Long Term Flux Profile of Implanon Birth Control Implant

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Executive Summary

Hormonal birth control methods have become increasingly popular since 2000, as the technology becomes more convenient for users, moving from daily pills, to weekly patches, to yearly implants. Implanon is an example of a long-term birth control implant. The goal of this project is to create an accurate computational model of Implanon's hormone diffusion over its standard prescription length: three years. Because Implanon is intended for long-term use, any potential improvements in the drug or release mechanism take several years to clinically test. It is time and cost inefficient to develop several new designs and test them all over this long time period. Instead, we can eliminate those designs that fail to reach specifications in our computer model and be more confident in the clinical success of those that function properly in our computer model, thus reducing the number of clinical trials needed and the time and money spent. We created a two-dimensional cross section model of the Implanon implant and surrounding tissue under mass transfer conditions model using COMSOL Multiphysics software. We confirmed our model's accuracy with comparisons to published Implanon hormone release rates at six weeks, one year, two years, and three years. Our model's hormone release rate was found to stay within a factor of 10 of the published data at all critical time periods. This data is significant in that it has the potential to expedite the hormone modification process. There were several assumptions made in the model's schematic design as well as material properties and boundary parameters. It is recommended that more *in vivo* experimentation and data gathering on Implanon implant placement and hormone diffusivity be conducted to improve this model's accuracy.

Introduction

Hormonal birth control includes a broad range of contraceptive methods that are fairly simple to use, have very few side effects, and when used correctly are very effective. These methods range from daily pills to monthly intrauterine devices to yearly implants. Hormonal birth control affects a woman by thickening the mucus membrane on the uterine walls such that sperm are not able to enter as well as preventing fertilized eggs from implanting on the uterine walls. In the case of a constant release of drug, ovulation is also suppressed in the patient.

The Implanon implant is a small (0.04 m by 0.002 m) cylindrical device that is placed under the skin of the upper arm of a woman. It is designed to release the hormone etonogestrel to lessen the risk of conception. The core of the implant contains sixty-eight milligrams of etonogestrel, which is released over a period of three years. While the device can be removed at any time it is recommended that it remain for the full three years. The drug released from the implant has the same general effects on a woman's body with regards to pregnancy prevention.

During the first six weeks after implantation, the experimental release rate of etonogestrel from the implant into the surrounding tissue is between 60 and 70 micrograms per day. At the one year mark, the release rate was measured to be between 35 and 45 micrograms per day, and between 30 and 40 micrograms per day at the end of two years. At the end of three years, the etonogestrel release rate was experimentally determined to be between 25 and 30 micrograms per day (Implanon, 2009). Even at these low release rates the contraceptive power is still effective enough to suppress ovulation.

Our project's goal was to model the etonogestrel release mechanism from Implanon over a three year period when implanted in human tissues (epidermis and dermis) to reduce the cost and time associated with testing future Implanon modifications. The model will take into account the thicknesses of the different tissues as well as their specific properties, both material and physical.

The computational model was a two-dimensional transient diffusion problem that monitored the concentration of hormone remaining in the implant and surrounding tissues before being removed by nearby blood vessels in dermis tissue. Our model differs from the manufacturer's experimentation because the manufacturer only released limited data on their experiment, excluding material properties such as diffusivity and flux values.

Since the material properties were not provided in literature, the material properties used were found from various hormones or drugs that were similar in size and structure. The three molecules used for material properties in the COMSOL model were etonogestrel (the working hormone), testosterone, and scopolamine. While the material properties were not available for the tissues, the diffusivities of etonogestrel in the implant core and in the membrane were found in published literature (van Laarhoven et al, 2002).

Considerations in the design of the model were that the Implanon implant is a perfect cylinder and is considered to be infinitely long with respect to the diameter, such that the effect of the ends of the implant was negligible. The model's domain was designed to include a representative cross section of the implant within the surrounding tissues.

Design Objectives

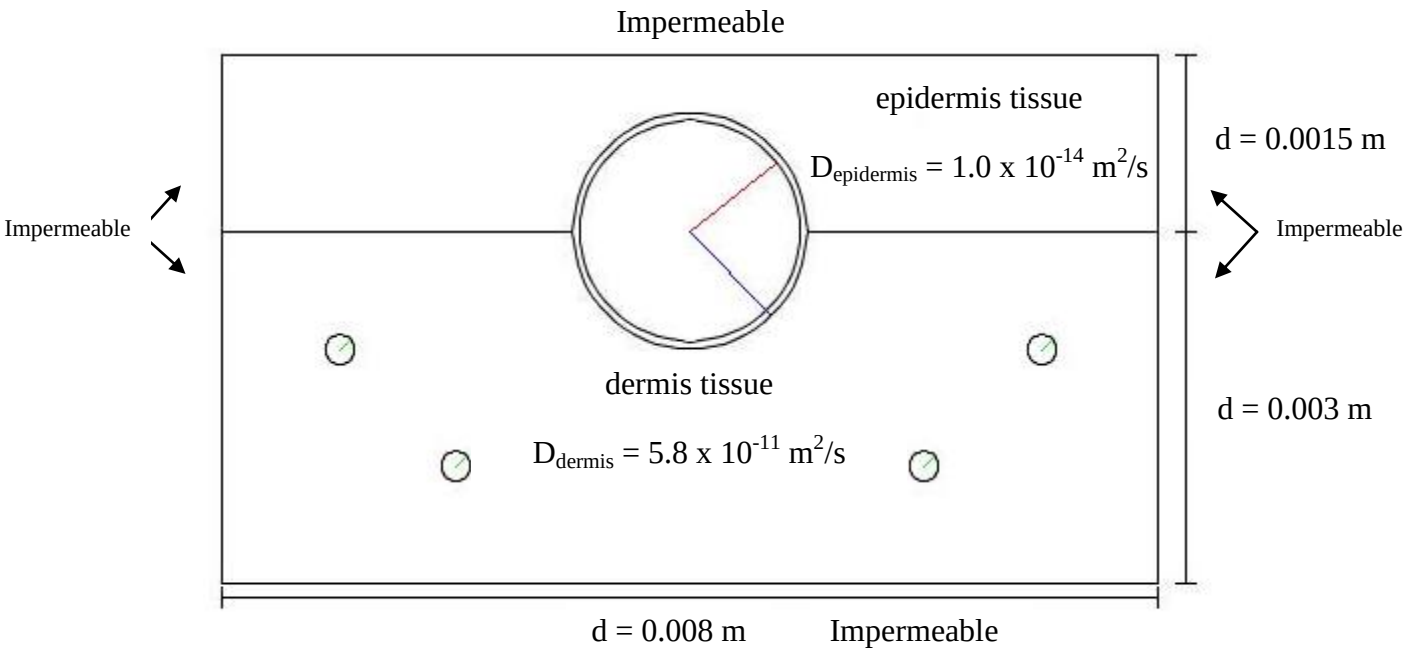
Our project had three design objectives:

- Determine if the diffusivities of similar drugs through tissues and blood are adequate approximations of the diffusivity of etonogestrel through tissues and blood
- Model the release of etonogestrel from the Implanon implant into the surrounding tissues and removal through blood vessels
- Compare the flux rates from the model to the experimental data provided by the specification sheet from the Implanon distributor

Problem Schematic

COMSOL Multiphysics was used to create a model of etonogestrel release over a period of three years in the skin surface tissues on the upper anterior portion of an adult female arm. The implant is modeled as a cylinder surrounded on all sides by tissues, both epidermis and dermis. In the model, the implant is considered to be an infinitely long cylinder, such that the effects of the ends are not considered in the model. The radius of the implant core is 0.94 mm and the radius of the implant core and the membrane, or the total radius, is 1.0 mm. The geometry of the implant was taken from Implanon, 2009. The epidermis is modeled to be 1.5 mm thick and the dermis is modeled to be 3.0 mm thick. This problem was formulated using a two-dimensional model that includes the Implanon implant, the dermis, the epidermis, and four blood vessels that are dispersed within the dermis. The geometry and dimensions of the model are shown in Figure 1.

Schematic of Implanon Implant in Tissue:



D_{core} = 1.84 x 10^{-13} m^2/s
$D_{membrane}$ = 9.2 x 10^{-15} m^2/s
Inward Flux $_{blood\ vessel}$ = -7.5 x 10^{-10} x c mol/m^2s

r_{red} = 0.00094 m
r_{blue} = 0.001 m
r_{green} = 0.000125 m

Figure 1: Schematic of Implanon implant in tissues as entered in COMSOL Multiphysics.

In our problem's governing equation, there is no reason to take convection into account due to the lack of fluid flow in the body tissues. There is no generation or degradation term because etonogestrel is only degraded and removed in a noticeable range in the liver (See Appendix A). All of the outer boundaries are set to have an impermeable condition, so that none of the drug is leaving the tissues through any method other than removal through the uptake into the blood stream through the blood vessels. The blood vessels have a boundary condition of inward flux, N_o, that is a function of the concentration of etonogestrel at the blood vessel/tissue interface at any given time.

The initial concentration of drug is located only in the Implanon core, and nowhere else. The drug concentrations in all of the tissues and in the implant membrane are all equal to zero.

The simulation was run over a three year period with a time step of one hour for the first six weeks then with a time step of ten hours from six weeks to the three year ending point. The simulation was run so that the flux at the boundary of the implant membrane can be calculated at given time points, six weeks, one year, two years, and three years, to compare with the data provided by the Implanon specifications sheet. The time step was smaller in the initial six week period because that was the time of greatest variation in hormone release from the Implanon, and was increased after the initial six weeks because there would be less variation in hormone release as time continued on.

The diffusivity of etonogestrel through the Implanon core was found to be 1.84×10^{-9} cm^2/s (van Laarhoven et al, 2002). This value is the diffusion coefficient of etonogestrel in ethylene vinylacetate (EVA) 9. EVA 9 is the copolymer through which many birth control implants are made out of, including Implanon. This value, however, was found experimentally for etonogestrel in an intrauterine device. Since the hormone and the material are the same, the diffusivity can be assumed to be accurate.

The diffusivity of etonogestrel through the Implanon membrane, we know, should be much smaller than the diffusivity through the core. The purpose of the membrane, which is also made out of EVA, is to further slow down the release of etonogestrel from the core into the tissues. According to, Implanon, 2009, the diffusivity of etonogestrel through the membrane is twenty times smaller than the diffusivity of etonogestrel through the core. This value was calculated to be, 9.2×10^{-11} cm^2/s.

The diffusivity of etonogestrel in the epidermis was not simple to find. Since the value was never calculated in literature, the next best option was to find the value of a similar molecule in the same tissue. For this, the diffusivity of the hormone testosterone through tissue was used. The value was found to be 1.0×10^{-10} cm^2/s (Ebert, 1992). Comparing etonogestrel to

testosterone, they have similar molecular substituent groups attached to central six-member carbon rings and the molar masses differ by 36.037 g/mol.

The diffusivity of etonogestrel in the dermis was also not found, again, the value was never calculated in literature. The solution to this was to use the value of scopolamine, a drug that is diffused through a patch into the skin to prevent motion sickness. The diffusivity of scopolamine through the dermis was found to be 5.8×10^{-7} cm^2/s (Datta et al, 2010). This value is a good approximation because the difference in the molar masses between etonogestrel and scopolamine is 21.104 g/mol.

To determine the amount of etonogestrel that was being removed from the tissue through the blood at a given time was calculated by determining the inward flux, N_o. First to do this, a value for the diffusivity of etonogestrel through the blood had to be found. Since this value was not available in literature, the next best option was to find the diffusivity of a different hormone through a material similar to blood. The diffusivity of testosterone through PDMS was found to be 1.8×10^{-5} cm^2/min (Pereira et al, 1987). To find the value of N_o the diffusivity was multiplied by the concentration, c. This means that the inward flux would vary over time, as the concentration at the blood vessel/tissue boundary would change over time.

Results and Discussion

The Implanon device contains 68 mg, or if expressed in concentration, 1668.0851 mol/m^3, of etonogestrel according to (citation). Using COMSOL Multiphysics, we modeled the 2D diffusion problem to observe how etonogestrel leaves the implant, and how long the implant could sustain an adequate dosage of hormone to prevent pregnancy. Using our model, we computed the diffusive flux of etonogestrel over a period of 3 years at the center of the Implanon core.

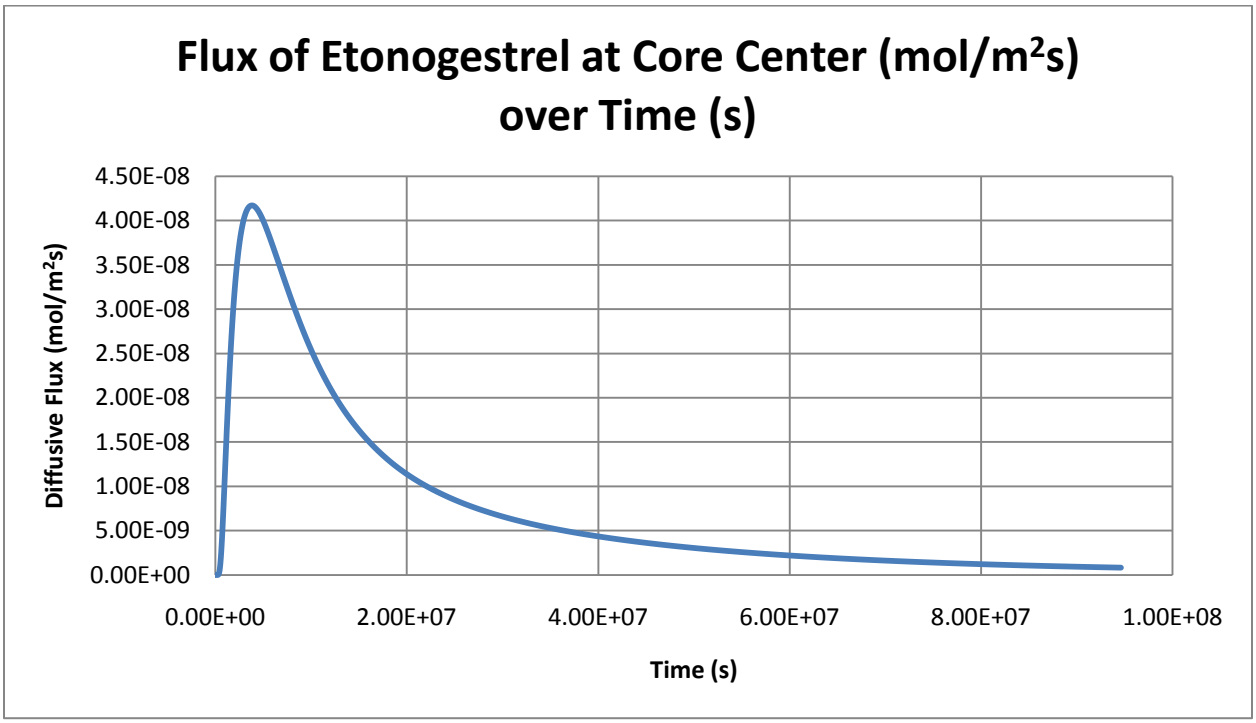


Figure 2: Etonogestrel Flux at Center of Implanon Core (0,0) over a Time Period of Three Years (94,608,000 s)

As Figure 2 shows, the flux of etonogestrel initially rises rapidly as because the initial concentration gradient of the drug between the core and tissue layers is very large. However, after only 45 days the flux reaches its maximum and starts to decrease. The peak occurring at the 45 day mark is significant because according to the manufacturer, Implanon achieved a maximum release rate after 42 days (6 weeks). The flux decreases rapidly after achieving its maximum because the concentration gradient of the etonogestrel between the core and tissue starts to decrease as more and more drug enters the bloodstream. The following surface plots, Figure 3a-e, shows how the drug diffuses out of the implant after 6 weeks, 1 year, 2 years, and 3 years.

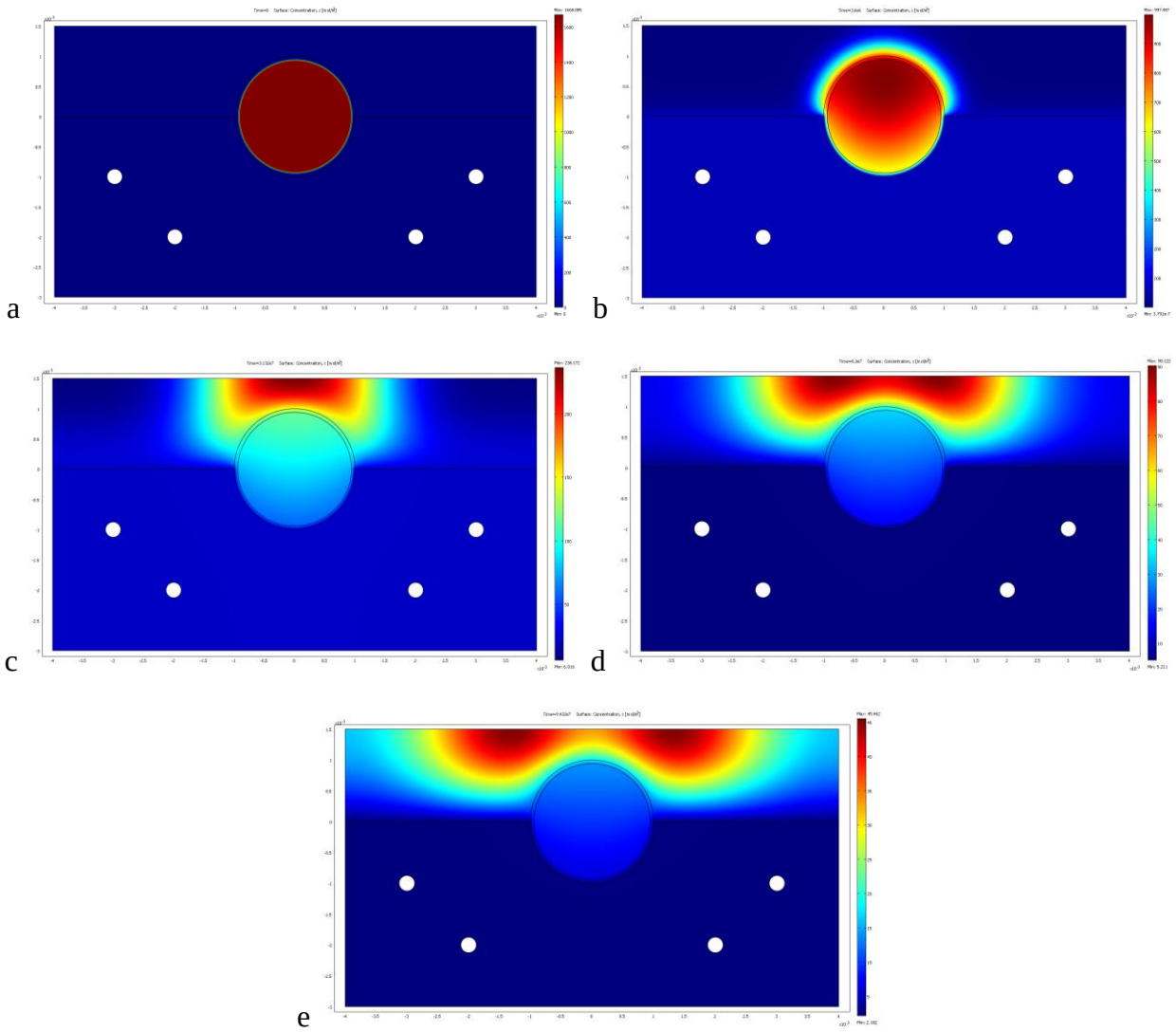


Figure 3: Surface Plots of Etonogestrel Concentration. (a) Initial surface plot of model (time = 0 s). (b) Surface plot of model after six weeks (3,628,800 s). (c) Surface plot of model after one year (31,536,000 s). (d) Surface plot of model after two years (63,072,000 s). (e) Surface plot of model after three years (94,608,000 s).

The etonogestrel concentration ranges for each of the surface plots in Figure 3 are tabulated in Appendix C. The hormone seems to diffuse out of the Implanon device towards the upper boundary of the epidermis, or the top layer of skin and accumulating. However, the diffusivity of etonogestrel is higher in the dermis, or the bottom layer of skin, than in the epidermis. Therefore, the hormone should be diffusing more into and through the dermis towards the blood vessels. Upon closer analysis, we see that etonogestrel is indeed diffusing towards the blood vessels, as shown in Figure 4.

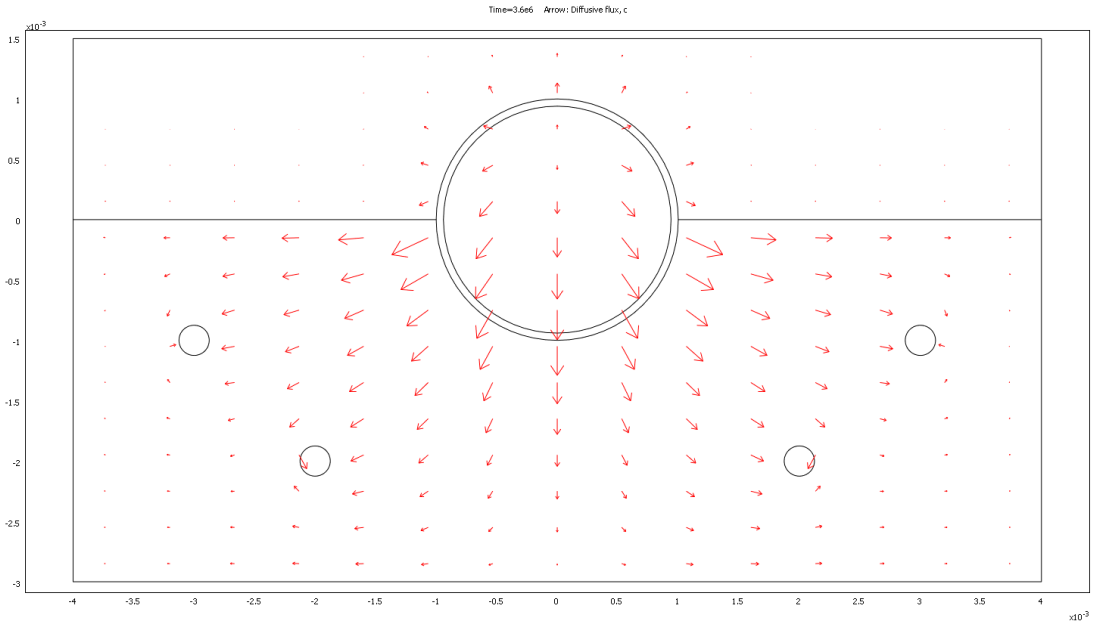


Figure 4: Etonogestrel Flux Pattern, Flow pattern after six weeks (3,628,800s).

Figure 4a shows the concentration flow pattern for the model at six weeks. It shows that etonogestrel in the upper section of the core is initially released towards the upper boundary of the epidermis. This explains why there are significant amounts of etonogestrel (see Appendix C for exact concentrations) still in the tissue at the end of the three year period tested. The hormone seems to settle in two different sections near the upper boundary of the epidermis. The two sections are equivalent due to the symmetries of the model. The hormone deposits near the boundary because the upper boundary of the epidermis has an insulated boundary condition. Therefore any etonogestrel released from the top of the implant diffuses towards the upper boundary and seems to settle there.

Figure 4 combined with Appendix C shows that the maximum concentration of etonogestrel decreases over time. Since the maximum concentration of etonogestrel is located at the upper boundary in Figures 3c, d, e, the hormone is clearly moving away from the upper boundary as time progresses. Also the etonogestrel flow pattern at the end of the three year period confirms that etonogestrel is diffusing towards the blood vessels.

Overall, the model behaved as predicted, with etonogestrel leaving rapidly during the early part of the three year period, then slowing down. The core had a low concentration of hormone (13.78 mol/m^3) left after three years, which is only 0.826% of the original concentration. The low concentration remaining in the core after three years was desired since the goal was to deliver all of the hormone into the body over the three year time frame.

The one unexpected result was etonogestrel accumulation in the upper tissue. The hormone settled here due to the setup of the model. Therefore, placing the implant at a slightly

different depth and/or placing the implant further into the dermis layer could limit the accumulation.

Accuracy Check

The release rates out of the Implanon device were calculated by performing a Boundary Integration around the membrane of the implant to calculate the diffusive flux at 6 weeks, 1 year, 2 years, and 3 years. The results from our model were confirmed by comparing the rates at specified times over the three years to published release rates by the manufacturer (Implanon, 2009).

Table 1: Accuracy check of Manufacturer Data as compared to COMSOL Simulation and Percent Error.

Accuracy Check Release rates ($x10^{-7}$ mol/day)			
	Manufacturer Data	COMSOL Simulation	Percent Error (%)
6 Weeks	2.16	5.69	163.425
1 Year	1.39	0.892	35.827
2 Years	1.23	0.312	74.634
3 Years	0.925	0.137	85.189

The percent errors are large for our accuracy check for two reasons. First, the values that we are comparing are very small, and therefore, the error is quite large for values that are actually quite close together. Second, we do not have actual experimental data for many of the parameters for our model, but instead were using approximate values based on similar molecules through similar materials. If we had the correct experimental data, we would expect the percent error to decrease.

Sensitivity Analysis

Because much of our model was based on molecules similar to etonogestrel, and not etonogestrel itself, it is important to conduct sensitivity analyses to determine the significance of these various parameters' uncertainty. We performed the sensitivity analysis on the inward flux of blood vessels, diffusivity in the dermis, and epidermis, as well as on the number of blood vessels surrounding the implant. We did not perform sensitivity analysis on the Implanon core and membrane diffusivities because we have published data from the manufacturer stating the diffusivity properties of these two regions. Since these values are particular to the drug, we are not going to change them. In each case of sensitivity analysis, a comparison was made between the newly calculated drug release rate and the original parameter's drug release rate at 6 weeks, 1 year, 2 years, and 3 years. In the figures below, the release rates of the drug were monitored over the course of the 3 years with variations on each of the parameters that were not fixed. These analyses will show how sensitive or nor the model is to each of the parameters with regards to the release rate of etonogestrel.

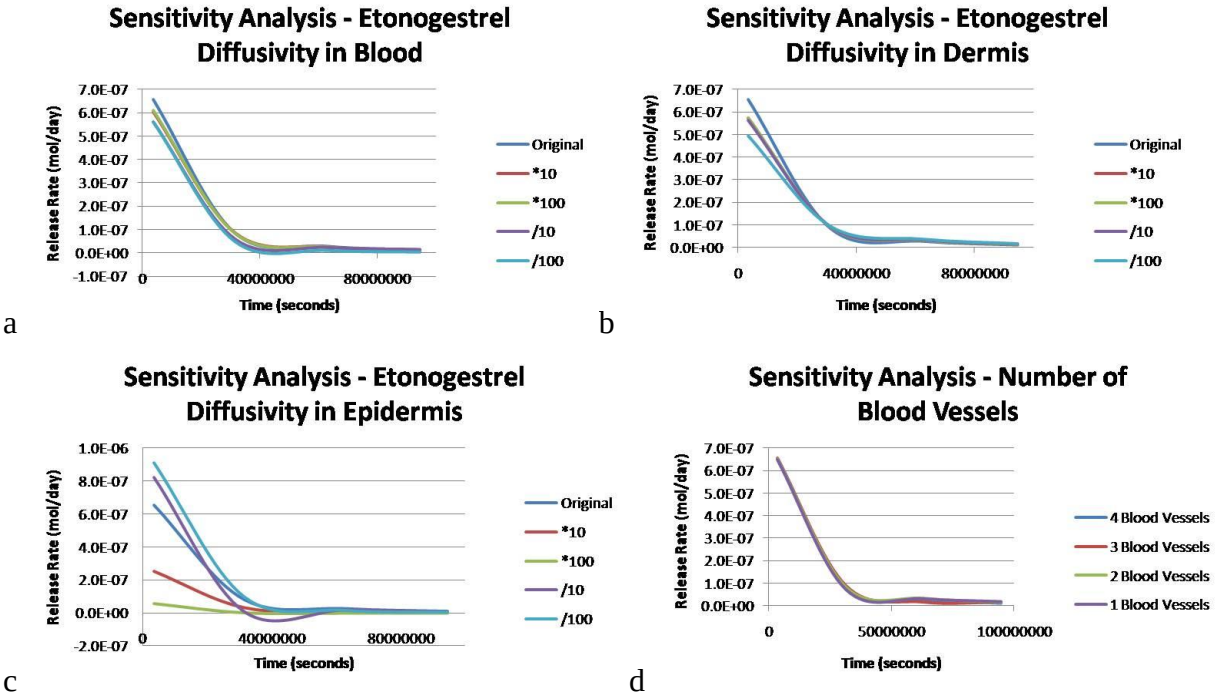


Figure 5: Sensitivity Analysis of Etonogestrel Diffusivity. (a) Sensitivity analysis of etonogestrel in blood. (b) Sensitivity analysis of etonogestrel in dermis. (c) Sensitivity analysis of etonogestrel in epidermis. (d) Sensitivity analysis of number of blood vessels.

The etonogestrel diffusivity in blood, in dermis, and epidermis all had a significant impact on the release rates of the hormone from the core. The etonogestrel diffusivity in blood had the greatest impact on the 6 week release rate, while the other release rates were impacted only slightly. The hormone diffusivity in the epidermis tissue layer had great impacts on all four

of the release rates (6 weeks, 1 year, 2 years, and 3 years), while the hormone diffusivity in the dermis had small impacts on each of the release rates. Surprisingly, the number of blood vessels did not have an impact on any of the release rates. This is unexpected because the blood vessels are the only way that the etonogestrel is able to leave the tissues, and the logical assumption would be that the fewer the blood vessels the lower the release rate (while all other properties remain consistent). However, if the number of blood vessels does not matter, then the uncertainty in our model on how the blood vessels actually interact with etonogestrel can be ignored.

Conclusion

The goal of designing an accurate model of etonogestrel diffusion from the implant and through the layers of tissue into the blood vessels was able to be achieved. Based on diffusion values calculated and the sensitivity analysis conducted to determine the relative amounts of uncertainty in the parameters selected, the model does exhibit release rates similar to those given in the literature, and the trend of decreasing rate of release over time is followed.

At the time of six weeks, the model gave a release rate of 6.56×10^{-7} mol/day, while the manufacturer claimed that there was a release of 2.16×10^{-7} mol/day. This difference in values between the data from COMSOL and the data from the manufacturer decreased for the period of one year (0.837×10^{-7} mol/day for the model versus 1.39×10^{-7} mol/day for the manufacturer), and then leveled off for two years (0.279×10^{-7} mol/day for the model versus 1.23×10^{-7} mol/day for the manufacturer), and three years (0.119×10^{-7} mol/day for the model versus 0.925×10^{-7} mol/day for the manufacturer). The model data shows that, as detailed by the manufacturer, the release rate of etonogestrel from the Implanon device decreases as the concentration of the drug inside the implant decreases. Given the relative simplicity of the model in relation to the intricate nature of human dermis and epidermis and the many assumptions made in the model, the accuracy of the results simulated from COMSOL is fairly high.

Although there was no readily available data for the diffusion of etonogestrel into the blood and testosterone is structurally a very similar molecule, improvements could be made to the model to prepare for future publications. This, as well as the other assumptions made in the model, will have effects on the results of the simulation as shown with the sensitivity analysis, but they were necessary to complete the current investigation into the release rates of etonogestrel from the Implanon birth control implant.

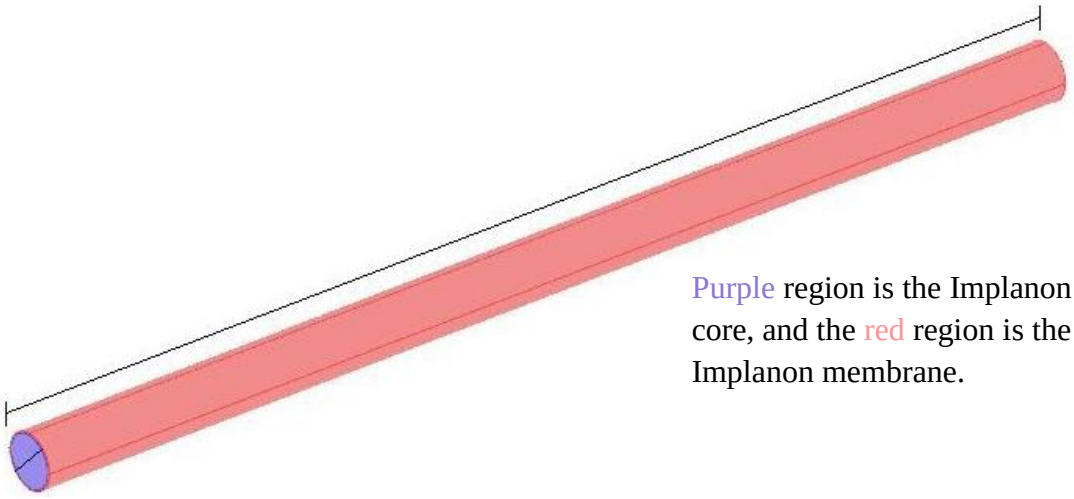
Design Recommendations

As the goal of this project was to model the current device's behavior, we did not consider improvements to Implanon's diffusion rates or methods. These release rates are set by doctors and pharmacologists to deliver the required amount of drug to prevent pregnancy and are not within the scope of this project. However, as engineers, we naturally see a need to improve the mechanical structure of Implanon. Due to the fairly fragile shape (a long, thin rod), Implanon is susceptible to becoming broken or damaged while in the body. Additionally, the implant should always be able to be felt through the skin, and when it is no longer palpable due to migration of the device or fibrosis, it can be a cause for alarm, and the removal process can become increasingly complicated. A possible improvement for this would be to re-evaluate the geometry of the device to a more sturdy shape that can handle mechanical stresses better. Additionally, use of a more flexible polymer to compose the scaffold of the device could improve structural properties of the device.

Implanon is not free of side effects, but the side effects associated with it are similar to those of other forms of hormonal birth control, such as oral contraceptive pills, implants, or Depo-Provera. These side effects include irregular periods, weight gain, abdominal pain, headaches, and acne, but they usually dissipate after the first few months of use in most women. Many women will no longer have periods while using Implanon, and few will have anxiety and depression. These side effects are not due to the Implanon device itself, however, but rather to the hormonal etonogestrel. Therefore, no design changes can mitigate these symptoms except the discovery of a new molecule that does not induce these effects in women.

Appendix A

Schematics and Mathematical Statement of Simulation



Purple region is the Implanon drug core, and the red region is the Implanon membrane.

diameter = 0.002 m

Figure A – A1: Schematic of Implanon Implant only.

Equation:

$$\frac{\partial C}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right)\right]$$

Boundary Conditions:

Insulation, at all outer boundaries, drug remains in the tissue and is removed through the blood vessels only

Initial Conditions:

C_o = 68 mg = 1668.0851 mol/m^3 initial drug concentration in the implant core

Input Parameters:

Table A – A1: Parameters Used in the Simulation

Property	Values Used	Units	Source
Core Diffusivity	$1.84x10^{-13}$	m^2/s	(van Laarhoven et al, 2002)
Membrane Diffusivity	$9.2x10^{-15}$	m^2/s	(Implanon, 2009)
Epidermis Diffusivity	$1.0x10^{-14}$	m^2/s	(Ebert, 1992)
Dermis Diffusivity	$5.8x10^{-11}$	m^2/s	(Datta et al, 2010)
Inward Flux	$-7.5x10^{-10}$ x c	mol/ m^2s	(Pereira et al, 1987)

Table A – A2: Conversion of Parameters from Literature to Parameters Used in Simulation

Property	Values from Source	Units Math Applied	Values Used	Units
Core Diffusivity	$1.84x10^{-9}$ cm^2/s	x (1 m^2 / 10000 cm^2)	$1.84x10^{-13}$	m^3/s
Membrane Diffusivity	$9.2x10^{-11}$ cm^2/s	x (1 m^2 / 10000 cm^2)	$9.2x10^{-15}$	m^3/s
Epidermis Diffusivity	$1.0x10^{-10}$ cm^2/s	x (1 m^2 / 10000 cm^2)	$1.0x10^{-14}$	m^3/s
Dermis Diffusivity	$5.8x10^{-7}$ cm^2/s	x (1 m^2 / 10000 cm^2)	$5.8x10^{-11}$	m^3/s
Inward Flux	$-1.8x10^{-5}$ x c mol/ cm min	x (1/0.04 m) x (1 min/ 60 sec) x (1 m^2 / 10000 cm^2)	$-7.5x10^{-10}$ x c	mol/ m^2s

Appendix B

Mesh Convergence

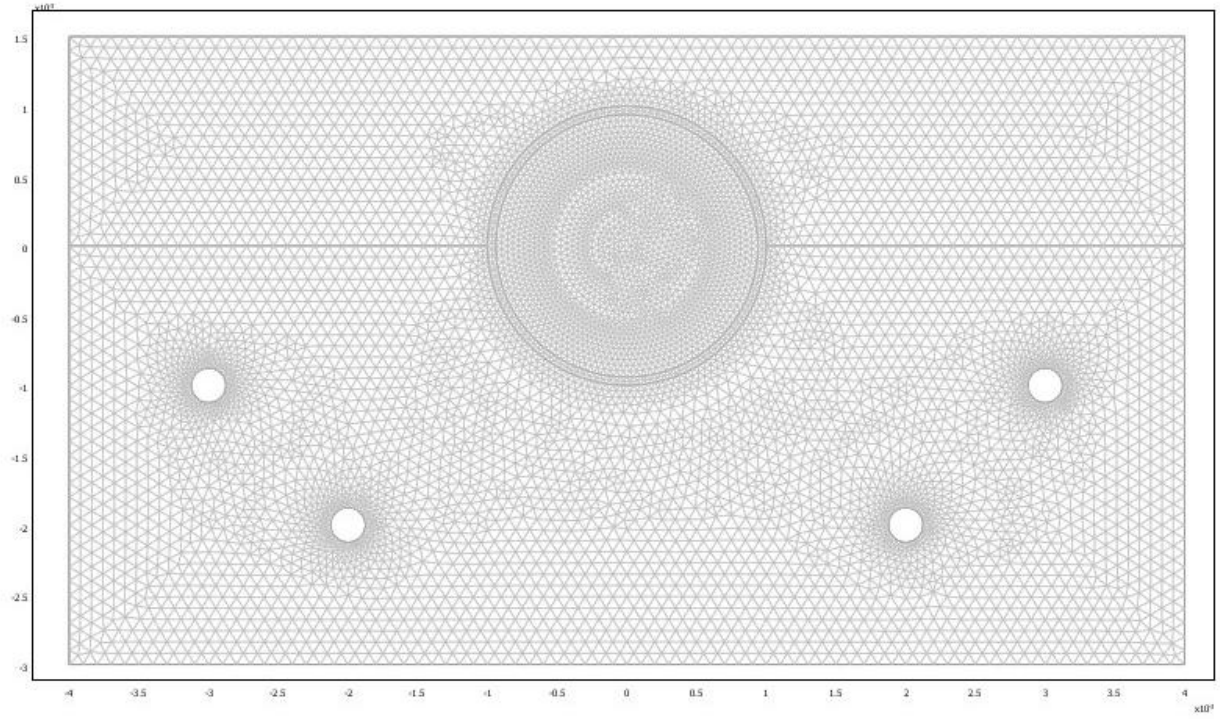


Figure A – B1: Image of Mesh after Convergence, used in the Problem Solution.

The mesh for this problem was created using the values for the mesh obtained from our mesh convergence. The free mapped mesh element size for the two skin layers, and the core had a maximum element size undefined, as COMSOL provided the best mesh size.

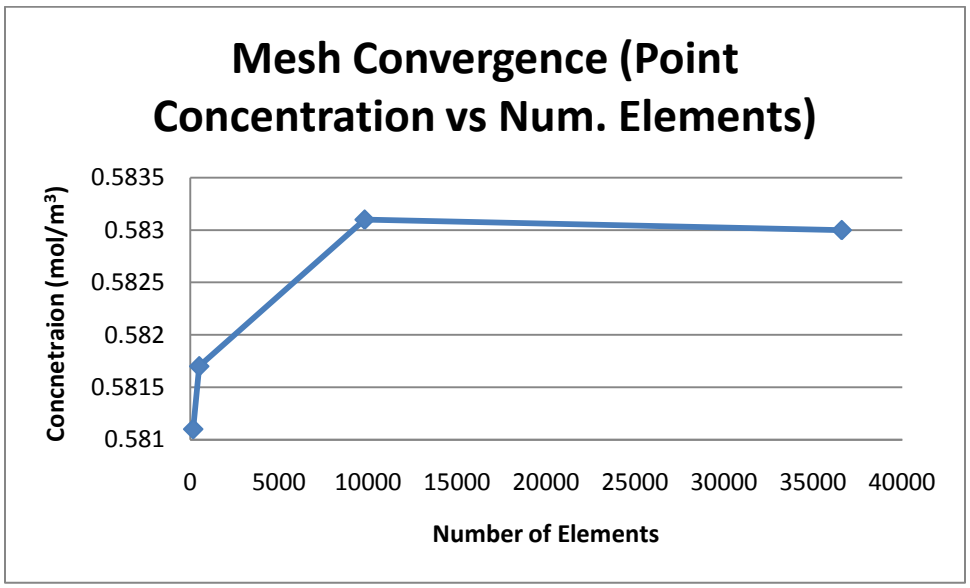


Figure A – B2: Mesh Convergence Determination, found in the Implant Membrane

Since there are different subdomains in our schematic, we decided to manually mesh converge in each subdomain separately. We compared element size to the concentrations at a single point within that specific subdomain. The subdomains pertaining to the skin layers and the core seemed to have a mesh convergence that always converged. Therefore it seemed that our solution is independent of the mesh in the two skin layers and core. However the membrane subdomain converged with an element size of 10000. Therefore our mesh has an element size of 10,000.

Appendix C

Additional Information

Table A – B1: Minimum and Maximum Concentrations of Etonogestrel in the Simulation.

Time of Surface Plot	Minimum Concentration (mol/m^3)	Maximum Concentration (mol/m^3)	Maximum Core Concentration (mol/m^3)
Initial (0 s)	0	1668.085	1668.085
6 weeks (3628800 s)	0	997.487	975.970
1 year (31536000 s)	6.016	236.172	115.820
2 years (63072000 s)	5.211	90.122	33.570
3 years (94608000 s)	2.182	45.462	13.780

Appendix D

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