-22

4. Khan OH, Enno T, Del Bigio MR (2003) Magnesium sulfate therapy is of mild benefit to young rats with kaolin-induced hydrocephalus. Pediatr Res. 53(6):970-6

About the Presenter. Marc Del Bigio received his MD in 1982 and began PhD studies related to the pathogenesis of hydrocephalus in 1983 at the University of Manitoba. Following graduation in 1987, he began training in neurosurgery. However, finding the professional lifestyle unsuited to his plans for a research career, he switched to neuropathology training at the University of Toronto from 1990-3. After postdoctoral training in Paris France, he took a position as neuropathologist in Winnipeg Manitoba. He is currently professor in the Department of Pathology and holds the Canada Research Chair in Developmental Neuropathology. Using human autopsy tissue and animal models he studies the pathogenesis of brain damage caused by hydrocephalus. He also studies brain damage due to hemorrhage and associated with in utero alcohol exposure.

WHAT CAN ANIMAL MODELS TEACH US ABOUT CSF FLOW DYNAMICS?

Mark E. Wagshul[1], Pat McAllister[2]

[1] Albert Einstein College of Medicine, Bronx, NY, USA

[2] University of Utah, Salt Lake City, UT

Abstract. Pulsatile flow of cerebrospinal fluid (CSF) can be accurately measured and quantified within the cranium, primarily at the cerebral aqueduct and the craniocervical junction. Quantification of CSF pulsatility at the aqueduct was demonstrated over 20 years ago [1], has been shown to be a sensitive diagnostic marker of normal pressure hydrocephalus [2], and has been suggested as a potential prognostic marker of response to surgical intervention [3-6]. Given the need for imaging methods as biomarkers for prediction of treatment outcome, this last category has received much attention over the last decade. Unfortunately, the collective results have been inconclusive, with roughly an equal number of studies showing good vs. poor predictive power. An important lingering question is the nature of elevated CSF pulsatility and its relationship to intracranial pressure (ICP). CSF pulsatility may be elevated due to decreased intracranial compliance, a natural product of raised ICP and the Marmarou pressure-volume relationship [7], or may reflect a more fundamental change in the distribution of pulsatile forces in the closed intracranial environment.

We have used a unique rodent model of communicating hydrocephalus to investigate these questions. Hydrocephalus is induced by injection of kaolin into the basal cisterns. Although the technique requires an anterior, "blind" approach into the basal cisterns, we achieve a success rate of about 60-70%, with animals developing clear signs of increased ICP within less than 24 hours, mild-to-moderate ventriculomegaly, and increased aqueductal pulsatility. MRI experiments investigating correlations between ventricular size and aqueductal pulsatility show a changing relationship over time, possibly reflecting changes in ICP or intracranial compliance. Two-photon microscopic techniques were used to explore potential association between macroscopic CSF pulsations and microscopic vascular pulsations, showing a positive correlation between increased capillary pulsation and CSF pulsations, as well as with increased astrocytosis on GFAP stains. To directly assess the effect of intracranial compliance on CSF flow dynamics, we performed cranial decompression with bilateral craniectomy. While these studies showed a dramatic effect on CSF pulsatility, the effect was highly variable showing percent changes in CSF pulsatility from +12% to -75%. Finally, an expected finding was the dramatic effect of respiratory rate on aqueductal CSF pulsatility, with as much as 3-fold pulsatility increases with decreased respiratory rate (from 60 to 35 breaths/minute); once again, we posit this to be a reflection of the decreased venous compliance with increased hypercapnia.

In summary, CSF flow dynamics can be investigated in hydrocephalus animal models. While our investigations have not yet definitively answered the questions raised above, they clearly show the importance of compliance in hydrocephalus. Methods for direct measurement of compliance may be needed to establish the role of compliance in the development and progression of ventricular dilation in hydrocephalus.

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2. Luetmer, P.H., et al., *Measurement of cerebrospinal fluid flow at the cerebral aqueduct by use of phase-contrast magnetic resonance imaging: technique validation and utility in diagnosing idiopathic normal pressure hydrocephalus.* Neurosurgery, 2002. **50**(3): p. 534-43; discussion 543-4.
3. Bradley, W.G., Jr., et al., *Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging.* Radiology, 1996. **198**(2): p. 523-9.
4. Kim, M.H., K.M. Shin, and J.H. Song, *Cine MR CSF flow study in hydrocephalus: what are the valuable parameters?* Acta Neurochir Suppl, 1998. **71**: p. 343-6.
5. Henry-Feugeas, M.C., et al., *CSF flow waveforms: MR analysis in chronic adult hydrocephalus.* Invest Radiol, 2001. **36**(3): p. 146-54.
6. Abbey, P., et al., *Shunt surgery effects on CSF flow across the aqueduct of Sylvius in patients with communicating hydrocephalus.* J Clin Neurosci, 2009. **16**(4): p. 514-8.
7. Marmarou, A., *et al*, *Compartmental analysis of compliance and outflow resistance of the CSF system.* J Neurosurg, 1975. **43**(5): p. 523-34.

Mark E. Wagshul

About the Presenter. Mark Wagshul is an Associate Professor of Radiology in the Gruss Magnetic Resonance Research center of the Albert Einstein College of Medicine in Bronx, NY. He has used MRI as a tool for investigating CSF pulsatility in clinical settings and in experimental models of hydrocephalus.

BIOMECHANICS OF DEMYELINATION PROCESSES: HOW SHEAR WAVE PROPAGATION CAN REVEAL MICROARCHITECTURAL CHANGES

Ralph Sinkus, Kings College London

The virtual “palpation” of the brain has become feasible using magnetic resonance elastography, which quantifies biomechanical properties of the brain parenchyma by analyzing the propagation of externally elicited shear waves. We assessed changes of viscoelasticity in a murine model of multiple sclerosis, inducing reversible demyelination by feeding the copper chelator cuprizone, and correlated our results with detailed histological analyses, comprising myelination, extracellular matrix alterations, immune cell infiltration and axonal damage. We show firstly that the magnitude of the complex shear modulus decreases with progressive demyelination and global extracellular matrix degradation, secondly that the loss modulus decreases faster than the dynamic modulus during the destruction of the corpus callosum, and finally that those processes are reversible after remyelination. We believe that the origin for the change in solid/liquid behavior is coming from multiple scattering effects which are sensitive to the details of the underlying microstructure. Basic experiments of polystyrene microbeads immersed in a non-attenuating gel are presented in order to validate the hypothesis.

SESSION F: MODELING 2

TUESDAY, JUNE 25, 2013 – 11:00 TO 12:30

Session Chair: Shaokoon Cheng, *Neuroscience Research Australia, Randwick, NSW, Australia*

Lynne Bilston **$11^{00} – 11^{30}$**

Neuroscience Research Australia, Randwick, NSW, Australia
Prince of Wales Clinical School, University of New South Wales, Randwick, NSW Australia

How To Use Experimental Data Effectively In Modeling

Vartan Kurtcuoglu **$11^{30} – 12^{00}$**

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

Near-Wall Ventricular Cerebrospinal Fluid Dynamics

Kent-Andre Mardal 12 **$^{00} – 12^{30}$**

Simula Research Laboratory, Oslo, Norway

On The Assumption Of Laminar CSF Flow In The Spinal Canal

BREAK FOR LUNCH, SESSIONS RESUME AT 1:30 PM

HOW TO USE EXPERIMENTAL DATA EFFECTIVELY IN MODELING

Lynne E Bilston[1,2]

[1] Neuroscience Research Australia, Randwick, NSW Australia

[2] Prince of Wales Clinical School, University of New South Wales, Randwick, NSW Australia

Abstract. Computational models of CSF hydrodynamics are often used to explore biomechanical mechanisms of neurological disorders that have a contribution from CSF flow.

Constructing and validating these models is a challenge, but is necessary to ensure that the models accurately capture the essential features of what is happening in the human system. Key issues for model development and validation include: (i) characterizing the anatomy of the CSF system being studied, (ii) determining the key physics principles that need to be included in the model and appropriate analytical frameworks (iii) determining the physical properties of the key components of the system, (iv) determining the most realistic boundary conditions for the model, and (v) testing the outputs of the model against measured behavior of the real system, independent of the data that was used to generate the model. These are well established biomechanical modeling procedures.

In CSF disorders, many of these steps involve the use of experimental data, either from animals or human subjects, and/or close collaboration with clinicians and other researchers who collect this data. This talk will discuss how to make best use of experimental data in modeling, including ongoing interaction and feedback between experimental and modeling approaches, using examples from the study of syringomyelia and hydrocephalus.

Lynne E Bilston

About the Presenter. Lynne Bilston is a biomedical engineer whose research focuses on how mechanical forces are involved in physiological and pathophysiological processes in the body. Her research encompasses injury biomechanics, neural and other soft tissue biomechanics, and the development of novel imaging methods for making mechanical measurements in vivo. She has a PhD in bioengineering from the University of Pennsylvania and is a National Health and Medical Research Council of Australia senior research fellow. She is a Senior Principal Research Fellow at Neuroscience Research Australia, and is a conjoint Professor at the University of New South Wales.

NEAR-WALL VENTRICULAR CEREBROSPINAL FLUID DYNAMICS

Bercan Siyahhan[1], Diane de Julien de Zélicourt[2], Vartan Kurtcuoglu[2]

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

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

Abstract. There is growing evidence that CSF flow induced by ependymal cilia is an important factor for neuronal guidance. However, the contribution of macroscale pulsatile CSF flow remains unclear. Here we use computational fluid dynamics (CFD) to investigate the interplay between macroscale and cilia-induced CSF flows and their relative impact on near-wall fluid dynamics. Physiologic macroscale CSF dynamics are reconstructed in the ventricular space using subject-specific anatomy, wall motion and choroid plexus pulsations derived from magnetic resonance imaging. Near-wall flow is quantified in a subdomain of the left lateral ventricle using dynamic boundary conditions obtained from the macroscale simulations.

Figure 1 shows a comparison of the tangential velocity profiles in the left ventricular subdomain when neglecting (top) or accounting for (bottom) cilia motion. The subdomain location is shown in green in the inset. Profiles are sampled on a line normal to the ventricular surface originating from point P and extending 2 mm into the CSF space. The shown profiles were sampled at the beginning of the ventricular filling (left) and at the end of the flushing phases (right), respectively. Without cilia, maximum velocity is reached beyond a distance of 0.5 mm from point P. With cilia, the maximum velocity location is shifted closer to the ventricular wall.

When cilia are neglected, CSF pulsation leads to periodic flow reversals along the ventricular surface, resulting in close to zero time-averaged force on the ventricle wall. In contrast, cilia action forces flow in the anterior direction throughout the cardiac cycle in the wall boundary layer, with sharper velocity gradients due to the local flow acceleration. This results in three orders of magnitude increase in wall shear stress.

Our findings indicate that near-wall CSF dynamics in the lateral ventricles are predominantly shaped by ependymal cilia, which may be critical for neuronal guidance. While cerebrospinal fluid flow in the center regions of the ventricles is determined predominantly by wall motion and choroid plexus pulsation, this area is nevertheless influenced by the cilia action as well. This may have implications for the investigation of substance transport in the ventricles, where small variations in the flow field can yield substantial changes in the distribution of the studied compound. Inclusion of the cilia in models of CSF dynamics should thus be carefully considered depending on the application.

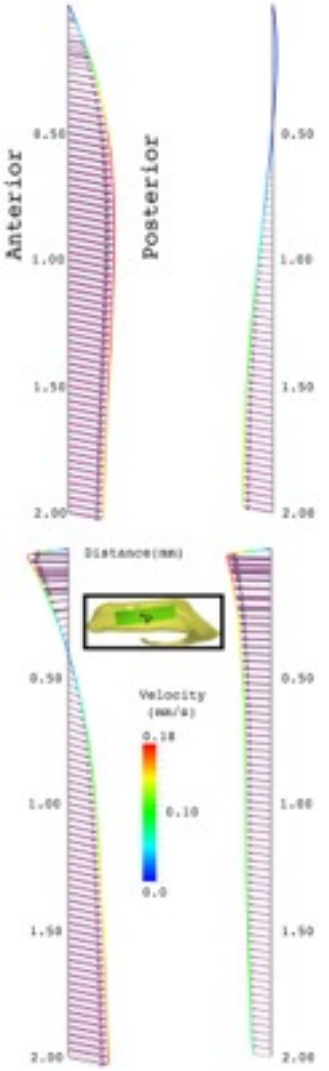


Fig. 1. Near-wall tangential CSF velocity distribution without (top) and with (bottom) contribution of cilia. See main text for detailed description.

Vartan Kurtcuoglu

About the Presenter. Vartan Kurtcuoglu received both his diploma in mechanical engineering and PhD in biomedical engineering from ETH Zurich. The subject of his dissertation was computational modeling of CSF flow in the human ventricular system. In 2011, he was a visiting scientist at Brigham and Women's Hospital and Harvard Medical School. He is currently an assistant professor of computational and experimental physiology at the University of Zurich, and chairman of the International Cerebrospinal Fluid Dynamics Society.

ON THE ASSUMPTION OF LAMINAR CSF IN THE SPINAL CANAL

Kent-Andre Mardal[1]

[1] Simula Research Laboratory, Oslo, Norway

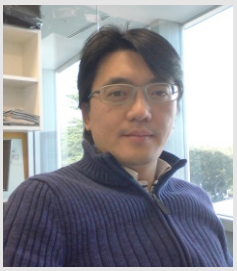
Abstract. CSF flow in the spinal canal is usually assumed to be laminar due to the relatively low Reynolds number, which is in the range 100-1000. However, the pulsatile nature of the flow as well as the complex anatomy of the subarachnoid space in the spinal canal have made us look critically at this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

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 interests include finite element methods, efficient solution algorithms, programming techniques for scientific computing, computational mechanics, blood flow in cerebral aneurysms, and cerebrospinal fluid flow in association with the Chiari I malformation, syringomyelia, and hydrocephalus.

SESSION G: SPINAL CORD

TUESDAY, JUNE 25, 2013 – 13:30 TO 15:00

Session Chair: Bryn Martin, *Conquer Chiari Research Center, University of Akron, USA*
Department of Mechanical Engineering, University of Akron, USA



Shaokoon Cheng **$13^{30} – 14^{00}$**

Neuroscience Research Australia, Randwick, NSW, Australia

Potential Cerebrospinal Fluid Flow Pathways In The Development Of Syringomyelia

Peter Cripton 14 **$^{00} – 14^{30}$**

Orthopaedic and Injury Biomechanics Laboratory, Department of Mechanical Engineering & Orthopaedics, University of British Columbia, Vancouver, BC, Canada
International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada

Cerebrospinal Fluid And Spinal Cord Morphology Changes In The Hours After Spinal Cord Injury: Results From Novel Porcine Model

Claire Jones 14 **$^{30} – 15^{00}$**

Orthopaedic and Injury Biomechanics Laboratory, Departments of Mechanical Engineering & Orthopaedics, University of British Columbia, Vancouver, BC, Canada
International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada

Dynamic Cerebrospinal Fluid Pressure During Experimental Contusion Spinal Cord Injury: Results From Novel Porcine And Synthetic SCI Models

AFTERNOON BREAK, SESSIONS RESUME AT 3:30 PM

POTENTIAL CEREBROSPINAL FLUID FLOW PATHWAYS IN THE DEVELOPMENT OF SYRINGOMYELIA

Shaokoon Cheng[1,4], David Fletcher[2], Sarah Hemley[3], Marcus Stoodley[3], Lynne Bilston[4]

[1]Department of Engineering, Macquarie University, Sydney, Australia.
[2]School of Chemical and Biomolecular Engineering, University of Sydney, Australia.
[3]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia.
[4]Neuroscience Research Australia, UNSW, Australia.

Abstract. As many as 30% of spinal cord injured patients develop post-traumatic syringomyelia months to years after the injury. The development of syrinxes in these patients has been associated with obstruction of the spinal subarachnoid space (SAS) and cerebrospinal fluid flow (CSF) into the spinal cord. However, there is a lack of understanding of how cerebrospinal fluid may flow into the spinal cord.

A base model was created based on axial anatomical images and cardiac gated phase-contrast flow measurements at the base of skull acquired from a healthy subject using a 3-T MRI scanner (Achieva 3TX, Philips Medical Systems, Netherlands). Three other models were then derived from the base model such that cross-sectional area of the SAS at T2 – T3 is reduced by 5 to 20% of the base model. The spinal cords were modelled as porous media with permeability of 1e-8 m^2 and void ratio of 0.2 to represent the extracellular spaces.

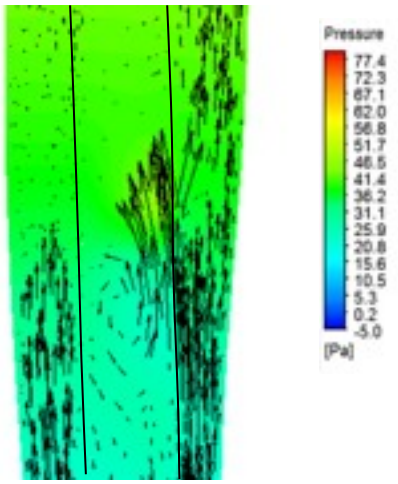


Figure 1. Panel shows the pressure field and CSF flow vectors in a model with stenosis of the spinal subarachnoid space at 35% of the cardiac cycle.

Results show that stenosis of the SAS increases CSF pressure differences between the SAS and spinal cord at T1 from 30% to 40% of the cardiac cycle such that pressure in the SAS is higher. Figure 1 shows CSF flow into the posterior side of the spinal cord at T1 and at 35% of the cardiac cycle. Results from this study may explain why syrinx is commonly found rostral to regions of SAS stenosis and may suggest potential CSF flow pathways into the spinal cord in syringomyelia.

About the Presenter. Shaokoon Cheng received his PhD in Biomedical Engineering from the University of New South Wales, Australia. He is a Senior Research Associate in Neuroscience Research Australia and a Senior Lecturer in the Department of Engineering, Macquarie University, Australia.

CEREBROSPINAL FLUID AND SPINAL CORD MORPHOLOGY CHANGES IN THE HOURS AFTER SPINAL CORD INJURY: RESULTS FROM NOVEL PORCINE MODEL

Claire F. Jones[1,2], Robyn R. Newell[1,2], Jae HT Lee[2], Brian K. Kwon[2,3], Peter A. Cripton[1,2]

[1] Orthopaedic and Injury Biomechanics Laboratory, Department of Mechanical Engineering & Orthopaedics, University of British Columbia, Vancouver, BC, Canada

[2] International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada

[3] Combined Neurosurgical and Orthopaedic Spine Program, Department of Orthopaedics, University of British Columbia, Vancouver, Canada

Abstract. Little is known about changes in the cerebrospinal fluid pressure (CSFP) profile and spinal cord morphology in the hours following traumatic SCI and surgical decompression. CSF drainage is currently used to prevent SCI during aortic surgery and has been investigated as an intervention for SCI. However, in SCI patients, extradural compression commonly occludes the thecal sac. This may generate a CSFP differential across the injury site, which cannot be appreciated with lumbar catheter pressure measurements in patients [1]. Furthermore, following decompression, although relief of compression of the thecal sac and cord can be confirmed intra-operatively, post-operative imaging often shows that the cord has swollen significantly. Little is known about the extent and timing of this response.

Anesthetized Yucatan miniature pigs received sham surgery (N=2), or a moderate (N=6, 20 g, 2.3 m/s) or high (N=6, 20 g, 4.7 m/s) severity weight-drop SCI followed by 8 hrs sustained compression (100g) and 6 hrs post-decompression monitoring. CSFP was measured cranial and caudal to the injury site. Sagittal-plane ultrasound images were used to quantify spinal cord, and thecal sac dimensions pre-injury and each hour after decompression.

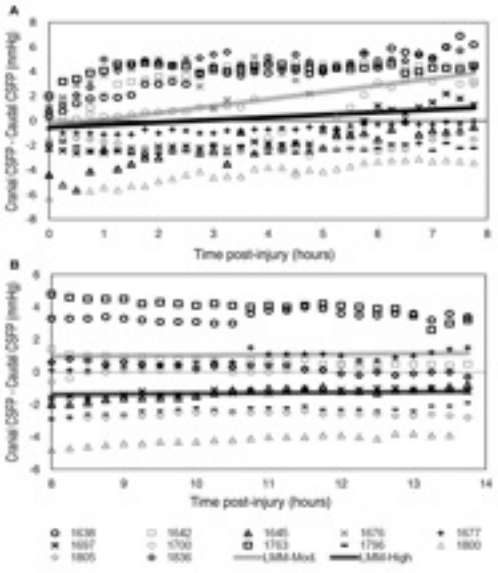


Fig. 1. Linear mixed model and individual animals' data points for cranial-caudal CSF pressure differentials for periods of (A) Compression and (B) Post-decompression. [2]

The cranial-caudal CSFP differential increased (mean 0.39 mmHg/hr), mostly due to increased cranial CSFP. Upon decompression, cranial CSFP decreased (mean -1.16 mmHg) and caudal CSFP increased (mean 0.65 mmHg). The differential did not change significantly after decompression (Fig. 1) [2]. Animals with moderate SCI exhibited a residual cord deformation of up to 0.64 mm within ten minutes of decompression, which tended to resolve over six hours. For animals with high severity SCIs, cord swelling was immediate and occluded the subarachnoid space within ten minutes to five hours; this occurred for only half of the moderate injury group [3]. In the presence of extradural compression, lumbar CSFP may not accurately indicate CSFP cranial to the injury. Decompression may provide immediate, though perhaps partial, resolution of the pressure differential. Decompression is followed by an injury severity dependent gradual or immediate spinal cord swelling which may lead to subarachnoid occlusion. These observations may partly explain the lack of benefit of decompression in some patients.

1. Kwon BK, Curt A, Belanger LM, et al. (2009) Intrathecal pressure monitoring and cerebrospinal fluid drainage in acute spinal cord injury: a prospective randomized trial. *J Neurosurg Spine* 10:181-93.

2. Jones CF, Newell RS, Lee JH, Cripton PA, Kwon BK. (2012) The pressure distribution of cerebrospinal fluid responds to residual compression and decompression in an animal model of acute spinal cord injury. Spine (Phila Pa 1976) 37(23):E1422-31.

3. Jones CF, Cripton PA, Kwon BK. (2012) Gross morphological changes of the spinal cord immediately after surgical decompression in a large animal model of traumatic spinal cord injury. Spine (Phila Pa 1976) 37(15):E890-9.

About the Presenter. Dr Cripton is an Associate Professor in the Departments of Mechanical Engineering and Orthopaedics at the University of British Columbia (UBC). He holds the Patrick Campbell Chair in Mechanical Design and he is a Principle Investigator at the UBC spinal cord injury centre, ICORD. His research interests are in the fields of injury prevention and neurotrauma especially of the head, spine and hip.

DYNAMIC CEREBROSPINAL FLUID PRESSURE DURING EXPERIMENTAL CONTUSION SPINAL CORD INJURY: RESULTS FROM NOVEL PORCINE AND SYNTHETIC SCI MODELS

Claire F. Jones[1,2*], Jae HT Lee[2], Brian K. Kwon[2,3], Peter A. Cripton[1,2]

[1] Orthopaedic and Injury Biomechanics Laboratory, Departments of Mechanical Engineering & Orthopaedics, University of British Columbia, Vancouver, BC, Canada

[2] International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, BC, Canada

[3] Combined Neurosurgical and Orthopaedic Spine Program, Department of Orthopaedics, University of British Columbia, Vancouver, Canada

Abstract. Despite considerable effort, research has failed to translate into effective treatment options for spinal cord injury (SCI). This is partly attributed to differences between the injury response of humans and rodent models. Some of this difference could be because the cerebrospinal fluid (CSF) layer of the human spine is relatively large, while that of the rodents is extremely thin. In these two studies, we sought to characterize the fluid impulse induced in the CSF by experimental SCIs of human-like severity, using novel porcine [1,2,3] and synthetic models of contusion SCI [4].

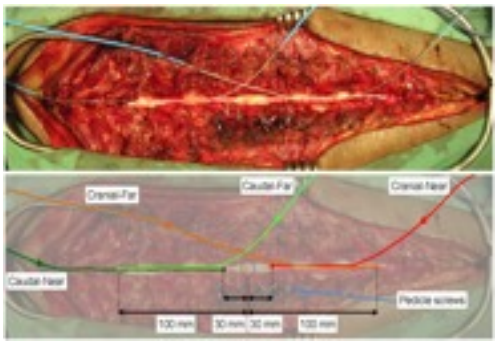


Fig. 1. Photo (top) and overlay (bottom) indicating the location of the four intrathecal pressure transducers and pedicle screws for attaching weight-drop device in the porcine model.

Study 1: Twelve miniature Yucatan pigs underwent experimental SCI (medium or high severity) via weight-drop method (n=6 per injury group, age 124.5 days, 20.9 kg). Four miniature pressure transducers were implanted in the subarachnoid space, cranial and caudal to the injury at 30 mm and 100 mm (Fig. 1). Tissue sparing was assessed via histology. The median peak pressures near the injury were 522.5 and 868.8 mmHg and far from the injury were 7.6 and 36.3 mmHg, for the moderate and high injury severities, respectively. High injury severity animals had less tissue sparing than the moderate injury severity animals, statistically significant only within 1.6 mm of the epicenter.

Study 2: A synthetic model, with mechanical properties similar to native tissues, was constructed to determine if the thickness of the CSF layer and the velocity of a 20 g impactor, affect mechanical predictors of SCI severity. Cord compression was directly proportional to impact velocity, inversely proportional to CSF dimension, and zero for the largest dura size. Impact loads were directly proportional to velocity, and inversely proportional to the thickness of the CSF layer. Peak CSF pressure decreased with distance from the impact epicenter for all dura sizes. Increased CSF dimension led to reduced CSF pressure near the impact epicenter but had little effect at the remote sites. The results suggest that a thicker CSF layer may reduce the stress induced in the cord, and therefore metrics of SCI risk, and computational and animals models of SCI, may be improved by incorporating human-like thecal sac dimensions.

1. Jones CF, Lee JH, Kwon BK, Cripton PA (2012). Development of a large-animal model to measure dynamic cerebrospinal fluid pressure during spinal cord injury. J Neurosurg Spine 16(6): 624-35

2. Jones CF, Lee JH, Burstyn U, Okon E, Kwon BK, Cripton PA (in press). Cerebrospinal fluid pressures resulting from experimental traumatic spinal cord injuries in a pig model. J Biomechanical Eng. Accepted 14 April 2013.

3. Lee JH, Jones CF, Okon EB, et al., (2013) A novel porcine model of traumatic thoracic spinal cord injury. J Neurotrauma 30(3):142-59

4. Jones CF, Kwon BK, Cripton PA (2012). Mechanical indicators of injury severity are decreased with increased thecal sac dimension in a bench-top model of contusion type spinal cord injury. J Biomech 45(6):1003-10.

About the Presenter. Dr Claire Jones received her PhD in Mechanical Engineering from the University of British Columbia in 2011, and is currently Senior Biomedical Engineer at the Adelaide Centre for Spinal Research (SA Pathology), and Adjunct Lecturer in the School of Mechanical Engineering and Affiliate Senior Lecturer in School of Medicine, University of Adelaide, Australia. Dr Jones' research interests focus on the orthopaedic and injury biomechanics of the spine and spinal cord. Dr Jones' travel is supported by the Australian Federation of University Women and the SA Pathology Medical Scientists Special Fund.

SESSION H: MODELING 3

TUESDAY, JUNE 25, 2013 – 15:30 TO 16:30

Session Chair: Lynne Bilston, *Neuroscience Research Australia, Randwick, NSW, Australia*

Corina S. Drapaka **15^{30} – 16^{00}**

Pennsylvania State University, Department of Engineering Science and Mechanics, University Park, PA, USA

A Fractional Pressure-Volume Model Of Cerebrospinal Fluid Dynamics: Marmarou's Model Revisited

Diane Dezelicourt 16 **^{00} – 16^{30}**

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

A Pilot, Multi-scale Numerical Framework For Brain Mechanics

CLOSING REMARKS FOLLOWED BY DISCRETIONARY PLENARY DISCUSSION AND CLOSING COFFEE

A FRACTIONAL PRESSURE-VOLUME MODEL OF CEREBROSPINAL FLUID DYNAMICS: MARMAROU'S MODEL REVISITED

Corina S. Drapaca[1], Justin A. Kauffman[1]

[1] Pennsylvania State University, Department of Engineering Science and Mechanics, University Park, PA, USA

Abstract. Hydrocephalus is a serious neurological disease characterized by abnormalities in the cerebrospinal fluid (CSF) circulation, resulting in an excessive accumulation of CSF in the ventricles of the brain, brain compression and sometimes an increase in the intracranial pressure. The treatment is surgical in nature and continues to suffer of poor outcomes. An important step in the design of better therapy protocols for hydrocephalus is the development of predictive mathematical models that better explain the fundamental science behind this clinical condition. One of the first mathematical models of CSF pressure-volume compensation introduced by Marmarou [1] provides a theoretical basis for studying hydrocephalus. However, the model is not able to fully capture the very complex CSF dynamics. In this talk we will present a generalization of Marmarou's model using fractional calculus. We use a modified Adomian decomposition method to solve analytically the proposed fractional order nonlinear differential equation. Our numerical simulations show a temporal multi-scaling behavior of the CSF dynamics, and propose *both* constant infusion of CSF *and* CSF bolus injection as possible mechanisms for the onset of hydrocephalus [2].

1. Marmarou A, Shulman K, Rosende R M (1978). A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics, J.Neurosurg., 48: 332-344.

2. Kauffman J A (2013). Mathematical models of brain and cerebrospinal fluid dynamics: application to hydrocephalus, Master's Thesis.

Corina S. Drapaca

About the Presenter. Dr. Drapaca is an Assistant Professor in the Department of Engineering Science and Mechanics at Pennsylvania State University since fall 2007. She has received her Ph.D. degree in Applied Mathematics from the University of Waterloo, Canada, in 2002 and held post-doctoral fellowships in the Department of Radiology, University of California, San Francisco, the Department of Applied Mathematics, University of Waterloo, and the Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester. She is a specialist in theoretical and computational mechanics, medical image analysis, and has particular interest in modeling brain diseases such as hydrocephalus, Chiari malformations, and brain tumors.

A PILOT, MULTI-SCALE NUMERICAL FRAMEWORK FOR BRAIN MECHANICS

Diane de Julien de Zélicourt[1], Bercan Siyahhan[2], Vartan Kurtcuoglu[1]

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

[2] Laboratory of Thermodynamics in Emerging Technologies, ETH Zurich, Zurich, Switzerland

Abstract. In this study, we present a multi-scale simulation-based pilot framework for brain mechanics built on the homogenization theory. The brain's structure is classified into meso- and macroscale domains. The mesoscale considers the anisotropic organization of fiber tracts and surrounding interstitial fluid, while the macroscale differentiates between brain tissue and cerebrospinal fluid. We explicitly model the mesoscale mechanics and apply the homogenization theory to derive the mean macroscale material properties and mechanical behavior. If one assumes porous material properties to remain constant throughout the deformation, our formulation reduces to the consolidation theory of Biot. However, while assuming constant properties is often valid in soil mechanics, it does not hold for brain mechanics where deformations can be large. In contrast, our multi-scale formulation allows for the dynamic adjustment of the local properties: Deformations at the macroscale impact the mesoscale structure, which in turn affects the average mesoscale properties. In addition, Biot's theory requires fitting of model parameters such as porosity, to experimental data, whereas in our approach these parameters are obtained from the mesoscale.

Our framework is implemented within the open-source platform OpenFOAM. Since resolving the mesoscale problems at each iteration is computationally expensive, we pre-compute the different mesoscale configurations and store the results in a look-up table. Finite deformations are handled using an updated Lagrangian formulation. When enforcing constant properties, excellent agreement is obtained in the validation of our computational framework against the analytical solution of an equivalent Biot problem. This framework is then applied to assess the impact of mesoscale and macroscale parameters on the observed dynamics. Fig. 1 exemplifies the impact of two different mesoscale configurations in a simplified 2D axisymmetric problem. Despite identical isotropic material properties and pressure loading, anisotropic macroscale behavior arises from the anisotropic fiber arrangement. Varying the macroscale loading rates (Fig. 2), we observe that the faster the loading, the higher the transient pressures and the longer the consolidation time required for the porous structure to reach its fully deformed state. In summary, while still preliminary, this framework holds promises to characterize the dynamics of the parenchyma which are multiphasic and multiscale in nature.

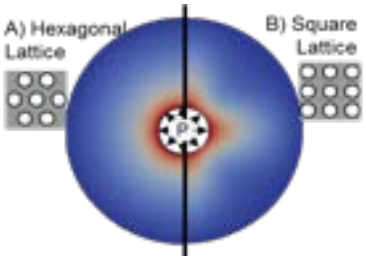


Fig. 1: Impact of the mesoscale fiber arrangement. The hexagonal structure (A) yields a homogenous load distribution and isotropic macroscale displacement field. With the square fiber arrangement (B), the resultant material is weaker along the pore alignment directions, yielding two preferred directions for macroscale deformations.

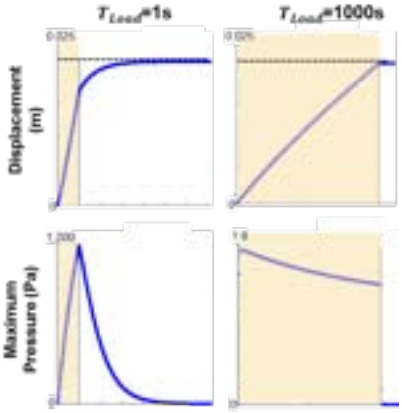


Fig. 2: Impact of the loading rate. A 10mmHg pressure is applied on the ventricular surface, with varying ramping up times (Tload). Short loading times (i.e. fast loading rates) yield large transient pressures followed by a consolidation and pressure relaxation phase, while slower loading rates are associated with low pressures and little to no relaxation.

Diane de Zélicourt

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

GENERAL INFORMATION

VENUE: SCIENTIFIC SESSIONS, BREAKFAST AND LUNCH

The symposium is held at the Feinstein Institute for Medical Research, located at 350 Community Drive, Manhasset, NY 11030.

A coach bus will pick up attendees at the Inn at Great Neck at 6:45am on Monday, June 24 and at 7:00am on Tuesday, June 25 and take attendees to the Feinstein Institute. Bus transportation will also be provided to return to the hotel at the conclusion of the sessions. Attendees should be on the bus 10-15 minutes prior to the listed departure time.

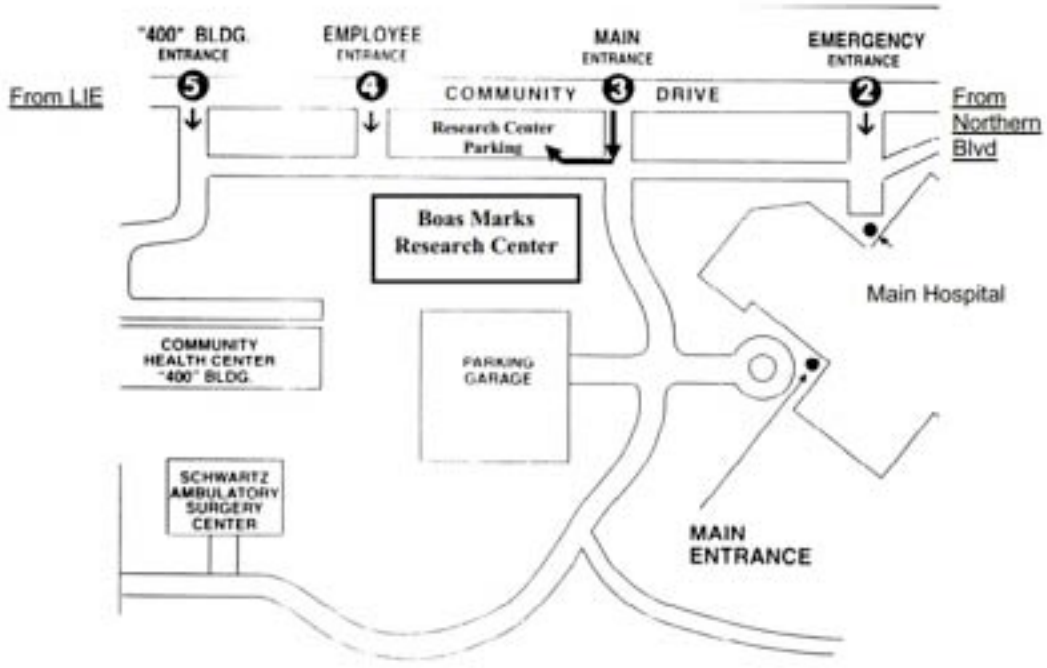
Travel east on the Long Island Expressway (Route 495):
To Exit 33. On the service road, at the second traffic light turn left (north) onto Community Drive. Approximately ½ mile turn right into the Hospital's main entrance (entrance #3). Then a quick right turn to the Research Institute.

Travel west on the Long Island Expressway (Route 495):
To Exit 33. Immediately get right and make a right turn (north) onto Community Drive. Approximately ½ mile turn right into the Hospital's main entrance (entrance #3). Then a quick right turn to the Research Institute.

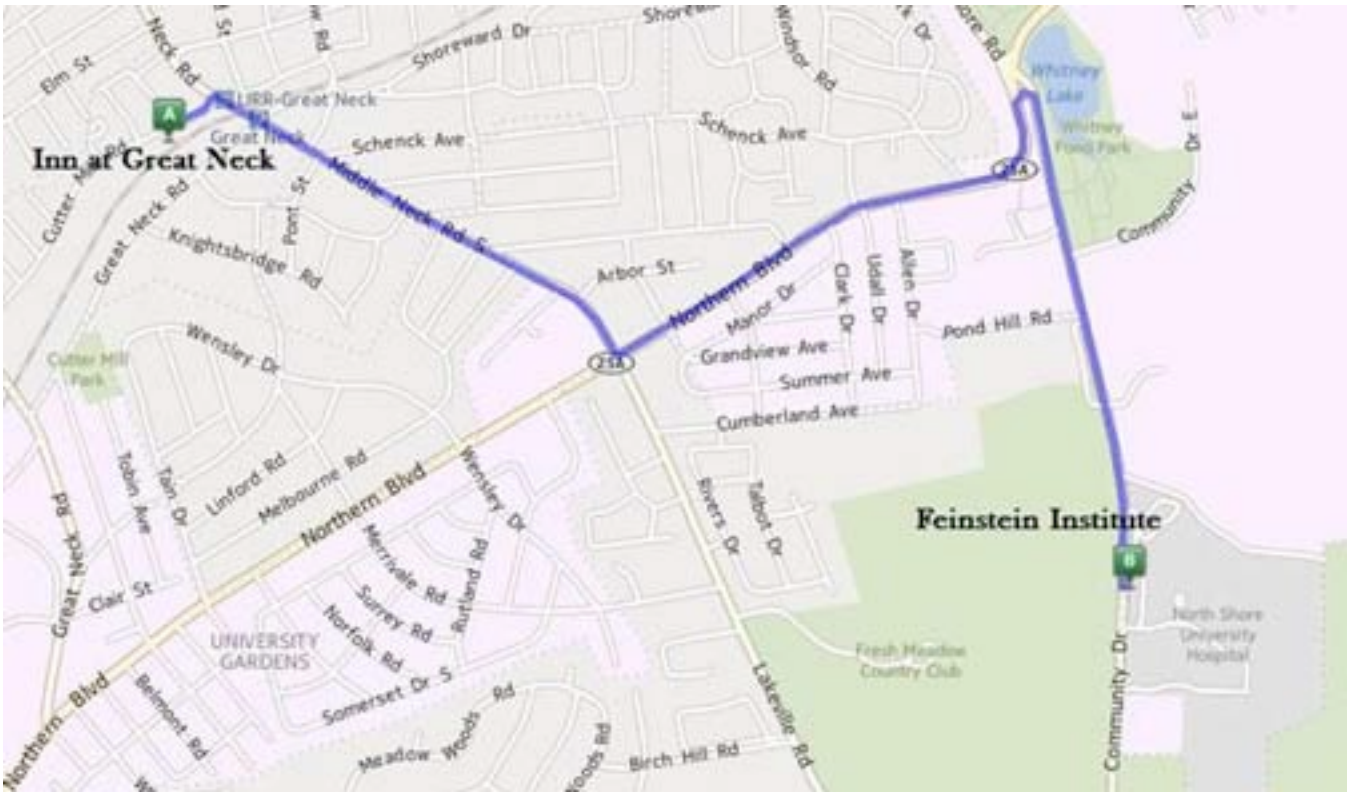
The Research Institute may also be reached via Northern Boulevard (Route 25A). Turn south off Northern Boulevard onto Community Drive. The Hospital's main entrance (entrance #3) is approximately ¾ mile down on the left-hand side.

Temporarily park in front of the Research Institute and ask at the reception desk for a pass to the parking lot (located in front of the Institute). You will also need to ask for the pass upon leaving to exit the lot.

Map 1. Map of the Feinstein Institute



Map 2. Map of the Inn at Great Neck and the Feinstein Institute



VENUE: SYMPOSIUM DINNER

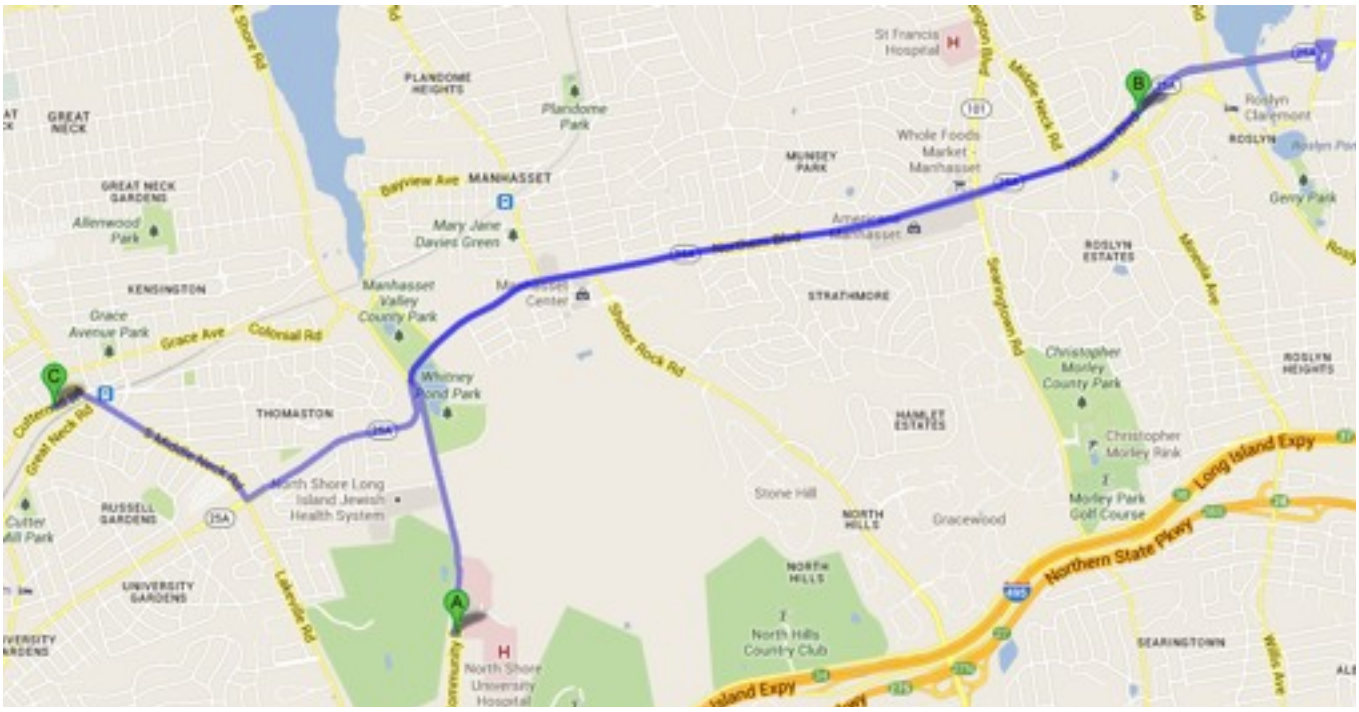
The symposium dinner will be held on Monday, June 24 at 7pm at Limani, located at 1043 Northern Blvd, Roslyn, NY 11576.

Bus transportation will be provided to and from the symposium dinner on Monday night for attendees via the Inn at Great Neck. The bus will depart for the dinner at 6:45pm. Please be on the bus 10-15 minutes prior to this departure time.

Directions to Limani from the Inn at Great Neck:
Head toward Gussack Plaza on Cutter Mill Rd. Turn right onto Middle Neck Road. Go for 0.7 mile. Turn left onto Northern Blvd (RT-25A). Go for 3.1 miles. Your destination on Northern Blvd (RT-25A) is on the left.

Directions to Limani from the Feinstein Institute:
Head toward Valley Rd on Community Drive. Go for 0.8 mile. Bear right onto Northern Blvd (RT-25A). Go for 2.3 miles. Your destination on Northern Blvd (RT-25A) is on the left.

Map 3. Dinner location: A. The Feinstein Institute, B. Limani, C. The Inn at Great Neck



CONNECTIVITY

There is free wireless internet available at the Feinstein Institute. Once you accept the terms and conditions via a web portal, the network is openly accessible.

INFORMATION FOR SPEAKERS

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 25 minutes. Keynotes presentations will be 60 minutes including time for discussion and transition.

CONDENSED SCHEDULE

Monday, June 24, 2013

7:00	BREAKFAST
8:30	OPENING REMARKS
8:45	PLENARY TALK
9:45	SESSION A: EFFECT OF MICROANATOMY ON CSF
10:45	MORNING COFFEE BREAK
11:15	SESSION B: MODELING 1
12:30	LUNCH
13:30	SESSION C: IMAGING 1
15:00	AFTERNOON COFFEE BREAK
15:30	SESSION D: CLINICAL
19:00	SYMPOSIUM DINNER AT LIMANI

Tuesday, June 25, 2013

7:30	BREAKFAST
8:30	PLENARY TALK
9:30	SESSION E: IMAGING 2
10:30	MORNING COFFEE BREAK
11:00	SESSION F: MODELING 2
12:30	LUNCH
13:30	SESSION G: SPINAL CORD
15:00	AFTERNOON COFFEE BREAK
15:30	SESSION H: MODELING 3
16:30	CLOSING REMARKS
17:00	DISCRETIONARY PLENARY DISCUSSION & CLOSING COFFEE

THANK YOU FOR MAKING THE 2ND INTERNATIONAL CSF DYNAMICS SYMPOSIUM A GREAT SUCCESS!