Corticosteroid Injection for the Treatment of Rheumatoid Arthritis in the Knee

BEE 4530: Computer-Aided Engineering:

Applications to Biomedical Processes

Kyoung Won Cho

Rebecca Bae

Yoon Soo Kim

George Markt

December 6, 2010

Table of Contents

I. Executive Summary

Rheumatoid Arthritis is a chronic inflammatory disorder that affect various tissues and organs, but principally synovial joints. Among the many affected joint regions, our model focuses on the knee, especially synovial fluid section where the actual inflammation occurs. For treatment, we use a corticosteroid drug named, methylprednisolone, via intra-articular injection, which is the most effective method during the severe state of the disorder. However, due to the high occurrence of side effects, mainly the seeping out of the drug and thus damage to the unwanted regions outside synovial fluid, a careful construction method in delivering the drug is necessary.

For our design, COMSOL was used to model the diffusion of corticosteroid in synovial fluid of the knee joint. We designed the model as 2D axialsymmetry with torus-shaped injection as a result of the symmetry. We aimed to achieve the thorough diffusion of the drug inside the inflamed synovial fluid by finding the optimum location of the injection site of the corticosteroid without any side effect. With all the parameters obtained from literature survey along with one calculated parameter, the diffusivity of the drug in synovial membrane, we were able to find the optimal location of the injection site as 0.02m from the axis of symmetry. Therefore, we can conclude that our optimal injection site occurs at 0.02m from the axis of symmetry that produces highest allowable drug concentration throughout the fluid without any side effect.

II. Introduction

i. Background

Our project entails designing and solving a mass transfer problem for corticosteroid injection in the knee for the treatment of rheumatoid arthritis patient.

Corticosteroids, a synthetically produced cortisol (a hormone produced in the adrenal cortex) or often just called "steroids", were once regarded as miracle-drug for their striking effect in the arthritis patients. The result was so remarkable that it was thought that the cure for arthritis has finally been discovered. However, as the use of corticosteroids increased substantially, its side effects started to emerge one by one and naturally, the use of it became more conservative to an extent of some patients declining any treatment using corticosteroid. Nonetheless, corticosteroids are powerful agents that hold a great potential and outcome when administered with proper guidelines.[1]

Corticosteroids are a class of medications that are related to cortisone. They reduce inflammation. When corticosteroids relieve pain, it is because they have reduced inflammation. Steroids work by decreasing inflammation and reducing the activity of the immune system. Inflammation is a process in which the body's white blood cells and chemicals can protect against infection and foreign substances such as bacteria and viruses. In certain diseases, however, the immune system doesn't function properly. This might cause inflammation to work against the body's tissues and cause damage. Steroids reduce the production of inflammatory chemicals in order to minimize tissue damage. Steroids also reduce the activity of the immune system by affecting the function of white blood cells.[2]

Corticosteroids are versatile in their mode of applications. They can be given:

- orally
- injected into the vein or muscle
- applied locally to the skin (ointment)
- injected directly into inflamed joints.[3]

We chose the method of injecting the corticosteroid directly into inflamed joints (knee joint). The benefit of corticosteroid injection is that the relief of localized inflammation is more rapid and powerful than with traditional anti-inflammatory medications given orally. A single injection also can avoid certain side effects such as irritation of the stomach that can accompany many oral anti-inflammatory medications. Cortisone injections can be administered easily in the doctor's

[1] Brezinschek et al., "Treatment of rheumatoid arthritis in the 21st century: targeting B-lymphocytes," *Wien Med Wochenschr* (2006) 156/1-2: 61-67.
[2] Santos et al., "The role of macrophage migration inhibitory factor in the inflammatory immune response and rheumatoid arthritis," *Wien Med Wochenschr* (2006) 156/1-2: 11-18.
[3] Leonard E. Lockman., "Knee joint injections and aspirations," *Canadian Family Physician* (2006) 52: 1403-1404.

office. Other advantages include the rapid onset of the medication's action, dependability, and minimal side effects. However, some side effects are followed by this method of corticosteroid injection.[4]

Most of the short-term side effects are uncommon but include weakening of tendon, soreness at the injection site, depigmentation of the skin at the injection site, and local bleeding from broken blood vessels in the skin or muscle. Long-term risks of corticosteroid injections depend on the dose and frequency of the injections. With higher doses and frequent administration, potential side effects become more severe including thinning of the skin, easy bruising, weight gain, puffiness of the face, elevation of blood pressure, thinning of the bones, and a rare but serious damage to the bones of the large joints.[5]

ii. Design Objectives

Most of the side effects occur because the corticosteroid cannot be contained within the synovial membrane where the inflammation occurs. Instead, the drug seeps out to other parts of the body, such as cartilage, tendon, and muscle. Thus, the dosage of corticosteroid and frequency of the injections must be scrutinized to prevent some of these side effects.[6] The main goal of this study is to design a model for the diffusion of a known initial concentration of corticosteroid in the knee by finding the optimal location of drug injection site. We must find the ideal position of the injection that is within the limit of the length of the syringe that allows for the spread of the drug throughout the synovial fluid in the shortest period of time with minimal spreading into surrounding tissue to prevent any side effects.

In order to find the optimal location of the injection site, we must know all the parameters in our model in advance so that our only varying parameter can be the distance of the injection site. Those parameters include the diffusivity of synovial fluid, synovial membrane, cartilage, muscle and the reaction rate of the drug. Also we must find out the minimum effective dosage of the corticosteroid in order to know if the drug is actually working when it diffuses in the synovial fluid while at the same time being ineffective outside the fluid.

We will design our injection with careful consideration of geometry. Since our model is 2D axialsymmetry (further explained in the following schematic section), we have to make the injecting point a circle-shape in order to contain the given volume of the drug when the model is rotated around the axialsymmetry. When it is rotated, the injection point would result in the shape of torus (doughnut-like structure). The resulting volume of the torus has an equation of $V = 2\pi^2 R r^2$ where R is the distance from the center of the circle to the axis of rotation and r is

[4] Lockman 1403-1404.
[5] George Schett, "Rheumatoid arthritis: inflammation and bone loss," *Wien Med Wochenschr* (2006) 156/1-2: 34-41.
[6] Gudbjornsson et al., "Synovial concentrations of the angiogenic peptides bFGF and VEGF do not discriminate rheumatoid arthritis from other forms of inflammatory arthritis*," Scandinavian Journal of Clinical & Laboratory Investigation* (2004) 64: 9-16.

the radius of the circle being rotated, in our case, the injection site. Thus, when we change the position of the injection site, we must also change the size of the circle in order to maintain the same volume needed for the drug. This would mean that the value r (radius of the circle) would have to be larger as the circle gets closer to the axis of symmetry since the value of R (distance from the center of the circle to the axis of rotation) would also get smaller in order to maintain the same V (volume of torus).

iii. Problem Schematic

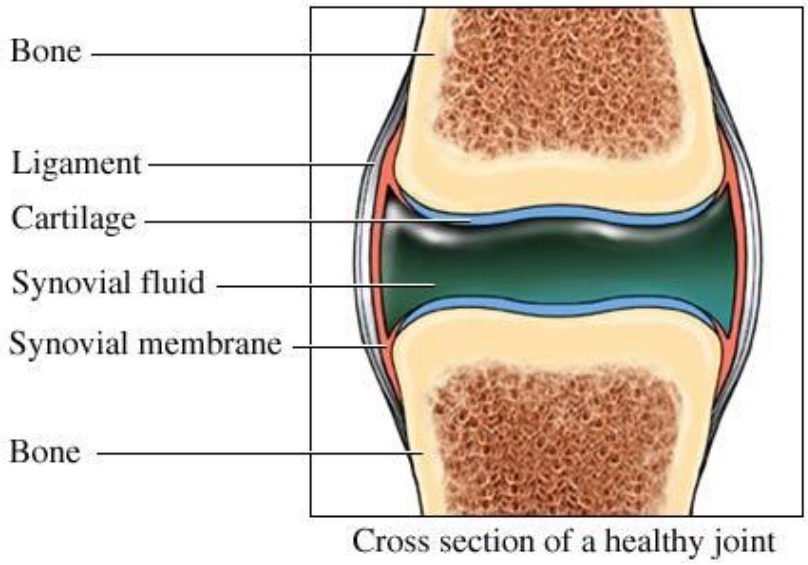


Figure 1. Cross section of a healthy knee joint

Figure 1 shows an image of the cross section of the knee with its various parts: bone, ligament, cartilage, synovial fluid, and synovial membrane. The area that we are most interested is synovial fluid since it is the place where injection takes place and where most inflammation occurs.

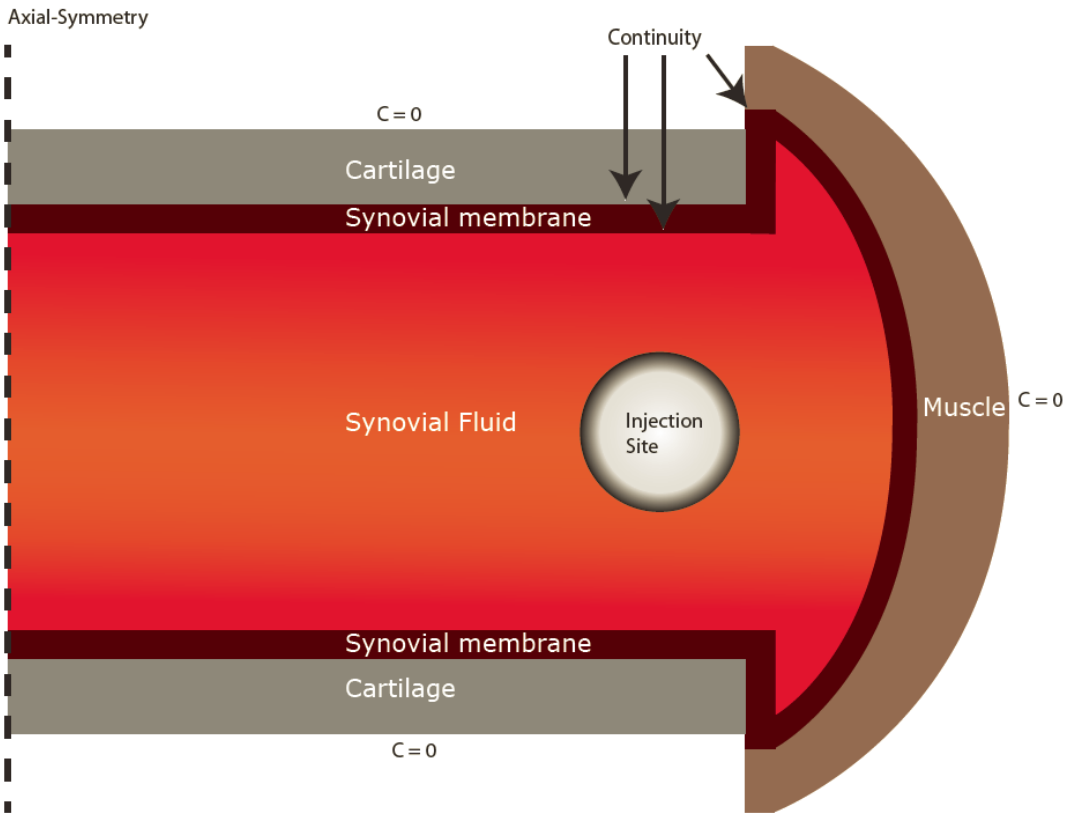
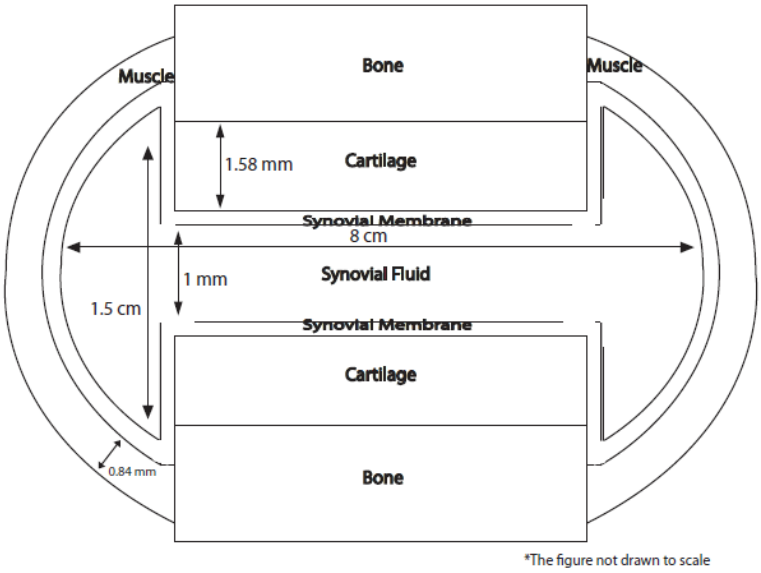


Figure 2. Simplified schematic of a knee joint with boundary conditions

The actual physical structure of the knee is obviously in 3D with irregular symmetry. But when we took a closer look at it from the side, we found a possibility of reducing it to a 2D model with axial-symmetry. The synovial fluid is located inside the joint capsule, in between the femur and the tibia. We get axial-symmetry geometry by cutting it vertically at the center and considering only the right half of the model. So when we put a circular injection site inside the fluid and rotate it 360 degrees around the symmetry, we would get a doughnut-like structure, or torus as mentioned in the design objectives section, that includes the effect of the drug in the whole synovial structure of the knee. In the geometry, we included as many anatomical parts as possible to account for the regions that would be affected (positively or negatively) by the drug. They are the synovial fluid, synovial membrane, cartilage, and muscle. We excluded bone because we assumed the drug to be harmful (causing side effect) once it reaches cartilage, which is located before bone. Also, the area of synovial fluid has increased from its original size because we are modeling the knee when the patient has rheumatoid arthritis and under the condition, the synovial fluid region expands due to high inflammation.



Synovial Fluid	
Diameter	8cm
Height	1.5cm
Muscle	
Thickness	0.84mm
Cartilage	
Thickness	1.58mm
Synovial Membrane	
Thickness	0.1cm

Figure 3. Simplified schematic of knee joint with dimensions[7,8]

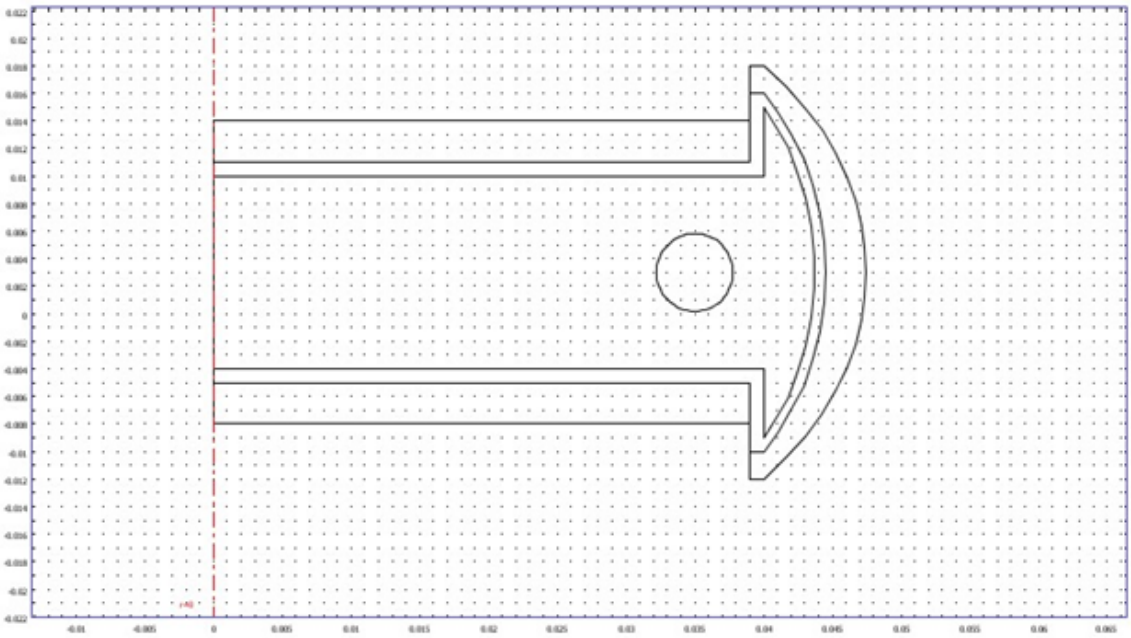


Figure 4. Simplified schematic of knee joint in COMSOL

Figure 4 depicts the actual design of the model used when it is implemented in COMSOL with the right dimensions from figure 3.

[7] Beattie et al., "Minimum joint space width and tibial cartilage morphology in the knees of healthy individuals: A cross-sectional study," *BMC Musculoskeletal Disorders* (2008) 9: 119.
[8] "Knee Anatomy," *eORIF.com* 17 Oct. 2010 <http://www.eorif.com/KneeLeg/KneeLeg%20anatomy/Kneeanatomy.html>

III. Results and Discussion

i. Solution Analysis

In order to make the location of the injection site as our only variable, we had to figure out all the other parameters from literature or given value. We were successful in obtaining all the parameters except for the diffusivity value of drug in synovial membrane. We could not randomly guess and continue with our model without this parameter especially since it has a crucial role of containing the inflammated synovial fluid and the drug inside. Thus, we had to do a separate calculation just to find this parameter. In order to find the optimal diffusivity value of drug in synovial membrane, we picked a point near the center of the synovial fluid and tested whether the drug reaches to the point at varying diffusivity values. The high concentration of the drug at the center would indicate the well spreading of the drug and validate its effectiveness in the synovial fluid.

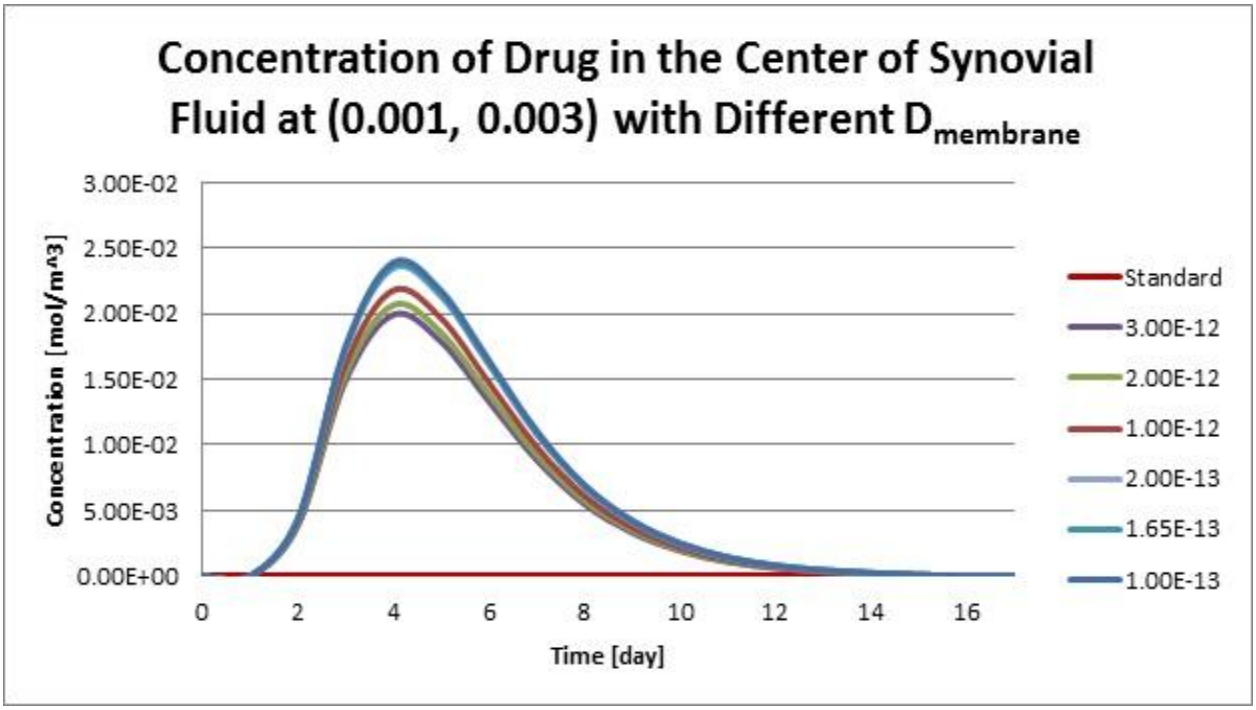


Figure 5. Solution to find the optimal diffusivity of the drug in synovial membrane

In order to validate the effectiveness of the drug, we found the minimum effective concentration of the drug in synovial fluid in horse (closest data we could find) to be $8 \times 10^{-5} \frac{mol}{m^3}$. From the range of diffusivity values tested, we can conclude that any value within the range allows the drug to spread to the center since the maximum concentration values are higher than the minimum effective dosage. We can also observe the trend that as the diffusivity increases, the concentration of drug near the center point decreases. From the trend we can conclude that it is

better to lower the diffusivity as much as possible to increase the concentration of drug that reaches the center.

Even though we want the drug to spread as much as possible to the center, we want it so that it does not cause any side-effects. In order to test whether the diffusivity value causes side-effect, we picked a point in cartilage where drug reaches first. We compared the concentration of drug at that point with the obtained value of the minimum effective dosage of the drug. It would have been ideal to obtain the minimum level of toxicity of the drug that causes harmful side effects in cartilage, but we just could not find it from our literature survey.

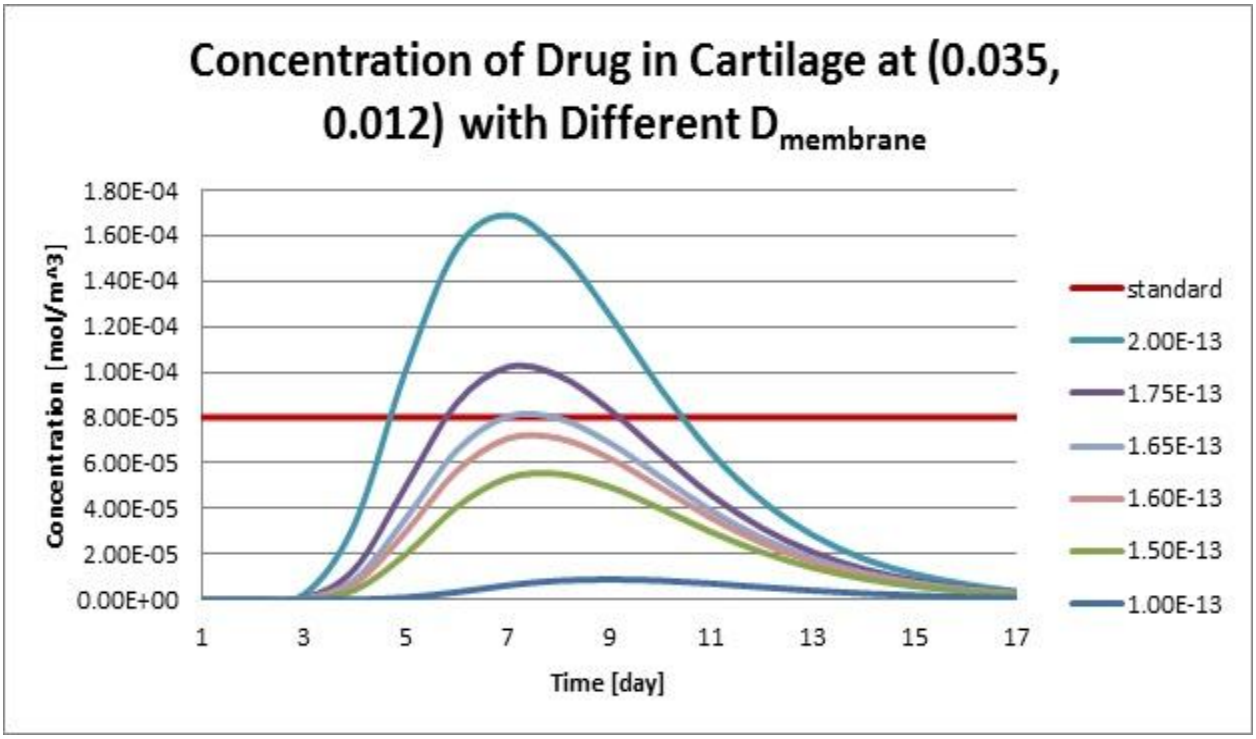


Figure 6. Solution to find the optimal diffusivity of the drug in synovial membrane using the data for the known concentration of the drug in cartilage that causes side effects

The graph suggests that diffusivity values above $1.60 \times 10^{-13} mol/m^3$ causes effective drug potency, which is harmful in the cartilage. Thus the diffusivity of membrane value was chosen to be $1.60 \times 10^{-13} mol/m^3$ for it is outside the range of dosage that causes side effect while having the highest allowed concentration for effective delivery in synovial fluid. We can also see a trend that as the diffusivity of the membrane increases, the concentration of the drug in cartilage also increases. This makes sense since higher diffusivity in the membrane would allow particles of the drug to pass more easily out of the fluid via membrane.

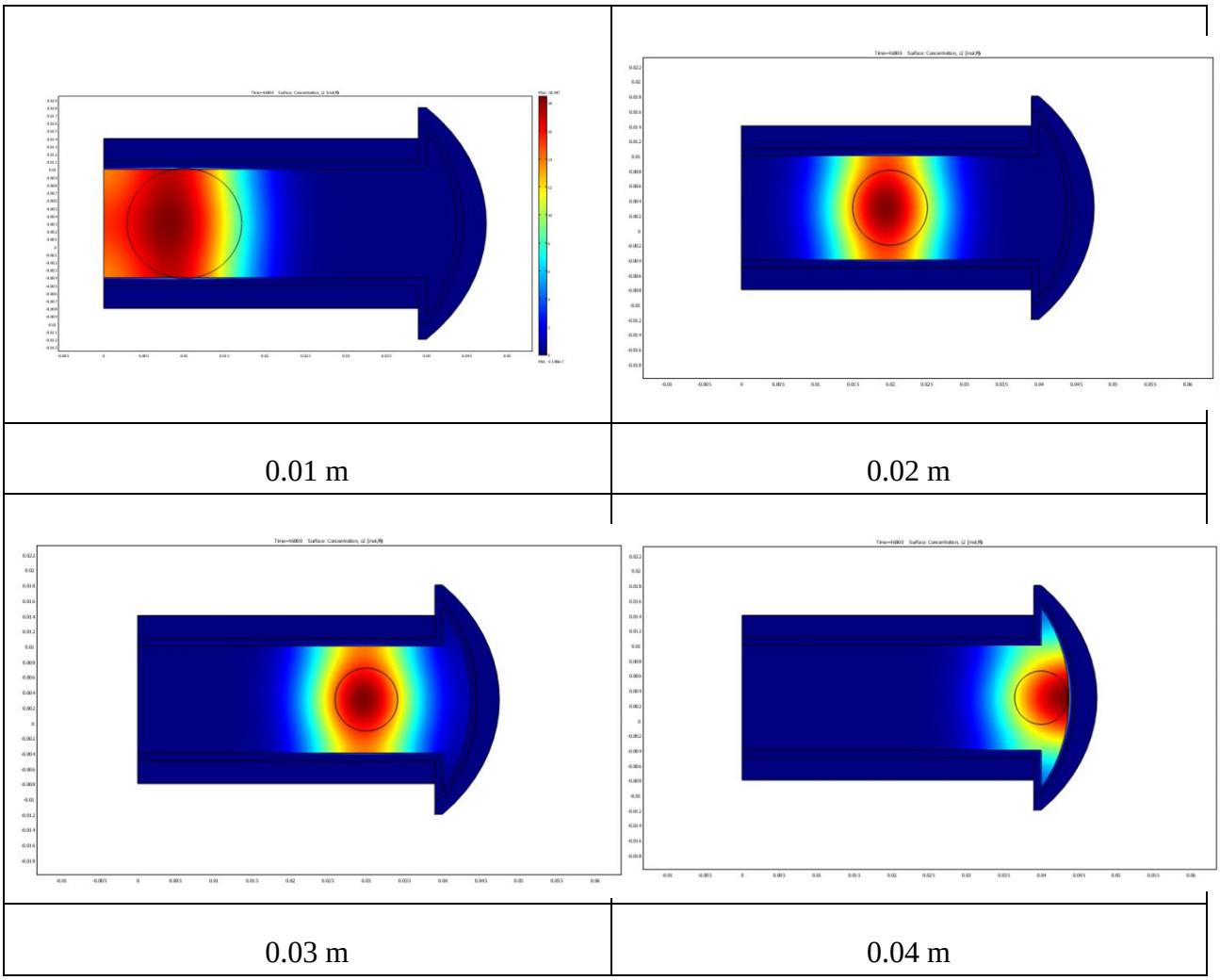


Figure 7. Contour plots that show the drug diffusion at maximum average concentration in the synovial fluid with various positions from the axis

The drug, methylprednisolone, is administered via syringe. Depends on the size of the knee, the length of syringe may vary from 1 in to 2 in. Most widely used syringe length is 1 ½ in which is approximately 0.038 m, thus, various models with different locations of injection site were tested.[9] Because the model is in axial symmetry, the formula of torus volume has to be implemented to calculate correct size of initial drug injection site. Thus, as the injection site closer to the axis symmetry the radius of injection site circle becomes larger (Refer to the Appendix *A2. Boundary & Initial Conditions*). However, the change of circle size (injection site) does not depend on the total initial concentration of the drug. The bigger circle of injection site

[9] "Knee Joint Injection," *Family Practice Notebook* 20 Nov. 2010 <http://www.fpnotebook.com/ortho/procedure/knjntinjctn.htm>

does not mean higher initial concentration than the smaller circle of injection site. However, according to the figure above, it seemed that the diffusion of the drug within the synovial fluid is more efficient at 0.01m than that at 0.04m. To find the most optimal location of the injection site that diffuses well and presents the highest drug concentration in the fluid, the average concentration of the drug in the synovial fluid, which is the most important structure where the inflammation is reduced by the drug, was calculated for each model at different injection sites

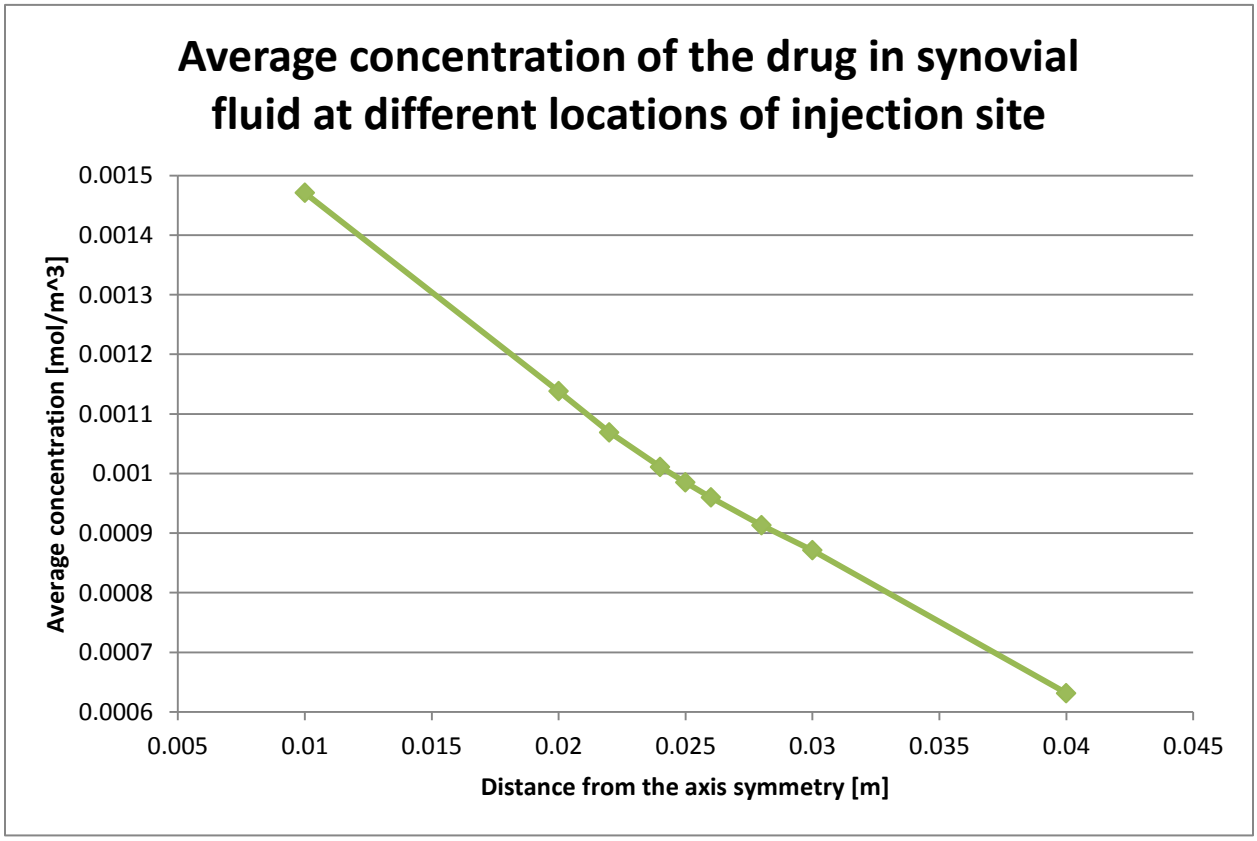


Figure 8. The change in average concentration of the drug in the synovial fluid depending on the injection site location from the center of the axis

As the injection site is closer to the axis, the more average concentration of the drug was present. Not only sites at 0.01 m, 0.02 m, 0.03 m, and 0.04 m, but more sites at between 0.02 m and 0.03 m also were tested to see any difference with minimal change in the locations of injection site. The decrease of the average concentration was relatively steady throughout from 0.01 m to 0.04 m. Although the concentration decreased as the injection site becomes farther away from the axis, the actual difference of the concentration from 0.01 m to 0.04 m was approximately 0.000839 mol/m^3. Not much difference of concentration was with changing the distance of the injection site from the axis or center. In other words, the locations of the injection site do not bring significant effect. Also, the minimum effective concentration for the drug is about 0.00008

mol/m^3. The results at all the different locations are higher than the minimum effective concentration.

Because there is not much difference of concentration at various locations of the injection and all the concentrations at different injection location are higher, the length of syringe was account to find the optimal location of injection site. 1 ½ inch syringe (0.038 m), which is most widely used, was account for the length of syringe. Because there is no specific dimension of the skin, subcutaneous fat, and muscle, the approximate thickness of layers outside of the synovium was considered. Since the closer injection site to the axis, the higher the concentration, the maximum point where the syringe can be injected into the synovial fluid was at 0.02 m from the axis. Thus, the most optimal location of injection site was at 0.02 m from the axis.

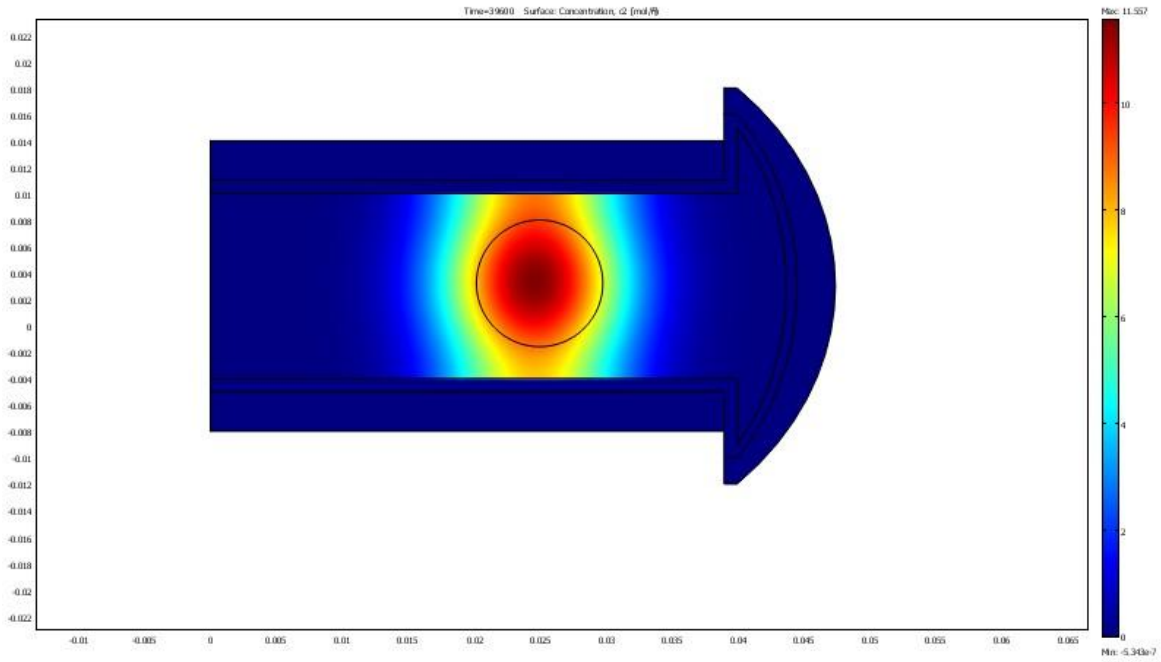


Figure 9. The contour plot with the injection site at the optimal location, 0.02 m from the axis, at maximum concentration, which is 11 hours after injection

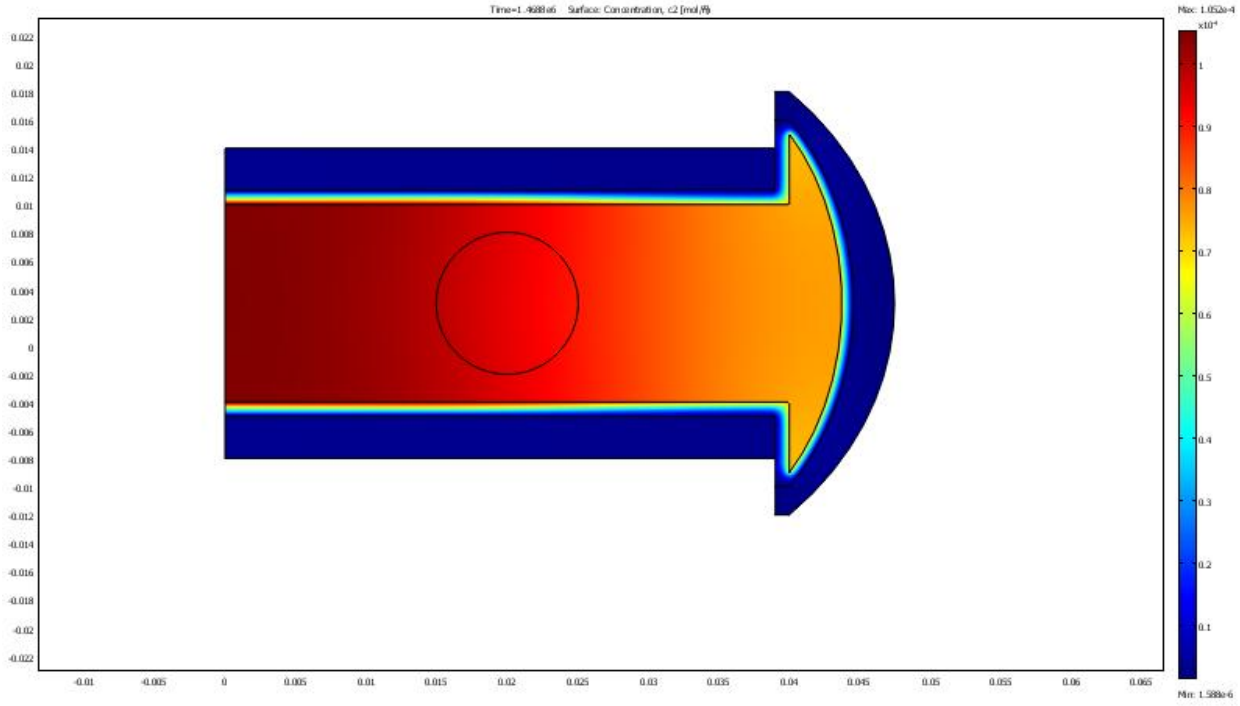


Figure 10. The contour plot with the injection site at the optimal location, 0.02 m from the axis, after 17 days

ii. Accuracy Check

Table 1. Mean maximum drug concentration and time of peak in Armstrong et al paper.[10]

Table 2 *Serum methylprednisolone* after intra-articular injections*

Group no.	*Patient no.*	*Amount of steroid injected into each joint (mg)*	*Maximum serum conc. of methylpred. (MP) (nmol/l)*	*Mean maximum serum conc. (nmol/l)*	*Time of peak (h)*
1	1	40	72·1	178·9	12
	2	1 knee	109·5		4
	3		475·3		4
	4		114·8		2
	5		122·8		2

An accuracy check of our design was conducted by comparing our results with results from related literature named *Serum methylprednisolone levels following intra-articular injection of*

[10] Armstrong et al., "Serum methylprednisolone levels following intra-articular injection of methylprednisolone acetate," Annals of the Rheumatic Diseases (1981) 40: 571-574.

methylprednisolone acetate by Armstrong et al. in the paper, they tested twenty one patients who have Rheumatoid Arthritis with two different concentration of the drug, 32 mol/m^3(40 mg) and 64 mol/m^3(80 mg). Then they obtained the maximum drug concentration along with the time of occurrence. From table 1, their results for 32 mol/m^3 concentration were 0.000178 mol/m^3 for the mean maximum serum concentration and 4.8 hours for the mean time of peak. Compared to our results, 0.001138 mol/m^3 and 12 hours, we have higher values for both the maximum drug concentration and time of peak.

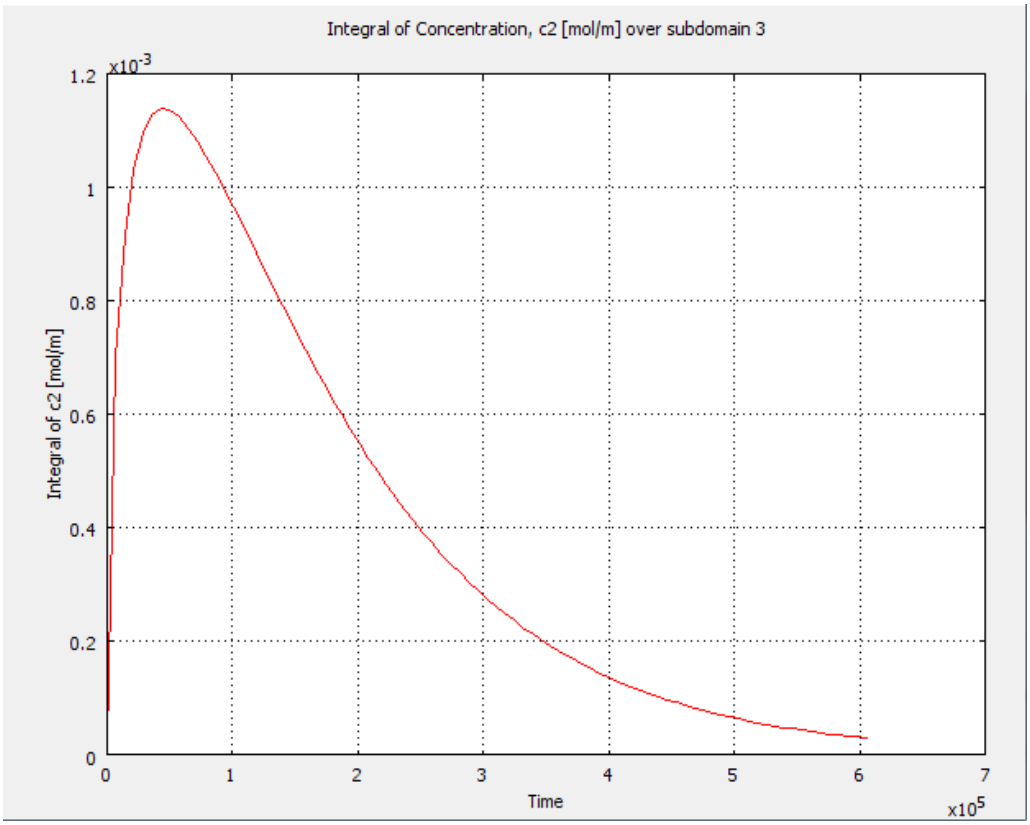


Figure 11. Maximum drug concentration in synovial fluid over 7 days

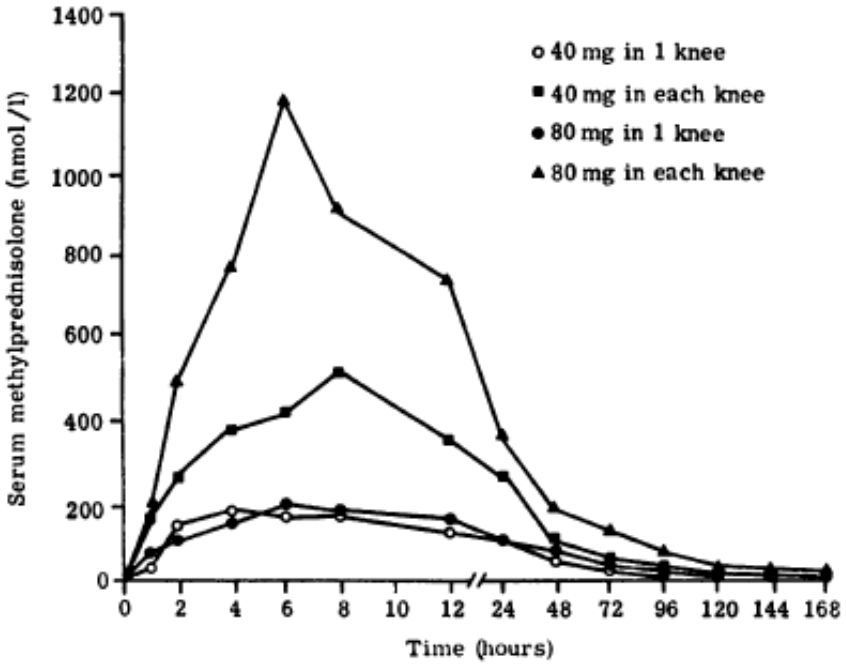


Figure 12. Mean serum methylprednisolone levels following intra-articular injections of methylprednisolone acetate with various dosages

However, when we take a look at figures 12 and 13, which depict the maximum drug concentration over 7 days for our model and that of paper, respectively, we see a very similar shape with a general pattern of steep rise in the first few hours and a complete depletion of the drug in the remaining days. Note that the general skewness might misleadingly look more centered in figure 13 due to the increased time step after 12 hours.

According to the paper, “in most patients the serum drug levels reached their maxima at times between 4 and 8 h after the dose and the drug cleared from circulation almost completely, depending on the size of the dose, within 3-5 days.” Although we obtained our maxima at 12 hours, it is clear that our drug concentration depleted almost completely after 3-5 days, which is in accordance with the paper.

iii. Sensitivity Analysis

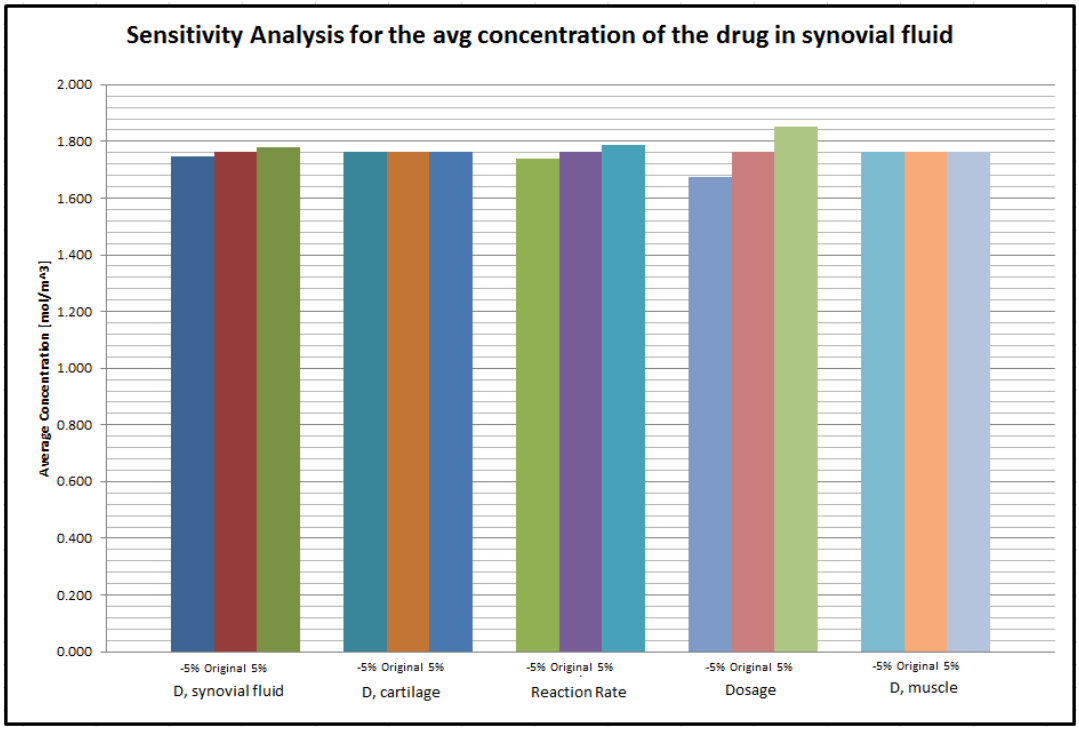


Figure 13. Sensitivity analysis of parameters used, such as $D_{synovial\ fluid}$, $D_{cartilage}$, reaction rate, dosage, and D_{muscle}.

To determine how the model is sensitive to each parameter, the sensitivity analysis was performed on each parameter: the diffusivity of the drug in synovial fluid, the diffusivity in cartilage, the reaction rate of the drug, the initial concentration of the drug, and the diffusivity in muscle. The variation of the value of each parameter was 5%. The average concentration of the drug in the synovial fluid was calculated for one variation at a time, while keeping constants for all other parameter values. The synovial fluid was chosen to examine the sensitivity because this region is where the most process of treatment occurs.

The sensitivity analysis shows that almost no change of average concentration with varying diffusivity values either in cartilage or in muscle. This result was predicted because the drug is supposed not to diffuse outside of the synovial membrane. The most sensitive factor is the dosage (initial concentration) of the drug. The 5% variation in initial concentration from the original value gave about 0.08871 mol/m^3 difference. Not as much as the dosage of the drug, but the next highest sensitive factor is the reaction rate. However, it seems the model is not too sensitive to reaction rate. Actually, the model is not highly sensitive to any of the parameters, except the initial concentration of the drug. In fact, the model is almost no sensitive to the diffusivities in cartilage or in muscle.

IV. Conclusion

i. Goals

Our goal for the design model was to obtain the optimal location of the injection site that most effectively delivers the corticosteroid in synovial fluid. Specifically, we defined this effectiveness as having a potent concentration throughout the fluid while not causing any side effects outside the targeted fluid region. We have calculated the diffusivity value of the drug in synovial membrane since it was the only unknown parameter needed in getting the optimal injection site. During the membrane diffusivity analysis, we found that at first all of the values were above the minimum effective concentration for the drug so they were all reasonable to use. However, when we considered the other objective, we could more selectively choose our value.

By giving a restraint in cartilage and thus take side effect into consideration, we found a diffusivity value that was below the minimum effective dosage but high enough to deliver the drug throughout the synovial fluid. Also we discovered the relationship that as diffusivity of the membrane increases, the concentration of the drug in cartilage also increases. This means that higher diffusivity of the membrane allows particles of the drug to pass more easily out of the fluid via more diffusive membrane into cartilage.

With the obtained diffusivity value of the synovial membrane, we could vary the location of the injection site to see the effect it has on the diffusion of the corticosteroid drug. We tested nine different injection spots from 0.04m to 0.01m away from the center (axis of symmetry). Although we saw a general increase in the average concentration of the drug inside synovial fluid as the injection site got closer to the center, the actual difference between the farthest point (0.04m) and the closest one (0.01m) was only 0.000839 mol/m^3. This suggests that the location of the injection point is not a significant factor affecting the diffusion of the corticosteroid inside synovial fluid. However, this proportional relationship is not useless when we consider physical limitation of the syringe to reach final conclusion. With the physical limit in the length of the syringe (0.038m), we can safely assume that our optimal injection site occurs at 0.02m from the axis of symmetry that produces highest allowable drug concentration throughout the fluid without any side effect.

ii. Realistic Constraints

The design for the corticosteroid injection into knee join cannot be implemented exactly into the real case. The dimensions of the knee joint, including synovium, cartilage, and muscle highly vary depends on an individual. Because there is no exact dimensions of each structure such as synovial fluid that can represent the general population, the exact solution cannot be utilized in real human. Also, size of inflammation in the synovium depends on the seriousness of arthritis. So, the initial concentration of the drug, methylprednisolone, and the length of syringe have to be used differently according to a patient.

Our model is in two-dimensional axial symmetry. In other words, if implementing this model in reality, the drug has to be injected all around the knee like a circle at the same time. Yet, administration of the drug all around the knee is almost impossible to be performed in real case. Also various location of injection site was tested to find the most optimal location for the injection. However, a physician is hard to inject the drug at specific location within the synovial fluid. Our model did not include the patella, the knee cap. However, because patella impedes the path of syringe to the synovial fluid, a physician, in reality, has to inject the drug diagonally. In other words, the syringe cannot be injected into the fluid directly from side way.

Some of parameters that were utilized in this model have been somewhat simplified, which might be different from reality. The reaction of the drug was account as first order reaction. However, the drug is reacted with the receptors in white blood cell by very complex process. It was impossible to find the correct value of reaction rate because the reaction rate depends on the number of white blood cells in the synovial fluid and each individual has different number of white blood cells depends on the symptoms.

It was crucial to find the minimum effective concentration of the drug, methylprednisolone or the minimum concentration that cause side-effects when the drug diffuses into cartilage. The toxicity of methylprednisolone at cartilage could not be found in literature, but the minimum effective concentration was able to be found. However, the minimum effective concentration, 0.03~0.04 μg/mL, was for horse, not for human. Among multiple types of corticosteroid that are used in reality, the drug that was implemented in this design was methylprednisolone. The model was designed with as most accurate properties of methylprednisolone as possible from the literature. Thus, this design may not work with the properties with other types of corticosteroid.

iii. Design Recommendation

Further works are necessary to improve the design more accurate and realistic. The dimensions of knee joint, including synovial fluid, membrane, cartilage, and muscle, subcutaneous fact and skin has to be determined that can be implemented to general population. The correct reaction rate of methylprednisolone with accurate number of white blood cells or number of steroid receptors is necessary to be scrutinized to ensure the quality of this design. Our design used simplified schematic that includes only synovial fluid, membrane, cartilage, and muscle. However, the future design, most importantly should include patella, designing in three-dimensional. Thus, the steroid injection can be more realistic with single point of injection, unlike our model that the steroid is injected on all around the knee.

Appendix A: Problem Formulation

A1. Schematic:

See the *Problem Schematic* section on page 5 – 8.

A2. Governing Equations:

We model a mass transfer process of the drug in the knee joint. Mass transfer equation was used in radial coordinate.

$$\frac{\partial c_A}{\partial t} + \left(v_r \frac{\partial c_A}{\partial r} + v_\theta \frac{1}{r}\frac{\partial c_A}{\partial \theta} + v_z \frac{\partial c_A}{\partial z}\right) = D_{AB}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_A}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2 c_A}{\partial \theta^2} + \frac{\partial^2 c_A}{\partial z^2}\right) + R_A$$

$\frac{\partial c_A}{\partial t}$ = Storage Term

$\left(v_r \frac{\partial c_A}{\partial r} + v_\theta \frac{1}{r}\frac{\partial c_A}{\partial \theta} + v_z \frac{\partial c_A}{\partial z}\right)$ = Convection Term

$D_{AB}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_A}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2 c_A}{\partial \theta^2} + \frac{\partial^2 c_A}{\partial z^2}\right)$ = Diffusion Term

R_A = Generation Term

From the general mass transfer equation, convection term can be ignored since we assume no fluid flow (only uniform diffusion) inside the synovial fluid. Also, since our model is 2D, we ignore the angular, θ term in the diffusion term.

Simplified Mass Transfer Equation:

$$\frac{\partial c_A}{\partial t} = D_{AB}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_A}{\partial r}\right) + \frac{\partial^2 c_A}{\partial z^2}\right) + R_A$$

$c_A = concentration\ of\ the\ drug$

$D_{AB} = diffusivity\ of\ the\ drug\ in\ various\ layers$
$(synovial\ fluid, synovial\ membrane, cartilage, muscle, and\ etc.)$

A3. Boundary & Initial Conditions:

<u>Boundary Conditions:</u>

- Because the steroid has side effects on the bone, the concentration of the steroid at the bone is set to zero $c_{bone}(t = \infty) = 0$.

- Continuity condition occurs at the synovium-cartilage interface.
- The synovial membrane is insulated outside the synovium-cartilage interface.

Initial Conditions:

- The radii of the injection site were calculated based on the varying distances from the center of the synovial fluid. The volume of the corticosteroid injection in practice is 10 mL. We set this as the volume of the torus as our model assumes.

  Volume of torus = 10 mL = 0.00001 m^3 = (cross-section area)(length)

  $$= (\pi r^2)(2\pi R) = 2\pi^2 R r^2$$

  where *r* is the radius of the circle being rotates, and *R* being the distance from the center of the circle to the axis of rotation.[11]

  The radii for varying R can be found using $r = \sqrt{\frac{0.00001 m^3}{2R\pi^2}}$.

Table 2. Corresponding *r*, radius of the injection site, for varying *R*, distance from the center

R, distance from the center, m	r, radius of the injection site, m
0.01	0.007117631
0.02	0.005032925
0.03	0.004109366
0.04	0.003558816
0.022	0.004798706
0.024	0.004594411
0.025	0.004501585
0.026	0.004414168
0.028	0.004253598

- The initial steroid (methylprednisolone) concentration is $32 \frac{mol}{m^3}$.

[11] "Volume of a Torus," Whistler Alley Mathematics 21 Oct. 2010 <http://whistleralley.com/torus/torus.htm>

A4. Parameters Used in Model:

Table 3. Input parameters

Parameter	Value
Diffusion constant in Synovial Fluid[12]	2.36×10-10 m^2/s
Diffusion constant in Cartilage[13]	7.84×10-10 m^2/s
Diffusion constant in Muscle[14]	1.20×10-11 m^2/s
Diffusion constant in Synovial membrane	Unknown
Time Range[15]	0 to 17 days
Time step	1 day
Number of mesh elements in synovial fluid	72,146
Number of mesh elements in all regions combined	98,960
Reaction Rate[16]	
*The reaction rate was first order and based on the half-life (27 hours) of the drug: $R = k * c * (c > 0)$ where $k = -7.13 \times 10^{-6}\ s^{-1}$	

[12] Goyal et al., "Determination of methylprednisolone acetate in biological fluids at gold nanoparticles modified ITO electrode," Journal of Pharmaceutical and Biomedical Analysis (2007) 44: 1147-1153.
[13] Plontke et al., "Cochlear Pharmacokinetics with Local Inner Ear Drug Delivery Using a Three-Dimensional Finite-Element Computer Model," Audiol Neurootol (2007) 12/1: 37-48.
[14] Plontke et al. 37-48.
[15] Goetzl et al., "Effects of intra-articular corticosteroids in vivo on synovial fluid variables in rheumatoid synovitis," *Ann. Rheum. Dis.* (1974) 33 – 62.
[16] "Methylprednisolone," Wikipedia 21 Oct. 2010 <http://en.wikipedia.org/wiki/Methylprednisolone>

Appendix B: Solution Strategy

B1. Solver:

The model was solved in the Direct (UMFPACK) finite element linear system solver in COMSOL.

B2. Time Stepping:

The time step of 86400 seconds (1 day) was used during the diffusion process of the drug after injected.

B3. Solver Tolerance:

We used the COMSOL default relative tolerance of 0.01 and absolute tolerance of 0.001 to solve the model.

B4. Mesh & Mesh Convergence:

Mesh convergence refers to the smallness of the elements required in a model to ensure that the results of an analysis are not affected by changing the size of elements. If the number of mesh elements is too low, the solution can be inaccurate. On the other hand, a high number of mesh elements will give an accurate solution, but at the expense of increased computation time.

Table 3. Average concentration was calculated for different number of elements

Number of Elements	Surface Integral in mol/m	Surface Integral in m^2	Average Concentration (mol/m^3)
5184	9.91E-08	2.47E-04	4.02E-04
10640	1.21E-07	2.47E-04	4.90E-04
42560	1.36E-07	2.47E-04	5.53E-04
62936	8.96E-08	2.47E-04	3.63E-04
77603	1.27E-07	2.47E-04	5.14E-04
99171	1.08E-07	2.47E-04	4.39E-04
139432	1.25E-07	2.47E-04	5.05E-04
160691	1.25E-07	2.47E-04	5.05E-04

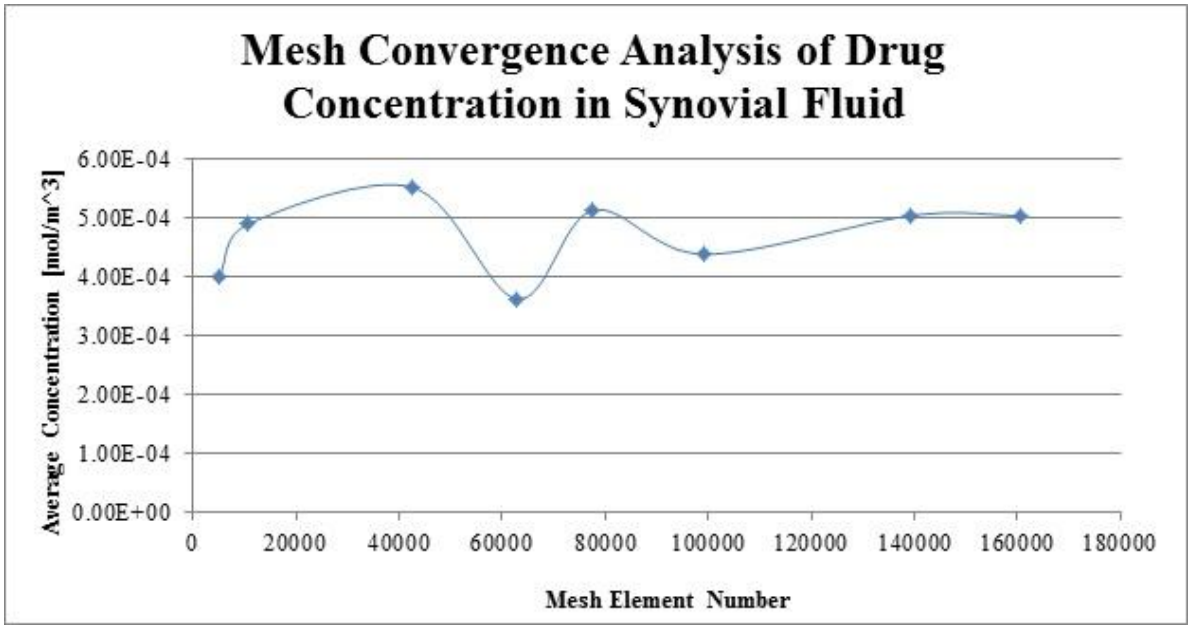


Figure 14. Mesh Convergence Analysis of Drug Concentration in Synovial Fluid

Our mesh convergence analysis suggests that when the number of elements exceeds 80,000, our solution is very close to being accurate. The average concentration of drug in synovial fluid region converges to $5.00 \times 10^{-4} \frac{mol}{m^3}$ from mesh element number of 80,000.

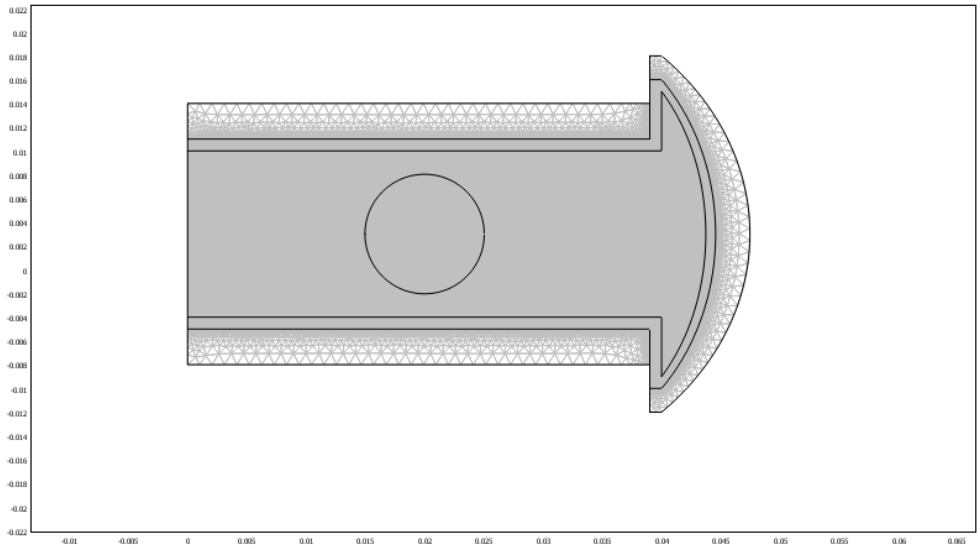


Figure 15. Constructed mesh used for solution with 98,960 elements

Appendix C: References

Goetzl E. J., Bianco N.E., Alpert J.S., Sledge C.B. and Schur P.H. “Effects of intra-articular corticosteroids in vivo on synovial fluid variables in rheumatoid synovitis.” *Annals of the Rheumatic Diseases* 33. (1974): 62. Web. 23 Sep 2010.

Leopold Seth S., Redd Brigham B., Warme Winston J., Wehrle Paul A., Pettis Patrick D. and Shott Susan. “Corticosteroid Compared with Hyaluronic Acid Injections for the Treatment of Osteoarthritis of the Knee.” *The Journal of Bone & Joint Surgery* 85-A. (2003). Web. 29 Sep 2010.

Santos Leilani L. and Morand Eric F. “The role of macrophage migration inhibitory factor in the inflammatory immune response and rheumatoid arthritis.” Wiener Medizinische Wochenschrift 156/1-2. (2006): 11-18. Web. 29 Sep 2010.

Schett Georg. “Rheumatoid arthritis: inflammation and bone loss.” *Wiener Medizinische Wochenschrift* 156/1-2. (2006): 34-41. Web. 29 Sep 2010.

Shimizu Masaki, Higuchi Hiroshi, Takagishi Kenji, Shinozaki Tetsuya and Kobayashi Tsutomu. “Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid.” *Journal of Orthopaedic Science* 15. (2010): 51-56. Web. 29 Sep 2010.

Walsh Nicole C., Crotti Tania N., Goldring Steven R. and Gravallese Ellen M. “Rheumatic diseases: the effects of inflammation on bone.” *Immunological Reviews* 208. (2005): 228-51. Web. 29 Sep 2010.

Frank Buttgereit, Rainer H. Straub, Marin Wehling, and Gerd Burmester. “Glucocorticoids in the Treatment of Rheumatic Diseases.” *Arthritis & Rheumatism.* Vol. 50. No. 11. (2004): 3408-3417

McAuley, David. "The Clinician's Ultimate Reference."The GlobalRPH. GlobalRPH Inc., 03 Jul 2009. Web. 3 Nov 2010. <http://www.globalrph.com/corticocalc.htm>.