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Commentary

Electrical Impedance Mammography: the key to low-cost, portable and non-invasive breast cancer screening?

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Breast cancer is a major public health problem with 1.7 million cases diagnosed per year and is the leading cause of cancer deaths in women worldwide (Siegel, Miller & Jemal, 2016). The two main determinants of survival are early detection and optimal treatment. Despite the advances in medicine, breast cancer is detected at advanced stages in developing countries (DCs) because early detection, diagnosis and treatment cannot be efficiently promoted. Thus, disease burden is particularly high in DCs, where more than half of breast cancer cases and 62% of the deaths now occur. The "Breast Health Global Initiative" (BHGI) evaluated the complexity of healthcare systems in relation to breast cancer. Specifically, at the basic level, breast self-examination is encouraged, whereas diagnostic ultrasound and X-ray mammography are available at a limited level. At the increased level, patients have access to diagnostic mammography with opportunistic breast screening, and at a maximum level, the population undergoes organized screening for breast cancer (Anderson et al., 2006).

X-ray mammography detects breast cancer with sensitivity rates of up to 90%. This classical diagnostic method, however, yields rather unspecific results. Only one in five biopsies of suspicious lesions leads to a malignant histological diagnosis (Lee et al., 2010), which causes unnecessary distress amongst the patients and significant delays in establishing a diagnosis. Despite the unacceptably high rate of false positives, high-income countries initiated population based mammographic screening programs, but there continues to be a heated debate regarding their possible benefits as X-ray mammography is harmful due to the radiation exposure and very costly. Thus, many national cancer control programs recommend later and less frequent mammograms. In UK, for example, women who are aged 50–70 and registered with a GP are automatically invited for breast cancer screening every three years. However, the incidence of the disease in younger women is not rare. Breast cancer is the most diagnosed cancer in women between the ages of 25 and 35 and tends to be more aggressive and harder to treat (Cancer Mondial, http://ci5.iarc.fr/ci5plus/ci5plus.htm). According to World Health Organisation (WHO), if breast cancer can be detected and treated in its early stage, the mortality due to this disease can be decreased by one-third, and 400,000 lives could be saved every year globally. Current research is therefore aimed at developing alternative techniques to detect breast cancer more accurately and possibly earlier.

Electrical impedance tomography (EIT) is a non-invasive, portable, low-cost technology developed to image the distribution of electrical properties, conductivity and/or permittivity, within an object from measurements of electric currents and voltages on its surface (Borcea, 2002). Since *in vivo* studies discovered a difference of three times or more in the specific electrical conductivity between healthy and cancerous tissue (Rigaud, Morucci & Chauveau, 1996), EIT has been actively studied as a complementary imaging modality for early detection of breast cancer (Holder, 2004).

The EIT estimation problem is mathematically challenging being both nonlinear and extremely ill-posed in the Hadamard sense, thus requiring the measured data to have a high degree of precision. Substantial progress has been made in determining the class of conductivity distributions that can be recovered from the boundary data (Astala & Päivärinta, 2006; Calderón, 1980; Nachman, 1996), as well as in designing practical reconstruction algorithms applicable to noisy measurement data (Holder, 2004). Reconstruction procedures addressing the full nonlinear problem include a wide

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range of iterative methods based on formulating the inverse problem in the framework of nonlinear optimization (Gehre, Kluth, Sebu & Maass, 2014; Halter, Hartov & Paulsen, 2008; Hong et al., 2015; Pak et al., 2012; Sze, 2012; Ye et al., 2008). While these techniques are promising for obtaining accurate reconstructed conductivity values, they are often slow to converge and are quite demanding computationally particularly when addressing the three-dimensional problem. These concerns have encouraged the search for reconstruction algorithms which reduce the computational demands. Some use a priori information to reconstruct piecewise constant conductivity distributions (e.g. Harrach, 2013), while others are based on reformulating the inverse problems in terms of integral equations and/or linearization (Delbary, Hansen & Knudsen, 2012; Georgi, Hähnlein, Schilcher, Sebu & Spiesberger, 2013; Hähnlein, Schilcher, Sebu & Spiesberger, 2011; Perez, Pidcock & Sebu, 2017). This list is by no means exhaustive and new approaches are constantly being presented (Hauptmann, Santacesaria & Siltanen, 2017).

Several electrical impedance mammographic systems have been developed over the years: fixed 3D EIT systems (Halter et al., 2008; Sze, 2012; Ye et al., 2008), bedside data-acquisition systems (Georgi et al., 2013; Pak et al., 2012), and a fully portable and autonomous EIT IC system (Hong et al., 2015). The EIT device developed at Dartmouth College (Halter et al., 2008) has 64 electrodes incorporated into a mechanical framework optimized for breast imaging. The mechanical assembly uses multiple rings of electrodes that conform the breast to a specific geometry which provides information on both the location of electrodes (± 1 mm) and the shape of the breast. In contrast, the EIT system designed at Duke University (Ye et al., 2008) has a 3D applicator with 128 electrodes on a cone-shaped surface which is filled with liquid electrolyte whose electrical properties are similar to that of normal breast tissue and which encases the breast to be imaged. The principle behind the Sussex EIM Mk4 system (Sze, 2012) is very similar, the only difference being that the array of 85 electrodes is planar and is fixed at the bottom of the examination tank. The devices described in (Assenheimer et al., 2001; Georgi et al., 2013; Pak et al., 2012) are in some aspects similar in the sense that all of them use planar electrode arrays in a handheld probe geometry which is pressed against the breast during the examination (see Figure 1). Note, however, that the T-Scan technology (Assenheimer et al., 2001) does not produce tomographic reconstructions, it just maps the surface impedance using 256 electrodes. In all the aforementioned bed type and probe type systems, the electronic circuitry is contained in a big box, and a PC is used as the imaging device. The compact brassiere-shaped EIT

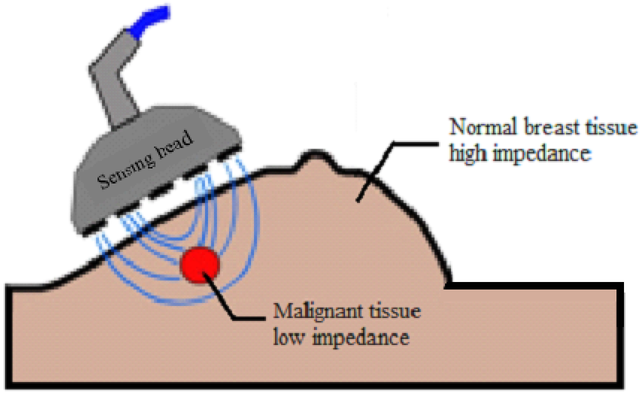

Figure 1: Data collection setup for EIM.

system introduced in (Hong et al., 2015) was designed for personal use at home without expertise. The EIT IC is integrated onto a fabric which has 90 soft electrodes fabricated using Planar-Fashionable Circuit Board technology. In addition, a portable smart device which can be connected via the USB port is used for imaging and displaying.

In spite of the tremendous development of electronic technologies, which has enabled a continuous modernisation and miniaturisation of electronic circuits (Hong et al., 2015), a higher degree of precision in the collected data (Terzopoulos, Hayatleh, Hart, Lidgey & McLeod, 2005), an extension of the operating frequency range of the EIT systems at lower power and improvements of the signal-to-noise ratios (SNRs) (Halter et al., 2008; Hong et al., 2015), Electrical Impedance Mammography (EIT) has raised only moderate interest in the medical community and has not yet made the transition from an exciting medical physics discipline into widespread routine clinical use. This is mainly due to its sensitivity to measurement errors and high computational demands, and to practical issues: errors in electrode positions or boundary shape, high and uncontrollable contact impedance of the skin (variations of 20% or more). While errors due to electrode position and boundary shape are of a technical nature, the problem of the contact impedance in medical applications is more fundamental.

Almost all previous EIT systems use the same electrodes for current injection and voltage measurement (Halter et al., 2008; Pak et al., 2012; Sze, 2012; Ye et al., 2008). The excitation current is injected (extracted) at one pair of electrodes at each time and the resulting voltage is measured at all or some of the remaining electrodes, e.g. (Halter et al., 2008; Pak et al., 2012). In this way, the problem with the high and uncontrollable skin-electrode contact impedance is avoided but at the price of aggravating the ill-posedness of the reconstruction. In other cases, the current is dispersed into the liquid before entering into the breast, which results in a low image resolution (Sze, 2012; Ye et al., 2008), or dry flexible electrodes are used (Hong et al., 2015) at the detriment of introducing errors in the electrode positions and boundary shape.

The novelty of the EIM devices designed by the author in collaboration with colleagues from University of Mainz, Germany, and Oxford Brookes University, UK, and hence of the image reconstructions proposed, consists in the distinct use of active and passive electrodes (Gehre et al., 2014; Georgi et al., 2013; Hähnlein et al., 2011; Perez et al., 2017). The active electrodes are used only for current injection while the passive electrodes only for voltage measurements, and thus there are no issues related to the contact impedance. The device has a fixed geometry and the positions of the electrodes are exactly known. Recently, this collaborative research group has made significant technical advances in EIM technology which could potentially bring breakthroughs to clinical acceptance. More precisely, the latest research project of the group funded by the Higher Education Innovation Fund HEIF5 (UK) was devoted to the design, construction and testing of a near-to-market electrical impedance mammographic sensor (see Figure 2) and to the development of computationally efficient image reconstruction algorithms which could be used to detect the size and the location of breast tumours in real-time. The numerical reconstructions obtained using data from *in vitro* experiments had very good spatial resolutions, and the algorithms were robust with respect to errors in the data (see Figure 3). The researchers are now establishing the experimental protocols for preliminary clinical trials. The next challenge though will be to embed the EIM system into a bra for home use whose results will be sent regularly via internet to a medical practitioner.

Figure 2: Sensing head of the EIM device developed at the University of Mainz in collaboration with the University of Malta and Oxford Brookes University.

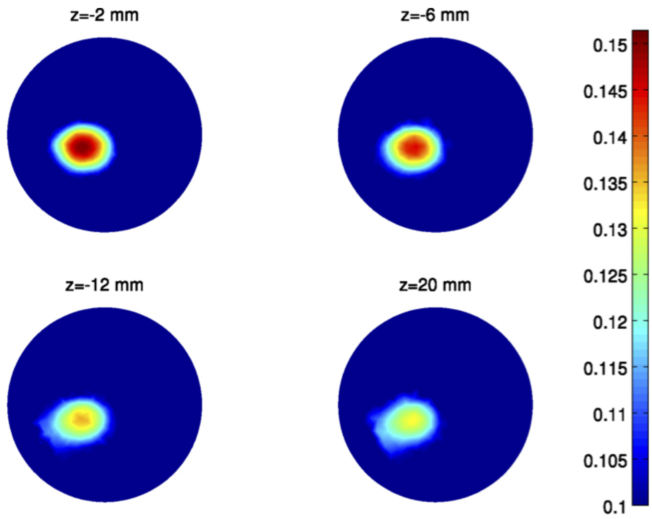

Figure 3: Cross-sections of 3D numerical reconstructions obtained from in vitro experimental data.

To summarize, the state of art of EIM research is still healthy and considerable efforts are continuously invested into the clinical trials and pilot studies to achieve widespread clinical acceptance. The advantages of EIM over traditional X-ray mammography - portability, low cost, little or zero patient discomfort, no known patient risk and no known side effects – will make this technology a welcome addition to the tools available in the fight against breast cancer. It will reduce the number of invasive X-ray and MRI mammograms, although of course, it will not fully replace them. Moreover, since the investigation could be performed by every medical practitioner without special training, EIM could be the key to mass breast cancer screening especially in the countries with underdeveloped medical facilities where it could even be used for provisional biopsy examinations.

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