BABYLUX

Programme	CIP – Competitiveness for innovation
Type of Action	Pilot B
Project Title	An optical neuro-monitor of cerebral oxygen metabolism and blood flow for neonatology
Acronym	BabyLux
Project n.	620996

D.7.2 REPORT ON STANDARDISATION ACTIVITIES – FIRST VERSION

Work Package	WP 7
Lead Partner	PoliMi
Contributing Partner(s)	…
Security Classification	PU (Public)
Date	03/01/15
Version	1.0

The BabyLux project (620996) is co-funded by the European Union under the CIP competitiveness and innovation framework program 2007-2013.

Document history

Version	Date	Comments	Authors
0.1	29.1.2016	first draft	A.Pifferi (PoliMi)
1.0	30.1.2016	Final revision	A.Torricelli (PoliMi)

Statement of originality:

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

The work leading to these results has received funding from the European Community's CIP competitiveness and innovation framework program under grant agreement nº. 620996.

Table of Contents

List of Figures

List of Tables

1. Executive Summary

The contribution of BabyLux to the reinforcement of the culture of standardized objective performance assessment and of quality control of diffuse optics instruments progressed along two parallel paths.

A first direction was the further elaboration and proposal of protocols, methodologies and phantom materials suitable for the performance assessment of brain imagers. In particular, a new concept phantom for assessing deep brain changes was designed, constructed, and characterized. This is a rugged, reliable and stable phantom, well suited for testing in a clinical environment and suitable for adoption in future standards.

Along a parallel path, prof. Antonio Pifferi and prof. Alessandro Torricelli served as technical experts in the IEC committee that worked to the preparation of the International Standard ISO/IEC 80601-2-71:2015, Medical electrical equipment - Part 2-71: Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment. The standard was approved in May 2015. This standard encompasses continuous wave NIRS instruments, and could be extended in the future to time-domain system, taking advantage also of the exploratory work performed under BabyLux.

For future activities, the aim is on one side to advance with the phantom construction and characterization for TRS, also in support of existing standards, and on the other hand to complete and publish the activity on DCS phantoms to be used as tools for objective performance assessment of DCS instruments.

2. Introduction

At present, there are no specific international industrial standards neither on Time-Resolved Spectroscopy (TRS) instruments, nor on Diffuse Correlation Spectroscopy (DCS) instruments. For what concerns, more in general, the clinical assessment of oxygenation by optical means – that is a key parameter provided by the BabyLux TRS – two standards are available, yet restricted to continuous wave (CW) instruments and for specific applications.

The first one is the ISO 80601-2-61, Medical electrical equipment – Part 2-61: *Particular requirements for the basic safety and essential performance of pulse oximeter equipment* [1]. It covers pulse oximeters widely used to assess non-invasively arterial oxygenation in intensive care units by simple devices attached to the finger tip. Besides safety issues, it addresses instrument performances using in vivo protocols.

The second one is the ISO/IEC 80601-2-71:2015, Medical electrical equipment - Part 2-71: *Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment* [2]. It is mainly related to safety issues, with a first attempt to address some basic instrument functionality using tissue-simulating phantoms. BabyLux members took part in the work that lead to this standard as described in Section 5.1.

The path towards standardization is now advancing to cover new applications and to encompass other techniques. Although TRS is still young among clinical instruments, with just initial commercial systems – BabyLux launched to set a new grade – still the work towards performance assessment and in the long-run standardization is open. BabyLux project is contributing in this direction, as specified in Section 4, starting from the sound foundations set forth by previous large international collaborations – as described in Section 3 – quite noticeably with strong involvement of EU Institutions and support from the EU Commission.

For what concerns DCS, the situation is quite different. Compared to TRS it is less mature and there are no multi-laboratory studies on basic performance assessments. Here the path is longer, with the need to design protocols, phantoms, cross-laboratory validation to build up a sound basis for the definition of standards. BabyLux is working in this direction, with the proposal of new concepts of phantoms for DCS and testing procedures. This activity with promising results is still ongoing and not yet published. Thus, due to the public nature of the present Deliverable, it will be updated in the final Deliverable D7.5 “Report on standardization activities – final version” at month 36. Consequently, the present Deliverable D7.2 is restricted to consolidated activities for TRS.

In the following, we will first resume the foundations on performance assessment of TRS, originated mainly by strong EU cooperation, which constitutes the basis of the specific BabyLux contribution (Section 3). Then, we will present an original concept and realization of a phantom for performance assessment of brain imagers that implements the previous protocols and could serve as viable tool in future standards (Section 4). Finally, we will document the involvement of BabyLux participants in standardization committees and international consensus conferences (Section 5).

3. Overview of Protocols for TRS

In the following, we will briefly overview the 3 protocols for performance assessment of diffuse optics instruments which have been elaborated in the course of the last decade by strong international interaction, mainly at EU level. These protocols clearly identify the key features of diffuse optics instruments relevant for clinical applications. They can set the basis for deployment of practical tools for their implementation (phantom kit) and also serve for the formulation of specific standards.

3.1. BIP

The Basic Instrument Performance (BIP) protocol [3] addresses the key hardware specification of a TRS system which can impact on the outcome of a clinical measurement. The Protocol was elaborated by 7 Institutions and first tested on 8 instruments. The key tested features are:

- *source* specifications (e.g. power, wavelength, …);
- *responsivity*, i.e. overall detection efficiency for a spread Lambertian-like diffused source;
- *temporal response* (IRF), expressed in terms of full-width at half maximum and shape of the IRF;
- *differential non-linearity;*
- *afterpulsing*, that is the signal-related increase in the background;
- *stability* of the overall system.

These parameters have an impact on the clinical measurement since they affect the estimate of the optical parameters or of a focal optical change. A specific phantom was proposed and characterized to be used for the assessment of responsivity.

3.2. MEDPHOT

The MEDPHOT Protocol [4] addresses the performance assessment of diffuse optics instruments in retrieving the optical properties of a homogeneous turbid medium. The Protocol was elaborated by 5 Institutions and first tested on 8 Instruments. The instrument is treated as a black box, including also the analysis tool, and its performances are assessed against the key measurable quantities of the medium under study, which are the absorption and the reduced scattering coefficient. The following 5 parameters are identified:

- *accuracy*, i.e. discrepancy between the measured and expected optical properties;
- *linearity* of the retrieved optical properties as a function of the background absorption and scattering;
- *noise* addressing the uncertainty of the measurement;
- *stability* in the short and long term of the retrieved properties;
- *reproducibility* among measurement sessions performed in different days.

The protocol was complemented with a kit of 32 solid phantoms (a matrix of 8 absorption and 4 scattering values) which was circulated all over the world.

3.3. nEUROPt

The nEUROPt Protocol [5] addresses the Performance assessment of time domain optical brain imagers or monitor. The Protocol was elaborated by 6 Institutions and first tested on 8 Instruments. Like in the MEDPHOT Protocol, the instrument is treated as a black box, and its performances are assessed against the key measurable quantities of the medium under study. Yet, the goal is not to address the homogeneous properties of the medium, but rather the localized optical changes within an inhomogeneous environment. The Protocol is composed of 6 tests:

- *contrast*, i.e. the sensitivity to deep optical perturbations;

- *contrast-to-noise ratio* that is the capability to extract focal optical changes out of the background fluctuations;
- *lateral resolution;*
- *depth selectivity;*
- *accuracy* in retrieving absorption variations;
- *linearity* in tracking localized optical changes.

A first phantom was proposed implementing the nEUROPt protocol based on hybrid solid-liquid phantoms [6]. A further implementation based on a solid-solid approach was developed within the course of BabyLux and described in detail in the following Section.

4. Proposals of new phantom concepts applicable in standards

The assessment of a given feature of a Protocol or of a Standard for clinical instruments in diffuse optics can be obtained using a proper phantom mimicking the clinical problem under study. This approach, if proven reliable in clinical practice, can be extremely effective since it can replace expensive, time-consuming, complex and something subjective clinical tests on humans or animals. Within this scope, a new concept phantom was developed in the framework of an international collaboration with involvement in particular of PoliMi from the BabyLux Project and of the Medical Optics group of the German metrological institute Physikalisch-Technische Bundesanstalt (PTB) in Berlin [7]. The adoption of a solid-solid approach, together with an easy mechanical switch between the two operating conditions make this phantom a valuable candidate for adoption in routine tests in clinics. In the following, we will present the phantom design, followed by the phantom characterization.

4.1. Phantom Design

The new phantom is meant to implement the NEUROPT Protocol for performance assessment of Brain Imagers. It mimics a localized absorption change at the brain level, resulting for instance by a local brain hypoxia or hemorrhage. Within the assumption of a homogeneous scattering medium, only absorption changes are produces. Based on previous studies, we exploited the Equivalence Relation between realistic absorption perturbations and totally absorbing objects with a given volume. This equivalence was thoroughly validated on Monte Carlo simulations [8].

The new phantom concept is based on a solid-solid approach and is depicted in Fig. 1. A black PVC cylinder with a proper volume matching a given brain perturbation is hosted in a movable rod inserted within an otherwise homogenous diffusive medium. The injection and collection fibers of the instrument to be tested can be placed in different positions of the phantom surface. By moving the rod hosting the black object, a local optical perturbation can be produced either at a fixed depth with varying lateral offset from the source-detector axis, or beneath the source-detector couple at varying depths.

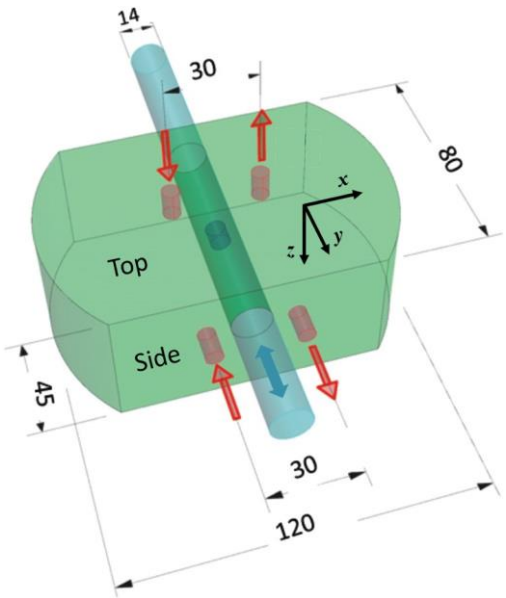

Figure 1: Schematic of the phantom.

The phantom can be equipped with an automated translation of the rod position along it axis, which adds functionality, with possible automated test procedures, and reliability to the kit. A photo of the kit is shown in Fig. 2.

Figure 2: Photo of the switchable phantom kit.

The choice of absorption perturbations over a given volume that can be reproduced are related to the volume of the black object, following an Equivalence Relations depending solely on the background scattering coefficient. As an example, in Table 1 we provide the effective absorption changes produced over a 1 cm^2 volume for a medium with a reduced scattering coefficient of 10 cm^{-1} using the black objects included in the kit.

Table 1: Equivalence table between black object and effective absorption perturbation over 1 cm^3.

diameter (mm)	length (mm)	volume (mm^3)	equivalent $\Delta\mu_a$ (mm^{-1})
3	3	21	0.05
4	4	50	0.10
5	5	98	0.17
7	7	269	0.40

4.2. Phantom Characterization

The background absorption and scattering properties of the phantom in the 600-1100 nm range are depicted in Fig. 3. The characterization was performed using a broadband workstation for time-domain diffuse optical spectroscopy [9].

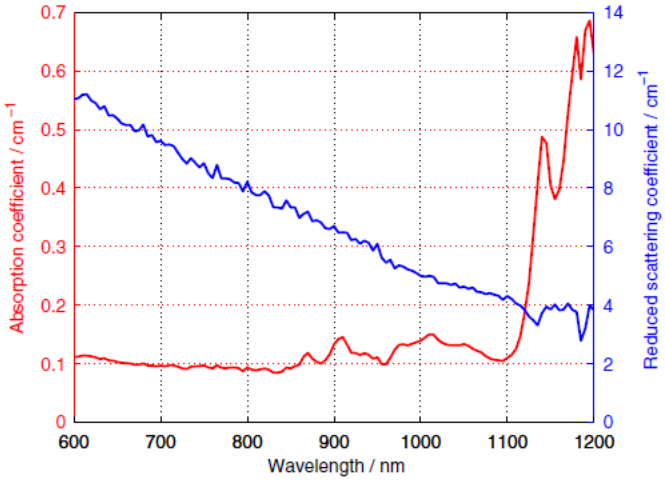

Figure 3: Absorption and reduced scattering spectra of the bulk material.

An example of the lateral scan obtained on the phantom using a TRS prototype for brain monitoring is shown in Fig. 4. The black object is translated at a fixed depth of 1.5 cm beneath the surface at different lateral locations with respect to the source-detector axis. Four inclusions are used, yielding the effective absorption perturbation described in the previous Table 1. Different panels represent the acquisition performed at increasing time-delays with respect to the injection pulse.

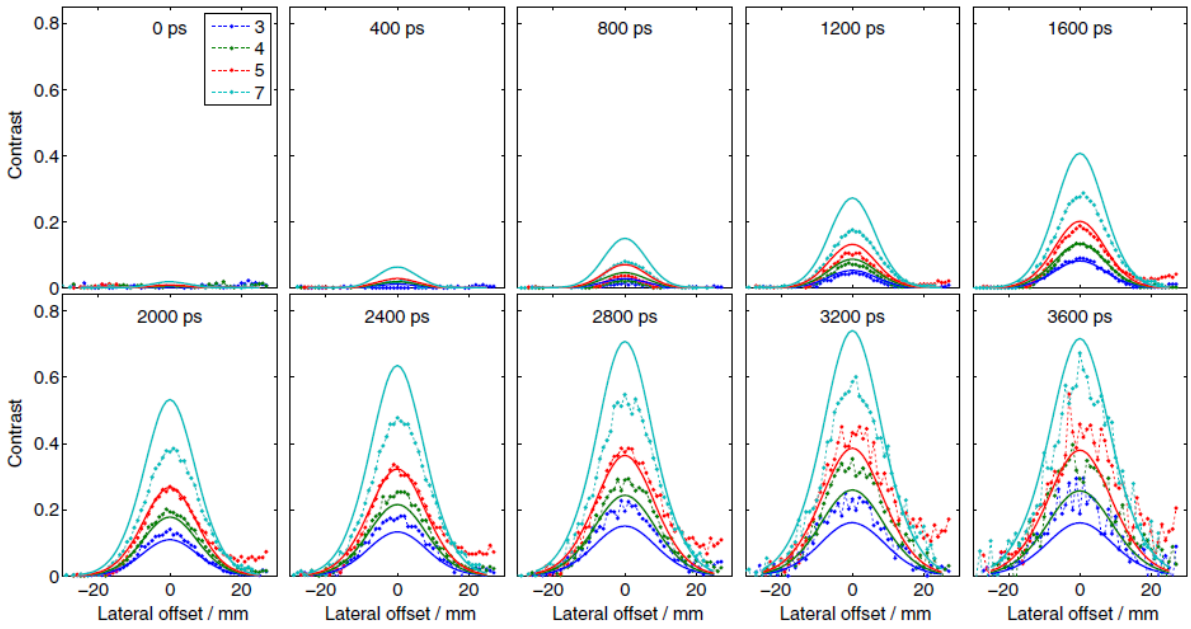

Figure 4: Lateral scan for increasing time delays.

An example of a depth scan is presented in Fig. 5. The inclusion was moving along the source-detector axis, at different depths from the surface. Increasing the time-gate of the acquisition (different panels), an increased depth sensitivity can be achieved.

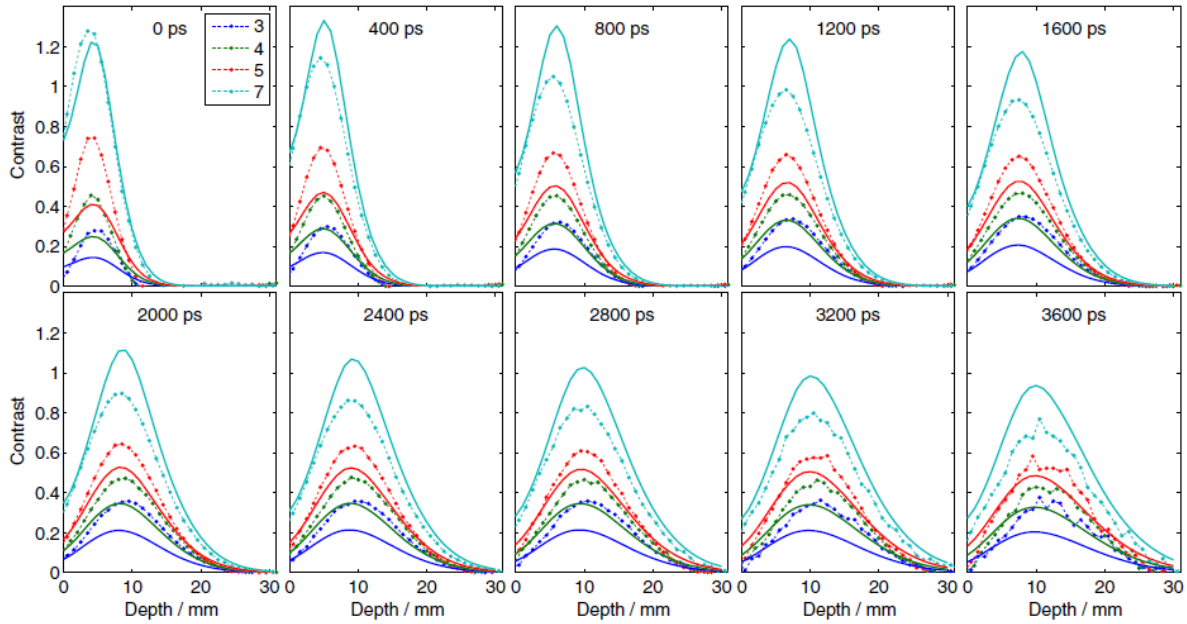

Figure 5: Depth scan for increasing time delays.

This phantom is extremely rugged, and it can be effectively used to mimic focal absorption changes at the human brain with different levels of intensity. As a possible extended use, it can also simulate optical attenuation changes for CW systems when used in transmittance geometry. Thus, it could be an alternative way to implement the specific test on signal attenuation prescribed by the standard ISO/IEC 80601-2-71:2015.

5. Contributions in Meetings and Standardization Committees

Participation to international committees and discussion panels at international levels permitted on one side to gain awareness on ongoing standardization and performance assessment processes, and on the other side to provide contributions arisen from the long-lasting experience on phantoms and instrument assessment gathered at the EU level. Specific actions are described below.

5.1. Contribution to standardization committees

Both prof.Antonio Pifferi and prof.Alessandro Torricelli served as local technical experts of the CEI Committee SC062 (local section of IEC) in the preparation of the standard ISO/IEC 80601-2-71:2015, Medical electrical equipment - Part 2-71: *Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment* [2]. In particular, their help was in strong connection with the coordinating activity of Dr.Heidrun Wabnitz from Physikalisch-Technische Bundesanstalt (PTB) in Berlin who gathered the expertise from the biomedical optics community and in particular from EU activities on performance assessment of diffuse optics instruments.

Concepts related to the phantom described in Section 4, as well as to the 3 EU Protocols described in Section 5 were presented at technical discussion tables. Although the proposed solutions were not undertaken in the final standard, being confined to purely CW instruments, yet they can be considered for future extension of the standard towards TRS systems or to new documents addressing the issue of tissue oxygenation. In addition, a contribution to the overall drafting of the standard with specific technical comments was provided.

5.2. Role at International meetings

The contribution of BabyLux to the reinforcement of the culture of standardized objective performance assessment and of quality control of diffuse optics instruments was pursued also through participation at International meetings. In particular, prof. Antonio Pifferi took part to a Conference within the framework of Photonics West 2015 – held in San Francisco, California in February 2015 – jointly organized by the National Institute of Health (NIH) and the National Institute of Standards and Technology (NIST) with the goal of gathering standardization and performance assessment initiatives for a more effective and reliable quality control of clinical trials. In that occasion, the new concept phantom for assessing deep brain changes was presented. As a consequence, an invited paper for a special issue of Journal of Biomedical Optics was requested, submitted and accepted for publication [7].

Conclusions and future work

In conclusion, within the BabyLux Project, the longstanding activity on performance assessment of diffuse optics instruments, which has been pursued at the EU level has been further advanced. This activity was founded on the 3 Protocols (BIP, MEDPHOT, NEUROPT) that have been proposed and shared at International level for the assessment of diffuse optics instruments particularly in the time-domain.

More specifically, a solid mechanically switchable phantom was developed permitting to implement the NEUROPT Protocol for performance assessment of time-resolved brain imagers using a rugged solid phantom suitable for testing in a clinical environment. Because of its reliability, this concept could be exploited in future standards.

In a parallel direction, PoliMi representatives contributed to the work leading to the ISO/IEC 80601-2-71:2015 standard on functional near-infrared spectroscopy (fNIRS) equipment. This standard is limited to CW instruments and to purely functional studies with no essential performance indicator on clinical diagnostics. It could evolve to encompass also TRS systems in future releases. Alongside, focus should be addressed also to clinically relevant parameters, and this is the goal of new ISO initiatives.

For future activities, the aim is on one side to advance with the phantom construction and characterization for TRS, also in support of existing standards, and on the other hand to complete and publish the activity on DCS phantoms to be used as tools for objective performance assessment of DCS instruments.

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