Treatment Planning for Magnetic Nanoparticle-Based Hyperthermia

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Superparamagnetic iron oxide nanoparticles (SPIONs) have been used as magnetic resonance imaging contrast agents. Coated and functionalized SPIONs can specifically target cancer cells, and, in combination with alternating magnetic fields, can be used to administer enhanced and targeted hyperthermic cancer treatment. A treatment planning platform featuring image-based personalized anatomical model generation, electromagnetic and thermal modeling, effect quantification, and field optimization has been developed and extended to include nanoparticle-field interaction and enhanced energy deposition with image-data information about particle density distributions. The impact of particle density, distribution sharpness and width, and perfusion vs. heat diffusion was investigated. The resulting platform can be used to design, optimize, and investigate nanoparticle-based hyperthermia treatment and personalize therapy.

BACKGROUND

SPIONs

Superparamagnetic iron oxide nanoparticles (SPIONs) are used as magnetic resonance imaging (MRI) contrast agents. Coated and functionalized nanoparticles can specifically target cancer cells and thus be used to visualize secondary tumors and metastases. As SPIONs exposed to alternating magnetic fields deposit energy through remagnetization losses (hysteresis), the targeting of functionalized nanoparticles can be used to apply localized hyperthermia therapy. When targeting is insufficient to produce the necessary particle density, particles can also be directly injected or be part of a cement formulation injected, e.g., into brittle, tumor-diseased bone.

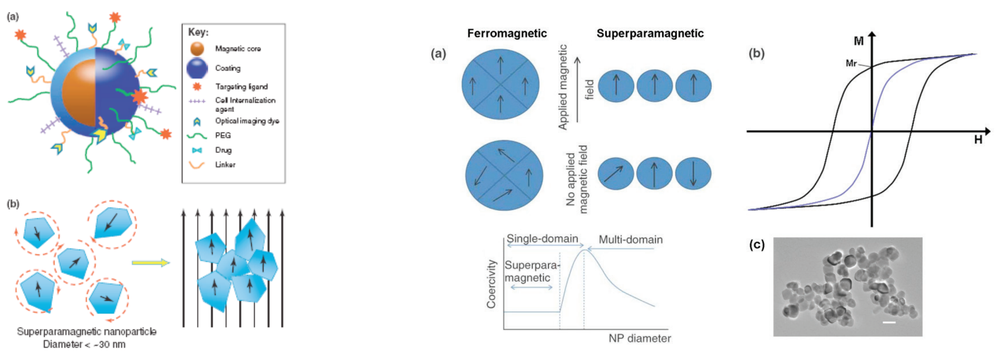


Figure 1: *Schematics of functionalized SPIONs (left, [Sezer 2012]) and their hysteretic behavior under magnetic field exposure (right, [Trindade 2011])*

Treatment Modeling and Planning

Treatment modeling and planning are required to determine the necessary SPION concentration, magnetic field strength, and expected outcome in terms of safety and treatment success. This information can be used to design the applicators and to optimize the magnetic field intensity and frequency, the size distribution and material properties of the particle formulations, and for quality assurance. Personalized treatment planning permits efficacy assessment, optimized dosage, and identification and avoidance of unwanted side effects.

To this effect, there needs to be an efficient generation of personalized patient model anatomy, physiology, and treatment setup, precise modeling of physics and related physiological reactions, and appropriate assessment of induced therapeutic effects. Computed tomography (CT) and magnetic resonance imaging (MRI) provides data on patient anatomy, nanoparticle distribution and potentially even tissue properties.

METHODS

Sim4Life

A platform (Sim4Life) for image-based hyperthermia modeling and treatment planning has been developed. Medical image data is segmented to generate patient-specific anatomical models. A magneto-quasistatic solver is used to determine the properties of the local magnetic field generated by the applicator coils and the specific absorption rate (SAR) distribution resulting from tissue conductivity losses. A physical model relating nanoparticle density, frequency, temperature, as well as SPION core and shell dimensions and magnetic properties to the specific loss power is derived. This analytical relationship, which takes Neel and Brownian relaxation mechanisms into consideration but neglects particle-particle interactions can be used in combination with the particle density distribution to generate additional heat sources in the thermal modeling. The thermal modeling is performed with an extended Pennes bioheat equation (PBE) in combination with body-core heating, thermoregulation, and vascular impact models to determine the transient temperature and associated thermal dose distribution expressed as CEM43, which informs about the treatment efficacy and collateral damage risk. The infrastructure is in place to co-visualize the images with the simulation model and results and to support nanoparticle distribution extraction.

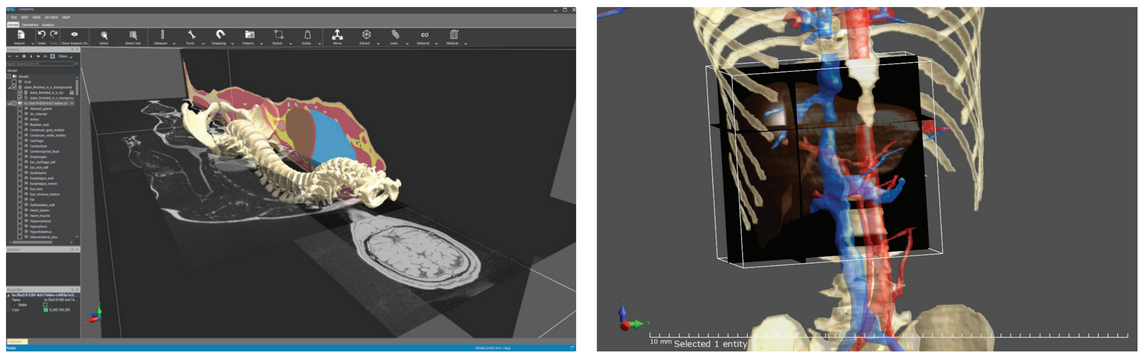


Figure 2: *Use of image data for model personalization. Image data is used for anatomy (left) and particle density distribution (right) extraction.*

$$EPFL(f,d,H) := \mu_0 \cdot \pi \cdot M_S \cdot \left[\left(\frac{\cosh\left(\frac{\mu_0 \cdot M_S \cdot H \cdot V_M(d)}{k \cdot T} \right)}{\sinh\left(\frac{\mu_0 \cdot M_S \cdot H \cdot V_M(d)}{k \cdot T} \right)} - \frac{1}{\frac{\mu_0 \cdot M_S \cdot H \cdot V_M(d)}{k \cdot T}} \right) \cdot \frac{2 \cdot \pi \cdot f \cdot \tau_0 \cdot 1 \cdot e^{\frac{K \cdot V_M(d)}{k \cdot T}}}{1 + \left(2 \cdot \pi \cdot f \cdot \tau_0 \cdot 1 \cdot e^{\frac{K \cdot V_M(d)}{k \cdot T}} \right)^2} \cdot H \cdot f \right]$$

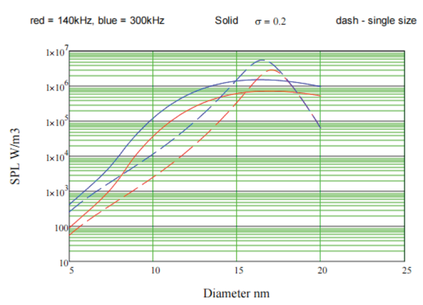
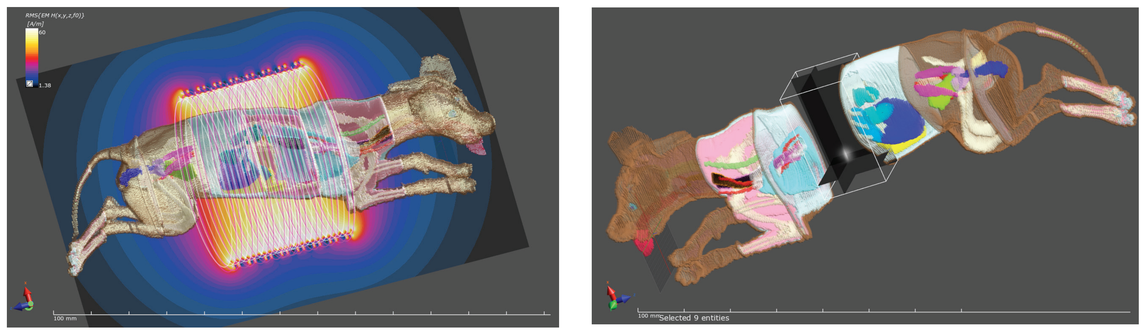


Figure 3: *Part of the computation of nanoparticle-related power deposition and visualization of particle-diameter dependence of specific power loss, with consideration of the tolerances in the particle manufacturing process, at two different frequencies.*

Setup



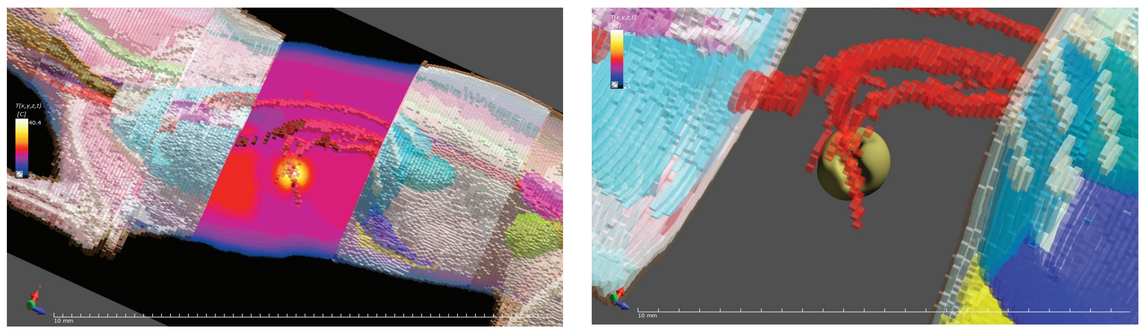


Figure 4: *Simulation of nanoparticle hyperthermia treatment in a dog. H-field (top, left), particle density distribution from image data (top, right), induced heating (bottom, left), and the resulting treatment volume as the thermal dose isosurface, with consideration of convective cooling by major vasculature (bottom, right).*

RESULTS

A comprehensive treatment modeling platform has been realized and applied to:

Particle optimization and coil design: The impact of frequency, particle size distribution, and coil design was investigated theoretically and provided input for the design process.

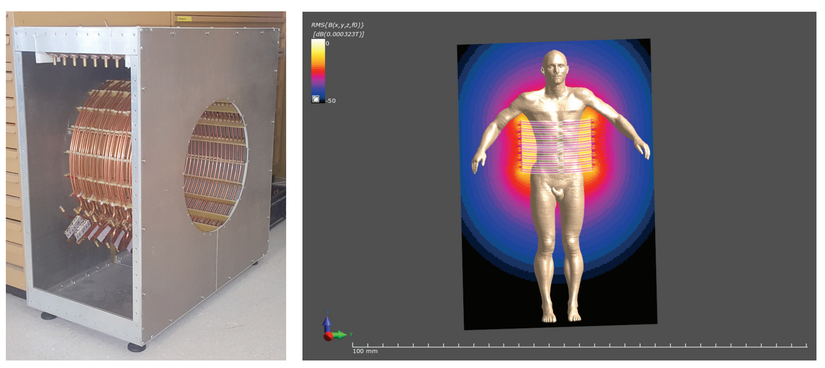


Figure 5: *Newly designed applicator prototype and simulated field distribution.*

Parameter impact: Modeling has been used to investigate the impact of nanoparticle size, distribution sharpness shape and width, density, and magnetic field strength and frequency. The temperature increase behavior is dominated by the interplay between diffusion and perfusion heat removal. In a well-perfused tissue such as liver, the temperature quickly reaches a perfusion dominated regime, where perfusion and particle density determine the temperature; the particle distribution affects only the width of the treatment area. However, in less-well-perfused tissues, e.g., fat and muscle, diffusion can become dominant, depending on the spatial extent and sharpness of the particle distribution, leading to more complex temperature increase relationships where particle distribution strongly impacts the resulting temperature. There is little temperature impact once the distribution width becomes larger than a fixed multiple of the characteristic Green's function length. A theoretical closed-form relationship was established. The impact of nearby major vasculature was also studied. The simulations permit the particle distribution density and tissue properties to be related to the extent to which nearby major vasculature prevents successful treatment through effective cooling by convective heat removal.

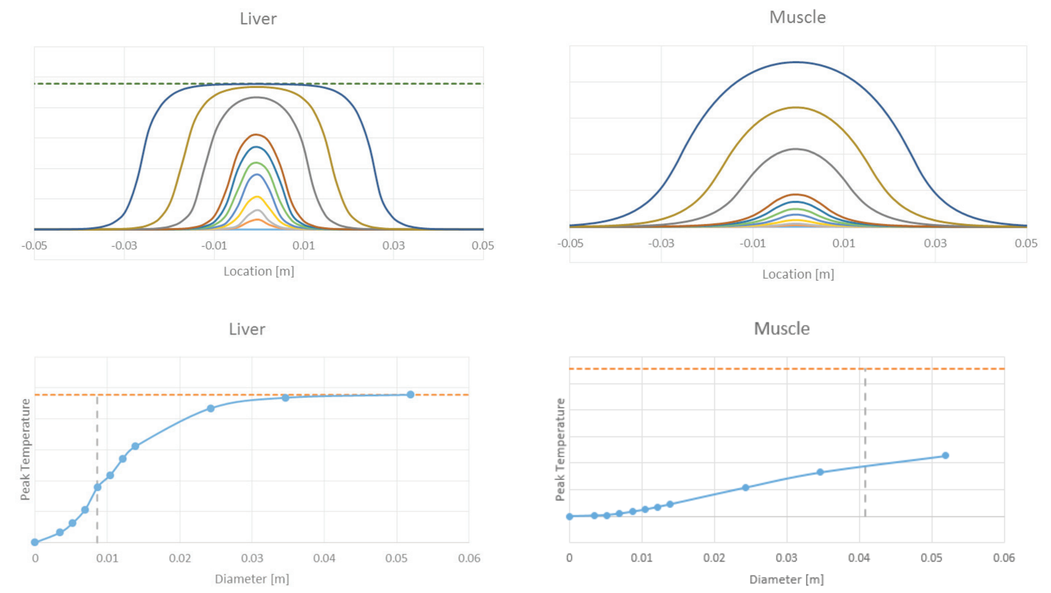


Figure 6: *Particle distribution width dependence of induced heating in liver (left, high perfusion), and muscle (right, lower perfusion). Where the distribution is wide compared to the Green's function characteristic length (grey, dashed lines), the temperature approaches a perfusion dominated maximum (orange, dashed line). For smaller diameters, the width-dependence is strong.*

CONCLUSIONS

Nanomedicine promises efficient, targeted therapies. A comprehensive treatment simulation tool for personalized SPION magnetic nanoparticle hyperthermia modeling was implemented in Sim4Life and used to study therapeutic applications with image-based modeling for anatomy and particle distribution coupled with multiscale / multiphysics simulations of electromagnetic exposure, particle power loss, thermophysiology, and treatment impact. This platform has been used to optimize particle size and applicator frequency and to gain understanding on impact of particle distribution, vasculature, and on model treatment.

Ongoing research is focused on the extraction of quantitative particle density information from MRI data and on experimental validation.

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