What Does a Brain Feel Like?

Zhengchu Tan,*[1] James P. Ewen,*[1] Antonio E. Forte,[2,3] Stefano Galvan,[1] Elena De Momi,[3] Ferdinando Rodriguez y Baena,[1] Daniele Dini[1]

1 - Department of Mechanical Engineering, Imperial College London, South Kensington Campus, Exhibition Road, London SW7 2AZ, U.K.

2 - John A. Paulson School of Engineering and Applied Sciences, Harvard University, 29 Oxford Street, Cambridge, Massachusetts 02138, U.S.A.

3 - Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan 20133, Italy.

* j.ewen@imperial.ac.uk, zhengchu.tan11@imperial.ac.uk

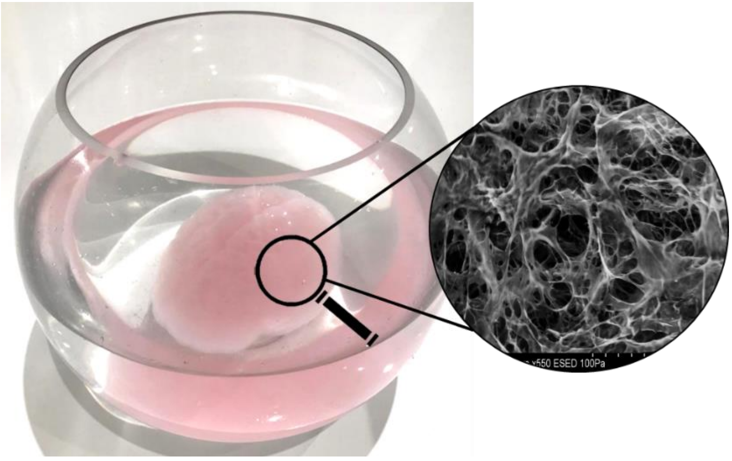
Abstract

We present a two-part, hands-on science outreach demonstration utilising composite hydrogels to produce realistic models of the human brain. The blends of polyvinyl alcohol and Phytagel closely match the mechanical properties of real brain tissue under conditions representative of surgical operations. The composite hydrogel is simple to prepare, biocompatible, non-toxic, and the required materials are widely available and inexpensive. The first part of the demonstration gives participants the opportunity to feel how soft and deformable our brains are. A second part allows students to perform a mock brain surgery on a simulated tumour. The demonstration tools are suitable for public engagement activities as well as for various student training groups. The activities encompass concepts in polymer chemistry, materials science, and biology.

Keywords

Demonstrations, Public Understanding/Outreach, General Public, High School/Introductory Chemistry, Hands-On Learning/Manipulatives, Polymer Chemistry, Materials Science

Graphical Abstract



Introduction

Hydrogels are a group of polymeric materials that can swell to absorb huge amounts of water. They are formed through the cross-linking of hydrophilic polymer chains, resulting in three-dimensional polymer networks.[1] Hydrogels are 'smart' materials that are able to respond to the environment and have been used in a variety of areas ranging from pharmaceuticals to biotechnology[2], most notably as pH responsive drug delivery mechanisms.[3] Applications of hydrogels that many of us encounter every day include soft contact lenses[4] and wound dressing.[5]

Much like our own bodies, hydrogels are mostly made of water and can be highly viscoelastic, that is they exhibit both viscous and elastic characteristics when they are mechanically deformed.[6] As a result, hydrogels are ideal materials to use as surgical phantoms, since they have similar mechanical properties with a range of organic tissues.[7,8] Phantoms are reproductions of human parts and organs that allow trainee surgeons to practice positioning of anatomical structures and hand-eye coordination.[9] They can also be used in prosthesis design, testing of robot-aided surgery systems, impact tests, and traumatic injury analysis.[9] If the phantom material is biocompatible, it can also be used for implants[10], tissue engineering[11] and drug delivery.[12]

Gelatin is a common hydrogel used to simulate organs for surgery and blast injury scenarios due to its ability to mimic the stiffness of soft tissues.[13] Previously, gelatin has been used as a surgical brain phantom despite the surgical tool penetration and cutting forces being much higher than what is experienced with real brain.[14] Composite hydrogels, which consist of a mixture of different polymers, can provide greater control of different mechanical responses, for example the stiffness can be modulated independently from the fracture strength, and can therefore drastically improve their tissue mimicking accuracy.[10]

Recently, we have developed a composite hydrogel that closely matches the mechanical response of brain tissue.[9] It consists of a blend of polyvinyl alcohol (PVA) and Phytagel (PHY), which is also known as gellan gum. PVA is formed from the vinyl acetate monomer, which is also commonly used in white craft glue. PHY is a high strength, water-soluble tetrasaccharide that is used as a gelling agent in plant and microbiological cultures.[15] The molecular structures of the PVA and PHY repeat units are shown in Figure 1.

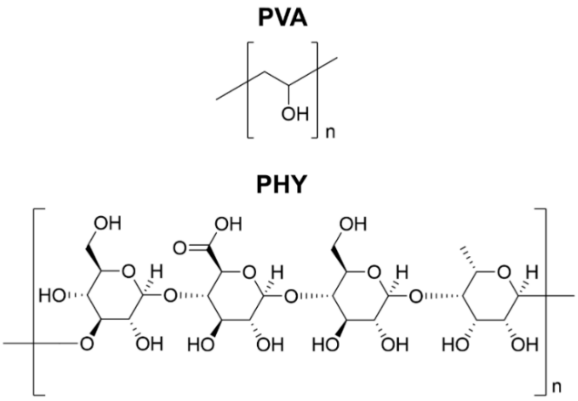


Figure 1. Molecular structures of polyvinyl alcohol (PVA) and Phytagel (PHY) repeat units.

By exploiting the hybrid mechanical capabilities of binary polymer blends, we produced a composite hydrogel with similar porosity, elastic, and viscoelastic properties to those of brain tissue. We used the composite hydrogel to create a life-sized phantom of an adult human brain, as shown in Figure 2a. Previous applications of PVA-PHY composite hydrogels include drug delivery[16] and tissue regeneration.[11] PVA creates a porous solid network that provides the stiffness (see Figure 2b), while PHY enables realistic rate-dependent properties.[9] Tuning the PVA and PHY ratios allowed us to create a composite hydrogel that mimicked brain tissue at different displacement rates and for different loading conditions.[9] No external cross-linking agents were used during the synthesis procedure. Therefore, the interactions between the two polymer networks are not expected to be due to chemical bonds, but rather physical hydrogen bonds between the OH groups of neighbouring PVA and PHY chains,[9] as shown in Figure 2c-d. The synthesis procedure can also be modified to create a transparent composite hydrogel that can be used for non-invasive optical measurements within the samples.[14] The composite hydrogel has also been successfully used as ink in a 3D-printer to produce porous scaffolds for tissue engineering.[17]

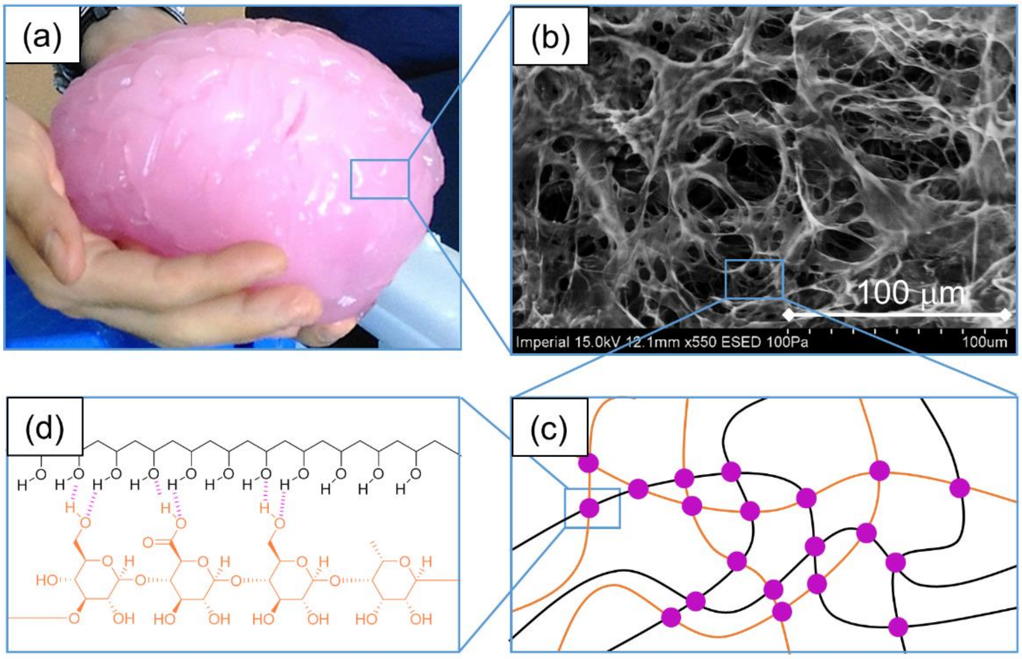


Figure 2. Life-sized phantom of the human brain (a). Scanning electron microscopy (SEM) image of the microstructure of the composite hydrogel (PVA 5.0 % + PHY 0.6 %) used in the first demonstration (b). Schematic showing the PVA (black) and PHY (orange) polymer network (c) and hydrogen bonds (purple) between the polymer chains (d).

In our previous study, we achieved the best match to the mechanical properties of porcine brain in compression, indentation, and shear tests by mixing 6.0 wt.% PVA and 0.85 wt.% PHY separate solutions in a 1:1 weight ratio.[9] A further investigation revealed that a composition of 5.0 wt.% PVA and 0.6 wt.% PHY closely matched the stiffness of brain tissue up to 95% engineering strain and demonstrated its use as a realistic brain phantom.[14] Reducing the PVA concentration to 2.5 wt.% and increasing the PHY concentration to 1.1 wt.% reproduced the mechanical response of the brain tissue during surgical puncture and cutting scenarios; the determination of this brain mimicking composition compared to real brain tissue is fully described in our previous work by Tan et al.[7] Different compositions have been devised that closely reproduce the mechanical properties of other organs such as the lungs and liver.[7]

In addition to its primary application as a realistic surgical phantom,[9,14] the model brain can be used as an engaging demonstration tool. Here we outline a two-part demonstration using slightly different PVA-PHY composite hydrogels. In the first part, we produce a life-sized phantom of an adult human brain that students can touch and manipulate. In the second part, we show how the composite hydrogel can be used for mock brain surgery with a simulated tumour. The composite hydrogel is inexpensive, simple to prepare, and its constitutive components are widely available, biocompatible, and non-toxic. The demonstration complements recent suggestions for applications of hydrogels[4,18,19] and other environment-sensitive polymers[20,21] in chemical education. The main purposes of the demonstration are:

1. To provide evidence that our brains are much softer and more fragile than most people expect.
2. To enable students to touch, manipulate, and perform mock brain surgery on realistic synthetic brain tissue.
3. To show how chemistry can be used to convert a common household material (PVA glue) into a useful functional material.

Pre-Demonstration

The Materials

PVA (146,000-186,000 g mol^{-1}, CAS: 9002-89-5), PHY (CAS: 71010-52-1), and deionised water were supplied by Sigma-Aldrich UK. Red or pink food dye was used to colour the composite hydrogel. For the negative brain mould required for the first demonstration, we used CS2 silicone rubber from Easy Composites Ltd. UK. For the second demonstration, glitter pompom balls (25 mm diameter) purchased from Amazon UK were used as simulated tumours.

We use different blend compositions for the two demonstrations. For the life-sized brain phantom, we use 1:1 weight ratio of 5.0 wt.% PVA and 0.6 wt.% PHY in water, which both matches the stiffness of brain[14] and is tough enough to maintain its structural integrity during the hands-on demonstration. For the surgical training demonstration, we use 1:1 weight ratio of 2.5 wt.% PVA and 1.1 wt.% PHY, since this composition more closely mimics the surgical cutting and penetration forces of brain.[7]

General Procedure

The procedure consists of three stages; preparing the composite hydrogel, casting the life-sized brain phantom, and casting the surgical training phantom. To make the composite hydrogel, PVA and PHY powders were added to separate solutions of deionised water in two different conical flasks of suitable size. A magnetic stirrer bar was placed inside each flask. The two separate solutions were heated to 90 ^{o}C under constant stirring using a magnetic stirrer hot plate until the PVA and PHY powders were completely dissolved (approx. 60 minutes), resulting in completely transparent solutions.[9] Care was taken to avoid excessive evaporation during the process; if using a conical flask, the screw cap should be loosely fitted and if using an open flask, aluminium foil should be fitted to cover the flask opening. The two solutions were then mixed together in a single flask (1:1 weight ratio) and stirred at 70 ^{o}C for

30 minutes. The masses required for each constituent material are shown in Table 1. No external cross-linking agents were used.

Table 1. Calculated weights for composite hydrogel constituents of the two different compositions

Composition	Total solution weight (g)	PVA powder weight (g)	DI water weight for PVA (g)	PHY powder weight (g)	DI water weight for PHY (g)
5.0 wt.% PVA, 0.6 wt.% PHY For life-sized brain mould	1400.0	35.0	665.0	4.2	695.8
2.5 wt.% PVA, 1.1 wt.% PHY For surgical training	500.0	6.2	243.8	2.8	247.2

To make the life-sized brain phantom, the 5.0 wt.% PVA, 0.6 wt.% PHY solution was poured into the silicone mould and allowed to cool down to room temperature (approx. 30 minutes). As in our previous study,[9] the reusable negative mould was made using a 3D-printed brain template[22] from a real MRI scan and a 3D image slicer.[23] Further guidance, as well as the standard triangle language (STL) file to 3-D print the life-sized brain template, are provided in the Supplementary Information. The weight of the life-sized phantom (1400 g) is representative of an adult human brain.[24]

To make the phantom for the surgical training demonstration, the 2.5 wt.% PVA, 1.1 wt.% PHY solution was poured into a clear plastic container of > 500 mL capacity. The glitter pompoms (approx. 16 for every 500 g of solution), used to simulate tumours for resection, were placed inside the solution and lightly pressed down to ensure submergence. For the purpose of public and classroom demonstrations, these glitter pompoms are eye catching and engaging. Their size (in the centimetre range) is close to that of the average brain tumour and the glittery protrusions are also representative of the diffuse nature of these tumours.[25]

The composite hydrogel containers were then stored in a freezer (approx. -25 ^{o}C) for 18 h and subsequently thawed at room temperature before the demonstration. The thawing time will depend on the volume of hydrogel made, although it should be at least 6 hrs to allow the physical crosslinks to form. To thaw the life-sized brain, the frozen phantom should be placed into a 60 L clear glass fishbowl and tap water should be added until fully submerged at room temperature, as shown in Figure 3. The demonstration may begin when the composite hydrogels are fully thawed. The hydrogel will remain fresh for up to 3 days after thawing when stored in a refrigerator at < 4 °C. We recommend that the preparation should begin 2-3 days before the demonstration.

The Demonstration

1. Feeling a Brain

The demonstration of the life-sized brain phantom stimulates the tactile response of real brain tissue to the audience. The audience should be encouraged to take turns to lightly touch and hold the brain phantom submerged in water with their bare hands, as shown in Figure 3. Paper tissues should be provided for the public to dry their hands after participation.

Figure 3. Experiencing what the brain feels like - the composite hydrogel brain phantom (left) and feeling the brain phantom immersed in water inside a fish bowl (right).

2. Cutting a Brain

The surgical training demonstration showcases how the composite hydrogel can be used to help surgical trainees practise dexterity and gain familiarity with the delicate forces required during open operations. In particular, participants can practice resecting tumours from highly sensitive anatomical regions of the body. The aim for the participants is to use mock surgical tools such as tweezers, small nail scissors, and safety scalpels to remove the mock tumours that were cast-moulded into the tissue phantom, as shown in Figure 4. Participants should be encouraged to cause the 'least damage' to the surrounding material that is mimicking the brain. Surgical gloves can be provided for the participants to more closely mimic a surgical scenario, although this is not necessary since the hydrogel is not hazardous.

Figure 4. *Surgical training using tools to remove tumours (pompoms) from a composite hydrogel.*

Hazards

PVA and PHY are not classified as hazardous substances, although normal lab practice should be followed. All solutions can be disposed of down the sink. The solid hydrogel material can be disposed of as general waste. If broken, the brain material may represent a choking hazard. The tools for the second demonstration (e.g. scissors) are sharp and should be used with care.

Results

This demonstration was originally developed and performed at outreach events at Imperial College London. It has since been implemented at schools, universities, and outreach events across Europe by the Enhanced Delivery Ecosystem for Neurosurgery in 2020 (EDEN2020) consortia. These events include; *New Scientist Live* (ExCeL, London, UK), *European Researchers' Night* (Natural History Museum, London, UK), *Great Exhibition Road Festival* (London, UK), *Natural History Museum Lates* (London, UK), *Maker Faire Rome* (Rome, Italy), and *Meet me Tonight* (Milan, Italy). Some examples are shown in Figure 5. Tens of thousands of students, parents, and teachers have viewed the demonstration at these events.

A lot of valuable feedback was received during the outreach events. Members of the public with previous experience touching the cadaveric tissue found the mock brain to be much softer and more delicate than they expected. This is because brain tissue quickly stiffens post mortem.[26] Moreover, cadaveric brain is usually fixed in formaldehyde solution (formalin), which further increases its stiffness.[26] Many participants were surprised at how heavy the brain is when lifted out of the water bath and by the fact that it is crushed under its own weight. This helped them to understand why our brains are surrounded in cerebral spinal fluid inside our skulls. During the surgical cutting demonstration, the public commented on how easy the material is to disrupt, as well as how difficult it is to remove the mock tumours without removing or damaging a large amount of 'healthy tissue'. This reinforced our message about the complex and arduous task that neurosurgeons face during surgery. The demonstration also showed the importance of developing surgical training systems to ensure that trainees receive the most accurate mock experiences possible to prepare them for real operations.

This demonstration also prompted thoughtful and engaging discussion about the underlying science of the demonstration as well as the work that the presenters do as scientists and engineers.

Figure 5. Demonstration of composite hydrogel brain at New Scientist Live 2019 at the ExCeL London (left) and European Researchers' Night 2019 at the Natural History Museum (right). Participants' faces are blurred to ensure anonymity.

Summary and Perspectives

The two-part demonstration detailed in this contribution involves a polymeric material whose mechanical properties mimic that of the brain and can therefore be used as a surgical training tool. This demonstration provides a unique first-hand and tactile experience for a wide range of audiences. The primary aim is to show young students how everyday materials can be usefully applied to provide novel solutions for important real life situations by understanding the science behind their origins and hence, to inspire them to pursue further studies in STEM fields. The demonstration can be easily scaled up for larger classes and events by simply making larger volumes of the hydrogel used in the surgical training application. Furthermore, the procedure may be appropriately modified to become a brain phantom for testing robotic surgical tools or as a medical surgical training tool by embedding a secondary hydrogel mass, dyed a different colour for example, inside the life-sized brain phantom to more accurately mimic a tumoral mass. Therefore, there is an extensive scope of impact that can be achieved by utilising the composite hydrogel material as a mechanically accurate, cost effective, and easily procurable presentation tool during brain mimicking demonstrations.

The team is currently working on the design of a dynamic lung phantom as training tool for lung surgeries and educational purposes, which can reproduce the respiratory cycle and the organ deformations realistically, besides mimicking the stiffness of lung tissue.

Supporting Information

A detailed description on how to obtain or create a life-sized, silicone brain mould. STL file to 3D-print brain template for the negative mould. Videos showing the two parts of the demonstration.

Acknowledgements

We thank all of the students, teachers, parents, administrators, and organizers from schools, universities, and outreach events located all over Europe for providing opportunities for our outreach demonstration. This project was supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 688279 for the funding call H2020-ICT-2015 Research and Innovation Action through the EDEN2020 project. D.D., J.P.E. and Z.T. thank the Engineering and Physical Sciences Research Council (EPSRC) for financial support via an Established Career Fellowship (EP/N025954/1). A.E.F. acknowledges that this project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 798244. All data and results will be made available upon request by email to the corresponding authors or tribology@imperial.ac.uk.

References

(1) Zhang, Y. S.; Khademhosseini, A. Advances in Engineering Hydrogels. *Science.* **2017**, *356*, eaaf3627. https://doi.org/10.1126/science.aaf3627.

(2) Schueneman, S. M.; Chen, W. Environmentally Responsive Hydrogels. *J. Chem. Educ.* **2002**, *79*, 860. https://doi.org/10.1021/ed079p860.

(3) Gupta, P.; Vermani, K.; Garg, S. Hydrogels: From Controlled Release to PH-Responsive Drug Delivery. *Drug Discovery Today*. 2002, pp 569–579. https://doi.org/10.1016/S1359-6446(02)02255-9.

(4) Chen, Y. H.; He, Y. C.; Yaung, J. F. Exploring PH-Sensitive Hydrogels Using an Ionic Soft Contact Lens: An Activity Using Common Household Materials. *J. Chem. Educ.* **2014**, *91*, 1671–1674. https://doi.org/10.1021/ed400833b.

(5) Kamoun, E. A.; Kenawy, E. R. S.; Chen, X. A Review on Polymeric Hydrogel Membranes for Wound Dressing Applications: PVA-Based Hydrogel Dressings. *J. Adv. Res.* **2017**, *8* (3), 217–233. https://doi.org/10.1016/j.jare.2017.01.005.

(6) Cacopardo, L.; Guazzelli, N.; Nossa, R.; Mattei, G.; Ahluwalia, A. Engineering Hydrogel

Viscoelasticity. *J. Mech. Behav. Biomed. Mater.* **2019**, *89*, 162–167. https://doi.org/10.1016/j.jmbbm.2018.09.031.

(7) Tan, Z.; Dini, D.; Rodriguez y Baena, F.; Forte, A. E. Composite Hydrogel: A High Fidelity Soft Tissue Mimic for Surgery. *Mater. Des.* **2018**, *160*, 886–894. https://doi.org/10.1016/j.matdes.2018.10.018.

(8) Carpenter, G.; Bozorgi, S.; Vladescu, S.; Forte, A. E.; Myant, C.; Potineni, R. V; Reddyhoff, T.; Baier, S. K. A Study of Saliva Lubrication Using a Compliant Oral Mimic. *Food Hydrocoll.* **2019**, *92*, 10–18. https://doi.org/10.1016/j.foodhyd.2019.01.049.

(9) Forte, A. E.; Galvan, S.; Manieri, F.; Rodriguez y Baena, F.; Dini, D. A Composite Hydrogel for Brain Tissue Phantoms. *Mater. Des.* **2016**, *112*, 227–238. https://doi.org/10.1016/j.matdes.2016.09.063.

(10) Ambrosio, L.; De Santis, R.; Nicolais, L. Composite Hydrogels for Implants. *Proc. Inst. Mech. Eng. Part H* **1998**, *212*, 93–99. https://doi.org/10.1243/0954411981533863.

(11) Norton, A. B.; Hancocks, R. D.; Grover, L. M. Poly (Vinyl Alcohol) Modification of Low Acyl Gellan Hydrogels for Applications in Tissue Regeneration. *Food Hydrocoll.* **2014**, *42*, 373–377. https://doi.org/10.1016/j.foodhyd.2014.05.001.

(12) Li, J.; Mooney, D. J. Designing Hydrogels for Controlled Drug Delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071. https://doi.org/10.1038/natrevmats.2016.71.

(13) van Veen, Y. R. J.; Jahya, A.; Misra, S. Macroscopic and Microscopic Observations of Needle Insertion into Gels. *Proc. Inst. Mech. Eng. Part H* **2012**, *226*, 441–449. https://doi.org/10.1177/0954411912443207.

(14) Leibinger, A.; Forte, A. E.; Tan, Z.; Oldfield, M. J.; Beyrau, F.; Dini, D.; Rodriguez y Baena, F. Soft Tissue Phantoms for Realistic Needle Insertion: A Comparative Study. *Ann. Biomed. Eng.* **2016**, *44*, 2442–2452. https://doi.org/10.1007/s10439-015-1523-0.

(15) Jaeger, P. A.; McElfresh, C.; Wong, L. R.; Ideker, T. Beyond Agar: Gel Substrates with Improved Optical Clarity and Drug Efficiency and Reduced Autofluorescence for Microbial Growth Experiments. *Appl. Environ. Microbiol.* **2015**, *81*, 5639–5649. https://doi.org/10.1128/AEM.01327-15.

(16) Agnihotri, S. A.; Aminabhavi, T. M. Development of Novel Interpenetrating Network Gellan Gum-Poly(Vinyl Alcohol) Hydrogel Microspheres for the Controlled Release of Carvedilol. *Drug Dev. Ind. Pharm.* **2005**, *31*, 491–503. https://doi.org/10.1080/03639040500215875.

(17) Tan, Z.; Parisi, C.; Di Silvio, L.; Dini, D.; Forte, A. E. Cryogenic 3D Printing of Super Soft Hydrogels. *Sci. Rep.* **2017**, *7*, 16293. https://doi.org/10.1038/s41598-017-16668-9.

(18) Hurst, G. A. Green and Smart: Hydrogels to Facilitate Independent Practical Learning. *J. Chem. Educ.* **2017**, *94*, 1766–1771. https://doi.org/10.1021/acs.jchemed.7b00235.

(19) Warren, D. S.; Sutherland, S. P. H.; Kao, J. Y.; Weal, G. R.; Mackay, S. M. The Preparation and Simple Analysis of a Clay Nanoparticle Composite Hydrogel. *J. Chem. Educ.* **2017**, *94*, 1772–1779. https://doi.org/10.1021/acs.jchemed.6b00389.

(20) Brown, C. L.; Barbee, M. H.; Ko, J. H.; Maynard, H. D.; Craig, S. L. Writing Without Ink: A Mechanically and Photochemically Responsive PDMS Polymer for Science Outreach. *J. Chem. Educ.* **2017**, *94*, 1752–1755. https://doi.org/10.1021/acs.jchemed.6b00806.

(21) Ting, J. M.; Ricarte, R. G.; Schneiderman, D. K.; Saba, S. A.; Jiang, Y.; Hillmyer, M. A.; Bates, F. S.; Reineke, T. M.; Macosko, C. W.; Lodge, T. P. Polymer Day: Outreach Experiments for High

School Students. *J. Chem. Educ.* **2017**, *94*, 1629–1638. https://doi.org/10.1021/acs.jchemed.6b00767.

(22) Naftulin, J. S.; Kimchi, E. Y.; Cash, S. S. Streamlined, Inexpensive 3D Printing of the Brain and Skull. *PLoS One* **2015**, *10*, e0136198. https://doi.org/10.1371/journal.pone.0136198.

(23) Fedorov, A.; Beichel, R.; Kalpathy-Cramer, J.; Finet, J.; Fillion-Robin, J. C.; Pujol, S.; Bauer, C.; Jennings, D.; Fennessy, F.; Sonka, M.; Buatti, J.; Aylward, S.; Miller, J. V.; Pieper, S.; Kikinis, R. 3D Slicer as an Image Computing Platform for the Quantitative Imaging Network. *Magn. Reson. Imaging* **2012**, *30*, 1323–1341. https://doi.org/10.1016/j.mri.2012.05.001.

(24) Dekaban, A. S.; Sadowsky, D. Changes in Brain Weights during the Span of Human Life: Relation of Brain Weights to Body Heights and Body Weights. *Ann. Neurol.* **1978**, *4*, 345–356. https://doi.org/10.1002/ana.410040410.

(25) Dempsey, M. F.; Condon, B. R.; Hadley, D. M. Measurement of Tumor “Size” in Recurrent Malignant Glioma: 1D, 2D, or 3D? *Am. J. Neuroradiol.* **2005**, *26*, 770–776.

(26) Weickenmeier, J.; Kurt, M.; Ozkaya, E.; de Rooij, R.; Ovaert, T. C.; Ehman, R. L.; Butts Pauly, K.; Kuhl, E. Brain Stiffens Post Mortem. *J. Mech. Behav. Biomed. Mater.* **2018**, *84*, 88–98. https://doi.org/10.1016/j.jmbbm.2018.04.009.