Magnetic bioferrofluids with tailored properties for biomedical applications

F. Palacio, A. Millán, E. Natividad, A. Arizaga, A. Urtizberea, N.J.O. Silva, R. Piñol, G. Ibarz, M. Castro and A. Mediano

Instituto de Ciencia de Materiales de Aragón.
CSIC - Universidad de Zaragoza. Zaragoza

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Outline

- Introduction: biomedical applications of magnetic nanoparticles
- Nano vs. Nano
- Superparamagnetic particles
- Hyperthermia
- Polymeric route to the production of iron oxide nanoparticles and ferrofluids

Interest of Magnetic Nanoparticles in Biomedical Applications

- Controllable sizes (≥ 100 nm - ≤ 10 nm) and shapes (spheres, needles, beads)
- Magnetic functionality => magnetic fields penetrate human tissues
- They obey Coulomb's law => can be controlled at a distance
- They transfer energy from an ac magnetic field and convert it into heat

Biomedical Applications of Magnetic Nanoparticles

Diagnosis

MRI

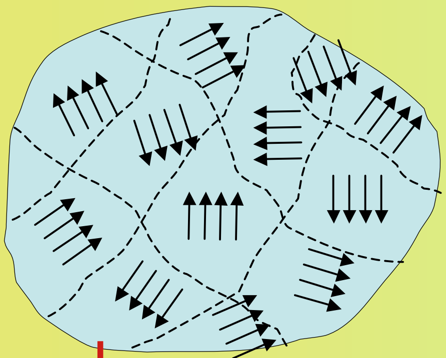
- Sensors
- Cell separation
- Enzyme tests
- Immunoassays

- Hyperthermia (MFH)
- Radiotherapy/ /Chimietherapy- -combined MFH
- Thermal ablation

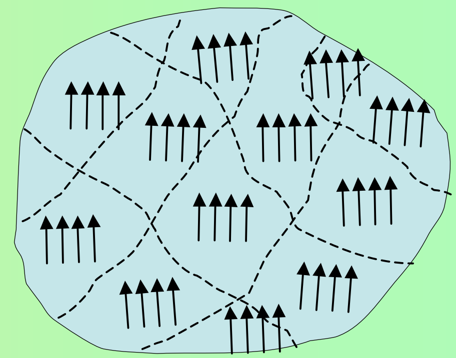
- Drug delivery
- Arthritic treatments
- Chronic disseases

Therapy

Magnetic (Nano)Particles

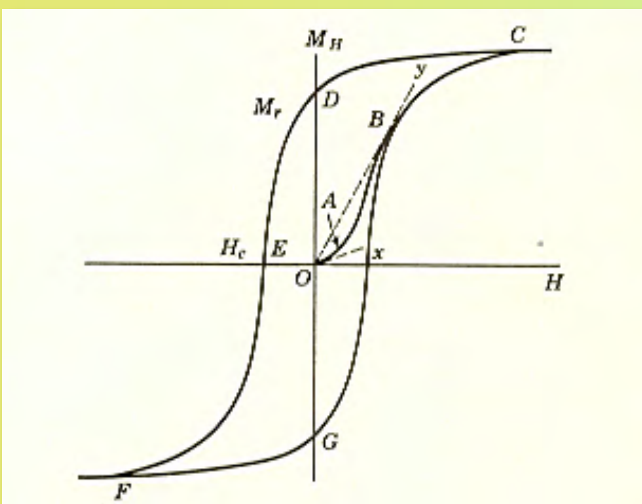


+ Magnetic field H



Magnetic domains

Magnetisation
$M = m/V_m$



Magnetic force

$$F_m = V_m (M/H) \nabla (B \cdot H/2)$$

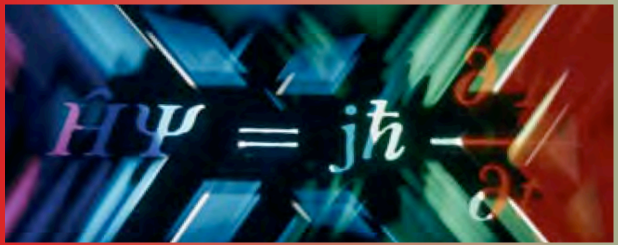
Introduction to nano-size

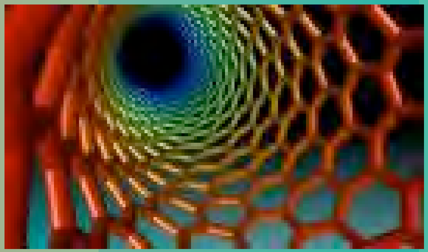
From the physics point of view Nano- is the interface separating the atomic from the macroscopic scales

Atomic World ruled by the laws of Quantum Mechanics

NANO WORLD

Macroscopic World as we perceive it, ruled by Classical Mechanics and Electromagnetism laws





In the atomic world there are properties whose critical lengths are at the nano-scale

Introduction to nano-size

At the scale below a critical length new properties arise that can give rise to new materials and new applications

Critical lengths such as

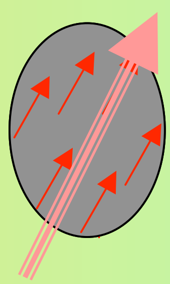
- one electron Fermi wavelength
- exciton Bohr radius
- single magnetic domain length

lead to Quantum Dots and Superparamagnetic particles

Single-domain particles => superparamagnets

When the size of a particle is smaller than the minimum allowing the formation of domains (≈ 20 - 30 nm), it becomes single-domain and

superparamagnetic



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Biomedical Applications of Magnetic Nanoparticles

- Cell separation
- Enzyme inmunoassay tests
- Sensitive detection of viral agents
- Drug delivery

} H → F_M

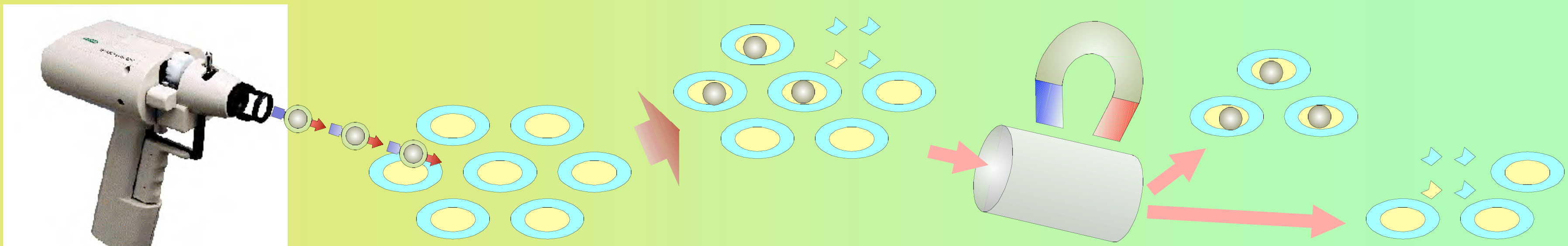
- Contrast agents for magnetic imaging — **M**
- DMS as luminescent sensors
- Hyperthermia — **SPM**

} d < critical size

- ··· the limit is the imagination ···

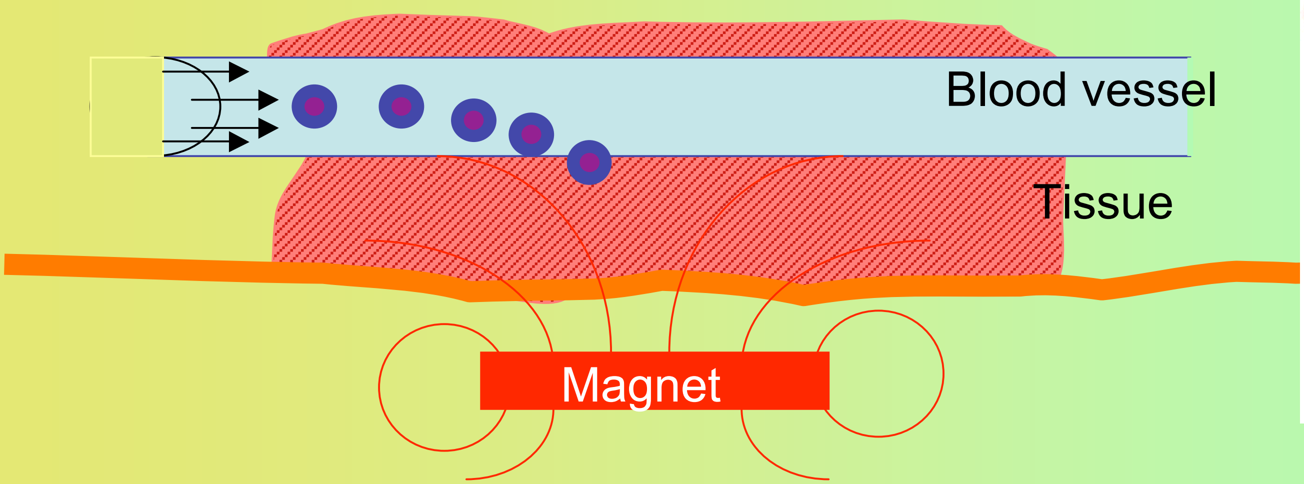
Magnetic force-driven applications

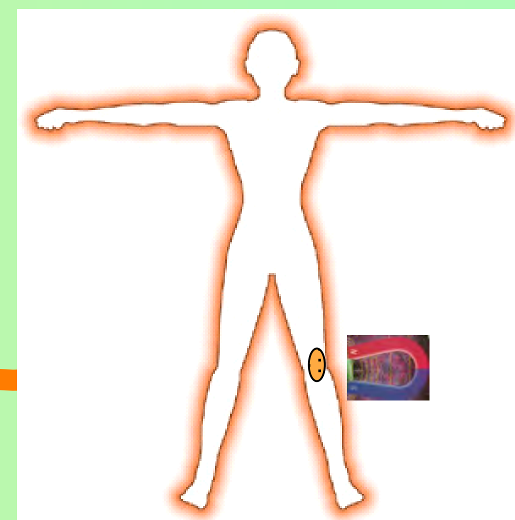
Magnetic separation



Transfected cell separation in gen therapy

Drug delivery





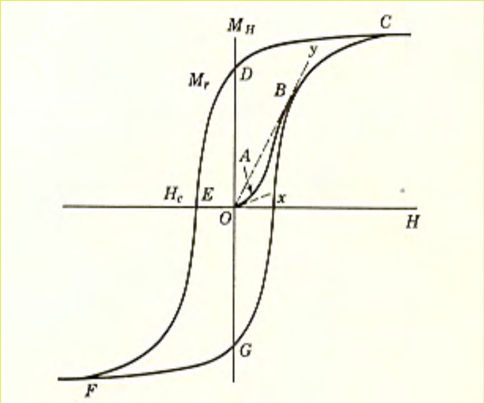
Magnetic nanoparticles as contrast agents for MRI

- Huge magnetic moments as compared to Gd chelates
- Proton relaxation is affected by the large magnetic field heterogeneity in the vecinity of the particles
- Can induce >10 fold increase in proton relaxivities
- Shortening of relaxation times, particularly T_2 (*negative contrast*)
- Very high resolution, close to molecular level

Hypertermia

Magnetic systems can convert energy into heat under the effects of an alternating magnetic field

- **inductive heating (eddy currents)**
- **hysteresis losses**



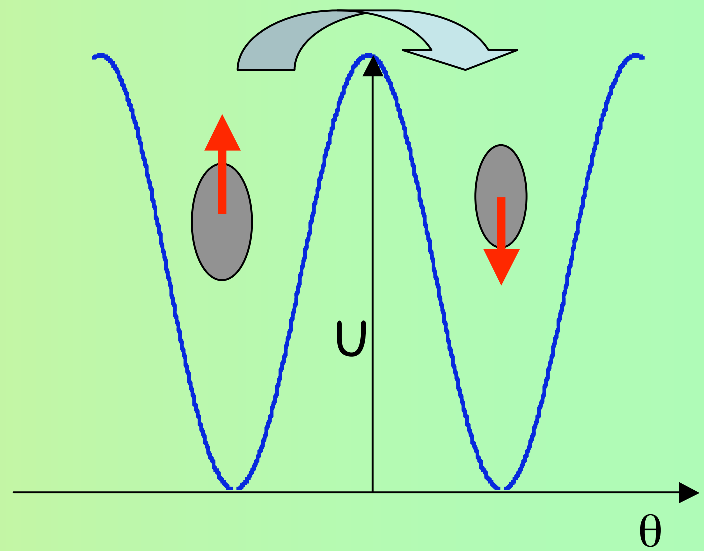
$$P_{FM} = -\mu_0 f \oint H dM$$

No relevant at low ac magnetic fields

Hypertermia

Superparamagnetic particles

- **Neél relaxation**
- **Rotational Brownian motion**



$$\chi'' = \chi_0 \frac{\omega\tau}{1+\omega^2\tau^2}$$

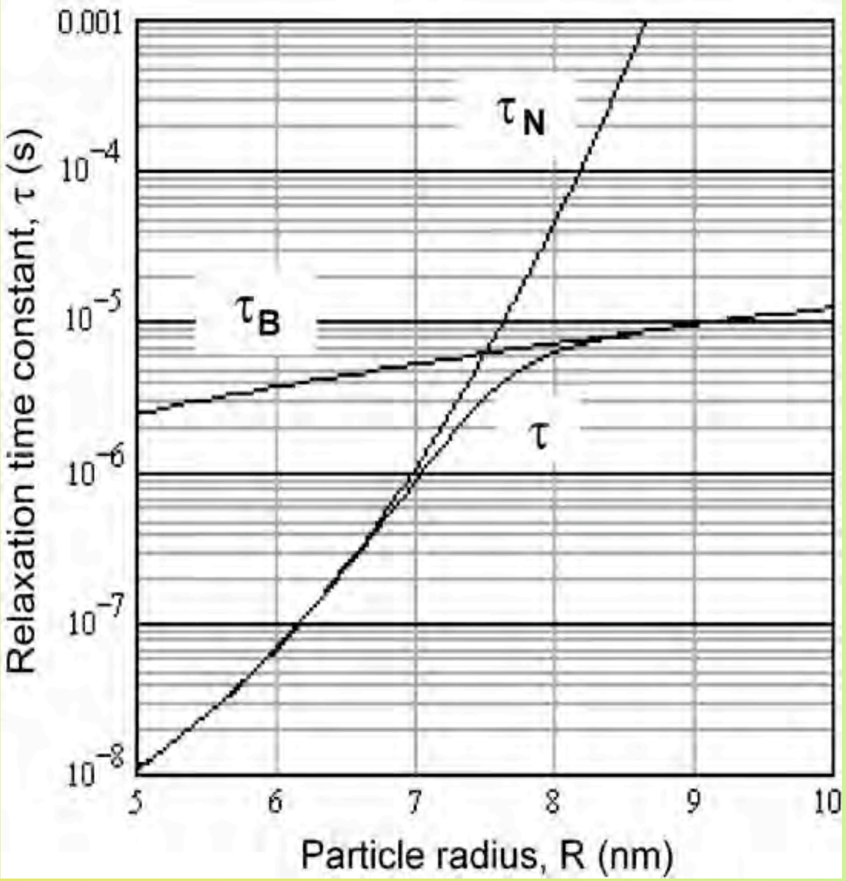
$$P_{SPM} = -\frac{1}{2}\mu_0\chi''\omega H_0^2$$

$\varpi\tau \sim 1 \Rightarrow E_{máx}$

$E_{máx}$ (γ-Fe_2O_3, 10 nm)
$\varpi \sim 1$ MHz

Biological range: 50 kHz ≤ f ≤ 1200 kHz, H < 15 kA/m and (H · f)max = 485 kHz·kA/m

Hypertermia



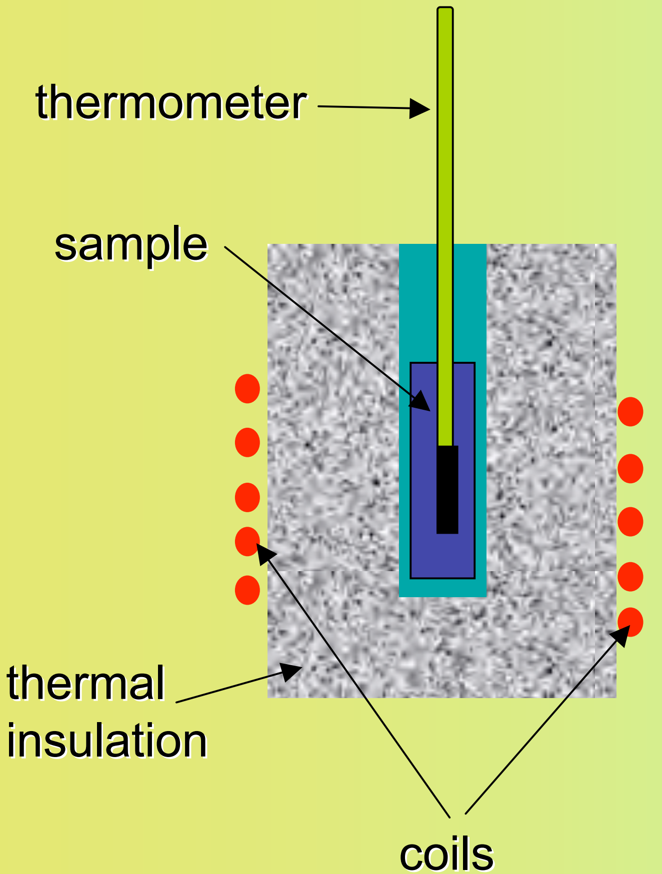
$$\tau_N = \tau_0 \exp\left(KV / kT\right)$$

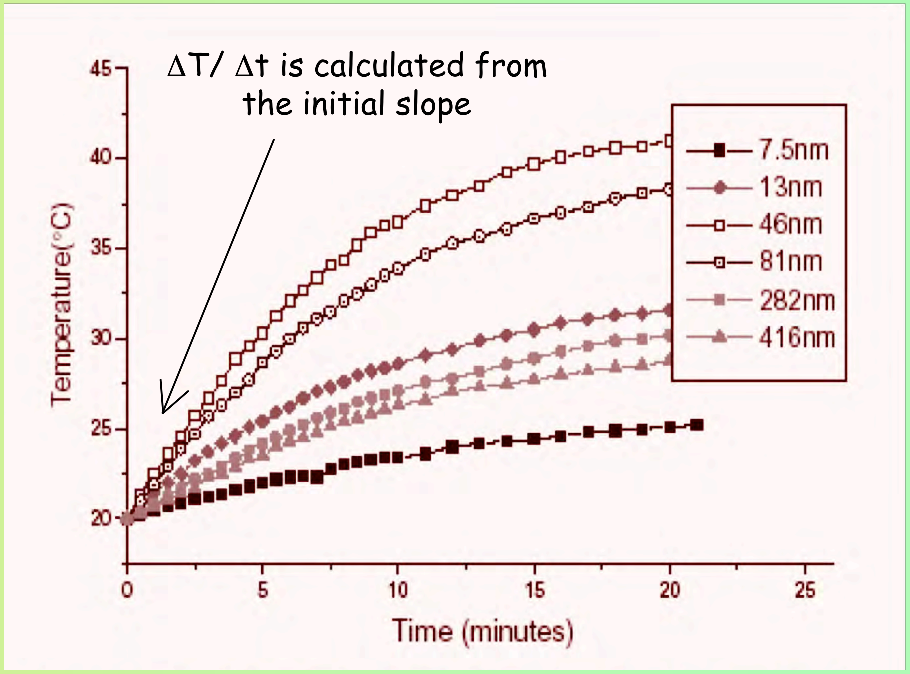
$$\tau_B = \frac{3\eta V_H}{kT}$$

$$\frac{1}{\tau_{eff}} = \frac{1}{\tau_N} + \frac{1}{\tau_B}$$

The shortest relaxation time constant tends to dominate the effective relaxation time

Hypertermia

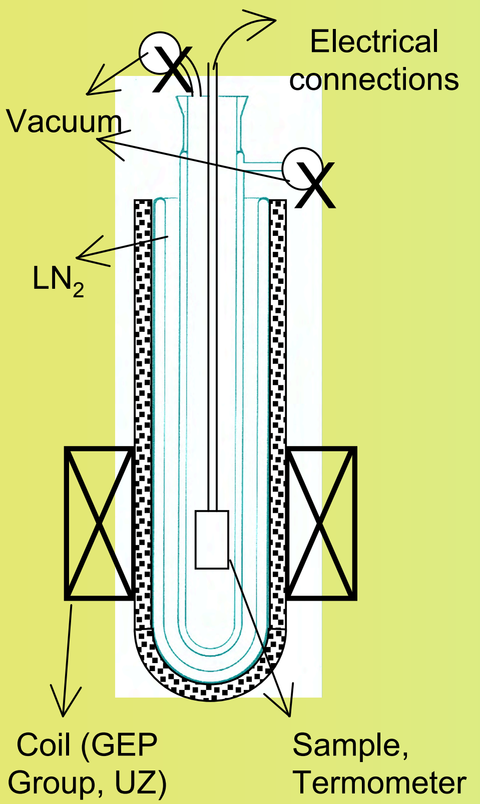




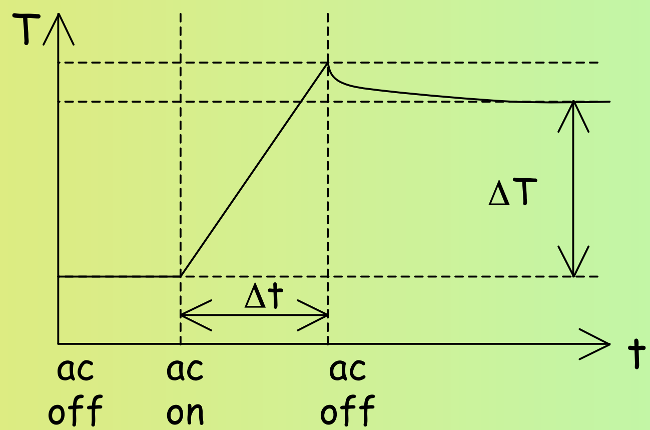
$$SAR_{(W/g)} = C\frac{\Delta T}{\Delta t} \cdot \frac{1}{m_{SPM}}$$

Non-adiabatic ----> heat losses ----> estimation of SAR

Adiabatic set-up for hyperthermia



(no metallic components)



Operation range:

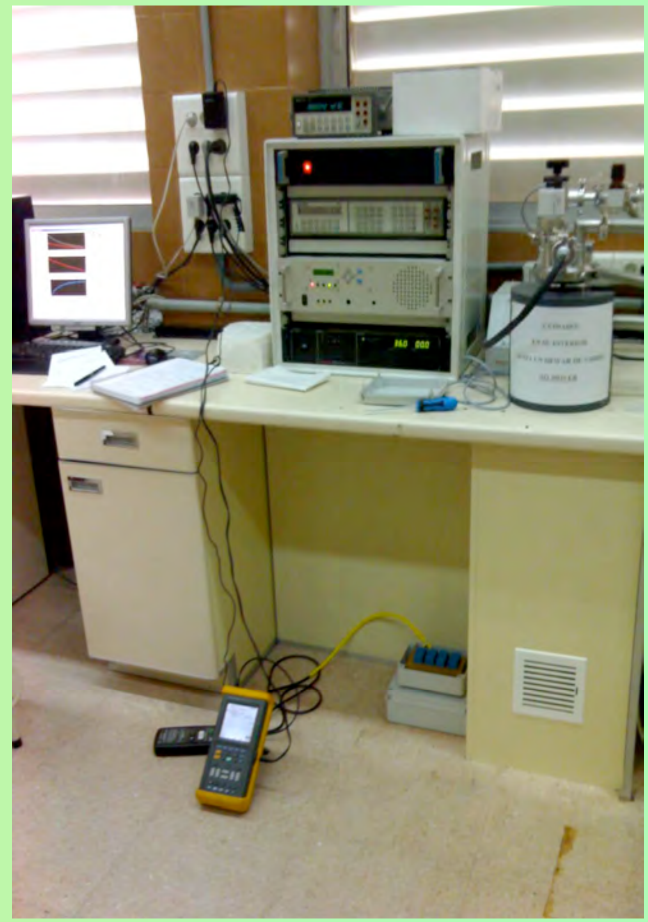
***H* = 0 - 8kA/m**

***f* = 50 – 300 kHz**

Biological applications:

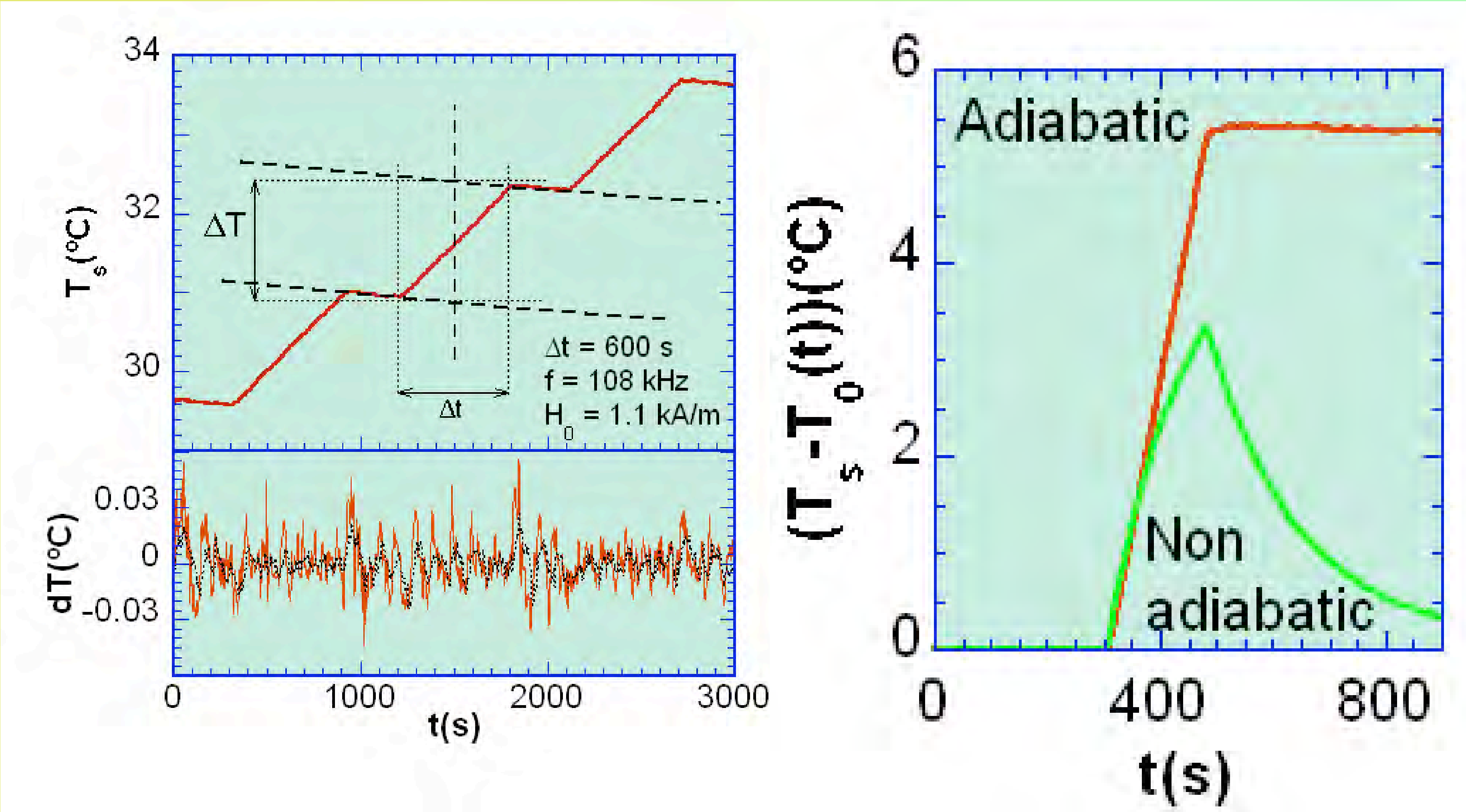
$H \cdot f < 4.85 \cdot 10^8$ A/m·s

H < 15 A/m, f < 400 kHz



Eva Natividad et al., Appl. Phys. Letters, **92**, 0991136 (2008)

Adiabatic set-up for hyperthermia

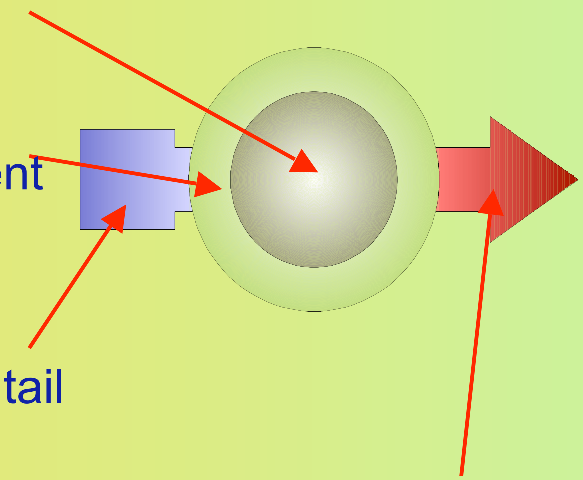


(see also poster from Ana Arizaga)

Superparamagnetic Particles for Biomedical Applications

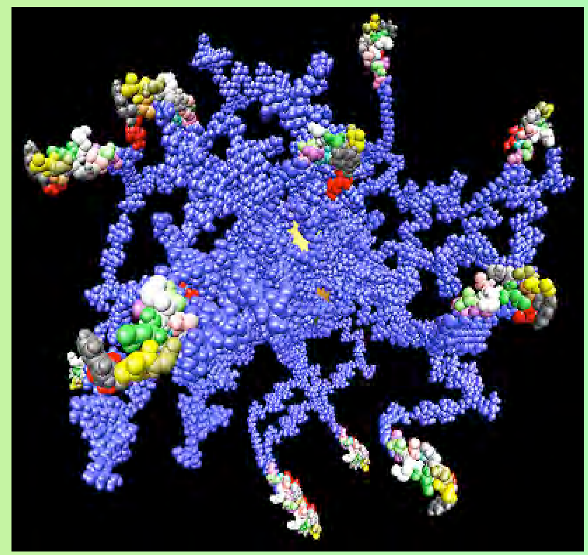
functionalized magnetic nucleus (maghemite, other)

Protecting core, anchoring element



Functionalized tail for therapeutic uses: drugs, enzyms, etc.

biological vector: antigens, etc.



Superparamagnetic Particles for Biomedical Applications

The magnetic nucleus should preferable be biocompatible, otherwise a strong protective coating (+ its validation!!) is required for *in vivo* applications

- Maghemite
- Magnetite
- Co-ferrites and other (*in vitro*)

Tailoring magnetic nanoparticles

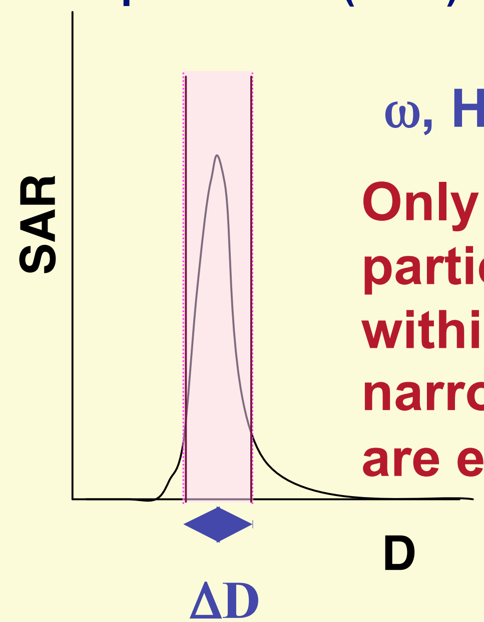
Interest:

- Important applications of magnetic nanoparticles are very exigent regarding size and shape dispersion
- Polymers can provide a way to avoid agglomeration and easy surface functionalisation

Production methods must focus on:

- narrow size dispersion
- variable size control
- variable shape control
- control of organization and particle-matrix interactions

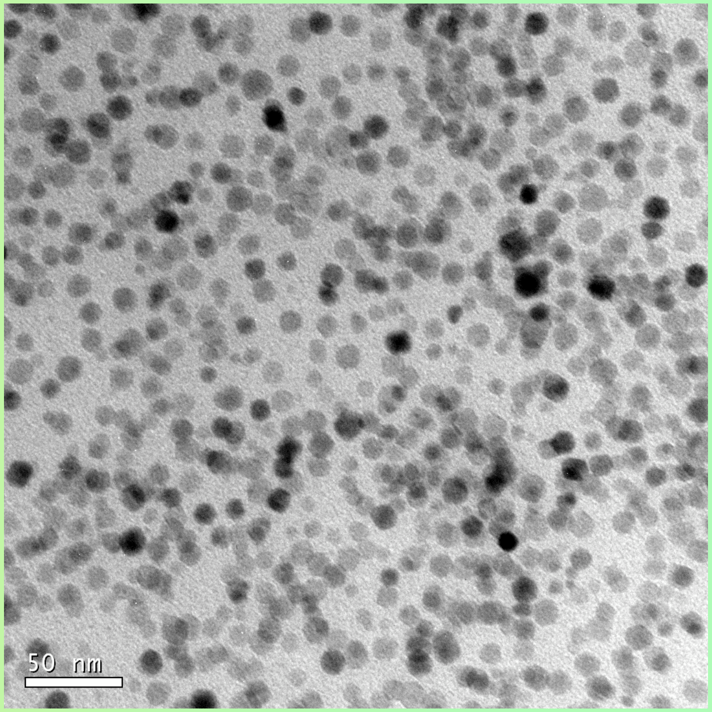
Size dependence of the Specific Absorption Rate (SAR)



Only particles within a narrow ΔD are efficient

Tailoring magnetic nanoparticles

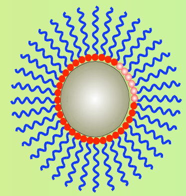
1. Synthesize the magnetic particles, normally magnetite or maghemite
2. Avoid agglomeration by keeping them dispersed in a surfactant
3. Eliminate surfactant to stabilise the particles either electrostatically or sterically
4. Functionalise the particles



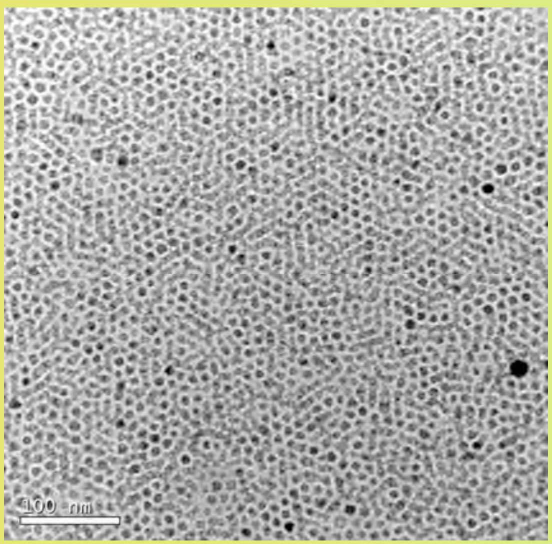
Thermal decomposition of $Fe(CO)_5$.

Tailoring magnetic nanoparticles

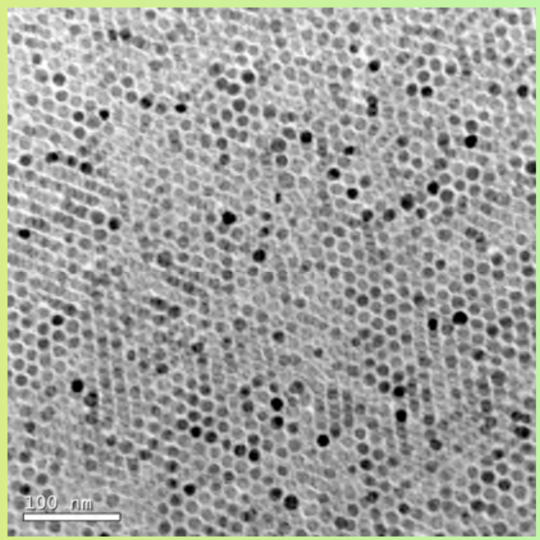
Solvent: octhyl ether

$Fe(CO)_5 \xrightarrow{\Delta}$ 

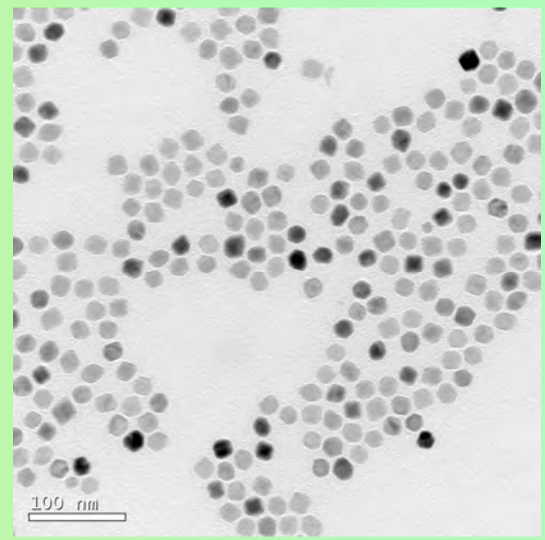
 Oleic acid



Maghemite, 10 nm



Maghemite, 14 nm

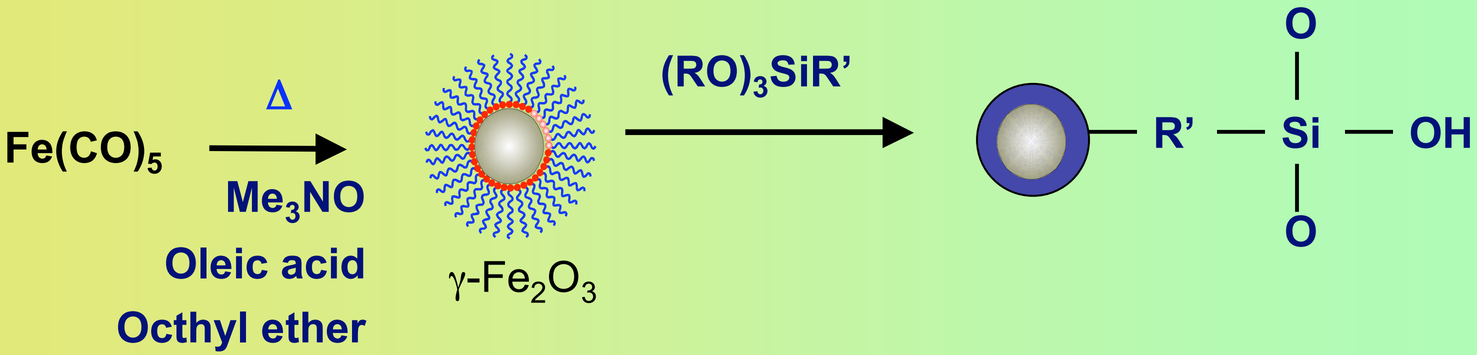


Maghemite, 20 nm

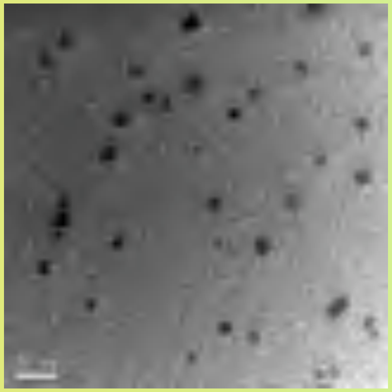
Size dispersion ≈ 5%

Size ranges: 4-20 nm

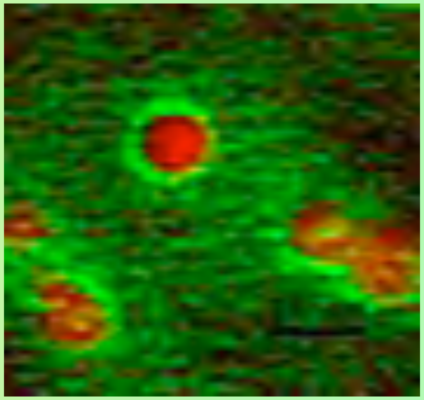
Tailoring magnetic nanoparticles



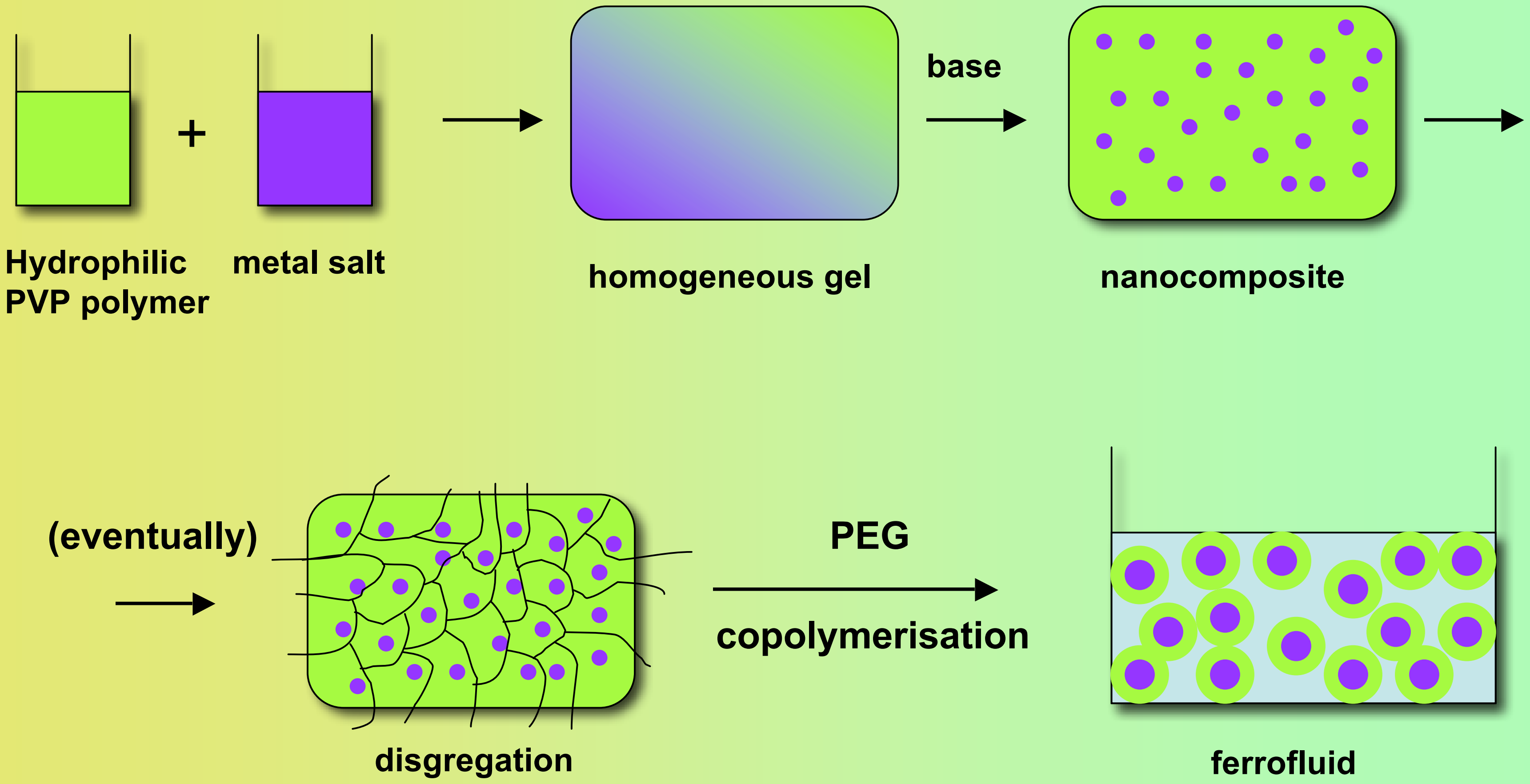
TEM



EFTEM



Tailoring magnetic nanoparticles with polymers



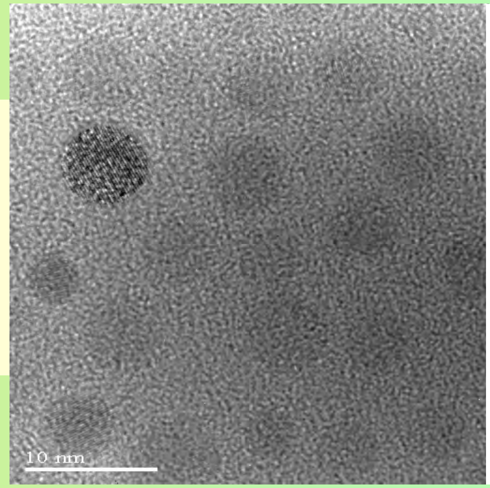
A. Millán and F. Palacio, Applied Organometallic Chemistry, **15**, 396-400 (2001)

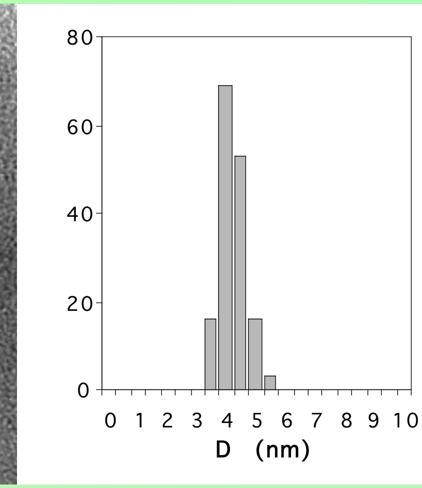
A. Millán et al., Acta Materialia **55**, 2201-9 (2007).

A. Millán, F. Palacio, G. Ibarz, Patent PCT/EP2007/058312

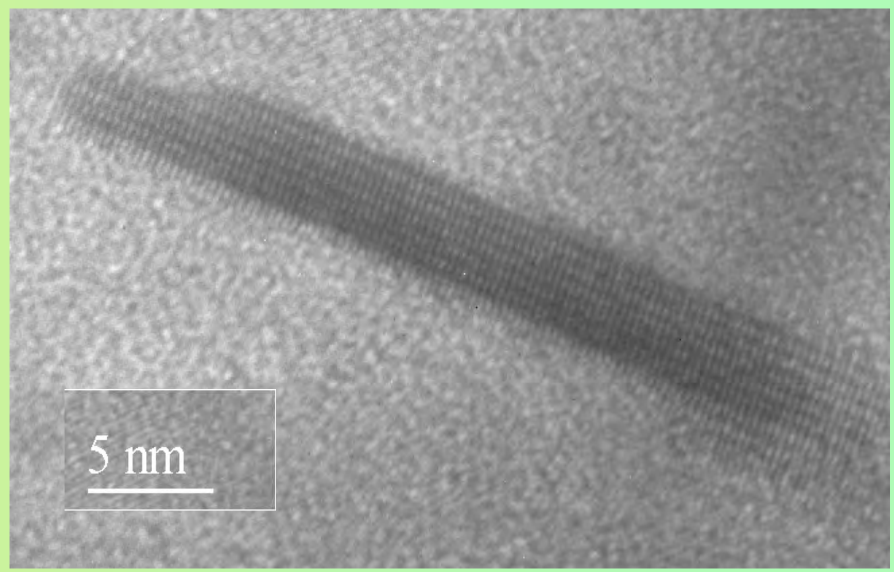
Tailoring magnetic nanoparticles with polymers

Simple and quick single-pot reaction
Spheric particle sizes 2 - 15 nm
Size dispersion ±10%
No aggregation. Uniform distribution.





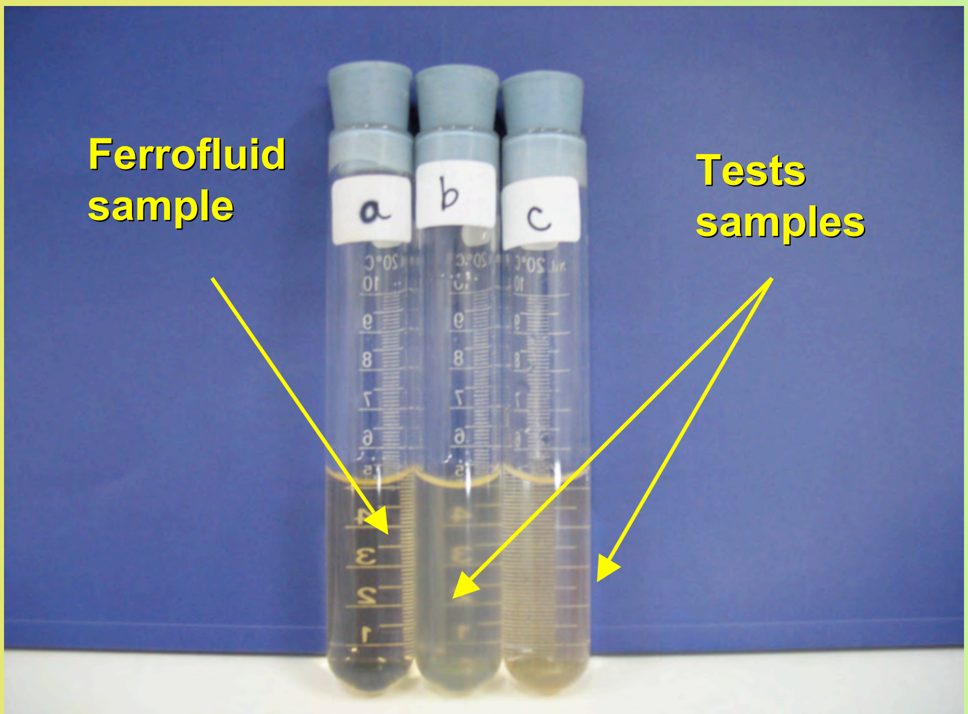
Either spheres and rods can be selectively prepared



Polymers can provide a way to avoid agglomeration and easy surface functionalisation

Maghemite ferrofluids

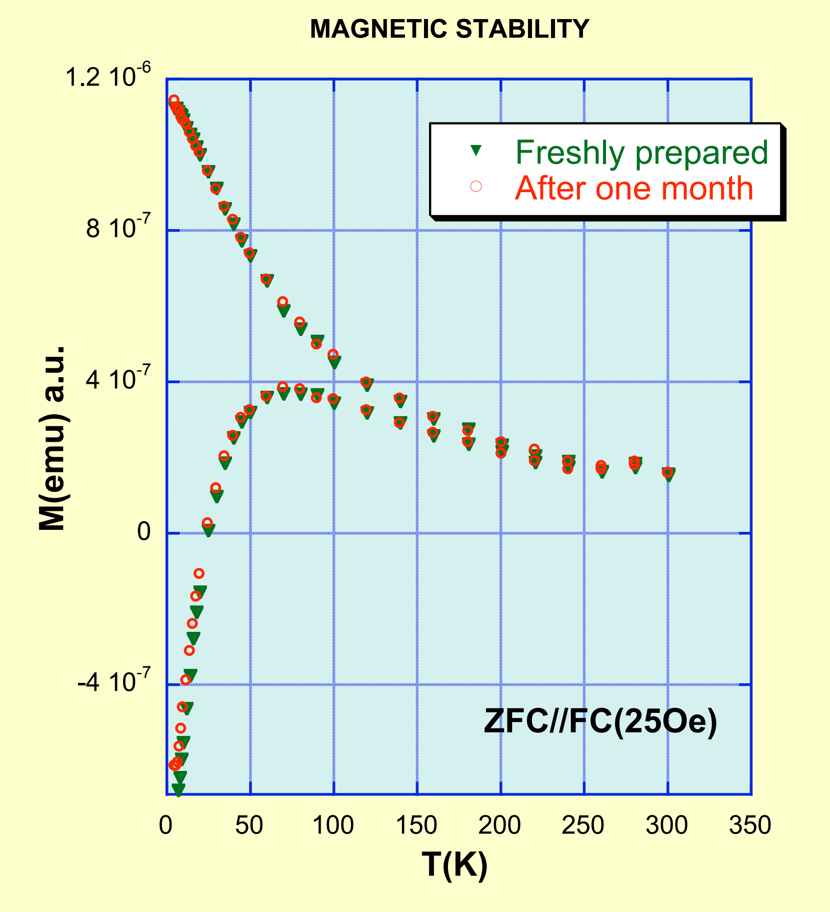
Adequate polymer design leads to nanocomposites which disperse in a phosphate buffer saline solution as nanoparticles coated with PEG

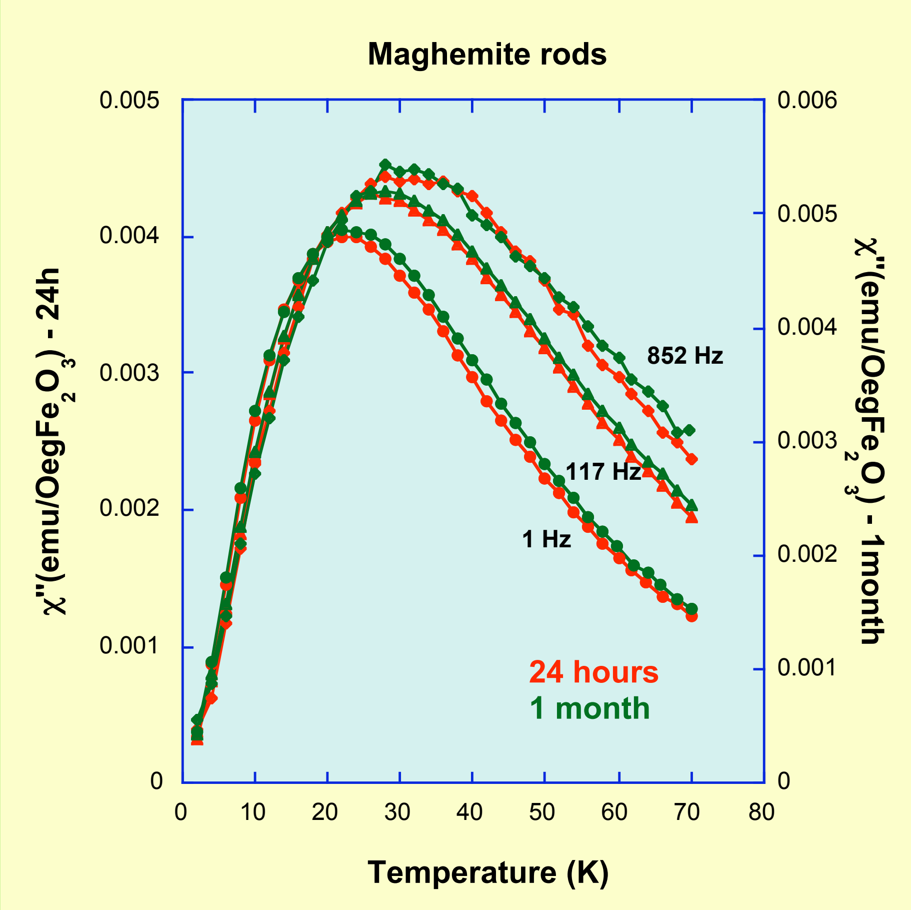


Bioferrofluids, pH = 7.4

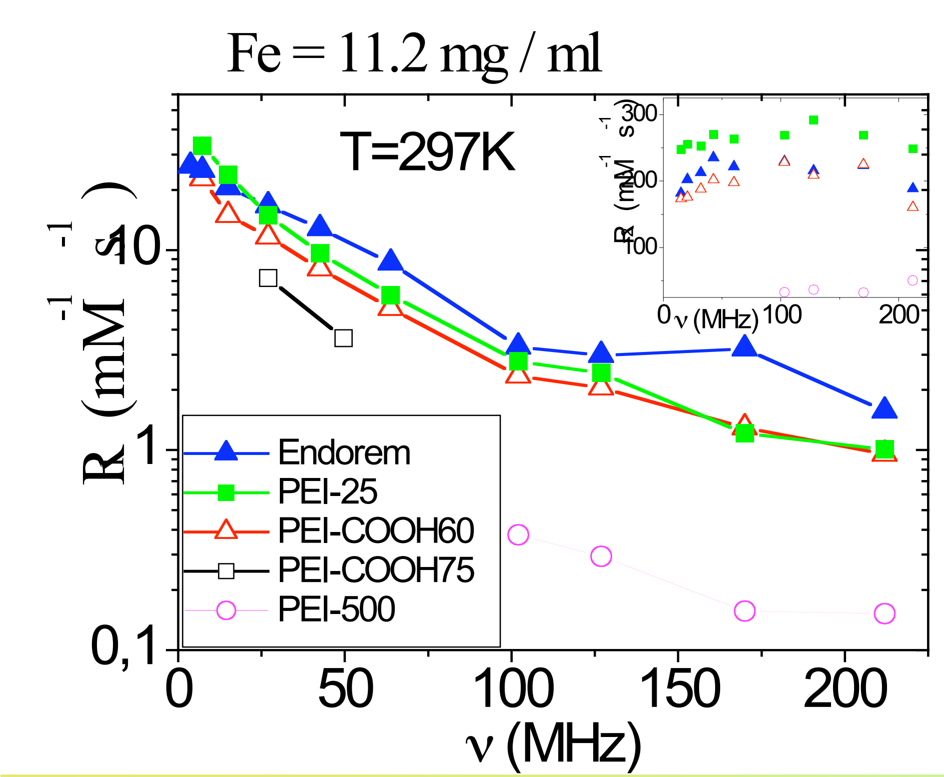
Maghemite ferrofluids

Ferrofluids are persistent for more than one month





NMR relaxometry



Relaxivities R_1 and R_2 quantifies the increased nuclear relaxation rates $1/T_1$ and $1/T_2$ of nuclei (typically protons) due to the presence of magnetic centers

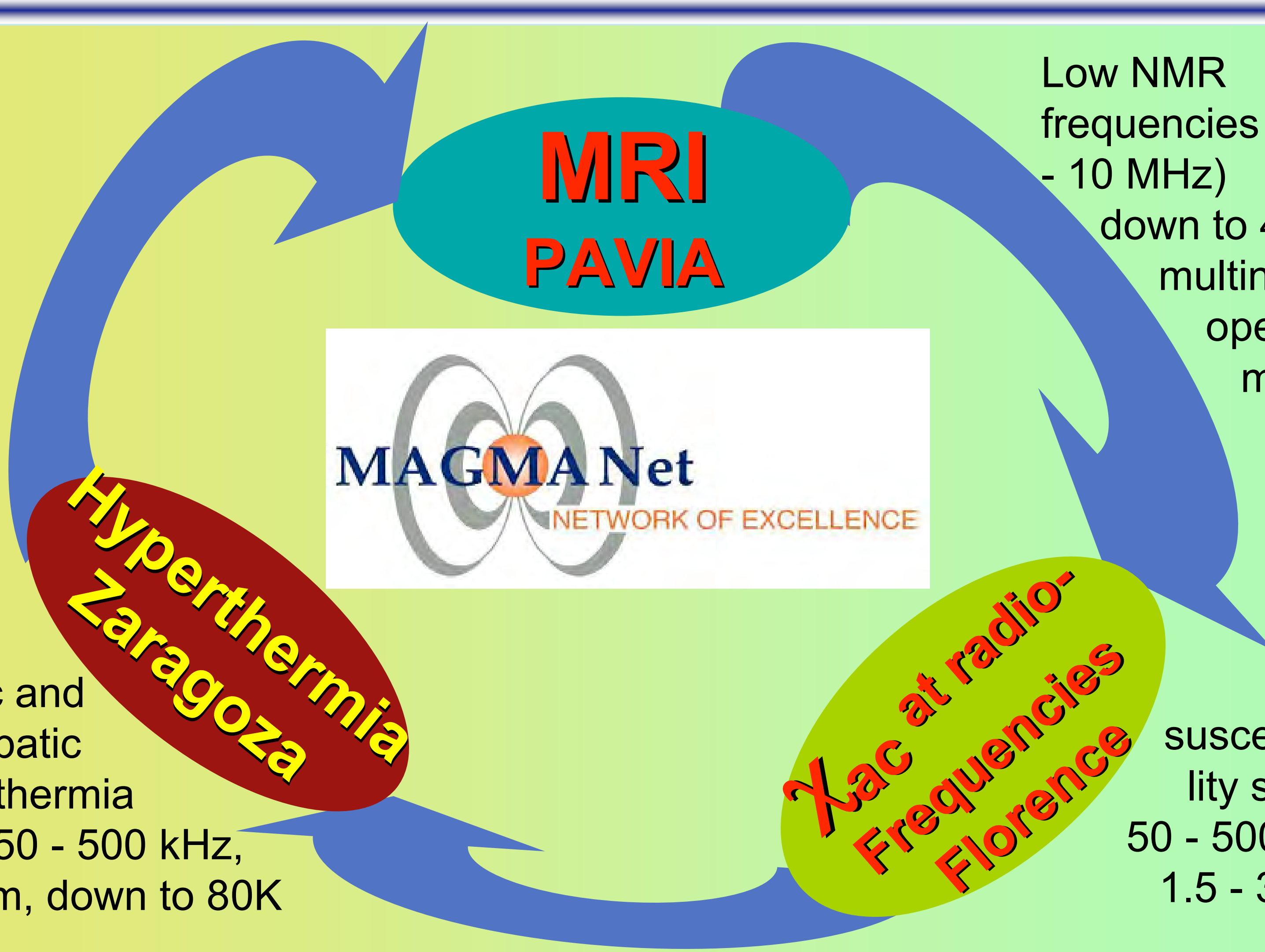
- **R_1 and R_2 relaxivities compared with commercial ENDOREM®**
- **PEI-25 R_1 relaxivity compares to ENDOREM®**
- **PEI-25 R_2 relaxivity higher over the whole field range.**

Hyperthermia values

Material	Size (nm)	H (kA/m)	f (kHz)	$Hf/(Hf)_{max}$	SAR (W/g)	SAR * (W/g)	Ref.
magnetite	8	1.4 - 6.3	410	1.2 - 5.3	78	**11.3**	Hiergeist et al, J. Magn. .Magn. Mat., 201 (1999) 420-422
magnetite	100	6.5	410	5.5	200	**27.2**	
maghemite	10 - 12	7.2	880	13.2	210	**10.8**	Brunsentsov et al, J. Magn. .Magn. Mat., 225 (2001) 113-117
magnetite	10	6.5	400	5.4	93	**12.9**	Hilger et al, Academic Radiology, 9 (2002) 198-202
magnetite	7.5 - 46	32.5	80	5.4	75.6	**2.1**	Ma et al, J. Magn. .Magn. Mat., 268 (2004) 33-39
magnetite	81 - 416	32.5	80	5.4	28.9	**0.8**	
maghemite	15	11.2	410	9.5	600	**27.4**	Hergt et al, J. Magn. .Magn. Mat., 270 (2004) 345-357
maghemite	7 - 18	15	410	12.7	900	**22.9**	ibid., 280 (2004) 358-368
magnetite	6 - 10	7	63	0.9	85	**93.7**	Wang et al, J. Magn. .Magn. Mat., 293 (2005) 334-340
maghemite	7.9 - 22.3	8	400	6.6	98	**14.7**	G. Glöckl, R. Hergt, M. Zeisberger et al., JP: CM 18 (2006) S2935–49
maghemite	16.5 - 24.8	24.8	700	35.8	1650	**9.2**	Fortin et al, J. Am. Chem. Soc., 129 (9) (2007) 2628-2635
maghemite	d ≈12 needles	5	150	1.1	158	**144**	A. Millán et al (in preparation)

(*) Referred to standard H = 4.85 kA/m, f = 100 kHz values

Nanomagnets for theragnostic



Low NMR frequencies (few kHz - 10 MHz) down to 4.2 K, multinuclear operatinal mode,

χ_{ac} susceptibi-lity set up
50 - 500 kHz
1.5 - 350 K

Adiabatic and non adiabatic magnetothermia set ups (50 - 500 kHz, 0 - 8 kA/m, down to 80K

Interested may contact: amillan@unizar.es or palacio@unizar.es

Group TERMOMAG

Ana ARIZAGA
Ramon BURRIEL
Javier CAMPO
Miguel CASTRO
Clara GONZALEZ
Miguel A. GONZALEZ
Gemma IBARZ
Ricardo LOPEZ
Emma LYTHGOE
Eva NATIVIDAD
Angel MILLAN

M Carmen MORON
Lucas OLO
Elias PALACIOS
Rafael PIÑOL
Ines PUENTE
Alberto RODRIGUEZ
Clara RODRIGUEZ
Cristina SAENZ de PIPAON
Jorge SANCHEZ
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Escalado de producción

Molecular Nanoscience

Programa Consolider
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