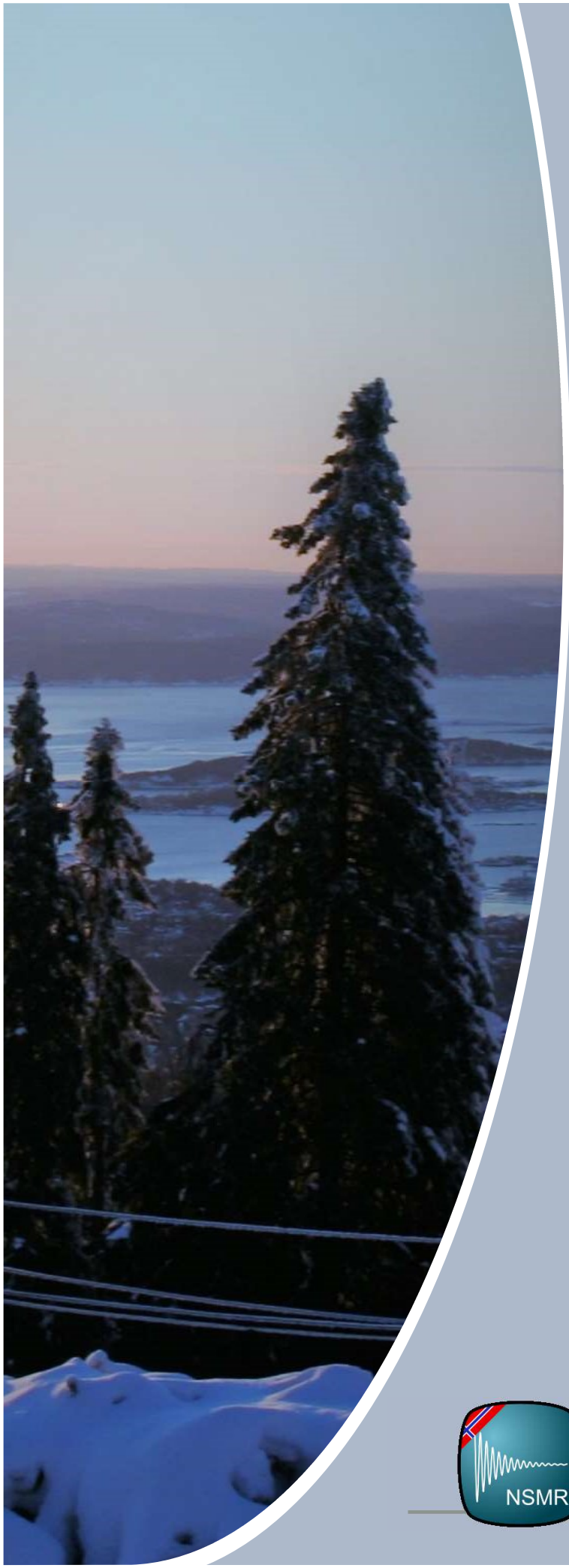

MR 2020

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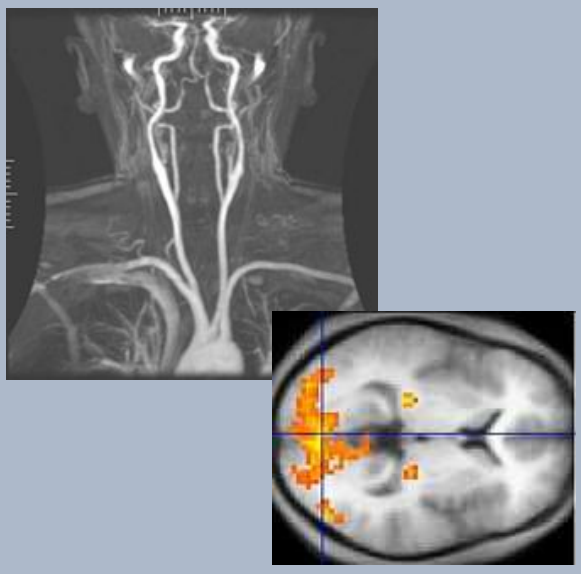
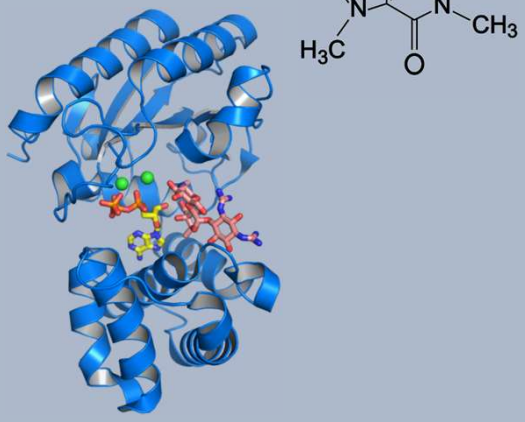




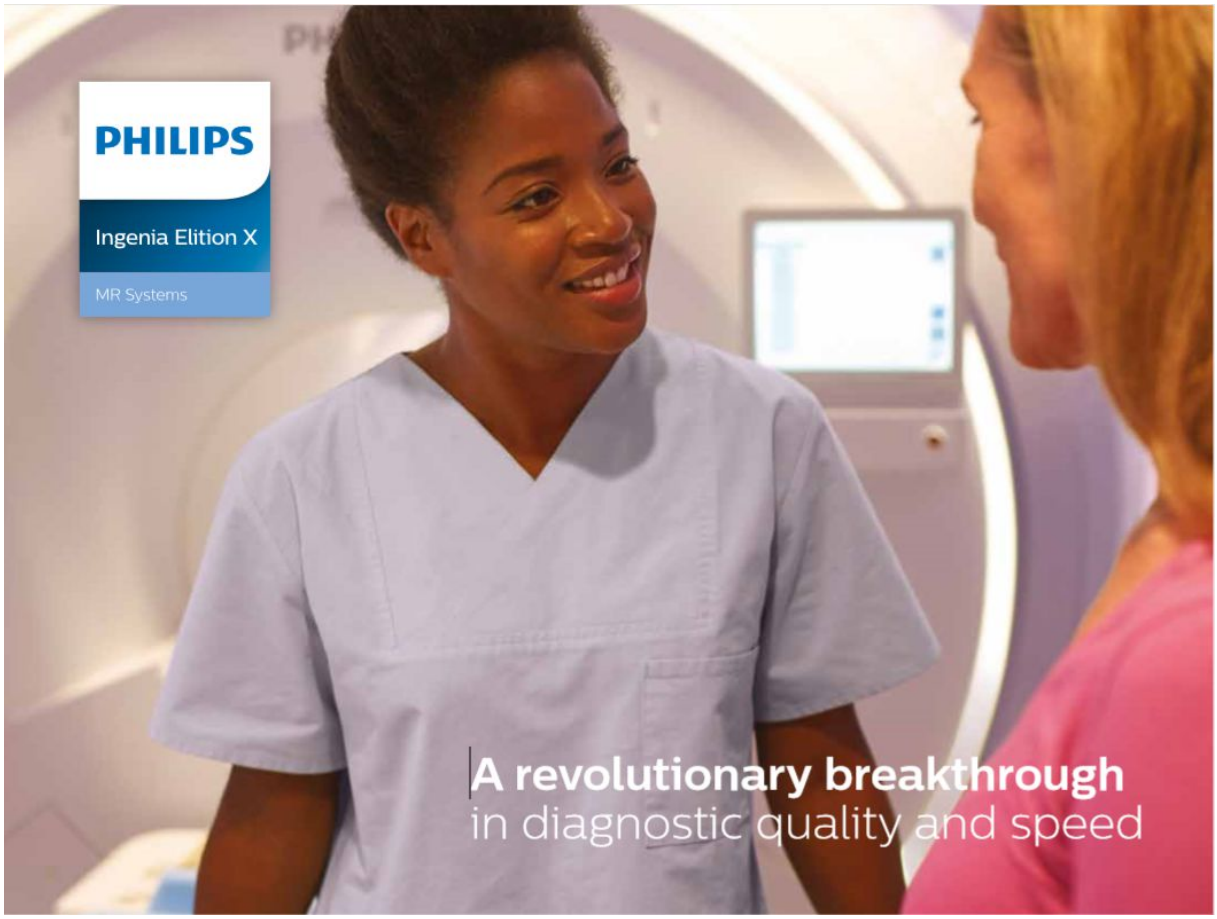
Tuesday, January 7th and
Wednesday 8th, 2020
in Oslo, Voksenåsen Hotel

NSMR

Norsk selskap for magnetisk resonans

Norwegian Society for Magnetic Resonance

PHILIPS



PHILIPS

Welcome to MR2020 in Oslo!

Dear participant at MR2020.

It is with great pleasure we welcome you to Oslo and Voksenåsen hotel for the biannual Norwegian MR meeting. This is the 16th consecutive national symposium. The venue – Voksenåsen hotel – was a gift from Norway to Sweden for humanitarian support during Second World War and has since been a center for cooperation between Sweden and Norway.

This year we have five keynote speakers; Melanie Britton (MRI and molecular processes), Timothy Claridge (NMR super sequences), Kyrre Eeg Emblem (MRI and cancer), Anders M. Fjell (MRI and brain development) and Reinhard Wimmer (NMR and biomolecules).

We have 18 orally presented contributions including the Norwegian history of MRI by Hans-Jørgen Smith and the NMR history by Bjørn Pedersen. Together with 14 poster presentations and seven vendor presentations MR2020 is covering most of the various sub disciplines in MR science and technology.

Since the MR2018 meeting in Tromsø the National NMR Platform (NNP, http://nmr.uib.no) has matured and is steadily producing results. A new 600 MHz NMR-instrument intended for metabolomics is installed in Bergen and a new 600 MHz NMR-instrument is incoming at NTNU.

The exciting addition of a 7 Tesla Siemens MR scanner at the Kavli Institute for Neuroscience in Trondheim opens up many new possibilities within the Norbrain III collaboration (Trondheim, Bergen and Oslo).

On the MR teaching front one of the universities has purchased two low field instruments which are included early in undergraduate teaching and another university is in the process of purchasing a low field instrument.

The organizing committee is very grateful to all that have chosen to visit Voksenåsen for MR2020 and we especially wish to acknowledge everyone participating with posters and oral presentations.

It is important to interact with our valued Business partners and Corporate members of the Norwegian Society for Magnetic Resonance (NSMR). Without them there would be no biannual MR meetings.

There will be a NSMR General Assembly late Tuesday. We urge you to participate. Anyone, including corporate members can participate, but only individual participants who have paid their individual membership dues can vote.

We wish you a stimulating meeting and an enjoyable stay at Voksenåsen.

Frode Rise

Frode Rise (UiO)
MR2020 Committee Leader

Bjørnar Arstad (Sintef), Morten Berntsen (UiO), Robin Bugge (OUS), Oliver M. Geier (OUS), Ingvild C. Hvinden (Oxford), Sissel Jørgensen (UiO), Massoud Kaboli (UiO), Fuad Karimov (Sintef), Per E. Kristiansen (UiO), Daniel Sachse (UiO), Kristian W. Trovik (UiO).

Norwegian National MR- and NMR-meetings

March 14 - 17 1983	Oppdal - Jostein Krane, AVH, UNIT.
May 10 - 12 1989	Geiranger - Jostein Krane, AVH, UNIT
	(Norsk Svensk NMR-diskusjonsgruppe)
October 07 - 08 1993	Ustaoset - Tore Skjetne, MR-senteret, Sintef Unimed
October 16 - 17 1995	Trondheim - Tore Skjetne, MR-senteret, Sintef Unimed
January 07 - 08 1998	Fefor - Dagfinn W. Aksnes, Einar Sletten, Nina Berg-Johannesen, UiB
January 05 - 06 2000	Geilo - Bjørn Pedersen, Frode Rise, UiO
January 09 - 10 2002	Beitostølen - Henrik W. Anthonsen, John G. Seland, Jostein Krane, NTNU
January 12 - 14 2004	Hafjell - Dagfinn W. Aksnes, Nils Åge Frøystein, Willy Nerdal, UiB
January 10 - 12 2006	Skeikampen - Frode Rise, Eddy W. Hansen, Per E. Kristiansen, UiO
January 16 - 18 2008	Oppdal - Alexander Dikiy, John Georg Seland, NTNU
January 18 - 20 2010	Storefjell - Nils Åge Frøystein, John Georg Seland, Willy Nerdal, UiB
January 11 -12 2012	Oslo - Frode Rise, Daniel Sachse, UiO
January 14 -15 2014	Trondheim - Øystein Risa, NTNU
June 16 - 17 2016	Bergen - Øyvind Halskau, Tina Pavlin, Jarl Underhaug, UiB
March 06 - 09 2018	Tromsø - Johan Isaksson, UiT
January 07 - 08 2020	Oslo
2022	Trondheim
2024	Bergen
2026	Tromsø
2028	Oslo

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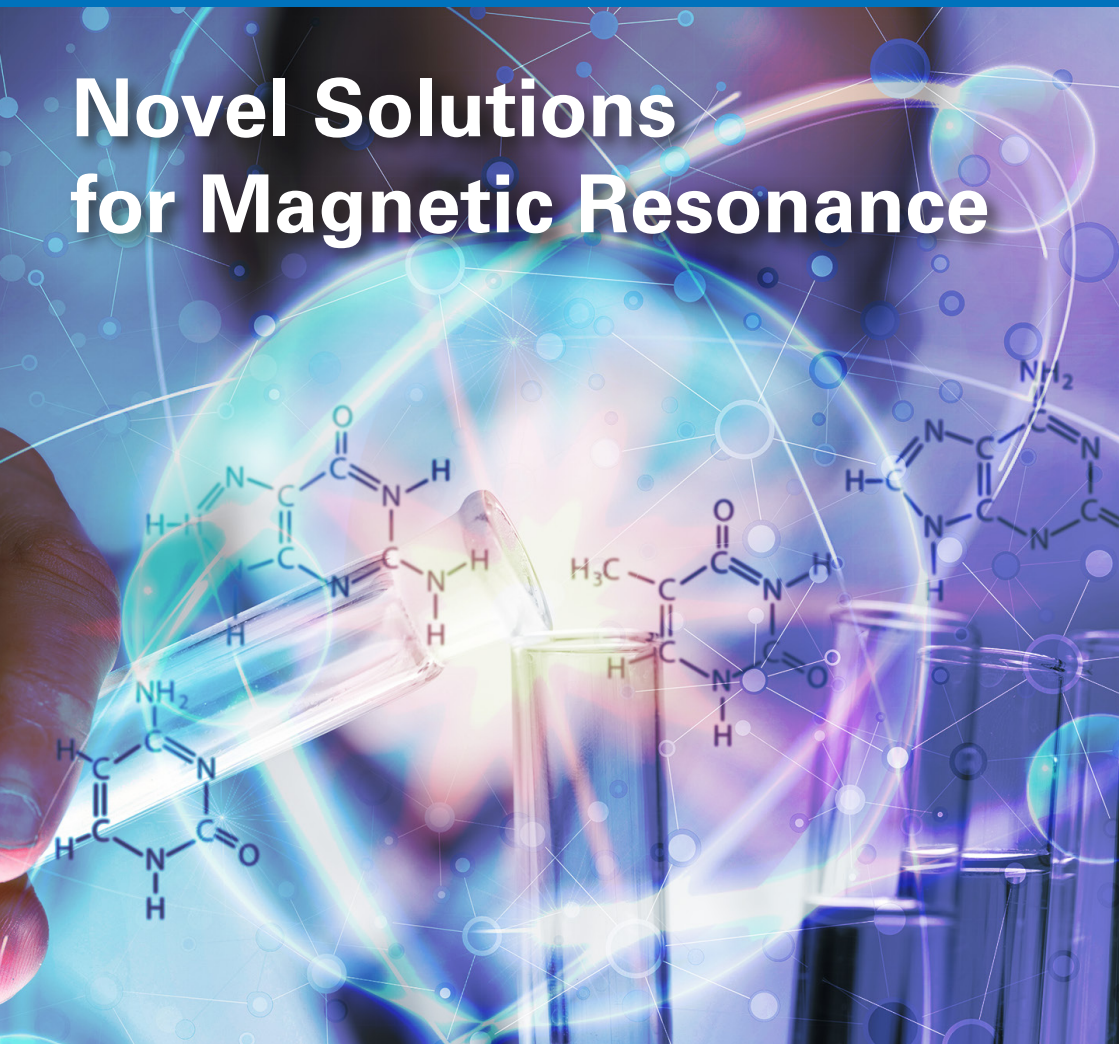

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Program MR2020

DAY 1 Tuesday 7th January

08:00 09:45 Registration/Coffe

09:45 10:00 Welcome, *Gøran Karlsson Swedish NMR Center*

Session 1, chair: *Tone Frost Bathen*

10:00 11:00 Plenary: Through the Chemical Looking Glass, what MRI can tell us about molecular processes in batteries, consumer products and engineering, *Melanie Britton*

11:00 11:30 When MRI came to Norway, *Hans-Jørgen Smith*

11:30 11:45 Workflow for Longitudinal evaluation of brain metastasis in response to gamma Knife surgery, *Lea Starck*

11:45 12:00 Echo planar imaging distortion correction and apparent relation to cerebral blood volume increase and tumor segments, *Ivar T. Hovden*

12:00 13:30 **Lunch**

13:30 13:45 Predictive Value of pre-treatment advanced DWI of intra- and peritumoral tissue in glioblastoma, *Oliver Geier*

13:45 14:00 MRI, prostate cancer and artificial intelligence, *Tone F. Bathen*

14:00 15:00 Plenary: Use of MRI to study lifespan changes in brain and cognition, *Anders Fjell*

15:00 16:00 Break, Voksenåsens "fika" *, Company presentations

Session 2, chair: *John Georg Seland*

16:00 16:15 Simultaneous diffusion weighting and editing of molecules using diffusion weighted MEGA-edited spectroscopy, *Emile S. Berg*

16:15 16:30 ^{2}H NMR study of propane and propylene mobility in ZIF-8, *Alexander E. Khudozhitkov*

16:30 16:45 NMR studies of the Na-sublattice of ionic conductors $Na_2Zn_2TeO_6$ and $Na_3Zn_2SbO_6$: How does structure relate to ionic conductivity, *Frida S. Hempel*

16:45 17:00 Raising the bar: New world-record 1.2 GHz NMR spectrometer, *Rainer Kümmerle*

17:15 18:00 Poster session

18:00 19:00 General assembly NSMR

19:30 23:00 Dinner

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DAY 2 Wednesday 8th January

Session 3, chair: *Marcella Orwick Rydmark*

09:00 10:00 Plenary: NMR supersequences for small molecule structure elucidation, *Timothy Claridge*

10:00 10:30 When NMR came to Norway, *Bjørn Pedersen*

10:30 10:45 News from JEOL lab: Elucidating novel crystalline structures with electron and NMR crystallography, *Emeline Barbet-Massin*

10:45 11:00 CSSF-CLIP-HSQMBC: Measurements of heteronuclear coupling constants in severely crowded spectral regions, *Johan Isaksson*

11:00 11:15 Break

Session 4, chair: *Johan Isaksson*

11:15 11:30 The utilization of NMR to assess the activity of formate dehydrogenase biocatalysts for CO2 utilization, *Kaiqi Xu*

11:30 11:45 NMR studies of the interaction between nitrogen bases and zinc complexes, *Knut T. Hylland*

11:45 12:00 NMR studies of biomimetic Cu(I) complexes, *Isabella Gerz*

12:00 12:15 An NMR study of carbohydrate binding module 14 and its interaction with chitin, *Eva Madland*

12:15 13:30 Lunch

13:30 14:30 Plenary: How single point mutations in Calmodulin can cause cardiac arrhythmia & How fluorine labelling can be a superior alternative to fluorescence labelling in peptide studies, *Reinhardt Wimmer*

14:30 14:45 Structural and functional insight into the mode of action of modular lytic polysaccharide monooxygenase, *Gaston Courtade*

14:45 15:00 The solution structure of the human brain-protein arc studied by NMR, *Helene J. Bustad.*

15:00 16:00 Break, Voksenåsens "fika" * Company presentations

16:00 17:00 Plenary: Functional MRI for brain cancer monitoring, *Kyrre E. Emblem*

17:00 17:15 Closure remarks

19:00 Dinner for people staying.

*** Company presentations during the Fika-break 15.00-16.00:**

Day 1, January 7th, each for 10 minutes

- Philips
- Bruker
- Magritek

Day 2, January 8th, each for 10 minutes except for Quantum which will use 5 minutes.

- Jeol
- Nerliens Mezanski
- Mestrelab
- Quantum

The first Presentation on each day starts 10 minutes into the "Fika". The other presentations follow successively.

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Invited lectures
MR2020

THROUGH THE CHEMICAL LOOKING GLASS, WHAT MRI CAN TELL US ABOUT MOLECULAR PROCESSES IN BATTERIES, CONSUMER PRODUCTS AND ENGINEERING

Melanie M. Britton
School of Chemistry, University of Birmingham, Birmingham, B15 2TT, U.K.

Britton is world known for her educational lectures at scientific meetings where she combines often seemingly disparate fields of NMR and MRI into a unified theme. Using a variety of NMR experiments, including T1 and T2 NMR relaxation measurements, spin echo imaging, pulsed field gradient measurements and velocity imaging, Melanie's group are providing unique insights in molecular processes underpinning systems found in a range of applications from structured materials, manufacturing and energy storage, to medical applications relevant in the diagnosis of cancer and the development of biomarkers.

Nuclear Magnetic Resonance (NMR) spectroscopy is widely employed to determine molecular structure and dynamics by using the signals of NMR active nuclei contained within a molecule. When NMR measurements are performed in the presence of magnetic field gradients, the NMR signal becomes spatially-dependent, resulting in images (MRI), with a spatial resolution in the order of 10-100 • m, as well as measurements of molecular flow and diffusion. As such, NMR is uniquely able to provide an integrated, non-destructive view of the structure, dynamics, and function of molecular systems where spectroscopic information at the atomic level can be integrated with information at the mesoscopic and macroscopic length scales via NMR imaging and diffusion methods. The synergy between these two modalities enables MR techniques to probe the broadest range of systems, many of which not accessible via other analytical techniques.

While MRI is a well-established analytical technique in biomedical research and clinical diagnosis, its ability to visualise the composition and behaviour of molecular materials is making it increasingly useful to study spatially-heterogeneous chemical systems in a diverse range of applications, including fast moving consumer goods (FMCG), pharma, manufacturing, materials science, reaction engineering, food technology, catalysis and energy storage. In talk I will explain the breadth of information available by MRI using examples from a diverse range of applications, including electrochemical energy storage, corrosion, electroplating, phase stability in surfactant solutions and reaction engineering.

USE OF MRI TO STUDY LIFESPAN CHANGES IN BRAIN AND COGNITION

Anders M Fjell
Center for Lifespan Changes in Brain and Cognition, University of Oslo

Fjell is interested in how the brain develops and changes during the life-span, and the cognitive consequences this development has. Fjell's research is focused on understanding the dynamic relationship between changes in brain structure, brain function, and cognitive abilities. Fjell use several different approaches to understand the relationship between brain and cognition, focusing on MR morphometry and diffusion tensor MRI. fMRI (functional MRI) of the brain is also included. An additional interest in Fjell's research is in how brain structure and function interact with CSF biomarkers in aging and Alzheimer's disease to produce cognitive changes.

Neuroimaging research over the last 20 years have shown that the brain changes throughout life. Some of these changes are positive, reflecting maturation and functional adaptation to changing environments, while others are negative, likely leading to reduced cognitive function and even dementia. To understand these life-span changes, MRI is an invaluable tool, and is used to probe different aspects of lifespan changes in the brain. I will show examples of use of different MRI modalities, including morphometry, diffusion tensor imaging and task-related fMRI, in lifespan studies. I will also show how MRI can be used in combination with other biomarkers in studies of cognitive decline and Alzheimer’s disease.

NMR SUPERSEQUENCES FOR SMALL MOLECULE STRUCTURE ELUCIDATION

Tim D W Claridge
Department of Chemistry, University of Oxford,
Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK

Claridge is the Director of NMR Spectroscopy for Organic Chemistry & Chemical Biology at Oxford University as well as professor of nuclear magnetic resonance spectroscopy. His research interests revolve around the application of solution-state NMR techniques, which address questions of structure, function and dynamics of "small" molecules in organic chemistry and chemical biology. Tim studies the interaction of small molecules with protein targets where NMR spectroscopy plays a key role, providing information on the behaviour of the small molecule and on structural changes in the protein itself. A variety of NMR techniques are used to probe such interactions, such as saturation transfer difference and WaterLOGSY as well as protein-observe methods with isotopically labelled macromolecules. He is also interested in developing and applying new methods for the characterisation of small molecules by NMR.

The structure characterisation of small organic molecules by NMR spectroscopy continues to represent one of the major applications of this analytical technique. NMR supports academic research into new synthetic methodology and its applications, and underpins advances in the pharmaceutical, agrochemical and fine chemical industries. Structure elucidation protocols now routinely employ well established 2D homonuclear and heteronuclear correlation experiments. Now recognised as the leading techniques, attention has turned to developing experimental methods that allow the faster collection of these data sets to speed characterisation and optimise spectrometer time. Herein, we describe an approach to data collection we term NOAH (NMR by Ordered Acquisition using 1H-detection) that records multiple 2D data sets nested as modules within a single “supersequence”. This requires only a single recovery delay for each series of modules, and so allows for significantly reduced data collection times. The concepts underlying multi-FID acquistion and the NOAH approach will be introduced and exemplified with a variety of supersequences.

References:

1. NOAH – NMR Supersequences for Small Molecule Analysis and Structure Elucidation Ē. Kupče and T. D. W. Claridge, *Angew. Chem. Int. Ed. Eng*., 2017, 56, 11779-11783.
2. Molecular Structure from a Single NMR Supersequence, Ē. Kupče and T. D. W. Claridge, *Chem. Comm*. 2018, 54, 7139-7142.
3. Triplet NOAH supersequences optimised for small molecule structure characterisation.T. D. W. Claridge, M. Mayzel, Ē. Kupče, *Magn. Reson. Chem*, 2019, 57, 946-952.
4. New NOAH Modules for Structure Elucidation at Natural Isotopic Abundance. Ē. Kupče and T. D. W. Claridge, *J. Magn. Reson*., 2019, [DOI: 10.1016/j.jmr.2019.106568]

HOW SINGLE POINT MUTATIONS IN CALMODULIN CAN CAUSE CARDIAC ARRHYTHMIA & HOW FLUORINE LABELLING CAN BE A SUPERIOR ALTERNATIVE TO FLUORESCENCE LABELLING IN PEPTIDE STUDIES.

Reinhard Wimmer
Aalborg University, Denmark Aalborg University, Denmark

Wimmer is the leader of the university's NMR center. His research covers broad areas of NMR spectroscopy, applied to biomolecular or biotechnological questions. A particular focus has been antimicrobial peptides, thought to offer a completely new class of antibiotics: widely abundant in nature, and very difficult for bacteria to acquire resistance against. Wimmer has also been involved in a number of collaboration projects with Aalborg and Aarhus university hospitals to utilize NMR metabolomics in medicine, for example in critical care or COPD patients.

Calmodulin is a mediator of calcium signalling and it is involved in countless processes in the human organism. Due to calmodulin's high degree of conservation in nature, calmodulin mutations were thought not to lead to viable organisms. However, recently, calmodulin mutations were discovered in humans with cardiac arrhythmia. Indeed, calmodulin plays a crucial role in the regulation of the human heartbeat by interacting with several ion channels. Mutations in calmodulin can significantly alter this interaction and cause a dysregulation of the heartbeat. By analyzing structural and thermodynamic details of the interaction between mutated calmodulin and its interaction epitopes, we can offer a mechanistic explanation of how this dysregulation actually happens.

The second part of the talk is dealing with cell-penetrating peptides. This class of peptides offers great benefits for use as drug vehicles. Currently, peptides are fluorescently labelled in order to follow their uptake across a cell membrane. We explored the possibility to apply fluorine labelling and follow peptide uptake by ^{19}F-NMR. Fluorine labelling leads to a minor change in peptide properties compared to fluorescence labelling. We explored different fluorine labels and investigated how they can be used to study the uptake of peptides into cells. If applied correctly, fluorine labelling in conjunction with 19F-NMR detection offers many advantages (and some disadvantages) compared to the currently used fluorescence-based methods.

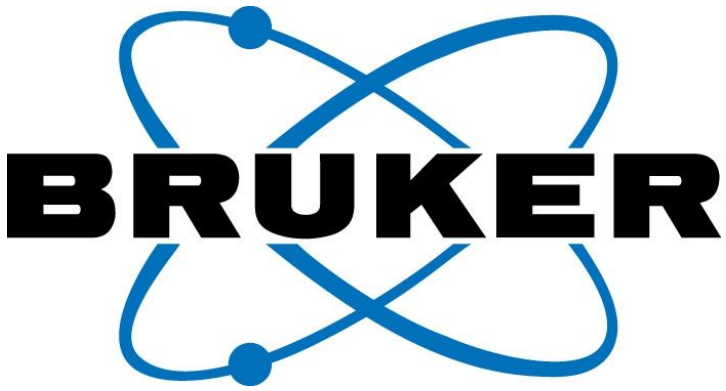
FUNCTIONAL MRI FOR BRAIN CANCER MONITORING

Kyrre E. Emblem
Department of Diagnostic Physics, Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway

Emblem is a famous young researcher in Norway mainly involved in MRI in Clinical Cancer Therapy. One of Emblems' goals is to solve one of the largest problems in cancer therapy. It is unknown who will benefit from treatment with a particular drug. Since only about half the patients who receive a typical anti-cancer drug benefit and the others just suffer side effects, knowing whether or not a patient's tumor is responding to a drug can bring us closer to truly personalized medicine. The main goal of Kyrre's research group is to find predictive and prognostic MRI-based biomarkers for better identification of patient-specific treatments and by this define how best to move the field of cancer therapy forward.

One of the major challenges in cancer treatment today is that we do not know who will benefit from a particular drug. Since only about half the patients who receive a typical anti-cancer drug benefit and the others just suffer side effects, knowing whether or not a patient's tumor is responding to a drug can bring us one step closer to truly personalized medicine – tailoring therapies to the patients who will benefit and not wasting time and resources on treatments that will be ineffective. Promising new anti-cancer treatments including vascular inhibitors and immunotherapy have made traditional diagnostic biomarkers insufficient because the cytostatic rather than cytotoxic nature of these therapies do no longer result in a simple reduction in tumor size. Moreover, following these therapies, the changes in tumor size do no longer correlate with survival and there is a critical need for new accurate biomarkers to assess the response to anti-cancer therapy.

The goal of my research is to find predictive and prognostic imaging-based biomarkers for better identification of judicious, patient-specific treatments and by this define how best to move the field of cancer therapy forward. The main focus of the research is the development and implementation of advanced MRI (Magnetic Resonance Imaging) techniques that uncover new, functional information of the disease during repeated monitoring. This includes perfusion, diffusion, mechanical forces and subsequent changes in vascular and morphologic structure.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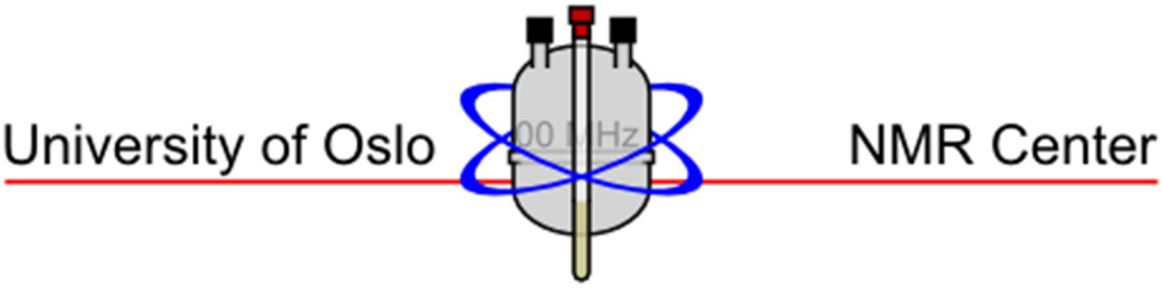
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Talks
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WHEN MRI CAME TO NORWAY

Hans-Jørgen Smith
Professor emeritus
Institute of Clinical Medicine
University of Oslo, Norway

The introduction of MRI in Norway was steered by the government and the national health authorities. For several reasons the steering was not very successful, and the intention of buying one MR unit ended up with the purchase of five units in a two-year period from 1986-1987. As a counterreaction, for several years only university hospitals were allowed to purchase MR equipment. In 1993, the strict regulations were abolished, and during the succeeding years Norway experienced an exponential growth in the number of MR units.

WHEN NMR CAME TO NORWAY

Bjørn Pedersen
Department of Chemistry UiO

Det første NMR-spektrometeret i Norge ble installert på Sentralinstitutt for industriell forskning (SI) våren 1960 ved fysikkavdelingen der som ble ledet av Henry Viervoll. Da hadde jeg vært ansatt på SI fra høsten året før og var sendt til Cornell University i Ithaca i USA for å lære om metoden. Der var Jeg ansatt ved Department of physics som research ascociate fra høsten 1959 til august året etter. Der hadde professor Donald Holcombs gruppe bygget sitt eget NMR-spektrometer så da jeg kom tilbake til SI hadde jeg aldri brukt det spektrometeret som Norge hadde kjøpt: ett Varian double purpose NMR spektrometer som kunne brukes til å ta opp NMR-spektra av både løsninger og faste stoffer. Et EPR-spektrometer var også anskaffet. Utstyret ble plassert på SI etter avtale med universitetene i Norge, og jeg opptok og tolket NMR-spektra og holdt forelesninger om NMR for potensielle brukere i de neste årene.

Jeg veiledet også hovedfagsstudenter i både fysikk og kjemi med oppgaver hvor bruk av NMR-spektroskopi inngikk. Etter noen år ble NMR-spektrometre anskaffet av universitetene i Bergen, Oslo, Trondheim og Tromsø. Fra 1970 var jeg professor 2 ved Kjemisk institutt og fra 1980 ble professoratet omgitt til et fulltids professorat i kjemi og jeg sluttet ved SI.


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WORFLOW FOR LONGITUDINAL EVALUATION OF BRAIN METASTASIS IN RESPONSE TO GAMMA KNIFE SURGERY

Lea Starck[1], Frank Riemer[2], Hauke Bartsch[2], Renate Grüner[1,2]

[1] *Dept of Physics and Technology, University of Bergen*
[2]*Mohn Medical Imaging and Visualization Centre, Dept of Radiology, Haukeland University Hospital*
[*]*Corresponding author (lea.starck@gmail.com)*

Introduction

An immediate response to gamma knife surgery in brain metastases may be an apparent tumor growth in the post intervention MRI follow-ups. This growth is not necessarily an indication of disease progression, but rather temporary disease pseudo-progression [1]. In order to investigate whether imaging biomarkers describing the microvasculature are able to differentiate true progression from pseudo-progression, a semi-automated workflow has been developed that includes processing of dynamic susceptibility weighted MRI (DSC-MRI) using blind deconvolution estimations of arterial input functions[2] and volumetric tumor volumes changes in time.

Methods

Longitudinal, multimodal MRI data from 43 adult patients were included. The workflow is here presented for one, randomly selected patient, with nine visits over a two-year period. All imaging was performed on a 1.5T whole body MRI system (Siemens Symphony 1.5T using a 8 channel head coil. DSC-MRI data were collected using a spin echo echo planar imaging sequence with a temporal resolution of 1.44s acquiring 60volumes in time. The contrast agent Dotarem (Guerbet, Villepinte, France) was administered using a power injector (injection speed 5 mL/s, 10 s after acquisition start). Structural pre- and post-contrast T1 weighted images were acquired.

Tumors were segmented semi-automatically. Image registration was performed using the Elastix [3,4] software. A pre-contrast image was subtracted from the post-contrast image, leaving only contrast enhanced regions. Following skull stripping, implemented with FSL [5,6] a binary mask was created by appropriate thresholding based on visual assessment. This mask was subsequently overlaid the original T1 structural post contrast image, and using the binary map as a guide, regions of interest covering the tumors were drawn manually. To arrive at regions of interest covering only the enhanced parts of the tumor, the binary map was multiplied by matrices now defining the regions of interest. The necrotic regions of interest were found by subtracting the enhanced region of interest from the total tumor region. Finally, the sizes of the various tumor parts were measured by counting the number of pixels contained in the regions of interest. Parametric perfusion maps, visualizing semi-quantifiable estimates of blood flow (BF), blood volume (BV) and mean transit time (MTT) were generated using the NordicICE (NordicNeuroLabs, Bergen, Norway) software package.

Results & Discussion

While times of treatment interventions are not yet linked back to the anonymous participant, the tumor under investigation seems to behave according to expectations from literature, in that it is growing as time progresses and exhibits possible signs of shrinking or pseudo-progression as response to gamma knife surgery intervention, Fig 1. Fig. 2 illustrates our approach to investigate the tumor properties by extraction of perfusion parameter maps.

These parameter values are to be related to clinical data and other markers of tumor progression.

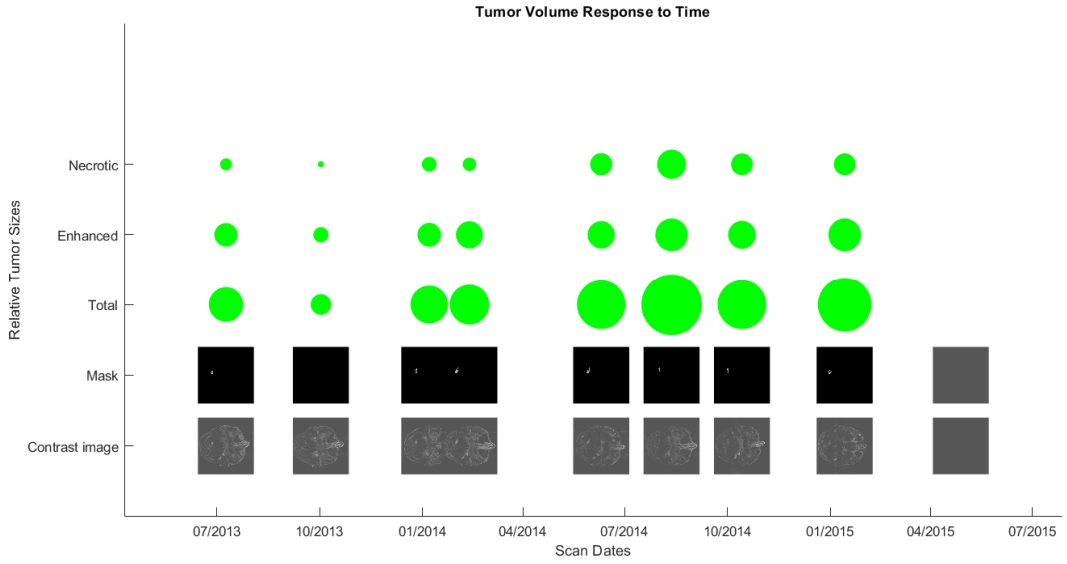

Figure 1: Using masks obtained from contrast images, different tumor parts are identified, and their relative sizes displayed as they evolve with time and treatment interventions.

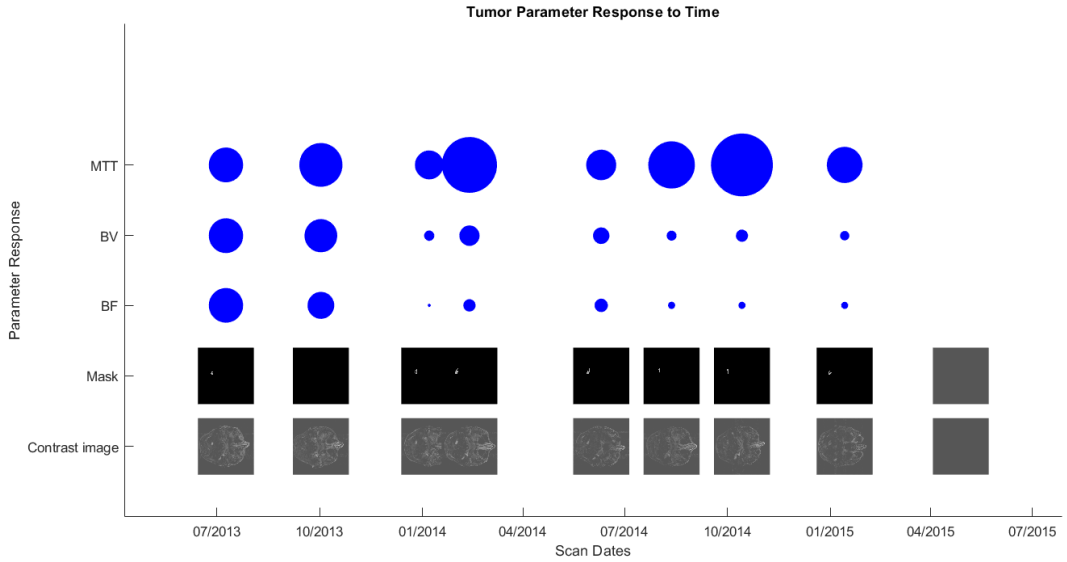

Figure 2: Perfusion parameters are extracted from perfusion maps as calculated with a blind deconvolution approach. The average parameter values (BF, BV and MTT) across the tumor are visualized according to their development in response to time and treatment.

Conclusion

We have presented a feasible workflow to investigate secondary brain tumor response to time and treatment interventions by adequate segmentation and, to our knowledge, first time application of blind deconvolution in characterizing brain metastases. This method must be applied to the entire patient cohort before calculated perfusion parameters can be related to immediate tumor responses to gamma knife surgery.

Acknowledgements
The work was supported by VIDI: Visual Data Science for Large Scale Hypothesis Management in Imaging Biomarker Discovery.

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ECHO PLANAR IMAGING DISTORTION CORRECTION AND APPARENT RELATION TO CEREBRAL BLOOD VOLUME INCREASE AND TUMOR SEGMENTS

Ivar T. Hovden[1], Oliver M. Geier[1], Ingrid Digernes[1], Elies Fuster-Garcia[1], Grethe Løvland[2], Einar Vik-Mo[3], Torstein R. Meling[3,4] and Kyrre E. Emblem[1]

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Abstract
Dynamic Susceptibility Contrast (DSC)-based estimation of cerebral blood volume (CBV) is indistinguishably a valuable tool in prognosis and treatment follow-up in Glioblastoma patients[1,2]. Like common fMRI, ASL and diffusion techniques, DSC-MRI is based on multiple echo planar images (EPIs) which possess severe geometric distortions as well as signal loss. We analyzed the impact of two established EPI distortion correction methods, FSL TOPUP[3] and EPIC[4], on gradient-echo and spin-echo based CBV from 45 Glioblastoma subjects in normalized (MNI) space.

After performing TOPUP and EPIC distortion correction, relative cerebral blood volume (rCBV) maps of uncorrected and corrected EPI-DSC were computed using nordicICE (NordicNeuroLab, Bergen, Norway) with mean white and gray matter normalization[5] and Weisskoff correction of contrast agent leakage extravasation[6]. The rCBV maps were then co-registrated and resliced to MNI space using SPM12 with the help of 3D T2-FLAIR images from the same MRI exam. Tumors were excluded from the rCBV maps on an individual basis, and ventricles and cerebrospinal fluid were excluded from the analysis. Symmetric left and right brain regions were merged for simplicity. A template from Neuromorphometrics, Inc. was used to measure rCBV change in the resulting 66 brain regions with the help of paired Wilcoxon signed rank tests with multiple comparisons correction.

Results indicated a general increase in CBV in some cortical and subcortical regions caused by correction, mainly pallidum, putamen, occipital pole and caudate nucleus ($P < 0.001$) (Figures 1-3). We also observed that there was more enhancing tumor in regions with CBV increase (56 % of the patients) than there was necrotic tumor (32 % of the patients) for spin-echo TOPUP correction (Table 1), which was the correction method to impose most CBV change.

In conclusion, CBV in the regions presented may be underestimated if EPI distortion correction is not performed. Moreover, enhancing tumor seemed to be more corrected than necrotic tumor in this patient group.

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Table 1: Number of patients with tumor in at least 4 cm^3 of significantly increased CBV caused by EPI distortion correction (n=45).

		GE TOPUP	GE EPIC	SE TOPUP	SE EPIC
	Number of significant regions	6	6	16	13
> 4 cm^3 signif. rCBV increase (P < 0.001)	Num. patients enhancing[7]	5 (11 %)	3 (7 %)	25 (56 %)	13 (29 %)
	-"- necrotic[7]	6 (13 %)	1 (2 %)	15 (33 %)	6 (13 %)
	- "- edema[7]	19 (42 %)	12 (27 %)	32 (71 %)	21 (47 %)

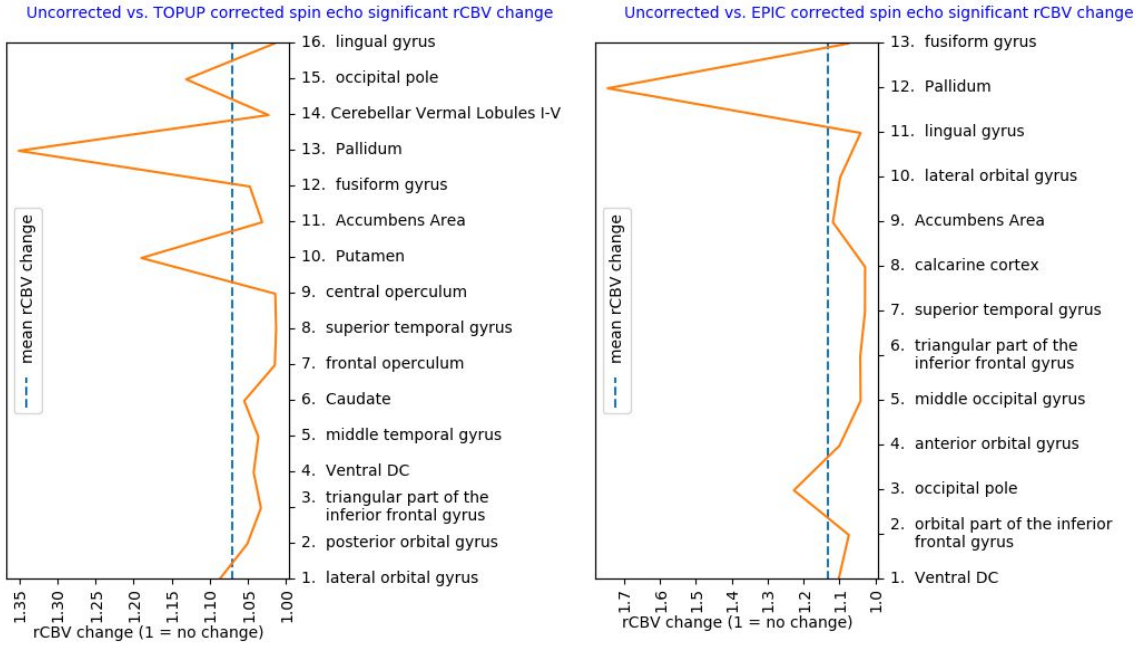

Figure 1: Regions with significant increase in CBV (1. most significant) by TOPUP (left) and EPIC (right) correction of **spin-echo** DSC ($P < 0.001$, n = [14, 34]). Blue lines: Mean rCBV change.

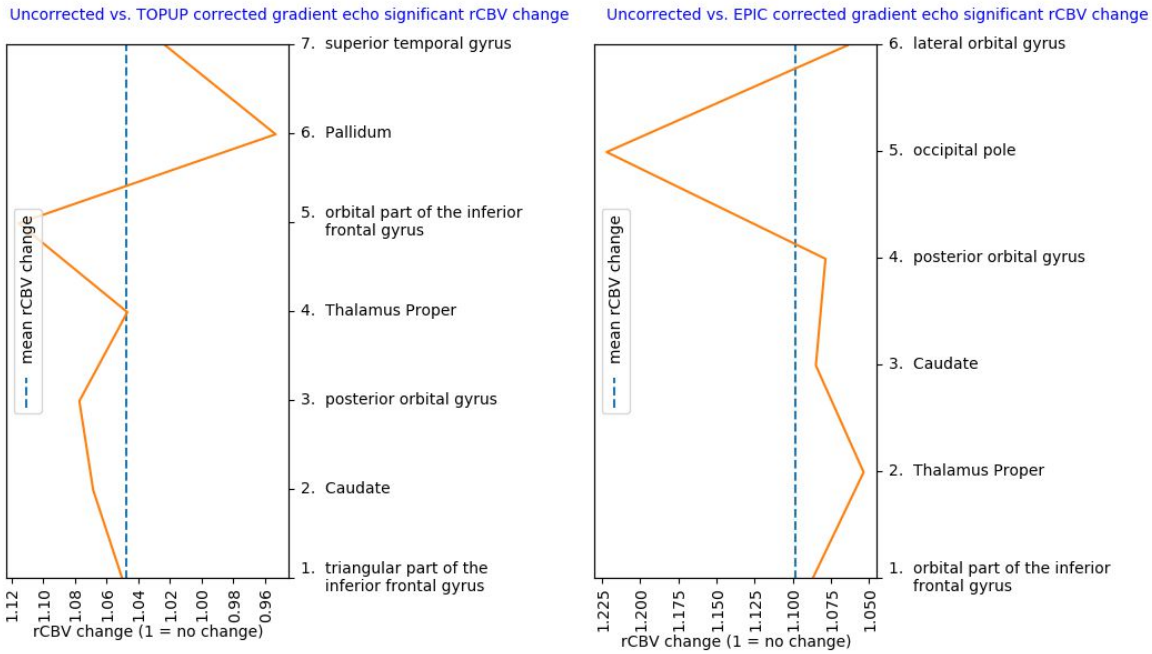

Figure 2: Regions with significant increase in CBV (1. most significant) by TOPUP (left) and EPIC (right) correction of **gradient-echo** DSC ($P < 0.001$, n = [22, 32]). Blue lines: Mean rCBV change.

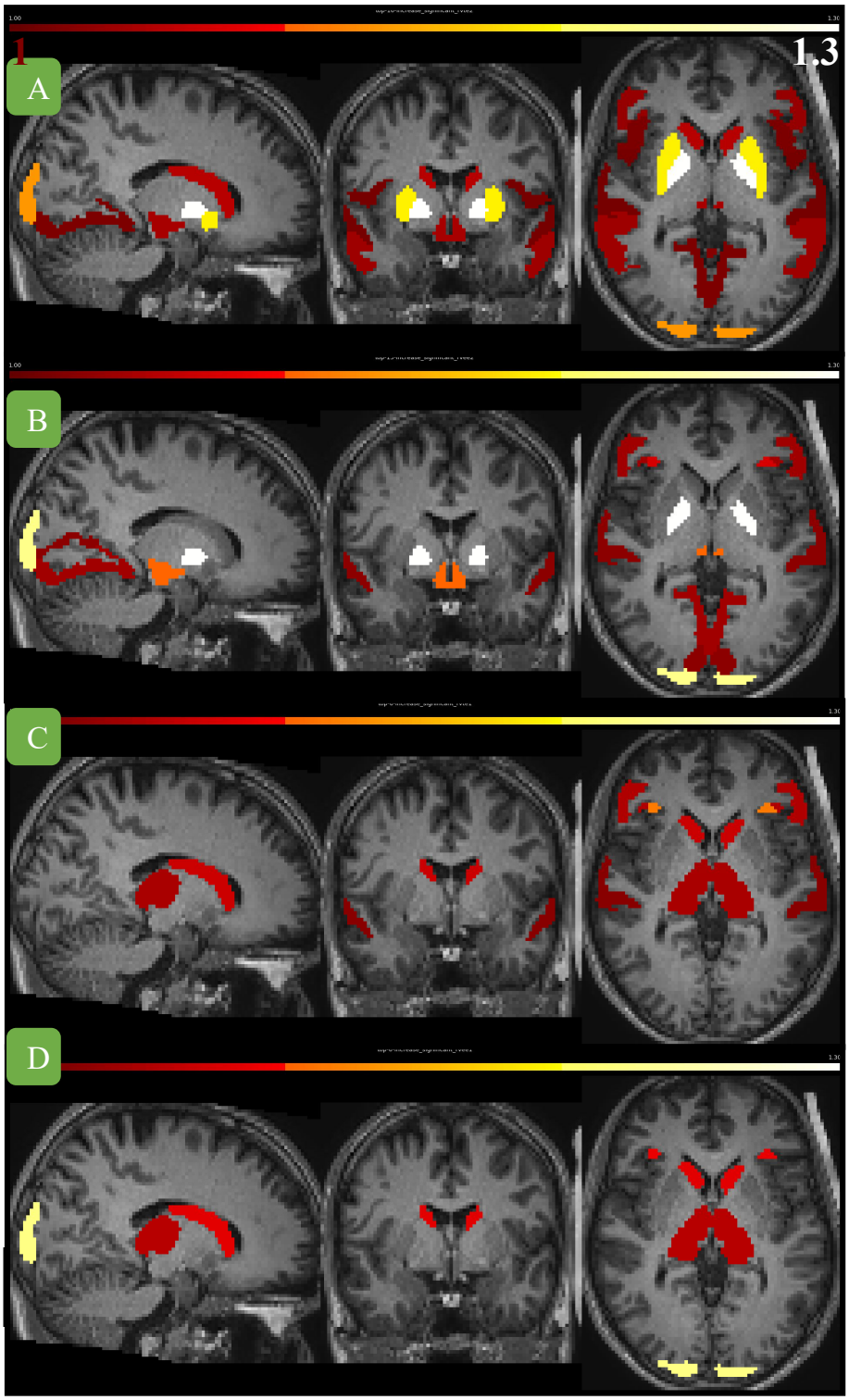

Figure 3. Regions with significant increase in CBV from EPI distortion correction (rCBV change > 1). The heat maps are medians of rCBV change for A, B: TOPUP and EPIC spin-echo correction (as in Figure 1); and C, D: TOPUP and EPIC gradient-echo correction (as in Figure 2). Pallidum is shown in white in A and B, while yellow regions in A depict putamen. The outermost posterior regions in A, B and D depict occipital pole.

PREDICTIVE VALUE OF PRETREATMENT ADVANCED DWI OF INTRA- AND PERITUMORAL TISSUE IN GLIOBLASTOMA

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Abstract
Purpose: Recently, it has been shown, that pretreatment apparent diffusion coefficient (ADC) analysis can be used for the prediction of tumor progression and overall survival [1]. In this study we would like to survey the prognostic value of advanced diffusion imaging techniques such as Restriction Spectrum Imaging (RSI) [2] and diffusion kurtosis imaging (DKI) [3]. These techniques may improve the assessment of the structural complexity and heterogeneity in intra- and peritumoral tissue. In contrast to standard diffusion weighted imaging the afore-mentioned techniques allow for the study of non-gaussian diffusion patterns (i.e. the deviation of the imaging signal from a purely mono-exponential behavior), which can be referred to malignant tissue. This is of particular interest in surrounding non-contrast-enhancing tissue, where infiltration and necrosis increase extracellular diffusion and consequently ADC values.
Material and Methods: RSI, DKI and ADC values were measured in forty-two patients with glioblastomas using a SE-EPI sequence with four b-values of 0, 200, 800 and 3000 s/mm^{-2} with 12 directions for each b-value. In addition a b=0 image in opposite phase direction was acquired in order to correct for spatial distortion caused by magnetic field inhomogeneity [4]. All examinations were performed on a 3T MR scanner (Skyra, Siemens Healthcare) with a 20 channel head coil. Prior to RSI and DKI analysis the images were corrected for noise and spatial distortion caused by field inhomogeneity and eddy currents. The region of interest was obtained using a postcontrast T1-MPRAGE acquisition. The prognostic value of ADC, RSI and DKI was analyzed using multivariate Cox and Kaplan-Meyer survival analysis.
Results: Greater increase in cellular index (CI) and FA with synchronal decrease in ADC in contrast-enhanced part of tumor was significant associated with shorter progression free survival and overall survival. This association was also consistent for values measured in close infiltration area and for FA values estimated in transitional area.
Conclusion: First results indicate that ADC, RSI and DKI can be used for stratification of overall survival and progression-free survival in patients with preoperative glioblastoma.

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MRI, PROSTATE CANCER AND ARTIFICIAL INTELLIGENCE

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Abstract
Prostate cancer affects approximately 1 in 8 men during their lifetime. This number is expected to increase substantially due to the aging population and excessive use of PSA-testing, and new clinical tools are urgently needed. Magnetic resonance imaging (MRI) has become a key component in the diagnostic workup. However, the interpretation of MRI images relies on the manual reading by experienced radiologists, which is a time and cost-intensive resource. Moreover, this process underuses the quantitative nature of the data. Our hypothesis is that better diagnostic performance is achievable by providing the radiologist with a decision support system based on artificial intelligence (AI). For such a system to work in clinical practice, it needs to be accurate as well as transparent and interpretable.

We are currently developing a decision support system that combines transparent AI methods, deep learning and model-based imaging features, and clinical information to provide the radiologist with a new set of interpretable tools to more accurately and efficiently detect prostate cancer, differentiate between high-risk and low-risk disease, and target prostate biopsies. The foundation of this project is formed by a unique Norwegian dataset of >1600 patients with MRI examinations and clinical variables, and an interdisciplinary project team with dedicated experience in MRI, AI, urology and radiology. Our collaboration with international experts in the field ensures access to similar data from The Netherlands and Taiwan, enabling solutions that also cover challenges related to demographic and multi-center variance.

The poster or talk will cover results from our group underpinning our hypothesis, and current results from the pipeline under development.

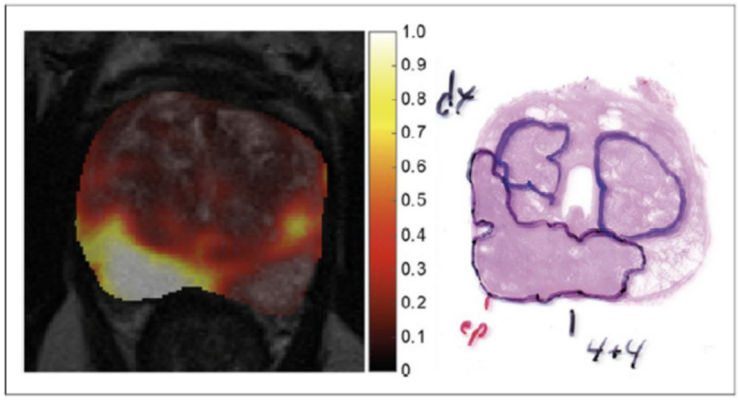

Figure 1: Tumor probability map from a machine learning model which can be used for targeting biopsies or focal treatment.

SIMULTANEOUS DIFFUSION WEIGHING AND EDITING OF MOLECULES USING DIFFUSION WEIGHTED MEGA

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Abstract

MRS is a widely used technique to examine metabolites in the brain tissue. By utilizing the information inherent in the chemical shift of the NMR signal, together with sensitive MR equipment, it is possible to examine intracellular metabolites. There are several severe limitations to quantify brain metabolites using MRS. Signals from different metabolites overlap with each other in the obtained spectrum, a problem to which the solution is currently to adopt editing sequences based on spectral J-coupling[1] to only detect signals from the metabolite of interest. Mescher-Garwood Point REsolved Spectroscopy (MEGA-PRESS) [1] is the main editing sequence used for metabolite editing. It uses two editing pulses centered around the metabolite of interest, in an ON-OFF scheme. By subtracting these, only signals from the edited metabolite will remain [1]. However, signals from metabolites also overlap with the signal from macromolecules reducing the accuracy of the metabolite quantification[2].

The macromolecules, being larger molecules, have a diffusion coefficient orders of magnitude smaller than that of the metabolites. We have therefore developed a sequence to utilize this difference in diffusion in order to suppress the macromolecule signal. Similar attempts of this suppression based on diffusion editing is found in the literature[3]. However, to enable a more accurate quantification of certain metabolites we have combined diffusion editing with MEGA-PRESS J-editing. This is achieved by combining editing gradients and diffusion gradients taking care to make sure the area of the diffusion parts of the gradients are equal. In this way the gradients are superimposed on each other and perform both tasks at the same time without having to separate them.

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^{2}H NMR STUDY OF PROPANE AND PROPYLENE MOBILITY IN ZIF-8

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Abstract
ZIF-8 is a metal-organic framework (MOF) renowned for its outstanding thermal and chemical stability [1]. This material is comprised of large spherical cavities with 11.4 A diameter connected by narrow windows with a size 3.4 A. Due to the dynamics of the linkers the effective size of the window increases allowing adsorption of the molecules larger than 3.4 A. Moreover, the flexible nature of the window leads to the high separation selectivity of light hydrocarbons. In particular, there are several reports showing the efficiency of ZIF-8 in propane/propylene separation. There have been several attempts to rationalize the ability of ZIF-8 to separate propane and propylene using adsorption methods and various computational techniques [2-5]. However, the diffusivity and the diffusional activation barrier of guest molecules obtained by different methods vary from 9.7 to 22 kJ/mol for propylene and from 26.8 to 74 kJ/mol for propane. In present work we clarified the mechanism of molecular transport inside ZIF-8 and determined the correct value of diffusivity by means of ^{2}H NMR method. Spin relaxation analysis allowed characterization of the intracavity mobility as well as the transport properties between cavities.
The reported study was funded by RFBR according to the research project 18-33-00048.

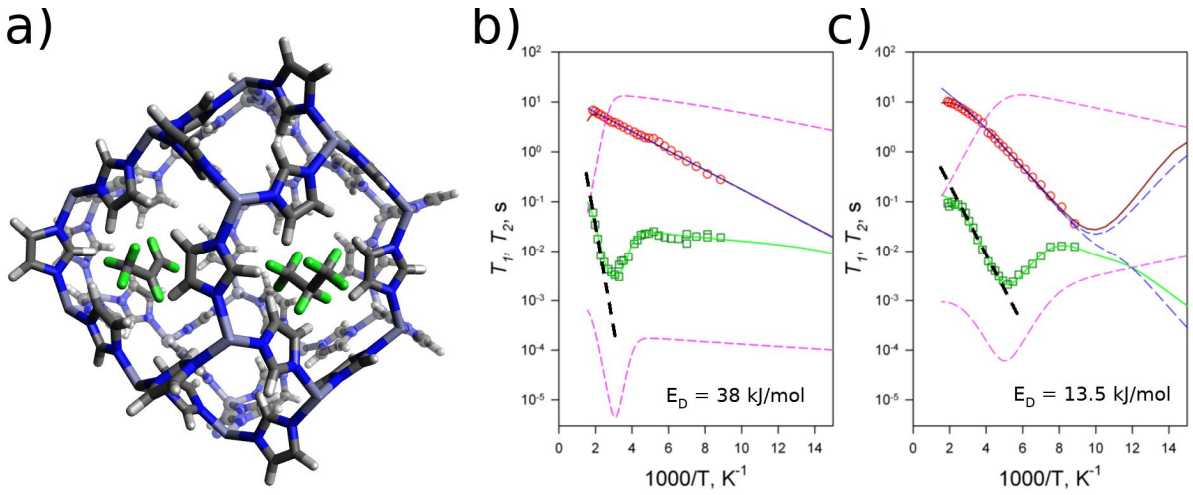

Figure 1: (a) Cage of ZIF-8. Spin relaxation of propane (b) and propylene (c) in ZIF-8.

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NMR STUDIES OF THE NA-SUBLATTICE OF IONIC CONDUCTORS $NA_2ZN_2TEO_6$ AND $NA_3ZN_2SBO_6$: HOW DOES STRUCTURE RELATE TO IONIC CONDUCTIVITY?

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Abstract
Solid-state electrolytes (SSE) propose a large improvement in existing battery technology, especially regarding battery safety. Degradation of the organic compounds in the liquid electrolyte on electrode surfaces is a major safety concerns and have already led to fires and explosions in commercially available batteries. Switching to a SSE will therefore remove these dangerous reactions, which is especially important for larger scale implementation of batteries, for example in electric vehicles and grid storage. It could also allow use of the elemental metal as the anode, which is one of the dreams of the battery community as it would drastically reduce weight and drastically improve capacity but is now much too unsafe.

The main issue with solid-state electrolytes is the limited ionic conductivity, which is currently orders of magnitude lower than the commercially available liquid electrolytes. There is currently a race of identifying new materials and improvement methods, with the modelling community supplying much of the needed understanding of the underlying conduction mechanisms. However, much too little time is spent looking into these mechanisms experimentally.

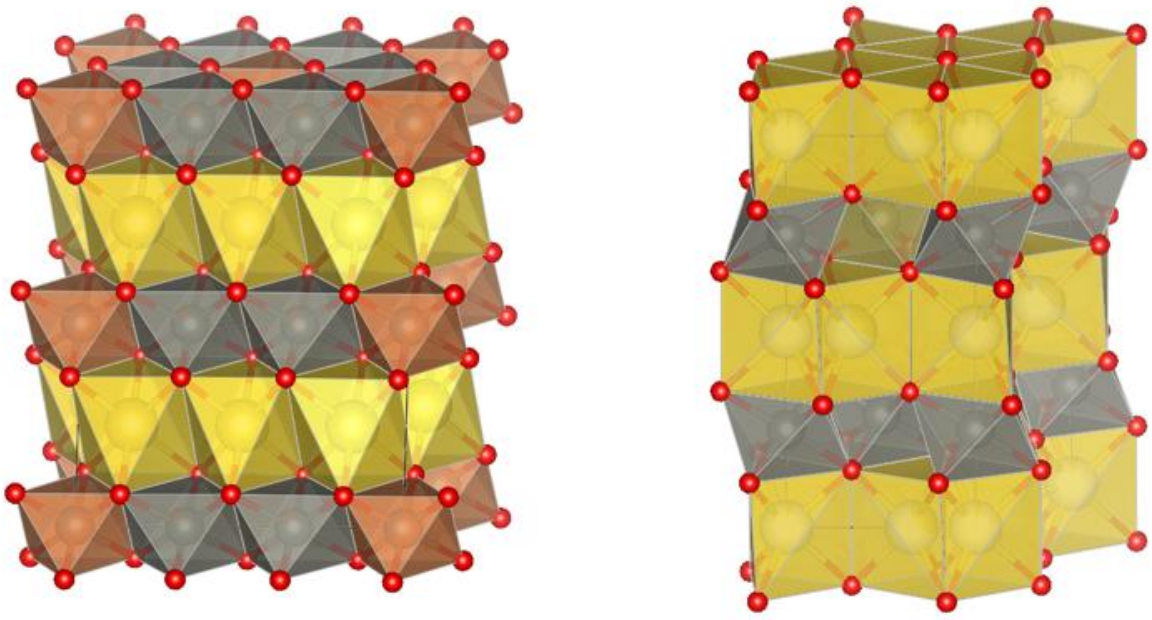

Figure 1: Structure of $Na_3Zn_2SbO_6$ (to the left) and $Na_2Zn_2TeO_6$.

This study presents an in depth look into the Na^+ sublattice in two layered compounds: $Na_2Zn_2TeO_6$ with a good ionic conductivity and the very similar $Na_3Zn_2SbO_6$, but with a very low conductivity. The first is a much-studied material for SSE. A goal with our studies of

these layered materials is to obtain knowledge on the structure-ionic conductivity relationship. We characterize both materials with X-ray diffraction and various NMR methods such as single pulse experiments and MQMAS NMR, as the single pulse spectra are clearly composite of many peaks. This allows us to resolve the actual Na-sites, the occupancy and the bonding characteristic of Na to the metal layer and discuss the different ionic conductivity in light of structure. This gives a vital insight into what limits and what increases Na-conductivity in this material class. NMR experiments at variable (higher) temperatures has been initiated and is in progress to obtain information on Na dynamics.

Raising the Bar: New World-Record 1.2 GHz NMR Spectrometer

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Abstract
For many years, high-resolution NMR was limited to a magnetic field of 23.5 Tesla, equivalent to a 1H resonance frequency of 1.0 GHz. This limit was set by the physical properties of metallic, low-temperature superconductors (LTS), and it was first reached in 2009 with a 1000 MHz spectrometer at the Ultra-High Field NMR Center in Lyon, France.

High-temperature superconductors (HTS), first discovered in the 1980s, open the door towards even higher magnetic fields, but considerable challenges in YBCO HTS tape manufacturing and in superconducting magnet technology made further ultra-high field (UHF) progress daunting until recently.

Novel 1.1 and 1.2 GHz magnet achievements now demonstrate the viability of new LTS-HTS hybrid magnet technologies with enormous technological progress in the areas of HTS materials manufacturing, testing and tape jointing, as well as in UHF magnet stabilization, homogenization, quench protection, and force management.

The aim of this presentation is to demonstrate the utility of NMR at >1 GHz for the study of molecular structure and dynamics both in liquids and solids, and how such investigations can expand the boundaries of molecular and materials research.


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NEWS FROM JEOL LAB: ELUCIDATING NOVEL CRYSTALLINE STRUCTURES WITH ELECTRON AND NMR CRYSTALLOGRAPHY

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Abstract
Here we present the novel development from Riken-JEOL Collaboration Center and Kyoto University iCeMS (Material-Cell Integrated System Center) to determine the molecular structures of low-molecular weight pharmaceutical compounds at natural abundance (without isotopic labelling), including the position of hydrogen atoms. This novel approach integrates electron diffraction (ED) for global structure analysis, solid-state Nuclear Magnetic Resonance (ssNMR) for local structure analysis, and first-principles quantum chemical calculations, to study microcrystals of 0.1 to 1μm.
We show that this combined approach circumvents the challenges of X-ray diffraction (XRD) and powder XRD for the crystal structure determination of low molecular weight active pharmaceutical ingredients, and highlights the importance of the positions of hydrogen atoms on the conformation and crystal packing of pharmaceuticals. Using this new electron and NMR crystallography technique, the structure of the model compound L-Histidine could be confirmed and the previously unknown structure of cimetidine crystal form B could be elucidated (1).

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CSSF-CLIP-HSQMBC: MEASUREMENT OF HETERONUCLEAR COUPLING CONSTANTS IN SEVERELY CROWDED SPECTRAL REGIONS

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Abstract
A new pulse program development, a chemical shift selective filtration clean in-phase HSQMBC (CSSF-CLIP-HSQMBC),[1] is presented for the user-friendly measurement of long-range heteronuclear coupling constants in severely crowded spectral regions. The introduction of the chemical shift selective filter makes the experiment extremely efficient at resolving overlapped multiplets and produces a clean selective CLIP-HSQMBC spectrum, in which the desired coupling constants can easily be measured as an extra proton-carbon splitting in f2. The pulse sequence is also provided as a real-time homonuclear decoupled version in which the heternonculear coupling constant can be directly measured as the peak splitting in f2. The same principle is readily applicable to IPAP and AP versions of the same sequence as well as the optional TOCSY transfer, or in principle to any other selective heteronuclear experiment that relies on a clean ^{1}H multiplet.

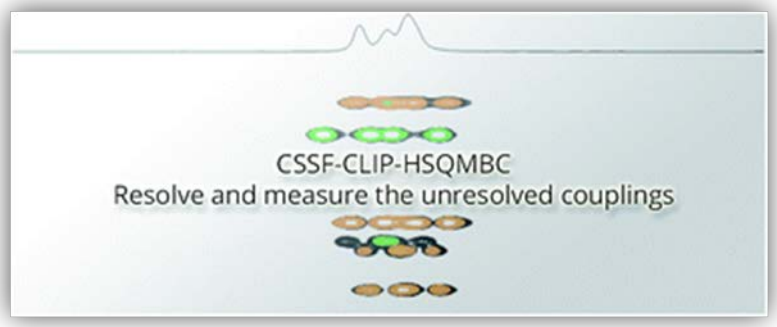

Figure 1: Individually filtered CSSF-CLIP-HSQMBC spectra of two overlapping protons only 1.8 Hz apart (green and orange) superimposed on the unfiltered CLIP-HSQMBC (black)

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The utilization of NMR in photo-assisted CO_2 utilization by formate dehydrogenase biocatalyst in a photoelectrochemical cell

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Abstract

We have assembled a photoelectrochemical (PEC) cell with efficient light-harvesting photoanode-Ta_3N_5 nanotubes, coupled with an oxygen tolerant formate dehydrogenase (FDH) enzyme to directly reduce CO_2 into formate by the assist from the sun light, as shown in Fig. 1 left. The PEC cell was operated continuously for 20 h, and a clear formate peak was found from the H^1 NMR spectra, as shown in Fig. 1 right. The emerged peak at chemical shift 8.44 ppm (red) is assigned to the presence of formate according to the internal reference spectrum by adding extra formic acid back to the solution (green), this is also in quite good agreement with the literature.[1] A control test operated under exactly the same condition but without the addition of FDH was also carried out, and the corresponding H^1 NMR spectrum (blue) shows no obvious peak of formate. We also quantified the produced formate indicated by the red H^1 NMR spectrum down to 4.85±0.24 µmol, this indicates a 100% faradaic efficiency.

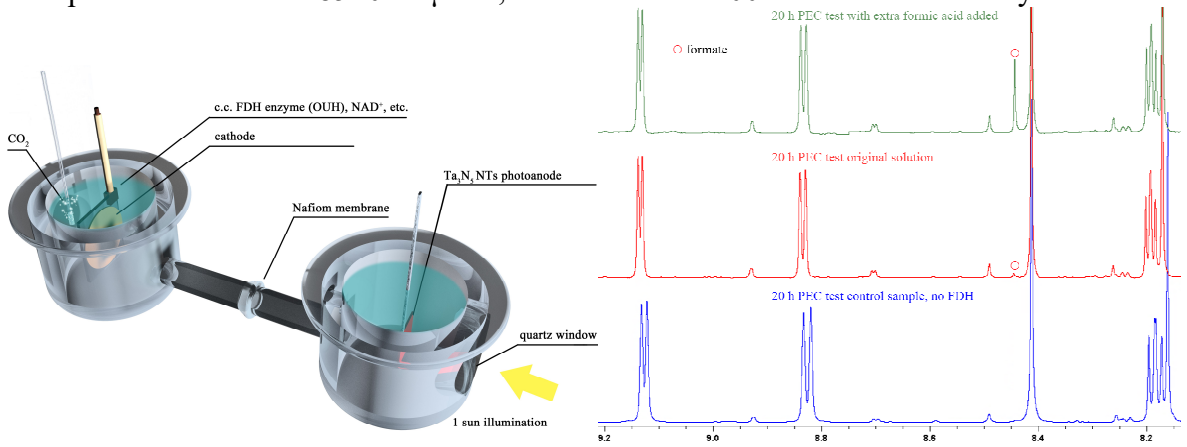

Figure 1 Left: schematic of the FDH integrated hybrid PEC cell. Right: H^1 NMR spectra of the solution at the cathode after 20 h PEC test for CO_2 reduction.

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NMR STUDIES OF THE INTERACTION BETWEEN NITROGEN BASES AND ZINC COMPLEXES.

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Abstract
Zn complexes of tetradentate Schiff base ligands are known to interact readily with nitrogen bases to form pentacoordinated complexes. Frequently studied Zn salen and salphen complexes are highly Lewis acidic and form stable adducts even with weak Lewis bases such as pyridine.[1] In our studies of related Zn complexes (Figure 1) towards different nitrogen bases, it was noticed that the stability of the corresponding adducts were highly sensitive to the nature of the nitrogen base. The adduct formation and stability was studied by NMR, and we here present NMR data that correlates the basicity of a series of nitrogen bases (Figure 1) with their ability to form stable complexes with Zn complexes **1**, **2** and **3** (Figure 1).

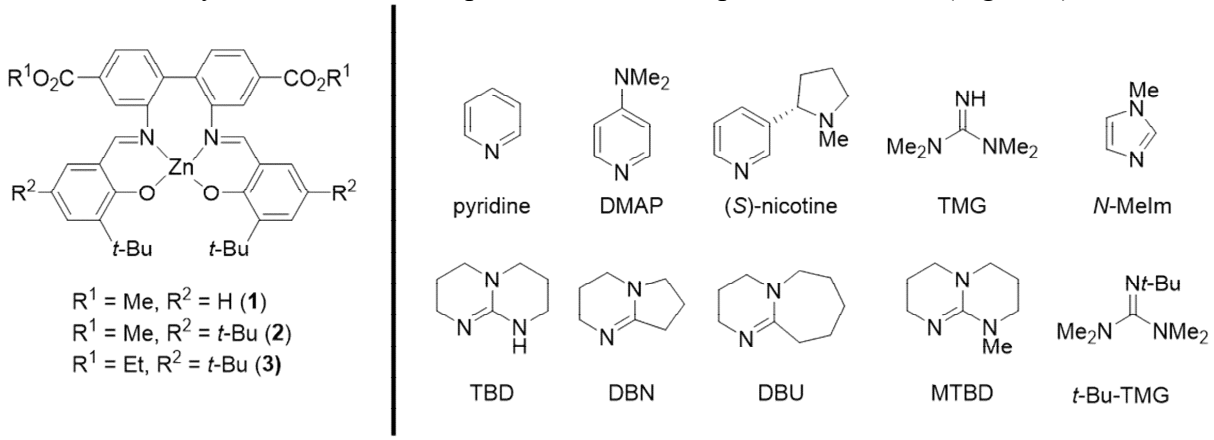

*Figure 1. Zinc complexes **1**, **2** and **3** (left). Different nitrogen bases studied within this work (right).*

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NMR STUDIES OF BIOMIMETIC CU(I) COMPLEXES

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Abstract
Lytic polysaccharide monooxygenase (LPMO) is capable of oxidizing various substrates selectively.[1] Its reactivity is attributed to a histidine-copper brace in its active centre.[2] We developed a series of complexes that mimic the active centre's features. Their facile synthesis through a one-pot synthesis allowed to access ligands that were too labile to be isolated without template. Characterising these compounds with NMR requires to work under rigorously air-free conditions, as traces of paramagnetic Cu(II) compounds lead to severe broadening and loss of fine structure.

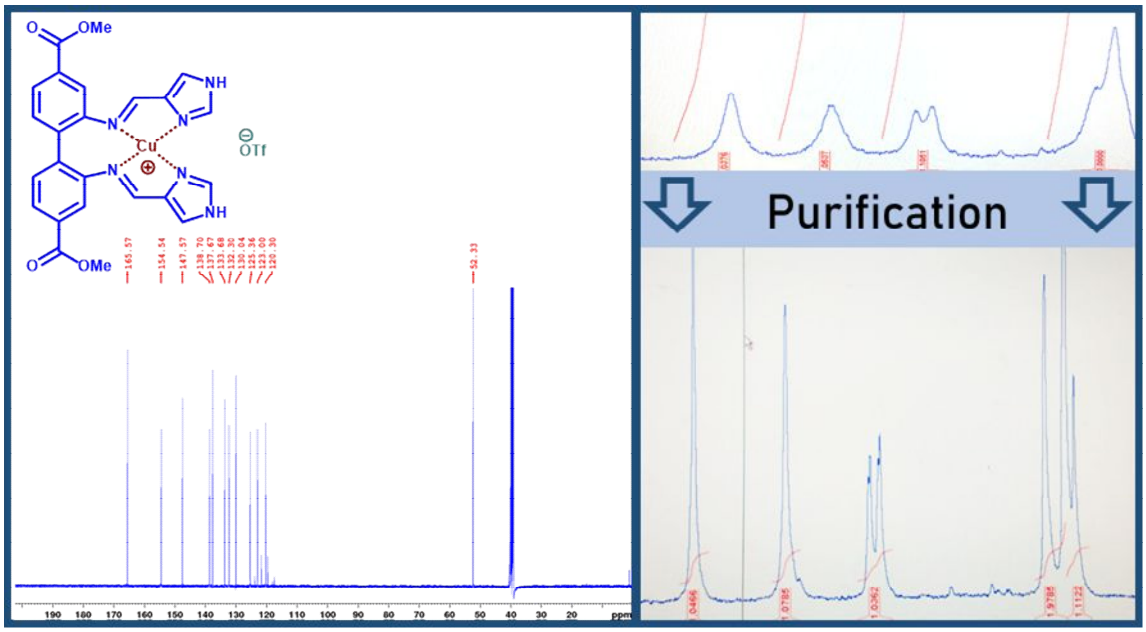

Figure 1: Left: ^{13}C spectrum of a LPMO mimetic complex. Right: Effect of the purification step on the ^{1}H spectrum appearance.

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AN NMR STUDY OF CARBOHYDRATE BINDING MODULE 14 AND ITS INTERACTION WITH CHITIN

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Abstract

Carbohydrate binding modules (CBM) have an important role in targeting and increasing the concentration of carbohydrate active enzymes on their substrates. Using NMR to get the solution structure of CBMs enables insight into secondary structure elements important for the stabilization of the structure, as well as a possibility to investigate how the CBM interacts with substrates.

We have investigated a CBM from family 14 (CBM14), a non-catalytic module of human chitotriosidase (HCHT) that recognize and binds chitin. The solution structure of CBM14 has been solved using NMR, and the interaction has been probed using two different substrates ($(GlcNAc)_3$ and β-chitin). From NMR titration experiments, we see that the same residues (Trp465 and Asn466) in CBM14 are affected for both $(GlcNAc)_3$ and β-chitin, stating that the binding site is the similar for both soluble and insoluble substrate.

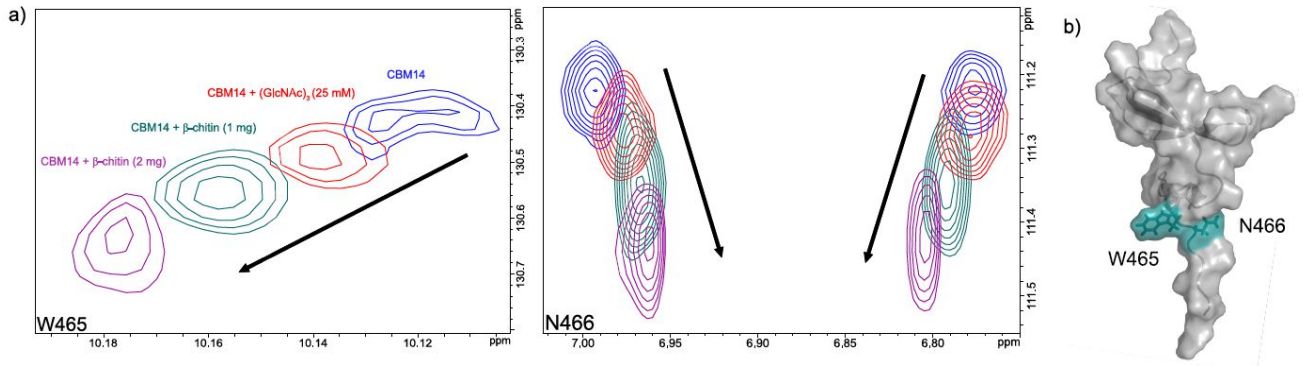

Figure 1 a) Area of interest in the ^{15}N-HSQC for the side-chain of Trp465 and Asn466 of CBM14. The arrows indicate the direction of the chemical shift change for the side-chain upon CBM14 interacting with (GlcNAc)3 (red) and -chitin (green and purple). b) Surface representation of CBM14 displaying the binding site in blue.

ITC experiments performed on the CBM14 – $(GlcNAc)_3$ system gave a K_d 3.1 ± 0.2 mM that corresponds to a relatively weak binding. This enabled investigation of the trimer's point of view by performing T_{1rho} experiments. Here we observed a slight preference towards the non-reducing end of the trimer, that could suggest a CH-π interaction between the sugar ring and the aromatic side-chain in Trp465.

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Madland, E., Crasson, O., Vandevenne, M., Sørlie, M., Aachmann, F. L. (2019) NMR and fluorescence spectroscopy reveal the pre-organized binding site in family 14 carbohydrate binding module from human chitotriosidase, manuscript under review (American Chemical Society, Omega).

STRUCTURAL AND FUNCTIONAL INSIGHTS INTO THE MODE OF ACTION OF MODULAR LYTIC POLYSACCHARIDE MONOOXYGENASES

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Keywords: LPMO, dynamics, NMR, MD

Lytic polysaccharide monooxygenases (LPMOs) are copper-dependent enzymes that bind to the crystalline surface of polysaccharides (e.g. chitin and cellulose) and cause cleavage of β-1,4 glycosidic bonds by an oxidative mechanism. Many LPMOs are composed of several domains, including a catalytic domain and one more carbohydrate-binding domains (CBMs). These structured domains are connected by linkers of varying length and sequence composition. Whereas most of our current understanding of LPMO activity is focused on the catalytic mechanism, the role of CBMs and linker regions in LPMOs is still poorly understood. Here, we have used NMR spectroscopy and SAXS, in combination with MD simulations to probe the distinct dynamic characteristics of multi-modular LPMOs, revealing conformational and functional properties of the linker as well as the overall structure and shape of the full-length proteins.

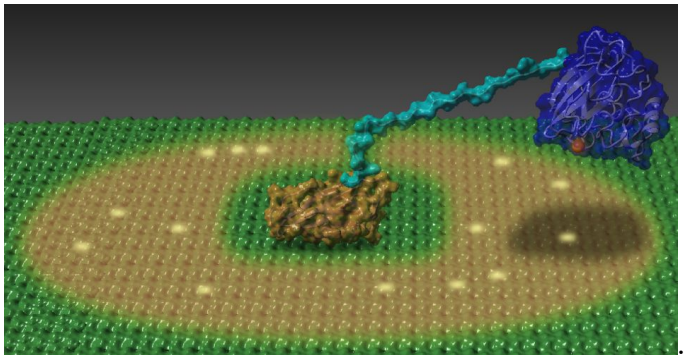

Figure 1. Illustration depicting a hypothetical model of cellulose oxidation by an LPMO consisting of a catalytic domain (blue) with a carbohydrate binding module (orange) and a linker composed of ~30 amino acids (cyan).

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THE SOLUTION STRUCTURE OF THE HUMAN BRAIN-PROTEIN ARC STUDIED BY NMR

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Abstract

The brain-protein Activity-regulated cytoskeletal associated protein (Arc) is essential for learning, memory formation and synaptic plasticity. Arc functions as an adaptable hub with several known binding partners, and has been implicated in neurological and neurodevelopment disorders such as schizophrenia and Angelman syndrome (1). Recently, Arc has been shown to form virus-like capsids, which encapsulate and transport mRNA to adjacent cells (2). In order to understand the molecular basis of Arc function and regulation of oligomerization and capsid formation it is essential to determine the protein 3D-structure. The structure of full-length human Arc is not yet known, however, a model of the protein shows a matrix domain connected to a capsid (CA) domain via a flexible linker (3). X-ray structures of two lobes of the CA-domain, N- and C-lobe and an NMR structure of the rat CA-domain have recently been reported (4, 5). The N- and C-lobes have shown to have homology with structural elements of Group-specific antigen (Gag) proteins found in retroviruses such as HIV. In our work, we express and purify ^{13}C and ^{15}N-labelled full-length human Arc, CA-domain, N- and C-lobes. We investigate the structure, dynamics and the influence of peptide binding to both the CA-domain and full-length Arc with using nuclear magnetic resonance (NMR) and electron microscopy (EM).

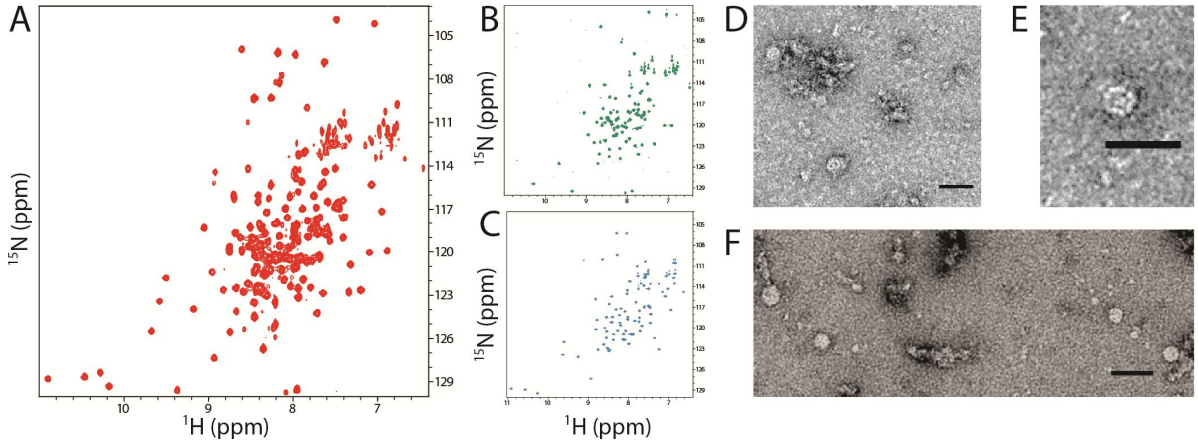

Figure 1: A-C) HSQC of ^{13}C,^{15}N-labelled CA, N- and C-lobe, respectively. D-F) EM images of purified full-length human Arc forming virus-like capsids. Scale bar represents 600 Å.

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SEGMENTAL ORIENTATION AND MOBILITY OF ULTRA HIGH MOLECULAR WEIGHT POLYETHYLENE

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Abstract

Formation of entanglements in Ultra-High Molecular Weight Polyethylene (UHMWPE) with average molecular weight exceeding 10^6 g.mol^{-1} limits their processability [1]. Entanglement characterization techniques mostly requires processing of nascent reactor powder, by melting. This will, however disturb the initial properties, and accordingly, the initial entanglement density in polymers. Therefore, Nuclear Magnetic Resonance (NMR) is an interesting alternative technique where the properties of UHMWPE can be explored in the solid state. However, during relevant NMR studies, the samples were either melted or characterized by using expensive and time-consuming ^{13}C NMR experiments [2]. Recently, simple low field, time-domain NMR with no need for isotope labeling, is gaining attention [3].

The aim of this study is to detect local mobility and orientation of chains across UHMWPE semi-crystalline network, in the solid state. The transverse relaxation time (T_2) is determined from the Free Induction Decay (FID) of samples synthesized during controlled catalytic Polymerisation. The method is used to detect differences in dynamic behaviour of UHMWPE samples by mapping the crystalline/amorphous topology [3]. However, due to inhomogeneity in the magnetic field, obtaining detailed information about local chain diffusion is difficult with said experiment. Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence is designed to overcome this issue by refocusing the dephased magnetization in the transverse plane [4]. Thus, CPMG will be used for accurate measurement of the T_2 distribution in UHMWPE samples at temperatures between 40-120 °C (below melting temperature).

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ABSTRACT TEMPLATE FOR THE 16TH NATIONAL MR MEETING

SOLID STATE NMR STUDIES OF THE STEPWISE TRANSFORMATION OF METHANE TO METHANOL OVER CU-ZEOLITES

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Abstract

The direct oxidation of methane to methanol is a potential key technology for converting stranded and flared methane into chemicals. A related topic is direct conversion of methane to chemicals by C-H bond activation and is by many one of the holy grails in chemistry. On the path towards the goal of direct conversion of methane the stepwise methane-to-methanol (MTM) conversion based on Cu-exchanged zeolites has received great attention recently [ref. 1 with references]. The MTM process consists of an initial catalyst activation step (in O_2/air), followed by a reaction step with CH_4 and then an extraction of methanol by H_2O. See Figure 1. Of the many porous zeolites investigated Cu-exchanged mordenite has shown a record high productivity close to the theoretical maximum of 0.5 mol MeOH/mol Cu [2]. Recently, key steps of the reaction have been intensely studied such as (a) the configuration of the active Cu-site and (b) the nature and location of the initial oxidation intermediate. In this work we will present a background of the topic, and work carried out in the SFI center iCSI the last four years on the configuration of the active Cu center and on point (b), the nature and location of the CH_x-moiety after CH_4's reaction with Cu. This last point is studied with a new combination of coupled *in-situ* IR spectroscopy in conjunction with solid-state NMR and results from this work will be presented in detail. The possible problems paramagnetic Cu-center imposes will be discussed and evaluated.

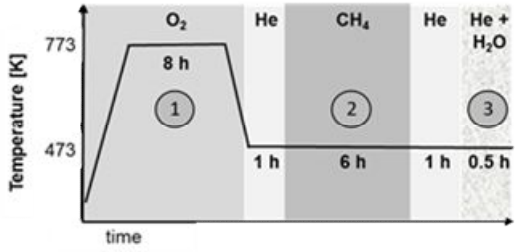

Figure 1. The temperature program of the stepwise MTM conversion divided into oxidation (1), reaction (2), and extraction (3)

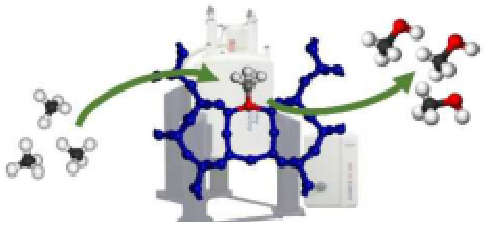

Figure 2. Schematic illustration of the MTM reaction

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Characterization of Water in Mesopores at sub-zero temperature

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Keywords: interfacial water, mesopores, spin diffusion, second moment, Cryo-NMR

Abstract: Combining proton spin-diffusion (SD) and Cryo-NMR measurements with proton line-shape analysis (second moment) of water confined in mesopores (MCM-41 and SBA-15) at subzero temperature (273K – 180K), the morphology of the co-existing solid ice (R) and interfacial water (M) is probed as a function of temperature. The magnetization transport within the two regions R and M – as characterized by their spin-diffusion coefficients D_R and D_M – showed the latter to be an order of magnitude smaller.
The rigid ice (R) core reveals a much broader spectral line (short T_2) compared to the more mobile interphase (M). Hence, the former magnetization component can be removed after applying a so-called "dipolar filter" (in the SD-pulse sequence), resulting in a magnetization transfer from the interfacial region and into the ice core, as illustrated in Figure 1.

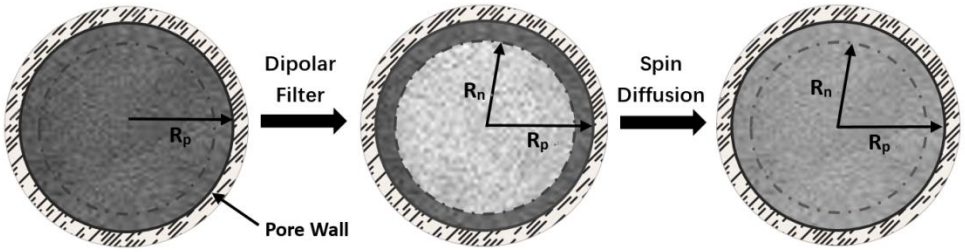

Figure 1. Illustration of the magnetization transfer (spin-diffusion) from the interfacial annular ring (dark grey; middle) and into the ice core until an equilibrium magnetization is established (light grey; right). R_p and R_n represent the dimension of the mesopore and the solid ice core, respectively.

In particular, the thickness d_I *(*$= R_p - R_n$) of the interface - as obtained independently from SD- and Cryo-NMR measurements, respectively (Fig. 2), are consistent.

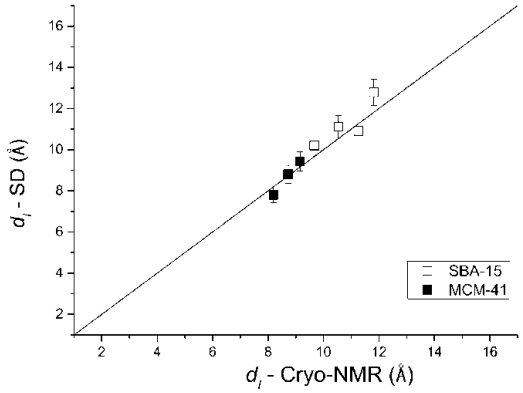

Figure 2. Average size (d_I) of the interfacial layer in MCM-41 and SBA-15 as derived by SD NMR and Cryo-NMR. The standard error is estimeted to be ±5%. Solid line represents $d_n(SD) = d_n(Cryo)$.

Acknowledgement: E. Hansen thanks the Physics Department at ECNU for financial support.

NMR studies of Aliquat 336 in toluene after contact with saline solutions. Determination of ionic content.

Author:, **Hans Vigeland Lerum*[1], Niels Højmark Andersen[1], Dag Øistein Eriksen[1], Eddy Walter Hansen[1], Jon Petter Omtvedt[1].**

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Abstract

The quaternary amine Aliquat 336 in toluene was mixed with aqueous solutions containing LiCl o HCl. Both NMR spectroscopy and acid-base titration were used to determine the amount of acid extracted into the organic phase. Likewise, the amount of Li^+ extracted into the organic phase was determined by ^{7}Li-NMR spectroscopy. A discrepancy in the estimated concentration of extracted acid from NMR spectroscopy analysis and acid-base titration was noted and explained by the assumption that HCl and H_3O^+ were both present in the organic phase under fast exchange conditions, as compared to the NMR sampling time. The best estimate of the HCl/H_3O^+-ratio at the highest extraction level of acid was found to be 0.42±0.02. The corresponding ratio of Li^+/Aliquat 336 and H_2O/Aliquat 336 were found to be 5.4±0.5 and 4.5±0.5, respectively. Also, the chemical shift of the -NCH3 protons was found to increase proportional to the Li^+ concentration. Finally, the NMR data suggests that the ions associate to the hydrophilic part of Aliquat 336.

NEW NMR METHODS AND TECHNOLOGIES TO ENHANCE YOUR RESEARCH

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Abstract

In this presentation, some of the recent hardware and software developments in Bruker's NMR division will be presented. New hardware has been introduced and important milestones have been set in the areas of e.g. high-field magnets and probe technology.

Further developments have been made regarding the automation concept, which now allows easy sample preparation, automatic instrument calibration and parameter optimization, and automatic or user-assisted data evaluation, thereby enabling a high throughput for both routine and specialized applications.

NUCLEAR MAGNETIC RESONANCE METHODS FOR CHARACTERISING MASS TRANSPORT IN HYDROGELS

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Department of Chemistry, University of Bergen
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Abstract

Characterization of the transport processes in drug delivery systems is critical in order to tune the drug loading and release. We present a simple and efficient NMR protocol [1] to investigate the transport of carrier molecules in hydrogels on micro- and macroscale under non-equilibrium conditions. The protocol is based on a combination of 1D NMR chemical shift imaging [2] and slice-selective diffusion experiments [3] (Figure 1).

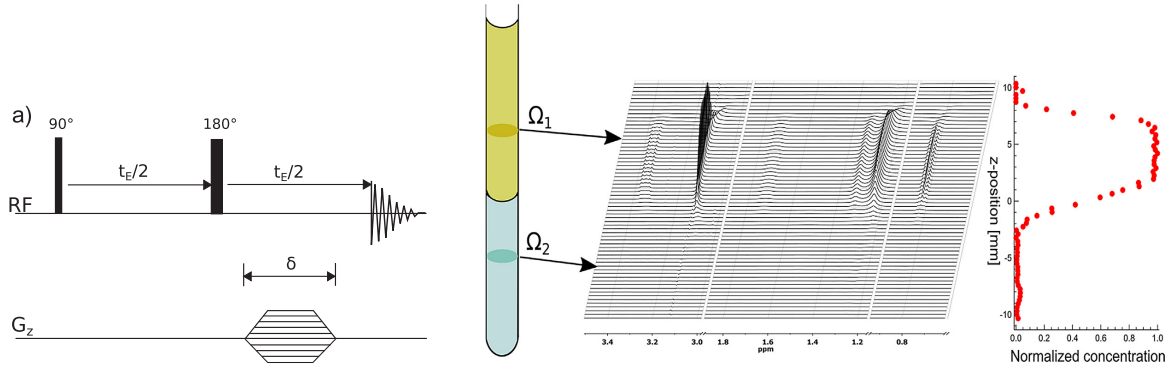

Figure 1: 1D NMR chemical shift imaging experiment (left) [2], leading to position dependent NMR-spectra (right). Slice-selective diffusion experiments [3] are performed at Ω_1 and Ω_2.

Furthermore, we present a combined Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) protocol (Figure 2) which allows to follow the shrinking of a hydrogel with subsequent determination of local concentrations of carrier molecules and transverse relaxation time and diffusion coefficient of water.

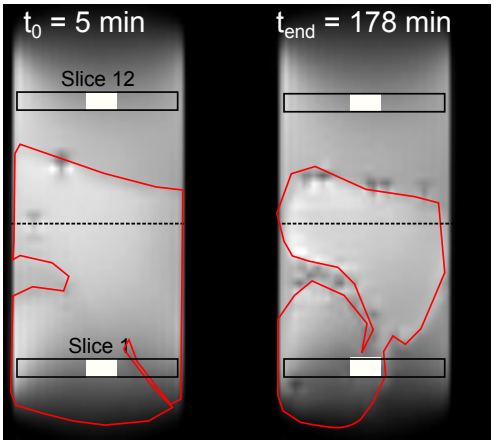

Figure 1: Positions of 1mm thick MRI slices in the hydrogel samples during drug release used for obtaining diffusion and relaxation maps of water. Slice 1: in hydrogel. Slice 12: in release medium. In addition, localized spectroscopy (MRS) of carrier molecules were performed in selected voxels in the hydrogel and release medium.

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REALTIME MONITORING OF ENZYMATIC HYDROLYSIS OF MARINE BYPRODUCTS USING BENCHTOP NMR SPECTROSCOPY

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Abstract

Increased interest in sustainability in marine resources has led to reasearch into ways to obtain more value from them without increasing catch sizes. Recently, functional peptides and amino acids have seen increased use in high value products such as functional foods, health food supplements, pharmaceuticals, and cosmetics. These molecules can be produced efficiently from marine by-products by enzymatic hydrolysis. Functional properties, such as foaming capacity, emulsification capacity and solubility, all have a dependence on protein size. Taste is another factor, as peptides that are too small will produce a bitter flavor that makes them unsuitable for use in food products. However, hydrolysis is a complicated process that is not fully understood. The hydrolysates depend on the starting materials, enzymes used, and the reaction conditions. A method to monitor the enzymatic hydrolysis process in real time would be valuable in order to consistently produce peptides of the desired size.

Benchtop diffusion nuclear magnetic resonance spectroscopy was used to perform quantitative monitoring of enzymatic hydrolysis. The study aimed to test the feasibility of the technology for characterization of enzymatic hydrolysis processes in real time. Diffusion ordered spectroscopy (DOSY) was used to measure the signal intensity and apparent self-diffusion constant of solubilized protein in hydrolysate, which was converted into an average protein molecular size and an estimate of degree of hydrolysis. These values were plotted as a function of time and the rate of both protein solubilization and breakdown could be calculated. Therefore, results indicate that monitoring by benchtop NMR spectroscopy would enable operators to more tightly control properties of products of enzymatic hydrolysis.

The “magnetic tongue” concept revisited: ^{1}H NMR-based multivariate statistics for unraveling sensory attributes of fish protein hydrolysates

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Enzymatic protein hydrolysis is a well-recognised biotechnology with a wide industrial application in recovery of peptides and proteins from food by-products.[1] The nutraceutical properties of protein hydrolysates have been successfully explored for development of high-value products, i.e., protein-based food formulations, mainly from dairy by-products. Although equally rich in nutrients, fish by-products are not exploited to the same extent for human consumption. Among the major challenges preventing such a utilisation is unwanted sensory attributes, such as bitterness. Therefore, understanding and identifying chemical constituents eliciting unwanted sensory attributes is a vital step in developing taste-neutral hydrolysates. In the present study, a series of mackerel by-product hydrolysates produced using different process settings (*i.e.*, type of enzyme, hydrolysis time and filtration setting) were analysed using ^{1}H NMR. The same hydrolysates were also subjected to qualitative and quantitative sensory descriptive analysis. Principal component analysis (PCA) of the ^{1}H NMR profiles was performed after performing peak shift alignment and normalisation to unit integration.[2] The classification observed in the ^{1}H NMR PCA score plot was strikingly similar to those observed in the qualitative sensory descriptive analysis. Among the major contributors (*i.e.*, variables (ppm)) to the variation along the principal component correlated with bitterness was the chemical shift region 0.86-0.96 ppm. These chemical shifts were tentatively assigned to side chains of hydrophobic peptides and amino acids. This is consistent with previous studies correlating bitter attributes to hydrophobic peptides.[3] In addition, lactic acid, trimethylamine (TMA) trimethylamine oxide (TMAO) were identified as metabolites potentially correlating to taste and smell of the mackerel protein hydrolysates. Prediction of magnitudes of selected sensory attribute (such as bitterness) were also attempted using ^{1}H NMR based PLS regression. Overall, the results showed that NMR is a promising tool for pinpointing taste-eliciting constituents of crude protein hydrolysates.

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Preclinical MRI for evaluation of regional wall thickness in a mouse model of hypertrophic cardiomyopathy

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Background: Experimental mouse models of hypertrophic cardiomyopathy (HCM) provide important insight into HCM pathophysiology. Our aim was to develop an MRI-based protocol to determine regional hypertrophy in mice during disease progression, and include this in the evaluation of the disease phenotype.

Methods: We used 10-11 week old male mice harboring a R403Q mutation in the *Myh6* gene encoding α-myosin heavy chain (R403Q) (Seidman laboratory, Harvard Medical School, Boston, MA, USA). Following an established protocol, Cyclosporine A (CsA) p.o. (0.16±0.01 mg/kg/d) was given for three weeks to induce HCM in mutated mice (R403Q/CsA, N=11). 129S6/SvEvTac wild type (WT) littermates exposed to the same protocol (WT/CsA, N=12), as well as R403Q (R403Q/Sham, N=11) and WT (WT/Sham, N=12) given sham feed served as controls. All mice were examined by cine and phase-contrast MRI before and after the feeding protocol, using a 9.4 T magnetic resonance system (Agilent Technologies, Inc., USA). Short axis sections covering the left ventricle (LV) were segmented to calculate total LV volume and mass. A customized MATLAB script was developed to calculate maximum, minimum, and mean myocardial thicknesses, in addition to free wall and septum thickness. Heart tissue was harvested at the end of the protocol.

Results: MRI-based analysis detected an increase in maximum wall thickness from baseline to endpoint in R403Q/CsA (1.25±0.15 mm to 1.65±0.31 mm, $p<0.01$), which was absent in the other groups. The same group had increased whole heart weights compared to all groups and LV weights compared R403Q/Sham, normalized to body weight at harvest. Calculated LV mass from MRI showed the same trend but did not pick up the significant differences seen in harvested tissue. Relevant mRNA markers for fibrosis and heart failure, as well as total collagen content by HPLC, was increased in the R403Q/CsA group.

Conclusion: We have developed an MRI-based protocol for characterization of regional hypertrophy in a mouse model of HCM. The increase in heart weight and fibrosis markers together with regional hypertrophy suggests a relevant model for HCM.

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Spectroscopic profiling of polysaccharides: Using ^{1}H-^{13}C HSQC spectra to assist with structure elucidation

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Abstract
Polysaccharides from natural sources, such as those found in marine algae, often display a variety of functional properties that can prove highly valuable for biotechnological applications. A complete structural characterisation is vital to study the structure-function relationship of molecules with reported biological activities. Due to their often-complex molecular structures, the NMR spectra of polysaccharides can become complicated and difficult to interpret. Variations in the position and configuration of glycosidic bonds, branching, and other modifications (e.g. acetylation, O-methylation, and sulfation), lead to variation in resulting spectra. Complexity is increased by the presence of more than one type of residue, and the picture becomes even more convoluted if all these features are incorporated in an irregular way. This builds up a very complex puzzle for the NMR structural chemist, and more complex and structurally irregular molecules require a more sophisticated approach to elucidate their structures. Here we propose the incorporation of two-dimensional NMR spectroscopic profiling, commonly applied to mixtures, as a tool to assist with the deconvolution of complex spectra. As a first step in polysaccharide structural elucidation the chemical shifts of H-C spin pairs can be obtained from ^{1}H-^{13}C HSQC spectra and compared to published data from known chemical structures. This enables the rapid assignment of residues that correspond to characterised structures. The benefits of this approach are twofold: firstly, the identification of known residues results in spectral deconvolution, and secondly it allows the rapid assessment of structural novelty.

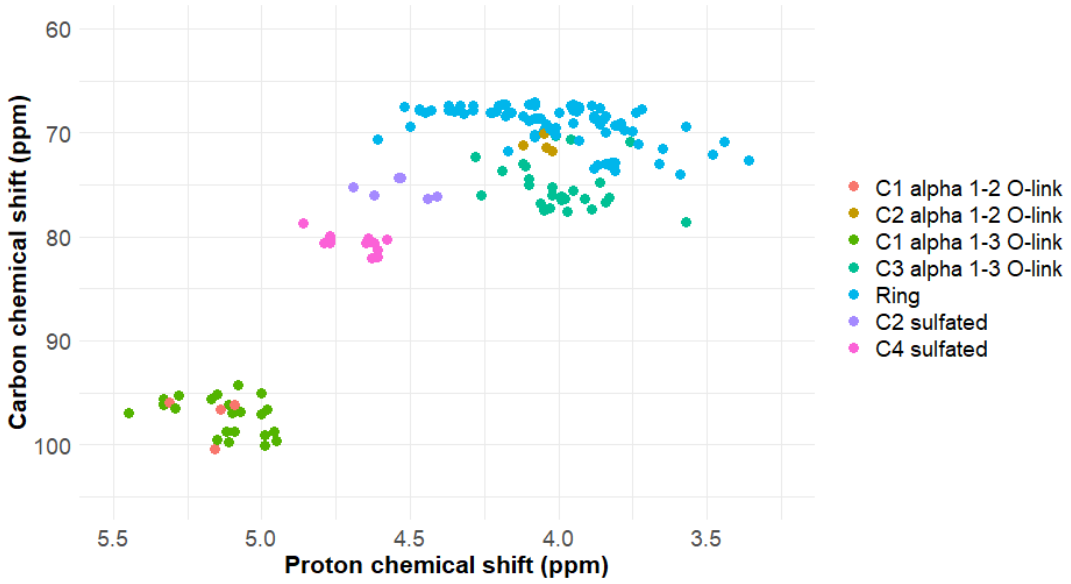

Figure 1: A 'Reconstructed' HSQC spectrum using literature reference data of fucose residues from fucoidans. H-C spin pairs are coloured corresponding to structural features.

ABSTRACT TEMPLATE FOR THE 16TH NATIONAL MR MEETING

TOWARDS THE STRUCTURE OF THE YERSINIA ADHESIN A MEMBRANE ANCHOR DOMAIN IN THE NATIVE ASSYMETRIC CELLULAR MEMBRANE

Marcella Rydmark[1], Florian Lindemann[2], Nandini Chauhan[1], Jayasubba Reddy Yarava[2], Hartmut Oschkinat[2], Michael Habeck[3], Barth van Rossum[2], Dirk Linke[1*]

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Abstract

Yersinia Adhesin A (YadA) is a protein found in the membrane of Yersinia Enterocolitica, which is involved in a number of food-borne diseases including enterocolitis, acute enteritis, diarrhea, and mesenteric limphadentisis. YadA plays an important role in the ability of Y. enterocolitica to colonize a host, by aiding in the autotransport of a head domain to the cell surface that can stick to host tissues[1]. A structure of the YadA anchor domain region (YadAM) in the microcrystalline form[2], and we know aim to solve structure in the e. coli outer membrane, which is asymmetric in nature, to gain insights on lipid interactions and dynamics. Preliminary results were published in 2015, which included 150 unique assignments[3]. By focusing heavily on both optimization of both the sample preparation and data acquisition we have over 800 unique assignments. We have now set up structure calculations, as well as begun dynamic measurements. This project, if successful, will provide the first *in situ* structure of a membrane protein, as well as its dynamics in the asymmetric outer membrane.

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LIPOPROTEIN AND METABOLITE RESPONSES TO PHYSICAL EXERCISE DURING ADJUVANT BREAST CANCER TREATMENT

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Background: Adjuvant breast cancer treatment may cause metabolic perturbations, such as dyslipidaemia, potentially exacerbating risk of cardiometabolic disease as well as risk of breast cancer recurrence. Physical exercise may have beneficial metabolic effects, but it's effect on serum lipoprotein- and metabolite profiles during adjuvant breast cancer treatment including chemotherapy is not yet well established.

Methods: The women participating in this pilot study of Energy Balance and Breast Cancer Aspects (EBBA)-II, were aged 38-69 years and diagnosed with stage I-II breast cancer. 60 breast cancer patients were randomized after surgery to a control group (n = 29, usual care) or an intervention group (n = 31, intervention), stratified by menopausal status. The patients in the intervention group received a detailed exercise program and met for supervised training sessions in groups of 10-12 women for 60 minutes twice a week during a 12 month period, and were in addition asked to perform at least 60 minutes of exercise at home (a total of 180 minutes of exercise weekly). Fasting serum samples were collected pre-surgery and after six months, and analysed by nuclear magnetic resonance (NMR)- spectroscopy and mass spectrometry. 170 metabolites and 109 lipoprotein subclass variables were quantified and analysed using orthogonalized partial least squares discriminant analysis. Statistical significance was assessed by permutation testing. Single variables were tested with Mann Whitney U- tests or multiple linear regression.

Results: The breast cancer patients (n = 60) had at pre-surgery the following means: Age at diagnosis of 55.4 years (38-69 years), low density lipoprotein (LDL)-cholesterol 145.4 mg/dl (3.76 mmol/L), high density lipoprotein (HDL)-cholesterol 70.4 mg/dl (1.82 mmol/L), and triglycerides 101.9 mg/dl (1.15 mmol/L), and 58.3 % of the patients underwent chemotherapy (paclitaxel/docetaxel/5- FU/epirubicin/cyclophosphamide based adjuvant chemotherapy). Physical exercise ameliorated chemotherapy-induced increases in very low density lipoprotein (VLDL)- and intermediate density lipoprotein (IDL)-associated lipids, and reduced triglyceride enrichment in LDL and HDL compared with chemotherapy controls ($p = 0.003$). Physical exercise also significantly increased apoA1 (4.6 % increase vs 11.3 % decrease, $q = 0.02$) and apoA2 (5.2 % increase vs 13.0 % decrease, $q = 0.01$) compared with chemotherapy control patients. The NMR-measured lipid signal at 1.55-1.60 ppm increased after six months in chemotherapy recipients, but this was attenuated among chemotherapy recipients in the intervention group. No statistically significant effect of physical exercise on serum levels of small- molecular metabolites was detected.

Conclusion: Our findings suggest that physical exercise may prevent atherogenic alterations in lipoprotein profile induced by chemotherapy. The results indicate increased HDL particle number- and function, as well as increased triglyceride clearance in the intervention group. Thus, atherogenic alterations in lipoprotein profile may play a role in evaluating breast cancer treatment, and could potentially be biomarkers of importance for breast cancer prognosis and co-morbidity.

Predicting chemoradiotherapy outcome and hypoxia-related tumor cell metabolism in cervical cancer by combining multimodality medical images.

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Background:

We have previously developed a tool to quantify hypoxic fraction by combining multiparametric MR-images related to oxygen consumption and supply. This tool, termed consumption and supply based hypoxia (CSH)-imaging, was developed in prostate cancer based on diffusion weighted (DW)-MRI. Its applicability in cervical cancer using dynamic contrast enhanced (DCE)-MRI was further demonstrated. We have also shown that we can quantify different levels of hypoxia (mild-severe) using the CSH-tool. When combined with other imaging modalities, the tool potentiates investigation of tumor biology responses to different hypoxia levels.

Aim:

We here investigated the prognostic potential of CSH-imaging with inputs from DCE- and DW-MRI in cervical cancer. We further combined CSH-images with fluordeoxyglucose (FDG)-PET to explore glucose uptake at different hypoxia levels within the tumors.

Methods:
Totally 120 patients with locally advanced cervical cancer were included. Diagnostic imaging with DCE-, DW-MRI and FDG-PET was available for 92 patients, whereas 38 patients without FDG-PET were used for validation. The MRI-parameters Ktrans and ADC and PET-parameter SUV were used as measures of tumor perfusion, cell density and glucose uptake, respectively. In-house developed software was used to co-register tumor delineations across image modalities for each individual patient, allowing pixel-by-pixel comparisons between the images.

Results:
Construction of CSH-images using images of ADC and Ktrans as measures of oxygen consumption and supply, respectively, was feasible. Hypoxic fraction derived from the CSH-images was strongly associated with outcome of chemoradiotherapy in both investigation and validation cohort (Log Rank: $P<0.01$). Pixel-by-pixel analysis of CSH- and SUV-images showed elevated glucose uptake in mild and moderate hypoxic areas compared to non-hypoxic areas. The glucose uptake was, however, decreased in severely hypoxic areas.

Conclusion:
CSH-imaging with DCE-MRI and DW-MRI is a promising prognostic tool in cervical cancer and provides novel understanding of tumor metabolism in relation to hypoxia level when combined with FDG-PET.

HIV-1 p6 –a multifunctional key molecule in HIV-1 biology

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The 52 amino acid HIV-1 p6 Gag protein is synthesized as the C-terminal part of the Gag polyprotein Pr55. p6 promotes virus release by its two late (L-) domains, and facilitates the incorporation of the viral accessory protein Vpr. However, the function of p6 in its mature form, after proteolytic release from Gag, has not been investigated yet.
There is a significantly higher risk for type II diabetes in HIV-1 carriers, albeit the molecular mechanism for this HIV-related pathology remains enigmatic.
We found that the mature p6 represents the first known viral substrate of the ubiquitously expressed cytosolic metalloendopeptidase insulin-degrading enzyme (IDE). IDE is sufficient and required for degradation of p6, and p6 is approximately 100-fold more efficiently degraded by IDE than its eponymous substrate insulin.
Permanent treatment with the IDE inhibitor 6bK reduced the replication of X4-tropic HIV-1 *wt*. Quantification of the replication capacity revealed a 50% reduction in the replication capacity of the *wt* under 6bK treatment. Structural features of p6 proteins with important sequence and point mutations leading to resistance towards IDE degradation are discussed.

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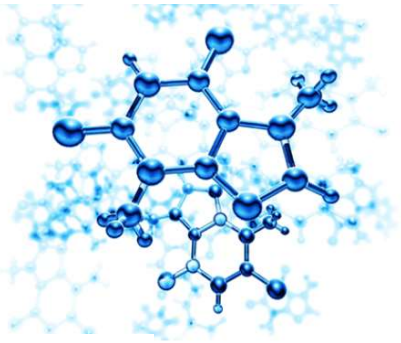

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