The Optimization of Gentamicin Concentration in Diffusion Analysis for Bone Cement of Total Hip Arthroplasty

BEE 4530: Computer-Aided Engineering

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Section 1.Executive Summary

Total hip arthroplasty is the surgical procedure to replace the damaged hip joint with an artificial prosthesis. PMMA bone cement has been used to anchor the metal prosthesis inside femur; however, with a postoperative infection rate of two percent, Gentamicin-loaded bone cement has been introduced as an innovative way of treating infection at the site of total hip replacement surgery.

Resultantly, the goal of our project is to visually and quantitatively study the degradation and diffusion of Gentamicin at the prosthesis site. This study can be used to calculate the optimal initial concentration of the antibiotic that has to be administered in the bone cement to treat infection, and also to establish the relationship with the heat induced-degradation of the antibiotic.As a result, we will establish a measurement of antibiotic degradation via the coupling of heat equation with mass transfer, in which the thermal effects will be quantified into the Gentamicin breakdown with respect to temperature of the bone cement.

The actual simulation study will be done in COMSOL by creating the simplified anatomy of the metal implant, bone cement, femur, and muscle layer. To solve our problem formulation of modeling antibacterial-loaded bone cement for total hip arthroplasty, we will implement the heat and mass transfer equations in COMSOL. Considering that the heat formation and dissipation in the bone cement is not uniform throughout the bone cement and femur, the model must be a two dimensional analysis of Gentamicin diffusionwith an axis of symmetry.

To validate the validity of our simulation, we initially performed a mesh convergence analysis to provide an accurate representation of the problem under the given conditions. Subsequently, with the confirmed mesh, we generated a typical solution of the temperature profile and diffusion gradient after a total of one week. Therefore, the Gentamicin concentration distribution can be visualized as a function of distance from the axis of symmetry. Furthermore, the sensitivity analysis concluded that the simulation data is relatively insensitive to all the major parameters except initial Gentamicin concentration, which validates our design objective to optimize this parameter. Finally, our COMSOL simulation has been validated with experimental data due to the superimposition of the experimental conditions in comparison with our computational model. b

With the validation of our simulation accuracy, we optimized the initial Gentamicin concentration by analyzing the average antibiotic in the femur after one week for the ideal therapeutic quantity. More specifically, we varied the initial concentration of Gentamicin in the bone cement to optimize the concentration in the bone for the treatment of postoperative infection. Therefore, for proposed future research, the adjustment of input parameters can be modeled to find the optimal initial antibiotic concentrations under different physical settings as well as for different antibiotics. In conclusion, we have successfully determined the effective dose of Gentamicin necessary to promote successful total hip replacement surgery.

Key words: Gentamicin, bone cement, total hip arthroplasty

Section II. Introduction

Background

Total hip arthroplasty is the surgical procedure to replace the damaged joint with an artificial prosthesis. More specifically, the orthopedic process involves the abscission of the head and proximal neck of the femur to resultantly create a simulated canal in preparation for the insertion of a metal femoral prosthesis and corresponding acetabular component (Siopack&Jergesen, 1995). Furthermore, to yield successful results of the total hip arthroplasty, the fixation of the artificial prosthetic component to the bony structures is achieved with the use of acrylic bone cement inserted proximally into the medullary region of the femur and enlarged acetabular space (Kavanagh, Deuritz, Ilstrup, Stauffer, & Coventry, 1989). With more than 193,000 total hip replacement surgeries performed in the United States annually, there is an undeniable need for safe and effective procedural practices (Rolfson, Dahlberg, Nilsson, Malchau, &Garellick, 2009).

Unfortunately, there is an incident rate of two percent for postoperative infection in the hip joint (Oussedik, Dodd, & Haddad, 2010). Therefore, in order to prevent and treat the infection, hip replacement prosthetics are fixated with antibacterial-loaded bone cement that allows the antibiotic to diffuse out of the bone cement over a prolonged period of time (Cummins, Tomek, Kantor, Furnes, Engesaeter, & Finlayson, 2009). Among a variety of antibiotics available, the mostly widely used treatment in the United States is Gentamicin, which is proven to be the best in qualifying the robust mechanical strength, and most importantly, thermal stability (Kumar, Himabindu, & Jetty, 2008). Considering that the heat released during bone cement polymerization is capable of destroying the loaded antibiotics, the initial Gentamicin concentration must be optimized to compensate for the effect of heat on degradation rate. By monitoring the concentration change in Gentamicin during the polymerization period and over time at body temperature (Lewis, 1997), we will have a better understanding of the antibiotic concentration in the femur at a specific time for the prediction of a safe and effective Gentamicin dosage necessary to promote successful total hip arthroplasty.

Design Objectives

The goal of this project is to model the mass transfer of antibiotic through loaded bone cement post total hip arthroplasty, where we will transiently analyze the diffusion of Gentamicin within the bone cement and femur. As a result, we will establish a measurement of antibiotic degradation via the coupling of heat equation with mass transfer, in which the thermal effects will be quantified into the Gentamicin breakdown with respect to temperature of the bone cement. Ultimately, with the determination of the degradation equation, we can establish an appropriate objective function to optimize the initial concentration of antibiotic by minimizing the Gentamicin breakdown for a successful surgical procedure.

In the mass transfer equation, Gentamicin is diffusing only through the bone cement and the adjacent femur. This is due to the assumed impermeability of the metal implant to the

antibiotic, and also that Gentamicin does not diffuse to the outer muscle layer due to the magnitude of distance and low diffusivity value of Gentamicin. Furthermore, there is only a specified initial concentration of antibiotic homogeneous throughout the bone cement. There is no fluid movement, and thus there is no convection term.

$$\frac{\partial c_g}{\partial t} = D_{g,bone}\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_g}{\partial r}\right)\right] + r_g \quad \text{(Mass Transfer of Gentamicin)}$$

Most importantly, Gentamicin degradation with respect to temperature can be expressed as a first order reaction as modeled with Arrhenius equation.

$$r_g = -kc = -\left(A\, e^{-\frac{E_a}{RT}}\right)c$$

As Gentamicin degradation rate changes with temperature, temperature gradient in the system has to be included as well. For heat transfer, the bone cement has completely polymerized, and thus the bone cement is subsequently applied in the surgical region at the maximum polymerization temperature. Thus, the initial condition for the bone cement is at maximum polymerization temperature, and the conditions for the implant, femur, and muscle specify the initial temperature at body temperature. Also, there is no fluid motion, and thus there is no convection term. Additionally, there is no heat generation, and thus this term, Q, can be ignored.

$$\rho C_p \frac{\partial T}{\partial t} = k\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)\right] \quad \text{(Heat Transfer of Gentamicin)}$$

To solve our problem formulation of modeling antibacterial-loaded bone cement for total hip arthroplasty, we will implement the heat and mass transfer equations in COMSOL. Considering that the heat formation and dissipation in the bone cement is not uniform throughout the bone cement and femur, the model must be a two dimensional analysis of Gentamicin diffusionwith an axis of symmetry (Okrajni, Plaza, &Ziemba, 2007). Furthermore, with an axisymmetric model, the centerline of symmetry is assumed to have a zero flux value for heat and mass transfer, whereas the distal side also has a zero designated flux due to the magnitude of distance from the center.Additionally, with the assumption that the heat and mass values do not vary in the vertical direction, the top and bottom edges of the model have zero heat flux. Ultimately, COMSOL will use the heat transfer equation to quantify the specific levels of Gentamicin degradation with respect to temperature, and the coupling of this equation will thereby determine the pharmacokinetics of the breakdown mechanism of antibiotic. As a result, we will systematically model the diffusion of Gentamicin and obtain the numerical computations of antibiotic concentration with temperature dependence.

Problem Schematic

The constructed two dimensional axisymmetric model is shown in Figure 1, with the quantified sizes displayed by the schematic. Moving outward from the center, the metal prosthesis, comprised of cobalt-chrome alloy, is implanted into the excised canal in the medullary region of the femur. Then, there is the antibiotic-loaded bone cement, which is the adhesive material between the implant and bone. Moreover, the femur is modeled with the dimensions of an average human bone structure (Robinson, Hendel, &Halperin, 1994), and the

muscle tissue is attached to the bone itself. Therefore, we model these four separate layers with different material properties according to the heat transfer or mass transfer equation, in which all parameters are considered to be constant throughout each specified layer.

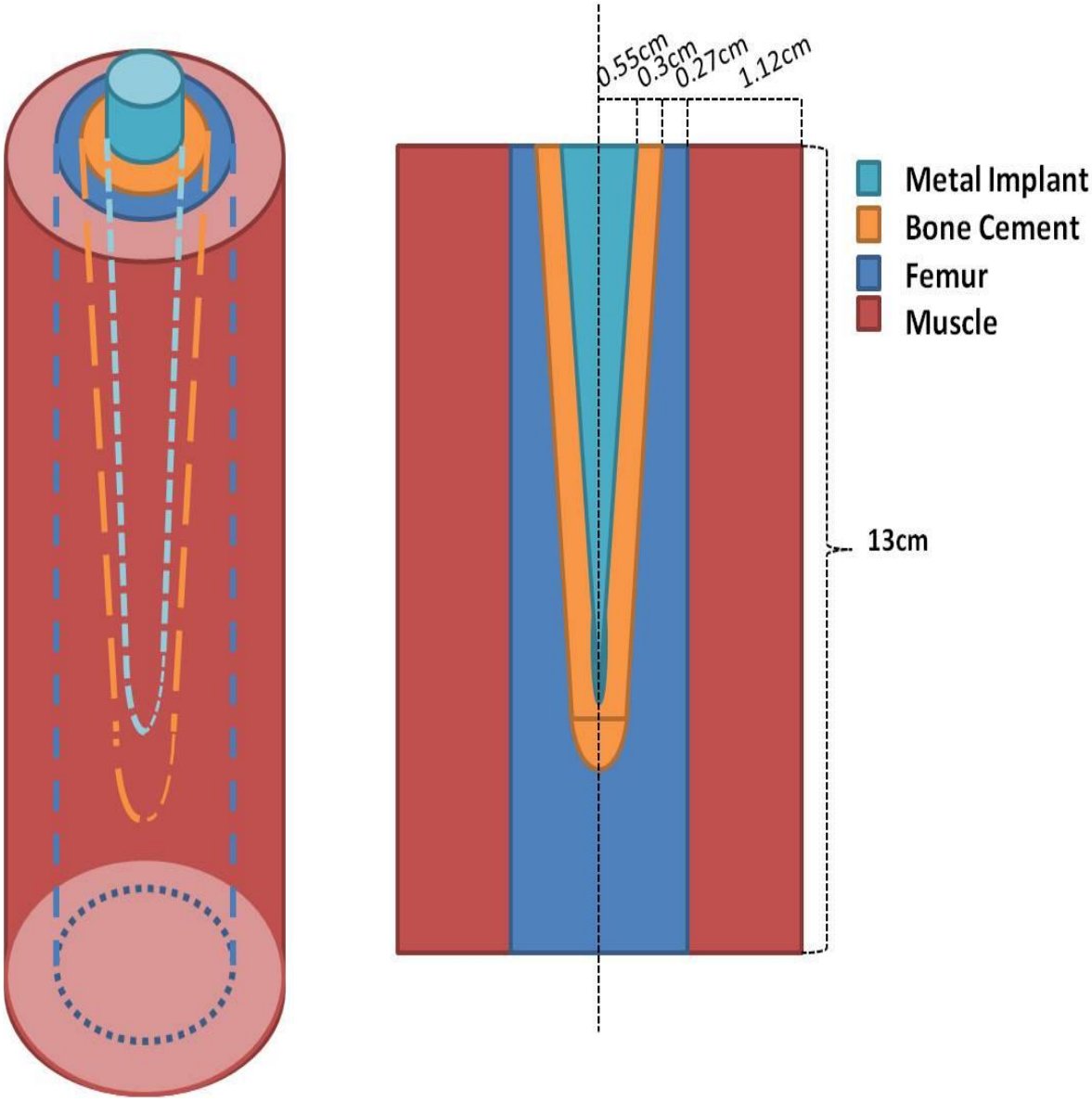

Figure 1: Schematic of the hip replacement system, with two dimensional axisymmetric about the inner dotted vertical line.

Our model assumes that our domain of the femur is perfectly cylindrical, in which the bone properties are comprised of a consistent substance without invariabilities. Therefore, the physical parameters of the bone are constant, and implemented in COMSOL according to literature values. Furthermore, the femoral bone is modeled with average American dimensions (Robinson, Hendel, &Halperin, 1994), and despite the variability among total hip arthroplasty

subjects, the geometry of the model is thereby assumed at a specific length and width.

In regards to the implant, the size of the prosthesis was obtained from Zimmer Orthopaedics (2010). The cobalt-chrome alloy is assumed to be a perfect mold without imperfections, and is fitted securely into the femoral excised canal. Moreover, the implant is simplified as an inverted cone with constant decreasing slope that is truncated by curved bottom edge. The bone cement is also modeled by a consistent substance with a homogenous mixture of antibiotic, and thereby has constant physical material properties; the bone cement is also assumed to be in direct contact with the prosthetic implant and femoral bone. Furthermore, the modeling of Gentamicin diffusion is assumed to transfer in one direction through the bone cement and femur, because the implant is assumed to be impermeable and is thereby inactive for the transient diffusion equation. As a result of these assumptions, we are able to provide a simplified model of the mass transfer of antibiotic, dependent on temperature, for the diffusion of Gentamicin after a total hip arthroplasty.

Section III. Results and Discussion

Typical Solution

With the simplified schematic and listed parameters from Table 1 in Appendix A, we implemented free mesh parameters to obtain an unstructured mesh. See Appendix B for mesh convergence. Therefore, we modeled the temperature profile of the complex for a total simulation time of one hourat a time step of 0.01, where the complex has an equilibrated temperature at this specified time. Therefore, the temperature profile demonstrates the minimal temperature gradient, in which can be explained by the high thermal conductivity of the materials that thereby promotes a uniform temperature profile. Also, see Appendix C for a plot of temperature as a function of time. Figure 2 displays the temperature profile with the initial temperature of bone cement modeled at maximum polymerization temperature.

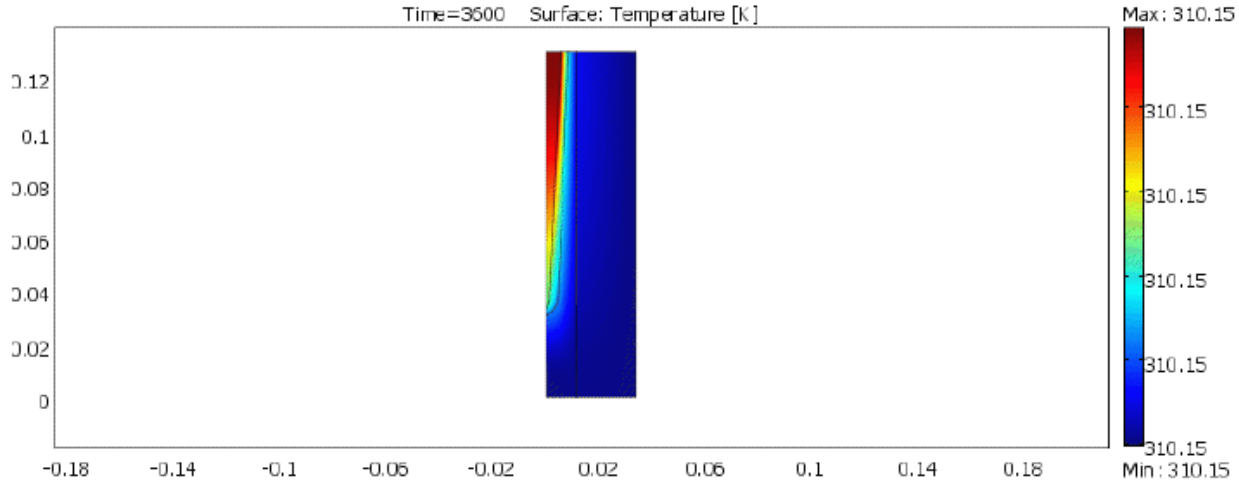

Figure 2: Surface plot of the temperature profile for thermal conductance through the complex at a simulated time of one hour.

The surface plot demonstrates the equilibrated temperature, in which effects the concentration of Gentamicin degradation through the bone cement complex.With the specified initial concentration homogeneous throughout the bone cement, the concentration profile was modeled after a simulation time of seven days at a time step of 0.01. Figure 3 displays the diffusion of the antibiotic through the complex.

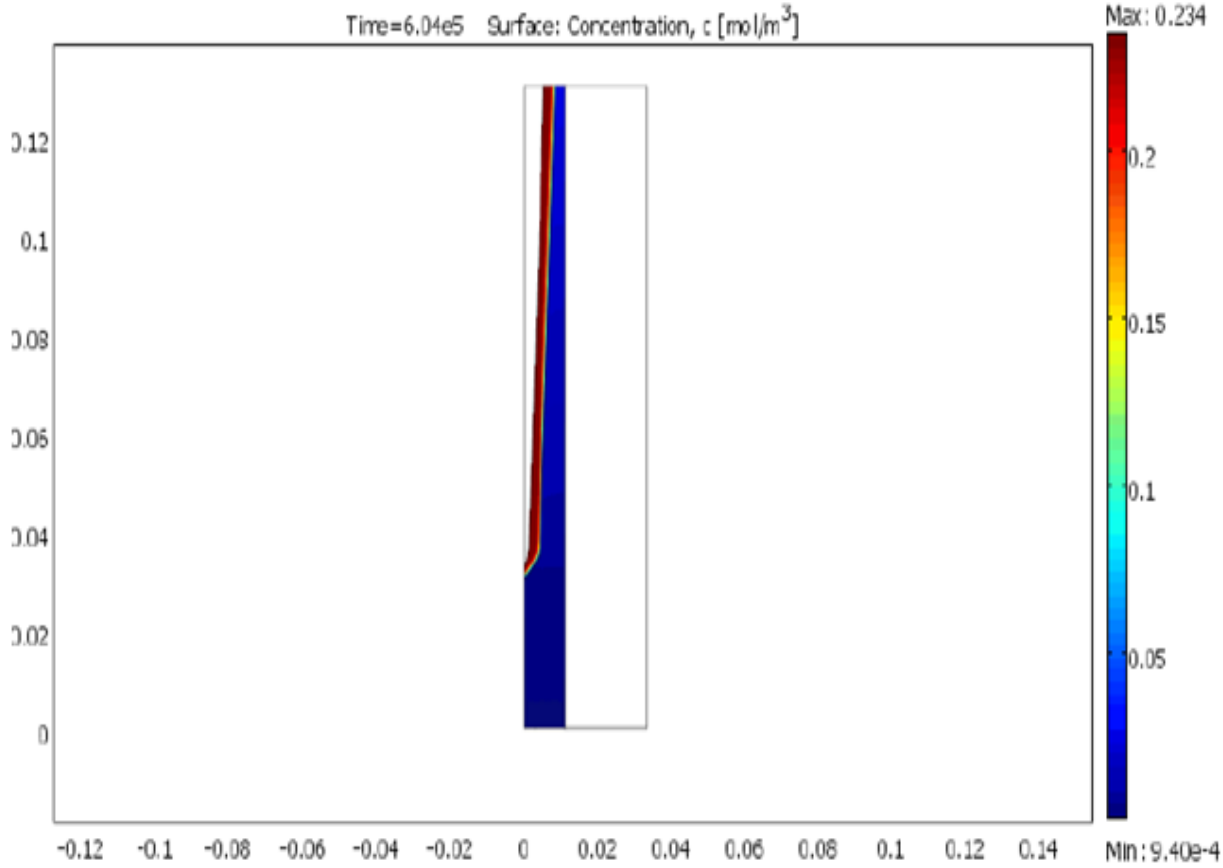

Figure 3: Surface plot of the concentration profile for diffusion through the complex at a simulated time of seven days.

With a sensitivity analysis of the initial concentration in the subsequent sections, we can optimize this parameter to deliver sufficient concentrations of Gentamicin to the surrounding femur region without reaching toxicity levels.

Concentration as a Function of Time

For the successful validation of our model, the concentration of Gentamicin is modeled as a function of time to analyze the antibiotic diffusion through the bone cement. Therefore, a concentration profile as a function of horizontal distance is plotted for a total of seven days (with intervals of 100,000 seconds). Figure 4 shows a decrease in concentration as the horizontal distance from the bone cement increases for all time intervals, in which the concentration is less with longer time intervals.

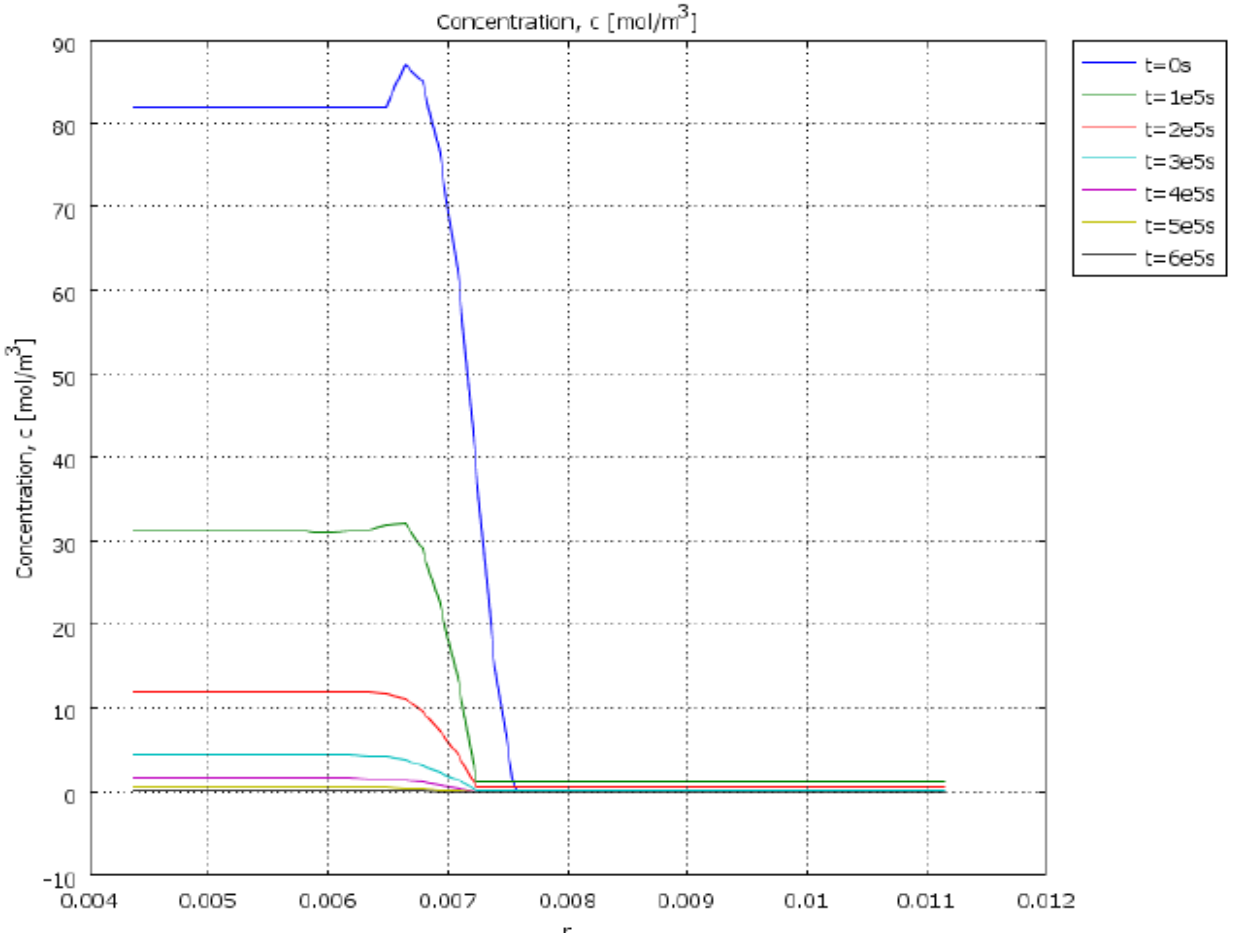

Figure 4: Concentration profile of Gentamicin versus distance at 4 day intervals for 16 days.

Although there are initial increases in concentration for the smaller time intervals, this is due to the disparity in diffusivity values for the bone cement and femur domains. Furthermore, as demonstrated by Figure 4, with longer time intervals, the concentration of Gentamicin decreases. Research studies conclude that the concentration of Gentamicin is therapeutically diffusing through the femur for one week (De Belt et al., 2002), and for the prevention of infection after total hip arthroplasty, the concentration of Gentamicin in the femur must not only remain below a toxic level, but also remain above the minimal effective level. Therefore, in subsequent sections, an accuracy check of our concentration behavior will be analyzed in comparison to experimental values. Furthermore, in the following section of sensitivity analysis, we analyze the effects of the initial concentration of Gentamicin on the average concentration, and further examine these values in the optimization section of the conclusion.

Sensitivity Analysis

To determine the sensitivity of our model on the accuracy of our parameters, it is necessary to perform a sensitivity analysis and thereby determine which parameters had the

largest effect on our results. Therefore, we changed one parameter at a time (initial concentration of Gentamicin, initial temperature of bone cement, and degradation rate of Gentamicin), and kept the other variables constant for each sensitivity analysis. Subsequently, we examined the resulting changes at a final time of 4 days, or 345,600 seconds, for the average concentration of antibiotic in a specified region of the complex.

Initial Concentration of Gentamicin

We performed a sensitivity analysis of the initial concentration of Gentamicin in the bone cement on the average concentration in the bone and bone cement after four days. We began our analysis using an initial concentration of 82.287 mol/m^3 Gentamicin (Marks, Nelson, and Lautenschlager, 1976). We decreased the initial concentration by 15% and 2.5% and found a corresponding decrease of 10.1% and 2.44% in average Gentamicin concentration, respectively. Similarly, we increased the initial concentration by 2.5% and 10% and found a corresponding the increase by 2.44% and 7.18%, respectively, of average Gentamicin concentration. The absolute change in the average concentration is shown below in Figure 5.

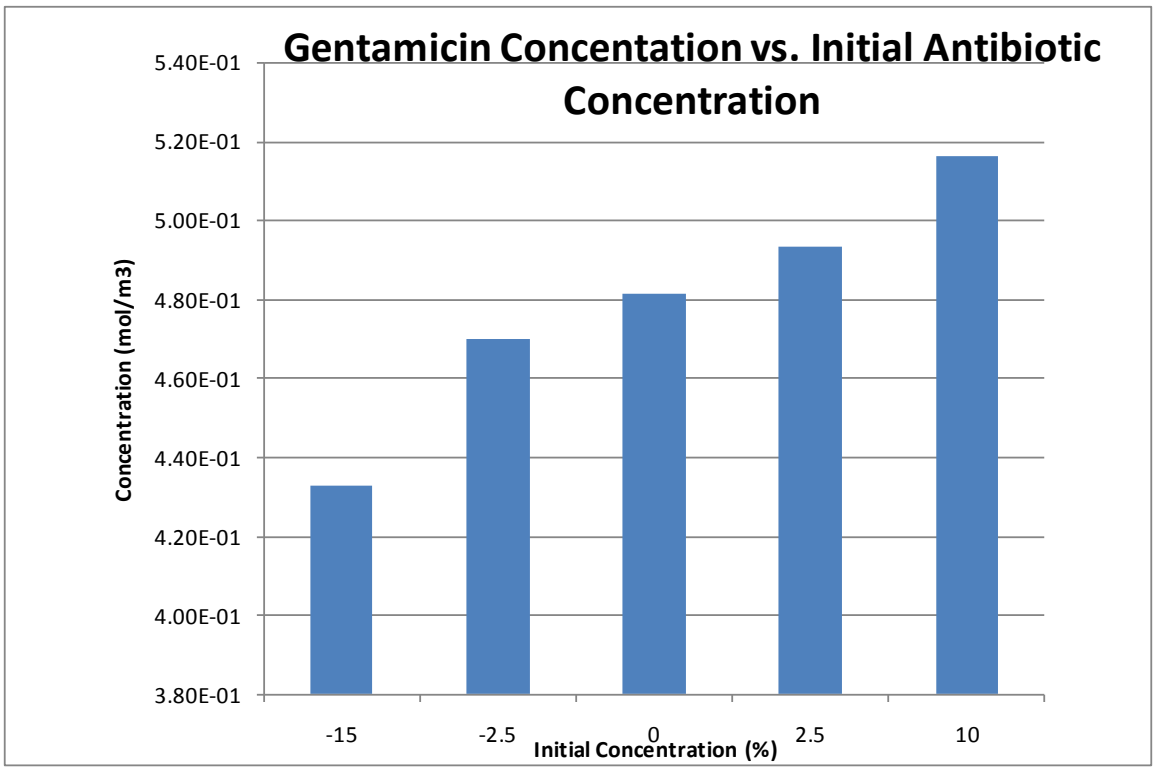

Figure 5: Sensitivity analysis of initial Gentamicin concentration for the average concentration of antibiotic in the bone cement and femur domains.

As expected, the initial concentration of Gentamicin was approximately linearly related the average concentration in the bone, and we can therefore further optimize the initial concentration

in the bone cement give a desirable average concentration in the bone. See the optimization section of the conclusion.

Initial Temperature of Bone Cement

The effect of the initial bone cement temperature was tested for sensitivity at a time of 4 days. This test reflects the possible variation in initial bone cement temperature, because this value profoundly depends on the surgeon's judgment during surgery. Three initial temperatures 70°C, 75°C, and 85°C were tested in addition to the standard 80°C over the femur and the bone cement domains, and the result is displayed in Figure 6.

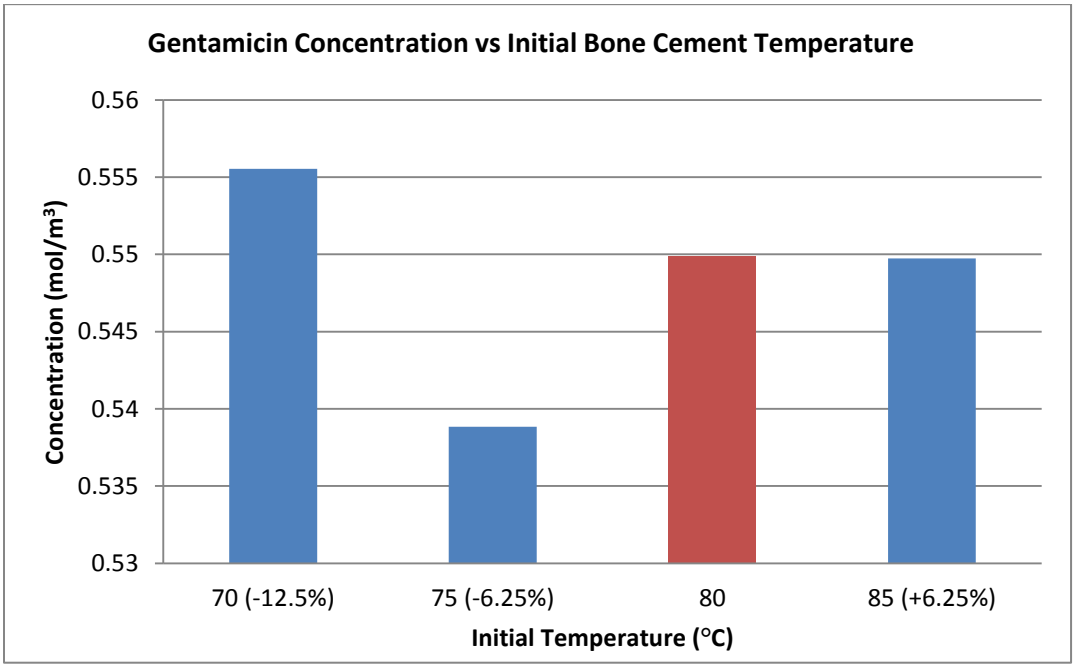

Figure 6: Sensitivity analysis of initial bone cement temperature for the average concentration of Gentamicin in the bone cement domains.

Figure 6 suggests that the initial bone cement temperature does not affect Gentamicin concentration significantly, with a maximum difference of 0.1 mol/m^3. Therefore, our simulation is relatively robust for the initial temperature of bone cement.

Degradation Rate of Gentamicin

In order to determine the Gentamicin degradation rate, the doubling temperature difference was arbitrarily set to 10°C according to Arrhenius equation with the rate term dependent on temperature. Although this value is assumed to be reasonable for Gentamicin, the significance of the Gentamicin degradation rate value was thereby checked via sensitivity analysis to determine the necessary accuracy. Two other values, 5°C and 15°C, of double temperature difference were tested. In the sensitivity analysis, the volumetric concentration of

Gentamicin within the bone cement layer was compared. The Gentamicin concentration with respect to different doubling temperature difference is displayed in Figure 7.

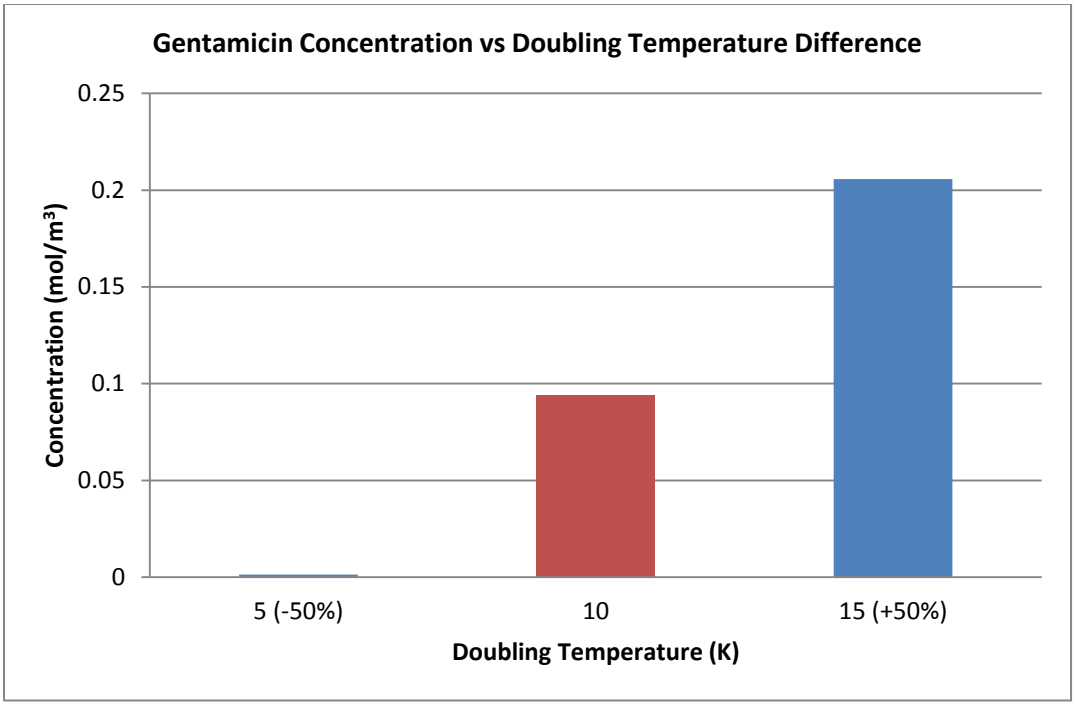

Figure 7: Sensitivity analysis of doubling temperature difference, and the resulting effect on the concentration of Gentamicin in the bone cement with an original value of 10°C difference.

From the Figure 7, the 5°C difference gives an unreasonably fast degradation rate of Gentamicin as almost all of the antibiotics are degraded after 4 days with a negligible amount of Gentamicin in the bone cement after cooling; thus, this value contradicts experimental data referenced in subsequent sections. In contrast, at 15°C difference, the concentration of Gentamicin in the bone cement is twice that at 10°C difference. Considering the two tested cases resulted in concentration values significantly different from the standard value, this data demonstrates that there is considerable sensitivity in the degradation term for Gentamicin. More specifically, this means that the model is strongly dependent on the half-life of the antibiotic, but with the degradation rate determined experimentally from literature values, this term does not compromise the validity of our model.

Accuracy Check

To validate our results, we compared our model to experimental data from literature. Therefore, to confirm the reliability of our assumptions, an accuracy check is necessary to determine the validity of our model. Considering that the degradation rate is dependent upon temperature, the comparison of Gentamicin diffusion with literature values will thereby validate the temperature equation due to the dependence of mass transfer on the coupling with the heat equation. In studies by Ruckdeschei, Hessert, & Schollhammer (1973), the research analyzed the

diffusion of Gentamicin through bone cement *in vitro*. More specifically, this study investigates the concentration profile of the antibiotic as a function of time, and in comparison with these results, we are thereby able to ensure that the assumptions of our model were valid. In the previously displayed plot in Figure 4, we plotted the concentration as dependent on time for our model in COMSOL. As an accuracy check, we superimposed our modeled curve with the data from Ruckdeschei, Hessert, & Schollhammer to thereby determine the validity of our model. This is presented data is presented in Figure 8.

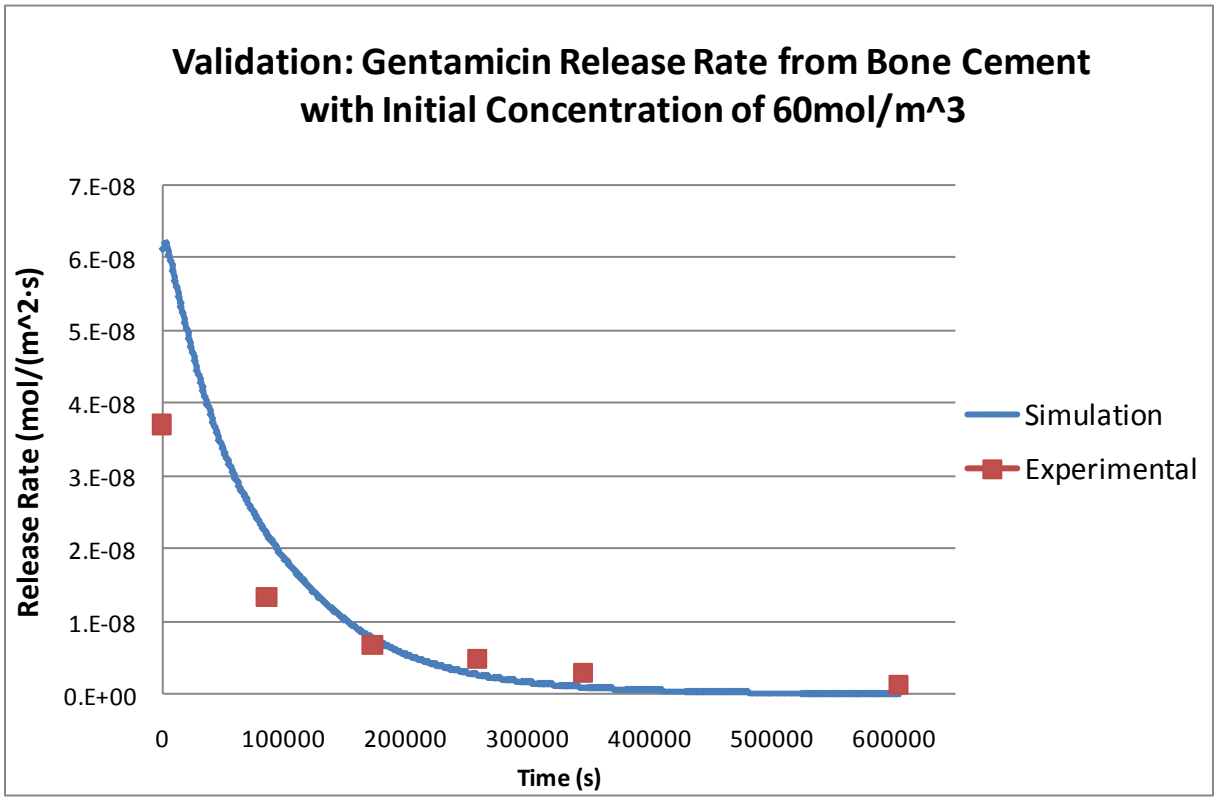

Figure 8: Accuracy Check with research from Ruckdeschei, Hessert, & Schollhammer (1973), plotted as concentration as a function of time.

There are obvious similarities between the experimental results and our COMSOL model. For both data sets, the transient model of mass transfer demonstrates a concentration profile with a decrease of drug, in which includes a more steady concentration decrease around 2 days (200,000 seconds).

Although there are discrepancies with the model, the experimental research study used florescence microscopy to detect the concentration of Gentamicin *in* vitro, while our model simulated an *in vivo* replica of total hip arthroplasty. Therefore, the intrinsic differences in testing scenarios create the variation in our results.

Section IV. Conclusion

Optimization

Our sensitivity analysis showed that the initial concentration of Gentamicin in the bone cement is very influential over the average concentration of the drug in the femur. It is desirable to have the average concentration in the bone cement be in the therapeutic range after one week (De Belt et al., 2002) to be maximally effective. However, we do not want the Gentamicin concentrations to reach toxic levels which will lead to bone cell death. More specifically, toxic levels of Gentamicin are known to be >10μg/ml or 21μmol/L (Beckman Coulter, 2002), while therapeutic levels are 5-10 μg/ml or 10.4-20.9 μmol/L (Beckman Coulter, 2002). Therefore, our model simulated the concentration of antibiotic as a function of distance, displayed in Figure 4, to thereby determine if our initial concentration of Gentamicin is within the specified range. Although the sensitivity analysis of the initial concentration (Figure 5) demonstrated that this parameter is not robust, the ability of the surgeon to mix a desirable amount of antibiotic into the bone cement allows for the optimization of this parameter. Therefore, with the initial concentration of 82.287 mol/m^3, we further modeled a variable initial concentration to optimize the average concentration of antibiotic in the femur. As displayed by Figure 9, the initial concentration of Gentamicin is modeled with respect to the ideal therapeutic level.

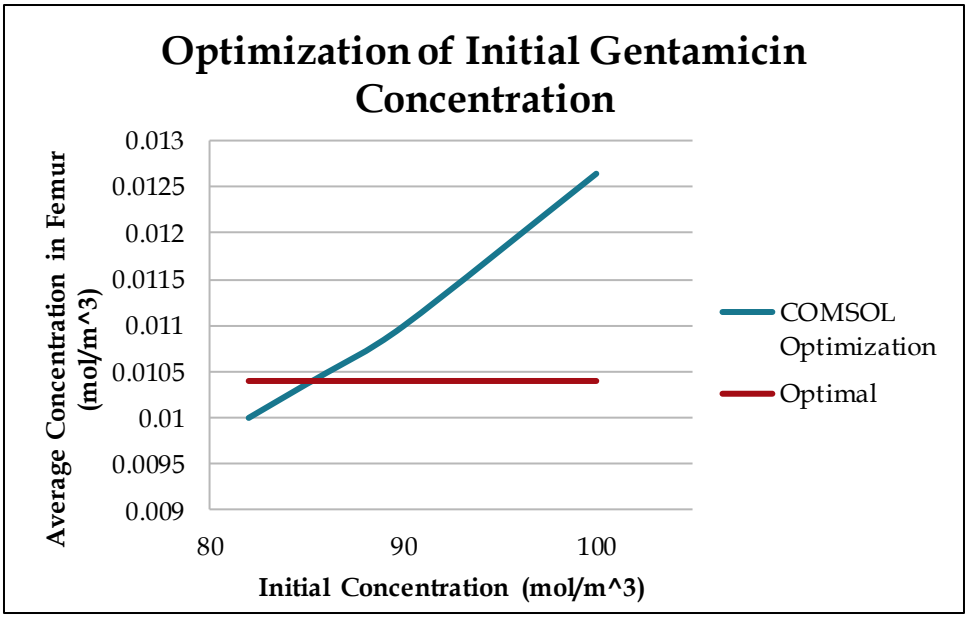

Figure 9: Function of initial concentration of Gentamicin in bone cement for optimal average concentration of antibiotic in femur, in which is plotted with reference to ideal therapeutic level.

From Figure 9, this plot demonstrates that the optimal concentration of Gentamicin is 85.3 mol/m^3. As a result, we have idealized the concentration of Gentamicin in the femur for a successful total hip arthroplasty.

Design Recommendations

The design used to construct this model opens many areas for further research with respect to procedures utilizing bone cement. With such further research, there are several recommended adjustments that could potentially generate more accurate and flexible results. The primary alteration deals with the determination of a quantitative method for inputting individual characteristics into the model. These could include the effects ethnicity, age, and gender on domain parameters, as well as the effects of personalized bone geometries on the model. Such consideration would allow for a more specific and accurate method for determining personalized optimization levels.

The current model also assumes a variety of measures that may require more detailed specifications. One such possibility is that the bone density changes over its geometry, therefore greatly affecting the diffusive results of Gentamicin. Other future models could implement small convective flows of heat in the tissue due to blood perfusion, or even take into account the complex nature of surrounding tissues. These modifications may require a great deal of processing time for the simulated model, however they will improve the accuracy of the generated results.

Realistic Constraints

The model constructed here is realistic with respect to current procedures performed in the medical field. As technology becomes increasingly more efficient and accurate, the most dangerous aspect to many surgeries is the potential for postoperative infection. This model allows for producers of bone cements to analyze the required level of Gentamicin provided the parameters of the surgery to remain within a specific range. The procedure involving Gentamicin may have an economic impact by increasing the price of bone cement; however, as infection is a major concern, that price is a negligent factor in comparison with the surgery as a whole.

In terms of health and safety, there may in fact be necessary precautions in order to prevent against the possibility of inducing an antibiotic resistance development. This concern does not demonstrate any significant realistic constraint with proper application and controls.

The final and most applicable constrain that would be incurred is the actual production of the bone cement. The addition of Gentamicin would involve a production process that occurs temporally very close to the procedure. The Gentamicin needs to be created and stored properly in order to prevent any significant levels of degradation before combination with the bone cement. This issue is one primarily of realistic logistics; however, it is a vital consideration that needs to be taken into account when truly analyzing the feasibility of this study.

In summary, out team believes that our model does indeed have the potential to be implemented in total hip arthroplasty procedures, and can greatly assist in the reduction in postoperative infection severity.

Section V. Appendices

Appendix A: Mathematical Statement of the Problem

Governing Equations

Governing equation for mass transfer of Gentamicin in bone cement and femur

$$\frac{\partial c_g}{\partial t} = D_{g,bone}\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_g}{\partial r}\right)\right] + r_g$$

Considering the degradation rate is dependent on temperature, the governing equation for heat transfer through bone cement and surrounding domains

$$\rho C_p \frac{\partial T}{\partial t} = k\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)\right]$$

Relevant Equations

With Gentamicin degradation dependent on temperature, the sink term can be expressed as a first order reaction as follows.

$$r_g = -kc$$

The reaction rate constant, *k*, can be modeled with the Arrhenius equation:

$$k = f(T) = A\, e^{-\frac{E_a}{RT}}$$

By taking a natural log on both sides,

$$lnk = lnA - \frac{E_a}{RT}$$

$$lnk_1 - lnk_2 = ln\frac{k_1}{k_2} = \frac{E_a}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

This equation can solve for *k* at a known temperature, given *k* at another known temperature and activation energy, E_a. Bates &Nahata (1994) research suggests that *k* at room temperature is:

$$k_{elimination}|_{T=25°C} = 0.00285\ (Creatinine\ Clearance) + 0.015$$

The first term involves creatinine clearance and describes the systematic clearance of Gentamicin by the kidney. The second term is exclusively attributed to natural degradation of the antibiotic. By ignoring the systematic clearance of Gentamicin, *k* at 25°C is:

$$k|_{T=25°C} = 0.015\ hr^{-1} = 4.1667E-6\ s^{-1}$$

In order to solve for the activation energy, it is assumed that (1) the activation energy stays that same within the temperature range of our problem and (2) *k* doubles from 25°C to 35°C. Considering that the second assumption is somewhat arbitrary, the doubling temperature can thereby be studied through sensitivity analysis. Using $k(T = 25°C) = 0.015$and $\frac{k(T=35°C)}{k(T=25°C)} = 2$, the activation energy over gas constant is:

$$\frac{E_a}{R} = -6368.28\frac{J}{mol\ K}$$

Using this constant, *k* at any temperature (ranging from room temperature to the highest bone cement temperature) can be found using the equation:

$$lnk_1 - lnk_2 = ln\frac{k_1}{k_2} = \frac{E_a}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right).$$

For instance, at 80°C:

$$ln\frac{k_1}{k_2} = \frac{E_a}{R}\left(\frac{1}{353K} - \frac{1}{298K}\right)$$

$$\frac{k_1}{k_2} = 27.84$$

$$k|_{T=80°C} = 0.4176\ hr^{-1}$$

Therefore, the equation can be solved for *k* with respect to temperature for implementation into COMSOL as follows,

$$k = 4.1667E-6\left(e^{-6368.28\left(\frac{1}{T}-\frac{1}{298K}\right)}\right)$$

Boundary Conditions

For mass transfer, only the bone and the bone cement layers are kept active. This is because the implant is assumed to be impermeable to Gentamicin, and the muscle layer is significantly far from the bone cement due to the low diffusivity of the antibiotic. Therefore, by keeping the metal implant domain inactive, the boundary condition specifies a flux at this interface equaling zero$\left(\frac{\partial c}{\partial r} = 0\right)$. Additionally, the same boundary condition is applied to the muscle layer (inactive mode). The vertical edges of the model are also assumed to have a zero flux as these boundaries due to the assumed horizontal diffusion of antibiotic, whereas the center of the implant has a boundary condition of zero heat flux due to the axisymmetry.

For heat transfer, heat diffuses relatively quickly through the bone. Thus, the original assumption to set the temperature of femur's distal side at body temperature was proven to be inappropriate, because this boundary acted as a great sink for heat and accelerated the heat loss. In order to resolve this problem, a muscle layer of significant thickness was added with the original boundary condition of $T = 37℃$. Notably, in contrast with mass transfer, all four domains were kept active due to the high thermal conductivity. The center of the implant has a boundary condition of zero heat flux because it is the axis of the symmetry. Similar to the mass transfer, all the other boundaries were set to zero heat flux as these boundaries do not have vertical conduction. The relevant schematic is shown in Figure 2.

Initial Conditions:

For heat transfer, the initial temperature of the bone cement is 353.15K (80°C) due to the polymerization temperature. As a part of surgical process, Cobalt Chromium implant is preheated to the body temperature before being placed in the bone cement. Also, the femur and the muscle layer are also at an initial body temperature. For the mass transfer, the entire bone cement region will be specified at an initial concentration of 82.287 mol/m^3 Gentamicin (Marks, Nelson, and Lautenschlager, 1976). Initially there is no Gentamicin in the femur. Similarly, the implant and the muscle layer do not have an initial Gentamicin concentration, but these domains are inactive, so these initial conditions do not have to be specified in COMSOL. In the sensitivity analysis and optimization sections, the initial concentration of Gentamicin in the bone cement

will be modified to determine the optimal amount. The boundary conditions and initial conditions are displayed in Figure 10.

Schematic

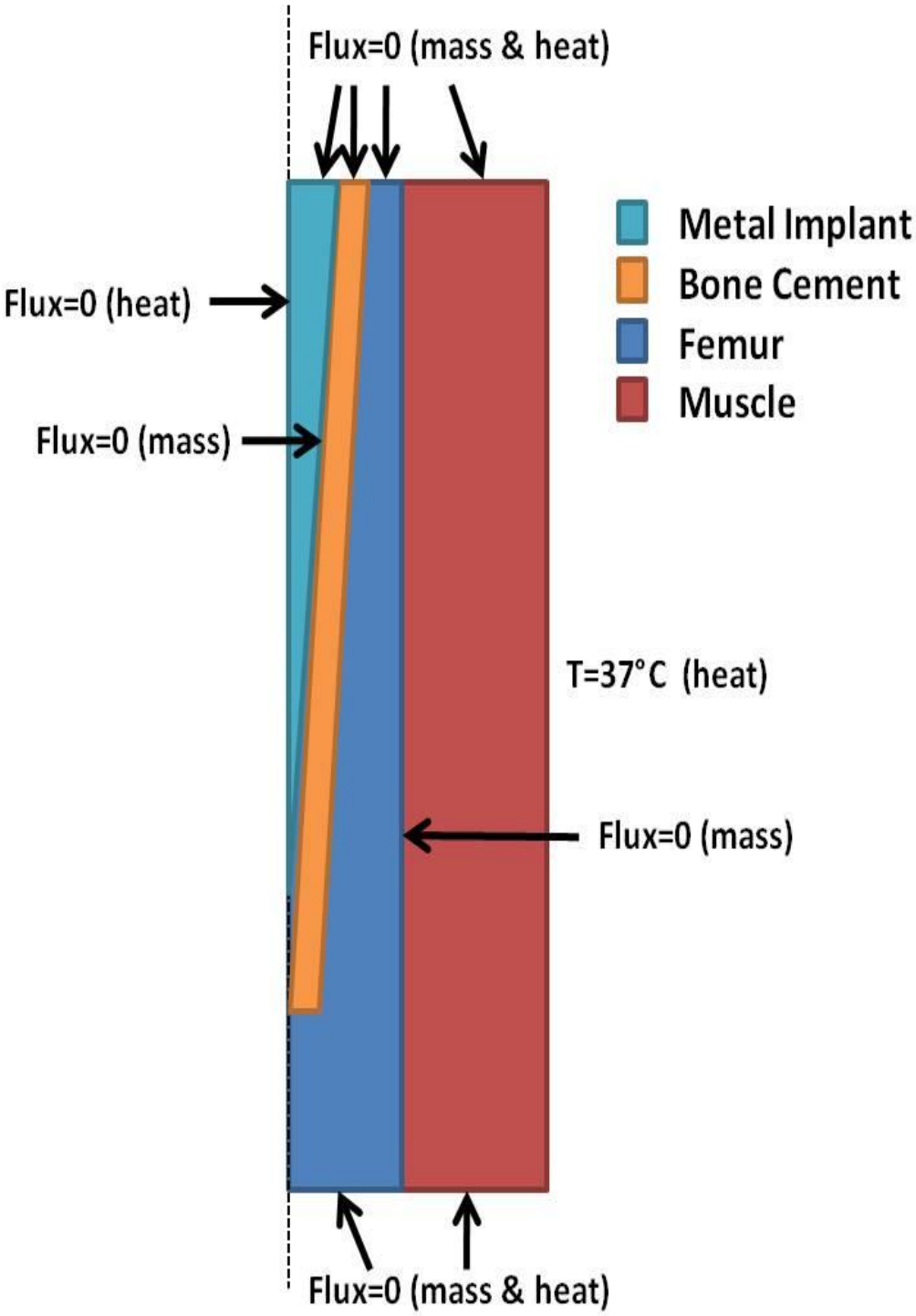

Figure 10: Schematic of the boundary conditions and initial conditions of the hip replacement system, with two dimensional axisymmetric about the inner dotted vertical line.

Material Properties

Table 1: Property values for materials simulated in COMSOL.

	Implant (CoCrAlloy)	PMMA Bone Cement	Bone	Muscle
Density ρ [kg/m^3]	8800 (Matweb)	1683(Hung et. al)	1850 (Cameron)	1060 (Urbancheka)
Specific Heat C_p [J/kg-K]	434 (Matweb)	310 (Hung et. al)	1500 (Suleyman)	3807.44(Urbancheka)
Conductivity k [W/m-K]	14.7 (Matweb)	0.12 (Hung et. al)	0.25 (Suleyman)	3.84(Urbancheka)
Mass Diffusivity D [m^2/s]	(impermeable)	2.5×10^{-9} (Law et al.)	46×10^{-7} (Singh)	(inactive)

Appendix B: Solution Strategy

To analyze Gentamicin diffusion and the resulting concentration profile, we used COMSOL Multiphysics with the implementation of UMFPACK direct solver. Therefore, COMSOL analyzed the transient diffusion equation discussed in Appendix A, and coupled this with the heat transfer equation for the dependence of degradation rate on temperature. Our time step was every 0.01 seconds for a total of seven days (604,800 seconds.) Calculations were performed with a 0.010 relative tolerance, and a 0.0010 absolute tolerance.

Mesh

The geometry, we used free mesh parameters to create an unstructured mesh, and thereby selectively refined the mesh around the cement regions due to the greatest magnitude of heat and mass transfer at these regions. The mesh simulated in COMSOL for mass transfer is displayed in Figure 11.

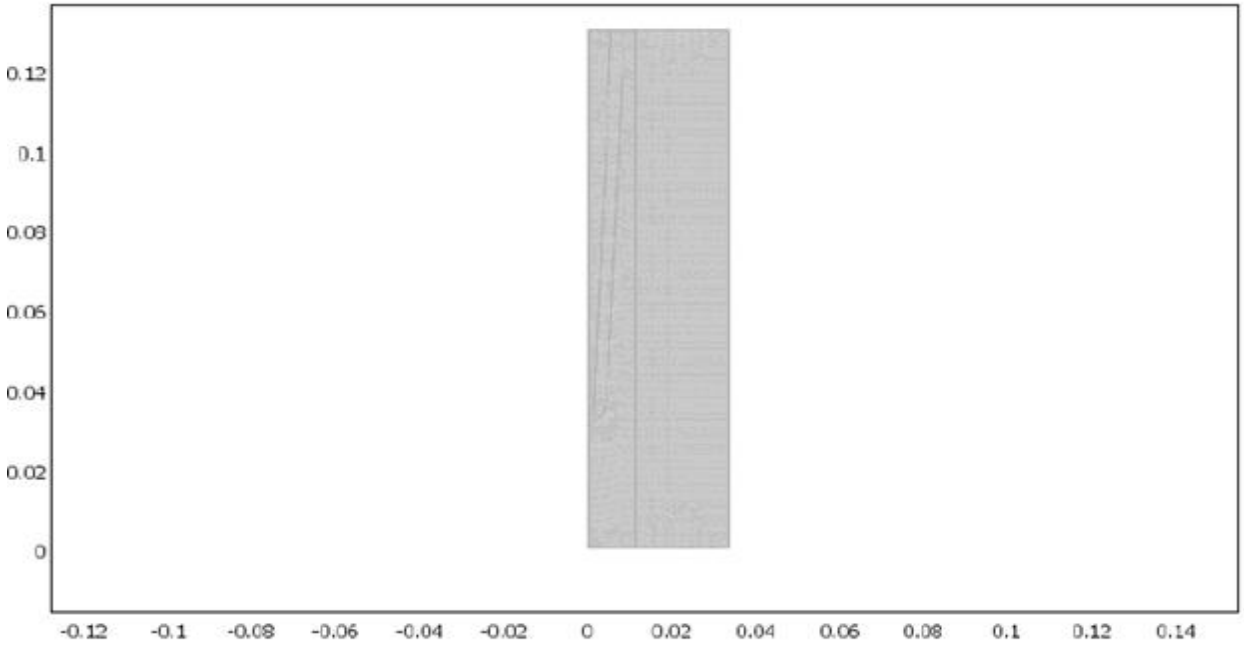

Figure 11: Mesh plot for total hip arthroplasty for mass transfer equation.

Mesh Convergence

To determine if the number of elements affected the solution, we performed a mesh convergence analysis for the heat and mass transfer equations. For both cases, the final time was 4 days, or 345,600 seconds, and the average was calculated by integrating over the specified region for the variant of interest, and then dividing by the total volume. With each subsequent mesh analysis, we made the mesh coarser.

For the mesh convergence analysis for heat transfer, we integrated over the femur domains. The results are displayed in Table 2.

Table 2: Mesh convergence analysis for temperature of Gentamicin after 4 days.

Number of Elements	Volume [m^3]	Temperature Integral [K* m^3]	Average Temperature [K]
665	3.82E-05	0.011847	3.10E+02
5309	3.82E-05	0.011847	3.10E+02
11870	3.82E-05	0.011847	3.10E+02

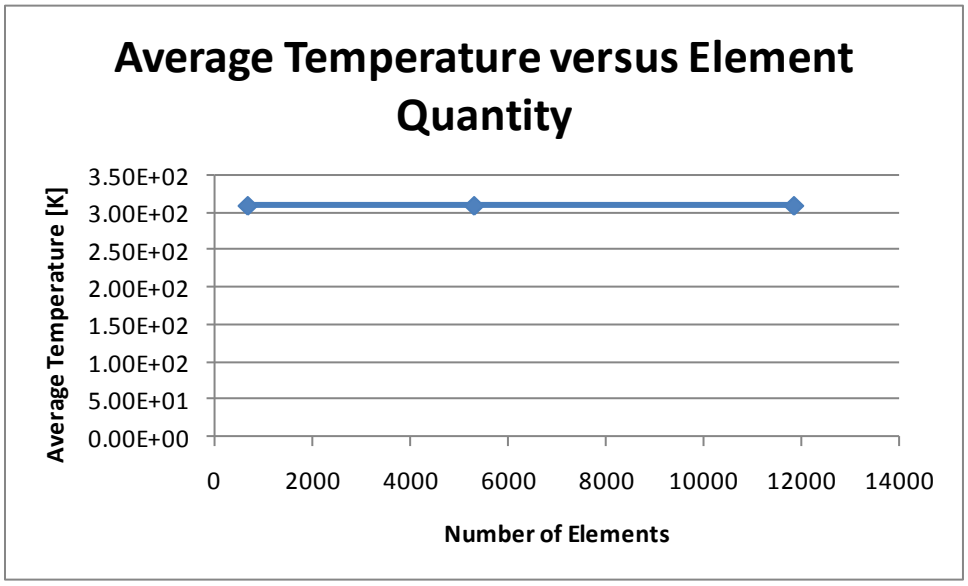

Figure 12: Plot of mesh convergence analysis for temperature of femur.

For the mesh convergence analysis for mass transfer, we integrated over the bone cement and femur region. The results are displayed in Table 3.

Table 3: Mesh convergence analysis for concentration of Gentamicin after 4 days.

Number of Elements	Volume [m^3]	Concentration Integral [mol]	Average Concentration [mol/m^3]
5309	4.72E-05	2.29E-05	4.86E-01
13211	4.72E-05	2.27E-05	4.82E-01
30805	4.72E-05	2.27E-05	4.81E-01

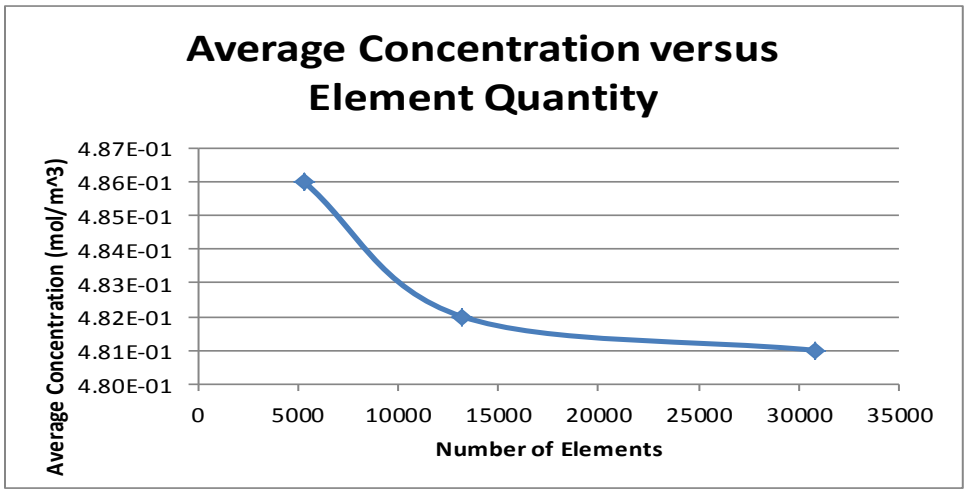

Figure 13: Plot of mesh convergence analysis for concentration of Gentamicin.

Therefore, with the results from the mesh convergence analysis of heat and mass transfer, the default solution was obtained using 665 elements for the heat equation and13,211 for the mass equation.

Appendix C: Additional Visuals

The dependence of the degradation rate of Gentamicin on the temperature thereby couples the heat transfer equation with the mass transfer equation. For a further examination into the temperature profile, a plot of temperature as a function of time is displayed in Figure 14, for a total time of 1100 seconds.

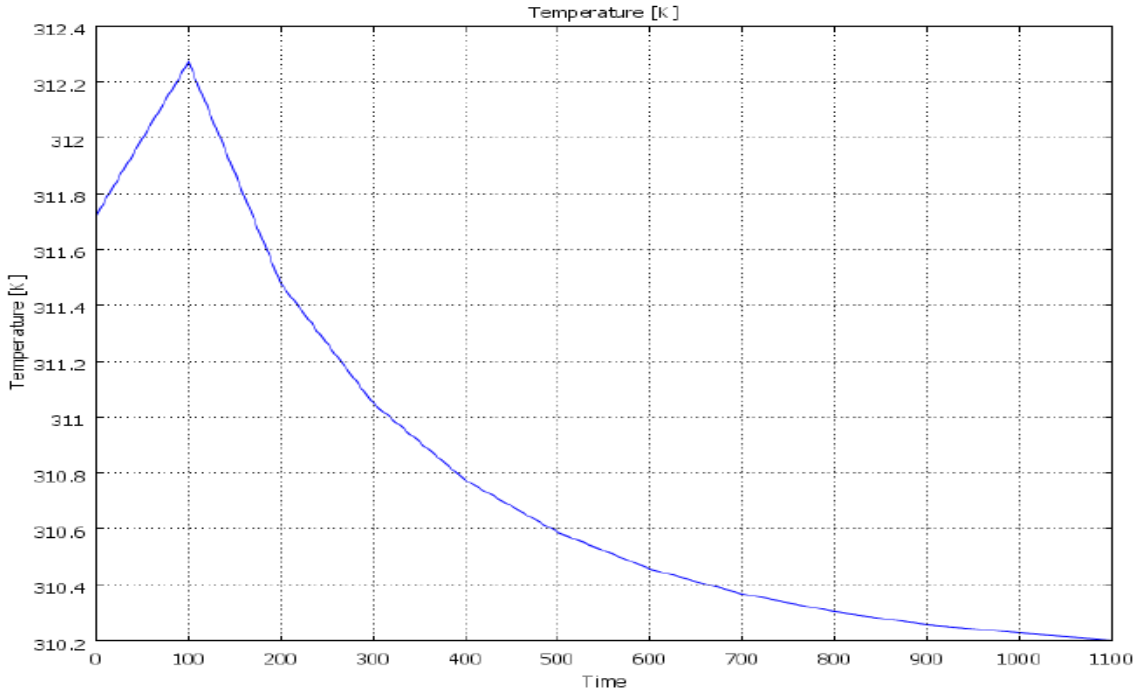

Figure 14: Temperature profile of all domains as a function of time.

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