

**COMPUTATIONAL INVESTIGATIONS ON  
THE HYPERTHERMIA THERMAL THERAPY  
OF CANCER TUMORS USING MAGNETIC  
NANOPARTICLES**

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INDIAN INSTITUTE OF TECHNOLOGY DELHI  
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*by*

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**Submitted**

**in fulfillment of the requirements of the degree of Doctor of Philosophy**

**to the**



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## CERTIFICATE

I am satisfied that the thesis entitled “**COMPUTATIONAL INVESTIGATIONS ON THE HYPERTHERMIA THERMAL THERAPY OF CANCER TUMORS USING MAGNETIC NANOPARTICLES**” presented by **Mr. NANDYALA MAHESH** is worthy of consideration for the award of the degree of **DOCTOR OF PHILOSOPHY** and is a record of the original bonafide research work carried out by him under my guidance and supervision, and the results contained in it have not been submitted in part or full to any other university or institute for the award of any degree/diploma.

I certify that he has pursued the prescribed course of research.

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NANDYALA MAHESH

## ABSTRACT

Cancer is one of the life-threatening diseases in the modern lifestyle. It has outspread throughout the world and gripped millions of lives. The major treatment methods for cancer are surgical removal, chemotherapy, and radiation therapy. However, only peripheral tumors are accessible for surgery, adverse side effects limit the chemotherapy, and radiation therapy is invasive to healthy tissues. With the advent of technology, nanomedicine as an interdisciplinary branch uses nanoparticles (NPs) with unique photothermal and electromagnetic properties. Nano-bio conjugates have shown substantial prospects in state-of-the-art techniques for detection, characterization, and therapeutic effect. Nanoparticles were used as drug carriers as well as adjuvant therapeutic agents along with the other modalities of treatments. *In-vivo* experiments are often complex and difficult to perform to evaluate therapeutic efficacy. Hence, mathematical models and computer simulations are widely used as methods of investigation.

Magnetic nanoparticle hyperthermia (MNH) is an adjuvant and independent thermal therapy to treat cancer tumors. It uses the alternating magnetic field and magnetic nanoparticles (MNPs) to generate heat locally and induce cellular damage without significant collateral damage to the surrounding healthy tissues. The energy dissipated into heat by MNPs, and the consequent temperature rise directly depends on the concentration profiles of MNPs in the tumor. Although different aspects of the treatment modality have been covered in the literature, a comprehensive model considering the infusion of nanoparticles into the tumor, and distribution of the particles, followed by heat transfer analysis to predict temperature elevation, is lacking. To this end, a mathematical model is presented to model intratumoral injection, post-injection distribution of MNPs, and corresponding tumor temperature elevations. Theories of fluid flow in porous tissues, mass transfer, and Pennes' bioheat equation combined with Rosensweig's theory of magnetic fluid heating are used to simulate magnetic nanoparticle hyperthermia. *In-silico* investigations were carried out with respective parameters of tumor and healthy tissues using finite element-based COMSOL Multiphysics® software.

Initially, a three-dimensional mathematical model has been used to study the interstitial fluid flow and post-injection nanoparticle distribution in tumors. A central

necrotic core without any capillaries and a viable tumor with highly permeable angiogenic vasculature regions were considered in the tumor. The effects of nanoparticle size, intratumoral single-site and multi-site injection methods, and vascular normalization on the distribution were investigated. Interstitial fluid pressure, velocity, and nanoparticle concentration in interstitial space were predicted by solving the mathematical models. It was found that the interstitial fluid pressure is elevated and uniform throughout the tumor region, inhibiting the convective transport of the nanoparticles. Post-injection distribution patterns of nanoparticles revealed that the smaller nanoparticles show faster diffusion and rapid clearance from the tissues, while larger particles are retained for longer periods. The multi-site infusion method results in better concentration levels in the viable tumor region than the single-site method. Vascular normalization has significantly affected the nanoparticle concentration in the viable tumor region. Consideration of necrotic core and transvascular transport is inevitable in modeling to replicate the *in-vivo* scenario in *in-silico* investigations.

Numerical modeling of the intratumoral infusion process and hyperthermia simulations were conducted to predict the nanoparticle distribution during intratumoral infusion and the tumor temperature elevations during the hyperthermia therapy. During the injection process, there is a significant increase in the pressure and velocity near the needle tip due to external pressure-driven infusion. Further, it was observed that the concentration profiles at the end of the injection are independent of the size of the nanoparticles illustrating the dominance of convection-enhanced transport due to higher velocity during the injection process. Bioheat transfer results demonstrate the feasibility of temperature elevations to destroy tumor cells. However, the majority of the tumor domain suffers the lower thermal dosages, which is attributed to the perfusion cooling and field parameters.

Further, a parametric investigation was performed to understand the effect of individual parameters such as particle distribution, dosage, size, and field parameters on the therapeutic effect. To this end, the values for different parameters varied within the ranges investigated in the literature. In addition, a clinical breast geometric configuration was employed in this parametric investigation. This study also compares the idealistic uniform distribution (UD), and Gaussian distribution (GD) of MNPs with the distributions predicted using the single-site intratumoral injection (SSIID). The predicted results

demonstrate that UD results in hyperthermia temperatures while GD and SSIID lead to ablative temperatures. For dosages investigated in this study,  $3 \text{ mg/cm}^3$  can result in therapeutic temperature in all three distribution patterns. Hence, this can be considered the optimum dosage required for an amplitude of  $10 \text{ kA/m}$  at  $100 \text{ kHz}$ . The  $16 \text{ nm}$  particle size results in the highest therapeutic temperature for amplitude in the range of  $8 \text{ kA/m}$  to  $16 \text{ kA/m}$ . The increase in amplitude monotonically increases the peak temperature for any particle size.

Lastly, the focus was given to estimating the power density required to achieve the defined therapeutic temperatures in the tumor, which is an important factor in deciding the nanoparticle dosage and delivery technique. A mathematical model is presented to estimate the power density requirement and to replicate the *in-situ* clinical scenario for a realistic breast geometry. This study investigates the effect of required therapeutic temperature, necrotic core, tumor size, and surrounding tissue in which the tumor is present. The results show that the therapeutic temperature and power density are directly proportional, while tumor size and power density are inversely related. The presence of a necrotic core reduces the power density requirements, and a tumor in highly perfused tissues demands higher power densities.

**Keywords:** Cancer; Breast Cancer; Interstitial fluid pressure; Interstitial fluid velocity; Bioheat transfer; Magnetic nanoparticles; Hyperthermia.



## सारांश

आधुनिक जीवनशैली में कैंसर जानलेवा बीमारियों में से एक है। यह पूरी दुनिया में फैल चुका है और लाखों लोगों की जान ले चुका है। कैंसर के लिए प्रमुख उपचार विधियाँ सर्जिकल रिमूवल, कीमोथेरेपी और रेडिएशन थेरेपी हैं। हालांकि, सर्जरी के लिए केवल परिधीय ट्यूमर ही सुलभ हैं, प्रतिकूल दुष्प्रभाव कीमोथेरेपी को सीमित करते हैं, और विकिरण चिकित्सा स्वस्थ ऊतकों के लिए आक्रामक है। प्रौद्योगिकी के आगमन के साथ, एक अंतःविषय शाखा के रूप में नैनोमेडिसिन अद्वितीय फोटोथर्मल और विद्युत चुम्बकीय गुणों के साथ नैनोकणों (एनपी) का उपयोग करता है। नैनो-जैव संयुग्मों ने पहचान, लक्षण वर्णन और चिकित्सीय प्रभाव के लिए अत्याधुनिक तकनीकों में पर्याप्त संभावनाएं दिखाई हैं। नैनोकणों का उपयोग दवा वाहक के साथ-साथ सहायक उपचारात्मक एजेंटों के साथ-साथ उपचार के अन्य तौर-तरीकों के रूप में किया जाता था। चिकित्सीय प्रभावकारिता का मूल्यांकन करने के लिए इन-विवो प्रयोग अक्सर जटिल और कठिन होते हैं। इसलिए, गणितीय मॉडल और कंप्यूटर सिमुलेशन व्यापक रूप से जांच के तरीकों के रूप में उपयोग किए जाते हैं।

मैग्नेटिक नैनोपार्टिकल हाइपरथर्मिया (एमएनएच) कैंसर ट्यूमर के इलाज के लिए एक सहायक और स्वतंत्र थर्मल थेरेपी है। यह वैकल्पिक चुंबकीय क्षेत्र और चुंबकीय नैनोकणों (एमएनपी) का उपयोग स्थानीय रूप से गर्मी उत्पन्न करने और आसपास के स्वस्थ ऊतकों को महत्वपूर्ण संपार्श्विक क्षति के बिना सेलुलर क्षति को प्रेरित करने के लिए करता है। एमएनपी द्वारा गर्मी में ऊर्जा का प्रसार होता है, और परिणामस्वरूप तापमान में वृद्धि सीधे ट्यूमर में एमएनपी की एकाग्रता प्रोफाइल पर निर्भर करती है। यद्यपि उपचार पद्धति के विभिन्न पहलुओं को साहित्य में शामिल किया गया है, ट्यूमर में नैनोकणों के जलसेक और कणों के वितरण पर विचार करने के लिए एक व्यापक मॉडल की कमी है, जिसके बाद तापमान वृद्धि की भविष्यवाणी करने के लिए गर्मी हस्तांतरण विश्लेषण की कमी है। यह अंत करने के लिए, एक गणितीय मॉडल मॉडल इंटरट्रामोरल इंजेक्शन, एमएनपी के पोस्ट-इंजेक्शन वितरण और संबंधित ट्यूमर तापमान उन्नयन के लिए प्रस्तुत किया जाता है। झरझरा ऊतकों में द्रव प्रवाह के सिद्धांत, बड़े पैमाने पर स्थानांतरण, और पेन्स के बायोहीट समीकरण को रोसेन्सविग के चुंबकीय द्रव ताप के सिद्धांत के साथ जोड़कर चुंबकीय नैनोपार्टिकल हाइपरथर्मिया का अनुकरण करने के लिए उपयोग किया जाता है। इन-सिलिको जांच ट्यूमर और स्वस्थ ऊतकों के संबंधित मापदंडों के साथ परिमित तत्व-आधारित COMSOL मल्टीफिजिक्स® सॉफ्टवेयर का उपयोग करके की गई।

प्रारंभ में, ट्यूमर में अंतरालीय द्रव प्रवाह और पोस्ट-इंजेक्शन नैनोपार्टिकल वितरण का अध्ययन करने के लिए एक त्रि-आयामी गणितीय मॉडल का उपयोग किया गया है। ट्यूमर में बिना किसी केशिका के एक केंद्रीय नेक्रोटिक कोर और अत्यधिक पारगम्य एंजियोजेनिक वास्कुलचर क्षेत्रों के साथ एक व्यवहार्य ट्यूमर माना जाता था। वितरण पर नैनोपार्टिकल आकार, इंटरट्यूमोरल सिंगल-साइट और मल्टी-साइट इंजेक्शन विधियों और संवहनी सामान्यीकरण के प्रभावों की जांच की गई। विकसित मॉडलों को हल करके इंटरस्टिशियल फ्लुइड प्रेशर, वेलोसिटी और इंटरस्टिशियल स्पेस में नैनोपार्टिकल कंसंट्रेशन की भविष्यवाणी की गई थी। यह पाया गया कि अंतरालीय द्रव का दबाव पूरे ट्यूमर क्षेत्र में ऊंचा और एक समान है, जो नैनोकणों के संवहन परिवहन को बाधित करता है। इंजेक्शन के बाद के नैनोकणों के वितरण पैटर्न से पता चला है कि छोटे नैनोकण तेजी से प्रसार और ऊतकों से तेजी से निकासी दिखाते हैं, जबकि बड़े कण लंबे समय तक बने रहते हैं। मल्टी-साइट इन्फ्यूजन विधि के परिणामस्वरूप व्यवहार्य ट्यूमर क्षेत्र में एकल-साइट विधि की तुलना में बेहतर एकाग्रता स्तर होता है। संवहनी सामान्यीकरण ने व्यवहार्य ट्यूमर क्षेत्र में नैनोकणों की एकाग्रता को काफी प्रभावित किया है। इन-सिलिको जांच में इन-विवो परिदृश्य को दोहराने के लिए मॉडलिंग में नेक्रोटिक कोर और ट्रांसवस्कुलर ट्रांसपोर्ट को ध्यान में रखना अपरिहार्य है।

इंटरट्यूमोरल इन्फ्यूजन प्रक्रिया और हाइपरथर्मिया सिमुलेशन के न्यूमेरिकल मॉडलिंग को इंटरट्यूमोरल इन्फ्यूजन के दौरान नैनोकणों के वितरण और हाइपरथर्मिया थेरेपी के दौरान ट्यूमर के तापमान में वृद्धि की भविष्यवाणी करने के लिए आयोजित किया गया था। इंजेक्शन प्रक्रिया के दौरान, बाहरी दबाव से प्रेरित जलसेक के कारण सुई की नोक के पास दबाव और वेग में उल्लेखनीय वृद्धि होती है। इसके अलावा, यह देखा गया कि इंजेक्शन के अंत में एकाग्रता प्रोफाइल इंजेक्शन प्रक्रिया के दौरान उच्च वेग के कारण संवहन-वर्धित परिवहन के प्रभुत्व को दर्शाते हुए नैनोकणों के आकार से स्वतंत्र हैं। बायोहीट ट्रांसफर के परिणाम ट्यूमर कोशिकाओं को नष्ट करने के लिए तापमान में वृद्धि की व्यवहार्यता प्रदर्शित करते हैं। हालाँकि, अधिकांश ट्यूमर डोमेन कम तापीय खुराक से ग्रस्त हैं, जो कि छिड़काव शीतलन और क्षेत्र मापदंडों के लिए जिम्मेदार है।

इसके अलावा, चिकित्सीय प्रभाव पर कण वितरण, खुराक, आकार और क्षेत्र मापदंडों जैसे व्यक्तिगत मापदंडों के प्रभाव को समझने के लिए एक पैरामीट्रिक जांच की गई। यह अंत करने के लिए, साहित्य में जांच की गई सीमाओं के भीतर विभिन्न मापदंडों के मान अलग-अलग हैं। इसके अलावा, इस पैरामीट्रिक जांच में एक नैदानिक स्तन ज्यामितीय विन्यास कार्यरत था। यह अध्ययन

एमएनपी के आदर्शवादी समान वितरण (यूडी), और गॉसियन वितरण (जीडी) की तुलना एकल-साइट इंटरट्रामोरल इंजेक्शन (एसएसआईआईडी) का उपयोग करके अनुमानित वितरण के साथ करता है। परिणाम प्रदर्शित करते हैं कि यूडी का परिणाम अतिताप तापमान में होता है जबकि जीडी और एसएसआईआईडी अपक्षयी तापमान का नेतृत्व करते हैं। इस अध्ययन में जांच की गई खुराक के लिए, 3 मिलीग्राम/सेमी<sup>3</sup> तीनों वितरण पैटर्न में चिकित्सीय तापमान का परिणाम हो सकता है। इसलिए, इसे 100 kHz पर 10 kA/m के आयाम के लिए आवश्यक अधिकतम खुराक माना जा सकता है। 16 एनएम कण आकार के परिणामस्वरूप 4 kA/m से 16 kA/m की सीमा में आयाम के लिए उच्चतम चिकित्सीय तापमान होगा। आयाम में वृद्धि किसी भी कण आकार के लिए शिखर तापमान को नीरस रूप से बढ़ाती है।

अंत में, ट्यूमर में परिभाषित चिकित्सीय तापमान को प्राप्त करने के लिए आवश्यक शक्ति घनत्व का अनुमान लगाने पर ध्यान दिया गया, जो नैनोकणों की खुराक और वितरण तकनीक को तय करने का एक कारक है। बिजली घनत्व की आवश्यकता का अनुमान लगाने और इन-सीटू क्लिनिकल परिदृश्य को दोहराने के लिए एक गणितीय मॉडल प्रस्तुत किया गया है, एक यथार्थवादी स्तन ज्यामिति का उपयोग किया जाता है। यह अध्ययन आवश्यक चिकित्सीय तापमान, नेक्रोटिक कोर, ट्यूमर के आकार और आसपास के ऊतक जिसमें ट्यूमर मौजूद है, के प्रभाव की जांच करता है। परिणाम बताते हैं कि चिकित्सीय तापमान और शक्ति घनत्व सीधे आनुपातिक हैं, जबकि ट्यूमर आकार और शक्ति घनत्व व्युत्क्रमानुपाती हैं। नेक्रोटिक कोर की उपस्थिति बिजली घनत्व की आवश्यकताओं को कम करती है, और अत्यधिक सुगंधित ऊतकों में एक ट्यूमर उच्च शक्ति घनत्व की मांग करता है।

**कीवर्ड:** कैंसर; स्तन कैंसर; अंतरालीय द्रव दबाव; अंतरालीय द्रव वेग; बायोहीट ट्रांसफर; चुंबकीय नैनोकण; अतिताप;



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## NOMENCLATURE

<b>Symbol</b>	<b>Description (Unit)</b>
$\varepsilon$	Tissue porosity (-)
$\rho$	Fluid density (kg/m <sup>3</sup> )
$t$	Time variable (s)
$\mathbf{u}_i$	Interstitial fluid velocity (m/s)
$Q_m$	Effective fluid source term (kg/m <sup>3</sup> ·s)
$\phi_B$	Transvascular fluid exchange rate (kg/m <sup>3</sup> ·s)
$\phi_L$	Translymphatic fluid exchange rate (kg/m <sup>3</sup> ·s)
$L_P$	Capillary hydraulic conductivity (m/Pa·s)
$\frac{S}{V}$	Transcapillary exchange area (1/m)
$P_b$	Capillary hydrostatic pressure (Pa)
$P_i$	Interstitial fluid pressure (Pa)
$\sigma_s$	Osmotic reflection coefficient (-)
$\pi_b$	Capillary osmotic pressure (Pa)
$\pi_i$	Interstitial osmotic pressure (Pa)
$\frac{L_{PL}S_L}{V}$	Effective lymphatic filtration (1/Pa·s)
$P_l$	Lymphatic hydrostatic pressure (Pa)
$\kappa$	Tissue permeability (m <sup>2</sup> )
$\mu$	Fluid viscosity (Pa·s)
$N_0$	Infusion mass flux at the needle tip (kg/m <sup>2</sup> ·s)
$C_i$	Nanoparticle concentration (mol/m <sup>3</sup> )
$D_{eff}$	Effective diffusion coefficient (m <sup>2</sup> /s)
$Q_s$	Effective solute source term (mol/m <sup>3</sup> ·s)
$D_0$	Diffusion coefficient in free liquid medium (m <sup>2</sup> /s)
$\kappa_B$	Boltzmann Constant (J/K)
$a$	Solute particle radius (m)
$T$	Temperature (°C or K)

$\Phi_B$	Rate of transvascular solute exchange (mol/m <sup>3</sup> ·s)
$\sigma_f$	Solute reflection coefficient (-)
$C_P$	Plasma concentration (mol/m <sup>3</sup> )
$P_m$	Capillary permeability for solute particles (m/s)
$Pe$	Peclet number (-)
$\Phi_L$	Rate of translymphatic solute exchange (mol/m <sup>3</sup> ·s)
$\epsilon$	Capillary wall porosity (-)
$\lambda$	Ratio of particle size to capillary pore size (-)
$\bar{L}$	Capillary wall thickness (m)
$r_p$	Capillary pore radius (m)
$J$	Solute diffusive flux (mol/m <sup>2</sup> ·s)
$J_0$	Solute infusion flux at the needle tip (mol/m <sup>2</sup> ·s)
$\rho_t$	Tissue density (kg/m <sup>3</sup> )
$c_t$	Tissue-specific heat (J/kg·K)
$k_t$	Tissue thermal conductivity (W/m·K)
$\omega_b$	Blood perfusion rate (1/s)
$\rho_b$	Blood density (kg/m <sup>3</sup> )
$c_b$	Blood-specific heat (J/kg·K)
$T_b$	Arterial blood temperature (°C)
$Q_{met}$	Tissue metabolic heat generation (W/m <sup>3</sup> )
$\alpha$	Correction factor (-)
$Q_{mnp}$	Heat generated by MNP in tissue (W/m <sup>3</sup> )
$P$	Power density of MNP in magnetic fluid (W/m <sup>3</sup> )
$\phi$	Magnetic nanoparticle volume fraction (-)
$\rho_{mnp}$	Nanoparticle density (kg/m <sup>3</sup> )
$\tau_B$	Brownian relaxation time (s)
$V_H$	Hydrodynamic particle volume (m <sup>3</sup> )
$\tau_N$	Néel relaxation time (s)
$\Gamma$	Calculation parameter (-)
$\tau_0$	Attempt time (s)

$\delta$	Liquid layer thickness (m)
$K$	Magnetic anisotropy constant (J/m <sup>3</sup> )
$V_M$	Particle magnetic volume (m <sup>3</sup> )
$\mu_0$	Vacuum magnetic permeability (H/m)
$f$	Magnetic field frequency (Hz)
$H$	Magnetic field amplitude (A/m)
$X''$	Loss component of the magnetic susceptibility (-)
$\tau$	Effective relaxation time (s)
$\chi_0$	Equilibrium magnetic susceptibility (-)
$\chi_i$	Initial magnetic susceptibility (-)
$\xi$	Langevin parameter (-)
$M_d$	Domain magnetization (A/m)
$\Omega$	Thermal damage parameter (-)
$A$	Effective collision frequency factor (1/s)
$E_a$	The molecular transition activation energy (J/mol)
$R$	Universal gas constant (J/mol/K)
$h$	Convective heat transfer coefficient (W/m <sup>2</sup> /K)
$S$	Objective function
$\mathbf{P}$	Unknown parameter vector
$\mathbf{Y}$	Measured or known temperature vector
$\mathbf{T}$	Predicted temperature vector
$\mathbf{J}$	Sensitivity or Jacobian matrix
$C_{mf}$	Nanoparticle concentration in magnetic fluid (mol/m <sup>3</sup> )
$\dot{V}$	Infusion rate ( $\mu$ l/min)
$A_{needle}$	Needle cross-section area (m <sup>2</sup> )
$C_{max}$	Maximum nanoparticle concentration in tumor (mol/m <sup>3</sup> )
$C_{min}$	Minimum nanoparticle concentration in tumor (mol/m <sup>3</sup> )
$r$	Radial position from tumor center (m)
$r_{50}$	Radial distance for 50% peak concentration (m)
$\Delta r$	Slope constant in curve-fit (m)

$C_{uniform}$	Uniform concentration (mol/m <sup>3</sup> )
$C_{peak}$	Peak concentration (mol/m <sup>3</sup> )
$\sigma$	Gaussian distribution's standard deviation (m)
$R$	Tumor size (m)



