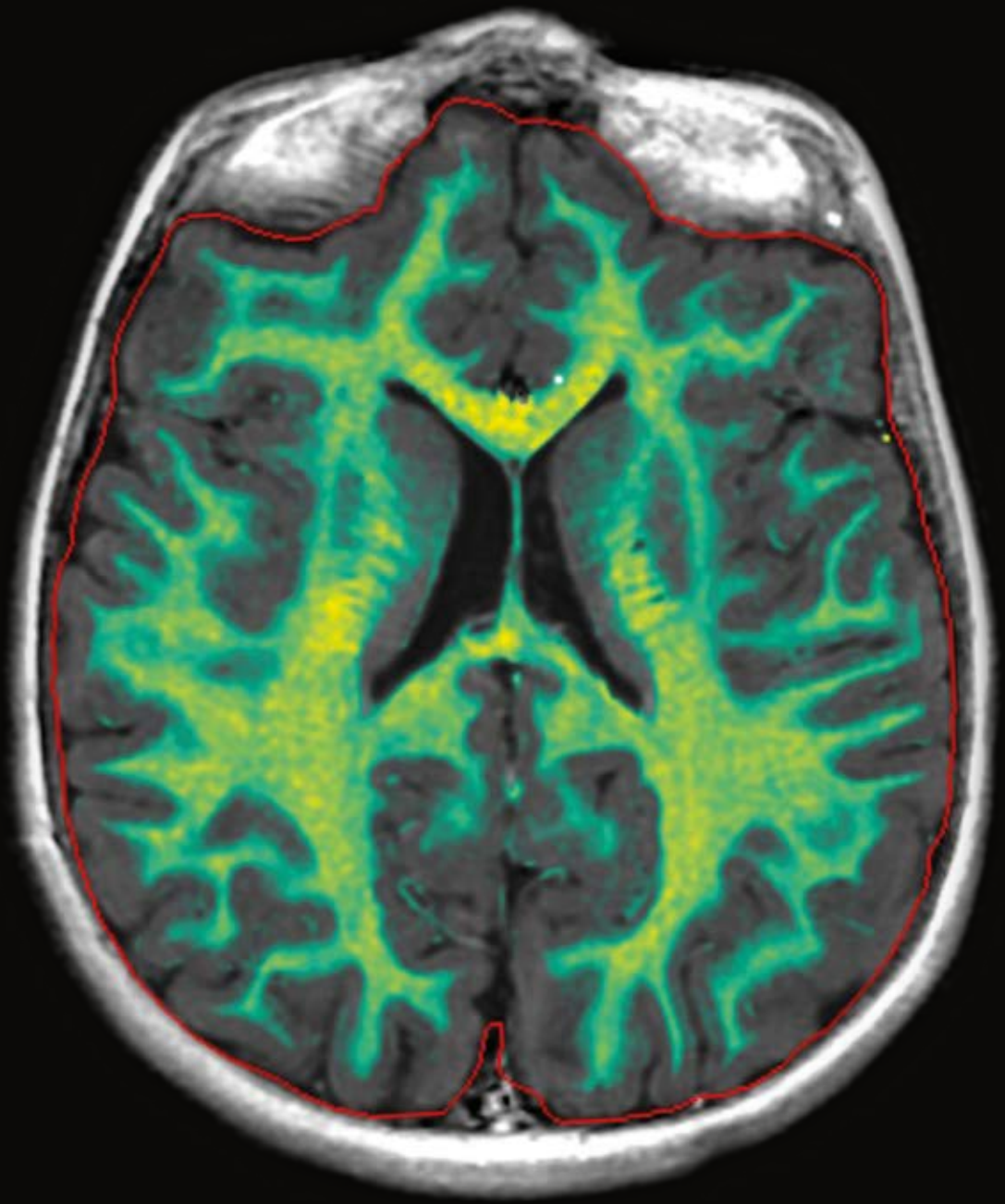
WELCOME TO THE EXCITING WORLD OF CMIV

ANNUAL SCIENTIFIC REPORT 2015

LINKÖPING UNIVERSITY



Project Leader, CMIV
Marie Waltersson

Production
Ariom Reklambyrå

Photography
CMIV
Oskar Lüren
David Einar
John Sandlund

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Visiting Address
Linköping University Hospital
Campus US
Entrance 1, floor 11
Linköping, Sweden

Postal Address
Linköping University
CMIV
581 85 Linköping
Sweden

info@cmiv.liu.se
www.liu.se/cmiv

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PREFACE

2015 was the busiest year ever for CMIV. The relocation into new facilities that we had prepared for during the last two years finally was effectuated. The new building taken into possession gives new opportunities to fulfill our goals and mission to conduct high-quality patient-centered interdisciplinary research.

The total available office space has increased four times and we now have room for three high-end magnetic resonance cameras, each optimized for different types of research, as well as two high-end computed tomography scanners. Furthermore, there are facilities for experimental purposes centrally placed in the department and separated from the rest of the facilities by airlocks, new meeting rooms and a virtual theater for up to 100 people with direct connection to the modalities. There are also new dedicated facilities for the digital pathology project with its own glass scanner, high-end monitors and pathology viewer.

Another exciting thing during the year was the start of the Swedish Heart-Lung Foundation study "SCAPIS" –Swedish Cardio Pulmonary bioImage Study in Linköping.

The goal is to find risk makers that predict who is at risk of developing heart or lung disease and how to prevent it through customized and personal treatment. The start of the trial has gone very well and the intended flow of volunteers, 10 per day was achieved during the year.

During the end of the year it was time to exchange the CMIV flagship projects to allow some of the other excellent projects to represent CMIV. The projects were selected by the scientific council. The new flagship projects are "Seeing organ function", which is a large Wallenberg project involving many CMIV researchers that aims to visualize the functions of the human body with focus on the heart and brain. "Liver function evaluation" a project that will develop new methods for diagnosing liver disease. The new technology is expected to result in safer liver surgery. Finally "Sleep abnormality network description" explores the neural networks of the human brain that are involved in the regulation of sleep. These are three outstanding projects that together continue to represent the multi-disciplinary research at CMIV.

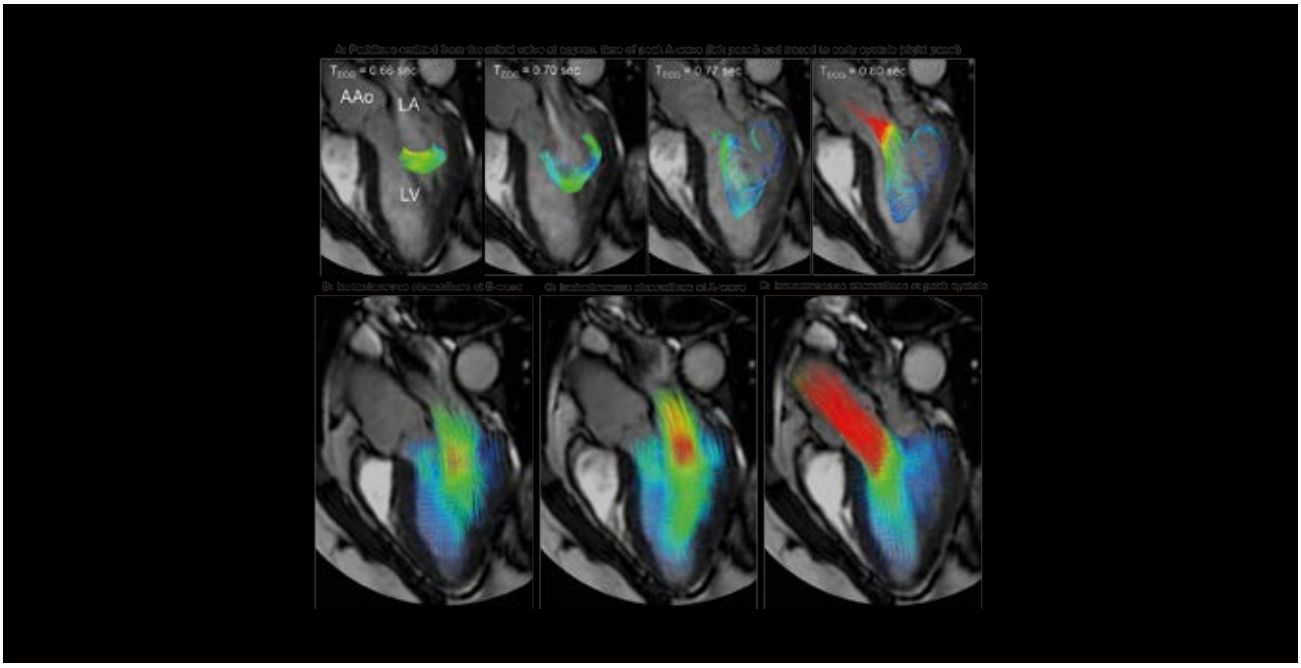
Sweden with Linköping in the front line is world leading in clinical use of digital pathology much thanks to the project "Optimized flow and IT tools for digital pathology". During the end of 2015 Region Östergötland, Linköping University and Sectra set up a research agreement to ensure continued research and innovation in the digital pathology field after the conclusion of the project.

This year many new scientists and PhD students were affiliated with CMIV and I am really looking forward to see what new collaborations will grow and spire during 2016.

Anders Persson
Director of CMIV

HIGHLIGHTS 2015

2015 has been an eventful year at CMIV with the move of the department and the start of SCAPIS. The research has expanded both with new projects and with an addition of new researchers. Here you will find the highlights of the year.



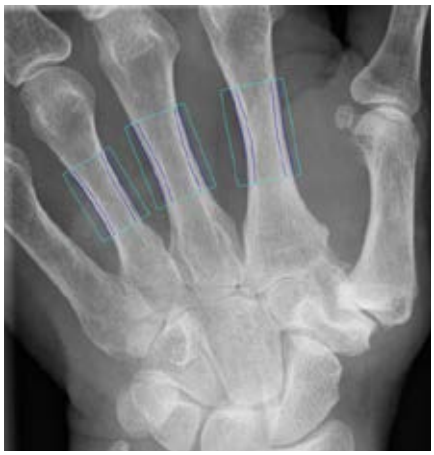
CONSENSUS STATEMENT ON 4D FLOW MRI

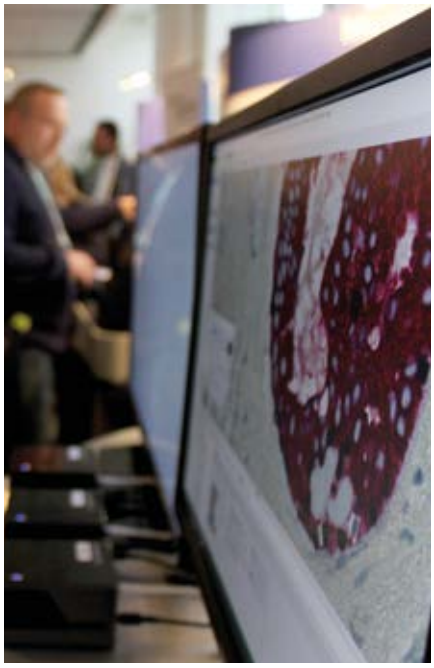
CMIV and the Department of Medical and Health Sciences scientists Petter Dyverfeldt, Carl-Johan Carlhäll and Tino Ebbers have published a consensus statement entitled "4D flow cardiovascular magnetic resonance consensus statement" with colleagues from Europe and the US.

The consensus statement addresses the current status and outlines future directions for research and clinical applications of advanced multidimensional MRI techniques for the assessment of cardiovascular blood flow. The article was published in Journal of Cardiovascular Magnetic Resonance.

MEDIA ATTENTION FOR OSTEOPOROSIS

A dissertation written by the CMIV PhD student Johan Kälvestens has received considerable media attention. The thesis describes a method to measure the risk of osteoporosis-related fractures and the possibility to use screening for early detection and treatment. Low-energy trauma and fragility fractures represent a major public health problem. The societal cost of the fragility fractures that occurred in Sweden 2010 has been estimated at €4 billion. The news has been addressed in several media including an interview on Swedish radio Östergötland.





NORDIC SYMPOSIUM ON DIGITAL PATHOLOGY 2015

The 3rd Nordic Symposium on digital pathology was held at Linköping Konsert and Kongress November 3-4 2015. There was a great interest and the symposium again had a new record with 190 visitors. CMIV has been the proud host since the beginning but the initiative for the symposium comes from the VINNOVA project "Optimized flows and IT tools for digitized pathology" with members in nine county councils and several industrial parts.

This year the keynote speakers were Nasir M. Rajpoot, PhD, SMIEEE, Qatar University, Qatar, University of Warwick, UK and Paul J. van Diest, MD, PhD, University Medical Center Utrecht.

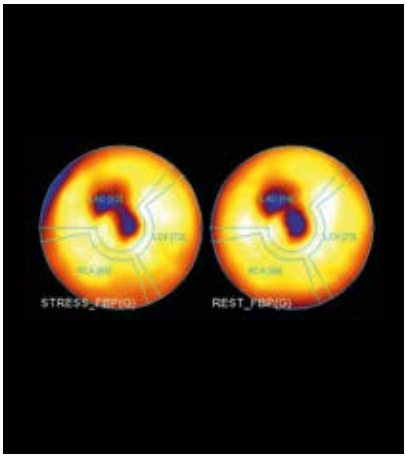
The subject of the digitization workshop where the audience was very much involved in creating the contents and sharing knowledge was validation. New this year was the breakfast seminars hosted by a selection of the exhibitors.

SURPRISING FINDINGS PRESENTED AT THE ECR CONGRESS

The study DOPPLER-CIP is a collaboration between researchers in six European countries and has been financed by the 7th Framework Programme. At CMIV the study is lead by Jan Engvall and Tino Ebbers.

DOPPLER-CIP has compared different non-invasive methods to determine the most useful tool at baseline for predicting risk of cardiac remodelling two years later. There are currently no guidelines for assessing a patient's risk for this type of deterioration. The general belief is that larger ventricles with thin walls (a typical 'infarct ventricle') would be at higher risk of remodelling, with a possible explanation for this being that there is increased wall stress in such hearts. But the findings in DOPPLER-CIP show that it is actually small hearts with thick walls that are more at risk.

If confirmed by other studies, this could completely change risk stratification among patients with stable coronary artery disease. These surprising results where presented at the ECR Congress 2015 in London.



SCAPIS

The national research initiative SCAPIS funded by the Heart-Lung Foundation and the Knut and Alice Wallenberg Foundation opened the doors for the first participants in Linköping. The goal is to be able to detect diseases in people's hearts, blood vessels and lungs with a simple blood test.

A total of 30 000 Swedes aged 50-64 years will undergo extensive studies at six university hospitals in Sweden. In Linköping 5000 of these will be examined over the next three years. Primarily, pulmonary and cardiac status, and so-called risk factors related to diseases of the heart, vascular and lung will be examined. At CMIV the participants will be examined with computed tomography and magnetic resonance tomography.

CMIV MOVES ON TO NEW FACILITIES

In September CMIV finalized the move from the old facilities to a new building nearby. With the new facilities CMIV increases its space considerable and the department now has room for two MR cameras and two CT:s. Despite the changed location the radiology department is still close by.

During the summer the CTs and 3T MRI were installed in the new labs while the 1.5T MRI was left in the old department to make space for a second 3T MRI that will be installed spring 2016.

The move means a lot for CMIV as it allows the research efforts to grow. The lecture hall Wranne with its VR theatre is now bigger and three new meeting rooms are available. In the middle of the department two labs approved for work with animals are built. The rooms have their own ventilation system and air locks for safe handling of animals.

VISIT FROM THE LIFE SCIENCE COORDINATOR

Anders Lönnberg, newly appointed national coordinator of life science by the Swedish government recently visited CMIV. On his agenda is to strengthen the collaboration between the healthcare, the academic research and the industry.

– The kind of close relationship between healthcare and research that is found at CMIV is not found in many places in the country. says Anders Lönnberg.

AUNT MINNIE

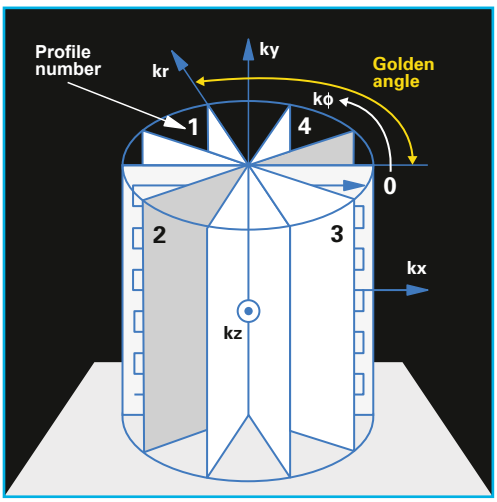
During ECR 2015 Aunt Minnie Europe interviewed Professor Anders Persson about the new Swedish National guidelines for post mortem imaging. It's the first systematic review done in the field worldwide. He was asked what makes a good forensic radiologist and answered that they need to be opened minded and curious. It's also important to have knowledge in forensic science as well as a good collaboration with a skilled forensic scientist.

Post mortem imaging is an important method that can complement the forensic investigation and possibly replace the medical autopsy in some cases.

CMIV IMAGING CHAIN

When CMIV was initiated, the vision was to gather all the components of medical imaging and visualization in one place. And at the same time create a whole new type of research environment where scientists, technicians and medical doctors could work close together with immediate access to the patients. A place where there was no distance between research and clinical needs. Since the start in 2002, CMIV has grown into the vision and it is now our everyday routine.

Information is gathered using novel imaging equipment

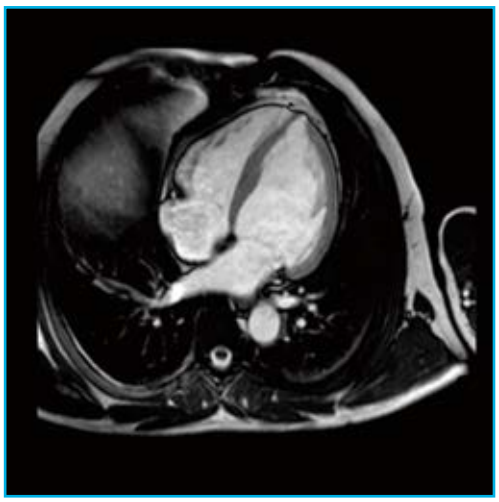


Raw data is processed using complex calculations and algorithms

Today, CMIV conducts focused front-line retsearch within multi-disciplinary projects providing solutions to tomorrow's clinical issues. The mission is to develop future methods and tools for image analysis and visualization for applications within health care and medical research.

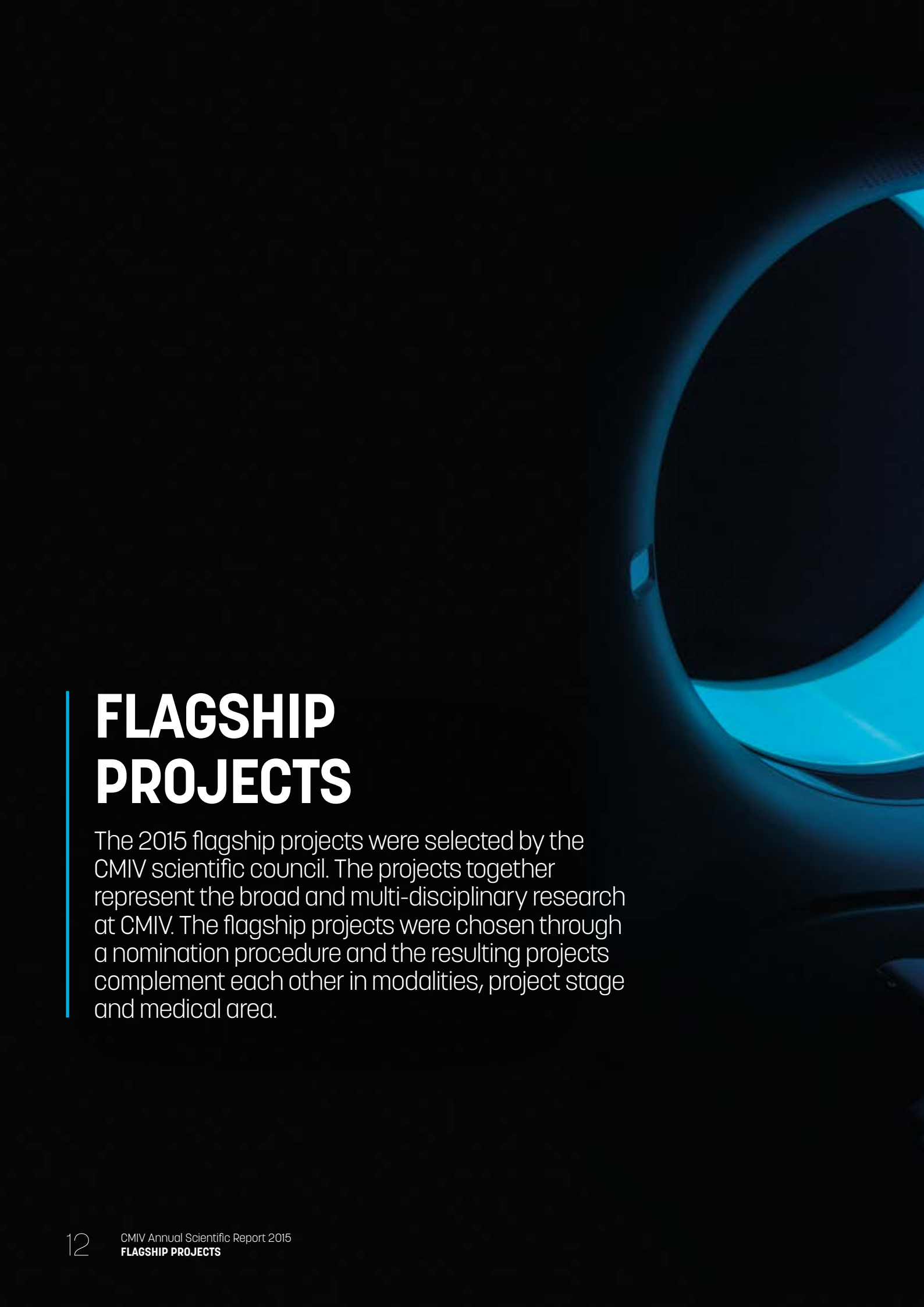
CMIV has a unique constellation in which research in the university provides the opportunity for clinical benefit in the region while the industry benefits nationally and internationally. The activities aim to combine different demands were the university seeks publications in high quality journals and the region wishes that the research and development comes to patient benefit. CMIVs organization centrally located within the university hospital creates conditions that combine these requirements. Results from basic research in universities can be utilized in clinical research which can then result in scientific publications, and patient cure.

The research projects at CMIV are all part of the imaging chain. Projects move dynamically through the chain and researchers from different disciplines work together to reach the goal of patient benefit. Focused research and development in all steps of the chain is important to continue to improve quality of care. In this way a technical solution in one medical field may be found useful in other fields as well. As it is or, moving back down the chain, inspire to new solutions no one even thought was possible.



Important findings are visualized in a comprehensive way

Images and findings are used in patient care



FLAGSHIP PROJECTS

The 2015 flagship projects were selected by the CMIV scientific council. The projects together represent the broad and multi-disciplinary research at CMIV. The flagship projects were chosen through a nomination procedure and the resulting projects complement each other in modalities, project stage and medical area.

SEEING ORGAN FUNCTION

The main cause of death in our part of the world is cardiovascular disease and the fastest growing cause of death is degenerative brain diseases. In this project, we hope to contribute to the health care fight against these diseases. The goal is to create image-based patient-specific models that explore organ function through simulation, enable breakthroughs in research on organ function and to use patient-specific functional organ models in the diagnostic workflow.

In the diagnosis of cardiovascular diseases anatomical measurement of arterial constriction may be supplemented with patient-specific estimates of the constriction effects on blood pressure and flow. Simulation and MRI measurements of the three-dimensional blood flow provide a deeper insight into disease mechanisms in e.g. heart failure.

To diagnose degenerative brain diseases the centers that control brain functions and the connections between them needs to be localized. New MRI techniques can provide this information and provide the basis for image-based measurement of disease severity in e.g. Alzheimer's disease.

-We choose to focus on the heart and brain, as they are both vital organs that are essentially different from each other, says Professor Anders Ynnerman, project manager of seeing organ function.

-Also, CMIV has substantial knowledge in both fields with proven track record of world-class research.

In both areas different types of functional imaging are progressively complementing the traditional imaging, and there is strong medical motivation for accelerating this progress. The project takes on the urgent task of developing new methods to capture,

PROJECT INFORMATION

PROJECT NAME
Seeing Organ Function

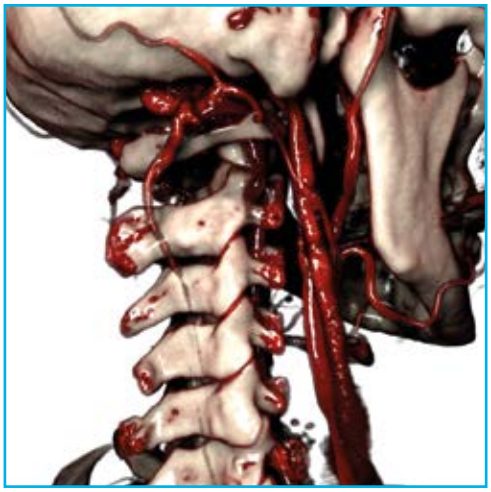
PROJECT LEADER
Anders Ynnerman

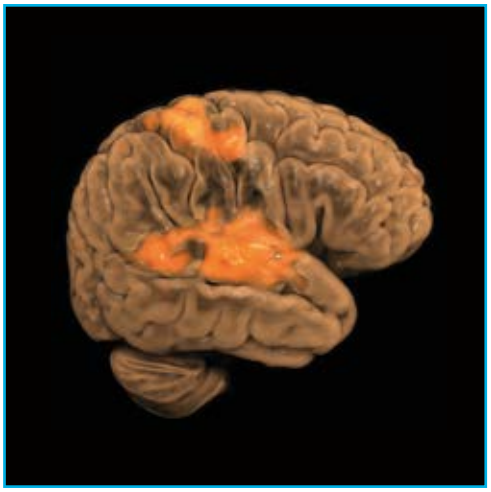
MAIN PROJECT PARTICIPANTS
Anders Ynnerman, Magnus Borga, Tino Ebbers, Maria Engström, Markus Heilig (MD), Ingrid Hotz, Matts Karlsson, Hans Knutsson, Peter Lundberg, Anders Persson (MD), Karin Wårdell

GRANTS
KAW

KEY PUBLICATIONS
Sigfridsson A, Petersson S, Carlhäll CJ, Ebbers T. 4D flow MRI using spiral acquisition. Magn Res in Med. 2012;68:1065-1073.

Markl M, Kilner PJ, and Ebbers T. Comprehensive 4D velocity mapping of the heart and great vessels by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2011; 13(1): 7.





> "To head a visionary project of this kind, with this high impact in the area of medical IT is a privilege"
>
> **- Anders Ynnerman**

process and present this rich functional information.

-We start with a medical problem and work interdisciplinary, linking medical research and clinical use with novel technical approaches, to find new solutions, Anders continues.

The project takes into account the complex mathematical concepts (vectors and tensors) that constitute the functional data and will specifically study the relation between structure and function of the body's organs.

An important problem for the sub-project *Data collection and enrichment* is to integrate functional and structural information from different scales.

Image based organ simulation will create patient-specific models of macroscopic and microscopic blood flow as well as the electrical activity of the heart and brain cells.

Interactive multi-dimensional organ visualization aims to create new visual representations to increase physicians and medical researchers' understanding of the functional information, for example by fusing data of different types from various image sources.

System Integration, finally, combines the results from the three technical sub-projects into integrated tools for studying cardiac and brain function. This includes image-based models of the function of the individual patient's heart and integration of data about brain activity, relations between the various centers and the concentration of neurotransmitters.

Seeing organ function is a visionary project with ambitious goals. It will bring together the expertise ranging from medicine, over medical visualization to image analysis and biomedical engineering found at CMIV. An advantage is that the research team has worked together in multidisciplinary projects for a long time.

-This is the first big project that engages CMIV as a whole, says Anders. The project is important for the development of image-based health care and takes on very important technical challenges.

-To head a visionary project of this kind, with this high impact in the area of medical IT is a privilege, Anders continues.

The project finances a number of Postdocs all working on part of the research agenda. CMIV as a center holds together the project parts in the common vision. The results will span from novel technical solutions to fundamental understanding of human organs and development of new clinical tools.

-CMIV provides the unique setting for this type of project by bridging the gap between technology and medicine, Anders explains.

LIVER FUNCTION EVALUATION

The liver is an important organ involved in vital processes as metabolism and removal of toxins. The western way of life is putting a high strain on the organ and liver diseases are consequently increasing. Liver Function Evaluation is a clinical research project that with the help of magnetic resonance (MR) will develop new methods for diagnosing liver disease. The new technology is expected to result in safer liver surgery and better treatment of diffuse liver diseases.

Many malignant liver diseases are diagnosed when they are in an advanced stage and the liver may be seriously damaged. At that time, surgery or liver transplantation is often the only curable treatment option. In order for the patient to survive a liver tumor operation, a healthy piece of the liver has to be left in the body. The liver is then growing during 4-5 weeks to regain almost full size and function. The first week after the surgery is a critical time since the small sized liver has to manage the job of a full liver.

Today, determination of how much of the liver to remove is difficult as only a rough estimate of the liver function can be made. Occasionally, patients may suffer from liver failure following radical surgery. On the other hand, some patients are wrongly judged unfit for surgery when the rough estimate suggests that they will not survive the procedure. With a better estimate of size and function in the liver residue more patients could be surgical candidates.

-The research project started when the hepatologist Stergios Kechagias asked me if I could help him to measure fat accumulation in the liver. After that the project has just continued to grow and evolve, says Professor Peter

PROJECT NAME
Liver Function Evaluation

PROJECT LEADER
Peter Lundberg, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Per Sandström, Stergios Kechagias, Mattias Ekstedt, Olof Dahlqvist Leinhard, Nils Dahlström, Mikael Forsgren, Markus Karlsson, Thobias Romu, Patrik Nasr, Johan Kihlberg, Anna Lindhoff Larsson, Gunnar Cedersund, Bengt Norén, Tommy Johansson, Torkel Brismar, Martin Henriksson, Lars-Åke Levin

GRANTS
Swedish Research Council (VR/NT) 2009-2011/2012
Swedish Research Council (VR/MH) 2013-2015/2016
VINNOVA 2013-2017
Swedish Research Council (VR/NT) 2015-2018/2019

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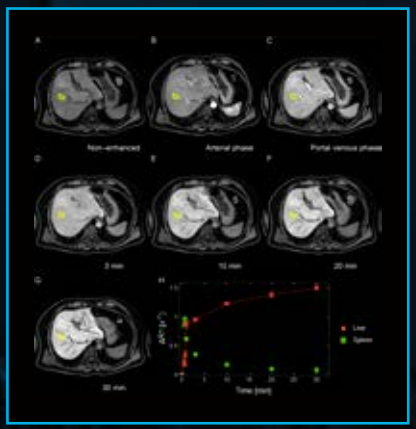
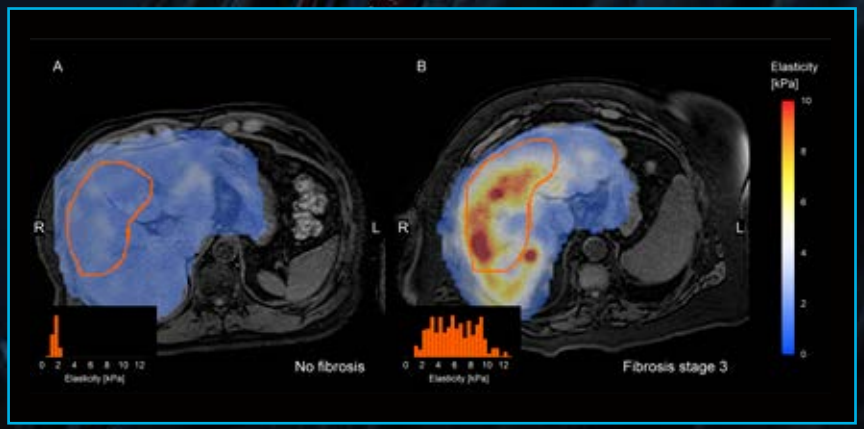
Norén B, Forsgren MF, Dahlqvist Leinhard O, Dahlström N, Kihlberg J, Romu T, Kechagias S, Almer S, Smedby Ö, Lundberg P (2013) Separation of Advanced from Mild Hepatic Fibrosis by Quantification of the Hepatobiliary Uptake of Gd-EOB-DTPA Eur Radiol 2013 Jan;23(1):174-81. doi: 10.1007/s00330-012-2583-2. Epub 2012 Jul 27.

Dahlqvist Leinhard O, Dahlström N, Kihlberg J, Sandström, P., Brismar TB, Smedby Ö, and Lundberg P. (2012) Quantifying differences in hepatic uptake of the liver specific contrast agents Gd-EOB-DTPA and Gd-BOPTA: a pilot study. Eur Radiol. 2012 Mar;22(3):642-53. Epub 2011 Oct 9.

Forsgren MF, Dahlqvist Leinhard O, Cedersund G, Lundberg P (2014) Physiologically Realistic and Validated Mathematical Liver Model Revels Hepatobiliary Transfer Rates for Gd-EOB-DTPA Using Human DCE-MRI Data PLoS ON, 2014 Apr 18;9(4):e95700. doi: 10.1371/journal.pone.0095700. eCollection 2014.

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Fibrosis stage 3

> "I'm passionate about my research being closely related to healthcare. I always want to do things that are of direct value for the patient."
>
> **- Peter Lundberg**

Lundberg, project manager of "Liver function evaluation".

With the help of MR it is possible to measure several parameters in the liver without invasive procedures. The MR also enables a better overview of the liver status as a whole compared to biopsies, as they only show status at the location where the sample is taken. If the biopsy is extracted from the wrong area there is a risk that important information is overlooked.

The magnetic resonance technology may, among other things, be used to measure the amount of fat in the liver, measure the uptake of a contrast agent to get an idea of how well the liver works and measure levels of many different elements, including iron and phosphorus compounds. Peter's research group has developed multimodal methods for analyzing the liver.

-Our MR protocol for analyzing the liver status is now ready to be tested in the workflow at other hospitals. Peter continues. This is an important step in showing that our method is ready for routine use. Health economists will then analyze if the method has an economical value, or may increase the quality of care.

One of the MR methods used is elastography. The examination shows fibrosis, formation of connective tissue, in the liver. The connective tissue makes the liver less flexible and impairs its normal elasticity. During MR mechanical vibrations are sent into the patient´s body. The vibrations are propagated differently depending on the flexibility of the tissue. Through registration of the different vibrations the MR-scanner can separate healthy from diseased tissue regions.

-Together with the CMIV spinoff AMRA AB we are developing a tool where data from different types of liver measurements may be gathered. The data will support the physician in determine how to treat the patient, Peter explains.

Apart from MR data the tool will also be able to collect other types of information. In line with this the project is investigating the possibility to use digital pathology in analyzing the biopsies and instead of a visual examination use image analysis to obtain a value of for example fat infiltration.

Peter says that the project is dependent on the collaboration between university, healthcare and industry.

-CMIV means everything for the project. Without the center it would be impossible to realize our ideas since we need the competence from all three cornerstones as well as advanced tools in an environment suitable for patients.

-I'm passionate about my research being closely related to healthcare. I always want to do things that are of direct value for the patient, Peter concludes.

SAND:MAN

Sleep is a naturally recurring state, which still is a mystery since its function and purpose is not fully understood. In this project we explore the neural networks of the human brain that are involved in the regulation of sleep and wakefulness. For this quest, patients with sleep disorders provide keys to the understanding of why we sleep and why we wake up.

In the early 20th century von Economo detected brain areas involved in the regulation of sleep and wakefulness by investigating patients with excessive sleepiness due to brain inflammation. Almost a century later, scientists discovered the important sleep-regulating substance, orexin, which is produced in a certain area of the brain: the hypothalamus. Loss of orexin causes the sleep disorder narcolepsy, which is characterized by involuntary daytime sleep attacks and poor nighttime sleep.

Kleine-Levin syndrome is another sleep disorder where the patients can sleep for extremely long periods, up to several weeks. Unlike narcolepsy, the cause of Kleine-Levin syndrome is still unknown. The relations between disease mechanisms and the symptoms in Kleine-Levin syndrome as well as in narcolepsy are still unresolved.

-The aim of this project is to investigate brain function and structure in these sleep disorders in order to explain the link between neurobiology, pathology, and the patients' symptoms, says Professor Maria Engström project manager of the SAND:MAN project.

Maria Engström is a former nurse who went back to school to study theoretical physics. Now she combines her

PROJECT INFORMATION

PROJECT NAME
Sleep Abnormality Network Description: Modeling and Analysis in Neuroimaging (SAND:MAN)

PROJECT LEADER
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Natasha Morales-Drissi, Suzanne Witt, Peter Lundberg, Anders Tisell, Sofie Tapper, Thomas Karlsson, Anna Wretman, Anne-Marie Landtblom, Tove Hallböök, Atilla Szakacs, Martin Ulander

GRANTS
The Research Council of South East Sweden (FORSS)
The Kleine-Levin Syndrome (KLS) foundation

KEY PUBLICATIONS
M. Engström, T. Karlsson, A-M Landtblom. Thalamic Activation in the Kleine-Levin Syndrome. Sleep, 37:379-386, 2014.

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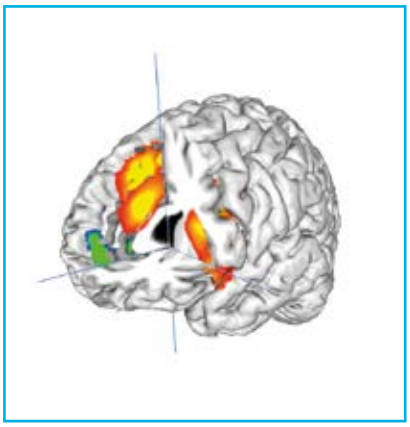


Figure 1 (sandman_WM): Brain activation in narcolepsy patients and healthy controls during working memory performance.

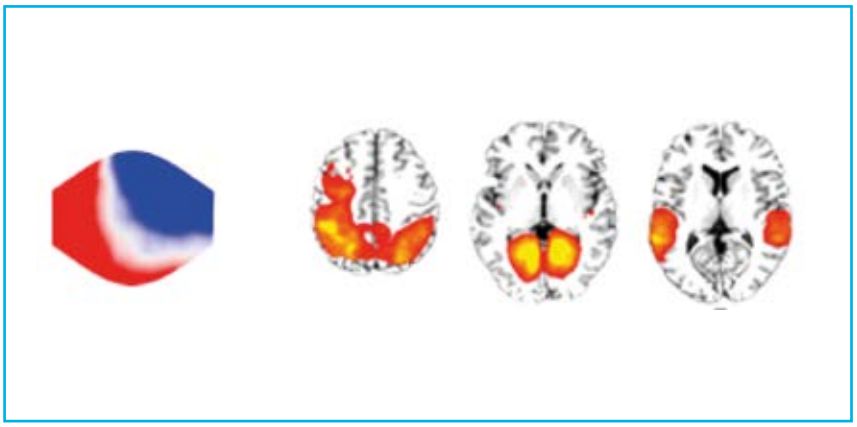


Figure 2 (sandmanMS-RS): EEG microstate A and the corresponding resting state networks into which narcolepsy patients have less transition probability.

knowledge in medicine and physics to investigate how the brain works.

-I have a genuine interest in finding out how things work. It is what pushes me forward in my research.

Brain function and structure is investigated by magnetic resonance imaging (MRI) and simultaneous electroencephalography (EEG). Brain activity can be monitored with a method called functional magnetic resonance imaging (fMRI). The method is based on the fact that the blood flow is increased in activated areas of the brain to supply energy and oxygen. It is the blood oxygenation differences between active state and rest that is measured with fMRI. In the beginning Maria optimized the method for surgery planning but when she met Professor Anne-Marie Landtblom who is interested in the Klein-Levin syndrome they started to collaborate.

-In the beginning it was difficult to know how to interpret the results. Is it good with high brain activity or should it be low? Maria explains.

To further understand what the method measures and how the brain works the research group uses mathematical modeling and system biology. What is biologically causing the increased blood flow? Maria is building theoretical models of the process and tests it against the data collected from patients.

To understand the sleep disorders are of equal importance as to understand how normal sleep works for the research group. Ultimately it's about understanding the brain.

-When trying to understand the normal function it can be very helpful to start with investigating something that is wrong. It's part of a detective work, Maria continues.

-We investigate brain function related to working memory and attention, as well as during rest. We also measure neurotransmitter GABA and glutamate concentrations by magnetic resonance spectroscopy (MRS) and tissue properties by quantitative MRI.

The results show that compared to healthy individuals, patients with the Klein-Levin syndrome have cognitive difficulties and a reduced working memory. Narcolepsy patients on the other hand have an intact working memory and the attention problems come from lack of sleep. Patients with narcolepsy have alterations in EEG micro states related to function in the brain's attentional network during rest and during working memory performance (figures 1 and 2).

Finding out more about the pathology behind sleep disorders is important for finding better treatments and better methods to monitor the effect of the treatment. CMIV offers the arena where professionals from different disciplines can meet that wouldn´t otherwise not naturally meet. To work with patients requires an environment that prioritizes the research and at the same time takes care of the individual patient.

"I have a genuine interest in finding out how things work. It is what pushes me forward in my research"

- Maria Engström

RESEARCH PROJECTS

The research within CMIV is based on innovations in medical image science and visualization. Future directions will strengthen the interdisciplinary approach to enhance the possibilities of image-based diagnosis and treatment. At CMIV research is conducted within several medical problem areas, combining a number of technologies for novel application within clinical routine, medical research and dissemination of information. Here you will find a selection of the research projects at CMIV.

Popular Scientific Summary
Tino Ebbers

PROJECT NAME
Assessment of cardiovascular blood flow using 4D flow MRI

PROJECT LEADER
Tino Ebbers, Department of Medical and Health Sciences, Division of Cardiovascular Medicine & Department of Science and Technology, Division of Media and Information Technology

MAIN PROJECT PARTICIPANTS
Senior research leaders: Tino Ebbers, Carl-Johan Carlhäll, Jan Engvall, Petter Dyverfeldt.

Post Doc: Jonas Lantz.

PhD students: Sven Petersson, Jonatan Eriksson, Belén Casas Garcia, Mariana Bustamante.

GRANTS
Swedish Research Council 2011-2013
European Research Council 2013-2017

KEY PUBLICATIONS (MAX 3)
Eriksson J, Bolger AF, Carlhäll C-J, and Ebbers T. Spatial heterogeneity of four-dimensional relative pressure fields in the human left ventricle. Magn Res in Med. 2015

Sigfridsson A, Petersson S, Carlhäll CJ, Ebbers T. 4D flow MRI using spiral acquisition. Magn Res in Med. 2012;68:1065-1073.

Markl M, Kilner PJ, and Ebbers T. Comprehensive 4D velocity mapping of the heart and great vessels by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2011; 13(1): 7.

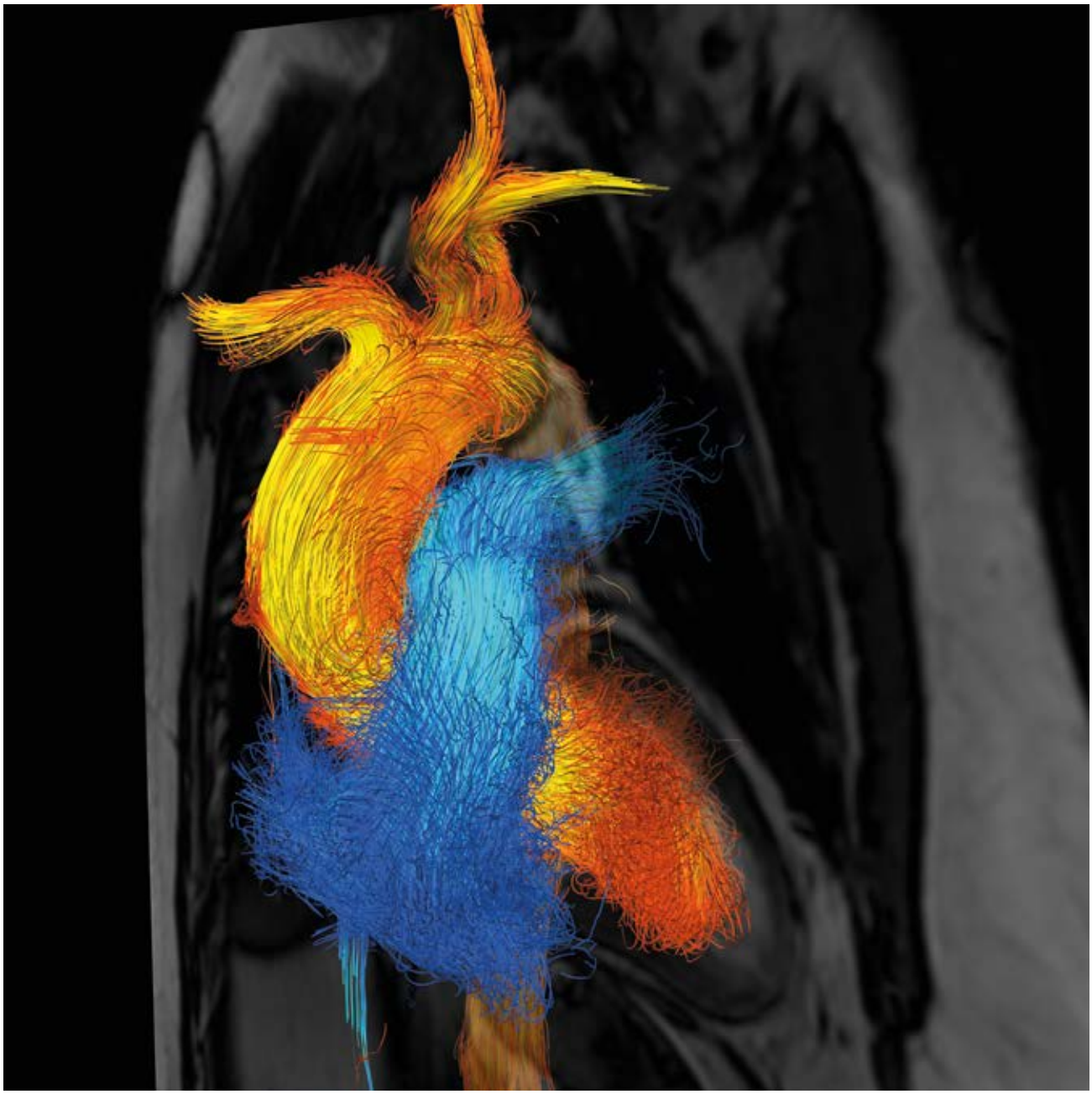
ASSESSMENT OF CARDIOVASCULAR BLOOD FLOW USING 4D FLOW MRI

The primary purpose of the cardiovascular system is to drive, control and maintain blood flow to all parts of the body. The heart acts as the pump in this system, and has as task to move blood through the body. Using a complex and ingenious interplay between muscle contraction and valve function, it fulfills this task amazingly efficient during rest and exercise for about a hundred years.

Sometimes small abnormalities occur at birth or by disease, cardiovascular diseases are often found in obesity, diabetes and an aging population. The heart can compensate for these to some extent, but they can also lead to inefficient pump function and sometimes to a cascade of more severe abnormalities.

Despite the primacy of flow, cardiac diagnostics still rely almost exclusively on tools focused on morphological assessment. Flow characteristics are often assumed rather than measured directly. Suitable non-invasive tools for characterizing and measuring flow dynamics are needed to push our medical effectiveness to the next level.

Imaging that is focused on answering the most relevant questions, with an



eye towards tangible improvements in diagnosis, therapy and outcomes can facilitate treatment of cardiac patients with higher quality and lower costs.

The objective of this project is to develop the next generation of methods for the non-invasive quantitative assessment of cardiac diseases and therapies by focusing on blood flow dynamics, with the goals of earlier and more accurate detection and improved management of cardiac diseases.

The project has developed a method for flow quantification using MRI which allows for simultaneous measurement of time-resolved, three-dimensional (time + 3D = 4D) blood flow velocity and turbulence intensity. This method reveals blood flow patterns in the heart and the large vessels.

Cardiovascular blood flow is still to a large extent unknown. In order to define relevant parameters, development of analysis and visualization approaches and studies of normal and abnormal blood flow have to be performed in chorus.

Studying cardiovascular blood flow dynamics in patients and healthy subjects will improve our understanding of the roles of flow dynamics in health and disease, leading to improved cardiac diagnostics, novel assessments of pharmaceutical, interventional, and surgical therapies, and promoting exploration of new avenues for management of cardiac disorders.

Popular Scientific Summary
Petter Dyverfeldt

QUANTIFICATION OF HEMODYNAMIC MARKERS WITH NOVEL 4D FLOW MRI

PROJECT NAME
Quantification of Hemodynamic Markers with Novel 4D Magnetic Resonance Flow Imaging

PROJECT LEADER
Petter Dyverfeldt, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

MAIN PROJECT PARTICIPANTS
Magnus Ziegler, Jonas Lantz, Carl-Johan Carlhäll, Tino Ebbers, Ebo de Muinck, Toste Länne

GRANTS
Swedish Research Council, Forskningsrådet i Sydöstra Sverige (FORSS)

KEY PUBLICATIONS

Dyverfeldt P, Bissell M, Barker AJ, Bolger AF, Carlhäll CJ, Ebbers T, Francois CJ, Frydrychowicz A, Geiger J, Giese D, Hope MD, Kilner P, Kozerke S, Myerson S, Neubauer S, Wieben O, Markl M. 4D Flow CMR Consensus Statement. J Cardiovasc Magn Reson 2015, 17(1):174.

Dyverfeldt P, Ebbers T, Länne T. Pulse Wave Velocity with 4D Flow MRI: Systematic Differences and Age-Related Regional Vascular Stiffness. Magn Reson Imaging 2014;32(10):1266–71.

Hope MD, Sigovan M, Wrenn SJ, Saloner D, Dyverfeldt P. MRI hemodynamic markers of progressive bicuspid aortic valve-related aortic disease. J Magn Reson Imaging 2014;40(1):140–5.

The main function of the arteries is to distribute blood flow to the organs of our body. Arteries can sometimes become constricted and this may affect the blood flow to downstream vasculature.

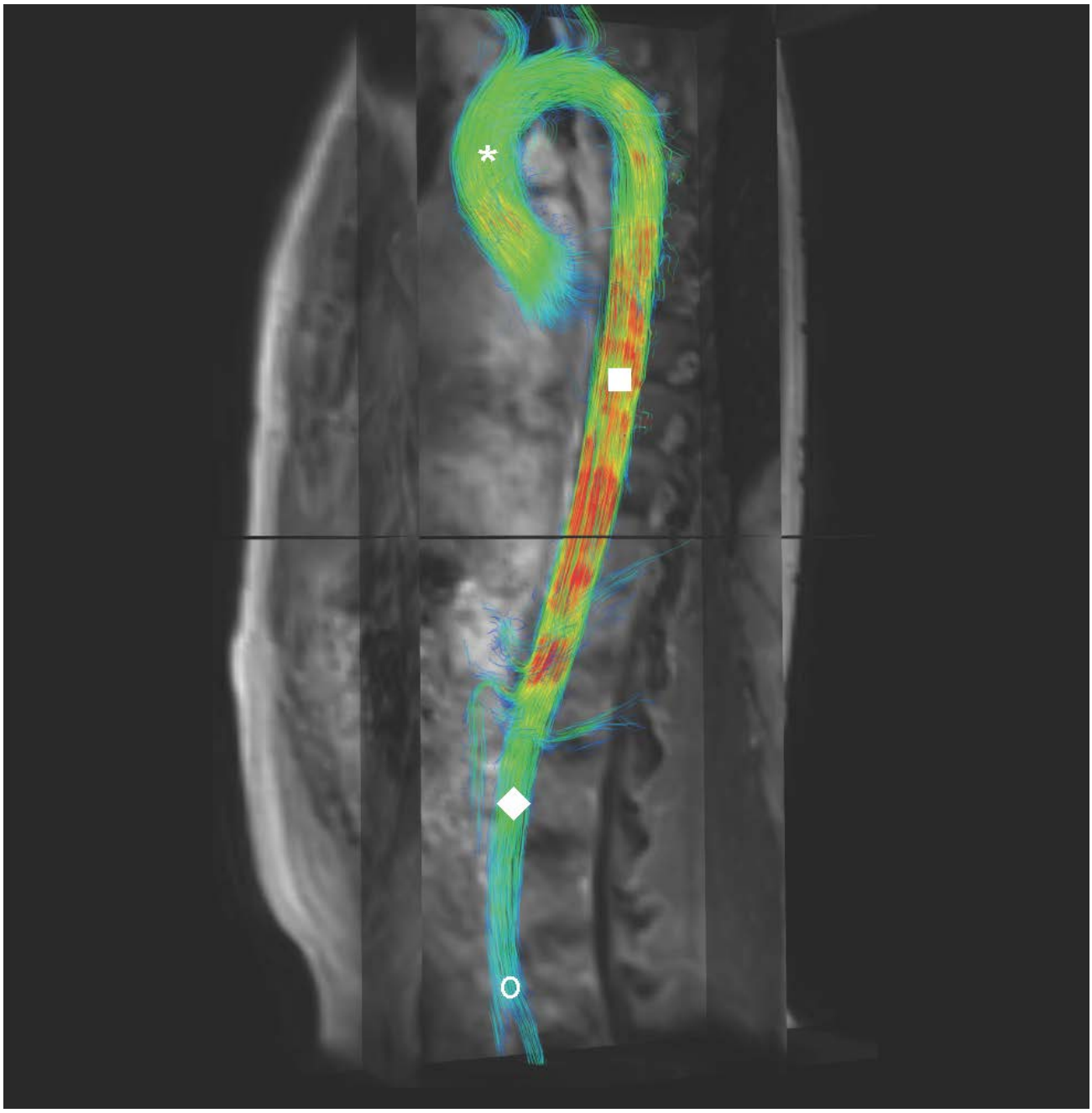
It has been known for quite some time that abnormal blood flow is both an indicator of arterial disease and a risk factor for disease progression. Unfortunately, appropriate tools for measuring these flow effects in humans have been lacking. Consequently, we still use measures such as the size of a constriction to assess the status of the blood flow.

The purpose of this project is to develop methods for the determination of some of the most important aspects of blood flow.

Many arterial diseases are related to atherosclerosis. The atherosclerotic disease process starts with deposition of fat in the arterial wall. This early process makes the arteries stiffer. Arterial stiffness alters the pressure wave that the heart generates when it contracts. Altered pressure wave is a strong marker of several cardiovascular diseases. If we could measure the pressure variations in the arteries we could increase and improve the clinical applicability of pressure wave measurements.

Advanced stages of atherosclerotic disease are characterized by large deposits of fat in the arterial wall. These deposits, plaques, constrict the arterial lumen. The plaques may rupture, which can cause stroke or a heart attack. The blood flow in constricted arteries can become turbulent. Several studies indicate that turbulent forces increase the vulnerability of the plaques and their risk of rupture. However, methods that permit assessment of the impact of turbulent forces do not exist.

We develop methods for the determination of pressure wave velocity and the effects of turbulent flow on the vessel wall. In achieving our goals we plan to



4D flow MRI visualization of blood flow in the whole aorta of a normal volunteer. Asterix: Ascending aorta. Square: descending aorta. Diamond: abdominal aorta. Circle: iliac bifurcation.

use an advanced magnetic resonance imaging (MRI) technique referred to as 4D flow MRI, which permits comprehensive assessment of time-varying three-dimensional (time + 3D = 4D) blood flows.

Additionally, we want to be able to measure these aspects of blood flow in the coronary arteries, where many of the most dangerous vascular diseases happen. 4D flow MRI is today used primarily to study blood flow in the heart and the greater vessels. We will improve the technique for application in coronary arteries. Successful application of MRI in the coronary arteries requires that the motion of the arteries due to breathing and cardiac contraction be taken into account. If this is not done the images get blurry.

Being able to measure aspects of blood flow that have previously not been measurable will lead to an increased understanding of the interrelationship between blood flow and vascular disease. It will also open up for new ways to assess and risk-stratify vascular disease. This will offer improved care for the vast population of patients with vascular disease and financial benefits for the health care system.

Popular Scientific Summary
Jan Engvall and Tino Ebbers

PROJECT NAME
DOPPLER-CIP

PROJECT LEADER
Tino Ebbers and Jan Engvall, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

MAIN PROJECT PARTICIPANTS
Johan Kihlberg, Petter Dyverfeldt, Eva Olsson, Carl-Johan Carlhäll, Lars-Åke Levin, Magnus Husberg, Magnus Janzon

GRANTS
EU grant, 2010-2014

KEY PUBLICATIONS
Kihlberg J, Haraldsson H, Sigfridsson A, Ebbers T, Engvall J. Clinical experience of deformation imaging using DENSE for detecting abnormal cardiac segments. Journal of Cardiovascular Magnetic Resonance 2015;17:50 doi: 10.1186/s12968-015-0155-8.

Fredriksson AF, Svalbring E, Eriksson J, Dyverfeldt P, Alehagen U, Engvall J, Ebbers T, Carlhäll C. 4D flow CMR can detect subtle right ventricular dysfunction in primary left ventricular disease. J Magn Reson Imaging. 2015 Jul 24. doi: 10.1002/jmri.25015. [Epub ahead of print] PMID: 26213253.

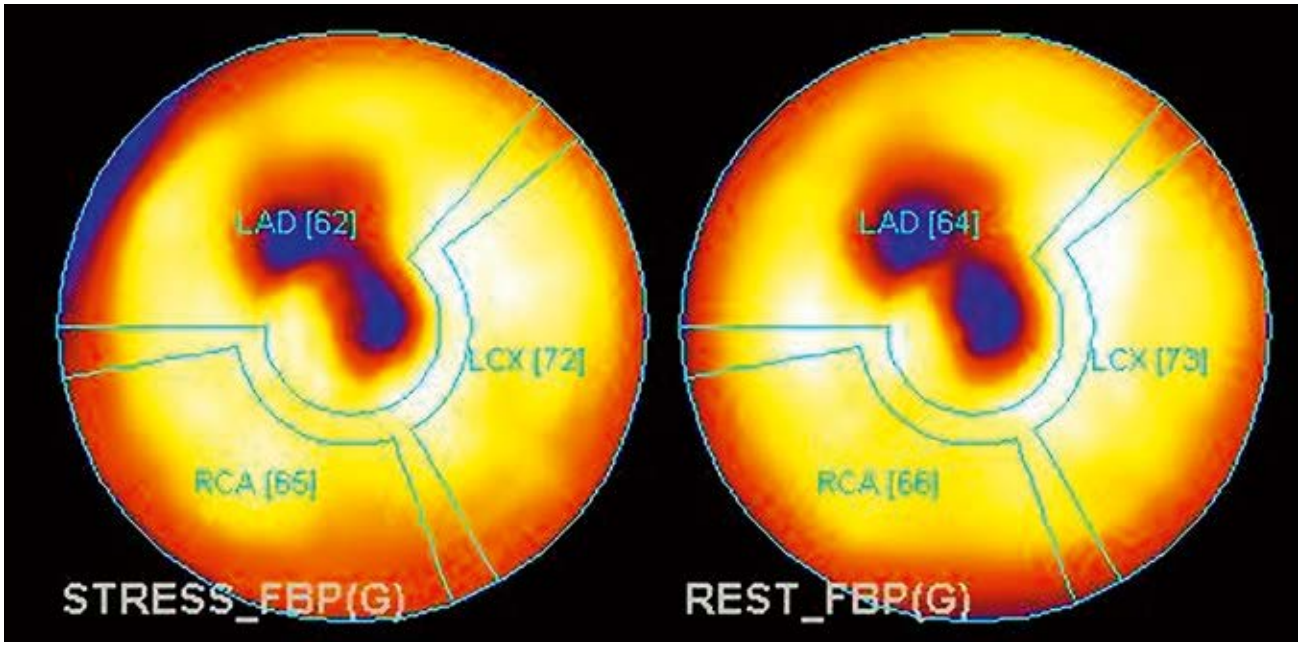
Queirós S, Barbosa D, Engvall J, Ebbers T, Nagel E, Sarvari S, Claus P, Fonseca J, Vilaça J, D'hooge J. Multi-center validation of an automatic algorithm for fast myocardial segmentation in 3D cine CMR datasets. EHJ Cardiovascular Imaging 2015 Advance Access published October 22, 2015, doi:10.1093/ehjci/jev247.

DOPPLER-CIP

Coronary artery disease is the most prevalent cause of cardiovascular disease. It is defined by the narrowing and occlusion of coronary arteries with subsequent imbalance between myocardial oxygen consumption and supply. This imbalance causes either myocardial cell death (infarction) or chronic ischemia (viable myocardium), both leading to changes in the shape of the heart (morphologic remodeling) and functional deterioration. In the long term, patients suffer from heart failure or die.

Restoring blood flow to a region of chronic ischemia can stop the process of remodeling and allow partial or full recovery of function. The current therapeutic approaches are either to restore blood flow by mechanical dilatation of the stenosed coronary vessel (i.e., balloon angioplasty, PCI) or by surgically bypassing the stenosis (coronary artery bypass grafting). Preprocedural investigations as well as the therapeutic measures undertaken are costly and carry a considerable risk for the patient.

The response of chronically ischemic myocardial cells to therapy depends on many factors. Little is known, however, about the exact relation between these pathophysiologic factors and functional recovery of the myocardium for a given therapeutic strategy.



Therefore, the purpose of DOPPLER-CIP is to determine the optimal noninvasive parameters (myocardial function, perfusion, ventricular blood flow, cell integrity) for the prediction of left ventricular morphologic and functional remodeling in chronic ischemic patients.

DOPPLER-CIP is a multi-center observational study. All patients with ischemic heart disease included in this study undergo at least two noninvasive stress imaging examinations at baseline. The presence/or absence of left ventricular (LV) remodeling will be assessed after a follow-up of 2 years, during which all cardiac events will be registered.

After completion, DOPPLER-CIP will provide evidence-based guidelines toward the most effective use of cardiac imaging in the chronically ischemic heart disease patient. The study will generate information, knowledge, and insight into the new imaging methodologies and into the pathophysiology of chronic ischemic heart disease.

In Linköping, almost all 192 patients have undergone at least three stress imaging tests. We will have an excellent opportunity to compare the different modalities in our local material. The patients in this study have helped us develop new MRI-based methods for the measurement of wall motion abnormalities and for 3D-visualization of intracardiac blood flow.

The study closed on March 31, 2015, and had a closing event in Leuven, Belgium, April 25-26 2015. Several manuscripts are in preparation from the different core-labs. Based on evidence-based efficiency of different imaging technologies, researchers at CMT in Linköping will provide a cost-effectiveness analysis of the methods used to image coronary heart disease.

Popular Scientific Summary
Jan Engvall and Anders Persson

MEASURING CARDIAC PERFUSION USING DYNAMIC CT ADENOSIN TESTING

Atherosclerotic coronary artery disease is caused by changes to the wall known as plaque. The plaque consists of deposits of cholesterol, cells and calcium sometimes causing obstruction to the coronary flow. The diagnosis of coronary artery disease rests on the visualization of atherosclerotic plaque or limitations to flow. Invasive investigation should be reserved for patients with a high likelihood of significant disease. Various exercise tests are employed to uncover effects of obstruction that may be silent at rest.

Myocardial blood flow may be visualized in different ways, most often using a gamma camera to trace the myocardial uptake of injected markers. The relationship between myocardial blood flow and the tracer molecules has been shown to be fairly linear within the range of normal resting coronary flow while uptake rolls off with increasing flow.

An alternative approach to calculating myocardial blood flow could be to use effects of angiographic contrast media in cardiac computed tomography (CT). Recent improvement in CT technology with higher temporal resolution and more advanced software has motivated a renewed interest in this method.

There are a number of critical prerequisites for using this approach: the scanning of the left ventricle must be fast to be able to detect the short-lived phase of increase in attenuation that comes with the wash-in of contrast, the X-ray detector has to be large enough to allow coverage of the entire heart and reconstruction and evaluation of the recording need to be fast and accurate. Ideally, the contrast medium itself should not induce any change in coronary flow. A number of smaller studies have been published but the method still

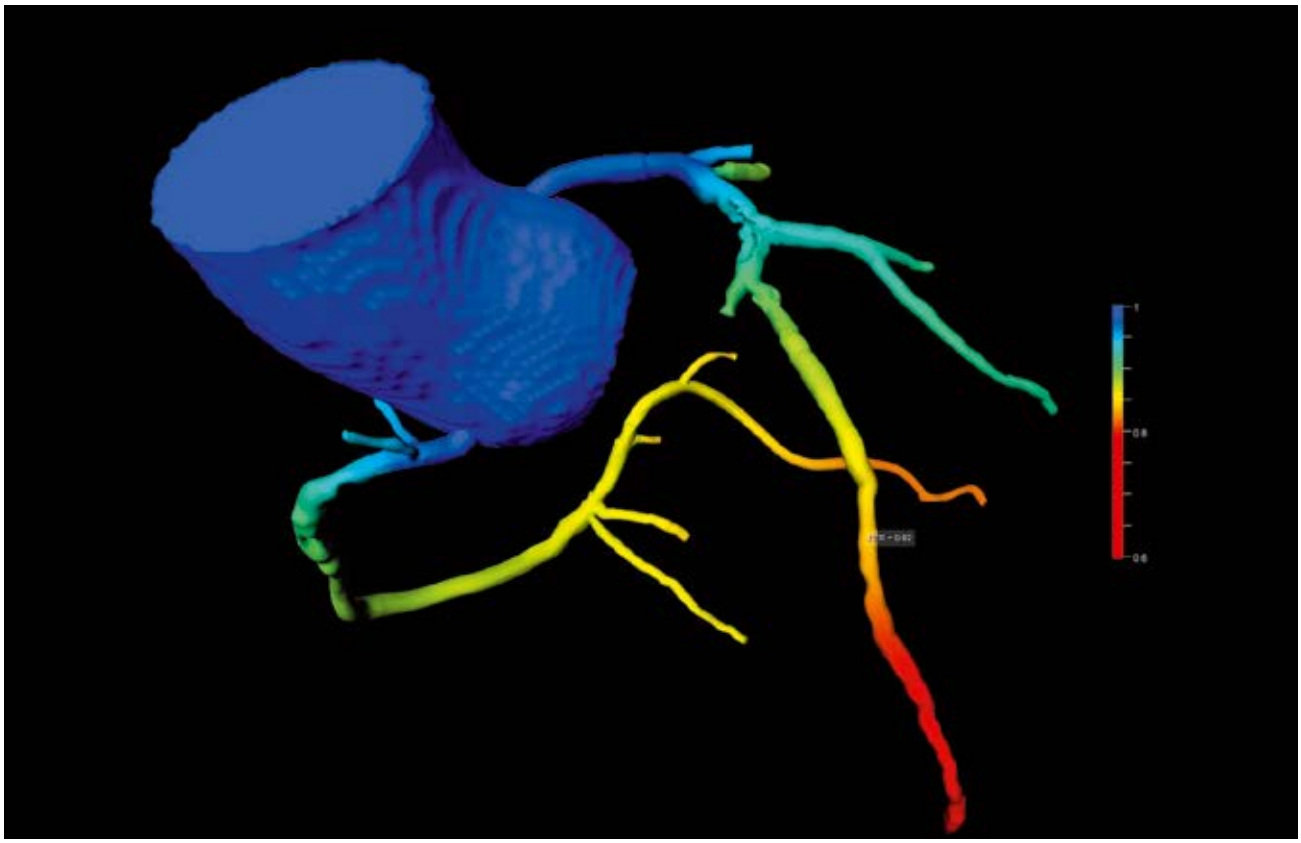
PROJECT NAME
Measuring cardiac perfusion using dynamic CT adenosin testing

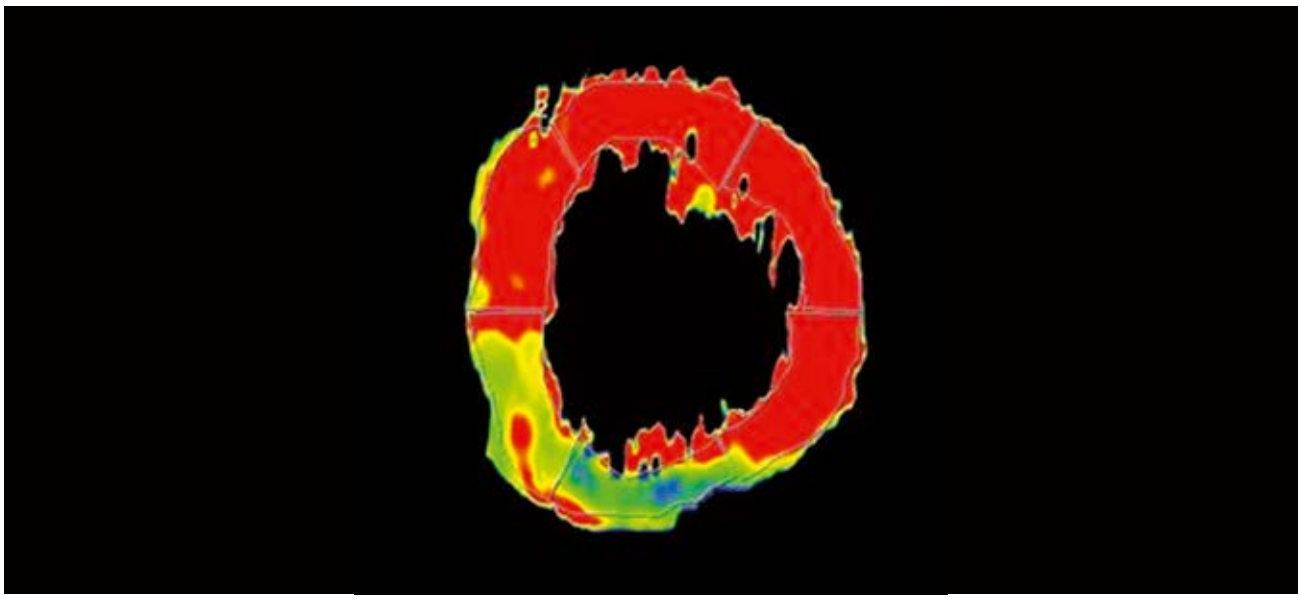
PROJECT LEADER
Jan Engvall, Department of Medical and Health Sciences, Division of Cardiovascular Medicine and Anders Persson, Department of Medical and Health Sciences, Division of Radiological Science

MAIN PROJECT PARTICIPANTS
Jakob de Geer, Marcus Gjerde, Petter Quick

GRANTS
Magnus Bergvalls stiftelse

KEY PUBLICATIONS
DeGeer J, Gjerde M, Olsson E, Brudin L, Persson A, Engvall J. Large variation in blood flow between left ventricular segments, as detected by Adenosine stress dynamic CT perfusion. Clinical Physiology and Functional Imaging 2014 May 19. doi: 10.1111/cpf.12163





needs extensive validation before being incorporated into clinical practice. Thus, the purpose of this study was to evaluate the variation in blood flow in cardiac segment determined to be normal or abnormal according to the gamma camera result. In addition, we wanted to compare CT blood flow values obtained with manual delineation of the cardiac wall with those obtained with automated software.

A positive but moderate correlation was found between CT and the gamma camera. Large variations in CT blood flow were detected which suggests that a single cut-off value for stress myocardial blood flow is inadequate to detect ischemic segments.

The study now continues along two different paths: one repeating the study with an improved CT-scanner with a larger detector, and the other along the path of using non-invasive calculation of fractional flow reserve, to improve the prediction of significance of coronary stenoses detected by CT.

Popular Scientific Summary
Ebo de Muinck

MAGNETIC RESONANCE AND CAROTID ULTRASOUND OBSERVATIONS

Worldwide, the most common cause of death is cardiovascular disease and the dominant cause of cardiovascular disease is atherosclerosis. Atherosclerosis is caused by accumulation of fat, primarily cholesterol in the wall of arteries. When the fat builds up in the arterial wall it causes thickening of the vessel wall and the thickened area bulges out into the vessel, causing narrowing of the artery.

The areas with fat accumulation are called atherosclerotic plaques. Sometimes these plaques rupture causing a blood clot to form. This causes a heart attack if it happens in the arteries of the heart or a stroke if it happens in the arteries feeding the brain.

We have developed an imaging method to identify plaques that are at high risk of rupture. We anticipate that this method will allow us to identify patients with rupture prone plaques and treat them before they suffer from a heart attack or stroke. The method uses magnetic resonance imaging (MRI) and can measure how much fat and blood there is inside atherosclerotic plaques (Figure 1). Plaques with a high fat content and a lot of blood are at higher risk of rupture since fat and blood increase inflammation inside a plaque and inflammation leads to rupture.

Atherosclerotic plaques lead to narrowing of arteries and when blood flows through such a narrowing there is a lot of turbulence immediately behind the narrowing. Turbulent blood flow acts on the vessel wall and increases inflammation inside the plaque (Figure 2).

In this project we study patients who are scheduled for surgical removal of atherosclerotic plaque. Before surgery, the patients undergo MRI of their carotid arteries and we measure the amount of fat and blood inside the plaque as well as the amount of turbulence. After surgery we study the plaque in a microscope. For this purpose the plaque is cut into a series of very thin sections and the amount of fat and blood as well as the amount of inflammatory cells is measured on each section. Then a 3D reconstruction of the plaque is generated based on these sections. This 3D rendering is compared with the MRI images by overlaying images (Fig. 3).

We have now validated the MRI method for quantification of fat and blood in plaques using 3D histology volumes from five patients who underwent MRI before carotid endarterectomy surgery. We have established that the volume of fat and blood in the plaque as measured by 3D histology correlates strongly to the fat and blood fraction as measured by MRI throughout the plaque. Thus, we show that fat and blood measured from Dixon MRI reliably quantifies the extent of hemorrhage and fat in atherosclerotic plaques as validated by 3D histology.

PROJECT NAME
Magnetic Resonance and Carotid Ultrasound Observations (MR CARUSO)

PROJECT LEADER
Ebo de Muinck, M.D., Ph.D, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

MAIN PROJECT PARTICIPANTS
Marcel Warntjes, Petter Dyverfeldt, Johan Kihlberg, Rodrigo Moreno, Daniel Forsberg, Toste Länne, Anne-Marie Landtblom, Darren Treanor

GRANTS
Swedish Heart and Lung Foundation

KEY PUBLICATIONS
Moreno R, Koppal S, de Muinck ED. Robust estimation of distance between sets of points. Pattern Recognition Letters 2013;34:2192-2198.

Sandeep Koppal, Marcel Warntjes, Jeremy Swann, Petter Dyverfeldt, Johan Kihlberg, Rodrigo Moreno, Derek Magee, Nicholas Roberts, Darren Treanor, Ebo D de Muinck. Direct in vivo Quantification of Intraplaque Hemorrhage and Fat in Atherosclerosis by Magnetic Resonance Imaging. American Heart Association Annual Scientific Sessions 2014, November 15 - 19, Chicago IL, USA.

Figure 1. Magnetic resonance image of a patient with atherosclerotic plaque in both carotid arteries. The plaque has caused a severe narrowing in the right carotid artery (arrow). The amount of fat in the plaques is shown in yellow and the amount of blood is in red.

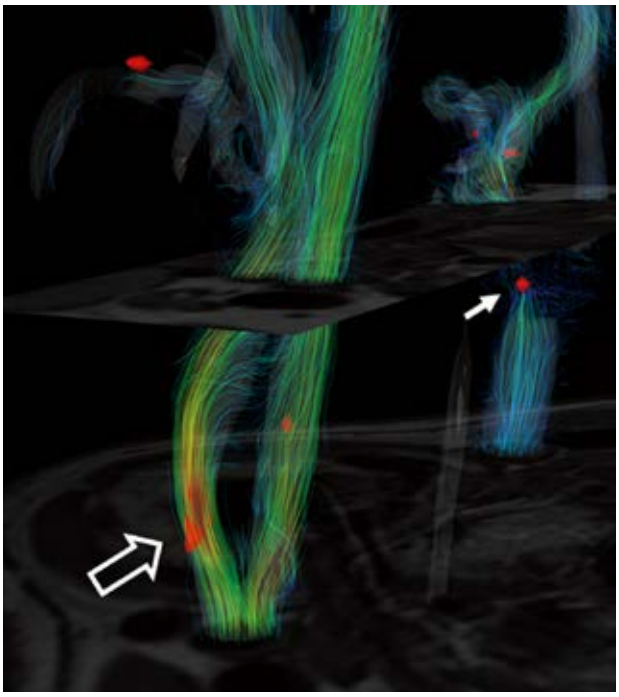


Figure 2. MRI turbulence data from a patient with carotid artery stenosis. The intensity of turbulence is graded according to a color scale, showing areas with a lot of turbulence in red and yellow downstream from a carotid artery stenosis (solid arrow) and at the outer wall of the contra-lateral internal carotid artery (open arrow).

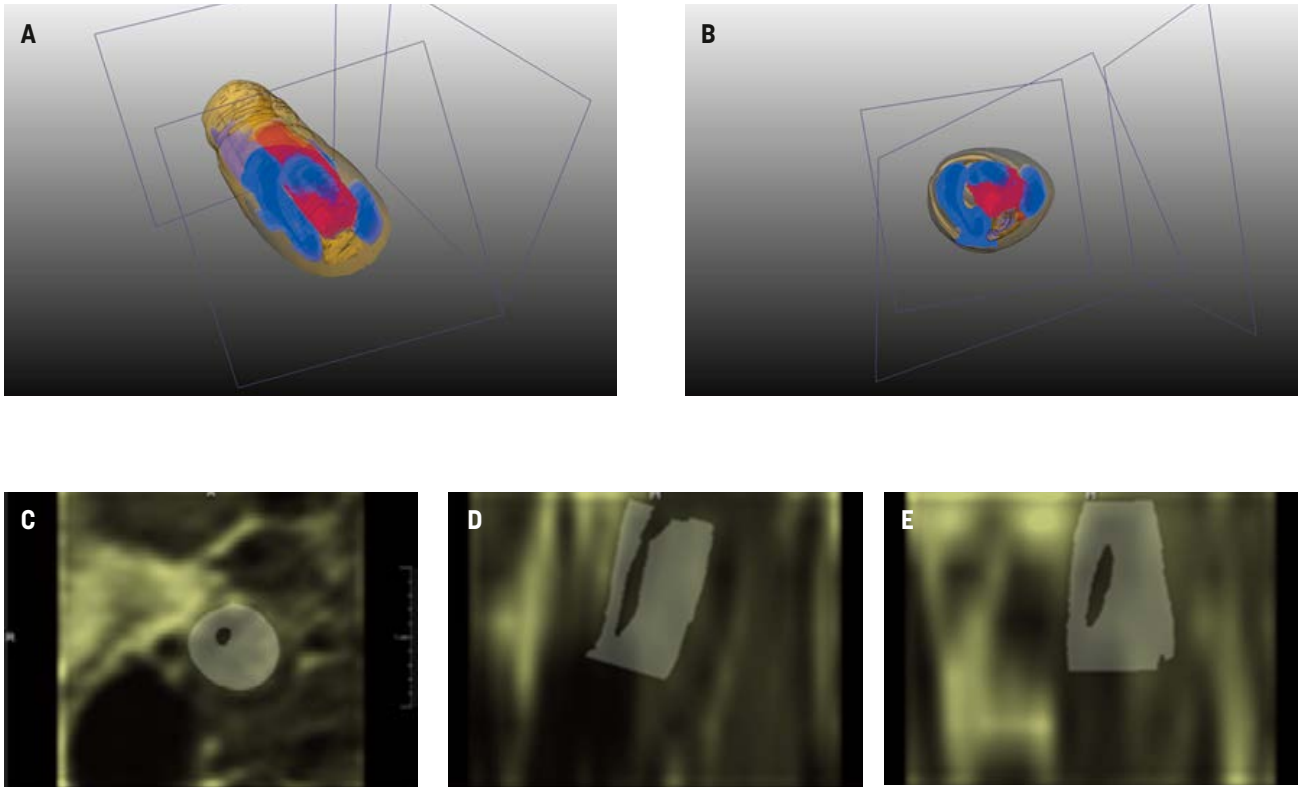


Figure 3. A-B 3D histology rendering of the atherosclerotic plaque showing the areas of internal hemorrhage (red) and lipid rich necrotic core (blue) within the lesion (yellow). C-E Spatial registration of 3D histology over 3D T1 weighted black blood sequence in an orthographic representation.

Popular Scientific Summary
Éva Tamás

HISTOLOGICAL AND FUNCTIONAL CHANGES IN LEFT VENTRICULAR FUNCTION DUE TO AORTIC STENOSIS

PROJECT NAME
Histological and Functional Changes in Left Ventricular Function Due To Aortic Stenosis

PROJECT LEADER
Éva Tamás, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

MAIN PROJECT PARTICIPANTS
Eva Nylander, Jan Engvall, Tino Ebbers

GRANTS
Svenska Läkarsällskapets Projektanslag 2014-2016

KEY PUBLICATIONS

Tamás É, Broqvist M, Olsson E, Franzén S, Nylander E. Exercise Radionuclide Ventriculography for Predicting Post-Operative Left Ventricular Function in Chronic Aortic Regurgitation. J. Am. Coll. Cardiol. Img. 2009;2;48-55.

Kvernby S, Warntjes MJ, Haraldsson H, Carlhäll CJ, Engvall J, Ebbers T. Simultaneous three-dimensional myocardial T1 and T2 mapping in one breath hold with 3D-QALAS. J Cardiovasc Magn Reson. 2014 Dec 20;16:102. doi: 10.1186/s12968-014-0102-0.

Aortic valve stenosis (AS) is the most common valvular heart disease in Europe (46.4%). Mostly elderly patients suffer from AS and due to the expanding population above 60 years this patient group is steadily increasing. Current treatment of aortic valve disease is prosthetic aortic valve replacement (AVR).

Operation is indicated when the valve disease affect hemodynamics and left ventricular function (LVF). Present guidelines suggest surgery when patients are presented with symptoms and/or echocardiographic parameters. These manifestations are fairly crude as both symptoms and left ventricular dilatation are appearing late in the natural history of the aortic valve disease. Furthermore, we showed previously that symptoms and LVF do not correlate.

In order to be able to keep up performance the LV compensates minor changes by hypertrophy. Further changes present even at histological level as diffuse fibrosis. It is known that regional fibrosis e.g. after myocardial infarction leads to impaired ventricular function. However, there is no informa-

tion available in the medical literature on exactly how diffuse fibrosis affects LVF and whether these are reversible. Thus, understanding how fibrotic changes of the heart muscle are connected to the impairment of LVF could give valuable information.

Previous studies have verified fibrotic regions following myocardial infarction on cardiac magnetic resonance imaging (cMRI). Thus cMRI was proved to be a useful diagnostic modality for myocardial viability and this knowledge has already been translated to clinical practice. While fibrosis is focal and concentrated in myocardial infarction there is no in-vivo information on the distribution of the fibrotic tissue in the mass of the human heart muscle in aortic valve disease which makes validation of cMRI images by means of histology necessary.

In our ongoing study we validate cMRI (special sequences developed at CMIV) as a diagnostic tool for diffuse myocardial fibrosis and to evaluate the effect of fibrosis on myocardial function. We hypothesize that the amount and the location of the fibrotic tissue can be connected to impairment of LVF in severe aortic valve disease. By using cMRI we intend to gain information on whether this impairment is reversible following surgery.

In addition to histological and functional studies at rest we plan to survey the anaerobe (physical) capacity by performing cardiopulmonary exercise testing pre- and postoperatively and study the relationship between physical performance capacity, fibrosis and LVF.

Popular Scientific Summary
Örjan Smedby

PROJECT NAME
Quantitative Assessment of Trabecular Bone Structure

PROJECT LEADER
Örjan Smedby, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Eva Klintström, Magnus Borga, Rodrigo Moreno (KTH), Torkel Brismar (KI)

GRANTS
Swedish Research Council (VR-NT) 2007-2009

KEY PUBLICATIONS 2015
Moreno R, Smedby Ö. Gradient-Based Enhancement of Tubular Structures in Medical Images. Medical Image Analysis 2015;26(1):19-29.

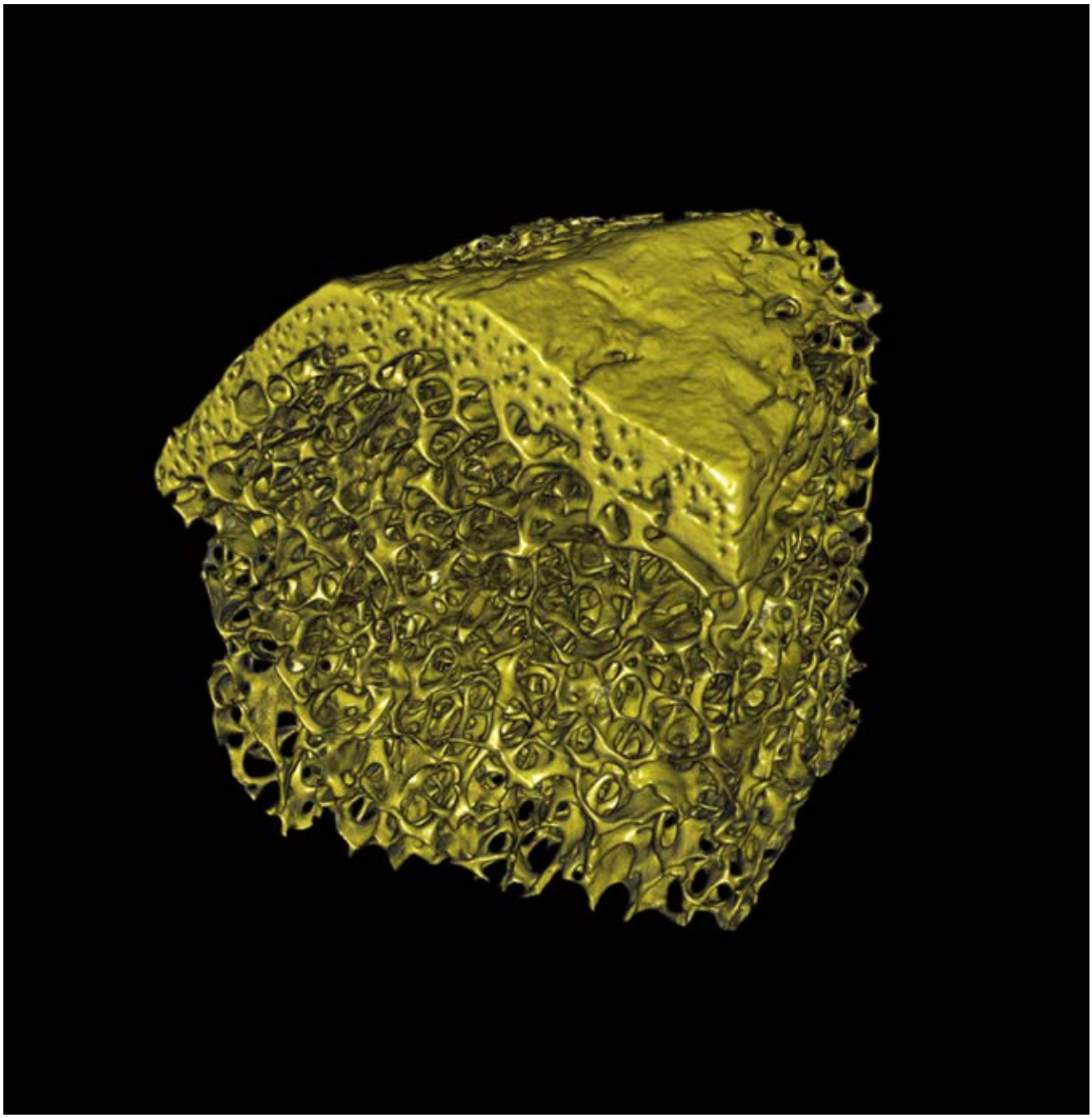
Moreno R, Smedby Ö, Pahr D. Prediction of Apparent Trabecular Bone Stiffness through Fourth-Order Fabric Tensors. Biomechanics and Modeling in Mechanobiology 2015:1-14.

Moreno R, Borga M, Klintström E, Brismar T, Smedby Ö. Anisotropy Estimation of Trabecular Bone in Gray-Scale: Comparison Between Cone Beam and Micro Computed Tomography Data. In: Developments in Medical Image Processing and Computational Vision / [ed] João Manuel R.S. Tavares and Renato Natal Jorge, Springer, 2015, 207-220.

QUANTITATIVE ASSESSMENT OF TRABECULAR BONE STRUCTURE

Patients suffering from osteoporosis have an increased risk of fractures. When studying this in patients the amount of calcium in the bone is usually measured since this is reduced in osteoporosis. However, the condition is also characterized by a change in the internal structure of the bone, which may be more important for its strength than the reduced calcium content. The internal structures of the bone are called trabeculae, and they are usually portrayed as either narrow rods or flat plates. Earlier, the 3D microstructure could only be studied in bone specimens removed from the body, where properties such as the spacing and thickness of the trabeculae and the number of branching points can be measured.

This project aims to study this structure in the living human by using methods available in a radiological department, in particular different types of



computed tomography (CT) methods. Since the trabeculae often are less than 0.2 µm thick, the limited resolution of the radiological methods may be a problem. Therefore, we have focused on developing new image processing techniques for as accurate measurements as possible in the available images.

To study how the structure of the bone differs between different directions we use mathematical concepts called tensors. With these rather abstract tools, we can estimate the strength of the bone, which is what really matters for the patient. We have shown that our predictions agree well with results from Finite element modeling (FEM), a computational method that requires much longer time even on very fast computers.

We have also studied how the type of tissue structure that is present in trabecular bone can be characterized and enhanced using tensor methods. In addition to bone structure this may be useful also for e.g. identifying vessels in CT or MRI images.

In the future, we hope that our methods will be useful in particular to evaluate the effects of treatment against osteoporosis. With better tools to measure the structure of the bone trabeculae it will be possible to draw such conclusions at an earlier stage, hence the number of subjects and the observation times in clinical trials may be reduced.

Popular Scientific Summary
Hans Tropp

QUANTITATIVE MUSCULOSKELETAL IMAGING FOR ASSESSMENT OF IDIOPATHIC SCOLIOSIS

Spinal deformities, such as idiopathic scoliosis, not only cause changes in posture but can also be associated with severe pain, breathing complications, as well as heart complications. Treatment options include braces for mild to moderate cases of idiopathic scoliosis, whereas severe cases often require surgery, both to halt progression and to preferably correct the already existing deformity.

Choice of treatment, monitoring of progression, follow-up after surgery are all activities that to a large extent are based upon a single measure called the Cobb angle. The Cobb angle measures the angle of the spine as seen on frontal radiographs. However, although widely used in clinical practice, the Cobb angle is incapable to fully describe a spinal deformity. This has motivated researchers and clinicians to pursue the development of new techniques to better describe and assess spinal deformities, which in turn will allow a better understanding of scoliosis on an individual level and, thus, be able to device personalized treatment plans.

To achieve this, we have focused our research on the combination of metrics describing the local deformation of each vertebra with metrics describing the overall deformation of the spine. For imaging, we are utilizing 3D imaging, as provided by computed tomography (CT), which provides excel-lent opportunities to measure and assess spinal deformities. Current state-of-the-art CT scanners with new low-dose examinations make the use of CT clinically feasible from a dose perspective.

Thus far, our work has focused on:

- Determining the relationship between the Cobb angle as observed from radiographs with the patient in standing and in supine position. This is relevant, since current clinical practice is based upon on the Cobb angle from radiographs with the patient in standing position and not in supine position as is the case for CT examinations.
- Developing computerized methods based upon advanced image analysis, which can be employed for measuring various metrics related to quantifying the 3D deformity in scoliosis. Automatic and robust methods are needed in order to limit the effects of intra- and inter-observer variability associated with manual methods.

Future work will focus on:

- Determining the relationship between the Cobb angle and the axial vertebral rotation. This is relevant, since the axial vertebral rotation is of many clinicians considered as a differentiating factor between different types of scoliosis.
- Investigating how the axial vertebral rotation is affected by different surgical techniques for correcting spinal deformities. In this study, we will collaborate with University Medical Center Utrecht in the Netherlands.

PROJECT NAME
Quantitative Musculoskeletal Imaging for Assessment of Idiopathic Scoliosis

PROJECT LEADER
Hans Tropp, Department of Clinical and Experimental Medicine, Division of Orthopaedics

MAIN PROJECT PARTICIPANTS
Ludvig Vavruch and Daniel Forsberg

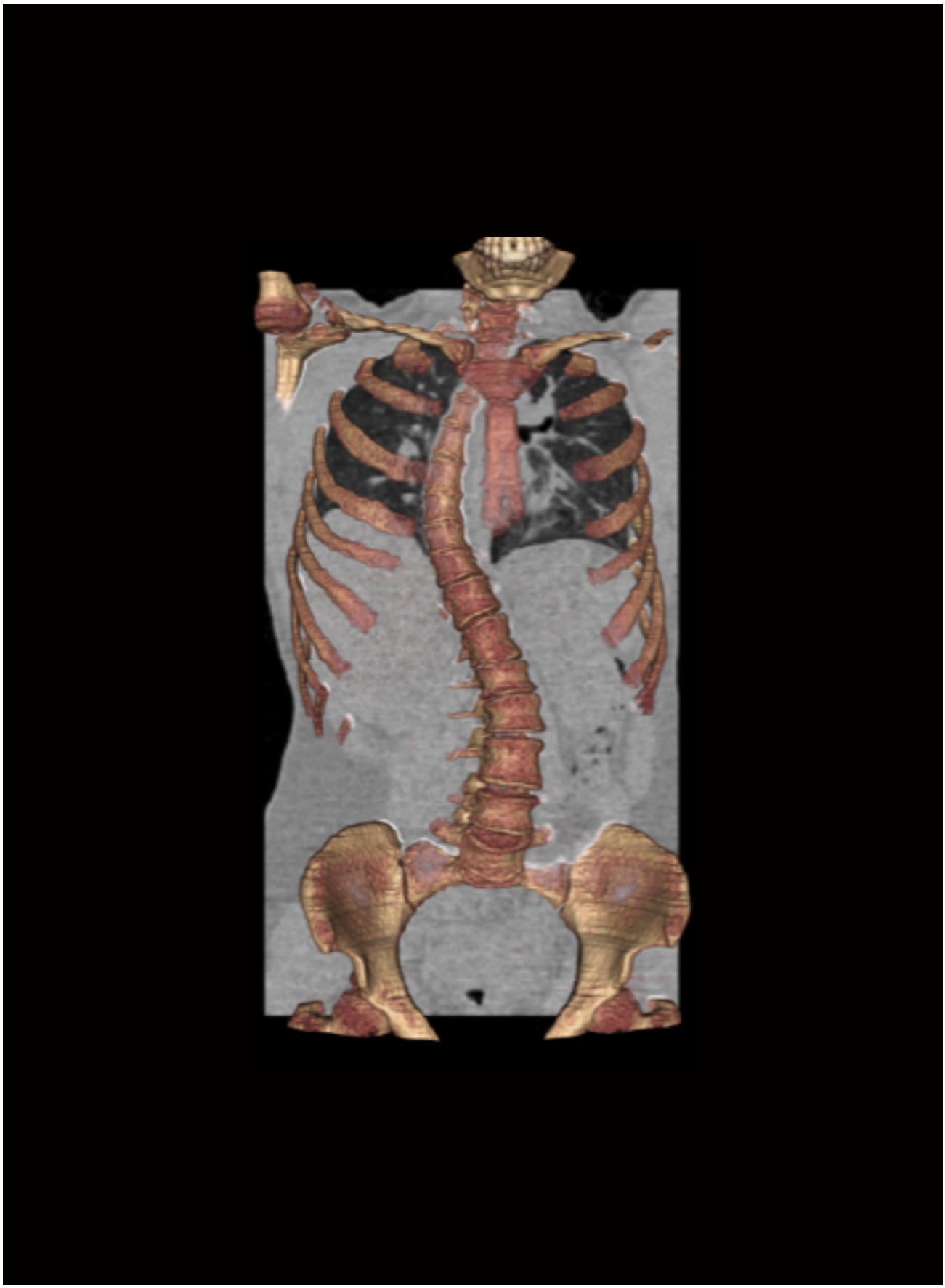
GRANTS
VR 2008-2013
VINNOVA 2012-2014

KEY PUBLICATIONS

L. Vavruch, and H. Tropp. A Comparison of Cobb Angle: Standing Versus Supine Images of Late-onset Idiopathic Scoliosis. Polish Journal of Radiology, 2016 (accepted for publication)

D. Forsberg, C. Lundström, M. Andersson, and H. Knutsson. "Model-based registration for assessment of spinal deformities in idiopathic scoliosis", Physics in Medicine and Biology, vol. 59, iss. 2, pp. 311-326, 2014

D. Forsberg, C. Lundström, M. Andersson, L. Vavruch, H. Tropp, and H. Knutsson. "Fully automatic measurements of axial vertebral rotation for assessment of spinal deformity in idiopathic scolio-sis", Physics in Medicine and Biology, vol. 58, iss. 6, pp. 1775-1787, 2013



A patient suffering from idiopathic scoliosis. Note that apart from the global sideways deformation of the spine, there are local deformations present. For example, vertebrae L1, T12 and T11 (i.e. vertebrae five, six and seven counted from the bottom) are deformed to have a so called wedge-like appearance.

Popular Scientific Summary
Daniel Forsberg

4D ORTHOPEDIC KINEMATICS

Dislocation of the kneecap is one of several knee problems that can cause significant negative impact on the life of an individual. The initial treatment is to engage the patient in physical therapy and/or provide a knee brace. However, if this treatment is unsuccessful or if the condition is very severe (the kneecap has been dislocated on multiple occasions), then surgery is needed. This typically includes a reconstruction of the medial patellofemoral ligament (a ligament on the inside of the knee, stabilizing the kneecap). The purpose of the surgery is to stabilize and thereby restore the "normal" motion pattern/range of the kneecap. Surgery is considered successful if the kneecap feels stable and if the patient no longer experiences dislocations. Today there exist no standardized methods for precise quantification of the kneecap's motion during continuous flexion and extension of the knee. The lack of quantitative metrics makes it very difficult to evaluate the large number of different surgical techniques that exists for treating patients suffering from dislocation of the kneecap. This is what we intend to remedy.

Over the last few years, computed tomography (CT) imaging has undergone a remarkable development. Today, state-of-the-art scanners can image the knee with a spatial resolution of 0.4x0.4x0.4mm3 and a temporal resolution of less than a second. Further, improved detector technologies and new image reconstructions algorithms ensure that dose is kept as low as reasonably achievable. This presents CT as a relevant technique for imaging the knee to allow a quantitative assessment of the continuous motion of the kneecap during flexion and extension of the knee.

Aided by the use of CT to obtain 4D datasets, i.e. a time sequence of 3D datasets, we aim to:

- Define metrics for quantifying the kneecap's motion pattern along with developing a method for measuring these metrics. By employing image analysis we intend the developed method to require as little user interaction as possible.
- Study the motion pattern of kneecaps from patients prone to dislocation of the kneecap and compare with control patients to determine what a healthy respectively pathological motion pattern/range of the kneecap is.
- Investigate how surgery affects the motion pattern of the kneecap for patients who have undergone surgery using the gracilis tendon (a tendon on the inside of the knee) to reconstruct the medial patellofemoral ligament.
- Evaluate the use of the developed method for assessing other knee problems, e.g. patients with injured anterior cruciate ligaments.

PROJECT NAME
4D Orthopedic Kinematics

PROJECT LEADER
Daniel Forsberg

MAIN PROJECT PARTICIPANTS
Maria Lindblom, Anders Persson and Håkan Gauffin

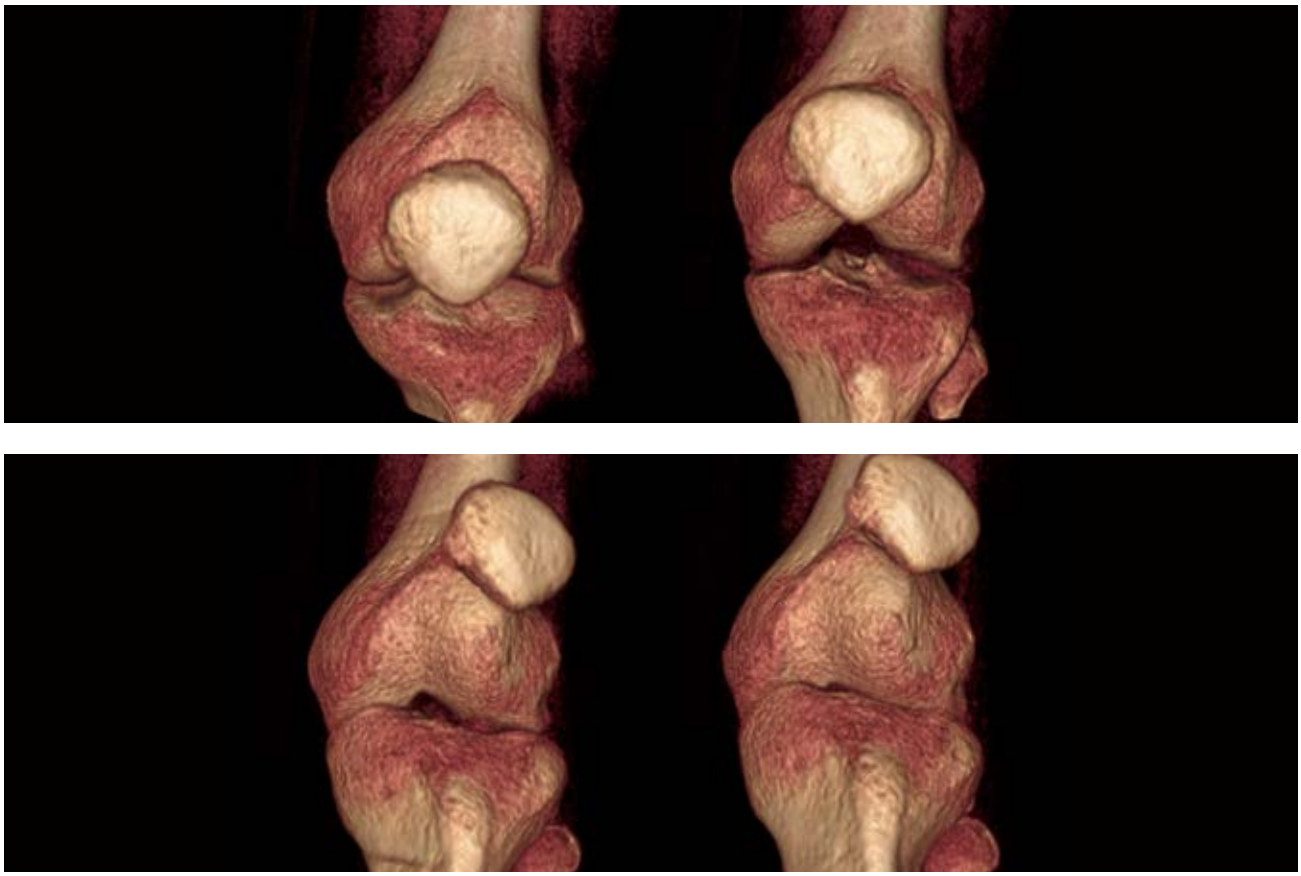


Figure 1. Preoperative imaging using CT for a patient with right knee prone to dislocation of the kneecap. Note how the kneecap moves to the side as the patient reaches full extension of the knee.

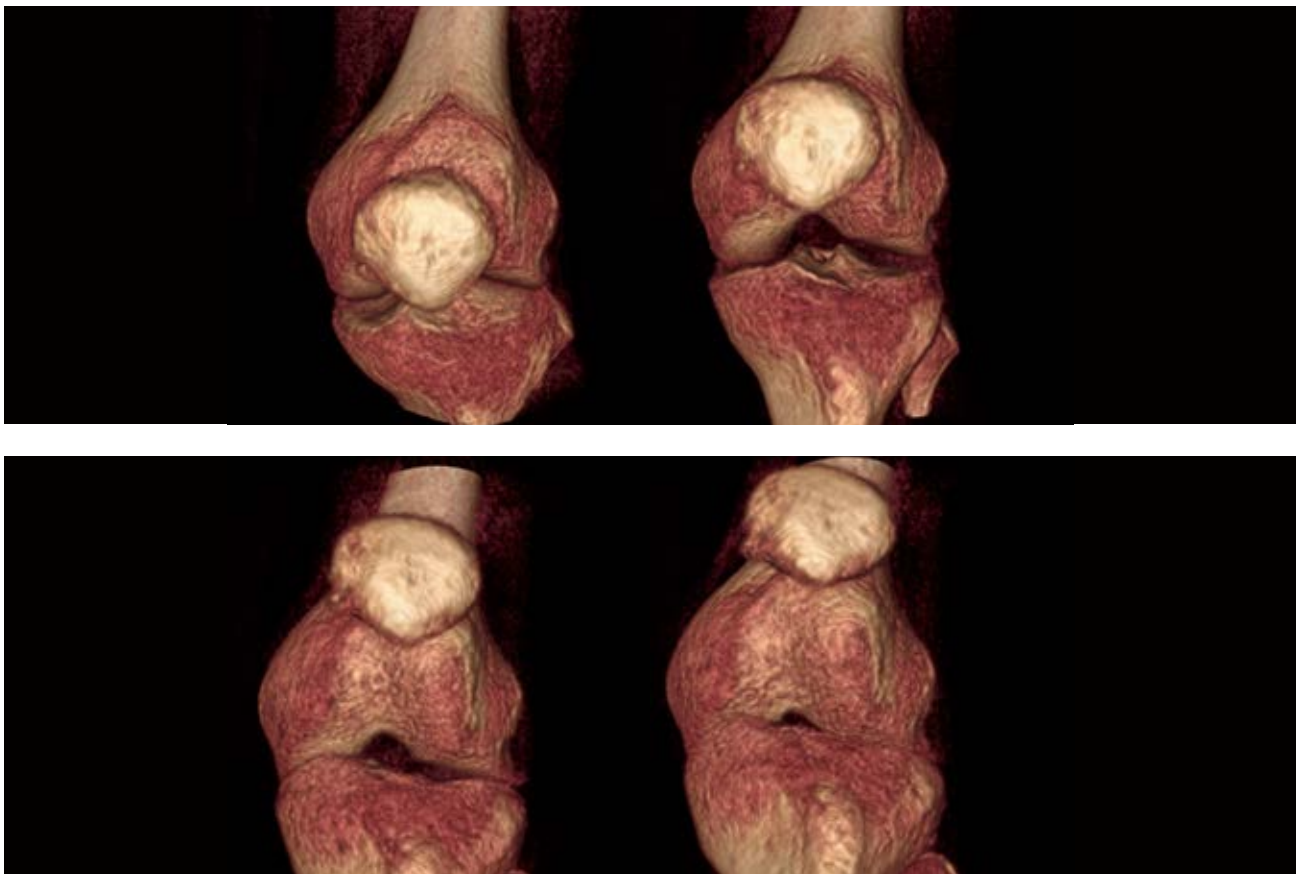


Figure 2. The same patient after reconstructive surgery. Now the kneecap stays much closer to the center of femur as the knee is extended.

Popular Scientific Summary
Mats Hammar and Magnus Borga

PROJECT NAME
Health effects of resistance training on postmenopausal women

PROJECT LEADER
Mats Hammar, Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynecology
Magnus Borga, Department of Biomedical Engineering, Division of Medical Informatics

MAIN PROJECT PARTICIPANTS
Anna-Clara Spetz Holm, Lotta Lindh Åstrand, Hanna Lindblom, Olof Dahlqvist Leinhard, Heriberto-Rodriguez-Martinez, Marie Rubér, Peter Söderkvist, Pontus Boström

GRANTS
Swedish Research Council

KEY PUBLICATIONS
Romu T, West J, Spetz-Holm A-C, Lindblom H, Lindh-Åstrand L, Hammar M, Dahlqvist Leinhard, Borga M. The effect of flip-angle on body composition using calibrated water-fat MRI. Submitted to ISMRM 2016, Singapore

Borga M., Virtanen Kirsi A., Romu T., Dahlqvist Leinhard O. Persson A., Nuutila P., Enerbäck S. Brown adipose tissue in humans: detection and functional analysis using PET (Positron Emission Tomography), MRI (Magnetic Resonance Imaging), and DECT (Dual Energy Computed Tomography), accepted for publication in: Methods in Enzymology Volume 537: Methods of Adipose Tissue Biology, 141-159, 2014.

Lindh-Astrand, L; Nedstrand, E; Wyon, Y; Hammar M.. Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy Maturitas; 2004; 48: 97-105

HEALTH EFFECTS OF RESISTANCE TRAINING ON POSTMENOPAUSAL WOMEN

Today's women will live more than a third of their lives after menopause, which is characterized by a series of clinical signs and symptoms including vasomotor symptoms (hot flushes and sweating), sleep and mental disturbances. Other important changes are osteoporosis and loss of muscle mass, which is replaced by accumulation of white fat. Inflammatory changes in the fat tissue also occur with immunologic and metabolic dysfunctions as consequences such as increased risk of cancer and cardiovascular disease.

Vasomotor symptoms like hot flushes and sweating are reported by about 75% of all menopausal women. Until about ten years ago almost every other middle-aged woman in the Western world used hormone therapy (HT) with combined estrogens and synthetic progesterone, which effectively diminishes vasomotor symptoms. Since HT, however, has been shown to increase the risk of cardiovascular and thrombo-embolic disease as well as breast cancer there is a need for alternative therapies.

Already in the early nineties (as the first group worldwide) we reported that vasomotor symptoms were less prevalent in women who participated in regular physical exercise. Women who were randomized to regular exercise reported decreased vasomotor symptoms and increased quality of life.

The purpose of this study is to establish health effects from 15 weeks of structured resistance training on postmenopausal women. The participating women are coached by a skilled physiotherapist and the training is individualized.

In the beginning and end of the study clinical outcomes as vasomotor symptoms, well-being, Body Mass Index, muscle strength and mass are measured. White and brown adipose tissue as well as browning of fat are measured with MRI. Also, production of myokines as irisin, immunological markers and genetic variables (length of telomeres) are analyzed. By means of structured interviews we investigate how to best stimulate people to change lifestyle and why some women will not be successful.

The study is a close collaboration between clinical medicine, the participating gym, laboratory biomedicine, caring sciences and physiotherapy, as well as advanced technology at CMIV. The results could easily and rapidly be implemented into clinical routine and may have extensive health benefits on the aging population.

Popular Scientific Summary
Lennart Persson

IMPACT OF VITAMIN D ON PHYSICAL TRAINING IN VITAMIN D DEFICIENT PATIENTS WITH COPD

PROJECT NAME
Impact of Vitamin D on Physical Training in Vitamin D Deficient Patients with COPD

PROJECT LEADER
Lennart Persson, Department of Pulmonary Medicine

MAIN PROJECT PARTICIPANTS
Magnus Kentson, Apostolos Sioutas, Mikael Forsgren, Kristina Tödt, Petra Jacobson, Linda Vainikka, Per Leanderson, Peter Lundberg

GRANTS
The Swedish Heart and Lung Foundation
Medical Research Council of Southeast Sweden (FORSS)

Muscle waste and inactivity is a great problem among patients with chronic obstructive pulmonary disease(COPD) and structured physical training is known to have many beneficial effects on these patients.

Many patients with COPD exhibit vitamin D deficiency, which in addition to COPD may act negatively on the skeletal muscle. Today it is still not well known how deprivation of this vitamin may interfere with muscle function and the ability of these patients to fully gain the benefits of physical training.
The goal of the present project is to identify mechanisms behind vitamin D deficiency- and COPD dependent muscle pathology applying the very latest technology, which include the 31P-MRS and serological biomarkers, and to find out the impact of vitamin D deficiency in an interventional double-blind trial of vitamin D3 supplementation and placebo.

If successful, the study will lead to a better understanding about the role

of vitamin D deficiency on the muscle waste observed among many COPD patients. Indeed, vitamin D may become a crucial vitamin to supplement before physical training is started.

The present study will include patients with stable but advanced COPD exhibiting deficiency of vitamin D and significant weakness of the breathing muscle. In a blinded fashion patients are randomized to physical training (at hospital supervised by physiotherapist twice a week and at home monitored by a training diary once a week for 8-10 weeks) with the study medication Vigantol (vitamin D3) or placebo (miglyol). Ongoing treatments with vitamin D and calcium are temporarily stopped at inclusion. Vigantol is administered orally as a daily dose of 4 000 IU starting from the day of randomization and continuing throughout the training period.

Primary outcome is respiratory muscle strength measured as the maximal inspiratory pressure (MIP). Among secondary outcomes studies on muscle strength and endurance of the dominant leg, metabolism of the quadriceps muscle of the dominant leg at rest and exercise (employing 31P-magnetic resonans (MR) spectrometry) and quantification of muscle, fat and bone tissues of the dominant leg (using MR) will be performed.

Popular Scientific Summary
Magnus Borga

IMAGING OF BROWN ADIPOSE TISSUE

PROJECT NAME
Imaging of Brown Adipose Tissue

PROJECT LEADER
Magnus Borga, Department of Biomedical Engineering, Division of Medical Informatics

MAIN PROJECT PARTICIPANTS
Anders Persson, Olof Dahlqvist Leinhard, Thobias Romu, Nils Dahlström

GRANTS
KAW 2012-2017

KEY PUBLICATIONS
Martin E. Lidell, Matthias J. Betz, Olof Dahlqvist Leinhard, Mikael Heglind, Louise Elander, Marc Slawik, Thomas Mussack, Daniel Nilsson, Thobias Romu, Pirjo Nuutila, Kirsi A. Virtanen, Felix Beuschlein, Anders Persson, Magnus Borga, Sven Enerbäck. "Evidence for two types of brown adipose tissue in humans", Nature Medicine, 19(5): 631-634, 2013.

Magnus Borga, Kirsi A. Virtanen, Thobias Romu, Olof Dahlqvist Leinhard, Anders Persson, Pirjo Nuutila, Sven Enerbäck. "Brown adipose tissue in humans: detection and functional analysis using PET (Positron Emission Tomography), MRI (Magnetic Resonance Imaging), and DECT (Dual Energy Computed Tomography)", Methods of Adipose Tissue Biology, Methods in Enzymology, No. 537, 2014.

Thobias Romu, Louise Elander, Olof Dahlqvist Leinhard, Martin Lidell, Matthias Betz, Anders Persson, Sven Enerbäck, Magnus Borga. "Characterization of Brown Adipose Tissue by water-fat separated Magnetic Resonance Imaging", Journal of Magnetic Resonance Imaging, 42(6): 1639-1645, 2015.

The human body contains different types of adipose (fat) tissue that play different roles in the metabolism. While white adipose tissue (WAT) act as energy buffer, brown adipose tissue (BAT) converts stored energy (WAT) directly into heat that keeps us warm at least as infants and is also most likely of importance to us for longer than that.

Today's sedentary life style has generated a cluster of obesity related health problems commonly referred to as the metabolic syndrome. A positive energy balance will eventually lead to insulin resistance and ultimately type 2-diabetes, which in turn may cause e.g. heart attacks, stroke, kidney problems and also many types of cancers.

In recent years, Brown Adipose Tissue (BAT) has emerged as a highly interesting object of study in the search for future solutions to many of the major health care challenges related to the metabolic syndrome. Also, recent publications have shown relations between BAT and osteoporosis and sarcopenia (age related loss of muscle mass).

The lack of efficient tools for studying BAT in vivo, however, is a serious limitation hindering large clinical studies related to BAT. Until recently the only available method for in vivo imaging of BAT was positron emission tomography, which requires injection of a radioactive substance in the subjects, clearly limiting its use in large prospective studies.

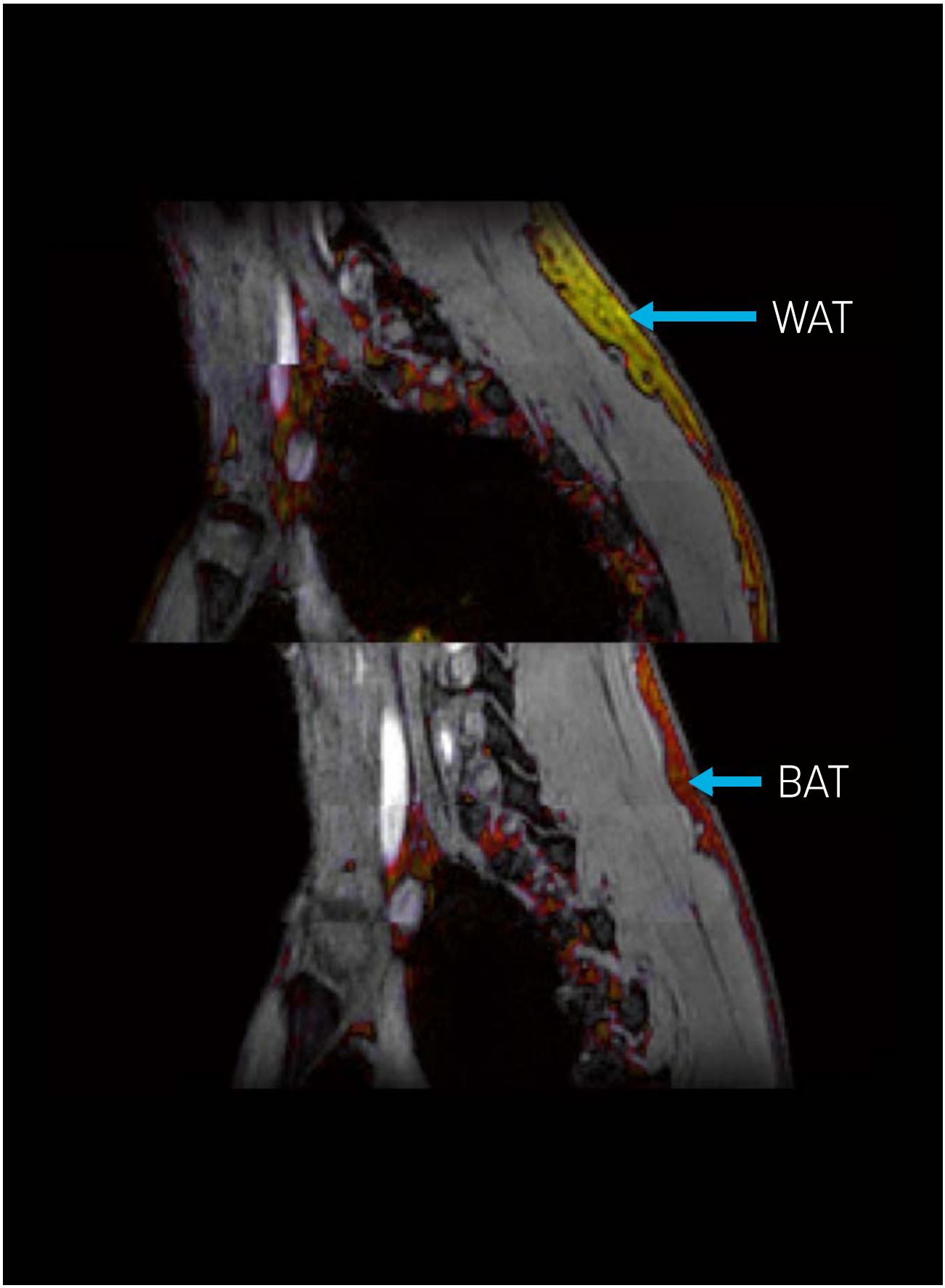
Manual assessment of the BAT images is extremely time-consuming, making larger studies impossible. Also, the reproducibility is limited in manual work. Computers on the other hand are very useful when it comes to reproducibility and speed.

The overall aim of this project is therefore to develop and evaluate accurate automatic methods for high-resolution in vivo imaging, classification and quantification of BAT using quantitative magnetic resonance imaging and dual energy computed tomography.

In parallel with the method development the project also studies the properties of brown fat and the possibilities to activate and even increase the amount of brown fat.

Results from the project show that it is possible to alter the constitution and amount of brown fat in rats by exposure to low temperatures. Studies are now performed on humans to see if it is possible to have the same effect.

The studies of brown fat involve professionals from multiple disciplines, patient recruitment and advanced equipment. Without a center as CMIV the project would be impossible to realize.



The image illustrates how BAT can be detected in the neck and shoulders using MRI that can quantify the amount of fat and water in the tissue. WAT contains almost 100% fat and is indicated in yellow. BAT contains approximately 50% water and is indicated in red.

Popular Scientific Summary
Nils Dahlström

SEMIAUTOMATIC LIVER VOLUME DETERMINATION

There are many types of liver diseases occurring through many different mechanisms. Diffuse liver disease for example is a rapidly growing problem in the Western world and includes conditions such as viral infection (hepatitis) and non- alcoholic fatty liver disease. Other types are alcohol induced liver disease and focal liver disease.

Common for all liver diseases is that they may lead to the formation of fibrosis, inflammation and ultimately, cirrhosis. Many forms are mainly discovered at a late stage when there is a loss of liver function. At this stage liver resection or transplantation may be the only available treatment. The evaluation of liver function is then crucial for reliable treatment planning.

Magnetic resonance imaging (MRI) offers a noninvasive method to monitor liver function using liver specific contrast agents. However, in developing system biology models for describing the pharmacokinetics of hepatocyte-specific contrast medium, it is important to estimate the total liver volume and preferably also liver segment volumes. Although tools for liver segmentation using datasets from computed tomography have become easily available, useful applications aimed at MRI datasets are lacking.

Thus, a sub-project within the Liver Function Evaluation project was formed to evaluate software that was compatible with the late hepatobiliary phase 3D datasets from examinations of patients with diffuse liver disease.

The first objective of this study is to compare the measured total liver volumes from several semi-automatic liver segmentation tools and a fully automatic application (developed in-house), with manual, detailed segmentation in a separate software environment serving as “ground truth”.

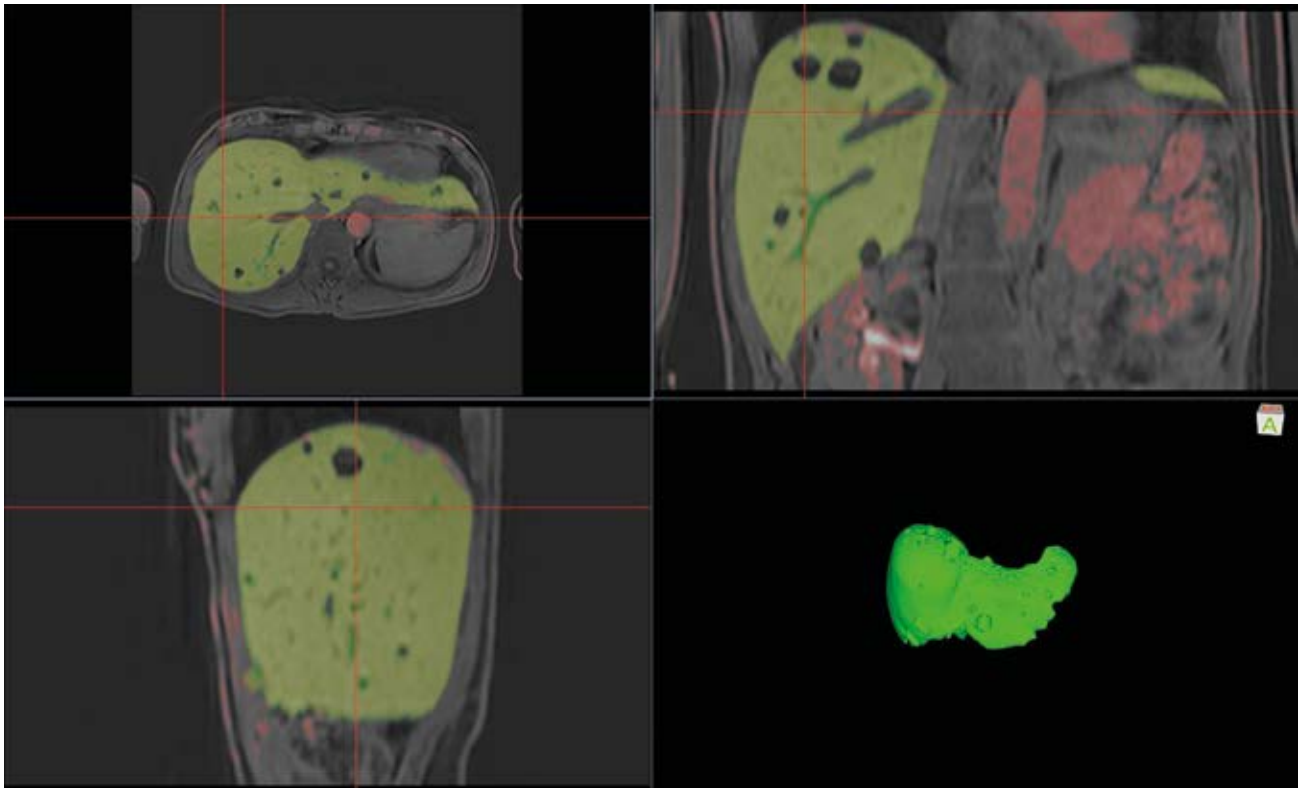
Preliminary results show that a fully automatic segmentation is feasible and has a precision that is sufficient for clinical use. Both semi-automatic softwares were found accurate but have quite different user interfaces, sometimes complicating the measurement task.

Another objective is to provide the total liver measurements needed for modeling the individual liver function estimates in the study, and also introduce the means for segment-based liver function modeling.

PROJECT NAME
Semiautomatic Liver Volume Determination

PROJECT LEADER
Nils Dahlström, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Mikael Forsgren, Chunliang Wang, Ola Persson



Sample view of semi-automatic segmentation of liver parenchyma using one of the software applications studied, MiaLite 2.0 (research software developed by Chunliang Wang, CMIV)

Popular Scientific Summary
Olof Dahlqvist Leinhard

WHOLE BODY MRI-BASED FAT AND MUSCLE MEASUREMENT

The metabolic syndrome is a disorder involving alterations of the normal biochemical processes of the body. High blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol increase the risk of heart disease, stroke and diabetes. In the metabolic syndrome several of these risk factors occur together, dramatically increasing the risk further.

Body Mass Index (BMI), weight and waist circumference do not tell the whole story about the metabolic syndrome. A better understanding of the effect of drugs and different life styles requires biomarkers reflecting where and how the body stores fat, build muscles and reacts on physical exercise. Fat stored diffusively in and in between the internal organs is much more dangerous than fat stored as subcutaneous fat and weight gain due to increased muscle mass is rather positive than negative for your health.

Body composition measurement with magnetic resonance imaging (MRI) enables safe and accurate quantification of fat and how it is stored in the body. The technology can determine diffuse storage of fat in the liver, pancreas and muscles, fat stored between the internal organs in the abdomen, and subcutaneous fat. The technique also allows quantification of the volume of muscles.

In this project we develop a technique for detailed analysis of fat and muscle tissue in the body based on whole body MRI examination (see figure). Recent technical development of MRI scanners enables high-resolution images of the complete body without exposing the subject to ionizing radiation or other known health risks. The technique can be applied in large-scale research studies to provide a better understanding about different body composition phenotypes.

We apply the technique in a number of clinical studies. In one project we study fibromyalgia where we recently showed an increased fat content in the thigh muscles of fibromyalgia patients. Another project regards whiplash associated disorders, where fat infiltration in deep neck muscles may affect the outcome of patient rehabilitation. We also study the effect of anti-obesity therapies and the role of abdominal and liver fat in diffuse liver disease.

Furthermore, we use the technique to provide better understanding of Sarcopenia, the decline of muscle tissue with age, which is one of the most important causes of functional decline and loss of independence in older adults.

Another important application area of the technique is imaging of brown adipose tissue (BAT). Recently, we demonstrated the presence of BAT between the shoulder blades in human infants. BAT is an organ that allows non-shivering thermogenesis in mammals and is a potential target for anti-obesity therapies.

PROJECT NAME
Whole body MRI-based fat and muscle measurement

PROJECT LEADER
Olof Dahlqvist Leinhard, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Magnus Borga, Professor, Thobias Romu, PhD Student, Anette Karlsson, PhD Student, Thord Andersson, PhD Student, Patrik Tunon, MSc Student

GRANTS
FORSS Research council of Southeast Sweden 2012-2014

KEY PUBLICATIONS

Lidell M, Betz M, Dahlqvist Leinhard O, Heglind M, Elander L, Slawik M, Mussack T, Nilsson D, Romu T, Nuutila P, Virtanen K, Beuschlein F, Persson A, Borga M, Enerbäck S. Evidence for Two Types of Brown Adipose Tissue in Humans. Nature Medicine, Volume 19(5):631-634, 2013, DOI:10.1038/nm.3017.

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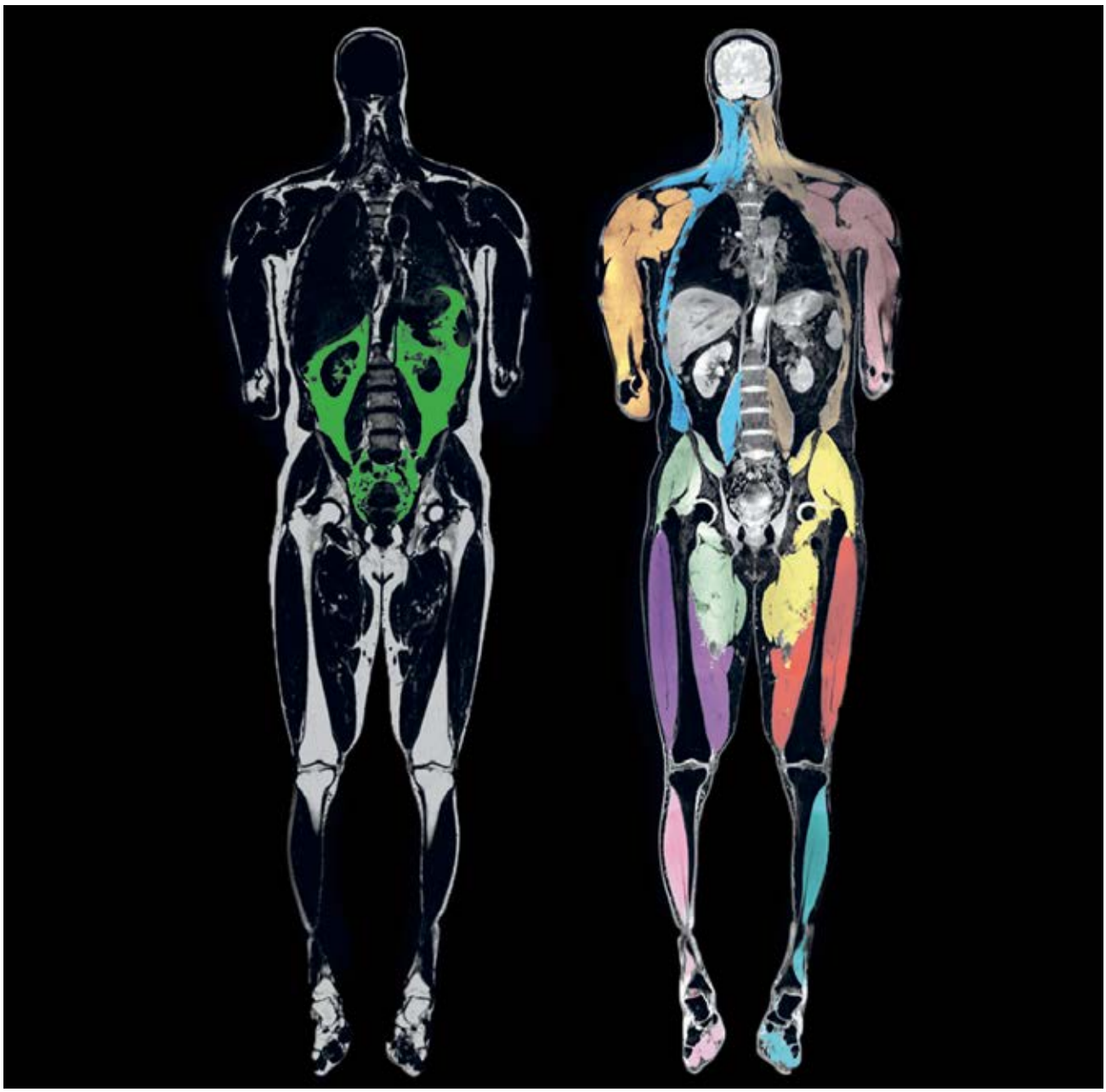
Dahlqvist Leinhard O, Johansson A, Rydell J, Smedby Ö, Nyström F, Lundberg P, Borga M. Quantitative Abdominal Fat Estimation Using MRI. 2008 19th International Conference on Pattern Recognition, ICPR 2008 , art. no. 4761764.



Automatically segmented whole body fat and water separated dataset from a 10 minutes MRI examination where abdominal fat (left) and different muscle groups (right) are shown in different colors.

Popular Scientific Summary
Claes Lundström

PROJECT NAME
Optimized flows and IT tools for digital pathology

PROJECT LEADER
Claes Lundström, Department of Science and Technology, Division for Media and Information Technology

MAIN PROJECT PARTICIPANTS
Senior research leaders: Claes Lundström, Darren Treanor, Martin Hallbeck, Peter Lundberg, Stergios Kechagias, Karin Wårdell, Daniel Forsberg, Nastaran Monsef, Ebo de Muinck, Per Carlsson, Lars-Åke Levin

Post-docs: Martin Falk, Nazre Batool

PhD students: Dharshana Jayewardene, Jesper Molin, Anna Bodén, Mattias Aronsson

Main clinical partners: Anna Bodén, Arrigo Capitanio, Helén Richard,Karin Skoglund

GRANTS
VINNOVA 2012-2014, 2015-2017

KEY PUBLICATIONS
Jesper Molin, Morten Fjeld, Claudia Mello-Thoms, Claes Lundström. Slide navigation patterns among pathologists with long experience of digital review, Histopathology 2014

Daniel Forsberg, Nastaran Monsef Evaluating Cell Nuclei Segmentation for Use on Whole-Slide Images in Lung Cytology, 22nd International Conference on Pattern Recognition (ICPR), 2014

Sten Thorstenson, Jesper Molin, Claes Lundström. Implementation of large-scale routine diagnostics using whole slide imaging in Sweden: Digital pathology experiences 2006-2013, Journal of Pathology Informatics 2014

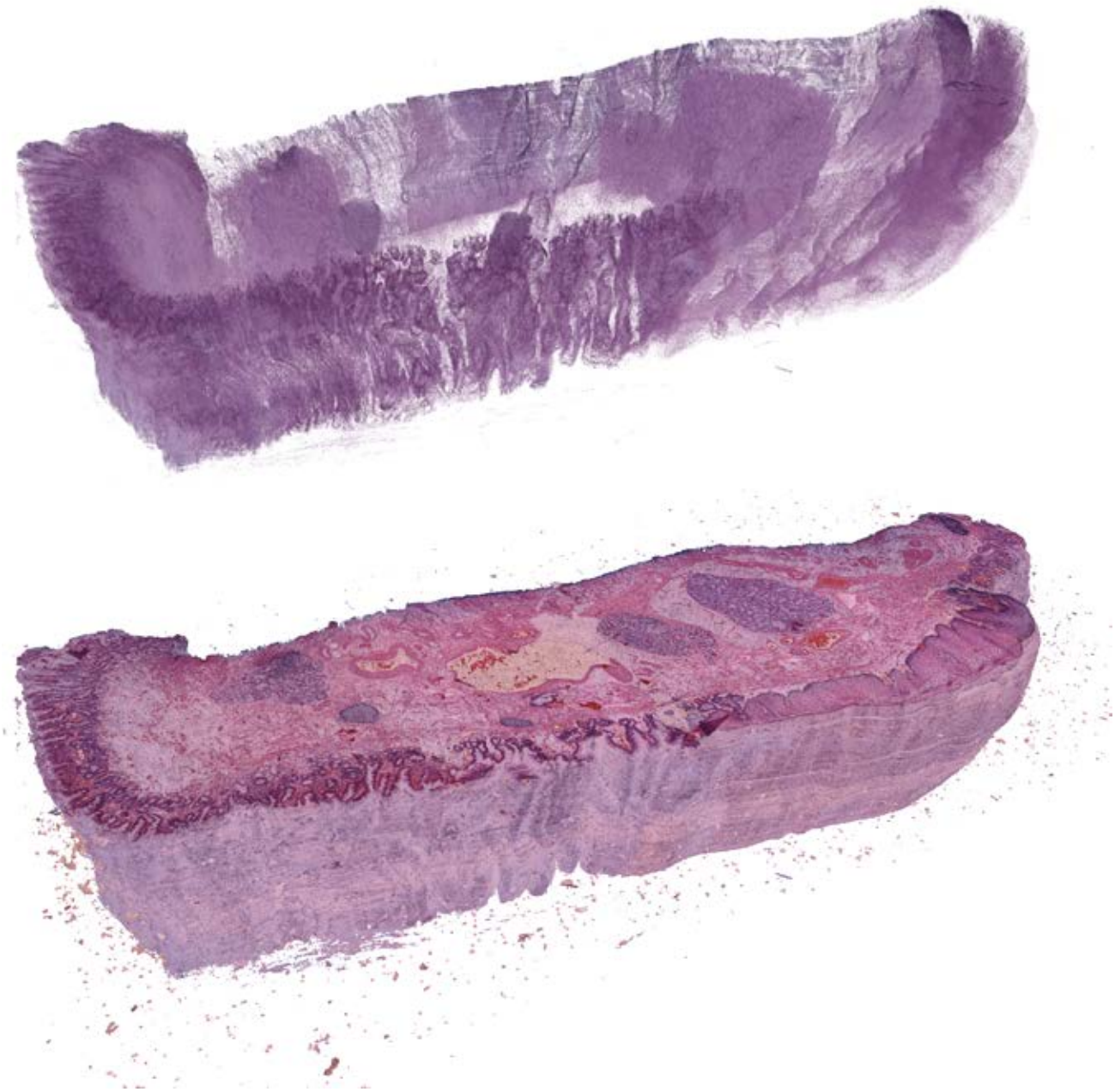
OPTIMIZED FLOWS AND IT TOOLS FOR DIGITAL PATHOLOGY

Diagnostic pathology is of crucial importance for health care, especially cancer care. Pathologists analyze tissue from the patient to determine its characteristics (histology). This knowledge is used to find the correct diagnosis and therapy. Due to lack of pathologists the waiting time for the pathology report is often long, with an anxious wait and delayed therapy for the patient as a result.

Digitization of the pathology workflow has the potential to increase both efficiency and quality of care.

In order to realize this potential, cross-disciplinary research efforts are needed that can combine clinical expertise with knowledge in image analysis and human-computer interaction.

This project aims to design an optimal workflow for digitized pathology, to develop IT tools such as the pathologist's workstation, and to bring the resulting innovations out into the clinical reality. Apart from CMIV the project consortium currently consists of Sectra AB, eleven regional care providers, Equalis, Interactive Institute Swedish ICT, and LRI Imaging AB. The main funding source



3D histology. Images of consecutive tissue slides from one sample are merged into a 3D volume

is VINNOVA (the Swedish Innovation Agency). CMIV efforts within the project are primarily focused on a number of research initiatives.
Today, most pathologists analyze histology samples in a microscope. In digital pathology the histology samples are instead scanned to create digital images of the tissue, which can be analyzed on a computer screen. While the pathologist is still responsible for the evaluation and diagnosis, the digital environment is a valuable tool for image analysis to detect, measure and grade diagnostic findings.

Analyzes of the pathology department show that digitization of the workflow from referral, finished preparation and scanning of samples to the pathologist´s workstation may result in a better overview of the workload, less administration and shorter turnaround times. Digital pathology also entails unique opportunities for collaborations between hospitals both regionally and worldwide as the digital samples can be sent instantly.

The CMIV research agenda in digital pathology tackles image analysis challenges such as correlating findings between radiology and histology in liver biopsies and carotid artery plaques, as well as breast cancer histological grading and lung cancer cytology screening. Visualization challenges for 3D histology are being addressed. Furthermore, the possibilities to validate the clinical work are investigated and human-computer interaction aspects are explored. A common ground for the research projects is the focus on finding digital solutions that will work in the clinical setting.

Popular Scientific Summary
Peter Lundberg

PRESTO-CAN FOR THREE-DIMENSIONAL FUNCTIONAL MRI

PROJECT NAME
PRESTO-CAN for three-dimensional functional MRI

PROJECT LEADER
Peter Lundberg, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Maria Magnusson, Olof Dahlqvist Leinhard, Helene van Ettinger-Veenstra

GRANTS
Swedish Research Council (VR), Cancerfonden, Knowledge foundation.

KEY PUBLICATIONS
Magnusson M, Dahlqvist Leinhard O, Brynolfsson P, Thyr P, Lundberg P. 3D Magnetic Resonance Imaging of the Human Brain – Novel Radial Sampling, Filtering and Reconstruction. In: Proceedings of the 12th IASTED International Conference on Signal and Image Processing, Acta Press, 2010.

Magnusson M, Dahlqvist Leinhard O, Brynolfsson P, Lundberg P. A 3D-plus-time radial-Cartesian hybrid sampling of k-space with high temporal resolution and maintained image quality for MRI and fMRI. In: Proceedings of the 19th Scientific Meeting & Exhibition of ISMRM, Montréal, Québec, Canada, 2011.

Magnusson M, Dahlqvist Leinhard O, van Ettinger-Veenstra, H, Lundberg P. FMRI Using 3D PRESTO-CAN - A Novel Method Based on Golden Angle Hybrid Radial-Cartesian Sampling of K-Space In: Proceedings of the 20th Scientific Meeting & Exhibition of ISMRM, Melbourne, Australia, Montréal, 2012.

The magnetic resonance images (MRI) are not produced directly by the MRI scanner. Instead raw data from the scanner is temporary stored in the so called k-space. The raw data comes in to k-space as sinus waves of different frequencies. These frequencies can then be transformed into images by a mathematical operation. This is called reconstruction. Normally, the frequency measurements are performed in thin 2D slices of the body which are reconstructed and combined in a stack to form an image volume. Occasionally, k-space is measured directly in 3D with a square pattern called Cartesian sampling pattern (figure 1, left).

In contrast to the 3D Cartesian geometry, our method PRESTO-CAN samples k-space using a hybrid between a radial geometry and a Cartesian geometry (figure 1, right). The large steps in the angular direction gives a fast recording of the important information located in the center of k-space.

As seen to the right in figure 1, there are more densely sampled data in the inner part of k-space. It has been shown that by removing parts of the inner over-sampled k-space at certain time points, the temporal resolution can be further increased. However, this gives a more complicated sampling pattern and a non-trivial reconstruction. PRESTO-CAN has shown to provide excellent temporal resolution and satisfactory image quality.

The method was developed having functional MRI (fMRI) applications in mind. In fMRI, MRI-volumes are recorded during a time period when a person/patient performs a particular task. By analyzing the MRI time sequence, it is possible to detect brain activity. Accordingly, it is desirable with a high time resolution.

A major advantage of the PRESTO-CAN sequence is that it allows for whole brain coverage. We are currently performing a comparative fMRI study between PRESTO-CAN and conventional techniques, like EPI. Figure 2 shows left and right fingers fMRI-activation computed from MRI-data based on PRESTO-CAN.

The rather simple geometry of PRESTO-CAN makes it easy to include standard procedures for speeding up the data acquisition further, such as parallel imaging which can be combined with unique 3D motion correction schemes. These possibilities will be investigated further.

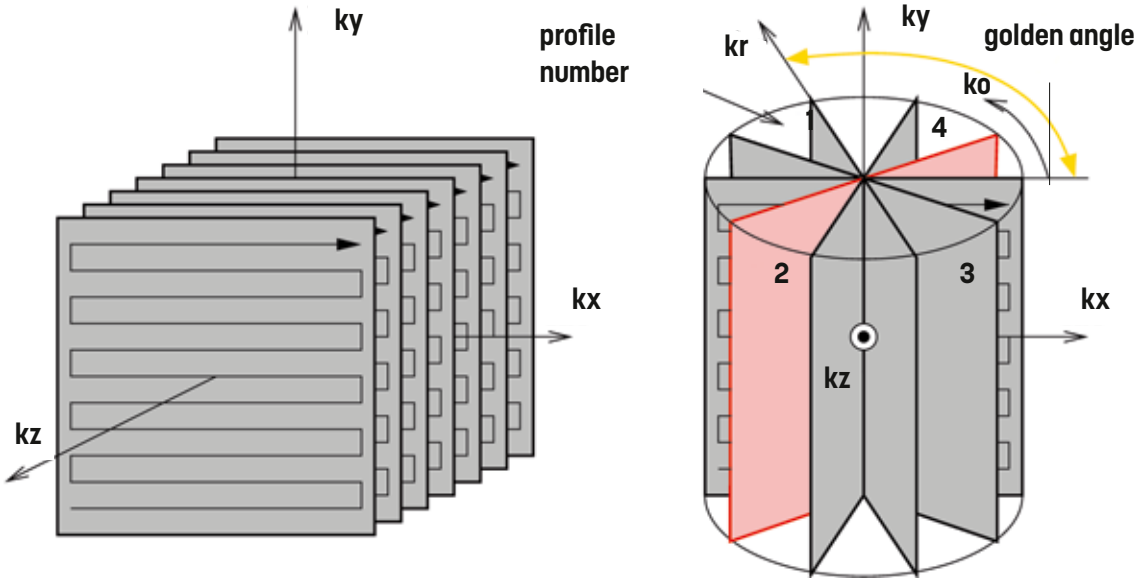


Figure 1. Left: 3D Cartesian sampling of k-space. Right: PRESTO-CAN sampling of k-space.

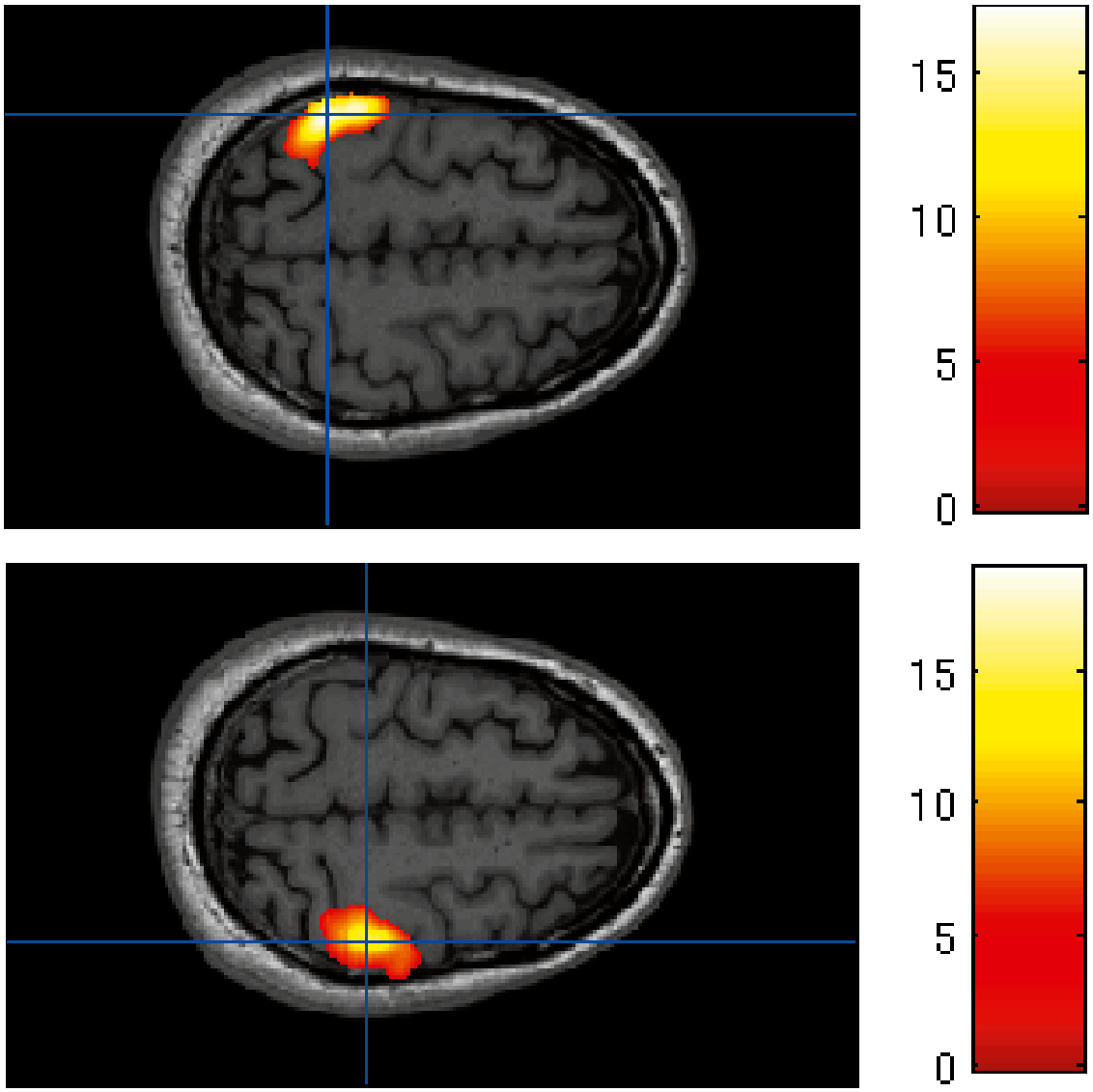


Figure 2 fMRI-activation computed from MRI-data based on PRESTO-CAN. Left: activation in left fingers motor cortex. Right: activation in right fingers motor cortex.

Popular Scientific Summary
Rozalyn Simon

THE NEUROCORRELATES OF MEDITATIVE PRACTICE

When an individual is in a quiet state of rest, thought-related activity in the brain does not cease. This activity can be recorded by functional magnetic resonance imaging (fMRI) and represented as constellations of anatomic regions in the brain that co-activate during cognition called resting state networks.

Although there are a number of such networks, the default mode network (DMN) became the first, and now the most extensively studied of the many known resting state functional networks. Network activation has been associated with specific mentation including autobiographical memory, self-reflective thought, envisioning future events, mind wandering, and considering the thoughts and perspectives of others.

Abnormal DMN activity – such as distractive mind wandering during tasks or excessive rumination – has been associated with a number of psychological disorders such as schizophrenia, anxiety, depression, attention deficit hyperactivity disorder (ADHD), and Alzheimer's disease (AD).

Meta-analyses examining the specific neurocorrelates of meditation have shown reductions in DMN activity as a primary outcome of meditation practices. In addition, modulation

PROJECT NAME
The neurocorrelates of meditative practice

PROJECT LEADER
Rozalyn Simon, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Maria Engström

KEY PUBLICATIONS
Rozalyn Simon and Maria Engström. The default mode network as a biomarker for monitoring the therapeutic effects of meditation. Frontiers in Psychology, 2015; 6:776.

M. Engström, J. Pihlsgård, P. Lundberg, and Birgitta Söderfeldt. Functional magnetic resonance imaging of hippocampal activity during silent mantra meditation. Journal of Alternative and Complimentary Medicine, 2010;16:1253-1258.

M. Engström and B. Söderfeldt. Brain activation during compassion meditation: a case study. Journal of Alternative and Complimentary Medicine, 2010;16:597-599.

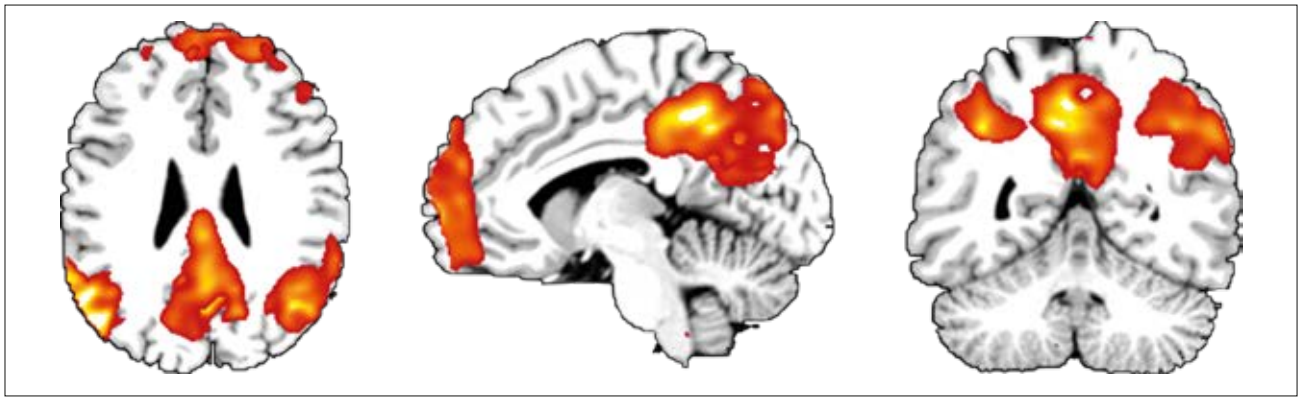


Figure 1. Data from five zen meditators showing differences in the Default mode network between focused attention meditation on breath versus resting state. Increases in red, decreases in activity in green.

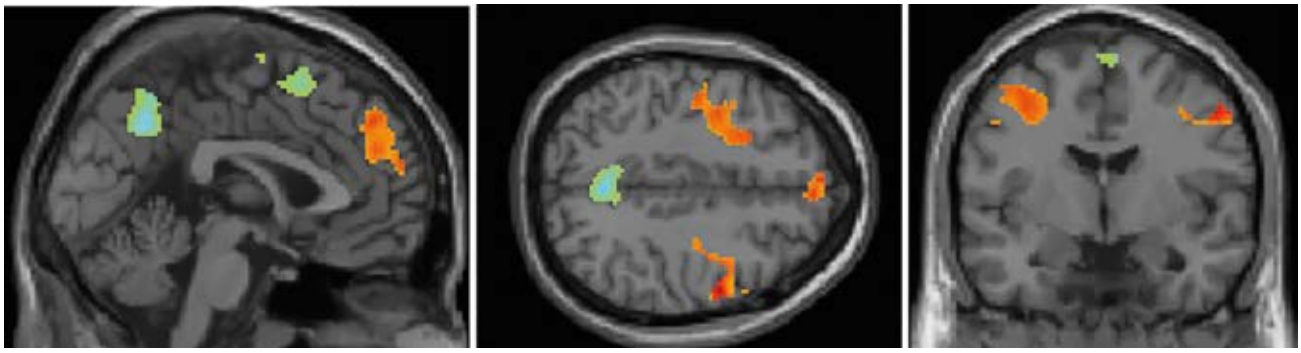


Figure 2. Activations in the default mode network for meditators during rest alone.

of DMN activity through meditative training has been demonstrated to help individuals concentrate and increase their present awareness, thus reducing mind wandering activities and improving cognition. Functional magnetic resonance imaging (fMRI) has been used to successfully visualize changes in the DMN resulting from meditative practices such as Vipassana and Mindfulness-based stress reduction (MBSR).

Although there is evidence that meditation practice alters DMN activity, the specific neurocorrelates based on the type of meditation practiced remain unclear. For example, what regions of the brain are active when one focuses their attention on the breath? How does open awareness of one's thoughts affect emotional centers of the brain?

In this project we are investigating the neural correlates of meditative practice in both experienced and novice meditators. Our goal is to identify specific regions of the brain affected by three specific types of meditation techniques by fMRI and EEG.

To date the project has examined 10 experienced meditators practicing techniques common to Buddhist meditation. We will be investigating cognitive activations, functional connectivity between regions, changes in gray and white matter, and changes in the quality of life resulting from meditative training.

Research-based evidence indicates that these practices, when used efficiently, could prove effective not only in the delay of cognitive dysfunction, but also in the enhancement of grey matter density and neuron plasticity in specific regions of the brain. By determining these neurocorrelates, it is our intention to effectively employ very specific meditative techniques as a means for the individual to regain control over irregular DMN activity and connectivity while providing a new perspective on the value of the present moment.

Popular Scientific Summary
Maria Engström

AB INITIO MATHEMATICAL MODELING OF MECHANISMS IN THE HUMAN BRAIN

By functional magnetic resonance imaging (fMRI), brain activity can be visualized and time dependent signals of the brain at work can be recorded. Despite the fact that fMRI is widely used in both research and health care, the relation between brain activity and the recorded signals remains elusive.

The aim of this project is to investigate different hypotheses that explain the relationships between brain activity and the fMRI signal using systems biology and mathematical mechanistic modeling. This approach offers the possibility to systematically investigate different theories on brain function and thereby increase the understanding of how the brain works (figure 1).

Several hypotheses of the neurobiology behind the fMRI signal are described in the literature. In this project we "translate" these hypotheses to mathematical expressions, so called differential equations. The mathematical models are then fitted to experimental data, which could be the fMRI signal but also measurements of blood flow, hemoglobin or neurotransmitter concentrations. By fitting a mathemati-

PROJECT NAME
Ab initio mathematical modeling of mechanisms in the human brain

PROJECT LEADER
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Karin Lundengård, Natasha Morales-Drissi, Sebastian Sten, Gunnar Cedersund, Fredrik Elinder, Susanna Walter

GRANTS
Swedish Research council

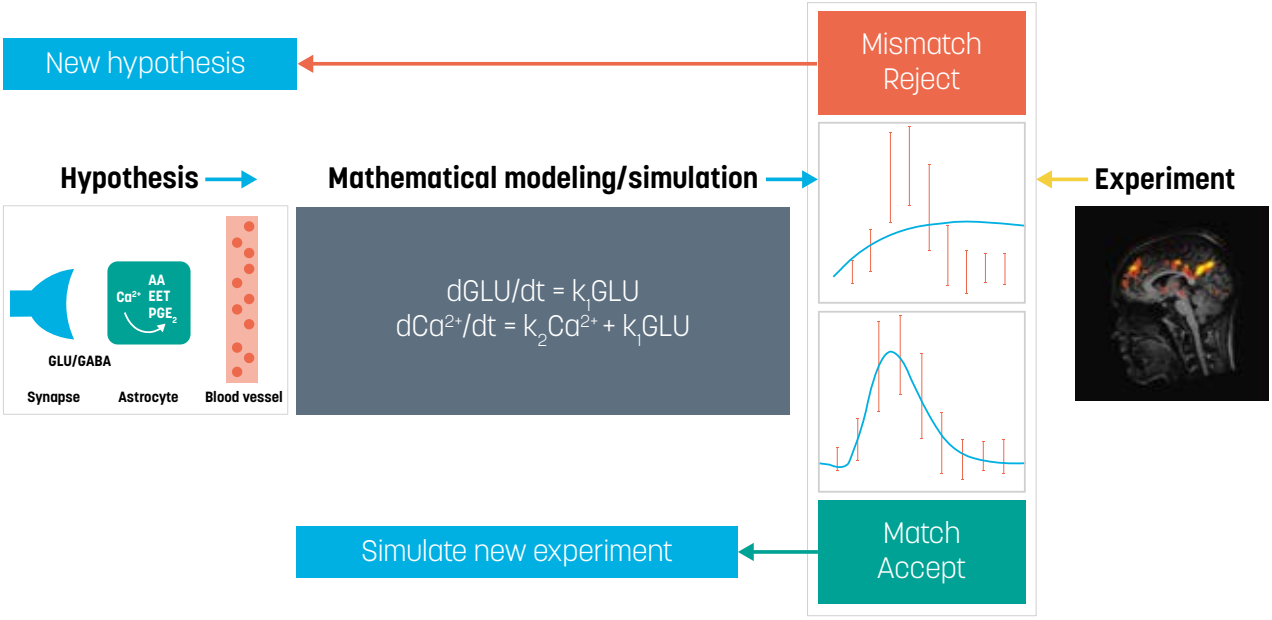


Figure 1. (ModelingOutline): Schematic overview of the project showing a simplified workflow from hypothesis to mathematical modeling, experimental data and hypothesis rejection or acceptance.

cal model to experimental outcome, we can evaluate if the model can or cannot explain data. Once we know that the model can explain data, we can use the model to predict brain function in response to different stimuli (figure 2).

In the first phase of the project we have investigated the "metabolic" and the "neurotransmitter" hypotheses, which currently are the most supported. According to the metabolic hypothesis, it is assumed that activated nerve cells have an increased energy demand and thereby an increased need for oxygen and glucose, which is supplied by increased cerebral blood flow. According to the neurotransmitter hypothesis, on the other hand, it is assumed that neurotransmitters, which are released when the brain is activated, trigger the release of substances that dilate or contract blood vessels. Preliminary data show that neither of these hypotheses alone can explain the fMRI signal. The metabolic hypothesis is necessary to explain the transient decrease in the fMRI signal immediately after a stimulus and the neurotransmitter hypothesis explains the response peak that occurs 6-8 seconds after a stimulus.

In the future we will use the mathematical models to investigate brain function in clinical studies. For this purpose, the project is directly linked to "Sleep abnormality network description: Modeling and analysis in neuroimaging", which investigates patients with sleep disorders.

Popular Scientific Summary
Maria Engström

FUNCTIONAL MRI STUDIES OF NORMAL AND IMPAIRED LANGUAGE FUNCTION

PROJECT NAME
Functional MRI studies of normal and impaired language function

PROJECT LEADER
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Thomas Karlsson, Anne-Marie Landtblom, Peter Lundberg, Helene Van Ettinger-Veenstra, Helena Gauffin, Anita McAllister

GRANTS
Henry och Ella Margareta Ståhls stiftelse

KEY PUBLICATIONS

H. Gauffin, H. van Ettinger-Veenstra, A-M Landtblom, D. Ulrici, A. McAllister, T. Karlsson, M. Engström. Impaired language function in generalized epilepsy: Inadequate suppression of the default mode network. Epilepsy & Behavior, 28:26–35, 2013.

H.M. Van Ettinger-Veenstra, M. Ragnehed, A. McAllister, P. Lundberg, M. Engström. Right-Hemispheric Cortical Contributions to Language Ability in Healthy Adults. Brain and Language, 120:395–400, 2012.

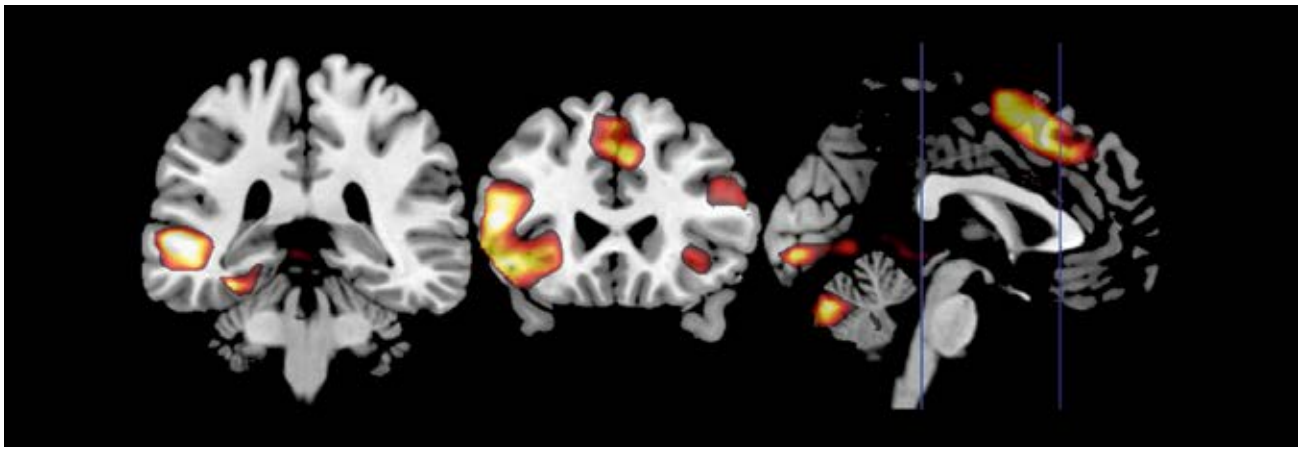
H.M. Van Ettinger-Veenstra, M. Ragnehed, M. Hällgren, T. Karlsson, A-M Landtblom, P. Lundberg, and M. Engström. Right-hemispheric brain activation correlates to language performance. NeuroImage, 49:3481-3488, 2009.

Language ability plays an important role when communicating with others. Although the most important areas of the brain that are involved in language function are identified, the relation between activation in these areas and language ability is not fully uncovered. That is to say, we do not know in detail the relation between the magnitude and extent of language activation as measured by brain scanning and individual performance on language tests.

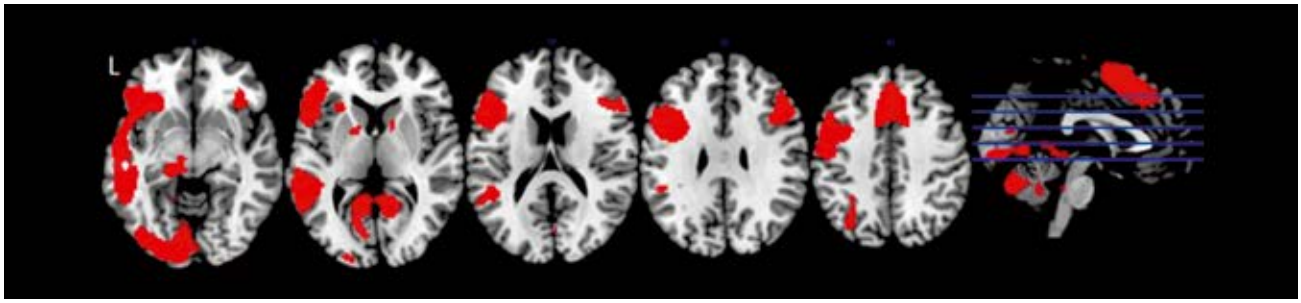
In this project we approached this research question by investigating healthy individuals and patients with epilepsy by functional Magnetic Resonance Imaging (fMRI) and standardized language tests.

For most people the brain's left hemisphere is dominant for language. This means that the left side of the brain executes language tasks, such as reading and talking. However, the brain's right side is also often activated during language tasks, but the role of the right hemisphere in language remains elusive.

We have shown that the right side of the brain plays an important role in supporting language ability. We have also shown that patients with generalized epilepsy have subtle language deficits related to inability to suppress the brain's default mode network during language processing. When performing executive tasks, such as language processing, this network should be suppressed for an optimal usage of the brain's resources. Preliminary data from patients with focal epilepsy in the left hemisphere indicate that these patients have a functional reorganization of language-related areas in the brain.



Language function in healthy subjects, coronal and sagittal slices: Brain activation is observed in typical language areas of the brain i.e., Broca's and Wernicke's areas, but also in medial frontal regions.



Language function in healthy subjects, axial slices: The left side is dominant; however, activation in the right hemisphere is also present.

Popular Scientific Summary
Nina Nelson

FUNCTIONAL NEUROIMAGING IN FORMER PRETERM CHILDREN WITH VERY LOW BIRTH WEIGHT

If a child is born preterm with a very low birth weight, it enters a life full of obstacles. After its struggle to survive, there is a struggle to keep up with its peers at school, as many preterm born children experience cognitive deficits, including language problems. These deficits are often related to risks for early brain insults, including periventricular leucomalacia, intraventricular hemorrhage and associated white matter disease. These insults together with adverse effects of other perinatal complications are responsible for a changed brain development in preterm born children.

In southeast Sweden, a group of preterm children with very low birth weight and a group of full-term born children as a control group was followed over time. Our interest in this functional magnetic resonance imaging (fMRI) study was to investigate components of reading ability in these groups, as reading is essential for school performance.

With fMRI, the activity level of the brain can be measured by looking at changes in blood flow transporting oxygen to active brain regions. During fMRI, our group of children did a series of language tasks, tapping semantic, orthographic, and phonological skills, all essential for reading ability.

As expected, the preterm very low birth weight group showed signs of altered development of their brain, and in effect altered pattern of activation

PROJECT NAME
Functional neuroimaging in former preterm children with very low birth weight

PROJECT LEADER
Nina Nelson, Department of Clinical and Experimental Medicine, Division of Pediatrics

MAIN PROJECT PARTICIPANTS
Helene van Ettinger-Veenstra, Carin Widén, Thomas Karlsson, Ingemar Leijon

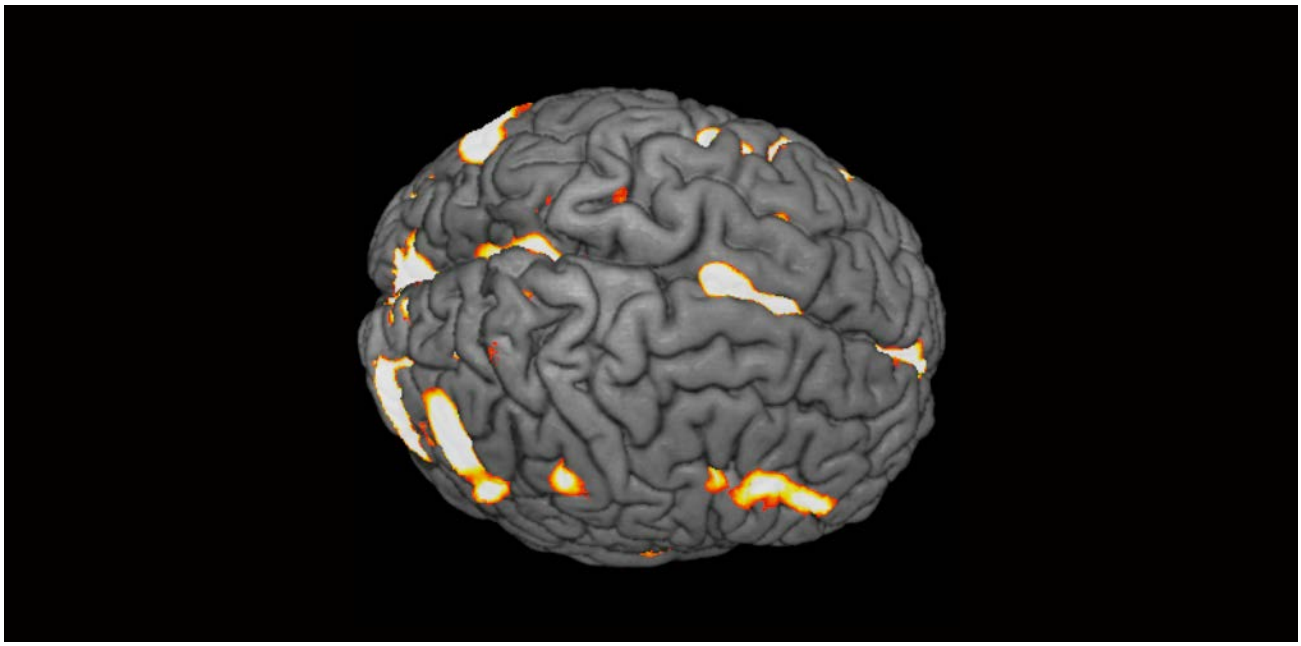


Figure 1. Sites of brain activity correlating (positively or negatively) with language tasks without regard to birth weight. (Head is facing rightward).

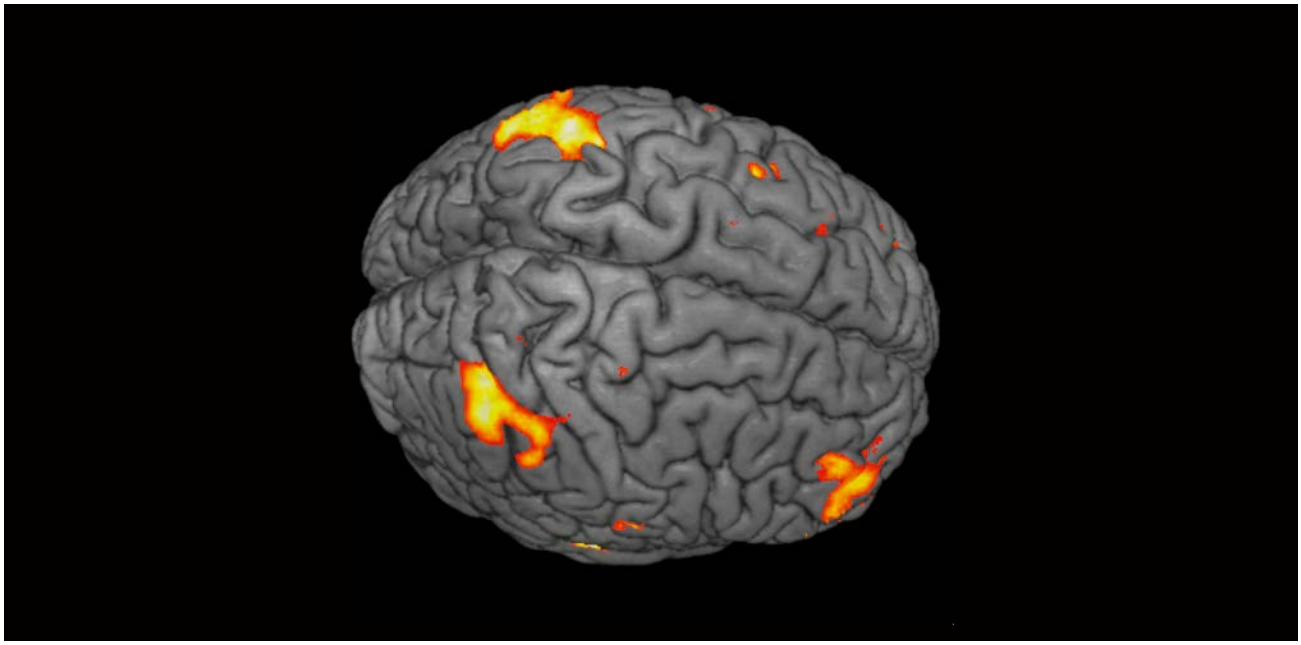


Figure 2. Difference in brain activity during language processing between normal birth weight and very low birth weight children in the fronto-parietal network.

during language processing. The preterm group had smaller brains, lower performance on language tasks and a performance IQ task.

Interestingly, the preterm very low birth weight group showed indication of an interchanged activation pattern for the semantic and the phonological tasks when compared to term-born children. This is indicative for a functional switch towards activating semantic processing regions for phonological processing. Alternatively, the very low birth weight group has less efficient neural processes during a task, and therefore recruits more brain regions to solve a task while the term-group may rely more on automated processes.

Subthreshold exploration has revealed an indication of less activity for preterm children in brain regions important for attention and voluntary control during tasks. The direct connection between these fronto-parietal regions - important for communication between brain regions - develops during childhood. We hypothesize that children born preterm lag behind in development of these connections. As an effect, they may show impaired ability to focus on their task, and thus show lower performance than the term-born group; this would be an alternative explanation to impaired cognitive functioning.

Popular Scientific Summary
Anne-Marie Landtblom and Maria Engström

PROJECT NAME
Clinical, psychosocial and imaging studies of fatigue in multiple sclerosis

PROJECT LEADER
Anne-Marie Landtblom, Department of Clinical and Experimental Medicine, Division of Neurology
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Anna-Christina Ek, Thomas Karlsson, Gullvi Flensner, Olle Söderhamn

GRANTS
Swedish Research Council (VR)

KEY PUBLICATIONS

Flensner G, Ek AC, Söderhamn O, Landtblom AM. Sensitivity to heat in MS patients: a factor strongly influencing symptomology – an explorative survey. BMC Neurol 2011;11:27.

Flensner G, Landtblom AM, Söderhamn O, Ek AC. Work capacity and health-related quality of life among individuals with multiple sclerosis reduced by fatigue: a cross-sectional study. BMC Public Health. 2013 Mar 15;13:224. doi: 10.1186/1471-2458-13-224.

Engström M, Flensner G, Landtblom AM, Ek AC, Karlsson T. Thalamo-striato-cortical determinants to fatigue in Multiple Sclerosis. Brain & Behaviour, 2013 November; 3(6): 715-728.

CLINICAL, PSYCHOSOCIAL AND IMAGING STUDIES OF FATIGUE IN MS

Multiple Sclerosis (MS) is an inflammatory disease affecting the nerve cells of the brain and spinal cord. The disease damages the nervous system communication resulting in a wide range of physical and mental symptoms. Fatigue, extensive tiredness and exhaustibility, is a common symptom of multiple sclerosis (MS). Fatigue is often found to be a more decapitating symptom than paresis. In this project we have aimed to describe fatigue from an epidemiological, psychosocial (effect on employment), physiological (coupling to heat sensitivity), clinical (effect on cognition) and interventional (cryotherapy) point of view.

Fatigue can be either peripheral or central. The neuronal mechanisms are not fully uncovered but the hypotheses for central fatigue involve the feedback loops between the basal ganglia and the motor cortex.

We have used functional magnetic resonance imaging of the brain (fMRI) to investigate the neuronal activity involved in the enhancement of cog-

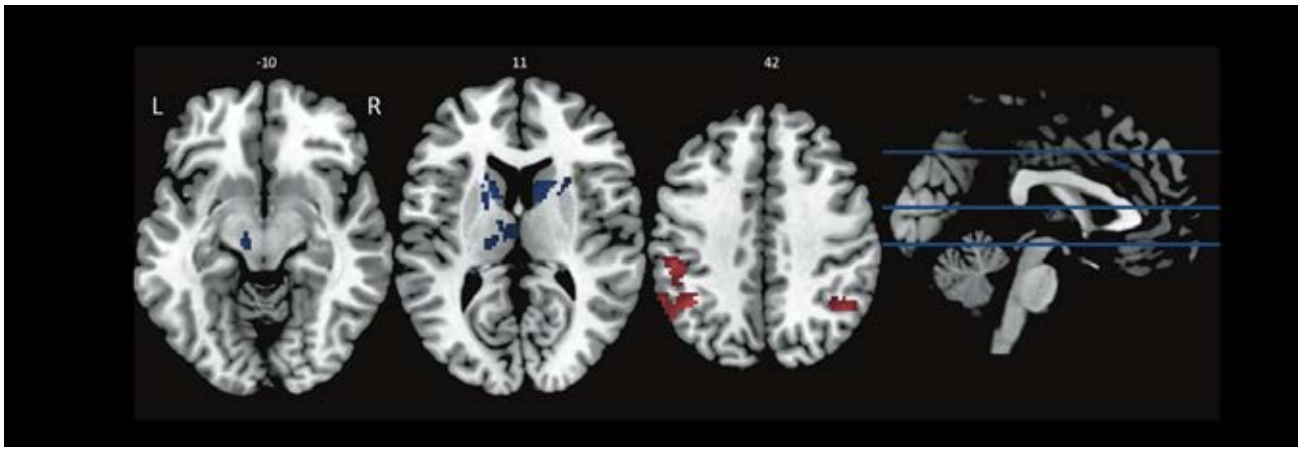


Figure 1. Differences in brain activation between MS participants and healthy participants in regions of interest in the brain. The red colour represents areas that were more activated in MS participants compared to controls, and the blue colour represents areas that were less activated in MS participants compared to controls.

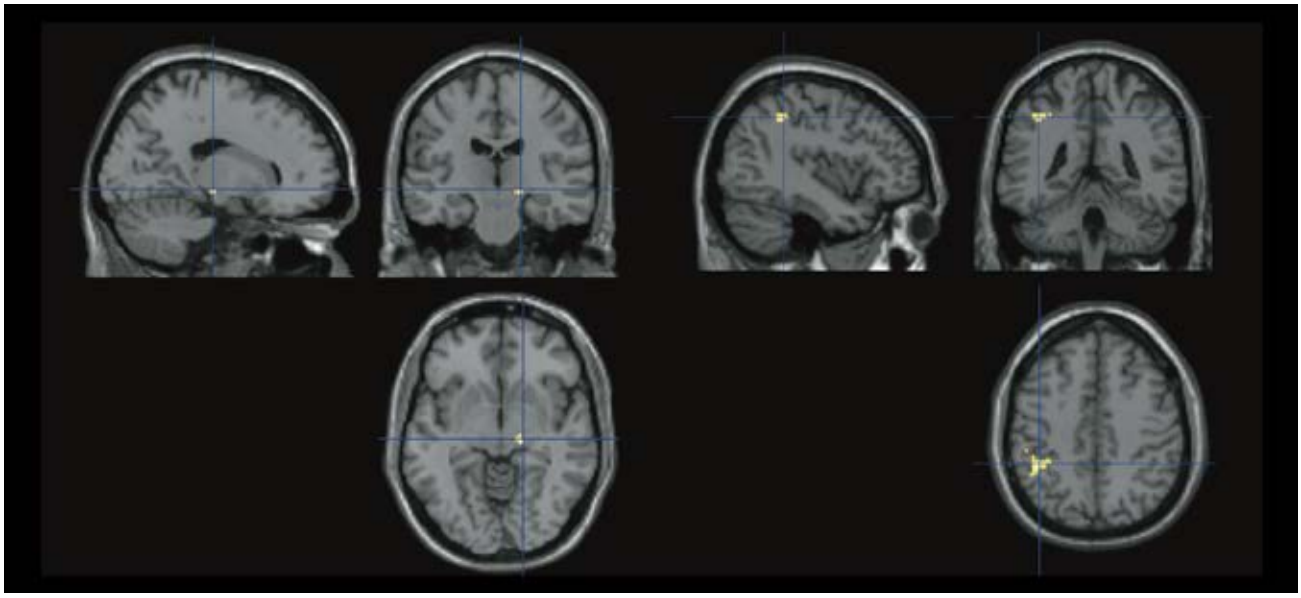


Figure 2. Brain activation with positive correlation to perceived fatigue during the working memory task. The images show activation in regions of interest: the right substantia nigra and the left posterior parietal cortex.

nitive problems due to fatigue among patients with MS. In fMRI, changes to the blood flow in the brain are measured. Increased blood flow corresponds to increased activity in that area of the brain. The patients were performing verbal tasks during the scan. A control group of healthy participants were also investigated. The patients were then examined in the same way after having a treatment with cryotherapy, i.e. having put on an active cooling garment with running cold water to lower the body temperature. The measurements were repeated to see if the cooling had improved the cognitive functions.

The fMRI experiments showed correlation between activation in specific areas of interest in the brain and perceived fatigue during the working memory tasks. The areas activated were the right substantia nigra and the left posterior parietal cortex. Neuropsychological investigations revealed clear effects on the working memory in the patients with MS and fatigue compared with the control group.

It is important to describe fatigue to gain acceptance for this decapacitating symptom. It is of great relevance to continue to investigate the physiological mechanisms behind the symptom. The results of this study have identified areas of the brain that are involved.

Analysis of results after intervention with a cooling garment is ongoing; here fMRI analysis is of great interest and can help in determining the physiological background of fatigue.

Popular Scientific Summary
Anne-Marie Landtblom and Maria Engström

CLINICAL, IMAGING AND MEMORY INVESTIGATION IN PATIENTS WITH THE KLEINE LEVIN SYNDROME

PROJECT NAME
Clinical, imaging and memory investigation in patients with the Kleine Levin syndrome

PROJECT LEADER
Anne-Marie Landtblom, Department of Clinical and Experimental Medicine, Division of Neurology
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Peter Lundberg, Thomas Karlsson, Olof Dahlqvist Leinhard, Anders Tisell, Patrick Vigren

GRANTS
Kleine Levin Foundation, USA

KEY PUBLICATIONS
Vigren P, Tisell A, Engström M, Karlsson T, Leinhard Dahlqvist O, Lundberg P, Landtblom AM. Low thalamic NAA-concentration corresponds to strong neural activation in working memory in Kleine-Levin syndrome.PLoS One. 2013;8(2):e56279. Epub 2013 Feb 25.

Engström M, Karlsson T, Landtblom AM. Reduced thalamic and pontine connectivity in Kleine–Levin syndrome. Frontiers in Neurology 2014;5:42.

Engström M, Karlsson T, Landtblom AM. Thalamic activation in the Kleine-Levin syndrome. SLEEP, 2014;37(2):379-386.

Sleep disorders in young individuals are acknowledged as a growing problem. Some disorders increase, especially delayed sleep phase syndrome (DSLP), but also narcolepsy as a consequence of the Pandemrix vaccinations. Some of the rarer sleep disorders are hard to diagnose, especially the periodically occurring hypersomnia, Kleine-Levin syndrome (KLS). The diagnostic tools used are mainly clinical, but in narcolepsy also laboratory.

We have developed laboratory tools to support the diagnosis of the Kleine-Levin syndrome, including neuropsychological testing to identify working memory deficits. We also used measures of cerebral blood flow in our diagnostic set up for KLS. Over the years we have gathered a large number of KLS patients from the Nordic countries (n=30) who take part in clinical and scientific procedures. This gives us the opportunity to compare young individuals with the disorder. Future goals are to investigate also other sleep disorders within a larger project, outlined by associate professor Maria Engström and in collaboration with colleagues in Gothenburg, see Engström's report the SAND:MAN project.

In this study we examined frequency, duration and type of sleep periods that the patient had. We also performed basic investigations including blood flow measurements in the brain (fMRI), where increased blood flow corresponds to increased activity in that part of the brain. The fMRI measurements were combined with cognitive tests of the working memory, and also neuropsychological investigations. The tasks had varying difficulty and therefore required different effort levels. Measurements were also performed in resting state.

Our results show that there are areas

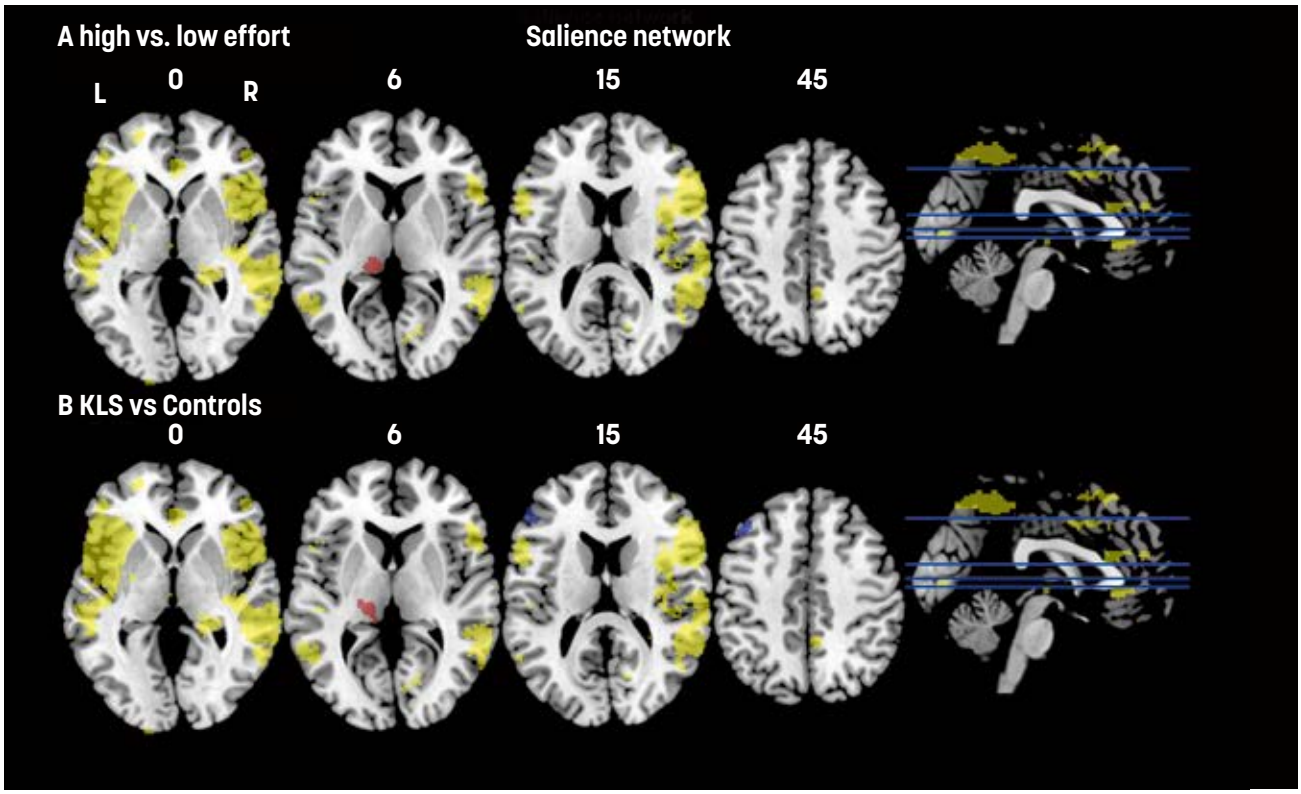


Figure 1. Functional connectivity in the salience network. Neural processing is often performed by an integrated network of several regions in the brain. Functional connectivity studies investigate the interaction of regions within these networks. Yellow areas show the network in selected slices. Red and blue areas show connectivity differences. (A) Red colour denotes regions that are more strongly coupled to the network at a high effort level compared to a low effort level. Blue colour denotes regions that are more strongly coupled to the network at a low effort level. (B) Regions that are more strongly (red) respectively more weakly (blue) coupled to the network in patients with periodic idiopathic hypersomnia (KLS) compared to healthy individuals at the high effort level.

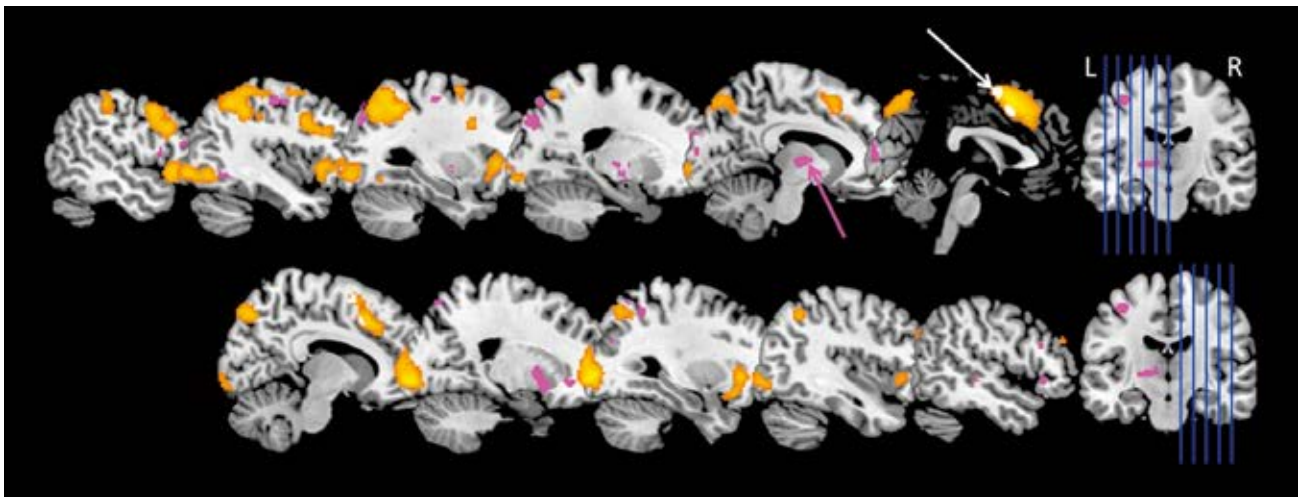


Figure 2. Typical working memory activation in healthy individuals and thalamic hyperactivation in KLS patients. In other parts of the brain KLS patients had less activation than healthy individuals.

in the brain that are activated differently in patients with KLS compared with healthy individuals. The differences between patients with KLS and healthy controls were demonstrated in the resting state. In activated state during the working memory test, patients with KLS showed increased activation in some parts of the brain while other parts were less activated compared with healthy individuals. The differences in activation in these areas could be used to part the KLS patients from the healthy individual in most of the cases; hence the techniques have the potential to be developed into diagnostic tools of KLS.

As mentioned above our present goals are to investigate also other sleep disorders within a larger project. We also plan additional studies regarding genetics and physiology. For example we will investigate the role of body temperature in relation to sleep episodes.

Popular Scientific Summary
Anne-Marie Landtblom

PROJECT NAME
Clinical and Imaging studies of multiple sclerosis

PROJECT LEADER
Anne-Marie Landtblom, Department of Clinical and Experimental Medicine, Division of Neurology

MAIN PROJECT PARTICIPANTS
Peter Lundberg, Olof Dahlqvist Leinhard, Marcel Warntjes, Anders Tisell, Örjan Smedby

GRANTS
Swedish Research Council (VR)

KEY PUBLICATIONS
Tisell A, Leinhard OD, Warntjes JB, Aalto A, Smedby Ö, Landtblom AM, Lundberg P. Increased concentrations of glutamate and glutamine in normal-appearing white matter of patients with multiple sclerosis and normal MR imaging brain scans. PLoS One. 2013 Apr 17;8(4):e61817. doi: 10.1371/journal.pone.0061817.

West J, Aalto A, Tisell A, Dahlqvist Leinhard O, Landtblom AM, Smedby Ö, Lundberg P. Normal and Diffusely Abnormal White Matter in Patients with Multiple Sclerosis, Assessed with Quantitative MR. PLOS one 2014 Apr 18;9(4):e95161. Doi:10.1371/journal.pone. 0095161. eCollection 2014.

Warntjes M, Tisell A, Landtblom AM, Lundberg P. Effects of gadolinium contrast administration on automatic brain tissue segmentation of multiple sclerosis patients. Am J Neurorad 2014;35(7):1330-6

CLINICAL AND IMAGING STUDIES OF MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is an inflammatory disease affecting the nerve cells of the brain and spinal cord. The disease damages the nervous system communication resulting in a wide range of physical and mental symptoms. The symptoms may occur in isolated attacks or build up over time.

Inflammation is, together with destruction, destruction of the insulating covers of nerve cells and the formation of lesions in the central nervous system the main characteristics of MS. However, not all MS patients have the typical lesions in the brain. In fact, MS could be seen as a generic group for a variety of disease patterns and this perspective may help the endeavors to find more specific treatment in the future.

Since not all patients have lesions in their brain, they cannot be the only explanation for the neuronal damage. Patients without lesions have almost equal disability from the disease. New methods that can look deeper into

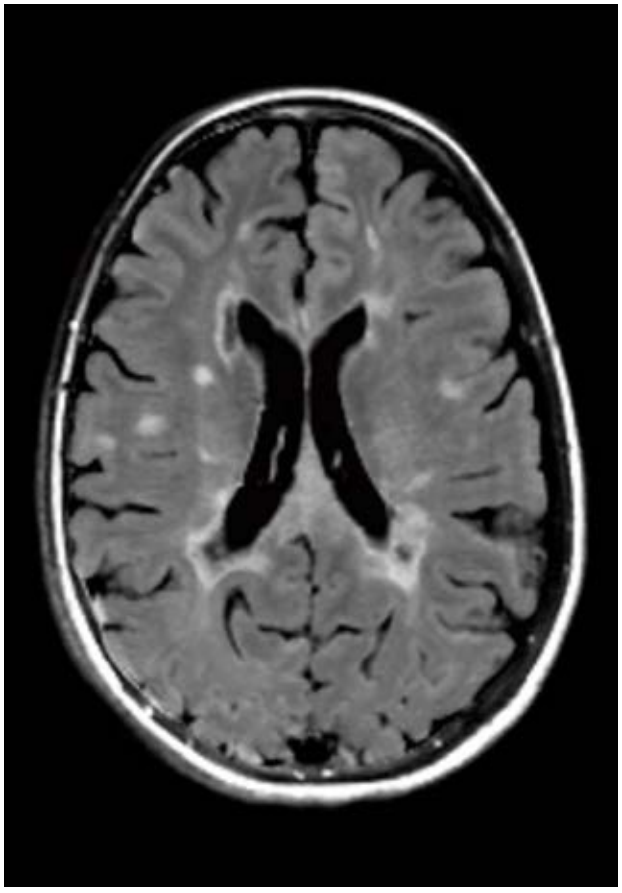


Figure 1. Image of the brain using MRI with conventional technique, showing lesions in the brain which can be a sign of MS, arteriosclerosis or insignificant signs in a healthy person over the age of 40.

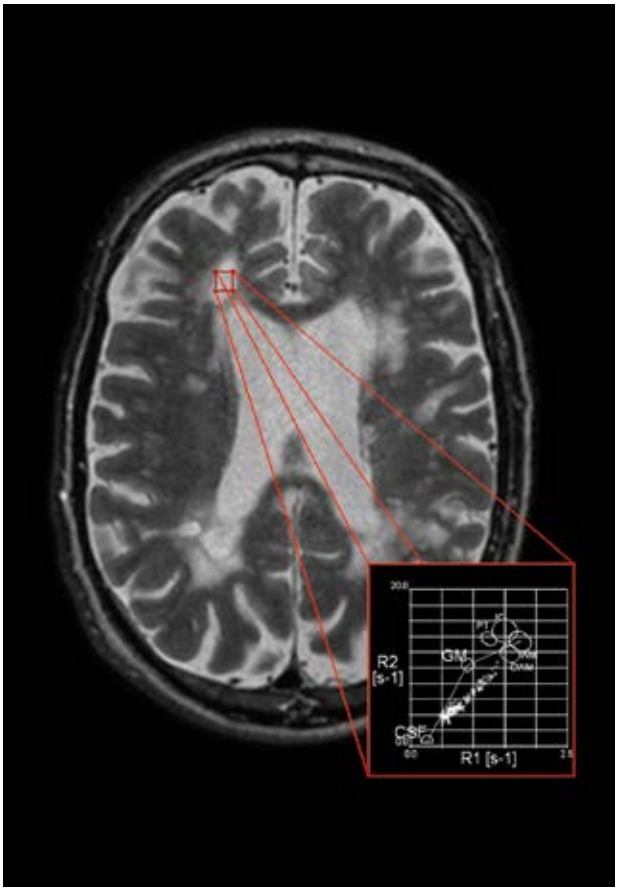


Figure 2. MR based method to discriminate between different types of brain lesions. Image by Örter and Warntjes, 2008.

the cause of MS is therefore of great interest.

Using magnetic resonance (MR) technique we can measure the levels of different metabolites in the brain. High levels of some substances reflect healthy tissue whereas others reflect damage. Using this method we have followed MS patients treated with the pharmaceutical Copaxone. Copaxone has been shown to decrease the lesions and slows down the progression of the disease. The results showed that the treatment slowed down the biochemical development of the disease.

Unspecific lesions in cerebral white matter can be seen both in MS and cerebral arteriosclerosis and is therefore often hard to use as basis for a diagnosis. A possibility to discriminate these lesions regarding their origin would be a valuable tool for diagnosis and we have therefore performed a pilot project aiming to develop an MR method to determine such differences.

This project has until now examined about 10 patients with MS, 10 patients with known cerebral arteriosclerosis with ischemia, and a few patients with diagnostic problems, where MS or arteriosclerosis could not be decided from the clinical and laboratory study. Preliminary results revealed a trend that may help in differentiating these two conditions and this will be investigated further. The project will proceed further including cooperation with Uppsala University.

Popular Scientific Summary
Markus Heilig

NEUROAFFECTIVE EFFECTS OF ELECTROCONVULSIVE THERAPY FOR MDD

Major depressive disorder (MDD) is a highly debilitating psychiatric condition that affects 20-30% of people at some point during their lifetime. Major depression leads all diseases in terms of years of productive life lost due to illness.

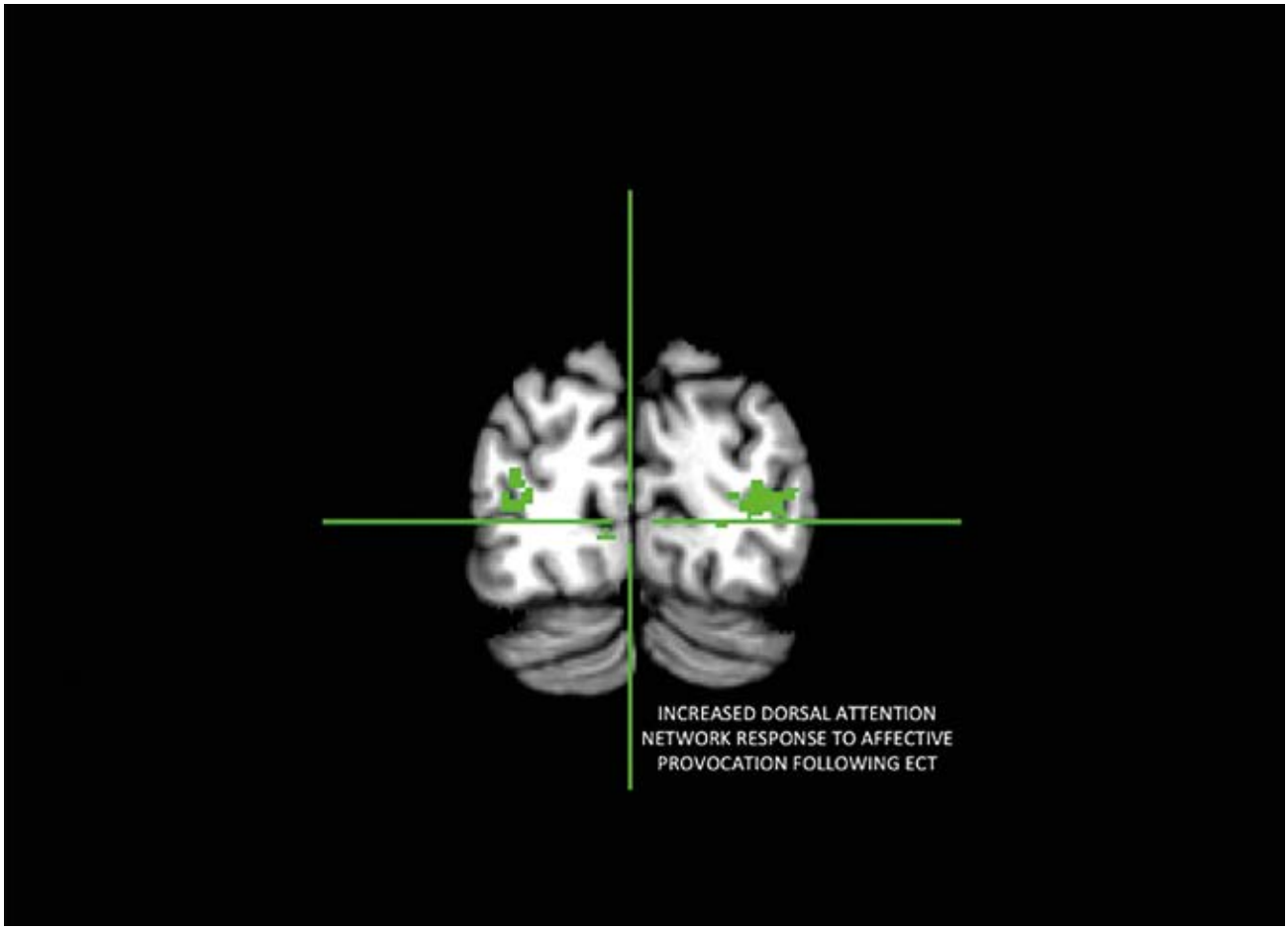
In acute cases of MDD, individuals can become entirely incapacitated or worse; pose a significant danger to themselves. In such acute cases, immediate amelioration of depressive symptomatology is required. Only a small handful of currently implemented courses of treatment can achieve such immediate effects—among these treatments, the most broadly applied is electroconvulsive therapy (ECT).

While effective, ECT is burdensome, requiring the patient to be anesthetized and to receive electrical stimulation sufficient to cause a grand mal seizure and concomitant side effects, including significant (but transient) autobiographical memory impairment. Given this, it is desirable to investigate the neural underpinnings of ECT's therapeutic effects so that we might develop equally effective treatments that are less burdensome to patients.

PROJECT NAME
Neuroaffective Effects of Electroconvulsive Therapy for Major Depressive Disorder

PROJECT LEADER
Markus Heilig, Department of Clinical and Experimental Medicine, Center for Social and Affective Neuroscience

MAIN PROJECT PARTICIPANTS
Paul Hamilton, Pia Nordanskog, Åsa Axén, Robin Kämpe



In a study currently underway, we are collecting neural structural and functional data in depressed patients during a course of ECT—just prior to receiving ECT for the first time, following eight weeks of receiving ECT, and eight weeks after completion of the course of ECT.

Preliminary analyses of functional neuroimaging data show intriguing functional changes in the brain as a result of ECT. Before ECT, for example, depressed patients show a pattern of affective flattening in which they react little, either neurally or behaviorally, to affective provocation with pictures. After ECT, however, depressed patients show robust response in the brain's visual attention network (see Figure 1) to emotionally provocative stimuli.

Further, in a task requiring patients to perform a challenging task to receive money, prior to ECT patients strongly activate a network subserving self-relational processing when they believe they are about to fail at the task. Following ECT, however, patients no longer strongly activate these structures as they anticipate failure at this challenging task.

As we continue collecting and analyzing these neuroimaging data, we will further delve into the neural underpinnings of ECT effects and how to implement them with less burdensome treatment modalities such as transcranial magnetic stimulation, which can focally stimulate a brain region of interest without detrimental side effects.

Popular Scientific Summary
Gudrun Alm Carlsson

PROJECT NAME
Tissue Classification Using Dual Energy CT and Iterative Reconstruction

PROJECT LEADER
Gudrun Alm Carlsson, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Alexandr Malusek, Maria Magnusson, Michael Sandborg, Gudrun Alm Carlsson

GRANTS
Cancerfonden 2013-2015

KEY PUBLICATIONS
Magnusson, M., Malusek, A., Muhammad, A. and Alm Carlsson, G. Iterative Reconstruction for Quantitative Tissue Decomposition in Dual-Energy CT. In: Proceedings of the 17th Scandinavian Conference, SCIA 2011, Ystad, Sweden, May 2011, (pp. 479-488). Springer Berlin/ Heidelberg.

Malusek, A., Karlsson,M., Magnusson, M., and Alm Carlsson, G. The Potential of Dual-energy Computed Tomography for Quantitative Decomposition of Soft Tissues to Water, Protein and Lipid in Brachytherapy. Physics in Medicine and Biology 58, no. 4 (February 21, 2013): 771.

Malusek, A., Magnusson, M., Sandborg, M., Westin, R. and Alm Carlsson, G. Prostate tissue decomposition via DECT using the model based iterative image reconstruction algorithm DIRA. In: Proceedings of the SPIE conference Physics of Medical Imaging, San Diego, California, USA, February 16-20, 2014

TISSUE CLASSIFICATION USING DUAL ENERGY CT AND ITERATIVE RECONSTRUCTION

Today's computed tomography (CT) images are affected by artifacts caused by the X-ray spectrum (beam-hardening artifacts). Due to the artifacts the CT-images are not completely quantitatively accurate. We have developed a mathematical method, an iterative algorithm, which eliminates these artifacts. With our dual energy iterative image reconstruction algorithm (DIRA) the pixels of the image are first classified into bone and soft tissue.

Bone pixels carry information about percentages of compact bone, red and yellow bone marrow. Soft tissue pixels carry information about percentages of water, protein and lipid. Consequently, DIRA provides quantitative information that can be used for improved medical diagnosis and treatment. As an example, DIRA can be used for determination of calcium content in the prostate.

The method is particularly important in radiation treatment planning using brachytherapy for prostate cancer where low-energy photons are used. A high calcium content in the prostate gland will change the spatial distribution of absorbed dose since it depends strongly on tissue's atomic number, Z.

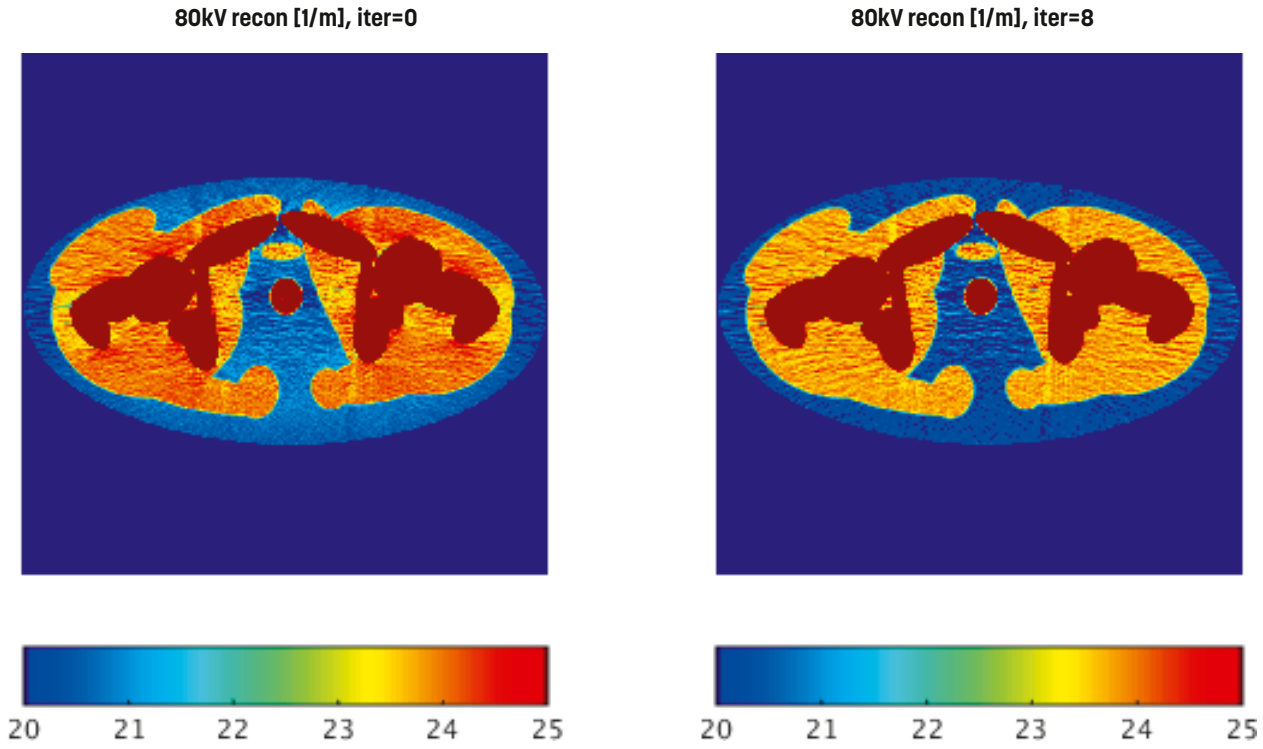


Figure 1. Suppression beam hardening artifacts in the human pelvic region from iteration 0 to iteration 8 in DIRA.

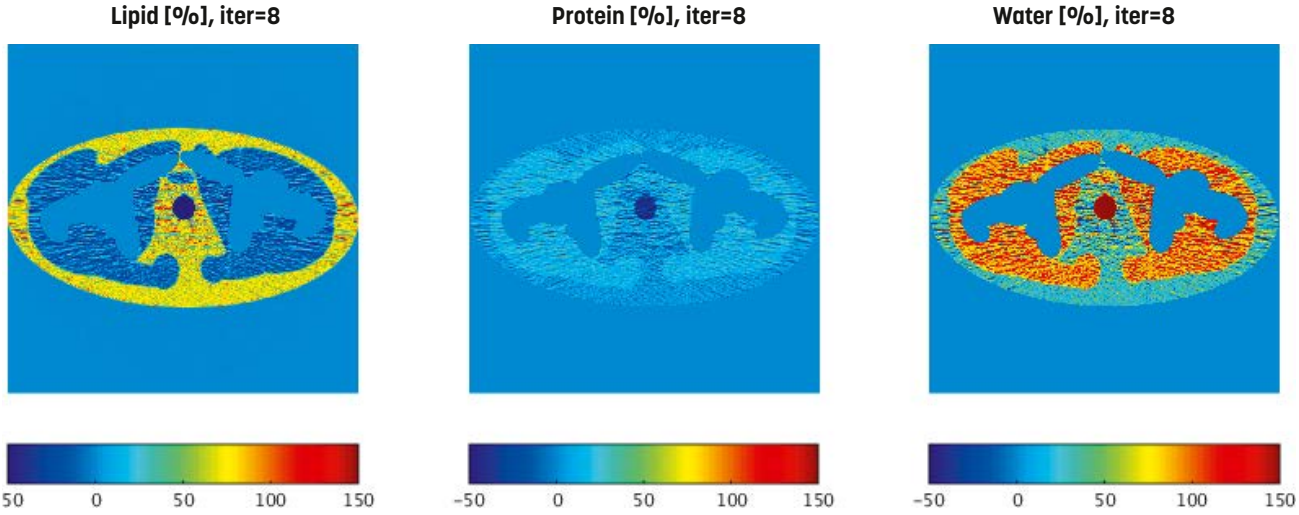


Figure 2. Soft tissue classification into lipid, protein and water (LPW) after 8 iterations of DIRA.

Our quantitative CT algorithm is important also in proton radiation therapy where the spatial location of the dose maximum is sensitive to the atomic numbers of the patient tissues.

To verify the method, we applied DIRA to simulated projection data of the human pelvic region. The X-ray spectra were 80 and 140kV, photon noise was included, and the geometry was basically the same as for the CT-Scanner at CMIV.

Figure 1 shows conventionally filtered back-projection 80kV reconstructed images of the human pelvic region after 0 iterations in DIRA (left) and after 8 iterations in DIRA (right). It is apparent that the beam-hardening artifacts corrupt the image causing streaks after 0 iterations (corresponding to the conventional Filtered Back Projection (FBP) with water beam hardening correction) (left). These artifacts are to a large extent reduced after 8 iterations (right).

One key point in DIRA is to classify the soft tissue of the reconstructed images for 80 and 140kV into the base material triplet lipid, protein and water (LPW). The classification based on the 8th iteration is consistent with the true values and provides important quantitative information of the tissue, see figure 2. Ongoing research includes more advanced segmentation, test of different noise levels and implementation on parallel CPU architecture.

Popular Scientific Summary
Michael Sandborg

OPTIMISING RADIOGRAPHIC TECHNIQUES – DOSE VERSUS IMAGE QUALITY

Minimizing radiation exposure in an x-ray examination while maintaining sufficient image quality for a correct diagnosis is called dose optimization. It requires that both image quality and patient absorbed doses can be measured and balanced against each other. The dose efficiency is defined as the ratio between image quality and absorbed dose (see figure below). It can be measured or computed by modelling of the whole x-ray system including the patient.
Our research aims to find optimal settings on the X-ray unit that maximizes the dose efficiency. The results show that large efficiency gains (i.e. dose reductions) are still possible to balance the more frequent use of ionising radiation in modern health care.

Our objective is to use computer simulations of the complete X-ray imaging system to predict image quality and mean doses in the patient. To reach this goal, we are developing a virtual X-ray system, by searching for correlations between the subjective assessment of clinical image quality made by the radiologist and of objective image quality made by a so called computer model observer. The model observer computes a detectability index for a pathological task, for example the signal-to-noise ratio of a contrast-filled heart vessel or a chest or breast tumour. The signal-to-noise ratio measures how well this pathology can be detected by the radiologist in the images where its visibility is limited by quantum noise.

Our virtual X-ray system provides unique, cost-efficient possibilities not just to evaluate existing X-ray systems, but also to explore future imaging systems before constructing expensive prototype systems. The research therefore gives important design information to manufacturers of new X-ray imaging systems.

An example of a model observer is given in the graph. Here the dose efficiency (signal-to-noise ratio per mean absorbed dose [μGy-1]) is given for three different imaging techniques in an angiography examination. The three different techniques (the three curves in the graph) all indicate that the dose efficiency peaks at a tube potential of 50-60 kV in the x-ray tube. This is a lower value than commonly used and indicate that further efficiency gains are possible. Dose reductions of up to 50% are possible in clinical practice for the benefit of the patient.

PROJECT NAME
Optimising radiographic techniques - dose versus image quality

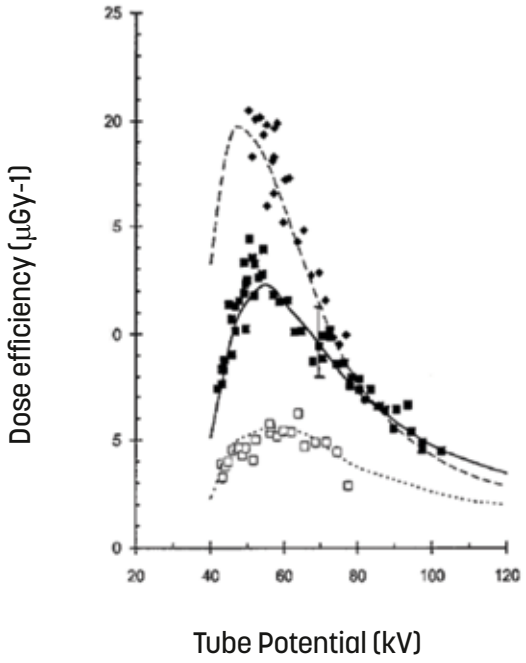
PROJECT LEADER
Michael Sandborg, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Gudrun Alm Carlsson, Erik Tesselaar, Alexandr Malusek

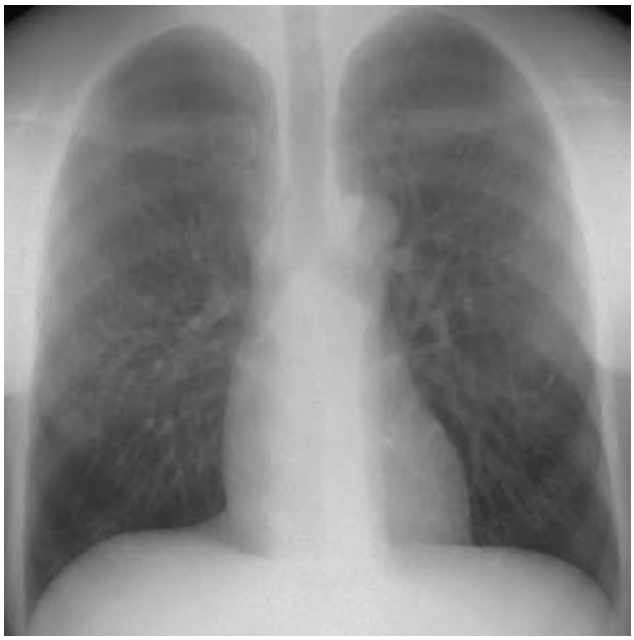
KEY PUBLICATIONS
Erik Tesselaar, Nils Dahlström and Michael Sandborg. Clinical Audit of image quality in radiography using visual grading characteristcs analysis. Radiat. Prot. Dosim. (2015) doi:10.1093/rpd/ncv411

Alexandr Malusek, Ebba Helmrot, Michael Sandborg, J-E Grindborg and Gudrun Alm Carlsson. In-situ calibration of clinical built-in KAP meters with traceability to a primary standard using a reference KAP meter. Phys. Med. Biol., 2014 (59), 7195-7210.

Michael Sandborg, Anders Tingberg, Gustaf Ullman, David R. Dance and Gudrun Alm Carlsson. Comparison of clinical and physical measures of image quality in chest and pelvis computed radiography at different tube voltages. Med. Phys., 2006, 33(11), 4169-4175.



The figure illustrates how our virtual x-ray system was validated since the measured (single marker points) and calculated (lines) data both coincide and indicate that dose efficiency peaks at a tube potential of 50-60 kV.



Popular Scientific Summary
Marcel Warntjes

CLINICAL IMPLEMENTATION OF SYNTHETIC MRI

Synthetic MRI is a technique to quantify physical properties of a patient using Magnetic Resonance Imaging (MRI). Based on these physical properties a range of conventional MR images can be recreated as well as tissue can be recognized and assessed automatically. This means that a relatively short scan time of 5-7 minutes is sufficient to reproduce a large part of a normal MR examination and, additionally, to provide more objective means of patient follow-up.

A close collaboration between researchers at CMIV and the university hospitals in Linköping, Umeå, Örebro, Uppsala and Göteborg ensured the clinical relevance of the technique. A number of technical and clinical studies were performed to validate the various aspects of synthetic MRI on scan time reduction and automatic brain segmentation. A spin-off company, SyntheticMR AB, was created to ensure an installable, safe product including the necessary regulatory requirements. After this initial prototype phase more hospitals became involved, among which a number in the EU and US, to introduce synthetic MRI as a standard procedure into the clinical workflow. For example, the Sahlgrenska University

PROJECT NAME
Clinical Implementation of Synthetic MRI

PROJECT LEADER
Marcel Warntjes

MAIN PROJECT PARTICIPANTS
Anne-Marie Landtblom, Peter Lundberg, Maria Engström, Tino Ebbers, Ebo de Muinck, Ida Blystad, Jan Engvall, Stefan Tell, Peter Johansson, Sten Bergström, Lisa Warnroth, Anders Swenningsson, Richard Birgander, Elna-Marie Larsson, Tobias Granberg

KEY PUBLICATIONS
M Warntjes, M Engström, A Tisell, P. Lundberg. Modelling the presence of myelin and oedema in the brain based on multi-parametric quantitative MRI. Frontiers in Neurology 2016, doi 10.3389

M Vågberg, T Lindqvist, JBM. Warntjes, P Sundström, R Birgander and A Svenningsson. Automated Determination of Brain Parenchymal Fraction in Multiple Sclerosis AJNR Am J Neuroradiol 2013;34:498-504

JBM Warntjes, O Dahlqvist Leinhard, J West and P Lundberg. Rapid Magnetic Resonance Quantification on the brain: Optimization for Clinical Usage. Magn Reson Med 2008;60:320-329

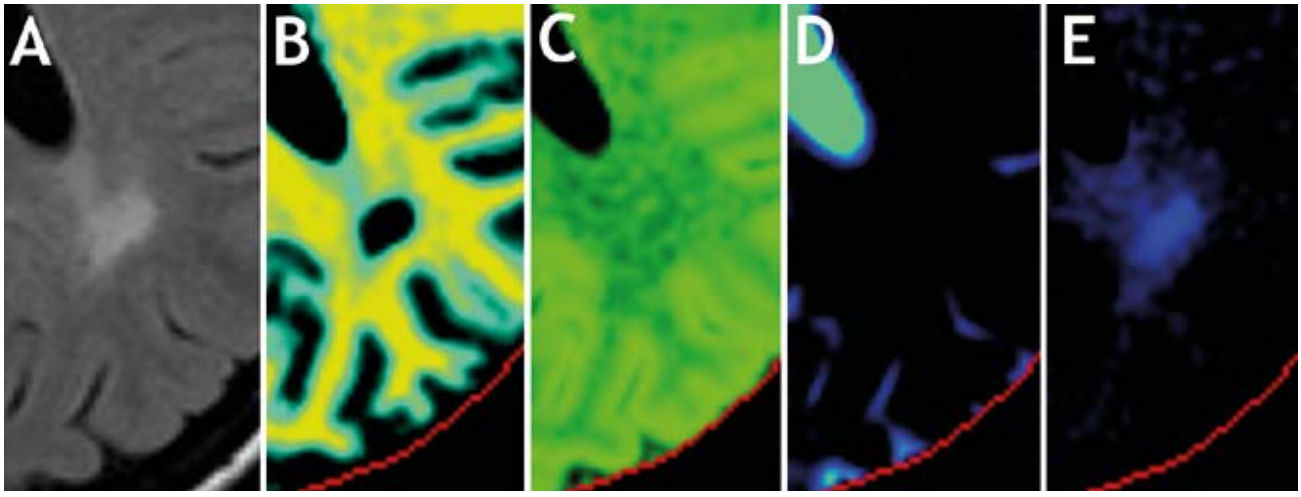


Figure 1. Example of synthetic MRI on an MS patient, showing new kinds of brain segmentation. Only a zoomed part of an axial slice is shown. Based on a single acquisition, different conventional images can be recreated such as a T1W, T2W or FLAIR (A). Using the same data, tissue can be assessed, in this case on the presence of myelin (B), cells (C), cerebrospinal fluid (D) and edema (E). Automatic tissue segmentation enables more objective patient monitoring since these values can be monitored over time and compared to a healthy reference.

Hospital and the entire County Council of Västerbotten use it as standard protocol for MS patients. Queen Silvia Hospital in Gothenburg and Cincinnati Children's Hospital apply the approach for their pediatric scanning.

The MR vendors General Electric (GE) Healthcare and Philips Healthcare now offer synthetic MRI as part of their product, based on the CMIV spin-off. More and more hospitals are starting to get familiar with the technique. An increasing number of evaluation projects are ongoing to validate the time reduction on the MR scanner and to assess the robustness of technique on diseases such as Multiple Sclerosis, hydrocephalus, cancer and dementia in clinical practice.

Exciting new research ideas are worked on such as brain myelination assessment. Synthetic MRI is also tested on other anatomies. Examples are the assessment of the prostate and of plaques in the large vessels. A new quantification sequence is developed which is so fast that the entire heart chambers can be measured within one single breath-hold.

In the history of MRI general images were acquired which were subjectively interpreted by radiologists. With the advent of synthetic MRI we believe that this is going to change dramatically: Scan times will be shorter and the decision support will be more based on numbers and statistics. Automated analysis can make the work of the radiologist both faster and more objective. The technique is available on the major scanner brands which will decrease the variation between different hospitals.

Synthetic MRI is a clear example of excellent cooperation between university, hospital and commercial companies, made possible by CMIV.

Popular Scientific Summary
Anders Ynnerman

METHODS FOR HIGH-QUALITY ILLUMINATION IN INTERACTIVE VOLUME GRAPHICS

An essential ingredient in understanding the structures found in volumetric data is the ability to interactively change rendering parameters and camera settings. In this project we strive to increase the clarity of images and improve the perception of depth and detail by developing efficient algorithms for shading of volumetric data in real time. However, being able to perform simulations of the ways light absorbs and reflects, while still being able to interactively explore the data, is a computationally daunting task.

Several approaches to this problem exist but they reduce the physical accuracy of the light transport in the volume in order to maintain interactivity. Our research is therefore focused on developing efficient methods for simulating physically based light interaction of volumetric objects from computed tomography (CT) scans, mimicking the real world matter-light interaction, while still allowing interactive data exploration.

This lifelike object-light interaction was previously not possible until we in this project were able to simulate realistic light interactions interactively using photon maps. The maps have a data structure that enables recording of the photons path history, thus avoiding costly recalculation of photon paths that did not change when altering light transport parameters.

By utilizing recent advances in hardware we have also shown how to perform selective light updates and reduce the memory footprint of a widely used light transport algorithm. This enables the user to create advanced light setups as shown in the screen shot above, which displays an interactive rendering of a CT scan of a mummy.

We are now extending our methods to time-varying CT scans and thereby enabling examination of organ functions with accurate shading. The key to this is to utilize the correlation between the changes of the data in time and incorporate the information in the light transport computation.

PROJECT NAME
Methods for high-quality illumination in interactive volume graphics

PROJECT LEADER
Anders Ynnerman, Department of Science and Technology, Division for Media and Information Technology

MAIN PROJECT PARTICIPANTS
Daniel Jönsson, Joel Kronander, Timo Ropinski

GRANTS
The Swedish Research Council 2011

KEY PUBLICATIONS
Efficient Volume Illumination with Multiple Light Sources through Selective Light Updates, Erik Sundén, Timo Ropinski, IEEE Pacific Visualization, To appear - 2015

Historygrams: Enabling Interactive Global Illumination in Direct Volume Rendering using Photon Mapping, Daniel Jönsson, Joel Kronander, Timo Ropinski, Anders Ynnerman, IEEE Transactions on Visualization and Computer Graphics (TVCG), Volume 18, Number 12, page 2364--2371 - December 2012.

Efficient Visibility Encoding for Dynamic Illumination in Direct Volume Rendering, Joel Kronander, Daniel Jönsson, Joakim Löw, Patric Ljung, Anders Ynnerman, Jonas Unger, IEEE TVCG, Volume 18, Number 3, page 447-462 - 2012.

Displaying a computed tomography scan of a mummy. By applying advanced shading and light setups it becomes intuitive to understand the shape, location and size of internal structures of the mummy.

Popular Scientific Summary
Anders Persson

LOW-DOSE COMPUTED TOMOGRAPHY BELOW 1 MILLISIEVERT

Medical imaging is useful and necessary when examining and taking care of patients. X-rays have been used for more than a hundred years for imaging of the chest and skeleton. With the invention of Computed Tomography (CT) X-ray in the 1970's, X-rays could be used to image all parts of the body. The first machines could produce only a few images (slices) of a limited region, e.g. the patient's head, but since the mid-90's a CT machine can scan the whole patient, and nowadays this takes just a few seconds.

The main problem is that X-rays are associated with a risk of cancer. The benefit of a well performed CT outweighs this risk, but it is important to continue improving the technique to limit the radiation dose the patients are exposed to.

Thanks to modern computers becoming more and more powerful, it is now possible to use advanced techniques and improved calculations on the CT data, resulting in high quality images. These so-called iterative techniques make it possible to use less X-rays in the CT scan and still obtain images of high quality.

An important research question is therefore how to lower the radiation dose as much as possible and still obtain acceptable images. This is important to study in real patients. Therefore, the 400 patients involved in this project receive an extra CT scan with very low dose together with their standard CT scan. The extra X-ray dose amounts to less than 1 mSv, which is about one third of the radiation dose we are exposed to each year from the earth and the sky.

The data from both the low-dose scan and the standard scan are stored in a digital archive. From this data, images can then be produced using both old and new techniques, in a number of ways. Generally, the low-dose images are of unacceptable quality when the old technique is used (see figure).

This project compares the best images we can reconstruct from low-dose data, using the best available iterative technique, with the standard-dose images. Since we have access to novel iterative techniques that are still in development, the research results will be relevant when these techniques are introduced on the market.

If the X-ray dose can be lowered in all or many of the very common CT examinations, CT will be a safer and more valuable technique, especially for patients that are young or have to go through many CT examinations.

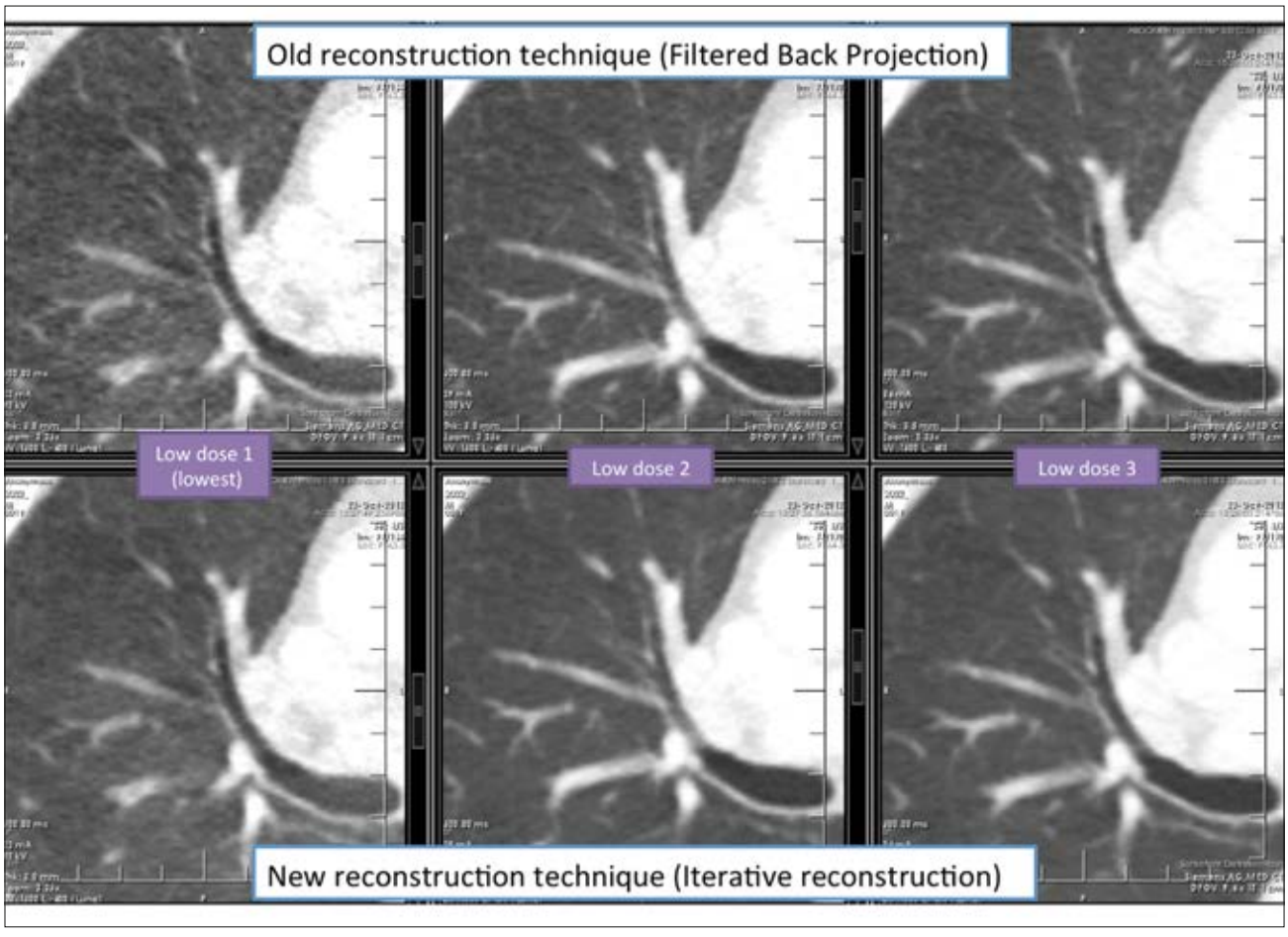
PROJECT NAME
Low-Dose Computed Tomography Below 1 milliSievert

PROJECT LEADER
Anders Persson, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Nils Dahlström, Mischa Woisetschläger, Lilian Henriksson, Petter Quick, Mannudeep Kalra

KEY PUBLICATIONS
Kalra M, Woisetschläger M, Dahlström N, Singh S, Lindblom M, Choy G, Quick P, Schmidt B, Sedlmair M, Blake MA, Persson A. Radiation Dose Reduction with Sinogram Affirmed Iterative Reconstruction Technique for abdominal CT. J Comput Assist Tomogr, 2012, 36(3):339-346.

Kalra M, Woisetschläger M, Dahlström N, Singh S, Digumarthy S, Do S, Pien H, Quick P, Schmidt B, Sedlmair M, Shepard J-A O and Persson A. Sinogram-Affirmed Iterative Reconstruction of Low-Dose Chest CT: Effect on Image Quality and Radiation Dose. American Journal of Roentgenology, 2013, 201(2), W235-W244.


Old reconstruction technique (Filtered Back Projection)
Low dose 1 (lowest)
Low dose 2
Low dose 3
New reconstruction technique (Iterative reconstruction)

Popular Scientific Summary
Anders Persson

FORENSIC SCIENCE – VIRTUAL AUTOPSY

A recent addition to the autopsy workflow is the possibility of conducting postmortem imaging using computed tomography (CT) and magnetic resonance imaging (MRI) in a virtual autopsy. The results from these modalities can provide additional information to the autopsy report. The images give a fast overview of damages to the skeleton, air pockets and foreign objects that is not possible to achieve with conventional methods. Blood cloths and bleedings can also be identified in the images.

At CMIV postmortem imaging has been used in routine work since 2003. Mostly homicides are analyzed and the imaging gives the police an early report allowing the traditional autopsy to wait for the crime scene investigation to finish. During the scan the body stays sealed in the bag preserving any evidence, as fibers and body fluids, present on the body. The images produced during the virtual autopsy are conveniently presented and easy to understand in court.

This project has focused on optimizing the total workflow for the post mortem imaging and developing a new type of software that can visualize full body data-sets and three-dimensional visualization. The conditions when scanning a dead body is not the same as for a living patient. When using the CT it is possible to use high radiation doses without concern for long term effects and there are no artifacts caused by movement. This allows images with high resolution. The bodies are scanned at two different energy levels at the same time, dual energy CT, improving soft tissue discrimination and visualization.

The MRI examinations are sensitive to the body temperature and it is difficult to generate images with good contrast when scanning a cold body. At CMIV the clinically established protocols has been adjusted for optimal image quality at any given temperature. If a natural death is suspected the heart is examined using specific MRI protocols revealing heart attacks.

The number of autopsies performed is decreasing and natural deaths are rarely investigated. The virtual autopsy is therefore not only a useful complement to the traditional autopsy in the forensic investigation. It could be used instead of autopsy for natural deaths which would otherwise not be investigated to improve medical education, quality assurance and reliable mortality statistics. It is also an alternative when the invasive autopsy is not agreed by the next of kin due to personal or cultural reasons.

PROJECT NAME
Forensic Science - Virtual Autopsy

PROJECT LEADER
Anders Persson, Department of Medical and Health Sciences, Division of Radiological Sciences

MAIN PROJECT PARTICIPANTS
Christian Jackowski, Maria Lindblom, Mischa Woisetschläger, Johan Berge, Anna Bodén

GRANTS
KK-stiftelsen 2008-2010
RMV forskningsfond 2008-2010
RMV forskningsfond 2009
Konung Gustav V:s och Drottning Victorias frimurarstiftelse 2008-2012

KEY PUBLICATIONS
Ljung P, Winskog C, Persson A, Lundström C, Ynnerman A. Full Body Virtual Autopsies Using A State-of-the-art Volume Rendering Pipeline. IEEE Transactions on Visualization and Computer Graphics. 2006;12(5):869-876.

Persson A, Lindblom M, Jackowski C. A state-of-the-art pipeline for postmortem CT and MRI visualization: from data acquisition to interactive image interpretation at autopsy. United Kingdom: Informa Healthcare; Acta Radiologica. 2011; 52 no. 5 522-536.

C. Jackowski, N. Schwendener, S Grabherr, A. Persson. Postmortem cardiac 3T magnetic resonance imaging: Visualizing the sudden cardiac death? Journal of the American College of Cardiology, 2013; Volume 62, Issue 7, 13 August 2013, Pages 617-629.

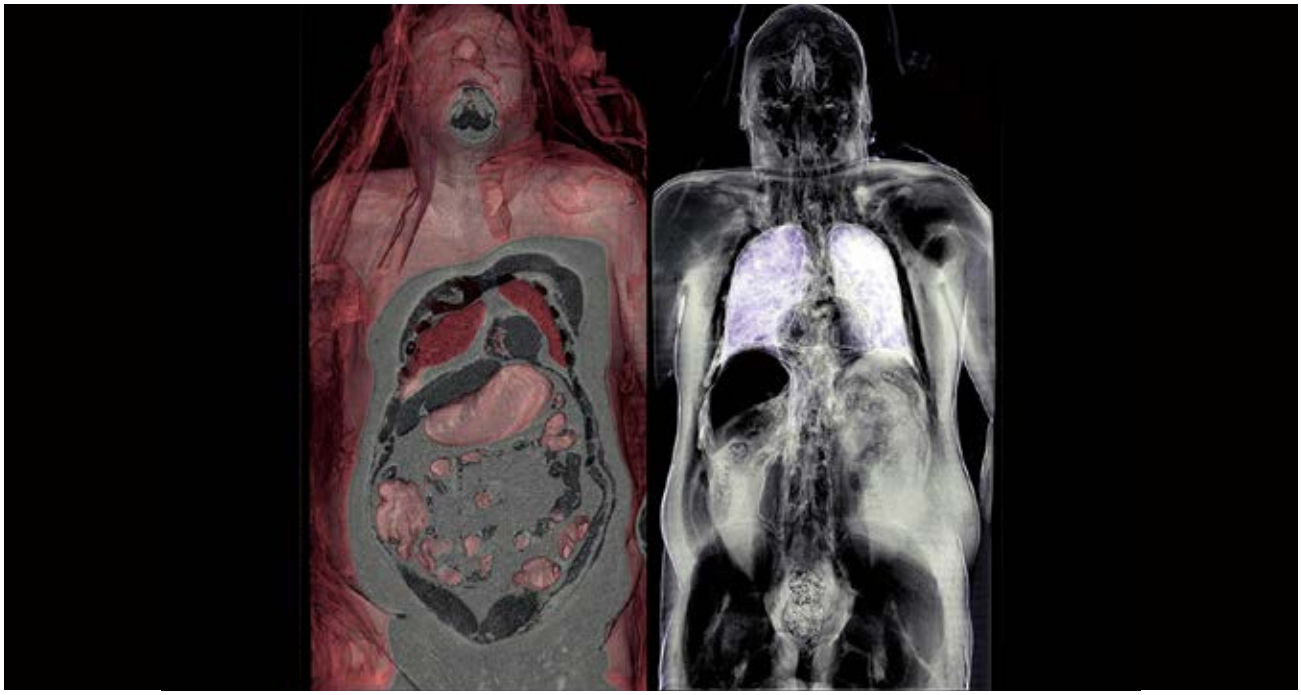


Figure 1. Postmortem Dual Energy computed tomography angiography. The captured data rendered with two different translucencies settings so that soft tissue and air in the body can be visualized by volume rendering 3D.

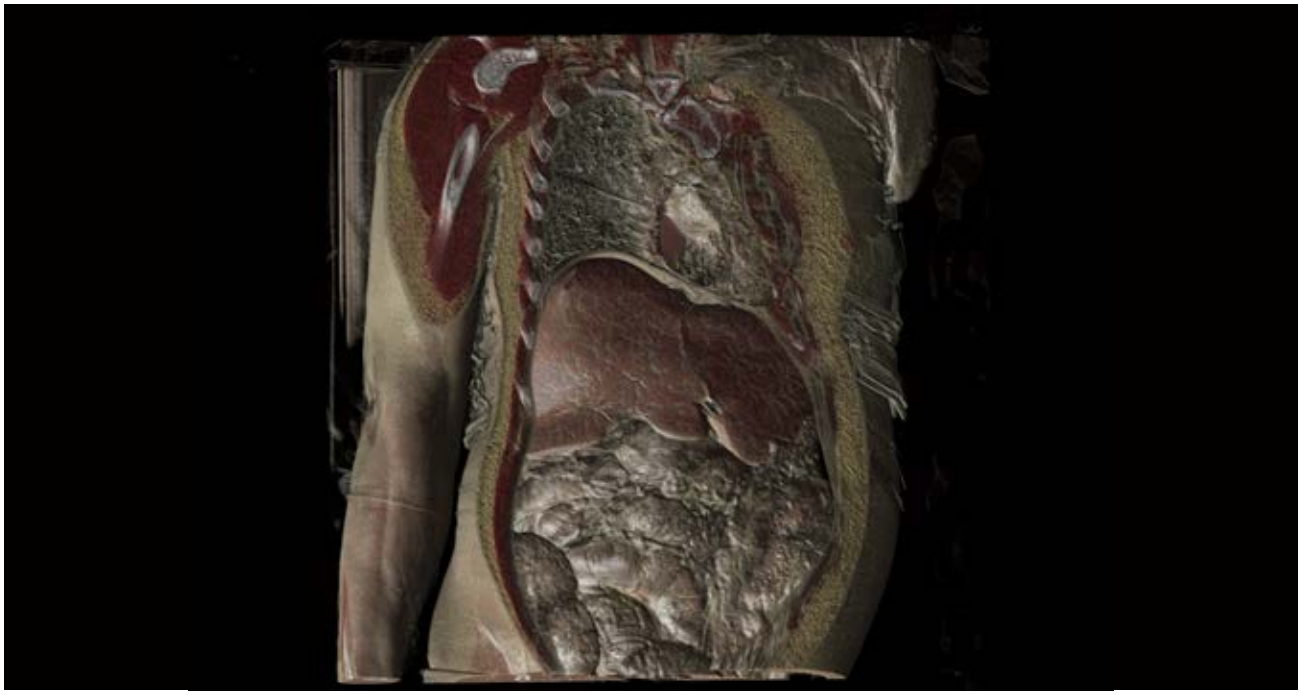


Figure 2. Postmortem Dual Energy computed tomography of a deceased person. Soft tissue rendered with different colours and different translucencies. Part of the anterior tissue virtually removed from the body so that the underlying organs can be studied.

Popular Scientific Summary
Wolf-Dieter Zech and Anders Persson

QUANTITATIVE MRI AS A GROUND-BREAKING TOOL FOR POST MORTEM IMAGING DIAGNOSES

Autopsies are fundamental to current post-mortem information acquisition for medical education, validation of therapeutic strategies, medical quality control and national cause of death statistics. Nevertheless autopsy rates have dramatically declined over the last decades.

A solution to overcome this problem was thought to be provided by non-invasive imaging techniques such as post-mortem computed tomography and post-mortem magnetic resonance imaging (MRI). However, so far several natural and unnatural causes of death and relevant forensic findings cannot be visualized or recognized via post-mortem imaging. Hence, to this date the classic autopsy remains the gold standard for acquisition of relevant post-mortem data, especially in determining natural causes of death such as acute heart attack.

A substantial advancement required for post-mortem imaging to equal classic autopsy is related to post-mortem quantitative MRI. This approach is based on a recently developed MRI sequence that allows for rapid quantification of parameters called relaxation times and proton densities. These parameters can be measured by placing measuring fields in regions of interest in MR images.

It was found that each relevant pathology such as infarction, inflammation or tumors exhibit unique combinations of parameters. Therefore, the measured values can provide the radiologist and the forensic pathologist with relevant information for the determination of the cause of death.

In 2015 a research collaboration between CMIV, the Forensic Institute in Linköping and the Institute of Forensic Medicine in Bern / Switzerland had been started assessing post-mortem quantitative MRI data validated by autopsy findings. The data assessed in this international research collaboration will be used to create a whole body reference database for the quantitative MRI approach. The database will be used for advanced post-mortem MRI diagnostics of relevant pathologic findings. Moreover the database will provide a fundament for development of software that is able to automatically detect pathologic tissue.

The overall-goal of the research collaboration is to develop a fully automatic workflow that acquires quantitative MR post-mortem information from corpses that do not undergo a traditional autopsy. Once implemented in a wide-spread manner, post-mortem quantitative MR imaging is expected to result in more deceased people undergoing investigations of the cause of death and thereby increase the quality of medicine in general and substantiate the mortality statistics of our society.

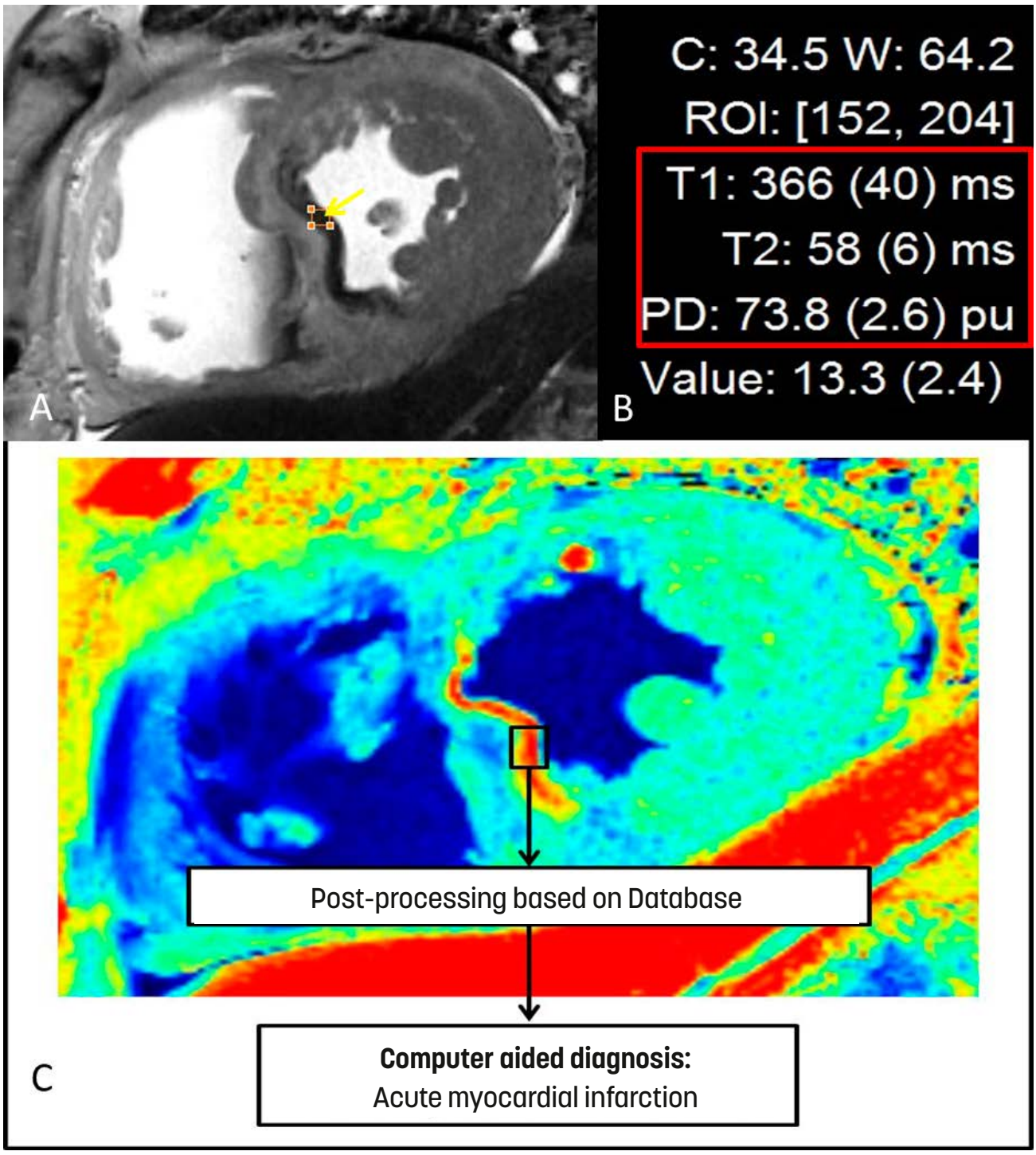
PROJECT NAME
Quantitative MRI as a ground-breaking tool for post mortem imaging diagnoses

PROJECT LEADER
Anders Persson, Department of Medical and Health Sciences, Division of Radiological Sciences
Wolf-Dieter Zech, Department of Medical and Health Sciences, Division of Radiological Sciences / Institute of Forensic Medicine Bern, University of Bern, Switzerland and

KEY PUBLICATIONS
Warntjes JB, Dahlqvist O, Lundberg P (2007) Novel method for rapid, simultaneous T1, T*2, and proton density quantification. Magn Reson Med 57:528-537

Jackowski C, Warntjes MJ, Kihlberg J, Berge J, Thali MJ, Persson A (2011) Quantitative MRI in isotropic spatial resolution for forensic soft tissue documentation. Why and how ? J Forensic Sci 56:208-215

Zech WD, Schwendener N, Persson A, Warntjes MJ, Jackowski C (2015) Postmortem MR quantification of the heart for characterization and differentiation of ischaemic myocardial lesions. Eur Radiol 25:2067-73



(A) Acute heart attack (yellow arrow) measured in synthetically calculated MR images. (B) Based on measurements of quantitative parameters (red frame) the nature of the pathology can be clearly defined. (C) The quantitative MR data may also be used for computer aided detection by automatically marking the heart attack with a designated color and providing a proper diagnosis.

CARDIO- VASCULAR DISEASE
Cardio- vascular diseases are the most common cause of death in Sweden as it is in most of the world. The diseases involving the heart and vessels include conditions as stroke and heart attacks. The risk of developing a cardio-vascular disease can be reduced by life style changes as healthy eating, exercise, avoiding tobacco smoke and limiting alcohol intake.

LUNG DISEASE
Also lung diseases cause a considerable part of the hospitalizations and deaths in the western world. They are however versatile and include conditions from the common cold and asthma to lung cancer. Some of the most severe lung diseases are lung cancer and chronic obstructive pulmonary disease (COPD). Both are closely related to exposure to cigarette smoke and air pollution.

SCAPIS

SCAPIS is a unique Swedish research initiative aiming for improved diagnosis and treatment of cardiovascular and lung disease. In total 30 000 healthy individuals will be examined in the study. The participants' lungs and cardiovascular system are examined with computed tomography and ultrasound.

Swedish Cardio Pulmonary bioImage Study (SCAPIS), is a large-scale national population study initiated by The Swedish Heart and Lung Foundation and supported by the Wallenberg Foundation. The study is lead by a national research group in collaboration with the University Hospitals in Sweden.

There are many different heart and lung diseases and this study will focus on identifying risk markers for conditions as sudden cardiac arrest and heart attacks. It will also try to find a way to identify COPD in an early stage for better treatment options.

In total 30 000 individuals in the age of 50-64 years will participate in thorough health examinations with focus on their heart, vessels and lungs. All the collected data will be saved in a knowledge bank, which will be a national resource used for research.

The study involves all the university hospitals in Sweden except Örebro and the first step was a pilot study at Sahlgrenska University Hospital in Gothenburg. During the pilot alone, four out of 1000 participants were found sick and in need of immediate care to avoid an acute condition in the nearest future.

WELCOME TO SCAPIS

The doors to the SCAPIS clinic in Linköping opened in October 2015. Here 5000 of the 30 000 participants will be examined. Carl Johan Östgren has the overall responsibility as principal investigator while Elisabeth Logander is the project manager handling the day-to-day business.

-We invite participants that are randomly selected from the population register, Elisabeth explains. About half of those who are invited accept the invitation.

Its important for the study to have a representative selection from the population and therefore the invited individuals live in all parts of the city with surroundings and have varying backgrounds.

-Many of the participants are excited about the study and happy to contribute to the research, says Elisabeth.

Kerstin Wenner is one of the participants in the study. She visits the clinic for the first day of examinations.

-It feels really good to be here. I have


SIEMENS

never done a health check-up before so it's a great opportunity. Of course I'm a little nervous that they will find something that is wrong.

Kerstin is an anesthesiology nurse at the hospital so she is used to the environment. She came in on her day off to do the examinations.

-It´s for a good cause and it´s fantastic to be able to produce a knowledge bank of this size.

BREAKFAST IS SERVED

The participants are fasting when they arrive to the clinic the first day. Their blood pressure, ECG and blood samples to measure, e.g. cholesterol and blood sugar, are taken before breakfast is served. After breakfast the neck arteries are examined with ultrasound and a survey with questions regarding health, diet and physical activity is filled in. The day finishes up with a test of the lung function.

If a larger plaque is found in the neck arteries the participant is asked to come back for an additional magnetic resonance (MR) investigation.

Between the first and second visit the participants measure their blood pressure twice a day at home and wear a pedometer to register how much they walk around.

The examinations take around three days in total for the participants. After the first day at the SCAPIS clinic the participants are sent to CMIV for examination in the computed tomography scanner (CT). In the CT the coronary arteries, the lungs and the aorta are examined. The fat content around the heart, in the liver and abdomen is also measured.

At CMIV a new CT is installed just for the purpose of SCAPIS. The CT is financed by the Swedish Heart and Lung Foundation and will be used only for the project during the three years it will take to examine all 5000 participants. A dedicated team of seven radiology nurses under the lead of Lilian Henriksson performs the CT scans.

-We have ten participants per day both at the clinic and at CMIV so we´re on a tight schedule, Elisabeth continues. But the staff has worked together for many years at other clinics so everything runs smoothly.

LOCAL RESEARCH ENDEAVORS

Most of the examinations in SCAPIS are the same at all University Hospitals but there is also a possibility to add investigations to support local research projects.

The local investigations are performed during the third day when the participants come back for an ultrasound examination of the heart and an investigation of the blood vessel elasticity. After that the circulation in the capillaries are analyzed.

-We want to combine data from the heart, the neck arteries and the capillaries to create a more reliable risk assessment for cardiovascular disease, says Professor Jan Engvall assistant PI in the SCAPIS group for local research.

The elasticity of the vessels may be reduced by continuous high blood pressure and this alone is a risk factor for stroke. The microcirculation in the capillaries is measured with a micro-doppler on the skin. Microcirculation is a new method in the context of risk assessment of cardiovascular disease.

-We don´t know yet what a disturbed microcirculation says about the heart. It´s part of the research to find out, says Jan.

The ultrasound investigation of the heart on day three is part of a project that wants to find out more about what the heart looks like in seemingly healthy individuals when they have reached a certain age.

-The ultrasound is better at analyzing the function of the heart compared to CT, explains Jan. With ultrasound we can see the heart valves move while the CT produces a still image.

Another study analyzes the hair, which gives a good picture of what has happened in the body during the last couple of months. The study focuses on stress. All participants are asked if they are willing to cut of a small amount of hair from the roots.

As an addition it is possible to participate in a study on fatty liver. The liver is then analyzed with MR on a separate occasion. At the same time the heart is analyzed with MR to study the importance of smaller deformities that show up on the image as small white spots. The changes could be e.g. macro fibrosis or edema.

-All pathological conditions found during the examinations are noted and passed on to the primary care, Jan continues.

HOPES FOR THE FUTURE

Most of the local projects were ongoing before SCAPIS started. Now SCAPIS is giving them the opportunity to grow from around a hundred participants to potentially thousands. SCAPIS is supplying the selection of participants and a valuable collection of basal data about the individuals.

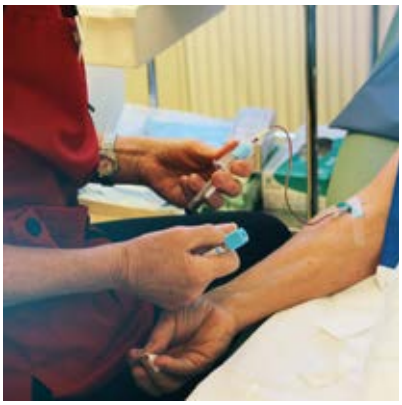
-Having a larger study group means that we can find important differences even if they are small, says Jan.

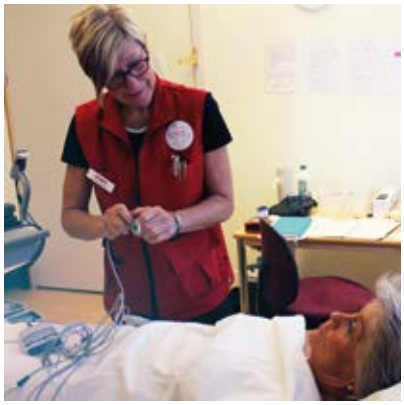
Several of the CMIV projects are involved in SCAPIS and the day-to-day business is affected with around 500 extra MR examinations every year during the time SCAPIS is running. And of course the addition of 10 CT scans a day has a great impact on the department.

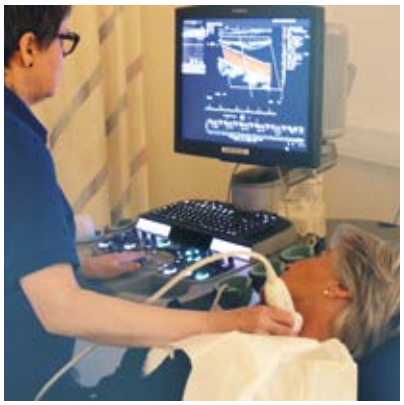
The study aims to find new risk markers for heart and lung disease that may enable a more personalized care in the future. SCAPIS hope to improve the individual's health through better diagnostics, care and treatment.

When the national study is finished and the first 5-year follow-up data is analyzed it will be possible for the local research groups to use the full knowledge bank, which will give unique opportunities for Swedish research during the following decades.

SPENDING A DAY AT SCAPIS →




Kerstin is one of 5000 volunteers entering the study in Linkoping.

SPENDING THE DAY AT SCAPIS

Kerstin Wenner, one of the invited Linköping residents who decided to join the study, fills in the paperwork needed to enter the study. At the same time she is offered to ask further questions before the examinations start.

Eva-Britt Ekelund then works through the initial tests with blood samples, ECG and blood pressure while explain everything to Kerstin. She also cuts a piece of Kerstin's hair after checking her weight and length.

Before the lung function is tested Kerstin inhales a medicine that expands her airways. During the spirometry Kerstin is guided through a series of breathing exercises where she alternate breathing as hard or long as she can with breath holds.

Kerstin's neck arteries are examined with ultra sound to find any plaque. If she has plaques larger than 2.7 mm she will be asked to do an MR for a more thorough examination.

Finaly, Elisabeth Logander shows Kerstin how to use the equipment that she will use at home to measure blood pressure and explains what will happen on her next visit.

THE CMIV RESEARCH SCHOOL

The CMIV research school offers a doctoral program with both medical and technological entries and coherent research education. A basic principle for our doctoral program is the close connection between different disciplines as medicine and technology. Currently there are around thirty PhD students admitted to the research school. Here a selection of them presents their research.


CMIV

Anette Karlsson

ASSESSING MUSCLE VOLUME USING MAGNETIC RESONANCE IMAGING

SUPERVISORS
Magnus Borga, Olof Dahlqvist Lein¬hard, Ola Friman

PROJECT
Fat- and Water Imaging Project
Quantitative Muscle Project
Brown Adipose Tissue Project

BACKGROUND
Master of Science, Engineering Biology, specialization in Biomedical Engineering The Institute of Technology, Linköping University, 2005-2011

Research Engineer, Department of Biomedical Engineering, Linköping University, Linköping 2011-2012

We have developed a method that can determine a patient's entire muscle volume, as well as the volume of separate muscle groups based on images from a 10 minute MR-scan. The method can also determine the amount of fat within the muscle, which is a sign that the muscle is injured.

The greatest health challenges of today are either obesity related or ageing related. While getting older, you start loosing muscles, a syndrome called sarcopenia. This may lead to immobility, falls, hip fractures, diabetes and more. In order to understand more about these kinds of syndromes and diseases we need detailed measures of muscle volume and fat infiltration. The possibility to measure the muscle volume and the amount of fat in the muscles is also a useful tool in finding the right treatment and rehabilitation for specific patients.

With an MR-scanner, images are created where all the soft tissue, for example liver, fat and muscles may be shown separately. A pair of images where the first only shows fat tissue while the second shows all the tissue containing water is shown in figure 1.

For the human eye, it is easy to distinguish e.g. the liver from the muscles, as the human knows where the liver is located and its shape. However, when calculating the volume of the muscles, each small image element must be included for each muscle group. This is too expensive why automatic solutions are needed.

For a computer, organs like the liver and the muscles look very similar as they have similar intensity values in the images (figure 1). The computer has no knowledge about where the liver is located or its shape. This method's solution is to manually pre-define the muscle groups within an image. When a new image with no pre-defined muscles is produced the old images are adapted so that they become as similar to the new image as possible. The adapted labels are in that process overlaid onto the new image and an automatic solution for the new muscles is achieved. The volume is calculated by a sum of all the small image elements. A typical result from our automatic muscle tissue segmentation method is shown in figure 2.

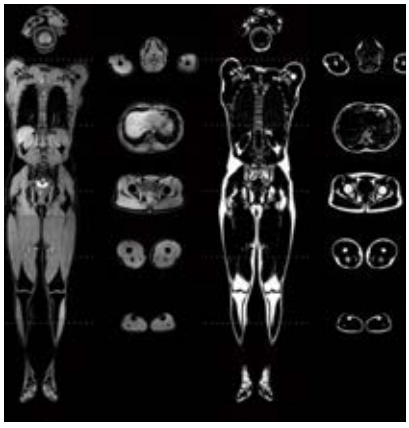


Figure 1. A paired magnetic resonance image where the left shows all the water within a whole body and the right shows all the fat.

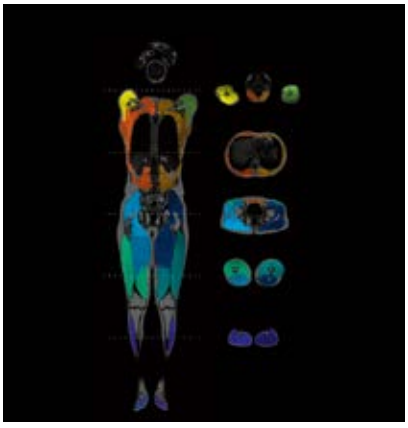


Figure 2. A typical result from the automatic method. The different muscle groups are shown in different colors. Grey color indicated that the automatic method has not considered that tissue as muscle tissue.

Thobias Romu

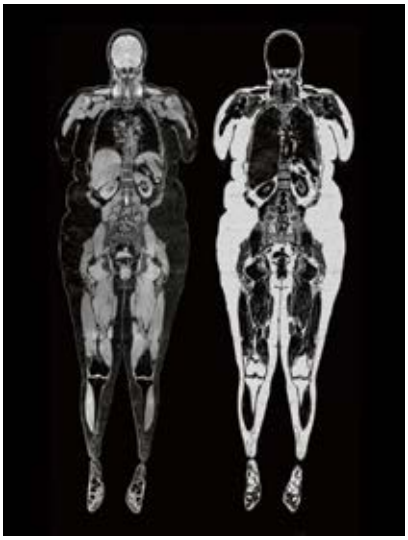
QUANTITATIVE WATERFAT IMAGING

To study the distribution of various tissues within the human body we use a technique that separates water and fat in magnetic resonance (MR) images. An example of such images is seen in the figure. We calibrate the images in a way that every pixel in the fat image corresponds to the actual adipose tissue concentration. Furthermore, we use automatic segmentation through anatomical atlases to study the amount of fat in different compartments in a cost effective way.

White adipose tissue (fat tissue) volume is very hard to measure by imaging since it is the most variable tissue in the human body. Its total volume varies from a few per cent of a person's total volume, to several times the volume of other tissues. An application of regional adipose quantification is that excess of visceral adipose tissue (belly fat) indicates a heighten risk of diabetes type 2, cardio vascular disease and cancer, whilst subcutaneous adipose tissue may even act protectively. Thus, it becomes important to separate the two fat compartments when assessing the risk of obesity.

The problem is that current methods, such as waist circumference, are not accurate enough to make predictions on an individual level. At the same time, competing image based methods are too expensive and time consuming.

We have created an inexpensive method for analyzing water and fat separated images as well as protocols for speedy MRI accusation. We can cover the abdomen in 5-6 min, and the entire body in less than 10 min, making it possible to add the sequences to existing protocols without much cost. After the data acquisition the abdominal fat can usually be measured without user interaction, by a system which learns from prior examinations. However, no bodies are identical to each other, so we have developed tools for those few cases where the automatic method fails, and by using those tools the abdominal fat can be measured in 1-3 min. For every new case the method learns a bit more about the possible variations, so it will handle those variations better in the future.



A water and fat image from a set of images covering the whole body.

Abdominal fat is not the only fat of interest. The same method is used to measure the amount of brown adipose tissue, a tissue which burns energy to produce heat. It is also used to quantify the subcutaneous adipose tissue volume, the liver and pancreatic fat concentration as well as the breast density, which is a strong predictor of breast cancer.

SUPERVISORS
Magnus Borga
Olof Dahlqvist Leinhard

BACKGROUND
MSc from Linköping University

Mikael Forsgren

DETERMINING HEPATIC FUNCTION IN DIFFUSE AND FOCAL DISEASE USING MULTIMODAL MAGNETIC RESONANCE IMAGING

SUPERVISORS
Bengt Norén (co-supervisor), Gunnar Cedersund (co-supervisor), Olof Dahlqvist Leinhard (co-supervisor), Peter Lundberg (supervisor)

PROJECT
Non-Invasive Liver Biopsy (NILB)
Liver Intrinsic Function Evaluation (LIFE and 4LIFE)
Hepatic Inflammation and Fibrosis (HiFi)

BACKGROUND
Master of Science (MSc; 2006-2011), Engineering Biotechnology, Systems Biology, Linköping University

Applications Engineer (October 2012-Present), Wolfram MathCore AB

Research Assistant/Engineer (2009-2012), County Council of Östergötland, CKOC, Department of Radiation Physics

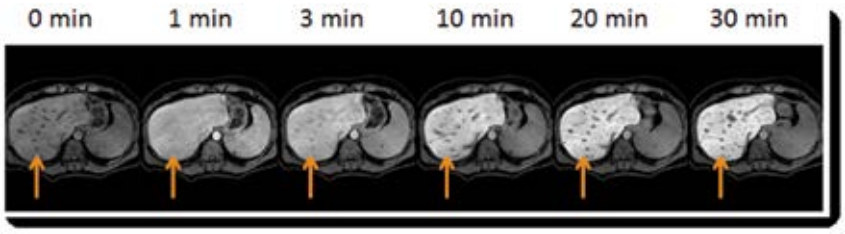
The liver is one of the largest organs in the human body and it handles many vital tasks such as nutrient processing, toxin removal, and protein assembly. In our modern society the number of people suffering from liver diseases is on the rise and there is an ever growing need to develop novel diagnostic techniques that can be used for accurate and non-invasive investigation of the liver. Such diagnostic techniques are the primary focus of my research.

The conventional methods for diagnosing liver disease suffer from several drawbacks. One such method is based on analyzing a small sample of the liver, which is extracted from the patient with a sharp needle. Due to the minute size of sample, about 10 to 20 microliters, it is not necessarily representative for state of the entire liver; a typical liver is about 1.5 liters in volume. As with any invasive method, there is of course an added risk of complications that might lead to hospitalization.

A common problem with many liver diseases is that they develop undetected. Once the symptoms become noticed the disease has often advanced so far that an operation might be the only option. Importantly, as the disease progresses there is ultimately a loss of liver function, and diagnostic tools that can accurately measure this loss are in high demand. For instance, when surgeons plan resective liver surgery they need to be sure that there will be enough 'liver function' after the surgical removal of the diseased portion of the liver, so that the risk of liver failure is minimal.

In our projects we use a set of novel magnetic resonance (MR) imaging methods in order to determine liver function. We start by injecting a contrast enhancing agent into the blood stream and image the liver for about 30 minutes – in the figure you can see how the accumulation of contrast agent makes the liver appear brighter. The contrast agent is taken up by the liver cells, but only in areas of the liver that are healthy enough. Basically the healthy parts of the liver are very bright in the images compared to the areas suffering from major disease. Once the images are processed we use mathematical models to determine liver function.

The goal of my projects is to be able to present a comprehensive understanding of the overall status of the liver, to for instance surgeons planning liver surgery, or to doctors treating patients, by combing our set of liver specific MR methods.



An example of the images we use to calculate liver function. This image shows how the contrast enhancing agent is taken up by the liver (the orange arrows points to the liver), and increases the brightness in the images over time as the contrast agent is accumulated in the liver.

Carina Stenman

AN ALTERNATIVE WORKFLOW METHOD FOR ULTRASOUND EXAMINATIONS

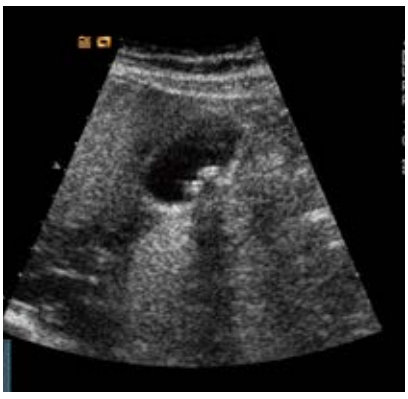
Ultrasound is often a first choice for radiological examinations. It is a quick and safe diagnostic method. Thanks to recent technical progress in regard to image quality ultrasound is used to diagnose, for example, focal changes in the liver.

The most common way to document ultrasound examinations is to store still images. This method offers very limited possibilities for re-evaluation of an ultrasound examination. Especially when new clinical questions arise after the examination, re-evaluation is often not helpful. A possible solution is to use standardized examination protocols and store as cine-loops. The purpose of this project is to evaluate the introduced ultrasound method that is used at the radiology department in Linköping, with special consideration to reproducibility.

The Radiology department in Linköping uses a standardized method for ultrasound examinations. The examination is performed according to an examination protocol and then stored as cine-loops. Cine-loops are films where the scan covers 5-10 centimetres in 5-10 seconds depending on the target organ. The documentation should include both longitudinal and transversal views covering the whole organ or region of interest. The dynamic scans are saved in the Picture Archiving and Communication System (PACS) from where the films can be retrieved and reviewed on a later occasion at dedicated workstations.

The ultrasound examination is in suitable cases, such as technically uncomplicated normal ultrasound scans with a clear clinical question, performed by a radiographer. The advantage is that examinations performed by a radiographer can be evaluated later by a radiologist, thus increasing the availability of the radiologist for more advanced examinations.

A prerequisite for recommending this routine for general use is that no diagnostic information is lost in the process. The professional roles may become more clear-cut, with the radiographer concentrating on perfecting the examination technique and the radiologist on improving diagnostic skills, just as in other radiological modalities.



SUPERVISORS
Staffan Wirell (co-supervisor), Marcus Ressner (co-supervisor), Örjan Smedby (supervisor)

BACKGROUND
Bachelor of Science in diagnostic radiography nursing 2001

Master of Diagnostic imaging and physiology, 2008

Medical Ultrasound, 2009

Licentiate of Medical Science, 2011

Radiology nurse and sonographer, Department of Radiology, County Council of Östergötland, Linköping 2000-present

Johan Kihlberg

MAGNETIC RESONANCE IMAGING OF PERFUSION AND DEFORMATION IN CARDIAC DISEASE

SUPERVISORS
Jan Engvall, Tino Ebbers, Anders Persson

PROJECT
Cardiovascular blood flow assessment, Determining Optimal non-invasive Parameters for the Prediction of Left Ventricular morphologic,
Early detection of cardiac effects induced by treatment for breast cancer, Heart4flow

BACKGROUND
Nursing degree from the University College of Health and Caring Sciences, Uppsala, in 1996

Bachelor degree 2000, Master of nursing in 2003, Linköping University.

Region Östergötland, Department of Medicine, Norrköping, 1996-1999,

Department of Radiology, Norrköping, 1999-2004.

2004-present CMIV, Linköping, radiographer responsible for the MRI scanners.

The treatment of myocardial infarction has advanced enormously in the last decade but is still one of the leading causes of death. The larger the scar is, the more likely that patients develop heart failure. Preventive treatment with ACE-inhibitors and diuretics is used to unload cardiac work and improve survival.

When an exact determination of infarct size is required, magnetic resonance (MR) is the best method. Still, many difficulties with cardiac MR exams remain, especially problems related to motion artifacts. However, MRI is versatile and segmented approaches requiring breath hold may be replaced by single-shot acquisitions, thus avoiding motion artifacts.

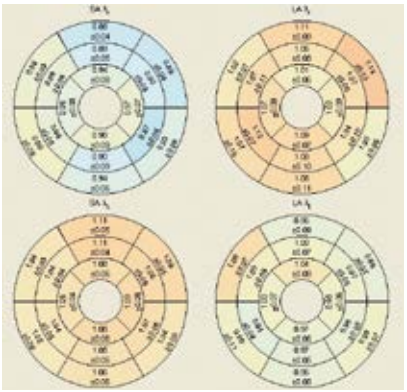
An important parameter that has to be determined during the cardiac MRI exam is the inversion time, which is critical for scar imaging. We have developed a sequence allowing a simulation of relaxation that in effect allows any inversion time to be used in scar imaging. We could show that synthetic scar images showed a good agreement with the conventional images in terms of scar size.

Scar size determines systolic pumping function. The contraction of the LV muscle can be analyzed in terms of cardiac strain which provides an additional aspect on systolic contraction beyond what can be obtained from the determination of ejection fraction. We have developed "Displacement Encoding with Stimulated Echoes" (DENSE) which measures the displacement of the cardiac wall during systole.

In my studies, DENSE has been validated for its ability to detect scar in 125 patients participating in the "Doppler-Cip" study. The results showed that circumferential strain could detect major scar with a sensitivity of 95% and a specificity of 80% with a clear cut off between healthy and scared myocardium. The strain was well aligning with the left ventricular ejection fraction.

A competing MRI technique that can measure cardiac strain is "tagging", which can be analyzed with the software "Harmonic Phase", (HARP). Since HARP is considered the gold standard, we have compared DENSE with HARP (manuscript in preparation).

Many diseases and treatments affect cardiac deformation. Therefore, it is interesting to follow a pathophysiological process with an accurate method like DENSE. One such condition is breast irradiation in cancer treatment. In this project we investigate breast cancer patients with DENSE before, during and after treatment. The overarching goal is to reduce radiation ("ALARA, As Low As Reasonably Achievable") to avoid cardiac impairment in both short and long term.



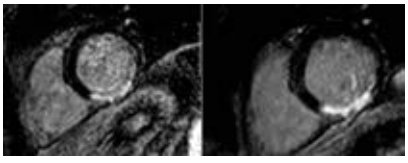


Image 1. Synthetic image of a myocardial scar using the adaptive inversion time technique to the left and the conventional late gadolinium image to the right.

Image 2. Stain values output as a bull´s eye from DENSE data.

Karin Lundengård

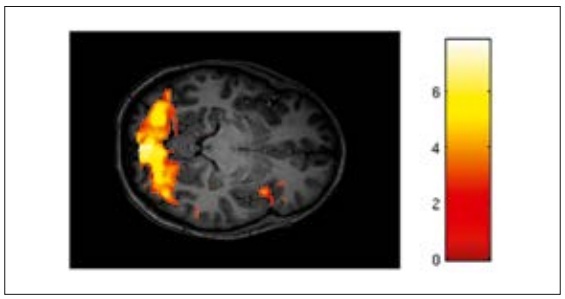
BUILDING COMPUTER MODELS OF THE BRAIN TO LOOK AT HOW HUNGRY NEURONS CONTROL THE BLOOD SUPPLY

The activity in the brain can be measured in a magnetic resonance scanner, using a technique called fMRI (functional magnetic resonance imaging). fMRI is often used in brain research, since it is safe for the person being examined and the whole brain can be examined at the same time.

Unfortunately, fMRI has some limitations. One of those limitations is that the fMRI-scanner only measures changes of the oxygen level in the different areas of the brain, instead of the electrical signals that neurons send to each other, the signals that we usually refer to when we talk about brain activity.

But how are the nerve signals and the oxygen level connected? When the nerves in an area of the brain start to signal each other they need more oxygen and nutrients, because they work harder. More blood is then sent to that brain area, carrying oxygen and nutrients. This changes the oxygen level. Since the oxygen level is controlled by the nerve signals it is used as a measurement of the activity in the brain.

However, it is not completely known how the nerve signal governs the oxygen levels and it is not possible to measure this. We know that the time it takes for the blood and oxygen to get to the active area (about 10 seconds) is much longer than the time it takes for the electric nerve signal to get there (a few milliseconds), and we want to find out what happens during that time. Therefore we are building computer models of the human brain, which can fill the knowledge gap between nerve signal and oxygen level. The models can then be used for looking at the nerve signals even though all we can measure is the oxygen level. We hope that by using these models we can get a better understanding of how the brain works and develop a good tool for diagnosing and investigating complicated brain disorders with fMRI images.



fMRI image where the active areas in the visual centra are highlighted as the person is looking at a picture.

Anatomical image of the brain.

SUPERVISORS
Maria Engström, Gunnar Cedersund, Fredrik Elinder, Susanna Walter

PROJECT
SAND:MAN

BACKGROUND
MSc from Linköping University

Belen Casas

IMPROVED DIAGNOSIS AND MANAGEMENT OF HEART DISEASE BY 4D BLOOD FLOW ASSESSMENT; STENOTIC BLOOD FLOW

SUPERVISORS
Tino Ebbers (supervisor)
Petter Dyverfeldt (co-supervisor)
Jonas Lantz (co-supervisor)
Carl-Johan Carlhäll (co-supervisor)

PROJECT
Cardiovascular blood flow assessment

BACKGROUND
MSc in Biomedical Engineering
August 2010-March 2013, Linköping University (Linköping, Sweden)

MSc in Telecommunication Engineering
October 2003-March 2010,
Universidad de Oviedo (Oviedo, Spain)

Systems engineer trainee
April 2010-July 2010,
EADS Astrium (Madrid, Spain)

Narrowing of the valves of the heart, valve stenosis, prevents the valves from opening fully which obstructs the blood flow. The blood flow after the valve will be turbulent and produces a pressure drop across the valve. Such pressure drop will cause the heart to perform additional work to increase the driving pressure and maintain the blood flow through the vascular system. Over time, this causes adverse remodeling of the heart muscle. In many patients with valve stenosis, the heart´s short-term compensatory mechanisms become less and less effective, ultimately leading to heart failure. It appears that the pressure drop over the valve is a crucial marker of the severity of the stenosis.

The current gold standard for measuring the pressure drop is catheterization, but this is an invasive procedure and cannot be applied routinely. In practice, the pressure drop is instead estimated non-invasively based on ultrasound measurements. This approach, however, does only work well for severe stenoses since mild pressure drops are masked by a pressure recovery phenomenon downstream of the stenosis. The irreversible pressure drop over the stenosis is directly related to the amount turbulence and a method monitoring this would be useful in detecting also mild stenoses.

The aim of this project is to propose and validate a non-invasive method to estimate irreversible pressure loss based 4D magnetic resonance imaging (MRI) measurements of the turbulent blood flow. Such a method should be suitable for assessment of mild, moderate and severe stenoses. In particular, it would be especially helpful for assessment of moderate and mild stenoses, for which current non-invasive methods often fail to provide a correct estimate of the pressure drop.

Mariana Bustamante

AUTOMATIC QUANTIFICATION AND VISUALIZATION OF BLOOD FLOW IN THE HEART

The main purpose of the project is to develop a semi-automatic method to quantify, analyze and visualize blood flow patterns in the whole heart. It is part of HEART4FLOW, a collaboration between researchers in different areas, whose aim is to develop the next generation of methods for noninvasive quantitative assessment of cardiac diseases and therapies.

The project intends to reach its goal by optimizing the most promising technique for intracardiac blood flow assessment at the moment, 4D flow MRI, and to utilize this technique to improve understanding of intracardiac blood flow dynamics in health and disease.

Analysis of 4D flow data is extremely time-consuming, especially during the heart segmentation stage. In spite of this limitation, some approaches have used the information available in the acquisitions to analyze values like flow components, kinetic energy, linear momentum and early vs. late diastolic inflow.

All of these methods require segmentation of the heart's chambers and large vessels, which present a problem in velocity MRIs, since the contrast between myocardium and blood is usually not very good (see fig. 3).

The first goal of the project was to develop an automatic atlas-based vessel segmentation method that can be used on 4D flow MRI. Atlas-based segmentation involves deforming an already labeled image by means of registration in order to extrapolate the labels into another unsegmented image. In this study, atlas-based segmentation was used in combination with registration between the timeframes of the 4D flow MRI dataset in order to obtain a 4D segmentation of the great thoracic vessels.

The atlas also includes information about 2D plane locations at which flow volume analysis will be performed.

In future projects, a 3D atlas of a heart will be used as base for the registration and subsequent segmentation of the input heart image. Where available; other acquired MRI data, such as angiography or velocity information, will be used to improve the quality of the method.

A successful result will be a delineation of the cardiac chambers, large vessels and valves of the heart. Some manual interaction with the obtained delineation may be necessary to assure robustness.

The technique's results will be validated visually on dilated cardiomyopathy patients and healthy volunteers, with a focus on blood flow analysis.

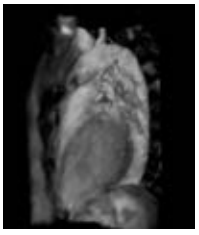


Figure 1. 3D rendering of a flow magnitude image

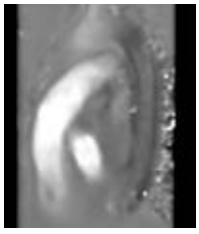


Figure 2. Flow velocity

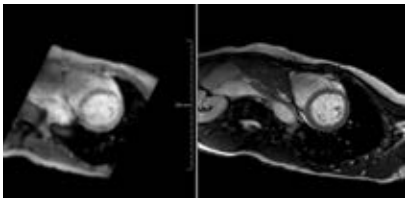


Figure 3. Flow Magnitude (left) and Short Axis balanced (right)

SUPERVISORS
Tino Ebbers, Carl-Johan Carlhäll, Petter Dyverfeldt

PROJECT
Cardiovascular blood flow assessment

BACKGROUND
MSc Computer Science
Uppsala University, Sweden, 2010-2012

Computer Engineering
Simon Bolivar University, Venezuela, 2001-2006

Jens Sjölund

ADVANCED MRI TECHNIQUES FOR FUNCTIONAL AND STEREOTACTIC NEUROSURGERY

SUPERVISORS
Hans Knutsson (supervisor), Mats Andersson (co-supervisor)

BACKGROUND
M.Sc. in Engineering Physics, KTH Royal Institute of Technology 2007-2012

Research Scientist, Elekta Instrument AB, Stockholm, Sweden (2012-present)

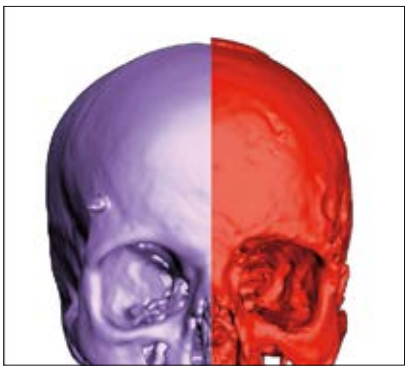
Many brain disorders–e.g. tumors, vascular malformations and Parkinson's disease–can be treated either surgically or by focused radiation. The treated areas are often small and it is of course vital not to harm the surrounding healthy tissue. This places extremely high demands on the accuracy of the tools used by neurosurgeons; for example the Leksell Gamma Knife (a Swedish invention) can deliver focused radiation with accuracy better than one millimeter.

To take full advantage of this accuracy you need to know where to direct it, which is why you need imaging. This project deals with the imaging technique known as Magnetic Resonance Imaging (MRI). It was developed in the early 1970's by the chemist Paul Lauterbur and the physicist Sir Peter Mansfield, a feat for which they were awarded the Nobel Prize in physiology or medicine in 2003.

Since its introduction, the principles and applications of MRI have been subject to intense research. We strive to take these scientific land winnings and put them at the hands of those who make it matter–the neurosurgeons. Our emphasis is on segmentation, which means that an MR image is, more or less automatically, provided with a "map" that describes the locations of different anatomical and functional structures in the image. This map can comprise both the target of the treatment (e.g. a tumor) and normal, healthy, brain structures.

Accurate and robust segmentation methods have several clinical uses. The most obvious is to aid in defining the target of a treatment and identifying nearby structures which must be protected. To evaluate the effects of a procedure, new MR images are acquired and compared to the prior ones. Segmentation methods can facilitate this comparison by, for example, quantifying how much a tumor has shrunk. Yet another important application, specific to radiation therapy, is the need to accurately compute the radiation dose. This is something that typically requires additional X-ray imaging with little diagnostic gain, in particular for brain disorders. It is therefore desirable to do the dose calculations using only MR images. An important step in this direction is to use segmentation to identify tissue types that have different effect on the radiation (Figure).

A specific MR technique with an important role in this project is so called diffusion imaging, which provides means to segment nerve fibers by taking advantage of the fact that water travels easier along nerve fibers than across them. This could provide the neurosurgeon with a valuable insight into the wiring of the brain; allowing critical nerves to be spared, improving understanding of how epileptic seizures spread throughout the brain and facilitating treatment of conditions in which a nerve itself is the culprit (e.g. trigeminal neuralgia–one of the most painful conditions known to mankind).



Daniel Jönsson

SCALABLE VOLUME RENDERING

Radiologists love images! Their daily work consists of looking at images of a patient's internal organs and determining if the patient is sick or healthy. The images of the internal organs are produced by magnetic resonance (MR) and computed tomography (CT) scanners at the hospital.

The scanners of the early nineties could only produce a handful of images for the radiologist to make a diagnosis. Scanners today can scan the whole body and produce thousands of images with millimeter resolution of a single patient. Upcoming scanners are able to scan over time and thereby record movements inside the body. This is a fantastic opportunity since it allows a radiologist to make a diagnosis based on the function of the organs as they are moving.

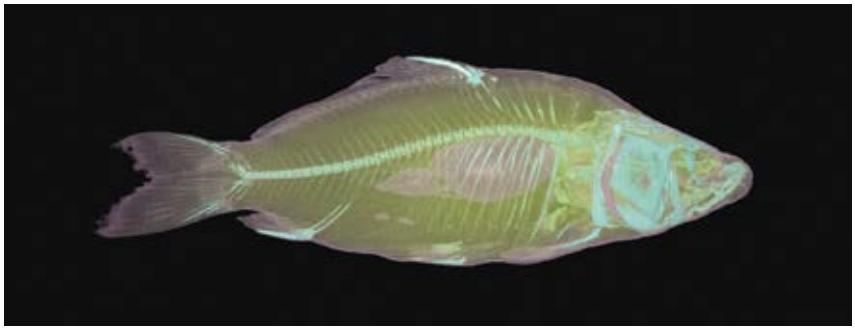
However, it is impossible for the radiologist to use the same workflow to investigate hundreds of thousands of images that can be produced by the new scanners. New tools are needed that can visualize relevant information and at the same time manage the enormous amount of data that is produced.

To support the radiologists in their work I do research on methods that can deal with the large amount of data that is produced by the scanners while maintaining high image quality. Algorithms that produce high image quality require expensive computations, which prevent large amount of data to be handled. In order to solve this puzzle we try to answer the question: If the images look similar over time, can we reduce the amount of work by making use of computations that was made before?

We first try to identify which part of an algorithm that can be changed such that computations can be reused. We then investigate what information that needs to be supplied in order to know which computations that should be redone. Given these two pieces of the puzzle we face the challenge of determining how to alter the algorithm and implementation such that it becomes more efficient than redoing everything in the first place. In addition to these two pieces of the puzzle we can add a third piece that tells us which information the radiologist is interested in. This last piece allows us to focus on giving the best representation of the relevant data and to filter away the unnecessary parts.

Another part of my research is of a softer nature. Radiologists require easy to use tools in their daily work but at the same time they must be powerful enough to visualize the desired information. The challenge here lies in combining the design of the tool with the underlying technique. The quest is to have few and easy to understand parameters to change. We therefore investigate how we can either change the algorithms to make the input more intuitive by nature, or how we can create intuitive parameters that are mapped to the input of the algorithm.

These two research directions aim to enable the radiologist to be able to explore organ function and doing so in an efficient manner.



PROJECT INFORMATION

SUPERVISORS
Anders Ynnerman

PROJECT
Methods for High-quality Illumination in Interactive Volume Graphics

BACKGROUND
Master of Science in Media Technology, Linköping University, 2004-2009

Research Exchange, Simon Fraser University, Vancouver, Canada, 2012 Feb-Apr

Research Engineer, Linköping University 2009-2010
Founder and CEO, Vistinct AB, 2013-present
Visualization Consultant, Context Vision AB, 2014-2015

Bharti Kataria

EVALUATION OF OPTIMIZATION METHODS FOR ABDOMINAL COMPUTED TOMOGRAPHY

SUPERVISORS
Prof. Michael Sandborg
Co-supervisors:
Prof. Örjan Smedby
Prof. Anders Persson
Docent Hannibal Sökjer

BACKGROUND
Diagnostic radiographer, Bristol School of Radiography in Great Britain April, 1980.

Diagnostic Radiographer Nairobi, Kenya 1980-1985

Radiology department Vrinnevi Hospital in Norrköping 1986-2014 during which I graduated with a Bachelor´s (2008) and Master's (2013) degree in Medicine.

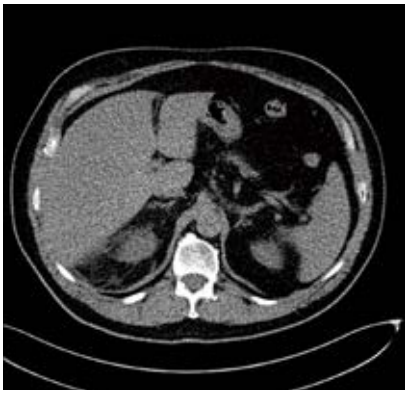
Radiology Department in Linköping March 2014-present

For all diagnostic radiology examinations using radiation there is a desire for the best possible image quality (AHARA principle) and at the same time endeavor to keep the radiation dose as low as reasonably achievable (ALARA principle). The higher the dose the better the image quality as image noise is reduced, but this is not always necessary to make a diagnosis.

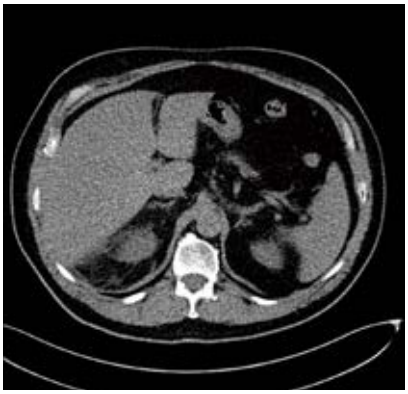
The main subject of this project is the relationship between radiation dose and image quality in abdominal Computed Tomography (CT) examinations, which deliver a high radiation dose to the patient. The purpose is to find ways of optimizing abdominal CT examinations by evaluating the dose reduction potential of different reconstruction and post-processing methods and the diagnostic value of a low-dose CT.

The first study evaluated the dose reduction potential of an iterative (mathematical) reconstruction method, SAFIRE, which reduces image noise and thereby allows 5-9% dose reduction. Further investigation of this algorithm and other post-processing methods using visual grading experiments will reveal the amount of dose reduction that is possible in order to optimize abdominal CT examinations.

Optimization is also about choosing the best imaging method to facilitate the diagnostic process by shortening time from presentation to treatment. Therefore evaluation of a low-dose abdominal CT to determine its diagnostic value compared to two other methods will be studied. The value of this project is to optimize protocols and reduce the radiation dose to all future patients undergoing abdominal CT examinations.



Filtered Back Projection 35 mAs



SAFIRE 35 mAs

Siemens SOMATOMForce

Ludvig Vavruch

IDIOPATHIC SCOLIOSIS – DEFORMITY IN THREE DIMENSIONS

Scoliosis is a deformity of the spine with curvatures in the frontal plane as well as in the sagittal plane. In addition, the vertebras in the deformity are rotated in the axial plane. Thus, scoliosis is a three dimensional spinal deformity. Traditionally the severity of each curvature has been evaluated by measuring the Cobb angle from standing radiographs. This angle is measured between the endplates of the vertebras in each curvature. It is desirable to be able to measure the vertebra rotation in order to fully understand the scoliotic curve. There are methods for doing this using ordinary radiographs although these methods are difficult to perform and not very precise.

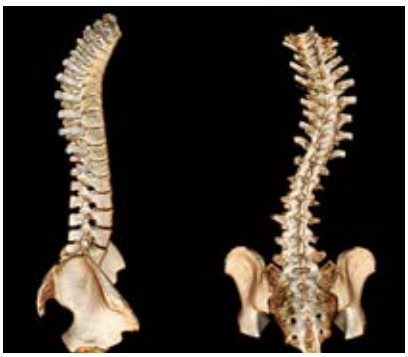
Since scoliosis is a three dimensional deformity, the importance of three dimensional imaging has been pointed out as a necessity to better understand the condition, as well as getting better preoperative information.

One way to obtain three dimensional images is to use low dose computed tomography images of the spine and then make three dimensional reconstructions. Using this technique it is easy to assess the spinal deformity as well as make precise measurements of each vertebra with concern to vertebral rotation and vertebral morphology.

The Cobb angle changes when going from standing to supine position (lying down). This is due to lesser gravitational loads in the supine position compared to when standing up. Since the patient is lying down during the CT examination we want to investigate how the Cobb angle changes from standing to supine position. This enables further studies based on images taken from low dose CT, in supine position.

The vertebras in scoliosis are not just rotated, they are also deformed. Therefore we will analyze how the morphology is changed in scoliotic vertebras compared to vertebras from a control group without any known back disorder. We hope to obtain a better understanding of the etiology of idiopathic scoliosis.

At our clinic most scoliosis patients undergo corrective surgery with an anterior approach. This is an established technique, but little is known about the changes in three dimensions as a result of the surgery. To learn more images from preoperative low dose CT are compared with postoperative low dose CT images in three dimensional reconstructions.



SUPERVISORS
Hans Tropp, Nils Dahlström, Daniel Forsberg, Per Aspenberg, Staffan Wirell

PROJECT
Quantitative musculoskeletal imaging for assessment of idiopathic scoliosis

Filipe Marreiros

VISUALIZATION AND TRACKING FOR SURGERY

SUPERVISORS
Prof. Michael Sandborg
Co-supervisors:
Prof. Örjan Smedby
Prof. Anders Persson
Docent Hannibal Sökjer

BACKGROUND
Diagnostic radiographer, Bristol School of Radiography in Great Britain April, 1980.

Diagnostic Radiographer Nairobi, Kenya 1980-1985

Radiology department Vrinnevi Hospital in Norrköping 1986-2014 during which I graduated with a Bachelor´s (2008) and Master's (2013) degree in Medicine.

Radiology Department in Linköping March 2014-present

The goal of this work is to explore new visualization and tracking techniques for surgery, particularly neurosurgery. The main interest is in brain tumor surgery to provide the surgeon visual information regarding tumors and eloquent areas, e.g. speech, motor and visual areas.

A central problem for all neuronavigation systems is the fact that, once the operation has started, the brain will be deformed to such an extent that the MRI image acquired preoperatively will no longer be a geometrically correct map of the area where the operation is carried out. This "brain shift" problem has attracted considerable attention, and the solutions proposed often involve some kind of tracking, e.g. by ultrasound, intraoperative MRI or camera stereovision systems. Our approach is to use a multi-view camera (three cameras) system to track brain superficial blood vessels and extract their 3D centerlines position. The intraoperative information is used to guide a deformation applied to the preoperative image, in order to compensate for brain shift. This deformation is necessary since the most relevant information (tumor extent, functional centers, and vessels) usually is present only in MRI, the real-time images cannot replace the preoperative images.

If the correct deformation is applied to the preoperative MRI image, it is still necessary to render it in such a way that the surgeon will perceive the important structures in the right position. Since the tumor can be located totally inside the brain the selection of the opacity levels and rendering types plays an important role. For instance if the tumor is rendered totally opaque then it will look like it is outside the brain, this is due to the occlusion depth-cue that can be stronger in stereoscopy.

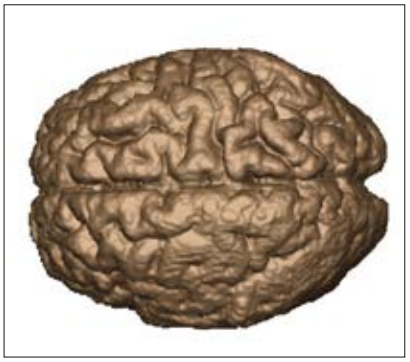


Figure 1. Pre-operative situation before brain shift.

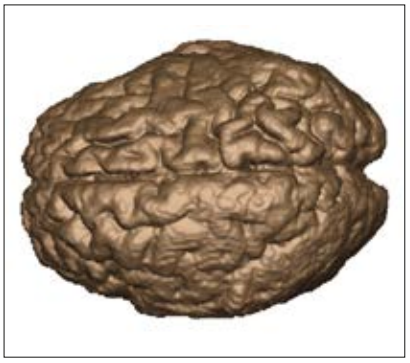


Figure 2. Intra-operative situation. Volume deformation for compensation of brain shift.

Stephanie Franzén

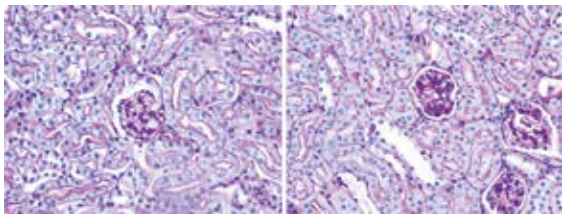
THE ROLE OF HYPOXIA IN THE DEVELOPMENT OF KIDNEY DAMAGE

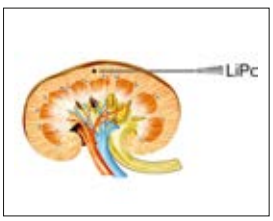
One third of all diabetes patients develop kidney damage during the course of their disease. The underlying mechanisms are, however, not yet completely known. Diabetes complication such as cardiovascular events is today one of the most common causes of death in the industrial world, whereas one in four Americans have metabolic syndrome which is indicated by obesity, diabetes, high blood pressure and high levels of plasma cholesterol.

The kidneys main function is filtration of the blood, reabsorption of the filtered substances that are necessary such as glucose and sodium, and excretion of substances that the body doesn't need into the urine. In early kidney damage the filtration rate is increased i.e. glomerular hyperfiltration, and there is a small leakage of proteins to the urine, i.e. proteinuria. This has been demonstrated to be reversible with antioxidant and citrulline treatment. Continued development of kidney damage causes the filtration rate to reach a top peak and further on decline with elevated proteinuria, which at this stage is irreversible.

Our hypothesis is that oxygen metabolism is the main underlying mechanism for developing kidney damage. It is known that diabetic kidneys present decreased oxygen tension, i.e. hypoxia. We are investigating if the hypoxia is caused by the increased consumption of oxygen that is occurring in a diabetic state. Therefore, we have performed several studies investigating the changes in oxygen consumption and oxygen tension with different treatments and can with that conclude that oxygen metabolism plays a key role in the development of kidney damage in diabetes.

We have recently presented an optimized methodology with electron paramagnetic resonance (EPR) oximetry and lithium phthalocyanine (LiPc) probes to repetitively monitor intrarenal oxygen tension and can with this method conclude that intrarenal tissue hypoxia occurs before the clinical marker for kidney damage, proteinuria. This indicates that tissue oxygenation plays an important part in the development of kidney damage, and monitoring of tissue oxygenation may be used as an initial marker for indications of kidney disease.





PROJECT INFORMATION

SUPERVISORS
Professor Fredrik Palm, IMH
Professor Mårten Segelmark, IMH
Professor Anders Persson, CMIV

BACKGROUND
MSc. in Biomedicine, started PhD in June 2012

Jesper Molin

SMARTER DIGITAL PATHOLOGY BASED ON DIAGNOSTIC TASKS AND COGNITIVE PROCESSES

SUPERVISORS
Morten Fjeld, Claes Lundström

PROJECT
Optimized flows and IT tools for digital pathology

BACKGROUND
Linköping University: Engineering degree in Applied Physics and Electrical Engineering with a minor in French, combined with a Master's degree in Biomedical Engineering, 2007-2012

Polytech'Montpellier: Exchange year at Electronique, Robotique et Informatique Industrielle, 2009-2010

New cancer treatment strategies have advanced rapidly during the last decades. The treatments have gone from a one-size fits all approach towards becoming more and more personalized. This development has put pressure on the diagnosing pathologists to deliver more detailed characterizations of the tumor biopsies. Together with the current lack of pathologists in Sweden this risks causing, if not severe implications, at least unnecessary emotional distress of patients waiting weeks on the lab results of their suspected cancer.

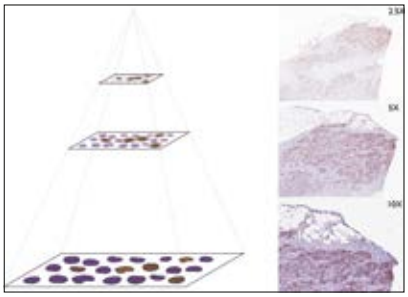
In recent years, the possibility of diagnosing cancerous tissue samples digitally has become available for clinical use. This makes it possible to create automatic systems that can aid and speed up the work of the pathologist.

This project focuses on analyzing the thinking processes of the pathologist to gain new insights to how such automatic systems should be constructed and then using these insights to create prototype systems and evaluate their performance.

So far three subprojects have been completed. We started out reviewing the current state of the art in digital pathology and analyzed navigation patterns when pathologist performed diagnoses with a prototype digital workstation. Based on these findings, we have developed two prototype systems. First, we implemented support for four different input devices and performed a comparative user study. Second, we developed a new image processing based visualization technique to help pathologists estimate the proliferation rate of breast cancer.

The findings from these projects are now used to develop new interactive visualization systems to facilitate the incorporation of results from image processing algorithms. The goal is to develop generic design patterns that can be used to put existing algorithms in use, rather than developing new algorithms.

These projects use a human centered design approach to assure that the outcomes can be used in routine clinical practice. A few of the solutions have already found its way out in clinical practice and are today used in pilot installations in Swedish pathology labs.



An interactive system that shows different amount of detail at different zoom levels that help pathologists to estimate the growth rate of cancer.

Jakob De Geer

THE USE OF CT IN CARDIAC IMAGING

During the last decade coronary computed tomography (CCTA) has become an important tool in the work up of coronary heart disease, especially in cases where the pre-test likelihood has been deemed low to intermediary.

However, as technology evolves a number of methods have emerged which take the diagnostic value of CT in coronary artery disease even further.

In one study we have evaluated dynamic CT perfusion, using SPECT as a reference. Our results showed only a moderate correlation between the methods, probably mainly due to the very different mechanisms involved. In addition, we observed a large variation in CTP blood flow in supposedly healthy cardiac segments, both within each patient but also between patients, leading to the conclusion that it is difficult to establish a single cut-off value for myocardial ischemia.

Another emerging technology is the evolution of software being able to estimate the fractional flow reserve (FFR), i.e. the pressure drop over a stenosis, using CCTA data only (cFFR). FFR is the ratio between pre- and poststenotic flow in the coronary arteries and has hitherto been determined by measuring pre- and poststenotic pressure during invasive coronary angiography. A ratio of < 0.80 is considered to constitute a significant stenosis and thus, FFR is a valuable tool when determining whether the patient needs treatment or not. However, invasive procedures are costly and potentially risky. If the cFFR technology proves reliable, it could be an important tool in the triage to invasive procedure.

In a small retrospective pilot study, we have compared invasively obtained FFR-values with those derived from CCTA in the same patient. The result showed a sensitivity and specificity for significant stenosis of 0.80 and 0.76 respectively. Spearman rank correlation between the methods was 0.77 and the intraclass correlation coefficient was 0.73. The same method is also being further evaluated in an on-going prospective study.

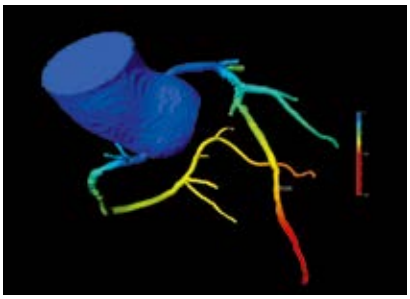


Figure 1 CT-based fractional flow reserve (cFFR) colour with cFFR = 0.82 in the LAD. The point of cFFR evaluation is freely adjustable.

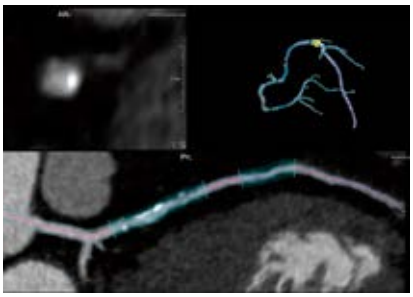


Figure 2 Overview of segmentation process, with the left anterior descending artery (LAD) in cross-sectional and curved MPR view, and the coronary tree mesh. Stenotic segments are manually defined. Vessel contours are automatically outlined but can be manually adjusted.

SUPERVISORS
Anders Persson, Jan Engvall, Örjan Smedby, Michael Sandborg

Eva Klintström

QUANTIFICATION OF OSTEOPOROSIS WITH COMPUTED TOMOGRAPHY

SUPERVISORS
Örjan Smedby, Torkel Brismar, Rodrigo Moreno

PROJECT
Quantification of osteoporosis with computed tomography

Fractures related to osteoporosis are common in Sweden, in particular among women. This means suffering for the individual and great costs for the community. In order to be able to minimize the number of fractures, it is important to detect osteoporosis at an early stage. The technique most frequently used for diagnosing osteoporosis is DXA (dual energy X-ray absorptiometry). With this method it is possible to measure the mineral content, but it is not possible to describe the internal structure of the bone. There are several studies showing that also the internal structure of the bone is of great importance for bone strength and risk for bone fractures.

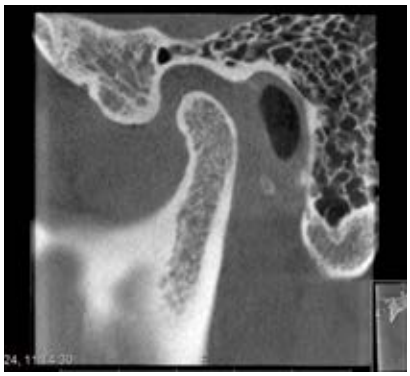
The aim of this project is to investigate the possibility to use the X-ray method computed tomography (CT) to image and measure the internal structure of bone, which would give a more complete picture of the osteoporosis. The aim is to find methods to measure osteoporosis and bone structure in patients. We started, however, with imaging small pieces of bone from the human forearm.

We have used 15 pieces of bone, all cubes with a side of 10-15 mm. The cubes were placed in test tubes filled with water, and the tubes were placed in a paraffin cylinder to mimic soft tissue. Imaging was performed with different types of CT methods and compared with the results from a method called micro-CT, which is considered the reference method. Micro-CT can only be used on small samples and in animal testing.

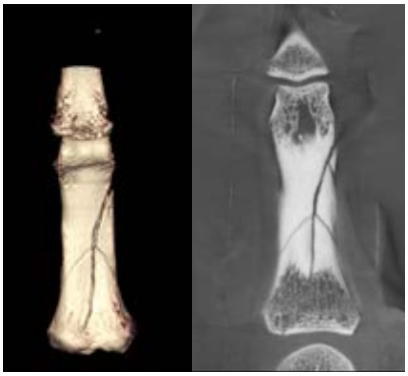
After imaging with the different X-ray methods, extensive image analysis is required. This analysis aims to identify all the small bone structures inside the bone. We analyse how many, how thick, how far apart the bone parts are, how many branches they have, how many free ends there are and the total amount of bone. For this purpose, a segmentation method is used that makes it possible to differentiate bone from the other structures, like blood vessels, fat and marrow inside the bone.

One of the tested methods, CBCT (cone beam CT), showed a very high correlation with micro-CT when analysing the bone pieces. CBTC is most often used in imaging teeth, jaws and people in need for implants in the jaws. The machine can also be used in diagnosing finger fractures both ordinary imaging and 3D visualisation.

In future studies, we want to compare the bone structure in the jaws with DXA results on patients examined for osteoporosis.



Left jaw and ear cells imaged by CBCT.



Left fractured first finger, CBCT image and 3D from CBCT.

Ida Blystad

CLINICAL APPLICATIONS OF SYNTHETIC MRI OF THE BRAIN

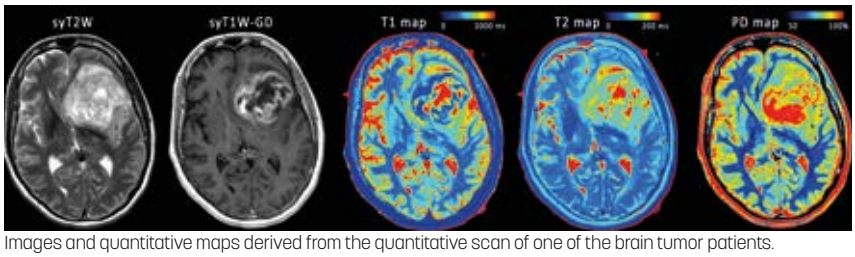
Conventional magnetic resonance (MR) images are assessed visually by the radiologist for diagnosis or evaluation of treatment effects. With new MR sequences it is possible to quantitatively assess the physical properties of the tissue, which gives a more objective evaluation tool. Synthetic MR is a quantitative MR sequence developed at CMIV and has a scan time of approximately 6 minutes. In this PhD-project the aim is to apply this sequence in different clinical settings, mainly in patients with multiple sclerosis (MS) and primary brain tumors.

Contrast-enhancing MS lesions are important markers of active inflammation in the diagnostic work-up of MS and in disease monitoring with MRI during follow-up. Since intravenous contrast agents involve an expense and a potential risk of negative side effects for patients, it would be desirable to identify active lesions without using a contrast agent. Using synthetic MR we have showed that active brain lesions in MS patients differ significantly from non-enhancing lesions, but that there is also a great overlap, which makes it difficult to rely on quantification alone.

Patients with high grade malignant gliomas (primary brain tumors) are treated with surgery, chemo- and radiotherapy and then followed with MR-examinations to evaluate treatment response and to detect early signs of tumor recurrence. Almost 25% of the patients react to the oncological treatment with edema and contrast-enhancement in the affected area of the brain, and although this pattern is benign it is difficult to distinguish visually from tumor recurrence.

Since the conventional image is non-specific, radiologists use quantitative methods in these cases, for example MR Spectroscopy, MR Perfusion and PET-CT, but there are still cases where it is unclear if the patient has tumor recurrence or treatment related changes. Since synthetic MRI is a quantitative MR-method it enables quantitative measurement of the tissue; relaxometry.

In this study we follow patients with malignant gliomas from diagnosis, during the follow-up after surgery and to oncological treatment. If it is possible to find tumor specific quantitative values, it might be possible to distinguish tumor from treatment effects and thereby improving the diagnostic arsenal in these difficult cases. This would be of great significance for the radiologists as well as the neurosurgeon and oncologist in treatment planning, and also of benefit for the patient.



Images and quantitative maps derived from the quantitative scan of one of the brain tumor patients. From left: synthetic T2W image, synthetic T1W image post-contrast agent injection, T1-, T2- and PD-maps.

SUPERVISORS
Elna-Marie Larsson, Peter Lundberg, Örjan Smedby, Marcel Warntjes, Anne-Marie Landtblom

PROJECT
Clinical Application of Synthetic MRI on Patients with Malignant Gliomas

BACKGROUND
Medical school Linköping University 1996-2002

Internship Enköping Hospital 2002-2005

Resident in Radiology 2005-2010,

Fellowship Neuroradiology 2010-2013,

Consultant Neuroradiologist, Department of Radiology, Linköping University hospital 2013-

Markus Karlsson

EARLY CHARACTERIZATION OF HEPATIC INFLAMMATION, FIBROSIS AND FUNCTION

SUPERVISORS
Peter Lundberg, Gunnar Cedersund, Nils Dahlström, Stergios Kechagias

PROJECTS
Non-invasive liver biopsy (NILB)
Liver intrinsic function evaluation (LIFE)
Hepatic inflammation and fibrosis investigation (HiFi)

BACKGROUND
M.Sc. in Engineering Biology, Linköping University (2015)

A problem with liver diseases is that the symptoms in the early stages are often weak and ambiguous. The physicians are often forced to do a liver biopsy to make a correct diagnosis. A biopsy however, has several drawbacks. Firstly, it is an invasive procedure that carries a risk for complications. Secondly, the biopsy also has a sampling error, since it only samples a tiny fraction of the liver. Therefore, there is a need for new diagnostic techniques.

Such new techniques could be based on magnetic resonance imaging (MRI). MRI can be used to characterize the diseased liver by a number of different parameters: inflammation, fibrosis, iron loading, fat loading, and function.

These parameters are not only of interest when investigating the early stages of liver diseases. Measures of hepatic function can, for instance, also be useful for liver surgeons deciding how much of the liver can be removed during surgery.

The main focus of this project is hepatic inflammation and function. We will explore if magnetic resonance elastography (MRE) can be used to detect and quantify inflammation.

MRE is a technique that measures the elasticity, by inducing shear waves into the liver, via an external vibrator. It is already established that MRE can be used to diagnose hepatic fibrosis. There is also strong evidence suggesting that inflammation also affects the elasticity of the liver. We hypothesize that by doing MRE at multiple frequencies, it will be possible to separate the contributions from fibrosis and inflammation.

The other focus of the project is hepatic function, which is measured using a contrast agent that increases the MR signal. The contrast agent used is liver specific, which means that it is taken up specifically by the hepatocytes and then secreted into the bile. The idea is that if the hepatic function is reduced, then less contrast agent will be taken up by the hepatocytes and the signal from the liver will not increase as much. Once the images are processed, they are analyzed using mathematical modeling.

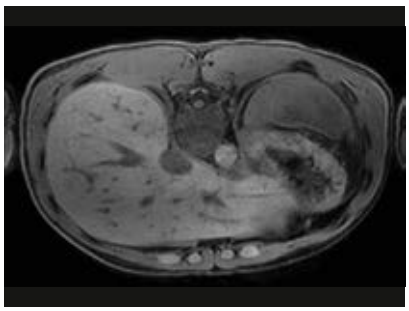


Figure 1. Image of a liver slice.

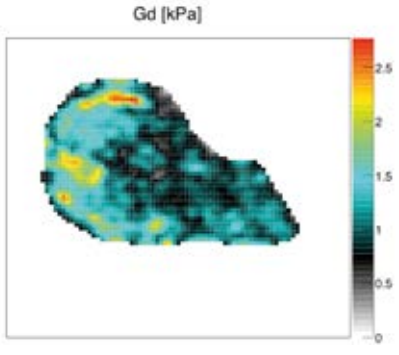


Figure 2. Elastogram showing the elasticity (Gd) of a liver slice.

Sofie Tapper

NEUROTRANSMITTER IMAGING OF THE HUMAN BRAIN

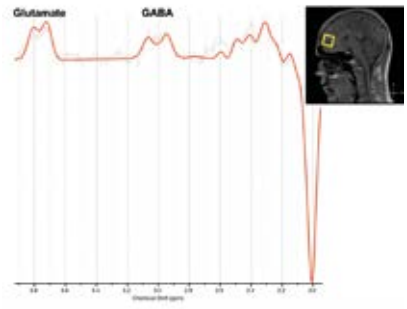
Magnetic Resonance Spectroscopy is a non-invasive technique that can be used to study metabolic changes in the diseased brain.

The neurotransmitters GABA and Glutamate, which are the main inhibitory and excitatory neurotransmitters in the central nervous system, should coexist in a healthy human brain. An imbalance between these neurotransmitters may have a significant influence on the development of neurological diseases. Therefore it is important to develop a clinical tool for reliable quantification of these neurotransmitters.

However, the challenges are exceptional, as the concentrations of the neurotransmitters are about 40,000 times less than that of water, and there is an additional overlap in the spectrum with signals from other metabolites. The technique has to handle effects from frequency drifts that occur when the MR-system is heated and signal artifacts such as those that originate from subject movements during the measurement. Additionally, in clinical applications it is desired that a measurement should be as short as possible and that the measurement region should be very small, both of these without loosing any quality in the resulting spectrum. It is therefore important to develop a novel method that reliably quantifies metabolites and at the same time handles all the factors described above.

The first step in this project has been to implement a method for artifact reduction that corrects for subject movements and at the same time can handle measurement data without any larger artifacts and without loosing any reliability in the computed concentrations. The results obtained so far show that it is important to handle these subject motions with corrections to obtain reliable concentrations.

The developed methodology will be applied in different clinical applications; diseases related to pain within the brain-gut axis (IBS), patients with essential tremor or Parkinson's disease that undergoes Deep Brain Stimulation (DBS) intervention, patients with sleep disorders such as Narcolepsy, and accumulation of manganese in the human brain affecting cognitive function.



The GABA and Glutamate signals that originate from the measurement region are visible in the resulting spectrum.

PROJECT INFORMATION

SUPERVISORS
Peter Lundberg
Anders Tisell
Peter Zsigmond

PROJECT
Seeing Organ Function

BACKGROUND
Master of Science (MSc) Applied Physics and Electrical Engineering, Signal and Image Processing, Linköping University 2008-2013

Research preparing course I-II 2013-2014

Research Assistant/Engineer, County Council of Östergötland, Department of Radiation Physics, 2014-2015

DISSERTATIONS

During 2015 three of the CMIV PhD students have finished their studies and defended their dissertations. The PhD students and the research school are an important part of CMIV and we are proud to present their dissertations here.

JOHAN KÄLVESTEN
Linköping University, Department of Medical and Health Sciences, Division of Radiology

AUTOMATIC IMAGE ANALYSIS FOR DECISION SUPPORT IN RHEUMATOID ARTHRITIS AND OSTEOPOROSIS

Low-energy trauma and fragility fractures represent a major public health problem. The societal cost of the fragility fractures that occurred in Sweden 2010 has been estimated at €4 billion. In rheumatoid arthritis (RA), patient outcomes have improved greatly in recent years. However, the therapeutic decision making is still hampered by a lack of effective validated biomarkers. The cost of RA in Sweden 2010 has been estimated at €600 million, of which biologic drugs was €180 million. Digital X-ray radiogrammetry (DXR) is a method to measure bone mineral density (BMD) in the metacarpals of the hand. It can be applied opportunistically in several workflows where a person is already at an X-ray machine, including fracture repositioning follow up, mammography screening and hand imaging in RA. This thesis explored DXR-BMD as a marker to identify individuals who would benefit from anti-osteoporotic treatment, change rate of DXR-BMD as a biomarker in RA and under what conditions historical X-ray images can be used to estimate DXR-BMD. An automated method for measurement of joint space width in metacarpophalangeal and interphalangeal joints was also developed and evaluated as a biomarker in RA.

MATS LOWÉN
Linköping University, Department of Clinical and Experimental Medicine, Division of Medical Gastroenterology

IRRITABLE BOWEL SYNDROME: STUDIES OF CENTRAL PATHOPHYSIOLOGICAL MECHANISMS AND EFFECTS OF TREATMENT

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by abdominal pain and altered bowel habits. The societal costs of the disorder are significant, as are its negative effects on quality of life. Medical treatment options are limited, but psychological treatments such as hypnotherapy have proven to be effective. Important pathophysiological mechanisms include disturbances in brain processing of visceral sensation and expectation of visceral sensation. Increased sensation of stimuli (hypersensitivity) is present in a subset of IBS patients to distensions in the lower part of the gastrointestinal tract, indicating a probable important pathophysiological mechanism in IBS. The overall aim of the thesis was to further study the central pathophysiological mechanisms involved in IBS. The results indicate that a subpopulation of IBS patients lacks the ability to habituate to repeated rectal distensions and expectation of these stimuli. The results also indicate that the abnormal processing of visceral stimuli in IBS can be altered, and that the treatments probably had a normalizing effect on the central processing abnormality of visceral signals in IBS.

FREDDIE ÅSTRÖM
Linköping University, Department of Electrical Engineering, Division of Computer Vision

VARIATIONAL TENSOR-BASED MODELS FOR IMAGE DIFFUSION IN NON-LINEAR DOMAINS

This dissertation addresses the problem of adaptive image filtering. Although the topic has a long history in the image processing community, researchers continuously present novel methods to obtain ever better image restoration results. One step in this pipeline is to use sophisticated imaging software including, e.g., noise reduction to reduce manufacturing costs, while maintaining image quality. This thesis is based on traditional formulations such as isotropic and tensor-based anisotropic diffusion for image denoising. The core contributions of this work is the introduction of a novel tensor-based functional which unifies and generalizes standard diffusion methods. Additionally, the explicit Euler-Lagrange equation is derived which, if solved, yield the stationary point for the minimization problem. Several aspects of the functional are presented in detail, which include but are not limited to, tensor symmetry constraints and convexity. Also, the classical problem of finding a variational formulation to a given tensor-based partial differential equation is studied. The presented framework is applied in problem formulation that includes non-linear domain transformation, e.g., visualization of medical images.

EQUIPMENT

Through unique collaborations with the industry it is possible for CMIV to always have the latest and most advanced equipment. This is a prerequisite for the successful research carried out at CMIV.

CT

The Siemens SOMATOM Force enables routinely performed exams at low kV settings (70-90 kV), even in adults. This is due to the system being equipped with powerful generators and X-ray tubes. The low kV settings allow for substantial reductions in contrast medium dose. Improvements have been made on the detector side as well with an increased number of detector rows and upgraded collimation.

The Force renders images with high spatial resolution and soft-tissue contrast. It contains two X-ray sources and two detectors which can be used simultaneously. This in combination with a broader detector enables faster scans than before. High speed scanning is necessary for cardiac examinations as well as for restless patients. The two X-ray sources also provide the possibility for dual energy examinations with improved spectral separation.

The Siemens SOMATOM Definition Flash dedicated to the SCAPIS project also performs at low kV settings and has two x-ray sources and two detectors allowing the use of dual energy.

MRI

The Philips Ingenia 3.0T has a 70 cm bore. It is equipped with Xtend gradient system (up to 45mT/m - 200 T/m/s) and two parallel RF transmissions (Multitransmit 4D), which adapt RF signals to each patient.

Multitransmit facilitates an increased image uniformity, contrast, and consistency, as well as faster imaging. A full range of receiver coils is available with analog-to-digital converters inside the coils (dStream RF). This samples the MR signal directly in the coil on the patient, and sends it to the reconstructor via a fibre-optic cable.

Our Philips Achieva 1.5T has a 60 cm bore and is equipped with Nova Dual gradients (up to 66 mT/m – 160 T/m/s), a 16-channel Freewave data acquisition system, and the latest software release. The 1.5T was recently upgraded to dStream resulting in up to 40 % higher SNR, and a dynamic range that exceeds 185dB.

A full research agreement with Philips Medical Systems allows all possible clinical as well as technical research applications.

In addition, we have access to a GE Signa 1.5T HDxt and Discovery 750 3.0T MRI system.

ULTRASOUND

CMIV has access to several clinical ultrasound scanners, Vivid E 9 with Echopac BT 13 software for echocardiography and Siemens S2000 for vascular studies, as well as a dedicated scanner GE Logic E9 and a Vevo high frequency scanner for vascular research.

PACS

Sectra radiology PACS is a comprehensive workstation, designed to optimize the workflow. It ensures quick and easy access to patient data and images and provides instant access to all the tools needed integrated on the desktop – including RIS and clinical applications.

For storage and handling of echocardiographic image data (for both research and clinical use), one of the largest installations of the GE EchoPAC system in the world is available. A number of advanced diagnostic workstations are available for clinical and research purposes.

VISUALIZATION

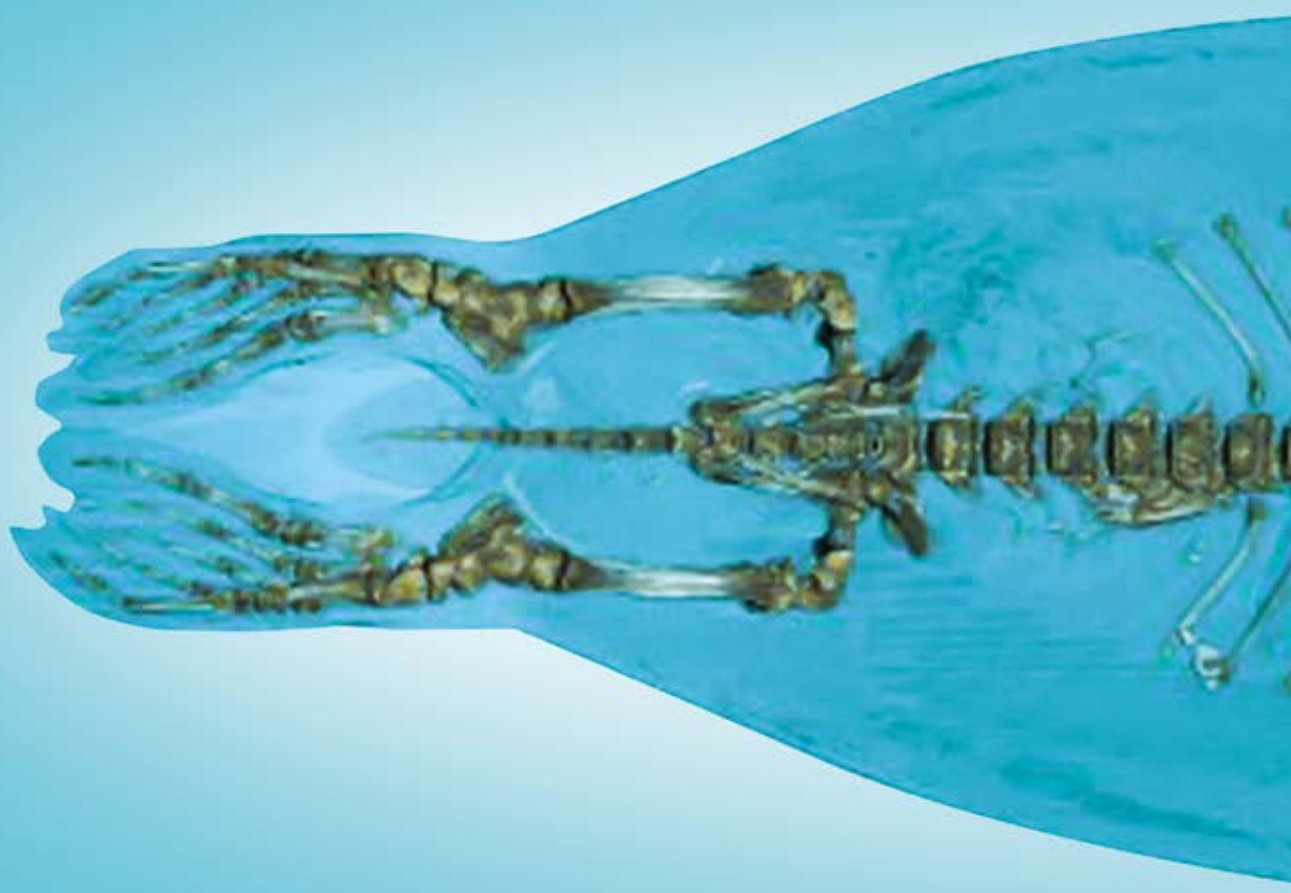
CMIV has its own Virtual Reality theatre with a capacity of 90 persons. The theatre is built around Barco Galaxy NW-12 projector (12 000 lumens light output, WUXGA (1920x1200) resolution.) The NW-12 has an integrated active Infitec 3D stereo filter, allowing for optimal 3D visualization with passive stereo glasses. Using a Barco XDS 150 and an EXTRON DMS 3600 DVI switch, all computers at CMIV's network can be used for video conference system, allowing for 1080p HD conference meetings or video broadcasting. A Smartboard Interactive Whiteboard is available for interactive presentations and meetings.

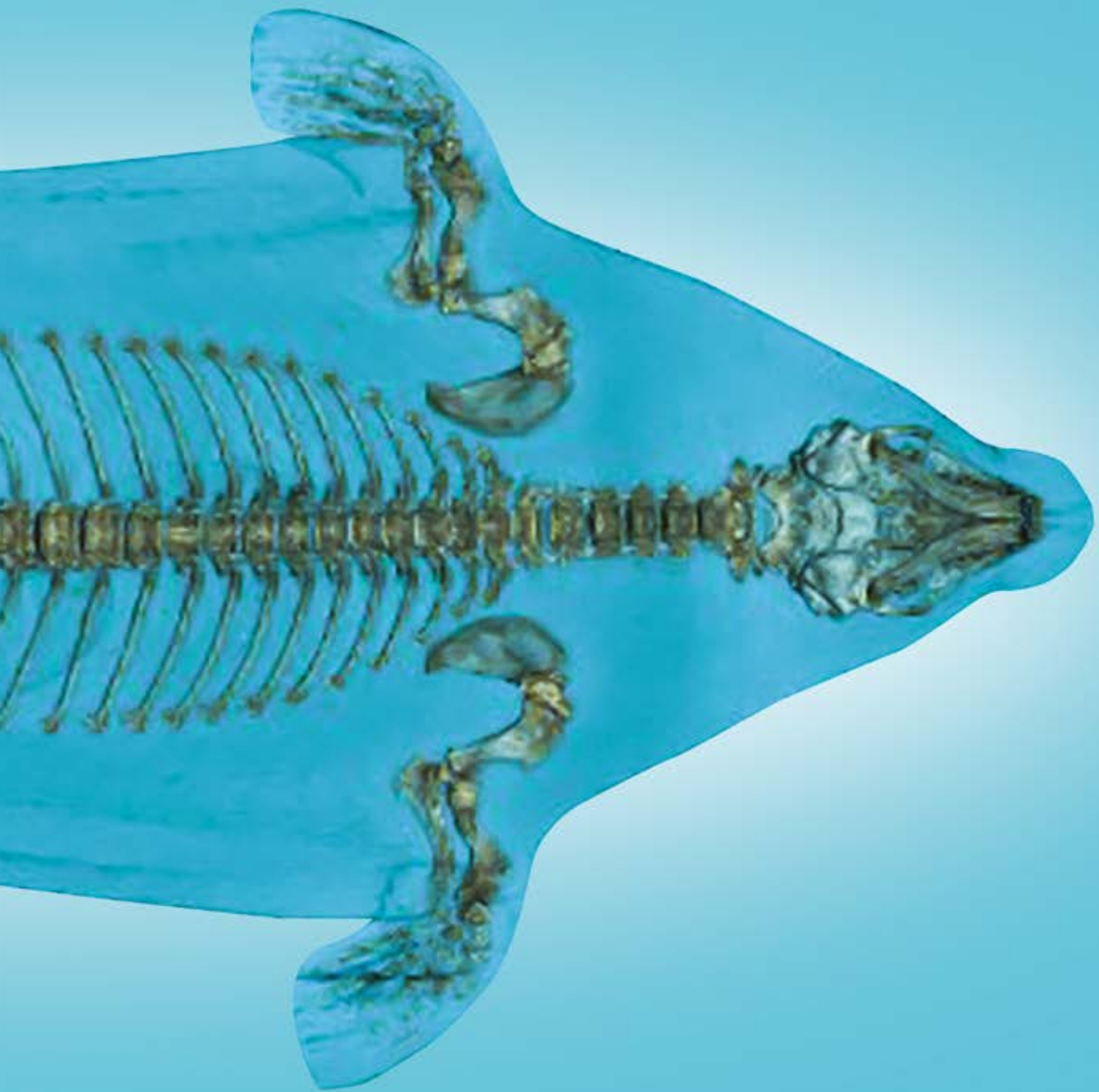
Several Advantage Workstations from GE Medical Systems are available at the hospital.

In addition to the theatre there is also a Sectra visualization table complete with Sectra PACS. The Visualization Table is a large interactive screen with an image display system that enables interaction with 3D human body images rendered from CT or MR.

DIGITAL PATHOLOGY SCANNER

A recent technical addition at CMIV is a pathology glass scanner from Hamamatsu. The Nanozoomer 2.0HT convert glass slides into high-resolution digital data by high-speed scanning and has a capacity of scanning up to 210 slides automatically.





ORGANIZATION

CMIV is governed by its Board of Directors, with representatives from academia, health care and industry. The Scientific Council, appointed among the senior researchers affiliated with CMIV, manages the research agenda of CMIV. The day-to-day operations of CMIV are handled by a group of core staff.

RESEARCHERS

Gudrun Alm Carlsson	IMH, Radiological sciences
Mats Andersson	IMT, Medical informatics
Nazre Batool	ITN, Media and information technology
Magnus Borga	IMT, Medical informatics
Carl-Johan Carlhäll	IMH, Cardiovascular medicine
Åsa Carlsson Tedgren	IMH, Radiological sciences
Olof Dahlqvist Leinhard	IMH, Radiological sciences
Nils Dahlström	IMH, Radiological sciences
Petter Dyverfeldt	IMH, Cardiovascular medicine
Tino Ebbers	IMH, Cardiovascular medicine
Gillian Einstein	IKE, Clinical sciences
Anders Eklund	IMT, Medical informatics
Maria Engström	IMH, Radiological sciences
Jan Engvall	IMH, Cardiovascular medicine
John-Peder Escobar Kvitting	IMH, Cardiovascular medicine
Daniel Forsberg	ITN, Media and information technology
Håkan Gustafsson	IMH, Radiological sciences
Vikas Gupta	IMH, Cardiovascular medicine
Mats Hammar	IKE, Clinical sciences
Markus Heilig	IKE, Neuro and Inflammation Sciences
Ingrid Hotz	ITN, Media and information technology
Camilla Josephson	IEI, National economy
Hans Knutsson	IMT, Medical informatics
Matts Karlsson	IEI, Applied thermodynamics & fluid mechanics
Thomas Karlsson	IBL, Disability research
Anne-Marie Landtblom	IKE, Neurology
Jonas Lantz	IMH, Cardiovascular medicine
Peter Lundberg	IMH, Radiological sciences
Karljohan Lundin Palmerius	ITN, Media and information technology
Claes Lundström	ITN, Media and information technology
Toste Länne	IMH, Cardiovascular medicine
Maria Magnusson	ISY, Computer vision
Alexandr Malusek	IMH, Radiological sciences
Rodrigo Moreno	IMH, Cardiovascular medicine
India Morrison	IKE, Neuro and Inflammation Sciences
Ebo de Muinck	IMH, Cardiovascular medicine
Nina Nelson	IKE, Pediatrics
Peter Nilsson	IFM, Chemistry
Eva Nylander	IMH, Cardiovascular medicine
Håkan Olausson	IKE, Neurology
Fredrik Palm	IMH, Drug research
Anders Persson	IMH, Radiological sciences
Lennart Persson	IMH, Cardiovascular medicine
Hans Ringerz	IMH, Radiological sciences
Timo Ropinski	ITN, Media and information technology
Michael Sandborg	IMH, Radiological sciences

Folke Sjöberg	IKE, Clinical sciences
Örjan Smedby	IMH, Radiological sciences
Rozalyn Simon	IMH, Radiological sciences
Éva Tàmas	IMH, Cardiovascular medicine
Darren Treanor	IKE, Neuro and Inflammation Sciences
Hans Tropp	IKE, Orthopaedics
Helene Veenstra	IMH, Radiological sciences
Susanna Walter	IKE, Gastroenterology
Marcel Warntjes	IMH, Cardiovascular medicine
Karin Wårdell	IMT, Biomedical instrumentation
Anders Ynnerman	ITN, Media and information technology
Wolf-Dieter Zech	IMH, Radiological sciences

PHD STUDENTS

Thord Andersson	IMT, Medical informatics
Ida Blystad	IMH, Radiological sciences
Mariana Bustamante	IMH, Cardiovascular medicine
Belèn Casas Garcia	IMH, Cardiovascular medicine
Olivier Cros	IMT, Medical informatics
Jakob de Geer	IMH, Radiological sciences
Mikael Forsgren	IMH, Radiological sciences
Stephanie Franzen	IMH, Drug research
Diana Fraser	IKE, Psychiatry
Charalampos Georgiopoulos	IMH, Radiological sciences
Marcus Gjerde	IMH, Cardiovascular medicine
Daniel Jönsson	ITN, Media and Information Technology
Anette Karlsson	IMT, Medical informatics
Bharti Kataria	IMH, Radiological sciences
Johan Kihlberg	IMH, Radiological sciences
Eva Klintström	IMH, Radiological sciences
Sandeep Koppal	IMH, Cardiovascular medicine
Sofia Kvernby	IMH, Cardiovascular medicine
Johan Kälvesten	IMH, Radiological sciences
Mats Lowén	IKE, Medical Gastroenterology and Hepatology
Karin Lundegård	IMH, Radiological sciences
Filipe Marreiros	ITN, Media and Information Technology
Jesper Molin	Chalmers and Sectra AB
Natasha Morales Drissi	IMH, Radiological sciences
Eva Olsson	IMH, Radiological sciences
Thobias Romu	IMT, Medical informatics
Jens Sjölund	IMT, Medical informatics
Carina Stenman	IMH, Radiological sciences
Sofie Tapper	IMH, Radiological sciences
Ludvig Vavruch	IKE, Orthopedics
Magnus Ziegler	IMH, Cardiovascular medicine
Jakob De Geer	IMH, Medical Radiology

BOARD

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Curt Karlsson	Linköping University
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Jan Marcusson	Region Östergötland
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Katrine Åhlström Riklund	Umeå University, Diagnostic Radiology

SCIENTIFIC COUNCIL

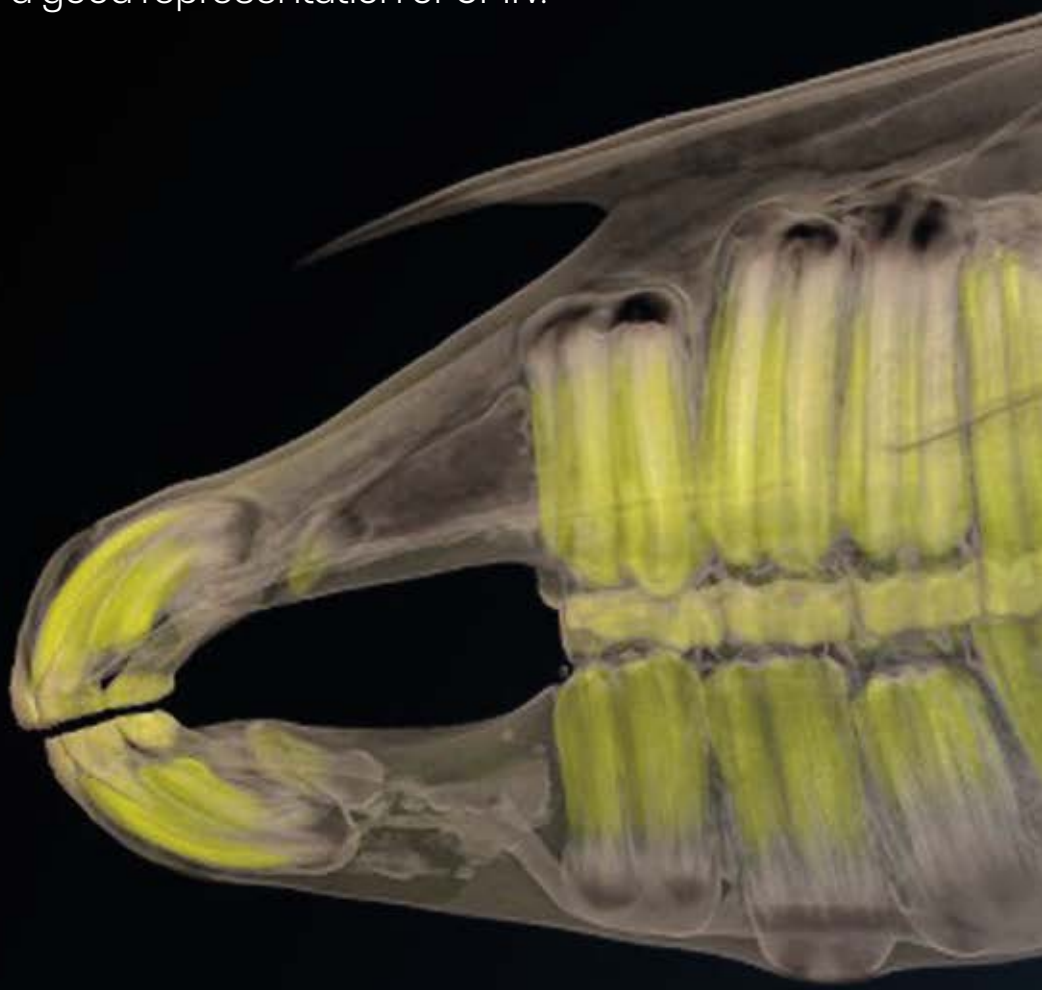
Magnus Borga	IMT, Medical informatics
Carl-Johan Carlhäll	IMH, Cardiovascular medicine
Olof Dahlqvist Leinhard	IMH, Radiological Sciences
Nils Dahlström	IMH, Radiological Sciences
Petter Dyverfeldt	IMH, Cardiovascular medicine
Tino Ebbers	IMH, Cardiovascular medicine
Håkan Gustafsson	IMH, Radiological sciences
Maria Kvist	CMIV
Peter Lundberg	IMH, Radiological Sciences
Claes Lundström	ITN, Media and Information Technology
Maria Magnusson	ISY, Computer vision
Fredrik Palm	IMH, Drug research
Anders Persson	IMH, Radiological Sciences
Karin Wårdell	IMT, Biomedical Instrumentation
Anders Ynnerman	ITN, Media and Information Technology

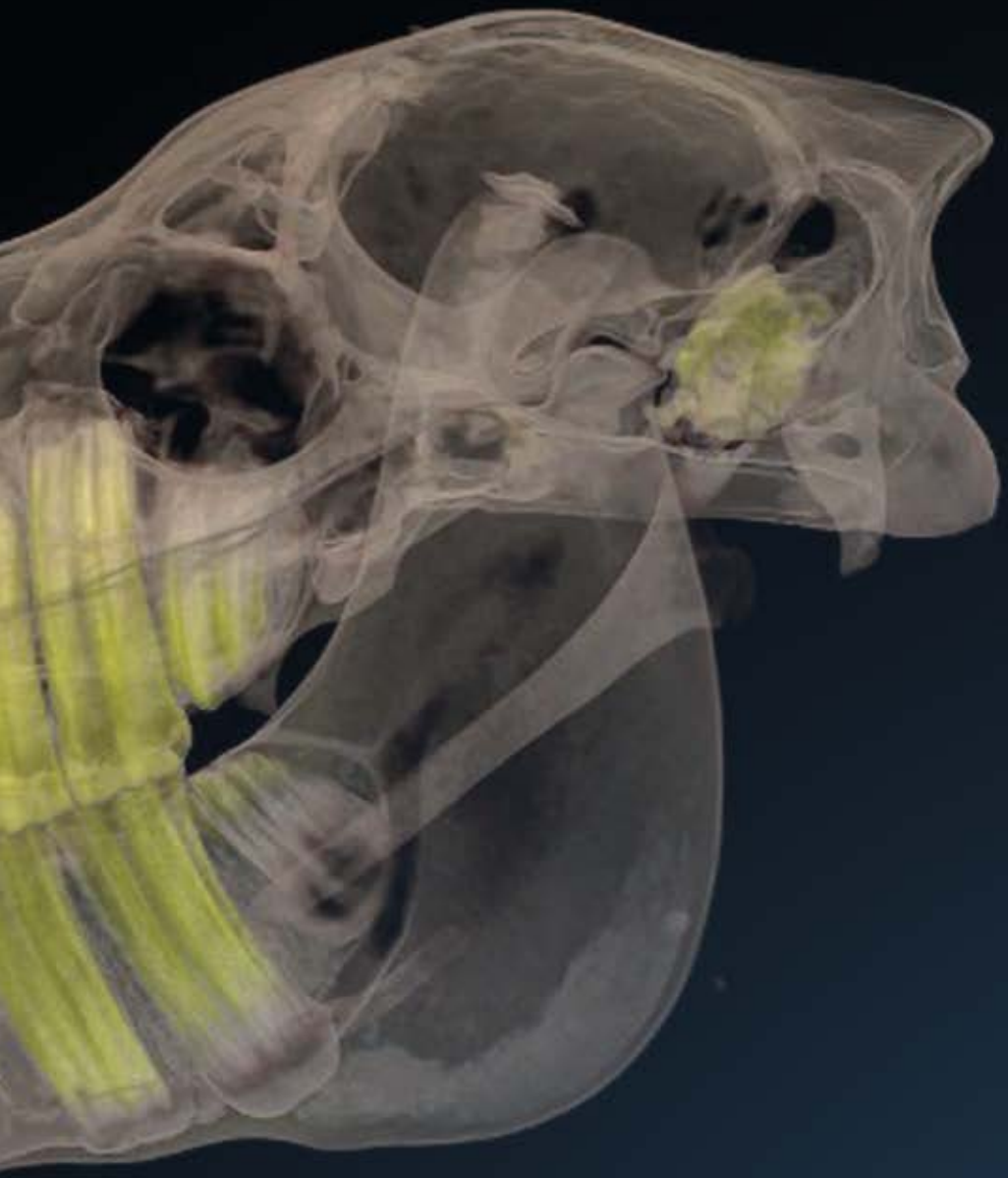
CORE STAFF

Anders Persson	Director
Maria Kvist	Research Coordinator
Marie Waltersson	Research Coordinator/ Communicator
Björn Broo	IT Manager
Marie Waltersson	Director of Doctoral Studies
Catrin Nejdeby	Coordiantor
Marcel Warntjes	Clinical Scientist
Petter Dyverfeldt	Clinical Scientist
Suzanne Witt	Clinical Scientist

PUBLICATIONS

As the CMIV researchers are also affiliated to a home department at Linköping University or another university and their research is primarily registered there it can be difficult to overview. We have made an attempt at putting together a list with the publications produced during 2015. Although not complete it still shows a good representation of CMIV.





BIBLIOMETRIC ANALYSIS

The bibliometric analysis has been provided by the Linköping University Library, department of Publishing Infrastructure. The citation data used in the analysis has been supplied by CWTS, Leiden University; data source: Thomson Scientific/ISI.

Table 1
Norwegian Model

	2010-2015	
	Number of publications	**Number of fractions**
Journal articles - refereed	308	152,5
Chapters - other academic	29	16,8
Books - other academic	0	0,0

The model combines productivity and impact. It is intended to be applicable to all areas of science, and therefore includes journal articles as well as books and chapters. Comment: Proceeding papers are included if they have been published in an approved publication channel, and are counted as chapters or journal articles.

Results

Publication points	**212,5**
Average number of publications points per year	35,4
% author shares level 2	14%
Author shares, sum	169,3

% author shares level 2: Percentage of fractionalized publications published in journals / publishers of the highest scientific quality.

Table 2
Open access

Articles:	**2015**
Share of green open access	35%
Share of hybrid open access	21%
Share of gold open access	0%
Share of conference articles with green open access	36%
Share of chapters with green open access	100%

Green open Access refers to articles, conference articles and chapters published in full text in DiVA. Gold open access is defined as publications where the article ISSN is registered in the Directory of Open Access Journals (DOAJ). Hybrid open access is defined as publications where registration in DOAJ is missing but open access may be availible through the DOI link.

Tablel 3
Coverage in Web of Science

Publications in Web of Science (including Conference Proceedings Index)	**Number of publications**	**Number of fractions**
Articles, reviews, letters, proceedings papers	277	133,4

Figure 1
Number of fractionalized publications

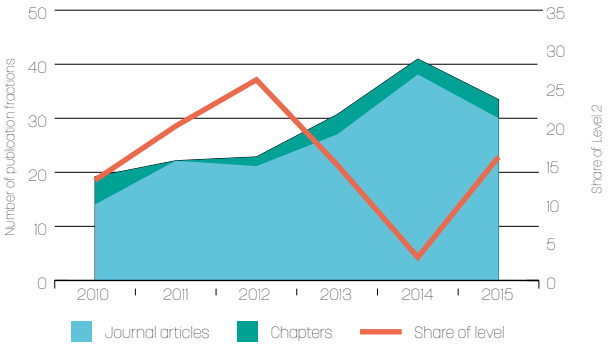


Figure 2
Open access articles

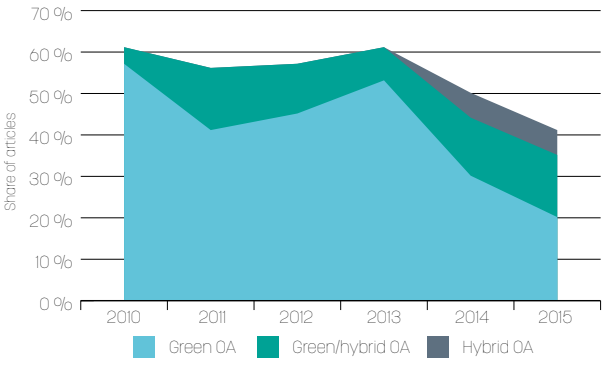


Figure 3
Number of fractionalized journal articles: Coverage in WoS 84%

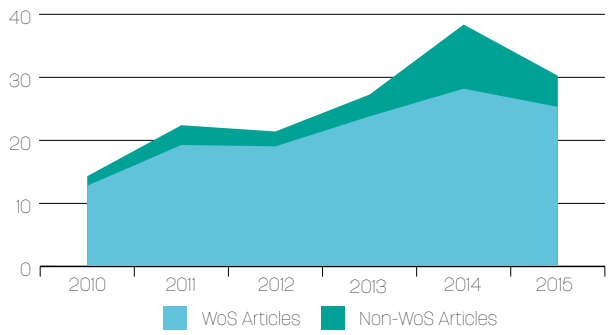


Figure 4
Impact

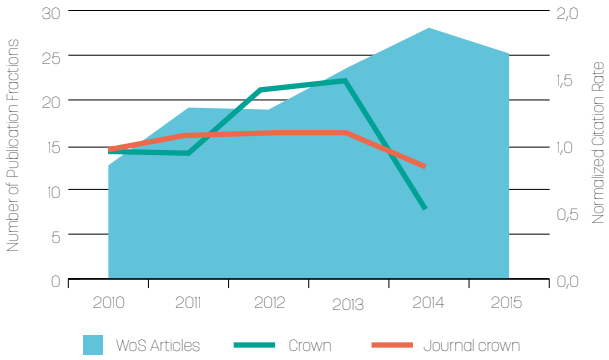


Figure 5
Fractionalized journal articles in WoS: Co-authorships

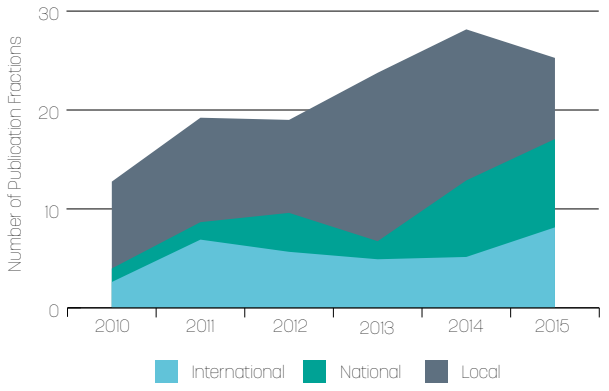


Figure 6
Parallel publishing

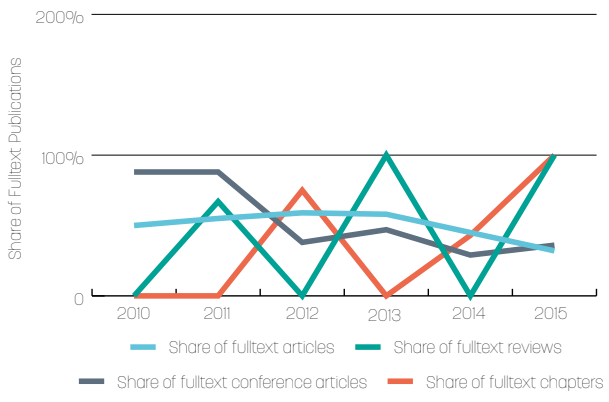


Table 4
Citation analysis

	2010-2015	
"Publications in Web of Science (excluding Conference Proceedings Index)"	**Number of publications**	**Number of fractions**
Articles, reviews, letters	175	82,8

Results

	2010-2014
Field-normalized citation rate (crown)	**1,06**
Share of top 10 %	14%
Share of uncited publications	22%
Field-normalized journal citation rate (journal crown)	1,01
Journal Impact Factor (JIF) ranking, mean	0,66

Crown: A measure of the impact of the articles included in the analysis. Provides a comparison value with an international average for the same field, year and article type, and where the value 1 corresponds to a world average.
Share of top 10%: The percentage of publications that are among the 10% most cited in the subject area during the time period
Journal Crown: A measure of the impact of the journals that the department published in. JIF Ranking mean: All journals within each subject category are ranked based on the JIF, and the number indicates how the journal in question is placed in the rankings. Ex 0.8 indicates that the journal is among the 20% highest ranking.

Table 5
Co-authorship

	2010-2015
Share of articles with international co-authors	**26%**
Share of articles with national co-authors	20%
Share of articles with local co-authors	54%

Table 6
Interdisciplinary authorship (LiU faculties)

	2010-2015
Number	**67**
Share	**20%**

PUBLICATIONS 2015

CMIV affiliated researcher are written in bold

Peer-reviewed Original Article

Adolfsson E, White S, Landry G, Lund E, Gustafsson H, Verhaegen F, **Alm Carlsson G** et al. Measurement of absorbed dose to water around an electronic brachytherapy source : Comparison of two dosimetry systems: lithium formate EPR dosimeters and radiochromic EBT2 film. Institute of Physics Publishing (IOPP); Physics in Medicine and Biology, ISSN 0031-9155, E-ISSN 1361-6560, Vol. 60, nr 9, 3869-3882 s. No of citations: - JIF: 2.761

Alonso F, **Wårdell K**, Hemm-Ode S. Influence on Deep Brain Stimulation from Lead Design, Operating Mode and Tissue Impedance Changes – A Simulation Study. Brain Disorders and Therapy, ISSN 2168-975X BDT. No of citations: -

Andersson M, Burdakov O, **Knutsson H**, Zikrin S. Sparsity Optimization in Design of Multidimensional Filter Networks. Springer; Optimization and Engineering, ISSN 1389-4420, E-ISSN 1573-2924, Vol. 16, nr 2, 259-277 s. No of citations: - JIF:1.233

Andersson M, Jagervall K, Eriksson P, **Persson A**, Granerus G, **Wang C**, **Smedby Ö**. How to measure renal artery stenosis - a retrospective comparison of morphological measurement approaches in relation to hemodynamic significance. BIOMED CENTRAL LTD; BMC Medical Imaging, ISSN 1471-2342, E-ISSN 1471-2342, Vol. 15, nr 42 No of citations: - JIF:1.312

Andersson M, Lantz J, Ebbers T, Karlsson M. Quantitative Assessment of Turbulence and Flow Eccentricity in an Aortic Coarctation - Impact of Virtual Interventions. Cardiovascular Engineering and Technology, ISSN 1869-408X, E-ISSN 1869-4098, Vol. 6, nr 6, 281-293 s. No of citations: -

Andersson T, Romu T, Karlsson A, Norén B, Forsgren M, Smedby Ö, Kechagias S, Almer S, **Lundberg P, Borga M, Dahlqvist Leinhard O.** Consistent intensity inhomogeneity correction in water–fat MRI. John Wiley & Sons; Journal of Magnetic Resonance Imaging, ISSN 1053-1807, E-ISSN 1522-2586, Vol. 42, nr 2, 468-476 s. No of citations: - JIF:3.210

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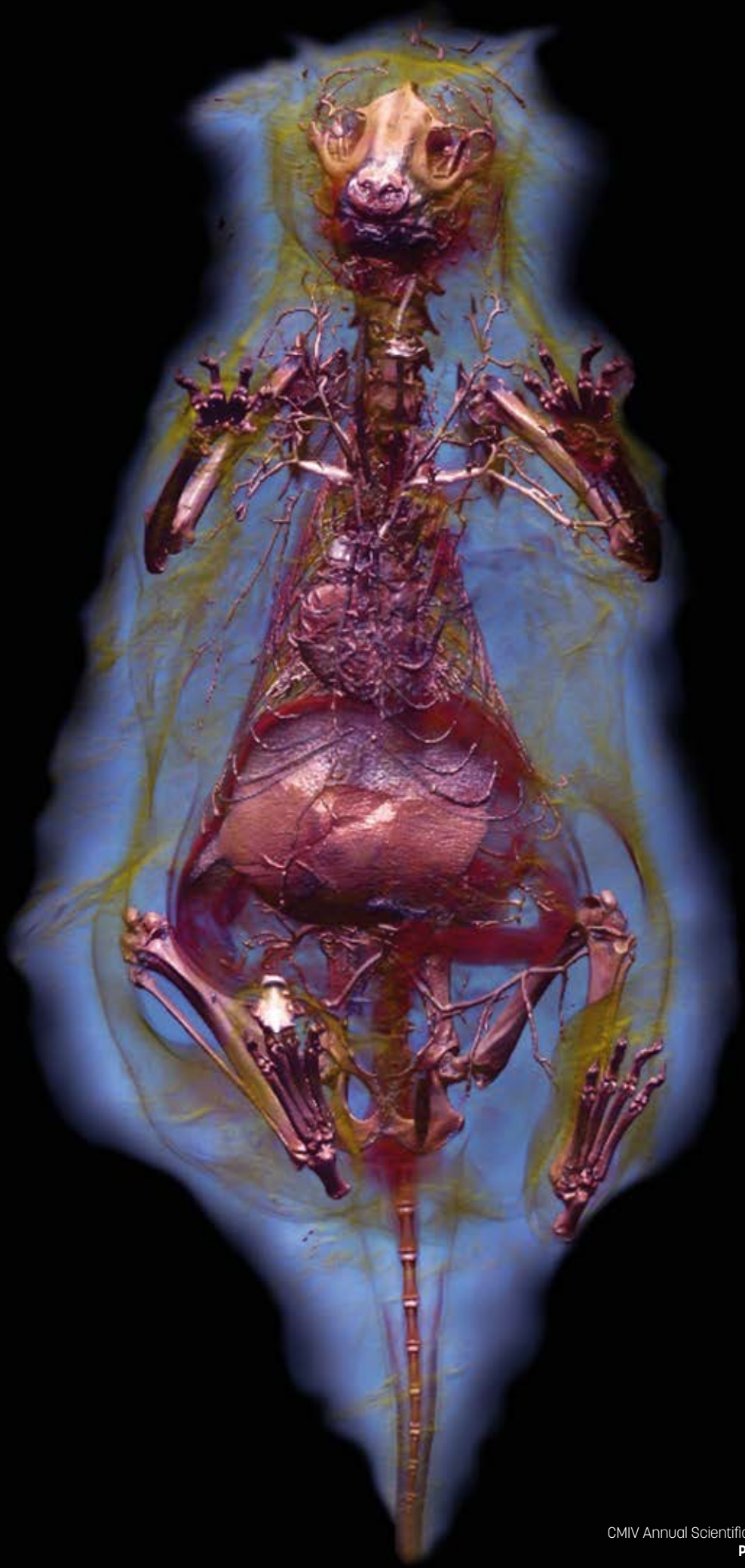


ANNUAL ACCOUNTS

During 2015 CMIV had a turnover of more than 39 million. The financial results for CMIV in 2015 was 1.2 million SEK in surplus.

This fiscal year several efforts have been made within the MRI area. The previously installed Philips 1.5T Achieva was upgraded to dStream. The center moved to new facilities and a Philips Ingenia 3T was installed at the new premises. A procurement is underway to purchase a neuro specialized MRI to be placed at the new premises, this MRI will be installed during 2016.

During 2015 CMIV had two ongoing grant projects, digital pathology and orthopedics. The project "Optimized flows and IT tools for digital pathology" was started up early in 2015 and will continue until 2017. The smaller project "Bringing orthopedic implant surgery to the era of precision medicine" started up in the second half of the year and is a smaller pilot project that ends during 2016.

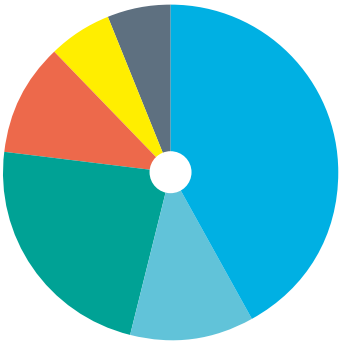
Economic summary

	2011	2012	2013	2014	**2015**
TOTAL REVENUE	32 800	32 629	35 576	48 762	**39 298**
EXPENSES					
Staff expenses	-14 645	-15 102	-16 756	-19 507	**-18 593**
Cost of premises	-1 975	-2 145	-2 034	-2 058	**-2 869**
Misc. operating expenses	-9 549	-7 653	-8 876	-17 334	**-11 483**
Depreciation expenses	-5 883	-4 938	-5 336	-5 629	**-4 980**
Financial expenses	-403	-125	-185	-102	**-123**
TOTAL EXPENSES	-32 455	-29 963	-33 187	-44 630	**-38 048**
RESULT OF OPERATIONS	345	2 666	2 389	4 133	**1 250**

Numbers in thousands of SEK

BASIC GRANT OVERVIEW

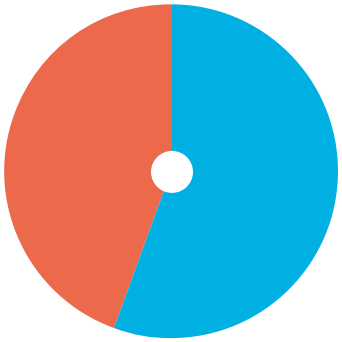
The annual basic grant from Linköping University and Region Östergötland is 3.5 million SEK distributed as 1 million each from technical and medical faculty and 1.5 million from the county council. The diagram shows an overview of how the grant is being used in the CMIV administration.



Salaries, CMIV staff	42%
Research school	12%
Clinical Scientists	23%
Central administration	11%
Travels and conferences	6%
Office supplies and computers	6%

RESEARCH FUNDING

CMIV receives funding from research funds and the industry both directly to the R&D platform and to specific research projects. In addition, the affiliated researchers have their own funding; however these grants will not be presented here.

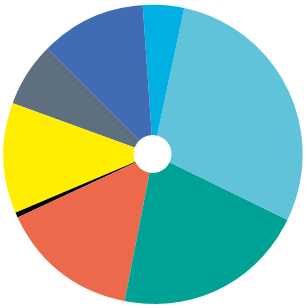


External funds: 67 854 Tkr
Industrial funds: 53 954 Tkr

External funds	
Industrial funds	

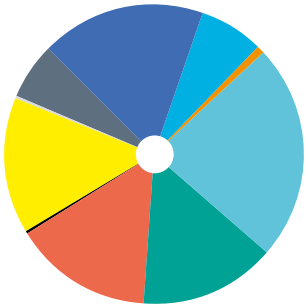
DISTRIBUTION OF RESEARCH ON THE MRI CAMERAS

2014



Full body scan	4,5%
Logistics	28,7%
fMRI neuro	21%
Cardiovascular	15,1%
Industry	0,3%
Combined Clinic/research	12,1%
Spectro neuro	6,8%
Development time	11,6%

2015



Full body scan	7,1%
Logistics	23,4%
fMRI neuro	14,8%
Cardiovascular	15%
Industry	0,3%
Combined Clinic/research	14,6%
Spectro neuro	6%
Development time	17,8%
Neuro	0,3%
CSAN neuro	0,7%

CENTER FOR MEDICAL IMAGE SCIENCE AND VISUALIZATION

LINKÖPING UNIVERSITY

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