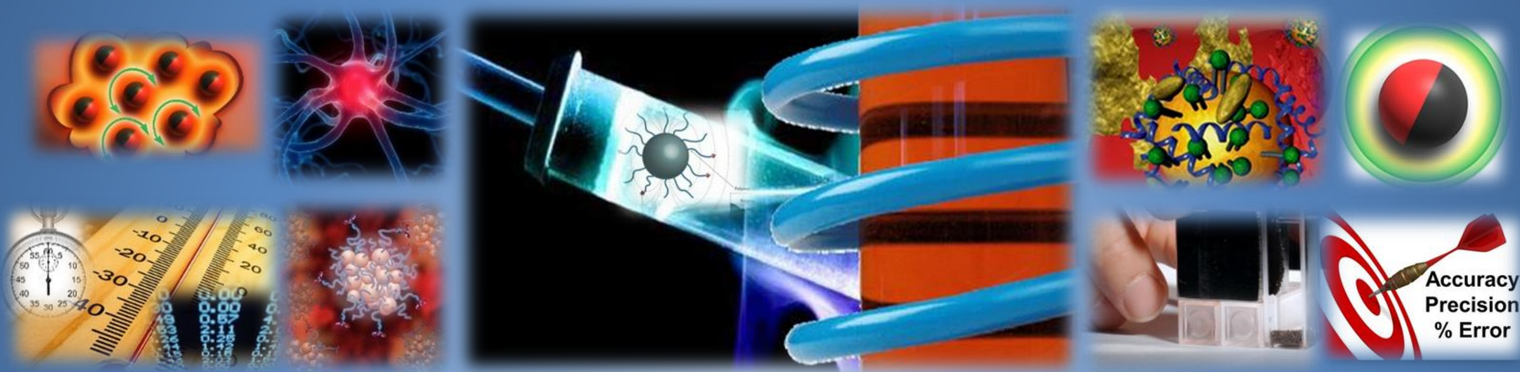
Magnetic Nanohybrids for Cancer Therapy



Hints and Tips in Magnetic Hyperthermia Measurements

MaNaCa Weekly Seminars

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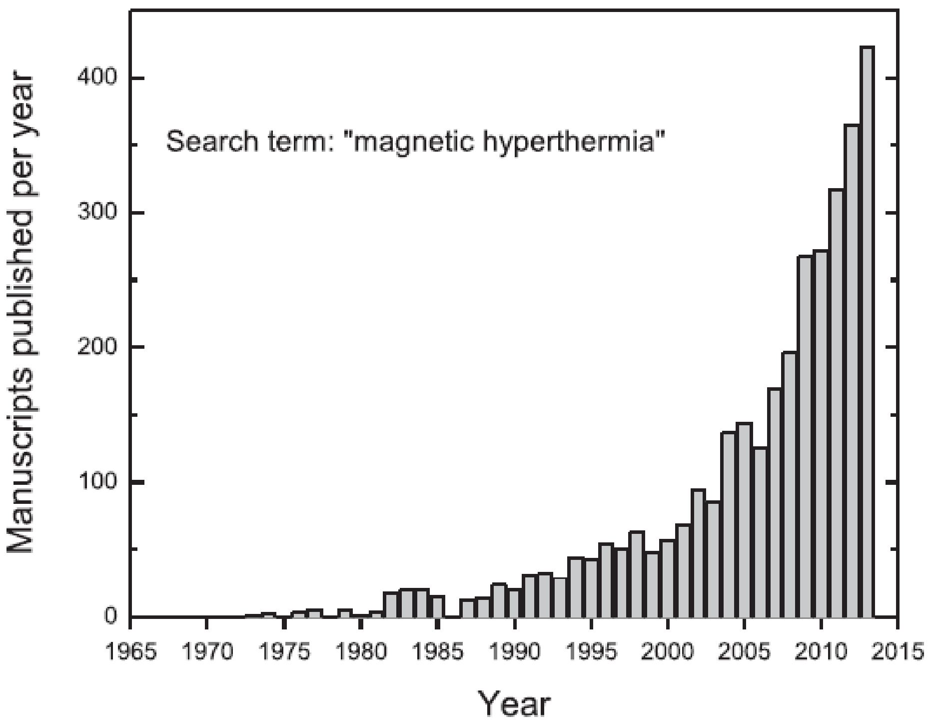
Contents

Magnetic hyperthermia experiments today

- It is important that the MNPs display the best possible heating properties and generate as much heat as possible for a given AMF strength and frequency.
- A critical factor here and one that is not always taken into account, is that most measurements are performed under non-adiabatic experimental conditions.
- It is also important to be able to directly compare the results reported by different research teams, even when they are using substantially different measurement apparatus and experimental conditions.

MH has never been so much in the spotlight as now.

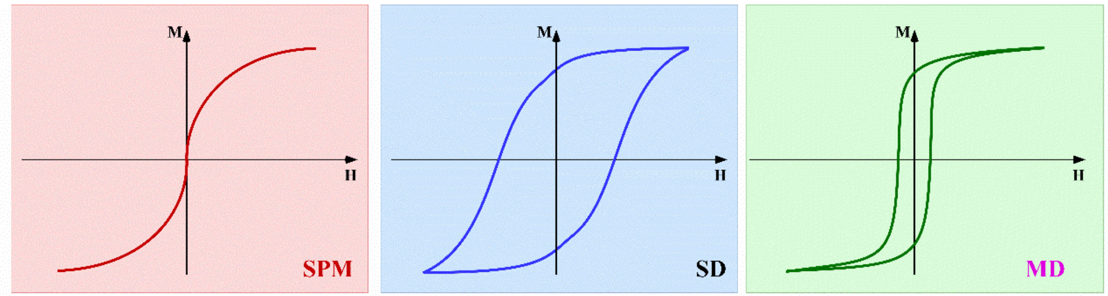


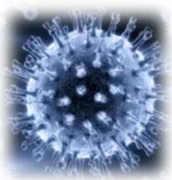
Perigo, Elio Alberto, et al. "Fundamentals and advances in magnetic hyperthermia." *Applied Physics Reviews* 2.4 (2015): 041302.

There is a chronic need for a more standardised approach.

Magnetic Nanoparticles

Size, coercivity and magnetic domains of magnetic nanoparticles

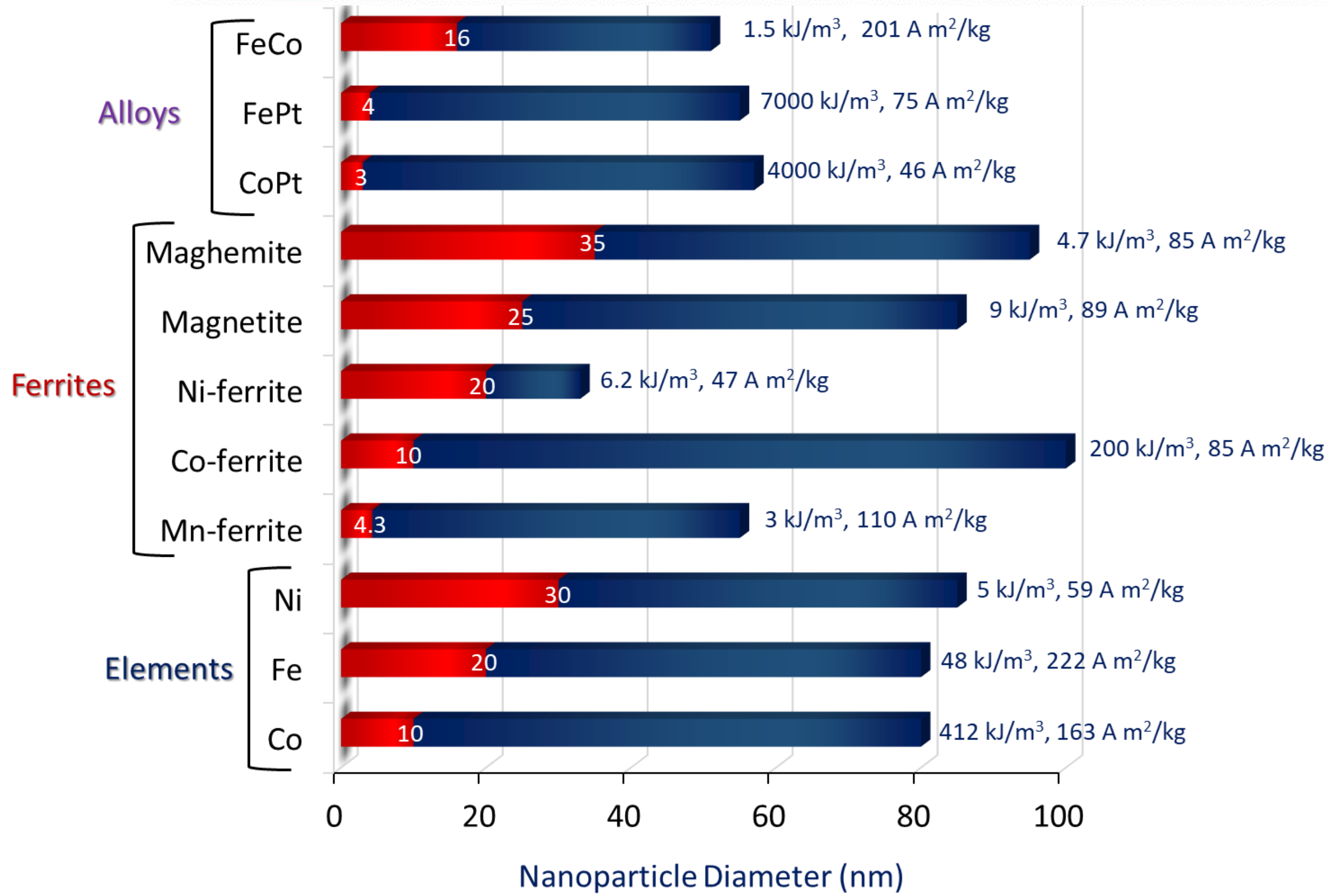




Size ↓

↑ % surface atoms

Surface & Interface Magnetism

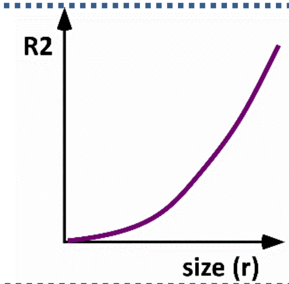


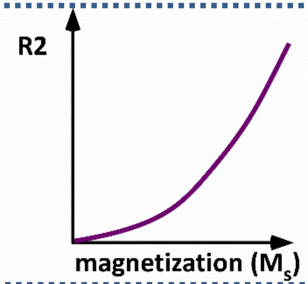
Magnetic Nanoparticles

MNPs properties affect specific indexes

MRI Relaxivity: R2

$$R2=\frac{1}{T2}=\frac{256\pi^2\gamma^2}{405}M_s^2V\frac{r^2}{D(1+\frac{L}{r})}$$

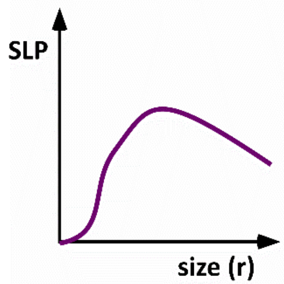


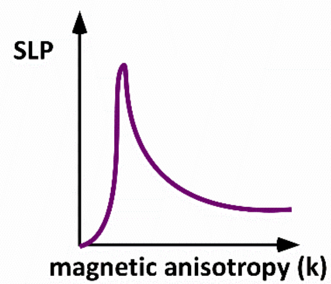


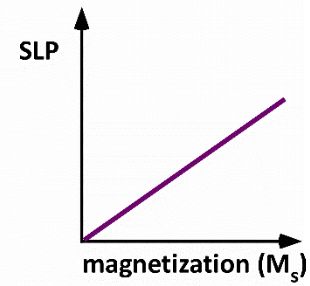
Specific Loss Power: SLP

$$SLP=\frac{\mu_o HM_s}{2\rho}L(\xi)\frac{\omega^2}{1+(\omega\tau)^2}$$

$$\frac{1}{\tau}=\frac{1}{\tau_o e^{KV/kT}}+\frac{kT}{3nV}$$

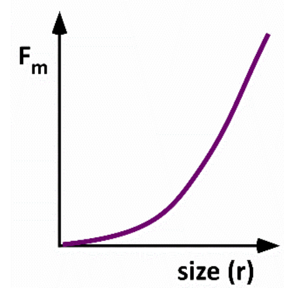


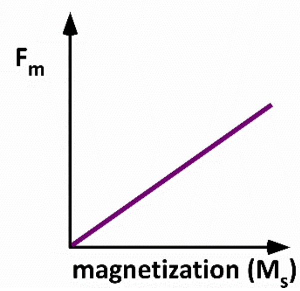




Translational Attractive Force: F_m

$$F_m=\sum m_s\cdot\nabla B$$





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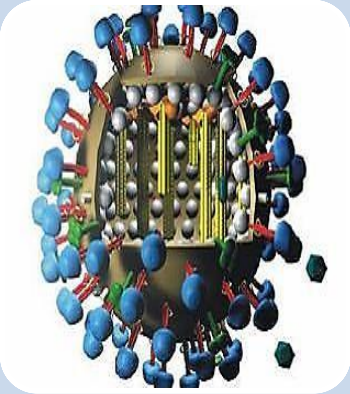


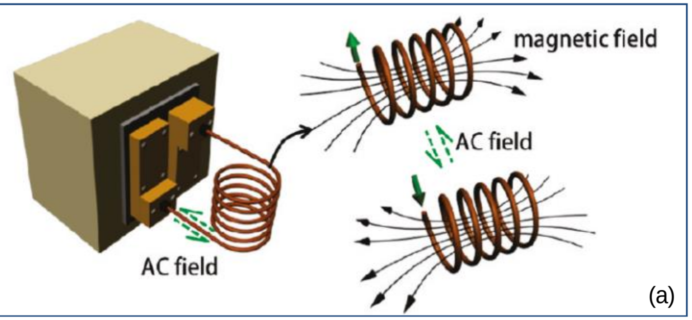
Introduction

- Biomedical Applicability
- Magnetic Nanoparticles
- Features & Properties

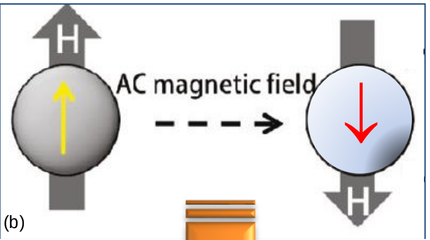
Magnetic Hyperthermia

- Setup Calibration & Specifications
- Uncertainty Evaluation
- Heating Efficiency

Heating via Magnetic Losses
Magnetic Hyperthermia



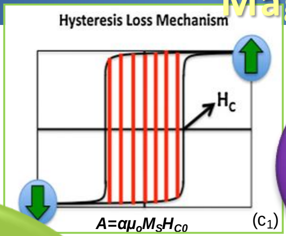
different processes of magnetization reversal



different manners on

the applied magnetic AC: *field amplitude and frequency*.

the structure: *mean size, width of size distribution, particle shape and crystallinity.*



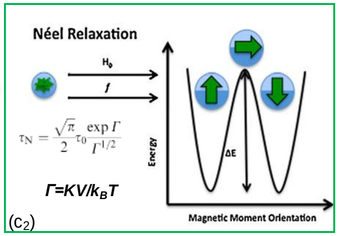
Induced Heating Power

$\sim H^2 f^2 D^2$

Hysteresis losses

~2 K

Ferromagnetic particles



Magnetic losses

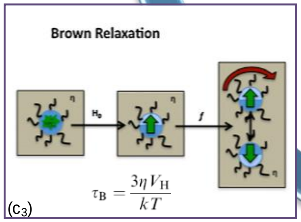
Viscous losses

$\sim 2\pi\mu_0 M_R H V$

Néel relaxation

$\tau_N=\tau_0 e^{KV/kT}$

Superparamagnetic particles



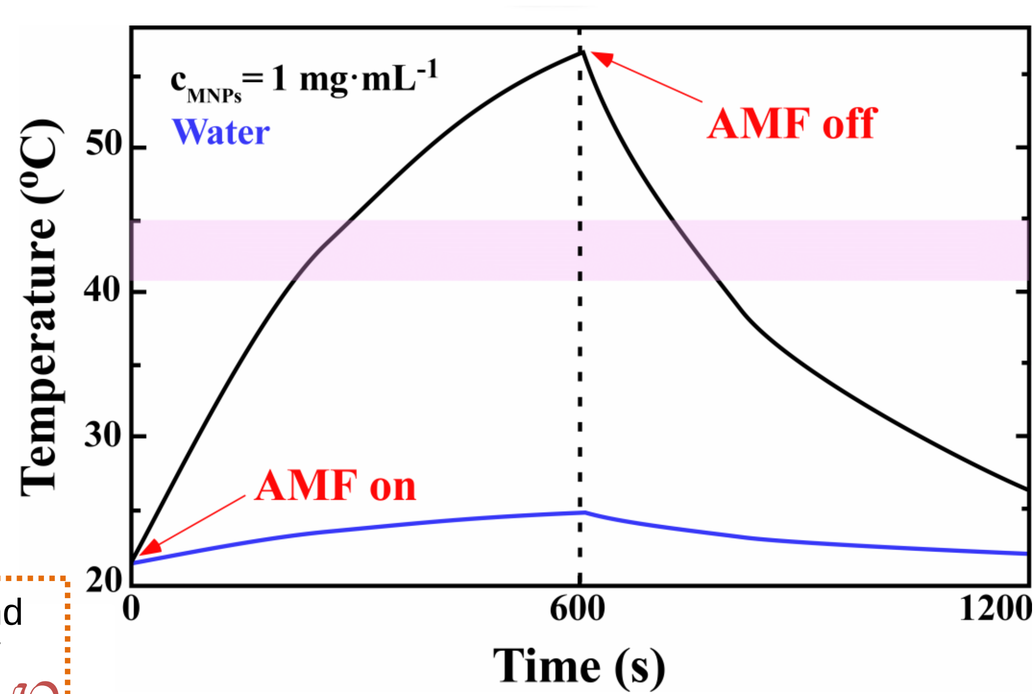
Brown relaxation

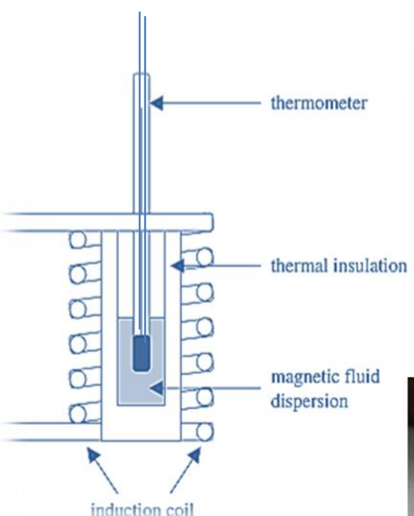
$\tau_B=4\pi n r_h^3/kT$

Effective relaxation

$\tau_{eff}=\tau_N\tau_B/(\tau_N+\tau_B)$

Frequencies: 50kHz - 800kHz
Field Strength up to 80mT (64kA/m)





Tips

Powder: is weighed and dispersed in solution/ ferrofluid

+

Ultrasonic bath

+

Remember to start when you are at the steady state

Hints

$Time_{exp}$: 10min 10min

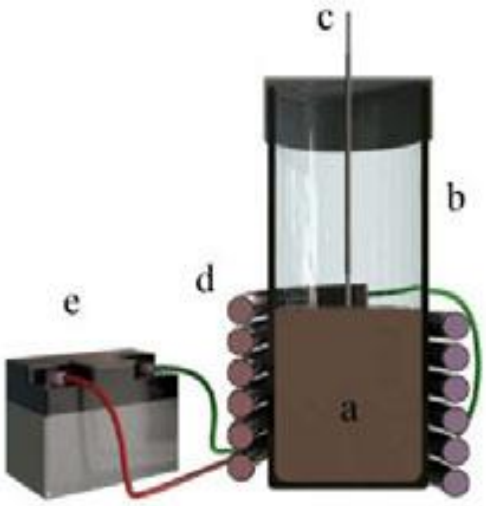
Specific Loss Power

$$SLP = \frac{W}{m_{magn}} = \frac{\Delta Q}{\Delta t \cdot m_{magn}} = c\,\frac{m_f}{m_{magn}}\,\frac{\Delta T}{\Delta t}$$

A. Chalkidou et al., J. Magn. Magn. Mat. ***323*** *775-780 (2011) .*

M. Kallumadil et al. JMMM ***321*** *1509 -1513 (2009).*

Differences between laboratories

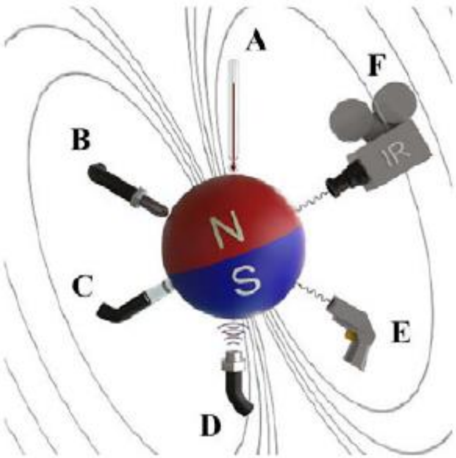


Schematic representation of a simple non-adiabatic measurement set-up with a) ferrofluid sample; b) sample holder; c) temperature sensor; d) coil system; and e) power supply.

Frequency range: 0.1-1 MHz

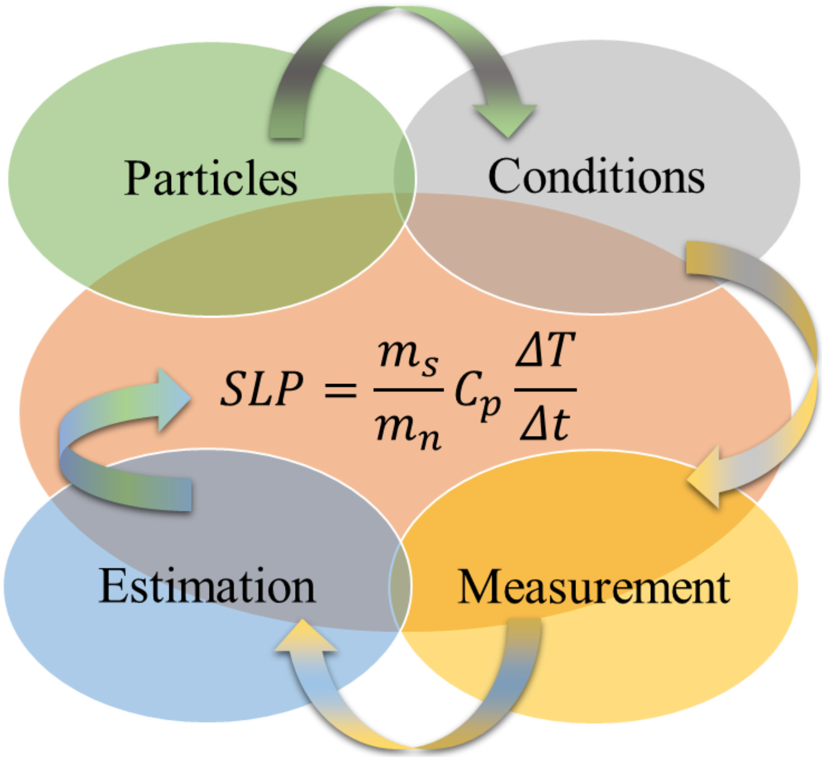
Coils: 2-70 loops

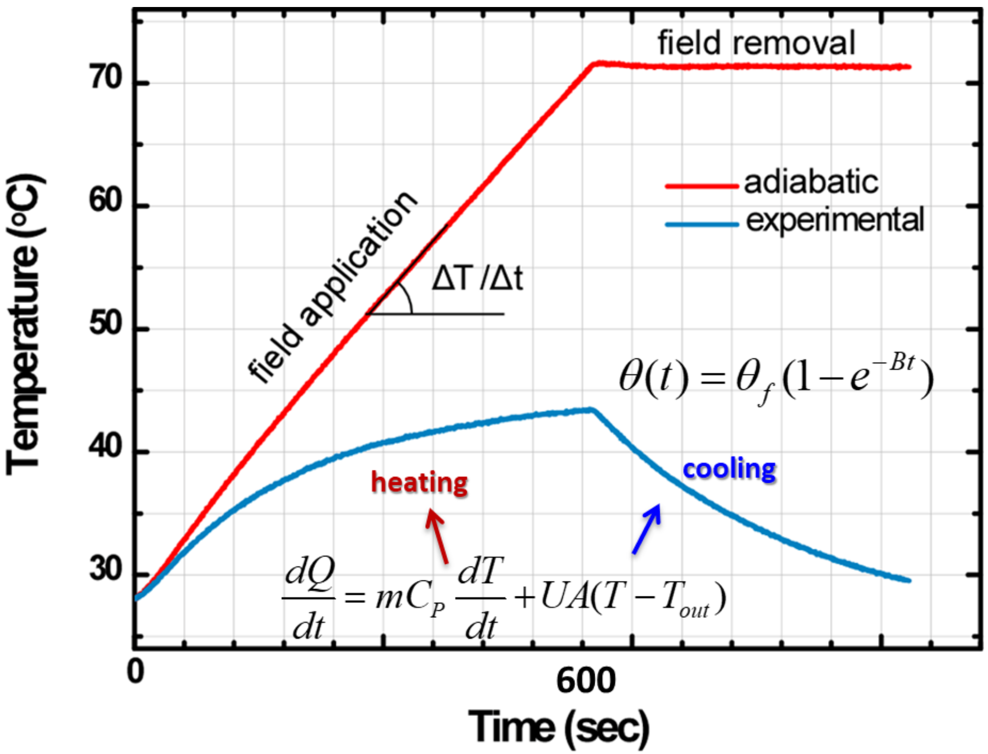
Field Strength up to 64 kA/m



Schematic representation of used calorimetric temperature sensors. Probes which require contact with the sample are A) Alcohol thermometer, B) Thermocouple, C) Fiber-optic cable, and D) Ultrasonic sensor. Contactless sensors are E) Pyrometer and F) IR camera

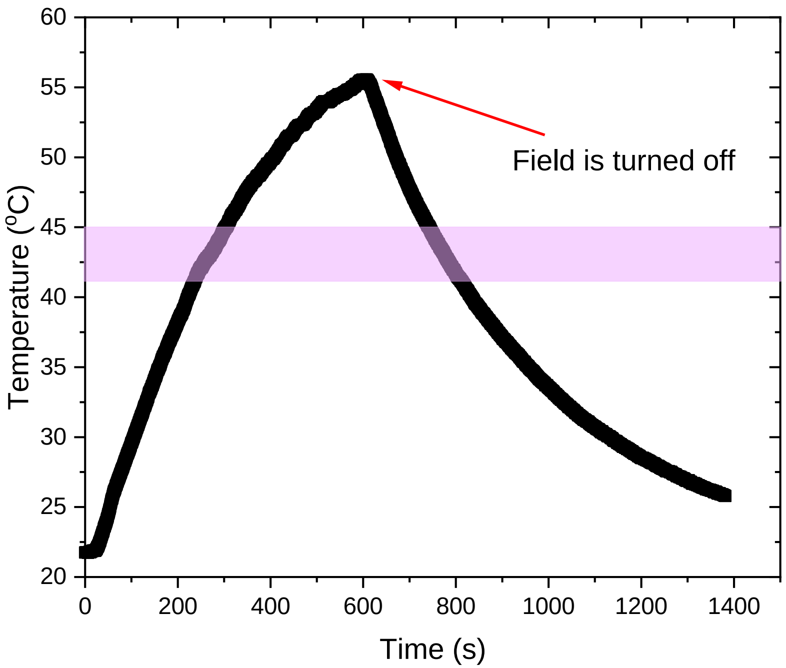
What affects heating efficiency of MNPs?

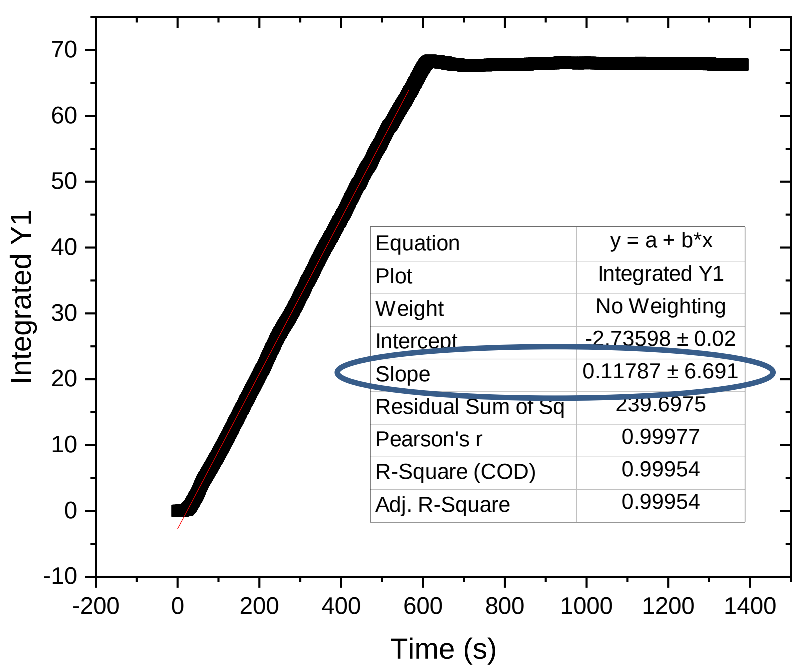




Modified Law of Cooling

Magnetite nanoparticles of 40 nm
Concentration: 2mg/mL
Frequency: 765 kHz
Magnetic Field Amplitude: 30 mT

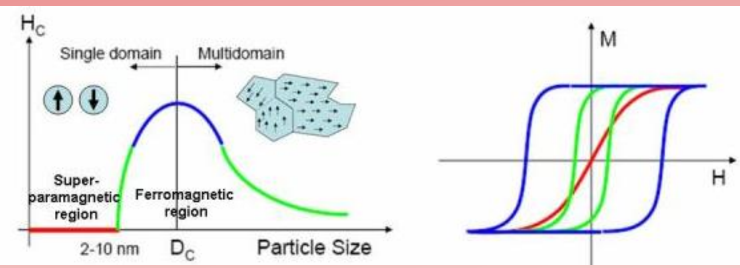




$$\frac{dQ}{dt} = mC_P \frac{dT}{dt} + UA(T - T_{out})$$

What affects heating efficiency of MNPs?

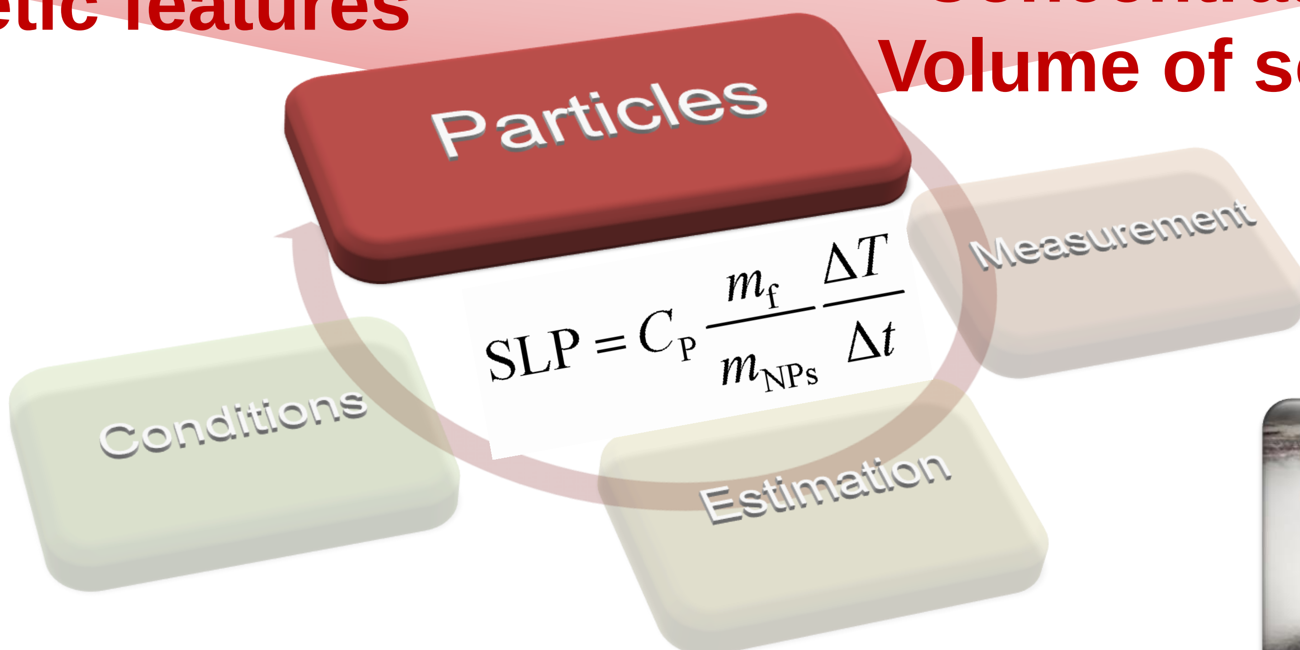
SPM or FM MNPs in the region of 20 nm



Solution Volume ~ 1mL
Varying concentration 0.1-10 mg/mL

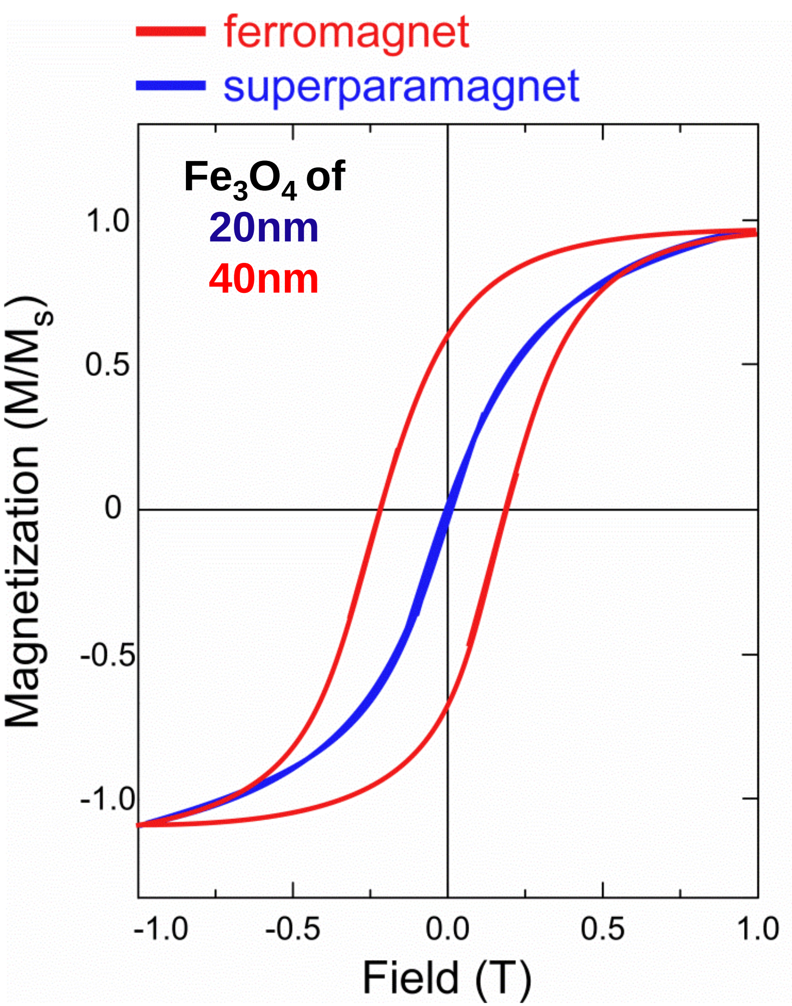
Magnetic features

Concentration & Volume of solution

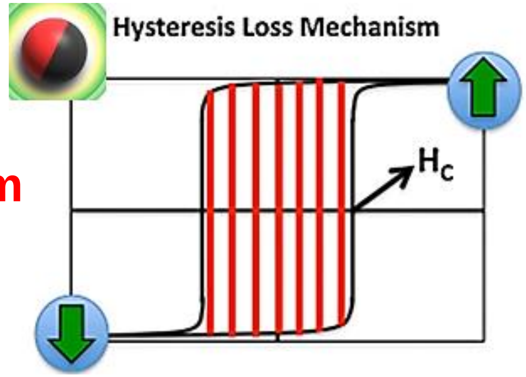


$$SLP = C_P \frac{m_f}{m_{NPs}} \frac{\Delta T}{\Delta t}$$

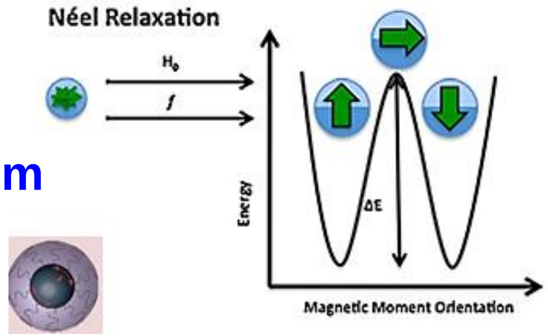
Particles- Magnetic Features



Ferromagnetism

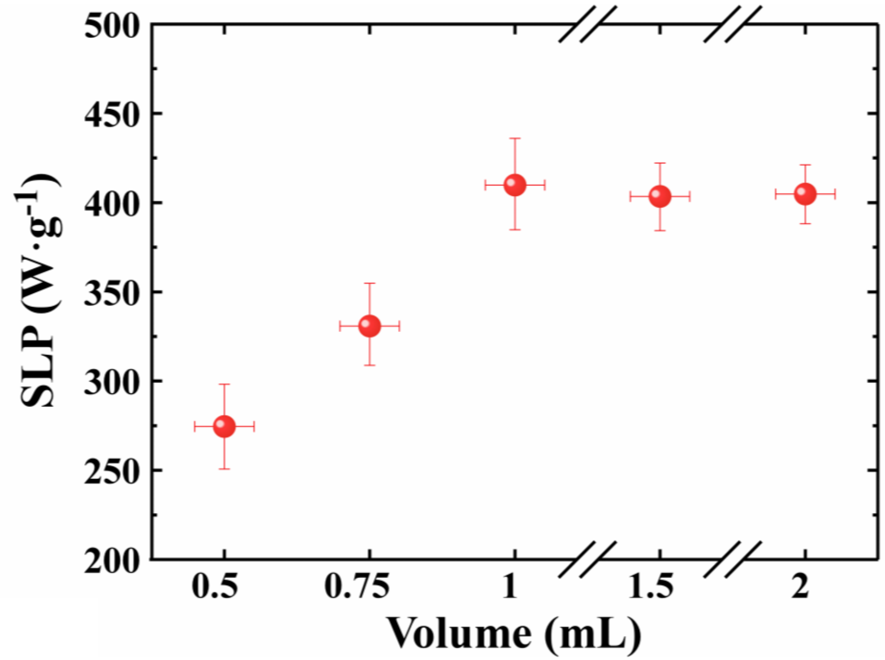


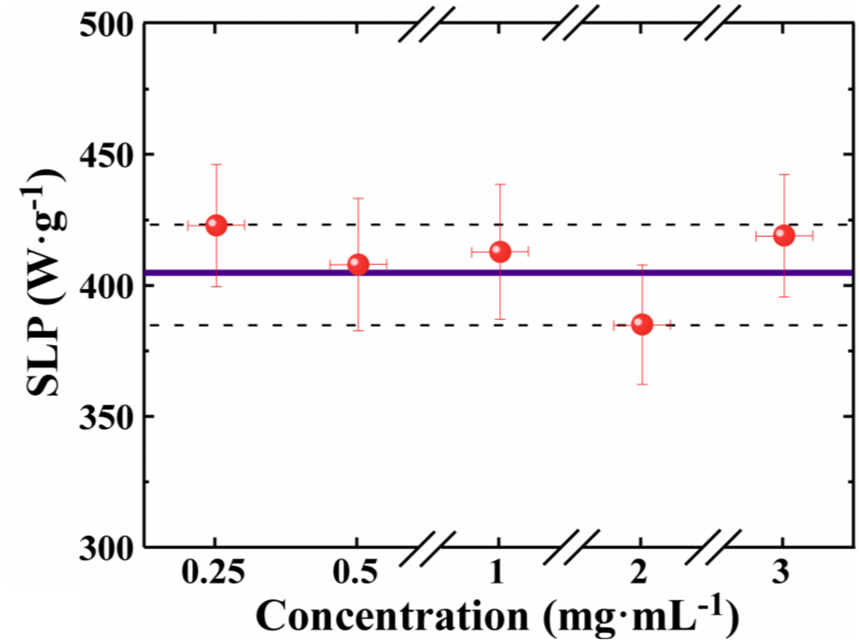
Superparamagnetism



Particles - Concentration & Volume of solution

f = 765 kHz
H = 20 kA/m





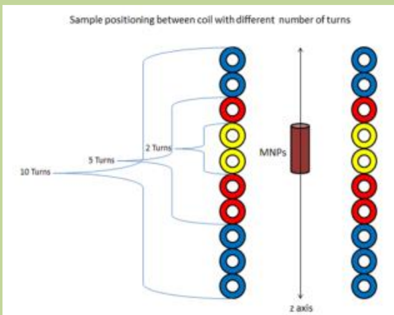
0.5 mL ≤ V ≤ 1.0 mL → Significant SLP dependence

1.0 mL ≤ V → SLP stabilization

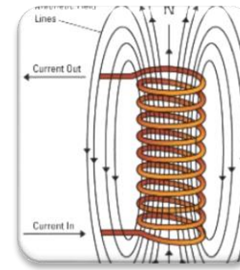
0.25 mg/mL ≤ c ≤ 3.0 mg/mL → Nearly constant SLP value

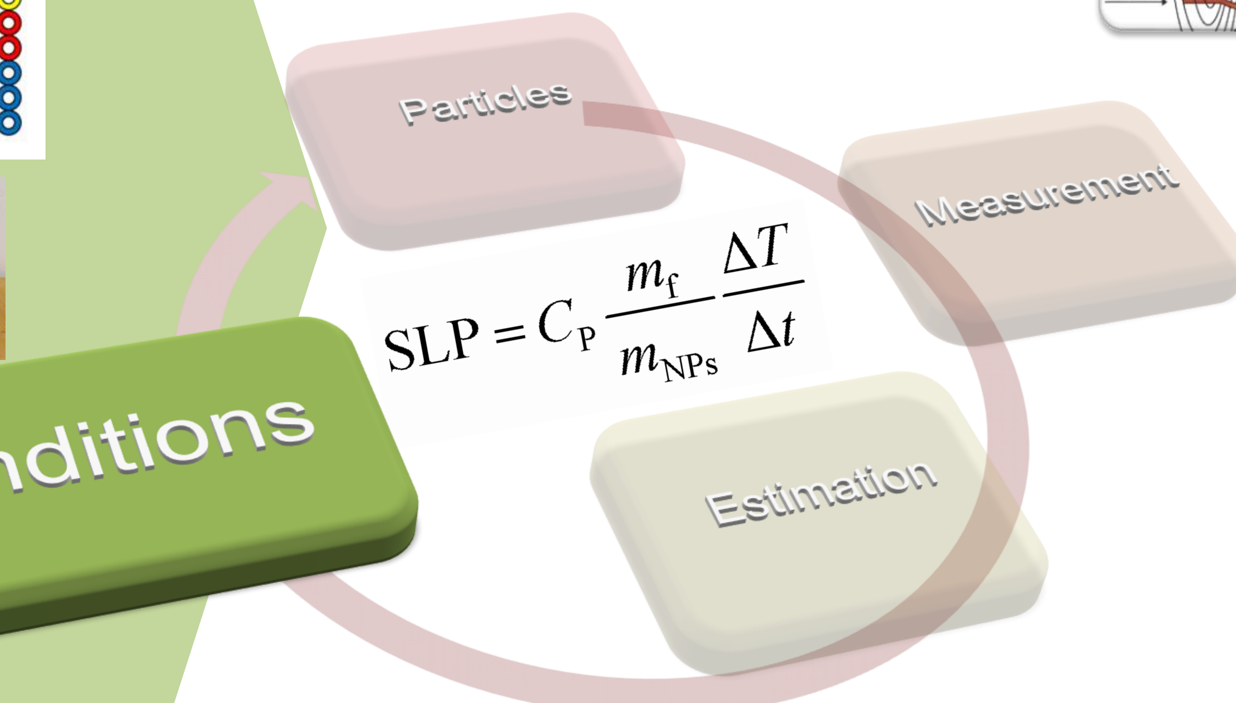
What affects heating efficiency of MNPs?

AC Frequency: 0.1-1 MHz
AMF Amplitude ≤ 50 kA/m
Coils:



Magnetic field homogeneity
Frequency & Amplitude





$$\mathrm{SLP} = C_{\mathrm{P}} \frac{m_{\mathrm{f}}}{m_{\mathrm{NPs}}} \frac{\Delta T}{\Delta t}$$

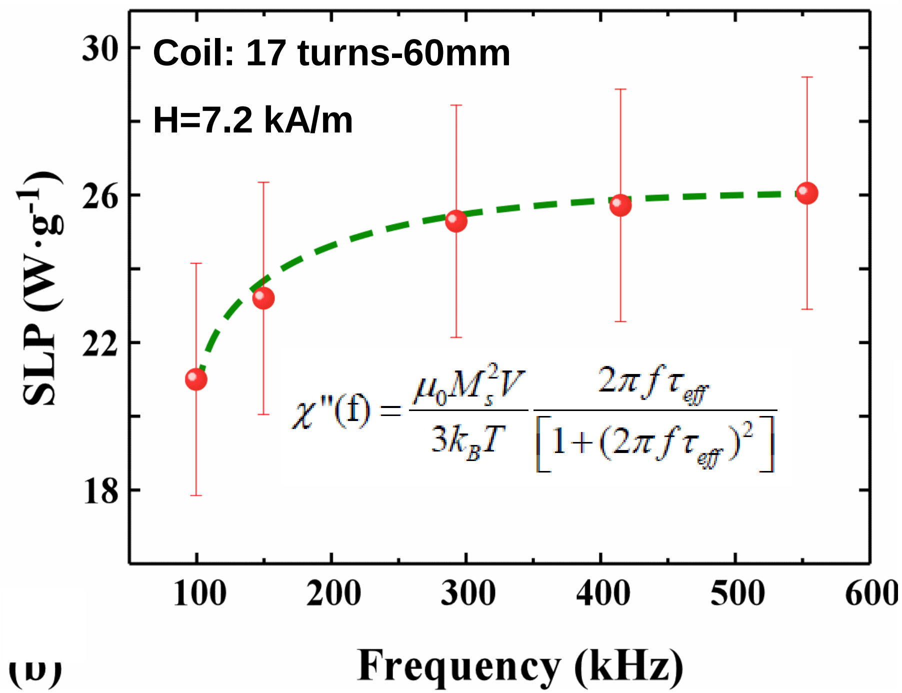
Conditions - AMF frequency & amplitude dependence

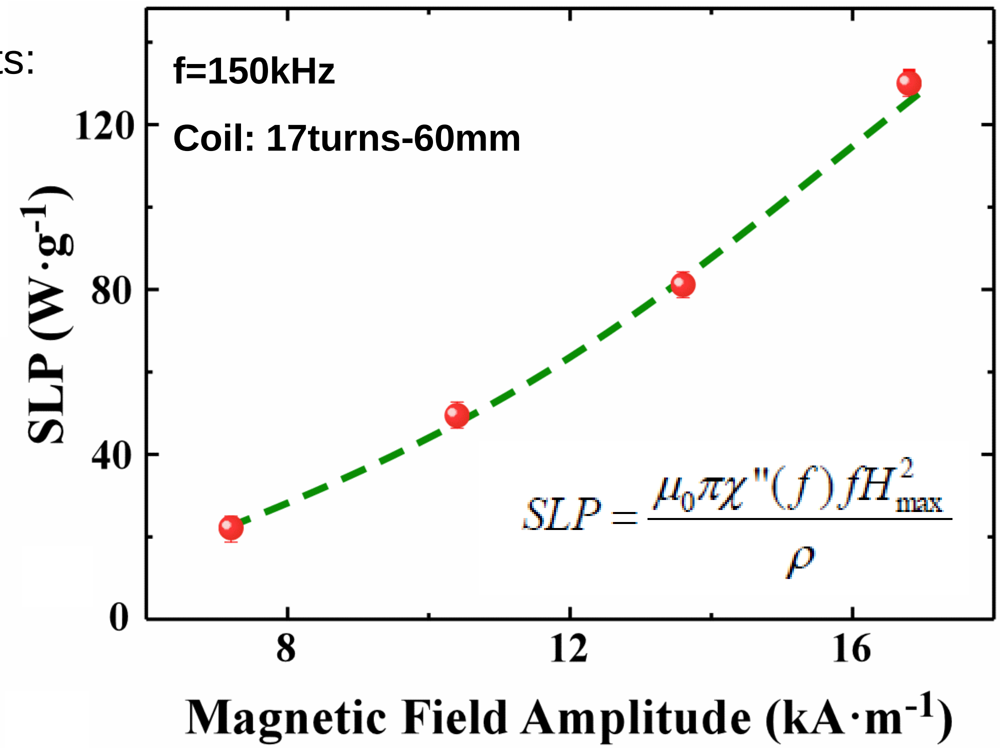
Superparamagnetic particles

What Linear Response Theory (LRT)* suggests:

$$SLP \sim H^2$$

$$SLP \sim f^2/(1+f^2)$$

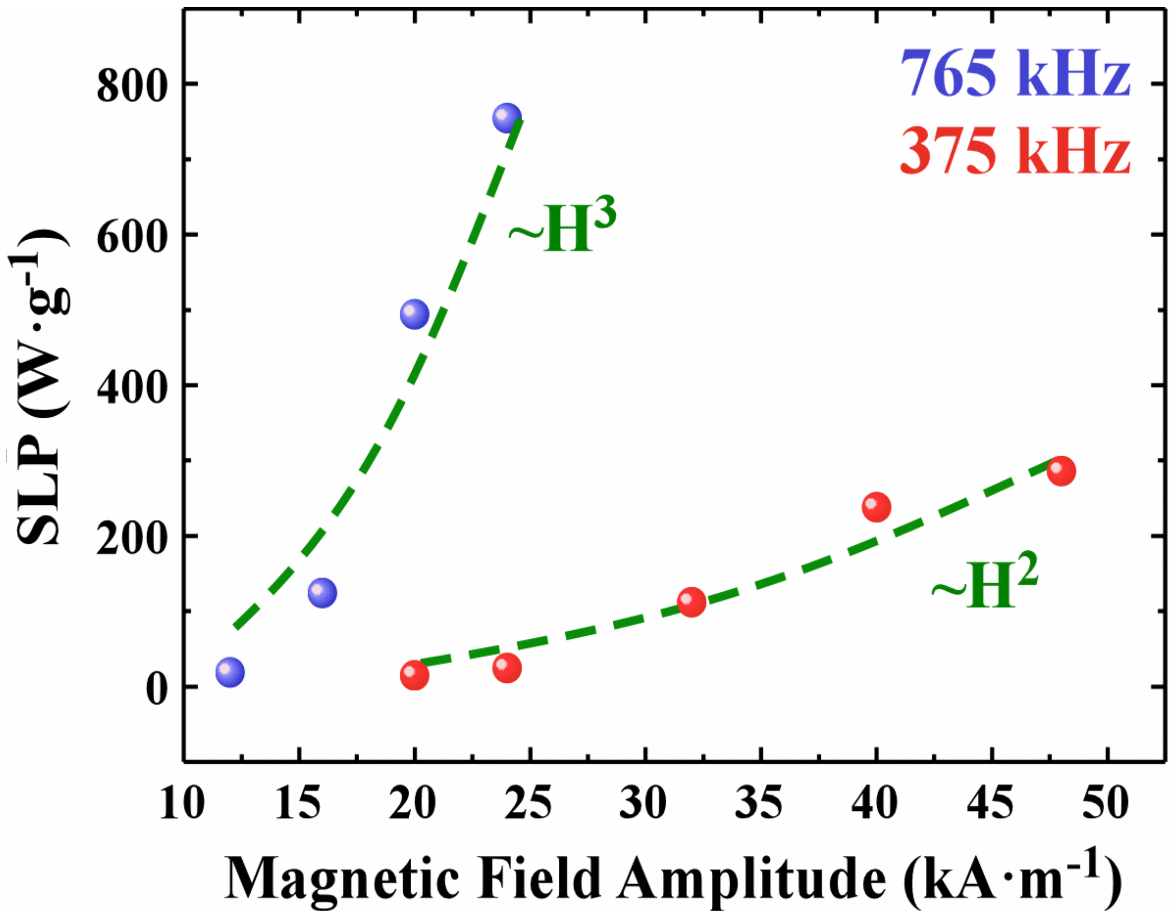




*R. Rosensweig Heating magnetic fluid with alternating magnetic field. J. Magn. Magn. Mater. 252, 370–374 (2002)

Conditions - AMF frequency & amplitude dependence

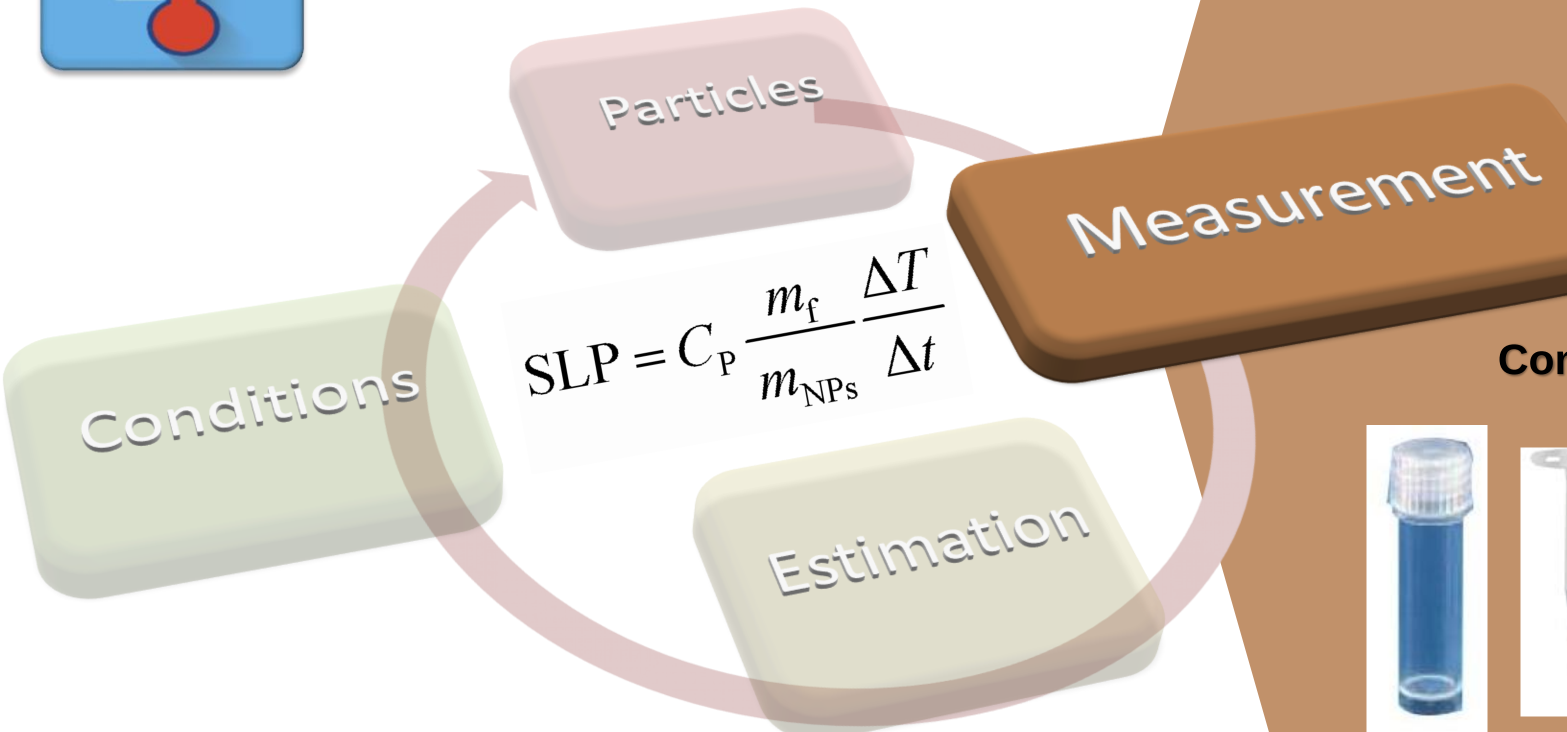
Ferromagnetic particles



Linear Response Theory is not applicable for MNPs with low anisotropy energies where the magnetization is saturated at low applied fields.

What affects heating efficiency of MNPs?

Temperature & Heat exchanges



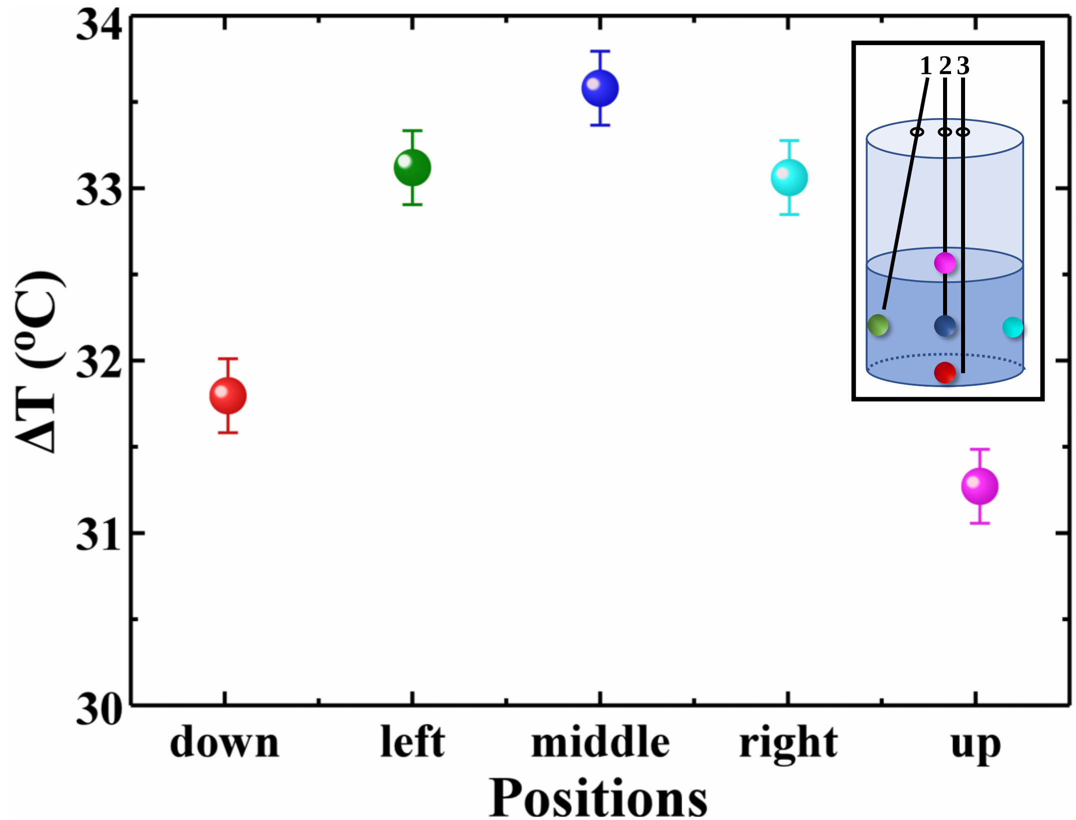
$$\mathrm{SLP} = C_{\mathrm{P}} \frac{m_{\mathrm{f}}}{m_{\mathrm{NPs}}} \frac{\Delta T}{\Delta t}$$

Temperature Recording

Common Vials:

Measurement - Temperature recording

f = 525 kHz, H = 16.8 kA/m, Coil: 9/50



Why is temperature distribution so important?

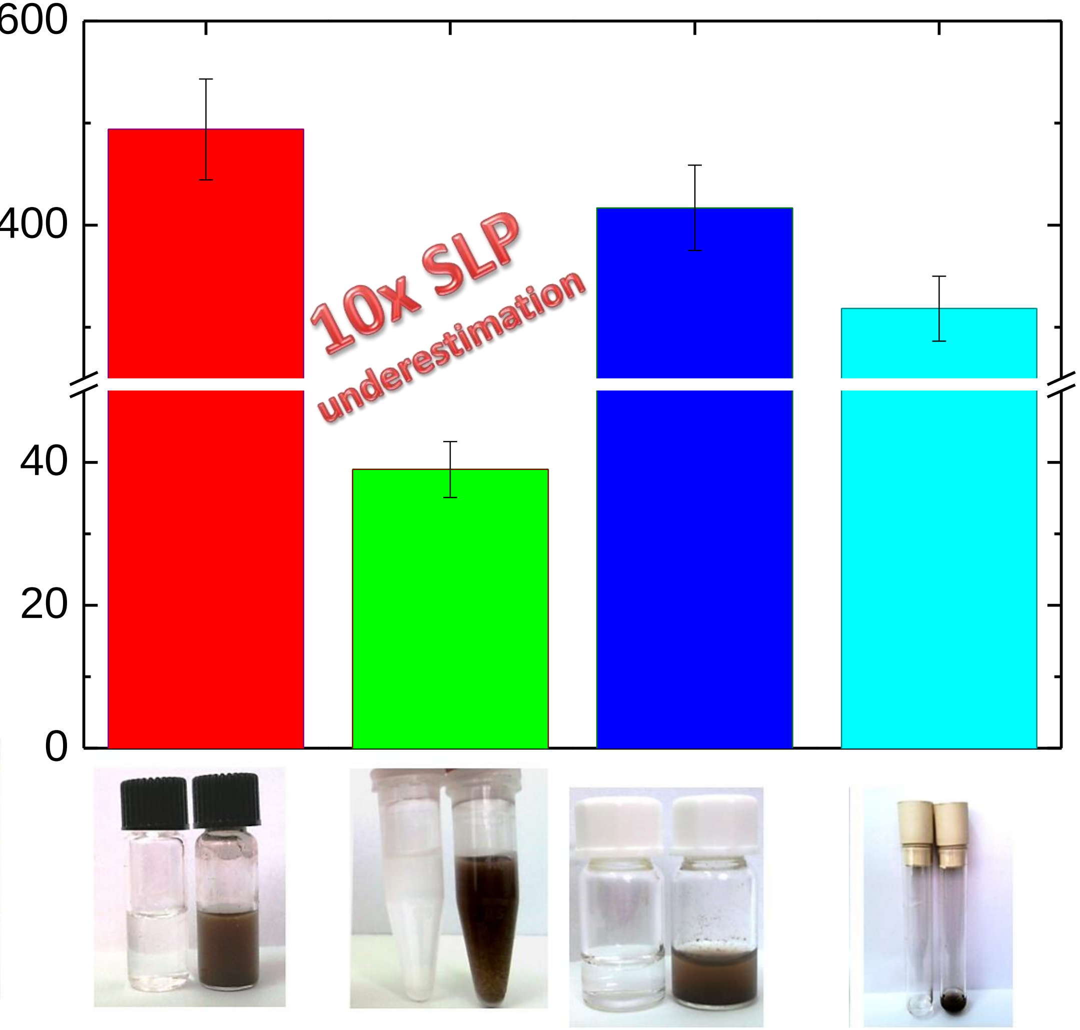
- Great importance in determining how successful the treatment is
- How much of the tumor is heated to therapeutic temperatures
- How much of the surrounding normal tissue is damaged by the heat

Vessel size and shape

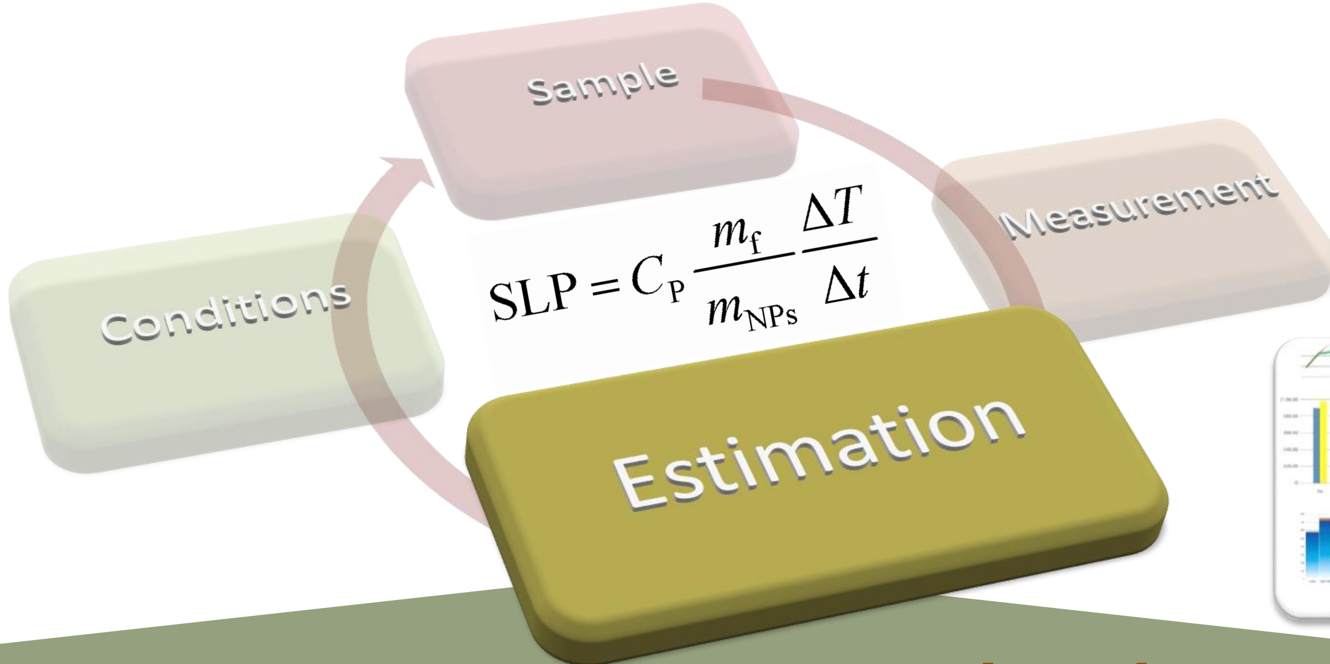
Two commonly used sample holders:

a plastic Eppendorf tube with a tapered bottom section

a glass flatbottomed cylindrical vial



What affects heating efficiency of MNPs?

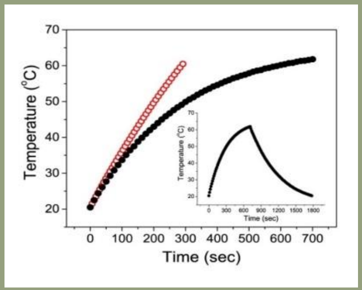


$$SLP = C_P \frac{m_f}{m_{NPs}} \frac{\Delta T}{\Delta t}$$

Experimental Errors

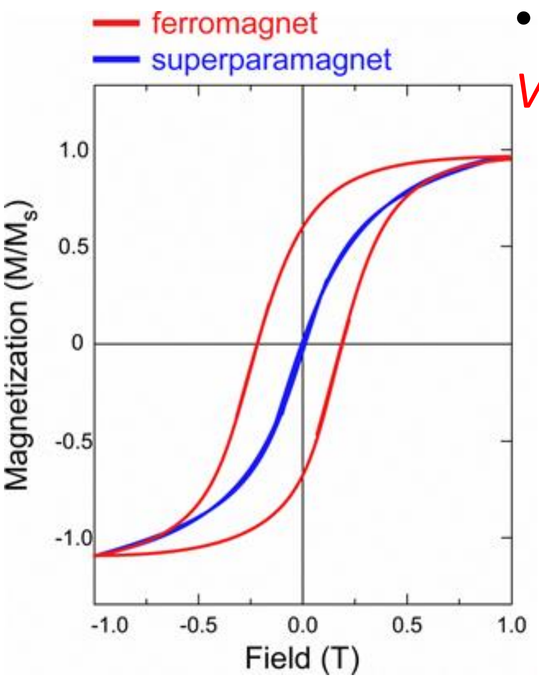
Estimation Procedure

Most commonly used method:



No experimental uncertainties are taken into account!

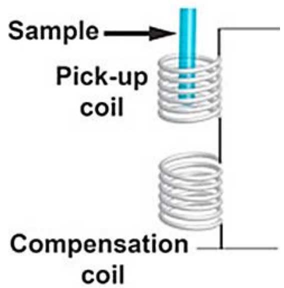
Magnetometry Method

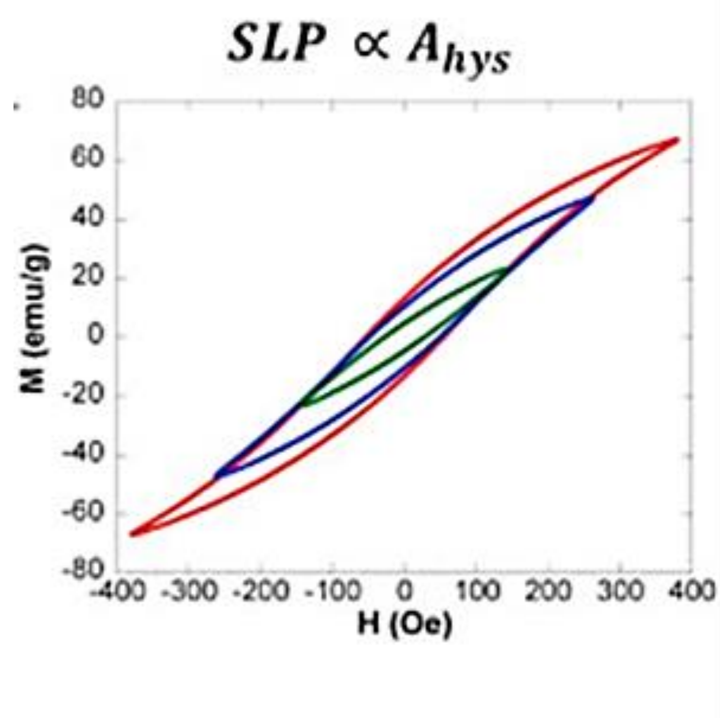


- *Hysteresis Loops*

Valid for ferro/ferri-magnetic hysteresis!

$$A = \int_{-H_{max}}^{+H_{max}} \mu_0 M(H)\, dH \qquad SLP = Af$$





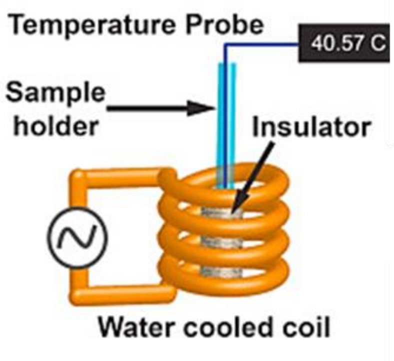
- *AC Susceptibility*

Valid for superparamagnetic particles

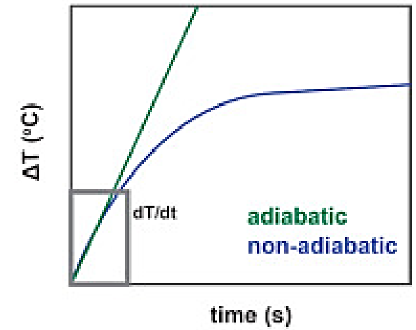
$$\chi''(f) = \frac{\mu_0 M_s^2 V}{3 k_B T} \frac{2\pi f \tau_{eff}}{\left[1 + (2\pi f \tau_{eff})^2\right]}$$

$$SLP = \frac{\mu_0 \pi \chi''(f) f H_{max}^2}{\rho}$$

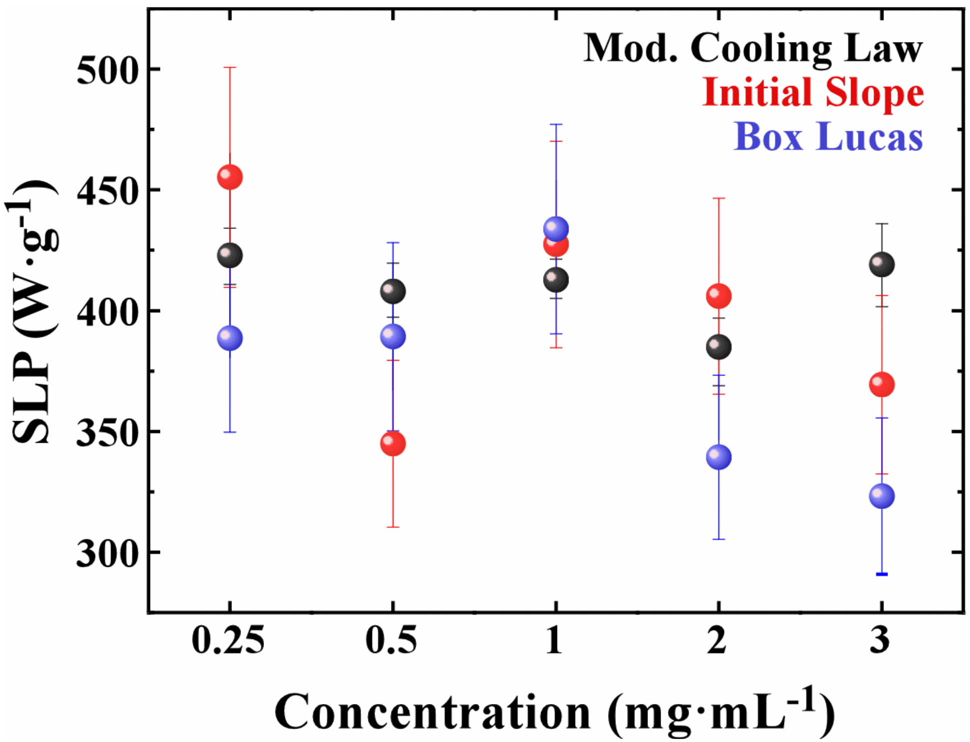
Calorimetric Method



$$SLP \propto \left.\frac{dT}{dt}\right|_{t=0}$$



Initial slope method: $SLP = \frac{C}{m_{MNP}} \cdot \left.\frac{dT}{dt}\right|_{t \to 0}$



Modified Law of Cooling

$$SLP = C_p \frac{m_f}{m_{MNPs}} \frac{dT_{eff}}{dt}$$

Box-Lucas method: $SLP_{Box-Lucas} = \frac{\alpha \lambda C_p}{m_{MNPs}}$

in the linear-loss regime the heating curve should follow a Box–Lucas equation $\Delta T = \alpha(1 - e^{-\lambda t})$

Simeonidis, K., et al. "Fe-based nanoparticles as tunable magnetic particle hyperthermia agents." Journal of Applied Physics 114.10 (2013): 103904.
Wildeboer, R. R., P. Southern, and Q. A. Pankhurst. "On the reliable measurement of specific absorption rates and intrinsic loss parameters in magnetic hyperthermia materials." Journal of Physics D: Applied Physics 47.49 (2014): 495003.

Experimental Errors

We define SLP as a function of six independent variables, namely the density of solvent (d), the solution volume (V), the nanoparticles mass (m), the specific heat (C_p), the temperature variation (ΔT), and the time variation:

$$SLP = f(d, V, m, C_p, \Delta T, \Delta t)$$

Each of these variables is a source of an uncertainty δx (where x can be d, V, m, C_p, ΔT or Δt) for the estimation of SLP and in order to quantify the propagation of these uncertainties we introduced the following formula by using the root sum-of-the-squares approach.

The overall uncertainty of the SLP values can be given by:

$$\delta SLP = \delta f = \sqrt{\left(\frac{\partial f}{\partial d}\delta d\right)^2 + \left(\frac{\partial f}{\partial V}\delta V\right)^2 + \left(\frac{\partial f}{\partial m}\delta m\right)^2 + \left(\frac{\partial f}{\partial C_P}\delta C_P\right)^2 + \left(\frac{\partial f}{\partial \Delta T}\delta \Delta T\right)^2 + \left(\frac{\partial f}{\partial \Delta t}\delta \Delta t\right)^2}$$

where δSLP is the uncertainty of SLP

Uncertainty sources contribution to the final SLP uncertainty

Conditions

Particles

Measurement

Description	Uncertainty value (%)	Probability distribution	Divisor	Sensitivity factor	Standard uncertainty (%)
Parameters of the setup influencing the measurand quantity (SLP)					
Magnetic Field Amplitude	0.56	N	1.00	2.00	1.11
Frequency	0.33	N	1.00	1.00	0.33
Solution concentration	0.10	R	1.73	0.00	0.00
Solution volume	5.00	R	1.73	1.00	2.89
Measured values used in the calculation of the SLP					
Fiber position uncertainty (vertical)	6.67	R	1.73	0.76	2.93
Fiber position uncertainty (eccentric)	6.67	R	1.73	0.10	0.39
Mass density of the solution	0.10	N	1.00	1.00	0.10
Solution concentration	10.00	R	1.73	1.00	5.78
Specific heat capacity	0.03	N	1.00	1.00	0.03
Temperature	0.03	R	1.73	1.00	0.02
Time	0.04	R	1.73	1.00	0.02
Combined standard uncertainty		RSS			**7.20**
Expanded uncertainty (95% confidence interval)					**14.40**

Makridis, A., et al. "A standardisation protocol for accurate evaluation of specific loss power in magnetic hyperthermia." *Journal of Physics D: Applied Physics* 52.25 (2019): 255001.

Uncertainty sources contribution to the final SLP uncertainty

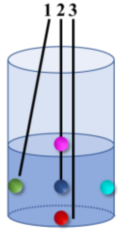
Concentration → < 9 %

Solution Volume → < 33% for 0.5-1 mL
Stable for 1-3 mL

Magnetic Field Amplitude

Magnetic Field homogeneity

→ *Depends on MNP type*
SPM: <12%
$SLP \sim H^2 \sim f^2/(1+f^2)$
FM: <18%
$SLP \sim H^2 - H^3$



Positions of the fibre probe → < 6 %

Vessel material → 40 % between vessels
Over 1 order of magnitude for plastic Eppedorf

$$SLP = C_P \frac{m_f}{m_{NPs}} \frac{\Delta T}{\Delta t}$$

SLP equation → < 30 %

Makridis, A., et al. "A standardisation protocol for accurate evaluation of specific loss power in magnetic hyperthermia." *Journal of Physics D: Applied Physics* 52.25 (2019): 255001.

Error free evaluation of SLP?

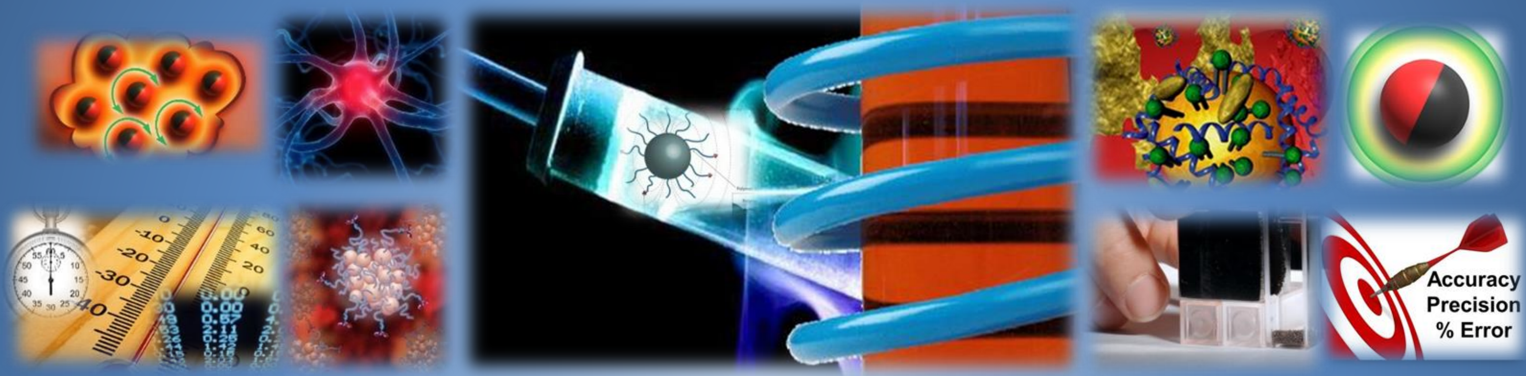
- **Sample:** Choice between superparamagnetic and ferromagnetic NPs depends on experimental conditions.
- **Conditions:** Suitable strength and frequency of the alternating magnetic field.
- **Measurement:** Calorimetric methods: lack of matching between measuring conditions, thermal models, and experimental setups.
- **Estimation:** SLP measurements are mainly conducted in non-adiabatic systems which lead to inaccurate estimations.

$$SLP = C_P \frac{m_f}{m_{NPs}} \frac{\Delta T}{\Delta t}$$

Possible sources of the inaccuracy in SLP measurement:

- spatial inhomogeneity of temperature ⇒ location of the thermal probe crucial.
- Heat delay.
- Variation heat capacity with temperature.
- Magnetic Field inhomogeneity.
- Peripheral heat exchanges.

Magnetic Nanohybrids for Cancer Therapy



Hints and Tips in Magnetic Hyperthermia Measurements

MaNaCa Weekly Seminars

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