The Effect of Vascularization and Tissue Type on Cryosurgical Procedures

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Table of Contents

1. Executive Summary

Cryosurgery is a minimally-invasive surgical procedure that is used in the treatment of multiple types of cancer. Although cryosurgical treatments, which involve the application of extreme cold to diseased or cancerous tissue, are often used in the treatment of near-surface skin cancer, they have also been used to treat several other types of internal cancers, including those in the prostate, liver, and kidney. Although fundamentally similar, many of these tissues differ significantly in properties such as density, vascularization, and thermal conductivity. A major issue in cryosurgery is adapting the procedure to different tissue types. In this study, the effect of tissue perfusivity on the outcomes of cryosurgery was modeled using the COMSOL software. For the purposes of comparison, the properties of lung tissue, which is highly perfused and not as conductive, and liver tissue, which is mildly perfused and more conductive, were used. The procedure was modeled as a 10 mm diameter cryoprobe set at a temperature of -196°C in a cylindrical region of tissue 8 cm in height and 8 cm in diameter. The time required for a 26mm diameter spherical tumor to reach -45°C was determined in four scenarios, lung tissue and liver tissue both with and without blood perfusion. Although metabolic heat generation was also included, sensitivity analysis showed it to be a minor factor in the cooling process. Results showed blood perfusivity to have a significant effect on freezing time in lung tissue and a relatively minor one in liver tissue: although the addition of perfusion caused freezing time in the liver to increase from 200 to 250 seconds, the addition of perfusion in the lung tissue caused the freezing front to never reach the tumor edge. Sensitivity analyses also revealed the freezing process to be highly sensitive to conductivity as well. It was therefore concluded that although blood perfusion is one of the most important heat transfer processes in cryosurgery, tissue conductivity is just as, if not more important. We recommend that cryosurgery continue to be used as a treatment for liver tumors, but further studies are needed to determine its efficacy in highly perfused, porous tissue such as the lung.

Key words: cryosurgery, lung cancer, vascularization

2. Introduction and Design Objectives

2.1 Background Information

Cancer is a leading cause of death in America, with lung cancer having the greatest occurrence. This year there will be 215,020 more cases diagnosed and 161,840 deaths in the United States alone[9]. These statistics emphasize the need for more effective methods of treatment. Traditional treatments for malignant tumors include surgery, radiation therapy, chemotherapy, targeted therapies, immunotherapy and angiogenesis inhibitor therapy. However, cryosurgery has recently been suggested as an effective and more successful treatment than previous methods. Cryosurgical benefits are multifold. It is a relatively noninvasive surgery for the removal of cancerous tissue. In addition, the procedure has fewer side effects, is less expensive and has a shorter recovery time compared to more conventional treatments. However, the technique is still under study and long-term effectiveness is unknown[11].

Cryosurgery works by taking advantage of the destructive force of freezing temperatures on cells. At temperatures below -45°C, the cell destruction caused by freezing is permanent. This procedure hasbeen used to treat several types of internal cancers, including those in the prostate, liver, and kidney. Although fundamentally similar, many of these tissues differ significantly in properties such as density, vascularization, and thermal conductivity. For example, lung tissue is highly perfused, porous, and thus less conductive compared to denser tissue types such as liver tissue: Liver tissue has a blood flow rate of 0.83 ml/min/gwith a density of 1000 kg/m^3 whereas lung tissue has a blood flow rate of 1.38 ml/min/g with a density of 332 kg/m^3(Appendix A). Cryosurgical procedures must take these tissue properties into account in order to determine the most effective freezing time. Indeed, a major issue in cryosurgery today is adapting the procedure to different tissue types.As clinical trials to determine proper freezing times are expensive and time-consuming, several models have been proposed to predict the

effects of cryosurgical procedures on tissues with differing material properties. Still, the procedure is still not fully optimized for different tissue types.

2.2 Problem Schematic

In this study, we aimed to develop a model for cryosurgical procedures in lung and liver tissues in order to quantify the optimal freezing times. As shown in Figure 1, the cryosurgical probe was modeled as a 10mm diameter cylinder set at a temperature of -196°C.The probe was set in a cylindrical region of tissue 8cm in height and 8cm in diameter with a 26mm-diameterspherical tumor in the middle. Liver, lung and cancerous tissue regions had different material properties. The governing equation, boundary conditions, initial conditions, and material properties can be found in Appendix A. Simulations were performed in COMSOL, a computational fluid dynamics (CFD) program.

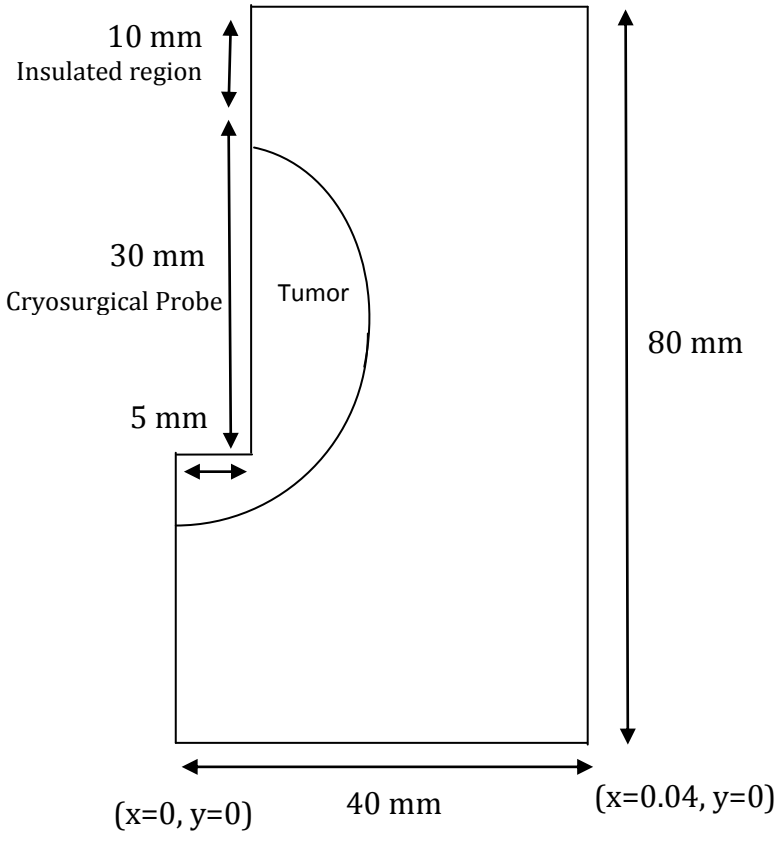


Figure 1: Schematic of cryoprobe in tissue. Model is axisymmetric.

2.3 Design Objectives

In this study, the required time for the tumor edge to reach -45°C in both lung and liver tissue was determined. This model incorporated the effects of blood perfusion to more realistically find freezing times. The results were then used to determine in which tissue types, specifically lung or liver tissue, cryosurgery can be used as an effective treatment.

3. Results and Discussion

3.1 Results

In order to determine the effect of tissue type and blood perfusion on the time required to reach -45°C throughout the geometry of the tumor, we compared the surface plots at 1000 seconds for four different conditions:

- liver tissue without blood perfusion
- liver tissue with blood perfusion
- lung tissue without blood perfusion
- lung tissue with blood perfusion

This allowed us to compare the size of the freezing region for each condition. We also analyzed temperature vs. time plots at (0.013, 0.045), a point 8 mm from the cryoprobe surface that was chosen to represent the outer boundary of the 26mm diameter tumor, for each of the four conditions outlined above. From these plots, we were able to compare the time required for the tissue to reach -45°C at the tumor edge for each of the 4 conditions.

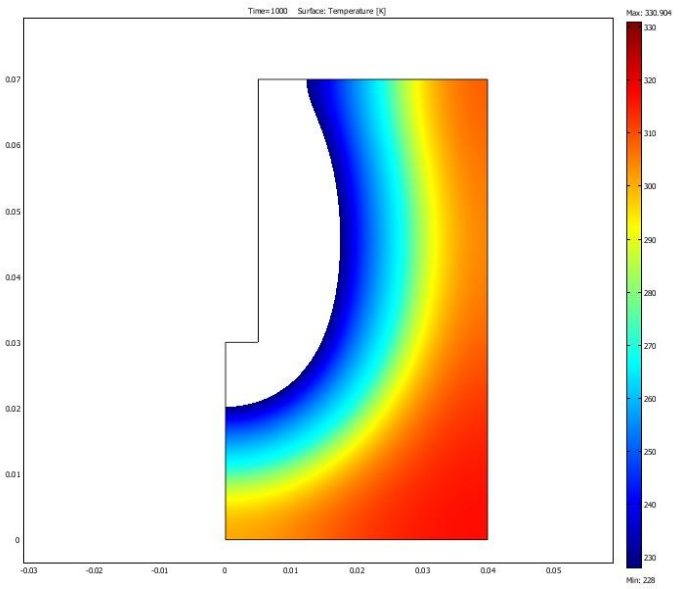


Figure 2: Surface plot of liver tissue without perfusion at 1000 seconds

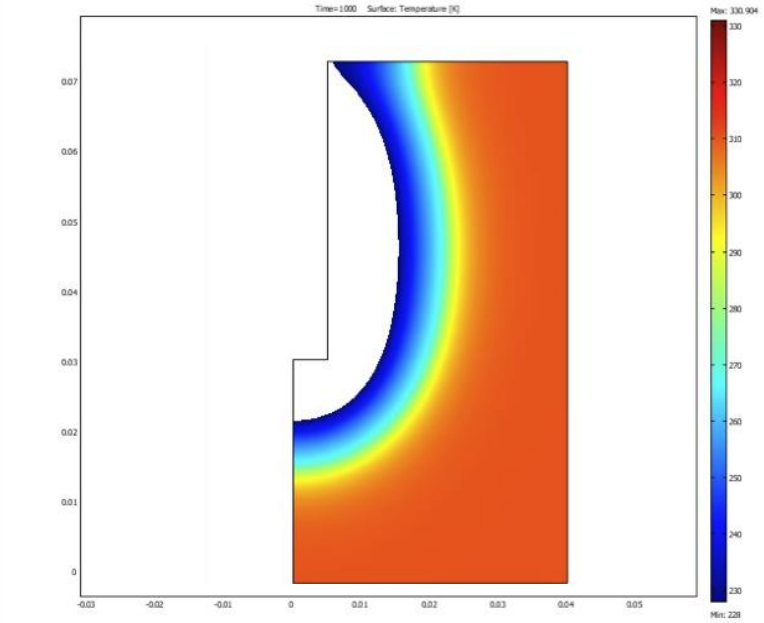


Figure 3: Surface plot of liver tissue with perfusion at 1000 seconds

By comparing Figures 2 and 3, it can be seen that there was a larger freezing region in the condition without perfusion. Therefore, taking the effect of blood perfusion into account shows that a smaller freezing region can be achieved in the same time period. In both cases, the freezing region reached the tumor edge within 1000 seconds.

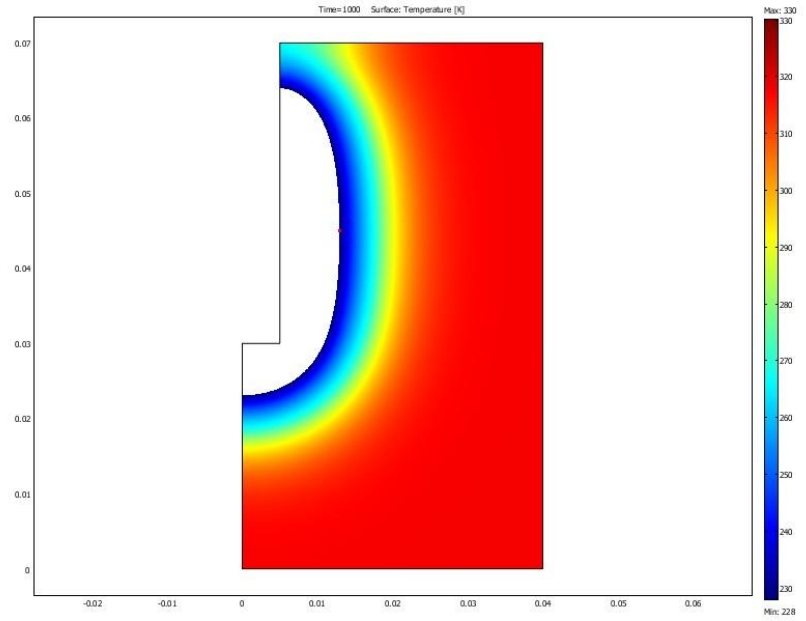


Figure 4: Surface plot of lung tissue without perfusion at 1000 seconds

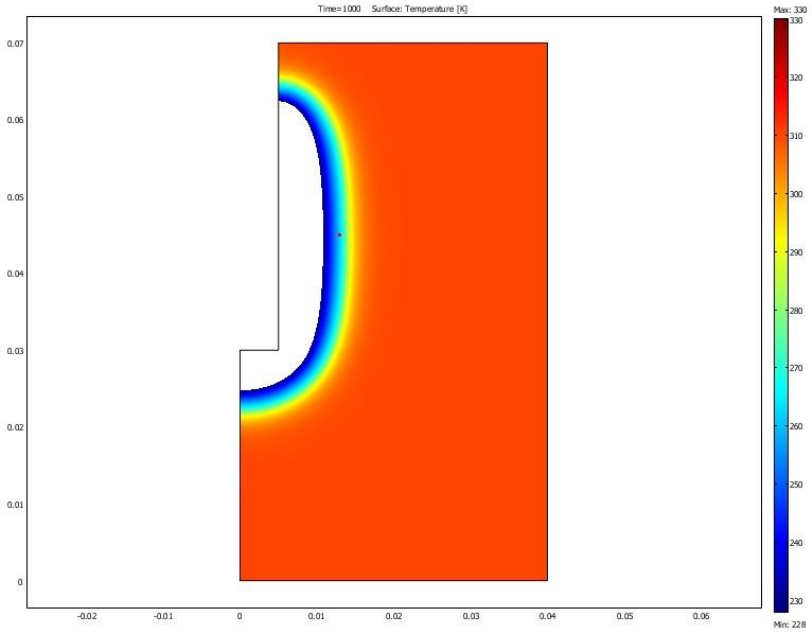


Figure 5: Surface plot of lung tissue with perfusion at 1000 seconds

As can be seen above, in the plot with perfusion (Figure 5), the freezing region was significantly smaller than in the plot without perfusion (Figure 4).This showed perfusion to be a much more significant factor in lung tissue than liver tissue. This is likely due to the much higher blood flow rate and higher degree of vascularization in lung tissue compared to liver tissue. Of additional interest is the heating of the

tissue by about 8°C in the case without perfusion. When perfusion is included however, the tissue remains at body temperature. Although this demonstrates some of the inaccuracies in a model which ignores perfusion, it also reveals the importance of perfusion as both a heating and a cooling mechanism.

The results of all four simulations are summarized below in Figure 6, which shows the temperature profiles at the tumor edge for both lung and liver tissue with and without perfusion. As seen below, there was not a large visible effect between the condition with perfusion and the condition without perfusion for liver tissue. For the liver tissue without perfusion, the tissue at the tumor edge reached a temperature below 228K after 250 seconds. For the liver tissue with perfusion, the tissue at that point took about 300 seconds to reach a temperature below 228K. In comparison, for the lung tissue with perfusion, the tumor edge only reached a temperature of approximately 260K, an insufficient temperature for complete freezing. Blood perfusion had a very significant effect in the lung tissue as evidenced by the large temperature difference between the two conditions at t=1000s.

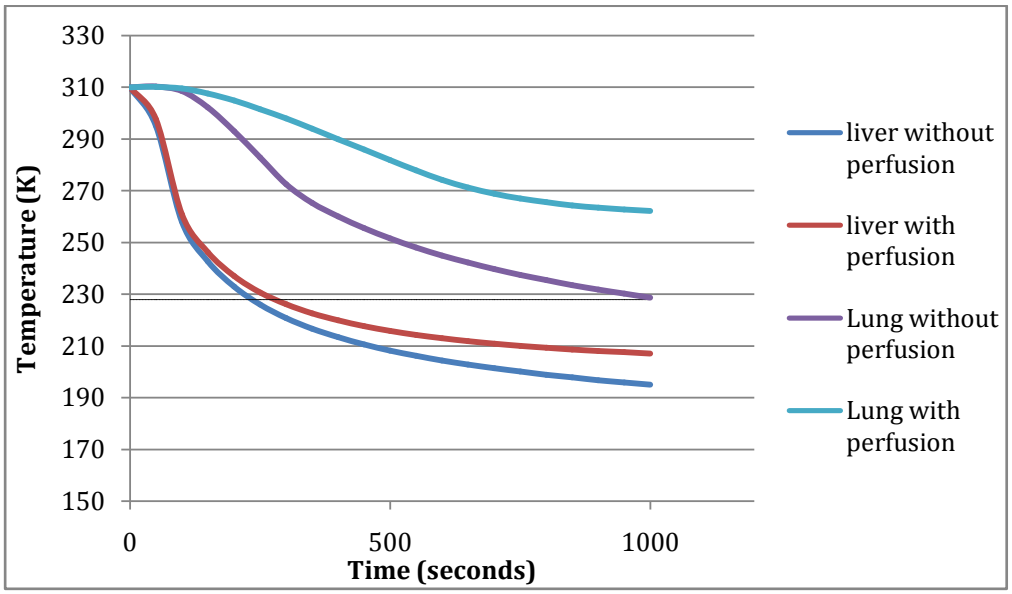


Figure 6: Surface plot of lung tissue with perfusion at 1000 seconds

The results of all four conditions reveal significant differences between the freezing times in lung and liver tissues. When perfusion is ignored, the freezing time in lung

tissue is much greater (1000s) than the freezing time in liver tissue (200s). Since perfusivity is not a factor in these two cases, this must be due to the difference in thermal conductivity as proven in the sensitivity analysis. When perfusion was included, a significant change occurred in lung tissue freezing time and only a minor change occurred in liver tissue freezing time. This shows perfusivity to be a much more significant factor in lung tissue than in liver tissue.

3.2 Sensitivity Analysis

The sensitivity of our solution was determined for four parameters using the condition of liver tissue with blood perfusion:

1. Specific heat capacity of the tissue
2. Metabolic heat generation
3. Thermal conductivity of the tissue
4. Blood perfusion rate

Each of the above parameters was modified by ±10% and ±25%. The resulting change in temperature at the point (0.013, 0.045), the tumor edge, was then observed. A direct comparison of the sensitivities of each condition was made using the temperature at t=1000 seconds.

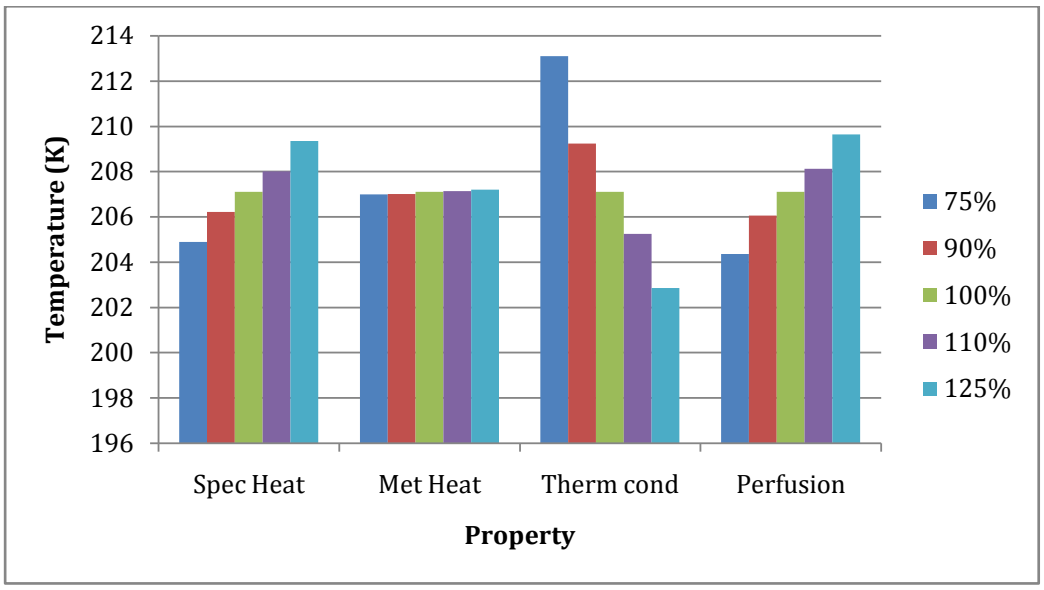


Figure 7: Sensitivity of temperature at (0.013, 0.045) at 1000 seconds to changes in various material properties

As can be seen in Figure 7, the experiment is most sensitive to changes in the thermal conductivity of the tissue. It is least affected, on the other hand, by changes in metabolic heat generation. This clearly shows that blood perfusion, not metabolic heat generation is the dominant source term in the bioheat equation (Appendix A). This is further demonstrated in the difference between results in the lung and liver tissues. Although the liver tissue is much denser than the lung tissue and therefore has significantly more heat generation, the perfusivity of the lung as well as its lower conductivity makes it much more difficult to freeze. The lower metabolic heat generation of the lung has very little effect on this outcome.

3.3 Comparison with Experimental Results

The accuracy of our results was determined via comparison with in vivo results as discussed in Baust, J. et al[8]. In the Baust study, 3mm and 8mm cryoprobes were both used in separate cryosurgical procedures. As seen in Figure 9, the study found that it took approximately 7.5 minutes for a point 8mm from the probe to reach -40°C (233K).

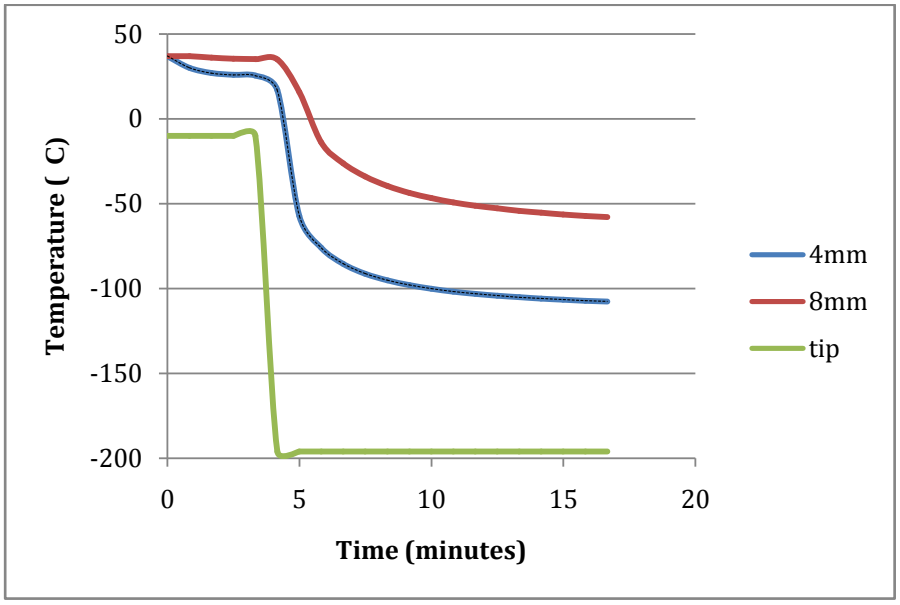


Figure 8: Liver tissue temperature as function of time based on our model at distances 0mm, 4mm, and 8mm from the probe.

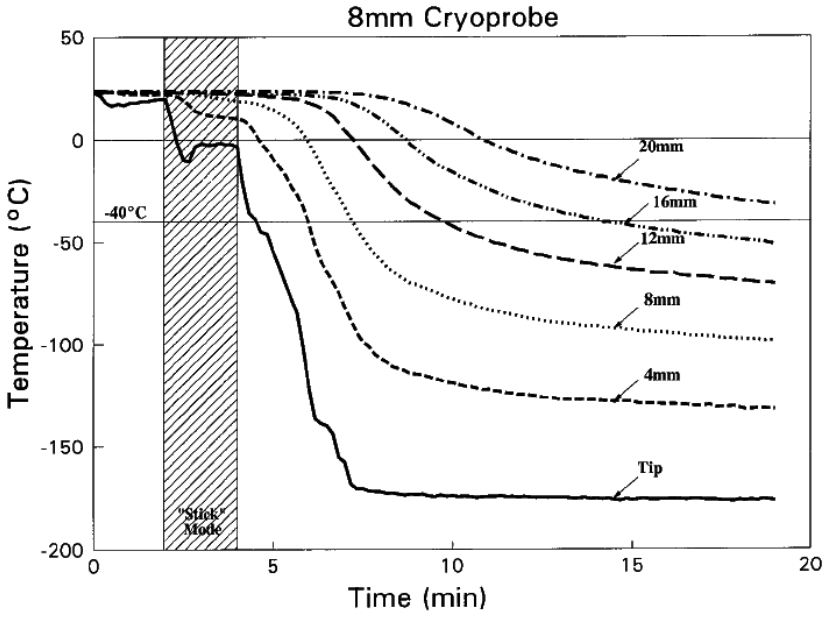


Figure 9: Experimental results from Baust, J. et al. used as comparison to our model

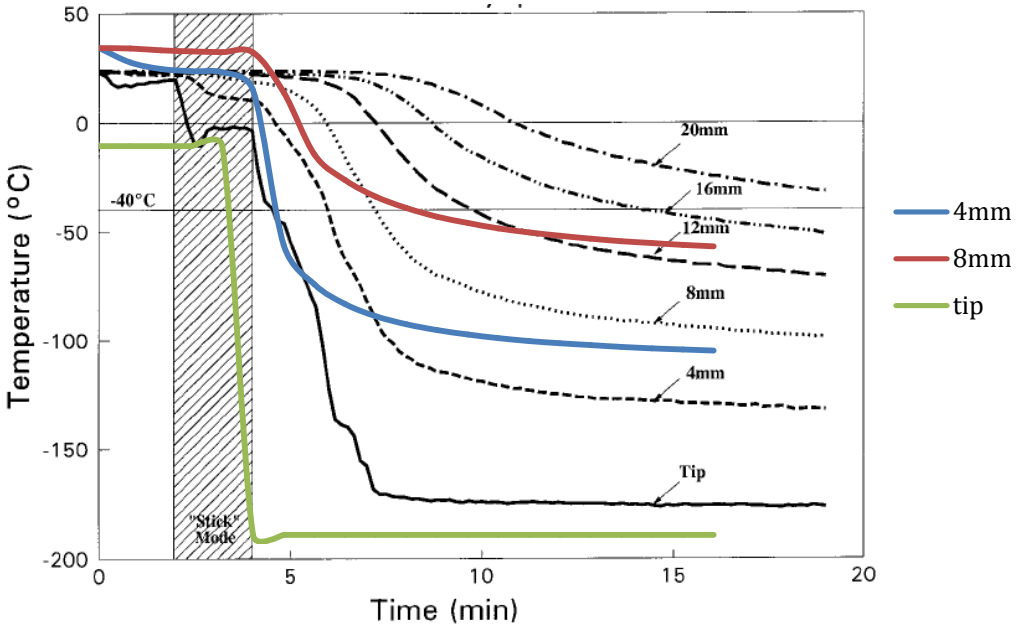


Figure 10: Overlay of results from our model and experimental results

In order to make a comparison, we modified our geometry from that of a 1cm cryoprobe to an 8mm cryoprobe. In addition, the in vivo model used a "stick mode" for approximately the first four minutes, a period in which the probe is set at -10°C to get it to "stick" to the surrounding tissue. In order to simulate the stick mode, we imposed a time-dependent boundary condition on our model, with the cryoprobe surface temperature at -10°C for the first 4 minutes, and -196°C after that. The results are shown above.

As can be seen in Figures 8-10, it took approximately 7.5 minutes for a point 8mm from the probe to reach -40°C (233K). This is very close to the values found in the experimental data.

4. Conclusions and Design Recommendations:

The results showed that tissue properties such as perfusivity and conductivity have significant effects on the efficacy of cryosurgical procedures in different tissue types. Unlike most predictive models which do not account for the heat being added by blood perfusion, ours showed that this is indeed an important factor to consider. Although this additional heat generation is always present, it has differing impacts depending on the density and the blood flow rate of the tissue. In tissues such as the lung where blood flow rate is very high, the difference between including blood perfusion and ignoring it is extreme. Conversely, in tissues such as the liver with a lower blood flow rate, perfusivity plays a much smaller effect. In addition to perfusivity, tissue properties such as thermal conductivity played a significant role in freezing times. Even when perfusion was ignored, the liver and lung tissues showed significant differences due mostly to differences in conductivity. This further demonstrates the importance of tissue properties in determining freezing time during cryosurgery.

While this model is better than those not including the effects of blood perfusion it is not necessarily an accurate predictor. The primary physical constraint in this model is the uncertainty about the physical parameters for the different tissues of the body. Values for thermal conductivity, density, and blood perfusion are difficult to find and are rarely agreed upon by different scientific papers. Another physical constraint is that physical properties of tumors differ from the surrounding normal tissue. We did not account for this difference, which may have an effect on the time it takes for the tumor edge to reach-45^{o}C.

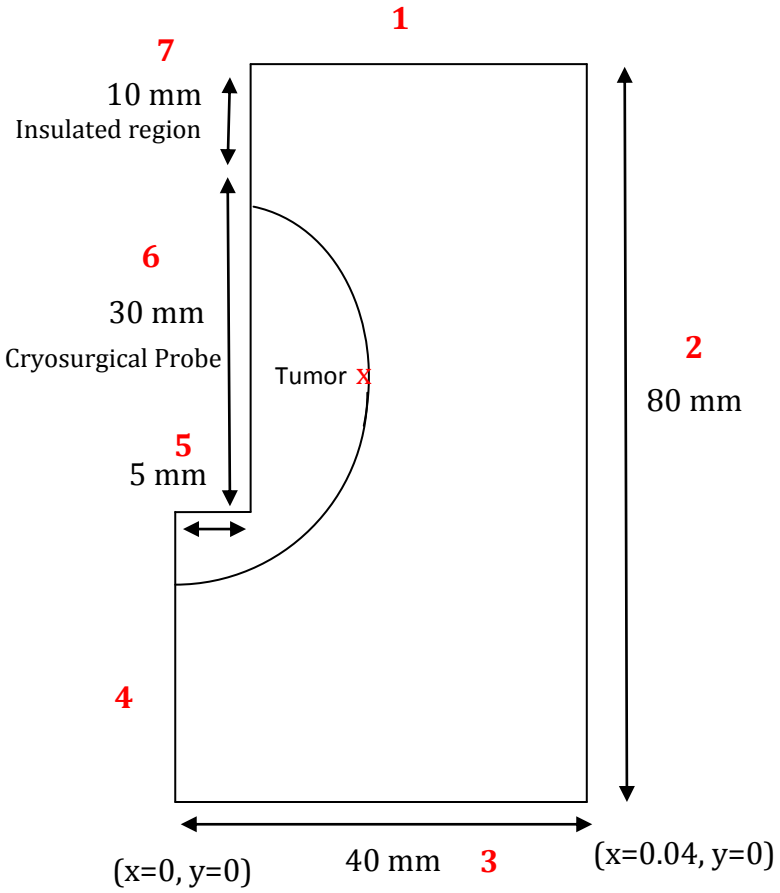
Even without addressing some of these issues, our model shows that cryosurgery is an effective treatment although one that varies significantly in its efficacy for different tissue types. As seen in our model, the procedure performs well in denser, less-perfused tissue types such as the liver, and fails to perform well in less dense, highly-perfused tissue such as the lung. Although we recommend the application of cryosurgery for liver and other similar tissues, we suggest that further models be

developed to assess the efficacy of cryosurgery in the lung. Future models would require more specific information regarding the various physical properties of all the tissues and tumors in the human body. In addition, these models could take into account the different cryoprobe tip sizes and shapes which exist in clinical practice.

In our recommendation to continue the use of cryosurgery for liver tissue, we acknowledge the existence of several realistic constraints which may impact future decisions. For example, the financial burden of increasing the use of cryosurgery for liver tumors could be considerable. Significant expenses such as the training of physicians, purchasing of equipment and insurance costs must be considered. Another important constraint to consider is the social impact of increasing the use of cryosurgery. Patients will now have to make the decision between a safer, but more localized treatment in the form of cryosurgery and more traditional treatments such as chemotherapy and conventional surgery. In order for cryosurgery to become a common treatment for cancer, the public would need to be informed about its advantages and disadvantages in comparison to current, commonly used treatment options.

Appendix A: Mathematical Model

A.1 Schematic:



Xdenotes the point (0.013, 0.045) where plots of temperature vs. time were created.

A.2 Governing Equation:

The governing equation for this model is the heat transfer equation. We added two source terms for metabolic heat generation, Q, and blood perfusion, $\rho c V^{v}(T_a - T)$.

$$\rho c \frac{\partial T}{\partial t} = k\nabla^2 T + \rho_b c_b \dot{V}_b^{v}(T_a - T) + Q$$

A.3 Boundary Conditions:

1. Flux = 0
2. Flux = 0
3. Flux = 0
4. Flux = 0 (symmetry)
5. T_{probe}^2 = -196°C = 77.15K
6. T_{probe}^2 = -196°C = 77.15K
7. Flux = 0 (insulated)

A.4 Initial Conditions:

T_{tissue} = 37ºC = 310.15K

A.5 Material Properties:

Table 1: Material Properties

Property	Value	Reference
Specific Heat Capacity of blood	3594J/kg-K	5
Blood flow rate in liver	0.83ml/min/g	6
Blood flow rate in lung	1.38ml/min/g	7
Density of blood	1060kg/m^3	3
Average Density of lung tissue	332kg/m^3	4,10
Density of liver tissue	1000kg/m^3	4

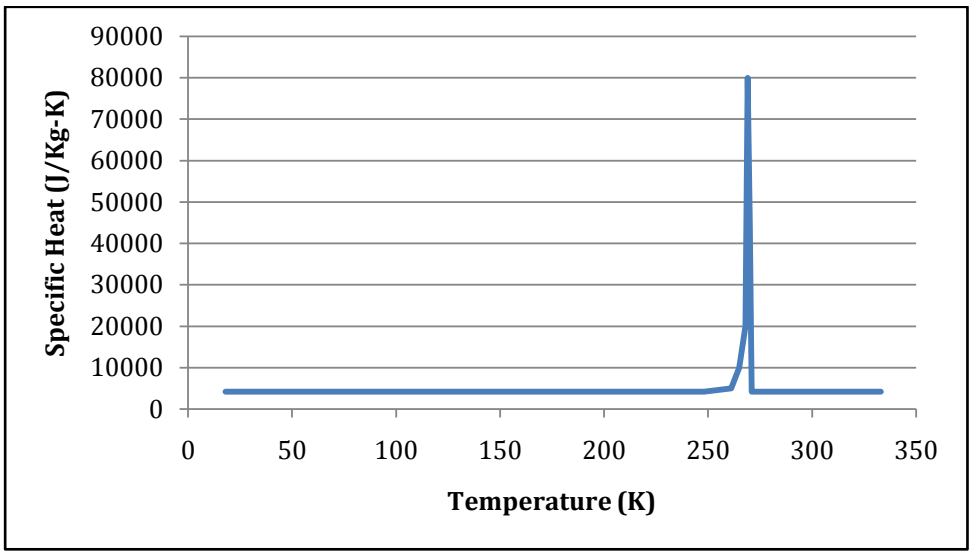


Figure 11: Specific heat of lung and liver tissue as a function of temperature[1]

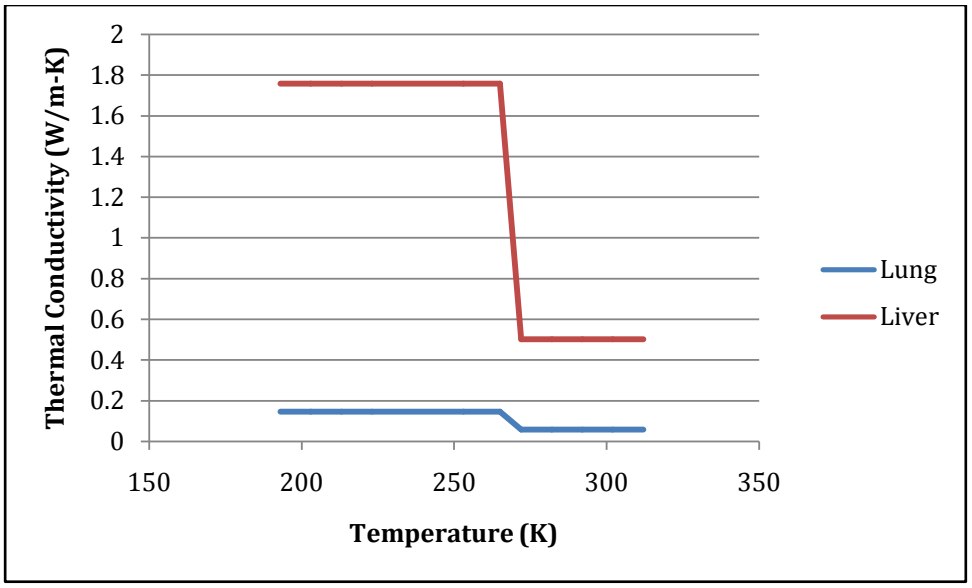


Figure 12: Thermal conductivity of lung and liver tissue as a function of temperature[4]

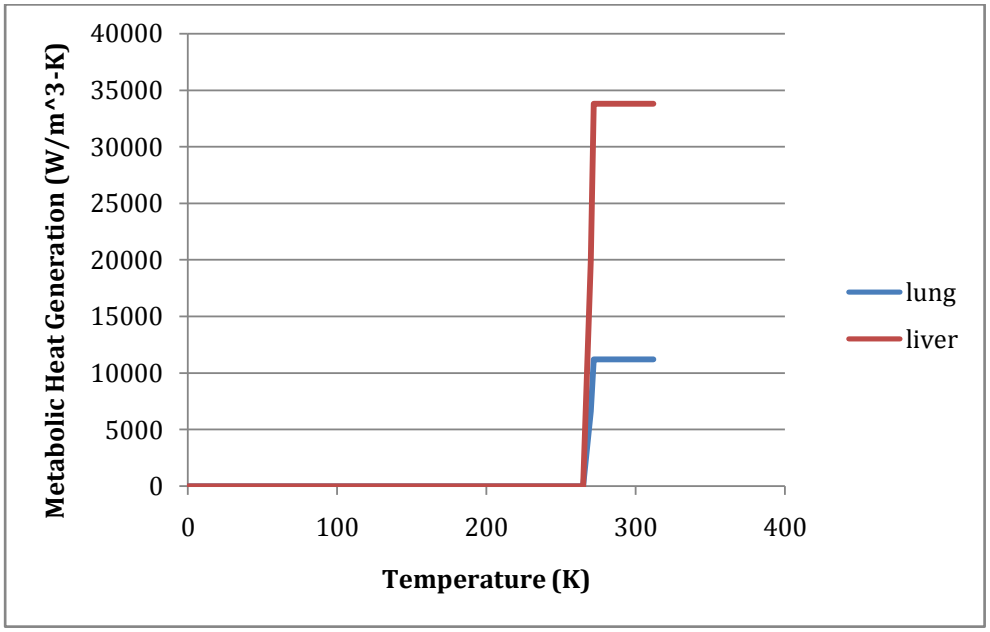


Figure 13: Volumetric metabolic heat generation of lung and liver tissue as a function of temperature[2]

Note: Since the density of lung tissue is 33% the density of liver tissue, the volumetric metabolic heat generation for lung tissue was obtained by multiplying the heat generation of normal non-porous tissue (liver) by .33.In addition, it is assumed that metabolic heat generation approaches zero as the phase change begins to take place between 265K and 272K.

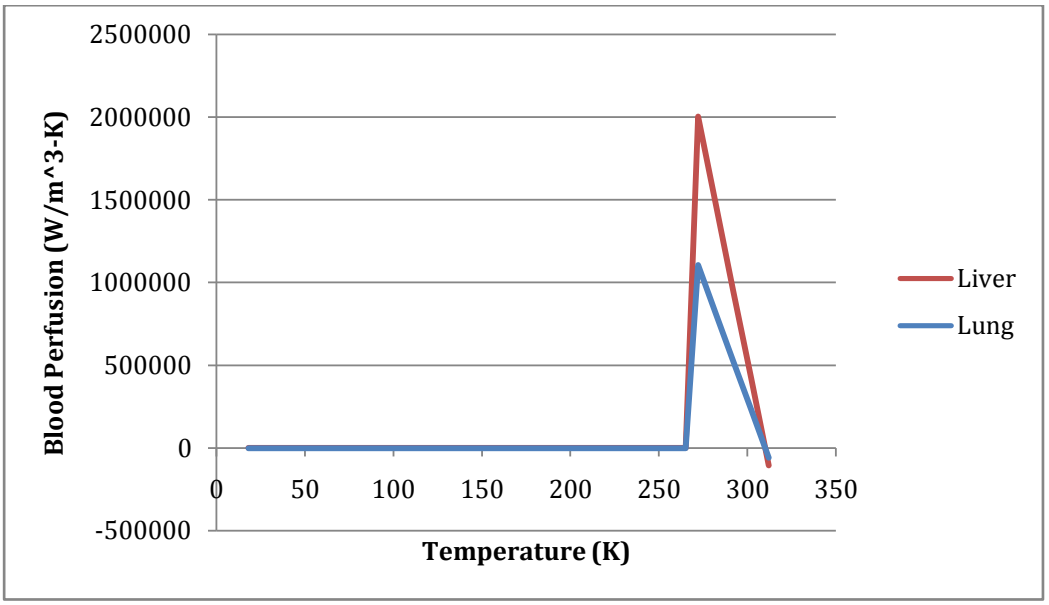


Figure 14: Blood perfusion in liver and lung tissue as a function of temperature

Note: Although lung tissue has a much higher perfusivity than liver tissue per gram of tissue, factoring in the lower density of lung tissue gives it a lower perfusivity per m^3. In addition, it is assumed that blood perfusion approaches zero as the phase change begins to take place between 265K and 272K.

Appendix B: Problem Statement

B. 1 Solver:

The solver used to solve the algebraic equations was a direct UMFPACK solver.

B.2 Problem Settings:

The problem settings used in COMSOL for our model were as follows:

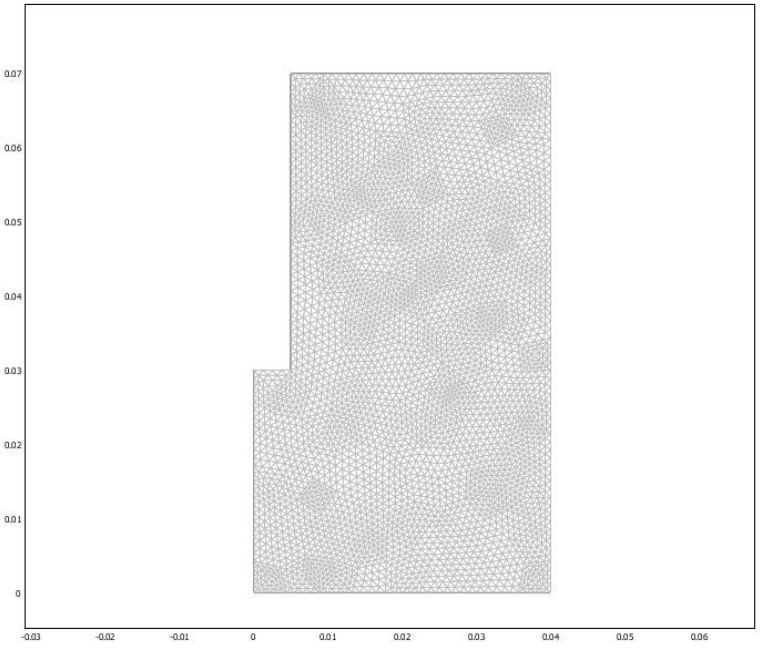
- Space dimention – 2D Axisymmetry
- Application Type – Heat Transfer
- Mode of Transfer – Conduction
- Simulation Type – Transient

B.3 Time Step/Tolerance:

A time step of 0:50:1000 seconds was used for the transient problem. We used a relative tolerance of 0.001, an absolute tolerance of 0.0001 and a maximum time step of 1 second.

B.4 Mesh:

We used a free (unstructured mesh) with 7968 triangular elements as shown below.



B.5 Mesh Convergence Analysis:

In order to perform a mesh convergence analysis, the average temperature throughout the domain (for liver tissue without blood perfusion) was calculated.

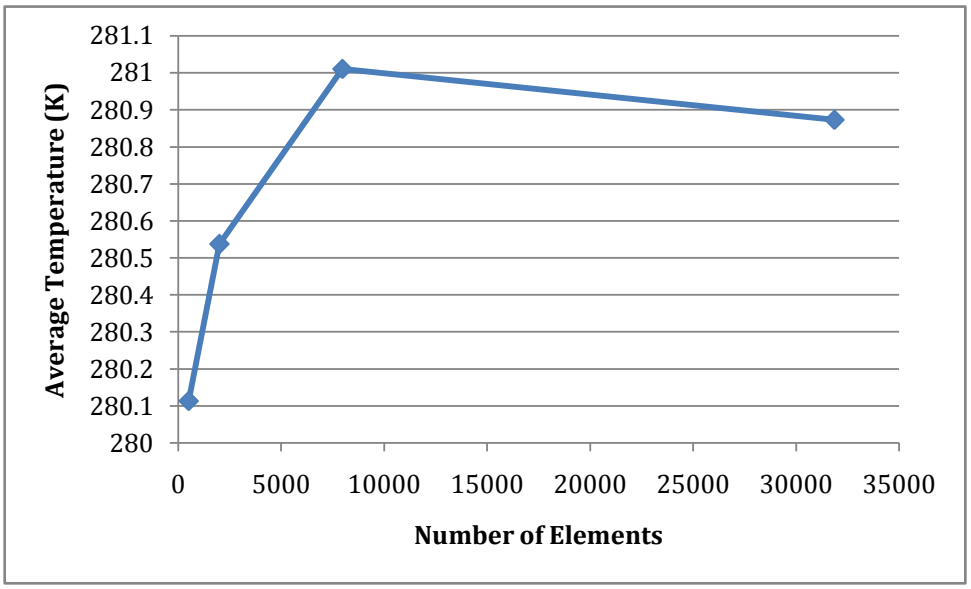


Figure 6: Mesh convergence

1. Default Mesh:
   Value of volume integral: 0.09768[m^3*K], Expression: T, Subdomain: all
   Value of volume integral: 3.487168e-4[m^3], Expression: 1, Subdomain: all
   Average Temperature = 280.1127
   Number of elements = 498

2. Refined 1x
   Value of volume integral: 0.097828 [m^3*K], Expression: T, Subdomain: all
   Value of volume integral: 3.487168e-4 [m^3], Expression: 1, Subdomain: all
   Average Temperature = 280.5371
   Number of elements = 1992

3. Refined 2x
   Value of volume integral: 0.097993 [m^3*K], Expression: T, Subdomain: all
   Value of volume integral: 3.487168-4 [m^3], Expression: 1, Subdomain: all
   Average Temperature = 281.0103
   Number of elements = 7968

4. Refined 3x
   Value of volume integral: 0.097945[m^3*K], Expression: T, Subdomain: all
   Value of volume integral: 3.487168e-4 [m^3], Expression: 1, Subdomain: all
   Average Temperature = 280.8726
   Number of elements = 31872

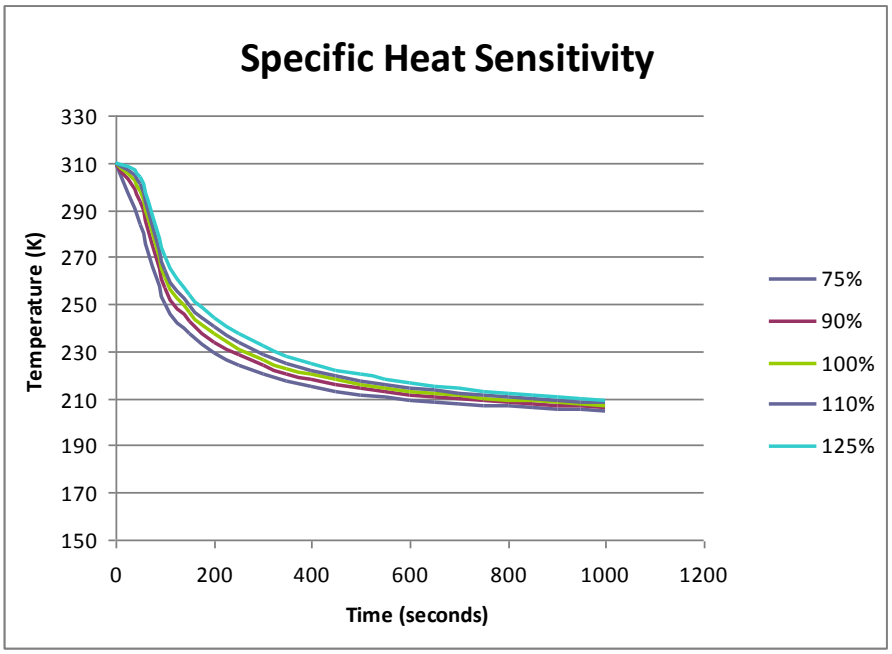
As shown in figure 17, changing the mesh resulted in relatively small changes in the average temperature. The graph shows convergence after refining the mesh 2 times. After this point, the average temperature is independent of the mesh. Thus, we selected to use the mesh with 7968 elements.

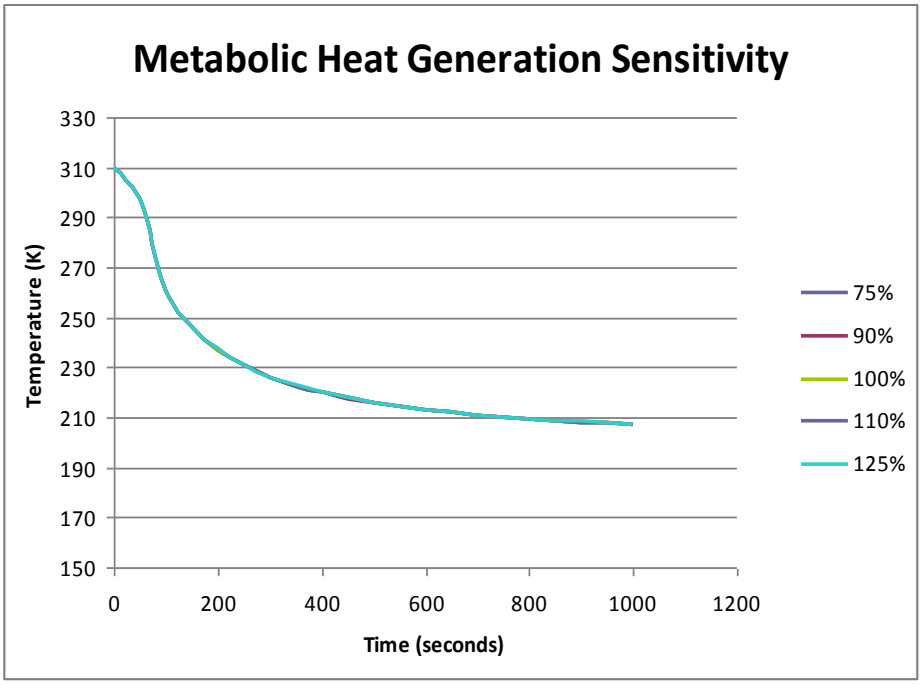
Appendix C: Additional Sensitivity Analysis Data

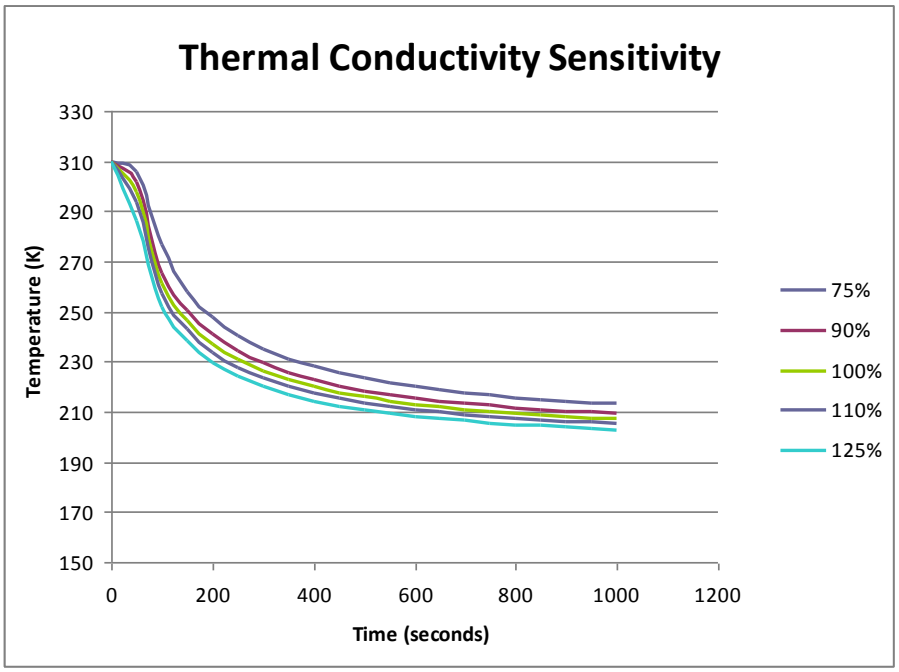
The sensitivity of our solution was determined for four parameters for the condition of liver tissue with blood perfusion:

1. Specific heat capacity of the tissue
2. Metabolic heat generation
3. Thermal conductivity of the tissue
4. Blood perfusion rate

Each of the above parameters was modified by ±10% and ±25%. The resulting change in temperature at (0.013, 0.045), the tumor edge, was then observed. The graphs below show the temperature at (0.013, 0.045) for the entire 1000 second range.




Metabolic Heat Generation Sensitivity
330
310
290
270
250
230
210
190
170
150
Temperature (K)
0
200
400
600
800
1000
1200
Time (seconds)
75%
90%
100%
110%
125%


Thermal Conductivity Sensitivity
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310
290
270
250
230
210
190
170
150
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200
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600
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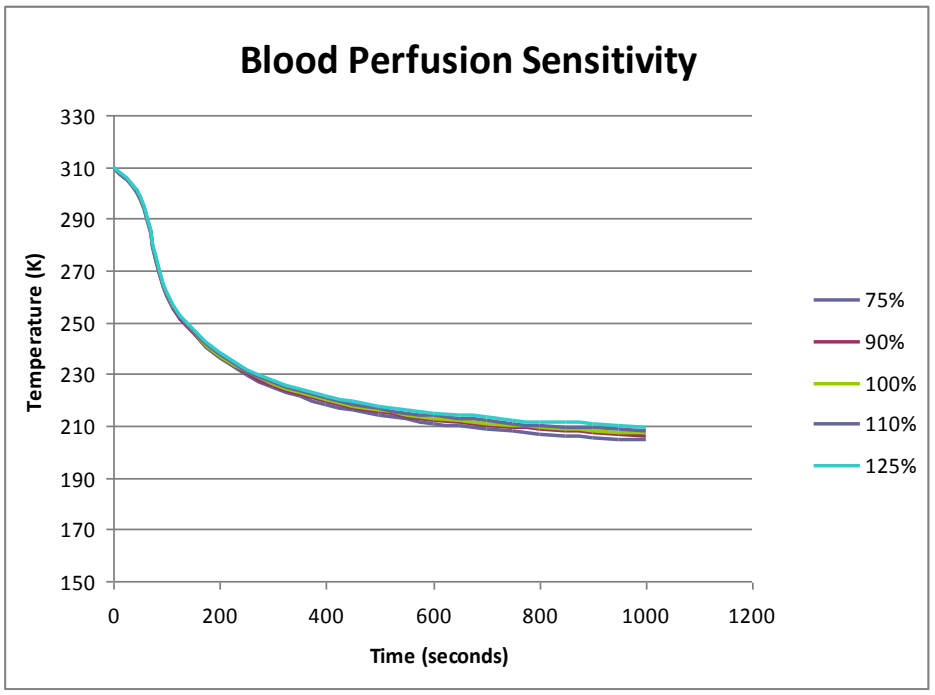
1200
Time (seconds)
75%
90%
100%
110%
125%


Blood Perfusion Sensitivity
330
310
290
270
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210
190
170
150
Temperature (K)
0
200
400
600
800
1000
1200
Time (seconds)
75%
90%
100%
110%
125%

Appendix D: References

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