Modeling Direct Drug Injection in the Kidney

Abstract:

End Stage Renal Failure can occur from several renal diseases, for which kidney transplantation is the only long term treatment. This solution can still be unreliable due to the chance of organ rejection. Direct injections of Rapamycin can significantly reduce the risk of kidney rejection by the body's immune system. An Ansys axisymmetric model of an ellipse was used to represent drug injection in the kidney to find the best injection site. The top, center and bottom of the kidney were tested as injection sites. Patches with three different initial temperatures of $10\,°C$, $20\,°C$, and $30\,°C$ were made at each injection site to see which site is best for the drug to diffuse throughout. The results showed the center of the kidney with a patch of $20\,°C$ diffused more than half of the drug throughout the entire kidney. This case was chosen to be the most viable option because a high concentration of Rapamycin is recommended in direct injection(Zhou, Peng, et al., 2014), but too high of a concentration can lead to adverse effects. Since no studies have numerically quantified what amount of Rapamycin can lead to these negative effects, the patch of $20\,°C$, was chosen for safety and ethical concerns.

Motivation:

Chronic kidney disease, a persistent medical problem, affects roughly 14% of Americans today. This disease is hard to diagnose as no viable symptoms arise until it becomes very advanced ("Kidney Disease Statistics for the United States.", 2016). Because of the difficulty in identifying those with the disease, the fraction of people affected continues to grow each year worldwide. End Stage Renal Failure (ESRF) affects about 750,000 people each year in the United States ("The Kidney Project Statistics.", 2019). Once diagnosed with ESRF, patients can receive dialysis treatment, or undergo a kidney transplant. Under 30% of those diagnosed with ESRF, receive a transplant. After receiving a kidney transplant, patients are at risk of rejecting the transplant. Rapamycin, also known as sirolimus, is a drug found to decrease the number of viral infections, prevent inflammation, inhibit T and B cell proliferation, and antibody production. This drug is more promising than current calcineurin inhibitors (CNIs) used to decrease the chance of rejection, because of Rapamycin's decreased toxicity in the kidneys (Moes, Dirk Jan A.r., et al., 2015). Direct injection into the kidneys after transplantation has been shown to improve targeting efficiency(Zhou, Peng, et al., 2014). Perfecting this procedure can lead to increased survival rates after kidney transplantation.

Problem Formulation:

To improve rapamycin injection a kidney was modeled, in Ansys, as an axisymmetric 2D ellipse on the x and y plane. The following equation was used to model diffusion of the drug.

$$\frac{1}{r}\frac{\partial}{\partial r}\left(D_{ij}\, r\frac{\partial C_i}{\partial r}\right) + \frac{1}{r^2}\frac{\partial}{\partial \phi}\left(D_{ij}\, r\frac{\partial C_i}{\partial \phi}\right) + \frac{\partial}{\partial z}\left(D_{ij}\frac{\partial C_i}{\partial z}\right) + R_i = \rho C_p \frac{\partial C_i}{\partial t}$$

r = radius

C_i = initial concentration
D_{ij} = thermal conductivity
R_i = metabolic rate of the kidney
ρ = density
C_p = specific heat
The terms with respect to ϕ and z were crossed out because the concentration in our model depended only radius. The new equation is as follows:

$$\frac{1}{r}\frac{\partial}{\partial r}\left(D_{ij}\, r\frac{\partial C_i}{\partial r}\right) + R_i = \rho C_p \frac{\partial C_i}{\partial t}$$

In our model, we ignored the z axis, and therefore the thickness of the kidney. Additionally, the kidney was modeled as an ellipse in order to simplify the geometry of our model. The equation for the radius of an ellipse is as follows:

$$r = \sqrt{\frac{ab}{a\cos^2(\theta)+b\sin^2(\theta)}}$$

r = radius
a = length from center of ellipse to vertical vertex
b = length from center of ellipse to horizontal vertex
The ureter was not modeled in this project.

Solution Method:

In order to model a kidney injected with medicine, a 2D axisymmetric ellipse was used in Ansys fluent. A half ellipse was drawn axisymmetric around the y axis. A major axis length of 0.127m and a minor axis length of 0.05715m were used to model a human size kidney (Glodny, Bernhard, et al., 2009). A small half circle of radius 5.34mm was drawn at a height of 114.3mm from the x axis. The same half circle was drawn at a height of 63.5mm and 12.7mm as well. The 3 different geometries can be seen in Figure 1. The circle represents the volume of medicine injected and the three heights represent the three injection sites tested. A mouse model of direct drug injection of 50 microliters into the kidney was used to calculate the volume needed for a human which was 635 microliters (Manaph, Nimshitha Pavathuparambil Abdul, et al., 2018). This was calculated by finding the ratio of drug volume to kidney size for the mouse model and then applying it to the human kidney(Huang, Linghong, et al., 2013). These calculations can be seen in Figure 5. The ellipse face was meshed with an element size of 0.005m, the circle was meshed with an element size of 0.0001m, and a face meshing with quadrilaterals was applied. In the model set up, thermal conductivity, density, and specific heat were set to 1 to give a non-dimensional problem. Viscosity was set as the default value. The energy model was turned on and the flow equation was turned off. Gravity on the y axis was set to -9.8 m/s^2 . The boundary condition for the kidney wall was 0 $°C$ and the half circle was patched to 10 $°C$, 20 $°C$, and 30 $°C$ for each of the injection site positions to represent the concentration of the injection. These values were estimated after a patch with a concentration of 1 $°C$, as previously used in models, was too little to diffuse throughout the kidney. Previous studies showed that a high concentration in the kidney is necessary for the drug to be effective, yet a high dosage could lead to adverse effects, such as, abnormal glomerular filtration, tubular secretion, or proteinuria (Zhou, Peng, et al., 2014). Data was exported every 0.25 seconds with a time step of .25 for 1s

and analyzed on the center axis of the ellipse which had the coordinates (0m, 0m) and (0m, .127m).

Results:

Figures 2A, 2C, and 2E show the concentration of rapamycin along the line in the center of the ellipse with the injection site patched at 10 °*C* , 20 °*C* , and 30 °*C* respectively. The highest concentration in the figures listed appear at y position = .0127m which is reasonable because that was the position where we injected the rapamycin for those trials. With an injection to the bottom of the kidney, it is seen in figures 2B, 2D, and 2F for t = 1s, the more stable solution, that the concentration at the bottom of the kidney is much higher than at the top. Comparing figures 2A-F, it is seen that the magnitude of concentration is higher with a higher injection site patch, therefore the injection site patched at 30 °*C* has the highest ending concentration throughout the kidney.

Figures 3A, 3C, and 3E show the concentration of rapamycin along the line in the center of the ellipse with the injection site patched at 10 °*C* , 20 °*C* , and 30 °*C* respectively. The highest concentration in the figures listed appear at y position = .0635m which is reasonable because that was the position where we injected the rapamycin for those trials. With an injection to the middle of the kidney, it is seen in figures 3B, 3D, and 3F for t = 1s, the more stable solution, that the concentration throughout the kidney is pretty similar. The bottom section of the kidney has a slightly higher concentration than the top which could be due to gravity. Comparing figures 3A-F, it is seen that the magnitude of concentration is higher with a higher injection site patch, therefore the injection site patched at 30 °*C* has the highest ending concentration throughout the kidney.

Figures 4A, 4C, and 4E show the concentration of rapamycin along the line in the center of the ellipse with the injection site patched at 10 °*C* , 20 °*C* , and 30 °*C* respectively. The highest concentration in the figures listed appear at y position = .1143m which is reasonable because that was the position where we injected the rapamycin for those trials. With an injection to the top of the kidney, it is seen in figures 4B, 4D, and 4F for t = 1s, the more stable solution, that the concentration at the top of the kidney is much higher than at the bottom. Comparing figures 4A-F, it is seen that the magnitude of concentration is higher with a higher injection site patch, therefore the injection site patched at 30 °*C* has the highest ending concentration throughout the kidney.

Conclusions:

Due to the semi-evenly distributed concentration of rapamycin from the injection site in the middle, it is evident that the middle site would be the most applicable place to inject the drug. Assuming that the drug should be in a high concentration to work effectively but not too high to cause abnormalities, the injection site patched at 20 °*C* would be the most appropriate answer. Therefore, figures 3C and 3D show the most effective solution to rapamycin injection in the kidney. To further our experiment, we would use a 3D model of the kidney with more accurate geometry, test more injection sites, add the ureter, and find the limit between an adequate amount and a harmful amount of rapamycin concentration in the kidney. Another extension of our project would be to look at longer time periods to model how long it would actually take for the

medicine to spread throughout the kidney. Although there were assumptions in the experiment, we believe that Ansys modeling of medical problems is an important part in improving the treatment and knowledge of medical practices.

Contributions Section:

Jonathan Pierre modeled in Ansys and helped write the paper.
Anna Ashford attempted to model in Ansys and helped write the paper.

References:

Glodny, Bernhard, et al. "Normal Kidney Size and Its Influencing Factors - a 64-Slice MDCT Study of 1.040 Asymptomatic Patients." *BMC Urology*, vol. 9, no. 1, 2009, doi:10.1186/1471-2490-9-19.

Huang, Linghong, et al. "Development of a Chronic Kidney Disease Model in C57BL/6 Mice with Relevance to Human Pathology." *Nephron Extra*, vol. 3, no. 1, 2013, pp. 12–29., doi:10.1159/000346180.

"Kidney Disease Statistics for the United States." *National Institute of Diabetes and Digestive and Kidney Diseases*, U.S. Department of Health and Human Services, 1 Dec. 2016, www.niddk.nih.gov/health-information/health-statistics/kidney-disease.

"The Kidney Project Statistics." *UCSF*, The Regents of the University of California, 19 Sept. 2019, pharm.ucsf.edu/kidney/need/statistics.

Manaph, Nimshitha Pavathuparambil Abdul, et al. "A Direct and Non-Invasive Method for Kidney Delivery of Therapeutics in Mice." *MethodsX*, vol. 5, 2018, pp. 1440–1446., doi:10.1016/j.mex.2018.10.019.

Moes, Dirk Jan A.r., et al. "Sirolimus and Everolimus in Kidney Transplantation." *Drug Discovery Today*, vol. 20, no. 10, 2015, pp. 1243–1249., doi:10.1016/j.drudis.2015.05.006.

Zhou, Peng, et al. "Kidney-Targeted Drug Delivery Systems." *Acta Pharmaceutica Sinica B*, vol. 4, no. 1, 2014, pp. 37–42.

Images:

Geometry:

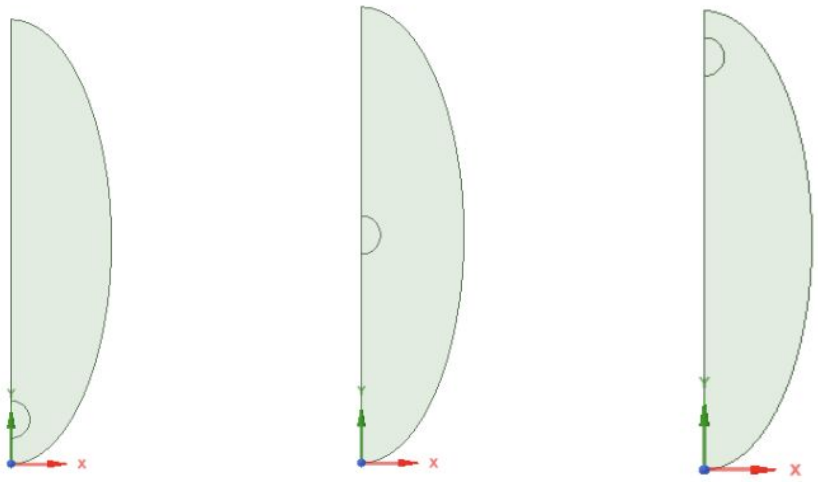

Figure 1: Axisymmetric geometries of kidney with injection site at the bottom (12.7mm), middle (63.5mm), and top (114.3mm).

Bottom Injection Site:

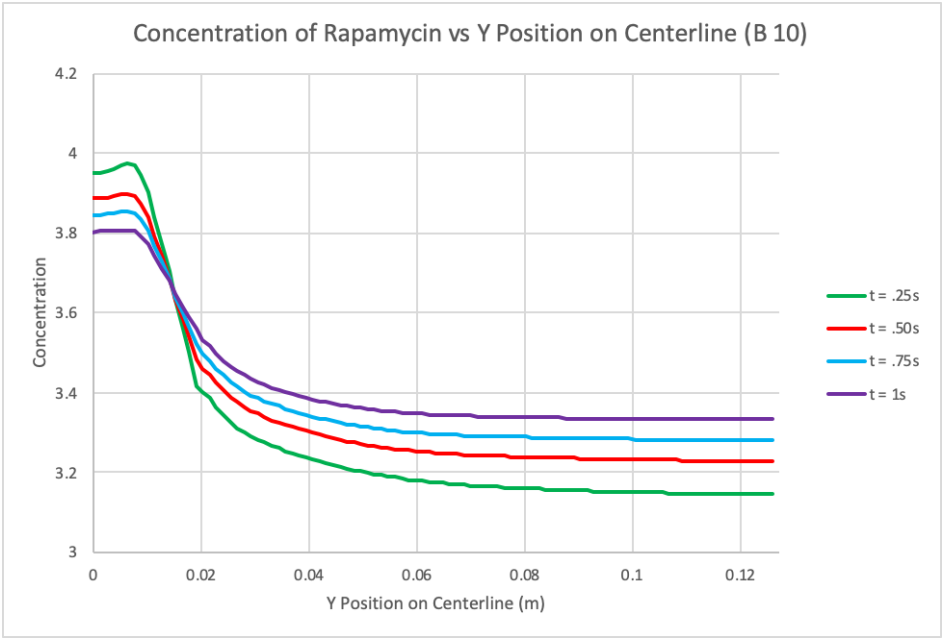

Figure 2A: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the bottom position patched at 10 °C .

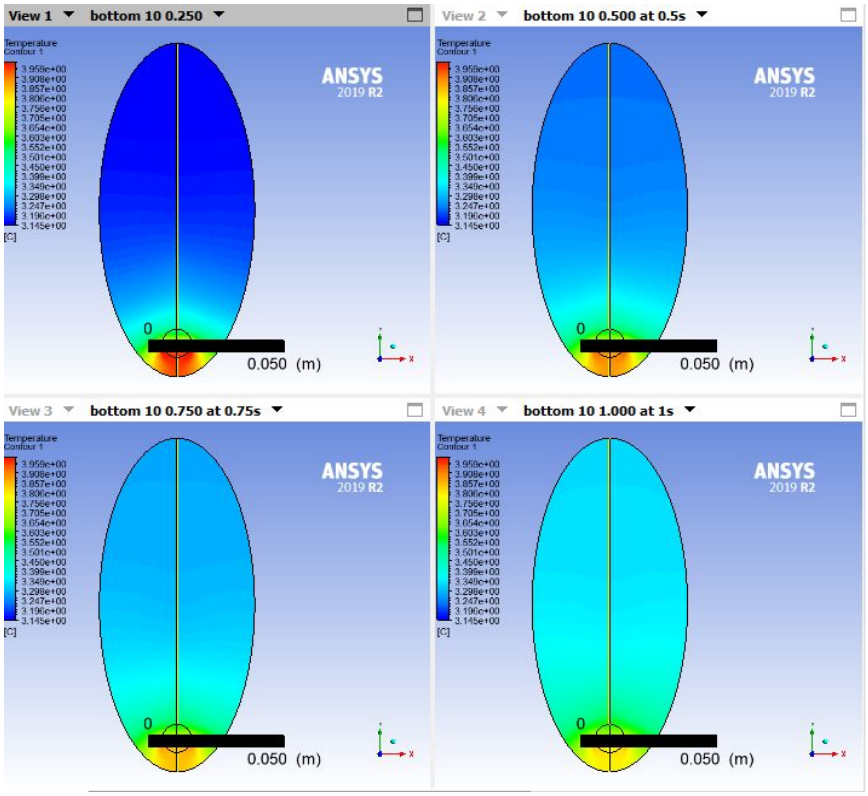

Figure 2B: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the bottom position patched at 10 °C .

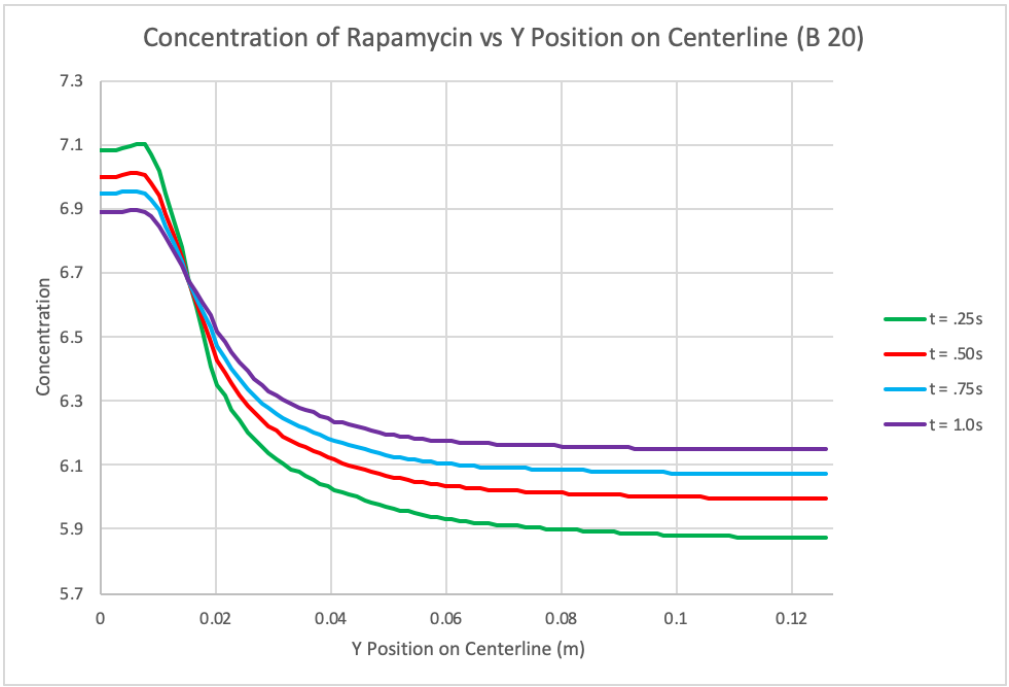

Figure 2C: Plot of Concentration of Rapamycin vs vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the bottom position patched at 20 °C .

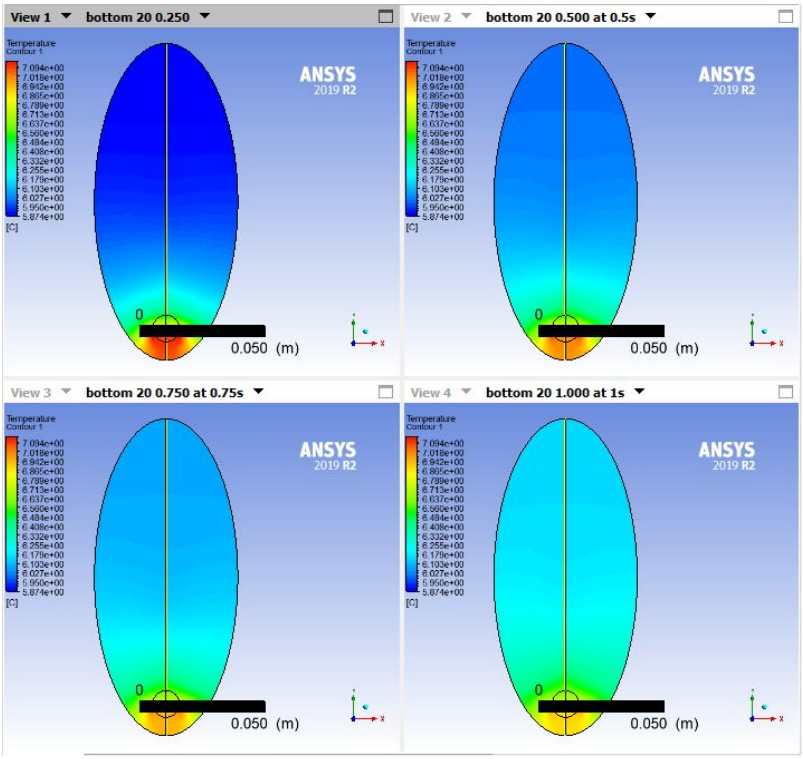

Figure 2D: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the bottom position patched at 20 °C .

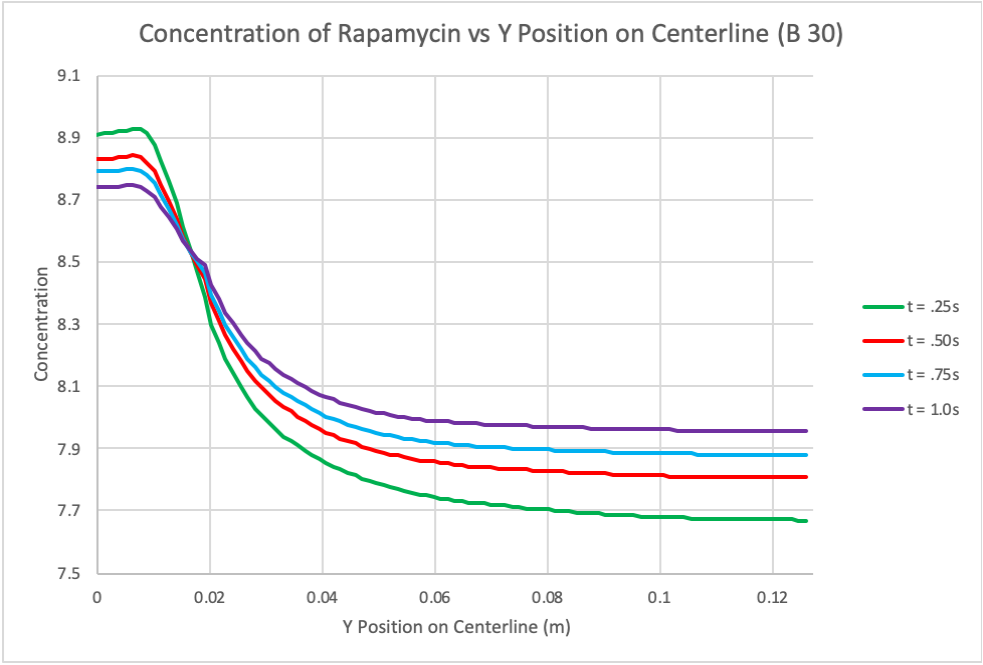

Figure 2E: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the bottom position patched at 30 °C .

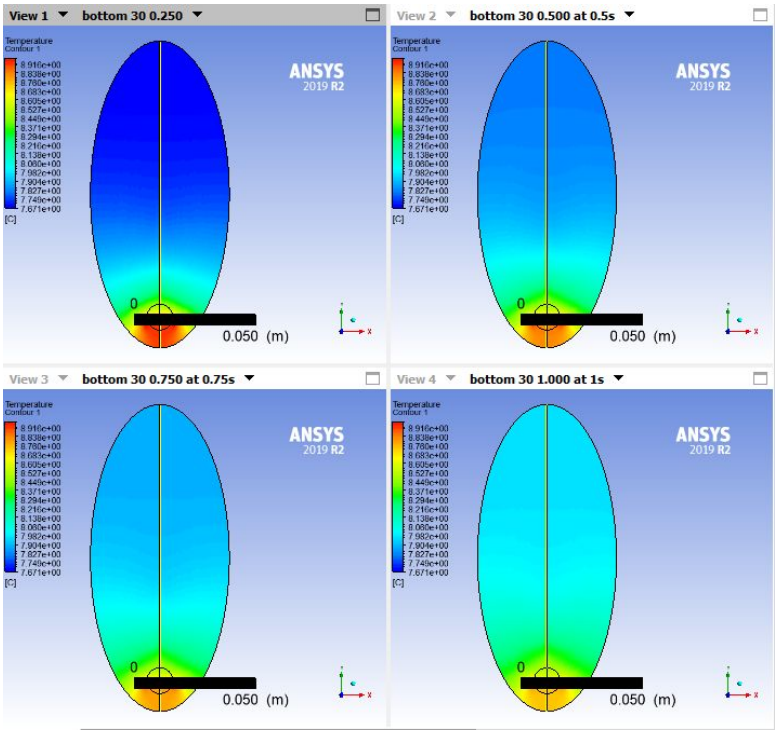

Figure 2F: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the bottom position patched at 30 °C .

Middle Injection Site:

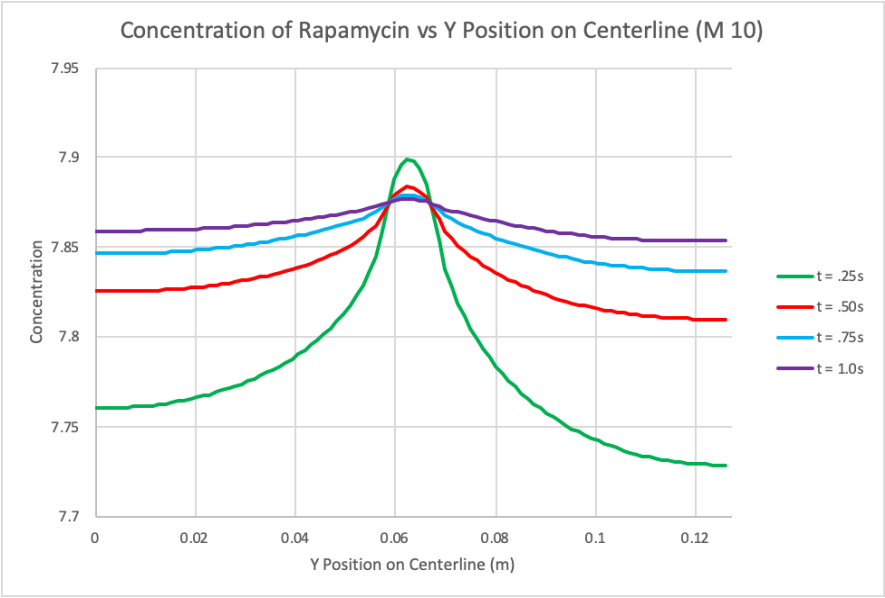

Figure 3A: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the middle position patched at 10 °C .

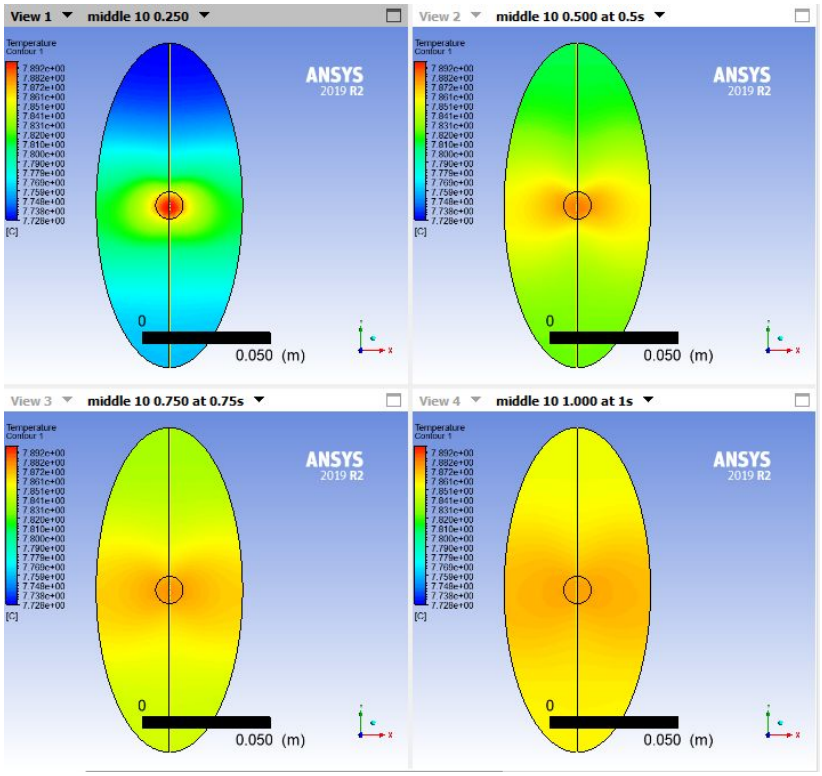

Figure 3B: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the middle position patched at 10 °C .

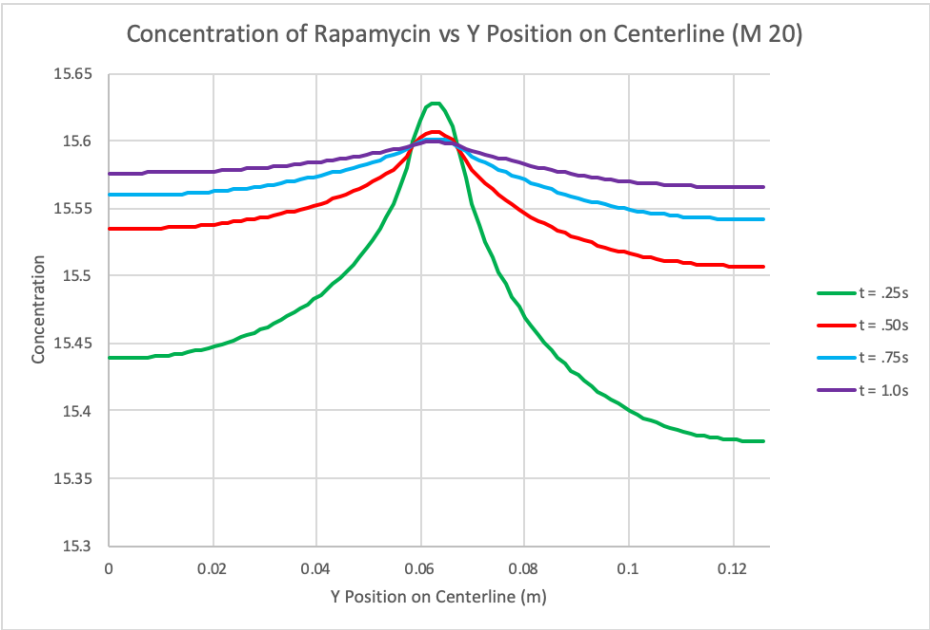

Figure 3C: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the middle position patched at 20 °C .

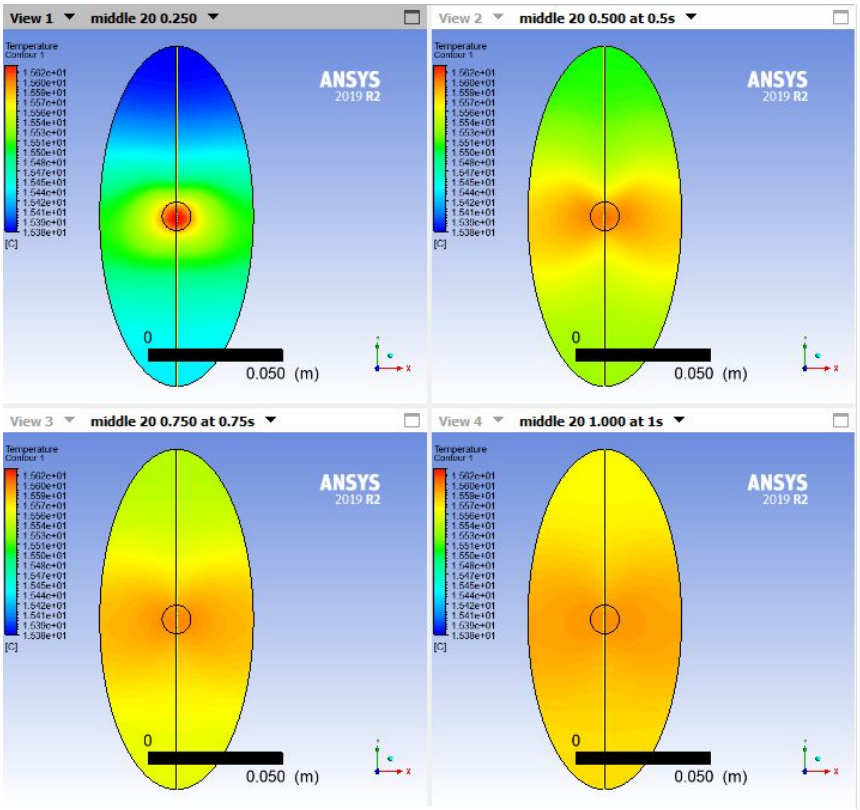

Figure 3D: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the middle position patched at 20 °C .

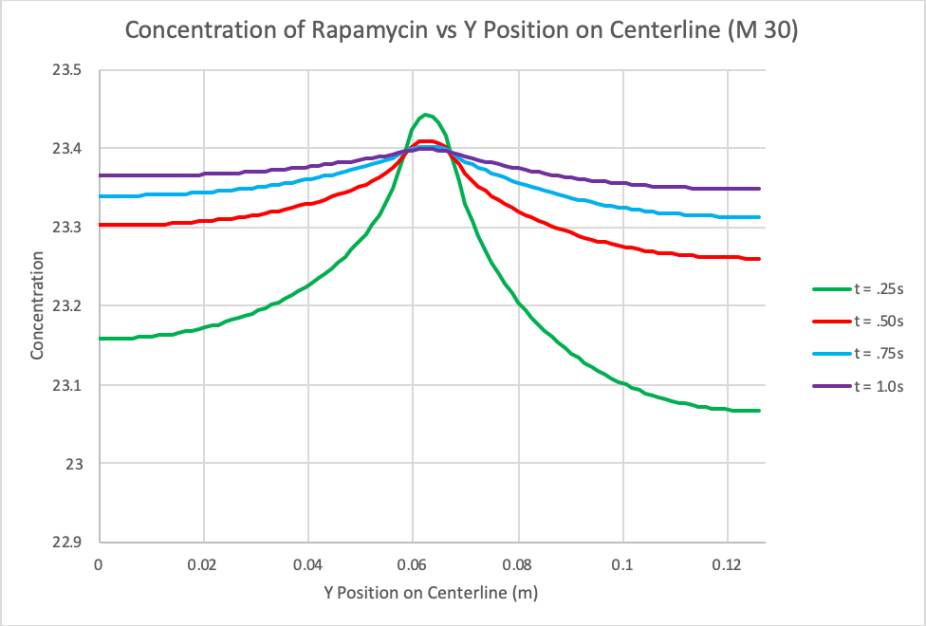

Figure 3E: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the middle position patched at 30 °C .

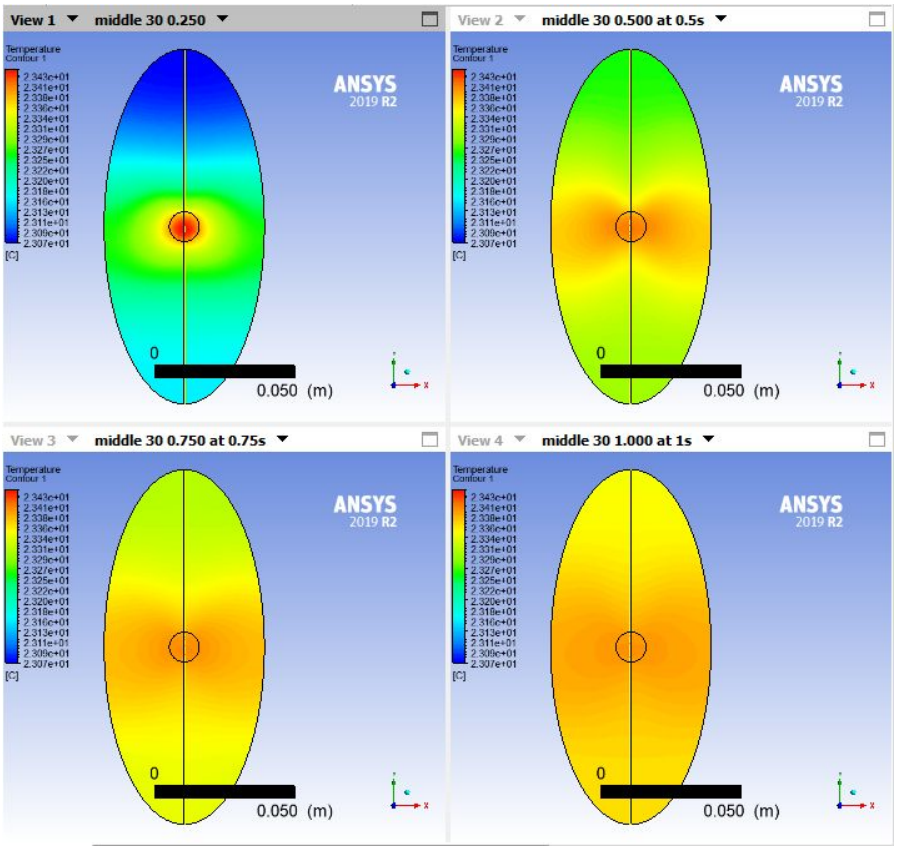

Figure 3F: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the middle position patched at 30 °C .

Top Injection Site:

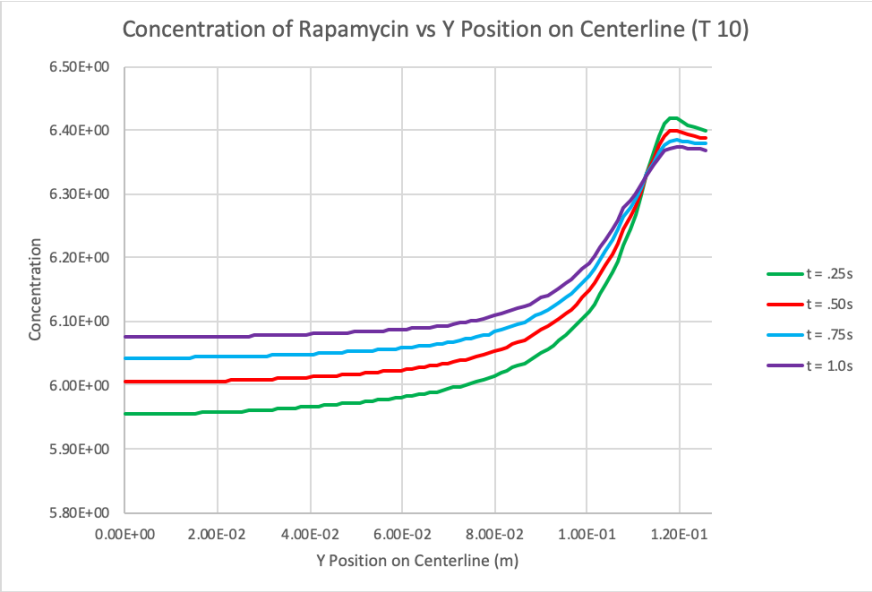

Figure 4A: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the top position patched at 10 °C .

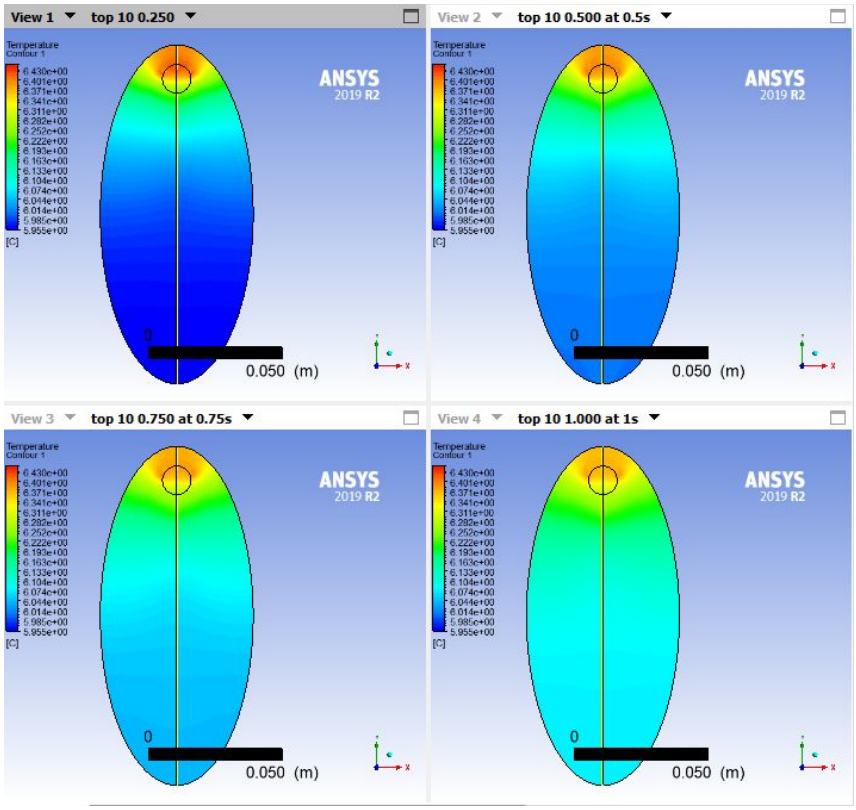

Figure 4B: Image of the temperature contours fort = .25s, .50s, .75s, and 1.0s at the top position patched at 10 °C .

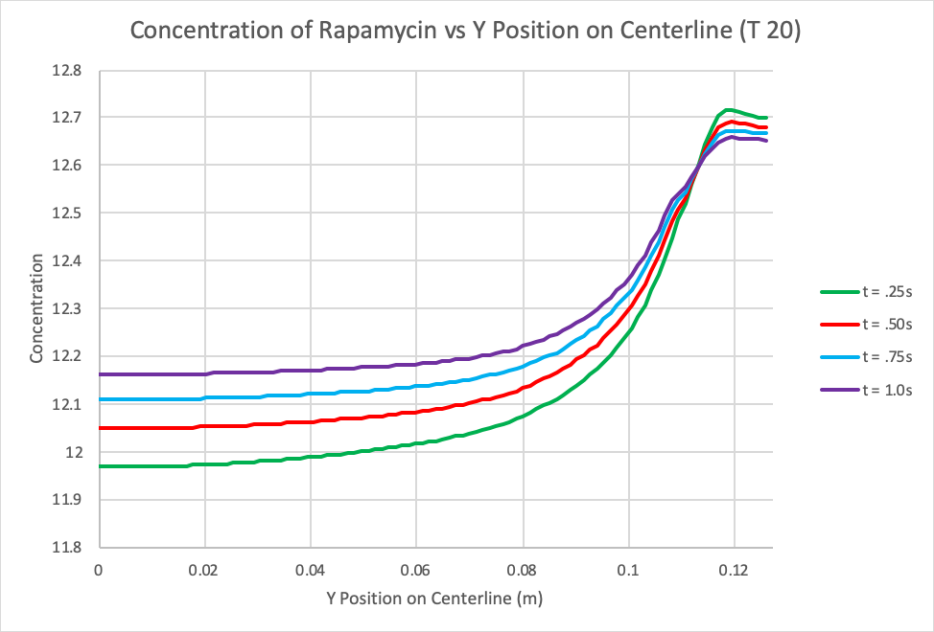

Figure 4C: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the top position patched at 20 °C .

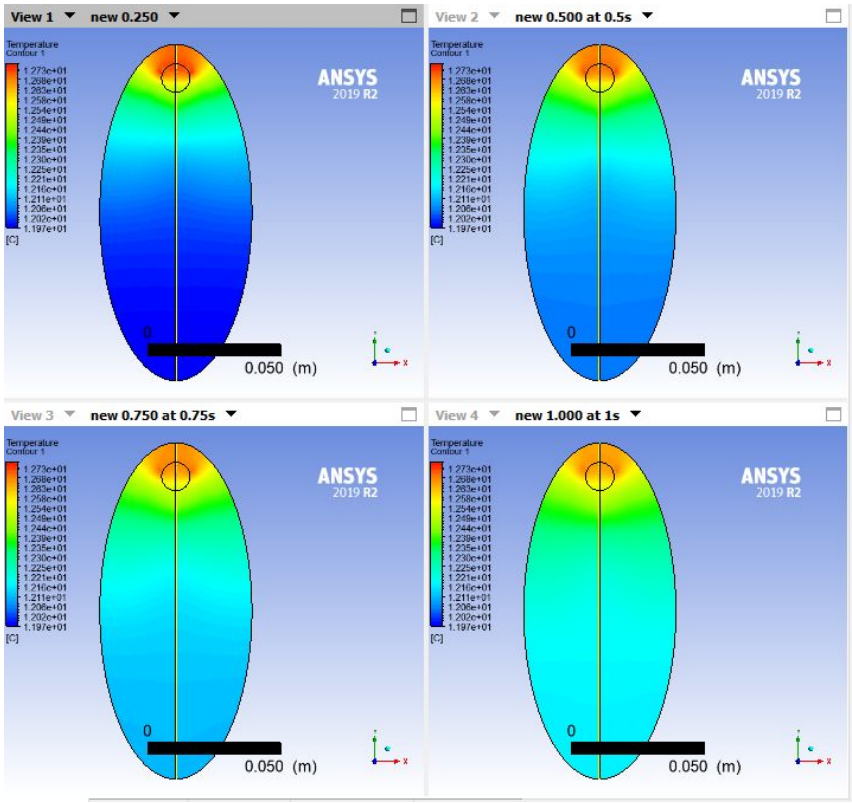

Figure 4D: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the top position patched at 20 °C .

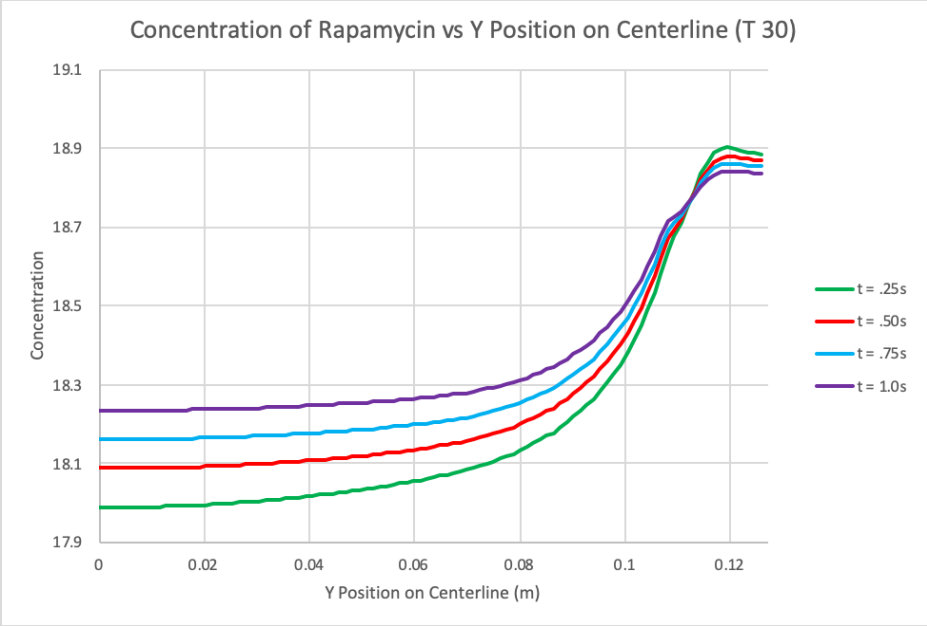

Figure 4E: Plot of Concentration of Rapamycin vs Y Position on Centerline for t = .25s, .50s, .75s, and 1.0s at the top position patched at 30 °C .

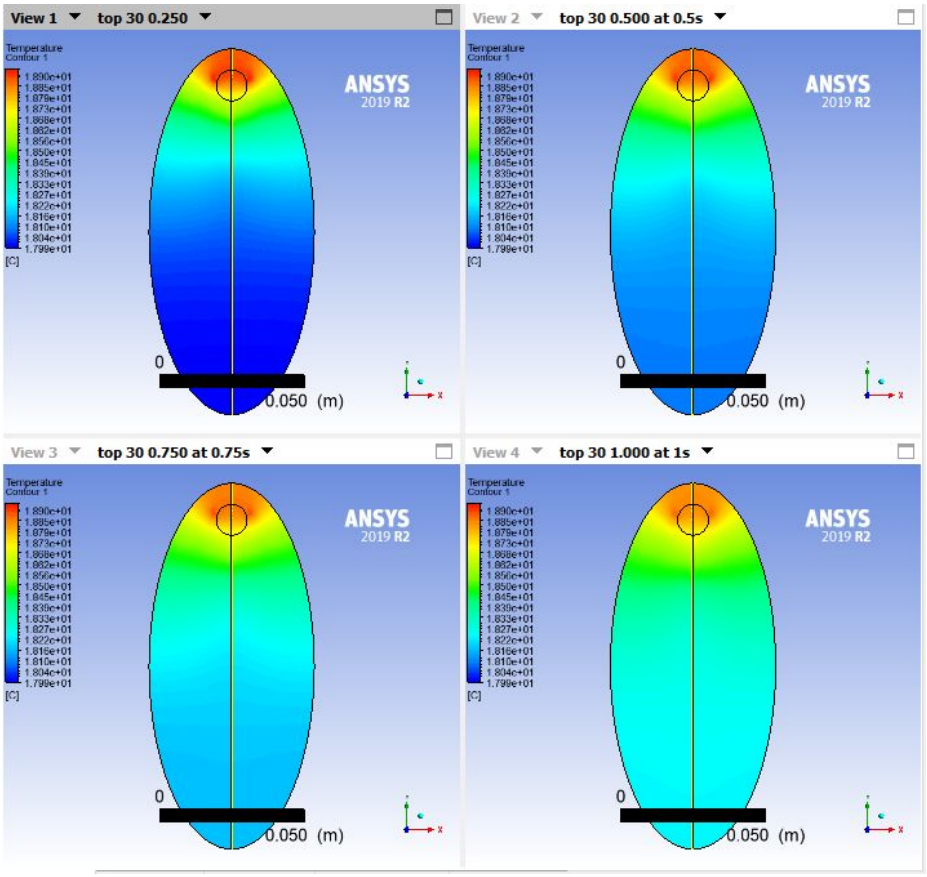

Figure 4F: Image of the temperature contours for t = .25s, .50s, .75s, and 1.0s at the top position patched at 30 °C .

Calculations:

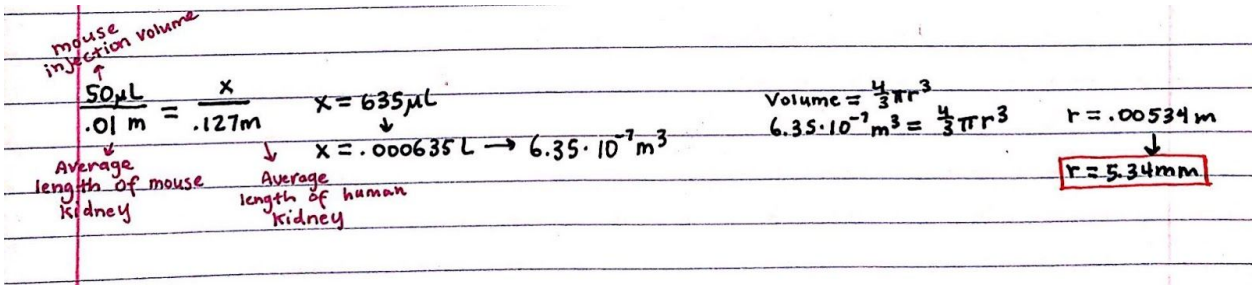

Figure 5: Image of the calculations used to find the appropriate radius of the injection site. This was used to form an accurate amount of the volume of rapamycin needed.