Modeling Heat Transfer of Intradiscal Electrothermal Catheter Therapy for Low Back Pain

BEE 4530

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1. Executive Summary

Lower back pain is a pervasive problem, affecting more than 31 million Americans at any given time. Current treatments for disc pain include standard physical therapy, and, if the pain is more severe, intradiscal electrothermal therapy. This therapy involves the threading of an electrothermal catheter through the intervertebral disc between the annulus fibrosus (outer disc) and the nucleus pulposus (inner disc). The catheter is heated, causing contraction of collagen fibers in the annulus and destruction of pain receptors in the nucleus. The temperatures required for each of these pain relieving mechanisms are 45°C and 60°C respectively. Avoiding heat damage to spinal nerve tissue is also an important consideration. Damage occurs at a temperature of 43°C. Though this therapy has been shown to be effective for most, some patients do not experience any pain relief due to insufficient heating. Our project focused on creating a computer model of electrothermal catheter therapy in order to optimize treatment conditions.

We created a 3D model in COMSOL representing an intervertebral disc and catheter. Our model showed a similar temperature distribution to experimental measurements made by the Department of Orthopaedic Surgery at Boston Medical School, demonstrating validity of our computational model. Our results showed appropriate temperature profiles for effective therapy after 16.5 minutes (recommended treatment time). Temperatures of 60°C, believed to be sufficient to cause contraction of collagen fibers can be reached up to 4 mm away from the catheter in the nucleus, and 2 mm away from the catheter in the annulus. The results were analyzed to optimize treatment time.

The sensitivity analysis showed that geometry was the most important factor for temperature distribution. Because of this we believe that optimization should be based on an individual’s disc geometry. Models like ours lead to a better understanding of heat distribution and its relationship to pain relief. This understanding and the ability to model based on individual disc geometry can allow for optimization of intradiscal electrothermal therapy treatment time and ultimately lead to higher success rates in patients suffering from back pain.

2. Introduction:

The back is the very core of the human body. Since it is involved in many movements ranging from light to heavy exercises, the back is very vulnerable and has a high possibility of injury, leading to disc pain. Disc pain can result from a variety of reasons, including aging, gaining weight, weight lifting, and sitting improperly. A minor disc injury can be treated with continuous stretching, physical therapy, and icing/heating. However, a severe disc injury requires more serious therapies.

One of the main treatments for disc injury is intradiscal electrothermal therapy, a minimally invasive procedure for managing chronic discogenic low back pain [1]. This therapy does not require a significant incision or extensive surgery, but rather involves only the small injection of an electrothermal catheter into the intervertebral disc. The catheter is heated in order relieve pain in the disc by causing contraction of collagen fibers and destruction of afferent nociceptors. After
undergoing intradiscal electrothermal therapy, most patients reach maximal improvement within three months. An average of 71% of patients experienced significant pain relief after the procedure [1]. Our project aims to improve this success rate by better understanding the mechanisms of pain relief, spinal damage, and heat distribution within the disc.

It is important to understand the specifics of the procedure in order to model it correctly. During the procedure, the electrothermal catheter is inserted using a 17-guage introducer needle. It is threaded between the nucleus pulposus (inner disc) and annulus fibrosus (outer disc) and sits on the posterior end of the intervertebral disc (see Figure 1-2). The position of catheter is very important and its placement is monitored by using fluoroscopy. During a standard procedure, the heating begins at about 65°C and is increased gradually 1°C every 30 seconds to achieve a final temperature of 80-90°C [1]. The process is conducted while the patient is conscious in order to check pain response.

Our project involves a computational model of this procedure which we created using COMSOL. The goals for our model involved causing contraction of collagen fibers in the annulus (outer disc) by heating the annulus tissue to 45°C (pain relieving mechanism 1) [2] and destroying pain receptors in the nucleus (inner disc) by heating the nucleus to 60 °C (pain relieving mechanism 2) [2]. Another important guideline was prevent damage to the spinal nerve root by maintaining a temperature below 43°C, which is the temperature that can cause tissue damage [2]. By successfully creating a model of intradiscal electrothermal therapy, we hoped to show that the procedure could be prototyped and optimized in order to increase the success rate, and subsequently increase the number of patients who experience significant pain relief.

3. Goals/Design Objectives:
   - The goal is to cause contraction of collagen fibers in the annulus of the intervertebral disc by heating the annulus tissue to 45°C (pain relieving mechanism 1) [2].
   - Destroy pain receptors in the nucleus of the intervertebral disc by heating the nucleus to 60 °C (pain relieving mechanism 2) [2].
   - Make sure the healthy tissue near the spinal cord is not damaged, which means the temperature of this tissue must stay at 43°C or below [2].

a. Geometry/Schematic:

We modeled the heat transfer of this process in three dimensions through different materials in the disc by applying the appropriate governing heat transfer equation for 3D Cartesian geometry using COMSOL. The materials include the nucleus and annulus of intervertebral disc, and the surrounding muscle tissue, which are heated by a catheter. We modeled the catheter as a 5 separate cylinders, which add up to a total length of 5 cm, which is the standard length of the heated catheter [3]. Average intervertebral disc diameter values for the nucleus (inner disc) and annulus (outer disc) were used to create our model and can be found in Table A1 and Figure 1 below.
Figure 1: **Model Geometry:** The dimensions of our computational model are shown above. The catheter (red) has a diameter of 0.9652 mm and is placed between the nucleus (inner portion) and the annulus (outer portion) of the disc. The catheter is composed of 5 small cylinders to approximate the curvature of the catheter. The disc is surrounded by muscle tissue (not pictured above).

*Schematic:*  
The following schematic was used in order to compute the temperature profile in the intervertebral disc.

Figure 2: **3D Schematic** Computational domain of interest is the disc and surrounding tissue. Catheter is located in the center (z = 6.5mm). Boundary conditions include heat flux (h=500 W/(m$^2$°C)) on all edges of the muscle tissue, and continuity for all edges of the intervertebral disc. The temperature profile of the catheter is also defined in the schematic above.
The type of catheter we modeled (SpineCATH by Smith & Nephew) can operate via multiple settings, the standard setting involves setting the maximum temperature. SpineCATH operates by adjusting the heat flux based on thermocouple reading of the catheter temperature. The computer algorithm adjusts this temperature to follow with fairly high accuracy the temperature function given in our schematic. The standard temperature profile involves heating the catheter linearly from 65°C to 90 °C for 12.5 minutes, holding the temperature steady at 90 °C from 12.5 to 16.5 minutes. The value for the diameter of the catheter was 0.9652 mm, which is the exact dimensions of the standard spineCATH [4].

The surrounding muscle tissue simulates the body tissue that surrounds the intervertebral disc, psoas and paraspinal musculature. Our outer boundary condition models convective heat flux from a surrounding circulating saline bath, which matched the conditions in a study that we used to check the accuracy of our results. This saline bath is maintained at 37°C to simulate body temperature [3].

4. Results and Discussion

a. Solution:

We obtained a solution over $t=16.5$ minutes for temperature variation throughout the intervertebral disc. The temperature profile at the final time can be seen in Figure 3 below.

![Temperature Profile](image)
Figure 3: Surface Plots of Temperature Distribution in Model after 16.5 min. (a) x-y plane (slice through z-axis) (b) slice through x-axis: These plots contain a visual representation of the temperature distribution within the various tissues surrounding the catheter.

It is clear from Figure 3a that the temperature decreases as the distance from the catheter increases, with more concentrated heat in the areas where the catheter is curving in. Figure 3b shows that the heat travels out radially from the catheter, with the heat being more concentrated near the surface of the catheter.

Temperatures of 60°C, believed to be sufficient to cause contraction of collagen fibers (pain relieving mechanism 1) [2] can be reached up to 4 mm away from the catheter in the nucleus, and 2 mm away from the catheter in the annulus. Destruction of pain receptors is believed to occur at 45°C [2]. It is clear from the temperature profile over time in Figure 3 above that the muscle tissue stays below 45°C at all times.

In order to better quantify the temperature distributions within the model, we graphed a single point in the annulus of the disc, nucleus of the disc, and the muscle tissue. This allowed us to see if each portion was being heated to an appropriate temperature (see Figure 4).
Figure 4: Temperature vs Time at 3 Points: The graph shows the temperature profile over 16.5 minutes at a point in the annulus and nucleus both 5 mm from the catheter, as well as a point in the muscle tissue 9 mm from the catheter. Temperatures reach up to 57.9°C in the nucleus, 53.10°C in the annulus, and 43.84°C in the muscle tissue.

This temperature distribution data gives us some insight into the process of Electrothermal Catheter Therapy and how the pain relieving mechanisms are achieved. Before this model can be used to optimize therapy conditions, it is important to check the accuracy of the model compared to experimental results.

b. Accuracy Check:

In order to check the accuracy of our model, we compared the final temperature of our model with data obtained from a study using 14 cadavers at 37°C by the Department of Orthopaedic Surgery at Boston Medical Center. This study used the spineCATH at standard protocol, as well as meat to simulate surrounding tissue, and a circulating saline bath at 37°C to simulate spinal fluid [3]. We matched our model’s catheter size, placement, and temperature profile exactly with the properties of the catheter used in the study, as well as added the surrounding muscle tissue and circulating bath. We also ensured that our run time was the same as treatment time in the study, 16.5 minutes. We checked the final temperature of our model after 16.5 minutes every millimeter up to 7-10 mm away from the catheter in either direction (in the nucleus or in the annulus).
Figure 5: Accuracy Check in the Annulus and Nucleus: Distance from catheter vs temperature of our model’s calculated temperature and mean experimental temperature. Vertical deviation bars represent the confidence interval [3].

The temperatures observed were close to the temperatures from the experiment conducted in the literature. Most observed temperatures fell within 0-5 °C of the experimental value, except for the temperatures 1 mm away from the catheter. We hypothesize that this discrepancy is due to pocket created by the introducer needle or slight tissue injury around the catheter path (also due to the introducer needle). This additional thermal resistance could explain the lower temperatures in the experimental model compared to our computer model. Our sensitivity analysis (below) does not show significant effects of varying the nucleus thermal diffusivity properties on the temperature distribution in the annulus and the nucleus. This does not support our hypothesis, but does also not necessarily refute it. In order to investigate this phenomenon fully, an injury region around the catheter would have to be modeled and implemented and various material properties would have to be tried to see if this tissue injury hypothesis is plausible.

Another potential cause of this discrepancy could be that the actual catheter is continuous, while our catheter consists of five discontinuous catheters. This difference could cause errors in regions close to the catheter. Higher temperature in our model could be explained by the increased surface area on ends of the catheter pieces.

C. Sensitivity Analysis:

Our sensitivity analysis focused on varying the material properties and geometry to see how the results were affected. It was most important to perform sensitivity analysis for our muscle tissue value of thermal diffusivity because this value was approximated and not available in the literature. We varied this value by 20% based on variation of other muscle values found in the literature. We also varied the thermal diffusivity of the nucleus and the annulus by 20%, though there is more data on these values in the literature and they don’t vary that widely. Then we
plotted the temperature at points of interest in the nucleus tissue (5 mm from catheter), annulus tissue (5 mm from catheter), and muscle tissue (9 mm from catheter) to determine how changing these diffusivity values affected the results. Our sensitivity analysis was based on range due to lack of statistical data on exact distribution of thermal diffusivities. Varying only one parameter at a time gives us less information than varying multiple parameters would, but we can still draw conclusions about the effect of varying each parameter on the solution. Sensitivity of the disc size was done for +/- 10%, 15%, and 20% of the original dimensions. In order to compare the results before and after variation, we calculated the percent difference over the total temperature change:

\[
% \text{ Difference} = 100\% \times \frac{T_{\text{new}} - T_{\text{original}}}{T_{\text{original}} - T_{\text{initial}}}, \text{ where } T_{\text{initial}} = 37\text{C}
\]

The resulting % differences can be seen in Figures 6-7 below.

Figure 6: Variation of thermal diffusivity in the nucleus, annulus, and muscle tissue, \( t=16.5 \text{ min} \). Temperature is taken at 5 mm from catheter for annulus and nucleus, and 9 mm from catheter in the muscle tissue. Baseline material property values can be found in Table A2. All thermal diffusivity values are varied +20% and -20% and the corresponding % difference in the results is shown for each situation.
Figure 7: Variation of geometry in the nucleus, annulus, and muscle tissue, t=990s. Temperature is taken at 5 mm from catheter for annulus and nucleus, and 9 mm from catheter in the muscle tissue. The disc (and muscle tissue) size was changed to +/- 10%, 15%, and 20% of the original dimensions. Baseline values for the normal size of the disc can be found in Table A1, and corresponding % difference in the results is shown for each situation.

Based on our sensitivity analysis we determined that variation among the material properties does not significantly impact the results. Temperature results do not vary more than 14% (2°C) in any tissue at the final time (16.5 minutes). This means that our model should be reliable regardless of any natural variation in thermal diffusivity.

The sensitivity analysis of disc size had a more significant effect on the final temperature reading. Disc size proved to be the most significant determining factor in treatment time, with percent differences ranging from 1-22% increase or decrease in temperature. Because of the variation in disc size between people, personalized treatment could be used to optimize treatment time based on the individual’s size (and corresponding disc geometry).

d. Optimization

After the model was validated, we were able to focus on optimization. By varying parameters and observing the effects on the temperature distribution, the most effective treatment parameters can be determined. For example, geometry of the disc, orientation of the catheter, diameter of the catheter, or time could be optimized. We were interested in preserving the surrounding muscle tissue near the spinal cord (T < 43°C), destroying the pain receptors in the nucleus (T > 60°C), and contracting collagen fibers in the annulus (T > 45°C). Instead of implementing a simple optimization function in which the desired tissue destruction would be weighted positively, and the destruction of surrounding muscle tissue would be weighted negatively, we graphed the function independently to observe the desired tissue destruction over time. We then graphed the cumulative number of equivalent minutes of thermal injury. Between these two graphs we gained more insight into the procedure. This allows us to make informed recommendations for treatment.
time and the corresponding effects on each tissue.

In order to understand the effectiveness of the treatment, we began by implementing the following equation in COMSOL to represent the desired tissue destruction:

\[ F_{\text{nucleus}}(T) = \begin{cases} 
0 & T < 60 \\
(T - 60) & T \geq 60 
\end{cases} \]

\[ F_{\text{annulus}}(T) = \begin{cases} 
0 & T < 45 \\
(T - 45) & T \geq 45 
\end{cases} \]

Pain relief function (quantified destruction of pain receptors and contraction of collagen fibers):

\[ J = \sum_i F_n(T_i) + \sum_i F_a(T_i) \]

For the nucleus tissue, any part of the tissue that is over 60°C contributes to the value of the function because this destruction of pain receptors contributes to our goal of pain relief. Because higher temperatures are more effective at destroying these pain receptors, there is a higher pain relief function value for higher temperatures. For the annulus tissue, any part of the tissue that is over 45°C contributes to the value of the function because of the contraction of collagen fibers, which again contributes to our goal of pain relief. This function allowed us to observe the desired effects of treatment over time (see Figure 8).

![Figure 8: Pain Relief Function vs Treatment Time](image)

*Figure 8: Pain Relief Function vs Treatment Time: Quantification of the destruction of pain receptors and contraction of collagen fibers over a full treatment cycle. The graph is labeled at 13.45 minutes to note the decrease in slope (decrease in effectiveness of treatment).*
From the graph we gained a good understanding of the effectiveness of treatment over time. There is a clear plateau in the graph after 13.45 minutes, indicating a decrease in effectiveness over time after this point.

Our main concern in optimization was to avoid damage to the central nervous system. It was important to monitor the temperature distribution near the spine in order to ensure that no motor function impairment occurred. The cumulative number of equivalent minutes of thermal injury was modeled using the following equation:

\[ CEM_{43°C} = \int R^{(43−T)} \, dt \]

In this function, \( R \) is the ratio of the times that produce equal thermal injury when the temperature is increased by 1°C. \( R \) for the spinal nerve root is one-half [5]. The thermal damage threshold on the central nervous system for temperatures of 43°C is equal to 60 minutes [6]. After this point, irreversible motor damage is likely to occur. We implemented \( CEM_{43°C} \) as a diffusion species in COMSOL with a diffusion coefficient of 0 and a generation term equal to \( R^{(43−T)} \). The function was graphed at a point 9 mm from the catheter in order to determine the thermal damage at a point near the nerve root (see Figure 9).

![Figure 9: Equivalent Minutes at 43°C vs Treatment Time](image)

This measurement was taken at a point 9 mm from the catheter in order to determine the thermal damage at a point near the nerve root. Damage in the nerve root occurs after 23 minutes of treatment (60 equivalent minutes at 43°C).

From the graph of the function we observe temperatures sufficient for spinal nerve root damage (equivalent 60 minutes at 43°C) at a treatment time equal to 23 minutes. Since we observed a plateau in treatment effectiveness after 13.45 minutes and spinal damage occurring after 23 minutes, we can agree with the standard recommendations for the electrothermal catheter procedure (16.5 minute treatment time). This model gives us a time interval for most effective treatment and allows us to better understand the mechanisms of pain relief and of spinal damage.
Given this greater understanding of treatment mechanism, we can optimize the procedure for an individual using our computational model. This type of optimization can allow for less conservative treatments and more efficient treatment intervals. Our sensitivity analysis supports the idea that personalized treatment could be useful because of the large effect geometry has on the solution.

5. Conclusions and Design Recommendations

Our results show that the temperature profile within the disc is largely dependent on time. Change in temperature was greater at earlier times in all three tissues. Temperatures of 60°C, believed to be sufficient to cause contraction of collagen fibers (pain relieving mechanism 1) [2] can be reached up to 4 mm away from the catheter in the nucleus, and 2 mm away from the catheter in the annulus at the end of treatment time. Optimization for standard disc geometry showed a plateau in effectiveness of treatment after 13.45 minutes of treatment and showed harmful damage to spinal nerve tissue after 23 minutes.

The temperature distribution does not seem to depend much on thermal diffusivity of the tissues based on sensitivity analysis, yet change in size of the disc significantly affects the temperature distribution. Based on this conclusion, treatment time could be optimized based on individual disc geometry using a computational model such as the one we designed. This would require measuring geometry of a person’s intervertebral disc before treatment and plugging geometry the computational model. Being able to model the heat distribution throughout the disc before treatment would allow for optimization based on the individual. Though this would result in higher success rates, the cost of such technology may make it unfeasible.

a. Constraints

A constraint to our recommendation for personalized treatment based on disc size measurements would be cost and feasibility. It may be difficult to collect the exact dimensions needed for input in the model from a CT scan or MRI. Another very real constraint is cost; MRIs are very expensive and hospitals tend to only use them when it is completely necessary. However, in this case it may still be feasible to consider since most patients require a MRI to diagnose the need for Intradiscal Electrothermal Therapy.

b. Model Improvement Recommendations

We hypothesize that differences between experimental temperatures and our model’s temperatures near the catheter were due to tissue injury from catheter insertion. By further investigating the thermal resistance of this injury, we could try to implement this region into our model in order to gain a more precise temperature distribution. Another difference between the experimental model and our model is that our model uses a discontinuous catheter in five separate pieces, while the true model uses a continuous catheter. More surface area in the discontinuous catheter could contribute additional heat flux, thereby explaining the increase in temperatures close to the catheter. Since our sensitivity analysis showed a large impact of geometry on the solution, our last recommendation is to use a CT scan or MRI in order to implement geometry.
Appendix A: Mathematical Statement of the problem

a. Mathematics/Equations:

Cartesian 3-D governing equation ( transient, no generation):

\[
\frac{k}{\rho C_p} \left( \frac{d^2T}{dx^2} + \frac{d^2T}{dy^2} + \frac{d^2T}{dz^2} \right) = \frac{dT}{dt}
\]

There is a convective boundary condition \((h=500 \text{ W/(m}^2\text{°C)})\) at each edge of muscle tissue, and continuity boundary conditions for all edges of the intervertebral disc.

- \(T_{\text{disc, initial}} = 37^\circ\text{C}\)
- \(T_{\text{muscle tissue, initial}} = 37^\circ\text{C}\)
- \(T_{\text{catheter, initial}} = 65^\circ\text{C}\)
- \(T_{\text{catheter, final}} = 90^\circ\text{C}\)
- Equation for \(T_{\text{catheter}}\) (°C):

\[
T_{\text{catheter}}(t) = \begin{cases} 
65 + 0.333t & \text{t < 750} \\
90 & \text{t \geq 750}
\end{cases}
\]

The catheter temperature is set to vary linearly with time. It is being heated up from 65°C to 90°C for 750 seconds, and then is held steady at 90°C from 750 to 990 seconds (16.5 minutes). This temperature variation mimics true treatment conditions \([1]\). The catheter was modeled by creating five small cylinders to approximate the curvature of the catheter (see Figures 1-2).

b. Input Parameters:

Table A1: Values used for disc geometry \([2]\). We used researched values in order to find the most accurate values for both nucleus (inner disc) diameter, and annulus (outer disc) diameter.

<table>
<thead>
<tr>
<th>Property</th>
<th>Nucleus (Human)</th>
<th>Annulus (Human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Diameter (mm)</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>Minor Diameter (mm)</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Height (mm)</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Table A2: Material Properties \([2, 7]\): Material properties were gathered for the annulus and nucleus disc tissues as well as for standard muscle tissue.

<table>
<thead>
<tr>
<th>Property</th>
<th>Nucleus</th>
<th>Annulus</th>
<th>Muscle Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k \text{[kg*mm/(s}^3\text{*K)}])</td>
<td>1008</td>
<td>1472</td>
<td>642</td>
</tr>
<tr>
<td>(\rho \text{[kg/mm}^3\text{]})</td>
<td>1.12e-6</td>
<td>1.09e-6</td>
<td>1.05e-6</td>
</tr>
<tr>
<td>(C_p \text{[mm}^2/(s}^*\text{K)})</td>
<td>3e9</td>
<td>3e9</td>
<td>3.75e9</td>
</tr>
</tbody>
</table>
Initial disc temperature= 37 °C
Catheter temperature °C (varies) = \begin{cases} 65 + 0.3333t & \text{if } t < 750 \\ 90 & \text{if } t \geq 750 \end{cases}

Appendix B: Solution Strategy

a. Solver
We used the direct finite element method with the UMFPACK solver to solve our model in 3D geometry.

b. Time Stepping/Tolerance
Our problem was solved over 990 seconds, using a time step of 1 second. We noticed that using a time step of 0.1 seconds created a much longer solution time, but did not change the temperature profile. We used a relative tolerance of 0.01 and an absolute tolerance of 0.0010. These were the default values in COMSOL, and they worked well to solve our problem. Changing the tolerance values also did not change our temperature profile solution.

c. Mesh
Our mesh consists of 37093 elements. We used the free mesh parameters function in COMSOL to automatically calculate the mesh elements due to the complicated geometry.

Figure B1: Visual Representation of Mesh, slice through z-axis: Contains 37093 elements (“coarse” under free mesh parameters), pictured as a wire representation of mesh element size.
It is clear from the mesh representation above that areas of higher heat flux have more concentrated elements. The mesh elements around the catheter and in the curved areas are smaller so that the temperature profile in these areas can be calculated as precisely as possible.

Table B1: Mesh convergence by temperature for 4 different meshes. Temperature is calculated at two different places, one in the annulus and one in the nucleus, both 5mm from the catheter.

<table>
<thead>
<tr>
<th>Number of Elements</th>
<th>Annulus (5mm from catheter) (°C)</th>
<th>Nucleus (5mm from catheter) (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10718</td>
<td>53.452957</td>
<td>58.142597</td>
</tr>
<tr>
<td>26045</td>
<td>53.14002</td>
<td>57.91242</td>
</tr>
<tr>
<td>37093</td>
<td>53.104946</td>
<td>57.876392</td>
</tr>
<tr>
<td>75700</td>
<td>53.138798</td>
<td>57.851315</td>
</tr>
</tbody>
</table>

Figure B2: Mesh Convergence for Temperature: Temperature vs number of elements for points in both the annulus and nucleus, both 5mm from the catheter. The graph converges at the number of elements we used, 50695.

We plotted number of elements vs the final temperature (t=990 s) at two points, one in the annulus, and one in the nucleus, both 5 mm from the catheter. Since these are important points to consider for destroying pain receptors, we used the mesh convergence to make sure the final temperature was not varying due to the mesh size. After 37000 elements, the temperature converged, so we used the “coarse” option under free mesh parameters (37093 elements).
Appendix C:

References
