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In vivo validation of time domain optical mammograph with high-sensitivity detection chain

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Summary. — Optical mammography is an application of diffuse optics that combines the advantages of cost-effectiveness, non-invasiveness, no significant dependence on breast density and capability to derive information about breast composition. Literature reports promising preliminary results when employed for breast cancer risk assessment, lesion characterisation, therapy monitoring and prediction of therapy outcome. In view of a clinical trial on the monitoring of neoadjuvant chemotherapy, we upgraded our time domain multi-wavelength optical mammograph exploiting new technology based on silicon photomultipliers and high throughput time-to-digital conversion. The setup is presented, together with the validation of its performances via laboratory and *in vivo* tests.

1. – Introduction

Breast cancer is the most diffused neoplasia among women, representing the 30% of female cancers [1]. Breast imaging is the first approach to identify a lesion. Currently, the main breast imaging techniques are X-ray mammography, ultrasounds, magnetic resonance imaging and positron emission tomography. They all have relevant advantages, but none is optimal. Optical mammography is an emerging imaging method that contributes to the unceasing clinical efforts aiming at improving breast diagnostics [2].

Optical mammography is relatively cost-effective, devoid of side effects, efficient on dense breast and, most importantly, it is sensitive to the breast tissue composition. This means that it is able to identify and quantify the concentrations of the main breast tissue constituents: oxy- and deoxy-haemoglobin, lipid, water and collagen. These components correlate with the tissue pathophysiology. Thanks to these peculiarities, optical mammography is suitable for different possible applications: breast density assessment, discrimination of benign and malignant lesions, therapy monitoring and prediction of therapy outcome [3].

The physics behind optical mammography is diffuse optics, which investigates photon migration in highly diffusive tissues. Diffuse optics can have different implementations [3]. For example, in time domain, under transmittance geometry, picosecond laser pulses at selected wavelengths are injected into the tissue and the output pulses —broadened by

tissue scattering (μ_s) and modulated by absorption (μ_a)— are collected on the opposite surface. The Distribution of photon Time Of Flight (DTOF) is then experimentally acquired using a Time-Correlated Single-Photon Counting (TCSPC) technique [4]. Exploiting the spectral dependency of absorption, information about the tissue composition is retrieved, while scattering is related to tissue micro-structure.

In this paper, we present our time domain multi-wavelength optical mammograph, exploiting recent advances on Silicon PhotoMultipliers (SiPMs) as detectors and high throughput Time-to-Digital Conversion (TDC) for TCSPC. The setup is described, together with the validation of its performances through laboratory and *in vivo* tests.

2. – Material and methods

2˙1. *Instrument architecture.* – The optical mammograph developed at Politecnico di Milano operates in time domain, under transmittance geometry and emits at 7 different wavelengths in the red and infrared spectral range (600–1100 nm). Light is sent to the compressed breast through an optical fibre, the breast is raster-scanned and the re-emitted photons are then collected by 8 SiPMs, axially aligned to the source. Then, the signal is addressed to an 8-channel TDC. The initial instrument setup employed a model from Surface Concept (SC-TDC 1000/08 S). Finally, data are transferred to the PC and from the distribution of transmittance curves at different wavelengths, it is possible to reconstruct the 2D maps of the breast constituents' concentrations and scattering parameters [5].

SiPMs and the TDC are the novel technologies composing the detection chain [5]. SiPMs are an alternative to the more widespread photomultiplier tubes and avalanche photodiodes. They are compact, cheap, robust and efficient over a wide spectral range (350–1100 nm). On the other hand, TDCs are an alternative to traditional TCSPC boards. They can accept multiple input channels and tolerate very high throughput (tens of Mcps). However, they could suffer from a far from optimal differential non-linearity, which refers to the non-uniformity of the channels width in the TCSPC histogram.

2˙2. *Data analysis.* – The parameters of interest are the breast constituents' concentrations (haemoglobin [μM], lipid, water and collagen [mg/cm^3]) and the scattering parameters (a [cm^{-1}] and b [adimensional]). a is related to the density of the scattering centres, while b to their size. Breast constituents' concentrations and scattering parameters are related to the absorption and scattering coefficient respectively through the Lambert-Beer law (eq. (1a)) and a Mie empirical model (eq. (1b)) [2, 3]:

$$\mu_a(\lambda) = \sum_i \epsilon_i(\lambda) C_i, \tag{1a}$$

$$\mu_s'(\lambda) = a \left(\frac{\lambda}{\lambda_0} \right)^{-b}, \tag{1b}$$

where λ is the wavelength, ϵ_i the extinction coefficient, C_i the concentration of the i-th constituent, λ_0 a reference value.

2˙3. *Procedure for instrument validation.* – We planned to employ our optical mammograph in a clinical trial on neoadjuvant chemotherapy monitoring and prediction of therapy outcome [6]. An accurate validation process should be articulated in multiple

steps, each one testing the instrument in a more complex setting. We decided to proceed applying three stages.

1. *Performance assessment protocols:* the BIP [7] and MEDPHOT [8] protocols investigate the key features of photon migration instruments. They comprehend many tests, but we briefly focus only on Differential Non-Linearity (DNL), that we mentioned in sect. **2**˙1, and reproducibility. DNL is calculated as the ratio between the peak-to-peak photon counts variation and the counts average over time bins, in a measurement with a battery-powered source. Reproducibility consists in measuring the optical properties of the same phantom (*i.e.*, a reference model, with specific μ_a and μ_s) on different days.

2. *Scan of breast-shaped phantom:* together with the curvilinear profile, a breast-shaped phantom reproduces the reduction in thickness on the borders of a compressed breast. The goal is to scan only and wholly the breast area, maintaining an optimal synchronisation between the probe movement and the acquisition.

3. *Preliminary in vivo measurements:* we organised a test involving three healthy women. Each volunteer participated in three sessions within a week. Each session was made of four measurements: Cranio-Caudal (CC) Right (R) and Left (L), Oblique (OB) right and left. The main goal of the study was to assess the reproducibility of measurements on a real breast, which is evaluated in terms of Coefficient of Variability (CV). The CV is the ratio between the standard deviation and the mean value of a parameter over the three sessions.

The described procedure is applied recursively, meaning that in case of issues outlined at a given phase, hardware modifications are implemented, then the new instrumental setup undergoes again the whole validation process, starting at stage 1.

3. – Results

The validation process was applied to the experimental setup described in sect. **2**˙1. However, while stage 1 and 2 returned positive outcomes, *in vivo* measurements were not as reproducible as desired. Moreover, sometimes the TDC throughput was insufficient to scan the whole breast area. Therefore, a hardware modification was implemented: the Surface Concept TDC was replaced with an innovative device from PicoQuant (MultiHarp 150 8N), conceived for high-throughput (180 Mcps) operations. Then, the validation process was applied again to the upgraded instrument.

3˙1. *Performance assessment protocols.* – A jigshaw DNL pattern denotes an irregularity in the time channel widths, which can be corrected applying a compensation algorithm, as occurs for the initial setup (DNL reduces from 88% to 4%). On the contrary, the new DNL for the upgraded instrument is below 1% even without corrections.

As regard reproducibility, the variation of the phantom's optical properties with respect to the mean value stays within a 3% band for both absorption and scattering in the case of the initial setup and becomes lower than 1% with the new one.

3˙2. *Scan of breast-shaped phantom.* – The scan of the breast-shaped phantom was flowing and accurate with both versions of the optical mammograph, thanks to the synchronization between the probe movement and acquisition.

TABLE I. – *Reproducibility results for subject #1, CC R view.*

	Session 1		Session 2		Session 3		CV	
	V1	V2	V1	V2	V1	V2	V1	V2
a [cm^{-1}]	13	11	14	12	13	11	2%	2%
b	1.1	0.9	0.8	0.8	1.1	1.0	16%	10%
Collagen [mg/cm^3]	50	58	78	57	33	53	42%	5%
Water [mg/cm^3]	251	198	259	181	220	180	8%	6%
Lipid [mg/cm^3]	627	674	648	671	647	697	2%	2%
Haemoglobin [μM]	8.9	7.9	9.0	8.1	10.2	7.2	10%	6%

3˙3. *Preliminary in vivo measurements*. – Stage 3 was the most decisive one, since, as stated in sect. **3**, its initial unsatisfactory results due to incomplete breast scans, in some cases caused by the limited throughput of the electronics, forced us to develop the new instrument setup. Following upgrade, we repeated the test on the very same volunteers using the new setup, always obtaining a complete breast scan.

Table I illustrates the reproducibility on *in vivo* measurements. It compares the values of the breast constituents concentrations and scattering parameters obtained for subject #1 using the initial setup (Version 1, V1) and the new one (Version 2, V2).

For subject #1 we can see that the CVs retrieved with the new setup (V2) are in general significantly lower than the V1 counterparts, especially as regard collagen, that moves from 42% down to 5%. Moreover, we can notice that variations are higher *in vivo* than on phantoms (sect. **3**˙1), which was expected due to the breast intrinsic heterogeneity and its variability over time. Together with the inter-subject variability, these are the reasons why a careful thorough validation process is important. Similar considerations are observed also for subjects #2 and #3.

Overall, these preliminary results met our expectations and the instrument was declared ready to be engaged in a clinical study.

4. – Conclusion

In conclusion, we discussed our optical mammograph's validation process. *In vivo* measurements highlighted the need for a significant setup upgrade, that finally allowed to begin the clinical trial. We confirmed that a systematic laboratory characterisation is important, but preliminary *in vivo* measurements on volunteers remain unavoidable.

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