A multimodal system for the diagnosis of breast cancer: the SOLUS project

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Breast cancer is the most common cancer in Europe; it is estimated that about one in eight women in Europe will develop breast cancer before the age of 85 [1, 2]. Early diagnosis of breast cancer maximizes the chances of survival so the availability of diagnostic tools with a high sensitivity for early cancer detection and with high specificity to minimize false positive results is vital.

The International Agency for Research on Cancer has confirmed the effectiveness of mammographic screening in reducing breast cancer mortality [3]. However, screening programs also result in the detection of a significant number of false positive cases [4], which lead to unnecessary additional imaging and invasive procedures such as fine needle aspirations or biopsies. On average about 50% of positive breast screening outcomes turn out to be false positives meaning that further invasive examination could have been avoided. These not only have a negative impact on patients' quality of life but also are a high economic burden on healthcare systems. There is thus a clear need for an affordable and highly specific point-of-care system to substantially improve in-depth diagnosis of breast lesions detected by ammography.

Several imaging modalities are currently being used or evaluated or as an adjunct to mammography.

This article summarizes the rationale behind the Solus project whose aims are the development of a multimodal breast imaging system involving diffuse optics, ultrasound and shear wave elastography.

ULTRASOUND

Ultrasonography (US) is the first choice technique to assess both non-palpable lesions visible at mammography and also palpable lesions, as well as to guide breast biopsy. For routine clinical applications, grey scale B-mode US is generally used. Morphologic features identified on US can be categorized to enable distinction between malignant and benign lesions. Thus, ellipsoid shapes, thin capsules and gentle lobulations are typically characteristic of benign lesions whereas spiculation, taller-than-wide orientation, angular margins and microcalcifications are generally associated with malignant lesions.

The Breast Imaging Reporting and Data System (BI-RADS) with US [5] provides standardized terminology to describe and assess masses found in breast tissue, as well as recommendations for further follow-up. BI-RADS category 3 are considered probable benign lesions, with a very low rate of malignancy (<2%). However BI-RADS category 4 covers a wide range of lesions whose malignancy status is less predictable.

Thus currently, the diagnostic results of conventional B-mode US are frequently unsatisfactory.

Improved characterization of lesions might allow better BI-RADS categorization which could lead to more non-invasive follow-ups rather than biopsies.

SHEAR WAVE ELASTOGRAPHY

Recently, the more advanced US technique known as shear wave elastography (SWE) has been introduced and provides a quantitative and reproducible measurement of tissue stiffness. This can reflect the increased deposition of extracellular matrix in neoplastic tissue and serve as a marker of malignancy.

A recent meta-analysis has evaluated the performance of SWE for the diagnosis of breast cancer [6]. The specificity of conventional US alone was 55%, but the addition of SWE to conventional US increased the specificity to 80%, while maintaining sensitivity essentially unaltered at 95%. However, even further improvement in specificity is desirable to achieve a significant reduction in the false positive rate and so generate a real impact on both patients and healthcare systems.

DIFFUSE OPTICAL IMAGING

Optical methods can give insight into tissue physiology and alterations, thus providing information complementary to US. Diffuse optics can probe tissue to a depth of a few centimetres, which makes it an appealing potential candidate for the non-invasive diagnosis of breast cancer, either as

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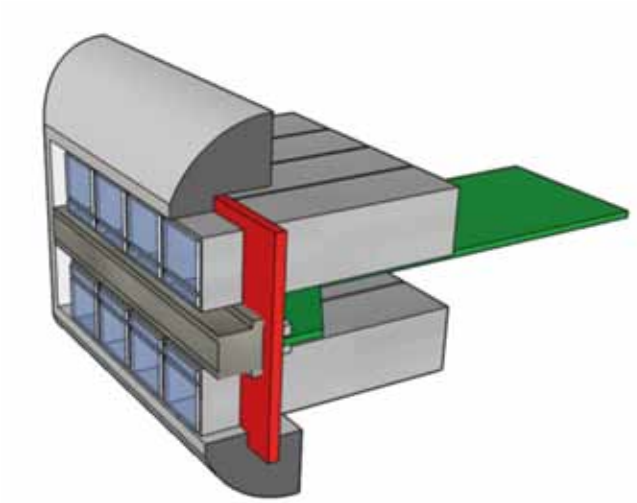

At the heart of the system is a multimodal probe capable of carrying out diffuse optical tomography, by means of a newly designed small device known as a smart optode, as well as US and SWE measurements

a stand-alone modality or in combination with other imaging modalities.

With diffuse optics, it is possible to measure the light absorption and scattering properties of breast tissue. Tissue composition and functional blood parameters, such as hemoglobin and oxygen saturation, as well as water and lipid content, are derived from the knowledge of the absorption properties at multiple wavelengths, while scattering provides information on tissue structure. Cancerous breast tissue is typically characterized by high hemoglobin and water content, while lipid content is correspondingly low. High light scattering has also often been detected in malignant lesions [7, 8]. Cancerous breast tissue is typically characterized by high hemoglobin and water content, while lipid content is correspondingly low. High light scattering has also often been detected in malignant lesions [7, 8].

These observations have a solid basis in tumor biology, as they all correlate with tissue changes associated with tumor development, such as neoangiogenesis, alterations of stromal components and increased extracellular matrix deposition among others.

Collagen — the structural element of the extracellular matrix which provides tissue with its mechanical strength and elasticity — can also be measured using diffuse optics. Alterations in stromal architecture and composition are well-known aspects of pathological breast conditions and a causal link between stromal collagen and tumor formation and progression has been established [9]. Thus, information on the collagen content in breast tissue could provide useful information for breast lesion classification.

A pioneering research team in the Politecnico di Milano, Italy, has been investigating the non-invasive optical characterization of biological tissues for more than two decades [12, 13] and has recently obtained encouraging preliminary clinical data, showing that collagen may be even more crucial than hemoglobin in the differentiation between malignant and benign breast lesions [10, 11]. Up till now collagen, as quantified by optical means has never been exploited in clinical practice for breast diagnostics.

Diffuse optics operating in the so-called time-domain, i.e. with short light pulses of the order of picoseconds, allow complete optical characterization of tissue in a single measurement.

However diffuse optical imaging has a well-known limitation, namely its limited spatial resolution, which is inherently due to the highly diffusive nature of biological tissues. To better exploit the information from diffuse optics, and to overcome its limited spatial resolution, morphologic data obtained from other imaging modalities, such as mammography, MRI, PET or US, have been used to provide prior information in diffuse optical tomography reconstruction procedures, or fused with optical images to provide anatomical landmarks [14].

Contrary to mammography or PET, US does not involve the use of ionizing radiation and does not have many of the disadvantages of these modalities (complexity, cost, long examination times, use of contrast agents, limited patient acceptance). This makes US an ideal method from which to derive anatomical information and to complement diffuse optics.

THE SOLUS PROJECT

The SOLUS project aims to develop an innovative, multimodal tomographic system, combining diffuse optics, US and SWE, to support the *in vivo* diagnosis of breast cancer. Specifically, our multimodal system hopes to improve the classification of breast lesions after a positive result on mammographic screening, and specifically at improving the discrimination of lesions that are borderline between benign and malignant (BI-RADS 3 vs. 4a) and which presently result in screening studies having high false positive rates.

Combining diffuse optics with US can be achieved via the development of a portable, cost-effective, non-invasive, point-of-care diagnostic tool.

We aim to attain the project's overall objectives by exploiting innovative photonics concepts and developing new components. By employing time-domain diffuse optics with a small source-detector distance, and a high dynamic range time-gated approach, the SOLUS system should achieve unprecedented sensitivity, spatial resolution, and depth penetration, thereby providing effective, diagnostic information on tissue composition and functional blood parameters to complement the anatomical information and characteristics of tissue stiffness provided by conventional US and SWE, respectively.

To reach our general goal, we are developing an innovative photonic module, called a smart optode to perform diffuse optical tomography to a depth of a few centimeters. The smart optode includes a novel laser driver and a newly developed fast-gated detector and acquisition electronics. The smart optode itself will be small in size (about 1x1x4 cm) and will be combined with a US transducer into a multimodal probe capable of carrying out diffuse optical tomography, as well as US and SWE measurements.

This multimodal probe is at the heart of the SOLUS system for high-specificity, multi-parametric breast imaging and diagnosis of breast cancer.

From the point of view of the patient and clinical user, the breast examination procedure will be very similar to current standard US practices. This should facilitate acceptance by the patient

and the clinician. A more comprehensive characterization of breast tissue, a higher diagnostic specificity, and a reduction in the number of further invasive examinations are expected.

After assessment of the sensitivity and spatial resolution of the system in laboratory trials, we plan to validate the SOLUS system in real clinical settings. A pilot clinical study on patients with benign and malignant breast lesions (20 each) has been designed to demonstrate the overall feasibility of the proposed approach, the practical usability of the multi-modal instrument, and at the same time to provide insights into the real diagnostic advantages that can be achieved.

The Solus system will be incorporated into a commercially available ultrasound system (the Aixplorer system from Supersonic Imagine).

IMPACT OF SOLUS

The SOLUS system should achieve substantially improved breast cancer diagnosis and reduction in unnecessary biopsies. The improvement in the characterisation of breast lesions also leads to higher specificity in non-invasive breast cancer diagnosis. Women receiving a negative report after their examination will be spared unnecessary additional examinations.

The system will also allow more effective treatment and therapy management. New and improved therapy response prediction and monitoring enable personalized decision-making, therapy planning and optimization for each patient. This also contributes to a significant decrease in the total cost of breast cancer diagnosis.

FIRST RESULTS AND ACHIEVEMENTS

The project members are currently designing and developing the components for the system. Ultimately, these will be incorporated into an existing, commercially available ultrasound system (the Aixplorer system from the French company SuperSonic Imagine).

In the first 18 months of the project, we've already developed a fast, compact laser driver and a new time-gated single-photon detector for the diffuse optics. These will be integrated into the smart optode, for which the overall design has been completed.

We're also working on the integration of the optode into the multimodal probe. The practical ergonomics of the probe are very important, so special attention is being paid to feedback from our collaborating clinicians on this aspect.

Highly automated image processing and reconstruction algorithms are being developed, whereby anatomical information from US will be used as priors for the reconstruction of the diffuse optics measurements.

We've also recently designed multimodal phantoms for optical tomography and ultrasound, necessary to assess the performance of the smart optode, multimodal probe and the overall system.

The protocol for the clinical pilot study has also been designed.

FACTS AND FIGURES

SOLUS is a four-year project that started in November 2016, and so will conclude in October 2020. The project is coordinated by Prof. Paola Taroni from the Politecnico di Milano, Italy. The consortium brings together physicists, engineers, clinicians and four industry partners to develop the SOLUS system for improved breast cancer diagnosis.

The consortium consists of nine partners from five European countries:

- Politecnico di Milano, Milan, Italy
- CEA-Leti, Grenoble, France
- SuperSonic Imagine, Aix-en-Provence, France
- Vermon, Tours, France
- University College London, London, UK
- Micro Photon Devices, Bolzano, Italy
- Ospedale San Raffaele, Milan, Italy
- European Institute for Biomedical Imaging Research, Vienna, Austria
- iC-Haus, Bodenheim, Germany

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REFERENCES

1. International Agency for Research on Cancer, "Global Cancer Observatory," 2018. [Online]. Available: http://gco.iarc.fr.

2. Curado M, Edwards B, Shin H, Storm H, Ferlay J, Heanue M & Boyle P. Cancer Incidence in Five Continents, Vol. IX. IARC Press, Lyon, 2007.

3. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F & Straif K. Breast Cancer Screening — Viewpoint of the IARC Working Group,. New England Journal of Medicine. 2015; 372: 2353

4. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012; 380: 1778

5. Mendelson E, Baum J, Berg W, Merritt C & Rubin E, Breast imaging, Reporting and Data System, BI-RADS: ultrasound. in American College of Radiology, Reston, VA, US, 2003.

6. Liu B, Zheng Y, Huang G, Lin M, Shan Q, Lu Y, Tian W, & Xie X. Breast Lesions: Quantitative Diagnosis Using Ultrasound Shear Wave Elastography—A Systematic Review and Meta-Analysis. Ultrasound in Medicine and Biology, 2016 ; 42: 835

7. Durduran T, Choe R, Baker W & Yodh A. Diffuse optics for tissue monitoring and tomography,. Reports on Progress in Physics. 2010; 73: 1

8. Leff D, Warren O, Enfield L, Gibson A, Athanasiou T, Patten D, Hebden J, Yang G & Darzi A. A diffuse optical imaging of the healthy and diseases breast: a systematic review. Breast Cancer Research and Treatment, 2008; 108: 9.

9. Luparello C. Aspects of Collagen Changes in Breast Cancer J of Carcinogenesis & Mutagenesis, p. S13, 2013.

10. Quarto G, Spinelli L, Pifferi A, Torricelli A, Cubeddu R, Abbate F, Balestreri N, Menna S, Cassano E & Taroni P. Estimate of tissue composition in malignant and benign breast lesions by time-domain optical mammography, Biomedical Optics Express, 2014; 5: 3684.

11. Taroni P, Pifferi A, Salvagnini E, Spinelli L, Teoricelli A & Cubeddu R. Seven-wavelength time-resolved optical mammography extending beyond 1000 nm for breast collagen quantification. Optics Express, 2009; 17: 15932

12. Dalla Mora A, Contini D, Arridge S, Martelli F, Tosi A, Boso G, Farina A, Durduran T, Martinenghi E, Torricelli A & Pifferi A. Towards next-generation time-domain diffuse optics for extreme depth penetration and sensitivity. Biomedical Optics Express, 2015; 6: 1749.

13. Konugolu Venkata Sekar S, Beh JS, Farina A, Dalla Mora A, Pifferi A & Taroni P. Broadband diffuse optical characterization of elastin for biomedical applications. Biophys Chem. 2017; 229: 130

14. Pearlman PC, Adams A, Elias SG, Mali WP, Viergever MA, Pluim JP. Mono- and multimodal registration of optical breast images. J Biomed Opt. 2012; 17: 080901