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High-Magnetic-Moment Nanoparticles for Biomedicine

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Abstract— **Magnetic nanoparticles play an important role in biomedical applications, such as MR imaging, drug delivery and hyperthermia. Nanoparticles made of high-moment materials like Fe-Co and Fe have become active in the field due to superior performance. Protected by a biocompatible shell (Au/Ag/Si/C), high-moment nanoparticles can retain their magnetic property over a long time and disperse well. By using a physical gas condensation technique, such high-moment nanoparticles and core-shell structured nanoparticles can be made and used for biomedicine.**

I. Introduction

Nanoparticles have started to draw a great deal of attention in a wide range of biomedical area. Unique properties introduced or enhanced by the small size of nanoparticles are studied widely to achieve desirable optical, mechanical and magnetic capabilities[1]-[3]. The large surface to volume ratio gives favorable active interactions[4]. Magnetic nanoparticles have become one of the most appealing candidates for use in biomedical applications, anywhere interactions with magnetic fields present. These include MRI, drug delivery and magnetic fluid hyperthermia applications.

From both magnetic and biomedical points of view, superparamagnetic nanoparticles have a number of favorable properties. They have a single magnetic domain structure and their magnetization fluctuates, assisted by thermal energy, giving rise to a negligible magnetic moment in the absence of any applied magnetic field. In the presence of a magnetic field, their magnetization can be described by the Langevin equation[5]. This intrinsic property makes them preferable because aggregation can be avoided without sacrificing magnetic signal [4].

Superparamagnetic iron oxide nanoparticles (SPIO), maghemite (γFe_2O_3) and magnetite (Fe_3O_4) are widely used due to their relatively easy synthesis process and established biocompatibility. They have been studied for several decades and have contributed to both diagnostic applications such as MR imaging and therapeutic applications such as hyperthermia[6][7]. However, the low saturation magnetization of iron oxide nanoparticles limits their applications, in some cases not even achieving the optimal level[8]. Increasing the magnetic moment of nanoparticles is the key for improving their application in biomedicine. Under size restrictions in a biological system, to achieve the possible highest magnetic moment of individual nanoparticle is desired for higher signal to noise ratio, lower dosage and higher efficiency. Although attempts to increase saturation magnetization have been made by doping iron oxides to form spinel metal ferrites, magnetic property still needs to be enhanced for future applications [8].

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II. High Magnetic Moment Fe-Co and Fe Nanoparticles

Our group first proposed the application of bio-compatible high-magnetic-moment nanoparticles for biomedicine application by preparing FeCo-Au(Ag) nanoparticles in gas phase in 2005 [9]. Bulk Fe-Co alloy has the highest saturation magnetization 240 emu/g at Fe:Co composition ratio of around 60:40, which makes it a promising material. Considering a single isotropic $Fe_{0.6}Co_{0.4}$, γFe_2O_3 and Fe_3O_4 superparamagnetic nanoparticle with the same size (say 13nm in diameter), the corresponding hysteresis loops follow the Langevin equation[5]:

$$m = m_0\left[\coth s - \frac{1}{s}\right], s = \frac{m_0 H}{kT} \qquad (1)$$

where m_0 is magnetic moment of a single domain particle, H is applied field, k is Boltzman constant and T is temperature. Using bulk saturation magnetization of $Fe_{0.6}Co_{0.4}$, Fe_3O_4 and γFe_2O_3, M-H loops for a single superparamagnetic nanoparticle at room temperature are calculated assuming unoxidized $Fe_{0.6}Co_{0.4}$ and are shown in Fig1. At 20 Oe external field, the moment of an isotropic $Fe_{0.6}Co_{0.4}$ nanoparticle is $2.4*10^{-15}$emu, which is 17 times larger than that of a Fe_3O_4 nanoparticle and 28 times than that of a γFe_2O_3 nanoparticle. It is important to notice that in this ideal case a single Fe-Co nanoparticle response to the applied field much faster in the low field region, leading to a quick rise in magnetic moment value. This indicates that high-magnetic-moment Fe-Co nanoparticles can be used more efficiently as compared to same size iron oxide nanoparticles. Because oxidation usually takes place for unprotected Fe-Co nanoparticles, a comparison of oxidized Fe-Co nanoparticle with iron oxide nanoparticle is also made. Under consideration of the natural oxidation layer (approximately 1.5nm thick), the calculated hysteresis loop of one such Fe-Co nanoparticle is shown in Fig 1 (dashed line). The moment of Fe-Co nanoparticle is still 6 and 10 times larger than that of the same size Fe_3O_4 and γFe_2O_3 nanoparticle. Therefore, even with a certain amount of oxidation, Fe-Co nanoparticles surpass iron oxide nanoparticles in terms of the critical magnetic property. As a matter of fact, natural oxidation layer leaves compatibility to biological environment and capability for functionalization. Iron can also be considered as another alternative choice of high-magnetic-moment material given its high saturation magnetization of 220 emu/g. Thus Fe-Co or Fe nanoparticles with their important characteristic are more promising for superior biomedical engineering systems.

Exploration of synthesis of Fe-Co alloy or Fe nanoparticles with controllable size and shape has been done by different methods (See Table 2). A unique physical gas condensation method was developed by Wang's group[29]. Fe-Co nanoparticles with narrow size distribution can be fabricated through control of thermal environment during fabrication

process[10][11]. Typical morphology and size distribution are shown in Fig 2(a)(b). Specific saturation magnetization of these unoxidized Fe-Co nanoparticles is determined to be around 226 emu/g, which is comparable to the bulk value[10].

III. FECO AND FE BASED CORE-SHELL NANOPARTICLES

Exposed Fe-Co and Fe easily oxidize and cannot be used for in vivo applications directly. Core-shell nanoparticles having an Fe-Co or Fe core and a biocompatible shell solves this problem of oxidation. Nobel metal, Silica and Carbon have been studied as prospective shell materials (See Table 2). Besides providing protection from oxidation, these shell materials have good chemical affinity for subsequent functionalization and may offer opportunities to approach multifunctional design.

We successfully synthesized nanoparticles having Fe-Co core and Au, SiO_x shell directly through a diffusion control based gas condensation method[14][17][30]. These nanoparticles are much more stable after exposure in air and simple chemistry can be applied to make them water soluble after modification of the shell material. Fig 2(c) shows the stable solution of $Fe_{0.7}Co_{0.3}$/Au core-shell nanoparticles dispersed in water. Experimental observation indicates that dispersion of these core-shell nanoparticles is better compared to Fe-Co nanoparticles with natural oxidation. Therefore, it can be concluded that Fe-Co or Fe core with an inorganic shell is a simple but effective design to obtain stable high-moment nanoparticles.

IV. BIOMEDICAL APPLICATIONS OF HIGH MAGNETIC MOMENT NANOPARTICLES

A. Magnetic Resonance Imaging Contrast Agents

In magnetic resonance imaging, a net moment from a collection of protons in biological tissues is obtained under a large external field. Based on the Larmor procession of the moment subjected to a time varying magnetic field, relaxation of the moment is scanned after the application of an RF pulse which causes the moment to flip[31]. Relaxation time of moment along field direction and in-plane are called T1 and T2, respectively, and reduction of either one of them can enhance the contrast. Superparamagnetic nanoparticles are commonly used as T2 MRI contrast agents[32]. T2 relaxation depends on the loss of phase coherence of the processing protons. An inhomogeneous local magnetic field environment can accelerate the phase coherence loss. In these circumstances, relaxation time T2 is replaced by T2* which includes the contribution from the inhomogeneity of the local field. Thus the decaying stray field from superparamagnetic nanoparticles shortens the relaxation time by introducing a local field gradient. Stray field of a nanoparticle is expressed as[33]:

$$H=\sum_{\vec{ij}} \frac{3\vec{n}(\vec{m}_j \cdot \vec{n})-\vec{m}_i}{\left|r_{ij}\right|^3} \tag{2}$$

where m_j and m_i are moment of the i_{th} and j_{th} atom, n is the field direction, and r_{ij} is the distance between i_{th} and j_{th} atom. A simulated stray field distribution of a Fe-Co nanoparticle using FEMLAB is shown in Fig 3(a). Decrease of stray field strength in the direction away from the nanoparticle can be observed. For high magnetic moment nanoparticles, the stray field decays faster. In this way, they provide better contrast by accelerating the relaxation more effectively.

The effectiveness of Fe-Co nanoparticles as MRI contrast agents and cell labels was demonstrated by tracking cells labeled with Fe-Co nanoparticles. High resolution MR imaging was shown in Fig 3(b)(top) while the unlabeled control sample (bottom) didn't show any contrast.

B. Magnetic Hyperthermia

Magnetic hyperthermia is a therapy that makes use of heat generated by nanoparticles under an AC magnetic field to kill malignant tumors[34]. Superparamagnetic nanoparticles release heat through Néel relaxation and Brownian relaxation[35]. The former one is due to magnetization relaxation with respect to crystal axis and the latter one is due to frictional rotation of the whole particle. The heat, or specific power loss is expressed as[36]:

$$P=\frac{\chi_0 \mu_0 H^2 \varpi}{2}\frac{\varpi\tau}{1+(\varpi\tau)^2} \tag{3}$$

where, μ_0 is the free space permeability, H is the AC field amplitude, ω is the field frequency and τ is the effective relaxation time. χ_0 is the susceptibility from Langevin function[36],

$$\chi_0=\frac{M_s}{V'H}\left(\coth s-\frac{1}{s}\right) \tag{4}$$

where, s is described in (1), V' is volume fraction of nanoparticles, M_s is the saturation magnetization of the ferrofluid and H is the applied field. According to the equation (4), nanoparticles with high magnetic moment such as Fe-Co show higher susceptibility χ_0 at the same volume concentration and hence more heat will be generated as compared to those having lower magnetic moment. Or equivalently, sufficient heat can be generated by a smaller amount of high-moment nanoparticles. This reduced dosage meets the criteria of in vivo application.

In Fig 3(c)[37], our system set-up for magnetic hyperthermia experiments is schematically illustrated. The sample is located in a copper coil connected to AC power supply. Temperature is measured by an optical fiber probe. Fig 3(d) is a plot of temperature change of water solution with a concentration of 8mg/ml $Fe_{0.7}Co_{0.3}$ nanoparticles versus time. The solution was placed in an AC magnetic field having frequencies at 191 kHz and 312 kHz and a peak magnetic field strength of 6 kA/m. These results indicate the capability of Fe-Co nanoparticles for use in magnetic hyperthermia.

To realize local heating in magnetic hyperthermia, positioning nanoparticles in a specific location is another challenge that requires proper design. Controlling the position by magnetic field is a promising way. The force felt by a nanoparticle is given by [31]

$$F=(m\bullet\nabla)B \tag{5}$$

where B is the applied field. The force is thus proportional to the moment of the nanoparticle as well as the gradient of the field. A high-moment nanoparticle can reach farther targeting

location as the field decays during penetration through the tissue.

C. *Biomarkers for Magnetic Sensor Detection*

Detection of a magnetic biomarker relies on stray field, emanating from the nanoparticle bonded to the sensor surface, which will cause a resistance change of GMR/MTJ based sensor. According to the equation (2), stray field strength is proportional to the magnetic moment of individual nanoparticle. A high moment nanoparticle will give a large value of signal to noise ratio. Recently we achieved zeptomole sensitivity detection of strepavidin labeled by cubic Fe-Co nanoparticles using GMR sensor[38]. This demonstration shows the potential of magnetic sensor detection scheme for future personalized health care device.

V. SUMMARY

High-magnetic-moment nanoparticles (Fe-Co and Fe) point out one direction to go in future biomedicine for improvement of nanoparticles' performance and efficiency. The intrinsic magnetic property of the material leads to high moment of individual nanoparticle in low magnetic field regime. Core-shell nanoparticles consisting of high magnetic moment core and chemically stable, biocompatible shell materials provide more opportunities to tailor property of nanoparticles. Improvements in MRI contrast agents, magnetic hyperthermia heat sources, and biomarker have been obtained using high- magnetic-moment nanoparticles.

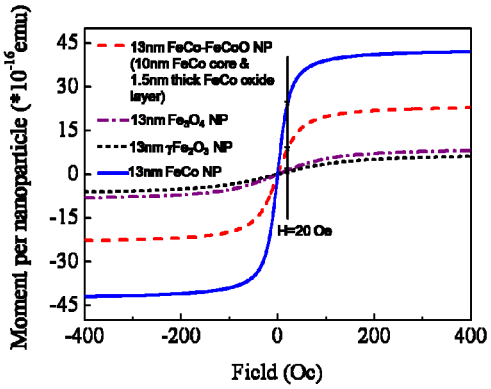

Fig.1 Calculated single particle M-H loops of unoxidized Fe-Co, Fe_3O_4, γFe_2O_3 and FeCo-FeCoO

TABLE1 CALCULATED MAGNETIZATION VALUES

Nanoparticle type	Saturation magnetic moment of a single nanoparticle	Magnetic moment of a single nanoparticle at H=20Oe
Unoxidized FeCo (13nm)	$4.3*10^{-15}$ emu	$2.4*10^{-15}$ emu
Fe_3O_4 (13nm)	$9.1*10^{-16}$ emu	$1.36*10^{-16}$ emu
γFe_2O_3 (13nm)	$7.1*10^{-16}$ emu	$0.83*10^{-16}$ emu
FeCo-FeCoO (10nm FeCo core &1.5 nm FeCoO shell)	$2.38*10^{-15}$ emu	$8.65*10^{-16}$ emu

TABLE2 HIGH -MOMENT NANOPARTICLES

Nanoparticle type	Property	Synthesis Method
$Fe_{60}Co_{40}$	~24nm, 226emu/g	Gas phase condensation[10][11]
	20nm , 230emu/g after annealing	Reductive decomposition of $Fe(acac)_3$ and $Co(acac)_2$[12]
	20nm, 183emu/g	Organometallic approach[13]
$(Fe_{60}Co_{40})_3Si–SiO_x$ core-shell	~20nm, 1140emu/cm^3	Gas phase condensation[14]
Fe_xCo_{1-x}-C(x=0.55, 0.60, 0.65, 0.70, and 0.75) core-shell	~50nm	RF plasma torch reaction[15]
Fe_xCo_{1-x} -C core shell	7nm, 215emu/g, x~0.4; 4nm, 162emu/g, x~0.15	Chemical vapor deposition[16]
Fe_xCo_{1-x}-Au/Ag core-shell	~21-23nm x=0.6 ; ~30nm x=0.7	Gas phase condensation[9][17]
Fe-Fe3O4	4nm core 2.5nm shell, 66.7emu/g	Thermal decomposition of $Fe(CO)_5$[18]
Fe-Fe oxide	7nm/9nm/11nm, 175/200/132 emu/g	Iron carbonyl decomposition[19]
	3nm-85nm,80-205emu/g	Gas phase nanocluster deposition[20]
Fe-Silica core-shell	~50nm	Hydrolysis of TEOS in mircroemultions[21]
	10-30nm, ~162emu/g	Arc discharge[22]
Fe-SiO_2 core-shell	~35nm, 70-165emu/g	Wet chemical[23]
Fe(Fe_3C)-C core-shell	30nm	Pyrolysis of $Fe(CO)_5$ and C_2H_2[24]
Fe-C core -shell	4.7±1.3 nm	High pressure CO (Hipco) approach[25]
Fe-Au core-shell	12.5nm, 145emu/g Fe	Chemical reduction[26]
	18±4nm, 81emu/g Fe	Reverse micelle reaction[27]
	21nm, 210emu/g Fe	Wet chemistry and laser irradiation deposition of Au[28]

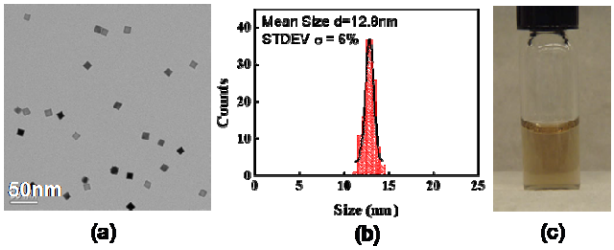

Fig. 2 (a) Bright field TEM image of Fe-Co nanoparticles (b) Size distribution (c) Water solution of $Fe_{0.7}Co_{0.3}$/Au core-shell nanoparticles

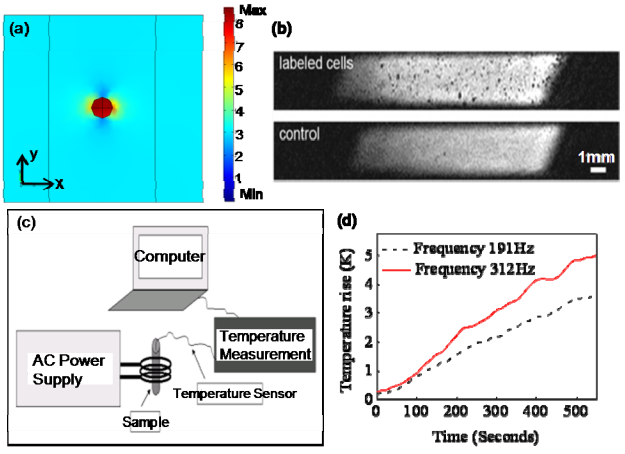

Fig. 3 (a) Simulated stray field distribution of one $Fe_{0.7}Co_{0.3}$ nanoparticle viewed from the top of the particle. Qualitative stray field strength is indicated by the color bar. (b)MR image of cells labeled Fe-Co nanoparticles (top) and unlabeled cells (bottom). Sample was prepared by Prof. Arkadiusz Dudek and MR image was collected by Prof. Patrick Bolan. (c) Schematic illustration of magnetic hyperthermia experimental set-up (d) Temperature rise versus time of 8mg/ml $Fe_{0.7}Co_{0.3}$ nanoparticle water solution under external AC field of 6kA/m peak field strength.

REFERENCES

[1] Gary Hodes, "When small is different: some recent advances in concepts and applications of nanoscale phenomena", Adv. Mater., Vol. 19, pp. 639-655, 2007

[2] Yuanzhe Piao, Andrew Burns, Jaeyun Kim, Ulrich Wiesner and Taeghwan Hyeon, "Designed fabrication of silica-based nanostructured particle systems for nanomedicine", Adv. Mater., Vol. 18, pp. 3745-3758, 2008

[3] Stéphane Mornet, Sébastien Vasseur, Fabien Grasset and Etienne Duguet, "Magnetic nanoparticle design for medical diagnosis and therapy", J. Mater. Chem., Vol. 14, pp. 2161-2175, 2004.

[4] An-Hui Lu, E. L. Salabas, and Ferdi Schüth, " Magnetic Nanoparticles: Synthesis, Protection, Functionalization, and Application", *Angew. Chem. Int. Ed.*, Vol. 46, pp. 1222 – 1244, 2007

[5] Robert C. O'Handley, *Modern Magnetic Material: principles and applications*, Wiley-InterScience, 2000, pp.74-76.

[6] Ajay Kumar Gupta and Mona Gupta, "Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications", *Biomaterials*, Vol. 26, pp. 3995-4021, 2005.

[7] Claire Corot, Philippe Robert, Jean-Marc Idée and Marc Port, "Recent advances in iron oxide nanocrystal technology for medical imaging", *Advanced Drug Delivery Reviews*, Vol. 58, pp. 1471–1504, 2006 .

[8] Conroy Sun, Jerry S.H. Lee, Miqin Zhang, "Magnetic nanoparticles in MR imaging and drug delivery" *Advanced Drug Delivery Reviews*, Vol. 60, pp. 1252–1265, 2008.

[9] J.M. Bai and J. P. Wang, "High-magnetic-moment core-shell-type FeCo–Au/Ag nanoparticles", *Appl. Phys. Lett*., Vol. 87, pp.152502(3pp), 2005

[10] Y. H. Xu, J. M. Bai and J. P. Wang, "High-magnetic-moment multifunctional nanoparticles for nanomedicine applications", *J. Magn. Magn. Mater.*, Vol. 311, pp. 131-134, 2007

[11] J. M. Bai, Y. H. Xu and J. P. Wang, "Cubic and spherical high-moment FeCo nanoparticles with narrow size distribution", *IEEE Trans. Magn*., Vol. 43, No.7, pp. 3340-3342, Jul. 2007

[12] Girija S. Chaubey, Carlos Barcena, Narayan Poudyal, Chuanbing Rong, Jinming Gao, Shouheng Sun, and J. Ping. Liu, "Synthesis and Stabilization of FeCo Nanoparticles", *J. Am. Chem. Soc.*, Vol. 129 (23), pp. 7214-7215, 2007

[13] Céline Desvaux, Frédéric Dumestre, Catherine Amiens, Marc Respaud, Pierre Lecante, Etienne Snoeck, Peter Fejes, Philippe Renaud and Bruno Chaudret, "FeCo nanoparticles from an organometallic approach: synthesis, organisation and physical properties", *J. Mater. Chem.*, 2009, Available:

[14] J.M. Bai, Y. H. Xu, John Thomas and J. P. Wang, "$(FeCo)_3Si$–SiO_x core–shell nanoparticles fabricated in the gas phase", *Nanotechnology*, Vol. 18, pp. 065701(5pp), 2007

[15] Z. Turgut, J. H. Scott, M. Q. Huang, S. A. Majetich, and M. E. McHenry, "Magnetic properties and ordering in C-coated FexCo1-x alloy nanocrystals", J. Appl. Phys., Vol. 83, pp. 6468-6470, 1998

[16] Won Seok Seo, Jin Hyung Lee, Xiaoming Sun, Yoriyasu Suzuki, David Mann, Zhuang Liu, Masahiro Terashima, Philip C. Yang, Michael V. Mcconnell, Dwight G. Nishimura and Hongjie Dai,"FeCo/graphitic-shell nanocrystals as advancedmagnetic-resonance-imaging and near-infrared agents", Nature materials, Vol. 5, pp. 971-976, 2006

[17] Y. H. Xu and J. P. Wang, "FeCo–Au core-shell nanocrystals", *Appl. Phys. Lett.*, Vol. 91, pp. 233107(3pp), 2007

[18] Sheng Peng, Chao Wang, Jin Xie, and Shouheng Sun, "Synthesis and Stabilization of Monodisperse Fe Nanoparticles", *J. Am. Chem. Soc*., Vol. 128 (33), pp. 10676-10677, 2006

[19] Dorothy Farrell, Sara A. Majetich, and Jess P. Wilcoxon, "Preparation and Characterization of Monodisperse Fe Nanoparticles", *J. Phys. Chem. B*, Vol. 107 (40), pp. 11022-11030, 2003.

[20] You Qiang, Jiji Antony, Amit Sharma, Sweta Pendyala, Joe Nutting, Daniel Sikes and Daniel Meyer, "Iron/Iron Oxide Core-Shell Nanoclusters for Biomedical Applications", *J. of Nanoparticle Research*, Vol. 8, pp. 489-496, 2006

[21] Pedro Tartaj and Carlos J. Serna, "Synthesis of Monodisperse Superparamagnetic Fe/Silica Nanospherical Composites", *J. Am. Chem. Soc*., Vol. 125 (51), pp. 15754-15755, 2003

[22] Rodrigo Fernández-Pacheco, Manuel Arruebo, Clara Marquina, Ricardo Ibarra, Jordi Arbiol and Jesús Santamaría, "Highly magnetic silica-coated iron nanoparticles prepared by the arc-discharge method", *Nanotechnology*, Vol. 17, pp. 1188–1192, 2006

[23] Mingzhong Wu, Y. D. Zhang, S. Hui, and T. D. Xiao, Shihui Ge, W. A. Hines, J. I. Budnick and M. J. Yacaman, "Magnetic properties of SiO2-coated Fe nanoparticles", *J. Appl. Phys*., Vol. 92, pp. 6809-6812, 2002

[24] Cheng Fa Wang, Jian Nong Wang, and Zhao Min Sheng, "Solid-Phase Synthesis of Carbon-Encapsulated Magnetic Nanoparticles", *J. Phys. Chem. C*, Vol. 111, pp. 6303-6307, 2007

[25] Yuhuang Wang, Wei Wei, Daniel Maspoch, Jinsong Wu, Vinayak P. Dravid, and Chad A. Mirkin, "Superparamagnetic Sub-5 nm Fe@C Nanoparticles: Isolation, Structure, Magnetic Properties, and Directed Assembly", Nano Lett., Vol. 8 (11), pp. 3761-3765, 2008

[26] Dorothy Farrell, and Sara A. Majeticha, "Gold-coated iron nanoparticles for biomedical applications, Min Chen, Saeki Yamamuro", *J. Appl. Phys*., Vol. 93, pp. 7551-7553, 2003

[27] Sung-Jin Cho, Benjamin R Jarrett, Angelique Y Louie, and Susan M Kauzlarich, "Gold-coated iron nanoparticles: a novel magnetic resonance agent for *T*1 and *T*2 weighted imaging", *Nanotechnology* Vol. 17, pp. 640–644, 2006

[28] Jin Zhang, Michael Post, Teodor Veres, Zygmunt J. Jakubek, Jingwen Guan, Dashan Wang, Francois Normandin, Yves Deslandes, and Benoit Simard, "Laser-Assisted Synthesis of Superparamagnetic Fe@Au Core−Shell Nanoparticles", *J. Phys. Chem. B*, Vol. 110 (14), pp. 7122-7128, 2006

[29] J. M. Qiu and J. P. Wang, "Tuning the Crystal Structure and Magnetic Properties of FePt Nanomagnets", *Adv. Mater*., Vol. 19, pp. 1703-1706, 2007

[30] Y. H. Xu and J. P. Wang, "Direct Gas-Phase Synthesis of Heterostructured Nanoparticles through Phase Separation and Surface Segregation", *Adv. Mater*. Vol. 20, pp. 994–999, 2008.

[31] Q. A. Pankhurst, J. Connolly, S. K. Jones and J. Dobson, "Applications of magnetic nanoparticles in biomedicine", *J. Phys. D: Appl. Phys*., Vol. 36, pp. R167-R181, 2003

[32] Hyon Bin Na, In Chan Song and Taeghwan Hyeon, "Inorganic nanoparticles for MRI contrast agents", *Adv. Mater*., Vol. 21, pp. 1-16, 2009

[33] Fawwaz T. Ulaby, Fundamentals of applied electromagnetic, Pearson Prentice Hall, pp.216-218

[34] Timothy Kline, Y.H. Xu, Y. Jing and J. P. Wang, *J. Magn. Magn. Mater*., Vol 321, pp. 1525-1528, 2009

[35] Rudolf Hergt, Wilfried Andrä, Carl G. d' Ambly, Ingrid Hilger, Werner A. Kaiser, Uwe Richter and Hans-Georg Schmidt, "Physical limits of hyperthermia using magnetic fine particles", IEEE Trans. Magn., Vol. 34, No. 5, pp. 3745-3754, Sep. 1998.

[36] R. E. Rosensweig, "Heating magnetic field with alternating magnetic field", J. Magn. Magn. Mater., Vol. 252, pp. 370-374, 2002

[37] Timothy Kline Thesis

[38] Balasubramanian Srinivasan, Yuanpeng Li, Ying Jing, YunHao Xu, Xiaofeng Yao, Chengguo Xing, and Jian-Ping Wang, "A Detection System Based on Giant Magnetoresistive Sensors and High-Moment Magnetic Nanoparticles Demonstrates Zeptomole Sensitivity: Potential for Personalized Medicine", *Angew. Chem*. Vol. 121, pp.1 – 5, 2009