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Magnetic nanoparticles: synthesis, properties and biomedical applications

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@olive_free



MAGNETIC NANOPARTICLES: SYNTHESIS, PROPERTIES AND BIOMEDICAL APPLICATIONS

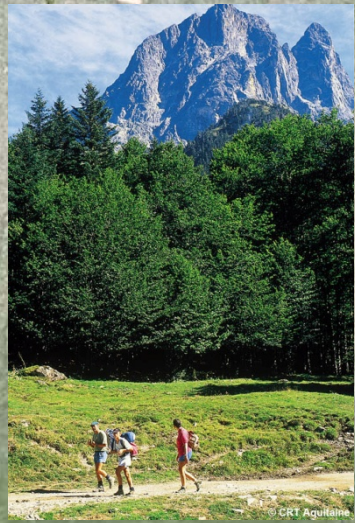
Olivier Sandre, senior CNRS researcher at Univ. Bordeaux, France



UGR

Universidad
de Granada





Magnetic nanoparticles (MNPs) Part 1: Synthesis and physical properties

- Part 1A: Chemistry of iron oxides and oxo-hydroxides:

Diversity of methods to prepare colloidal nanoparticles, either in non aqueous solvents: hydrothermal synthesis, polyol synthesis, thermal decomposition... or in water: alkaline co-precipitation of iron salts (also in EG, DEG...)

- Part 1B: Magnetic behavior (ferro- /ferri- /antiferro- /superpara– magnetism...) and optical properties of MNPs (UV-vis absorption, magnetic birefringence)

- Part 1C: MNPs as contrast agents in Magnetic Resonance Imaging
Universal law for relaxometry (T_1/T_2 of water H spins near MNPs)

All properties are highly sensitive on MNP's size and shape (poly)dispersity!

- Part 2A Magnetic Hyperthermia ('Tumor catabolism')

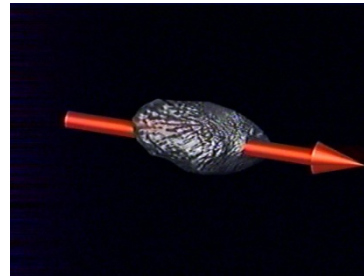
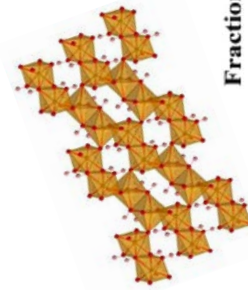
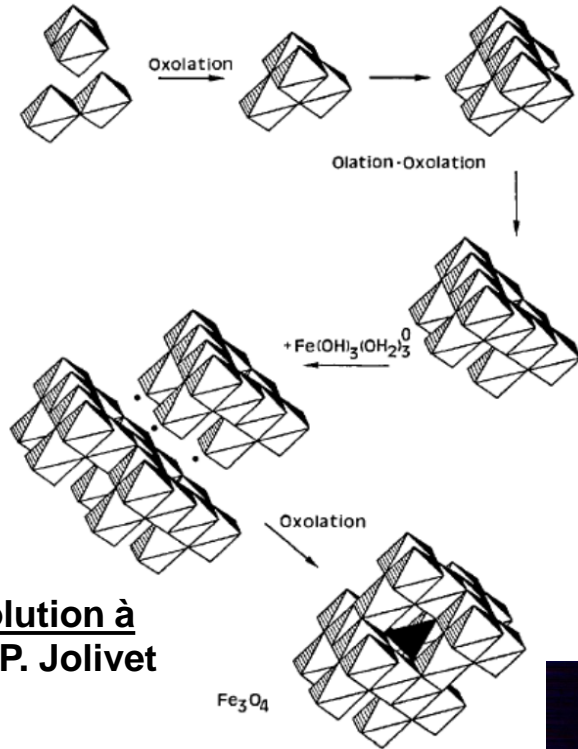
- Part 2B Nanomedicines – Magnetic carrier – Magnetic Guiding ('Tumor homing')

- Part 2C Drug Delivery Systems (DDS) based on Magnetic Core@Polymer Shells, Magnetic Polymer Shells, Magnetic Micelles, or Vesicles ('Polymersomes')

The Iron Oxides (Rochelle M. Cornell, Udo Schwertmann)

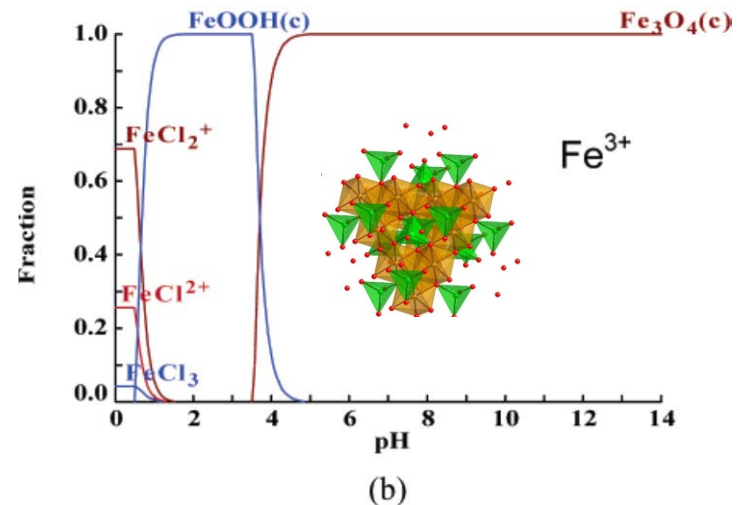
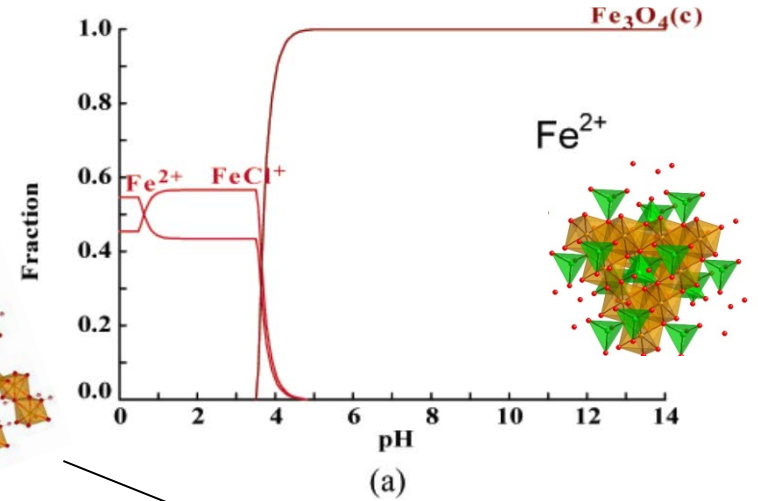


From solution of Fe^{2+} et Fe^{3+} salts towards solid phase



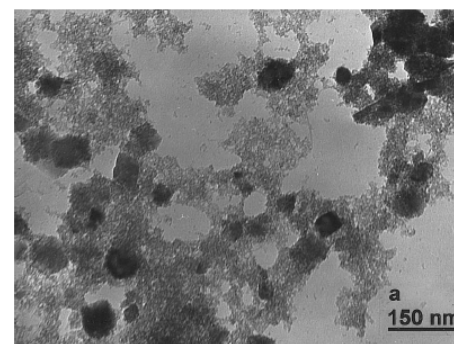
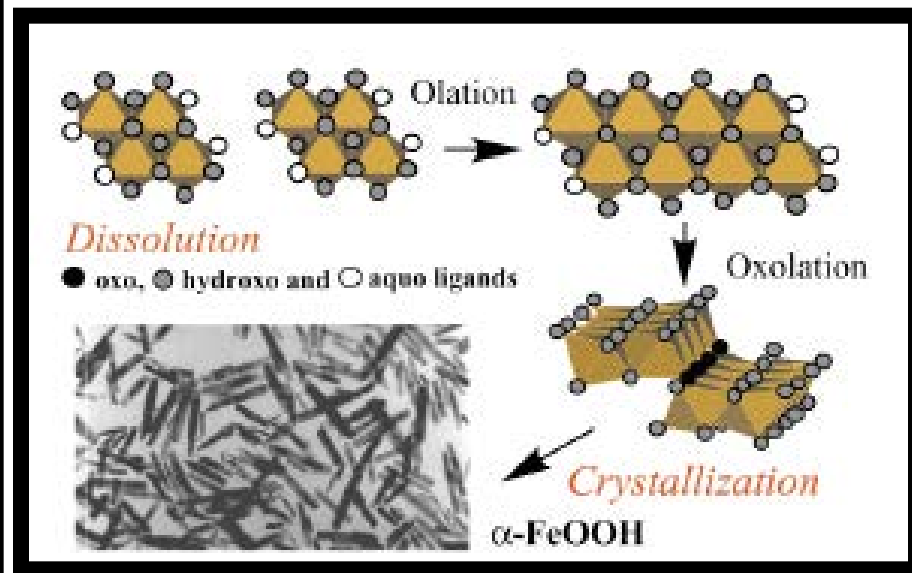
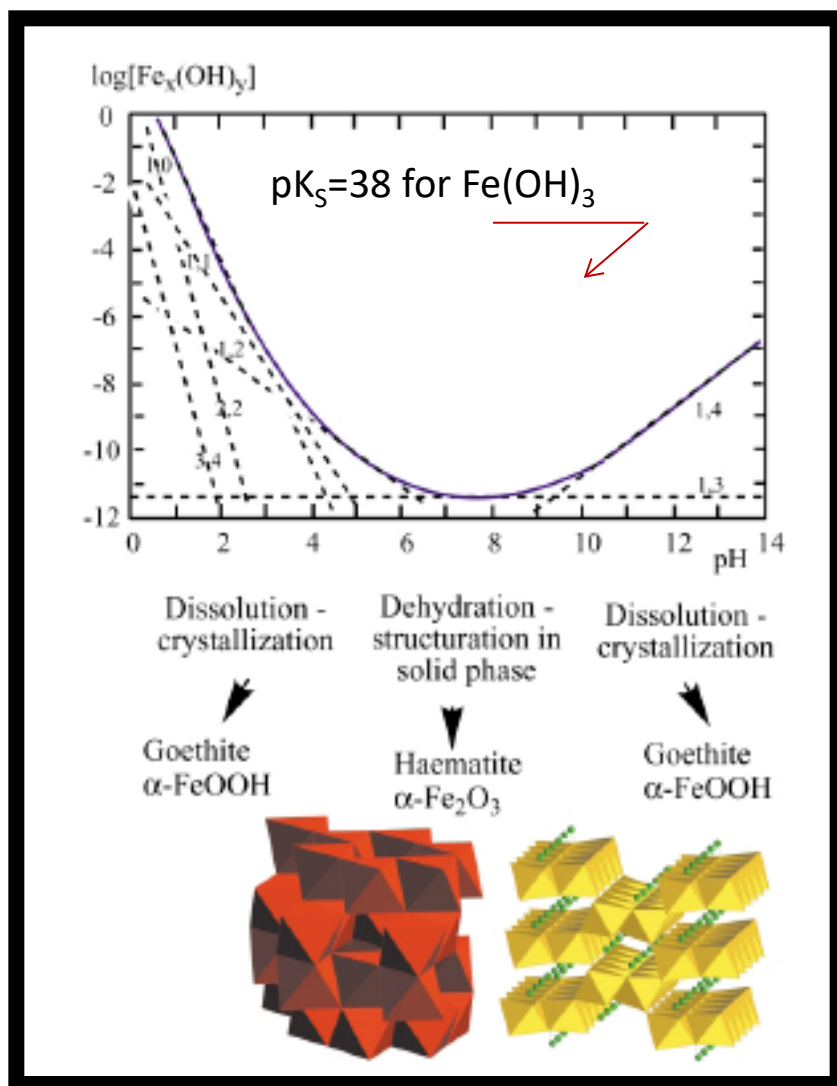
- ⊕ O^{2-}
- Fe^{3+} tetrahedral site
- Fe^{2+}/Fe^{3+} octahedral site

Spinnelle structure



D.K. Kim et al.,
Chem. Mater. 2003, 15, 1617-1627

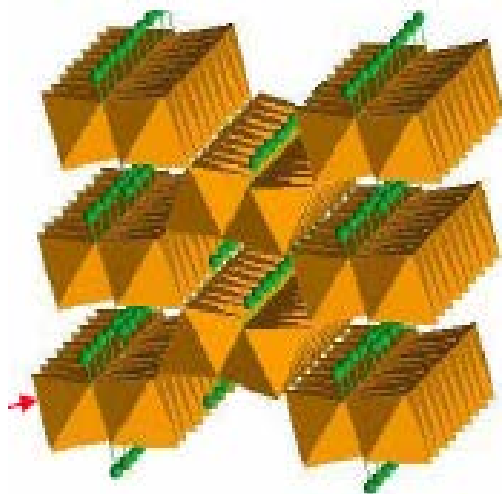
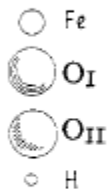
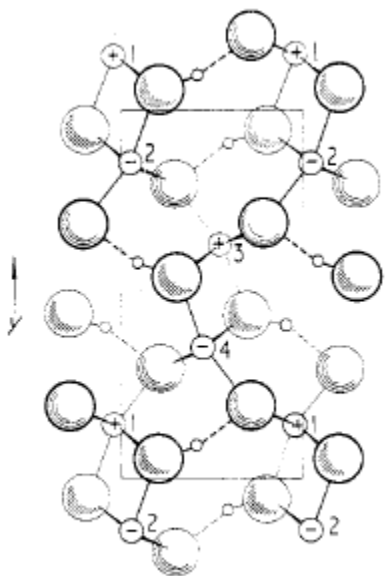
Very narrow pH stability of $\text{Fe}^{3+}(\text{H}_2\text{O})_6$ soluble ion



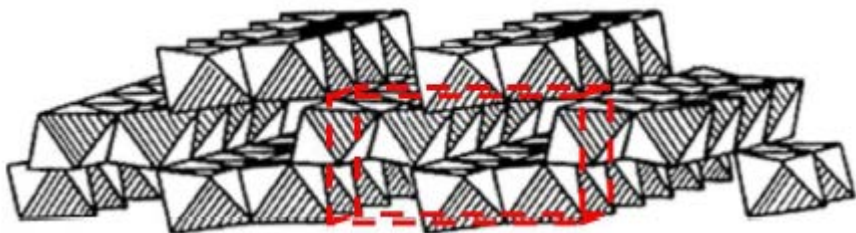
Jean-Pierre Jolivet,

Chem. Commun., 2004, 481-487

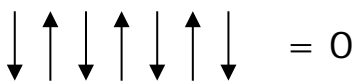
Antiferromagnetic clays made of iron^{III} oxo-hydroxides



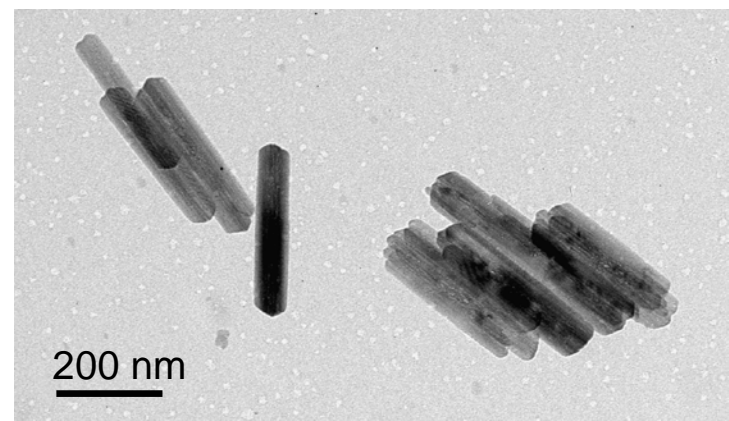
Orthorhombic structure of $\gamma\text{-FeOOH}$
(Fe³⁺ in octahedral sites)



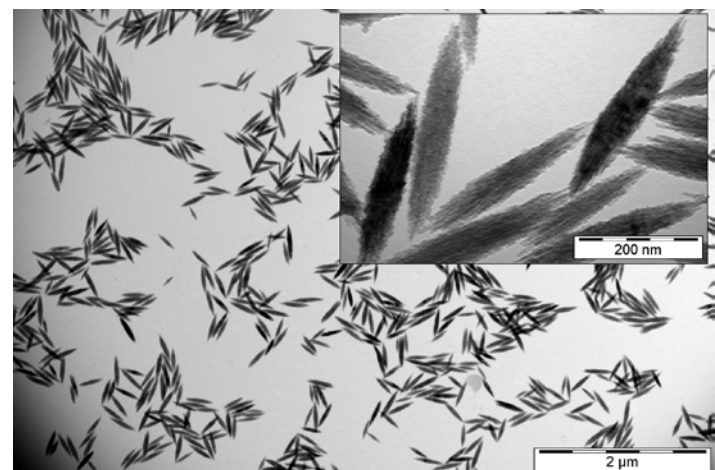
Goethite is **antiferromagnetic**



Resulting
magnetization



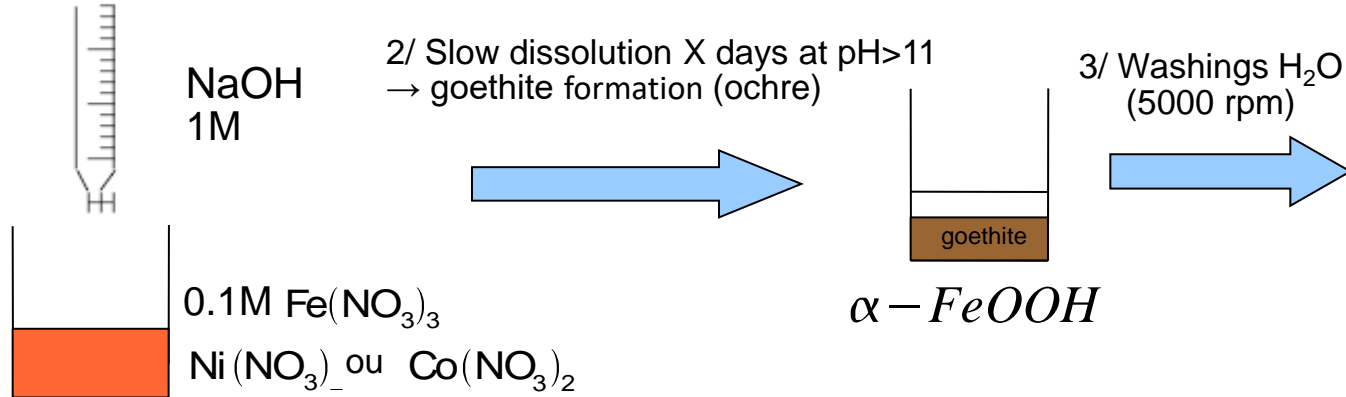
Goethite nanolaths $\gamma\text{-FeOOH}$
(rod-like)



Accicular Haematite $\alpha\text{-Fe}_2\text{O}_3$
(spindle-like)

Synthesis of antiferromagnetic goethite nanorods

1/ ferrihydrite alkaline precipitation



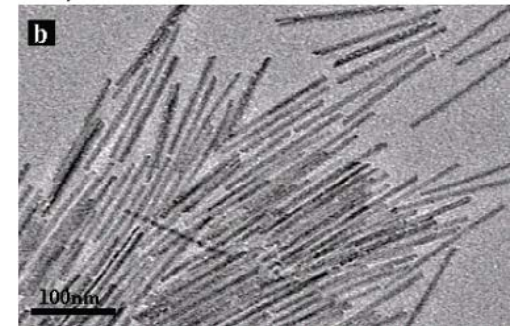
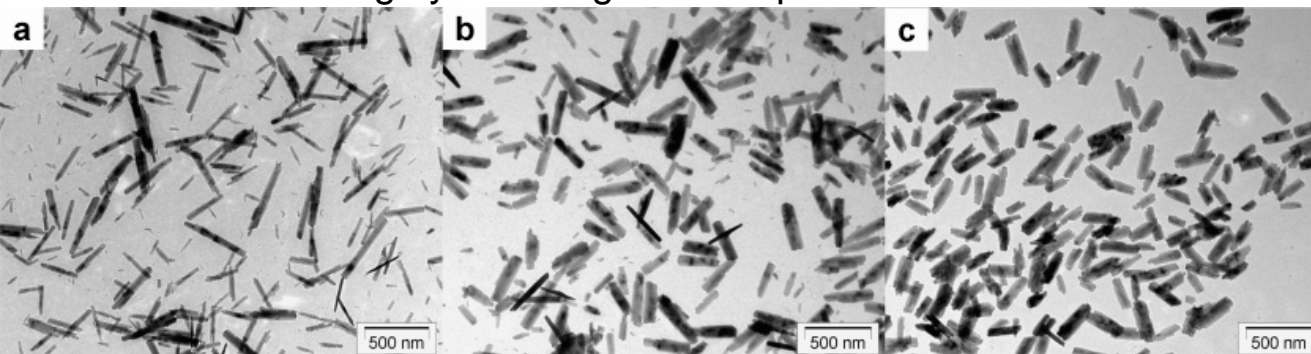
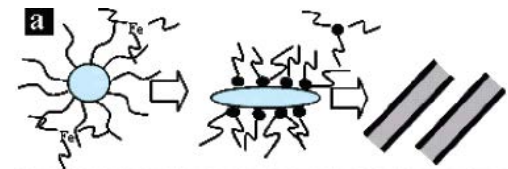
Dispersion in HNO_3 at pH=3

- PhD thesis J. Hernandez (UPMC 1998):
10 days ageing at $T=25\text{C}$ & pH13

- S. Krehula et al. (Mat. Lett. 2002): hydrophobic base (TMAOH)
Ageing during 1 – 21 days + “forced hydrolysis” ($T=60 - 160\text{C}$)

- D. Thies-Weesie et al. (Chem. Mater. 2007)
Size-sorting by centrifugation steps

- Thermal decomposition Fe^{III} -oleate
Taekyung Yu et al. (JACS 2007)



Doping of goethite nanorods with M^{n+} cations

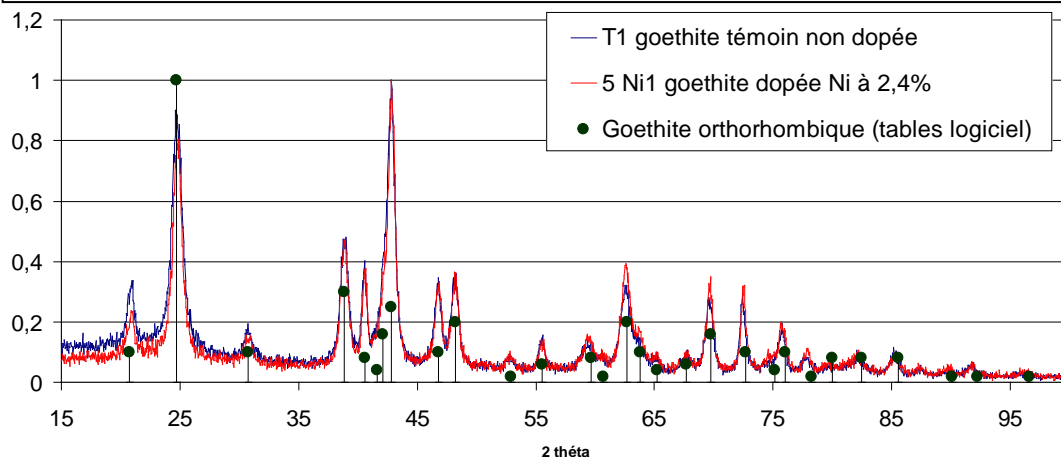
- U. Schwertmann & R.M. Cornell, Iron Oxides in the Laboratory (1991)
- B. Sing et al., Clay Minerals 2002 → Cr^{3+} , Mn^{3+} , Ni^{2+}
- M. Mohapatra et al., Hydrometallurgy 2002 → Cu^{2+} , Ni^{2+} , Co^{2+} , Mat. Chem. Phys. 2005 → Ce^{4+}

Ageing conditions: 24h in oven at 70° C – pH=11-12

Sample	pH _{ageing}	Ni/Fe	Φ v/v	D _{hyd} nm
T	11.1	0	0.21%	205
1Ni	11	0.6%	0.19%	198
5Ni	11.9	2.4%	0.17%	142
10Ni	12	2.8%	0.10%	168

Sample	pH _{ageing}	Co/Fe	Φ v/v	D _{hyd} nm
T	11.1	0	0.21%	205
1Co	12	1.0%	0.25%	284
5Co	12.2	2.6%	0.15%	169
10Co	12.2	9.6%	0.02%	238

XRPD: no trace of $Ni(OH)_2$ → nickel on surface



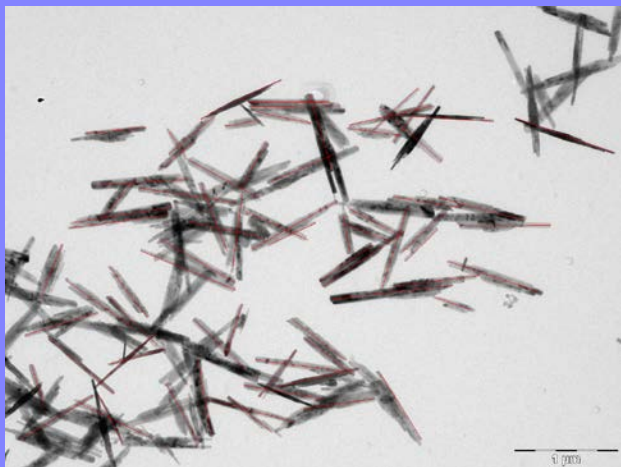
α -FeOOH: orthorhombic mesh $a=9.95\text{\AA}$ $b=3.01\text{\AA}$ $c=4.62\text{\AA}$

1 μ m

1 μ m

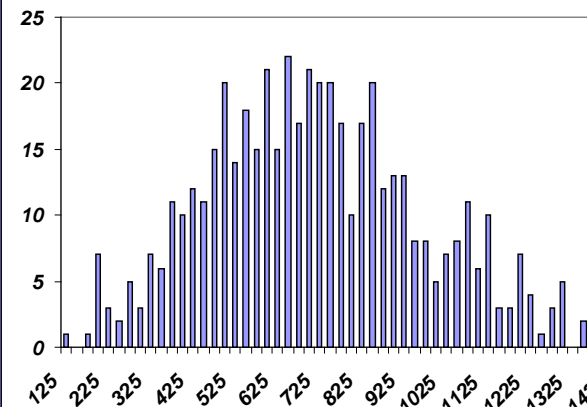
Goethite nanorods doped with Co^{2+}

Goethite doped at 1%Co

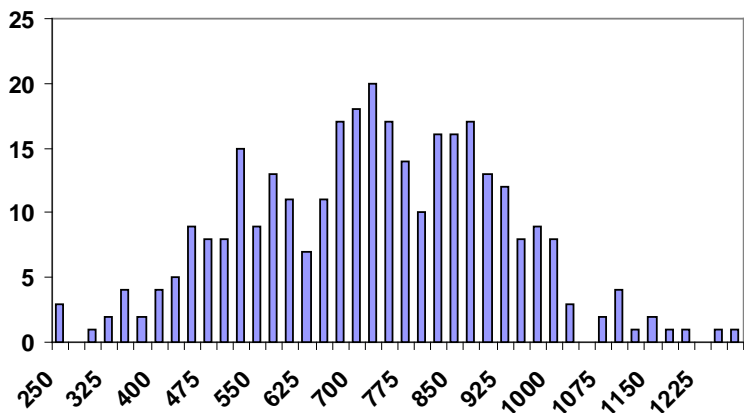


Hydrodynamic diameter = 284 nm
Mean length by TEM = 715 nm

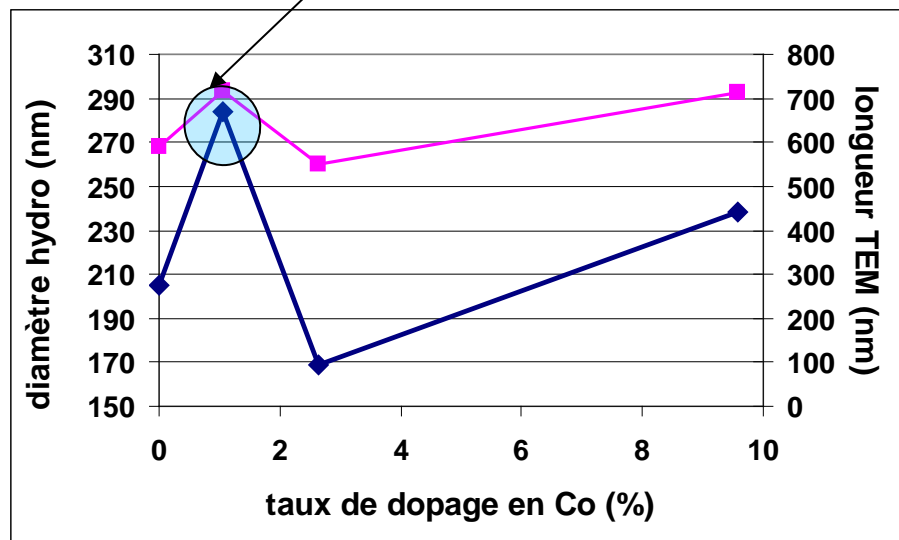
Goethite doped at 10%Co



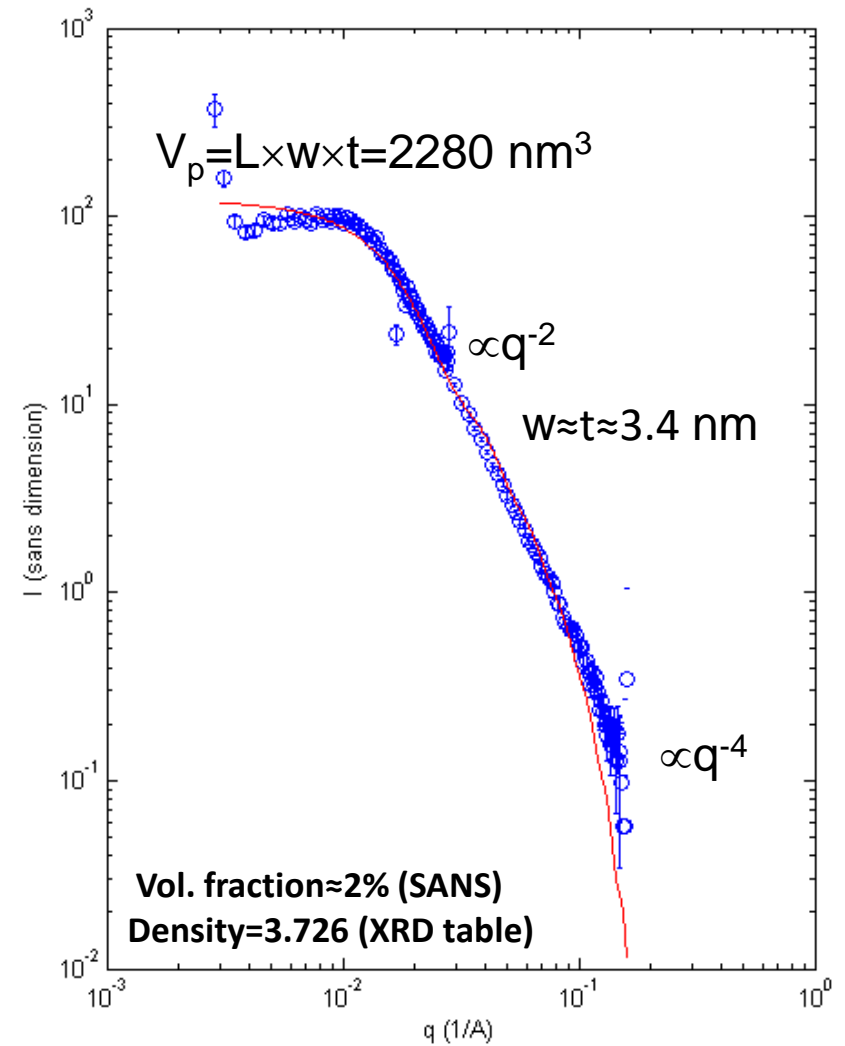
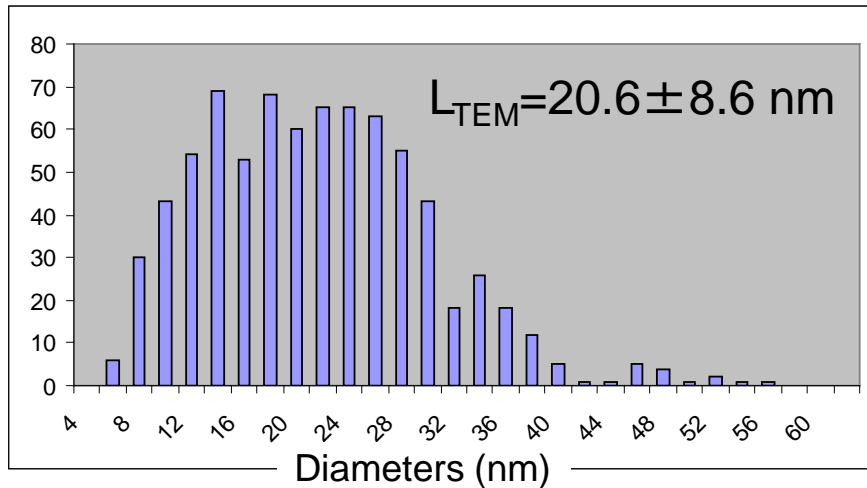
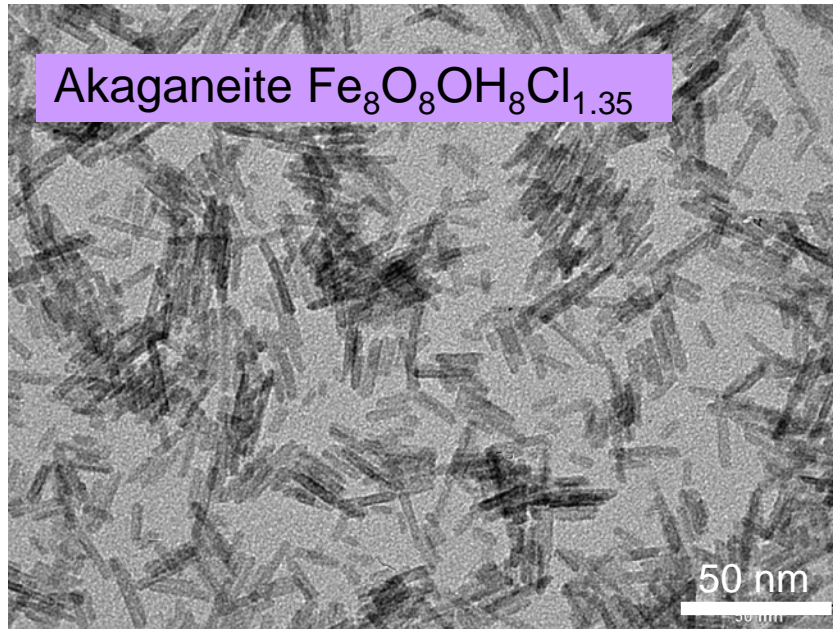
Large size associated with interesting magnetic properties (1Co1 sample)



Non monotonous effect of Co doping on rods' size:



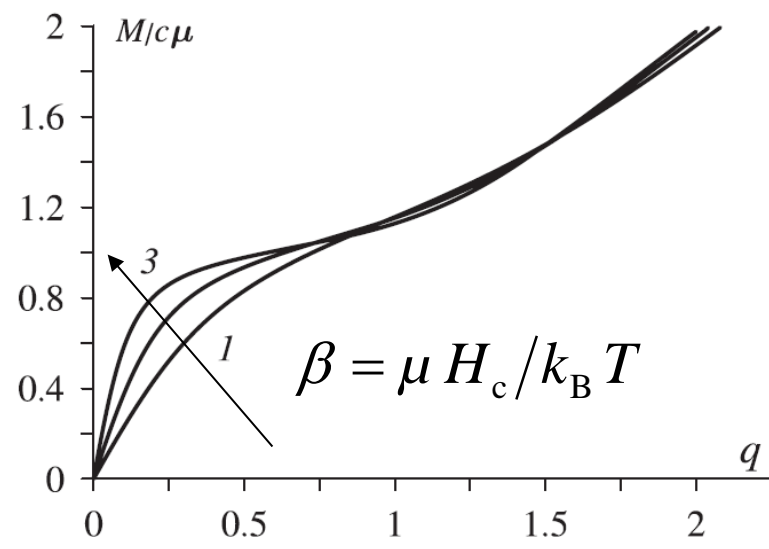
Antiferromagnetic nanorods of even smaller sizes



SANS on PAXY LLB-Saclay (oct. 2008)

Magneto-orientational behavior of a suspension of anti-ferromagnetic nanoparticles (NAF)

J. Phys.: Condens. Matter **20** (2008) 204120 Yu L Raikher, V. I. Stepanov (Perm, Russia) :

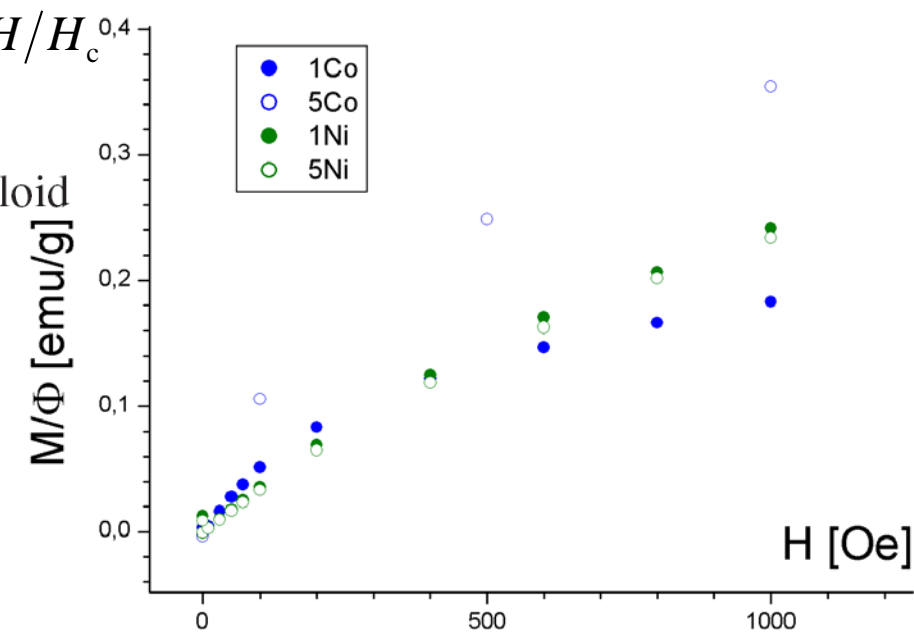


$$U = -\mu (\vec{e} \cdot \vec{H}) + \frac{1}{2} \chi_A V (\vec{e} \cdot \vec{H})^2$$

Figure 1. Reduced static magnetization of a NAF colloid

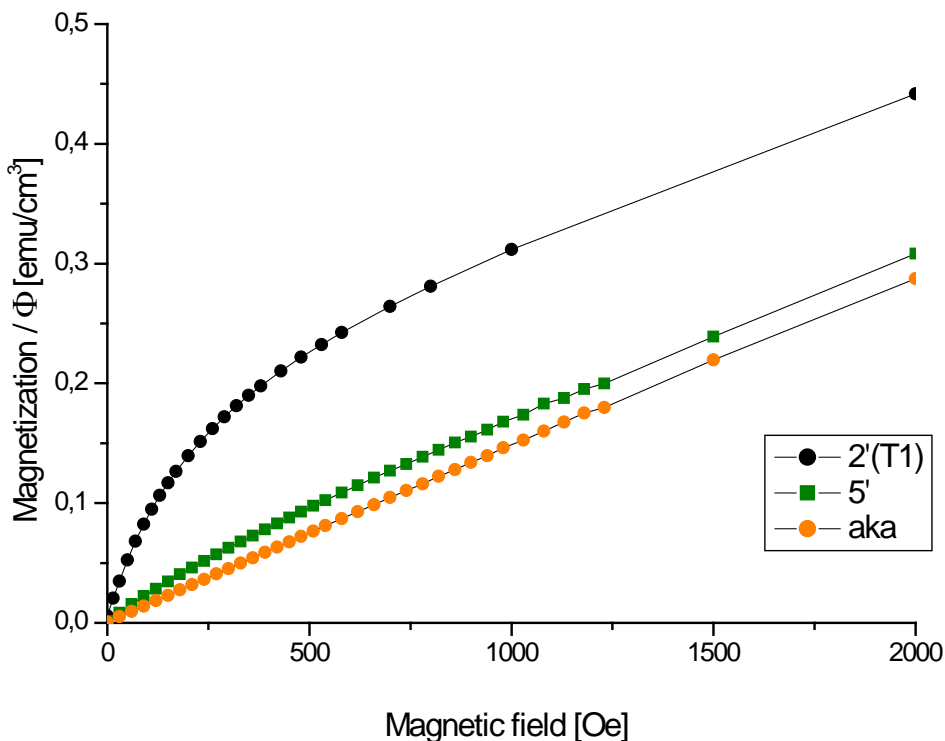
$$H_c = \mu / \chi_A V$$

$$\chi_A = \chi_{||} - \chi_{\perp}$$

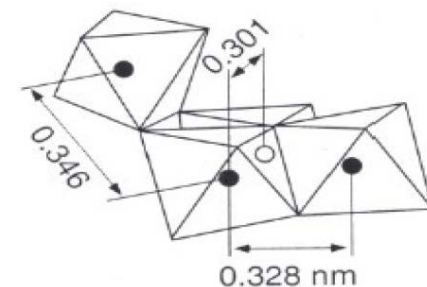


Magnetic behavior of antiferromagnetic nanorods

SQUID magnetometry at ambient temperature*

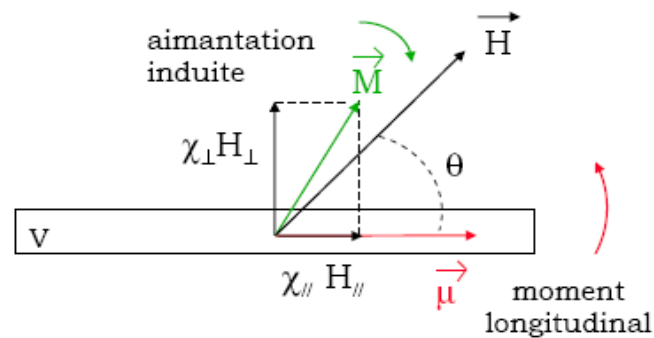


*measurement at INSP lab. (UPMC)



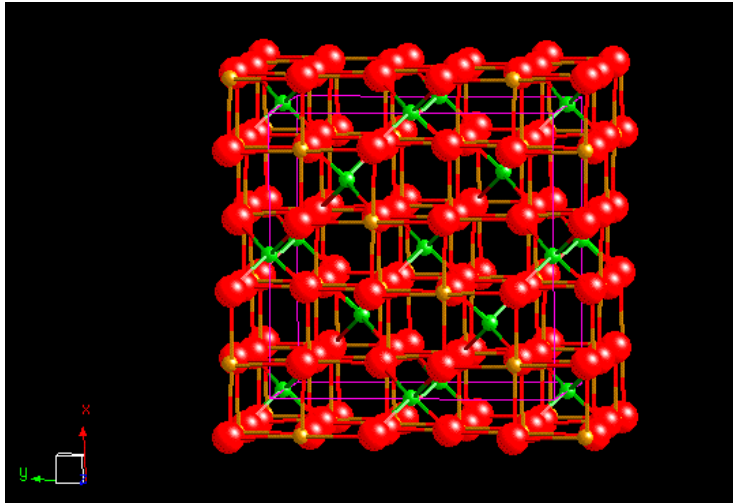
$$\mu_{\text{Fe+III}} = 5 \mu_B$$

$$\mu \approx 10000 \mu_B \approx (N_{\text{Fe}})_{\text{surf}}^{1/2} \mu_{\text{Fe}}$$

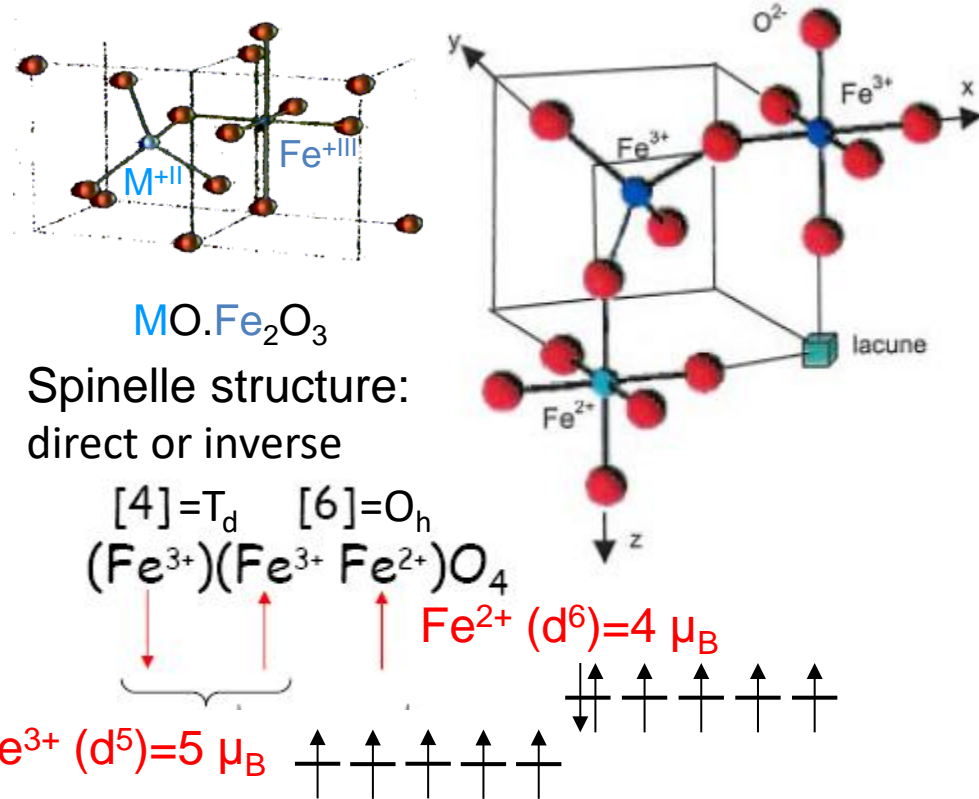
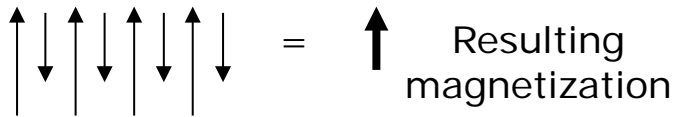


B. Lemaire, P. Davidson (LPS Orsay)

Magnetite: Crystalline Structure



Magnetite is **ferrimagnetic**



Exercise: 1/calculate specific volume ($cm^3 \cdot mol^{-1}$) and mesh size a

Data: one unit cell is cubic and contains 8 Fe_3O_4 molecules

Mass density $\rho = 5.18 \times 10^3 \text{ kg} \cdot m^{-3}$, Molar mass $M = 231.535 \text{ g} \cdot mol^{-1}$

1 Bohr magneton $\mu_B = 9.274 \times 10^{-24} \text{ A} \cdot m^2$

2/calculate the specific magnetization M_S of bulk Fe_3O_4 in $A \cdot m^{-1}$

Answers:

$v = 45 \text{ cm}^3 \cdot mol^{-1}$

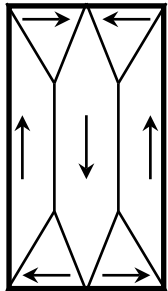
$a = 8.396 \text{ \AA}$

$M_S = 5 \times 10^5 \text{ A} \cdot m^{-1}$

Magnetic domains and Bloch boundaries (walls)

Macroscopic magnets (bulk materials) are multi-domains

Size of mono-domain: ~ 30-50 nm for iron oxides



Rosensweig 1965, Néel 1955, Kittel 1946, Elmore 1938

Curie-Weiss
domains



One ~ 10 nm nanoparticle is a magnetic single domain

Bloch walls

Exercise:

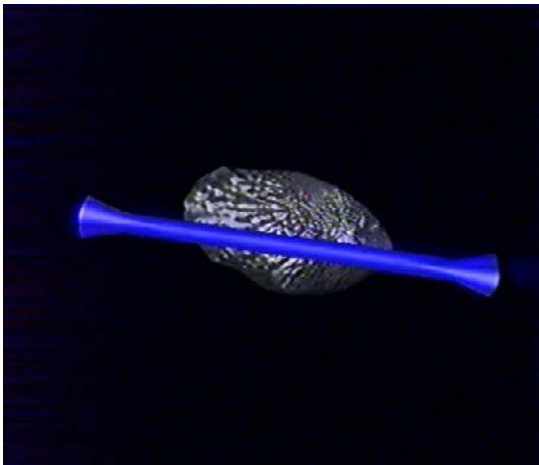
- 1: calculate magnetic moment (in nb of μ_B /MNP) for diameters: $d=4 / 8 / 16$ nm
- 2: calculate total nb of Fe ions per MNP for all d 's
- 3: calculate nb of Fe ions on surface per MNP for all d 's

Data:

- 1 Bohr magneton $\mu_B=9.274 \times 10^{-24}$ A·m²
- For nano-crystalline Fe_3O_4 , $M_S = 4 \times 10^5$ A·m⁻¹

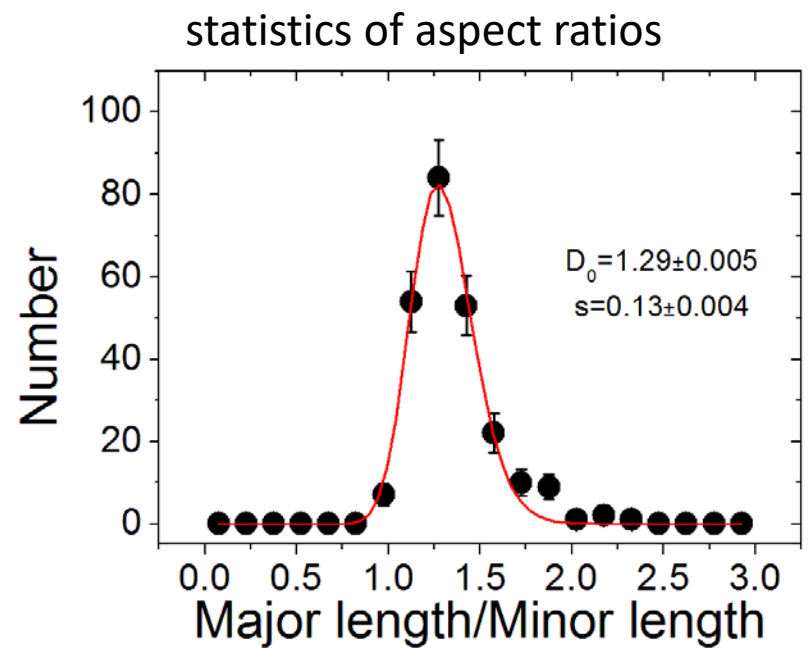
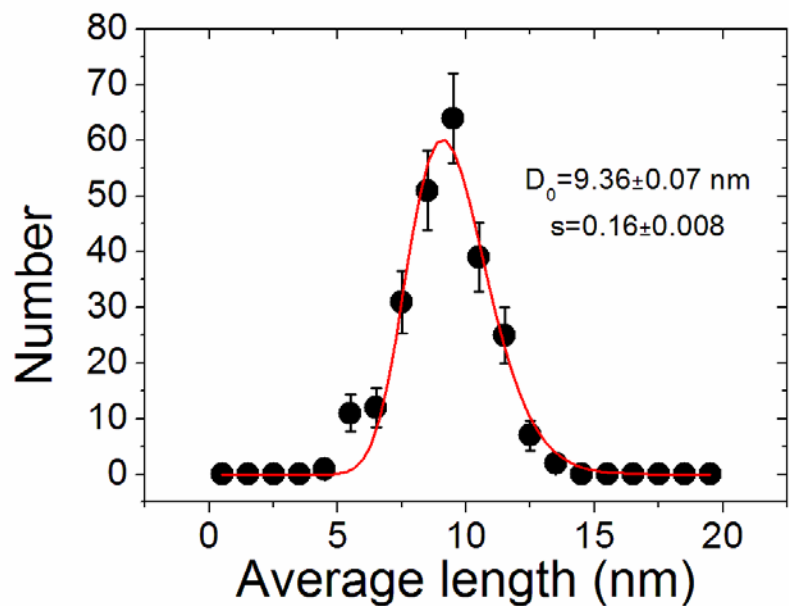
Answer:

- 1: 1500 / 11000 / 90000 2: 1400 / 10700 / 87000
- 3: 290 (20%) / 1100 (10%) / 4500 (5%)



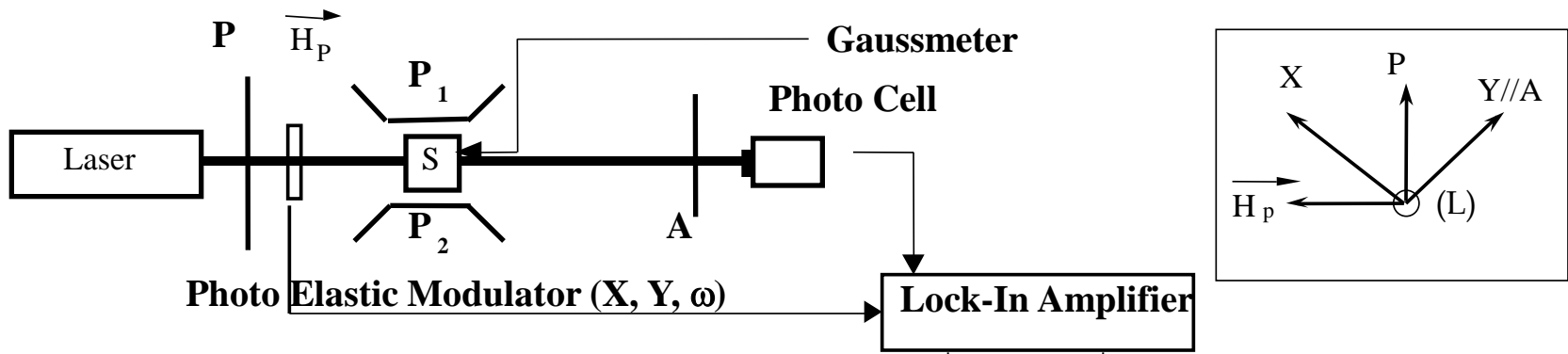
Shape anisotropy contribution to birefringence

"Rock-like" particles: S1C fraction, coated with PAA_{2k}

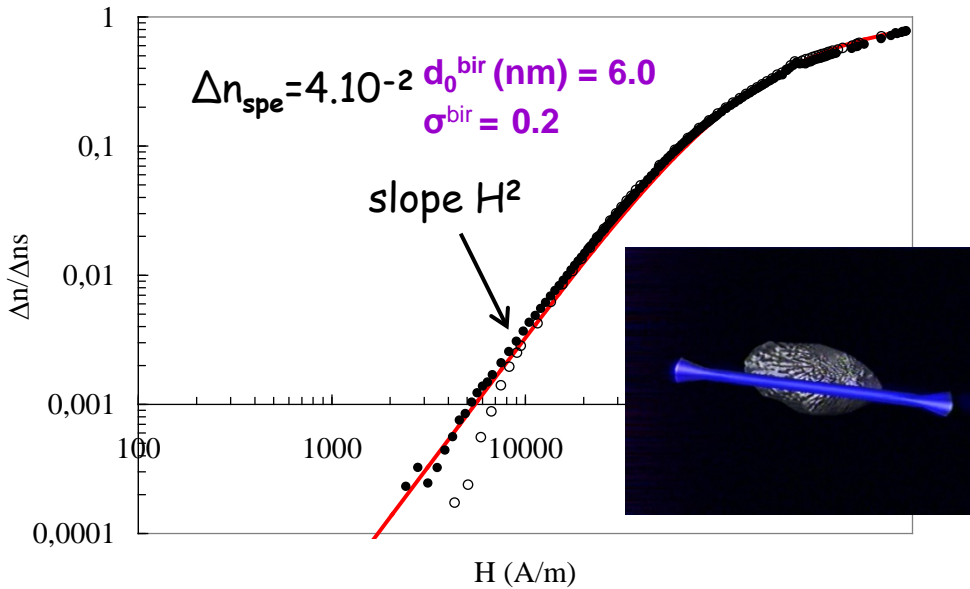


50 nm

Birefringence measurement under H field



E. Hasmonay et al. EPJB 1998



$I_1(\omega) \propto |\sin(\varphi)|$ $I_2(2\omega) \propto (t_{\parallel} - t_{\perp})$ dichroism

$\varphi = 2\pi \Delta n e / \lambda$ $\Delta n = (n_{\parallel} - n_{\perp})$ birefringence

Plateau: $\Delta n_{sat} = \Delta n_{spe} \Phi$

Ferrofluid sample (maghemite $\gamma\text{-Fe}_2\text{O}_3$)

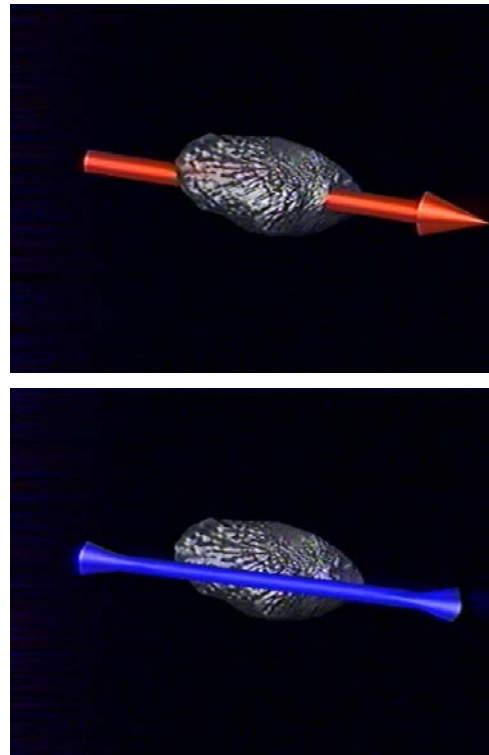
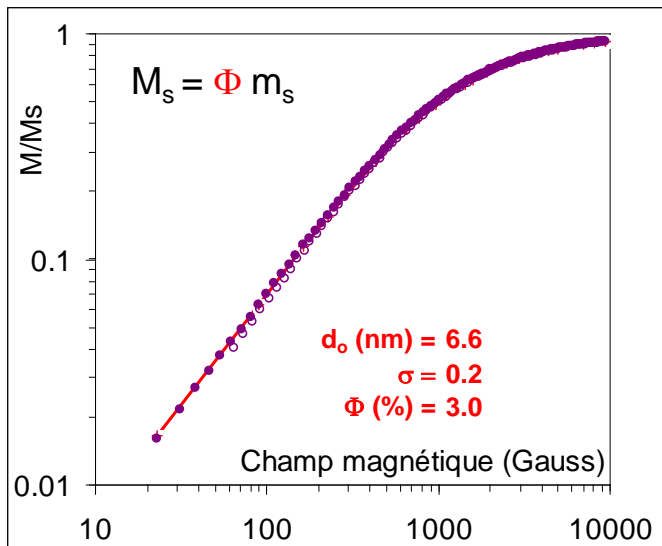
Starting materials : "True" ferrofluid

Ferrofluid = colloidal suspension of magnetic nanoparticles
 which remains stable whatever the intensity of applied magnetic field

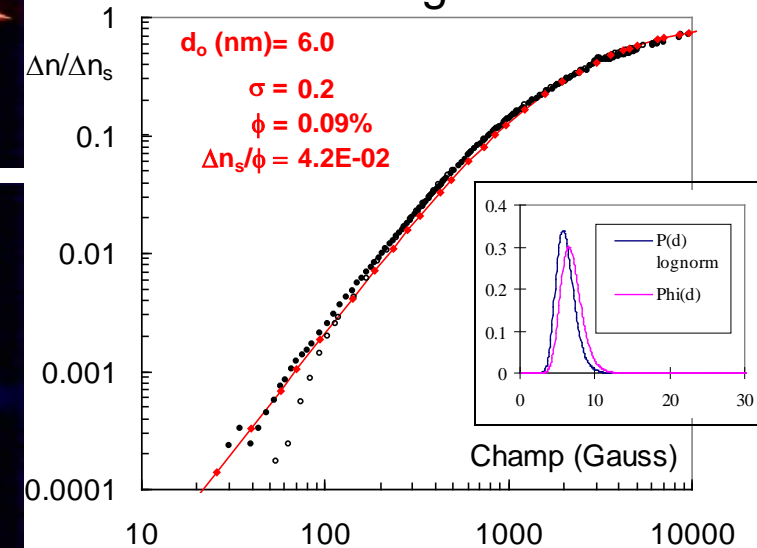
- no attraction of nanoparticles under B field gradient nor chaining by dipolar interaction
- but progressive orientation of dipoles according to Langevin's laws:

Magnetization

$m_s = 3,1 \cdot 10^5 \text{ A/m (SI)}$ $m_s / 4\pi = 300 \text{ G (CGS)}$

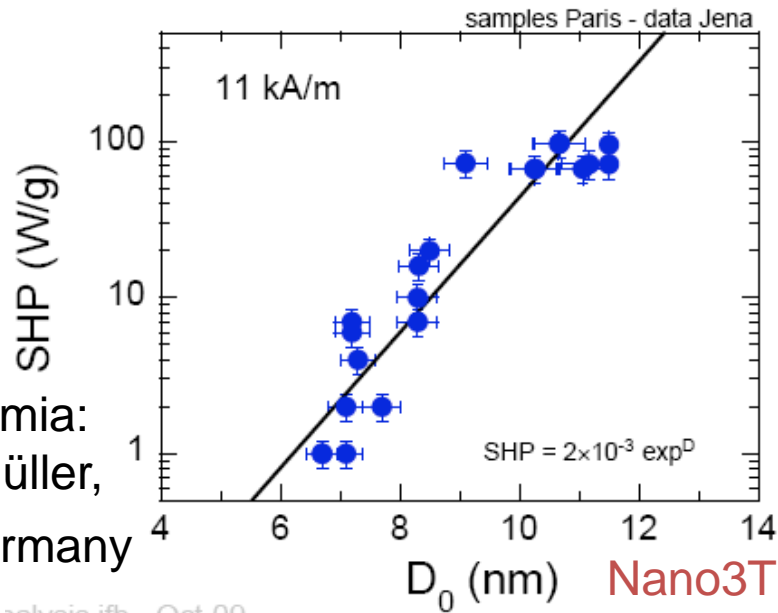


Birefringence

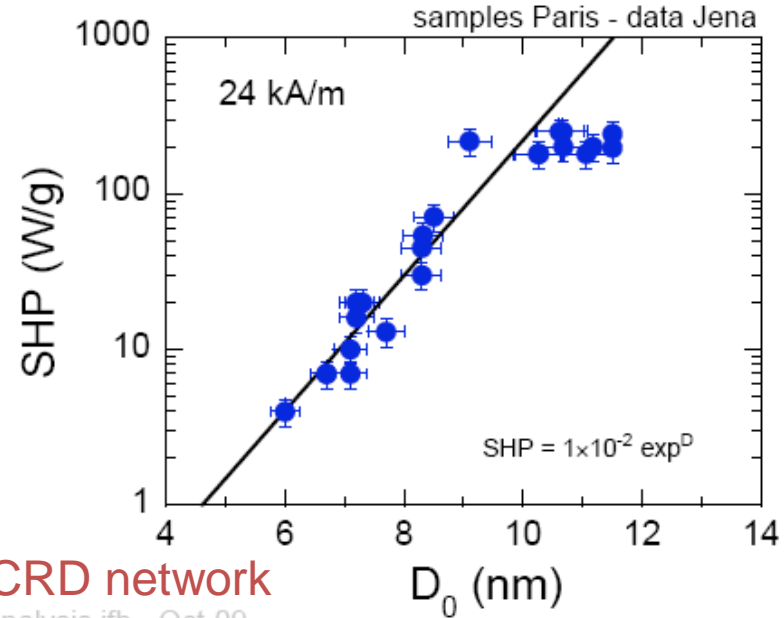


Improved properties of the larger magnetic NPs

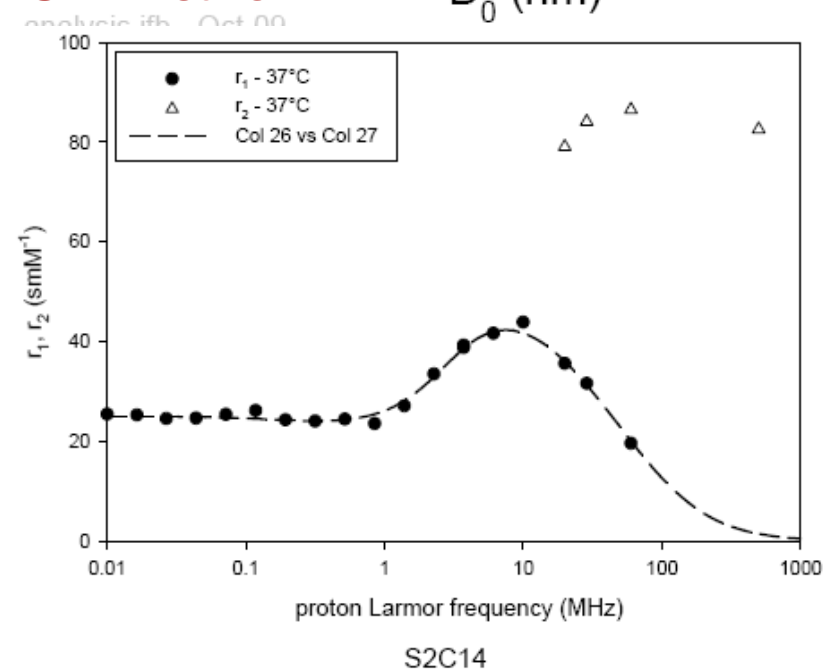
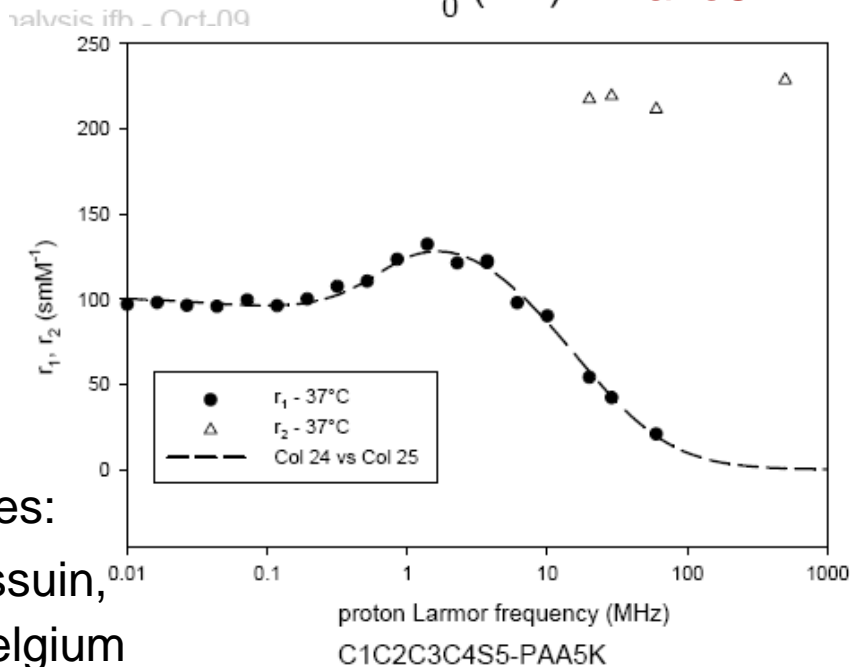
Hypethermia:
Robert Müller,
Jena, Germany



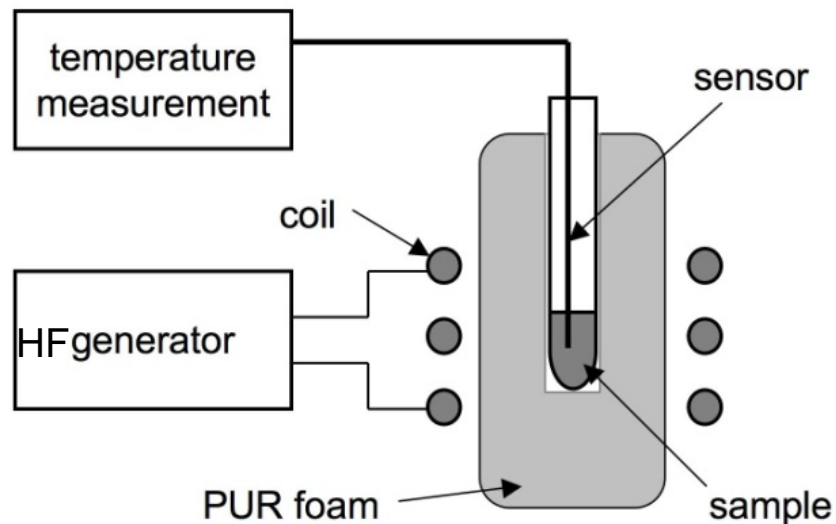
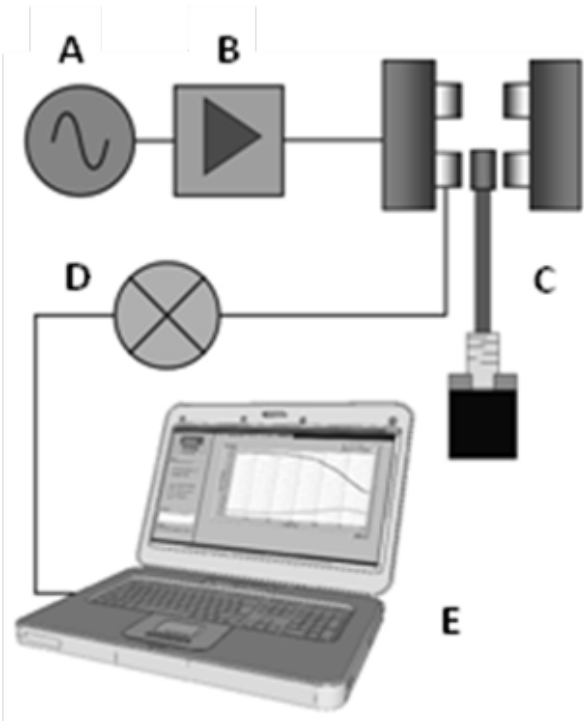
Nano3T 7th PCRD network



Relaxivities:
Yves Gossuin,
Mons, Belgium



Astalan, A.; Ahrentorp, F.; Jonasson, C.; Blomgren, J.; Yan, M.; Courtois, J.; Berret, J.-F.; Fresnais, J.; Sandre, O.; Müller, R.; Dutz, S.; Johansson, C., AIP Conf. Proc. Series 2010

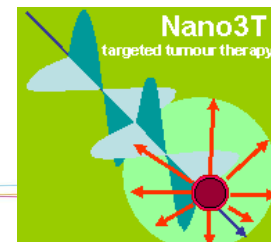


Hyperthermia set-up built by
R. Müller, Jena (Germany)

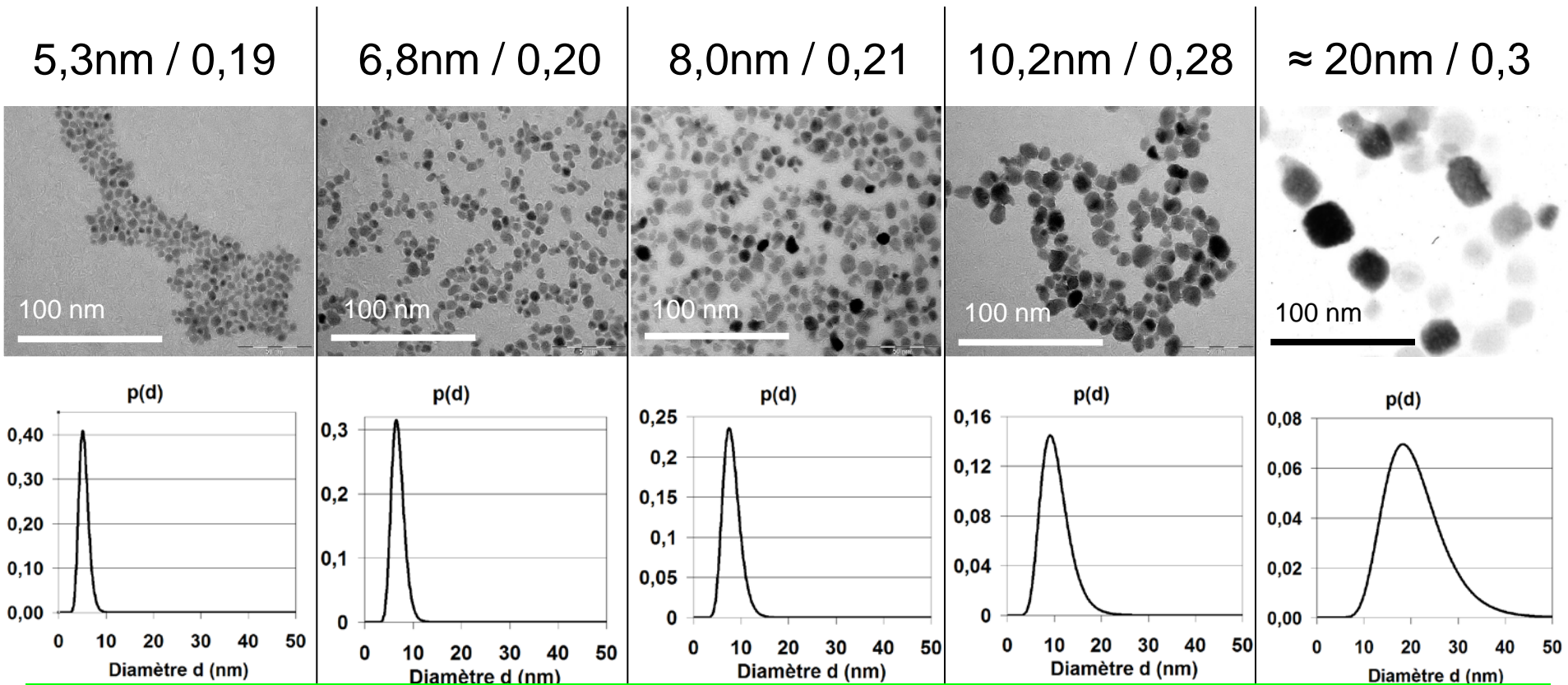
High frequency AC susceptometer built at
the IMEGO company (Sweden)

AC signal source (A), current amplifier (B),
coil system and mechanics (C), lock-in
amplifier (D) and user interface software (E)

$$SHP = \pi \mu_0 \chi'' f_{RF} H_0^2 V_S$$



G. Glöckl, R. Hergt, J. Phys.: Condens. Matter 18 (2006) S2935–S2949: resonance effect



SHP (at $f = 700$ kHz, $H_0 = 24.8$ kAm⁻¹) =

4 W/g

14 W/g

37 W/g

275 W/g

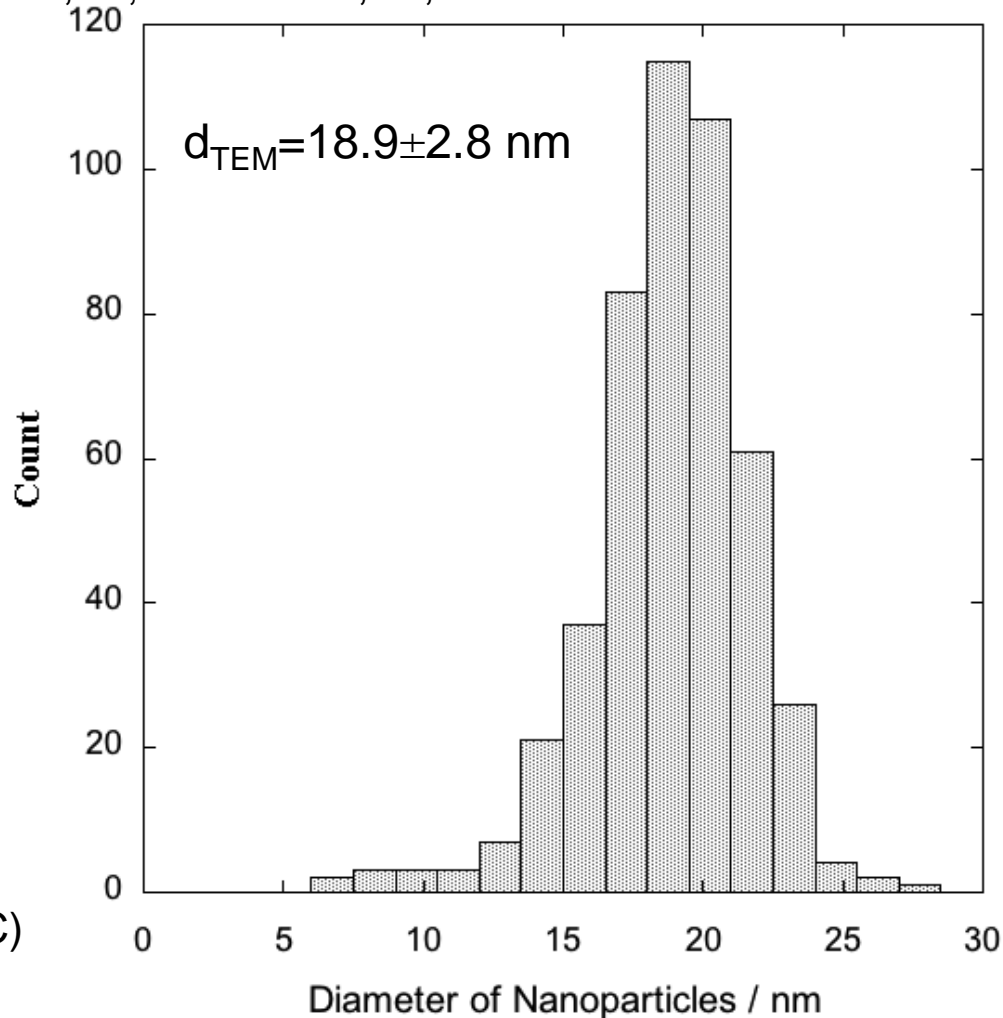
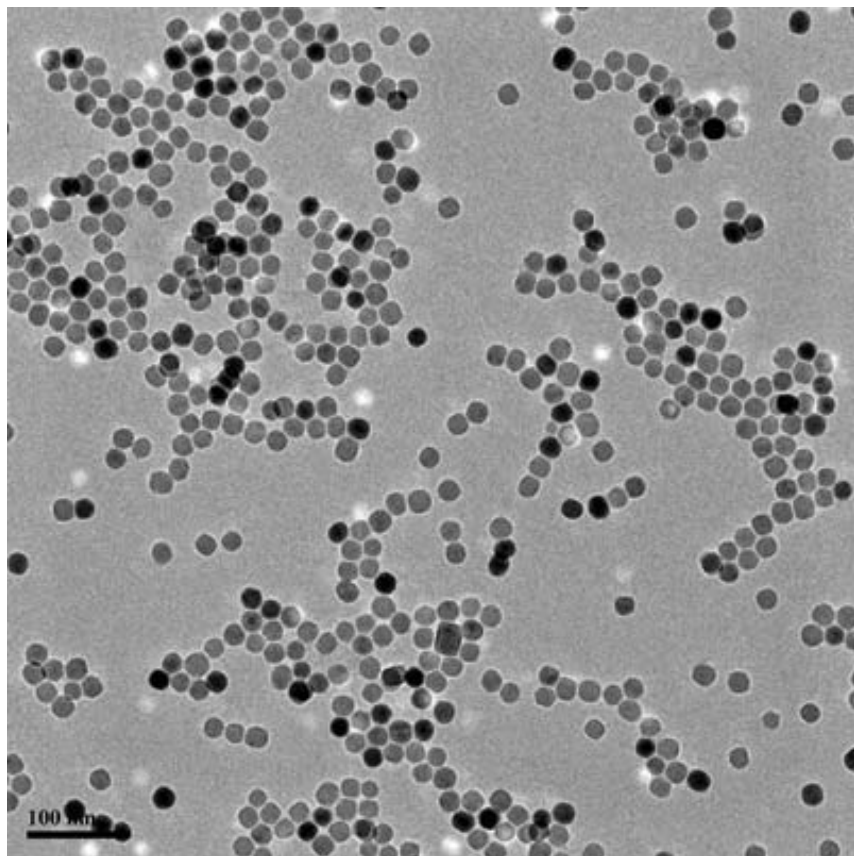
1650 W/g

J-P. Fortin, C. Wilhelm, J. Servais, C. Ménager, J-C. Bacri, F. Gazeau, J. Am. Chem. Soc. 129 2628 (2007)

M. Lévy, C. Wilhelm, J-M. Siaugue, O. Horner, J-C. Bacri, F. Gazeau, J. Phys. Cond. Mat. 20 204133 (2008)

Calibration sample: monodisperse Fe_3O_4 nano-spheres

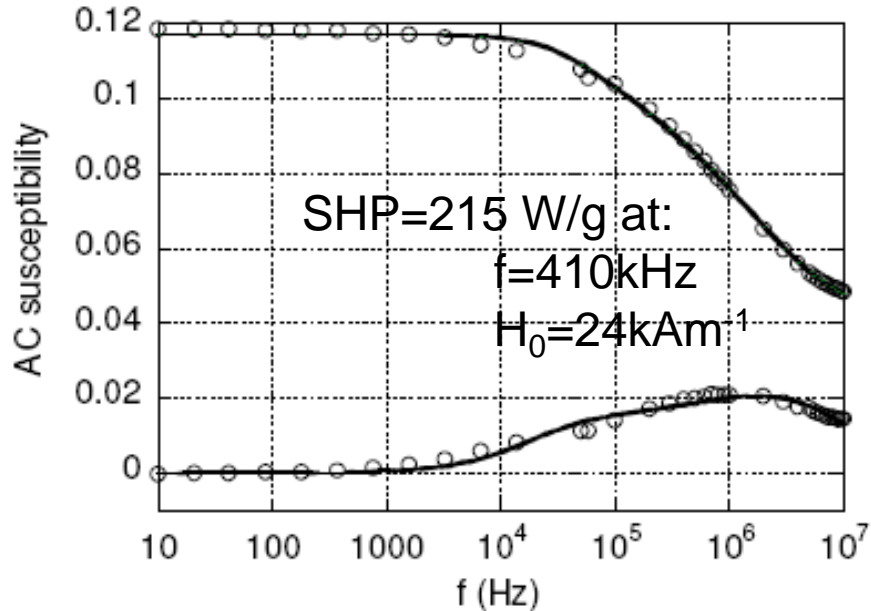
Astalan, A.; Ahrentorp, F.; Jonasson, C.; Blomgren, J.; Yan, M.; Courtois, J.; Berret, J.-F.; Fresnais, J.; Sandre, O.; Müller, R.; Dutz, S.; Johansson, C., AIP Conf. Proc. Series 2010



Fe-oleate decomposition in n-hexane (4h 70°C)
Q. Bin, O. T. Mefford (Clemson Univ, USA)
according to Park et al, Angew. Ch. 2005)

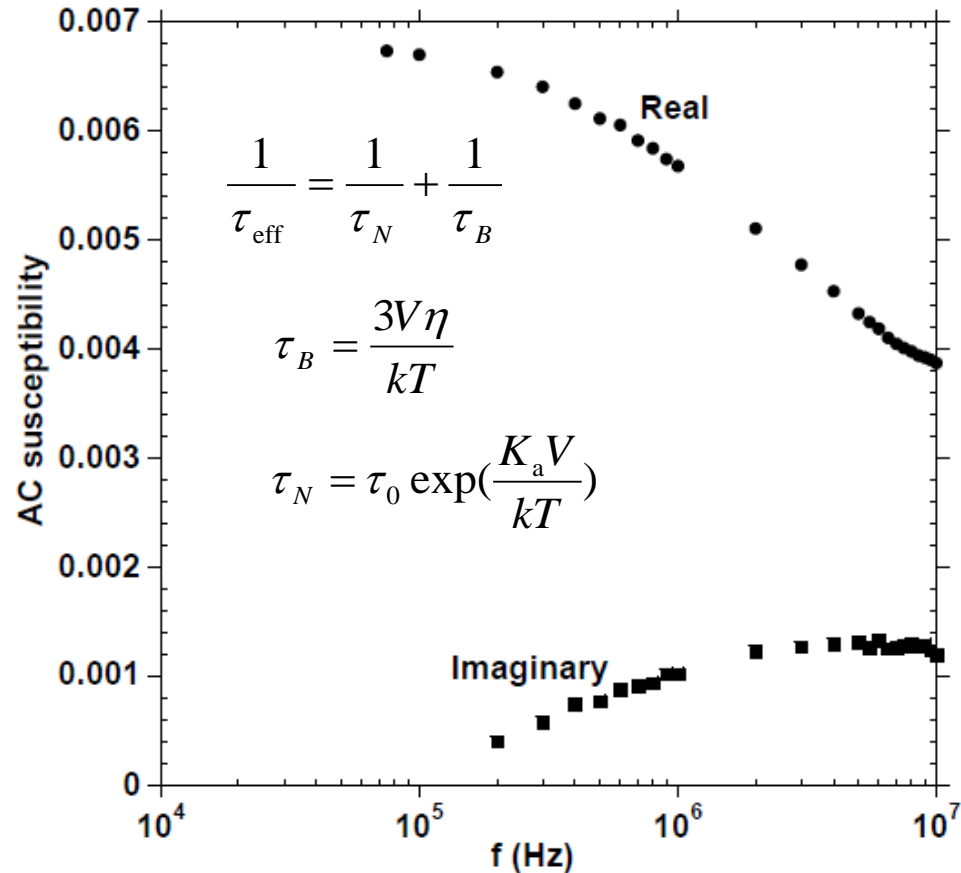
Role of MNP shape on the magnetic anisotropy K_a

Astalan, A.; Ahrentorp, F.; Jonasson, C.; Blomgren, J.; Yan, M.; Courtois, J.; Berret, J.-F.; Fresnais, J.; Sandre, O.; Müller, R.; Dutz, S.; Johansson, C., AIP Conf. Proc. Series 2010



rock-like particles $\text{\O}16\text{nm}$:
large χ'' , Néel's band $\sim 2\text{MHz}$

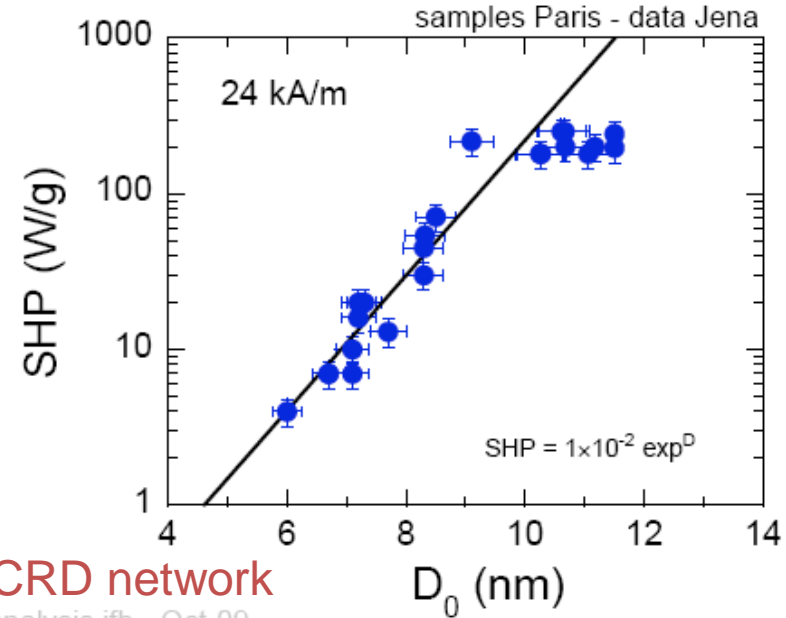
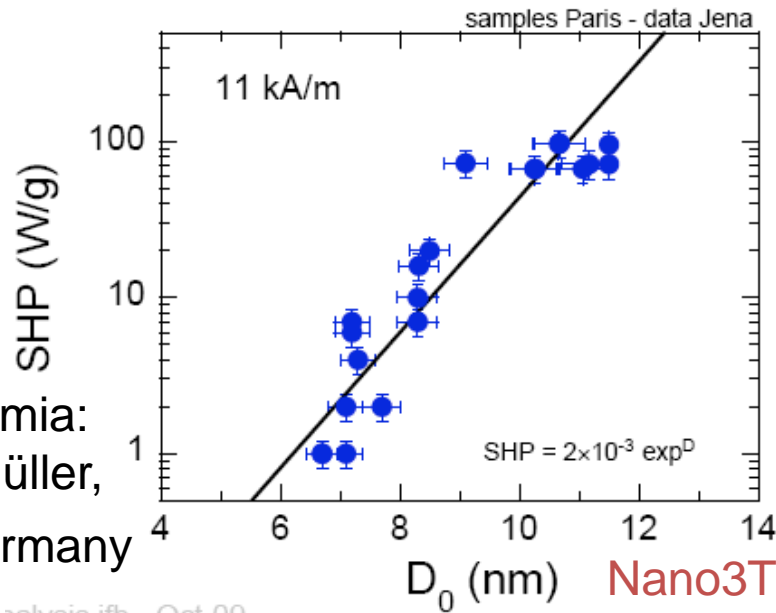
$$\chi(\omega) = C \int \frac{r_c^6}{(1 + j\omega\tau_{\text{eff}}(r_H))} f(r_H) dr_H + \chi_{\text{high}}$$



spheres $\text{\O}19\text{nm}$: weak χ'' , Néel's band $\sim 5\text{MHz}$

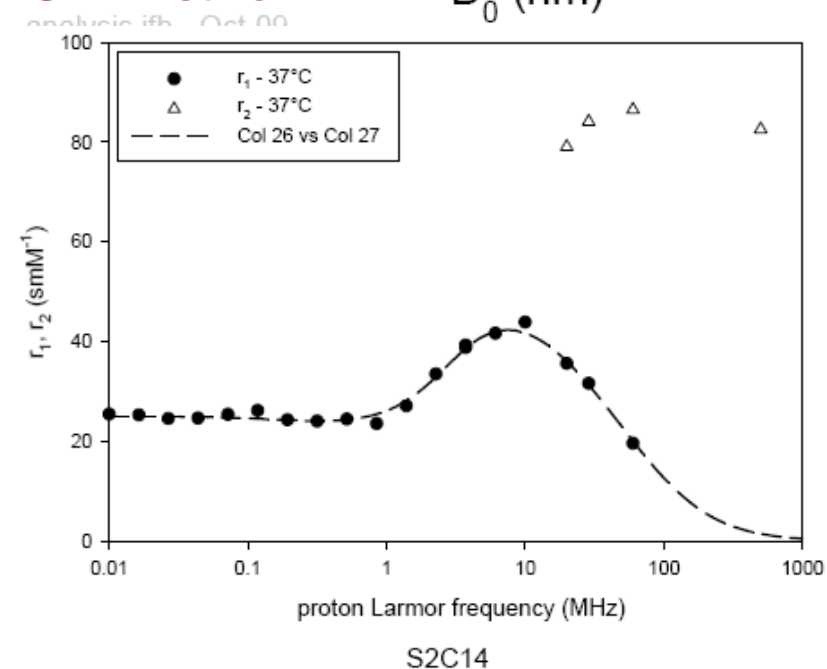
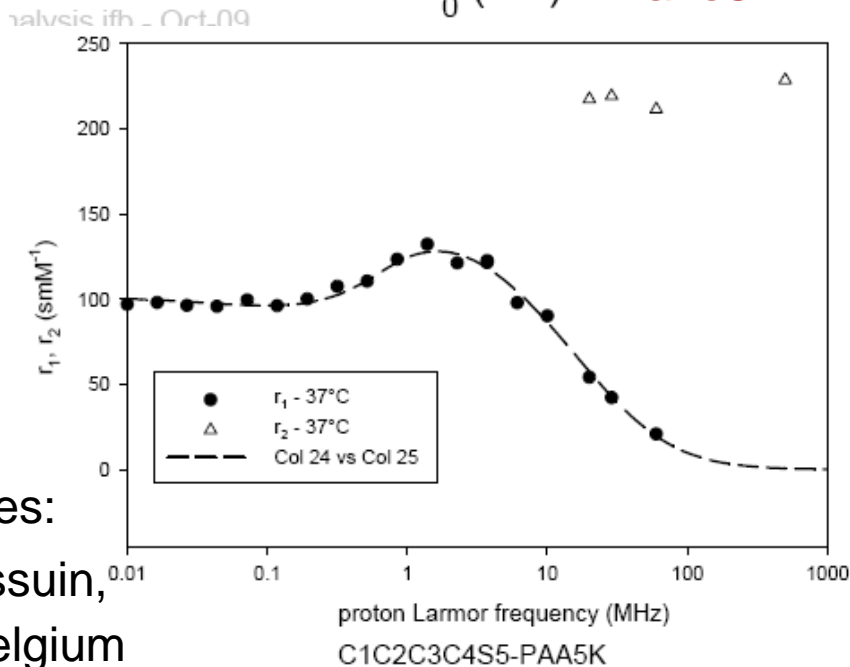
Improved properties of the larger magnetic NPs

Hypethermia:
Robert Müller,
Jena, Germany



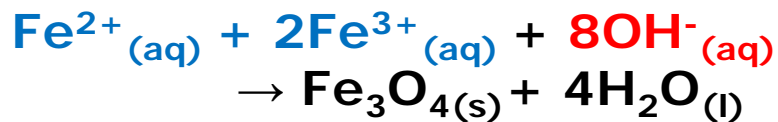
Nano3T 7th PCRD network

Relaxivities:
Yves Gossuin,
Mons, Belgium

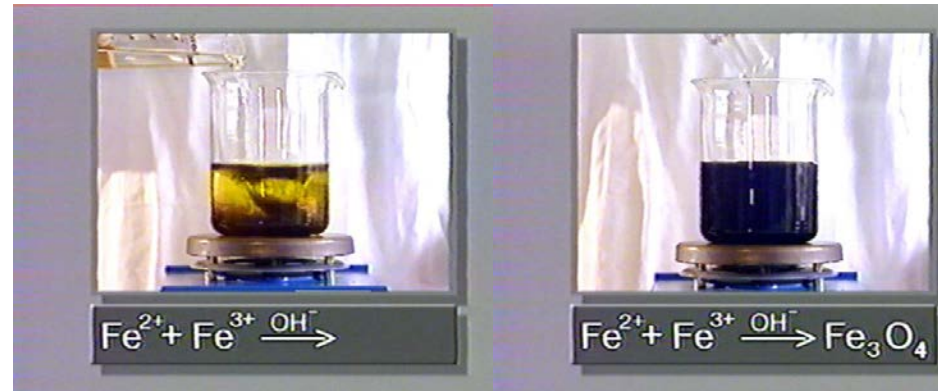


Ionic Ferrofluids: the coprecipitation synthesis

- Massart's process:
Alkaline coprecipitation of FeCl_2 & FeCl_3
→ magnetite Fe_3O_4 nanoparticles

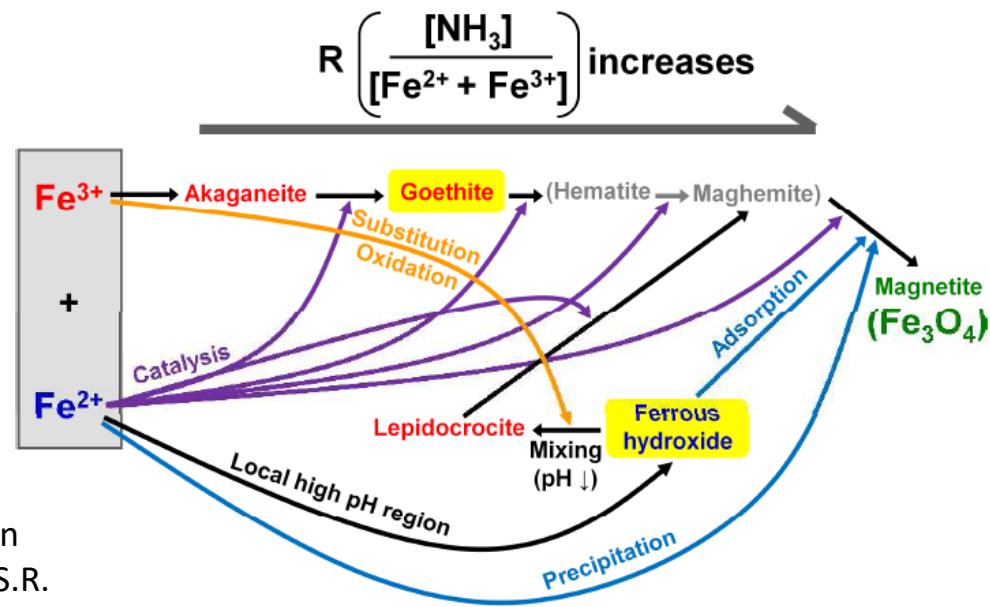


R. Massart *IEEE Trans. Magn.* **17** 1247 (1981)



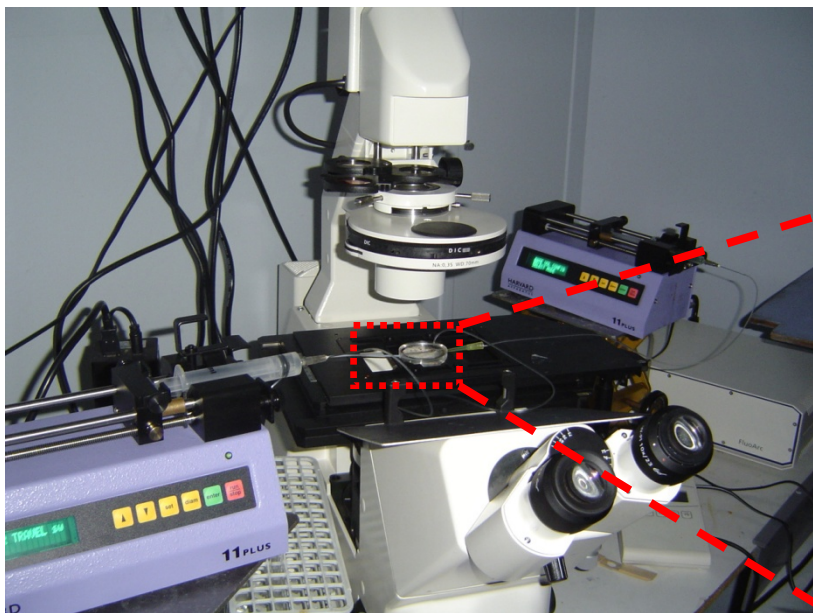
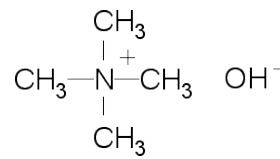
- Oxidation by $\text{Fe}(\text{NO}_3)_3$
→ maghemite $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles
in acidic medium (HNO_3): stabilized by
electrostatic surface charges ($\text{PZC} \approx 7$)

A. Abou-Hassan, O. Sandre, and V. Cabuil, *Chapter 9: Microfluidics for the synthesis of iron oxide nanoparticles, in Microfluidic Devices in Nanotechnology: Applications*, C.S.S.R. Kumar, Editor. **2010**, John Wiley & Sons, Inc: Hoboken, NJ, USA. p. 323-360

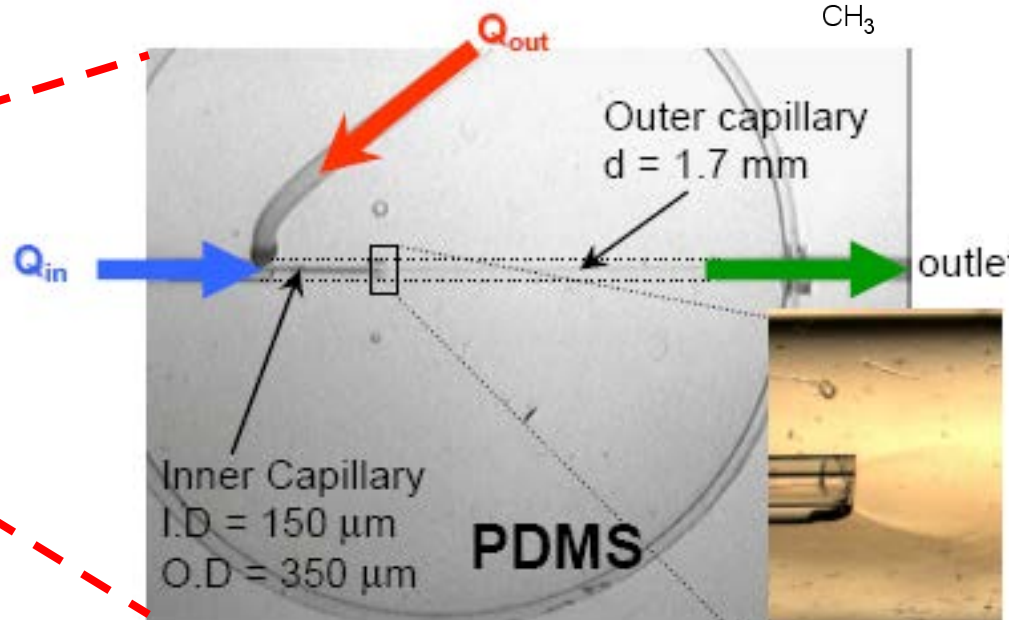


T. Ahm et al. *J. Phys. Chem.* (2012) pre-print

Microfluidics as a tool to get an insight of the kinetics of the coprecipitation reaction

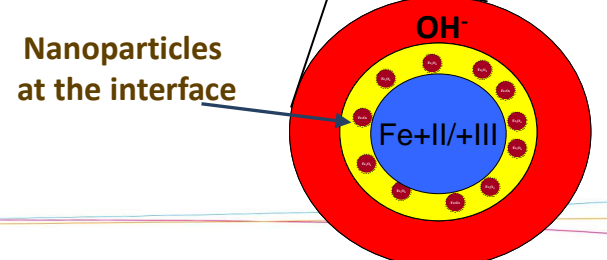
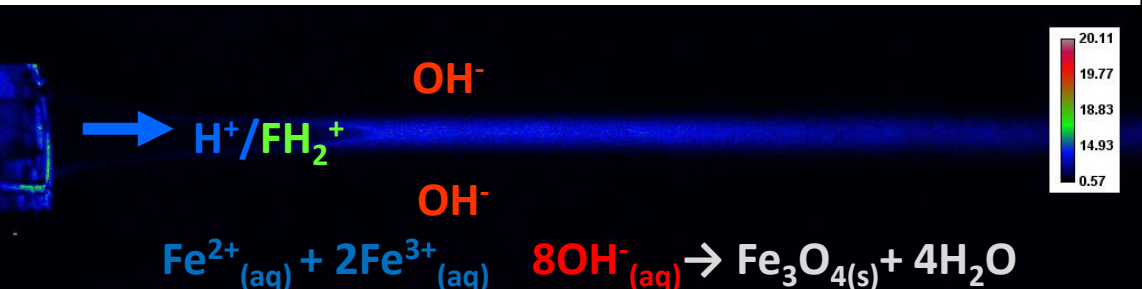


Answer to clogging issue: 3D geometry and non flocculating counterion of base TMA⁺



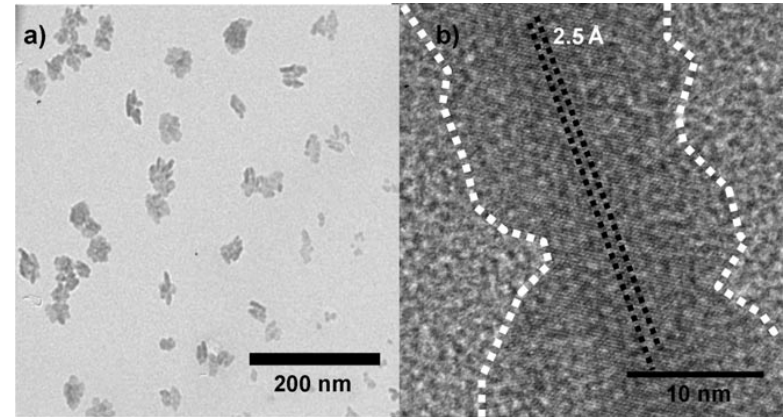
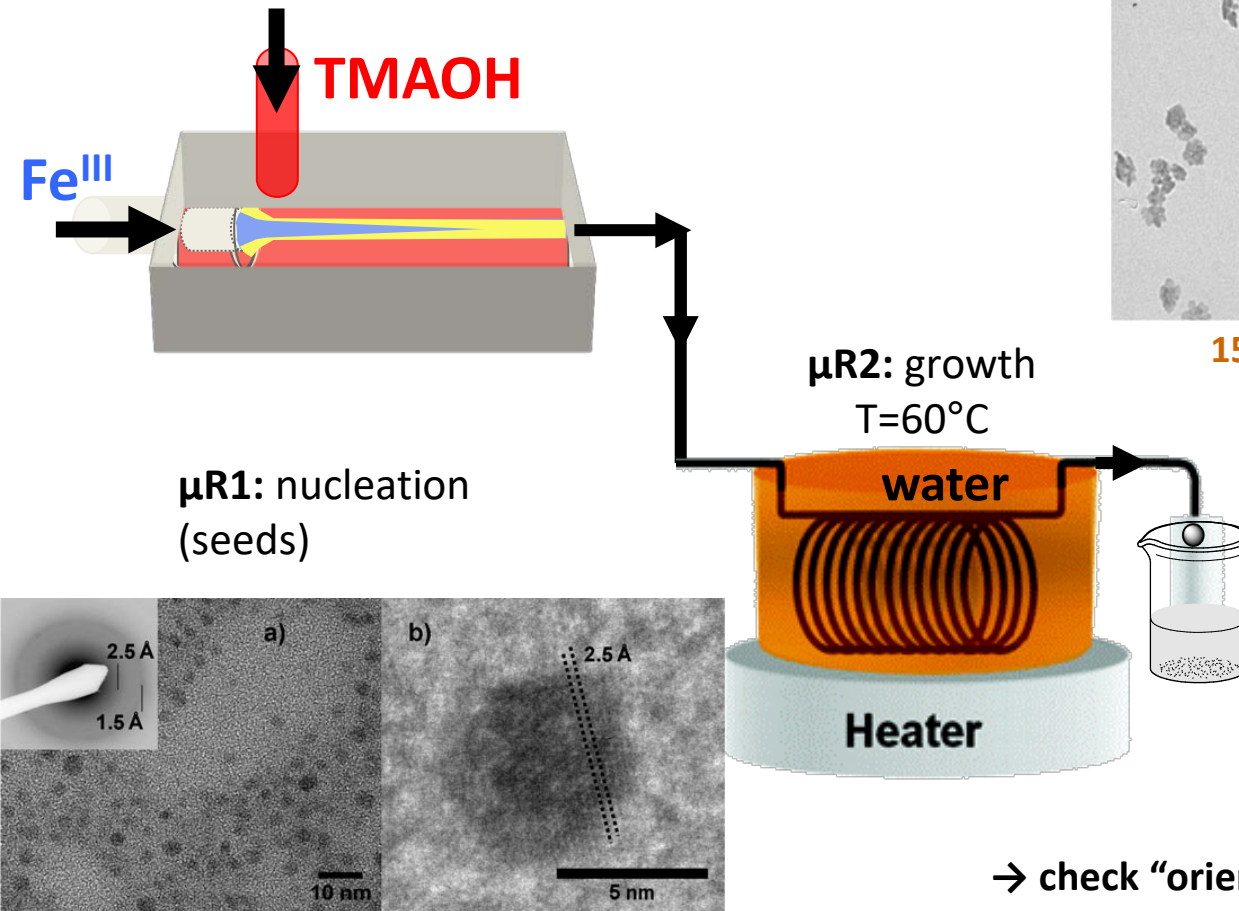
PhD thesis Ali Abou Hassan (2 oct 2009)

A. Abou Hassan, O. Sandre, V. Cabuil, P. Tabeling, *Chem. Commun.* 2008, 1783



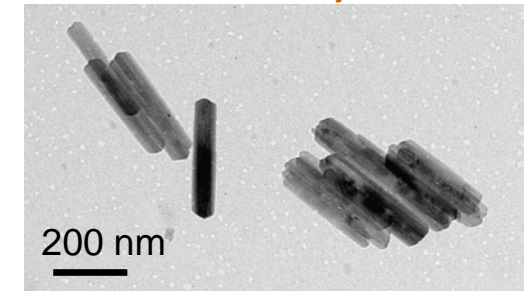
Microfluidics as a tool to get an insight of the mechanism of goethite formation

Two micro-reactors in-line



15 min / 60°C: Goethite nanorods
L=30±17 nm and w=7±4 nm

Final state as in macro synthesis



→ check “oriented aggregation” mechanism

J. F. Banfield et al. *Science* 2000, 289, 751

“2-lines ferrihydrite” nanodots $\varnothing = 4 \pm 1$ nm

A. Abou-Hassan, O. Sandre, S. Neveu, V. Cabuil, *Angew. Ch.* **48** 1-5 (2009)

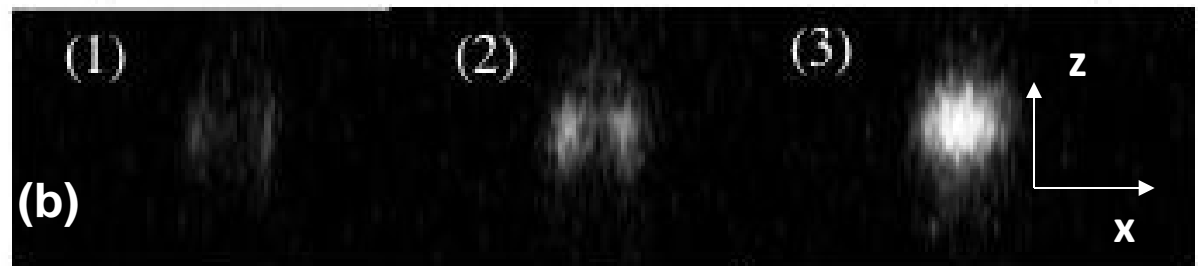
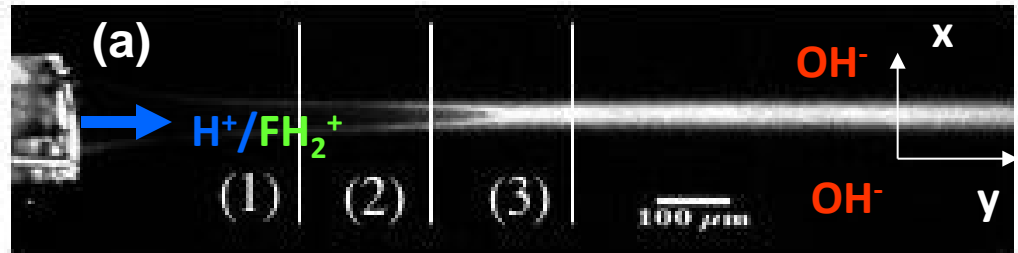
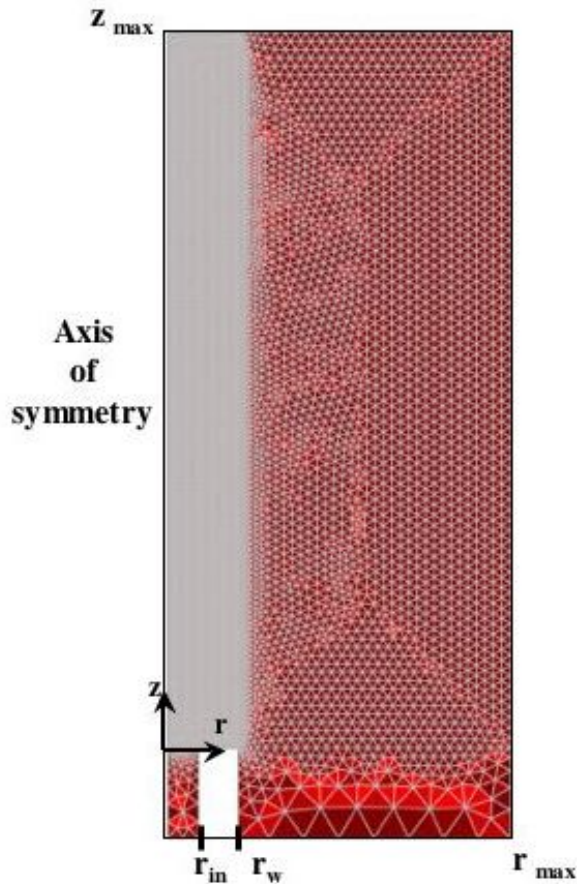
Microfluidics as a tool to get an insight of the mechanism of goethite formation

▪ FEM lab simulations

$$\frac{\partial C_i}{\partial t} + \text{div}(C_i \mathbf{u} + \mathbf{j}_i) = \sigma_i$$

$$\mathbf{j}_i = -D_i \text{grad} C_i + \frac{D_i}{k_B T} C_i Z_i e \mathbf{E} \quad (\text{Nernst-Planck})$$

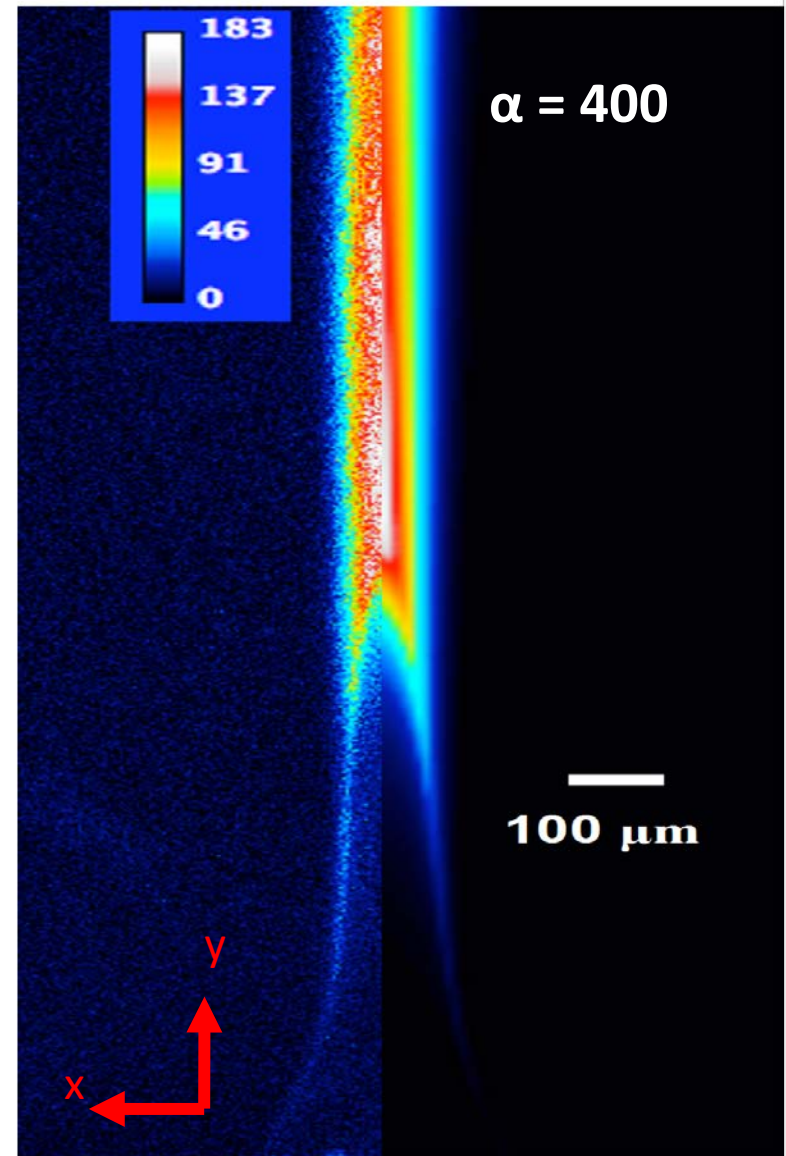
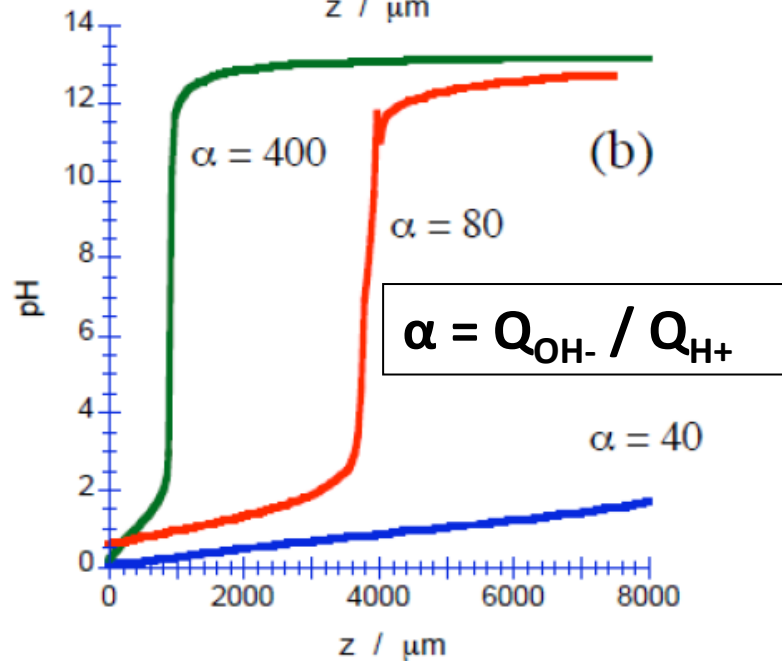
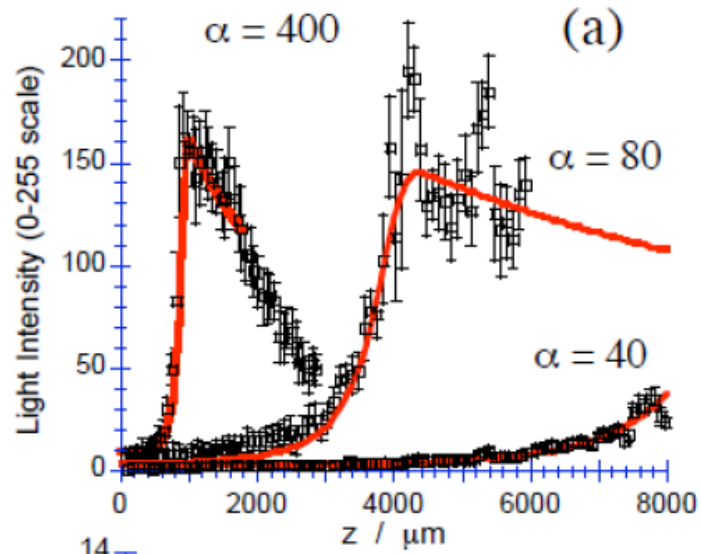
▪ Confocal Laser Scanning Microscopy: Fluorescein as pH reporter dye



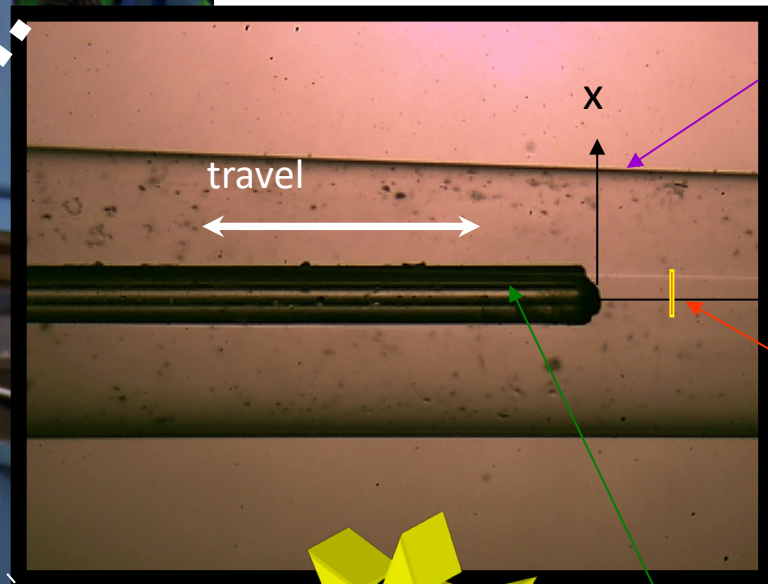
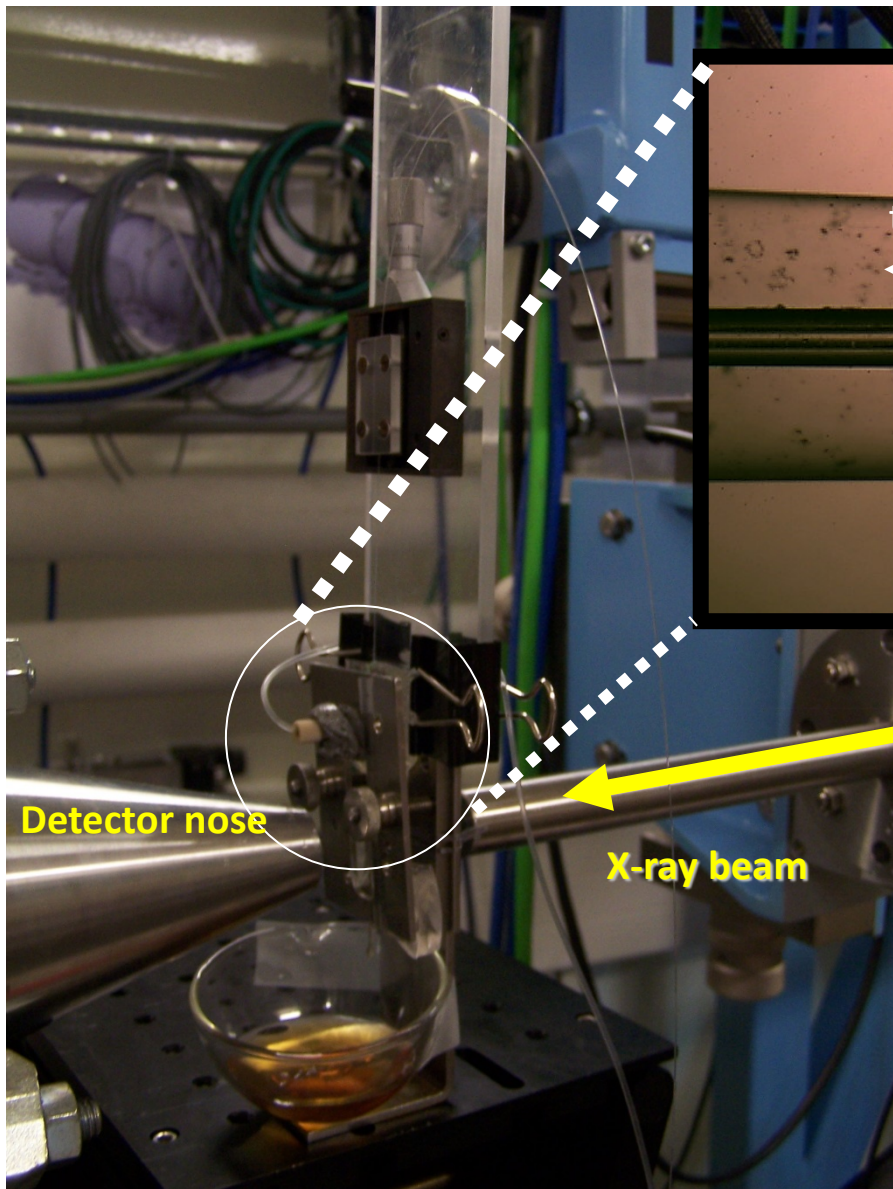
$$\text{pH} = f(\alpha) \text{ with } \alpha = Q_{\text{OH}^-} / Q_{\text{H}^+}$$

A. Abou-Hassan, J-F. Duf r che, O. Sandre, G. M riguet, O. Bernard, V. Cabuil, *J. Chem. Phys. C* 2009

Microfluidics as a tool to get an insight of the mechanism of goethite formation

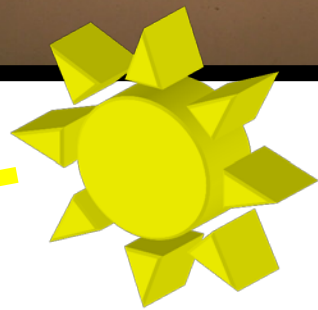


Detection of first seeds using SAXS in microfluidics



Lindemann
glass capillary
 $\varnothing = 1,6 \text{ mm}$
(wall thickness
 $= 10 \mu\text{m}$)

beam $300 \times 100 \mu\text{m}$
cross-section at fixed
position



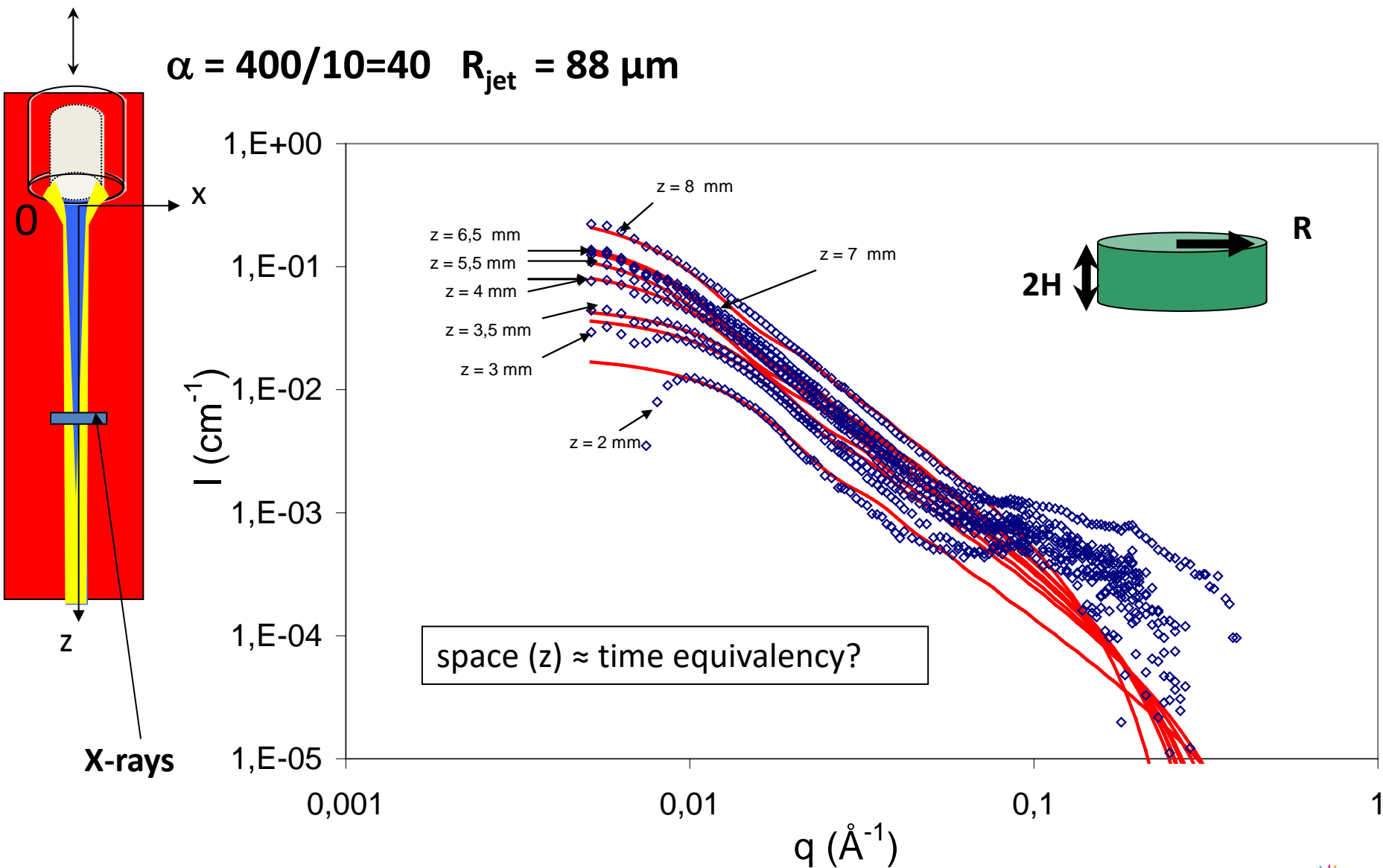
Internal capillary
 $\varnothing_{\text{int}} = 100 \mu\text{m}$
 $\varnothing_{\text{ext}} = 350 \mu\text{m}$

SAXS measurements on SWING line at
SOLEIL synchrotron (July 2009)

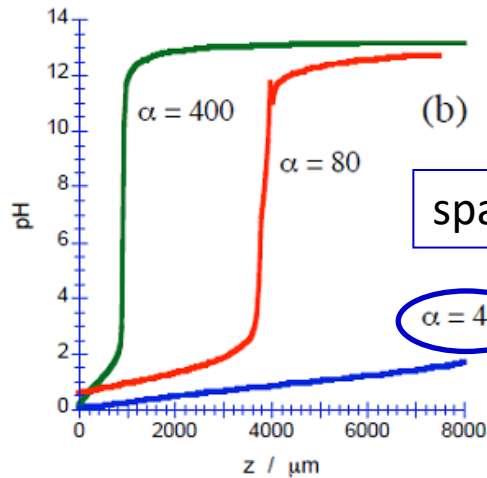


Abou Hassan, O. Sandre,
V. Dupuis, Olivier Spalla

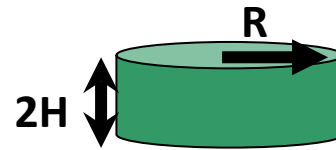
Preliminary SAXS results: intensity curves along z



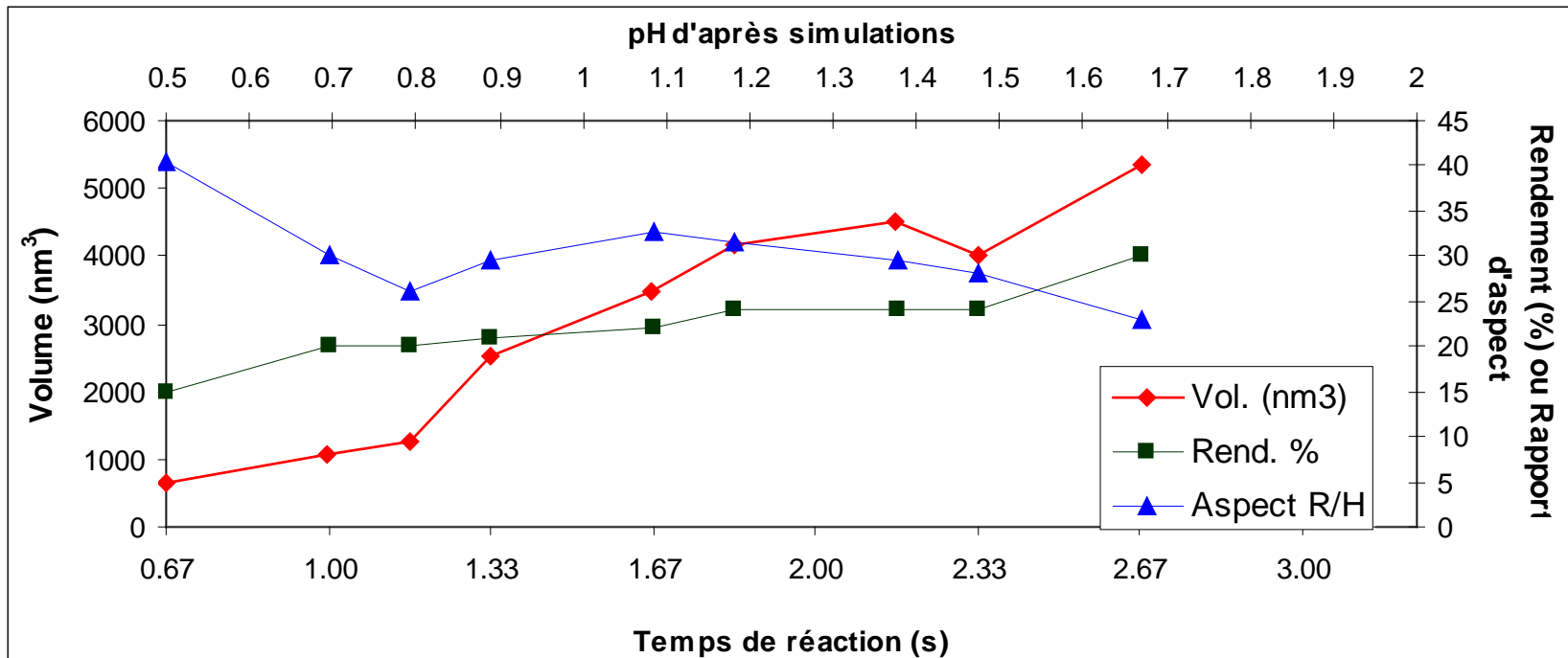
Preliminary SAXS results: fits as disk form factor



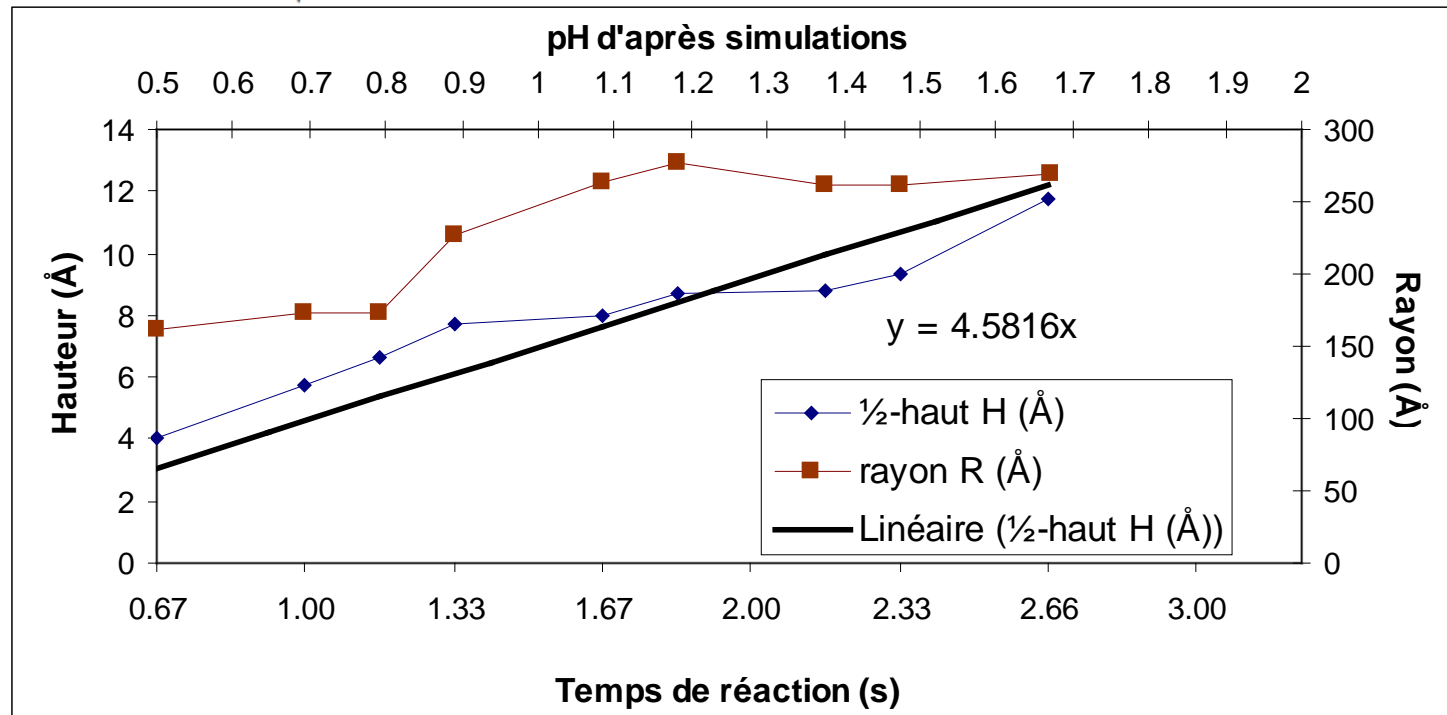
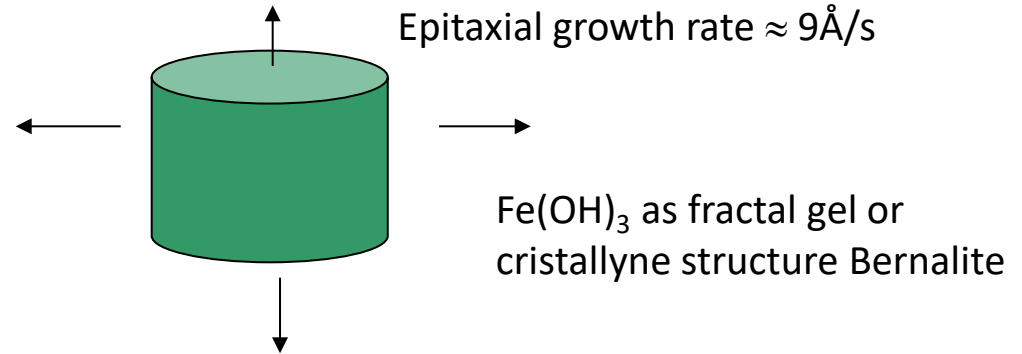
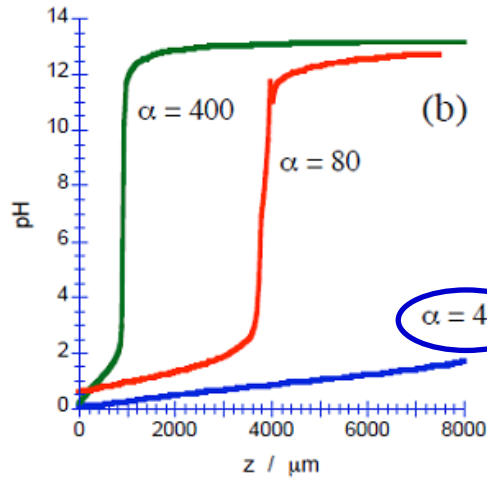
space (z) \approx pH equivalency



Anisotropy R/H



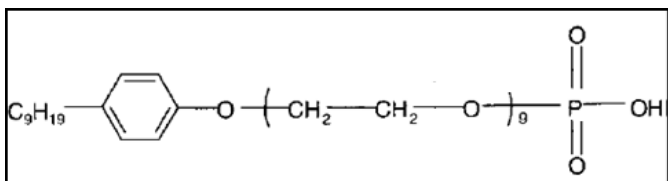
Preliminary SAXS results: fits as disk form factor



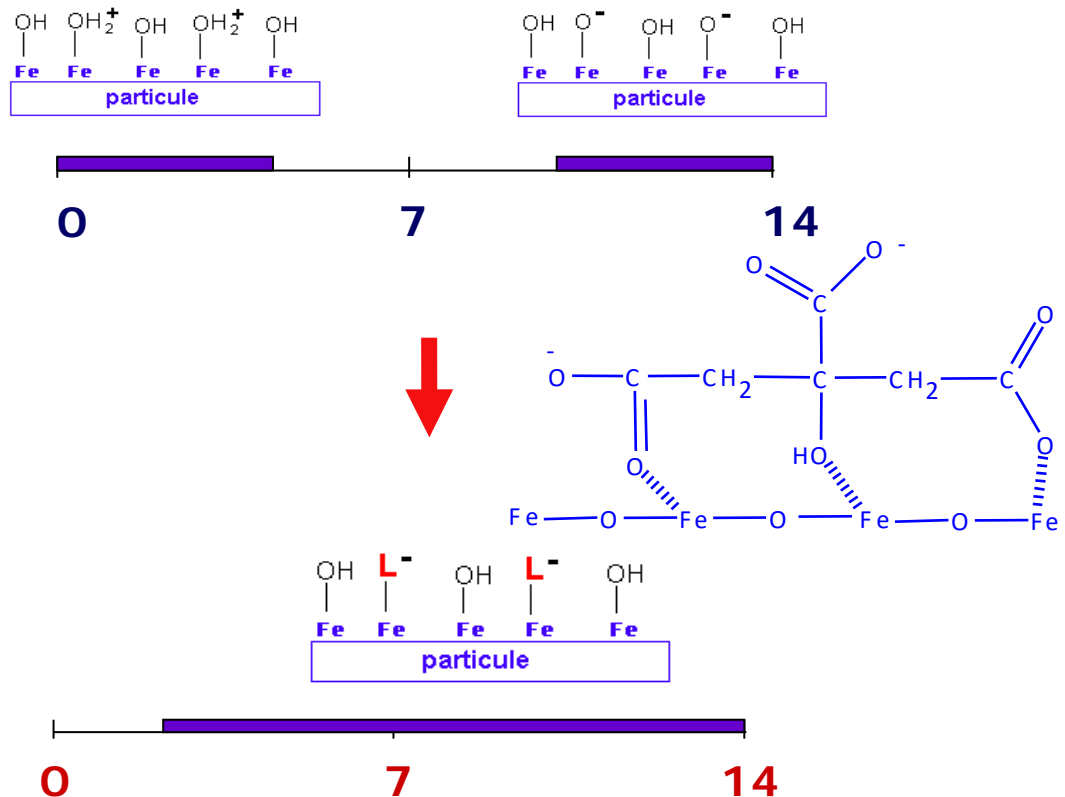
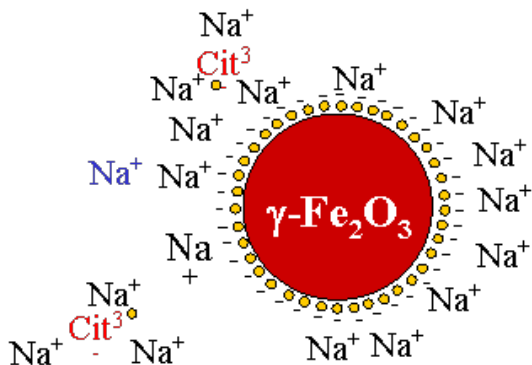
Coatings of iron oxide and oxo-hydroxide NPs for their dispersion in various media

Different coatings to insure colloidal stability :

- surfactants (oleic acid, phosphoric di-ester, ...) for organic solvents (alkanes, chlorinated,...)



- sodium citrate in aqueous neutral medium (pH=7.2) or sodium polyacrylate (2000 or 5000 g/mol)

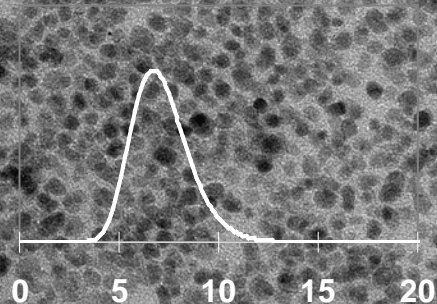


20 mol%/Fe addition precipitation-redispersion

J. A. Galicia, O. Sandre, F. Cousin, D. Guemghar, C. Ménager, V. Cabuil, *J. Phys.-Cond. Mat.* **2003**, 15 S1379.

Ionic Ferrofluids: demixtion & size sorting

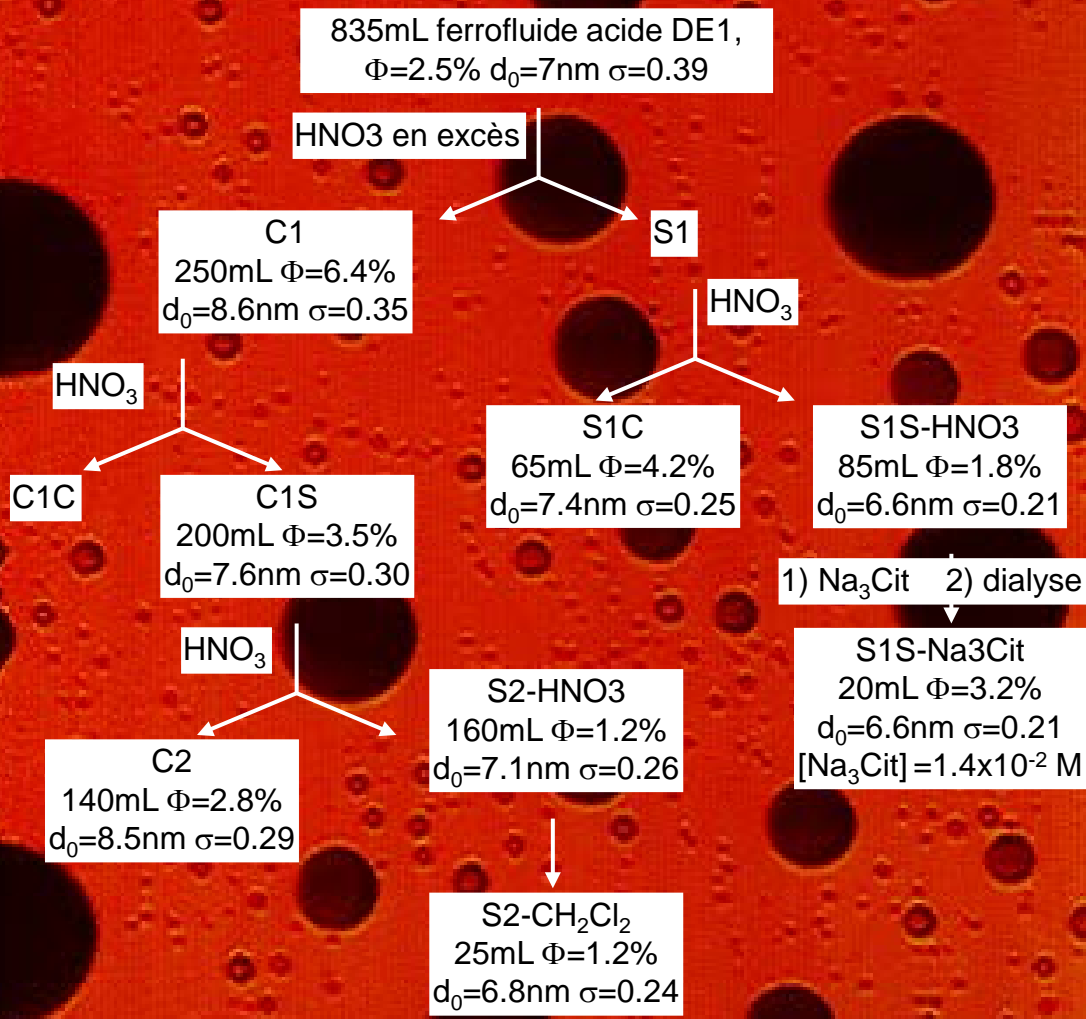
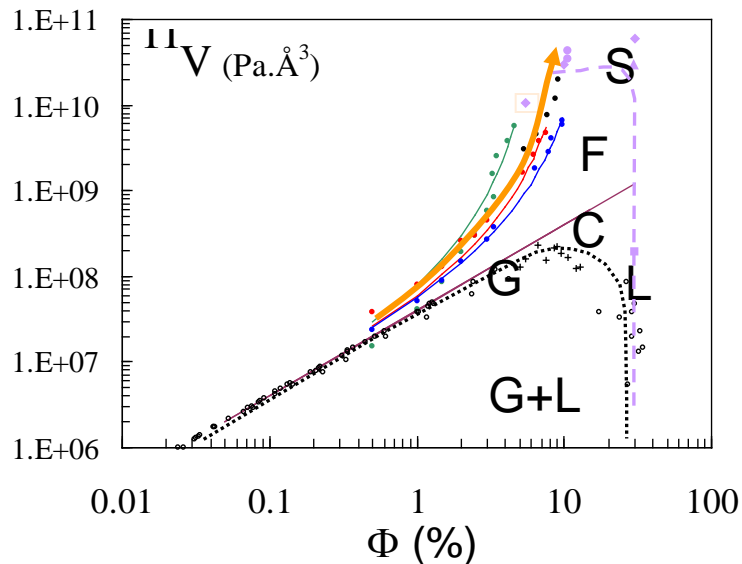
Size Polydispersity: $P(d, \text{nm})$



Fractionated separations

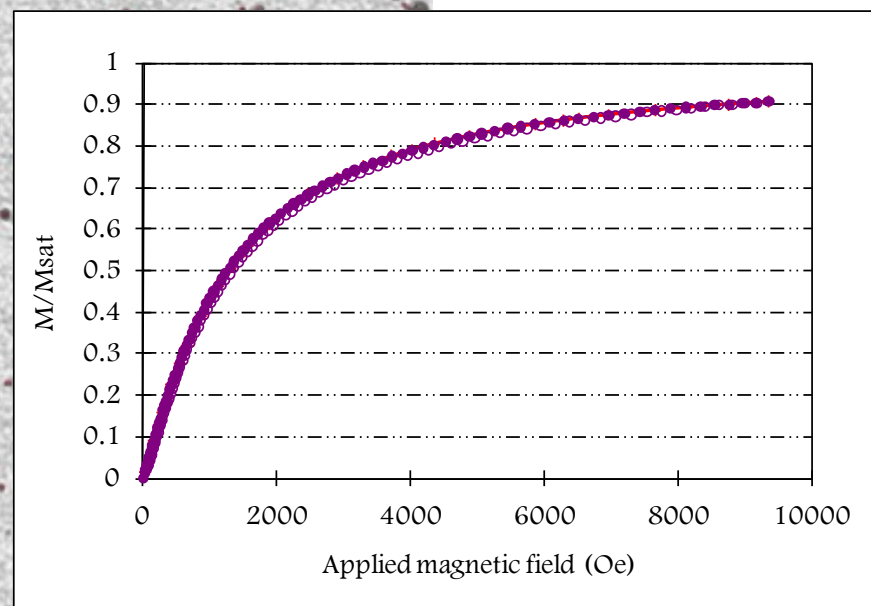
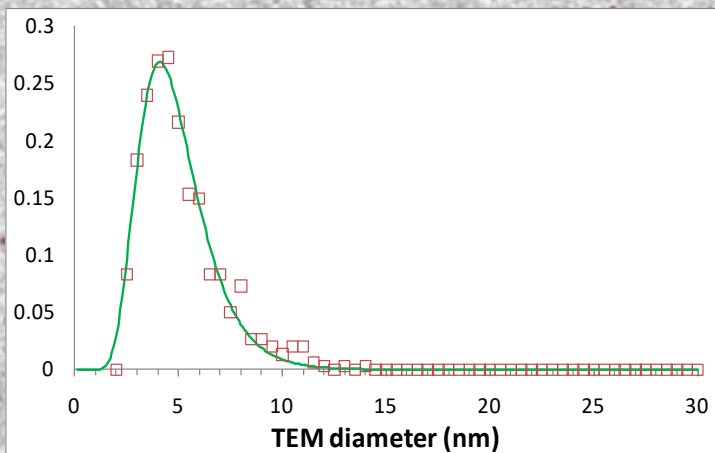
50 nm

R. Massart, E. Dubois, V. Cabuil, E. Hasmonay, J. Magn. Mater. 149 1 (1995)



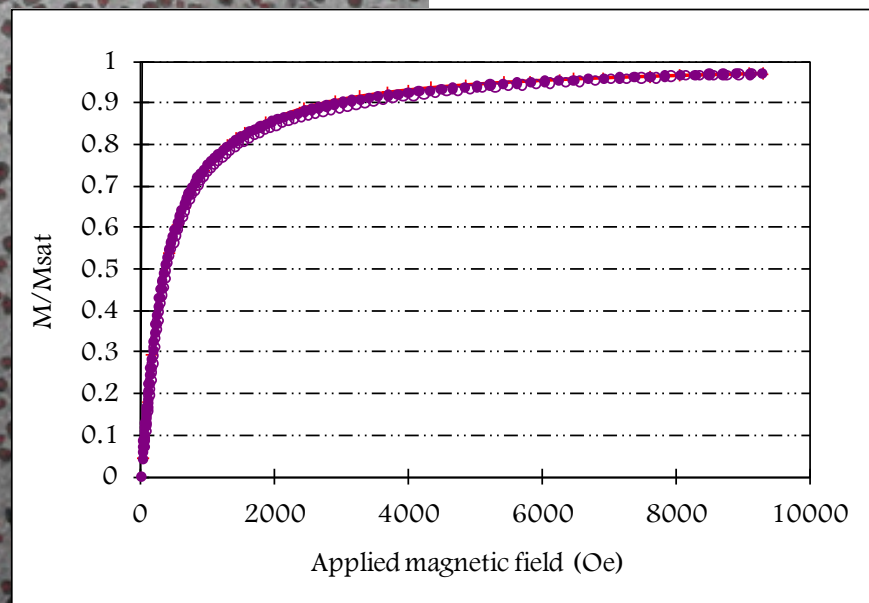
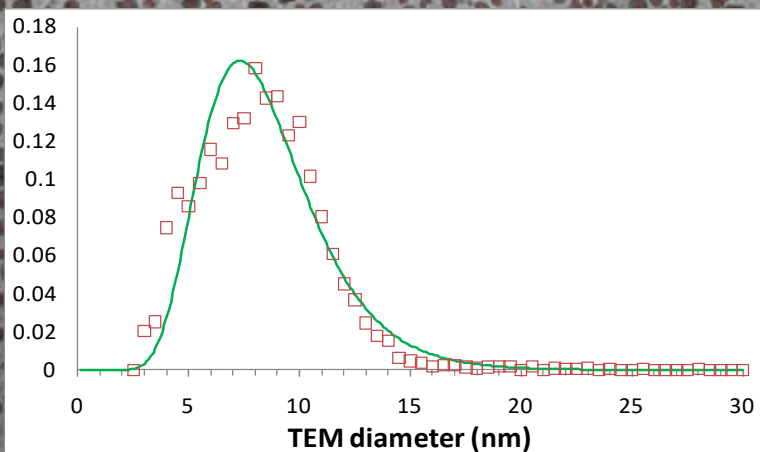
Size-sorted "ionic ferrofluid" as elementary bricks

USPIO fraction	Given name in this work	D_H of bare MNPs in HNO_3 nm / PDI	Average diameters by TEM	Average diameters by VSM	Saturation magnetization emu/g A/m	r_2 (4.7T) $s^{-1}mM^{-1}Fe_e$	SLP at $f=800$ kHz, $H_0=11$ kA/m W/g
S1S2S3	6-7 nm	11 / 0.12	$d_n=4.9$ nm, $d_w=6.9$ nm ($N=600$)	$d_n=6.5$ nm, $d_w=7.5$ nm	55 ± 1 2.8×10^5	70	2 ± 1



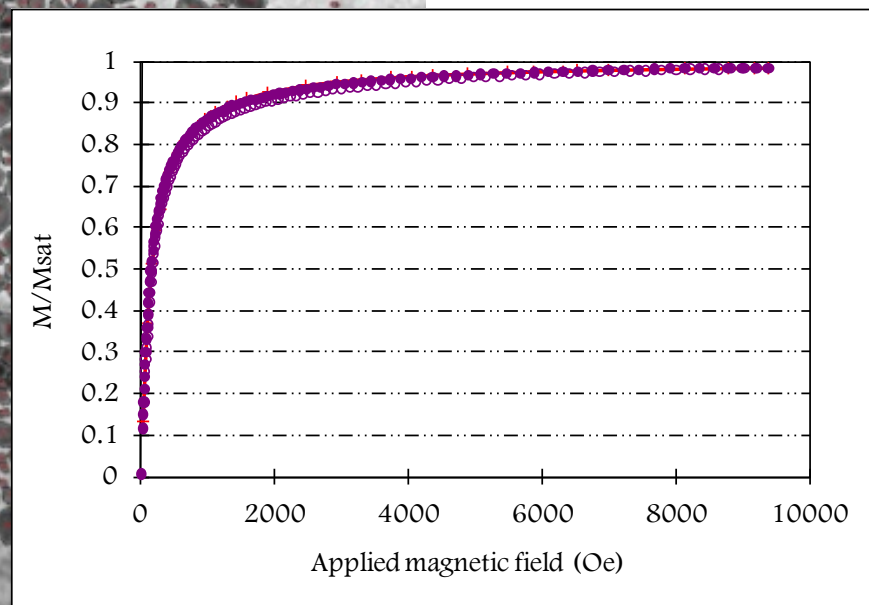
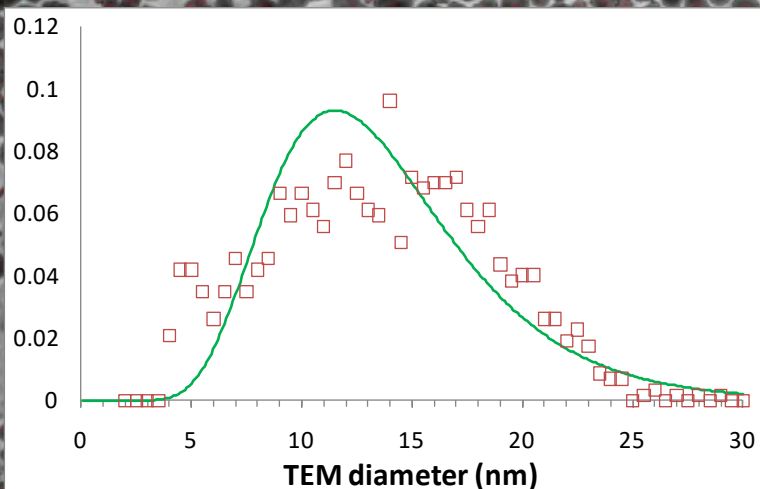
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S1C2	8-10 nm	23 / 0.16	$d_n=8.5$ nm, $d_w=11.6$ nm ($N=3800$)	$d_n=8.2$ nm, $d_w=10.0$ nm	60 3.0×10^5	104	9 ± 1

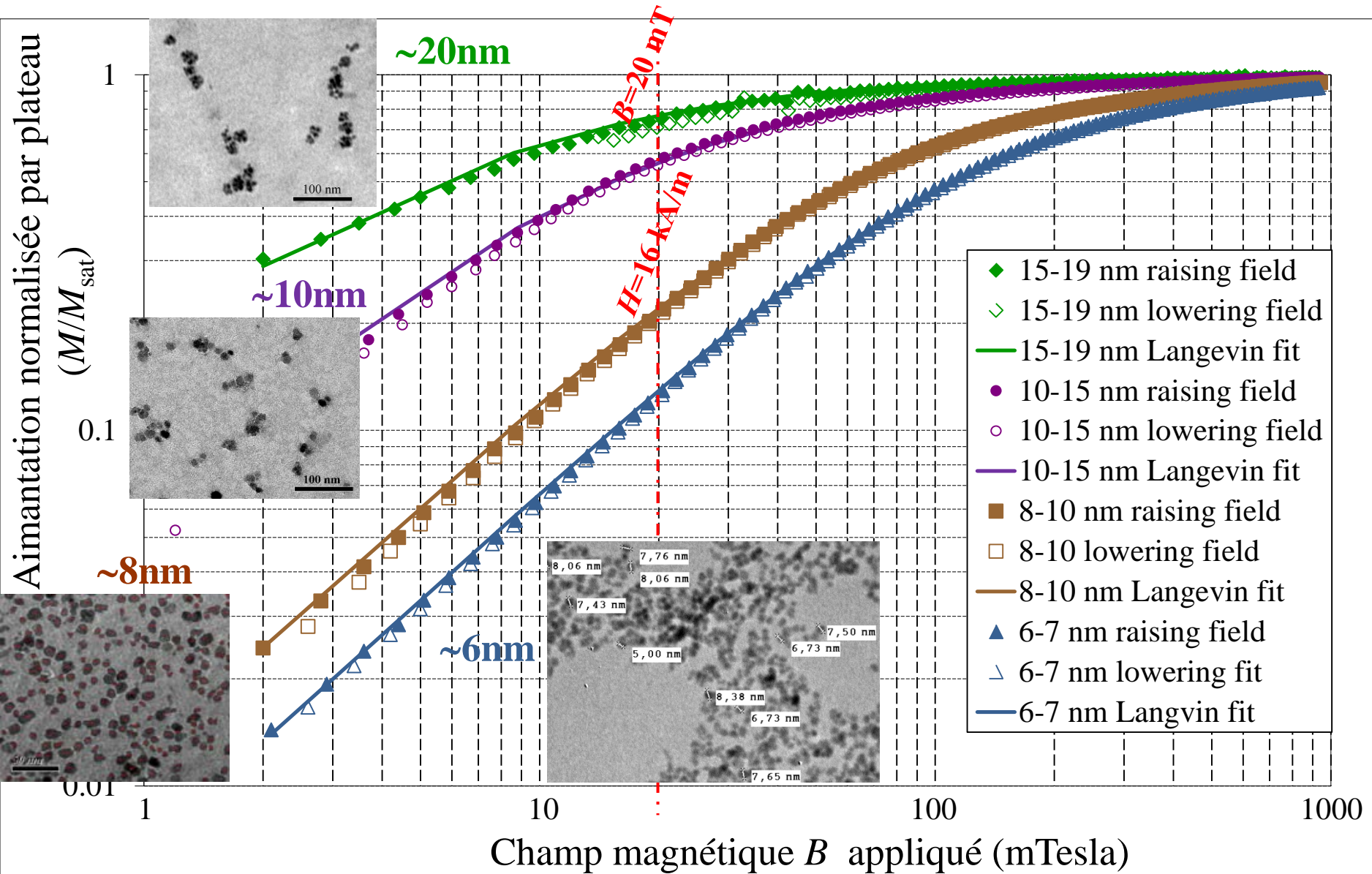


Size-sorted "ionic ferrofluid" as elementary bricks

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S1S2S3	6-7 nm	11 / 0.12	$d_n=4.9$ nm, $d_w=6.9$ nm ($N=600$)	$d_n=6.5$ nm, $d_w=7.5$ nm	55 ± 1 2.8×10^5	70	2 ± 1
S1C2	8-10 nm	23 / 0.16	$d_n=8.5$ nm, $d_w=11.6$ nm ($N=3800$)	$d_n=8.2$ nm, $d_w=10.0$ nm	60 3.0×10^5	104	9 ± 1
C1C2S3S4	10-15 nm	38 / 0.26	$d_n=13.8$ nm, $d_w=20$ nm ($N=1140$)	$d_n=10.4$ nm, $d_w=14.8$ nm	70 ± 1 3.5×10^5	293	80 ± 5



Magnetization curves along the size-grading process

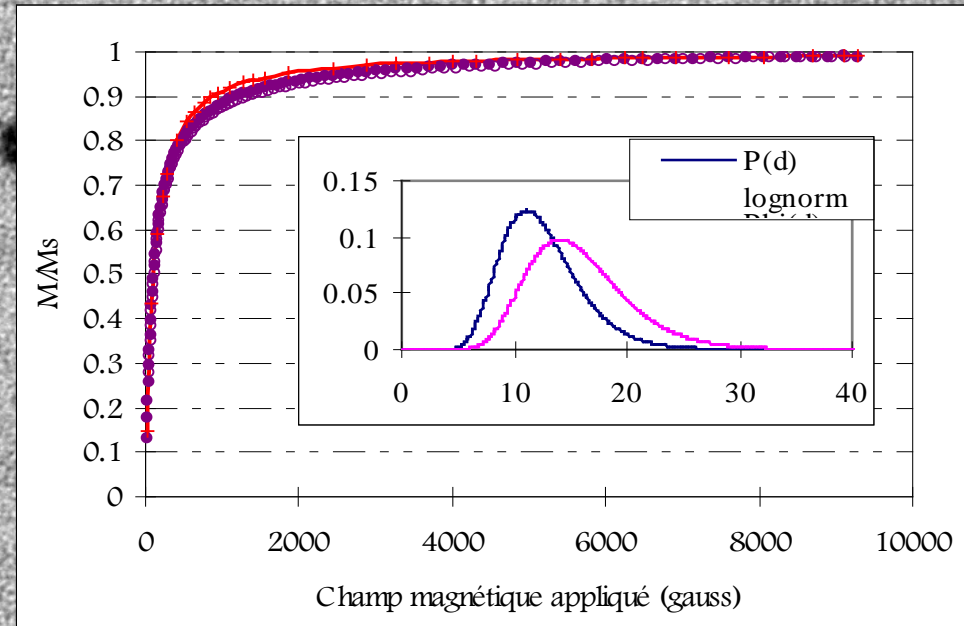
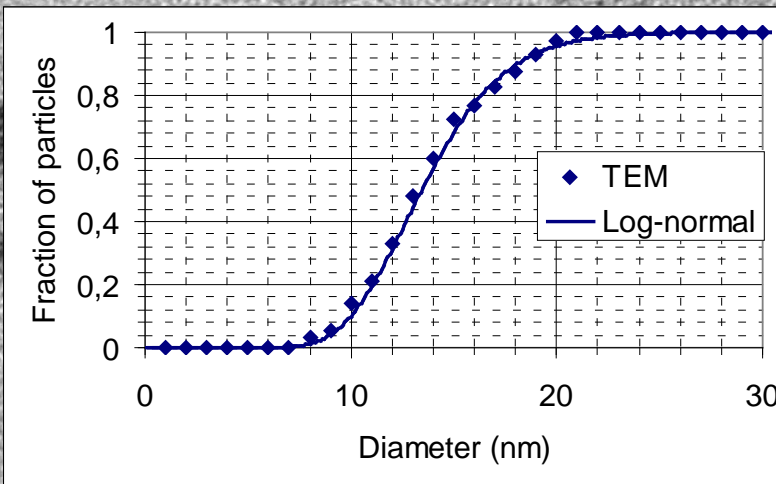
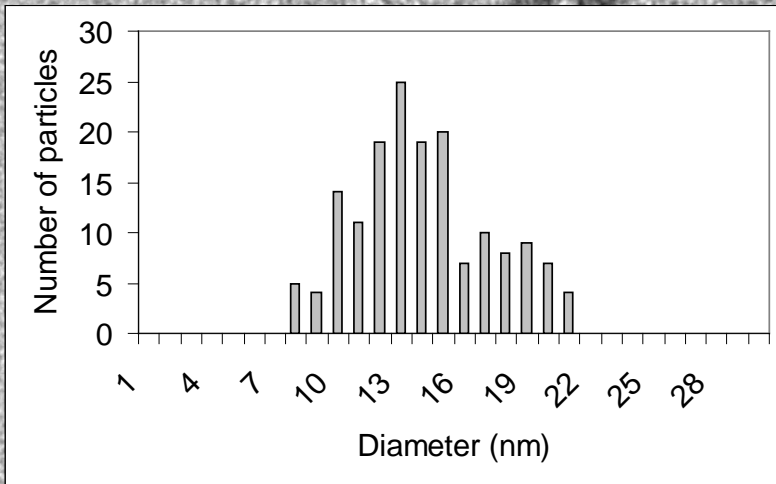


Larger nanoparticles for larger physical effects?

Obtained by multiple phase separation (C1C2C3C4)

$$\langle d \rangle_{\text{TEM}} = 13.9 \text{ nm}$$

$$\langle d \rangle_{\text{VSM}} = 11.8 \text{ nm}$$



$$d_w = \langle d^4 \rangle / \langle d^3 \rangle_{\text{VSM or TEM}} \approx 16 \text{ nm}$$

$$\langle d^n \rangle = d_0^n \exp(n\sigma^2/2) \rightarrow d_w = \langle d^4 \rangle / \langle d^3 \rangle = d_0 \exp(3.5\sigma^2)$$

100 nm

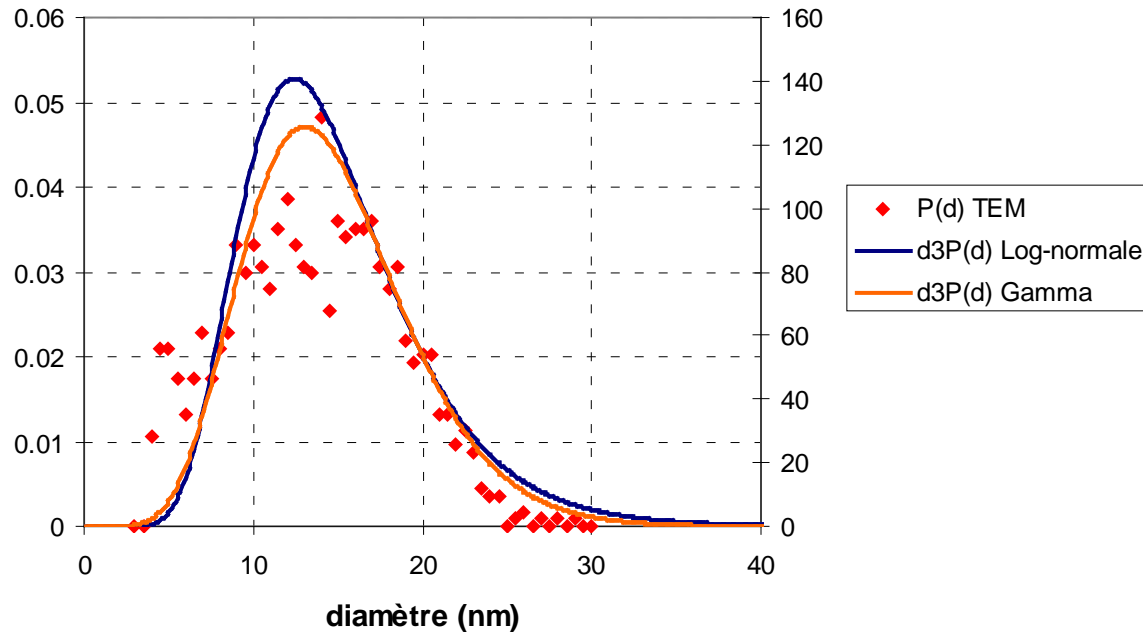


Size-sorted fraction: C1C2S3S4

$\langle d \rangle_{\text{TEM}} = 13.3 \text{ nm}$

$d_w = \langle d^4 \rangle / \langle d^3 \rangle_{\text{VSM}} = 14.8 \text{ nm}$

Distributions des diamètres de l'échantillon RP1-C1C2S3S4@BNE-A d'après TEM et fits VSM

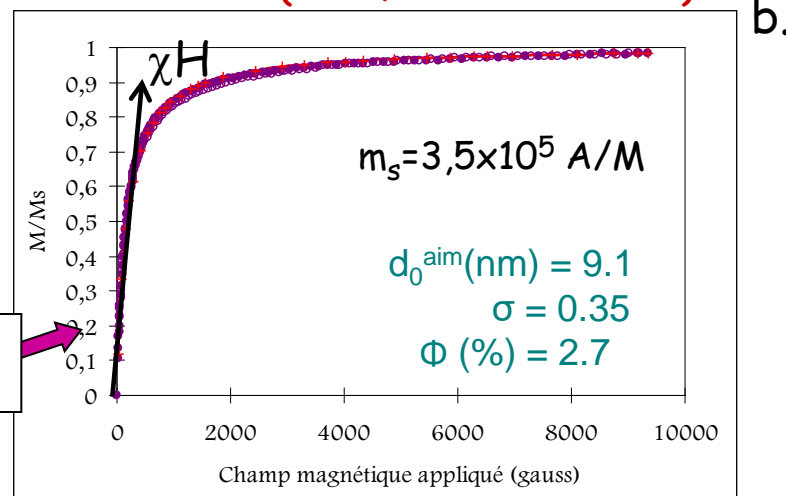
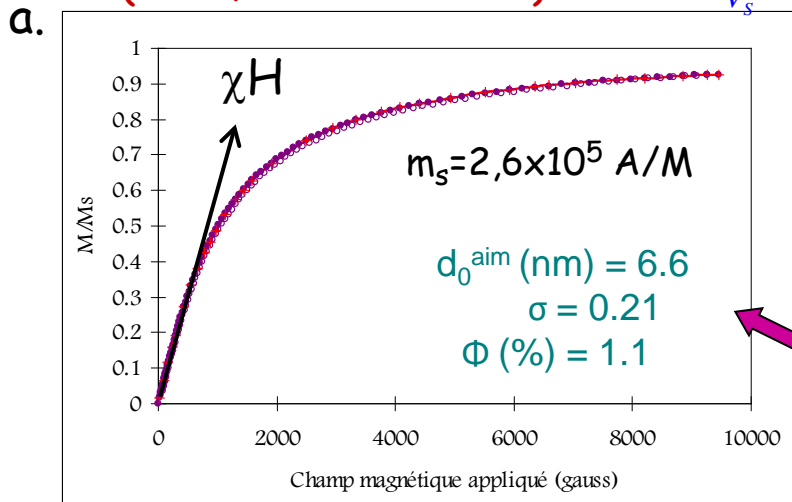


Vibrating sample magnetometry

$$M = \frac{1}{V_s} \int M_s \frac{\pi}{6} D^3 L\left(\frac{\mu_0 M_s \pi D^3 H}{6kT}\right) f_{LN}(D) dD$$

Smaller NPs
(S1S fraction d=6nm)

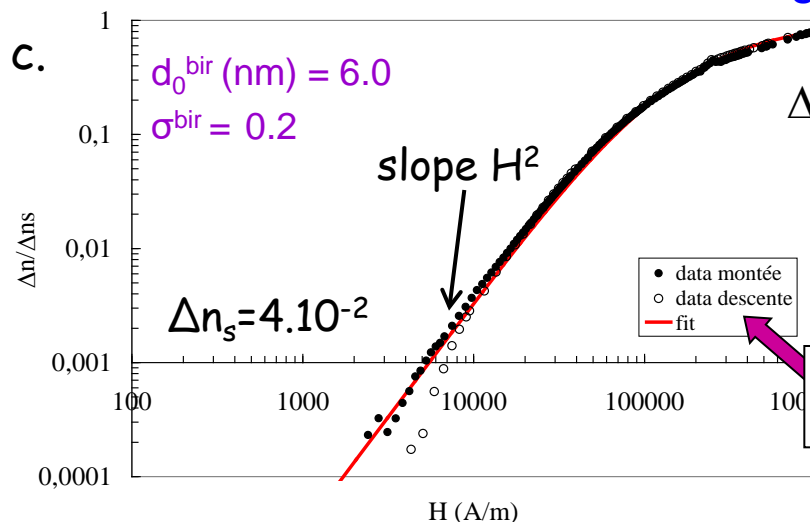
Larger NPs
(C1C fraction d=9nm)



$$M_{\text{sat}} = m_s \Phi$$

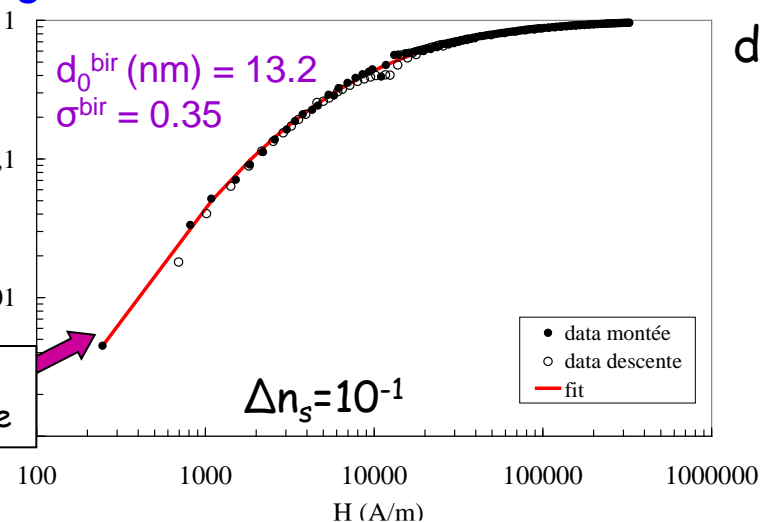
1st order
Langevin's curve

Static Magneto-birefringence



$$\Delta n_{\text{sat}} = \Delta n_s \Phi$$

2nd order
Langevin's curve



→ more monodisperse and superparamagnetic

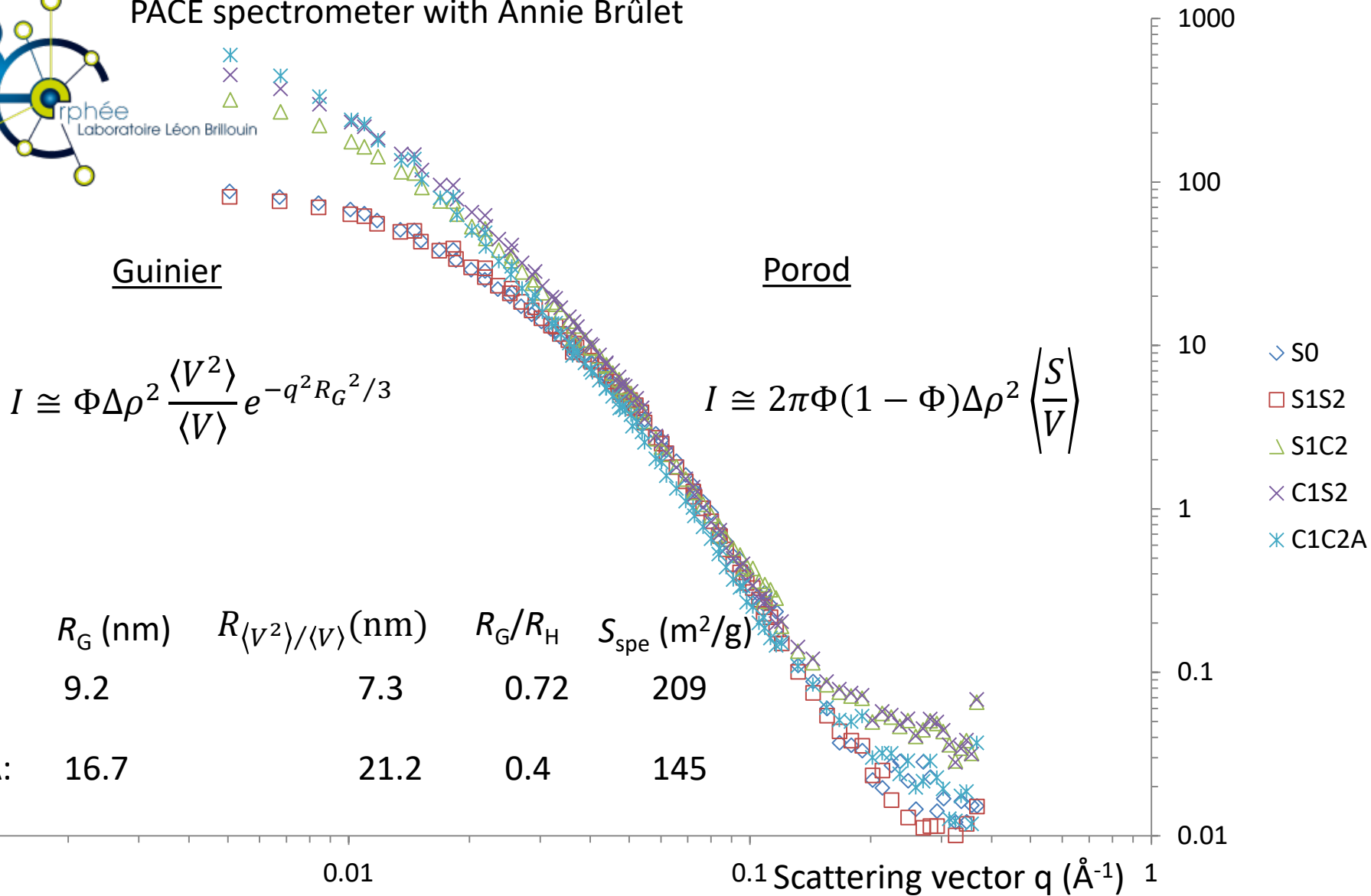
→ larger, ferrimagnetic and more anisotropic

Particle form factors by small angle neutron scattering

SANS Intensity normalized by volume fraction Φ (cm⁻¹)

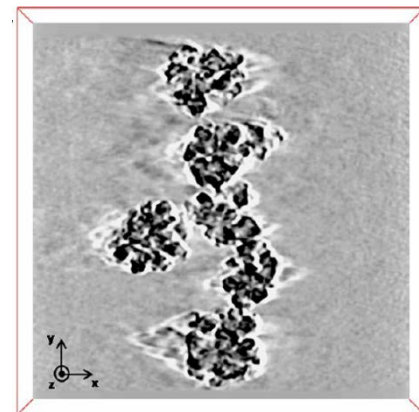
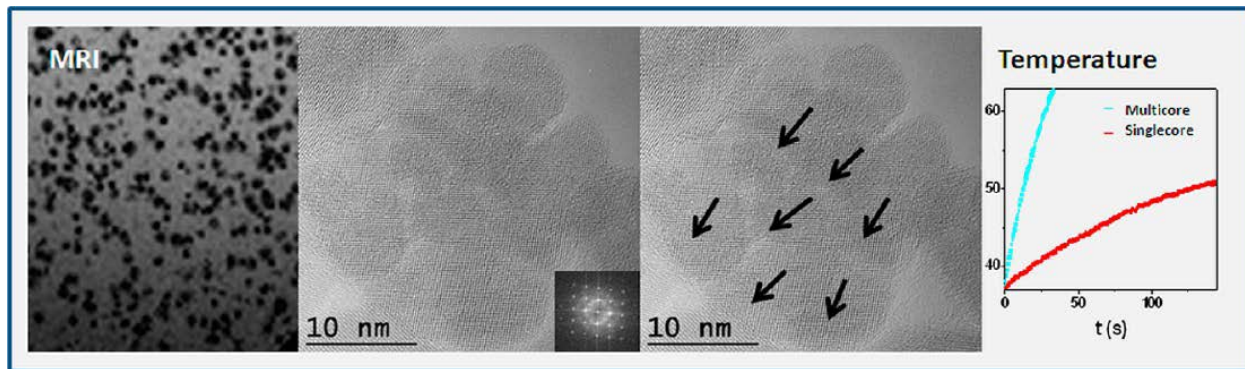


PACE spectrometer with Annie Brûlet

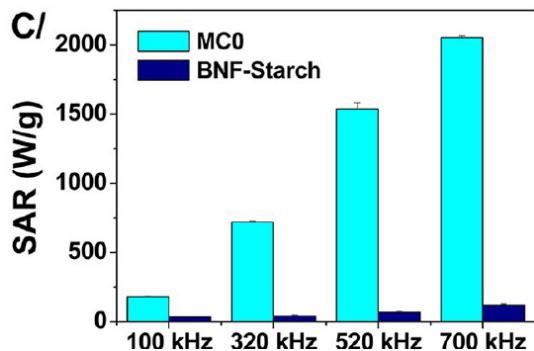


Synthesis & properties of multi-core "nanoflowers"

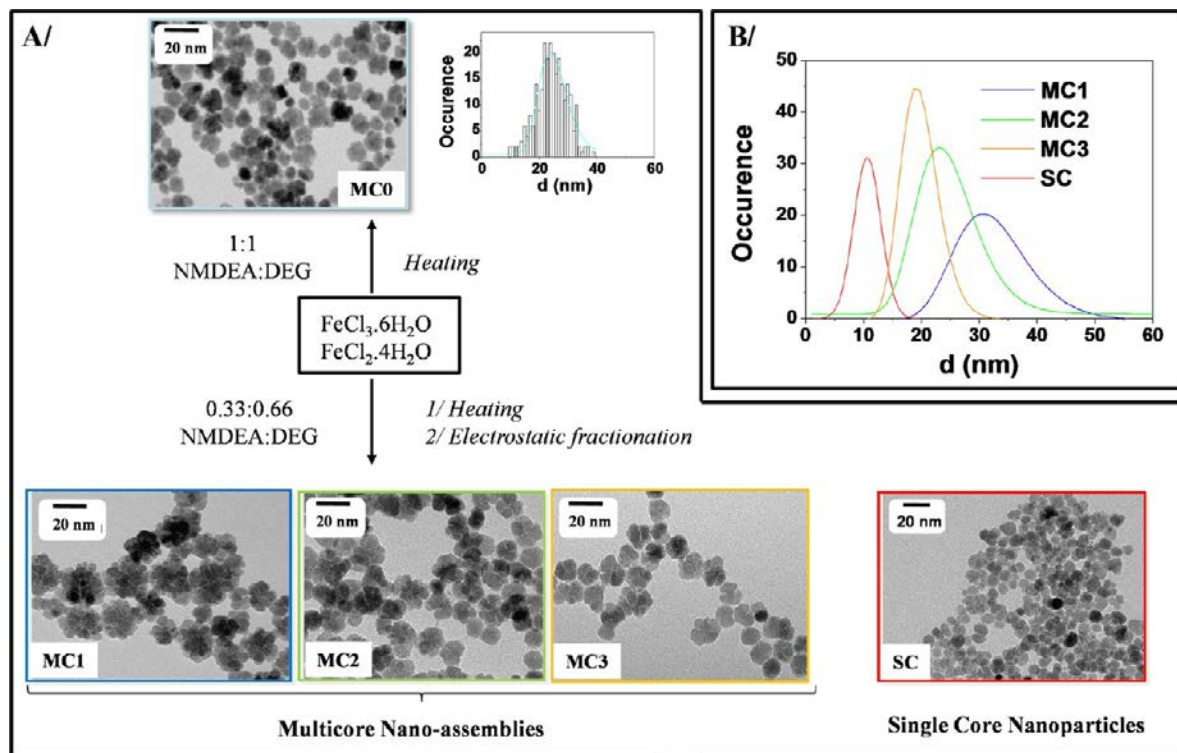
L. Lartigue, P. Hugounenq, D. Alloyeau, S. P. Clarke, M. Lévy, J-C. Bacri, R. Bazzi, D. F. Brougham, C. Wilhelm, F. Gazeau, ACS Nano 6, 10935–10949 (2012)



→ superior heating properties
(here values at $H_{max} = 29$ kA/m)

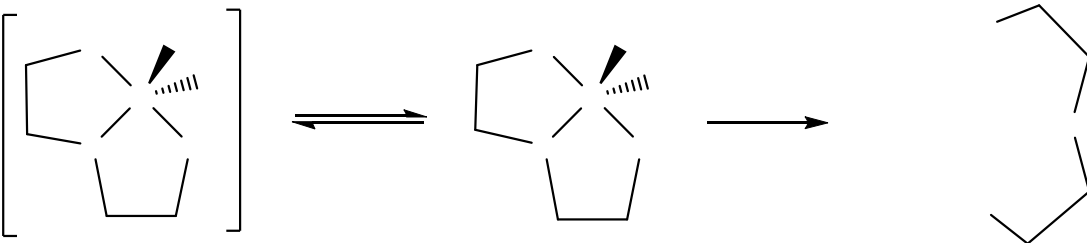


→ also high transverse relaxivity:
 $r_2 = 365 \text{ s}^{-1} \text{ mM}_{\text{Fe}}^{-1}$ at 9.25 MHz
(0.22 T / 37°C)

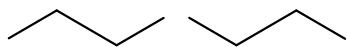


Nanoflower synthesis: the New Orleans method

D. Caruntu, G. Caruntu, Y. Chen, C. J. O'Connor, G. Goloverda,
V. L. Kolesnichenko, *Chem. Mater.* **2004**, *16*, 5527-5534



Polyol mixture: N-methyl diethanolamine / DEG (1:1)



- 2 mmol FeCl₂
- 4 mmol FeCl₃
- 16 mmol NaOH
- 40 g DEG
- 40 g NMEDA
- 220°C 5h

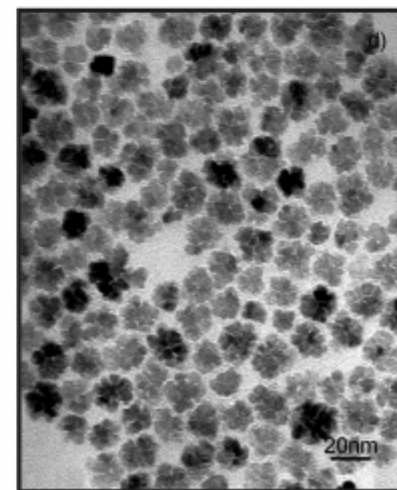
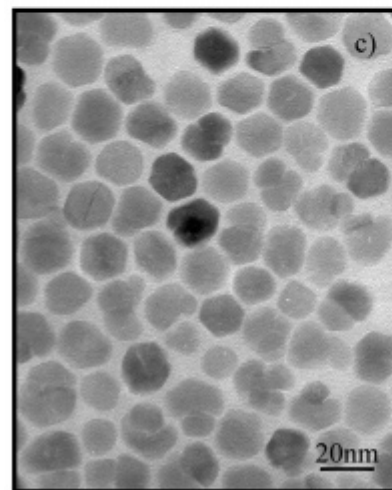
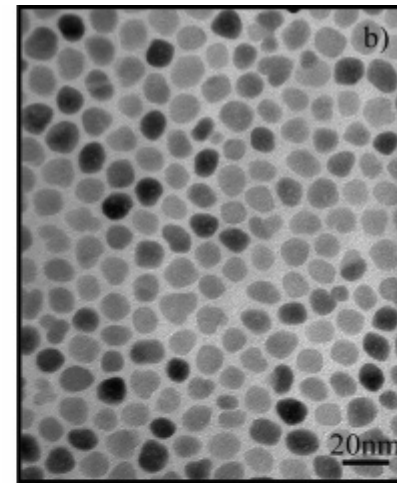
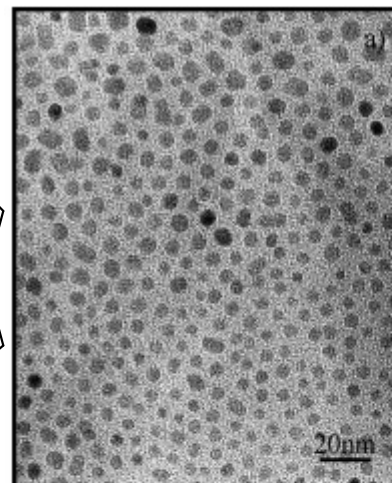
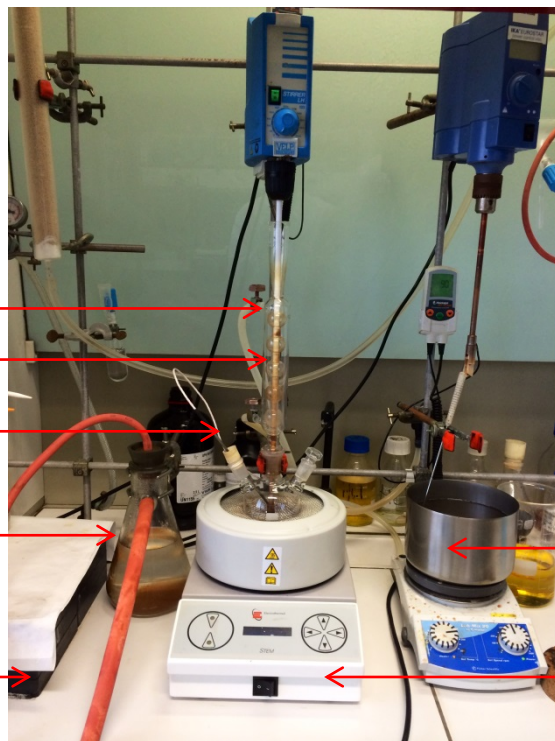
Reflux

Stirring shaft

Internal T-probe

Aspiration flask for
washing steps

Ferrite slab for magnetic
sedimentation

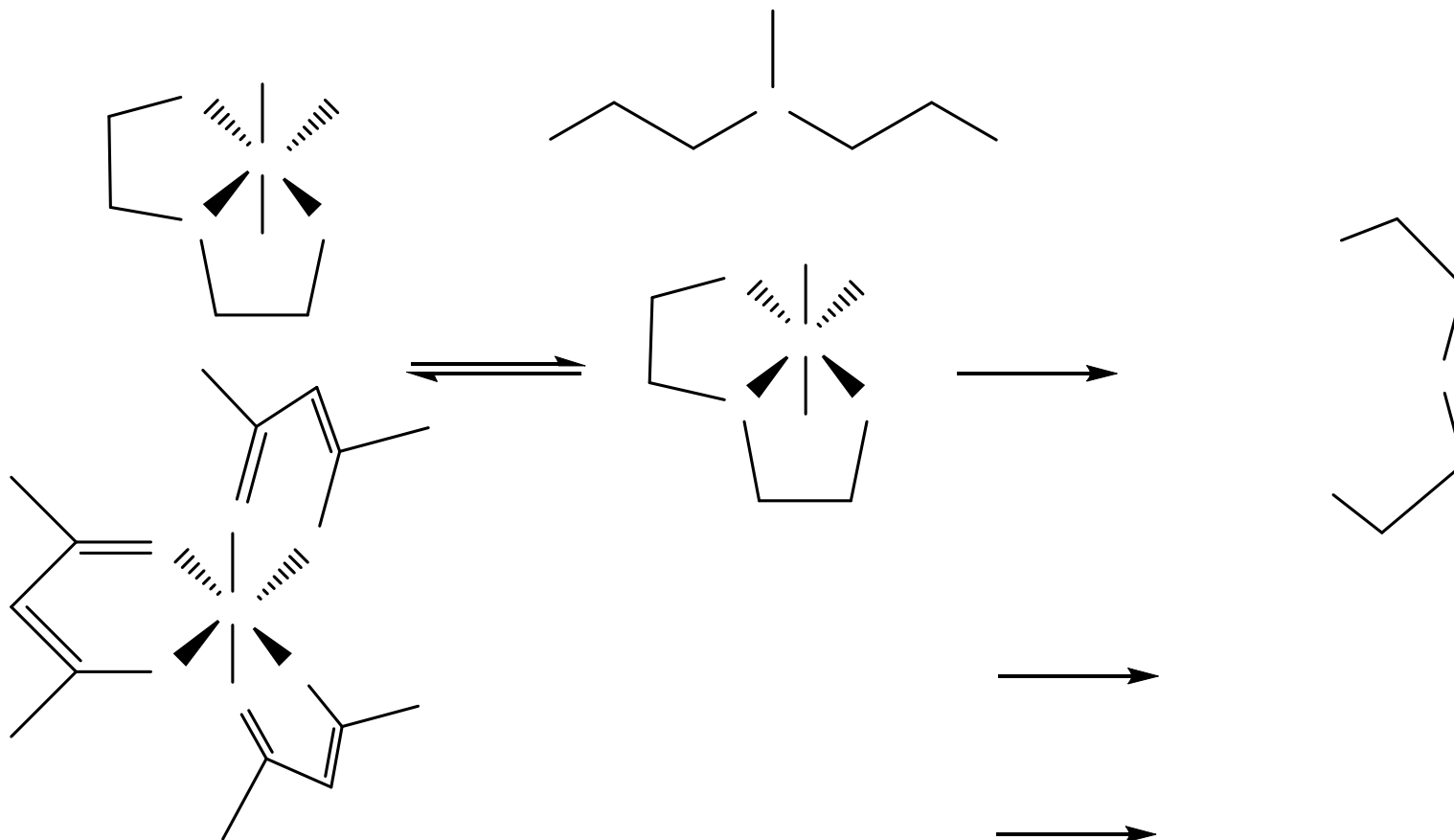


2nd heat/stirrer for
precursor dissolution

Dry heating mantle
(up to 250°C)

- Precursor
- Polyol composition
- Temp/Duration
- Water content

Forced hydrolysis mechanistic pathway (Caruntu)



- 1) D. Caruntu, G. Caruntu, Y. Chen, C. J. O'Connor, G. Goloverda, V. L. Kolesnichenko, *Chem. Mater.* **2004**, *16*, 5527-5534;
- 2) S. Sun and H. Zeng et al, *J. A. C. S.*, **2002**, *124*, 8204-8205 and **2004**, *126*, 273-279
- 3) F.A. Tourinho, R. Franck, R. Massart, *J. Materials Science* **1990**, *25*, 3249-3254

Large library of sample batches

Batch name	Nomenclature
15ff	DN1000 _{HU} -5h
17ff	D5000 _{HI} -20m
25ff	DN500 _{HU} -4h
30ff	DN1000 _{HU} -5h
31ff	DN500 _{HU} -1h
32ff	DN500 _{HU} -5h
34ff	DN100 _{HU} -5h*
35ff	DN100 _{HU} -5h
36ff	DN100 _{HU} -5h

Batch name	Nomenclature
28AA	DN100 _{HU} -220-5h-Cl
29AA	DN200 _{HU} -220-5h-Cl
02MA	DN300 _{HU} -220-5h-Cl
09MA	DN400 _{HU} -220-5h-Cl
10MA	DN500 _{HU} -220-5h-Cl
11MA	DN50 _{HU} -220-5h-Cl
27MA	DN0-220-5h-Acac
12MA	DN100-220-5h-Acac
17MA	DN200-220-5h-Acac
18MA	DN300-220-5h-Acac
19MA	DN400-220-5h-Acac
20MA	DN500-220-5h-Acac
15JA	DD100-250-5h-Cl
10JA	TD100-250-5h-Cl

Vary μ L water in 120 g polyol mixture:

EG: Ethylene Glycol D=pure DEG
 DEG: Diethylene Glycol DN=DEG/NMDEA (1:1)
 TEG: Triethylene Glycol DD=DEG/DEA (1:1)
 DEA: Diethanolamine TD=TEG/DEA (1:1)

NMDEA: N-methyldiethanolamine

TEA: Triethanolamine

DIA: N-ethyl Diisopropylamine

HU=heating up

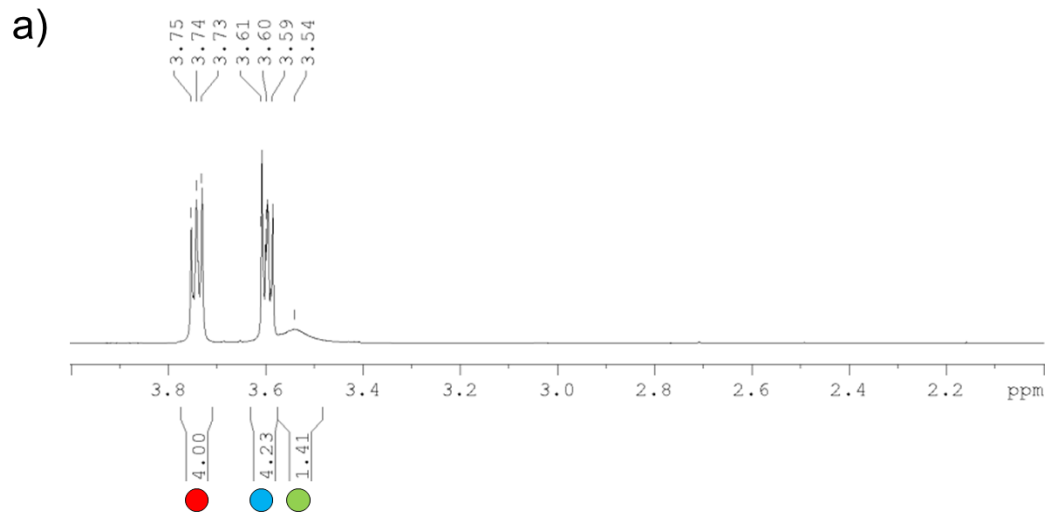
HI=hot injection

* no stirring

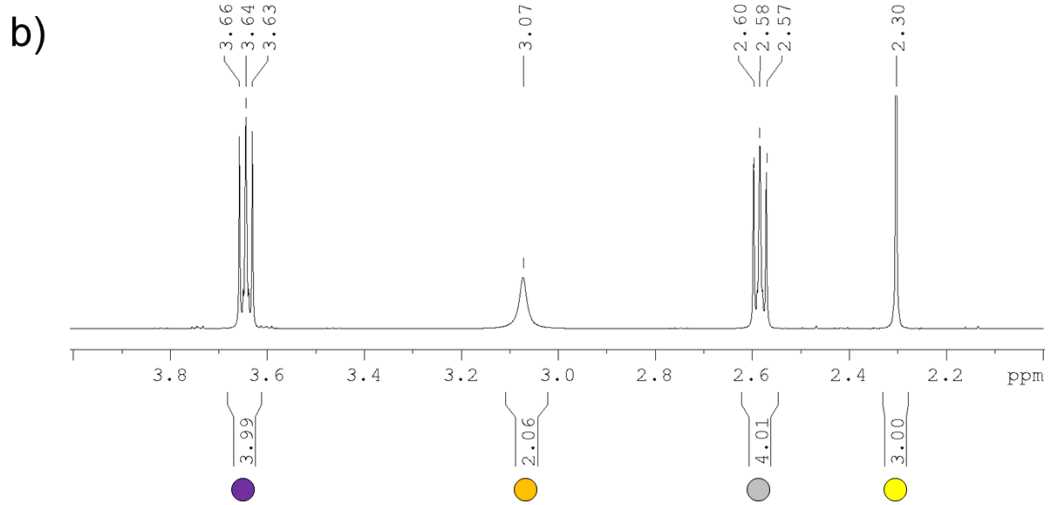
Cl=2 mmol FeCl₂, 4 mmol FeCl₃, 16 mmol NaOH

Acac=6 mmol Fe(acac)₃, 16 mmol NaOH

Study of polyol route: fate of solvent molecules

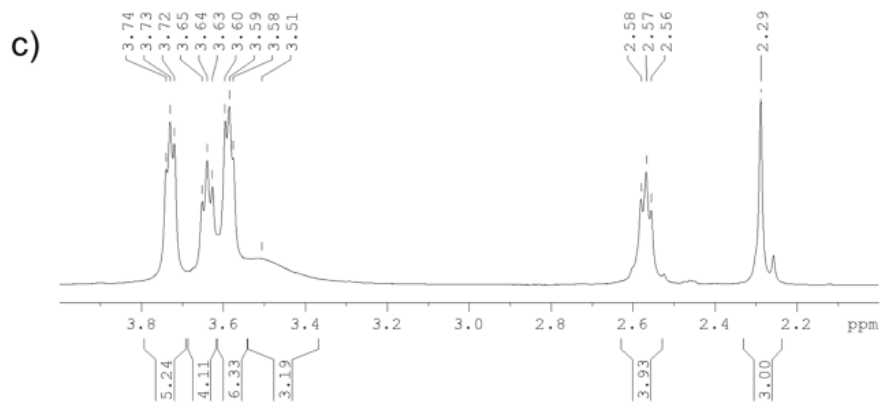


Diethylene glycol (DEG)

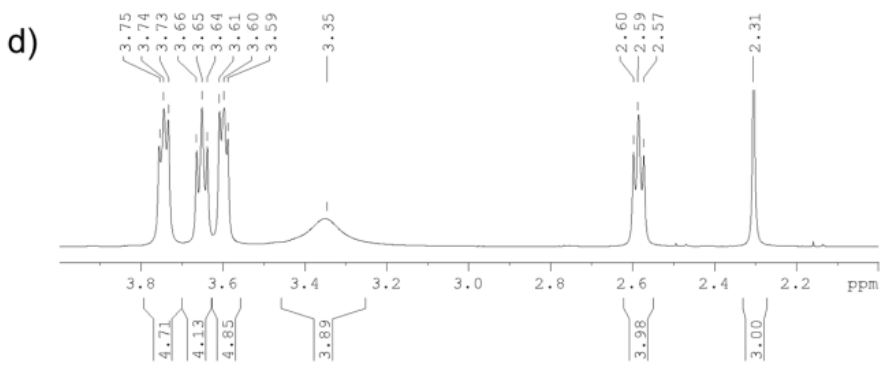


N-methyldiethanolamine (NMDEA)

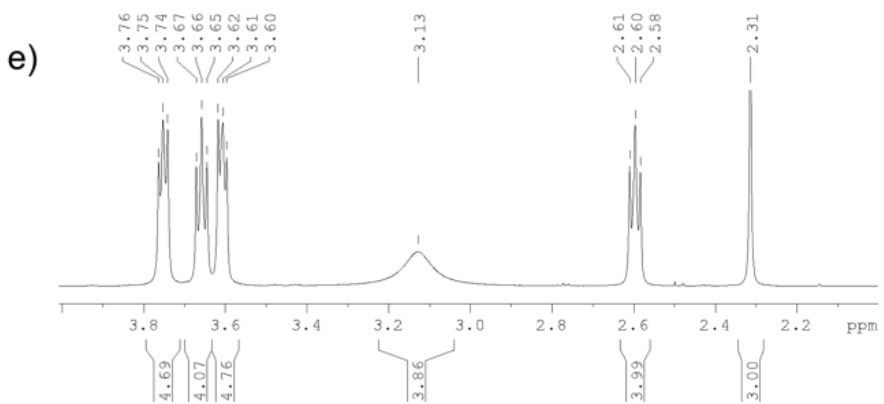
Study of polyol route: fate of solvent molecules



DEG, NMDEA, NaOH, FeCl₂, FeCl₃

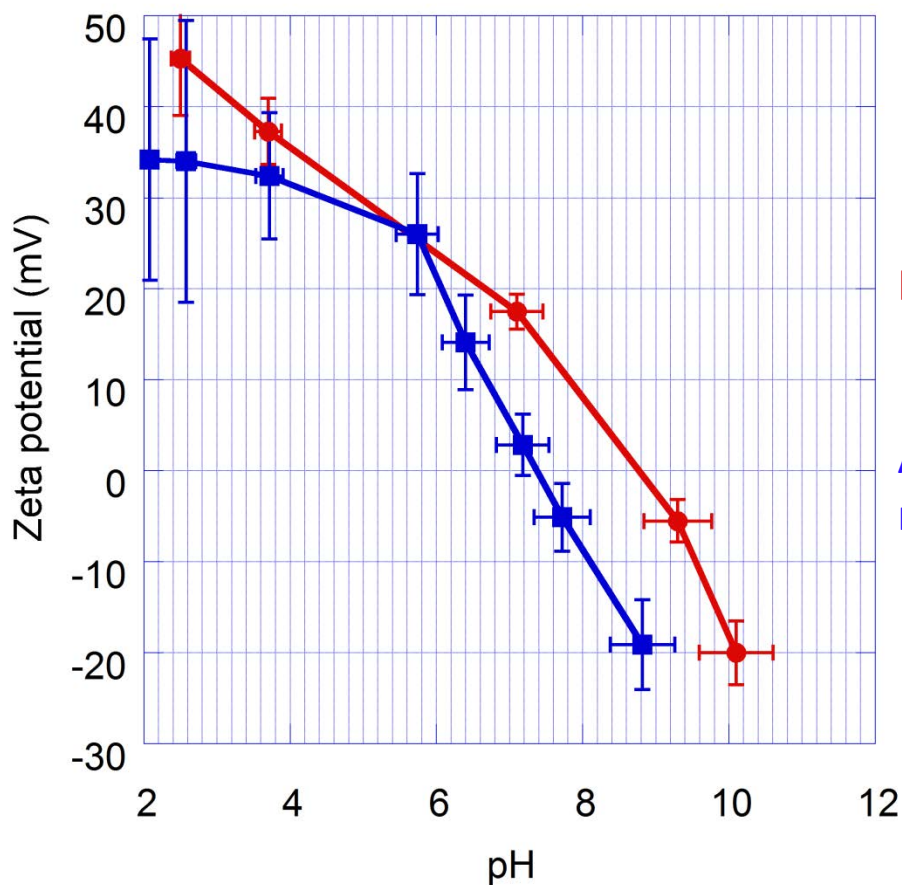


DEG, NMDEA, NaOH, FeCl₂, FeCl₃, H₂O
Before reaction



DEG, NMDEA, NaOH, FeCl₂, FeCl₃, H₂O
After reaction

Study of polyol route: fate of solvent molecules

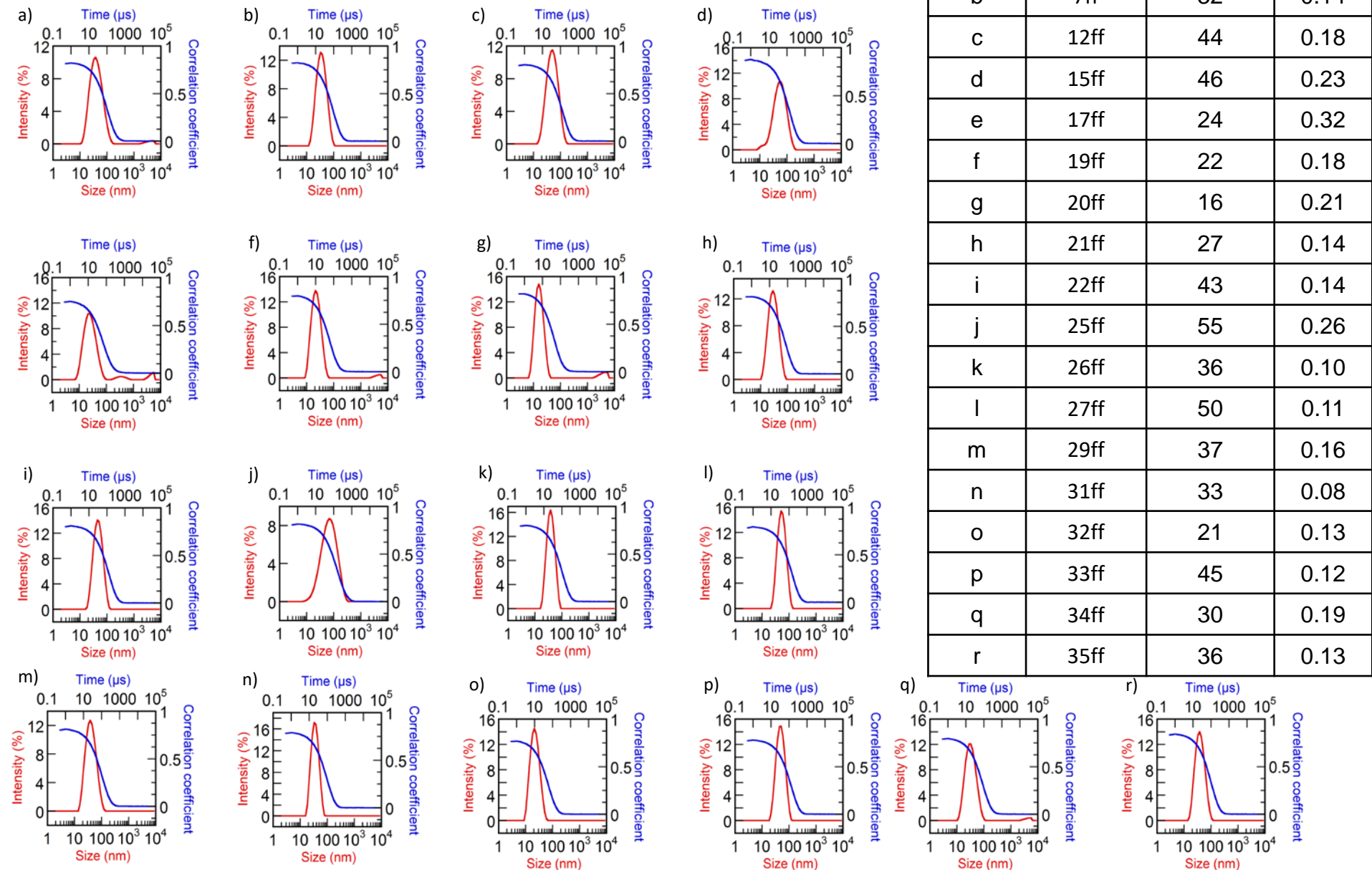


Right after synthesis
→ PZC = pKa of NMDEA

After washings (precipitation-
redispersion cycles at alkaline pH)

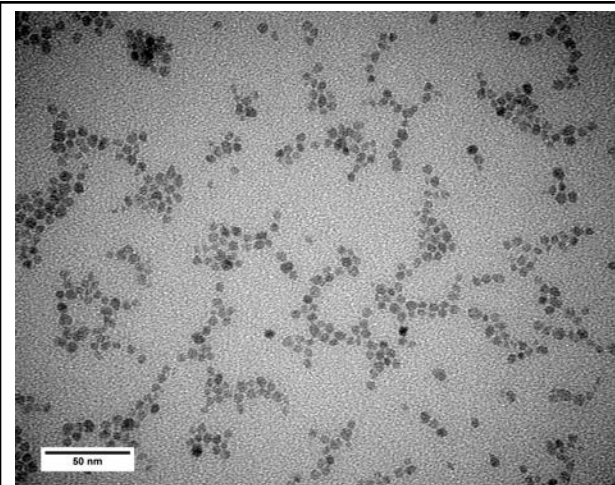
- Can be oxidized in boiling $\text{Fe}(\text{NO}_3)_3$: $\text{Fe}_3\text{O}_4 \rightarrow \gamma\text{-Fe}_2\text{O}_3$
- Washed and stabilized in water at $\text{pH} \sim 7$ with citrate ligand or PEG-phosphonate

Hydrodynamic size by DLS

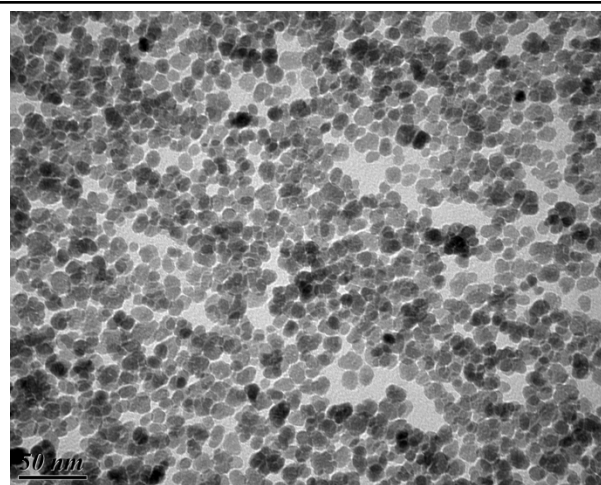


Variety of Fe_3O_4 NP batches synthesized in DEG:NMDEA

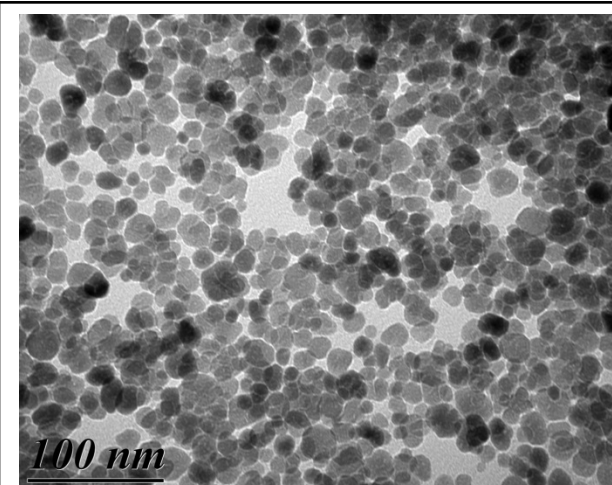
$$\langle d \rangle = d_0 e^{\sigma^2/2} \quad \text{var}(d) = d_0^2 (e^{\sigma^2/2} - 1)$$



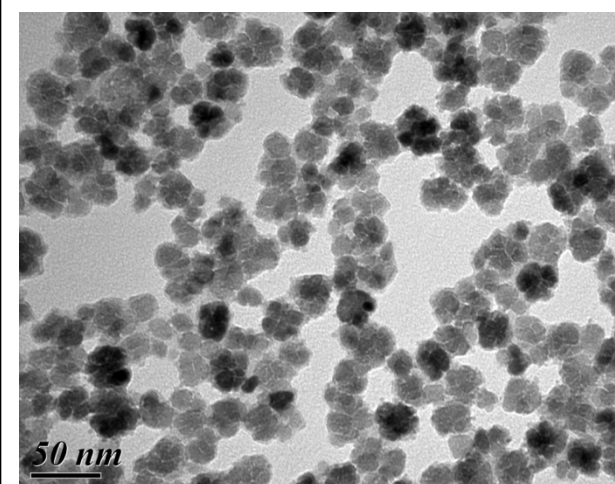
4FF: $d = 6.2 \pm 1.0$ nm



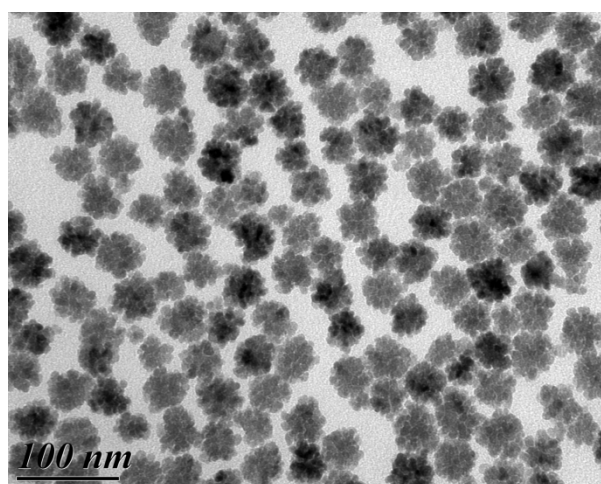
23FF: $d = 10.5 \pm 1.9$ nm



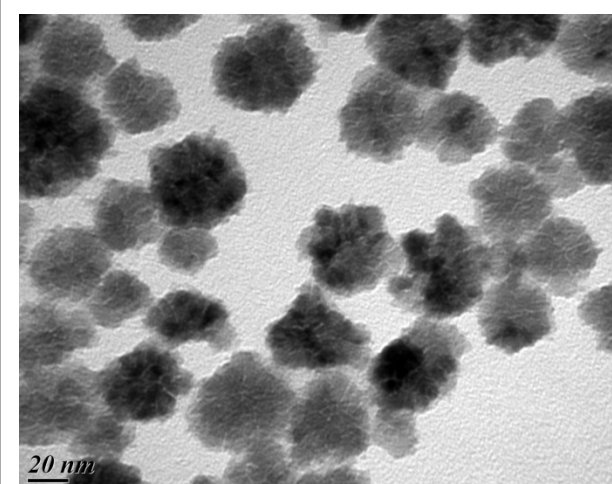
25FF: $d = 14.2 \pm 3.2$ nm



29FF: $d_{\text{out}} = 26.6 \pm 4.2$ nm



15FF: $d_{\text{out}} = 36.3 \pm 4.8$ nm

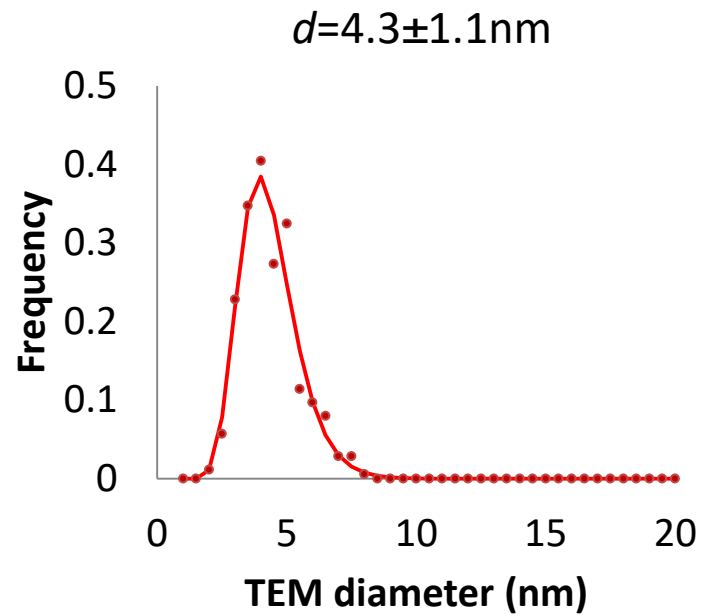
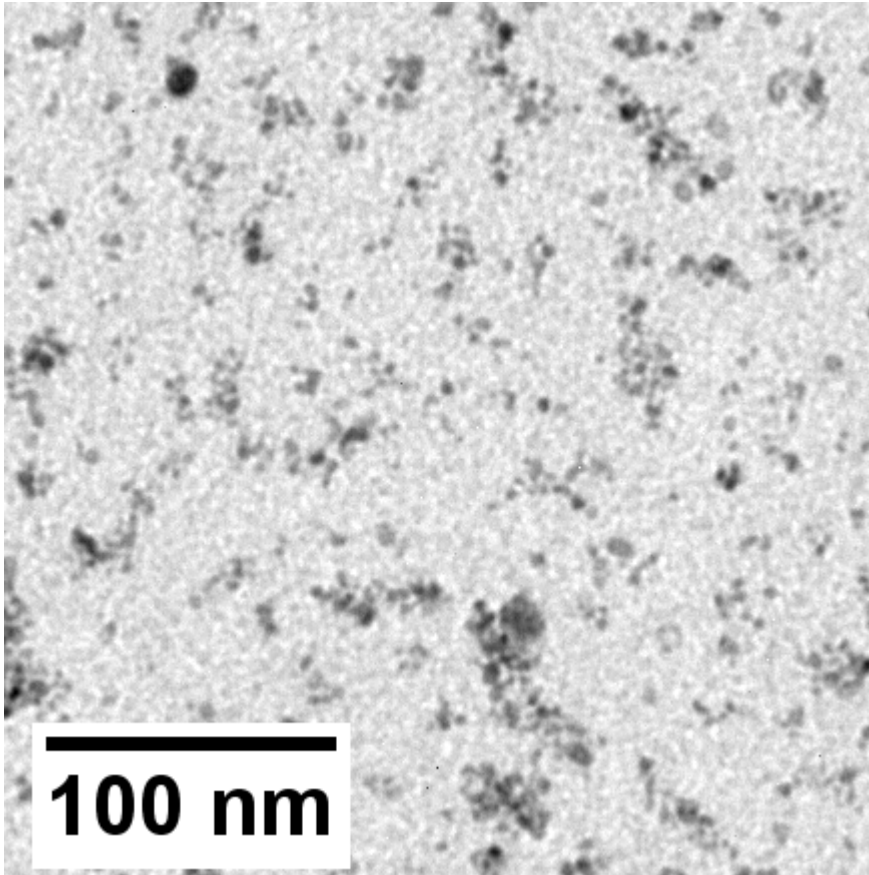


30FF: $d_{\text{out}} = 41.1 \pm 8.6$ nm

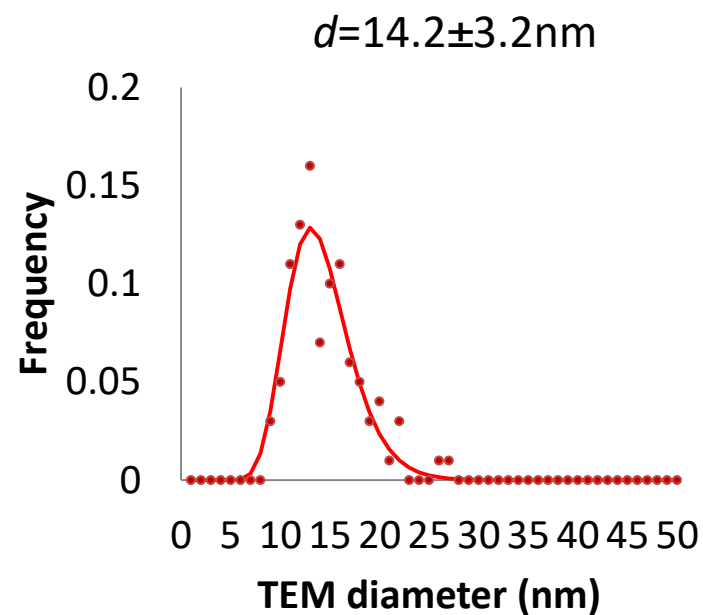
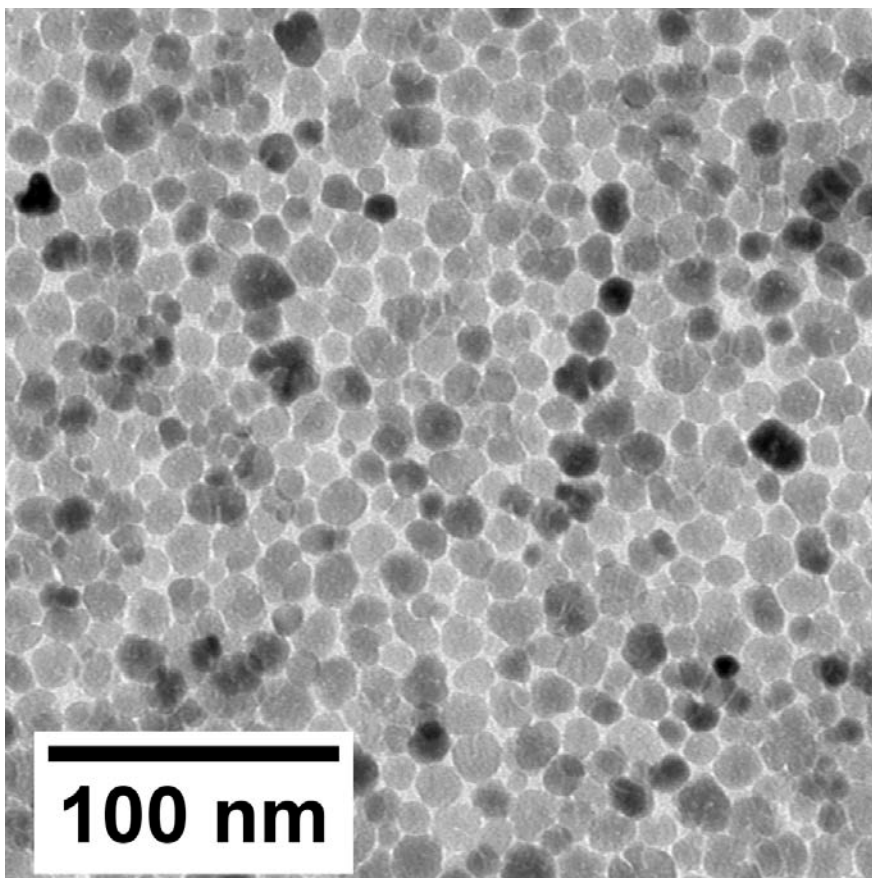
G. Hemery, A. C. Keyes Jr., E. Garaio, I. Rodrigo, J. A. Garcia, F. Pazaola, E. Garanger,

O. Sandre, arXiv preprint: [1701.05858](https://arxiv.org/abs/1701.05858)

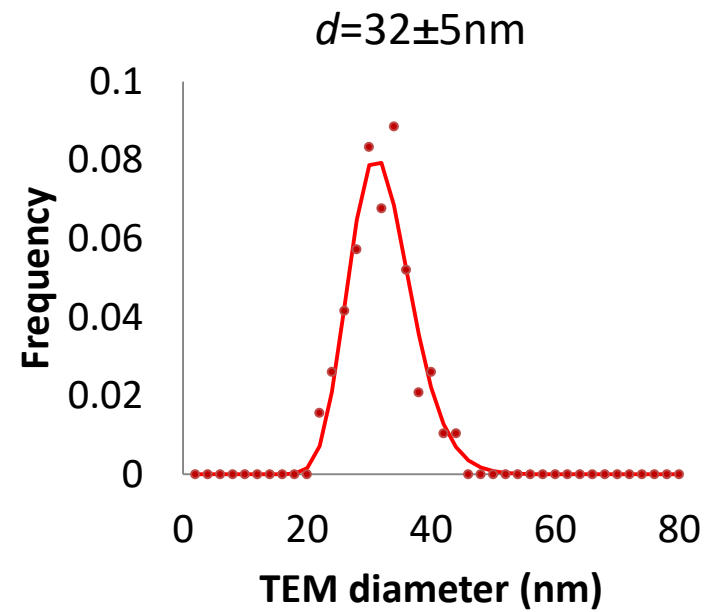
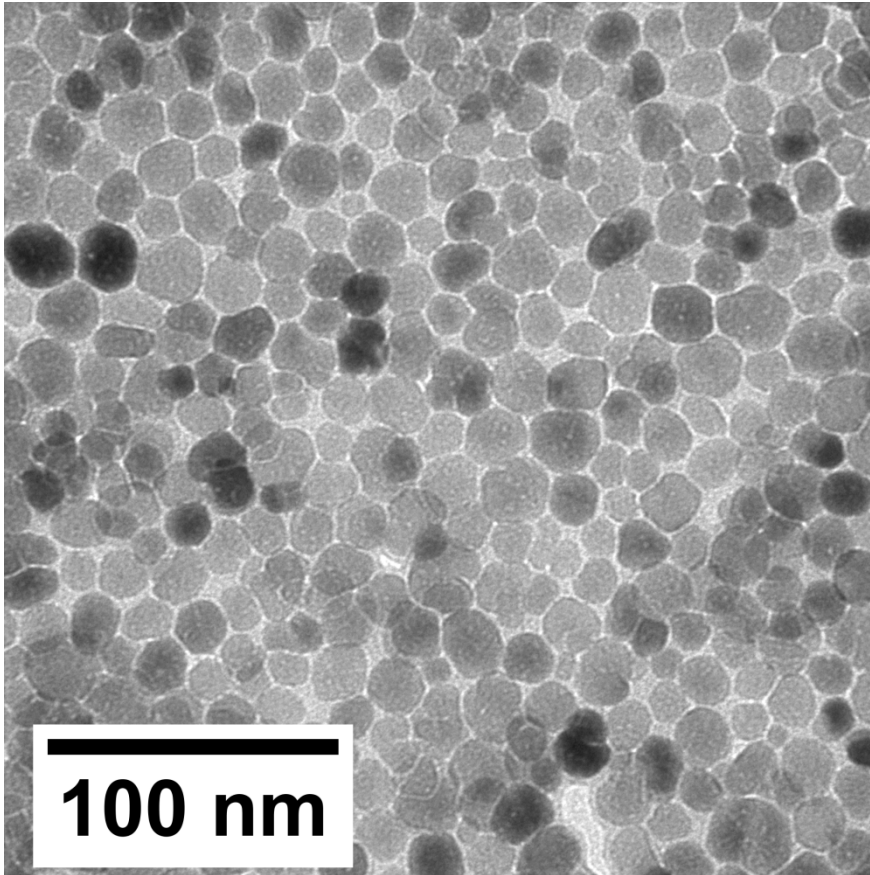
Example of ultra-small nanosphere sample: 17FF



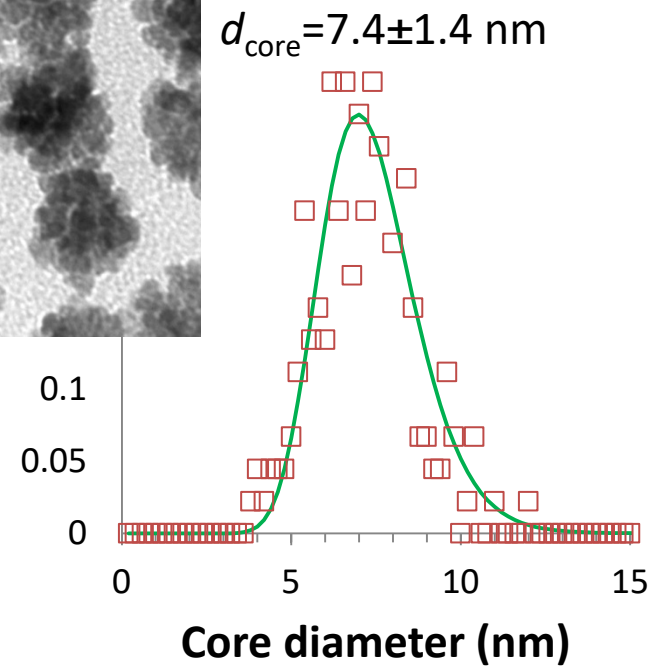
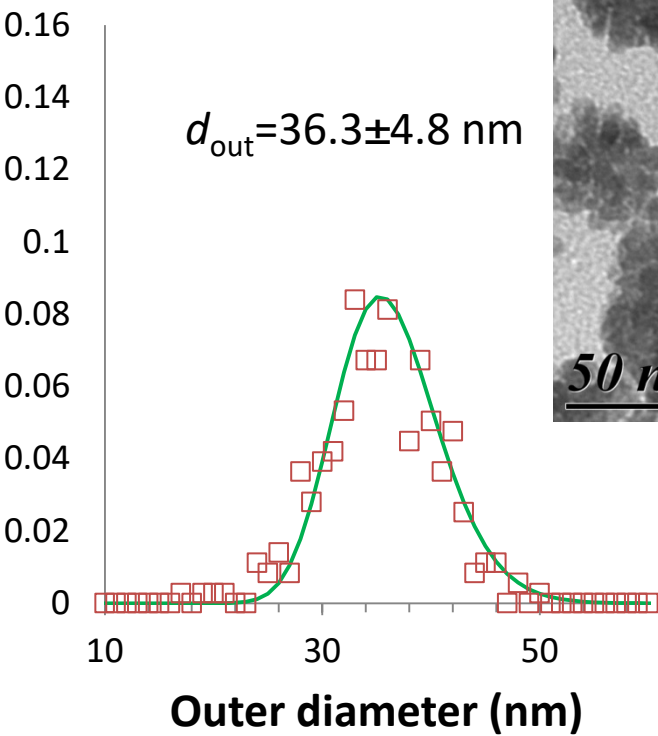
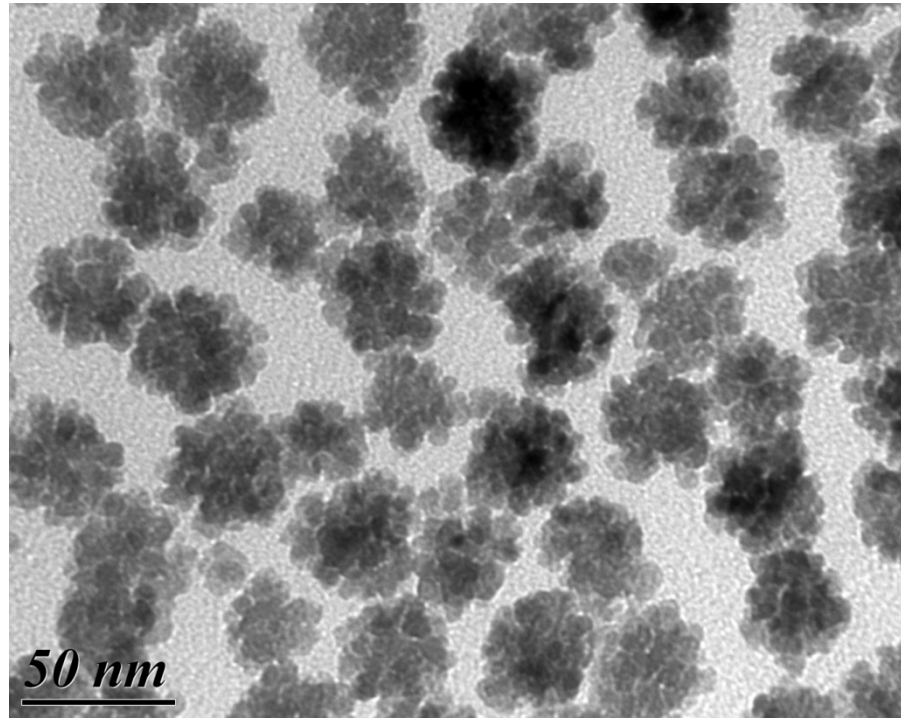
Example of medium size nanosphere sample: 25FF



Example of very large size nanosphere sample: 34FF

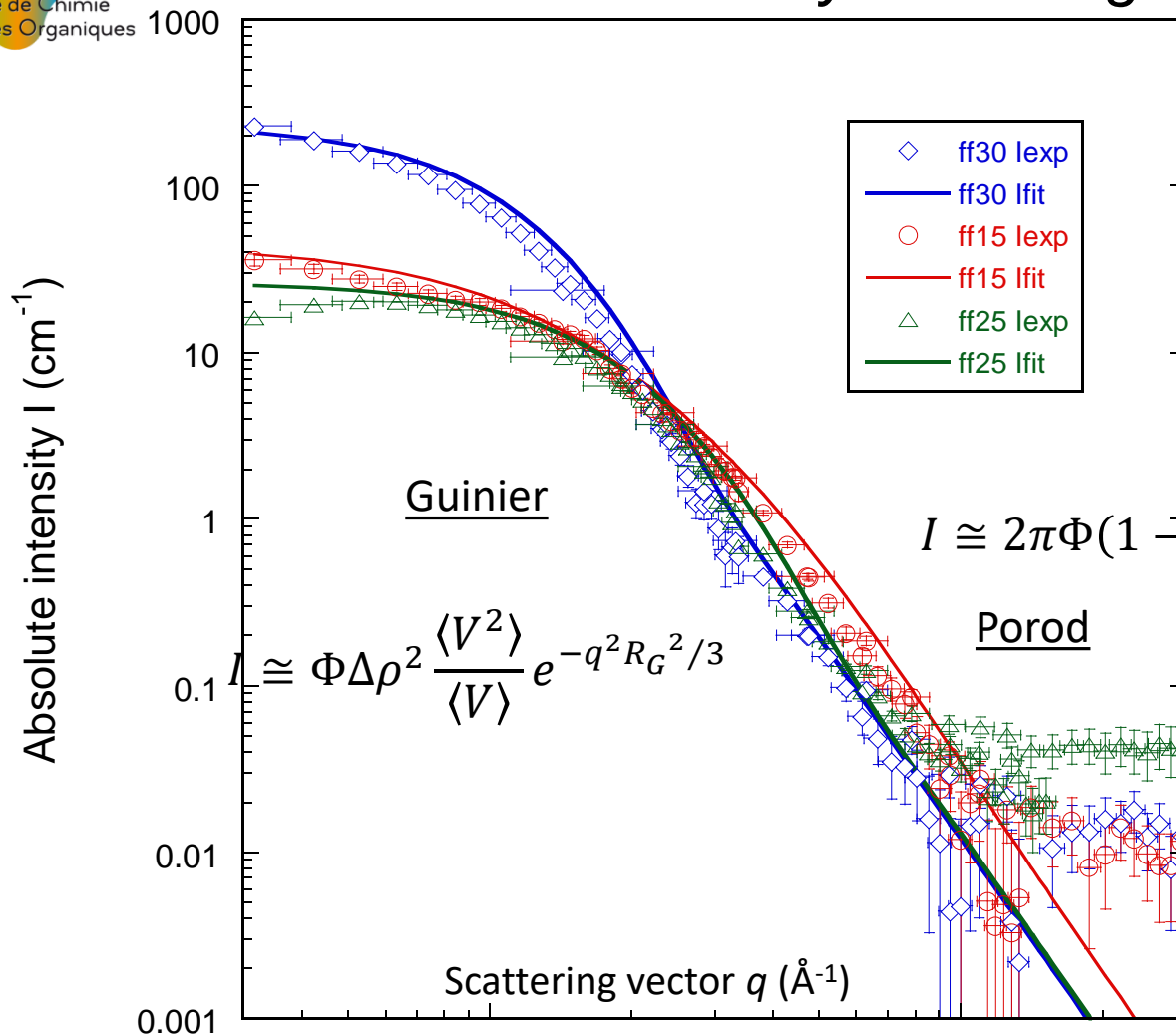


Example of nanoflower sample: 15FF



Particle form factors by small angle neutron scattering

PACE spectrometer
with Annie Brûlet



$$I \cong 2\pi\Phi(1 - \Phi)\Delta\rho^2 \left\langle \frac{S}{V} \right\rangle$$

$$I \cong \Phi\Delta\rho^2 \frac{\langle V^2 \rangle}{\langle V \rangle} e^{-q^2 R_G^2 / 3}$$

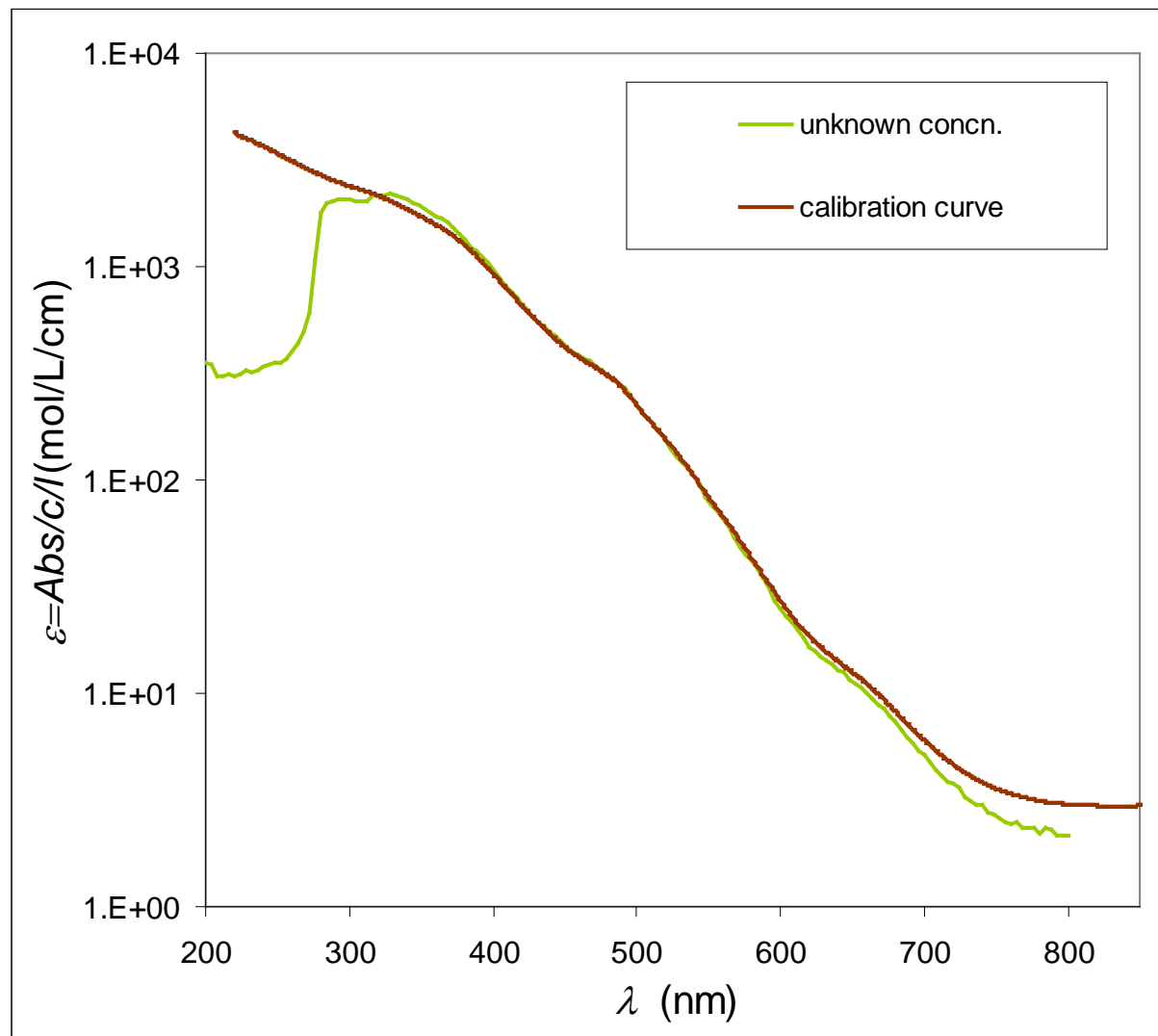
$$\left\langle \frac{S}{V} \right\rangle^{\text{the}} = 3 / \left(R_{\langle V^2 \rangle / \langle V \rangle} \right)$$

	0.01	R_G (nm)	$R_{\langle V^2 \rangle / \langle V \rangle}$ (nm)	R_{TEM} (nm)	S_{spe} (m ² /g)	$S_{\text{spe}}^{\text{the}}$
30ff:		18.9	18.1±3.9	23.5 ± 4.2	31.7	33.1
25ff:		10.5	10.4±2.3	7.1 ± 1.6	52.6	57.7
15ff:		19	10.6±3.9	17.5 ± 2.4	89.9	56.6

Experimental measurement of all properties (m_S , Δn_S , SHP, $P(q)$, r_1 , r_2 ...) require the total iron concentration.

Available methods are:

- Atomic Absorption Spectroscopy (or ICP): sensitive ($10^{-5}M$) but $\pm 5\%$
- Redox titration (Charlot) by $K_2Cr_2O_7/SnCl_2$: precise ($\pm 1\%$) but not sensitive ($10^{-1}M$)
- Whole UV-Vis curve: precise ($\pm 1\%$) and sensitive ($10^{-4}M$)
- “Ferrozine assay”: highly sensitive ($10^{-7}M$) from OD_{562nm} according to *Small* 5 (2009) 256



UV-Vis extinction is independent on MNP size distribution

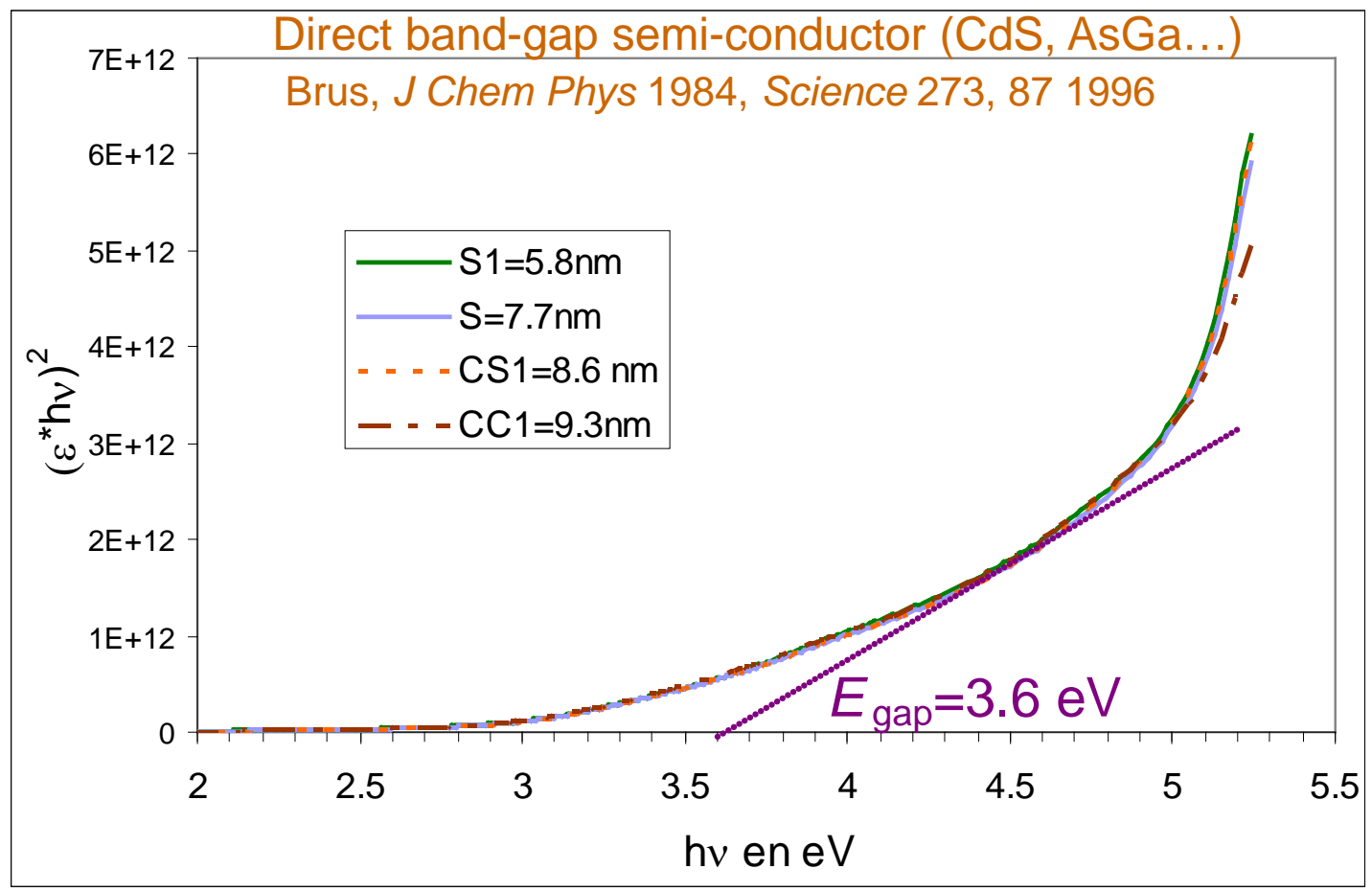
Constant →

UV-Vis molar extinction coefficient →

$$\epsilon = \frac{c(h\nu - E_g^{bulk})^{1/2}}{h\nu}$$

3,6 eV for Fe₂O₃
Shannon, *J. Phys. Chem. Ref. Data* 2002

A. Abou-Hassan
UPMC thesis 2009
2010 Best thesis
prize in physical
chemistry
(SFP/SCF)
→ no size-dependent
gap in the case of γ -
Fe₂O₃
(the exciton
diffusion length is
presumably much
smaller than the size
of the USPIOs, thus no
confinement)



- Since 30 years, the aqueous route (alkaline coprecipitation) leads to a quantitative production ($\sim 100\text{g}$ dry $\gamma\text{-Fe}_2\text{O}_3$) of magnetic nanoparticles that can be further functionalized (organic solvent, polymer matrix, biological coatings...). Today the up-scalable method is polyol route.
- Samples have inherent size / shape polydispersity, which can be a drawback for long-range ordering (e.g. colloidal or liquid crystals) but, according to Curie's principle, this is a great advantage to get large physical properties!
- The outlooks for biological applications (MRI contrast agents and magnetic hyperthermia) might be to play on the anisotropy constant K_a (shape anisotropy or other "irregularity") rather than on the size only, because of the difficulty to stabilize large MNPs (e.g. $\text{Ø} > 20\text{nm}$) in biological media (ionic strength and flocculent proteins).