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Hierarchical materials based on polydimethylsiloxane as tissue-like phantoms for photoacoustic imaging and diffusive optics

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ABSTRACT

The rise of multimodal imaging and treatments, particularly with optical tools, promises to make a disruptive impact on clinical problems such as cancer and infectious conditions, especially in critical sites like the lungs. However, ethical concerns and the high costs of using lab animals represent significant barriers in the early stages of development. In this context, significantly enhancing the relevance of multimodal phantoms for unbiased technical specification validation within a controlled lab setting may constitute a major advancement. Here, we propose a concept of hierarchical manufacturing as an approach to encode multiple mechanisms of physical contrast based on water-in-elastomer micro-emulsions made of a continuous phase of hydrophobic polydimethylsiloxane and micro-droplets of hydrophilic solutions. Specifically, we investigate the potential to engineer the overall morphology of the ensemble to mimic the intricate anatomical structure of complex organs, such as the unique porosity of lung tissue. Concurrently, we aim to precisely control the optical properties of the system in critical scenarios, such as enabling the recreation of diverse skin tones and varying levels of vascularization in relevant applications. We believe that a hierarchical approach to fabricating anatomical phantoms represents a robust and adaptable alternative to animal models in the early stages of translational research involving hybrid or multimodal imaging techniques. This approach will prove particularly valuable in developing artificial intelligence solutions for emerging modalities like photoacoustic imaging, which face fundamental challenges due to the limited availability of accurate ground truth data from animal studies.

Keywords: Anatomical phantoms, agarose hydrogel, PDMS, Porous elastomers, Optical spectroscopy

1. INTRODUCTION

The rise of multimodal imaging and treatments, particularly involving optical technologies, promises to make a disruptive impact on clinical problems such as cancer and infectious conditions. However, the need for extensive use of lab animals from the outset of the development of highly innovative methods represents a significant obstacle due to an interplay of technical, ethical and financial considerations.

In this context, increasing the relevance of anatomical phantoms is crucial. These phantoms should accurately and comprehensively encode multiple biophysical features to enable an impartial validation of the technical specs of interest.[1–3] This will facilitate their routine use in lab settings and play a strategic role in research and development.

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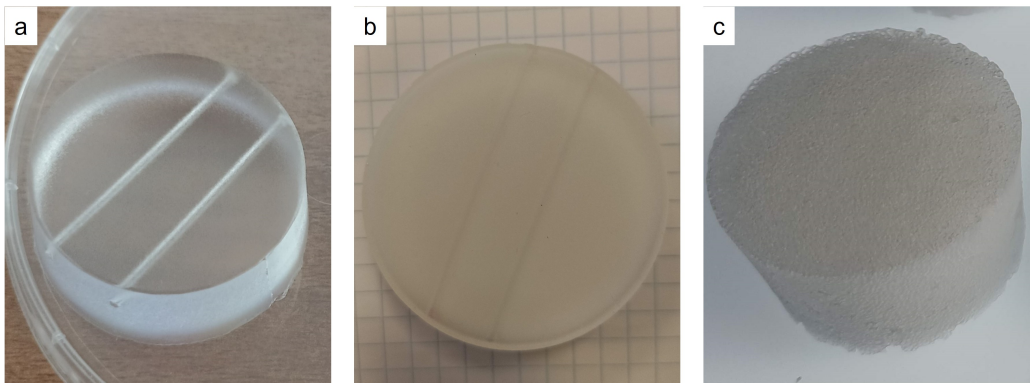

Figure 1. Photograph of a) a pure PDMS block, b) an example of Agarose@PDMS block, and c) an example of Agarose@PDMS sponge.

Here, we propose a hierarchical manufacturing approach to encode multiple mechanisms of physical contrast based on an innovative building block centred on water-in-elastomer micro-emulsions. These micro-emulsions are made of a continuous phase of hydrophobic polydimethylsiloxane (PDMS) and micro-droplets of hydrophilic solutions. These hydrophilic solutions are designed to accommodate various dyes and other contrast agents in a physiological environment.[4–6] This composite material inherits some properties from the elastomeric matrix, such as the speed of sound and acoustic attenuation coefficient, some from the hydrophilic inclusions, such as the optical absorbance, and some from their overall ultrastructure, such as the intensity of optical scattering.

We focus in particular on the possibility to tailor the overall morphology of the ensemble to mirror the anatomical features of various organs. We investigate two complementary scenarios of topical interest within the broader field of medical applications: skin and lung.

For skin, by precisely tuning the optical and thermodynamic properties of our materials, we aim to develop tissue models that take into account the variety of tones and levels of vascularization. These models will be invaluable for the development and assessment of optical methods such as photoacoustic imaging or pulse oximetry, ensuring inclusiveness in their design and performance.[7,8]

Furthermore, we aim to replicate the characteristic porous structure of lung tissue by repurposing the technology for fabricating PDMS sponges to obtain phantom materials. PDMS sponges fabricated by casting the polymer precursor onto a water-soluble sacrificial template have demonstrated significant promise in diverse fields such as water purification, flexible electronics, and energy technologies.[9] Significantly, these materials demonstrate a porosity of around 80%, resembling that of the lungs, and possess a pore size on the order of 100 micrometers, comparable to the dimensions of alveoli. By incorporating elastomers and hydrogels to represent extracellular and cellular compartments and establishing an interconnected network of pores, we aim to develop a more accurate and physiologically relevant lung model, also suitable for testing optical methodologies.

2. RESULTS AND DISCUSSION

We focus on optimizing a novel composite material consisting of an emulsion of hydrogel particles within an elastomeric monolith (PDMS). Our approach leverages two independent existing technologies: a general one for the formation of water-in-oil emulsions adapted to the case of agarose hydrogel in PDMS (Agarose@PDMS) and another for the fabrication of sponges with a PDMS frame.

Detailed experimental procedures are outlined in Ref. 10. Briefly, the Agarose@PDMS emulsion is prepared by dissolving 2% agarose in deionized water with 0.02% Triton X at 100°C. This solution is then mixed with a 1:1 mixture of hexane and PDMS base (mod Sylgard 184) at 37°C and emulsified. After hexane evaporation, the PDMS curing agent is added (10% of PDMS base), and this mixture is put into a vacuum chamber at room temperature for at least 30 min. Subsequently it is cured in the desired mold at 37°C for another 48 hrs.

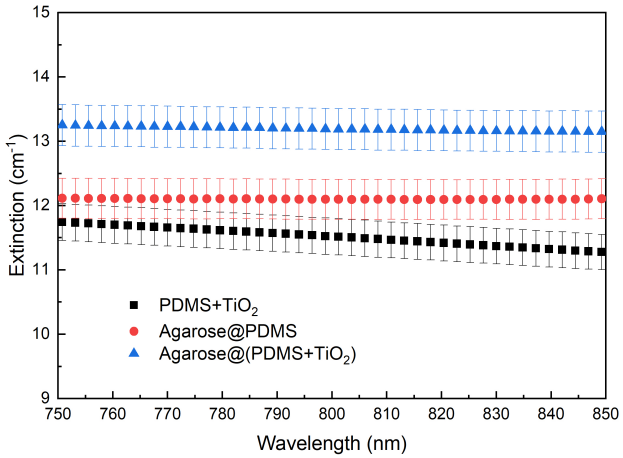

Figure 2. Experimental spectra of optical extinction, i.e. absorbance plus scattering, of PDMS+TiO_2 sample (black squares), Agarose@PDMS sample (red circles), and their mixture Agarose@(PDMS+TiO_2) sample (blue triangles).

Fig. 1 illustrates the distinct appearance of the resulting Agarose@PDMS system (b) compared to pure PDMS (a). The milky appearance of the Agarose@PDMS emulsion is characteristic of similar systems, such as those incorporating glycerol[4,5] or polyvinyl alcohol (PVA)[6] instead of the hydrogel used in this work.

To assess the potential for fine-tuning optical scattering, we compared the extinction spectra of the Agarose@PDMS system with that of PDMS mixed with TiO_2 powder (PDMS+TiO_2), which is a common standard for phantom materials.[11–13] PDMS+TiO_2 was prepared by incorporating about 1.6% TiO_2 powder (anatase, Sigma-Aldrich, CAS number 1317-70-0) into the PDMS curing agent. Extinction spectra were measured using a spectrophotometer (model Jasco V-770 UV-Visible/NIR).

The results are reported in Fig. 2. Both systems exhibited comparable optical extinction values within the range 750-850 nm, relevant for biomedical applications. However, in contrast to the wavelength-dependent scattering exhibited by the PDMS+TiO_2 system, the Agarose@PDMS alternative displayed a more consistent and uniform extinction profile.

When the two systems were mixed in a 50:50 ratio (Agarose@(PDMS+TiO_2), blue triangles in Fig. 2, a significant increase in overall extinction was observed, suggesting a change in the structure of the mixture that warrants further investigation.

Finally, we produced PDMS-based sponges following the protocol reported in Ref. 10.

Existing methods often employ sacrificial templates like sugar or salt,[14] which are dissolved in warm water after curing. Nonetheless, in our case, the high affinity exhibited by these templates for the agarose hydrogel necessitates the exploration of alternative methodologies to circumvent the coalescence of the functional droplets within the sacrificial component. In an attempt to introduce a water-insoluble porogen, a protocol employing sub-millimeter sized wax beads was devised.

Briefly, we mix the above water-in-oil emulsion (1 part), PDMS curing agent (10% of PDMS base), and wax granules (2 to 3 parts) with a spatula, and cure the mixture at 37°C for at least 2 days. The wax template is then removed by immersing the cured mixture in a vegetable oil bath at 65°C for at least five times. The sponges are then washed in an aqueous solution of a detergent such as Mucasol, followed by abundant rinsing with deionized water. The rinse water is finally expelled by gentle squeezing and left to dry for a couple of days.

In Fig. 1c an example of PDMS-sponge prepared in this way is shown. The resulting PDMS sponge exhibits high elasticity and compressibility, closely mimicking the mechanical properties of lung tissue.

3. CONCLUSION

In conclusion, we propose a hierarchical approach to fabricating anatomical phantoms as a versatile model to replicate different tissues, such as skin and lung. This system enables the seamless integration of hydrophilic and lipophilic materials, facilitating the creation of complex phantoms. It also provides a foundation for future incorporation of living elements, enhancing the biological relevance of these models.

We posit that this technology may garner widespread acceptance as a robust, resilient, and rigorous alternative to the utilization of lab animals in the early phases of translational research involving hybrid or multimodal imaging methodologies, such as ultrasound/optical/photoacoustic modalities. This approach holds the potential to substantially facilitate the development and validation of novel imaging techniques, as well as their augmentation with artificial intelligence-driven reconstruction algorithms.

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