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Tissue phantoms in multicenter clinical trials for diffuse optical technologies

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Abstract: Tissue simulating phantoms are an important part of instrumentation validation, standardization/training and clinical translation. Properly used, phantoms form the backbone of sound quality control procedures. We describe the development and testing of a series of optically turbid phantoms used in a multi-center American College of Radiology Imaging Network (ACRIN) clinical trial of Diffuse Optical Spectroscopic Imaging (DOSI). The ACRIN trial is designed to measure the response of breast tumors to neoadjuvant chemotherapy. Phantom measurements are used to determine absolute instrument response functions during each measurement session and assess both long and short-term operator and instrument reliability.

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1. Introduction: phantoms are important components of clinical translation

1.1. Phantoms in the development of biomedical optics

Tissue-simulating phantoms are an important part of technology development, validation and translation. From the early years of biomedical optics, phantoms have provided controls of "known" optical properties (i.e., absorption and scattering). In the near infrared (NIR) spectral region (i.e., 650-1000 nm) phantoms must have a high level of turbidity to simulate the multiple scattering of NIR photons in biological tissues [1,2]. Phantoms can simulate tissue features by controlling the magnitude and spectral dependence of their optical properties. While tissues are assumed to be "homogeneous," more accurate geometries can be modeled. The states of absorbing molecules, such as hemoglobin [3,4] or water and lipids [5,6] can be modeled via phantoms. As optical imaging technologies move towards the clinic, groups have documented phantom use for training operators [7] and for comparing instrument performance across different imaging platforms [8]. Phantom materials and fabrication strategies for biomedical optics have been summarized in a comprehensive review [9].

In Diffuse Optical Spectroscopic Imaging (DOSI), or any diffuse optical approach (e.g., diffuse optical tomography, DOT, diffuse optical spectroscopy, DOS), instrument calibration is required. Such practices are nothing new: examples include reflectance standards for wavelength calibration or scattering solutions for phase and amplitude calibration in fluorescence lifetime measurements. For diffuse optical approaches, typically phantoms with "known" optical properties are used to remove unknown source and detector characteristics. The instrument response function (for time domain), phase offsets/amplitude scale factors (for frequency domain) or intensity variations (for multi-spatial domain) can all be assessed using tissue-simulating phantoms. However, there is no formal consensus for this calibration process; typically each instrument has its own calibration procedure and phantoms.

1.2. Use of phantoms in ACRIN 6691

Phantoms in the context of multicenter clinical trials are not only needed for calibration, but are further needed to ensure that instrument performance is maintained across multiple research sites, each with different phantoms, instruments and operators. Performance must also be documented over extended periods of time, especially in the case of longitudinal measurements on human subjects. For DOSI and related approaches, the robustness of the calibration process in light of these changing experimental conditions has not been well documented. The validity of any clinical trial depends upon instrument and operator precision, stability, and accuracy, all of which can be assessed using phantoms.

DOSI is now undergoing standardization and validation on neoadjuvant chemotherapy patients in an investigator-initiated, hypothesis-based multi-center clinical trial supported by the NIH and the American College of Radiology Imaging Network (ACRIN). ACRIN 6691 employs identical, "frozen" DOSI technology at each site and was activated on April 1, 2011. Identical DOSI platforms have been placed at Dartmouth, the University of Pennsylvania, Massachusetts General Hospital, UC San Francisco, and UC Irvine. The goal of the study is to measure breast tumor response to neoadjuvant chemotherapy, and compare the velocity of the optically-measured tumor response to the surgically-determined tumor pathological state at the conclusion of chemotherapy [10]. One of the aims of ACRIN 6691 is to establish procedures and methods for multi-center Quality Control and Instrumentation (QC/I). This aim is critical because DOSI is used at 4 time points (pre-therapy, 1 week after starting therapy, midway through therapy and at the conclusion of therapy) that span several months. In addition, data will be combined from 5 DOSI instruments, using at least 5 different operators with 5 sets of phantoms. In this paper we document our phantom construction methods and provide preliminary results on instrument calibration stability.

2. Phantoms used in the ACRIN 6691 study

2.1. Diffuse Optical Spectroscopic Imaging technology

The current clinical DOSI instrument employed in ACRIN 6691 combines frequency-domain and steady-state spectroscopies to provide quantitative broadband absorption and reduced scattering spectra from 650 to 1000 nm using a single source-detector pair [11]. The frequency-domain portion of the instrument employs multiple amplitude-modulated laser diodes at discrete wavelengths (660, 680, 785, 810, 830, and 850 nm). A network analyzer measures the phase and amplitude of the detected modulated electronic signal from an avalanche photodiode (APD) over a broad range of source modulation frequencies (401 points spanning ~500MHz). The steady-state portion of the instrument is a combination of a broadband lamp and spectrometer. A combined broadband measurement currently takes about 5 seconds to complete. The entire system is cart-based. The only component in contact with the patient is a handheld probe which contains optical fibers and the APD inside a black plastic case.

2.2. General overview of ACRIN 6691 phantom use

Each ACRIN site is required to measure 2 different tissue-simulating phantoms per clinical measurement. One set of five identical phantoms (one for each ACRIN site) was constructed by the UC Irvine team (a.k.a. the “ACRIN” phantom series). The other set of identical phantoms was the “biomimic” soft phantom which was purchased from INO (Quebec, Canada), a.k.a. the “INO” phantom series. We purchased 2 sets of 5 phantoms from INO; one set was distributed to the ACRIN sites (1 phantom per site) and the other set is a backup. Note that by working in a strongly diffuse regime at depth, scattering in our context is always meant to be the “reduced scattering” (i.e., scattering $\times (1 - g)$, where g is the anisotropy).

The use of two phantoms offers both redundancy and validation insurance [12]. For the purposes of redundancy, either the ACRIN or INO phantom can be used as calibration for tissue measurements. Both phantoms have “similar” optical properties at the six laser diode wavelengths which require the calibration. For the purposes of validation, one phantom is used as the calibration for the other to test optical property recovery. Instrument performance and operator compliance can be monitored at each clinical measurement date. The measurement protocol is built into the DOSI instrument control software. At the start of the clinical measurement, the operator measures both ACRIN and INO phantoms 3 times, each time picking up and re-placing the probe onto the phantom. These values are averaged together at each laser diode wavelength. This process is repeated after the first breast is scanned and repeated again at the conclusion of the measurement.

2.3. UC Irvine phantom construction method

Solid phantoms made at the Beckman Laser Institute contain the following four components: P4 silicone rubber base and p4 silicone activator (Eager Polymers, Chicago, IL), along with anatase titanium(IV) oxide and water-soluble nigrosin ink (Sigma-Aldrich, St. Louis, MO) for scattering and absorption features. Components were mixed together in a specific manner to achieve optimal homogeneity. First, 3.5 g of titanium(IV) oxide was stirred into 300 g of the silicone activator by hand. Next, the mixture was placed in a Branson 1200 ultrasonic cleaner (Branson Ultrasonics, Danbury, CT) for 3 hours to break apart coagulated titanium(IV) oxide particles. In a separate container, 5 mL of nigrosin solution (1.5 g/l Liter H₂O) was added to a 3000 g of the silicone base and mixed with a plunge mixer (Freeman Manufacturing & Supply Company, Avon, OH) for 5 minutes at 2000-2500 rpm. The titanium(IV) oxide suspension was then mixed into the nigrosin and silicone base mixture. The full set of components was mixed for 2 additional minutes with the plunge mixer and immediately placed into a Gas Vac II industrial vacuum degassing unit (Freeman Manufacturing & Supply Company, Avon, OH). The phantom mixture sat in the degassing chamber for approximately 2 minutes until a pressure of -29 mmHg was achieved. When the pressure reached -29 mmHg, bubbles began to collapse and the mixture was returned to normal atmospheric pressure. The mixture was

evenly divided into five identical plastic containers and all containers were returned to the degassing unit for further degassing. After a pressure of -29 mmHg was reached, the chamber was vented, the containers were removed and placed on a flat surface, and phantoms were allowed to cure for 24 hours.

2.4. Commercial phantoms

Phantoms purchased from INO were specified to have absorption and reduced scattering in the range of 0.01 mm^{-1} and 1 mm^{-1} . The phantoms were prepared from a soft polyurethane matrix. Titanium dioxide particles (mean particle size 3 μm) were added as a scattering agent. A NIR dye was added to obtain an absorption feature at 750 nm. Carbon black was further added to raise the absorption at other wavelengths. INO made the phantom dimensions the same as the “ACRIN” phantoms using a mold supplied by the UC Irvine team (Fig. 1).



Fig. 1. Setup for calibration measurement. In order to measure the same phantom volume each time, a mask was prepared to fit the phantom (left) and lock the probe in place (right).

3. Phantom optical property measurement

Standard DOSI measurements of all phantoms were initially performed at UC Irvine and subsequently at each study site with the local DOSI instrumentation. All initial phantom measurements were performed using another calibration phantom developed at UC Irvine that has been extensively characterized using a multi-distance and multi-frequency measurement protocol [13]. We note that each set of “ACRIN” and “INO” phantoms displayed nearly identical optical properties within their class ($<2\%$ variation) using this method.

The DOSI handheld probe at each study site has a “jig” that locks the source and detector separation at either 22 , 28 or 34 mm (Fig. 1). All clinical measurements were performed at 28 mm, whereas calibration was performed at 22 mm. The jig ensures consistent contact between the probe and the phantom surface and simplifies the measurement process. The molded case and probe mask surrounding the phantom ensures that the same region of the phantom is measured each time. All operators were trained by the UC Irvine team to teach proper measurement technique (see <http://acrin.bli.uci.edu/> for training manuals and videos).

4. Measurements of phantoms in the multi-center environment

4.1. Diffuse Optical Spectroscopic Imaging stability assessed by phantom measurement

Figure 2 provides stability measurements for each DOSI instrument measured over a one hour timeframe. The one hour timeframe is the typical patient measurement time in the study. For this “drift test” the probe is fixed onto a phantom for the measurement. The percent deviation of the optical properties from their mean values at each laser diode wavelength is then calculated. The laser diode wavelengths are slightly different (several nm) for each DOSI system; hence we averaged the optical property values at similar wavelengths because the phantom optical properties are not sharply-varying at these wavelengths. The data confirms

DOSI instrument stability is very high during the measurement timeframe: average absorption changed $\sim 0.4\%$ and average reduced scattering changed $\sim 0.2\%$ for all sites. Using this protocol method we detected a problem with 2 laser diodes which were subsequently repaired.

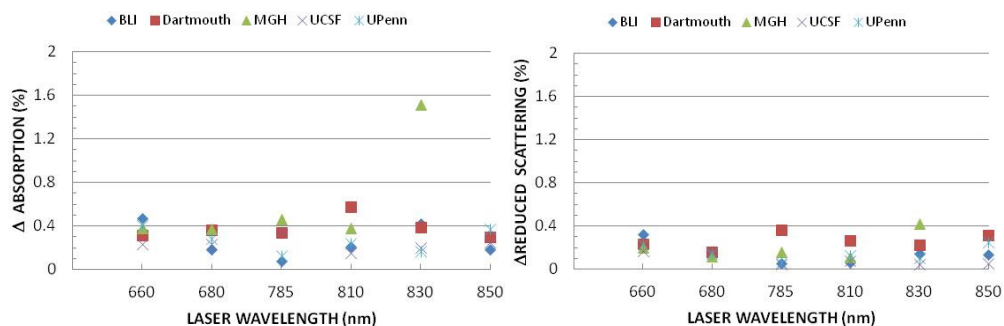


Fig. 2. Drift tests for all DOSI instruments in ACRIN 6691. The percent change in optical properties for each laser diode measured over a 1 hour timeframe is presented for absorption (left) and reduced scattering (right).

4.2. Phantom measurements performed during clinical measurements

Figure 3 provides a summary of 180 different phantom measurements performed during an 8 month period in the ACRIN 6691 study. The “INO” class of phantoms was used as the calibration and the “ACRIN” class of phantom was used as the “tissue.” The results come from 2 measurement sites (UC Irvine and Dartmouth) with the majority of patient measurements to date. The calculated variance is the standard deviation of this sample population. Only laser diode data is shown because this is the data used for the calibration of the frequency-domain portion of the DOSI instrument, which is the most critical step. Broadband optical property values will be reported in a subsequent manuscript.

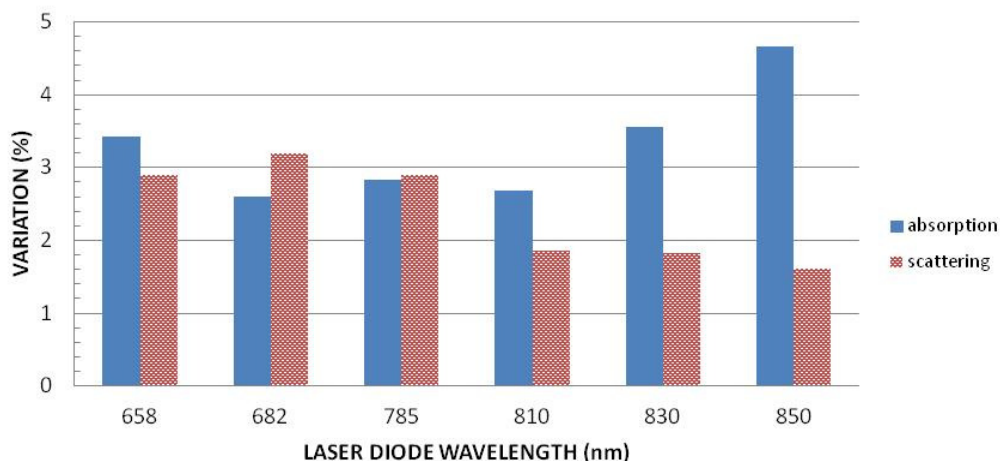


Fig. 3. Measured differences of 180 different phantom measurements at UC Irvine and Dartmouth. Overall the differences in absorption were on average $\sim 3.3\%$ and the differences in reduced scattering were on average $\sim 2.4\%$.

The results of Fig. 3 reveal that DOSI instrument performance, as assessed by inter-site and inter-operator variability in a phantom measurement task over an 8 month period, is $<5\%$. The average variation across all phantom measurements in absorption is 3.3% (max 4.7% @ 850 nm) and the average variation in the reduced scattering is 2.4% (max 3.1% @ 690 nm). A small percentage (7.7%) of measurements were not included in the analysis; these data were

rejected for not passing our S/N criterion for acceptability. In these cases the fits of real and imaginary components (i.e., phase and amplitude) versus modulation frequency were poor. More will be described about this quality control filter in a subsequent manuscript.

5. Discussion

While there are diverse choices for phantoms (matrix, absorbing and scattering agents) [9] several criteria are essential for streamlining clinical translation in a multi-center environment. We require phantoms that are stable over a defined period of time (e.g., the length of the trial). Phantoms must be simple to use and cannot rely upon chemical mixtures that are prepared for each clinical measurement. Phantoms should represent reasonable approximations to the absorption and scattering properties of breast tissues [11]. Although it would be advantageous to have similar tissue and phantom spectral shapes, this has not yet been realized in a manner suitable to the multi-center clinical environment. Thus, our phantoms do not take into account precise anatomical/spectral characteristics of real breast tissues, but instead represent bulk averages of their optical properties. In addition, our phantoms are also relatively large in size (~1 L volume) because our interest is breast imaging, and thus precise concentrations of microspheres to accurately model tissue scattering is impractical.

Our primary concern is measurement repeatability, not exact tissue feature replication. Data presented here strongly suggests that the frequency-domain calibration procedure employed for DOSI in ACRIN 6691 is precise enough for the multi-center environment. Given that these measurements were taken over the course of several months, this enhances our confidence that longitudinal multi-center measurements are possible for DOSI. There are still challenges to navigate, as evidenced by the rejection of some of the data points in our analysis. We are investigating the origins of these errors and pursuing strategies to distinguish between instrument vs. operator error during each measurement session. One way to assess this is by stability testing (e.g., Fig. 2). Our preliminary results show that there is less than 2% variation in absorption and <0.5% in scattering for 1 hour acquisitions. This suggests that using proper QC/I methods, operator error can be identified and reduced.

6. Conclusion

While this use of tissue-simulating phantoms cannot safeguard against all possible problems, proper phantom use for quality control is essential for multi-center studies. In this pilot study we have demonstrated that the frequency-domain calibration process for DOSI is stable, with less than 5% variance over the course of several instruments, operators, phantoms, and time points (~8 months). Importantly, tissue simulating phantoms allow us to reliably compare DOSI patient results during longitudinal studies across multiple sites.

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