Recommendations for a photoacoustic imaging phantom material

IPASC-PD Consensus Document - Version (DRAFT)

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This document defines essential material properties of a tissue mimicking (TMM) phantom material for use in photoacoustic imaging (PAI)/optoacoustic imaging (OAI). Phantom material properties are specified that need to be fulfilled for a PAI phantom material candidate to comply with IPASC standards. The document focuses on general material properties only, as phantom geometry and design are dictated by application and system type.

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Definitions

Table 1: Definition of relevant material properties parameters in PAI.

	Parameter	Symbol	Unit	Definition	Ref
Optical	Optical absorption coefficient	μ_a	cm^{-1}	Probability of photon absorption per unit length travelled by the photon	1,2
	Refractive index	n	-	Ratio of the velocity of light in a vacuum to the velocity of light in a medium	1,2
	Anisotropy factor	g	-	Average of the cosine of the scattering angle which represents the effects of directionally dependent scattering	1,2
	Reduced scattering coefficient	μ_s'	cm^{-1}	Probability of photon scattering per unit length travelled by the photon	1,2
Acoustic	Acoustic attenuation coefficient	α	$dB \cdot cm^{-1} \cdot MHz^{-y}$	Extent of reduction of an acoustic wave when propagating within a medium	3
	Speed of sound	c	$m \cdot s^{-1}$	Velocity of acoustic wave propagation within a medium	3
	Backscattering coefficient	μ_{bs}	$m^{-1}sr^{-1}$	Differential scattering cross section per unit volume at a scattering angle of 180◦	4
Mechanical	Density	ρ	$kg \cdot m^{-3}$	Measure of mass per unit volume	3
	Young's Modulus	E	$N \cdot m^{-2}$	Ratio of stress applied to a material to the strain that results from the stress	3
Thermoelastic	Grüneisen Parameter	Γ	-	Measure of thermoelastic efficiency	5,6

Note: Measured methods for characterizing the acoustic backscatter properties and Grüneisen Parameter of tissue or tissue-like materials are not as well-developed as techniques for other material properties. This document will be revised as progress is made in determining these quantities.

1. Scope

Phantoms are essential to establish consensus performance test methods and support future standards development in PAI, allowing quality assurance, quality control, and indirect comparison of the performance of different PAI equipment during development and marketing. Here, IPASC recommendations are outlined on material properties of a stable PAI phantom (solid and fluid) designed for device characterization and calibration purposes. A standard phantom or material may be approved by consensus after evidencing that the properties laid out herein have been achieved. A review of existing material candidates used for opto-acoustic phantom applications can be found elsewhere[7,8].

1.1 Use cases

The following use-cases of PAI phantoms made from a suitable phantom material have been identified:

- Conducting quality assurance/quality control (QA/QC) tests:
  - Verifying device specifications;
  - Technically validating device performance in controlled test-bed environments; assessing drift in accuracy and precision of the PAI device over time ("routine quality performance", or "constancy testing"); providing a "reference sample" for quality control (over time, device-to-device, and site-to-site variations);
  - Performing inter-device comparisons and benchmarking;

    - Facilitating system design optimization (hardware or software/algorithm); quantifying/assessing impact of system upgrades;
    - Comparison between different diagnostic modalities.
- Additional purposes:
    - Perform standardized biomarker readouts from multiple and distinct PA instruments;
    - Validation of research and development in photoacoustic technology;
    - User training;
    - Marketing;
    - Technical demonstrations;
    - Testing to support regulatory evaluation.

2. General material recommendations

A PAI phantom should ideally be composed of a bulk material that fulfills the following properties[9] (ranked in no preferential order):

- Defined, biologically relevant optical properties: optical absorption and reduced scattering coefficients (Annex 8.1);
- Defined, biologically relevant acoustic properties: speed of sound, attenuation (Annex 8.1);
- Safe to prepare in a laboratory environment; no expert training required for material fabrication;
- Components are widely available from commercial chemical vendors internationally, ideally with known intra- and inter-batch variation where available;
- Fabrication possible with commonly available chemical lab equipment (Annex 8.2) and basic experimental skills under protocol guidance;
- Long-term temporal stability (>6 months[5]) of optical, acoustic and mechanical properties (structural robustness and durability) in a realistic range of ambient room temperatures (18-25°C) and humidities (30-80%) to allow convenient storage across the globe;
- Short-term tolerance and maintenance of structural integrity for handling and transportation in a temperature range between 4° and 40°C based on appropriate transportation and handling procedures;
- Structural and material integrity is maintained when in contact with an aqueous medium;
- Photostable at the visible and near-infra red (NIR) wavelength range (532 nm - 1064 nm) under safe exposure limits as encountered during imaging, handling and storage.

A candidate material should evidence fulfillment of the properties outlined above as required by the target use of the phantom. Additionally, a candidate material should allow the embedding of target inclusions without their degradation to enable quantitative assessment of image quality metrics for specific applications. Ideally, the material should allow for the inclusion of targets made out of the same material type as well as of targets made out of different material types (e.g. microspheres, wires, etc.). Phantom geometry, target type, target properties, and target arrangement will depend on the application, type and configuration of the imaging system (e.g., microscopic vs macroscopic systems). The IPASC phantom development working group will provide recommendations on phantom geometrical properties and target requirements in a future consensus document.

The candidate material should ideally be accessible to everyone in the scientific community. If it cannot be procured in a “ready to manufacture” state at more than one standard scientific material supplier, its ingredients (including chemical abstract service (CAS) numbers) and detailed manufacturing process should be openly published. Reproducible fabrication should be evidenced by a multi-center study (see Section 6) to ensure that the material is accessible to the whole scientific community, achieving desired properties within acceptable uncertainty limitations (Annex 8.3).

[5] Based on typical service cycles seen in commercial photoacoustic devices on the market

3. Optical properties

QA/QC PAI phantoms require defined optical properties that are biologically relevant. In the following, the recommended optical properties are outlined that the background (bulk) material should fulfill at 800 nm (or as required by the application). 800 nm has been chosen as the defining wavelength as it approximates the isosbestic point of hemoglobin. The background material should ideally be characterized by low optically attenuating values to allow tunability for a variety of tissue types[2]:

- Absorption coefficient (μ_a): ~<0.02 cm^{-1}
- Reduced scattering coefficient (μ_s'): ~ <2 cm^{-1}

For specific applications, these values should be increased to match average optical values of the biological tissue of interest (Annex 8.1). For example, for application in breast imaging, μ_a is recommended to be at least 0.02 cm^{-1} and μ_s' to be at least 10 cm^{-1} (both ± 10%)[2] at 800 nm. Deviations from these recommendations may be made on an application specific basis.

Target inclusions should exhibit a photoacoustic response at a wavelength relevant to the target system/application. Recommended wavelengths are stated below, but the final value is device- and application-specific. Fluorescence effects of the material at these wavelengths are not considered, but phantoms should ideally not exhibit any fluorescence or other optical behaviors that reduce photoacoustic conversion efficiency.

- 532 nm (for microscopy or mesoscopic systems)
- 540 nm and 576 nm (oxyhemoglobin peaks)
- 758 nm (deoxyhemoglobin peak)
- 800 nm (isosbestic point of hemoglobin)
- 850 nm (above isosbestic point)
- 1064 nm (many systems use fundamental wavelength of Nd:YAG lasers)

Other biologically relevant properties include the anisotropy factor g, which is accounted for by the reduced scattering coefficient ($\mu_s' = \mu_s(1-g)$), and the refractive index, n (see Section 5 for characterization). Ideally, the material should exhibit forward scattering comparable to the tissue of interest, resulting in values of g >0. The refractive index n should also mimic soft tissues if possible (Annex 8.1).

4. Acoustic properties

Existing diagnostic ultrasound standards for acoustic properties of tissue-mimicking materials have been adapted to respective ultrasound imaging applications, e.g.:

- Conventional B-mode imaging: speed of sound = 1540±15 $m \cdot s^{-1}$, acoustic attenuation = 0.5 – 0.7 ± 0.05 dB $cm^{-1}MHz^{-1}$ (for frequency range 2 – 15 MHz[10,11] , due to the frequency dependence of acoustic properties).
- Continuous wave Doppler systems: acoustic attenuation = 0.5–1.0 dB $cm^{-1}MHz^{-1}$ [12].
- Blood mimicking fluids: speed of sound = 1570 ± 30 $m \cdot s^{-1}$ [13].

For PAI, the consortium proposes to include the following parameters:

- Speed of sound: The speed of sound value should preferably lie in the range of 1430 - 1550 $m \cdot s^{-1}$ [14] (for background material). This range is chosen to account for (1) the wide range of values observed in biological tissues (Annex 8.1) and (2) for the fact that PAI systems are often designed towards a specific application (e.g., a specific tissue type), thereby requiring phantom materials to have specific acoustic properties targeted towards the application of interest. The larger contributions of fat and water in common tissues of interest for PAI (e.g. breast tissue) legitimate an extension of the acceptable range towards the lower speed of sound[15]. The target speed of sound should be chosen based on literature values for the application.
- Acoustic attenuation: The acceptable range is determined to be 0.5 dB $cm^{-1}MHz^{-1}$ - 2 dB $cm^{-1}MHz^{-1}$ based on the range of acoustic properties measured in relevant human tissues[5] (Annex

8.1).

NOTE: Acoustic "attenuation" has been chosen as the parameter of interest (rather than acoustic absorption or scattering), as the key interest lies in characterizing the ability of the material to transmit acoustic waves from the target to the detector. Therefore, determining the amplitude of the losses is more important than analyzing the fate of the encountered losses.

Deviations can be argued on an application specific basis. The chosen values should be repeatable with high precision (uncertainty defined in Annex 8.3).

Further acoustic properties, such as density, ultrasound non-linearity parameter (B/A) and acoustic back-scattering coefficient or echo reduction, as well as thermoelastic properties, such as the Grüneisen parameter are not considered as mandatory parameters at this stage. If quantification of these parameters can be performed, it is recommended that the values approximate the values of the target tissue of interest (Annex 8.1). Guidance on techniques to measure the density[16], non-linearity parameter[17], the acoustic back-scattering coefficient[18], echo reduction[19] and Grüneisen parameter[6,20] can be found elsewhere.

5. Characterization of optical properties

Optical properties should be verified through spectrophotometric characterization. Various methods have been proposed for optical property measurements. Some recommended approaches include (ranked in no preferential order):

- Integrating sphere (such as single or double integrating spheres) setups that measure total transmittance and diffuse reflectance of samples[21,22];
- Time resolved diffuse optical measurement systems[23];
- Spatial frequency domain imaging (SFDI)[24];
- Frequency domain photon migration (FDPM) measurements[25];
- Fiber-optic diffuse reflectance measurements[26].

For the optical measurement technique of choice, sufficient characterisation and calibration data should be given to provide confidence in the measurement results (e.g., by including open port measurements for integrating sphere measurements at same exposure times and stabilized light source). The temperature at which the characterisation measurements were performed should be reported (preferably at room temperature [18-25°C]). Estimated values for the refractive index *n* and anisotropy factor *g* should ideally be given alongside the reduced scattering and optical absorption coefficient.

6. Characterization of acoustic properties

Well-established approaches for measuring acoustic properties include:

- Through-transmission techniques[27];
- Pulse-echo techniques[28].

Further details on how to characterize the acoustic properties are given elsewhere[19]. Characterisation measurements should be performed at room temperature (18 - 25°C), with validated corrections being applied for measurements made outside of this range. For reporting of measured values, the frequency range of the transducers used to perform acoustic characterization of material samples needs to be stated. Moreover, the method for extraction of the acoustic properties from the data needs to be detailed (or referenced). *NOTE: Stating the exact characterisation method is necessary, since, due to dispersion, a single 'sound speed' does not exist. Different measurement approaches may measure different 'sound speeds', e.g., time-of-flight picking that focuses on the first arrival of a pulse will measure the signal velocity; time-of-flight picking that focuses on the peak of a pulse envelope will measure the group velocity; taking the Fourier transform of a pulse and using the phase will extract the*

frequency-dependent phase velocity. Fourier techniques are particularly useful as they allow the frequency dependent properties (both speed of sound and attenuation) of the TMM to be determined over a broad frequency range[29,30].

7. Requirements for validation study

If the TMM material cannot be obtained from a commercial supplier that can certify its properties, it is recommended to conduct a multi-center study to verify the compliance of a material candidate with the aforementioned requirements. This ensures that the candidate material can be reproduced and characterized reliably using a provided protocol.

The following requirements must be fulfilled by such a study:

- Three batches of the material should be repeatedly (n≥3) manufactured by ≥3 independent institutions to enable statistical analysis. Optical (reduced scattering coefficient and optical absorption coefficient) and acoustic properties (speed of sound and acoustic attenuation) of the resulting material batches shall be verified by at least two institutions. Variations of the phantom properties should fall within the specified acceptance ranges (Annex 8.3).

8. Annex

8.1 Acoustic and optical properties of soft tissues

Table 1: Overview of representative acoustic and optical properties found in soft tissues. Optical properties cover a spectrum from 600 to 900 nm. For values outside this wavelength range, please refer to the literature[2].

Tissue type	**Acoustic properties**		**Optical properties**		**Ref**
	c ($m \cdot s^{-1}$)	**α ($dB \cdot cm^{-1}$) at f(MHz)**	**μ_a (cm^{-1})**	**μ_s' (cm^{-1})**	
Soft tissue	1450–1575	0.5–30 at 1-10 MHz	0.1–0.5	10–20	[8,11]
Breast fat	1430–1480	1–18 at 1-10 MHz	0.05–0.4	3–8	[8,11]
Breast parenchyma	1460–1520	2–25 at 1-10 MHz	0.1–0.3	5–15	[8]
Blood	1560-1570	0.1-0.2 $dB \cdot cm^{-1} \cdot MHz^{-1}$	2.0–10.0	10–15	[2,31,32]
Brain	1550	0.6 at 1 MHz	0.2–9	8–90	[32–34]
Liver	1510–1590	0.5-0.9 $dB \cdot cm^{-1} \cdot MHz^{-1}$	1.15–1.56	22–30	[2,31,35]
Prostate	1614	1.86 $dB \cdot cm^{-1} \cdot MHz^{-1}$	0.05–0.72	1–40	[2,32]
Skin	~1600	2-4 $dB \cdot cm^{-1} \cdot MHz^{-1}$	0.05–1.11	2–21	[2,32,35]
Muscle	1540-1580	1.3 – 3.3 at 1 MHz	0.05-0.17	6-10	[2,31]
Tendon	1670	4.7 $dB \cdot cm^{-1} \cdot MHz^{-1}$	*		[32]
Water	1480	0.0022 at 1 MHz	0.006-0.07	0.003	[32,36]

*****No specific reference found.

Table 1: Summary of average values of tissue properties relevant in PAI.

	Parameter	Symbol	Unit	Range in soft tissue*	Ref
Optical	Optical absorption coefficient	μ_a	cm^{-1}	0.1 - 0.5	[1,2]
	Refractive index	n	-	1.33 - 1.51	[1,2]
	Anisotropy factor	g	-	0.7 - 0.9	[1,2]
	Reduced scattering coefficient	μ_s'	cm^{-1}	10 - 20	[1,2]
Acoustic	Acoustic attenuation coefficient	α	$dB \cdot cm^{-1} \cdot MHz^{-y}$	0.1 - 1.6	[34]
	Speed of sound	c	$m \cdot s^{-1}$	1450 - 1730	[34]
	Backscattering coefficient	μ_{bs}	$m^{-1} \cdot sr^{-1}$	3.5×10^{-4} - 9×10^{-4}	[4]
Mechanical	Density	ρ	$g \cdot cm^{-3}$	0.95 - 1.15	[34]
	Young's Modulus	E	$N \cdot m^{-2}$	1×10^{2} - 1×10^{6}	[37]
Thermoelastic	Grüneisen Parameter	Γ	-	0.25 - 0.9	[5,6]

Note 1: These are just representative values. See literature for values that pertain to specific samples and controls. The properties may vary with the experimental conditions.

Note 2: Acoustic properties are temperature-dependent.

8.2 List of basic laboratory equipment

Table 2: List of general laboratory equipment for phantom fabrication.

Fabrication step	Equipment examples
Mixing	Bath sonicator, vortex, (blade) mixer, mechanical stirrer
Heating	Hot plate, oven, heating bath, heating mantle
Weighing	Electronic laboratory scales / scientific balances
Handling	Glassware
Vacuuming	Vacuum oven, vacuum chamber, Vacuum Pump
Personal protection	Lab coat, googles, gloves

8.3 Accepted uncertainty of phantom properties

The temporal variation/stability of the material properties should be determined under prescribed characterization and material storage conditions. Properties should ideally remain stable for a time-period of at least six months. Accurate and precise assessment of material properties requires detailed knowledge of the characterisation systems and, in particular, an assessment of the uncertainty associated with each characterisation measurement. The criteria employed for stability should be explicitly stated for each test, but it will typically involve any drift in the parameter being less than 2 x the accepted uncertainty figure. At present, we only provide guidance on uncertainty for acoustic properties (Table 3). The measurement of optical properties in turbid samples with high accuracy and precision is more challenging, and uncertainty values will highly depend on the measurement technique used[9,21,38] and the final properties of the phantom. For this reason, users are advised to adapt the optical uncertainty limits as appropriate to their final application.

Table 3: List of accepted uncertainty ranges for acoustic properties.

The uncertainty values align to IEC 61391-1:2017. Please note that the values only act as rough benchmark numbers providing general guidance (Coverage factor k=1).

Parameter	Accepted uncertainty
Acoustic attenuation coefficient α	±7%*
Speed of sound c	±1%*

*within a ±1.5 MHz bandwidth

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