Heat Transfer Model for Cryosurgery

Thesis submitted in the partial fulfillment of the requirements for the degree of

Master of Technology

In

BIOMEDICAL ENGINEERING

By:

VARSHA RANI CHIKANJURI

Roll. No. 209BM1002

Under the guidance of

DR. AMITESH KUMAR

Department of Biotechnology and Medical Engineering

National Institute of Technology, Rourkela (Odisha)

Heat Transfer Model for Cryosurgery

Thesis submitted in the partial fulfillment of the requirements for the degree of

Master of Technology

In

BIOMEDICAL ENGINEERING

By:

Varsha Rani Chikanjuri

Roll No.209BM1002

Under the guidance of

Dr. Amitesh Kumar

Department of Biotechnology and Medical Engineering

National Institute of Technology, Rourkela (Odisha)

National Institute Of Technology
Rourkela

C E R T I F I C A T E

This is to certify that the thesis entitled "**HEAT TRANSFER MODEL FOR CRYOSURGERY**" by Miss. **Varsha Rani Chikanjuri** submitted to the **National Institute of Technology**, Rourkela for the Degree of Master of Technology in Biotechnology, is a record of bonafide research work, carried out by her in the Department of Biotechnology and Medical Engineering under my supervision. I believe that the thesis fulfils part of the requirements for the award of Master of Technology. To the best of my knowledge, the matter embodied in the thesis has not been submitted to any other University / Institute for the award of any Degree or Diploma.

Date:

Place:

Dr. Amitesh Kumar
Department of Biotechnology and Medical Engineering
NIT Rourkela

ACKNOWLEDGEMENT

This dissertation would not have been possible without the guidance and help of several individuals who in one way or another, contributed and extended their valuable assistance in the preparation and completion of this work.

First and foremost, my utmost gratitude to my supervisor Dr. Amitesh Kumar, Assistant Professor, Department of Biotechnology and Medical Engineering, for his supervision, advice and guidance as well as sharing his extra-ordinary experiences throughout the work. Above all and the most needed, he unflinchingly encouraged and helped me.

I am thankful to my lab mates and colleagues Ms. Dibya Devismita, Mr. Sadanand Jinna, Ms. Prerna Dixit, and Mr. Teepireddy Sudeep, who were a great moral support during my work.

Last, but not the least, I would thank the God and my family, whose love and trust on me has brought at this stage of my life.

Varsha Rani Chikanjuri

ABSTRACT

Cryosurgery is a surgical technique which employs extreme freezing to treat diseased or abnormal tissue. Here, a new numerical approach is devised to simulate the heat transfer process in cryosurgery in order to assess the propagation of ice front's positions and thermal history inside the ice ball. The developed numerical code is validated against the published experimental results. The emphasis is placed on minimizing the computational time so that the devised approach can be used in planning of cryosurgery treatment. The phase change phenomenon is solved using finite volume method on a fixed multiblock structured grid. An enthalpy method in addition to two-dimensional axisymmetric model is used to approximate the process of cryoablation. The model has used constant thermal properties for both the unfrozen region and the frozen region. In this study, we predicted thermal profile of tissue simulating gel during freezing and holding after certain time duration, while considering various dependent parameters. In addition, effect of cryoprobe size on the propagation of ice front positions and thermal history inside the ice ball is studied. And, it is found that ice volume varies almost linearly with time as well as with cryoprobe size.

Keywords: Cryosurgery, Finite volume method, Multiblock Technique, Ice- front position

CONTENTS

List of Tables

List of figures

Nomenclature

c Specific heat capacity, J/ (kg ^{0}C)

H Total enthalpy, J/ kg

h Sensible enthalpy, J/ kg

k Thermal conductivity, J/ (m s ^{0}C)

L Dimensional length, m

$\dot{m}_b$ Blood perfusion rate, kg blood/m^3 tissue/s

$\dot{q}_{met}$ Metabolic rate, J/ (m^3 s)

r Radial co-ordinate

T Temperature, ^{0}C

t Time, s

z Axial co-ordinate

Greek Symbol

ρ Density, m^3

Subscripts

B Boundary

b Blood

f Frozen gel or tissue

p Probe

u Unfrozen gel or tissue

CHAPTER 1

INTRODUCTION

1.1 Background

Cryosurgery, also referred as cryotherapy or cryoablation, is a novel surgical technique which employs extreme freezing to destroy diseased tissue [1]. Modern era of cryosurgery began with the development of automated cryosurgical equipment in the 1960s. Using freezing as the means to destroy undesirable tissues, modern cryosurgery presents many remarkable merits over its competitive modalities. Cryosurgery is conducted by means of a cryoprobe either by placing its continuously cooled tip on or into the tissue to be frozen. Cryogens (used as a cooling medium) which have been used in cryosurgery include liquid nitrogen, nitrogen oxide, solid carbon dioxide, liquid argon having boiling temperature of -196^0C, -89.5^0C, -78.5^0C and -187^0C respectively [1]. Generally liquid nitrogen is used for cryogen because of minimum boiling temperature. Cryosurgery is widely applied in the treatment of various undesired cancerous and non-cancerous tissues in liver, lung, kidney, prostrate, brain, skin, breast, bone etc. One of the key advantage of cryosurgery is that cell destruction is localized which minimizes damage to surrounding healthy tissue [12]. The goal of this surgical technique is to maximize the destruction of target tissue while minimizing the damage to surrounding healthy tissue. Two mechanisms of tissue injury, immediate and delayed, are associated with cryosurgery. The immediate destruction involves direct destruction of cells while the delayed invokes post application damage due to the destruction of blood vessels or delayed immune system [1, 2, 3]. The basic technique requires fast freezing to lethal temperature of tissue, slow thawing, and repetition of the freeze-thaw cycle. Ice-front's positions, holding time duration, freeze-thaw cycles, freezing rate and induced thermal stress should be properly monitored for the optimal destruction of undesired tissue. The cryosurgeon monitors the freezing process by means of medical imaging such as ultrasound or MRI and adjusts the cooling power of the individual cryoprobe accordingly to maximize the cell death and minimize the destruction of surrounding normal tissue or organ.

For the purpose of cryosurgical planning, it is highly desirable to compute the process of ice propagation and thermal history inside the ice-ball, which cannot be determined by imaging. Computerized planning helps surgeons in pre-planning of surgery. To determine the effect of cooling rate, exposure of cryoprobe temperature, freeze-thaw cycle and arrangement of cryoprobe on the degradation of cancerous cells and thermal history within the tumor, numerical

simulations can be valuable help. Such a tool resonates well with surgeons, providing them with the capacity to maximize the efficacy of the surgery. Numerical simulation can become more advantageous in real time operation to predict the internal thermal history of the target tissue.

1.2 Review of Literature

In 1961, first cryosurgical system was invented by an American neurosurgeon Irving Cooper [2, 3]. They built a cryosurgical probe capable of freezing brain tissue, with good control over target region. Originally developed for the treatment of parkinson and other neural disorders, the probe was found with great value for broad use in destroying undesirable tissues deep in the body. The field of cryosurgery therefore experienced a rapid growth after the introduction of the first cryosurgical probe. Many new applications of cryosurgery have been introduced between years 1961 and 1970. Cahan and his associates applied cryosurgery to uterus with the inclusion of heating element [4]. Rand et al. [5] reported the use of cryosurgery in neurology. Markcover and his colleagues extended the use of cryosurgery in orthopedics [6]. Torre made contributions in cutaneous cryosurgery [7].

To apply cryosurgery precisely it is necessary to know the mechanism of tissue destruction during cryosurgery, thermal history within frozen tissue, and methods to evaluate extent of freezing.

1.2.1 Mechanisms of cryosurgery

The destructive effect of freezing tissue has been categorized into two major mechanisms (figure 1), one immediate and the other delayed. The immediate destruction is due to the direct destruction of cells while the delayed invokes post application damage due to the destruction of blood vessels or delayed immune system. The immediate process involves formation of intracellular and extracellular ice- crystals. As tissue temperature falls below zero degree, ice-crystals form in extracellular space and in microvasculature; this removes water from biological system and invokes hyperosmotic drying of the tissue, further tissue ablation starts. Higher rate of freezing produces intracellular ice crystals which causes progressive cell destruction [1, 2, 3,11]. Delayed mechanism is operative during thawing. The cryogen circulation is stopped for certain time duration which causes the failure of microcirculation. Furthermore, rupture of blood

vessels and platelets aggregation lead to cell injury due to thrombosis, vascular occlusion and necrosis [1, 2, 3, 11].

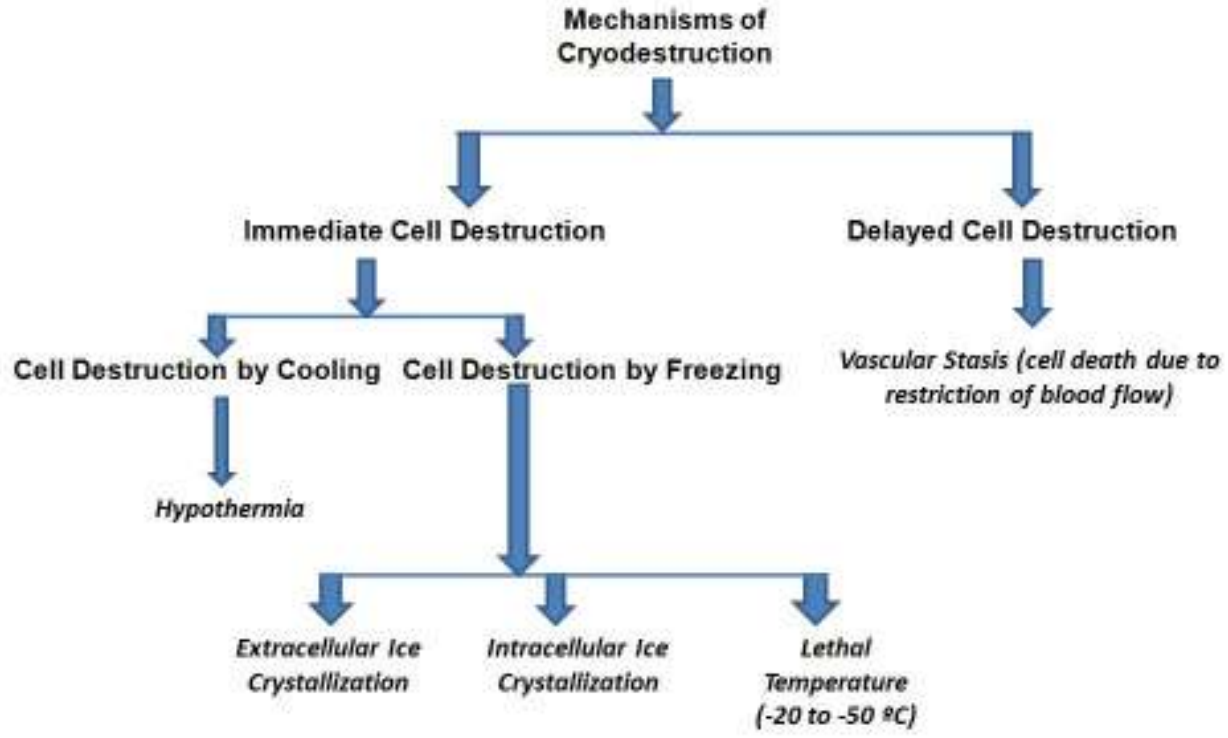


Figure 1: Mechanism of Cryosurgery [11]

Tissue response varies with intensity of cryogenic injury. Less cryogenic injury produces inadequate tissue destruction while more cryogenic injury may extend deleterious effects to surrounding normal tissue. For optimal cryoablation of the diseased tissue, it is necessary to be concerned on following controlling parameters:-

Cooling rate

In cryosurgery, rapid cooling rate i.e. more than 50^0C/min produces intracellular ice- crystals which is more destructive. Review of experimental data suggested that cooling rates of 3^0C/min, 22^0C/min and 50^0C/min are required in order to induce intracellular ice in neoplastic cells, liver and dunning AT-Tumor [3]. Such higher rates of cooling can only be achieved close to the cryoprobe and further away it lowers, and whole tissue is not subjected to rapid cooling. Farrant, Walter and Mazur support that cooling rate is not a prime factor for cryosurgery. They suggested that the cells are exposed to diverse thermal profiles for different times [3, 22, 23, 24].

Temperature

Cryosurgical treatment requires that lethal tissue temperature should be achieved in all parts (whole) of the tumor. The lethality of freezing increases as temperature falls more and more. Mazur stated that the lethal temperature range is between -5^0C to -50^0C [22]. According to Cooper, -20^0C temperature for 1 min time duration is sufficient to produce necrosis [25]. Rivoire et al. [32] found -15^0C temperature is needed to produce complete necrosis. In experiment with rat liver, Smith and Fraser suggested that necrotic effect activates at -15^0C, but they also observed that some undesired cell survival was possible at this temperature [3, 33, 34]. The treatment of tumor requires a tissue temperature at which all the abnormal cells are certainly dead. It shows the importance of lethal tissue temperature in cryosurgery, especially for the treatment of cancer. However, varieties of experiments have provided many range of lethal temperature for corresponding type of tissue (Table 1) [3].

Table 1

Lethal Temperatures for Cells Experiments *in Vivo*—Single Freeze–Thaw Cycles [3]

First Author	Year	Cell/Tissue	Lethal Temperature(^{0}C)	Freeze-thaw program
Gage	1966	Osteocytes, bone, dog	-2	5-min F–slow T
Gage	1979	Melanocytes, skin, dog	-4	4-min F–slow T
Smith	1974	Liver, rat	-15	3-min F–slow T
Rivoire	1996	Liver, pig	-15	5-min F–slow T
Lefebvre	1975	Cheek pouch, hamster	-18	1-s F–slow T
Dow	1970	Prostate, dog	-20	1-min F–slow T
Gage	1982	Skin, dog	-40	3-min F–slow T
Yamada	1976	Skin,mouse	-40	1-min F-slow T
Gage	1978	Palate, dog	-40	3-min F–slow T
Neel	1971	Sarcoma,mouse	-60	6-min F–slow T
Steren	1997	Adenocarcinoma, rat	-70	7-min F–slow T

F-T is Freeze- thaw

Due to variations in sensitiveness and thermophysical properties of normal and cancerous tissue, it is quite complex to achieve the lethal temperature of the diseased tissue. From the review of all experimental studies the end point temperature below -40^{0}C has been considered prime factor for tissue destruction [3, 24].

Hold Time/ freeze-duration

A measure of optimal freezing duration, i.e. how long tissue should be held in a frozen state, is not known prior to the surgery. Mazur stated that the rate of cell death is greatest when tissue is held at temperature above than -30^{0}C [23]. Below that temperature, little water remains unfrozen, so duration is less important. However, other cryosurgical experiments showed its importance. Prolongation of freezing was thought to be advantageous in experiments with breast tumors in animals. Longer freezing also produced more damage to the cartilage of the ears of pigs. Gage and Baust suggested that freeze-duration is unimportant if the tissue is held at temperatures colder than -50°C, but holding tissue at warmer temperature i.e. more than -40^{0}C, will increase destructive effect [3, 24].

Thawing rate

Thawing rate should be slow and continued for longer time period; rapid thaw rates allow cell survival. Within temperature range of -20^{0}C to -25^{0}C, thaw is more important due to maximal growth of ice-crystals. If tissue is held at this temperature for longer duration, cell death is more effective due to recrystallization process which produces large ice crystals. Prolongation of thaw is advantageous in cell damage only if it is processed completely [3, 12, 24].

Repetitive freeze-thaw cycles

Rapid freezing and slow thawing do not guarantee effective cell destruction. Therefore, the cryosurgery process should be programmed in such a way to produce appropriate lethal effect to certain volume of tissue. Now freeze-thaw cycle came into concept, each of which cycle is injurious to cells [12]. During repetition of cycles, several times cells undergo through disturbed thermal conditions than the thermal conditions for their survivability, this leads to more volume of cell death. Freeze-thaw cycle is more destructive if repetition is performed within temperature range of -20^{0}C to -30^{0}C. Intracellular ice formation is progressive in repeated cycles, which

causes tissue abrasion. Use of repeated freeze-thaw cycle is also beneficial in treatment of cancerous tumor [3, 24].

1.2.2 Monitoring cryosurgery

Improper monitoring of cryosurgical process may lead to either incomplete surgery or an additional undesired damage to healthy tissue. Therefore, for optimal destruction of diseased object, monitoring should be performed precisely and simultaneously extent of freezing should be evaluated. There are following ways of cryosurgery monitoring:-

1. Local Monitoring of Cryosurgery: -

Local monitoring techniques are based on thermometry and impedancemetry. In first case, thermocouples are inserted inside the tissue to be frozen for direct measurement of local temperature and in second case electrode needles are placed inside the target tissue to detect freezing-induced changes in local impedance. While thermometry and impedancemetry have a valuable contribution to cryosurgery, they also have some major drawbacks. Both are invasive and have localized thermal information (only for inserted site) [2]. Therefore, lack of detailed knowledge may forward to fault result.

2. Imaging Monitoring Technique: -

In cryosurgery, ultrasound was the first imaging technique used in clinical cryosurgery because it was easier to use and economical. Several techniques are available for acoustic imaging of the body. A short pulse of electrical energy is converted into a burst of acoustic energy with a piezoelectric transducer. The pressure wave that is produced propagates through the body. When the pressure pulse encounters the boundary between regions with different acoustic impedance, part of the wave is reflected back to the transducer where it is converted back to an electrical impulse. The piezoelectric transducer functions both as an emitter and a detector. In whole-body imaging it is assumed that the velocity of the acoustic wave is approximately 1450 m/s. When pressure waves return to the piezoelectric element, the measured time of flight of these waves can be combined with knowledge of the tissue wave speed to determine the location of the acoustic impedance discontinuity. Two-dimensional images of acoustic discontinuities in tissue can be produced using multiple piezoelectric elements and computer analysis of the data. The

accuracy of ultrasound images is limited by the assumption of the wave velocity in tissue. Freezing interfaces can be conveniently monitored with conventional ultrasound because there is a large difference in acoustic impedance between ice and water. Ice essentially reflects all the acoustic energy, therefore entire freezing area looks dark. Ultrasound can only capture the image of the freezing interface in front of transducer, this is the problem associated with ultrasound. Magnetic resonance imaging (MRI) produces an image of the body organ by applying an alternating magnetic field. It produces an image of proton density, which closely relates to tissue structures. MRI produces a precise three-dimensional image of freezing interface; therefore it can be used to calculate the temperature distribution in the frozen region. MRI has solved the problem encountered by ultrasound as it is able to produce real-time three-dimensional image of frozen tissue without acoustic shadowing. However, high cost and special surgical environment may limit its usage.

Another imaging technique is optical monitoring; it overcomes the problem of ultrasound and is also less expensive. It employs two methods: one uses the time of flight of a proton through the tissue, and other is based on scattering characteristics of the tissue. In both the methods, light is emitted on one tissue-surface and detected on other. Tomography is then used to reconstruct the image from the optical properties of the tissue. Sufficient optical contrast should exist to capture the frequent changes in tissue while freezing.

Electrical impedance tomography (EIT) is another new technique that may provide an inexpensive and flexible supplement to existing cryosurgical monitoring techniques. Injecting small sinusoidal electrical currents into the body and measuring the resulting voltages through an electrode array produces a typical EIT image. An impedance image of the tissue is then produced from the voltage data using a reconstruction algorithm [2].

3. Mathematical models: - Above imaging techniques only monitor the outer freezing front and those are not able to provide thermal information inside the frozen tissue. Then mathematical models came into existence to predict the thermal history within the target object and the extent of freezing. Based on bio-heat equation, heat transfer model has been developed to describe cryosurgical process numerically. Many scientists have imposed mathematical techniques to evaluate and optimize the cryosurgical planning. It can be used by surgeons in real-time

cryosurgery. However, to make it more effective there is need for the inclusion of advanced mathematical techniques [2].

1.2.3 Advantages of cryosurgery over other surgical treatment

1. Minimal invasion of tissue
2. Less bleeding
3. Local application
4. Less time taking
5. Anesthetic capabilities
6. Repetition of procedure
7. Minimal hospitalization
8. Less expensive

1.2.4 Analysis of Experimental and Numerical Study

Historical review of cryosurgery and involvement of advanced techniques in its development are presented by Rubinsky [2]. Major concern was on mechanism (both biophysical and biochemical) of tissue destruction during cryosurgery and monitoring technology. Baust et al. [1] discussed the minimal invasiveness of cryosurgery and mechanisms of cryodestruction. The focus was on advanced technologies associated with cryosurgical instruments, monitoring techniques and clinical applications. A large volume of research efforts have been conducted in cryosurgery to improve its efficacy and to promote the applications. Popken et al. [13] experimentally studied thermal response of pig liver, human liver, and human colorectal cancer liver metastases using cryoprobes of 3 mm and 8 mm diameters, and compared the size of ice-balls produced by those cryoprobes. The ice-ball diameters and the temperatures at different distances from the cryoprobe were measured. There was no significant difference in ice-ball size in the different tissues. The diameter of frozen region enclosed by -40°C temperature or less was noticed approximately 44 mm using 8-mm cryoprobe in porcine liver and between 27-31 mm using 3-mm cryoprobe in the different tissues. The results suggested various cryoprobe's placement configurations which may help in pre-planning of the cryosurgical treatment of liver metastases. From the review of experimental studies it is analyzed that experimental results were not sufficient to determine exact lethal cell volume, temperature distribution throughout the

tumor, effect of moving ice-fronts etc. These factors have a vital role to optimize cryosurgery protocol in operating room. Thus, to study the phase change phenomena and heat transfer process inside an ice-ball numerical methods have become an important tool.

In cryosurgery, it is important to control the cooling/thawing rate over some critical range of temperatures in order to regulate the spatial extent of injury during freezing. An analytical model has been developed by Chua et al. [11] to study the temperature profiles within a liver tumor undergoing freeze-thaw cycle. The simulation algorithm was based on solving the transient bio-heat equation using the finite volume scheme for a single or multiple-probe geometry. The calibrated model has been employed to study the effects of different freezing rates, freeze–thaw cycle(s), and multi-probe freezing on cell damage in a liver tumor. Results from the model show the potential of freeze-thaw cycles to enhance cell destruction within the cancerous tissue. The proposed model also helps in preserving surrounding healthy tissue. In another study, they devised a simulation algorithm to provide essential information for estimating the extent of freezing during cryosurgery [12]. The validation of the bio-heat model with in-vitro experimental data derived from an experimental setup showed a good agreement of up to 6.8%. Deng et al. [29] presented a new tumor ablation technique based on immediate freezing followed by a rapid and strong enough heating. Three-dimensional phase-change problems (combining both freezing and heating) have been solved using an algorithm based on heat capacity method. They tried to solve the problems encountered during cryosurgery which include complexity due to irregular shape of the frozen region, propagation of ice-fronts, and temperature distribution within ice-balls. A numerical algorithm based on the dual reciprocity boundary element method (DRBEM) was developed to solve multidimensional phase change problem in biological tissues subjected to cryosurgery [26]. In addition to this, they proposed a method for controlling the extent of freezing by percutaneously injecting some solutions with particular thermal properties into the target tissues [27]. A new numerical algorithm was developed to solve multidimensional freezing problem of biological tissues injected in situ with functional solutions. Two specific cases were investigated: the injection of solutions with high thermal conductivity; the injection of solutions with low latent heat. It was found that the injection of such solutions enhances the freezing effect and controls the direction of growth of ice-ball. They pointed out the effect of large blood vessels in biological tissue which resulted in non-uniform temperature distribution during cryosurgery treatment [28]. The thermal model combines the Pennes bio-heat transfer equation describing

perfused tissues and the energy equation for single or countercurrent large blood vessels with a constant Nusselt number. A finite-difference algorithm was used to model the complex heat transfer process with phase change in biological tissues embedded with large blood vessels. The results suggested that careful treatment planning is necessary to operate the tumor close to or with large blood vessels transmitting through it. Later, the thermal effects of large blood vessels during cryosurgery were experimentally investigated with the use of infrared tomography [14]. The experimental results suggested that the heat source effect of large blood vessels may result in improper freezing power and then contribute to failed-killing of tumor during cryosurgery. Zhao at el. [15] also characterized the effect of thermally significant blood vessels (TSBV) on heat transfer inside the tissues during cryosurgery. The tissues were treated as non-ideal materials with temperature dependent thermophysical properties regarding the effects of blood perfusion and metabolic heat generation in the unfrozen region. It was found that the thermally significant blood vessel had much influence on the temperature distributions inside the normal and the tumor tissues; and isotherms reshaped differently from the case in the absence of blood vessel. Fortin et al. [10] numerically studied phase change process during cryosurgery. They predicted the freezing front's positions and the thermal effect experienced within ice-ball. A three-dimensional mesh was reconstructed at each time step to match at exact moving ice-fronts. Stefan condition was imposed on moving frozen interfaces to predict the time-evolving position of freezing front; at the same time, the temperature is computed everywhere in the computational domain giving access to the complete thermal history. The numerical results were matched with in-vivo experimental data of porcine cryosurgery. An experiment of approximately 1 minute freezing followed by a passive thaw was performed on rat prostate tumor by placing cryoprobe of nearly 1 mm diameter [30]. Thermal information obtained from this experiment was used to investigate the validity of two models based on freezing and thawing behaviours within the ice-ball. The first model was a two-dimensional transient axisymmetric numerical solution using an enthalpy method and incorporating heating due to blood flow. The second model was a one-dimensional radial steady state analytical solution without blood flow. It has been analyzed that two-dimensional model sufficiently captured the freezing and thawing parameters recorded by the thermocouples which were used to estimate the thermal history throughout the ice-ball.

A multi-cryo-needle surgery was performed on gel considering it as a tissue-simulating medium and three-dimensional numerical model has been developed by Magalov et al. [18]. It was

observed that it took only first few minutes of operation to form lethal ice volume enclosed by -40^0C isotherm. The new term "ablation ratio" was included which is percentage of volume enclosed by certain temperature to the volume of total frozen region. The result showed that for one, two and three cryo-needles, ablation ratio attained 3%, 3-6%, and 3-8% respectively after 30 minutes of application. Using high pressure argon gas as a cryogen, an experiment was conducted on gel and the phase change problem on gel was numerically solved by ANSYS7.0 software, based on enthalpy method by Magalov et al. [8]. They found that cylindrical structure of cryoprobe was effective for ice fronts growth in upward and radial directions. The analysis provided essential information regarding various probes placements and insertion depths in target tissue which is helpful in pre-planning of cryosurgical procedures. Yang et al. [17] devised finite element method for simulating both thermal and mechanical aspects of a multiprobe prostate cryosurgery. The quantitative and graphical results can help to plan cryosurgical protocols. Fixed grid finite element based enthalpy formulation was used by Bhattacharya et al. [19] for computing phase change related problems. Rewcastle et al. [16] introduced finite difference method to track ice ball formation using an axisymmetric model around a single cryoprobe. To develop computerized planning tools for cryosurgery, Rossi et al. [31] developed an efficient numerical technique for bio-heat transfer simulations using finite difference scheme. The goal was to develop computerized tool which takes 3D construction of a target region and to generalize best cryoprobe placement configuration. In another computerized study, they focused on insertion depth of cryoprobe in prostate cryosurgery [9]. Investigations performed in order to judge the benefit of active length of cryoprobe by comparing the results of variable insertion depth planning with uniform insertion depth planning. The result stated that variable insertion depth is effective in case of more number of cryoprobes.

For optimizing the cryosurgery protocol in real-time application, this research has concerned on computer runtime, thermal history within ice-ball and position's of ice-fronts propagation. The aim of current study is to devise an efficient numerical method for simulating the phase change phenomena and heat transfer process during cryosurgery to determine the exact volume of cell death. The main emphasis is on minimum computational time to mimic cryosurgery process. The numerical method thus developed can be used in planning of a real time cryosurgery treatment. Also, some new features have been brought out in connection with the effect of cryoprobe size

on thermal history inside the ice ball. It is hoped that results presented in this paper can assist clinical practitioners in dealing with the limitations of cryosurgery.

CHAPTER 2

MATHEMATICAL FORMULATION

Cryosurgery process can be accomplished using system as represented in figure 2; a cryoprobe is inserted inside diseased body part (for an example kidney) and simultaneously the process is monitored with the help of imaging device. The cryoprocedure starts by turning the cryoprobe on to initiate the freezing process; an ice-ball forms surrounding the closed end of cryoprobe which is in contact with tissue which causes them to die. The current study focused on heat transfer modelling during freezing of a biological tissue in order to determine internal thermal history within ice-ball, propagation of ice front's positions and the extent of ice volume. In this context, the gelatin solution (1.4%) in a cylindrical perspex phantom is considered as the tissue-simulating medium. Because of the axisymmetry of the problem, we have considered only right half of the cross-section.

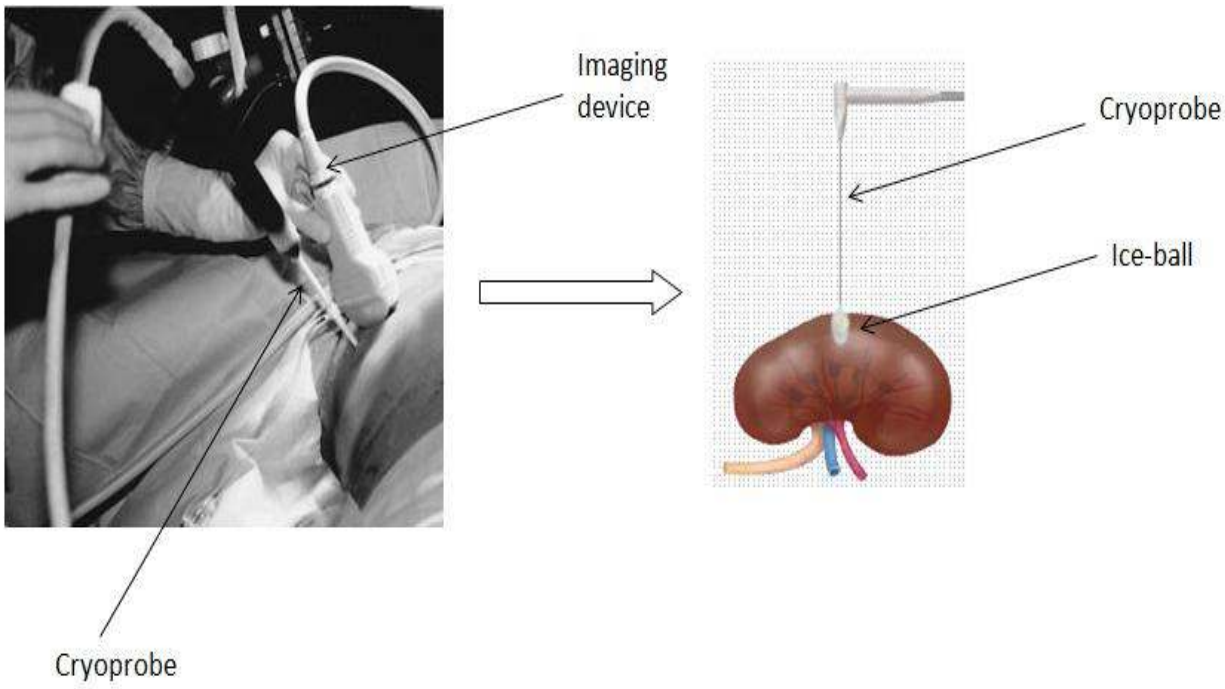


Figure 2: Cryosurgery Process

2.1 Model Description

The schematic diagram of cryoprobe setup is shown in figure 3. The geometrical configurations of domain are: domain radius L_{dw}, domain length L_{dh} and cryoprobe radius r_p and length L_p. Because of the axisymmetrical nature of the problem only right cross-section is considered for the simulation. The domain size is taken as $100mm \times 60mm$. The insertion depth of the cryoprobe is $L_p = 66mm$; the lower half is insulated while remaining exposed half is provided extreme cold condition. The temperature of the exposed part is a function of temperature and space. The detailed temperature profile for exposed half can be found in Rewcastle et al. [16] . The gelatin solution is initially refrigerated to a temperature of $T_i = 1.5^0C$.

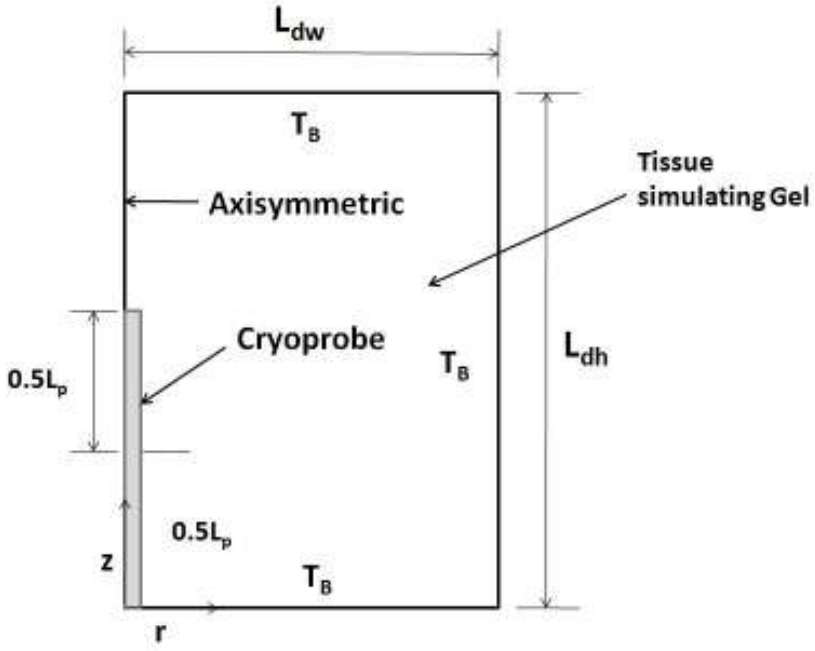


Figure 3: Schematic diagram of cryoprobe setup

2.2 Bio-Heat Equation

Heat is defined as flow of energy from one physical entity to another physical entity, when entities are at different temperatures. It transfers from higher temperature system to lower temperature system. The transfer process proceeds towards thermal equilibrium.

Several heat transfer mechanisms occur during cryosurgery, including conduction, convection, metabolism and phase change.

1. Conduction:

Conduction is heat transfer by means of molecular agitation within a material without any motion of the material as a whole. The heat conduction is governed by Fourier's Law, which states that the time rate of heat transfer through a material is proportional to the negative gradient in the temperature and to the area, at right angles to that gradient, through which the heat is flowing.

For one-dimensional heat conduction in x-direction-

$$q_x = -k \frac{\partial T}{\partial x}$$

where q_x is heat flux in x-direction

k thermal conductivity

T temperature

2. Convection:

Convection is the transfer of heat from one place to another by the movement of fluids. This motion is due to collective movement or aggregation of large numbers of molecules. Free or natural convection results from the density variations due to variations of temperature in the fluid.

Heat transfer by conduction has been assumed to be the primary heat transfer process during cryosurgery since the cryoprobe operates at an extremely low temperature. Bio-heat transfer is the study of heat transfer in biological system. The fundamental heat transfer equation in biological tissue was firstly suggested by Pennes.

Pennes suggested that the rate of heat transfer between blood and tissue is proportional to the product of the volumetric perfusion rate and the difference between the arterial blood temperature and the local tissue temperature [21, 22]. He expressed that relationship as follows

$$h_b = V\rho_b c_b(1-K)(T_a - T)$$

where

h_b is the rate of heat transfer per unit volume of tissue,

V is the perfusion rate per unit volume of tissue,

ρ_b is the density of blood,

c_b is the specific heat of blood,

K is a factor that accounts for incomplete thermal equilibrium between blood and tissue ($0 \leq K \leq 1$, for some cases $K = 0$)

T_a is the temperature of arterial blood, and

T is the local tissue temperature.

In this study we have used following form Pennes bio-heat equation:

$$\frac{\partial(\rho H)}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(kr\frac{\partial T}{\partial r}\right) + \frac{\partial}{\partial z}\left(k\frac{\partial T}{\partial z}\right) + \dot{m}_b c_b (T_b - T) + \dot{q}_{met}$$

Where

ρ is density of the tissue

H is total enthalpy

c_b is specific heat capacity of the blood

T_b is temperature of the blood

T is temperature of the tissue

$\dot{q}_{met}$ is metabolic rate

$\dot{m}_b$ is blood perfusion rate

t is time

r is radial co-ordinate

z is axial co-ordinate

2.3 Boundary and Initial Conditions

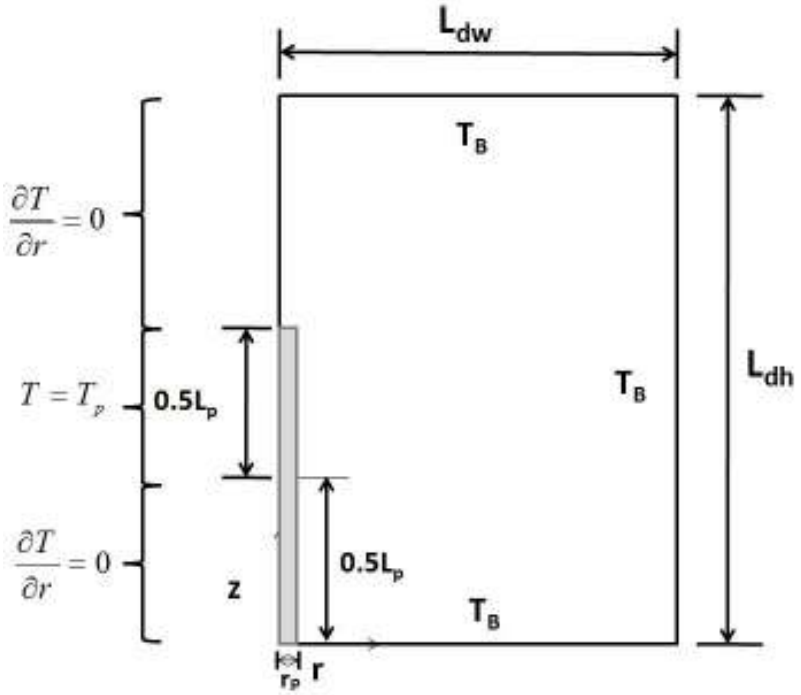


Figure 4: Geometrical Model of cryoprobe setup with boundary conditions

For the above described model, following boundary conditions are imposed:

$$r = r_p, 0 \le z < 0.5L_p, \frac{\partial T}{\partial r} = 0$$

$$r = r_p, 0.5L_p \le z < L_p, T = T_p$$

$$r = 0, L_p \le z < L_{dh}, \frac{\partial T}{\partial r} = 0$$

$$r_p \le r \le L_{dw}, z = 0, T = T_B$$

$$0 \le r \le L_{dw}, z = L_{dh}, T = T_B$$

$$r = L_{dw}, 0 \le z \le L_{dh}, T = T_B$$

In the above conditions, T_B is the domain boundary temperature which is kept fixed at 1.5^0C throughout the simulation. Initially the whole domain is kept at $T(\Omega, 0) = 1.5^0C$.

2.4 Solution Approach

The two-dimensional axisymmetrical Pennes equation has been discretized on a structured, multiblock grid system using finite volume approach. The finite volume method is a method for representing and evaluating partial differential equations in the form of algebraic equations. Finite volume refers to the small volume surrounding each node point on a mesh and in this method values are calculated at discrete places on a meshed geometry.

The grid with three blocks used for this simulation is shown in figure 5. The diffusive term and the unsteady term are discretized using central difference scheme and implicit three time level method (a quadratic backward approximation) respectively giving second order accuracy in space and time. A typical computational time for a simulation run is 40s on a personal computer (Pentium IV processor).

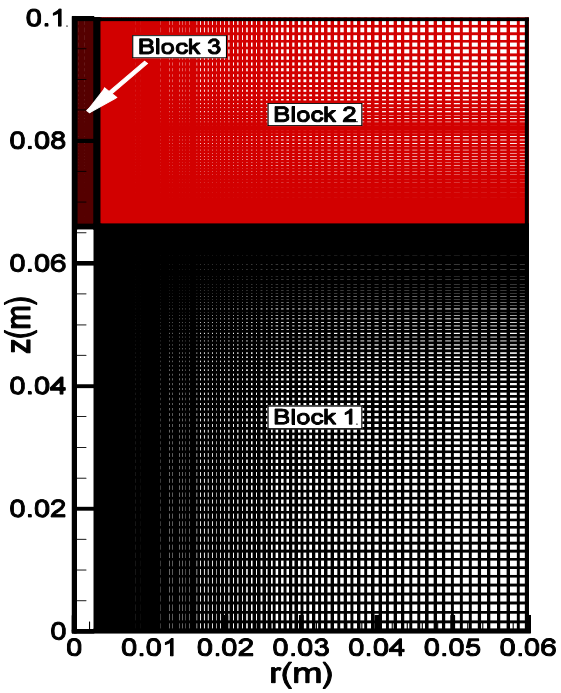


Figure 5: A typical multiblock structured grid

2.5 Code Validation

The present numerical code is validated against the published experimental result of Rewcastle et al. [16]. In the experiments, the temperature was recorded at 4 thermocouples placed at 10mm from the axis of the probe. Figure 6 shows a comparison between the computed temperatures, at the three thermocouples having coordinates (10mm,36mm), (10mm,46mm) and (10mm,56mm), and the experimental temperatures. The numerical results agree quite well with the experimental results.

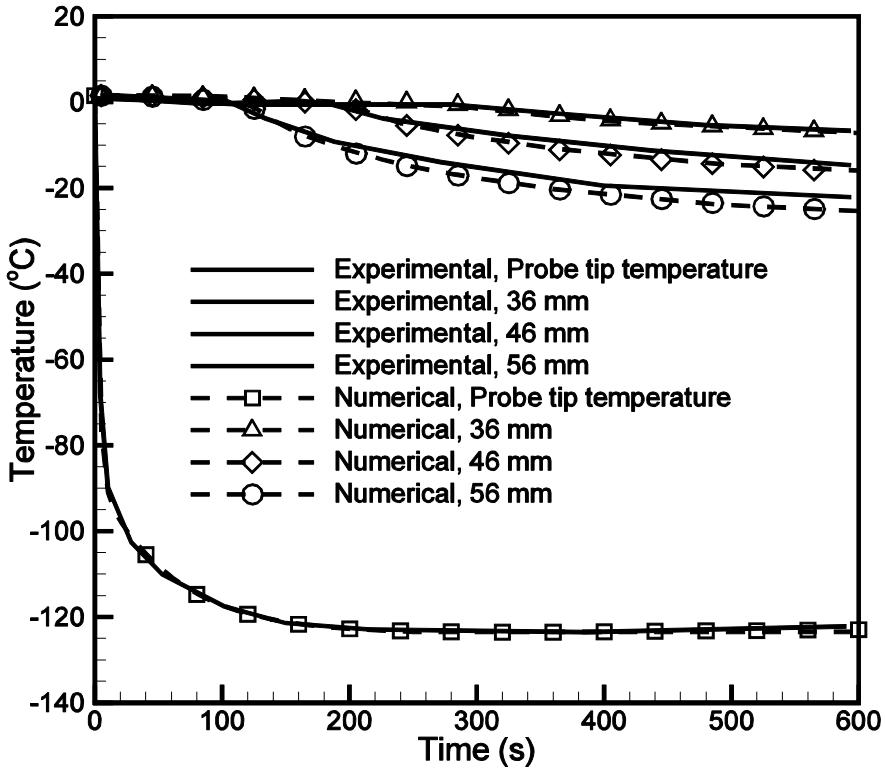


Figure 6: Validation of present numerical code

CHAPTER 3

RESULTS AND DISCUSSION

The gelatin solution (1.4%) in a cylindrical perspex phantom is considered as the tissue-simulating medium. The thermal properties of which are given in Table 2. It should be noted here that the blood perfusion term and the metabolic term appearing in equation (3) are neglected for numerical simulations while considering gel as a tissue simulating medium. A two-dimensional axisymmetrical methodology is applied to prescribed grid geometry. Numerical results have obtained for cryoprobe radii of 1mm, 2mm and 3mm. Cancerous cell destruction occurs due to extracellular ice formation (between temperatures of -4^{0}C to -21^{0}C) and intracellular ice formation (temperature less than -40^{0}C) [11]. To assess the effect of cryoprobe radius on the thermal history inside the solution, isothermal volume contours, propagation of freezing front (0^{0}C) and two other sub-cooled fronts (-20^{0}C and -40^{0}C) with time and variation of ice volume with time are numerically obtained for a single freeze-cycle of 600s.

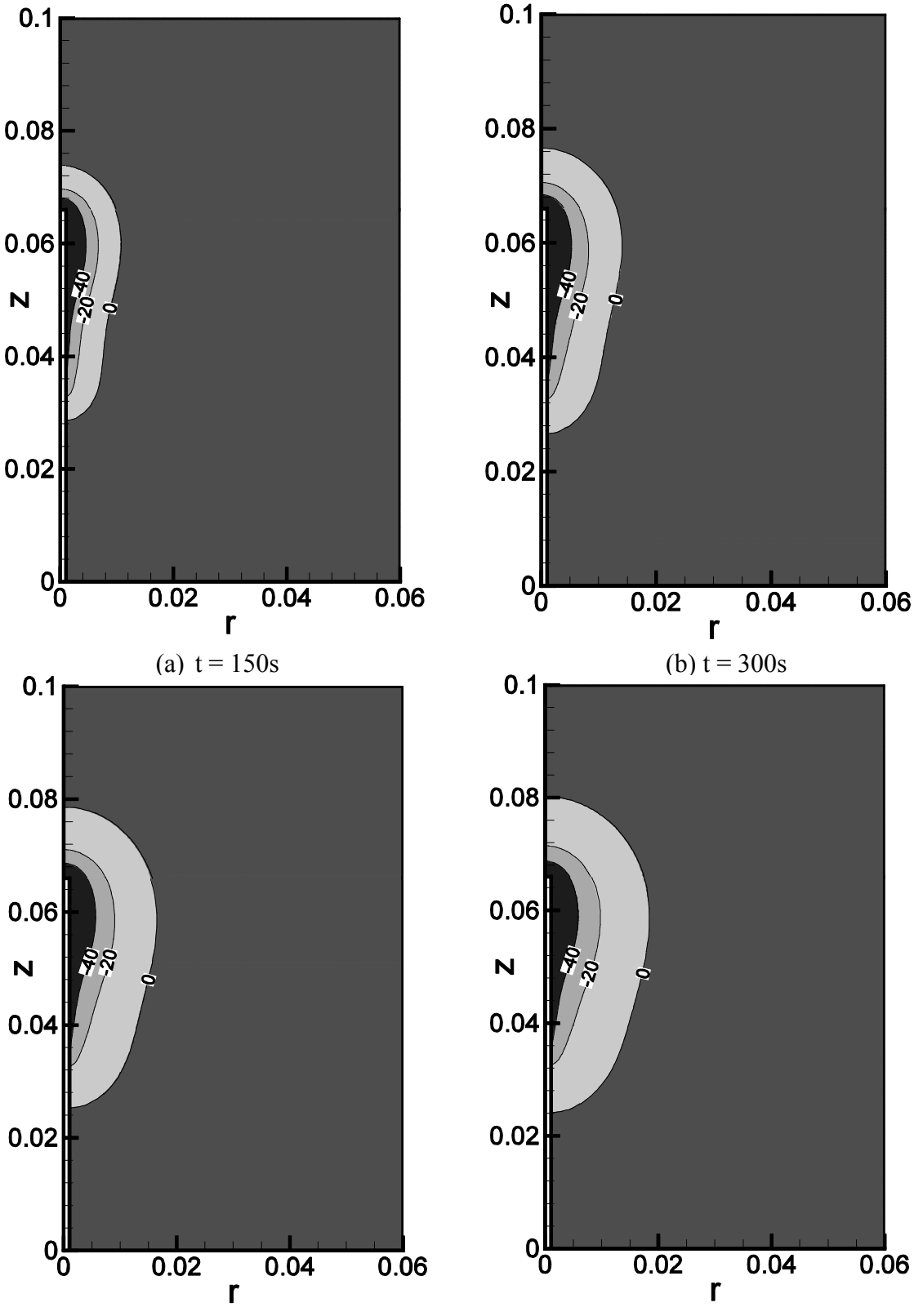
Table 2

Thermal properties from Rewcastle et al. [16]

$\rho c_f = 1.95 \times 10^6$	$J/(kg°\text{C})$
$\rho c_u = 4.186 \times 10^6$	$J/(kg°\text{C})$
$k_f = 2.22$	$W/(m°\text{C})$
$k_u = 0.603$	$W/(m°\text{C})$
$\rho_u \lambda = 3.33 \times 10^8$	J/m^3
$T_f = -4$	°C
$T_u = 0$	°C

3.1 Isothermal Contours for Different Cryoprobe radii

Figures 7, 8 and 9 show the isothermal contours of 0^{0}C, -20^{0}C and -40^{0}C at four different time instances (150s, 300s, 450s and 600s) during freeze-cycle for cryoprobe radius of 1mm, 2mm and 3mm respectively. This information is important to determine the regions of total cell destruction. For all the cases, it is found that the formation of ice (volume enclosed by 0^{0}C temperature contour) is faster than the formation of other two sub-cooled ice (volume occupied by -20^{0}C and -40^{0}C temperature contours). Heat transfer surface area increases with increase in the cryoprobe radius. Therefore, ice formation increases with increase in the cryoprobe radius (figure 8, 9).



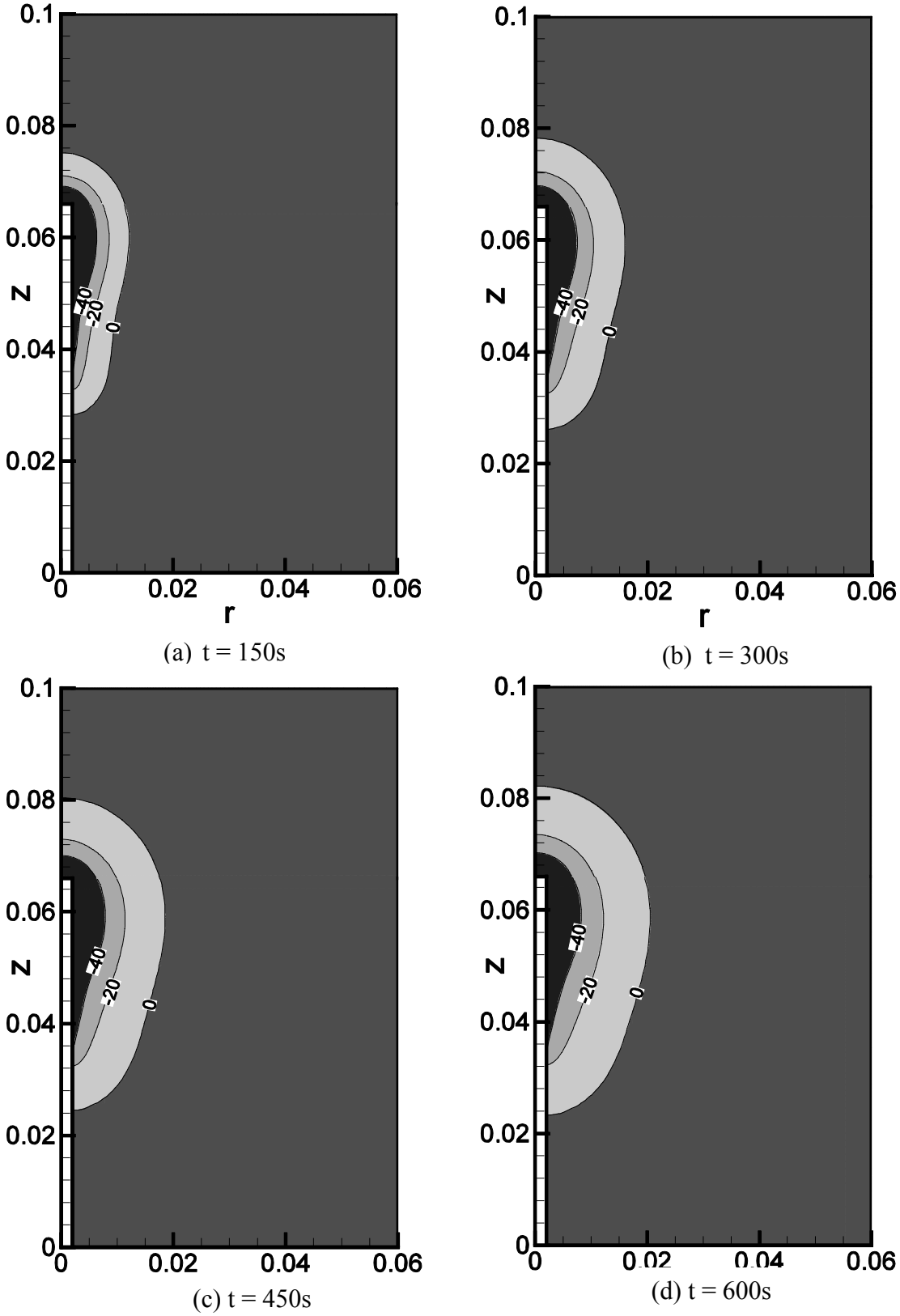
(a) t = 150s

(b) t = 300s

(c) t = 450s

(d) t = 600s

Figure 7: Isothermal Contours of 0^0C, -20^0C and -40^0C for 1mm cryoprobe radius



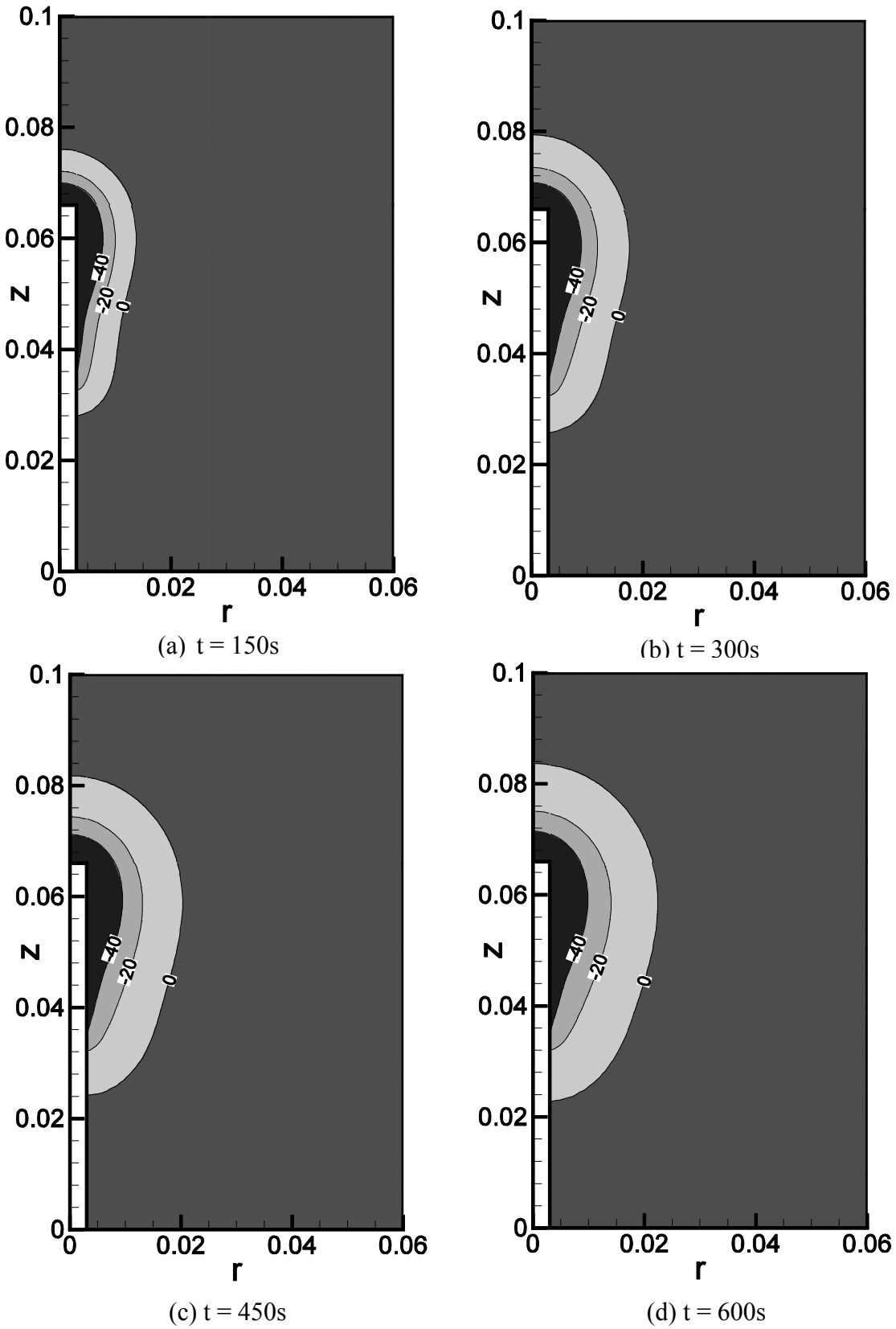
(a) t = 150s

(b) t = 300s

(c) t = 450s

(d) t = 600s

Figure 8: Isothermal Contours of 0^0C, -20^0C and -40^0C for 2mm cryoprobe radius



(a) t = 150s (b) t = 300s

(c) t = 450s (d) t = 600s

Figure 9: Isothermal Contours of 0^0C, -20^0C and -40^0C for 3mm cryoprobe radius

3.2 Evolution of Ice volume and Ice-front's Positions

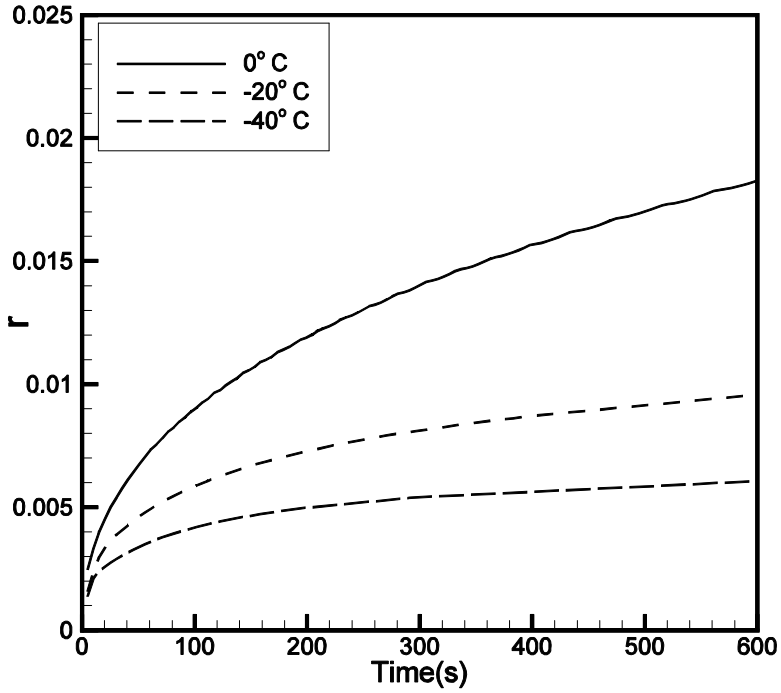


Figure 10(a) Positions of ice-fronts for Cryoprobe radius of 1mm

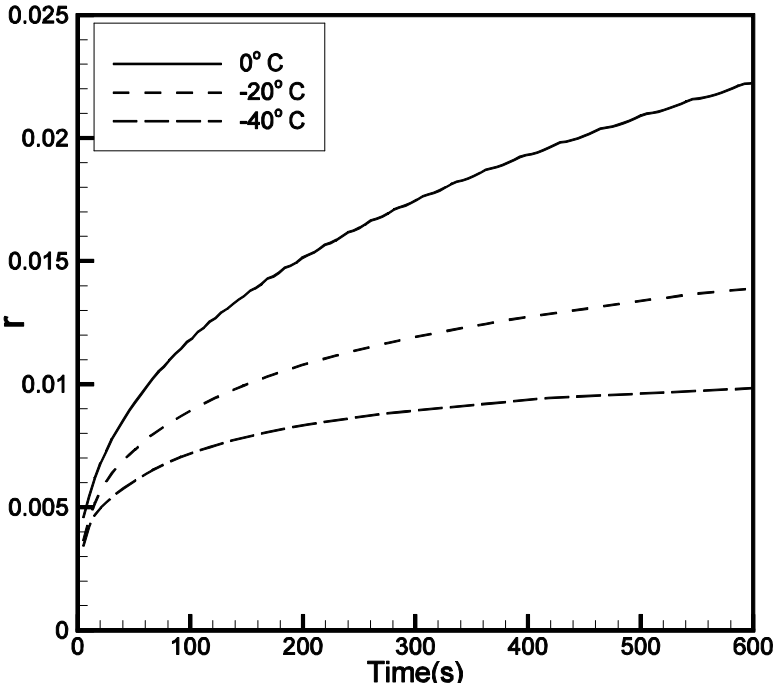


Figure 10(b) Positions of ice-fronts for cryoprobe of radius 2mm

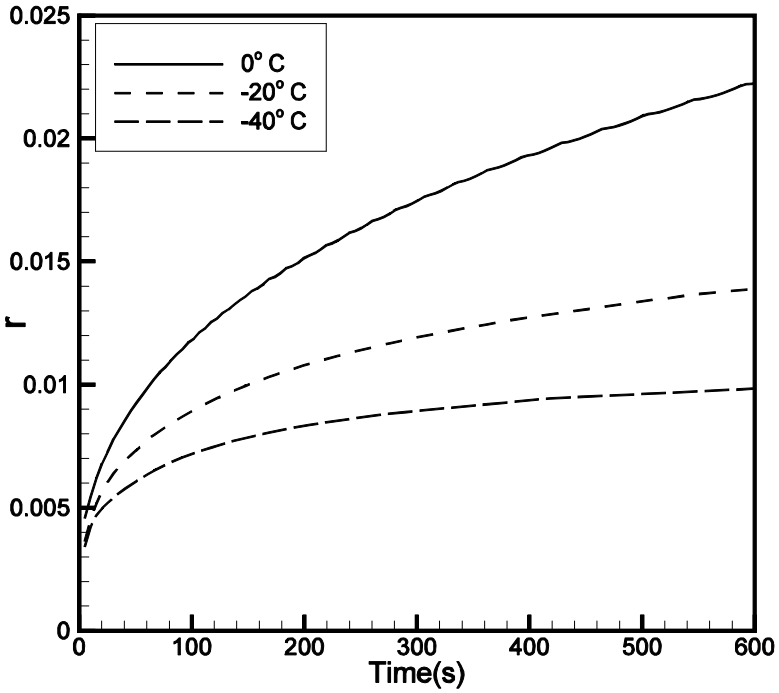


Figure 10(c) Positions of ice-fronts for cryoprobe of radius 3mm

Figure 10 shows the different front positions at an axial distance of 60mm from the origin of the domain (i.e., bottom-left corner of the domain) for a freeze-cycle of 10min. The propagation of freezing front (0^0C) and sub-cooled fronts (-20^0C and -40^0C) positions for a cryoprobe radius of 1mm, 2mm is shown in figure 10(a), figure 10(b) while figure 10(c) corresponds to a cryoprobe radius of 3mm.

It can be noticed that throughout the freeze-cycle location of freezing front is always ahead of the other two sub-cooled front's positions. Also, the rate of freezing front propagation is more at the beginning of the freeze-cycle while it attains a fixed value at the end as reflected in figure 10. The remaining two fronts show different patterns: at the beginning, the rate of front propagation is more while it is almost zero at the end of the freeze cycle.

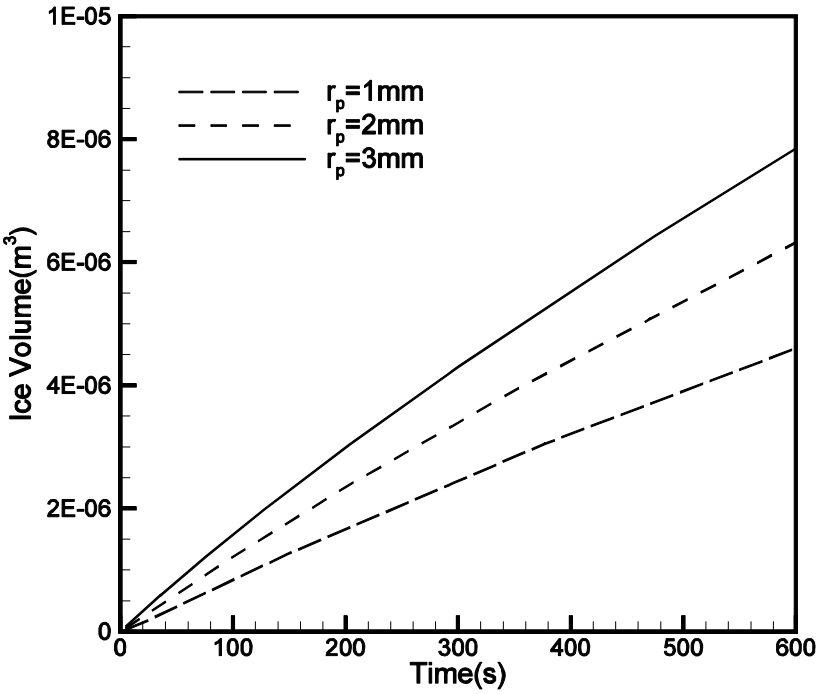


Figure 11: variation of ice-volume with time

Figure 11 represents the variation of ice volume with time for cryoprobe radii of 1mm, 2mm and 3mm. It is found that ice volume increases almost linearly with increase in cryoprobe size at any instant of freeze-cycle. It is also interesting to observe that the variation of ice volume is almost linear with time.

3.3 Conclusion

A new numerical approach has been devised to predict the temperature contours and freezing front positions inside the ice ball. It has been shown that the developed two-dimensional axisymmetric model is capable of solving a phase change problem in a complex geometry within 40s on a Pentium IV personal computer. The complex geometry is easily subdivided into small sub domains using multiblock structured grid which resulted in less computational time. Use of larger radius cryoprobe increases the surface area of heat transfer with the surrounding and consequently, there is an increase in lethal volume (volume below -40^0C temperature contour) inside the ice ball. Also, it has been found that ice volume increases almost linearly with increase in cryoprobe radius as well as with increase in time. The developed approach can be applied in

cryosurgical protocol for decision making in real time application. To make it applicable to cryosurgery, still some improvements are required (i.e., incorporation of blood perfusion rate in the numerical model).

References

1. J. Baust, A. A. Gage, H. Ma and C. M. Zhang, Minimally invasive Cryosurgery-Technological Advances, *Cryobiology* 34 (1997), pp. 373-384.

2. B. Rubinsky, Cryosurgery, *Annu. Rev. Biomed. Eng*. 2 (2000), pp. 157-187.

3. A. Gage, J. Baust, Mechanisms of tissue injury in cryosurgery, *Cryobiology* 37(3) (1998), pp. 171-186.

4. W. Cahan, Cryosurgery of the uterus: description of techniques and potential applications, *Am. J Obstel. Gynecol* 88 (1964), pp.410-414.

5. R. W. Rand, A. M. Dashe, D. E. Paglia, L. W. Conway, D. H. Solomon, Stereotactic Cryo-hypophysectomy, *JAMA* 189 (1964), pp.255-259.

6. R. Marcove, T Miller, The treatment of primary and metastatic bone tumors by cryosurgery, *Surg Clin N Am* 49 (1969), pp.421-430.

7. D Torre, Cutaneous Cryosurgery, *NY State J Med* 70 (1970), pp.2551-2554.

8. Z. Magalov, A. Shitzer, D. Degani, Experimental and numerical study of one, two and three embedded needle cryo-probes simultaneously operated by high pressure argon gas, *ASME J. Heat Transfer* 130 (2008), pp. (032301-1--032301-12).

9. M. R. Rossi, D. Tanaka, K. Shimada, Y. Rabin, Computerized Planning of Prostate Cryosurgery using variable Cryoprobe Insertion Depth, *Cryobiology* 60 (2010), pp. 71–79.

10. A. Fortin, Y. Belhamadia, Numerical prediction of freezing fronts in cryosurgery: Comparison with experimental results, *Computer Methods in Biomechanics and Biomedical Engineering* 13(3) (2010), pp. 241-249.

11. K. J. Chua, S. K. Chou, J. C. Ho, An analytical study on the thermal effects of cryosurgery on selective cell destruction, *Journal of Biomechanics* 40 (2007), pp. 100–116.

12. K. J. Chua, S. K. Chou, On the study of the freeze-thaw thermal process of a biological system, *Applied Thermal Engineering*, 29 (2009), pp. 3696-3709.

13. F. Popken, J. K. Seifert, R. Engelmann, P. Dutkowski, F. Nassir, and T. Junginger, Comparison of Iceball Diameter and Temperature Distribution Achieved with 3-mm Accuprobe Cryoprobes in Porcine and Human Liver Tissue and Human Colorectal Liver Metastases in Vitro, *Cryobiology* 40 (2000), pp. 302-310.

14. Z. S. Deng , J. Liu , H. W. Wang, Disclosure of the significant thermal effects of large blood vessels during cryosurgery through infrared temperature mapping, *International Journal of Thermal Sciences* 47 (2008) pp. 530-545.

15. G. Zhao, Q. F. Yu, Z. F. Liu, Cryogenic Heat Transfer inside the Tissues with Thermally Significant Blood Vessels during Cryosurgery, *2nd International Conference on Bioinformatics and Biomedical Engineering* (ICBBE) (2008), pp. 1690-1693.

16. J. C. Rewcastle, G. A. Sandison, L. J. Hahn, J. C. Saliken, J. G. McKinnon, B. J. Donnelley, A model for the time-dependent thermal distribution within an ice ball surrounding a cryoprobe, *Phys. Med. Biol.* 43 (1998), pp. 3519–3534.

17. B. Yang , R. G. Wan, K. B. Muldrew, B. J. Donnelly, A finite element model for cryosurgery with coupled phase change and thermal stress aspects, *Finite Elements in Analysis and Design* 44 (2008), pp. 288-297.

18. Z. Magalov, A. Shitzer, D. Degani, Isothermal volume contours generated in a freezing gel by embedded cryo-needles with applications to cryo-surgery, *Cryobiology* 55 (2007), pp. 127-137.

19. M. Bhattacharya, T. Basak, K. G. Ayappa, A fixed- grid finite element based enthalpy formulation for generalized phase change problems: role of superficial mushy region, *International Journal of Heat and Mass Transfer* 45 (2002), pp. 4881–4898.

20. Pennes, H. H. Analysis of tissue and arterial blood temperature in the resting human forearm. *J. Appl. Physiol*. 1(1948), pp.93-122.

21. E. H. Wissler, Pennes' 1948 paper revisited, *J Appl Physiol* 85 (1998) pp. 35-41.

22. Mazur, P. Freezing of living cells: Mechanisms and implications. *Am. J. Physiol* 143 (1984)**,** pp. C125–C142.

23. Mazur, P. Physical-chemical factors underlying cell injury in cryosurgical freezing. *In* "Cryosurgery" (R. Rand, A. Rinfret, and H.von Leden, Eds.), Thomas, *Springfield IL*, (1968), pp. 32–51.

24. L.C.M. Keijser, Cryosurgery of bone tumors (2001).

25. Cooper, I. S. Cryobiology as viewed by the surgeon, *Cryobiology* 1 (1964), pp. 44–54.

26. Z. S. Deng, J. Liu, Modeling of multidimensional freezing problem during cryosurgery by the dual reciprocity boundary element method, *Engineering Analysis with Boundary Elements* 28 (2004), pp. 97–108.

27. Z. S. Deng, J. Liu, Numerical simulation of selective freezing of target biological tissues following injection of solutions with specific thermal properties, *Cryobiology* 50 (2005), pp. 183–192.

28. Z.S. Deng, J. Liu, Numerical study of the effects of large blood vessels on three-dimensional tissue temperature profiles during cryosurgery, *Numerical Heat Transfer Part A* 49, (2006) pp. 47–67.

29. Z.S. Deng, J. Liu, Numerical simulation of 3-d freezing and heating problems for combined cryosurgery and hyperthermia therapy, *Numerical Heat Transfer Part A: Applications* 46: 6 (2004), pp.587 – 611.

30. N. E. Hoffmann, J.C. Bishof, Cryosurgery of Normal and Tumor Tissue in the Dorsal Skin Flap Chamber: Part I-Thermal Response, *Journal of Biomechanical Engineering* vol.123 (2001), pp.301-309

31. M. R. Rossi, D. Tanaka, K. Shimada, Y. Rabin, An efficient numerical technique for bioheat simulations and its application to computerized cryosurgery planning, *Computer methods and programs in biomedicine* 85 (2007), pp.41–50.

32. M. L. Rivoire , E. J. Voiglio, P Kaemmerlen, G Molina, I Treilleux, J Finzy, E Delay, F Gory, Hepatic cryosurgery precision: evaluation of ultrasonography, thermometry, and impedancemetry in a pig model, *J Surg Oncol* April (1996), pp. 242-248.

33. J. J. Smith and J. Fraser, An estimation of tissue damage and thermal history in the cryolesion. *Cryobiology* 11 (1974), pp. 139–147.

34. J. Smith, J. Fraser, and MacIver, A. G. Ultrastructure after cryosurgery of rat liver. *Cryobiology* 15 (1978), pp. 426–432.

35. H. K. Versteeg and W. Malalasekera, An introduction to computational fluid dynamics, Longman Scientific and Technical (1995).