Mathematical Modeling and Simulation of Cryo-Probe for Tumor Removal Surgery (Cryo-Surgery)

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Abstract— Cancer is a dangerous disease accounting for the highest number of deaths by a single cause all over the world. There are several ways to treat cancerous cells are available and new ways are regularly being proposed. Cryosurgery is one of them and offers many advantages. Cryosurgery is the destruction of undesired biological tissues by freezing. For remove of undesired biological tissue i.e. tumor modern cryosurgery is frequently performed as a simply persistent procedure, in which multiple, hypodermic needle-shaped cryoprobes are inserted into the target area to be treated. It causes freezing the tumor inside body below its critical temperature and forming ice-ball, so tumor being inactive and removed from the body. To use this technique effectively the rate of cooling and extent of cooling needs to be controlled. It helps in achieving total destruction of tumor and minimum harm to adjoining healthy tissue. The aim of the cryosurgeon is to place the cryoprobes so as to maximize cryoinjury within the target region, while minimizing damage to healthy surrounding tissue. The quality of the cryoprobe arrangement, which has a direct impact on the success of the procedure, is dependent upon the cryosurgeon's own skill and experience. From a mathematical point of view, the problem is to predict the time-evolving position of freezing or melting position where phase change occurs. At the same time, the temperature is computed everywhere in the computational domain giving access to the complete thermal history. Bio-heat equation can be solved by using one of various simulation techniques for a single or multi-probes. Simulated results greatly match with the experimental outputs. Thus, the model used can be extrapolated to study the effects of different freezing rates.

Key words: Cryo-Probe, Cryo-Surgery

I. INTRODUCTION

Cancer has become one of the major causes of mortality in our modern society and it has over taken cardiovascular diseases to become the number one killer in the world. Hitherto, the common treatments for cancer include surgical removal, radiation therapy and chemotherapy. These treatments can have devastating side effects which can potentially weaken cancer patients. In the last half of the previous century, another method of cancer treatment, known as cryosurgery, was developed. Cryosurgery, sometimes referred to as cryotherapy or cryoablation, is a surgical technique that employs freezing at cryogenic temperatures to destroy undesirable tissue. Cryosurgery is conducted by means of a cryoprobe either by placing its continuously cooled tip on or into the tissue to be frozen. One of the key advantages of cryosurgery is that cell destruction is localized which minimizes damage to surrounding healthy tissue. There is, however, one drawback of this surgical technique. The minimally invasive nature of cryosurgery poses some difficulties in controlling the procedure. As the freezing front propagates from the cryoprobe outward, the extent of the tissue effected by freezing at times cannot be easily determined by the surgeon, resulting in a loss of precision and control.

The current resurgence of interest in cryosurgery has allowed countless new applications to surface. This, in turn, has brought about numerous investigations on the mechanisms of cryoinjury with the aim of better defining the appropriate or optimal temperature–time dosimetry of the freezing process. Currently, there is an urgent need in cryosurgical research to develop tools and methods that can maximize cell death within the tumor and yet maintain high cell survivability in the periphery of the cryolesion where cells can either live or die. It is imperative to understand the mechanisms of cell damage during cryosurgery and the thermal history of the frozen lesion in order to evaluate the efficacy of each surgical protocol.

Since the introduction of the cryosurgical technique, the unintended destruction of the surrounding healthy tissue has been a vexing problem which tended to limit the application of cryosurgery. Unnecessary freezing can lead to a host of lethal and chronic complications. Generally, when a tumor is irregularly shaped, the ice-ball formed by employing a single cryoprobe cannot optimally cover the tumor without causing excessive damage to surrounding healthy tissue. This detrimental freezing is of paramount concern when the diseased region is located close to critical organs and blood vessels. Solving the problem of detrimental freezing, or at least minimizing healthy tissue destruction, requires more than good surgical judgment or reliance on visual monitoring. It may involve the use of multiple cryoprobes that can shape ice-balls near the tumor contour. A mathematical model has been developed to study the process of freezing in liver tissue under controlled thermal conditions and the response of liver cells to changes in cooling rate[1]. The application of multi-probe cryosurgery requires judicious planning based on the optimization of cryoprobe placements for maximum destruction in neoplasms and minimum cell death in healthy tissue as illustrated by many researchers. However, optimization of multi-probe placement is presently not within the scope of this study. Instead, the efficacy of multiple cryoprobes in relation to cell destruction in the tumor and cell survival in the surrounding healthy tissue has been investigated.

It is important to be able to predict and control the cooling rate over some range of temperatures and freezing states, whether in single or multi-probe freezing, in order to regulate the spatial extent of injury for any freezing and thawing protocol.[2] Therefore, the principal objective of this paper was to construct an accurate analytical

cryosurgical model to predict the ice-ball formation and the internal cooling rates and thereby correlate the degree of cell destruction/ survival within the tumor/healthy tissue region. The model was simulated to study the effectiveness of employing different cryoprobes in destroying cancerous tissue or minimizing cell damage in the peripheral healthy tissue. It is hoped that results presented in this paper can assist clinical practitioners in dealing with the limitations of cryosurgery.

II. CELL DESTRUCTION UNDER CRYOGENIC CONDITION

The mechanism of tissue injury during cryosurgery has to be understood in order to connect the freezing process to degree of cell destruction within the tumor. The destructive effects of freezing tissue can be categorized into two major mechanisms, namely immediate and delayed. The causes of immediate cell destruction are due to direct cell injury from the effect of temperature and the cooling and freezing processes while the delayed cause of freezing injury that can last up to several hours upon the completion of a cryosurgery with the most dominant form of cell destruction being vascular stasis[1]. Tissue response depends on the cryogenic injury. The coldest tissue temperature is a key factor in cell death and −50℃ is recommended for sure cell death. Experiments conducted to determine the survivability of cells during cooling show for temperatures equal to or above −196℃, cells survive the cryoinjury [3].

A. Extracellular Ice Crystallization

This mechanism, also known as "solution effect" is the main cause of cell death from freezing. Extracellular crystallization cell destruction occurs between temperatures of −4℃ to −21℃. Low cooling rates and moderately low temperatures dominate the process. The extra-cellular spaces start freezing and ice crystals are formed. The core of the cell stays unfrozen due to cell membrane. To achieve equilibrium, water in the cells passes out through the cell membrane by osmosis. This loss of water causes cells to shrink, damaging their membranes and constituents. Eventually, cell shrinkage reaches a maximum even though extracellular concentration continues to increase. This creates a concentration gradient between the two sides. A point in time arrives when the concentration gradient is significant and the solutes from the extracellular fluid are allowed to pass into the cell. This generates a mechanical force on the cells, which damages and destroys the cells.

B. Intracellular Ice Crystallization

When cooling rates are high, there is less time for extracellular ice crystallization. Theoretically, this means that there would be a reduction in cell destruction. However, another ice formation phenomenon takes place-intracellular ice. When this occurs, water cannot leave the cells fast enough to maintain osmotic equilibrium across the cell membrane. Therefore, equilibrium is achieved by the formation of ice crystals within the cells as well as outside. In cryobiology, heterogeneous nucleation of intracellular ice can form at temperatures of −15℃ and below whereas homogeneous intracellular ice crystals form at temperatures of −40℃. As the temperature drops, the intracellular solution becomes thermodynamically super cooled and becomes increasingly unstable. This instability causes ice nucleation to take place, leading to the formation of ice crystals within the cell membrane. The intracellular ice crystals irreversibly rupture the cell membrane due to an expansion in volume. At the same time, it disrupts the proper functioning of cell organelles, thereby destroying the cancerous cells.

III. KEY FACTORS IN CRYOSURGERY

A. Cooling Rate

The extracellular ice crystallization happens between temperatures of −4℃ to −21℃. As the cooling rate goes up, lesser time is available for the cells in this temperature range. This apparently decreases the number of cells died. As the cooling rate further increases, intracellular ice crystallization dominates and abetting cell death. There exists a critical cooling rate depending on the cell type being frozen for which cell survival is optimum. Rapid cooling rate is lethal and causes intracellular ice crystallization resulting in faster cell death.

B. Lowest Tissue Temperature

The lowest temperature attained during cryosurgery has strong bearing on the efficacy of the process. When cryoprobe is touches the tumor, temperature profiles are developed in region of interest. The lowest temperature is attained by the cells near the tip of cryoprobe. Care needs to be taken to ensure that critical temperature of −50℃ is attained throughout the tumor.

C. Duration of Freezing

The duration of freezing is unimportant if the tissue is kept at temperature below critical temperature of −50℃. However, the holding time for temperatures above critical temperature of −50℃ enhances the cell death.

D. Thawing Rate

Slow thawing abets tremendous harm to the cells than the rapid cooling. Slow thawing provides enough time for the growth of large ice crystals through recrystallization. Large crystals have intruding abrasive action disrupting cells.

E. Number of Freeze-Thaw Cycles

The repeated cycles ensure certain and complete cell death. Each following cycle adds up to the volume of cells frozen and that too at faster rate. The lowest temperatures obtained moves away from the cryoprobe towards the periphery of the tumor.

IV. MODEL FORMULATION

Cryosurgery involves numerous heat transfer mechanisms and a phase change from liquid to solid. The phase change of cellular fluid complicates the matters for mathematical formulation. As cryosurgery operates at very low temperatures, the other forms of heat transfer except conduction can reasonably be assumed to be negligible.[4] This assumption is corroborated by the experiment performed by Pennes[5] finding that there are no noticeable discrepancies between the application of this assumption and the end results obtained . Heat sources due to the processes of metabolism and blood perfusion which regulate the body temperature almost constant at 37℃ are needed to be included.

The following assumptions have been made in developing the bioheat thermal model[6] :

1) Heat transfer in the cryosurgical model occurs purely by conduction.
2) Latent heat of fusion is constant and is applied in the region of phase change.
3) Thermo-physical properties vary at the point of complete phase change from liquid to solid.
4) Heat flow occurs in one-dimensional manner.
5) Liquids and solidus tissue temperature are 272 K and 265 K respectively.
6) Heat Source due to blood perfusion and metabolism is present when tissue is not frozen.

Pennes formulated bio-heat transfer equation that considers all significant contributions and is as follows.[7]

$$(\rho c)_t \frac{\partial T(r,t)}{\partial t} = \nabla k_t \nabla T(r,t) + S_b + Q_m \qquad (4.1)$$

Where $(\rho c)_t$ represents the product of density and specific heat for the tissue, $T(r,t)$ is temperature at t time and at r distance from cryo probe, t is time, k_t is the tissue thermal conductivity, S_b is the heat source term due to blood perfusion and Q_m is the heat source term due to metabolism. The heat source term due to blood perfusion (S_b) is difficult to quantify unless certain assumptions are made. Pennes postulates that the heat source term due to blood perfusion (S_b) is directly proportional to the temperature difference between blood entering the tissue and the tissue. The local blood temperature T_b is treated as constant and rate of blood perfusion is considered uniform. Perfect heat exchange between blood and tissue is presumed as the rates and distances involved are small. The Pennes model provides good approximation which pans out as follows,[7]

$$S_b = (\rho c)_b \omega_b (T_b - T(r,t)) \qquad (4.2)$$

Where (ρc) represents the product of density and specific heat for blood, ω_b is the volumetric flow rate of blood perfusion per unit volume of the tissue, T_b is local blood temperature and $T(r,)$ is the local tissue temperature.

The following fig.4.1 shows various freezing zones in radial geometry [3]. When cryo-probe is introduced, temperature gradient is set up in the tissue. As the cryoprobe is maintained at temperatures far below that of the tissue, the tissue temperature starts falling. As the tissue temperature near the cryoprobe falls below its freezing temperature, the tissue starts solidifying. Iceball formation starts and it propagates away from the cryoprobe. Three regions i.e. frozen, mushy and unfrozen can be seen in the schematic representation. In the mushy region, the tissue temperature lies between the liquidus (272 K) and solidus (265 K) tissue temperatures.

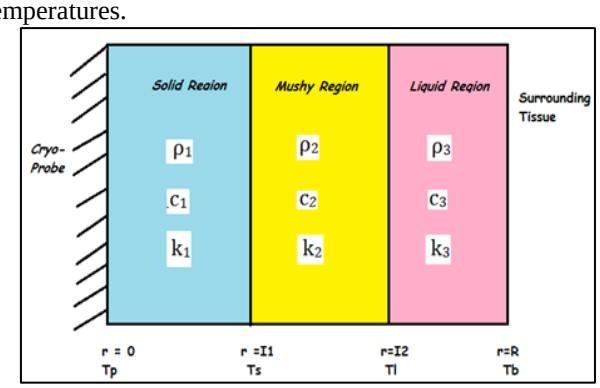

Fig. 4.1: Schematic layer representation

Different terms from the bioheat transfer equation appear and disappear depending on for which region the equation is applied to.

A. In the frozen region, due to absence of blood perfusion and metabolic rate, the heat balance equation may be expressed as

$$\rho_1 c_1 \frac{\partial T_1(r,t)}{\partial t} = k_1 \frac{1}{r}\frac{\partial}{\partial r}\left(r \frac{\partial T_1(r,t)}{\partial r}\right) \qquad (4.3)$$

B. In the mushy rerion, both blood perfusion and metabolic rate contribute to the energy balance and phase change occurs. So, we can write

$$\rho_2 c_2 \frac{\partial T_2(r,t)}{\partial t} = k_2 \frac{1}{r}\frac{\partial}{\partial r}\left(r \frac{\partial T_2(r,t)}{\partial r}\right) + \rho_b c_b \omega (T_b - T_2(x,t)) + S_m + \rho_2 h_L \frac{df_s}{dt} \qquad (4.4)$$

where, $$f_s = \frac{(T_2(x,t) - T_l)}{(T_f - T_l)} \text{ if } T_s < T_2(x,t) < T_l \qquad (4.5)$$

Where h_L is the total latent heat in J/Kg required for phase change across the mushy region. T_2 is the local tissue temperature. T_l and T_s symbolize liquidus (272 K) and solidus (265 K) tissue temperatures respectively.

C. For the unfrozen region, both blood perfusion and metabolism exists and are accounted for as follows.

$$\rho_3 c_3 \frac{\partial T_3(r,t)}{\partial t} = k_3 \frac{1}{r}\frac{\partial}{\partial r}\left(r \frac{\partial T_3(r,t)}{\partial r}\right) + \rho_b c_b \omega (T_b - T_3(x,t)) + S_m \qquad (4.6)$$

The boundary conditions at various interfaces can be expressed as follows,

1) At the interface between cryoprobe and the frozen region : T_P is the boiling point of the cryogenic fluid.

$$T_1(r,t) = T_P \qquad (4.7)$$

Where T_P is temperature of surface of cryoprobe.

2) At the interface between the frozen and mushy regions which is one of the two moving boundaries:

$$T_1(r,t) = T_2(r,t) = T_s \qquad (4.8)$$

$$K_3 \nabla T_3(r,t)\hat{n} = K_2 \nabla T_2(r,t)\hat{n} \qquad (4.9)$$

Where $\hat{n}$ is the unit normal vector to the frozen and mushy regions interface.

3) At the interface between the mushy and unfrozen regions which is second of the two moving boundaries:

$$T_2(r,t) = T_3(r,t) = T_l \qquad (4.10)$$

$$K_2 \nabla T_2(r,t)\hat{n} = K_3 \nabla T_3(r,t)\hat{n} \qquad (4.11)$$

Where $\hat{n}$ is the unit normal vector to the mushy-unfrozen zone interface.

4) At the end of the unfrozen region i.e. at the interface between unfrozen region and the surrounding tissue:

$$T_3(r,t) = T_B \qquad (4.12)$$

Where, T_B is surrounding tissue Temperature which is temperature of Blood equal to 310.15 K .

V. Discretization

For discretize above differential equations we used finite difference method and made an assumption that heat flow in radial direction only. For discretize purpose we use central difference Implicit method as it is unconditionally stable.

The challenging task in this process is three region and two moving boundary. For three region we made three different discretize equation but for moving boundary it is not that much easy because it has different thermal property on each of the side of boundary. So we consider node on

boundary and taking backward difference in left side region and forward difference in right side region and applying constant heat transfer equation for conduction.

VI. Solve the mathematical model

For Solving this mathematical model we doing programming in matlab 2014. And getting the result by matrix inversion method.

The bio thermal property used in simulation process have been obtained from published literature and listed in

Property	Quantitative Value
Thermal conductivity for liver tissue	Unfrozen = 0.50208 Wm-1K-1 Frozen = 1.75728 Wm-1K-1
Specific Heat of Liver tissue	Unfrozen = 3347.2 J kg-1K-1 Frozen = 1673.6 J kg-1K-1
Density of liver tissue	Unfrozen = 1000 kg m-3 Frozen = 998 kg m-3
Metabolism of liver	80 W (based on a 70 kg man)
Perfusion of liver	0.01872 s-1
Thermal Conductivity of Blood	0.492 Wm-1K-1
Specific heat of blood	3640 J kg-1K-1
Density of Blood	1050 kg m-3
Probe Temperature	98.15 K
Blood Temperature	310.15 K
Latent heat in mushy region	4200 KJ
Liquids Temperature	272 K
Solidus Temperature	265 K

Table 1:

Flow chart for solving the equation in matlab is as shown in Fig.6.1

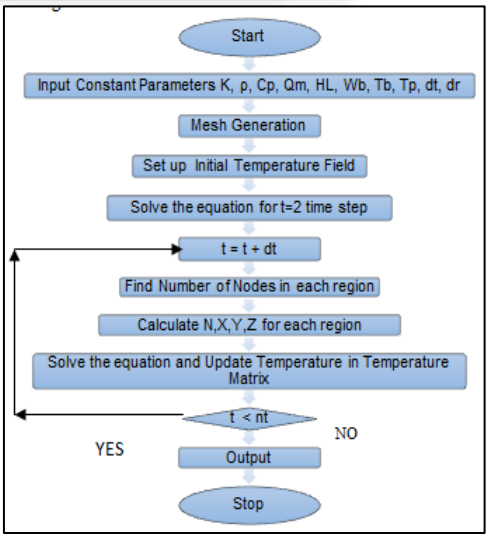

Fig. 6.1: Flowchart for Program

VII. Results and discussion

To validate the the numerical code the results from the simulation has been compared with results of K.J.Chua et. al. (2007). It shows from the comparison that simulation results matches their data well. Hence it can be used further to find optimized freeze thaw cycle.

A comprehensive grid independent study has been performed to study the model stability with regard to model meshing size. Test has been carried out using two mashing scheme with the ratio of 1: 2. The coarser grid size 1 mm and finer grid size 0.5mm. Temperature difference between this two is shown in fig. The maximum deviation is about 6.4% as shown in fig.7.1. So further refinement in grid size will not improvement in accuracy.

Now we compare our result of temperature profile of 15 mm diameter tumor tissue at 10 mm away radial distance from cryo probe for 20 min. Here we use three different probe of 3 mm, 5mm and 8mm diameter. All curve have same features rapid initial drop in temperature and get final temp. of -37 to 70 ℃. Also shows that 8 mm probe has much steeper curve than 5 and 8 mm probe.

Another comparison is made of freezing front position using different diameter probes. This both graphs are also almost same. From this study we can say that freezing front position with 8 mm with compare to 5mm and 3 mm diameter is approximately 30% and 52% more as shown in fig.7.3. It is because of more surface contact area and due to it more heat transfer is possible.

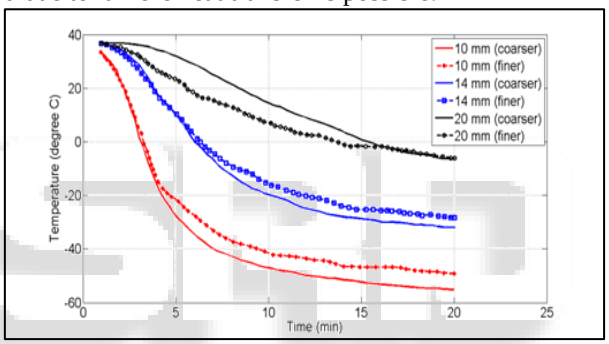

Fig. 7.1: Grid size Comparision

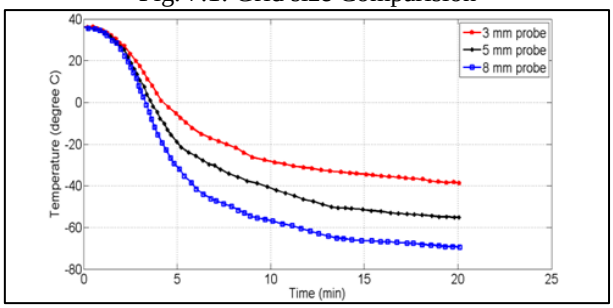

Fig.7.2: Temperature profile at 10 mm radial distance from surface of cryoprob

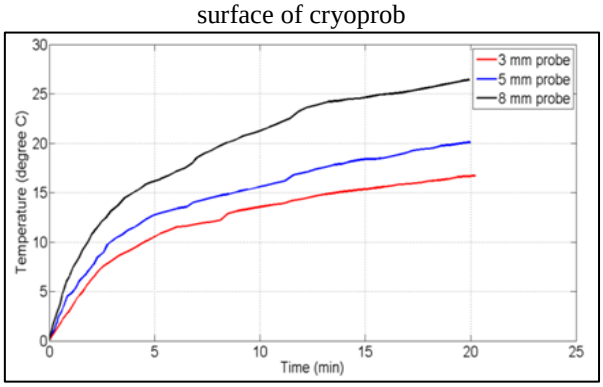

Fig. 7.3: Freezing Front position in radial direction in 15 mm tumor

Comparison of temperature profiles between simulated and in vivo experimental results Experimental data were obtained by a single freeze cycle of 20 min on a liver organ using a 8 mm-AccuProbe Cryoprobe held at an approximate temperature of -175 C with thermocouples positioned at 10, 15 and 20mm away from cryoprobe as shown in fig.7.4

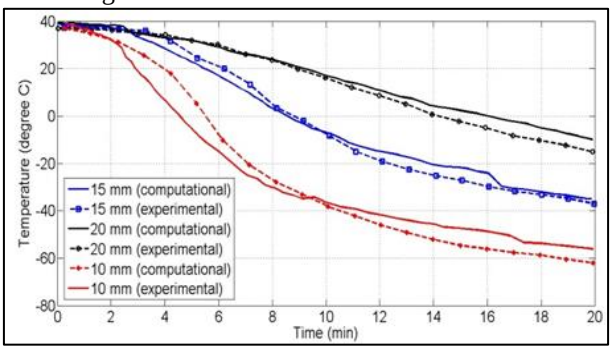

Fig. 7.4: Comparison with experimental data

VIII. Conclusion

In present work bio-heat equation has solved numerically to simulate the cryo surgery's thermal aspects. Pure implicit finite difference scheme has been used to solve non-linear partial deferential equations in cylindrical domain. Numerical results has been validated against published paper results. It shows that when increase diameter of probe, it has more contact area for heat transfer so we get fast cooling and more freezing propagation from probe in same time.

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