Clemson University

TigerPrints

All Theses | Theses

5-2024

Advancements of a Breast Tissue Marker and Localization System

Azrin Jamison
azrinj@g.clemson.edu

Follow this and additional works at: https://tigerprints.clemson.edu/all_theses

 Part of the Bioimaging and Biomedical Optics Commons, Biomaterials Commons, and the Biomedical Devices and Instrumentation Commons

Recommended Citation

Jamison, Azrin, "Advancements of a Breast Tissue Marker and Localization System" (2024). *All Theses*. 4243.
https://tigerprints.clemson.edu/all_theses/4243

This Thesis is brought to you for free and open access by the Theses at TigerPrints. It has been accepted for inclusion in All Theses by an authorized administrator of TigerPrints. For more information, please contact kokeefe@clemson.edu.

ADVANCEMENTS OF A BREAST TISSUE MARKER AND LOCALIZATION SYSTEM

A Thesis

Presented to

the Graduate School of

Clemson University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

Bioengineering

---

by

Azrin M. Jamison

May 2024

Accepted by:

Delphine Dean, Ph.D., Committee Chair

Jordon Gilmore, Ph.D.

Alexey Vertegel, Ph.D.

ABSTRACT

Breast cancer has become the most prominent cancer worldwide in women. Annual mammograms are encouraged for women of high risk to increase early detection, allowing for lumpectomies rather than mastectomies. Prior to a lumpectomy, a biopsy must be taken to determine if the tissue is cancerous, and a breast cancer biopsy marker (BBM) is placed in the region of possible cancerous tissue. Wire localization has been the gold standard for localizing these BBMs. However, due to the reported patient discomfort and logistical inefficiencies faced by healthcare providers (HCP), non-wire localization solutions have been recently developed.

This study aims to build upon the development, fabrication, and assessment of a novel BBM and localization system first introduced by Scott Slaney in 2019 that allows for perioperative imaging without wire localization.

The first portion of this study focused on optimizing the novel BBM to a feasible size to be deployed during a breast cancer core biopsy and fit within a 2.5 cm incision site. A four-week degradation and proximity study was conducted *in vitro* to evaluate the performance of the magnetic and degradable properties of the novel BBM (Figure 1).

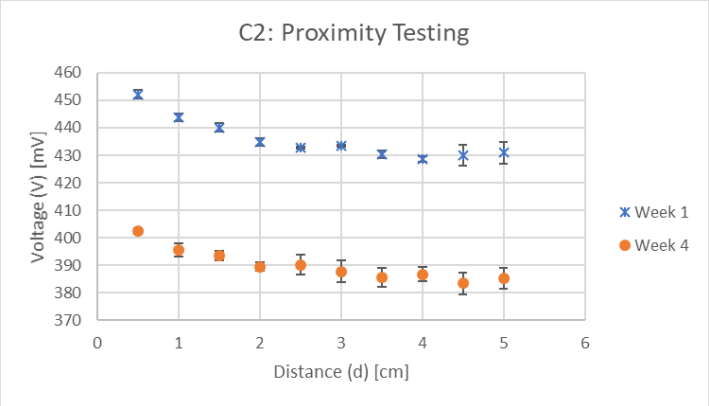

Figure 1. Voltage attenuation curve produced from proximity testing of marker over four weeks.

The second element of this study further optimized the localization system described by Scott Slaney in 2019. COMSOL Multiphysics was used to evaluate different combinations of design parameters so that a sensitive and accurate system could be achieved to detect our novel BBM. Alternative localization methods were explored for the novel BBM using ultrasound imaging. The novel BBM was embedded in gel tissue phantoms, and ultrasound was used to locate the novel BBM in this study successfully.

The results of this study have shown that the nonpermanent BBM has met the design constraints of our clinical collaborators at the Medical University of South Carolina (MUSC). The novel BBM and localization system has shown that it can effectively eliminate the need for preoperative imaging and wire localization.

ACKNOWLEDGMENTS

I begin with heartfelt gratitude to God and my Savior, Jesus Christ, without whom this incredible opportunity would not have been possible. I am thankful for the trials and tribulations He guided me through during this research, leading to the testimony that emerged. I express my deepest thanks to my parents for the unwavering support and care they have shown me along this journey. Though our paths sometimes diverged, thank you for allowing me the freedom to trust in charting my course. This journey has been enriching for each of us in our walks with the Lord.

I appreciate the remarkable individuals God has blessed me with throughout this journey. They have contributed to my growth as a scientist, mentor, friend, brother, and follower of Christ. Dr. Delphine Dean, I am grateful for the opportunity to pursue this project under your guidance and continued support. Dr. Melissa McCullough, your mentorship during my undergraduate years inspired this project, and I am thankful for your influence.

A special thanks to Scott Slaney for his assistance in advancing the project and for his previous work. To Dr. Gilmore, Dr. Vertegel, Dr. Harvey, Dr. Schmidt, Dr. Mulwee, Dr. Medfford, Alexander Malaj, Dr. DeMore, Dr. Jeryl Jones, Dr. Cerano Harrison, and Mr. Travis Pruitt, your technical guidance and support were invaluable.

To everyone in the Multiscale Bioelectromechanics lab—Ellie, Arianna, Drew, Calvin, Diego, and Jeremiah—your collaboration and camaraderie made this journey truly rewarding. I also thank my undergraduate research mentees: Ella, Lauren, Megan,

and Aaron. Your dedication was instrumental. Maria Eduarda-Camargo and Taya Lee, thank you for your assistance in developing the biosensor for antiretroviral drug detection. Your support, encouragement, and wisdom have shaped me into a better researcher and individual.

To the PEER & WISE family, your ongoing support and encouragement have been a constant source of strength.

I express profound gratitude to my family at Freeway Church for your prayers and unwavering support. To my brother Quan, thank you for leading me to this church and being a guiding light in my spiritual journey.

I'd also like to thank the bioengineering staff, Ms. Leigh and Ms. Lauren, for their support in ensuring my progress through my classes. Your assistance was invaluable.

To my brothers and all my family members in the low country, your unwavering support throughout life has been a constant source of strength and encouragement.

Lastly, to my family at The Outdoor Goods Store—James, Conner, Blake, Bryce, Quinntin, TJ, Andrew, and Ms. Liz—I am deeply thankful for your unwavering support while conducting this research.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Overview of Breast Cancer

Breast cancer has become one of the top three leading cancers worldwide while being the most prominent malignancy found in women.[1,2] Worldwide, it has been shown that one in eight women will develop breast cancer in their lifetime.[1] The World Health Organization (WHO) has established that early detection of breast cancer helps increase the patient's outcome and is the foundation for breast cancer regulations.[3] Annual mammograms are encouraged for women of high risk to increase early detection, and in 2012, of the 1.7 million diagnoses made, 80% were eligible for a lumpectomy.[1,4] Prior to a lumpectomy, a biopsy must be taken to determine if the tissue is cancerous, and a breast biopsy marker (BBM) is left in the region of possible cancerous tissue, allowing physicians to locate and excise the cancerous tissue, as seen in figure 1.

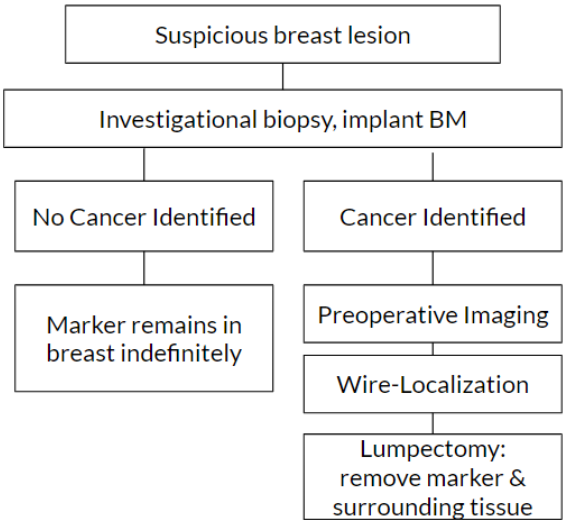

Figure 1. Traditional process of investigational biopsy, includes preoperative imaging & wire localization

Non-Cancerous Lesions & Migration BMs

As seen in Figure 1, a BBM is implanted regardless of whether a patient has cancer or not. This creates a long-term health concern for patients due to the impacts on their bodies as they keep these BBMs within their bodies indefinitely. Patients have reported rashes, itchiness, and long-term discomfort at the sites of their implanted BBM. Additionally, long-term physicians can follow up on these BBMs to see if cancerous tissue has appeared. However, this would require a future investigational biopsy to be done. Studies have been done on the BBMs migrating from their original positions of implantation.[5] Due to this, it has been encouraged to create BBMs with unique geometrical shapes to help decrease the chances of migration and increase the ability of physicians to distinguish between BBMs placed at different periods.[5]

Procedure of Wire-Guided Localization

Since the 1970s, wire-guided localization (WGL) has been the gold standard for localizing these BMs. A typical wire used can be seen in Figure 2. An imaging modality is used, typically ultrasound, to guide the wire through the breast tissue to the implanted BBM, figure 3. The remaining portion of the wire is left exposed outside of the breast tissue and is then taped to the outside of the breast tissue so surgeons can use it as a guide to excise the cancerous tissue and BBM.

Figure 2. Kopans Wire used for guidance during a WGL procedure.

https://itsinterventional.com/

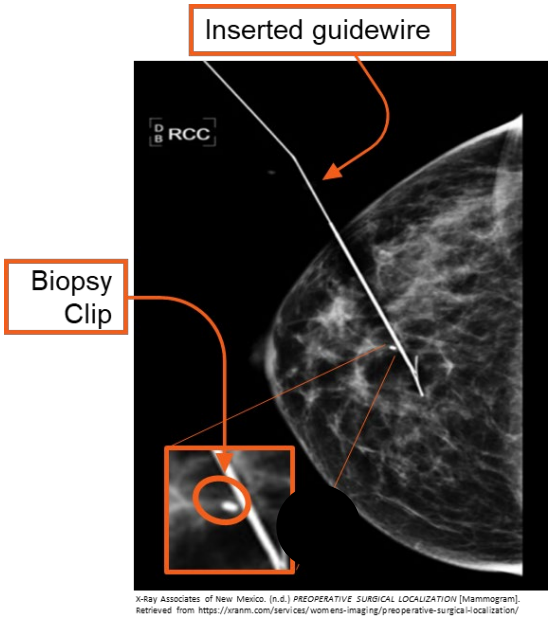

Figure 3. Imaging of a WGL procedure

With the recommended increase in routine imaging of patients an increasing awareness of the disadvantages have become more widely discussed. More patients are speaking about the discomfort and stress they face when having the wire localization procedure done. It should be noted that the procedure does include the use of local anesthetics to help relive patients pain but often this is not enough as it doesn't diminish the stress, anxiety, and discomfort they feel. With this study we were able to hear personal experiences of patients who've undergone WGL procedures. For one patient we spoke to they received three BMs implanted concurrently and in turn had to receive three different WGL procedures the day of their lumpectomy procedures. They talked about the painfulness, stress, and discomfort they felt from the overwhelming procedure. From a health care providers (HCP) perspective these procedures can be very challenging. There have been studies shown that the wires have unknowingly fragmented into the

breast tissue during WGL procedures and caused long-term discomfort for patients.[6] It's essential that HCPs provide excellent care during WGL to help manage their patients stress and anxiety. Lastly, HCPs have the added pressure to ensure that their logistically prepared to handle WGL procedures effectively as it requires them to perform the procedure in an imaging suite and then transport patients to an operating room after. Due to the reported patient discomfort and logistical inefficiencies faced by HCPs, non-wire localization solutions have been recently developed starting in the 2010s.

Novel Wire-Free Localization Systems

These non-wire localization solutions currently have disadvantages, which has kept them from becoming the new gold standard as HCPs slowly accept them, as seen in Table 1.

	Localization Systems		
Device Name	Scout Radar System	Magseed/Sentimag System	LOCalizer System
Device Description	Nickel based radiofrequency marker & infrared light-emitting probe	Metal detection of stainless steel marker with metal detection probe	RFID marker and RFID detection probe
Advantages	Approved for long-term placement	Low migration or marker in the body	Numerous markers can be placed at once
Disadvantages	Costly equipment; nickel allergy patients can't use; theatre lights & blood can impair signals	Marker insertion needle incompatible with MRI; non-magnetic instruments must be used; not approved for long-term placement	Unsuitable for marking lymph nodes; avoided with in situ defibrillators or pacemakers

Table 1. Novel Wire – Free Localization systems available on market today.[7]

These procedures often require a primary marker and a secondary marker placed at the biopsy site due to the localization system being developed only for the secondary clip. As seen in Figure 4, a primary clip is implanted during the investigational biopsy, and the novel wire-free localization systems BBMs are placed either 30 days before the lumpectomy or the day of. The Scout Radar system would be excluded from this as it has been approved for long-term placement and can be placed instead of a primary clip. However, this disadvantage arises as the patients we interviewed for this study are not keen on a BBM remaining in their body indefinitely. The preoperative placement of these localization systems can still contribute to patient stress and logistical inefficiencies for HCPs.

Figure 4. Scout Radar System: a nickel based radiofrequency primary BM and infrared light-emitting probe.[7]

The Findings of Scott Slaney

In 2019, Scott Slaney, along with the help of many others, first tackled this clinical technological gap and posed a novel idea that would take inspiration from existing FDA-approved devices on the market. This approach of not reinventing the wheel but utilizing what is out there to create a simplistic novel technology was encouraged by Melissa McCullough and her own experiences with battling breast cancer. Due to the ingenuity of this team, they identified a critical disadvantage to the existing novel wire-free localization systems. Yes, they all gave an alternative to wire localization, but they still didn't address the problem of a BBM remaining indefinitely in the breast tissue, which the majority of patients would have concerns about their long-term health. Slaney and others identified that along with a wire-free localization system, a novel biopsy marker that allowed for non-permanence in the body over a designated period was essential and could be a viable competitor to the existing solutions on the market. The group's thorough market analysis showed the novel approach as a viable commercialization device. Funding and assistance were acquired from CURF, MUSC, and many other agencies to provide initial proof of concept for this novel BM and localization system they presented. More in-depth knowledge of breast cancer, breast cancer treatments, biopsy procedures, and existing BMs can be found in his thesis (Appendix A.)

The novel BBM, referred to as the McCullough Biopsy Marker (MBM), was designed to feature the biodegradable properties of Poly Lactic-co-Glycolic Acid (PLGA) and the magnetic susceptibility properties of Iron Oxide Nanoparticles (IONPs). PLGA was chosen due to its well-established and documented application in biodegradable sutures. It has been shown that the ratio of Lactic to Glycolic Acid can be varied to enhance or decrease the degradation rate. For the MBM, it was found that a 50:50 ratio would allow for a three to four-week degradation period. The group's clinical collaborator at MUSC, Dr. Nancy DeMore, it was recommended that this would be a feasible period because of the urgency to remove cancerous tissue after the investigational biopsy.

Additionally, using PLGA would allow for the embedded IONPs to be held together and slowly released into the body. The initial size of the MBM was 8 mm in diameter and 3 mm in depth.[8] Varying concentrations of PLGA: IONP MBMs were fabricated and validated through proximity testing. The optimal ratio for a MBM of reduced size would be 30% wt. of PLGA and 70 % wt. of IONPs.[8] Reducing the size of the MBM would allow it to be properly deployed through a core biopsy needle into the breast tissue.[8]

IONPs have been introduced into the medical industry in many different applications because of their low toxicity to the body and natural routes of degradation through the renal system. The use of IONPs as a contrast agent for imaging showed that they could possibly be used in the application of being a BBM. Based on the magnetic susceptibility properties of IONP, Scott's work showed that a localization system similar to a metal detector, like the MagSeed/Sentimag system, could be used to detect the IONPs within the body. Proximity testing showed that the localization system could detect the MBM at the specified depths in Table 2 and that the voltage response attenuated as the distance decreased from the MBM, as seen in Figure 5.[8]

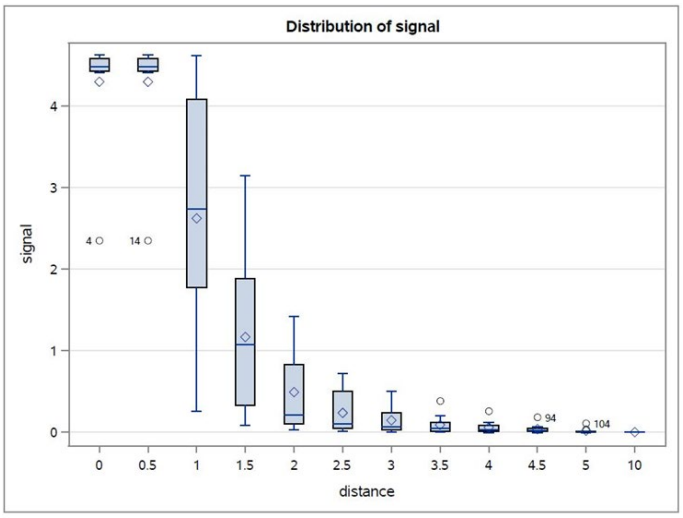

Figure 5. Voltage signal attenuating with distance utilizing a localization system developed by Slaney et al., 2019.

Slaney prepared a localization system based on the principles of metal detection, Appendix A. Validation of the metal detection was done *ex vivo* on a nitinol BBM, figure 6. The localization system detected the nitinol BM within a 3-5 cm range.[8] However, the signal-to-noise ratio of the localization system still needs to be adequate for clinical application. It was recommended from this study that the coil parameters needed to be enhanced to generate a more practical signal-to-noise ratio.[8]

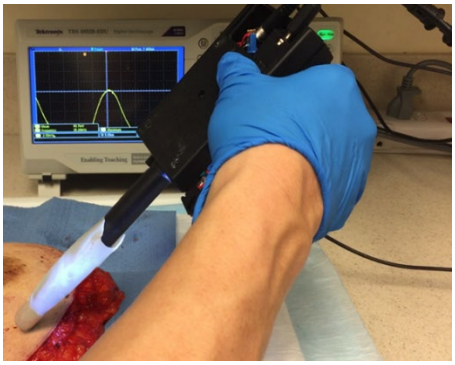

Figure 6. *Ex vivo* validation of localization system in mastectomy samples by Slaney et al, 2019.

Scott Slaney's work showed that this novel approach of a nonpermanent primary marker and localization system would address the need to eliminate preoperative imaging and wire localization. Further work needed to be done to bring the proof of concept to a more practical clinical grade before further work in commercializing the idea could be done.

Project Aims

This study aims to build upon the development, fabrication, and assessment of a novel localization system first introduced by Scott Slaney in 2019. By designing this novel MBM and localization system, we aim to address the disadvantages of wire-free localization systems on the market and WGL. Our design of a nonpermanent primary BBM will allow physicians to localize our novel MBM without the use of wire-localization preoperatively.

The first portion of this study focused on optimizing the novel MBM to a feasible size to be deployed from a nine or 11-gauge biopsy needle.[4] A four-week investigational study was conducted *in vitro* to evaluate the performance of the magnetic and degradable properties of the novel MBM.

The second element of this study further optimized the localization system described by Slaney. COMSOL Multiphysics was used to evaluate different combinations of design parameters so that a sensitive and accurate system could be achieved to detect our novel BM. Outside industrial collaboration from Woodruff Scientific was sought to help further develop our localization system, as shown in Appendix B.

Lastly, alternative localization methods were explored for the novel MBM. Ultrasound imaging is traditionally used in wire-localization procedures and is a favorable means of locating the novel MBM. The novel MBM was embedded in gel tissue phantoms, and ultrasound was used to locate the novel BM successfully in this study.

The results of this study have shown that the nonpermanent primary MBM has met the design constraints of our clinical collaborators at MUSC, table 2. The novel MBM and localization system has shown that it can effectively eliminate the need for preoperative imaging and WGL.

User Needs	Design Specifications		
Use of FDA-approved materials	PLGA and IONPs has shown safety and efficacy in the body		
Compatibility with existing BM technology	Localization system must be able to fit within a 2.5 cm incision site.		
Perioperative Localization	Allow physicians a 3-4-week period to operate on a patient after implantation of MBM	Use of a metal detector localization system requires the use of non-metal instrumentation	The design of the handheld ultrasound probe will allow for the localization of MBM
Non-permeance of MBM	BM will dissolve from the body 1 month after implantation while remaining detectable		
Accurate & Sensitive Localization System	Detection depth of 3-5 cm; 5 cm preferred	Localization of BM within +/- 1 to 2 mm; +/- 1 mm preferred	

Table 2. Design Criteria for BM and localization system provided by clinical collaborators at MUSC.

METHODS

Fabrication of MBM

Poly(Lactide-co-glycolide) (PLGA) (50:50) acid endcap, 15,000 – 25,000 Da, was acquired from PolySciTech. Iron (III) oxide nanoparticles (IONPs), <50 nm particle size (BET), were acquired from Aldrich Scientific. Varying concentrations of MBM composed of PLGA and IONPs were fabricated, as seen in Table 3.

PLGA: IONP (wt%)	C1 (30:70)	C2 (50:50)	C3 (40:60)
PLGA (g)	0.6	1	0.8
IONP (g)	1.4	1	1.2

Table 3. PLGA & IONP make-up of MBM

MBMs were first prepared by weighing the respective portions of PLGA and IONP. PLGA was then diluted in 20 mL of absolute ethanol (EtOH) for 1 hour under intense stirring, figure 7.

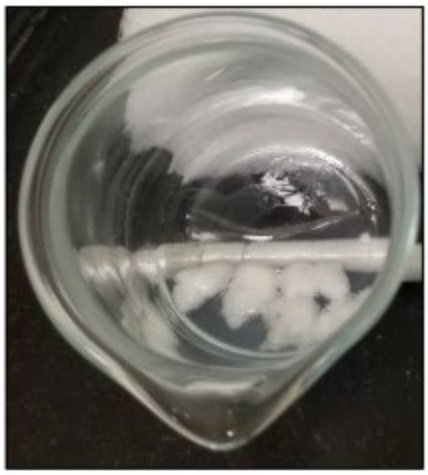

Figure 7. PLGA is dissolved in EtOH.[8]

A corresponding amount of IONPs was added to the PLGA/EtOH mixture and stirred. Samples were then placed under a vacuum chamber for 24 hours. After incubation under vacuum, Figure 8 shows samples removed from the beakers using a metal spatula, Figure 9. A metal mold was prepared by drilling a 1/8th inch drill bit through a metal disk, as seen in Figure 10. The coiled side of the drill bit was placed into the opening of a drill press machine so that the blunt conical end was exposed, as seen in Figure 11.

Figure 8. Vacuum-dried samples after solvent casting.[8]

Figure 9. Vacuum-dried samples after solvent casting and removed with a spatula.[8]

Figure 10. Mold for fabrication of MBM

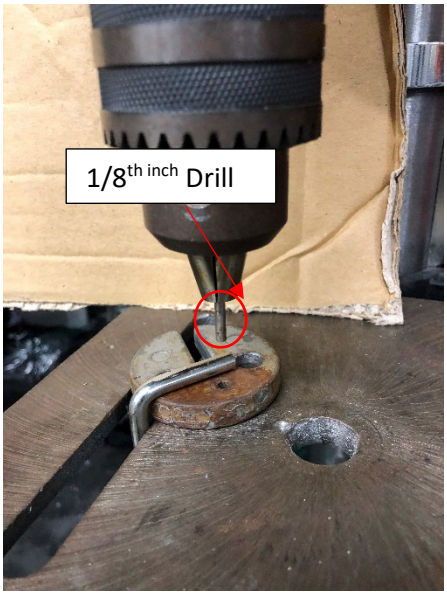

Figure 11. Drill bit to press PLGA: IONP material into MBM mold.

The drill bit and mold were aligned so that the drill bit could fit into the through hole. Prepared PLGA: IONP samples were pressed into the molds through the hole, heated with a heat gun, and pressed down with the drill press. This process was repeated until the whole hole was filled with the PLGA: IONP sample. The drill bit was then used to push the MBM through the whole, resulting in the MBM seen in Figure 12. Before and after each MBM fabrication, the mold was cleaned using a cotton swab and EtOH.

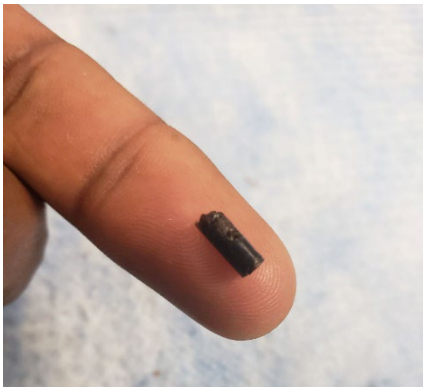

Figure 12. Smaller fabricated MBM

Degradation Study – MBM Weight Change

The degradation study occurred over four weeks. MBMs were placed in 15 mL centrifuge tubes with phosphate-buffered saline (PBS) media. Weekly media changes were conducted and analyzed for pH change and the presence of IONPs. The initial weights of the MBMs were taken, as shown in Table 4, by placing a weight boat on a scale, then zeroing the scale and placing the MBM in the weight boat to be weighed. Additionally, an empty 15 mL centrifuge tube was weighted as well.

Concentrations	Samples	Weight of Centrifuge Tube	Weight of MBM
C1 (30:70)	A	7.1648	.3653
	B	7.0728	.2283
	C	7.0253	.2258
C2 (50:50)	A	7.3462	.5467
	B	7.1298	.3303
	C	7.2898	.4903
C3 (40:60)	A	6.9443	.1448
	B	7.0320	.2325
	C	7.0626	.2631

Table 4. Initial MBM weights were recorded at the beginning of the degradation study.

At the beginning of each study week, the unabsorbed PBS was pipetted into a new 15 mL centrifuge tube to be studied later. The 15-mL centrifuge tube containing the MBM without PBS was then weighed, and the MBM weight was calculated using Equation 1 and recorded in Figure 16. During the 4-week study, all samples were stored in an incubator at an average physiological temperature of 37ºC.

$$Equation\ 1.\ MBM_{weight} = MBM_{sample,weight} - 15\ mL\ centrifuge\ tube_{weight}$$

Degradation Study – PBS pH Change

To ensure the physiological *ex vivo* environment remains non-toxic during the 4-week study. PBS collected from the degradation study samples was evaluated using the Mettler-Toledo pH probe each week, as seen in Figure 21.

Degradation Study – Release of IONPs

The release of IONPs into the physiological environment was tracked to ensure toxic levels were not detected in the PBS media. Upon collection of the PBS media from degradation samples, a nanodrop spectrophotometer was used to detect the presence of IONPs each week, as seen in Figure 20.

Degradation Study – SEM Surface Characterization

The overall morphological composition of the MBM was evaluated using scanning electron microscopy. Separate smaller samples were prepared for this so that they could be secured to a 26 mm SEM pedestal. The samples were 1/3rd of the original length of the MBM samples. They were stored in centrifuge tubes containing 15 mL of PBS in physiological temperature. The PBS was changed each week during the study, and samples were imaged. They were secured to the SEM pedestal using double-sided tape and copper. Specific parameters were placed in the Aztec EDS software to properly image the samples in Table 5.

EDS Software Parameters	
Spot Intensity	50
BSE	Electron Dense Higher Color
Pressure	50 Pa
Pull Line for EDS	15 kV

Table 5. Parameters were used to set up imaging using 3400 SEM. Mr. Donald assisted the group at the ARML Lab in setting these parameters based on the material composition of the MBM.

Degradation Study – Proximity Testing

Benchtop validation of the MBM was carried out utilizing a Harbor Freight handheld metal detector (HFMD). Degradation samples were placed 10 cm away from the HFMD on top of a foam block to help displace any interference from metal objects in the testing vicinity, as seen in Figure 13. The metal detector was hooked to the oscilloscope to measure and record the voltage response. Responses were obtained by recording the maximum voltage received on the oscilloscope after a minute at each designated distance. Baseline data was collected at 10 cm, 5 cm and every 0.5 cm until 0 cm was reached. The degradation sample was held at a fixed position while the metal detector was marched closer to the degradation sample.

During this benchtop validation, a 9-volt battery was used to power the metal detector over the first three weeks. During the fourth week of the degradation study, a new 9-volt battery was placed in the metal detector.

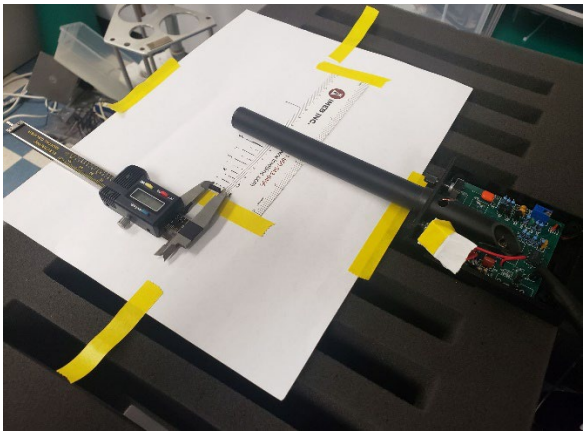

Figure 13. Proximity testing benchtop set-up.

COMSOL Multiphysics Localization Optimization

A 2-D axis-symmetrical model was created using COMSOL Multiphysics to evaluate the magnetic flux of the MBM at a fixed position (Appendix C). A metal detector was created in COMSOL utilizing the electromagnetics package. Global parameter variables, ferrous core diameter, transmitting/receiving coil turns, and transmitting/receiving coil layering, were tested in various combinations through a parametric sweep to determine the optimum magnetic flux achieved. A current of 1 A was distributed evenly throughout the coils. An iron material marker similar to our MBM was replicated in the 2-D system at a distance of 4 mm x-direction and 4 mm y-direction at the rightmost edge of the coils for each parametric sweep combination.

Global Parameter Variables	Initial Value	Step Value	Final Value
Ferrous Core [mm] Material: Iron	20	1	80
Transmit Coil Turns [-] Material: Copper	500	100	5000
Receive Coil Turns [-] Material: Copper	500	100	5000
Transmit Coil Layers [-] Material: Copper	1	1	10
Receive Coil Layers [-] Material: Copper	1	1	10

Table 6. Global parameter variables were tested through a parametric sweep where all possible combinations of variables were tested

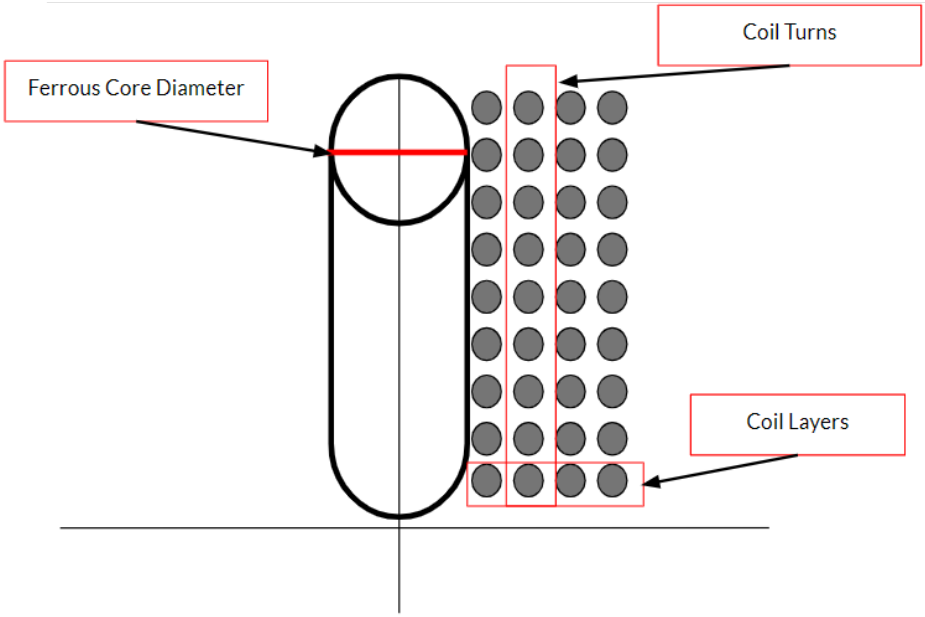

Figure 14. COMSOL 2-D simulation showing the positions of the global parameter variables. Coil layers correspond to the rows, while the turns correspond to the columns of coils. The coil diameter was set at 0.3 mm with a distance of 0.6 mm between each coil.

Next, the current was adjusted with the established optimized parameters, and the MBM was placed in three different locations in the 2-D plane as seen in Figure 26. The distances of each marker were set to adjust as the overall 2-D localization system changed size through the parametric sweeping and can be seen in Table 7. The r,z coordinate system correlate with conventional cartesian coordinates. Only the current was set as the global parameter variable, while the ferrous core radius, transmitting/receiving coil turns, and transmitting/receiving coil layers were fixed at the optimum values determined.

Global Parameter Variables	Initial Value	Step Value	Final Value
Current [mA]	1	10	100
Parameter Variables			
Ferrous Core [mm]	Transmit/Receive Coil Turn [-]	Transmit/Receive Coil Layers [-]	Coil Diameter [mm]
10	500	5	0.3
Point A	Point B	Point C	
r-direction: 1 cm z-direction: 100 mm	r-direction: 4 cm z-direction: 150 mm	r-direction: 5 cm z-direction: 50 mm	

Table 7. Global and local parameter variables are used to determine the optimum current to be placed through the coils

Alternative Methods for Localization

A portable ultrasound machine was used to visually locate the MBM in a gel tissue phantom with assistance from a trained technician. The gel-tissue mold was created by dissolving one pack of gelatin in 1 cup of warm water. Next, Fibrin was added to the dissolved gelatin solution to add texture to the mold. A small round tubaware bowl was used as a mold. The prepared solution was poured into the mold until the solution reached 3 cm depth. The solution was allowed to solidify for 1 hour. The MBM was placed in the mold, and then more gel solution was prepared and poured over the MBM until it reached the top of the mold. The mold was allowed to continue to solidify overnight frigerated.

Ultrasound Gel was placed on the top of the gel mold, and the ultrasound probe was placed on the surface of the gel mold. Images were captured during the localization procedure on the gel mold, as seen in Figures 28-30. Lastly, the gel mold was flipped upside down and imaged on the bottom face and concave side.

RESULTS & DISCUSSION

Degradation Study – MBM Weight Change

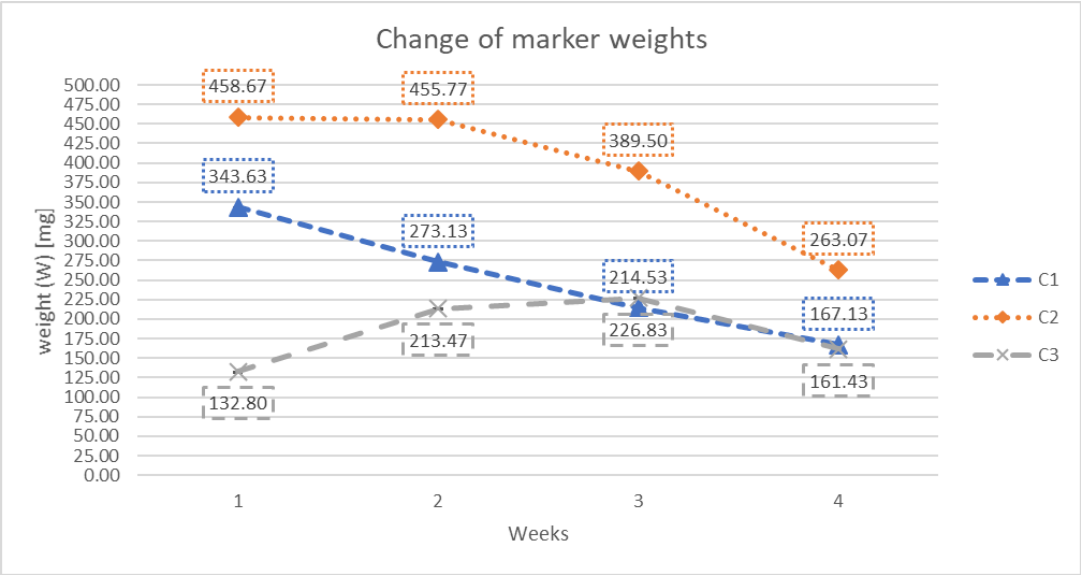

Figure 15. Change of MBM weights over the four-week degradation study.

Each sample of the respective MBM concentrations tested was averaged and reported in Figure 15 over four weeks. From initial weight measurements, it was found that C2>C1>C3. This was due to C2 being able to pack more of the PLGA:IONP material into the mold seen in Figures 10 & 11, which resulted in a heavier MBM than C1 & C3. For C1, the group saw a linear decrease in the weight while C2 showed a consistent bulk release of weight over weeks 2 and 3. However, for C3, the group saw an initial uptake in the weight of the marker followed by a bulk release at week 3. This can be attributed to the PLGA absorbing water into the MBM until hydrolysis degrades most PLGA.

Degradation Study – Proximity Testing

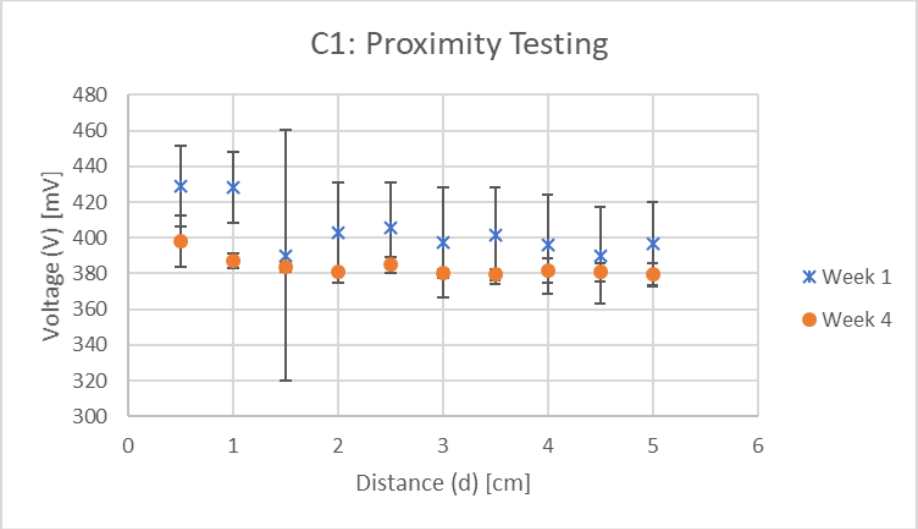

Figure 16. MBM C1 proximity testing over four-week degradation study. Only weeks 1 and 4 were reported due to a low battery during weeks two and three.

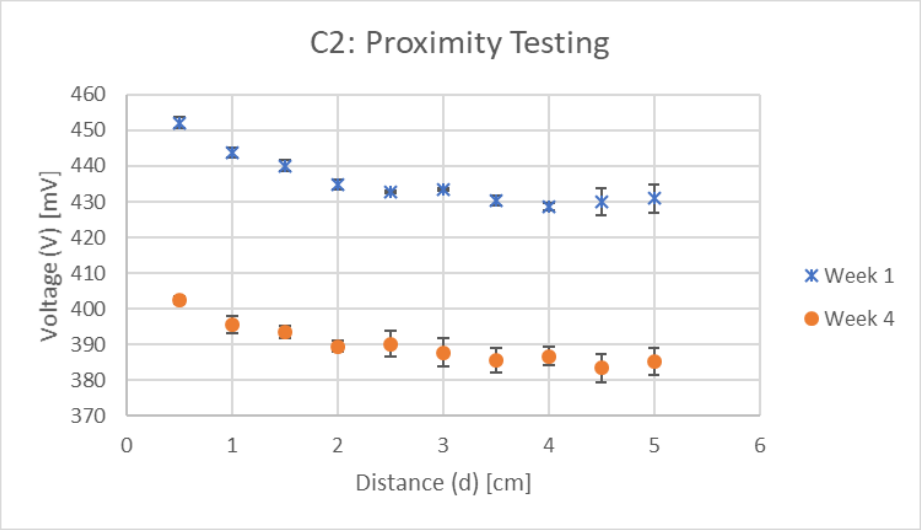

Figure 17. MBM C2 proximity testing over four-week degradation study. Only weeks 1 and 4 were reported due to a low battery during weeks two and three.

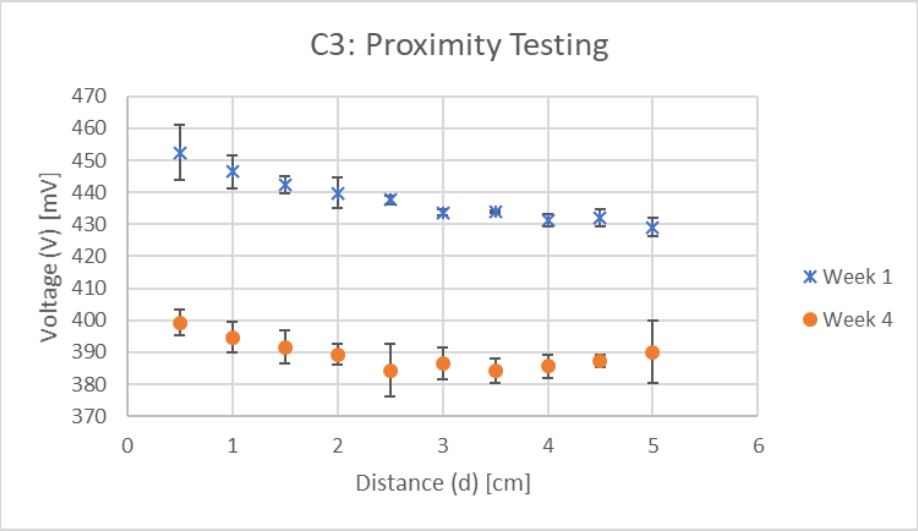

Figure 18. MBM C3 proximity testing over a four-week degradation study. Only week 1 and 4 were reported due to a low battery during weeks two and three.

For MBM C1, we see a decrease in voltage response from week 1 to week 4. Additionally, it can be seen that the voltage attenuates with distance from the MBM. The data obtained from C1's proximity presented a higher variance than what is seen in Figures 16 and 17. This can be attributed to the movement of the harbor freight metal detector while attempting to collect results. After this initial trial, it was noted that a better connection between the oscilloscope and metal detector was needed. After this adjustment, the variance was reduced throughout the rest of the proximity testing for the remaining samples.

MBM C2 showed a significant decrease in voltage response from weeks one and four, with slight variance reported.

MBM C3, similar to C1 and C2, shows the voltage attenuates with distance while also showing a decrease in voltage between weeks one and four. Variance in this data set can be attributed to the movement of the harbor freight metal detector while recording data.

Degradation Study – Release of IONPs

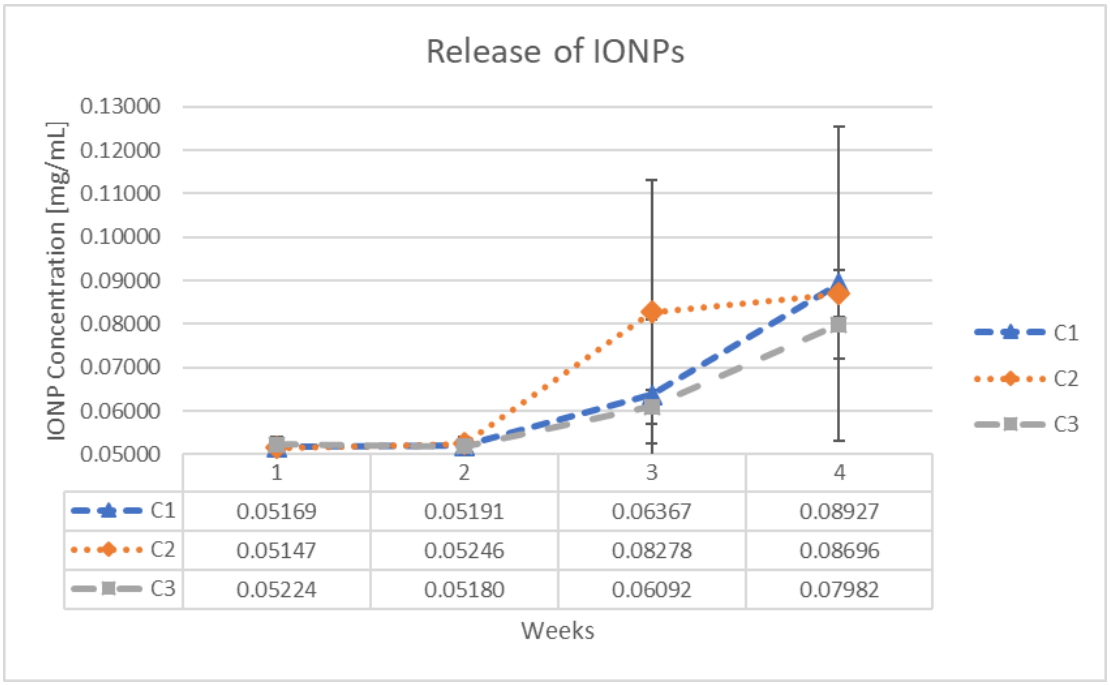

Figure 19. Measured release of IONPs into the PBS media over the four-week degradation study.

From the literature, it is deemed that a concentration of IONPs up to 0.1 mg/mL is deemed non-toxic in the body. For each of the MBM concentrations tested, the PBS media collected from each week was shown to remain below this recommended non-toxic level. MBMs C1 and C3 gradually increased IONPs over weeks two and four. Meanwhile, in MBM C2, we see a bulk release of IONPs in week three. These results reflect similarly to the MBM weight change as the group saw a bulk release of the C2 at week two and three seen in figure 16. With these results, variances increased in the data at weeks three and four. This can be attributed to inconsistent pipetting of the PBS media out of the 15-mL centrifuge tube. Over-pipetting resulted in small portions of the MBM being drawn into the pipette.

Degradation Study – Change of pH

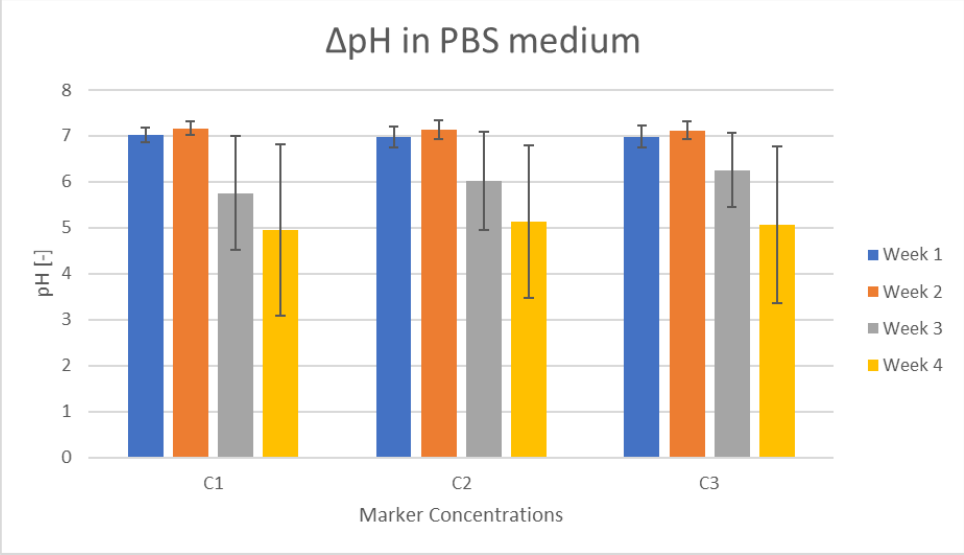

Figure 20. Change of PBS media over a four-week degradation study.

From the data collected, each of the MBM concentrations followed the same pattern. In more detail, we see C1 during weeks three and four having lower pH values than C2 and C3, which is what we would expect since PLGA contributes to the change in pH. MBM C2 and C3 have higher ratios of PLGA than that of C1. Additionally, similar to Figure 20, variance increases during weeks three and four due to over-pipetting of the PBS media and drawing up bits of the MBM.

Degradation Study – SEM Surface Characterization

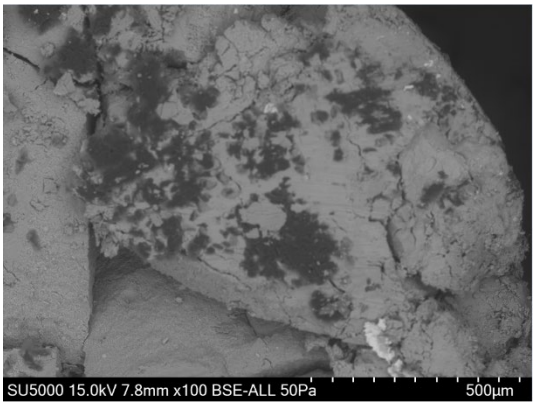

Figure 21. Week one of SEM imaging of prepared MBM samples.

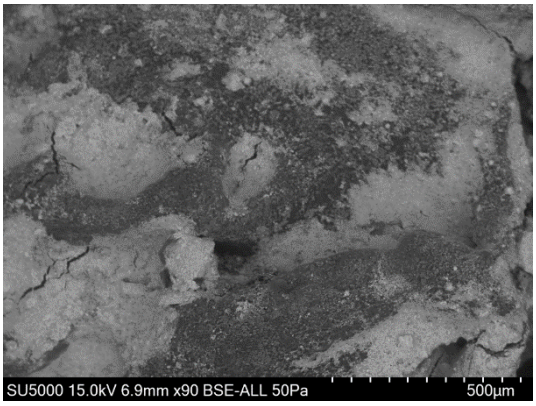

Figure 22. Week three of SEM imaging of prepared MBM samples.

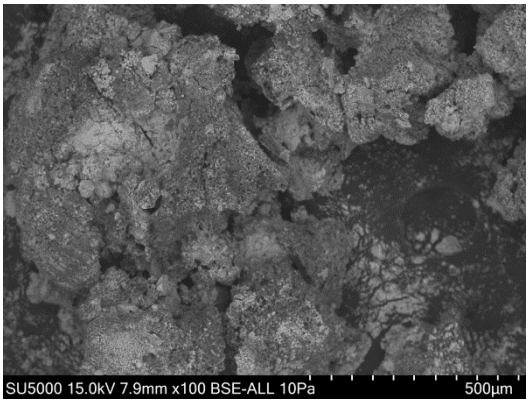

Figure 23. Week four of SEM imaging of prepared MBM samples.

In figure 21 the dark artifacts signify PLGA while the lighter ones signify IONPs. Figure 21 shows an ununiform mixture of PLGA:IONPs with IONPs being the predominant material in the image. The surface is flat and compact, and no erosion can be seen.

From week one to week three, the surface morphology becomes more eroded while a more significant presence of PLGA is exposed as the IONPs and PLGA are degraded. Spherical air bubbles can also be seen in Figures 22 and 23 due to the mixing process during the fabrication of the MBMs.

Finally, figure 23 shows the further surface erosion of the MBM sample. The surface appears to have more porous pits than in Figures 21-22.

COMSOL Multiphysics Localization Optimization

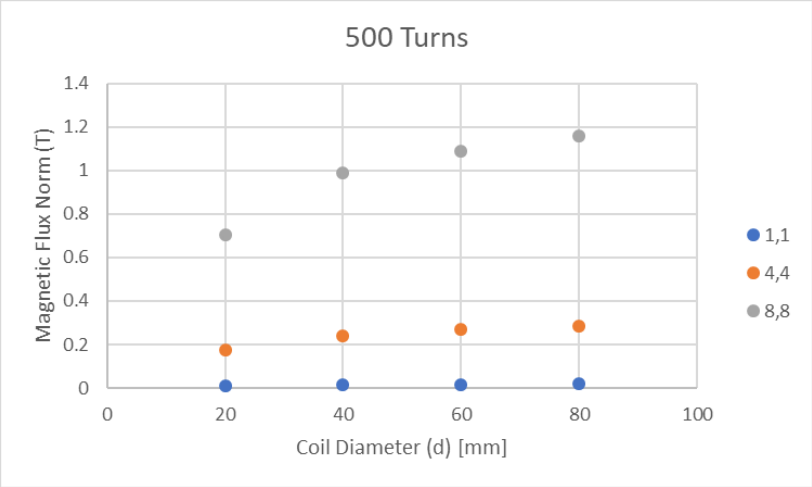

Figure 24. 2-D COMSOL simulation testing with Transmit/Receive Coil Turns at 500 while performing parametric sweep with current, coil diameter, and coil layers. The legend reports the unique layer, and current combinations tested.

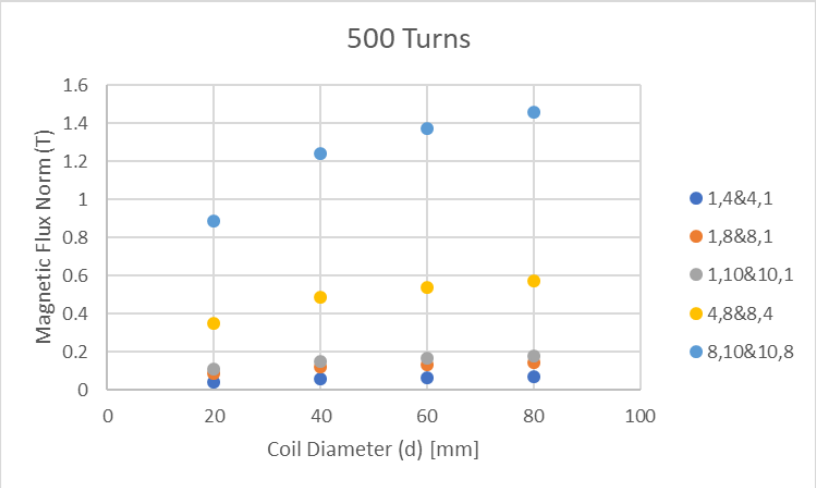

Figure 25. 2-D COMSOL simulation testing with Transmit/Receive Coil Turns at 500 while performing parametric sweep with current, coil diameter, and coil layers. The legend reports the common layer, and current combinations tested.

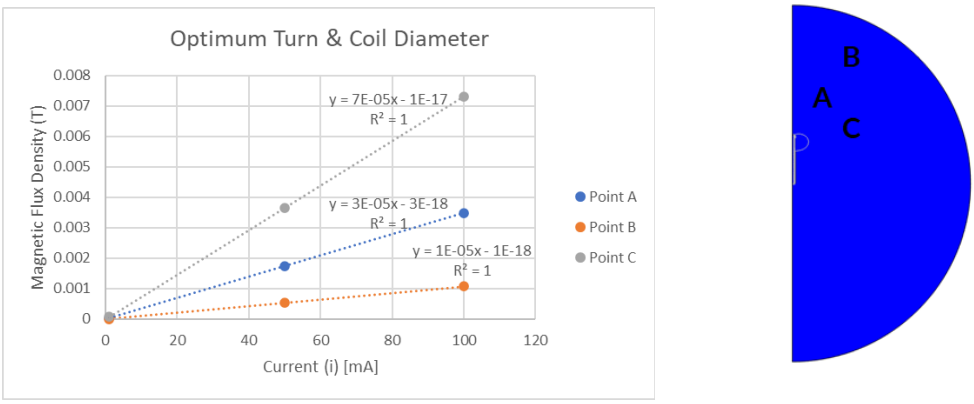

Figure 26. 2-D COMSOL simulation testing with optimum turn and coil diameter while performing parametric sweep with current.

Figure 27. Localization system parameters and total coil diagram were shared with Woodruff Scientific.

The COMSOL Multiphysics packet was a difficult portion of this entire study. Based on the recommendations and developments of Scott Slaney's localization system, the group wanted to establish the optimum parameters for creating a double-coupled coil system to detect the Eddie currents induced in the MBM. Due to the localization system needing to fit within a 2.5 cm incision, the group was able to test various arrangements of coil layer, coil winding, ferrous core radius, and current that would fit within the parameters given. From the initial study, figures 24 and 25, the group knew that any turn more significant than 500 would create a shaft of the localization system that was too long. With the parametric sweep performed, we see that each of the conditions tested gives a linear response as you increase the ferrous core diameter. We also saw that the magnetic flux norm increased as you increased the layers and current. Figures 24 and 25 show that some values achieved magnetic fluxes greater than 0.5 T. These possible parameter combinations were excluded due to their high strength, as an MRI machine typically generates 0.5-1.5 T. A much lower magnetic flux must be achieved for our application to place it safely in the body. From these simulations, the group also found that in Figure 25, common layers and current combinations reported the same data. This also allowed the group to eliminate possible combinations further, as the common combination that could fit within the 2.5 cm incision while achieving a magnetic flux less than 0.5 T needed further evaluation.

The second portion of the COMSOL simulation study focused on taking the parameters we found feasible in the first study and determining what practical current would give us a safe magnetic flux density when the Eddie currents are induced in three separate markers at different points, as seen in Figure 26. The group could see that the magnetic flux density remained safe for all the currents tested at each of the three points. These parameters were then shared with Woodruff Scientific to validate the work done in the COMSOL study, as seen in Figure 27. Appendix B includes a complete summary of Woodruff's Scientific work and findings. They found that the inductive voltage established would not be able to be supported by the wire gauge we gave them. They suggested that a thicker wire gauge, fewer layers and a smaller ferrous core would be able to achieve our goal.

Alternative Methods for Localization

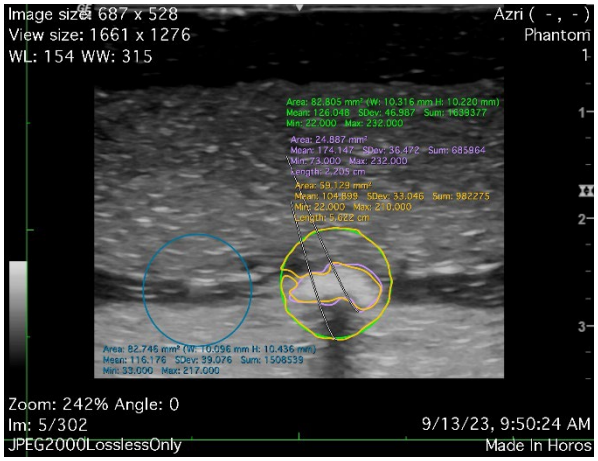

Figure 28. Ultrasound Image of breast tissue model taken from the bottom of the mold with little compression applied.

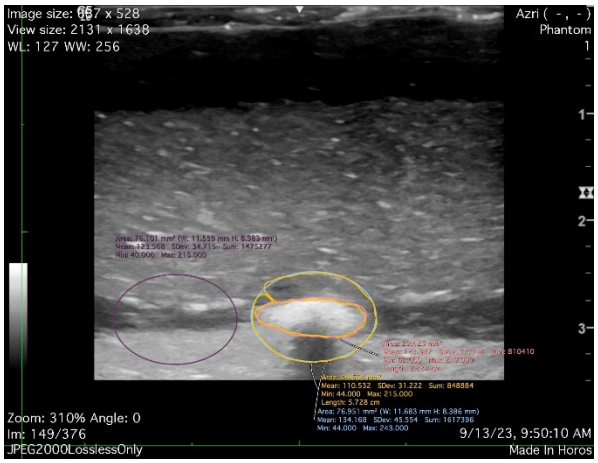

Figure 29. An ultrasound image of the breast tissue model was taken from the bottom of the mold with compression applied.

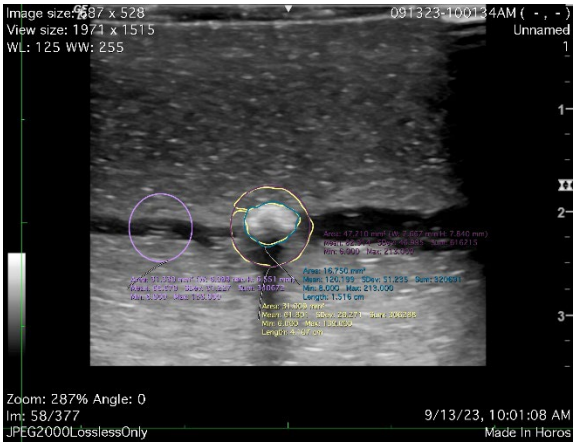

Figure 30. An ultrasound image of the breast tissue model was taken from the top of the mold with no compression applied.

Visualization of the MBM under ultrasound was successful. In Figure 29, the group was able to visualize the MBM along its longest side from the bottom of the mold, and it can be seen that it is at a depth of 3 cm. With Figure 30, the ultrasound technician then applied mild pressure to the mold to get a better visual image of the marker from its longest side from the bottom view. The MBM can still be seen at a depth of around 3 cm. Lastly, the ultrasound technician flipped the mold over, imaged it from the top down, and was able to visualize the face of the marker at 2 cm of depth from the top, figure 30.

CONCLUSION

Since the 1970s, wire-guided localization has been the gold standard in preoperative imaging of breast cancer biopsy markers. This procedure continuously results in a painful and traumatic experience for patients. At the same time, physicians face the logistical inefficiencies of scheduling an imaging suite and operating room on the day of or before the lumpectomy. In conjunction with the rise of concerns, the increase in mammogram screenings has resulted in wire-free localization systems being introduced into the current market. Many of these solutions do present advantages over wire-guided localization but have their drawbacks that slow the introduction of these novel systems into healthcare facilities. The main disadvantage of these novel wire-free localization is that if a patient receives a benign biopsy diagnosis, these wire-free localization system markers will remain in their body indefinitely. Patients may still have anxiety and concern about the long-term effects of the marker in their body.

The McCullough Biopsy Marker and localization system will be a novel-wire-free localization system that can be implanted thirty days before the operation and localized using ultrasound, MRI, or the developed localization system. Lastly, the McCullough Biopsy marker will allow for nonpermanent placement as it degrades naturally throughout the body. This study evaluated and determined the optimum ratio for the McCullough Biopsy marker to be composed of a 50:50 ratio of PLGA:IONPs. It was recommended that a more extended degradation period for the marker could be achieved by utilizing PLGA with a 75:25 ratio of L:G or using L-PLGA. It was also recommended that the shape of the marker be adjusted to a T-shape to increase the surface area,

decrease the adsorption rate, and keep the marker from migrating and having a bulk release.[5] An alternative marker shape can be achieved by creating a silicone mold, placing the prepared PLGA:IONP solution under vacuum for 24 hours, and then removing the marker from the mold. A specialized deployment system would additionally need to be created to fit the new marker shape. To increase the uniformity of the MBM it has been suggested to use a homogenizer this however could increase the presence of spherical bubbles which could be advantageous for ultrasound imaging. Lastly, utilizing the L/D chirality of Poly Lactic Acid (PLA) will allow for a more lengthened degradation time and increase the MBM's porosity internally and externally. The increased surface area will allow the marker to degrade internally and externally more uniformly, decreasing the chances of a bulk release.

The localization system designed and described by Scott Slaney and optimized in this study will be able to be fully developed with the assistance of Woodruff Scientific if collaborators at MUSC and CURF determine it to be a financially solvent strategy to finalize patenting the novel technology. The McCullough Biopsy Marker's ability to be imaged with several modalities allows it to be a potential patented and novel technology alone. Further validation should be done with MRI and ultrasound imaging utilizing tissue phantoms that mimic soft and dense tissue. A small-scale animal study should also be conducted to evaluate how the McCullough Biopsy Marker interacts subcutaneously and in tissue.[9] If ultrasound imaging is deemed superior to the methods of localization for the MBM, developing a uniaxial handheld ultrasound probe or ultrasonic range finder that can fit within the 2.5cm incision site should be explored as a possible option.

Overall, this study has further developed a nonpermanent primary marker and localization system, eliminating the need for preoperative imaging and wire localization while easing patients' and physicians' anxieties, discomfort, and frustrations.

REFERENCES

1. Szynglarewicz, B., Dołęga-Kozierowski, B., Szulc, R., Kasprzak, P., & Matkowski, R. (2021). Identification of a localization wire tip in an occult breast lesion using a handheld magnetometer. Advances in Clinical and Experimental Medicine, 30(3), 273–278. https://doi.org/10.17219/ACEM/131751
2. Kolak, A., Kamińska, M., Sygit, K., Budny, A., Surdyka, D., Kukiełka-Budny, B., & Burdan, F. (2017). Primary and secondary prevention of breast cancer. Annals of Agricultural and Environmental Medicine, 24(4), 549–553. https://doi.org/10.26444/aaem/75943
3. Akram, M., Iqbal, M., Daniyal, M., & Khan, A. U. (2017). Awareness and current knowledge of breast cancer. In Biological Research (Vol. 50, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s40659-017-0140-9
4. Scarth, H., et al. (2002). Clinical practice guidelines for the care and treatment of breast cancer: Mastectomy or lumpectomy? The choice of operation for clinical stages I and II breast cancer (summary of the 2002 update). CMAJ, 167(2), 154-155.
5. Funaro, K., Prather, A., Niell, B., & Jared Weinfurtner, R. (2020). Tissue marker migration after MRI-guided breast biopsy: Migration frequency and associated factors. Breast Journal, 26(3), 440–445. https://doi.org/10.1111/tbj.13486
6. Martaindale, S., Scoggins, M., Bassett, R. L., & Whitman, G. (2022). Retained Localization Wire Fragments in the Breast: Long-term Follow-up. Current

Problems in Diagnostic Radiology, 51(3), 313–316. https://doi.org/10.1067/j.cpradiol.2021.03.015

7. Norman, C., Lafaurie, G., Uhercik, M., Kasem, A., & Sinha, P. (2021). Novel wire-free techniques for localization of impalpable breast lesions—A review of current options. Breast Journal, 27(2), 141–148. https://doi.org/10.1111/tbj.14146
8. Slaney, S., et al. (2019). “Development of a breast tissue marker and localization system.” Clemson University.
9. Haim Zada, M., Gallimidi, Z., Schlesinger-Laufer, M., Nyska, A., & Domb, A. J. (2020). Biodegradable Breast Tissue Marker Clip. ACS Applied Bio Materials, 3(11), 7439–7453. https://doi.org/10.1021/acsabm.0c00655

APPENDICES

Appendix A: Scott Slaney Thesis

https://clemson.box.com/s/zujimb9t2bykwqs2jnbe40mbxwe4kwov

Appendix B: COMSOL Simulation Data

https://clemson.box.com/s/3nzq12fu9rd8v5cpqxngfmaeimi0wsld

Appendix C: Ultrasound Imaging Protocol

https://clemson.box.com/s/u1wcudnhanevfbn46vwuo4rqq6gqozlm