Mechanical Simulation of Human Pleura for Medical Training by Crosslinked Polyurethane

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Abstract

Mechanical Simulation of Human Pleura for Medical Training by Crosslinked Polyurethane

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Due to the absence of abundant mechanical data on human tissues, currently used medical training materials and devices are not well simulated by synthetics, which hampers the ability of trainees such as soldiers to best master first-aid methods. The present study is to use crosslinked polyurethanes (PU) to simulate mechanical properties of human tissues, starting with pleura, to develop an appropriate synthetic simulator for military medical training. As a result, two partial crosslinked PUs are proved to be promising candidates for pleura simulator, with perfect matches on ultimate tensile strength (UTS) and stretch ratio (SR) of human pleura, indicating the great potential to use PU synthetics to mimic the mechanical behavior of pleura and other human tissues for medical training purpose.

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Chapter 1. Introduction

1.1 Tissue Simulation

Medics are required to take adequate medical trainings before performing operations on patients. Similarly, combat medics and soldiers are required to master first-aid approaches in austere environments without basic life support equipment [1]. However, it is suggested that medical errors lead to a death rate of 251454 patients annually, the third leading cause of death in the United States [2]. In spite of this grim statistic, the military expects more lives to be saved on the battlefield by improved training to non-surgeons. The current difficulty here is the inadequacies of medical simulators, in particular, the significant differences in mechanical properties between human tissues and their corresponding simulators for medical training. The lack of fidelity of synthetic simulators is largely a result of the absence of quantitative guidance towards their synthesis. Little data on the mechanics of human tissues is found in literature and previous simulator synthesis normally relied on animal data, such as from the rabbit. Unfortunately, data acquisition of human tissues is another challenging task. Due to the decay of cadaver tissues and subsequent altered properties, tissues from fresh cadavers should be measured within 72 hours of death to maintain their fidelity [3]. In addition, the properties of human tissues are not readily described, in that they are influenced by age, gender, race, location, disease history and hydration levels. These factors, combined with the anisotropic architectures of tissues [1], make it extremely difficult to establish a standard to direct material synthesis for tissue simulation. Although cadavers and animals are currently used for medical training and they surpass synthetic simulators, the existence of various flaws, including cost, storage and ethical difficulties, makes them less optimal for training [3]. To address this issue, since 2015, the Army Research Laboratory (ARL) has teamed with academia and industry to better define and describe human tissues and to apply those characteristics to medical simulation systems. The present study is focused on developing alternative synthetic simulators by polymer synthesis with the guidance of newly acquired human tissue data from collaborators. Pleura is the first tissue to start with for using human mechanical data to develop mechanically accurate simulator polymers.

1.2 Pleura

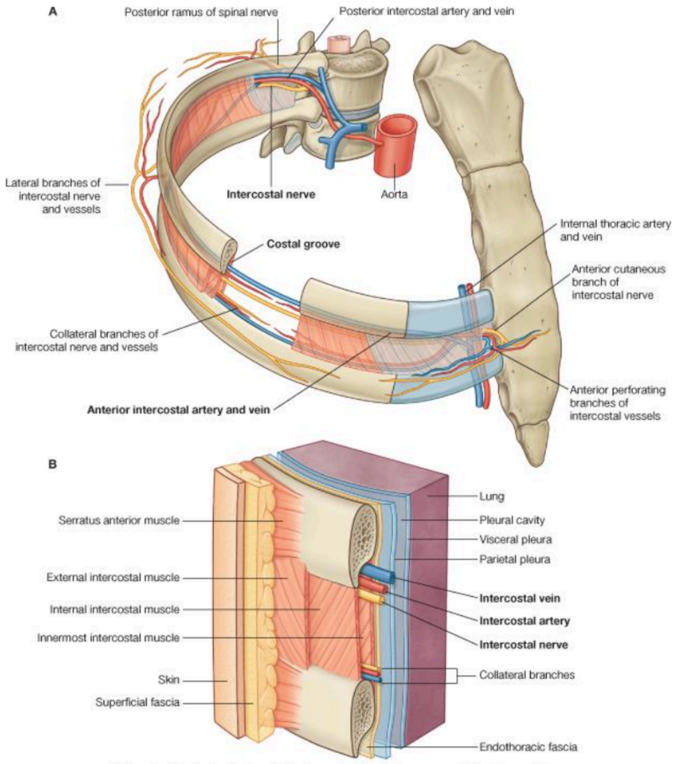

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Figure 1.1. Chest wall tissues [1]

Tension pneumothorax, or collapsed lung, accounts for 3-4% of total combat fatalities, the second most common cause of death on the battlefield which is preventable by timely proper first-aid [4]. Needle decompression (thoracentesis) and chest tube insertion are the basic approaches, in which a needle is inserted between the ribs and into the thorax to gain access to the intercostal space, and then a tube is inserted to drain trapped fluids and air from the chest cavity [1,4]. As shown in Fig. 1.1, several layers of muscle, fascia and pleura must be penetrated during insertion, without hurting other organs and tissues, and a characteristic “pop” is supposed to occur when the needle enters the pleural cavity, indicating the resistance of the parietal pleura and the pressure release [4]. Therefore, in contrast to skin and muscle, pleura is the most important tissue with unique elasticity when dealing with tension pneumothorax, both on the battlefield and in the hospital, and its mechanical properties should be first studied and simulated. The corresponding simulator should have the characteristic “pop” when penetrated and provide the trainees with feedbacks on the force range they are required to apply.

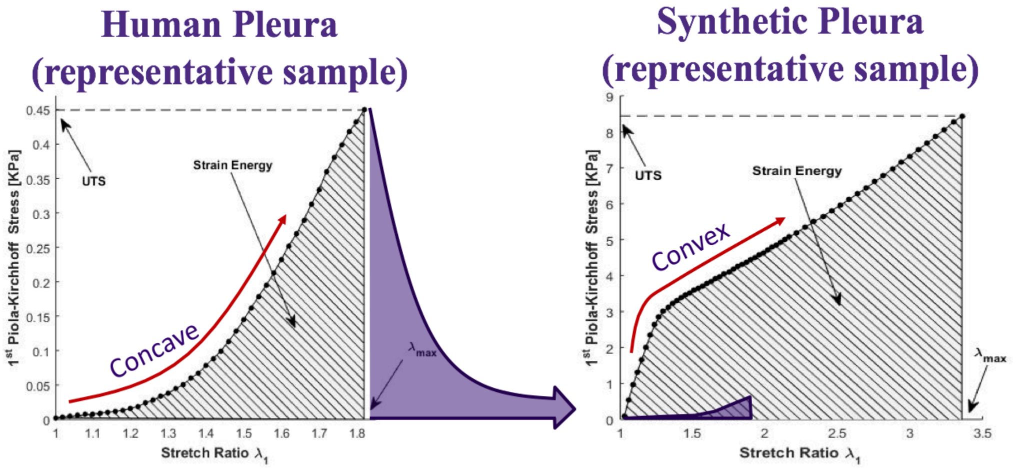


Figure 1.2. Gap between human pleura and synthetic pleura [5]

However, as shown in Fig. 1.2, compared to human pleura, currently used training simulator polymer has a significant performance gap in mechanical properties, with in orders of magnitude differences, resulting in the comment that military medical training is usually like “treating a piece of plastic” [1]. The inaccuracy here is not only the isotropy and the convex shape of curve, but also the huge magnitude differences in stress and strain. Also, no data had been reported on mechanical properties of parietal pleura before the project and collaborations started [5]. Although recent studies have shown the promising results of myocardial tissue simulation by poly(glycerol sebacate) (PGS) [6] and PGS/poly(L-lactic acid) (PLLA) core-shell [7] materials, polyisocyanopeptides (PICs) based hybrid polymer networks simulating mechanical environment of cells [8], complicated poly(dimethylsiloxane) (PDMS) materials mimicking strain-stiffening characteristics of jellyfish and lung [9], silicone based 3D printed organ models [2] and simulations by natural rubber nanocomposites [10] on selected human tissues, no study has been done on pleura simulation by an easily synthesized material. The aim here is to present a relatively simple and affordable protocol based on the polyurethane family to simulate mechanical behaviors of human pleura, developing an alternative pleura simulator for medical training on thoracentesis.

1.3 Polyurethanes

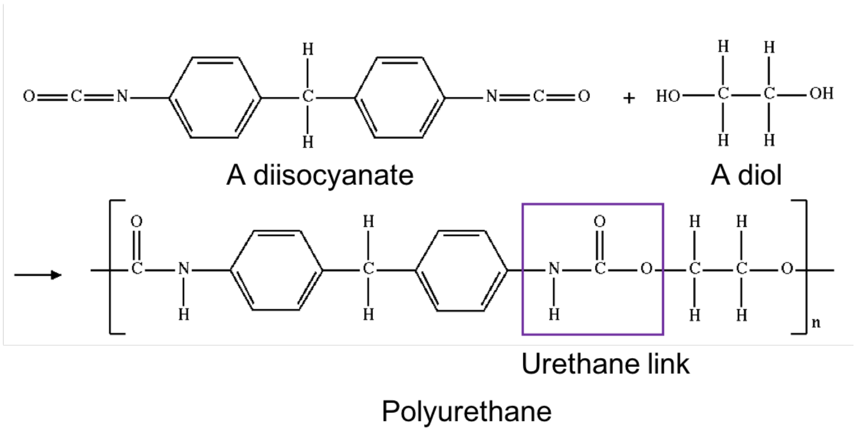


Figure 1.3. Polyurethane structure [11]

As shown in Fig 1.3, polyurethanes (PU) are a class of polymers consisting of organic units joined by carbamate links which can be made both as thermosetting polymers and thermoplastic polymers [11]. Thermoplastic PU can be defined as copolymer containing blocks of hard segment (HS) and soft segment (SS). HS is comprised basically of urethane groups developed from di- or polyisocyanate terminating in isocyanate (NCO) groups and hydroxyl (OH) groups from both relatively high molecular weight (MW) oligomer and low MW polyol used as either a crosslinker (CL) (if it is multifunctional) or as a chain extender (CE) (if it is difunctional). Thus, HS consists of an isocyanate component along with either CL or CE, while the SS is generally all other components in the carbon chain. In other words, PU elastomer consists, typically, of three parts: polyol, dissocyanate and CE for linear PU or CL for crosslinked PU. The mechanical properties of PU including tensile stress, strain and Young's modulus can be readily altered within a wide range by simply changing the ratios or concentrations of the three initial components. For example, PU can possess a Young's modulus from less than 5 MPa to nearly 200 MPa, providing a large amount of materials from millable elastomers to rigid foams [12]. The manufacturing of PU has become mature since its original discovery in 1937 [12] and several practical protocols are being used in industry for various applications. Therefore, the alterable property of PU, as well as its accessible commercialization, makes it a promising candidate and the target polymer in the study of tissue simulation.

In general, linear PU possesses more elasticity due to the long carbon chain of SS, while crosslinked PU shows more stiffness resulting from more aggregated and rigid crosslinked network. In the study, both linear and crosslinked PUs were developed for simulating pleura mechanically. Based on the recently obtained data of human pleura from collaborators, several linear compositions and a bunch of crosslinked compositions were synthesized. Two crosslinked compositions of PU were proved to be promising candidates for pleura simulator by mechanical testing and characterization of ATR-FTIR.

Chapter 2. Materials and Methods

2.1 Materials

Poly(tetramethylene oxide) (PTMO) (MW=1000) was purchased from BASF. N, N-dimethylacetamide (DMAc), 4,4’-methylenebis(phenyl isocyanate) (MDI), 1,6-hexamethylene diisocyanate (HDI), 1,4-butanediol (BU), 1,1,1-trimethylolpropane (TMP), pentaerythritol (PETT) and tin(II)·2-ethylhexanoate (SnOc) were purchased from Sigma-Aldrich. Silanol terminated PDMSs (DMS-S15, DMS-S14, and DMS-S21) and carbinol terminated PDMSs (DMS-C16 and MCR-C61) were purchased from Gelest. Glycerol was from AMRESCO and 1,3-bis(4-hydroxybutyl)-1,1,3,3-tetramethyldisiloxane (BHTD) was from Silar. DMAc was dried using 10 wt.% of 4 Å molecular sieves. All other materials were used as received. All chemicals were purged with nitrogen after use. Teflon trays in two sizes (8.2 cm×3.7 cm×1.9 cm and 18.6 cm×10.9 cm×5.8 cm) were purchased from VWR.

2.2 Synthesis

Linear PUs in small size (8.2 cm×3.7 cm) were synthesized by one-shot system [12] based on PTMO, MDI or HDI, and BD. Assuming the density of PU is 1 g mL^{-1}, about 1.7 g of polymer was made for each composition to eventually give a film in the thickness of approximate 0.5 mm (similar with pleura). Specific amount of every reactant was calculated based on the total amount of polymer and molar ratio of each composition. PTMO and BD were first added into a nitrogen-purged 50 mL three-neck round-bottom flask with 8 mL of DMAc as solvent and a stir bar. MDI or HDI was then added and the mixture was reacted in the oil bath at 70 °C for 4 h under stirring and protection of nitrogen flow. Afterwards, the 20 wt.% solution was rested under room temperature for about 20 min to remove the developed bubbles. Glycerol was added into some compositions as an additive (plasticizer). The solution was then poured into a small Teflon tray, which was subsequently put into a vacuum oven for solvent evaporation at 70 °C for overnight. The oven was pre-purged by nitrogen and its door was supposed to have a gap left to let the solvent vapor out. High vacuum (30 in. of Hg) was applied lastly for 2 h at 70 ^{o}C to finalize the evaporation process.

Crosslinked PUs were also synthesized by one-shot system in both small size and large size (18.6 cm×10.9 cm) based on PTMO or BHTD or PDMS, MDI, PETT or TMP, with or without BD for different compositions. Specific amount of every reactant was calculated based on the total amount of polymer and molar ratio of each composition. For small samples, about 1.7 g of polymer was made to give a 0.5 mm film. TMP or PETT, as CL, was first added into a nitrogen-purged 20 mL scintillation vial with 8 mL of DMAc as solvent and a stir bar. After complete dissolution of CL by stirring at room temperature, polyol (PTMO or BHTD or PDMS) was added into the vial. BD was also added as CE for some partial-crosslinked compositions. The stirring continued until the solution became homogeneous. One drop of SnOc was added for some compositions as catalyst. MDI was lastly added, and the mixture was stirred until MDI dissolved completely, giving a 20 wt.% solution. The solution was then poured into a small Teflon tray, which was subsequently put into a vacuum oven for simultaneous reaction of polymerization and evaporation of solvent at 80 ^{o}C for 24 h. The oven was pre-purged by nitrogen and its door was supposed to have a gap left to let the solvent vapor out. High vacuum (30 in. of Hg) was applied afterwards for 2 h at 80 ^{o}C to finalize the evaporation process. For large samples based on certain promising compositions, about 12 g of polymer was made to give a 0.5 mm film. PETT as CL was first added into a nitrogen-purged 100 mL round-bottom flask with 50 mL of DMAc as solvent and a stir bar. After complete dissolution by stirring at room temperature, polyol (PTMO or BHTD) was added into the flask. BD was also added as CE for some partial-crosslinked compositions. The stirring continued until the solution became homogeneous. MDI was lastly added, and the mixture was stirred until MDI dissolved completely, giving a 20 wt.% solution. The solution was then poured into a large Teflon tray, which was subsequently put into a vacuum oven for simultaneous reaction of polymerization and evaporation of solvent at 80 ^{o}C for 4 days. The oven was pre-purged by nitrogen and its door was supposed to have a gap left to let the solvent vapor out. High vacuum (30 in. of Hg) was applied afterwards for 2 h at 80 ^{o}C to finalize the evaporation process.

2.3 Mechanical Testing

2.3.1 Uniaxial Testing

The method for uniaxial testing is modified from ASTM D412 method. As shown in Fig. 2.1, the synthesized film was punched into dogbone-shape specimen by a standard punch die, with a gauge length of 22 mm and a width of 5 mm. The thickness of each specimen was measured by a caliper. Uniaxial tensile testing was conducted for each specimen at room temperature and dry condition using an Instron 5543 mechanical tester equipped with a 500 N load cell. The tensile rate (crosshead speed) was selected to be 10 mm min^{-1} and the specimen was stretched at this speed until it broke. Three specimens were tested for each composition. Raw data was exported from the attached software for further analysis.

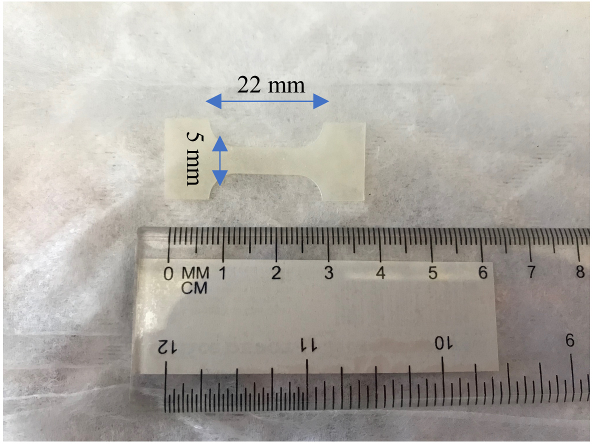


Figure 2.1. Dogbone-shape specimen

2.3.2 Puncture Testing

Puncture testing was conducted on large samples by collaborators from University of Washington’s Center for Research in Education and Simulation Technologies (CREST) using Dexter, a procedural based instrument developed at CREST. As shown in Fig. 2.2, Dexter features a rotatable manual-driven main stage allowing for a maximum travel distance in the y-axis of 46 cm. A smaller rotatable motor-driven sub-stage with a maximum travel distance of 36 cm is attached to the main stage allowing for angled punctures. The motor drives the stage at a maximum speed of 9 mm sec^{-1}.

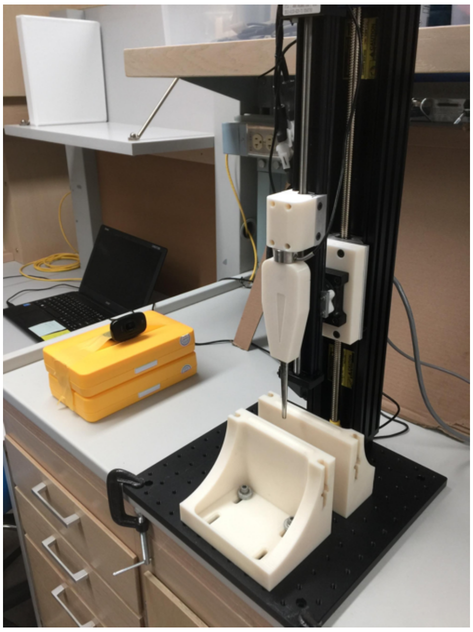


Figure 2.2. Dexter layout for puncture testing

For blunt puncture testing, a large hemostat was affixed to Dexter. The sample was loaded into the sample holder and then preloaded using a 500 g weight while sample thickness measurements were recorded. The hemostat was then positioned 1 cm away from the sample ensuring constant velocity during puncture. A video camera was positioned 15 cm from the test apparatus. The test was then performed at the maximum speed (9 mm sec^{-1}). Data was recorded via the loadstar software and analyzed through lab-developed MATLAB scripts.

2.4 ATR-FTIR

Several compositions were characterized by attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectrum at room temperature using a Nicolet-560 spectrophotometer with a resolution of 2 cm^{-1} and a scanning number of 16 from 400 cm^{-1} to 4500 cm^{-1}. Raw data was exported from the attached software for further analysis.

Chapter 3. Results and Discussion

3.1 Desired Properties

The present study is based on the hypothesis that a material matching the stress-strain behavior and tensile strength of the human pleura will be an appropriate choice for pleura simulator in medical training [4]. Therefore, the desired mechanical properties of PU are developed from human pleura data. The pleura testing was conducted by collaborators at ARL and CREST, which provided the desired mechanical properties of PU simulator defined by two critical parameters: ultimate tensile strength (UTS), the measured stress at failure, and stretch ratio (SR), the ratio of specimen length at failure to initial specimen length, as shown in Table 3.1. Pleura samples perpendicular or parallel to the rib were assigned as the "CROSS" direction or the "RIB" direction, respectively. The data suggests the expected polymer a soft material with low tensile strength and little extension.

Table 3.1. Desired mechanical properties from human pleura testing

Parameter	Definition	CROSS (perpendicular)	RIB (parallel)	Unit
Ultimate Tensile Strength (UTS)	Measured stress at failure	0.26-2.02		MPa
Stretch Ratio (SR)	Length at failure/initial length	1.18-2.34	1.23-1.71	Mm for length, ratio

3.2 Linear PUs

As shown in Table 3.2, several linear PUs were first synthesized at the beginning of the study to initially find a direction to further polymer development. The total ratio of the two functional groups in the reactants, OH groups and NCO groups, is 1/1 for each linear composition.

Table 3.2. Summary of linear PUs

Polymer	Composition	OH/NCO	HS (wt.%)
PU-815	PTMO/MDI/BD=1/2/1	1/1	37.41
PU-816	PTMO/MDI/BD=1/1.8/0.8	1/1	34.91
PU-817	PTMO/MDI/BD=1/1.6/0.6	1/1	31.86
PU-823	PTMO/HDI/BD=1/2.1/1.1	1/1	31.75
PU-825	PTMO/MDI/BD=1/1.2/0.2	1/1	31.25
PU-826	PTMO/MDI/BD=1/1.1/0.1	1/1	25.08

Fig. 3.1 shows typical stress-strain curves of linear PUs by a representative composition PU-817 (molar ratio of PTMO/MDI/BD=1/1.6/0.6). It is obvious that the UTS and SR of this composition are much higher than the expected values. The addition of glycerol as plasticizer is able to lower the UTS to about 5 MPa while SR almost remains identical. All other linear compositions have the similar behavior when stretched, as shown in Fig. 3.2 with another representative composition PU-825 (PTMO/MDI/BD=1/1.2/0.2).

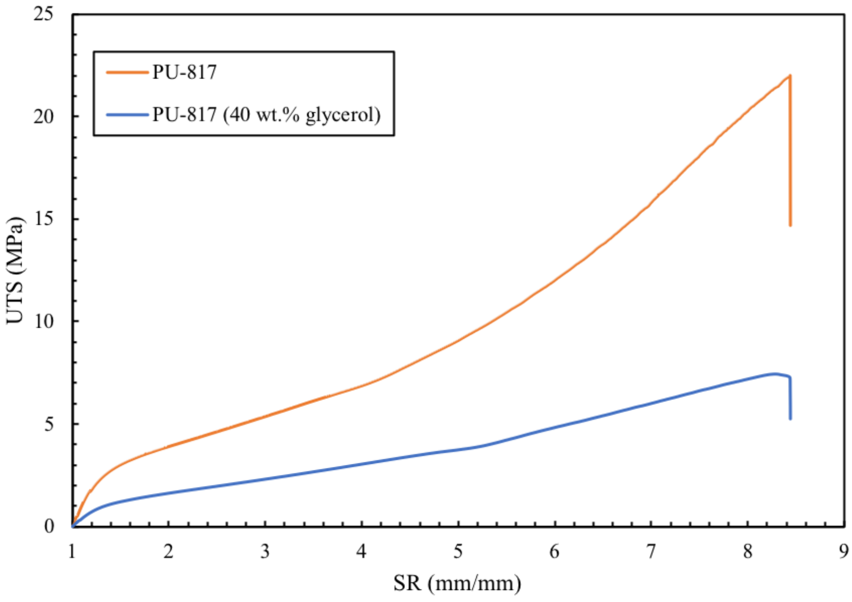


Figure 3.1. Stress-strain curves of PU-817

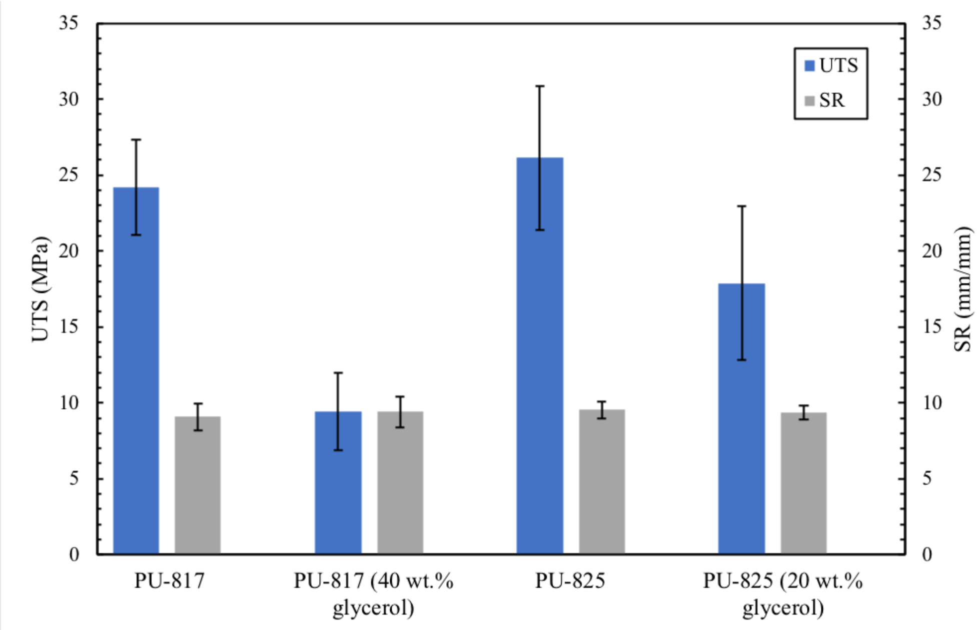


Figure 3.2. Mechanical properties of representative linear PUs

It is concluded that more glycerol added into the polymer solution as plasticizer will further reduce UTS while has no influence on SR, which is nearly one order of magnitude higher than desired value. Other than introducing plasticizer in the polymer, it is expected that UTS can also be decreased by using PTMO or other polyol with higher MW. Theoretically, polyol with higher MW provides longer chain of SS and lowers the mass fraction of HS (MDI or HDI with BD) in the linear structure, resulting in a softer material with lower tensile stress at failure. However, longer chain of SS will simultaneously make the material more elastic with an even higher SR. Therefore, linear PU is not an appropriate choice for the study.

3.3 Crosslinked PUs

As mentioned before, crosslinked PU is expected to possess lower UTS and SR comparing to linear PU even at the similar HS and SS content, which is primarily attributed to its rigid and regular crosslinking network structure. The non-covalent intermolecular attractive forces are interrupted by increased chemical crosslinking, losing their effectiveness on resistance when being stretched due to the lower effect of forced crystallization. It has been demonstrated that increased degree of crosslinking in PU is accompanied by decreases in tensile strength, elongation at break, modulus and hardness [12]. In the study, TMP was first introduced as a trifunctional CL, and then PETT as a tetrafunctional CL. Silicone-based materials are widely used in the field of artificial organ and tissue engineering. Therefore, PDMS and BHTD were used for some crosslinked compositions as SS instead of PTMO.

3.3.1 TMP-based crosslinked PUs

Table 3.3. Summary of TMP-based crosslinked PUs

Polymer	Composition	OH/NCO	HS (wt.%)
PU-851	TMP/MDI/DMS-S14=1/3/1.5	1/1	35.10
PU-852	TMP/MDI/DMS-C16=1/3/1.5	1/1	45.00
PU-853	TMP/MDI/MCR-C61=1/3/1.5	1/1	37.95

As shown in Table 3.3, three compositions based on TMP, MDI and PDMS were developed for initial trial of crosslinked PUs and Fig. 3.3 illustrates the mechanical properties of two tested compositions, PU-852 (based on linear PDMS) and PU-853 (based on branched PDMS). As seen in the figure, the UTS of this kind of crosslinked PU drops to around 10 MPa, and SR has an even greater decrease, nearly reaching the desired range, which demonstrates that the crosslinking network derived from trifunctional TMP has more resistance when being stretched, providing little extension and low stress in a material with less elasticity. To further reduce UTS and minimize SR, PETT was used instead of TMP to increase the crosslinking density, and therefore possess mechanical performance closer to that of human pleura.

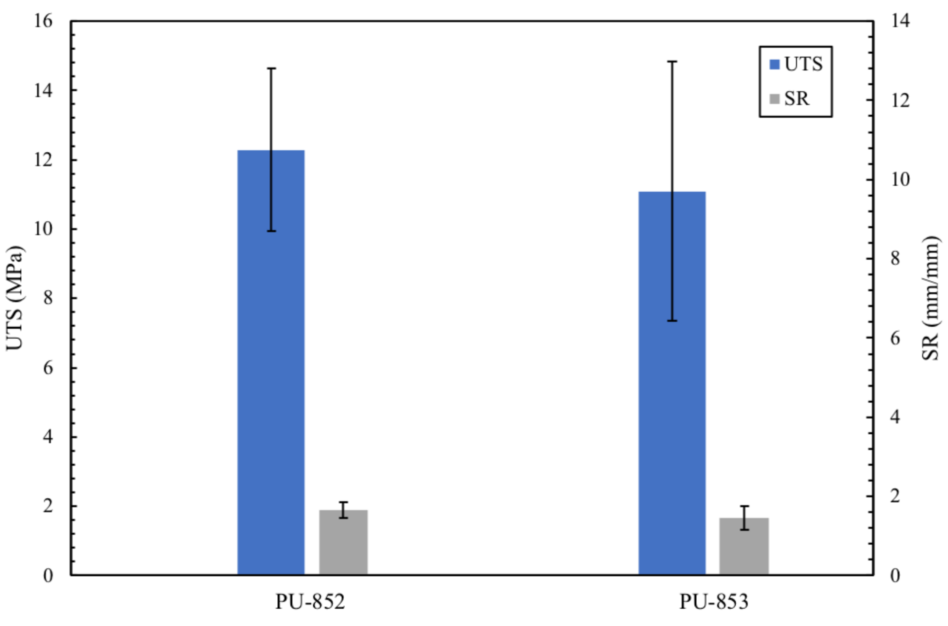


Figure 3.3. Mechanical properties of TMP-based crosslinked PUs

3.3.2 PETT-based crosslinked PUs

Table 3.4. Summary of PETT-based crosslinked PUs

Polymer	Composition	OH/NCO	UTS (MPa)	SR (mm/mm)
PU-857	PETT/MDI/MCR-C61=1/4/2	1/1	3.3	1.11
PU-859	PETT/MDI/MCR-C61=1/2/1	1.5/1	3.8	1.17
PU-860	PETT/MDI/BHTD=1/4/2	1/1	1.8	2.15
PU-862	PETT/MDI/BHTD=1/2/1	1.5/1	0.4	2.71
PU-863	PETT/MDI/MCR-C61/BHTD=1/4/1/1	1/1	5.2	1.12
PU-868	PETT/MDI/BHTD=1/4/2.4	1.1/1	2.1	1.62

Several crosslinked PUs were made using tetrafunctional PETT as CL and some representative compositions are listed in Table 3.4. PDMS and BHTD are here served as polyols to form the chain of SS in the polymer. Some compositions have a molar ratio of OH and NCO groups greater than 1/1 and it is believed that an excess in OH groups can reduce the UTS by increasing mass fraction of SS. As shown in the chart, comparing to trifunctional TMP, tetrafunctional PETT provides the material with lower UTS by increased crosslinking density, while SR remains in the range of expected value. The excess in OH groups has some effect on reducing UTS in certain compositions. The promising properties of PETT-based crosslinked PUs indicate the right direction of synthesis and composition modification, which is introducing CL into the polymer. Among these crosslinked PUs, PU-860 and PU-868 have the best mechanical performance when comparing to human pleura. PU-860 was then chosen for further validation by another uniaxial testing conducted at ARL and puncture testing on a large sample conducted at CREST. Results are shown in Fig. 3.4 and Fig. 3.5, respectively.

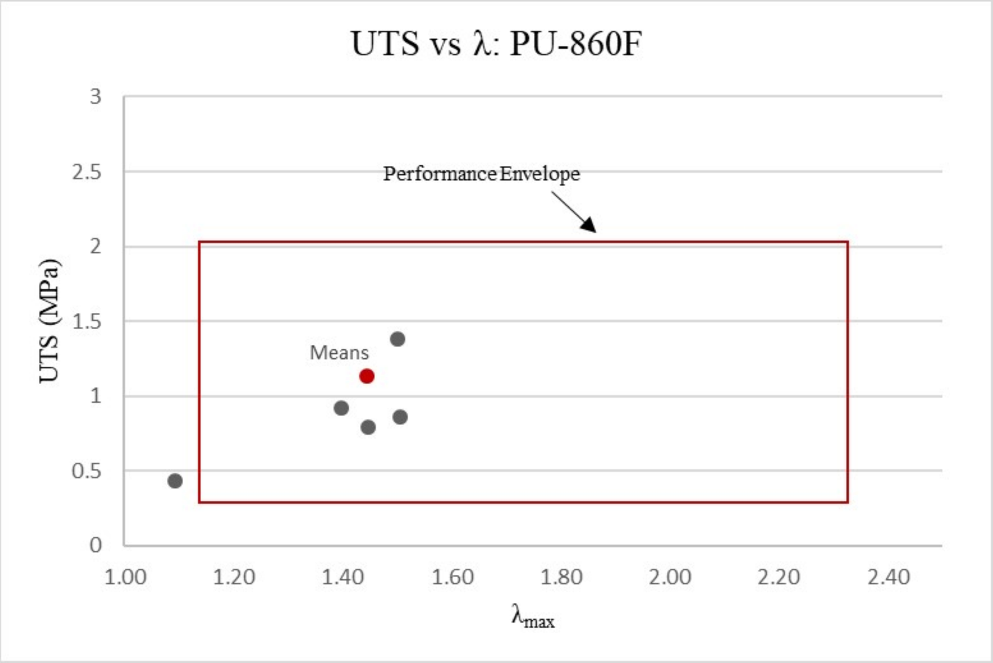


Figure 3.4. Uniaxial testing results from ARL

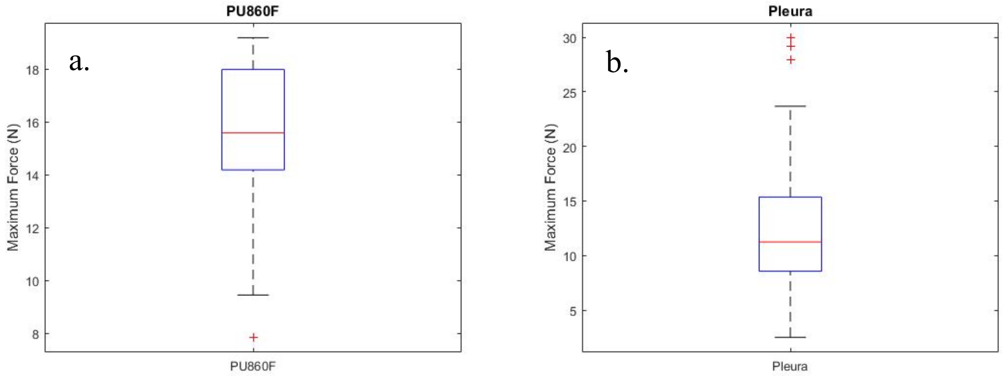


Figure 3.5. Puncture testing results of PU-860 (a) and pleura (b) from CREST

It is demonstrated again that PU-860 is a promising candidate for pleura simulator with mechanical properties, UTS and SR, fitted in the performance envelope of human pleura. Although the maximum puncture force against the polymer is a little higher than that against pleura, it possesses the mechanical properties closest to the required values and proves the possibility to simulate mechanical behavior of nature tissue by crosslinked PU.

However, problems and difficulty arose when repeating synthesis of PU-860, and reproducibility was hard to achieve between different batches, which led to the following discussion.

3.3.3 Troubleshooting

During repetition synthesis of PU-860 for further testing, there was a tendency that longer evaporation time resulted in stiffer material. Typically, evaporation for overnight gave a soft and elastic material while evaporation for 3 days ended in an extremely stiff and brittle material with high UTS and nearly no SR, which was impossible to do the uniaxial tensile testing. To solve the problem, two samples of PU-860 synthesized from different curing time were characterized by FTIR, as shown in Fig. 3.6.

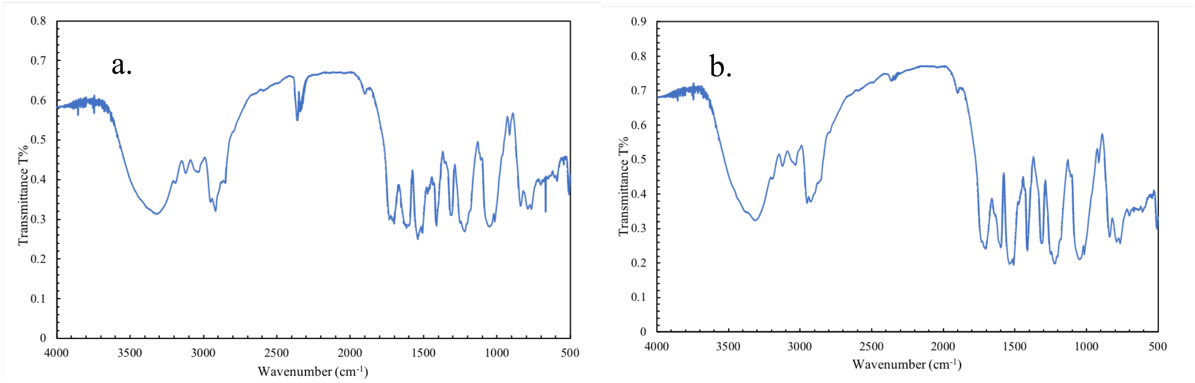


Figure 3.6. FTIR spectra of PU-860 with curing time of overnight (a) and 3 days (b)

As seen in the figure, there is a peak around the wavenumber of 2350 cm^{-1} in the sample evaporated for overnight (Fig. 3.6.a), which corresponds to free NCO groups, but no peak exists in that area of the sample cured for 3 days (Fig. 3.6.b). Therefore, this difference between two samples indicates the incompletion of polymerization after overnight reaction and evaporation, which is responsible for the final altered properties between two samples. Side reactions such as formation of allophanate groups are unlikely here since higher temperature (at least 120 °C) is required [12], and 80 °C is relatively safe. To accelerate the reaction, SnOc as the catalyst was added to some compositions. However, the presence of catalyst sped up the reaction rate so much that either the solution became gel during mixing or the polymer film shrunk after curing. Therefore, the difficulty of controlling catalyzed reaction system led to alternatively longer curing time of the polymer without catalyst.

Although prolonged evaporation time can ensure the completion of reaction, which is proved by IR spectrum, properties difference still exists between batches, resulting in poor reproducibility. Other than polymerization, solvent residue is another key factor of the final properties of the polymer. It is suggested that DMAc as the solvent has strong affinity to the polymer, and the tiny residue of DMAc trapped in the crosslinked polymer network is able to significantly alter the mechanical properties.

Therefore, to complete the reaction and solvent evaporation, standard synthesis procedures were developed as mentioned before in Chapter 2. The curing time is 24 h for small samples and 4 days for large samples. It is believed that, in this way, polymerization can be completed and nearly all solvent are removed from the polymer. The reaction completion has been validated by IR spectrum. Gas chromatography-mass spectrometry (GC-MS) will be utilized in the future for quantitative determination of solvent residue in the PU film.

Based on the standard procedures, however, all the crosslinked compositions developed from BHTD as SS provided stiff and weak polymers with little elasticity, and no soft material similar with the original batch was able to made, even with the addition of BD as CE for partial crosslinked compositions. Thus, it is finally concluded that BHTD is not an appropriate choice for SS, which is theoretically reasonable. Elastic PUs are typically developed from polyols with MW from 600 to 1200, and poor elastic products are obtained when the MW falls below 600 [12]. The short chain of SS derived from polyols with low MW has no contribution to material elasticity, especially in the crosslinked network. BHTD has a MW of 278.54 and is therefore not a proper candidate for SS in theory. PTMO was then used for developing crosslinked PUs and some partial crosslinked compositions are promising for pleura simulation.

3.3.4 Promising candidates

Table 3.5. Summary of promising crosslinked PUs based on PTMO

Polymer	Composition	OH/NCO	UTS (MPa)	SR (mm/mm)	HS (wt.%)
PU-909	PETT/MDI/PTMO=1/4/2	1/1	2.87	2.82	36.33
PU-910	PETT/BD/MDI/PTMO=0.9/0.2/4/2	1/1	2.21	2.00	36.49
PU-911	PETT/BD/MDI/PTMO=0.8/0.4/4/2	1/1	1.69	1.51	36.67
PU-912	PETT/BD/MDI/PTMO=0.7/0.6/4/2	1/1	1.18	1.15	36.72

PTMO is believed to be a suitable material as polyol, whose MW is 1000 and therefore provides some elasticity in the tetra-crosslinked PU by forming long chain of SS. As shown in Table 3.5, starting from the fully-crosslinked composition PU-909, several partial crosslinked PUs were developed and have shown great potential to simulate pleura mechanically. PU-909 has slightly higher values of UTS and SR, while the other three compositions all possess similar mechanical performance with human pleura. Fig. 3.7 illustrates the comparison of mechanical properties among these compositions. It is clear that with the increasing addition of BD as CE and decreasing PETT as CL resulted from their different ratios, crosslinking density falls and subsequently reduces the UTS and SR, giving a softer material even at the same concentration of HS. The presence of BD provides the polymer with linear parts, which interrupts the crosslinking network and its continuity, resulting in a weaker physical property. As shown in the figure, this tendency is well-proved by the compositions with decreasing crosslinking density, and the promising properties once again demonstrate the possibility to simulate mechanical behavior of nature tissue by crosslinked PU.

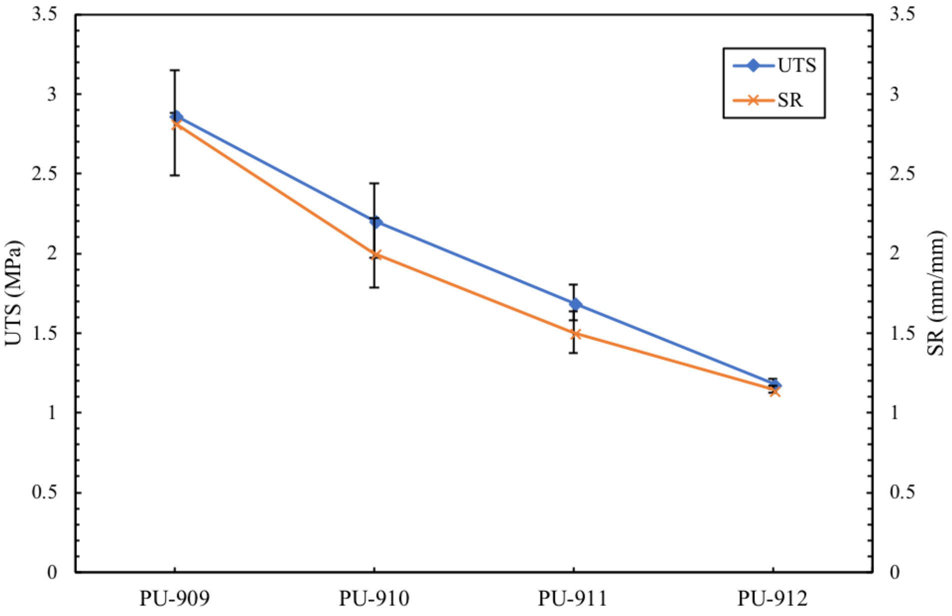


Figure 3.7. Comparison of mechanical properties of crosslinked PUs with different crosslinking density

Fig. 3.8 and Fig. 3.9 show the comparison between representative samples of linear PU (PU-817) and crosslinked PU (PU-911). Both UTS and SR decrease significantly by one order of magnitude from linear PU to crosslinked PU, demonstrating the variety of PU elastomers and the feasibility of the present study.

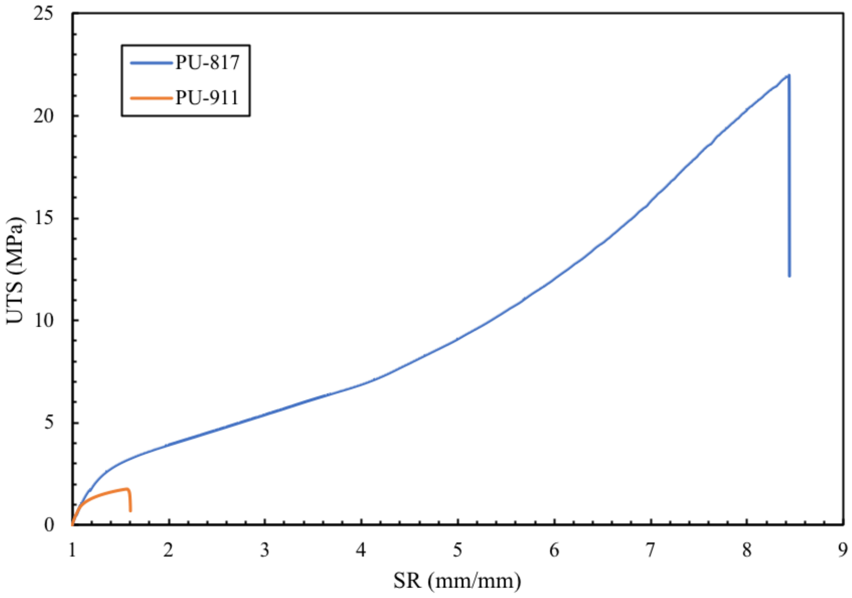


Figure 3.8. Stress-strain curves of representative linear and crosslinked PUs

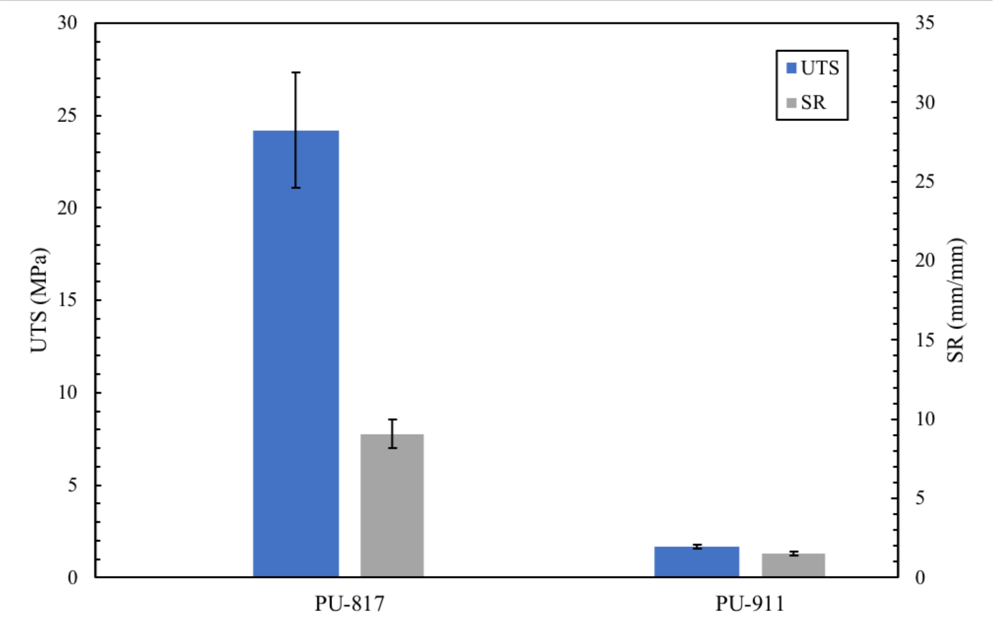


Figure 3.9. Mechanical properties of representative linear and crosslinked PUs

Fig. 3.10 illustrates the mechanical comparison of the PTMO-based partial crosslinked PUs and the expected performance envelope from human pleura, which is shown as the red rectangle in the figure. It is concluded that among these three compositions, PU-911 has the best mechanical performance, perfectly mimicking the human pleura mechanically. PU-912 also possesses desired UTS while has slightly lower SR. Both two compositions are believed to be promising candidates for pleura simulator, and puncture testing has been conducted on PU-911 at CREST lab, as shown in Fig. 3.11.

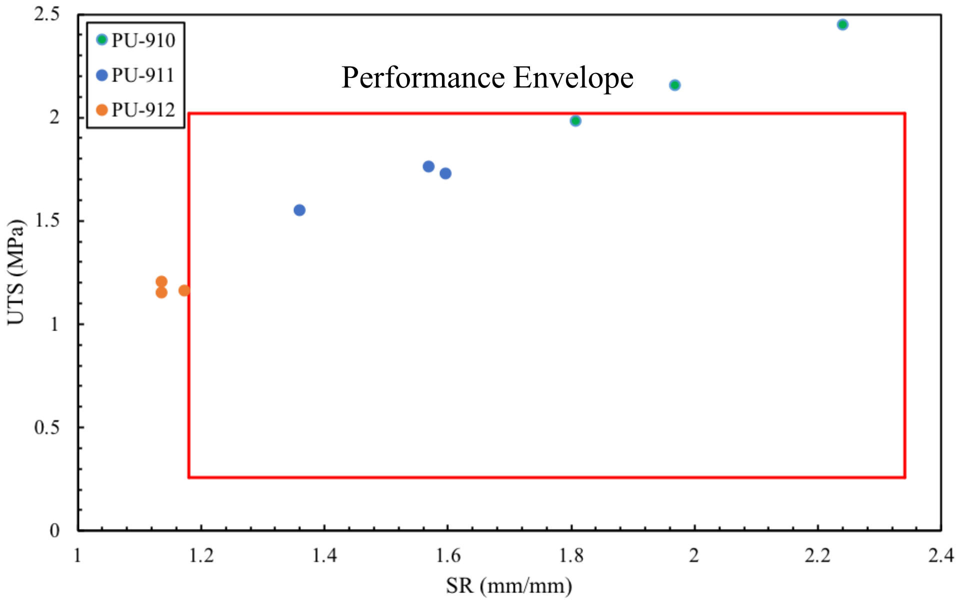


Figure 3.10. Mechanical properties of partial crosslinked PUs and the desired performance envelope

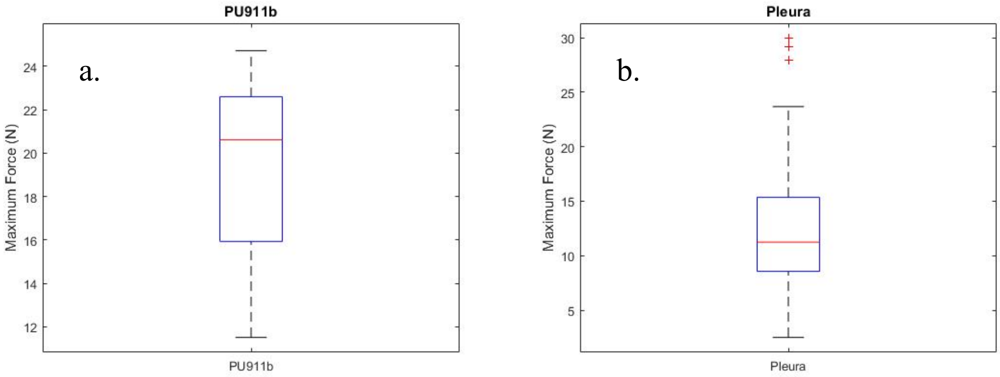


Figure 3.11. Puncture testing results of PU-911 (a) and pleura (b) from CREST

As seen above, although PU-911 possesses the best mechanical behavior, the large sample of it (PU-911b) does not perform well in the puncture testing. The force against puncture is higher than that of human pleura. The undesired results can be attributed to the difference in thickness between synthetic material and nature tissue. More puncture testing will be conducted in the future to validate the simulation feasibility on these two compositions.

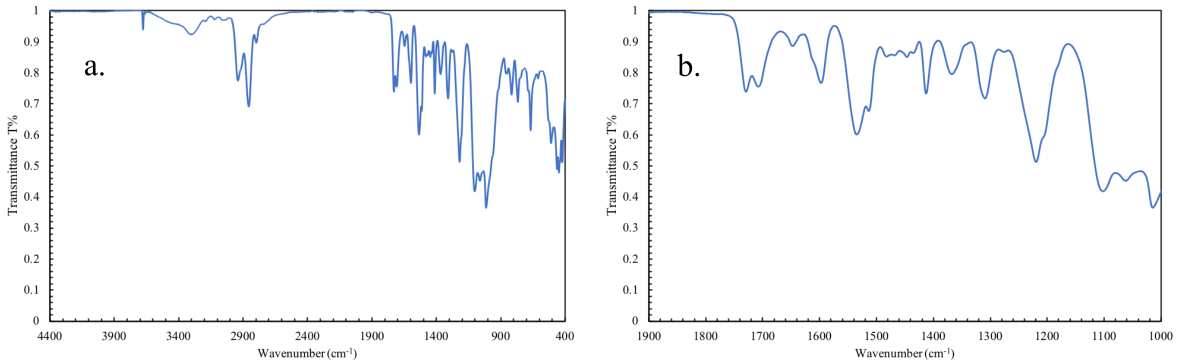
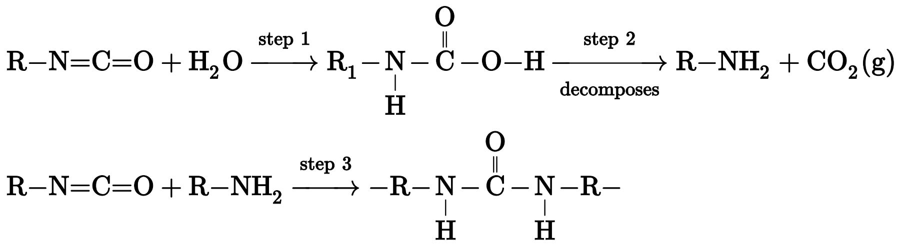


Figure 3.12. IR spectrum of PU-911(a: whole spectrum. b: spectrum from 1000 to 1900 cm^{-1})

As shown in Fig. 3.12, PU-911 was characterized by ATR-FTIR spectrum to validate its PU polymer structure. As seen in Fig 3.12.a, there is no peak at around 2350 cm^{-1}, indicating the absence of free NCO group and the completion of reaction. In Fig. 3.12.b, a peak around 1700 cm^{-1} is associated with carbonyl stretching vibration (amide I band) in PU. Also, it can be seen that around 1720 cm^{-1} there is a medium peak indicating the free carbonyl group in urethane. For amide II band, a medium peak at around 1620 cm^{-1} can be regarded as another evidence of primary urethane, and a strong peak at 1530 cm^{-1} may indicate the secondary urethane.



$$\mathrm{R{-}N{=}C{=}O + H_2O \xrightarrow{step\ 1} R_1{-}\underset{\underset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}O{-}H \xrightarrow[decomposes]{step\ 2} R{-}NH_2 + CO_2(g)}$$

$$\mathrm{R{-}N{=}C{=}O + R{-}NH_2 \xrightarrow{step\ 3} {-}R{-}\underset{\underset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}\underset{\underset{H}{|}}{N}{-}R{-}}$$

Figure 3.13. Side reactions with water forming urea group [11]

The medium peaks at around 1640 cm^{-1} and 1010 cm^{-1} may be related to the presence of urea groups in the PU polymer, which is generated from side reactions when free NCO groups react with water contamination from the air or from the undried PTMO, as shown in Fig. 3.13. However, the 1010 cm^{-1} peak can also be the C-N-C backbone from DMAc, and there is no peak around 1640 cm^{-1} which is associated particularly with diaryl urea in solid phase. More data is required to determine the urea existence, but fortunately, the existence of little amount of urea in PU polymer will not have effect on mechanical property.

Another interesting finding is that the peak at 1725 cm^{-1} indicating free carbonyl groups is typically only a shoulder in fully-crosslinked compositions, and the peak associated with hydrogen-bonded carbonyl groups has greater transmittance than fully-crosslinked ones. These two peaks indicate the similar amount of the two kinds of carbonyl groups while in fully-crosslinked compositions, more hydrogen-bonded carbonyl groups are characterized. The difference is quite reasonable, since the addition of BD interrupts the regular crosslinking network and makes it harder to develop hydrogen bonds between two urethane groups in different chains, as shown in Fig. 3.14, and therefore more free carbonyl groups are present in the polymer.

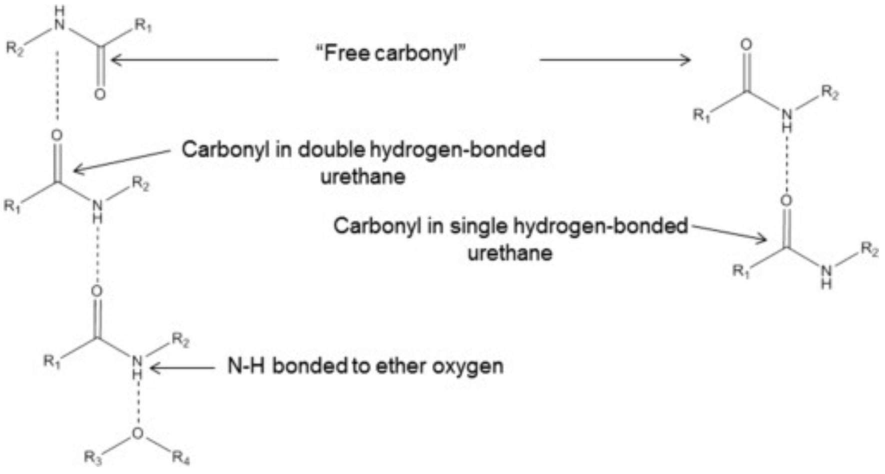


Figure 3.14. Free and hydrogen-bonded carbonyl groups [13]

To determine the residue amount of DMAc in the solid polymer film, MS-GC is going to be utilized in the future testing. As mentioned before, DMAc has strong affinity to the polymer and little residue can significantly change the mechanical properties. It is believed that any liquid additives distributed in the solid polymer works as a plasticizer. Such additive takes some internal volume in a polymer structure and increases a free space between polymer molecular chains resulting in breaking weak bonds, and therefore a polymer material weakens. For future synthesis, PTMO is required to be pre-dried before use to remove the water contamination.

Solid NMR characterization will also be conducted to validate the polymer structure for future experiment.

Chapter 4. Conclusion

It is proved that two specific partial crosslinked PUs based on PETT, BD, MDI and PTMO are promising candidates for pleura simulator in medical training. The mechanical properties of these two compositions, PU-911 (PETT/BD/MDI/PTMO=0.8/0.4/4/2) and PU-912 (PETT/BD/MDI/PTMO=0.7/0.6/4/2), perfectly match the UTS and SR of human pleura, and the puncture test further shows the feasibility of this kind of synthetic polymer. The crosslinked PUs are easily to be made in manufacturing for large amount of use in medical training. Although some other complicated synthetic materials, as mentioned before, have better simulation performance than the crosslinked PUs developed, and some of them can even mimic the shape of stress-strain curve of human tissue, they are hard to be commercialized for applications such as medical training. In addition, medical training only requires the trainees to master the sense of conducting thoracentesis. They are required to understand how much force they should apply when doing the operation. The process of stretching or puncture, such as the stress-stiffness behavior normally observed in nature tissue, is less important than the final properties when they are penetrated. Therefore, the key factors for medical training are the final mechanical properties, UTS and SR, and the crosslinked PUs performing similar mechanical behaviors are believed to be great candidates for pleura simulators.

More mechanical testing will be conducted to further validate the feasibility of the developed crosslinked PUs as pleura simulator and more characterizations including GC-MS and solid-NMR will be done for further validation of the polymer structure. It is believed that these crosslinked PUs can be practically used in medical training in the future, and is possible to make them implantable biomaterials, based on their great simulation on mechanical behavior of human tissue. The readily altered property of PU by changing the molar ratio of reactants, provides it with the great potential to simulate other human tissues for various applications in the future.

References

[1] Norfleet, Jack, Fluvio Lobo Fenoglietto, and Mark Mazzeo. "Simulated Human Tissue Performance." *MODSIM World Meeting 2015*. 2015.

[2] Qiu, Kaiyan, et al. "3D Printed Organ Models with Physical Properties of Tissue and Integrated Sensors." *Advanced materials technologies* 3.3 (2018): 1700235.

[3] Norfleet, Jack, et al. "Thoracostomy Simulations: A comparison of the mechanical properties of human pleura vs synthetic training pleura." (2017).

[4] Barocas, Victor, et al. "A Paradigm for Materials Design for Surgical Simulators, With Specific Application to the Pleura and Needle Decompression." *Journal of Medical Devices* 10.3 (2016): 030934.

[5] Tenorio, L. (2016). "Biomechanics of Human Parietal Pleura: Laying the Groundwork towards a Model for Material Selection in Surgical Training Simulators." Master of Science. University of Minnesota.

[6] Chen, Qi-Zhi, et al. "Characterization of a soft elastomer poly (glycerol sebacate) designed to match the mechanical properties of myocardial tissue." *Biomaterials* 29.1 (2008): 47-57.

[7] Xu, Bing, et al. "Mechanically tissue-like elastomeric polymers and their potential as a vehicle to deliver functional cardiomyocytes." *journal of the mechanical behavior of biomedical materials* 28 (2013): 354-365.

[8] Jaspers, Maarten, et al. "Nonlinear mechanics of hybrid polymer networks that mimic the complex mechanical environment of cells." *Nature communications* 8 (2017): 15478.

[9] Vatankhah-Varnosfaderani, Mohammad, et al. "Mimicking biological stress–strain behaviour with synthetic elastomers." *Nature* 549.7673 (2017): 497.

[10] Murniati, Riri, et al. "Natural Rubber Nanocomposite as Human-Tissue-Mimicking Materials for Replacement Cadaver in Medical Surgical Practice." *Procedia*

engineering 170 (2017): 101-107.

[11] "Polyurethane", https://en.wikipedia.org/wiki/Polyurethane

[12] Hepburn, Claude. "Polyurethane elastomers", *Applied Science Publishers*. 1982.

[13] Huacuja-Sanchez, J. E., K. Müller, and W. Possart. "Water diffusion in a crosslinked polyether-based polyurethane adhesive." *International Journal of Adhesion and Adhesives* 66 (2016): 167-175.