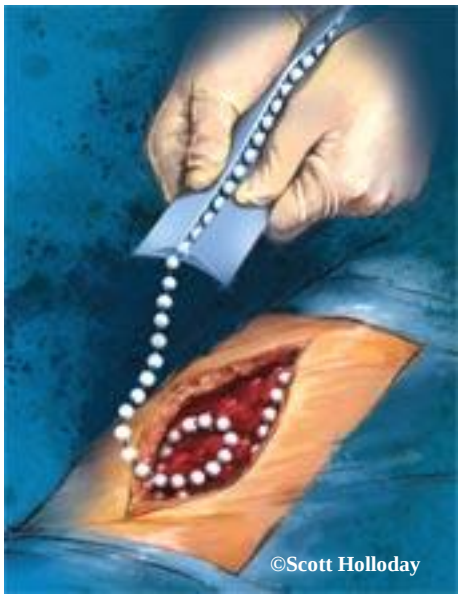
Modeling of Antibiotic Diffusion from Implanted Absorbable Beads in Localized Injured Tissue



BEE 4530: Computer Aided Engineering in Biomedical Processes

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SECTION I: EXECUTIVE SUMMARY

Prevention of infection during the healing process in tissue is a major concern and is especially crucial for the health of the patient. In order to combat infection due to bacteria, antibiotics must be deployed in the tissue at a high enough concentration for a long enough period of time in order to be deemed effective. Historically, systemic antibiotics have been administered to diminish the threat of infection, either through intravenous injection or oral ingestion. However, toxicity levels of the drug in the entire body must be taken account, lowering the efficacy of systemic antibiotics. Implanted antibiotic beads provide an attractive alternative by locally administering the antibiotics to the injured soft tissue, allowing higher concentrations of antibiotics to be delivered over a longer period of time, thus increasing the efficacy and safety of the drug. Although these beads must be physically placed into the injured soft tissue, a string of them can easily be implanted as the last step of surgery as a protective measure against future infections.

The goal of this project is to model the delivery of vancomycin-impregnated biodegradable antibiotic beads as the vancomycin diffuses into the injured soft tissue.
We constructed the model using 2D-axisymmetric geometry in COMSOL. Our bead was comprised of two separate layers, one made of Polylactic Acid containing the initial drug concentration of vancomycin of 12.9 mol/m^3, and an outer layer of Polylactide-Polyglycolide Copolymer (PLA-PL:CG), containing no vancomycin.

We successfully modeled the shrinking of the biodegradable bead and were able to get results that agreed with other experimental data. These results included collecting data for concentrations of vancomycin in the tissue over time and space. For vancomycin to be successful in fighting infection, the concentration needs to be above the minimum effective level while remaining below the toxic level. Using these requirements, we determined the optimal spacing between multiple beads to be 0.56cm.

Our model can be used in place of experimentation to determine the optimal combination of parameters that meet a patient's needs. This model allows estimation of concentration profiles in the tissue that would otherwise be difficult to gather in an experimental setting. Therefore, our model can be used as a tool for physicians to better prevent infection in traumatic injuries and surgeries.

Key words: *antibiotic bead implants, vancomycin treatment, PLA bead, PLA-PL:CG polymer coating, antibiotic diffusion*

SECTION II: INTRODUCTION AND BACKGROUND

2.1 Introduction and Background

Open Wound Surgery and Infection

During open wound surgery, the prevention of wound site infection is paramount to the healing and recovery process of injured soft tissue. Bacteria residing in the dead space of tissue debridement present the biggest threat of infection in the healing tissue. Consequently, significant preventative measures must be taken. Otherwise, infections may cause complications such as prolonged hospital stays, increased rehabilitation periods, repeated debridements, morbidity, and mortality (Edwards, et al 2008, 770-777). Although advances in aseptic and sterilization technologies have vastly diminished the threat of infection, the prevention of infection still remains a significant issue in patient health.

Staphyloccocus aureus is the gram-positive bacteria most commonly found to cause infections during and after open would surgery. *S. aureus* is normally found living on human skin, but can be life-threatening to the patient (Kluytmans, et al 1997, 505-520). when entering the body through the wound site. In a study done by Khan et al., it was determined that *S. aureus* was the main causative bacterial agent in infection during open wound surgery at least 50% of the time (Khan, et al 2008, 23-25). Therefore antibiotic treatment against *S. aureus* would likely be sufficient in preventing most bacterial infections. Vancomycin, an antibiotic effective against gram-positive bacteria, could therefore be an effective treatment for infections resulting from surgery or traumatic injuries.

Antibiotic Bead Implants

Systemic antibiotics are normally used for treatment against bacterial infection after open wound surgery. These can be administered intravenously or orally. However, intravenous injection can be seen as invasive or tedious because of repetitive injections, while oral administration of antibiotics often yields unpredictable concentrations. Because systemic drugs circulate throughout the entire body, there is a risk of reaching toxic levels in the kidney. Antibiotic bead implants provide an attractive alternative to systemic antibiotics by supplying a prolonged, controlled release of antibiotics over longer periods of time. Antibiotic beads also supply drug to localized tissue, increasing the effective amount of antibiotics reaching the injury site while avoiding the risk of kidney toxicity. Biodegradable beads also resorb slowly into the body, eliminating the need for secondary surgery for bead removal (Liu, et al 2002, 807-813). As shown in Figure 1, multiple antibiotic beads can be strung together and placed inside the wound site during the open wound surgery.

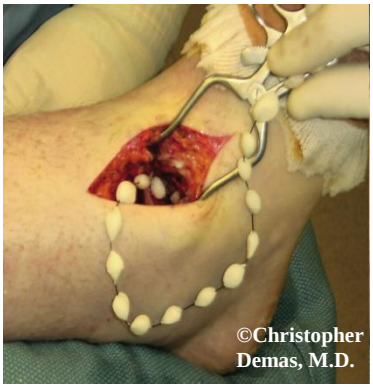

Figure 1. *Insertion of multiple antibiotic beads during open wound surgery*

2.2 Design Objectives

Due to the unpredictable behavior of drugs in the body, accurate modeling of the diffusion of vancomycin in the injured tissue is necessary before surgery. Modeling can reduce the need for experimentation while also providing more insight into the diffusion process. To avoid reaching toxic drug levels while still maintaining minimum effective concentrations in the tissue, we need to consider spatial and transient concentration profiles. Therefore, we plan to:

1) Model the diffusion of vancomycin out of the bead into the injured soft tissue
2) Determine the effective time period and diffusion distance of the drug
3) Model the physical shrinking of the antibiotic bead over time
4) Determine the optimal spacing between beads
5) Validate our model using published experimental data

2.3 Problem Schematic

We used COMSOL Multiphysics software to model the diffusion of vancomycin into the tissue over time. Because the shape of our antibiotic bead is spherical, we used 2D-axisymmetric geometry. The rotational symmetry of the bead allowed us to simplify the model to include only a quarter of the sphere. Our antibiotic bead model was comprised of two separate layers; the inner layer was made of PLA and the outer layer (polymer coating) was made of PLA-PL:CG. Only the inner layer contained an initial drug concentration.

As shown in Figure 2, we modeled the bead with an inner radius of 4mm and an outer polymer coating layer with a thickness of 1mm. Surrounding the bead is a region of soft tissue that extends 1cm from the center of the bead, which is sufficiently large to model the entire concentration behavior of the vancomycin diffusion in the tissue. As indicated on the schematic, the bead and polymer coating shrink over time.

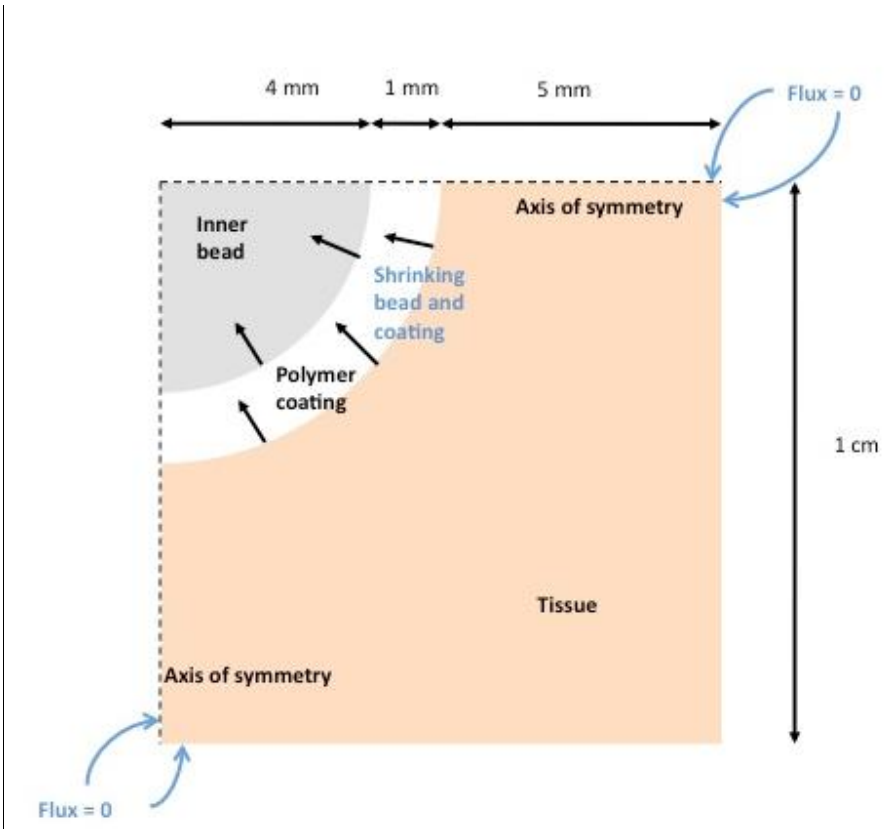

Figure 2. *Problem schematic of vancomycin bead in tissue*

The top and left boundaries have a mass transfer flux of zero due to symmetry. The right and bottom boundaries also have a mass transfer flux of zero, because they can be considered at a far enough distance where the drug never reaches the boundary. The initial inner bead concentration is 12.9mol/m^3. The concentration of vancomycin in the tissue was also assumed to be zero initially.

We used this schematic, along with the appropriate governing equations, as the basis for our COMSOL model.

2.4 Governing Equations

The governing equation for the antibiotic bead model is the generalized mass transfer governing equation in cylindrical coordinates without the convection term. Cylindrical coordinates are required for this problem because we needed two dimensions for a moving boundary in COMSOL. The convection term is omitted as there is no flow present in our model. Because COMSOL uses a finite mesh and the software does not allow mesh to disappear over time, the shrinking of the bead is modeled as a moving boundary. The governing equation is:

$$\frac{\partial c_A}{\partial t} = D_{AT}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_A}{\partial r}\right) + \frac{\partial^2 c_A}{\partial z^2}\right) - R \qquad (1)$$

The diffusion of vancomycin in the tissue needs to also include a clearance term to account for metabolic degradation and removal of vancomycin due to blood flow (not to be confused with convective flow). In order to account for this behavior, clearance of vancomycin is modeled as a first-order reaction based on the half-life of vancomycin, which has been adapted from the vancomycin microcapsule elution model done by Pettiti et al (Pettiti 2009, 859-866).

$$\boldsymbol{R = k\left[\frac{1}{s}\right] * c\left[\frac{mol}{m^3}\right]} \quad (2)$$

$$\boldsymbol{k = \frac{\ln(2)}{t_{1/2}}} \quad (3)$$

R is the clearance term, k is the rate constant, and $t_{1/2}$ is the half-life of vancomycin (Ducharme, et al 1994, 513-518).

2.5 Model Design and Conditions

As stated earlier, the physical geometry of the bead shrinks over time as the vancomycin diffuses into the tissue. We used a moving boundary to account for the disappearance of the outer layer by having the bead boundary shrink at a constant velocity up to a certain point in time. The mesh of the outer layer cannot completely disappear, so once the shrinking outer layer has nearly reached the inner bead, the region that was designated as the outer layer was then given the properties of the surrounding tissue. At this time, the inner bead began to shrink at a constant velocity, although different from that of the outer layer. We also included the regrowth of tissue to account for the shrinking of the bead over time. See Appendix A for numerical values and calculations of parameters. Our shrinkage and tissue growth values were based on previous experimental data using vancomycin antibiotic beads (Mader, et al 1997, 415-418). The minimum effective concentration of vancomycin for antibacterial activity is $0.0021 mol/m^3$ (Hook 1978, 411-415). The maximum concentration of vancomycin before reaching toxic levels is $0.4 mol/m^3$ (Edin, et al 1996, 245-251). All other parameters involved in the solving of the model are detailed in Appendix A.

We made some simplifying assumptions for the model. These included uniform and constant tissue and bead properties and perfect spherical geometry of the bead. The string connecting the beads was also considered negligible. The shrinkage velocities of the bead layers were assumed to be constant. Finally, the input parameters were estimates from experimental data collected from literature (Mader, et al 1997, 415-418), (Ducharme, et al 1994, 513-518), (Hook 1978, 411-415).

SECTION III: RESULTS AND DISCUSSION

3.1 Modeling Vancomycin Concentration Profile

We modeled the concentration profile of the vancomycin bead using the above schematic and listed parameters. In COMSOL, we constructed the schematic using an unstructured fine mesh. See Appendix C for mesh convergence analysis. We ran the simulation for a total of 28 days at a time step of 1 hour which closely approximates the entire healing process of tissue recovery after surgery. Figure 3 shows a surface plot of the vancomycin concentration in the tissue after the full 28 day treatment with the vancomycin bead.

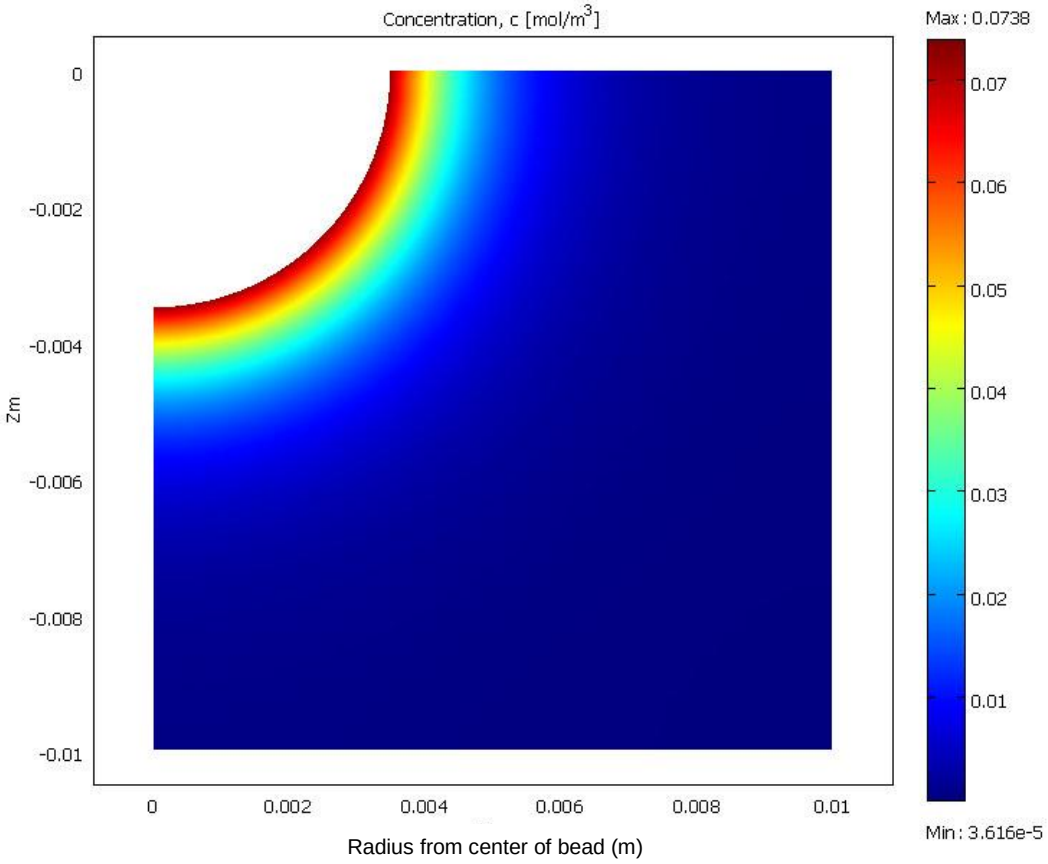

Figure 3. *Surface plot concentration profile of vancomycin diffusion only in soft tissue after 28 day treatment*

Analysis of the surface plot confirms that concentration levels of vancomycin are in fact above the minimal effective level well outside the radius of the bead in the tissue region. Once the model was confirmed to deliver sufficient concentrations of vancomycin to the surrounding tissue region, we analyzed how the diffusion of vancomycin into the tissue changed over time.

3.2 Analysis of Vancomycin Diffusion as a Function of Distance

For our model to be deemed successful, the concentration of vancomycin in the tissue must remain below the toxic level while remaining above the minimal effective level. A concentration profile for vancomycin over an increasing radial distance from the bead was plotted for several weeks. Figure 4 shows a relatively constant concentration behavior curve for one to four weeks of vancomycin treatment. The vancomycin concentration decreases as the radial distance from the bead increases. As expected, the concentration of vancomycin in the tissue gradually decreases over the treatment span of four weeks.

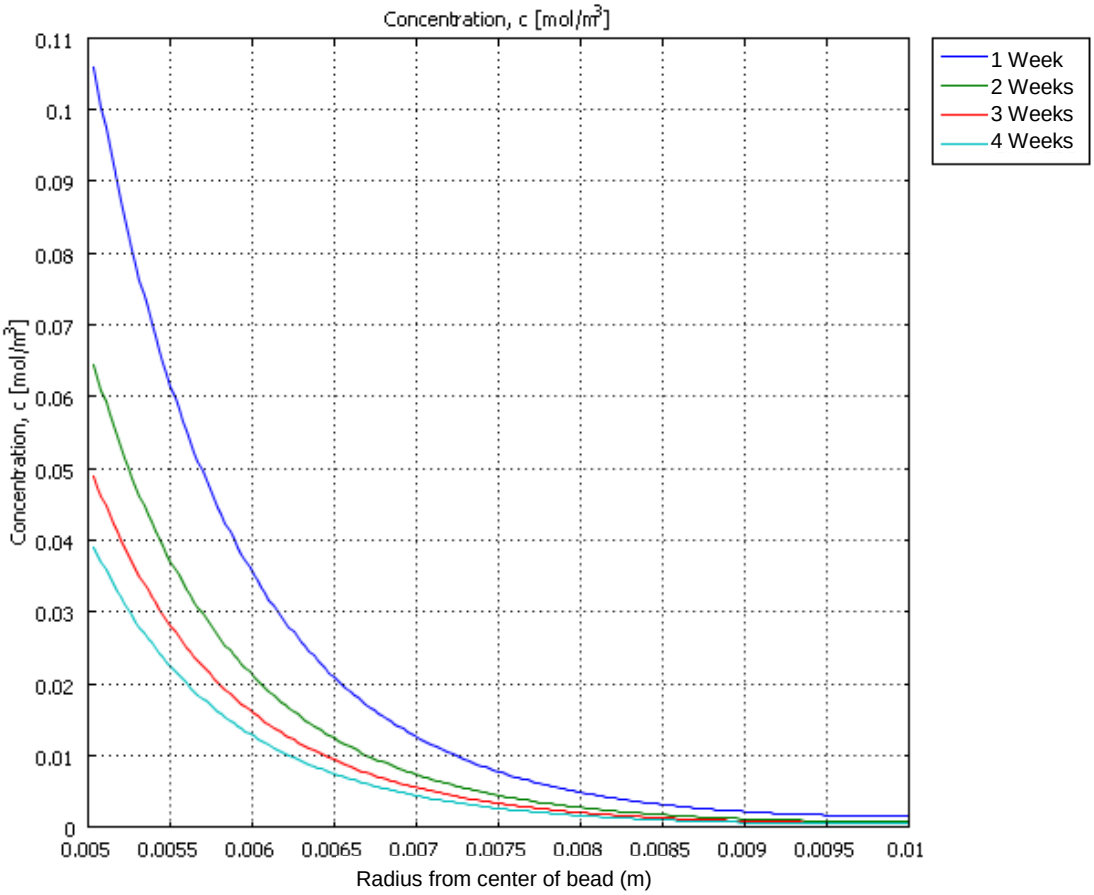

***Figure 4**: Concentration profile of vancomycin over radial distance from the center of the bead (initial bead radius = 5mm) at weekly intervals.*

For all four weeks, the concentration of vancomycin consistently stayed below the toxic level of 0.4mol/m^3 in the tissue. The maximum vancomycin concentration in the tissue was at the bead-tissue interface after one week of treatment, with a value of approximately 0.17mol/m^3. Based on these concentration profiles, we were then able to optimize the bead spacing.

3.3 Optimization of Individual Antibiotic Bead Spacing

Our next step was to determine the optimal amount of spacing between multiple vancomycin beads for placement during surgery. After determining that the toxic level for vancomycin was not reached over the treatment span, our main concern became keeping the vancomycin level in the tissue above the minimum effective level through the fourth week. Figure 5 shows a magnified view of Figure 4, specifically the concentration curves over the range of 7mm to 8.2mm from the bead center. Figure 5 shows that after four weeks, vancomycin concentration in the tissue drops below the minimum effective level of 0.0021mol/m^3 at 2.8mm from the edge of the bead, which is 7.8mm from the center of the bead. At this distance, the concentration drops below the minimum effective level after week four.

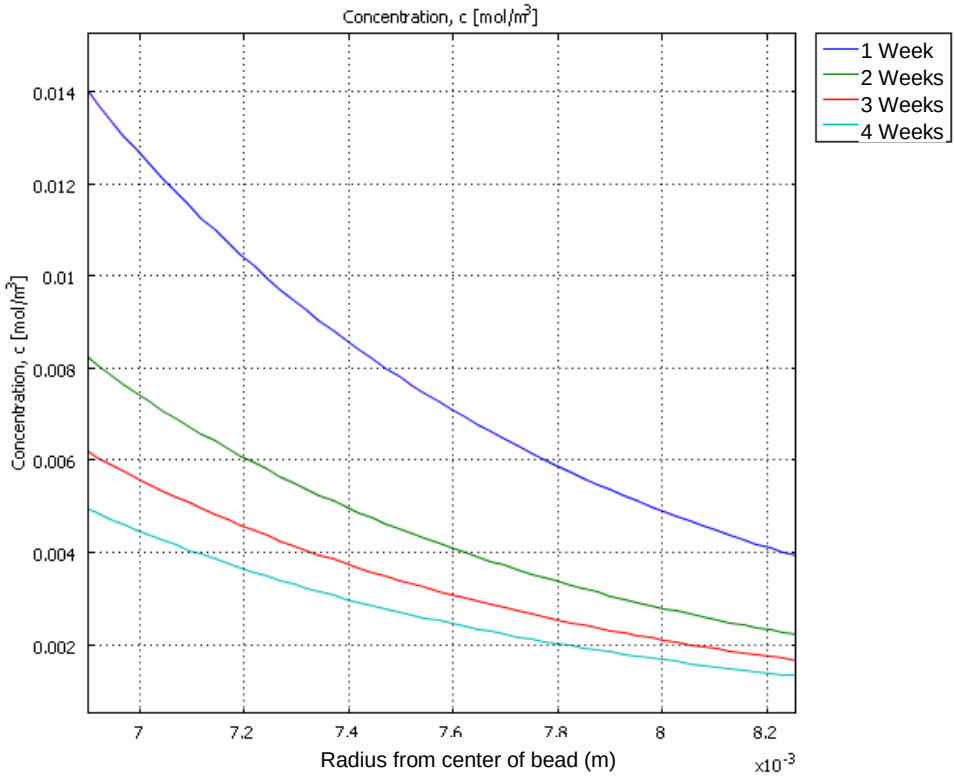

Figure 5: *Concentration profile of vancomycin over radial distance from the center of the bead at weekly intervals.*

Based on this data, the next bead must be placed approximately 0.56cm away from the initial bead in order to ensure that all tissue between the beads has an effective level of vancomycin. If antibiotic treatment requires a longer treatment span than four weeks, a bead with a higher initial concentration would be needed in order to minimize the number of beads needed. Because this plot shows concentrations only at discrete times, we found it necessary to also analyze concentrations as a function of time.

3.4 Analysis of Vancomycin Diffusion as a Function of Time

Analyzing the concentration behavior of vancomycin at specific radial distances from the bead provided a better understanding of the diffusion of the antibiotics. We analyzed the results for the entire duration of treatment rather than at interval weeks. We had to confirm that the concentration of vancomycin remained within the effective range. Therefore, we plotted the concentration of vancomycin over time at the bead tissue interface, at 1 mm from the interface, and at 2.5 mm from the interface. In Figure 6, these locations are represented as points A, B and C, respectively.

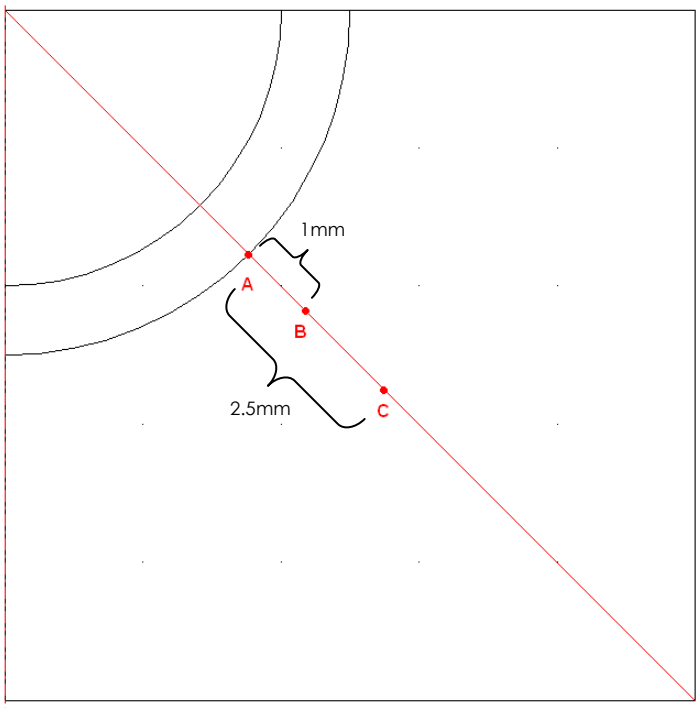

Figure 6: *Depiction of points A, B and C, used for concentration profiles over time.*

Figure 7 shows concentration profiles at the points shown in Figure 6. The three curves in Figure 7 represent the concentrations at the points over the 28 day period. The minimum effective concentration is also depicted on the graph.

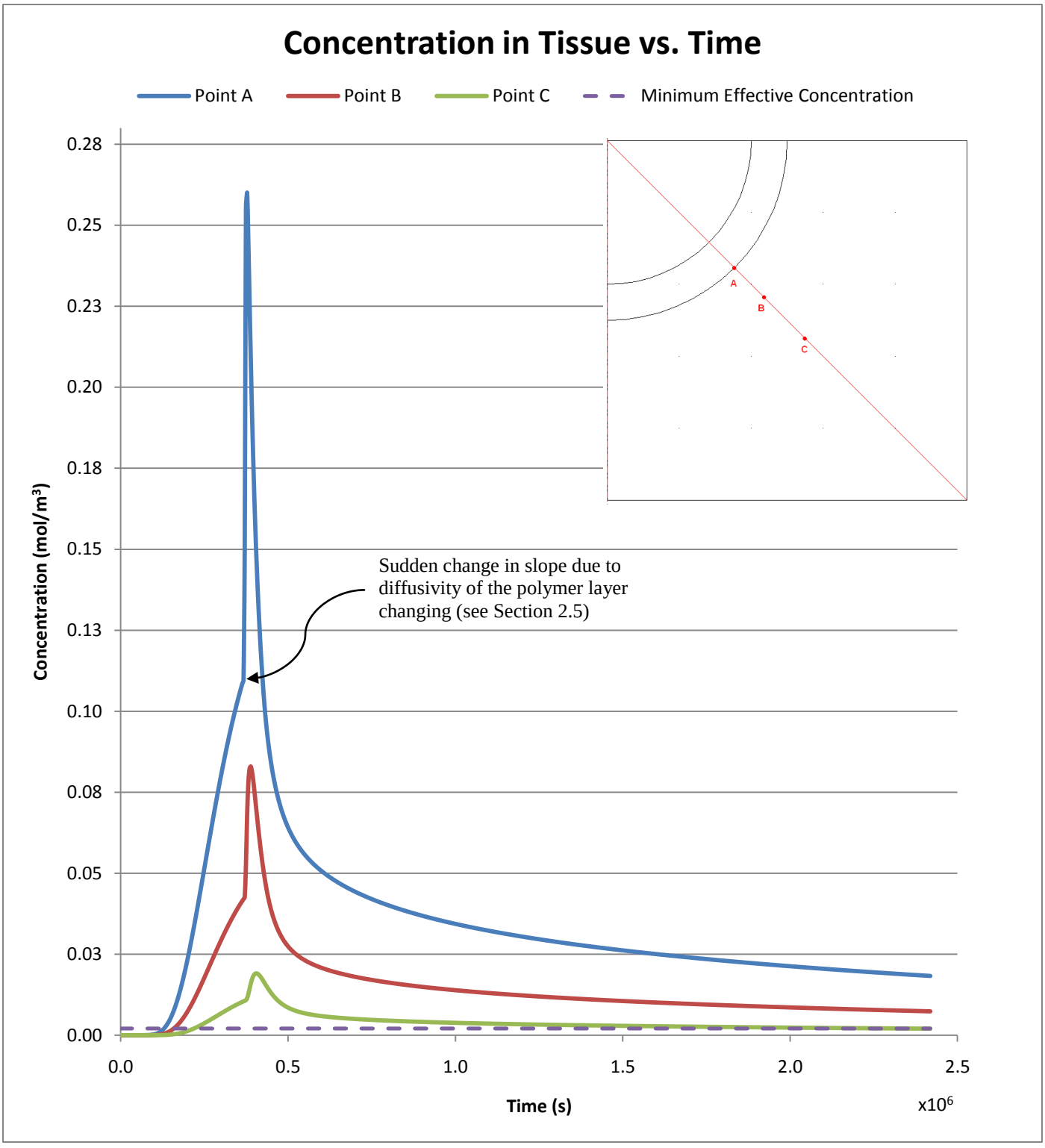

Figure 7: *Concentration over time for Points A, B, and C. Minimum effective concentration, of 0.0021 mol/m^3, is also shown.*

Figure 7 shows that at early times, the drug has yet to diffuse through the polymer layer and reach the tissue. Therefore, the concentration in the tissue is approximately zero for the first few days. At around 4.5 days ($0.4x10^6$s on the graph), the polymer coating is completely dissolved which corresponds to the change in slope of the peak. This slope change is due to the change in diffusivity values, resulting from the way we handled the mesh limitation in COMSOL. This was discussed earlier in Section 2.5. As time increases after this peak, the concentration gradient decreases as more vancomycin diffuses out of the bead and into the tissue. The decrease in concentration gradient of vancomycin combined with the metabolic clearance mentioned earlier causes vancomycin concentration to gradually decrease over time.

The concentration in the tissue remains within the desirable range, $0.0021 mol/m^3$ to $0.4 mol/m^3$, for the duration of the treatment of four weeks. Based on the profiles for these three points, we can assume that all points will have the same concentration profile shape overtime. Therefore, this confirms our solution of 0.56 cm as the optimum spacing between beads.

3.5 Accuracy Check

In order to validate our results, we compared our model to experimental data from literature. An accuracy check is necessary in order to validate the assumptions we used to construct our model. Ueng et al. studied biodegradable alginate antibiotic beads used to deliver vancomycin in rabbits *in vivo* (Ueng, et al 2004, 592-599). This study looks at the concentrations in the femoral bone cavity over time. We used these results to ensure that our assumptions were valid.

We compared our results to that of Ueng et al. by superimposing the concentration curve from this data over our own data, previously depicted in Figure 7. This is presented as the accuracy check curve in Figure 8.

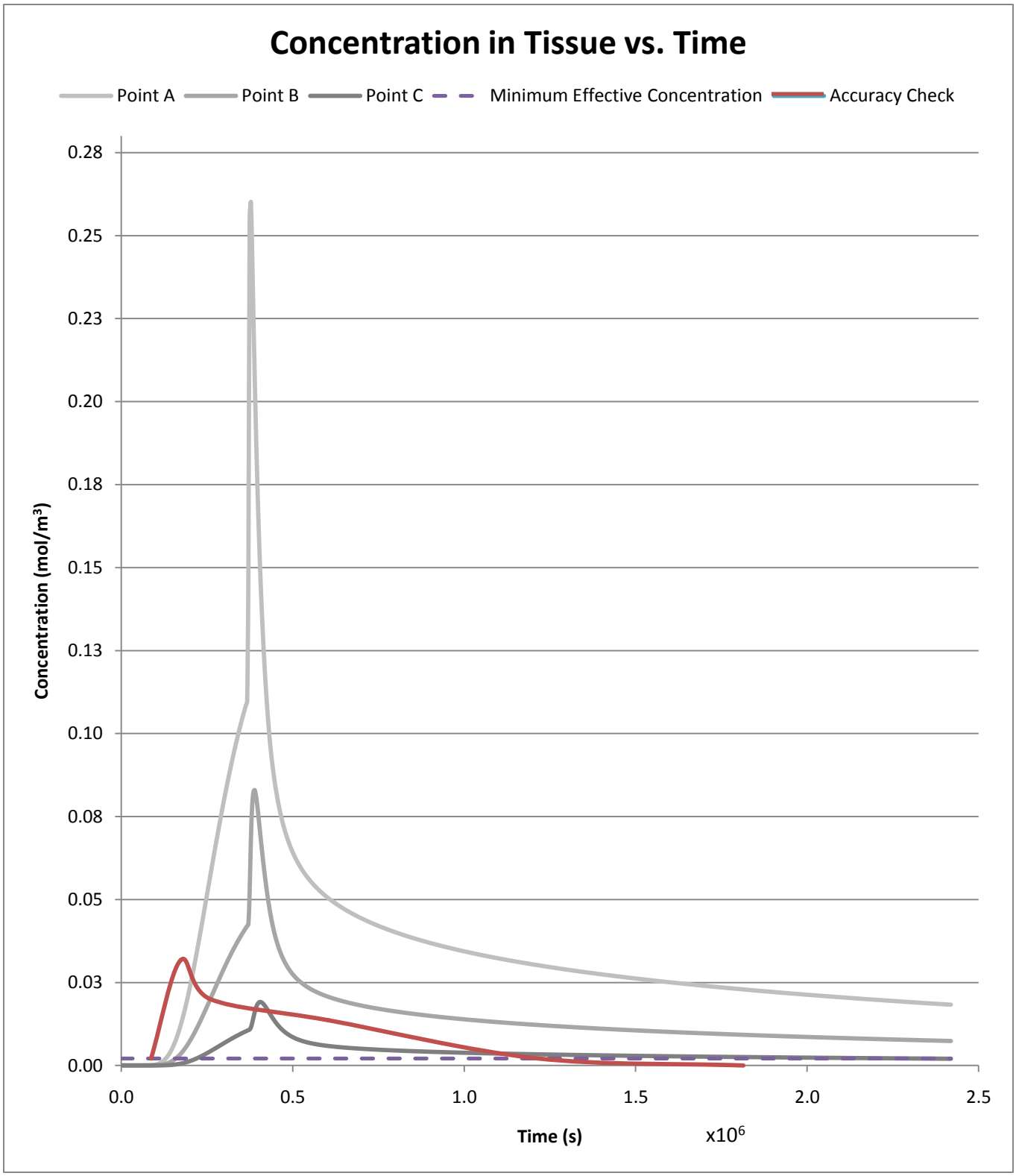

Figure 8. *Result graph with accuracy check data from Ueng et al.*

There are obvious similarities between our COMSOL model and the experimental results. In both data sets, the concentration curve shows a significant rise in concentration, peaking around three or four days (0.25-0.45 x 10^6 s), and then a steady decrease of drug concentration. As shown in Figure 8, the accuracy check curve best resembles the curve for Point C. This makes sense because the concentrations in the study were measured in the bone cavity, not very close to the bead. This corresponds best to Point C because it is at the distance farthest from the bead.

Discrepancies between the experimental set up of Ueng et al. and our model should be noted. Their antibiotic bead design uses poly-L-lysine sodium alginate as their coating layer while we use PLA-PL:CG polymer coating. They used a bead of diameter 3mm, whereas our bead had a diameter of 10mm. This difference may play a role in the concentration behavior over time. Furthermore, instead of placing their antibiotic beads within tissue as we have modeled, Ueng et al. placed them within the femoral bone cavities of rabbits. The femoral cavity in rabbits may have a different effect on vancomycin behavior than would the tissue in humans. All of these discrepancies may contribute to the variation in results.

3.6 Sensitivity Analysis

After we validated our solution with experimental data, it was important for us to determine the parameters that had the largest effect on our results. For our sensitivity analysis, we altered the values of the following parameters by $\pm 5\%$: diffusivity of antibiotics in the bead, diffusivity of antibiotics in the tissue, initial concentration of antibiotics in the bead, and the clearance term for vancomycin. We changed one parameter at a one, while keeping all others the same. We examined the resulting changes at a distance of 6mm from the center of the bead after four weeks.

Figure 9 shows that our simulation is relatively robust in terms of tissue diffusivity and bead diffusivity, but is more sensitive to the initial concentration in the bead and clearance term for vancomycin.

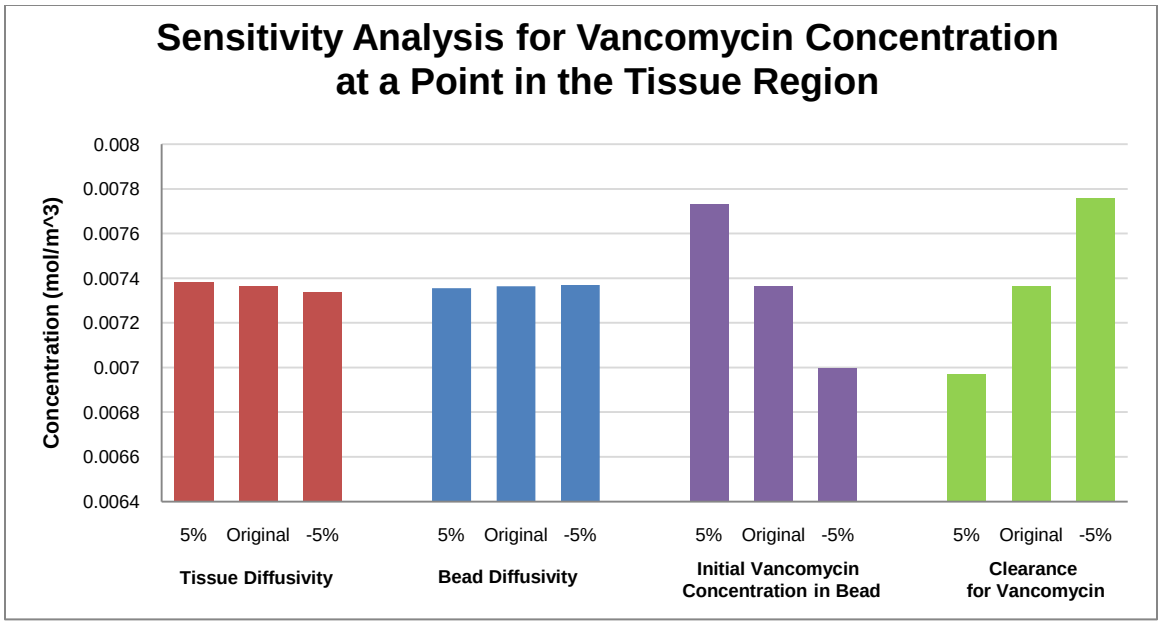

Figure 9: *Sensitivity analysis for selected model parameters*

As shown in Figure 9, each parameter has a different effect on the concentration in the tissue. Changes in tissue diffusivity and bead diffusivity are relatively unimportant. This is reassuring because the exact values of the diffusivities are unknown. On the other hand, the model is very sensitive to initial concentration. This is convenient because it is it is one of the easiest parameters to adjust when manufacturing the beads. There is also a considerable amount of sensitivity in the clearance term for vancomycin. This means that the model is heavily dependent on the half-life of vancomycin in the tissue. Although the clearance term has a significant impact on the results, the half-life can be determined from experimental data, and therefore the clearance term does not compromise the validity of our model.

SECTION IV: CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions and Design Recommendations

We successfully created a model of an antibiotic bead that shrinks and releases antibiotics over time. For our specific model parameters, with an initial concentration of 12.9mol/m^3 in the inner bead, we found concentration profiles over both time and space. This led us to determine the optimal bead spacing of 0.56cm, which allows for effective drug delivery without reaching toxic levels.

From the sensitivity analysis, we learned that the initial concentration of vancomycin in the inner part of the bead and the clearance term are important parameters of the model.

Both affect the final concentration in the tissue and the treatment duration. While the clearance term is patient-dependent and thus unalterable, the initial concentration can easily be changed during manufacturing.

This model can be used by medical professionals to test different properties and parameters and determine the optimal combination of bead materials, drug composition, bead spacing, number of beads, etc., that meets each patient's needs. Our model is flexible enough so that given a specific bead material, the medical professional can alter these other properties and parameters to optimize treatment. We recommend determining the appropriate initial concentration first, then refining the bead design by changing the other properties and parameters.

4.2 Realistic Constraints

Antibiotic beads have been clinically used for over thirty-five years. In 1974, the first antibiotic beads were placed into patients, however these were not absorbable. They were commonly made of polymethyl methacrylate and were required to be removed from the patient after the antibiotics had completely diffused into the surrounding tissue (Freed and Demas 2010). Concerns regarding the use of nonabsorbable beads included the need for a second surgery to remove the bead, potentially harmful foreign body responses, and possible development of antibiotic-resistant organisms (Zalavras, et al 2004, 86-93).

In order to address these issues, absorbable antibiotic beads were developed. These absorbable beads are often made of biodegradable polymers, such Polylactic acid and Polygylcolic acid, mixed with antibiotics, such as vancomycin or tombramycin (Liu, et al 2002, 807-813). Absorbable antibiotics beads are currently being manufactured by companies such as OsteoSet®. Traditionally, the beads are manufactured by hand using molds of specified dimensions. Different materials are used to customize antibiotic beads.

While some of the concerns related to the non-absorbable beads were addressed, other concerns regarding the use of absorbable beads have developed. The consistency of biocompatibility of the beads is a concern, as well as maintaining effective antibiotic concentrations for prolonged periods of time. However, the benefits of using absorbable beads outweigh the possible consequences, thus over the past ten years absorbable beads have mostly replaced the use of nonabsorbable beads.

In comparison to systemic antibiotics, absorbable antibiotic beads have been reported to have reduced costs (Zalavras, et al 2004, 86-93). Studies have shown that a 35-day intravenous treatment using vancomycin cost over $13,000 (Susman, 2005). The cost of antibiotic bead treatment has been estimated to be around $500 (Wright, et al 2007, 129). Due to the reduced costs as well as associated advantages with using beads, this method of antibiotic administration is preferable.

4.3 Future Work

There are several possibilities of expanding and improving upon our vancomycin bead model. One includes developing an equation for the optimal bead spacing for given parameters. We would need to run the simulation using different sets of parameters, and then develop an equation that relates those parameters to the bead spacing. Developing such an equation would improve usability of the model, allowing others to determine optimal spacing solutions without complex knowledge of COMSOL. Other future work may involve incorporation of multiple layers with differing vancomycin concentrations. This could allow us to analyze the effect of multiple layers on drug delivery to the tissue. Finally, the implementation of the shrinking bead could be improved. The shrinking bead in our model has significant limitations in its COMSOL meshing implementation, due to restrictions of the COMSOL software. Although changing the parameters of the outer bead layer at different shrinkage points is the most adaptive solution given COMSOL meshing requirements, the fact still remains that the simplification is a crude approach.

SECTION V: APPENDICES

5.1 Appendix A – Input Parameter Values and Calculations

Table 3. *Input Parameter Values for Vancomycin PLA-PL:CG Bead*

Parameter	Symbol	SI Units	Value	Reference
Velocity of Bead Shrinkage	v_{bead}	*m/s*	-2.572×10^{-10} for $t \leq 432000$ seconds	(Mader et al 1997, 415-518)
Velocity of Tissue Growth	v_{tissue}	*m/s*	-2.316×10^{-9} for $t > 369250$ seconds	(Mader et al 1997, 415-518)
Half-life of Vancomycin	$t_{1/2}$	*s*	*23400 s*	(Ducharme, et al 1994, 513-518)
Diffusivity of PLA-PL:CG copolymer	$D_{polymer}$	m^2/s	2.5×10^{-13} *for* $t < 369250$ *seconds;* 5.502×10^{-11} *for* $t \geq 36950$	(Hook 1978, 411-415)
Diffusivity of inner bead layer	$D_{inner\ bead}$	m^2/s	2.5×10^{-13}	(Hook 1978, 411-415)
Diffusivity of tissue	D_{tissue}	m^2/s	5.502×10^{-11}	(Hook 1978, 411-415)

Calculations for Velocity of PLA-PL:CG copolymer

From the experimental data, it was given that the copolymer shrunk 8mm after 40 days in PBS solution (Mader et al 1997, 415-518).

$$\frac{\partial r}{\partial t} = \frac{8mm}{40\ days}\left(\frac{1\ day}{86400\ s}\right)\left(\frac{10^{-3}m}{1mm}\right) = 2.316x10^{-9}m/s$$

Calculations for the Velocity of Bead Shrinkage

From experimental data, it was given that the inner part of the bead solution with vancomycin shrunk 4mm after 180 days in PBS solution.

$$\frac{\partial r}{\partial t} = \frac{4mm}{180\ days}\left(\frac{1\ day}{86400\ s}\right)\left(\frac{10^{-3}m}{1mm}\right) = 2.572x10^{-9}m/s$$

5.2 Appendix B – COMSOL Specifications

We used COMSOL Multiphysics software, implementing the UMFPACK direct solver. The time step used was 3600 seconds (one hour) and was run for a total of 28 days. The relative tolerance used was 0.01, and the absolute tolerance was 0.0010.

5.3 Appendix C – Mesh Convergence

Table 4. *Mesh Convergence Values for Antibiotic Bead after 28 Days*

Elements	Concentration Integral in Tissue(mol/m^3)	Surface Area (m^2)	Average concentration in tissue (mol/m^3)
408	3.687919E-07	8.65049E-05	4.263249E-03
552	3.678681E-07	8.65049E-05	4.252570E-03
720	3.677822E-07	8.65049E-05	4.251577E-03
1110	3.681135E-07	8.65049E-05	4.255406E-03
1698	3.680327E-07	8.65049E-05	4.254472E-03
4208	3.680390E-07	8.65049E-05	4.254545E-03

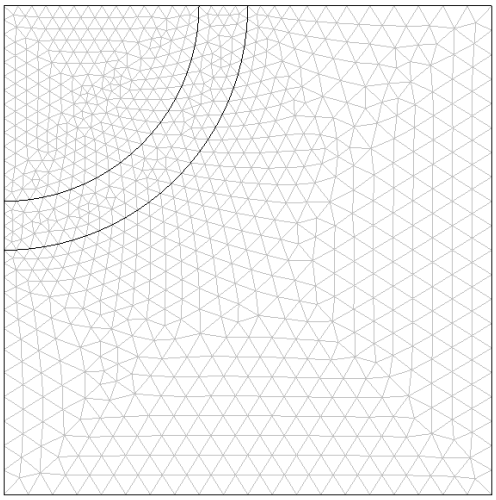

Figure 12. Mesh with 1698 elements

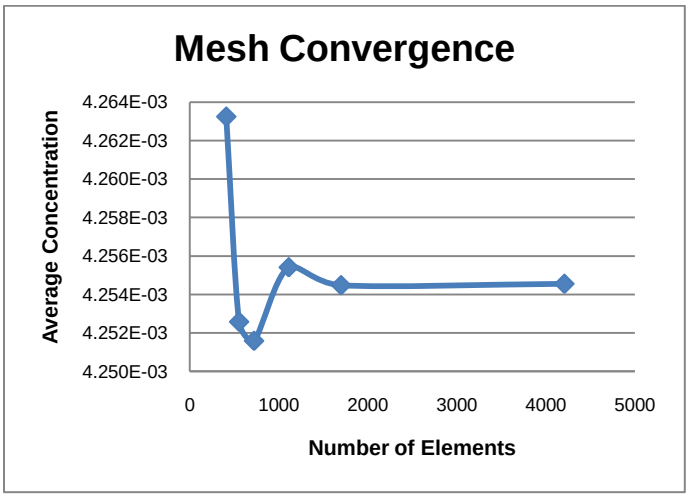

Figure 13. *Mesh Convergence Graph of Average Concentration*

5.4 Appendix D - References

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