SOLUS | SMART OPTICAL AND ULTRASOUND DIAGNOSTICS OF BREAST CANCER

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Deliverable 4.3: Definition of procedures for routine tests

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Abbreviations

BIP	Basic Instrument Performance
DO	Diffuse Optics
DOT	Diffuse Optical Tomography
DTOF	Distribution of Times of Flight
FWHM	Full-Width at Half Maximum
IRF	Instrument Response Function
TD	Time-Domain
TG	Time-Gated
US	Ultrasound

1. Introduction

This deliverable defines standard procedures for daily routine tests to be performed on the SOLUS system prototype during the clinical validation stage in order to ensure the acquisition of high quality data and to guarantee consistency between measurements performed on different days. In particular, these tests have a dual scope: i) the monitoring of the instrument performance in real settings, and ii) the check of the instrument working condition to detect possible degradation or malfunctioning before each *in-vivo* session in order to avoid the acquisition of *in-vivo* data in case of unexpected loss of performances. This is crucial for the validation in clinical settings, since it is expected that the 40 adult women enrolled for the study (see D5.1 Definition of the clinical protocol, M3) will undergo the SOLUS examination on different, possibly not consecutive, days. It is worth noting that the SOLUS prototype performances will be already verified on phantoms before starting the validation in clinical settings, but being a radically new device based on newly devised photonic technologies, it is important to approach the first clinical validation with standardized daily procedures that can highlight possible degradation of performance or instabilities. Additionally, the comparison of tests carried out on different days can be useful to identify possible ageing of components or subsystems. Even in case of degrading performances, a standardised reference measurement can be used to re-align the system with respect to small, subtle variations in properties due for instance to temperature change or aging. These small alterations can be tracked back by e.g. a machine learning approach to account for system-specific contributions.

The identification of the daily routine tests can be useful also to specify the general pipeline and protocol of the clinical measurements. Some aspects could be inserted in the SOLUS software sequences (pre-defined sets of operations/acquisitions to be performed sequentially following a fixed scheme).

The procedures reported here are a subset of the tests identified as relevant for the validation of SOLUS in laboratory settings, and previously reported in D4.2 "*Definition of protocols for system characterization*" (M12). They have been defined following the recommendations from the M12 project consortium general assembly (in particular by OSR) about the maximum duration of such procedures and the recommendations received from the external advisory board (see D.8.6 First report of the external advisory board, M13) about the relevance of these tests and the need to keep them as simple as possible, thus enabling their execution by technicians.

This report is organized as follows: Section 2 contains the proposed daily tests, while Section 3 reports the conclusions.

2. Daily routine tests

This section reports the list of proposed tests for daily check of the SOLUS prototype working conditions.

MEASUREMENT OF THE INSTRUMENT RESPONSE FUNCTION

The measurement of the Instrument Response Function (IRF) is part of the Basic Instrument Performance (BIP) Protocol, which has been devised to test the hardware specifications of a Time-Domain (TD) Diffuse Optics (DO) system [1]. The IRF shape is given by the combination of the shapes of the laser pulse, of the detector single-photon response, of the broadening due to possible different optical paths of photons inside the collection optics before being detected and of the jitter and distortions introduced by the time-to-digital converter. Hence, it provides a wide view of the operating conditions of many parts of the SOLUS prototype in parallel.

The acquisition of the IRF is relevant since it characterizes the time resolution of the instrument as a whole, which is an important parameter in TD-DO. Indeed, a loss of resolution can give rise to confounding effects during the analysis due to the resulting crosstalk between information coming from different depths of the investigated tissues, which is encoded at different arrival times of photons along the distribution of photons times of flight (DTOF). Moreover, a precise knowledge of the IRF is mandatory for model-based reconstruction of optical properties. For this reason, it is crucial to measure it every day of operation in order to be able to exclude effects coming from possible changes in its shape due to e.g. possible slow degradation of components, which can be revealed thanks to the comparison of IRFs taken at different times.

In order to guarantee the measurement of the IRF with good signal-to-noise ratio, the BIP protocol recommends the acquisition of a number of photons of at least 1 million, which can be usually detected in just 1 second. However, this recommendation is generally for free-running operation (i.e. not time-gated) of the detection chain, while in SOLUS the time-gated (TG) operation can extend the measurement dynamic range by few orders of magnitude. For this reason, it would be desirable to have orders of magnitude more photons in the IRF to acquire it with wider dynamic range. This will severely affect the measurement time since in measurements dominated by Poisson noise the dynamic range increases by one order of magnitude upon increasing the acquisition time by two orders of magnitude [2]. In fact, TG operation can extend the dynamic range of the measurement without such a large increase in the acquisition time [3]. With TG acquisition, few slices of the DTOF are acquired at different temporal positions, which are then combined to reconstruct the waveform in post-processing [2]. It is therefore possible to have about 1 million of photons in each slice. Hence, for each wavelength and for each source-detector pair, the required measurement time is in the order of 1-second times the number of delays employed for the TG acquisitions (e.g. 10). This will guarantee the required dynamic range to be able to monitor the IRF. Since different lasers and detectors will compose the SOLUS system, the acquisition of all the IRFs should require about 10 minutes.

It is worth noting that the figure of merit for the evaluation of the IRF is indeed not only its Full-Width at Half Maximum (FWHM), but also its width at 1/10, 1/100, etc., of the maximum, since some fingerprints of TD-DO devices can be identified only well below the peak of the IRF. For instance, the memory effect [4] of the detector is expected 4-8 decades below the peak, the diffusion tail of the detector single-photon response [2] usually affects the IRF one decade below the main peak, and the LED-mode emission of the laser diodes can be present few orders of magnitude below the emission peak (see D.1.1 “Specifications of smart optode components, M4”).

In a classical fiber-based TD-DO system the IRF is typically measured by directly facing the injection and collection fibers, with a thin diffuser in between (e.g. a piece of Teflon tape or a piece of paper) in order to ensure that the input acceptance angle of the detection fiber is fully filled, similarly to what happens when the fiber is placed in contact with the tissue under investigation. However, SOLUS does not use optical fibers, and a proper experimental procedure for the measurement of the IRF needs to be designed during the following stages of the project. For instance, the IRF could be measured by placing the SOLUS probe in contact with a custom designed surface allowing the laser light to directly reach each detector. This can be a reflective surface, shaped to match the SOLUS probe, with a thin layer of US gel in between in order to provide a direct light path from sources to detectors. Optical scattering particles can be added to the gel in order to uniformly distribute the light on the probe area. This and other solutions will be tested once the SOLUS probe will be available.

MEASUREMENT OF AN HOMOGENEOUS PHANTOM

The instrument performance in recovering optical properties of homogeneous media is evaluated by applying the MEDPHOT Protocol [5]. Although the breast is a heterogeneous medium, the performance in the measurement of a homogeneous medium provides additional guard against possible performance degradation. As stated above, the SOLUS instrument will be completely characterized on phantoms before its routine operation in the clinical setting, therefore its performance in recovering the optical properties of homogeneous media will be known (D4.8 “Final characterization of the SOLUS prototype,” M36). Hence, the measurement of a single suitable homogeneous phantom using the SOLUS probe will allow comparison of the performance of each source-detector pair with the benchmark (i.e. the full characterization performed previously to accomplish the validation in laboratory settings).

The measurement of the homogenous phantom will last 30-60 seconds, thus acquiring waveforms with the same dynamic range as the final measurement on the breast. Optical properties will be estimated from all the source-detector pairs, possibly discarding the information recorded with null or short separation between source and detector since, on a homogeneous phantom, they provide DTOFs too similar to the instrument response function, impairing the quantification of the optical properties [2]. The figure of merit to evaluate the system performance on homogeneous phantoms is the relative error in recovering the

optical properties (both absorption and reduced scattering coefficient) of the phantom. Further, this test will permit to measure the change in signal level as compared to the initial reference values.

Being homogeneous, there are no structures inside the phantom to be recognized by simultaneous US investigation, therefore the phantom to perform this test can be either a classical epoxy resin or silicone rubber phantom, as well as a homogeneous phantom fabricated with the same technique used to build the SOLUS phantom kit (see "D4.4 Provision of multi-modal phantom kit," M18).

MEASUREMENT OF AN HETEROGENEOUS PHANTOM

The instrument performance in detecting, localizing and quantifying spatially confined absorption-changes is evaluated in the NEUROPT Protocol [6]. However, in order to properly address the performance in Diffuse Optical Tomography (DOT) an additional effort was taken to include a more comprehensive standardization (this is not considered within NEUROPT but relevant for SOLUS). To this purpose, we defined the SOLUS Protocol to standardize the test of the performance in detecting, localizing and quantifying three-dimensional optical perturbations embedded inside a highly scattering medium (see D4.2 "Definition of protocols for system characterization," M12).

The full characterization of the system with the SOLUS Protocol (D4.8 "Final characterization of the SOLUS prototype," M36), implemented using the phantom kit developed within this project (D4.4 "Provision of multi-modal phantom kit," M18), will provide the benchmark for future evaluations of the performance of the SOLUS system. Hence, a daily check of the DOT performance on a heterogeneous phantom will be useful to assess the instrument performance in a scenario that is closer to the final measurement.

The measurement will have the duration of 1-2 minutes as *in-vivo* breast measurements, thus acquiring waveforms with the same dynamic range as the clinical measurement, but will include also the initial phase (expected 10-60 s) of best attenuation search. The figures of merit we identified to evaluate the system performance on the heterogeneous phantom are: i) contrast and ii) contrast-to-noise ratio produced by the perturbation, iii) displacement and iv) broadening of the reconstructed perturbation; v) relative error in recovering optical properties (both absorption and reduced scattering coefficient) of the perturbation.

In this case, the measurement will be performed by guiding the investigation with US to locate the perturbation position and shape. Hence, this measurement will be performed using a phantom fabricated with the same technique of the SOLUS phantom kit, being suitable to both US and optical investigations.

SUMMARY TABLE

The daily routine tests are summarized in Table 1. This is a first attempt to identify the key requirements and specifications. The choice of the phantom and detailed operative conditions is not the goal of the present deliverable (which defines the Protocol and the key Figure of Merits), but rather of the implementation phase, which will the probe validation in the lab. The table will be updated when the smart probe is ready and fully tested to adapt to the further needs and limitations emerged during the extensive lab validation.

Table 1 – summary procedure for the daily routine tests.

Test	Goal	Protocol	Specs	Phantom	Figures of merit	Ext. time
IRF	Tests: i) jitter ii) shape iii) reflexes iv) memory v) background	BIP [1]	λ=all, source_det_pair=all, #delays=10, #counts=1M	IRF phantom (TBD)	▪ width @ 1/2, 1/10, 1/100 ▪ peak position ▪ memory noise level ▪ background level	10 min

HOMO	Tests: i) loss in signal ii) retrieval of homogeneous properties	MEDPHOT [5]	λ=all, source_det_pair=all, #delays=3, t_{acq}=1 s for each λ & source, fixed attenuation	Homog. phantom (e.g. μ_a = 0.05 cm^{-1}, μ_s' = 10 cm^{-1}, TBD)	▪ fitted μ_a ▪ fitted μ_s' ▪ signal level	1 min
TOMO	Test capability to: i) detect, ii) localize and iii) quantify a local optical perturbation	NEUROPT [6] (updated by SOLUS)	λ=all, source_det_pair=all, #delays=3, 5 ms acquisition time, 60 repetitions, adaptive attenuation (same sequence of the clinical measurement)	Hybrid US + Optics phantom (TBD)	▪ contrast ▪ contrast-to-noise ratio ▪ spatial offset ▪ spatial broadening ▪ accuracy in $\Delta\mu_a$ and $\Delta\mu_s'$	2 min

3. Conclusions

This document provides the procedures for daily routine test of the SOLUS system during the clinical validation to ensure the acquisition of high quality breast data. In about half an hour, as recommended by OSR, the system will be used to acquire: i) an instrument response function; ii) a measurement on a homogenous phantom; iii) a measurement on a heterogeneous phantom. This set of data can be used to detect possible degradation or malfunctioning of the system, thus avoiding acquiring clinical *in vivo* data in case of unexpected loss of performance.

Daily tests have been defined well in advance, since the validation in clinical setting will start during the third year of the project. This permits to meet WP4 goals timely and to anticipate reasoning and discussion in an early phase of the project.

4. References

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