

MI Lab Scientific Advisory Board Report March 2010

The MI Lab Scientific Advisory Board consists of:

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

MI Lab Site Visit, 18 January 2010

Overview

The remit of this review was to provide informal feedback to the leadership of MI lab on:
The scientific quality and originality of MI Lab's ongoing research and future research plans;

Evaluation of the research against international trends;

Advice on changes to research plans and/or suggestions for other research activities.

It was understood that our advice and comments were to be considered as the Lab prepared for an external review by the Research Council of Norway this spring of 2010, the mid-way point in MI Lab's first round of funding of approximately €32 million over 8 years.

For the meeting, we were given an overview of the MI Lab concept; brief written descriptions of each of the 9 subprojects in four groups; during the meeting presentations were made by senior investigators, each of which we followed by a discussion. Our host and MI director, professor Haraldseth, facilitated frank and open access of the review group to the project facilities and investigators.

Summary of Reviewers' Discussions

1. Research environment

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, fetal 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 NTNU'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.

Investigators

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, fetal-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.

Training environment

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.

Programmatic Aspects

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.

But we do see some problems with this. First, it is reasonable to expect that a budget as large as €30 million would indeed be capable of having the 'clout' to shift emphasis of a scientific program, and it may be right to expect that it should. For example, it was pointed out that with an exceptional record in cardiac imaging and a strong and original MRI program, why is there no cardiac MR in the program? 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.

A final point about this programmatic structure was also discussed. If projects and funds and ideas come from outside and are mingled with MI Lab resources, how will the MI Lab leadership - or the Research Council of Norway - measure its success? What publications, patents and innovations can be said to have been bought by MI Lab's budget, and no-one else? What scientific aims the group as a whole has achieved, and how can further funding be justified from a scientific point of view? For education, the answer is clear; for scientific progress, this may be more difficult to measure.

Recommendations

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.

A major challenge appears to be the measurement of success and productivity in its setting of mixed funding and leadership.

It might be useful to create a kind of matrix of the interactions between industry, NTNU investigators, trainees and clinical groups to identify the overlapping areas that MI Lab funds.

A definition of the scientific boundaries of MI Lab may help define an area in which its progress can be assessed.

It would be helpful for MI Lab to work with its investigators to create measures of productivity and success: eg, publications, endpoints for scientific projects.

A balance needs to be struck between commercial opportunities (which might be short term and relate to money) and scientific objectives (which might be long term and relate to knowledge) in MI Lab's plan. This may help justify long term funding.

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.

The review panel thanks professor Haraldseth and MI Lab for inviting our opinions.

Technical annexes on projects

1.1 Ultrasound image improvement & flow quantification

The road map of this key and wide frame research axis aims to leverage most advanced technologies of beamforming building up new algorithms and software. Critical to diagnosis tissues and flow imaging and quantification improvements are both addressed in plans;

On the hardware side, project is taking benefit from advanced systems from Norwegian partner (GE-Vingmed is a worldwide leader in cardiology market) and others commercial systems. In addition, a massive RF signals parallel acquisition tool is planned. This constitutes one of the most advanced hardware research platform I am aware of in the world in this environment. Last but not least the support commitment of industrial partners guaranties sustaining in the state of the art level of this platform. Overall, an impressive basement for research plans!

Software activities and plans covers major opportunities for improvements identified so far at both academic and industrial level as software beamforming and massive parallel processing, taking benefit from advanced processing based pc world architectures. These software plans are covering both management of these new hardware and improved modeling of ultrasound waves propagation (linear and non linear, scattering in inhomogeneous medium...), finally merging it into innovative imaging modes (regular and synthetic beamforming).

Lastly, plans are including effort in transducer arrays, cooperating with others NTNU labs, covering design tools and prototypes built in house in piezoelectric or cMUT technologies. This plan is ambitious but I support strongly it as array and sensors physical limitations need to be perfectly understood to drive realistic imaging approaches. This area will also benefit to the industrial partners that need improved modeling tools for these device and will be a unique opportunity to train engineers and imagine new concepts.

The project looks well balanced between the 3 feet of MiLab: technical application development, design and verification utilizing realistic computer models, and a clinical feasibility validation.

Industrial benefit is clearly identified we would recommend to pursue and/or intensify cooperation on the long-term road map backbone.

1.2 Ultrasound Probe Hardware

Project is focus on evaluating solution for 4D ICE applications. Ultrasound imaging with catheters has proven usefulness over decades with 2D imaging. Now high integration technologies become available for moving toward 4D imaging, the so-called 4D ICE being dedicated to intra cardiac imaging.

Industrial 2D solutions (Acunav) showed potential of ICE approach in simplifying EP procedures workflow and increasing safety for patient.

It is believed that a true 4D solution will be a breakthrough in this area. Given the state of the art at Vingmed and the close cooperation with the project team, all conditions are present to end up with tangible progress in understanding the need and exploring feasibility, enabling industry to move forward with practical solutions.

2.1 Cardiac Ultrasound

The main foci are 3-D cardiac imaging including strain measurements in the myocardium as main subject, but also automated volume and cardiac mass calculations as subsets. One sub goal is also automatic view identification and improved segmentation algorithms. Parallel computing is improving and one ambition of the group is to take advantage of these using new graphic processing units in performing delineated surfaces.

The clinical and physiological problems are to take new technologies into the clinic concerning the questions feasibility, reproducibility and diagnostic capacity. This needs big population studies which partly could be fulfilled by the HUNT population including 1266 healthy volunteers. So far prognostic data from velocity and strain data are missing, but this population could contribute to solve this problem.

The validation of data are performed both MRI and also other techniques like SPECT. Studies that are of great public interest are the studies performed to evaluate the effect of physical training in already diseased people. Around ten PhD projects are presented with realistic plans for being presented during the next years all of them of high quality and unique for the research environment at NTNU.

2.2 Pocket sized Ultrasound

This device 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.

This very new approach today materialized by the GE-Vingmed innovation device: Vscan is now calling for investigation of potential for healthcare benefit. Project are covering main question about, from usability by non-expert medical staff to implementation of relevant imaging mode (BFI for instance) and assessment of diagnosis capabilities. One of the success indicators is if this product could be included in the general education of medical staffs.

The level of cooperation with the industrial partners is huge and MilLab configuration is ideal and unique here. We believe in expected outputs of projects, also including dedicated transducers architectures design and realization (vascular and cardiac multipurpose probe).

There is here a potential for one of the major breakthrough in ultrasound health care model.

3.1 Neurosurgery

The aim of the project is to remove as much of an intracerebral tumour process without removing non-involved functional brain tissue. The project uses MR functional imaging (BOLD imaging), MR diffusion imaging obtained preoperatively with peroperative UL, and combines the image information in the neuronavigation system. Peroperative occurring brain shift obtained with UL is converged to the preoperative obtained MR images, allowing continuous use of important MR image information during an operation. The project is very advanced combining UL and MR elegantly and showing its clinical usefulness and complimentary information provided by these modalities. It seems that computer processing time needs to be increased in order to fully take advantage of this set-up in the operation theatre.

3.2 Thoracic surgery & vascular surgery

This research part works with solutions more to use ultrasound for monitoring cardiac and vascular function. For finding optimal variables for cardiac and vascular coupling to optimize stroke work. But also to use ultrasound as an eye into the tissue for the surgeon. Including development of new transducers. The neurosurgical department at NTNU has been very successful in this concept so perhaps some of that could be applied also in cardiac and vascular surgery. This type of high specialised equipment has definitely an advantage to have the surgeons around the corner for testing but also for the engineers to take ideas from the operating room. In the future an engineer will be a part of the therapeutic and diagnostic team. We need more skills in modern health care than we have today.

Focusing on part of the project aiming to design an pericardial transducers filling a gap in the current offer application wise ergonomic and high resolution: transducer specification are challenging and well suited for an advance research including exploration of potential of cMUT new technology and benchmarking it with current ones. The project is consistent with the transducer road map already discussed in 1.1. Again the Milab configuration gathering clinical feedback and industrial partner support is unique and promising.

4.1 Advanced MR methods in clinical diagnosis

In this segment a variety of important brain diseases are investigated using advanced functional MR imaging methods, such as BOLD imaging, diffusion imaging and perfusion imaging, with the aim of improving early diagnosis, predicting clinical outcome and measuring the efficacy of treatment. Relevant hardware and software has been created as needed. The projects are near the clinics and patients are also characterised and studied with relevant clinical and para-clinical measurements. The entire set-up benefits from the well-organised integrated university hospital infrastructure. The projects are following the international trends of increasingly using MRI to study neurodegenerative diseases. A critical mass with regards to the number of researchers and MR scanners has been met, allowing the investigation of large groups of patients. This is relevant for the more epidemiological assessment of disease profiles in the population.

Still, outside the financial sphere of MI Lab, I would emphasise that the translational aspect is secured by the fact that similar animal studies can be and are performed on experimental (animal) MR scanners. One study focuses on the hemodynamic response function in BOLD imaging, which is good. Generally, a basic understanding of the physiology behind BOLD imaging and vascular reserve capacity are sparse, and I recommend continued effort in that direction. Also, the usefulness of the general linear model, often used in order to quantify BOLD results should be considered. A couple of projects are focused on the development of basic MR sequences, which I consider both valuable and important with a strong innovative potential. The reason being that basic MR research is a fundamental requirement for continued improvement of clinical MR imaging. The project related to faster imaging acquisition using the so-called 'compressed sensing' is an ambitious project and benefits from the strong tradition of physics and mathematics at the NTNU. With regard to the project related to physiological noise in BOLD imaging, I recommend considering the program RETROICOR (Glover, MRM 2000), which is able to correct movement due to respiration and heart pulsation.

4.2 Fetal Ultrasound

Focusing again on transducer development part, project is based on a dedicated transducer for fetal heart imaging. Quite challenging at transducer level, it is in line with evolution of modern front end designed for wider bandwidth, and will open new diagnosis capabilities on fetal heart. A promising longer term option improving resolution in elevation plan will certainly take benefit from built in probe housing beam forming electronics as already done in Pocket sized ultrasound project

Project 4:2

In the presentation only technical developments are presented with a new probe design for foetal monitoring. Even in this field a close cooperation between the clinic and the technical development is of big importance. No such projects are presented in the research review from MI-lab which is a shortage, because I am convinced that such cooperation exists. This is definitely something that needs to be corrected for a later evaluation.

In conclusion the scientific work is of high quality and shows an extreme good cooperation between engineers and the medical staff. Few other centres in the world have this close integration of technique and medicine, which I think is the key for MI lab.

4.3 MR in regenerative medicine & MR nanoparticles

This section consists of two ambitious and innovative projects which, if successful, would have an enormous clinical potential. Both projects are at the level of in vitro and/or in vivo animal experiments. The first project aims at using MR imaging for guidance of stem cell therapy with the aid of MR contrast agents. The other project is employing targeted nanoparticles as molecular imaging agents. Both projects are very recommendable and indispensable for future development of the MR imaging modality for becoming capable of molecular imaging. The success of these projects, when it comes to clinical feasibility, is not guaranteed because nuclear medicine methods have an inherently higher sensitivity in this area. These projects could benefit from having partners involved in radiopharmaceutical production and micro-PET systems, in order to get basic information regarding detection limits and sensitivity.

Conclusion Transducers (Gelly)

As a representative of industry in Medical Ultrasound Transducer linked to Cardiac application, I am a strong believer in MiLab structure and plans. As quite important spin off for industry are expected and given the high level of ambition of the projects, I would encourage MiLab team, industrial partners, and medical expert stakeholders to pursue effort in identifying key deliverables and associated risks (with back up solutions for instance) to facilitate “consortium” management. Also given the long-term profile of backbone road map, it seems to me important to imagine a resource plan supporting it beyond the identified projects reviewed so far.

It is also obvious that this structure will generate highly skilled and with unique training engineers for industry.

Conclusion on cardiology (Brodin)

One of the most important keys to the scientific success and high quality of the scientific work at NTNU concerning image related research are the close integration, between basic technical applied research and its connection to the clinic. The research environment with the technical development working with the testing facility situated just around the corner. This communication is also for taking clinical needs to technical solutions. These research areas are of great interest with studies both working with high

end machines for improved diagnosis but also working with small ultrasound machines for finding their usability in general health care.

Conclusion MR (Larsson)

In conclusion, the MR projects to a large extent comply with the success criteria defined by RCN. 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. Finally, I see a possible value of a more direct integration between MR and UL. Overall I am impressed and strongly recommend continued financial support.

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