Lecture 3

Magnetic particles in fluids

Magnetic particles in fluids

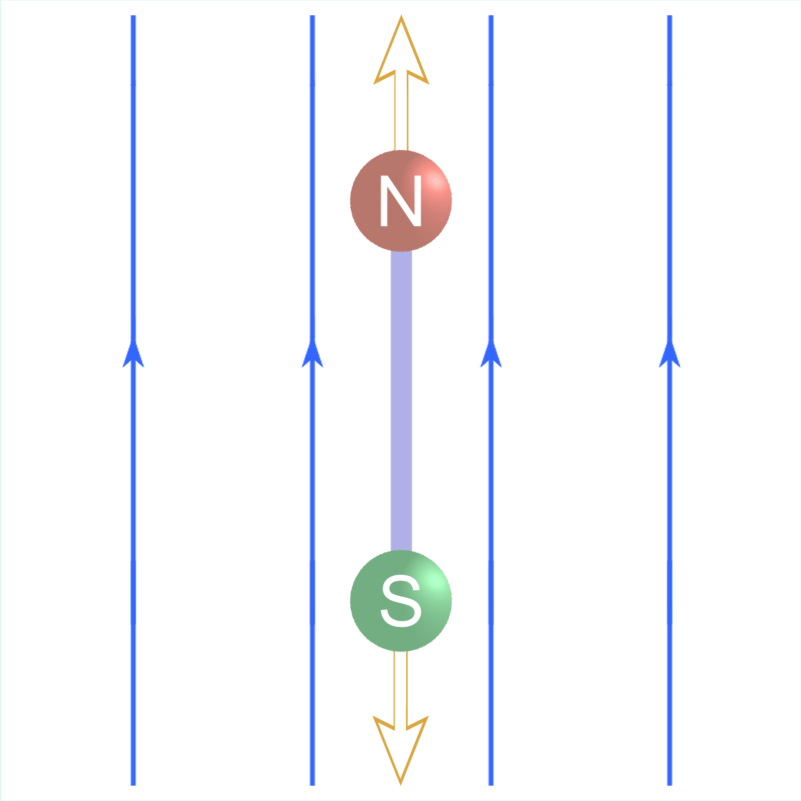
- **Most clinical and biotechnological applications of magnetic carriers involve suspensions of particles in fluids**

- **Here we review some of the basic principles governing the behaviour of magnetic particles in fluids**

Magnetic particles in fluids

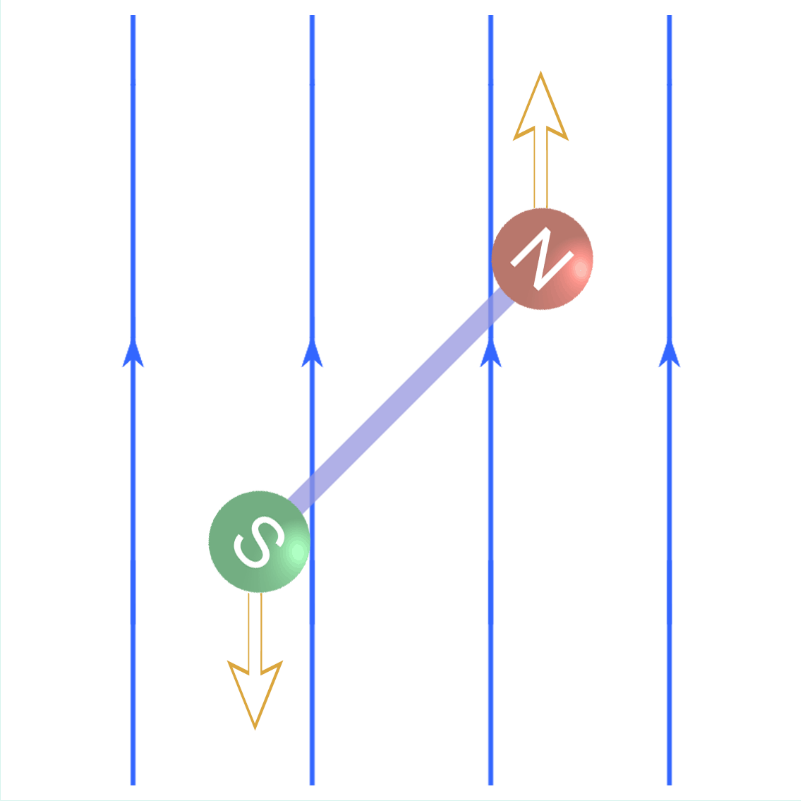
- **Several forces involved**
  - Force of applied magnetic fields on particles
  - Viscous drag forces
  - Interparticle magnetic forces
  - Interparticle electrostatic forces
  - Interparticle entropic "forces"

Single magnetic particle in fluid



- **A uniform magnetic field tends to orient a magnetic dipole**
- **Uniform field does NOT exert translational force on dipole**
- **Forces on North and South pole balance**

Single magnetic particle in fluid



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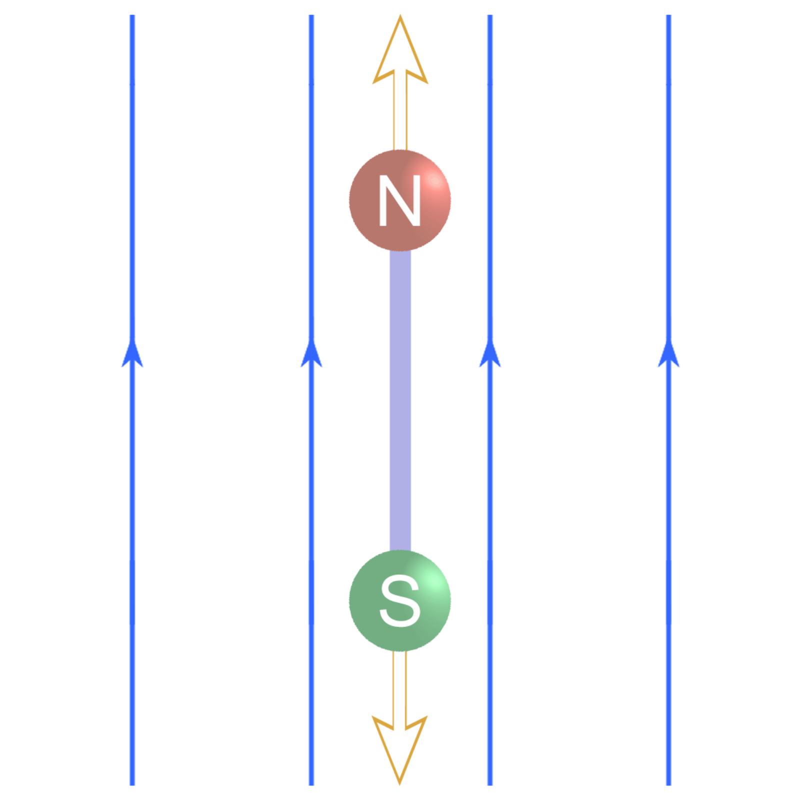
Single magnetic particle in fluid



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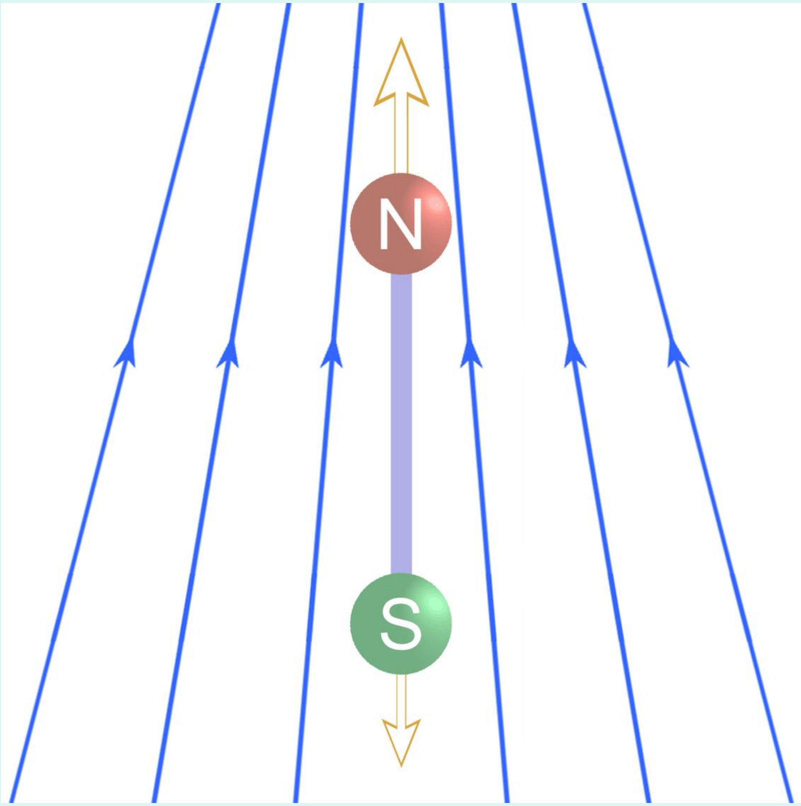
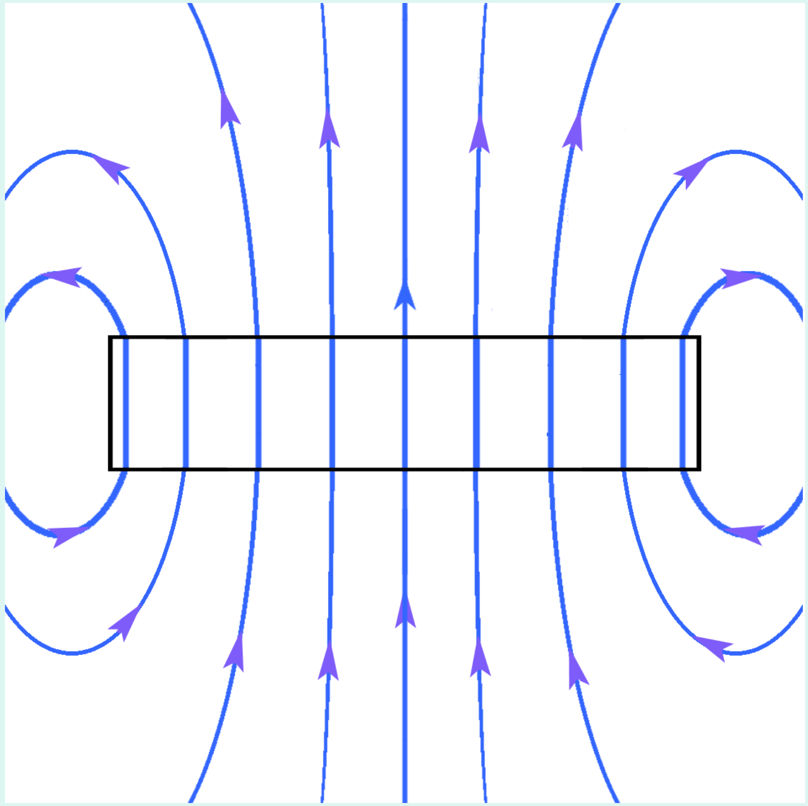
Single magnetic particle in fluid



- **A field gradient is required to exert a translational force on dipole**
- **Figure shows a stronger force on the North pole than the South pole**
- **Net force causes translation**

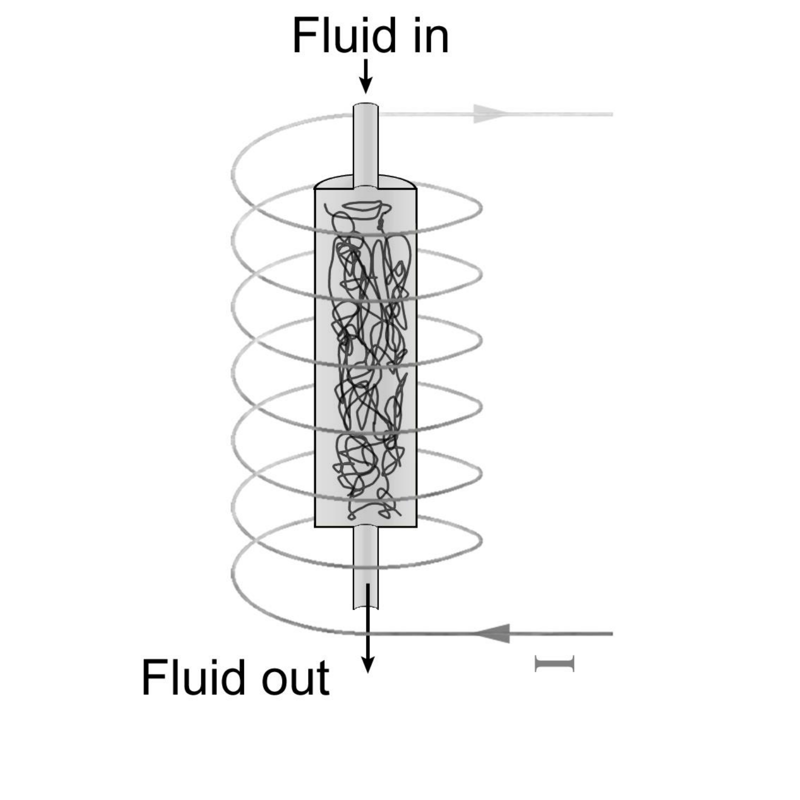
Magnetic Field Gradients



Disk-shaped magnet

- **A simple bar magnet generates magnetic field gradients**
- **Gradients tend to be larger at sharp corners of magnet**
- **Fine or sharply pointed magnetized objects generate high field gradients**

High field gradients used in magnetic separators



- **Fine wire with high mag susceptibility and low remanence used in a column**
- **Magnetic particle bearing fluid passed thru column with applied field**
- **Particles attracted to wire**
- **Particles can be released by removing applied field to demagnetize wire**

Cell magnetic separation

- **Cells with intrinsic or extrinsic magnetic components are forced to pass through magnetic field gradient leading to a separation and to a concentration of the magnetic phase.**
- **Examples: Red blood cells (RBC) infected with malaria and lymphocytes labelled with magnetic antibody**

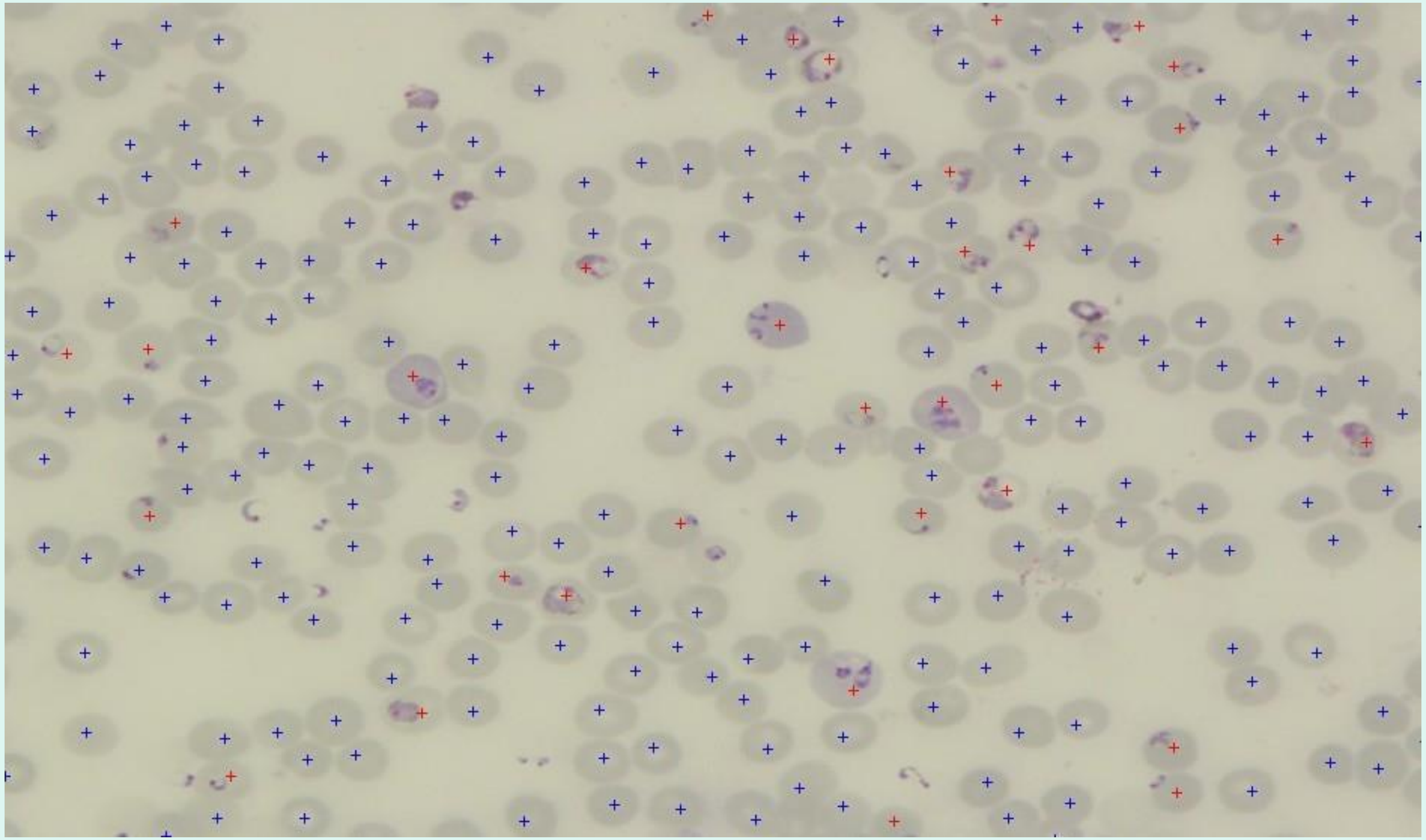
Malaria infected erythrocytes
(Am. J. Clin. Pathol. 103:57 (1995))

- **The erythrocytes infected with malaria contain hemozoin, which is a paramagnetic molecule originating from hemoglobin degradation. This allows that a magnetic field can be used to separate the erythrocytes infected with P. falciparum of health RBC.**

Haemozoin

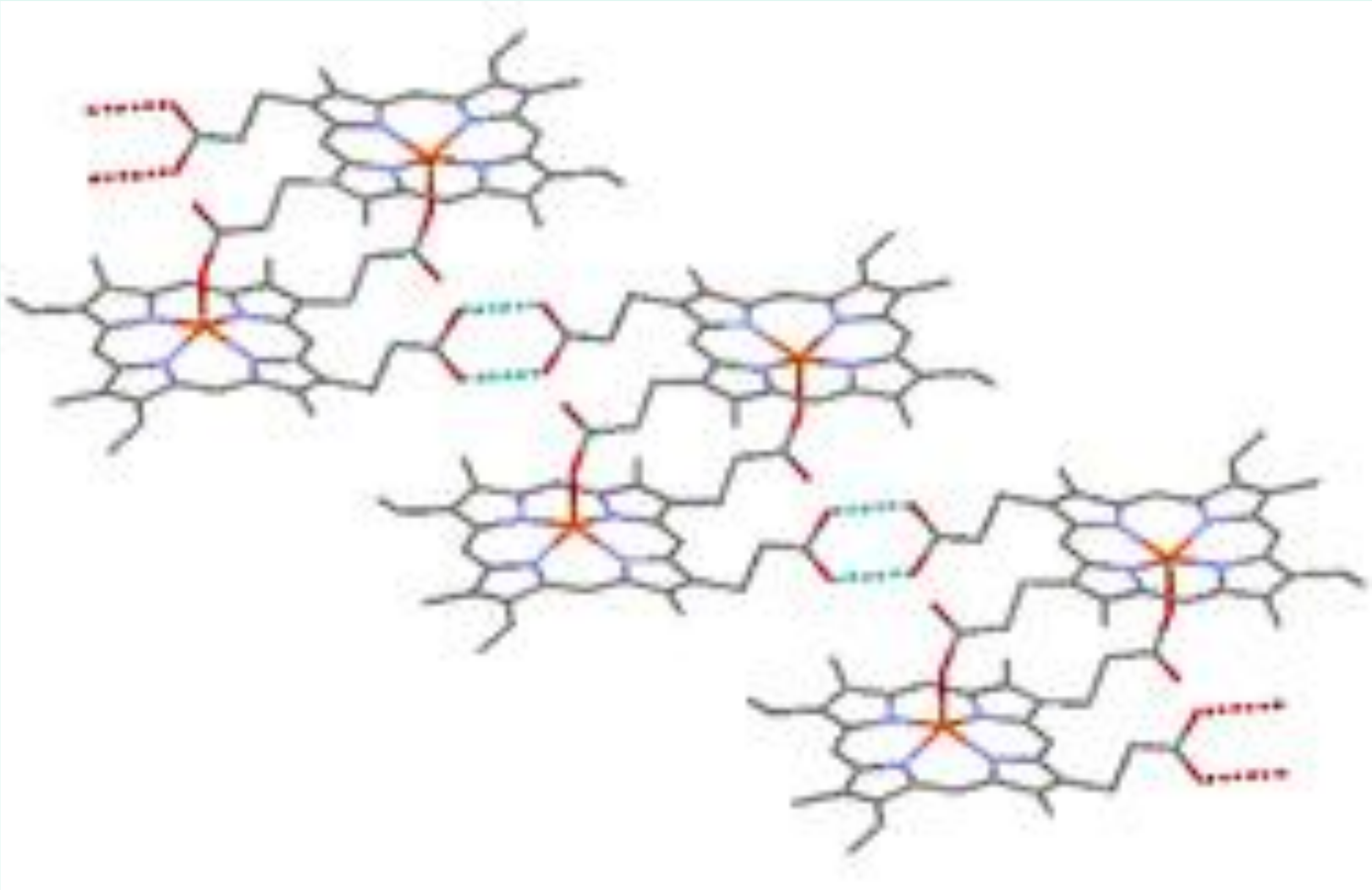
- **Is a disposal product formed from the digestion of blood by some blood-feeding parasites. These hematophagous organisms such as Malaria parasites (*Plasmodium spp.*), *Rhodnius* and *Schistosoma* digest haemoglobin and release high quantities of free heme, which is the non-protein component of hemoglobin. A heme is a prosthetic group that consists of an iron atom contained in the center of a heterocyclic porphyrin ring. Free heme is toxic to cells, so the parasites convert it into an insoluble crystalline form called hemozoin. In malaria parasites, hemozoin is often called *malaria pigment*.**

Malaria parasitemia

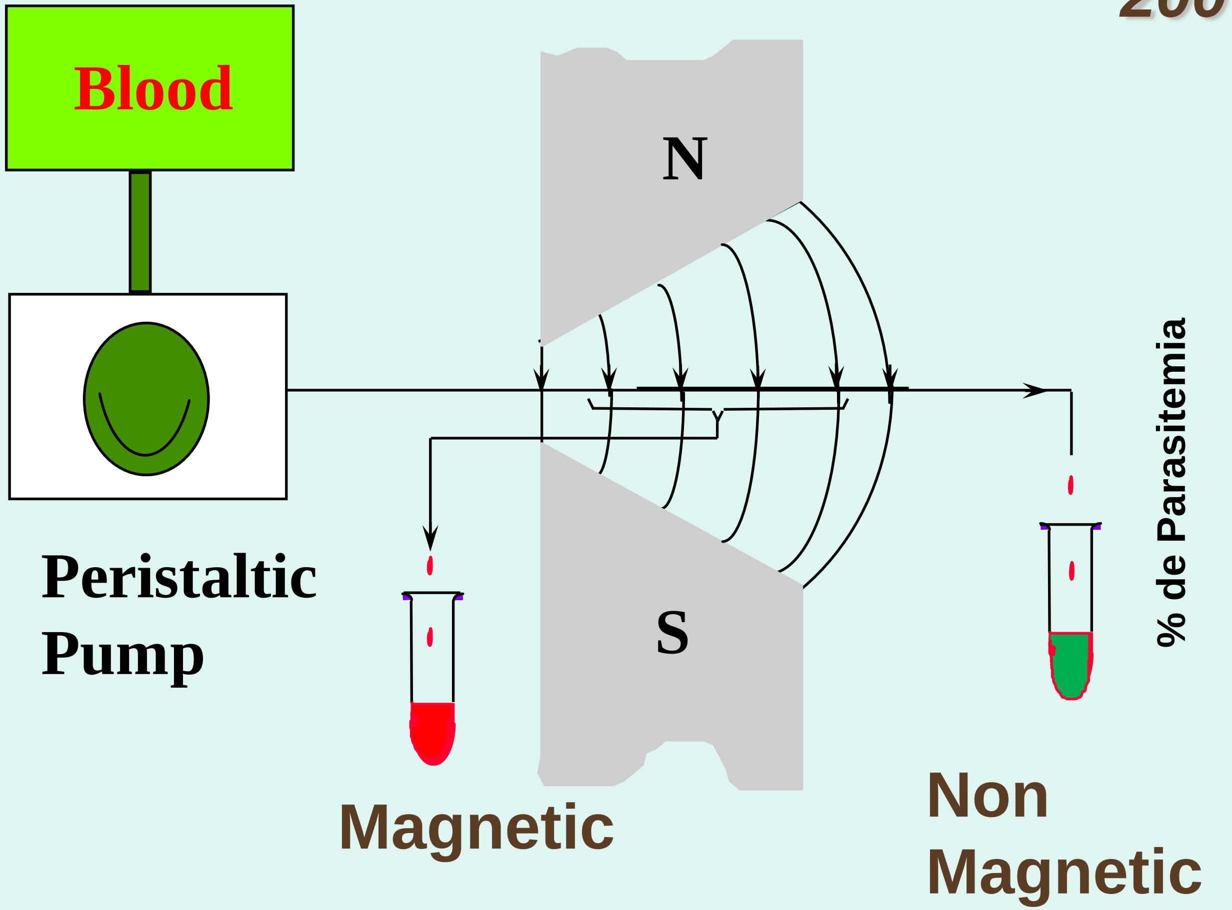


Normal cells are marked in blue and infected cells with red crosses.

Haemozoin

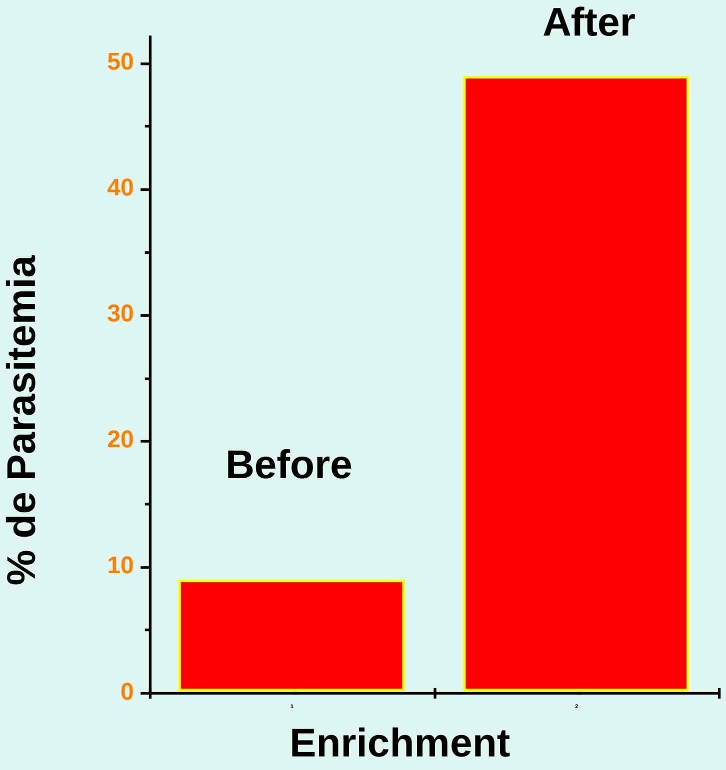


Instrumental and Results



6.4 x enrichment

200 ⇨ 30 visual fields



Reynolds Numbers

- **The Reynolds number of an object in a fluid is the ratio of inertial to viscous forces experienced by the object**
- **Micron and sub-micron particles in water have very low Reynolds numbers**
- **Velocity $\propto$ externally applied force**
- **i.e. objects reach their terminal speed almost instantaneously**

Field gradients applied to small magnetic particles in fluids

- **Speed of particle $\propto$ field gradient force**
- **Field gradient force $\propto$ moment on particle**
- **Moment on particle $\propto$ volume of particle**
- **$\therefore$ Speed $\propto$ volume of particle**
- **LARGER PARTICLES MOVE FASTER IN FIELD GRADIENT**

Field gradients applied to small magnetic particles in fluids

- **Magnetic separation techniques preferentially remove aggregates of particles**

- **Magnetic microspheres will move faster than nanospheres**

Interparticle interactions: Aggregation

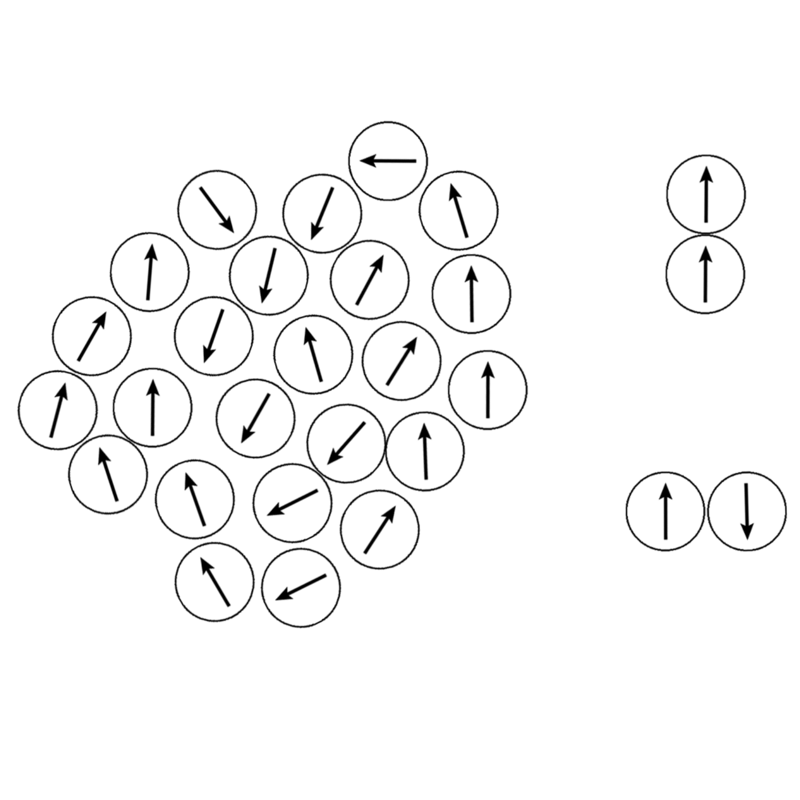
- **More likely to occur as magnetic moments on particles increase (due to interparticle magnetic dipole interactions)**

- **Very large aggregates→precipitation (i.e. gravitational forces significant)**

Reversible and irreversible aggregation

- **Reversible**
  - Particles aggregate under applied field. Removing field lowers moments on particles sufficiently that repulsive forces dominate
- **Irreversible**
  - Applying field causes aggregation. Proximity of particles to each other results in mutual induction of dipole moments even in zero applied field. Attractive magnetic interactions within aggregate dominate

Demagnetizing interactions in clusters

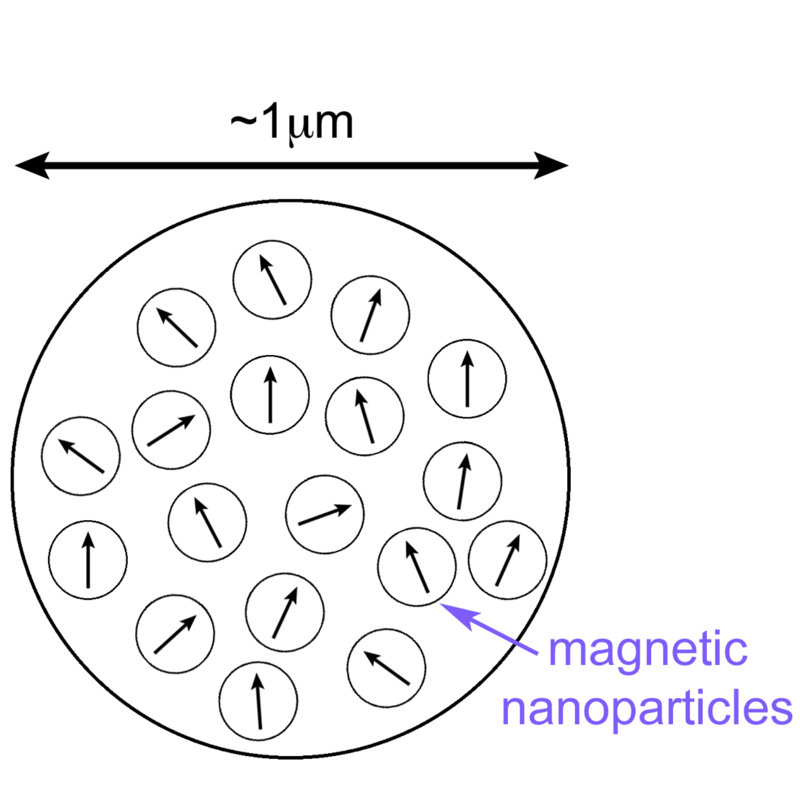


- **Particles in close proximity with each other**
- **Moments tend to arrange themselves such as to minimize magnetization of aggregate**
- **Clusters of particles may show reduced susceptibility in low fields**

Design of magnetic carriers

- **High χ generally desirable**
- **Low M_r desirable so that magnetic moments can be "switched off"**
- **High interparticle repulsion to reduce aggregation**
  - Electrostatic repulsion forces
  - Entropic repulsion forces
  - These forces are needed to overcome interparticle attractive magnetic forces. Determined by chemistry of particle coatings.

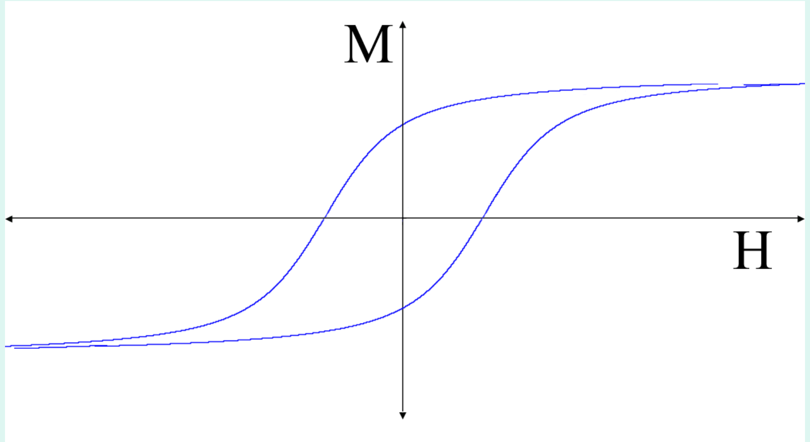
Design of magnetic microspheres



- **Make microsphere from aggregate of superparamagnetic nanoparticles**
- **SP particles give high χ and zero M_r**
- **Aggregate micron size yields faster movement in fluid**

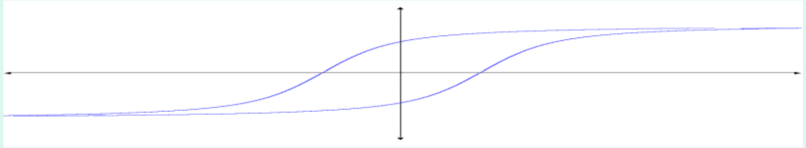
Particles for Special Applications

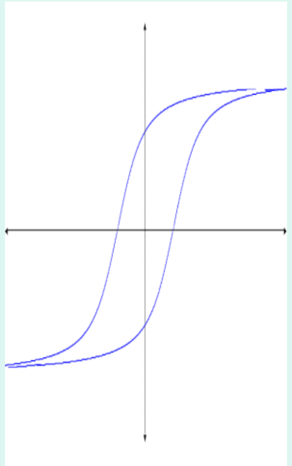
Particles for hyperthermia therapy



- **Magnetic hyperthermia therapy involves application of ac field to heat particles**
- **Heat generated per field cycle ∝ area within hysteresis loop**

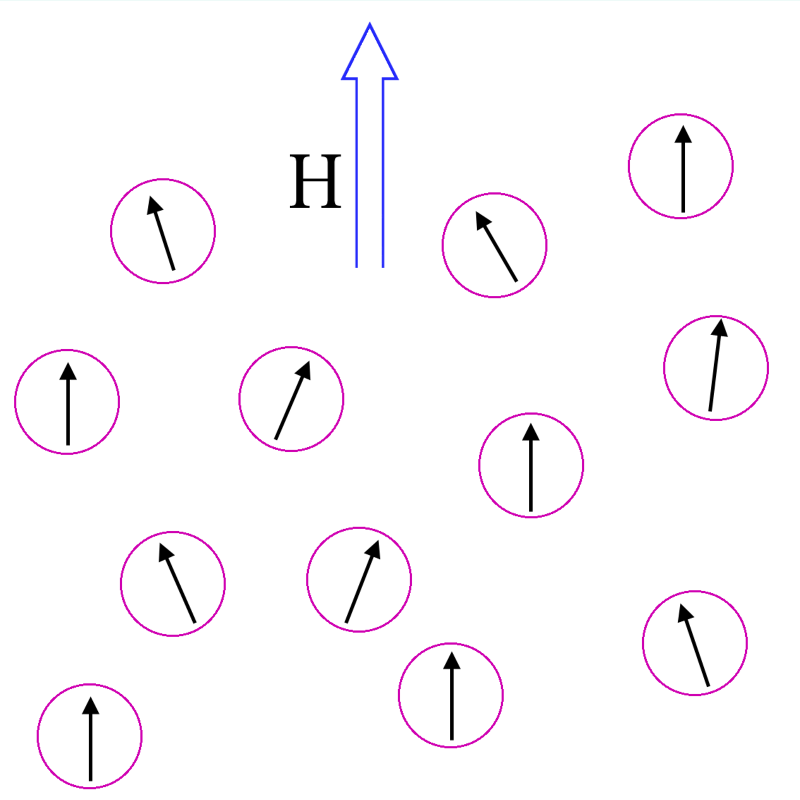
Particles for hyperthermia therapy





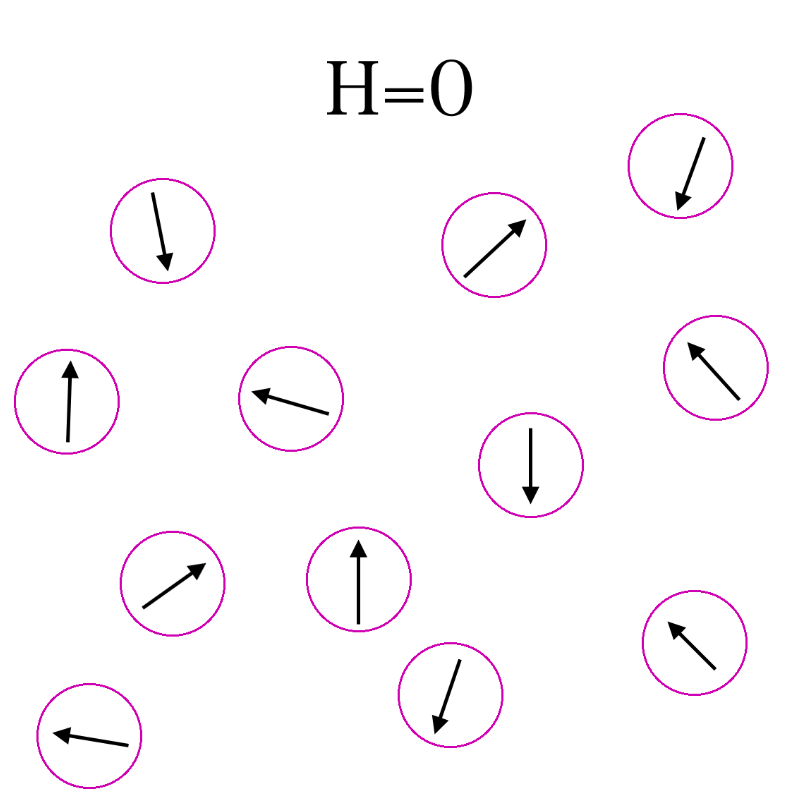
- **Therapeutic ac field amplitudes are limited (to avoid nerve stimulation)**
- **Particles with low coercivity but high M_s are preferred**

Particles for Brownian rotation studies



- **Magnetically blocked particles required**
- **Must stay in suspension**
- **Observe time dependent magnetic behaviour of fluid due to physical Brownian rotation of blocked dipoles**

Particles for Brownian rotation studies



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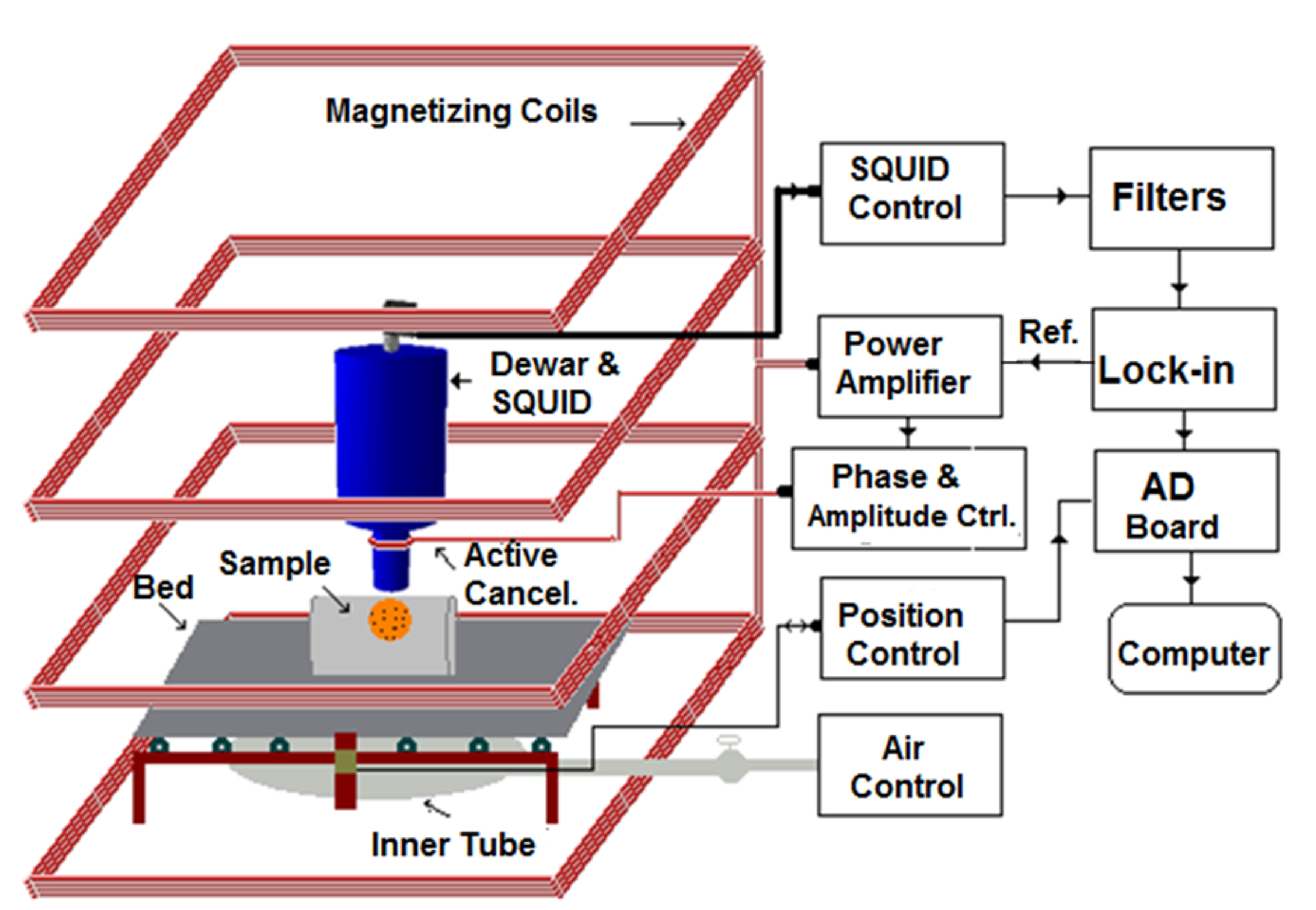
DETECTION OF MAGNETIC NANOPARTICLES WITH A LARGE SCALE AC SUPERCONDUCTING SUSCEPTOMETER

- Magnetic nanoparticles are being used in several applications in medicine such as hyperthermia, magnetic particle imaging, *in vitro* and *in vivo* bioassay, and still there are many other possibilities of use of these particles. One crucial step of its use it is the detection of these particles when present in a certain tissue. For *in vitro* bioassay, the sample can be harvested and placed inside the detector in optimal conditions to favor sensitivity. However, for *in vivo* human measurements the system must be noninvasive and conform to the anatomic restrictions requiring sensitive detectors and dedicated setups. In this study, we detect nanoparticles with an AC biosusceptometer

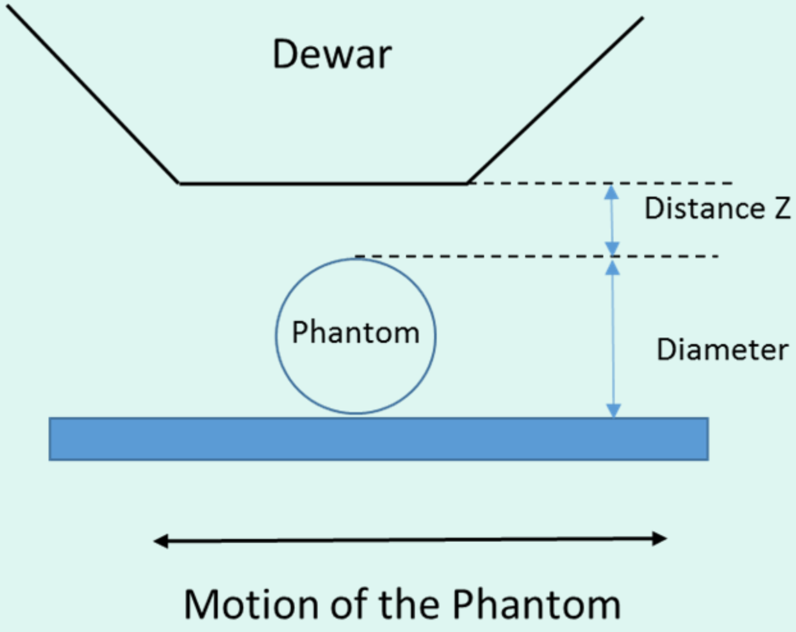
A block diagram of the large-scale AC superconducting susceptometer

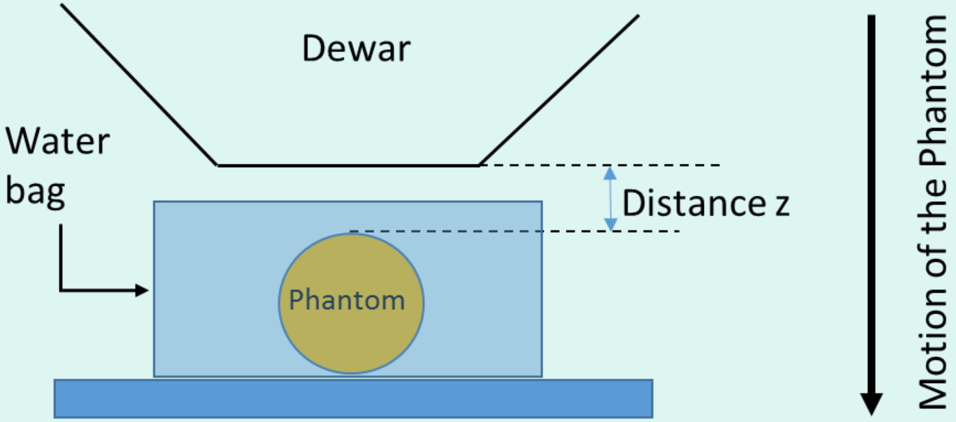


Detail of the Dewar, bed, magnetizing coils and water reservoir.

Sketch of the measurement methods used

- $\chi_{total} = -\chi_{air} + \chi_{water} + c\chi_{MNP}$



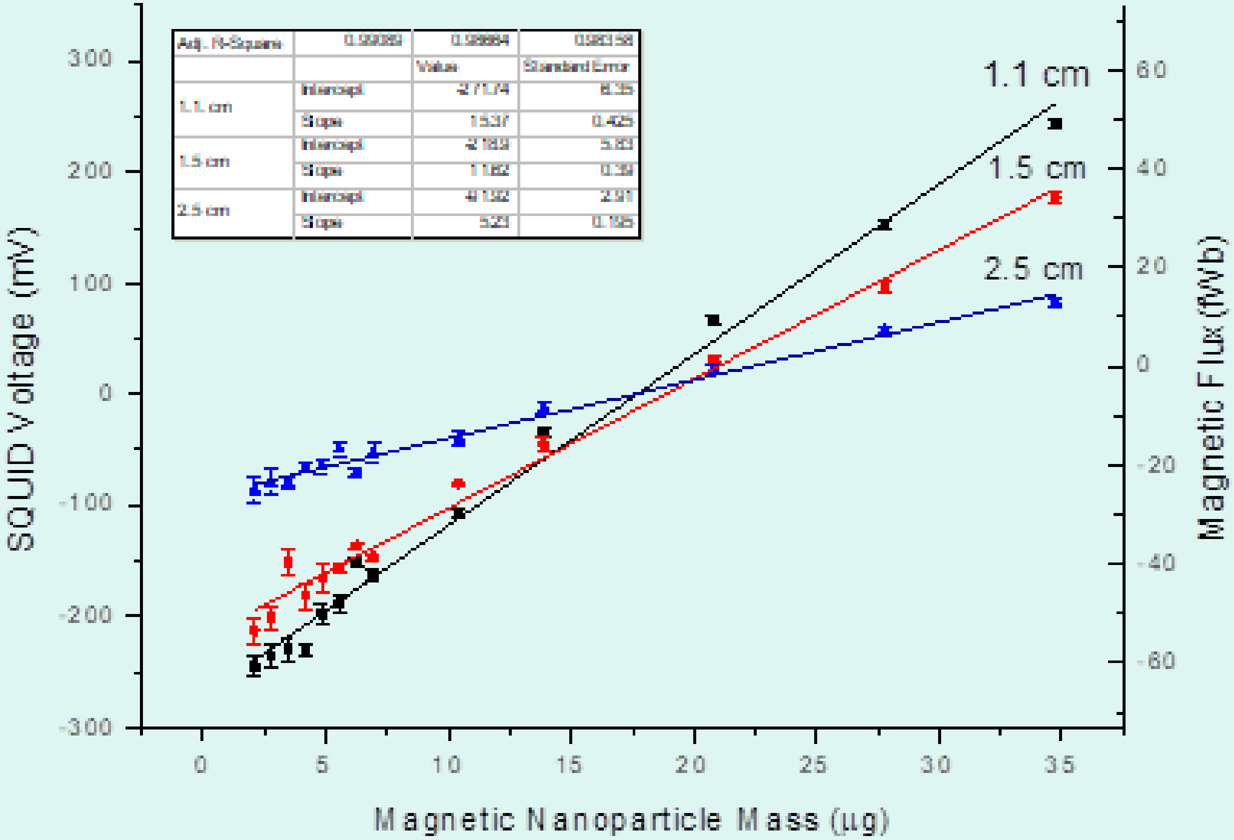


Modelling

- Squid Voltage $V = \alpha \Delta B$
- $\Delta B = \frac{\mu_0}{2\pi} \frac{<m_d>_{sample}}{r^3} \cong \frac{\mu_0}{2\pi} \frac{N M_s v L(x)}{r^3}$
- Langevin function *L(x)= cotanh(x)-1/x*, where x stands for the ratio of the Zeeman term to the thermal energy, i.e. x=$M_s v_p B / k_B T$

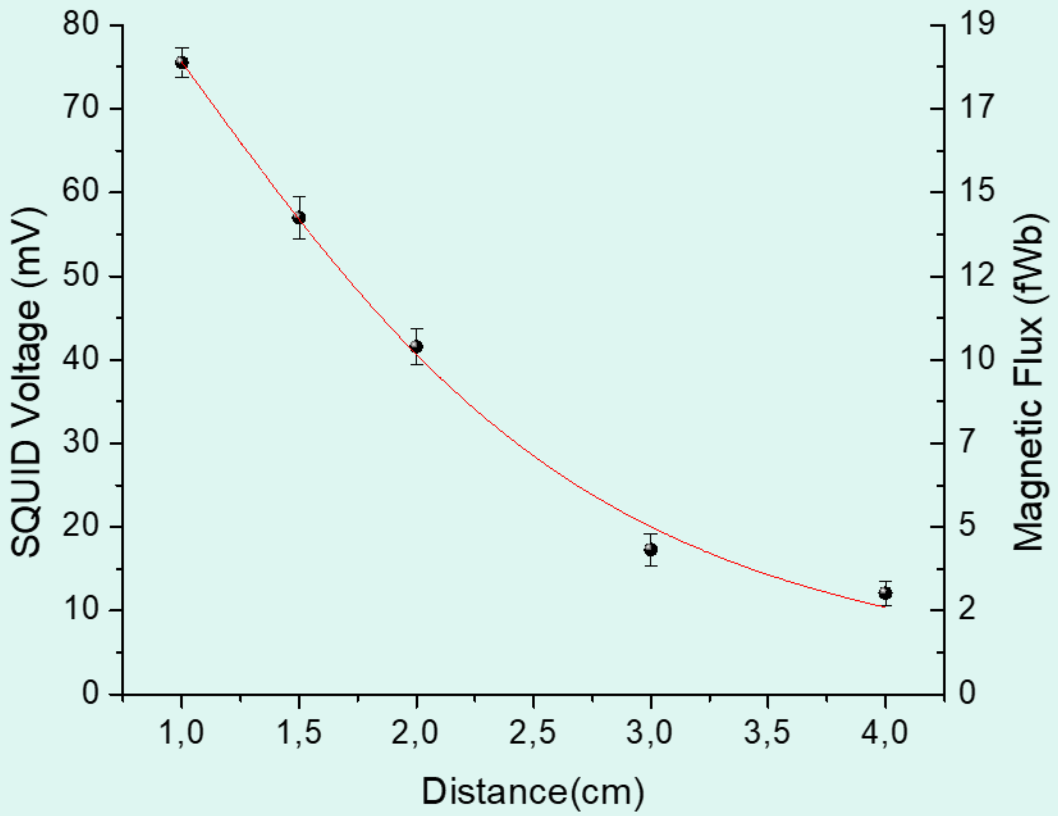
- At the low field condition, the Langevin function is $(x) \cong \frac{x}{3}$
- $< m_d >_{sample} = NM_s vL(x) \cong v\frac{NM_s^2 v_p B}{3k_B T} = \frac{v\chi_L B}{\mu_0}$
- $V = \alpha\frac{\mu_0}{2\pi r^3} \ \frac{\chi_L vB}{\mu_0} = \alpha\frac{\chi_L vB}{2\pi r^3}$
- Where $\chi_L = \frac{2\pi r^3 V}{\alpha vB} = \beta V$ and $\beta = \frac{2\pi r^3}{\alpha vB}$

Response of biosusceptometer for different masses of magnetic nanoparticles



Distances of 1.1 (squares, black), 1.5 (circle, red) and 2.5 cm (triangles, blue) from the gradiometer obtained by the methods 1. The table shows the linear fitting parameters of the data

Dependence of the measured signal on the distance sample-gradiometer



Curve corresponds to the fitting of a $1/z^3$ function with a correlation coefficient $R^2 = 0.985$

Limit of detection (LOD) and sensitivity of MNPs for three distance sample-gradiometer

Sample distance (cm)	LOD (μg)	Sensitivity ($fWb/\mu g$)	Sensitivity ($10^9\ NP/ml$)
1.1	3.3	3.7	8.1
1.5	4.0	2.8	9.5
2.5	4.5	1.3	11

Assuming that the cell contains the order of 100pg of magnetic material one can estimate the limit of detection to be above $3x10^3$ cells at 1 cm up to $4.5x10^4$ cells at 2.5 cm. This sensitivity value is in the same order of magnitude expected for MRI, but two orders higher than MPI, which can detect up to 100 cells

Functional Magnetic Nanoparticle Imaging by AC Biosusceptometry

Laboratório de Biomagnetismo, Instituto de Biociências de Botucatu, Unesp, SP - Brazil,
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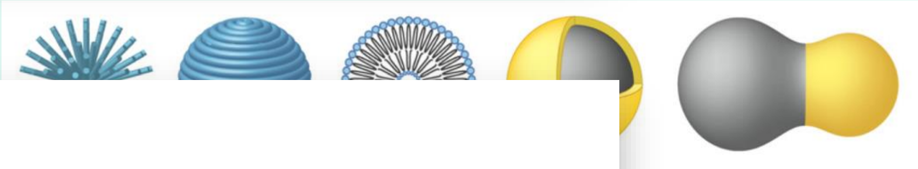
Instituto de Física, Universidade Federal de Goiás, Goiânia, GO - Brazil
Departamento de Física, FFCLRP, USP, Ribeirão Preto, SP - Brazil

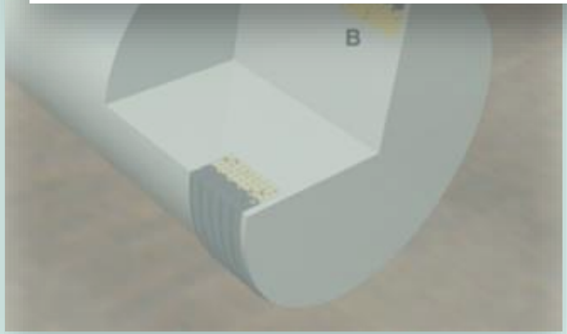
Research Team

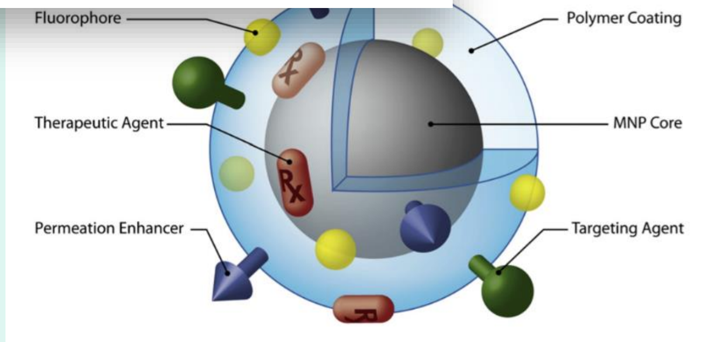
- José Ricardo Arruda Miranda-UNESP
- Caio Quini-UNESP
- Andris Bakusis -UFG
- Madileine F. Americo-UFMT
- Oswaldo Baffa-USP

Outline of the presentation

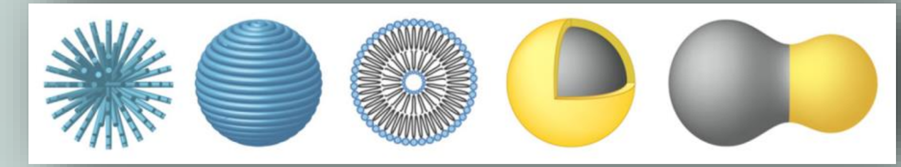


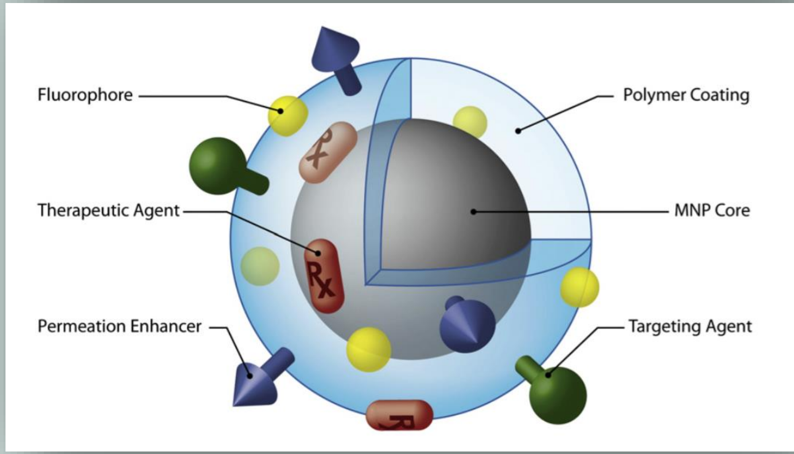
- Motivation for the use of MNPs
- AC Biosusceptometry
- Animals & Experimental protocol
- Results & Discussion





Magnetic Nanopartciles (MNPs)





Versatility

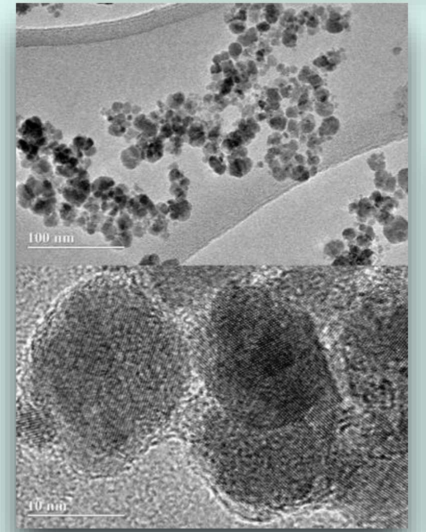
- Magnetic Particle Imaging
- Magnetic Resonance Imaging
- AC Biosusceptometry

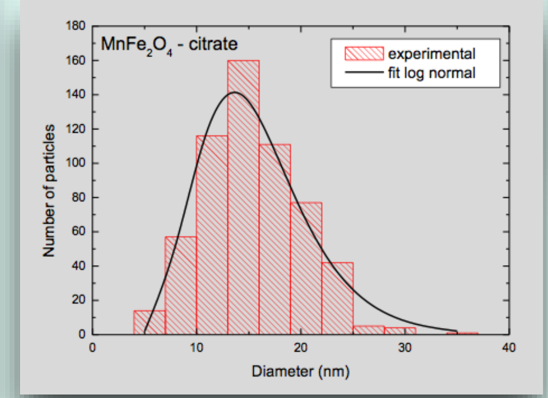
- Simplicity
- Versatility

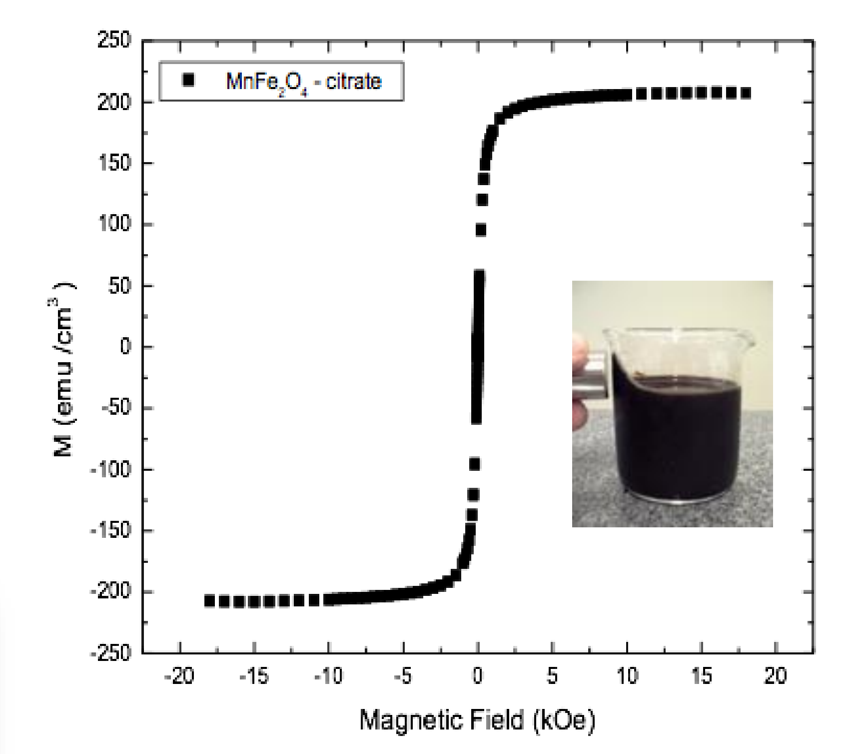
Magnetic Nanopartciles (MNPs)

Superparamagnetic Iron Oxide Nanoparticles

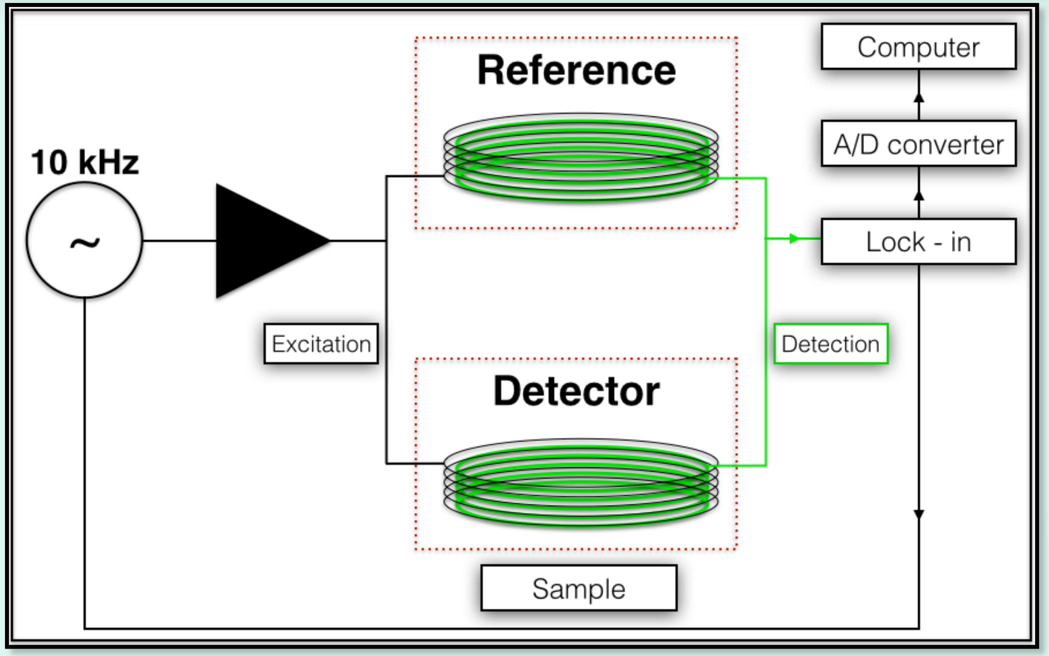
- Ci-$MnFe_2O_4$
  - 13 ± 4 nm
  - - 27.8 mV
  - 23 mg/mL - $1.17x10^{15}$ part/mL







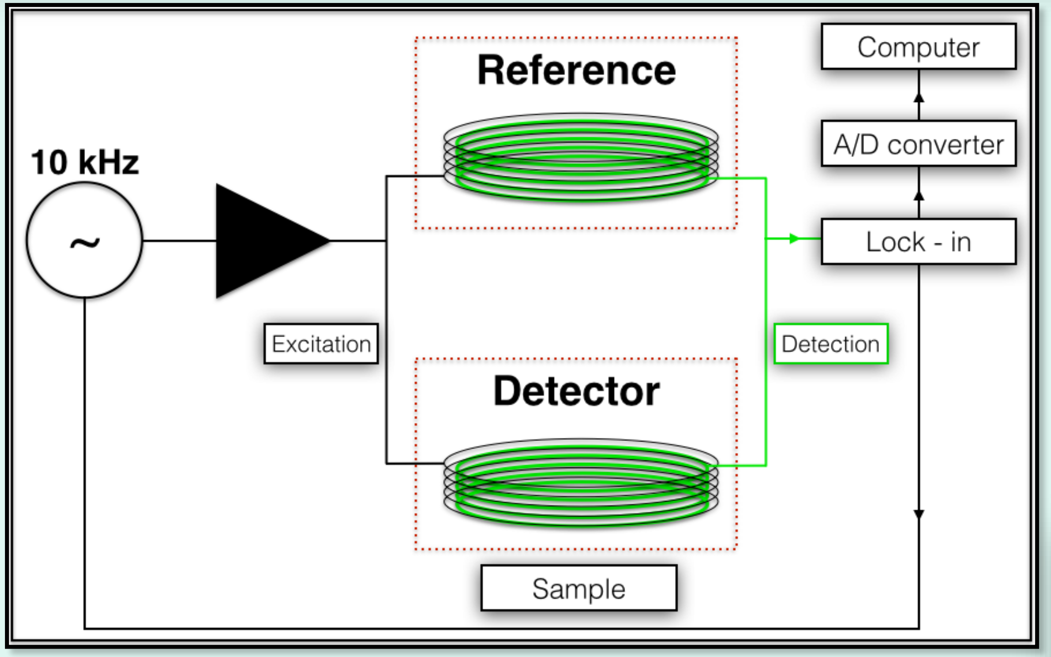
AC Biosusceptometry (ACB)



$$\Phi_d = \frac{1}{\mu_0 I_d} \int \chi(\vec{r})\, \overrightarrow{B_a} \cdot \overrightarrow{B_d}\, dV$$

A set of coils (black) generate a signal that is detected by a lock-in amplifier. When properly balanced, no voltage is detected at the lock-in. However when a magnetic substance is near one pair of coils a net voltage is detected.

AC Biosusceptometry (ACB)

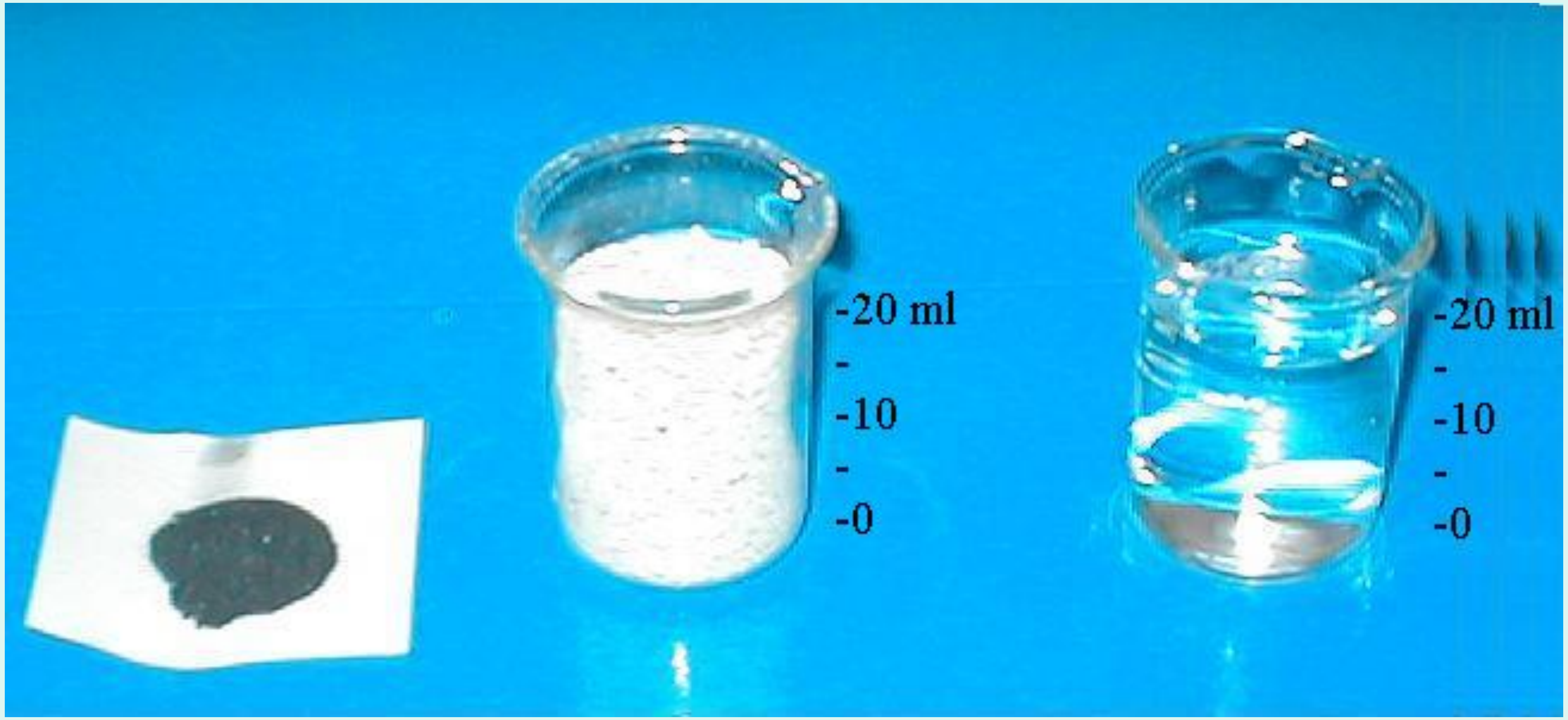


- First order gradiometer system
- Signal Decays Fast (r^{-6})

$$\Delta\Phi = \frac{N_S N_E \chi \mu_0 \delta V (A_s . A_e) I}{4\pi}\left[\frac{1}{r^6} - \frac{1}{(r+b)^6}\right]$$

Why Nano?

- GI motility tests require a test meal



3 g ferrite (Fe_3O_4) 15 g Oat Flour Water

Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

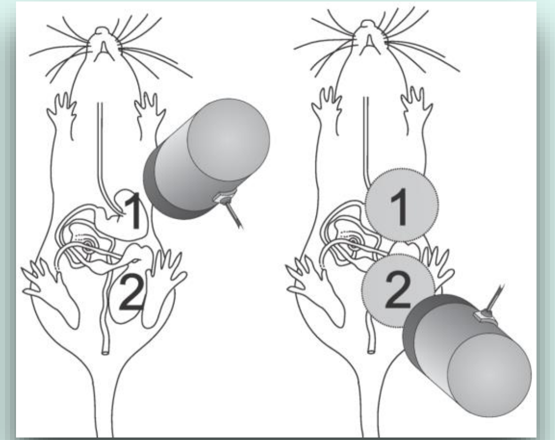
Quini *et al. Journal of Biological Engineering* 2012, **6**:6
http://www.jbioleng.org/content/6/1/6

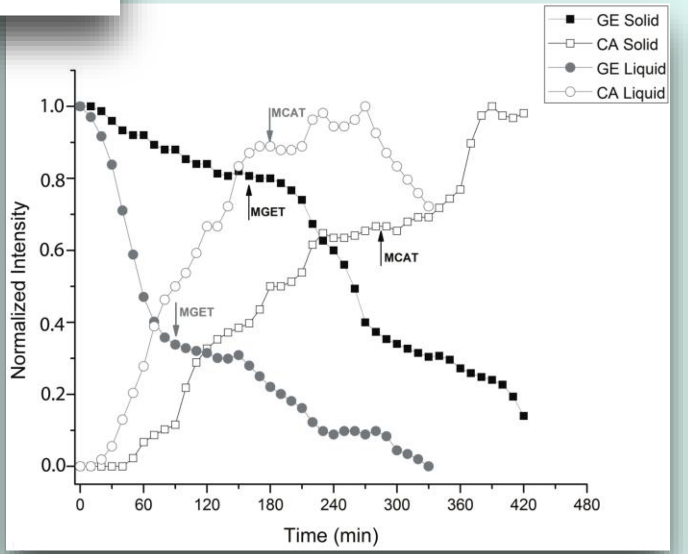
JOURNAL OF BIOLOGICAL ENGINEERING

METHODOLOGY Open Access

Employment of a noninvasive magnetic method for evaluation of gastrointestinal transit in rats

Caio C Quini[1], Madileine F Américo[2], Luciana A Corá[3], Marcos FF Calabresi[1], Matheus Alvarez[1], Ricardo B Oliveira[4] and Jose Ricardo A Miranda[1*]





Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

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Renal perfusion evaluation by alternating current biosusceptometry of magnetic nanoparticles

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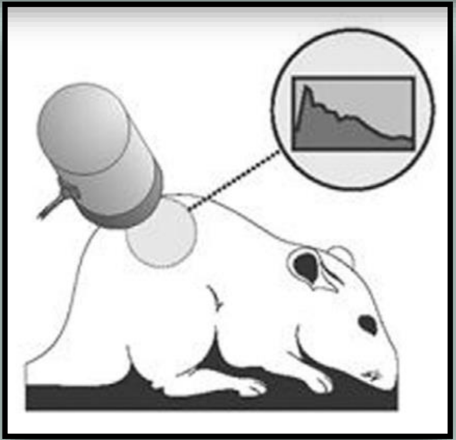
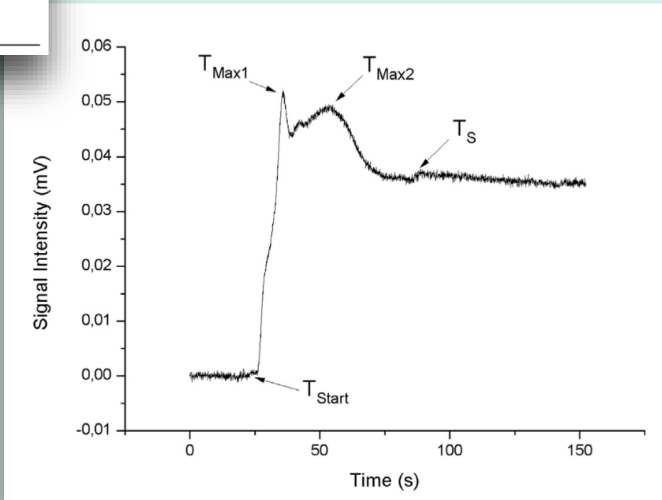
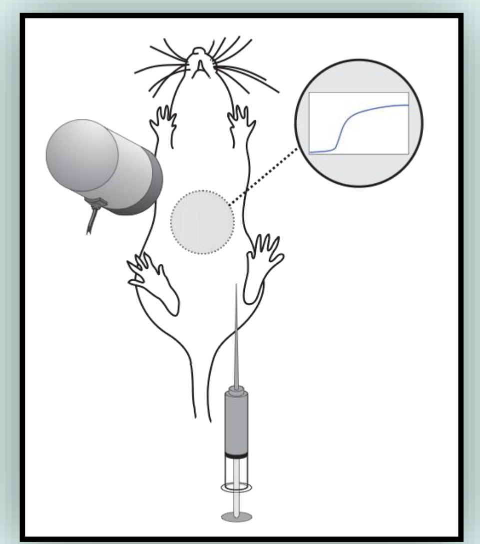


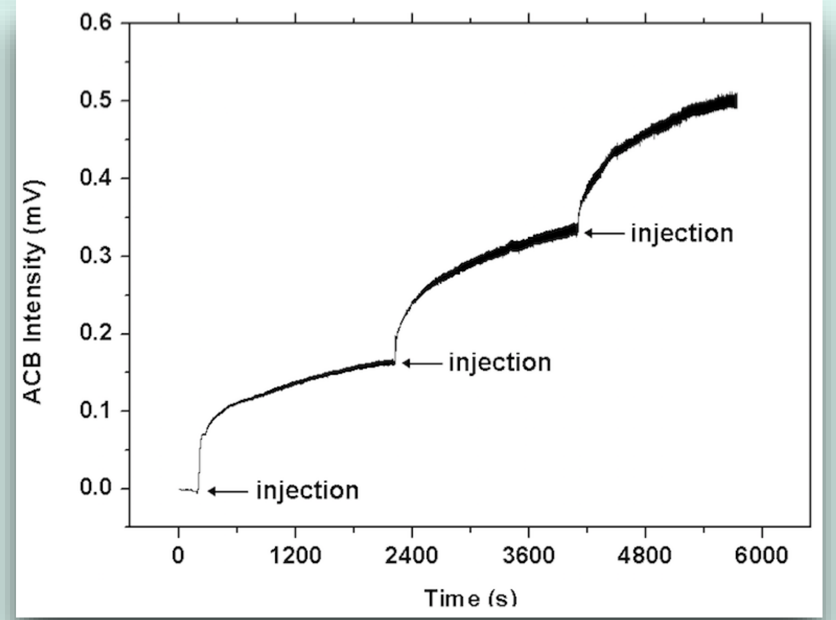


Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

Real Time Liver Uptake and Biodistribution of Magnetic Nanoparticles assessed by AC Biosusceptometry

Caio C. Quini[a], André G. Próspero[a], Marcos F. F. Calabresi[a], Gustavo M. Moretto[a], Nicholas Zufelato[b], Sunil Krishnan[c], Diana R Pina[d], Ricardo B. Oliveira[e], Oswaldo Baffa[f], Andris F. Bakuzis[b], Jose R. A. Miranda[a]





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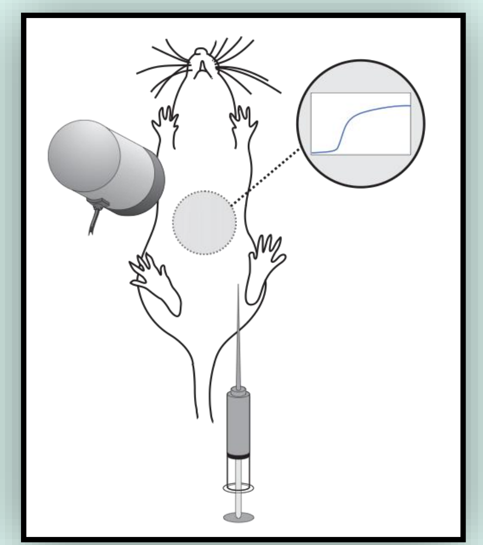
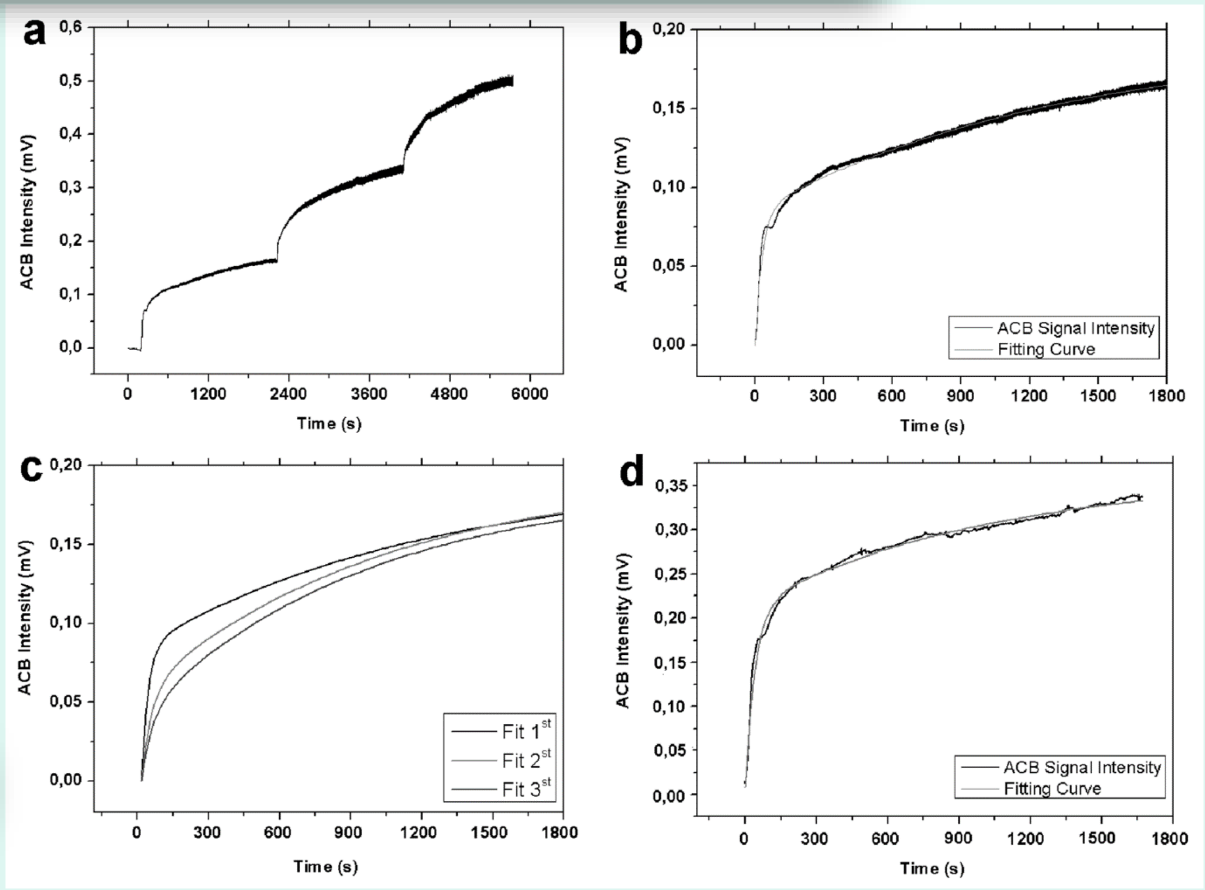
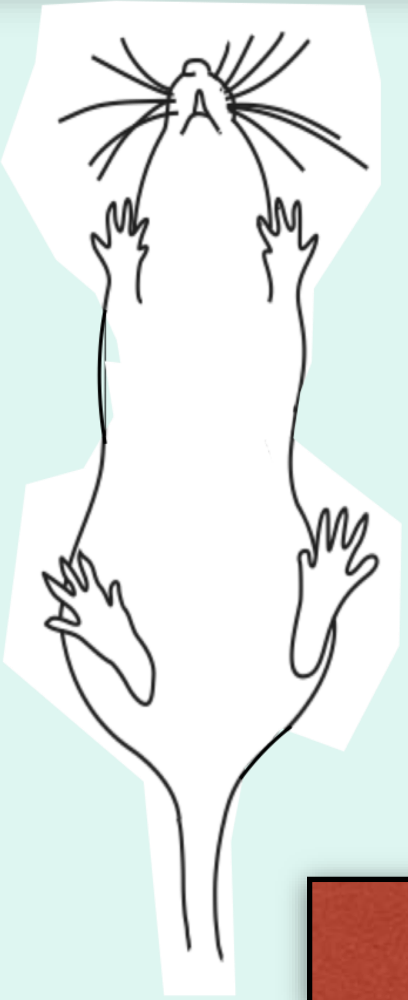
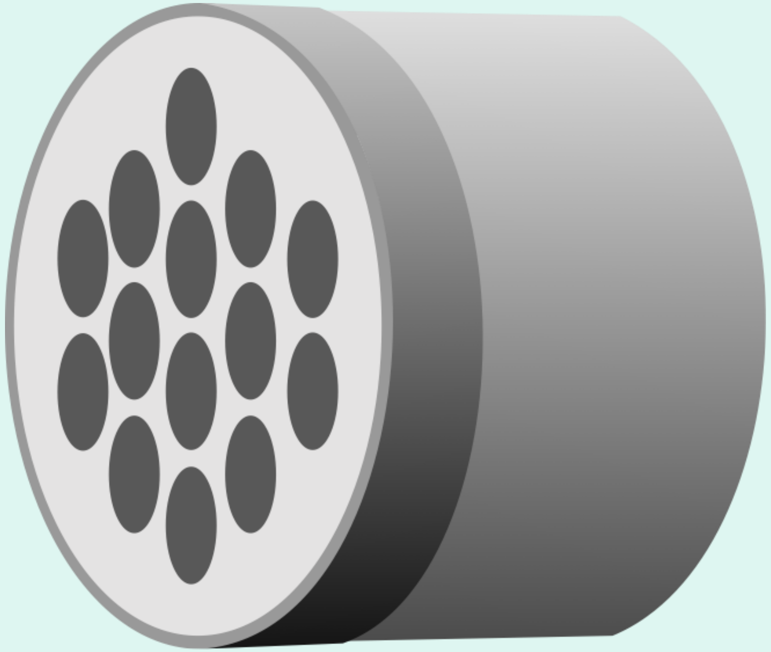


$$Y = Y_0 + A_1\left[1 - e^{-x/t_1}\right] + A_2\left[1 - e^{-x/t_2}\right]$$



Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

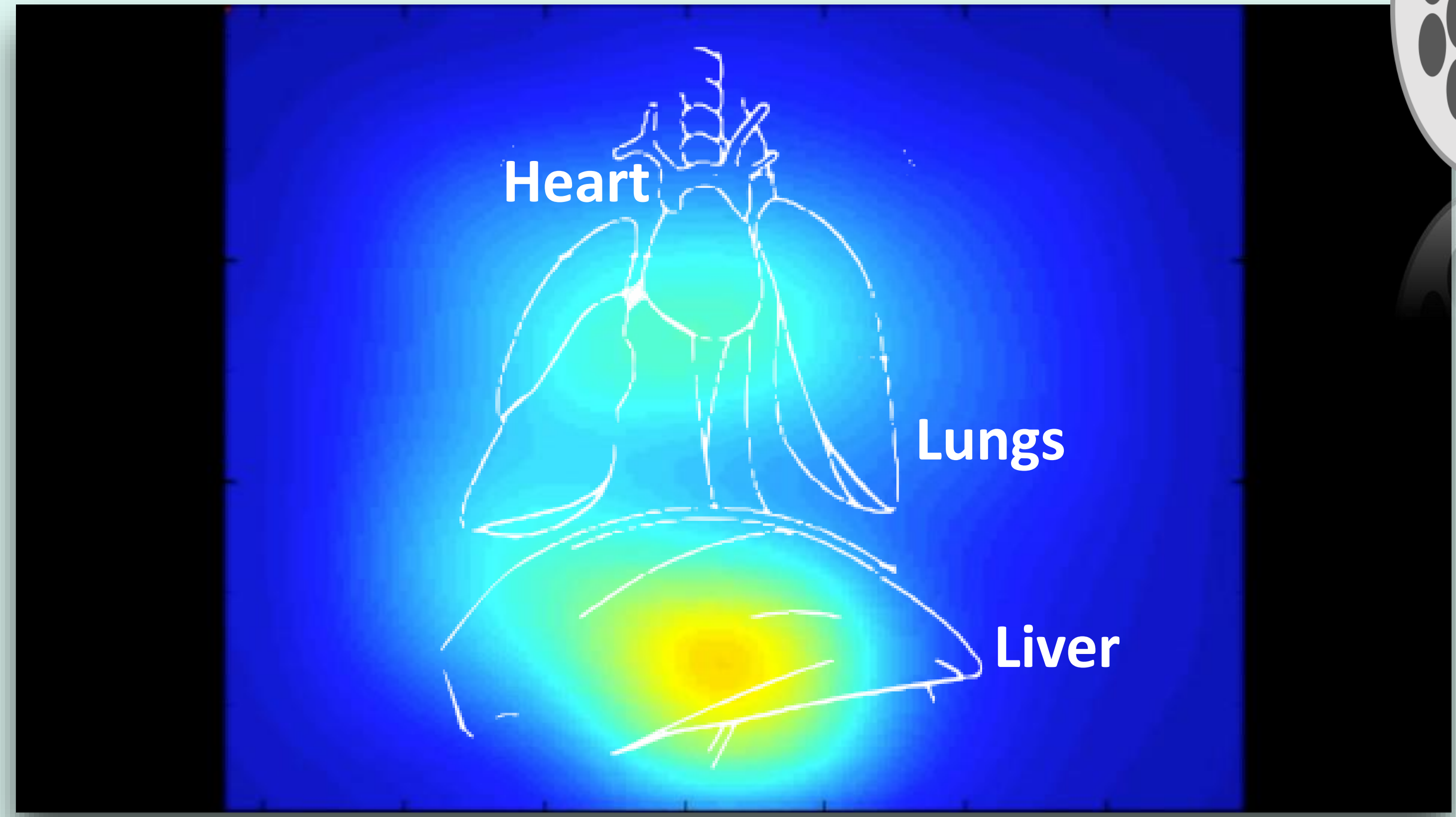


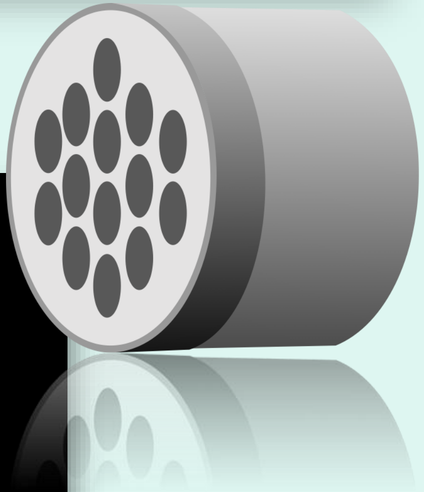


Multi-channel ACB system

Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

Multi-channel ACB system





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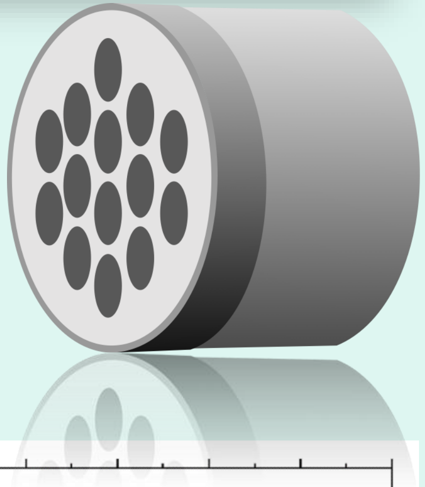

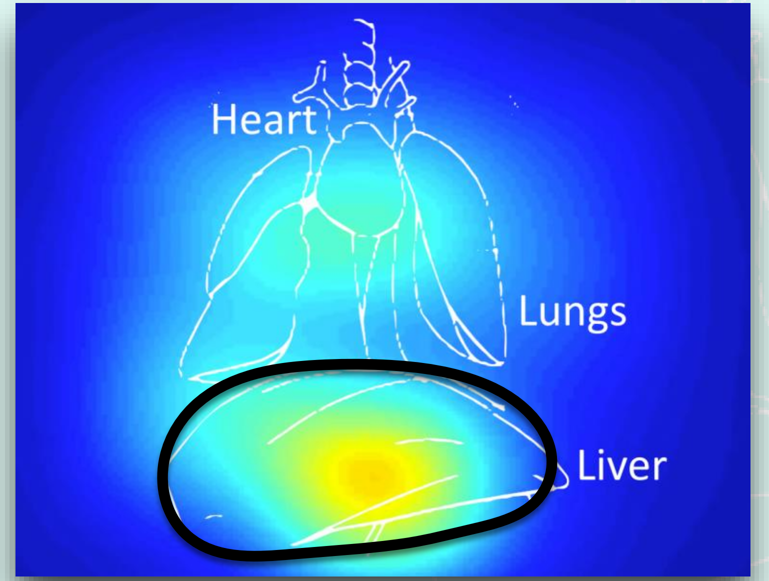

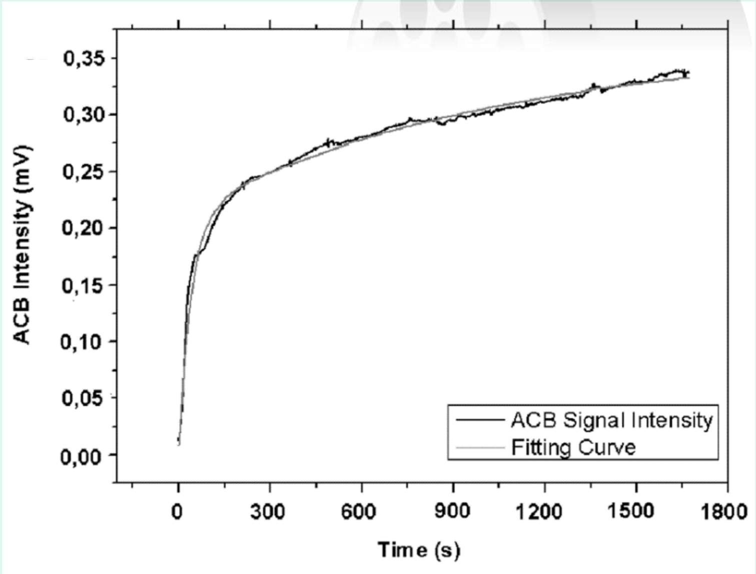

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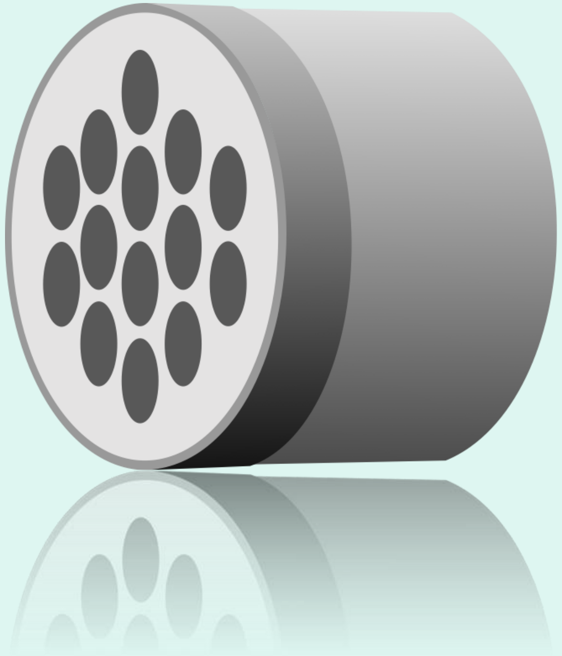
Multi-channel ACB system

Great Temporal Resolution

Accumulation profile on organs of interest

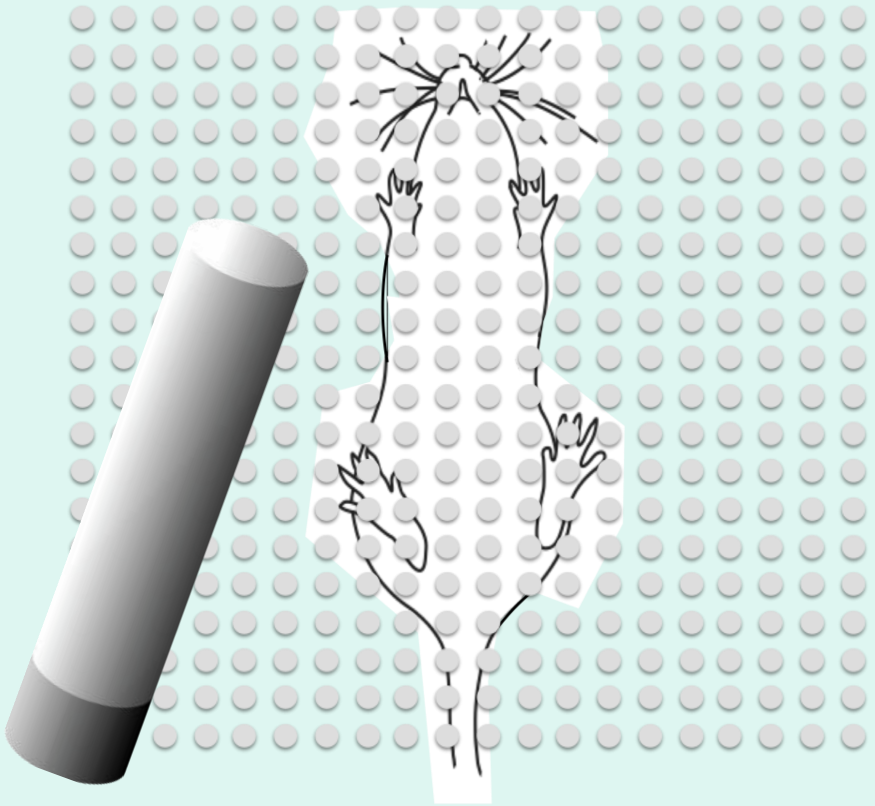
Poor Spatial Resolution

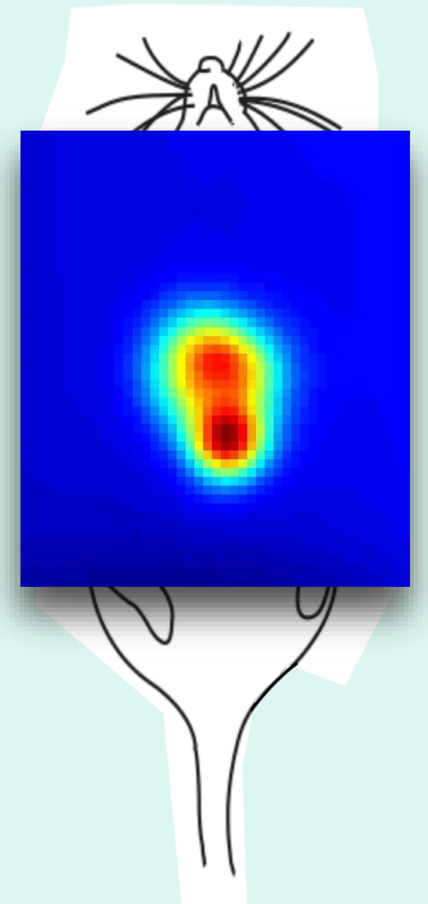


Liver

Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

ACB scanning system





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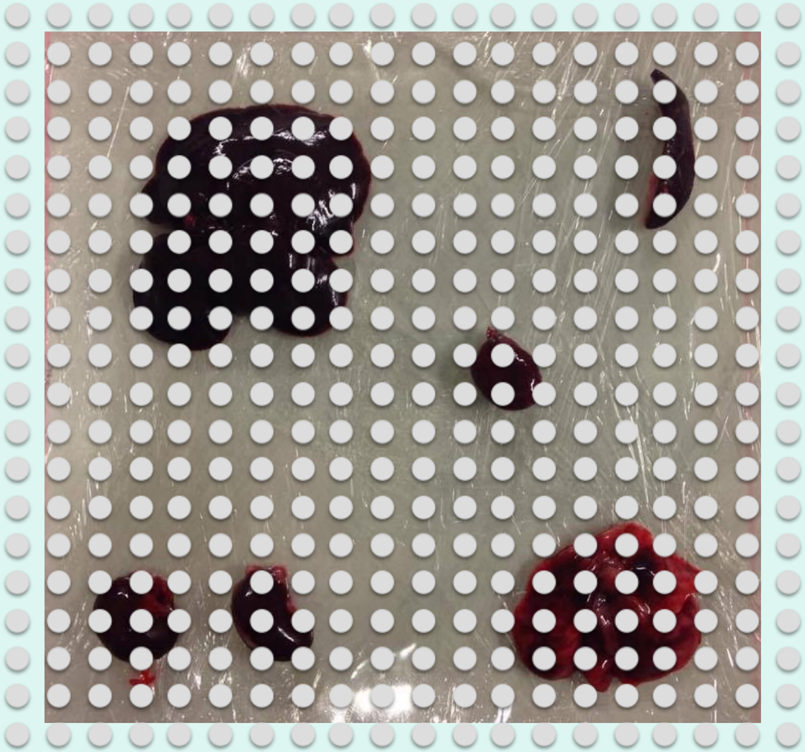
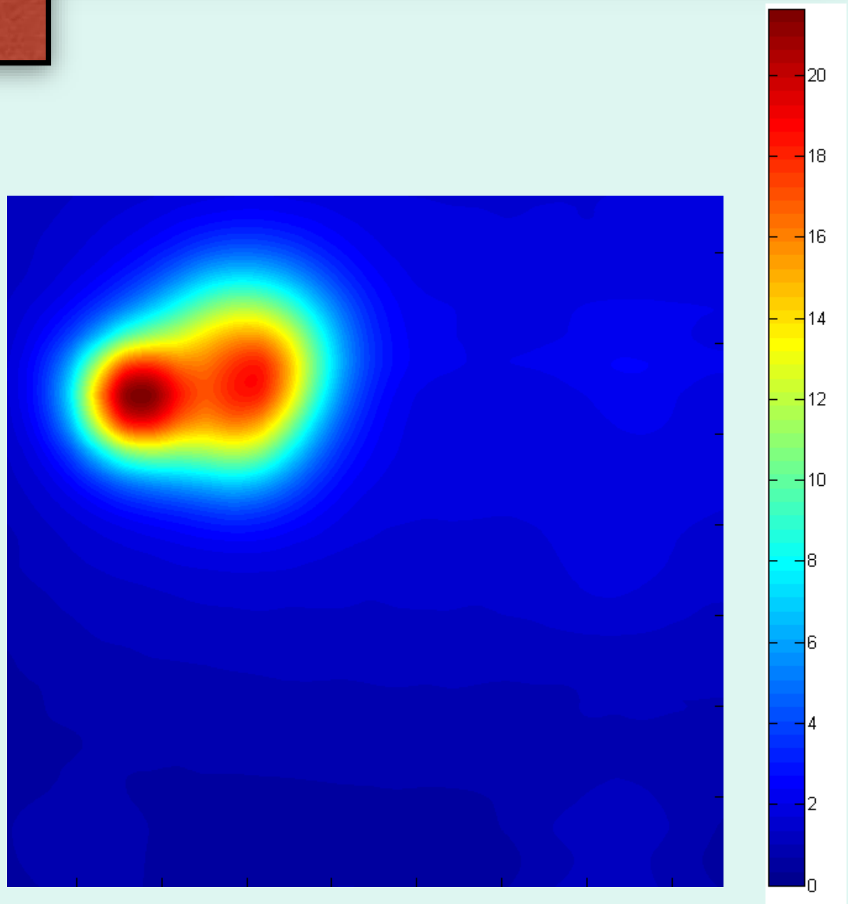
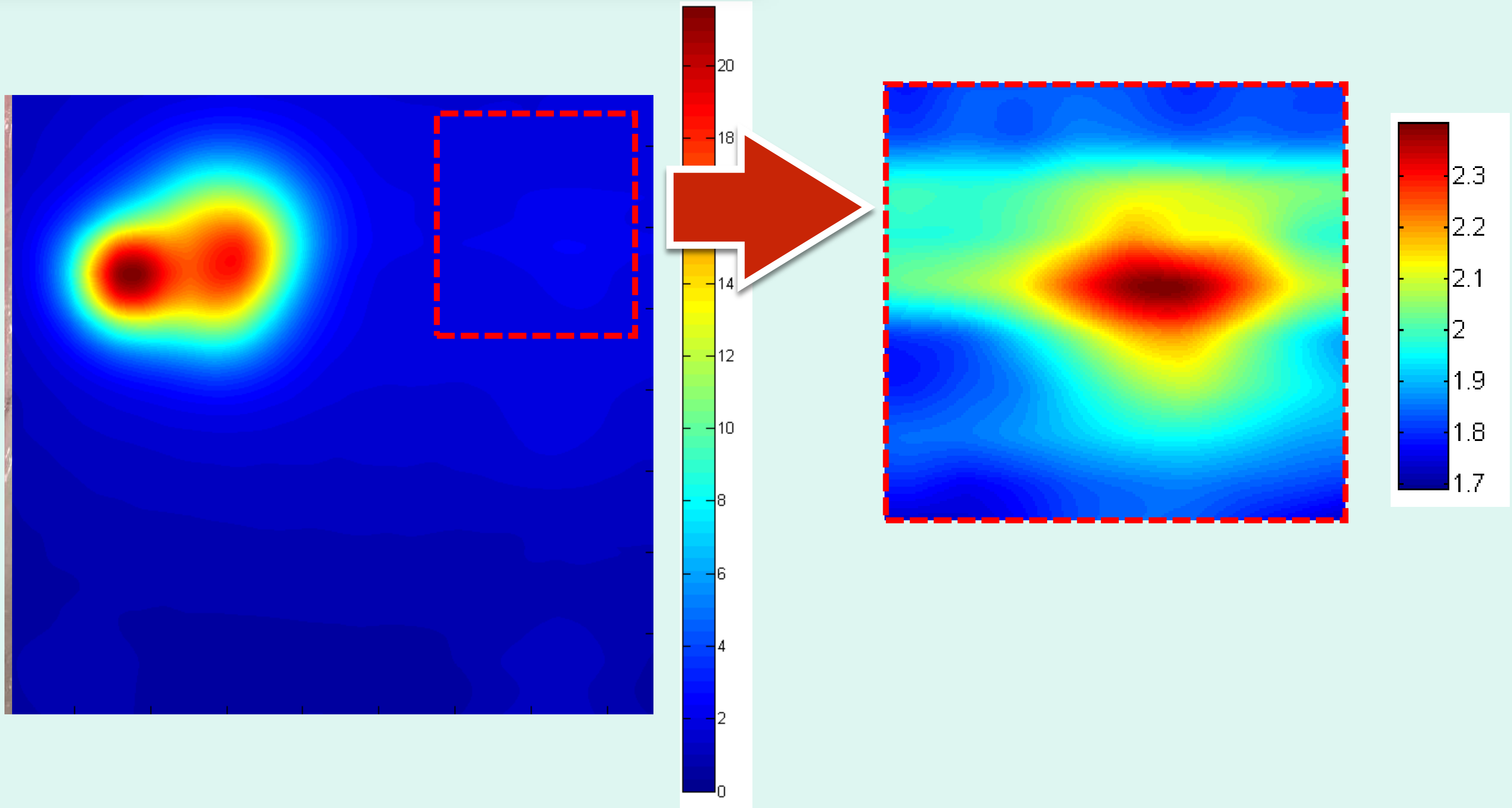
ACB scanning system





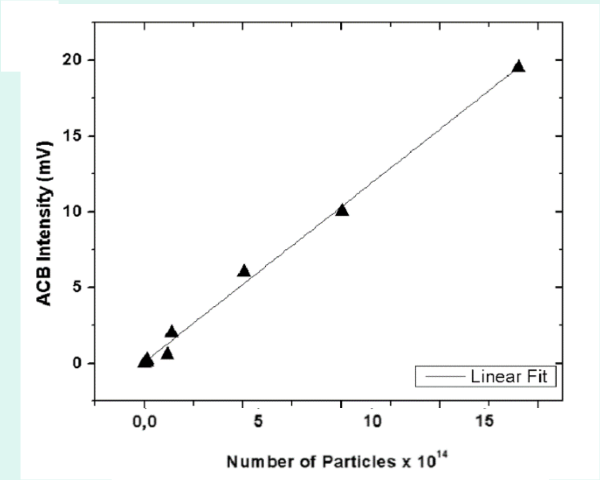
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

ACB scanning system

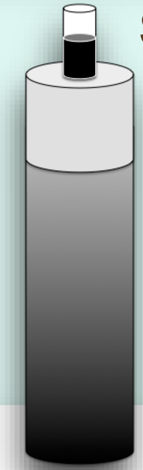


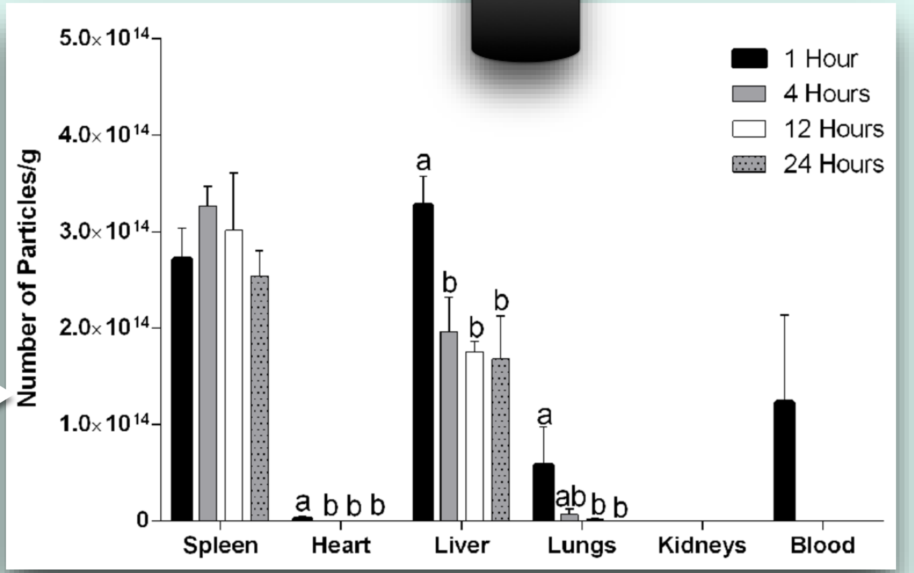
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

Nanoparticles quantification by ACB



Calibration Curve





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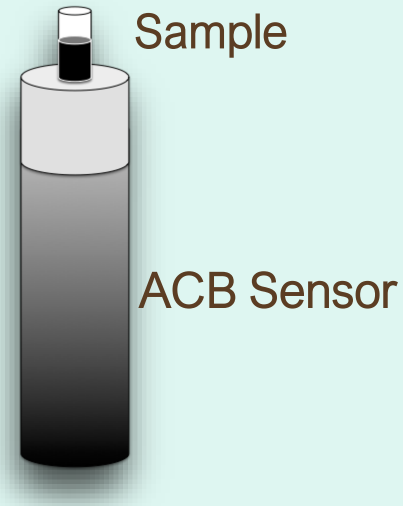
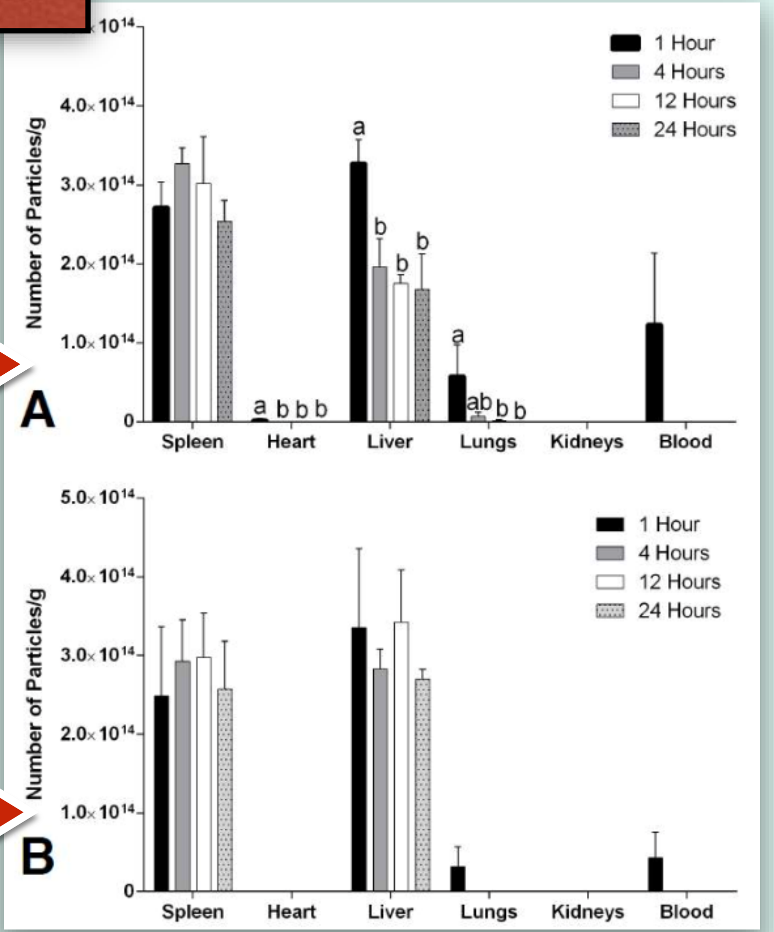
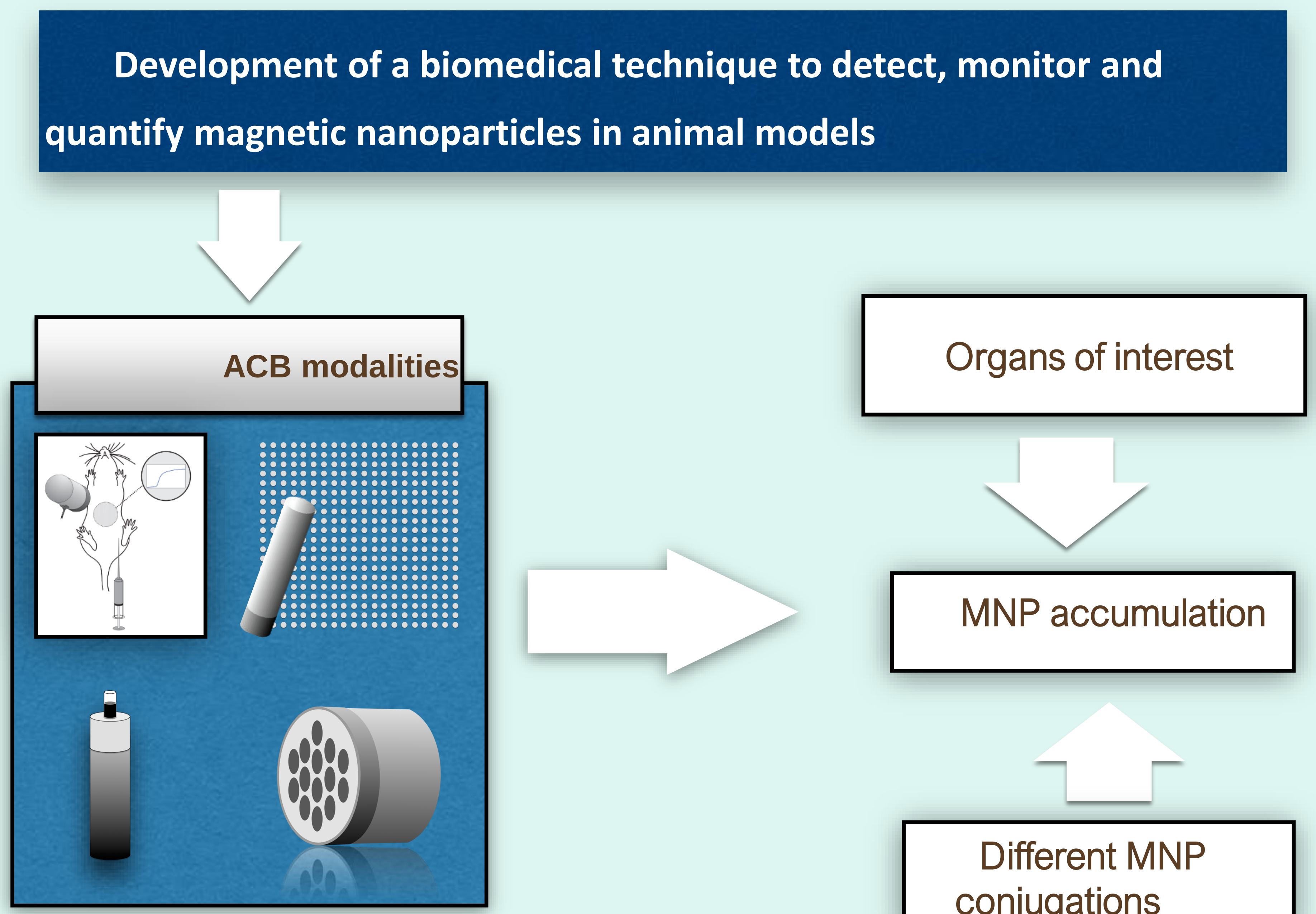
Nanoparticles quantification by ACB



ACB

ESR




Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models
ACB modalities
Organs of interest
MNP accumulation
Different MNP conjugations

Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

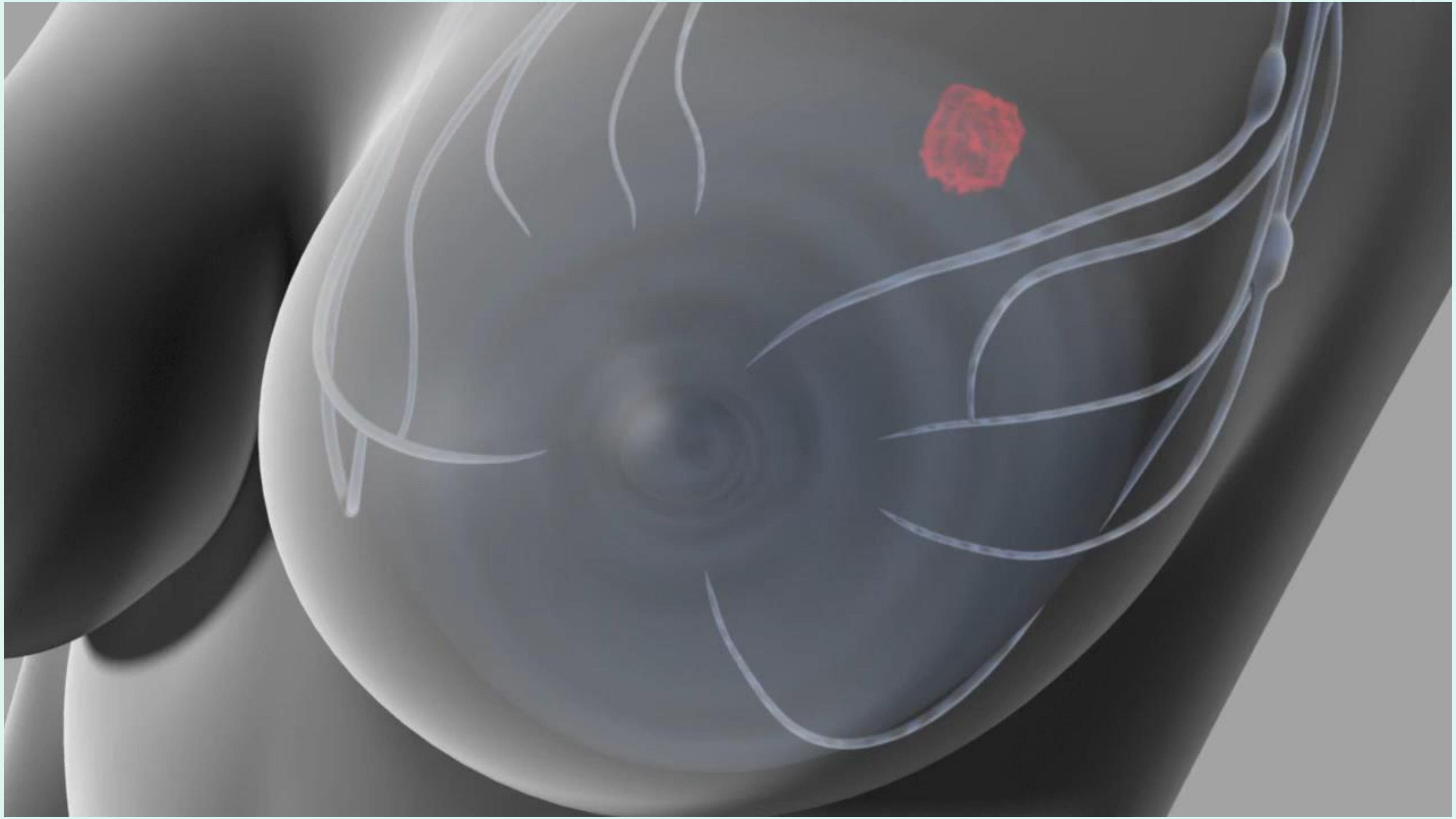
ACB modalities

- Simplicity
- Versatility
- Non-Invasive
- Association with other techniques
- Already employed on human studies

AC Susceptibility in Sentinel Node detection

- The **sentinel lymph node** is the hypothetical first lymph node or group of nodes draining a cancer. In case of established cancerous dissemination, it is postulated that the sentinel lymph node/s is/are the target organs primarily reached by metastasizing cancer cells from the tumor.
- **https://www.endomag.com/**
- **https://www.youtube.com/watch?v=a6xRx329lxw**

AC Susceptibility in Sentinel Node detection



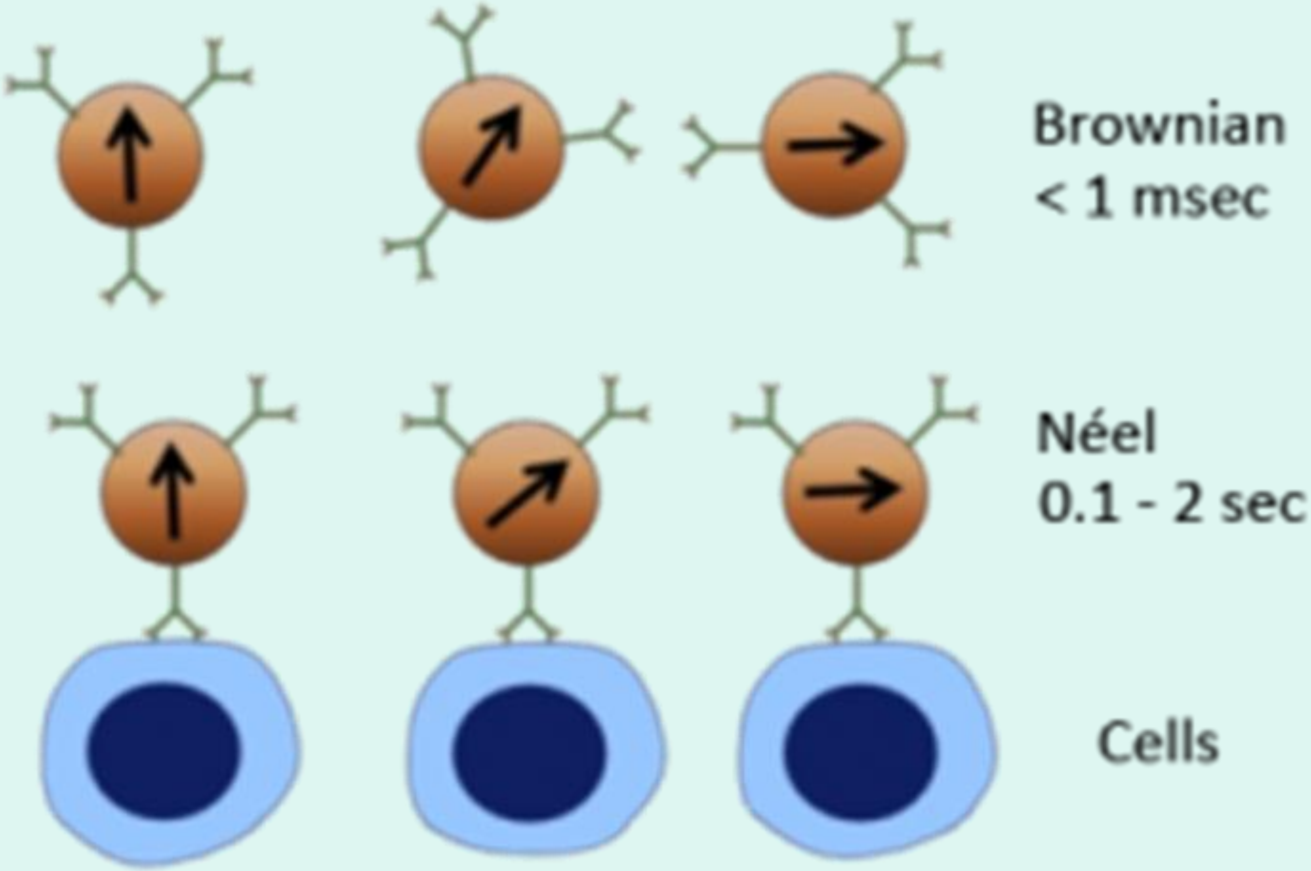
RELAXOMETRY STUDIES OF NANOPARTICLES IN BIOLOGICAL SYSTEMS

- Magnetic particles in a biological media can relax by two mechanisms, Brownian Motion and Néel, that depending on the particle size can have distinct values. The basic idea is that the functionalized magnetic nanoparticles attached to cancer cells will only relax by Neel mechanism which in the present case produce a longer relaxation time than Brownian motion. Thus, by measuring the relaxation of these particles it is possible to detect and calculate the concentration of cancer cells as depicted below.

- A key parameter is the number of MNPs take can be detected. The smaller the better to have a precise and earlier detection of a tumor.

- Highly sensitive magnetometers are necessary.

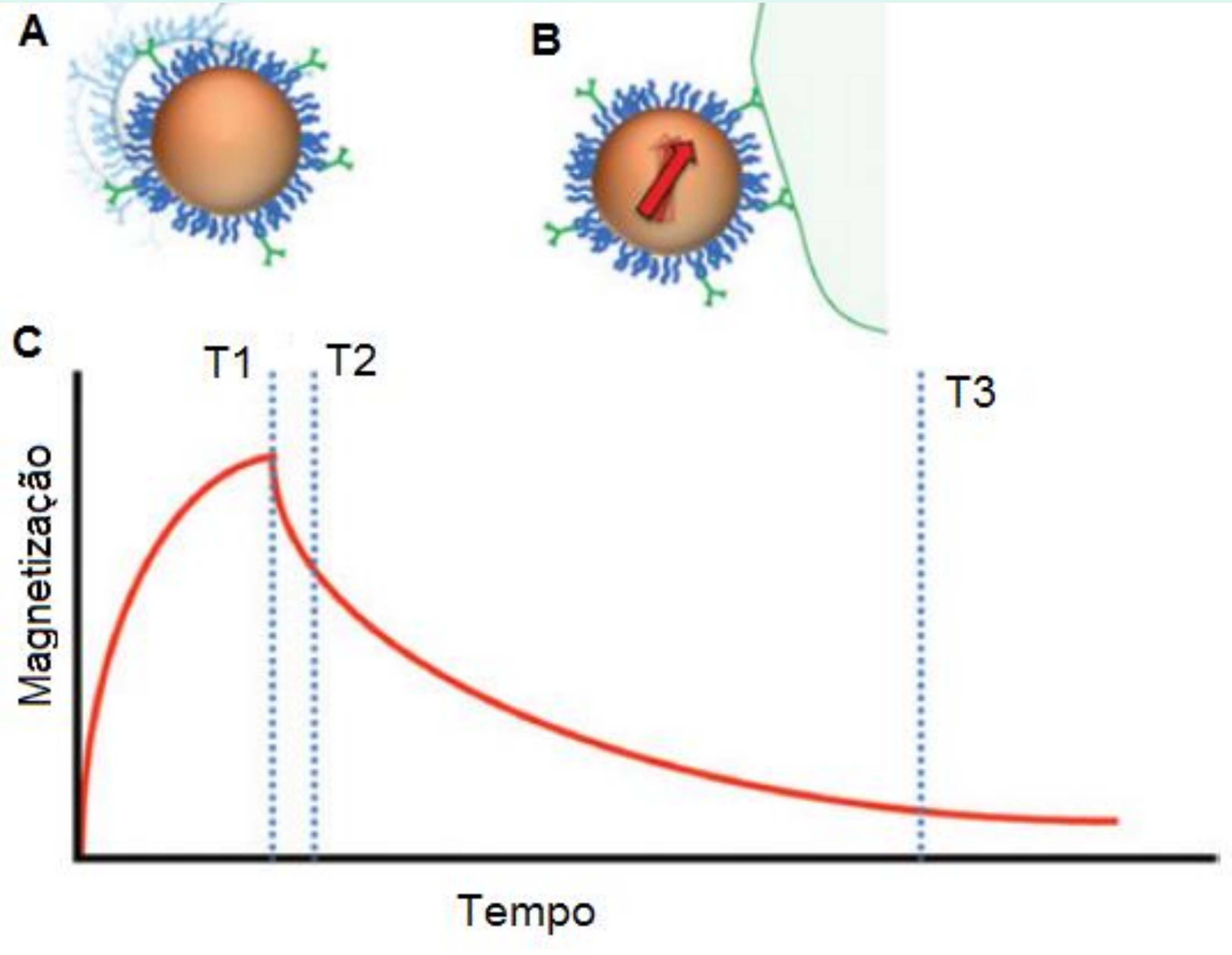
Relaxation Processes MNPs



Magnetic nanoparticles with 25 nm diameter and narrow size distribution

(Image adapted from http://www.seniorscientific.com)

Magnetization (A) & Relax MNP (B)



MNP Total Relaxation Time

- $\tau_{MNP} = (\frac{1}{\tau_N} + \frac{1}{\tau_B})^{-1}$
- $\tau_N = \tau_0 e^{\frac{KV}{kT}}$
- $\tau_B = \frac{3\eta V_h}{k_B T}$

Atomic Magnetometer (AM)
now
Optically Pumped Magnetometers

General Principles of Operation

- **Optical pumping polarizes atoms**
- **Detect Larmor precession of atoms in B field**
- **Relaxation processes limit sensitivity**

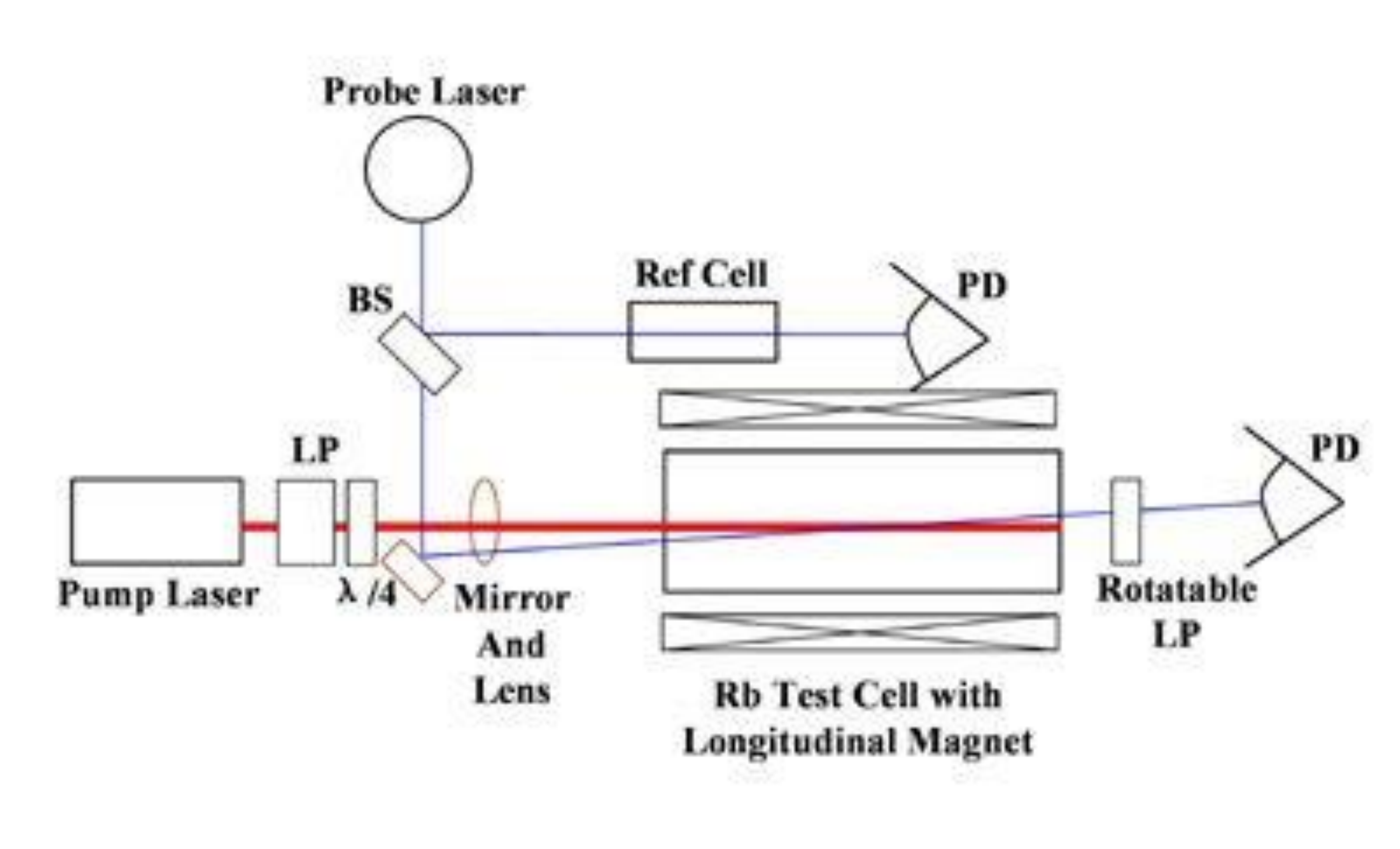
OPM-Working Principle

Measuring field strength with an optically pumped magnetometer

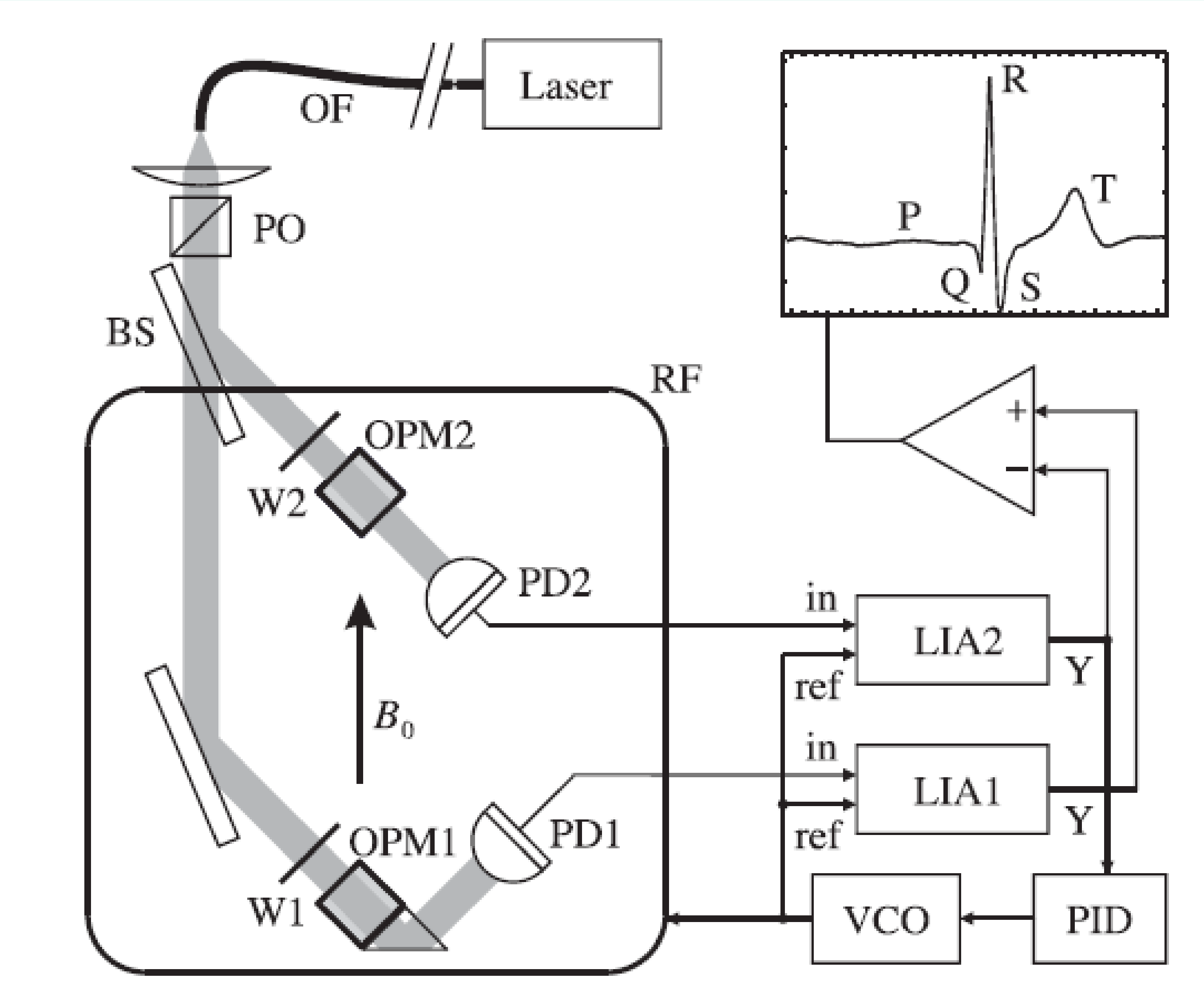
PML
PHYSICAL MEASUREMENT LABORATORY

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

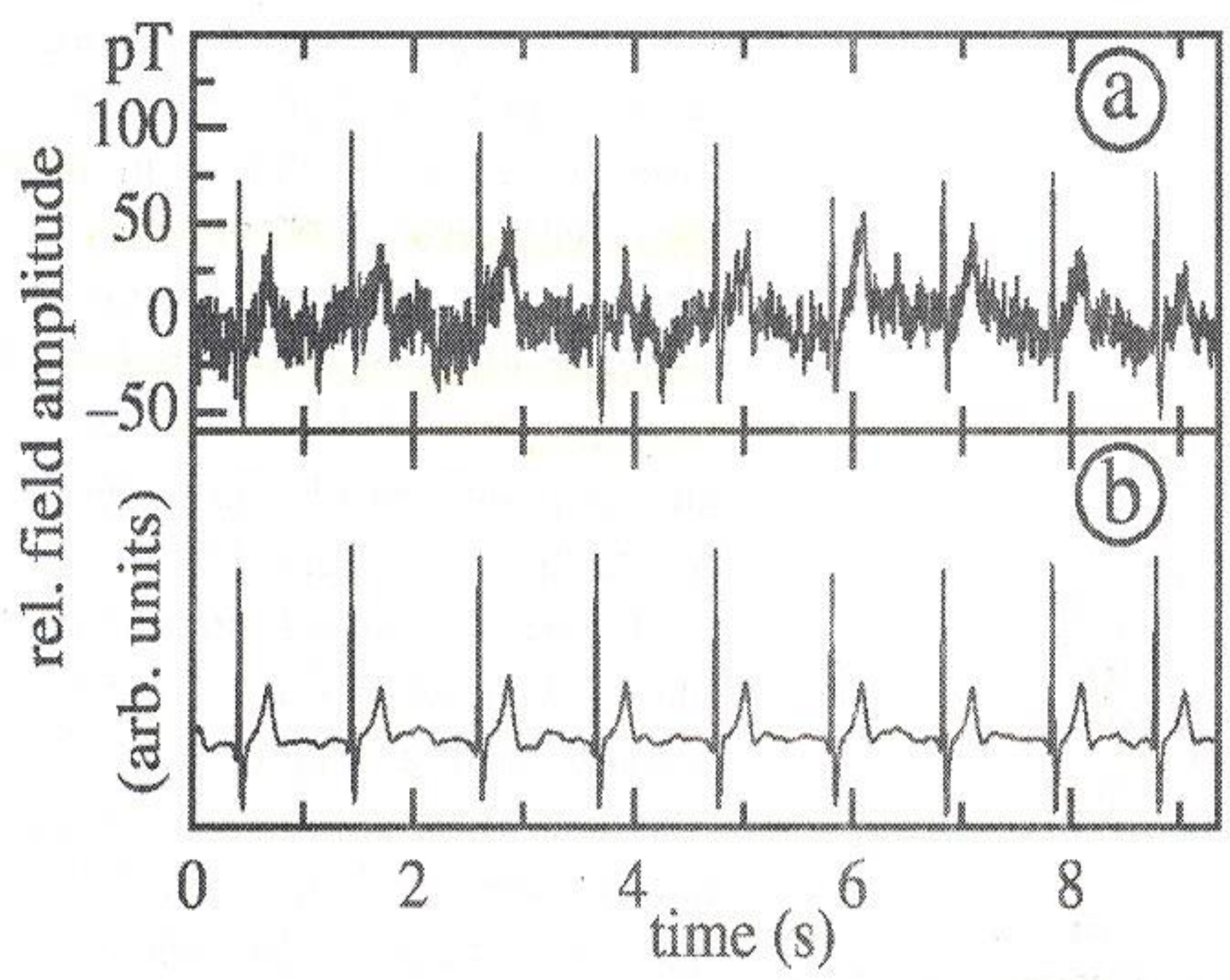
Optical Pumped Magnetometer-Rubidium Cell



Experimental array for a first order electronic gradiometer based on OPMs



Optical and electronic components: optical fiber (OF), polarizer (PO), beam splitter (BS), quarter wave plates (W1,W2), photodiodes (PD1, PD2), cesium-vapor cells (OPM1, OPM2), lock-in amplifiers
(LIA1, LIA2), servo amplifier (PID), voltage-controlled oscillator (VCO).



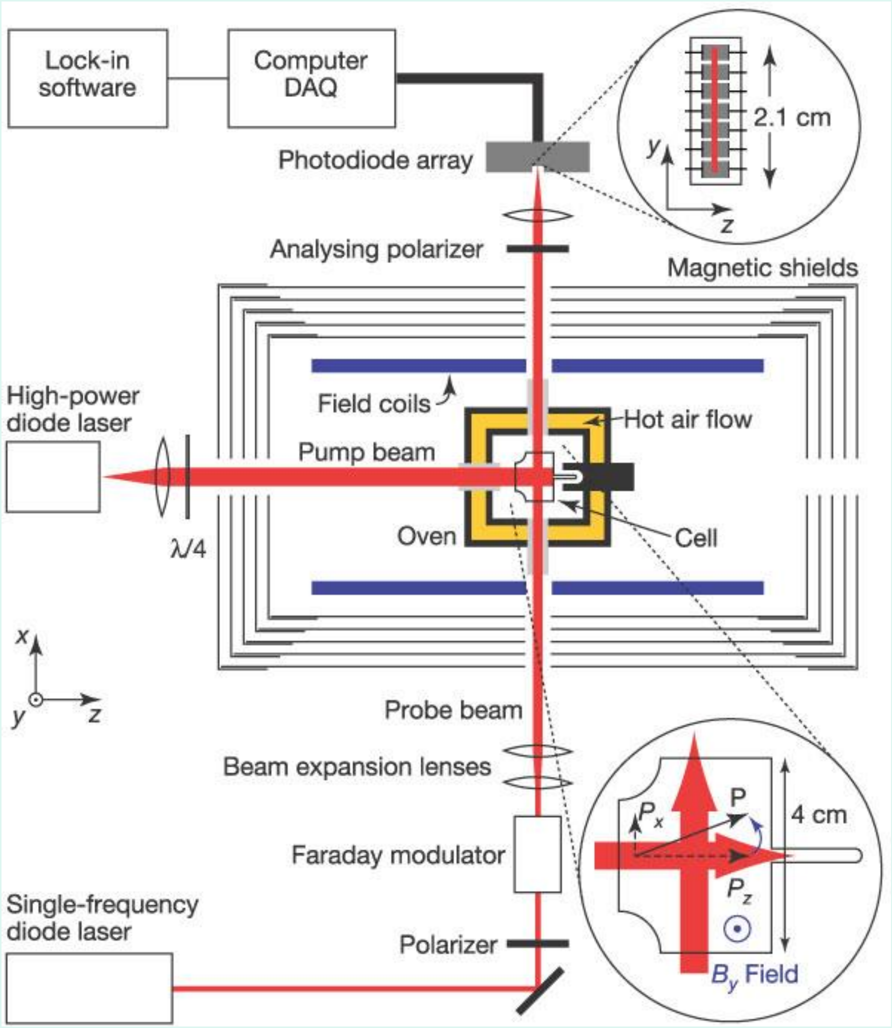
raw signal

~100 fT/(Hz)$^{1/2}$

processed signal

Bison et al., Optics Express 11:904 *(2003)*

The SERF Magnetometer

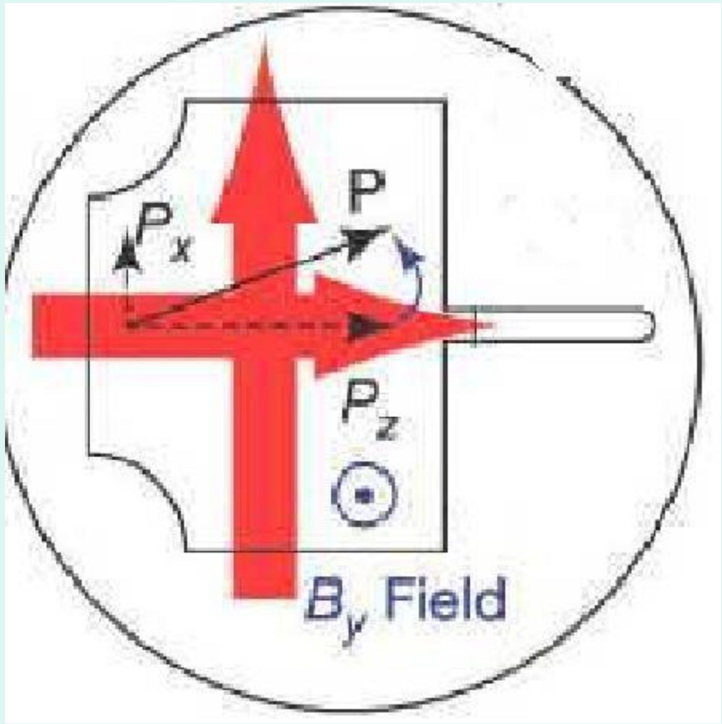


- **Pump laser and probe laser**
- **Heavy magnetic shielding**

I. K. Kominis, T. W. Kornack, J. C. Allred & M. V. Romalis, "A subfemto-tesla multichannel atomic magnetometer." Nature **422**, 596 (2003).

Detection

- optically pumped atoms are polarized along z
- B_y rotates the spin; polarization acquires x component
- P_x can be detected by probe beam



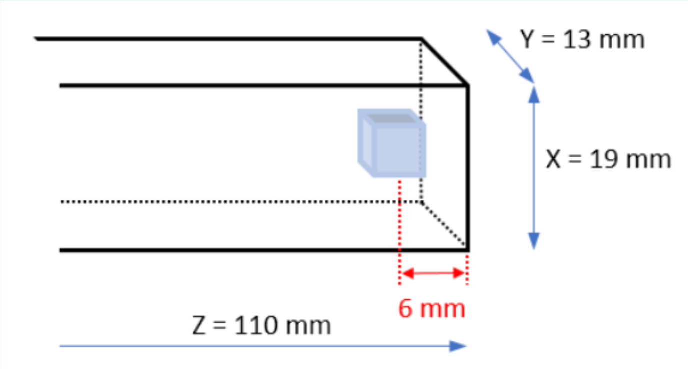
Advantages of Rubidium

- **Higher relaxation rate → lower sensitivity, but higher bandwidth**

- **Suitable diode lasers are mass produced**

MRX & OPMs

OPM Technical Specifications



Field Sensitivity: less than 15 fT/√Hz in 1-100 Hz band
Dynamic Range: ±5 nT
Measurement Axes: Z-axis only / Y-axis only / Dual Z & Y axes (simultaneous)
Calibration: Internal reference (automated)
Signal Outputs: Analog, USB Digital
Power consumption: 5W total (0.7 W sensor head)
Atomic species: Rubidium

Magnetic Shielding

ZG-206

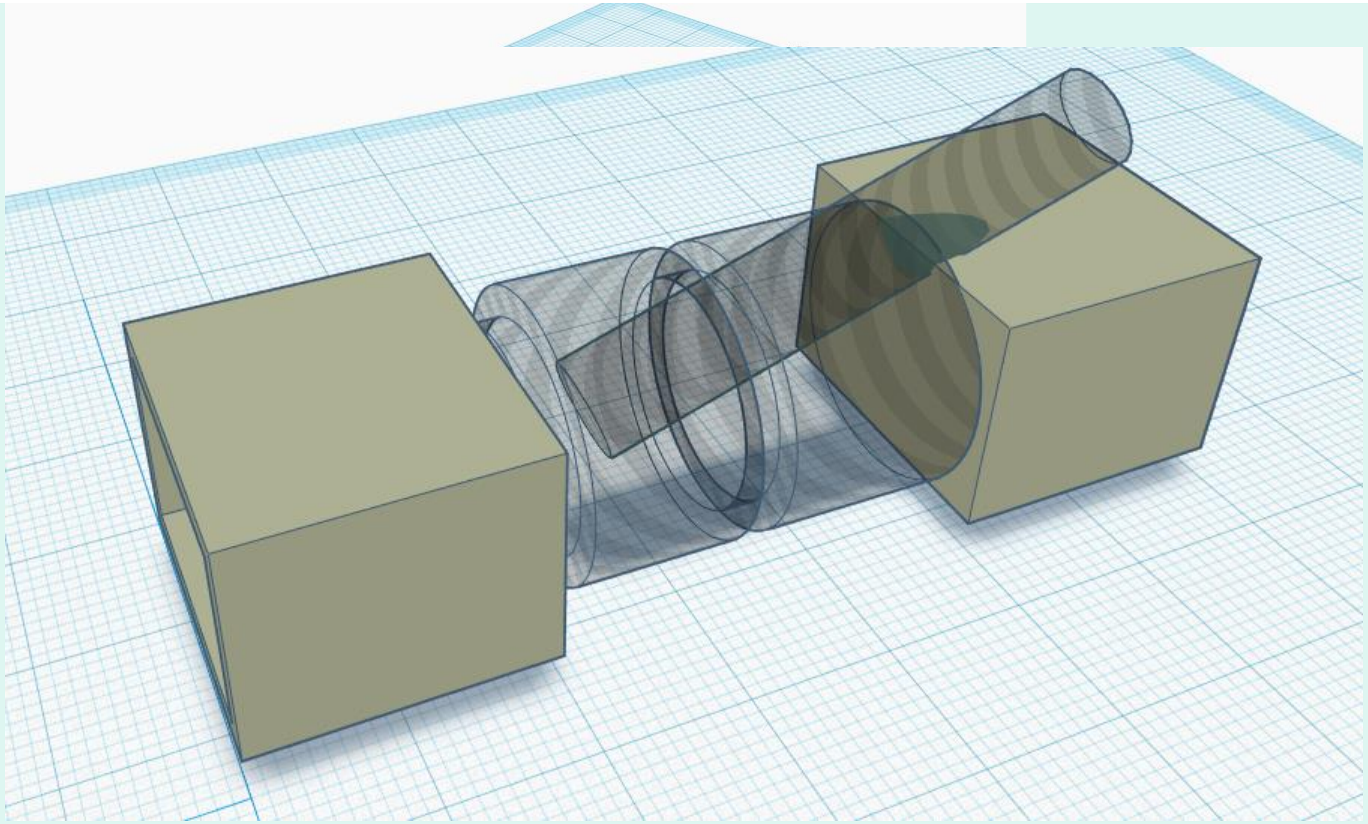
- Internal diameter 152mm
- Inside Depth 381mm
- Outside diameter 210mm
- Overall length 438mm

- 3 layer of thickness 0.64mm
- Attenuation ~1,500

Zero Gauss Chamber

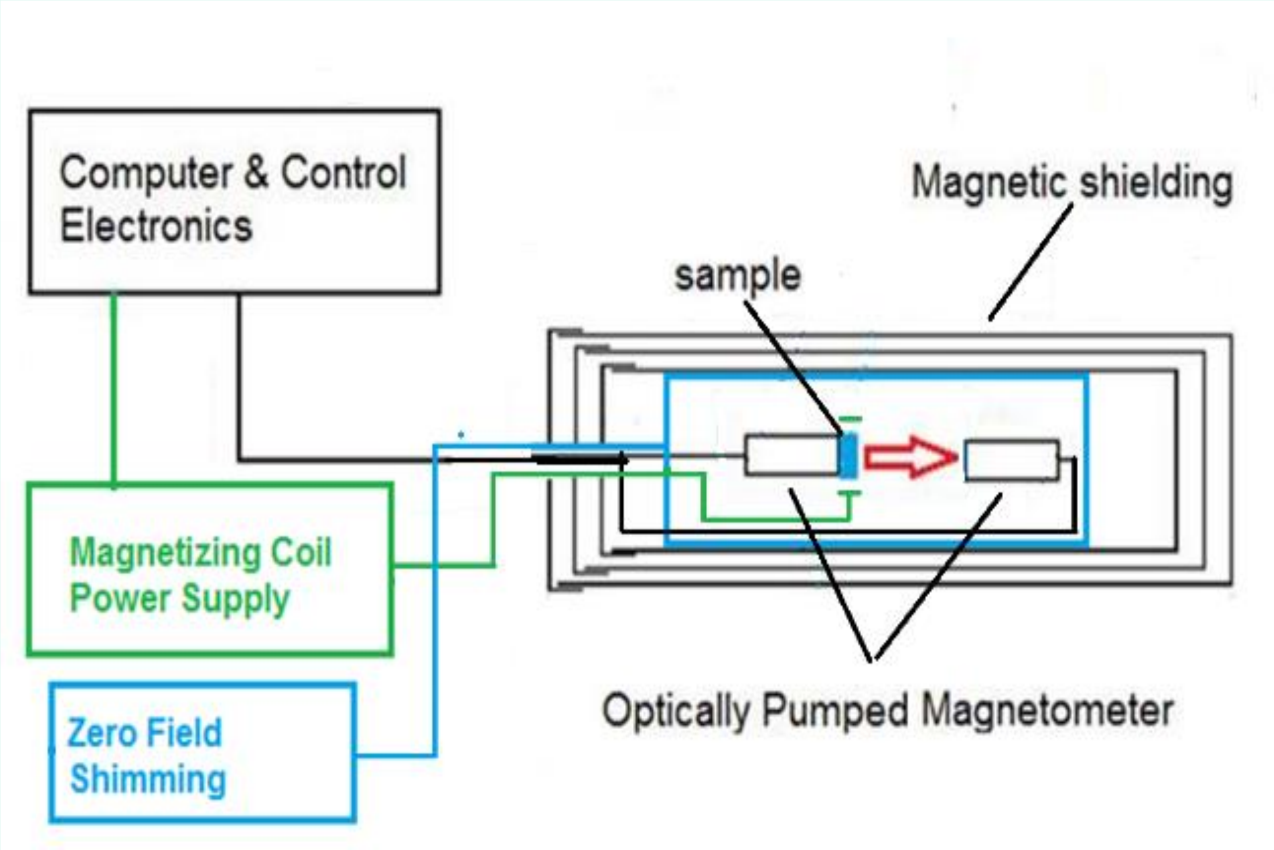
MAGNETIC SHIELD CORPORATION

Sample set up



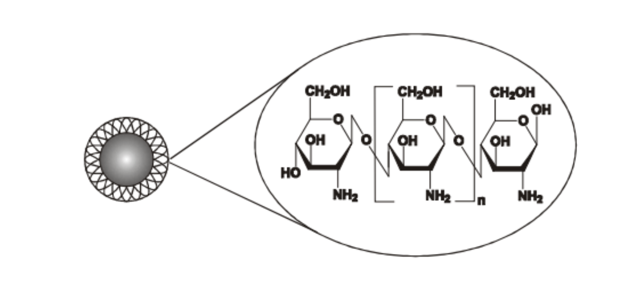
General view of the set up

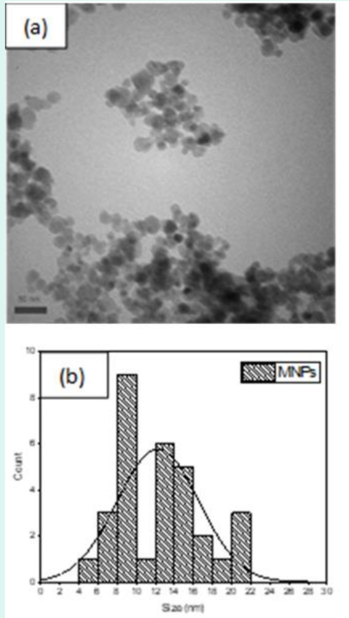
Schematics for MRX Acquisition

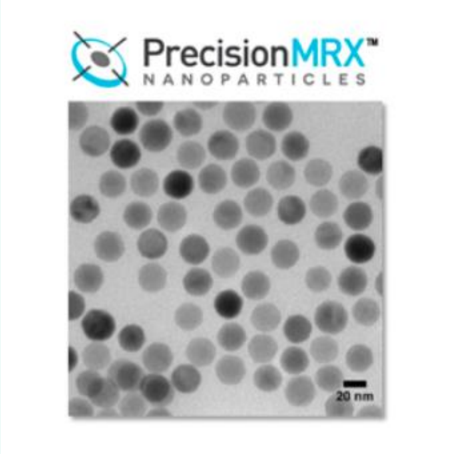


Magnetic Nanoparticles

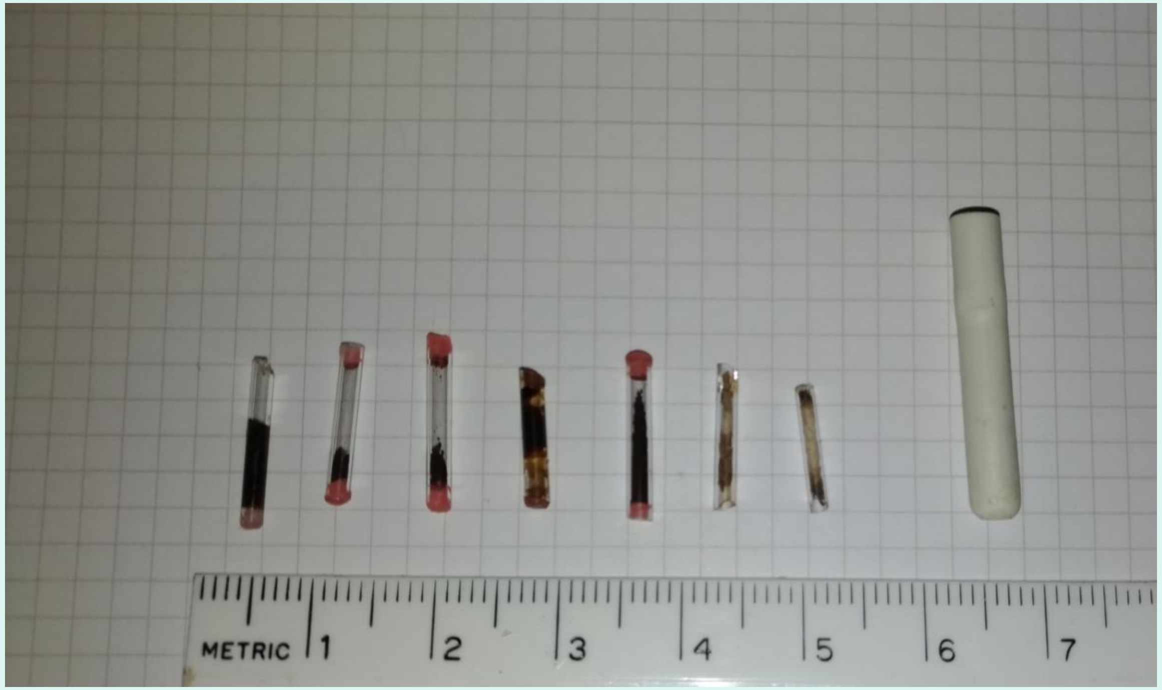
- **1-Chemicell fluidMAG-Chitosan Φ = 2μm**
- **2-Home made magnetic Fe_3O_4 nanoparticle, synthesized by the co-precipitation method at 90ºC**
- **3- PrecisionMRX® Superparamagnetic Nanoparticles Φ = 25nm**





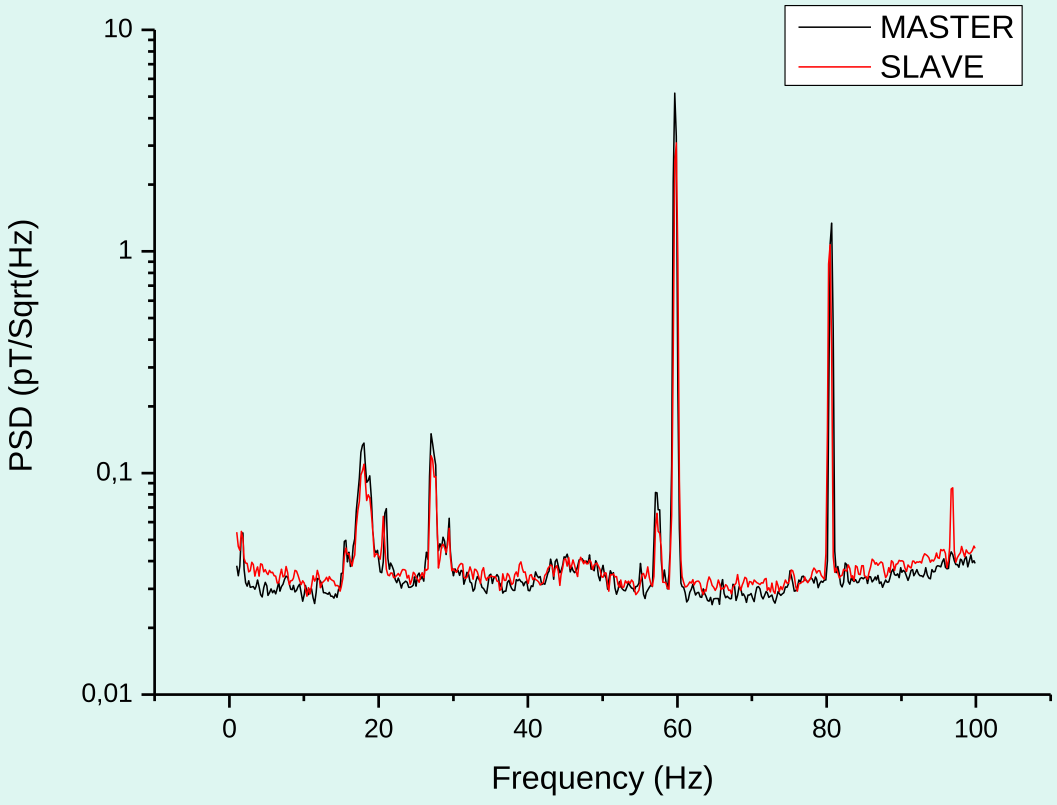


Samples

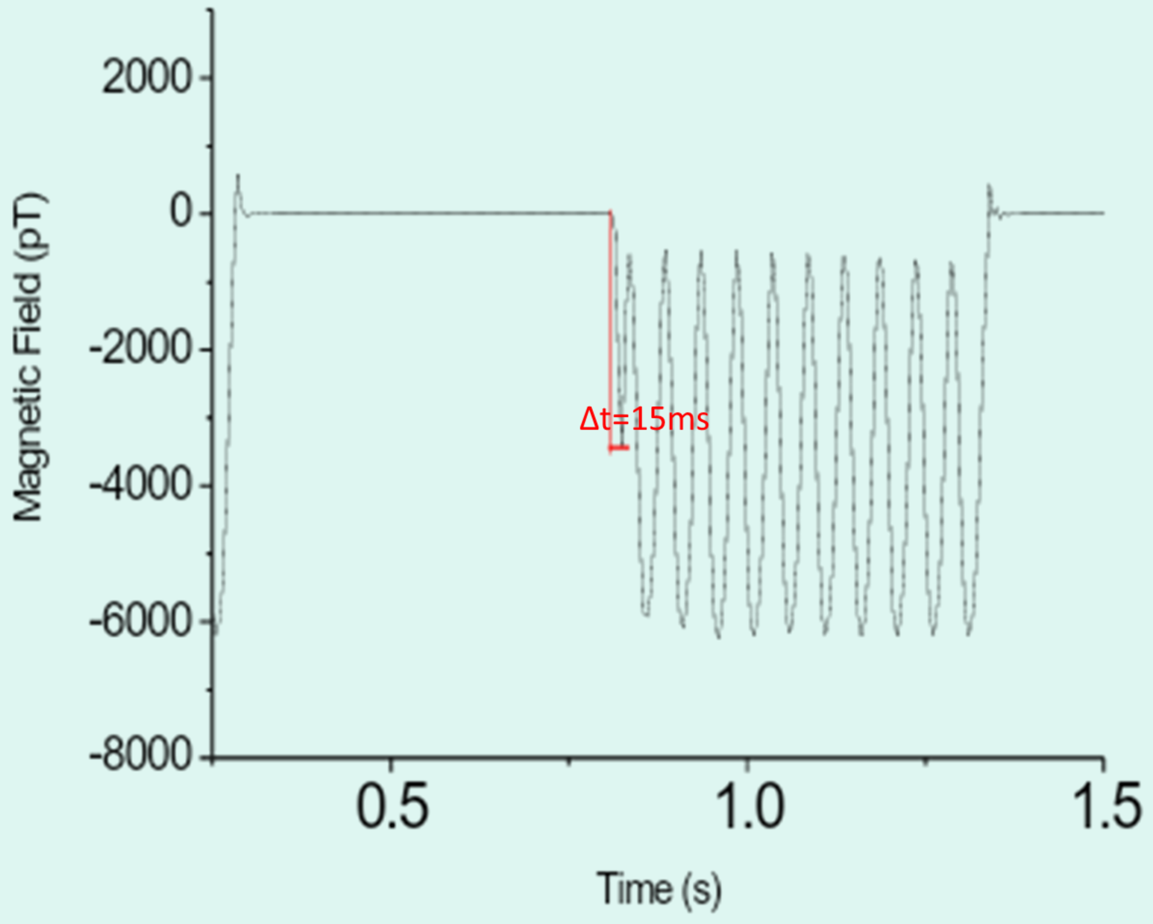


Hematocrit glass capillary tube internal diameter 1mm & PVC Sample holder.

A typical noise floor of the QZFM sensors in our laboratory



Time response

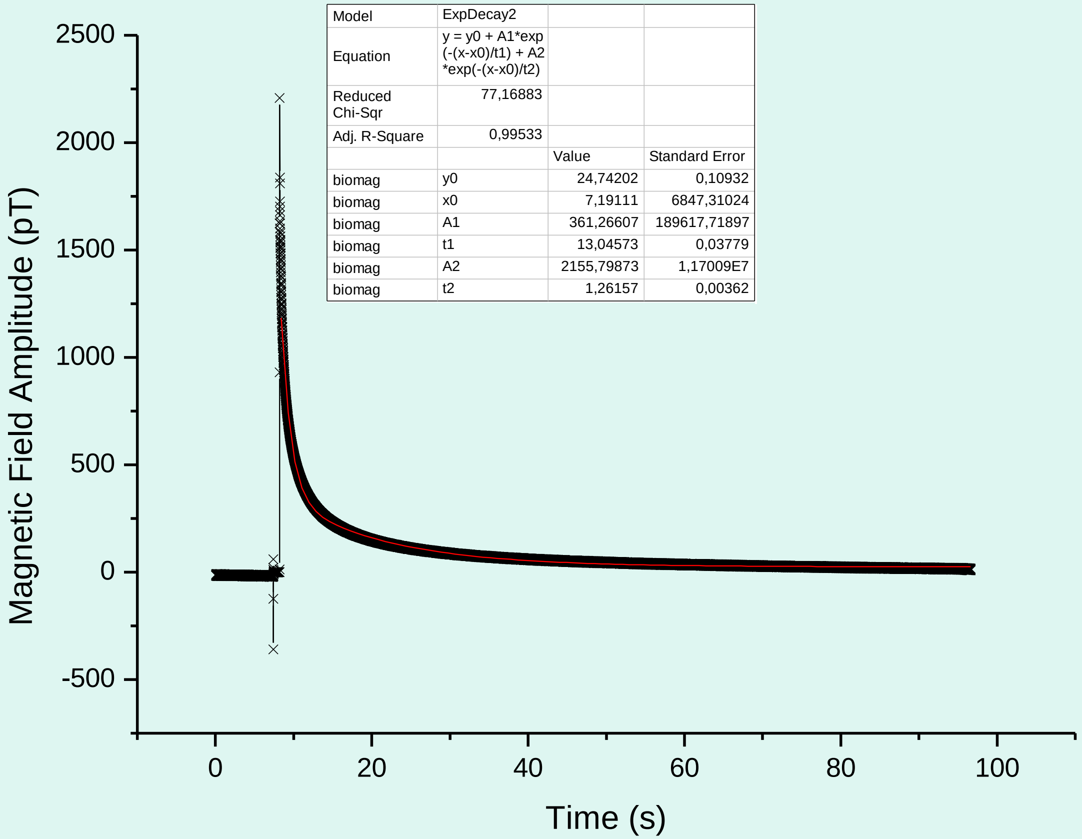


MNP in Solution

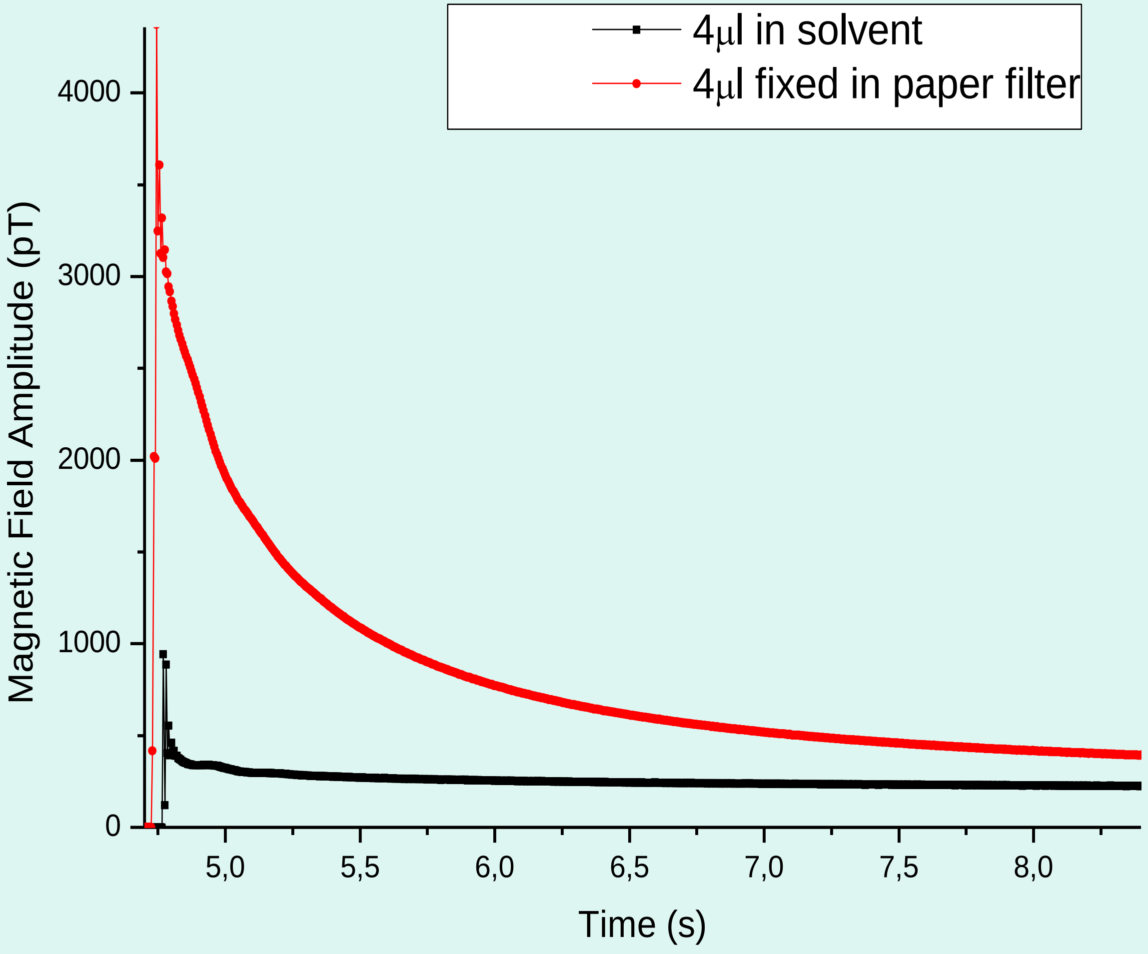
- **MNP 1 in water solution undergoing Brownian motion**

$$\tau_B = \frac{4\eta\pi r^3}{k_B T}$$

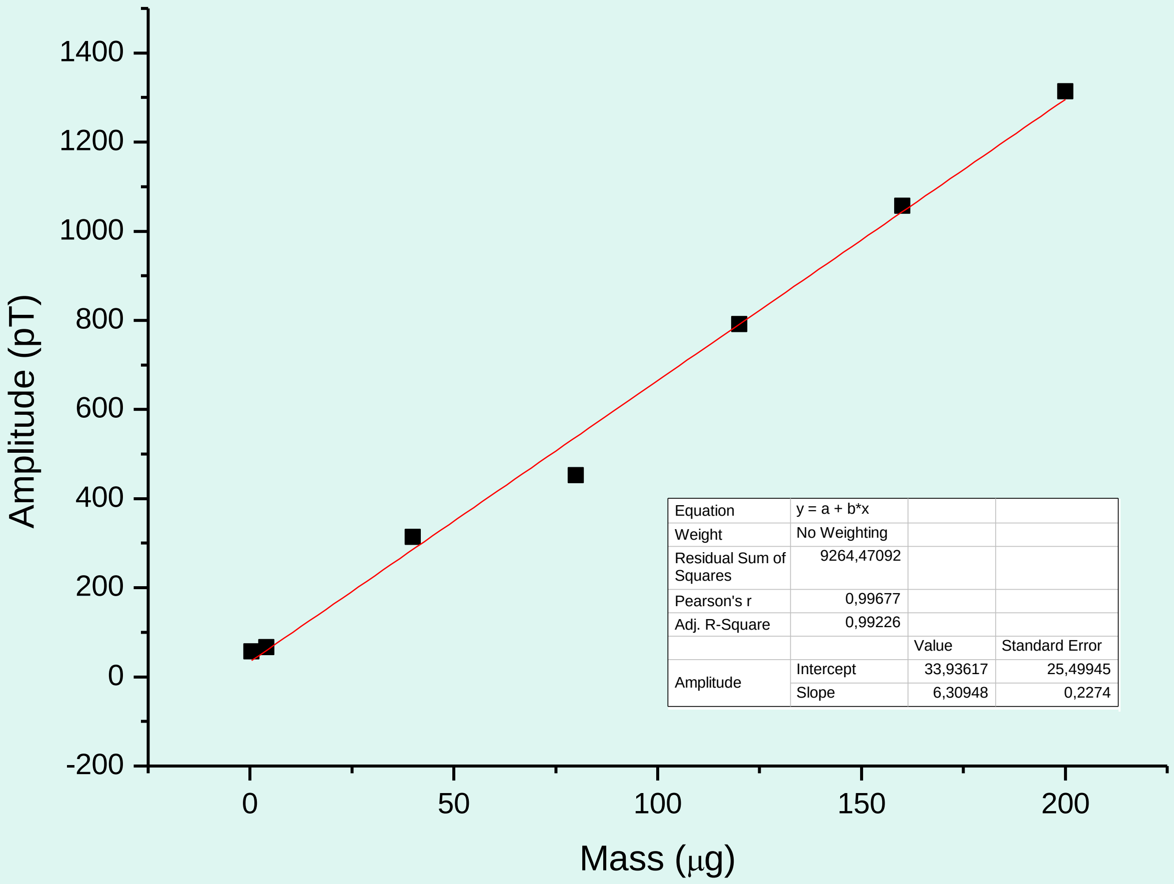
- **Using the time constant of 1.26s and assuming the viscosity is the same as water we get a radius of r = 0.77μm.**
- **DLS measurements gave a radius r = 0.812 μm.**



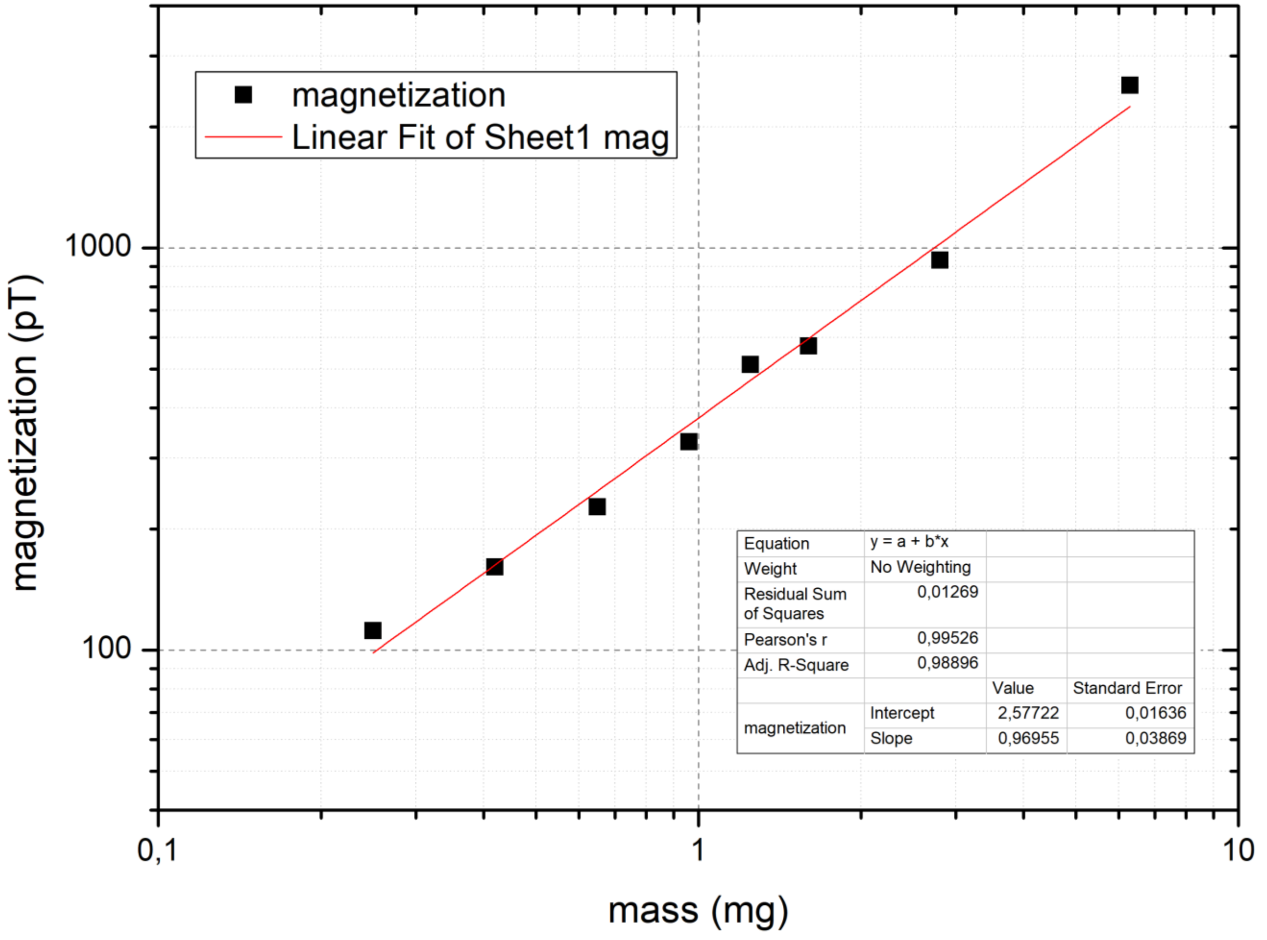
Comparison of signals of MNPs in a liquid and fixed in paper filter



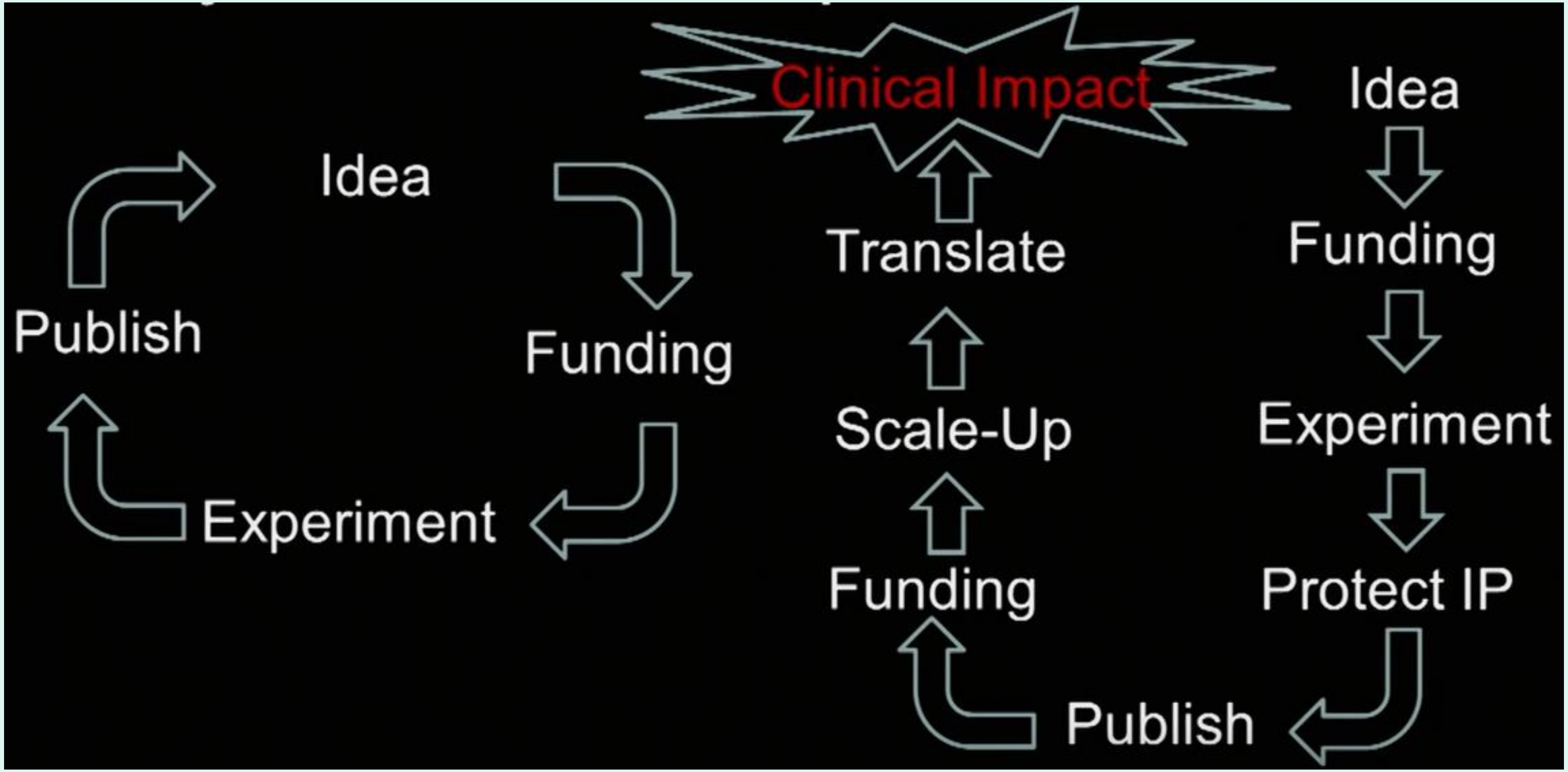
Calibration for MRx MNPs 25nm



Calibration for Home made MNPs

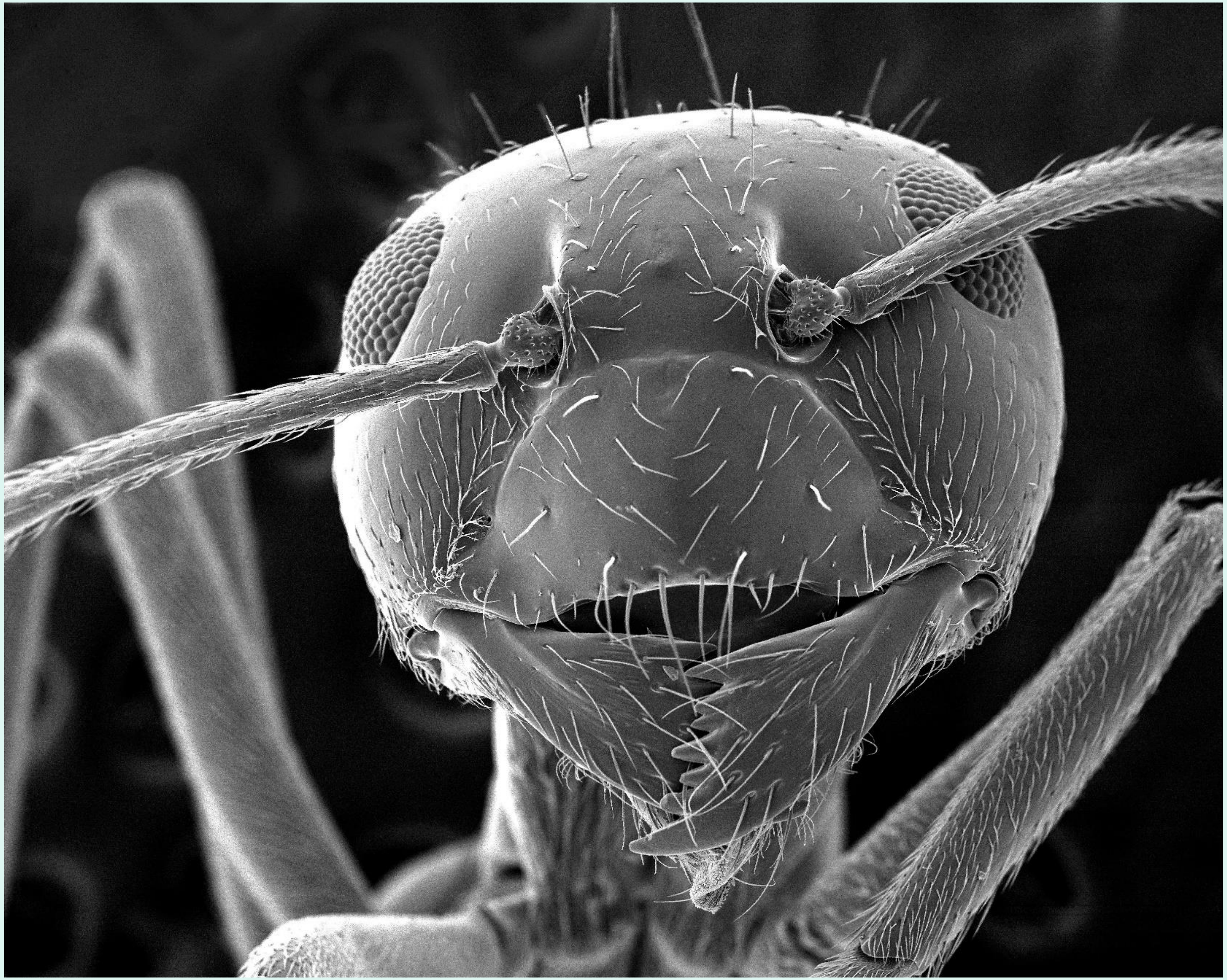


Translational Research



Origin- TEDx

Bye, for now !



Stefan Eberhard, Complex Carbohydrate Research Center, University of Georgia. Ant head