HealthManagement.org
The Journal
LEADERSHIP • CROSS-COLLABORATION • WINNING PRACTICES

VOLUME 19 • ISSUE 1 • 2019 • € 22
ISSN = 1377-7629

UnBLOCK the Chain

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

SOLUS is developing a multimodal breast imaging system involving diffuse optics and ultrasound.

The SOLUS project develops a novel multimodal system that significantly improves the characterisation of breast lesions.

Paola Taroni
Project Coordinator
SOLUS
Professor
Department of Physics,
Politecnico di Milano (POLIMI)
Milano, Italy

paola.taroni@polimi.it

Peter Gordebeke
Project Manager
SOLUS
Project Manager
European Institute for
Biomedical Imaging Research
Vienna, Austria

pgordebeke@eibir.org

@EIBIR_biomed

Alberto Dalla Mora
Associate Professor
Department of Physics,
Politecnico di Milano (POLIMI)
Milano, Italy

Alberto Tosi
Assistant Professor
Department of Electronics,
Politecnico di Milano
Milano, Italy

Breast cancer is one of the most common cancers in the world. It is estimated that about one in eight women in Europe will develop breast cancer before the age of 85 (International Agency for Research on Cancer 2018; Curado et al. 2007). The chances for survival increase substantially upon early diagnosis of breast cancer, so the availability of diagnostic tools with a high sensitivity and specificity is vital.

The International Agency for Research on Cancer has confirmed the effectiveness of mammographic screening in reducing breast cancer mortality (Lauby-Secretan et al. 2015). Unfortunately, such screening programmes return a significant number of false positive cases (Lancet 2012). These require further examination, such as additional imaging or invasive procedures such as biopsies. Approximately 50% of positive breast screening outcomes turn out to be false positives, meaning that a large number of additional examinations could have been avoided.

These additional examinations not only have a negative impact on the patient's quality of life, they also represent a high economic burden. Thus, there is a clear need for an affordable point-of-care system with a high specificity to improve the in-depth characterisation of breast lesions.

This article summarises the rationale behind the SOLUS project whose aims are the development of a multimodal breast imaging system involving diffuse optics and ultrasound.

Ultrasound

Ultrasonography (US) is the first-choice technique to assess the morphology of breast lesions and guide breast biopsies. Based on the morphological features of a lesion, a distinction between malignant and benign lesions is possible using the Breast Imaging Reporting and Data System (BI-RADS) (Mendelson et al. 2003). BI-RADS provides standardised terminology to describe and assess breast lesions, as well as recommendations for further follow-up.

> "THE SOLUS PROJECT IS DEVELOPING AN INNOVATIVE, MULTIMODAL TOMOGRAPHIC SYSTEM, COMBINING DIFFUSE OPTICS, US AND SWE, TO SUPPORT THE IN VIVO DIAGNOSIS OF BREAST CANCER"

BI-RADS category 3 are considered benign lesions, with a very low rate of malignancy. However, BI-RADS category 4 covers a wide range of lesions whose malignancy status is less predictable.

The diagnostic results of conventional US are frequently unsatisfactory. Improved characterisation of lesions might allow better BI-RADS categorisation and decrease invasive follow-ups.

Shear wave elastography

Recently, shear wave elastography (SWE) has been introduced as an advanced US technique. SWE provides a quantitative and reproducible measurement of tissue stiffness. Tissue stiffness can serve as a marker of malignancy, as malignant tissue generally contains more extracellular matrix, increasing its rigidity. A recent meta-analysis has evaluated the performance of SWE for the diagnosis of breast cancer (Liu et al. 2016). The specificity of conventional US was 55%. The combination of SWE and conventional US resulted in a specificity of 80%.

This is a promising increase, but further improvement in specificity is desirable to achieve a significant reduction in the false-positive rate.

Diffuse optical imaging

Optical imaging is an appealing candidate as a method complementary to US. Optical imaging methods can give insight into tissue composition, which US is unable to do.

With diffuse optics, a form of optical imaging, it is possible to measure the light absorption and scattering properties of tissue. The absorption and scattering properties of light at different wavelengths provides information about tissue structure, composition and functional blood parameters, such as haemoglobin concentration, oxygen saturation, and water and lipid content. Diffuse optical imaging can probe tissue to a depth of a few centimetres, which makes it suited for the non-invasive diagnosis of breast cancer.

Cancerous breast tissue is typically characterised by high haemoglobin and water content, while lipid content is correspondingly low. High scattering has also often been detected in malignant lesions (Durduran et al. 2010; Leff et al. 2008). These observations all correlate with known changes associated with tumour development, such as neoangiogenesis, alterations of stromal components and increased extracellular matrix deposition.

Collagen can also be measured using diffuse optics. Alterations in the composition of the extracellular matrix are well-known aspects of pathological breast conditions and a causal link between collagen and tumour formation and progression has been established (Luparello 2013). Thus, information on the collagen content in breast tissue could provide useful information for breast lesion classification.

Pioneering research on the optical characterisation of tissue by the Politecnico di Milano, Italy, has recently shown encouraging preliminary results that collagen may be even more crucial than haemoglobin concentration in the differentiation between malignant and benign breast lesions (Quarto et al. 2014; Taroni et al. 2009; Dalla et al. 2015; Konugolu et al. 2012).

With diffuse optical imaging using multiple extremely short light pulses at different wavelengths, a complete optical characterisation of tissue is possible in a single measurement. However, its spatial resolution is a well-established limitation. To better exploit the information from diffuse optical imaging, 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 so-called prior information for the diffuse optical tomography reconstruction, or for combined imaging to provide anatomical landmarks.

Contrary to conventional x-ray mammography or PET, US does not involve the use of ionising radiation and does not have many of the disadvantages of these modalities (complexity, high cost, size of equipment, 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 is developing an innovative, multimodal tomographic system, combining diffuse optics, US and SWE, to support the *in vivo* diagnosis of breast cancer. Our multimodal system will improve the classification of breast lesions, more specifically the discrimination of lesions that are borderline between benign and malignant (BI-RADS 3 vs. 4a). These presently have 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.

The SOLUS project is exploiting innovative photonics concepts for the development of new components. By employing diffuse optics with a small source-detector distance and a time-gated approach, the SOLUS system will 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.

We are developing an innovative photonics module, called a smart optode to perform the diffuse optical tomography. The smart optode

Antonio Pifferi
Professor
Department of Physics,
Politecnico di Milano (POLIMI)
Milano, Italy

Jean-Marc Dinten
Head of CEA-LETI
Grenoble, France

Mathieu Perriollat
Optical systems project manager
CEA-LETI
Grenoble, France

David Savery
Research Engineer
SuperSonic Imagine
Aix-en-Provence, France

Hélène Sportouche
Clinical Product Specialist
SuperSonic Imagine
Aix-en-Provence, France

Bogdan Rosinski
Research Engineer
VERMON
Tours, France

Simon Arridge
Professor
Centre for Medical Image Computing, University College London
London, UK

Andrea Giudice
CTO
Micro Photon Devices
Bolzano, Italy

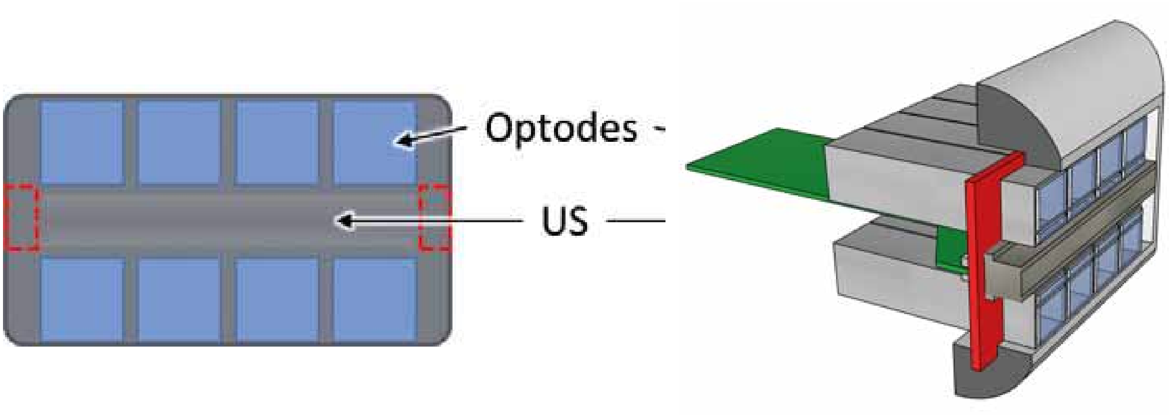
Simone Tisa
Research Engineer
Micro Photon Devices
Bolzano, Italy

Elena Venturini
Radiologist
San Raffaele Hospital
Milano, Italy

Pietro Panizza
Head of the Breast Imaging Unit
San Raffaele University Hospital
Milano, Italy

Pamela Zolda
European Research Manager
European Institute for Biomedical Imaging Research
Vienna, Austria

Ing. Alexander Flocke
Sales / Application specialist
iC-Haus GmbH
Bodenheim, Germany



Left: front of the multimodal probe with the eight optodes in two banks of four, with the ultrasound transducer in the middle. Right: mockup of the multimodal probe.

includes a novel laser driver and newly developed detector and acquisition electronics. The smart optode itself will be small in size (measuring about 1 cm^2 at the front). Multiple smart optodes will be combined with a conventional US transducer into a multimodal probe capable of carrying out diffuse optical tomography as well as US and SWE measurements all at once.

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

The examination procedure will be very similar to current standard US practices. This facilitates acceptance by both patients and clinicians.

A more comprehensive characterisation of breast tissue, a higher diagnostic specificity, and reduction in the number of invasive follow-up examinations are expected.

After assessment of the specificity, 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.

Impact of SOLUS

The SOLUS system will achieve substantially improved breast cancer diagnosis, leading to a reduction in unnecessary biopsies and decreasing the economic burden on our healthcare systems. The system will also allow more effective treatment and therapy management. New and improved therapy response prediction and monitoring enable personalised decision-making, therapy planning and optimisation for each patient. This also contributes to a significant decrease in the total cost of breast cancer diagnosis.

> “SOLUS WILL SUBSTANTIALLY IMPROVE BREAST CANCER DIAGNOSIS, LEADING TO REDUCTION IN UNNECESSARY BIOPSIES & DECREASING THE ECONOMIC BURDEN ON HEALTHCARE SYSTEMS”

Conclusion, first results and achievements

The project partners are currently finishing the development of the components for the system.

The overall design of the smart optode has already been completed. Subcomponents of the smart optode, such as the compact laser driver and the time-gated single-photon detector, have been developed and are currently in the final stages of testing prior to their integration.

Furthermore, phantoms and protocols for performance assessment have been completed.

Work on the integration of the multimodal probe is currently ongoing. 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 and tested with promising early results. These use anatomical information from US for the reconstruction of the diffuse optics measurements. Additional software for the operation of the entire system is also under development.

Ultimately, the multimodal probe will be incorporated into an existing, commercially available ultrasound system from project partner SuperSonic Imagine.

Facts, figures and acknowledgement

The SOLUS project is coordinated by Prof. Paola Taroni from the Politecnico di Milano, Italy. It started in November 2016 and will conclude in October 2020. The consortium brings together physicists, engineers, clinicians and 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

SOLUS has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 731877. The SOLUS project is an initiative of the Photonics Public Private Partnership. ■

KEY POINTS

- ✓ A high number of breast lesions, detected by screening programmes, are false-positives.
- ✓ Better discrimination between benign and malignant breast lesions is necessary to reduce the number of unnecessary procedures and the economic burden.
- ✓ Optical imaging methods provide an excellent addition to conventional ultrasound imaging.
- ✓ The SOLUS project is developing an innovative, multimodal tomographic system, combining diffuse optics and ultrasound to support the in vivo diagnosis of breast cancer.

REFERENCES

Curado M, Edwards B, Shin H, Storm H, Ferlay J, Heanue M, Boyle P (2007) Cancer Incidence in Five Continents. IARC Press, Lyon Vol. 9

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

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

International Agency for Research on Cancer. "Global Cancer Observatory" (2018) Available from gco.iarc.fr.

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

Konugolu Venkata Sekar S, Beh JS, Farina A, Dalla Mora A, Pifferi A, Taroni P (2017) Broadband diffuse optical characterization of elastin for biomedical applications. Biophys Chem 229: 130 14.

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

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

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

Luparello C (2013) Aspects of Collagen Changes in Breast Cancer J of Carcinogenesis & Mutagenesis S13.

Mendelson E, Baum J, Berg W, Merritt C, Rubin E (2003) Breast imaging, Reporting and Data System, BI-RADS: ultrasound. American College of Radiology.

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

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

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