Effect of photothermal therapy on nuclear magnetic resonance imaging during concurrent use

C. Rousseau[1], Q.L. Vuong[2], Y. Gossuin[2], B. Maes[1] and G. Rosolen[1]

[1] Micro- and Nanophotonic Materials Group, Research Institute for Materials Science and Engineering, University of Mons, 20 Place du Parc, B-7000 Mons, Belgium

[2] Biomedical Physics Unit, University of Mons, 20 Place du Parc, B-7000 Mons, Belgium

Theranostics, the integration of diagnosis and treatment in medicine, has gained significant popularity. For these applications, innovative hybrid nanoshell platforms have emerged. A promising platform consists of a particle composed of a magnetic core that influences proton relaxation, combined with a gold shell that converts light into heat. This enables the particles to be utilized for both photothermal therapy and magnetic resonance imaging concurrently. In our studies, we compare our numerical findings with reported experiences and analytical modeling, showing that the collective thermal interaction of the nanoshells leads to a modification of the transverse relaxation rate, a constant that plays a role in magnetic resonance imaging contrast. The modification of the transverse relaxation rate is highly dependent on the geometry of the nanoshells. This investigation underscores the promising potential of the hybrid nanoscale platform to advance the use of both MRI and plasmonic photothermal therapy. This paves the way for innovative and multifaceted biomedical interventions.

Introduction

In recent years theranostics, a medical discipline trying to integrate the diagnostic and therapeutic aspects within medicine, has experienced notable expansion. Numerous combinations of imaging methods and treatment approaches are possible using different platforms. To illustrate, one can explore the integration of fluorescence and chemotherapy with quantum dots [1], or the combination of Raman scattering and mitochondria targeting with carbon nanotubes [2]. Within the vast array of nanoplatforms, the nanoshell (NS) platform stands out with its magnetite core and gold shell, providing numerous advantages. Firstly, this composite material alloy enables nanoparticle tracking via nuclear magnetic resonance imaging (MRI) with the magnetite core, and facilitates cancer cell destruction through photothermal therapy, leveraging the plasmonic properties of the gold shell [3]. Secondly, the nanoshell configuration demonstrates a remarkable tunability of its plasmonic resonance. This allows convenient adaptation to the near-infrared biological window in humans, the wavelength range where light most effectively penetrates tissues. This feature facilitates efficient heating when nanoparticles internalized within the tumor are illuminated with lasers. Lastly, the gold shell offers opportunities for the functionalization of the nanoplatform, enabling efficient targeting of cancer cells. In this study, we combined thermoplasmonic theory with the theory of relaxation induced by iron oxide nanoparticles, allowing us to assess the potential impact on image contrast of concurrently employing photothermal therapy and nuclear resonance imaging.

Nanoshell particles as heaters

In the field of plasmonics, the denomination 'localized surface plasmon' refers to a normal mode of collective oscillation of the free electrons contained in metal nanoparticles [4]. From the wave theory point of view, light can generate excitations of free electrons when its frequency matches the plasmonic resonance of a nanoparticle. The resonance frequency is influenced by different factors such as the nanoparticle's composition, geometry, and the surrounding medium. Due to the Joule effect, this collective oscillation within the nanoparticle will convert incident light energy into heat. The thermal energy will subsequently disperse into the surrounding medium, leading to a temperature rise in the environment. By solving the steady-state heat transfer differential equation, with laser irradiance (I_0) set at 0.33 W/cm^2, it is shown that the temperature rise around a single NS is negligeable: only 0.0003 K elevation at the surface of the NS. This finding is unexpected in contrast to experimental observations indicating a macroscopic temperature rise of about 20 K when a nanoshell solution is exposed to low-irradiance laser illumination [3] (Figure 1). To understand the macroscopic temperature increase, it is necessary to consider the collective thermal interaction of the nanoparticles. Each nanoparticle elevates its temperature independently through Joule heating caused by its plasmonic excitation. Moreover, it experiences heating from all other nanoparticles within the solution. For a sample with a high concentration of nanoparticles, we can use the following integral taken on the volume of the laser beam to calculate the temperature rise at any points in the sample:

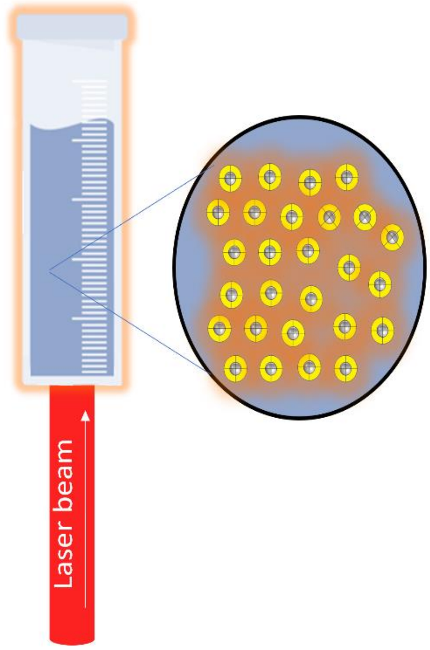

Figure 1: ***Simulated experimental setup:*** *a nanoshell solution illuminated by a continuous wave laser.*

$$\boldsymbol{T_{collective}(\vec{r})} = \iiint_{\boldsymbol{laser\ beam}} \frac{\boldsymbol{q(\vec{r'})}}{\boldsymbol{4\,\pi\,\kappa_{sur}\,\left|\vec{r'}-\vec{r}\right|}}\,\boldsymbol{dr'} \text{ with } q(\vec{r'}) = I_0\, N\, \sigma_{abs}\, e^{-\sigma_{ext}\, N\, z} \qquad \textbf{(1)}$$

The constant κ_{sur} is the thermal conductivity of the surrounding medium, N the number of NS per m^3 and I_0 is the irradiance of the laser beam, σ_{abs} and σ_{ext} are respectively the absorption cross-section and the extinction cross-section of the NS and z the distance in the sample. We can map the temperature increase within the sample as shown in Figure 2.

Influence of temperature gradient on the relaxation time

To quantify the impact of the macroscopic temperature gradient due to the laser illumination on the MRI we map, within the sample, the change in transverse relaxation rate (R_2). The latter is a constant that describe the progressive dephasing of proton's spinning magnetic dipoles of the solution and have a direct impact on the contrast of MRI images. To acquire the spatial distribution of the change in R_2, we implemented the following procedure. We first compute the absorption cross-section and the extinction cross-section of the nanoparticles using COMSOL Multiphysics. We then input these data into the collective models, enabling us to numerically calculate the temperature increase at all points in the sample using Eq. (1). We then discretize this temperature map to mimic the voxel-by-voxel acquisition of the MRI signal. The grid on Figure 2 illustrates this discretization. The average temperature of each voxel is numerically calculated using a sub-discretization of each voxel. Now, we choose the appropriate relaxation model for each voxel. Three different transverse relaxation models are available to describe relaxation induced by superparamagnetic nanoparticles. These models will not be detailed here, but their complete description is available in reference [5]. The choice of the model is guided by the size of the nanoparticle, its magnetization, and the water diffusion coefficient. The latter is directly related to temperature, which explains the influence of temperature on R_2. Having executed this process for every voxel within the sample, we generate a transverse plane of the sample that includes the center of the laser beam. We thus finally obtain the desired map of the spatial variation of R_2 in the solution (Figure 3).

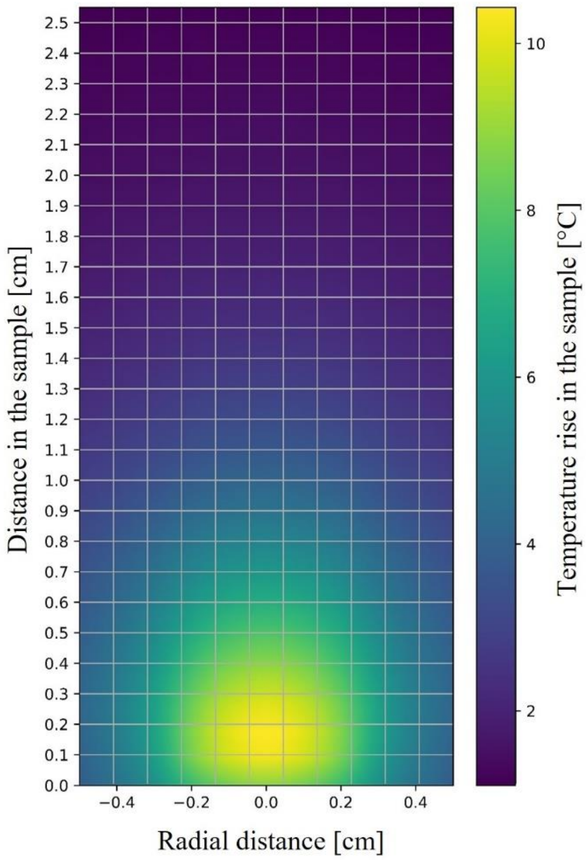

*Figure 2: **Map of temperature elevation within the sample under laser irradiance** of 0.33 W/cm^2. The radius of the laser beam is equal to 0.28 cm. Nanoshell parameters are: magnetite core radius: 55 nm, gold shell thickness: 10 nm.*

Figure 3 represents the spatial variation of R_2 for three geometries of the NS. We observed that the alteration of R_2 by the laser illumination is highly dependent on the geometry of the NS. Figure 3a displays the results obtained for small NS with a magnetite core radius equal to the thickness of the gold shell. NSs exhibiting this geometry lose approximately 20% of their impact on the solution's relaxation when subjected to laser illumination, hence degrading the MRI contrast. Figures 3b and 3c reveal that for larger NS, two regimes coexist. One regime where the laser illumination does not influence the transverse relaxation Figure 3b, and another where, contrary to the case of small NS, laser illumination increases the transverse relaxation Figure 3c. The proportion between the volume of gold and the volume of magnetite determines whether the NS falls into one regime or the other. The geometry of the nanoshell can be modified to achieve the desired effects on the transverse relaxation time of the solution. For example, if larger contrasts are required for MRI imaging, particles with thicker shells should be designed (Figure 3c). On the other hand. if one wishes to ensure that phototherapy does not impact the images taken in MRI, a geometry with thinner shells can be employed (Figure 3b).

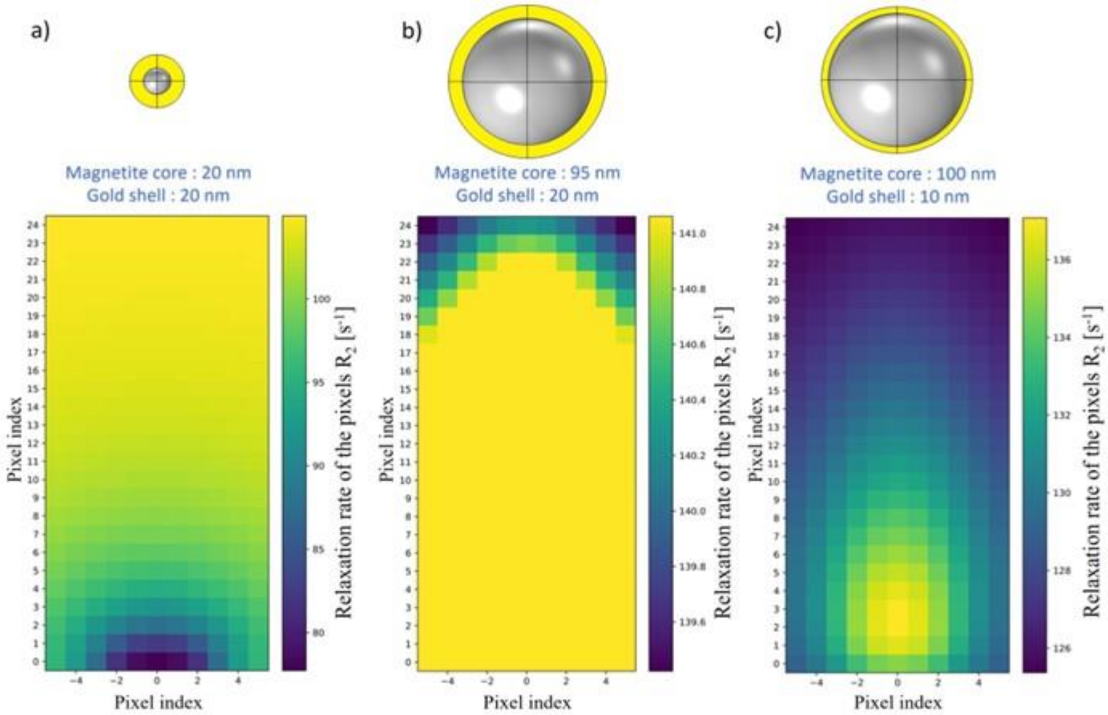

Figure 3: ***MRI signal is highly dependent on the geometry of the nanoparticles under laser illumination****. Maps of the transverse relaxation within the sample for an incident laser power of 0.33 W/cm^2. A diagram of the considered geometry is presented above each map. The radius of the magnetite core and the thickness of the shell are: (a) 20/20 nm, (b) 95/20nm, (c) 100/10nm.*

Conclusion

In this paper, we combine two research areas: thermoplasmonics and relaxation induced by iron oxide nanoparticles. This was done to explore the implications of phototherapy on MRI, a question that has become pertinent with the advent of theranostics. To do this, the behavior of a NS solution under laser illumination was studied. The results establish that the collective effects between nanoparticles must be considered to describe the temperature rise in the sample, which influence the relaxation rate through proton diffusion. Notably, the influence on the relaxation rate is highly dependent on the geometry of the NSs. We believe that our study sets the stage for a systematic optimization of various NS parameters to attain the desired effect on MRI.

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