Modeling Brain Cooling Helmets for Ischemia Patients

BEE 4530: Computer-Aided Engineering: Biomedical Processes

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1. Executive Summary

In this project, we modeled the effectiveness of a cooling cap designed to lower brain temperatures by approximately 3°C in order to cause temporary hypothermia in the brain and thereby prevent further injury caused by cerebral ischemia. Cerebral ischemia is a condition in which blood flows preferentially through certain blood vessels in the brain and not through others, resulting in certain sections of the brain receiving insufficient blood flow for nutrient uptake and waste removal, potentially resulting in a stroke. Using the modeling program COMSOL Multiphysics, we simulated the brain temperature that results from the use of a cooling helmet consisting of a cap containing flowing coolant. The model incorporates convective flow of the coolant in the cap, and heat conduction through various modeled layers of the head. Our model showed that cooling occurred by the predicted conduction and convection mechanism and our results matched closely with those obtained from the literature, therefore validating our model. Initial results showed appropriate brain cooling; however, damage to the scalp occurred. Time of application and temperature of coolant were then successfully optimized to eliminate scalp damage while maintaining effective brain cooling. Even cooling the brain just a few degrees, as achieved in our model, reduces the extent of brain damage following cerebral ischemia. The use of this model provides insight into the optimal treatment conditions for using the cooling cap in a clinical setting.

2. Introduction

2.1 Background Information

A cerebrovascular accident (CVA), or more commonly, a stroke, is the loss of brain function due to a disturbed blood supply to the brain. This is most often due to a hemorrhage resulting from a blocked or burst blood vessel, and less commonly due to ischemia, a loss of oxygen in local areas due to vasoconstriction (Bamford 1991, 1521). Deprived of oxygen, the affected area of the brain time-dependently suffers neurological damage that is oftentimes permanent, qualifying a CVA as a medical emergency. CVAs are the number two cause of death worldwide and the leading cause of adult disability in the US (Feigin 2005, 2160).

Treatment for stroke patients varies according to the severity of the neurological damage suffered. Severe cases are often treated with an “optimal comfort” philosophy, and most hospitals are equipped with stroke units. Patients suffering mild strokes typically receive “supportive care” (Straus 2002, 1388), which includes speech, physical, and occupational therapies, along with practicing blood pressure control and taking antiplatelet medication (secondary prevention).

A new and alternative method of treatment proposes using “brain-cooling helmets” to induce local hypothermia in the stroke-affected area and deep brain (Neimark 2008, 333). Researchers have demonstrated the benefits of inducing local hypothermia, which is defined by the temperature range 32-34°C. Inducing a state of local hypothermia slows down cellular metabolism in that region, thereby lowering the oxygen demand. This can be particularly effective for stroke patients whose ischemic regions cannot be permanently alleviated by thrombolysis or conventional surgical methods. This includes most patients.

The brain damage accrued following a stroke is critically dependent on the amount of time the tissue’s oxygen supply is disturbed. For the cooling to be an effective therapy for patients, the time limit of treatment after the CVA incident cannot exceed three hours (Neimark 2008, 333). After this amount of time it is held that the neurological damage suffered is too great, and is therefore irreversible. This puts a marked restriction on the model, as it may be difficult to achieve the necessary temperature deep in the brain in this time without causing cryo-damage to intervening layers.

The aim of our study is to implement this model using COMSOL and evaluate its viability for the treatment of stroke patients, and evaluate alternate applications if this intended use is not ultimately viable.

2.2 Schematic

A 2D axisymmetric depiction of the cap and layers of the head, shown in Figure 1, details the model implemented in COMSOL.

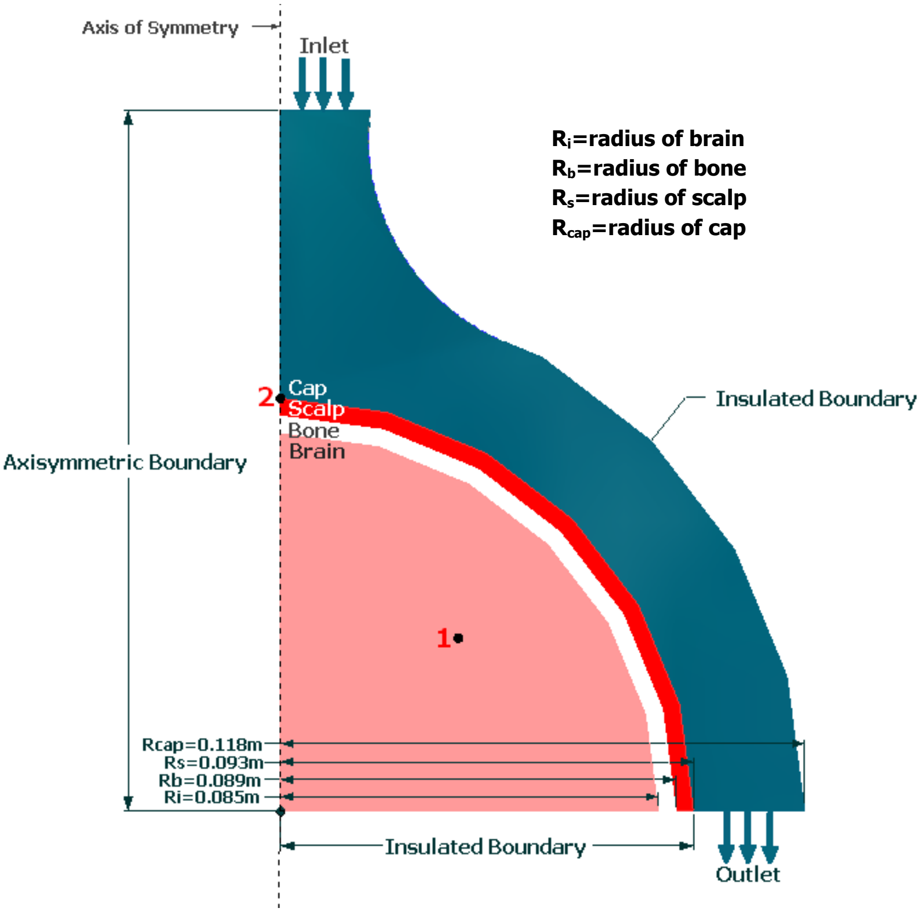


Figure 1. Schematic of the Brain and Cooling Cap. Utilized in COMSOL as a 2D axisymmetric geometry. Physical dimensions of modeled layers used from Neimark et al (2008). All external boundaries are considered insulated or no flux due to axisymmetry except for the inlet with a defined temperature of -8°C, and the outlet with a defined pressure equal to 0 atm.

The vertical axis of symmetry, boundary conditions, and direction of fluid flow are all indicated on the schematic, as well as the different layers and their respective radii. Though not shown, the inlet has a constant boundary temperature equal to the fluid temperature, and the initial temperature of the brain, bone, and scalp layers is 37°C. Point 1 is located at the coordinates (0.04m, 0.04m), and Point 2 is located at (0m, 0.093m).

2.3 Governing Equations

There are several governing equations solved by COMSOL in this 2D axial symmetrical problem which incorporate two physics- Navier-Stokes governing fluid flow and Conductive and

Convective Heat Transport. Ultimately, COMSOL will solve for temperature, pressure, and velocity (both u and v for two dimensional flow) using these equations in each subdomain. Modifications to these equations, for example using only conduction and no convection, are required for each layer of our model, resulting in the specific equations included in Appendix A. Before applying these equations we determined the geometries, parameters, and nature of the boundaries that define our model. In doing so, we made several necessary assumptions and simplifications:

- the region of the head treated is the shape of a perfect hemisphere
- the cooling cap completely covers the head and fits snugly with no air gap
- no hair is present, so any effect it has on shielding radiative heat is ignored
- the head is divided into three distinct, uniform layers, each with unique parameters constant throughout the layer
- the inner brain is one uniform area with no distinction between white and grey matter
- the parameters of the cranial layers are independent of temperature
- the properties do not fluctuate from patient-to-patient

2.4 Design Objectives

There are two main requirements of the cooling cap. First, to be an effective method of preventing secondary strokes, the cap must cause deep brain temperature to reach 32-34°C. The temperature at the target point, Point 1, will reveal whether or not this requirement has been achieved. The other requirement of the cooling cap is that it must not result in skin or tissue damage. Therefore, the skin surface temperature and all sub-surface regions must be maintained above 5°C. The temperature at the coolest point on the scalp, Point 2, is used as an indication of our success in achieving this requirement.

We attempt to satisfy these objectives by modifying cap application time and coolant fluid temperature. The application time is limited in its variability, as it cannot exceed three hours in order to be therapeutically effective. If our efforts prove to be unsuccessful, either due to unacceptable scalp conditions or the system being unable to achieve a low enough temperature in the allotted three hour time period, we will investigate if the temperature reached is appropriate for other uses, allowing our model other applications. For example, alopecia prevention requires that only the scalp layer is cooled, and has no cooling requirements for deep brain (Janssen 2005, 4065).

3. Results and Discussion:

3.1 Results from Initial Model

The initial model of a cooling cap helmet with convective flow and conductive heat transport yielded what appeared to be reasonable results based on the surface temperature and velocity plots after 3600 seconds, as seen in Figure 2. Notice that as expected the most dramatic temperature changes occur across the scalp and bone layers, making temperature changes inside the actual brain much less extreme despite the large temperature gradient between the cap and inner brain. As for velocity, even though the inlet has a maximum speed of 0.03m/s, since the cap is actually three dimensions, the area through which the fluid flows increases dramatically as it flows down the cap causing the velocity to be very small in the majority of the cap as shown below in Figure 2B.

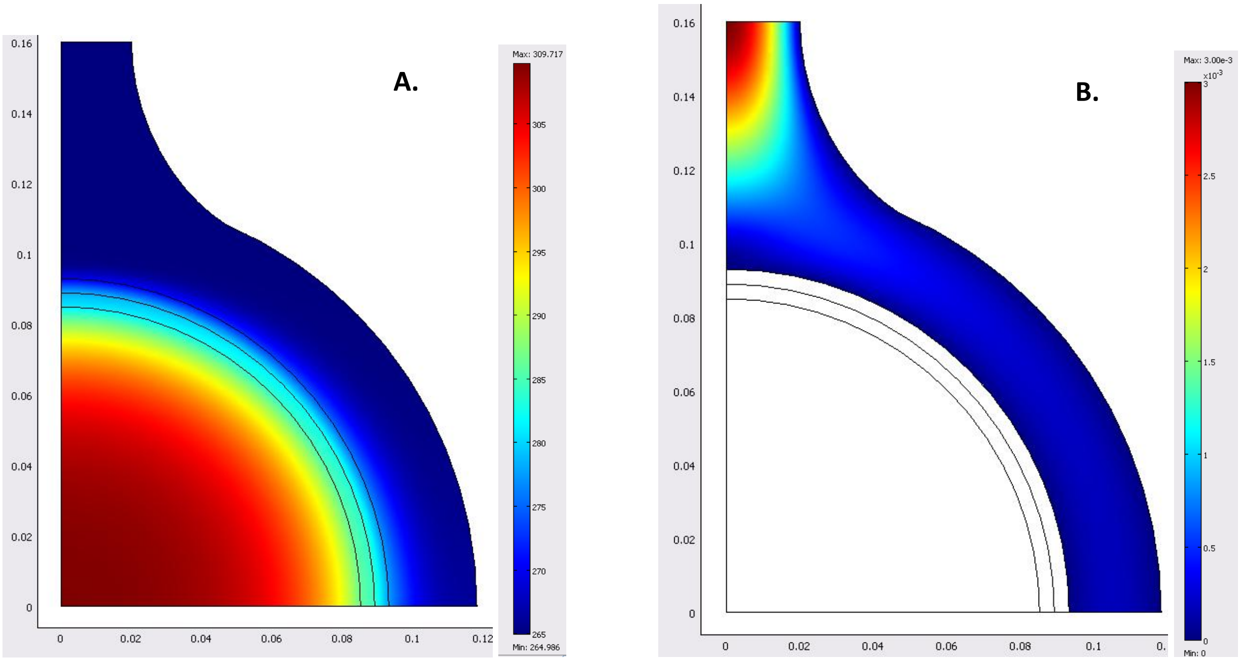


Figure 2. Temperature and Velocity Profiles at t= 3600s. A-Surface temperature solution solved using both Navier-Stokes and Conductive and Convective Heat Transfer. B-Velocity profile of coolant in cooling helmet.

The surface plot above in Figure 2A and the contour plot presented in Appendix C.1 demonstrate the temperature distribution in the modeled head regions. As could be predicted, the maximum temperature occurs at the center of the brain, a region where heat generation is high and the distance for heat transfer between the cold cap and hot biological material is greatest. Yet this is the region of greatest concern for clinical use as ischemia occurs in neural tissue inside the brain, not in the scalp or bone which may be quickly cooled. According to Zhu & Diao, effectiveness of brain cooling methods has previously been monitored approximately 7.5 mm beneath the brain tissue surface (2001, 681). However, this does not appear to be a deep enough measurement in order to verify that the region where an ischemia is likely to occur, deep in the brain, will be cooled enough. This measurement only seems to consider the surface of the brain, not the gray matter which is most vulnerable to tremendous loss of neural function following an untreated cerebral ischemia. Therefore, the quantitative analysis of this model has focused on achieving the necessary temperature cooling at a more internal point, Point 1, which is at a radial distance of 0.056569m from the model's origin. This should provide a more accurate depiction of the effectiveness of the cooling helmet.

Additionally, the velocity profile in Figure 2B verifies that fluid flow remains consistent over the hour of the simulation. This enables the cold fluid to stay in motion and continuously remove the efflux of heat from the head. The velocity remains highest at inflow where velocity is forced in and the area through which the coolant may flow is the smallest. However, as the fluid spreads out over the cap, it is flowing through a much larger area and therefore slows down dramatically as shown above.

The formation of visibly warmer contour lines near the coolant cap outlet in Appendix C.1 shows how the flowing coolant collects the heat leaving the head. Closer to the inlet, the coolant will not be warmed nearly as much by the extracted heat. In these areas, the actual temperature touching the scalp is of great concern. Sustained contact with the scalp at temperatures below 2 °C could cause tissue damage. Therefore, Point 2 was chosen to monitor the scalp temperature. Because the coolant is entering just above this location, this point represents one of the coolest spots on the scalp.

While the final temperature profiles given above are helpful to determine if the brain reaches the desired temperature during therapeutically relevant times, visualizing the temperature with respect to time provides another way of understanding the heat transfer. Monitoring the temperature change over time, as seen below in Figure 3, helps to identify optimal treatment options that incorporate sufficient brain cooling without imposing scalp damage.

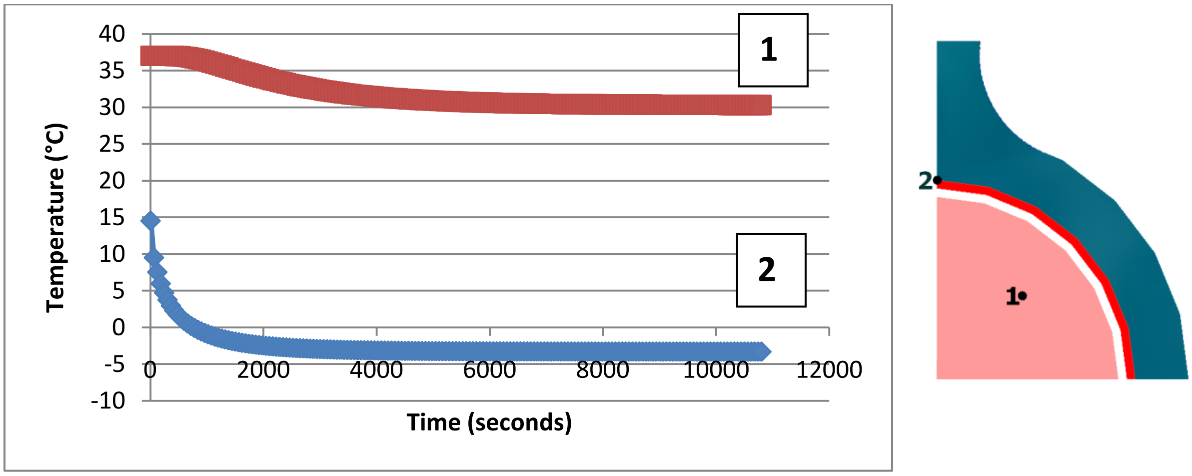


Figure 3: Heat transfer effects in critical locations- inner brain and scalp- The temperature of the coldest point of the scalp, measured at Point 2, decreases and levels off to approximately -3°C within an hour. B-The temperature at Point 1, an inner brain location, steadily declines over an hour and reaches the desired therapeutic temperature.

Figure 3-line 1 shows temperature vs. time for Point 1, which is the point used to monitor if the ischemia prone region of the brain reaches the necessary temperature. After a few minutes of relatively little change, the temperature showed a steady decline from 37°C to 32°C over the course of about an hour. The first few moments of little change represent time during which the cold is first affecting the scalp and bone layers, which act as an insulator to the actual brain. The five degree temperature reduction in just one hour is more rapid cooling than desired. Most medical applications of this cooling cap will require maintenance of approximately 32-34°C for a sustained amount of time to induce the necessary hypothermia without causing other damage.

Figure 3-line 2 shows the temperature as it changes with time at the coldest point of the scalp, which is just inside the boundary of the cooling cap. Our aim was to keep the temperature at all points above 5°C, so that the patient would not sustain any tissue damage due to freezing. However, as can be seen in the graph above, the temperature at the coldest point drops below 5°C after approximately three minutes, which is much earlier than we had anticipated. Also, the temperature plummets to approximately -3°C at steady state, which is much too cold for sustained exposure. We plan to raise coolant fluid temperature in order to achieve a less dramatic, and potentially safer, temperature profile.

3.2 Comparison of Standard Model Results with Literature

Models like ours are used to numerically solve non-linear, complex solutions that cannot be solved with a simple analytical calculation. Additionally, our model makes dramatic assumptions regarding geometry and physical parameters. Without the ability to obtain a simple analytical solution, it is difficult to assess the validity of our model beyond recognizing reasonable, expected trends in the solutions. Therefore, in order to confirm our model justly represents the actual heat transfer through the cap and cranium, we compare our results to previously published models. Each model uses a slightly different method, yet if appropriate they should all yield similar results for the same overall problem. Results found in literature for brain temperature following the application of a cooling cap that closely resemble similar findings to those obtained using our model, as shown below in Figure 4, strongly suggest that our model accurately depicts the heat transfer.

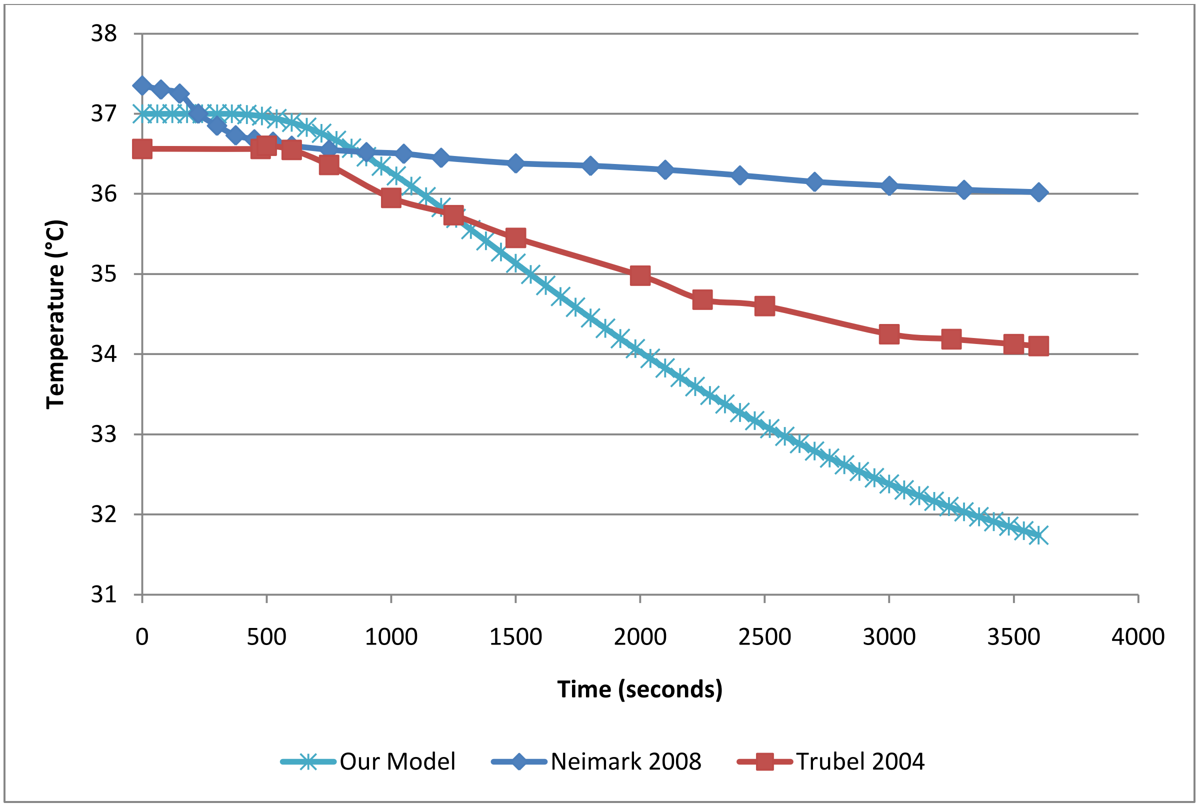


Figure 4: Validation through Comparison to Literature. This figure includes temperature profiles in the internal brain region obtained through three different models for a brain cooling cap. General trends are similar suggesting a decrease of a few degrees over one hour even though the ultimate temperatures vary between each model by at least 2 °C. (Neimark et al. 2008, 339 & Trübel et al. 2004, 1831).

Literature comparison most obviously demonstrates how modeling yields variations. The three curves presented in Figure 4 are results from our model, light blue 'X's, and two found in literature for the application of a cooling cap to treat brain injury. While no model provided the exact same temperature profile over one hour, our relatively simple model yields the same trend and overall few degree temperature reduction as the two more sophisticated models performed by Neimark, 2008, and Trübel, 2004. The general trends of gradual temperature decline of a few degrees persist in all three models with ours and Trübel's matching most closely. The Neimark model suggests a more dramatic initial temperature decrease and then a steadier decline over time. Some of this variation may be attributed to different models taking temperature measurements at slightly different locations. For example, our model measures brain temperature at a radius of 0.056569m while the Neimark study records the temperature at the ipsilateral anterior territory but does not cite a specific distance from the center of the brain (2008, 339). Additionally, each model utilizes slightly different assumptions regarding how to define the cranial layers and what parameters values to use which may contribute to how well the scalp and skull layers insulate or conduct the heat transfer between the cooling cap and then internal brain tissue.

Variation is inevitable in complex modeling like this that incorporates innate calculation errors due to iterative convergence for time and discretization of space calculations in addition to the assumptions made regarding the actual geometry and properties that are necessary to convert a biological situation into a mathematically solvable schematic. However, showing that our model does not vary from others more than the alternative models vary from each other suggests accuracy in how we depicted the situation and solved heat transfer to obtain a brain temperature after time. Although our results after one hour differ approximately 4 °C from the Neimark study, they differ approximately 2 °C from the Trübel paper, which is the same as the difference between final temperatures calculated in the two published papers. Thus, ours is definitely in the same range as theirs, emphasizing the validity of our model.

3.3 Combined Variability:

Firstly, we performed an overall sensitivity analysis to determine the combined effect of variability of several parameters. For each layer, specific heat, mass density, thermal conductivity, and where appropriate, heat generation, were calculated at two values based on an appropriate range in data as found in literature. The following equation was used to calculate combined variability:

$$\Delta T = \sqrt{\left(\frac{\partial T}{\partial c_p}\Delta c_p\right)^2 + \left(\frac{\partial T}{\partial \rho}\Delta \rho\right)^2 + \left(\frac{\partial T}{\partial k}\Delta k\right)^2}$$

where $\frac{\partial T}{\partial c_p}$ represents how sensitive the temperature is to that parameter and is calculated by $\frac{T^* - T_0}{{c_p}^* - c_{p_0}}$. Δc_p represents the amount of variation for each parameter based on the range of each parameter value in literature. This is calculated by ${c_p}^* - c_{p_0}$. Thus $\frac{\partial T}{\partial c_p}\Delta c_p$ can be solved as $T^* - T_0$using an appropriate range for each parameter. Appendix C.2 provides the table of values used and calculated to determine an overall sensitivity variation of 0.2373.

3.4 Sensitivity Analysis:

Biological parameters inherently exhibit tremendous variability dependent upon factors such as source and methods of measurement. Even among published results, variability exists in reported parameter values. To understand the effect and significance of this variability on the results of the model, a sensitivity analysis was performed to monitor the responsiveness of the model to a 5% deviation to each parameter. Overall findings displayed in Figure 5 suggest the minor variations for physical parameters found in literature would not significantly alter the outcome of the model.

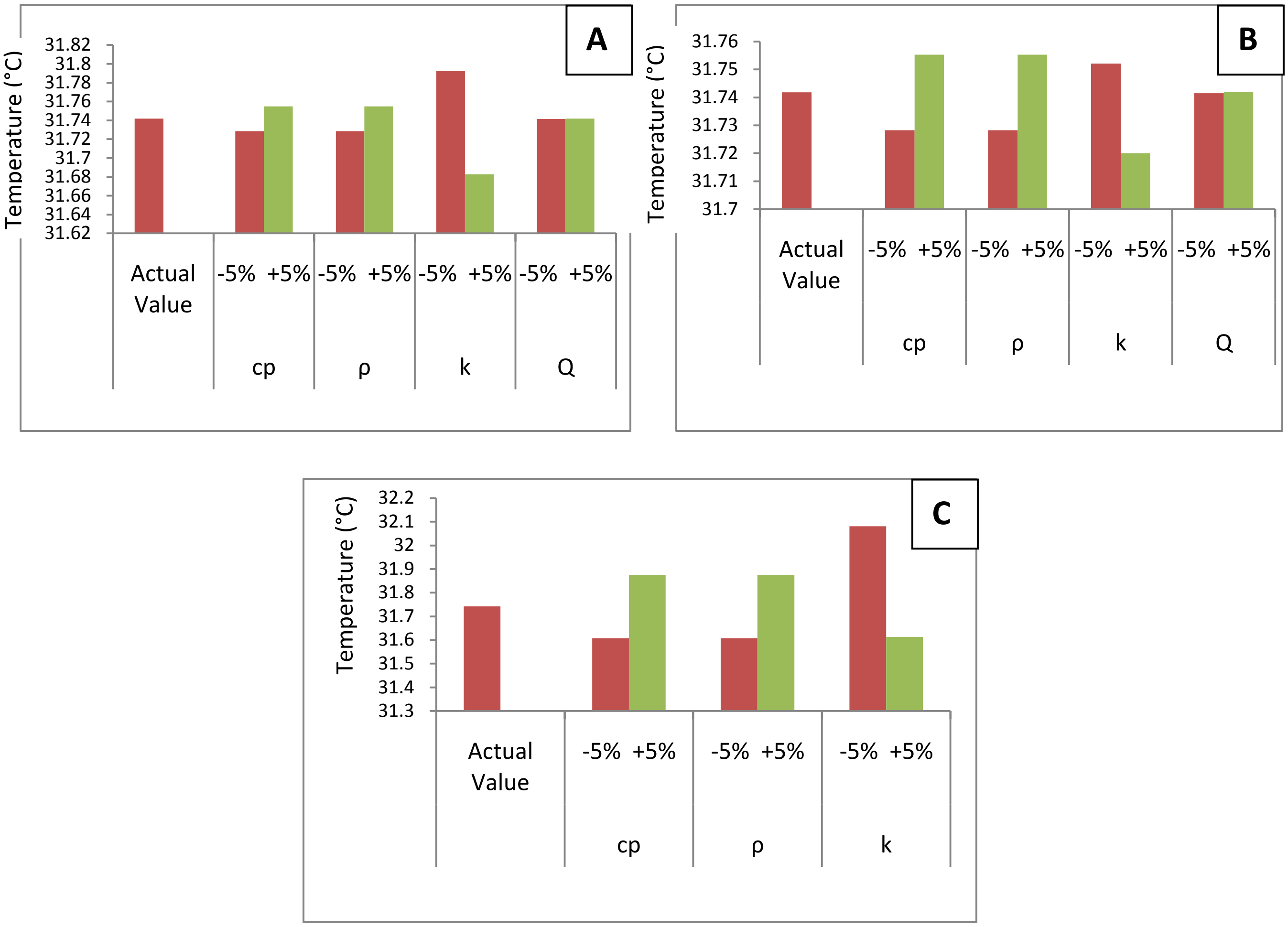


Figure 5. Sensitivity Analysis for Parameter by Layer. Plots indicate actual value of temperature found using original parameters and then the temperatures obtained by varying each parameter independently by ± 5%. Each plot represents the calculation by layer in the brain: A-Scalp B- Bone C-Brain.

The graphs above show relative insensitivity of the temperature change based on these parameters, as even the most sensitive parameter, heat conductivity, k, varied by 5% only changes the temperature approximately 0.2 °C in the brain which appears to be the region most sensitive to these changes. This finding is promising since differences in genetic makeup that occur from patient to patient will result in slight differences in individual parameters. Additionally, these physiological parameters likely vary with temperature even though our model assumes they remain constant. If a change in one parameter was found to cause dramatic differences in the final brain temperature, the use of this model would not produce accurate temperature representations of individual cases.

4. Conclusion and Design Recommendations

4.1 Conclusion

Visualizing the overall temperature change throughout the system helps to understand exactly how heat transfers through each region. It reveals where the temperature is changing most and presents the overall profile of heat transfer through the system, ultimately yielding an understanding of the property effects of the included layers of scalp, bone, and brain. Furthermore, comparing the initial temperature distribution with the final profile helps to verify the actual effect due to the cooling cap. In Figure 6, two model experimental designs are included, with coolant fluid at T= -8°C and T= 2°C, to reveal how influential this parameter is in determining final temperatures. Importantly, this reveals that within an hour, the use of the colder coolant sufficiently cools the brain but leaves the scalp at dangerous temperatures. It appears as though the slightly warmer coolant temperature may not sufficiently reduce brain temperatures within the hour. However, further analysis reveals that this coolant temperature is still therapeutically effective at two hours.

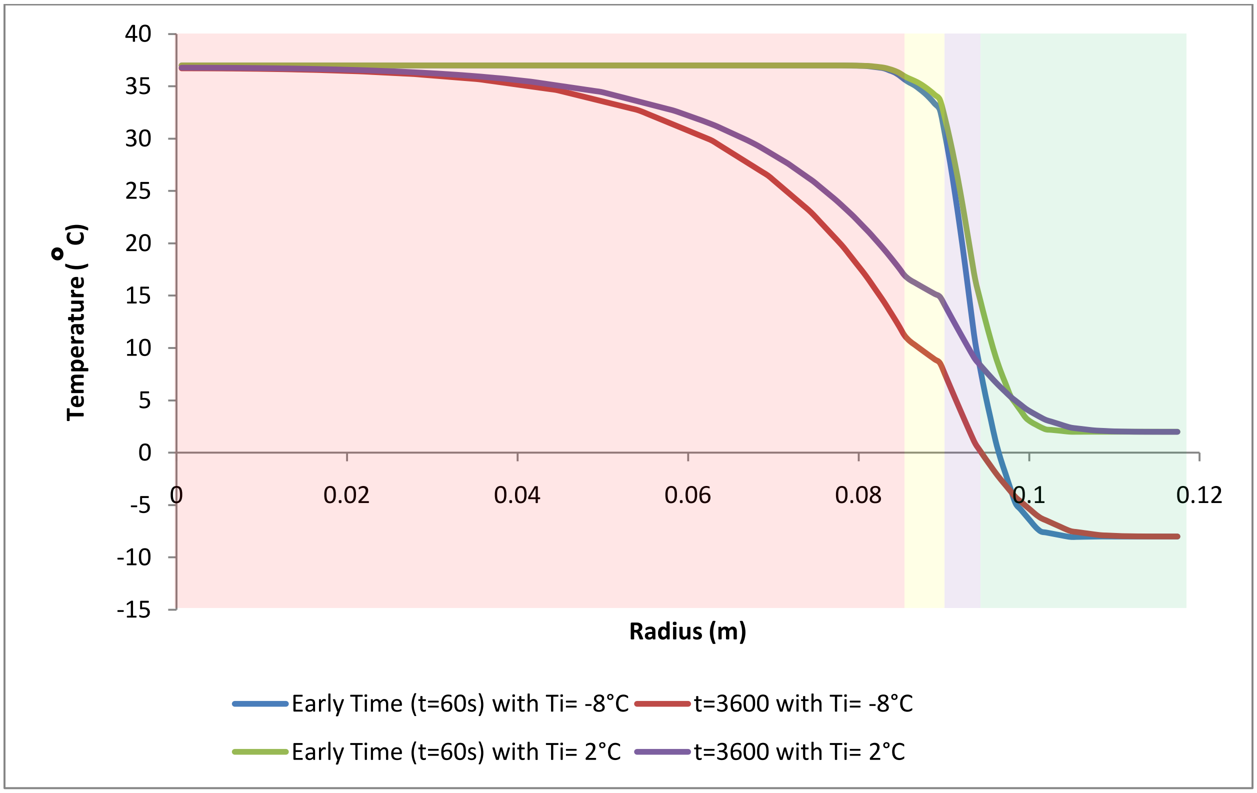


Figure 6. **Temperature Profile Through Brain and Cap.** This profile demonstrates the temperature change across the entire brain within an hour. Region I for the Brain, Region II is the cranial bone, Region III is the scalp, and Region IV represents the cap.

Monitoring the temperature throughout the system clearly identifies how each layer affects the heat transfer. Although the delay in immediate temperature reduction seen above in

Figure 4 suggests the scalp and skull layers provide insulation, Figure 6 explicitly reveals that the scalp is the layer provided the most insulation, as seen by the smaller slope in temperature over this region. The skull layer actually presents a very dramatic temperature change, suggesting this layer helps increase the heat transfer from the cap to the brain. Additionally, Figure 6 reveals the importance of coolant temperature and leads to the design recommendations explained below that a warmer coolant temperature than initially used, 2°C rather than the first attempted -8°C coolant, should be used to optimize the negative and positive effects.

4.2 Design Recommendations

For clinical use: the cap should be applied for two hours with a coolant temperature of 2°C

The design goals state that the desired brain temperature must be between 32 and 34°C. In addition to this, the skin temperature must not drop below 5°C, otherwise significant tissue damage may occur.

Keeping these two temperature goals in mind, an initial coolant fluid temperature of -8°C was used, based on a modeling experiment by Janssen et al (Janssen 2005, 4065). With this coolant temperature, as shown by the triangular points in Figure 7, the target brain temperature is achieved, but the scalp temperature is far too low. This would result in significant tissue damage. The coolant temperature was then increased in increments of 5 degrees in order to determine a temperature that satisfies the cooling requirements. A coolant temperature of 2°C, denoted by the solid lines, was selected as the optimal temperature. After one hour of wearing the cap at this temperature, the brain and scalp temperatures reach 32.82°C and 6.64°C, respectively, both of which sufficiently satisfy the cooling requirements.

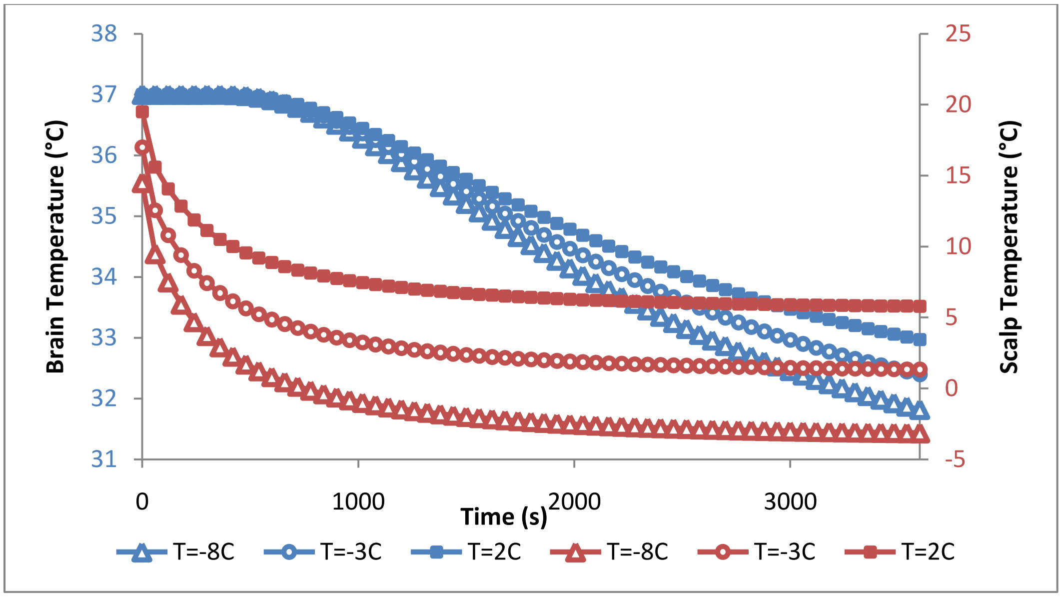


Figure 7. Effect of Varying Coolant Temperature. Brain temperatures were measured in the internal brain, Point 1, over 1 hour. Scalp temperatures were measured at Point 2. The coolant temperature was varied in increments of 5° from -8°C to 2°C.

Figure 7 shows that after one hour, the scalp temperature essentially levels off, but the brain temperature appears to continue decreasing. Therefore, increasing the time the patient undergoes cap therapy has the potential to even further reduce brain temperature while still maintaining a safe scalp tissue temperature. The maximum therapeutic time for a cooling cap is three hours (Neimark et al. 2008, 333). The effect of increasing the treatment time to three hours was then investigated.

As shown in Appendix C.3, after approximately 2 hours, the temperature begins to level off. The temperatures at each location after 2 and 2.5 hours were compared, as seen in Appendix C.4, and in all cases resulted in a temperature decrease less than 0.1°C. Therefore, it can be concluded that a coolant temperature of 2°C and a treatment time of 2 hours would result in optimal therapeutic effects.

Further, simple optimization calculations were performed with a computed objective piece-wise function to demonstrate the optimum time for balancing the positive effects of cooling the brain below 34°C with the negative effects of freezing scalp and tissue layer below 5°C. Below is the objective function used:

$$J = \sum_{i} F_b(T_i) + \sum_{i} F_s(T_j)$$

where $F_b(T) = \begin{cases} (T - 307)^2 & T > 307 \\ 0 & T \leq 307 \end{cases}$ represents the nodes of the brain needing to be lowered in temperature and

$F_s(T) = \begin{cases} 0 & T > 278 \\ 278 - T & T \leq 278 \end{cases}$ represents the nodes of the skin which need to remain unfrozen.

Results, represented graphically in Appendix C.5, reinforced the above findings that using a coolant temperature of -8°C causes tremendous damage to the scalp tissue that sits just below the cap even within an hour treatment. During times when the tissue is not terribly frozen, the brain has not reached low enough temperatures and thus would be therapeutically inefficient. Promising though, the use of coolant at 2°C never causes the skin to go below 5°C within three hours of treatment. Additionally, the brain successfully cools 3°C in just 2520 seconds as demonstrated by the minimum of 0 for the objective function at this time. We still choose to keep cooling the brain for nearly two hours as described above to guarantee the brain is maintained at this colder temperature long enough to harness the beneficial cooling effects.

4.3 Realistic Constraints

As previously mentioned, biological systems naturally contain unavoidable variability that may pose a health risk in extreme cases. A sensitivity analysis was performed on each parameter in efforts to reveal these potential hazards. The results suggest the brain temperature is not overly sensitive to minor variations in biological parameters, thus reducing concern for the potential safety threat. However, Figure 4 shows the tremendous variability that exists from model to model. While our model presents a more simplified approach which may partially explain the temperature difference, even the complicated published models exhibit differences in their final temperatures. Although the variability in individual parameters did not have a significant effect on the final brain temperatures, the presence of this model variability raises concern as just a few degree deviation from expected temperatures may result in tissue injury. Applying this model in a clinical setting requires caution and should be used only as a guide for estimating the temperature changes. Constant monitoring of patient brain temperature must be performed during treatment to ensure safety.

Additionally, the model contains an outlet but does not consider the fate of the fluid once it exits the cap. This poses a manufacturing constraint as to how to handle the effluent. Ideally, the used coolant would be restored to its initial temperature and recycled back to the inlet, creating a closed system. This may require additional equipment to remove the added heat and to actively pump the fluid back into the system. These modifications may increase costs and equipment size which may reduce portability and consequently overall availability to patients.

5. Additional Applications

The initial intention of this model was to determine times and temperatures significant to ischemia treatment. Cooling caps have additional clinical applications such as the prevention of alopecia, or hair loss, in chemotherapy patients, and the use of COMSOL makes it almost effortless to adjust our model for such an application. Alopecia has been shown to be temperature dependent, and its prevention requires a scalp temperature below 22°C before, during, and after the administration of cytotoxic drugs (Gregory 1982, 1674). This temperature-dependent interaction is due to vasoconstriction, which occurs at low temperatures. Vasoconstriction reduces blood flow and consequently decreases the amount of available cytotoxic drugs that the hair cells can uptake, eliminating the occurrence of alopecia (Janssen et al. 2005, 4065). A commercially made cooling cap, the Penguin Cold Cap system™, is often used in this application, and remains on the head for a total of 2 hours and 10 minutes in clinical treatments (Peck 2000, 246). With our model at a coolant temperature of 2°C, it can be seen in Figure 8 that in 5 minutes or less, the entire scalp is below 22°C. Furthermore, the scalp temperature remains below the required alopecia-preventing temperature during the entire treatment. This application demonstrates the versatility of the model to predict temperature changes in various heat transport simulations.

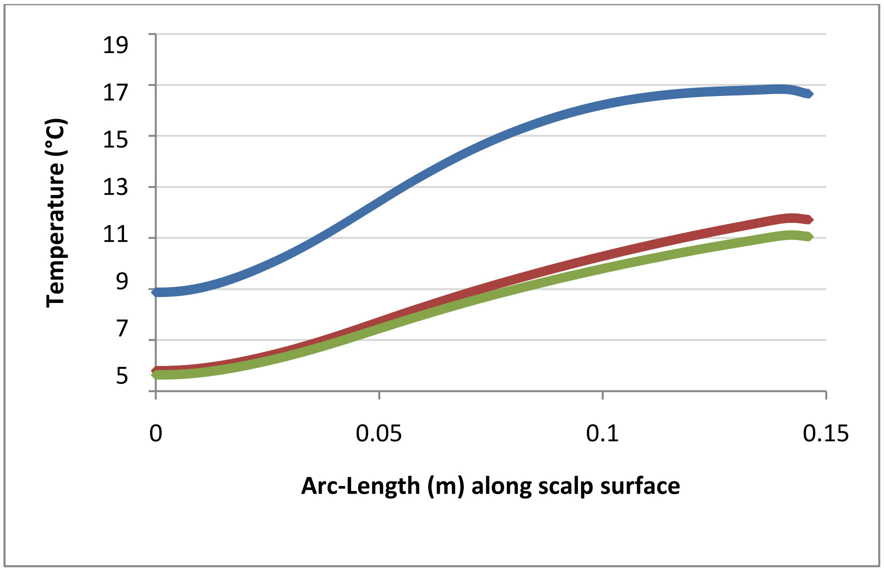


Figure 8. Surface Temperature of Scalp. Scalp temperature cools almost immediately to a clinically effective temperature for alopecia prevention. The therapeutic temperature is maintained along the entire scalp for the duration of treatment.

6. Appendix A: Mathematical Statement of the Problem

6.1 Governing Equations, Boundary Conditions and Initial Conditions

1. **Cap to scalp:**

   The cap region incorporates two physics due to the flowing coolant in the cap. For the time period we are concerned with, steady-state Navier-Stokes for fluid flow in addition to transient conductive and convective heat transfer into the scalp must be solved. Navier-Stokes must be solved first to provide a velocity, in r- and z- direction to incorporate into the heat transfer equation.

   Conservation of energy with convection: $\frac{k}{\rho c_p}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)+\frac{\partial^2 T}{\partial z^2}\right)=\frac{\partial T}{\partial t}+v_r\frac{\partial T}{\partial r}+\frac{v_z \partial T}{\partial z}$

   Boundary Conditions:

   - **Inlet-** at the top of the cap, the inlet is defined as constant temperature of the flowing fluid. T= -8°C
   - **Outlet-** the bottom edge of the cap serves as an outlet for the flowing fluid and therefore in COMSOL is defined as a Convective Flux which will be defined by solving the heat flux equation using the material properties and velocity profile of the cap region.

   Initial Conditions: $T(t=0)=T_{cap}=-8°\text{C}$

   Navier-Stokes: $\rho\left(\frac{\partial v_r}{\partial t}+v_r\frac{\partial v_r}{\partial r}\right)=-\frac{\partial P}{\partial r}+\mu\left[\frac{\partial}{\partial r}\left(\frac{1}{r}\frac{\partial}{\partial r}(r v_r)\right)+\frac{\partial^2 v_r}{\partial z^2}\right]$

   Boundary Conditions:

   - **Inlet-** at the top of the cap, must define the velocity profile modeled for flow through a tube with v_{max}=0.03 m/sec
     - $v = -75r^2 + 0.03$
   - **Outlet-** the bottom edge of the cap serves as the outlet for the coolant fluid and is defined as atmospheric pressure.
     - $P_{z=0} = 0\ atm$

   Initial Conditions:

   Throughout the cap, zero initial velocities or pressure values are included

2. **Scalp to bone:**

   G.E.: $\frac{k}{\rho c_p}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)+\frac{\partial^2 T}{\partial z^2}\right)+\frac{Q}{\rho c_p}=\frac{\partial T}{\partial t}$

   Left B.C.: $-k\frac{dT}{dr}=0$ due to axial symmetry

   Bottom B.C.: $-k\frac{dT}{dr}=0$ due to use of assumption that this is insulated

   I.C.: $T(t=0)=37\ °\text{C}$

3. **Bone to brain:**
   G.E.: $\frac{k}{\rho c_p}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)+\frac{\partial^2 T}{\partial z^2}\right)+\frac{Q}{\rho c_p}=\frac{\partial T}{\partial t}$
   Left B.C.: $-k\frac{dT}{dr}=0$ due to axial symmetry
   Bottom B.C.: $-k\frac{dT}{dr}=0$ due to use of assumption that this is insulated
   I.C.: $T(t=0)=37\ ℃$

4. **Within brain matter:**
   G.E.: $\frac{k}{\rho c_p}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial T}{\partial r}\right)+\frac{\partial^2 T}{\partial z^2}\right)+\frac{Q}{\rho c_p}=\frac{\partial T}{\partial t}$
   Left B.C.: $-k\frac{dT}{dr}=0$ due to axial symmetry
   Bottom B.C.: $-k\frac{dT}{dr}=0$ due to use of assumption that this is insulated
   I.C.: $T(t=0)=37\ ℃$

Variable	**Property**	**SI units**
T	Temperature	K
K	Heat Conductivity	W/mK
P	Density	kg/m^3
c$_p$	Specific Heat Capacity	J/kg K
H	Convective Heat Transfer Coefficient	W/m^2 K
V$_r$	Radial Velocity	m/s
Q	Heat Generation	W/m^3

Table 1: Variable Definitions and Units.

6.2 Input Parameters

Parameter	**Domain**			
	BRAIN/BLOOD	**SKULL**	**SCALP**	**CAP**
k (W/m K)	0.5	1.16	0.34	0.5
ρ (kg/m^3)	1050	1500	1000	1000
c$_p$ (J/kg K)	3700	2300	4000	4300
Q (W/m^3)	10,437	368.3	363.4	0
T$_{initial}$ (K)	310	310	310	265
μ$_{coolant}$ (Pa·s)	NA	NA	NA	1.61x10^{-2}
ρ$_{coolant}$ (kg/m^3)	NA	NA	NA	1113.2

Table 2. Input Parameters. Cap values are based on properties of Anti-freeze and information provided in literature (Janssen et al. 2005, 4065). All other parameters used in the head model were supplied by literature (Zhu & Diao 2001, 681).

7. Appendix B: Solution Strategy

7.1 Solver, Time Stepping, and Tolerance

The algebraic equations were solved using the Direct (UMFPACK) solver, meaning that for each matrix of equations for the Navier-Stokes and Conduction and Convection Heat Transfer the matrices were inverted by directly modifying the equations and substituting them into each other to ultimately obtain values for temperature, pressure and u and v velocities at each node. Thus, algebraic equations were solved together rather than iteratively testing values and measuring their convergence.

Both physics required transient calculations as the objective is to understand temperature change within one hour and then within a still therapeutically appropriate three hour range. Therefore, time step calculations were done for both transient equations at each node. The BDF method was used, storing the values at specified times of every 60 seconds up to 3600s (one hour). However, calculations were done using a maximum time step of one and an initial time step much smaller at 0.001 since in the very beginning when a lot of changes are occurring it is important to solve many more times to improve accuracy and reduce error. A large time step during periods of dramatic change will overlook a lot of the minute temperature changes that may especially occur at the boundary layer of the flowing fluid and therefore disregard even small heat transfer across the layers.

Relative and absolute tolerances of 0.001 were used. This relatively small tolerance is important since we are solving for temperatures which are expected to only change a few degrees. So each time step needs to achieve temperatures in a very small range to actually prove a significant change, not just one due to error. The mesh convergence above for temperature in the convective sub-domain demonstrates the very small temperature changes that occur but still need to be addressed. The fluid is dramatically colder than the natural tissue so the boundary layer for velocity and temperature profiles is very important in this region. The low tolerance is critical for reducing iterative error and showing temperature changes are actually due to the treatment and principles we are considering.

7.2 Mesh

The mesh used for model calculations included free meshed triangular elements with smaller units on the boundaries. At the boundaries are where temperature change is most dramatic due to conduction and convection as properties change, especially in the cap where convective flow occurs so that there is a boundary layer. Thus it is important to include many nodes in this region. Additionally, it is important to make sure all the mesh remains fine even in the middle of the brain since there is high heat generation in the internal regions of the brain that will cause temperature changes and need to be considered in very closely. Figure 10 shows the final mesh of 10958 elements. Mesh used for the solution calculation with 10958 elements:

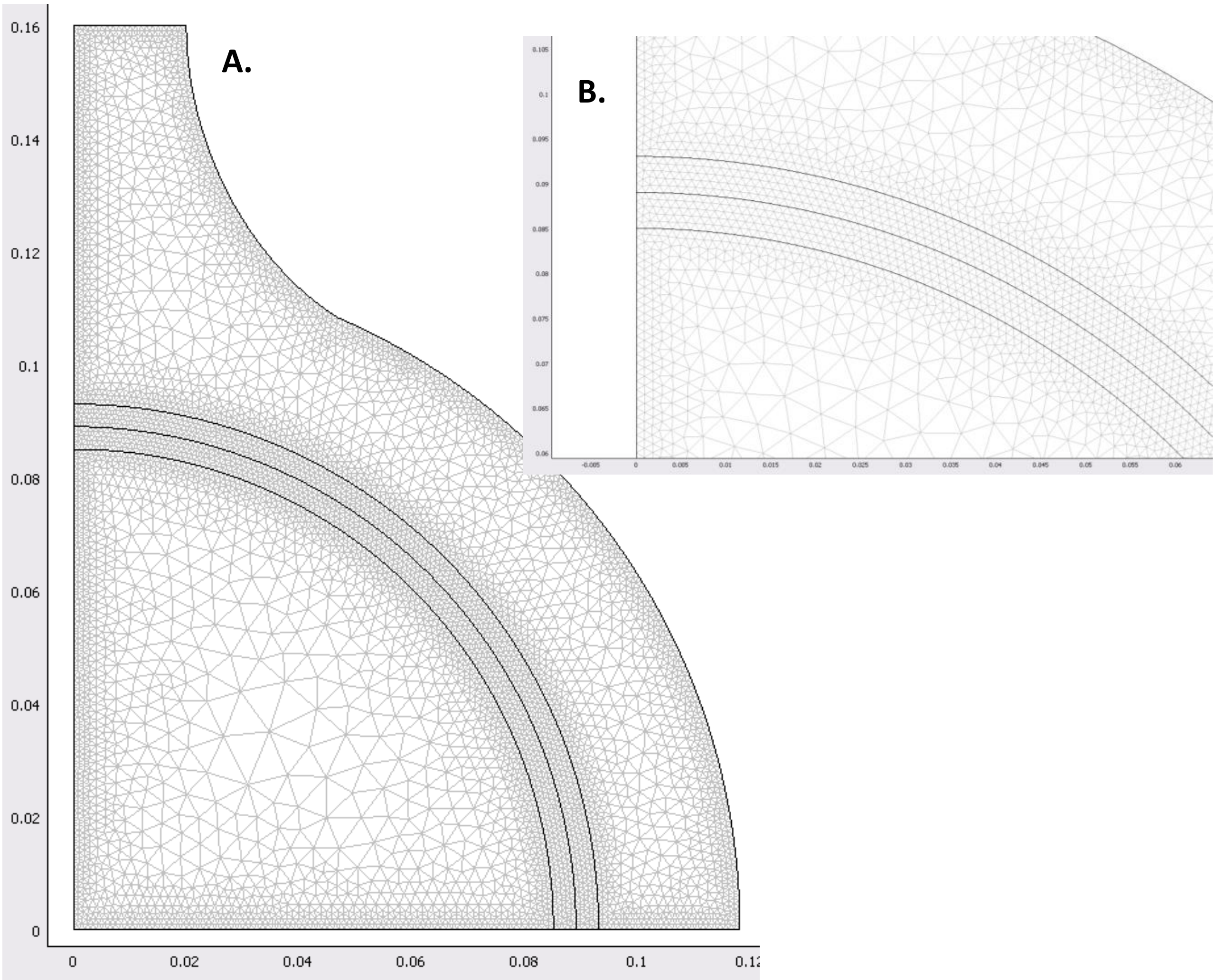


Figure 9: Complete Mesh. A- Final mesh includes 10958 elements, with high concentrations at boundaries- regions of high large temperature changes. B- A magnified image of the mesh at the boundaries to reveal fine elements where heat transport changes most.

7.3 Mesh Convergence

In order to verify the independence of the solution from the mesh, mesh convergence analysis was performed by calculating the temperature at the point (0.08, 0.02), a point with potential high changes due to the changing between layers and therefore diffusive and heat generation properties, for several mesh sizes. The overall mesh design remained the same but was mode finer to show the effect on the temperature by solving the equations at even more points. Showing relatively little change in temperature even as the number of elements increases as seen in Figure 10A suggests the solved temperature is appropriate for the model and parameters used. The solution is not simply a function of the number of points used to solve but an overall solution.

Since we are concerned with making sure the brain temperature at the specific point of stroke occurrence is reduced by at least three degrees, we performed the convergence for specific temperature. While naturally the average brain temperature needs to be reduced to induce hypothermia to the brain and protect the patient just following a stroke, this is not the most important. Thus, we took point temperatures.

The temperatures converge fairly quickly, after 5000 elements. Therefore our mesh of 10958 elements is appropriate to include enough points to attain an accurate answer without performing too many excessive calculations.

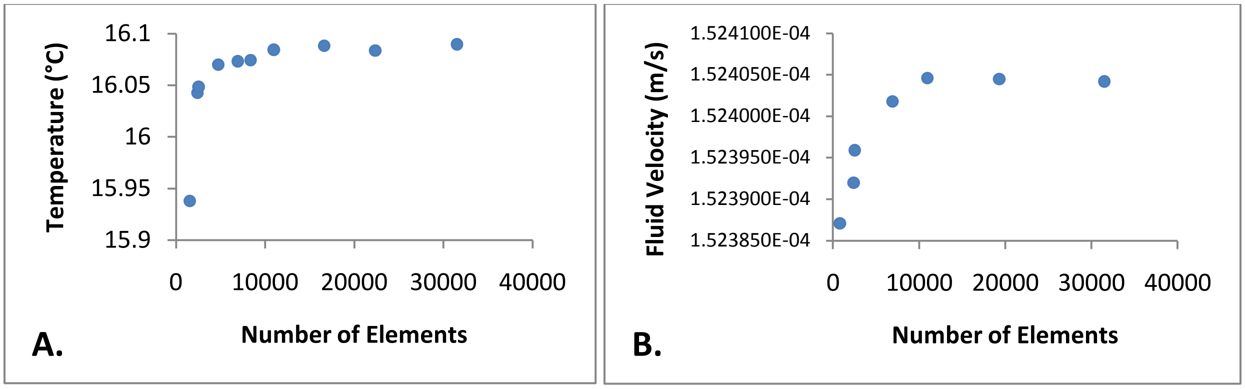
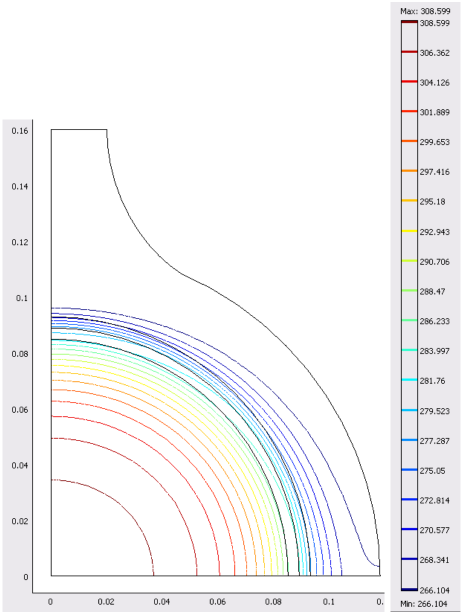


Figure 10: Mesh Convergence. A-Mesh convergence based on temperature at (0.08m, 0.02m). B-Mesh convergence for the fluid velocity measured at point near outlet.

Including fluid flow convection requires careful consideration of boundary layers since over a very short distance fluid may go from 0 m/s to 0.03 m/s. The use of large elements in this region will cause significant error. Therefore, mesh convergence also needs to be completed within the cap to assure that the velocities converge and do not produce an unexpected profile that would not properly model convective heat form from this region. Although Figure 2B visually shows an appropriate velocity profile, quantitative calculations showing velocity is not dependent on the mesh further supports the model's validity. Figure 10B reveals that at 10958 elements, the fluid velocity in the cooling cap converges, suggesting the mesh used is also appropriate for these parameters as well. These values were obtained at a point near the outflow and near the scalp boundary where there is the greatest variation in velocity.

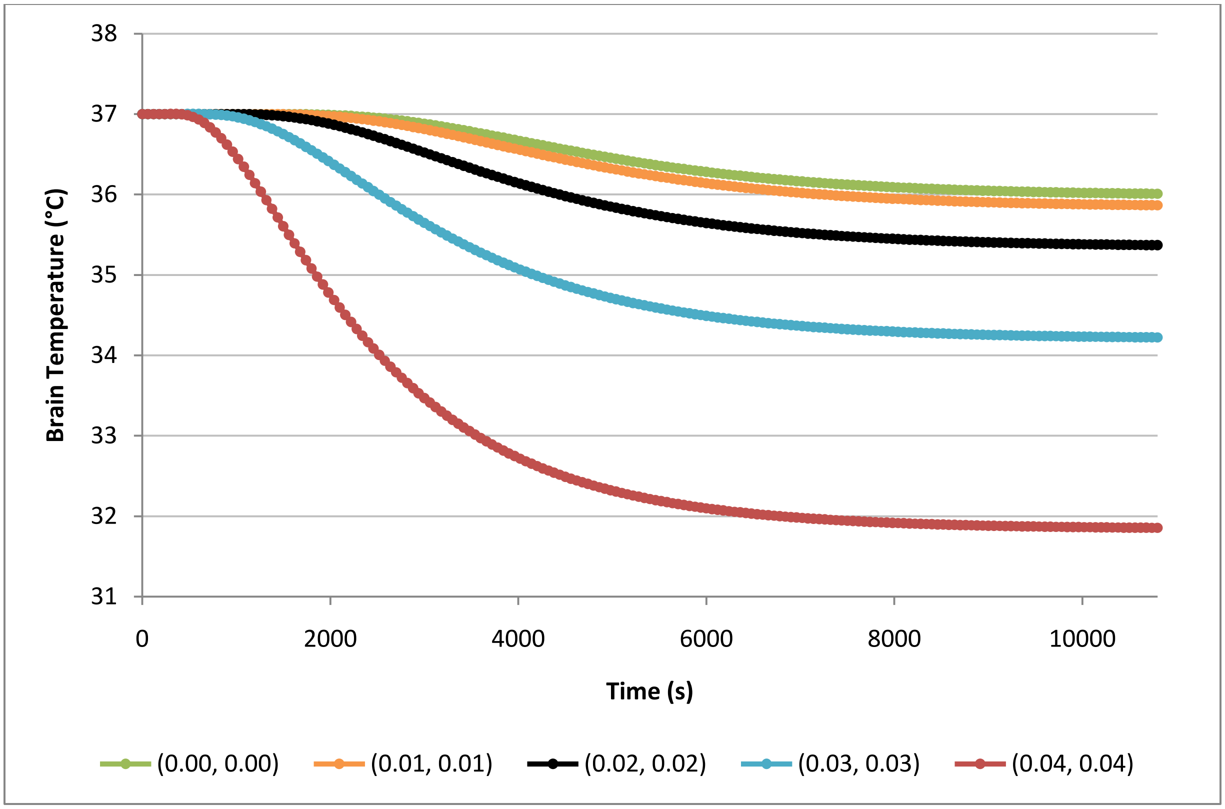
8. Appendix C: Additional Visuals



Appendix C.1. Contour plot of temperature after t=3600s. This plot shows more closely how the temperature is actually changing in each layer based on the convection in the cap and diffusion in each layer based on the different properties and heat generation.

Parameter		**Janssen (2005)**	**Zhu (2001)**	**Konstas (2006)**	**Temp** $_{\text{low}}$	**Temp** $_{\text{high}}$	**dT**
Specific heat (W kg^{-1}K^{-1})	*scalp*	3570	4000	4000	31.7137	31.7418	0.028072
	bone	1700	2300	2300	31.6720	31.7418	0.069734
	brain	3800	3700	3700	31.7418	31.8141	0.072346
Mass density (kg m^{-3})	*scalp*	1130	1000	1000	31.7418	31.7761	0.034359
	bone	1500	1500	1520	31.7418	31.7454	0.003603
	brain	1000	1050	1030	31.6147	31.7418	0.127033
Thermal conductivity (W mK^{-1})	*scalp*	0.384	0.34	0.342	31.7418	31.6132	0.128572
	bone	1	1.16	1.16	31.7926	31.7418	0.050831
	brain	0.5	0.5	0.49	31.8365	31.7418	0.094728
Metabolic heat gen. (Wm^{-3})	*scalp*	500	363.4	363.4	31.7418	31.7430	0.001251
	bone	130	368.3	368.3	31.7389	31.7418	0.002836

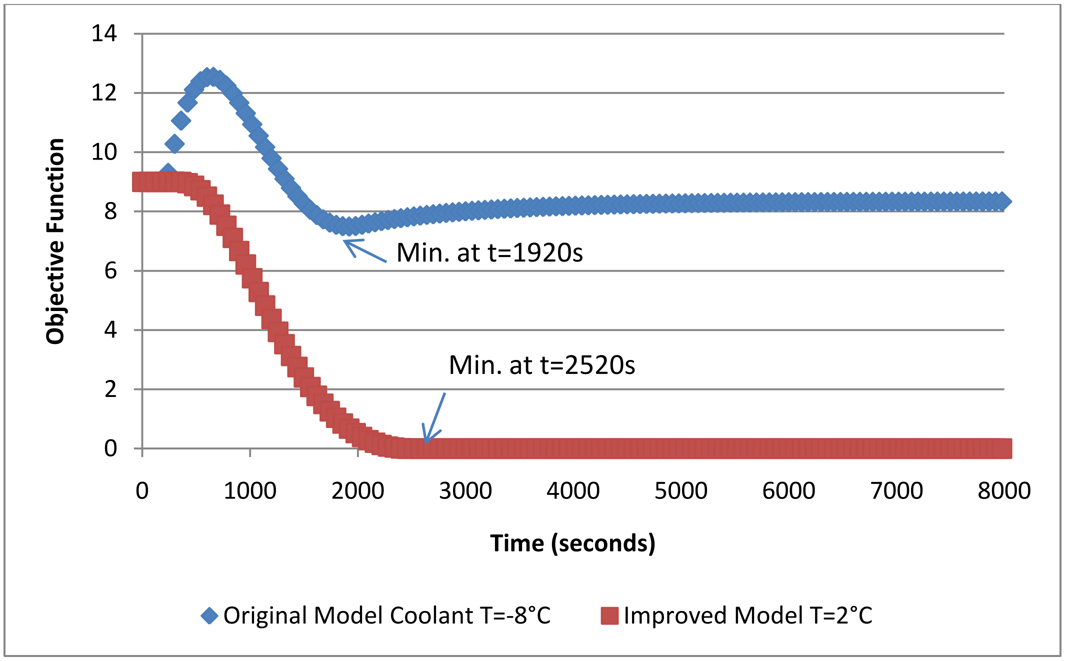
Appendix C.2. Sensitivity Analysis Parameter Variations. Included are values from several literature sources, used to define the variability of the individual parameters (for example dc_p). The temperatures at the lowest and highest values of each parameter were calculated. The resulting difference between these temperature extents yielded the dT for each individual parameter, which was used in the overall sensitivity calculation.



Appendix C.3. Effect of Time and Distance on Brain Temperature. The temperature at different distances from the center of the brain was examined over the course of three hours.

Location (m)	**Temperature (°C)**		
	At 2 hours	*At 2.5 hours*	*Difference*
(0.00, 0.00)	36.1456	36.0458	0.09979
(0.01, 0.01)	36.0028	35.9032	0.09958
(0.02, 0.02)	35.5032	35.4052	0.09805
(0.03, 0.03)	34.3477	34.2549	0.09285
(0.04, 0.04)	31.9638	31.8821	0.08179

Appendix C.4. Brain Temperature at Various Locations for Optimizing Treatment Length. The difference between temperature after 2 hours and 2.5 hours was calculated and found to be insignificant, suggesting that 2.5 hour treatments would not provide a significant advantage over a 2 hour treatment.



Appendix C.5. Objective Function Optimization. The objective function detailed in section 4.2 weights the importance of cooling the brain below 34 °C with the negative effects of reducing the scalp temperature below 3 °C. Squaring the brain temperature function was necessary to adjust for the necessity of lowering the brain below 34 °C to have any therapeutic effects. There would be no reason to use this therapy if it lowered the brain temperature but not enough to induce the necessary hypothermia. Additionally, exposing the scalp to sub-optimal temperatures for a short time may be tolerable if the brain achieves the necessary cooling. These functions therefore weight for the priority of reducing brain temperature over protecting the scalp tissue.

From the graph, one can see the initial model used with coolant temperature of -8°C reaches its optimal condition, the minimum of the objective function, after just 1920 seconds, but even this minimum has a relatively high value, suggesting traumatic damage to the scalp. A coolant temperature of 2°C provides more beneficial results. Within an hour, after just 2520 seconds, this graph achieves it minimum suggesting the brain is at or below the necessary 34°C while the scalp maintains a safe temperature. For optimum treatments, we still suggest applying the cap for two hours since this will provide somewhat of a “safety zone” to consider the patient-to-patient variability this model inherently possesses. No negative effects occur with sustained application, for example the scalp still does not freeze after two hours of application, and the additional time can only provide greater guarantee that effective hypothermic conditions reach the stroke region.

9. Appendix D: References

1. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. 1991 Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 337: 1521–1526.
2. Feigin VL. 2005. Stroke epidemiology in the developing world. *Lancet* 365: 2160–2161.
3. Straus SE, Majumdar SR, McAlister FA. 2002. New evidence for stroke prevention: scientific review. *JAMA* 288: 1388–1395.
4. Neimark, MA et al. 2008. Brain cooling maintenance with cooling cap following induction with intracarotid cold saline infusion: A quantitative model. *Journal of Theoretical Biology* 253: 333-344.
5. Janssen, FEM, Van Leeuwen, GMJ, Van Steenhoven, AA. 2005. Modeling of temperature and perfusion during scalp cooling. *Physics in Medicine and Biology* 50: 4065-4073.
6. Zhu, L, Diao, C. 2001. Theoretical simulation of temperature distribution in the brain during mild hypothermia treatment for brain injury. *Medical and Biological Engineering & Computing* 39: 681-687.
7. Trübel, H et al. 2004. A novel approach for selective brain cooling: implications for hypercapnia and seizure activity. *Intensive Care Medicine* 30: 1829-1833.
8. Peck, H.J. 2000. Evaluating the efficacy of scalp cooling using the Penguin cold cap system to reduce alopecia in patients undergoing chemotherapy for breast cancer. *European Journal of Oncology Nursing* 4: 246-248.
9. Gregory, RP. 1982. Prevention of doxorubicin-induced alopecia by scalp hypothermia. *British Medical Journal* 284: 1674.