# A Computer Model for Evaluating the Efficiency of Cryosurgery for Prostate Cancer

BEE 4530

Michael Horsfield, Ritvik Sarkar, Sam Reffsin, Woo Jin Seog

## Executive Summary

We model the effects of the cryosurgery process for prostate cancer in COMSOL Multiphysics® (ver 5.1) using imaging and manufacturing data to generate 3D realistic geometry for the prostate and cryoprobe. By imposing a freezing temperature at the probe-tumor boundary, we can observe the impact on healthy tissue over the freeze-thaw cycles of the surgery procedure.

By varying the number and locations of probes, as well as the rate of the freeze-thaw cycle, we find the optimum cryosurgery procedure that kills as much cancer as possible while minimizing damage to the remainder of the prostate.

We find that, for an "average" spherical tumor roughly 1 cm in radius found in the center of the prostate, a single probe piercing the tumor's center fully treats the cancerous tissue without harming healthy tissue more than 1 mm away from the tumor's edge. This assumes two freeze-thaw cycles at -196°C. This proves that the simulation methodology can predict the optimum surgery procedure. With proper imaging data, this same procedure can be used to treat individuals with differently-shaped and oriented prostate tumors.

## Problem Statement

Modern prostate cryosurgery practice requires the surgeon to visually monitor the treated region during operation to ensure the minimal loss of healthy tissue. There is no adequate model to predict cell death during this procedure.

## Introduction to Cryotherapy and Literature

Prostate cancer is one of the most common forms of cancer found in men. It is a slowly growing cancer that is usually diagnosed in men of age 65 or older [1]. Cryotherapy is a common treatment method used for men who are in the early stages of this cancer. During the procedure, argon gas is passed through the inserted hollow needles into the prostate [2]. Ice ball formation, which can be adjusted by changing the flow rate of argon, occurs at the tips of the needles to freeze and destroy as much of the tissue at the cancer site as possible. In order to prevent too much of the nearby tissue from being destroyed, the doctors actively monitor the prostate using ultrasound images during the procedure.

The needles are usually inserted into the middle of the prostate, the urinary sphincter, and the neurovascular bundles during the same procedure. The urinary sphincter thermocouple is kept at a temperature of 15°C or greater while those in the midgland and the neurovascular bundles reach temperatures of -40°C or lower. The neurovascular bundles are often destroyed by such

low temperatures leading to erectile dysfunction, one of cryotherapy's most common long term side effects [3].

Although the prostate is mainly affected after the procedure, healthy tissue surrounding the prostate can also be affected from this freezing technique. A side effect is that it can lead to long term urinary incontinence [4]. The freezing can lead to a risk of fistulas and can affect the bladder and intestines that lead to pain when needing to empty the bladder and bowels [4]. There have been models made to trace the heat transfer process that occurs between the probe and the tumor. According to the model created by researcher Baohong Yang, the model focused on the heat transfer between the probes and the prostate gland [5]. The actual geometries of the prostate gland were used in that model. However, it was seen in those models that the heat transfer went beyond the prostate gland. Because the researcher lacked a healthy tissue domain, it was not possible to see the damage that would be done to the surrounding tissue of the prostate.

Our project will improve on this model by not only showing the heat transfer occurring between the prostate and the probe, but also a domain considering the healthy tissue around the prostate, and modeling the damage that the tissues in this domain may face.

There is always a risk in developing such long term side effects after receiving the cryotherapy treatment. Mapping the heat transfer and how the temperature of the tissue around the probe changes is useful in reducing the chances of the cold temperatures damaging the healthy tissue while also making sure the tumor is being destroyed completely. When modeling, it will be noted that because of the low temperatures the needles during the procedure, the heat transfer that can occur around the prostate, not involving the probe, is negligible. With better mapping and localization of the tumor region, it may be possible to increase the treatment's effectiveness while decreasing its likelihood for complications.

## Model Formulation

### Design Objectives and Goals

Our goal is to experiment and then optimize the system in order to minimize healthy cell death and maximize tumor death.

Our project proposes to use a model to develop not only a heat map of a prostate and the surrounding organs in-vivo during one of these procedures, but also to model the spatial and temporal variations that may occur. Using the heat map, we will then determine the volume of healthy cells unintentionally killed during the cryosurgery procedure.

**Assumptions**

To begin formulating the model, we must make a few assumptions to focus our design goals and to simplify the problem. Model formulation methodology was based on work by Datta [6].

1. We will use an imaging database for an accurate 3D rendition of the prostate.
2. We will assume the tumor cells to be located deep inside of the prostate gland.
3. We will assume the tumor cells congregate to form a spherical tumor within the prostate.
4. We will assume that there is no heat transfer between the tissue and its surroundings a large distance away from the prostate.
5. We will assume the cryoprobes have a cylindrical shape and will begin freezing within the tumor itself.
6. We will assume that healthy tissue and tumor tissue have the same material properties.

With these assumptions we can design an initial model for investigation. It should be noted that these assumptions were chosen to simplify the problem significantly.

**Schematic of 3D Model**

Figure 1 shows our 3D model schematic and its relation to the cryosurgery process. Dimensions are estimated from available clinical data [7]. Realistic 3D models were built from public imaging data [8].

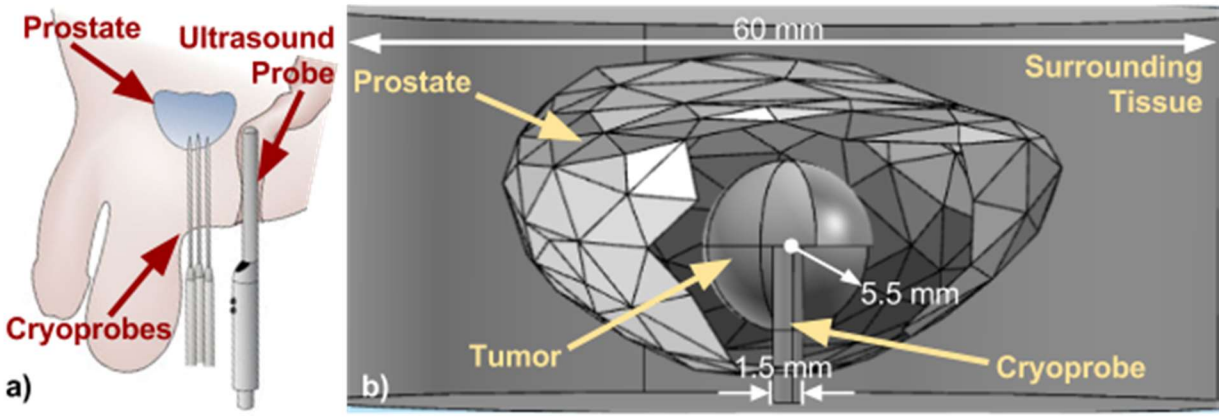


**Figure 1.** (a) A drawing of the prostate in the body and the insertion of cryoprobes [9]. The Ultrasound probe is used to observe the state of the prostate during surgery. (b) COMSOL generated schematic of the prostate gland, tumor, and inserted cryoprobe with realistic geometry.

A sphere was used to represent the tumor inside of the prostate. A cylinder was used as a simplified model to represent the cryoprobe. The larger cylinder surrounding the prostate represents healthy tissue which extends far enough to be unaffected by heat transfer in the tumor region.

**Governing Equation**

The following is the heat transfer equation including generation terms for metabolic heat and blood perfusion:

$$\rho C_p \frac{\partial T}{\partial t} = k\nabla^2 T + Q_{blood\ perfusion} + Q_{metabolism} \tag{1}$$

Both $Q_{blood\ perfusion}$ and $Q_{metabolism}$ are valid only at temperatures over freezing. Both terms can be decomposed as follows:

$$Q_{blood\ perfusion} = \begin{cases} \rho_{blood} C_{p,blood} \dot{V} \left(T_{body} - T\right); & T > 273 \\ 0 & T < 273 \end{cases} \tag{2}$$

$$Q_{metabolism} = \begin{cases} Q_{met}; & T > 273 \\ 0 & T < 273 \end{cases} \tag{3}$$

**Boundary Conditions**

To specify Equations 1-3, two spatial boundary conditions are required. It should be noted that our governing equation will be solved along the tumor/healthy tissue region.

Our first boundary condition will be at the probe-tumor interface. We will assume that the probe maintains a constant temperature of -196°C. This dictates that the boundary condition at the probe-tumor surface will be a constant temperature boundary condition of -196°C. This is a necessity in order to maintain the freezing temperatures surrounding the probe, allowing for greater ice ball formation.

The second boundary condition makes use of our assumption that the surrounding tissue domain extends far beyond the prostate gland. We can assume that there will be no heat transfer toward the outer surface of our domain. Hence, our assumption for this initial model justifies a zero flux boundary condition at the outer surface of the healthy tissue (Figure 2).

**Initial Conditions**

At the beginning of the simulation, all tissue (healthy and tumor) will be at normal body temperature (37°C, 310K).

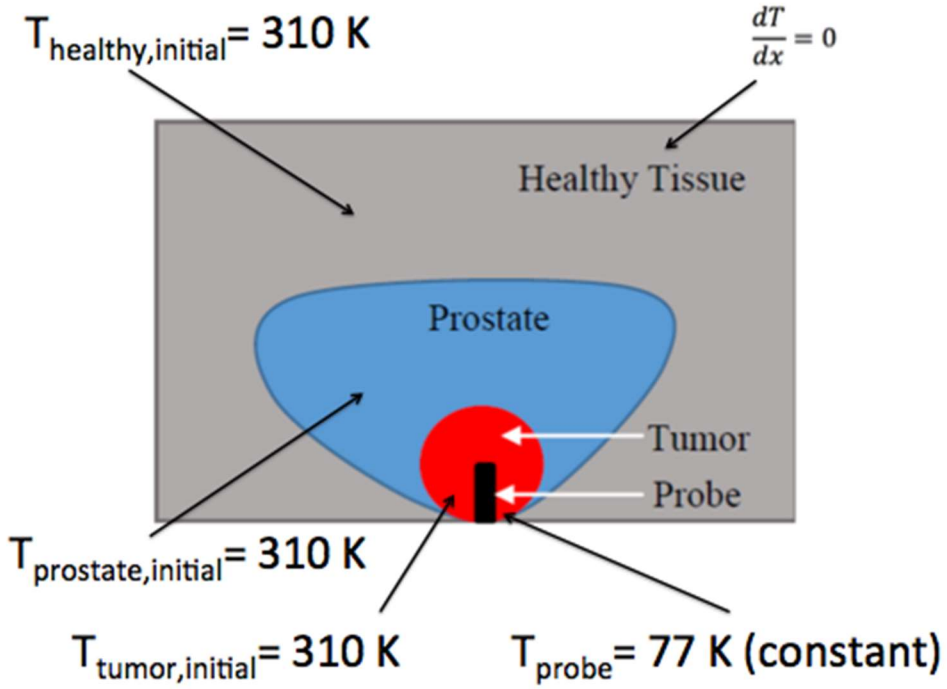


**Figure 2.** A 2D drawing of our model set-up. All body tissue starts at 310K (37 C). The probe maintains a temperature at 77K (-196 C).

**Properties**

Material property data was taken from a model formulation textbook [6].

**Table 1.** Summary of material properties [6].

| **Property** | **Value** |
|---|---|
| Tissue density, $\rho$ | 1500 kg/m$^3$ |
| Thermal conductivity, $k$ | Temperature dependent, see Table 2 |
| Specific heat, $C_p$ | Temperature dependent, see Table 3 |
| Blood density, $\rho_{blood}$ | 1060 kg/m$^3$ |
| Blood specific heat, $C_{p,blood}$ | Assumed to be the same as tissue specific heat |
| Blood perfusion rate, $\dot{V}$ | $0.5\times10^{-7}$ 1/s |
| Body temperature, $T_{body}$ | 310 K (37°C) |
| Metabolic heat generation, $Q_{met}$ | 1400 W/m$^3$ |

The thermal conductivity, $k$, and the specific heat, $C_p$, were computed using interpolation functions in COMSOL, as defined in Tables 2 and 3, to represent their temperature-dependence. The spike in $C_p$ at 263 K (-10°C) represents the latent heat of freezing.

**Table 2.** Temperature dependence of thermal conductivity. The dependency was calculated using an interpolation function between these values.

| Temperature, $T$ (K) | Thermal Conductivity, $k$ (W/m-K) |
|---|---|
| 18 | 0.627 |
| 250 | 0.627 |
| 273 | 0.209 |
| 333 | 0.209 |

**Table 3.** Temperature dependence of specific heat. The dependency was calculated using an interpolation function between these values.

| Temperature, $T$ (K) | Specific Heat, $C_p$ (J/kg-K) |
|---|---|
| 253 | 4180 |
| 263 | 10000 |
| 273 | 4180 |
| 333 | 4180 |

## Mesh

We used COMSOL's default meshing system for both the healthy tissue and tumor domains. To ensure mesh convergence, we plotted the average temperature over the tumor domain at t = 120s (2 min) against the number of mesh elements. Details of the mesh and resultant temperature can be seen in Figure 3.

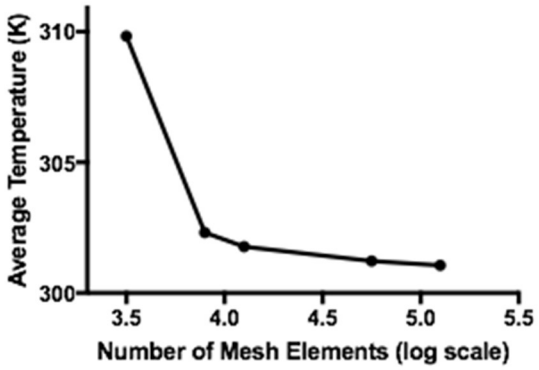


**Figure 3.** Mesh convergence of our 3D domain. The plot of temperature vs mesh resolution used to determine mesh convergence. The average tumor temperature stops changing significantly after 40,000 mesh elements.

Figure 3 shows that the average temperature steadies at about 40,000 elements. This means our mesh converges at the default "Finer" setup. However, we decided to continue with the Fine default instead. While it is possible to add more elements and get a more accurate mesh, the run-time of our model was not feasible at these greater element numbers. Due to external time constraints, the change in average temperature and marginal increase in accuracy is not worth the extra hours of computation time needed to resolve the Finer and Extra Fine meshes.

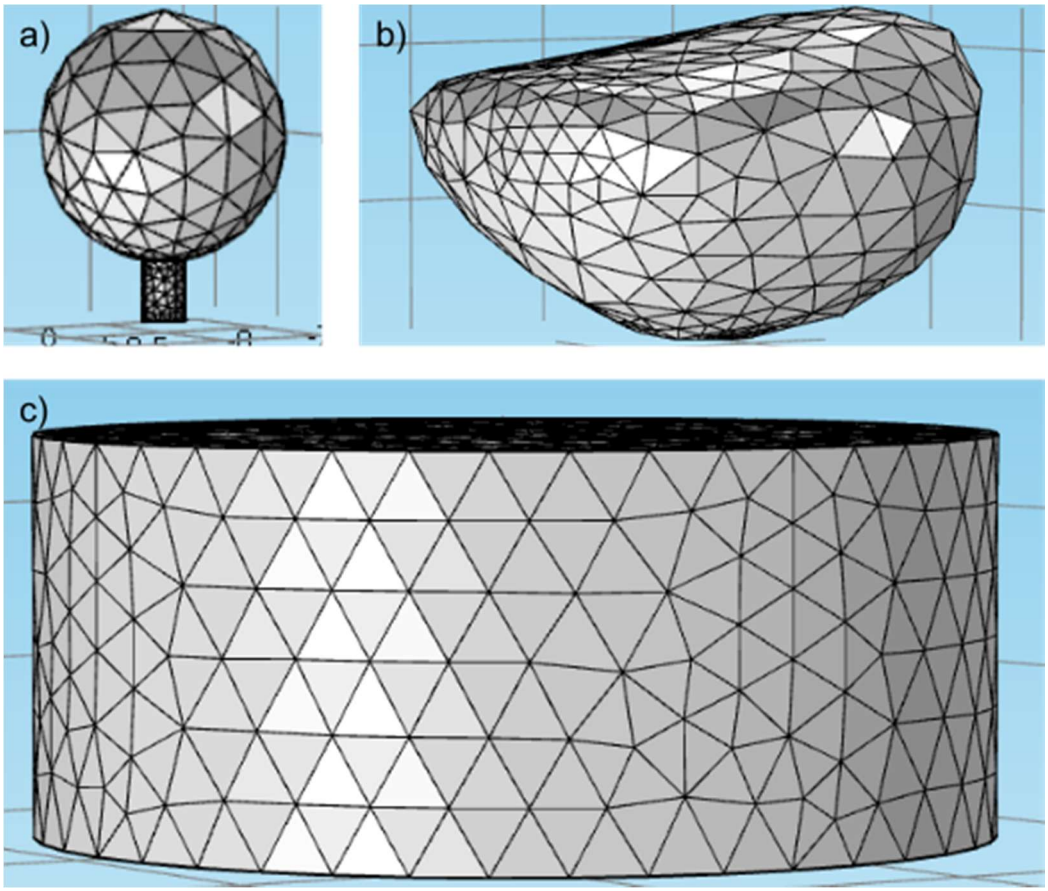


**Figure 4.** (a) 3D model of the spherical tumor under the Fine mesh. (b) 3D model of the prostate gland under the Fine mesh. (c) 3D model of the surrounding healthy tissue domain under the Fine mesh.

Figure 4 shows the results from the Fine mesh, where we believe the solution has converged. The temperature distribution at the probe is smooth.

**Sensitivity Analysis**

The specific heat, $k$, and thermal conductivity, $C_p$, were calculated using an interpolation (see Tables 2-3). To test the sensitivity of the model to these parameters, the parameters were varied by ±10% of the interpolation parameter values. These models were tested for sensitivity by analyzing the changes in the fraction of frozen tumor. It can be seen in Figure 5 that the frozen tumor tissue percentage vary by approximately 4% for each change in the specific heat and thermal conductivity. Therefore, because of this small change, the percentage of frozen tissue is not particularly sensitive to these parameters. More precise values are not needed for an accurate model.

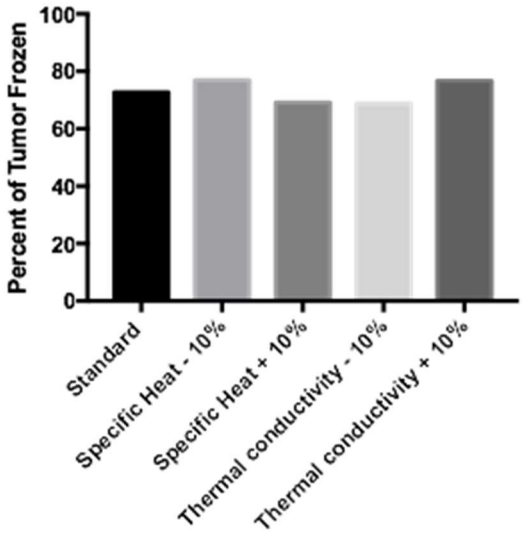


**Figure 5.** Sensitivity Analysis was computed for various parameters. Bar graph of percentage of frozen tissue for various combination of specific heat and thermal conductivity values.

## Results

### Exploring the Use of Multiple Probes

The goal in prostate cryosurgery is ultimately to maximize the amount of tumor tissue we destroy and minimize the amount of healthy prostate tissue destroy. In this section we explore the use of multiple probes in optimizing prostate cryosurgery. We begin by simulating cryosurgery with a single probe. The results from the single probe surgery are shown in Figure 6.

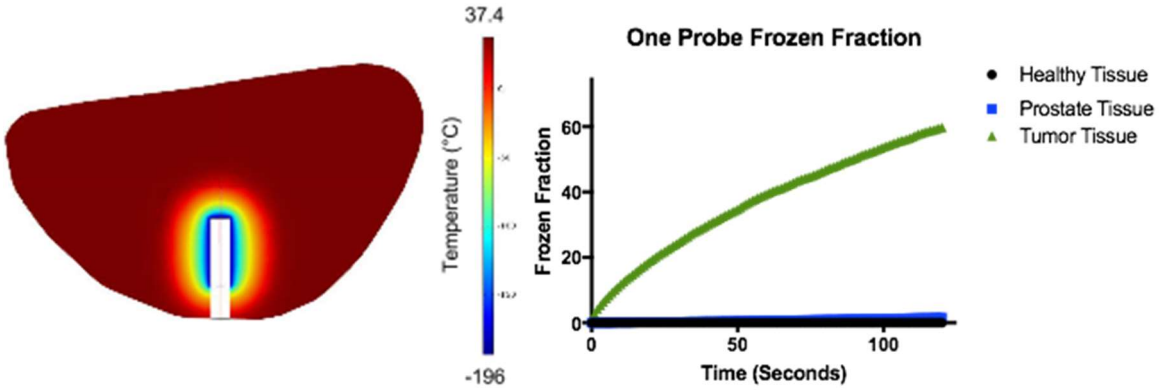


**Figure 6.** (Left) Temperature profile from one-probe surgery simulation. (Right) About 60% of the tumor and 2% of healthy prostate tissue is destroyed after 120s. The surrounding tissue remains unaffected.

The results from the single probe simulation show that only about 2% of the healthy prostate tissue is destroyed and that the surrounding tissue is unaffected. However, only 62% of the tumor tissue is destroyed. This will not suffice. If more than 10% of the tumor remains, the surgery was not successful. Ideally we would like all of the tumor to be destroyed. Based on our results, we

decided it would be necessary to explore the expected results of using numerous probes in cryosurgery (Figure 7).

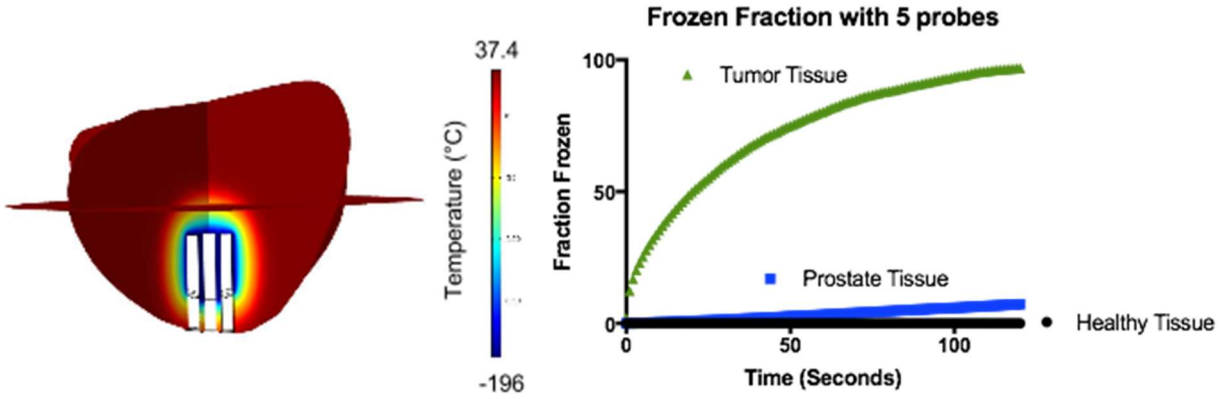


**Figure 7.** (Left) Temperature profile from five-probe surgery simulation. Five probes are inserted from the bottom in a regular cross-shape. (Right) Over 90% of the tumor is destroyed, but so is about 7% of healthy prostate tissue. The surrounding tissue remains unaffected.

While a large amount of the tumor mass is destroyed with five vertical probes inserted into the prostate, about 7% of healthy prostate tissue is also damaged. In order to try to minimize this healthy tissue death, we explore the use of even more probes for shorter freezing times in the hopes of getting the same amount of tumor frozen while sparing healthy tissue (Figure 8).

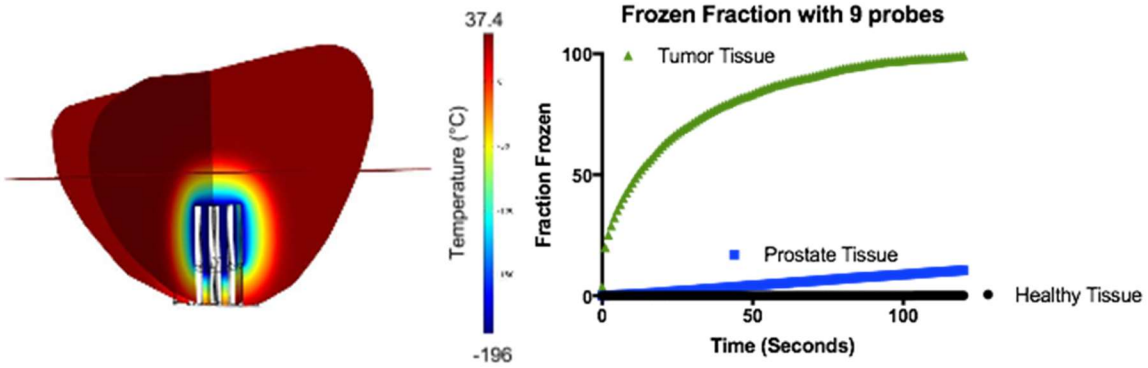


**Figure 8.** (Left) Temperature profile from nine-probe surgery simulation. Nine probes are inserted from the bottom in a regular 3-by-3 array. (Right) Nearly all of the tumor is destroyed, but so is about 12% of healthy prostate tissue. The surrounding tissue remains unaffected.

Nine probes results in nearly 100% of tumor tissue death, but it also leads to a large amount of healthy tissue being damaged. We can optimize the process in order to determine the maximum time to keep the probe in, limiting this healthy tissue death.

**Optimization Methodology**

We find our optimum probe setup with the objective function F.

$$F = \sum Healthy(T) + \sum Tumor(T) \tag{4}$$

$$Healthy(T) = \begin{cases} -1, & T \leq -40°C \\ 0, & -40°C < T < -10°C \\ 1, & T \geq -10°C \end{cases} \tag{5}$$

$$Tumor(T) = \begin{cases} 5, & T \leq -40°C \\ -5, & -40°C < T \end{cases} \tag{6}$$

$Healthy$ and $Tumor$ are functions of local temperature $T$. They assign positive or negative weights based on whether the temperature at a location is desired or not. In the tumor domain, apoptotic freezing temperatures are desired and the -40°C temperature is a common cut-off for irrecoverably inducing cell death [10]. In the healthy tissue region, reaching such temperatures is undesirable.

We will use weighted values to obtain the most efficient process. The weights represent the increased importance of eradicating the tumor relative to damaging healthy cells. In other words, it is better to damage healthy tissue if it means removing more of the tumor. For example, for every tumor cell that is killed, a weight of +5 will be assigned. For every healthy cell that is damaged by the probe (reversibly), we will assign a score of 0. For every healthy cell killed, we will assign a score of -5.

By maximizing $F$, we can find the best arrangement of cryoprobes.

**Optimization Results**

Here we apply our optimization methodology to our five-probe scenario. The five-probe scenario was chosen because the one-probe model doesn't freeze enough tumor tissue to justify a successful surgery and the nine-probe model doesn't significantly alter freezing of the tumor.

Our goal is to use this optimization function to determine the optimal amount of time the cryosurgery should be performed i.e. the time at which our defined optimization function is maximized. First, we allow the simulation to run for 120 seconds (Figure 9).

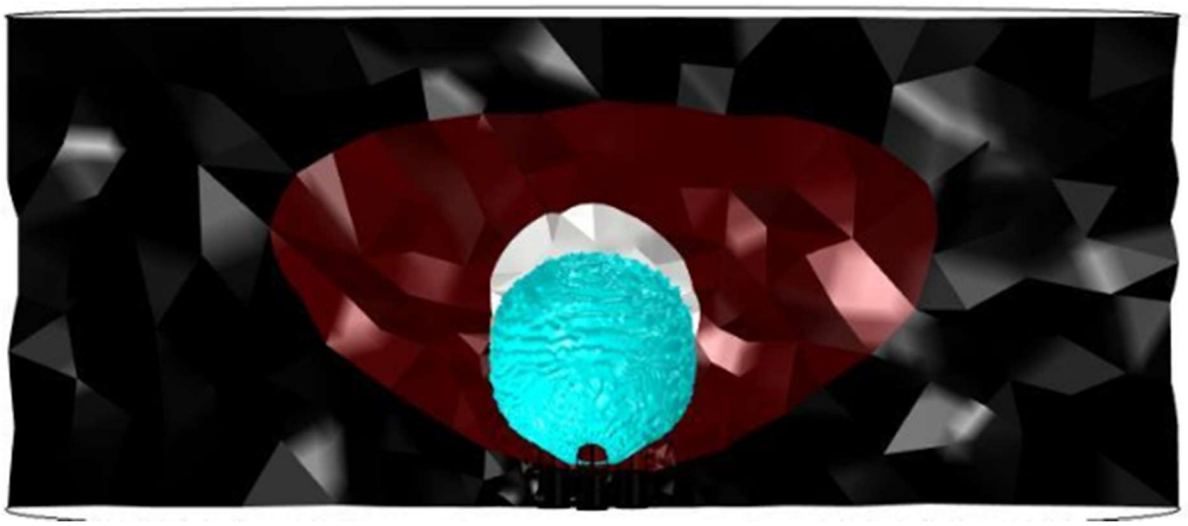

**Figure 9.** Results from single cryoprobe surgery simulation after 120 seconds. The cyan colored ellipse indicates frozen tissue. White region represents tumor tissue. Red region represents healthy prostate tissue. Black region indicates surrounding healthy tissue.

Our results suggest that this simulation kills a significant portion of the tumor tissue. However, closer investigation reveals that some of the healthy prostate tissue is being frozen as well. These results were also seen in Figure 7.

The value of our optimization function over the 120 seconds of simulated freezing was determined from our results (Figure 10).

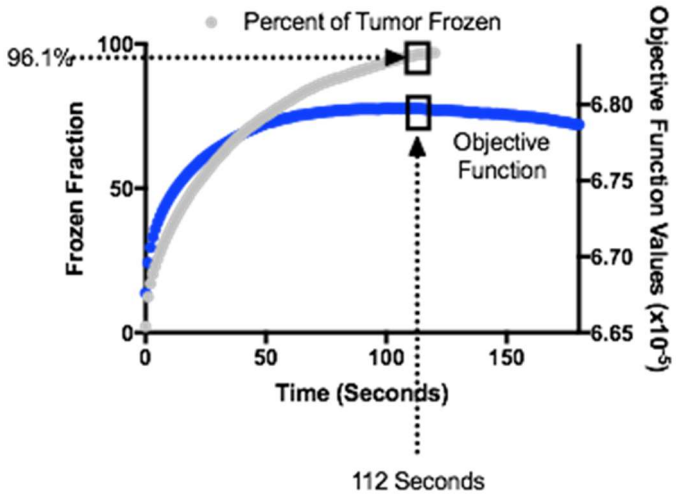


**Figure 10.** The objective function reaches a maximum at 112 seconds, which corresponds to 96.1% tumor freezing in the five-probe scenario. The objective function is plotted for 180 seconds to better identify the maximum.

The optimization function seems to be taking a maximum value at around 112 seconds. After 112 seconds, it appears that the benefit from killing more tumor tissue is outweighed by the

drawback of killing healthy tissue. Therefore, this simulation suggests that, with the five-probe set-up, the time for cryosurgery should no more than around 112 seconds.

However, if we observe the frozen region shown in Figure 11, we see that a large portion of the tumor is not killed after only 112 seconds. Leaving this volume of tumorous tissue behind after surgery will only allow the tumor to grow back. This makes the case for exploring the use of more probes and/or different probe tip styles in order to maximize the volume of tumor tissue destroyed while minimizing the volume of healthy tissue destroyed.

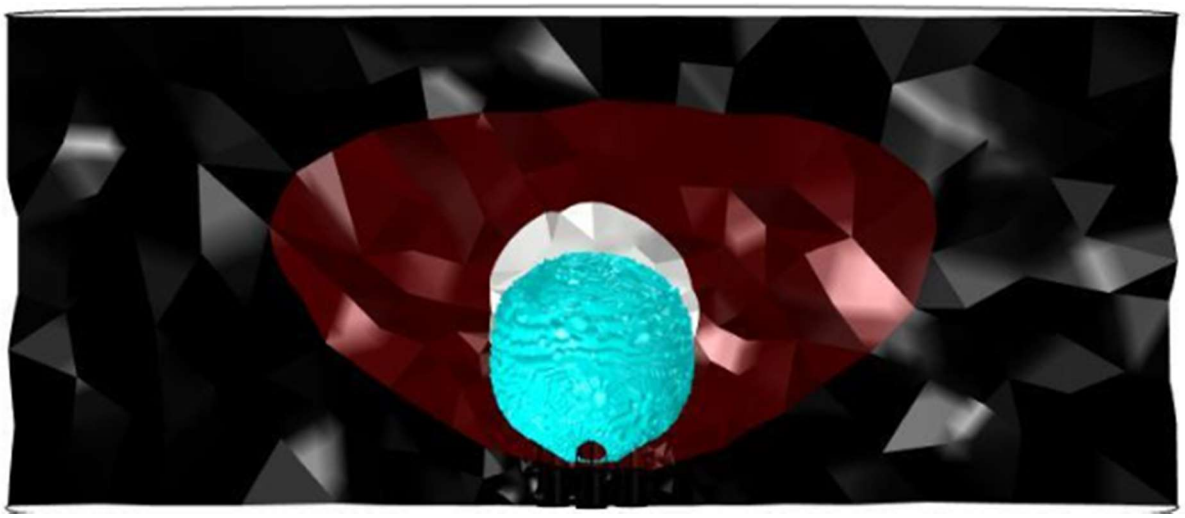

**Figure 11.** Results from single cryoprobe surgery simulation after 112 seconds. Cyan colored ellipse indicates frozen tissue. White region represents tumor tissue. Red region represents healthy prostate tissue. Black region indicates surrounding healthy tissue.

**Design of a Safer Probe**

The use of nine probes inserted into the prostate results in 100% of tumor frozen, but it also leads to 12% of the surrounding healthy prostate to be frozen. 12% of prostate frozen may results in severe side effects that differ from patient to patient depending on the location of the tumor. The issue with the current system is the fact that numerous probes need to be inserted, all from the same vertical orientation. Since the freezing is directed in only one direction (from the tip of the probe), it is necessary to position them near the boundary of the tumor-prostate interface in order to freeze the margins of the tumor.

We propose a probe design that makes optimal use of surface area, as well as one that cools in all directions, from the inside out. This probe tip features a spherical head, with various extrusions coming out from the center (Figure 12). The probe was designed by our team using SOLIDWORKS®. In this system, we have much more surface area than compared to the classic probe design, eliminating the necessity for multiple probes.

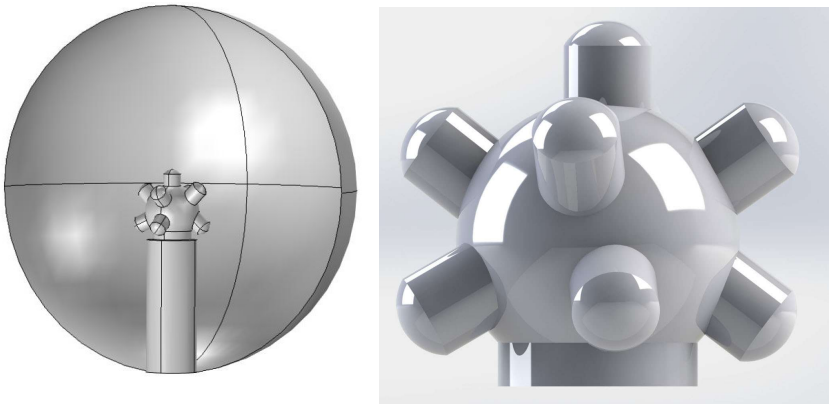

**Figure 12.** 3D model of new probe tip. Featuring a spherical head, as well as numerous extrusions, cooling is achieved in all directions. For an animation showing the complete design of this new probe tip please visit: https://www.youtube.com/watch?v=VUWnC5Kbjtw.

Using the same constant freezing temperature of -196 C, we simulate tissue freezing using this new probe design (Figure 13).

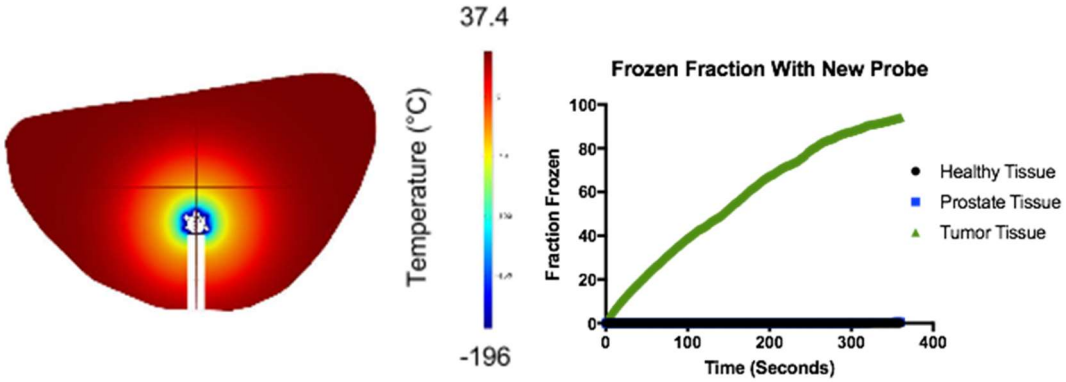


**Figure 13.** Multi-slice plot of temperature gradient within the tumor**.** Fraction of tissue frozen in all domains of interest (healthy, prostate and tumor tissues).

Our new probe is extremely effective. Its spherical design and extrusions allow for efficient cooling, keeping the amount of healthy and prostate tissue frozen non-existent. This allows for longer freezing times, in this case for three minutes. At the three minute mark, our fraction of tumor frozen reaches 93%, while healthy prostate frozen is a trivial 0.3%. The current practice of using multiple probes results in healthy prostate frozen amounts of approximately 10% for the same amount of tumor frozen (Figure 7). With 90% of tumor frozen the criteria for a successful surgery, our new model can reach this threshold without the same risk of healthy prostate damage.

**Validation and Comparison to Cryosurgery Procedures**

Modern cryosurgery practice dictates that a minimum freezing temperature of -40°C needs to be maintained for at least three minutes for complete eradication of the tumor [10]. The objective

function of our model indicates an optimum surgery duration of only 112 seconds (just under 2 minutes) for a five-cryoprobe set-up (Figure 10). However, this is largely due to the amount of healthy tissue being killed beyond that time.

The change between Figures 9 and 11 show that, after 112 s, the frozen tissue region (cyan) extends into the healthy prostate (red). The five-probe model reaches a steady state where the frozen region within the tumor stops expanding, but the surrounding normal tissue can continue to freeze for a while longer. Consequently, after 112 s, the five-probe model kills more healthy tissue than cancerous tissue with increased time. Our optimization procedure as currently implemented does not guarantee complete eradication of the tumor, only the point of maximum tumor death relative to unharmed normal tissue.

During cryosurgery, some of the healthy tissue around the tumor is also frozen due to limitations in precision and to totally eradicate the tumor. Because of the damage to the healthy prostate tissue, impotence is a common complication seen in 91% of patients [11]. Incontinence and rectal fistulas are also seen in 2.9% and 0.4% of patients, respectively, due to the freezing of healthy urethral and rectal tissue surrounding the prostate [11]. It is unknown how much of the healthy tissue is killed during the actual procedure, as the current technique has no way to measure this. Surgeons must monitor ultrasound images during surgery to gauge tumor and tissue death [10]. However, because some of the healthy prostate tissue is inevitably killed during the procedure, impotence is commonly seen. In our model, 6.7% of the healthy prostate tissue was killed while killing 96.1% of the tumor (Figure 7). Therefore, the correlation between healthy prostate death and tumor death is seen and contributes to the impotence complication.

## Future Plans

In order for a cylindrical shaped probe to completely kill a spherically shaped tumor, healthy prostate tissue must freeze (Figure 14a). However, a spherically shaped probe, if positioned properly, can completely kill a spherically shaped tumor without damaging healthy prostate tissue (Figure 14b). Our results highlight an important point: the amount of healthy prostate tissue killed is dependent on the geometry of the cryoprobe. Probes shaped the same way as the tumor will perform better than probes that are not shaped the same way as the tumor. If probe tips can be engineered to the shape of the prostate tumor to be frozen, we can improve the effectiveness of cryosurgery (Figure 14c).

A potential method of creating these custom probe tips is to image the tumor prior to surgery using MRI techniques. This image could then be rendered into a 3D model of the tumor. This 3D model could then be used to 3D print a probe tip to the exact shape of the tumor. Aluminum, a highly conductive metal, could be used as the printing material for the custom probe. With these

custom probes, a validation experiment should be conducted to test the hypothesis that a probed shaped to the geometry of the tumor will more efficiently freeze the tumor during cryosurgery.

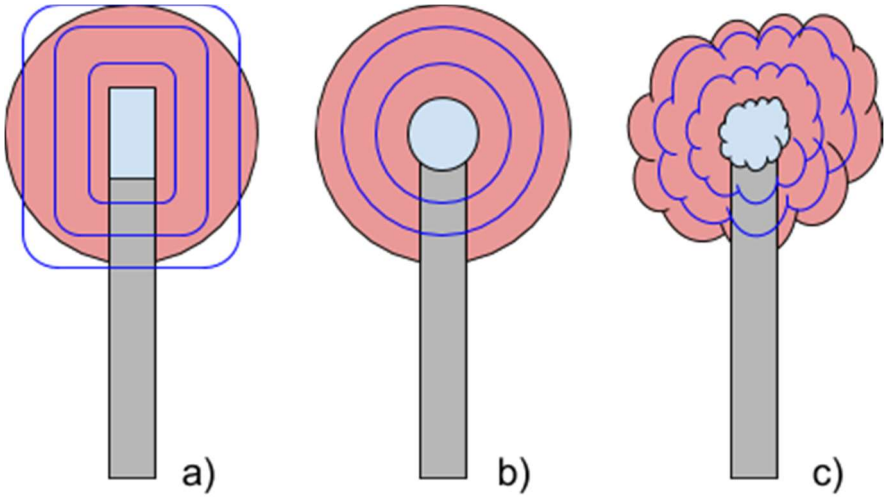


**Figure 14.** A probe tip that matches the shape of the tumor will be better at minimizing healthy tissue death.

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