In silico experiments as a tool to reduce preclinical tests of magnetic hyperthermia

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Abstract

In silico models can be useful tools to guide preclinical tests of magnetic hyperthermia, which employs Magnetic Nanoparticles (MNPs) excited by AC magnetic fields, as heat mediators for cancer cure. We virtually reproduce the heating process induced by magnetic hyperthermia in murine models, as a function of field applicator features, properties and size of target tissue, MNP dose and animal size.

Introduction

Magnetic hyperthermia is an oncological therapy, typically employed in combination with radiotherapy or chemotherapy; this uses magnetic nanoparticles (MNPs), activated by magnetic fields with frequency of 50-500 kHz, to release heat in diseased tissues. The heat deposited in the tissue is responsible for a local increase in temperature, which should be in the order of 4-5 °C.[1] In preclinical trials, generally conducted on murine models, several factors have to be taken into account to optimize heat deposition and reduce side-effects. These comprise undesired electromagnetic induction phenomena, field applicator configuration, heat transfer with the external environment and MNP spatial distribution within the target tissue.

Here, we present a physics-based modelling approach to address *in vivo* tests of magnetic hyperthermia,[2] providing information on how plan and optimize treatments in view of a possible reduction of the number of animals involved in preclinical trials. To this aim, we have developed *in silico* models for the evaluation of eddy currents induced in the body during hyperthermia sessions and the calculation of thermal effects, consequent to magnetic field application and MNP excitation. The study is focused on computational anatomical murine models with different size, changing the target tissue where the MNPs are dispersed (with variable dose) and its location in the body.

Materials and Methods

The study is performed by using in-house finite element models aimed at determining the thermal effects correlated, first, to the exposure to the only AC magnetic field and, second, to the MNP excitation. To evaluate eddy current effects produced in biological tissues during field application, we have developed a low-frequency electromagnetic field solver, in which displacement currents are neglected. To calculate the thermal effects induced in the animal body due to field exposure and MNP excitation, we have implemented a numerical code that solves the Pennes' bioheat transfer equation.[2] The analysis is conducted on murine models released by IT'IS Foundation.[3]

Results

The attention is first focused on the design of the applicator that generates the AC magnetic field for MNP activation. Different applicators are compared, studying the influence of their geometry and position on the field distribution within the target tissue. To avoid undesirable eddy current effects, we consider the Hergt-Dutz limit for selecting field frequency and amplitude.[4] *In silico* experiments are performed to estimate the Specific Adsorption Rate (SAR) and temperature increase under critical conditions, to provide safety advise for preclinical trials, sometime performed without fulfilling the Hergt-Dutz limit.[5] The results obtained on a 28 g weight mouse[3]

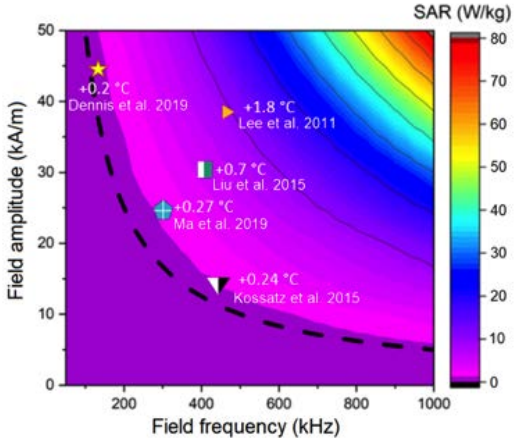

Figure 1. Whole-body SAR deposited in a 28 g mouse, as a function of the frequency and amplitude of the field (applied parallel to the body longitudinal axis). The maximum temperature increase is calculated for field parameters of pre-clinical studies (markers) exceeding Hergt-Dutz limit (dotted line).

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Key words: Magnetic hyperthermia; magnetic nanoparticles; computational animal models; bio-heat model.

Acknowledgments: This work is developed in the framework of the Project 18HLT06 RaCHy that received funding from the European Metrology Programme for Innovation and Research (EMPIR).

Disclosures: The authors declare no conflicts of interest.

Conference presentation: This paper was presented at the Third Centro 3R Annual Meeting - L'era delle 3R: modelli *in silico, in vitro* e *in vivo* per promuovere la ricerca traslazionale - 30 September - 1 October 2021, Evento online organizzato dal Politecnico di Torino.

Received for publication: 9 July 2021.
Accepted for publication: 7 September 2021.

Biomedical Science and Engineering 2021; 4(s1):199
doi:10.4081/bse.2021.199

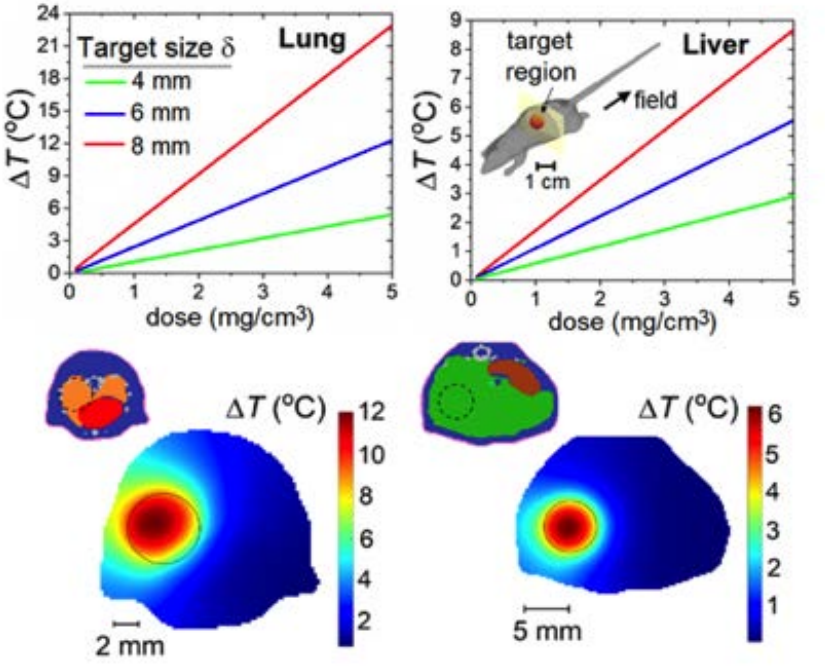

Figure 2. Top: Maximum temperature increase reached in a 28 g mouse at the end of hyperthermia heating transient, as a function of MNP dose and size (δ) of target region (placed in lung or liver). Bottom: Maps of the temperature increase calculated in transversal sections of the mouse body.

are shown in Figure 1. *In silico* experiments are also conducted to evaluate the heating effects produced by MNP excitation, as a function of MNP dose and target tissue location and size, as reported at the top of Figure 2 for the 28 g weight mouse. Bio-heat simulations enable us to establish whether MNPs heat only the target tissue, or generate hot spots in the surrounding healthy tissues, as shown at the bottom of Figure 2. The results have been obtained by assuming a uniform distribution of the MNPs within the target tissue. As a future work, we plan to introduce a more realistic MNP spatial distribution, depending on the tumor microenvironment (*e.g.* vascular network).

Discussion and Conclusions

The results of this work have demonstrated the utility of *in silico* experiments in guiding and finally reducing animal tests in magnetic hyperthermia studies, thanks to a proper choice of parameters and prediction of adverse effects. From SAR estimation, modelling has proved that a careful selection of field frequency and amplitude is necessary to keep to a safe level the exposure to magnetic fields, in relation to the size and position with respect to applicator of the treated animals. With field parameters little exceeding the Hergt-Dutz limit, a 28 g mouse presents a negligible temperature increment, whereas a 503 g rat experiences a maximum temperature increase of 6 °C. The bio-heat simulations of the heating process induced by MNPs have shown that in murine models temperature increments comparable to that obtained in calorimetric measurements under quasi-adiabatic conditions can be achieved only by using an order of magnitude larger dosage of MNPs, due to blood perfusion effects.

Finally, the simulations have demonstrated how thermal properties of tissues strongly influence the heating response; in particular, the maximum temperature increase is observed in the tissues with reduced thermal conductivity and lower blood perfusion rate, such as lung and fat.

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