MI Lab Research Plan 2011-2014

1. Background and Process

MI Lab started March 2007, and had during the period 2007-2009 a gradual build up to full budget capacity at the end of 2009.
MI Lab started in 2009 a process towards a revised research plan for the 4-years period 2011-2014. This process has included the following criteria and activities:

MI Lab wants to have a main focus on good interaction with the industrial partners and a main challenge for 2011-2014 is to achieve increased participation from the partners' R&D departments in long-term high quality and high ambition research activities inside MI Lab. During 2009 the MI lab leadership visited all the main industrial partners (GE Vingmed Ultrasound MediStim, Sonowand, Arctic Silicon Devices, NordicNeuroLab), and similarly had a meeting with The CEO of Fast Search & Transfer, Bjørn Olstad. The goals of these visits were:

- to get an update on each industrial partner's business activities and R&D strategies
- to discuss how to strengthen the interaction between the partner and MI Lab
- to discuss possible new research activities in MI Lab

MI Lab established in 2009 an international Scientific Advisory Board with the following members:

- Professor Peter Burns, Department of Medical Biophysics, University of Toronto, Canada
- Professor Lars-Åke Brodin, The Royal Institute of Technology (KTH), Stockholm, Sweden
- Researcher Jean-Francois Gelly, Parallel Design SA, Sofia Antipolis, France
- Professor Henrik Larsson, Unit for Functional Image Diagnostics at Glostrup University Hospital, Copenhagen, Denmark

Burns and Brodin have no scientific collaboration with MI Lab, while Gelly and Larsson are attached to MI Lab as international professor/guest researcher.

The Scientific Advisory Board had the first meeting in Trondheim January 2010 with the following mandate:

- Evaluate the scientific quality and scientific originality of the on-going research and future research plans
- Evaluate if the research is according to international trends
- Discuss the research activities with some of the key professors and post docs
- Advice on changes to the research plans and/or suggest other research activities and new research ideas
- Make a written report on the evaluation and recommendations

MI lab established in 2009 an extended leader group consisting of the senior NTNU personnel that are most involved in the MI Lab activities as subproject leaders and main supervisors for PhD students hired by MI Lab:

- Professor Olav Haraldseth, MD, PhD
- Professor Hans Torp, PhD
- Associate professor Asta Håberg, MD, PhD
- Associate professor Asbjørn Støylen, MD, PhD
- Professor Trond Ytterdal, PhD
- Research Scientist Lasse Løvstakken, PhD
- Research Scientist Bjørn Olav Haugen, MD, PhD

This new MI Lab research plan for 2011-2014 builds on these three main sources:

- The discussions with the industrial partners
- The written report from the Scientific Advisory Board
- Discussions in the MI Lab leader group

The research plan for 2011-2014 was formally approved by the MI Lab Board in June 2010.

2. Overall Framework

It was agreed to keep most of the main framework from the original MI Lab research plan from March 2007, with some adaptations from MI Lab Board decisions during 2007-2009.
These include (se below): vision, main research tasks, strategy, main success criteria, interaction with the partners, integration with the medical imaging community in Trondheim, focus on researcher training.

Vision

To facilitate cost efficient health care and improved patient outcome through innovation in medical imaging, and to exploit the innovations to create industrial enterprise in Norway.

Main research tasks

The research plan is based on the understanding that the most important challenge for the future healthcare is how to exploit the great achievements in medical research in order to improve patient treatment and outcome while containing costs. Medical imaging is central to meeting this challenge, and new technology for improved cost efficacy should be a main focus for imaging research and industrial innovation.

Innovation in medical imaging can contribute to improved cost-efficiency on several levels, and MI Lab has chosen to focus on three important areas:

- high quality medical imaging products and applications for non-expert users at the initial point of care
- less complications and more rapid patient rehabilitation with image-guided minimally invasive surgery
- more rapid and more precise choice of efficient treatment through decision-making based on advanced medical imaging.

As Trondheim has a long history of basic ultrasound technology research with successful industrial spin-offs, this is a fourth main area, and MI Lab has the following main research tasks:

- Research Task 1: Ultrasound technology
- Research Task 2: Advanced imaging applications for non-expert user
- Research Task 3: Image guided minimally invasive surgery
- Research Task 4: Imaging based information to support medical decision making

Strategy

The strategy is to establish a creative melting pot for medical imaging research through:

- bringing together on a daily basis researchers from university, hospital and industry
- establish a large multi-disciplinary research environment including medicine, ICT, physics, mathematics, cybernetics, electronics, physiology, molecular biology, neuroscience, psychology etc.

And that successful innovation for next generation technology will emanate from this integration between research on new technology and research on new clinical practice.

Main success criteria

MI Lab has focused on the following success criteria (taken from the RCN “official” list of success criteria for Centres for Research-based Innovation):

- The centre engages in long-term industrial research of a high international calibre, and demonstrates its high quality through its production of doctorates, scientific publications, papers for presentation at recognized international conferences and other forms of scientific merit.

- Researchers from the host institution and partners participate actively in the centre's research. The centre has achieved mutual mobility of personnel between the centre and the user partners.
- The centre's user partners have increased their research activities both through participation in the centre's activities and their own R&D activities on topics of relevance to the centre.
- The centre attends to researcher training effectively, and helps to train highly skilled personnel in the centre's special fields.
- The centre's research has engendered or is expected to engender possibilities for innovation and enhanced competitiveness among user partners and expectations about social ramifications over and above the partners' direct participation in the centre's activities.

Interaction with the partners

Centres for Research-based Innovation are a new construction where several industrial partners and the university work together in an open research environment. A main goal for MI Lab is to build an arena for open innovation and long-term industrial research combining high scientific quality with good commitment from the partners.
An important tool to achieve this goal is the MI Lab consortium agreement which is tailored to facilitate innovation in an open research environment with many industrial partners.

Other main tools are:

- active involvement from the MI Lab Board in all major decisions
- regular all-day seminars for science and mingling between all the involved PhD students, post docs, researchers, professors, hospital doctors and industrial partners
- regular project meetings
- mobility of researchers

Integration with the medical imaging community in Trondheim

MI Lab wants to be an integrated part of the total ultrasound and MR research environment in Trondheim, and the MI Lab subprojects collaborate with related research activities financed from other sources. A goal is to obtain seamless collaboration, scientific discussions, idea creation and co-publication throughout this large group of PhD students, post docs, researchers, professors and hospital doctors.

Focus on researcher training.

The MI Lab board decided that most of the budget should be allocated to hiring of PhD students and post docs, and MI Lab thinks that recruitment of the best students is the main success factor to obtain the scientific goals. Furthermore, these persons obtain experience in medical R&D in the crossroad between university, industry and hospital, and will be a future pool for recruitment of high-quality personnel for Norwegian industrial R&D, health care and academia.

Overall Framework

Evaluation and advice from the Scientific Advisory Board

This overall framework was also strongly supported by the Scientific Advisory Board evaluation.
Some relevant citations from their written report:

“The reviewers were uniformly impressed with the research environment at NTNU. Medical technology researchers have built an enviable network that reaches on the one hand into strong collaborations with commercial partners, both local, national and - in the case of GE - multinational; and on the other hand into clinical care in interventional medicine, foetal maternal health, radiology, cardiology, neurology and neurosurgery. The seamless discussion of projects between scientists, engineers and clinicians we met reflected the high level of integration of basic science and engineering and clinical research that has become part of the culture of NTNU in medicine. Indeed Niño’s international reputation is founded on a strong record of success in the translation of ideas into both clinical care and commercial innovation. No amount of planning can create a culture of this quality: it has arisen out of the work of several generations of visionary researchers at NTNU, and represents the fundamental asset upon which MI Lab is designed to build. We regard this as representing excellence at an international level.

As the NTNU investigators from whom MI Lab draws expand in number, new facilities have been created for them. It was noted that in the new hospital, research is situated on the second floor of each building, effectively sandwiching researchers in the middle of clinical facilities. This is an original and somewhat courageous move, reflecting the importance placed by the institution on the retention of this unique culture.

MI Lab is governed by a board in which researchers, commercial partners and clinical collaborators are represented. The difficult issue of IP ownership appears to have been resolved by formal agreement among partners, though the success of such an arrangement may need to withstand the test of the translation of a new commercial product to be convincingly demonstrated.”

“MI Lab is composed of world-class investigators working in a uniquely collaborative environment with clinicians and industry. It is to be congratulated on its culture for multidisciplinary research and training: it is a clear leader in its field.”

“The expertise of the investigators participating in MI Lab is dominated by the extremely strong ultrasound group (~70%), with MR research occupying most of the remaining researchers. The ultrasound scientists form one of the leading research groups worldwide, with very strong expertise in cardiac imaging, Doppler, foetal-maternal imaging and technology development. They have led innovations that created and sustained Vingmed - and later GE echocardiography - as a global commercial force. Their pace of innovation never seems to slacken, as evidenced by the success of their most recent foray into miniaturized ultrasound, now marketed strongly by GE as the VScan, as well as work in new methods of blood flow imaging. The MR group is perhaps less mature as investigators but is focusing on neuroimaging and intervention with excellent progress. MI Lab is exploiting the opportunity to bring in smaller, more local companies involved in processing and

microfabrication, for example. This is clearly beneficial to both NTNU researchers and the local commercial sector."

"It is striking that the majority of the quite large budget of MI Lab is devoted to the funding of graduate education and training, with 22 PhD students and Postdoctoral fellows funded already to the combined amount of about 43 man-years of training. The MI Lab budget also supports 8 guest professors. While this is an obvious benefit to a training program that is already the strongest of its kind in Norway and beyond, it became clear that the choice to fund students and training alone was a broader strategic one for MI Lab. First, it is evident that the projects and labs that comprise MI Lab are already viable financially, so that funding research projects directly was not necessary. In addition, MI Lab has chosen to build on an existing, successful structure rather than create a new one, which would effectively create a considerable perturbation of a somewhat delicate - and very successful - existing collaborative culture between NTNU labs and the clinical and private sectors. The injection of these funds into graduate training creates a powerful stimulus for the project to produce a generation of highly trained personnel that will help sustain NTNU and its local industrial partners. The students we met, and whose publications we have read, impressed us with their high academic and intellectual level, their commitment and their maturity. We see this as a very positive aspect of the project."

3. Changes

Recommendations from the Scientific Advisory Board

The main criticism and advice from the Scientific Advisory Board were linked to what they called "Programmatic aspects".
Cited from their written report:

"It is fair to say, however, that the structure that MI Lab has arrived at, while understandable and clearly well-functioning, presents possibly the greatest challenge to its review and scientific assessment. While there are laudable aims to stimulate training, clinical and commercial translation; by definition, MI Lab does not appear to have a scientific goal, or even agenda. It seems to serve more the function of an umbrella, under which investigators bring their own projects, collaborations and funding. This is the 'bottom up' approach that professor Haraldseth described as a principle of MI Lab's governance, which is based on realistic and pragmatic considerations: the well-established research programs of the investigators, the business plans of the various partner companies, and so on. MI Lab does not call the scientific and commercial tune of these projects, but accepts them into its fold."

"A 'top-down' initiative to create a chosen new program from MI Lab resources may be precisely the impetus needed to drive new innovation. This may involve bringing in new personnel at a senior level, but this is surely possible. It could also be argued that a commercial partner cannot be relied upon to create strategic goals for a group of this size and independence: their agenda is by needs different and indeed, is likely to be shorter in term. Thus strategic thinking, in science and in long term planning, should be brought to the second-term plan. We do not see this as excluding the

existing structure; indeed, a blend of 'bottom-up' projects in an umbrella with its own intramural program opens up a new type of collaborative interaction."

"MI Lab should consider choosing an area of focus where it can be the synergistic agent for the creation of new program(s). This would be a departure from the current model, but could be in addition, rather than a replacement of the existing structure."

However, for the MR activities, in the subchapter "Conclusion MR" it was also stated that the broadness of the MR projects is strength:

"The MR projects are in accordance with the international trend, some projects are very innovative and some are very ambitious with a great clinical potential. I find the broadness of the MR projects is strength, especially because the overall focus is coherent and the projects mutually benefit from each other."

Main subproject structure in Research Plan 2011-14

MI Lab will in the allocation of resources also in 2011-2014 have a main emphasis on ultrasound with app. 70% on ultrasound activities (including image-guided surgery with ultrasound as main intra-operative modality) and app. 30% on MR activities. A main reason for this is that the majority of the industrial partners are ultrasound companies.

MI Lab will in 2011-2014, as advised by the Scientific Advisory Board, have one "area of focus where it can be the synergistic agent for the creation of new program(s)". That is in basic ultrasound technology, and with a main emphasis on integrating research on hardware, software and transducer arrays. In ultrasound there will in the coming years be some major improvements of image quality linked to new technology, and MI lab wants to be one of the world leaders in this research area. Participation in R&D on this next generation ultrasound technology will also have long-term benefit for all the MI Lab ultrasound industrial partners as well as the university and hospital research groups involved in R&D on new ultrasound methods and clinical applications. The R&D on hardware, software and transducer arrays will also to a large extent be able to tailor solutions to specific challenges and goals for each industrial partner and research group. This activity will be organized in a new subproject 1.1 called "Ultrasound image improvement" which includes R&D on transducer arrays, ultrasound electronics, software beamforming, parallel imaging (compressed sensing), minimum diffractive wave imaging, model powered acquisition and new technology for flow imaging/quantification, and will also include a transducer workshop.

MI Lab will also in 2011-2014 have five subprojects linked to clinical applications of ultrasound technology:

- Cardiac ultrasound
- Pocket-sized ultrasound
- Neurosurgery
- Cardiac and vascular surgery
- Foetal ultrasound

These subprojects are placed under the four main research tasks according to whether the activity is mainly linked to advanced imaging applications for non-expert user,

image guided minimally invasive surgery or imaging based information to support medical decision making.
Pocket-sized ultrasound is a new clinical subproject based on GE Vingmed Ultrasound's release in 2009 of the new pocket-sized ultrasound scanner, Vscan. The research group of Professor Hans Torp, both inside and outside of MI Lab (including the RCN funded project SIFU), has contributed to the product, and further R&D on clinical application and further technology refinements will be an important area for MI Lab. Also cited from the MI lab Scientific Advisory Board:
"This device [the pocket sized ultrasound scanner] *is developed with one of the industrial partners General Electric and the preliminary ambition is to see if the use of the equipment improves the diagnosis and outcome in different patient groups both for cardiac, vascular and general imaging This subject has earlier been addressed in several studies, but the success with this product has definitely been improved with the new product because of improved image quality and easy handling ….. There is here a potential for one of the major breakthrough in ultrasound health care model."*

For the MR research activities MI lab will, as advised by the Scientific Advisory Board, keep the present broadness inside the two subprojects:

- Advanced MR methods in clinical diagnosis
- MR in regenerative medicine & nanoparticles for imaging

Thus MI Lab will in 2011-2014 have the following project structure:

Research Task 1: Ultrasound technology
- 1.1 Ultrasound image improvement

Research Task 2: Advanced imaging applications for non-expert user
- 2.1 Cardiac ultrasound
- 2.2 Pocket-sized ultrasound

Research Task 3: Image guided minimally invasive surgery
- 3.1 Neurosurgery
- 3.2 Cardiac & Vascular surgery

Research Task 4: Imaging based information to support medical decision making
- 4.1 Advanced MR methods in clinical diagnosis
- 4.2 Foetal ultrasound
- 4.3 MR in regenerative medicine & nanoparticles for imaging

4. Research Plan 2011-2014 – details

1.1 Ultrasound image improvement

Aims and goals

The main aim is to perform research on several new strategies for improvements of ultrasound image quality integrating research on hardware, software and transducer arrays & electronics. Other aims are improved methods for faster image acquisition and for ultrasound based visualisation and quantification of blood flow. The research will combine basal technology R&D, preclinical testing and clinical feasibility studies.

Research activities

Planned subprojects (including continuation of on-going activity):

- *Transducer electronics*. This is enabling technology for real-time 3D ultrasound imaging, as well as pocket size ultrasound devices. The goal is to increase understanding of fundamental limitations of noise and power dissipation in the transducer readout and driver electronics and to develop new hardware technologies where the performance power dissipation ratio is improved compared to current solutions. To obtain this, a theoretical model of the noise requirements along the signal chain will be made. This model will be used to make a noise budget that will be utilized for optimizing the power dissipation and performance for a given configuration. The model will be built in a high level modelling language and supported by analytical calculations. The results from the model will be used to implement new and innovative circuit solutions based on the results of the theoretical model.
- *New beamformer strategies for real-time 3D imaging.* Beamformer hardware with improved computational capacity enables new possibilities for increased frame-rate in 3D ultralsound imaging. The object (e.g. human heart) can be sufficiently illuminated by a reduced number of transmit beams with limited diffraction to avoid loss in signal to noise ratio. Transmit focussing can be performed retrospective, by coherent processing of data from several transmit beams. In order to apply these methods for 2D matrix array transducers, part of the beamforming must be performed in the ultrasound probe, using simpler algorithms. An important part of this project is to evaluate different transducer-topologies to limit the number of channels in the digital beamformer. Evaluation will be performed by computer simulations, including non-linear wave propagation, but also in vitro and in vivo, using ultrasound scanner with the option to store echo data from single elements/ single subapertures.
- *Quantification of valvular regurgitation*. This is an ongoing project, where the regurgitant jet crossectional area is visualized and estimated by a newly developed 3D ultrasound technique. Further developments include a new scan sequence which enables simultaneous velocity measurements, which means that a full quantification can be performed in one heart beat. Experimental validation includes an in vitro pump model, simulated data sets based on CFD (computational fluid dynamics), and patient studies with MR imaging as reference method.
- *Biomechanical modeling linked with ultrasound imaging*. In the development of new image modalities, a proper method validation before clinical trials is important to 1) establish the true potential and limitations of the given modality, 2) save time, patient discomfort, and human resources, and cost by avoiding unnecessary clinical investigations. This task has previously been done using simplified computer simulations and in vitro models, providing an important but limited answer. Recent work has shown that by linking advanced biomechanical models with ultrasound imaging simulations, new and existing modalities can be tested for more realistic scenarios. Biomechanical models will specifically be (further) developed to aid in the development and validation of new potential tissue deformation and flow imaging modalities. Examples include models of mitral regurgitation and vulnerable plaque deformation.

- *Improved flow imaging and quantification.* With recent advances in ultrasound imaging technology, the image acquisition rate can be increased substantially for a broad range of clinical applications. A real-time high-frame rate imaging was developed at MI Lab based on emitting plane ultrasound waves and generating 16 image lines in parallel. This setup provides the means to increase both the frame rate and image quality in conventional Doppler modalities, and also provides opportunities for new modalities overcoming the traditional limitations in Doppler imaging, such as angle-dependencies and aliasing. Improvements of both conventional colour-Doppler imaging as well as the recently introduced Blood Flow Imaging modality will be investigated. Further, using a high rate acquisition new quantitative flow imaging modalities overcoming well-known Doppler imaging limitations (aliasing and angle-dependencies) become feasible and will be investigated
- *Transducer workshop.* A transducer workshop is established to support ongoing and new research projects on transducer stack acoustics. The workshop will be able to produce transducer arrays based on stacked piezoelectric composites. The target for the workshop is not to make full arrays for clinical use, but rather arrays with limited number of elements to support theoretical and simulation studies of ultrasound transducers. A special emphasis will be on wide band transducer using multilayer piezocomposites and mechanical cross talk in arrays.

Other potential subprojects:

- *CMUT.* This is an interesting technology for disposable, invasive probes for surgical applications in the frequency range 10 – 30 MHz. The advantage is lower production cost, and the possibility to make complex 2D array transducers with small physical dimensions, suitable for a number of invasive surgical procedures. Feasibility for this new transducer technology will be investigated in collaboration with Arne Rønnekleiv (MUSIC program, IME faculty)
- *Nonlinear wave propagation in heterogeneous soft tissue.*
  This activity will be focused on fast numerical simulations to be used for evaluation of new transducer design, and beamformer strategies for real-time 3D imaging. Experimental verifications by hydrophone measurements, as well as comparison to established computer simulation tools will be performed.

2.1 Cardiac ultrasound

Aims and goals

The main aim is to evaluate the clinical benefit of improved 3D ultrasound on some specific clinical problems including infarct size, myocardial wall strain, left ventricular endocardial visualization, left atrium size and aortic regurgitation. Cardiac MRI will provide accurate functional and morphological information, which will be used both for validation and to explore possible advantages of image fusion. Another aim is further improvement of methods for automatic and real-time view detection of cardiac ultrasound images.

Research activities

Planned subprojects (including continuation of on-going activity):

- *3D strain*. 3D echo has the potential to overcome major limitations in 2D deformation imaging. Although technological developments still are important for 3D echo to improve, we are now beginning to see clinical results. The goal in this subproject is to validate 3D strain measurements by high-quality MRI methods in a clinical relevant population of patients with regional dysfunction at rest (myocardial infarction), but ischemia induced during stress.
- *Sensitivity and specificity for regional dysfunction of 3D ultrasound compared to tissue Doppler and speckle tracking by conventional 2D echocardiography.*
- *Measurement of infarct size by 2D regional function parameters, as well as 3D ultrasound.*
- *Integration of 2D/3D echo and cardiac MRI*. New probe- and acquisition technology in ultrasound can give detailed functional measurements from anatomically specified regions in the heart, and due to the 3D nature of the datasets, fusion of this information with detailed functional and morphological information from cardiac MRI will be possible. The goal of this subproject is to study the best presentation of these combined datasets, and evaluate the possible diagnostic and prognostic benefits.
- *Ultrasound 3D heart model*
  This subproject is an extension of an existing Kalman filter-based image segmentation and tracking framework to support new modes of operation, as well as applying the framework to new and innovative applications within 3D echocardiography. The model adaption can be performed in real-time, which enables immediate feedback to the user, and optimized data acquisition. The underlying motivation is to increase the clinical value of 3D echocardiography, by making the modality easier and more productive to use, as well as extending the range of clinical applications.
- *New imaging methods in paediatric echocardiography*
  Clinical studies will continue on the use of Blood Flow Imaging (BFI), an angle-independent flow visualization supplemented to conventional colour-Doppler imaging. This includes both transthoracic imaging during the normal examination, as well as using BFI in transesophageal imaging during catheter intervention. With recent advances in ultrasound imaging technology, the image acquisition rate can be increased substantially for a broad range of clinical applications. A large potential exist for improving both the frame rate and image quality for Doppler imaging in several applications, i.e. paediatric echocardiography. Improvements of both conventional colour-Doppler imaging as well as the recently introduced Blood Flow Imaging modality will be investigated. Further, using a high rate acquisition new quantitative flow imaging modalities overcoming well-known Doppler imaging limitations (aliasing and angle-dependencies) become available which will be investigated.

Other potential subprojects:

- *3D echo and cardiac MRI in patients with non-ST elevation myocardial infarction (NSTEMI).* This study will investigate the effects of a new interleukin-6 antagonist on inflammatory markers and left ventricular function in patients with NSTEMI undergoing revascularization. The imaging sub-

study will provide important functional data, and also high-quality follow-up data well-suited for methodological studies.
- *Cardiac ultrasound in the HUNT population study.* In the HUNT3 (Health Survey of North-Trøndelag) population advanced cardiac ultrasound was performed in a subgroup of app. 1300. This unique database that will be used in several studies. A first study was to establish normal values for two dimensional deformation measurement, and a planned activity is to use the data to modify normal values according to heart rate, blood pressure and body size, as well as cardiac risk factors and fitness data. In addition, the data will serve as a source of matched control data for patient studies.

2.2 Pocket-sized ultrasound

Aims and goals
The main aim is to perform research on new applications of pocket-sized ultrasound for improved hospital workflow and validate the use of pocket-sized ultrasound among non-expert and expert users in a variety of clinical settings in general practice, nursing homes, emergency medicine and intensive care, and also including training of medical students in the use of pocket-sized ultrasound.

Research activities

Planned subprojects (including continuation of on-going activity):
- *To validate if the use of pocket sized ultrasound in general practice will improve diagnosis of heart failure among risk patient groups.* Assessment of left ventricular global contractility with echocardiography is mandatory in patients with suspected heart failure**.** The main aim is to validate if it is possible for non-experts to assess left ventricular contractility with a limited amount of training using pocket-sized ultrasound and to develop applications for automation. An important part of this subproject is further technology refinements directed at improved user-friendliness through soft-ware programs for automatic quality assessment and quantitative analysis.
- *To validate if the use of pocket sized ultrasound by non- expert and expert users will change diagnosis and treatment among patients admitted to a medical department.* Ultrasound is widely used as a diagnostic tool in a hospital setting. In a medical department, diagnosis like heart failure, pericardial effusion, hypovolemia, pleural effusion, ascites, diseases in the gall bladder/bile tract and hydronephrosis are common. Ultrasound is the key diagnostic tool in these diagnoses, and an early diagnosis is crucial for the patient's well being and for hospital logistic reasons.
- *To validate whether the use of pocket sized ultrasound during resuscitation in hospitals will help identifying reversible causes.* The prognosis following in-hospital cardiac arrest is poor. Approximately 70 % of the initial heart rhythms detected in these cases are pulse less electric activity or asystole. Not much is known about the aetiology and causes of these incidents. Some examples of potential reversible causes of circulatory failure that could be identified using ultrasound are tamponade, hypovolemia and pulmonary embolism.

Other potential subprojects:

Other subporjects are being planned, but currently we do not want to make public these research ideas at the present moment.

3.1 Neurosurgery

Aims and goals

The main aim is further improvements of image-guided neurosurgery combining advanced neuronavigation, preoperative MR image information about anatomy and function, and intra-operative ultrasound imaging during the neurosurgery.

Research activities

Planned subprojects (including continuation of on-going activity):

- *Improved intraoperative 2-D and 3-D imaging of flow in neurosurgery*. Research on new ultrasound methods for intraoperative blood flow visualization and quantification in the cerebral vascular system in general, and tailored to specific needs for arterio-venous malformations, aneurysms and in tumour resection. This includes improved 3-D angiographic flow imaging of smaller vessels, and navigated 2-D and 3-D mapping of flow velocity and direction.
- *R&D on automatic real-time brain shift (brain deformation) correction and display during the operation*, including mathematic modelling of the brain deformation, use of ultrasound angiography for co-registration with preoperative MR angiography, and development of robust algorithms for the real-time image warping.
- *Research on low grade astrocytomas with clinical evaluation of resection grades, survival and complications* with the use of intra-operative ultrasound guided surgery. Clinical series comparing results from our centre using our current technology with results reported in the literature.
- *Clinical evaluation of the benefits of ultrasound angiography for surgery of intracranial aneurysms*. Evaluation of aneurysm morphology and to what extent vessels related to the aneurysm can be identified, and if there is flow in the vessels after aneurysm clipping. Evaluation of the technology for this purpose.
- *Validation of registration of the patients head to the neuronavigation system based on preoperative MRI*. The current standard with the SonoWand® system is with fiducials and we are comparing it to registration of external anatomical landmarks. Comparison of methods.
- *Research on intra-operative ultrasound guidance in surgery of lumbar disc herniation*. A new ultrasound probe has been developed in Trondheim for trans-nasal imaging of pituitary gland, and will be used in order to visualize the nerve root, dura and the disc herniation – and to visualize if there are remnants left.
- *Research on use of ultrasound imaging for guidance of catheterisation of brain ventricles*. With the use of a probe that can visualize the ventricles through a burr hole and make a 3D ultrasound acquisition. We want to evaluate the accuracy of catheter placement with this technique. A technical project is planned to start in spring 2011. Further studies will be done if the

technique is feasible with comparing it to current standard (without image guidance).

Other potential subprojects:

- *Research on comparison between volume measurments of gliomas based on MRI and ultrasound imaging.* The measured volumes based on the different techniques are currently used as if they were similar, although this is not known. Comparing the volumes of preoperative MRI and perioperative ultrasound with accurate tools would help the surgeon in the resection of tumours with a diffuse growth pattern. The project will include research on new methods for improved tumor rim detection both with MR and ultrasound, and also study potential methods for detection of peri-tumour cancer infiltration and islets.

3.2 Cardiac and vascular surgery

Aims and goals

The main aim is to develop new technology and novel applications of existing technology in ultrasound imaging for

- Preoperative evaluation and risk assessment
- Perioperative quality evaluation
- Postoperative minimal invasive monitoring and guiding of treatment

Some of the activities also include MR Imaging methods.

Research activities

Planned subprojects (including continuation of on-going activity):

- *Development and evaluation of non-invasive echocardiography indexes that can be used during cardiac surgery to optimize stroke work and cardiac output in failing hearts.* Specifically, we evaluate echocardiography derived indexes that reflects, and can replace, ventricular elastance as a description of ventricular function in the equation defining ventriculoarterial coupling, thus making it possible to optimize stroke work without the present invasive measurements (requiring intra-arterial catheterisation). This index must detect alterations in ventriculoarterial coupling during different physiological and pathological settings, such as volume-load, alterations in vascular resistance, heart failure and inotropic stimulation. Furthermore, these measurements calls for new hardware and software that can incorporate different non-invasive hemodynamic measurements, thus making it possible to have an integrated approach to guiding the treatment of the failing circulation. In eg. the intensive care unit, the patient is monitored with numerous more or less invasive methods, such as intra-arterial and intravenous pressures, pulmonary arterial pressures and cardiac output. The use of transoesophageal echocardiography has yielded insight into the postoperative failing heart. However, to have a full overview of the patients' circulation, echocardiographic- and catheter based flow and pressures need to be integrated in a novel technology.
- *Clinical feasibility studies of new equipment for perioperative integrated anatomical and functional quality assessment of cardiac bypass grafts* based

on perioperative blood flow measurements and high-resolution visualisation of vessel lumen. This equipment also has numerous other potential applications that need to be evaluated, e.g. perioperative use of the high resolution imaging modality on the native coronary vessels to locate ideal landing zones for bypass grafts, perioperative quality assessment of the ascending aorta before cannulation for cardiopulmonary bypass etc. These applications of this novel equipment need to be investigated in a clinical setting.

- *Improved vascular imaging modalities.* Research on how recent advances in high frame rate ultrasound imaging can be used to improve non-invasive plaque characterization, vessel wall stiffness, and flow related parameters such as wall shear stress. A new method for real-time high-frame rate imaging developed at MI Lab based on plane ultrasound waves and 16x parallel receive beamforming not only provides a very high frame rate (10-16x conventional imaging), but also gives new flexibility with regards to scan sequencing. Longer ensembles of data can be acquired for improved processing of velocity and deformation measurements, and also provide angle independent flow imaging based on compounding flow images from several angles.
- *Biomechanical modelling of bypass anastomoses for improved understanding and prediction of graft failure*. Using biomechanical modelling tools it is possible to recreate the flow field in an anastomosis. This can be done with high accuracy by using geometrical shapes and measured boundary conditions extracted from experimental animal models. Having such a model available allows us to investigate the flow conditions in detail for various scenarios linked to long-term graft failure, such as for instance competitive flow from the native coronary. An aim is to explore which flow conditions and which vessel regions that are prone of endothelial dysfunction, atherosclerosis and graft failure.

Other potential subprojects:

- *Research on new materials for ultrasound probes that enable improved sterilisation* between investigations and thus practical reuse of probes for open surgery and intravascular ultrasound.
- *Research on methods for individual assessment of the functional consequences of carotid stenosis on brain perfusion*. The subproject will use MRI based methods for measuring hemodynamic response function in the brain after respiratory challenges (breath holding, hypercapnia, hyperoxia etc) with the aim to find the best procedure for patient diagnostics.

4.1 Advanced MR methods in clinical diagnosis

Aims and goals

The main aim is to perform research on the potential of using different advanced MR imaging methods to gain new knowledge about the pathophysiology and functional deficits of several important brain diseases and use this knowledge to develop and evaluate new methods for early subclinical diagnosis, monitoring of treatment and/or rehabilitation efficacy, monitoring of disease progression and prediction of outcome. Another aim is improved methodology for functional MRI including research on improved spatial and temporal resolution and the brain hemodynamic/vascular response.

Research activities

Planned subprojects (including continuation of on-going activity):

- *Clinical utility and feasibility of MRI in more precise diagnosis and prediction of outcome and potential benefit of rehabilitation in moderate to severe traumatic brain injury (TBI).* This is part of a large interdisciplinary follow-up study of a cohort of >100 moderate to severe TBI patients and 60 matched controls. On the behavioural level extensive neuropsychological, psychiatric, and motor function tests have been performed repeatedly from acute to chronic phase. The imaging research integrates several advanced methods: Diffusion Tensor Imaging, attention task fMRI, resting state fMRI, mapping of vascular response, and automatic segmentation of MRI based brain volumes & brain morphometry including use of NeuroQuant software.
- *Clinical utility and feasibility of MRI in more precise diagnosis and prediction of outcome and potential benefit of rehabilitation after premature birth.* Premature birth is connected to significant risk for neurocognitive problems and reduced academic performance. Furthermore, there is an increase in the prevalence of psychiatric symptoms. By combining extensive clinical and neuropsychological testing, MRI and EEG, we explore the effect of premature birth and factors adversely affecting the longterm consequences of it. We also assess the effect of interventions aimed at improving cognitive performance. The aims are to increase our understanding of brain-behavior interaction in preterms and thereby develop predictors that allow for improved diagnosis and optimized intervention to amend neurocognitive deficits and psychiatric symptoms.
- *Vascular response / hemodynamic response function.* The activity includes both research on changed hemodynamic response (altered neurovascular coupling) as a cause of false negatives in fMRI, and the use of the vascular response as a possible diagnostic method and/or imaging biomarker. The main patient groups are Traumatic Brain Injury, brain tumour and carotid artery stenosis.
- *MR-sequences for high-resolution fMRI.* A main aim is to develop tools for functional MRI at 3T with sufficient spatial resolution and sufficient precise anatomical localization to fully explore different memory functions in the medial temporal lobe (including hippocampus) in order to gain new knowledge about impaired memory functions and dementia, and use this knowledge to develop MR based early (subclinical) diagnosis and new imaging biomarkers for Alzheimer’s disease. The two main areas of technology research are optimization and validation of a balanced SSFP (Steady State Free Precession) sequence for fMRI and optimization and validation of different methods for correction of geometrical distortions and magnetic susceptibility artefacts both in balanced SSFP and in Single-shot Echo Planar Imaging sequences.
- *Compressed sensing in MRI and ultrasound.* The main focus is to be an additional approach to obtain functional MRI at 3T with sufficient spatial resolution and sufficient precise anatomical localization to fully explore different memory functions in the medial temporal lobe (see point above). Compressed sensing, including several potential MRI signal undersampling techniques, will be used to improve temporal resolution of the image

acquisition (which may reduce artefacts/distortions, improve spatial resolution, and increase brain volume coverage). Another aim is to use the experience and competence developed also to look at compressed sensing in ultrasound.
- *HUNT MRI of white matter disease.* In the HUNT-MRI project advanced MR Imaging has been performed on a cohort of 1005 participants in the HUNT3 (Health Survey of North-Trøndelag) population survey, and with the main inclusion criterias of age 50 - 65 years and previous participation in HUNT1 (1984-86) and HUNT2 (1995-97) population surveys allowing longitudinal study design. The MR Imaging data has been collected and genetic analysis of the same participants will be performed during 2011. One of the planned studies on these unique data from this HUNT MRI cohort is MR based mapping of white matter connectivity and microstructure (Diffusion Tensor Imaging) and lesion mapping (T2/FLAIR imaging) and obtain new knowledge about the relationship between white matter microstructure/connectivity and disease/risk factors/genetics with special focus on risk factors for cardiovascular disease and some known candidate gene SNPs for white matter disease.

4.2 Foetal ultrasound

Aims and goals

The main aim is to perform research on the potential of using ultrasound methods with improved image quality and spatial resolution to gain new knowledge about early intra-uterine development of the foetus.

Research activities

Planned subprojects (including continuation of on-going activity):
- *New high frequency trans-vaginal probe for ultrasound imaging of embryos at 5-9 weeks gestation.* The resolution has been targeted at a minimum embryo length of 4mm, and we have currently designed such a probe optimized for this purpose. The new focus on ultrasound technology in the 1.1 Ultrasound Image Improvement task (se page10 above) includes a new transducer workshop with a technician and a PhD student. They will look into transducer stack specification and optimization with focus on a close match between specified and effective element size, establish contact with a transducer manufacturer for prototype production, and perform laboratory testing (matching the probe to the scanner and tuning the imaging parameters for optimal resolution and image quality throughout the depth range), and safety approval (water tank measurements of the transducer field to ensure that the probe is following the safety regulations for transvaginal foetal imaging).
- *Initial clinical testing of the new high frequency trans-vaginal probe for ultrasound imaging of embryos at 5-9 weeks gestation*. This is a pilot study to identify which embryo anatomy we are able to resolve and at which ages.
- *Larger scale study with the new high frequency trans-vaginal probe for ultrasound imaging of embryos at 5-9 weeks gestation*. The aim is to establish

normal values for embryo anatomy at weeks 5-9 of gestation. Major anatomic structures to image will be brain, heart, spine, hands and legs.

Other potential subprojects:

- *Improved elevation characteristics of the new high frequency transvaginal probe for ultrasound imaging of embryos at 5-9 weeks gestation.* 1.25D or 1.5D arrays might be an option if the current design does not give sufficient resolution in the elevation plane. These types of arrays increase the cost of the probe with approx 40% or more, but allows for a finer resolution elevation plane. Hanafy lens is another design option to improve the resolution in the elevation plane. This type of design could be less expensive, but involves a larger risk since the technique is not as well established as 1.25D and 1.5D arrays.
- *Investigation of cardiac and circulatory development using high frame rate, high resolution Doppler imaging.*
- *Advanced acquisition and image processing techniques for improved resolution, image quality and frame rate.* E.g. retrospective transmit beamforming, coded excitation and plane wave imaging.

4.3 MR in regenerative medicine & nanoparticles for imaging

Aims and goals

One main aim is to study the potential of several new MR methods for non-invasive guidance and monitoring of cell therapy (stem cells, other relevant cell types, scaffolds etc) in regenerative medicine of the brain.
The other main aim is to perform research on multifunctional and multi-modal nanoparticles for imaging with main emphasis on improved MR sensitivity and better understanding of in-vivo bioavailability and receptor targeting in order to obtain new knowledge about which properties that affects crossing of tissue barriers and receptor binding and use this knowledge for optimal design of the nanoparticles.

Research activities

Planned subprojects (including continuation of on-going activity):

- *Multimodal MRI for image guidance of transplant-mediated repair of brain and spinal chord white matter degeneration and injury*. The main imaging methods are Manganese-Enhanced MRI (MEMRI), tracking of transplanted cells labelled with MR sensitive contrast agents and Diffusion Tensor Imaging. The transplant-mediated repair integrates stem cells, scaffolding cells (Olfactory Ensheathing Cells) and alginate scaffolds and the ability of the MR imaging for monitoring and guidance of the repair will be optimized and validated in three rat models of brain and spinal chord degeneration/injury.
- *Research on multi-modal and multi-functional nanoparticles for MR Imaging including image-guided drug delivery.* The chosen nanoparticles are “oil-in-water nanoemulsions” type with multi-modality for both MR Imaging and optical imaging (fluorescence) resepcti and with ligands binding to intravascular and tissue receptors. A window chamber model of rat tumours allow excellent co-localization between the MR and optical images, and will

be used to focus on research on some basic mechanisms: what size of the nanoparticles gives optimal MR sensitivity, the ability and the reproducibility of the nanoparticles to cross the biological barriers between the main tissue compartments, and mechanisms for binding to the receptors.

- *LUPAS project.* Participation in the EU 7^{th} FP project "*Luminescent polymers for in vivo imaging of amyloid signatures*". Novel contrast agents (based on luminescent conjugated polymers, LCPs) and methods tailored to in-vivo diagnostic imaging of amyloid plaques (the main pathophysiology in Alzheimer's disease) has been developed. The contrast agents are multi-modal for optical imaging (fluorescence) and MR Imaging to combine high sensitivity (fluorescence) with good anatomical localization (MRI).

Other potential subprojects:

- *Tumour specific therapy and improved drug and gene vector delivery by ultrasound.* Currently we do not want to make public the planned details in this research activity.