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High-throughput multi-wavelength time-resolved optical mammograph: Importance of *in vivo* performance assessment

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ABSTRACT

The use of technologies still under development for the upgrade of our multi-wavelength time-resolved optical mammograph, such as silicon photomultipliers and a Time-to-Digital Converter (TDC), highlighted the crucial need for a thorough and progressive instrument characterization: from extensive laboratory tests on phantoms to *in vivo* measurements. Despite satisfying results on phantoms, *in vivo* tests urged a significant instrumental change to obtain high-quality breast scans. The setup was upgraded with the adoption of a just-released high-throughput TDC and now grants much wider scan area, better day-by-day reproducibility, and improved signal quality. These results point out the importance of *in vivo* performance assessment as a general approach for instrument characterization, not limited only to our optical mammograph. After the successful outcomes of the preliminary tests, a clinical study on neoadjuvant chemotherapy monitoring is now ongoing at the San Raffaele Hospital, Milan.

Keywords: optical mammography, *in vivo* measurements, performance assessment, instrument validation, Time-to-Digital Converter, diffuse optics

1. INTRODUCTION

Neoadjuvant chemotherapy is a more and more widespread treatment to manage breast cancer [1]. It consists in the administration of systemic therapy prior to surgery to downstage the tumor size. Among others, its main advantage is the facilitation of a breast-conserving surgery. The possibility to assess the treatment efficacy underway, thus allowing its early interruption or modification if unsuccessful, would certainly be of great value. The response to neoadjuvant chemotherapy is mainly evaluated by means of breast imaging measurements. X-ray mammography and ultrasounds proved not sensitive enough to quantify changes in tumor size, while magnetic resonance imaging and positron emission tomography are not recommended for frequent application, though providing useful information regarding the tumor metabolism. Nevertheless, recurring imaging sessions, intended to portray both tumor morphology and physiology, are needed to follow the disease progression.

In this respect, optical mammography has been researched as an alternative breast imaging technique for neoadjuvant chemotherapy monitoring, being able to retrieve information about tumor composition and dimensions non-invasively by diffuse optics [2].

The optical mammograph developed at Politecnico di Milano was recently upgraded with in mind its potential use for neoadjuvant chemotherapy monitoring [3]. The major purpose was to improve the signal level especially in the infrared region (up to 1060 nm) to put emphasis on collagen, that is characterized by significant absorption above 1000 nm and is considered a representative tissue constituent for breast cancer. Further aim was to provide robustness to stray light, for improved compatibility with a clinical environment. Efforts were made to implement the upgrade employing emerging technologies, that are currently attracting attention thanks to their relevant technical potential and versatility: Silicon PhotoMultipliers (SiPM) as detectors, and a Time-to-Digital Converter (TDC) for time domain data acquisition through Time-Correlated Single-Photon Counting (TCSPC) [4].

The use of technologies still under development further highlights the already crucial need for a gradual and thorough process for the instrument validation. The standardization of the performance assessment in laboratory settings has already

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been exhaustively optimized via the BIP [5], MEDPHOT [6] and NEUROPT [7] protocols. These procedures contribute to the accomplishment of the Technology Readiness Level (TRL) 4: "Technology validated in lab" [8]. In this paper, we want to put emphasis on the leap from TRL4 to TRL5: "Technology validated in relevant environment". In our case, we prepared the instrument for a clinical trial on neoadjuvant chemotherapy monitoring at the San Raffaele Hospital in Milan. We believe that systematic *in vivo* measurements prior to a clinical trial are essential to verify whether the instrument guarantees the required robustness and reproducibility to adapt to the heterogeneity of the human body (female breasts, in our specific case), simulating the conditions of a clinical environment. We also believe that this approach could be potentially of general interest.

2. METHODOLOGY

2.1 Experimental architecture

At the beginning of the validation process, our time-resolved optical mammograph worked in transmittance geometry at 7 different wavelengths (635, 680, 785, 905, 933, 975 and 1060 nm, 10 MHz, 1-5 mW), which were delivered to the compressed breast through a single optical fibre. During the raster scan, the re-emitted photons were harvested by an 8-SiPM detection probe (S13360-1350PE, Hamamatsu Photonics, Japan). Then, the transmitted signal was addressed to a multi-channel TDC from Surface Concept (SC-TDC-1000/08 S, Surface Concept, Germany [9]), after proper amplification and conversion to Low Voltage Transistor-Transistor Logic (LVTTL) [3].

2.2 Performance assessment procedure

We structured the validation process of the optical mammograph in three steps [10]:

1. characterization of the setup through standard performance assessment protocols (BIP and MEDPHOT);
2. test of the optical mammograph's capability to fully scan a breast-shaped phantom;
3. validation of the optical mammograph through preliminary *in vivo* measurements on healthy volunteers.

The BIP [5] and MEDPHOT [6] protocols comprise many different tests, that require to carry out point measurements on a set of homogeneous phantoms of well-known optical properties. Among the available tests, Differential Non-Linearity test (DNL) and reproducibility are two meaningful assays that help us to underline the evolution of our instrument in light of the validation results. DNL measures the irregularity of the TCSPC histogram channels, while reproducibility refers to the variation with respect to the mean value of the measured optical properties of a specific phantom over time.

While the BIP and MEDPHOT phantom kits drive attention to the optical properties, the breast-shaped phantom shifts focus on the compressed breast geometry. In fact, it serves to verify whether the probe efficiently raster scans the breast without exceeding its border, to save measurement time and avoid potential damage of the detector caused by direct illumination.

Finally, the measurements on three healthy women are the core of the validation process. They have been subject to four measurements (cranio-caudal right and left, oblique right and left views) on three different days within a week. The goal was to assess the quality, the robustness and the reproducibility of a scan. Robustness (here intended both as endurance to stray light and adaptability to different breast sizes and compositions) is evaluated by comparing the extension of the scanned area with the effective breast area. Reproducibility is measured by computing the Coefficient of Variability (CV, over the three sessions) of the average breast constituent concentrations (hemoglobin, water, lipids, collagen) and scattering parameters (*a* and *b*).

2.3 Data analysis

The distribution of transmittance curves at different wavelengths collected during a raster scan results in a set of bidimensional maps, one for each of the parameters of interest mentioned above. The conversion from output light pulses to breast constituent concentrations or scattering parameters is achieved by applying a spectrally constrained data fit approach [11]. In particular, Eq. 1 and Eq. 2, derived from Lambert-Beer and Mie theory respectively, are directly replaced in the diffusion equation. μ_a is the absorption coefficient, μ_s' is the reduced scattering coefficient, λ is the wavelength, ϵ_i is the extinction coefficient, C_i is the *i*-th constituent concentration, λ_0 is a reference wavelength.

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

$$\mu_s'(\lambda) = a\left(\frac{\lambda}{\lambda_0}\right)^{-b} \tag{2}$$

Once the bidimensional maps have been obtained for each parameter, their mean values are retrieved over a reference area that encloses the pixels associated with a distribution of time of flights with a barycenter greater than the median one.

3. RESULTS

Step 1) has been successfully performed with the setup described in Section 2.1. In fact, after the application of proper compensation algorithms, DNL was lower than 4% and reproducibility for μ_a and μ_s' lower than 3%.

In laboratory, measurements on breast-shaped phantoms (step 2) also returned satisfying outcomes. The probe movement well adapted to the curvilinear profile of the phantom and the TDC maximum throughput was able to process the signal even on its borders.

However, after preliminary *in vivo* tests on healthy volunteers (step 3), it became clear that the TDC maximum throughput (namely 40 Mcps) was not high enough to efficiently scan all kinds oTf breasts. In fact, scans sometimes recorded only portions of the breast, without including its periphery (Figure 1, top). That made the instrument inadequate to sustain a clinical trial properly. Although laboratory tests had successful outcomes, *in vivo* measurements brought out limitations that could not show up otherwise. Therefore, only those preliminary *in vivo* measurements allowed us to modify the setup to better fit the requirements of a clinical setting.

In fact, the replacement of the TDC with another model, become available recently on the market and optimized for high-throughput applications (the 8-channel MultiHarp 150 8N, PicoQuant, Germany [12]), has been resolutive [10]. The validation process has then been repeated from step 1. The direct effect has been a great increase of the maximum throughput (180 Mcps), that allowed robust and complete *in vivo* scans (Figure 1, bottom). Further positive effects were the simplification of the setup (*i.e.* the removal of the LVTTL stage), a marked reduction of the DNL and, most importantly, a significant improvement in reproducibility for measurements performed on the same subject over different days.

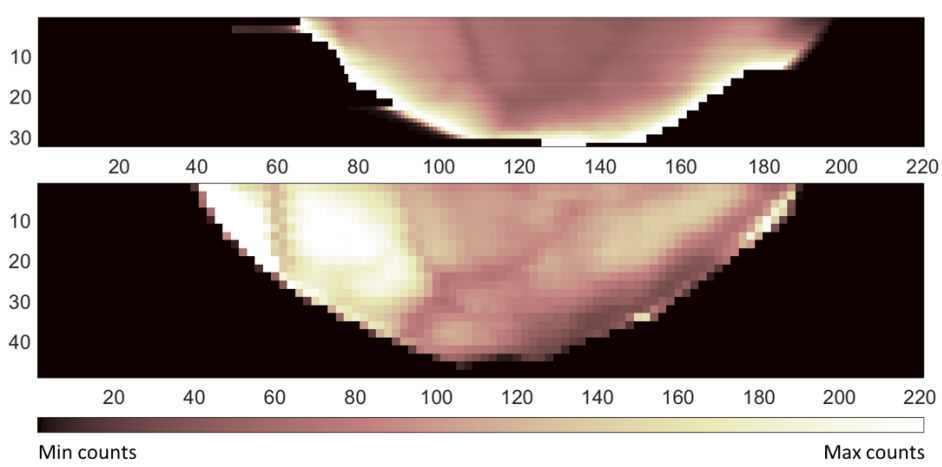

Figure 1. Example of cranio-caudal view scans of the left breast of a healthy volunteer, obtained with the first TDC model (Surface Concept, top) and the second (PicoQuant, bottom). Labels on axes report the extension in millimeters. The imaged area with the new TDC is 4 times larger than with the previous one.

The DNL measured with the new setup is lower than 2% without applying any compensation algorithm. Reproducibility on phantoms is now better than 1% for both coefficients. Scans of the breast-shaped phantom were carried out without difficulties once again.

As regard step 3, *in vivo* reproducibility shows a significant improvement too (Table 1). This is especially evident for collagen, which, due to its weak absorption, is more critical to quantify than other constituents. We can observe that its CV reduces relevantly from 43% to 5%. The other volunteers show similar trends.

In vivo measurements on different days exhibit higher CVs than phantoms, as expected. Actually, phantoms, however useful they may be, are simplified models and they could never properly simulate the breast heterogeneity and the effects of metabolism and age on its composition. Another criticality where phantoms fail is the variability in size and composition

among different women. For these reasons, the instrument could not be transferred to clinics without prior check on some volunteers. Only after the accomplishment of step 3, the transfer was finally possible.

Table 1. Comparison of average breast constituent concentrations of a healthy volunteer, from cranio-caudal right views, obtained with both TDC models (initial setup, V1 – Version 1, and new setup, V2 – Version 2). The unit of collagen, water and lipids is mg/cm^3, of hemoglobin μM, of saturation %, of a cm^{-1}, b is adimensional.

	Session 1		**Session 2**		**Session 3**		**CV**	
	V1	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**
Collagen	50	58	78	57	33	53	42%	5%
Water	251	198	259	181	220	180	8%	6%
Lipids	627	674	648	671	647	697	2%	2%
Hemoglobin	8	8	9	8	10	7	10%	6%
Saturation	51	63	71	69	59	58	17%	8%
a	13	11	14	12	13	11	2%	2%
b	1.08	0.85	0.83	0.77	1.13	0.95	16%	10%

4. CONCLUSION

In conclusion, groundwork for high-throughput time-resolved optical mammography has been laid. We showed how it can be effectively implemented exploiting novel emerging technologies, such as SiPMs and a high-throughput TDC. Furthermore, this study has pointed out the key role of a thorough and gradual methodical approach, from laboratory to *in vivo* testing, as a general guideline for instrument characterization, that could also be beneficial to instruments other than our optical mammograph. In particular, *in vivo* rehearsals proved crucial to certify the instrument readiness to an effective clinical study. Our instrument is now engaged in a clinical trial on monitoring of neoadjuvant chemotherapy at the San Raffaele Hospital in Milan.

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