



Northeastern University

CenSSIS Annual Reports

Bernard M. Gordon Center for Subsurface Sensing
and Imaging Systems (CenSSIS)

January 01, 2008

ACT-4 : A Gordon-CenSSIS MedBED Component

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Recommended Citation

Bernard M. Gordon Center for Subsurface Sensing and Imaging Systems (Gordon-CenSSIS), "ACT-4 : A Gordon-CenSSIS MedBED Component" (2008). *CenSSIS Annual Reports*. Paper 9. <http://hdl.handle.net/2047/d10015954>

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Year Eight Project Report



Project ID: MedBED-B					
Title: ACT-4: A Gordon-CenSSIS MedBED Component					
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I. Brief Overview of the Project and Significance

We design, construct, and test electrical impedance tomography (EIT) systems to screen for breast cancer. These systems apply electrical currents through electrodes on the surface of the breast and record the voltages that result on these electrodes. From this electrical data we reconstruct and display approximations to the electrical conductivity and permittivity inside the breast. These reconstructed conductivity and permittivity maps are expected to be useful for diagnosing breast cancer, since many breast tumors have different electrical conductivity and permittivity characteristics than surrounding normal tissue or other inhomogeneities. We are collaborating with Daniel Kopans' laboratory at MGH to develop an imaging system for breasts that can take mammograms and EIT images simultaneously and in register by placing EIT electrodes on the mammograph instrument plates. We also collaborate with Tom Szabo at BU to develop a fused sensor single probe to make combined EIT and ultrasound images of the breast.

This project has obtained the loan of an ultrasound instrument from Terason Inc., along with its development software package.

Our principal task is the development of a breast tumor diagnostic system. We have completed the initial testing of hardware and software for an impedance imaging system with 60 electrodes and sources that can produce 3-D images of conductivity and permittivity in real time using frequencies between 3 kHz and 1 MHz. The system has several probes to be applied to the breast, and is of a size and operational design suitable for clinical testing. It is able to apply arbitrary patterns of voltage or currents. The operator can select various combinations of image rate and measurement precision, including real-time operation to visualize cardiac-frequency events. We have developed electrode designs that include single planes of different sizes and two parallel planes, as in x-ray mammography. We are developing, implementing and testing reconstruction algorithms to form images in the planar geometries in real time, and display them. These will use data from each current pattern studied, and incorporate conductivity and permittivity displays. We have studied 72 patients using radiolucent electrodes in the mammography geometry in screening and in biopsy patients at MGH.



Figure 1. The ACT 4 instrument

II. State-of-the-Art, Technical Approach and Major Contributions

This work is at the cutting edge of the technology of breast impedance imaging. The Moscow group has produced a system with 256 electrodes, but with only one current source and a back-projection reconstruction algorithm. This system is limited by having to multiplex its single source among all electrodes. It was being prepared for marketing in the US, but this effort has ceased. It is being sold in Russia and Malaysia [3, 4]. The Israeli group has produced a breast surface impedance measuring device that it has marketed only in Europe, but the device does not have any depth sensitivity, and displays only a map of surface conductivity. It applies a fixed voltage to all electrodes simultaneously, and measures and displays current at each electrode. It is no longer being marketed, but a technically-improved version may be being tested in anticipation of being marketed in the US. A US startup firm is exploiting and expanding the original TScan technology [1]. The Dartmouth group uses a multiple-current source system, but with less accuracy and a less-accurate reconstruction algorithm than we use. They use a complex circular electrode array, rather than the planar probe used by us and the other groups mentioned [2]. Our system will operate and display data in real time. This feature, which may allow pulsatility of hypervascularized tumors to be visualized, is unique among systems reconstructing images. Several new systems are being developed in Korea, at least one of which is similar to our planar system [5]. These have not yet reported clinical results in patients, but will likely do so soon.

Our work advances the state-of-the-art by combining a robust reconstruction algorithm tailored to the electrode array it is used with, and a multi-frequency, real and reactive, multi-source imaging instrument with high precision operating in real-time. No other existing system has this ability. What follows provides further details about these technical developments.

We have developed a reconstruction algorithm that accepts voltage and current data from two parallel

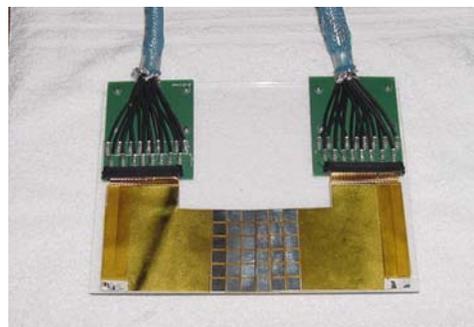


Figure 2. One of two planes of 32 radiolucent electrodes used with ACT 4. The active part of the array measures 65 mm x 65 mm.

planes of 32 electrodes each and produces images of the block of tissue between these planes. It has been tested in a breast-shaped saline tank with a 10 mm cubic copper inhomogeneity, and produced the images in Figure 3. The target was moved to four different locations in the tank, at

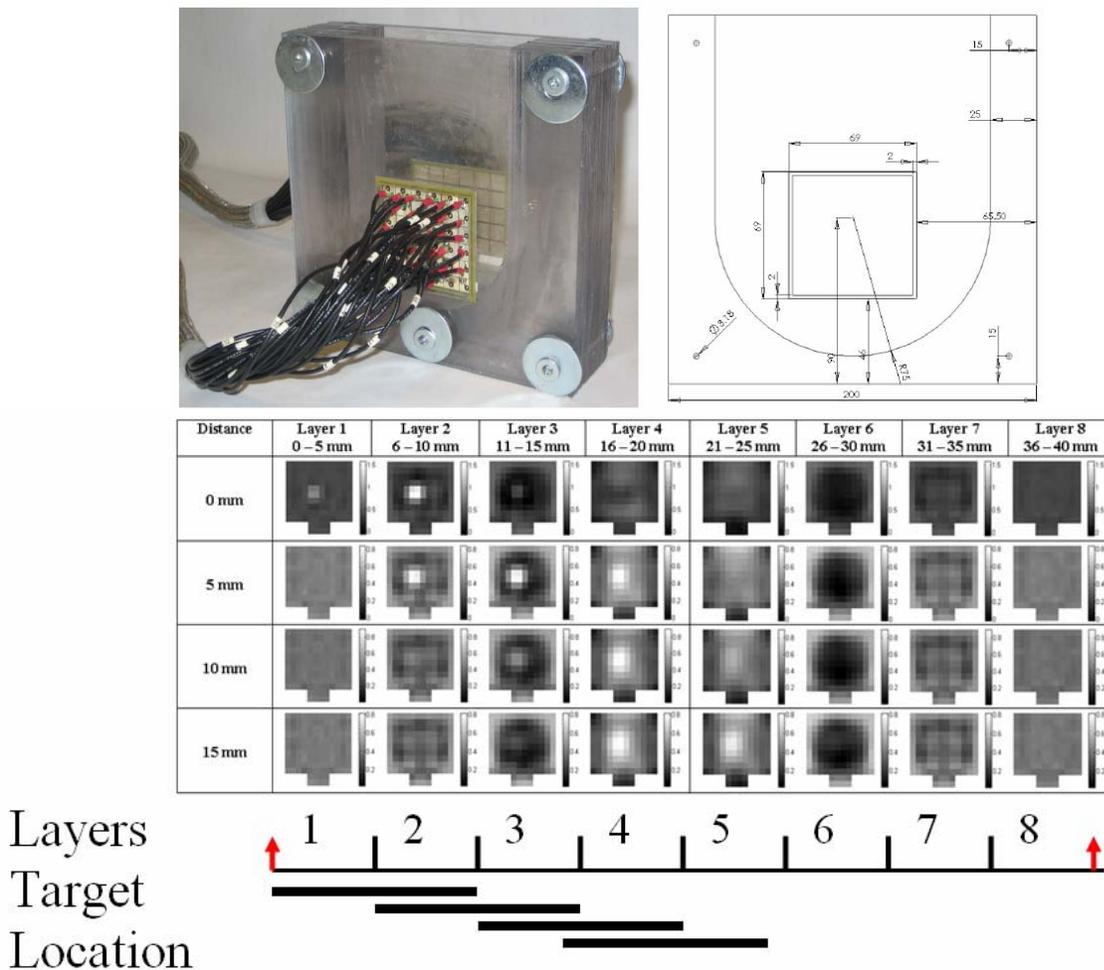


Figure 3. Upper left: A photograph of the test tank, showing two parallel planes of electrodes. Upper right: A drawing showing the tank dimensions. Bottom: Conductivity images in each of eight layers of voxels representing the interior of the tank. A conductive target was located in each of four depths, as shown in the diagram below the images, at the x-y position seen in the 0 mm (top row) image. The electrode planes are at each end of the diagram, adjacent to layers 1 and 8.

the same x-y coordinates, but different depths below an electrode plane.

The images are sharpest when the target is closest to the electrodes, but usable images are obtained from the middle of the tank as well.

This year, we have continued our study of breast cancer patients at the Massachusetts General Hospital Breast Imaging Center. We have accrued 72 patients to date, 45 of whom have biopsy results available and 27 of whom are routine screening patients. Analysis of the first 55 patients studied yielded 48 breasts with usable data. Of these, four had cancer and 44 did not. We developed an analysis scheme called the Linear Correlation Measure (LCM) as an assessment of the likelihood of malignancy. When a threshold LCM value of 700 was established, the sensitivity of the LCM for cancer was 100% and the specificity was 89%. These preliminary results have been submitted for publication, and included in our amended NIH grant application, now in review. Figure 4 shows a mammogram of a breast with invasive ductal carcinoma at the left. In the center is a black-and-white image of the regional values of the LCM parameter in

that breast. At the right, a color image of the LCM has been superimposed over the mammogram.

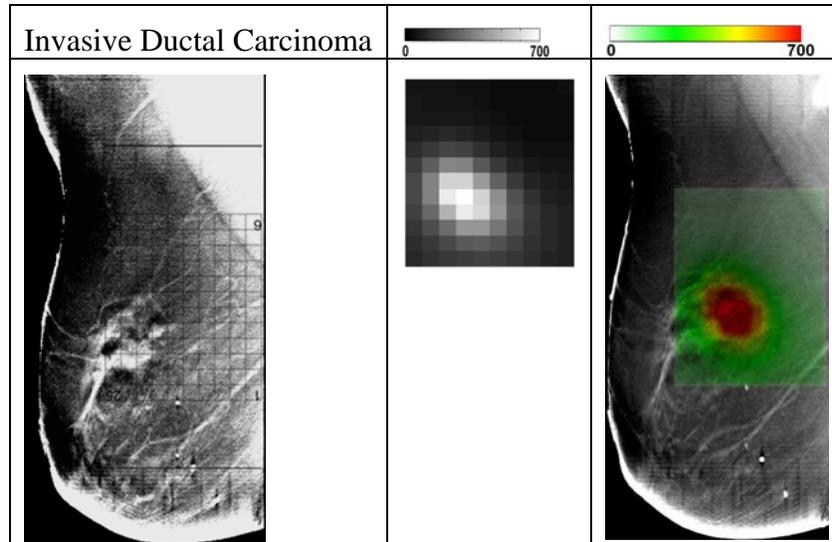


Figure 4. Tomosynthesis images, gray scale LCM images, and a color LCM image of the region of interest superimposed on the tomosynthesis images from the middle layer in a typical breast. Note that larger LCM values appear brighter in the gray scale LCM image and these regions correspond to voxels that have a more linear EIS spectrum. At the right in each case, the tomosynthesis image is reproduced, with a semi-transparent overlay of the colorized LCM image. The LCM scale for both the gray scale and color images is 0 to 700 in both cases.

A number of issues were raised and addressed during this study. The 32-electrode arrays used originally were not ideal because the extra two electrodes in the sixth row provided artifacts to the reconstruction algorithms. We deleted these electrodes, and now use two $5 \times 6 = 30$ electrode arrays. We have written a simplified operator's interface for the entire system, so as to make it operable by the MGH Tomosynthesis Technologists, rather than the investigators themselves. We also modified the electrode connection cables to make them easier to use and more immune to errors. These steps should greatly increase our future productivity, and at lesser cost. We have begun to address some subtle errors in the programs that acquire data. These errors are small, but produce some noise and increase the data acquisition time. New software is being developed that will be faster and cleaner. The principal ongoing development task is the refinement of the reconstruction algorithm to work more effectively in the presence of the skin on the breast. Our development work to date has been based on an assumption of homogeneity of the target, but our results are finding a sufficiently high resistivity at the skin that it appears that this should be explicitly accounted for in the algorithm. We are using numerical finite-element simulations, and experimental data from breasts to investigate this possibility and improve the algorithm's performance.

In summary, the start of a clinical investigation is an iterative process that involves studying a number of patients, changing the system to remedy the problems encountered, returning to the clinic, back to the lab etc. We have made about 4 cycles of this so far, and will start the fifth shortly. We will return to the clinic with a new set of cables, two new electrode arrays, and two new discrete dummy loads to test the electrode arrays, and a new operating system interface for the technologists.

III. Center Strategic Goals and Legacy

This project is a critical element of the Gordon-CenSSIS concentration on breast cancer diagnosis. The error rate for the best-available means of breast cancer detection, x-ray

mammography, is significant. This results in many unnecessary biopsies and needless patient stress. The risk of x-ray exposure in younger women is too high to warrant its routine use in screening women under 40. A risk-free electrical screening method could improve the results of mammography, and may replace mammography in younger women. The S3 project to use EIT as an adjunct to mammography, forming simultaneous, co-registered images from which to derive impedance spectra for diagnostic use, is central to this multidisciplinary effort.

Ultrasound is the next choice of breast tumor imaging modalities after mammography. It can help resolve uncertainties when suspicious regions are identified by mammography, palpation, or other means, but its capacity is limited and subject to distortion. A fused mode display of EIT information with the M-mode ultrasound image may contribute information not available by either mode alone, since ultrasound structural data will be used to provide prior information to the EIT reconstruction algorithm. Similarly, electrically suspicious regions may be identified for more complete study by ultrasound.

Although less central to the Center's mission, our research may also make another important scientific contribution toward solving the inverse problem of electrocardiography. Missed and mistaken diagnosis of cardiac disease is still a major problem despite over 100 years of development of the electrocardiogram (ECG). One approach which has seen a lot of research but only very limited clinical application is inverse electrocardiography, or cardiac electrical imaging (CEI), which has the potential to greatly increase accuracy and reliability of non-invasive diagnosis. A major impediment to wider acceptance of CEI is the need for a patient-specific map of the conductivity of the thorax as an input. An interface between EIT and CEI has the potential to overcome this barrier and make a significant contribution to the medical field. Similarly, although effectiveness of electrical defibrillators depends on their ability to produce the desired patterns of current density in the heart, placement of electrodes is done empirically or based on generic anatomical models. Patient-adaptive on-line models based on incorporation of EIT technology could provide a tremendous benefit.

IV. Future Plans

We are presently refining our reconstruction algorithms to obtain regional 3-D admittivity data. That data will then be analyzed to give regional spectra, and these results will be compared with the pathology results in the biopsy patients. We will resume clinical studies at MGH in February 2008. The data obtained will be examined for diagnostically-specific impedance spectral information. Careful correlation between the pathology reports from biopsy and the impedance spectra will be carried out. Tissue lesion size, diagnosis, location and other relevant findings will be related to complex impedance data at several frequencies.

We will also continue to refine the ACT-4 system, developing additional reconstruction algorithms and refining the user interface, based on clinical experience. The system has already been refined to some extent and is now operated by the technologists at MGH.

The major development goal is a custom mammography probe that includes EIT electrodes on its faces. This will enable the addition of electrical property information obtained simultaneously and in registration with the x-ray image. Achievement of this goal will require close collaboration with vendors of this equipment, but it is an investigation with significant commercial potential.

The principal deliverable for the first EIT study will be a clinical operating protocol for the EIT instrument, and knowledge of the electrical properties and pathology reports of the breasts

studied. Operating procedures for the use of the instrument, definitions of the circumstances when it should be applied and objective criteria to interpret its results must be produced.

With these protocols available, we will then design a multi-center large-scale clinical trial of the system. This will require construction of several more copies of the instrument. At least three different protocols will be designed. In one, a double-blinded experimental design will ask whether EIT is better than chance in detecting breast cancer. It will also ask whether EIT can improve the results of mammography. The second study will be a targeted study, examining by EIT those patients with positive mammography findings. The third study will be an intended use study, in which EIT will be used to provide adjunctive diagnostic information in patients with ambiguous mammograms.

A second major goal will be integration of EIT electrodes into an ultrasound probe, in collaboration with Tom Szabo at BU. This sensor fusion will allow EIT information obtained simultaneously and in registration with the ultrasound images to enhance the ultrasound images and add information about the electrical properties of the structures seen by ultrasound.

V. Broader Impact

Success of this project would result in a reduction in the number of unnecessary biopsies for breast cancer, and a decrease in the number of missed cancers in mammography screening. The consequences of these outcomes would be a reduction in breast cancer morbidity and mortality, and a reduction in the societal cost of breast cancer care. There will be opportunities for significant financial benefit to whatever entities can implement these goals successfully.

VI. Technology Transfer

The first commercial application will probably be a technical add-on to existing digital mammography machines and tomosynthesis machines. The intent will be to provide a useful adjunct to mammography. If that is successful, the EIT technology may be able to be developed as a stand-alone screening technique, using a hand-held probe. Such a probe might also include ultrasound imaging, and be a dual-mode rather than stand-alone system.

VII. Project Budget and Sustainability

We need to maintain our present funding level for this year. Our second NIH proposal that was pending last year was in fact funded, but only for one year, and only for 75% of the approved budget. The consequence of that is that the costs of conducting that study are likely to be greater than the amount of added funding, and our need for Gordon-CenSSIS funds remains unrelieved. We presently support a student, part of a post-doc and significant operational expenses with Gordon-CenSSIS funds.

Our amended application to NIBIB of NIH for three years of support was funded three years ago with a budget of \$924k for the three-year period, supporting both MGH and RPI efforts. We submitted a revised application to NCI of NIH for four years of support with a budget of \$1.6 million supporting both BU and RPI efforts. This proposal was not funded on first application, but a revised application was submitted on Nov. 1, 2005. This was funded for only the first year, at a reduced level of 75% of the approved amount, or \$186,000.

We have applied for two years of continued NIH support for the EIT with mammography project. This proposal was not funded in 2007, but we submitted a revised proposal in November 2007 for funding in August 2008.

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IX. Documentation

A. Technology Transfer (Project Inception to Dec. 31, 2007)

Invention Disclosures:

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B. Publications Acknowledging NSF Support (Dec. 1, 2006 to Dec. 31, 2007)

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C. Relevant RICC 2007 Posters

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