Our PhD research scholar **Mahesh Nandyala** has successfully defended his research work titled, "**Computational Investigations on the Hyperthermia Thermal Therapy of Cancer Tumors Using Magnetic Nanoparticles**". He is joining as a Postdoctoral fellow at the University of Texas at Austin, Texas, USA. He will be working on clinical data-driven computational modeling of magnetic hyperthermia in collaboration with The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Mr. Nandyala Mahesh was born on July 8th, 1993, in Byrapuram, a small village in Kurnool district, Andhra Pradesh, India. e obtained his bachelor's degree in mechanical Engineering from Rajiv Gandhi University of Knowledge Technologies (RGUKT), R K Valley Campus, with a distinction grade. He also has a minor in Management Studies from the same institution. Later he attended Dr. B. R. Ambedkar National Institute of Technology Jalandhar, Punjab, for his master's degree in mechanical engineering. After finishing his master's degree, he joined the Indian Institute of Technology (IIT) Delhi, India, to pursue his doctoral research in the field of computational cancer investigations. Along with academics, he has a great interest in sports such as badminton, cricket, and cycling.

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 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 kA/m at 100 kHz. The 16 nm particle size results in the highest therapeutic temperature for amplitude in the range of 8 kA/m to 16 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.

LIST OF PUBLICATIONS

JOURNALS

1. **Mahesh, N.**, Singh, N., and Talukdar, P., 2023, "A Mathematical Model of Intratumoral Infusion, Particle Distribution and Heat Transfer in Cancer Tumors: In-Silico Investigation of Magnetic Nanoparticle Hyperthermia," Int. J. Therm. Sci., 183, p. 107887. DOI:10.1016/j.ijthermalsci.2022.107887.
2. **Mahesh, N.**, Singh, N., and Talukdar, P., 2023, "In-silico investigation of magnetic Nanoparticle Hyperthermia Treatment to Estimate the Power Density and Concentration Required to Achieve the Therapeutic Effect," Int. Commun. Heat Mass Transf., 137, p. 106295. DOI:10.1016/j.icheatmasstransfer.2022.106295.
3. **Mahesh, N.**, Singh, N., and Talukdar, P., 2021, "A Mathematical Model for Understanding Nanoparticle Biodistribution after Intratumoral Injection in Cancer Tumors," J. Drug Deliv. Sci. Technol., 68, p. 103048. DOI:10.1016/j.jddst.2021.103048.
4. **Mahesh, N.**, Singh, N., and Talukdar, P., 2023, "Investigation of Breast Cancer Magnetic Hyperthermia Through Mathematical Modeling of Intratumoral Nanoparticle Distribution and Temperature Elevations," *Therm. Sci. Eng. Prog.*, *40*, p.101756. DOI:10.1016/j.tsep.2023.101756