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SOLUS: An innovative multimodal imaging system to improve breast cancer diagnosis through diffuse optics and ultrasounds

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ABSTRACT

To improve non-invasively the specificity in the diagnosis of breast cancer after a positive screening mammography or doubt/suspicious ultrasound examination, the SOLUS project developed a multimodal imaging system that combines: B-mode ultrasound (US) scans (to assess morphology), Color Doppler (to visualize vascularization), shear-wave elastography (to measure stiffness), and time domain multi-wavelength diffuse optical tomography (to estimate tissue composition in terms of oxy- and deoxy-hemoglobin, lipid, water, and collagen concentrations). The multimodal probe arranges 8 innovative photonic modules (optodes) around the US transducer, providing capability for optical tomographic reconstruction. For more accurate estimate of lesion composition, US-assessed morphological priors can be used to guide the optical reconstructions. Each optode comprises: i) 8 picosecond pulsed laser diodes with different wavelengths, covering a wide spectral range (635-1064 nm) for good probing of the different tissue constituents; ii) a large-area (variable, up to 8.6 mm^2) fast-gated digital Silicon Photomultiplier; iii) the acquisition electronics to record the distribution of time-of-flight of the re-emitted photons. The optode is the basic element of the optical part of the system, but is also a stand-alone, ultra-compact (about 4 cm^3) device for time domain multi-wavelength diffuse optics, with potential application in various fields.

Keywords: breast cancer, diffuse optics, multimodal imaging, optical mammography, diffuse optical tomography, shear wave elastography, ultrasound.

1. INTRODUCTION

Breast cancer is the most common female cancer. Early diagnosis through mammographic screening plays an important role to increase the patients' chances of survival and improve their quality of life. However, X-ray mammography suffers from low specificity, with false positive detections leading to further imaging and frequently even to unneeded biopsies. Ultrasound (US) imaging and Magnetic Resonance Imaging (MRI) are considered as complementary diagnostic

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techniques, but a clinical need exists for diagnostics tools characterized by non-invasiveness, cost-effectiveness, high specificity and sensitivity to reduce the patient's discomfort following false positive screening results, and to make breast cancer diagnosis more sustainable for the health care systems.

2. THE SOLUS PROJECT

In the above framework, the SOLUS project ("Smart OpticaL and UltraSound diagnostics of breast cancer) [1], supported within the EU Horizon 2020 Framework Programme, aims at developing an innovative multimodal breast imaging system to improve the non-invasive discrimination between lesions that are borderline between benign and malignant ones.

The SOLUS system combines different non-invasive techniques: B-mode US, Color Doppler (CD), Shear Wave Elastography (SWE), and time domain diffuse optical tomography (TD-DOT). Up to now, none of them have proven specific enough to be adopted as a stand-alone technique. Still, they all proved useful for breast cancer diagnosis, and each provides specific information on tissue. B-mode US imaging identifies morphologic features that are already routinely exploited in clinical diagnosis.[2] CD visualizes tissue vascularization.[3] SWE evaluates tissue stiffness that showed to be higher in malignant lesions than in surrounding healthy tissue.[4] TD-DOT is performed at multiple wavelengths in the range 635-1064 nm to estimate tissue composition (i.e. oxy- and deoxy-hemoglobin, lipid, water, and collagen concentrations) in the lesion as compared to the surrounding breast tissue.[5] Thus, the combination of the different techniques aims at yielding a more specific diagnosis than achievable when each of them is operated individually.

B-mode US imaging, CD, SWE and TD-DOT are combined in a novel multimodal probe, developed arranging 8 innovative photonic modules (smart optodes) around the US transducer (Fig.1). This configuration allows the acquisition of light diffusely reflected along different paths for optical tomographic imaging of the same tissue volume as imaged by US.

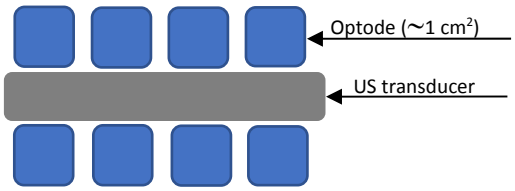

Fig. 1: Arrangement of optodes and US transducer in the multimodal probe.

2. THE "SMART OPTODE"

The smart optodes are basic elements of the probe. They were designed and fabricated specifically for the project to achieve high performances in diffuse optical measurements, still fitting in a very small footprint (~1 cm^2) and length (~4 cm), so to allow a multi-modal hand-held probe to be developed. At the same time, a single optode can also operate as an ultra-compact stand-alone device to perform TD diffuse optical measurements at 8 wavelengths, with a wide range of potential applications, also independent of medical imaging.

Each optode comprises:

- 8 picosecond pulsed laser diodes emitting at different wavelengths;
- a large-area fast-gated digital Silicon Photomultiplier (gated-SiPM);
- the acquisition electronics to record the distribution of time-of-flight (DTOF) of the re-emitted photons.

The wavelengths of the 8 light sources were selected to cover a wide spectral range (635-1064 nm) for good probing of the different tissue constituents. The integrated laser driver was designed to provide illumination picosecond pulses with negligible exponential tail or secondary peaks. With pulse duration <240 ps FWHM, average output powers of 1.5-6 mW (depending on wavelength) are obtained at 80 MHz repetition rate.

The time-gated digital SiPM detector [6] developed for the SOLUS optodes has 4.9 x 4.7 mm^2 collection area, and its active area can be controlled up to a value of 8.6 mm^2. The Photon Detection Efficiency (PDE) is 35% (peak value, not including the fill-factor of 37%) at 430 nm and decreases progressively down to ≈3% around 800 nm. The measured risetime (20% to 80%) of the gate window opening depends on the active area, but is about 500 ps even for large (≥ 3 mm^2) active areas. The temporal response depends on the active area, going from 235 ps (FWHM) for a single active pixel to about 500 ps for an active area of around 4 mm^2.

The temporal fast-gating capability of the detector (available up to a frequency of 80 MHz) enables performing measurements with increased dynamic range and allows managing different source-detector separations (from few millimeters to few centimeters), with collected signal spanning over several orders of magnitude. Indeed, time slicing of the DTOF curve is feasible by means of fast-gating, where each portion of the curve can be acquired at the same count-rate, thus increasing the number of collected late photons significantly and the dynamic range by one to two decades, depending on the wavelength as compared to free running detectors. [7]

The integrated Time to Digital Converter (TDC) features a 128-channel histogram builder with average channel width (i.e. least significant bit) of 78 ps and full scale range of ≈10 ns. The dead time is <100 ns and histograms can be transferred at a rate up to 30 kHz with no additional dead-time.

The single optode was characterized following shared protocols for diffuse optics instruments (BIP, nEUROPt, and MEDPHOT), [8, 9, 10] to assess its basic performances (*e.g.*, light harvesting, instrument response function (IRF) shape and temporal stability, etc.), as well as its capability to detect an optical perturbation buried in depth and recover its optical properties. [11] Due to the large detector area, the light harvesting is at least one order of magnitude larger than for state-of-the-art systems, with responsivity $>10^6$ m^2sr at 600 nm already for an active area of about 2 mm^2.

The performances in terms of recovery of the absorption properties is in line with state-of-the-art systems, while worse performance was obtained on the retrieval of the scattering properties. Specifically, absorption μ_a and scattering μ_s' were varied over the range of interest for tissue measurements (absorption μ_a = 0.06-0.4 cm^{-1} and reduced scattering μ_s' = 4-17 cm^{-1}). The relative error (%) on the retrieved μ_a showed a median discrepancy of 10%, while for the scattering it reached 40%. Furthermore, the retrieved scattering suffers from marked coupling with the absorption value. Work is on-going to improve the estimate of the scattering properties.

For the use of the optodes in the SOLUS probe, the sensitivity to deep absorption perturbations and the estimate of their value are of special interest, as they determine the capacity to retrieve lesion composition. Following the nEUROPt protocol, a totally absorbing perturbation (black PVC cylinder) with 100 mm^3 volume (featuring an absorbing perturbation $\Delta\mu_a$ = 0.16 cm^{-1} over a 1 cm^3 volume) was embedded at varying depth in an otherwise homogeneous medium (μ_a = 0.1 cm^{-1} and μ_s' = 10 cm^{-1}). Longer gate delays reach higher contrast for deeper position of the perturbation, as the later photons are re-emitted the higher is the probability they travelled deep in the medium. The longest delay, allows one to discriminate the presence of the perturbation down to 35 mm with a contrast of 2%, when source and detectors belong to separate optodes, placed at the distance of ~2 cm. Measurements with source and detector within the same optode (source-detector distance of few mm) show lower penetration depth (~2 cm), likely due to a background floor ("memory effect"), which is proportional to the number of early photons impinging on the detector when it is off. [12]

3. THE MULTIMODAL PROBE AND THE FULL SYSTEM

To assemble a multimodal system, suitable for use by medical staff in a clinical environment, multi-wavelength TD-DOT capability was added to the Aixplorer® MACH 30, a high-end commercial instrument for US imaging and SWE by SuperSonic Imagine S.A., as shown in Fig. 2, so that clinical examinations can be performed using the system in sequence with a regular probe for US imaging and with the multimodal SOLUS probe.

Water-cooling is embedded in the probe to control internal and surface temperature, thus ensuring safe and reliable operation. The probe also hosts skin contact sensors (to prevent operation when the probe is not is good contact with skin) and a 3D probe position sensor.

Preliminary phased-array scans of a standard US phantom (ATS model 549) were performed and confirmed that the multimodal probe arrangement does not affect negatively the US imaging capability. The full performance assessment of the multimodal probe and integrated system has just started.

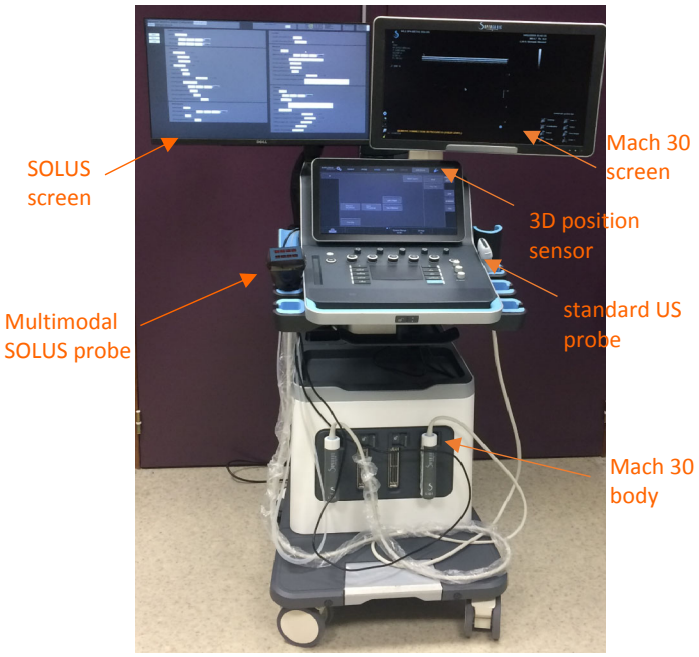

Fig. 2: Picture of the multimodal SOLUS system.

Concerning data analysis for optical imaging, after manual segmentation performed on US images, a routine extracts a 3D prior, which can be used to guide diffuse optical reconstructions, together with the enforcement of a spectral constrain. Several strategies were investigated and tested on simulations and phantom measurements. The adoption of a pure analytical model based on the Born approximation requires the availability of a reference measurement (taken, *e.g.*, from the contra-lateral breast or from a region nearby the lesion). Alternatively, a FEM-based non-linear fitting would not require any reference measurement, but it would be more computationally intensive and time consuming. Both approaches will be challenged for the analysis of clinical data. In particular, the first one will provide a quick initial feedback for the operator, leaving further refinement at a post-processing stage.

In conclusion, an innovative multimodal imaging system was developed as the major goal of the SOLUS project and will be challenged in the next months in a clinical validation involving patients with malignant and benign breast lesions. The single optode, designed as a key element of the SOLUS probe, also represents an innovative, very compact and cost-effective stand-alone device to perform time domain multi-wavelength diffuse optical spectroscopy, of potential interest in various fields, from the development of wearable devices for monitoring of sports training to on-the-field non-destructive assessment of the internal fruit quality.

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