A Conceptual Introduction to the Physics of Magnetic Particles

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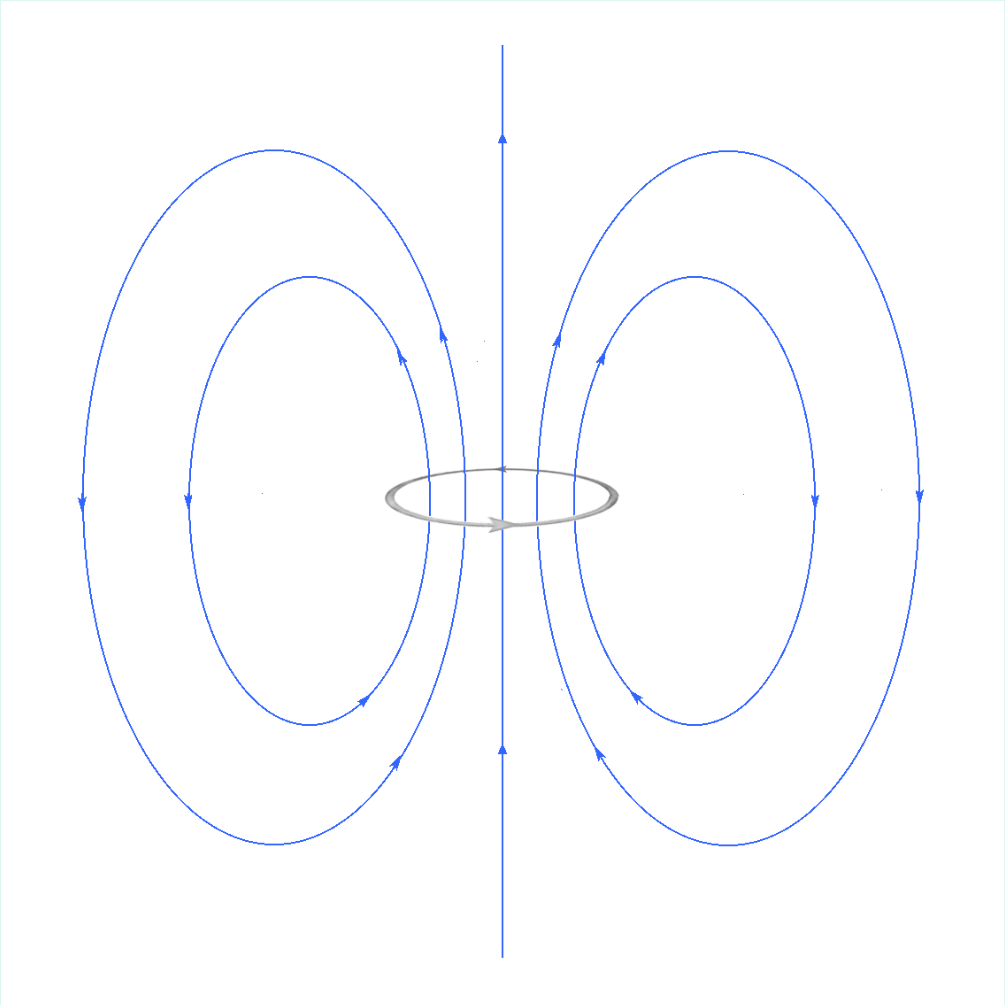
Outline of Lectures

- **Lecture 1**
  - Magnetic Moments and Magnetic Fields
  - Magnetic Materials - an Empirical Approach
- **Lecture 2**
  - Magnetic Materials - the Microscopic Picture
  - Small Particle Magnetism
- **Lecture 3**
  - Magnetic Particles in Fluids
  - Design of Magnetic Carriers
  - Applications of Magnetic Particles

Lecture 1

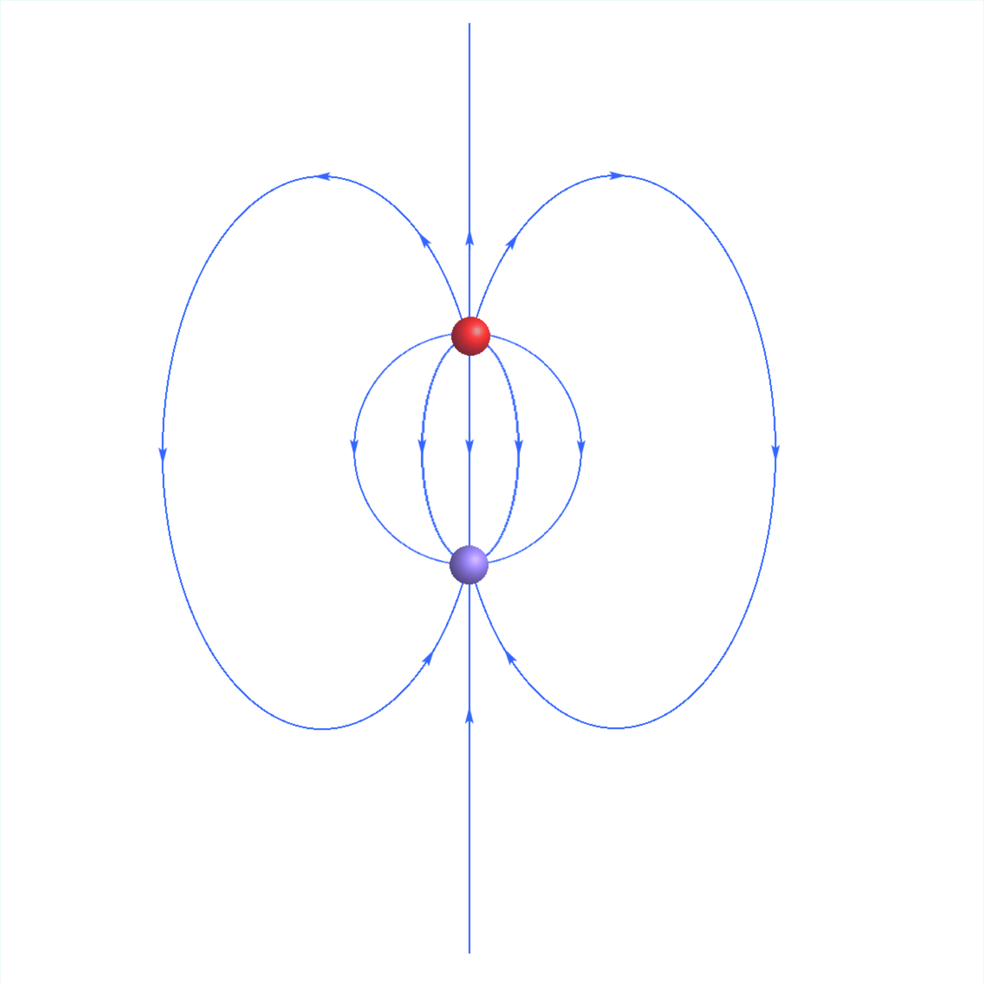
Magnetic Moments and Magnetic Fields

Magnetic fields are generated by movement of electric charges



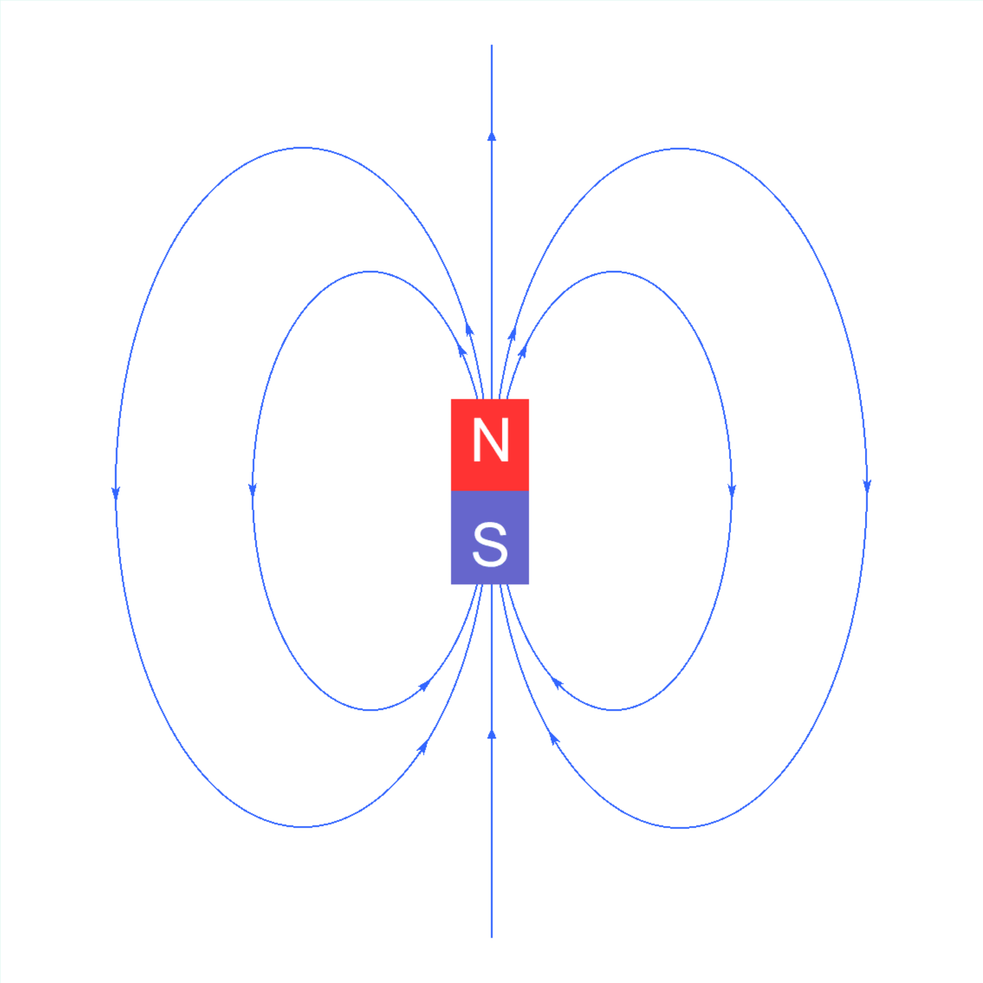
A loop of electric current generates a magnetic dipole field

A magnetic dipole



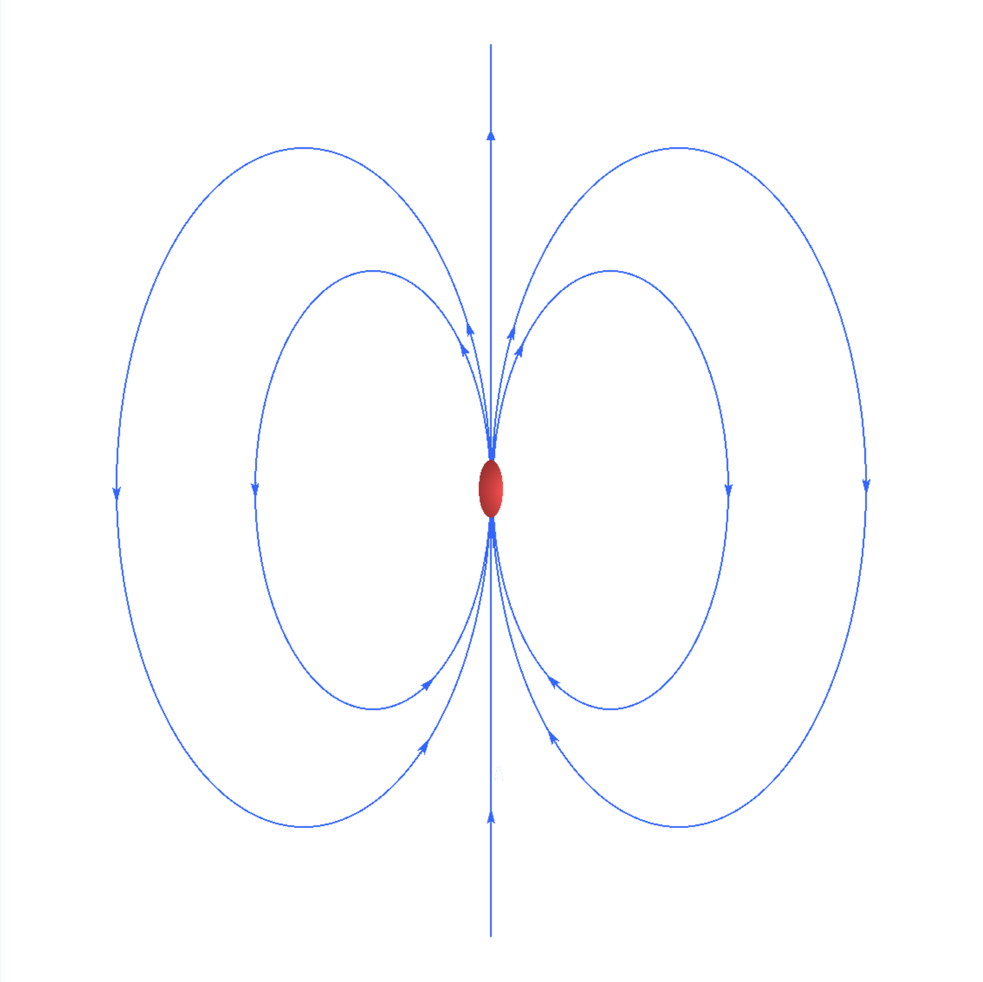
- **Field lines run from the North pole to the South pole**
- **Field lines indicate the direction of force that would be experienced by a North magnetic monopole**

A bar magnet



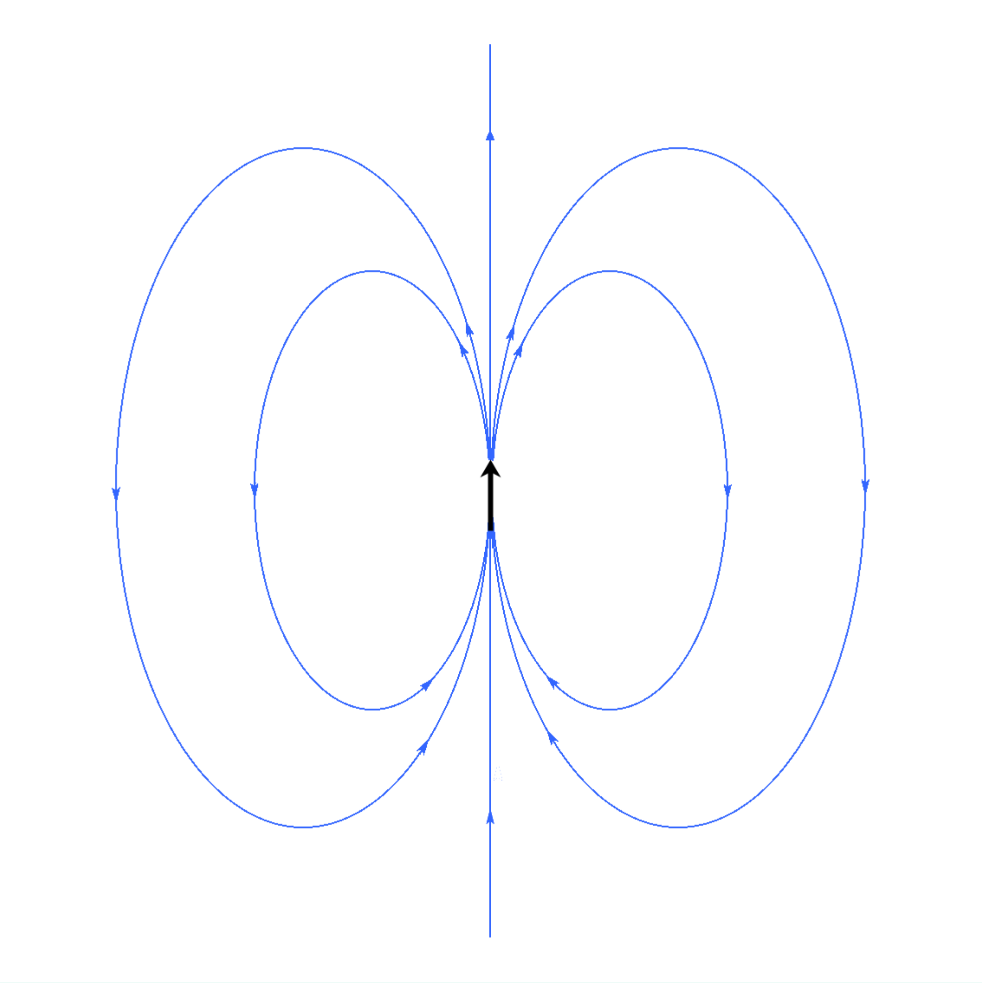
A simple bar magnet behaves like a magnetic dipole

Far field picture



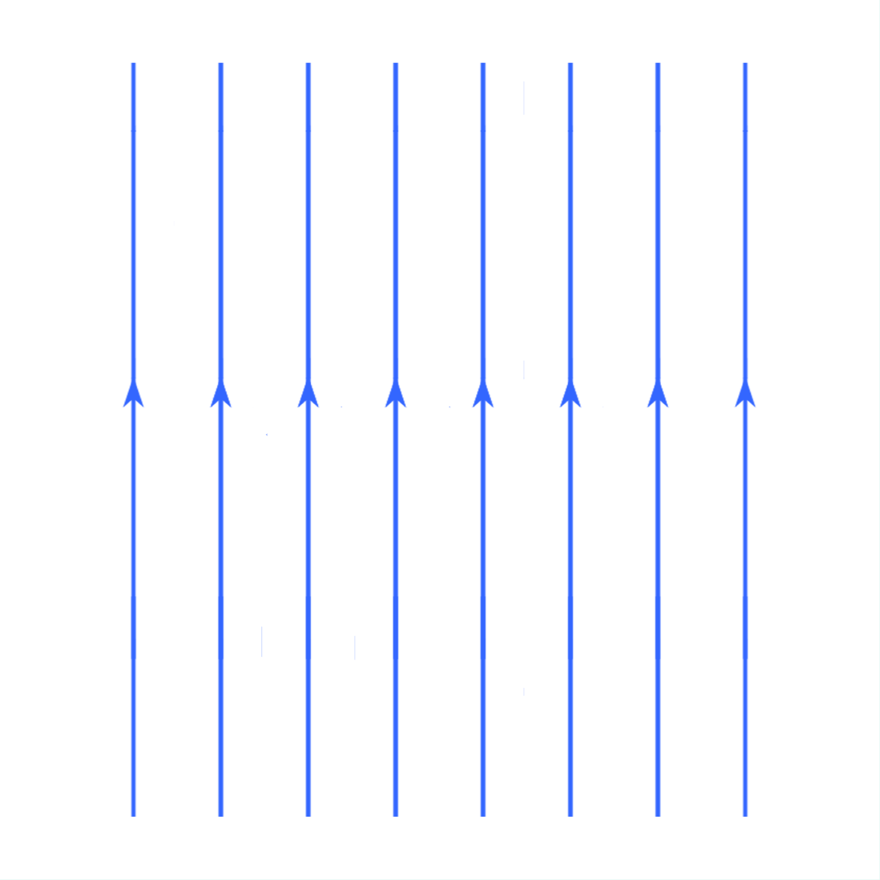
- Sometimes the dipoles are very small compared with their spatial field of influence
- An electron, for example

Schematic representation



- **A magnetic dipole is often represented schematically as an arrow.**
- **The head of the arrow is the North pole.**

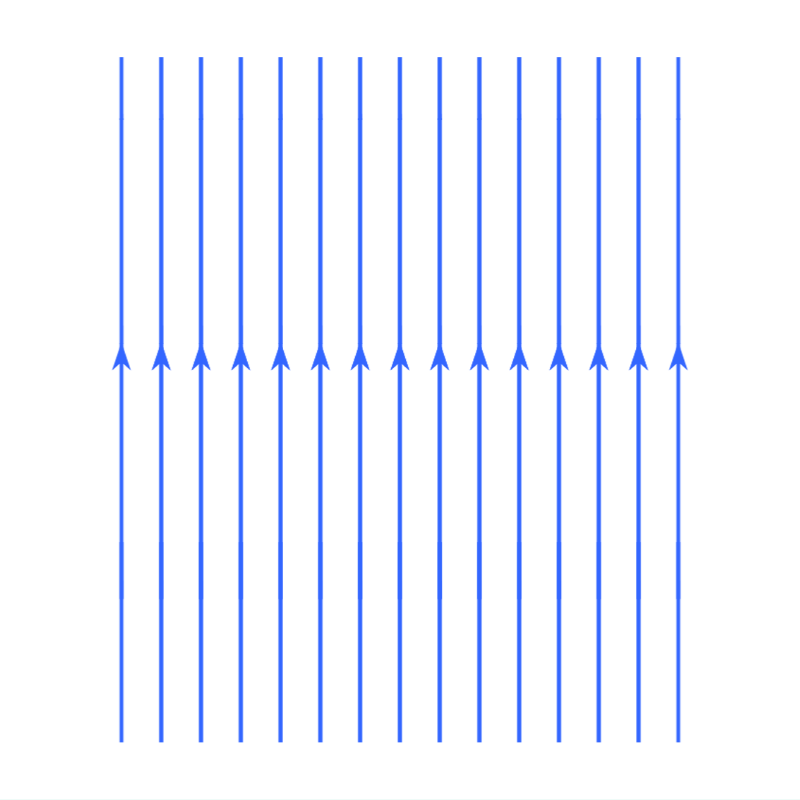
Flux density, $\boldsymbol{B}$



- Density of flux (or field) lines determines forces on magnetic poles
- Direction of flux indicates direction of force on a North pole

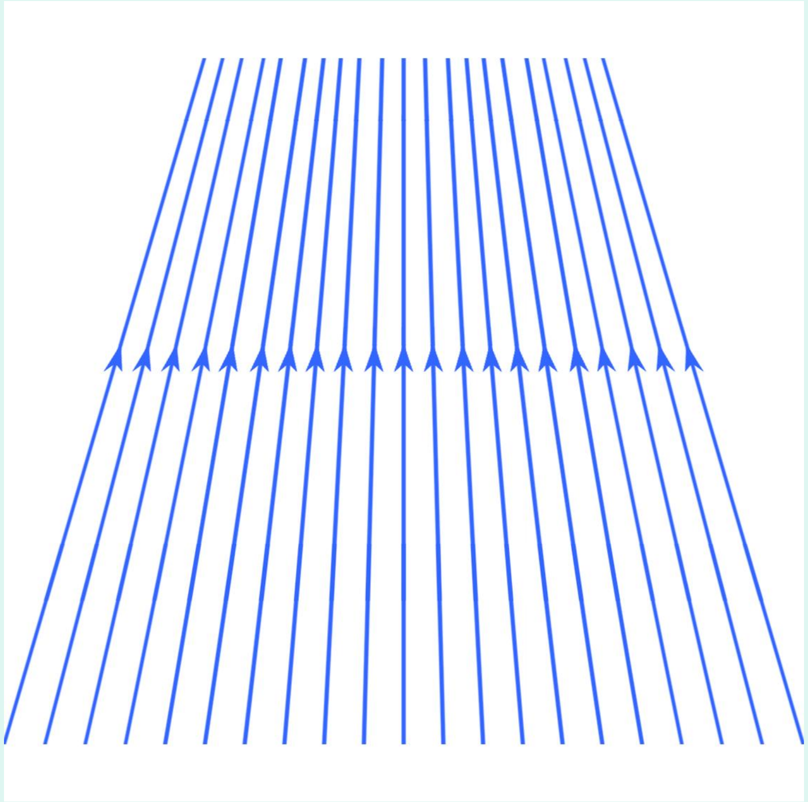
$$B = \phi / A$$

Flux density, $\boldsymbol{B}$



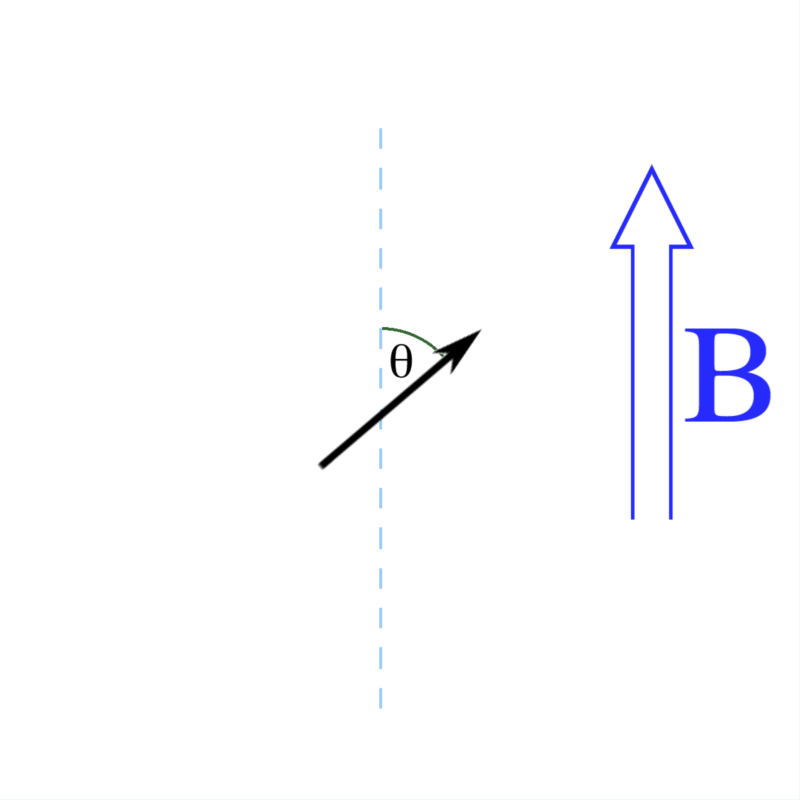
- **Higher flux density exerts more force on magnetic poles**

Magnetic field gradients



- **Magnetic field gradients exist when flux lines converge of diverge**

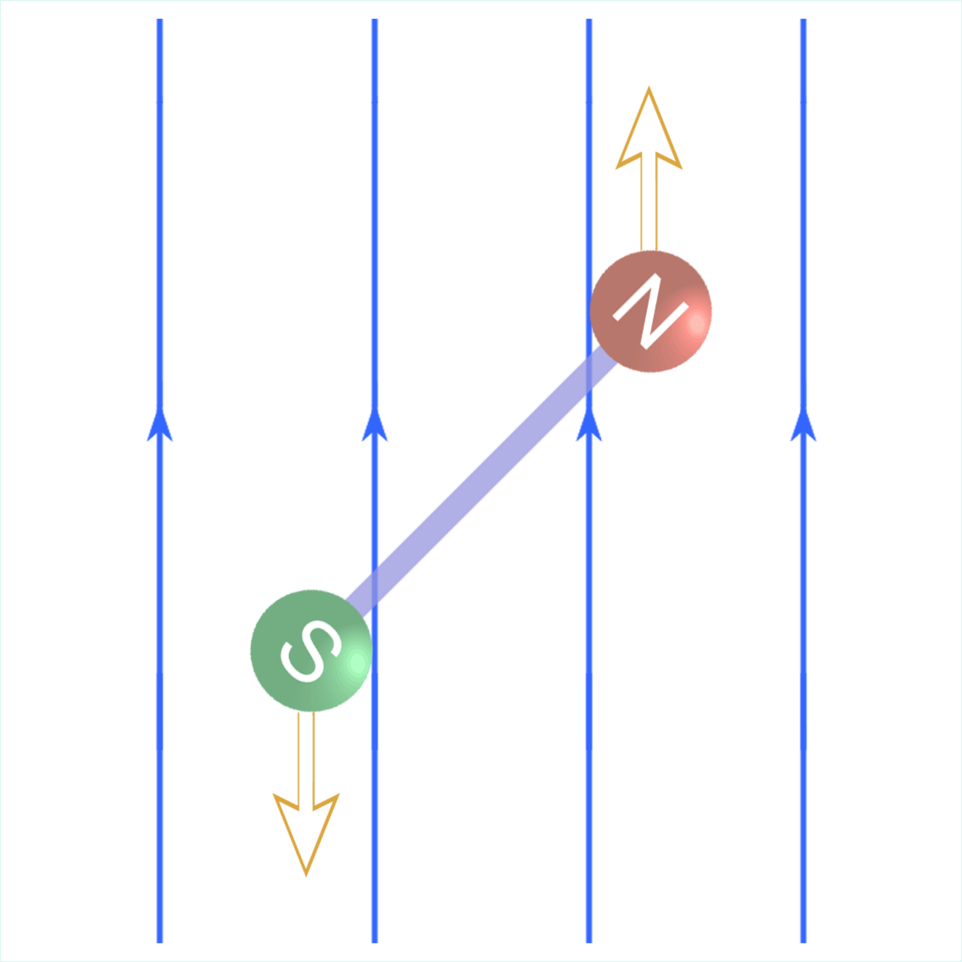
Magnetic Moment



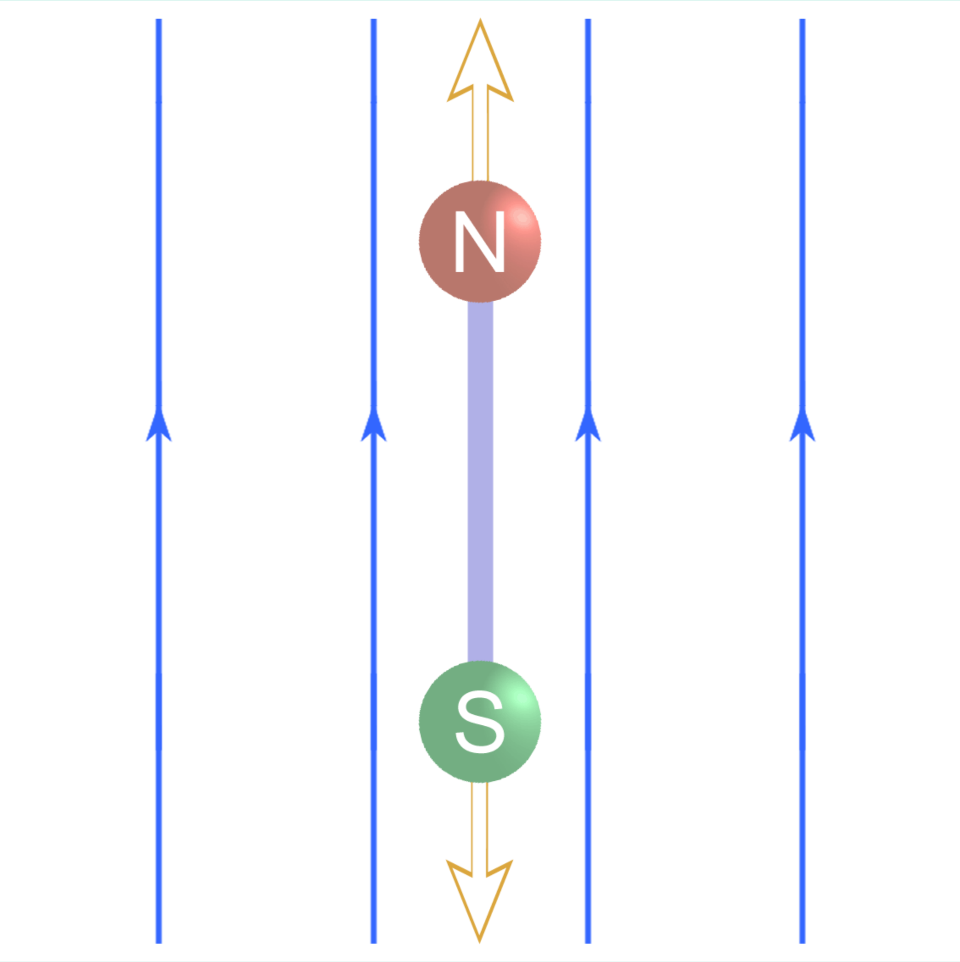
- **A magnetic dipole in a field *B* experiences a torque, τ**
- **Magnitude of τ depends on B and magnetic dipole moment, *m*.**

$$\tau = mB\sin(\theta)$$

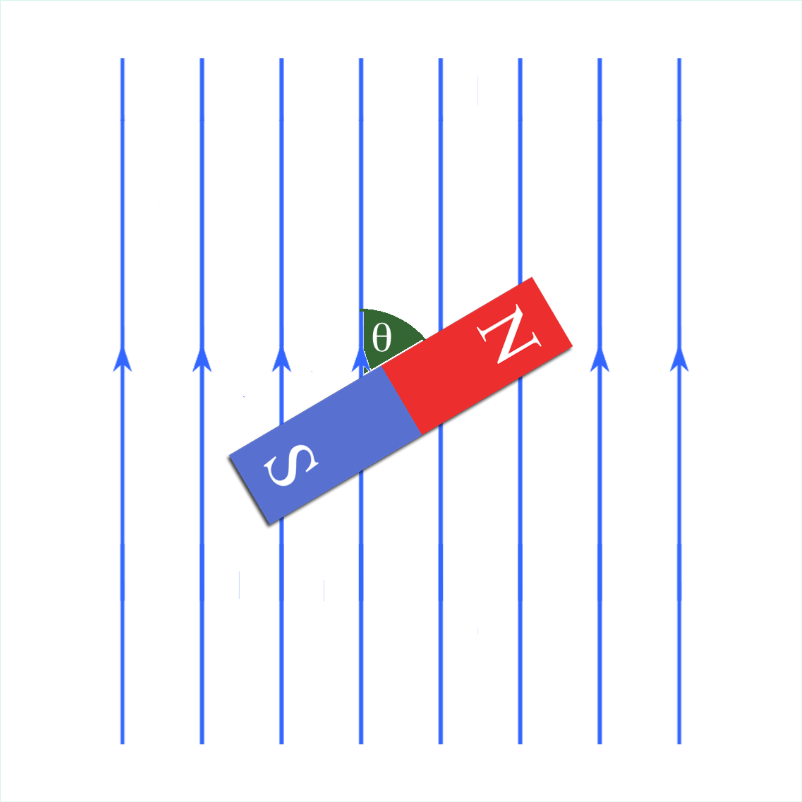
Magnetic dipole in a field



Magnetic dipole in a field



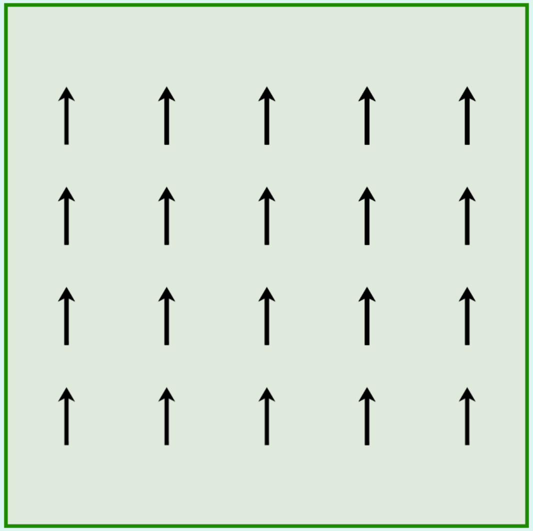
Compass needles



- A magnetic compass needle has a magnetic moment
- Needle is oriented in the Earth's magnetic field.
- Note that both magnetic moment and field are vectors

Magnetic Materials -
an Empirical Approach

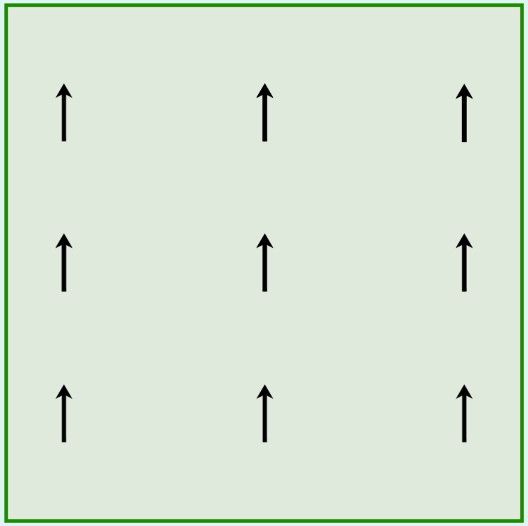
Magnetization, $\boldsymbol{M}$



- **Material with a net magnetic moment is magnetized**

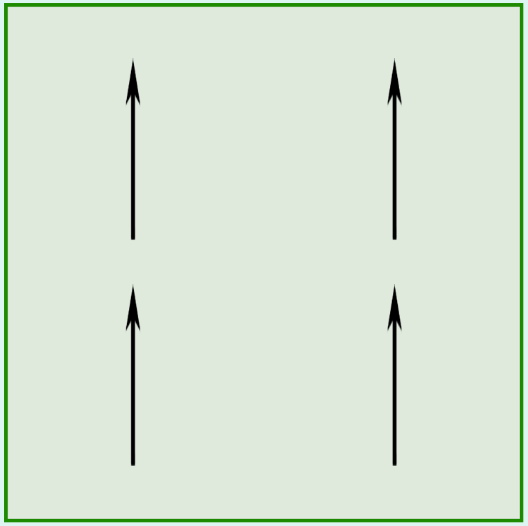
- **Magnetization is the magnetic moment per unit volume within the material**

Magnetization depends on……..



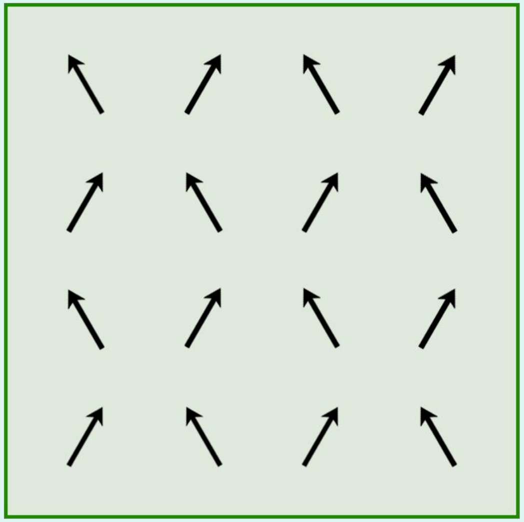
- **Number density of magnetic dipole moments within material**

Magnetization depends on……..



- **Magnitude of the magnetic dipole moments within the material**

Magnetization depends on……..



- **The arrangement of the magnetic dipoles within the material**

Magnetization in materials arises from…….

- **unpaired electron spins mainly**
- **the orbital motion of electrons within the material to a lesser extent**

Langevin Function

- **Assembly of single domain particles, each with total magnetic moment μ and vanishingly small anisotropy.**
- **Assembly at a temperature *T* in na applied field *H*, achieved a thermodynamic equilibrium: Boltzmann distribution of μ with respect to *H* $\rightarrow$ identical to classical paramagnetism.**
- **Each magnetic moment has a certain potential energy E_p, given by:**

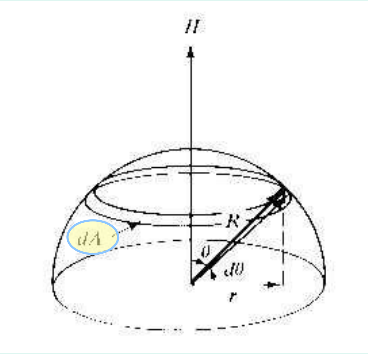
$$E_p = -\vec{\mu}\cdot\vec{H} = \mu H\cos\theta$$

- **The number of moments between θ and θ+dθ is proportional to dA, multiplied by the Boltzmann factor:**

$$\mathrm{d}n = K\mathrm{d}A\exp\left\lfloor -E_p/k_BT \right\rfloor = 2\pi K\exp\left[\left(\mu H\cos\theta\right)/k_BT\right]\sin\theta\,\mathrm{d}\theta$$

- **where *K* is a proportionality factor, determined by the**
- **fact that:**

$$\int_0^n \mathrm{d}n = n$$



Langevin Function

- **If** $a = \dfrac{\mu H}{k_B T}$ **we have:**

$$2\pi K \int_0^{\pi} \exp(a\cos\theta)\sin\theta \,\mathrm{d}\theta = n$$

- **multiplying the number of magnetic moments d*n* by the contribution μ cosθ of each moment, and integrating over the total number, one obtains the magnetization *M* :**

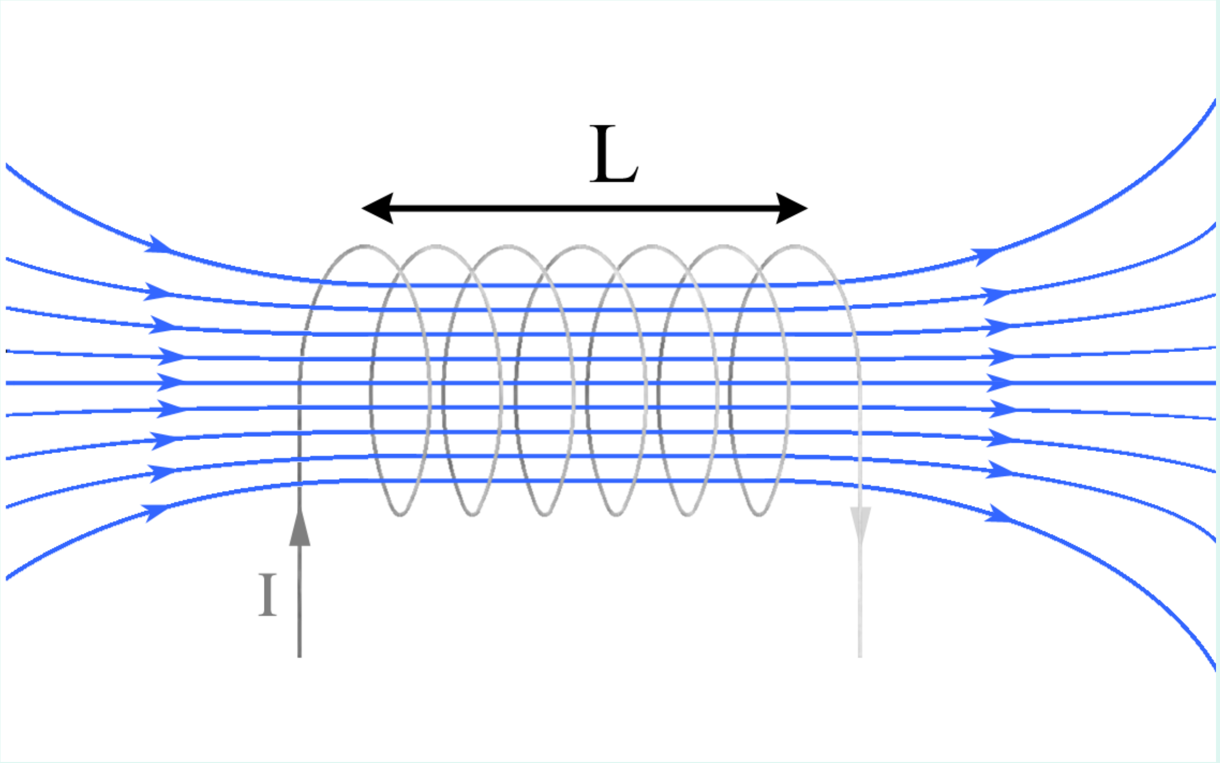
$$M = \int_0^{n} \mu \cos\theta \,\mathrm{d}n$$

$$M = 2\pi K\mu \int_0^{\pi} \exp(a\cos\theta)\sin\theta\cos\theta \,\mathrm{d}\theta =$$

$$= \frac{n\mu \int_0^{\pi} \exp(a\cos\theta)\sin\theta\cos\theta \,\mathrm{d}\theta}{\int_0^{\pi} \exp(a\cos\theta)\sin\theta \,\mathrm{d}\theta}$$

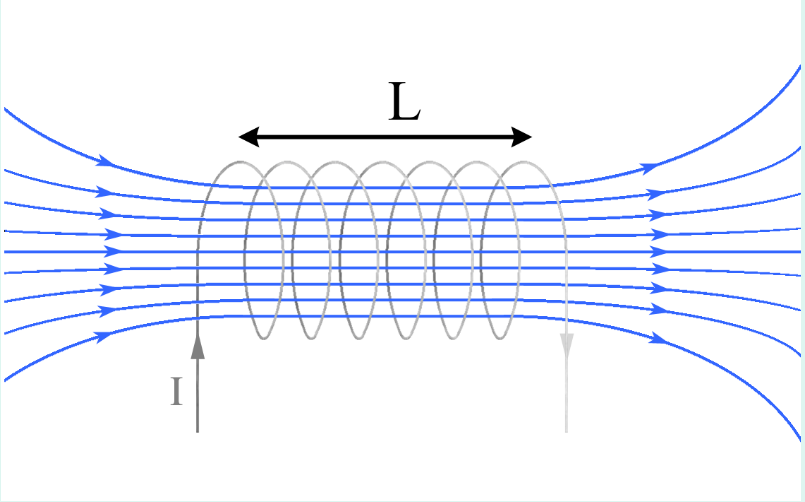
$$M = n\mu\left(\coth a - 1/a\right)$$

Generating a uniform magnetic field in the laboratory



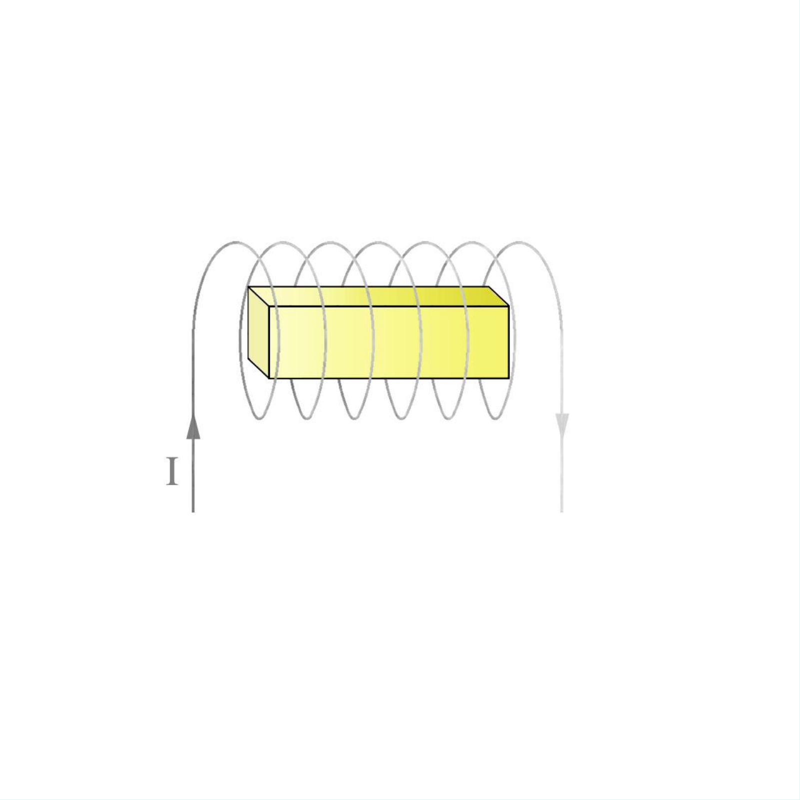
- **An electric current run through a conducting coil (solenoid) generates a uniform flux density within the coil**

Flux density in vacuum (or air) within coil……..



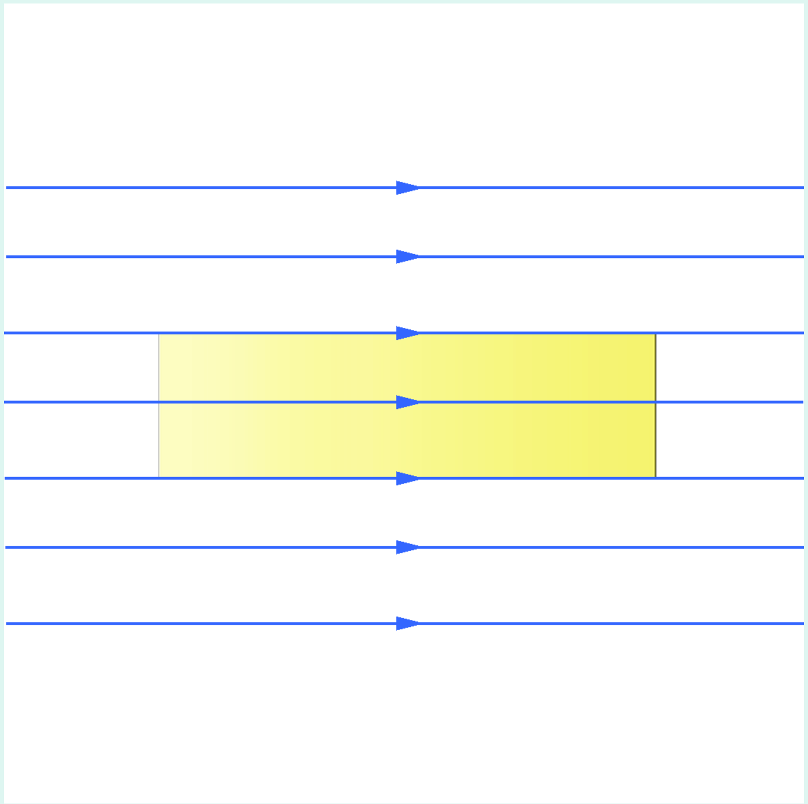
- **Increases in proportion to the electric current**
- **Increases in proportion to the number of turns per unit length in the coil**

Inserting a specimen into the coil



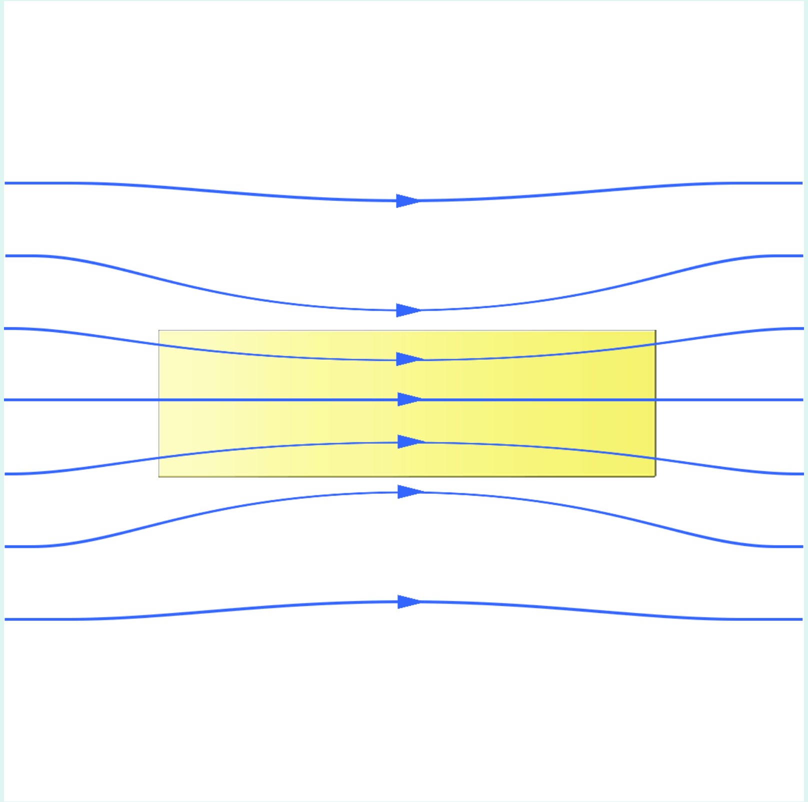
- **Generally, the orbital and spin magnetic moments within atoms respond to an applied magnetic field**
- **Flux lines are perturbed by specimen**

Specimen in magnetic field



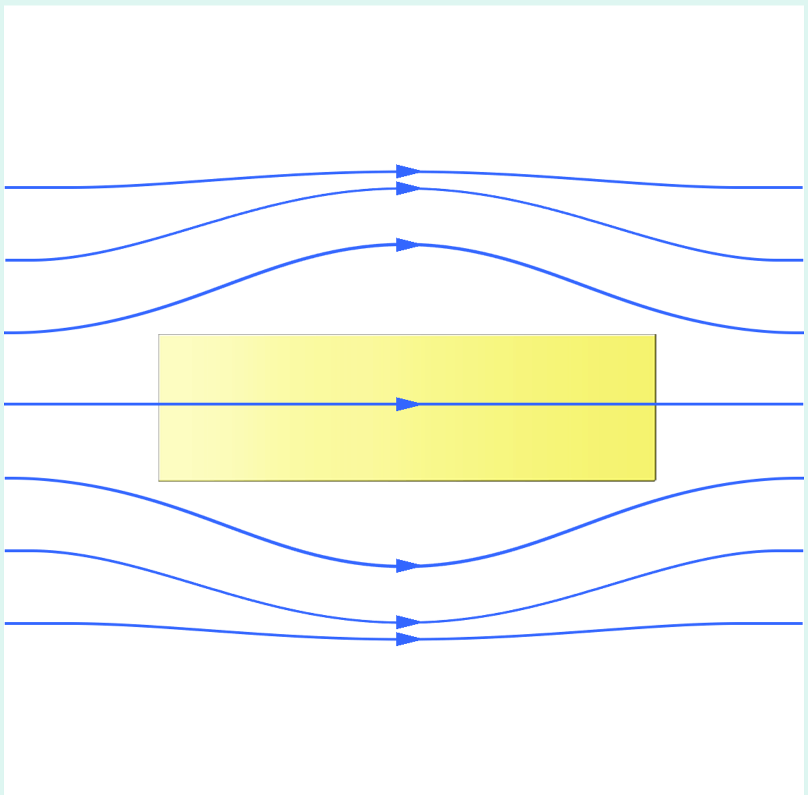
- **If specimen has no magnetic response, flux lines are not perturbed**

“Magnetic” materials



- **“magnetic” materials tend to concentrate flux lines**
- **Examples: materials containing high concentrations of magnetic atoms such as iron, cobalt**

Diamagnetic materials

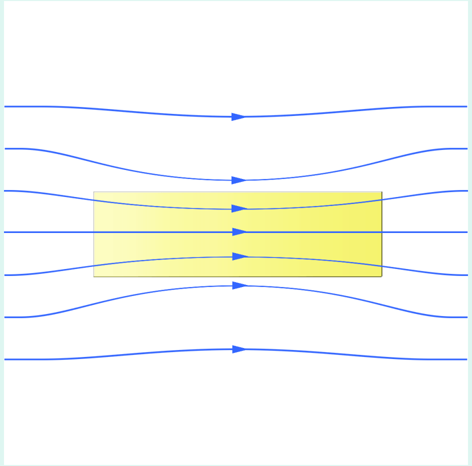


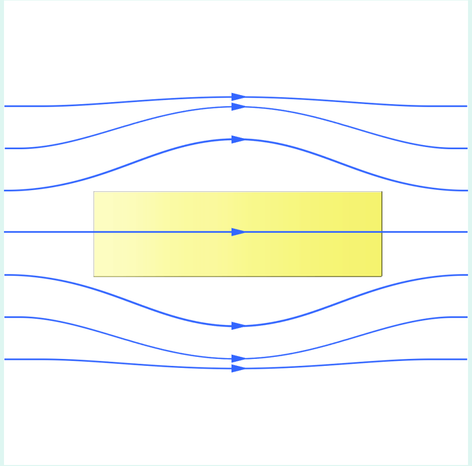
- **Diamagnetic materials tend to repel flux lines weakly**
- **Examples: water, protein, fat**

Flux density *B* within material determined by both……

- **Geometry and current in solenoid**
- **Magnetic properties of the material**
- **Geometry of material**

$$\boldsymbol{B} = \mu_0\left(\boldsymbol{H} + \boldsymbol{M}\right)$$



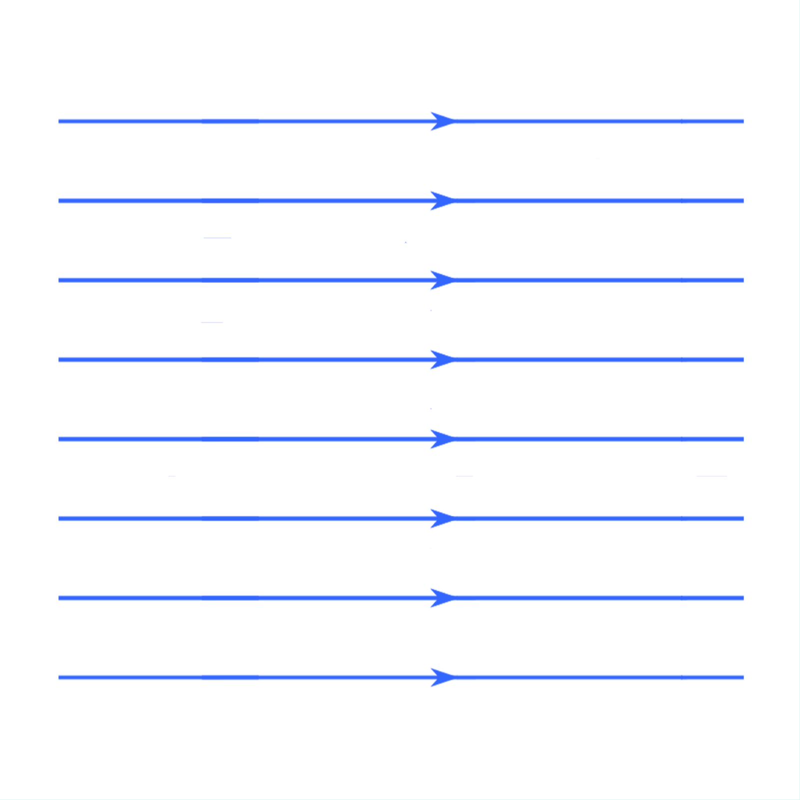


The $\boldsymbol{H}$ Field

- **$\boldsymbol{H}$ is called the magnetic field strength**

- **μ_0 is a constant called the permeability of free space**

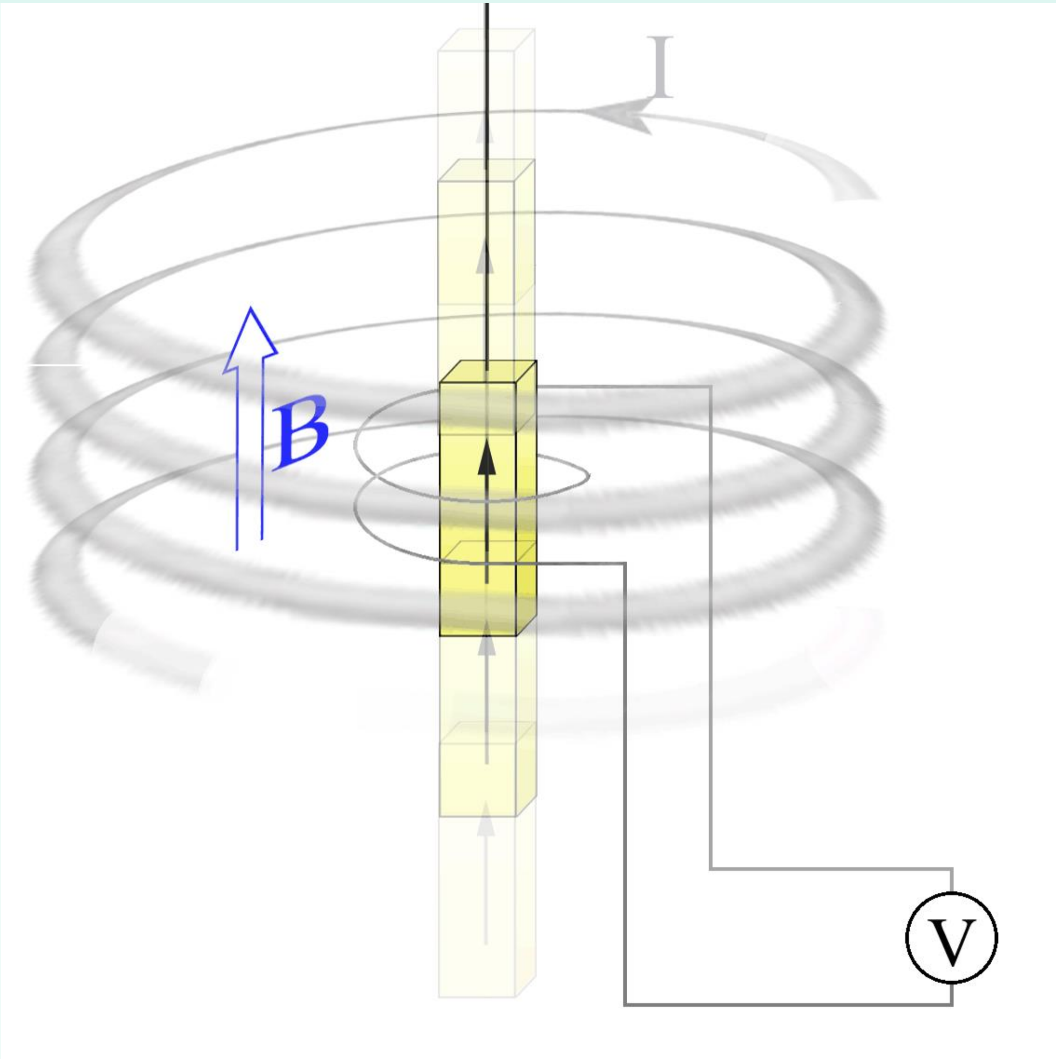
In the absence of material in the solenoid……



- **There is no magnetization *M***
- **So…..**

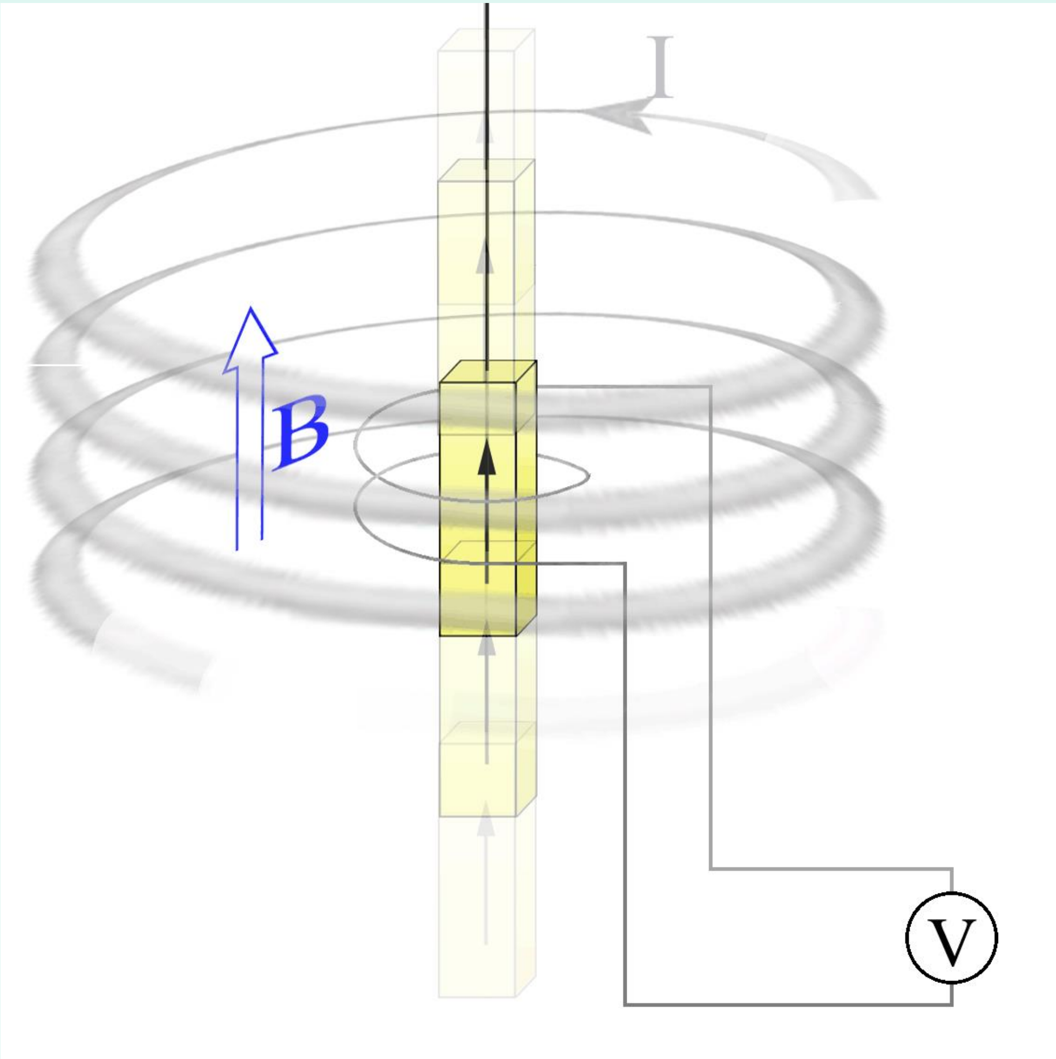
$$\boldsymbol{B} = \mu_0 \boldsymbol{H}$$

Measuring magnetic moment of specimen



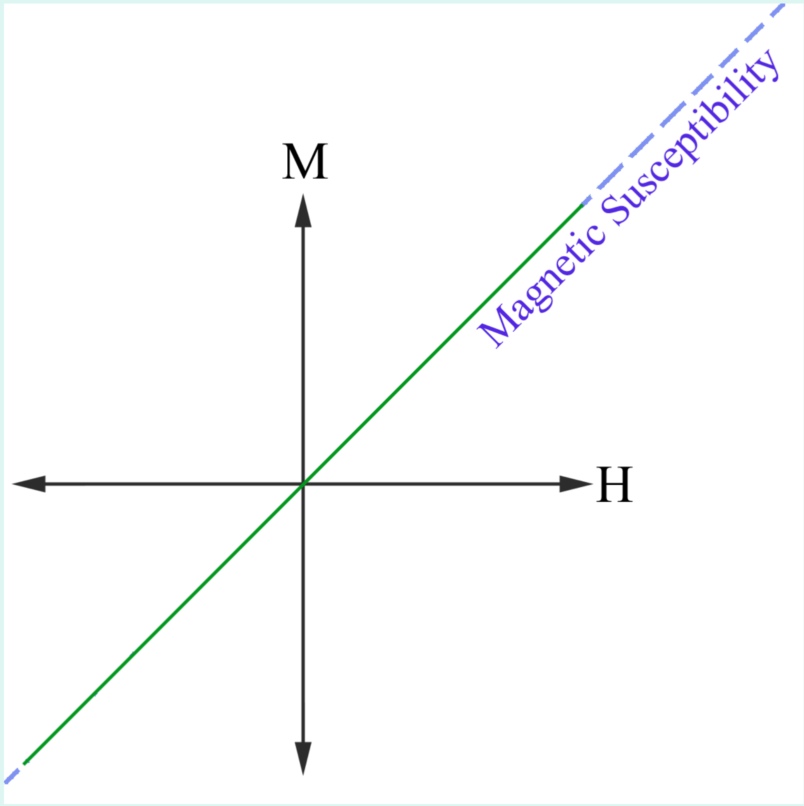
- **Pass specimen thru small "sensing" coil**
- **Measure voltage generated across coil**
- **Voltage proportional to moment on specimen**

Measuring magnetic moment of specimen



- **Use large coil to apply magnetic field to specimen**
- **Use a cryostat or furnace to vary temperature of specimen**

Response of material to applied magnetic field strength $\boldsymbol{H}$



- **Generally, $\boldsymbol{M}$ changes in magnitude as $\boldsymbol{H}$ is varied.**
- **Magnitude of response is called the “magnetic susceptibility” of the material**

Response of material to applied magnetic field strength $\boldsymbol{H}$

- **Diamagnetic materials have a very weak negative response**

- **i.e. they have a small negative magnetic susceptibility**

Magnetic susceptibility, χ

- **Magnetic susceptibility is sometimes written as**

$$\chi = {M}/{H}$$

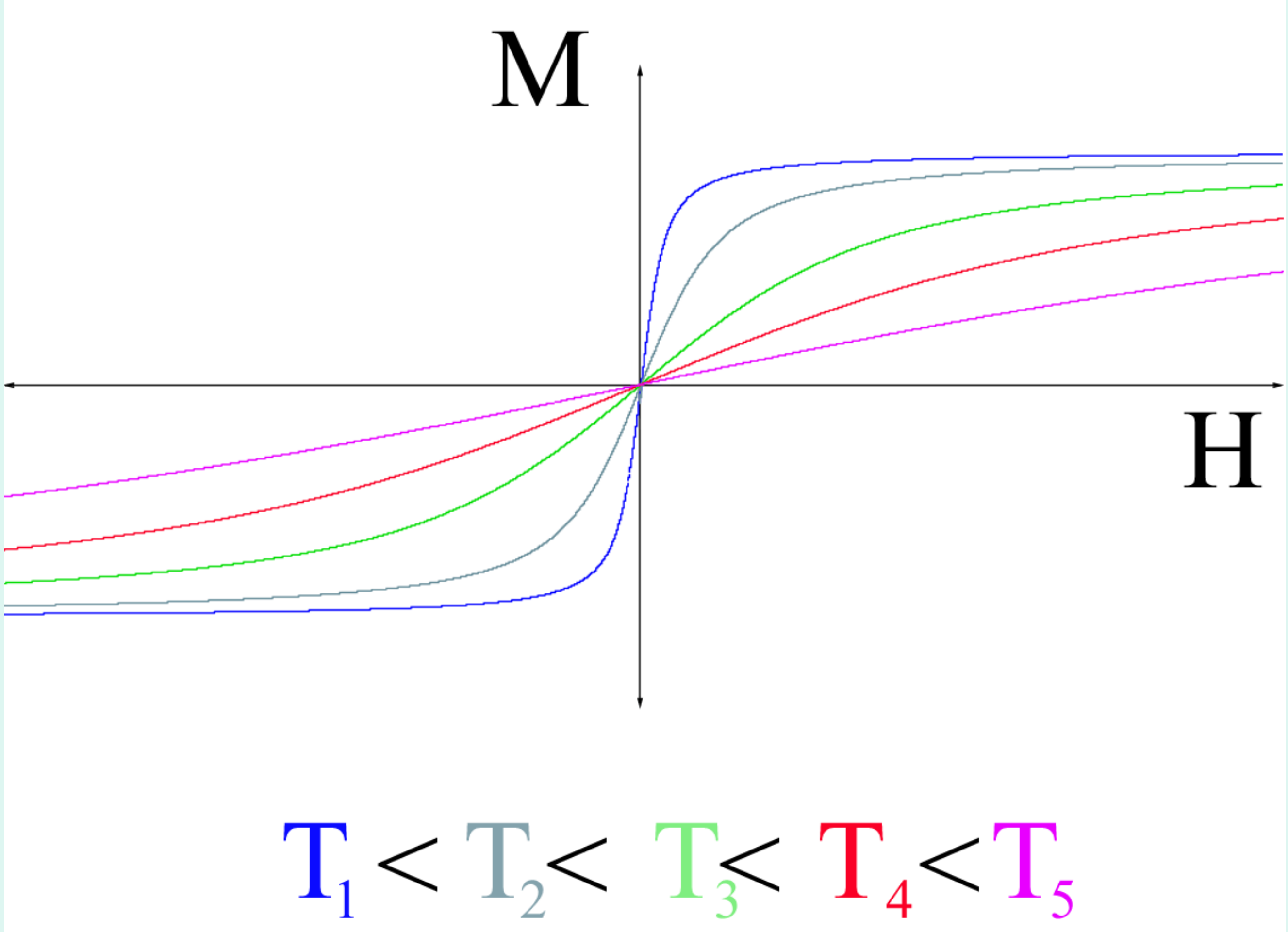
- **And sometimes as the slope of *M* vs *H***

$$\chi = {dM}/{dH}$$

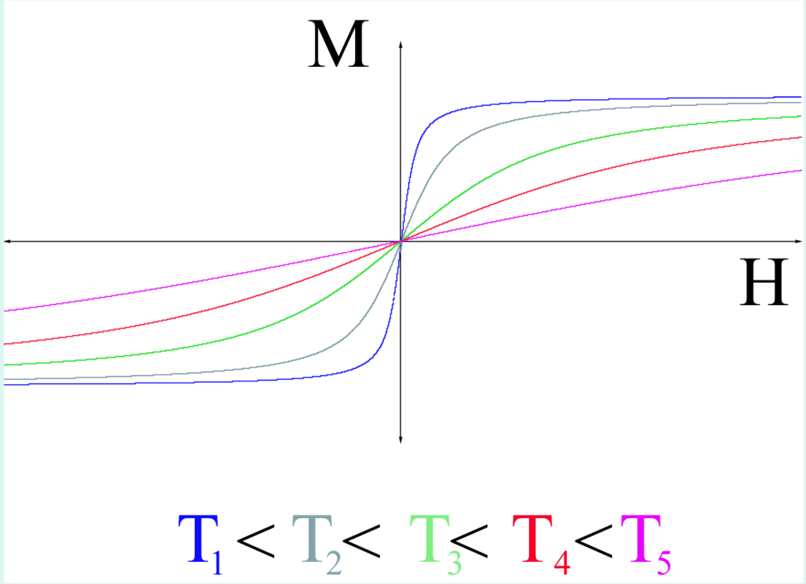
How does $\boldsymbol{M}$ respond to $\boldsymbol{H}$?

- **There is a variety of ways that M responds to H**
- **Response depends on type of material**
- **Response depends on temperature**
- **Response can sometimes depend on the previous history of magnetic field strengths and directions applied to the material**

Non-linear responses

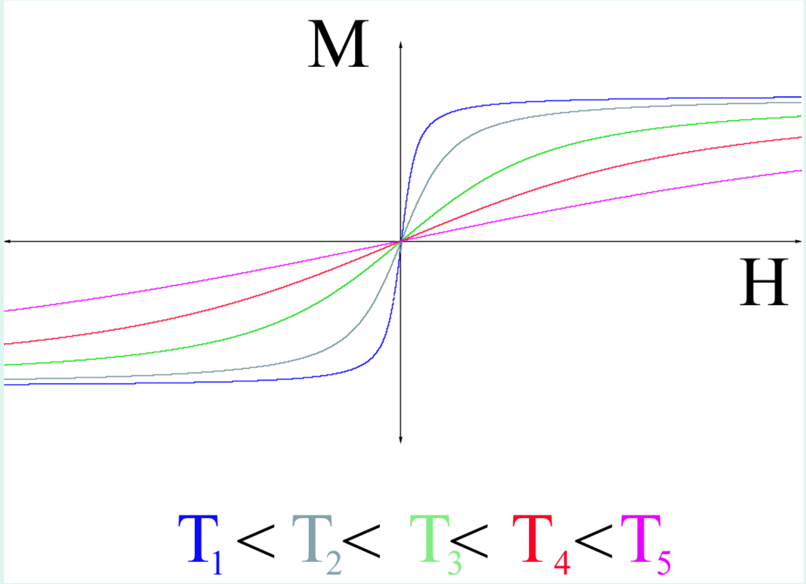


Non-linear responses



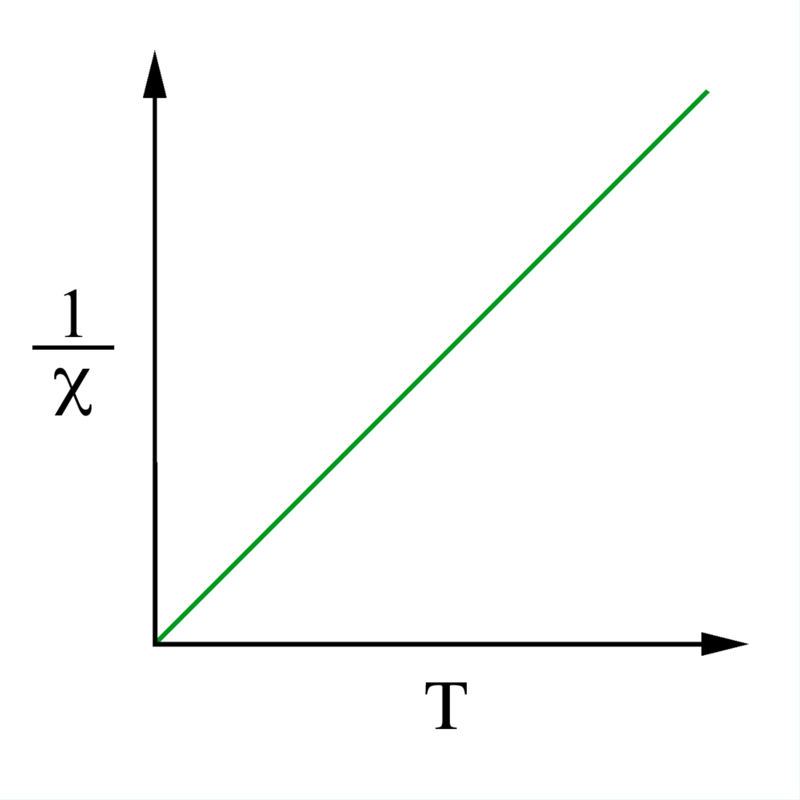
- **Generally, the response of *M* to *H* is non-linear**
- **Only at small values of *H* or high temperatures is response sometimes linear**

Non-linear responses



- ***M*** **tends to saturate at high fields and low temperatures**

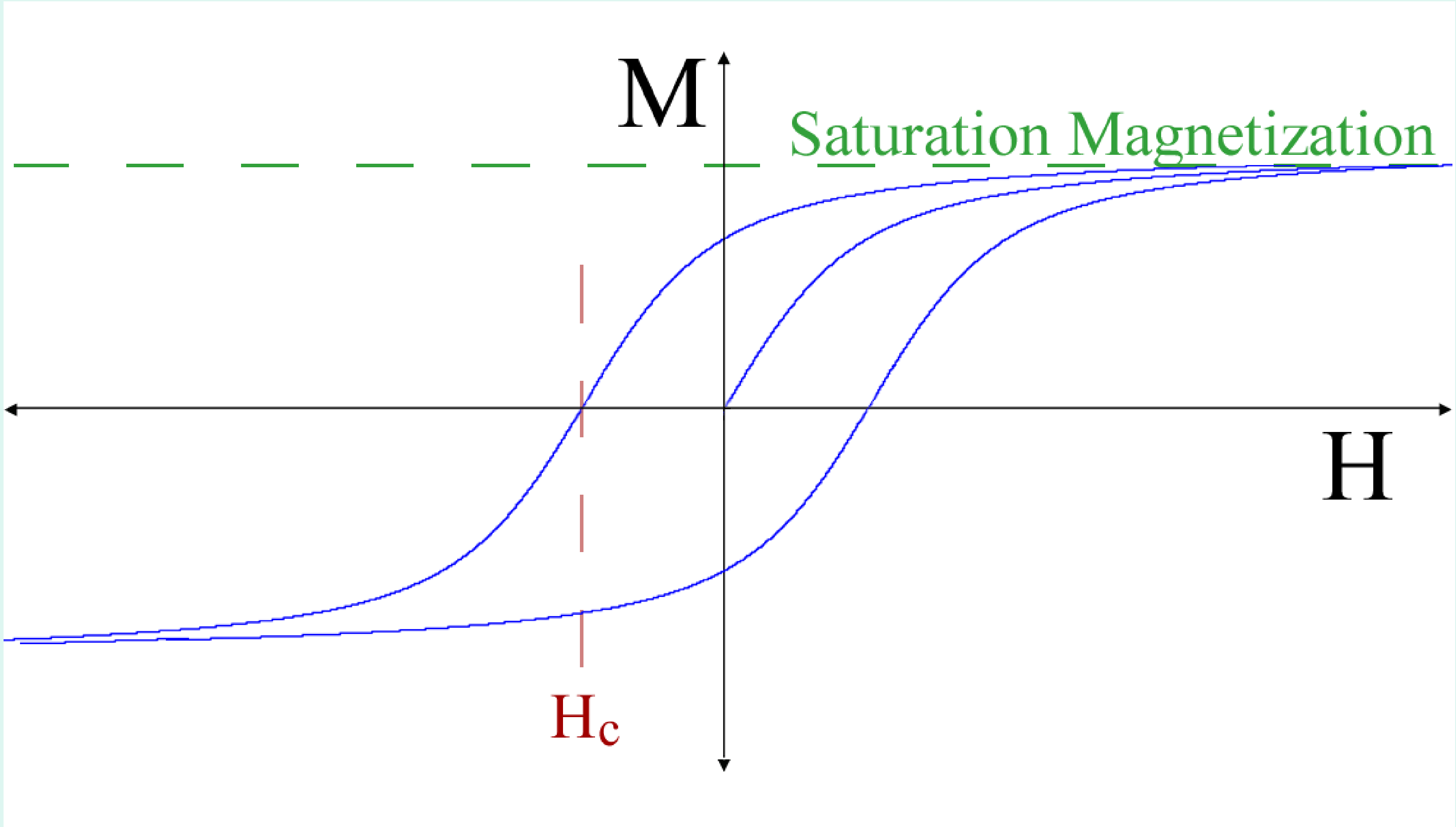
Low field magnetic susceptibility



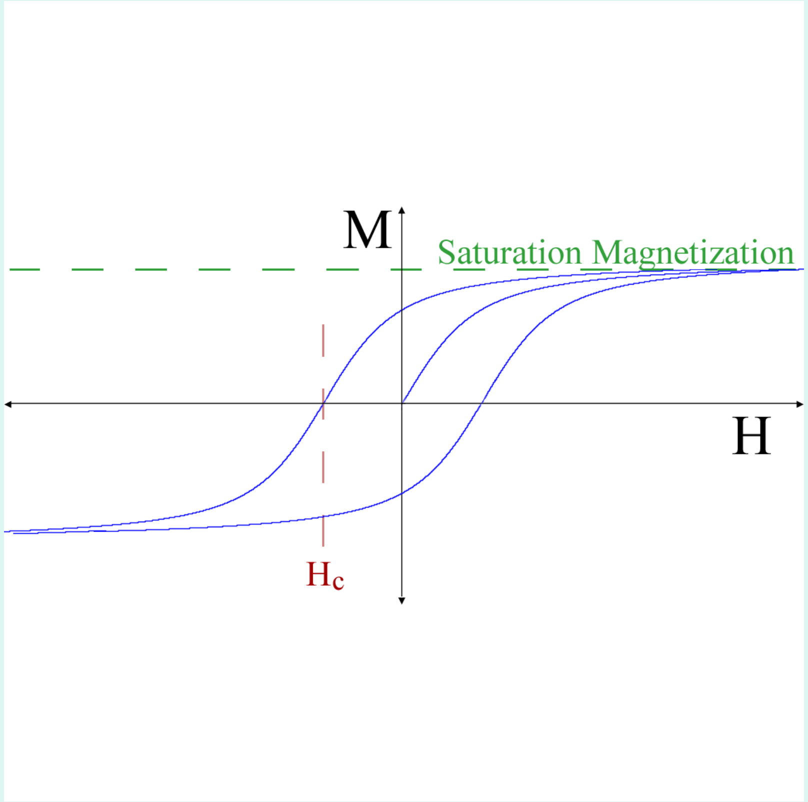
- **For some materials, low field magnetic susceptibility is inversely proportional to temperature**

- **Curie's Law**

Magnetic hysteresis

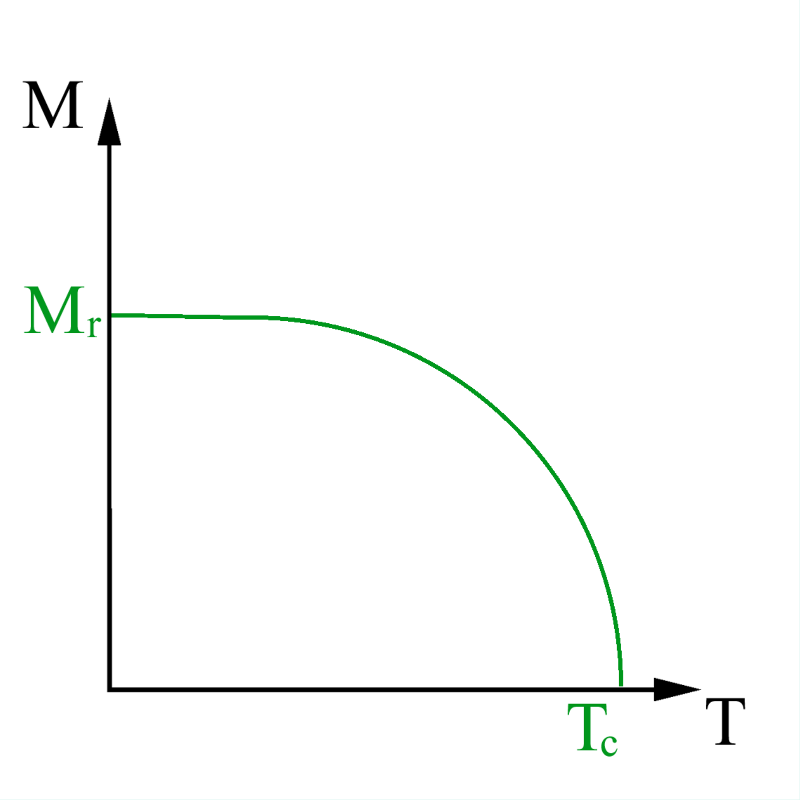


Magnetic hysteresis



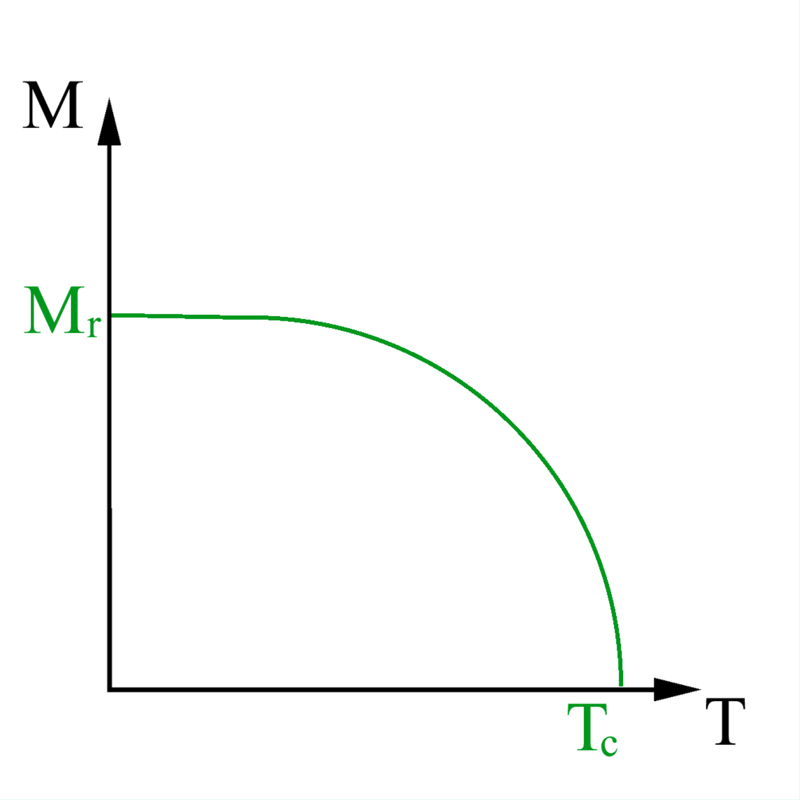
- ***M*** **depends on previous state of magnetization**
- **Remnant magnetization** M_r **remains when applied field is removed**
- **Need to apply a field (coercive field) in opposite direction to reduce** ***M*** **to zero.**

Effect of temperature on remnant magnetization



- **Heating a magnetized material generally decreases its magnetization.**
- **Remnant magnetization is reduced to zero above Curie temperature T_c**

Effect of temperature on remnant magnetization



- **Heating a sample above its Curie temperature is a way of demagnetizing it**

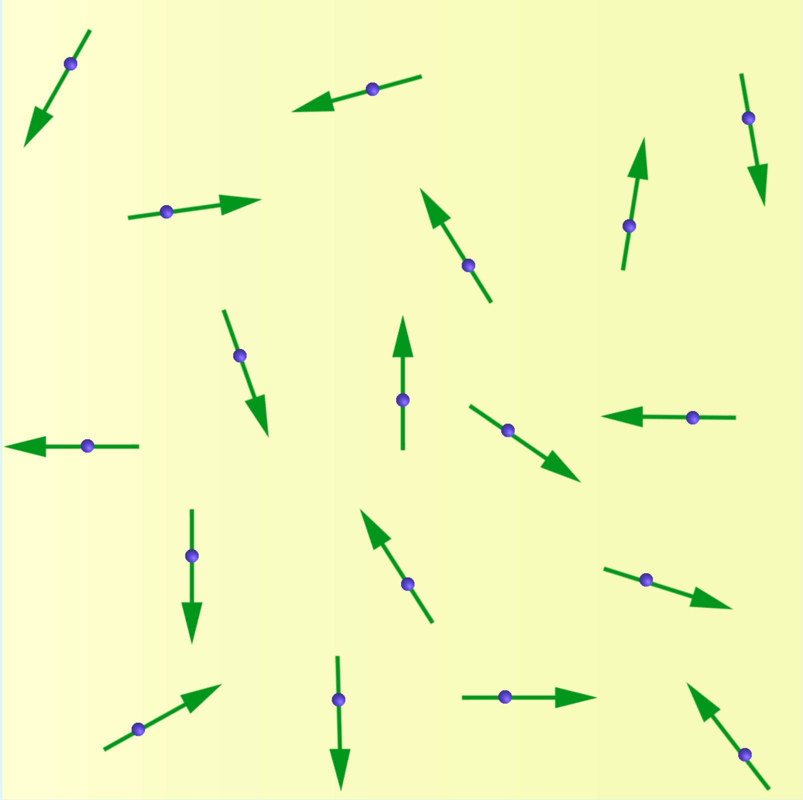
- **Thermal demagnetization**

Lecture 2

The Microscopic Picture of Magnetic Materials

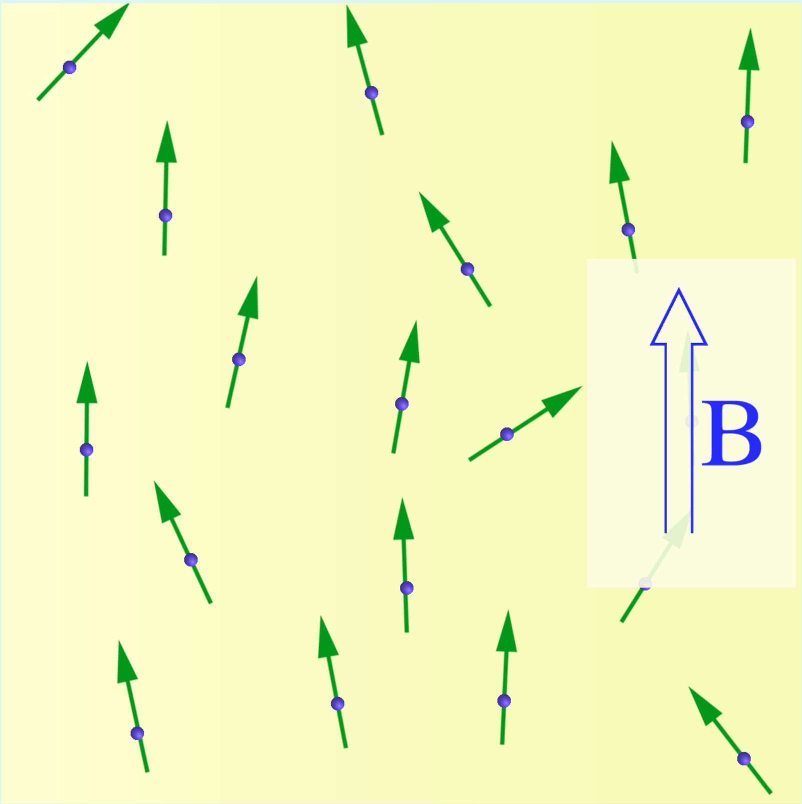
- **We will now revisit the experimentally observed magnetic behaviours and try to understand them from a microscopic point of view**

Paramagnetic gas



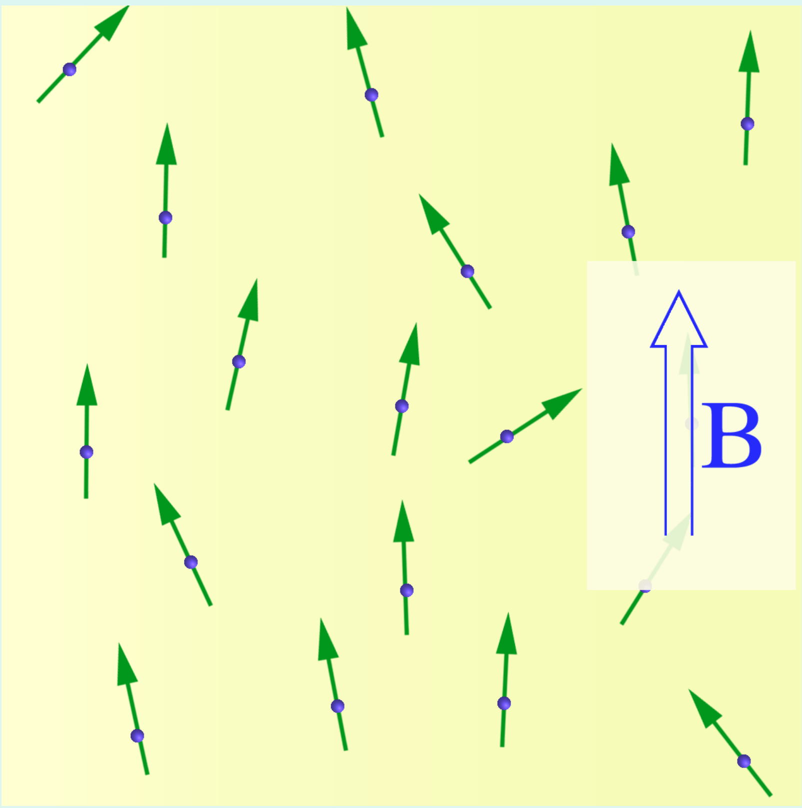
- **Imagine a classical gas of molecules each with a magnetic dipole moment**
- **In zero field the gas would have zero magnetization**

Paramagnetic gas



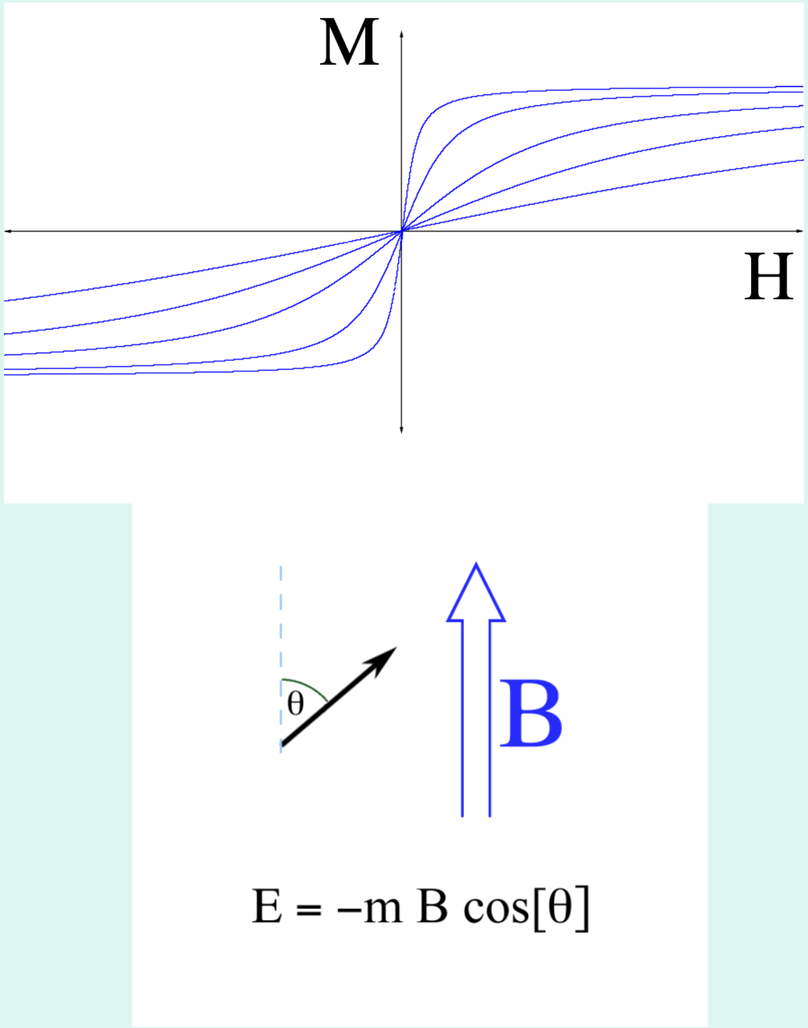
- **Applying a magnetic field would tend to orient the dipole moments**
- **Gas attains a magnetization**

Paramagnetic gas



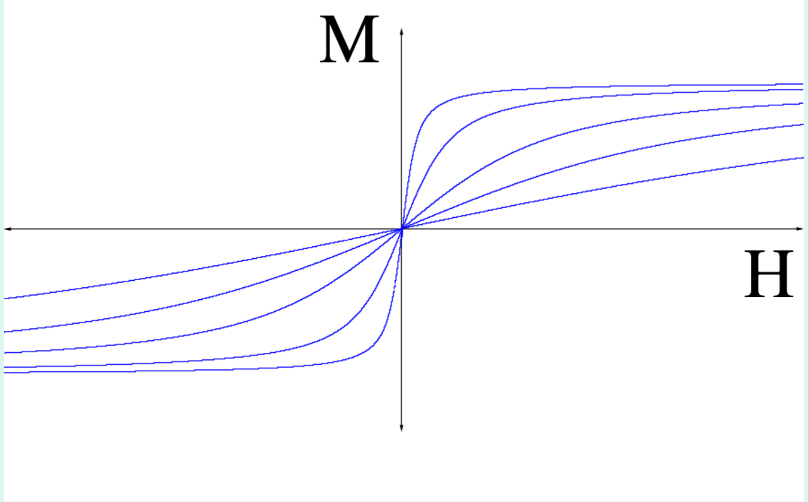
- Very high fields would saturate magnetization
- Heating the gas would tend to disorder the moments and hence decrease magnetization

Paramagnetic gas

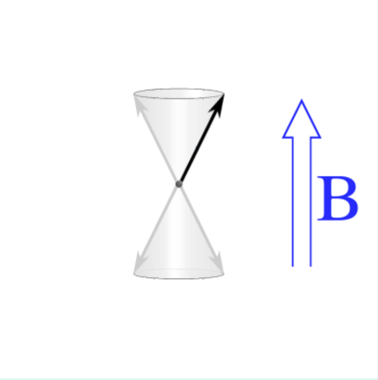


- **Theoretical model**
- **Non-interacting moments**
- **Boltzmann statistics**
- **Dipole interaction with *B***
- **Yields good model for many materials**
- **Examples: ferrous sulfate crystals, ionic solutions of magnetic atoms**

Paramagnetic gas



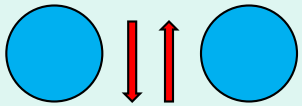
- **Classical model yields Langevin function**
- **Quantum model yields Brillouin function**



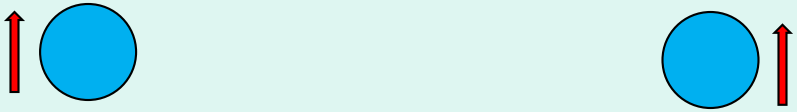
Exchange Interaction

- **Direct exchange**

Direct exchange operates between moments, which are close enough to have sufficient overlap of their wavefunctions. It gives a strong but short range coupling which decreases rapidly as the ions are separated. An initial simple way of understanding direct exchange is to look at two atoms with one electron each. When the atoms are very close together the Coulomb interaction is minimal when the electrons spend most of their time in between the nuclei. Since the electrons are then required to be at the same place in space at the same time, Pauli's exclusion principle requires that they possess opposite spins. According to Bethe and Slater the electrons spend most of their time in between neighboring atoms when the interatomic distance is small. This gives rise to antiparallel alignment and therefore negative exchange. (antiferromagnetic).



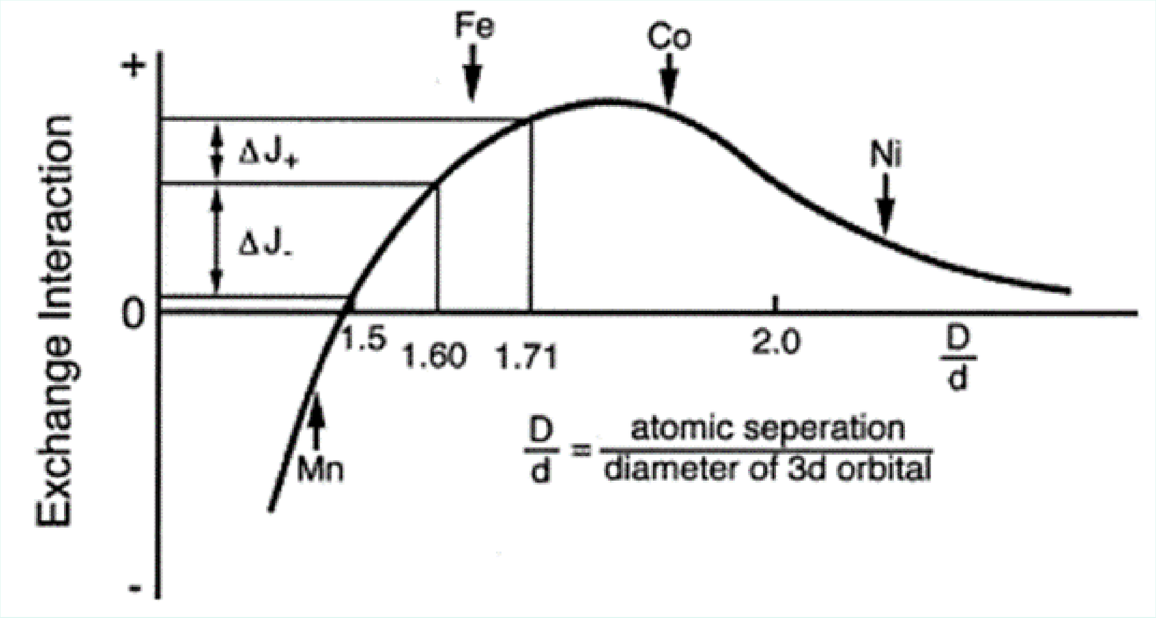
If the atoms are far apart the electrons spend their time away from each other in order to minimize the electron-electron repulsion. This gives rise to parallel alignment or positive exchange (ferromagnetism)



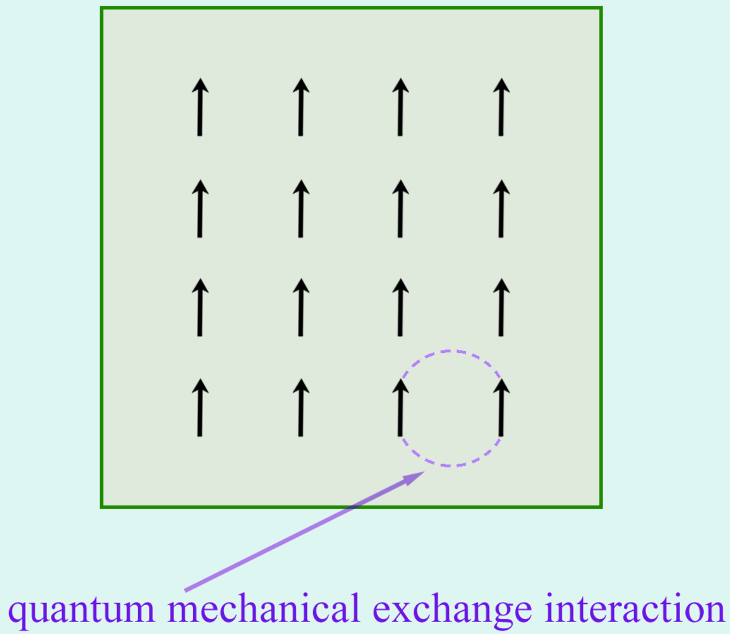
Bethe-Slater curve

- **The exchange Heisenberg energy, suitably scaled, replaces the Weiss molecular field constant in the mean field theory of ferromagnetism to explain the temperature dependence of the magnetization**

$$E_p = -J_{ex} S_i \times S_{i+1}$$

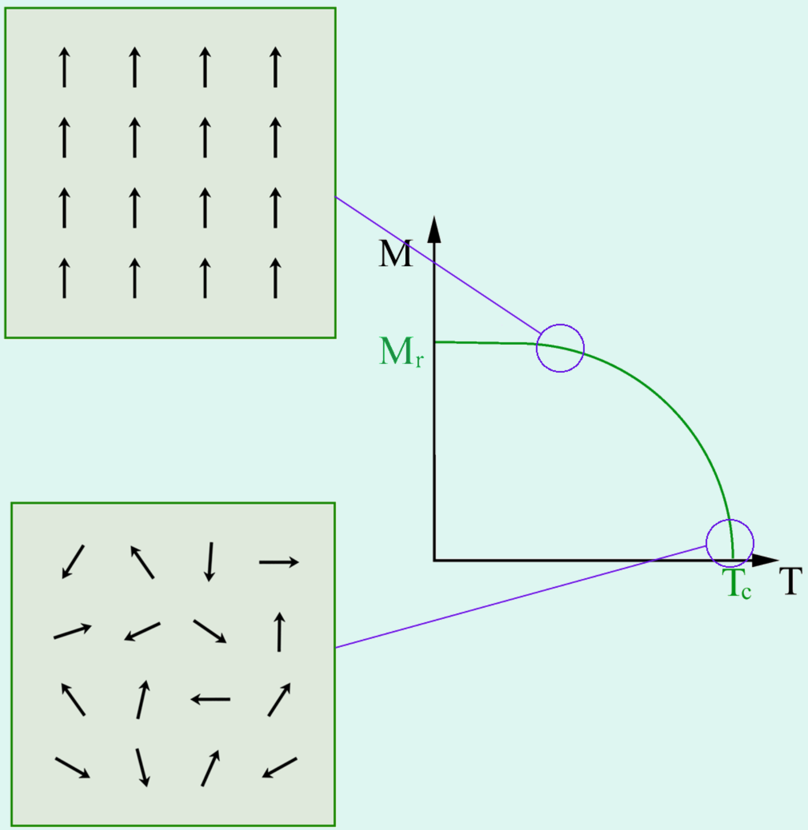


Ferromagnetism



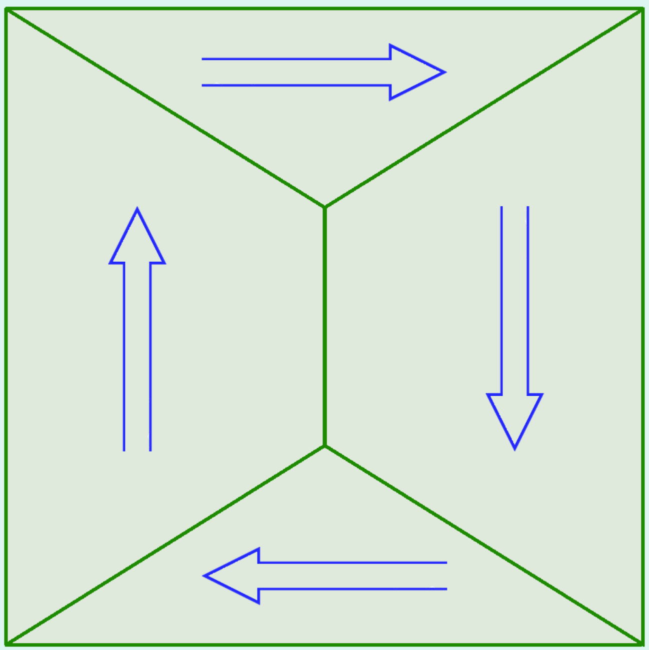
- **Materials that retain a magnetization in zero field**
- **Quantum mechanical exchange interactions favour parallel alignment of moments**
- **Examples: iron, cobalt**

Ferromagnetism



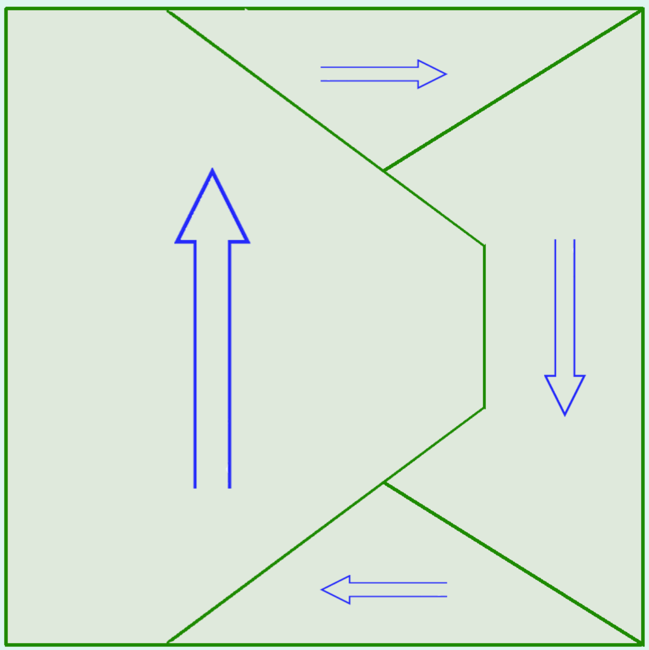
- **Thermal energy can be used to overcome exchange interactions**
- **Curie temp is a measure of exchange interaction strength**
- **Note: exchange interactions much stronger than dipole-dipole interactions**

Magnetic domains



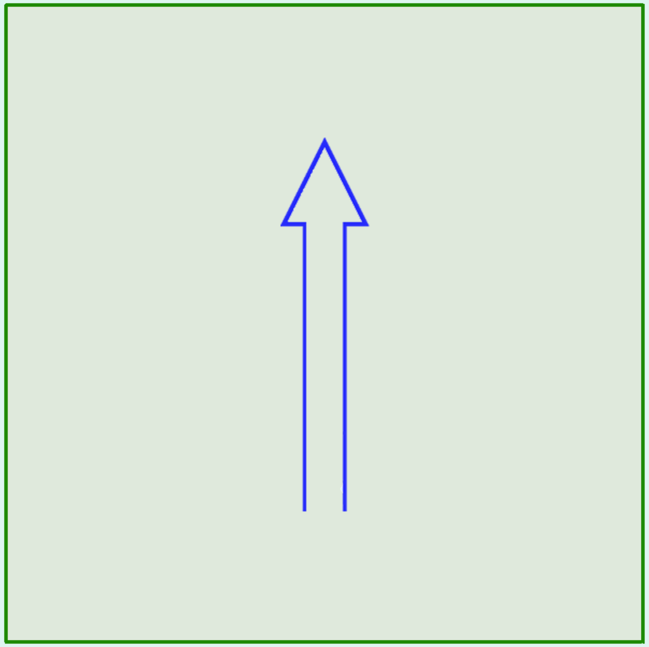
- Ferromagnetic materials tend to form magnetic domains
- Each domain is magnetized in a different direction
- Domain structure minimizes energy due to stray fields

Magnetic domains



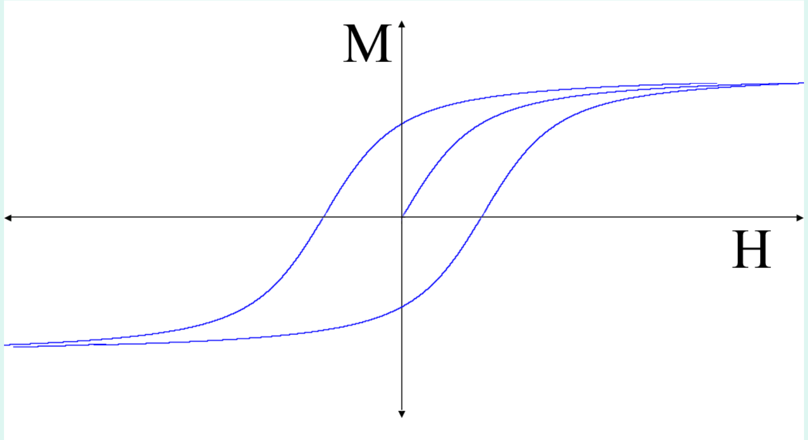
- **Applying a field changes domain structure**
- **Domains with magnetization in direction of field grow**
- **Other domains shrink**

Magnetic domains



- **Applying very strong fields can saturate magnetization by creating single domain**

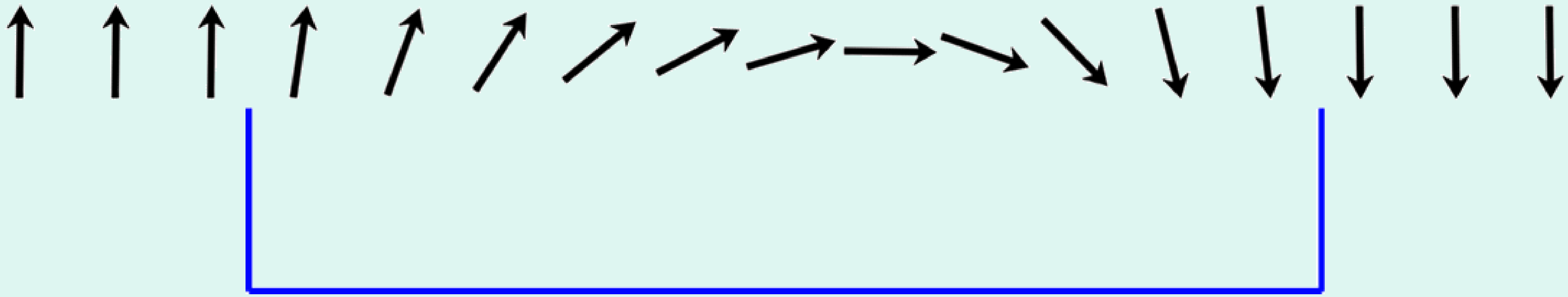
Magnetic domains



- **Removing the field does not necessarily return domain structure to original state**

- **Hence results in magnetic hysteresis**

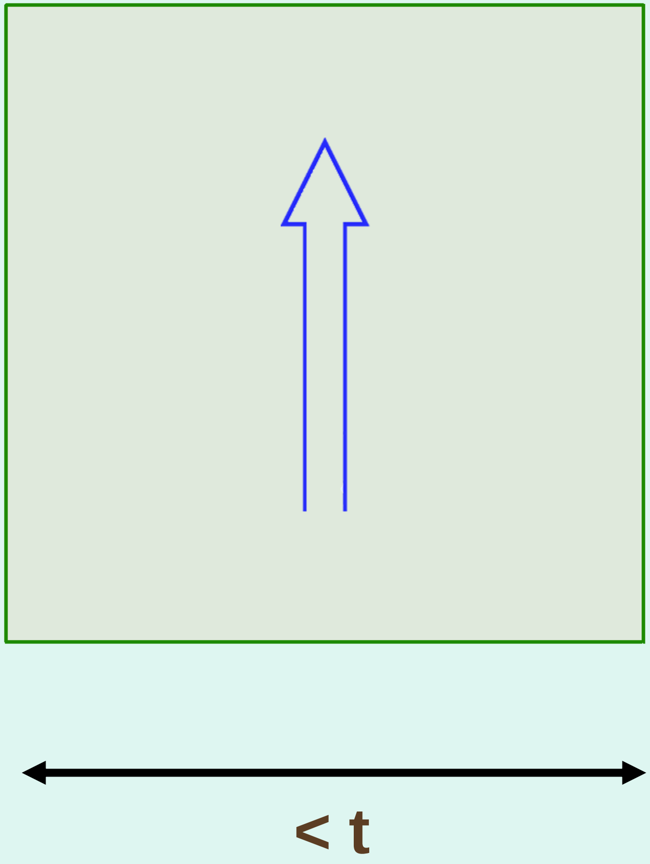
Magnetic domain walls



Wall Thickness "t"

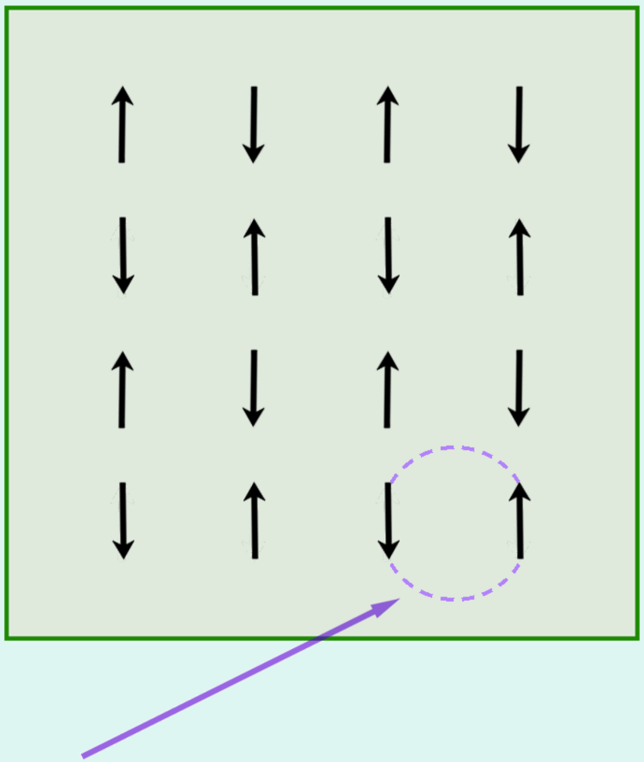
Wall thickness, t, is typically about 100 nm

Single domain particles



- **Particles smaller than “t” have no domains**

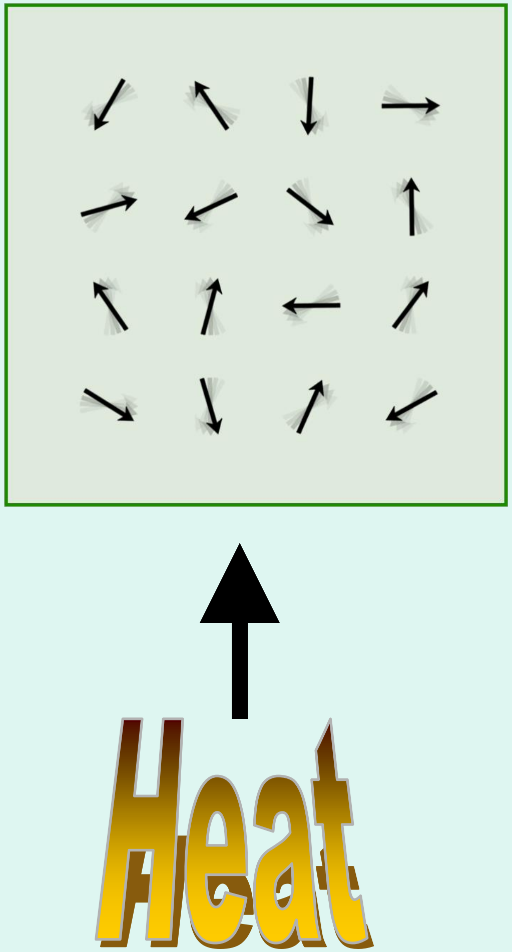
Antiferromagnetism



quantum mechanical exchange interaction

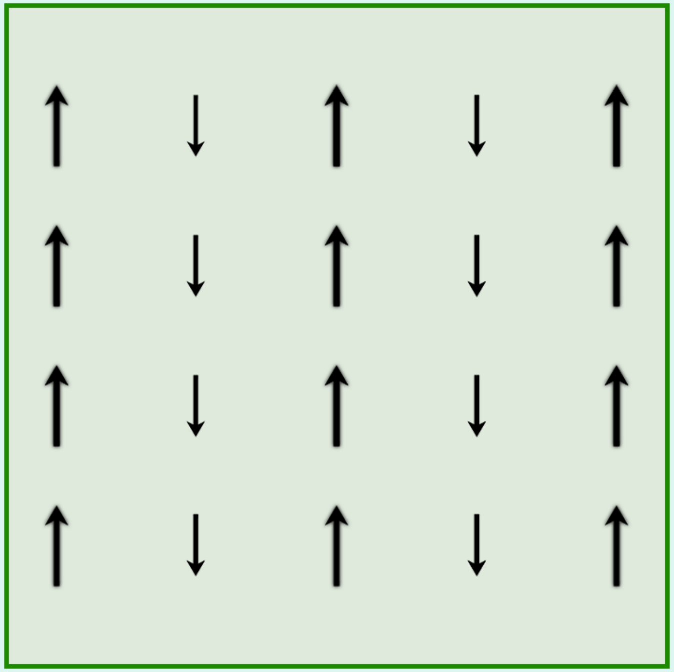
- **In some materials, exchange interactions favour antiparallel alignment of atomic magnetic moments**
- **Materials are magnetically ordered but have zero remnant magnetization and very low χ**
- **Many metal oxides are antiferromagnetic**

Antiferromagnetism



- **Thermal energy can be used to overcome exchange interactions**
- **Magnetic order is broken down at the Néel temperature (c.f. Curie temp)**

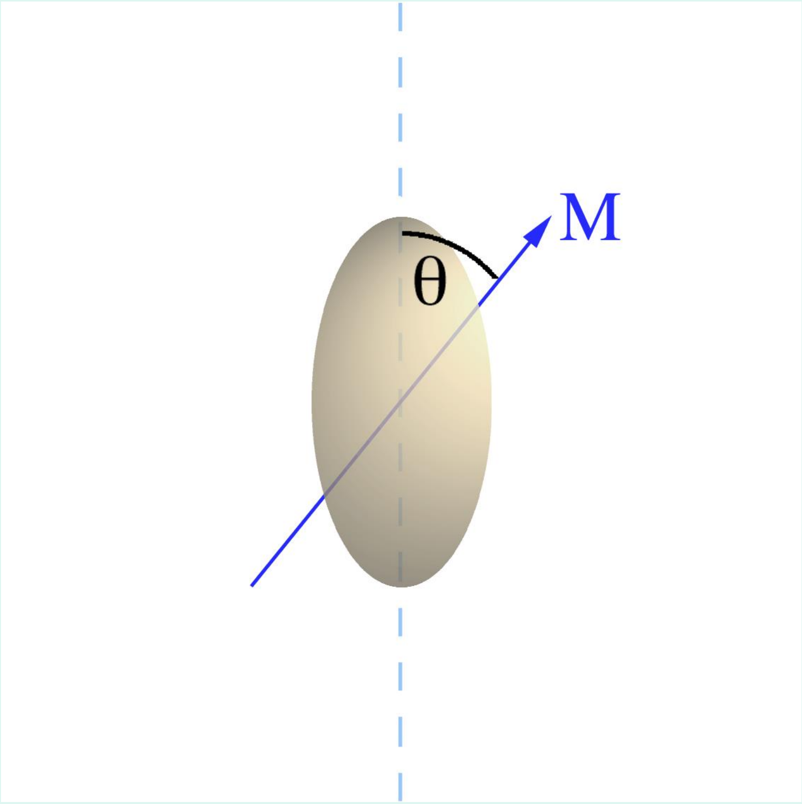
Ferrimagnetism



- **Antiferromagnetic exchange interactions**
- **Different sized moments on each sublattice**
- **Results in net magnetization**
- **Example: magnetite, maghemite**

Small Particle Magnetism

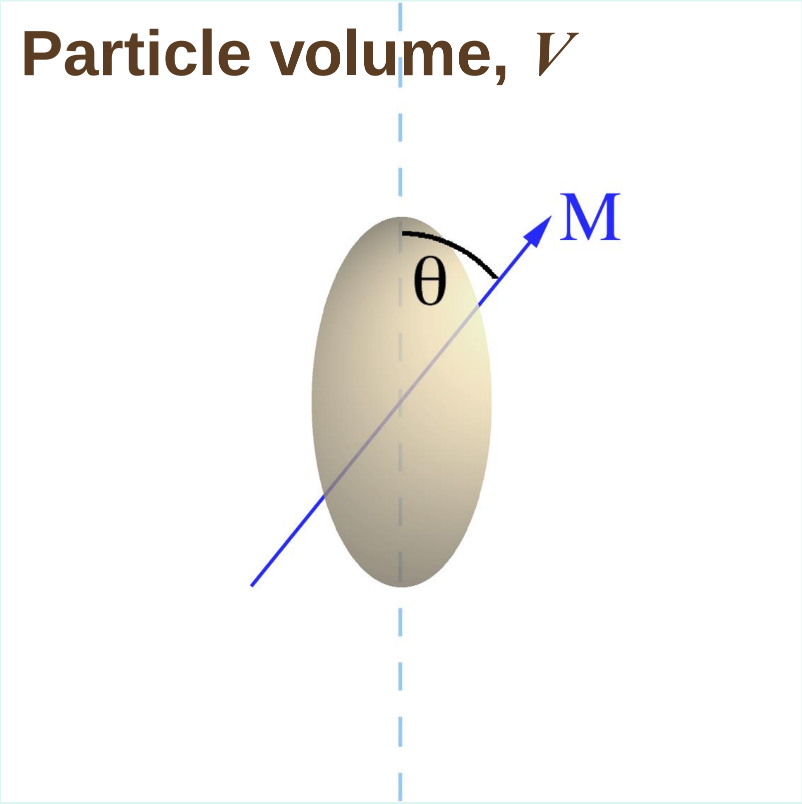
Stoner-Wohlfarth Particle



- **Magnetic anisotropy energy favours magnetization along certain axes relative to the crystal lattice**

Easy axis of magnetization

Stoner-Wohlfarth Particle

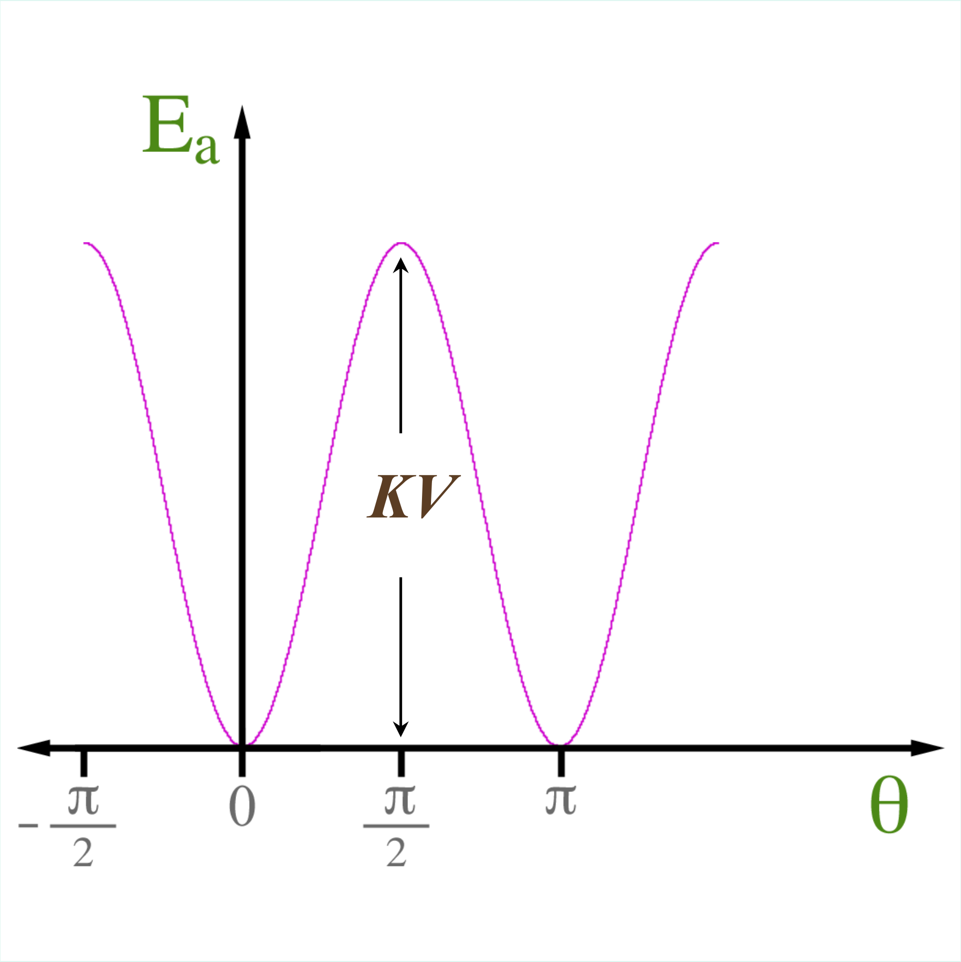


- **Uniaxial single domain particle**
- **Magnetocrystalline magnetic anisotropy energy given by**

$$E_a = KV \sin^2(\theta)$$

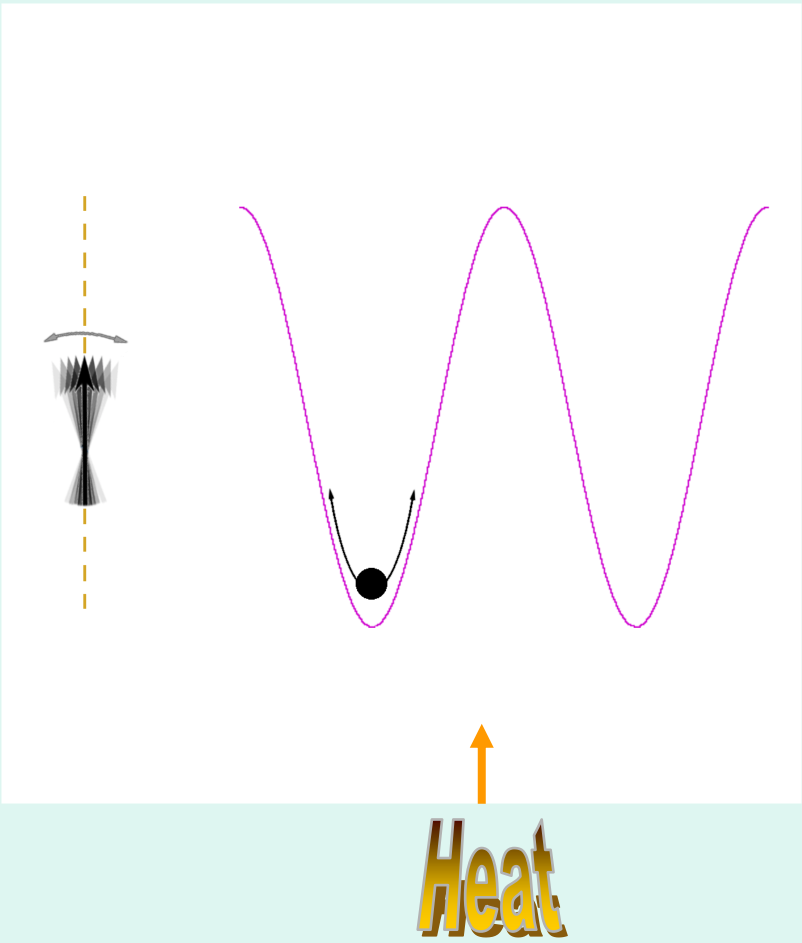
- ***K* is a constant for the material**

Stoner-Wohlfarth Particle



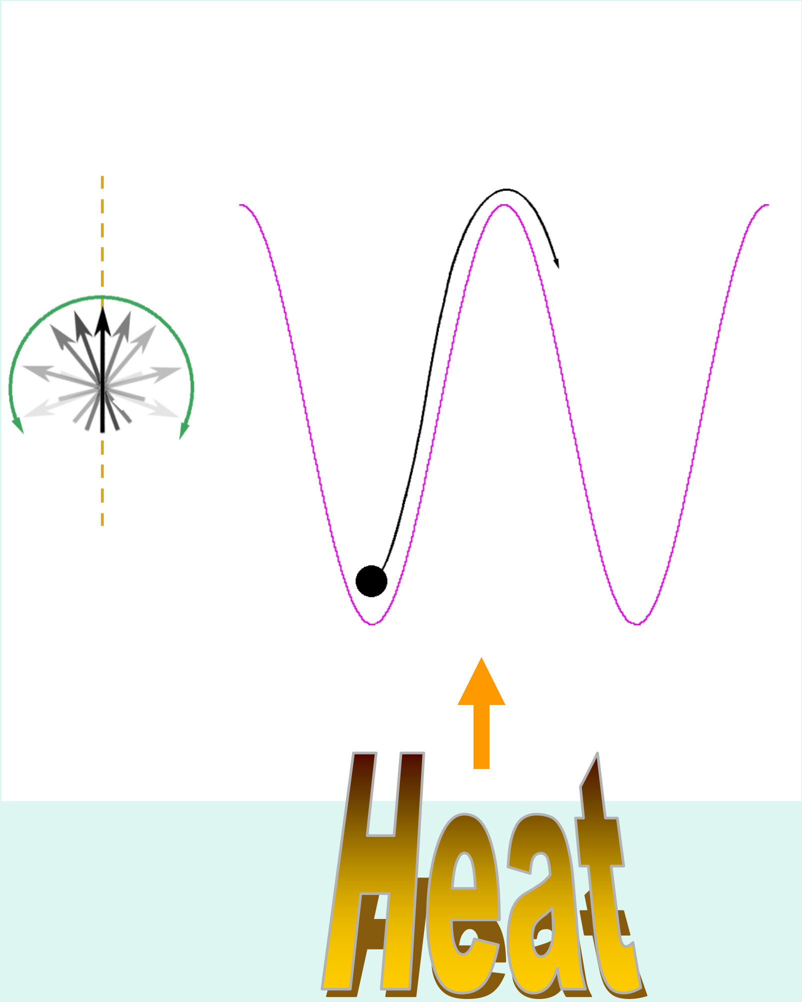
$$E_a = KV \sin^2(\theta)$$

Thermal activation



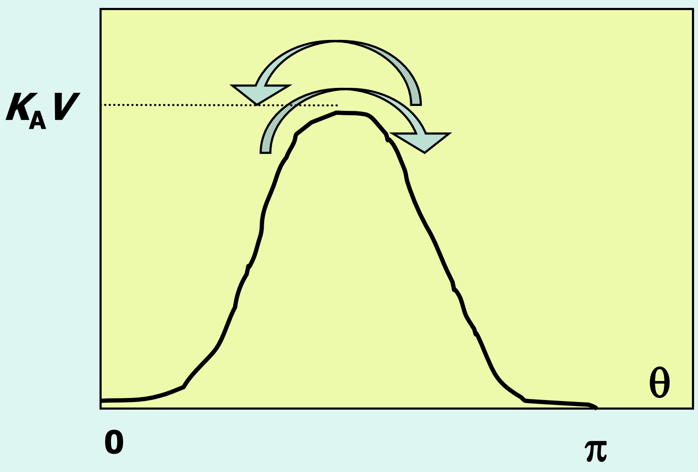
- **At low temperature magnetic moment of particle trapped in one of the wells**
- **Particle magnetic moment is “blocked”**

Thermal activation

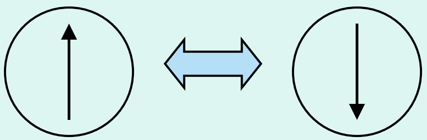


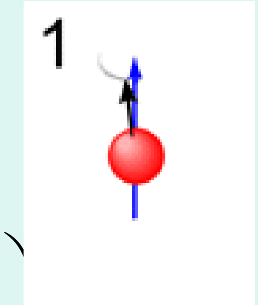
- **At higher temps, thermal energy can buffet magnetic moment between the wells**
- **Results in rapid fluctuation of moment**
- **Particle moment becomes “unblocked”**

Thermally Activated Jump



Thermally Activated Jump (Classical Behaviour!!)





- **Jump frequency**: $\upsilon = \tau_0^{-1} \exp\left(-\frac{K_a V}{k_B T} \right)$
- **Relaxation time:** $\tau = \tau_0 \exp\left(\frac{K_a V}{k_B T} \right)$
- **theoretical predictions:** $\tau_0 = 10^{-9} \div 10^{-10}$ **(see later)**

Demagnetization rate of an assembly of uniaxial particles

$$-\frac{dM}{dt} = f_0 M e^{-KV/kT} = \frac{M}{\tau}$$

f_0 : frequency factor (≈ 10^9 sec^{-1})
τ : relaxation time

Turn-off external field at t = 0 with M_i

$$M_r = M_i e^{-t/\tau}$$

τ : time for M_r to decrease to 1/e of its initial value

$$\frac{1}{\tau} = f_0 e^{-KV/kT}$$

For Co (K = 4.5×10^6 ergs/cm^3) at room temp. (T = 300 K)

D = 68 Å (V = 1.6 × 10^{-19} cm^3)

$$\frac{1}{\tau} = 10^9 \cdot e^{-(4.5\times10^6 \times 1.6\times10^{-19}/(1.38\times10^{-16}\times300))} \approx 279.9\ \frac{1}{\sec}$$

$$\tau \approx 3\times10^{-2}\ \sec$$

An assembly of such particles would reach thermal equilibrium state (M_r = 0) almost instantaneously.
No hysteresis

Magnetization Relaxation

- **Two Regimes:**

$\tau < t_m$ $\quad t_m \quad$ $\tau > t_m$ $\quad$ ***time***

Superparamagnetic

Measuring time (time needed to do a measurement)

Blocked

- **Standard Magnetic Measurements: $t_m \approx 100$ s**
- **Mössbauer: $t_m \approx 10^{-8}$ s**

- **Define a critical volume at constant T (e.g., RT≡T_0) by requiring $\tau = t_m$:**

$$\ln \tau = \ln \tau_0 + \frac{K_a V_{crit}}{k_B T_0} = \begin{cases} \ln 10^2 \\ \cdots \\ \ln 10^{-8} \end{cases}$$

$\approx 10^{-10}$

For $t_m \approx 100$ s:

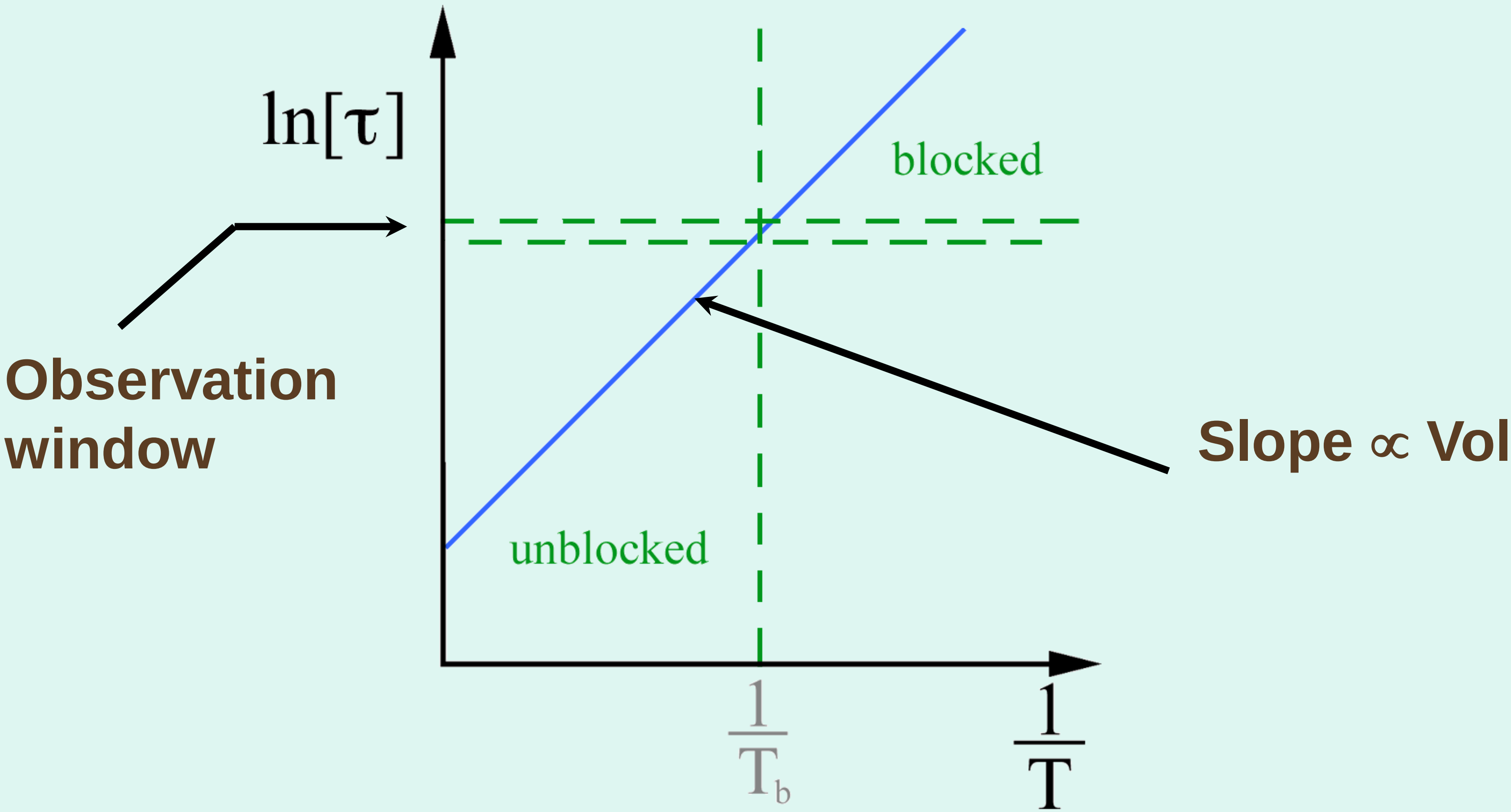
$$V_{crit} \approx \frac{25 k_B T}{K_a}$$

$$D_{crit} = \left[\frac{6}{\pi} V_{crit} \right]^{1/3}$$

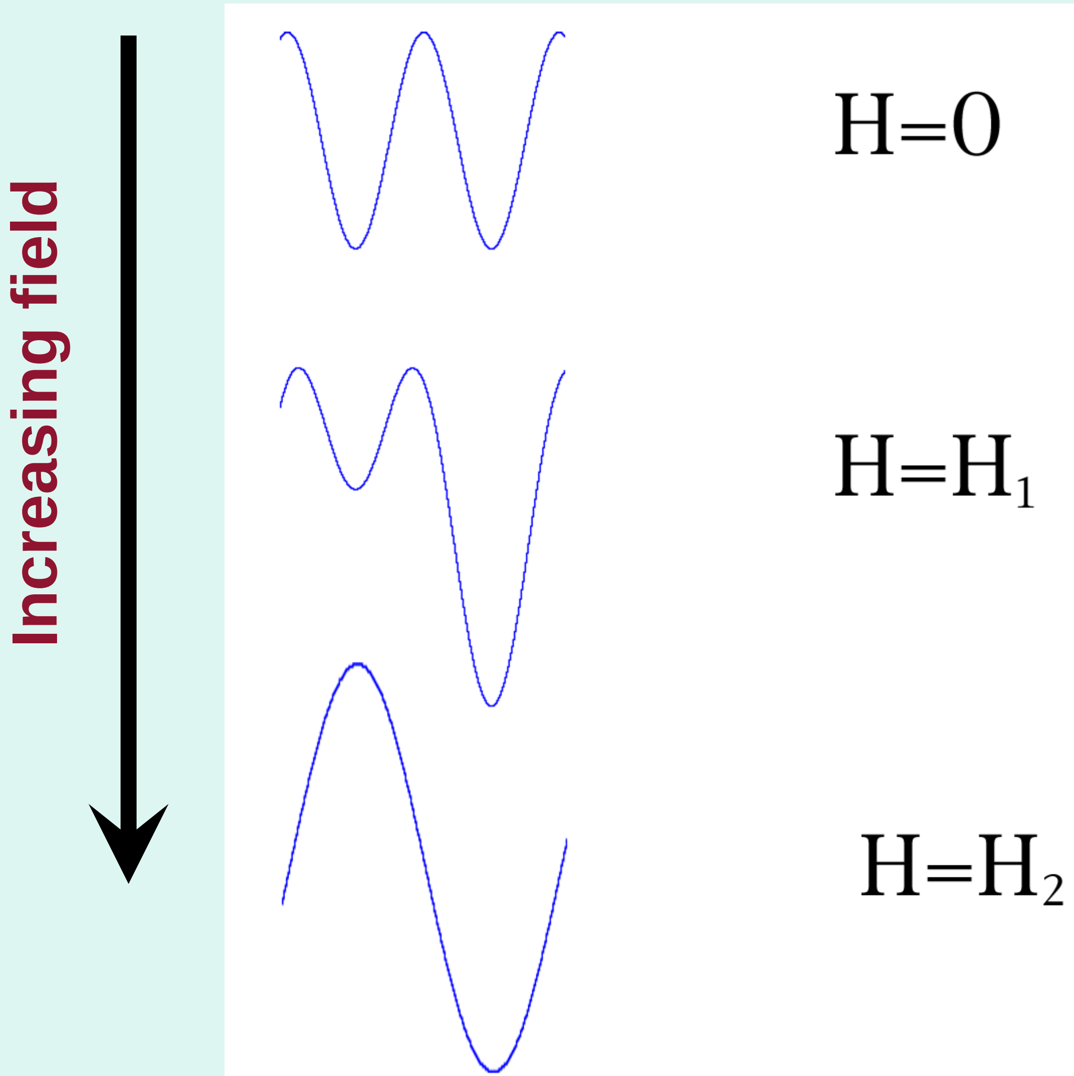
Magnetic blocking temperature

- **The magnetic blocking temp, T_b, is the temp below which moment is blocked**
- **Blocking temperature depends on particle size and timescale of observation**
- **Larger particles have higher blocking temperatures**
- **The longer the observation time, the more likely it is that the moment will be observed to flip**

Fluctuation timescales, τ

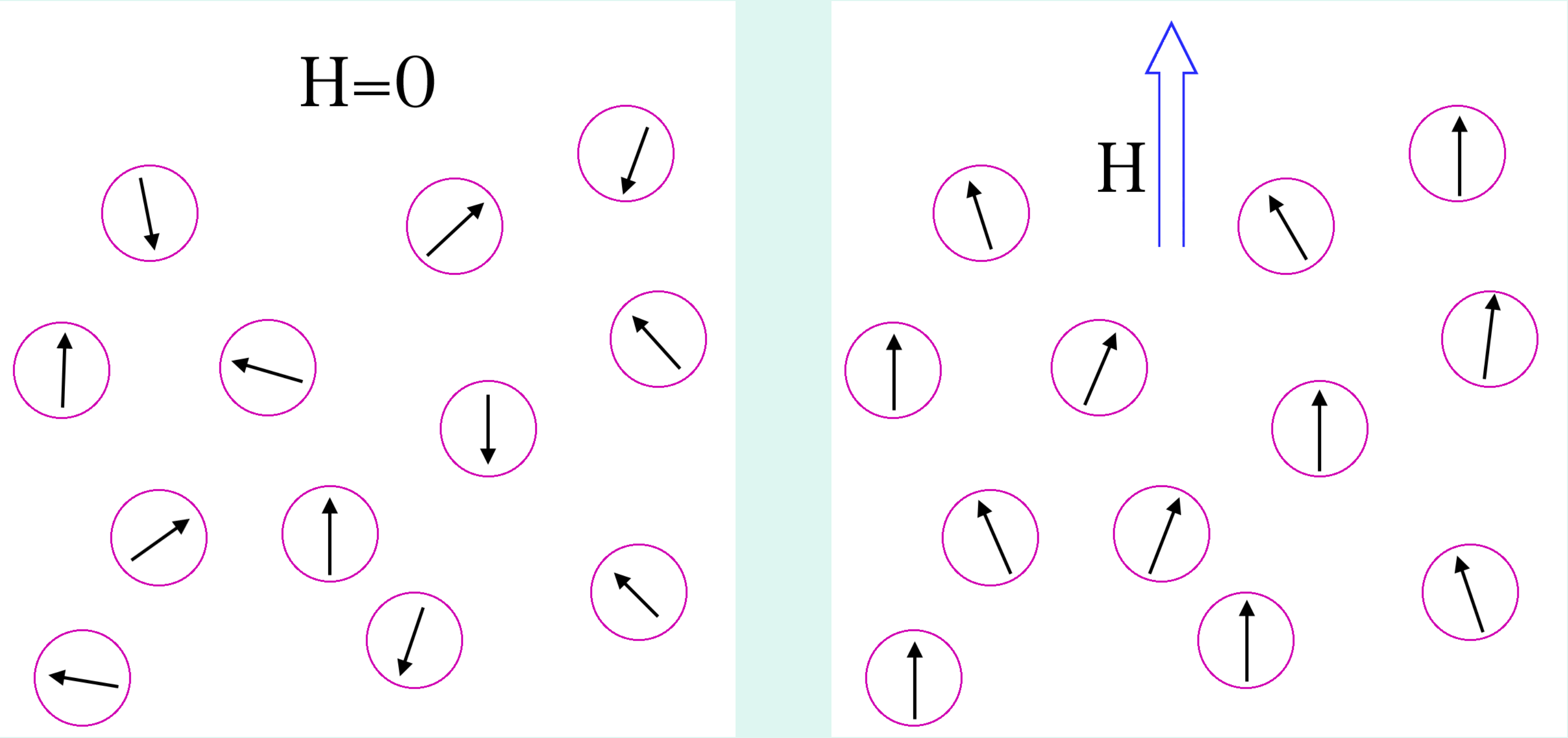


Effect of applied field on single domain particles



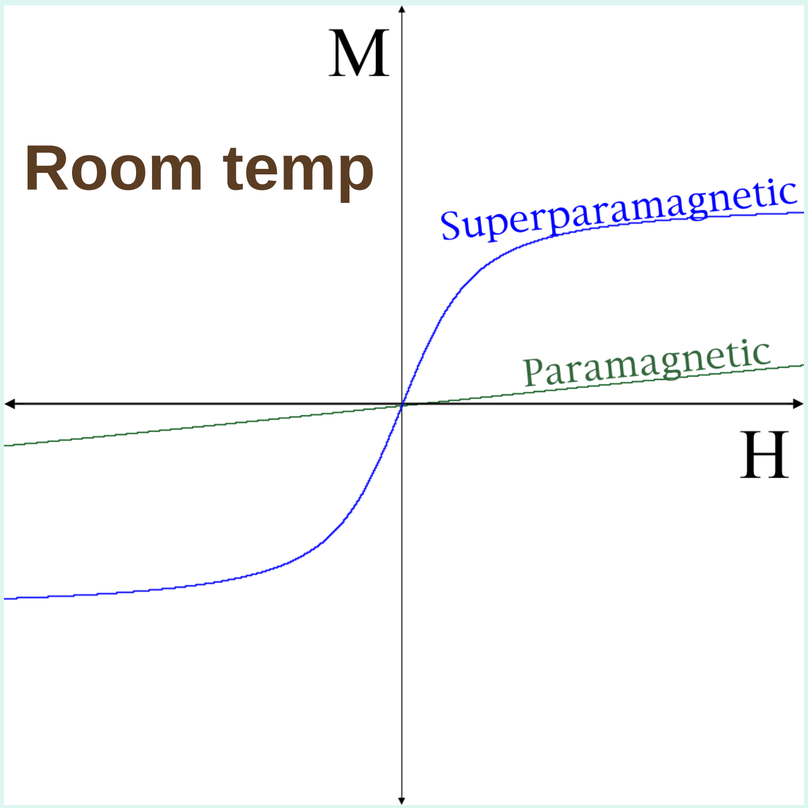
- **Applying field along easy axis favours moment aligned with field**
- **Above T_b this results in moment spending more time in lower well**
- **Particle exhibits time averaged magnetization in direction of field**

Superparamagnetism



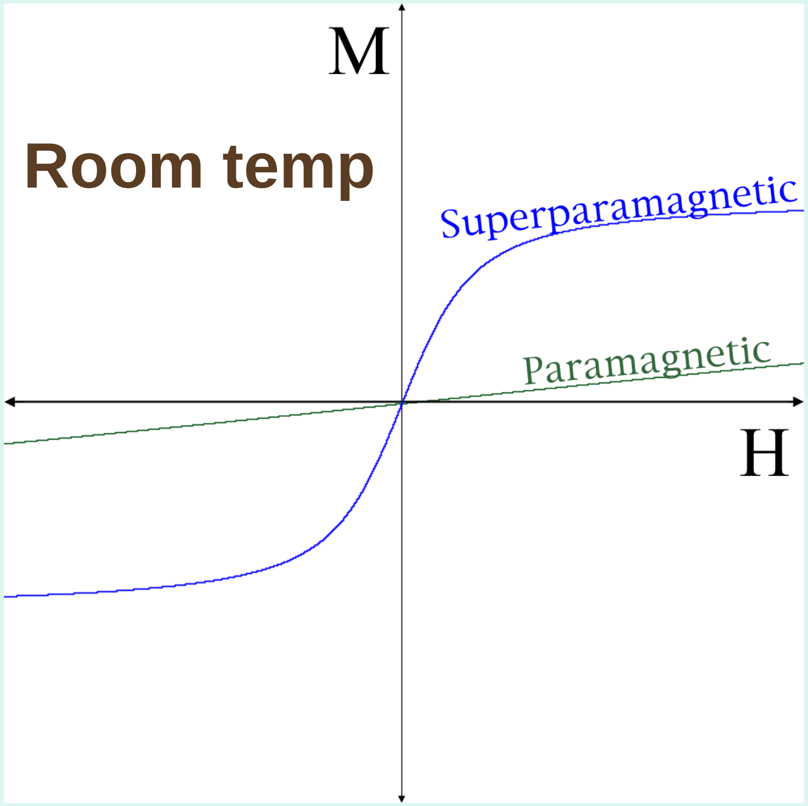
- **Unblocked particles that respond to a field are known as superparamagnetic**

Superparamagnetism



- **Response of superparamagnets to applied field described by Langevin model**
- **Qualitatively similar to paramagnets**
- **At room temperature superparamagnetic materials have a much greater magnetic susceptibility per atom than paramagnetic materials**

Superparamagnetism



Superparamagnets are often ideal for applications where…

- **a high magnetic susceptibility is required**
- **zero magnetic remanence is required**

Lecture 3

Magnetic particles in fluids

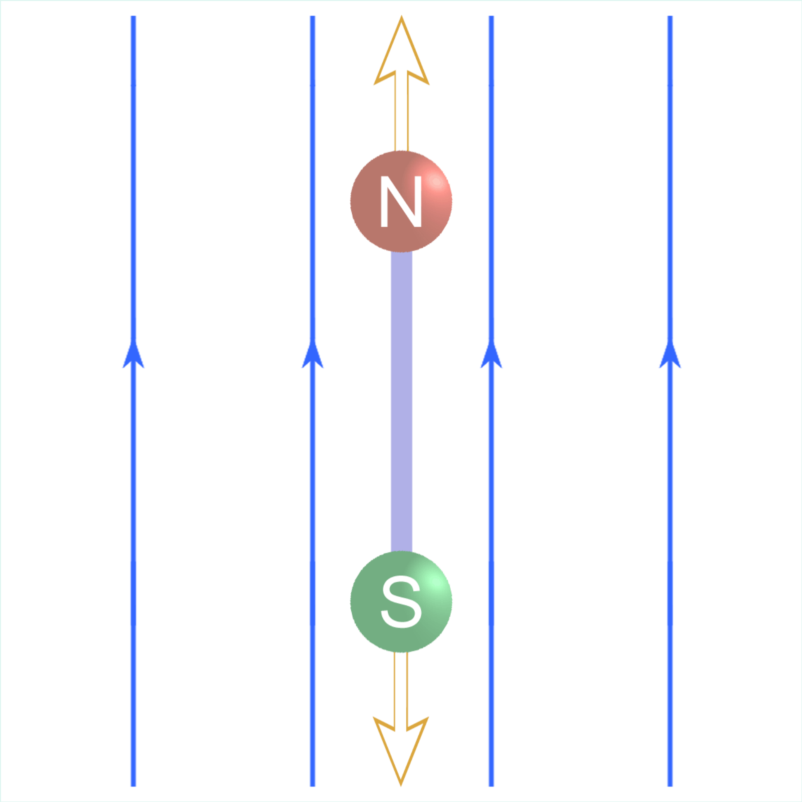
Magnetic particles in fluids

- **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

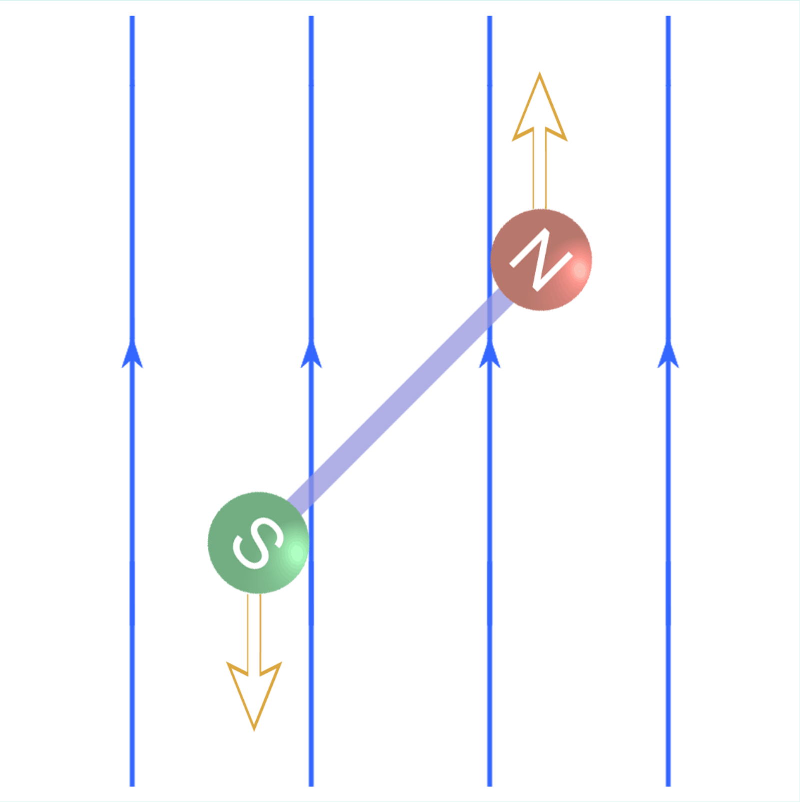
- **Several forces involved**
  - Force of applied magnetic fields on particles
  - Viscous drag forces
  - Interparticle magnetic forces
  - Interparticle electrostatic forces
  - Interparticle entropic “forces”

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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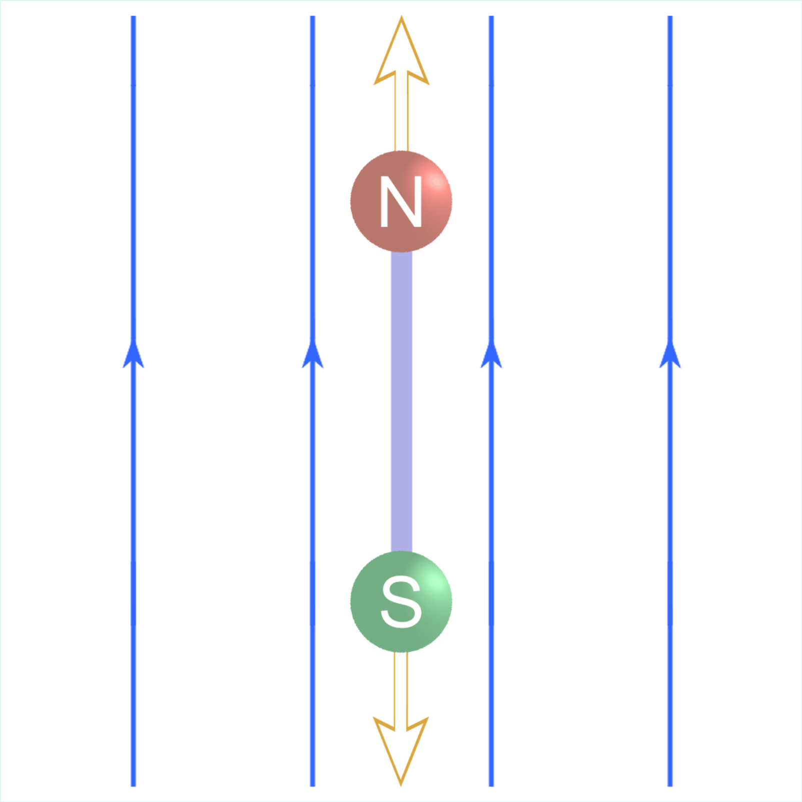
Single magnetic particle in fluid



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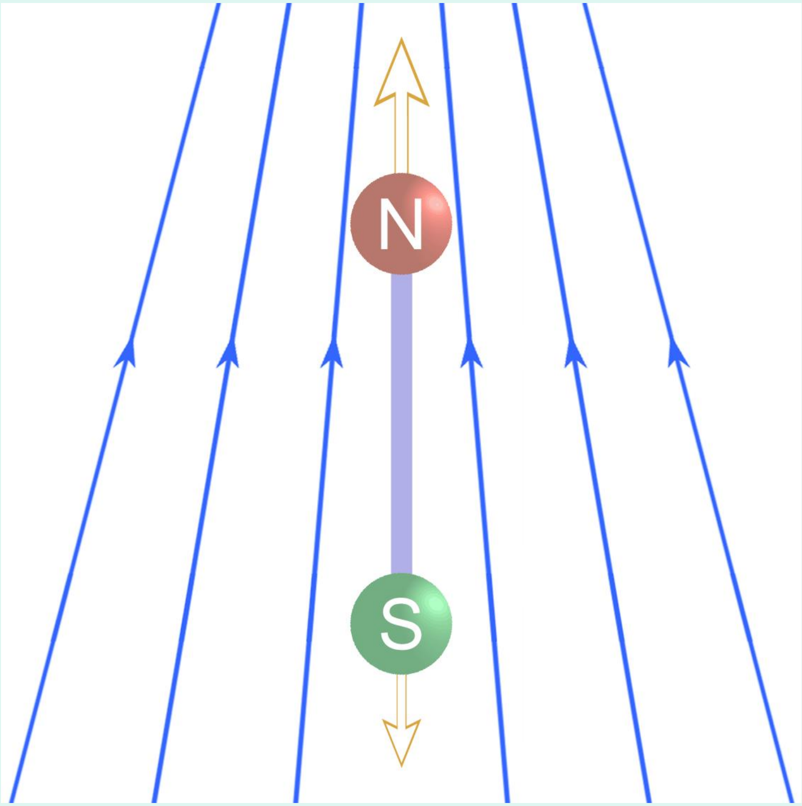
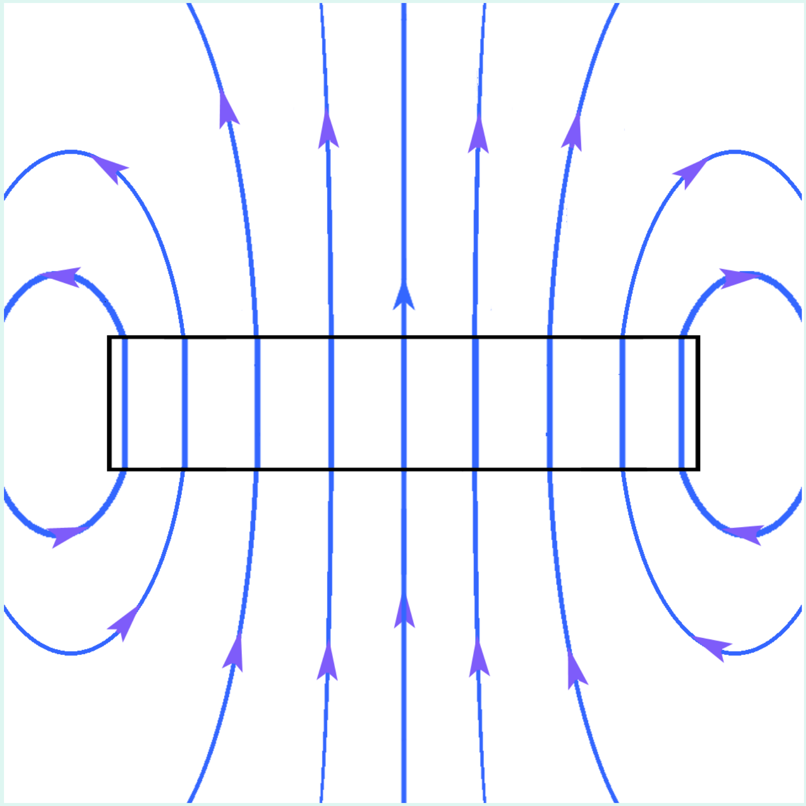
Single magnetic particle in fluid



- **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**

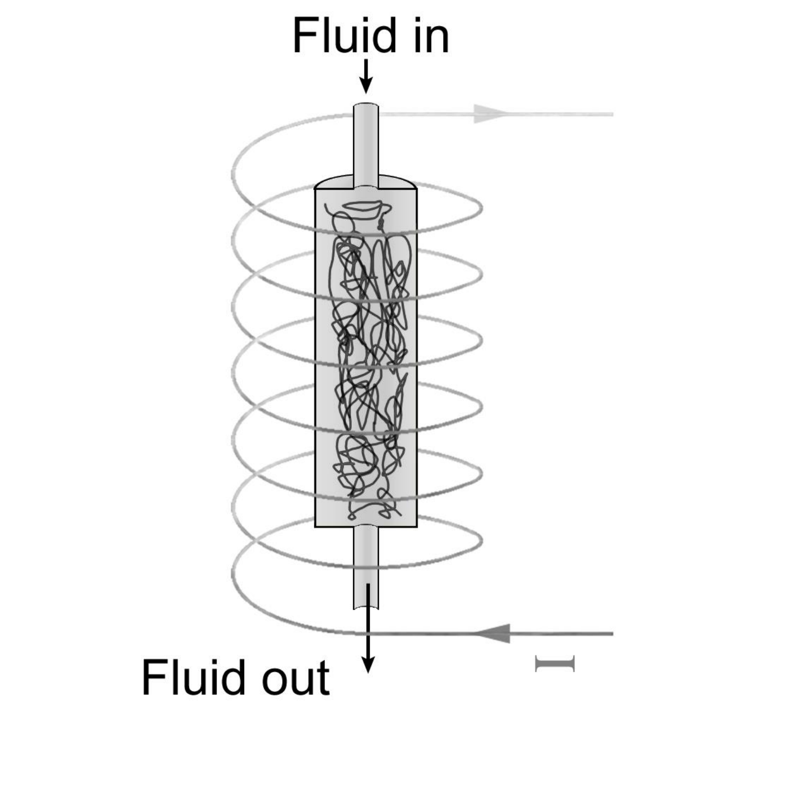
Magnetic Field Gradients



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**

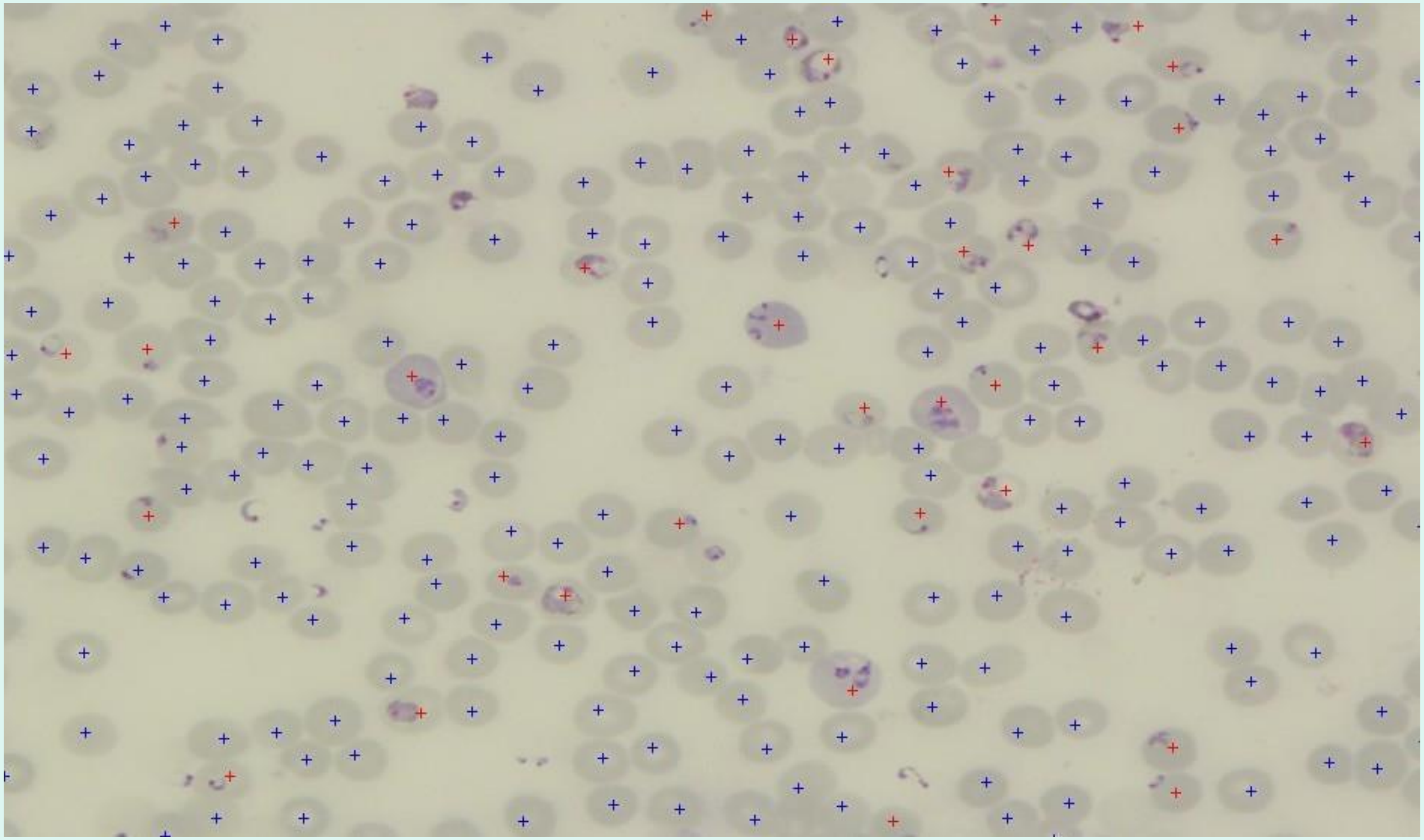
Malaria infected erythrocytes
(Am. J. Clin. Pathol. 103:57 (1995))

- **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 <u>P. falcipurum</u> of health RBC.**

Haemozoin

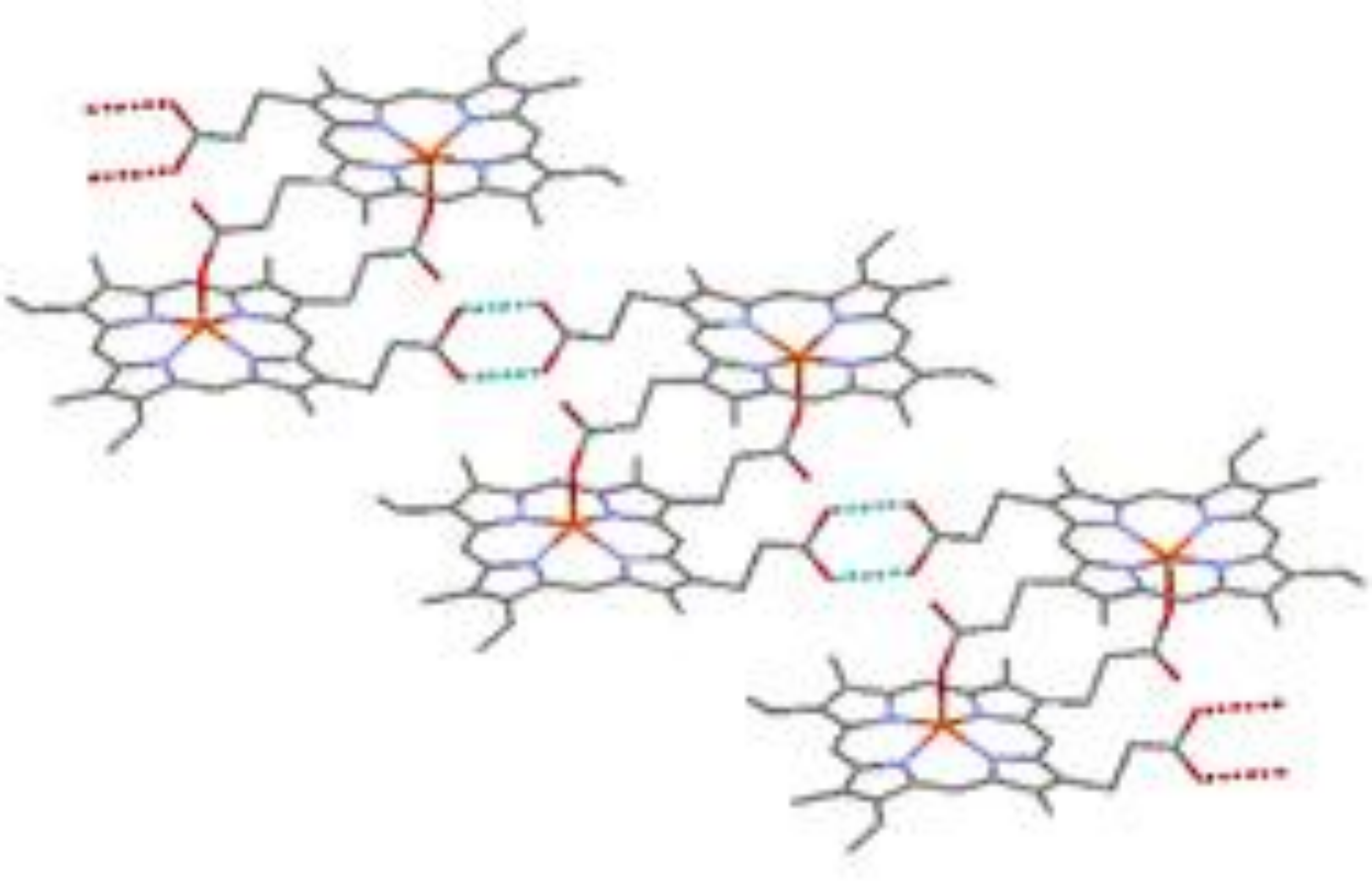
- **Is a disposal product formed from the digestion of blood by some blood-feeding parasites. These hematophagous organisms such as Malaria parasites (*Plasmodium spp.*), *Rhodnius* and *Schistosoma* digest haemoglobin and release high quantities of free heme, which is the non-protein component of hemoglobin. 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



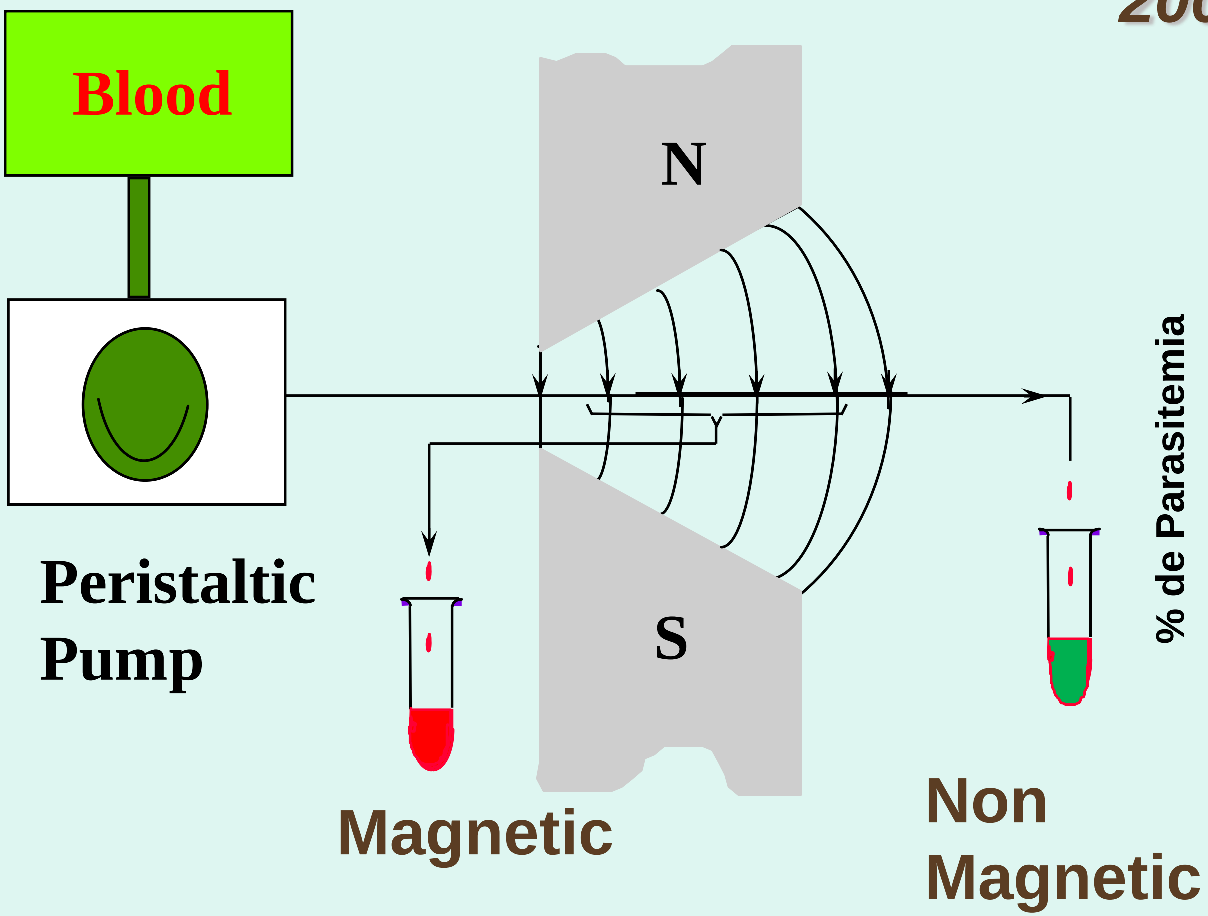
Normal cells are marked in blue and infected cells with red crosses.

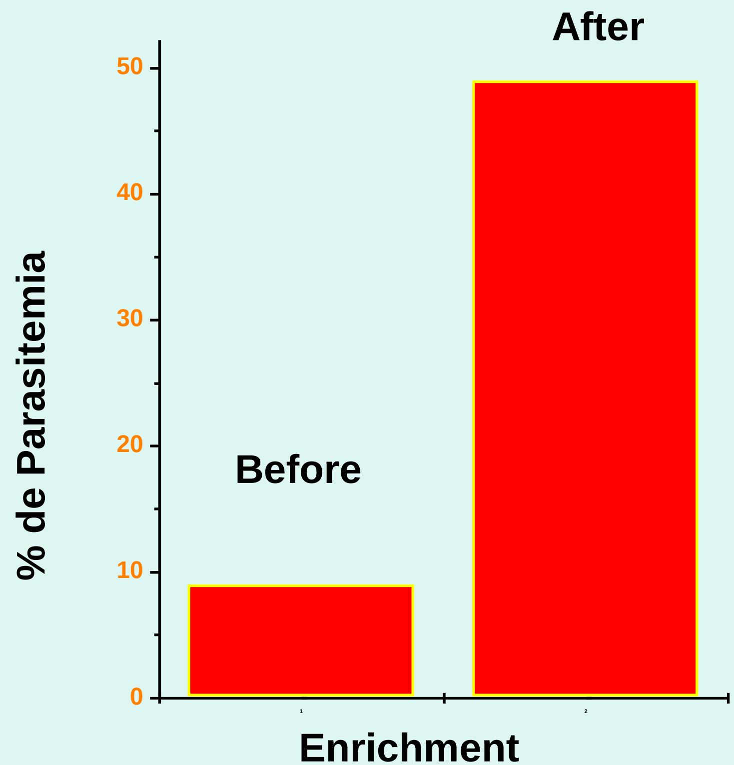
Haemozoin



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**

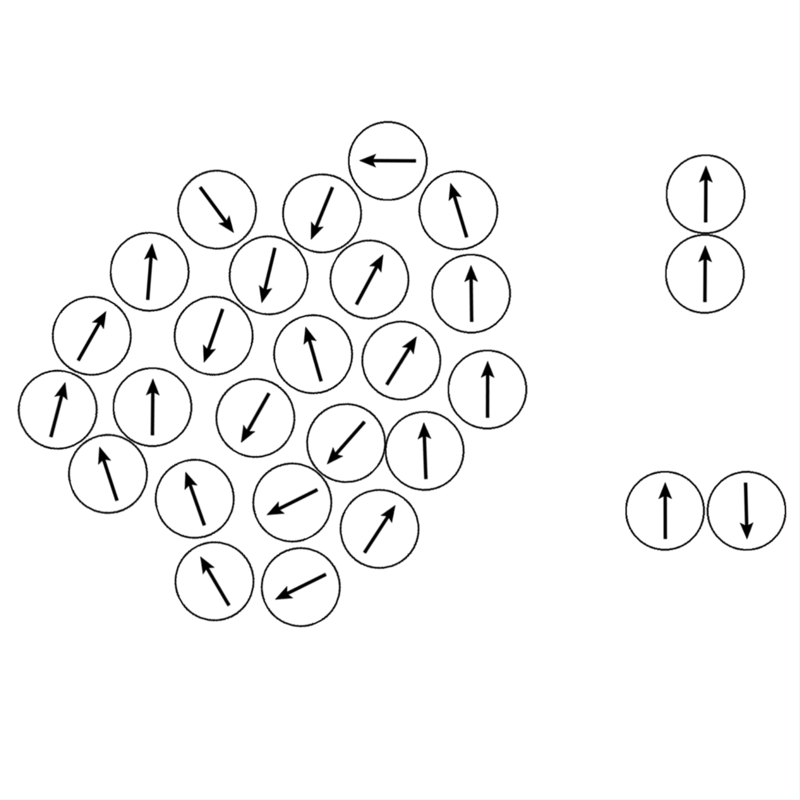
Interparticle interactions: Aggregation

- **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

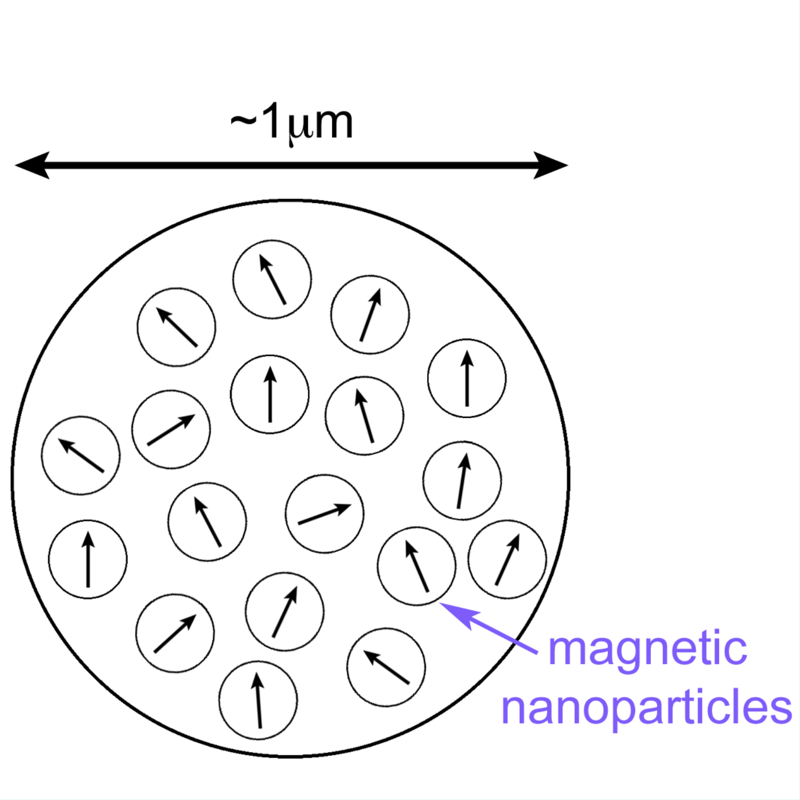


- **Particles in close proximity with each other**
- **Moments tend to arrange themselves such as to minimize magnetization of aggregate**
- **Clusters of particles may show reduced susceptibility in low fields**

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.

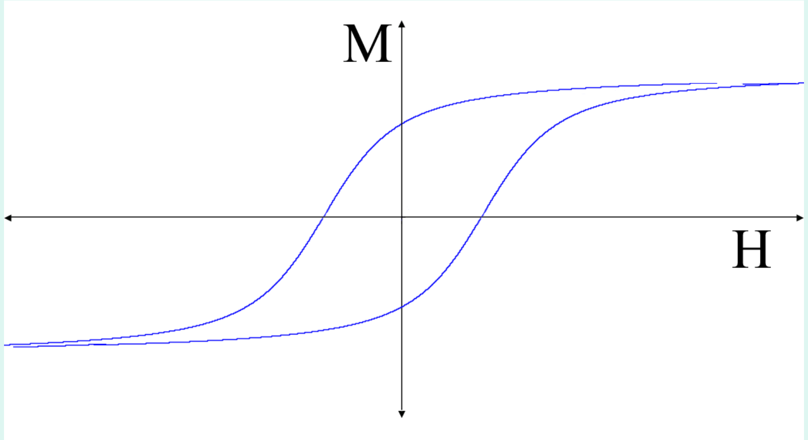
Design of magnetic microspheres



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

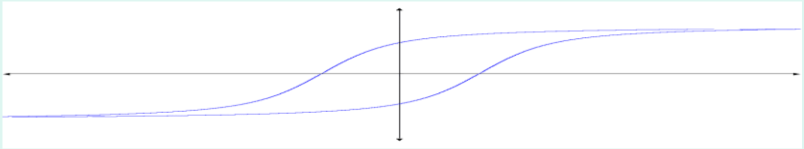
Particles for Special Applications

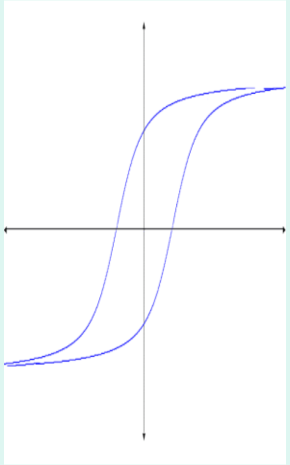
Particles for hyperthermia therapy



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

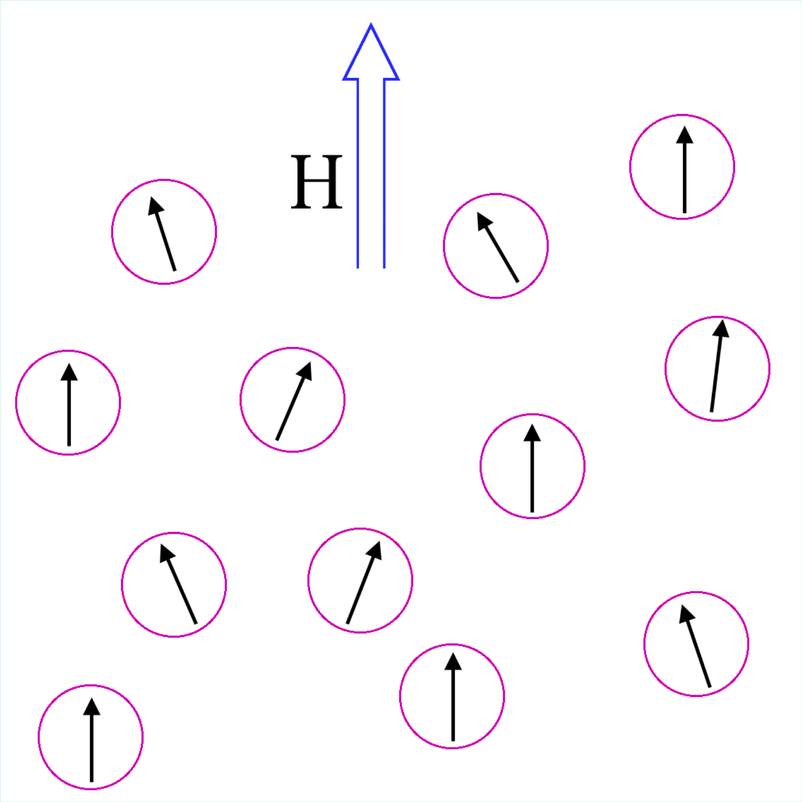
Particles for hyperthermia therapy





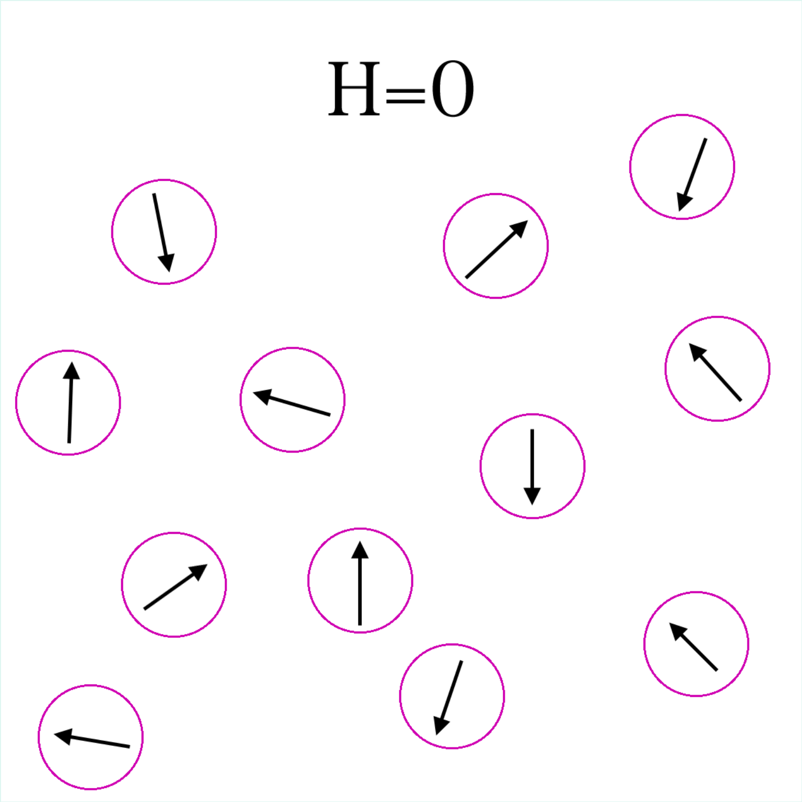
- **Therapeutic ac field amplitudes are limited (to avoid nerve stimulation)**
- **Particles with low coercivity but high M_s are preferred**

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



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

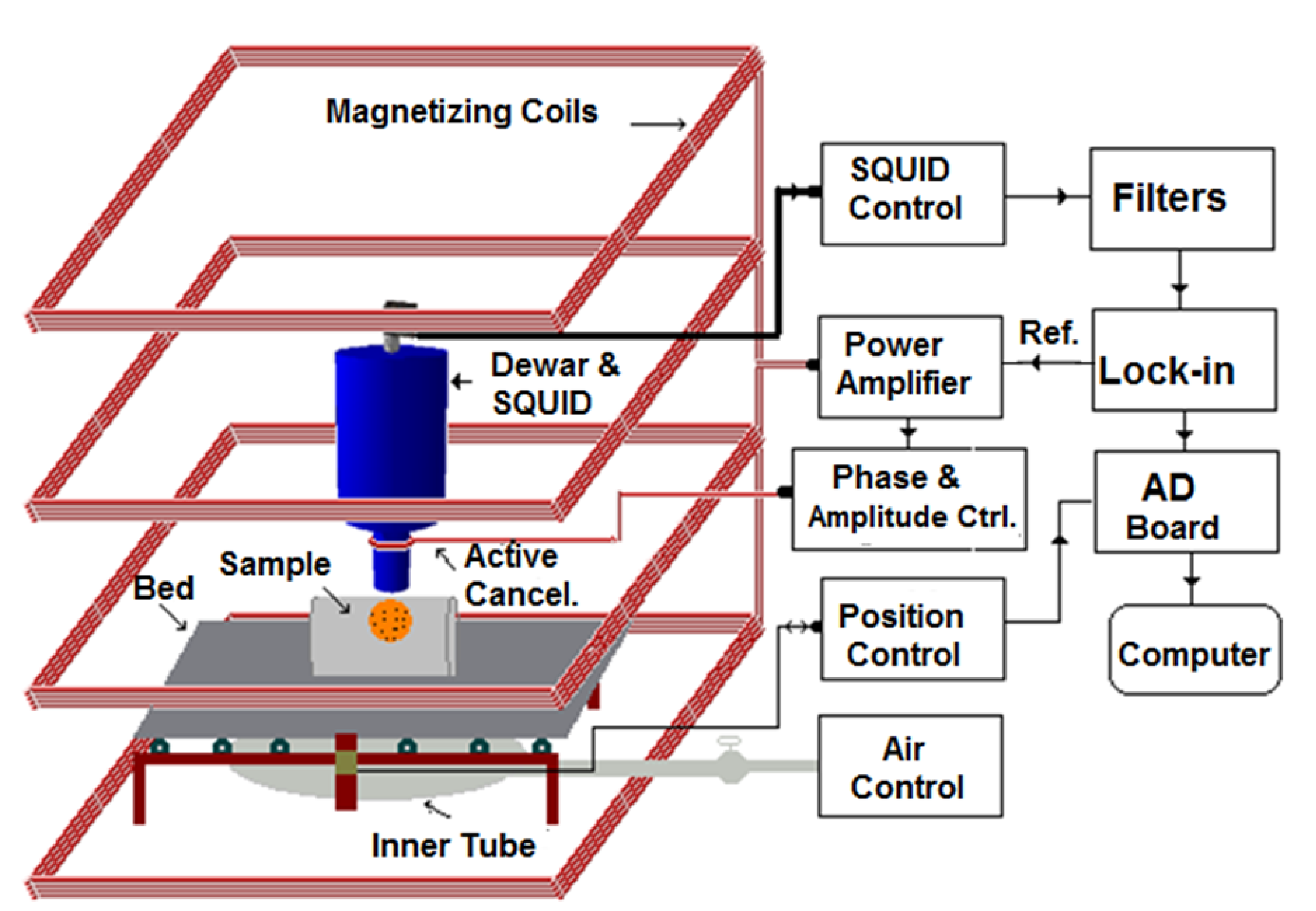
Scientific and Clinical Applications of Magnetic Carriers

- **Magnetic separation applications**
- **Magnetically targeted drug delivery**
- **Magnetic labelling**
- **Magnetic hyperthermia therapy**

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

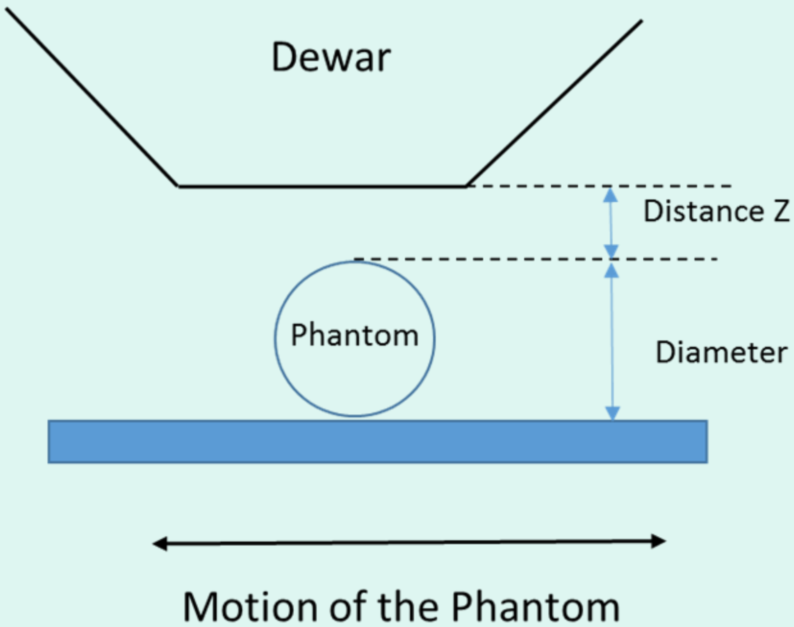
A block diagram of the large-scale AC superconducting susceptometer

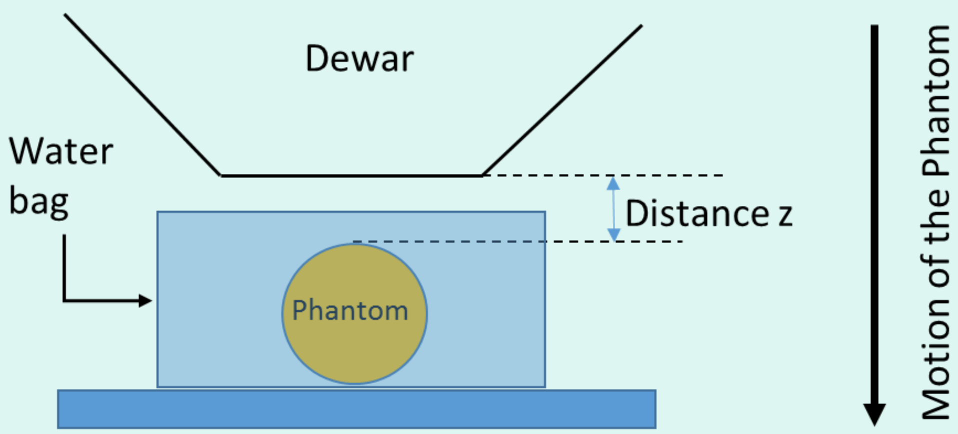


Detail of the Dewar, bed, magnetizing coils and water reservoir.

Sketch of the measurement methods used

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



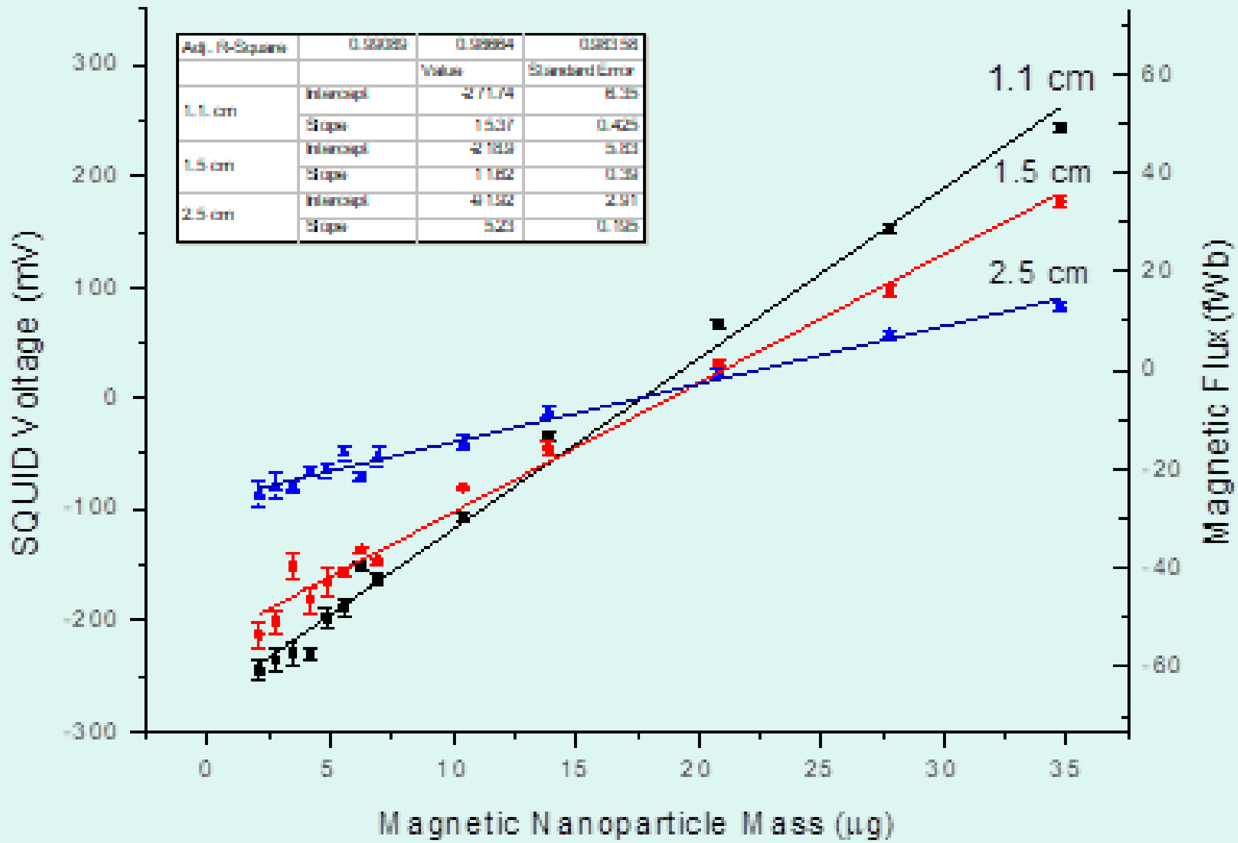


Modelling

- 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*=$M_s v_p B / k_B T$

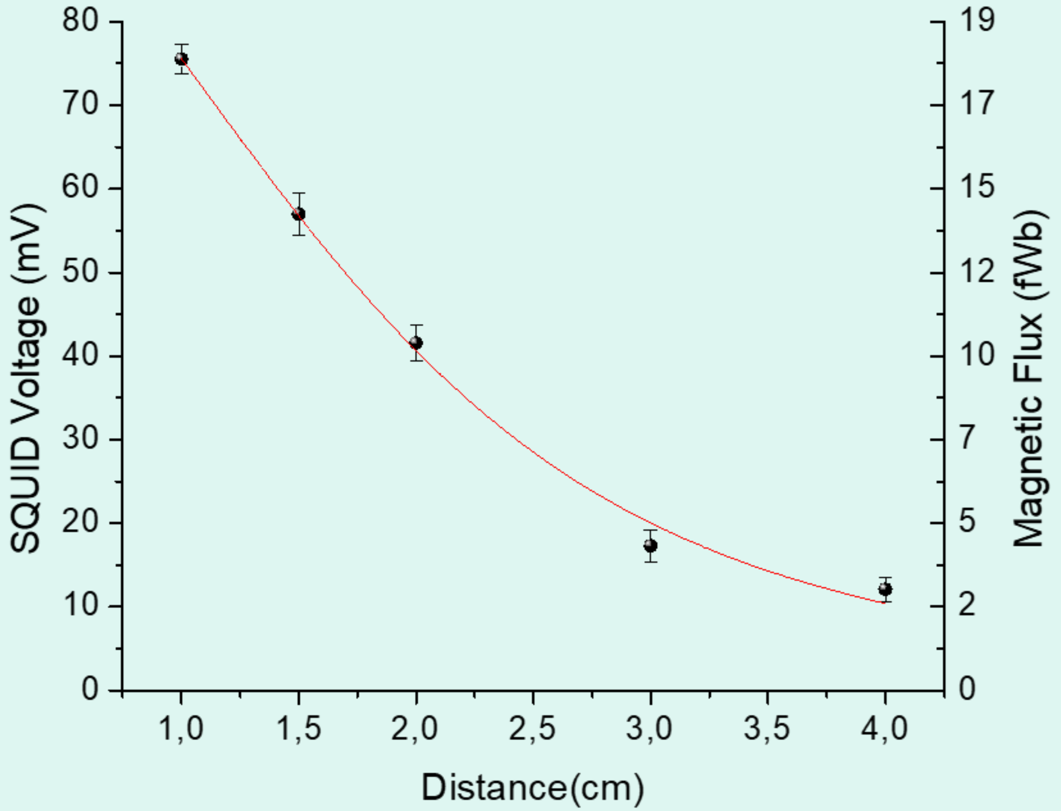
- At the low field condition, the Langevin function is $(x) \cong \frac{x}{3}$
- $< m_d >_{sample} = N M_s v L(x) \cong v \frac{N M_s^2 v_p B}{3 k_B T} = \frac{v \chi_L B}{\mu_0}$
- $V = \alpha \frac{\mu_0}{2\pi r^3} \; \frac{\chi_L v B}{\mu_0} = \alpha \frac{\chi_L v B}{2\pi r^3}$
- Where $\chi_L =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

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 ($fWb/\mu g$)	$10^9\ NP/ml$
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

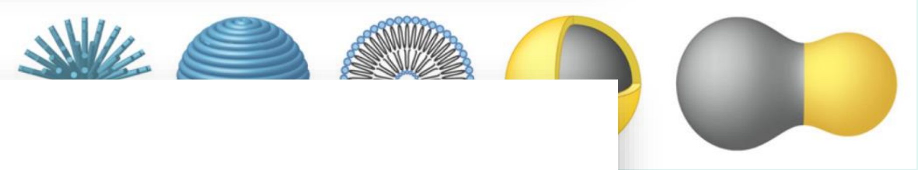
Functional Magnetic Nanoparticle Imaging by AC Biosusceptometry

Laboratório de Biomagnetismo, Instituto de Biociências de Botucatu, Unesp, SP - Brazil,
Universidade Federal do Mato Grosso, Campus Barra do Garça, MS - Brazil
Instituto de Física, Universidade Federal de Goiás, Goiânia, GO - Brazil
Departamento de Física, FFCLRP, USP, Ribeirão Preto, SP - Brazil

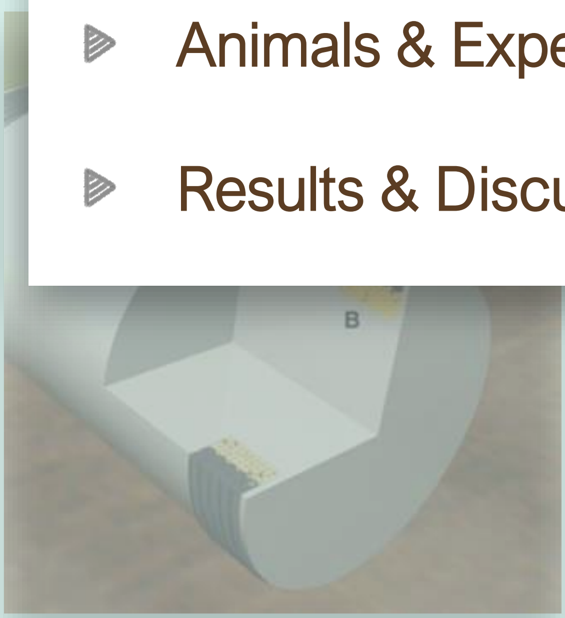
Research Team

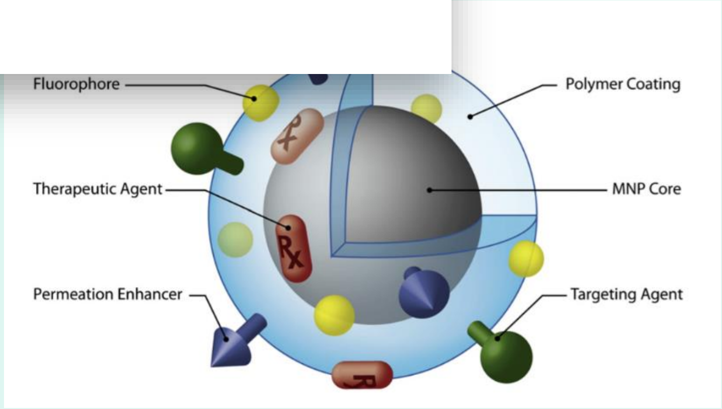
- José Ricardo Arruda Miranda-UNESP
- Caio Quini-UNESP
- Andris Bakusis -UFG
- Madileine F. Americo-UFMT
- Oswaldo Baffa-USP

Outline of the presentation

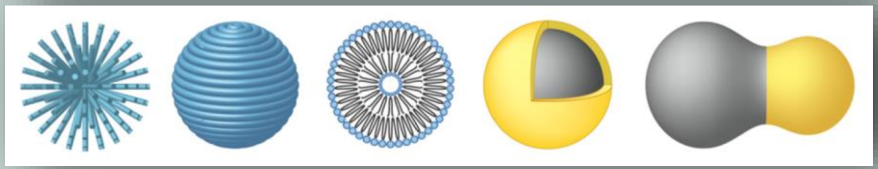


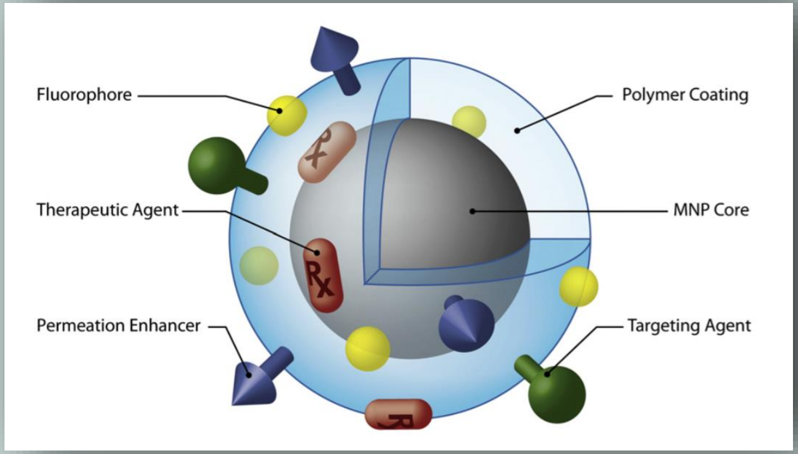
- Motivation for the use of MNPs
- AC Biosusceptometry
- Animals & Experimental protocol
- Results & Discussion





Magnetic Nanopartciles (MNPs)





Versatility

Magnetic Particle Imaging

Magnetic Resonance Imaging

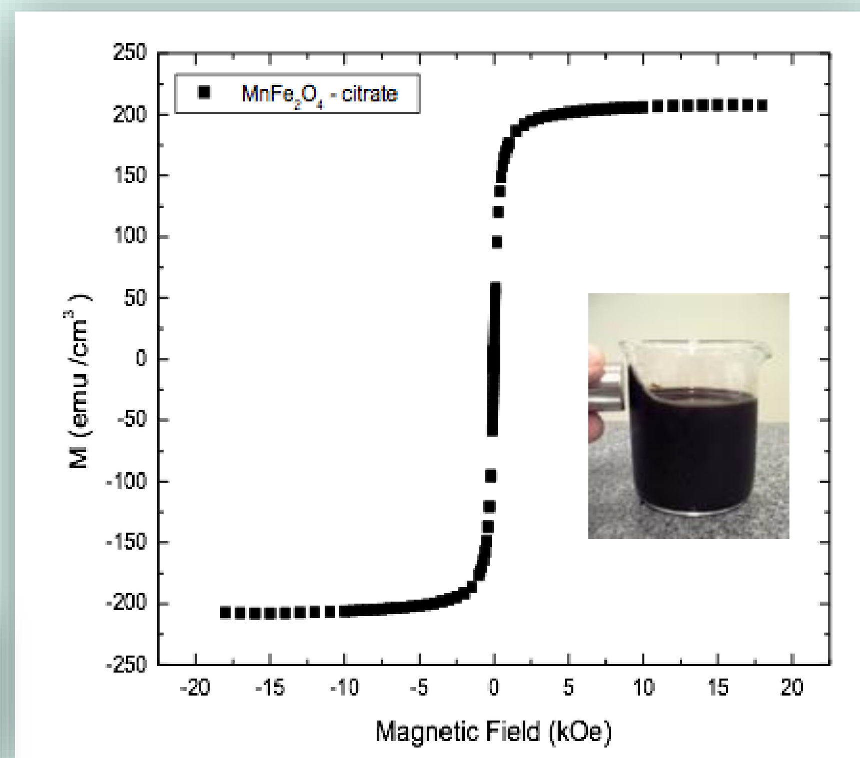
AC Biosusceptometry

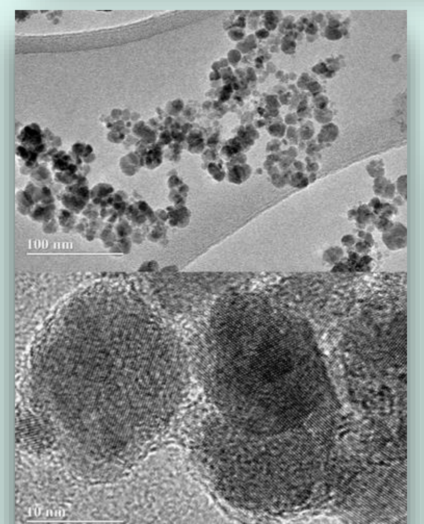
- Simplicity
- Versatility

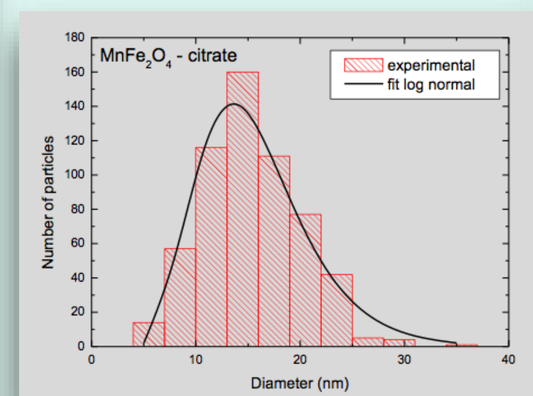
Magnetic Nanopartciles (MNPs)

Superparamagnetic Iron Oxide Nanoparticles

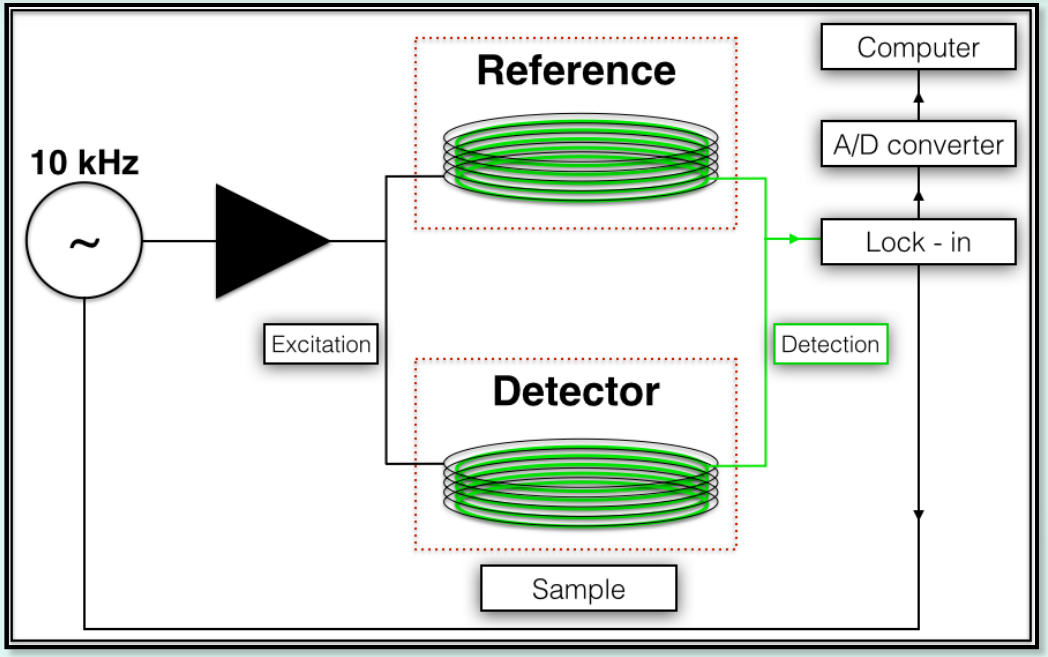
- Ci-$MnFe_2O_4$
  - 13 ± 4 nm
  - - 27.8 mV
  - 23 mg/mL - 1.17x10^{15} part/mL







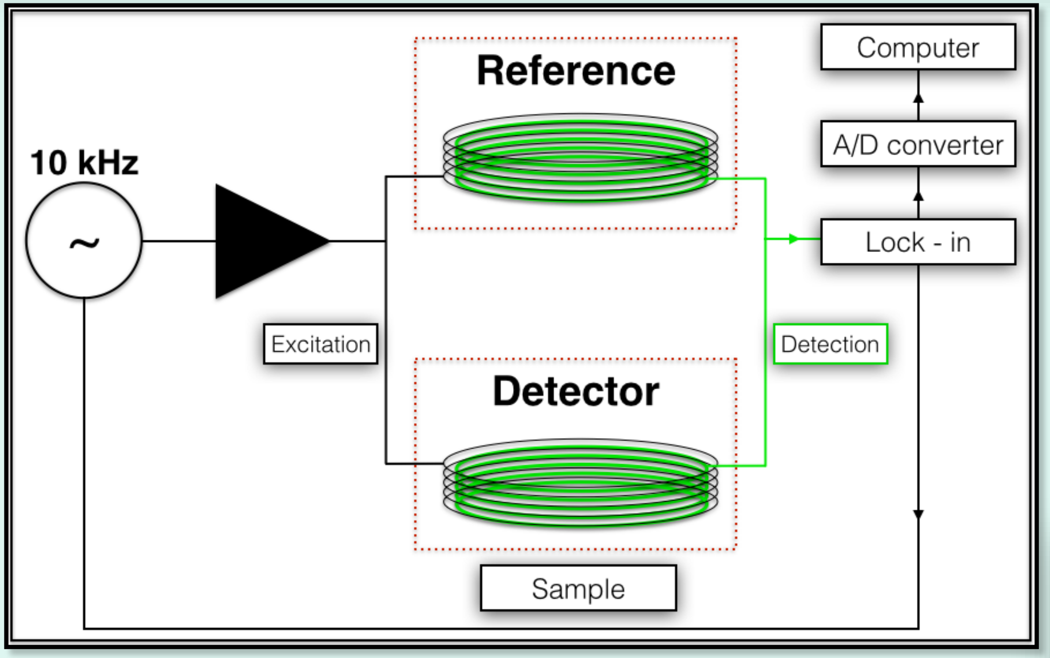
AC Biosusceptometry (ACB)



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

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)

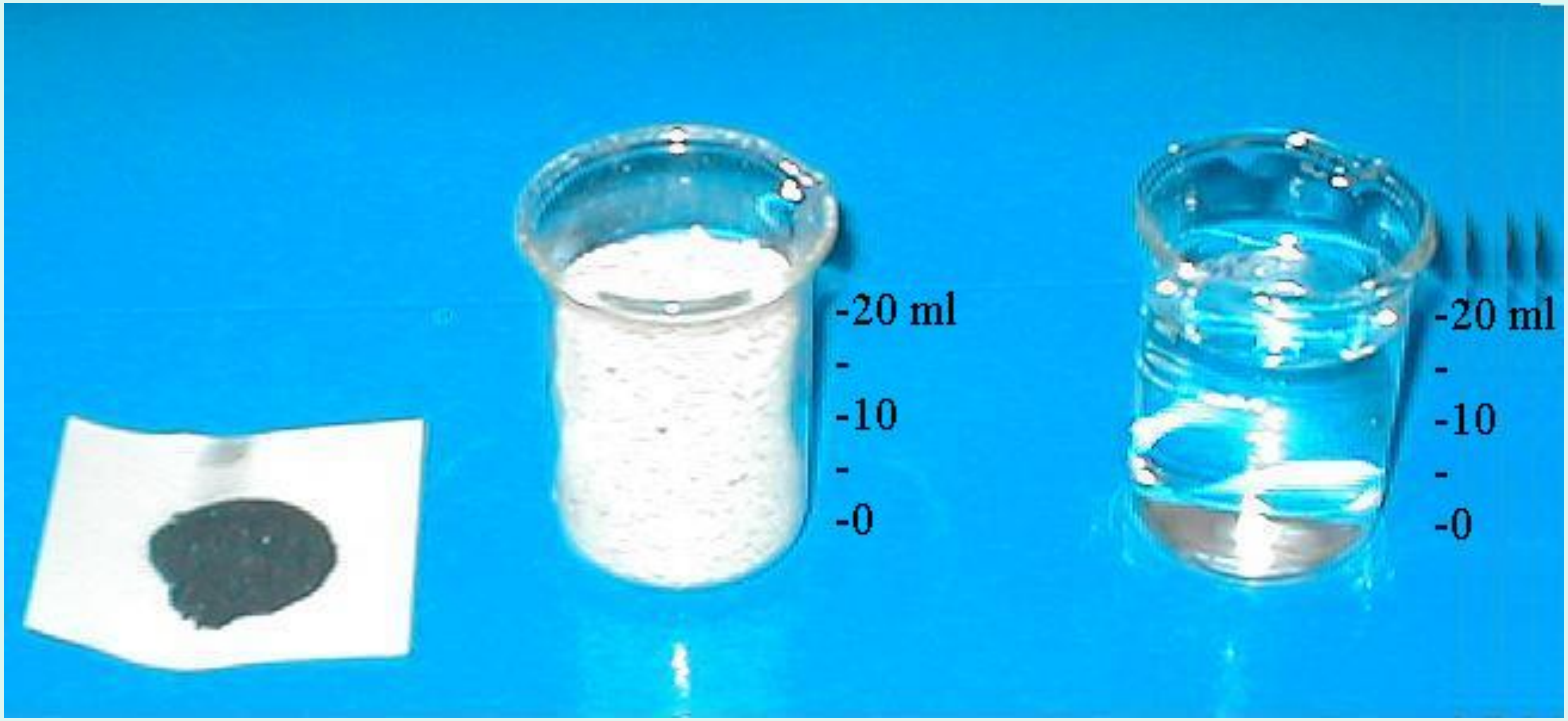


- First order gradiometer system
- Signal Decays Fast (r^{-6})

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

Why Nano?

- GI motility tests require a test meal



3 g ferrite (Fe_3O_4) 15 g Oat Flour Water

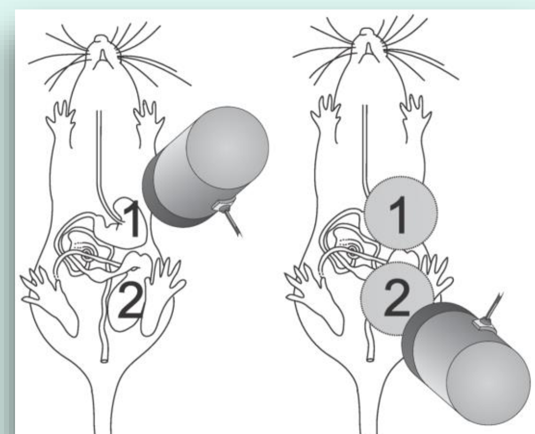
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

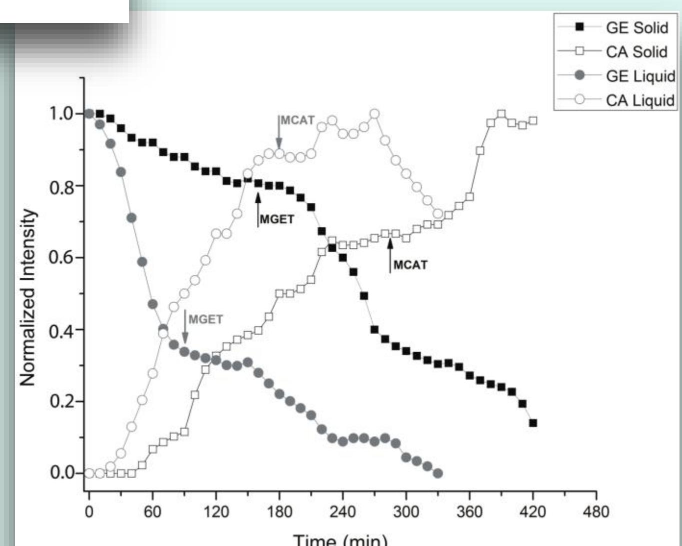
Quini et al. Journal of Biological Engineering 2012, 6:6
http://www.jbioleng.org/content/6/1/6
JOURNAL OF BIOLOGICAL ENGINEERING

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

Journal of Magnetism and Magnetic Materials 380 (2015) 2–6

Contents lists available at ScienceDirect

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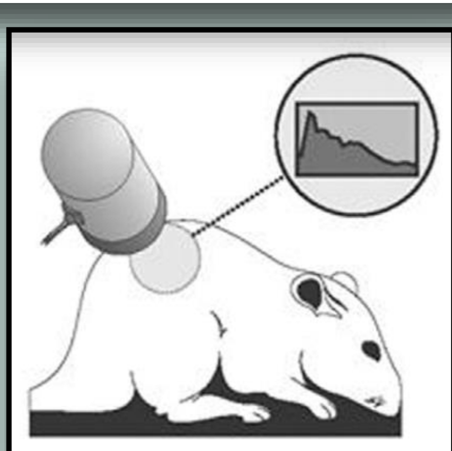
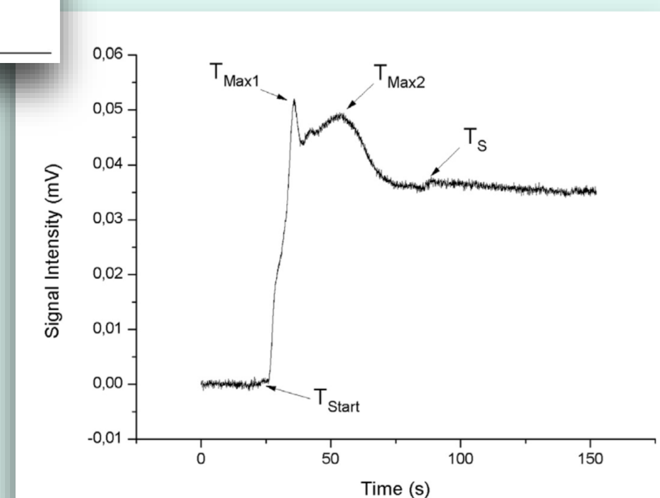
journal homepage: www.elsevier.com/locate/jmmm

Renal perfusion evaluation by alternating current biosusceptometry of magnetic nanoparticles

Caio C. Quini [a,*], Juliana F. Matos [a], André G. Próspero [a], Marcos Felipe F. Calabresi [a], Nicholas Zufelato [b], Andris F. Bakuzis [b], Oswaldo Baffa [c], José Ricardo A. Miranda [a]

[a] Departamento de Física e Biofísica, Instituto de Biociências, UNESP, Botucatu, SP, Brazil
[b] Instituto de Física, UFG, Goiânia, GO, Brazil
[c] Departamento de Física, FFCLRP, USP, Ribeirão Preto, SP, Brazil

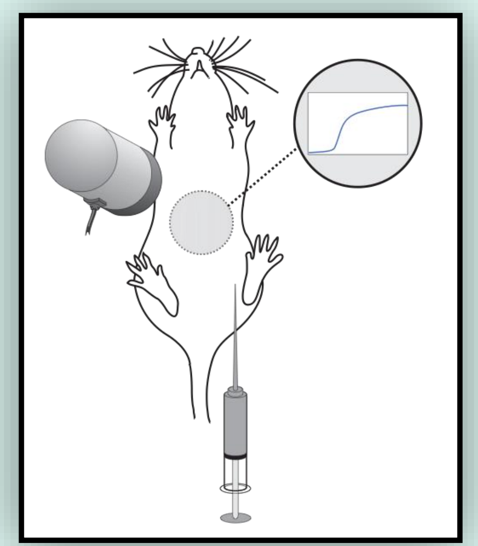


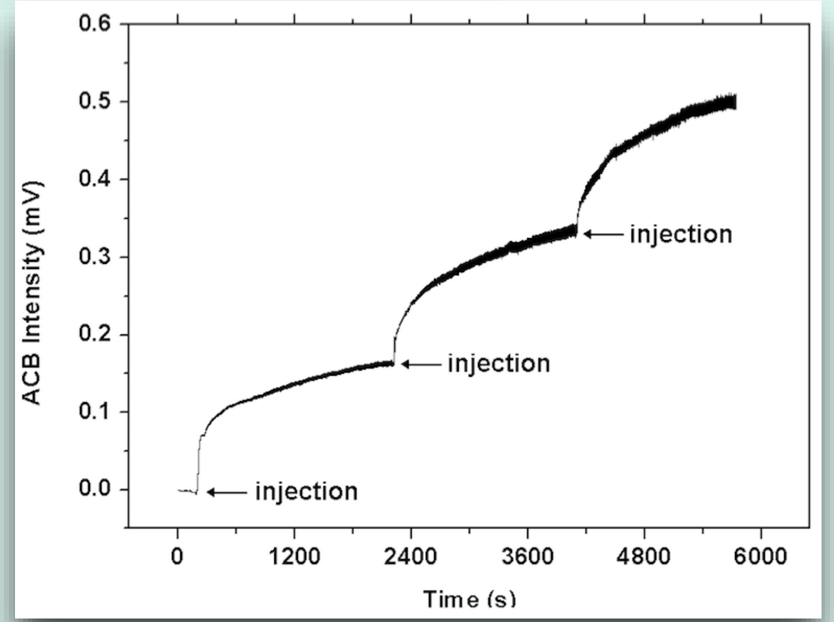


Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

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

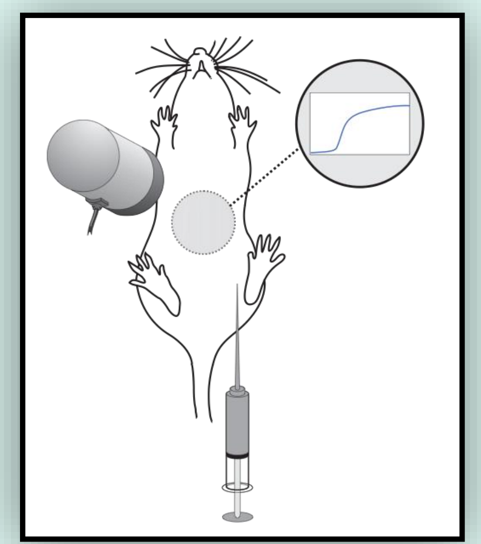
Caio C. Quini[a], André G. Próspero[a], Marcos F. F. Calabresi[a], Gustavo M. Moretto[a], Nicholas Zufelato[b], Sunil Krishnan[c], Diana R Pina[d], Ricardo B. Oliveira[e], Oswaldo Baffa[f], Andris F. Bakuzis[b], Jose R. A. Miranda[a]

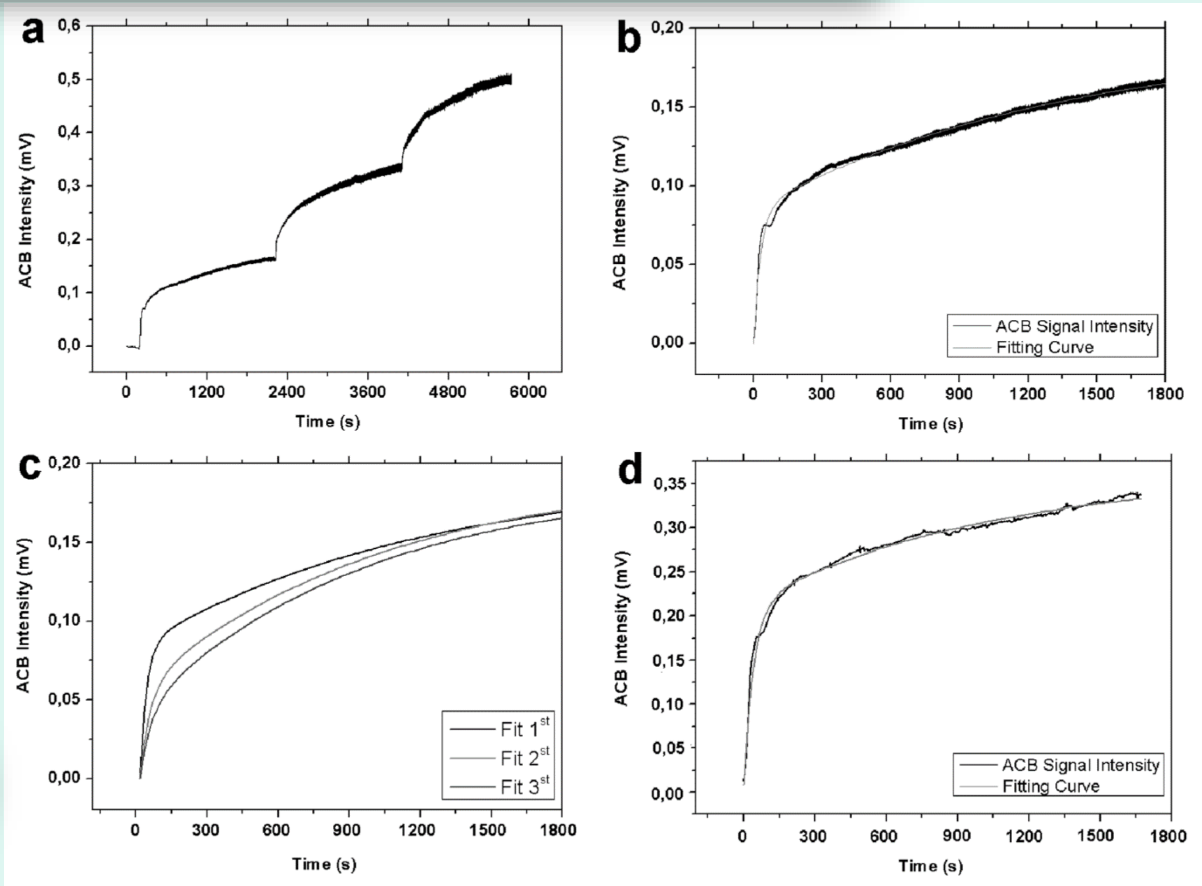




Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

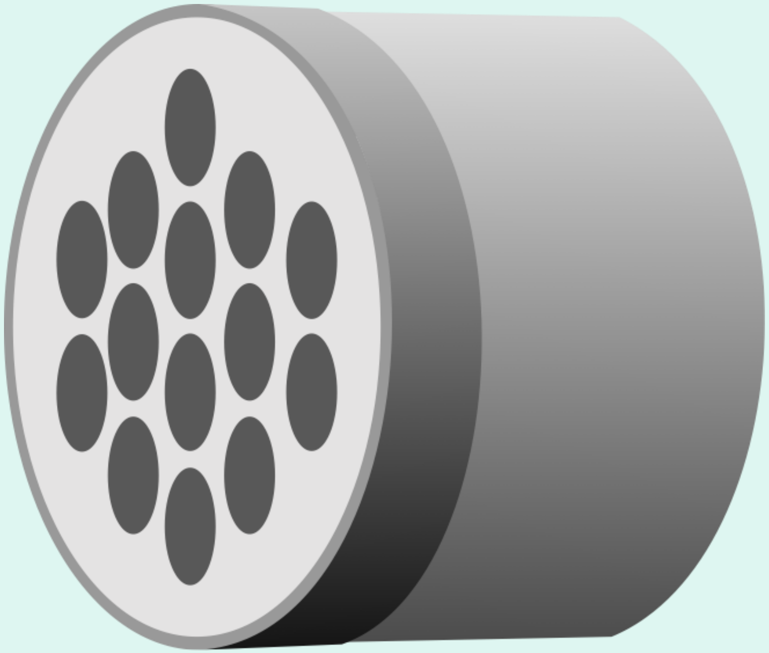
Real Time Liver Uptake and Biodistribution of Magnetic Nanoparticles assessed by AC Biosusceptometry





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

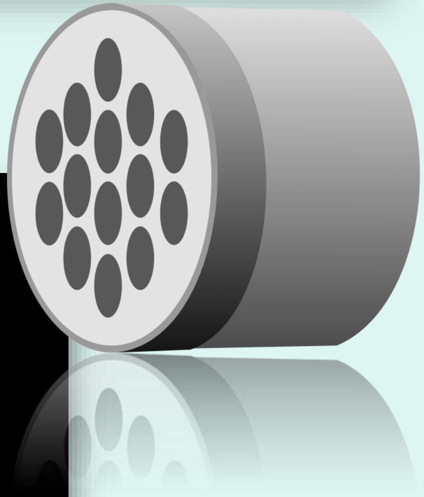
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

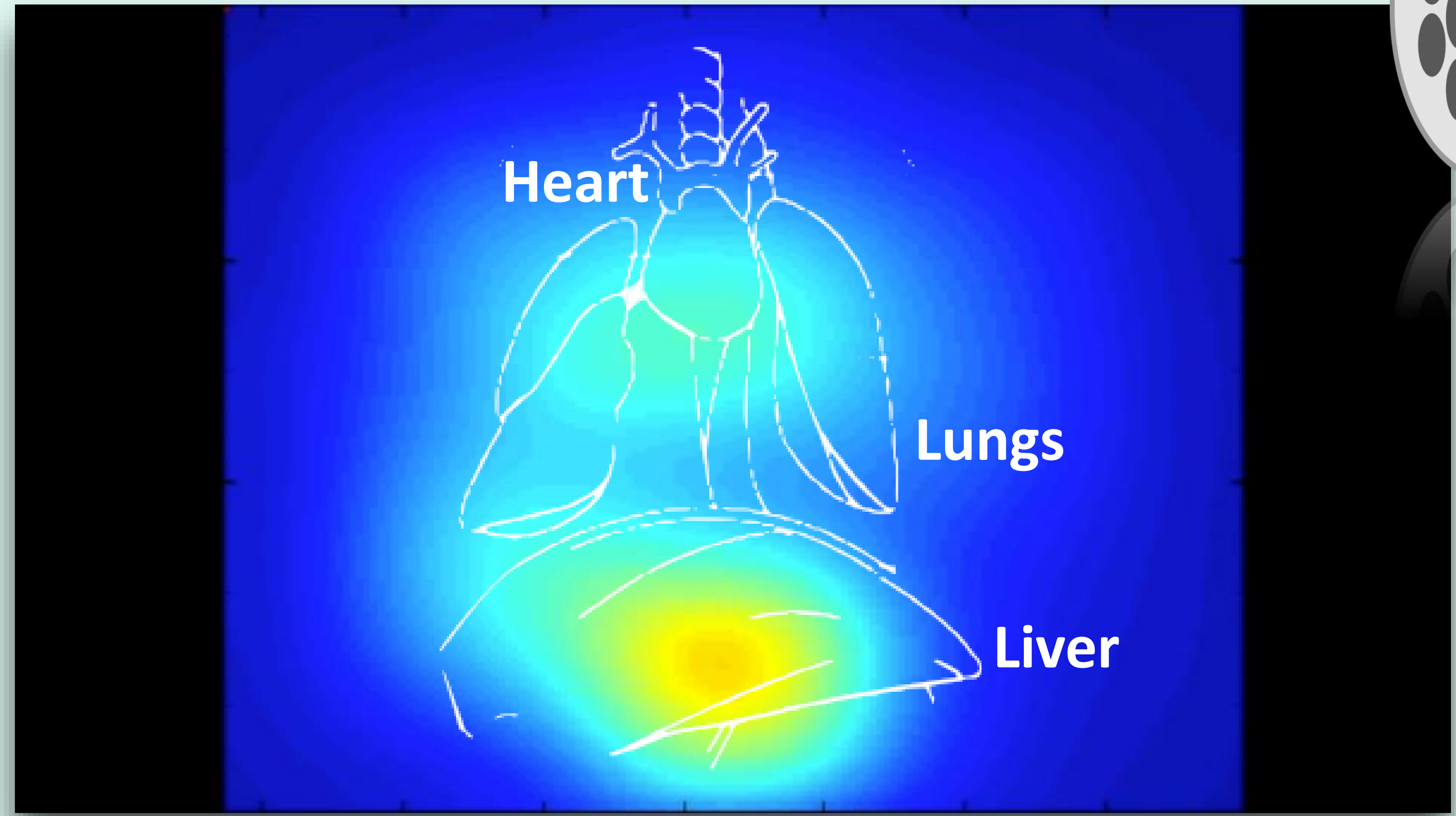


Multi-channel ACB system

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

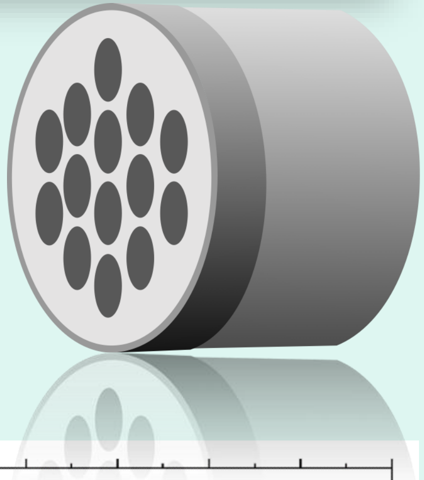
Multi-channel
ACB system

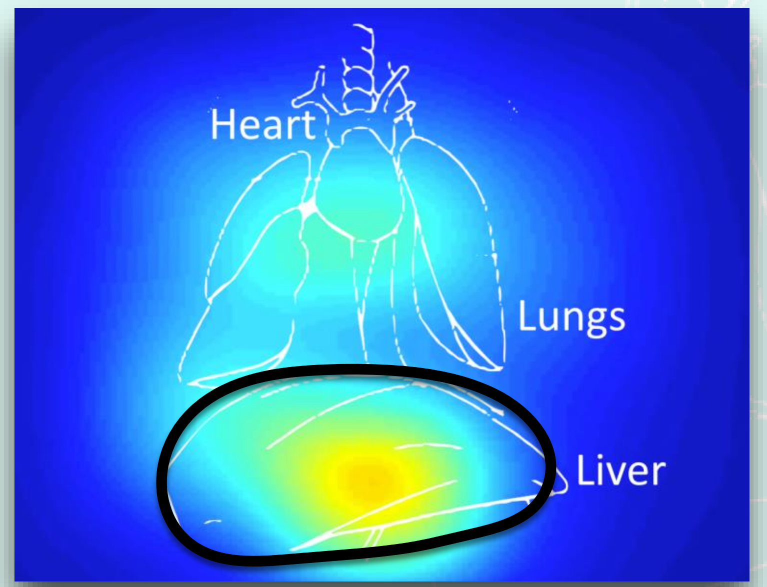


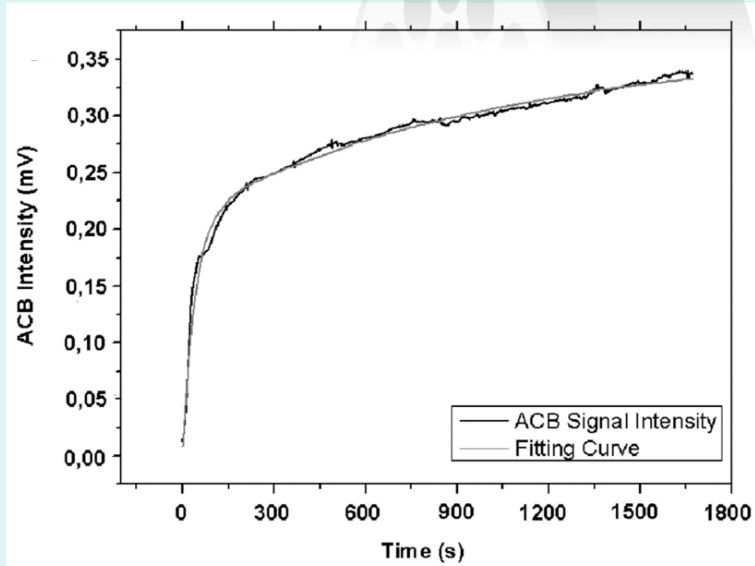


Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

Multi-channel ACB system





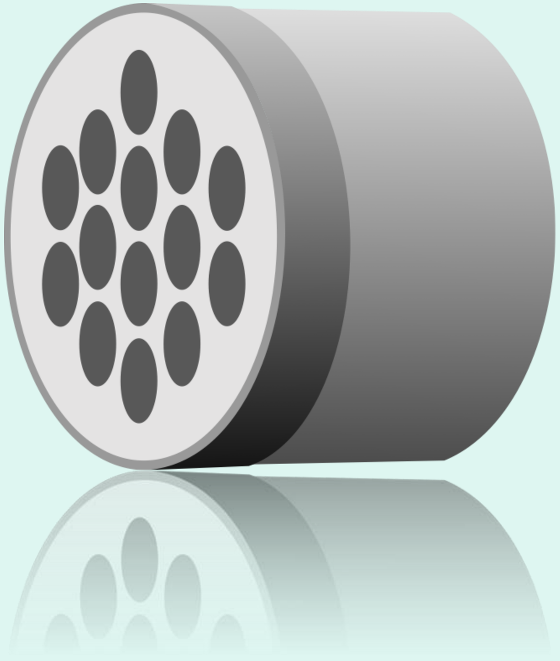


Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

Multi-channel ACB system

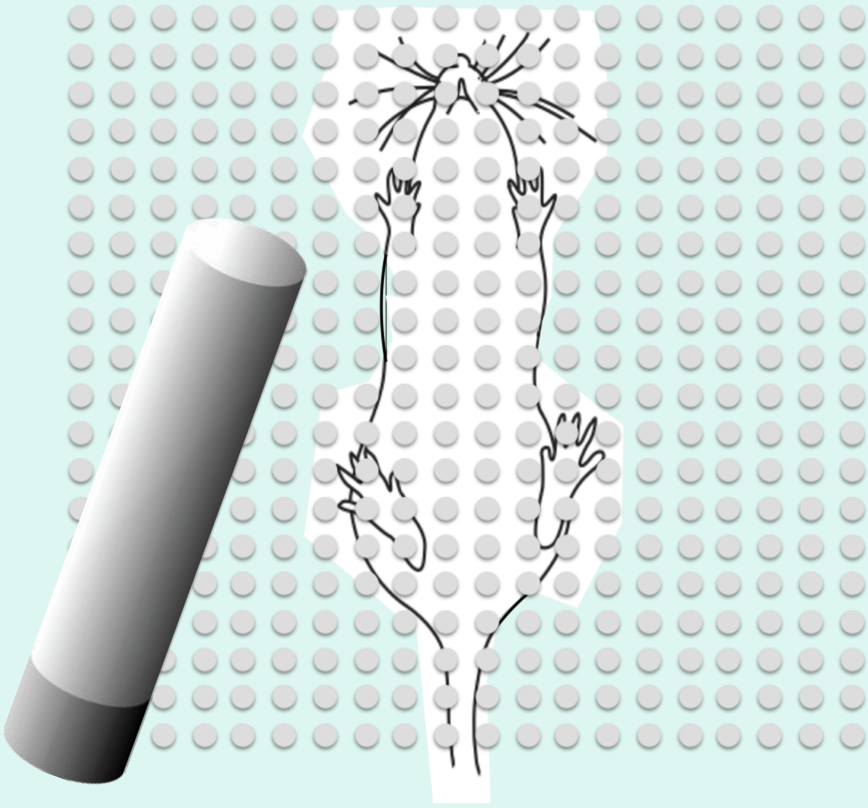
- **Great Temporal Resolution**
- **Accumulation profile on organs of interest**
- **Poor Spatial Resolution**

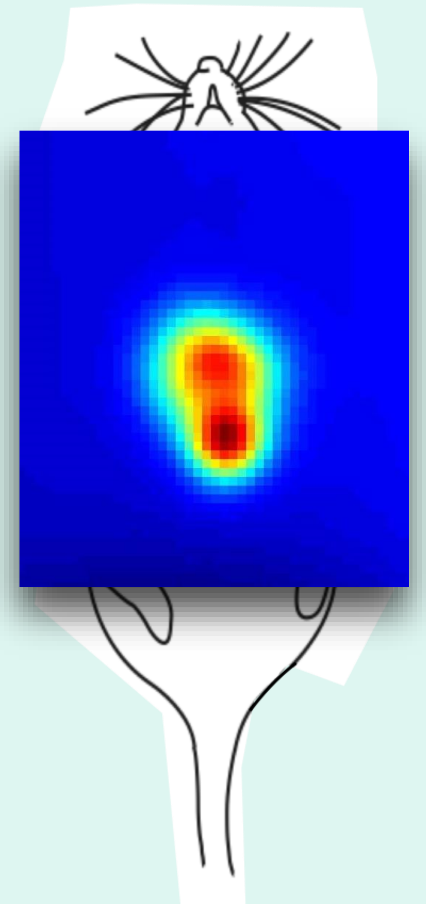
Liver



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

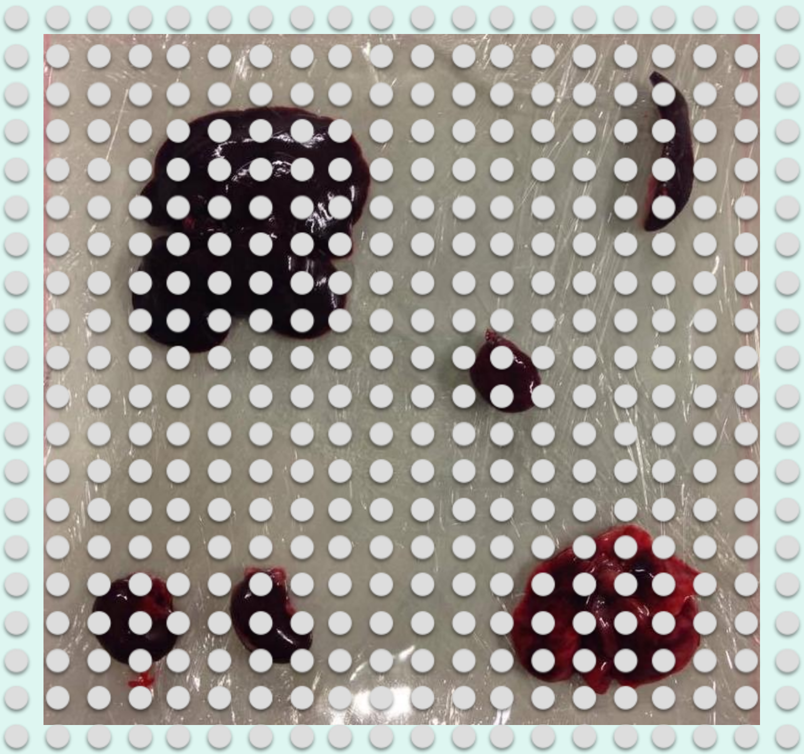
ACB scanning system

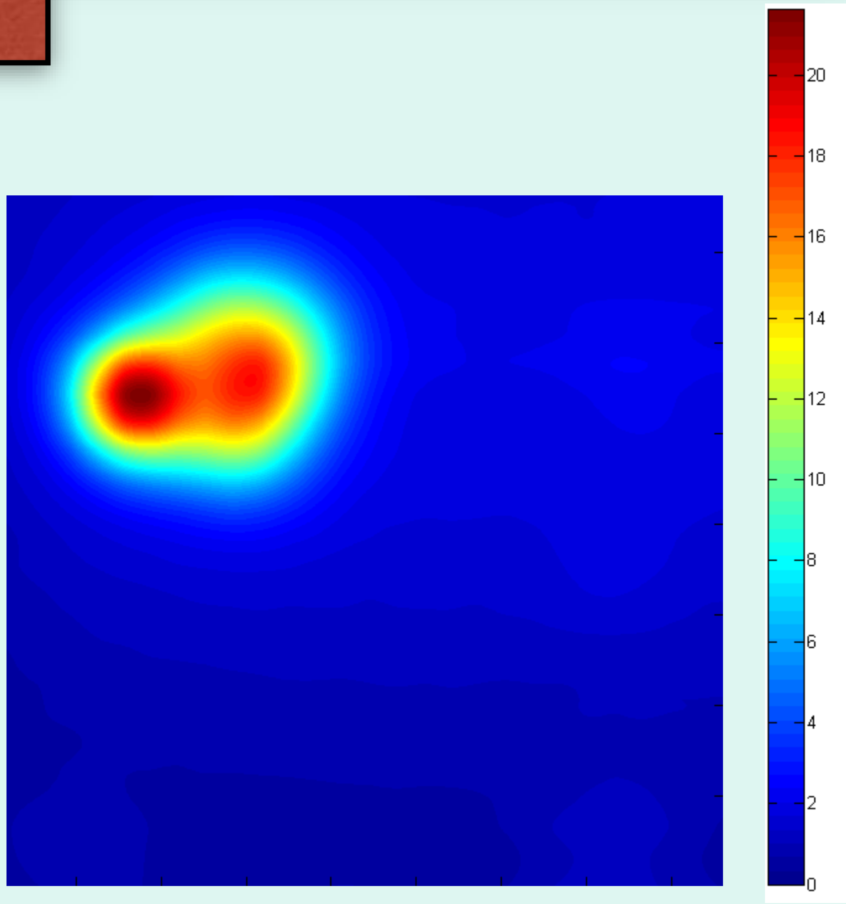




Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

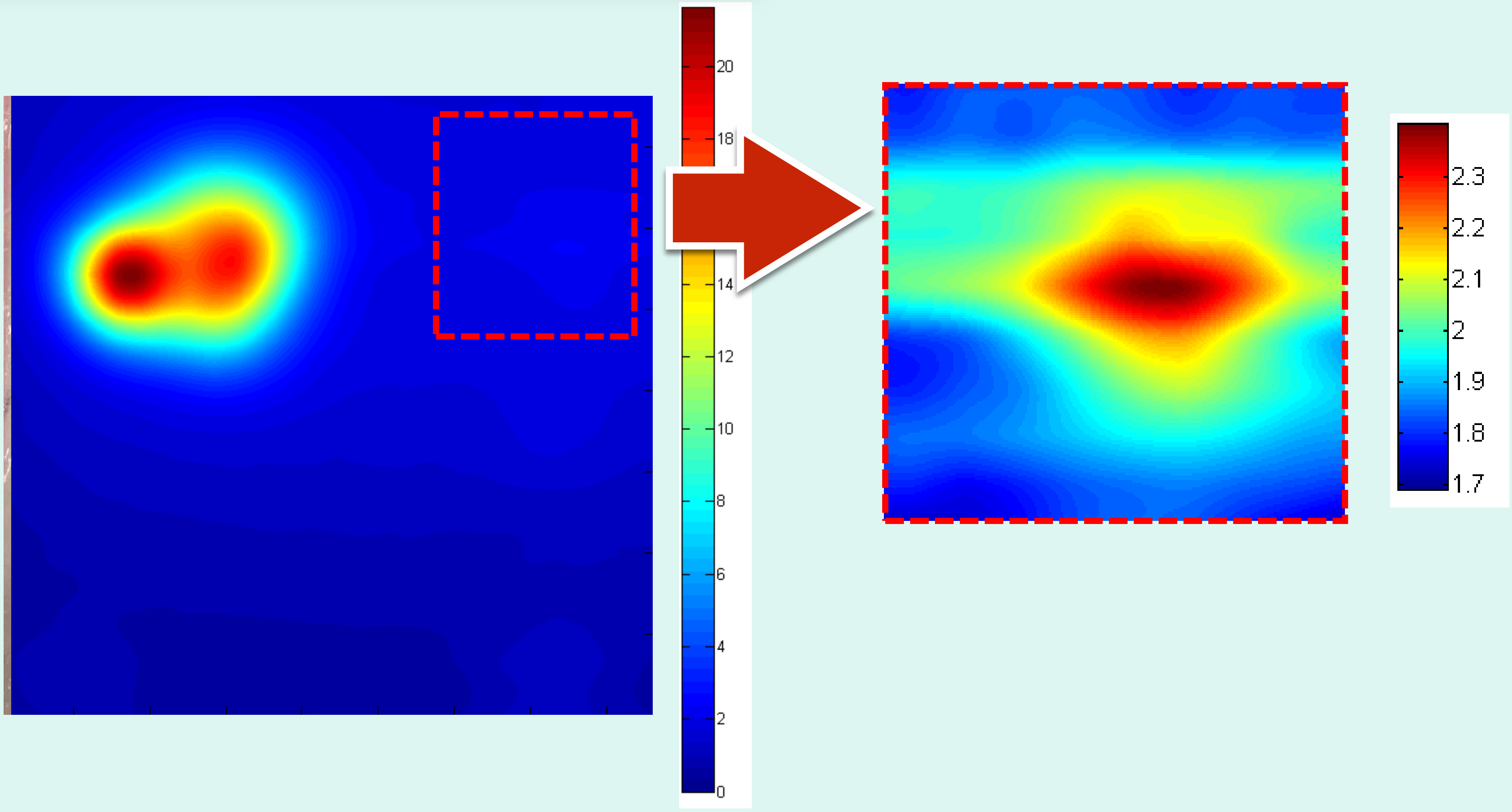
ACB scanning system





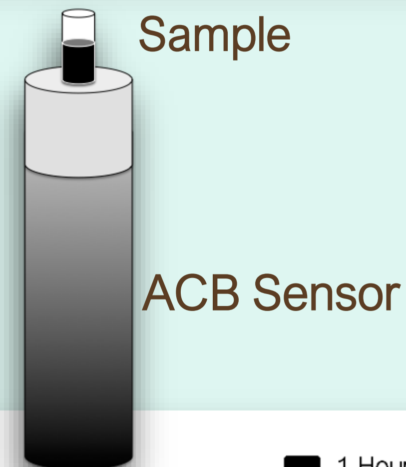
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

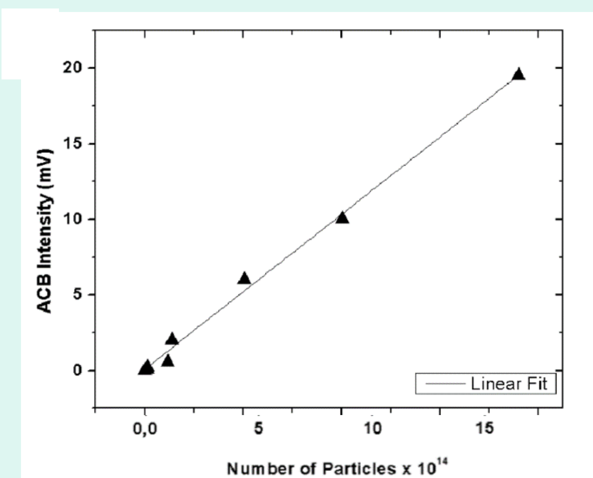
ACB scanning system



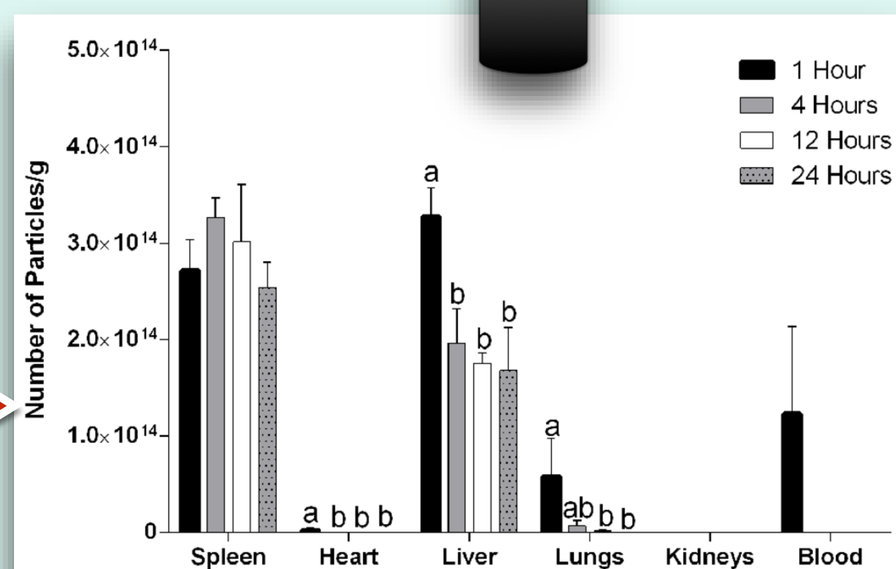
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

Nanoparticles quantification by ACB



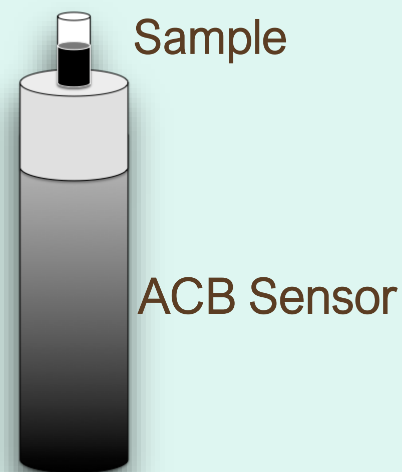


Calibration Curve



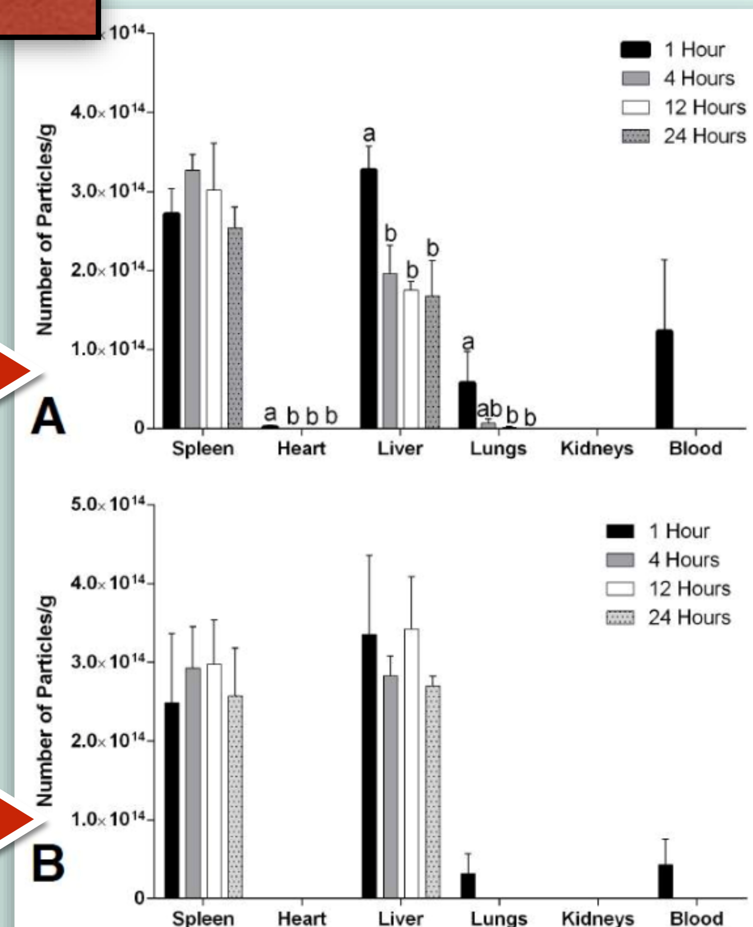
Development of a biomedical technique to detect, monitor and quantify magnetic nanoparticles in animal models

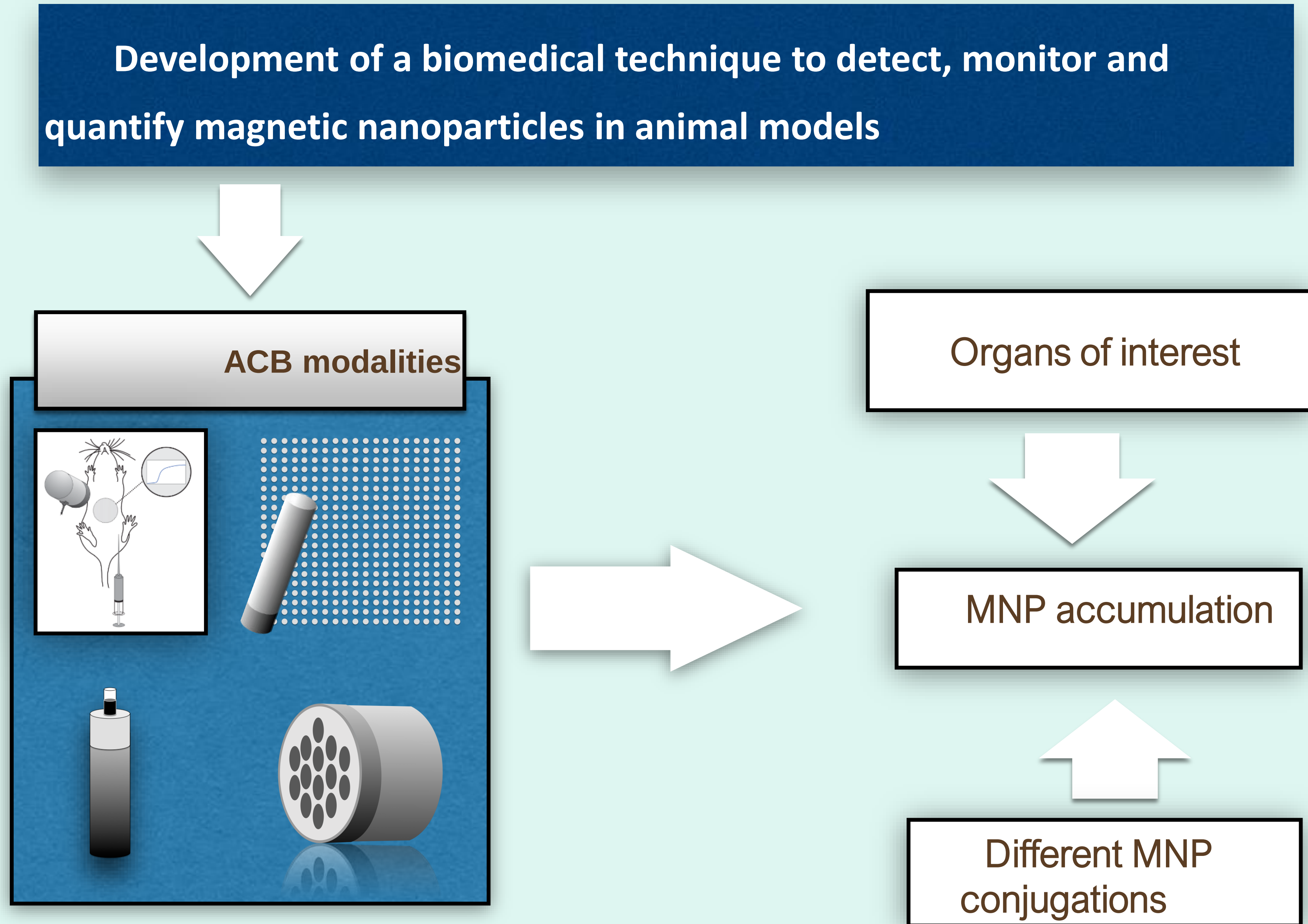
Nanoparticles quantification by ACB



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

Seoul BIOMAG2016

The 20th International Conference on Biomagnetism

October 1(Sat.) - 6(Thu.), 2016

Coex, Seoul, KOREA

Biomag

Lab. Biomagnetismo - Unesp

UNIVERSIDADE DE SÃO PAULO

SCIENTIA VINCES

Thank you!

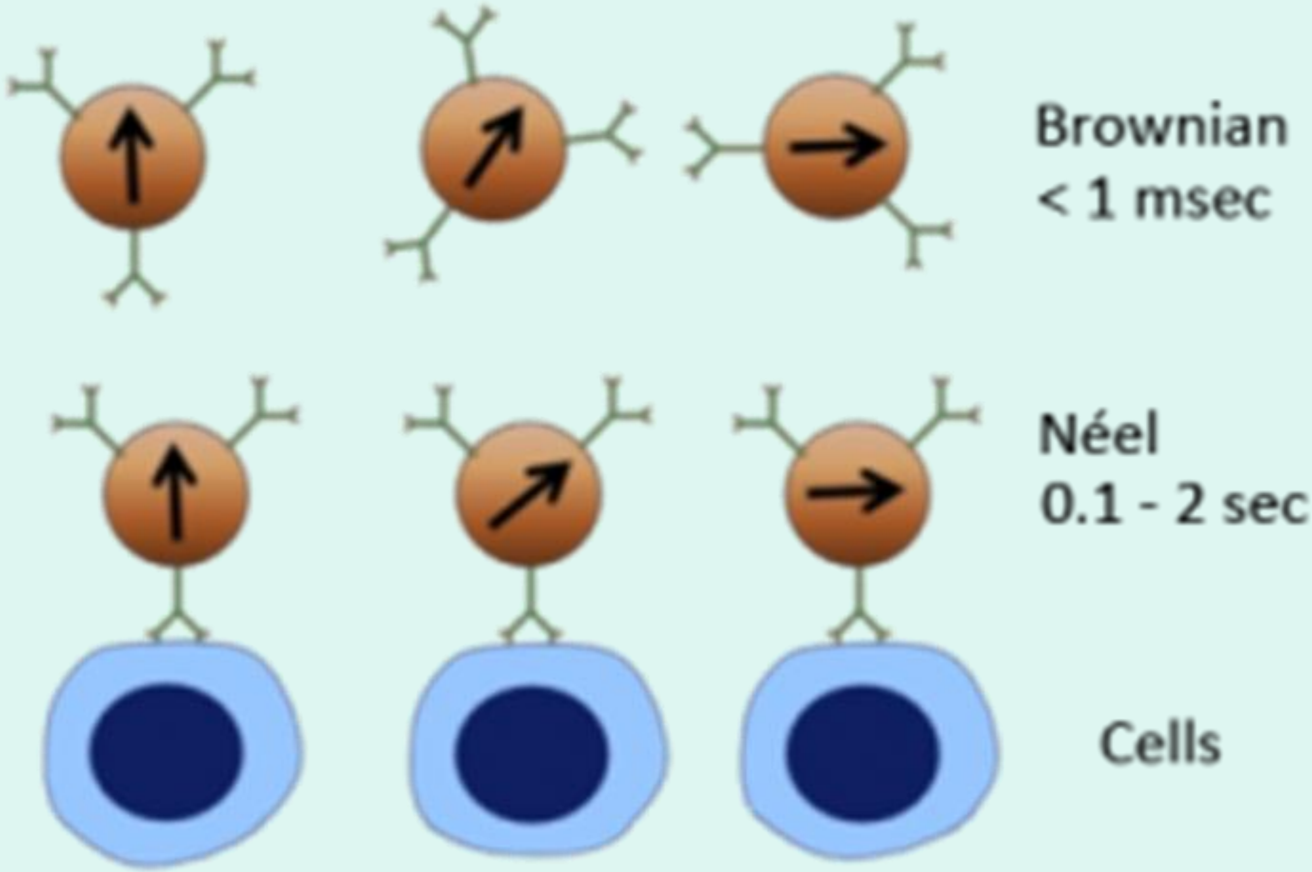
Gomawo!

Obrigado!

RELAXOMETRY STUDIES OF NANOPARTICLES IN BIOLOGICAL SYSTEMS

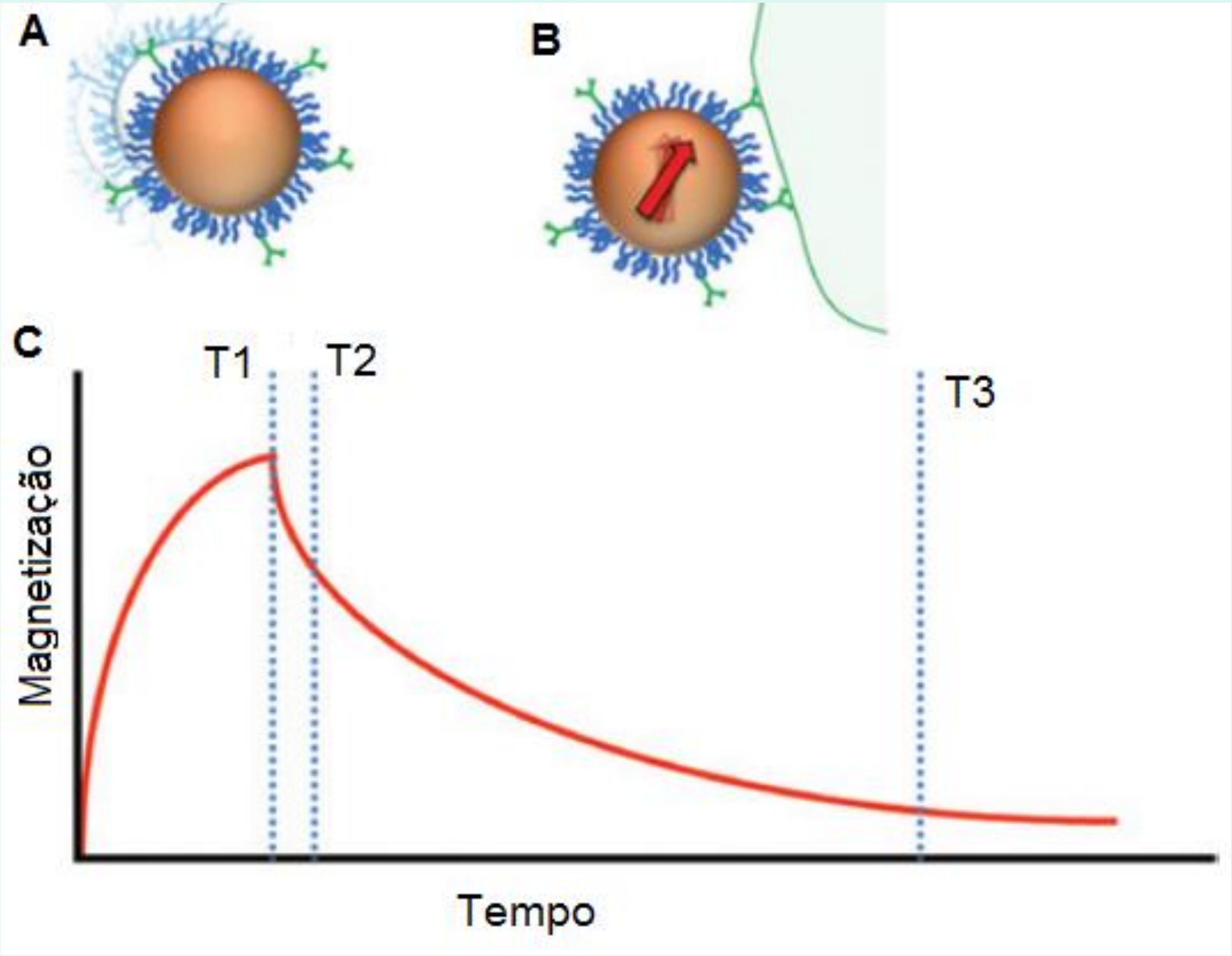
- Magnetic particles in a biological media can relax by two mechanisms, Brownian Motion and Néel, that depending on the particle size can have distinct values. For 25nm diameter particles the values are shown below. The basic idea is that the functionalized magnetic nanoparticles attached to cancer cells 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.

Relaxation Processes MNPs



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

Magnetization (A) & Relax MNP (B)

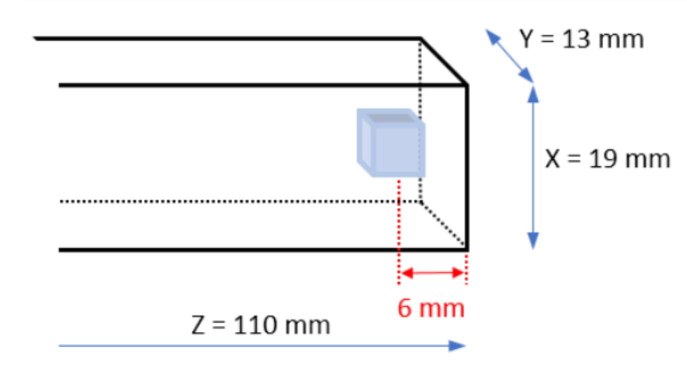


MNP Total Relaxation Time

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

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

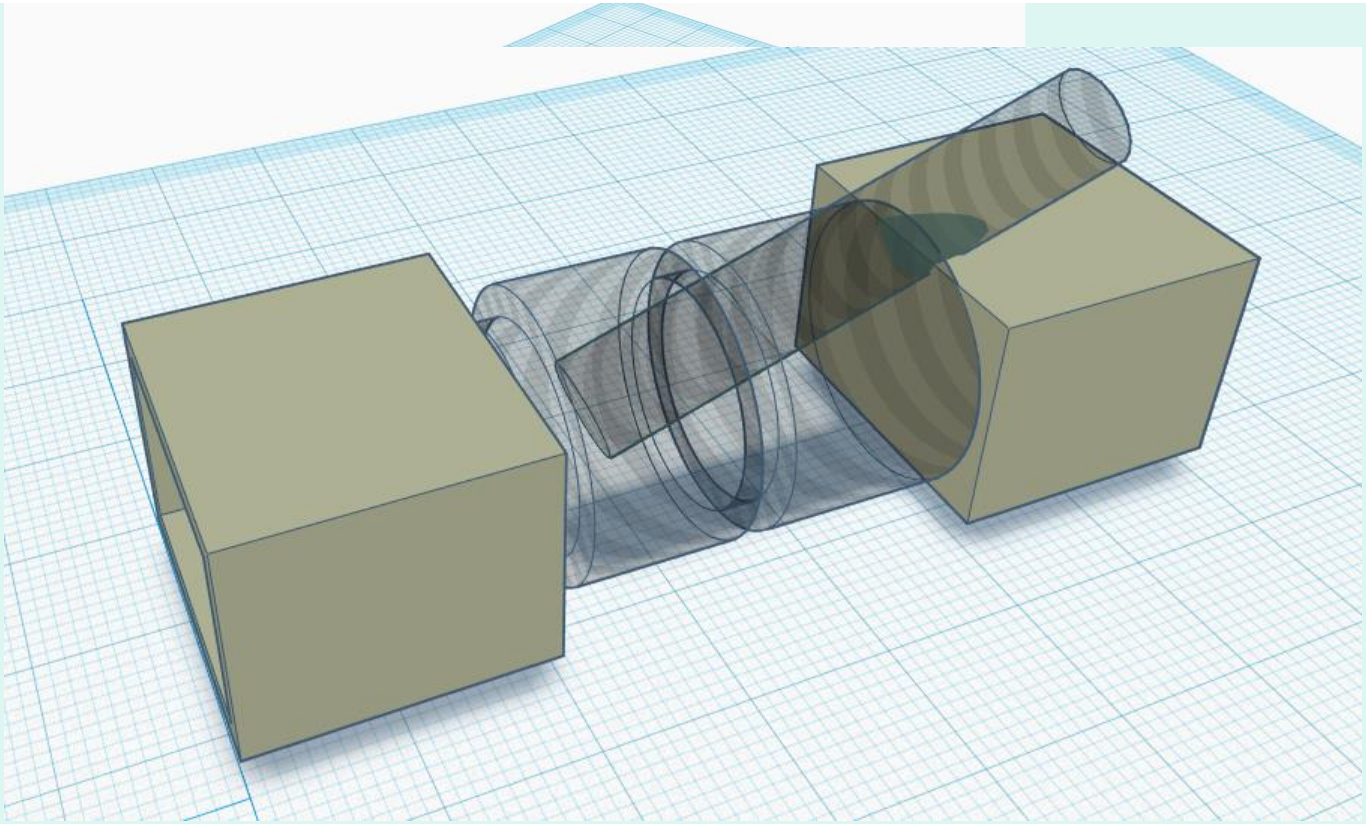
- Internal diameter 152mm
- Inside Depth 381mm
- Outside diameter 210mm
- Overall length 438mm

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

Zero Gauss Chamber

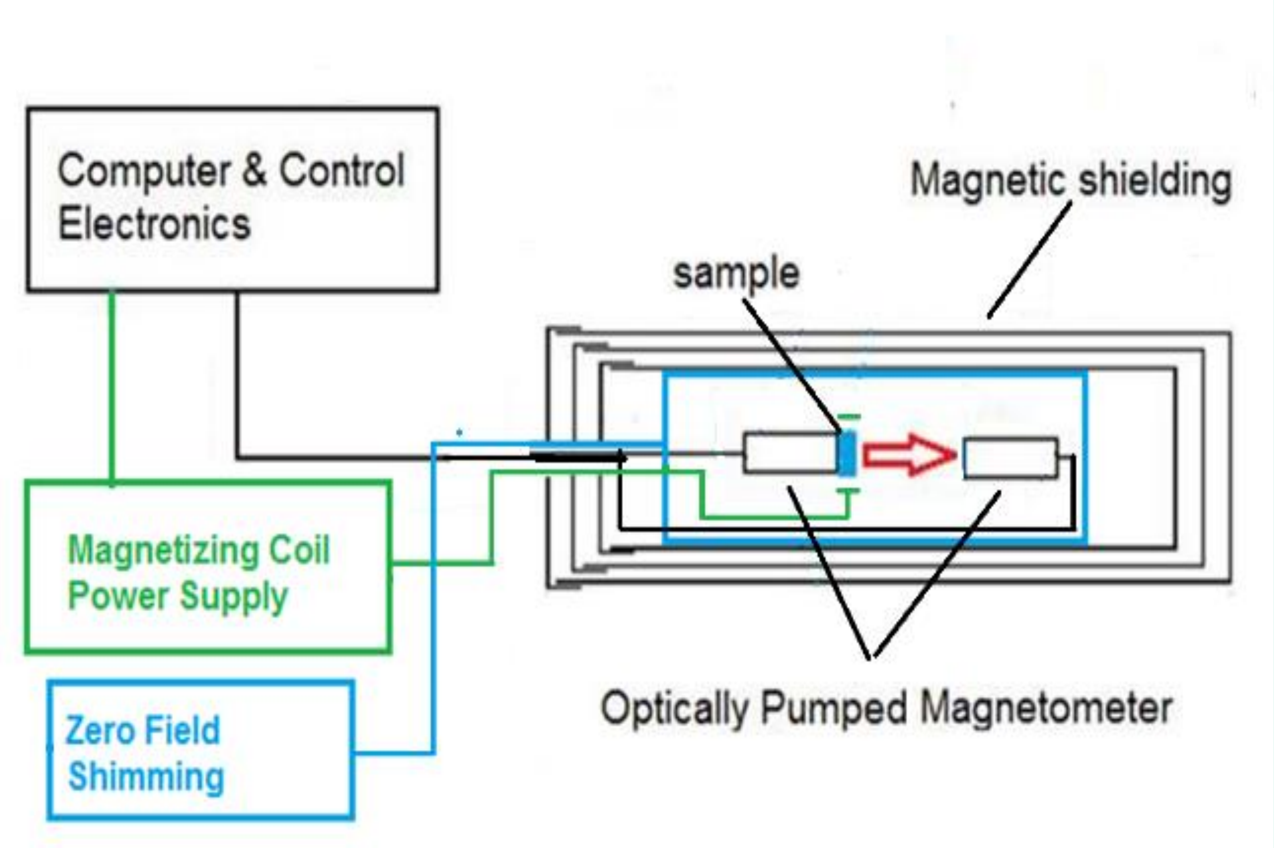
MAGNETIC SHIELD CORPORATION

Sample set up



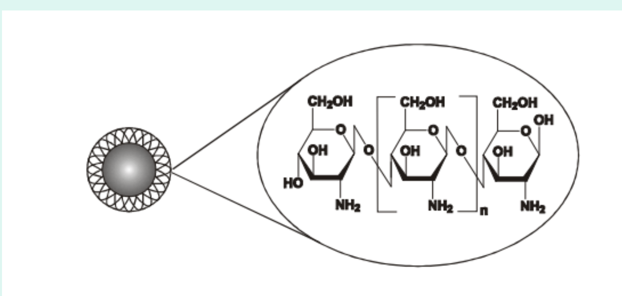
General view of the set up

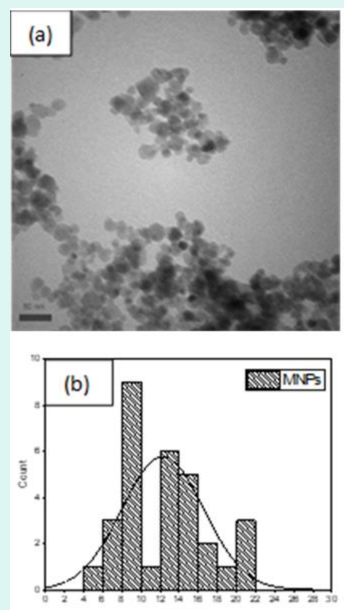
Schematics for MRX Acquisition

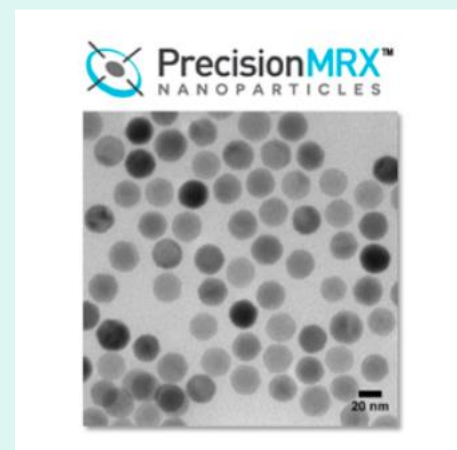


Magnetic Nanoparticles

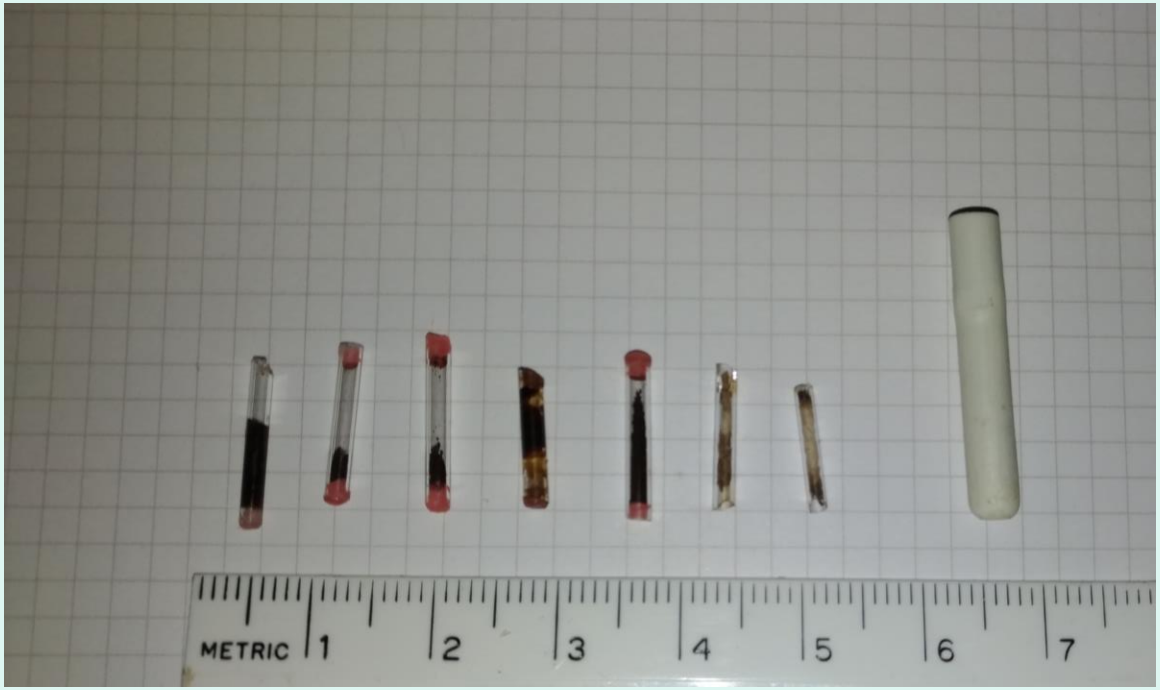
- 1-Chemicell fluidMAG-Chitosan $\Phi = 2\mu m$
- 2-Home made magnetic Fe_3O_4 nanoparticle, synthesized by the co-precipitation method at 90ºC
- 3- PrecisionMRX® Superparamagnetic Nanoparticles $\Phi = 25nm$





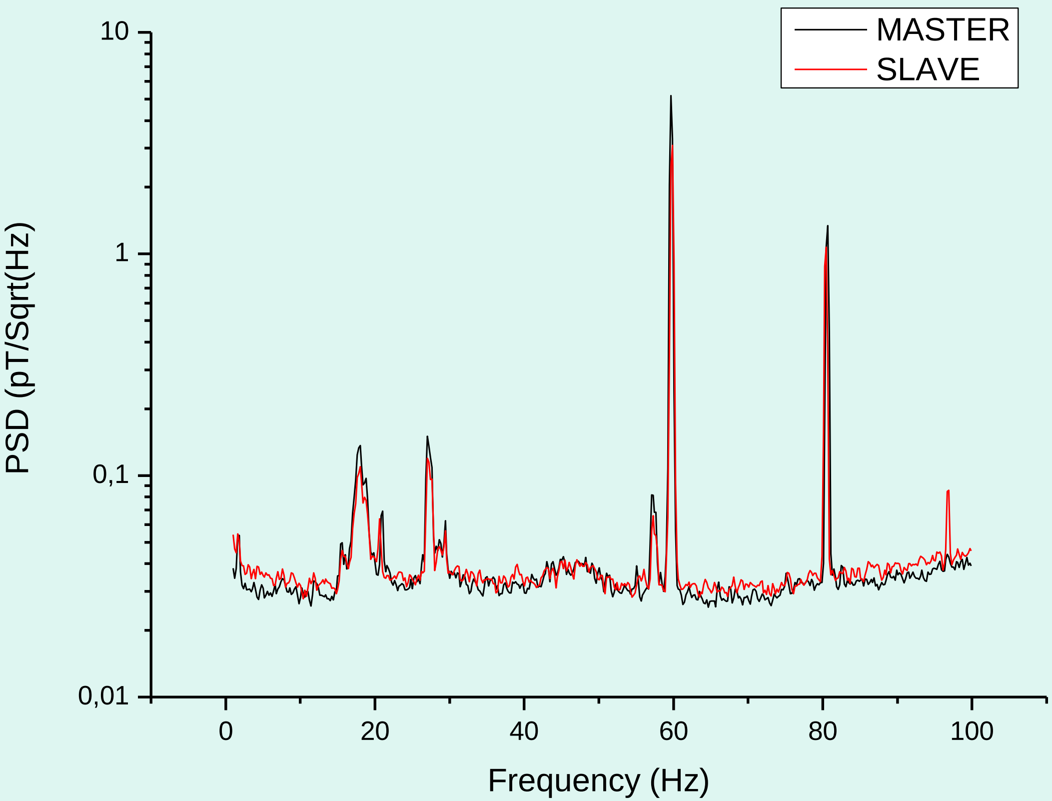


Samples

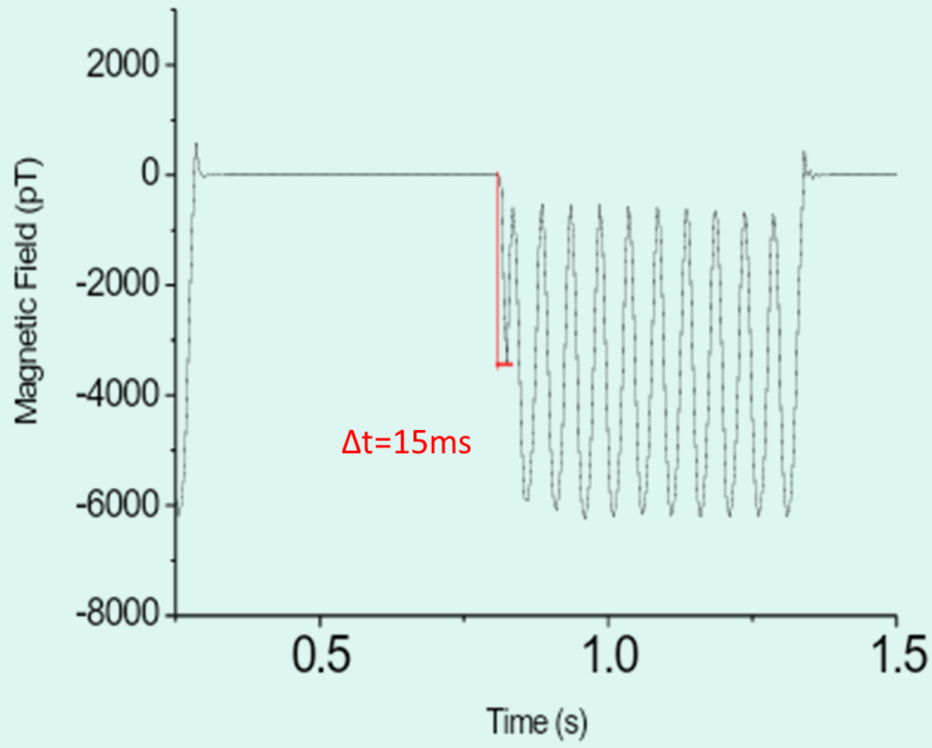


Hematocrit glass capillary tube internal diameter 1mm & PVC Sample holder.

A typical noise floor of the QZFM sensors in our laboratory



Time response

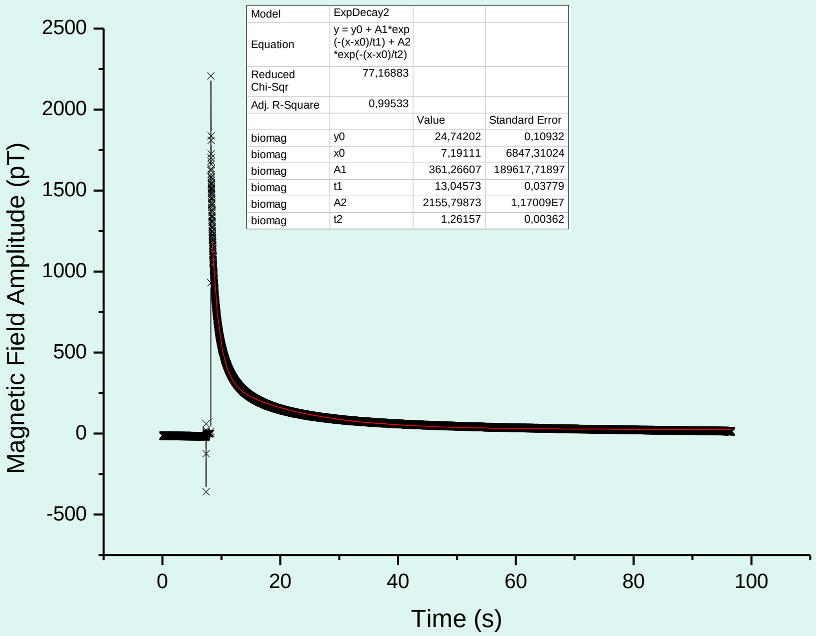


MNP in Solution

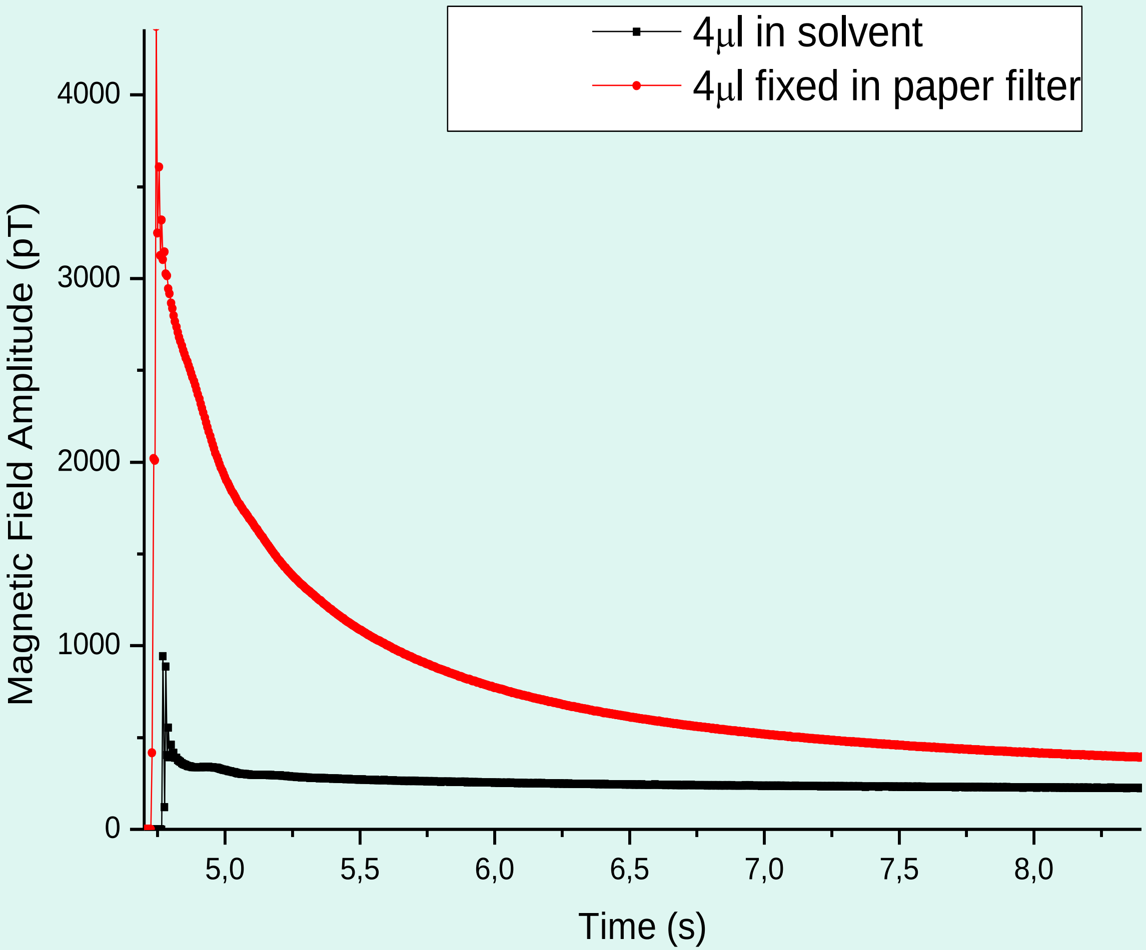
- **MNP 1 in water solution undergoing Brownian motion**

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

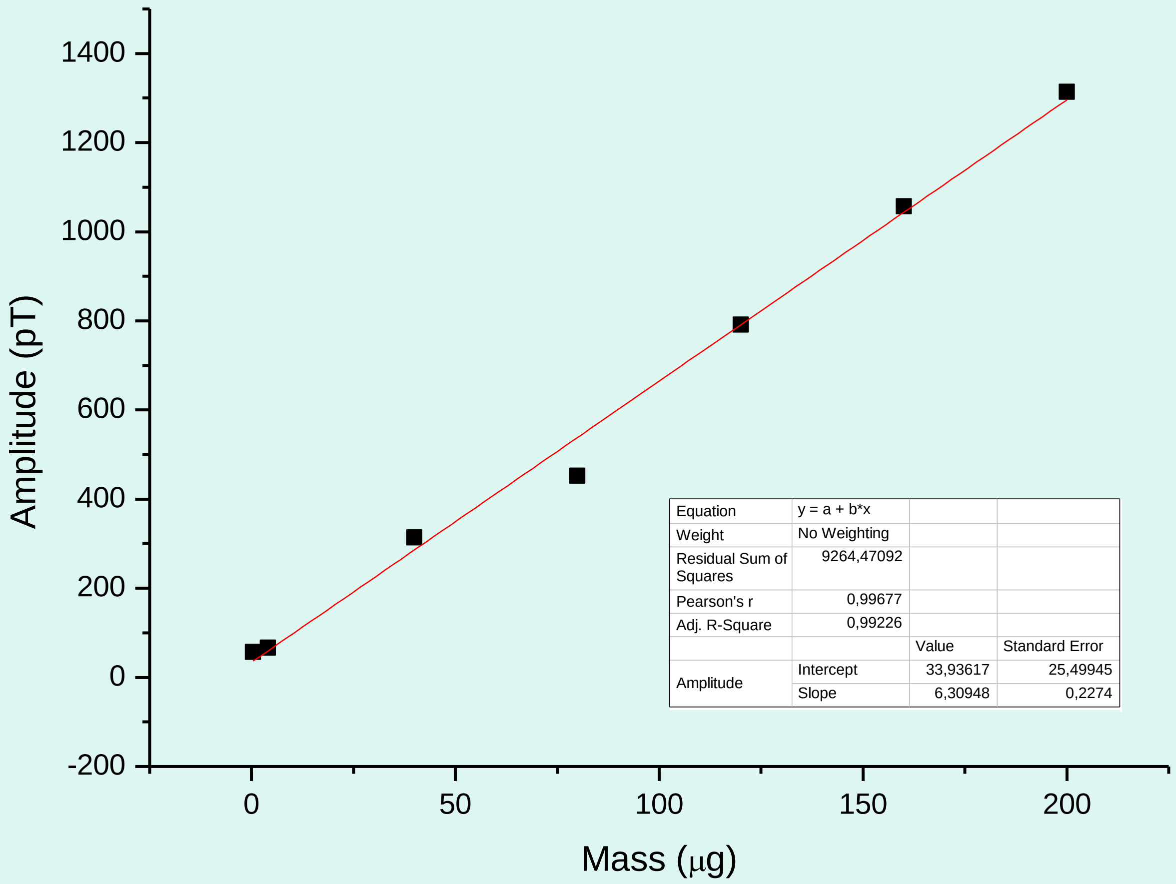
- **Using the time constant of 1.26s and assuming the viscosity is the same as water we get a radius of r = 0.77μm.**
- **DLS measurements gave a radius r = 0.812 μm.**



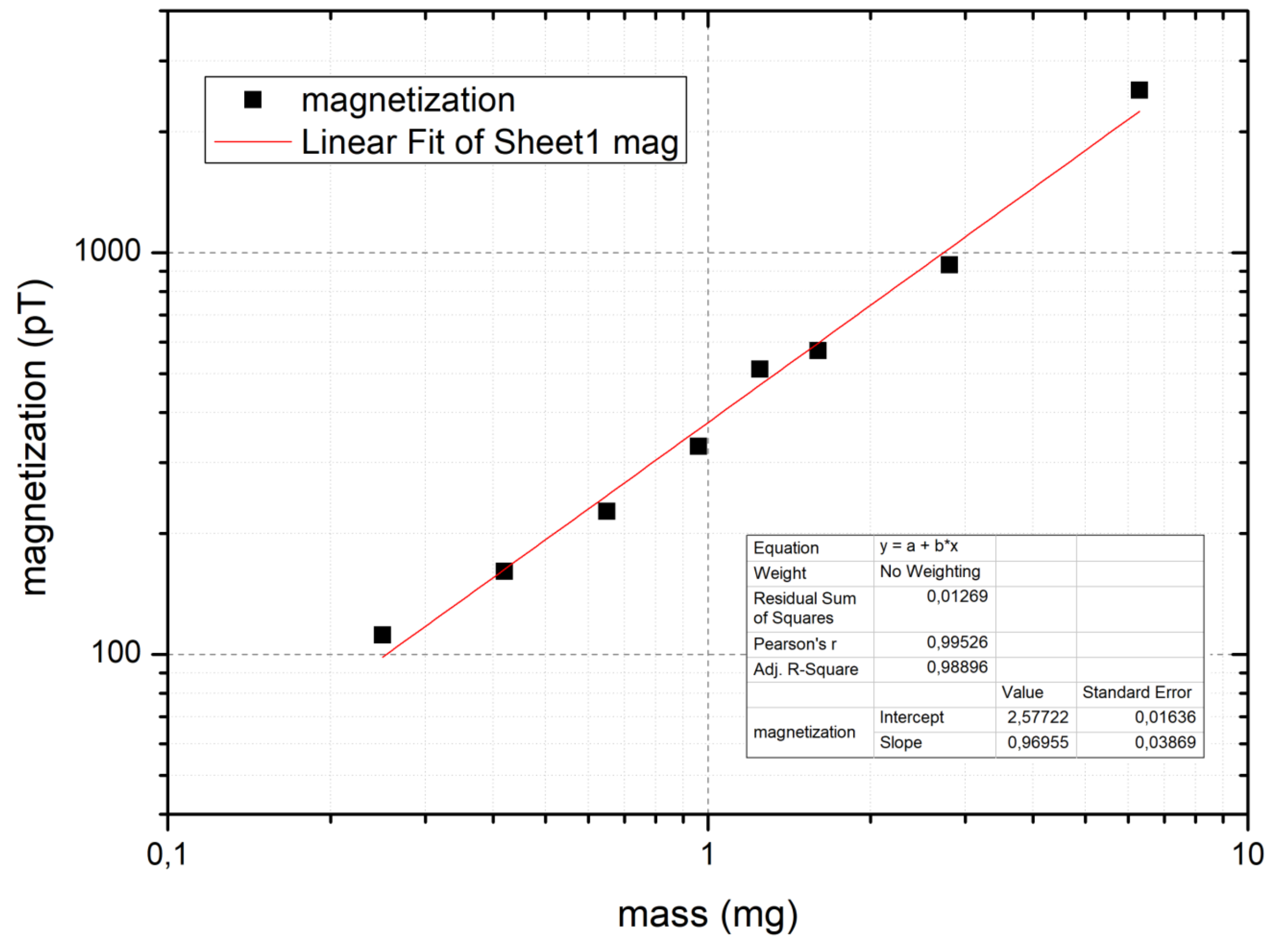
Comparison of signals of MNPs in a liquid and fixed in paper filter

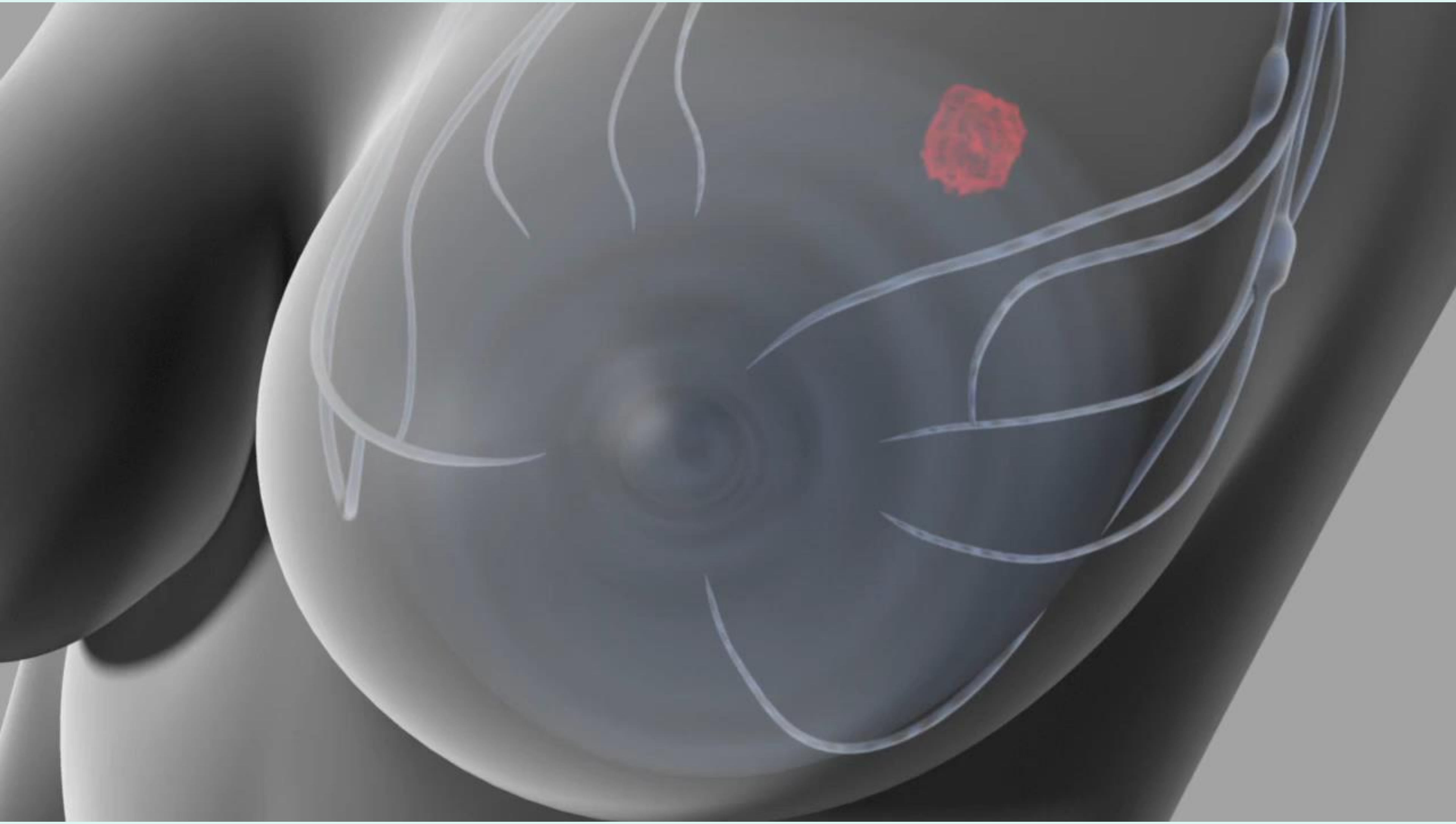


Calibration for MRx MNPs 25nm



Calibration for Home made MNPs

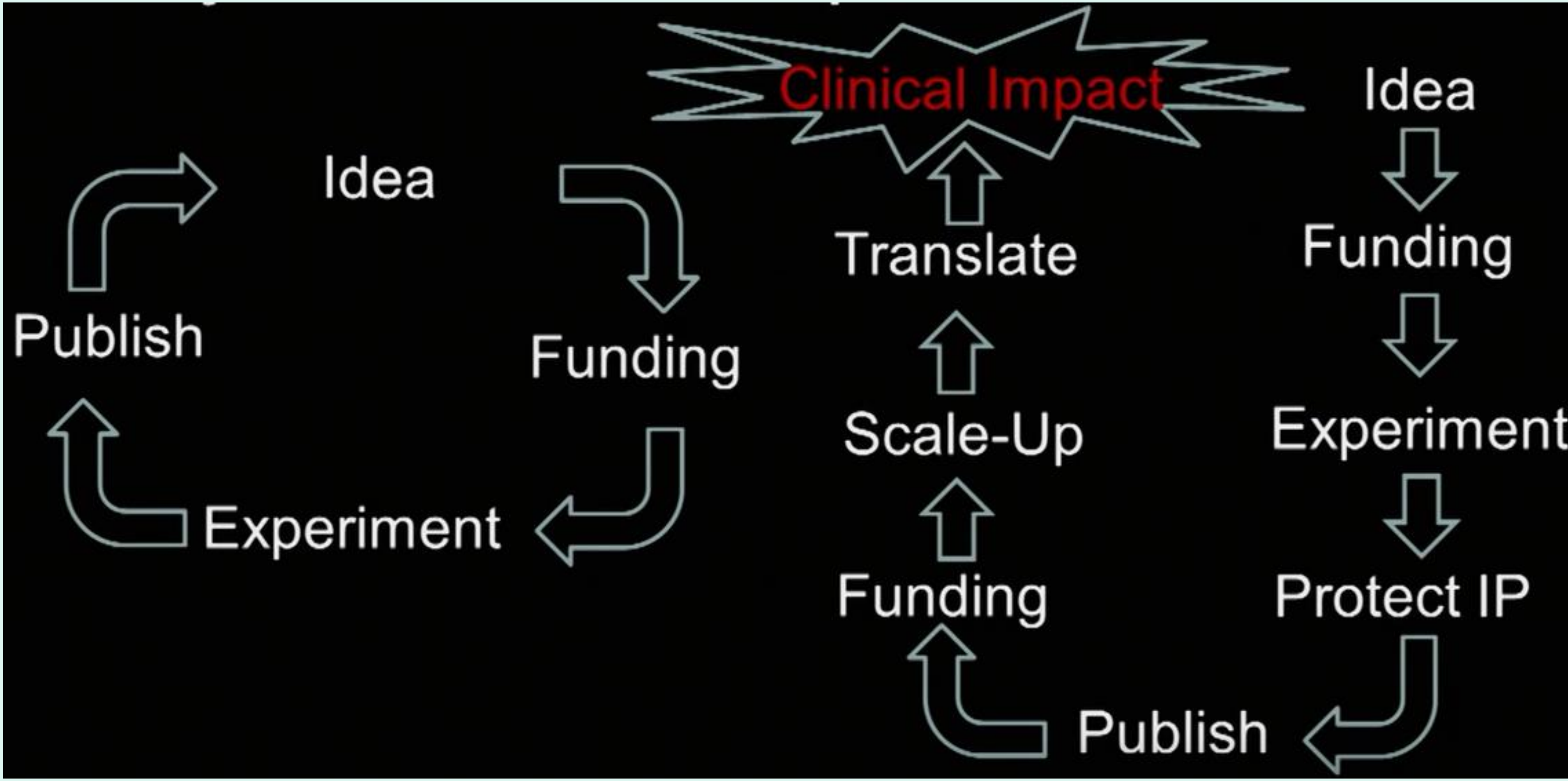




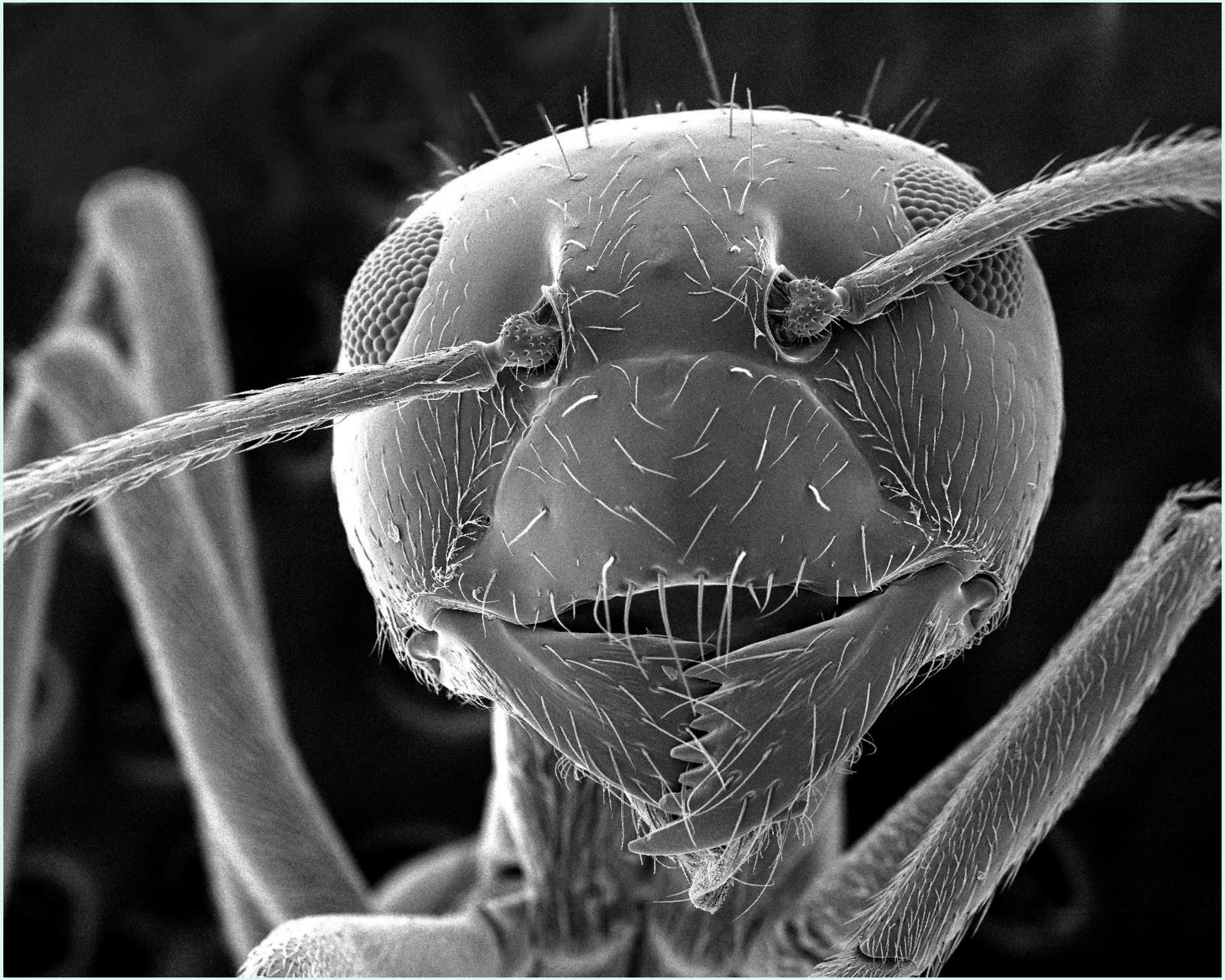
- https://www.youtube.com/watch?v=a6xRx329lxw

- http://www.endomag.com/content/sentimag-procedure

Translational Research



Bye, for now !



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