Nanomagnetism
Part 2: Magnetic Nanoparticle Applications

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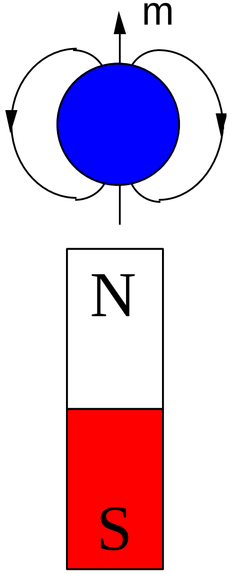
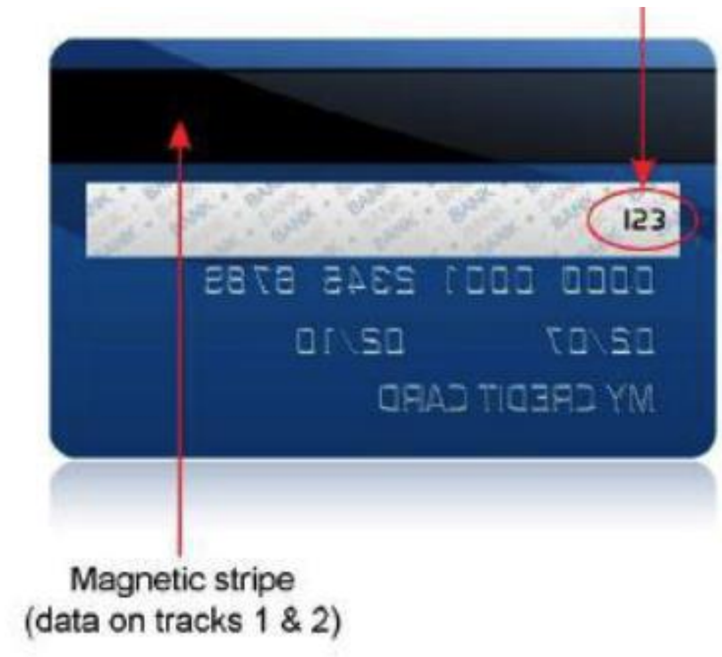
Applications of Magnetic Nanoparticles

1. Intro and key nanoparticle properties
2. Magnetic manipulation
3. Magnetic sensing
4. Magnetic hyperthermia
5. Magnetic Particle Imaging (MPI)
6. Magnetic Resonance Imaging (MRI)



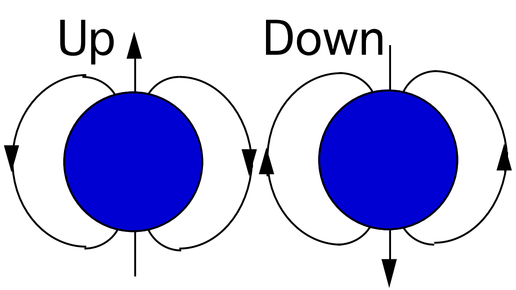
Where Do You Have Magnetic Nanoparticles?

Magnetic Hard Disk Media



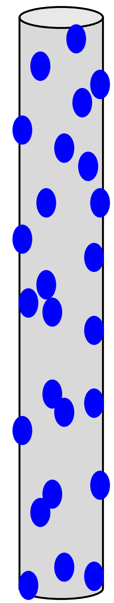
Credit Card Magnetic Stripe

$$D = \frac{KV}{k_B T}$$

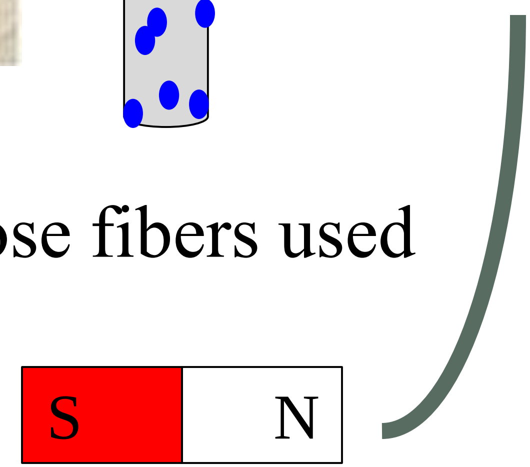


Monodomain, not superparamagnetic

Where Do You Have Magnetic Nanoparticles?



Iron oxide nanoparticles grown in cellulose fibers used in $ as anti-counterfeiting measure



Use a NdFeB magnet to exert a force

Have You Ever *Eaten* Magnetic Particles?

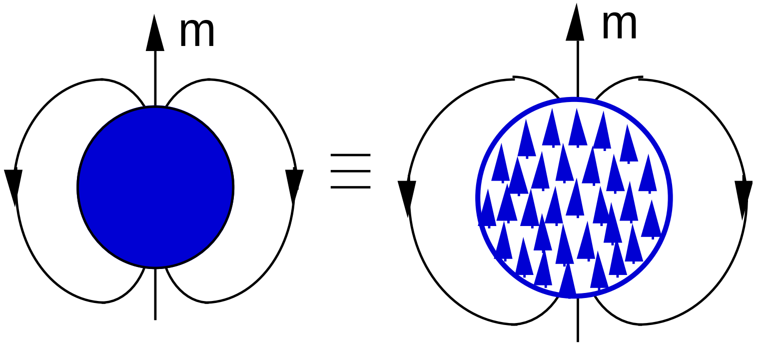
Iron-fortified cereals have < 45 μm food-grade Fe particles

- dissolve in stomach acids so the Fe can be absorbed

- $Fe(PO)_4$ and $FeSO_4$ also used for fortification

Magnetic Particle Review

Monodomain: no domain walls, so acts like giant spin



Ferr**o**magnet　　　Ferr**i**magnet

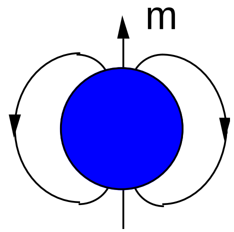
Fe　　　γ-**Fe**$_2$O$_3$, **Fe**$_3$O$_4$

Superparamagnet: monodomain particle where there are rapid fluctuations in the magnetization *direction*

Important Magnetic Features

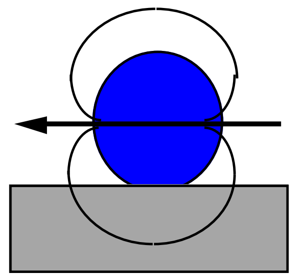
Magnetic moment

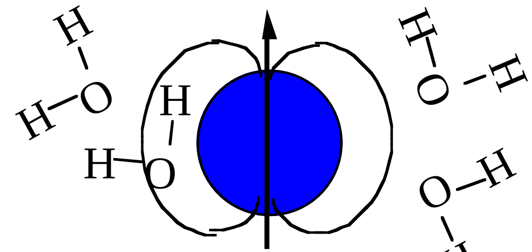
$\mu = M_s V$



Generate a Magnetic Field H ~ μ

Magneto-resistive Sensor

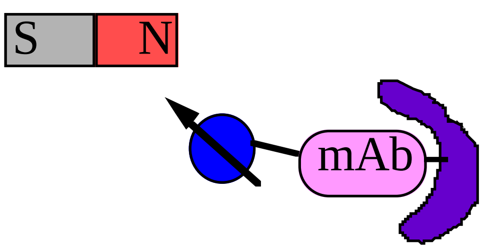




MRI contrast agent

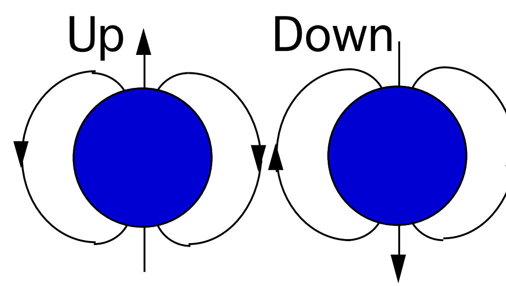
Move in response to a magnet

Force $F = \mu \bullet \nabla H$



Specific Cell Type

$$D = \frac{KV}{k_B T}$$



Thermal stability enables information storage

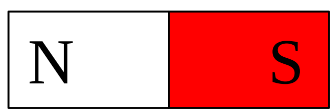
Important Magnetic Features for Specific Applications

Application	Generates Field	Moves in Field	Magnetically Metastable
Magnetic Manipulation	N	Y	N
Magnetic Sensing	Y (for detection)	N	Y(over measurement time)
Magnetic Hyperthermia	N	N	N (for DC), but Y (for AC field used)
Magnetic Particle Imaging	Y (for detection)	N	N
Magnetic Resonance Imaging	Y	N	N
Ferrofluids	Y (to form chains)	Y	N
Magnetic Recording Media	Y (for reading)	N	Y (for a long time)

Biomedical Applications of Magnetism

• Magnetic fields disturb normal biological function much less than electric fields.

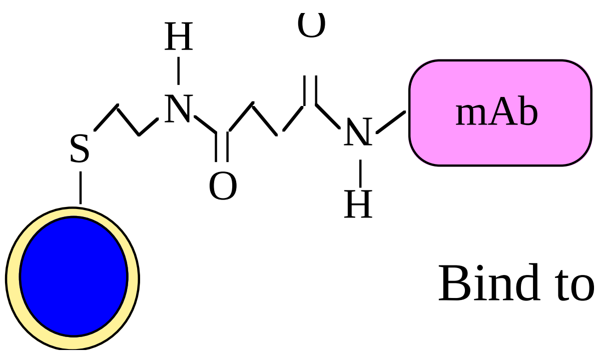
• Use the power of nanomagnetism as a tool, with some constraints, in complex biological systems



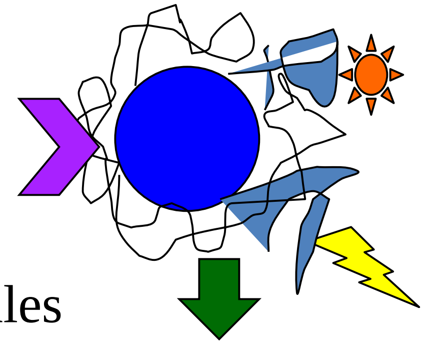
Requirements *Beyond* Magnetism

Toxic? Mutagenic? Carcinogenic?

- Stricter requirements for **in vivo** than for **in vitro**
- **LD50** (Median lethal dose, per kg of body mass) – *In vitro* cell exposure test – determine exposure for half of cells to die
- Co, Ni demonstrated carcinogens
- Biocompatible (no immunoresponse) vs. biodegradeable (body excretes)
- **Only superparamagnetic iron oxide** (Endorem[R], Feridex[R], Resovist[R]) has in vivo approval



Bind to targeting molecules



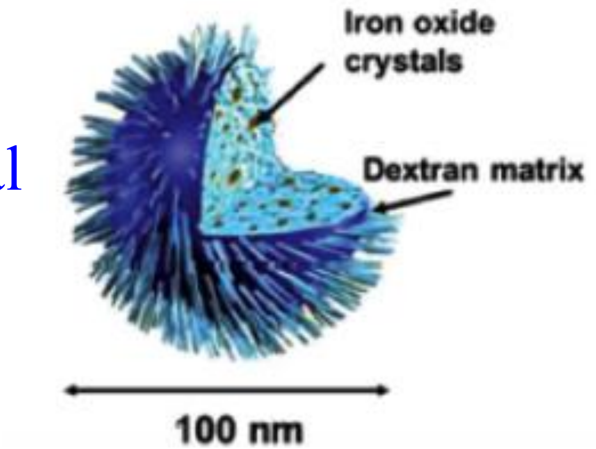
Importance of Particle Coatings

Coatings are used to **enhance dispersion stability**, to **functionalize for selective binding**, and (for in vivo use) to **prevent rapid removal**

- The Reticulo-endothelial system (RES) recognizes "intruders", coats with proteins, so they are recognized and removed by macrophages (opsonization)

• Coating magnetic nanoparticles with "friendly" molecules essential

(Cindi Dennis, NIST)

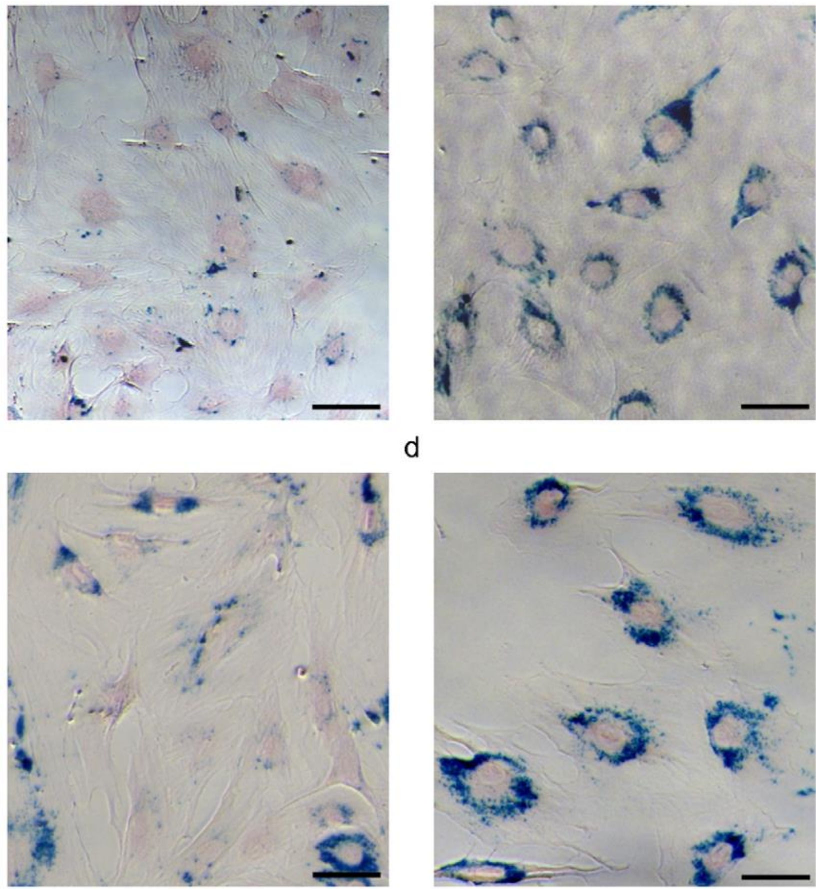


C. C. Berry and A. S. G. Curtis, J. Phys. D: Appl. Phys. **36** R198-R206 (2003).
V. P. Torchilin, Amer. Assoc. Pharmaceut. Sci. Journal **9** E128-E147 (2007).

Coating and Stem Cell Uptake Efficiency

Endorem[R] (dextran-coated)

Poly(lysine)-coated Endorem[R]



Uncoated γ-Fe_2O_3

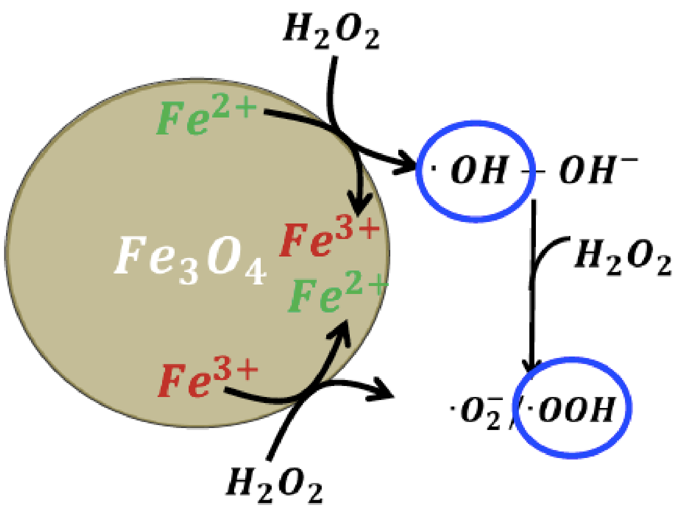
D-mannose-coated γ-Fe_2O_3

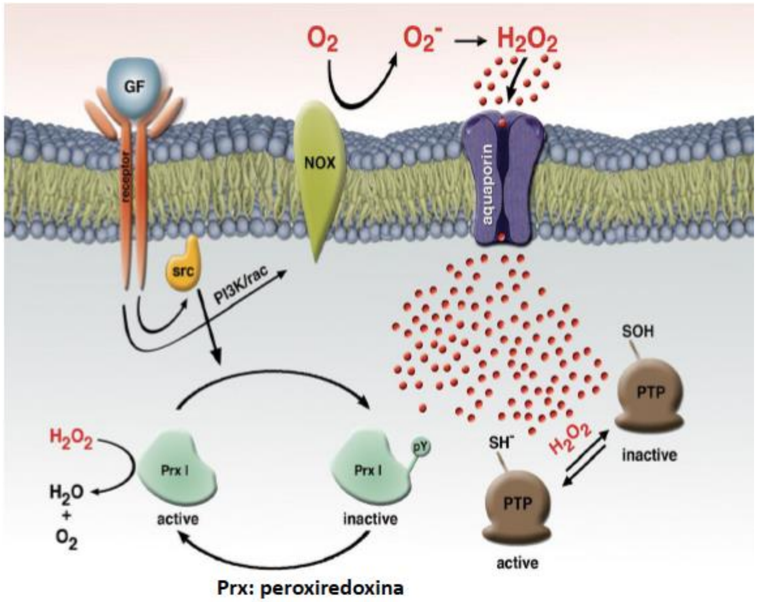
Prussian Blue stain for Fe, Optical microscopy

D. Horak, et al. J. Magn. Magn. Mater. **321** 1539-1547 (2009).

Fe^{2+}, Fe^{3+} Catalysis at NP Surfaces

Cells regulate the balance between creation and destruction of free radicals, but NPs can shift the balance

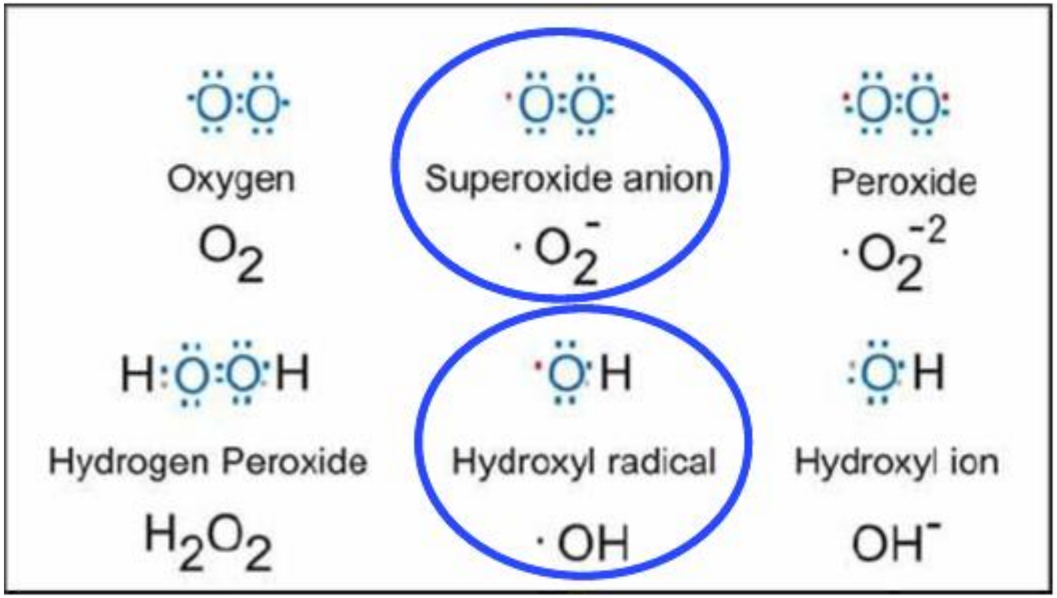




Roberto Zysler, INN Bariloche

Reactive Oxygen Species (ROS)

60% of DNA damage due to X-rays from ROS (75% from •OH)



•OH can cause oxidative stress and damage

If Fe^{2+} can alter the ROS concentration, are Mn ferrite ($Mn^{2+}Fe^{3+}O_4$) NPs better than Magnetite, ($Fe^{2+}Fe^{3+}O_4$)?
Is γ-Fe_2O_3 (no Fe^{2+} , but lower M_s) better?

Roberto Zysler, INN Bariloche

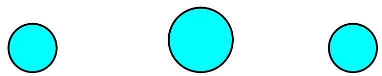
Particle Dispersion

- If particles form large agglomerates in biological media, they could cause heart attacks or strokes in living organisms

- What happens in biological media? (Phosphate Buffered Saline solution used is equivalent to 154 mM NaCl --- need steric stabilization)

- Primary particle size from TEM, clustering from dynamic light scattering (DLS)

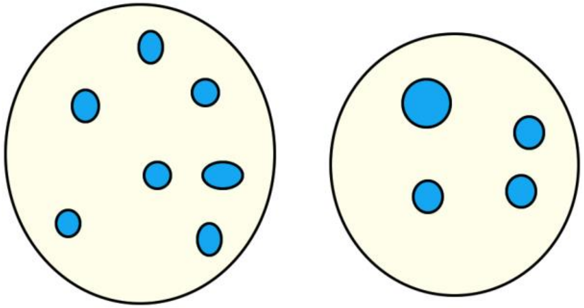
Two Main Types of Nanoparticles



Fe_3O_4 or γ-Fe_2O_3 ; ~10 nm

Individual particles

MRI, hyperthermia, ferrofluids



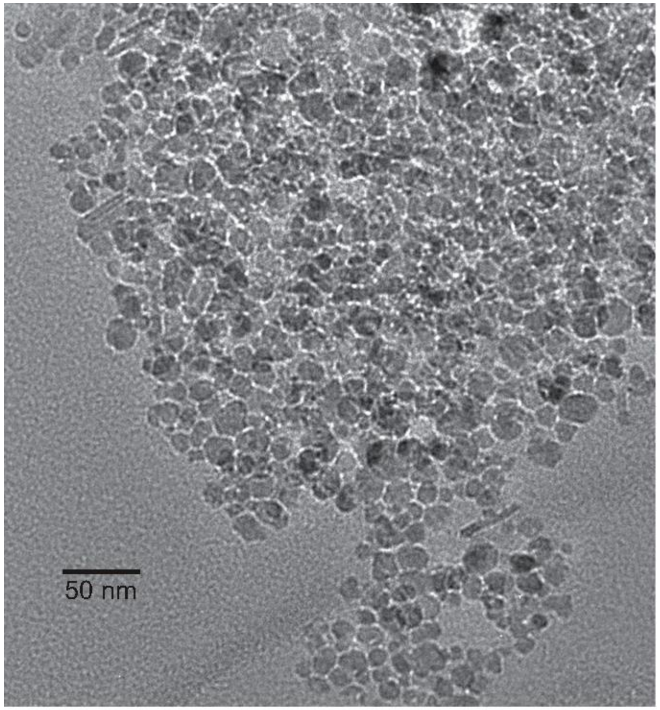
Magnetic beads with many particles bound in a polymer matrix; ~ 0.5-10 μm

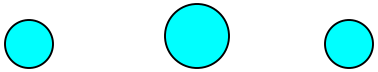
Magnetic separation, sensing

Coatings important for both types

Superparamagnetic

Coprecipitation or Hydrothermal Synthesis





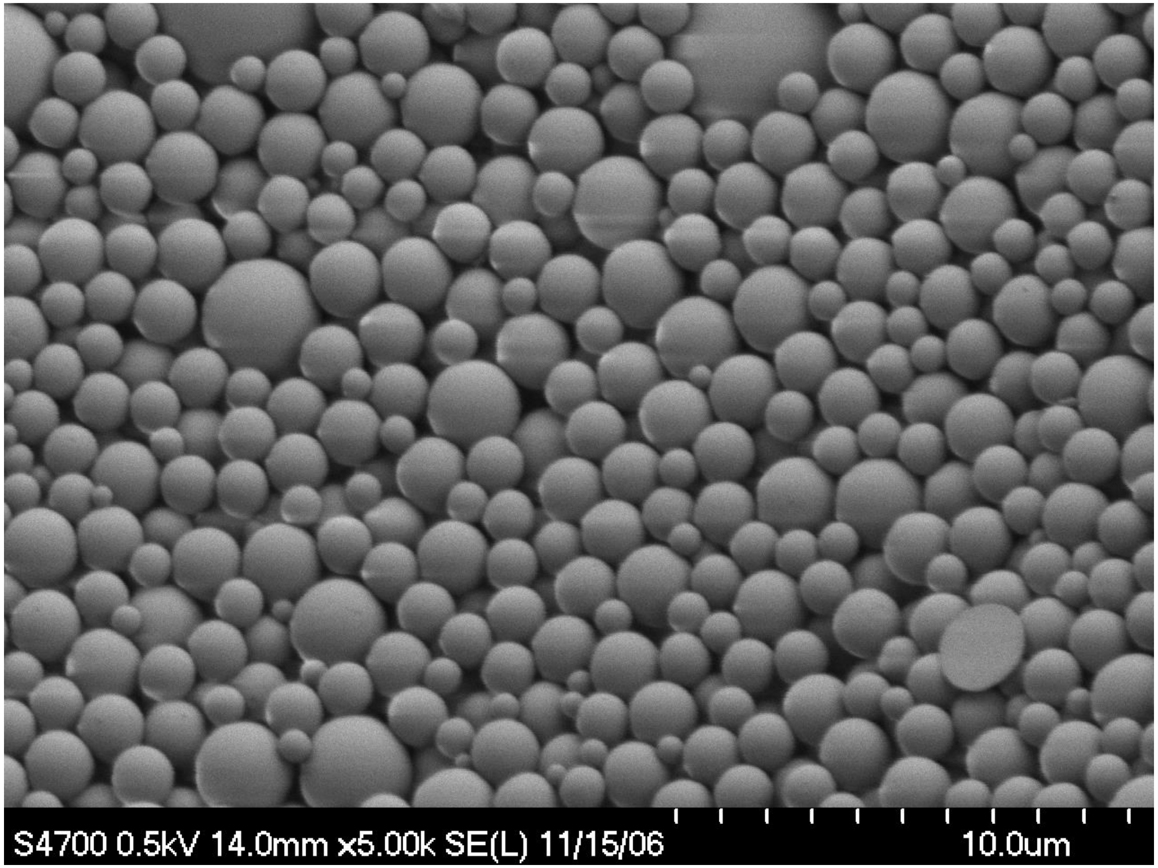
Mix Fe (II), Fe (III) salts in aqueous solution, add base

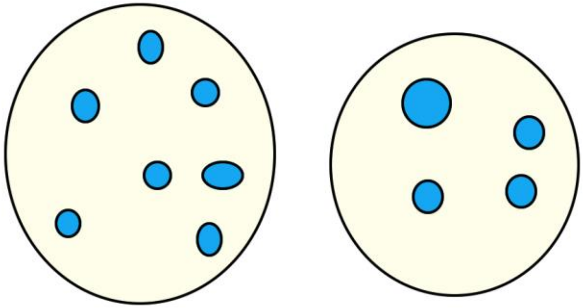
Easy, all reagents can be biocompatible, makes ~10 nm particles, 20-50 emu/g

GMP: Good manufacturing practices

R. Massart and V. Cabuil, J. Chem. Phys. **84** 967 (1987).

Magnetic Beads





Commercially available (Dynal, Miltenyi,…)

H. Zhao, K. Saatchi, U. O. Hafeli, J. Magn. Magn. Mater. **320**, 1356 (2009).

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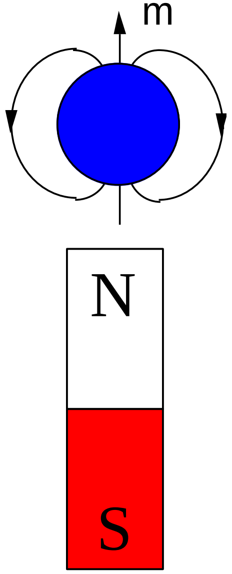
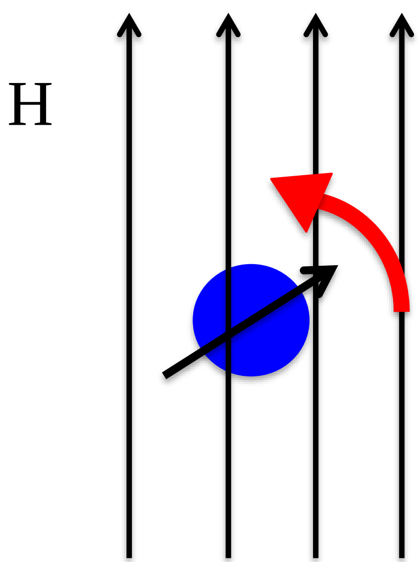


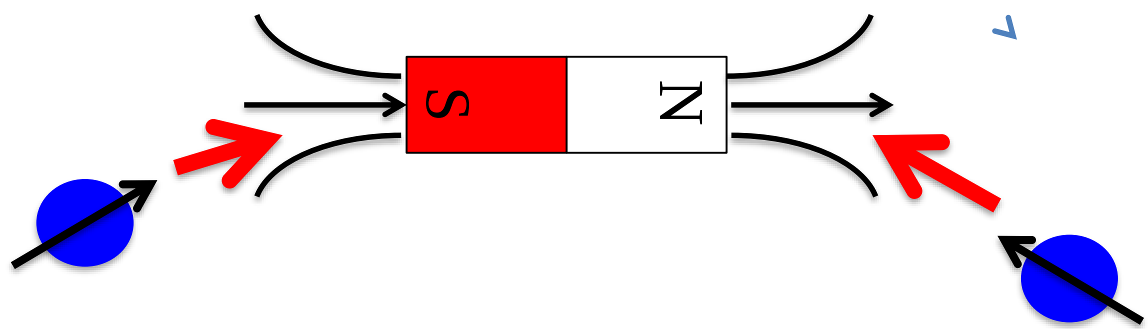
2 Kinds of Magnetically Controlled Motion

Particle moment μ rotates in a uniform field



Torque $\tau = \mu \times H$

Spatially varying translates particles toward poles



Force $F = \mu \bullet \nabla H$

Torque on Vortex Discs for Cancer Treatement

nature materials

ARTICLES

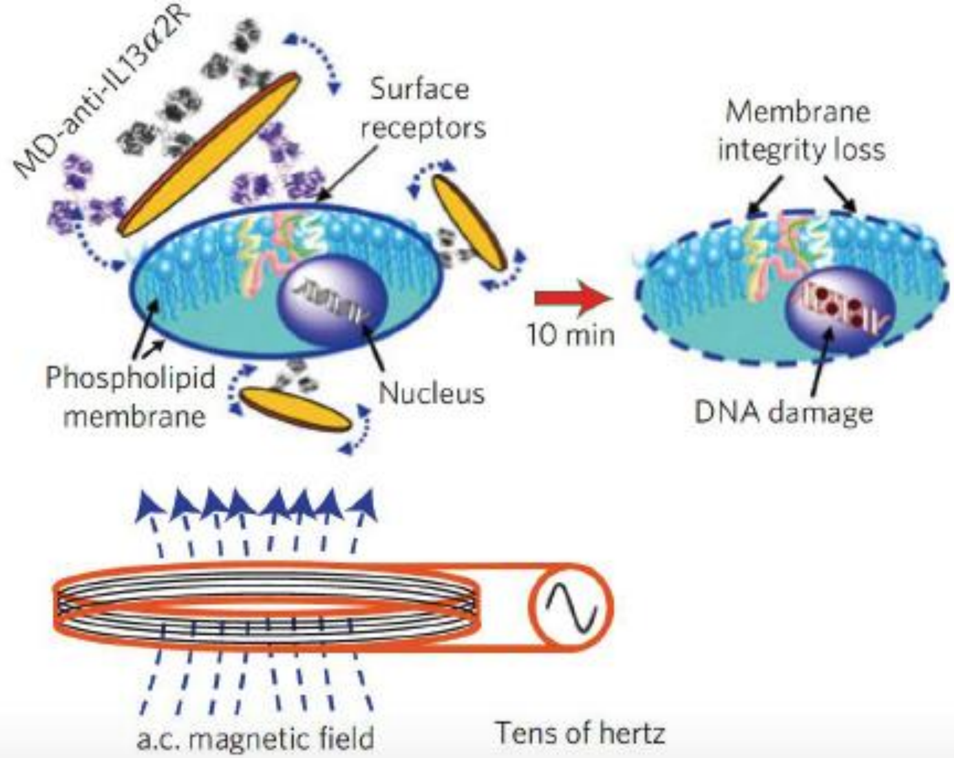
PUBLISHED ONLINE: 29 NOVEMBER 2009 | DOI: 10.1038/NMAT2591

Biofunctionalized magnetic-vortex microdiscs for targeted cancer-cell destruction

Dong-Hyun Kim[1], Elena A. Rozhkova[2]*, Ilya V. Ulasov[3], Samuel D. Bader[1,2], Tijana Rajh[2], Maciej S. Lesniak[3] and Valentyn Novosad[1]*

Torque $\tau = \mathbf{m} \times \mathbf{H}$

Oscillation of the disks induces programmed cell death



Kim, Nature Mater. 9 165, (2010)

Magnetophoresis

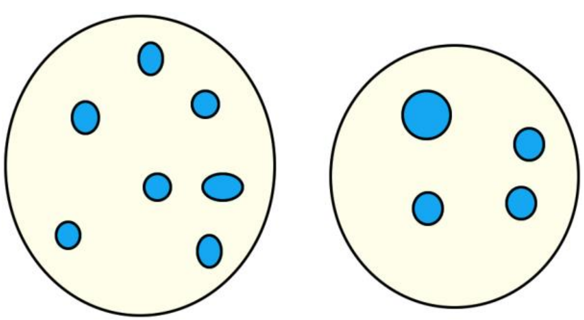
- Drag forces large for small particles, relative to magnetic force

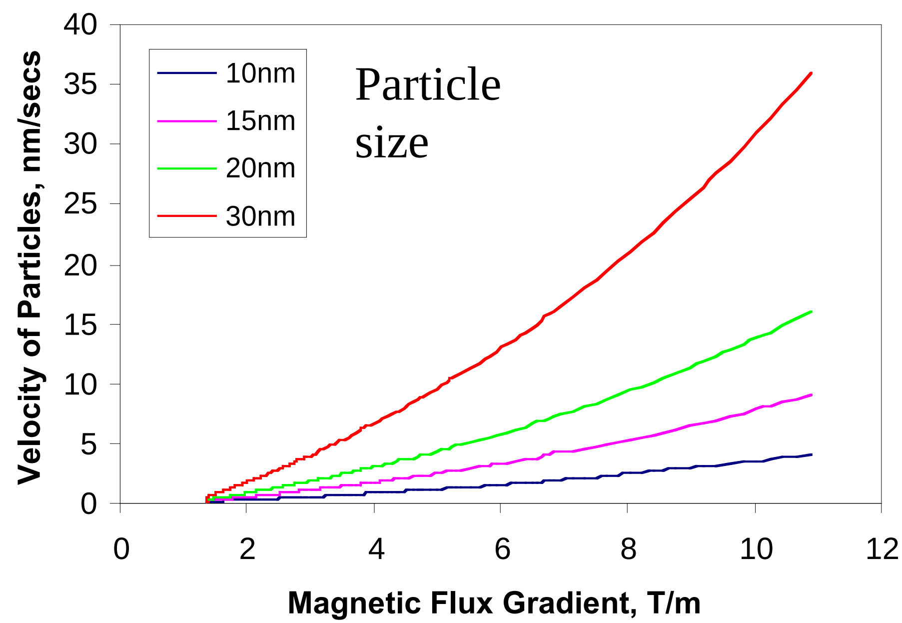
$$F_{drag} = 6phur_{hyd} \qquad \vec{F}_{mag} = (\vec{\mu} \bullet \nabla)\vec{B}$$

- Terminal velocity

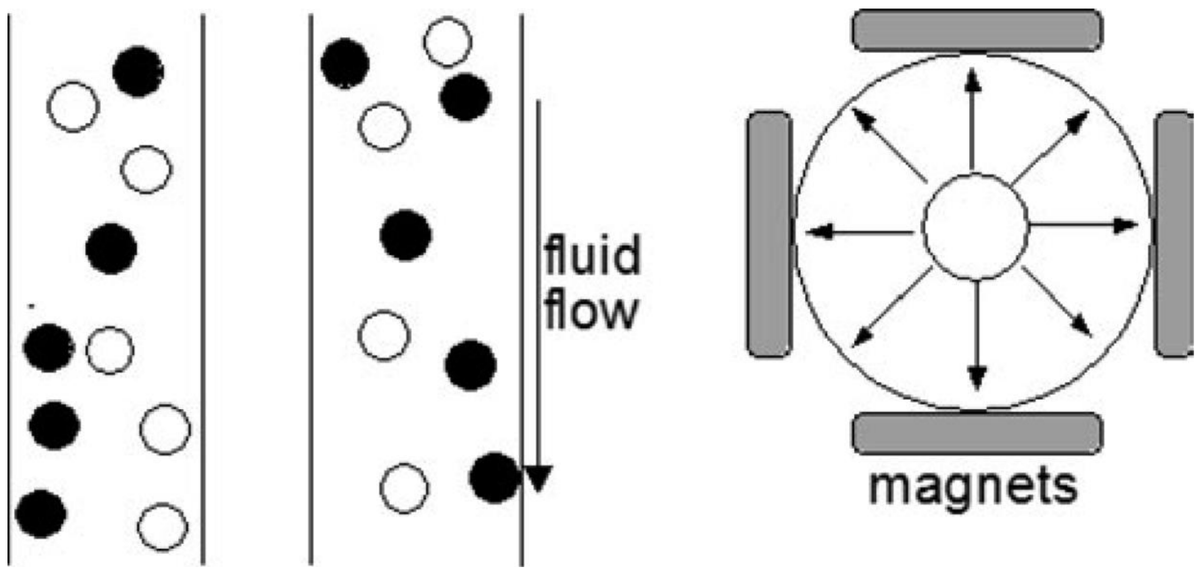
$$u_{mag} = \frac{F_{mag}}{6phr_{hyd}}$$

- Use magnetic beads





Quadrupole Magnetic Separation of Circulating Tumor Cells



F. Carpino, et al. J. Magn. Magn. Mater. 311 383 (2007).
S. Nagrath , et al., Nature 450 20 (2007) - < 10 cells/10 mL blood, Stage I breast cancer trial

Circulating Tumor Cells

Primary cancers shed cells even when tumor seems to be organ-confined, cause of metastasis

- E. Racila, et al., PNAS **95** 4589-4594 (1998).

Detection of tumor cells in blood could be used for diagnosis, choice of treatment, prognosis

Challenge: find 10 cancer cells among $5x10^9$ red blood cells $5x10^6$ white blood cells/mL of blood

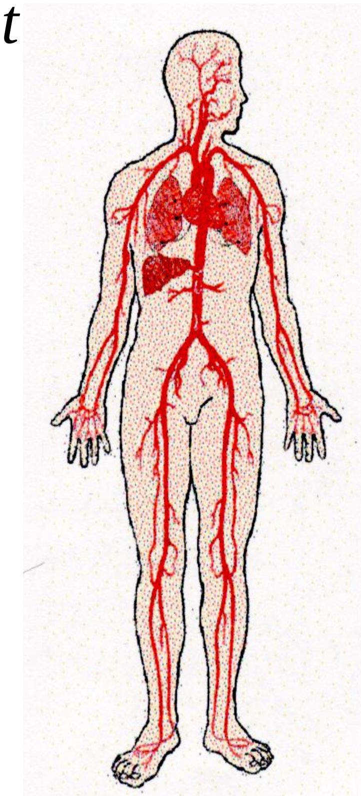
Targeting Magnetic Particles *in vivo*

No **magnetic** drug delivery *yet*

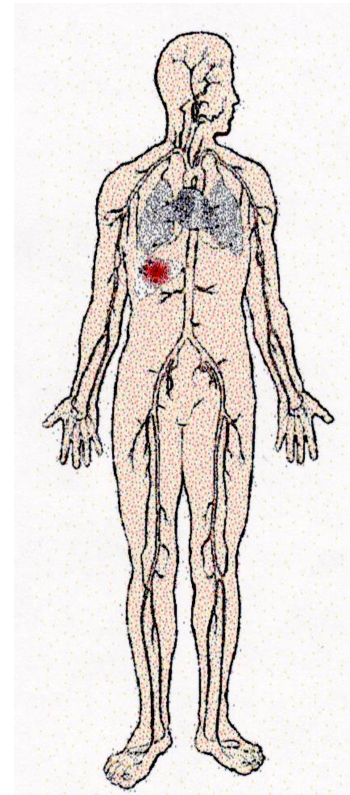
-Hard to guide to deep locations
- Can hold in place with external magnets

-Selective chemical binding very inefficient

-Best delivery by injection upstream of tumor



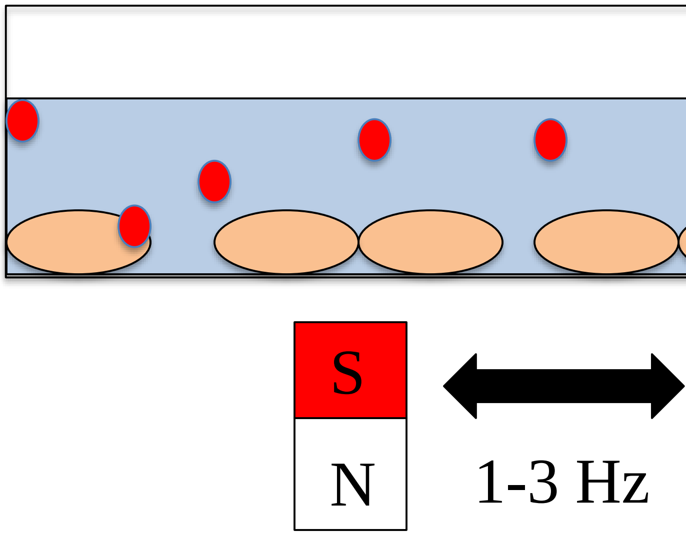
Systemic Therapy



Drug Targeting

Urs Hafeli, Univ. of British Columbia
www.magneticmicrosphere.com/hafeli_lab

In Vitro Magnetic Gene Delivery



Oscillate field, stimulate endocytosis of 1 μm beads

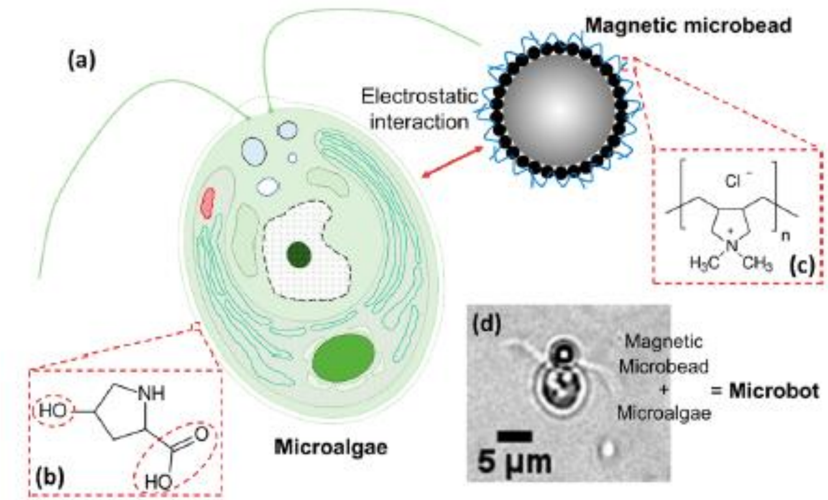
- C. Plank, Molec. Therapy **6,** 106-112 (2002); Nature Biotech. **18**, 893-895 (2000).

100 nm magnetic pts. coated with DNA coding for green fluorescence protein transfected

- S. C. McBain, et al., Gene Therapy **15**, 902 (2008)

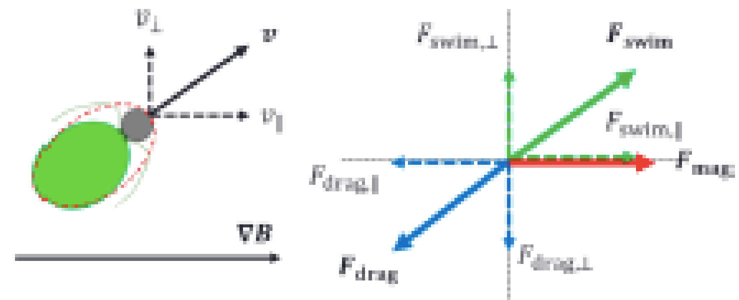
Feline fibrosarcoma trial – J. Vet. Med. A Physiol. Pathol. Clinical Med. **54** 599-606 (2007); human trials started in 2009

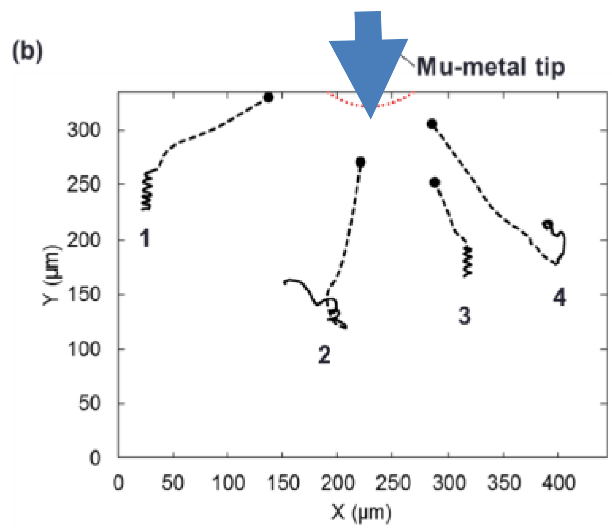
Magnetic Swimmers



W. M. Ng, et al., Langmuir **34**, 7971 (2018)

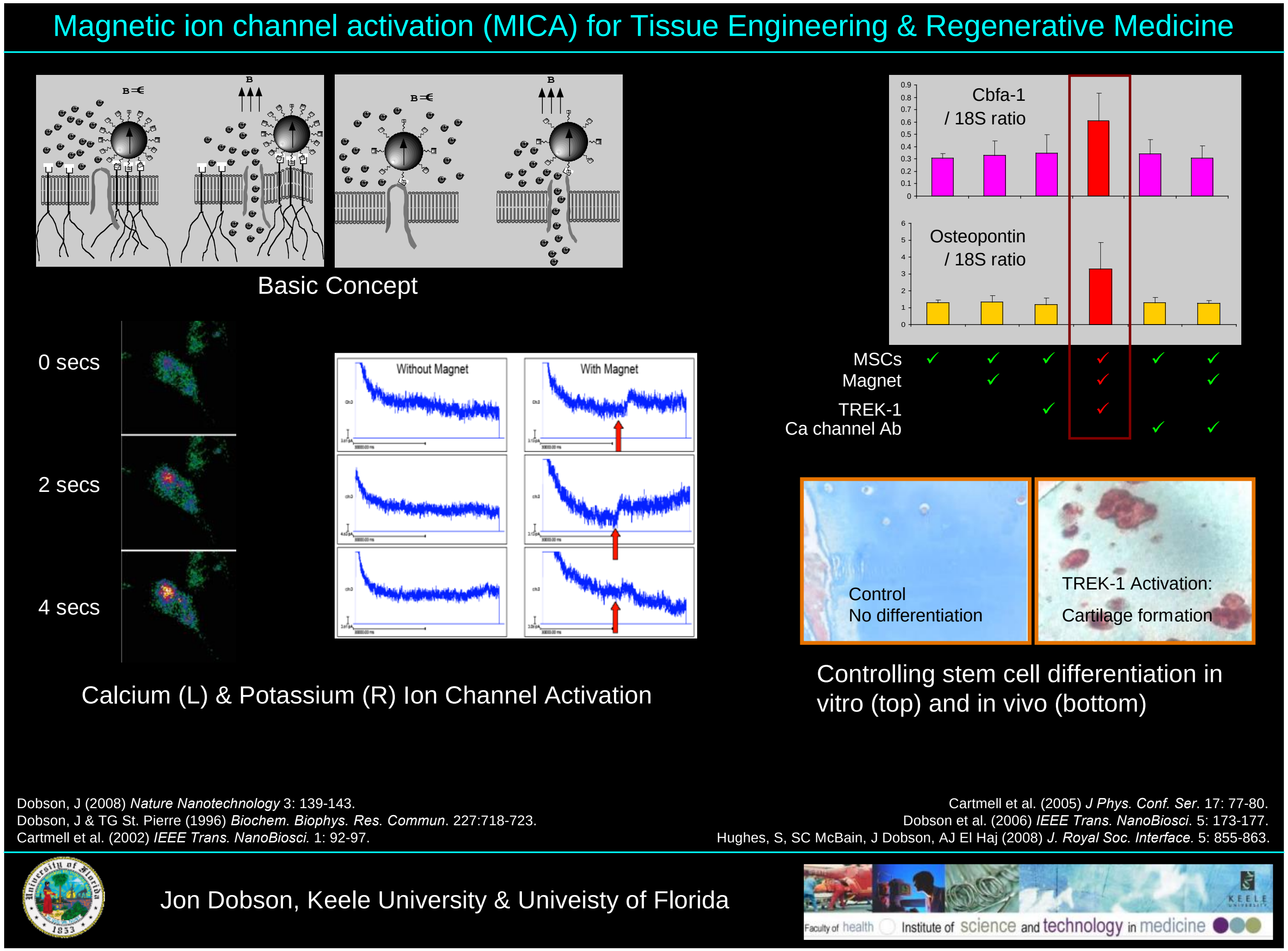
Algae swim in response to field gradient





Helical trajectory due to flagella, but magnetic guidance

In Vitro Magnetic Control of Ion Channels



J. Dobson, Nature Nanotech. **3**, 139-143 (2008); H. Huang, et al. Nature Nanotech **5**, 602 (2010).

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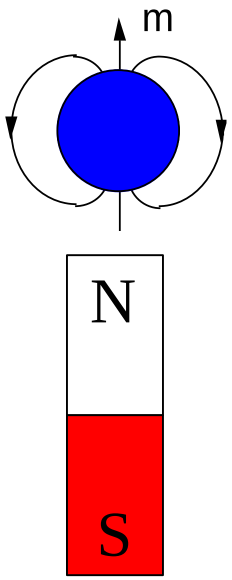
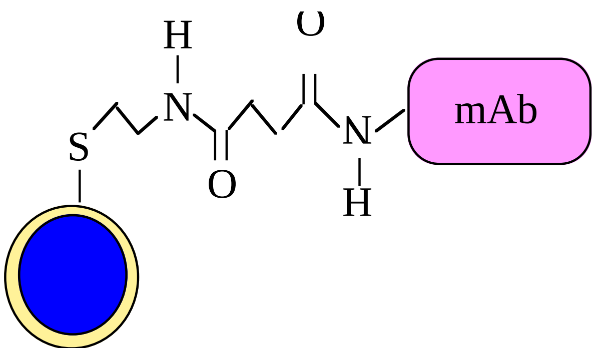
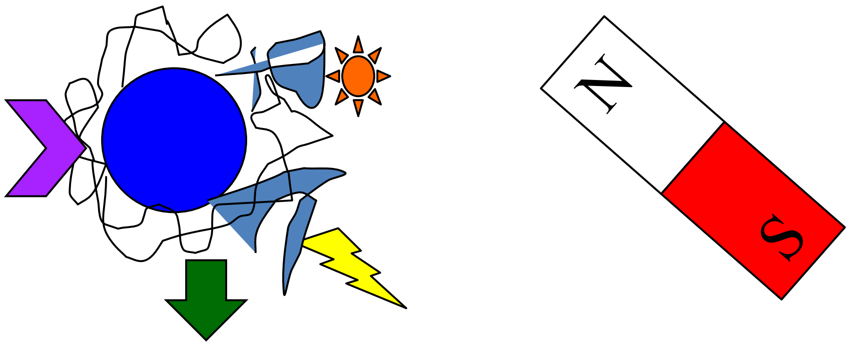


Magnetic Sensing

Use functionalized particles selectively bind analytes, then concentrate magnetically, then detect by:

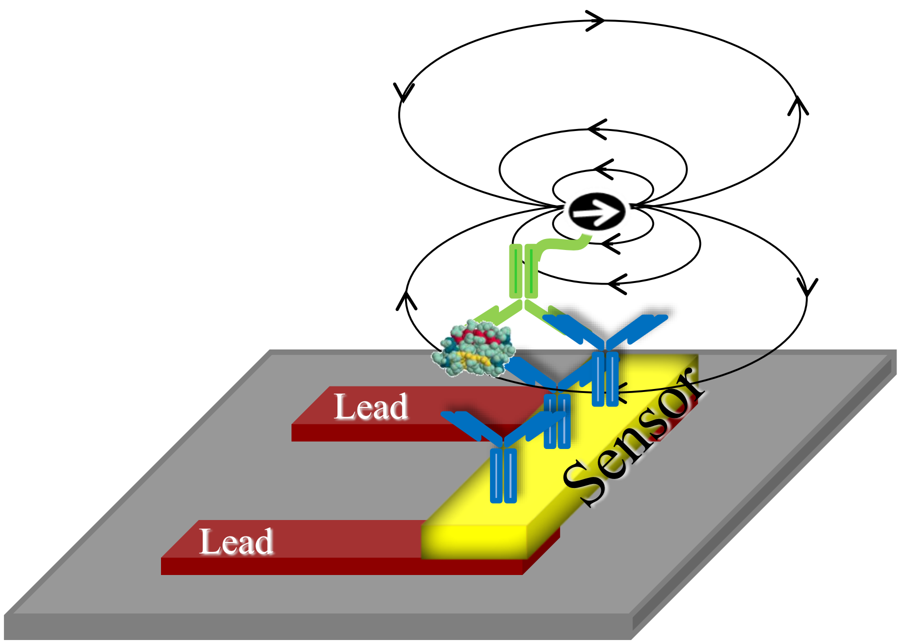
- Magnetoresistance (GMR, TMR)
- Relaxometry (SQUID, fluxgate)

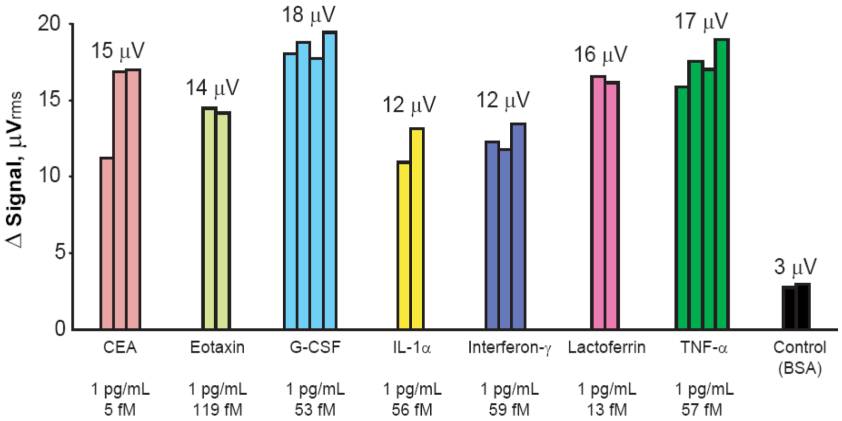




Magnetoresistive Sensing: Sandwich Assay

Need selective binding of analyte to NP + binding of NP to magnetic field sensor



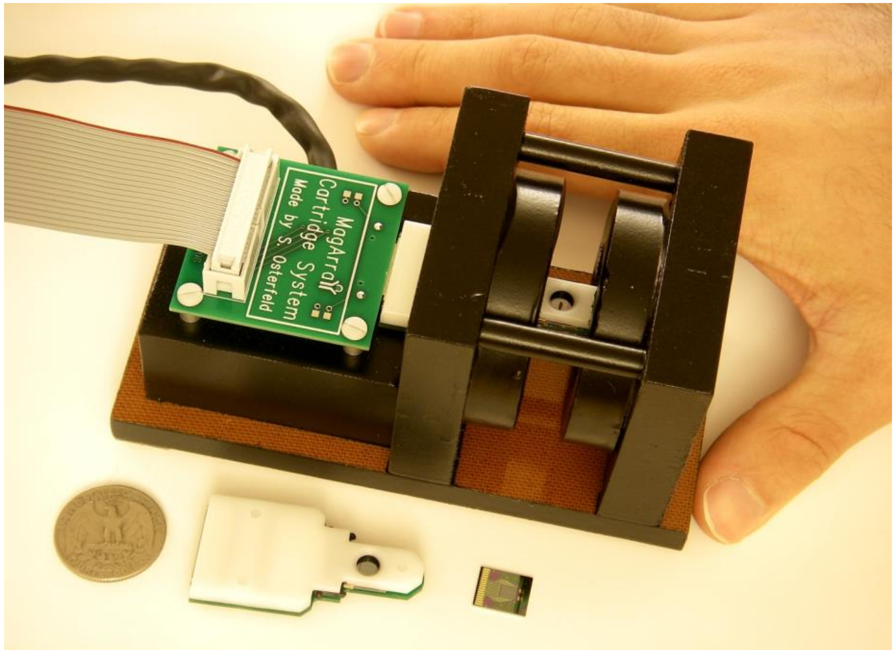


S. J. Osterfeld, et al., PNAS, **105**, 20637, (2008)

Magnetic Blood Scanner for Cancer

• Uses magnetic magnetic beads to ‘tag’ proteins indicative of cancer and reading them out using magnetic sensors

• Higher sensitivity (1 picogram/mL) than conventional optical fluorescence assays, enabling earlier cancer detection.



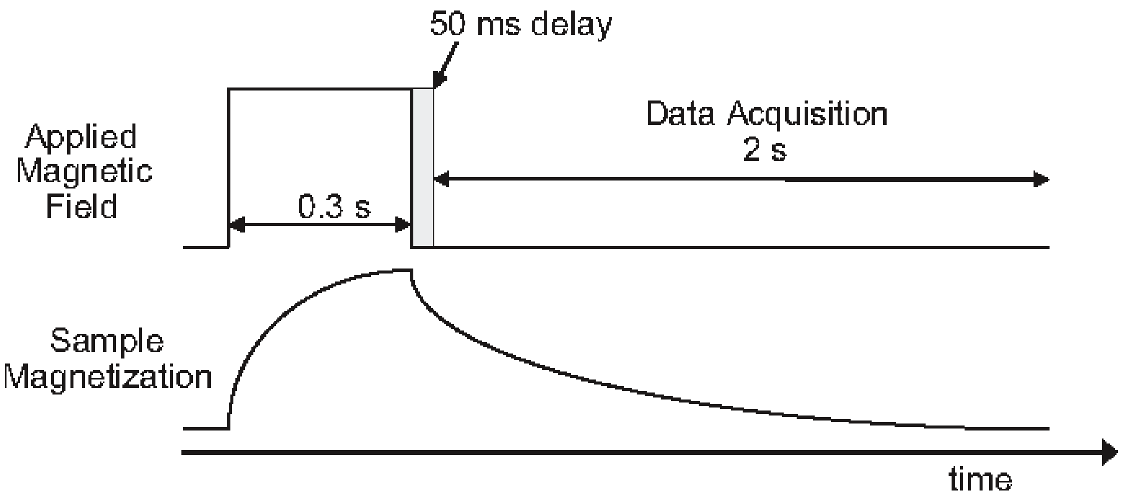
• Could be done quickly in a doctor’s office

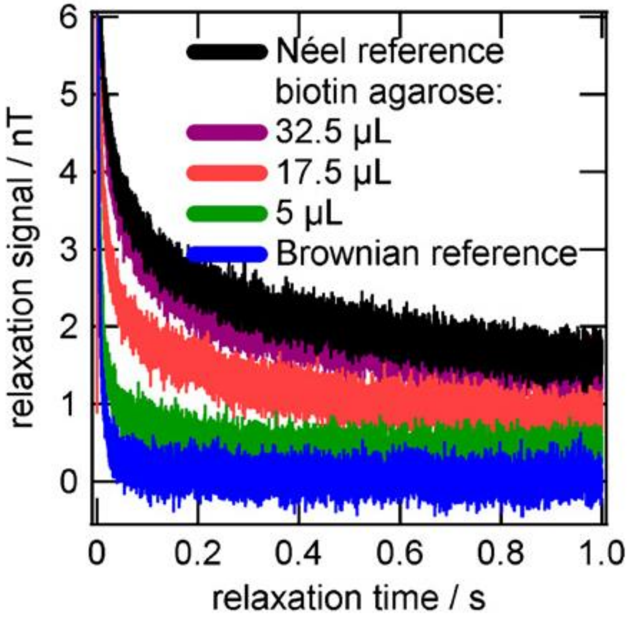
J. Choi, et al., Biosens. Bioelectron. 85**, 1 (2016)**

Relaxometry

3D sensor (microSQUID array) **– doesn't require particles to be within a few nm of a sensor surface**

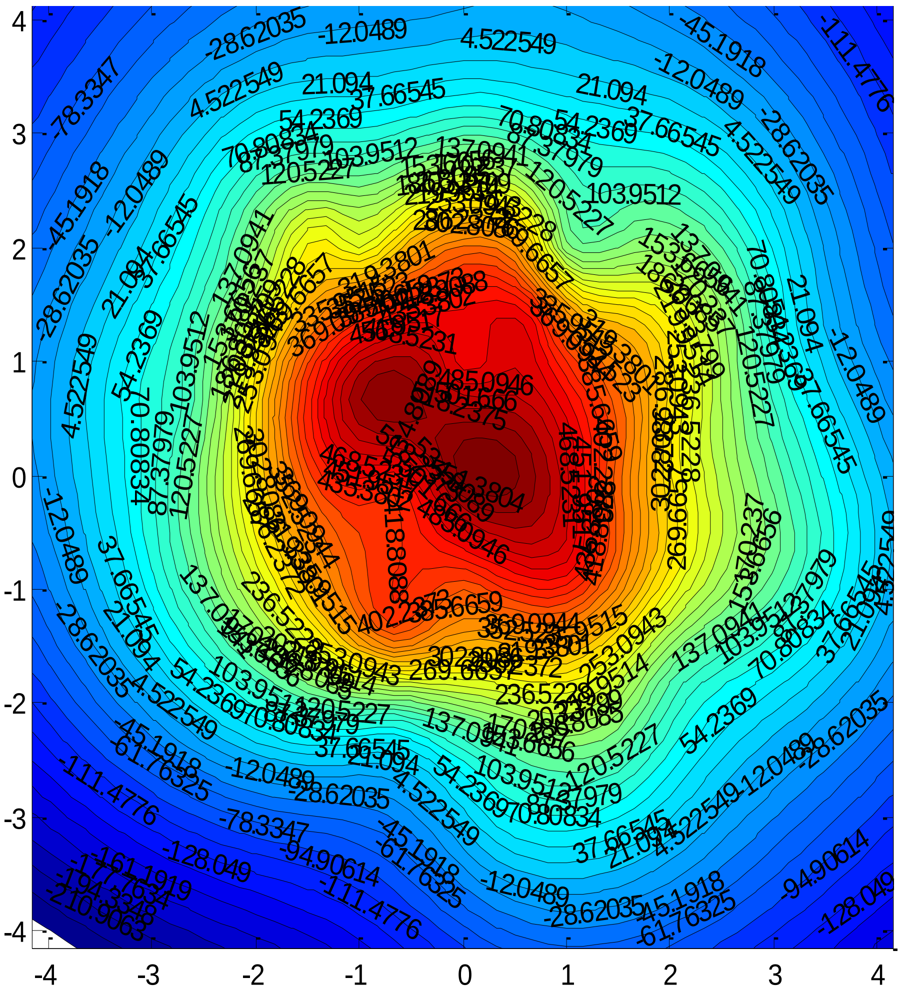
Can do measurements on whole blood





N. L. Adolphi, et al., Contrast Media Molec. Imaging **7**, 308 (2012).
D. Eberbeck, et al., J. Magn. Magn. Mater. **321** 1628-1631 (2009).
W. K. Peng, et al., Nature Medicine **20**, 1069 (2014).

SQUID Relaxometry Detection of Breast Cancer



From mouse with two human breast tumors injected with anti-Her-2/neu labeled nanoparticles (Ocean Nanotech SHP-30)

Natalie L. Adolphi, Kimberly Butler, Debbie M. Lovato, Richard S. Larson **(Univ. New Mexico**) Trace E. Tessier, Howard C. Bryant, **Edward R. Flynn (Senior Scientific, LLC)**

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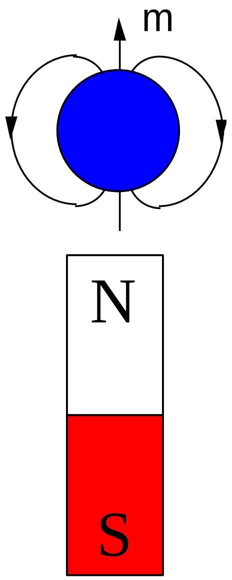
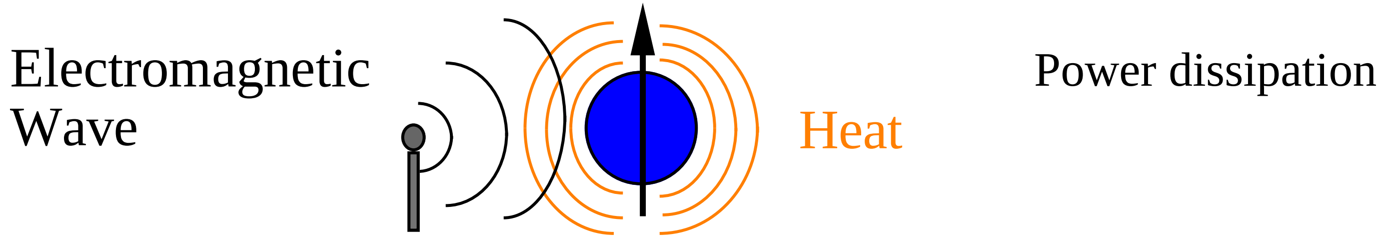


Magnetic Hyperthermia

Dissipate Energy – Hyperthermia



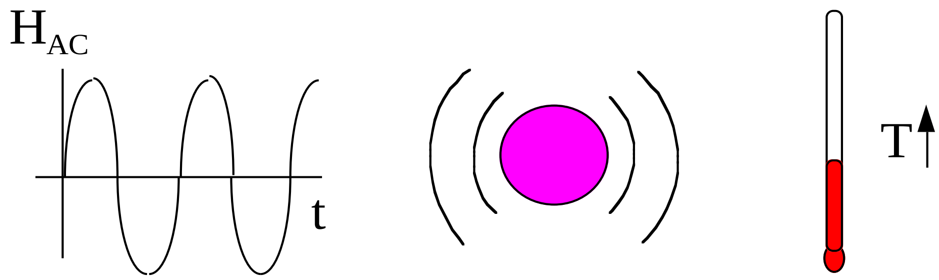
Hyperthermia – > 43 ° C – cells more sensitive to chemotherapy drugs and radiation

Ablation - > 50 ° C – kill cells directly by heating

Many types of hyperthermia: Direct, electrical, ultrasound, photothermal, magnetic (where is magnetic hyperthermia superior?)

Clinical trials: Charité Hospital Berlin, University College London

Magnetic Hyperthermia



Magnetic dissipation

$$\Delta U = -\mu_0 \oint M dH$$

$$P = f\Delta U = \mu_0 \pi \chi'' f H^2$$

Power loss ~ ΔT

FDA requirements: $H_{max} f < 4.85 \times 10^8$ A-turns/m-s

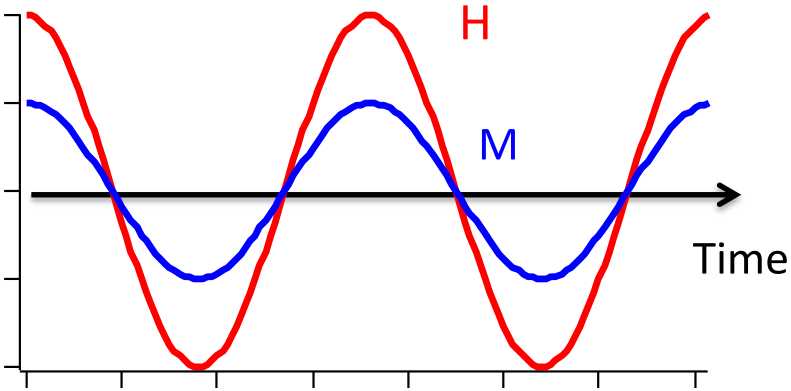
- with typical fields, $f_{max} < 1.2$ MHz

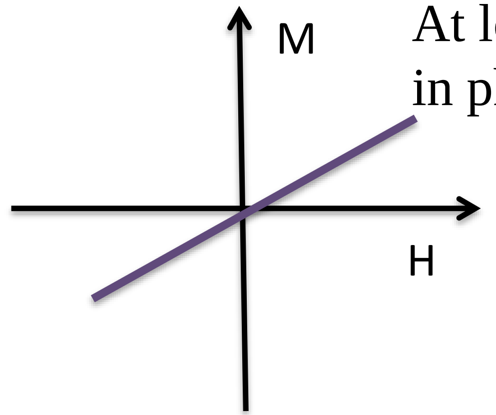
- Otherwise stimulate nerves and cause pain

W. J. Atkinson, et al., IEEE Trans. Biomed. Eng. **31** 70-75 (1984).

Magnetic Susceptibility $c = M/H$

Low amplitude AC field H(t) drives magnetization M(t)

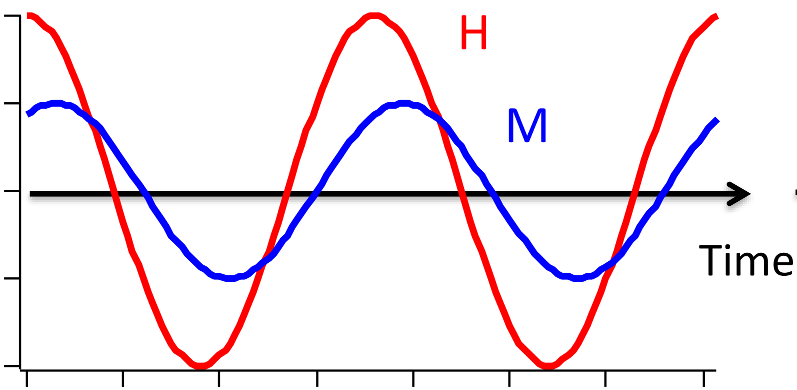


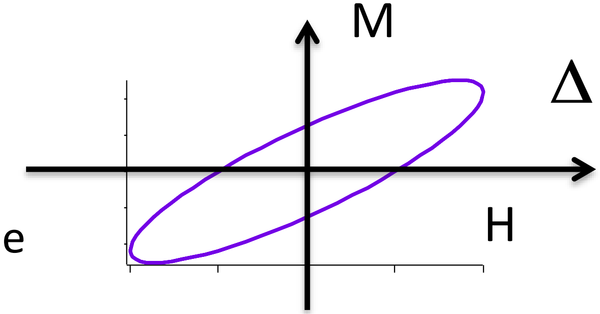


At low frequency, M(t) in phase with H(t)

Superparamagnetic

At higher frequency, M(t) lags H(t)

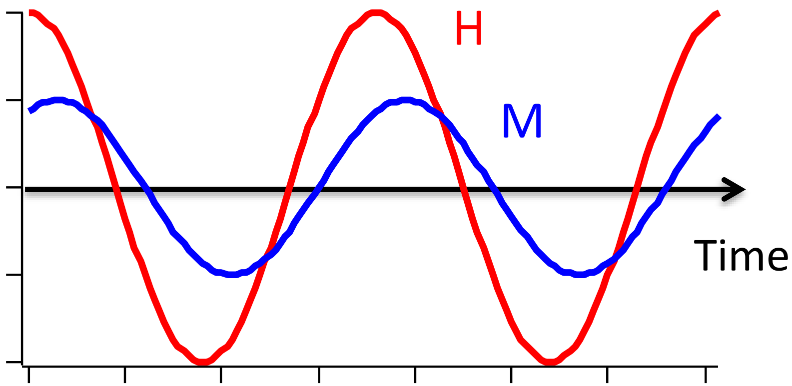


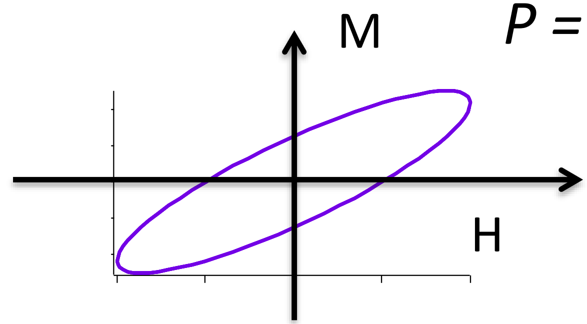


$$\Delta U = -\mu_0 \oint M dH$$

Hysteresis means energy dissipation

Imaginary Susceptibility

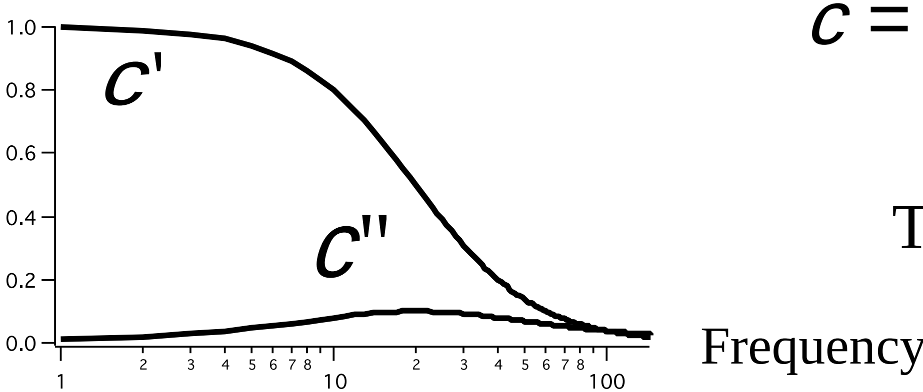




$P = f\Delta U = \mu_0 \pi \chi'' f H^2$

Can break M(t) into components in-phase and 90° out-of-phase with H(t), leading to the real and imaginary terms in the susceptibility, respectively

$$c = \frac{M}{H} = c' - i\,c''$$

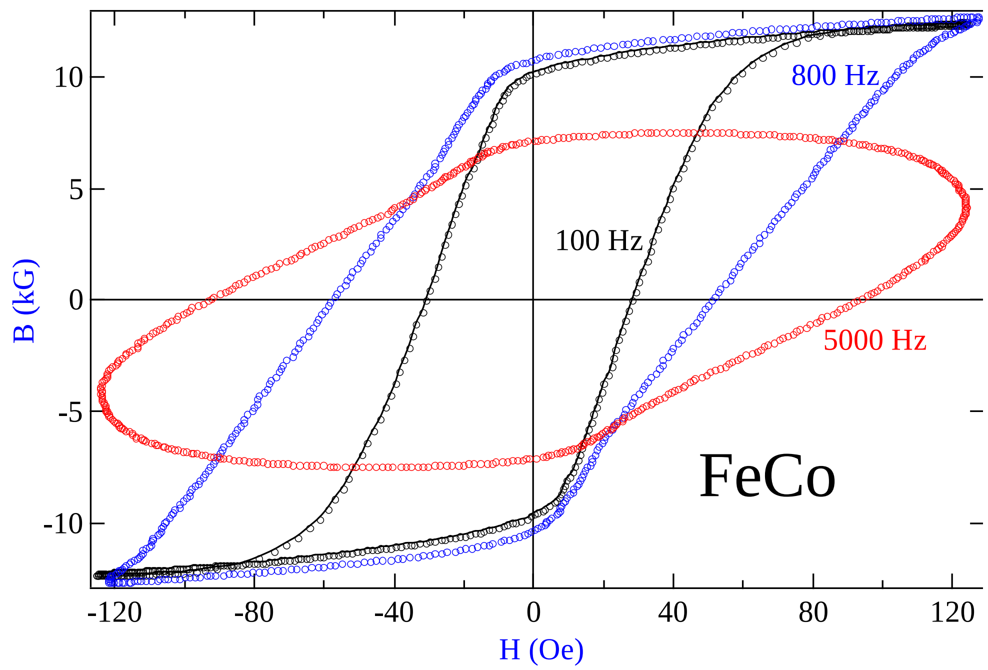


Typical hyperthermia frequencies
100-500 kHz

Are Superparamagnets Best?

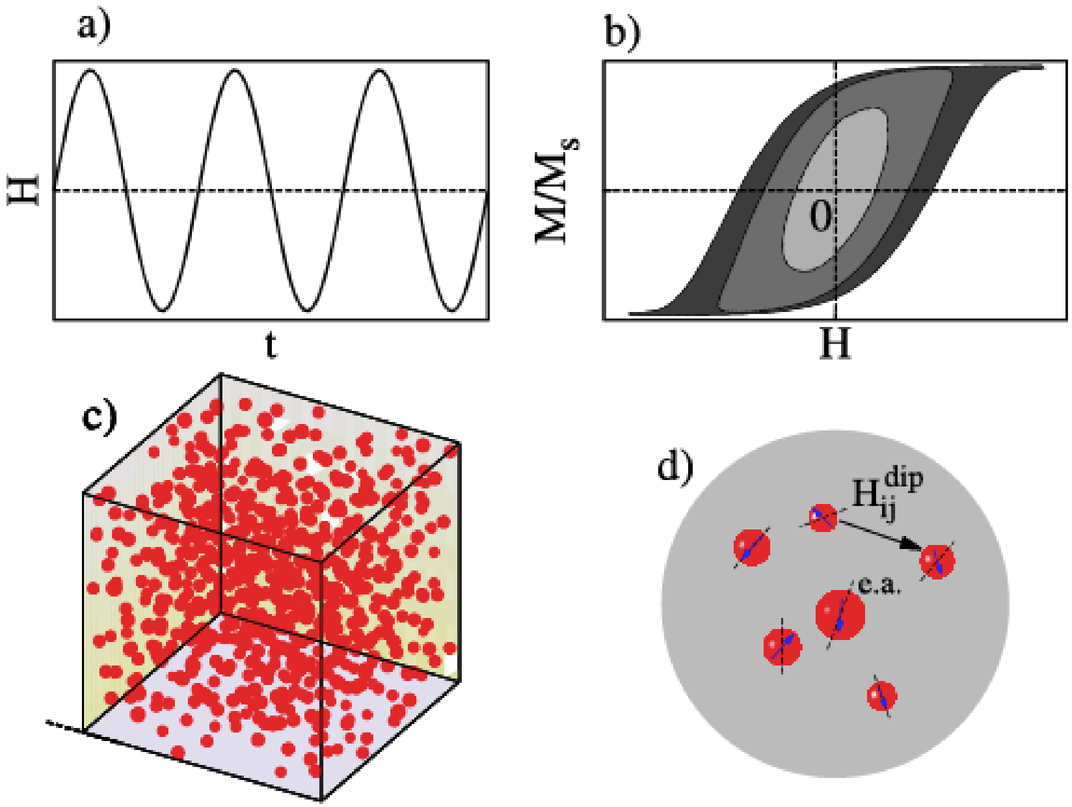
• Many papers claim that SP particles are best for hyperthermia, but these particles have no magnetic energy losses

• Particles are SP in nearly DC measurements, but loops open up at AC frequencies used for hyperthermia



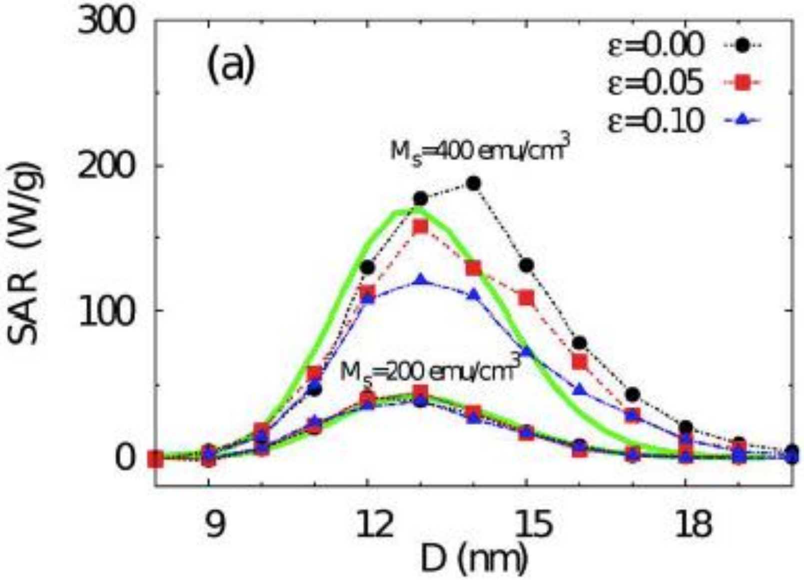
A. K. Giri, K. M. Chowdary, and S. A. Majetich, *Mater. Physics and Mechanics* **1**, 1-10 (2000).

Hyperthermia Simulations

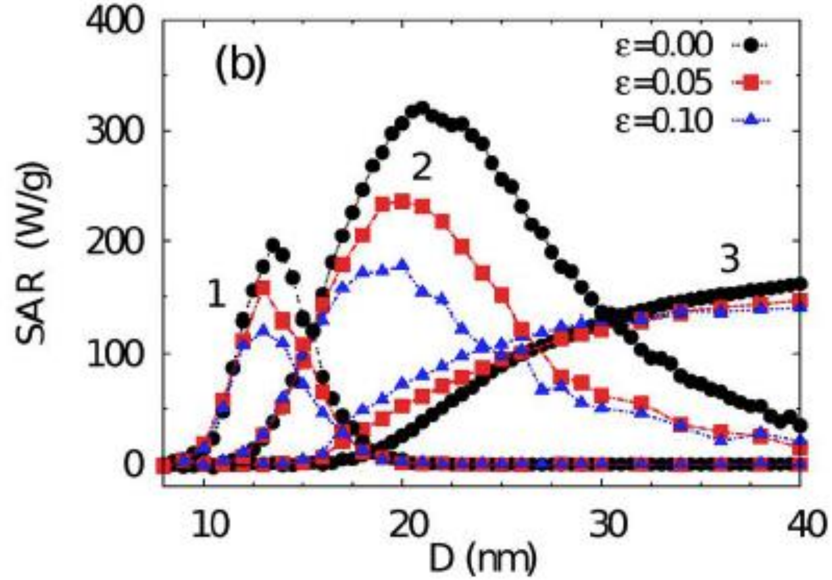


S. Ruta, et al., Sci. Rep. (2015), DOI: 10.1038/srep09090

Hyperthermia Simulations: Magnetostatic Interactions and K



Vary packing fraction ε

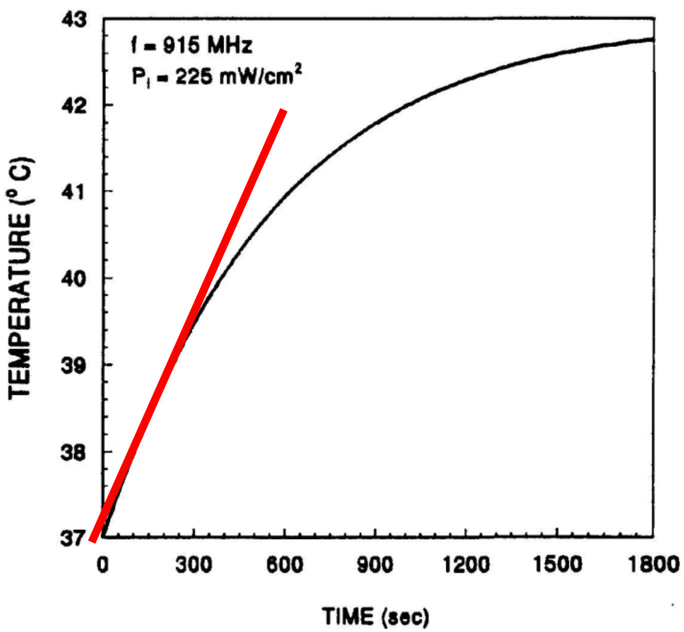


Vary anisotropy

1: 3 x 10^5 erg/cc
2: 1.5 x 10^5 erg/cc
3: 0.5 x 10^5 erg/cc

S. Ruta, et al., Sci. Rep. (2015), DOI: 10.1038/srep09090

Quantifying Heating Power



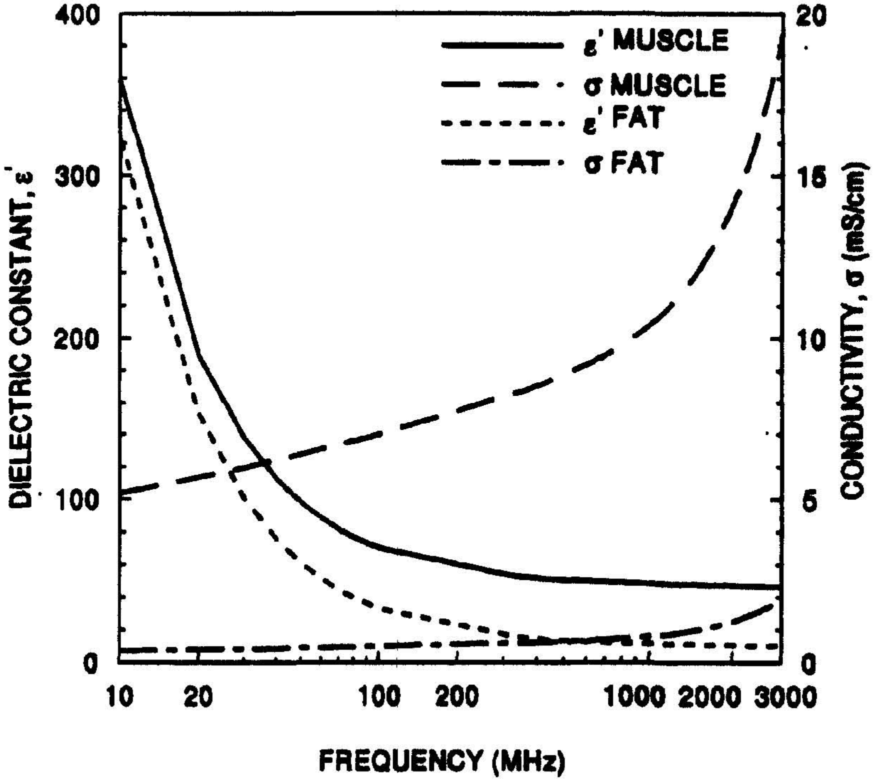
Ex vivo measurement of heating rate

- measure initial slope of T(t)
- depends on particle concentration
- depends on whether particles immobilized (Brownian vs. Néel rotation)
- use IR T sensor, not thermocouple

Figures of Merit

SAR – Specific absorption ratio – Power absorbed *per kg tissue*
SLP – Specific loss parameter – Power absorbed *per g Fe*
Thermal dose – *Should* be total power transferred, but not yet standardized

Electromagnetic Properties of Biological Tissues



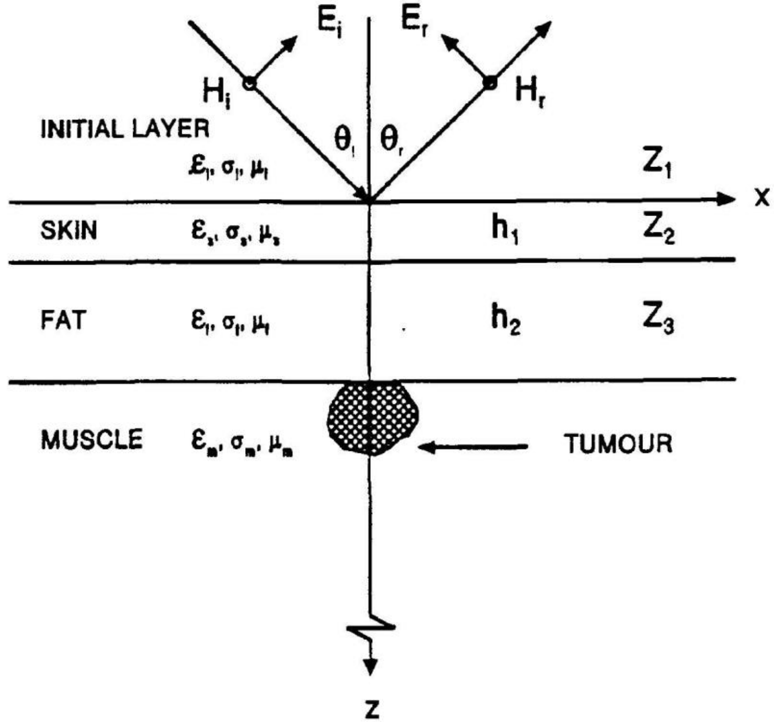
Low electrical conductivity at low frequencies, but not at high

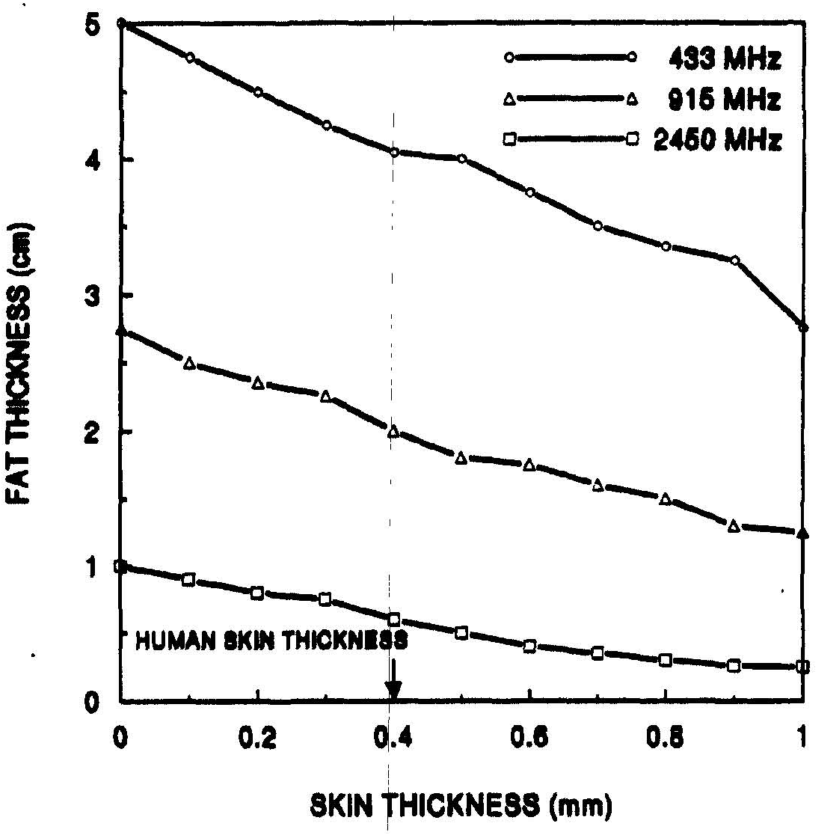
- like a Capacitor

Muscle and fat have different electrical properties

- AC EM field hyperthermia can create hot spots in fat

Boundary Value Problems





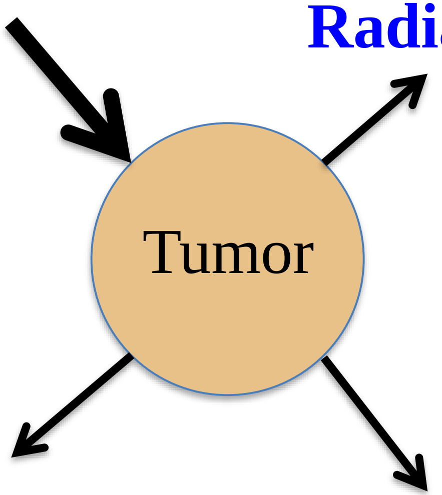
EM field penetration depends on frequency, material, and thickness

Must tailor hyperthermia treatment to individual

Bioheat Transfer Mechanisms

Power Deposition

Heat Convection, Radiation

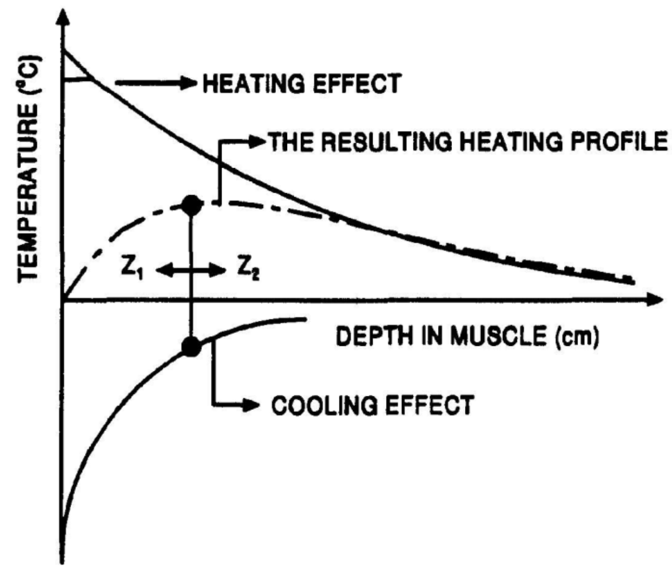


Blood Perfusion, Sweating

Heat Conduction

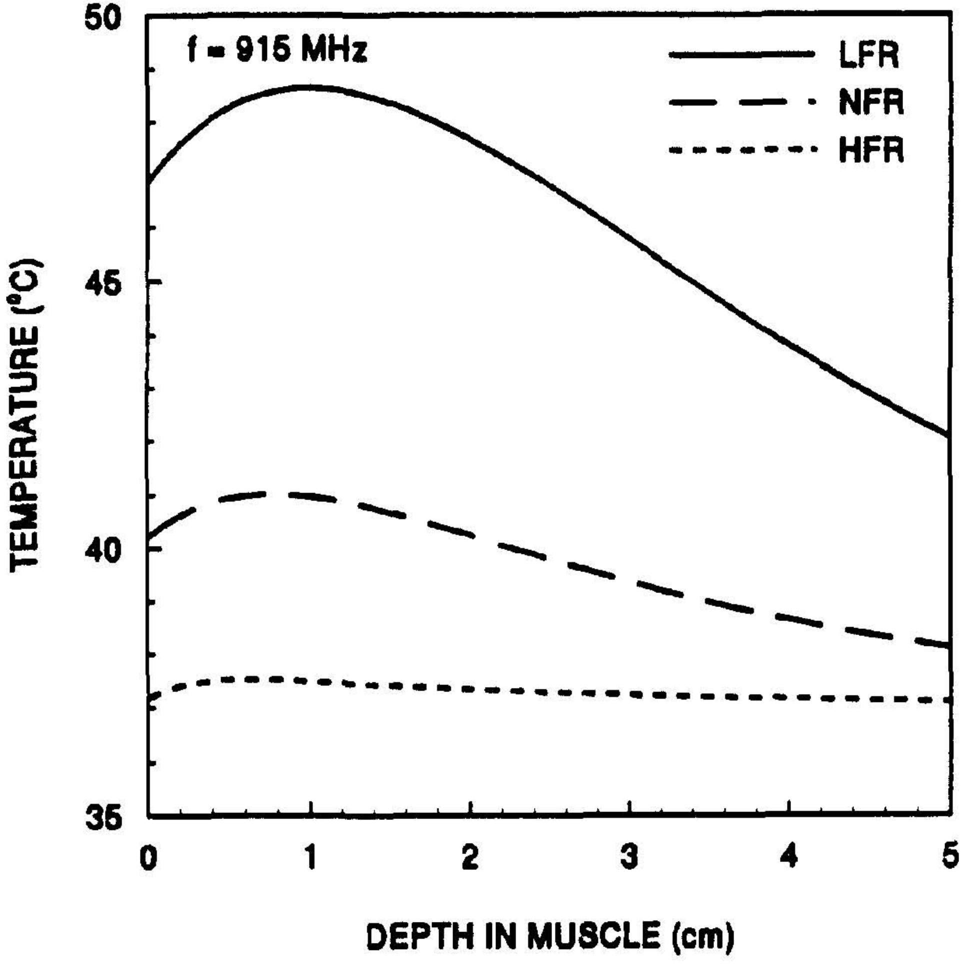
$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot \left(k \nabla T \right) + P$$

Bioheat Equation



Don’t want to damage healthy tissue

Blood Perfusion



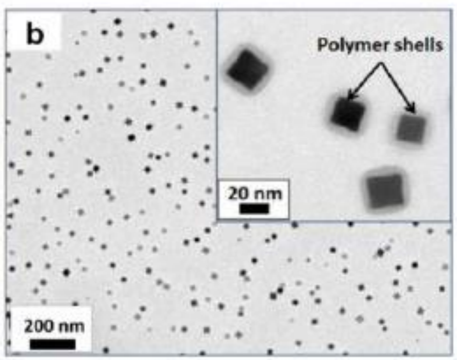
Low flow rate

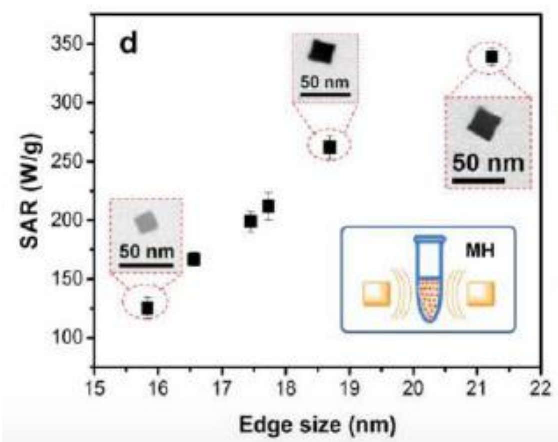
Normal flow rate (typical of muscle)

High flow rate (typical of brain, kidneys)

Hyperthermia harder in regions with high blood flow rates

Nanocubes for Hyperthermia





17 – 21 nm Fe_3O_4 nanocubes currently have high SAR under conditions approved for in human application

Coatings to limit magnetostatic interactions are important

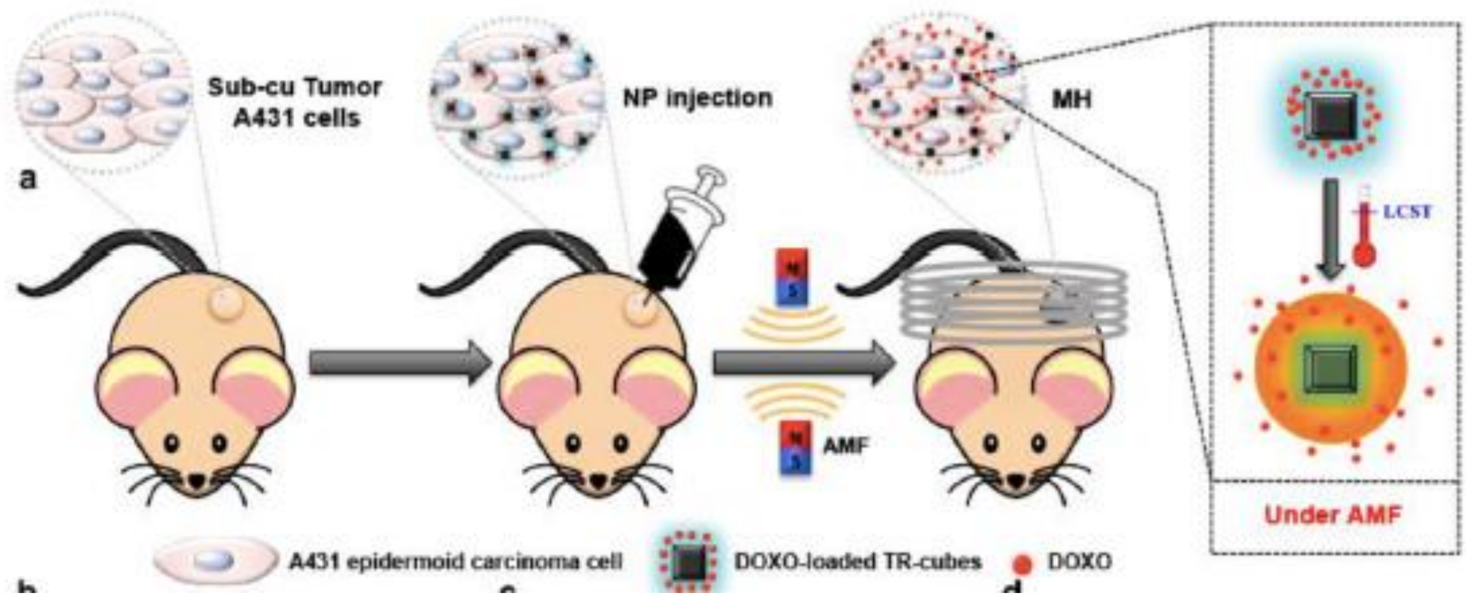
When particles taken up into endosomes, forming magnetosomes, they interact more strongly and the surface coating is often degraded. The stronger interactions reduce the SAR. This is also found with multicore NPs for hyperthermia.

B. T. Mai, et al., ACS Appl. Mater. and Interf. **11**, 5727 (2019)

J. Kokosnjaj-Tabi, et al., ACS Nano **8**, 4268 (2014).

Nanocubes for Hyperthermia

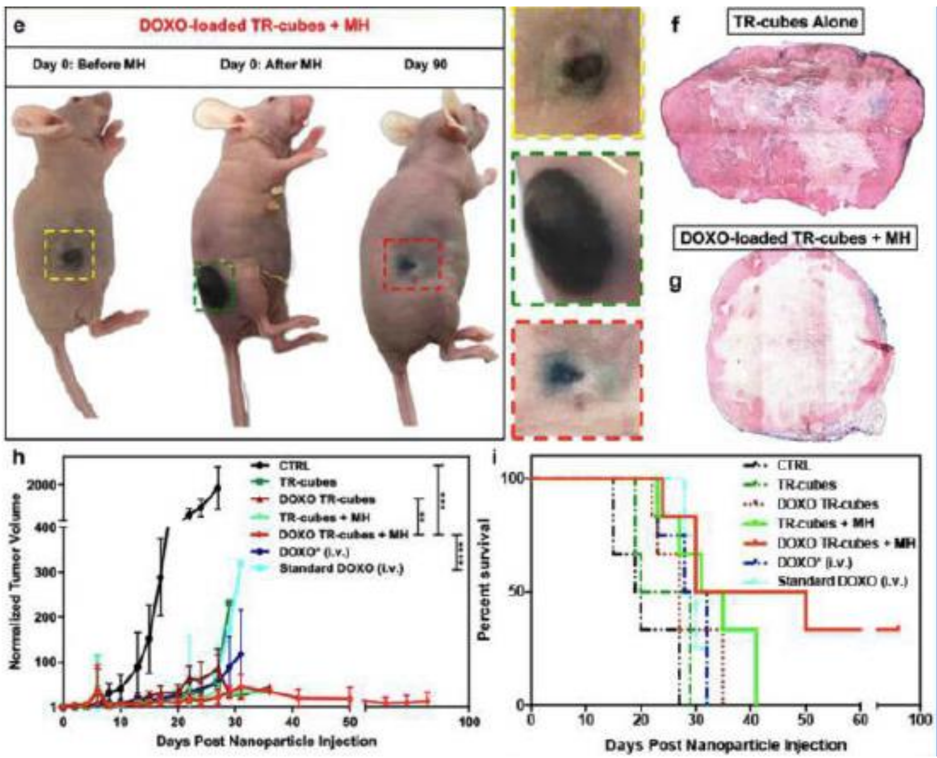
AC magnetic field heats through the particles, and at the same time releases the chemo locally



Complete clearance of NPs after 5 months

B. T. Mai, et al., ACS Appl. Mater. and Interf. **11**, 5727 (2019)

Nanocubes for Hyperthermia



Hyperthermia plus localized drug release (doxorubicin) eliminates skin cancer tumors

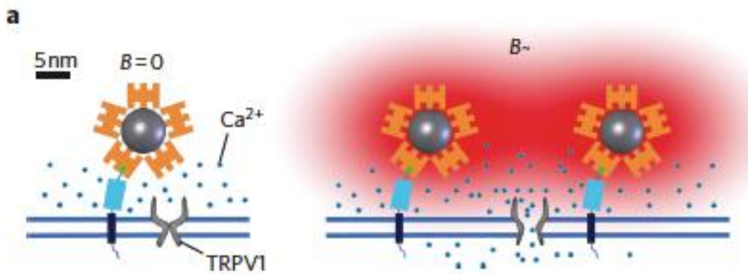
DOXO has FDA approval for release through liposomes, and is used to treat breast, prostate, stomach, and colon

DOXO loaded in thermally responsive polymer coating the nanocubes

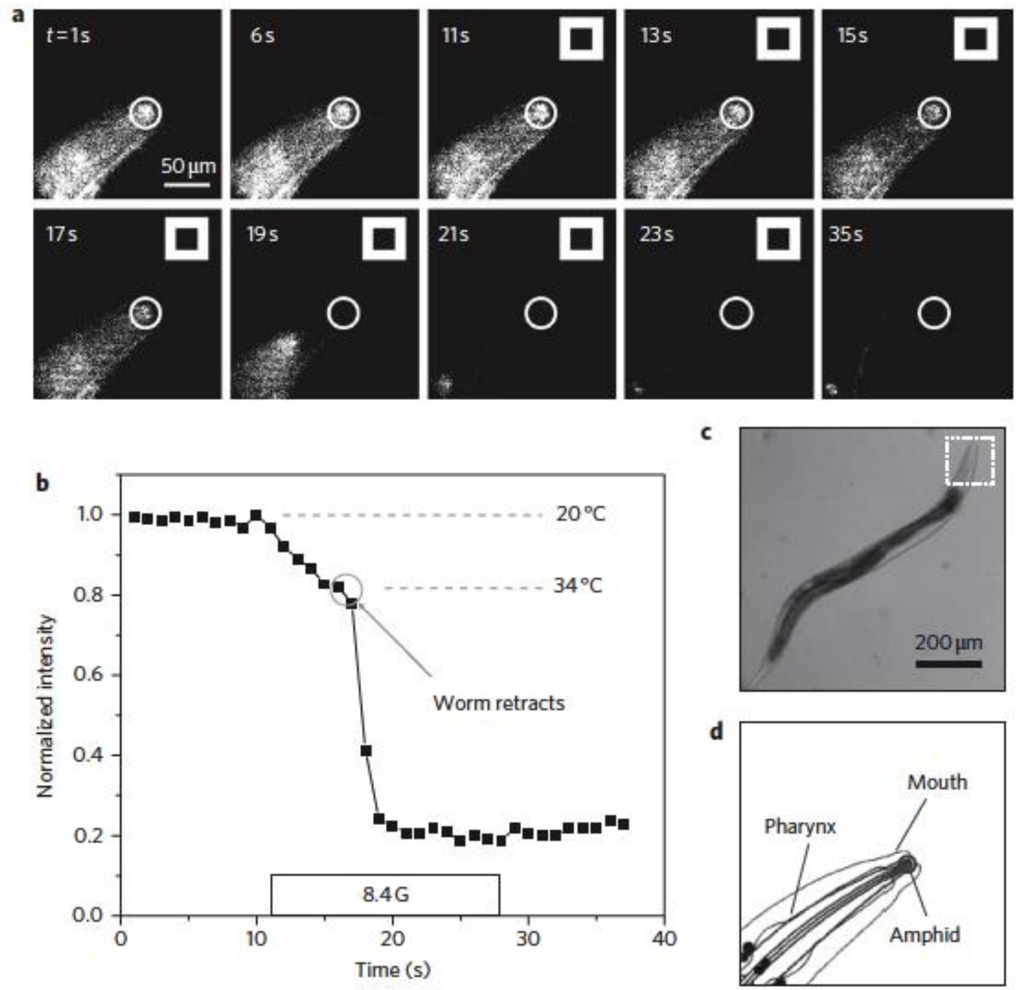
AC magnetic field heats through the particles, releases the chemo

B. T. Mai, et al., ACS Appl. Mater. and Interf. **11**, 5727 (2019)

Hyperthermia Control of Ion Channels



H. Huang, et al., Nat. Nanotech. (2010), DOI: 10.1038/NNANO.2010.125

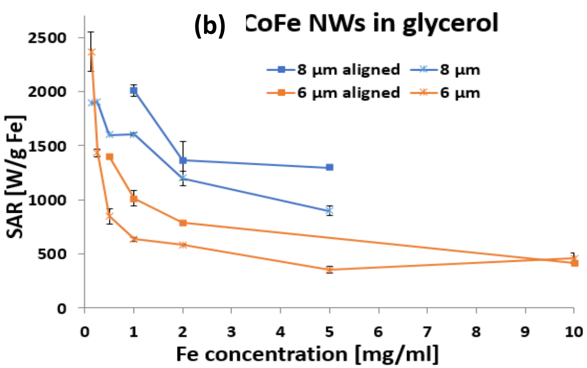


Use AC field to heat nanoparticles attached to sites near ion channels, see living C. elegans respond to AC magnetic field stimulus

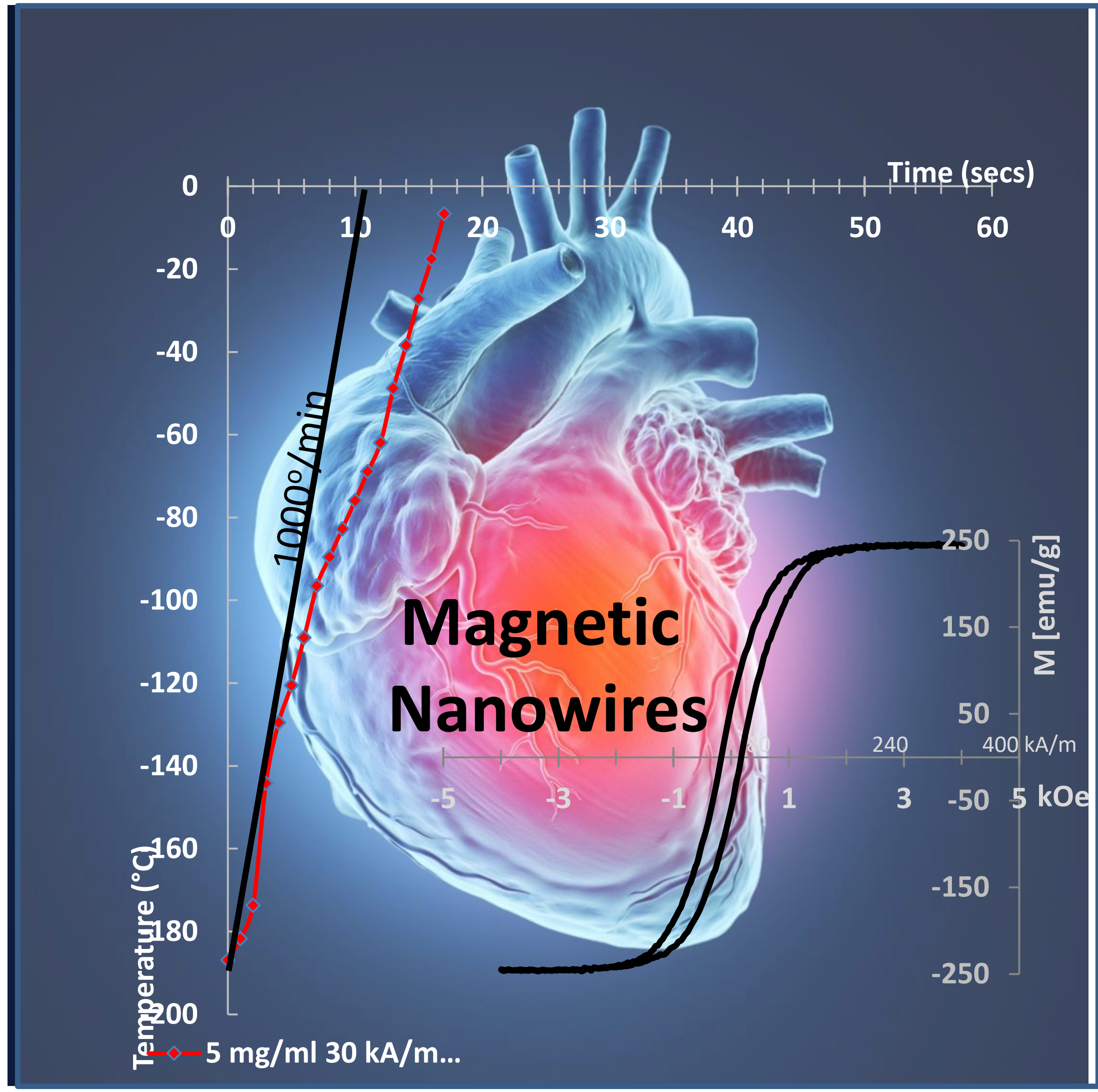
Hyperthermia for Organ Transplantation

The lifetime of harvested organs is extended by exchanging the blood with a liquid such as DMSO that doesn't crystallize when cooled

Rapid re-heating is needed prior to transplantation, or the glassy DMSO can recrystallize and damage the tissue

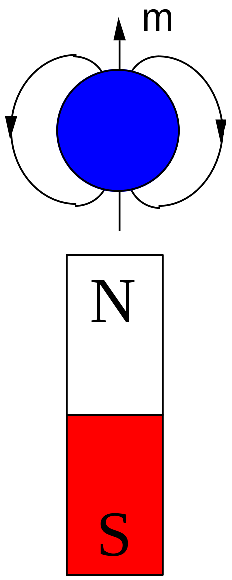


Beth Stadler and John Bischof, U. Minn., Oana Dragoa-Pinzaru, Iasi, Romania



Applications of Magnetic Nanoparticles

1. Intro and key nanoparticle properties
2. Magnetic manipulation
3. Magnetic sensing
4. Magnetic hyperthermia
5. Magnetic Particle Imaging (MPI)
6. Magnetic Resonance Imaging (MRI)

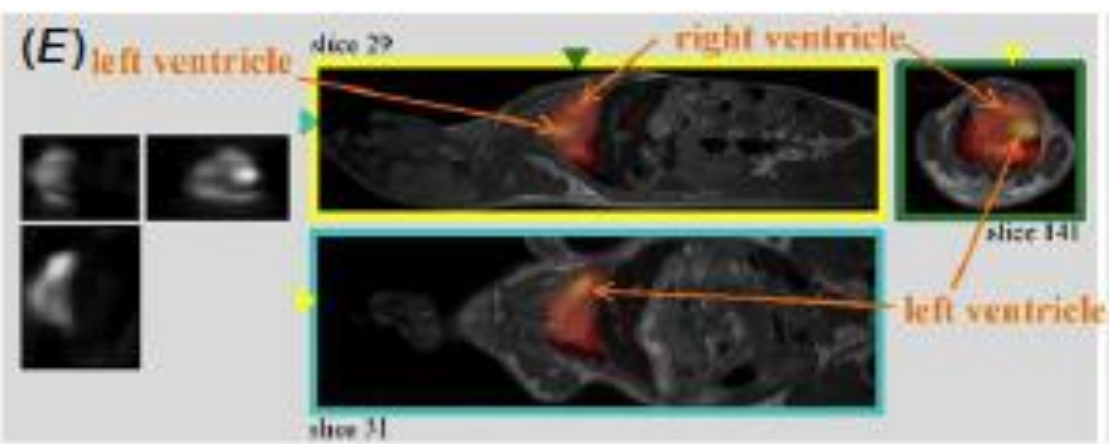


Magnetic Particle Imaging (MPI)

MRI – Detect protons (^{1}H) whose NMR frequency is perturbed by the field of a magnetic particle

MPI – Detect magnetic particles themselves

- 50 frames/s
- see particles *move* through mouse heart



B. Gleich, J. Weizenecker, Nature **435** 1214 (2005).

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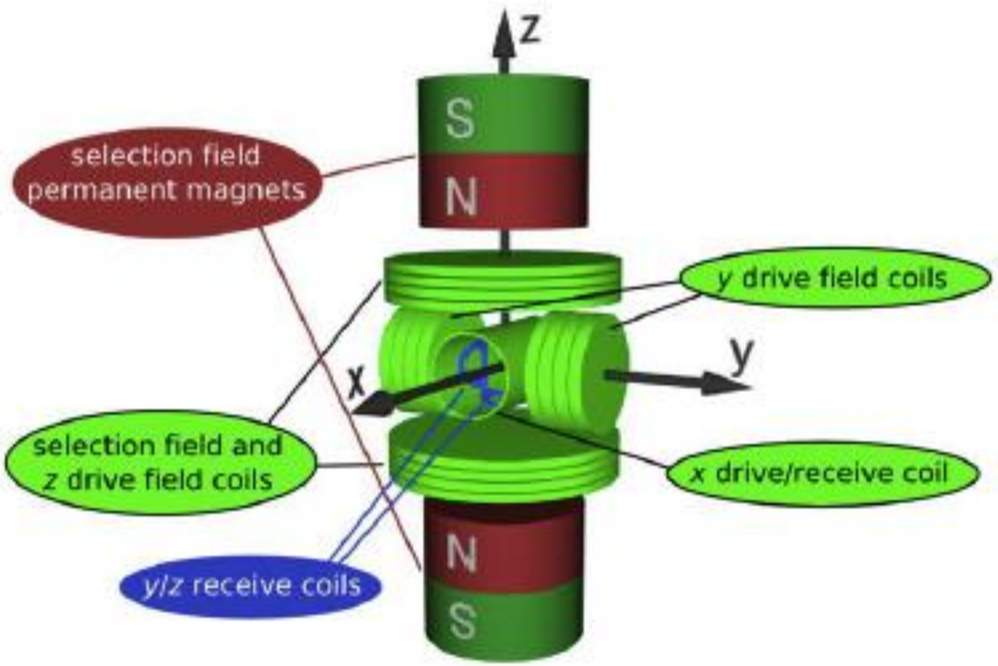


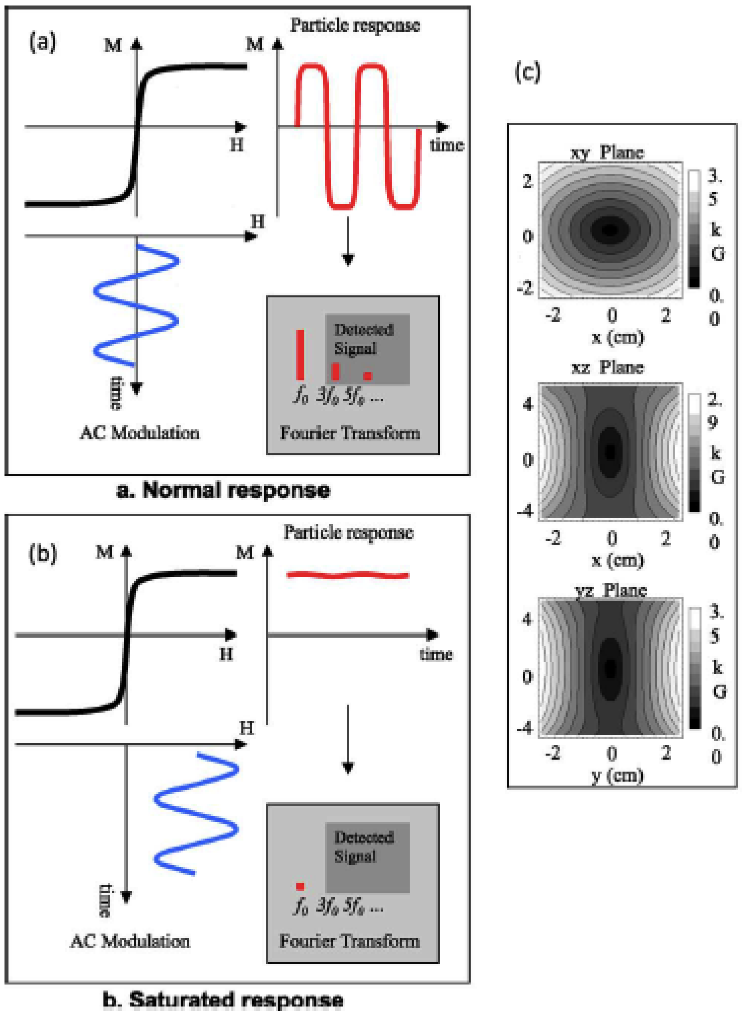
3 orthogonal DC fields determine Field Free Point (FFP)

Near H = 0, NPs have a nonlinear response

Apply high amplitude AC field, and response is dominated by NPs near the FFP

Scan FFP through sample and repeat to form 3D image

MPI – Nonlinear Response

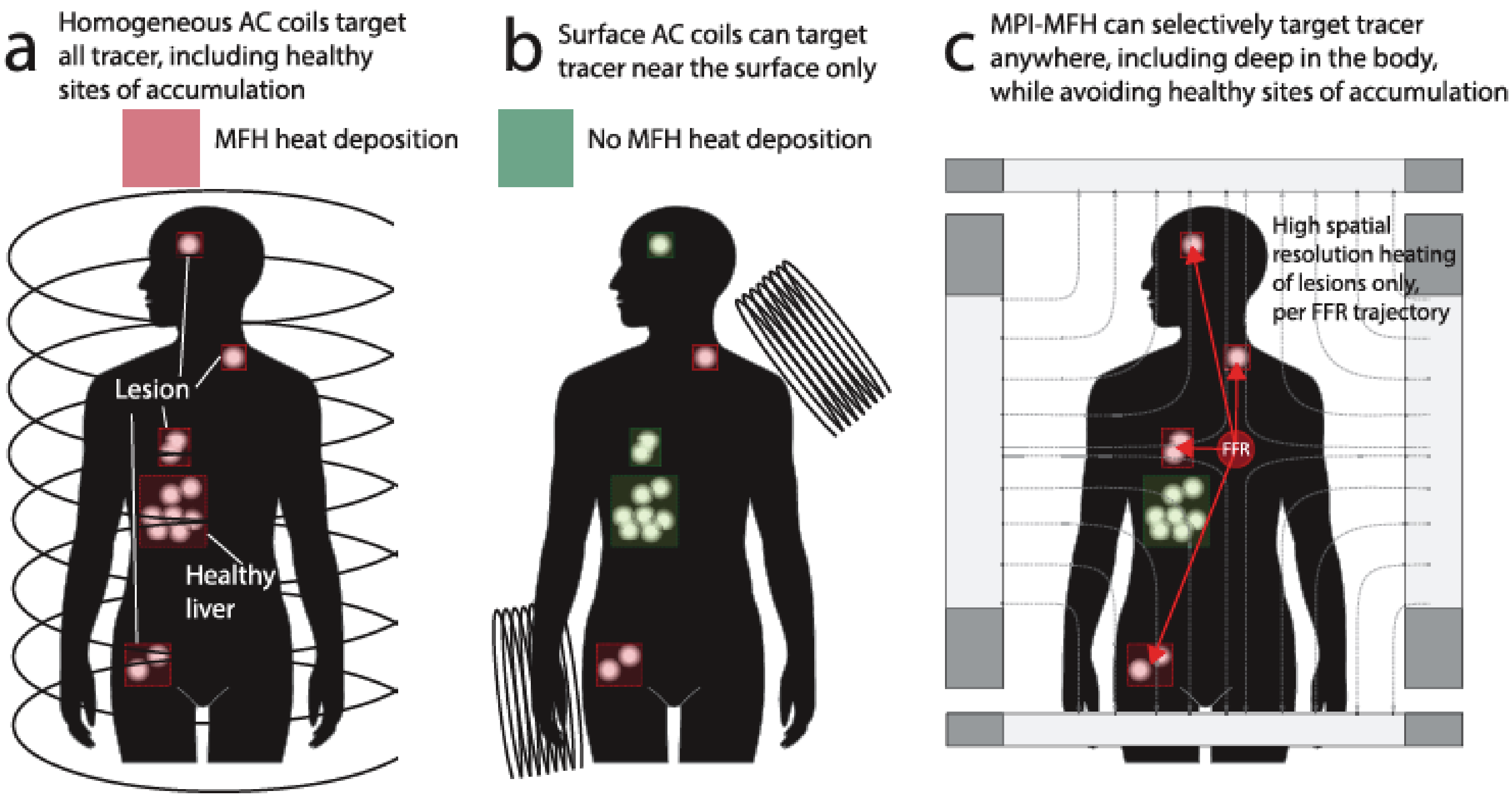


Excite with AC field about H = 0, FT has **high** amplitude in many harmonics

Excite about H near saturation, FT has **low** amplitude in many harmonics

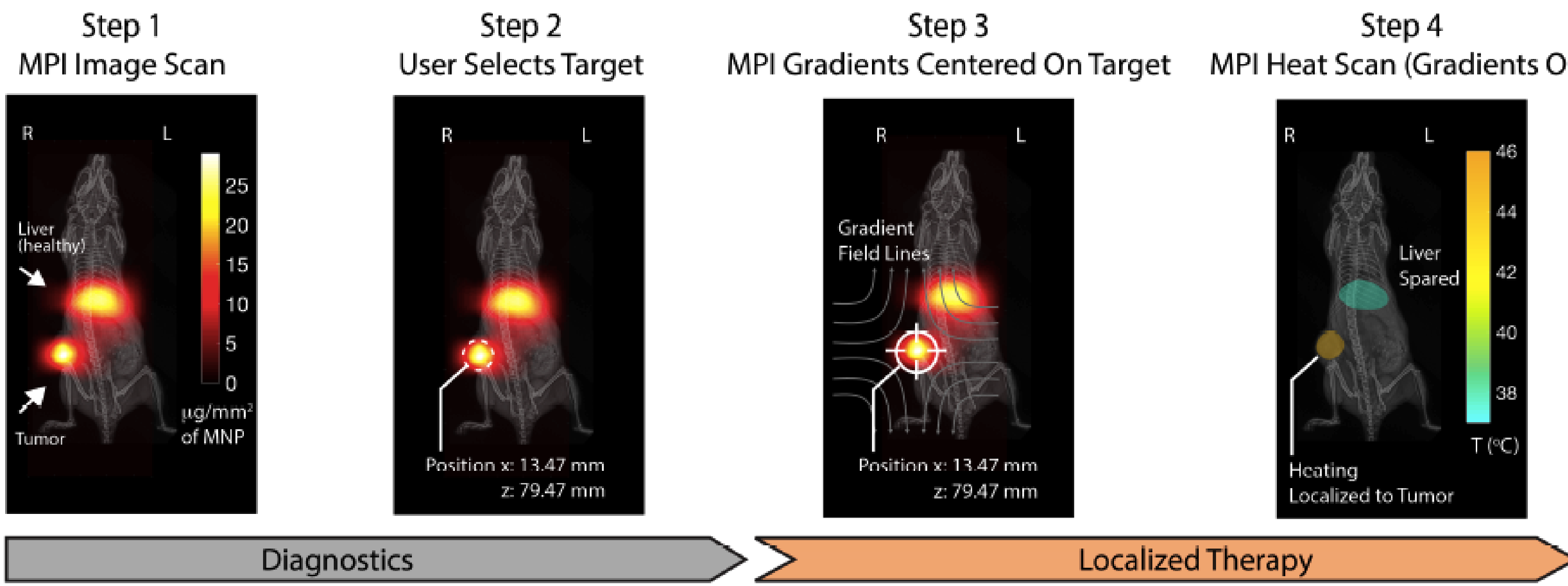
K. M. Krishnan, IEEE Trans. Magn. **46**, 2523 (2010)

Combining MPI and Hyperthermia for Deep Targeting



D. Hensley, et al., Phys. Med. Biol. **62**, 3483 (2017)

More MPI and Hyperthermia



Z. W. Tay, ACS Nano (2018), DOI: 10.1021/acsnano.8b00893

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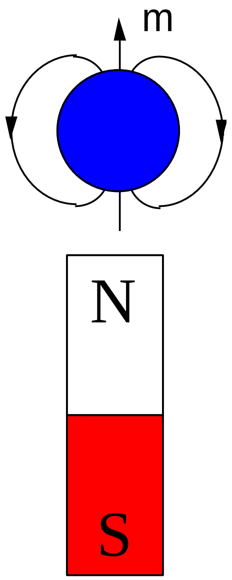
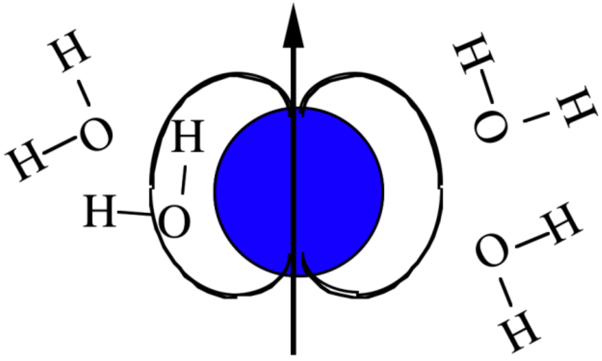


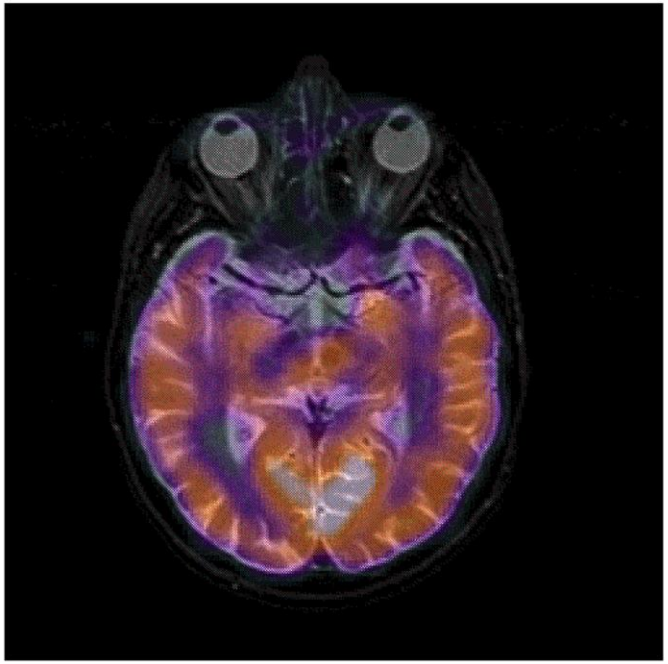
MRI CONTRAST AGENTS

Particle moment generates a Magnetic Field



- Magnetic particle fringe field changes relaxation rate of nuclear moments of hydrogen atoms (^{1}H) in nearby water molecules

- Remove water background for higher contrast



Magnetic resonance imaging (MRI)

^{1}H Nuclear Magnetic Resonance (Proton NMR)

• Very sensitive method for detecting hydrogen nuclei in different chemical (and magnetic) environments

• **Nuclear spins** act like paramagnets with high saturation field

- At DC field of 1.5 T, only *slight* imbalance
- ^{1}H magnetic field is very weak, so detect by dynamic measurements
- FMR typically in GHz range, ^{1}H NMR typically in MHz range

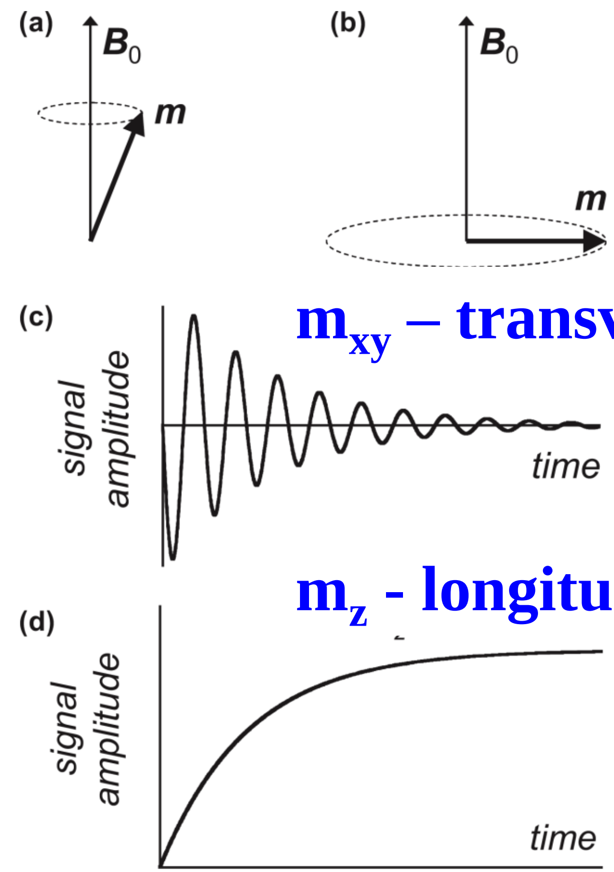
• Magnetic resonance imaging (MRI) = spatial mapping of NMR signal

Longitudinal and Transverse Relaxation

m precesses about a static field B_0

Apply rf field pulse to rotate by $\pi/2$

m precesses back to lie parallel to B_0



m_{xy} – transverse

m_z - longitudinal

Q. A. Pankhurst, et al., J. Phys. D **36**, R167 (2003)

Bloch-Bloembergen equations

$$\frac{\partial m_z}{\partial t} = -\gamma\left(\vec{m} \times \vec{B}\right)_z = \frac{m_s - m_z}{T_1}$$

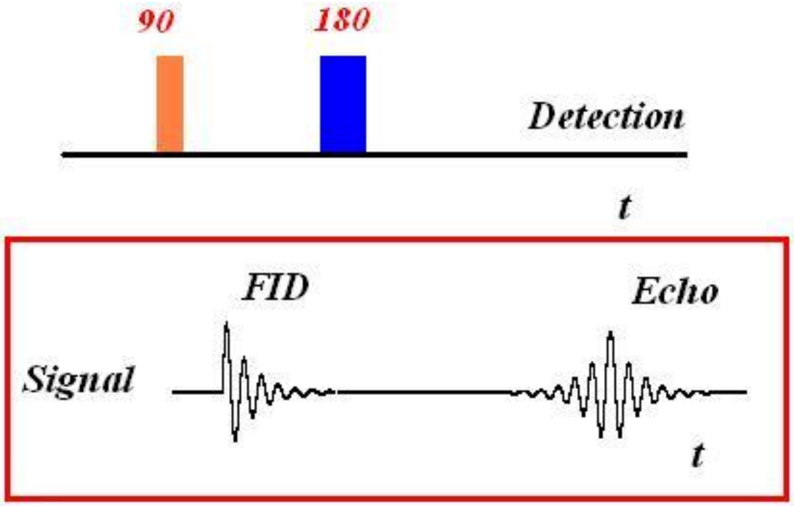
$$\frac{\partial m_{x,y}}{\partial t} = -\gamma\left(\vec{m} \times \vec{B}\right)_{x,y} = \frac{m_s - m_{x,y}}{T_2}$$

2 characteristic times, T_1 and T_2

Dephasing and T_2

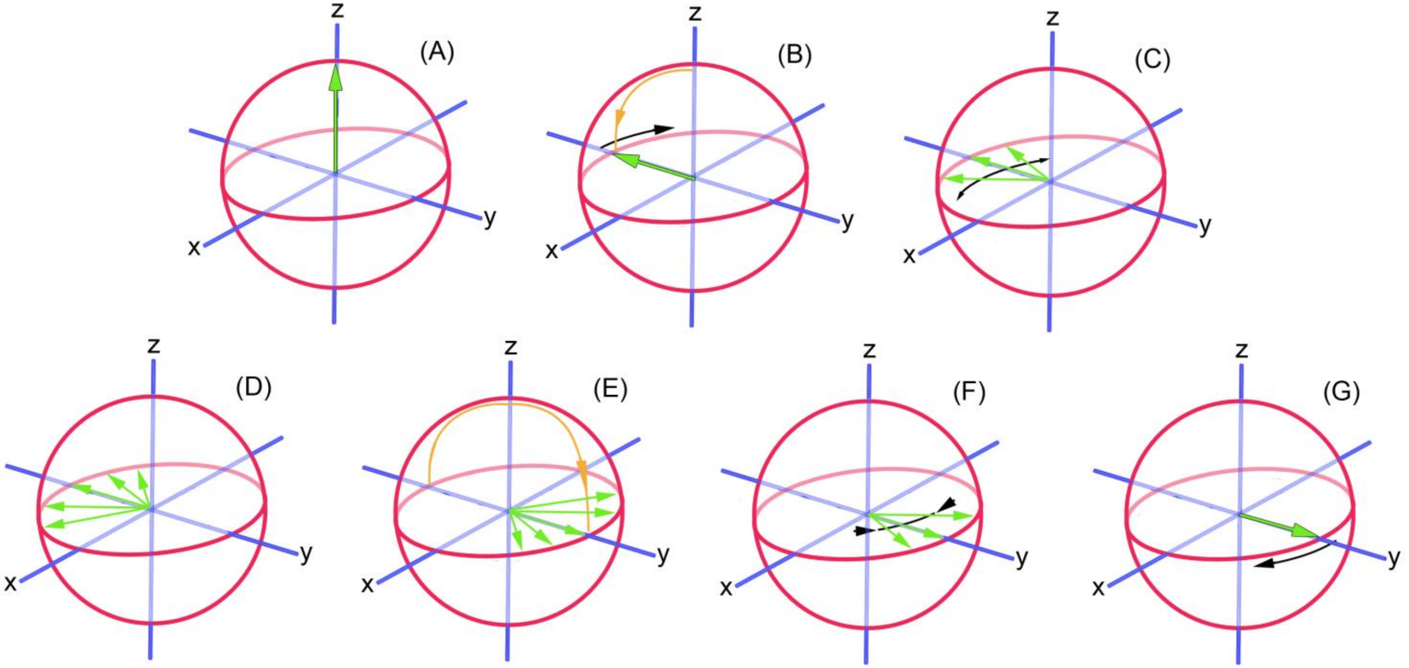
Spin Echo rf pulse sequence

$\pi/2$ rotation π rotation



$$\vec{B}_{tot} = \vec{B}_0 + \vec{B}_{rf} + \vec{B}_{local}$$

NPs change B_{local}, affect dephasing rate



$$w = gB_{eff}$$

T_1 and T_2 Relaxation

$$m_{x,y} \propto \exp(-t/T_2)$$

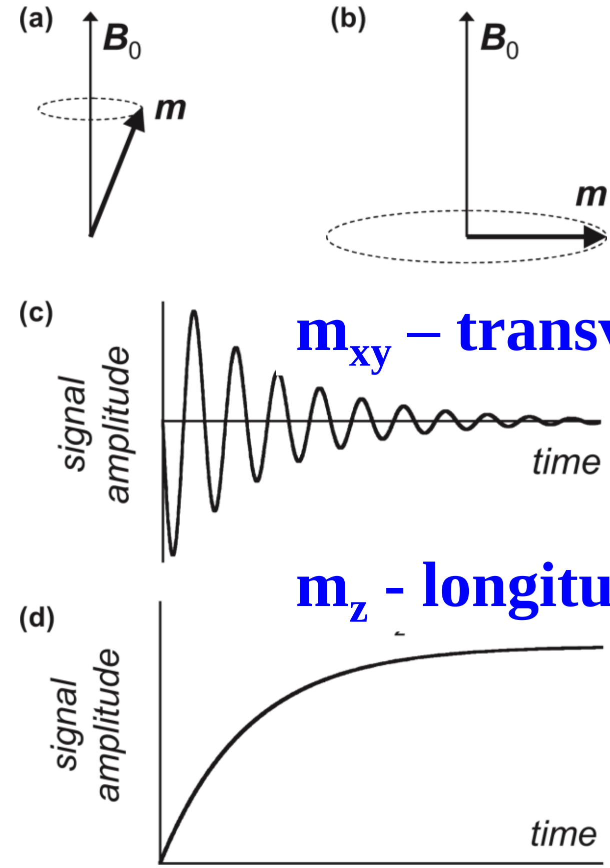
Decrease T_2 of water protons and signal decreases – **image gets darker**

- **Use iron oxide nanoparticles**

$$m_z \propto \left[1 - \exp(-t/T_1)\right]$$

Decrease T_1 of water protons and signal increases – **image gets brighter**

- **Use Gd^{3+}**DTPA



m_{xy} – transverse

m_z - longitudinal

Figure of Merit:

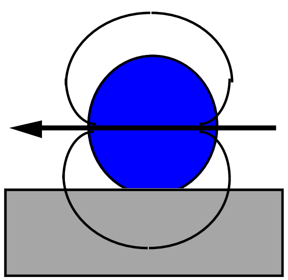
$$\omega = \gamma B_{eff}$$

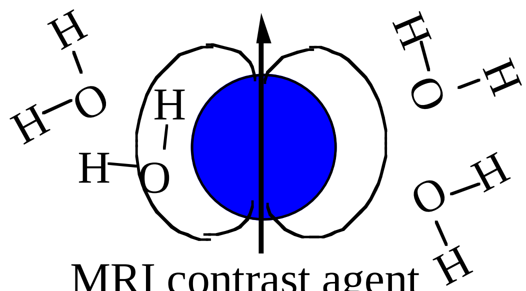
Relaxivity R_1 (or R_2)= change in T_1 (or T_2) per concentration of contrast agent

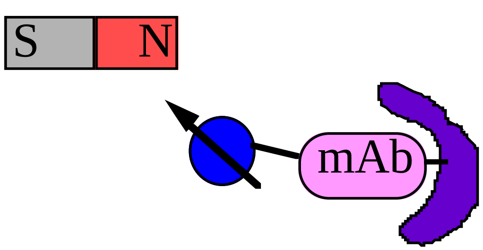
Summary

Most magnetic particle applications arise because they can generate magnetic fields, can move or change properties in response to a magnetic field, and can easily be bound to other things

Magneto-resistive Sensor







Specific Cell Type

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Kannan Krishnan – Univ. Washington
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JitKang Lim – U. Sains Malaysia
Beth Stadler – U. Minnesota