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A composite hydrogel for brain tissue phantoms

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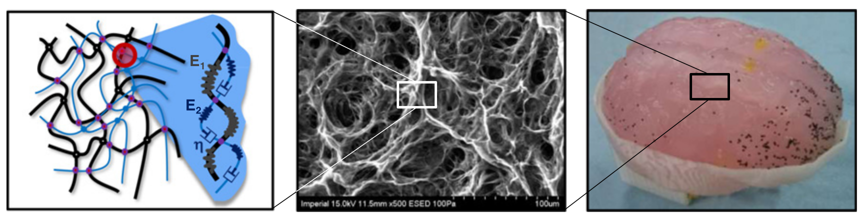
HIGHLIGHTS

- Design and development of a composite hydrogel to mimic brain tissue
- Testing, material characterisation and comparison with brain tissue
- Manufacturing and testing of life-size phantom
- Optimisation of mechanical response of the composite hydrogel

GRAPHICAL ABSTRACT



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ABSTRACT

Synthetic phantoms are valuable tools for training, research and development in traditional and computer aided surgery, but complex organs, such as the brain, are difficult to replicate. Here, we present the development of a new composite hydrogel capable of mimicking the mechanical response of brain tissue under loading. Our results demonstrate how the combination of two different hydrogels, whose synergistic interaction results in a highly tunable blend, produces a hybrid material that closely matches the strongly dynamic and non-linear response of brain tissue. The new synthetic material is inexpensive, simple to prepare, and its constitutive components are both widely available and biocompatible. Our investigation of the properties of this engineered tissue, using both small scale testing and life-sized brain phantoms, shows that it is suitable for reproducing the brain shift phenomenon and brain tissue response to indentation and palpation.

1. Introduction

Surgeons are required to reach high standards and perform complex technical tasks in a short training period [1]. However, early in their career, trainees are not given the opportunity to operate on a sufficient number of patients, nor to perform an exhaustive mix of procedures. The reduction of assisted training hours in Europe (since 2009) and the USA (since 2011), along with a growing attention on patient safety [2], have further worsened this scenario. Cadaveric training is still considered the gold standard in order to achieve technical proficiency [3], as it provides details on the anatomical structures and their positions, practice on skin incisions and tactile feedback. However, an absence of specimens, ethical issues, and high costs of handling, storage and preservation of the tissue all contribute to offsetting the advantages of this method. Animal models are cost effective, and they are characterised by a certain degree of realism owing to the presence of soft tissue [4]. On the other hand, they are not free of drawbacks. For example, anatomic structures are often different from human specimens to an extent which depends on the combination of organs and animals. Ethical restrictions are also involved in the utilization of the samples, and specific equipment requirements must be met when handling and testing animal tissues.

Haptic virtual-reality simulators are used to overcome the drawbacks of animals and human specimens. Recent advances in computer graphics have made it possible to design simulators with a level of fidelity that makes it possible to reproduce real surgical environments. Simulations such as these may be used for training in minimally invasive procedures (MIP), such as laparoscopy and endoscopy, but their ability

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to accurately reproduce complex, dynamic interactions is questionable. Additionally these systems are expensive [5], the transfer of simulator-based skills to the real operating theatre remains doubtful [6,7], and the number of procedures available for simulation-based training is limited.

Phantoms are reproductions of human parts and organs that allow a trainee to practice positioning of anatomical structures, as well as hand-eye coordination. In addition, the applicability of reliable synthetic organs extends well beyond training purposes, as they can be employed in, for example, prosthesis design, design and testing of robotic aided surgery systems, impact tests and traumatic injury analysis. Furthermore, if the phantom material is biocompatible, it can be used for bio-implants [8–11] and tissue development [12–16]. In fact, in specific cases, cell differentiation and regeneration is promoted in scaffolds that exhibit mechanical properties similar to those of the real tissue [12–16]. Although the impact of successfully designing advanced bioengineered materials that are able to mimic the mechanical behaviour of native tissues is evident, this is not a straightforward task, especially when the aim is to reproduce the behaviour of organs.

Some human tissues, like the brain, present non-linear elastic mechanical responses, in addition to rate-dependent characteristics [17] (*i.e*. the tissue stiffness changes depending on the strain/displacement-rate). This behaviour is due to the interaction between the cerebrospinal fluid (CSF) and the solid matrix of the tissue, as well as the viscoelastic properties of the solid matrix itself [18]. For this reason, the brain deforms differently during trauma (fast rate), indentation and palpation (medium rate), and brain shift (slow rate) phenomena. In particular, brain shift is a non-rigid deformation occurring during surgical procedures when a craniotomy is performed. Due to changes in the boundary conditions, the brain starts to "shift" along the direction of gravity. The loss of CSF during surgery, and consequentially of buoyancy forces surrounding the brain, is recognised as the main cause of brain shift [19,20]. It has been shown that brain can shift up to two centimetres in a non-rigid fashion [21]. This introduces a non-negligible error in target location, which would results in loss of accuracy if not accounted for. Conventional phantom materials are not designed to mimic such a complex response, and thus the research aimed at identifying suitable natural and synthetic compounds that are capable of achieving this task is of immediate significance.

A number of strategies and material candidates for brain phantom fabrication are available in the literature, although to-date the attention has been focused mainly on drug delivery and near-infrared spectroscopy [22–24]. In the last decade, synthetic materials such as Agarose gelatine, Sylgard 527 silicone gel, Hyaluronic Acid (HA) and Polyvinyl Alcohol (PVA) have been developed for soft tissue mimics; these recent efforts are briefly reviewed here. Cloyd et al. [25] analysed a composite gel produced with Agarose, Alginate and HA for human nucleus pulposus measuring compression peaks of about 4000 Pa at 0.05/s strain rate for 25% deformation; however, this value is considerably higher than the experimental results shown by Miller [17] for porcine brain samples. De Lorenzo et al. [26] used Sylgard 527 (Dow Corning, USA) as synthetic surrogate of brain tissue, designing a brain phantom and evaluating the deformations predicted by their novel simulation algorithm. However, no experimental evidence was provided for the characterisation of the mechanical properties of the gel. The same gel was also used by Brands et al. [27] to compare its mechanical properties with the brain tissue. A rheometric analysis revealed that the gel exhibited linear viscoelastic behaviour for strains up to 0.5 and frequencies up to 460 Hz; this is far from capturing the established characteristics of brain tissue. Dumpuri et al. [20] used PVA at 7% concentration to validate the fidelity of their constrained linear inverse model but no detailed material studies are reported in their contribution in order to compare the mechanical properties and loading response of the synthetic material and brain tissue.

The present contribution focuses on the design of a brain phantom made of a novel composite hydrogel (CH) that can reproduce the dynamic mechanical response of brain tissue, providing an accurate mimicking of the organic tissue at different displacement rates and for different loading conditions. Taking advantage of the hybrid mechanical capabilities of binary polymer blends, we generate a novel porous composite hydrogel (see Methods for more details about the CH composition and fabrication). The strategy adopted by the authors relied on the identification of individual components whose properties could be combined to form a stable coupled network with porosity, elastic and viscoelastic properties representative of brain tissue. Testing and characterisation of a number of individual compounds led to the realisation of a superior construct obtained by combining the elastic characteristic of PVA and the viscoelastic response of Phytagel (PHY). The gel is simple to prepare and its components are widely available, inexpensive and biocompatible [28–33]. By means of molecular bindings a coupled binary network is synthesised [34], which guarantees that the mechanical characteristics of the synthetic material can be easily tuned. The result is a non-linear hyper-elastic, rate-dependent material suitable for reproducing the tissue dynamic mechanical behaviour, as demonstrated in the following section. The adaptability of the CH in terms of reproducing the mechanical response of brain tissue is also demonstrated by a further tuning process that allows the material to reproduce brain tissue cutting for surgical applications. Preliminary studies of the puncturing resistance of the CH have also been presented in [35].

Finally, we study the behaviour of a life-sized human brain-skull phantom, and describe its manufacturing process. This is the first synthetic replica of a human brain that provides an accurate reproduction of geometric features and a reliable dynamic response. Furthermore, the loss of CSF can be regulated by a dedicated draining system, enabling the experimental simulation of the brain shift phenomenon in a laboratory.

2. Methods

2.1. Sample preparation

PVA (146,000–186,000 molecular weight), PHY and deionised water were supplied by Sigma-Aldrich, USA. Sylgard 184 and 527 were provided by Dow Corning, USA. Gelatine powder was provided by Dr. Oetker, Germany. All the concentrations in the following sections are expressed as a percentage by mass (wt%). Samples of porcine brain were provided by a local supplier within 24 h post-mortem.

PHY is a high strength, water-soluble tetrasaccharide generically used as gelling agent in plant and microbiological culture. PHY powder (concentration 2.2%) was dissolved in deionised water under constant stirring. The solution was progressively heated to 90 °C, under which complete and homogeneous dispersion of the material was obtained after 30 min. The samples were stored at room temperature for 24 h before testing.

Gelatine gels are frequently used in the food industry to thicken and stabilise various products such as desserts, yogurts, candies and jellies. Gelatine gels were produced by mixing deionised water and beef gelatine in powder form at 90 °C for 5 min under vigorous stirring at 5 and 10% concentrations. The solution was then poured in Petri dishes and allowed to cool down to reach room temperature. Afterwards the samples were stored for 18 h at 13 °C before testing.

PVA is a non-toxic, hydrophilic, synthetic polymer recently introduced in tissue engineering for its biocompatibility [36]. PVA was dissolved in deionised water at 90 °C for 1 h under vigorous stirring at 7 and 15%concentrations. The dissolving time normally varies with the concentration adopted. The solution was then poured in Petri dishes and allowed to cool down to room temperature. The samples were then stored for 18 h at −25 °C and subsequently thawed for 6 h before testing.

Sylgard 184 (also known as PDMS) is a silicone elastomer that has been extensively used as casting material for soft lithographic replications. The elastomeric part and curing agent were mixed together in a 10:1 ratio and cured at room temperature for 24 h before being tested.