SOLUS | SMART OPTICAL AND ULTRASOUND DIAGNOSTICS OF BREAST CANCER

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Abstract

This document is the report relative to the deliverable D3.5. It describes the validation of the SOLUS prototype for the clinical validation.

Key Words

SOLUS prototype, functional validation, clinical validation

Tables of contents

Abbreviations

DOT	Diffuse Optical Tomography
IRF	Instrument Response Function
UUID	Universally Unique IDentifier

1 Introduction

The SOLUS project aims to develop a new imaging system to improve the breast cancer diagnosis. It combines conventional ultrasound imaging with emerging diffuse optical tomography (DOT). To push this technology toward an industrial product, it relies on the smart optodes, a new fully integrated time resolved component developed in the course of the project. Thanks to these components, the SOLUS prototype features a bimodal ultrasound/optical probe. Apart from the technical developments of the prototype, a clinical validation is also planned in the project to evaluate the usability of the prototype in the clinical workflow and to start assessing the benefits of the bimodal information from a clinical perspective.

This document shortly describes the SOLUS prototype. Then it reviews its operation during the clinical validation. Finally, the set of data that will be collected in clinics are reported and the Key Performance Indicator (KPI) relative to the prototype is evaluated.

2 Presentation of the prototype

2.1 Hardware

The SOLUS prototype takes profit of the commercial Aixplorer Mach 30 from Supersonic Imagine to mount all the external devices required for the whole system. Figure 1 shows the resulting system. The prototype is composed of:

1. The Aixplorer Mach30 from Supersonic Imagine: it is a fast ultrasound imaging system featuring shear wave elastography to assess tissue stiffness in complement with first class Doppler and B-mode imaging. This commercial system is CE marked. It thus complies with all regulatory rules required for clinical validation. It is equipped with a standard SuperLinear™ SL18-5 probe to provide the 'state of the art' reference of breast cancer diagnosis. The ultrasound part of the SOLUS probe is connected to this machine.
2. The SOLUS bimodal probe: it embeds both the US and optical modalities in a single handheld housing. The probe also features two skin contact sensors located at two opposite zones of the probe end face. Even though laser safety does not require it (laser class 1), for additional caution and not to raise unneeded concerns for the operator or patient, the optical emission is only enabled when the probe end face is fully in contact with the skin. The manufacturing of the probe complies with VERMON standards for ultrasound probes. The probe also complies with current regulations concerning electric insulation, ultrasound emission and thermal management. It is rated class 1 for laser emission. The optical part is driven and powered through an usb-C connexion to the SOLUS computer (a power injector delivers the required power to the electronics).
3. The position sensor: a solution from NDI based on the controller driveBay, the mid-range transmitter and the sensor Model 800. It provides the position and the orientation of the probe during the examination. It is approved for clinical use.
4. The water cooling system EXT-440 from Koolance: it serves to cool down the SOLUS probe by circulating water inside the probe. It is mandatory to fulfil the thermal regulation on medical devices and to prevent any damages to the electronics integrated in the probe.
5. The Lenovo Tiny P330 computer: it drives the bimodal acquisitions and it performs the online data processing to characterize the suspicious lesion. An extra screen is also added on the prototype to operate the SOLUS software.
6. The REO Reomed 600 power supply isolator: it ensures the safety of the users and it prevents the prototype to perturb the nearby equipment in clinical environment.

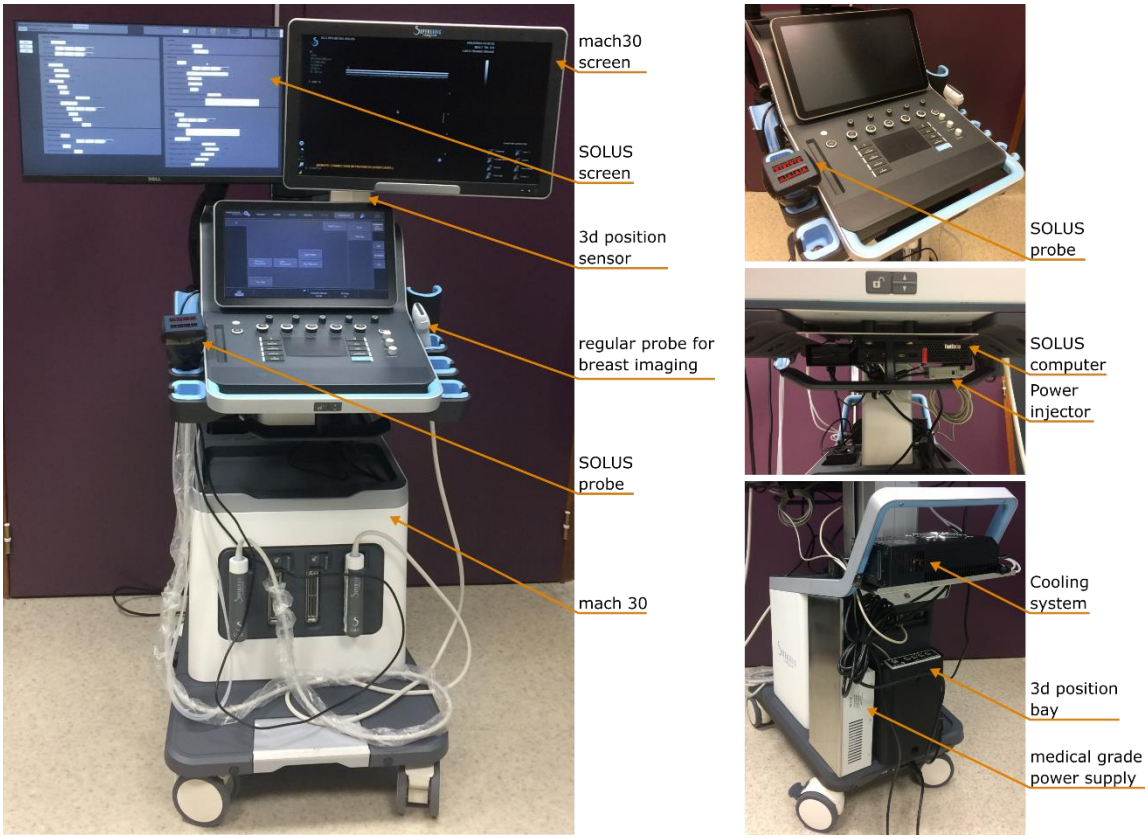

Figure 1. The SOLUS prototype

The connections between these elements are depicted in the scheme presented on Figure 2. The development of the hardware of the SOLUS prototype is reported in Deliverable 3.3.

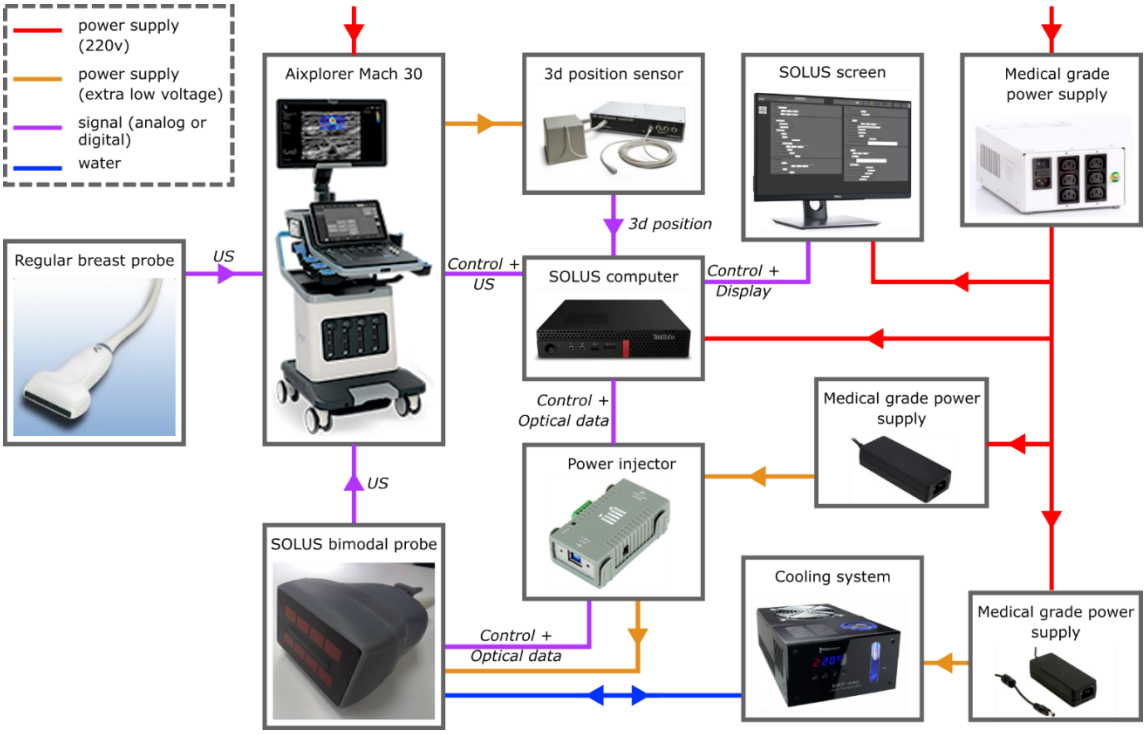

Figure 2. Connections between the devices of the prototype.

2.2 Software

The SOLUS software runs on the prototype. It drives the acquisitions, it processes the data and it collects the patient information during the clinical tests. It is attended to be operated by the researchers from the field of diffuse optics to tune the prototype and by the radiologists to conduct the clinical validation. It is written in Matlab to fit the skills and the habits of the partners of the consortium involved in coding activities. It has a modular structure to preserve the confidentiality of the software libraries released by the partners. A user interface helps the user to configure and to operate the prototype, see Figure 3 for an illustration.

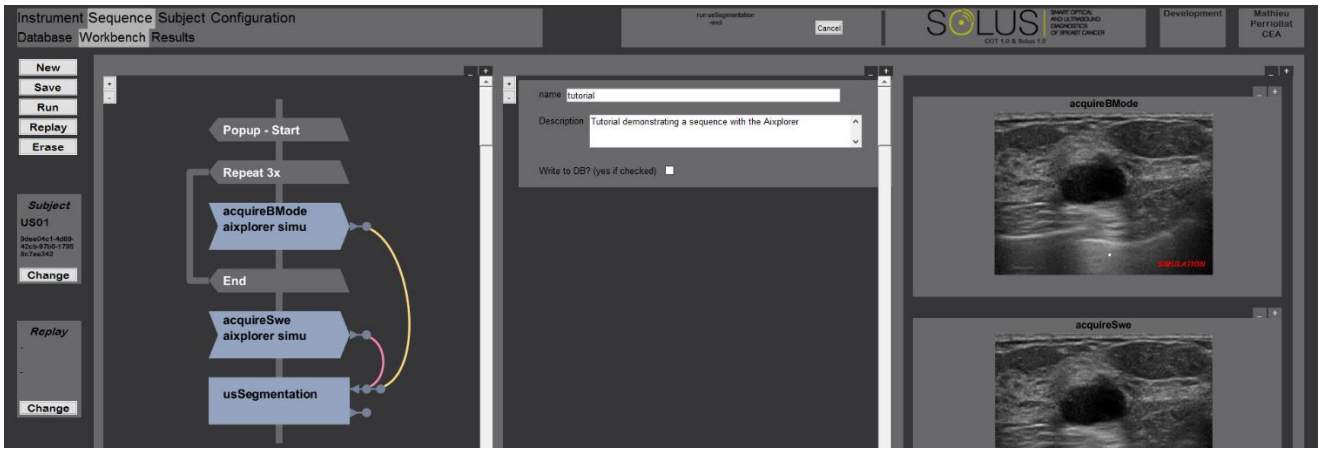

Figure 3. The SOLUS software. This workbench serves to define (left) and to parameterize (middle) the sequence. It also displays the outputs of the sequence during execution (right).

The software presents two technical menus. The first one serves to configure the devices of the prototype (connection details to communicate with the Aixplorer Mach30, initialisation of the smart optodes and initialisation of the position sensor). The other one presents an interface to define and to run the tasks performed by the prototype. In this menu, the user designs a sequence composed of acquisition actions and data processing. He also sets up the outputs that display while running the sequence, see Figure 3. The software also includes a clinical menu to collect the patient medical data required to conduct the clinical validation.

The software relies on a database to manage all the data relative to the experiments: experimental data acquired or computed during the experiment and metadata giving the context of the experiment (like the version of the prototype, the current software revision or the name of the user). The database is formed by a hierarchical structure of folders and files which is described in Deliverable 8.3. Figure 4 illustrates the structure of the database.

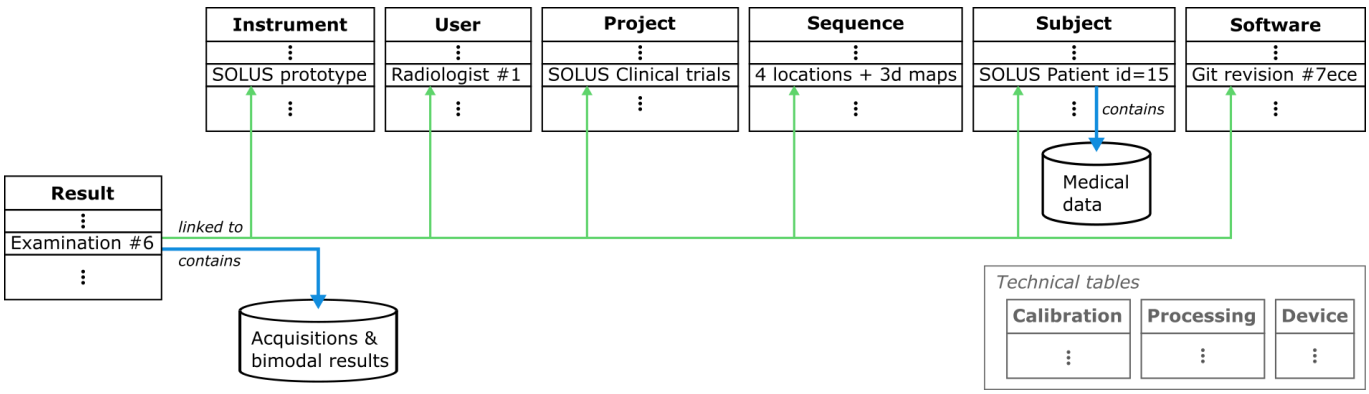

Figure 4. Structure of the SOLUS database. The boxes are the tables of the database. Examples of entries are given in the tables. The results (generated by the execution of the sequence) are linked to the other tables to give the context of the experimentation.

Even though it has been developed during the SOLUS project, the design of the software is generic to ease its reuse in studies involving similar prototypes. The implementation is described in Deliverable 3.4.

3 Clinical use of the prototype

3.1 Protocol

The clinical validation serves to quantify the gain of coupling the ultrasound imaging with diffuse optical tomography over the standard ultrasound imaging. It also aims to evaluate the use of the bimodal technology in a clinical workflow. To achieve these goals, the clinical partners and the technical teams agreed on the protocol depicted in Figure 5. In this protocol, the state of the art of the breast cancer diagnosis from ultrasound imaging is provided by the Aixplorer Mach 30 equipped with the standard breast imaging probe. Moreover, three radiologists examine each SOLUS patient independently from each other to evaluate the variability induced by the practitioner. Even though the system is designed to be operated by the radiologist alone, for better control, in this initial clinical validation, a technical operator supports the radiologist by operating the SOLUS software, while the medical doctor examines the patient (including full control of the Aixplorer).

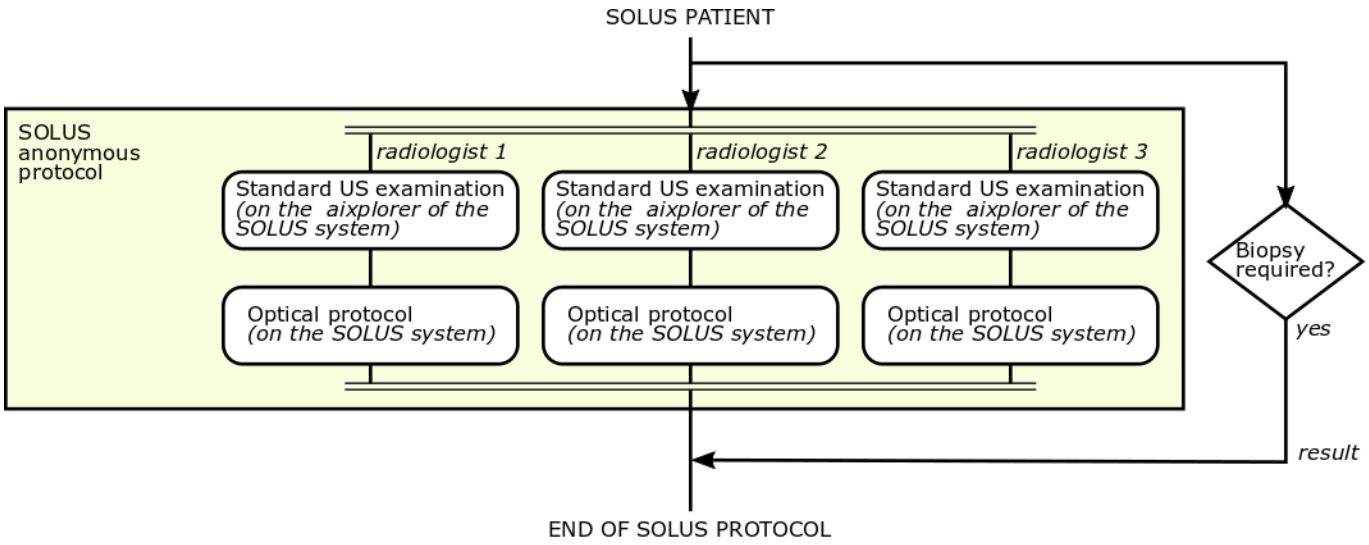

Figure 5. The protocol for the clinical tests.

The full clinical protocol is reported in Deliverable 5.1. From a practical perspective, an examination conforms to the following procedure:

1. SOLUS patient recruitment
2. Registration of the patient in the SOLUS database including its medical history, Figure 6 illustrates the form available in the software for this purpose. An anonymous identifier is used to preserve the anonymity of the medical information. The medical staff manages the anonymization procedure.
3. The radiologist logs in the SOLUS software and loads the patient in the system.
4. The radiologist uses the Aixplorer to examine the patient with the standard probe. The ultrasound images taken by the radiologist during this examination are exported and they are saved as DICOM images in the SOLUS database. The practitioner fills its conclusions in the fields of the menu for the standard examination in the software. They also spots the four locations to focus on during the bimodal acquisition as depicted in Figure 7.
5. The SOLUS operator launches the sequence. Then, he or she acquires the instrument response function (see paragraph 3.2 for details).
6. The radiologist switches probe. Then, he or she tunes the parameters for the B-mode, the colour Doppler and the shear wave elastography on the SOLUS probe.
7. The SOLUS operator guides the radiologist through the bimodal sequence (see paragraph 3.2 for details).

8. If applicable, the results of the biopsy are appended to the patient's medical information in the database.

Figure 6. Close-up on the clinical form to collect medical data.

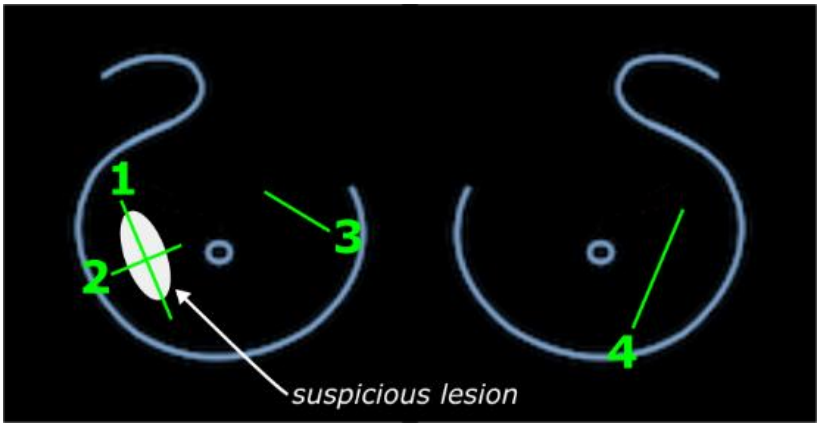

Figure 7. The four locations of examination with the SOLUS probe: 1 is the main axis of the lesion; 2 is the minor axis of the lesion (orthogonal to 1); 3 is a homogeneous (supposedly healthy) zone on the same breast; 4 is the mirror position of location 1 on the contralateral breast. The white zone is the suspicious lesion.

3.2 SOLUS sequence

The SOLUS sequence collects and processes the data from the bimodal probe (see Figure 8). It has six parts:

1. The Instrument Response Function (IRF) acquisition and validation
2. The data acquisition and validation on the main axis of the lesion
3. The data acquisition and validation on the orthogonal axis of the lesion
4. The data acquisition and validation on a homogeneous zone out of the lesion on the same breast
5. The data acquisition and validation on the mirror position of the contralateral breast
6. The estimation of the tissue composition and the display of the results

The sequence stops before starting each part and a window pops up with specific instructions for the user. The user must validate the message for the sequence to continue (example on top right of Figure 8).

The optical acquisitions are also subject to verification. The SOLUS operator must diagnose the quality of the optical data from a table of graphics showing the different combinations of firing optode, wavelength and detecting optode (example on middle right of Figure 8). In case the quality is degraded, the last region of interest is acquired once again and the validation process restarts.

To acquire the IRF, the probe is positioned in a dedicated holder (IRF box), specifically designed for the purpose and located in a handy position on the Aixplorer body.

When the acquisitions are complete, the radiologist manually segments the lesion in the B-mode image (example on bottom right of Figure 8). This provides the spatial prior to the optical reconstruction, which starts automatically after the segmentation. The results of the bimodal analysis are displayed in two screens. In the first one, the user navigates through the reconstructed volume in three dimensions with a slicing capability to explore the dataset. The second one focuses on the contrast in optical properties and in tissue composition between the lesion and the surrounding area. These graphics intend to show that the new bimodal analysis brings specific information related to the medical grade of the lesion, see Figure 9 for an example.

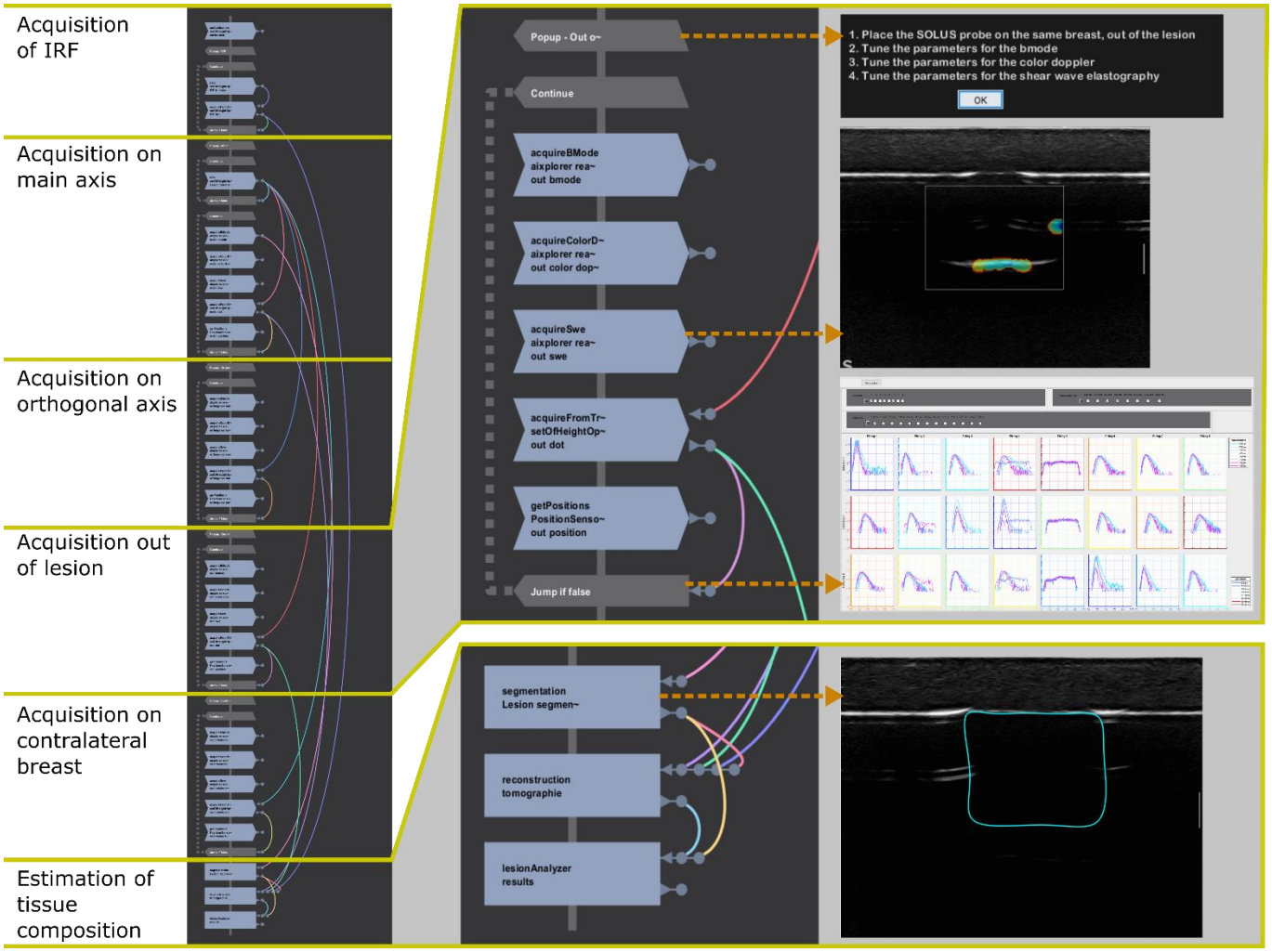

Figure 8. Clinical sequence. The six parts of the sequence are labelled on left. Two close-up views depict the bimodal acquisition on the out location (top) and the reconstruction (bottom). Specific steps are illustrated on right.

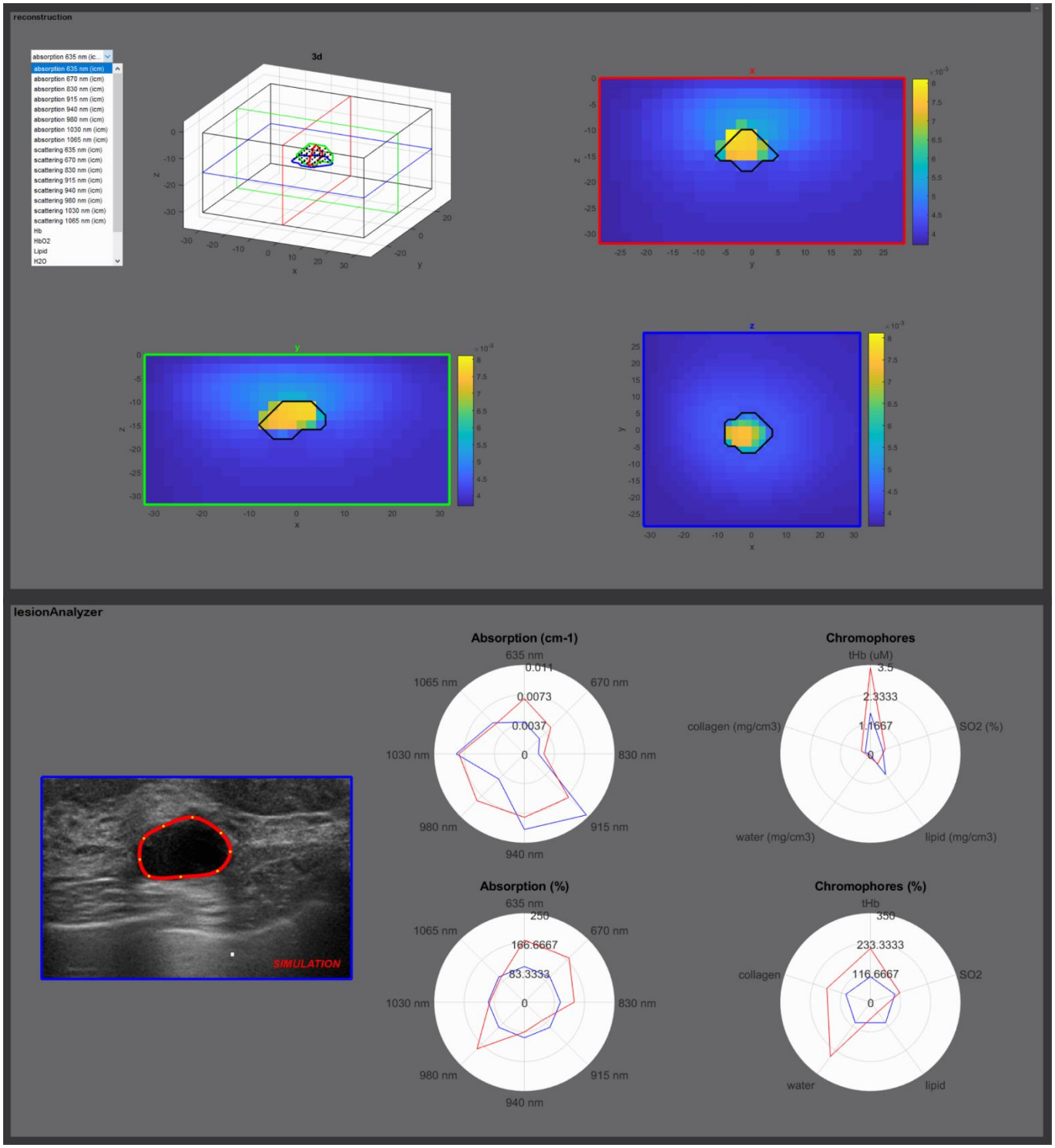

Figure 9. Results of the SOLUS analysis. Top: the 3d reconstructed maps and slices. Bottom the tissue composition inside and outside the lesion.

3.3 Optical acquisition

The SOLUS probe integrates eight smart-optodes. A smart-optode is an optoelectronic component that measures the statistical distribution of the times of flight of photons in the biological tissue, see Deliverable 1.4 for an extensive description and Deliverable 4.6 for its full characterization. It is composed by a time-gated detector, eight pulsed laser sources at different wavelengths and a timing electronics. In the SOLUS probe, the eight smart-optodes work together and the detectors are sensitive to 64 lasers of the probe (8 optodes x 8 wavelengths). Setting up an optical acquisition consists in selecting the subset of lasers that

fire, the integration time to capture the distribution, the temporal position of the time gates, plus other technical parameters.

The sensitivity of the detectors can be adjusted to maximise the number of collected photons without saturating the sensor. At each wavelength, the sensitivity depends on the optical properties of the tissue subject to the examination, to the temporal position of the time gates, as well as the distance to the firing source. The firmware driving the smart-optodes implements an automatic method to tune the sensitivity of the eight detectors regarding the configuration of the acquisition.

The processing of the optical data jointly exploits the data from the different locations on the breasts. It is thus required to acquire these data in the exact same configuration of the optical acquisition. The acquisition on the patient thus starts with a preliminary optical acquisition. The latter defines the configuration of the optical acquisition and it computes the sensitivity of the detectors for this configuration. These settings are then used for the optical acquisition on the four locations, see Figure 10.

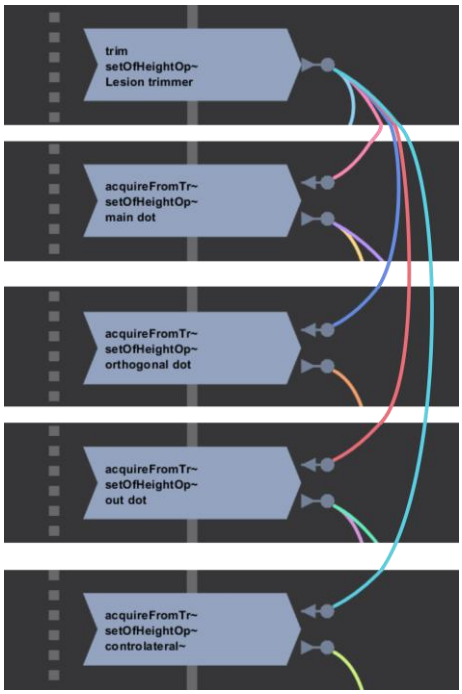

Figure 10. Optical acquisition in the sequence (sub-parts). The first block defines the sensitivity of the detector for the optical acquisition. These parameters are then used by the acquisitions on the four locations.

4 Collected data and online processing

4.1 Data description

The data collected during the acquisition steps are summarized in Table 1. As previously explained, the user can redo the acquisition if the quality of the data is not sufficient. However, all the data are saved in the database whatever their quality, but they are marked with a quality flag.

Table 1. Summary of acquired data.

	B-mode image	Colour Doppler	SWE	Optical data	Position
IRF	NA	NA	NA	X	NA
Lesion main axis	X	X	X	X	X
Lesion orthogonal axis	X	X	X	X	X
Same breast, out of lesion	X	X	X	X	X
Contralateral breast	X	X	X	X	X

The Aixplorer Mach 30 provides the B-mode image, the colour Doppler image and the shear wave elastography image. They are saved along with a set of metadata giving the settings of the ultrasound machine, the spatial resolution of the image and the scale of measurements. The radiologist tunes the parameters of the ultrasound images on the Aixplorer system prior to launch the acquisitions on the SOLUS system – the blocking popup windows in the sequence give time for these settings.

The position sensor was foreseen to be used to register the four locations regarding each other and to invalidate a measurement in case a large displacement occurs while acquiring the data. The position data comprises the history of positions (three coordinates) and directions (three angles) of the probe during the acquisition phase. The ultrasound images and the optical measurements being tagged over time, it is then possible to extract the location of the probe for a specific acquisition.

The elementary optical data is an array of 128 values giving the number of detected photons per time channel. Such an array is related to the acquisition by one detector of the light emitted by one firing optode at a specific wavelength (i.e. one physical laser source) for a given time gate. All combinations of sources, detectors and gates are possible. Moreover, to get rid of external perturbations like ambient light during the data processing, each acquisition is doubled with an acquisition having the same settings but without firing the laser (i.e. the background acquisition). Finally, the whole process can be repeated to improve the signal to noise ratio by averaging the acquisitions made with identical configurations. At each location on the breast, the optical data is a matrix having seven dimensions: the detector (8), the firing optode (8), the firing wavelength (8), the position of the gate (up to 13), the foreground (i.e. with lasers ON) or background mode (2), the repetitions (usually 2) and the time channels (128).

4.2 Access the data

The execution of the sequence creates a new record in the table *TABLE_result* of the database. All the data generated while the sequence runs are saved in this record. The record is indexed by a unique key (Java Universally Unique Identifier – UUID). A Matlab tool has been implemented to easily retrieve the data in the database. It provides them as a structure which fields are the steps of the sequence.

The data are currently saved on disk using the regular Matlab format (mat files). However, a new format might be used in the future for the open access database, see Deliverable 8.3.

5 Key attribute for the system

Table 2 gives the key attribute relative to the bimodal acquisition with the SOLUS system defined in the amendment AMD-731877-12. The in-vivo measurements have not yet started – in accordance with the project plan, they will start during the mockup session at the Ospedale San Raffaele – and one relies on the measurement on phantom to derive the operational performances of the SOLUS prototype.

Table 2. The key performance indicator of the SOLUS prototype.

KPI number	**Key Performance Indicator**	**Check point**	**Y1**	**Y2**	**Y3**	**Y4**	**3y after project end**
KPI4	SOLUS prototype – Operational performances: acquisition time for complete DOT, acquisition time for complete examination (US+SWE+DOT)	D3.5	-	-	-	30 s 60 s	-

Table 3. Durations of acquisitions for an acquisition on phantom.

Bmode	Colour Doppler	Shear wave elastography	DOT	Position
14 s	14 s	14 s	54 s	5 s

Table 3 provides the estimates of the durations of the sequence extracted from an acquisition on a bimodal phantom (Ecoflex phantom, see Deliverable 4.4). These measurements have been performed in the following conditions:

- The phantom has been designed to have realistic optical properties to mimic breast tissue in the wavelength range of interest, and to mimic the geometry of a breast with a lesion (D2.1 - Definition of paradigms representing exemplary breast lesions cases),
- The SOLUS probe is the probe #1. Unfortunately, it has a broken optode that does not fire the lasers. The measured acquisition time is thus underestimated by one eighth regarding a full operative probe. A second probe is currently in development to tackle this limitation.
- The number of time gates is set to 13 to allow the best retrieval of the time distribution of collected photons. The analysis of the acquired data shows that one can reduce the number of gates to 6 during the clinical validation without losing quality on the dataset.

The acquisition time is linear against the number of gates and the number of firing lasers. The extrapolated key attributes for in-vivo measurement are thus:

- acquisition time for complete DOT = 28.5 s
- acquisition time for complete examination (US+SWE+DOT) = 75.5 s

The time for the DOT acquisition fulfils its key attribute. The ultrasound imaging takes slightly more time than expected. This is related to the implementation of the image retrieval from the SOLUS computer that offers different modes to set the ultrasound parameters – one prioritizes the flexibility over the acquisition time. An optimization could be planned in the future when the use of the prototype is more mature.

Lastly, the position sensor was not foreseen in the KPI for the acquisition and it also contributes to the overall acquisition time. Once again, the duration could be drastically reduced in a more advanced version of the prototype.

6 Conclusion

The prototype fully integrates the technologies developed in the other work-packages of the project. The different devices have been mounted on the ultrasound machine and a software has been implemented to drive these devices and to analyse the data. The prototype is now ready to be transferred to Ospedale San Raffaele and enter the clinical validation. A training session has also been organized to learn how to use of the prototype during the clinical validation.

The acquisition time of a complete DOT with the current version of the prototype is in line with the target of KPI4, while the overall acquisition time is slightly higher than the target defined in the KPI. However, it is still compatible with the duration of the examination foreseen for the clinical validation. Actually, the flexibility of the prototype has been preferred against the duration of examination, especially to be able to fine tune the sequence to achieve a good quality of in-vivo measurements.

The clinical validation will push the bimodal acquisition and the data processing to more mature solutions. It will then be possible to optimize the prototype to improve its performances.