Automated Uretero-Intestinal Anastomosis with Absorbable Staples

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Abstract

Bladder cancer is the 5th most common cancer in the United States. When cancer cells invade the bladder muscle, surgical removal of the bladder, called radical cystectomy, is the desired treatment. A neobladder is formed from a portion of intestine, and the ureters are currently attached via absorbable sutures. The team has developed a rigid absorbable staple comprised of 85:15 poly(lactide-co-glycolide) (PLGA). The copolymer is compression molded into a sheet, then cut to the desired shape with an Epilog Mini CO_2 laser cutter. Degradation testing shows that the staples will retain strength for at least 20 days, which is long enough to promote healing of the tissue. Functional testing shows comparable grip strength relative to Vicryl sutures.

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Introduction

Background & Motivation

Bladder cancer is the 5th most common cancer in the United States. According to the National Cancer Institute, there will be over 69,000 new cases reported in the United States and 15,000 people will die from bladder cancer in 2011 [1]. The causes are unknown, but it is more prevalent among smokers. Occupational exposure to rubber, dyes, aluminum, leather, and pesticides also increases the risk of developing bladder cancer. Bladder cancer is more common in males than females.

Because the tumors spread quickly and are difficult to remove, bladder cancer is the most expensive cancer to treat over time. When the tumors invade the bladder muscle, the desired treatment is radical cystectomy, which is the surgical removal of the entire bladder [2]. Following removal of the bladder, there are 2 options for urine storage: a urostomy bag or neobladder. A urostomy bag resides outside of the body under the patient's clothes, and urine drains into the bag. This bag must be emptied and changed daily. The second method, as used by the client, is the formation of a neobladder using a portion of the intestine. The intestine is formed into a bladder and is placed back into the abdominal cavity.

Currently, the ureters are attached to the neobladder with absorbable sutures as shown in Figure 1. This attachment should be watertight so urine does not leak into the abdominal cavity and a tight seal will help promote anastomosis. Because surgeons must manually suture the ureters to the neobladder with only a small working area, results are often inconsistent between surgeons and the procedure is relatively lengthy.

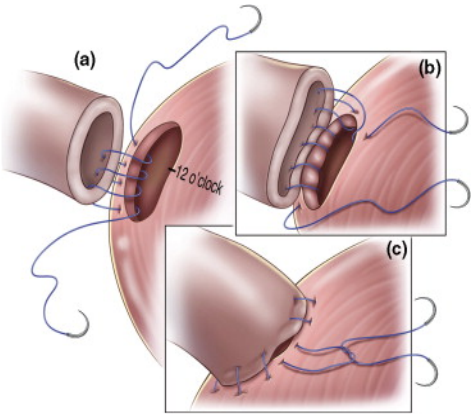


Figure 1: Attachment of ureters to neobladder with absorbable sutures [3]

The client desires an automated method to attach the ureters to the neobladder. This will reduce procedure time and ensure more consistent results between surgeons. Increased consistency and reduced procedure time will translate into fewer complications for patients, shorter hospitalization times, and minimized need for subsequent interventions.

Current Devices

There are currently no absorbable staples specifically designed to secure a ureter to a neobladder; however, there are some devices that are utilized for similar procedures. These devices do not translate directly into the applications of this project but will be discussed regardless.

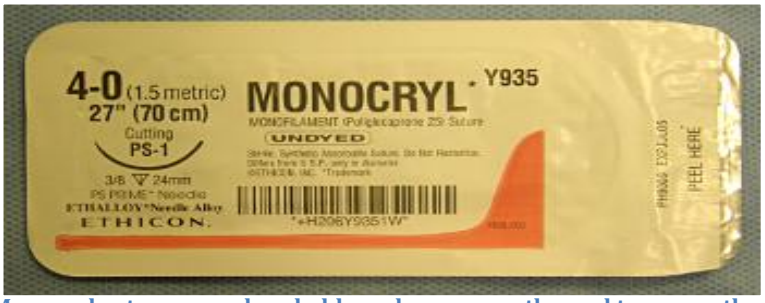


Figure 2: Ethicon Monocryl sutures are absorbable and are currently used to secure the uretero-intestinal anastomosis [4]

The client currently uses Ethicon Monocryl and Vicryl sutures, shown in Figure 2, to secure the anastomosis. The ureters are joined to the neobladder using approximately 7-9 stitches around the circumference of the anastomosis. While these sutures are absorbable, it is time consuming to suture the tissue together and a quicker method is desired. There is also considerable variation in suture insertion depending on the surgeon, and a more consistent method would be advantageous.

Both Ethicon and Covidien manufacture circular staplers, which are utilized for colorectal or intestinal anastomosis. The Ethicon Intraluminal Stapler is pictured in Figures 3 and 4. These staplers insert multiple staples simultaneously around the anastomosis in a circular fashion. However, the staples that are compatible with these staplers are made of titanium which, when used in the urinary tract, may lead to kidney stones or urinary tract infections. This is why an absorbable material is the desired material for this project. These staplers are also too large to use in the 7 mm diameter ureters.

Figure 3: Ethicon Endo-Surgery Intraluminal Staplers have a curved neck to improve the surgeon's access to the anastomosis site through a small entry wound [5]

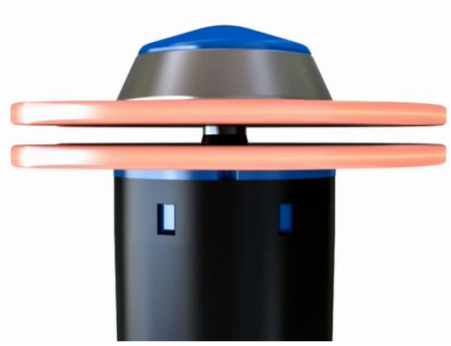


Figure 4: Close-up of the Ethicon Intraluminal Stapler head. This image shows the stapler just before securing the two pink sheets of tissue [6]

Covidien offers a stapler that inserts an absorbable staple for use in meniscal repair, as pictured in Figure 5. The staple is made out of the absorbable proprietary Polysorb™ polymer. This polymer is a PLGA copolymer composed of 82% poly-lactic acid (PLA) and 18% poly-glycolic acid (PGA). The staples have two barbed posts which are 10 mm long and are connected by a 4 mm long braided piece which is too large for the applications of this project [7]. PLGA was investigated as a potential material for this project because it is FDA approved and is currently used for many absorbable staples.

Figure 5: Covidien stapler and staple used for meniscal repair [7]

Insorb sells a stapler containing absorbable staples for use in skin closure following subcutaneous incisions (pictured in Figures 6 and 7). This stapler inserts one staple at a time in a linear fashion. This method of staple placement would not be compatible with a circular anastomosis and individual staple placement would not help to reduce procedure time. However, the staples contained in this stapler are made of PLGA and are absorbable. The staples are approximately 3 mm × 4 mm and have a barb on each leg to secure the staple within the tissue. Although none of these current devices are suitable for the clients needs, they offer a good insight for designing absorbable staples and a stapler for uretero-intestinal anastomosis.

Figure 6: The Insorb Subcuticular Skin Stapler inserts stables to secure subcutaneous skin incisions [8]

Figure 7: The staples contained in the Insorb stapler have to barbs and are absorbable [8]

Design Criteria

There are several important specifications that must be taken into consideration for the absorbable staple design. Although the stapler is also an essential component of the final product, it has not been considered in detail this semester due to time limitations. Since the staples will be used within the abdominal cavity, it is extremely important that they are biocompatible and elicit little or no immune response. They should withstand the bladder environment, which may include any pH from 4.5 to 8.0, the normal pH range for urine. The staples must secure the ureter to the neobladder for a minimum of thirty days, which is enough time for the anastomosis to heal. In addition, the staples must be

completely absorbable and degrade over a period of 30-90 days. The staples should also create a watertight seal to prevent fluid leakage at the anastomosis site. Furthermore, the seal must withstand normal bodily forces, such as fluid pressure inside the ureters and any foreseeable force in the abdominal cavity. There should be little to no damage to the surrounding tissue as a result of staple insertion or degradation. Finally, the staples should be sterile, as they will be used within the body. Complete design specifications can be found in the Product Design Specifications in Appendix A.

Previous Work

The previous design team that worked on this project focused mainly on the stapler. Figure 8 shows their final design for the stapler head. The firing mechanism (not shown) was cannibalized from an Ethicon stapler. To operate this stapler, the tissue would be secured in place and, when fired, two concentric rings of staples would pierce the tissue and bend to close much as traditional metal staples do. Portions of stapler head were prototyped using Aluminum 6061 T-651, and other portions were prototyped with Accura 60.

Figure 8: Stapler head designed by previous design team [9]

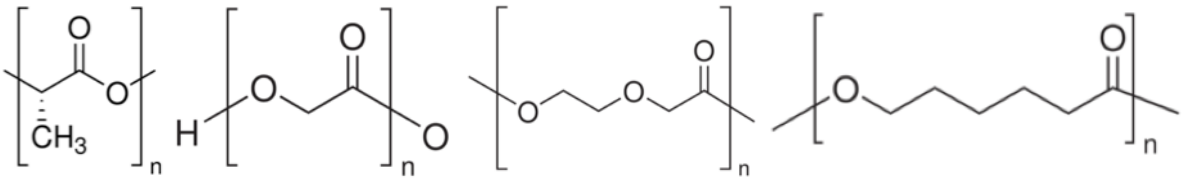
This team also developed a staple by mixing poly(lactic acid) (PLA) and polycaprolactone (PCL) in a 90:10 ratio and crosslinking with 10 parts per hundred (phr) of dicumyl peroxide (DCP). The team showed that the polymer constructs would be strong enough to withstand tensile strengths in the body, but they were too brittle to be bent and formed into staples after firing.

Semester Work

This semester the team decided to focus primarily on the staple design, because designing a stapler to accommodate the designed staples would allow the group to optimize staple properties, which are essential for the success of this method. The stapler design was considered briefly, but it will be investigated in more detail in the future.

Material Selection

There are many absorbable polymers that have been used for medical purposes in the past, and many factors contribute to the final properties of the materials. To select an absorbable polymer that is suitable for use in this staple, three properties were considered: mechanical strength, degradation rate, and biocompatibility. Some synthetic degradable polymers that have been used in medical applications such as staples, sutures, or stents include poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and copolymers (PLGA), polycaprolactone (PCL), polydioxanone (PDS) [10] (see Figure 9 for chemical structure). These polymers are all polyesters, which are broken down by bulk hydrolysis [10]. The previous design team chose to use a blend of PCL and PLA to make their staples, but the



PLA *PGA* *PDS* *PCL*

Figure 9: Chemical structure of common absorbable polyesters [11]

resulting staples were too brittle. Instead of continuing to pursue PCL/PLA, the team chose to pursue PLGA as the staple material.

PLGA has a number of features that make it a suitable choice for this application. To begin with, PLGA is generally biocompatible because it breaks down into lactic acid, which is produced naturally by the body, and glycolic acid, which is easily cleared from the body. PLGA has also been used for many medical applications; it is used for both Insorb and Polysorb staples [12] [13], which suggests that it is a suitable staple material. Furthermore, PLGA is generally accepted by the FDA for use in medical devices.

After selecting the polymer to use, the team also had to consider properties of the PLGA polymer such as molar ratio (PLA:PGA) and molecular weight. PGA is the most simple, linear polyester and is highly crystalline. Unfortunately, it degrades quickly via hydrolysis, losing most of its strength over a period of 2 to 4 weeks in vivo. PLA is more hydrophobic and can be added to PGA to decrease degradation rate. A 50:50 ratio of PLA:PGA has the quickest degradation rate due to changes in crystallinity when PLA and PGA are combined, and any deviation away from a 50:50 molar ratio can increase or decrease the degradation rate [10] (Figure 10). Rather than blending PGA and PLA to form the staples, which may result in variability and phase separation, the team decided to use a commercially available PLGA copolymer.

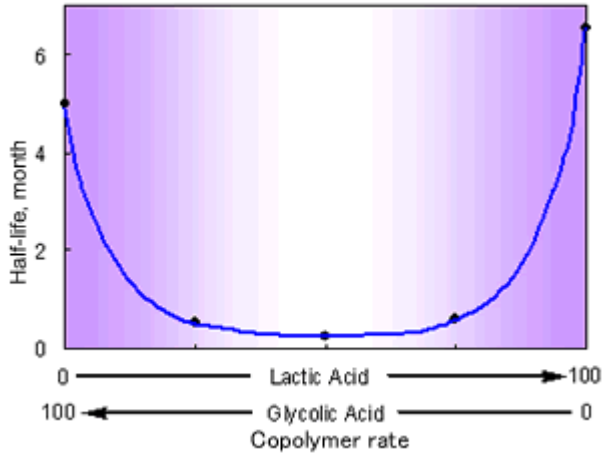


Figure 10: Half-life of PLGA copolymer at various molar ratios of PLA and PGA [14]

To select the proper molar ratio of PLA to PGA, published data on degradation of various molar ratios was examined. Polysorb sutures, which have a molar ratio of 82:18 PLA:PGA, are reported to lose 20% of strength after two weeks, lose 70% of strength after three weeks, and absorb completely over 56 to 70 days [15]. Vicryl sutures, which have a molar ratio of 10:90 PLA:PGA and are sometimes used by the client for anastomosis, lose 25% of strength after two weeks and lose 80% of strength after four weeks [16]. A US

patent for a two-piece absorbable staple made of PLGA suggests that the optimal molar ratio is 85:15 PLA:PGA [17].

Another important consideration was how the neobladder environment could affect the degradation rate of PLGA staples. A study measuring the degradation of Vicryl sutures in various body environments suggests that the degradation rate in the bladder tissue is only slightly faster than the published Vicryl rates above (losing 10% strength after 5 days) and that the degradation rate in urine is significantly faster (losing 22% strength after 5 days) [18]. All things considered, it seemed that the best option for molar ratio was 85:15 PLA:PGA because it should maintain its strength long enough for the anastomosis to heal; however, the actual degradation rate can only be determined by testing this polymer in the specific application and environment.

With molar ratio being the most important factor in selection of PLGA copolymers, the team had limited choices when it came to molecular weight or chain terminating groups because the materials were being ordered from chemical vendors rather than synthesizing a custom copolymer. Given the choice of molecular weights around 60 kDa or 225 kDa, the larger molecular weight is preferred because it should have greater mechanical strength; it is also closer to the viscosity of 1.6-1.9 dl/gm suggested in the previously mentioned patent [17]. The material selected was 85:15 PLA:PGA, ~225kDa molecular weight, alkyl ether terminated poly(D,L-lactide-co-glycolide) from Sigma Aldrich (product #739979)[11]. However, to reduce project costs, 85:15 PLA:PGA having a viscosity of 2.3 dl/gm was donated by Purac Biomaterials and was tested to ensure appropriate properties for mechanical strength and degradation rate.

Staple Design

With an absorbable PLGA polymer as the staple material, the design of the staple shape is essential for a successful anastomosis. Polymers have properties that are significantly different than metals; most notably, polymers are not as malleable and cannot bend to the same extent as metals while retaining strength. Thus, the staple cannot take the same shape as a typical metal staple, instead it must securely hold the tissue without bending. The previously discussed Insorb staples are a good example of polymeric staple design which does not require bending. Whereas the Insorb staples are designed to hold together two sides of a skin wound [12], the staples for uretero-intestinal anastomosis will perform a slightly different function. These staple will be introduced from inside the neobladder, through the neobladder tissue and finally through the ureter tissue (see Figures 11 and 12 for comparison).

The staples for uretero-intestinal anastomosis have been designed to account for this different mechanism of securing tissue. While the Insorb staples function well for holding skin wounds together, their design is insufficient for this project because the single barb would not allow for variability in tissue thickness and would not provide enough mechanical support to hold the tissues together. To address these issues, a number of designs were developed and are pictured in Figure 13. For the purposes of deciding which design to ultimately pursue, dimensions were not included because they can be easily changed as necessary. Designs were limited to be 2-dimensional for ease of fabrication with the laser cutter and ease of use with a stapler, which is yet to be designed. The simple barbs

and alternating barbs designs are relatively simple in that they only have one piece and are inserted into the tissue without modification; the barbs then secure the staple and the tissue in place. The zip tie design is different because it has two pieces; the horseshoe shaped piece pierces through the tissue and the top piece is placed over the legs of the other and will lock the staple in place with a mechanism similar to a zip tie.

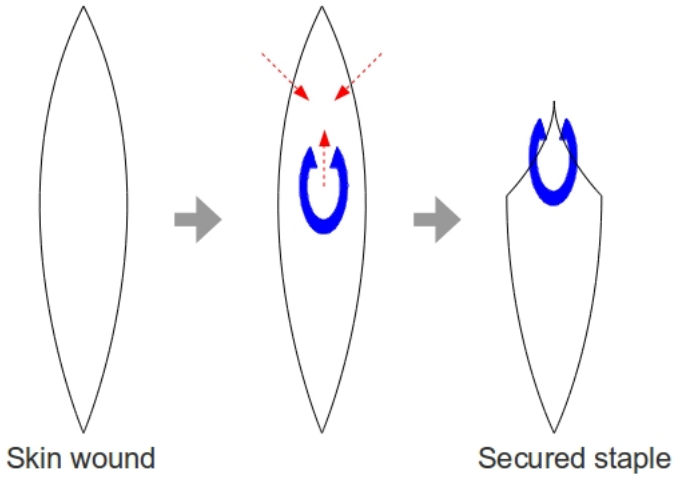


Figure 11: Diagram of Insorb staple illustrating the role of the staple in holding tissue together. The staple uses a horseshoe shape with a single barb on each staple leg (not to scale)

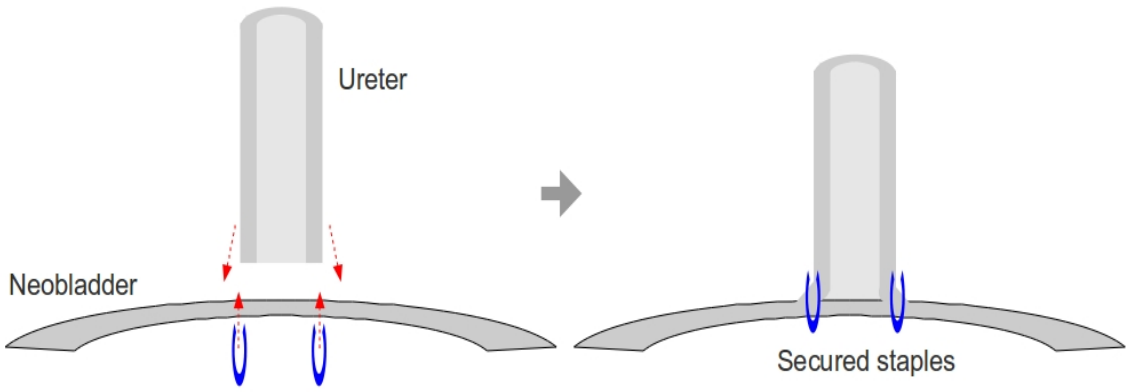


Figure 12: Diagram of proposed staples for uretero-intestinal anastomosis illustrating the role of the staples in holding the tissue together (not to scale)

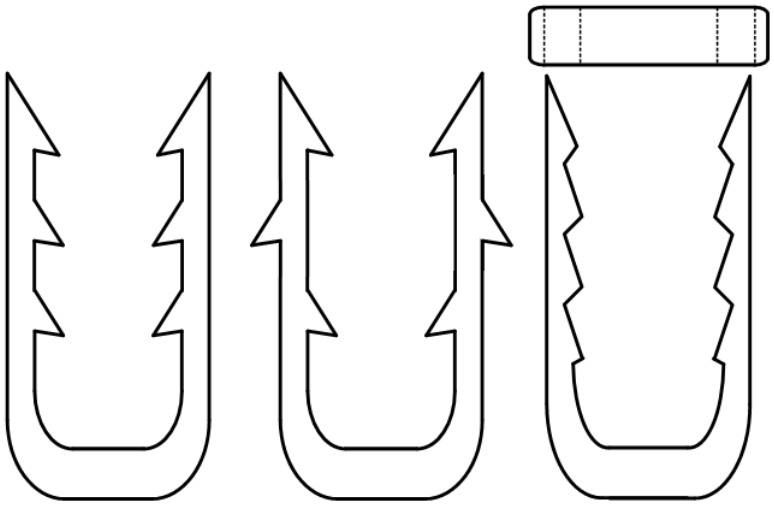


Figure 13: Staple designs considered for uretero-intestinal anastomosis

To evaluate the staple designs, the main considerations were the strength of anastomosis and the feasibility of creating a stapler to introduce these staples into the tissue. Other considerations in the design matrix (Table 1) include the ability to limit tissue damage and the manufacturability. Material selection and cost were also important factors; however, differences in cost are negligible due to the similar sizes of each staple and material selection is covered more thoroughly in the Material Selection section of this report. The complete design matrix is shown in Table 1 and indicates that the alternating barbs design is likely the best choice of designs. Although the simple barbs and the alternating barbs are very similar in design, the alternating barbs will provide more structural support to hold the tissue together for anastomosis. Furthermore, the alternating barbs design is much more feasible than the zip tie design, especially when considering stapler designs in the future. Since the alternating barbs design is a single-piece staple, it will be much easier to design a stapler to place these in the body. On the other hand, the zip tie design has two pieces and will ultimately complicate the design of the stapler. Thus, the alternating barbs staple design was chosen for the final staple design. If testing indicates that this staple does not provide sufficient strength for the anastomosis, the other designs could be considered.

Table 1: Design Matrix

Design Consideration	Weight	Simple Barbs	Alternating Barbs	Zip Tie
Strength of Anastomosis	35	20	25	33
Feasibility of Stapler Design	35	30	30	15
Ability to Limit Tissue Damage	15	12	10	14
Manufacturability	15	12	12	5
Total	100	74	77	67

The dimensions of the chosen staple design need to fit the target tissue characteristics. According to the client, ureters average about 7-10 mm in diameter and 5-7 mm in thickness. Furthermore, the intestinal tissue used to create the neobladder is about 12-14 mm thick. Based on this information, to place staples in two concentric rings around

the circumference, assuming 6 staples per ring, the staples should be about 3.0-3.5 mm in width. The length of the staples should be about 14.0 mm in order to pierce through both the neobladder and ureter tissue, assuming a slight decrease in tissue thickness due to the force of the staples. Finally, the staples should be about 0.5 – 1.0 mm in thickness and each leg should be about 0.5 – 1.0 mm wide to provide sufficient strength. Given these dimensions, the initial staple design shown in Figure 14 was drawn for use with the Epilog Mini CO_2 laser cutter [19]. Using this laser cutter, samples of these staples were cut and given to the client for feedback. It was decided that the staples should be 3-4 mm shorter, so the staple was redesigned slightly for this purpose. Additionally, it was noticed that the dimensions given to the laser cutter and the actual dimensions of the cut staple were slightly different; namely, the laser cutter has a finite width to its cut which caused the barbs and the legs to be much thinner than desired. To account for this, the staple was drawn with thicker legs and barbs so that the laser would cut the staples to be the desired dimensions. This improved staple image is shown in Figure 15 and is the staple design used for functional testing.

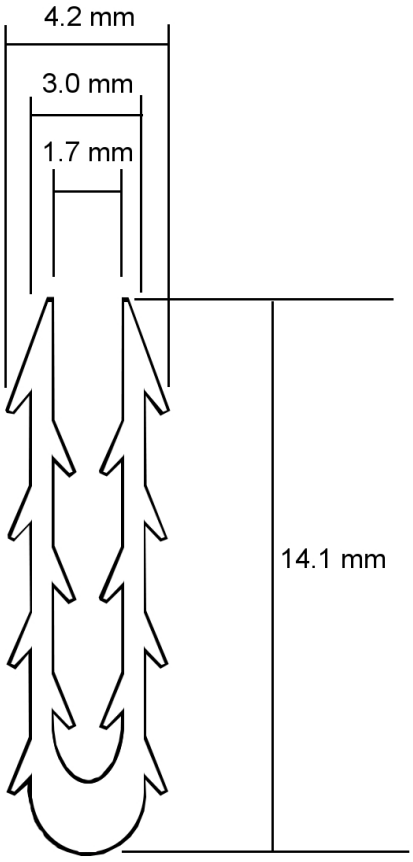


Figure 14: Initial staple design for use with laser cutter

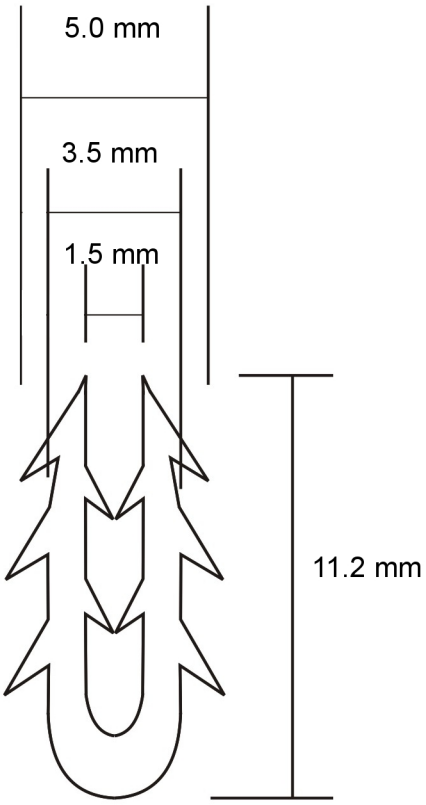


Figure 15: Improved staple design to account for laser width and client's feedback

Fabrication

To fabricate the staples and specimens for material testing, the team first designed a compression mold to form a 1mm thick sheet of PLGA. The group then used an Epilog Mini CO_2 40 Watt laser cutter, courtesy of the UW-Department of Biomedical Engineering teaching lab, to cut staples and tensile test specimens from the sheets of PLGA.

Fabrication of the Compression Mold

The group used a CNC mill in the UW-College of Engineering Student Shop to fabricate a compression mold from aluminum. The mold consisted of two pieces, a base and a lid, which fit together to compress the material into 1mm thick, 45mm x 16mm sheet of PLGA, from which the team could cut approximately 6 staples. The dimensions of the mold are shown in Figures 16 and 17, while a picture of the final mold is shown in Figure 18.

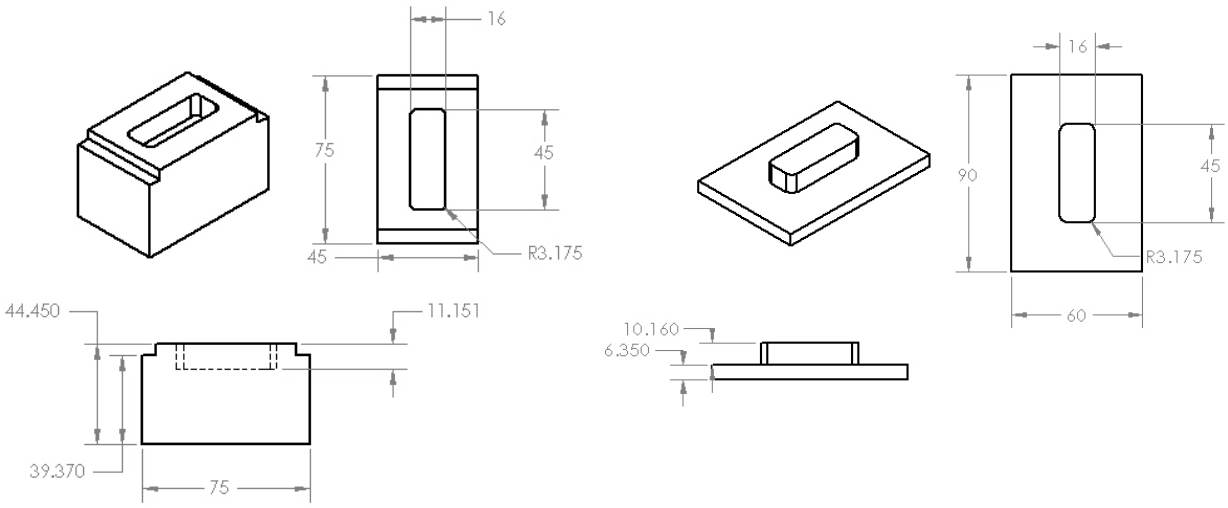


Figure 16: Drawings for the base and lid of the team's compression mold. The base (left) contains a cavity into which the raw material is placed. The two cuts on either end are for prying the mold open after the piece has cooled. The lid (right) contains an extrusion matching the cavity in the base. Overall the lid and base were cut very thick to help prevent warping of the mold during repeated use.

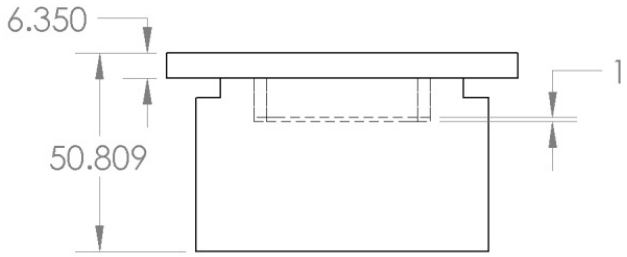


Figure 17: A drawing of the two assembled mold pieces. When the two pieces are placed together they create a roughly rectangular cavity that measures 45mm x 16mm x 1mm.

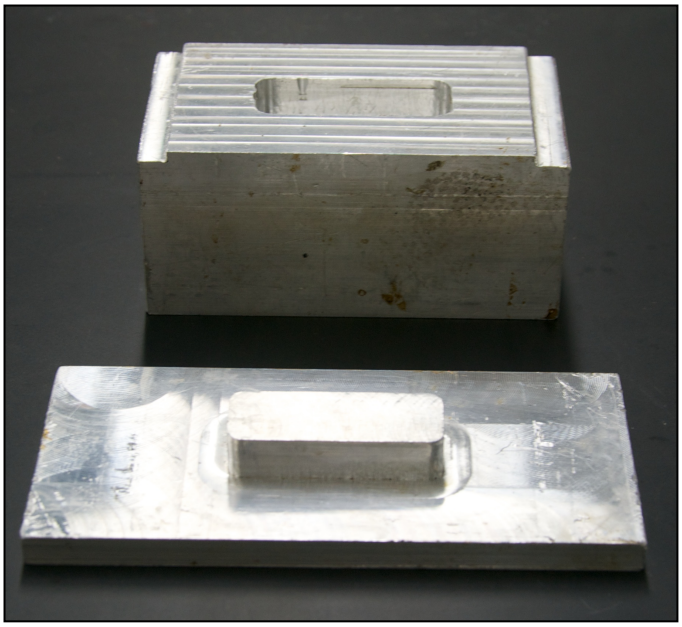


Figure 18: A picture of the final mold made from aluminum, with the base above and the lid below.

Compression Molding the Sheets

Before beginning the molding process, the group preformed a differential scanning calorimetry (DSC) test to determine the melting point of the material (Figure 19). The large dip on the DSC indicates the melting point is 149°C. Following instructions from a Purac representative, the team added 20°C to the melting temperature to obtain the desired processing temperature of 169°C. The additional 20°C above the melting point ensures that any material within the mold will melt completely and therefore flow evenly. Because PLGA degrades thermally, it was important to minimize the temperature used during molding and minimize the time the material spent at high temperatures.

After the volume of the mold was calculated to be 0.71mL, the team used the material density (as provided by Purac) to calculate the amount of material required to fill the mold. PLGA has a density of 1.24g/mL, so the team used approximately 0.88g of PLGA per sheet.

To mold the material, the team pre-heated the mold to the processing temperature then added approximately 0.88g of material to the mold cavity. The group then placed the lid on the base and compressed the material at 169°C for 10 minutes (Figure 20). After 10 minutes, the mold was allowed to cool slowly at room temperature with a weight on the lid. After the mold was cool enough to touch, the team removed the PLGA sheet from the mold.

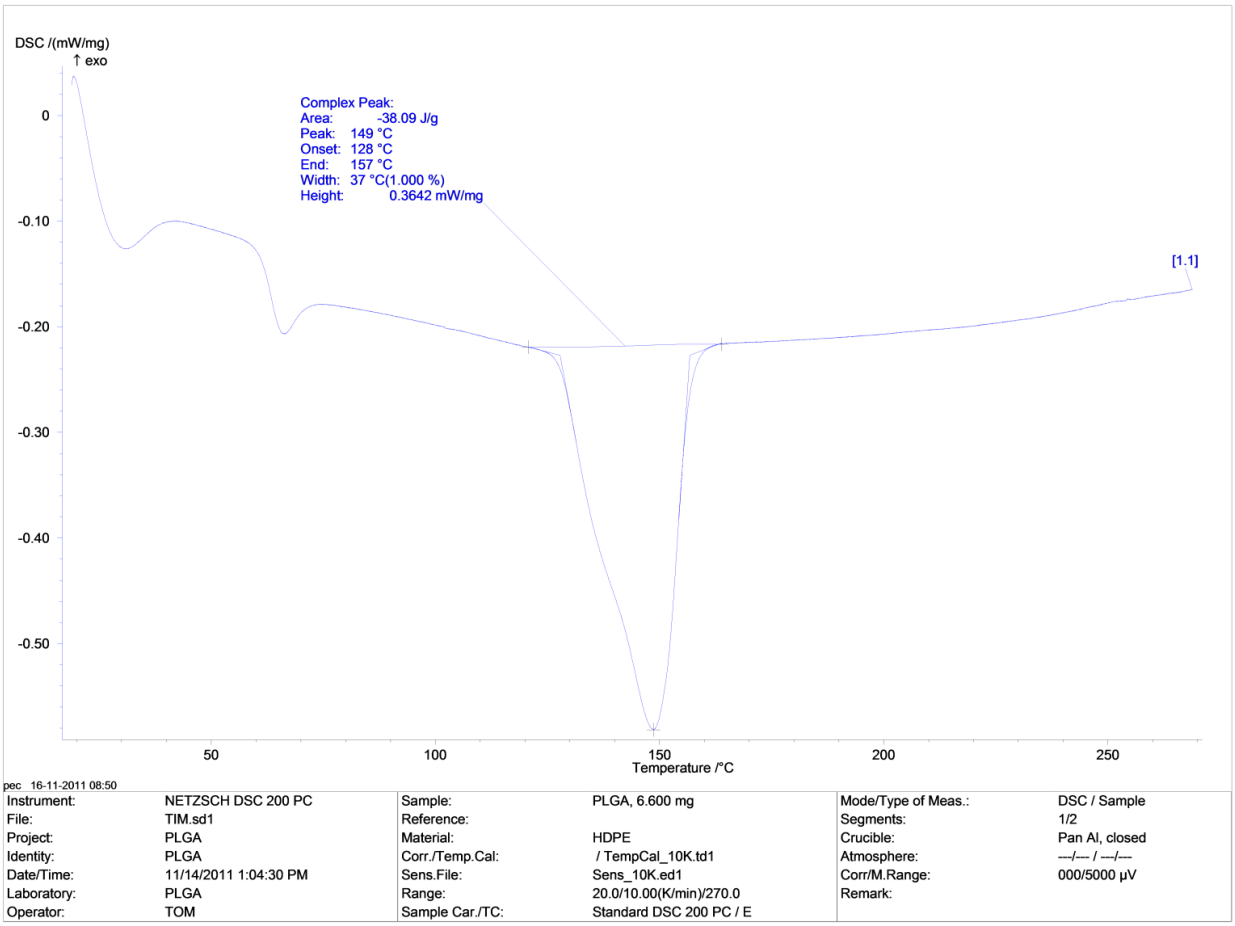


Figure 19: Using a DSC test, the team determined that the melting point of the PLGA is 149°C. The DSC test was based on ASTM standards with at starting temperature of 20°C, an ending temperature of 260°C, and a heating rate of 10°C/min.

This method produced sheets with consistent sizes and thicknesses; however, the sheets contain bubbles which could affect the strength of the staples and tensile test specimens (Figure 21). In the future, the team hopes to research methods to eliminate bubbles during the molding process.

Cutting the Sheets with a Laser Cutter

After compression molding PLGA sheets, the team used the Epilog Mini laser cutter to cut out the final staples and tensile test specimens. The drawings for the staples and test specimens were made using Corel Draw X3 and are shown with dimensions in Figure 22. To cut the staples, the team set the laser parameters to 100% power, 60% speed, and maximum frequency.

Dimensions for the test specimens were determined using ASTM standards for a Type I material, as explained later in the testing section.

The final staples can be seen in Figure 23.

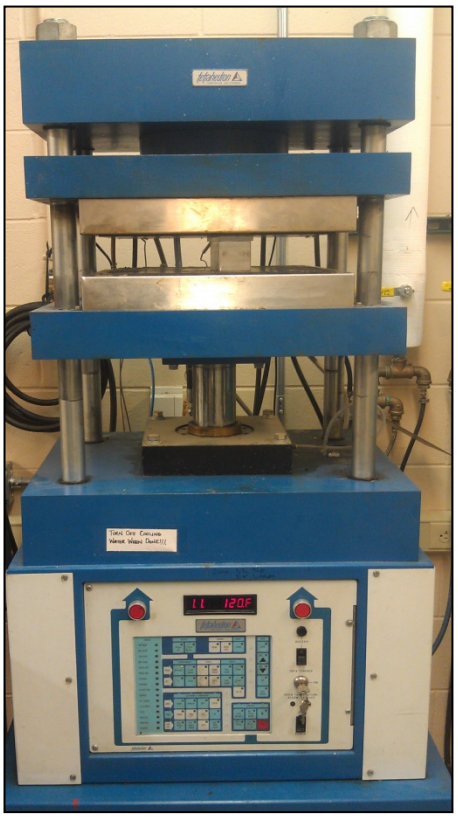


Figure 20: Image of the mold in the compression molder, which simultaneously heats and compresses the PLGA to form it into the desired shape

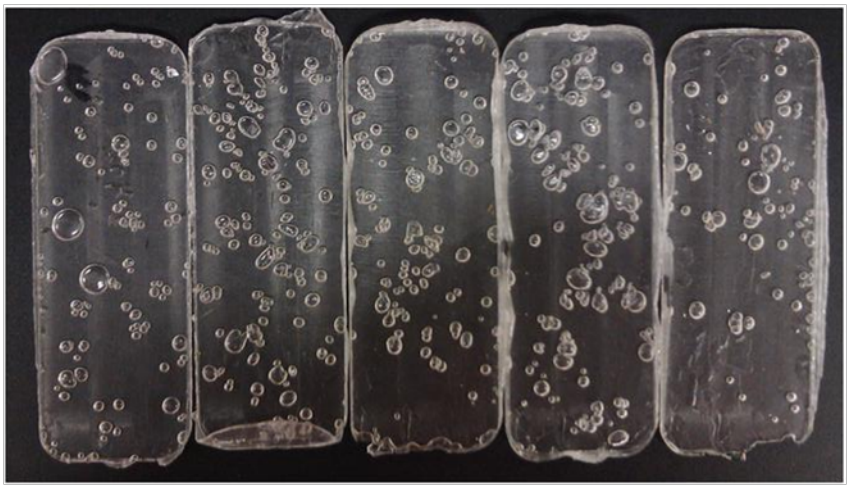


Figure 21: Compression molded PLGA sheets used to produce staples and test specimens

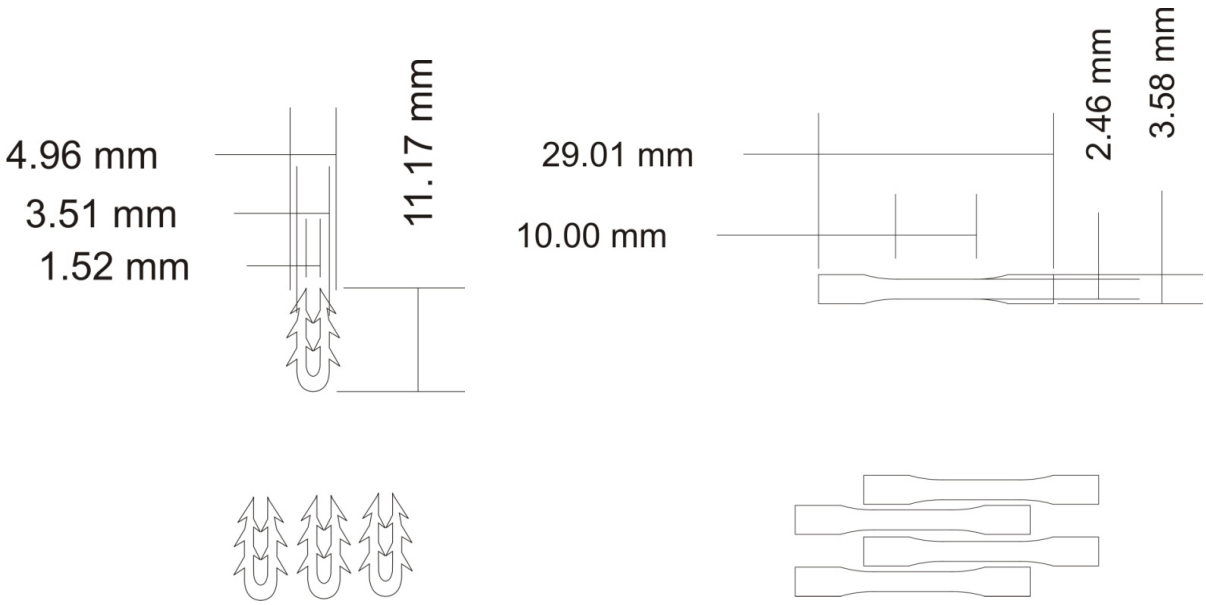


Figure 22: Dimensions for staples and test specimens as drawn in Corel Draw X3

Figure 23: Picture of staples after being cut with the laser cutter

Testing

Degradation Testing

The team analyzed the mechanical properties of the staples during degradation to ensure that the staples can hold the tissue together throughout the healing process. The samples used in this test were tensile bars made of PLGA. The dimensions of these test samples were calculated using the specimen dimension requirements in ASTM D638-10 Standard Test Method for Tensile Properties of Plastics, as shown in Figure 24. The specimens were classified as Type I which is preferred for molded rigid and semirigid plastics where the material thickness is 7 mm or less. The staples are 1 mm thick, so they fall under this category. The dimensions given in the standard had to be scaled down to fit the molded PLGA sheet. The scaled dimensions are listed in Table 2. Using the laser cutter,

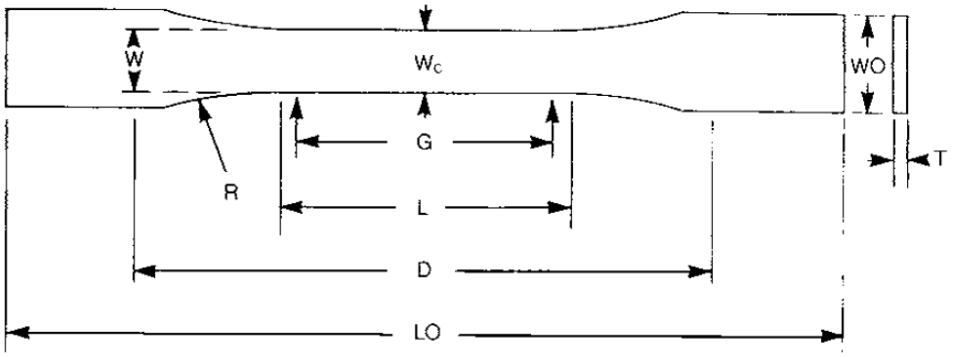


Figure 24: The shape of a tensile bar specimen for Type I molded rigid and semirigid plastics as required by ASTM D638-10. See Table 2 for dimension values [20].

Table 2: The dimensions of a test specimen for Type I molded rigid and semirigid plastics as required by ASTM D638-10 and scaled down for this project. See Figure 24 for dimension definitions [20].

Symbol	ASTM Value (mm)	ASTM Tolerance (mm)	Scaled (mm)
W	13	±0.5	2.28
L	57	±0.5	10.00
WO	19	+6.4	3.33
LO	165	no max	28.95
G	50	±0.25	8.77
D	115	±5	20.18
R	76	±1	13.33
T	≤7	≤7	1.00

four tensile bar specimens were cut out for each compression molded PLGA sheet as described in the fabrication section.

Since the staples will contact urine, which has a pH ranging from 4.5-8.0, degradation testing would ideally be performed at a variety of pH's within this range [21]. However, due to limited material, only the two extreme pH's (4.5 and 8) were tested, since these extreme pH conditions are most likely to increase the degradation rate. 200 mL of 0.1 M phosphate buffered saline (PBS), which was set to the desired pH of 8.0 using NaOH. 0.1 M acetate buffer was made by mixing 1.75 g of sodium acetate (13.6 g/L), 0.433 mL of 16.5 M acetic acid, and about 200 mL of water. It was set to the desired pH of 4.5 using HCl.

Ethicon size 4-0 Vicryl sutures (product number J773D) were used as a comparison to the PLGA test specimens since these are the sutures currently used by the client for uretero-intestinal anastomosis. Three PLGA specimens and three sutures were tested per degradation time point at each pH. ASTM D638-10 requires at least five specimens to be tested; however, the sample size needed to be smaller due to limited PLGA material. Specimens were left in the respective pH solution for 0, 10, or 19 days. Ideally, degradation testing would have been performed at more time points, extending past 30 days; however, this was not possible due to time constraints and limited material. The specimens for Day 0 were not put in any buffer solution and serve as a base for comparison. The other twelve PLGA and twelve suture specimens were each put in one well of a 6-well plate. Half of the specimens were immersed in 3 mL pH 4.5 acetate buffer and the other half were immersed

in 3 mL pH 8.0 PBS. The plates were put into an incubator that was kept at 37 °C. The buffer solutions were changed every five days.

Once the respective degradation time had passed, a simple tensile test was conducted on the specimens. The test was conducted on an Instron 5566 Universal Testing Machine. The test configuration is pictured in Figure 25. The sutures were cut to a length of 50 mm before beginning the tensile test. A crosshead velocity of 5 mm/min was used as per the ASTM standard, and the specimens were tested to failure.

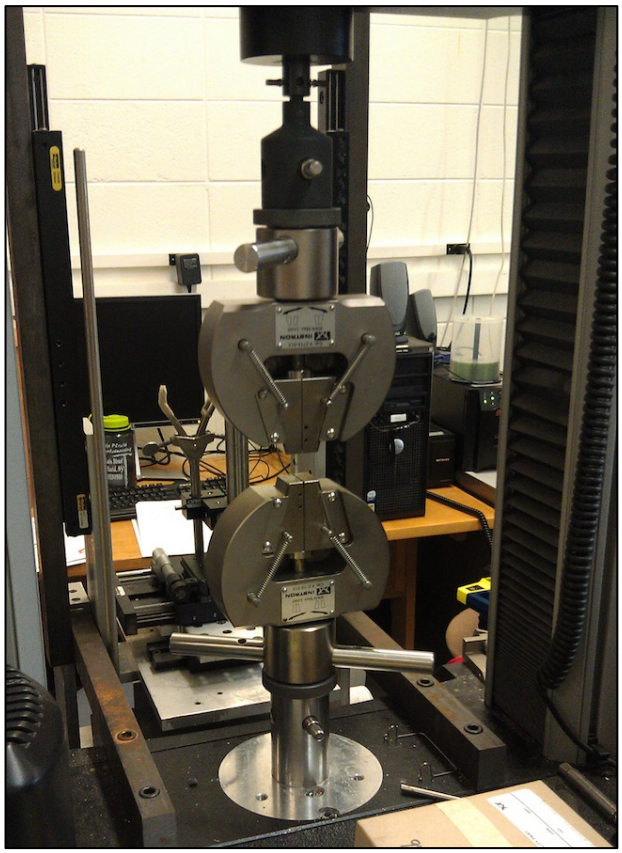


Figure 25: Tensile testing configuration using an Instron 5566 Universal Testing Machine

Figure 26 and Table 3 give the data from tensile testing of the PLGA specimens, while Figure 27 and Table 4 give the data from tensile testing of the Vicryl sutures. Additional tensile test data is provided in Appendix B. The different pH conditions for both the PLGA and sutures do not significantly impact the mechanical strength when comparing within respective days. This is encouraging because it indicates that the staples should be able to withstand the wide range of pH's of the urine. As Figure 28 shows, the ultimate strength of the PLGA specimens is between 33 and 38 MPa value for days 0 and 10, but there is a more dramatic drop in ultimate strength at day 19 where the ultimate strength was 23.8 ± 7.0 MPa for pH 4.5 and 25.7± 5.7 MPa for pH 8.0. As Figure 29 shows, the ultimate strength of the sutures decreased from 843.0 ± 79.4 MPa at day 0 to 820.4 ± 31.8 MPa for pH 4.5 and 702.3 ± 42.4 MPa for pH 8.0 at day 19. The PLGA degrades slightly more quickly than the sutures, as the ultimate strength of the PLGA decreased by about 25% by

day 19 and the ultimate strength of the sutures decreased by about 16% by day 19. This indicates that the staples and sutures have begun to degrade by day 19, and in the future, degradation testing will be conducted over a longer time period to find when the burst effect occurs. The burst effect is the time when the mechanical strength of the PLGA decreases dramatically. It will also be important to conduct tensile testing up through 30 days because one of the design criteria is that the staples should be able to withstand the bladder environment and secure the ureter to the neobladder for a minimum of thirty days.

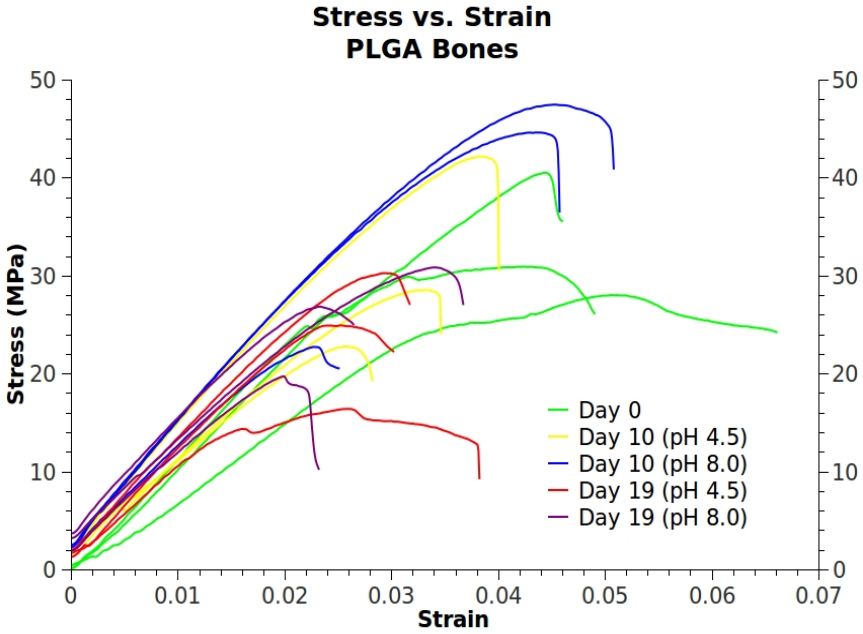


Figure 26: Stress-strain curves of the tensile test data for PLGA specimens

Table 3: A summary of the tensile test data for PLGA specimens

Degradation of PLGA Specimens				
Average (standard deviation)				
Day		0	10	19
Ultimate Strength (MPa)	pH 4.5	33.1 (6.5)	33.9 (8.6)	23.8 (7.0)
	pH 8.0		38.2 (13.5)	25.7 (5.7)
Yield Strength (MPa)	pH 4.5	25.0 (1.0)	27.7 (4.6)	20.7 (6.1))
	pH 8.0		30.0 (8.7)	22.3 (2.9)
Yield Strain	pH 4.5	0.027 (0.006)	0.027 (0.005)	1.018 (0.004)
	pH 8.0		0.024 (0.005)	0.019 (0.002)
Elastic Modulus (GPa)	pH 4.5	1.04 (0.19)	1.03 (0.21)	1.07 (0.07)
	pH 8.0		1.17 (0.09)	0.97 (0.11)

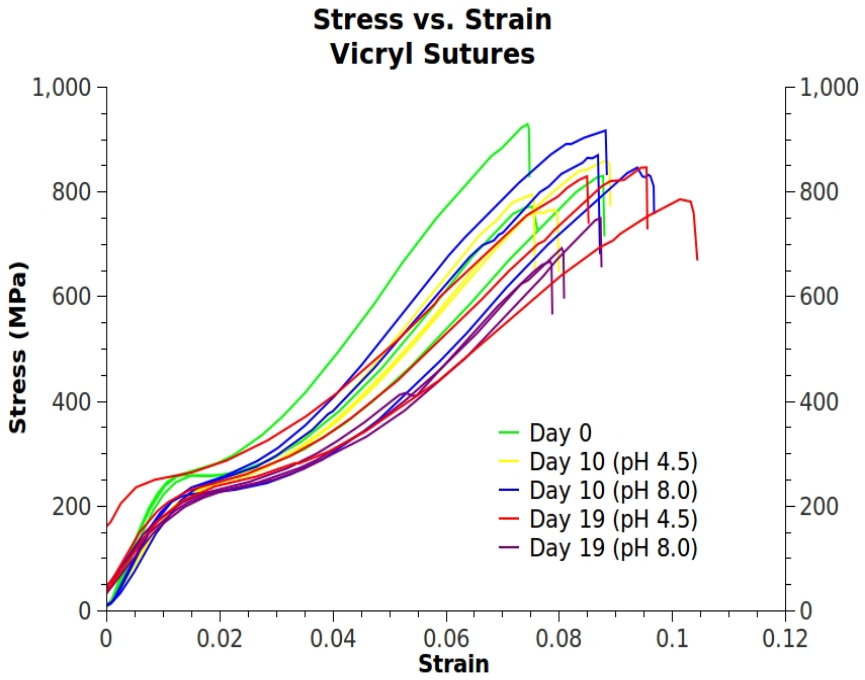


Figure 27: Stress-strain curves of the tensile test data for Vicryl specimens

Table 4: A summary of the tensile test data for Vicryl sutures

Degradation of Vicryl Sutures				
Average (standard deviation)				
Day		0	10	19
Ultimate Strength (MPa)	pH 4.5	843.0 (79.4)	805.5 (47.5)	820.4 (31.8)
	pH 8.0		872.4 (42.4)	702.3 (42.4)
Yield Strength (MPa)	pH 4.5	803.3 (45.1)	753.3 (32.1)	760.0 (65.6)
	pH 8.0		750 (26.5)	680.0 (20.0)
Yield Strain	pH 4.5	0.074 (0.009)	0.072 (0.005)	0.084 (0.006)
	pH 8.0		0.074 (0.010)	0.081 (0.005)
Elastic Modulus (GPa)	pH 4.5	12.90 (1.45)	12.60 (0.78)	9.85 (0.48)
	pH 8.0		12.50 (0.69)	10.84 (0.09)

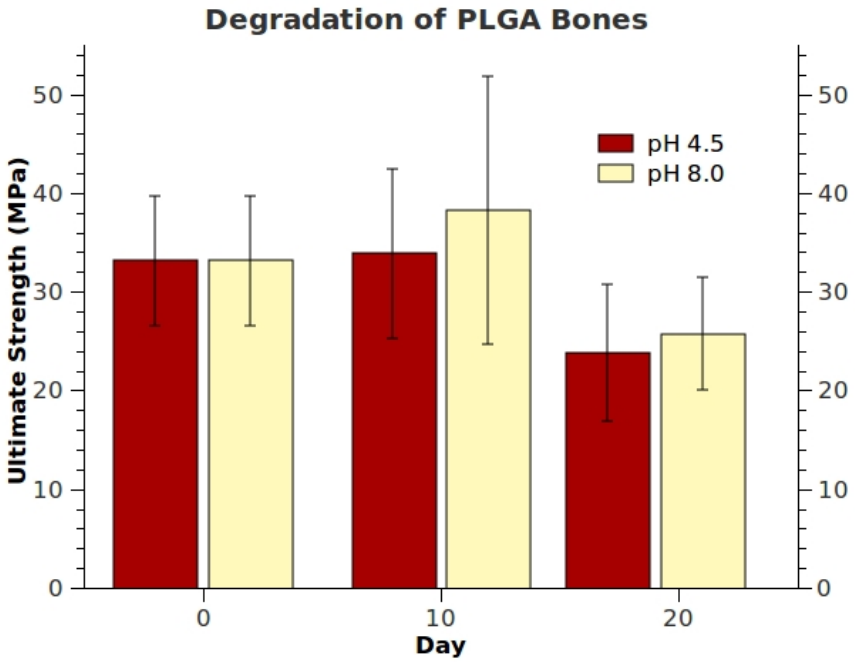


Figure 28: Tensile test data showing the average ultimate strength of PLGA specimens after various degradation times

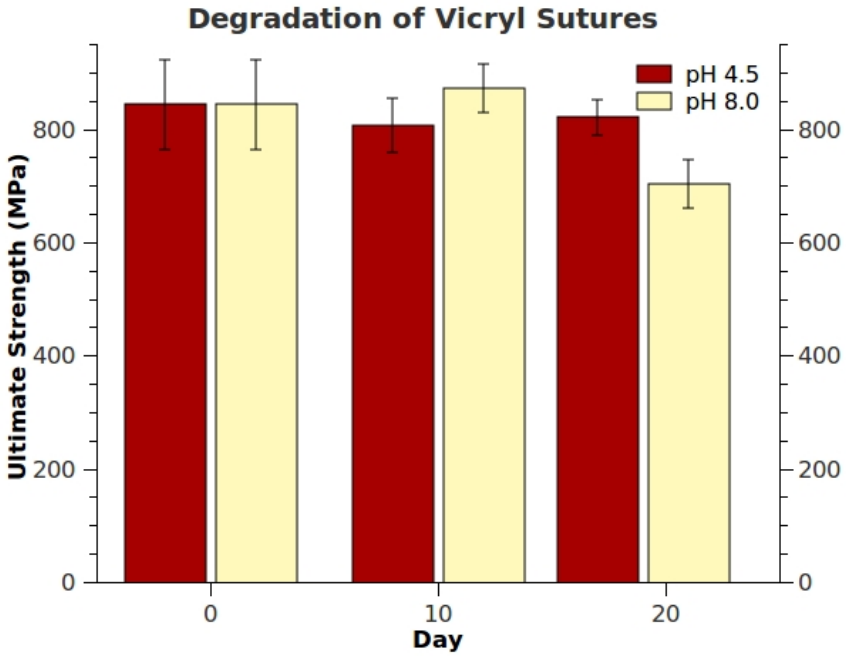


Figure 29: Tensile test data showing the average ultimate strength of Vicryl sutures after various degradation times

The sutures had a much higher ultimate strength than the PLGA specimens over the testing duration. This is to be expected because the sutures are mass manufactured by a well-defined process. However, since the PLGA staples have a larger cross-sectional area than the Vicryl sutures, the load-bearing capacity is actually comparable between the two. PLGA still maintains a significant amount of strength at day 19. This indicates that the

staples should maintain enough mechanical strength to secure the ureter to the neobladder at least through day 19, at which point significant tissue healing has already occurred.

Functional Testing

A test was conducted in order to test the functionality of the staples. The initial test setup is pictured in Figure 30, which measures the force it takes to pull a staple out of a raw, boneless chicken breast. An Ethicon Vicryl suture was formed into a loop by tying the ends together. The suture loop was put in between the legs of the staple and the staple was pushed into the chicken breast until all of the barbs were in the tissue. The hook of an OHAUS spring gauge (Model 8014-N) was then hooked on the suture loop. The spring gauge was then pulled vertically while the chicken breast was held to the table, and a camera was used to film the test. Multiple trials were performed, but the force it took to pull the staple out could not be measured on the spring gauge, which measures forces from 0-20 N. A more sensitive measuring device was not available, so another test method was sought out.

Figure 30: The initial test setup to measure the force it takes to pull a staple out of a chicken breast

The final test setup is pictured in Figure 31, which measures the force it takes to pull a staple out of foam packing material. Since a measurable force was obtained for this test, this was the final test setup. The suture loop was put in between the legs of the staple and the staple was pushed through eight layers of the packing material, having an approximate thickness of 7 mm, until all of the barbs were in or through the packing material. The same test was performed with the OHAUS spring gauge. For comparison, sutures were also tested by threading the suture through eight layers of the packing foam, tying a loop with the ends, attaching the spring gauge to the loop, and pulling the spring gauge vertically while holding down the packing foam to the table. The distance between the insert into the foam and exit from the foam of the suture was approximated to be the distance between the two legs of the staple. Five samples of both staples and sutures were tested, and the results are listed in Table 5. The average force it took to pull a staple out was 3.74 ± 1.01 N,

which is only slightly larger than the average force of 3.56 ± 1.82 N that it took to pull a suture out. A two-tailed Student's t-test was performed on the data and a p value of 0.85 was obtained; therefore, there is no significant difference between the force it takes to pull the staples and the sutures out of the packing material.

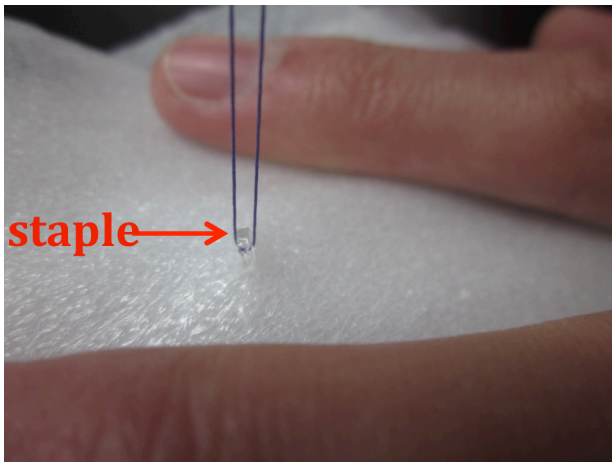


Figure 31: The final test setup in which the force it takes to pull a staple out of foam packing material was measured

Table 5: Results obtained from functional testing of the staples compared to the sutures

	Force to Remove Staple (N)	Force to Remove Suture (N)
	2.4	2.0
	2.9	2.6
	4.4	2.2
	4.5	6.0
	4.5	5.0
Average	3.74 ± 1.01	3.56 ± 1.82

It should be noted that the foam packing material is not a physiologically relevant model of the anastomosis; one reason being that the anastomosis only consists of two layers of tissue about 12 mm in total thickness, not eight layers 7 mm thick as for this test. Although a better representation, the chicken breast is also not a completely relevant model, since the structure of skeletal muscle is very different from that of the smooth muscle that the ureters and intestine are composed of. A future test should employ a more physiologically relevant model so that more meaningful results can be obtained. A future test should also use a more sensitive force gauge, since it was demonstrated in the test with the chicken breast that the force to remove the staple from tissue could be less than 1 N.

SolidWorks Modeling

The staple design was drawn in SolidWorks to analyze various mechanical loading scenarios. The results of these tests are shown in Figure 32. As expected, when a 1N test load is applied to the tip of the staples, the Von Mises stress is highest where the legs meet the base of the staple. Therefore, if a load was applied in the area specified (as indicated by

the purple arrows), failure would occur first at these points. These areas should be reinforced with more material to prevent premature failure; however, it can only be determined whether this is necessary after mechanical testing is performed on the actual staple.

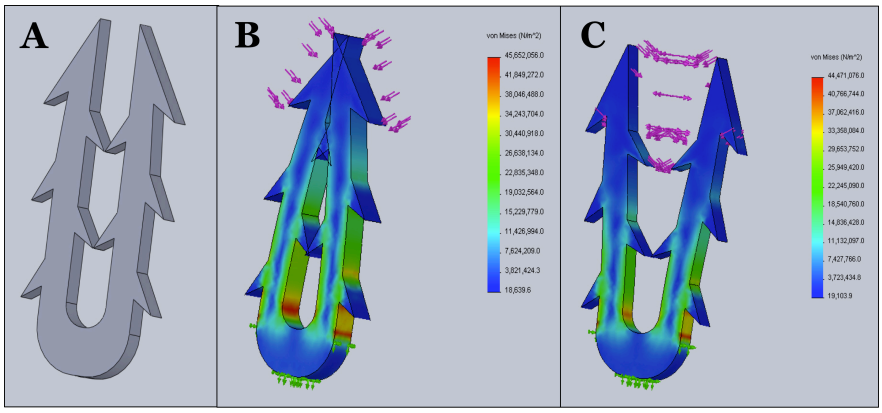


Figure 32: (A) SolidWorks drawing for the final staple design. (B) and (C) Von Mises stresses for fixture (shown in green) and loading (shown in purple).

Future Work

The team's work with the staples this semester has provided insight into the difficulties of processing PLGA. Air bubbles in the PLGA sheets this semester were a major concern, so more research will need to be conducted into why these bubbles form and ways that they can be avoided. Once a bubble-free sheet has been produced, the team plans to repeat degradation and strength testing.

The previous team focused almost exclusively on the stapler; therefore, the current team has a working model. Unfortunately, this stapler will require redesign as the staples designed by the previous team for the stapler were deemed unworkable. The client also requested a few additional changes regarding the ease of use of the stapler.

The team plans to continue degradation testing to a full time period of at least 60 days. Functional testing will also be continued to test the strength and quality of the anastomosis. Animal models will most likely be used for this testing.

Ethical Concerns

Patient safety is a primary concern with the staples and stapler. According to the FDA, surgical staples qualify as a class II medical device and must therefore comply with FDA standards for patient safety. Class II medical are subjected to more stringent control from the FDA than class I devices, which typically present minimal risk to users. Special controls for class II devices often include labeling requirements, post-market surveillance, and additional performance standards. Some common examples of class II devices include surgical needles, sutures, and other surgical staplers [22]. Staples for this project are made of PLGA, which has already been approved by the FDA for use in the body, while the stapler

design would likely qualify for a 510(k) since many previously approved staplers use similar materials and firing mechanisms for alternative applications within the body.

To ensure patient safety, the absorbable staples should hold tissue in place within the body as expected and should degrade at a rate compatible with healing time. This will ensure the staple will indeed hold the tissue in place. The staple material should also be biocompatible and should not elicit an immune or inflammatory response. Since the staples are biodegradable, the degradation products should not be cytotoxic and should be cleared naturally by the body. Finally, the material should minimize fibrosis of the surrounding tissue during healing and should not increase the patient's risk of infection, by promoting bacterial growth. This is a potential concern for the staples, since neobladders are commonly constructed from the small intestine, which, unlike a urinary bladder, promotes bacterial growth.

Ergonomics

Because surgical staples must remain sterile prior to surgery, two sets of staples (enough to staple both ureters to the neobladder) will be pre-loaded in the stapler and will therefore not be a concern with regards to ergonomics. However, ergonomics will be a significant concern in stapler design, since the goal of the product is to simplify the surgical procedure and to reduce operating time. The entire surgery may be performed endoscopically, which means the surgeon will have only a small area to access the bladder and ureters. For this reason, the neck of the stapler should be curved to allow the surgeon better access to ureters and neobladder (Figure 3 on page 5). This would be a modification from the stapler design of the previous group, which had a completely straight neck. Secondly, the stapler's firing mechanism should be simple and intuitive for the surgeon. This means that the surgeon should be able to pull the trigger to place the staples using only one hand and a comfortable grip. Finally, the stapler should be compatible with both left and right-handed users.

Cost Analysis

Biomaterials was able to donate 10g of 85:15 PLGA, and the group obtained aluminum stock for building the compression mold from the UW College of Engineering Student Shop free of charge. Finally, the testing materials included: two 500mL sterile filter bottles, four 6-well plates, 200mL PBS, four Pasteur pipettes, eight 5mL serological pipettes, eight 15mL conical tubes, and gloves. The cost for these materials is unknown at this time. In whole, the team had no major expenditures.

Conclusion

This semester, the team has designed an absorbable staple comprised of 85:15 poly(lactide-co-glycolide) (PLGA) to assist with the surgical treatment of bladder cancer. The PLGA was compression molded into a sheet and then cut into staples using an Epilog Mini CO_2 laser cutter. Degradation, tensile, and functional testing was performed using PLGA to determine the properties of the material. Data showed that the staples can hold forces comparable to the sutures the client currently uses, and should maintain sufficient strength to hold the tissues together to promote anastomosis for at least 19 days. The team plans to continue testing the chosen material and staple design, optimize the fabrication process, and focus on designing a stapler, which will deliver the staples during the surgical procedure.

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Appendix A – Product Design Specifications

Absorbable Staples for Use in an Automated Uretero-Intestinal Anastomosis

September 28th, 2011

Leader: Samantha Paulsen
BSAC: Vanessa Grosskopf
BWIG: Matt Bollom
Communicator: Jeff Theisen

Problem Statement:

In patients with bladder cancer, the bladder can be either partially or completely removed. A procedure called a radical cystectomy is required to completely remove the bladder when cancer has invaded the muscle layer of the bladder. Afterwards, a section of the small intestine can be used to form a new bladder (neobladder). If the neobladder is not constructed, a ureostomy bag is implemented instead. However, in both procedures the ureters must be connected to the new bladder tissue; this is currently done using absorbable sutures. There are several complications associated with this approach due to the invasiveness and length of the procedure. Our goal is to design absorbable staples to be used in an automated uretero-intestinal anastomosis, to be used with a specialized stapler. The staples should be strong enough to secure the ureters to the neobladder or ureostomy bag and should degrade to avoid the need for a second intervention.

Client requirements:

- Must be completely absorbable to allow for full tissue healing and regeneration
- Must form a water tight seal on the intestine-ureter linkage
- Must be biocompatible – no immune reaction
- Must be able to withstand the caustic environment of the ureter when it is filled with urea.
- Must hold their shape
- Must be strong/sturdy but flexible enough to be bent
- Must work in conjunction with the stapler

Design requirements:

1. Physical and Operational Characteristics

a. *Performance requirements*: Will be used with a single use stapler to perform an automated anastomosis to secure two ureters to a neobladder.

b. *Safety*: Must not damage surrounding tissue in the abdominal cavity, bladder, or ureters. Must create a secure water-tight seal with both ureters to allow for normal use of the kidneys post-surgery. Must not cause infection or immune response.

c. *Accuracy and Reliability*: The seal created must be water-tight.

d. *Life in Service*: Will be single use and should degrade in a period of 30-90 days in vivo.

e. *Shelf Life*: Should last at least 1 month in storage.

f. *Operating Environment*: The device will be inserted into the abdominal cavity for a surgical procedure. More specifically, the staples will be inserted into the ureters and will be exposed to temperatures around 37 ^{o}C and urine, which has a high salt content. The staples must be sterile to avoid cross-contamination.

g. *Ergonomics*: The user will not handle the staples, so ergonomic considerations will be focused on the stapler.

h. *Size*: The staples should be large enough to secure the ureter to the neobladder, but small enough to fit two concentric rings of staples into the tissue. The diameter of the ureter ranges from 7-10mm in diameter.

i. *Weight*: Negligible

j. *Materials*: The final material will be a bioabsorbable polymer FDA approved for use in the human body.

k. *Aesthetics*, *Appearance, and Finish*: Not applicable

2. Production Characteristics

a. *Quantity*: To be determined based on final staple design.

b. *Target Product Cost*: Undetermined, under $1 per staple.

3. Miscellaneous

a. *Standards and Specifications*: Must be approved for safety and function by the surgeons utilizing the device. Must have IRB approval once used in humans.

b. *Customer/Patient related concerns*: Must create a water tight seal after anastomosis is performed. Must not do damage to any other tissues in the body. The staples should degrade eventually to promote tissue healing and regeneration. Since the staples will be contacting high salt concentrations, the material should not promote the formation of kidney stones.

d. *Competition*: There is currently no product made specifically for sealing the ureter to the neo-bladder during anastomosis.

Appendix B – Additional Testing Data

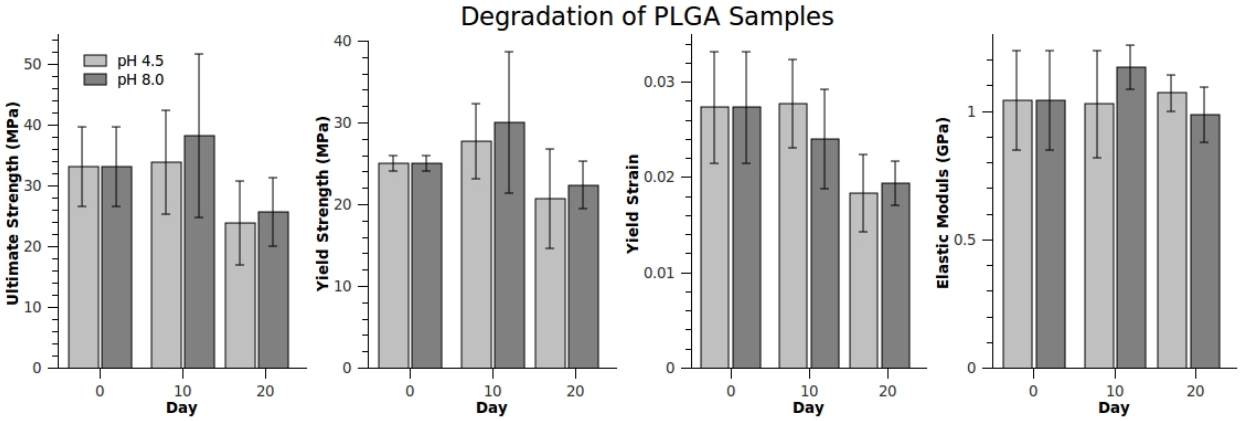

Figure 1: Additional tensile test data showing the average ultimate strength, average yield strength, average yield strain, and average elastic modulus of PLGA specimens at the respective degradation times

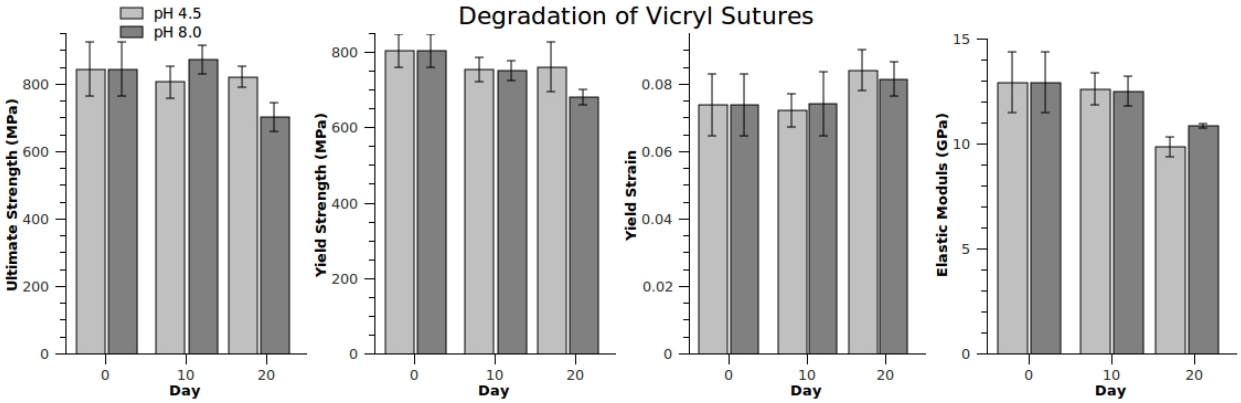

Figure 2: Additional tensile test data showing the average ultimate strength, average yield strength, average yield strain, and average elastic modulus of Vicryl suture samples at the respective degradation times