HABILITATION THESIS

MODELING OF THE COMPLEX PHYSICAL PROCESSES IN THE MAGNETIC HYPERTHERMIA
SUMMARY

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SUMMARY

The Habilitation Thesis entitled „Modeling of the complex physical processes in the Magnetic Hyperthermia” presents the most important scientific results published by the author since obtaining the title of doctor in Physics. The work is targeted on both my academic career development, the scientific concerns and contributions, by published works in the field of physics. In the presentation of the didactic and research activity were included details about the academic profile, supervision of the students for their final thesis for bachelor and master studies, member of the commissions of guidance for PhD students.

CHAPTER I presents my professional evolution and the most important achievements in the research and teaching activities. **CHAPTER II** is dedicated to my development plan that divides between teaching and research activities. The list of teaching objectives containes: updating electronic support materials for courses, continuous guidance of undergraduate and master students and supervising doctoral students. A careful attention will be paid for the strengthening the collaborations by engaging young researchers and PhD students in the research activities related to the proposed topics. Attracting financial resources from national and international programs will be one of the most important goals. **CHAPTERS III ÷ V** describe a part of the scientific contributions to the physics, in the Magnetic Hyperthermia field.

Modeling physical processes using analytical and/or numerical methods helps to better understand the behavior of a system and make predictions about its future evolution. From this point of view, this work presents important results regarding the modeling of the complex processes of magnetic hyperthermia with potential applications in the treatment of malignant tissues such as tumors and cancers.

Hyperthermia is a promising medical technique for the treatment of the malignant tissues (tumors, cancers). This therapy received a considerable attention in the theoretical and experimental researches. Hyperthermia method uses the heat from various sources to destroy the malignant tissues. The thermal damage (cancer cell death) starts when the tissue temperature reaches the hyperthermic range (40 ÷ 45oC). The control of the temperature field within malignant tissues is an important task in this therapy. Magnetic Hyperthermia uses the targeted therapeutic heat developed from the magnetic nanoparticles when an external alternating electromagnetic field high frequency was applied to destroy the malignant tissues (due to their small thermal resistance). The thermal energy deposited within the malignant tissue provides from the MNP distributed as result of convection-diffusion-deposition of the particles after their injection inside tissue. The ferrofluid infusion rate influences significantly the spatial distribution of the nanoparticles and consequently the temperature field. The control of the thermal damage of the malignant tissue by the choice of the best magnetic material is really important in Magnetic Hyperthermia. The particle doses can be computed using a (numerical/analytical) complex model. The following parameters as: (i) ferrofluid infusion rates, particle zeta potential, particles size, ii) tissues` porosity and iii) blood perfusion rate have a fundamental role in this temperature analysis.

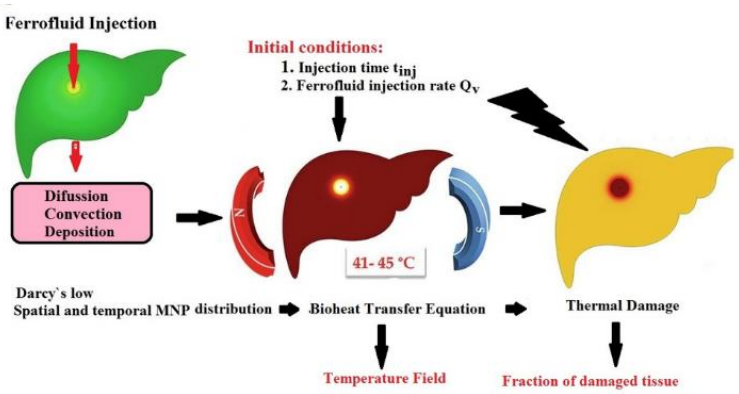

Figure 1.
Graphical Abstract for Magnetic Hyperthermia

CHAPTER III focuses the main parameters with a fundamental role in the thermal damage of the malignant tissue with intravascular structure. The numerical model developed in this chapter has the advantage to describe the therapeutic temperature field and the thermal damage of the malignant tissues in correlation by the parameters as: i) ferrofluid infusion rates, particle zeta potential, the magnetic nanoparticle (MNP) size (paragraph III.2.1), ii) tissue porosity, (paragraph III.2.2) c) blood perfusion rate (paragraph III.2.3). The spatial MNP distribution, the temperature field and thermal damage were computed considering the convection-diffusion-deposition of the particles within tissues, the bioheat transport equation and Arrhenius formulation for tissue thermal damage. The particles with higher velocity moves on larger distances on radial direction from the injection site within tumor. This important effect determines a temperature field with small temperature gradients. The paragraph III.2.2 describes the influence of the tissues' porosity on the therapeutic temperature field which determines the thermal damage of the malignant tissues. The supplementary effect related to the spatial re-distribution of the nanoparticles was discussed in the following cases: i) the constant and ii) thermal damage dependent porosity of the tissues. Using the realistic data from the computed tomography scan (2D – CT scan), the therapeutic temperature field in the hyperthermic range (40 ÷ 46oC) was analyzed using the proper physical characteristic parameters. In the Arrhenius formulation, the thermal analysis based on the thermal damage dependent blood perfusion was compared to the one with constant blood perfusion. The strong dependence of the perfusion profile on the cooling mechanism is discussed based on the temperature model results. A collection of CT-data was studied to recognize and to reconstruct the tumoral regions localized in organs. A temperature analysis on liver tissue was developed using these CT-scan data. In the Magnetic Hyperthermia, the segmentation of the tumoral region helps to elaborate a temperature model with the particular data (shape, size) specific to each patient. The main goal was to obtain a good temperature control and to compute the MNP doses needed for elaboration of the Hyperthermia Planning Therapy (HPT) specific to a patient. The model developed is a thermal analysis tool which uses a medical image computing and visualizations (2D CT-scan data) to evaluate as precisely as, the thermal damage of the malignant tissue from the healthy region for various magnetic field parameters. A small healthy region (0.5 mm) around tumor is little bit destroyed (10-20%) as result of the therapeutic temperature on the tumor border vicinity. The cooling mechanism due to perfusion profile acts as a heat sink and should be considered in the real – time analysis with advanced simulations. This extended study focuses the essential role of these parameters to compute and predict accurately the optimum MNP dosage which induces a hyperthermic temperature field. The optimum position of the ferrofluid injection site (IS) which induces the maximum thermal damage within tumoral tissue volume was computed for three materials: maghemite, magnetite and FePt (paragraph III. 3). The main goal was to identify the optimum magnetic material which induces the larger hyperthermic range and maximizes the thermal damage of the malignant tissues. Capability of the magnetic materials as:

magnetite, maghemite and FePt to maximize the thermal damage of the malignant tissues was demonstrated. The complex model developed computes the optimal position of the ferrofluid injection sites (in the arrangement with 2IS and 4IS) which give the maximum thermal damage of the tumoral tissue related by the magnetic field parameters (frequency, amplitude), tumor (characteristics, size). The control of the tumoral tissue thermal damage can be done by the control of this parameter x_1 for a specific magnetic material. The range of the specific particles sizes which give the therapeutic temperature can be selected for each material. The maghemite particles destroy more efficiently a larger tumoral tissue volume. This analysis allows the understanding capability of the magnetic material to be used in this therapy. The maghemite particles offer larger possibilities for sizes and doses to maximize the thermal damage of tissues.

CHAPTER IV analyzes the hyperthermic effects determined by the magnetic particles with low Curie Temperature (Tc) within a tumoral configuration from healthy tissue when an alternating magnetic field is applied. As the results shows, the Fe-Cr-Nb-B system determines an automatic control of tumor heating. The temperature field increases from 37oC to the Curie temperature of the particles which becomes the maximum temperature within tumor. Small quantities of ferrofluid in the range 0.1 - 0.3 cm^3 determine a temperature rise in the therapeutic temperature range in a tumor. The heat generation by Néel and Brown relaxations was modeled using the thermal and magnetic properties of the FeCrNbB particles experimentally determined. Interconnection between particle parameters (composition, size, magnetic and thermal properties), optimum dosage (volume concentration) and the magnetic field parameters (frequency and magnetic field intensity) was studied. The FeCrNbB magnetic systems have a particular behavior with the frequency and amplitude of the AC magnetic field. The temperature gradients induced within the tumor as a result of the heating in the magnetic field are smaller than ones induced by the magnetite systems. This temperature behaviour can be an advantage in the controlled heating of the tumors. Taking into account the results of these studies one can design new materials better adapted to this type of application. The particle size dependent temperature field corresponds to three stages: i) the temperature increases with the particle size, ii) the temperature reaches a maximum value for a specific particle diameter (Ds) and iii) the temperature decreases with particle size. Néel relaxation mechanism is dominant in the stage i) and Brown relaxation mechanism is dominant in the stage iii). Both heating mechanisms are equally at the stage ii) when the maximum value of temperature is reached. The absorbed energy of the FeCrNbB particles in the magnetic field lead to a maximum temperature for the particles having the diameter of 16-20 nm. This temperature maximum depends strongly on the frequency of the magnetic field. The therapeutic temperature field within tumoral region (T) can be obtained by using the particles with size in a larger range (7 - 30) nm if the tunning of the frequency is realized. Ferrofluids with small viscosity which contain particles with size of 20 nm can determines the therapeutic temperature in the small applied magnetic fields (f = 200 kHz and Ho = 3 kA/m). The FeCrNbB magnetic systems have good thermal and magnetic properties to be used in the Magnetic Hyperthermia. These magnetic systems open new borders in the Magnetic Hyperthermia researches.

CHAPTER V shows a thermo-mechanical analysis considering the local displacements of the tissue during the ferrofluid injection. The temperature field can be controlled by the infusion parameters as: i) ferrofluid infusion rate; and ii) needle gauge size of the syringe. The ferrofluid infusion rate induces some local deformations within tissue which influences significantly the convection-diffusion-deposition of the particles and implicitly the MNP distribution. The elastic parameters of the tumoral tissue have an important role in the study of the MNP distribution and temperature field. The ferrofluid injection within tissue with high infusion rate and small needle diameter determines a temperature field with smaller temperature gradients. Analytical correlations between the following parameters : i)

the particle velocities, ii) the pressure developed in geometry during the ferrofluid infusion and iii) the particle concentration were done in order to understand and predicts the temperature field within tissues when an external magnetic field is applied. The therapeutic temperature field is concentrated within the malignant tissue. The temperature on the tumor border (approximately 38-39^{o}C) not affects the healthy tissue. Analytical heat transfer computations within a tumoral tissue (with intravascular structure) are essential for the optimization of the hyperthermia treatment planning. The magnetic nanoparticles (MNP) distribution after their injection depends on the vascularization of the malignant tissue. The paragraph V. 3 analyzes the influience of the intravascular structure on the therapeutic temperature field within a malignant tissue. An analytical model which considers the ferrofluid transport, the spatial MNP distribution and heat transfer was developed in this paragraph. The temperature field given by the MNP heating as thermal sources (when an alternating electromagnetic field was applied) was analyzed for different values of the magnetic field parameters (frequency, amplitude), intravascular tumor and MNP characteristics. The therapeutic temperature field and thermal damage of the malignant tissue depends strongly on the tumor tissue vascularization and the needle size used for the delivery of the ferrofluid within tumor. The temperature values within tumor volume decrease with the increase of the radius of the needle. The therapeutic temperature values depends strongly on the tumor intravascular structure. The higher intravascular pressure was developed within the intravascular tumor, when the ferrofluid injection was done using a small radius of the needle. In this case, the magnetic nanoparticles moves at the larger distances from the injection sites and the therapeutic values of the temperature covers a larger volume of the solid tumor. A higher percentage of the tumor volume was thermally damaged. The analytical model developed in this paper allows to optimize the MNP doses used in the magnetic hyperthermia therapy. The control of the spatial MNP distribution within the tumoral tissue can be realized more eficcient if the ferrofluid injections with small needle sizes are used.