NUMERICAL AND EXPERIMENTAL STUDY OF BIOHEAT MODELS DURING CRYOSURGERY

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INDIAN INSTITUTE OF TECHNOLOGY DELHI
JULY 2026

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Numerical and Experimental Study of Bioheat Models during Cryosurgery

by

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Submitted

In fulfilment of the requirements of the degree of

Doctor of Philosophy

to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI
July, 2026

CERTIFICATE

This is to certify that the thesis entitled **"Numerical and Experimental Study of Bioheat Models during Cryosurgery"**, submitted by **Mr. Hitesh Kumar Gupta**, to the **Indian Institute of Technology Delhi**, for the award of the degree of **Doctor of Philosophy**, is a bona fide record of the research work carried out by him under our supervision and guidance. The contents of this thesis, in full or in part, have not been submitted to any other Institute or University for the award of any degree or diploma.

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ACKNOWLEDGEMENT

At the very outset, I bow in reverence to Maa Kamakhya and Golu Devata, whose divine blessings and spiritual strength guided me through every stage of this doctoral journey. Their grace provided resilience, clarity, and inner strength during moments of challenge and uncertainty.

I would like to express my deepest and most sincere gratitude to my supervisor, Dr. Debabrata Dasgupta, Professor, Department of Mechanical Engineering, Indian Institute of Technology Delhi, for his unwavering guidance, constant encouragement, and invaluable mentorship throughout the course of my doctoral research. His profound knowledge, intellectual clarity, and meticulous attention to detail have been a continuous source of inspiration for me. I am immensely grateful for his patience, thoughtful insights, and invaluable suggestions, which have significantly strengthened both the technical depth and scientific rigor of this work. His trust in my abilities and his consistent motivation during challenging phases of the research journey have played a pivotal role in the successful completion of this thesis.

I would also like to convey my heartfelt gratitude to my esteemed co-supervisor, Prof. Prabal Talukdar, Professor, Department of Mechanical Engineering, IIT Delhi, for his constant support, valuable suggestions, and enriching technical discussions throughout my doctoral journey. His broad vision, analytical perspective, and deep understanding of thermal sciences have significantly enhanced the quality and direction of this research. I am especially grateful for his encouragement and motivating guidance at crucial stages of my PhD, which strengthened my confidence and inspired me to approach complex research challenges with clarity and determination. His positive outlook, insightful remarks, and belief in my work played a vital role in sustaining my enthusiasm and commitment during demanding phases of the study.

I sincerely acknowledge the members of my Doctoral Research Committee, Dr. Bahni Ray, Dr. Sangeeta Kohli, and Dr. Neetu Singh, for their valuable guidance, insightful suggestions, and academic inputs provided at various stages of my doctoral research. Their feedback greatly helped in refining the scope, methodology, and presentation of this thesis.

I am deeply grateful to the Oncology Department, AIIMS New Delhi, for kindly providing the DICOM imaging data that formed the foundation for the patient-specific tumour modelling presented in this research. Their support significantly enhanced the clinical relevance and practical applicability of this work.

I also acknowledge the support of the Department of Mechanical Engineering, IIT Delhi, for providing a stimulating research environment and access to the computational and experimental facilities essential for carrying out this work. I am thankful to the technical and laboratory staff for their assistance during experimental setup, instrumentation, and data acquisition.

I would like to thank my fellow research scholars and colleagues at IIT Delhi for their cooperation, insightful discussions, and encouragement, which made this research journey intellectually enriching and professionally rewarding.

Finally, I owe everything to my family for their unconditional support, patience, and unwavering belief in me throughout this long academic journey. Their constant encouragement and sacrifices have been the foundation upon which this work stands.

ABSTRACT

Cryosurgery is a clinically established, minimally invasive thermal therapy in which tumour destruction is achieved through controlled freezing and thawing. Despite its widespread clinical use, reliable cryosurgical planning remains challenging because cryogenic heat transfer in living tissue is governed by a complex interplay of heat conduction, phase change, and vascular heat transport. Conventional planning approaches continue to rely heavily on simplified bioheat formulations, empirical probe-placement heuristics, and visual assessment of ice-ball extent, which are insufficient for accurately predicting lethal thermal injury under realistic physiological conditions. The present thesis addresses these limitations by developing an integrated numerical–experimental framework that advances cryosurgical understanding and planning through physically rigorous bioheat modelling, thermal-field-guided multi-probe placement strategies, and systematic experimental investigation.

To establish a physically realistic foundation for cryosurgical simulation, a transient computational framework is developed to perform a systematic comparison between the classical Pennes bioheat equation and a Local Thermal Non-Equilibrium (LTNE) porous-media model under cryogenic freezing and rewarming conditions. The numerical model incorporates temperature-dependent thermal properties, phase change via an apparent heat-capacity formulation, and a time-dependent cryoprobe temperature boundary condition comprising cooling, low-temperature holding, rewarming, and final holding stages. Physiologically relevant microvascular parameters, including tissue porosity and blood velocity, are varied over wide ranges, and freezing performance is quantified using temperature histories, liquid-fraction evolution, lethal-isotherm morphology, and frozen damage volume. The LTNE framework predicts destruction volumes approximately 7–38% larger at low porosity ($\varepsilon = 0.005$), 55–80% larger at moderate porosity ($\varepsilon = 0.01$), and up to 120% larger at high porosity ($\varepsilon = 0.05$)than those obtained from the Pennes formulation. These results demonstrate that the equilibrium assumption inherent to the Pennes formulation is not valid during cryogenic cooling, particularly in moderately to highly vascularized tissue, and that the LTNE framework provides more physiologically realistic estimates of ice-front propagation and lethal-zone extent.

Building on this improved thermal modelling framework, the thesis next develops a thermal-field-guided cryoprobe placement strategy for multi-probe cryosurgery applied to patient-specific tumour geometry. Rather than relying on geometric rules or frozen-volume

overlap, probe number, spatial arrangement, and active length are determined using full three-dimensional temperature fields, lethal-isotherm continuity, and quantitative destruction metrics. For the patient-specific tumour of total volume $6114\ \mathrm{mm}^3$, the three-cryoprobe configuration with a 10 mm active cooling length achieved complete lethal-temperature coverage at probe-to-centre distances of 5–8 mm, whereas the corresponding two-cryoprobe configuration produced approximately 35–40% lower tumour destruction volume across the investigated distances. The analysis establishes that single-probe cryosurgery is inherently insufficient for clinically realistic tumour volumes, and that effective ablation is achieved primarily through thermal superposition in multi-probe configurations. The results further reveal a fundamental trade-off between maximising tumour destruction and limiting collateral freezing of surrounding healthy tissue, underscoring the need for balanced, physics-based planning rather than aggressive overcooling.

To complement and physically ground the numerical findings, controlled cryoablation experiments are conducted using agarose-based tissue-mimicking gel phantoms with systematically varied glycine concentration, probe number, and inter-probe spacing. Spatially resolved temperature–time histories obtained for single-, double-, and triple-probe configurations reveal clear evidence of probe–probe thermal interaction, including synergistic cooling, ice-ball coalescence, and spacing-dependent suppression of residual warm regions. In the single-cryoprobe experiments at the 5 mm radial location, the end temperature decreased from $-31.98°\mathrm{C}$ for the 1% w/v agarose phantom to $-43.31°\mathrm{C}$ for the 4% w/v glycine phantom, while the radial ice-ball diameter expanded from 27.9 mm to 32.2 mm, representing an increase of approximately 15%, and the longitudinal extent increased from 48.4 mm to 52.1 mm, representing an increase of approximately 7–8%. The experimental observations provide direct insight into multi-probe freezing dynamics and reinforce the physical mechanisms captured by advanced bioheat models, thereby strengthening confidence in thermal-field-guided cryosurgical planning.

Overall, this thesis advances cryosurgical treatment planning from heuristic and geometry-based practice toward a quantitative, physics-guided framework. By demonstrating the necessity of non-equilibrium bioheat modelling, developing thermal-field-guided multi-probe placement for patient-specific tumours, and experimentally characterising probe-interaction effects, the present work provides a robust foundation for accurate, physiologically realistic, and clinically relevant cryosurgical planning.

सार

क्रायोसर्जरी एक चिकित्सकीय रूप से स्थापित, न्यूनतम आक्रामक ऊष्मीय उपचार पद्धति है, जिसमें नियंत्रित हिमन एवं पिघलन के माध्यम से ट्यूमर का विनाश किया जाता है। इसके व्यापक नैदानिक उपयोग के बावजूद, विश्वसनीय क्रायोसर्जिकल उपचार-योजना अभी भी चुनौतीपूर्ण है क्योंकि जीवित ऊतकों में क्रायोजेनिक ऊष्मा स्थानांतरण ऊष्मा चालन, अवस्था परिवर्तन तथा रक्त-वाहिकीय ऊष्मा परिवहन के जटिल पारस्परिक प्रभावों द्वारा नियंत्रित होता है। वर्तमान उपचार-योजना पद्धतियाँ मुख्यतः सरलीकृत बायोहीट मॉडलों, अनुभवजन्य प्रोब-स्थापन नियमों तथा आइस-बॉल के दृश्य आकलन पर निर्भर करती हैं, जो यथार्थवादी शारीरिक परिस्थितियों में घातक ऊष्मीय क्षति का सटीक पूर्वानुमान करने के लिए पर्याप्त नहीं हैं। प्रस्तुत शोधप्रबंध इन सीमाओं को संबोधित करते हुए एक समेकित संख्यात्मक–प्रायोगिक रूपरेखा विकसित करता है, जो भौतिक रूप से सुदृढ़ बायोहीट मॉडलिंग, ऊष्मीय-क्षेत्र-निर्देशित बहु-प्रोब स्थापना रणनीतियों तथा व्यवस्थित प्रायोगिक अध्ययन के माध्यम से क्रायोसर्जरी की समझ और उपचार-योजना को उन्नत बनाता है।

क्रायोसर्जिकल सिमुलेशन के लिए एक भौतिक रूप से यथार्थवादी आधार स्थापित करने हेतु, इस शोध में क्रायोजेनिक हिमन एवं पुनःतापन परिस्थितियों के अंतर्गत पारंपरिक पेनेस बायोहीट समीकरण तथा लोकल थर्मल नॉन-इक्विलिब्रियम (LTNE) पोरस-मीडिया मॉडल के बीच एक व्यवस्थित तुलनात्मक अध्ययन करने के लिए एक क्षणिक संगणकीय रूपरेखा विकसित की गई है। संख्यात्मक मॉडल में तापमान-निर्भर ऊष्मीय गुण, प्रत्यक्ष ऊष्मा-धारिता सूत्रीकरण के माध्यम से अवस्था परिवर्तन तथा समय-निर्भर क्रायोप्रोब तापमान सीमा-शर्त सम्मिलित की गई है, जिसमें शीतन, निम्न-तापमान स्थिरावस्था, पुनःतापन तथा अंतिम स्थिरावस्था चरण शामिल हैं। ऊतक रंध्रता तथा रक्त वेग जैसे शारीरिक रूप से प्रासंगिक सूक्ष्म-रक्तवाहिकीय मापदंडों को विस्तृत सीमाओं में परिवर्तित किया गया है तथा हिमन प्रदर्शन का आकलन तापमान इतिहास, द्रव-अंश विकास, घातक समताप रेखा की आकृति तथा जमे हुए क्षति आयतन के माध्यम से किया गया है। LTNE रूपरेखा निम्न रंध्रता ($\varepsilon = 0.005$)पर पेनेस मॉडल की तुलना में लगभग 7–38% अधिक, मध्यम रंध्रता ($\varepsilon = 0.01$)पर 55–80% अधिक तथा उच्च रंध्रता ($\varepsilon = 0.05$)पर अधिकतम 120% अधिक विनाश आयतन का पूर्वानुमान करती है। ये परिणाम प्रदर्शित करते हैं कि क्रायोजेनिक शीतन के दौरान, विशेष रूप से मध्यम से उच्च रक्त-वाहिकीय ऊतकों में, पेनेस सूत्रीकरण में निहित ऊष्मीय संतुलन की धारणा मान्य नहीं है तथा LTNE रूपरेखा आइस-फ्रंट प्रसार एवं घातक क्षेत्र के विस्तार का अधिक शारीरिक रूप से यथार्थवादी पूर्वानुमान प्रदान करती है।

इस उन्नत ऊष्मीय मॉडलिंग रूपरेखा के आधार पर, शोधप्रबंध में रोगी-विशिष्ट ट्यूमर ज्यामिति के लिए बहु-प्रोब क्रायोसर्जरी हेतु एक ऊष्मीय-क्षेत्र-निर्देशित क्रायोप्रोब स्थापना रणनीति विकसित की गई है। ज्यामितीय नियमों अथवा जमे हुए आयतन के अतिव्यापन पर निर्भर रहने के स्थान पर, प्रोबों की संख्या, स्थानिक व्यवस्था तथा सक्रिय लंबाई का निर्धारण पूर्ण त्रि-आयामी तापमान क्षेत्रों, घातक समताप रेखा की निरंतरता तथा मात्रात्मक विनाश मानकों के आधार पर किया गया है। $6114\ \mathrm{mm}^3$के कुल आयतन वाले रोगी-विशिष्ट ट्यूमर के लिए, $10\ \mathrm{mm}$ सक्रिय शीतन लंबाई वाले तीन-क्रायोप्रोब विन्यास ने ट्यूमर केंद्र से $5–8\ \mathrm{mm}$ की दूरी पर पूर्ण घातक-तापमान कवरेज प्राप्त किया, जबकि संबंधित दो-क्रायोप्रोब विन्यास ने अध्ययन की गई सभी दूरियों पर लगभग $35–40\%$ कम ट्यूमर विनाश आयतन प्रदान किया। विश्लेषण से यह स्थापित होता है कि चिकित्सकीय रूप से यथार्थवादी ट्यूमर आयतनों के लिए एकल-प्रोब क्रायोसर्जरी स्वाभाविक रूप से अपर्याप्त है तथा प्रभावी एब्लेशन मुख्यतः बहु-प्रोब विन्यासों में ऊष्मीय सुपरपोज़िशन के माध्यम से प्राप्त होता है। परिणाम ट्यूमर विनाश को अधिकतम करने और आसपास के स्वस्थ ऊतकों में अनावश्यक हिमन को सीमित रखने के बीच एक मूलभूत संतुलन को भी दर्शाते हैं, जो आक्रामक अतिशीतन के बजाय संतुलित, भौतिकी-आधारित उपचार-योजना की आवश्यकता को रेखांकित करता है।

संख्यात्मक निष्कर्षों को पूरक एवं भौतिक रूप से सुदृढ़ करने हेतु, एगारोज-आधारित ऊतक-सदृश जेल फैंटम का उपयोग करते हुए नियंत्रित क्रायोएब्लेशन प्रयोग किए गए, जिनमें ग्लाइसिन सांद्रता, प्रोबों की संख्या तथा अंतर-प्रोब दूरी को व्यवस्थित रूप से परिवर्तित किया गया। एकल-, द्वि- तथा त्रि-प्रोब विन्यासों के लिए प्राप्त स्थानिक तापमान–समय इतिहास प्रोब–प्रोब ऊष्मीय अंतःक्रिया के स्पष्ट प्रमाण प्रदान करते हैं, जिनमें सहक्रियात्मक शीतन, आइस-बॉल का सहसंयोजन तथा दूरी-निर्भर अवशिष्ट ऊष्ण क्षेत्रों का दमन शामिल है। एकल-क्रायोप्रोब प्रयोगों में $5\ \mathrm{mm}$ की रेडियल स्थिति पर, $1\%\ \mathrm{w/v}$ एगारोज फैंटम के लिए अंतिम तापमान $-31.98^{\circ}\mathrm{C}$ से घटकर $4\%\ \mathrm{w/v}$ ग्लाइसिन फैंटम के लिए $-43.31^{\circ}\mathrm{C}$ हो गया, जबकि रेडियल आइस-बॉल व्यास $27.9\ \mathrm{mm}$ से बढ़कर $32.2\ \mathrm{mm}$ हो गया, जो लगभग 15% की वृद्धि दर्शाता है। इसी प्रकार, अनुदैर्ध्य विस्तार $48.4\ \mathrm{mm}$ से बढ़कर $52.1\ \mathrm{mm}$ हो गया, जो लगभग $7–8\%$ की वृद्धि है। प्रायोगिक अवलोकन बहु-प्रोब हिमन गतिकी की प्रत्यक्ष समझ प्रदान करते हैं तथा उन्नत बायोहीट मॉडलों द्वारा निरूपित भौतिक तंत्रों को सुदृढ़ करते हैं, जिससे ऊष्मीय-क्षेत्र-निर्देशित क्रायोसर्जिकल उपचार-योजना में विश्वास और अधिक मजबूत होता है।

समग्र रूप से, यह शोधप्रबंध क्रायोसर्जिकल उपचार-योजना को अनुभव-आधारित एवं ज्यामिति-आधारित पद्धतियों से आगे बढ़ाकर एक मात्रात्मक, भौतिकी-निर्देशित रूपरेखा की ओर अग्रसर करता

है। गैर-संतुलन बायोहीट मॉडलिंग की आवश्यकता प्रदर्शित करते हुए, रोगी-विशिष्ट ट्यूमर के लिए ऊष्मीय-क्षेत्र-निर्देशित बहु-प्रोब स्थापना रणनीति विकसित कर तथा प्रोब-अंतःक्रिया प्रभावों का प्रायोगिक चरित्रीकरण प्रस्तुत कर, यह कार्य सटीक, शारीरिक रूप से यथार्थवादी तथा चिकित्सकीय रूप से प्रासंगिक क्रायोसर्जिकल उपचार-योजना के लिए एक सुदृढ़ आधार प्रदान करता है।

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LIST OF SYMBOLS

Symbol	Description
T_t	Tissue temperature.
T_b	Blood temperature.
T_a	Arterial blood temperature.
T_{probe}	Cryoprobe surface temperature.
T_{ext}	External ambient temperature.
t	Time.
r, z	Radial and axial coordinates.
k	Thermal conductivity.
k_t	Thermal conductivity of tissue.
k_b	Thermal conductivity of blood.
ρ	Density
ρ_t	Tissue density
ρ_b	Blood density
c	Specific heat capacity
c_t	Tissue specific heat
c_b	Blood specific heat
Q_{lf}	Latent heat of fusion
λ	Liquid fraction
ω_b	Blood perfusion rate
u_b	Blood velocity
ε	Tissue porosity
h_{bt}	Interfacial heat transfer coefficient
a	Volumetric interfacial area
Q_m	Metabolic heat generation
Nu	Nusselt number
d_v	Blood vessel diameter
x,y,z	Spatial coordinates
T_l	Liquidus temperature
T_s	Solidus temperature

LIST OF ABBREVIATION

Abbreviation	Full Form
BHE	Bioheat Equation
PBM	Pennes Bioheat Model
LTNE	Local Thermal Non-Equilibrium
LN_2	Liquid Nitrogen
N_2O	Nitrous Oxide
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
2D	Two-Dimensional
3D	Three-Dimensional
ROI	Region of Interest
OD	Outer Diameter
EIF	Extracellular Ice Formation
IIF	Intracellular Ice Formation
IMRT	Intensity-Modulated Radiotherapy
IGRT	Image-Guided Radiotherapy