

Bioactive Interference Screw for ACL Reconstruction

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Abstract:

The objective of this project is to develop a novel ACL interference screw that not only secures a graft in place, but incorporates a material intended to promote bone tissue growth. This material is composed of a mineralized alginate scaffold that mimics natural matrix environment. Using this material along with the selected growth factors in an interference screw may greatly improve recovery and longevity of the graft. A potential solution has been developed that utilizes a structurally sound thermoplastic while optimizing the amount of mineralized alginate scaffold present in the screw. Preliminary work has been done testing the feasibility of the fabrication process for this type of biphasic screw using model materials. Comparative mechanical testing has begun to ensure that the structural integrity of the screw has not been compromised by the addition of alginate. Future work includes the production of a metal cast mold from a rapid prototyped model and testing with desired materials.

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Design Problem

Interference screws are used during reconstructive anterior cruciate ligament (ACL) surgery to secure the graft in the femur and tibia. Current interference screws are either completely metal or partially biodegradable. All screws contain foreign materials and both metal and degradable have their disadvantages. The metal screws can cause lacerations to the graft, may hinder future reconstructions, and may be problematic during MRI scans of the knee. The disadvantages of the biodegradable screw are that they may fracture during the implantation or there may be adverse reactions to the material. Most importantly, current screws do not promote bone re-growth, subsequently leaving voids in the tissue once the screw has fully degraded.

Product Function

The interference screw that will be designed should be biphasic and bioactive. A biphasic screw should have a degradable plastic phase that is strong enough to withstand the stress during implantation and post-operative activity, and a mineralized hydrogel phase that acts as a scaffold for bone growth. The screw must also be bioactive, which means that it must promote tissue growth at a rate that is comparable to the degradation of the screw. The screw must also secure the ACL graft just as its predecessors do. Finally the screw must be biocompatible; in other words, it must not cause an inflammatory or immune response in the body.

Background

ACL Reconstruction Surgery

Four ligaments connect the femur to the tibia and allow for stabilization and control within the knee: the anterior cruciate ligament (ACL), the posterior cruciate ligament (PCL), the medial collateral ligament (MCL), and the lateral collateral ligament (LCL) (Freedman). The MCL and LCL work together to keep the knee from bending inward (medially) and outward (laterally). The PCL keeps the tibia from sliding behind (posteriorly) the femur and the ACL keeps the tibia from sliding in front of (anteriorly) the femur. Both the ACL and PCL also provide rotational stability. Figure 1 shows a diagram of the knee and the ligaments.

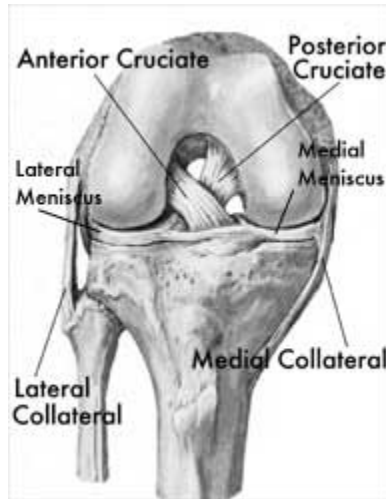


Figure 1: The bones and ligaments of the right human knee (Avery).

Injuries to the ACL are very common. About 90,000 ACL reconstructions occur each year worldwide, with 50,000 of them taking place in the United States. Injuries are caused by strong blows to the knee, quickly stopping and pivoting, or hyper-extension. Participants in sports like skiing, soccer, basketball, and football are at high-risk for ACL related injuries (Chen). When ACL injuries occur, the injured usually hears a “pop” sound and experiences mild pain and swelling; instability is another complaint (Brown).

Doctors can diagnose a torn ACL injury quickly and non-invasively. They perform a Lachman shift test, in which they have the patient relax their leg and the doctor pulls forward on the tibia to see if bone is restricted from moving in the anterior direction (Barber). If the bone is not restricted then it is very likely the ligament has been torn. MRI’s can also be used to detect ACL tears.

The reconstruction of the ACL involves replacing the old ligament with a graft, a tissue used for transplantation, usually harvested from a hamstring tendon or patellar tendon (Brown). Harvesting the graft is the first part of the surgery. In the case of a patellar graft, the surgeon makes an incision on the anterior side of the leg slightly inferior to the patella. A central part of the tendon and attached, cylindrical cut outs of the femoral and tibial heads, called bone plugs, are removed. The remaining part of the tendon is sutured in order for it to re-grow and continue to function. After harvesting, sutures are added to the bone segments of the graft which will be used in placing the tendon. Next, the remaining ACL is removed from the knee, and parts of the

intercondylar notch are burred away so that the surgeon has a better chance of making a more precise and accurate placement of the tendon. Upon completion of burring, the surgeon drills two pilot holes starting at the tibia up into the joint and then into the femur (Figure 2). Each pilot hole is initially drilled using a small bit for accuracy. Once the initial pilot hole is drilled a larger bit is used to over-drill the hole which is the same diameter as the cylindrical bone plug.



Figure 2: Holes are created in both the tibia and femur bone where the graft will eventually be attached. (Brown)

After the holes are smoothed, a sutured end of the graft is pulled through the knee from the head of the tibia to the head of the femur (Brown). The graft is secured by interference screws which are hollow and headless. The interference screws wedge the tendon into the bone providing a firm hold (Figure 3). Once the screws are in place, the joint is irrigated and flushed and the incision is sutured. After surgery the patient will experience moderate pain and have difficulty flexing and extending the knee. With limited post-operative activity and a rigid rehabilitation program, the patient will successfully recover from the operation.

Limited post-operative activity is suggested because the graft is in the process of transforming into a tendon. During this process the graft becomes extremely weak and the knee is somewhat unstable. If activity is too intense, the graft may tear and the patient will need to have another reconstruction performed. It is also necessary to limit

post-operative activity because the graft is only secured by the interference screw. Therefore, as the graft is being pulled on by the tibia or femur, the screw is also being pulled on, and this may cause the screw to be pulled-out from the pilot hole. This scenario would also lead to another reconstruction.

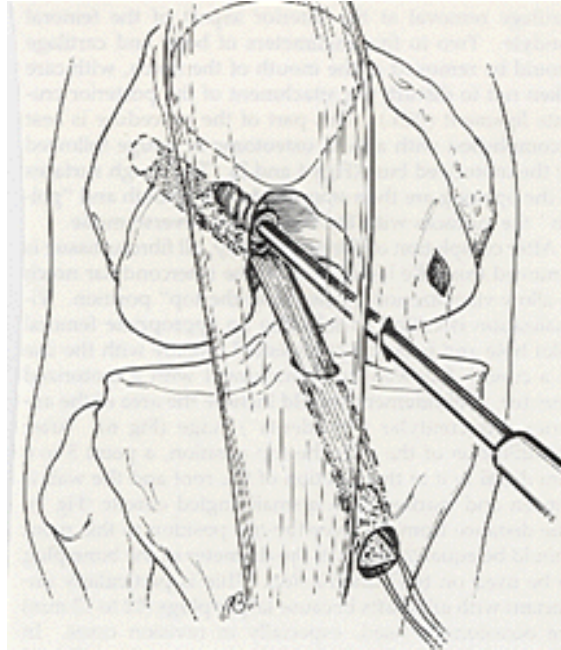


Figure 3: A hand-held driver wedges the interference screw between the graft bone plug and the wall of the drilled hole to create a secure fit. (Brown)

Interference Screws

In orthopedic ACL reconstruction surgery, the interference (or wedge) screw is utilized to hold a replacement ligament/tendon in a drilled bone hole while tissues heal. The screw is driven in the gap between the bone plug and drilled tunnel wall. A variety of sizes are usually available to accommodate different size patients, and appropriate size drills and bone plug bores are made to go with them. To insure proper insertion angle, a guide wire (about 1.5mm in diameter) is often employed that extends through the hollow interference screw and the drilled hole (Figure 4). The guide wire also prevents the screw from disengaging during insertion and being lost within the patient. The interference screw not only has to provide a wedging action, but must be self-tapping to keep it securely in place (Luks et al.). Most screws make their own threads in the bone tunnel and plug by cutting with the screw threads during insertion. The screws lack “heads” so

they do not protrude out of the drilled hole. The hollow socket down the middle of the screw is in the specific shape of a driver, which can be inserted with the guide wire.

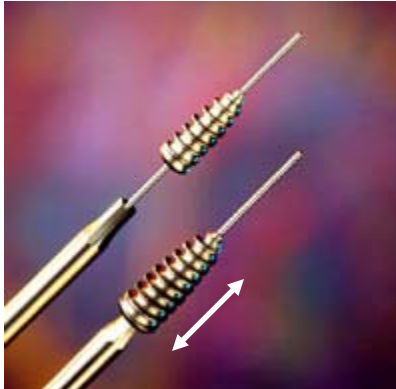


Figure 4: Examples of interference screws, including the driver and guide wire in the screw socket. Length of screw is 25 millimeters (white arrowheads) <www.stryker.co.uk>

Currently there are many companies that manufacture interference screws for use in ACL surgery. While most screws in the industry utilize a similar hollow socket for the driver application, there are a large number of variables in interference screw designs that differ between companies. For example, some of the options that usually differ between manufacturers are: size availabilities (diameter and length), screw tapering, thread geometry, thread pitch, and materials. One of the biggest differences is the material what the interference screw is fabricated out of. Traditionally interference screws were made from metal, usually titanium for its biocompatibility, but in the last ten years alternate compositions have become available. The majority of these new screws offer a material that is bioabsorbable, which is one that will eventually break down in the body, unlike metal which is permanently embedded within the bone. Studies have shown no statistical significance in failure strengths between the metal and bioabsorbable screws (Johnson and vanDyk; Pena, et al.).

The two conventional interference screw types, titanium and bioabsorbable, both have their fair share of disadvantages as implantable devices. Titanium screws do not degrade over time inside the body leaving two major post-operative issues to contend with. First, once a titanium screw is in the body, that region cannot be imaged using magnetic resonance imaging (MRI), a widely used device to image and assess the post-operative condition of a biological tissue, especially ligaments and tendons. Metallic materials implanted in the body can distort the image produced by other techniques of

adjacent and surrounding tissue with artifact that cause a sharp decrease in resolution (Shellock, et al.). Secondly, metallic interference screws can interfere with revision surgery for ACL reconstructions (Kurzweil, Frogameni and Jackson). Because metallic screws do not degrade over time, when a screw must be removed from the bone during a revision surgery it leaves a large void where the screw was housed. These voids compromise the structure of the bone and complicated the placement of the new graft (Miller). For these important reasons, the use of bioabsorbable interference screws has been developed.

Bioabsorbable interference screws have not yet proven to be without inherent problems. It is widely reported that such screws, even of the same composition, have high variability in degradation rates. A comparison study of different compositions of absorbable interference screws showed that poly (L-lactide) (PLLA) had not fully decomposed 20 months following implantation, poly (D,L-lactide-co-glycolide) (PDLLA-co-PGA) was completely decomposed at 12 months, and poly (D,L-lactide) (PDLLA) showed no degradation at 6 wks post-implantation but no traces were found at 10 months (Stahelin, et al.). In the study, the molecular weight and percent composition (L:G) ratio were undefined.

Moreover, as screw types do not necessarily degrade at defined rates, biological tissue regeneration remains a slow and asynchronous process in relation to the degradation. A study done by Bach, *et al.*, assessed the condition of the tissue growth surrounding the surgical polyglycolic (67.5%) and trimethylene carbonate (32.5%) graft. The study showed that the screws were completely reabsorbed within 1 year of implant (Figure 5 and Figure 6), leaving new fibrous and fatty tissue in the graft site that was not new bone (Figure 7). Fink, *et al.*, also did not see any re-growth of bone in the first year following surgery. They reported the first bone regeneration occurred three years after the surgery and within five years, the graft was completely grown in with new bone.

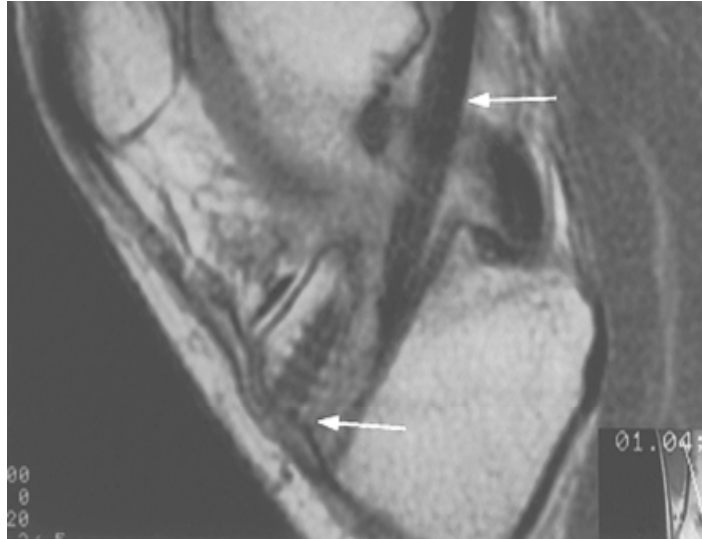


Figure 5: This MR image shows the interference screw (bottom arrow) has not degraded at 6 months following implantation (top arrow indicates the graft tissue) (Bach, et al.).



Figure 6: This MR image shows that the interference screw is completely degraded at 12 months post-implantation (arrow points to implantation site) (Bach, et al.).

Another potential problem with bioabsorbable interference screws results from their degradation. As the screws break down, they release composite molecules that can cause inflammatory foreign-body reactions. These reactions may be minor with a small release of non-bacterial sinus or may be major requiring immediate attention. Screws that take longer to break down inside the body elicit fewer foreign body reactions, but at the same time require a longer period for complete bone regeneration. Although the majority

of cases show the body does not completely reject the screws when a foreign body reaction occurs, these locations are often associated with osteolysis and cyst formation (Bostman).

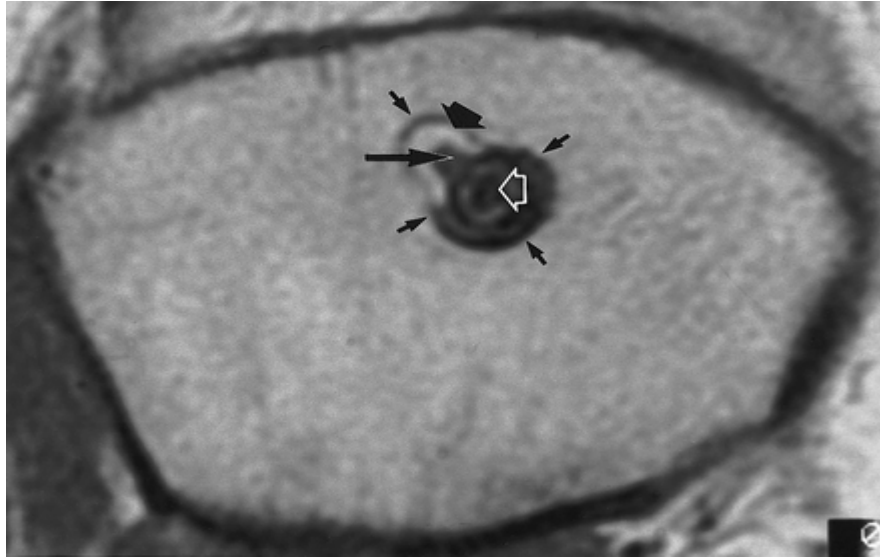


Figure 7: This MR image shows a surgical graft after the screw has completely degraded. The tunnel where the screw used to be implanted is indicated by the small arrows. New tissue that formed around the bone plug (open arrow) was determined to be a fibrous tissue (long skinny arrow) with fatty tissue surrounding it (thick short solid arrow) (Bach, et al.).

Biomaterials

Hydrogels

Hydrogels are three-dimensional polymer scaffolds used in several applications of tissue engineering. A particularly important technique is that of *in vivo* tissue regeneration. In this case, a patient's own cells are combined with the polymer, and held *in vitro* until ready to be implanted. The hydrogel acts as a natural extra-cellular matrix that subsequently promotes cell proliferation and tissue re-growth. The pseudo-extra-cellular matrix, comprised of growth factors, metabolites and other materials, brings cells together and controls tissue structure with the ultimate goal of replacing the natural tissue that was lost or damaged (Lee and Mooney).

Under the given circumstances of creating a scaffold that promotes bone re-growth, our client has chosen an alginate hydrogel. Alginate has been shown to be a useful tool for producing bone and cartilage tissues (Alsberg, et al.). It is very

biocompatible in humans and peptides can also be covalently coupled to the molecules. Alginate is a naturally occurring polymer found in kelp (seaweed) that is commonly used in gel formation. In varying ratios, alginate's two primary residues, seen below in Figure 8, greatly affect properties, such as pore size and degradation rate (Prakash and Soe-Lin).

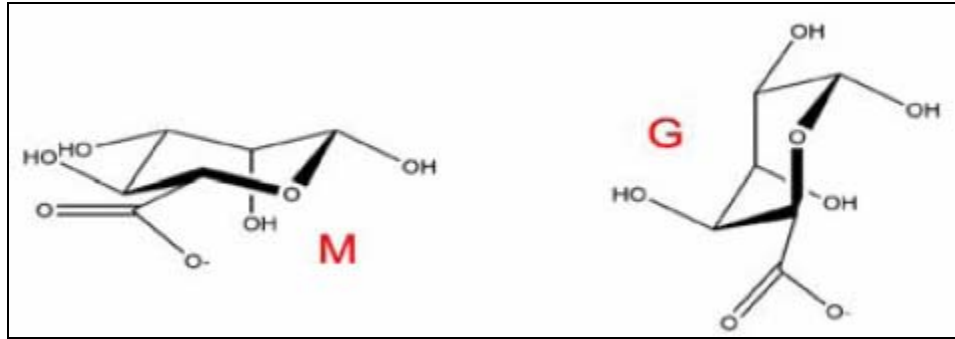


Figure 8: Molecular structure of alginate monomers. The M residue is β -D-mannuronic acid. The G residue is α -L-guluronic acid. Variations in the ratios of the two molecules facilitate desired properties in the gross behavior of the gel, such as rigidity and degree of porosity (Prakash and Soe-Lin).

Calcium Cross-linking

The primary feature of interest concerning alginate polymers is their ability to crosslink with divalent cations, such as calcium. When combined, the negatively charged viscous polymer bonds to the calcium ions forming a gelled network that possesses structural integrity. Simplified schematics of alginate's polymeric arrangement and the calcium cross-linking reaction can be seen below in Figure 9 and Figure 10, respectively.

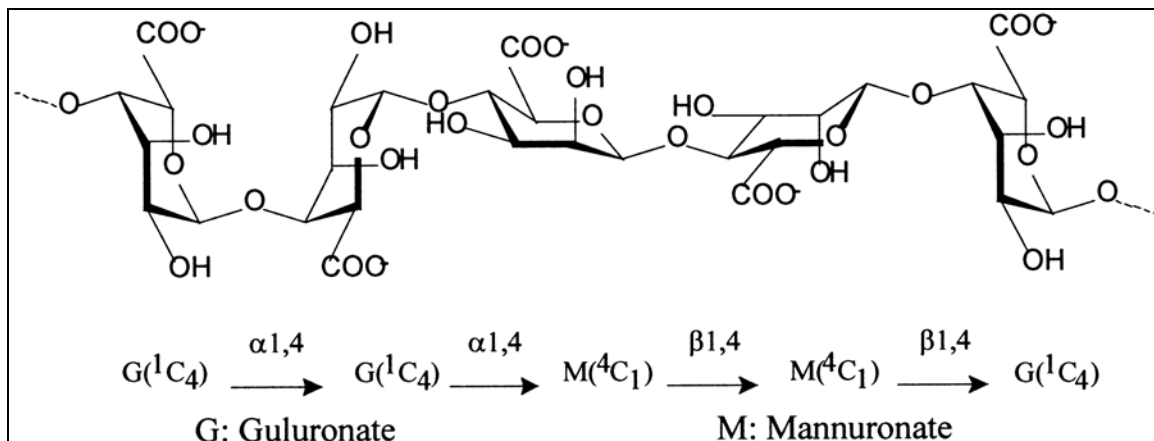


Figure 9: Polymeric arrangements of alginate. The G-block arrangement typically binds with the calcium ions, because two adjacent guluronic acid residues form a binding site for the polyvalent ion (Dornish, et al.).

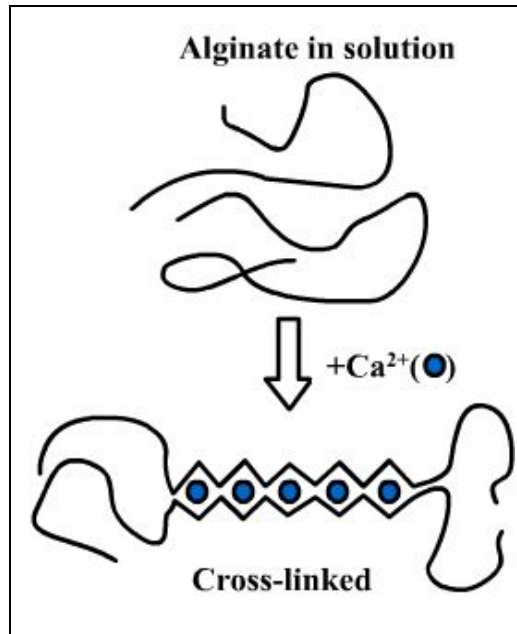


Figure 10: Schematic of calcium cross-linking process. The calcium bonds to the negatively charged portions of the G-blocks.

The alginate gels are typically obtained through diffusion setting, internal setting, or setting by cooling. Our client is interested in devising a method to accommodate the first of those methods. Diffusion setting occurs by allowing calcium to diffuse slowly into the alginate solution through a filter membrane. The time for the calcium to completely diffuse into the alginate depends on the thickness/geometry of the gel, but is generally on the order of one day to completely cross-link the alginate. In doing this, a homogeneous calcium-alginate network can be achieved. The relatively slow rate of this process limits its applications to smaller solution sizes, for which designing screw threads (at a very small volume) is not perceived to be a problem (International Specialty Products).

Another advantage to this cross-linking process is that growth factors or other proteins can be in solution with the alginate polymer during the reaction so that they are integrated into the matrix. This is because the reaction only needs calcium to be added and can be carried out at room temperature; therefore proteins will retain their natural activity during the process. An example of why this is useful is the possibility of adding VEGF (a growth factor that promotes angiogenesis or vascular growth) into the alginate to promote bone tissue growth into the matrix. By promoting blood vessel growth in the matrix, osteoblast and osteoblast precursor cell growth may be enhanced by the increased flow of nutrients and signals (Murphy, et al.). This is just one example of the many

possible enhancing reagents that could be integrated into the alginate matrix to promote bone regeneration.

Mineralization

After calcium cross-linking is accomplished, the mineralization process must be carried out to not only ensure a sufficient amount of mechanical stability within the screw, but to compose a screw that mimics natural scaffolding for bone tissue to grow into. In its broadest biological sense, mineralization is a complex process that involves deposition of anionic mineral nuclei onto a scaffolding framework (in our case, the alginate polymer) that allows for nucleation and growth (Murphy and Mooney). For example, in vertebrates, collagen fibrils are organized to have anionic “hole zones” which are thought to bring in mineral nuclei and initiate growth. Ultimately, mineralization processes will build an entire mineral network upon the scaffold matrix. In the case of interference screws, it will be desired to grow a mineral structure upon the cross-linked alginate matrix. This step is essential to the screw material because it has been shown that bone-like mineral is a prerequisite to bonding implanted materials to natural bone tissue (Murphy and Mooney).

Ideally, growth of carbonated hydroxyapatite (HA) would occur in the alginate scaffold. HA is the major mineral component in human bone extra-cellular matrix (ECM) (Murphy and Mooney). Our client is currently performing research to characterize the minerals he has been growing on alginate scaffolds. If our material mimics the ECM of bone, with a porous mineralized matrix, relatively quick bone tissue regeneration could be achieved. To grow mineral on the alginate scaffold, the gel is incubated in a simulated body fluid (SBF). The major mineral components of this solution are: NaCl, KCl, MgSO₄, MgCl₂, NaHCO₃, CaCl₂, and KH₂PO₄. This solution, at a pH of 7.4 and a temperature of 37°C, closely resembles the environment that bone matures under. Incubation time is on the order of two weeks to achieve complete mineralization.

Thermoplastic

In our novel design, a biphasic screw will provide bioactivity and structural support in a biological environment. The mineralized portion of the screw offers an ECM-mimicking structure that bone tissue can grow into and regenerate. Ideally, a screw

composed of solely mineralized alginate would maximize bone re-growth, which is the goal of this project. The thermoplastic is necessary, though, in providing more strength under operative and post-operative actions, in other words it acts as a substructure upon which the functional component (mineralized alginate) is formed. Thermoplastics are synthesized polymers and some exhibit mechanical properties comparable to metals currently being used for interference screws. These thermoplastics, as suggested by the name, can be cast in liquid form and then allowed to cool into desired dimensions, making their possible application quite diverse. An exceptionally important feature of thermoplastics is their ability to degrade over time under biological settings. Hydrolytic splitting of the polymers breaks down the plastics, which are eventually removed via phagocytosis by the immune system all over the course of several months to a couple years (Staelin).

The thermoplastic being considered for the portion of our screw is poly(lactic-co-glycolic acid) (PLGA), whose molecular structure can be seen below in Figure 11. The L-enantiomer of lactide occurs naturally in the body, but synthetic processes of making the polymer can produce a racemic mixture of L- and D-enantiomers. Depending on the makeup of enantiomers present, the mechanical properties and degradation rate of the plastic will vary. For example, an arrangement of the poly-L-lactic acid (PLLA) polymer creates a highly crystalline structure, while the poly-L-D-lactic acid (PLLDA) polymer is amorphous and degrades faster in the body. However, the makeup of PLGA is typically random (Gleason). In addition, the ratio of lactic to glycolic acid also affects the mechanical properties and degradation rate of the polymer plastic. While poly(glycolic acid) degrades faster than both poly(lactic acid), the copolymer composition of the plastics (PLGA) does not have a linear relationship to the degradation rate (Figure 12) (Middleton and Tipton).

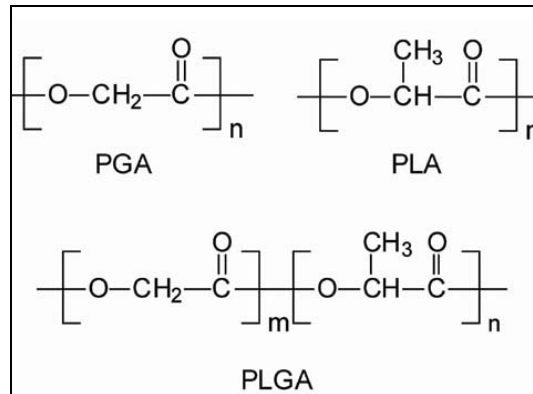


Figure 11: Chemical structures of poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and poly(lactide-co-glycolic acid) (PLGA). <<http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=152>>

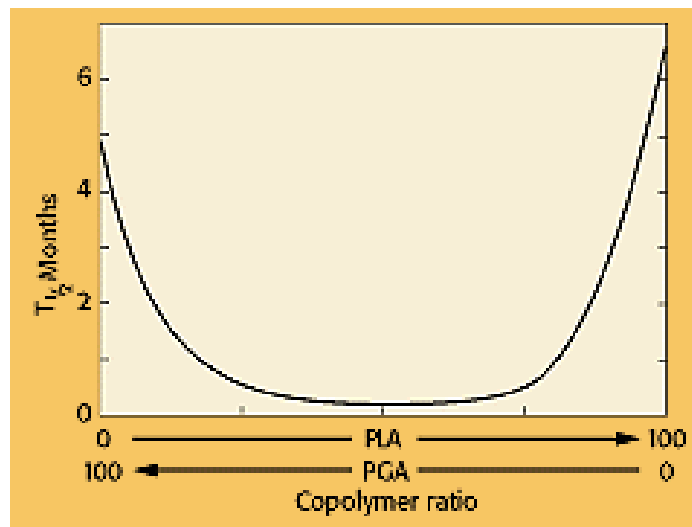


Figure 12: Half-life of PLGA copolymer in rat tissue compared to the ratio of polymer components in the plastic (Middleton and Tipson).

Client Requirements

- Biphasic
 - Constructed from synthetic, but degradable thermoplastic which provides strength
 - Mineralized material offers maximal ability for positive biointeractions
- Biocompatible
 - Material must be recognized as self once implanted
- Bioactive
 - Material must promote and foster tissue regrowth

- Biodegradable
 - Material must degrade over time to be completely replaced by natural tissue
- Sterilizable
- Able to withstand the forces involved in surgery and post-operative activity
- A technique to reproduce the screw consistently
 - Molding technique must be accurate and reproducible for production purposes, and that maintains the integrity (activity) of any integrated growth factors or proteins.

Final Design

Our initial design involved thermoplastic threading supported by axial spines in which an alginate core was situated in an interlocking mechanism (Figure 13). This design, however, became infeasible when it was determined, through consultation with our client, that the mineralized alginate was not structurally sound enough to bear the insertion torque created during surgery. This was largely due to the fact that the alginate was being frozen to increase porosity for fostering additives, such as growth factors and osteoblasts. Unfortunately, increasing porosity also meant weakening the already questionable hydrogel strength.

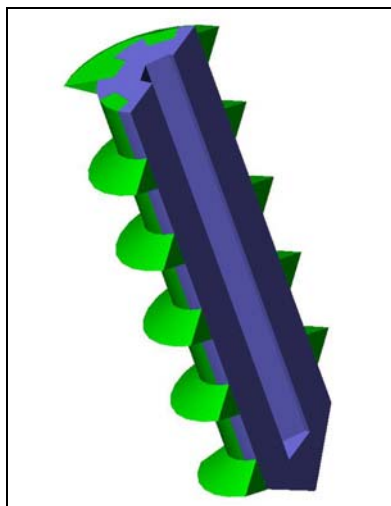


Figure 13: Illustration of a cross-sectional view of the old biphasic screw design. The green section represents PLGA, while the blue section represents mineralized alginate gel.

Our focus, therefore, was to redesign our screw so the PLGA would not only comprise the threading, but the core as well. In doing so, we aim to make a sufficiently strong screw that integrates alginate into less load-bearing areas.

Components

Thermoplastic core/structure

The first step taken in redesigning the screw was considering the entire screw as PLGA, and then examining where alginate could be put without compromising the screw structure. The core needed to be thermoplastic, because as previously mentioned, the alginate is not strong enough to accommodate the torque generated for insertion (Figure 14). Also, the threading of the screw needed to be PLGA due to the obvious shearing forces that the screw will endure during insertion.

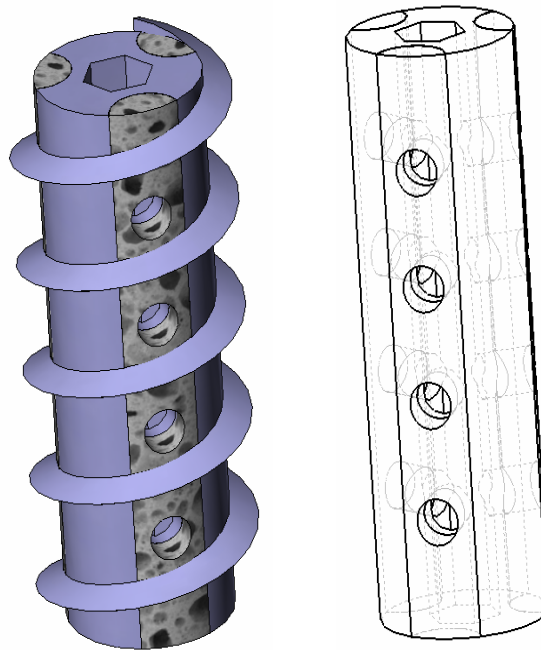


Figure 14: Computer model representations of the final interference screw design. Left: thermoplastic structure (purple), with alginate pockets (grey). Right: Model without the threading for better visual of alginate pockets.

The novelty of our design lies in its biphasic nature. Ideally, for tissue in-growth and bone formation, the interference screw would be solely comprised of mineralized alginate, however, as stated before, that would severely impair the mechanical integrity of the overall design. Incorporation of the PLGA allows for a much stiffer, stronger screw

that still exhibits degradable properties while promoting tissue growth. The PLGA copolymer that will ideally be used for this purpose will have a lactide to glycolide ratio of approximately 85:15. The large amount of lactide gives the screw mechanical strength, while the glycolide portion increases degradation rate. This ratio is still pending, though, and may be altered after further testing. The ideal composition will degrade at a rate that complements the rate of bone regrowth, while still providing enough strength until the new bone can fully handle associated loads and hold the graft in place. Figure 15 shows an example of plastic degradation that is designed to last just long enough until biological healing can take over. However, this product will mainly be replaced by fibrous and fatty tissue, while our design would allow for bone tissue to grow onto the alginate scaffold.

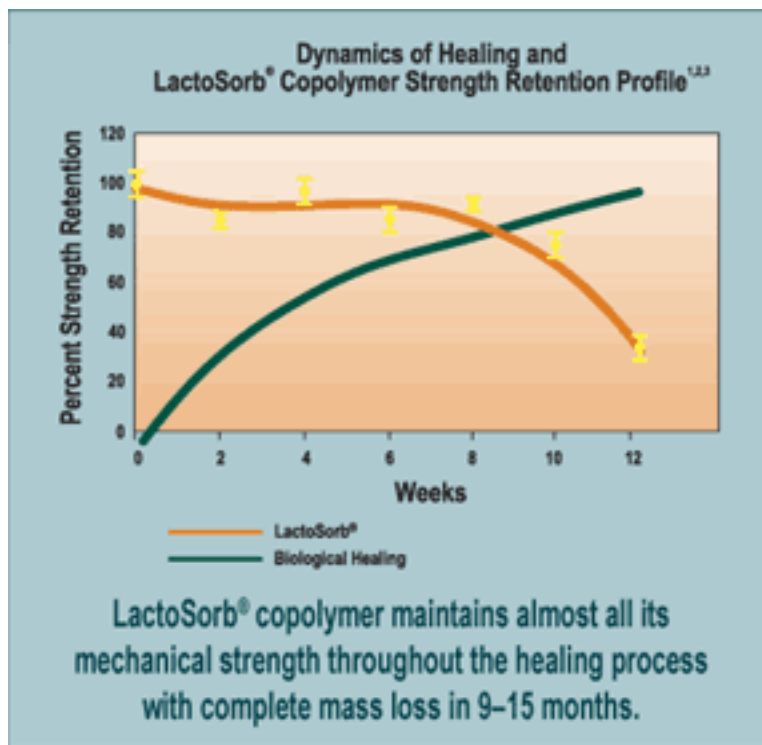


Figure 15: A graphical representation of plastic degradation rate versus healing for a product from Arthrotek. <<http://www.arthrotek.com/products/lisorb.cfm>>

Mineralized Alginate Pockets

The novelty of our design demands the incorporation of alginate into the screw in order to promote natural bone regrowth. We decided to create alginate “pockets” that would allow for this material to be included. Three semi-circular cavities in our design are now embedded in the thermoplastic, located along the circumference of the screw.

This location, seen in Figure 16, was chosen because the alginate between the threads will be in direct contact with surrounding bone tissue. With further testing, it will be determined if this arrangement will give the overall screw sufficient strength. The important aspect of the alginate pockets is that they are almost completely surrounded by PLGA, and so will not have to be responsible for any direct support. Finally, these pockets will be connected with the driver shaft using transverse growth holes. This entire system will be continuous, maximizing bone regrowth after inserted.

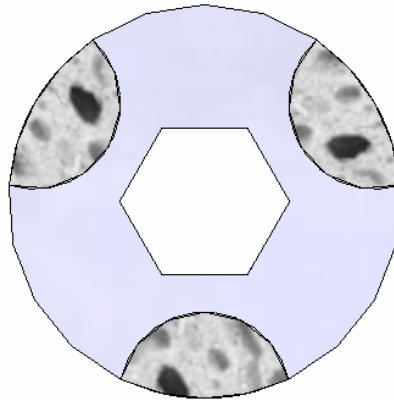


Figure 16: Top view of the interference screw with the threading not incorporated. The alginate pockets (porous grey) are located along the periphery for direct contact with tissue.

Growth Holes

Growth holes have been incorporated into the final design to allow the bone tissue to have direct access to the driver cavity (Figure 14, 17). These holes permit in-growth of the tissue to surround the plastic before degradation begins. Having the in-growth of tissue increases the osteo-conductive environment and improves the support before the tissue degrades. Also, with the possibility of in-situ addition of alginate into the driver cavity, the growth holes allow further distribution of the alginate's tissue-promoting growth capabilities.

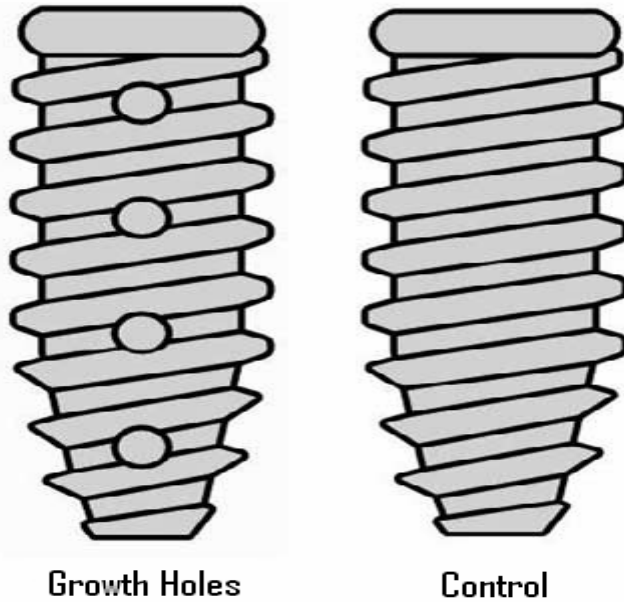


Figure 17: Depicts the screw with holes drilled between the exterior into the driver shaft to promote inward tissue growth compared to controls (Hunt, *et al.*, 2005)

Design Calculation

Alginate Radius

Since alginate is such an important part to our final design, it was important to maximize the amount of alginate present in our screw. But due to the mechanical properties of the alginate contributing almost nothing to the structural integrity of the screw, it was decided to treat this as a void space during analysis. Professor Michael E. Plesha was consulted on how to accurately account for the alginate cavities when determining shear stress. Figure 18 represents the information found in Roark's Formulas for Stress and Strain under the direction of Professor Plesha.

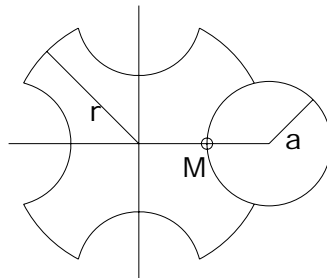


Figure 18: Shape used for maximum shear stress analysis

Equations were given for shapes with 2 or 4 holes in the previously mentioned reference, where r is given as the radius of the shape, a is given as the radius of the cut-out and M is the point where maximum shear stress will occur. Although the final design incorporated only 3 holes, the 4-hole equation was used as it included a factor of safety. Equation 1 represents this relation, where the value for B is the substituted into Equation 2.

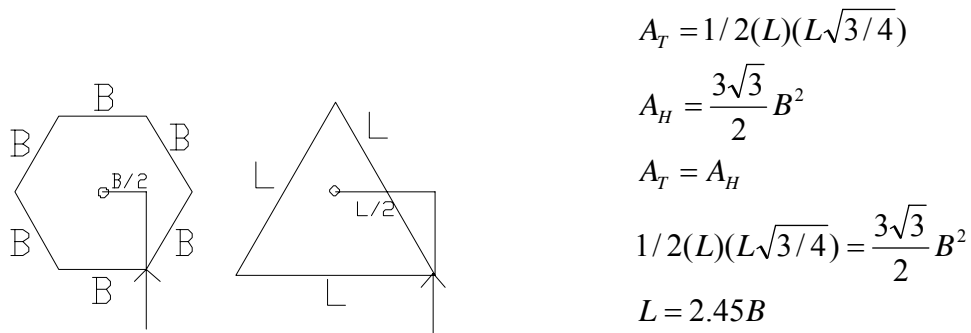
$$B = 1.2135 - 2.9697 \frac{a}{r} + 33.713 \left(\frac{a}{r} \right)^2 - 99.506 \left(\frac{a}{r} \right)^3 + 130.49 \left(\frac{a}{r} \right)^4 \quad \text{Equation 1}$$

$$\tau = \frac{TB}{r^3} \quad \text{Equation 2}$$

Preliminary calculations using an insertion torque of 1.5Nm (reference) and a PLGA maximum shear stress of 14 MPa (need to double check value and find MW), give a value of roughly 0.5 mm. **This amounts to approximately 2% of total cross-section that could be incorporated as alginate into the screw.**

Torque Analysis

In order to determine the ideal shaft of the driver insert, torque analysis was used. Two different shapes were investigated, namely a hexagonal core and a triangular core. Free body diagrams of the shaft cross-sections were then analyzed with the area held constant between the two different options. First a relation was found between the length of a triangular side and a hexagonal side as outlined in Figure 19.



$$A_T = 1/2(L)(L\sqrt{3}/4)$$

$$A_H = \frac{3\sqrt{3}}{2} B^2$$

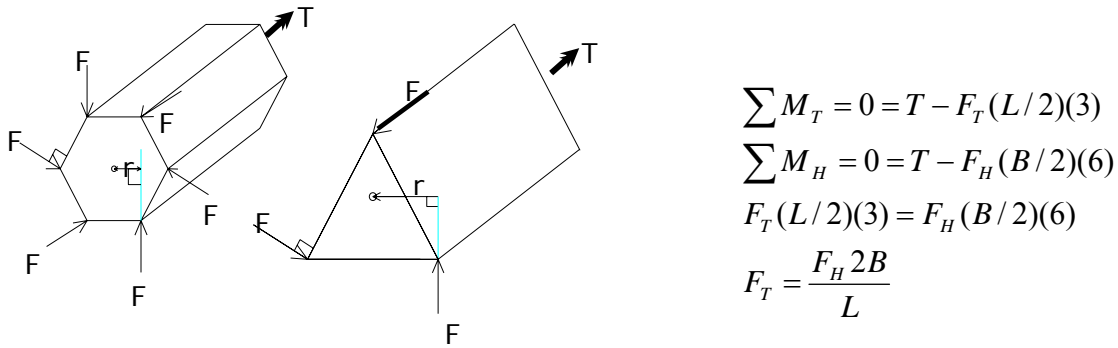
$$A_T = A_H$$

$$1/2(L)(L\sqrt{3}/4) = \frac{3\sqrt{3}}{2} B^2$$

$$L = 2.45B$$

Figure 19: Calculations to determine the relationship between the length of a triangular side and a hexagonal side to be used in torque comparisons.

Next a relation was found between the force acting on each triangular face and the force acting on each hexagonal face as outlined in Figure 20.



$$\sum M_T = 0 = T - F_T(L/2)(3)$$

$$\sum M_H = 0 = T - F_H(B/2)(6)$$

$$F_T(L/2)(3) = F_H(B/2)(6)$$

$$F_T = \frac{F_H 2B}{L}$$

Figure 20: Summing of the moments was used to find the relationship between forces acting on the faces of the driver shafts.

Finally, the two equations were combined and common variables were eliminated. This resulted in a direct relation between the force acting on each triangular face versus each hexagonal face as presented in Equation 3 and 4.

$$F_T = \frac{F_H 2B}{L}; L = 2.45B \quad \text{Equation 3}$$

$$F_T(1.225) = F_H \quad \text{Equation 4}$$

Thus, it was determined that if both shapes were limited to the same area, the **hexagonal shaft would experience less force.**

Screw Fabrication Process

A major part of our design is creating a feasible process to produce the desired screw geometry and makeup. We needed to test the fabrication process that we developed to prove if our design could even be created before we made a significant financial investment in the desired materials. Therefore, we constructed a scaled-up rudimentary screw mold from a 8.89 cm metal coupling nut with 1.91 cm inside diameter (Figure 21A). **The diameter is scaled up by roughly a factor of two and the length by a factor of three.** A scaled-up model is easier to work with than the smaller surgical sized screw because of the model's size, and it helps identify structural and fabrication failure points. We machined a base for this mold from a bolt that screwed into the coupling nut (Figure 21E) and had an indented end to produce a conical tip on the screw.

Experimentation has been critical in our success with designing the scaled-up model screw. We have tried a variety of heating techniques: oven, Bunsen burner, and heated mineral oil bath. Our most successful technique has been the heated mineral oil bath due to the fact that we are able to achieve uniform heating.

This process begins by preparing the mineral oil to utilize as a heat source. Mineral oil is added to a glass bowl to a level that lies just below the top of the mold (preventing it from spilling into the mold) and heated on a hot plate. Once the mineral oil has reached 100° Celsius, the mold, filled with seven grams of polypropylene (PP) beads and sealed with a solid metal screw cap, is placed into the bath. (PP beads were used in place of PLGA due to the high quantity required and less expensive cost; at least until the fabrication process is sound). The bath continues to heat until it reaches 175° – 180° Celsius. At this point, the cap is removed and pieces of PP that haven't reached their transition temperature are removed from the mold using forceps. Then the molten PP is slightly compressed with the forceps and recapped with a special screw cap that has a hole in the center and three slots equally spaced around the circumference (Figure 21D). The mold then remains in the bath until the mineral oil reaches 185 degrees Celsius.

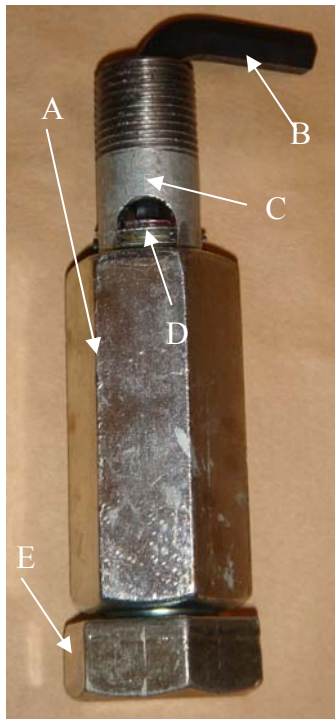


Figure 21: Side view of our metal mold (A), with driver shaft (allen wrench, B), alginate pocket plug (C), three-slot screw cap (D), and bolt base (E).

A plug is then inserted through the special cap and into the mold. The plug displaces the PP to form three alginate pockets in the screw. The plug was fabricated from one solid piece of piping so that each displacement shaft is connected at the top and held in the correct position (Figure 21C). The displaced PP is removed using the forceps, and the driver shaft (Figure 21B) is jammed through the cap into the mold. At this point the mold can be quenched using ice or cool water. Once this process is finished, the product is screwed out of the mold and the shaft is removed. Finally, once the screw has reached room temperature, it is taken down to the lab and growth holes 1.2 mm in diameter are drilled from the outside of the screw, into the alginate pockets until they reach the driver shaft.

There are two problems we had with this process that we have been working on fixing. First, many of the screws that were made were not completely uniform; many had air bubbles all along the side. Our current solution for this problem is to remove any PP that has not reached the transition temperature (are not rubbery or looked like they have melted) when we take off the solid screw cap; our rationale is that these may provide the air bubbles. This change has seemed to be successful, but more experimentation is necessary to be certain. The second problem we have encountered has been with “burning” the bottom of the PP. We do not know the exact mechanism, but we hypothesize the bottom of the mold, the side closest to the hot plate, experiences hotter temperatures. Our current solution has been to limit the temperature to 185° Celsius and to make sure that it is only at that temperature for a small amount of time.

We have also been working on adding alginate to our current model. Thus far we have successfully injected gelatin into the alginate pockets as a model material (Figure 22C). Gelatin was initially used as a model material for alginate due to the ability to thermally cross-link as opposed to chemically (less expensive cost). Also, for our purposes, gelatin displays similar properties to alginate until we begin using mineralized alginate. Our next step is going to be injecting a hydrogel into the pockets, cross-linking it, and then mineralizing it. Looking forward, a major challenge with mold development will be cross-linking and mineralizing the alginate. To cross-link the alginate polymer, a micropore filter will be secured on top of the mold and the entire system will be placed into a bath of calcium chloride for 24 hours. The final procedure to undertake is

mineralizing the alginate. This is done by bathing the screw in a modified simulated body fluid (mSBF) solution for the course of one week. Mineralizing the alginate gel will stiffen it and will emulate bone extra-cellular matrix properties. It is also expected that mineralization will improve the interface between the two materials. Minerals should grow on the surface of the PLGA at the interface, possibly providing adhesion between the two materials.

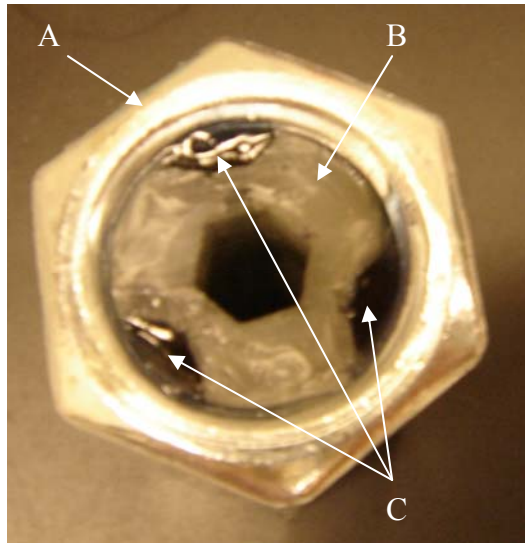


Figure 22: Top view of the mold (A) with solidified PP structure (B) and filled alginate pockets, using a purple gelatin model material (C).

Storing the screw brings up another issue. When we first injected gelatin into the mold we found that it quickly dried up (approximately 48 hours). Our solution to this problem is to store the screws in a humid environment so the gelatin/hydrogel will not dry. Thus far we are using a plastic container with a wet paper towel; once the screw has been developed we will look into this issue more closely.

Mechanical Testing

Once our screw fabrication process was working, we wanted to compare the structural properties of the different screws. Therefore, a small amount of mechanical testing was done on the screws to allow for a comparative analysis. We used the mechanics lab to test the axial and radial compressive strength of the screws. Preliminary data from the axial compression test compared a solid screw with to the alginate pocket

screw (pocket screw) in Figure 23. Data was analyzed as a function of force (Newtons) versus strain (percentage). It is important to note that the sample size of the data was two for each type of screw and therefore a standard deviation could not be calculated. Figure 23 shows that the two screws differ by approximately 100 N at 2% strain, **a factor of 1.2**. Measurements are taken at 2% strain because, generally speaking, biological materials have exceeded their yield strength after they surpass 2% strain. The factor obtained through axial compressive analysis (1.2) will be used to help select the type of PLGA (molecular weight and ratio) for the final screw. Once the L:G distribution and molecular weight of the PLGA being used is decided upon, a literature search can be done to find the maximum axial compressive force that that type of PLGA can withstand. Once found, this value will be divided by the factor that was empirically gathered to get the maximum compressive force that the same material can withstand while having alginate pockets. If this value is more than what the knee, itself, experiences then the given alginate to PLGA ratio should work.

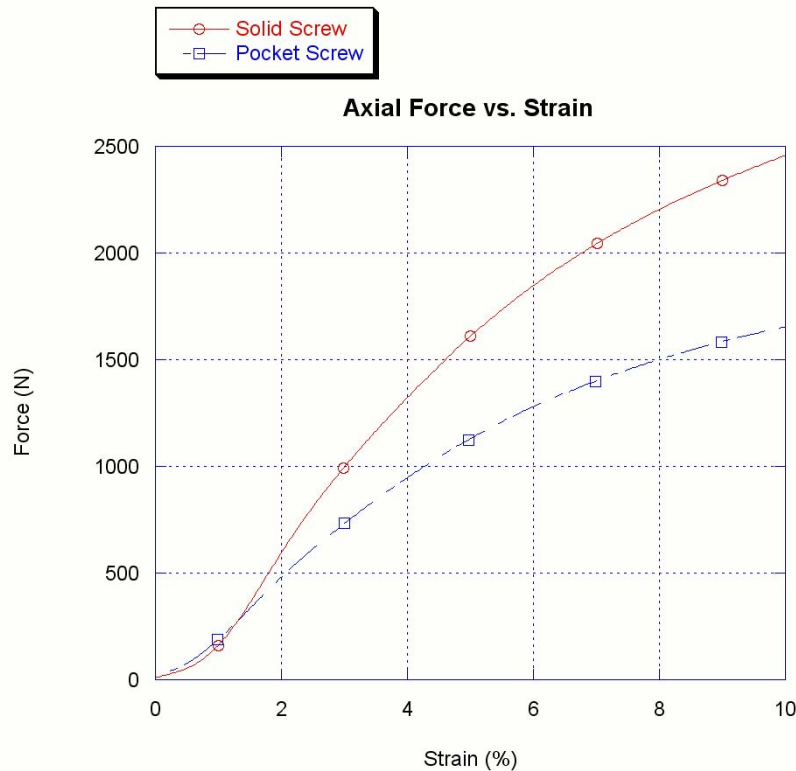


Figure 23: Axial compression test comparing a screw with the driver shaft cavity to the properties of a screw with both the driver shaft cavity as well as alginate pockets.

The second test that we ran in the mechanical testing lab was a radial compression test. Again the sample size was only two for each type of screw, but the forces were averaged together to get graphs. The solid screw in Figure 24 appears to reach its yield force at approximately 13% strain, with a force around 2200 N. On the other hand, the alginate pocket screw (pocket screw) in Figure 24 appears to reach its yield force at 3% strain, with a force around 300 N. However, the pocket screw graph has a non-traditional appearance, and from observation during the testing, this occurred because alginate pockets collapsed and were easily compressed. This compression took place because we only have three alginate pockets, the line of force could not be spread out evenly to the solid pieces of the screw. Our solution to this problem is to create a plug that has four legs and then run more radial compressive tests in hopes that force will be distributed more evenly.

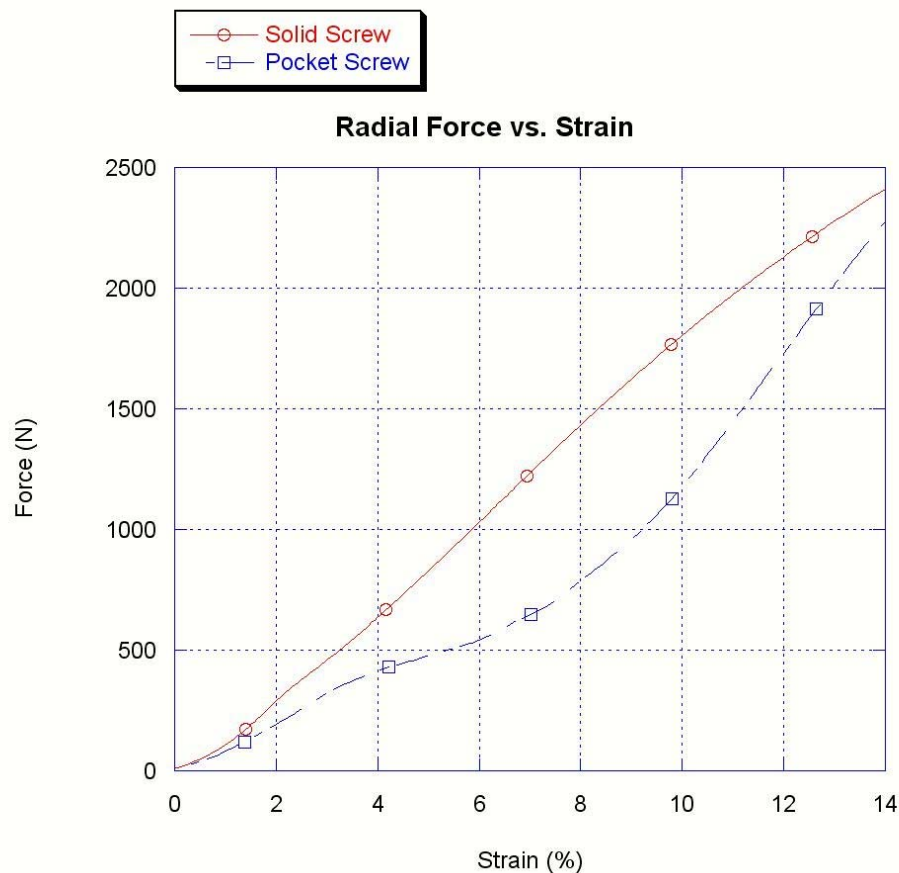


Figure 24: Radial compression test comparing a screw with the driver shaft cavity to the properties of a screw with both the driver shaft cavity as well as alginate pockets

The factors obtained through mechanical analysis (1.2 for compression, 1.4 for radial) will be used to select the type of PLGA (molecular weight and ratio) for the final screw.

The last test that was performed on the screw was an insertion torque test. The model being tested was screwed into the mold until it came in contact with the base of the mold and could not be screw any further. The mold was then secured into a vice and a torque wrench was inserted into the shaft cavity of the screw. Torque applied to both the solid screw and the alginate pocket screw. The solid screw was able to withstand 67.79 Nm of torque before the wrench started to slip within the shaft cavity. However, we were unable to get any data from the alginate pocket screw because the wrench slipped inside the shaft cavity when any amount of torque was applied. We observed that the part of the screw in contact with the wrench was slightly deforming into the pocket and causing the wrench to slip (the shaft would slightly transform into a circle). Therefore, in order to determine a proportionality constant, we intend on developing a screw with a triangular driver cavity and rerunning the test.

Mold Development: Rapid Prototyping

After showing that our screw fabrication process is feasible with a rudimentary metal mold made from a coupling bolt, we are looking to the next step of making a mold specifically for our interference screw. Fabrication of a mold will be accomplished through casting of a designed model. The mold will be constructed using a form of rapid prototyping. Rapid prototyping is a technology that takes images directly from three-dimensional computer-aided designs (CAD), transforming data into a physical model (PM Engineer). After designed, the CAD file is converted into a .stl (stereolithography) format, which has become the industry standard. After physical dimensions are dictated, the construction is carried out one layer at a time using polymers, paper, wax or powdered metal. Finishing steps include sanding, polishing or sealing the material, however this step will probably not be necessary for our application, because the prototyping will be followed by investment casting, and thus degradation.

Investment casting will allow for a mold to be created that fulfills the above constraints set forth. This common process involves coating of the prototyped material

with a refractory material that is heat resistant, followed by replacement of the prototyped material with molten metal. The molten metal can be poured using gravity, pressure or a vacuum system (Harvest Technologies). Once the metal is cooled, a reusable mold will be obtained (Figure 25). Investment casting offers the benefit of precision, because direct machining of the metal is not needed. When working with such a small volume of material that has a large degree of structural complexity, this process will be ideal.

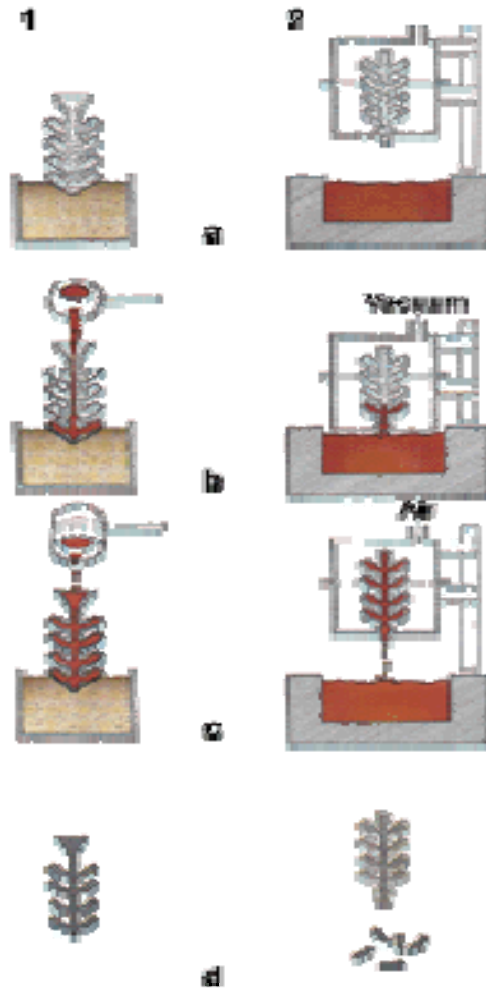


Figure 25: (a) Mold casing (b) Molten metal is poured into casing; method 1 uses gravity, where method 2 uses vacuum (c) Excess molten metal is removed and allowed to cool (d) Cooled positive metal mold is obtained (Harvest Technologies).

A computer model of the desired interference screw mold was created using Solid Works (Figure 26A). It includes two halves which have bolt holes that will be used to hold the mold together during fabrication. A conical tip will allow for centering of the driver shaft before the melted plastics set around it. The cylindrical shape of the shaft of

the screw (not including the threads) will make the fabrication of a tool to displace the plastic for alginate cavities much more feasible. The flat sides will make the cavity formation at the surface much easier with a tool made from a cylindrical shaped piece of metal (like piping). In addition, this model was scaled up from the actual size for initial fabrication work. Actual interference screws only have a diameter of approximately 1 centimeter, therefore an actual size mold would be difficult to work with.

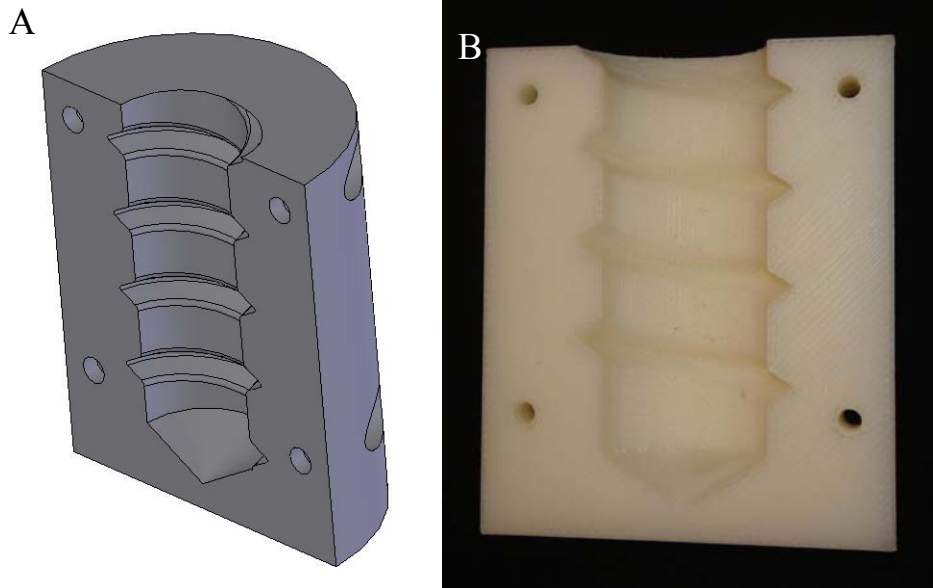


Figure 26: Solid Works model of one half of the interference screw mold (A); rapid prototype model from test run made of ABS plastic (B).

These designs were given to Todd Kile of the Mechanical Engineering Department who has access to a rapid prototype machine. It was unknown whether the machine could produce the contours of the threads on the interference screw that were needed, but Mr. Kile suggested that we attempt a run of one half of the mold to test the feasibility. This was done using ABS plastic (not a wax, which would be used for eventual casting). The rapid prototype machine successfully created the half mold we designed (Figure 26B).

From the initial rapid prototyping test run we learned that our design can be accurately produced, but also used a substantial amount of material to create. This amount of material means the design is expensive and takes a considerable amount of time for the machine to fabricate. Therefore, we are going to redesign our mold to have thinner sidewalls so that less volume of material is needed when we create our final mold. The thickness of the walls was initially made somewhat thick to allow space for the bolt

holes, but we should be able to reduce the thickness while still incorporating holes to line up the two halves. In addition, we may make a mold that is as scaled up as our first run to save material and cost. We would still make a scaled-up model, but not to the same extent. Our final design will be fabricated from a wax material that can be utilized in an investment casting process.

Potential Problems

The most imminent issue is determining how well the information gained from the tests and fabrication process of the PP model will correlate with the properties of the intended design. If this information does not translate to the surgical device; the current design will need to be reworked. However, if our assumptions are valid then the following potential problems will need to be taken into consideration:

Thermoplastic properties

The feasibility of our alginate-pocket design resides upon the ability of the thermoplastic structure being able to withstand the forces incurred during implantation and rehabilitation. Understandably, as greater amounts of thermoplastic are removed for integration of alginate, mechanical strength of the device decreases. Two key issues arise in trying to solve this predicament. First, in order to provide enough space for sufficient alginate, the molecular weight and/or PLA:PGA ratio must be increased; increasing the degradation time of the thermoplastic and conflicting with the tissue growth. Secondly, mechanical properties reported in the literature do not list the essential values needed to estimate how our alginate-pocket design will behave under loading. Thus, the design will have to be thoroughly tested to quantify its limits and make comparisons with other ACL interference screws on the market. This detailed testing will be time-consuming, but it is important to maximize the amount of alginate, minimize the degradation time, and maintain safety of the device.

Heating Process/Uniformly consistent screw composition

As the aforementioned alginate pockets characteristics continually get refined, it is also important to develop a method of thermoplastic heating that is efficient and yields a more homogenous melting and is reproducible. The current mineral oil bath protocol is

time consuming and inconsistently melts the thermoplastic in the mold. The non-uniform melting is the greater of the two problems because it leads to inconsistencies in the screw. Referring to the mechanical testing discussed above, the produced screws must have a homogenous makeup to have confidence in the results and make solid conclusions about their safety. Further research into polymer melting practices may reveal steps to methods that can be added to fix this problem.

Scaling Down

Our current work has been done using a scaled up model of the device. This larger model makes it easier to build in the alginate pockets and test its mechanical properties. Machining the mold and plugs on that small of scale will be difficult and the melting method may need to be modified as well. Once scaled down to surgical size, it will be important to repeat the mechanical testing to assure sufficient strength, hopefully not changing significantly from the large model.

Degradation of thermoplastic

One area that has only been explored through literature research is that of *in vivo* degradation of the PLGA and other commonly used biodegradable polymers. An issue is raised with our screw design in that its uniqueness does not have exact degradation behaviors well characterized in the literature. It is important that the bulk phase degradation of the thermoplastic structure be sufficiently long to allow for tissue growth to secure the graft. The degradation is thus another unknown that must be safely approximated during the healing process. Additionally, we will only be able to quantify the degradation with *in vivo* testing of the alginate-pocket screw design; an aspect of the project that will be difficult to produce during the final semester of work.

Driver shape

Calculations of the hexagonal driver shape shows that it requires less force per unit area to screw in the device. Preliminary torque analysis using the hexagonal driver shape indicates that this may not be optimal for use in the alginate-pocket design. When the hexagon driver (Allen wrench) is rotated, it displaces the thermoplastic outward into the alginate-pockets, allowing the driver to slide through the cavity without turning the

screw. One caveat is that these screw models were composed of a softer thermoplastic (PP) than the actual design. In the event that the hexagonal driver still slips through the hole too easily, a triangular shaped driver will have to be substituted. This new shape necessitates a greater insertion force per unit area that has to be distributed throughout the cross-section, possibly causing problems during the insertion.

Chemical modifications to the alginate, both cross-linking and mineralizing, could also pose problems by rendering incomplete results. The cross-linking, as explained earlier, will be performed by diffusing a calcium chloride solution through a micropore filter at the top of the mold. Although the screws are small in magnitude, the cross-linking solution still has a relatively large distance to travel. Because the filter covers a small area to volume ratio, incomplete diffusion could occur. The same situation can be said about the mineralizing process, where regions of the alginate not in contact with any direct surfaces may get neglected. Possible solutions to address this problem would be to modify the alginate in a stepwise fashion. Diffusing the correct chemicals into the alginate in several steps would decrease the distance needed to travel, however, fusion of each subsequent block would then become a problem. Another possible answer would be to design a porous mold for more ubiquitous delivery of the calcium chloride.

Another potential problem is our ability to test the screw. We will initially have to test *in vitro*. After the initial testing we would like to move to animal testing and eventually test the design in humans. In order to do this testing we will need to get a variety of forms filled out and permissions granted. We will start looking into this scenario as soon as possible to give us a head start.

Future Work

The current status of the project leaves several aspects to be completed in the future semester. The first order of business is to have a rapid prototyped mold created, from which we can cast a metal mold. Expected completion is early in the next semester. We have contracted the Mechanical Engineering department to do the rapid prototyping and a local foundry to cast the mold. As soon as this is done, scaled-up screws can be produced and followed by mechanical testing. After the structural properties in the scaled-up model are safely defined, the next phase is to remove the scaling factor to reach

an actual surgical size. Again, rapid prototyping and investment metal casting will be utilized to create the smaller size of mold.

There are two other types of testing that need to be conducted to prove the success of this device. Degradation testing is something that is best done *in vivo* using animal models to study the behaviors and tissue growth from the alginate incorporation also needs to be assessed. There is substantial literature on *in vivo* ACL interference screw degradation and tissue growth models. When the time is appropriate, our own model can be developed from these and implemented to study the alginate-pocket device. The latter of the two is best studied with *in vivo* animal models, but data may also be generated *in vitro* using osteoblast-like cell lines seeded on the alginate screws. Our client's work specializes in this area, presenting us with expert assistance and resources to complete this *in vitro* testing.

In the event that an adequate amount of thermoplastic can not be removed from the screw structure to maintain the safety of the screw, other approaches will need to be investigated. For example, our client has suggested the possibility of mineralizing the external surface of a solid degradable thermoplastic screw. This can be achieved by chemically treating the surface of PLGA, for example, to form functional groups that allow for mineral crystal nucleation. After incubation in a mineralizing solution, the plastic surface develops a thin layer of mineralization. This technique has already been shown to work by our client in previous work. This type of altered thermoplastic screw would have a great advantage over current screws because the mineralization has been shown to foster bone cell growth. In addition, we may be able to alter the screw geometry in ways to optimize surface area of mineralization, or area that for tissue in-growth (e.g. growth holes).

Thermoplastic Degradation

To date, previous *in vitro* degradation testing of PLGA interference screws can not be found. Moreover, there is minimal documentation of *in vivo* degradation of PLGA interference screws. The data that is reported is basic in content and does not provide sufficient background from which to confidently understand the degradation process of such screws. Thus, it is our intention to develop and execute an *in vitro* degradation

model using the PLGA reinforced threads. It is important to have the degradation properties of the thread model in order to tailor the correct copolymer ratios to tissue growth.

The protocol of this degradation assay would be carried out following the completion of a large number (>12) complete thread sets detailed in a previous section. The PLGA threads would then be submerged in a bath of Simulated Body Fluid (SBF), the contents of which are best described by Murphy and Mooney. The SBF provides a means to mimic the milieu a screw would endure inside the body and more importantly provide an aqueous environment to carry out hydrolytic degradation. Each week, the change in weight and volume would be measured and used as a parameter for degradation. Additionally, at two, four, six, twelve months, three of the screws would be randomly selected to undergo mechanical strength testing like compression and tension loading as well as shear stress analysis. The data acquired from such analyses would be used as another gauge of the degradation and also used to make comparisons of strength reduction over time to size reduction over time.

The proposed *in vitro* model has several advantages over *in vivo* models using PLGA or other polymer interference screws. The most obvious is there is no need for difficult, invasive surgical procedures or animal subjects. Second, SBC is a controlled environment with minimal variability thus keeping the degrees of freedom as small possible. Third, the screws can be easily weighed and measured and replaced back into the SBC. Lastly, simplicity of the entire operation makes it feasible with respect to the limited manpower, budget, and time that this project has available. There is no doubt that the quantitative data collected *in vitro* would not perfectly mimic the data collected in a similar analysis done *in vivo*, but the aforementioned motivation and advantages provide sufficient rationale for the comparative *in vitro* model.

Mineralized Alginate Mechanical Properties

Currently, mineralized alginate hydrogel has not underwent mechanical property testing and been reported. This seems likely since mineralized alginate is a relatively new biomaterial that has not been used before as a structural element. The biphasic interference screw detailed in this project does just that, uses the mineralized alginate as a

structural element. Thus, there is a sufficient need to quantify the compressive, tensile, and shearing strengths of the mineralized alginate core. Most importantly, the shearing modulus must be sufficient to withstand shearing failure at the gear-grip thermoplastic interface as well as the hexagonal driver interface (assuming the thermoplastic and driver would have larger shearing moduli).

Mechanical property testing is relatively simple and can be done on most solid objects. The protocol for the testing would include having at least 3-6 specimens per property and interface test. A standard set of material testing machines can be used to perform different tests. The quantitative data collected from the necessary tests could then be compared to known insertion torque and pull-out strength requirements documented in the literature.

Tissue Regrowth

The bioactivity of the screw is one of its novel elements. Therefore, it is necessary to have some understanding of how well the screw will promote and foster the growth of tissue. The screw will act like a scaffold, thus it will mimic the extracellular matrix. It is the hypothesis of the group and the client that this structure will foster tissue growth. Approximately 12 experiments would be run at once to ensure integrity of the collected data. These experiments would utilize the SBF described in the Thermoplastic Degradation section of the paper. In addition to the SBF, the alginate would be seeded with osteoblasts and growth factor to simulate the bone environment and what will be on the screw. The growth factor that will coat the alginate will be vascular endothelial growth factor (VEGF). These pieces of alginate will be examined daily for any type of growth and weighed to note any changes in mass.

If the *in vitro* tissue regrowth test is successful, the next will be to test it in living subjects. With permission from the Institution Review Board (IRB), we will start implanting mineralized alginate in the bones of rodents. This alginate will no longer be seeded with osteoblasts since it will be in direct contact with bones, but it will still be coated with VEGF. The rodents would be kept in a controlled environment and bi-weekly specimens would be taken to determine the rate of growth in the bone. The

pieces of alginate would undergo mechanical testing to determine how strong the newly formed tissue is.

Screw Dimensions

Upon optimization of a molding technique, a shape for the threading, driver shaft and screw, itself, must be established. Basic screw specifications can be seen in Figure 27. Because there is no industry standard, the overall screw will not replicate any specifications, only resemble them. Typical interference screws range from 20-30 mm in length (Mitek) and 6-12 mm in major diameter, which is what our design will emulate. These dimensions, however, will need to be analyzed in more detail, because of their influence on pullout strength and other mechanical properties (Duke Orthopaedics). Pullout strength is defined as the maximum uniaxial tensile force applied to a screw that is necessary for failure of a bone or a screw to occur (Johnson et al.). Other factors influencing pullout strength are minor diameter and thread depth (outer to inner diameter ratio) which must also be tested. Overall, a design with the most amount of bone in contact with the screw is the most effective way to maximize pullout strength (Sanden). This implies a substantial thread depth to increase outer surface area.

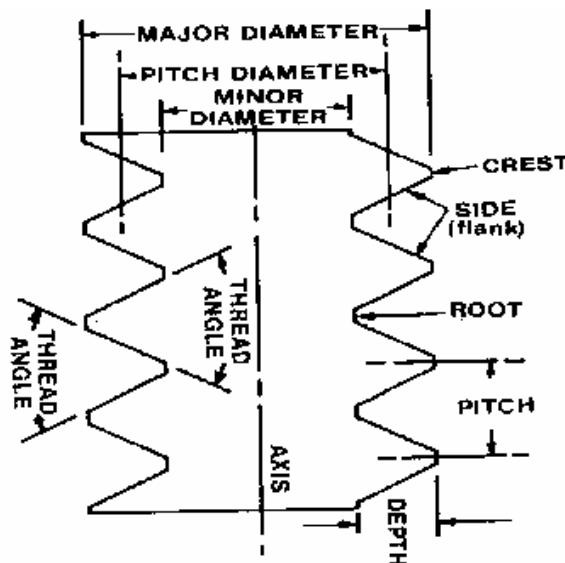
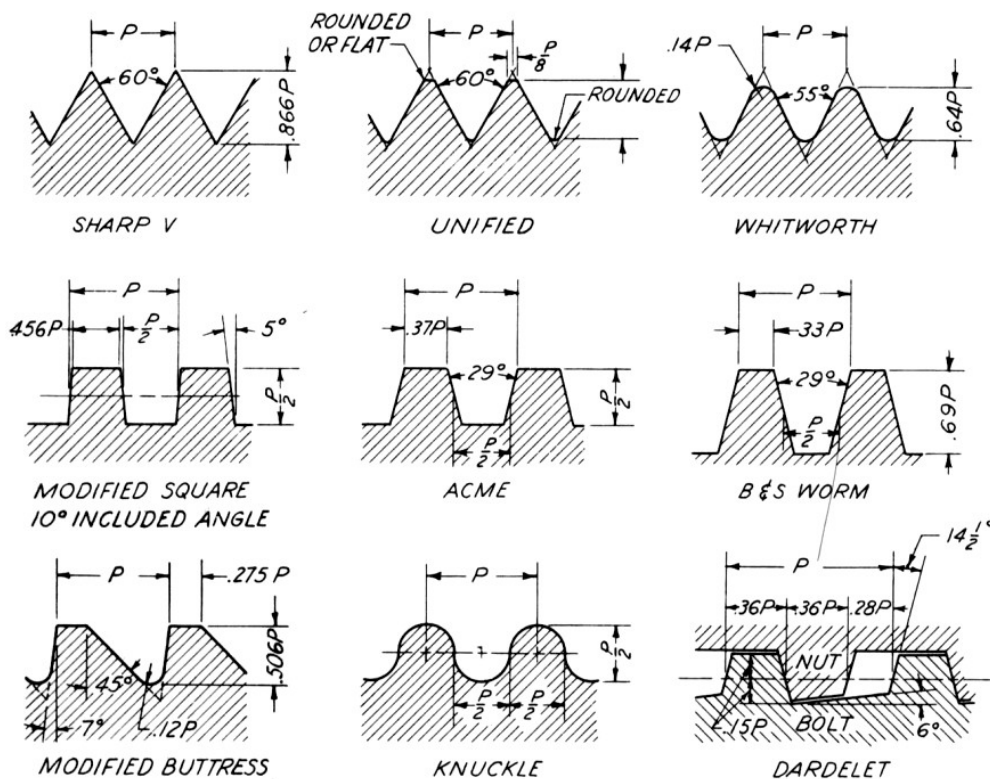


Figure 27: Basic dimensions of a screw <www.americanmachinetools.com>.

Further mechanical testing must be done to determine what magnitude and types of forces the screw is subjected to. Tensile, compressive and shear forces are all present within the knee and must be considered when finalizing a design. Specifically, tensile and compressive forces have been found to be proportional to the square of the minor diameter. Also, shear forces are proportional to the cube of the minor diameter, making this an important design component (Duke Orthopaedics).

The threading shape must also be taken into consideration during the design process due to the presence of the graft. Too dull of threading will not be effectively implanted into the stiff bone, however, too sharp of a threading design will lead to lacerations in the graft, and thus mechanical degradation. Current designs under scrutiny can be seen below in Figure 28. These shapes can be experimented with in the lab by using collagen-mimicking material placed into a pilot hole of bone or comparable wood and then recording the degree of damage administered by the various threads.



Screw threads.

**Figure 28: Various thread geometries previously designed <
<http://www.u.arizona.edu/ic/ce210/images/fastener/screw.JPG>>**

A final consideration necessary in designing the anatomy of the screw is that of the driver shaft shape. There are many of these present on the market today, with no design deemed as objectively the most effective. Several shapes can be seen below in Figure 29. The purpose behind careful selection of the driver shaft shape is to achieve maximal distribution of torque during insertion. The more area that the driver is spread out upon, the less pressure the screw will experience at any one point, assuring mechanical strength and less breakage. A large amount of surface area is also important in promoting bone re-growth. The more mineralized alginate directly open to the cancellous bone environment, the quicker tissue re-growth can occur. Currently, we are looking at simple triangular and hexagonal driver shafts. Since slipping was observed in the hexagonal shaft, and the triangular shaft was calculated to need a great deal of force, all together new shapes may need to be considered.

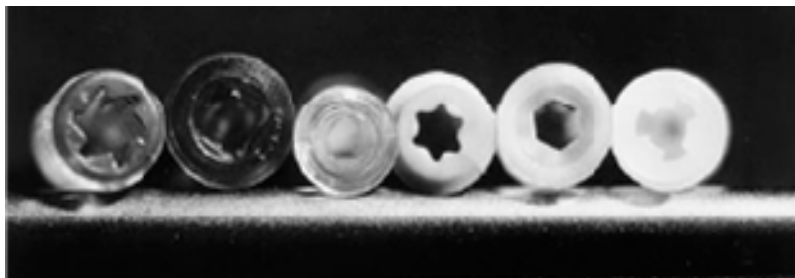


Figure 29: Assorted driver shaft shapes currently available on the market. From left to right: turbine-like drive, quadrangular drive, triangular drive, star-shaped drive, hexagonal drive, tri-lobe drive <<http://ajsm.highwire.org/cgi/reprint/26/1/119>>.

Ethical/Safety Concerns

There are clear ethical concerns involved in advancing this product to market. When the time comes, animal testing must be performed to better gauge the behavior of the interference screw. Therefore, a two hour training session on animal care must be attended by all group members in order to receive the Animal User Certificate (Research Animal Resources Center). After successful results are recorded with animal experimentation, human subjects become an issue. Although this is in the distant future, further research on how to legally pursue and carry out this testing will be studied when it is more applicable.

Also related to ethical concerns is the issue of proper safety. Biocompatibility becomes an issue of paramount concern when using newly introduced materials. Many new biomaterials can unexpectedly cause problems if not PLGA and its degradation products have been approved by the FDA for human use. The mineralized alginate, in contrast, has not been approved; therefore, it is important that the proper steps are taken to either research mineralized alginate's FDA status and/or apply for approval when the time comes. In doing so, the materials that are integrated in our screw will be fully compliant with FDA standards, ensuring a high degree of patient safety.

A safety issue that has already been considered and is currently being practiced is the lab protocol that our group is following. Presently, PP is replacing PLGA and gelatin is replacing alginate. Although the gelatin is harmless, the PP, once heated, emits noxious fumes that need to be handled carefully. For this reason, melting procedures are carried out in the fume hood for safe ventilation. Further, in general terms, safe lab procedures are stressed when dealing with the 180 °C oil bath and melted materials in order to minimize the chance of wasted material or personal injury.

Summary

ACL reconstructive surgeries are common-place in hospitals in the United States and the world. The main components used to secure the graft are interference screws. Currently these screws are made of titanium or a biodegradable plastic. The main disadvantage with both these screws is that tissue growth is not promoted or fostered by the materials in the screws. Therefore, the goal of this project is to design a screw that will secure the graft and increase the rate of tissue growth around the graft.

Thus far, a large amount of literature research has been completed in order to increase the knowledge of the group pertaining to biomaterials. A design has been finalized in Solid Works that incorporates thermoplastic, alginate pockets, a hollow screwdriver shaft, and growth holes for uniform, continuous growth. Attempts to maximize the amount of alginate incorporated were accomplished by the previously stated design calculations. This, along with our preliminary design, has solidified a course of action that relates to our initial goal of promoting tissue growth through the

inclusion of alginate. Rapid-prototyping was extensively researched and pursued in order to fabricate a casted steel model created for more reproducible testing.

Meanwhile, scaled-up models of this design were fabricated using common materials, and successful screw-making techniques have been established. Screw models are currently being subjected to mechanical tested in Engineering Hall. Both axial and radial compression tests have been completed and quantified, which can be seen in former sections of this paper. These tests, because performed on scaled versions of model materials, do not yield significance quantitative results. The purpose, rather, was to illustrate the discrepancy in strength created by adding alginate pockets to the screw, expressed as a ratio. Overall, much work was accomplished recently that has materialized the novelty of our screw and will allow us to take the next step in our design.

A rapid-prototype mold will be created and eventually used to cast a metal mold that will help fabricate surgically sized screws. Thermoplastic degradation and tissue regeneration testing are necessary to ensure the novelty and eventual success of the design. Eventually, animal testing will be integrated to validate the design before it goes on the market. Ultimately, the design of this biphasic screw will improve current problems in the field of ACL reconstructions.

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Appendices

Appendix A: Product Design Specification

Title: Bioactive Interference Screws for ACL Reconstruction

Group Members:

- ∞ Katherine Davis
- ∞ Aaron Huser
- ∞ Cole Kreofsky
- ∞ Dana Nadler
- ∞ Joe Poblocki

Advisor: Professor Kristyn Masters

Client: William Murphy, Ph.D.

Function:

Currently, during an ACL reconstructive surgery, titanium or partially degradable plastic interference screws are used to secure the graft within the femur and tibia. These screws or parts of these screws will remain in the patient's knee for the rest of his or her life and can potentially cause problems. The current screws are also not conducive for tissue re-growth. It is therefore our client's desire to develop an interference screw for ACL reconstruction that will promote and foster the growth of surrounding bone tissue, as well as limit any potential problems a patient may incur due to these screws in his or her body.

The interference screw that we will design should be biphasic and bioactive. A biphasic screw consists of a thermoplastic that is strong enough to withstand the stress during implantation and post-operative activity, and a mineralized hydrogel phase that acts as a scaffold for and promotes bone growth. The screw must also be bioactive. It must promote tissue growth at a rate that is comparable to the degradation of the screw. The screw must also secure the ACL graft just as its predecessors, and it must be biocompatible, in other words it must not cause an inflammatory or immune response in the body.

Client Requirements:

The screw must be:

- ❖ Biphasic, in that one half is bioactive alginate hydrogel that effectively promotes and fosters bone tissue re-growth, and the other half is PLGA/PLLA thermoplastic which provides mechanical strength, however, ultimately degrades
- ❖ Biocompatible in that it does not evoke an immune response when implanted and is relatively inert with respect to the body
- ❖ Biodegradable in that it is biologically absorbed over time without producing harmful byproducts in the process
- ❖ Easily sterilized or autoclaved
- ❖ Must be able to withstand the stresses involved during surgery and post-operative activity

Design Requirements

1. Physical and Operational Characteristics

a. *Performance requirements:* The screw must withstand the stresses involved with the surgery and activities performed by the patient post-surgery. More specifically, the screw must withstand a pullout-strength of 1300 N and shear failure strength of 430 N.

b. *Safety:* The screw should allow bone tissue to re-grow and anchor the graft within the bone. The material of the screw should not be harmful to the body. The threads of the screw should not shear the graft.

c. *Accuracy and Reliability:* The screw should successfully anchor the graft, and stay secure until sufficient bone tissue re-growth has occurred. The screw should be able

to be manufactured with a high rate of precision and accuracy with room allowed for only minor error.

d. *Life in Service*: The PLGA/PLLA portion of the screw must structurally support the graft until enough tissue has grown to support the graft. Ideally, the screw will degrade at a rate equal to the tissue growth rate. This is typically on the order of several months but could last up to one year. Thus in order to include an adequate factor of safety, the screw should be able to last for two full years after implantation.

e. *Shelf Life*: Optimal shelf life would be between six months and one year due to the maintenance of chemicals within the hydrogel. The screw should also be stored in a secure, cool place out of direct sun-light.

f. *Operating Environment*: The screws need to be kept in a sterile, possibly cool storage area before being used. After surgery, the screw will be secured in the knee, anchored in bone and must not interfere with homeostatic conditions.

g. *Ergonomics*: The screw must not interfere with the motion of the tibia, femur, patella, or graft.

h. *Size*: The screw will be between 22-30 mm long and will have diameter of 6-10 mm.

i. *Weight*: The weight of the screw will be dependent on the materials chosen and their relative densities. Care should be taken, however, to minimize the weight of the screw.

j. *Materials*: The threads and main components of the screw will be fabricated out of a PLGA/PLLA composition. The semi-circle pockets will be composed of mineralized alginate.

k. *Aesthetics, Appearance, and Finish*: The screw should be uniform in shape and density and have minimal amounts of rough edges, increasing the ease for insertion into the bone.

2. Production Characteristics

- a. *Quantity*: Current mechanical testing requires a small quantity of surgically sized prototypes as well as a scaled-up model, diameter approximately larger by a factor of 2.5. Ideally, 10-15 screws should be manufactured for both sizes used in testing.
- b. *Target Product Cost*: The cost of the screw will be dependent on the mold and the materials used in the screw. The PLGA/PLLA will be the most expensive.

3. Miscellaneous

- a. *Standards and Specifications*: All nations have strict rules and regulations pertaining to medical devices. In the United States, the Food and Drug Administration (FDA) is mainly responsible for product safety and performing regulatory actions. They have very detailed and thorough regulations for medical devices, especially implantable ones, which requires additional research to attain the details.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=888.3040>

- b. *Customer*: The customer will be the surgeons that will be using the interference screws during surgery. The consumer (patient) should be unaware of the screw after it has been inserted.
- c. *Patient-related concerns*: The screw must not initiate an immune system response. The screw will need to be sterilized before it is secured in the body. The doctors should make sure the patient is not allergic to any of the materials in the screw. The doctor must advise the patient on proper care during post-surgical recovery. Excessive force on the screw before full healing could cause damage to the screw and to the patient.
- d. *Competition*: There are many health care companies that manufacture interference screws for orthopedic applications. The size geometry of the current products is somewhat similar, but can have small differences. These include the amount of

tapering, the size and angle of the threads, and the shape of the tip. Many designs are patented and further research is needed to investigate the various patents and screw geometries in general.

The original material standard for interference screws was metal, usually a titanium alloy because of its biocompatibility. Many companies currently offer titanium interference screws, including Stryker (www.stryker.com), Sulzer Medica (www.sulzerortho.eu.ch), and DePuy Mitek (a Johnson & Johnson company, www.mitek.com). However, there have been recent advances in the materials used to fabricate interference screws. Newer materials are not just biocompatible, but bioabsorbable, where they will break down starting 6 weeks to 6 months after surgery. Following is a list of companies and the bioabsorbable interference screw they offer:

- Stryker Corporation (www.stryker.com)
 - Bioabsorbable Wedge Interference Screw
 - 100% Poly-L Lactic Acid (PLLA)
 - Biosteon™ (HA/PLLA) Wedge Interference Screw
 - 25% Hydroxyapatite
 - 75% PLLA
 - Patented wedge design
 - Osteo-conductive potential of bone
- Arthrotek, Inc. (www.arthrotek.com)
 - LactoSorb® resorbable copolymer
 - 82% PLLA
 - 18% glycolic acid
 - Retains most of its strength for 6-8 weeks
- Steiner & Martins, Inc. (www.steminc.com)
 - DrixMed™ PLDL TB bioabsorbable interference screw
 - Poly (L-DL-Lactide) 70-30
 - Total resorption at more or less 2 years
- Sulzer Medica (www.sulzerortho.eu.ch)
 - Sysorb – bioresorbable interference screw

- Poly (D,L-Lactide)
- DePuy Mitek (www.mitek.com)
 - Milargo interference screw
 - 30% osteoconductive β TriCalcium Phosphate (TCP)
 - 70% faster resorbing poly(lactide-co-glycolide) (PLGA)
 - ABSOLUTE Absorbable Interference Screw
- Atlantech Medical Devices LLC (www.atlantech-md.co.uk)
 - Bilok® ceramic/polymer interference screw
 - PLLA and β -Tricalcium phosphate
- Linvatec (a ConMed Company) (www.linvatec.com)
 - SmartScrew®
 - ACL – self reinforced 96L/4D copolymer
 - BioScrew®
 - PLLA