Abstract

In this Thesis, we focus on the application of magnetic nanoparticles (MNPs) in magnetic hyperthermia, with the aim of presenting a modeling approach to provide information to plane and optimize *in vivo* experiments conducted on small animals. Magnetic hyperthermia is a therapeutic technique, which is generally applied as an adjuvant to standard therapies for the cure of cancer, e.g. radiotherapy or chemotherapy. With this technique, MNPs are excited by the application of an AC magnetic field (with frequency from 50 kHz to 1 MHz) to release heat in diseased regions and thus promote the damage of cancer cells, enhancing their sensitivity to standard therapies. The target temperatures should be in the range of 40-45 °C). Although promising results have been obtained in clinical trials, further research is required to optimize this therapeutic technique and acquire a deeper knowledge of its potential advantages and limitations. The main critical aspects are the capacity of guaranteeing safe levels of field exposure, the achievement of a proper MNP thermal dose, and the monitoring of temperature distribution within the tumor and the surrounding tissues.

In this context, we have developed a set of in-house numerical tools for the simulation of the heating process generated by magnetic hyperthermia (also considering side effects) and of the MNP transport in microvascular networks and their release to target tissues. For each solver, we present its implementation and the numerical validation by means of comparison to analytical solutions or solutions obtained with commercial solvers. The first solver simulates the eddy current effects induced by the exposure to low-frequency electromagnetic (EM) fields, evaluating the electric field induced in the body/domain of calculation. The second solver is based on the heat transfer equation and calculates the spatial-temporal distribution of temperature of MNP-containing samples to support thermometric measurements and the characterization of MNP heating efficiency, as a function of MNP concentration and heating time. The third solver is based on the Pennes' bioheat equation and evaluates the thermal response of living tissues as a result of blood perfusion, metabolic heat, EM field exposure (whose contribution is calculated with the EM solver), and MNP activation under AC magnetic fields. The simulations are performed on two high-resolution digital phantoms of murine models, a 28 g mouse and a 503 g rat. The last solver is based on classical Newtonian dynamics and simulates the motion of an ensemble of spherical micro/nanoparticles circulating in a 3D

reconstruction of a real blood vessel segment, under the influence of an external magnetic field.

The first three models, all based on the finite element method (FEM), enable us to test the heating efficiency of MNPs, and to select the treatment conditions to guarantee a proper temperature increase in tumor-affected regions and to avoid the appearance of hot-spots in healthy tissues. Specifically, with the EM solver and the thermal solver based on the Pennes' equation, we have investigated the effects of the only EM field exposure, in terms of specific absorption rate (SAR) and temperature increase, in relation to the field parameters (frequency and peak amplitude), the animal size, the body-field orientation (considering uniform fields), and the applicator geometry (i.e. non-uniform field distribution). Then, we have analyzed the heating effects of several MNP types as a function of diseased region type (size and position in the body), MNP concentration, and field configuration. Finally, with the last model, we have investigated the importance of magnet configuration (size and position with respect to the blood vessel geometry) and particle properties (size and magnetic moment) to properly guide particle motion towards the target regions, comparing the trajectories of three different particle types, with radius from 10 nm to 500 nm.