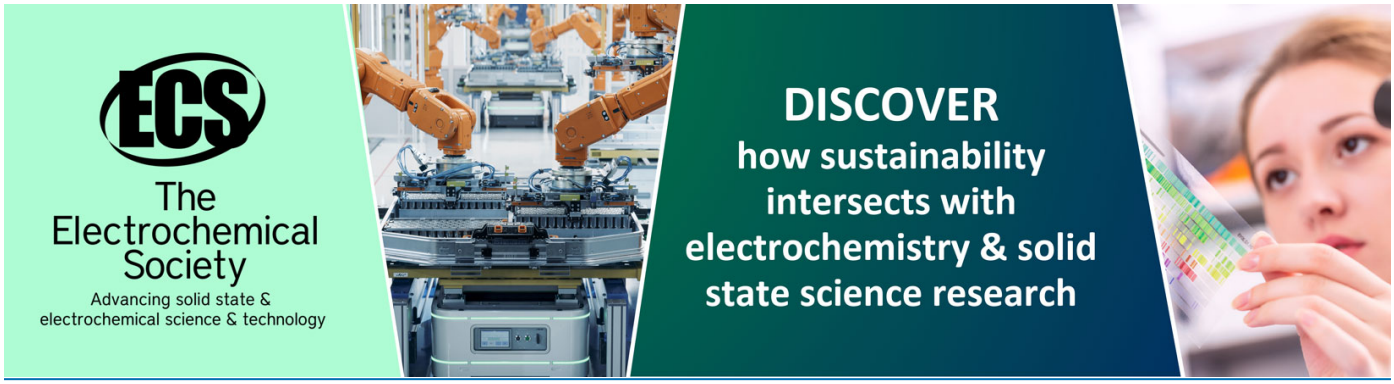
# Computational study on superparamagnetic hyperthermia with biocompatible SPIONs to destroy the cancer cells





# Computational study on superparamagnetic hyperthermia with biocompatible SPIONs to destroy the cancer cells

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**Abstract**. Superparamagnetic hyperthermia (SPMHT) appears nowadays as the most promising method of the future, non-invasive and with low toxicity, for destroys the cancer cells through the magnetic relaxation in superparamagnetic nanoparticles. In our research we focused on finding the *optimal* conditions using a 3D computational study to obtain a *maximum* specific absorption rate (SAR) by the magnetic relaxation in $Fe_3O_4$ and $\gamma$-$Fe_2O_3$ superparamagnetic iron oxide nanoparticles (SPIONs), which give the most pronounced SAR and with low toxicity on cells. The effect of the diameter of the nanoparticles, frequency and amplitude of external alternating magnetic field and the thickness of biological coating of nanoparticles in the case of their encapsulation in biocompatible membranes, like liposomes (Ls) and cyclodextrins (CDs), on Néel-Brown magnetic relaxation and maximum SAR, are presented and discussed in this paper, within the biological admitted limit.

## 1. Introduction

Superparamagnetic hyperthermia (SPMHT) [1], obtained as a result of magnetic relaxation in superparamagnetic iron oxide nanoparticles (SPIONs), is a very suitable method for destroying cancer cells [2], by increasing the temperature to *42-43 °C* in the targeted tissues. This method is non-invasive and apparently without toxicity when nanoparticles are encapsulated in biocompatible membranes, such as liposomes (Ls) or cyclodextrins (CDs), which are used today as a possible nanocarriers in drug delivery [3,4]. One of the most important issues in the use of SPMHT is finding the *optimum* conditions for obtaining a *maximum* specific absorption rate (SAR). Several research studies have been conducted on the effect of the nanoparticles' diameter upon the magnetic hyperthermia [5,6]. However, finding the *optimal physical* conditions for obtaining a *maximum* SAR, within the accepted biological limit [7] is still an open issue, which must be clarified before moving on to the next stage, of *in vitro* or *in vivo* studies and, finally, to the clinical studies. The success of the *in vitro*/*in vivo* magnetic hyperthermia highly depends on the results from the first stage. In this regard, we conducted a 3D computational study of SAR, considering simultaneously the diameter of the nanoparticles (D), the frequency (f) and amplitude of the magnetic field (H) in the case of SPIONs of $Fe_3O_4$ and $\gamma$-$Fe_2O_3$, when they are encapsulated in Ls or bioconjugated with CDs (using CDs in SPMHT is a new strategy of ours). Our 3D study allows us to *rapidly* find the *optimum* values of the *D, f, H* parameters, the viscosity of the dispersion environment of the bionanocapsules, etc., by simply modifying their values in the calculation program, thus optimizing the superparamagnetic hyperthermia, by simulating real conditions. The study focused on finding the optimum diameter of the nanoparticles, which is a critical parameter, and on the way in which the thickness of the biological

membrane of the Ls and of the layer determined by the CDs at the surface of the biocompatible nanoparticles, when dispersed in water, influence the contribution of the Neel-Brown relaxation processes in obtaining the maximum SAR. Furthermore, for this study, we took into consideration a very small volume fraction of the nanoparticles, of only *1.7 vol%*, which allows the maintenance of the superparamagnetic behavior of nanoparticles [8], without the appearance of the hysteresis loop caused by the interactions between nanoparticles [9], and the application of the Neel-Brown relaxation theory; in static conditions (where the measuring time is *~100 s* [10]), in the lack of the interactions between nanoparticles, and as a result of the reduced magnetic anisotropy of the $Fe_3O_4$ and $\gamma$-$Fe_2O_3$ nanoparticles, the superparamagnetic (SPM) behavior is maintained for rather large diameters (*<20 nm*), because the Neel-Brown relaxation times (in the order of nano - microseconds) are much lower than the measuring time (tens – hundreds of seconds). Consequently, considering the Neel-Brown magnetic relaxation, we aimed to find the *optimum* conditions in which the *highest maximum* SAR is *obtained* for the nanoparticles of $Fe_3O_4$ and $\gamma$-$Fe_2O_3$, when they are encapsulated in Ls or bioconjugated with CDs, *without exceeding the biological limit* [7].

## 2. Theory

Volumetric power dissipated in superparamagnetic nanoparticles in alternating harmonic magnetic field, with frequency $f$ and amplitude $H$ [1], can be written based on the static magnetic susceptibility $\chi_0$ and magnetic relaxation time $\tau$ [11]: $P = \mu_0 \pi f \frac{2\pi f\tau}{1+(2\pi f\tau)^2}\chi_0 H^2$. In low magnetic fields, $\chi_0$ can be approximated by the initial magnetic susceptibility $\chi_i = \varepsilon\mu_0\pi M_s^2 D^3/18k_BT$, deduced from the Langevin function [12], for the approximation of the spherical nanoparticles, and the relaxation time is $\tau = \tau_N\tau_B/(\tau_N+\tau_B)$, with the following components: $\tau_N = \tau_0 \exp\left(\pi KD^3/6k_BT\right)$, for the Néel relaxation time, and $\tau_B = 3\pi\eta D_h^3/6k_BT$, for the Brown relaxation time. In the above mentioned formulas, $M_s$ is the spontaneous magnetization, $D$ is the magnetic (mean) diameter, $\varepsilon$ is the (volume) magnetic packing fraction of nanoparticles, $\mu_0$ is the permeability of vacuum, $k_B$ is the Boltzmann constant, $T$ is the room temperature, $K$ is the magnetic anisotropy constant, $\tau_0$ is the time constant (*~$10^{-9}$ s*), $\eta$ is the viscosity coefficient and $D_h$ is the hydrodynamic diameter of nanoparticles: $D_h = D + 2d$, $d$ being the biological coating thickness. Specific absorption rate (SAR), under adiabatic conditions, can be expressed in terms of power dissipation, expressed in *W/g*, by the formula: $SAR = P/\rho$, where $\rho$ is the material density.

## 3. Results and discussions

SAR was studied in 3D for the monodispersed $Fe_3O_4$ and $\gamma$-$Fe_2O_3$ nanoparticles, which are suitable for magnetic hyperthermia. SAR was also studied when the nanoparticles are encapsulated in Ls or bioconjugated with CDs, while considering the hydrodynamic diameter of the nanobiocapsules ($D_h$). In these conditions, we aimed to find the most suitable nanoparticles, regarding the diameter (optimal diameter in the range of *1- 30 nm*), depending on the frequency and amplitude of the external magnetic field, which are leading to the *highest maximum* SAR, without exceeding the biological limit. Data used in calculations, according to the formulas in Section 2, are given in Table 1.

**Tabel 1:** *Characteristic observables of nanoparticles and alternating magnetic field parameters*

| *Samples* | $M_s$ *(kA/m)* | $K$ *(kJ/m$^3$)* | $\rho$ *(g/cm$^3$)* | $\varepsilon$ | $d_{Ls}$ [3] *(nm)* | $d_{CDs}$ [14] *(nm)* | $\eta$ *(kgm$^{-1}$s$^{-1}$)* | $f$ *(kHz)* | $H$ *(kA/m)* |
|---|---|---|---|---|---|---|---|---|---|
| $Fe_3O_4$ [13] | 477 | 11 | 5.24 | 0.017 | 35 | 0.8 | $7\times10^{-4}$ | 100-1000 | 10-20 |
| $\gamma$-$Fe_2O_3$ [1] | 416 | 4.6 | 5.20 | 0.017 | - | - | - | 100-1000 | 10 |

Due to the very low (*0.017)* volume magnetic packing fraction of nanoparticles ($\varepsilon$) and to the thickness of the biological coating of the nanoparticle, the nanoparticles are well isolated from one another and, therefore, the interactions between them (Van der Waals and dipole-dipole) may be neglected [8,15].

In the case of $Fe_3O_4$ nanoparticles (figure 1), for the *10 kH/m* amplitude of the magnetic field, it has been found that the maximum SAR can be obtained if the magnetic diameter of the nanoparticles is *~15-17 nm*, depending on the frequency (*100 - 1000 kHz*); at lower frequencies the diameter has a higher value. Highest maximum for SAR is *~27 W/g* and it can be obtained at the diameter of *~15 nm* and frequency of *1 MHz*.

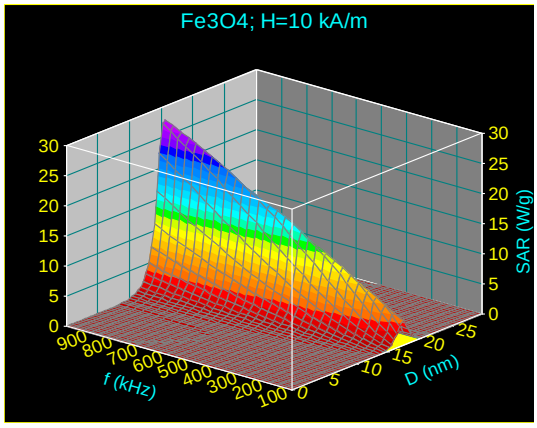



**Figure 1.** (colour online) 3D diagram of SAR in the case of $Fe_3O_4$ nanoparticles.

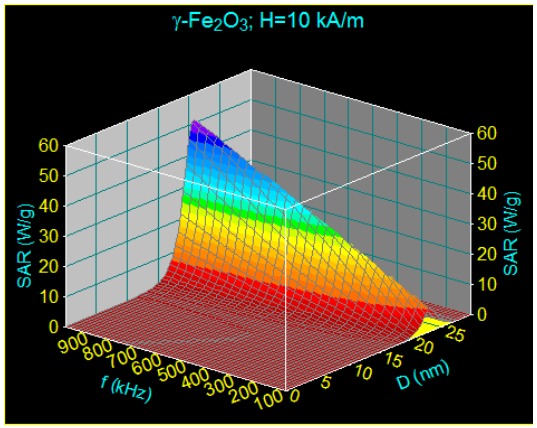
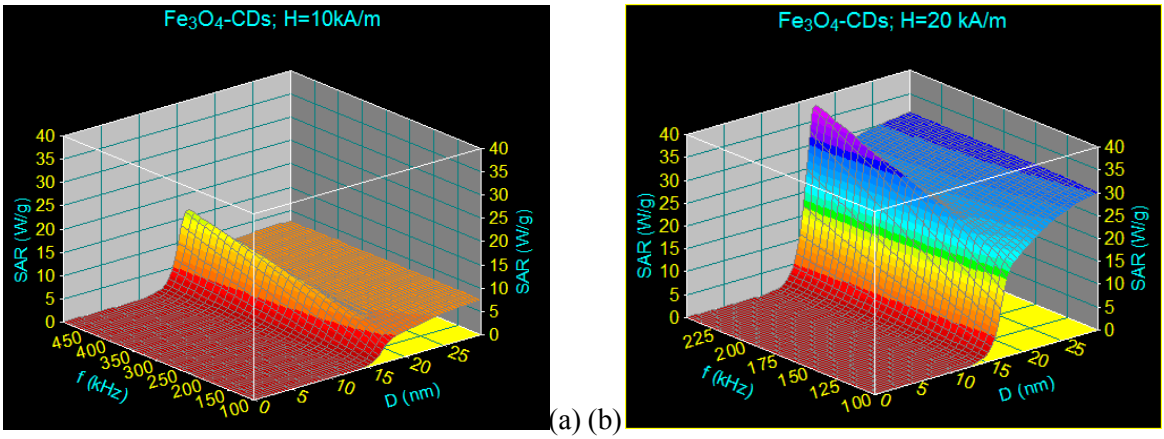



**Figure 2.** (colour online) 3D diagram of SAR in the case of $\gamma$-$Fe_2O_3$ nanoparticles.

In the case of $\gamma$-$Fe_2O_3$ nanoparticles (figure 2), the SAR increase, reaching the highest value of *50 W/g*, under the same field conditions and frequency, but at considerably larger diameter of nanoparticles, i.e. *~20.5 nm*. However, although a higher maximum SAR it is obtain for $\gamma$-$Fe_2O_3$ nanoparticles, the high value of the nanoparticles' diameter determines their behaviour in external magnetic field to not be superparamagnetic (Néel magnetic relaxation time increases rapidly with diameter between *19-25 nm*), and thus appear a small hysteresis loop. Consequently, the formula for SAR cannot be used in this case. For this reason, $Fe_3O_4$ nanoparticles are more suited than those of $\gamma$-$Fe_2O_3$ in *superparamagnetic* hyperthermia. Other authors have shown that, in the case of $\gamma$-$Fe_2O_3$ nanoparticles, the maximum specific loss power (SLP) is obtained for smaller diameters, namely *14 nm* [5]. This is probably due to the value of the magnetic anisotropy constant higher than the known one [1,16]; a higher anisotropy constant leads to a maximum of the SLP at a smaller diameter.

Having in view this result, we studied the SAR for $Fe_3O_4$ nanoparticles when they are made biocompatible in order to be used in practice. Further on, we consider two cases: (i) $Fe_3O_4$ encapsulated in Ls and (ii) $Fe_3O_4$ bioconjugated with CDs, strategy currently used in research on targeted therapy. When the nanoparticles are encapsulated in Ls (i), Brown relaxation time becomes much higher than the Néel relaxation time ($\tau_B$ $(167\times10^3\ ns)$ >> $\tau_N$ $(122\ ns)$), and the relaxation time will be: $\tau = \tau_N/(1+\tau_N/\tau_B) \cong \tau_N$ (see chapter 2). In this case the SAR diagram obtained is similar to that in figure 1, these being determined only by the Néel dissipation processes.

The results for $Fe_3O_4$-CDs are shown in figure 3 for two values of the magnetic field, considering biological accessibility limit, $Hf \le 5\times10^9\ Am^{-1}Hz$ [7]. In this case, two magnetic relaxation processes contribute to the SAR, both Néel and Brown, for magnetic diameters greater than *15 nm*. Néel relaxation processes become dominant with the increasing frequency to the upper limit at the *~15.5-17 nm*. At lower frequencies, such as *150 kHz*, contributions to the SAR of the Néel and Brown relaxation processes become comparable and at the frequency of *100 kHz*, Brown relaxation prevail, especially in




(a) (b)

**Figure 3.** (colour online) 3D diagram of SAR until the biological limit in the case of $Fe_3O_4$ nanoparticles bioconjugated with CDs, for magnetic field amplitude of (a) 10 kA/m and (b) 20 kA/m.

large diameters. When the magnetic field reaches to *20 kA/m* (figure 3(b)), the highest maximum of SAR increases significantly from *~15 W/g* to about *~38 W/g*, at the biological limit, for the *17 nm* diameter. In this case, the SAR still remains high (*~30 W/g*) for $D > 22$ *nm*, due to Brown relaxation.

## 4. Conclusions

The 3D study allowed us to optimize superparamagnetic hyperthermia, in order to apply it in practice: by finding the most suitable bionanoparticles, as material and size, and also as magnetic field parameters (*f* and *H*), in order to obtain the highest SAR within the biological accepted limit.

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