Modelling irradiation by EM waves of multifunctionalized iron oxide nanoparticles and subsequent drug release

Feng Wang, Florent Calvayrac, Véronique Montembault, and Laurent Fontaine
Université du Maine (le Mans), Institut des Molécules et Matériaux du Mans, France
E-mail: florent.calvayrac@univ-lemans.fr

Abstract. Thermal transport in the environment close to the periphery of the nanoparticle, from a few angstroms to less than a nanometer scale, is becoming increasingly important with the advent of several biomedical applications of multifunctional magnetic nanoparticles, including drug delivery, magnetic resonance imaging, and hyperthermia therapy. We present a multiscale and multiphysics model of the irradiation by electromagnetic waves of radiofrequency of iron oxide nanoparticles functionalized by drug-releasing polymers used as new multifunctional therapeutic compounds against tumors. We compute ab initio the thermal conductivity of the polymer chains as a function of the length, model the unfolding of the polymer after heat transfer from the nanoparticle by molecular mechanics, and develop a multiscale thermodynamic and heat transfer model including the surrounding medium (water) in order to model the drug release.

1. Introduction
Magnetic nanoparticles can chemically anchor or physically adsorb specific polymers for further functionalization, depending on the desired application[1]. Functionalized magnetic nanoparticles with certain polymers as drug carriers are very promising for applications in magnetic-field-directed drug targeting and magnetic-field-controlled drug delivery[2, 3, 4]. The magnetic-field-directed drug targeting is to guide functional magnetic nanoparticles to a chosen site under the localized magnetic field gradients, while magnetic-field-controlled drug-releasing is based on the fact that remote release of drugs is initiated by the heat generated upon alternating magnetic field exposure. The controlled placement and drug delivery of these functional magnetic nanoparticles by means of an external magnetic field enables their biomedical application of having the potential to achieve high local concentration, and avoiding toxicity and other adverse side effects arising from high drug doses in other parts of the organism. Readers who are interested in a more detailed understanding of the physical properties and behavior of these magnetic nanoparticles, or biomedical and biotechnology applications, are referred to specific reviews[5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. In the following, after briefly showing a diagrammatic representation of research ideas in the context of functional iron oxide magnetic nanoparticles (IONPs) with hyperthermia-induced drug-releasing of recent interest, we focus mainly on how heat is transferred through the polymer chains between the drug linker and the nanoparticle surface in such functional IONPs.
2. Diagrammatic Representation of Research Ideas

To build an suitable computational model of functional IONPs, we employ a reported design scheme\cite{15} that contains a phosphonic acid group for the binding to the iron oxide surface of IONPs, and two orthogonal clickable groups: an alkyne moiety for installing an azide end-functionalized hydrophilic polymer through 1,3-dipolar cycloaddition to impart aqueous dispersability/stability, antifouling property, and biocompatibility to the IONPs; and a furan ring that serves as a drug linker for a biologically active molecule through reversible Diels-Alder (DA) chemistry (as shown in Figure 1 and Figure 2).

![Diagram](image)

**Figure 1.** A reported design scheme of functional iron oxide magnetic nanoparticles with hyperthermia-induced drug-releasing.

![Diagram](image)

**Figure 2.** The structure to be considered for modeling.

It is well known that the microscopic reverse of the DA reaction, namely the retro-Diels-Alder (retro-DA) reaction, can be accomplished spontaneously with a supply of activation of heating. Consequently, one can speculate that when such functional IONPs are exposed to a varying magnetic field, the particles would become powerful heat sources, and sufficient heat could be brought in close proximity to the furan ring to initiate the retro-DA reaction. Indeed, recent experiments have shown that localized heating is observed without any significant heating of the medium\cite{15, 16, 17} when IONPs are exposed to alternating magnetic field, forming very high temperature gradient from the nanoparticle surface. Obviously, for the given magnetic field frequency and the size of the IONPs, the chain length between the drug linker and the nanoparticle surface should be precisely designed/optimized to bring enough heat to engage the retro-DA reaction, (as shown in Figure 3). Theoretical studies of the possible heat transfer mechanisms have been initiated, but to date obtaining an atomic- and microscale-level
understanding of how heat is transferred through the polymer chains between the furan ring and the nanoparticle surface remains the greatest challenge that must be overcome in order to realize the full potential of this new class of functional magnetic nanoparticles.

![Diagram](image1)

**Figure 3.** To look at the influence of the chain length between the drug linker and the nanoparticle onto heat transfer.

3. **Atomic-level Modeling of Heat Transfer of Polymer Chains**

![Diagram](image2)

**Figure 4.** Atomic-level modeling of heat transfer of polymer chains from density-functional-theory-based ab initio molecular dynamics simulations.
Figure 5. Heat conduction model with negligible internal resistance.

Figure 6. Checking velocity rescaling method with different relaxation time.

This study develops one of the most comprehensive series of molecular dynamics simulations to gain insight into thermal transport between the thermoreversible linker and the nanoparticle.
surface for functional IONPs in more realistic atomic-level modeling. Our approach is to hold the nanoparticle of the simulation structure at some desired temperature by rescaling velocities of nanoparticle atoms as a heat source while investigating temperature rising process of the drug linker as a function of time and chain length (as shown in Figure 4).

An approach is described by Figure 5 for determining thermal conductivity of polymer chains. The approach idea, which is directly analogous to the lumped thermal capacity model[18], is that the resistance to heat transfer within the drug-releasing part is negligible when compared with the resistance to heat transfer with the polymer chains.

The velocity rescaling method has been checked with different ‘relaxation time’ (as shown in Figure 6), which gives a rough estimates of the time needed to achieve the given target temperature, and controls the global temperature fluctuation intensity around the given target temperature.

4. Results and Discussion

To investigating temperature rising process of the drug linker as a function of chain length, we have optimized three geometries of iron oxide nanoparticles functionalized by polymers with different chain length (as shown in Figure 7).

![Figure 7. Optimized geometries of iron oxide nanoparticles functionalized by polymers with different chain length.](image)
Figure 8. The temperature rising process of the drug linker in cases of A, B and C, keeping the nanoparticle temperature at 500 K.

Figure 9. The polymer folding occurs with increasing temperature in cases of A, keeping the nanoparticle temperature at 500 K.

Keeping the nanoparticle temperature at 500 K, the temperature rising process of the drug linker of case A is obviously different from cases of B and C (as shown in Figure 8). This shows that the chain length between the drug linker and the IONP can influence the drug delivery.
deeply. After checking the time evolution of geometric structure, we find that the polymer folding occurs with increasing temperature in the case A (as shown in Figure 9).

The polymer folding can enhance the heat transfer rate between the IONP and drug linker by adding heat transfer pathway and decreasing heat transfer distance. One of the key findings of this study is that there is a significant thermal transport dependence on the polymer chain folding, invoked by heat accumulation in the polymer. Our calculations suggest that a new/existing heat transfer pathway is activated/inactivated by an increased/decreased link between the nanoparticle and the folded polymer chain, as indicated by the qualitative change of temperature rising process of the polymer drug-releasing part (as shown in Figure 10).

![Figure 10.](image)

**Figure 10.** The qualitative change in temperature rising process of the drug linker might indicate opening/closing of a new/existing heat transfer pathway, in case of A, keeping the nanoparticle temperature at 500 K.

5. Summary and Conclusions
In summary, thermal transport in the environment close to the periphery of the nanoparticle, from a few angstroms to less than a nanometer scale, is becoming increasingly important with the advent of several biomedical applications of multifunctional magnetic nanoparticles, including drug delivery, magnetic resonance imaging, and hyperthermia therapy. Can we look at the influence of the distance between the drug linker and the IONP onto the debonding? How heat is transferred from the IONP to the drug linker through polymer chain? Stimulated by above interesting and unanswered questions, we have built a model method for the heat transfer investigation in novel functional IONPs showing unprecedented, active control over drug release by retro-DA reaction by using hyperthermia effects, and achieved following conclusions: 1) The polymer folding can enhance the heat transfer rate between the IONP and drug linker by adding heat transfer pathway and decreasing heat transfer distance; 2) The chain length between the drug linker and the IONP can influence the drug delivery deeply.
References

[1] Lu A H, Salabas E L and Schüth F 2007 Angew. Chem. Int. Ed. 46 1222
[2] Shubayev V I, Pisanic T R, Jin S H 2009 Adv. Drug Delivery Rev. 61 467
[3] Ho D, Sun X L and Sun S H 2011 Acc. Chem. Res. 44 875
[4] Mura S and Couvreur P 2012 Adv. Drug Delivery Rev. 64 1394
[5] N’Guen T K T 2012 Magnetic Nanoparticles: From Fabrication to Clinical Applications (Boca Raton, FL: CRC)
[6] Cheng Z L, Al Zaki A, Hui J Z, Muzykantov V R and Tsourkas A 2012 Science 338 903
[7] Reddy L H, Arias J L, Nicolas J and Couvreur P 2012 Chem. Rev. 112 5818
[8] Amstad E, Textor M and Reimhult E 2011 Nanoscale 3 2819
[9] Hao R, Xing R J, Xu Z C, Hou Y L, Gao S and Sun S H 2010 Adv. Mater. 22 2729
[10] Boyer C, Whittaker M R, Bulmus V, Liu J Q and Davis T P 2010 NPG Asia Mater. 2 23
[11] Gao J H, Gu H W and Xu B 2009 Acc. Chem. Res. 42 1097
[12] Frey N A, Peng S, Cheng K and Sun S H 2009 Chem. Soc. Rev. 38 2532
[13] Laurent S, Forge D, Port M, Robic C, Elst L V and Muller R N 2008 Chem. Rev. 108 2064
[14] Lu A H, Salabas E L, Schüth F 2007 Angew. Chem. 119 1242
[15] N’Guen T T T, Duong H T T, Basuki J, Montembault V, Pascual S, Guibert C, Fresnais J, Boyer C, Whittaker M R, Davis T P and Fontaine L 2013 Angew. Chem. Int. Ed. 52 14152
[16] Huang H, Delikanli S, Zeng H, Ferkey D M and Pralle A 2010 Nat. Nanotechnol. 5 602
[17] Creixell M, Bohorquez A C, Torres-Lugo M and Rinaldi C 2011 ACS Nano 5 7124
[18] Mellor P H, Roberts D and Turner D R 1991 IEE Proceedings B (Electric Power Applications) 138(5) 205