EVALUATION OF TIME-DEPENDENT PROPERTIES OF BIODEGRADABLE MATERIALS FOR TRANSIENT IMPLANTABLE BIOSENSORS

BY

ELLIOTT P. RILL

THESIS

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Adviser:

Professor John A. Rogers
Current magnesium and silk materials used in transient devices limit the design possibilities. Proper material choice will give transient electronics greater functionality and a wider range of applications. Time-dependence of electrical and physical properties due to dissolution was tested for Al, Zn, W, and Fe, alone and in combination with magnesium. PLGA, collagen, gelatin and a gelatin/PVA hydrogel were tested for physical degradation. Aluminum was the best choice for extending the lifetime of magnesium traces, and tungsten had the slowest dissolution rate of any pure materials tested. Slowly degrading metals could enable fully degradable devices with direct contact with external tissue. PLGA and collagen were moderately functional as encapsulation materials. PLGA was detrimental to magnesium when used as a substrate, but gelatin and the gelatin/PVA hydrogel are both fully biodegradable and have potential as flexible or stretchable (respectively) substrates.
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CHAPTER 1: INTRODUCTION

Improvements in medical technology enable new procedures to combat health problems, and new detection methods shed light on previously unknown medical issues. Detection and diagnostic methods are equally important as treatments to successful treatments. An inherent obstacle to diagnosis is the limitations in data collection. Unlike a mechanic, who can disassemble an engine to find and fix the problem, a doctor cannot disassemble a human body only to put it back together with no ill effects. Explorative surgery is one possible diagnostic tool, but non-invasive means are generally preferable to surgery. Non-invasive imaging methods are common tools in a diagnostic toolbox; external imaging is appropriate in many instances, but requires skilled interpretation and appropriate use conditions. Biopsies and blood samples are means of taking data directly from body tissue, but again, the applicable scenarios are limited. No one technique is universally useful, and doctors are trained to know which to choose.

In addition, many of these tools are unsuitable for long term monitoring. Implantable biosensors are a topic of significant research as potential improvements and additions to current medical diagnostic capabilities. In order to be useful as diagnostic tools, implantable sensors must be small enough to be tolerated by the body, able to transmit data out of the body (or store it in a retrievable manner), and be sensitive enough to warrant an (minimally) invasive procedure. This becomes a more viable option when a surgical procedure is already necessary; for example, a biosensor could be implanted during an organ transplant and used to monitor organ rejection.

As artificial replacement or assistive medical implants gained wider clinical use, it became clear that certain situations caused the devices to lose their beneficial functionality, or
even cause harmful effects. This is often seen with the use of stainless steel coronary stents: the presence of the foreign material can cause restenosis (renarrowing of the blood vessel) over time, even though the vessel wall has strengthened so as to no longer need the stent [1, 2]. Surgical removal of the stent is possible in some cases, but increases the risk of surgical complications [3]. Furthermore, properties that are necessary for short-term healing may be detrimental to long-term health, as can be seen in bone implants that cause bone loss by not allowing natural bone to bear weight because of a modulus mismatch [4]. These situations would benefit from implant materials that can provide the desired healing function but then disappear when their presence would be harmful, and do so without the complications and cost of another surgical operation.

The relevance of magnesium as an implantable material began as an effort to replace existing biocompatible, but permanent, materials. The majority of surgical implants currently in use are structural components (bone fixtures, stents, artificial joints etc.). As such, magnesium was first explored as an alternative material for these applications [5, 6]. Since magnesium is a fairly soft but light metal, it garnered extra attention for applications where strength was not a primary concern or the requirement was low, such as stents used in angioplasties, which must be able to provide enough force to hold open the blood vessel but be soft enough to collapse and bend for easy insertion. Stent geometry and delivery type can promote these effects, allowing the material choice to encompass other factors [7, 8].

Silk (from silkworms, e.g. *Bombyx mori*) was the initial choice for a transient substrate material [9-11]. Silk has been used for numerous biomedical applications, including bone regeneration [12], drug delivery [13, 14], and tissue scaffolding [15-17]. It has also been recognized as a biocompatible material by the FDA (U.S. Food and Drug Administration). Its dissolution rate can be tuned from minutes to years by varying the degree of crystallinity [18,
Silk is composed of 2 forms: the alpha (α) helix and crystalline beta (β) sheet. β sheets slow the dissolution rate by providing physical crosslinks [20]. β sheet content can be increased by a number of methods, including thermal, solvent (i.e. methanol), and water vapor methods [21].

Film thickness also controls the degradation rate of silk. As a result, previous demonstrations [9] preferred thick silk films (10-100 µm) over spincast films from a dilute aqueous (~7% w/v) silk solution. These films surrounded the device, and were bonded along the edges with silk solution and applied heat. In this format, the silk-silk edge interface is the weak point, and ultimately leads to failure of the encapsulation before the silk films have failed individually [9].

While silk can be tuned within a wide range of degradation rates, it also requires particular processing methods when used as a device substrate. With the exception of specific solvents, it generally degrades or deforms when exposed to common photolithographic chemicals, including acetone, TMAH (tetramethylammonium hydroxide, the active chemical in many common photoresist developers), metal etchants, and even water if not crystalline enough [10, 11]. Furthermore, high temperatures will cause degradation of silk films, limiting possible deposition methods [20]. However, proper processing can mitigate some of these flaws; for deposition, this requires the use of shadow masks for patterning instead of photolithography.

The goal of this work is to provide initial evaluations for a number of alternative materials for transient electronic devices. The scope is meant to be broad and not highly focused on any one material type. It is not meant as a full evaluation of these materials, but rather to identify which materials are worth pursuing further and which should be eliminated from additional testing. A variety of materials will eventually allow for a wider range of applications for transient devices; for example, new, slowly degrading yet conductive materials could allow
for electrodes with direct contact to biological tissue. Materials, not just processing conditions or device types, could be changed to suit individual applications as well. New materials may also allow for different processing methods that are more compatible with biodegradable formats. The materials presented below do not make an inclusive list of biodegradable materials; they are only a select few that represent a wide range of materials classes.
CHAPTER 2: THEORY OF DISSOLUTION

The kinetics of reactive dissolution can be modeled analytically [9] by considering the two limiting cases: the diffusion of water to the dissolving material, and the reaction between a water molecule and atoms of the thin film. The soluble product of the reaction is then assumed to diffuse away from the surface of the film. The model summarized below is presented in full in [9]. This model enables the resistivity measurements as a tool by which the degradation can be measured and understood. Additionally, this model can be used in a predictive manner to understand device level changes in functionality during degradation.

The boundary conditions are the concentration of water at the surface of the film (1) and the flux of the water at the base of the film (2) [9].

\[
\begin{align*}
\frac{\partial w}{\partial y} \bigg|_{y=0} &= 0 \\
w \bigg|_{y=h_0} &= w_0
\end{align*}
\]

(1) 
(2)

The analytical solution that follows from these boundary conditions is quite complex. Assuming an approximately linear loss of thickness produces the following result (3),

\[
h = h_0 - \frac{M(\text{mat})}{M(H_2O)} \frac{w_0}{\alpha \rho} \sqrt{kD} \tanh \sqrt{\frac{k \rho h_0^2}{D}} t
\]

(3)

where \( k \) is the reaction constant, \( D \) is the diffusivity of water in the dissolving material, \( M(H_2O) \) and \( M(\text{mat}) \) are the molar masses of water and the material being dissolved, respectively, \( w_0 \) is the initial water concentration, \( \rho \) is the density of the material being dissolved, \( \alpha \) is the ratio of the number of atoms of the dissolving material to the number of water molecules, \( h_0 \) is the initial thickness, \( h \) is the thickness, and \( t \) is the time. Both \( k \) and \( D \) are determined from
fitting the model to experimental data. This model is fit to the thickness data presented in Chapter 5, along with the predicted critical time to dissolution (4).

\[ t_c = \frac{M(mat) w_0}{M(H_2O)} \alpha \rho \sqrt{kD} \tanh \left( \frac{k h_0^2}{D} \right)^{-1} \]  

(4)

For all of the materials presented here, the material and any oxides will all react with water to form soluble species. The presence of any surface oxide layer can be accounted for in the dissolution model by inputting individual boundary conditions for the film and the oxide layer separately, then coupling the two with a continuity equation. This method can be further modified by including a time-dependent rate constant to capture additional features of the dissolution mechanism. The model can also be applied to resistance measurements as well as film thickness. However, for the cases presented here, the simple linear model is adequate, and the predicted critical time to dissolution from (3) is presented with each set of thickness measurements.
3.1 Interconnect Materials

3.1.1 Magnesium

The research on metallic biodegradable stents revolves around magnesium. It is fully biocompatible, being present naturally in the body, and is fully biodegradable, reacting with water as shown below [5].

\[ Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2 \]

The product, magnesium hydroxide, is fully soluble in water; in biosolutions, where extra chlorine is present, the hydroxide can be converted into magnesium chloride, which is also highly soluble. Analysis of the degradation products and the amounts produced from the dissolution of transient devices (which have significantly less mass than magnesium stents) show that the concentrations in vivo are within reasonable limits and are nontoxic [9].

3.1.2 Magnesium alloys

Magnesium alloys are being researched as solutions to perceived flaw with pure magnesium stents: rapid loss of that strength due to fast corrosion [22]. Magnesium alloys come in many different varieties, though all have several traits in common. Alloying elements are added in small quantities (generally \( \leq 10\% \) by weight), most alloys are ternary, and few have been evaluated on their electrical properties. Tested elements include: aluminum [5, 8, 23], silver [24], calcium [5, 23], lithium [5, 23], manganese [5, 23], silicon [24], tin [24], yttrium [5, 8, 23], zinc [5, 23], zirconium [5, 8, 23], and rare earth elements [5, 8, 23].

Magnesium-aluminum-zinc alloys are some of the more common alloys studied. Magnesium alloys are designated by the alloying elements and the amounts added (in weight
percent), plus one optional designation for miscellaneous information, such as heat treatments or impurity limits. For example, AZ31B is nominally 3% aluminum (AZ31B) and 1% zinc (AZ31B), where B denotes specific limits on iron, nickel, and copper impurity content. AZ31 is more easily cast and has a higher ultimate tensile strength (UTS) than pure magnesium [5]. The bulk degradation rate is slower than pure magnesium [22] (1.3 mm/year versus 2.0 mm/year [25, 26]).

3.1.3 Zinc

Very little work has been published on the degradation/corrosion of zinc in vivo. The majority of work involves magnesium-zinc alloys. Zinc oxide is also biodegradable, and has considerable potential to enable transparent thin film transistors as a transparent semiconductor. Zinc is usually added to magnesium alloys in very small amounts. The bulk resistivity of zinc is higher than that of magnesium ($5.9 \times 10^{-8} \Omega \text{m}$ versus $4.4 \times 10^{-8} \Omega \text{m}$). The bulk degradation rate of zinc is less than that of magnesium as well ($\sim250 \mu\text{m/year}$ versus $\sim50 \mu\text{m/year}$ at a pH of 7) [27]. However, in magnesium alloys zinc does provide some strengthening effects [5]. Magnesium can be added to zinc as well, but the influence on degradation rate is very small [27].

In vitro testing of zinc alloys reveals toxic effects on human cell cultures only at very high concentrations of zinc [28].

3.1.4 Tungsten

Unlike magnesium, tungsten is a very dense material. It is usually overlooked for biomedical implant applications in favor of titanium and other lightweight metals, due to its lower strength-to-weight ratio. It is much more likely to be found ex vivo, as a component of an x-ray source. However, tungsten has some niche uses as an implant, notably as one possible material choice for an embolization coil. Embolization coils are used to stop blood flow through
a blood vessel, which can be useful in a number of different medical procedures; embolization may be required to treat an aneurysm, prevent excessive bleeding during surgery, or restrict blood flow to a tumor [29, 30]. As an embolization coil, tungsten has shown to be degradable, though the degradation rate is much slower than that of magnesium [31]. Pure magnesium stents commonly degrade in 6 to 18 months [23, 32], while tungsten embolization coils usually take a minimum of 30 months [33] and can take up to 72 months [31] to fully degrade.

Tungsten is generally considered to be insoluble in water. However, in small amounts and over long time periods, tungsten will be converted into tungstic acid. Tungstic acid is the final product of tungsten dissolution in vivo. Initially, tungsten oxidizes into tungsten trioxide (WO$_3$). In an aqueous solution, this oxide will react further to form tungstic acid (H$_2$WO$_4$) [34].

$$WO_3 + H_2O \rightarrow WO_4^{2-} + 2H^+$$

Tungsten may also react directly with water to form tungstic acid in the event that the surface oxide is completely dissolved. The anodic and cathodic reactions are shown below [34]:

$$W + 4H_2O \rightarrow WO_4^{2-} + 8H^+ + 6e^-$$

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$$

$$2H_2O + 2e^- \rightarrow H_2 + 2OH^-$$

Tungsten is naturally present in human serum in small quantities (~0.2 µg/L) [33]. Serum tungsten levels have been monitored in vivo as tungsten embolization coils degrade; though the levels increased dramatically (from 0.2 µg/L to 10.7 µg/L in humans [33] and from 0.48 µg/L to 12.4 µg/L in rabbits [35]), no biological response was found. In addition, no inflammatory response was seen at the implantation sites [33], and histological examinations of rabbits with implanted tungsten coils showed no evidence of local or systemic toxicity [35]. This agrees with in vitro findings that extremely high levels of tungsten are needed to cause cytotoxicity [31, 36].
While this points to the biocompatibility of tungsten, tungstic acid has been identified as an epileptogenic material when applied directly to parts of the brain [37]. In fact, tungstic acid gel has been used to induce seizures in animals for clinical studies on epilepsy [38]. For this reason it is recommended that the local concentrations of tungstic acid be evaluated versus minimum levels necessary to induce seizures before tungsten is used in neural sensors.

The electrical properties of tungsten compare favorably to magnesium. The bulk resistivity of tungsten is very similar to magnesium ($5.0 \times 10^{-8} \Omega \text{m}$ versus $4.4 \times 10^{-8} \Omega \text{m}$), so replacing or capping magnesium with small amounts of tungsten will not significantly impact device performance. Tungsten has been previously investigated as a long-term electrode material for neuroprosthetic applications; the study determined that the in vivo degradation, while slight, made tungsten inferior to platinum and unsuitable for permanent electrodes despite its good electrical conductivity [34]. Furthermore, tungsten is currently used as an interconnect material for integrated circuits [39]; the presence of existing processes for large-scale IC fabrication is one less barrier for commercial development of transient electronics and a benefit over magnesium interconnects.

3.1.5 Iron

Like magnesium, iron has also received interest as a biodegradable stent material. The structural properties of iron exceed those of magnesium, and are much closer to 316L SS (stainless steel), the non-degradable standard in stents [8, 23]. Like magnesium, iron degrades by first oxidizing, forming iron (II) oxide (ferrous oxide, FeO), iron (III) oxide (ferric oxide, Fe$_2$O$_3$), or a combination iron(II,III) oxide (Fe$_3$O$_4$) [40]. These oxides further dissolve to produce ferric or ferrous ions ($\text{Fe}^{2+}$ or $\text{Fe}^{3+}$); iron can switch between the two oxidation states easily by gaining or donating an electron to other ions in solution [40]. Both forms are soluble in water.
Iron is extremely common within the body, and the final products of the dissolution are naturally present as well, up to ~450 mg/L in human blood [23]. Iron is critically important for many biological processes. *In vitro* testing has shown degradation rates that are slower than magnesium. However, *in vivo* degradation rates are far less than predicted by *in vitro* studies. This has been attributed to passivation of the iron surface by some compound other than iron oxide. Iron phosphide is one possible candidate; phosphate ions are readily present in the body, and iron phosphide is insoluble in water, which may explain the dramatically reduced degradation rate [41].

3.2 Encapsulation Materials

Encapsulation is another way to extend a device’s lifetime. An encapsulation material allows a rapidly dissolving but highly conductive material like magnesium to be used in transient devices for useful amounts of time. This also allows the devices lifetime to be changed without affecting the electrical properties, effectively decoupling the device performance from its lifetime. A properly designed encapsulation layer provides a time period in which the devices properties are invariant. This is extremely important in order to maintain the accuracy of any device calibration. For a device made with quickly degrading materials, the encapsulation material effectively determines the overall (total and functional) degradation time scales. Since desired degradation times can vary from application to application, it is important to have control over this device parameter. For this reason it is important that the encapsulation layer can be tuned independently to shorten or lengthen the degradation time, all without impacting the device it protects.
3.2.1 PLGA

While silk meets many of these requirements, it requires very stringent processing methods to prevent premature degradation. In order to circumvent these problems, other materials with better resilience to standard processing conditions have been investigated. Thermoplastic polymers have well understood processing requirements in both small and large scale formats, and so were the first class of materials considered as a replacement for or a complement to silk. Of biocompatible and biodegradable synthetic, thermoplastic polymers, poly(lactic-glycolic) acid (PLGA) and its derivatives are some of the most commonly used [42], for both structural [43, 44] and drug delivery [45, 46] applications. PLGA is a copolymer of lactic acid and glycolic acid, which individually form biodegradable polymers as polylactic acid (PLA) and polyglycolic acid (PGA). PLGA can be tuned using a number of parameters, including ratio of lactic to glycolic acid, molecular weight, and end groups [47, 48]. PLGA can also be blended or copolymerized with other polymers. Blend composition and crosslinking type and amount can also influence properties. These variables result in degradation rates that can be changed significantly. Among these variables, molecular weight has the most influence on degradation rate [48].

3.2.2 Collagen

Collagen is a naturally occurring group of proteins. It is present in humans and many other animals, especially in connective tissue. Collagen is produced from animal sources rather than being synthesized, and has been used for various medical applications, including promoting bone growth [49], guiding tissue regeneration, and preventing adhesion during surgery [50]. The manufacturing process for obtaining collagen is complex, since the raw sources of collagen are
animal tissues. Collagen is categorized by type (I, II, III etc.) and by source (cow, pig, mouse etc.).

Collagen is comprised of a triple helix structure, two chains of which are the same (α1) with the third being slightly different in composition (α2) [51]. Each chain is made up of amino acids, with the number and order varying between the different types and sources of collagen. The triple helix structure, stabilized by hydrogen bonds between the polypeptide strands, helps give collagen its strength and chemical resistance [52]. Collagen shares many characteristics with silk fibroin, including a high amount of glycine in the constituent protein strands. Collagen also contains a large amount of proline and hydroxyproline [52].

Collagen degrades enzymatically into gelatin and shorter strands. Collagenase is the enzyme that first attacks the collagen fibrils. First, the three strands that make up the triple helix are separated by the collagenase enzyme [53]. Denaturation can also occur due to excessive heat [53]. Once separated, the enzyme can attack individual strands, separating them into ¾ and ¼ length pieces. Further scissions of the pieces can then take place, and gelatinase and other protein-dissolving enzymes can become involved as the fragments get smaller and smaller [54].

Collagen is generally only soluble in highly acidic or basic solutions. It is resistant to acetone and many of the other solvents used in photolithography. However, collagen fibrils will swell in basic solutions [55], including TMAH-based photoresists developers. The fibril structure of collagen may also swell in certain acidic wet etchants as well.

3.3 Substrate Materials

Silk can also be used as a device substrate. Because silk is sensitive to many parts of the photolithographic patterning process, polyimide stencils are used to pattern films on silk. However, polyimide stencils can be fragile and difficult to handle, especially when they contain
small features. These stencils cannot reach feature sizes possible with photolithography. Other materials have been explored as possible replacements for silk. New substrates could enable more robust patterning methods and facilitate the use of currently unavailable deposition methods.

3.3.1 PLGA

PLGA has been evaluated as a biodegradable substrate for organic electronics [56]. However, the PLGA substrate is the only material in common with materials presented here. The silver and gold contacts are not biodegradable, and the semiconductor and gate dielectric are both organic materials. As a result, the fabrication methods are very different from the liftoff and transfer printing methods used to create silicon- and magnesium- based transient electronics. PLGA has been shown to be completely biodegradable over a few months [56], so the focus of future tests will be on the compatibility of PLGA with the fabrication steps used for magnesium and silicon devices.

3.3.2 Gelatin

Gelatin is the name given to hydrolyzed collagen. The fully denatured, short strands lack the triple helix structure of collagen and are highly soluble in water as a result. The resulting hydrophilicity allows gelatin to form a hydrogel (i.e. Jello). This has a profound effect on processing; gelatin can be easily dissolved, spin cast, and blended with other polymers. Like collagen, gelatin is insoluble in acetone, and glassy gelatin (dried rapidly so that all bound water is evaporated) is stable up to 200 °C. However, like collagen, gelatin is susceptible to swelling in basic solutions [57], such as TMAH. This presents a different challenge to photolithography on gelatin films.
3.3.3 Gelatin/PVA Hydrogel

Polyvinyl alcohol (PVA) is a highly water soluble polymer. Its biodegradable nature has been leveraged for eco-friendly product packaging [58], and its high dielectric constant has made it an often used gate dielectric material for organic electronics [59]. PVA is biocompatible and biodegradable. It has been investigated as a material for tissue engineering [60] and drug delivery [61] and in blends with other biodegradable materials [62].

The hydroxyl groups along the chain backbone of polyvinyl alcohol, in addition to making PVA highly hydrophilic, allow PVA to react with a number of other molecules. The reaction of a hydroxyl group of PVA with a carboxyl group on one of the proteins of gelatin via an esterification reaction (catalyzed by a proton) produces an ester bond, which acts as a crosslink between the two molecules [63-65]. Since PVA has many hydroxyl groups, and the most common amino acids in gelatin strands (glycine, proline, and hydroxyproline) contain carboxyl groups, many crosslinks are possible; the end result is a very hydrophilic network of chemically-crosslinked gelatin and PVA. The hydrophilicity drives the gelatin/PVA to dissolve, but the crosslinks prevent this, resulting in a swollen network, or a hydrogel.

The properties of the resulting hydrogel are dependent on the ratio of gelatin to PVA. Increasing gelatin content increases the tensile strength and the strain at failure for hydrogel films [64, 65]. For a PVA:gelatin ratio of 4:1 (20% gelatin, by weight), the tensile strength is ~14 MPa, and the hydrogel swells to ~260% (measured by weight, not volume) when placed in water [63]. While the components and physically-crosslinked blends [66, 67] have been shown to be biodegradable, ester crosslinked hydrogels have not. In vitro testing of biodegradation for this particular hydrogel will be shown in section 5.3.3.
CHAPTER 4: FABRICATION AND TESTING METHODOLOGY

4.1 Experimental Design

Materials were tested for three different functions in transient devices: interconnects, encapsulation layers, and substrates. The effects of new interconnect and encapsulation materials were referenced to a pure magnesium control. Substrate materials were evaluated based on processing. Table 4.1 describes the sample configurations for interconnect and encapsulation materials. The table references Fig. 4.1, which illustrates sample cross-sections, for each of the five general sample geometries.

4.2 Sample Fabrication

4.2.1 Interconnect Materials

Resistive trace patterns for testing encapsulation and interconnect materials were fabricated using a liftoff method. 1x1.5 inch glass substrates were cleaned and coated with a negative photoresist, AZ nLOF 2070 (AZ Electronic Materials, USA), by spin coating (Headway Research, USA). A pre-exposure bake was done according to the manufacturer’s recommendations, as was the following UV exposure and post-exposure bake. The exposure was done using a Karl Suss MJB-3 mask aligner (SUSS MicroTec, Germany) through an iron oxide mask. The pattern was developed in AZ 327 MIF (AZ Electronic Materials, USA), a TMAH-based photoresist developer, to achieve a negatively sloped sidewall profile suitable for liftoff.

Magnesium (99.99% pure), chromium (99.9% pure), titanium (99.995% pure), aluminum (99.95% pure), tungsten (99.95% pure), and iron (99.95% pure) (Kurt J. Lesker Company, USA) were deposited onto the photoresist patterned glass substrates using an electron beam evaporator (Temescal, USA). AZ31B (composition in Table 1), titanium (99.97% pure), zinc (99.99% pure),
and tungsten (99.95% pure) were deposited using a DC magnetron sputtering system (AJA International, USA) from standard sputtering targets (Kurt J. Lesker Company, USA). For encapsulation testing, 300 nm thick magnesium films were deposited on 5 nm of titanium (as an adhesion promoter). Interconnect materials were all 300 nm thick and deposited onto 5 nm of chromium or titanium adhesion layers, with the exception of sputtered tungsten. Sputtered tungsten was deposited onto an e-beam evaporated Cr/Mg (5/5 nm) adhesion layer due to the inability to sputter the adhesion layer in situ. The fabrication process finished with a 1-2 hour soak in acetone to dissolve the photoresist and allow undesired metal to fully lift off.

4.2.2 Encapsulation Materials

4.2.2.1 PLGA

PLGA (lactide:glycolide 85:15, Mw 50,000 - 70,000, Sigma-Aldrich, USA) was dissolved into ethyl acetate (≥99.5%, Sigma-Aldrich, USA) to achieve a final concentration of 4 g/mL. A barrier fabricated from poly(dimethylsiloxane) (PDMS, Sylgard 184, 10:1, Dow Corning, USA) was used to confine the PLGA solution to the desired area. The PLGA was allowed to dry until it could support its shape and then the PDMS well was removed. The PLGA was dried in air for an additional 2 hours before testing. Thermally cast PLGA was melted directly onto the glass substrates on a hotplate at 200 °C, also confined using a PDMS well. The PLGA was allowed to cool and the PDMS was removed.

4.2.2.2 Collagen

Collagen films (Devro, USA) were cut to size and attached to the glass substrates with PLGA or carbon tape. A concentrated PLGA solution (10 g/mL) was used to secure the collagen to the glass. The solution was spread around the edge of the collagen film (on 3 sides, leaving the leads exposed) and allowed to dry for a few minutes. The film was then pressed and held against
the glass substrate. Once the PLGA was sufficiently dry, a second coat of PLGA solution was applied to the seam between the collagen and glass. Carbon tape was used in a similar manner; one piece was placed between the collagen and glass, and a second was placed on top of the collagen film across the edge between the film and the glass substrate.

4.2.3 Substrate Materials

4.2.3.1 PLGA

Thermally cast PLGA substrates were formed by melting PLGA particles on a hotplate at 200 °C. The PLGA was placed between two silicon wafers to produce flat and thin circular PLGA substrates (∼0.5 mm thick and ∼2 cm in diameter). The silicon wafers were fluorinated to reduce the surface adhesion for easier removal of the PLGA. Thin magnesium films (300 nm) with and without a titanium adhesion layer (5 nm) were evaporated from an e-beam system through a 12.5 µm thick polyimide stencil (Kapton, Dupont, USA). The stencil was fabricated by first attaching a polyimide film to a glass slide coated with PDMS. A 150 nm gold film was deposited onto the polyimide using an electron beam evaporation system, with a 10 nm chromium layer to improve adhesion. The metal film was patterned using photolithography and standard wet etching. This patterned metal served as an etch mask during dry etching of the polyimide by reactive ion etching (RIE) in oxygen gas (Nordson MARCH, USA). After fully etching the exposed polyimide, the metal mask was removed by wet etching and the patterned polyimide stencil were peeled from the PDMS/glass carrier substrate and placed on the PLGA surface.

4.2.3.2 Gelatin

Gelatin powder (bovine type B, Sigma-Aldrich, USA) was first dissolved in deionized water at 80 °C to achieve a final concentration of 20% (by weight). A magnetic stirrer was used
to ensure that a homogeneous solution was produced. The solution was maintained at 80 °C during formation of the gelatin films. This solution was spin cast onto cleaned glass slides (1”x1”) and dried at 110 °C for 1 minute to produce 8-10 μm thick films. The edge bead of each film was removed using a razor blade. The gelatin films were then protected by depositing various thicknesses of SiO₂ by PECVD (Plasma-Therm, USA) at 200 °C. Patterning on these gelatin/SiO₂ substrates was done using the liftoff method described in section 4.1.1.

4.2.3.3 Gelatin/PVA Hydrogel

The gelatin/PVA hydrogel was formed in accordance with previously published recipes [63-65]. Gelatin powder (bovine type B, Sigma-Aldrich, USA) was dissolved in a 9% by weight PVA solution (Celvol, Sekisui Specialty Chemicals America, USA) to achieve a ratio of PVA to gelatin of 4 to 1. The resulting mixture was stirred with a magnetic stirrer while maintained at 70 °C. When the gelatin was fully dissolved, 0.5 mL of concentrated hydrochloric acid (HCl, electronic grade, ScienceLab, USA) was added per 100 mL of solution to catalyze the crosslinking reaction. The solution was stirred for an additional 30 minutes, and then let sit for 30 minutes to prevent bubbles from stirring to remain during casting.

The hydrogel solution was cast into glass petri dishes; approximately 2.5 mL of solution was required per square inch of petri dish to produce a 50 μm thick film. The solution was allowed to dry in air for 24 hours. When fully dry, pieces of the resulting film were cut and removed from the petri dish; the remainder was stored in humidity and temperature controlled environment. Individual pieces were rinsed thoroughly in deionized water and then dried in air before using.

Devices for transfer printing onto the hydrogel substrates were fabricated as follows. Single crystalline silicon nanomembranes were fabricated from silicon-on-insulator wafers (SOI,
SOITEC, France). The in plane dimensions of these nanomembranes were defined using RIE in sulfur hexafluoride (SF$_6$). The oxide beneath the nanomembranes was removed by etching with hydrofluoric acid (HF, 49% electronic grade, ScienceLab, USA). Single membranes were then transfer printed onto a polyimide/poly(methyl methacrylate) (PI/PMMA) coated silicon wafer. The subsequent deposition, photolithographic patterning, and etching steps were done using this silicon wafer as a temporary substrate. Various metal and dielectric layers were used to complete the devices.

Devices were released from the temporary carrier substrate by dissolving the sacrificial PMMA layer in hot acetone. The devices were then transfer printed from the silicon wafer to the hydrogel substrate using a PDMS stamp. No additional adhesion layer was used to complete the transfer printing process; a few drops of water were added on the hydrogel surface, allowing it to swell slightly, which dramatically increases the adhesive properties of the surface. An encapsulating layer of hydrogel was added by pouring additional gelatin/PVA solution onto the device, sandwiching the device between two hydrogel layers. This second layer was allowed to dry in the same manner as before.

4.3 Testing Methodology

The dissolution testing was done by placing the resistive traces into a dish filled with deionized water or a phosphate buffered saline solution (PBS, pH 7.4, Sigma-Aldrich, USA). Resistances were measured from contact pads extending out of the water using a digital multimeter (Fluke, USA). Images during dissolution were taken using an optical microscope (Mitutoyo, USA). Thickness measurements were done using a stylus profilometer (Veeco, USA). To reduce the risk of delamination by handling samples, resistance measurements were done on a different sample from those used for imaging and thickness measurements.
The resistance measurements of encapsulated magnesium traces were done in the same manner as described above. The encapsulation layers prevented the measurement of thickness and imaging the magnesium during dissolution.

*In vitro* degradation testing of the gelatin/PVA hydrogel was done by incubating hydrogel samples in PBS (with Mg\(^{++}\) and Ca\(^{++}\), Sigma-Aldrich, USA) at 37 °C with added collagenase (from *Clostridium histolyticum*, Type I, Sigma-Aldrich, USA). Collagenase was added to the solution to degrade the gelatin strands. The 2 mg/mL of collagenase was dissolved into the PBS to give a final concentration of ≥250 CDU (collagen digestion units) per mL of PBS. Calcium dihydrate was also added to the solution to ensure that the concentration of Ca\(^{++}\) was greater than 5mM (per instructions included with the collagenase). The hydrogel samples were dried under vacuum and weighed prior to incubation. Samples were removed every 24 hours, rinsed to remove any excess solvent or digested pieces, and dried under vacuum before weighing. The solution was also changed each time the sample was weighed.
### 4.4 Tables

<table>
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<tr>
<th>Material</th>
<th>Sample Geometry (from Fig. 4.1)</th>
<th>Adhesion Layer Material</th>
<th>Adhesion Layer Thickness (nm)</th>
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</thead>
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<td>Magnesium oxide</td>
<td>5</td>
</tr>
<tr>
<td>AZ31B</td>
<td>1</td>
<td>Titanium</td>
<td>5</td>
</tr>
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<td>Chromium</td>
<td>5</td>
</tr>
<tr>
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<td>3</td>
<td>Chromium</td>
<td>5</td>
</tr>
<tr>
<td>Zinc, single layer</td>
<td>2</td>
<td>Titanium</td>
<td>5</td>
</tr>
<tr>
<td>Zinc, pure</td>
<td>1</td>
<td>Titanium</td>
<td>5</td>
</tr>
<tr>
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<td>2</td>
<td>Titanium</td>
<td>5</td>
</tr>
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<td>1</td>
<td>Chromium/Magnesium</td>
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<tr>
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<tr>
<td>Collagen encapsulation</td>
<td>5</td>
<td>Titanium</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4.1: Description of experimental samples for interconnect and encapsulation materials
4.5 Figures

Figure 4.1: Sample cross-sections for different sample configurations (thicknesses not to scale). In all cases grey denotes the glass substrate and blue the adhesion layer. For configurations 1, red illustrates the location of the material being tested. For cases 2-5, the red denotes magnesium. In cases 2 and 3, the green denotes the material being tested (in a capping format). For cases 4 and 5, orange denotes PLGA and purple denotes collagen.
CHAPTER 5: RESULTS AND DISCUSSION

In order to understand how standalone electrical properties of simplified test structures will translate to real, functioning devices, proper metrics must be established. For resistance measurements, the recorded resistances are normalized by the trace length (50 mm for the test structures presented here). An upper limit is established at 25 Ω/mm; beyond this value the trace resistance will be considered to have a non-negligible effect on device performance by introducing parasitic resistances when the given material is used as an interconnect. For the test trace design used here, this corresponds to an absolute resistance of 1250 Ω. In addition, each presented material will be compared to pure magnesium.

Pure magnesium loses “functionality” (i.e. R/L > 25 Ω/mm) in approximately 30 minutes for a 300 nm thick trace (Fig. 5.1, panel B). Full degradation, as judged visually, occurs in approximately 6 hours for a 300 nm thick trace (Fig. 5.1, panel A). Non-uniformity during dissolution is expected to some small extent with large traces. Images during dissolution provide a qualitative means of judging this non-uniformity, which can have an impact on accurately predicting dissolution time scales. This non-uniformity can also be recognized in measurements of trace thickness during dissolution; rough surfaces or large variations in thickness result in larger errors in thickness measurements. All thickness measurements presented in the following sections are the average of a minimum of 3 individual measurements, normalized to remove the thickness of the insoluble adhesion layers used. In all cases, the width reduction due to dissolution of the trace sidewall (or undercut, if a capping layer is present) is negligible compared to the thickness loss due to dissolution of the top surface.
These resistance test structures can also be used to measure the encapsulation ability of different materials. By placing an encapsulation material around a magnesium trace, a resistance increase will be an indication of failure of the encapsulation layer. This technique was used successfully to measure the performance of magnesium oxide and silk as encapsulation layers. It is applied here for collagen and PLGA in the same manner, as is described previously.

As a simple example of functional devices made with silicon integrated with magnesium, a system of a silicon diode shunted by a magnesium resistor is presented in Fig. 5.1, panel C. More complex systems can be made as well (transistors, logic gates, etc.), but this system serves as an example of a functional change due to transience. The system initially shows the IV characteristics of a resistor (left graph). When this magnesium shunt resistor dissolves, the system reverts to the diode characteristics (right graph). This functional can be applied to other systems by separately controlling the degradation rates of individual areas of a device.

5.1 Interconnect Materials

5.1.1 AZ31B

AZ31B, the only homogeneous magnesium alloy presented here, is the most directly related to pure magnesium. AZ31B was sputtered to produce a homogenous thin film. The composition of the sputter target used is presented in Table 1. The traces are very similar visually to those of pure magnesium, but the properties do differ, despite the low amount of added aluminum and zinc. Like magnesium, AZ31B degrades rather uniformly, even for a 300 nm thick trace. Figure 5.2, panel A, shows the degradation of a 300 nm thick AZ31B trace (with a 5 nm thick titanium layer used as an adhesion promoting layer). The initial, as deposited trace is shown upper row, far left, with increasing degradation shown from left to right, finishing with the fully degraded state after 14 hours (lower row, far right), where only the titanium adhesion
layer remains (as determined visually and from thickness measurements). Like magnesium, AZ31B can be deposited directly on glass without the use of an adhesion promoter, though the use of titanium improves yield.

Figure 5.2, panel B, shows the electrical resistance per millimeter of a 300 nm thick trace of AZ31B (black squares, also with a 5 nm thick titanium adhesion layer). The resistance reaches the upper limit of 25 Ω/mm in approximately 3.5 hours. This is a marked improvement over the 30 minutes of pure magnesium (data shown in Fig. 5.2, panel B, as red circles). While the initial resistance is larger than that of pure magnesium (~2 Ω/mm vs ~1.5 Ω/mm, due to the difference in bulk resistivity), the resistance of the pure magnesium trace quickly increases and surpasses the initial resistance of AZ31B in only a few minutes. AZ31B is much more stable; the resistance increases by only 4% in 1 hour, and quick increases in resistance begin only after 2.5 hours.

Figure 5.2, panel C, details the trace thickness during degradation. The thickness data shows the full degradation of the trace, unlike the resistance data which is only shown until functional degradation is achieved. The thickness data confirms the total dissolution of AZ31B, and the total lifetime agrees with the images presented in Fig. 5.2, panel A. As expected, the thickness uniformity decreases as degradation proceeds, which is manifested in the variation in the thickness measurements at the end of the test.

For applications that can tolerate a slightly higher initial resistance, AZ31B is a capable replacement for pure magnesium. It requires no different patterning methods, and sputter deposition is compatible with current industry practices. This alloy maintains the full transience of magnesium but at a slower rate; however, this rate is still relatively fast compared to the other components (silicon, silicon dioxide, silk, etc.) used in transient devices.
5.1.2 Single Layer Aluminum

One alternative way to extend the dissolution time of magnesium metal interconnects is to “cap” the metal lines with a second, conductive material that has a much slower degradation rate. Essentially, the capping layer acts as a conductive, localized encapsulation material. As silk enables controllable degradation for an entire device, capping materials have the potential to play the same role for magnesium metallization. This can be done with any trace material compatible with the deposition of the capping layer; the capping materials presented here are all metals deposited by evaporation or DC sputtering.

The first metal chosen as a capping material was aluminum, partly due to a study done on PVD deposited aluminum on AZ31B [68]. While aluminum is not biodegradable on its own, it degrades when alloyed into magnesium up to approximately 12% (the solubility limit of aluminum in magnesium [69]). Figure 5.3, panel A, shows the images of a 300 nm thick, pure magnesium trace capped with approximately 6% by weight aluminum film (~12 nm). Because the aluminum layer is very thin it will eventually corrode; however, it does not corrode completely, even for times much longer than the functional lifetime. The leftmost image of Fig. 5.3, panel A, shows the as deposited aluminum-capped magnesium trace. As time progresses the aluminum clearly degrades (moving left to right in Fig. 5.3, panel A). When enough of the aluminum has degraded, the magnesium is no longer exposed only along the sidewall, but from the top surface as well. This large increase of exposed surface area is also evident in the resistance data, shown in Fig. 5.3, panel B.

The initial resistance of the aluminum-capped magnesium is slightly lower than that of pure magnesium, resulting from the extra conductive material and lower resistivity of aluminum. The resistance data shows a large improvement over pure magnesium, increasing significantly
after 3.5 hours, and only reaching the limit of 25 Ω/mm after 5 hours. This surpasses AZ31B, though it is important to note that AZ31B has half of the aluminum content (3% versus 6%) and starts at a higher resistance. Thickness data is also provided in Fig. 5.3, panel C. The large error is due to non-uniform pitting in the aluminum layer. Even after long periods of time, this uneven pitting and uncorroded aluminum still remains, as can be seen in the last (bottom, rightmost) image of Fig. 5.3, panel A, and in Fig. 5.3, panel C. It is clear that 12 nm of aluminum is too thick to be fully biodegradable. This uneven degradation also represents the lack of stability in the trace as it degrades; while slow degradation is the first priority, predictable failure is important for device level use. Still, 5 hours represents a 10 fold increase over pure magnesium. Even with the addition of a generous safety factor, aluminum-capped magnesium still represents an improvement in corrosion resistance over magnesium alone, though at the expense of total biodegradability.

5.1.3 Multilayer Aluminum

In order to solve the uneven pitting issue to gain better predictability and to regain full biodegradability, the single, 12 nm aluminum layer was redistributed throughout the magnesium by splitting the aluminum layer into four, 3 nm layers, evenly spaced and surrounded by magnesium (750 nm per magnesium interlayer). The total aluminum amount is kept constant, so each aluminum layer is only 1.5% by weight. With six additional magnesium-aluminum interfaces, the aluminum atoms are in closer proximity to magnesium atoms, on average. This produces a structure that is closer to a magnesium-aluminum alloy while still maintaining a top layer of aluminum. This “quasi-alloy” can be produced in situ from bulk magnesium and aluminum sources without the use of a custom deposition source; four layers were chosen so that
the individual aluminum layers would significantly decrease in thickness without making the processing extremely tedious.

The second version of aluminum-capped magnesium was dissolved and monitored as in the previous two tests. Figure 5.4, panel A, from top left to bottom right shows the degradation from start to finish. Complete degradation occurs in 28 hours. Unlike the first iteration, the trace surface shows an even degradation with only minor pitting. More importantly, the entire trace fully degrades. The time to total dissolution is much longer than the end of degradation for the single-layer aluminum; this is attributed to the stabilization that aluminum provides to magnesium when in solid solution.

This effect is also seen in the resistance measurements shown in Fig. 5.4, panel B (red circles). For direct comparison, the data from Fig. 5.3, panel B, is also included (black squares). The multilayer aluminum scheme provides an extra 5 hours of stable operation and 6.5 hours of functionality compared to magnesium. In addition, the effects of uniform dissolution can also be seen from the degradation rate after failure of the top aluminum layer. The dissolution rate is faster for the multilayer scheme as the entire trace is degrading, while in the single layer case only the magnesium that is exposed where the aluminum has fully corroded degrades, while the rest is still protected.

Figure 5.4, panel C, also shows the extended lifetime of the traces and confirms the total dissolution of the multilayer aluminum system. Despite the modest inhomogeneity in the images of panel A, the thickness data shows that this is due to the chromium adhesion layer, not pitting. Some small amount of pitting is present, but the amount and size is not nearly as large as in the single layer aluminum case. The multilayer scheme fully degrades in ~28 hours; the thickness of the individual layers may control this effect. Additional testing could identify a maximum layer
thickness to allow for full biodegradation and an optimum layer thickness for slowest degradation rate. However, this system is limited by the amount of aluminum that can be added to magnesium; more complex magnesium-aluminum alloys will likely be the eventual route to circumvent this limit.

5.1.4 Zinc

While the multilayer aluminum stack showed improved degradation resistance over a single aluminum layer and was able to achieve complete dissolution, a single layer is highly preferred from a processing standpoint. In order to accomplish this, the aluminum capping layer could be made very thin, but this decreases its usefulness. A more attractive solution is to replace the aluminum with a material that is degradable on its own. Going back to AZ31B, the partial inspiration for choosing aluminum, zinc is a logical next choice.

The initial results of zinc-capped magnesium are disappointing compared to the aluminum results. Where the aluminum increases the trace lifetime from hours to days, the same 12 nm thickness of zinc extends the lifetime by only minutes. Figure 5.5, panel A, shows the degradation of this trace. The zinc layer, which gives a coppery color to the trace, quickly fades to the dull grey that is typical of magnesium. The trace only survives for ~6 hours, which is no different than the lifetime of pure magnesium.

Figure 5.5, panel B, shows the resistance data during dissolution and confirms the conclusion drawn from the previous images. The zinc top layer extends the functional lifetime a mere 15 minutes. While this is a 50% increase over the 30 minutes of magnesium alone, it is still far less than what is necessary for exposed electrodes. In fact, the extra lifetime may be largely a result of the extra material. Figure 5.5, panel C, shows the rapid loss of thickness during
dissolution. All three methods reach the same conclusion: zinc is best left as an alloying element for magnesium, not as an external protective layer.

To elucidate the reason for the slight increase in lifetime for the zinc-capped case, pure zinc was also tested. As before, the first panel of Fig. 5.6 shows the degradation images. The dark, coppery appearance seen in Fig. 5.5 is also present here. The brown, coppery color remains throughout the dissolution, but the trace gets lighter and lighter as the zinc dissolves and only the adhesion layer remains (Fig. 5.6, far right).

The normalized resistance data (Fig. 5.6, panel B) shows that the change in resistance is nearly identical to pure magnesium. The initial resistance is higher, as was expected; the zinc degrades marginally slower than magnesium. The rate of thickness loss can be seen in Fig. 5.6, panel C. From this slightly longer lifetime over the capping method, the additional 12 nm used in the previous scenario would extend the dissolution rate slightly. However, because the dissolution rate of pure zinc in thin film form does not differ significantly from the rate of magnesium, the gain from capping or replacing magnesium with zinc is small. Again, it appears from all three methods that zinc shows no significant improvement over only magnesium and comes at the expense of a higher resistivity. Furthermore, ZnO is a semiconductor, rather than the insulating magnesium oxide (MgO), which may cause unintended consequences in actual devices.

5.1.5 Tungsten

Moving away from alloying elements for magnesium, tungsten also represents a move away from stent materials. Tungsten is still used as an implant material in the form of embolization coils, though it is not the exclusive choice for these coils. Since tungsten embolization coils are actively used to treat patients, there is data on bulk degradation in human
patients [33]. Furthermore, tungsten is used in the semiconducting industry for vias and interconnects for integrated circuits, so the processing capabilities for depositing thin films already exist in industry, an important advantage over magnesium. However, since the bulk degradation rate of tungsten is significantly slower than that of magnesium [31], tungsten is first explored as a capping material. Like zinc, the degradation characteristics of pure tungsten thin films is also presented as a route to understanding the degradation kinetics of the tungsten capping layer.

Tungsten is similar in appearance to magnesium, as can be seen in Fig. 5.7, panel A (top left). Like zinc and aluminum, the deposited tungsten layer only protects the top surface of the magnesium trace but not the sidewalls. The resistance values (Fig. 5.7, panel B) show that the sidewall degradation and undercut is not a dominant factor in the dissolution process. The 12 nm thick tungsten layer extends the functional lifetime to 2.5 hours, approaching the 3.5 hour functional lifetime of AZ31B.

The total lifetime of tungsten-capped magnesium is longer than unprotected magnesium at 8 hours and, like the resistance data, is comparable to AZ31B. Even though tungsten is not as effective as aluminum as a capping layer, it has a history of being biodegradable, unlike aluminum. The thickness data shown in Fig. 5.7, panel C, confirms the full degradation of the tungsten-capped magnesium trace. The rate is consistent with the images presented in panel A. Surface roughness was not significant until very low thicknesses, where the chromium adhesion layer began to be exposed. Overall the degradation rate was fairly even locally, even though some thickness variation appears in Fig. 5.7, panel A. This is likely due to an uneven deposition, not uneven dissolution.
Because tungsten has a very high melting point, evaporation of tungsten for thin films is difficult and generates large amounts of heat. While this was acceptable (though at the expense of yield) for the very thin films used as a capping layer, evaporating tungsten films would produce far too much heat to be used in any application with temperature sensitive substrates (such as silk). Instead, the pure tungsten films tested here were sputtered in argon.

Fig. 5.8, panel A, shows the dissolution of a pure tungsten trace in water. The trace delaminated after 12 hours due to a failure of the adhesion layer. The initial image (left) shows the intact tungsten trace; the middle image shows the trace in the process of delamination at approximately 12 hours, and the final image (right) shows the remaining adhesion layer after full delamination of the tungsten trace. Despite this undesired failure mode, the trace still survived 12 hours with no noticeable changes, indicating that very little degradation occurred before delamination. This slow degradation rate is also expressed in the resistance data in Fig. 5.8, panel B.

Because the resistivity of tungsten is only slightly higher than that of magnesium, the difference in normalized resistance of a 300 nm trace between tungsten and magnesium is negligible, as can be seen in the data of Fig. 5.8, panel B. The tungsten resistance is quite stable, only changing after 12 hours due to partial delamination of the trace from the glass substrate. The resistance increases seen after 12 hours is due to progressive delamination of the tungsten film; the entire submerged portion of the tungsten trace eventually delaminated, but stayed connected to the dry tungsten, both physically and electrically. The last data point at 16 hours was taken with the entire resistive portion of the trace floating in the water. After this point the trace broke away from the dry portion. Despite this delamination, the trace lasted for 16 hours,
and likely could have lasted longer if it had not delaminated. The thin film degradation is slower than magnesium, as was expected from the bulk degradation rates.

The trace thickness measurements (before delamination) are in agreement with the resistance data (Fig. 5.8, panel C). The tungsten appears to undergo very slow degradation, evidenced by a gradual decrease in thickness over the span of the 12 hours. At this point the delamination occurs, and further measurements reveal information only about the adhesion layer. Pure tungsten should be further evaluated with a proper adhesion layer to ensure accurate measurement of the dissolution kinetics, especially since tungsten appears to be very promising as a replacement/complement to magnesium.

5.1.6 Iron

Iron is the last metal investigated here, and represents a return to alternative stent materials. However, unlike the previous materials which improve corrosion resistance when alloyed with magnesium (or at least are neutral in that regard), iron actually has a negative effect on the degradation of magnesium [69-71]. Iron impurities increase the degradation rate of magnesium and its alloys; many of the miscellaneous designation codes for magnesium alloys specify limits on iron, copper, and nickel, all of which increase corrosion in magnesium [70, 71]. However, on its own, iron is investigated as an alternative to magnesium stents because of its mechanical properties.

Since literature reports vastly different degradation rates for in vitro and in vivo degradation, investigations on iron thin films were done to see if this could be replicated with in vitro tests, as in vivo passivation could extend the trace lifetime well past what is desired for transient electronics. Since iron capping would negatively affect magnesium films, iron films must be used in a standalone format. Figure 5.9 presents R/L data for three separate cases: pure
iron in deionized water, pure iron in PBS, and pure magnesium (as a reference). Resistance data is not shown for an iron-magnesium combination; the time to failure for magnesium with an iron capping is extremely short and occurred within a few minutes, much faster than either of the two materials alone.

The resistance data for pure iron also differs from the usual trends seen in other materials. First, the dissolution in water is slow to reach the limit of 25 Ω/mm (approximately 8 hours, longer than any magnesium combination). Yet, the resistance begins to change much sooner, and as a result is much less stable than any other case shown previously. Finally, the initial resistance is also much higher than the magnesium cases. The dissolution in PBS is below the detection limit of the equipment used here. Any change in resistance appears to be variations due to the measurement, not the trace. The dissolution test was stopped after 20 hours, with a total change in R/L of ~1 Ω, or 0.3%. This dramatically slower dissolution rate in biological conditions is consistent with literature. Since PBS contains phosphate ions, and iron phosphide is insoluble in water, it is suspected that the lack of dissolution is due to an iron phosphide film that passivates the surface instead of iron oxide [41]. Iron may be a potential interconnect material for ex vivo applications, but for in vivo use the formation of iron phosphide should be confirmed, and a long term study done to determine if iron thin films can fully degrade with a passivating layer of iron phosphide. For this reason, iron films were not pursued further.

Figure 5.11, panel A, summarizes the lifetimes (functional and total) for interconnect materials. Tungsten produces the longest lifetimes of pure materials, while the aluminum multilayer provides the longest lifetimes of magnesium-based traces.
5.2 Encapsulation Materials

5.2.1 PLGA

Because magnesium dissolves rapidly in aqueous solutions, transient devices with magnesium interconnects and contacts must be isolated from aqueous environments in order to allow functionality over reasonable and useful timescales. To do so without sacrificing transience (as would happen by using polyimide or other insoluble encapsulant materials), the encapsulation layer must also be transient but on a longer timescale than magnesium. A number of synthetic, biodegradable polymers fit this description; PLGA is presented here as one possible polymer encapsulation material.

In order to measure the effectiveness of various encapsulation materials, each tested material was used to protect a submerged magnesium resistive trace. The resistance of the trace was used to evaluate the penetration of water through the transient barrier.

The length-normalized resistance values for PLGA encapsulated magnesium traces are shown in Fig. 5.10, panel A. Different thicknesses of solvent cast PLGA are compared to unprotected magnesium. The molecular weight and ratio of the PLGA was kept constant, as was the thickness of the magnesium (300 nm). As expected, thicker layers of PLGA extend the lifetime of the magnesium trace from 30 minutes to 3, 12, and 39 hours, for 1, 2, and 3 mm thick PLGA layers, respectively. In all three cases of solution cast PLGA, water penetrates the PLGA and reaches the magnesium before any degradation of the PLGA can be seen. Solution cast PLGA, unlike the hard and brittle thermally cast PLGA, is soft and flexible, and with a less dense structure, water molecules are able to diffuse through much faster. Bubbles formed by evaporating solvent also cause open areas within the structure, presenting localized areas with a very small thickness of PLGA as a barrier between the water and magnesium. These bubbles
could not be avoided, as the PLGA dried unevenly. Solvent evaporates much faster from the air-exposed surfaces, allowing a “skin” of PLGA to form that trapped unevaporated solvent in the bulk of the PLGA layer. This skin may break or instead trap bubbles, leaving the PLGA with a non-uniform, porous structure. The 3 mm thick PLGA layer was significantly thicker than any bubbles that had formed, leading to significant thicknesses of PLGA across the entire trace. This produced the nearly 40 hour increase in trace lifetime.

Thermally cast PLGA was investigated as a solution to the problems with solution cast PLGA. However, thermally cast PLGA had poor adhesion to the glass substrates used in testing, resulting in rapid delamination, well before the PLGA itself experienced any degradation. Thermally cast PLGA could not be tested on currently available silk substrates due to its high melting temperature (~200 °C) without damaging the silk, and surface treatments were unable to improve the adhesion to glass substrates. Because delamination began after only 3 minutes and destroyed the magnesium due to full delamination after only 6 minutes, the resistance data is not shown in Fig. 5.10.

5.2.2 Collagen

Collagen films were chosen as an encapsulation layer that was water insoluble yet still biodegradable in vivo. The triple helix structure of collagen makes it fairly resistant to water and other solvents while still being susceptible to enzymes in the body. The low solubility makes processing a challenge, but eventually thick (50-100 µm) films were sourced from a food products vendor.

Collagen films were initially attached to the glass substrates using PLGA from solution and then tested in the same manner as the PLGA encapsulation layers. The resistance values are shown in Fig. 5.10, panel B. Like PLGA and silk, the failure after 1 hour occurred at the
interface between the encapsulation layer and the device substrate. The solution cast PLGA “glue” was previously shown to have a lower than expected water resistance; since the amount of PLGA used here was much less than before, it was expected that the encapsulation layer would be less effective, though not due to the failure of the collagen. To test this theory, further tests were done using non-transient materials to attach the collagen to the glass substrate; Fig. 5.10, panel B, (red circles) shows the results of a collagen film attached with double-sided carbon tape. The carbon tape seals the interface better than PLGA, and as a result the encapsulation effectiveness is greatly increased, protecting the magnesium for 11 hours. Still, the interface proved to be the location of failure, and at 11 hours the pocket formed between the collagen film and the glass filled with water. If this interface issue can be solved or circumvented with the use of transient materials or different encapsulation geometries, collagen has potential to protect devices in aqueous solutions but still maintain in vivo transience.

Figure 5.11, panel B, summarizes the functional lifetimes for encapsulation materials. PLGA gives the longest lifetime, with the lifetime being proportional to the thickness of the PLGA layer.

5.3 Substrate Materials

5.3.1 PLGA

PLGA has been previously used as a degradable substrate material [56], but not in a fully biodegradable system. Because the liftoff procedure used for patterning magnesium films requires soaking in acetone (an excellent solvent for PLGA), deposition of magnesium onto PLGA was done using PI stencils. Magnesium traces were first deposited using a titanium adhesion layer (consistent with samples fabricated on glass substrates). Images of these traces dissolving in water are shown in the right column of Fig. 5.12. PLGA is soluble in water, but it will degrade
much slower than magnesium; in the timescale necessary for complete dissolution of magnesium (i.e. hours), only the surface of the PLGA will exhibit degradation. This degradation, while slight, will cause the titanium adhesion layer to eventually delaminate, though well after the magnesium has completely dissolved. The final image of degradation (Fig. 5.12, right column, bottom) shows this after 12 hours.

For magnesium deposited without a titanium interlayer, the results are very different. Immediately after evaporation the magnesium appears normal (ignoring shadowing effects from the stencil), as can be seen in the top of the left column of Fig. 5.12. However, the magnesium trace degrades over time, even before submersion in water. The trace becomes fainter and fainter until it is completely gone (Fig. 5.12, second image from the top, to the bottom, left column). This phenomenon is not seen when magnesium is deposited onto glass, silk, or other substrates, and it is not observed when there is a layer separating the magnesium from the PLGA. It appears that this dissolution of magnesium by the PLGA is both chemical and diffusive in nature. Both glycolic acid and lactic acid can form stable complexes with magnesium atoms, largely due to the positive charge carried by magnesium ions and the net negative charge on the carboxylic oxygen atoms in each of the monomer units. Furthermore, the structure of PLGA can put multiple negatively charged oxygen atoms in proximity, providing a stable spot for a magnesium atom. This same phenomenon can be seen with zinc (a similarly charged and reactive metal); zinc oxide (ZnO) dissolves more rapidly when PLGA is added to the solution [72]. This is attributed to complexation between zinc and PLGA. This complexation between PLGA and magnesium could also explain the rapid delamination seen in the encapsulation tests. This unusual and unexpected result adds a new design criterion when using organic materials (especially synthetic polymers) with magnesium or other reactive thin films.
5.3.2 Gelatin

The goal of using gelatin substrates was to show high resolution patterning via photolithography on a biodegradable substrate. The degradation rate of gelatin is not as variable as that of silk (though gelatin can be modified to some extent), but it is resistant to acetone, even for the long soaks needed for liftoff processes. Initial testing on gelatin substrates revealed one large flaw: gelatin swells during the development step. The TMAH-based developer solution is highly basic, which causes any gelatin exposed to it to swell. However, gelatin that was still covered by photoresist was not prone to swelling, only areas where the photoresist had been removed to allow the magnesium film to remain. Testing with unpatterned photoresist (all processing steps but the UV exposure) showed little to no swelling. The solution, therefore, was to separate the gelatin from the developer.

The eventual solution was to use low temperature (200 °C) PECVD deposited SiO$_2$ as a protective barrier. Figure 5.13 shows a series of patterns on SiO$_2$ protected gelatin. The first image (A, top left) shows patterned 400 nm thick SiO$_2$ on gelatin. This pattern was made by dry etching the oxide with a positive photoresist etch mask. The positive photoresist required a much shorter development step, and the 400 nm protective oxide layer was able to prevent diffusion of the developer solution to the gelatin during that short time. Image B (top right) shows the same 400 nm SiO$_2$ layer with magnesium features deposited using liftoff. The gelatin has swollen significantly, though the patterned features are still intact and conductive; however, in this condition the samples cannot tolerate further fabrication steps.

The third image (C, bottom left) shows a high resolution pattern (3 µm thick magnesium features) on 600 nm SiO$_2$. The 600 nm layer does a much better job of protecting the gelatin substrate. 37 of 84 patterns survived the processing with no defects. Low magnitude swelling
was present in much of the area of the 600 nm samples, in contrast with the large swelling seen around defects in the 400 nm samples. This indicates swelling is due a small amount of diffusion through the barrier, not due to point defects in the layer. The final image (bottom right) shows liftoff patterned magnesium on a 800 nm SiO₂ coated gelatin substrate. Finally, 800 nm is thick enough to prevent the gelatin from swelling during the development step. Yield is improved, with 53 out of 84 patterns being defect free. Since 800 nm is not an insignificant thickness for integrated circuits, this method of protecting the gelatin will not work in all situations. Provided that this barrier layer can be incorporated into the process flow, gelatin may have potential as a biodegradable substrate material, especially since it can tolerate higher temperature processes better than unannealed silk films. In addition, other biodegradable materials may also function as barriers and allow the barrier thickness to be reduced.

5.3.3 Gelatin/PVA Hydrogel

One downside to silk substrates is the lack of stretchability. Silk films are flexible, but stretchable substrates can allow for better conformal contact with tissue, which can be far from flat.

Before the hydrogel was used as a device substrate, it was first confirmed that the hydrogel is in fact biodegradable. Figure 5.14 shows the mass of a 75 mg (initially) hydrogel sample during incubation in a simulated biosolution (PBS plus collagenase). The collagenase will attack the gelatin strands, breaking them and destroying the network structure of the hydrogel. Since gelatin and PVA are highly soluble, the separated pieces can dissolve in the solution. Miscellaneous additional proteins will further digest the short peptide strands. The solution was incubated at 37 °C and changed every day. The hydrogel sample was rinsed and dried under vacuum before weighing. The rate of digestion appears to be fairly constant at ~8.5%
loss per day, with the exception of the initial mass loss after 24 hours (likely due to pieces of gelatin or PVA unincorporated into the network structure). Because the number of collagen digestion units (CDUs) was kept constant during, a fixed amount of digestion is possible in a fixed amount of time. However, the degradation rate presented here may not be the maximum rate possible; the collagenase requires oxygen to function, and the apparatus used here did not allow for constant oxygenation of the solution. The collagenase may have used up all the available oxygen before the solution was changed, thereby stopping degradation. Since the procedure was not ideal (though consistent), the important result is that the gelatin/PVA hydrogel does completely degrade in vitro.
Composition of AZ31B sputtering target

<table>
<thead>
<tr>
<th>Element</th>
<th>Mg</th>
<th>Al</th>
<th>Zn</th>
<th>Mn</th>
<th>Si</th>
<th>Pb</th>
<th>Sn</th>
<th>Ca</th>
<th>Cu</th>
<th>Fe</th>
<th>Ni</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount (wt%)</td>
<td>95.2</td>
<td>3.5</td>
<td>1.3</td>
<td>0.2</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 5.1: Composition data (by weight) of the AZ31B sputtering target (data provided by Kurt J. Lesker Co., USA)
Figure 5.1: Dissolution of pure magnesium. Panel A shows images during dissolution, panel B shows resistance during dissolution, and panel C shows a simple magnesium-based system where functionality change (evidenced by IV curves) is driven by dissolution of a magnesium resistor.
Figure 5.2: Dissolution data for 300 nm AZ31B resistive trace, including images (panel A), resistance data (panel B), and thickness data (panel C) over time.
Figure 5.3: Degradation of a 300 nm magnesium trace capped by a single layer of 12 nm aluminum. Degradation images are shown in panel A, resistance data in panel B, and thickness data in panel C.
Figure 5.4: Degradation of a multilayer magnesium-aluminum trace. Total magnesium thickness is 300 nm, and total aluminum thickness is 12 nm. Panel A shows images of dissolution, panel B measurements of resistance, and panel C measurements of thickness.
Figure 5.5: Dissolution of a zinc-capped 300 nm magnesium trace. A) Dissolution images; B) normalized resistance data compared to pure magnesium; C) thickness loss during dissolution.
Figure 5.6: Dissolution data of a pure zinc resistive trace (300 nm). Panel A shows images during dissolution, panel B shows the resistance during dissolution, and panel C shows the thickness during dissolution.
Figure 5.7: Degradation of a tungsten-capped magnesium trace. Images, resistance, and thickness during dissolution are presented in panels A, B, and C, respectively.
Figure 5.8: Dissolution of pure tungsten. Images (panel A), resistance data (panel B), and thickness data (panel C) were stopped after delamination was complete.
Figure 5.9: Dissolution of pure iron resistive traces in deionized water and PBS.
Figure 5.10: Length-normalized resistance data for PLGA (panel A) and collagen (panel B) encapsulated 300 nm magnesium traces.
Figure 5.11: Summary of trace lifetimes for interconnect (panel A) and encapsulation (panel B) materials.
Figure 5.12: Magnesium traces on a PLGA substrate. The left column is magnesium without an adhesion layer, while the right column includes a 5 nm titanium adhesion layer.
Figure 5.13: Photolithographic patterns on SiO₂ covered gelatin substrates.
Figure 5.14: The enzymatic degradation of a gelatin/PVA hydrogel.
CHAPTER 6: CONCLUSION

In order to decrease the dissolution rate of metal interconnects in transient electronics from the rapid ~ 50 nm/hr rate of thin films of magnesium, nine different metals/schemes were tested. Aluminum produced the longest degradation times of all the magnesium-based schemes (as an alloying element or in “quasi-alloy” form). Aluminum must be used in small amounts though, as it will not degrade without magnesium. Tungsten proved to be the best (slowest dissolving) pure metal, surviving well past pure magnesium, zinc, or iron. Though thin layers of tungsten were not as effective as aluminum when used as a capping layer, the tungsten thickness can be increased because it is fully biodegradable. PLGA and collagen were both functional as encapsulation materials, though practical use will require careful planning and thorough research to ensure a strong interface between the encapsulation layer and the device substrate. PLGA was shown to be a poor substrate for magnesium-based devices due to the complexation with and gradual dissolution of magnesium films. New interlayer diffusion barrier materials may mitigate this, but careful research should be done as most biodegradable materials are also quite reactive. Gelatin and a gelatin/PVA hydrogel showed promise as alternative flexible or stretchable (respectively) substrates to silk. The gelatin/PVA hydrogel was also shown to be fully biodegradable in vitro.

Future work should begin with device level testing (diodes, transistors, logic gates etc.) using the most promising new materials, especially tungsten and magnesium-aluminum alloys. It is especially important to evaluate integration with silicon nanomembranes. Tungsten should also be tested with a proper adhesion layer to accurately measure the degradation kinetics. In vivo testing would be an appropriate study following development of functioning devices. Finally,
these new materials should be evaluated for integration with silk or other biodegradable substrates; the ability to process these new materials with different methods (especially dry etching) may allow the use of new substrates or expand the capabilities of the silk substrates. The interconnect materials should also be evaluated in forms that include exposed electrodes, as slowly degrading contacts could allow exposed electrodes to directly contact tissue without jeopardizing device functionality while still allowing the device to degrade in a reasonable amount of time. Capping magnesium, including the sidewall, may be a possible method of achieving this.
REFERENCES


