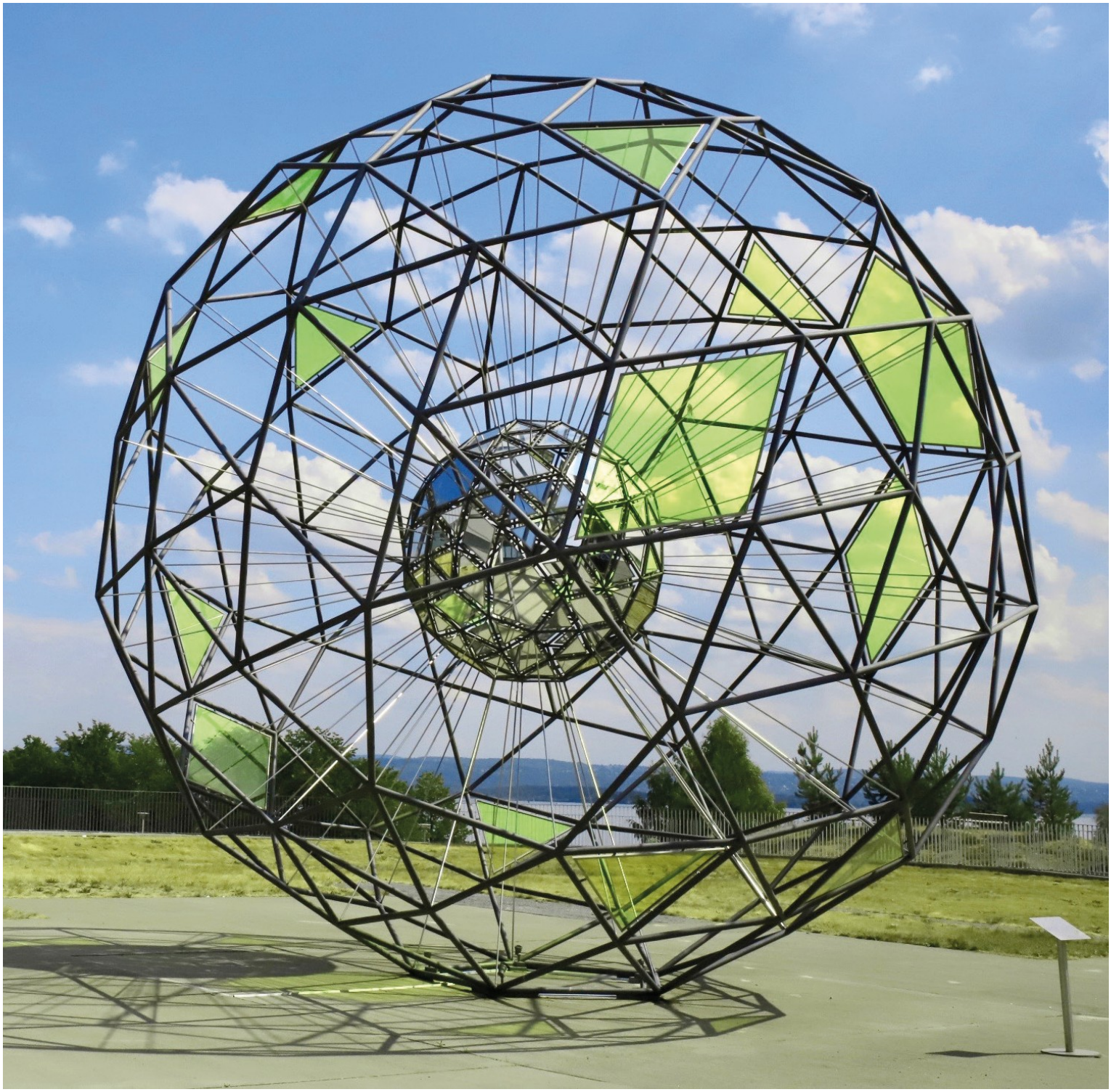
PRELIMINARY PROGRAM

FOR THE 2019 CSF DYNAMICS SYMPOSIUM

Simula Research Laboratory

Oslo, Norway June 30 - July 2 2019



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RELIMINARY PROGRAM FOR THE 2019 CSF DYNAMICS SYMPOSIUM

Simula Research Laboratory

Oslo, Norway

June 30 - July 2 2019

Sunday June 30	
19:00-21:00	Welcome reception at Simula Research Laboratory
Monday July 1	
08:30-09:00	Light breakfast and coffee served in Pusterommet at Simula
09:00-09:15	Welcome in Storstua at Simula
09:15-10:15 Session 1	CSF DYNAMICS IN INDIVIDUALS WITH CSF CIRCULATION DISORDERS P. K. Eide
10:15-11:15 Session 2	POWER AND LIMIT OF MRI TO INVESTIGATE CSF AND CEREBRAL BLOOD FLOWS O. Balédent PHYSIOLOGICAL DRIVERS OF FLUID FLOW IN THE SPINAL SUBARACHNOID SPACE AND SPINAL CORD M. Stoodley
11:15-11:30	Morning coffee break in Pusterommet
11:30-12:30 Session 3	REVISED CONCEPTS OF CSF DYNAMICS FACILITATED BY REAL-TIME FLOW MRI S. Dreha-Kulaczewski CSF FLOW DURING RESPIRATION IS INFLUENCED BY BOTH THORACIC AND ABDOMINAL PRESSURES L. E. Bilston
12:30-14:00	Lunch at Scandic Hotel Fornebu

Program last updated June 24 2019. Subject to changes. All talks will take place in Storstua at Simula Research Laboratory.

14:00-15:30 Session 4	MRI OF RAT BRAIN PERIVASCULAR NETWORK SHOWS CONNECTIVITY TO VENTRICLES M. Sartinoranont CSF DYNAMICS IN PERIVASCULAR SPACES: FLOW MECHANISMS AND CHARACTERISTICS D. H. Kelley CONVECTIVE INFLUX/GLYMPHATIC SYSTEM. TRACERS INJECTED INTO THE CSF ENTER AND LEAVE THE BRAIN ALONG SEPARATE PERIARTERIAL BASEMENT MEMBRANE PATHWAYS R. O. Carare
15:30-16:00	Afternoon coffee break in Pusterommet
16:00-17:30 Session 5	FLOW RESISTANCE OF THE BRANCHED NETWORKS OF CEREBRAL PERIVASCULAR SPACES M. K. Sharp CSF DYNAMICS: MODELING, CLINICAL MEASUREMENTS AND IS IT ABNORMAL IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS COMPARED TO HEALTHY? A. Eklund UNCERTAINTY QUANTIFICATION OF PARENCHYMAL TRACER DISTRIBUTION USING RANDOM DIFFUSION AND CONVECTIVE VELOCITY FIELDS M. E. Rognes
17:30-18:00	Aperitif and mingling in Pusterommet
18:00-22:00	Conference dinner at Dyna Fyr. Pick-up by boat at the Sea Plane Harbor at 18:00.
Tuesday July 2	
08:30-09:15	Light breakfast and coffee served in Pusterommet
09:15-10:15 Session 6	CSF PRODUCTION – NOW WITH COTRANSPORT OF WATER N. MacAulay

Program last updated June 24 2019. Subject to changes. All talks will take place in Storstua at Simula Research Laboratory.

10:15-11:15 Session 7	IN VITRO MODELING OF CEREBROSPINAL FLUID SOLUTE TRANSPORT B. Martin INTRACRANIAL PRESSURE ELEVATION ALTERS CSF CLEARANCE PATHWAYS V. Vinje
11:15-11:30	Morning coffee break in Pusterommet
11:30-12:30 Session 8	IMAGING AND MODELING GLYMPHATIC RESPONSES AFTER DIABETES Q. Jiang A GENERAL, CONSOLIDATED PIPELINE FOR INVESTIGATING THE TRAJECTORY OF ALZHEIMER'S DISEASE: INSIGHT INTO THE UNDERLYING MECHANISMS OF THE NEUROVASCULAR UNIT IN DIFFERENT REGIONS OF THE BRAIN J. C. Vardakis
12:30-14:00	Lunch at Scandic Hotel Fornebu
14:00-15:30 Session 9	DEPENDENCE OF INTRACRANIAL PRESSURE ON PRESSURES IN OTHER BODY COMPARTMENTS V. Kurtcuoglu CRANIAL PULSE MODULATION: FROM BLOOD FLOW TO DRUG DELIVERY M. Luciano
15:30-16:00	Afternoon coffee break in Pusterommet
16:00-17:00 Session 10	EXPLORING THE TRANS-MANTLE PRESSURE GRADIENT IN HYDROCEPHALUS H. Rekate EXPLORING THE CEREBROSPINAL FLUID DYNAMICS OF THE AMERICAN ALLIGATOR B. A. Young

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CSF DYNAMICS IN INDIVIDUALS WITH CSF CIRCULATION DISORDERS

P.K Eide[1,2]

[1] Department of neurosurgery, Oslo university hospital – Rikshospitalet, Oslo, Norway
[2] Department of neurosurgery, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway.

Abstract. The talk addresses clinical CSF circulation disorders in light of new observations of CSF circulation disturbance in idiopathic normal pressure hydrocephalus (iNPH) and idiopathic intracranial hypertension (IIH). We have used MRI before/after intrathecal administration of a MRI contrast agent (gadobutrol) acting as a CSF tracer to visualize movement of molecules in CSF spaces and glymphatic pathways. The studies haven given evidence that CSF is in direct communication with the extravascular space of the entire CNS, including visual pathways. The CSF seems to be an integral part of the entire central nervous system (CNS). Phase-contrast MRI for assessment of CSF movement in CSF spaces has provided evidence that direction and magnitude CSF movement may be very different from the traditional concept. In modeling studies, we have explored mechanisms behind CSF movement, high-lightening the role of respiration for CSF movement. Results from studies in iNPH and IIH patients have given evidence that the basement membrane of the glia-vascular interface may be an important region for CSF circulation disturbance. It is concluded that we are now witnessing a paradigm shift regarding our concept of CSF circulation. The third circulation concept, coined by Harvey Cushing about 100 years ago, is challenged.

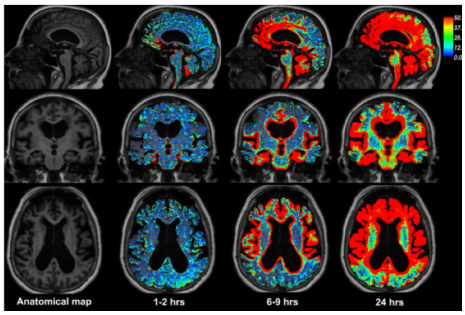


Fig. 1. A MRI contrast agent (gadobutrol) applied intrathecal to the CSF and serving as a CSF tracer distributes to the entire brain in a centripetal direction, and illustrates that the subarachnoid CSF spaces communicates with the extravascular spaces of the entire brain.

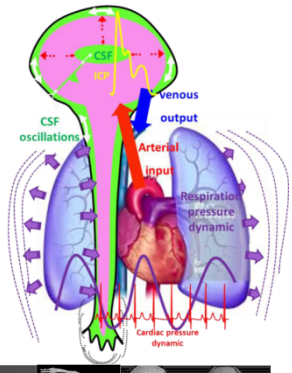
About the Presenter: Per Kristian Eide is Professor of Medicine (Neurosurgery), Institute of Clinical Medicine, University of Oslo, senior consultant neurosurgeon/head of section, Department of Neurosurgery, Oslo University Hospital – Rikshospitalet, and head Neurovascular-Hydrocephalus Research Group, Department of Neurosurgery, Oslo University Hospital. He has ha broad interest in CSF circulation disorders, from basic mechanisms to clinical practice.

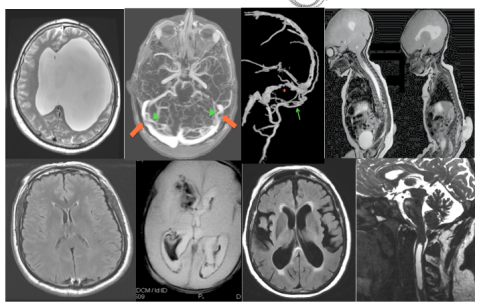
POWER AND LIMIT OF MRI TO INVESTIGATE CSF AND CEREBRAL BLOOD FLOWS

O. Balédent

University hospital of Picardie Jules Verne, CHIMERE EA 7516, Amiens, France

Abstract. The large and rapid amplitude change of cerebral arterial input flow increases the brain volume over the intracranial subarachnoid spaces (large red arrows). In these areas, resistance to flow is low and as CSF viscosity is low, CSF is quickly displaced out of the cranium toward the compliant spinal canal; ICP increase is therefore limited. Nevertheless, this first CSF response is scanty and has to be supplemented with the cerebral blood venous outflow. Due to blood viscosity, this venous contribution is slower but brings a greater volume displaced. Finally, the decrease in pressure at the brain periphery induces a CSF ventricular flow, out of the fourth ventricle and through the aqueduct of Sylvius, resulting in a small inner displacement of the brain directed toward the ventricles (small red arrows). After this series of flow events during the systolic phase of cardiac cycle, arterial inflow equals venous outflow and cervical CSF flush stops. After this brief equilibrium pressure moment, venous heart aspiration increase the cerebral venous outflow, decrease ICP and reverse the cervical CSF flow to fill the cranium and prepare the next cycle. For the last twenty years Cerebral hydrodynamic's knowledge has benefited considerably from the introduction of phase-contrast magnetic resonance imaging (PCMRI). CSF and blood flows can be easily quantified. The objective of this presentation is to describe power and limit of this tool to investigate cerebral hydrodynamic and to highlight how CSF and blood flows impact or are impacted in some cranio spinal pathologies not yet well understood.





1. *Feinberg D.A., Mark A.S. Human brain motion and cerebrospinal fluid circulation demonstrated with MR velocity imaging. Radiology 1987 (163) : 793–799.*
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3. *Stoquart-Elsankari S, Lehmann P, Villette A, Czosnyka M, Meyer ME, Deramond H, Balédent O. A phase-contrast MRI study of physiologic cerebral venous flow. J Cereb Blood Flow Metab. 2009 Jun;29(6):1208-15*
4. *Chen L , Beckett A ,Verma A, Feinberg D. Dynamics of respiratory and cardiac CSF motion revealed with real-time simultaneous multi-slice EPI velocity phase contrast imaging. NeuroImage 2015 ; (122) : 281–287*
5. *Daouk J, Bouzerar R, Baledent O. Heart rate and respiration influence on macroscopic blood and CSF flows. Acta Radiologica, 2016*

Olivier Balédent

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 group in the CHIMERE EA7516 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.

PHYSIOLOGICAL DRIVERS OF FLUID FLOW IN THE SPINAL SUBARACHNOID SPACE AND SPINAL CORD

Shinuo Liu,[1] Lynne Bilston,[2] Neftali Flores Rodriguez,[3] Courtney Wright,[3] Marcus Stoodley,[1] Sarah Hemley[1]
[1] Department of Clinical Medicine, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia
[2] Neuroscience Research Institute, Sydney, NSW, Australia
[3] Australian Centre for Microscopy and Microanalysis, The University of Sydney, Sydney, NSW, Australia

Background: There is mounting evidence that disruption to CSF circulation and CSF/interstitial fluid exchange is likely to contribute to a number of CNS diseases including syringomyelia. However, the physiological factors that govern CSF flow in the subarachnoid space (SAS) and fluid transport in the spinal cord are poorly understood.

Aims: The aims of this study were to determine the effects of heart rate, blood pressure and respiration on the flow of fluid in the subarachnoid space, as well as into and out of the spinal interstitium.

Methods: In Sprague Dawley rats, physiological parameters were carefully manipulated such that the effects of free breathing (negative intrathoracic pressure), mechanical ventilation (positive intrathoracic pressure), tachy/bradycardia, as well as hyper/hypotension were separately investigated. To investigate spinal CSF hydrodynamics, *in vivo* near infrared imaging of intracisternally infused indocyanine green was performed. Spinal fluid inflow at a microscopic level was characterised by *in vivo* two-photon intravital microscopic imaging of fluorescent ovalbumin and microspheres injected into the SAS. Complementary quantitative data was obtained in *ex vivo* epifluorescence studies employing ovalbumin. To assess fluid outflow, ovalbumin was injected into the cervicothoracic spinal grey or white matter.
Results: Compared to controls, free-breathing animals had significantly greater flow of CSF in the SAS as well as inflow of tracer into the spinal cord. Hypertension and tachycardia had no significant effect on SAS CSF flow. Hypertension resulted in reduced tracer inflow, whereas increased tracer influx was observed with tachycardia. Both tachycardia and hypertension stimulated tracer efflux, but respiration was not found to affect spinal interstitial clearance.
Conclusions: Intrathoracic pressure has a significant effect on spinal subarachnoid CSF flow and parenchymal fluid ingress. Cardiovascular pulsations play a smaller role in SAS hydrodynamics but have profound effects on spinal interstitial fluid homeostasis.

About the Presenter: Professor Stoodley is head of neurosciences at Macquarie University. Professor Stoodley's clinical subspecialty qualification is in neurovascular surgery. In addition to his neurovascular expertise, Professor Stoodley is recognised internationally for clinical management of Chiari malformation and syringomyelia. He graduated with honours from the University of Queensland. After completing neurosurgery training in Australia, he undertook further subspecialty training in vascular neurosurgery at Stanford University and the University of Chicago in the United States. In addition to his clinical interests, Professor Stoodley heads the neurosurgery research team at Macquarie University. This is one of the largest neurosurgery research groups in Australasia, with world-leading research efforts in syringomyelia and CSF physiology, and in the development of new treatments for brain AVMs. This work has attracted over $4 million in research funding, including support from Australia's major medical research funding body the NHMRC and The Column of Hope, a US-based organisation dedicated to advancing the understanding and treatment of syringomyelia. He has produced more than 100 publications and has supervised over 15 research students. He has delivered over 70 invited lectures at national and international scientific meetings. In 2012, Professor Stoodley was awarded the John Mitchell Crouch Fellowship by the Royal Australasian College of Surgeons, the premier surgical research award of the RACS.

REVISED CONCEPTS OF CSF DYNAMICS FACILITATED BY REAL-TIME FLOW MRI

Steffi Dreha-Kulaczewski[1], Arun Joseph[2], Jost Kollmeier[2], Hans-Christoph Ludwig[3], Jutta Gaertner[1], Jens Frahm[2]

[1] Department of Pediatrics and Adolescent Medicine, University Medical Center, Goettingen, Germany
[2] Biomedizinische NMR am Max-Planck-Institut für biophysikalische Chemie, Goettingen, Germany
[3] Department of Neurosurgery, Division of Pediatric Neurosurgery, University Medical Center, Goettingen, Germany

Abstract. Current concepts of CSF dynamics presume a constant downward flow from the lateral ventricles towards subarachnoid spaces, which are in contrast to neurosurgical observations and findings of MRI flow-studies. New insights revealed respiration as the dominant driving force of CSF dynamics using inflow-sensitive real-time MRI. In particular, forced inspiration has been identified as the dominant regulator of CSF dynamics in all its compartments, while flow adjustments in relation to the heart beat represent a continuous albeit minor component. Forced inhalation prompted an upward surge of CSF from the thecal sac in the lumbar region along the entire spinal canal, into the cranial vault and passing through the aqueduct further upwards. The upward motion of CSF into the head and brain is explained by the necessity to counterbalance inspiratory-regulated venous outflow out of the head/neck region. The interplay between the CSF and venous blood system is part of a tightly adjusted fluid equilibrium essential to ascertain a constant intracranial volume in accordance with the Monro-Kellie doctrine (1). In the spinal canal concomitant forced expiration revealed downward CSF flow which resulted in a watershed pattern with the dividing point at about the level of the heart. Upward direction prevailed cranial to thoracic level Th1, while CSF flow pointed downwards at level Th6 and below (2). Flow in the aqueduct has been found to be comparatively small. In full agreement with previous reports CSF movement during deep inspiration here was upward, while forced expiration elicited very low or no CSF flow. It is tempting to speculate that the aqueduct holds a regulatory function in order to prevent irregular volume variations into the ventricles of the brain. Recent findings of differential CSF flow in the aqueduct of healthy subjects and patients with normal pressure hydrocephalus and intracranial aneurysms may be in support of this hypothesis (3). The ability of the CSF system to accommodate a broad physiological range of pressure conditions as shown during thoracic vs abdominal breathing is of high clinical importance for patients with disturbed CSF circulation like hydrocephalus, pseudotumor cerebri and others. Real-time MRI access to quantitative CSF flow in these patients will therefore contribute to unravel underlying pathophysiological mechanisms and to open new approaches to therapeutic interventions.

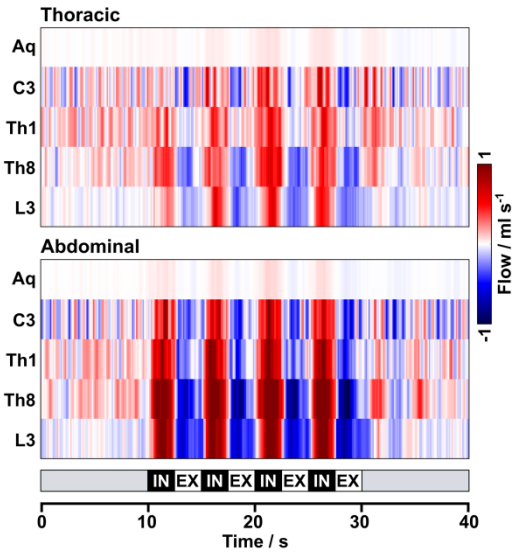

Fig. 1: CSF flow rates (ml s-1) during forced respiration. Mean color-coded flow rates averaged across 18 subjects in aqueduct, C3, Th1, Th8, L3 for **Top:** forced thoracic and **Bottom:** abdominal breathing. Onset of forced inspiration prompts increase of CSF flow in upward direction (red) at all locations, while downward movement (blue) prevails during expiration at all spinal levels. Forced abdominal breathing consistently causes higher flow rates compared to thoracic breathing.

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3. Lindstrom EK, Ringstad G, Mardal KA, et al. Cerebrospinal fluid volumetric net flow rate and direction in idiopathic normal pressure hydrocephalus. Neuroimage Clin. 2018;20:731.

S. Dreha-Kulaczewski

About the Presenter: Steffi Dreha-Kulaczewski, a pediatric neurologist, focuses on disorders of disturbed of CSF circulation in children and on childhood leukodystrophies. Research activities comprise application of novel MR-techniques i.e. real-time flow MRI to unravel underlying pathophysiologic mechanisms of perturbed CSF dynamics giving raise to hydrocephalus, pseudotumor cerebri, and syringomyelia.

CSF FLOW DURING RESPIRATION IS INFLUENCED BY BOTH THORACIC AND ABDOMINAL PRESSURES

Robert A. Lloyd[1,2], Jane Butler[1], Simon C. Gandevia[1], Marcus Stoodley[3], Lynne E Bilston[1,2]

[1] Neuroscience Research Australia, Sydney, NSW Australia
[2] University of New South Wales, Sydney, NSW Australia
[3] Macquarie University, Sydney, NSW, Australia

Abstract. Flow of CSF into the spinal canal is largely driven by the Monro-Kellie doctrine, where blood flowing into the cranium displaces CSF through the foramen magnum into the spinal canal. Both cardiac and respiratory cycles have an effect via arterial and venous blood flows. Forced inspiration has been shown to increase cranial CSF flow in the spinal canal, presumably via negative intrathoracic pressure drawing venous blood into the thorax. However, other CSF movement patterns have been observed during inspiration, including reports of caudal CSF flow [1,2].

This study aimed to determine how intrathoracic pressure, epidural venous flows, and CSF flows are related during controlled respiratory manoeuvres in healthy control subjects (N=10, 5M, 5F). Real time phase contrast MRI was used to measure CSF flows in the spinal canal at C3 and L2 during short inspiratory and expiratory efforts (sniff, cough). Intrathoracic and abdominal pressures were measured during the same manoeuvres using a pressure catheter inserted nasally.

During a sniff (short inhalation), intrathoracic pressure is negative, but abdominal pressure is positive. During a cough (short exhalations), both pressures are positive. CSF displacement was regularly cranial during both maneouvres, despite negative intrathoracic pressures in the sniffs. (See Fig 1).

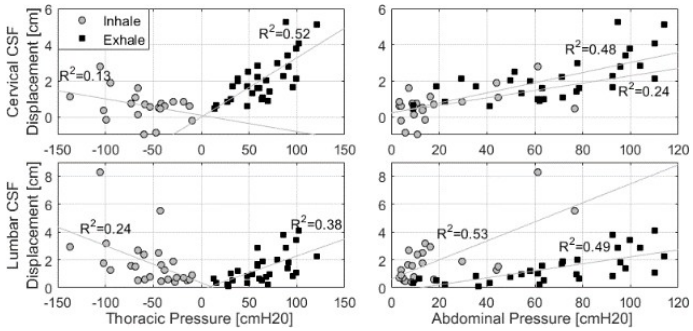

Fig. 1. Peak CSF displacement in the cervical and lumbar spinal canal varies with thoracic and abdominal pressures during inhalation and exhalation manoeuvres.

The cervical CSF displacement was significantly associated with abdominal pressure, whereas lumbar CSF pressure was significantly associated with both thoracic and abdominal pressures. Increased abdominal and thoracic pressure coincided with an increase of blood flow into the epidural veins, and cranial displacement of CSF. Decreased thoracic pressure coincided with increased venous return via the cervical epidural veins, and generally CSF was displaced cranially. However, in some subjects the cervical CSF was displaced caudally.

These results suggest that CSF flows in response to respiratory activity are driven by the net effect of intrathoracic and lumbar pressures, likely via their effects on epidural veins.

References:

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2. Dreha-Kulaczewski, S., et al., (2018). Sci. Rep., 8(1) 5594.

Lynne Bilston

About the Presenter: Professor Lynne Bilston is Lynne Bilston is a biomedical engineer whose research focusses on neural and soft tissue biomechanics, and applications to CSF flow disorders, injury and sleep apnoea. 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 Scientist at Neuroscience Research Australia and a conjoint Professor at the University of New South Wales.

MRI OF RAT BRAIN PERIVASCULAR NETWORK SHOWS CONNECTIVITY TO VENTRICLES

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

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

Abstract. Mechanisms by which metabolic wastes are cleared from CNS is important for understanding natural function and the pathophysiology of several neurological disorders. Recent evidence suggests clearance may be the function of perivascular spaces (PVS), annular gaps that exist between cerebral blood vessels and brain parenchyma. PVS provide potential transport routes for cerebrospinal fluid (CSF) surrounding the brain to exchange with interstitial fluid in the brain interior. In this study, an MRI-based methodology was developed that allowed us to visualize PVS within the brain interior and reconstruct the PVS network in whole rat brain[1]. There is a need to quantify connectivity of perivascular channels at the tissue level in order to better understand the physics of PVS flow[2], as well as study the effects of abnormalities in these networks with disease.

MR visible tracer (gadolinium-DTPA bound to albumin) was infused *in vivo* into the lateral ventricle followed by *ex vivo* high-resolution MR imaging at 17.6 T with an image isotropic voxel size (40 microns) two orders of magnitude smaller than previously reported. Next, imaged tracer distribution patterns were reconstructed to obtain brain PVS networks. After MRI, the presence of the tracer in PVS was confirmed using confocal fluorescence imaging. We found several types of PVS connections repeatedly highlighted across animals, and new PVS connections were revealed between ventricles and different parts of the brain parenchyma. This suggests a possible role for the ventricles as a source or sink for solutes in the brain. In future studies, high-resolution PVS networks can be incorporated into computational models that account for transport between subarachnoid, ventricle, and interstitial spaces [2,3].

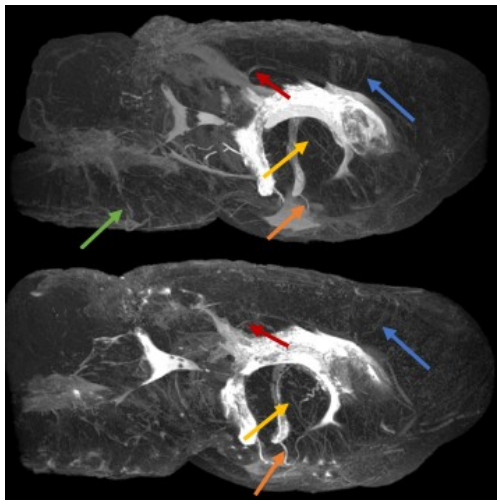

Fig. 1. *2D maximum intensity projections of the reconstructed perivascular network in tracer infused rat brains. Common PVS in two different rats are highlighted. PVS connecting lateral ventricles to the dorsal brain surface (red and blue arrow), ventral brain surface (orange arrow), deep brain structures (yellow arrow) are highlighted along with PVS in the brainstem (green arrow).*

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2. Rey J and Sarntinoranont M (2018). Pulsatile flow drivers in brain parenchyma and perivascular spaces: a resistance network model study. Fluids Barriers CNS 15:20.
3. Kim JH, et al. (2012) Voxelized computational model for convection enhanced delivery in the rat ventral hippocampus: Comparison with in vivo MR experimental studies. Ann. Biomed. Engi. 40(9): 2043-58.

Malisa Sarntinoranont

About the Presenter. Dr. Sarntinoranont is an Associate Professor in the Department of Mechanical & Aerospace Engineering at the University of Florida. Her research is driven by a vision to develop translational tools for patient-specific drug therapy. The focus of her lab has been the development of image-based computational models that predict flows and 3D drug distributions within the brain, spinal cord and tumors. Dr. Sarntinoranont received her undergraduate degree from Georgia Tech. She completed her M.S. and Ph.D. degrees in mechanical engineering at U.C. Berkeley. Her post-doctoral training was at the National Institutes of Health (NIH) in Bethesda, MD. She is a fellow of the American Society of Mechanical Engineers.

CSF DYNAMICS IN PERIVASCULAR SPACES: FLOW MECHANISMS AND CHARACTERISTICS

Douglas H. Kelley[1], Jeffrey Tithof[1], Humberto Mestre[2,3], John H. Thomas[1], and Maiken Nedergaard[2,4]

[1] Department of Mechanical Engineering, University of Rochester, Rochester, NY USA
[2] Center for Translational Neuromedicine, University of Rochester, Rochester, NY USA
[3] Department of Neuroscience, University of Rochester, Rochester, NY USA
[4] Center for Translational Neuromedicine, University of Copenhagen, Copenhagen, Denmark

Abstract. Primarily active during sleep[1], the glymphatic system drives CSF through perivascular spaces (PVSs) surrounding arteries, then into deeper brain tissue, to sweep away cellular waste. The glymphatic system may prevent neurological disorders, such as Alzheimer's and Parkinson's diseases, associated with accumulation of waste proteins. However, the mechanisms and characteristics of CSF flow in PVSs have been topics of debate in recent publications, with disagreement over the size of the spaces through which CSF flows, its direction of flow, its rate of pulsation, and how flow is driven. In results recently published,[2] we use in vivo particle tracking to measure CSF flow in PVSs surrounding pial arteries in mice. We show that the flow pulses in synchrony with the cardiac cycle, consistent with "perivascular pumping" in which CSF is driven by the motion of the adjacent artery wall.[3] We alter that motion by inducing high blood pressure to stiffen the wall, and we show that the mean CSF flow speed is reduced ~40%. Perivascular pumping appears to be the primary driver of CSF flow in healthy mice, and its disruption by high blood pressure may relate to the fact that early-onset hypertension is a known risk factor for Alzheimer's disease in humans.

We injected 1-μm tracer particles into the cisterna magnas of anaesthetized mice, then imaged particle motion using two-photon microscopy. Automated particle tracking yielded
hundreds of thousands of measurements from each experiment. We calculated the root-mean-square flow velocity v_{rms} as it varied in time and compared it to the ECG and respiration signals recorded simultaneously. Statistics of delay times among v_{rms} peaks, ECG peaks, and respiration peaks, show that CSF pulses in synchrony with the cardiac cycle. Synchronization suggests that motion of artery walls drives CSF via perivascular pumping. To test that hypothesis, we changed the wall motion by inducing high blood pressure. High pressure causes muscular artery walls to flex harder in order to maintain the same diameter, stiffening the tissue, and presumably changing wave propagation. The measured wall deformation and velocity did change significantly,
as we expected. The mean flow speed also changed significantly, as Figure 1 shows, dropping on average from 30 μm/s to 18 μm/s. Our measurements further show that when blood pressure is normal, pulsations vary the flow speed between faster and slower, but when blood pressure is high, pulsations typically cause backflow during part of the cardiac cycle, reducing overall pumping efficiency.

1. Xie, L. et al. *Science* **342**, 373–377 (2013).
2. Mestre, H. *et al. Nat. Comm.* **9:1,** 4878 (2018).
3. Hadaczek, P. *et al. Mol. Ther.* **14,** 69–78 (2006).

About the Presenter: Douglas H. Kelley is an Associate Professor of Mechanical Engineering at the University of Rochester. His research considers fluid dynamics in contexts ranging from cerebrospinal fluid removing waste from the brain to mixing and instabilities in liquid metal batteries. He is the recipient of a CAREER Award from the National Science Foundation. Before coming to Rochester, he earned a PhD in Physics at the University of Maryland and held postdoctoral research positions at Yale University and Massachusetts Institute of Technology.

CONVECTIVE INFLUX/GLYMPHATIC SYSTEM. TRACERS INJECTED INTO THE CSF ENTER AND LEAVE THE BRAIN ALONG SEPARATE PERIARTERIAL BASEMENT MEMBRANE PATHWAYS

Nazira J Albargothy[1], David A Johnston[1], Matthew MacGregor-Sharp[1], Roy O Weller[1], Ajay Verma[2], Cheryl A Hawkes[3]*, Roxana O Carare[1]*

[1]Faculty of Medicine, University of Southampton, U.K
[2]Biogen, U.S.A
[3]Open University, U.K

*Contributed equally to the study

Abstract.
Tracers injected into CSF pass into the brain alongside arteries and out again. This has been recently termed the "glymphatic system" that proposes tracers enter the brain along periarterial "spaces" and leave the brain along the walls of veins. The object of the present study is to test the hypothesis that 1) tracers from the CSF enter the cerebral cortex along pial-glial basement membranes as there are no perivascular "spaces" around cortical arteries, 2) tracers leave the brain along smooth muscle cell basement membranes that form the Intramural Peri-Arterial Drainage (IPAD) pathways for the elimination of interstitial fluid and solutes from the brain. 2μL of 100μM soluble, fluorescent fixable amyloid β (Aβ) were injected into the CSF of the cisterna magna of 6-10 and 24-30 month-old male mice and their brains were examined 5 and 30 mins later. At 5 mins, immunocytochemistry and confocal microscopy revealed Aβ on the outer aspects of cortical arteries colocalized with α-2 laminin in the pial-glial basement membranes. At 30 mins, Aβ was colocalised with collagen IV in smooth muscle cell basement membranes in the walls of cortical arteries corresponding to the IPAD pathways. No evidence for drainage along the walls of veins was found. Measurements of the depth of penetration of tracer were taken from 11 regions of the brain. Maximum depths of penetration of tracer into the brain were achieved in the pons and caudoputamen. Conclusions drawn from the present study are that tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. The exit route is along IPAD pathways in which Aβ accumulates in cerebral amyloid angiopathy (CAA) in Alzheimer's disease. Results from this study suggest that CSF may be a suitable route for delivery of therapies for neurological diseases, including CAA.

Roxana Carare qualified in Medicine in Bucharest in 1994. During her basic clinical training, she became fascinated by anatomy and completed her PhD in experimental neuropathology in 2006, in the University of Southampton, UK. She was appointed lecturer in 2001, associate professor in 2014 and professor of clinical neuroanatomy in 2016. The main international recognition for Roxana Carare has come from the interdisciplinary research she leads, investigating the cause of Alzheimer's disease and suggesting therapeutic strategies. Roxana is a member of the MRC Dementia Platform UK Vascular Experimental Medicine committee and the UK government advisory committee for the effects of pollution on the brain. The Carare team has won prestigious awards, including a Dementia Research Leader award from Alzheimer's Society UK. Roxana has enjoyed teaching anatomy for 20 years, with a passion for neuroanatomy. Roxana chairs the committee for equality, diversity, intersectionality and inclusivity in the Faculty of Medicine, University of Southampton and is Co-Chair for The International Alliance of Women Alzheimer's Researchers in Alzheimer's Association.

FLOW RESISTANCE OF THE BRANCHED NETWORKS OF CEREBRAL PERIVASCULAR SPACES

M. Keith Sharp[1], Mohammad M. Faghih[1]

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Abstract. Transport of tracers has been documented in the "glymphatic" (outer, paravascular space surrounding cerebral arteries and veins between the pial membrane and the astrocyte end feet (Fig. 1) and along basement membranes between arterial smooth muscle cells (inner, periarterial space inside the pial membrane). Direct observation of convection in these spaces is limited to the larger pial vessels. Measurements in smaller vessels is challenging due to the small sizes and to limited optical access through the surrounding tissue. Thus, to evaluate the potential for flow in these spaces, one-dimensional network models were constructed [1]. Measured dimensions of arteries from the vertebral and internal carotid to the middle, anterior and posterior cerebral arteries were used, while dimensions of smaller vessels down to the capillaries were scaled by a Murray's model. The annular perivascular gaps were also scaled from reported values. Total resistance of the periarterial, paraarterial and paravenous networks were quantified with and without porous media in the channels.

It was found that for a pressure difference from the capillaries to dural lymphatic ducts of 14 mmHg to drive a flow of 0.13 ml/min (extrapolated from estimates in rat brains and from systemic lymphatics in humans) in the human periarterial space, the resistance without porous media is about 4 million times too large, and with porous media is about 2 billion times too large. Because the hypothesized glymphatic circulation begins and ends in the cerebral subarachnoid space, the available pressure difference to drive steady flow is limited to the transmantle pressure difference of about 0.03 mmHg. For the same flow rate to be driven in the paraarterial space, a pressure difference of 0.15 mmHg would be required, which is higher than the transmantle pressure difference. With porous media, the required pressure difference becomes 99 mmHg. The required pressure differences for the paravenous space is only 0.00023 mmHg without porous media, but is 0.36 mmHg with porous media.

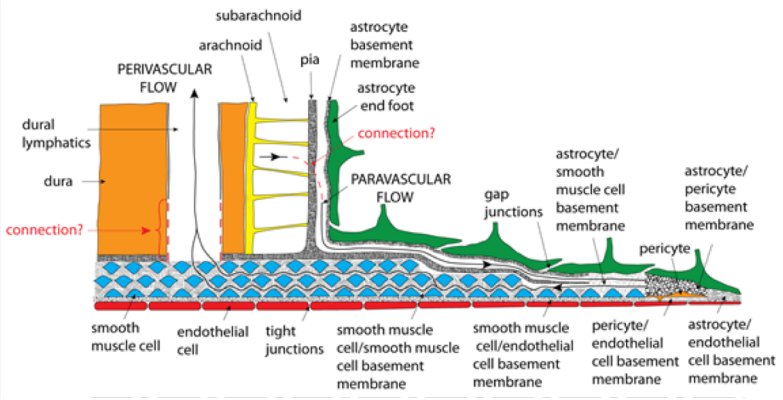
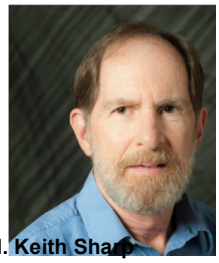


Fig. 1. Hypothetical periarterial and paraarterial flow channels in a cerebral artery.

Even given the uncertainties associated with the models and parameter values, significant flow in the periarterial space seems highly unlikely. For the glymphatic circulation, plausibility of flow depends on the absence of porous media, because resistance with porous media is much too high to support the estimated flow. Without porous media, the paraarterial resistance estimated by the model is within an order of magnitude of that available to drive the flow, thus further study is required to definitively judge the likelihood of significant flow in these channels. Paravenous resistance is low enough that flow may be driven by the transmantle pressure difference.

1.Sharp MK, Faghih MM (2018). Is bulk flow plausible in perivascular, paravascular and paravenous channels? Fluids Barriers CNS 15:17. https://doi.org/10.1186/s12987-018-0103-8



M. Keith Sharp

About the Presenter: M. Keith Sharp, ScD, PE, ASME Fellow, is an Emeritus Professor of Mechanical Engineering at the University of Louisville. He received BS, MS and ScD degrees in mechanical engineering from the University of Cincinnati, Colorado State University and Massachusetts Institute of Technology, respectively. Research interests include flow and transport in cerebrospinal fluid in the brain and in the spine, flow-induced blood damage, and passive heating and cooling of buildings.

CSF Dynamics: Modeling, clinical measurements and is it abnormal in idiopathic normal pressure hydrocephalus compared to healthy?

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Abstract.

With respect to the dilated ventricles and that CSF shunting is an effective treatment it is natural to hypothesize and expect that patients with Normal pressure hydrocephalus (NPH) have a disturbance in their CSF dynamics. However, the specifics of the CSF dynamic disturbance have not been clearly documented. One reason for this is that measurements of the main parameters in CSF dynamics, intracranial pressure (ICP) and CSF outflow resistance (Rout), requires infusion investigations which involves invasive lumbar puncture, data on healthy is therefore sparse. This makes both the diagnosis and selection of patients for shunt surgery challenging.

CSF dynamics can be assessed with infusion investigation. Rout is determined from the relationship between ICP increase and infusion rate, while the compliance can be determined from the cardiac-related ICP pulsations at different pressure levels. Typically, the pulse pressure amplitude increases as the pressure is raised. To analyze infusion pressure and flow data we use lumped models of the CSF dynamic system.

In this talk we will present the infusion method that we use in the clinic in Umeå[1], together with the Marmarou-Avezaat lumped model[2] that we use for the analysis. The validity[3,4] of the assumptions in the model will be discussed and a study investigating if the CSF hydrodynamic profile of INPH is disturbed in relation to healthy elderly will be presented[5]. We will furthermore reflect on how the lumped model can be extended in order to include the glymphatic pathways.

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2. Marmarou A, Shulman K, Rosende RM. (1978) A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. J Neurosurg. 1978 Mar;48(3):332-44
3. Andersson N, Malm J, Eklund A. (2008) Dependency of cerebrospinal fluid outflow resistance on intracranial pressure. J Neurosurg. Nov;109(5):918-22
4. Qvarlander S, Lundkvist B, Koskinen LO, Malm J, Eklund A. (2013) Pulsatility in CSF dynamics: pathophysiology of idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 2013 Jul;84(7):735-41.
5. Jacobsson J, Qvarlander S, Eklund A, Malm J. (2018). Comparison of the CSF dynamics between patients with idiopathic normal pressure hydrocephalus and healthy volunteers. J Neurosurg. 2018 Nov 1:1-6.

About the Presenter: Anders Eklund is Professor in Biomedical at the Department of Radiation Sciences Umeå University and also has a position at the R&D-department of Biomedical Engineering at Umeå University Hospital. His research field is models and measurement techniques concerning the physiological fluid dynamics, specifically for the brain and the eye. Eklund has published more than fifty journal papers within the field of hydrocephalus.

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UNCERTAINTY QUANTIFICATION OF PARENCHYMAL TRACER DISTRIBUTION USING RANDOM DIFFUSION AND CONVECTIVE VELOCITY FIELDS

Matteo Croci[1, 2], Vegard Vinje[2], Marie E. Rognes[2]

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[2] Department of Numerical Analysis and Scientific Computing, Simula Research Laboratory, Fornebu, Norway

Abstract. Over the last decade, there has been a significant renewed interest in the waterscape of the brain; that is, the physiological mechanisms governing cerebrospinal fluid and interstitial fluid (ISF) flow in (and around) the brain parenchyma. A number of new theories have emerged including the glymphatic system, the intramural periarterial drainage theory, and the Bulat-Klarica-Oreskovic hypothesis, along with critical evaluations. A great deal of uncertainty and a number of open questions relating to the roles of diffusion, convection and clearance within the brain parenchyma remain. Replacing partial differential equation (PDE) parameters subject to uncertainty with spatially correlated random fields is a common modelling choice in the uncertainty quantification literature to quantify how uncertainty in model input propagates to uncertainty in model output.

With this study, we aimed to rigorously quantify how the aforementioned uncertainties in the physiological parameters and in ISF flow affect the spread of a tracer from the SAS into the brain parenchyma. We assumed movement of tracer in the brain parenchyma to occur by diffusion and/or convection. To account for uncertainty and variability, we circumvented the lack of precise parameter values by modelling velocity and diffusivity as Mat\'ern stochastic fields (Fig. 1). We then set up a PDE model with these stochastic fields as coefficients and quantify the uncertainty in the model prediction via the Monte Carlo (MC) method.

In models of pure diffusion, the expected amount of tracer in the gray matter reached peak value after 15 hours, while the white matter does not reach peak within 24 hours with high likelihood. Models of the glymphatic system behaved qualitatively similar as the models of pure diffusion with respect to expected time to peak but displayed less variability (Fig. 2.). However, the expected time to peak was reduced to 11 hours when an additional directionality was prescribed for the glymphatic circulation. Even when uncertainties are taken into account, we find that diffusion alone is not sufficient to explain transport of tracer deep into the white matter as seen in experimental data. A glymphatic velocity field may increase transport if a directional structure is included in the glymphatic circulation.

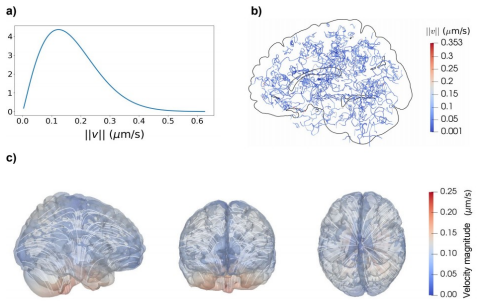

Fig. 1. Stochastic model of a glymphatic velocity field with and without additional directionality. **(a)** Probability density of the velocity magnitude. **(b)** Streamlines of a velocity sample. **(c)** Velocity magnitude and streamlines for the additional directional field. The flow field is assumed to follow cardiovascular pulses upwards along the brain stem.

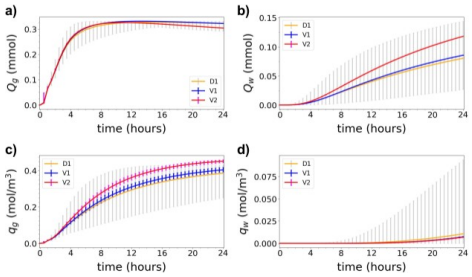

Fig. 2. Glymphatic velocity with directionality model (V2) in comparison with pure diffusion model (D1) and without directionality (V1). The integrated amount of tracer in the **a)** gray matter and **b)** white matter over time. The average tracer concentration in a subregion of **c)** gray matter and **d)** white matter over time. The curves show the expected values while vertical bars indicate the 99.73% confidence intervals of the different models.

1. M. Croci, V. Vinje and M.E. Rognes Uncertainty quantification of parenchymal tracer distribution using random diffusion and convective velocity fields. bioRxiv 665109 https://doi.org/10.1101/665109

About the Presenter: Marie E. Rognes, PhD in applied mathematics and numerical analysis, is Chief Research Scientist at Simula Research Laboratory, Norway. Rognes research revolves around numerical methods for partial differential equations, with particular emphasis on modelling cerebral mechanics. She is recipient of the 2015 Wilkinson Prize for Numerical Software, the 2018 Royal Norwegian Society of Sciences and Letters Prize within the Natural Sciences and a 2016 ERC Starting Grant.

CSF PRODUCTION – NOW WITH COTRANSPORT OF WATER

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Abstract. The mammalian brain is bathed in the cerebrospinal fluid (CSF), which is continuously secreted by the choroid plexus located in each of the four ventricles. The CSF production was generally assumed to take place by transepithelial transport of ions followed by osmotically obliged, passive movement of water, partly via the water channel aquaporin 1 (AQP1) expressed at the luminal membrane of the choroid plexus. The limitations of such a conventional osmotic model for CSF production are apparent from the minimal effects of genetic deletion of AQP1 and the ability of the choroid plexus epithelium to transport water *uphill* against a transepithelial osmotic gradient. A number of cotransporter proteins have the inherent ability to cotransport water along with the ions/solutes in the translocation mechanism in a manner that permits water to be transported independently of an osmotic gradient. This talk will introduce the water-translocating Na^+,K^+,$2Cl^-$ cotransporter, NKCC1, as a key contributor to CSF production in the murine choroid plexus. The NKCC1 cotransport protein is located in the luminal membrane of the choroid plexus and is poised for ion and water transport *from* the choroid plexus epithelial cell to the ventricle. With its inherent ability to transport water along with the ion translocation, NKCC1 is able to move water independently of the osmotic gradient and in this manner contribute approximately half of the CSF secretion across the luminal membrane.

Nanna MacAulay

About the Presenter: Nanna MacAulay is Professor of molecular neurophysiology at Department of Neuroscience at University of Copenhagen. Professor MacAulay is trained in water transport across cell membranes and has in the past decades aimed at revealing the molecular mechanisms governing transmembrane water movement in different cellular structures and compartments in the mammalian brain.

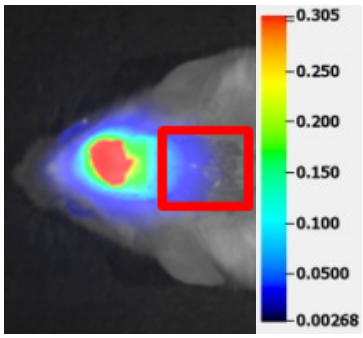

Fig. 1. This figure illustrates a mouse placed in the Li-Cor scanner with dye injected into the lateral ventricle. Movement of the dye is employed as a read-out of CSF secretion and movement.

IN VITRO MODELING OF CEREBROSPINAL FLUID SOLUTE TRANSPORT

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Introduction: CSF-based therapeutics are under development for treatment of devastating central nervous system (CNS) diseases such as leptomeningeal cancer, adrenomyoneuropathy, Tay Sachs disease, subarachnoid hemorrhage, multiple sclerosis, spinal muscular atrophy, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and others. These therapeutics all leverage CSF to either deliver or remove solutes to the CNS system. Unfortunately, a major barrier to therapeutic optimization is the lack of an animal model that represents human CSF dynamics. Also, large animal models are costly and only allow limited information about spatial-temporal characteristics of tracer distribution. The goal of this study was to develop a subject-specific in vitro CSF system that allows spatial-temporal quantification of solute concentration over 24 hours.

Methods. Subject-specific T2-weighted MRI images were segmented to define the 3D geometry of the intracranial and spinal CSF space. 31 pairs of anatomically realistic spinal cord nerve roots and filum terminale were then added by hand. The intracranial CSF spaces included key CSF cisterns and ventricles. To allow CSF production, ports were added to the lateral ventricles. Pulsatile CSF motion was accommodated by ports added to the superior and inferior aspect of the model. The model was 3D printed in an optically clear material, assembled, and connected to a custom oscillatory CSF flow pump.

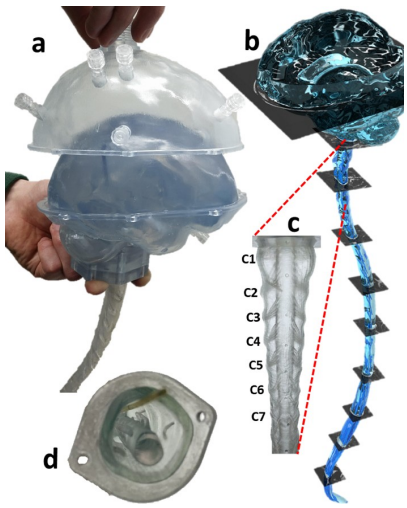

Fig 1. (a) 3D printed CSF model, (b) digital reconstruction of CSF system, (c) cervical spine detail showing 3D printed nerve roots, and (d) interior view.

The following imaging method was developed to quantify fluorescein solute spatial-temporal distribution. The model was setup in a dark enclosure to remove ambient light sources and fluorescein excitation was achieved with blue wavelength LEDs. To correct for photooxidative decay, time-lapse imaging was obtained over 24-hours with the model containing fluorescein at a known concentration. An analogous series of images were then collected with fluorescein injected at multiple locations under various injection scenarios (e.g. bolus volume, injection location, flush volume, filtration loop, and others) with various CSF flow waveforms (e.g. magnitude, frequency, respiratory vs. cardiac). Fluorescein concentration was computed for each experiment based on the ratio of signal intensity at each time-point compared to the baseline decay.

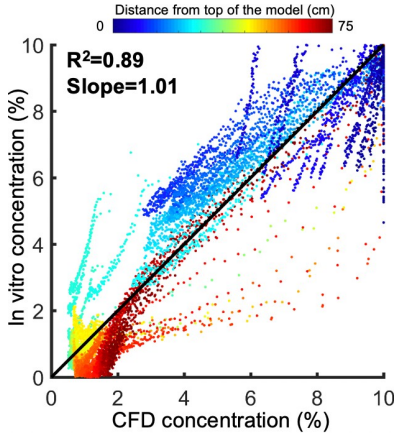

Fig 2. Regression of in vitro versus CFD concentration results over 24h.

The following computational fluid dynamics (CFD) study was performed to help verify the in vitro solute concentration results. The pulsatile in vitro CSF flow field was solved using ANSYS Fluent and then used to obtain the steady-streaming velocity field throughout the model. The steady-streaming velocity field was used as a "frozen flow" in the ANSYS mixture multi-phase fluid model to solve the volume fraction equation to obtain spatial-temporal tracer concentration over 24-hours with the solute modeled as a bulk fluid phase within the CSF. In vitro results for a specific injection scenario were compared to CFD by linear regression of the average tracer concentration for 3 mm thick axial slices.

Results. The final 3D printed MRI-compatible CSF system model is shown in **Fig 1**. Total spinal CSF volume was 100.3 mL. Intracranial CSF volume was 221.6 mL. Hydraulic diameter and Womersley number had an average value of 6.2 mm and 9.8 within the subarachnoid space, respectively. Maximum Reynolds number was 461. Steady-streaming velocity magnitude predicted by CFD in cranial CSF was ~50X smaller than the spine. Agreement between in vitro and CFD spatial-temporal solute concentration was relatively strong for all injection scenarios examined (sample results, R^2 = 0.89, slope 1.01, **Fig 2**).

Dr. Bryn Martin

Conclusion. The in vitro CSF system model allows quantification of spatial-temporal solute concentration for various CSF therapeutics. Agreement of CFD and in vitro concentration results help verify the imaging and CFD methods.

About the Presenter: Bryn Martin is an Associate Professor of Biological Engineering at the University of Idaho (2015-present). Martin earned a PhD in Mechanical Engineering at the University of Illinois (2008) and completed post-doctoral studies at the Swiss Federal Institute of Technology, EPFL (2009-2012) (http://www.niml.org).

INTRACRANIAL PRESSURE ELEVATION ALTERS CSF CLEARANCE PATHWAYS

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[2] Department of Radiation Sciences, Umeå University, Umeå, Sweden
[3] Department of Mathematics, University of Oslo, Oslo, Norway

Abstract. In a manner similar to a clinical infusion test, investigations of the glymphatic system often include an infusion protocol demonstrated to increase intracranial pressure by several mmHg [1]. During an infusion test in humans, fluid is assumed to exit through the arachnoid granulations, while in the glymphatic theory, flow into paravascular spaces also play a major role. In this work we aimed to model cerebrospinal fluid distribution to different outflow routes at baseline and at elevated intracranial pressure. We used a two-compartment model consisting of the subarachnoid space and the paravascular spaces. For the arachnoid granulations (AG), the cribriform plate (Crib), capillaries (Cap) and paravascular spaces (PVS), resistances were calculated and used to estimate flow before and during a standard infusion test. In addition, pressure in the subarachnoid space and paravascular spaces were computed. Different variations to the model were also tested to evaluate the sensitivity of selected parameters. At baseline, we found a very small paravascular flow directed into the subarachnoid space, while 60% of the fluid left through the arachnoid granulations and 40% left through the cribriform plate. However, during the infusion, paravascular flow reversed and 25% of the fluid left through these spaces, while 60% went through the arachnoid granulations and only 15% through the cribriform plate. The relative distribution of CSF flow to different clearance pathways depends on intracranial pressure, with the arachnoid granulations as the main contributor to outflow. Paravascular flow was reversed during an infusion test.

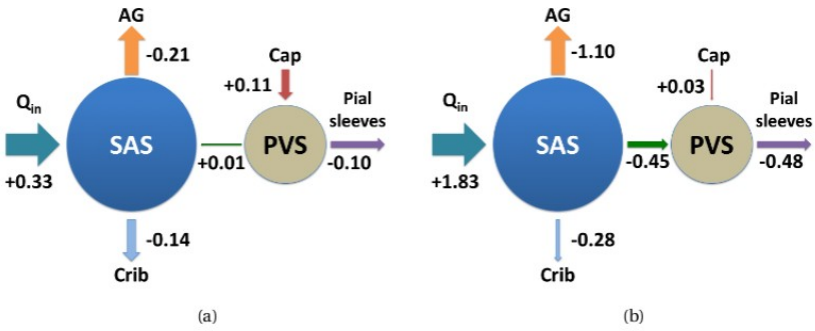

Figure 1: Illustration of the outflow distribution in mL/min (a) before and (b) during infusion. The size of the arrows are proportional to Q_{in}. Note that the net CSF flow from the PVS to the SAS changes direction and magnitude during infusion.

1.J. J. Iliff, M. Wang, D. M. Zeppenfeld, A. Venkataraman, B. A. Plog, Y. Liao, R. Deane, and M. Nedergaard. Cerebral arterial pulsation drives paravascular CSF–interstitial fluid exchange in the murine brain, *Journal of Neuroscience*, 33(46):18190–18199, 2013.

About the Presenter: Vegard Vinje has a MSc in mathematics and fluid mechanics from the University of Oslo, and is currently a PhD-student at Simula Research Laboratory. His work is mainly focused around pulsatile CSF dynamics in the central nervous system, and in particular mechanisms for waste removal from the brain over different time scales.

IMAGING AND MODELING GLYMPHATIC RESPONSES AFTER DIABETES

QuanJiang, Esmaeil Davoodi-Bojd, Li Zhang, Guangliang Ding, Michael Chopp and Zhenggang Zhang

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Abstract. Brain was long considered to be devoid of a conventional lymphatic system. Recent studies[1, 2] have fundamentally altered the traditional function of cerebrospinal fluid (CSF) hydrodynamics and led to the conceptualization of a new system, the glymphatic system[1], responsible for clearance of interstitial solute from the brain parenchyma. The glymphatic system plays an important role in neurological diseases[1-3].

The glymphatic system is preferably studied in the living system and to-date, most studies of the glymphatic system have been performed with two-photon laser scanning microcopy, which is excellent for a predetermined small para-vascular space; however, this approach is invasive and not a suitable tool for whole brain study, especially for deep brain tissues. In current talk, whole brain dynamic real time imaging of the glymphatic system will be demonstrated and different quantitative analysis and modeling will be discussed with and without neurological diseases. We will also introduce a new model of the glymphatic system from the kinetics of Gd-DTPA tracer measured by MRI in order to: 1) map the glymphatic system path, 2) derive kinetic parameters of the glymphatic system, and 3) provide quantitative maps of the structure and function of this system. We use the MRI data of healthy and Diabetes mellitus (DM) animals to assess the performance of the model in differentiating affected tissues. The results from this new model exhibit its better sensitivity to differential diabetic and control animals than previous two-compartment kinetic model and show increased clearance time and binding of tracers in diabetic compared with control animal brain (Figure 1). Our results show that modeling glymphatic system using dynamics of the tracer can reveal characteristic maps of the paravasculatures. The resulted parameters may be used in diagnosis and treatment evaluation of brain diseases.

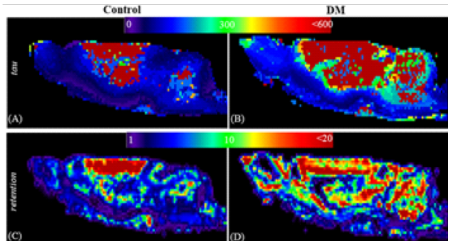

Fig. 1. The maps of quantitative modeling the glymphatic system for control and DM animals. Fig 1 shows the visual comparison of the clearance time constant, tou (minutes, A, B) and the retention (C, D) maps under control (A, C) and DM (B, D) conditions. Comparing with the control, DM animal exhibits longer clearance time constant (slower clearance of the tracer from the tissue) and high retention values (large fraction of the tracer remains in brain tissue).

1. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013;342:373-377
2. Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, et al. Cerebral arterial pulsation drives paravascular csf-interstitial fluid exchange in the murine brain. J Neurosci. 2013;33:18190-18199
3. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates csf flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Science translational medicine. 2012;4:147ra111.

Quan Jiang

About the Presenter: Quan Jiang. He received the B.S. degrees in physics from Zhejiang University, Hangzhou, China, in1982 and the M.S. degrees in nuclear physics from Idaho State University, Pocatello, ID, in 1987 and Ph.D. degrees in medical physics from Oakland University, Rochester, MI, in 1991, respectively. Since 1991, he has been with the Department of Neurology, Henry Ford Health System, Detroit, MI, where he is currently a Senior Staff Scientist. Since 2003, he has been with the Department of Neurology of Wayne State University where he is currently a full adjunct Professor. He has published over130 papers in peer reviewed journals and book chapters. He has served on the study sections of the National Institutes of Health (NIH) and other funding agencies.

A GENERAL, CONSOLIDATED PIPELINE FOR INVESTIGATING THE TRAJECTORY OF ALZHEIMER'S DISEASE: INSIGHT INTO THE UNDERLYING MECHANISMS OF THE NEUROVASCULAR UNIT IN DIFFERENT REGIONS OF THE BRAIN

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Abstract. Alzheimer's Disease (AD) can be deemed as a heterogeneous mixture of multiple age-related neurodegenerative factors and vascular related pathologies. The hallmark pathological features of the disease are the extracellular deposition of amyloid-β peptide into parenchymal senile plaques or within the walls of arteries and capillaries, in addition to the aggregation of hyperphosphorylated tau into intracellular neurofibrillary tangles and neuropil threads. Evidence also suggests that AD may be a vascular disorder, caused by impaired cerebral perfusion, which is observable at the early stages of the disease (Mild Cognitive Impairment (MCI) - an intermediate state between normal ageing and dementia). Hypoperfusion may be promoted by cardiovascular risk factors, and these are known to be strongly influenced by lifestyle. In order to develop an understanding of the exact nature of such a hypothesis, a biomechanical understanding of the influence of lifestyle factors is pursued. Specifically, we statistically analyze the influence of the level of physical activity, on: (i) the clearance of CSF/ISF; (ii) blood perfusion; and (iii) swelling and drainage of CSF/ISF in 10 regions of the brain (such as the hippocampus, brainstem etc.). A consolidated pipeline (see Fig. 1) that integrates three key components: a 3D multiporoelastic-based model of perfused parenchymal tissue; an accurate, fully automated image-based model personalization workflow (subject-specific meshes, permeability tensor maps); and a subject-specific boundary condition model is used to obtain the solution fields of interest. The subject-specific datasets used in the modelling were collected as part of prospective data collection. For this work, a cohort size of 35 subjects (20 controls and 15 MCI subjects - stratified with respect to gender) were used to conduct the analysis. Key results garnered from this study include: (i) For perfusion in the right ICA, there was a statistically significant (SS) simple two-way interaction of cognitive status and gender during high activity (p < 0.0005), a SS simple main effect of gender for MCI subjects during high activity (p < 0.0005); (ii) SS differences in hippocampal (the right portion) neurovascular unit swelling between CHC males and MCI females during both activity states (p = 0.025). Furthermore, a combination of the Kruskal-Wallis H-Test and Wilcoxon Signed Rank Test was used to analyze all the data at our disposal, giving rise to a plethora of SS findings for the ten regions of interest.

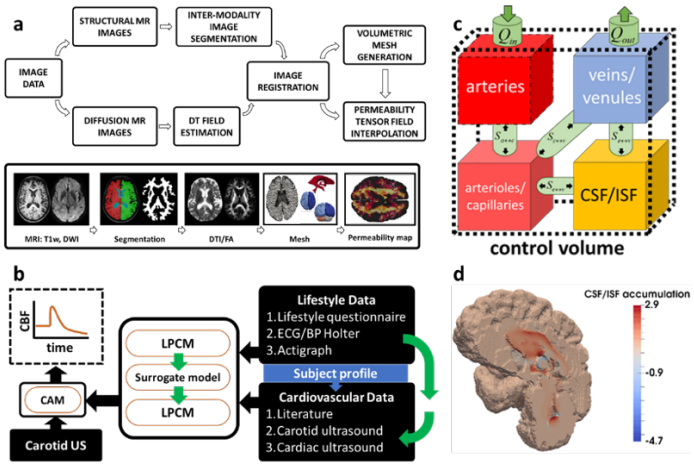

Figure 1. The consolidated pipeline that incorporates: (a) an image-based model personalization module; (b) a subject-specific modelling pipeline for acquiring personalised cerebral blood flow waveforms that are fed into the 3D MPET solver (c). A typical solution field (swelling of CSF/ISF) is shown in (d). Ageing and lifestyle related patient-specific boundary conditions are generated following the data collection and subject-based model parameterization. The personalization of the lumped parameter circulation model (LPCM) was accelerated via a surrogate model to approximate its input-output response. LPCM = Lumped parameter circulation model, CAM = cerebral autoregulation model.

John C. Vardakis

About the Presenter: John Vardakis holds a PhD in Integrative Cerebral Dynamics from the University of Oxford. He is a Postdoctoral Research Scientist in the field of Brain Biomechanics, working within the Fluidics & Biocomplexity Group at UCL. His focus is on developing computational frameworks that will aid in the understanding of cerebral diseases within the realm of Dementia. The foundations of the mathematical modelling that he works on lie in Multiple-Network Poroelastic Theory, adapted to patient specific cases and simulated through a combination of CFD and in-house FEM-based numerical templates.

Dependence of intracranial pressure on pressures in other body compartments

B. Bausch[1, 2], V. Kurtcuoglu[1], M. Schmid Daners[2]

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

Abstract. The exact pathogenesis of hydrocephalus is still unknown. There is limited data on the physiology of healthy intracranial pressure (ICP) and its interaction with pressures in other body compartments such as the large body cavities (e.g. thorax, abdomen), the cardiovascular system or the lymphatic system. Imbalance of cerebrospinal fluid (CSF) production and reabsorption, which may be a reflection of, in part, local changes in said interaction, can manifest itself in hydrocephalus. Current shunt systems for the treatment of this pathologic condition may cause CSF overdrainage or induce unphysiological fluctuations in CSF drainage during changes in body posture. A potential solution are adaptive shunts, i.e. ones that dynamically adjust the drainage rate to the patient's current physiologic need. However, adaptive shunts require quantitative knowledge of the underlying pathophysiology. The goal of this study is to contribute towards developing this knowledge.

We have established a method for measuring ICP in rats at an acquisition rate of 500 Hz. We acquired telemetrically ICP and pressures in various body compartments of 68 healthy rats, and examined these data. Radio telemetric transmission enables data collection in real time in absence of the researcher, allowing animals to move and change body position freely and naturally in the cage. Additionally, the experimental animals were trained to perform specific posture changes, imitating upright and supine human body positions. Since the transmitters can broadcast at two different frequencies, it is possible to keep the animals in pairs during the experiments. This allows a staggered experimental setup with 8-12 animals per experimental group. Pressure data were acquired over a period of 4 weeks for each animal and their activities were additionally video-monitored.

With our rat model, we intend to lay the basis for a deeper understanding of the physiologic interactions of individual body compartments influencing ICP and fluid volume shifts. The results of this study shall contribute to the development of new shunt systems that adapt automatically to the real physiological needs of the patient. Our findings serve as a basis for investigations of these parameters in a large animal model (sheep). Those results will be used for in-vitro and in-silico models and corresponding simulations.

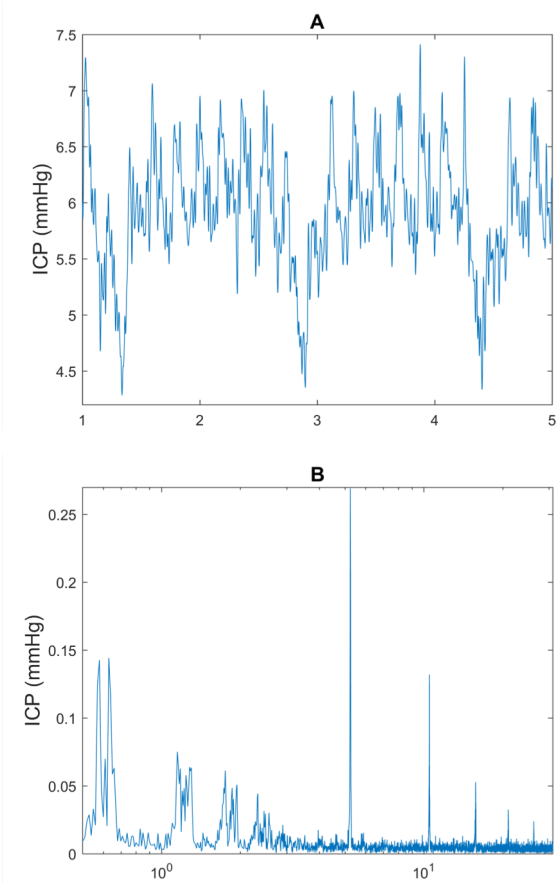
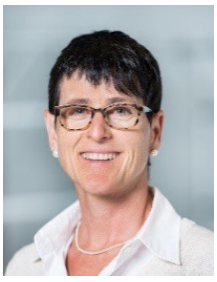


Fig. 1 Example of intracranial pressure (ICP) recording of a rat showing ICP fluctuations (A) due to cardiovascular action and respiration. In B the corresponding frequency content is given (cardiac action: 5 Hz (300 bpm) and respiration: 0.6 Hz (36 bpm)).



Dr. Marianne Schmid Daners

About the communicating author:
Marianne Schmid Daners heads the Biomedical Systems group of the Product Development Group Zurich. Her research interests are the modeling and control of biological systems and the development and control of biomedical devices. She graduated in 2006 as a mechanical engineer at ETH Zurich, Switzerland, and received her PhD in 2012 at the Institute for Dynamic Systems and Control at ETH Zurich on the topic of "Adaptive Shunts for Cerebrospinal Fluid Control".

Cranial pulse modulation: from blood flow to drug delivery

Mark G. Luciano[1], Stephen Dombrowski[2], Sara Qvarlander[3], Francis Loth[4], Riccardo Serra[1]

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[2] Department of Neurosurgery, Cleveland Clinic, Cleveland , OH, USA
[3] Department of Radiation Sciences- Biomedical Engineering, Umea University, Umea, Sweden, Country
[4] Department of Mechanical Engineering, University of Akron, Akron, OH, USA
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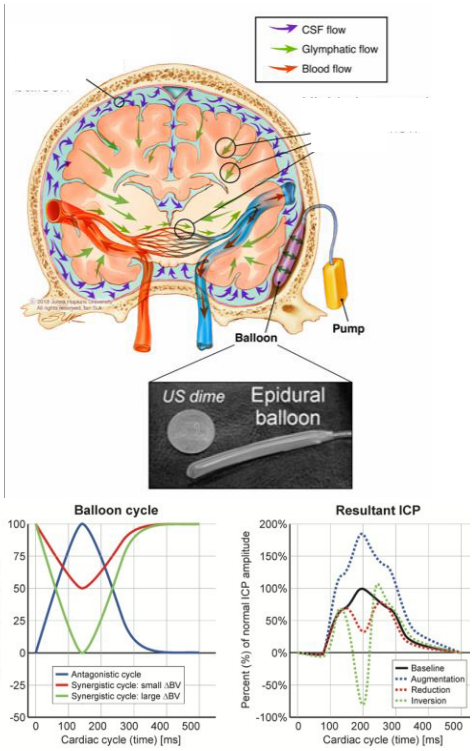
Abstract. The amplitude and pattern of intracranial pressure pulsation can be modified with a cardiac-gated cranial balloon implant. This approach may be used as a tool to evaluate the potential physiological effects of intracranial pulsation, including changes in brain morphology, cerebral blood flow, and CSF/solute movement. In this study we compare three forms of pressure modulation: augmentation, reduction, and inversion of the ICP waveform for effects on cerebral blood flow and systemic dynamics. The study utilizes a randomized individual-controlled, longitudinal comparison of the three ICP pulse modulation effects in dogs. We found differential effects on intracranial pressure, cerebral blood flow (thermodilution), and systemic dynamics, with pulse inversion resulting in the greatest change in cerebral blood flow. In addition, laser-doppler blood flow measurement suggests alteration in pulsatility of tissue blood flow. These studies reinforce the potential physiological influence of intracranial pressure oscillation in a rigid cranium. The changes in ICP pressure oscillation on blood and CSF flow may be of clinical interest, not only for increasing blood flow, but also in brain clearance and drug delivery. Current studies are aimed at evaluating the effect of pulsation changes on CSF tracer distribution.



About the Presenter: Mark G. Luciano, MD, PHD is the Berry-Brem Professor of Neurosurgery at Johns Hopkins University and Director of the CSF Disorders Center. He is a Pediatric and Adult Neurosurgeon centering his clinical interests on the variety of CSF disorders including hydrocephalus, intracranial hypertension and intracranial hypotension, Chiari malformation and neuroendoscopy. He is a founding member of the Adult Hydrocephalus Research Network and has participated in multiple clinical studies including directing a current multi-national trial on shunting in NPH. His transitional laboratory work includes testing of new materials, devices and methods for shunt diversion and his experimental work includes NIH-supported studies on cerebral angiogenesis and ICP dynamics.

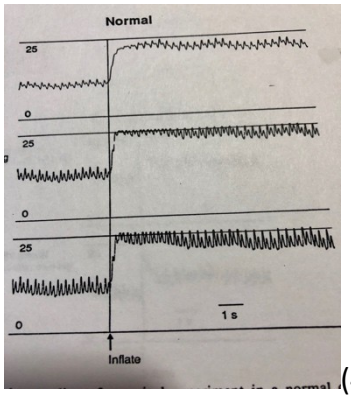
SESSION 10, TUESDAY, JULY 2, 16:00-17:00

EXPLORING THE TRANS-MANTLE PRESSURE GRADIENT IN HYDROCEPHALUS

H. Rekate MD Hofstra, Northwell School of Medicine, Hempstead, NY USA
I. Kurtcuoglu PhD Institute of Physiology, University of Zurich, Switzerland

Abstract: Despite over a century of scientific efforts to fully understand the pathogenesis and pathophysiology of hydrocephalus a great deal of controversy and confusion remain to be fully elucidated. Challenging issues in hydrocephalus research include the unique nature of infantile hydrocephalus, normal pressure hydrocephalus, normal volume hydrocephalus and negative pressure hydrocephalus. The purpose of this presentation is to move away from the concept that hydrocephalus is explained fully by what is happening to the cerebral ventricles to opening up the discussion to include the volume of the brain and the volume of the cortical subarachnoid spaces in understanding these complex conditions.

Since the seminal work of Walter Dandy in the early years of the 20th century researchers have been able to assess the changes in ventricular volume and more recently to actually measure it. The important issues that have been more difficult to define relate to the actual volume of the brain as hydrocephalus develops, the volume of the cortical subarachnoid space (CSAS) and most importantly the ability to measure a pressure differential between the cerebral ventricles and the CSAS called the "trans-mantle pressure gradient (TPG)." Whether or not the TPG actually exists has been a matter of controversy. Multiple researchers have attempted to measure this parameter and concluded that there was no TMP in either communicating nor obstructive hydrocephalus. (1, 2) More recently a TPG was measured in an acute model of hydrocephalus to be an average of 3 cm of water. (3) As seen in Figure 1 our work on the attempt to find pressure differentials in multiple CSF compartments was first interpreted to show an absence of a TPG. In retrospect however a TPG of approximately 1 mmHg can be seen in the recordings. It is likely that the TPG in hydrocephalus is present but small and very sensitive transducers are needed to measure it. Understanding of the maintenance of brain volume in acute hydrocephalus and the importance of the TPG will demystify all of the controversial issues in hydrocephalus



(4)

Fig: 1 measurements of ICP in ventricles and CSAS

Dr. Rekate is Emeritis Pofessor of neurosurgery
Studied hydrocephalus with help of engineers for 40 years
One of the founders of the International Hydrocephalus Imaging Working Group
Author of over 200 works on hydrocephalus

1. Shapiro K, Kohn IJ, Takei F, Zee C. Progressive ventricular enlargement in cats in the absence of transmantle pressure gradients. J Neurosurg. 1987;67(1):88-92.
2. Stephensen H, Tisell M, Wikkelso C. There is no transmantle pressure gradient in communicating or noncommunicating hydrocephalus. Neurosurgery. 2002;50(4):763-71; discussion 71-3.
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4. Rekate H, McCormick JM, Ko W. Failure to demonstrate a Brain Transmissibility Factor. In: Marlin AE, editor. Concepts in Pediatric Neurosurgery. 10. Basel, Switzerland: S. Karger; 1990. p. 235-42.

EXPLORING THE CEREBROSPINAL FLUID DYNAMICS OF THE AMERICAN ALLIGATOR

Bruce A. Young[1]

[1] Kirksville College of Osteopathic Medicine, A.T. Still University, Kirksville, Missouri, U.S.A.

Abstract. My long-term goal is to develop a "complete" model of cerebrospinal fluid dynamics in the American alligator (*Alligator mississippiensis*); this talk will explain my rationale for using the alligator as my model organism, summarize the results obtained to date, and describe the next round of experiments.

The compartmentalization of the CSF in *Alligator* is very different from what is seen in a healthy mammal. The spinal cord of the alligator extends to the very tip of the tail, there is no anatomical or functional equivalent to the lumbar cistern in *Alligator*. The meningeal roof of the 4th ventricle is continuous, neither a median nor lateral apertures are present. Thus from an anatomical point of view, the CSF within the ventricles and spinal central canal is segregated from the subarachnoid CSF. Previous studies have claimed that the arachnoid of reptiles is avascular; to date there is no evidence about the rate of CSF absorption at the venous sinuses associated with the meninges. Exchange between the ventricular and subarachnoid pools of CSF depends on transport across the tela choroidea. I have been exploring factors that influence transport across the tela choroidea; when the tela choroidea functions as a barrier the isolated ventricular system of the alligator approaches the system seen in obstructive hydrocephalus in humans.

Previous studies have argued that the choroid plexi are relatively larger in reptiles (presumably including *Alligator*) than in mammals. To date the Intracranial pressure recordings taken from the cranial subarachnoid CSF have not demonstrated any pressure waves that correlated with choroid arterial pulsations. I maintain the alligators on a mechanical ventilator during the experiments, and there is a clear linkage between the induced ventilatory movements and ICP pulses. While these pulses are distinct, the underlying causal mechanisms linking ventilation and ICP pulsations in *Alligator* are not clear.

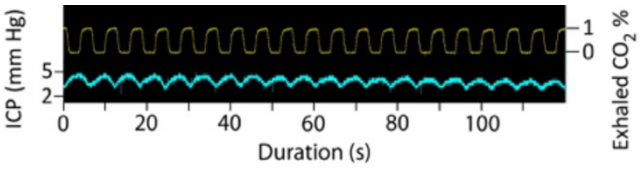

Fig. 1 Simultaneous recordings of the ventilator cycle (upper trace) and pulsations in the intracranial pressure (lower trace) from *Alligator*.

Alligators have a well-developed myodural bridge. Several researchers have postulated that the myodural bridge may function as a CSF pump, but there is no experimental evidence for this. By surgically isolating the muscles associated with the myodural bridge, the displacement of the *Alligator* dura produced by muscle contraction can be quantified. By adding a micro-bubble contrast agent to the CSF, a quantitative flow profile of the CSF can be generated. By combining quantitative flow profiles of the cerebrospinal fluid generated through orthostatic gradients, exchange at the tela choroidea, ventilatory displacements, the myodural bridge, and choroidal arterial pulsations (if any) a complete picture of the cerebrospinal fluid dynamics may begin to form. Ultimately, the goal is to compare the profile of CSF flow in *Alligator* to the flow profile found in the healthy and pathological states in humans.

About the Presenter: Bruce Young is a Professor of Anatomy at the Kirksville College of Osteopathic Medicine. His research work involves experimental analyses of complex biophysical systems. Perhaps reflective of deep-seated psychological issues, most of his research involves venomous snakes and other reptiles.


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