Abstract Book
Foreword

Bergen, Bikuben Conference Center, September 7th

We cordially welcome you to Bergen to the 10th MedViz Conference, jointly organized with the 6th Eurographics Workshop on Visual Computing for Biology and Medicine (VCBM 2016) at Haukeland University Hospital.

Advanced medical imaging and visualization is crucial for the best-possible diagnosis and treatment of patients, and clinical decision-making is increasingly based on information that is provided by medical imaging and visualization. Interventions and image-directed therapies are also increasingly employed, guided by findings from imaging and diagnostic procedures preceding the customized therapy.

MedViz has a decade of exciting experiences from annually assembling more than 100 technologists and physicians, both from Bergen, Norway, and from abroad for the MedViz conference. VCBM was first organized in 2008 in Delft, The Netherlands, then becoming a very successful series of events, happening again in 2010 in Leipzig, Germany, then in 2012 in Norrköping, Sweden, and then in 2014 in Vienna, Austria. Due to its increased success, VCBM was then improved into an annual event—organized in 2015 in Chester, UK, before then coming here to Bergen, Norway, in 2016. We are very enthusiastic about the combination of both events, this year, with fruitful discussions and the exchange of scientific ideas between researchers and users of medical imaging and visualization. Furthermore, this conference provides a forum in which students and PostDocs can interact with scientists, clinicians and engineers to enable translational communication, research and innovation.

We are particularly grateful to the many international faculty members for coming to Bergen and sharing their expertise with the conference. Their talks are complemented by the important contribution from national speakers and from our local organizing committee.

The conference is scheduled for three days with a social program in addition to the scientific content. The scientific program consists of five joint oral presentation sessions, four parallel MedViz –VCBM sessions, and a poster session. The presentations covers the following topics: visualization, MR modality, visual exploration and analysis of biological data, novel visualization techniques, translational imaging, ultrasound modality, visual computing for blood flow & motion analysis, medical data analysis and visualization, PET / MR modality, illustrative and comparative medical visualization, perfusion imaging, simulation and visual analysis in medicine, and computational imaging.

The conference audience is also presented Prof. Ingrid Haldorsen playing “Kjempeviseslåtten” (“Ballad of revolt” by Harald Sæverud) on the piano, before Nils Erik Gilhus, Head of Department of Clinical Medicine, University of Bergen, opens the conference. The social program includes a dinner at Galleri Nygaten, where the choir Stram sets the right mood among pieces of modern art, dominated by Eser Afacan.

At the end of the conference, prizes for the best paper, best poster, and best presentation, as well as the winner of the MedViz image contest are awarded.

Thank you all for coming to Bergen and we wish you a pleasant stay.

Sincerely yours,

Prof. Ragnar Nortvedt
MedViz
Joint Organizing Chair

Prof. Helwig Hauser
University of Bergen
General Chair, VCBM

Prof. Odd Helge Gilja
Haukeland Univ. Hospital
General Chair, MedViz
Program

Conference Venue: Bikuben Conference Center, Haukeland University Hospital, Bergen, Norway
See also http://MedVizVCBM.UiB.no/venue.php

Wednesday September 7
12:00   Start registration (posters might be displayed from 08:00)
1300 – 1345 Lunch
1345 – 1400 Welcome by Head of Department of Clinical Medicine, University of Bergen, Nils Erik Gilhus

Joint Session I: Visualization
Chairs: Helwig Hauser & Odd Helge Gilja (“Storstuen” = large room)
1400 – 1445 Hans-Christian Hege, Zuse Institute, Berlin:
Visual Computing for Connectomics - Achievements and Challenges
1445 – 1530 Panel discussion: Future topics in Medical Visualization, moderated by Helwig Hauser
1530 – 1600 Coffee break and Posters

Two parallel Sessions II:
MR modality
Chairs: Ingfrid Haldorsen & Jarle Rørvik (“Storstuen” = large room)
1600 – 1630 Tijl van der Velden, UMC, Utrecht:
Advanced MR diffusion and metabolic models characterizing tumors
1630 – 1640 Arvid Lundervold, Department of Biomedicine, University of Bergen:
Brain imaging and machine-learning to explore brain gut axis in irritable bowel syndrome
1640 – 1650 Eli Eikefjord, Department of Radiology, Haukeland University Hospital, Bergen:
Quantification of single kidney function and volume in living kidney donors using dynamic contrast-enhanced MRI
1650 – 1700 Sigmund Ytre-Hauge, Department of Radiology, Haukeland University Hospital, Bergen:
In vivo MR spectroscopy predicts high tumor grade in endometrial cancer
1700 – 1730 Atle Bjørnerud, University of Oslo:
MR perfusion for tumor characterization

Visual exploration and Analysis of Biological Data
Chair: Timo Ropinski (“Auditorium”)
1600 – 1620 Ivan Kolesar, Dept. of Informatics, University of Bergen:
Unfolding and Interactive Exploration of Protein Tunnels and their Dynamics
1620 – 1640 Nicholas Waldin, Vienna Technical University:
Chameleon: Dynamic Color Mapping for Multi-Scale Structural Biology Models
1640 – 1700 Johannes Sorger, Vienna Technical University:
Illustrative Transitions in Molecular Visualization via Forward and Inverse Abstraction Transform
1700 – 1720 Martin Hess, Technical University Darmstadt:
Visual Analysis and Comparison of Multiple Sequence Alignments
1730 – 1800 Coffee break and Posters
Joint Session III: Short papers – Novel Visualization Techniques
Chairs: Stefan Bruckner (“Storstuen” = large room)
1800 – 1815 Benjamin Behrendt, Otto-von-Guericke University, Magdeburg:
Semi-Automatic Vessel Boundary Detection in Cardiac 4D PC-MRI Data Using FTLE fields
1815 – 1830 Serban Pop, University of Chester:
Real-Time Guidance and Anatomical Information by Image Projection onto Patients
1830 – 1845 Salaheddin Alakkari, Trinity College Dublin:
Volume Visualization Using Principal Component Analysis

Thursday September 8

Joint Session IV: Translational imaging
Chairs: Martin Biermann & Lars R. Reisæter (“Storstuen” = large room)
0900 – 0930 Andreas J. Tulipan, Dept. of Radiology and Nuclear Medicine, Oslo University Hospital:
Diagnosing prostate cancer with PET
0930 – 0950 Habib Baghirov, Department of Physics, NTNU, Trondheim:
Focused ultrasound-mediated transport of poly (alkyl cyanoacrylate) nanoparticles across the blood-brain barrier in a melanoma brain metastasis model
0950 – 1030 Samer Ezziddin, Department of Nuclear Medicine, Saarland University Hospital, Bad Homburg:
Radiopeptide treatment for prostate cancer
1030 – 1100 Coffee break and Posters

Two parallel Sessions V:

Ultrasound
Chairs: Odd Helge Gilja & Roald Flesland Havre (“Storstuen” = large room)
1100 – 1130 Paul Sidhu, King's College Hospital, London:
Clinical Applications of Elastography: My Experience
1130 – 1145 Roald Flesland Havre, National Centre for Ultrasound in Gastroenterology, Dept. of Medicine, HUH:
Endoscopic strain imaging of the pancreas
1145 – 1200 Mette Vesterhus, National Centre for Ultrasound in Gastroenterology, Dept. of Medicine, HUH:
Elastography of the liver in Primary Sclerosing Cholangitis
1200 – 1215 Trond Engjom, National Centre for Ultrasound in Gastroenterology, Dept. of Medicine, HUH:
Comparing secretin stimulated ultrasonography and MRI in cystic fibrosis patients and healthy controls
1215 – 1230 Elisabeth Steinsvik, National Centre for Ultrasound in Gastroenterology, Dept. of Medicine, HUH:
Proximal stomach function in patients with IBS compared to Functional Dyspepsia using Ultrasound
1230 – 1300 Bjørn Angelsen, NTNU, Trondheim:
SURF elastography for improved ultrasound

Visual computing for Blood Flow & Motion Analysis
Chairs: Bernhard Kainz (“Auditorium”)
1100 – 1130 Niels de Hoon, Technical University Delft:
Temporal interpolation of 4D PC-MRI blood-flow measurements using bidirectional physics-based fluid simulation
1130 – 1200 Arjan Broos, Eindhoven University of Technology:
A framework for fast initial exploration of PC-MRI cardiac flow
1200 – 1230 Rickard Englund, Linköping University:
Coherence Maps for Blood Flow Exploration
1230 – 1300 Ali Sheharyar, Jacobs University Bremen & Texas A&M University at Qatar:
Spatio-temporal Visualization of Regional Myocardial Velocities

1300 – 1400 Lunch
Joint Session VI: Poster summary and Short papers – Medical Data Analysis and Visualization
Chairs: Lars Linsen (“Storstuen” = large room)
1400 – 1415 Nico Merten, University Magdeburg:
Illustrative PET/CT Visualization of SIRT-Treated Lung Metastases
1415 – 1430 Dennis Eschweiler, RWTH Aachen University:
A Feasibility Study on Automated Protein Aggregate Characterization Utilizing a Hybrid Classification Model
1430 – 1445 Alberto Corvo, Technical University Eindhoven:
PATHONE: From one thousand patients to one cell
1445 – 1500 Veronika Šoltészová, Christian Michelsen Research and Dept. of Informatics, University of Bergen:
A summary of the posters

1530 – 1600 Coffee break and Posters

Two parallel Sessions VII:
PET/MR
Chairs: Renate Grüner & Thomas Schwarzmüller (“Storstuen” = large room)
1600 – 1630 Bernhard Sattler, University Hospital Leipzig:
PET/MRI – Technology and performance, challenges and applications
1630 – 1640 Pedro Silva, Eindhoven University of Technology:
Visualization of Variability in Radiotherapy Dose Planning
1640 – 1700 Hans-René Bjorsvik, Dept. of Chemistry, University of Bergen:
Synthesis of 11C labeled sulfasalazine for PET imaging of drug delivery across the blood brain barrier and uptake in tumor tissue
1700 – 1720 Live Eikenes, NTNU, Trondheim:
Experiences with PET/MR in Norway

Illustrative and Comparative Medical Visualization
Chairs: Ivan Viola (“Auditorium”)
1600 – 1620 Patrick Saalfeld, University of Magdeburg:
Semi-immersive 3D Sketching of Vascular Structures for Medical Education
1620 – 1640 Nils Lichtenberg, University of Koblenz-Landau:
Sline: Seamless Line Illustration for Interactive Biomedical Visualization
1640 – 1700 Gabriel Mistelbauer, Vienna Technical University:
Aortic Dissection Maps: Comprehensive Visualization of Aortic Dissections for Risk Assessment
1700 – 1720 Sylvia Glasser, University Magdeburg:
How to Evaluate Medical Visualizations on the Example of 3D Aneurysm Surfaces

Joint Session VIII: Posters
1730 – 1830 Posters in the poster area (“K1”)

1900 Conference Dinner: Galleri Nygaten
Common bus transport from the Conference venue (18:40). You may alternatively find the location by taxi to Nygaten 7 or look it up at http://gallerinygaten.no/om-oss/
Friday September 9

Two parallel Sessions IX:

**Perfusion Imaging**

Chairs: Torfinn Taxt & Erlend Hodneland (“Storstuen” = large room)

0900 – 0930  Radovan Jiřík, Institute of Scientific Instruments of the CAS, Brno:
Recent Advances in MRI and Ultrasound Perfusion Imaging

0930 – 0950  Erik Hanson, Department of Mathematics, University of Bergen:
Discretization dependency of classical models for perfusion - a simulation study

0950 – 1010  Kim Nylund, National Centre for Ultrasound in Gastroenterology, Dept. of Medicine, HUH:
Ultrasound imaging of perfusion

1010 – 1030  José Manuel Prats Montalbán, Universidade Politécnica de Valencia:
Multivariate image analysis for multiparametric phenotyping and prognosis in cancer

**Simulation and Visual Analysis in Medicine**

Chairs: Claes Lundström (“Auditorium”)

0900 – 0920  Philip Voglreiter, Graz University of Technology:
Visualization-Guided Evaluation of Simulated Minimally Invasive Cancer Treatment

0920 – 0940  Oliver Mattausch, Swiss Federal Institute of Technology, Zurich:
Monte-Carlo Ray-Tracing for Realistic Interactive Ultrasound Simulation

0940 – 1000  Sergej Stoppel, Department of Informatics, University of Bergen:
Graxels: Information Rich Primitives for the Visualization of Time-Dependent Spatial Data

1000 – 1020  Renata Raidou, Technical University Eindhoven:
Visual Analytics for the Exploration and Assessment of Segmentation Errors

1030 – 1100  Coffee break and Posters

**Joint Session X: Computational Imaging**

Chairs: Arvid Lundervold & Antonella Zanna Munthe-Kaas (“Storstuen” = large room)

1100 – 1115  Carola-Bibiane Schönlieb, Dept. of Applied Mathematics & Theoretical Physics, Univ. of Cambridge:
Dynamic image analysis: from tracking of cells to dynamic MRI

1115 – 1130  Erlend Hodneland, Christian Michelsen Research and MedViz, Bergen:
Image registration for early detection of fibrosis

1130 – 1145  Hiroshi Noborio, Dept. Computer Science, Osaka Electro-Communication University:
Evaluation of depth-depth matching algorithm for following human liver whose motion is practical and also is occluded by human body

1145 – 1200  Alexander Lundervold, Faculty of engineering and business administration, Bergen University College:
Imaging-based modeling of the human larynx for simulation of airflow during exercise

1200 – 1215  Kent-Andre Mardal, Department of Mathematics, University of Oslo:
Brain & Water - computational modelling of the aging brain

1240 – 1315  Awards for the best PhD Poster, PhD oral presentation and for Image Contest

Concluding remarks

by Ragnar Nortvedt, MedViz, Bergen and Helwig Hauser, VCBM

1315 – 1400  Lunch
International Faculty
Samer Ezziddin, Department of Nuclear Medicine, Saarland University Hospital, Bad Homburg, Germany
Eduard Gröller, Vienna University of Technology, Austria
Hans Christian Hege, Zuse Institute, Berlin, Germany
Radovan Jiřík, Institute of Scientific Instruments of the CAS, Brno, Czech Republic
José Manuel Prats Montalbán, Universidad Politécnica de Valencia, Spain
Bernhard Sattler, University Hospital Leipzig, Germany
Carola-Bibiane Schönlieb, Dept. of Applied Mathematics & Theoretical Physics, Univ. of Cambridge, UK
Paul Sidhu, King’s College Hospital, London, UK
Tijl van der Velden, UMC, Utrecht, The Netherlands
Ivan Viola, Vienna University of Technology, Austria

Local Organizing Committee
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Stefan Bruckner
Helwig Hauser
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Judit Haász
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Abstracts for Session II
MR modality

Abstracts are organized in the order of presentations
Advanced MR diffusion and metabolic models for characterizing breast tumors

Tijl van der Velden – T.A.vanderVelden@umcutrecht.nl

With breast cancer being the most prevalent form of cancer among women, being able to accurately characterize breast tumors helps in the treatment planning of many patients. A wide variety of imaging modalities are available for breast tumor imaging, such as mammography, ultrasound, PET/CT and MRI, each with its advantages and disadvantages. The topic of this presentation will be how MRI can be used for characterization of breast tumors.

The main advantage of MRI over other modalities is the high contrasts that can be obtained between different soft tissue types. In the case of cancers, this contrast can be increased by administering a gadolinium containing contrast agent. Tumors will get a hyper intense signal, compared to healthy tissue, due to high vascularization. Figure 1a shows a breast tumor after the injection of a contrast agent.

Figure 1: (a) Post contrast enhanced MRI of a woman with a invasive ductal carcinoma. The tumor, containing a relatively high concentration of contrast agent, is hyper intense compared to healthy tissue. (b) Enhancement curve of the tumor. The wash-in and wash-out of contrast agent in the tumor is an indicator of aggressiveness of the tumor.

Besides morphological images, information on a cellular and metabolic level can be obtained as well with MRI, of which four will be discussed: dynamic contrast enhanced (DCE) MRI, diffusion weighted imaging (DWI), phosphorous spectroscopy (31P MRS) and chemical exchange saturation transfer (CEST).

- With DCE MRI, multiple scans are acquired just after the injection of a contrast agent, from which an enhancement curve, shown in figure 1b, can be determined. By modeling of the uptake of contrast agent in the tumor, kinetic information can be obtained. Kinetics of contrast uptake gives information about the vascularization and the permeability of the vessel wall in the tumor region (1). These types of acquisitions are currently the standard in most breast MRI examinations. Special attention should be given to fat suppression. In particular at higher resolution, fat suppression is desired to prevent subtraction errors. Multiple fat suppression techniques are available, such as fat saturation, Dixon and water excitation, each with different limitations on different field strengths.

- Diffusion weighted MRI provides information of the cellular structure by measuring the diffusivity of water in tissue. With the unstructured organization of cells in tumors, a lower diffusivity can be measured, compared to healthy tissue (2). From multiple diffusion
weighted images, a quantitative measure representing the amount of diffusion can be calculated: the apparent diffusion coefficient (ADC) (fig 2b).

One of the main challenges in DWI is to deal with geometric distortions. The echo planer imaging (EPI) readout, often used in DWI, is very sensitive to inhomogeneities in the main magnetic field (B0 field). There are multiple techniques that allow to minimize this problem, which can be found both in sequence optimization as well as post processing techniques (3,4). Similar to DCE, a combination of fat suppression techniques can be used, to prevent any artifacts from fat tissue.

![Figure 2: (a) Coronal view of the post contrast enhancement acquisition of figure 1. (b) ADC map, calculated from multiple DWI images. Note the lower diffusion coefficient in the tumor, as a result of dense and unstructured cellular organization.](image)

- 31P MRS holds information on the cell membrane metabolism. With 31P MRS, different metabolites that contain phosphorous atoms can be distinguished. The ratio between phosphomonoesters (PME) and phosphodiester (PDE) gives information on the response on therapy (5,6).
  Due to the different resonance frequency of 31P (17.23 MHz/T) compared to 1H (42.58 MHz/T), dedicated radio frequency (RF) coils are required. Preferably, these RF coils can be combined with 1H RF coils for imaging. However, due to lower abundancy of 31P atoms and the lower resonance frequency, a much lower signal is measured. Therefore, special MR sequences are required which allow to acquire data with sufficient signal.

- Chemical exchange saturation transfer (CEST) gives information of protein contents. The proteins that are mostly observed in CEST imaging are the proteins with an amide group, since differences in the amide proton transfers (APT) effect might indicate if the patient is responding to chemotherapy (7–9).
  With CEST, the metabolite concentration can indirectly be determined by measuring the change in water magnetization because of the exchange of 1H atoms of the protein with water. This is done by applying a long RF pulse with a small bandwidth on the resonance frequency of the specific metabolite, followed by a conventional imaging sequence that measures the water signal. The exchange of the mobile protons between the water pool and the metabolite results in a lower intensity of the image compared to images acquired without a saturation RF pulse. By repeating this measurement for a series of frequencies, a so-called z-spectrum can be calculated.

In the presentation I will show our experiences with these techniques, applied on 7 tesla MRI. Furthermore, I will show how the different parameters from these scans can potentially be off aid in the treatment planning of breast cancer patients.


Brain imaging and machine-learning to explore brain gut axis in irritable bowel syndrome

Eivind A Valestrand¹,², Kiniena F Tekie²,¹, Trygve Hausken¹,³, Arvid Lundervold²,⁴

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⁴Radiology Department, Haukeland University Hospital, Bergen, Norway

Introduction

The brain-gut axis’ involvement in irritable bowel syndrome (IBS) has received increased attention recent years. One core network in the IBS brain is the salience network, which responds to subjective salience of stimulus, or the expectation of stimulus, reaching the brain. In our study we use powerful machine learning classification methods to analyze cortical thickness in key nodes of this network (see figure 1).

Method

Two successive 3D T1-weighted MRI acquisitions from 15 IBS patients and 15 healthy controls (HC) were recorded on a GE Signa 3.0T MR scanner and segmented with FreeSurfer v.5.3.0. Our imaging protocol also included diffusion tensor imaging and functional magnetic resonance imaging pre- and post-meal stimulation (see figure 2). These data are analyzed in different parts of the project. In this part, cortical thickness values from 6 x 2 anatomical regions (left and right hemisphere) in the salience network were extracted and analyzed in R v.3.2.3 with a two-layer neural network classifier (‘nnet’ in the ‘caret’ package with 7 neurons in the hidden layer and weight decay 0.05), predicting HC versus IBS for the 12-dimensional normalized cortical thickness pattern vectors. For training the network we used an hold-out
method including 75% of the total sample with resampling and cross validation (10 fold, repeated 10 times). For the assessment of classification performance and possible generalization abilities, we repeated the hold-out method 50 times, each with random sampling of 46 observations used for training (cross validation 10 folds, 10 repetitions) and with the remaining 14 observations (7 HC, 7 IBS) used for testing. For each hold-out experiment we computed the confusion matrix, classification accuracy, sensitivity, and specificity. The 12 cortical regions being analyzed were the caudal anterior cingulate, caudal middle frontal, lateral orbitofrontal, medial orbitofrontal, rostral middle frontal, and the insular cortex in left and right hemisphere respectively. We also assessed the importance of the regional variables across the series of experiments.

Results

The 50 hold-out experiments gave the following results: mean classification accuracy 0.687 (SD 0.125), mean sensitivity 0.643 (SD 0.178), mean specificity 0.731 (SD 0.118). Very similar performance measures were also confirmed by using a Random Forest classifier in the same repetitive hold-out procedure. The scores of regional importance for the classification results were very close to each other (see figure 5). The left and right insular regions had typically high scores, but no order or region in either hemisphere could be singled out as the most important for discrimination. This was also reflected in the class-specific feature density
plots. The discrimination ability was thus due to cortical thickness patterns rather than thickness of a single region.

Conclusions

Patients with IBS seem to have structural brain signatures that differ from healthy controls in terms of cortical thickness patterns within the salience network. The finding of such patterns, making it possible to discriminate between the IBS brain and the HC brain with a sensitivity / specificity of about 64% / 73% is highly interesting, both diagnostically and mechanistically. An overall change in the network could indicate an altered interoceptive function in IBS patients constituting of several minor non-significant findings.
Quantification of single kidney function and volume in living kidney donors using dynamic contrast-enhanced MRI

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¹Department of Radiology, Haukeland University Hospital, ²Department of Clinical Medicine, University of Bergen, ³Department of Clinical Engineering, Haukeland University Hospital, ⁴Christian Michelsens Research (CMR) AS, ⁵Department of Medicine, Haukeland University Hospital, ⁶Department of Biomedicine, University of Bergen.

Abstract

Objective: To investigate whether dynamic contrast enhanced MRI (DCE-MRI) can detect differences and potential adaption in single kidney parenchymal volume, blood flow, glomerular filtration rate (GFR), or filtration fraction in the remaining kidney of healthy donors compared to non-donors. Further, to evaluate the agreement in donors’ GFR measured by MRI versus iohexol.

Materials and methods: 20 living kidney donors (mean age, 51 years; age range, 38-67 years; mean years since donor nephrectomy 9 years, range 2-17 years) and 20 healthy controls (mean age 25 years; age range, 20-38) underwent DCE-MRI and iohexol-GFR. Renal parenchymal volume was assessed from maximum signal intensity maps. Single kidney MRI-measurements of blood flow and GFR were derived from parenchymal intensity time curves fitted to a two-compartment filtration model. Student t-test, Pearson correlation, mean differences, and limits of agreement were applied to analyze MRI-measurements between groups and agreement with iohexol-GFR, respectively.

Results: MRI found a significantly higher blood flow (54%, p = 0.001), GFR (78%, p < 0.0001) and parenchymal volume (65%, p < 0.0001) in donors’ kidney compared to the single kidney of healthy controls. In donors’ kidney, a proportional increase in blood flow and GFR resulted in comparable filtration fraction as observed in controls. Significant correlations were found between MRI-derived GFR (p= < 0.0001) and parenchymal volume (p < 0.0001) compared to iohexol-GFR. Mean difference and limits of agreement between MR-derived GFR and iohexol-GFR were 14 mL/min and [−24.1, 52.1] mL/min, respectively.
**Conclusion:** Significantly higher MRI-derived values for single kidney functional parameters in kidney donors compared to controls suggest a future potential benefit of dynamic contrast enhanced MRI in clinical work-up of living kidney donors, especially in donors with marginal GFR where optimal care is mandatory.
In vivo MR spectroscopy predicts high tumor grade in endometrial cancer

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INTRODUCTION AND PURPOSE OF STUDY
Endometrial cancer is the most common gynecologic malignancy in high-income countries, and the incidence is increasing. Current treatment algorithms have been criticized for insufficient individualization leading to overtreatment in low-risk patients and undertreatment in high-risk patients. Preoperative imaging may potentially provide biomarkers improving the preoperative risk stratification enabling individualization of patient treatment. In vivo magnetic resonance spectroscopic imaging (MRSI) enables non-invasive quantification of tumor metabolites preoperatively. Choline-containing metabolites (tCho) are previously reported to play a key role in tumor metabolism. We aimed to explore whether high risk histological features are reflected in preoperative MRSI tumor parameters in endometrial carcinomas.

MATERIALS AND METHODS
Preoperative multimodal pelvic MRI at 1.5T, including structural, diffusion weighted imaging (DWI) and multivoxel localized point-resolved spectroscopy (PRESS) 1H MRSI, was prospectively performed in 77 patients with histologically confirmed endometrial carcinomas. MRSI was acquired with the parameters; TR/TE = 690/120 ms, matrix size 12×12×12, voxel size 6.7×6.7×6.7 mm, 1.3 kHz spectral window and 512 points. Guided by the diagnostic conventional images, representative MRSI voxels were selected and analyzed from tumor tissue and adjacent normal tissue (myometrium). Spectral data were analyzed by the software jMRUI v5.2. To measure tCho concentration, three ratios were generated; tCho/Creatine, tCho/Water and tCho/Noise.

MRSI parameters were analyzed in relation to histological subtype and grade, surgicopathological staging parameters (deep myometrial invasion, cervical stroma invasion and lymph node metastases), MRI measured tumor volume and tumor apparent diffusion coefficient (ADC) value using Mann-Whitney U test, Kruskal-Wallis H test, Jonckheere-Terpsta trend test and Spearman’s bivariate correlation test. Comparison of MRSI features in tumor tissue and normal tissue was performed with Related-Samples Wilcoxon Signed Rank Test.

RESULTS
Tumor tissue had significantly higher ratios for tCho/Creatine, tCho/Water and tCho/Noise than normal myometrial tissue (p<0.001 for all). High tumor tCho/Water-ratio was significantly associated with high tumor grade in endometrioid tumors (p=0.02). Tumor tCho/Creatine-ratio was positively correlated to MRI assessed tumor volume ($r_s = 0.25; p=0.03$).
CONCLUSIONS
Tumor tCho/Water-ratio is significantly related to high tumor grade, which is an established risk factor in endometrial cancer. Thus, in vivo $^1$H MRSI may potentially aid in the preoperative tumor characterization for risk stratification guiding individualized surgical and adjuvant treatment. However, the benefits of MRSI should be considered along with the costs and technical challenges before implementation into routine clinical practice in endometrial cancer patients.

Figure 1: T2-weighted images and spectra for one high grade (a: grade 3 endometrioid tumor, tCho/Water-ratio 7.1) and one low grade endometrial cancer patient (b: grade 1 endometrioid tumor, tCho/Water-ratio 1.4). Notice the high level of choline metabolites (high tCho peak) in the high grade tumor.
MR perfusion for tumor characterization

Atle Bjørnerud
The Intervention Centre, Oslo University Hospital
Dept of Physics, University of Oslo

Perfusion weighted MRI (pwMRI) is a term used to describe a multitude of MR techniques designed to measure different aspects of tissue perfusion. Although tissue perfusion is strictly defined physiologically as volume of blood flowing through a given volume of tissue per unit of time, the term pwMRI is also commonly used for MR techniques used to measure a broad range of parameters also including tissue blood volume, tracer capillary transit times and capillary permeability. pwMRI has gained increasing attention since it offers additional information beyond what is available with conventional (structural) MRI, thereby potentially increasing both sensitivity and specificity in tumour diagnostics.

pwMRI techniques can be divided into different sub-categories, depending on the specifics of the method used, as shown in Figure 1.

Figure 1

Non-contrast enhanced pwMRI based on arterial spin labelling (ASL) is a relatively new method whereby the blood is used as an endogenous tracer to measure tissue perfusion without the need to inject contrast material. By magnetically labelling the blood (using special RF pulses) in a region upstream from the tissue of interest, tissue perfusion can be estimated based on the effect of the labelled blood on the measured MR signal in the tissue of interest (in contrast to the same signal measured without magnetic labelling of the blood). There has
been a tremendous development of ASL-techniques over the last couple of years, and the fact that the method is completely non-invasive (allowing repeated measurements, and application in patients where injectable contrast agents are contra-indicated) combined with its inherently quantitative nature has led to a rapid acceptance of ASL in neuroscience imaging research.

The disadvantage of ASL compared to contrast enhanced pwMRI is a lower sensitivity to the perfusion effect (the labelling only causes a small change in the measured MR signal). Further, ASL is extremely sensitive to motion which severely limits the utility of the methods outside the brain.

**Contrast enhanced pwMRI:** is currently the most established MR based approach for tumor characterization. Bolus injection of a (gadolinium based) contrast agent is combined with rapid dynamic imaging, capturing the effect (in terms of change in measured MR signal) of the tracer on the tissue of interest. A major strength of MRI in this context is that the MR signal can be sensitised to different properties of the contrast agent, reflecting different properties of tissue microstructure. Dynamic susceptibility contrast (DSC) is the term used when the MR sequence is made sensitive to the T2-relaxation effect of the contrast agent. DSC-MRI is particularly useful in tissues where the contrast agent is confined to the capillary space since high degree of compartmentalization enhances the T2-effect of the contrast agent. Hence, DSC-MRI has become the preferred method for brain tumor characterization. Here, relative maps of cerebral blood volume (CBV) have been shown in numerous studies to aid in characterization of primary brain tumors. For gliomas, higher tumor grade (higher malignancy) is associated with increased CBV and more heterogeneous CBV distribution in tumor, as shown in Figure 2.

![Figure 2](image.png)

**Dynamic contrast enhanced (DCE) MRI** is the term traditionally used when the T1-effect of the contrast agent is used in combination with heavily T1-weighted MR sequences. In the brain, in areas with intact blood brain barrier (BBB), the T1-effect of current contrast agent is limited since this effect will essentially only influence the signal of water protons present in the same intravascular compartment (contrary to the T2-effect which is long-range). Hence DCE-MRI has a much lower sensitivity.
sensitivity than DSC-MRI in intact brain. However, in pathological conditions where the BBB is disrupted, the T1-effect becomes much stronger and the measured increase in MR signal due to the T1-effect of the agent can then be used to estimate hemodynamic parameters related both to perfusion and capillary permeability. Figure 3 shows a sample case where DSC- and DCE-MRI are acquired in the same tumor (glioblastoma) and the time-intensity curves show the appreciable difference in the T2-response (left) and T1-response in tumor (red curves) versus unaffected cortex (green curves) for the two sequences. The same gadolinium based contrast agent and the same contrast agent dose was used in both cases.

Figure 3

In non-CNS tumors, DCE-MRI is the most commonly used approach for tumor characterization. This is due to the fact that all non-CNS tissues have a high permeability to current contrast agents, causing rapid extravasation to the extravascular-extracellular space (EES) and hence strong T1-enhancement. Since many pathological processes lead to alterations in both tissue perfusion and permeability, application of appropriate kinetic models then enables estimation several metrics related to pathological changes in tissue hemodynamics and capillary permeability.

To date, breast- and prostate cancer have been most extensively investigated with DCE-MRI outside the brain, but the methods has also shown utility in many other areas including head & neck, rectum and endometrium.

**Parameter estimation and the art of kinetic modeling:** Although many advanced kinetic models have been developed for DCE-MRI analysis, advanced analysis approaches have not yet gained widespread clinical acceptance due to the complexity of the analysis and lack of standardization between institutions and MR machine vendors. Quantitative analysis of perfusion related parameters with both DCE- and DSC-MRI has proven very challenging for several reasons. First, the dose-response (effect of the contrast agent on the measured MR signal) is not generally well defined.
in MRI. Unlike in CT where the contrast agent is detected directly, MRI agents can only be observed indirectly through its influence on surrounding water protons. This leads to complex (and generally non-linear) dose-response which can vary depending on tissue structure, contrast agent distribution-and dose and many other factors. Second, most kinetic models used for quantitative analysis requires accurate measurements of the arterial input function (AIF), representing the dose-response in an artery feeding the tissue of interest. Accurate AIF determination is quite often impossible due to e.g. limited spatial resolution, motion or excessive arterial contrast agent concentrations, resulting in severe artifacts in the AIF profile. It has therefore proved difficult to establish robust quantitative analysis approaches yielding comparative results across sites and MR systems. In spite of these challenges however, there is a large effort in the research community to develop (semi-) quantitative analysis approaches allowing estimation of kinetic parameters for use in tumor diagnostics that can be directly compared between patients and sites. The most commonly used kinetic model for (semi-) quantitative analysis a so-called two-compartment model (Figure 4) where the contrast agent is assumed to be present in one of two compartments; the intravascular (IV) space or the EES. There is then a bi-directional flux of tracer between these two compartments where the rate of exchange is a function of relative tissue compartment sizes, tissue perfusion and capillary permeability to the agent. This model enables (in theory) estimation of plasma volume ($V_p$), EES volume ($V_e$) and the bi-directional transfer constant ($k^{trans}$), all parameters which have been shown to be sensitive to pathological changes in tumors. More advanced models also enables estimation of tissue perfusion (flow) – which is many situations will be an important parameter driving the extent of contrast agent extravasation.

In the absence of quantitative analysis alternatives, the MR community has for a long time settled for a much more pragmatic approach whereby only the relative ‘shape’ of the dynamic signal response is considered. Although such ‘shape-analysis’ cannot be directly related to underlying tissue properties (e.g. perfusion and permeability) it is still clearly related to these properties and has thus been shown to add diagnostic value for tumor characterization. The verdict is therefore still open as to whether more advanced kinetic modeling approaches will become established in a clinical setting.
in the future or whether the more pragmatic qualitative approaches will remain the preferred approach due to higher reproducibility and ease of use.

In summary, pwMRI is a versatile range of techniques with the common aim of measuring tissue metrics reflecting perfusion and capillary permeability. A large range of pwMRI techniques are currently available, some of which are completely non-invasive (ASL) and some which requires injection of a gadolinium-based contrast agent (DCE-MRI and DSC-MRI). The choice of methods depends on many different factors as described above. All pwMRI techniques have limitations in relation to sensitivity, complexity of analysis and ability to obtain quantitative (or at least comparable) data. Many of these challenges will be overcome in the near future but it remains to be seen whether pwMRI will become an integral part of the diagnostic work-up of a wider range of cancer patients than what is currently the case.

Further reading

Abstracts for Session IV
Translational imaging

Abstracts are organized in the order of presentations
Diagnosing prostate cancer with Positron emission tomography (PET)

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Prostate cancer (PCa) is the most common type of cancer in men and the second leading cause of cancer mortality among Norwegian men (3). PCa is characterized by biological heterogenic behavior and controversies in the management of PCa are attributed to several unique biologic features. Due to the lack of reliable imaging methods to assess PCa aggressiveness, the ability to differentiate between low-risk and high-risk PCa patients is currently limited.

For localized PCa, both radical prostatectomy and external radiation therapy both offer long-term tumor control in the majority of patients. Imaging the risk of ten years-biochemical recurrence ranges from 15% for low-risk patients to 67% for high-risk patients following radiation therapy and from 10 to 50% after radical prostatectomy (5).

Biochemical recurrence (BR) is diagnosed mainly on the serum prostate-specific antigen (sPSA) level being above a threshold or on the PSA kinetic values (7). BR is not synonymous with local recurrence in the prostatic bed, but can be also be due to distant metastases. A persistently elevated sPSA level can also be due to residual glandular healthy tissue after prostatectomy or radiotherapy.

Confirmation of residual or local recurrent disease is critical because it may greatly influence the subsequent therapeutic strategy and survival. This needs to determine whether there is local or distant disease and triggers diagnostic imaging.
Multiparametric MRI (mpMRI) joins anatomic and biological information by combining morphological imaging and functional techniques and is widely used. At present, mpMRI is the most useful tool available for the detection of local PCa recurrence (8). Whole-body MR imaging enabling detection of distant metastases is feasible with whole body array coils or moving examination table, but the prolonged examination time has resulted in alternative imaging options.

As one alternative, whole body positron emission tomography (PET) is increasingly included in the diagnostic work-up of PCa patients. Imaging with PET have shown to improve the management of patients with early recurrence, although their accuracies are closely linked to sPSA level, sPSA dynamics and tumor characteristics.

For clinical use there are several different radiolabeled PET tracers available. During the presentation the main characteristics of choline, acetate, FDG (9), NaF (10), PSMA (11) and FACBC (12) (13) will be presented.

Simplified overview of metabolic processes targeted by PET and MRI. AA pool = amino acid pool; ChoK = choline kinase; FAS = fatty acid synthase; FR-1,6-BP = fructose-1,6-bisphosphate; G-6-P = glucose-6-phosphate; LAT = L-type amino acid transporter; LDH = lactate dehydrogenase; P-choline = phosphocholine; Ribose 5P = ribose-5-phosphate. Christian Plathow, and Wolfgang A. Weber J (4)
Urea-based inhibitors of the prostate-specific membrane antigen (PSMA) represent low-molecular-weight pepidomimetics showing the ability to image PSMA-expressing prostate tumors (1).

Homodimer of human Glutamate Carboxy Peptidase II (crystal structure), also known as N-acetyl-L-asparty-L-glutamate peptidase I (NAALADase I), NAAG peptidase, or prostate-specific membrane antigen (PSMA), an enzyme that in humans is encoded by the FOLH1 (folate hydrolase 1) gene (2). One monomer shown in semitransparent surface representation with individual domains of the extracellular part colored green (protease domain; amino acids 57 – 116 and 352 – 590), blue (apical domain; amino acids 117 – 351), and yellow (C-terminal; amino acids 591 – 750); the second monomer is colored gray. N-linked sugar moieties are colored cyan, and the active-site Zn$^{2+}$ ions are shown as red spheres. **Left panel** – residing at the plasma membrane of astrocytes/schwann cells, GCPII catabolizes NAAG, the most prevalent peptidic neurotransmitter in the mammalian nervous system. N-acetylaspartate and glutamate, the reaction products, are selectively transported into glial cells, metabolized and reused for NAAG synthesis in neurons. **Right panel** – GCPII (or folate hydrolase) at the plasma membrane of enterocytes in the proximal jejunum sequentially hydrolyzes the C-terminal $\gamma$-glutamate tail of dietary folates, finally leaving folate-monoglutamate, which can be then transported transcellularly into the blood stream (6).

2. Wikipedia. Glutamate carboxypeptidase II (PSMA).


7. EAU. European Association of Urology. 2014.


Focused ultrasound-mediated transport of poly (alkyl cyanoacrylate) nanoparticles across the blood-brain barrier in a melanoma brain metastasis model

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Introduction

Brain delivery of drugs is hindered by the blood-brain barrier (BBB), an interface at brain endothelium that protects the brain and maintains its homeostasis, but also restricts the passage of 98% of small and virtually all large molecular drugs [1]. Nanoparticles (NPs) can offer numerous benefits in drug delivery due to their high drug loading capacity, incorporation of poorly soluble drugs and novel therapeutics such as peptides and oligonucleotides, functionalization for sustained and controlled release and combination of therapeutics with imaging. In the case of solid tumors, nanoparticles can also benefit from the enhanced permeability and retention effect, whereby NPs are retained in the tumor due to its leaky neovasculature and reduced lymphatic drainage. The BBB, however, is a formidable obstacle for NPs as well, and their brain delivery can benefit from versatile BBB opening techniques. Focused ultrasound in combination with microbubbles (MBs) has been shown to open the BBB safely and reversibly [2]. In this study, we used a novel platform based on poly (isohexyl cyanoacrylate) (PIHCA) NPs wrapped around MBs [3] to open the BBB and deliver NPs into brain parenchyma in a melanoma brain metastasis model.

Methods

For FUS-mediated BBB opening we used a state-of-the-art ultrasound system able to generate FUS at 1.1 MHz and 7.8 MHz during the same experiment, allowing a very precise magnetic resonance imaging (MRI)-guided selection of the area exposed to FUS. We used FUS exposure at the lower frequency to disrupt the BBB. FUS at the higher frequency of 7.8 MHz was employed to enable the effect of the acoustic radiation force. This force is caused by a transfer of momentum between the ultrasound wave and the propagation tissue, and can hopefully facilitate NP transport in the extracellular matrix. Experiments were performed on immunodeficient mice with melanoma brain metastases developed four weeks after intracardiac injection of patient-derived human melanoma cells [4]. A NP-MB platform, similar to that reported in our earlier study [5] and based on PIHCA NPs forming a shell around perfluorocarbon MBs, was used for FUS-mediated BBB opening. PIHCA NP-MBs were injected immediately before the FUS exposure. BBB opening was assessed using a gadolinium-based contrast agent. After the experiments, the brains were either frozen or fixed in formalin. NP transport across the BBB and distribution in the brain tissue were assessed in
cryosections using confocal microscopy, while histopathological changes and cellular changes caused by FUS were evaluated using formalin-fixed paraffin embedded tissue sections.

**Results and Conclusions**

Successful BBB opening was verified by MRI (Fig. 1a). An optimal window for FUS-mediated BBB disruption using our NP-MB platform was found to be around a mechanical index of 0.31. Analysis of cryosections showed that the combination of FUS with our NP-MB platform allowed transport of NPs across the BBB in an opening-dependent manner (Fig. 1b). Histological evaluation showed some extent of red blood cell extravasation following FUS exposure. The effect of the acoustic radiation force of NP distribution in the brain parenchyma away from blood vessels and the effect of FUS exposure on P-glycoprotein, an efflux transporter that is an integral part of the BBB, are currently being analyzed. Overall, our results indicate that our platform based on PIHCA NPs and MBs can be used to deliver substantial amount of NPs across the BBB, showing its potential in NP-aided drug delivery to the brain.

![Figure 1: FUS-mediated BBB disruption and transport of NPs across the BBB. a) BBB opening mediated by FUS in combination with the PIHCA-MB platform. b) transport of PIHCA NPs across the BBB following FUS exposure. Red – PIHCA NPs, Green – blood vessels](image)

**References**

Abstracts for Session V
Ultrasound

Abstracts are organized in the order of presentations
Clinical Applications of Elastography – My Experience

Professor Paul S. Sidhu, King’s College London, United Kingdom

Elastography is a measure of tissue stiffness using the properties of modulation of the ultrasound wave as it passes through tissue. The transition from laboratory to clinical application as taken place with a number of well-established uses in particular the detection of liver fibrosis and in the detection of focal malignancy in the thyroid gland. The proviso for the use of elastography is the assumption that harder tissue is malignant or fibrotic, and guides the clinical team to proper patient management. The two predominant techniques; shear wave elastography (SWE) and strain elastography (SE) have often complimentary roles with each particular method finding use in different clinical scenarios. Many different manufactures have developed commercial techniques, both SWE and SE, with a major limitation of lack of transferable data between the machines. No particular method is superior, but the application is dependent on the clinical need, with quantification important in liver fibrosis and a subjective colour map helpful in thyroid disease. Combinations of colour mapping and shear wave velocity measurements are now available.

My experience of elastography extends from the assessment of liver fibrosis in chronic liver disease, using SWE on different machines and using different techniques. The application of SE to the assessment of focal testicular lesions potentially differentiating benign from malignant abnormalities, and the management of thyroid disease using SE to guide fine needle aspiration or biopsy will be discussed.

Example of liver cirrhosis

Point SWE using ARFI
The lecture will focus on SWE in the management of chronic liver disease, establishing the METAVIR or ISHAK scores of fibrosis, with illustrations of different machine techniques. Applications in the thyroid and testis will be discussed.
Endoscopic strain imaging of the pancreas

Roald Flesland Havre, Institute of Medicine, University of Bergen and National Centre for Ultrasound in Gastroenterology, Department of Medicine, Haukeland University Hospital, Bergen, Norway

Imaging of tissue stiffness may detect and describe tissue pathology. Tissue stiffness tend to increase in neoplastic and inflammatory diseases due to changes in tissue architecture, increasing cellularity, fibrosis or interstitial fluid pressure. Currently, there are two main methods for imaging tissue stiffness or elasticicity with ultrasound; strain imaging which tracks the local tissue deformation by image correlation under repeated minimal stress and shear wave imaging which detects the shear wave speeds after deposition of an acoustic or mechanical push-pulse in the insonified tissue.

This abstract deals with strain imaging combined with an endoscopic ultrasound which allows close contact with the pancreatic tissue. Endoscopic ultrasonography (EUS) is considered to be one of the best imaging methods for examinations of focal lesions in the pancreas. It also provides detailed imaging of inflammatory changes and enables minimal invasive tissue sampling by EUS guided fine needle aspiration (FNA) or biopsy. EUS of the pancreas is often used as a supplement to CT or MRI findings and may also detect pathological lesions missed by the other imaging modalities.

The EUS examination

Echo-endoscopes have either integrated radial or curvilinear transducers. Linear transducers are now being used to a greater extent because they provide possibility of scanning the tissue as well as providing EUS guided fine needle aspiration tissue sampling.

Pancreatic EUS-elastography

This strain imaging technique detects small-scale deformations created by the heart or the aorta allowing strain imaging in the upper GI tract. Harder tissue is less deformed than soft tissue, hence strain detection can be used to assess tissue stiffness. There are several pit-falls in strain imaging, and the method is based on an assumption that all tissue in the field-of view has been subject to a similar amount of stress. Since the local amount of stress is unknown, only the resulting axial stress is imaged in the elastogram (fig. 1 and 2). In endoscopic strain imaging some of the challenges are to achieve an adequate strain signal from the tissue and to avoid strain artefacts created by fluid filled spaces and sliding surfaces such as the peritoneum, the luminal side of the bowel or the pleura.

Several studies on EUS-elastography of focal lesions in the pancreas have been published. Giovannini et al. reported very high sensitivity in a limited material with high incidence of malignant lesions in the pancreas. Janssen et al. compared elastography images in patients with focal lesions of unknown histology with patients with chronic pancreatitis and normal pancreas using a novel visual categorical scale. They concluded that EUS-elastography findings were overlapping between half of the chronic pancreatitis cases and the malignant tumours. Pancreas elastograms in healthy individuals also overlapped to some degree with chronic pancreatitis. Hirche et al. examined only cases with focal pancreatic lesions without pancreatitis. They found that lesions larger than 35 mm and deeply situated lesions were difficult to image with adequate elastogram quality, and they were only able to evaluate 56 % of the lesions by elastograms. They also concluded that the ability to differentiate between malignant and benign lesions was low reporting sensitivity, specificity and accuracy of 41%, 53% and 45 %, respectively. Saftoui et al. used Neural Network Analysis on EUS-elastography images. They reported more optimistic results when using colour hue histograms.
of lesions. Sensitivity, specificity, and accuracy for differentiation of benign and malignant masses were 91.4%, 87.9%, and 89.7%, respectively. In a follow-up multicentre study Giovannini et al. reported 121 cases of focal pancreatic lesions and found that EUS-elastography performed equal to or better than conventional B-mode EUS for differentiation of malignant and non-malignant lesions. Sensitivity: 92.3% vs. 92.3% and specificity: 80% vs. 68.9%.

We performed EUS-elastography in 48 focal pancreatic lesions and found sensitivity 67% and specificity 71% for detecting malignancy when using strain ratio cut-off 4.4 between benign and malignant. In a sub-group analysis we found two microcystic serous adenomas (benign) that were harder than the malignant lesions. Our results are otherwise in line with the findings of several other researchers and a meta-analysis from 2012 who found a pooled sensitivity of 95% and a pooled specificity of 69%.

EUS in pancreatitis

Unless small CBD stones are suspected, EUS is rarely performed in acute pancreatitis. EUS may cause a pressure to the pancreas, and may thus provoke the inflamed tissue. After an acute pancreatitis, EUS may demonstrate hypoechoic areas, pseudocyst formation, calcifications, pancreatic duct calibre variation, visible side ducts and various degrees of lobulation or hyperechoic strands. These findings overlap largely with findings in advanced chronic pancreatitis. The most reliable EUS findings indicating chronic pancreatitis are calcifications, pancreatic duct stones, pancreatic duct-diameter variations, lobulation of the parenchyma and stranding. These findings represent scarring and calcium deposits in the gland and may unusually be visible only after prolonged symptoms. Early changes are more discrete and may be difficult to discriminate from normal tissue variations.

Tissue elasticity is often increased transiently during the period of acute inflammation and focal inflammatory lesions have proved to be less stiff than malignant tumors in some studies.
Some groups have found increased tissue stiffness more generally distributed in chronic pancreatitis (CP) with strain ratio values corresponding to the B-mode criteria of CP and with the degree of pancreatic insufficiency\(^\text{12,13}\).

**Summary**

EUS elastography is a useful tool in addition to B-mode imaging for characterising solid focal lesions in the pancreas. Harder lesions may be false positives, but a lesion with a soft appearance or stiffness equivalent to surrounding tissue, is likely to be benign lesion. Tissue stiffness shows great variability in focal lesions of inflammatory origin, but generally the stiffness is lower than in malignant tumours. Pancreatic cysts may appear with a hard signal, but usually cysts have no strain signal or they have a typical “Red-Blue-Green” artefact. In chronic pancreatitis, tissue stiffness may be increased due to fibrosis and ongoing inflammation, the pattern may be difficult to separate from increased hardness due to malignant neoplasms.

**References**


Elastography of the Liver in Primary Sclerosing Cholangitis

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Introduction

Ultrasound elastography is a noninvasive technique measuring liver stiffness or elasticity as an expression of fibrosis. Encompassing a range of methods and platforms, it has emerged as a highly useful tool in the assessment of liver fibrosis at diagnosis and during follow-up; in particular the use of transient elastography (TE) in chronic Hepatitis B and C has been well established.(1, 2) However, the role of ultrasound elastography in other liver diseases such as primary sclerosing cholangitis (PSC) has not been established.

PSC is a chronic disease of the bile ducts of unknown etiology, resulting in liver fibrosis and cirrhosis over time and, in the absence of effective therapy, leading almost universally to liver transplantation or death through a highly variable disease course.(3) Liver fibrosis is an important player in PSC pathogenesis and a treatment target in several clinical therapeutic trials; hence, evaluation and monitoring of liver fibrosis is of high interest in PSC. Liver stiffness as measured by TE was reported to be associated with clinical outcome in a single, monocenter study and was highlighted as a candidate surrogate endpoint in clinical trials in PSC in a recent position paper.(4, 5) Using ultrasound, we have investigated point shear wave elastography of the livers in PSC patients.

Method

We recruited 55 patients from a cohort of non-transplanted PSC patients in Western Norway. Patients were examined and patient records were searched for information on clinical data, including ascites, encephalopathy, esophageal varices, variceal bleeding and inflammatory bowel disease status. At the day of ultrasound elastography, blood was sampled and biochemical analyses were performed using standard routine laboratory protocols. In the fasting condition, a full B-mode scan of the liver and spleen was performed, and the elasticities of both liver lobes and the spleen were assessed by point shear wave elastography (pSWE) using a conventional ultrasound system (ElastPQ, iU22, Philips Healthcare, Andover, MA, USA) and a convex probe (C5-1). A 0.5 x 1.5 mm region of interest (ROI) was placed 2-6 cm deeper than the liver capsule in hepatic tissue, avoiding large vessels or bile ducts (Fig. 1). The median value of ten acquisitions with a success rate ≥60 % was defined as a valid measurement. In a subset of patients, follow-up liver elastography assessments were available. All ultrasound scans and pSWE were performed by a single operator (MV).
Results

Shear wave velocities (SWV) indicating liver fibrosis (any stage) was identified in 21 patients (38%). A subset of patients showed signs of advanced liver disease: splenomegaly in 19 patients (35%) and ascites in two patients (4%). Successful pSWE measurements were achieved in the right liver lobe of all individuals and in the left liver lobe of 36 patients (65.5%). The median SWV was significantly increased in PSC compared to controls for the right liver (median [range] SWV 1.26 [0.73–2.57] vs. 1.09 [0.88–1.25] m/s; P<0.001), whereas no significant difference was found for SWV in the left liver lobe or spleen. Bile duct dilatation was identified in 26 (47.3%) patients, but median right liver SWV did not differ between patients with or without bile duct dilatation (1.32 [0.93-2.57] vs. 1.24 [0.73-2.43] m/s, P=0.61). Median SWV of the right liver lobe in PSC patients correlated with a serum based liver fibrosis panel (ELF test; Fig.2).

Conclusions

We have shown that point shear wave elastography can be performed in PSC patients in both liver lobes; however, feasibility is higher in the right liver lobe. PSC patients have increased SWV compared to healthy controls on a group levels, but with wide variability between patients possibly reflecting a range of fibrosis stages. Platform specific, PSC-specific cut-off values for stages of fibrosis would be of value in clinical practice. The putative role both as a prognostic tool, a stratifier in clinical trials and as a surrogate endpoint of point shear wave elastography as well as other elastography techniques including 2D-shear wave elastography, should be further explored.

References


Comparing secretin stimulated ultrasonography and MRI in cystic fibrosis patients and healthy controls

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Introduction: Cystic fibrosis (CF) is an autosomal inherited disease caused by a wide range of mutations in the cystic fibrosis transmembrane receptor (CFTR) gene on chromosome 7. Exocrine pancreatic failure has been reported to affect 73-90% of CF patients. The primary effect of the mutation is defect or lack of the widespread CFTR protein and reduced pancreatic secretion of bicarbonate and fluid. Secretin-stimulated magnetic resonance cholangiopancreatography (s-MRCP) is considered the radiological reference standard in the evaluation of pancreas secretions. We have previously used secretin stimulated ultrasonography to evaluate the same parameters. We aimed to compare the results of the two methods using endoscopic secretin test as a reference standard for ductal failure.

Methods: We included 21 CF patients and 11 healthy controls (HC). The patients were earlier characterized by faecal elastase (FE) and secretin stimulated endoscopic short test (EST) with duodenal bicarbonate concentration. Patients having FE<100µg/g and bicarbonate concentration <80 mmol/L were considered pancreatic insufficient. Transabdominal ultrasonography (US) estimating fluid filled area of the descending duodenum was performed before and 1, 5, 10 and 15 minutes after secretin stimulation (Figure 1).

![Figure 1: Transabdominal US of the descending duodenum (yellow) demonstrating increasing fluid filling after secretin stimulation in a pancreas sufficient subject.](image)

The MRI imaging protocol included standard pancreatic MRI and MRCP (1.5 T). T2-weighted imaging and DWI were acquired before and 1, 5, 9 and 13 minutes after secretin administration and secreted pancreatic juice volumes were calculated based on these sequential images (Figure 2). Secreted volumes for both methods were calculated as the difference between the timed calculated areas/volumes and the calculated areas/volumes of fluid in the intestine before secretin stimulation. Area under the time-secretion curve (AUC) was used as an estimate for the secretion in the whole period.
Figure 2: T2-weighted MRI images demonstrating intestinal fluid before (left) and 13 minutes after (right) secretin stimulation (Images G Wathle).

Figure 3: Time-secretion curves for US and MRI. Box plots demonstrating median value, IQ range and 95% CI at relevant time intervals.

**Results:** Based on the biochemical tests of the CF patients (n=21), ten cases were categorized as pancreatic insufficient (CFI) whereas eleven cases were pancreatic sufficient (CFS). Results of exocrine function testing and estimates of exocrine volume secretions by the two methods are presented in the table. The time-secretion curves are presented in figure 3.

| Exocrine pancreatic function and secretion estimates in CF patients and Healthy controls. | CFI | CFS | HC | p
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<tr>
<td>D HCO3 (mmol/L)</td>
<td>11 (0-20)</td>
<td>110 (62-124)</td>
<td>115 (108-126)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>F- Elastase (µg/g)</td>
<td>0 (0-3)</td>
<td>575 (506-626)</td>
<td>558 (471-664)</td>
<td>&lt;0.001*</td>
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<tr>
<td>Peak sekr. MRI (mL)</td>
<td>7.3 (4.0-17)</td>
<td>75 (56-101)</td>
<td>94 (60-108)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>AUC MRI</td>
<td>71 (36-173)</td>
<td>696 (409-859)</td>
<td>727 (452-940)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>AUC UL</td>
<td>7.5 (4.5-13.8)</td>
<td>51.4 (19.0-63.0)</td>
<td>57.6 (40.3-68.0)</td>
<td>&lt;0.001*</td>
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Table: Values in medians (Inter quartile range)*Difference CFI vs others
The diagnostic accuracy of the two methods was compared by receiver operator (ROC) curves (Figure 4). Secretin stimulated ultrasonography demonstrated a sensitivity of 0.90 and a specificity of 0.86 for exocrine failure whereas sMRI demonstrated perfect sensitivity and specificity of 1. Spearman-rank correlation coefficient between the AUC values from the two methods were 0.55 (p<0.001).

**Conclusion:** Both methods demonstrate good diagnostic accuracy for exocrine pancreatic function in CF patients. Maximum secreted pancreatic juice volumes were significantly lower in the pancreatic insufficient CF patients compared to the pancreatic sufficient CF patients and the healthy controls. The absolute correlation between parameters obtained by the methods was not optimal.
Proximal stomach function in patients with IBS compared to Functional Dyspepsia using Ultrasound

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Background
Functional gastrointestinal disorders (FGID) such as Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD) are common conditions worldwide, with prevalences of 10-30% (1, 2). Patients suffering from these disorders report impaired quality of life (3, 4). They are frequent visitors of outpatient clinics, undergo multiple diagnostic tests, have an extensive use of prescription drugs, and a higher rate of sick leave compared to healthy controls (4, 5). FGIDs have not been linked to organic or biochemical defects, but motility disturbances in the stomach are well-known mechanisms in functional dyspepsia. There is a considerable overlap between the FGIDs. Gastric motility and sensitivity has been thoroughly studied in functional dyspepsia, but the gastric function has not been fully investigated in IBS.

The Ultrasound Meal Accommodation Test (UMAT) is a clinical test used to assess gastric accommodation, gastric emptying and visceral sensitivity. The patient ingests a low-calorie soup (500 mL/4 min, 37 °C), also being a contrast agent for ultrasound, allowing measurements of the proximal and distal stomach. The measurements are repeated at 0, 10 and 20 minutes. The UMAT has been used in the clinic at Haukeland University Hospital the last 20 years as a tool for investigating dyspepsia, nausea and other upper GI-related symptoms. The aim of this study was to compare findings from the UMAT in patients with IBS and FD, thus gaining more knowledge about gastric physiology in IBS patients.

Material and methods
In the period 1999 – 2014, 509 patients were consecutively included in a retrospective study of a clinical material. In total were 160 patients (31%) diagnosed with FD, and 154 (30%) were diagnosed with IBS(6). Sixty-six patients had both IBS and FD, and for the statistical comparison of the groups, these patients were treated as a separate group. Analysis were done using the Mann-Whitney-U test in IBM© SPSS Statistics Version 23.
Table 1: Measurements of the proximal stomach in the Ultrasound Meal Accommodation Test at Haukeland University Hospital in Bergen, Norway, obtained in standardized sections using transabdominal ultrasound after intake of 500 mL of a low-calorie, liquid meal.

<table>
<thead>
<tr>
<th>Measurements of the proximal stomach</th>
<th>FD (n=94)</th>
<th>IBS (n=88)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean proximal frontal diameter 0 min (cm)</td>
<td>5.4</td>
<td>6.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean proximal sagittal area 0 min (cm³)</td>
<td>26.5</td>
<td>29.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean proximal frontal diameter 10 min (cm)</td>
<td>4.5</td>
<td>5.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean proximal sagittal area 10 min (cm³)</td>
<td>22.4</td>
<td>25.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results
As presented in Table 1 and Figure 2, patients with FD had significantly lower frontal diameter and sagittal area of the proximal stomach than patients with IBS, both immediate postcibally and 10 minutes postcibally (p<0.005) indicating impaired accommodation. There were no significant differences in the antral area or antral emptying fractions.

Figure 2: Ultrasonographic measurements of the proximal stomach in patients with Irritable Bowel Syndrome (IBS, n=77) and Functional Dyspepsia (FD, n=74), 10 minutes after ingestion of a low-calorie liquid meal in the Ultrasound Meal Accommodation Test. Data obtained in a retrospective clinical material during 1999-2014 at Haukeland University Hospital, Bergen, Norway.

Conclusion
In this study, patients with IBS had better gastric accommodation to a liquid meal compared to patients with FD, but gastric emptying was equal between the groups. This shows that even though there are many similarities between FD and IBS, there are still physiological differences in gastric function. Ultrasound is a helpful tool in the assessment of gastric accommodation to a meal.
References
Abstracts for Session VII
PET / MR

Abstracts are organized in the order of presentations
Abstract

Combined PET/MRI systems have entered the clinical arena almost a decade ago with first proof of mechanism settings with MRI compatible PET-detector systems being inserted into stand alone MRI systems. Phantom measurements showed the feasibility and performance of the two imaging modalities operating in parallel without detrimentally impairing the performance of the one or other, respectively. The clinical operability of PET being integrated with a MRI system has been first shown with brain PET investigations in these days. Fall 2010 the first integrated whole body PET/MRI systems entered the clinical arena. Since then, the technical, clinical and organizational methodology has been improved by the introduction of major improvements in detector PET detector technology, MR-based attenuation correction approaches becoming available. The installed base of sequential and integrated PET/MRI systems is continuously growing and the worldwide search for key applications in clinical and research settings is going on, first of those have been identified and more are under evaluation. As for larger clinical trials data need to be acquired in multicenter trials, imaging protocols and data analysis/quantification need to be comparable and standardized across centers finally.

This talk will give an overview of the available instrumentation, technology and imaging as well as quantification protocols. Moreover, first insights in the approach towards standardization Applications of PET/MRI imaging protocols and quantification will be given as well as the challenges and issues still to be resolved will be touched on.
Visualization of Variability in Radiotherapy Dose Planning

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Introduction

In radiotherapy, the goal is to deliver high radiation doses to treat tumorous tissues, while sparing the adjacent healthy tissues [1]. To ensure a successful radiotherapy treatment, a dose planning is required. However, at each step of the pipeline performed before planning, different assumptions and/or parameterizations can be made, which may result in several alternative dose plans. It is not known a priori which of these assumptions or parameter settings lead to better results. Still, it is valuable for clinical researchers to understand how the different assumptions and parameterizations can affect the final result. In that way, they are aware of the variability and can evaluate whether different choices in the planning pipeline have an impact on the final treatment planning. Currently, variability assessment is not incorporated in the analysis, due to time and resource constraints. In the present work, we propose a visual framework that enables clinical researchers, working in radiotherapy dose planning, to interactively explore and analyse the variability in an ensemble of possible dose plans. It allows to gain insight into the variability at two different levels: first, based on the isodoses (i.e., the radiotherapy dose iso-contours) across the dose plans, and, secondly, directly at a voxel level. As a proof of concept, we demonstrate the use of our framework with prostate tumor patient data.

Method

The proposed visual framework aims at employing an effective strategy to visualize variability across an ensemble of possible dose plans. To this end, we identified a set of relevant questions that are important for clinical researchers to understand variability in radiotherapy dose planning:

(Q1) How different are the dose plans in relation to a particular isodose?
(Q2) How does the variability between dose plans changes for different isodoses?
(Q3) Along the isodoses, are there any dose plans that significantly differ from the rest?
(Q4) Where are the (regions of) voxels with higher (dis)agreement between dose plans?
(Q5) Given a (region of) voxel(s), what is the distribution of doses among the dose plans?

The first three questions are related to the analysis of variability among the dose plans at one or more specific isodose levels. These questions are based on the fact that clinical researchers may be interested in investigating how the dose plans vary within one isodose level, or across the overall isodose distribution (Contour-based approach). The last two questions are related to the analysis of variability among the dose plans at precise spatial locations. Here, the goal is to provide localized information on the variability (Voxel-based approach). Each one of these questions is addressed by a component of our framework, as shown in Figure 1.
The **Contour-based approach**, which is presented in Figure 2, incorporates the following three components:

**Exploration and analysis of isodose variability (C1)**. At a contour-level, the goal is to be able to identify major trends and outliers in an ensemble of isodoses. We use an adaptation of the contour boxplot method [2]. Instead of using the original visualization, we use opacity to encode the band depth value. As a result, isodoses with high band depth are encoded into high opacity, while isodoses with low probability are encoded into low opacity. Identically, the same concept is applied to the bands: the 50 percent band, since it contains the 50 percent of deepest isodoses, is encoded into higher opacity, while the 100 percent band is encoded into lower opacity. Additionally, the median isodose is rendered thicker and with a different color, while the outliers are kept dashed (Figure 2a). At the same time, the method must be compatible in a situation where multiple isodoses are displayed simultaneously. In the present case, a maximum number of three simultaneous isodoses was considered. The decision was to use yellow, red, and blue. Alpha blending is used to show the overlap of different isodose bands [3].

**Comparison of variability along isodoses (C2)**. The goal of the second component is to provide an overview of the variability, so that the user can identify and compare, immediately, which isodoses have higher or lower variability. Also, it is possible to pick interesting doses and interactively explore them, using a bar chart visualization (Figure 2b). The horizontal axis represents the discrete isodose levels, while the vertical axis represents a probability that is indicative of the variability at every isodose. This component is linked with (C1).

**Outlier detection (C3)**. In this part, the goal is to compare the dose plans through their isodoses in a global way. In this way, it is possible to identify which dose plans differ significantly from the rest along the range of isodoses. Every isodose of the ensemble has an associated band depth value, which we encode through a heatmap with a gray scale colormap. Isodoses with high
probability are mapped to white, while isodoses with low probability are encoded to black (Figure 2c). When hovering the mouse on the heatmap, tooltips pop-up with detailed information on the underlying cell.

The **Voxel-based approach**, which is depicted in Figure 3, incorporates the following two components:

**Global dose and variability overview (C4).** At a voxel-level, the goal is to be able to identify voxels or regions with higher or lower variability. To show the dose magnitude, we calculate an average dose plan by computing the mean at every voxel. To show variability, we calculate the standard deviation at every voxel. For a general overview of these two facets of the data we employ a 2D color map (Figure 3a), but also a scatterplot (Figure 3b). Every point in the scatterplot represents a voxel from the data, and is represented by the mean (horizontal axis) and the standard deviation (vertical axis). To diminish clutter from point overplotting, datapoints in the scatterplot are rendered with higher opacity. Additionally, to help locating dense regions, a bi-variate kernel density plot overlaid on top of the scatterplot was used as an additional visualization method [4]. Still, the scatterplot only is not able to provide any kind of spatial information. To overcome this limitation, we employ brushing and linking [5] from the scatterplot to the anatomy of the patient (Figure 3c).

**Local exploration of dose distribution (C5).** Additional visualization methods were incorporated to dynamically explore the distributions at every voxel. Based on 2D slices, we enable the user to interactively probe the voxels and get a detailed notion of the underlying distribution of values (Figure 3d). The resulting visualization depicts a simultaneous combination between a kernel density estimation (KDE) [4] and a rugplot [6], where the KDE curve provides an indication where the value density is greater. We also enable a region of interest (ROI) selection: instead of considering a single voxel, a ROI can be selected, and the distributions are displayed for every voxel inside the region.
Conclusions

We introduced a visual framework for the interactive exploration and analysis of variability in radiotherapy dose planning. It allows to visually assess the variability across multiple possible dose plans, as a result of different assumptions, parameter settings and choices that can be taken during the planning pipeline. The core aspect of the framework is the ability of providing insight on the variability at two different levels: through the iso-contours across the dose plans, and directly at a voxel level. An initial, informal discussion with domain experts resulted in a positive feedback for the developed framework, who considered the integration of both perspectives an enrichment to the analysis process, and a more complete perception of the underlying variability. However, a thorough evaluation still needs to be performed in order to validate these observations.

References


Experiences with PET/MRI in Norway

Presentation at the 10th MedViz Conference, Sept 7-9, Bergen Norway

Live Eikenes, Department of Circulation and Medical Imaging, NTNU, Norway.

Abstract

From the initial idea of using MRI to improve the resolution of PET it took around 10 years to develop the first devices capable of simultaneously acquiring preclinical PET and MRI data, and another 15 years to develop the first integrated clinical PET/MRI scanner, which was approved for clinical use in 2011. There are now approximately 100 installed clinical hybrid PET/MRI scanners worldwide, and the only PET/MRI scanner in Norway was installed at St. Olav's Hospital October 2013. Hybrid PET/MRI systems can theoretically take advantage of the high contrast resolution and functional information yielded by MRI together with the metabolic PET activity to enable better assessment of tumor burden in patients with malignancy or other pathological conditions when compared with standalone PET or MRI. The benefits of combined PET/MRI over PET/CT includes improved soft-tissue contrast, reduced ionizing radiation, the possibility of MR-based motion correction, and the acquisition of truly simultaneous multiparametric images that yield functional, morphologic, and molecular information.

While there are many theoretical advantages and potential clinical applications for PET/MRI when compared with standalone MRI and PET and hybrid PET/CT, it is not yet clear what the key applications will be for this new scanner. PET/MRI technology is also burdened with technical and methodological issues that need to be improved in order to obtain optimal use in a daily clinical setting. Research evaluating the diagnostic potential of PET/MRI together with novel PET tracers within various pathological conditions and improving technical issues are warranted for this new technology. Since installation at St. Olav's Hospital in 2013 the research environment at NTNU and St. Olav's Hospital has initiated several technical studies for evaluating and improving image quality and acquisition, clinical projects within the fields of lung cancer, prostate cancer, lymphoma and glioma, and are in the planning phase of studies involving sarcoidosis and traumatic brain injury. The glioma, sarcoidosis and traumatic brain injury studies will be the first to evaluate two new PET tracers together with simultaneous MRI acquisition. The overall aim of all the projects is to improve diagnosing, staging and therapy assessment in the various pathological conditions with the use of PET/MRI.
Abstracts for Session VIII: Posters

Some* abstracts are listed under oral presentations in the respective sessions. Posters are organized in alphabetical order according to first author’s family name:

Sergey Alyaev
*Habib Baghiro
Alexander Craven
Michael J. Doyle
*Trond Engjo
*Erik Hanso
William Haugland
*Roald Flesland Havr
*Erlend Hodneland (2
Kergann Le Cornec
*Alexander Lundervol
Cecilie Brekke Rygh
*Pedro Silv
Veronika Šoltészová
*Elisabeth K. Steinsvi
*Eivind A. Valestrand
Kaoru Watanabe
*Sigmund Ytre-Haug
Elucidating empty nose syndrome with CFD

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Introduction

Empty nose syndrome (ENS) appears when the nasal aerodynamics deviates from normal due to an operative enlargement of air pathways in the region of internal and middle turbinates [1]. “Empty nose” patients are suffering from chronic endonasal crusting and dryness. However, the most distinctive symptom of ENS is “paradoxical obstruction”-suffering from obstructed nasal breathing despite of the widely patent nasal cavity [2]. ENS patients often describe their feeling of nasal obstruction as constant and continuous: feeling of suffocation, inability or significant difficulty to breathe through nose, inability to inflate the lungs properly, and other undifferentiated breathing difficulties [3-5]. ENS pathology is not entirely understood, as the expansion of nasal channels would theoretically ease the propagation of air and thus promote breathing. From another side, unnatural vorticity induced by the channel modification may alter nasal residence time. This could potentially outcome with sensitive changes in microclimate and sensation. A detailed insight into the nasal flow patterns would improve knowledge on the problem. However, such precise measurements are presently sophisticated in-vivo. We therefore employ computational fluid dynamics to study ENS in-silico.

Methodology

The present paper analyses aerodynamics of an “empty nose” for a patient with ENS symptoms, which appeared after a partial resection of right turbinate during cystectomy. In addition to the first operation, the patient, 31-year old female Caucasian, was subjected to implantation aimed in narrowing channels. The implantation did not however influence ENS and the volume of empty cavities remains 28.7% larger than before operations.

Two 3D models of pre-operative and post-operative nasal configurations were reconstructed in the open-source segmentation code ITK-Snap. As shown in Fig.1, the models include paranasal sinuses. The accuracy of segmentation was examined comparing frontal areas in 12 coronal cross-sections of models, also shown in Fig.1, with experimental data given in [6]. The results of
validation are presented in Fig. 2 for different distances from the nostrils (coronal distances). It follows from the figure, that the pre-operative case complies with the averaged configuration of nasal channels given in [6] for Caucasians. The post-operative geometry outcomes with an artificial expansion in the nasal valve and close to the nasopharynx. Further, a contraction is located in the center of the nose, where the implant is mounted.

The CFD-models of both configurations were built in the commercial tool STAR-CCM+. Following [6], they were discretized by 1.5M 0.6-mm polyhedral control volumes (Fig. 1) with 33% prismatic near-wall refinement. The boundary conditions for the pre-operative case included: pressure at nostrils, negative volumetric flow inlet at 166.7 ml/min [6] at nasopharynx and no-slip wall at the rest of the surface. The overall pressure drop induced on the nasal channels in pre-operative case, was set as the negative pressure at the nasopharynx of the post-operative model, while the rest of boundaries was equivalent to the previous case. The normal breathing conditions were reproduced for the post-operative case in this way. The set of laminar, incompressible Navier-Stokes equations was solved with the standard SIMPLE technique (central differencing) till the residuals fell down to -7th order. The initial conditions included uniform zero velocity and pressure fields (relative to reference of 1 bar).

Results

At first, the pre-operative case was validated with pressure drop data given in [6,7] for the interval 100-700 ml/min through the nose, demonstrating relative discrepancies below 10%. The pressure drop of 10 Pa was detected at 166.7 ml/min. This value was mounted at the outlet of the post-operative case, which resulted with 46% increase of the volume flow rate through the post-operative channels. The comparison of the flow patterns for both cases, given in Fig. 3, demonstrates sufficient difference of secondary flow signatures. The pre-operative case is characterized by preferably straight streamlines directed from nostrils towards nasopharynx with the average air residence time of 2.4 s, the most intensive flow acceleration takes place yet to the entrance to nasopharynx caused by bending of nasal channel. In the post-operative case, the velocity magnitude maximum starts in the vicinity of nasal valve and persists to the nasopharynx due to the implant. A flurry of parasite secondary currents, clearly seen in this
region, are increasing mean residence time by up to 20%. The sinuses are ventilated with a low-magnitude air jet.

The secondary flow in the post-operative case is responsible for the formation of multiple vortices in the center of the nose. This is illustrated in Fig.4 where the vorticity, averaged in frontal cross-sections, is shown as a function of coronal distance.

The vorticity is generally higher by magnitude in the post-operative situation as the volume flow rate is also increased there. However, the maximum persists longer in the post-operative case when flowing from nostrils towards nasopharynx.

Conclusions

The aerodynamic analysis of the “empty nose” was conducted computationally with the use of CFD-model validated by data from literature. The main flow parameters obtained for ENS were compared with “normal”, pre-operative case. The following conclusions are drawn as the outcome of our comparative analysis:
• ENS is characterized by the significant modification of the flow patterns in the regions where the operative treatment of nasal channels took place; The intensive swirl motion observed there could sufficiently alter nasal microclimate.

• ENS caused by the operational expansion of nasal channels does not bring additional aerodynamic resistance to the flow. Speculating on the reason of suffocation, it is possible to propose that it is either caused by neurological reasons (partial loss of sensoric stimulation) or an atrophy of the diaphragm since in-halation requires less mechanical energy. An influence of easier ex-halation can not be also disregarded.

It ought to be finally noted that a complete physical description of the “empty nose” requires analysis of nasal microclimate.

References


Towards Functional MR Spectroscopy: Time-Resolved Assessment of tDCS-Induced Changes in Local GABA Concentration in the Brain

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Introduction

The ability to perform quantitative analyses of biochemical compounds in-vivo with Magnetic Resonance Spectroscopy (MRS) has afforded new insights into biological mechanisms underlying both healthy and diseased states. Of particular interest is the ability to measure γ-aminobutyric acid (GABA), as dysfunction of GABA-ergic transmission has been implicated as a contributing factor in many psychological conditions including the experience of auditory verbal hallucinations (AVH) in people with schizophrenia [1]. The purpose of this project is to develop a method for performing MRS in a time-resolved or functional manner (i.e. fMRS) in order to measure dynamic changes in GABA in response to tasks or stimuli. To this end, transcranial direct current stimulation (tDCS), a neurostimulation technique that may be used to excite or inhibit neural activity within a given area, was used in a facilitating capacity to increase activity in the posterior superior temporal gyrus (pSTG). The pSTG is a key node in the auditory processing stream and has been implicated in the experience of auditory hallucinations in schizophrenia, amongst other conditions. Excitatory stimulation has been shown in previous studies [2] to lower local cortical GABA concentration in the area of excitation. To better understand the relation between GABA variations and the experience of auditory hallucinations, the operational mechanisms of tDCS, and the possibilities for the latter to be incorporated in management of the former, the ability to quantify metabolite variations with improved temporal resolution is crucial.

Typically in MRS, in order to overcome the inherently low signal-to-noise ratio (SNR) of a single acquisition, a high number of individual spectra are acquired over a long period and averaged together to produce a single time-averaged spectrum. While this approach may be useful for improving SNR, the long scan time it necessitates limits usefulness for time-resolved or functional MRS designs.

Specialised spectroscopy sequences, such as the GABA-specific MEGA-PRESS spectral editing technique, exacerbate these problems; the technique requires the acquisition of two spectra from which a difference spectrum is calculated, effectively doubling scan time and halving temporal resolution. Furthermore, editing techniques are susceptible to issues of co-editing, and variations in editing efficiency due to frequency drift throughout the scan.

Here, we present a novel analysis approach for use with GABA-specific MEGA-PRESS spectroscopy data that adaptively combines data from multiple time windows to quantify
temporal dynamics; additionally, an algorithm will be proposed for blind group-wise analysis of such data.

**Method**

Data were collected from 20 healthy, right-handed subjects (10 female; age 18-35). Each subject underwent two MR sessions, an hour apart, incorporating either real or sham stimulus in randomised order (double blind). Spectroscopy data were collected using the MEGA-PRESS sequence, a spectral editing technique which allows meaningful assessment of GABA levels in-vivo [3]. In each session, one long MEGA-PRESS acquisition was performed (~31 minutes; TE=68ms, TR=1500ms, 616 edit on/off pairs), localised to the posterior superior temporal gyrus (pSTG); see Figure 1a.

tDCS was applied at 2mA with the anode over the pSTG and cathode over the orbitofrontal cortex (Figure 1b), for 10 minutes during spectroscopy acquisition, with 10 minutes of acquisition pre- and post-stimulation and 24 second ramp time (Figure 1c).

Data were analysed with an adaptive, multi-resolution windowing technique as illustrated in Figure 2a,b. Contiguous blocks of different lengths and offsets were averaged before quantification in LCModel. An aggregate of overlapping estimates, weighted according to window length and fit quality, determines the final estimate for each time point.

A blind, maximum-likelihood algorithm is used to classify each time course as “real” or “sham” stimulation. As a starting estimate, sham response is modeled as a flat line; no assumption is made as to the shape of the real stimulus response (Figure 2c). Acquisitions from each participant are classified as stimulus or sham according to distance from the sham model; the outcome of this initial classification is used to develop a new model for the stimulus response, which is used to iteratively refine the classification until steady state is reached (Figure 2d).
Data Quality

No spectral artifacts could be observed during steady-state tDCS stimulation; mild artifacts were seen during the ramp period. Although well out of the measured metabolite range and unlikely to influence estimates, these frames were omitted from analysis. Spectral line width (assessed from residual water signal) showed no observable change during stimulus.

Data were collected without macromolecule suppression, due to these techniques' increased susceptibility to frequency instability. Drift in the present dataset was however relatively mild: absolute linear drift ~3Hz (0.02ppm), with an SD across time of ~1.15Hz.

Individual time points identified as strong outliers, or having poor quality (as assessed by SD and SNR of constituent spectra) were omitted from the time course estimate; furthermore, acquisitions demonstrating abnormally high variation in metabolite estimate or frequency drift were automatically rejected (n=3, all female).

Results

A multi-factor ANOVA shows significant condition by time interaction, suggesting that the tDCS induced a measurable change. Analysis (see Figure 3) indicates a 9.7% decrease in measured GABA during stimulation (p_{adj}=0.0005, Tukey HSD adjusted), with partial recovery post-stimulus leaving a 5.5% (p_{adj}=0.06) reduction relative to baseline. Slight variations (0.5% pre vs post) in the sham data are non significant.

The direction and magnitude of the observed change (decrease in cortical GABA post-stimulus) are consistent with existing literature [2]. Therefore, we conclude that our method demonstrates good potential for capture and quantification of tDCS-induced GABA fluctuations. Despite the problems fMRS of GABA presents, it has great potential to elucidate biochemical events underlying changes observed both in normal processes and mechanisms of disease.

References


Fast Hardware-Accelerated Construction of Spatial Index Structures for Visualization of Time-Varying Medical Data

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Introduction

Direct Volume Rendering (DVR) [1] has been firmly established as an accurate and high-quality visualization method for volumetric datasets in medicine, such as those obtained in CT and MRI scanners. Direct volume rendering utilises what can be termed a ray-based approach to rendering, where geometric rays are cast from each pixel in the viewport into the volume data. The volume data is sampled and interpolated at intervals along the rays and the interpolated data is mapped to colour and opacity (often RGBA) data via a transfer function. By combining the colour and opacity values sampled along each ray, the colour value for each pixel in the image can be determined.

However, the visual quality that DVR can deliver is achieved at a significant cost. A high-resolution image can have well over a million pixels, and many volume datasets consist of tens of millions of voxels, requiring a high number of sampling and interpolation operations. Given the demanding nature of DVR, many optimizations have been proposed. Among the most widely employed, are the empty space skipping methods [2]. The basis of empty space skipping methods is that many combinations of datasets and transfer functions lead to substantial regions of the volume dataset which do not contribute to the rendered image, even if they are sampled by the rays. These regions are thus "invisible", and processing of these regions may be skipped. This can afford a significant acceleration, as less computation is needed to obtain the same end result.

In order to exploit such empty space in volume data, it is necessary to process the data and construct some data structure to "mark" these regions. Such a data structure should be readily searchable during visualization so that the renderer can quickly know which regions of the dataset it may skip. One way to achieve this is with the use of spatial index structures, such as octrees and kd-trees. Spatial index structures provide a searchable map of visible regions of the dataset which can be consulted during rendering to accelerate visualization.

The utility of spatial structures is not limited to volume rendering. In fact, they are ubiquitous in many fields of computing, such as computer graphics, image processing and computer vision. Although these structures can provide a high degree of acceleration to many algorithms, they are non-trivial and sometimes expensive to construct. For this reason, providing dedicated hardware support for these structures (typically in GPUs) is an emerging field of research.

In this work, we are examining the application of existing spatial index construction hardware accelerators, originally designed for polygonal data, to direct volume rendering. We have produced a custom DVR pipeline that employs hardware construction of a structure known as a BVH, to provide empty space skipping techniques to a CPU DVR pipeline.
Method

Doyle et al [3] were the first to propose a specialised hardware design for building spatial index structures. Specifically, this hardware design produces a structure known as the bounding volume hierarchy (BVH). The accelerator is designed for ray-tracing of polygonal geometry. However, in our current work, we are investigating how to adapt this accelerator for use in direct volume rendering of time-varying datasets. By employing the same accelerator for multiple forms of rendering (polygonal and volumetric), we can increase the utilisation of the unit, leading to an overall more efficient hardware platform.

Figure 1 shows our custom DVR pipeline. The middle stage is performed by the custom hardware accelerator. The BVH accelerator is designed to operate on polygonal geometry represented as an array of axis-aligned bounding boxes (AABBs). Therefore, to leverage the accelerator for DVR, we must devise a volume pre-process to represent visible regions of the dataset in this manner.

We first break the volume into a smaller number of cubes, with each cube containing several (8 - 64) voxels. To accommodate interpolation, each cube overlaps the next by one voxel. By computing the range of data in each cube, and by consulting the transfer function, we can determine if any visible samples could possibly reside in the cube. We keep the cubes that contain visible data, and discard the rest. We then compute the spatial extent of each of these cubes, and represent each of them as an AABB. We then feed these AABBs into the BVH construction unit in the middle stage of the pipeline. Once the BVH is built, instead of sampling the volume along the whole length of the ray, we can search the BVH for subsets of the ray's length that contribute to the final pixel colour. We thus implicitly skip non-visible regions, saving computation. To perform time-varying visualization, we can simply execute the pipeline for subsequent frames. This property allows our pipeline to support real-time data acquisition and visualization.

Although BVHs have been employed for DVR in the past [4], these methods are designed for only static datasets, they do not discard empty regions in the manner we do, and do not seek to employ hardware accelerators.

To test the efficacy of utilising the BVH accelerator for DVR, we tested our DVR system on two commonly available medical datasets, shown in Figures 2 and 3. Both datasets consist of $256^3$ voxels. The first dataset is that of an aneurysm, and the second is a skull dataset. We employed ramp-like transfer functions to the data to provide a clear view of the main structure of these datasets. To construct the BVH, we used an exact functional simulator of the BVH accelerator from our previous work [3]. We use the output of this simulator to drive our custom BVH-based CPU DVR pipeline. Rendering was performed on an Intel Xeon CPU E5-1620 v3 @ 3.50GHz with 16GB of RAM, with a resolution of 1024 x 1024 pixels.
Based on our previous experiments [3], we can expect an acceleration of at least 5 - 10X in constructing the BVH with the hardware accelerator. To test the benefit of the BVH for the actual rendering, we executed our software BVH-based DVR pipeline utilising the output of the BVH construction simulator. The aneurysm dataset exhibits a high degree of sparsity, and we see a large increase in rendering speed from 0.2 FPS to 1.8 FPS. While not quite as effective for the skull, we still see an increase from 0.32 FPS to 0.87 FPS. Furthermore, we expect these results can be improved by employing more advanced BVH traversal techniques. Beyond these two examples, many other datasets can take advantage of empty space. Many other parts of the skeleton (e.g. the bones of the ribcage) are highly suitable cases. Generally, the technique is effective with anatomy exhibiting any cavity or regions of homogeneous data. Of course, there are combinations of datasets and transfer functions for which different types of optimizations have a much larger impact due to a lack of sparsity in the dataset. We are also actively pursuing these as part of our DVR pipeline.

**Conclusions**

In our current work, we are examining the potential role of BVH hardware accelerators in empty-space skipping for direct volume rendering. Our initial results show that this approach has the potential to significantly reduce rendering time for many datasets exhibiting sparsity. We propose that by transforming the volume data in a manner suitable for use with existing accelerators designed for polygonal data, we can increase the utilisation of this unit in a processor by using it for multiple forms of rendering. This approach would also naturally support rendering of polygonal iso-surface geometry and mixed polygonal-volumetric scenes. Furthermore, our design is specifically designed to support time-varying visualization, and can support efficient visualization of datasets which are acquired in real-time.

There are many interesting areas for future work. We would like to investigate how the BVH structure can be efficiently updated over multiple frames in a time-varying dataset. We are also interested in exploring new methods for encoding the visible regions of the volume dataset and resulting BVH, for example, by using integer encoding to improve storage overhead, memory bandwidth and power consumption. Finally, we believe that other aspects of DVR, such as interpolation, are good candidates for hardware accelerators in future work.

**References**


Real time Image based stabilization for Dynamic Contrast-Enhanced Ultrasound

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Abstract

The quality of dynamic contrast-enhanced ultrasound (DCE-US) is often affected by movement artefacts. To improve the quality of datasets during the acquisition we propose a real-time image based tracking method capable of tracking a user defined target in DCE-US. The purpose of our algorithm and method is to allow the clinician to select a region of interest in the scan plane and evaluate the reliability of the tracking before contrast injection, changing the workflow and improving the quality of data collection. After the scan the tracking data can be used to stack the image data and streamline the computation of perfusion parameters.

Introduction

Ultrasound (US) imaging is one of the most commonly available medical imaging techniques [1]. This is due to negligible short and long term side effects, reasonable price, portability and general flexibility in clinical situations. In recent decades, significant research has been conducted in the field of US contrast agents (UCA) and associated acquisition protocols [2] and [3]. However this modality is not without its limitations since differences in settings of the ultrasound scanner, patient characteristics, injection technique, ultrasound contrast behavior, region selection and tissue motion are all factors that could potentially introduce variability [4].

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Motion artefacts and speckle noise make meaningful post processing of DCE-US scans very difficult and target tracking challenging. Currently this movement can be removed by speckle decorrelation analysis, using frame reduction for a specific point, splines, or manually [6][7][8]. The above methods have several complications; only adjusting for in-plane motion, requiring idealized cases or use in conjunction with large data banks [1]. A new non-specialized class or organ detection is required to compensate for motion [1].

Methods

DCE-US scans of disease affected bowel in patients with Crohn’s disease were used in this analysis. The scans were acquired using a linear ultrasound probe (9L, 6-9 MHz) and Logiq®E9 ultrasound scanner (GE Healthcare, Milwaukee, WI, U.S.A.). 90 second videos were recorded in general contrast mode after a bolus injection of 4.4 ml of SonoVue® (Bracco, Milan, Italy) had been administered. During the acquisition a bolus and burst regime was used to allow the calculation of absolute perfusion [9]. The dual view images were then loaded into Matlab® for analysis. The initial test was performed on a 2.8 GHz Intel core i7 MacBook pro with 16GB 1600MHz DDR3 memory (Apple, Cupertino, CA, U.S.A.).

Our proposed algorithm runs within the Matlab® environment and begins by converting the RGB images to grayscale images. This is done to reduce the number of image comparisons needed to find the most likely target. Next we create two series of images one containing the Normal Gray Scale Images (NG) and the other the logarithm of the NG image intensities (L). Our final step in pre-processing is to normalize both sets of image intensities to values between [0 1], in order remove any unintentional bias.

The algorithm asks the user to define a target (t) within the first NG B-mode image in the series, see Fig 2. In this application, the target is typically a Region of Interest (ROI), which will be used later for extraction of quantitative measurements. An initial scan of 20 consecutive frames is performed. To allow the user to evaluate the reliability of the target they have selected. If this initial target is unreliable, the user is prompted to select another target until the preliminary tracking results are satisfactory. This process is shown in Fig 3.
A bounding box can be defined by the user in the event that the tissue surrounding the target is very similar to the target being tracked. Starting from the location of the present position for the target, the algorithm scans patches in a uniform grid within a 5 pixel border from the current location of the target to find the most similar region (Winner, w). The winner’s centroid is required to be within the bounding box. If no winner is identified or the similarity is not high enough the algorithm expands the scope to a wider grid (11 pixel borders).

The similarity (S) between each patch and the target is calculated using the Dot Product (·). This comparison is shown in the equations to the right, where S can return a maximum value of 1 and minimum value of 0. This is repeated until all the patches (i) within all the frames (N) have been compared to the target. We expanded our algorithm to compare the patches not only to the user defined target but also to compare the patches to the last winner to account for organ deformations throughout the scan. Two biases were included in the comparison, one for the Normal vs. Logarithmic images, and one for the last winner comparison. The first bias is controlled by the user, but the second is automatically adjusted by the algorithm in order to maintain the highest winner similarity values.

The centroid locations from all of the winning patches are then used to globally shift the ultrasound frames in order to stabilize the target and hence the ROI within them. This stack of stable images is then exported to post-processing where the tissue’s perfusion characteristics are evaluated. If a reliable target is not found, however the contrast investigation is not performed.
Conclusions

Initial trials of our algorithm on pre-recorded DCE-US videos have shown that it is capable of tracking a given region of interest in a series of images. The tracking results shown in Fig. 4 show a high statistical similarity between the target and the winner in each frame. The centroid locations corresponding to the winning patch from each frame are shown in Fig. 5. The time required to scan the image frames is dependent on the number of images and the distance the target moves from frame to frame. Using the aforementioned computer our algorithm required 0.3 seconds (s) to scan one frame, 5-6 s to track the target in 20 subsequent frames during the initial target tracking evaluations. Loading the data and completing a full scan of 1145 images took on average 98 s. Repeating the scan once the data had been loaded, took between 30 to 50 s. This is significant improvement over current methods, especially manual stabilization.

We are currently working to compare the results to an established manual method quantitatively [1]. Initially we proposed testing the algorithm on DCE-US scans that have already been acquired in order to facilitate development, and are currently working to find a way to acquire the images in real time from the US machine directly, allowing us to fully implement our algorithm.
References


Automated microbubble detection for treatment of cancer

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Introduction

Microbubbles are commonly used in clinic as an ultrasound contrast agent\textsuperscript{1,2}. These microbubbles allow clinicians to visualize organ perfusion and determine the type and location of malignant tissue\textsuperscript{1,3}. Latest research has shown that such microbubbles can also be used to improve the delivery of therapeutic agents from \textit{in vitro}\textsuperscript{4–6} to \textit{in vivo}\textsuperscript{7–10} and even clinical trials\textsuperscript{11}.

Whilst in their current state, clinically used microbubbles are considered sub-optimal for therapeutic uses. Specifically, clinically employed microbubbles have a broad size distribution\textsuperscript{12–14}, variable physical properties\textsuperscript{15–17}, and do not allow drug loading. Consequently, numerous researchers have been working on developing novel microbubble formulations to solve these limitations. When producing such microbubbles, it is important to be able to correlate the novel formulations used to the physiochemical properties. Specifically, the particle size distribution and concentration are of great importance. Current tools available on the market are expensive, inaccurate, time-consuming, or complicated to use. Hence, there is a need for an easy-to-use technique that allows for quick, reliable, reproducible and low cost quantification of microbubble size distribution and concentration.

In our work here we demonstrate a fully automated technique that can be used to characterize and quantify microbubble size distribution and concentration requiring only a calibrated digital image of the microbubbles, and no \textit{a priori} knowledge other than the depth of the chamber containing the microbubbles, as well as the pixel size.

Methods

In general, the technique used to detect bubbles was a Hough transform sensitive to circular shapes in the image. A typical input image is shown in Figure 1, left panel. The Hough transform was applied to multiple intervals of bubble radii, resulting in a large set of detected circles, including false positive bubble candidates. Let us define the absolute gradient image $|\nabla f|$, used in the following.
Figure 1: Example of automated bubble detection. Left: Raw input image. Right: Detected bubbles by the algorithm outlined with blue circles.

For the removal of false positive bubble candidates we implemented the following ordered selection steps:

1. Among each set of bubbles $S$ with similar centers we selected the bubble with the largest boundary value on $|\nabla f|$. The remaining bubbles in $S$ were excluded from further analysis. Bubbles with similar centers were defined as the set of bubbles with centers less than 4mm apart. This step guaranteed the absence of multiple representations of the same bubble.

2. Sorting the bubbles from large to small, and starting with the larger bubbles, we excluded bubbles that were covered by larger bubbles with more than 40% of their area. This step limited the allowed overlap of bubbles.

3. The sorting step in (2) favours larger bubbles and therefore introduced minor location errors. To account for these location errors we applied a subsequent erosion step to each detected bubble, stopping the erosion when the boundary of the detected bubble had a local maximum on $|\nabla f|$. This local maximum corresponded to alignment of the detected bubble with the true bubble boundary.

An example of detected bubbles is shown in Figure 1, right panel. After detection, the bubbles were subject to statistical analysis.

Results

Results of microbubble detection in two data sets are shown in Figure 2 and Figure 3. The plots show count and volume frequency, cumulative frequency, mean, median, mode, $d_{90}/d_{10}$, PDI, bubble concentration, as well as skewness of the distribution. Data set 1 contained five pictures, and data set 2 contained six pictures.

Discussion and conclusions

The developed algorithm was able to detect bubbles in the two data sets fully automatically with no human intervention except from initial parameter settings. We found on average a larger bubble diameter in data set 2 then in data set 1. The findings are in agreement with initial expectations and suggest that we have an efficient and robust tool for automated detection of bubbles in future acquisitions. The results produced by the code will be important for tuning of the microbubble excitation parameters in upcoming experiments investigating efficacy of microbubble treatment of cancer, with a large potential for improved patient health care.
Previously, manual processing and quantification of the digital images took 2-3 hours per sample (e.g. 5 images) using image-based techniques. The currently described algorithm reduces the processing time to 1-2 min, i.e., the image capture time only. Taking into account the highly sensitive temporal stability of microbubbles, the time saved allows for more time using and testing the microbubbles, and validating size and concentration measurements. Other methods, (op. cit. introduction) that can produce such quantitative results require 20-60 min of preparation time and significant post processing, in addition they are burdened with high consumable and running costs. Here, there are no additional consumables, as the measuring chamber (glass microscope slide) is reusable, and microscopes with digital cameras are considered standard lab equipment. As a result, the described algorithm reduces cost, quantification variability, and saves times compared to other methods, thus significantly improving the post processing steps leading to the scientific results.
References

Python-based software for medical imaging and machine learning
- an example from brain imaging in IBS

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Background and aims

During the last years, there has been a great momentum in using free and open-source programming languages and environments in the analysis of medical images and scientific data. Driving forces in this is mainly the R Project for Statistical Computing (www.r-project.org) and the scientific Python (www.python.org, e.g. [1]) communities.

This work is part of a student ERASMUS\textsuperscript{+} project conducted at UoB / ISIMA during the Spring semester 2016 [2]. Here we present Python scripting and Python libraries being used as tools for analyzing brain MR imaging data from patients with irritable bowel syndrome (IBS) in order to assess the brain-gut axis and “brain signatures” in this functional gastrointestinal disorder. In our study we are addressing both structural T1-weighted 3D MRI brain imaging (sMRI), diffusion imaging (dMRI), and resting state BOLD fMRI (rs-fMRI) recorded at the same imaging session; see [3] for a recent review on neuroimaging in IBS, and [4] for closely related work on classifying IBS from cortical thickness patterns.

In the following we present some illustrative cases and processing stages (filtering, image registration, fiber tracking, and functional connectivity) showing how Python-based tools can be used in the processing pipeline from image acquisition to probabilistic prediction and decision - using actively developed and rapidly expanding open-source libraries for neuroimaging and machine learning. A major goal is to establish a Python-based code repository - within the framework of open science and reproducible research - that can be used to explore the possibility of distinguishing between IBS brains and healthy brains based on structural and functional “brain signatures” in IBS.

Pre-processing and filtering of 4D fMRI data

An important step in analyzing fMRI data in time and space is neuro-signal restoration using denoising and filtering. The fMRI-recordings are typically influenced by multiple sources of noise, such as thermal noise, scanner instability, head motion, cardiac and respiratory pulsations, and spin history. Moreover, the spectral band representing neuronal activity in the recorded BOLD-signal is considered to be located in the interval [0.02, 0.15] Hz. For such filtering and signal-to-noise calculation we have been using the core numerical algorithms implemented in the Python library Nitime [5,6], both in time and spectral domains. Figure 1 illustrates the effect of such filtering on a single voxel time course within the 4D fMRI recording from one of the subjects in the IBS study. The grey curve is the time series without any filtering. Two different filtering methods (FIR and IIR) were employed, and they might influence the calculation of functional connectivity (cf. Fig. 4) differently.

\textbf{Figure 1.} Filtering of recorded voxel time course in resting state fMRI using Nitime [5]. Grey = original recording, Red = FIR filtered, Green = IIR filtered. X-axis is frame number (TR=2 s); Y-axis is signal intensity (A.U.).
Coregistration of the structural and functional MRI data

An important part of the neuroimage analysis is to enable the filtered functional recordings to be associated and informed by their anatomical localization. This involves spatial alignment or coregistration of the (segmented) structural MRI recordings and the functional MRI recordings. Image registration is generally characterized by the class of admissible spatial transformations (e.g. rigid, affine, elastic), the similarity function measuring the goodness of spatial overlap (e.g. cross-correlation, mutual information), the type of interpolation being used (e.g. nearest neighbor, linear, spline), and in case of iterative methods, the optimization scheme for driving the registration towards a solution. A tool for assessing the goodness of registration is also important. Figure 2 illustrates such a tool using a Python interface to visually assess the alignment of structural and functional MRI recordings after automated registration. Widgets are used to restrict the inspection to a given anatomical region.

White matter tractography from diffusion MRI

To explore whether the IBS brain is subject to microstructural changes affecting the white matter pathways and structural connectivity of the brain, diffusion MRI recordings are used. With this measurement technique the MRI signal is sensitive to water diffusion along different encoded directions, probing the microstructure and degree of diffusion anisotropy in the brain voxels, enabling tractography of the white matter fiber pathways. This is typically based on constructing a tensor model (cf. “diffusion tensor imaging”) and associated streamlines on a 3D vector field joining the principal water diffusion directions, being obtained by eigen-decomposition of the vector-valued dMRI data at each location (voxel) in the brain. For these rather involved tractography calculations we mainly use the Python library Dipy [7], which contains a broad range of algorithms for denoising, registration, reconstruction, tracking, clustering, visualization, and statistical analysis of dMRI data. Figure 3 illustrates brain tractography from one of the subjects in the IBS study.

Figure 2. Python-based interface to assess the result of structural and functional coregistration.

A slider can be used to select sagittal slice position, and a drop-down menu to select tissue type or anatomical region according to image segmentation of the structural MRI recording.

Figure 3. White matter fiber tractography using Dipy [7]. Colorcoding according to fiber direction. Red = left-right; Green: anterior-posterior; Blue: superior-inferior.
Functional connectivity from denoised fMRI data and segmented sMRI

The functional connectivity between brain regions (or voxels) A and B is characterized by the statistical relationship (e.g., Pearson’s correlation) between the fMRI time courses anchored at A and B. High degree of time course similarity indicates high probability of functional communication. If A and B are multi-voxel regions, the time courses are typically taken as the mean time course of all voxel time courses within the region. For n labelled anatomical regions we obtain an \( n \times n \) correlation matrix \( X \) using Pearson’s correlation between pairs of time courses. \( X \) is also called the functional connectivity matrix, or the adjacency matrix when putting the anatomical regions and connections into the framework of nodes and edges in a graph theory, such that the symmetric matrix \( X \) corresponds to a weighted, undirected graph. For a given subject in the IBS study we have performed automated segmentation and anatomical labeling of the sMRI recording using Freesurfer (http://freesurfer.net) and selected the mean of the denoised fMRI voxel time courses (cf. Fig. 1) within each of the \( n = 34 \) labelled regions. Then, Pearson’s correlation was calculated between all pairs of regions. For visualization of this matrix we have used the Seaborn [8] Python library, providing a high-level interface for drawing attractive statistical graphics. Figure 4 illustrates the functional connectivity matrix from a subject, showing the labelled regions (i.e. nodes) being segmented and the pair-wise correlations \( \rho \in [-1, 1] \) (i.e. weights).

Figure 4. Functional connectivity matrix in one subject from the IBS study. See text for details.
Machine Learning predicting the IBS brain from healthy volunteer brain

To explore the possibility of performing neuroimaging-based predicting of IBS versus healthy controls (HC) using brain connectivity as input data, we employed machine learning methodologies from the scikit-learn [9] and the Keras [10] Python libraries. Based on previous processing, we had access to brain structural and functional connectivity measures from 15 IBS patients and 14 HCs. From these connectivity analyses each subject was represented by a real-valued feature vector in 51-dimensional feature space. Repeatedly, we randomly split the sample into 25 subjects used for training the machine learning classifiers and 4 subjects used for testing, i.e. evaluating the performance of the classifier. Using random forest ensemble learning implemented in scikit-learn and a simple feed-forward multilayer (51-9-1) neural network classifier implemented in Keras, and our cross-validation scheme, we obtained an average classification accuracy of ≈65% (which is moderately better than chance). We also assessed the ranking of feature importance for the classifiers.

Conclusion and perspectives

The main goal of this project was to establish a Python-based pipeline to explore possible “brain signatures” in IBS using multimodal MR image acquisitions and advanced data analysis. We are in the process of making these tools and scripts more easily available to students (in the context of e-learning modules, using Jupyter Notebooks [http://jupyter.org]) and researchers, facilitating further research in quantitative neuroimaging of the brain-gut axis in IBS. These open-source, powerful and scalable tools will also be important when analyzing larger collections of patients and when incorporating other sources of information such as microbiota profiling, symptom scores, and abdominal imaging. For the “brain signature” classification approach, exploration of the most important discriminative features might aid mechanistic hypothesis generation and facilitate characterization of imaging-based biomarkers in IBS.

Acknowledgements

This study is part of the “Brain-Gut” project, established by a multidisciplinary research collaboration between the Department of Clinical Medicine, University of Bergen, the Neuroinformatics and Image Analysis Laboratory, Department of Biomedicine, and the Department of Radiology, Haukeland University Hospital. We thank Eivind Valestrand, Kiniena Tekie and Trygve Hausken for recruiting patients and healthy volunteers for the MRI scanning and for useful discussions. We also acknowledge support from MedViz and the “Computational medicine” initiative [http://computationalmedicine.no].

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Healthy body, healthy mind: Multi-parametric evaluation of muscle function, performance and cognitive function – can images and biomarkers tell us what we need to know?

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Introduction and background

Physical activity has shown to be important in the prevention of various diseases, and to maintain cognitive function. A good and adequate muscle function enables us to participate in daily life activities and to maintain an active lifestyle. Respiratory and muscular fitness promotes physical development, childhood learning and cognitive function in the elderly [1,2], as well as contributing to successful ageing and increased life expectancy [3]. In 2014, the Norwegian Directorate of Health changed their recommendations regarding physical activity to also include muscle strengthening activities in addition to metabolic conditioning.

But there are gaps in the knowledge of the underlying mechanisms of the effect of muscle strengthening activity, and the project aims to study this. What is the effect of exercise measured by objective parameters? Can we characterize muscle tissue composition and muscle phenotype, and measure the effect of different types of exercise? Furthermore, may this give us an indication of which types of exercise that are appropriate for different population groups? We will also measure the effect of exercise on the brain, both in cognitive function and change of metabolites.

Methods and material

We will implement a multi-parametric imaging approach and subsequent image data analysis where we combine the results from magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), ultrasound, and blood samples (different blood markers and miRNA) and compare this with the tissue biopsy samples and physical performance. We aim to establish measurable and sensitive biomarkers, and to explain the effect of muscle strengthening exercise based on these biomarkers. Muscles in the thigh are important for walking, climbing stairs and sitting/rising, as well as an important muscle group for athletes, and will therefore be the focus area of this project.

There are three subprojects. In the two first projects, we aim to discover the optimal exercise program to increase muscle function and strength in 1) young women (20-25 years of age) and 2) postmenopausal women (60-70 years of age). Women who do little or no physical activity will be included. The healthy volunteers will be given a thorough introduction on how to perform the different exercises before starting. The healthy volunteers will be randomly divided into two groups. Both groups will conduct two weekly workouts with muscle strengthening exercises over a period of eight weeks. The subjects in the first intervention group will do between 3-5 repetitions, while subjects in the other intervention group will do
8-12 repetitions, but both groups do the same set of exercises. Figure 1 demonstrates an example of a muscle strengthening activity.

Figure 1: Demonstration of a muscle strengthening exercise

MRI, MRS, ultrasound, micro-biopsy, blood samples and performance tests will be performed at the start and end of the intervention:

1) T1 and T2 weighted images to obtain morphological information. In addition, the T1 and T2 relaxation times provide information on muscle characteristics,

2) MRS to measure metabolites such as lactate, choline, carnosine, GSH (glutathione), and creatine that provide information on various physiological and metabolic characteristics of the muscle tissue

3) Ultrasound to study blood flow

4) Blood samples to measure miRNA, hemoglobin, ferritin, myoglobin, testosterone / estrogen, cortisol and creatine kinase,

5) Micro biopsy to obtain histological data, and high-field spectroscopy data

6) Physical performance measures (squats, leg strength), flexibility and maximum oxygen uptake.

In the third subproject, we will examine activation in different parts of the brain after physical activity in healthy female volunteers between 60 and 70 years. In this subproject, we choose the training intervention that gave the best results from the previous subprojects. The healthy volunteers will be divided into two groups, where one group exercise and the other group live normally. Parameters we want to study is the brain's functional and structural network [4] using structural MRI, diffusion weighted MRI, fMRI, as well as MRS to study brain metabolites. In this study we want to perform imaging before and after cycling using a MR compatible bike at baseline (pre-test) and after completing the exercise intervention (post-test). We also aim to study the relationship between cardio-respiratory fitness (VO2 max) and cognitive function.

Discussion and outlook

Quantitative and sensitive measures of tissue properties, as well as both muscular and cognitive response to an exercise intervention can give us important knowledge about the mechanisms of altered function due to exercise. This is important from a public health perspective, and for the development of specific characteristics of athletes. Increased knowledge about underlying mechanisms may lead to long-term effects such as targeted and
improved rehabilitation of muscle function and muscular development after major accidents, as well as inform us about how to maintain good health in the elderly population.

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References


Interactive Visual Analysis of Microarray Data of Algae

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Introduction

In molecular biology, one of the major goals is to elucidate the function of genes in organisms. Different organisms are studied for different purposes. In our project, the organism of interest are microalgae, in particular diatoms Phaeodactylum tricornutum and Thalassiosira pseudonana. Diatoms are a group of unicellular photosynthetic microalgae that have a great ecological importance; They constitute about 20% of carbon dioxide fixation on a global scale [1]. The species P. tricornutum and T. pseudonana are the two main model species for molecular studies in diatoms. Some genes of the species have known functions, however, many genes with unknown function remain. Finding genes with known function that have similar behavior in particular experiments can help identifying the function of yet unknown genes.

Our goal is to develop an analysis tool that applies interactive visual analysis to analyze the data from molecular techniques, such as microarray data and annotations made by researchers. In our example, the microarray dataset for P. tricornutum contains gene expression measurements of 10,367 genes in 46 experiments. The experiments include different light settings (exposure to light of different wavelengths and intensity), pollution (Cadmium) or nutrient starvation.

Method

We propose to combine several interactive visualization techniques in multiple linked views and connecting them via brushing [2]. Brushing is a selection technique, in which the selection made in one view applies to all views. In this way, the analyst can overcome the shortcomings of using one visualization technique only.

The main view is the parallel coordinate view [3], in which data from each experiment are represented as dimensions. The second and third view visualizes the Pearson correlation matrix between genes. This matrix is very large -- rendering such a large matrix, even if it was possible on a commodity screen of a PC (more than $10^8$ elements), would not be useful, since a human observer cannot perceive that much information at once. In the second view, we display the maximal correlation of each gene with another gene in the database, and how many genes are highly correlated (see also Figure 1).
Figure 1: Selecting genes for which there are relatively few highly correlated pairs.

In the third view, we aggregate each correlation vector of each gene into a histogram with given bins. Each correlation vector of a gene is represented as connected line strips. Pearson correlation has range [-1.0, 1.0] and we chose bins of equal size 0.05. The line segments connect the histogram bins, that indicate the number of genes which have the correlation with the respective gene corresponding to the histogram bin. Figure 2 illustrates the histogram view of P. tricornutum dataset, with the same selection as in Figure 1 in the scatterplot view.

Figure 2: The selection rendered in the histogram view. Very unique genes will have few or none genes that are highly correlated, but many genes with low absolute correlation.
Finally, we show again the selection in the parallel coordinate view. The selection mechanism allows to make consecutive selections with set operators such as add, subtract, intersect and new.

*Figure 3: The selection rendered in the parallel coordinate view. In a subsequent operation, we select genes that have high expression in two light experiments and observe that their expression is highly correlated except of the experiments that compare expression in light conditions at different times of the day.*

In addition to the graphical view of the data and for interactive exploration using linking and brushing, the application has an option for textual search. Some genes in the database are annotated. Those with no annotation are marked "N/A". With the textual search, it is possible to quickly retrieve the genes without annotations and search for genes that are highly correlated with them, and their function is known. In Figure 4, we show genes with no annotation (175 genes). Further 3097 genes have the word “unknown” in their description.

*Figure 4: Genes that have no annotation.*
Conclusions

We presented an application for multidimensional microarray data, which combines multiple visualization techniques via brushing and linking. First users reported improved and more efficient workflow.

As further improvements, we plan to include cluster computation and interactive exploration of clusters.

References


A Mechanical System Directly Attaching beside a Surgical Bed for Measuring Surgical Area Precisely by Depth Camera

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Introduction

There are many methods for capturing surgical area including many kinds of organs and/or several medical tools in an abdominal or laparoscopic surgery by different types of surgical operative procedures [1],[2],[3]. In this study, we propose a new mechanical structure to capture a sequence of depth images during a surgery when the surgeon rotated the surgical bed to maintain a wider comfortable view over the surgical field. Because the camera and bed are directly connected in this structure, the relative position and orientation between the camera and surgical field are fixed and consequently depths corresponding to pixels around the liver surface are acquired with high precision by the camera. The corresponding depths are useful to investigate and simulate motion and deformation of the organ via many points on its surface.

Method

We pay especial attention to the environment where a surgeon can easily view and operate in the surgical field, especially when regarding the cancerous tissue inside the liver. Therefore, we always prepare a wider view to allow the surgeon to cut/deform the liver’s surface comfortably with both hands and several medical tools. To maintain a suitable view, the surgeon sometimes needs to move the surgical bed along the X-, Y- or Z-axes, both translationally and rotationally. From previous practical experiences in the operating room, the camera was independently located beside the surgical bed and so the relative position/orientation between the surgical field and the capturing camera irregularly changed and consequently the image pixel of the capturing sequence did not always correspond to the same

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{(a) A mechanical system for measuring the surgical area under an astral lamp. (b) Cover connecting Kinect v2 with a filter protecting against several kinds of halation.}
\end{figure}
position on the liver’s surface. As a result, the fixed liver deformation at each pixel cannot be calculated and consequently all the captured depths are to useless for real-time surgical simulation.

To overcome this drawback, we directly attach the camera to the surgical bed (Fig.1(a) and (b)). Thus, the surgical field and recording camera are cooperatively moved and therefore the relative position/orientation between the surgical field and its capturing camera are always fixed during the surgery, which can take place over 2–3 hours. In the following experiments, the initial distance between the camera and liver was always set at approximately 1 m. Our operating room is shown in Fig.1(a). By changing the lengths of the stainless sticks and aluminum pipes freely, we are able to flexibly adjust the camera position/orientation in a 3D XYZ coordinate system (Fig.2). We adjusted the stiffness of the mechanical system in a trial and error manner in order to limit vibration of the camera during surgery.
Finally, in order to eliminate a strong halation around the liver by the astral or xenon lamp, we use the light-shielding glass filter for welding. As shown in Figs 3 and 4, the strong halation around the liver completely disappears. As a result, we can capture a good sequence of depths whose pixels always correspond to the same positions of the liver’s surface.

Evaluating the average error of the measured 30 depths after rotation of the surgical bed under an astral lamp.

A surgeon operates while moving the surgical bed around the X- or Y-axis, to perform several surgical techniques (cutting, deforming, moving translationally and/or rotationally) using plastic and viscoelastic virtual livers. Synchronously, we evaluated the average precision of the 30 depths captured by the Kinect v2 system during the operation. Consequently, we obtained the graph shown in Fig.5. Because the trial and error is not enough yet in the present stage, the mechanical system with one pole unfortunately vibrates until 40 seconds (at most 30*40=1200 frames) after a surgeon moves the bed. Note that the depth image is captured by at most 30 fps (the frame rate is flexibly changed around 20 fps). For keeping the high rate of capturing all RGB/IR/Depth images of Kinect v2, we always change many Solid State Drives (SSD) with 512GB. Over the course of the experiment, the errors are no longer apparent. The
graph demonstrates a 2 mm distance error. In general, since the distance error of Kinect v2 is 1-2 mm, this error can be considered negligible.

Evaluating the average error of the measured 30 depths when the surgical bed is rotated under a xenon lamp.

A surgeon operated using our surgical bed, moving around the X- or Y-axis, while performing real surgical techniques using plastic and viscoelastic virtual livers (Fig.2). Simultaneously, we evaluated the average precision of the 30 depths captured by Kinect v2 during the operation. Consequently, we obtained the graph shown in Fig.6. As described in the previous paragraph, our structure with one pole vibrates until 40 seconds and then the vibration disappears after a surgeon operates a surgical bed. In the graph, we can see the initial errors were approximately 2 mm around the X- and Y-axis, respectively. As mentioned previously, the distance error of Kinect v2 is $1 \sim 2$ mm. Therefore, the recorded error was considered negligible.

Conclusions

We constructed a smart mechanism to sense the many surface points of the liver, brain, or other organs irrespective of translation or rotation of the surgical bed by the surgeon. In order to evaluate this mechanism in a real operating room in a hospital, we stably captured a lot of surface points around liver, brain, or other organs. The measuring error of many surface points are evaluated by their average which is estimated as 2 mm. As a result, even if a surgeon rotates or translates the surgical bed, sensing errors are negligible.

ACKNOWLEDGMENTS

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References


Abstracts for Session IX
Perfusion imaging

Abstracts are organized in the order of presentations
Recent Advances in MRI and Ultrasound Perfusion Imaging

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Perfusion imaging is an important diagnostic tool used mostly in oncology, neurology and cardiology, to assess the perfusion status of the tissue on a capillary level, e.g. assessment of angiogenesis, ischemic regions and inflammation. This contribution is a review of recent advances in dynamic contrast-enhanced magnetic-resonance and ultrasound imaging (DCE-MRI and DCE-US). In these methods, contrast-agent concentration time curves are derived from the acquired image sequences for each tissue region of interest. These tissue curves are then approximated by a pharmacokinetic model parametrized by perfusion parameters, such as blood flow, blood volume, vessel permeability-surface product, and extravascular-extracellular space volume.

In DCE-MRI, the pharmacokinetic model is a convolution of the arterial input function (AIF) and the impulse residue function (IRF). Selection of the appropriate IRF model for a given tissue remains an open question. Selection of the appropriate pharmacokinetic model for a given tissue has been supported by simulations and real data. Estimation of an examination-specific AIF has been one of the main challenges in DCE-MRI. Single- and multi-channel blind-deconvolution approaches based on non-parametric and parametric AIF formulation are reviewed.

The recent trend is to use more complex IRF models parametrized by more perfusion parameters which leads to the problem of ill-posed approximation task. This problem requires higher signal-to-noise ratio (SNR), higher temporal resolution and the need for additional information. One approach to improve the SNR and temporal resolution is to use compressed sensing acquisition and image reconstruction techniques. Additional information has been recently gained by application of several boluses of contrast agents with a different molecular weight.

In DCE-US, the challenge of absolute quantification of perfusion parameters has not been addressed by many research groups. One approach to absolute perfusion-parameter quantification is based on the same convolutional model as in DCE-MRI (and in DCE-CT, PET, SPECT), with simpler IRF models. This unified model can be applied to the burst-replenishment, bolus and bolus&burst acquisition techniques. The AIF can be measured or estimated by single-channel blind deconvolution.
Discretization dependency of classical models for perfusion – a simulation study

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Background

Perfusion can be defined as the rate of delivered arterial blood to a tissue volume [1]. Many medical conditions are accompanied by altered tissue perfusion, and image derived perfusion measurements can therefore serve as an important parameter in diagnosis and prognosis. Accurate estimates of perfusion are therefore of high importance. The traditional approach to perfusion, using one-compartment models, has mathematically no spatial reference where the extent of the model is applied to a larger region of interest, comprising the entire process of blood being transported from the arterial side to the venous side of the capillary bed. However, modern scanners typically provide high-resolution images where the capillary network is ranging across several voxels, leading to multiple feeding voxels. Traditional models are not able to handle connected systems since the applied distribution volume will be incorrect, and over-estimation of perfusion might take place. Improved methods for image derived perfusion have therefore recently gained reviewed attention [2]. In this work we focus on the modelling part of the perfusion estimation. We introduce a model suited for simulation of local perfusion in a connected system. The simulated flow maps were also subject to traditional perfusion estimation methods, and perfusion error estimations were computed based on the known ground truth for the entire domain.

Methods

Mathematical theory

We simulate blood flow and transport of contrast agent through a bounded tissue domain $\Omega$. The local flow in $\Omega$ is represented by a flux-vector $q$. In-line with standard theory for a steady-state incompressible fluid, the flux field $q(x)$ obeys the continuity equation

$$\nabla \cdot q = Q,$$

where $Q \left[ \text{m}^3/\text{s} \right]$ is a user-defined source- and sink term, which we assume to be only non-zero within the source or the sink. Combining the continuity equation for the fluid mass balance with Darcy’s law leads to the governing equation

$$\nabla \cdot \left( \frac{k}{\mu_b} \nabla p \right) = Q, \quad x \in \Omega,$$

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where \( p \) is the pressure, \( k \) is the intrinsic permeability tensor, and \( \mu_b \) is the blood viscosity. The equation is solved for \( p \), driving the flow. The tracer concentration was computed locally in line with mass conservation of the tracer

\[
\phi \frac{\partial c}{\partial t} + \nabla \cdot (cq) = c_a Q_{so} + c Q_{si} \\
c(x,t) = 0
\]

where \( Q(x) = Q_{si}(x) + Q_{so}(x) \).

The synthetic structure

As a simplified, but still realistic test case, we consider a three layered structure to imitate a multi compartment model: An upper layer representing the arterial compartment, a middle layer reflecting the capillary compartment, and a lower layer representing the venous compartment, as shown in Fig. 1. Blood flow through the middle layer can thereby be considered as perfusion. The model structure ensures that both arterial and venal flow, as well as the perfusion itself, is purely driven by pressure differences and constrained by locally varying permeabilities.

The domain was dissected into 16 discrete slices. Permeability and porosity were assigned a fixed value and then multiplied by a 2D image of a capillary network, with a mean of 1 and minimum and maximum values of 0.5 and 1.5. The capillary image was used to create a structure in the parameter maps. The 2D image was duplicated across the third dimension and then scaled across the third dimension according to an inverted Gaussian of zero mean and standard deviation of 2, and later scaled to minimum value of 0.5 and maximum value of 1. The gaussian scaling was performed in order to create varying parameters between arterioles, capillaries, and venules. In addition, one region of hyper- and one region of hypo-permeability were inserted into the permeability field to simulate pathological changes in the capillary ability to deliver blood. One slice of the obtained porosity and permeability fields are shown in Fig. 2.

Figure 1: Model for capillary perfusion. Oxygenated blood enters the tissue in the arterioles (upper, red layer), flows through to the capillaries (gradient between dashed lines), and is leaving the FOV via the venous system (lower, blue layer). The blood is entering and leaving the FOV in regions indicated by the arrows.

Figure 2: Parameter fields used for simulation. **Left:** Porosity field. **Right:** First component of the permeability field \([m^2]\) used in the structural phantom. Both the porosity and the permeability fields were inspired by the structure of a capillary network. Additionally, we assigned two regions of hypo-permeability (blue circle) and hyper-permeability (red circle) simulating pathological conditions leading to changes in the capillary ability to maintain perfusion.
Equation (2) was solved numerically for the flux $q$ along with Neumann boundary conditions using the TPFA method [3]. One slice of the obtained pressure field is shown in Fig. 3. Parameters used in the synthetic structure are summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
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<tr>
<td>Field of view (FOV)</td>
<td>$3 \times 3 \times 1.5$</td>
<td>mm</td>
</tr>
<tr>
<td>Voxel size</td>
<td>$46.875 \times 46.875 \times 93.75$</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>Matrix</td>
<td>$64 \times 64 \times 16$</td>
<td>-</td>
</tr>
<tr>
<td>Viscosity blood $\mu_b$</td>
<td>0.0035</td>
<td>$Pa \cdot s$</td>
</tr>
<tr>
<td>Average permeability arterioles</td>
<td>$1.01 \cdot 10^{-13}$</td>
<td>$m^2$</td>
</tr>
<tr>
<td>Average permeability capillaries</td>
<td>$8.17 \cdot 10^{-14}$</td>
<td>$m^2$</td>
</tr>
<tr>
<td>Average permeability venules</td>
<td>$8.30 \cdot 10^{-14}$</td>
<td>$m^2$</td>
</tr>
<tr>
<td>Average porosity arterioles</td>
<td>0.045</td>
<td>-</td>
</tr>
<tr>
<td>Average porosity capillaries</td>
<td>0.035</td>
<td>-</td>
</tr>
<tr>
<td>Average porosity venules</td>
<td>0.036</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1: Parameters used to create the synthetic structure.

The synthetic phantom

A synthetic phantom with local concentration time curves was created within the synthetic structure using a gamma variate arterial input $c_a$ [4]. Given $q$ from (2), (3) was solved by upwinding for time steps $\delta t = 0.002s$ within the time interval $[0, T]$. The synthetic phantom was resized to a temporal resolution of 0.2 seconds to be in line with a realistic time scale for clinical imaging equipment. For reconstruction of perfusion we used a classical one-compartment (1C) model by deconvolution [5]. In the numerical reconstruction phase of perfusion we collapsed all layers in the third direction of the structural phantom into one voxel layer in order to ensure the existence of arterioles, capillaries, as well as venules within every voxel. In other words, the concentration time curves were averaged over the third direction and used as input for deconvolution. Average, reconstructed perfusion was compared to the total ground truth perfusion $P$ previously used to create the synthetic phantom.

Results

Results from deconvolution analysis are shown in Table 2 and a computer perfusion map is shown in Fig. 3. The obtained average perfusion values $\bar{P}$ should be compared to the overall perfusion of value $P = 50ml/min/100ml$. The obtained, average porosity values $\bar{\phi}$ should be compared to the average porosity of the synthetic structure of $\phi = 0.038$. The simulation results show that voxelwise perfusion is discretization dependent, and that the error in perfusion values increases with smaller voxel size. On the other hand, the porosity is estimated with a low error independent of voxel size. Percentage error $E$ was computed as

$$E(P, \bar{P}) = 100\% \left( \frac{\bar{P} - P}{P} \right), \quad E(\phi, \bar{\phi}) = 100\% \left( \frac{\bar{\phi} - \phi}{\phi} \right). \quad (4)$$

Discussion and Conclusions

We have carried out estimates of porosity (CBV) and perfusion in a synthetic 3D multi compartment phantom using a traditional, state of the art one-compartment deconvolution model. According to our results are estimates of porosity reliable independent of
block size. On the other hand, serious discretization dependencies exist for perfusion measurements, and the error increases with smaller voxels. As an internal control, results for the entire ROI resulted in a low measurement error (5.6%), suggesting the use of traditional one-compartment for entire capillary systems. These results indicate that it can be error-prone to apply classical one-compartment models to fine-grained images with small voxel sizes in the range of the capillary system, and that traditional methods can induce serious errors in clinical perfusion studies. The traditional models should therefore only be used for larger regions of interest. This problem is expected to become even more pronounced in future applications where scanings are expected to generate images at even higher spatial resolution. As a remedy, we are focusing on the development of coupled and regularized PDE models where the perfusion concept is subject to a mathematically more strict and anatomically fine-grained formulation [2].

References

Ultrasound imaging of perfusion

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Imaging of organ perfusion is clinically relevant in conditions related to changes in blood flow such as ischemia (reduced or absent flow), inflammation (hyperaemia) and otherwise altered flow conditions or vasculature as seen in in the pathological tissue of tumours [1]. It can be used to aid disease detection and differentiation. Since perfusion often quickly changes with an intervention it is also an interesting parameter for treatment follow up [2, 3]. Unfortunately, the clinical application of such methods are challenging since the physiological variation of perfusion can be large both between and in the same individual. Also, a non-invasive method requires an imaging modality which means that both extensive standardization and data-modelling is required [3-5].

This lecture will focus on dynamic contrast-enhanced ultrasound (DCE-US) in which the intensity changes after UCA injection offer a direct opportunity for measuring tissue perfusion. Currently, using 2D ultrasound there are limited possibilities for multiple sampling even though continuous infusion of UCA or multiple injections are possible. DCE-US is, however, considerably cheaper, more flexible and with less side effects than similar measurements in CT or MRI. It can also offer both immense spatial and temporal resolution.

DCE-US can be performed using different techniques of contrast administration. In the disruption replenishment technique a continuous infusion is given and in steady state the microbubbles is destroyed with high energy ultrasound and the reperfusion is observed [6]. In bolus tracking a single bolus injection is observed over time in a region of interest [7]. The bolus and burst method is a combination of the two [8]. The evolution of intensity changes over time in a region of interest can be represented in a time intensity curve. As ultrasound data are inherently noisy they are usually fitted to an indicator dilution model [9]. It is still an ongoing discussion which UCA administration technique and indicator dilution model should be used.

There are several sources of variability when performing DCE-US. To summarize briefly, differences in settings of the ultrasound scanner settings such as mechanical index, focal depth, dynamic range and gain will all affect results. Also, differences in patient characteristics, injection technique, UCA behaviour, region selection and tissue motion are all factors that could potentially introduce variability [3-5]. Finally, the analysis of DCE-US requires post-processing which often is work intensive and inherently introduces more intra-reader variability [10, 11]. Standardization between vendors, of injection techniques and modelling together with a simplified analysis process is therefore necessary for a more generalized clinical use.
Figure 1: Panel a and b shows the B-mode and contrast image, respectively, during peak enhancement. The chosen section is a stenotic small bowel loop. In panel c the linearized intensity data are shown plotted over time (seconds). The data has been acquired using the bolus and burst technique. In panel d the intensity data (blue) are shown together with the fitted model. In this case there is a good fit between the actual data and the model.

Reference List


Multivariate image analysis for multiparametric phenotyping and prognosis in cancer

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INTRODUCTION

Imaging biomarkers are being developed for early cancer detection in several organs such as lung, breast, liver, colon, prostate, or brain. These imaging biomarkers, which act as indicators of a normal biological process, a disease or a response to a therapeutic intervention, rely on (hard) physiological models; making the interpretation difficult in some cases. Furthermore, these imaging biomarkers are obtained pixel-by-pixel, hence introducing an extra variability source. Therefore, developing new easy-to-interpret and robust imaging biomarkers becomes a challenge in order to help and improve clinical tasks, such as detection, phenotyping and prognosis.

In the chemometrics field, Multivariate Curve Resolution (MCR) models have been applied for chemistry applications (de Juan and Tauler, 2006). From early 2000’s, the applications of these models on images have increased, mainly in chemistry and pharmaceutical environments favored by the similitude between the image data structure (after proper unfolding) and the data arrays commonly analyzed. The wide applicability of MCR on chemical images comes from the fact that the spectrum at each pixel location can be modeled as the weighted sum of its pure chemical compounds present in the whole data structure (i.e. the unfolded image); where this weight is the relative concentration of each chemical compound at that pixel location.

This concept can be easily extrapolated to other environments, as is the case of Magnetic Resonance (MR) images in Medicine, where the registered signal, which depends on the type of MR sequence, can be modeled as a weighted sum of the relative relevance of each “pure” physiological behavior (phenomenon) at that pixel location. In this work, we present the application of MCR on Dynamic Contrast Enhanced (DCE) and Diffusion Weighted (DW) MR images for the voxelwise development of new imaging biomarkers able to detect and locate tumors at early stage, in the case of Prostate Cancer (PCa). Our main objective was to create nosologic images with prognostic clinical information that will help in establishing a personalized medicine approach.

DCE and DW MR

Main hallmarks indicators of tumoral processes are vascular proliferation and cell replication. Neoangiogenesis (creation of new vascular vessels) and neovascularization (development of existing ones) are phenomena that occur when a group of growing tumoral cells presents abnormally high oxygen demands. In order to improve diagnosis, tracking and tracing of these malignant tumor progression, different MR techniques have been developed to acquire complementary information to that obtained from conventional MR imaging (not able to discriminate the spread of invasive part of the tumor): DCE-MR and DW-MR imaging (Heijmink et al. 2011; Giannarini et al. 2012).
Pharmacokinetic modeling of DCE-MR images is based on the application of a mathematical analysis to tissue enhancement curves. One characteristic of these models is the lack of a priori knowledge about the tissue vascular environment, which leads to a series of assumptions that condition the use of different pharmacokinetic modeling approaches. Accordingly, and depending on the tissue dynamics patterns, the pharmacokinetic model may provide biased measurements which may not properly reflect the true physiology of the tissue. Furthermore they require patient-specific data such as T1 values and arterial input function (AIF) that can introduce variability. It is therefore desirable to have a priori knowledge about the dynamics of tissue to easily interpret the information provided by the pharmacokinetic parameters. Thus, it becomes necessary to have models that are able to directly extract such a priori knowledge from the data sequences; and create robust models that are able to cope with external artificial variability that can affect the biomarker computation.

Another way of facing the oncogenesis (combination of cellularization and vascularization) process is by studying the tissue local diffusion process (Charles-Edwards and De Souza, 2006), which is a physical process that occurs due to the thermal agitation of the water molecules inside the human body. Tumors are characterized by an increased cellularity, with cell swelling and rests of necrosis and fibrosis, all reducing the mobility of water molecules. When the tissue is highly cellularized, the molecules have more restrictions to movement due to a decreased interstitial space and higher cell membrane interfaces. However, when the tissue is highly vascularized, molecules are in a non-restricted high velocity environment within the vessels, and the spatial movements are random with fewer restrictions in all spatial directions.

The diffusion process can be evaluated with DW-MR, which is associated to a parameter known as $b$-value (Le Bihan, 1991). The signal of the image decreases with the increase in the $b$-value acquired. This attenuation depends on the characteristics of the tissue, being stronger if the tissue is vascularized and much more moderate if it is highly cellular. Within the different models to be used, a biexponential model called Intra-Voxel Incoherent Motion (IVIM) is able to separate these two effects. Nevertheless, the fact that the IVIM model is not a typical biexponential model because the two exponential decays are not independent as they are complementary weighted by the vascular fraction, $f$; joint to the normalization of the spectra, increases the difficulty in the interpretation of the results provided by its associated biomarkers (such as $D$, $D^*$ and $f$ parameters) and limits its applicability in clinical practice.

All these biomarkers from DCE-MR and DW-MR are obtained pixel-by-pixel, hence not taking advantage of the relation between pixels with the same behavior, increasing the uncertainty in their estimation; and degrading the corresponding imaging biomarkers used for clinical purposes.

This way, analysis of imaging biomarkers poses different problems:

- These biomarkers are obtained in a univariate way by fitting them to some mathematical models, not taking advantage of the internal correlation structures between pixels.
- The simultaneous evaluation of several biomarkers is difficult, even more when considering the different combinations that may be related to a tumor. This can be complicated and requires a priori knowledge.
- Some of the obtained parameters (e.g. the transfer coefficient of $K^{trans}$) have a complex physiological interpretation, since it mixes permeability and vascular flow. Therefore, it seems interesting to obtain biomarkers having an easy clinical interpretation.
- Likewise, there are different models of different levels of complexity both for perfusion and diffusion. Such models are justified in certain cases (e.g. IVIM in diffusion). In other cases
- (e.g. certain pharmacokinetic models) the complexity has not been justified yet. Therefore, it becomes necessary to have models that are able to extract such a priori knowledge from data directly extracted from the sequences.

- Also these biomarkers may suffer from bias in their estimation due to measurement errors introduced by the different devices ("ghosts"), and/or reproducibility errors associated with the values of some model input function from which are obtained (e.g. the Arterial Input Function AIF).

**NEW IMAGING BIOMARKERS DEVELOPMENT**

One way to address the above issues and challenges is to analyze the imaging biomarkers in a multivariate way. Multivariate statistical projection models allow analyzing large data sets; obtaining simplified structures that help to understand the relationships between the studied variables and the underlying physiological phenomena. The application of these techniques on images is called Multivariate Image Analysis (MIA) (Prats-Montalbán et al., 2011). In the case of medical images, the observations are formed by each of the pixels of the images, while columns contain the signal of each pixel at each time (pharmacokinetic perfusion), or b-values (diffusion).

The application of MIA in oncology (Bruwer et al., 2008; Prats-Montalbán et al., 2014; Aguado-Sarrió et al., 2015) allows extracting the sources of variation from a relevant number of sequenced images, which help in describing and explaining the behavior differences between healthy and affected tissues, as well as the physiological phenomena undergoing, better than the mathematical imposed model. These models reduce the uncertainty in the estimation of the parameters obtained from the computational models for the treatment of medical images. They provide new biomarkers, complementary to those commonly used and with clinical interpretation in the case of using MCR models, which directly point out to the pixels related to each physiological behavior and areas of starting active tumor growth, facilitating the clinical diagnosis; as well as other regions of interest in an objective and reproducible way (e.g. AIF (Sanz-Requena et al., 2015)).

MCR-ALS is an iterative method that performs a bilinear decomposition of matrix $S$ by means of an alternating least squares optimization, by imposing certain constraints related to some a priori knowledge, when available; hence being able to provide more clinically (or physiologically) interpretable results (in this case, non-negativity in the intensities and the dynamics)

$$S = CD^T + E$$  \hspace{1cm} (1)

Here, $D^T$ contains in its rows each one of the dynamic behaviors modeled, $C$ gathers in its rows the relative importance of each modeled dynamic behavior for each pixel, and $E$ is a residual matrix.

This way, by applying MCR-ALS models to both DCE and DW MR sequences, new imaging biomarkers are obtained, with complete clinical meaning. In the case of DCE, when a tumor is evolving in the prostate, three different dynamic behaviors can be expected:

1. Type AIF: abrupt initial peak and fast washout (blood flowing within the arteries), corresponding to the dynamics pattern in the artery (Figure 1a).
2. Type NT: slow progressive enhancement without washout, corresponding to a non-tumoral tissue (Figure 1b).
3. Type VT: delayed fast initial enhancement and slow washout, corresponding to a highly vascular tissue, such as a tumor (Figure 1c).
By applying MCR-ALS, not only these a priori known dynamics, but also an artificial (non-physiological) Contrast Media Arrival (CMA) related to the MR equipment (Fig. 2, left) are detected. Finally, by focusing in the local prostate area and eliminating the AIF related to the arteries, more refined dynamics (Fig. 2, right) and their corresponding biomarkers (Fig. 3) can be derived.

**Figure 1.** Dynamics patterns after the injection of a contrast media in dynamic contrast-enhanced magnetic resonance images. Abrupt initial peak and fast washout: AIF (a), slow progressive enhancement without washout (b) and delayed fast initial enhancement and slow washout (c). Curves b) and c) are often analyzed using the same pharmacokinetic model, which may lead to biased results in the estimated parameters.

**Figure 2.** Left: Dynamic behaviors provided by the MCR model: type AIF (black solid line), type NT (blue dotted line), type VT (red dashed line) and non-physiological Contrast Media Arrival (type CMA) effect (green dashed-dotted line). Right: Dynamic behaviors provided by the local MCR model: type NT (blue dotted line), type VT (red dashed line) and non-physiological Contrast Media Arrival (type CMA) effect (green dashed-dotted line).

**Figure 3.** Distribution maps of the dynamic behaviors from prostate MCR local model shown in Figure 3. Left: Type CMA. Middle: Type NT. Right: Type VT (c). Note that Type AIF has not been included as there are no arteries in the prostate area.

Performing in an analogous way for the DW-MR sequence, Figure 4 shows the corresponding exponential decays and their corresponding imaging biomarkers are obtained, as well as the outlying pixels (those that show a behavior that does not relate to any of those included in the model), gathered by the Residual Sum of Squares (RSS) image.

**Conclusions**

This work shows the capability of MCR models to extract biological behaviors with clinical meaning from the DCE-MR and DW-MR images by including a priori knowledge. MCR lets to
directly locate and grade the spatial expression of these behaviors, providing new imaging biomarkers complementary to those obtained from the theoretical models, to improve clinical diagnosis. MCR also helps in segregating those artifacts that may introduce uncertainty in the estimation of any biomarker, providing an evaluation tool for assessing the appropriateness of theoretical models, with a data driven model methodology that allows incorporating prior knowledge in a sequential fashion.

Figure 4. MCR prostate imaging biomarker related to d1 (slow diffusion, solid blue line) (top left). MCR imaging biomarker related to d2 (fast diffusion, dashed green line) (top right). RSS distribution map (bottom left). Modeled behaviors (bottom right).

References

Abstracts for Session X
Computational imaging

Abstracts are organized in the order of presentations
Dynamic image analysis: from tracking of cells to dynamic MRI

Data processing and analysis becomes increasingly important in the healthcare context. Much of this data consists of visual data such as cellular imaging data in cancer research and molecular imaging data in the clinic, used for prediction, diagnosis and treatment of diseases. This data needs to be processed, analysed, and classified, and very often is used to inform decisions based on the information extracted. Image data plays a special role in data science, as the information that it encodes is usually very complex and structured, and is prone for access by mathematical models and techniques. Indeed, images are a rich source of beautiful mathematical formalism and analysis.

In this talk we will discuss a collection of mathematical approaches and their use and realisation for solving particular image analysis and processing tasks such as image de-noising, de-blurring and segmentation, object tracking and motion estimation, as well as image classification. The talk is furnished with applications of the introduced models in biomedical and clinical imaging.
Image registration for early detection of fibrosis

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Background
The final stage of chronic kidney disease is renal fibrosis followed by sclerosis ultimately requiring renal replacement therapy, such as dialysis and/or kidney transplantation. However, the time point of advanced renal failure can potentially be delayed by several years through early fibrosis detection in conjunction with appropriate medical treatment. In vivo imaging methods for early detection of fibrosis are therefore useful tools to prescribe treatment slowing down this disease progress. New imaging techniques with excellent spatial coverage for in vivo diagnosis of fibrosis are emerging. In particular ultrasound (US) liver elastography as well as magnetic resonance elastography (MRE) are developing as promising clinical tools to detect fibrosis.

The pathological mechanisms underlying fibrosis lead to increased tissue stiffness. In order to further complement existing diagnostic tests, the main aim of this work was to study whether a T1-w dynamic MR sequence routinely used in dynamic contrast enhanced MRI (DCE-MRI) can be used to estimate deformations which might reflect an early stage increased tissue stiffness following fibrosis. As external force for deformation we use the patient's own breathing. We hypothesize that induced tissue stiffness following fibrosis will lead to altered elastic behaviour upon breathing that can be detected by methods for image registration.

Methods
We setup a mathematical model for deformation of elastic tissue. The same type of model is used both to simulate deformations in healthy and fibrotic tissue and as a regularizer in the image registration process.

Poroelastic model for deformation: Define the deformation field vector \( u : \Omega \times T \rightarrow \mathbb{R}^3 \), the hydrostatic pressure \( \rho : \Omega \times T \rightarrow \mathbb{R} \) of fluid, the identity tensor \( I \), a scalar \( \alpha \in [0,1] \), the first Lamé constant \( \lambda : \Omega \rightarrow \mathbb{R} \), and the shear modulus \( \mu : \Omega \rightarrow \mathbb{R} \) [1]. Furthermore, let \( q : \Omega \times T \rightarrow \mathbb{R}^3 \) be the flux per unit area \( [m^3 / s / m^2] \) and let \( \rho : \Omega \times T \rightarrow \mathbb{R} \) be the fluid density \( [kg/m^3] \). The poroelastic equations can be summarized as the set of equations [2,3]

\[
\epsilon = \frac{1}{2} \left( \nabla u + (\nabla u)^T \right),
\]

\[
\sigma = 2\mu \epsilon + \lambda (tr \epsilon) I - \alpha \rho \mathbf{l}
\]

\[
\nabla \cdot \sigma + \gamma b(x, u) = 0.
\]

and
\[-\nabla \cdot \left( \frac{k}{\mu_b} \nabla p \right) + \frac{X}{\rho} \frac{\partial p}{\partial t} + \alpha \frac{\partial}{\partial t} (\nabla \cdot u) = 0 \]

The above equations constitute the poroelastic deformation model, which is solved numerically for the deformation field $u$ and pressure $p$.

**Participants:** Data from ten randomly selected healthy volunteers and ten patients with various stages of biopsy-proven kidney fibrosis were used in this project. Exclusion criteria were standard exclusion criteria for MR examinations, dementia, as well as presence of cancer. The study was approved by the Regional Committee for Medical and Health Research Ethics (REC) (Approval 2014/1929).

**MR image acquisition protocol:** All MRI recordings were acquired at the Department of Radiology, Haukeland University Hospital, Bergen, with a Siemens Magneton Prisma 3.0T scanner. A dynamic T1-weighted 3D single gradient recall echo (GRE) FLASH3D pulse sequence was used to obtain signal-intensity time curves. The acquisition was undertaken with deep, calm breathing. The acquisition parameters were TR/TE/FA=2.41ms/0.87ms/12O, matrix size=256x256, FOV=425mm, voxelsize=2.08x2.08x3mm, and number of time points=40. Acquisition time between each 3D volume was 0.7s. For the current study only segmented images were used in addition to the first time point of the dynamic T1-weighted MRI sequence.

**Discretization:** Discretization was performed by the multi point stress approximation (MPSA) framework described elsewhere [2,3]. The implementation allows for rapid changes in parameters without entering a state of numerical instability.

**Parameter settings:** Tissue parameters used for discretization of the PDE system are shown in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Unit</th>
<th>Kidney</th>
<th>General organ</th>
<th>Lung</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shear modulus</td>
<td>$\mu$</td>
<td>Pa</td>
<td>5.00</td>
<td>5.00</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>First Lame parameter</td>
<td>$\lambda$</td>
<td>Pa</td>
<td>0.10</td>
<td>0.10</td>
<td>0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Permeability x,y,z</td>
<td>$k_{x,y,z}$</td>
<td>m$^2$</td>
<td>$2.60 \cdot 10^{-13}$</td>
<td>$1.30 \cdot 10^{-13}$</td>
<td>$1.30 \cdot 10^{-13}$</td>
<td>$1.30 \cdot 10^{-13}$</td>
</tr>
<tr>
<td>Porosity</td>
<td>$\phi$</td>
<td>-</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 1 Parameters used for discretization.

The reported parameters were assigned to each tissue class, resulting in piecewise constant parameter maps. The different tissue classes were defined using marker-controlled watershed segmentation with manually outlined markers. In addition, for the patient group, we assigned a stiffer kidney by imposing a random field of increased values of $\mu$ and $\lambda$. The random field was a smooth version of the first dynamic T1-weighted MR image. The random field was thereafter normalized to [1,10] and multiplied with the piecewise constant parameter maps. An example of the parameter map for $\lambda$ is shown in Figure 1 (left panel).

**Simulated deformation field and restoring it by image registration:** Based on the discretization we simulated patient breathing movement using a time varying and periodic volume force assigned to the upper horizontal row of pixels. The volume force was a 4th order polynomial

$$F(x,t) = -\frac{4M}{D^4}(l^2 - D^2)l^2 \sin(\pi t / 2)$$

where $D$ is horizontal domain length, and $l$ is the horizontal distance from the origo centered in the middle of the upper boundary. Provided the spine is in the middle of the image, this results in a force with local minima at the boundaries as well as at the spine location. A visual representation of the imposed force is shown in Figure 1 (right panel).
Figure 1 Left: Parameter map of $\mu$. The spine was treated as internal boundaries with Dirichlet conditions of $u = 0$, assuming no motion at these locations. The kidneys (bright, regions of varying intensity) were assigned a varying parameter map with increased values of $\mu$ and $\lambda$ to simulate a pathological condition consistent with fibrosis. Right: The first dynamic T1-weighted MRI volume used for forward simulations. The plotted curves show a scaled version of the force used to simulate breathing, and different colours correspond to various time points.

Using the first image in the original DCE-MRI time series as model image, the forward simulation resulted in a motion disturbed, discrete image sequence $f(x, t)$ in space and time. This setup represent an idealized case, where all subjects (patients and healthy) are breathing exactly similarly and thereby exposed to the same external forces.

As a final step, omitting the random parameter field within the kidney for the sick group and thus using the same discretization for all participants, we tried by image registration to recover the deformation field created in the forward simulation. For this task the deformation field, the imposed volume force $F(x, t)$, was replaced by a sum-of-squared differences (SSD) registration force $b$ in the poroelastic deformation model [4].

**Quantitative measures:** We extracted the following quantitative measures for statistical analysis: The absolute deformation $|u|$ reflecting total deformations, the absolute, linearized volume change $|\nabla \cdot u|$, the absolute determinant of the strain tensor $|\det(\varepsilon)|$ reflecting volume and shape change, fractional anisotropy (FA) as a measure of anisotropy in the vector field $u$, and the absolute pressure gradient $|\nabla p|$ as a measure of breathing induced flux. All extracted quantities were subject to a two-tailed t-test for comparison between healthy and the sick. All measures were extracted from the kidneys only.

**Results**
Results from image registration are shown in Figure 2 and Table 2.

**Discussion and conclusions**
We mathematically simulated a “fibrosis pathology” with heterogeneously distributed parameters reflecting a situation of up to 10x increased stiffness in the kidney for the patient group, and conducted forward deformations on a human geometry map. Results from reconstruction of the deformation field using image registration show that although the average deformation is comparable between healthy and patients, there are distinct differences to be observed in volume changes and in the determinant of the deformation upon exertion of an external force field. The image sequences that form the starting point for the image registration can be seen as a hybrid between real and simulated data. The geometries as well as the image intensities are from real recordings, while the breathing motion was simulated. In the same way the heterogeneity of the
tissue properties was somewhat simplified in the model. As a result of these simulations we suggest to further explore image registration as a quantitative tool for fibrosis.

![Figure 2 Results of forward simulations. From left to right: $|u|$, $|\nabla \cdot u|$, $|\det(e)|$, FA, and $|\nabla p|$ of healthy (H) and patients (P). Error bars show standard error.]

<table>
<thead>
<tr>
<th></th>
<th>Mean (healthy)</th>
<th>SD (healthy)</th>
<th>Mean (patients)</th>
<th>SD (patients)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$</td>
<td>u</td>
<td>$</td>
<td>0.469</td>
<td>0.094</td>
<td>0.507</td>
</tr>
<tr>
<td>$</td>
<td>\nabla \cdot u</td>
<td>$</td>
<td>4.390 · 10^{-3}</td>
<td>0.340 · 10^{-3}</td>
<td>1.927 · 10^{-3}</td>
</tr>
<tr>
<td>$</td>
<td>\det(e)</td>
<td>$</td>
<td>6.026 · 10^{-5}</td>
<td>1.242 · 10^{-5}</td>
<td>1.149 · 10^{-5}</td>
</tr>
<tr>
<td>$FA(c)$</td>
<td>0.886</td>
<td>0.012</td>
<td>0.875</td>
<td>0.008</td>
<td>0.803</td>
</tr>
<tr>
<td>$</td>
<td>\nabla p</td>
<td>$</td>
<td>6.452 · 10^{-7}</td>
<td>0.731 · 10^{-7}</td>
<td>6.680 · 10^{-7}</td>
</tr>
</tbody>
</table>

Table 2: Results of forward simulations. Mean and standard error (SE) of healthy and patients, and p-value from a two-tailed t-test comparing the two groups. Significant differences between healthy and patients are indicated in bold.

The next natural step will be to study full time series of real data recordings with breathing induced motion. In conclusion, dynamic T1-weighted MRI has a potential to visualize image changes related to renal fibrosis.

**Acknowledgement**

We want to thank Berit Sande for organizing the MR acquisitions of patients.

**References**

Evaluation of Depth-Depth Matching Algorithm for Following Human Liver whose Motion is Practical and also is Occluded by Human Body

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Introduction

Researchers have designed a number of approaches for matching the closest pairs from many 3D points for surface registration [1],[2],[3],[4]. In surgical navigation, it is necessary that the motions of the patient’s liver be translated to virtual liver motion on the PC in the operating room. However, because there are so many 3D points around a real liver, 3D registrations are time consuming. To overcome this drawback, we propose a new algorithm matching a small number of corresponding 2D depths. Furthermore, depth comparison is achieved very rapidly by processing all pixels in parallel using the GPU. Therefore, registration need not be time consuming.

In this framework, we can design and compare many types of 2D depth-depth comparison algorithms that evaluating pixels and images by their minimum, median, and average values and by changing the numbers of pixels and images, respectively. In this paper, in order to evaluate our algorithm without considering sensor errors, we use master and slave virtual livers on a PC in lieu of real and virtual livers in the operating room (Fig.1). The master liver corresponds to a real liver captured by a depth camera, while the slave liver corresponds to a virtual liver calculated by the Z-buffering of a GPU.

Previously, we discussed the basic advantages (fast speeds and no active or passive markers) of this type of algorithm [5]. Then, we evaluated its theoretical properties by changing pixel and image selections and numbers [6]. Further, in order to save calculation time, we divide
the search space defined by 6 degrees of freedom (DF) into 3 translational and 3 rotational [7]. In this study, by changing the number of pixels and images from 10 to 100, we check algorithm parameters for the average-pixel/median-image algorithm for tracking a master virtual liver whose motion is coincident to a real surgical patient's liver. We test our algorithm using several virtual occlusions mimicking the human body. As a result, we can see that 6D searching is perfect but very time consuming and 1D searching is useless for obtaining a reasonable path to follow. Therefore, we use 3 + 3D search, which is less time consuming and able to select a path to follow with no or few errors.

Figure 2: A real sequence of a human liver in the left, and its virtual sequence of its virtual liver in the right.

Figure 3: Pitch, yaw, and roll angles of the virtual liver illustrated in Fig. 16. They are described by red, green and blue lines, respectively. (Note that there is no translation of the virtual liver because x-, y- and z-translational movements are quite rare in real liver surgeries and also because our randomized algorithm is quite sensitive to translation motions).

Method

In this section, we describe the differences against our 2D depth-depth matching algorithms have been already published [5],[6],[7]. Firstly, in order to find a realistic sequence of liver motions for a master liver, we carefully watch several kinds of surgical videos shown in the left stroboscopes of Fig.2 and consequently design a practical sequence of master liver motions illustrated in the right stroboscopes of Fig.2. Secondly, a real liver is occluded by a human body during a surgery, and therefore we obstruct a master liver in PC by white some plate with a circle whose radius is flexibly changed (the right of Fig.2). In our previous evaluations of our algorithms [5],[6],[7], the 2D depth-depth image matching algorithm is robust for translational motion but unfortunately is not stable for rotational motion. In other
words, our algorithm has high sensitivity for translation movement but low sensitivity for rotation movement. Therefore, in this study, we especially pay attention to a practical sequence of rotational motions (Fig.3).

Realistic Experimental Results

For the realistic motion sequence of master virtual liver illustrated in Fig.2 and Fig.3, we change the search space, e.g., 1 DF search and 3 DF + 3 DF search, whose idea was already presented in [7], to track a master liver with its slave liver. Pixels are randomly evaluated by the average value in their distribution and images are evaluated as the median value in their distribution; the number of randomly selected pixels is changed to 10, 30, 50, and 100, respectively, and the number of images is changed to 10, 30, 50, and 100, respectively. Moreover, we change the occlusion to 0%, 30%, and 70%. Each algorithm generates quite different error sequences for pitch, yaw, and roll orientations, as illustrated in Fig.4 and Fig.5. Note that there is few translation errors along X, Y, and Z axes in all the above cases. In the 1 DF search, the error sequence increases when the occlusion percentage increases even though we use distances of 2 or 3. Therefore, this search cannot be used. The 3 DF + 3 DF search becomes much better. Even though we set the distance to 1, there are few errors. If and only if the occlusion percentage is set to 70%, we see a few errors of 2 degrees. This can be negligible in a real surgical operation. Needless to say, the 6 D search, whose computation cost is quite large, is the best (with no errors). However, although the 6 DF search is quite time consuming, the error difference compared with the 3 DF + 3 DF search is very small. In other words, in spite of a small computational cost, the 3 DF + 3 DF search algorithm generates a wonderful tracking sequence with few translation and rotation errors. Therefore, we can use the 3 DF + 3 DF search in place of 6 DF search. Finally, in our study, M is selected to be 100, and N is selected to be 10.

Conclusions

In this paper, for a realistic motion sequence of a master virtual liver with several kinds of occlusions, we evaluated many average-pixel/median-image algorithms whose pixel and
image selections and evaluations are changed. Our results show that 3 DF + 3 DF search whose optimal (M, N) pair is (10, 100) is the best. The algorithm is relatively fast and also gives few rotation errors. Furthermore, as long as GPUs become faster in the future, all remaining error problems will be solved.

ACKNOWLEDGMENTS

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References


Imaging-based modeling of the human larynx for simulation of airflow during exercise

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Background and aims

Obstruction of the central airways is typically expressed by exercise-induced inspiratory symptoms (EIIS) and is an important cause of exercise induced dyspnea in young and otherwise healthy individuals. This is a large, heterogeneous and vastly understudied group of patients, whose symptoms are often confused with those of asthma. Causal mechanisms for the symptoms are poorly understood, and the simplistic view that all EIIS is due to vocal cord dysfunction still hampers science and patient management.

The larynx (Figure 1) accounts for a significant fraction of total airway resistance at rest, and becomes even more important during exercise [1]. Laryngoscopy performed as symptoms evolve during increasing exercise is therefore pivotal. Furthermore, abnormalities vary between patients, and laryngoscopic findings are important for correct treatment and handling.

Surgical treatment of laryngeal obstruction has been shown to have a positive effect [2], but methods and protocols to guide the treatment algorithms for patients are needed.

We are constructing a computational model for the larynx, used to simulate the airflow. The aim is to understand the larynx’s role for breathing problems: which obstructions leads to problems, and why. The models and simulations will be guided and validated against results from the Continuous Laryngoscopy Exercise test, developed by researchers in Bergen. A realistic and flexible model of the larynx will give us a better understanding of the causal mechanisms behind inspiratory symptoms, which can be used as a guide in treatment.

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**Figure 1:** Normal larynx, as observed transnasally in a flexible laryngoscope, with the patient in the lower left corner.

**Figure 2:** Severe inspiratory adduction of the glottic space.
Method

The experimental measurements are collected using the Continuous Laryngoscopy Exercise (CLE) test, described in [3]. This method has been used for diagnosis and follow-up of patients with Exercise-Induced Laryngeal Obstruction (EILO) [4].

To reproduce the situation that provokes the symptoms, the patients run on a treadmill during transnasal laryngoscopy (Figure 4). In addition to the video from the laryngoscope, the patient’s upper body movements and breathing sounds are recorded, together with various physiological parameters like heart rate, heart rate reserve, O2/HR, and VO2/kg (Figure 5). See [3] for a detailed description. The second author and his group at Haukeland University Hospital is currently working to extend the measurements to include the pressure drop across the vocal folds.

We are collaborating with researchers from the Norwegian University of Life Sciences, where they are studying equine larynges using similar techniques [5]. Their pressure measurements from the airways of exercising horses are more detailed than the ones currently obtained by the CLE test for humans [5], and the researchers at NMBU have better access to excised (equine) larynges. We will use their data as a basis for constructing a detailed model of equine larynges. The geometry of equine and human larynges are similar, so the results from this study will be at least partly transferable.

To obtain the proper laryngeal geometry we use a combination of MRI and CT data acquired at HUS and public datasets available online (illustrated in Figure 5 with data from the Cancer Imaging Archive).

Based on this image data and data from the CLE test, we are in the process of constructing a computational model of the larynx using COMSOL Multiphysics, a finite-element based software package widely used in computer-aided engineering. This is done as a three-stage iterative process:

(i) Obtain a realistic geometry of the larynx for use in the simulation. This is achieved by using the image data from MRI together with techniques for segmenting the larynx from the images, and reconstructing a 3D model. (ii) Define the proper physics on the model, including the airflow through the larynx and its tissue-interaction. This involves techniques and results from computational fluid dynamics (CFD), in particular incompressible Navier-Stokes equations, turbulence modeling and fluid-structure interaction, guided by the experimental measurements and results from the literature on the respiratory system [6]. (iii) Simulate the airflow through various glottis geometries,
and compare the results with measurements from the CLE test. Based on the results in stage (iii), we update the model by tweaking stage (i)–(iii).

The model is cross-validated against datasets not used in the selection of model and simulation parameters.

The simulations will uncover the effect of geometry changes in the supraglottic region on the characteristics of the airflow through the larynx.

The project builds upon and extends various models and simulations of the larynx constructed by other researchers, e.g. [7], [8], [9].

**Discussion and outlook**

The current knowledge of the causal mechanisms for exercise-induced inspiratory symptoms is very limited. Using computational modeling and simulation we hope to increase our understanding of EIIS, and help guide treatment of the symptoms. A long-term goal of the project is to combine computational simulations with the CLE test and medical imaging of individual patients, enabling personalized intervention.

The methods used for modeling and simulation of the larynx can also be extended to other organ systems, extending the influence of engineering techniques in medicine.
Recognitions

The project is part of the multidisciplinary research group on Sports, Health and Function at Bergen University College. We thank the larynx working group based at Haukeland University Hospital and the research group of Eric Strand at NMBU for useful discussions. We also acknowledge support from the ICT engineering research program at Bergen University College, and the “Computational medicine” project (computationalmedicine.no).

References


Brain & Water - computational modeling of the aging brain

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Introduction

The role of water flow in the aging brain has recently received significant attention, as the water seems to play an important role in the development of dementia. One form of dementia, normal pressure hydrocephalus is characterized by hyperkinetic flow and abnormal pressure fluctuations of the cerebrospinal fluid in the water in the ventricles and subarachnoid space. Hyperkinetic flow is also involved in the disease Chiari, which often leads to remodeling of the spinal and the development of syringomyelia. Alzheimer disease on the other is associated with accumulation of plaque, called amyloid-beta in the extra-cellular water filled matrix inside the parenchyma. The accumulation is believed to be caused by reduced clearance by malfunctioning interstitial fluid flow. Both the cerebrospinal fluid and the interstitial fluid mainly consist of water and are continuously exchanging. The mechanisms behind the water transportation and exchange have been inadequately understood and recently new theories have been proposed. In particular, a pathway called the glymphatic system has been proposed. The proposed pathway is that water is driven through the parenchyma by hydrostatic pressure gradients arising from pressure difference in the arterial and venous part of the circulation. The pathway appears to be particularly active during sleep as the extracellular spaces are increase during this phase. In this talk we will present recent modeling studies that for the waterscape of the human brain. We will present both macro and micro-scale models that are used to understand the interaction of water and tissue and corresponding remodeling tissue. In particular we will try to demonstrate how modeling can add to and be combined with imaging.