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Reusable Surgical Phantoms with Self-healing Nanocomposite Hydrogel

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Reusable Surgical Phantoms with Self-healing Nanocomposite Hydrogel

A thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Bioengineering

by

Catherine Hannah Watson

Committee in charge:

Professor Adam Engler, Chair
Professor Karen Christman
Professor Ester Kwon
Professor Preetham Suresh

2021

The thesis of Catherine Hannah Watson is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2021

DEDICATION

To my boyfriend for his continued support

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ABSTRACT OF THE THESIS

Reusable Surgical Phantoms with Self-healing Nanocomposite Hydrogel

by

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Master of Science in Bioengineering

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Professor Adam Engler, Chair

Current medical education facilities use simulation training to educate medical residents and other healthcare staff. These centers typically rely on single-use soft training devices that use ballistics gel to simulate human tissue but that must be discarded after a single training session. This not only is an environmental burden but amounts to a tremendous cost for training programs. As such, I have adapted a self-healing nanocomposite hydrogel to make surgical phantoms and other medical education mannequins reusable. This hydrogel has similar storage and loss moduli to human muscle tissue and is acoustically similar to human tissue. Failure testing of the hydrogel material simulating trainer use, i.e., cycles of needle punctures and overnight healing, demonstrated that the hydrogel trainer can be used up to 10 times with successful healing. The hydrogel is initially intended to replace single-session clinical trainers for ultrasound-guided central line placement, so I created a perfusable, more anatomically accurate trainer where the device can be pressurized with liquid to simulate human blood vessels and bleeding. In a blinded study of training staff within the Simulation Training Center at the University of California, San Diego, qualitative ultrasound evaluation indicated that clinical experts could not, upon initial evaluation, correctly determine which training devices had previously been punctured and healed. These data suggest that a self-healing nanocomposite hydrogel may be an alternative to current single-use soft training materials.

Chapter 1.

Introduction

1.1 Introduction

Globally in 2020, there were 139,848 active first-year medical residents. This is a 3.5% increase from 134,951 in 2019 and 7.5% increase from 129,291 in 2018[1]. Each of these students are expected to complete years of training to learn the skills necessary for their medical careers. And due to this increasing number of medical residents, there is a high demand for readily available and inexpensive educational tools.

Technological innovations have vastly changed the way we teach surgical residents and other medical professionals, such as nurses and paramedics. From practicing on cadavers to using virtual reality, surgical education relies on a spectrum of technologies to provide realistic simulation learning experiences. Outside of physical education tools and simulation training, there is also a reliance on apprenticeships and mentor/mentee relationships[2]. There is no doubt that the use of cadavers is crucial in surgical education due to the anatomical realism cadavers provide when practicing surgical techniques[3]. However, this educational tool is expensive and limited by the quantity of cadavers available. Aside from cost issues stemming from availability, cadavers must be stored and maintained in special facilities, which limits their use to institutions that are able to invest in building and maintaining these cadaver storage facilities. Given that these educational tools are limited to well-funded training institutions, there exists an educational disparity within communities of medical residents. Educational facilities that receive less funding from public or private sources, generally, cannot maintain the upkeep of cadavers for education which leads to systemic inequities in higher education[24].

Due to the limited quantity and high associated cost of cadavers, educational institutions have turned towards the use of virtual reality in surgical education, largely in part to the widespread availability and recent advances in artificial intelligence technology[4]. Additionally, with the advent of the global COVID-19 pandemic, the desire to limit person to person contact has led to an increase in the use of internet-based educational resources [5,6]. Virtual reality is useful for simulation training because it allows many more students to be trained in a lower-cost, immersive environment with automatic results and feedback when compared to using human cadavers or single-use resources[4]. However, even with the instant feedback and low cost, virtual reality trainers are still not able to accurately simulate the stress medical personnel feel in an operating room or when working with a patient and are under pressure to perform quickly and accurately. Many studies have measured resident anxiety before and after training through metrics such as heart rate and qualitative assessments of anxiety. It has been documented that simulating operating room stress through simulation training such as on cadavers and in fully representative operating suites can alleviate a portion of the anxiety felt by medical residents once training has concluded[7,8]. For example, students presented with more stressful simulation training as measured by increased heart rate performed better on final assessments than their less stressed counterparts[8]. Thus, while virtual reality is a useful tool for educating multitudes of students cheaply while providing instant feedback, it must be used in conjunction with another educational tool[6].

This leads us to the most widely used option, surgical phantoms, which are mannequins that model the human body[9]. Surgical phantoms are anatomical recreations of the human body made from a variety of materials. These phantoms can be organ or tissue specific, oriented towards a specific technique, or can be whole body models to simulate full procedures[9]. The phantoms vary in realism and anatomical correctness based on the needs of the institution. There are many ways to recreate human tissue with synthetic materials. These tissue-mimicking materials (TMMs)[10] rely on changes in tensile moduli and acoustic properties to accurately represent specific tissues. For example, many surgical phantoms take advantage of the high tensile strength properties of materials such as ballistics gel and proprietary blends of synthetic polymers to accurately represent the elasticity of human skin. Additionally, adipose tissue or organ lining can be represented by less dense materials such as hydrogels or other synthetic polymer blends[10]. However, due to the properties of these materials, surgical phantoms tend to be single use to limited use items. Many companies have gotten around this by creating a long-lasting mannequin out of plastic or rubber with separate, replaceable inserts that are to be changed either with each use or after several uses. This, however, introduces a larger overhead cost for training facilities as the cost to replace each piece increases with the ever-increasing number of new students and returning staff. There is also a hugely negative environmental impact as the materials used generally are not recyclable[11,12]. Additionally, due to the large cost associated with replacing pieces, many educational institutions opt to reuse old materials which degrades education quality as students are no longer learning how to conduct a procedure but are just following the marks from the previous student. As such, there is much to be improved upon within the field of simulation learning in medical education.

1.2 Central Line Venous Catheter Systems

As documented above, the use of surgical phantoms to practice essential skills is widespread. For example, one well documented medical technique that is a necessity for all medical professionals to learn is the placement of central venous line catheters. This technique involves the placement of a catheter peripherally through a large vein such as the internal jugular and down into the superior vena cava, inferior vena cava, or right atrium of the heart[13]. This procedure is important as it is often used for long-term delivery of medicine and easy data collection for diagnosis using catheters[13]. It has been estimated that over 5 million central venous catheters are placed each year in the United States[14]. Each procedure brings the possibility of error with immediate complications resulting from mistakes in placement[14]. Although the procedure has not changed significantly since the 1970's[25], the advent of ultrasound imaging technology has significantly improved the ease of placement for central line catheters [15,16]. Ultrasound imaging is used to guide the needle into the vein and help with the placement of the catheter into its intended location[16]. Materials such as ballistics gel and synthetic polymers use additives and dyes to be acoustically similar to human tissue; however, needle tracks and catheter punctures can easily be seen in these materials after a few uses. Therefore, surgical phantoms that are acoustically like human tissue and can hide or repair perturbations would be widely beneficial for medical resident training as it would provide the most realistic simulation.

1.3 Self-Healing Smart Materials

Being able to mimic the tensile and anatomical properties of human tissue is an integral component of surgical phantoms. Different materials offer unique abilities which open opportunities for the creation of new types of surgical phantoms. Outside of the tensile properties explored earlier, another factor for consideration is the ability of a material to self-heal like how human tissue can heal itself. Self-healing is defined as the property of the material to autonomously repair perturbations without external influence[17]. Self-healing materials, or smart materials[17], have made a huge difference in how industry approaches the development of products[18]. Self-healing allows for products to automatically and spontaneously repair internal and external damage which increases the longevity of the product and affects the environmental impact. There is no longer a need to replace parts as damage is inflicted as the material can repair itself.

Several mechanisms exist to facilitate self-healing in smart materials and scientists continue to develop novel ways of self-healing. Current mechanisms include the embedding of healing agents, reversible cross-links, and the shape-memory effect. This is by no means an exhaustive list, only a snapshot of the mechanisms available for self-healing within smart materials. The most common technique by many materials currently on the market, such as plastics and rubbers, that advertise self-healing make use of materials known as healing agents. During the manufacturing process of these materials, pockets of these active healing agents such as monomers or hollow fibers are added into the polymeric systems. When the system is perturbed, the pockets of healing agents are broken and can be drawn through the cracks by capillary forces[17]. These healing agents then fill the cracks caused by the perturbation thereby healing them when the liquid healing agent hardens. This process is entirely autonomous which makes it a common mechanism for smart materials[18].

Another mechanism for healing is the use of reversible cross-links within a polymeric system. Typically used in hydrogels, reversible cross-links rely on noncovalent bonds, such as hydrogen bonds, between polymer chains to 'knit' perturbed surfaces back together[18]. However, these systems are not completely autonomous. Reversible cross links typically require chemical, thermal, or photo activation to proceed[17] which degrades their usefulness partially. The advantage of these materials presents itself in the efficiency of the healing process and the restoration of mechanical properties of the material post-healing[18]. In contrast, a different partially autonomous system relies on the shape-memory effect. Certain materials such as Nitinol (nickel-titanium) ‘remember’ their original shape and will return to it under the right conditions. These shape memory alloys can be deformed and perturbed, but when subjected to high temperatures or when an electric current is passed through will ‘remember’ their original shape and return to it[19]. Again, this system is not completely autonomous, but has been found to be extremely useful especially in the creation and deformation of springs[18].

1.4 Hydrogels

A material for which the tensile and mechanical properties have been well documented is the hydrogel[19-23]. With an ability to extensively swell with water, these networks of crosslinked polymer chains have emerged as a formidable tool for medical applications[22]. In the past, hydrogels have been utilized for drug delivery due to the controlled degradability of the hydrogel. Other uses have included contact lenses, surface coatings, and dressings[23]. Despite all these uses, little is known about the extent to which hydrogels can be applied to the application of surgical phantoms. In recent years, hydrogels have been developed as novel smart materials. Relying on reversible cross-linking and random interactions between carbon backbones and side chains, some hydrogels have the ability to re-heal after perturbation[20]. This automatic healing of damages allows a hydrogel to be applied to the realm of surgical education due to its ‘infinite’ reusability.

Many hydrogels, specifically those with carbon polymer backbones, already exhibit equivalent tensile properties to that of human tissue[20]. This anatomically correct tensile property is an important factor for creating a high-quality medical education tool, as discussed earlier. With the addition of dyes and additives such as reflective nanoparticles, hydrogels can also display the same acoustic properties as human tissue when viewed under ultrasound. As it is common practice for medical staff to rely on ultrasound imaging to guide procedures, such as described above with central line catheterization, it is important that surgical phantoms and medical mannequins have similar acoustic properties as human tissue.

1.5 Conclusion

As such, there is a necessity for inexpensive, anatomically correct medical education tools to continue educating the ever-growing number of medical residents. In the following chapters, I will demonstrate how a self-healing nanocomposite hydrogel can be used to create a reusable surgical phantom. Initially, I explored a chemical-based mechanism for self-healing that ultimately was not applicable to the world of surgical education. Chapter 2 focuses on this pH-based healing hydrogel system formulated from acryloyl-6-aminocaproic acid. Given that the pH-based system did not lend itself to creating a surgical phantom, I switched to a mechanically based healing mechanism that is thermally sensitive which lends itself nicely to creating surgical phantoms. I created an anatomically correct central line catheterization trainer with this hydrogel that has similar tensile and acoustic properties of human tissue. Ultimately, the goal is to apply this self-healing hydrogel to many different surgical phantoms to create a sustainable future for medical education. These future directions and conclusions are explored in Chapter 4.

Chapter 2.

Hydrogel formulated from nanocomposite clay for use in self-healing surgical phantoms

2.1 Abstract

Current medical education facilities use simulation training to educate medical residents and other healthcare staff. These centers typically rely on single-use soft training devices that use ballistics gel to simulate human tissue but that must be discarded after a single training session. This not only is an environmental burden but amounts to a tremendous cost for training programs. As such, I have adapted a self-healing nanocomposite hydrogel to make surgical phantoms and other medical education mannequins reusable. This hydrogel has similar storage and loss moduli to human muscle tissue and is acoustically similar to human tissue. Failure testing of the hydrogel material simulating trainer use, i.e., cycles of needle punctures and overnight healing, demonstrated that the hydrogel trainer can be used up to 10 times with successful healing. The hydrogel is initially intended to replace single-session clinical trainers for ultrasound-guided central line placement, so I created a perfusable, more anatomically accurate trainer where the device can be pressurized with liquid to simulate human blood vessels and bleeding. In a blinded study of training staff within the Simulation Training Center at the University of California, San Diego, qualitative ultrasound evaluation indicated that clinical experts could not, upon initial evaluation, correctly determine which training devices had previously been punctured and healed. These data suggest that a self-healing nanocomposite hydrogel may be an alternative to current single-use soft training materials.

2.2 Introduction

There is a clear need for creating an anatomically correct, reusable option for surgical education tools. Self-healing hydrogels can provide that option. After mining the literature for self-healing hydrogels, two options presented themselves as potential solutions. The first was a hydrogel created with an acryloyl-

6-aminocaproic acid (A6ACA) backbone. This hydrogel relies on reducing the pH of the system to facilitate hydrogen bonding between polymer side chains[26]. However, this type of healing mechanism introduces a hazard due to the nature of the low pH healing solution and was unsuitable for a clinical training environment.

The second option for a self-healing hydrogel used a dimethyl acrylamide (DMAA) carbon chain background and nanocomposite clay particles. The self-healing mechanism for this system is based on reconstructing networks of non-covalent bonds between polymer chains and nanocomposite clay particles[27] and is depicted by Figure 2.1. When perturbed surfaces are held together for an extended period, polymer chains diffuse through the hydrogel between the surfaces and interact with clay particles on the opposite side, forming non-covalent hydrogen bonds[27].

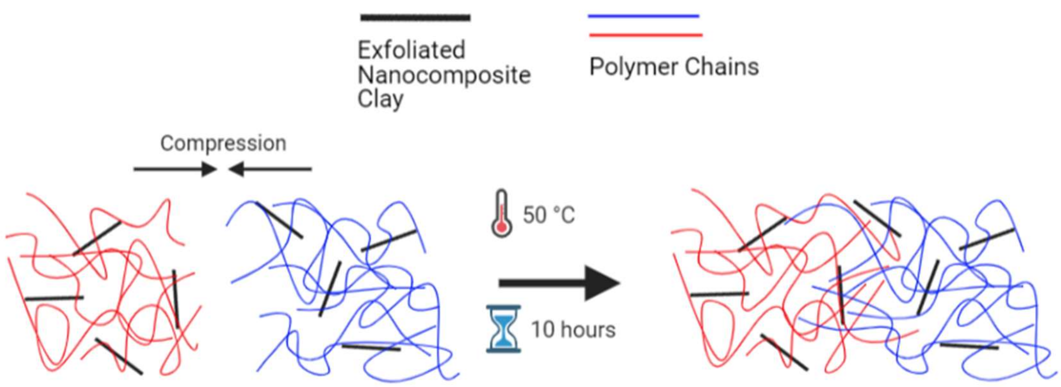


Figure 2.1. Depiction of healing mechanism at the microscale

This microscale process is accelerated by the addition of constant heat. As such, for the entirety of the experiments detailed in this chapter, Figure 2.2.A details the healing process used. After perturbation, a block of nanocomposite hydrogel is placed back into the compression device (see Figure 2.2.B) where the lid of the device is firmly fastened via a wing nut to ensure constant compression. From there, the entire compression device is placed in an oven at 50 degrees Celsius for 10 hours. The increased temperature allows for faster diffusion of the polymer chains across the separated sections of the nanocomposite hydrogel.

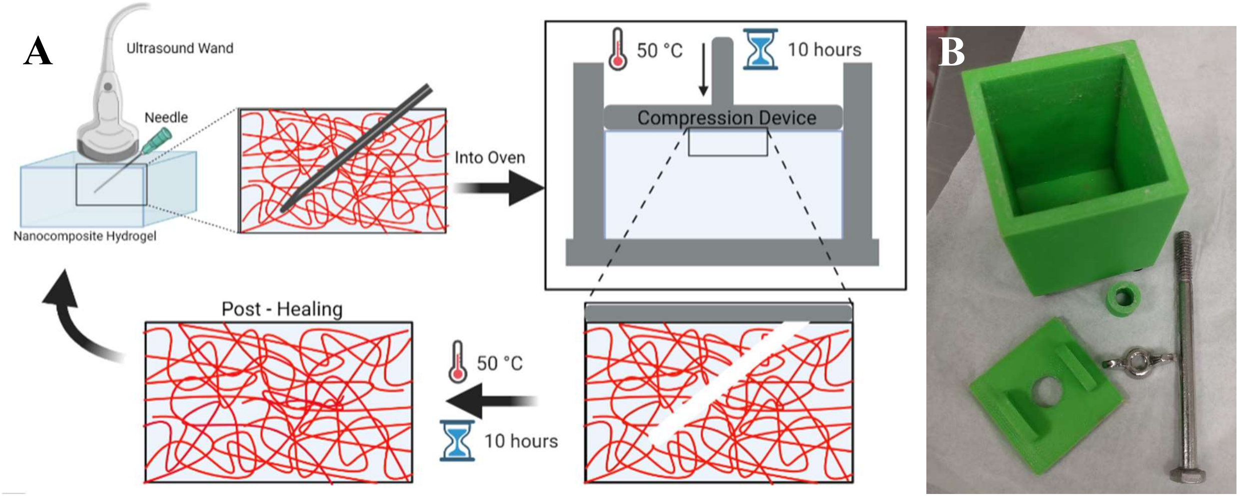


Figure 2.2. (A) Depiction of cyclic perturbation/healing process. Nanocomposite hydrogel is first perturbed via needle/catheter and then placed back into the compression device to maintain cut surface connections. The compression device is then placed in the oven at 50°C for 10 hours to facilitate healing. (B) Image of the 3D printed compression device

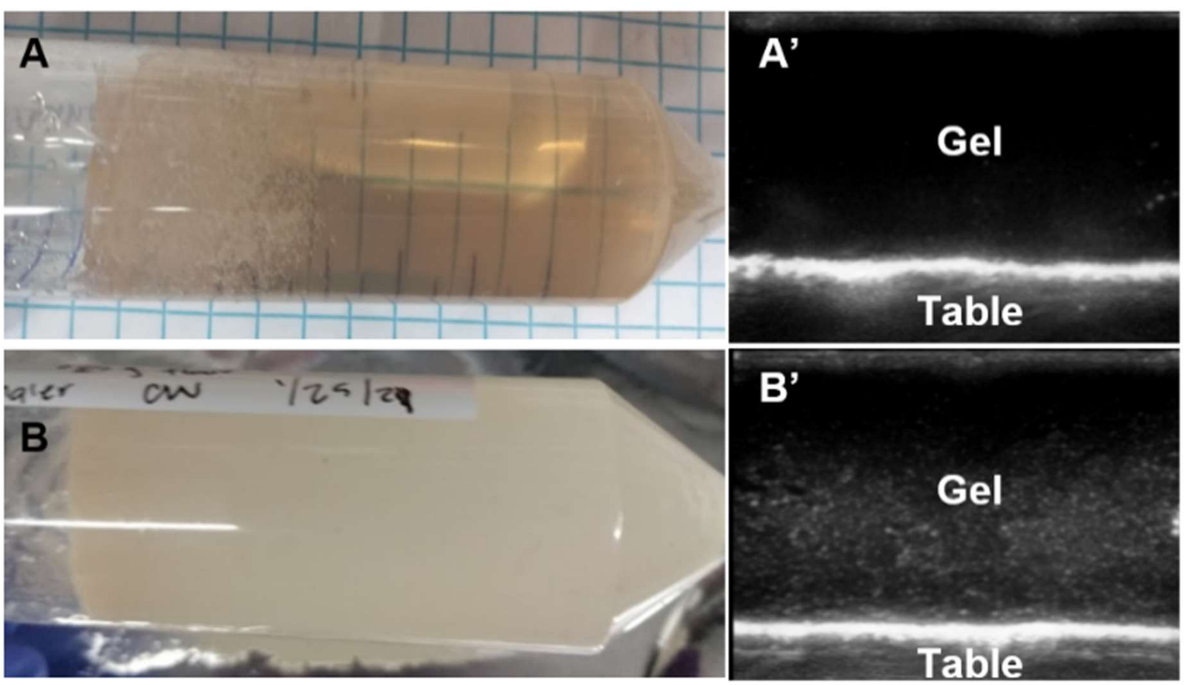


Figure 2.3. (A) Nanocomposite hydrogel polymerized in a conical tube with no contrast agent. (A') Ultrasound image of gel in (A) shows acoustic clarity. (B) Nanocomposite hydrogel with added all-purpose flour as a contrast agent. (B') Ultrasound image of the gel with the contrast agent.

The self-healing mechanism is an important consideration factor in choosing the material for creating surgical phantoms. Another factor of consideration is the material's adaptability such that it can be altered to portray human tissue more accurately. The nanocomposite hydrogel is acoustically clear given the hydrogel's high water content. Figure 2.3.A and 2.3.A' demonstrates this acoustic clarity under ultrasound. To create acoustic opaqueness in the hydrogel, it is necessary to add contrast agents or dyes during the polymerizing step of gel creation. Figure 2.3.B shows the hydrogel with all-purpose flour added as a contrast agent. Under ultrasound (see Figure 2.3.B'), the addition of flour results in an opaquer image with the flour particles reflecting the sound waves emitted by the ultrasound wand. With the addition of a contrast agent, the nanocomposite hydrogel is acoustically similar to human tissue and a suitable option for surgical education tools.

2.3 Results

2.3.1 Comparing material properties of the nanocomposite hydrogel to the industry standard

The current industry standard for creating surgical phantoms is a synthetic polymer blend similar to ballistics gel. As such, the nanocomposite hydrogel was compared to ballistics gel to determine if it has comparable tensile and acoustic properties. To measure the tensile properties, samples of ballistics gel and nanocomposite hydrogel were tested via oscillatory rheometry. As can be seen by Graph 2.1A, the nanocomposite hydrogel has a similar loss modulus, G'', to that of ballistics gel. That is both the hydrogel and ballistics gel dissipate a similar amount of energy when stress is applied to it. Ballistics gel can also be seen to have a higher storage modulus, G', than the nanocomposite hydrogel as the ballistics gel has a higher degree of cross linking. However, after repetitive cycles of perturbation and healing, the nanocomposite hydrogel stiffens due to increasing cross linking between the nanocomposite clay and DMAA polymer and due to dehydration during the healing process. Graph 2.1B demonstrates that the stiffening of the hydrogel is statistically significant in both the storage and loss moduli. This stiffening of the hydrogel brings it to a similar tensile modulus as ballistics gel. In the workable range of frequencies, the average elastic modulus for ballistics gel and healed nanocomposite hydrogel is 12.9 KPa and 9.56 KPa, respectively. Comparatively, human muscle tissue has an average elastic modulus of between 8 to 17 KPa[28,29].

Graph 2.1. Measuring the tensile modulus of the nanocomposite hydrogel versus ballistics gel (A) and an unhealed nanocomposite hydrogel versus a nanocomposite hydrogel that has been through ten cycles of perturbation and healing (B) using oscillatory rheometry

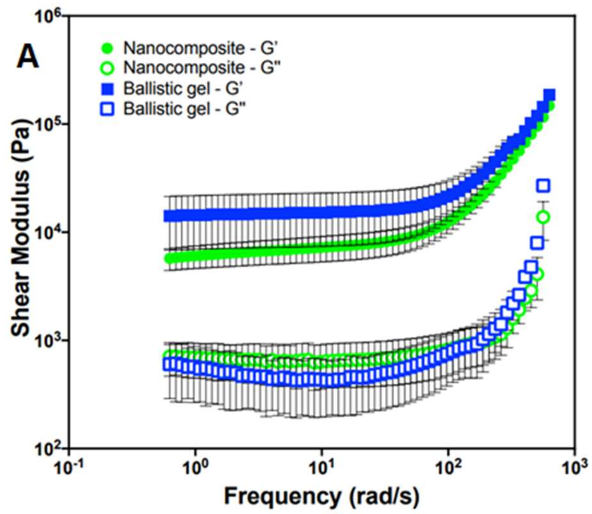


Figure 2.4 demonstrates that the nanocomposite hydrogel is also acoustically similar to ballistics gel. Originally, the high water content of the nanocomposite hydrogel rendered it 'invisible' under ultrasound. However, with the addition of a contrast agent (in this case, all-purpose flour), the nanocomposite hydrogel had sufficient contrast under ultrasound to effectively mimic human tissue and compete with the industry standard in surgical phantoms as measured qualitatively by industry professionals in the Simulation Training Center at the University of California, San Diego. Figure 2.4.A to 2.4.B demonstrates that a puncture mark left by a needle completely disappears after the hydrogel repairs itself as viewed under ultrasound. To achieve the same results in ballistics gel, the ballistics gel needed to be melted down and recast. As can be seen in Figure 2.4.C to 2.4.D, the guide suture shifts in position due to the remelting process. The self-healing mechanism of the hydrogel is quicker and easier to facilitate than having to remelt and recast the ballistics gel. The time cost associated with repairing the ballistics gel and the hazards in remelting and pouring the hot ballistics gel leads it to be the less desirable option. As a

comparison, Figure 2.4.E shows an ultrasound image of the muscles in a human forearm. The muscle striations reflect a similar level of acoustic waves such that the brightness of each image: nanocomposite clay, ballistics gel, or human tissue, are all similar.

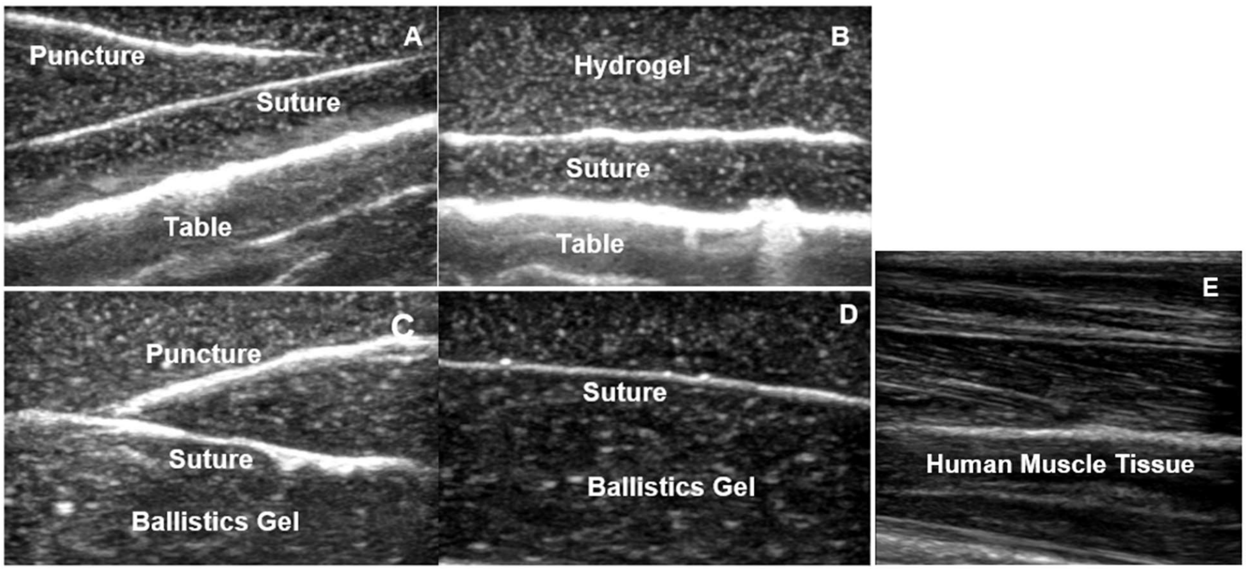


Figure 2.4. Ultrasound images of a single puncture mark in a nanocomposite hydrogel block before (A) and after (B) healing. Note the lack of perturbation mark post-healing in (B). Ultrasound images of ballistics gel with the same perturbation pre-melting and recasting (C) and after recasting (D). Note the change in suture position after remolding the ballistics gel in (D). For comparison, (E) is an ultrasound image of human muscle tissue.

2.3.2 Cyclic testing of the self-healing properties of the nanocomposite hydrogel

Next, the limit to which the nanocomposite hydrogel can be cyclically punctured with needles and healed was tested. The process included repetitive cycles of 15 needle punctures angled towards a guide suture under ultrasound. After perturbation, the hydrogel was healed for 10 hours under compression and constant heat. This process yielded that the nanocomposite hydrogel can undergo 10 cycles of perturbation and healing before there are detectable perturbations post-healing. After post-healing Cycle 10, as exhibited by Figure 2.5, bubbles could be seen in the ultrasound image in the location of prior needle tracks demonstrating that the nanocomposite hydrogel can be used effectively for 10 cycles.

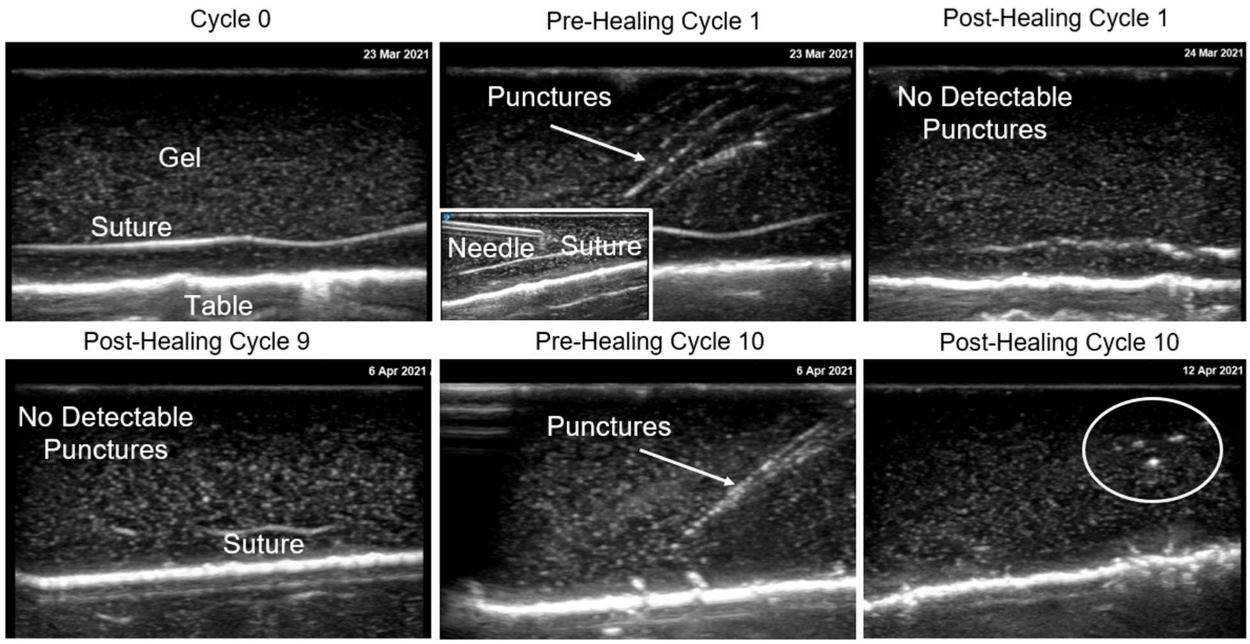


Figure 2.5. Ultrasound images of the cyclic puncture and healing process in a cylinder of nanocomposite hydrogel. Cycle 0 represents the hydrogel prior to any perturbations by needles. Each cycle consisted of 15 punctures by an 18-gauge needle and healing under compression in a 50°C oven overnight.

It is possible to continue using the hydrogel after 10 cycles as it is not obvious where perturbations have occurred from the surface of the hydrogel. However, given that this is a hydrogel made of mostly water and the healing mechanism is accelerated with increased temperatures, there is the advent of volume loss due to both dehydration and the hollow needles coring out material with each insertion. Figure 2.6 highlights this volume loss with 2.6.B being an unhealed nanocomposite hydrogel and 2.6.A being the hydrogel after 10 cycles of puncturing and healing. The hydrogel eventually becomes unusable due to the amount of volume loss within the hydrogel. However, providers of the current educational phantoms suggest that clinics send the phantoms back for repair once they have been punctured either 100 times by needles or 40 times by catheters. Given that the cyclic testing on the nanocomposite hydrogel has proven it can last for 10 cycles minimum with 150 needle punctures, this is a 150% increase in product use and performance.

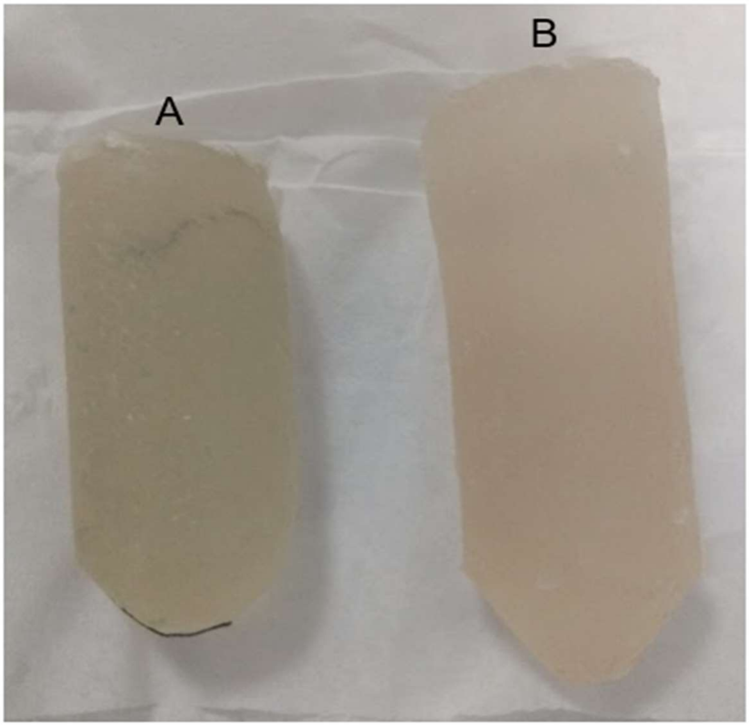


Figure 2.6. Volume loss in a nanocomposite hydrogel made in a 50mL conical tube before (B) and after (A) 10 cycles of perturbation and healing

2.3.3 Creating a lumen within the nanocomposite hydrogel

In a clinical training setting, it is useful for surgical phantoms to have integrated channels within them to represent blood vessels within the human body. This lumen can then be pressurized with fluid to simulate blood and bleeding during perturbation. The nanocomposite hydrogel easily extends to this application. The lumen is created by polymerizing the hydrogel in a mold containing a rod through the center. Figure 2.3 clearly shows this mold for lumen creation. Additionally, with the set-up in Figure 2.7 below, fluid can easily be passed through the hydrogel in either a pulsatile manner similar to how blood flows through blood vessels with each heartbeat or the fluid can remain static once the lumen is filled.

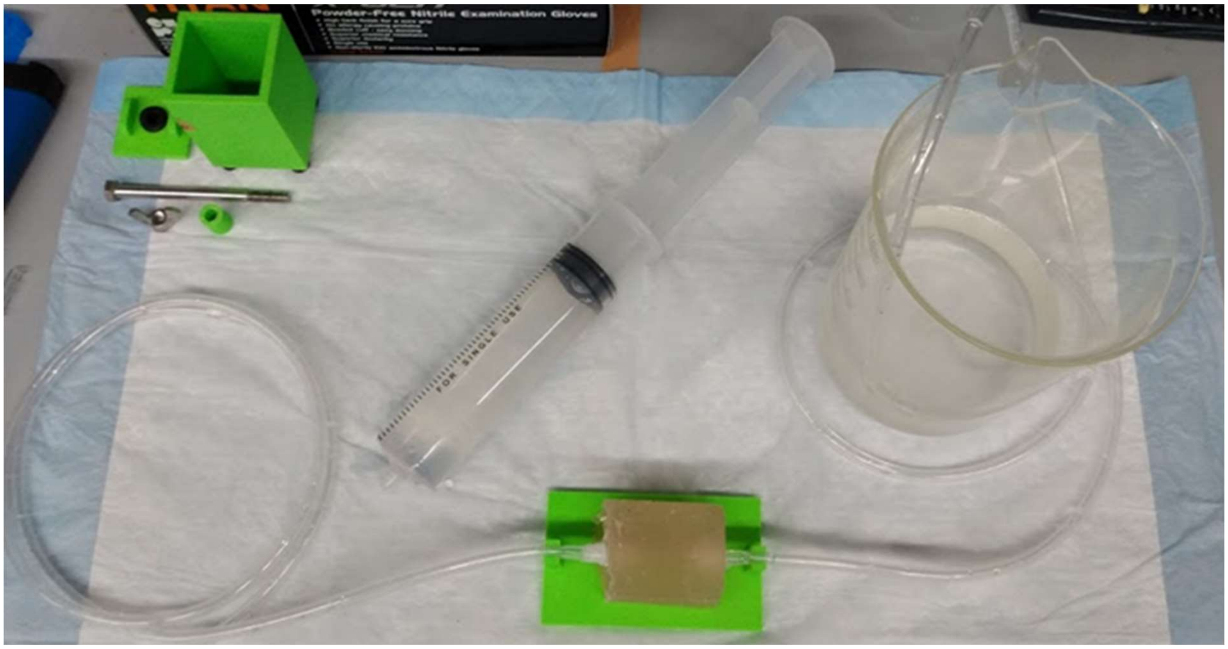


Figure 2.7. Complete set-up for creating an open pressurized fluid system within the nanocomposite hydrogel. A 100mL syringe is used to push deionized water coloured with food dye through rubber tubes. The rubber tubes have connections on each end that attach to each opening of the lumen within the hydrogel that prevent leaking when the fluid is pushed through.

Figure 2.8.A demonstrates that the lumen of the nanocomposite hydrogel can clearly be seen under ultrasound. This is acoustically similar under ultrasound to the lumen within the industry standard surgical phantom as seen in Figure 2.8.B. However, the nanocomposite hydrogel is superior to the industry standard in that the self-healing nature of the hydrogel eliminates the puncture marks after each use. The current industry standard cannot do the same. Perturbation marks can clearly be seen in Figure 2.8.B after several cycles of use in the clinic.

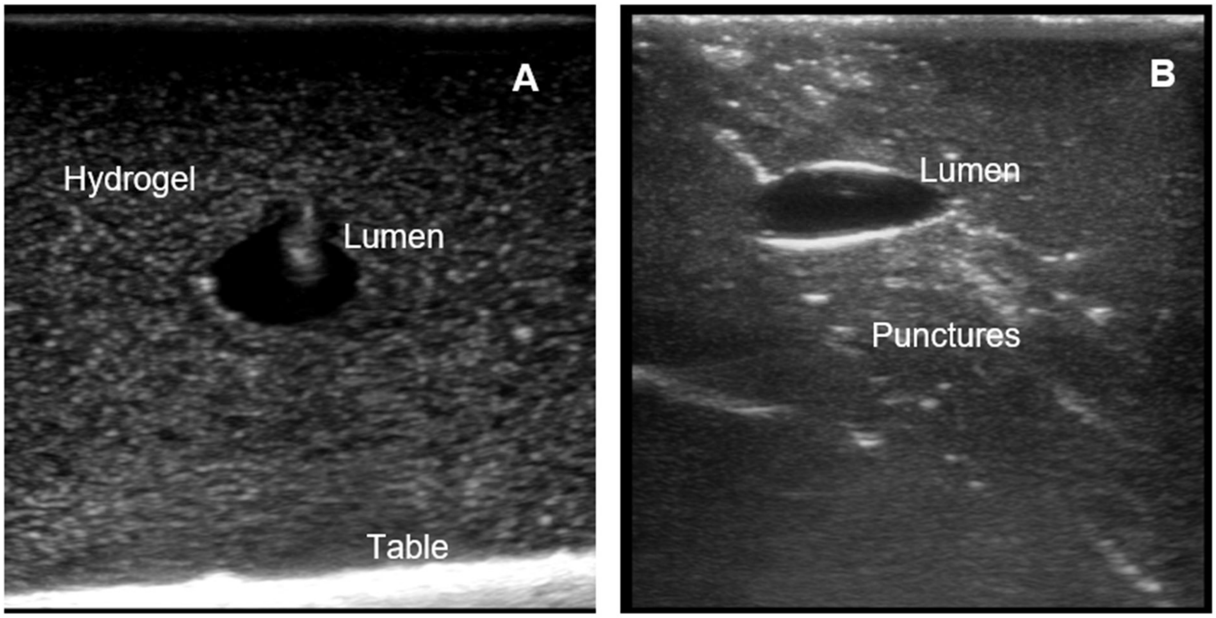


Figure 2.8. Ultrasound images of the lumen running through a nanocomposite hydrogel block (A) and the lumen in the current industry standard phantom (B).

The procedure and corresponding ultrasound image for inserting a needle into the nanocomposite hydrogel can be seen in Figure 2.9.A below. The nanocomposite hydrogel has shown to be durable enough to withstand up to 15 needle punctures in the same location on its surface before fluid seeps through to the surface. Additionally, the channel running through the block of hydrogel maintains structural integrity during the entirety of the test. Figure 2.9.B further illustrates the robustness of the nanocomposite hydrogel. In this image, a 5-French (1.67 mm diameter) catheter is inserted into the hydrogel block and passed through to an adjacent tubing. Tests have shown that the nanocomposite hydrogel can withstand this procedure several times in one use with minimal leakage. With each cycle, the nanocomposite hydrogel heals completely such that there is no indication of an entry point from prior insertions and the inner lumen is not damaged.

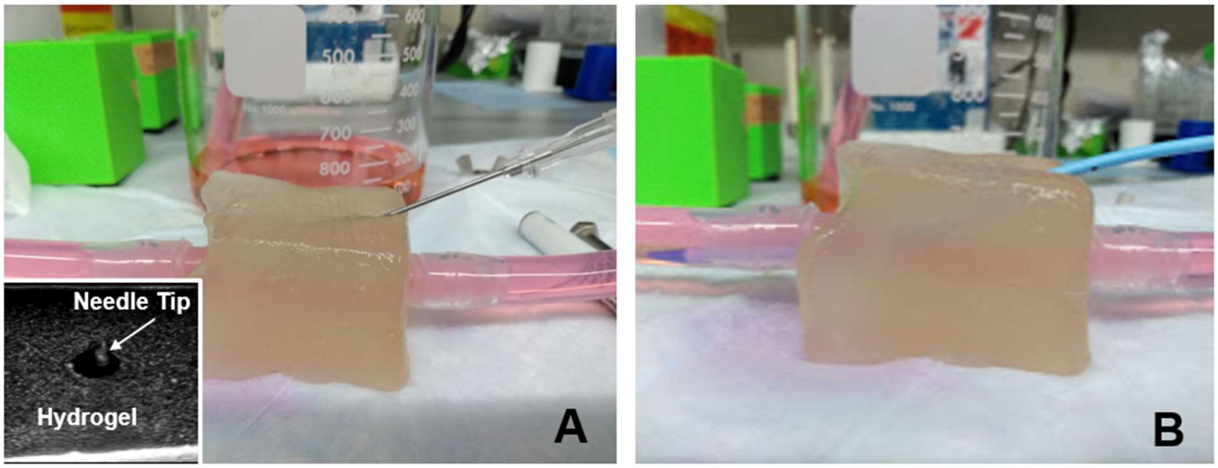


Figure 2.9. First image is of nanocomposite hydrogel block with 18-gauge needle inserted into the lumen (A) with the corresponding ultrasound image. Second image is of the same nanocomposite hydrogel block with a 5-French catheter inserted (B) into the lumen and through to the tubing on the left.

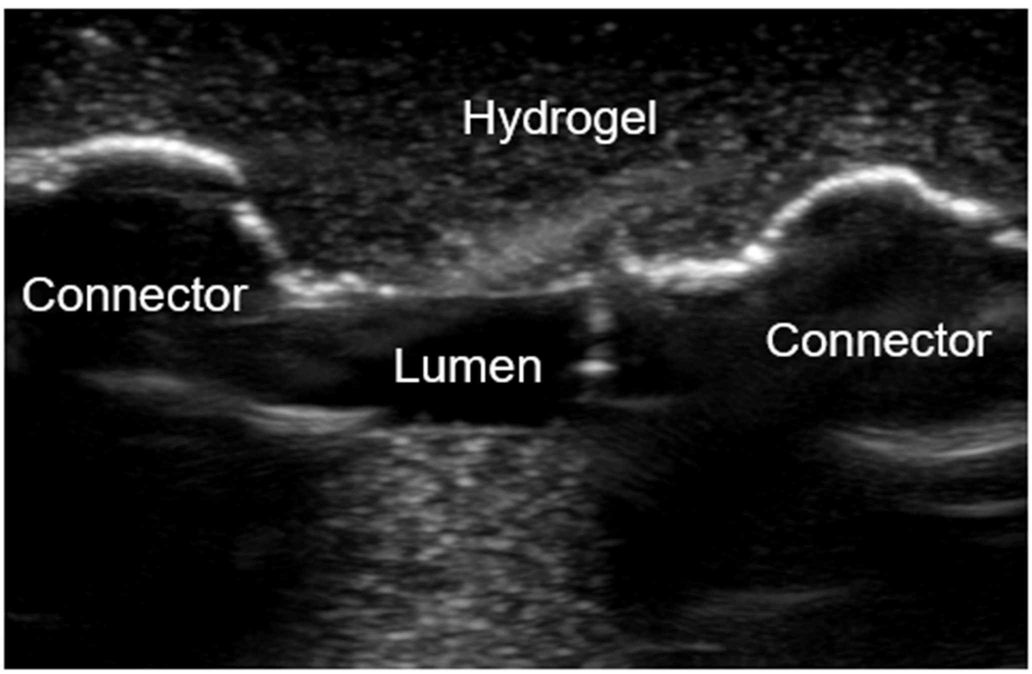


Figure 2.10. Ultrasound image of lumen within a nanocomposite hydrogel block. Ultrasound wand is oriented parallel to the main axis of the lumen

Cyclic testing for punctures and healing was also conducted on the hydrogel containing the lumen to determine if there is a finite stopping point before the hydrogel no longer heals itself and begins to leak from the site of prior perturbation. Testing was underway to determine how many cycles the hydrogel can withstand 15 needle pokes prior to healing before the integrity of the hydrogel is compromised. However, the testing was halted due to significant volume loss in the hydrogel block that eliminated the gap between tubing connectors. Figure 2.10 is an ultrasound image of the hydrogel block running parallel along the lumen. The end of the tubing connections can clearly be seen. With significant volume loss, the gap between those connections is lost. Figure 2.11 displays the before and after pictures of the hydrogel from Cycle 0 to Cycle 16. Before the hydrogel reaches the point of complete structural integrity degradation, the overall volume loss from dehydration and material loss from use of hollow needles renders the nanocomposite hydrogel unusable after 13 cycles. The graph in Figure 2.11 shows the steady decline in volume of a block of nanocomposite hydrogel with each cycle.

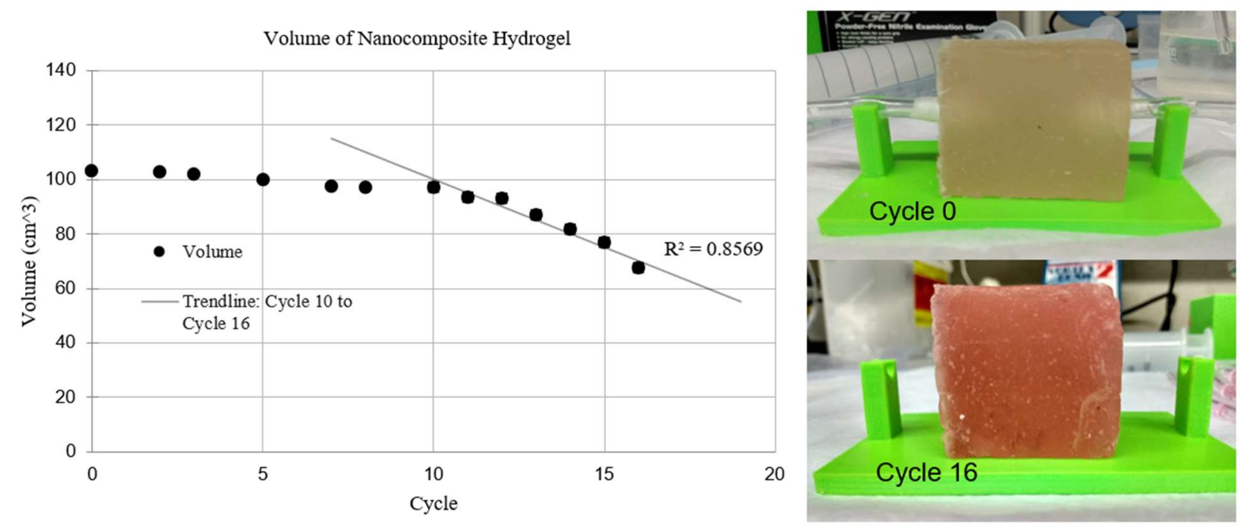


Figure 2.11. Volume of the nanocomposite hydrogel decreases over time due to dehydration and volume loss. Image on top right is of the nanocomposite hydrogel prior to any perturbation. Image on the bottom right is after 16 cycles of 15 needle punctures and overnight healing in a 50°C oven. Colour change is due to the dye in the water pumped through the channel being absorbed into the hydrogel.

After Cycle 12/13, there has been significant volume loss such that the hydrogel no longer maintains a separation between the tubing connections on either end of the block. This effectively puts an upper limit on the number of cycles the nanocomposite hydrogel can be used. Rehydration of the hydrogel brought the hydrogel back to its original volume; however, healed portions of the hydrogel split due to water molecules interfering with the weaker cross links at sites of prior perturbation. Furthermore, when scaled up and applied to surgical phantoms, significant volume loss would impede educational quality. First, the stiffening of the material eventually brings it to an elastic modulus stiffer than human tissue which makes it no longer anatomically accurate. Second, if the hydrogel is polymerized in a shape intended to fit within the walls of a plastic mannequin modeling the human body, volume loss would result in an improper fit and would no longer be usable as an educational tool. From an operational perspective, it is my recommendation that use of the nanocomposite hydrogel is stopped after Cycle 10.

2.4 Conclusion

Overall, the nanocomposite hydrogel demonstrates it is an effective alternative to current single-use products used for surgical education tools. This hydrogel has been shown to be anatomically accurate, simple to use in a clinical environment, and a cost-effective substitute for the current industry standard.

While initially, the nanocomposite hydrogel has a lower elastic storage modulus than ballistics gel, it was shown that once healed under compression at 50°C for a few cycles, the storage modulus of the nanocomposite hydrogel increases due to a rising number of crosslinks and eventual dehydration due to the healing process. This results in comparable tensile moduli between the hydrogel and ballistics gel allowing for the hydrogel to be anatomically similar to human tissue. Additionally, with the addition of contrast agents, the nanocomposite hydrogel is acoustically similar to both ballistics gel and human tissue as examined by ultrasound by industry professionals.

The self-healing mechanism of the nanocomposite hydrogel leads it to be more user-friendly than current solutions. The current solution relies on the trainers to be used until educational quality has degraded and repair is required. Options for repair are to either melt the ballistics gel down in the clinic and recast the gel into a prepared mold or send in the phantom to be repaired by the company. Both are expensive and time-extensive processes. Additionally, the remelting of the ballistics gel introduces a hazard within a teaching environment due to the high temperature required to melt the ballistics gel. In contrast, the self-healing mechanism of the nanocomposite hydrogel is much simpler. A user only needs to place the hydrogel in the compression device and leave it to sit for 48 hours. If accelerated healing is necessary, such as if there is a training class the following day, the hydrogel within the compression device can be placed into an oven at 50°C and left overnight to heal. The self-healing mechanism of the hydrogel provides each teaching session with an unperturbed trainer free of marks and indications of prior use. This allows each student a more optimal learning experience when practicing each technique as there are no prior needle tracks to follow. Furthermore, the longevity of the self-healing mechanism of the nanocomposite hydrogel as proven by cyclic testing allows the gel to be used for more training cycles than the current training option.

2.5 Methods

2.5.1 Polymerization of nanocomposite hydrogel with contrast agent

This polymerization protocol was adapted from Haraguchi, et al.[27]. In a 50 mL conical tube, add 30 mL of DI water, 1.1415 g exfoliated nanocomposite clay (Synthetic Hectorite, Laponite XLG) 30 nm in diameter and 1nm thick, and 0.1 g all-purpose flour. Shake vigorously to dissolve all the clay powder and flour. Next, add 3.087 mL poly(N,N-Dimethylacrylamide) (Sigma-Aldrich, cat # 274135) and 0.03 g potassium persulfate (Sigma-Aldrich, cat # 216224). Invert 3 times to mix. Finally, add 24 µL N,N,N',N'-tetramethylethylenediamine (Sigma-Aldrich, cat # T9281) and invert to mix. Leave at 20°C for 20 hours. For hydrogels polymerized in the 3D printed box mold with the channel running through, all values previously mentioned are multiplied by 3.

2.5.2 Cyclic testing

Place a standard suture through long axis of nanocomposite hydrogel using a straight needle. Suture should be placed no more than one centimeter below the surface of hydrogel and should be visible along the length of the hydrogel via ultrasound. With the ultrasound wand placed parallel to the suture, an 18-gauge needle is inserted into the hydrogel in the same plane as the suture. Figure 2.12 demonstrates this procedure with an ultrasound image of the needle in the same visual plane as the suture.

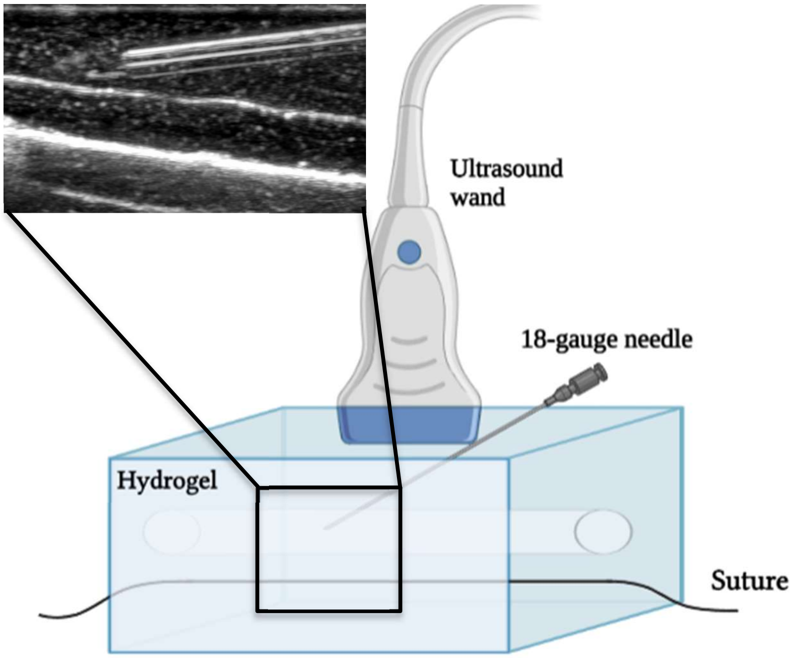


Figure 2.12. Procedure used for needle insertion under ultrasound

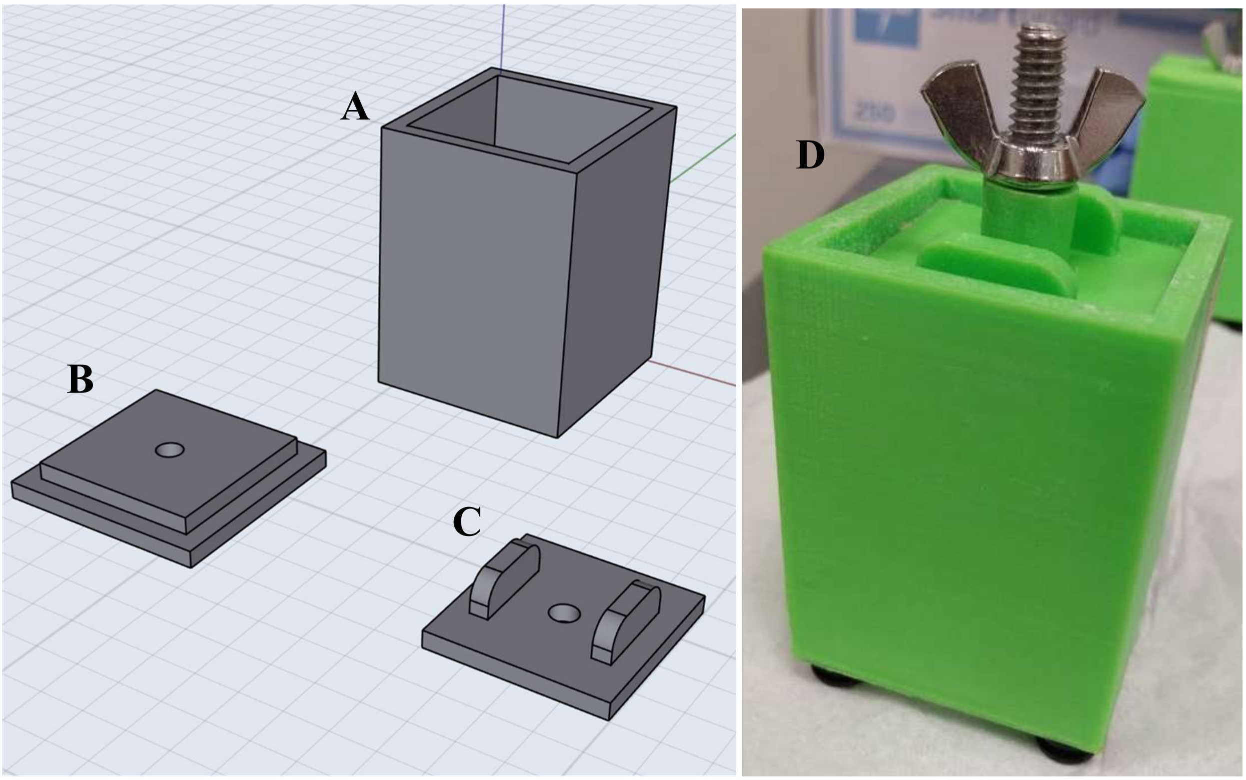
For each cycle, place the surface of the hydrogel closest to the suture on the table and place the ultrasound wand on the top surface oriented parallel to the suture. If there is resistance between the hydrogel and ultrasound wand, dispense a small amount of ultrasound transmission gel (Aquasonic 100, Ultrasound Transmission Gel) onto the surface of the hydrogel as a lubricant. With the ultrasound wand in place. insert an 18-gauge needle into the surface of the hydrogel on the opposite side of the suture. Both the needle and the suture should be visible under ultrasound. Refer to the ultrasound image in Figure 2.12 for correct positioning. Repeat cycle 15 times.

For healing, place nanocomposite hydrogel back into the 3D-printed compression device and tightly secure lid ensuring complete compression. Before placing lid onto hydrogel, add 3 drops of DI water to maintain a hydrated environment within the compression device. For accelerated healing, place compression device into an oven at 50°C for 10 hours. If accelerated healing is not required, compression device can be left on flat surface at room temperature for 48 hours. Hydrogel must be kept in a sealed container to prevent dehydration.

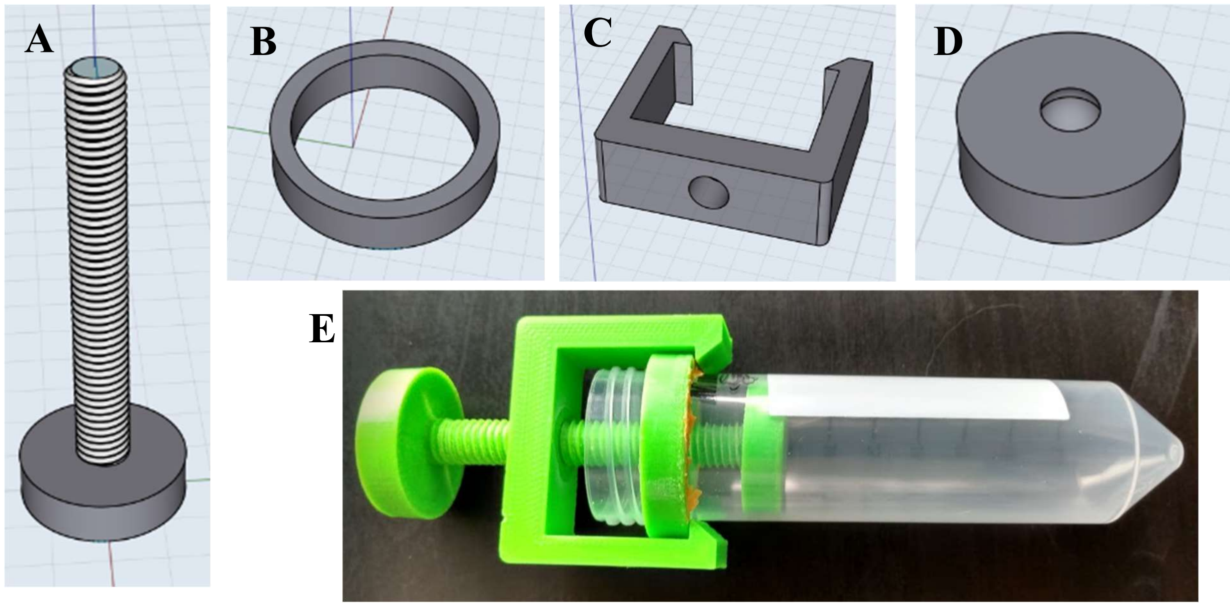
2.5.3 Oscillatory rheometer data collection

To measure the tensile modulus of the nanocomposite hydrogel, an AR G2 by TA Instruments oscillatory rheometer was used. The hydrogel and ballistics gel samples were cut into discs 14 mm in radius, 3 mm in thickness. A flat plate geometry with radius 10 mm was lowered until surface contact was made with very little deformation. Temperature was maintained at 25°C. Using an angular frequency sweep function from 0.1 rad/s to 100 rad/s allows the user to examine the hydrogel's response to a useful range of frequencies. Zero gap was established on the machine before placing the sample. Between samples, the plate was cleaned with DI water, acetone, and ethanol, in that order.

2.6 Supplementary Figures



Supplementary Figure 2.1. .stl file for 3D printed box mold. (A) Box mold with hole in the bottom for a ¼ inch diameter, 3-inch-long bolt to slide through. (B) Lid for box during polymerization stage to make sure bolt remains straight during gel polymerization. (C) Compression lid that slides into the box with wings for easy removal. Complete set-up can be seen in (D) with the threaded bolt and a wing nut for creating compression.



Supplementary Figure 2.2. 3D printed compression device for nanocomposite hydrogel polymerized 50mL conical tube. (A) Threaded bolt for pushing down compression disk. (B) Ring to slide around conical tube to keep compression device in place. (C) Holder for threaded bolt to maintain compression. (D) Compression disk in contact with hydrogel. Threaded bolt maintains contact in hole in middle of disk. (E) Complete set up with 50mL conical tube, no nanocomposite hydrogel

2.7 Acknowledgements

Illustrations in Figures 2.1 and 2.2 were created in Biorender. Supplementary Figures 2.1 and 2.2 created in Shapr3D for iPad. Funding for this work was provided by the National Institutes of Health grant R25EB023839(A.J.E.).

Chapter 3.

Conclusions

3.1 Introduction

The advent of global change drives an ever-growing responsibility for each sector to transition to sustainable and reusable products. Medical education is no exception. Unfortunately, the necessity for accurate, anatomically correct tools has led to research and development in products that must be thrown away or repaired with each use. Current standards for educational tools such as surgical phantoms highlight the importance of anatomical correctness and 'real-feel' technology[9,10]. However, many of the available tools on the market are limited-use or even single-use items. Not only environmentally damaging, these limited-use products are also a fiscally irresponsible choice for medical education centers. Each replacement or repair of a device costs money and with cohorts of students passing through educational centers, the net cost rises exponentially.

Current alternatives to expensive and limited-use pieces of equipment include human cadavers, virtual reality tools, and less accurate, inexpensive materials. Human cadavers present their own problems as discussed in Chapter 1, but they offer the highest level of anatomical realism. Virtual reality allows for multitudes of students to be trained efficiently, but the physical aspect of surgical training is lacking. For simulation training, lower cost materials such as ballistics gel have been explored to alleviate the financial burden associated with limited use, 'real-feel' devices. However, what lower cost materials bring in cost savings, they lack in educational quality. Ballistics gel requires the addition of contrast agents to give it the same acoustic appearance as human tissue. And although ballistics gel boasts a similar tensile modulus to human tissue, a ballistics trainer shows scars after the first use that multiply with each consecutive use. As such, each student that practices on a ballistics gel trainer loses educational merit due to being able to follow the tracks and perturbations of the previous student. The process to melt down and recast the ballistics gel to create a new trainer introduces a hazard to the clinical environment with the high melting temperature required and the fumes produced when melting the ballistics gel down.

With this information, we found it necessary to find an alternative to current surgical education tools. The demands are simple: the material needs to be anatomically accurate in both tensile and acoustic properties, the material should be competitively priced for the current market, and the material has to be self-healing.

3.2 Surgical phantoms made of nanocomposite hydrogel

After mining the literature for smart materials, it became apparent that self-healing hydrogels were a viable option for surgical education phantoms. Hydrogels are well studied materials capable of high diversity. With a high water content, hydrogels are easy to maintain and are easily modifiable. Due to this, modifications can be made to make a hydrogel self-healing after perturbations with minimal outside interference.

Two options for self-healing hydrogels were considered. The first, an acryloyl-6-aminocaproic acid (A6ACA) based hydrogel, was disregarded as the healing mechanism was unsuitable for a clinical environment. To facilitate self-healing, the A6ACA hydrogel needs to be immersed in an extremely low pH healing solution, such as 0.1M hydrochloric acid[26]. The second option was a nanocomposite clay polymer system within a hydrogel. Utilizing the non-covalent bonds between dimethyl acrylamide and exfoliated nanocomposite clay particles, this self-healing hydrogel uses a mechanical healing mechanism that is easy to facilitate. The healing mechanism involves diffusion of dimethyl acrylamide polymers across perturbed surfaces and non-covalent hydrogen bonds between the nanocomposite clay and dimethyl acrylamide chains[27]. By using compression to maintain contact between perturbed surfaces and increased temperature to speed up the healing process, this healing mechanism is easy to maintain within a clinical environment. This project focused on developing a central venous line catheter training system made from this nanocomposite hydrogel. A 3D printed mold acted as the initial site for hydrogel polymerization as well as the compression device for the subsequent healing cycles. A channel ran through the hydrogel block to simulate a human vein; fluid could be run through the lumen to simulate bleeding. Qualitative testing by industry professionals in the Simulation Training Center at the University of California San Diego determined that the nanocomposite hydrogel was a suitable alternative to the current industry standard. The healing mechanism was also determined to be simple to reproduce within the clinical training environment.

3.3 Future Directions

The nanocomposite hydrogel is applicable to a range of surgical education phantoms. For this thesis, the hydrogel was polymerized in a mold suitable to create a central venous catheter practice system. Currently, the system relies on a manual pump for pushing fluid through the channel which requires a second person to maintain fluid pressure during practice. With minor adjustments, an electronic pump can replace this manual system. This would eliminate the need for a second set of hands when using the central venous catheter trainer and could automate the fluid movement to simulate a human heartbeat.

In the future, different molds can also be created for other surgical procedure practice. For example, sheets of nanocomposite hydrogel can be applied to cricothyrotomy procedures and suture practice. The exfoliated nanocomposite clay content within the hydrogel can also be adjusted to change the tensile modulus of the gel. This would open other opportunities for trainers. Differing tensile modulus would more accurately match whole human system trainers, as the tensile modulus of skin is different than that of muscle, which is different to adipose tissue, etcetera[28,29]. Layering different concentrations of nanocomposite clay would mimic these tissue differences. More testing would need to be conducted to determine if the healing mechanism works between different concentrations of clay within hydrogel and if the time and temperature to heal is the same. Additionally, volume loss within the different layers would need to be measured to determine if the trainers could be used for the same length of time. With more testing, this nanocomposite hydrogel could apply to a broad range of surgical education tools.

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