

Biomedical applications for magnetic nanoparticles

glawes@wayne.edu

1. Introduction to magnetic nanoparticles

- 1a. What are nanoparticles?
- 1b. Synthesizing nanoparticles
- 1c. Characterizing nanoparticles

2. Biomedical applications

- 2a. Targeted drug delivery
- 2b. Magnetic hyperthermia
- 2c. MRI contrast agent
- 2d. Magnetic separation
- 2e. Controlled drug release

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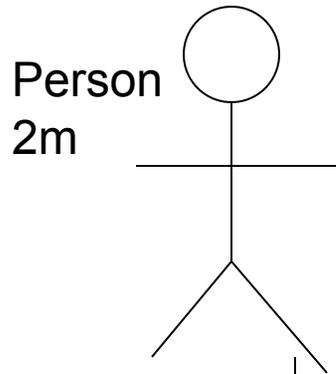
What are nanoparticles?

Broadly speaking, a nanoparticle is anything having a size varying from a few nm to approximately 100 nm.

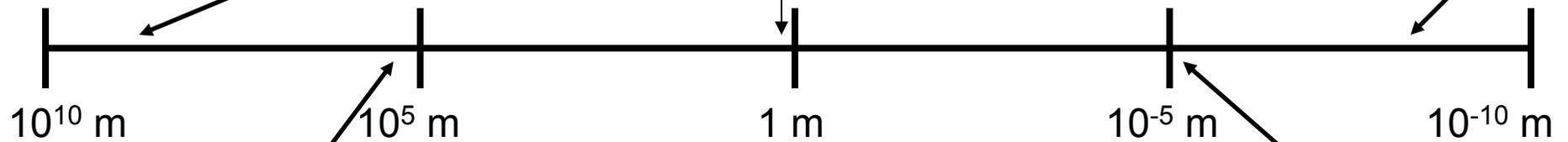
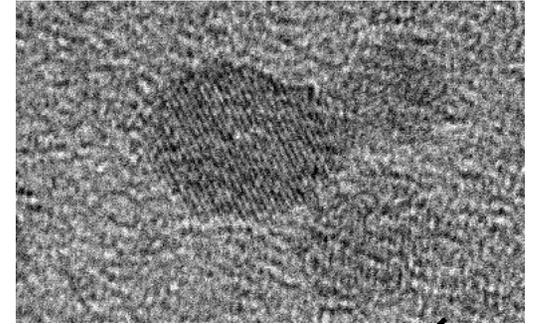
The small lengthscale of nanoparticles makes them suitable for a number of different biomedical applications, as they smaller, or similar in size, to many important intracellular objects (eg. Red blood cell: ~ 6000 nm , DNA strand: ~ 2 nm diameter [but much longer] , Cell membrane thickness: $\sim 5-10$ nm).

Because of their small size, nanoparticles have huge surface-to-volume ratios, which can strongly affect their reactivity. This is one example of how nanoparticles have different physical properties than bulk materials.

Earth-Moon distance
 4×10^8 m
(courtesy NASA)



Magnetic nanoparticle
 5×10^{-9} m

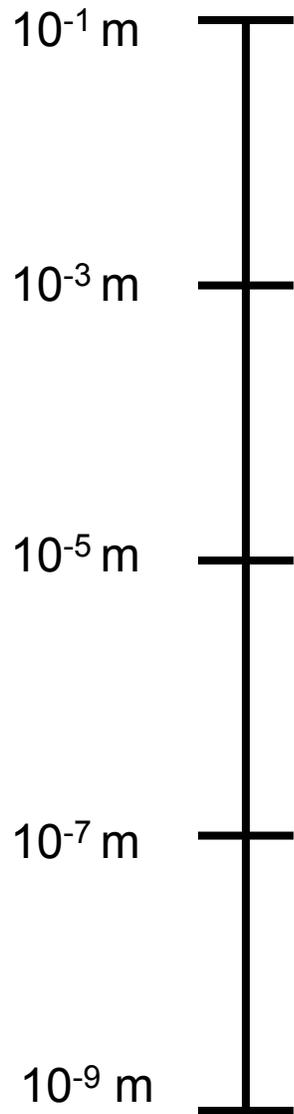


Michigan width
 2×10^5 m
(courtesy Google)



Red blood cell
 1×10^{-5} m
(courtesy PBS)

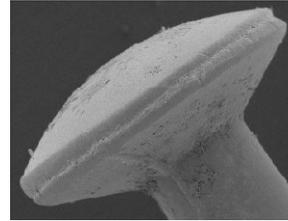




10^{-3} m = 1 mm

10^{-6} m = 1 μ m = 1 (micron)

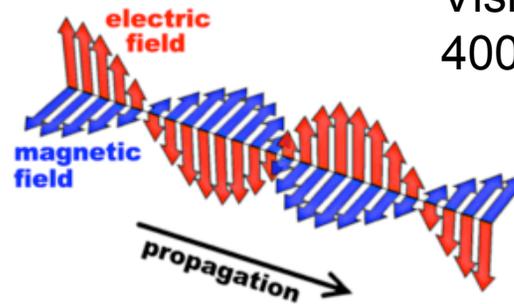
10^{-9} m = 1 nm (nanometer)



Head of a pin
1,000,000 nm

Courtesy CSU Hayward

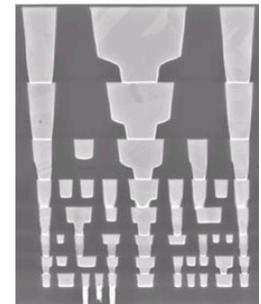
Thickness of a human hair: 100,000 nm



Visible light
400 to 700 nm

Transistors
65 nm

Distance between
atoms in a solid
~0.3 nm



Courtesy Intel

Magnetic nanoparticles

Nanoparticles made from magnetic materials are, rather unsurprisingly, referred to as “magnetic nanoparticles”.

This particles can be moved by applying magnetic fields, which allows them to be controlled inside the body.

Magnetic nanoparticles suspended in solution are called “ferrofluids” and have many applications in medicine, acoustics, and electronics.

Iron oxide (Fe_3O_4 , $\gamma\text{-Fe}_2\text{O}_3$). Very stable and easy to synthesize. Biocompatible, minimally toxic, used in many clinical studies, and FDA approved for some applications. Reasonably large saturation magnetization (~ 90 emu/g). The most widely investigated type of magnetic nanoparticle for biomedical applications.

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Synthesis

Surfactants

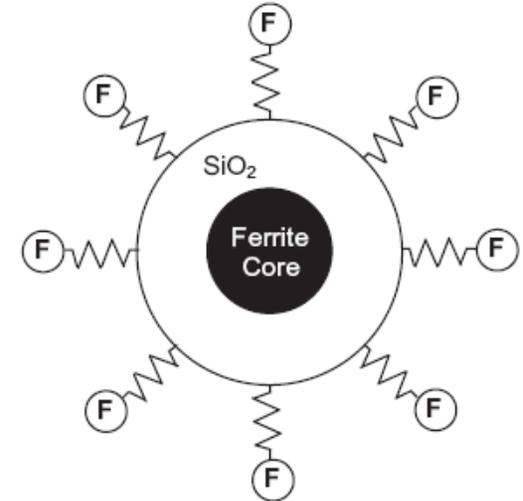
Magnetic nanoparticles can stick together if they collide. This can lead to agglomeration, which is generally detrimental for applications.

In order to prevent agglomeration, nanoparticles are often coated with some material to prevent agglomeration (either because of steric or electrostatic effects).

Organic surfactants. Normally long chain molecules, including fatty acids, dextran, alginate, or other polymers.

Inorganic surfactants. Generally non- or weakly-reactive materials, including Si, SiO₂, Au, or others. Core-shell nanoparticle structures can also have other types of functionalities (quantum dots).

Surfactants can also introduce additional binding sites to the magnetic nanoparticles.



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TOPICAL REVIEW

Applications of magnetic nanoparticles in biomedicine

Q A Pankhurst¹, J Connolly², S K Jones³ and J Dobson⁴

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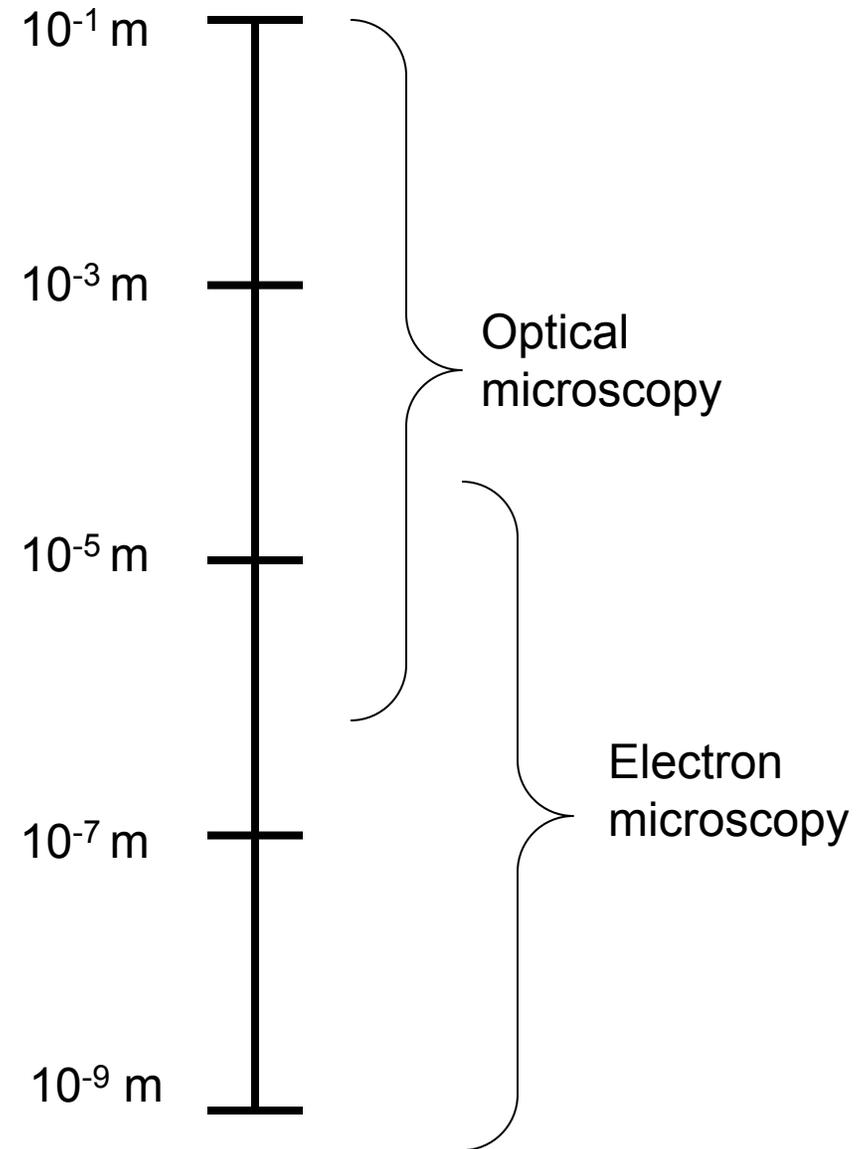
2d. Magnetic separation

2e. Controlled drug release

The *diffraction limit* sets a bound on the resolution of optical microscopes. Very roughly, the smallest separation d between two points that can be resolved varies as the wavelength of light used divided by some scaling factor of order 1. In practice, optical microscopes can normally only resolve objects down to approximately 200 nm.

- The development of scanning probe techniques (STM, AFM) in 1981 revolutionized the imaging of nanoscale systems.

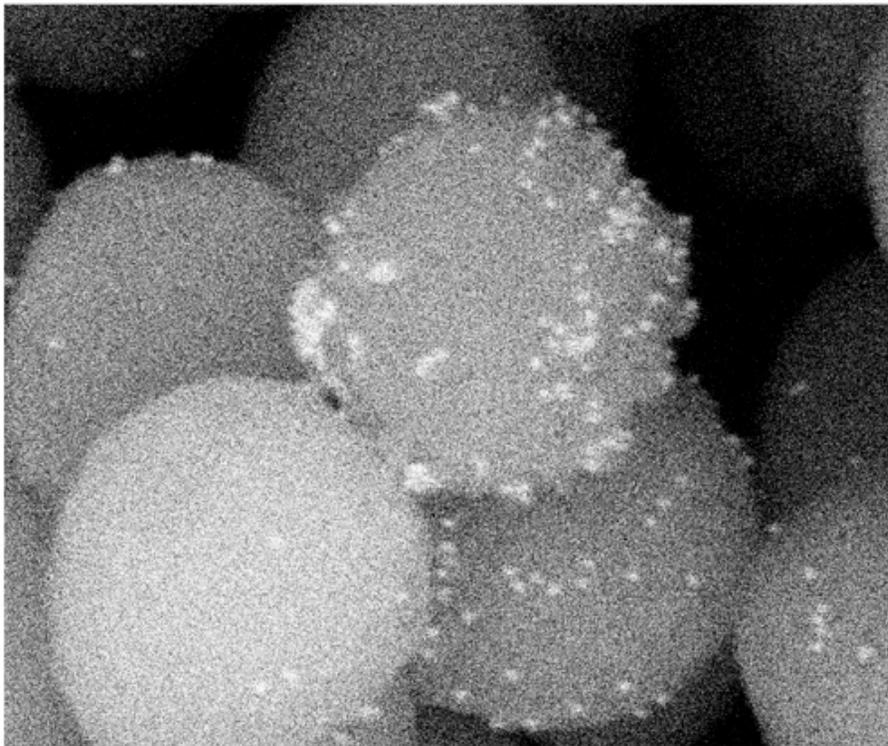
Nanotechnology



Scanning electron microscopy

SEM: Focus electron beam to a small sample spot. Scan beam over sample and collect secondary and backscattered electrons.

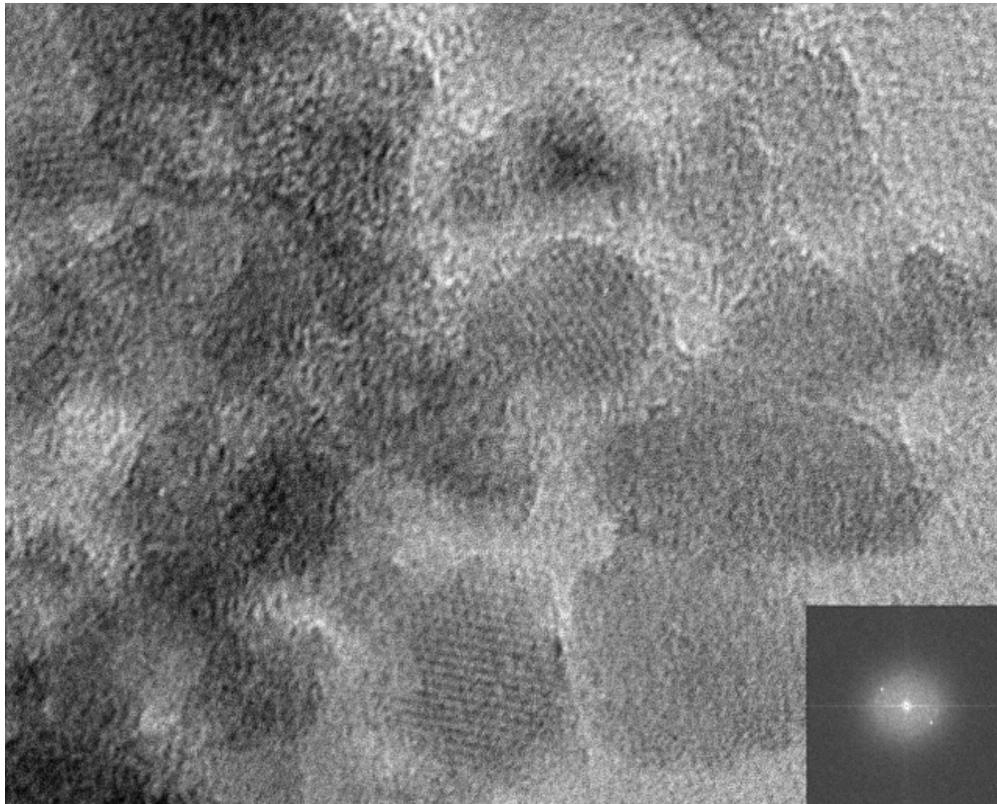
Typical electron energies are 1-50 kV with a spot size of 1-10 nm.



SEM Image of bacteria with attached protein

Transmission Electron Microscopy

TEM: Use electrons to image the specimen directly.

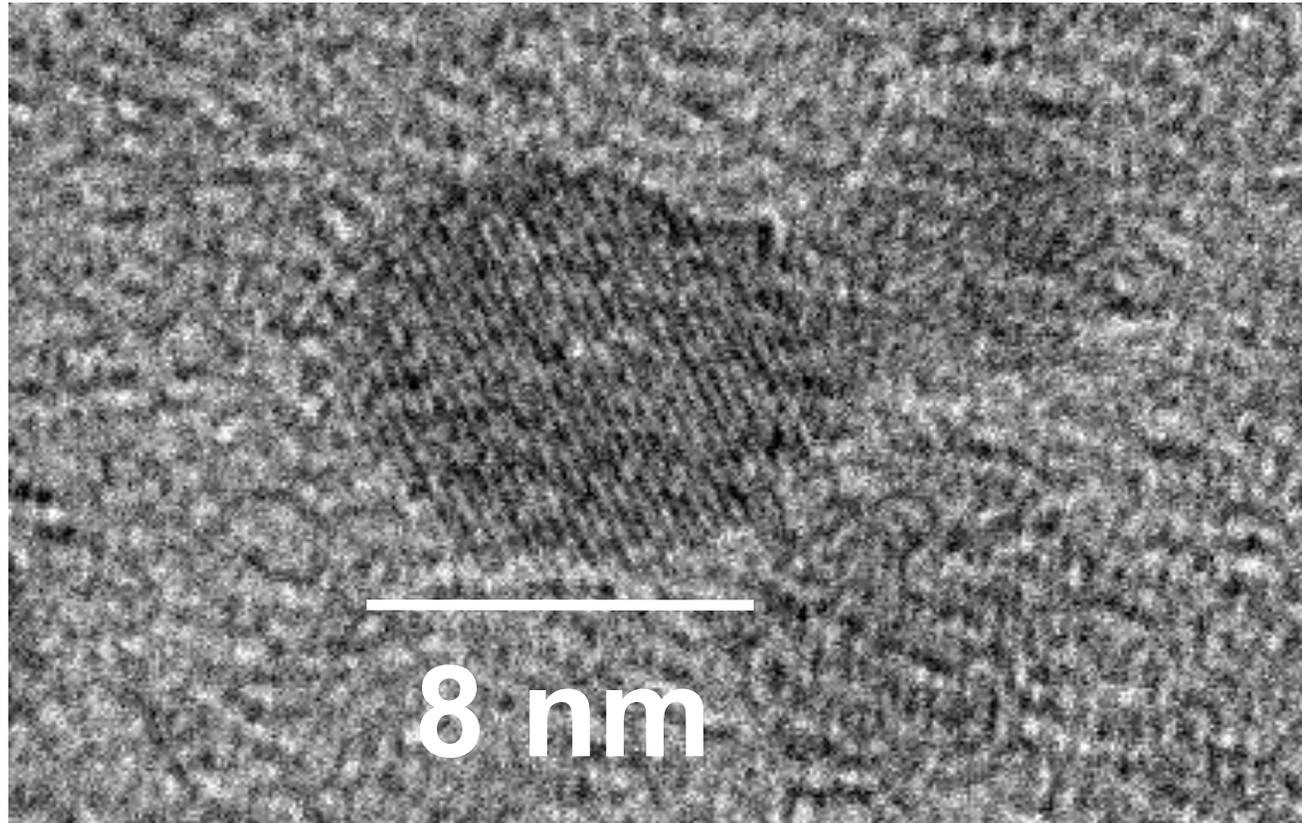


TEM image of iron oxide nanoparticles

Fe-6-A-ED-500k-500k-b.tif
Fe-6-A
Print Mag: 3720000x @ 7. in
15:10 02/03/06
TEM Mode: Imaging
Microscopist: Sudakar

5 nm
HV=200kV
Direct Mag: 500000x
Wayne State Univ.

TEM image of iron oxide nanoparticle



Note the regular crystal structure of the magnetic nanoparticle.

In order to be used for biomedical applications, magnetic nanoparticles must be injected into the body. For many proposed applications, this injection would be done intravenously, which requires a good understanding of the hydrodynamic response of the nanoparticles.

Because of their small size, magnetic nanoparticles often exhibit complicated hydrodynamic properties when suspended in solution. Fortunately, the problem of understanding small particles in solution was solved by Einstein many years ago.

However, since magnetic nanoparticles are sensitive to magnetic fields, applied fields can produce additional magnetohydrodynamic effects that are absent in non-magnetic nanoparticles.

Furthermore, since nanoparticles will often be functionalized by attaching surfactants, it is also necessary to understand how these surfactants will affect the hydrodynamic response.

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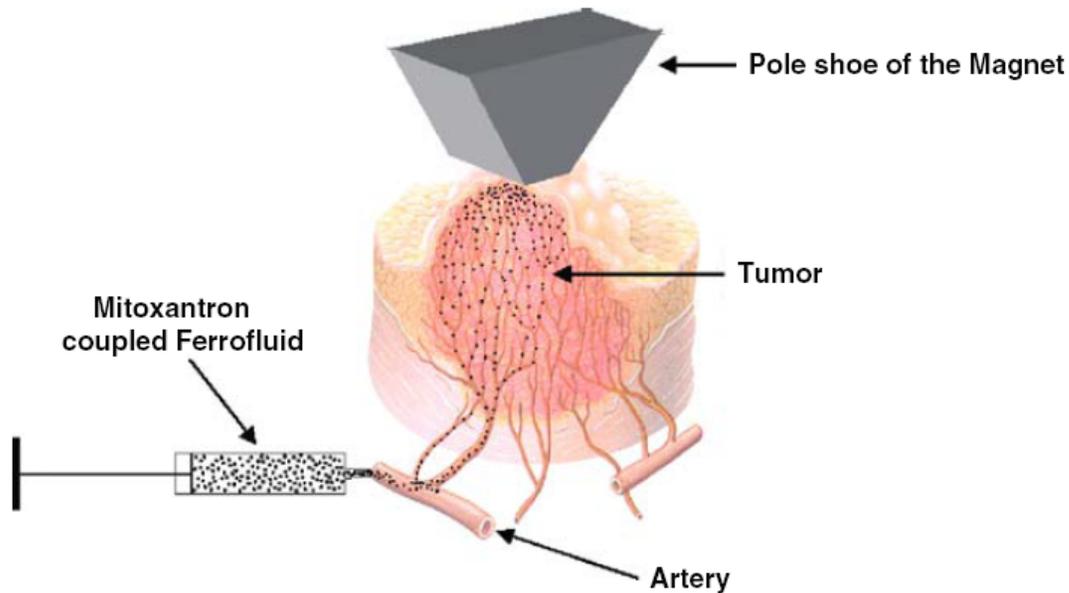
An external magnetic field gradient will produce a force on magnetic nanoparticles. There is considerable interest in using this effect for targeted drug delivery by attaching the drug to the magnetic nanoparticles, then applying a large magnetic field to the desired region (e.g. a cancerous tumor or damaged joint), which will attract the magnetic nanoparticles, hence also attract the attached drug.

This illustrates one of the recurring themes of many possible biomedical applications for nanoparticles: it is (believed to be) safe to apply relatively large static dc magnetic fields to patients. Furthermore, even ac magnetic fields may be safe, as long as the frequencies are not too high nor the field amplitudes too large.

This application requires attaching the drug to the magnetic nanoparticles without (strongly) deteriorating the magnetic response of the composite or the efficacy of the drug.

While detailed hydrodynamic modeling is difficult, this magnetic localization is expected to require very large field gradients, on the order of tens of T per m for even relatively low blood flow rates and large magnetic particles.

Principle of local Chemotherapy with Magnetic Drug Targeting



Magnetic nanoparticles will be attracted to regions of high field gradients.

The field gradients are largest close to the magnet, so this approach is most readily used to accumulate nanoparticles near external surfaces.

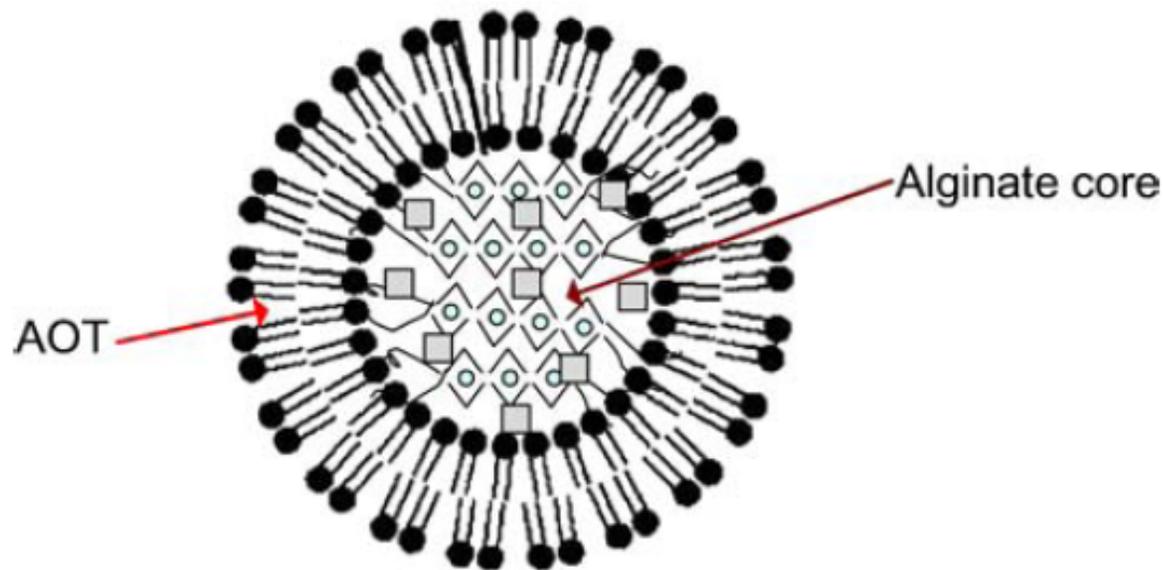
Biomedical Applications of Magnetic Nanoparticles

L. Trahms

Physikalisch-Technische Bundesanstalt, Berlin, e-mail: Lutz.Trahms@PTB.de

We will consider an example of incorporating magnetic with an established drug delivery platform, with the long-term objective of using this composite for targeted delivery.

Aerosol-OT nanoparticles



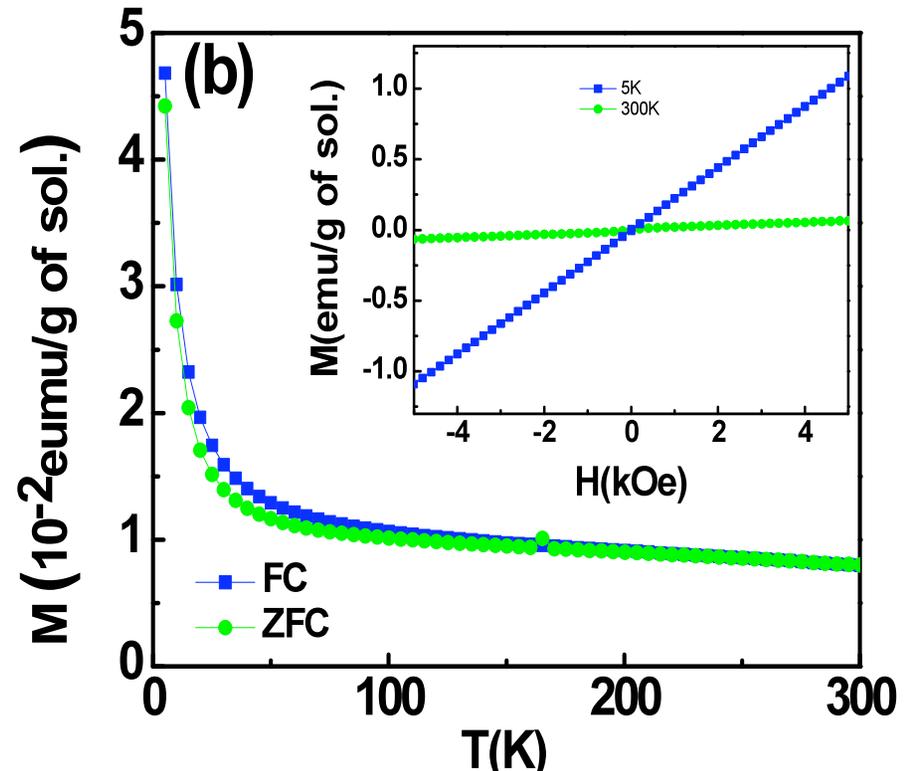
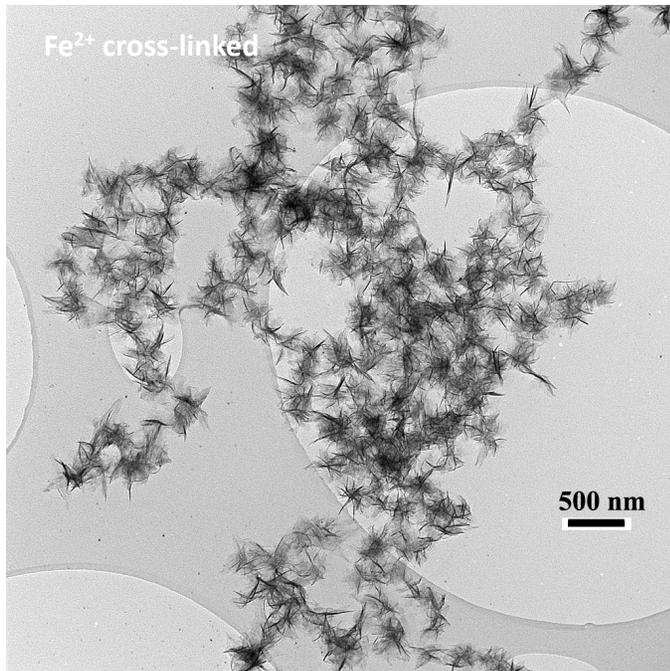
- Exhibit controlled and sustained release of doxorubicin
- Delivery improved relative to drug in solution

Mahesh D. Chavanpatil,¹ Ayman Khdair,¹ and Jayanth Panyam^{1,2,3}

Pharmaceutical Research, Vol. 24, No. 4, April 2007 (© 2007)

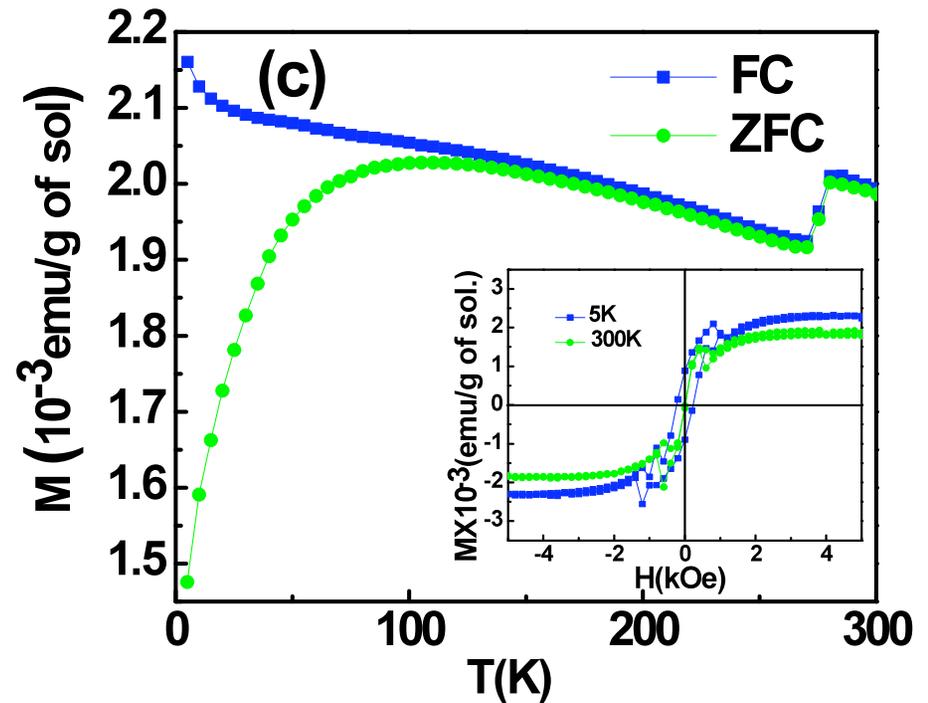
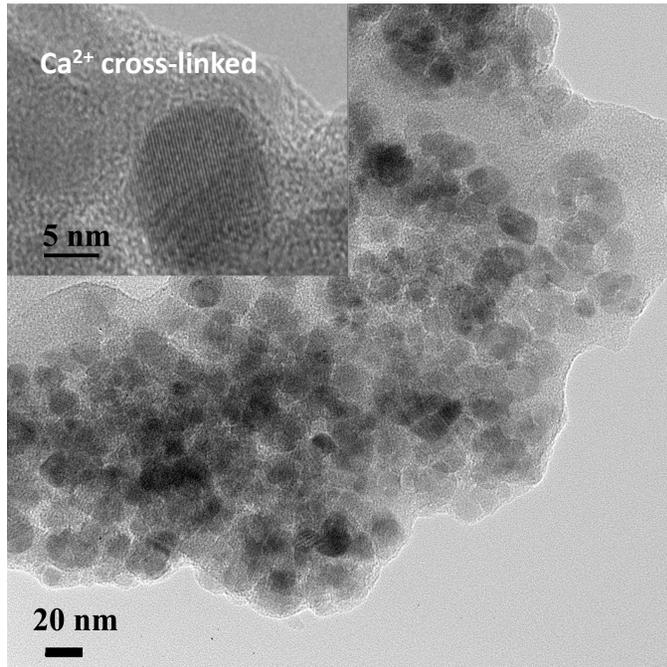
DOI: 10.1007/s11095-006-9203-2

Fe²⁺ crosslinked no nanoparticles



Using Fe²⁺ ions to cross-link the alginate leads to a non-magnetic material. The individual Fe ions do not order ferromagnetically.

Ca²⁺ crosslinked with nanoparticles



Crosslinking the alginate using Ca²⁺ in the presence of iron oxide magnetic nanoparticles produces a magnetic composite (which could be used for targeted drug delivery applications).

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Magnetic hyperthermia

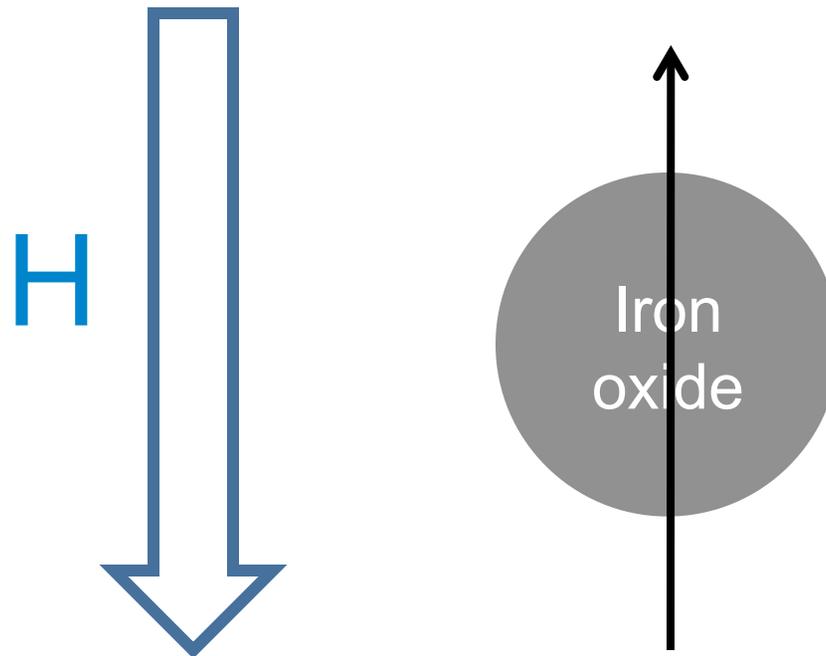
There are a number of therapeutic benefits in producing localized heating, for example, delivering toxic doses of thermal energy to tumors, or increasing the efficacy of certain anti-cancer drugs.

However, heating the surrounding tissue can also produce unwelcome side-effects so there are advantages to strictly controlling the region under treatment by using magnetic nanoparticles as the heating element.

For treating cancer tumors, the general measure of effectiveness is the cumulative equivalent minutes at 43 °C for 90% of the tumor volume (CEM 43 T₉₀).

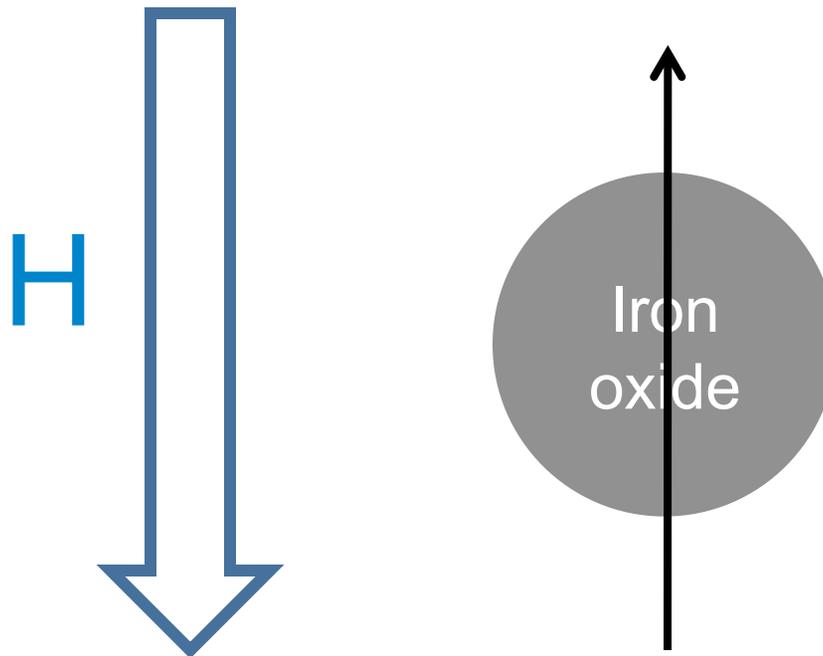
The magnetic moments on nanoparticles will align with an external magnetic field. As the external field changes direction, the magnetic moment will also change direction. This produces dissipation leading to heating. One of the major advantages of using magnetic fields to produce heating is that they readily penetrate tissue.

Relaxation in magnetic nanoparticles



In Brownian relaxation, the entire nanoparticle rotates to reverse the direction of the magnetic moment.

Brownian Relaxation



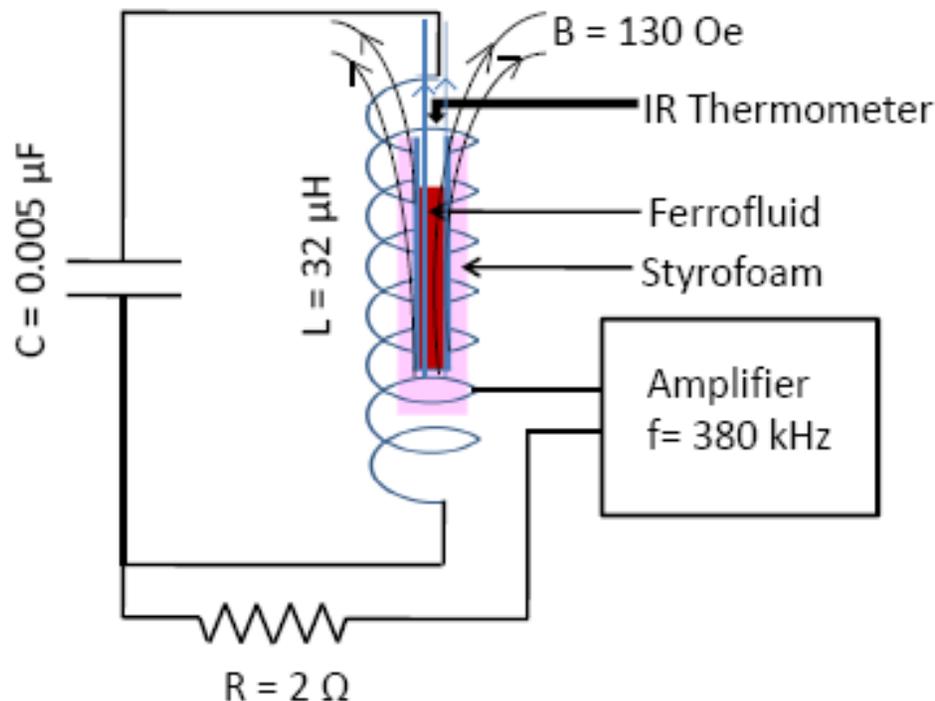
In Neel relaxation, the nanoparticle remains fixed in place, but the magnetic moment reverses direction to align with the external field.

Neel Relaxation

Practical aspects of magnetic hyperthermia

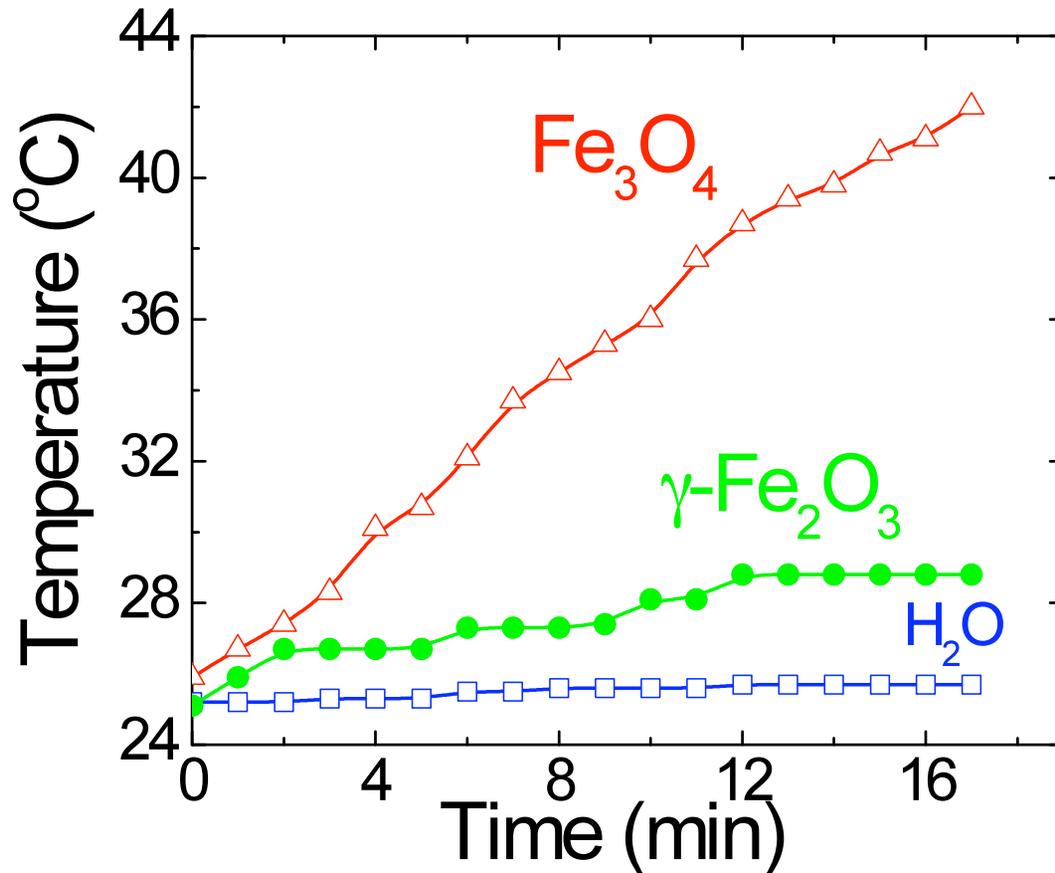
Magnetic hyperthermia requires large magnetic fields alternating at high frequencies to be effective. In practice it is challenging to meet these two requirements simultaneously.

The circuit diagram on the left shows one approach to designing apparatus suitable for hyperthermia. This particular system provides a field of just over 0.01 T at a frequency of almost 400 kHz (with a current of ~ 30 A flowing in the wire).



The high currents required for producing high magnetic fields lead to substantial resistive losses in the coil, and therefore significant radiative heating. This must be minimized to avoid heating the entire sample volume (e.g. by water cooling, etc).

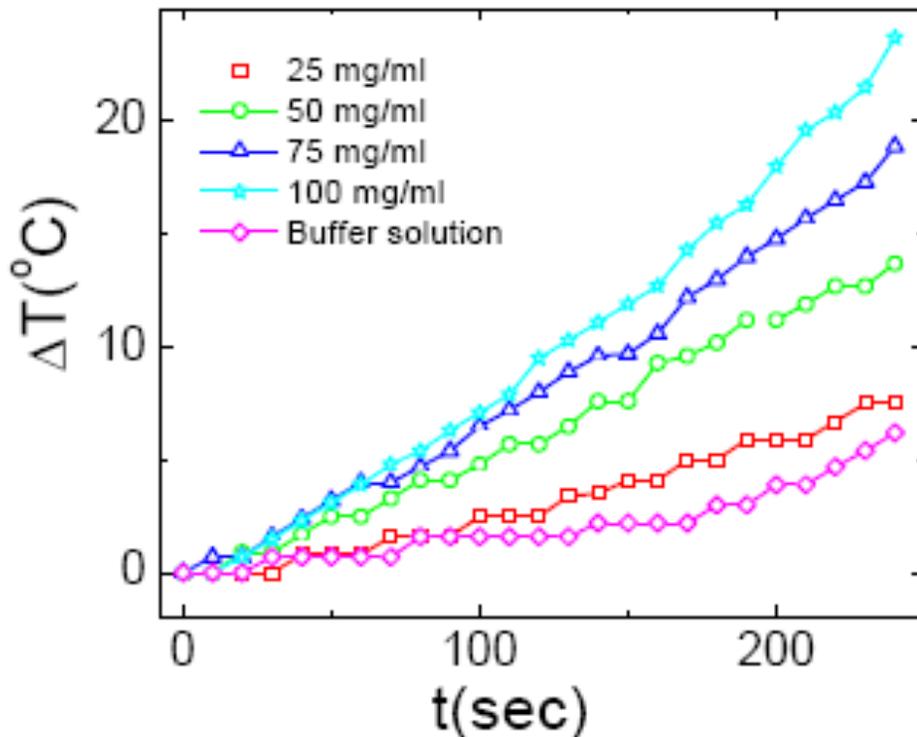
Magnetic hyperthermia



The sample consisting of individual nanoparticles (Fe₃O₄) heats 4-5 times faster than the sample with clustered nanoparticles (γ -Fe₂O₃).

This suggests that, at least for these experimental conditions (nanoparticle size, driving frequency, sample viscosity, etc), Brownian relaxation is a much more effective heating mechanism than Neel relaxation.

Concentration dependence of magnetic heating



Hyperthermia heating is normally scaled to the heat capacity and expressed as specific absorption rate (SAR) in units of W/kg.

A higher concentration of magnetic nanoparticles will lead to a greater amount of heating during magnetic hyperthermia (as illustrated on the left).

However, increasing the concentration of nanoparticles may lead to increased toxicity and other undesirable side-effects.

Understanding the heat flow from magnetic nanoparticles into the surrounding tissue, and then through the surrounding tissue will be important when designing specific applications.

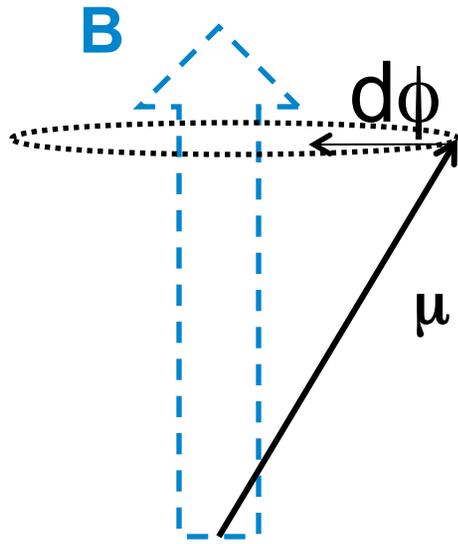
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Magnetic resonance imaging



Local magnetic moments (μ) will precess about a magnetic field B .

The rate of precession will depend on the magnitude of the magnetic field, so is sensitive to the magnetic environment.

Applying a gradient magnetic field over an object produces a gradient in precession rates, which can be correlated with position. This allows local changes in magnetic properties to be spatially localized.

Magnetic relaxation

When the local moments are perturbed, there are two main relaxation effects on the magnetic dynamics.

T1 (Longitudinal relaxation time) is a measure of how long the magnetization takes to recover to align along B after being flipped 90°. This depends on interactions of the moment with other particles and is referred to as “spin-lattice” relaxation.

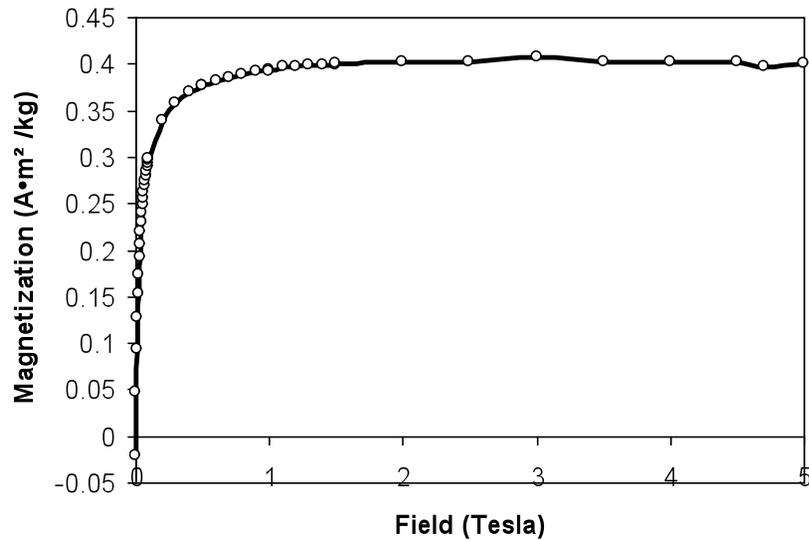
T2* (Transverse relaxation time) is a measure of how long spins will rotate together when flipped 90°. This is affected by the precession rate, which depends on the local magnetic environment. As T2* relaxation depends on the interaction of moments with the magnetic field, this is referred to as “spin-spin” relaxation.

Different types of tissue have different T1 and T2* relaxation times and can therefore be distinguished using MRI.

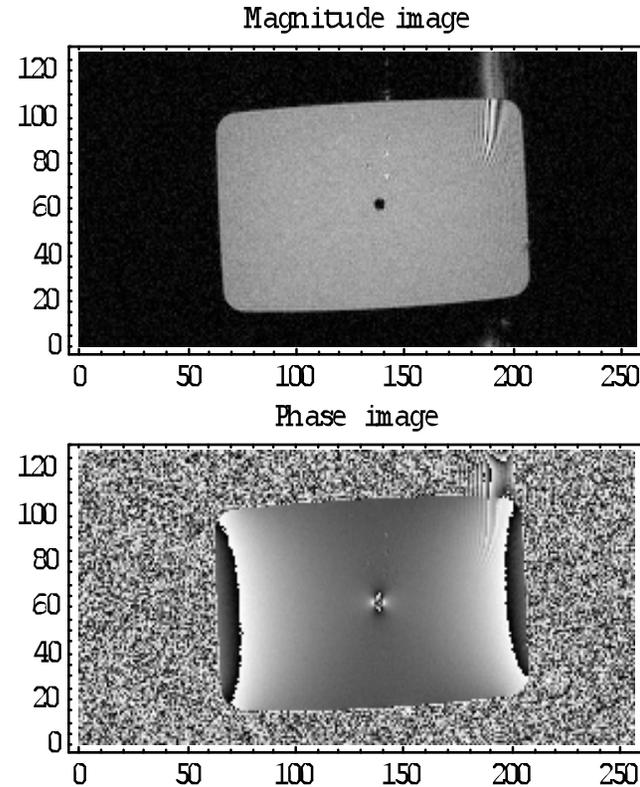
Contrast agents modify T1 and T2* and can provide clearer images. Superparamagnetic iron oxide nanoparticles greatly reduce T2*.

Static MR measurements

Quartz tube filled with ferrofluid (Fe_3O_4)



Bulk magnetization data
 $\chi=103$ ppm at 4.7 T



MRI data
 $\chi=112$ ppm at 4.7 T

Direct measurements of the ferrofluid susceptibility agree well with the value extracted from MRI studies. This allows a *quantitative* determination of nanoparticle concentration using MRI.

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As magnetic nanoparticles respond to external magnetic field gradients, it may be possible to magnetically tag certain objects, and then extract these from a flowing mixture using magnetic fields.

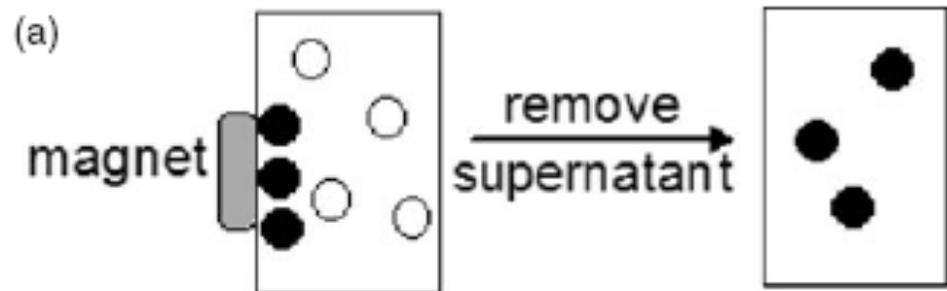
One advantage of this approach compared to other separation methods is that the external magnetic can be turned on and off, allowing the separation between tagged and untagged objects to be well controlled.

Also important to understand the magnetohydrodynamics for this application, since these will strongly affect the separation rate, etc.

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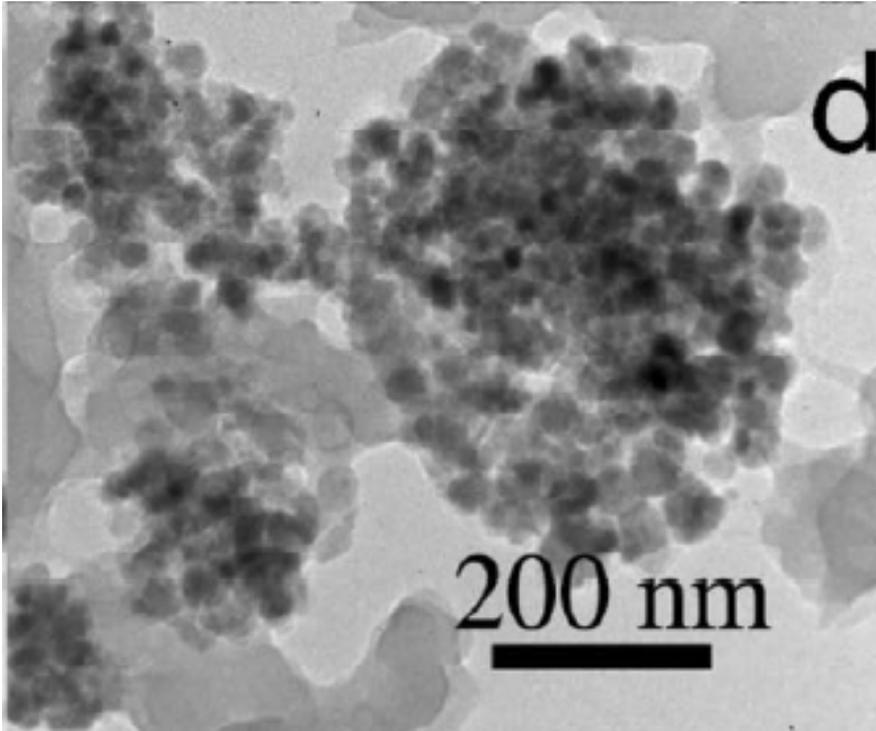
Using magnetic nanoparticles to trigger controlled drug release

Because magnetic nanoparticles show a large response to magnetic fields, they can be used to trigger reactions simply by using external fields. This functionality can be used for controlled drug release.

PNIPAM is a thermosensitive polymer, which has a significant volume collapse near 40 °C.

By integrating magnetic nanoparticles with PNIPAM, the resulting composite can be heated using external ac magnetic fields, which in turn can trigger the volume change.

This phenomenon can be exploited for controlled drug delivery. A drug that can be stably loaded into the PNIPAM matrix at low temperatures, but exits at high temperature, can be released by the expedient of applying a magnetic field.

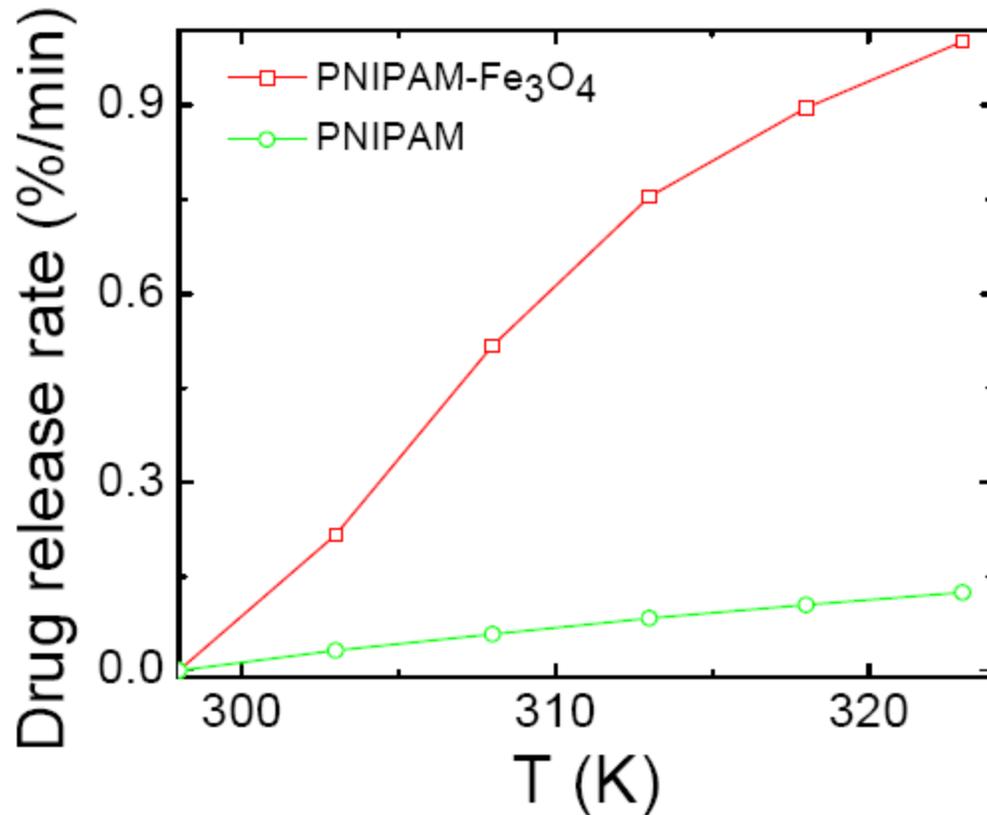


TEM image of magnetic nanoparticles attached to the surface of the PNIPAM microgel.

The magnetic nanoparticles seem to preferentially coat certain PNIPAM globules, rather than being distributed uniformly.

This may degrade the controlled response (as only a portion of the PNIPAM is targeted).

Drug release in PNIPAM and PNIPAM/Fe₃O₄ composites



Drug release rate from magnetically heated PNIPAM/Fe₃O₄ composite is much higher than from pure PNIPAM heated in a water bath.

Surprisingly, there is no significant change in the release rate associated with the structural transition (in either sample).

Points to importance of understanding chemical interactions in detail.

Summary

In addition to being small compared to most biological structures, magnetic nanoparticles have distinctly different magnetic properties from bulk materials, making them potentially very attractive for biomedical applications.

Magnetic nanoparticles have direct applications to medicine, including magnetic hyperthermia and as MRI contrast agents, but can also introduce new functionalities when combined with other materials, such as targeted drug delivery and controlled drug release.

One of the central ideas for magnetic nanoparticle applications is the ability to manipulate the particles using an external magnetic field.

There is still a great deal of work to be done on understanding how magnetic nanoparticles interact with the body (toxicity, excreting the nanoparticles, etc).

Other resources

General reviews

“Applications of magnetic nanoparticles in biomedicine”, Q A Pankhurst, J Connolly, S K Jones and J Dobson, *J. Phys. D: Appl. Phys.* **36** (2003) R167–R181

“Biomedical Applications of Magnetic Nanoparticles”, L. Trahms, *Biomedical Applications of Magnetic Nanoparticles. Lect. Notes Phys.* 763, 327–358 (2009)

Synthesis

“Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications”, A K Gupta, M Gupta, *Biomaterials* **26** (2005) 3995.

Drug delivery

“Magnetic nanoparticle carrier for targeted drug delivery: perspective, outlook and design”, R D K Misra, *Materials Science and Technology* **24** (2008) 1011.

Collaborators

Wayne State University

Physics

Ratna Naik

Chandran Sudakar

Ambesh Dixit

Rajesh Regmi

Ashis Mukhopadhyay

Vikas Gumber

Correy Black

Medical school

Norman Cheng

Mark Haacke

Ching-Yi Hsieh

David Oupicky

Shanta Raj

Bhanu Jena

University of Minnesota

Jayanth Panyam

Uday Toti

Kettering University

Prem Vaishnava

Corneliu Rablau