"BIOMEDICAL APPLICATIONS OF MAGNETIC NANOPARTICLES:

I: DRUG DELIVERY"

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II: ELECTROMAGNETIC RADIATION"

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ZARAGOZA (SPAIN)

http//:ina.unizar.es

OUTLINE OF THE TALK

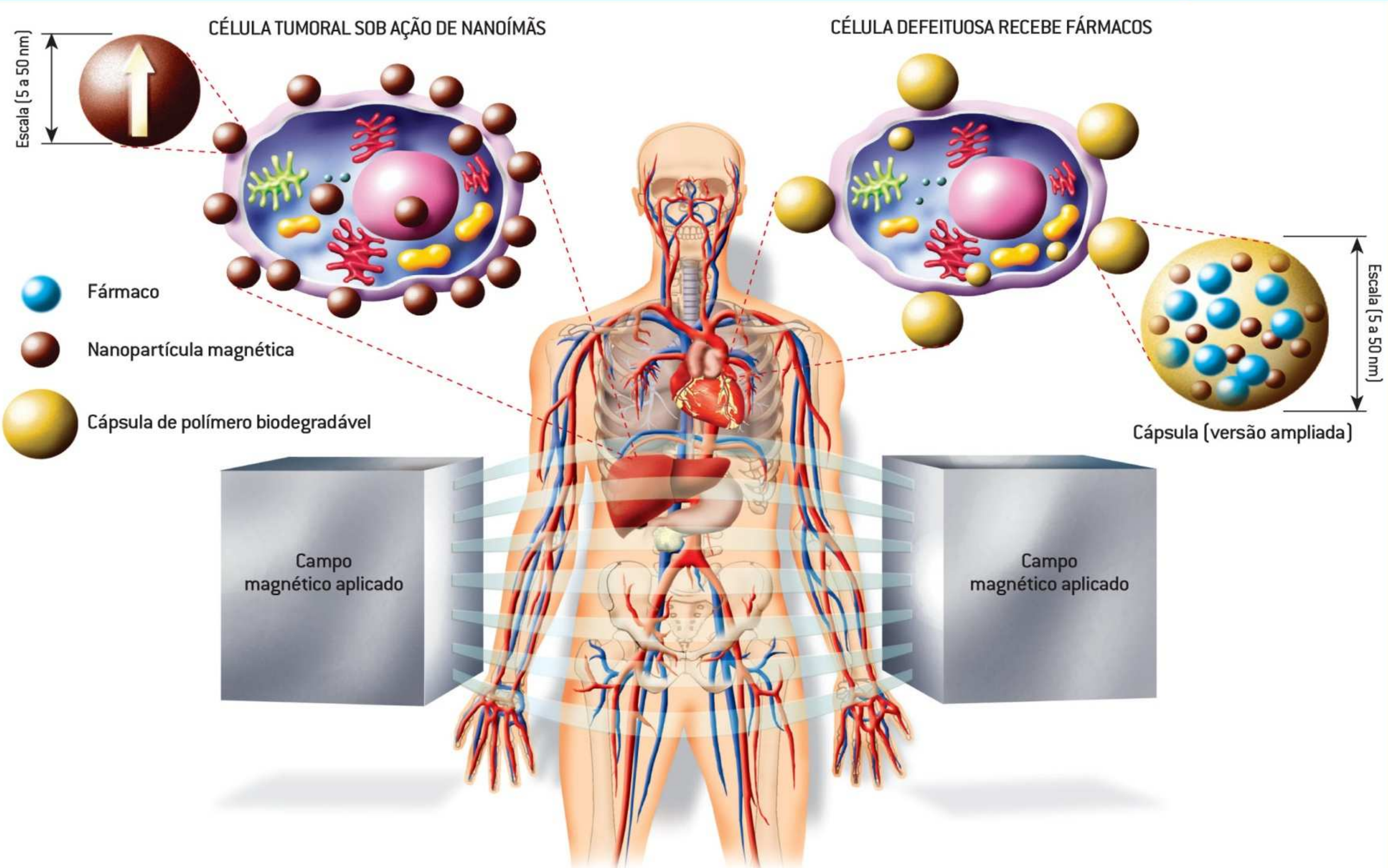
Biomedical applications of magnetic nanoparticles II: Electromagnetic radiation

-Introduction

-Therapy based in magnetic hiperthermia

-Diagnostic based in nuclear magnetic resonance effect: MRI

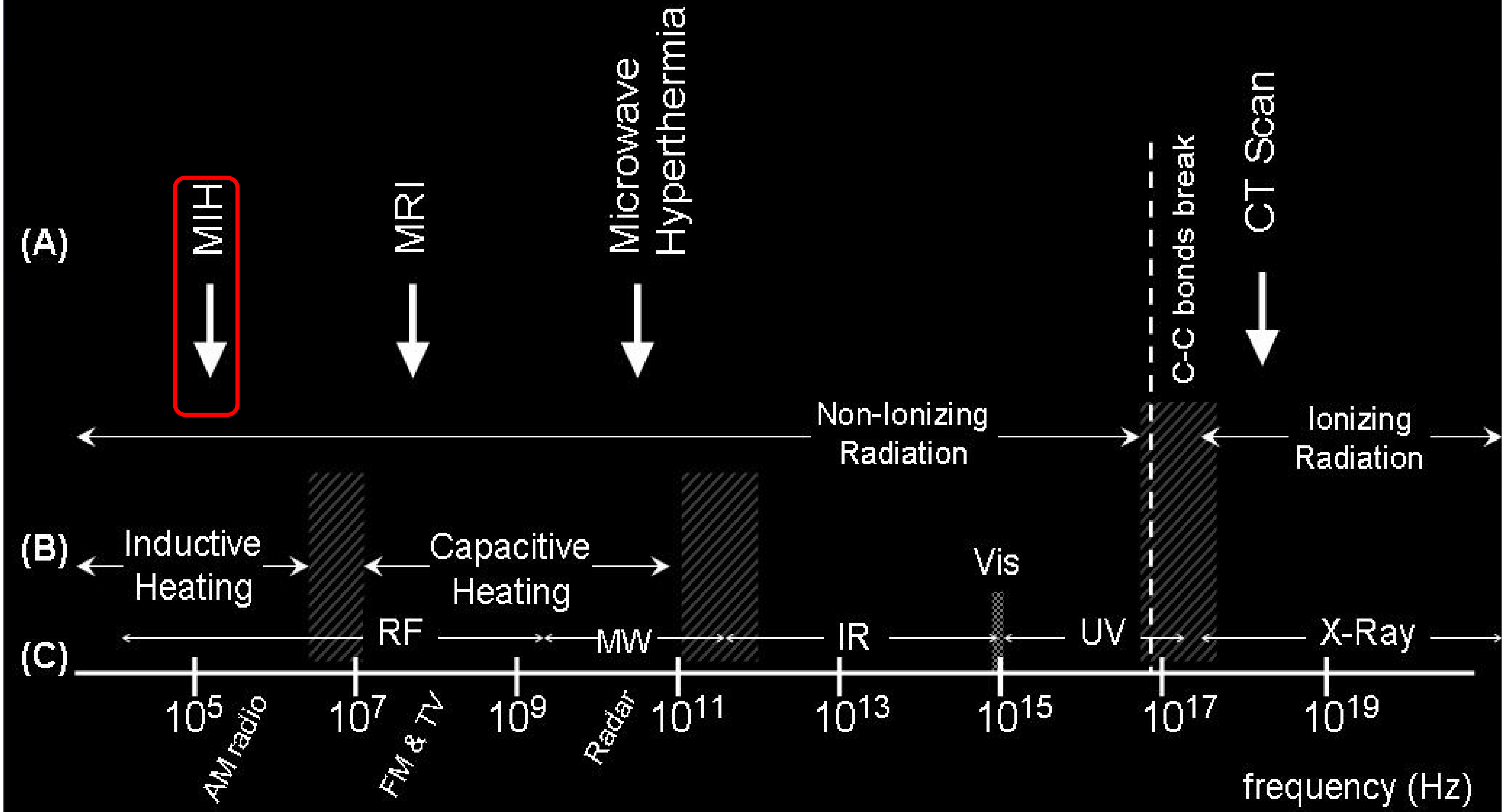
DUAS NANOESTRATÉGIAS CONTRA CÂNCER E OUTRAS DOENÇAS



Duas aplicações terapêuticas possíveis dos nanoímãs. Carregados pelo corpo com a ajuda de um campo magnético, eles poderiam ser levados até células cancerosas e agitados por alternações sucessivas do campo. O processo geraria calor e mataria as células doentes *(no alto, à esquerda)*. Em outro cenário, eles seriam agregados a um pacote que contém um fármaco e uma capa de polímero biodegradável. O campo magnético serviria para carregá-los até as células doentes, às quais entregariam o remédio com menor chance de erro *(no alto, à direita)*

Marcelo Knobel y Gerardo F. Goya , Scientific American. 31, DIC. 2004

Electromagnetic Spectrum



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Biomedical applications of magnetic nanoparticles II: Electromagnetic radiation

-Introduction

-Therapy based in magnetic hiperthermia

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What is hyperthermia?

Hyperthermia (thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to **45 ℃**). Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. By killing cancer cells and damaging proteins and structures within cells, hyperthermia may shrink tumors.

National Cancer Institute, USA

Core loss formulation

- Loss separation

  The formulation is the same for an alternating and rotating field

$$P_{core} = P_{hysteresis} + P_{eddy}$$

- Hysteresis loss

  Rate of change of energy used to affect magnetic domain wall motion

- Eddy-current loss (classical eddy currents)

  Due to induced currents flowing in closed paths within magnetic material

Losses in Colloids

1. In NPs suspensions (@ RT), the Brownian relaxation in viscous media is

$$\boxed{\tau_B = \frac{3\,\eta\,V_H}{k_B T}}$$

2. Néel relaxation is

$$\boxed{\tau_N = \tau_0 \exp\left(\frac{K\,V_M}{k_B T}\right)}$$

So the total (parallel) relaxation is

$$\boxed{\frac{1}{\tau} = \frac{1}{\tau_B} + \frac{1}{\tau_N}}$$

R.E. Rosensweig, **JMMM** **252** *(2002) 370.*

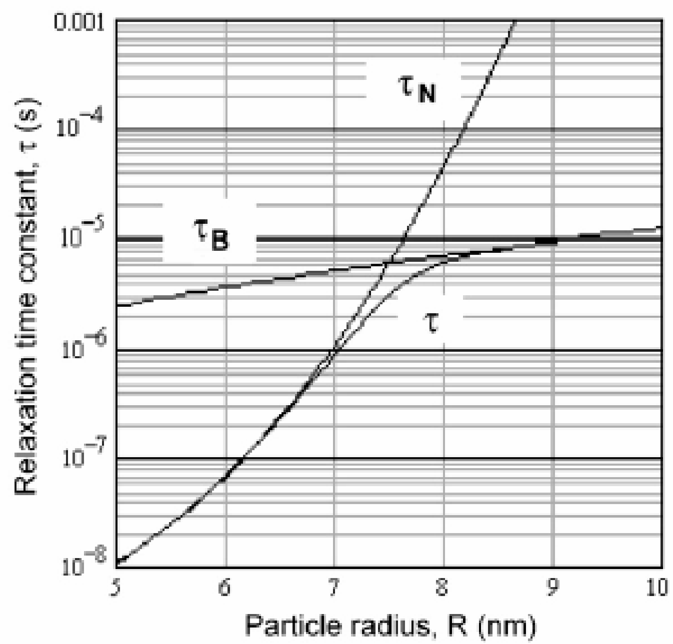


Fig. 2. Time constants vs. particle size for magnetite particles.

Heat Transfer

The "Bio-Heat Equation"

$$\rho_t \cdot c_t \cdot \frac{\partial T}{\partial t} = k_t \cdot \nabla T$$

ρ_t = tissue density
c_t = tissue specific heat capacity
k_t = thermal conductivity,

But living systems generates and dissipate heat by themselves, and these contributions lead to the "Pennes formulation" of the conventional "bio-heat equation":

Heat Transfer

Pennes' equation estimates the temperature field T(x,y,z,t) at nearby tissues

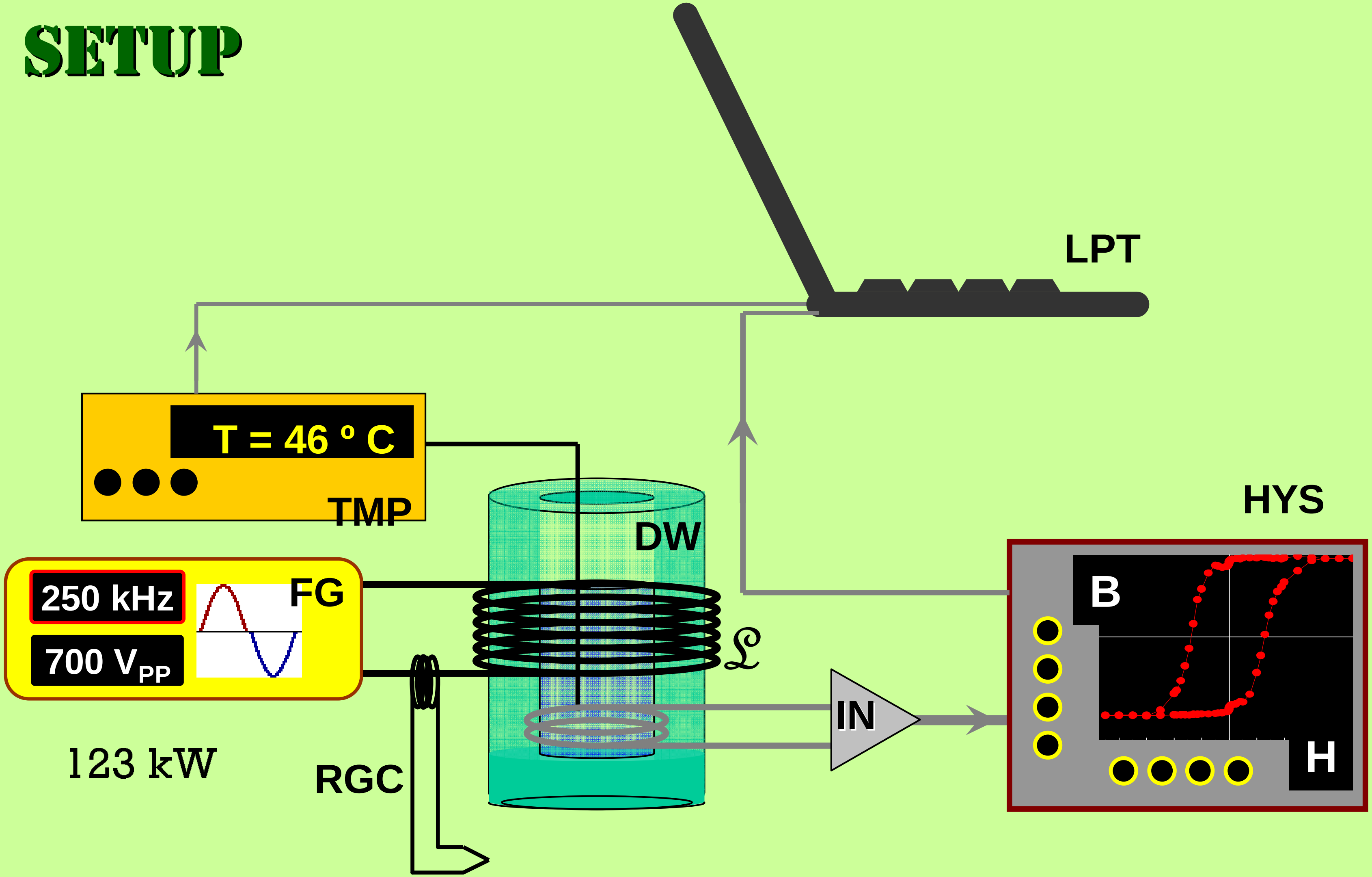
$$\frac{\partial T}{\partial t} = \frac{1}{\rho_t\, c_t}\left\{k_t \nabla^2 T - w_b c_b (T - T_a) + Q\right\}$$

ρ_t = tissue density
C_t = tissue specific heat capacity
Q = density of heat production rate,
T_a = temperature at infinite distances
w_b, = perfusion rate
c_b = blood specific heat capacity

It relates to the functional definition of Specific Absorption Rate (SAR): amount of energy converted in energy per time and mass

$$SAR = \frac{C_S}{m_{Fe}}\left(m_{FF}\frac{\Delta T}{\Delta t}\right) = \frac{Q}{\rho_t}$$

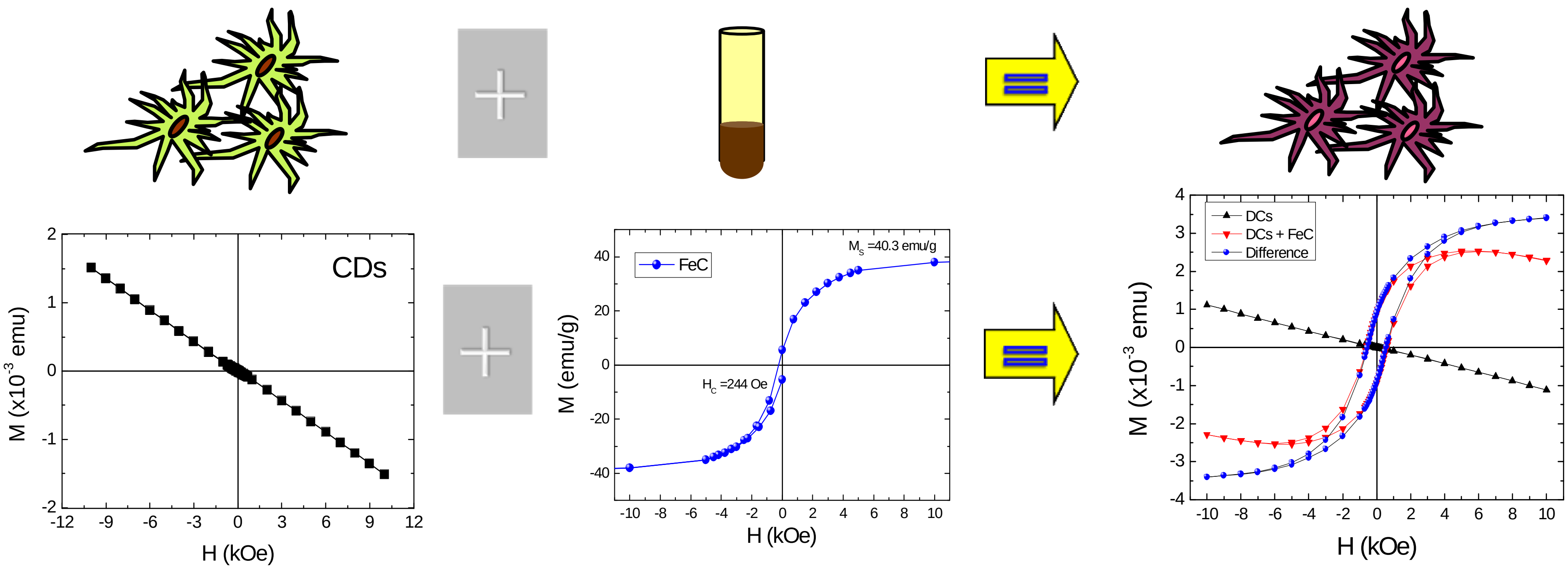
SETUP



G. F. Goya, V. Grazú and M.R. Ibarra, *Current Nanoscience, 2007.*

MAGNETIC CELLS

DENDRITIC CELLS **FE_3O_4 COLLOID** **NPS UPTAKE**



G.F. Goya et al. J.Exp.Med, submitted

Before

After

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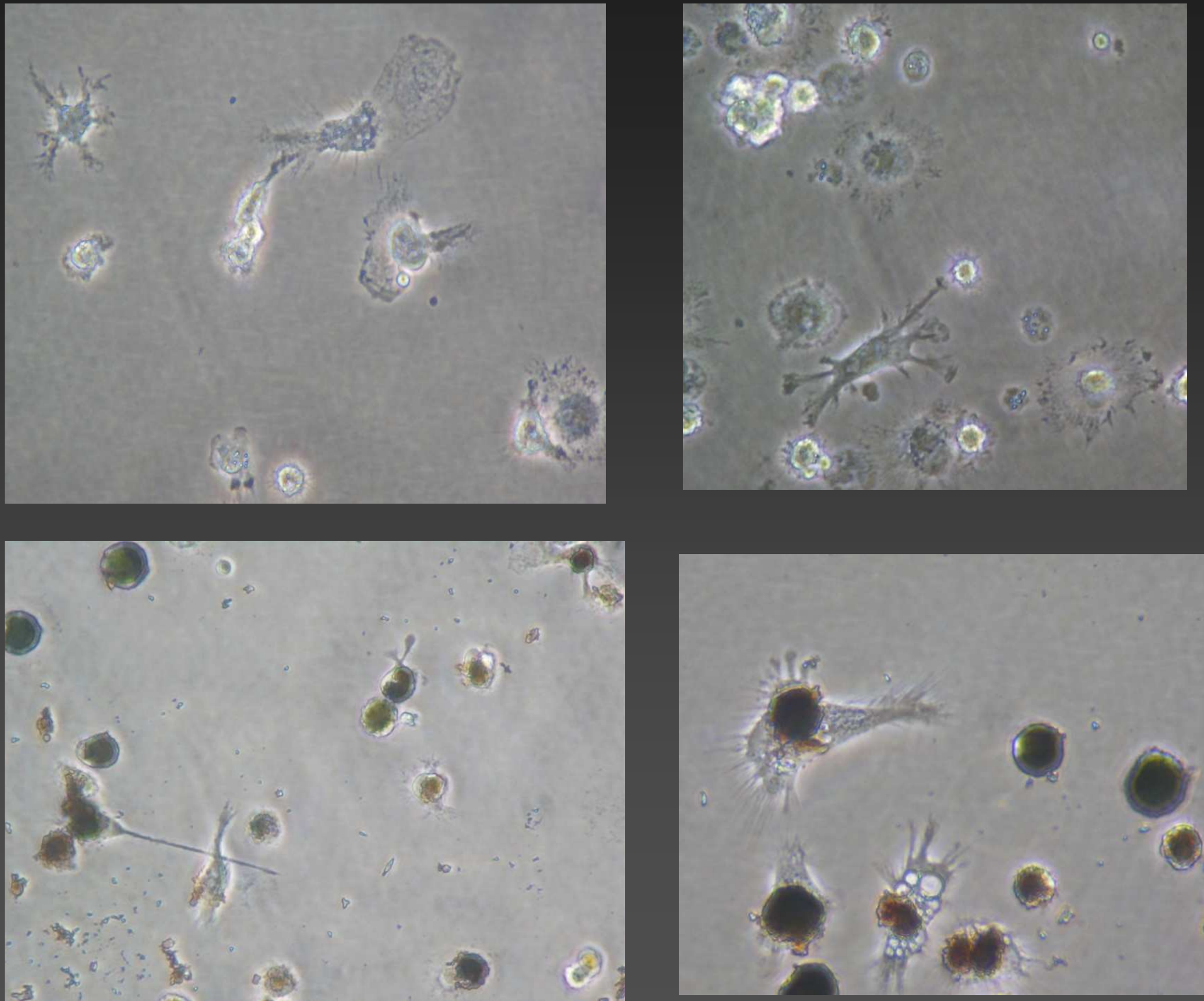

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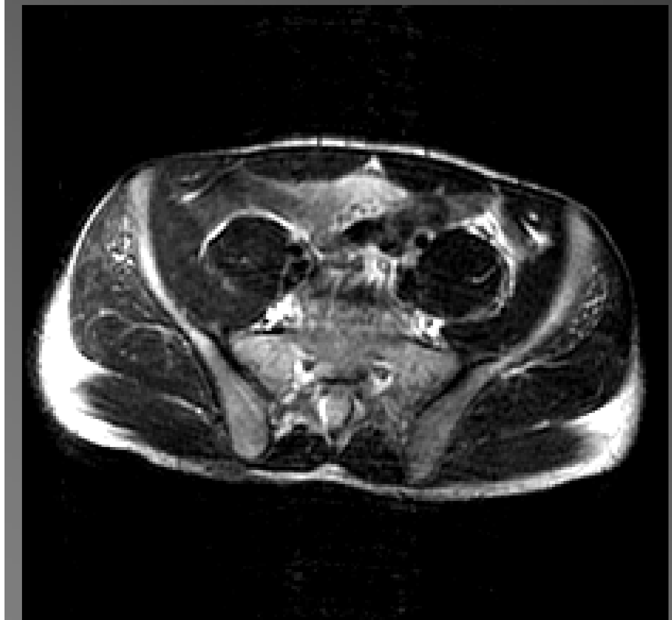
Magnetic Resonance Imaging

- Non-invasive medical imaging method, like ultrasound and X-ray.
- Clinically used in a wide variety of specialties.



Abdomen

Spine

Heart / Coronary

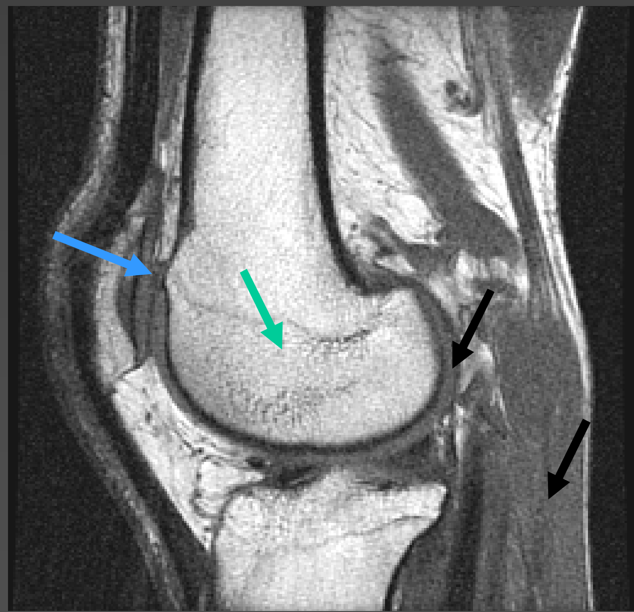
Magnetic Resonance Imaging

Advantages:

- Excellent / flexible contrast
- Non-invasive
- No ionizing radiation
- Arbitrary scan plane

Challenges:

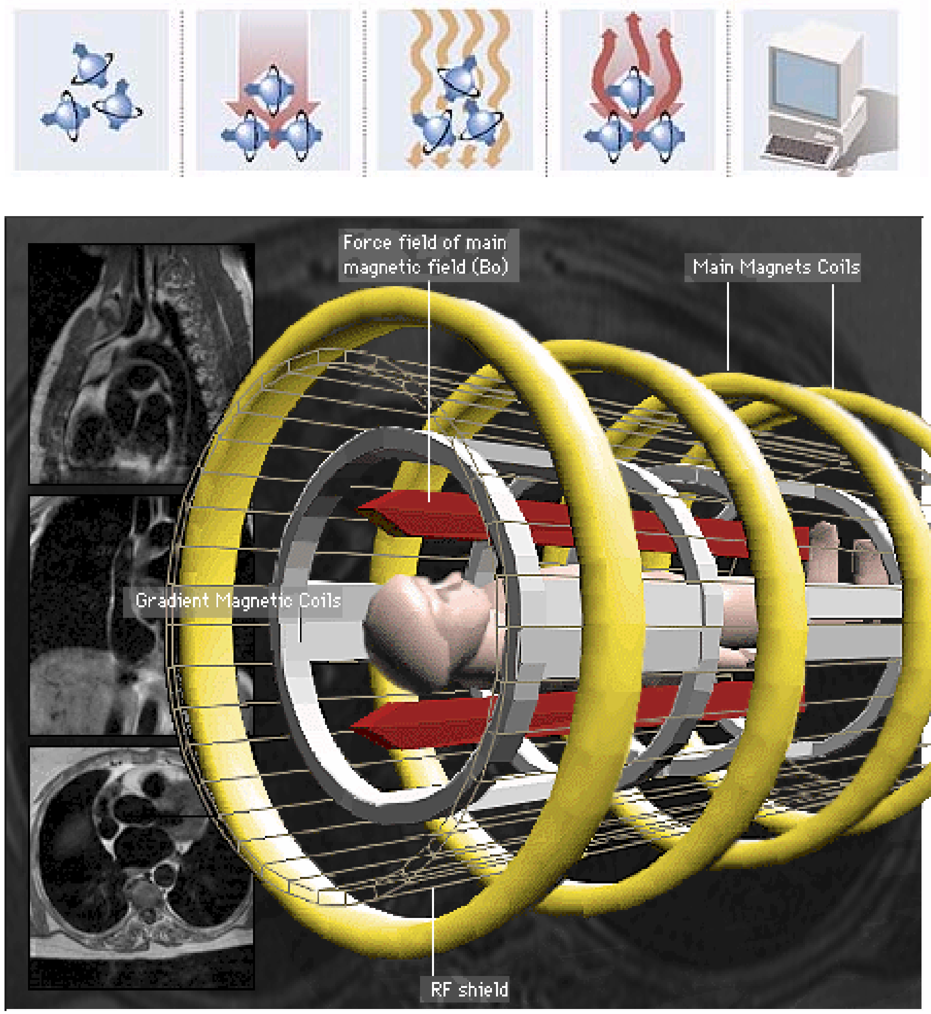
- New contrast mechanisms
- Faster imaging



MRI Systems

At $2 million, the most expensive equipment in the hospital…

Magnetic Resonance Imaging (MRI)



Artwork courtesy of Rebecca Cagle, National Library of Medicine-Lister Hill Center for Biocommunication

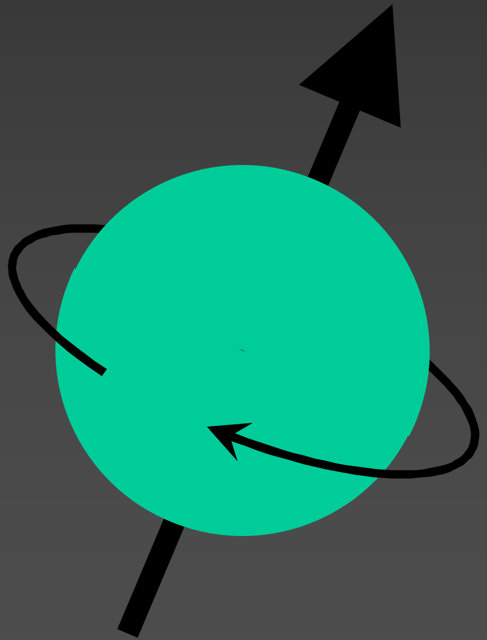
-Based on the magnetic relaxation of hydrogen water protons in tissues

-Resonance phenomena have different relaxation time depending of the active tissue under a radiofrequency signal. The radiation emited due to the relaxation can be detected and espatially localized within the body giving rise to contrast imaging

-The constrast is enhanced by paramagnetic or superparamagnetic nanovectors

Magnetic Resonance

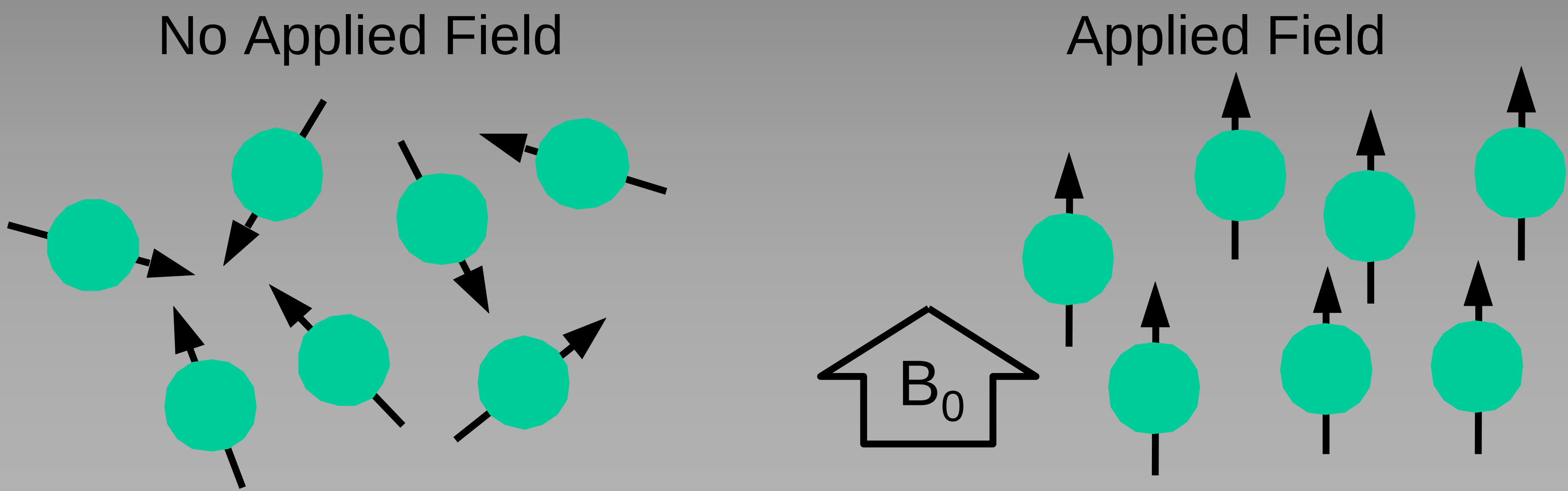
- Certain atomic nuclei including ^1H exhibit nuclear magnetic resonance.
- Nuclear “spins” are like magnetic dipoles.



^1H

Polarization

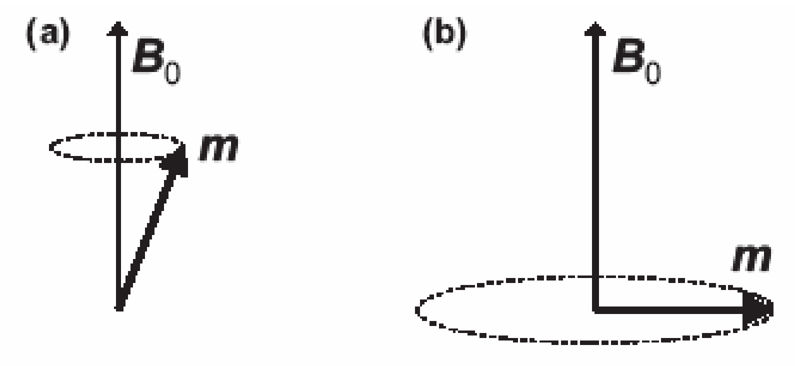
- Spins are normally oriented randomly.
- In an applied magnetic field, the spins align with the applied field in their equilibrium state.
- Excess along B_0 results in net magnetization.

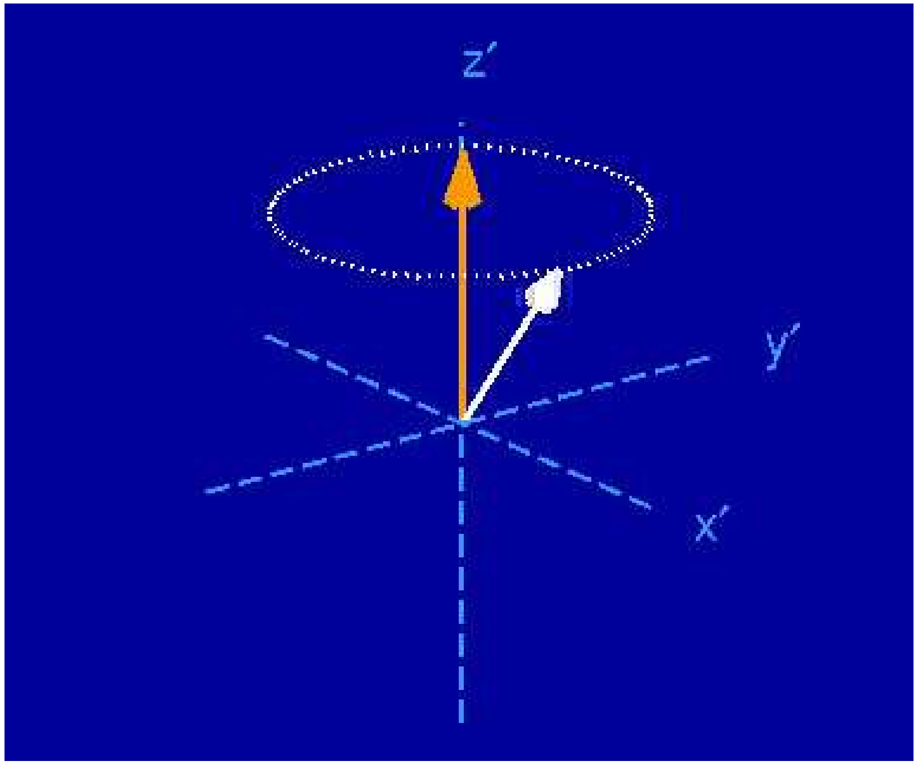


Precession

- Spins precess about applied magnetic field, B_0, that is along z axis.
- The frequency of this precession is proportional to the applied field:

$$\omega = \gamma B$$

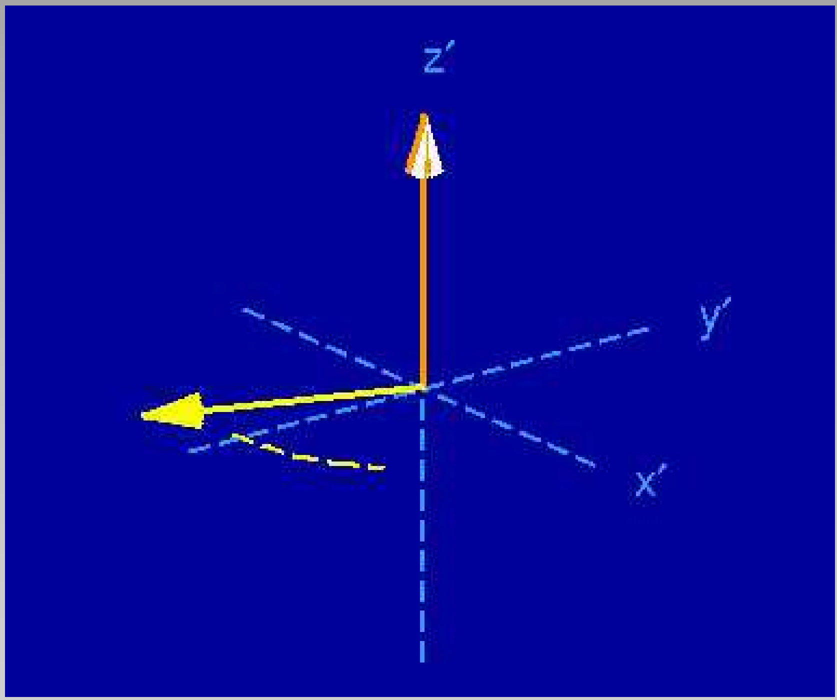


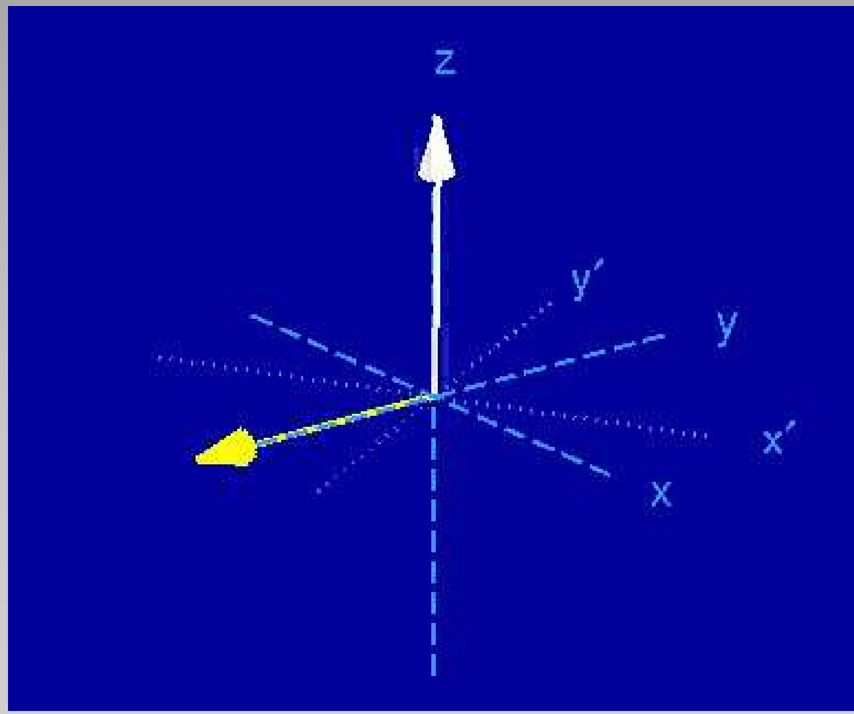


Excitation

- "Excite" spins out of their equilibrium state.
- Transverse RF field (B_1) rotates at γB_0 about z-axis.

B_1 B_0 Magnetization





Rotating Frame

RELAXATION

(Pankhurst et al. J. Phys. D: Appl. Phys 36 (2003) R167)

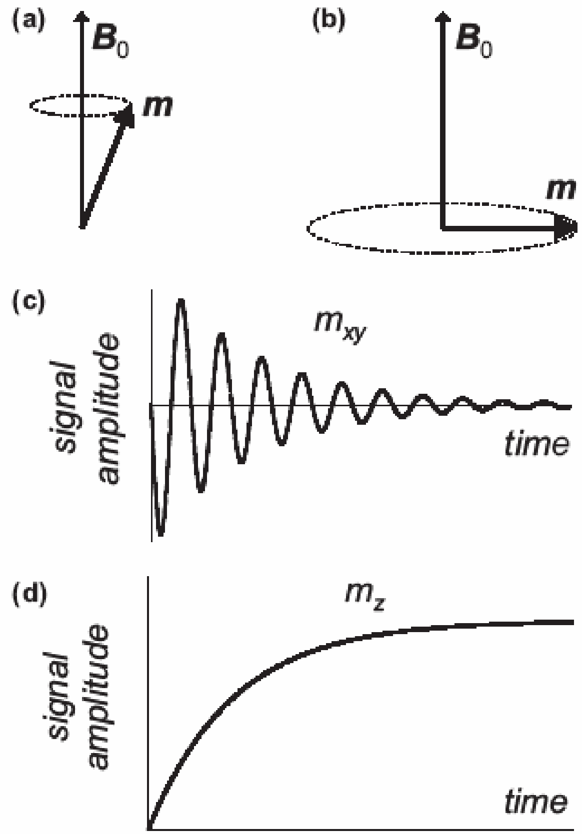


Figure 8. Illustration of magnetic resonance for a large ensemble of protons with net magnetic moment $\boldsymbol{m}$ in the presence of a external magnetic field $\boldsymbol{B}_0$. In (*a*) the net moment precesses around $\boldsymbol{B}_0$ at the characteristic Larmor frequency, ω_0. In (*b*) a second external field is applied, perpendicular to $\boldsymbol{B}_0$, oscillating at ω_0. Despite being much weaker than $\boldsymbol{B}_0$, this has the effect of resonantly exciting the moment precession into the plane perpendicular to $\boldsymbol{B}_0$. In (*c*) and (*d*) the oscillating field is removed at time zero, and the in-plane (*c*) and longitudinal (*d*) moment amplitudes relax back to their initial values.

$$m_z = m(1 - \mathrm{e}^{-t/T_1})$$

$$m_{x,y} = m\sin(\omega_0 t + \phi)\mathrm{e}^{-t/T_2}$$

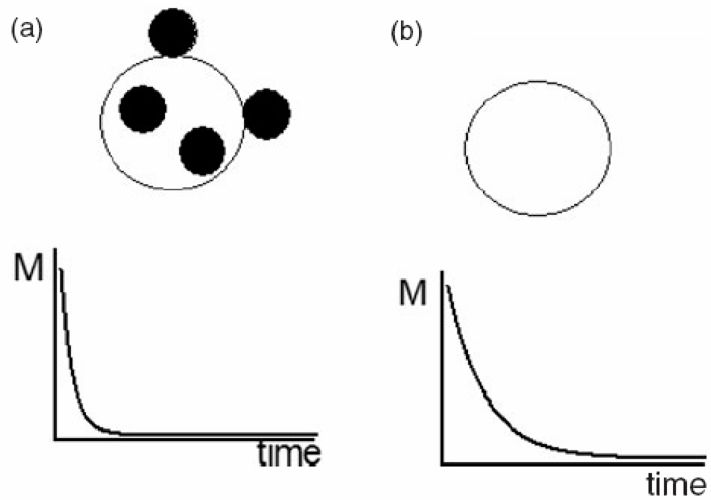
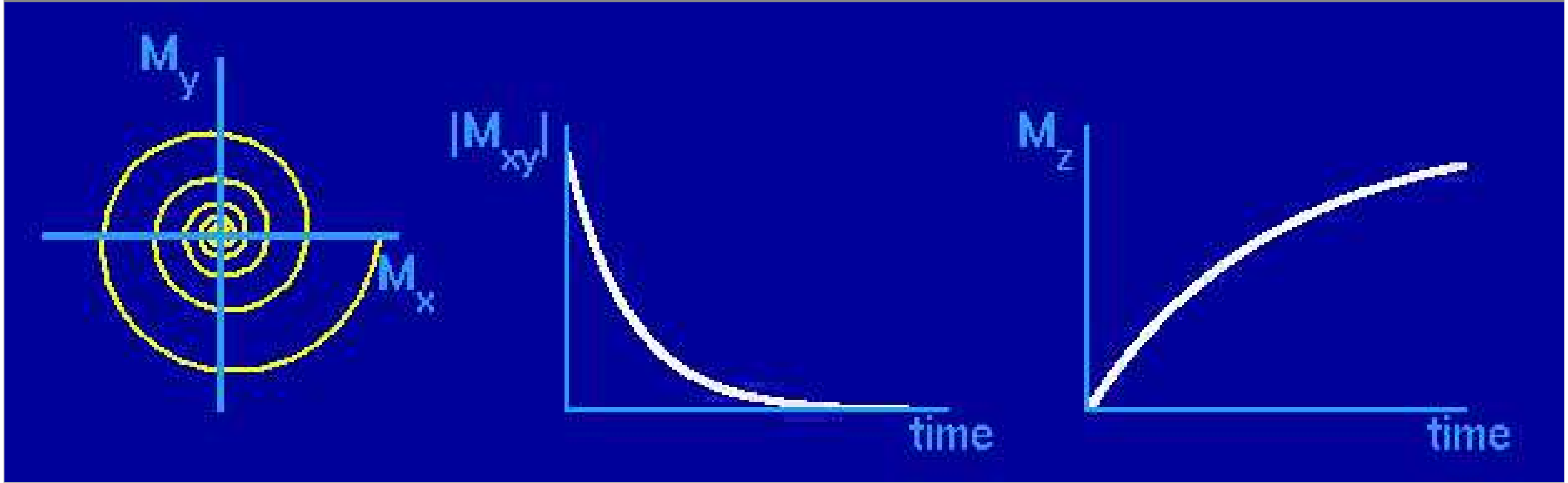


Figure 9. Effect of magnetic particle internalization in cells on T_2^* relaxation times: (*a*) the protons in cells tagged by magnetic particles have a shorter T_2^* relaxation time than those in (*b*) untagged cells.

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \gamma\frac{\Delta B_0}{2},$$

Relaxation

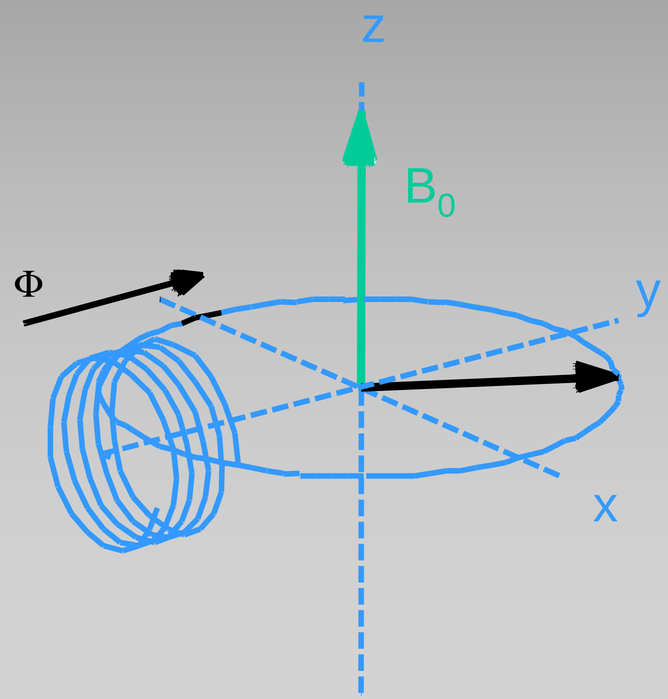
- Magnetization returns exponentially to equilibrium:
  - Longitudinal *recovery* time constant is T_1 (spin-lattice)
  - Transverse *decay* time constant is T_2 (spin-spin)
- Relaxation and precession are independent.



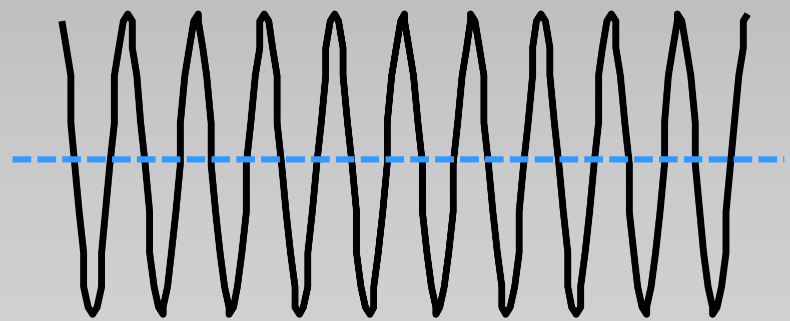
Precession Decay Recovery

Signal Reception

- Precessing spins cause a change in flux (Φ) in a transverse receive coil.
- Flux change induces a voltage across the coil.

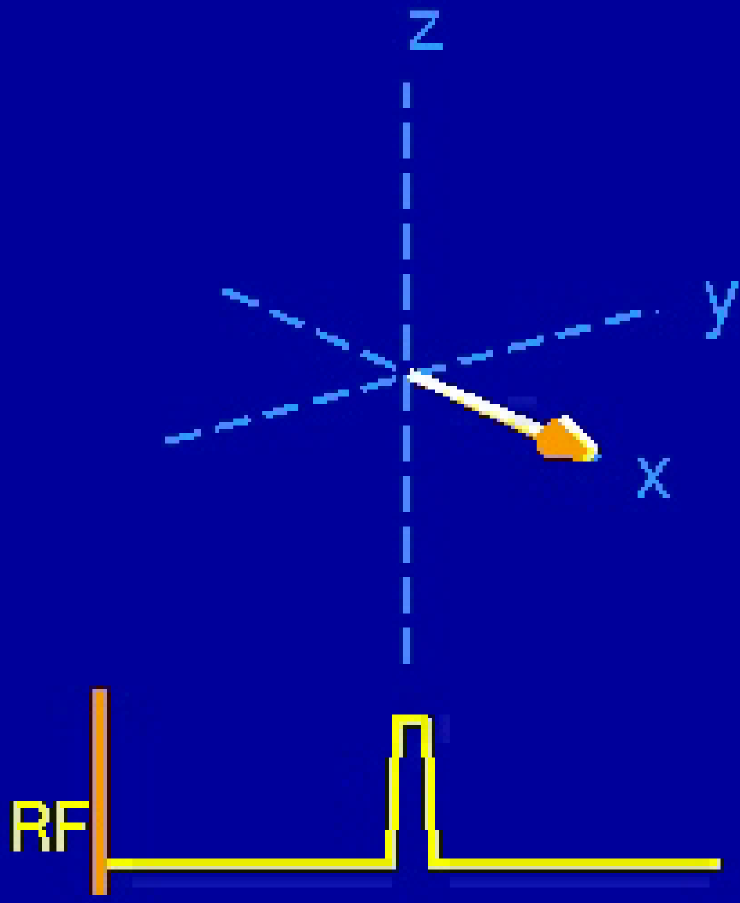


Signal



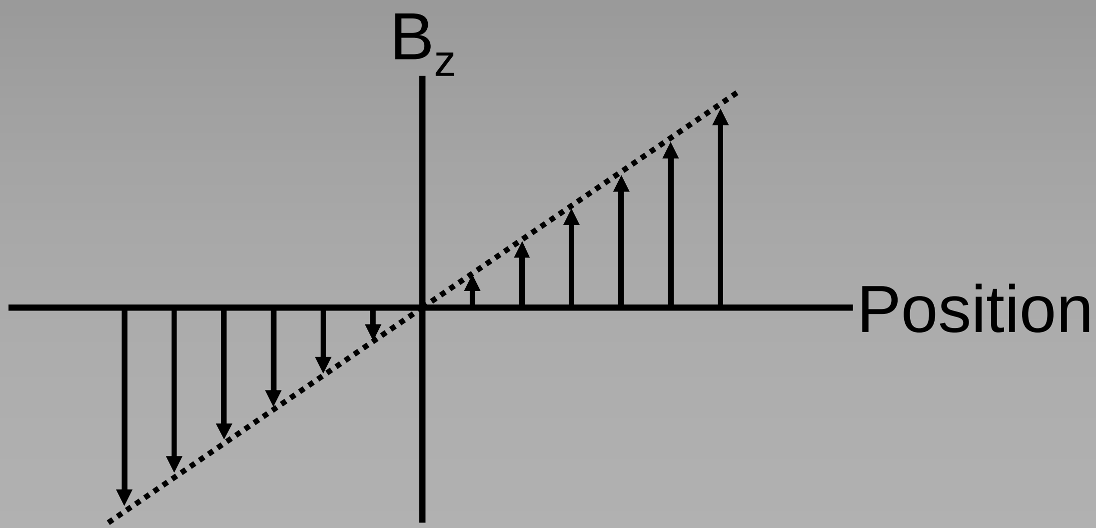
Spin Echoes

- 180° RF tip can reverse the dephasing effects of off-resonance.
- Spins realign at some time to form a *spin echo*

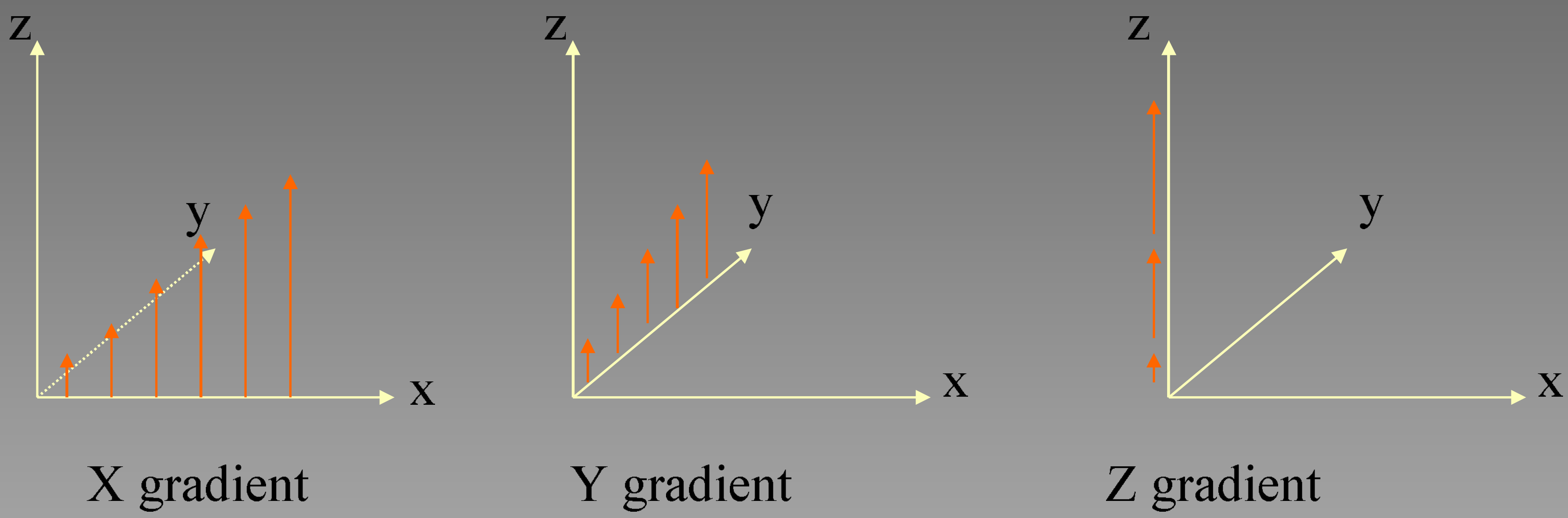


MR Image Formation

- Gradient coils provide a linear variation in B_z with position.
- Result is a resonant frequency variation with position.



Gradient Coils



Gradient coils generate spatially varying magnetic field so that spins at different location precess at frequencies unique to their location, allowing us to reconstruct 2D or 3D images.

Selective Excitation

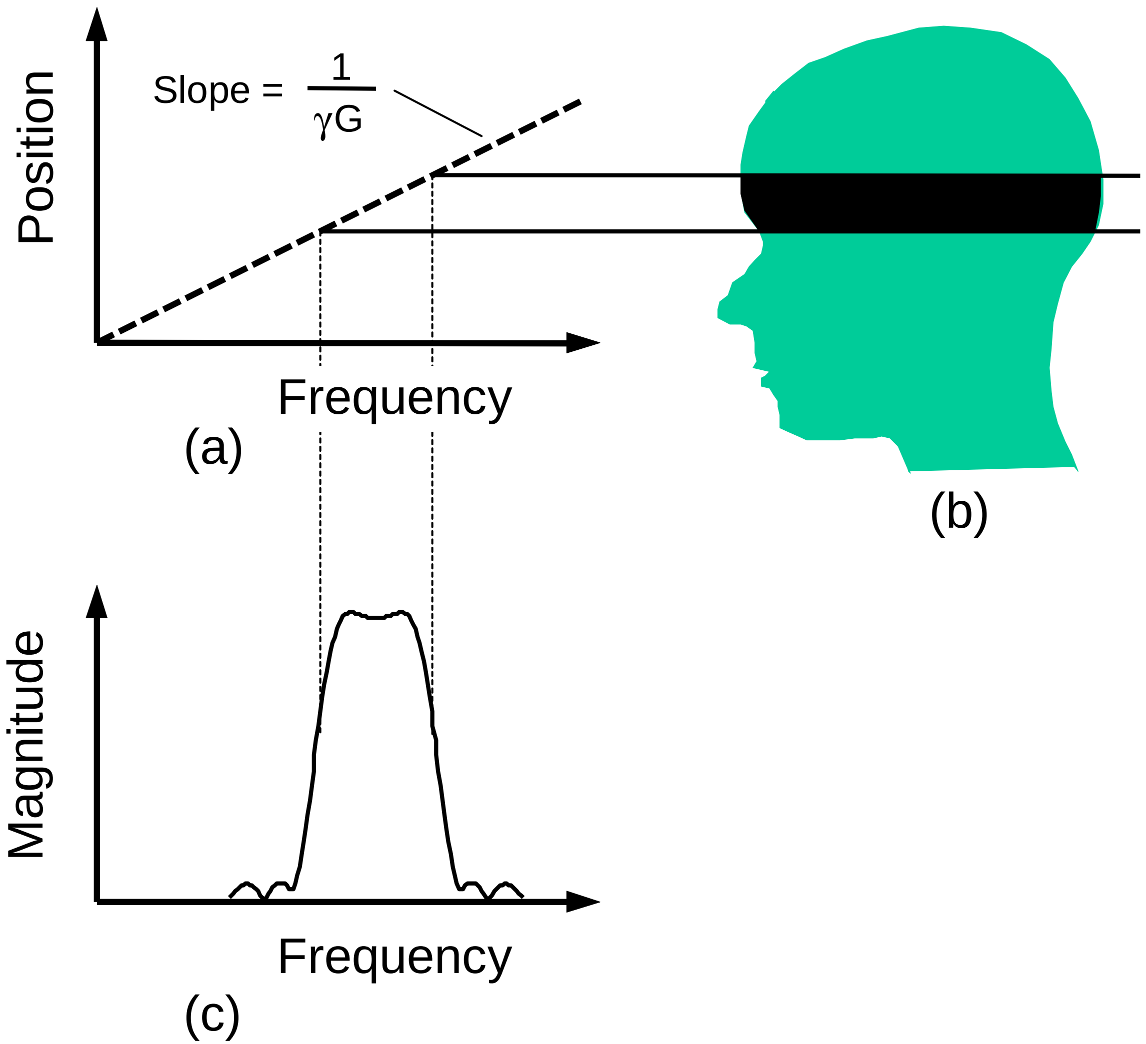
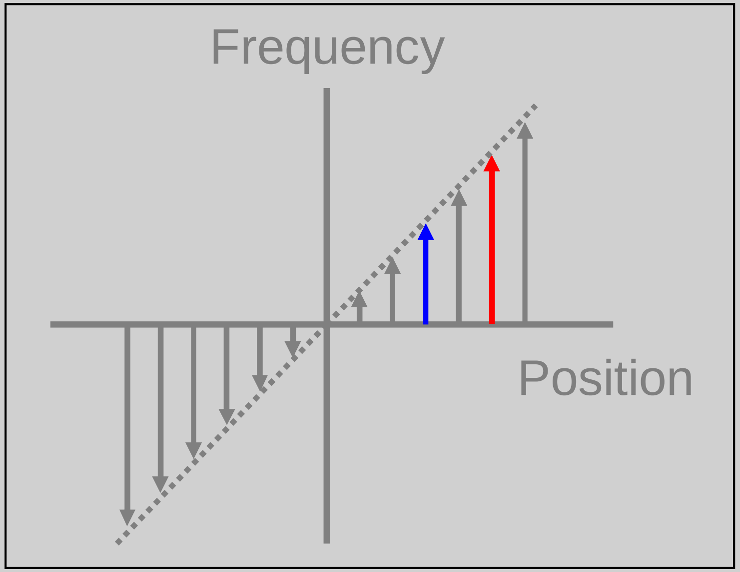
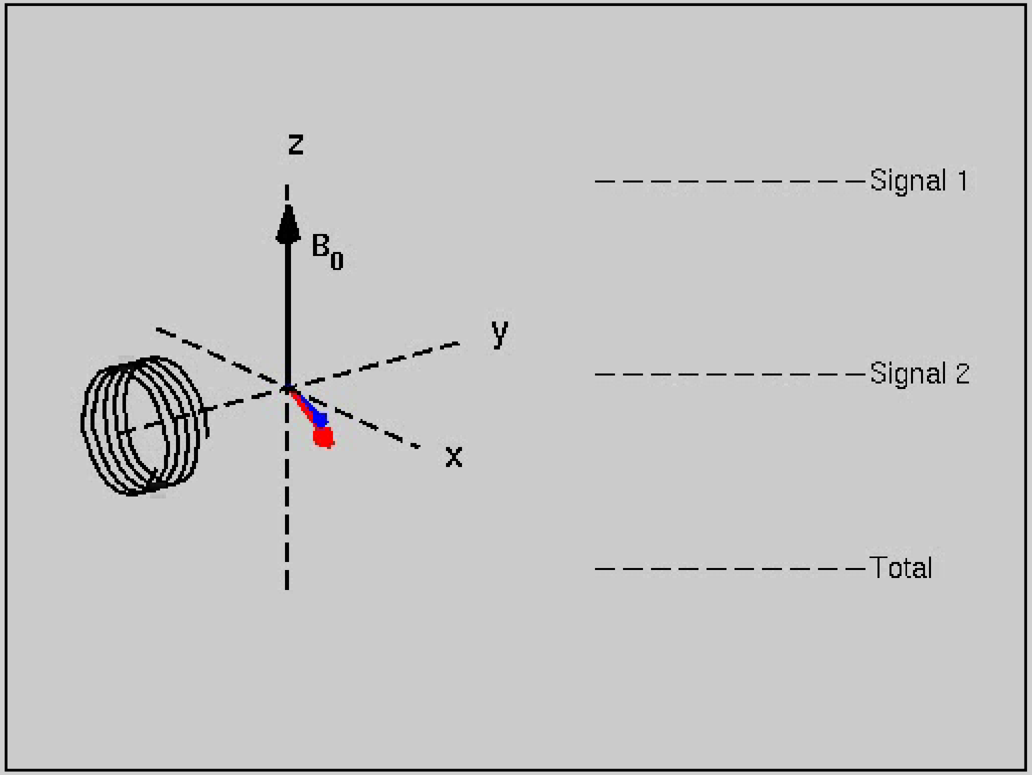


Image Acquisition

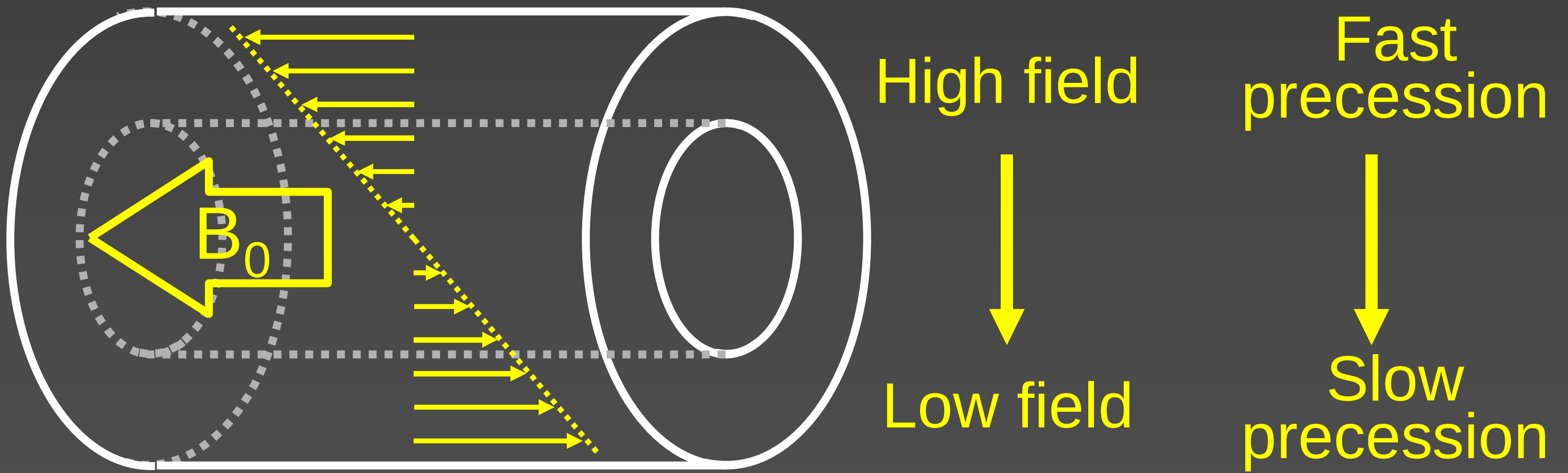
- Gradient causes resonant frequency to vary with position.
- Receive sum of signals from each spin.



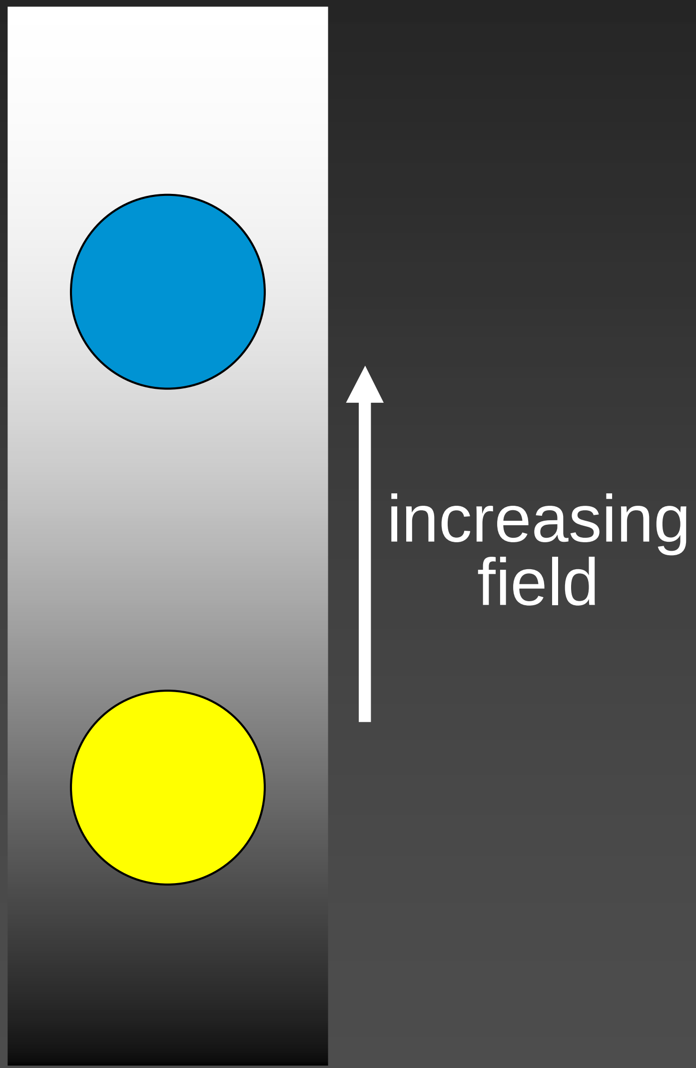


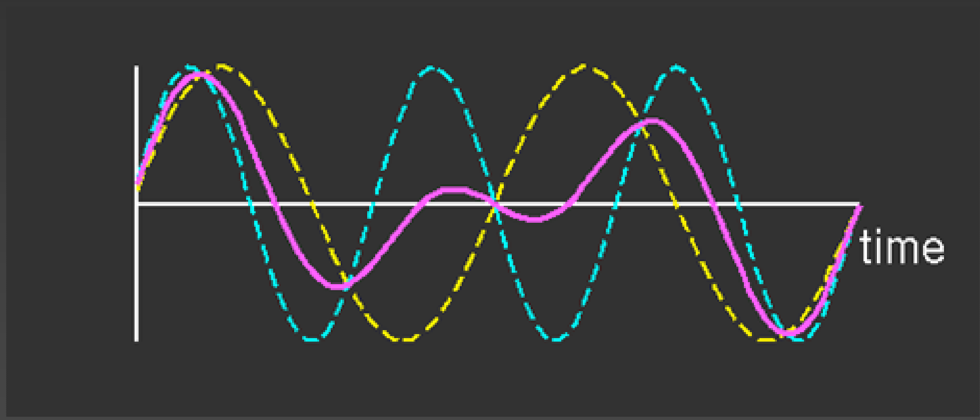
Magnetic Gradients

- Gradient adds to B0, so field depends on position
- Precessional frequency varies with position!
- “Pulse sequence” modulates size of gradient Spins at each position *sing* at different frequency
- RF coil *hears* all of the spins at once
- Differentiate material at a given position by selectively *listening* to that frequency



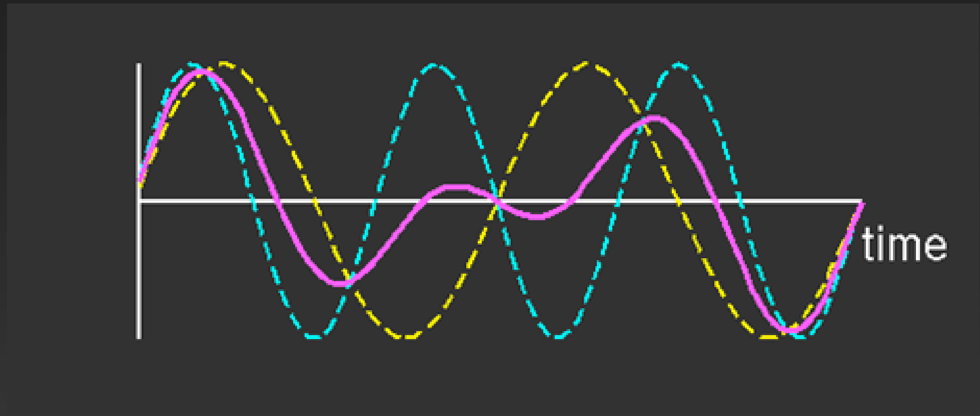
Simple “imaging” experiment (1D)





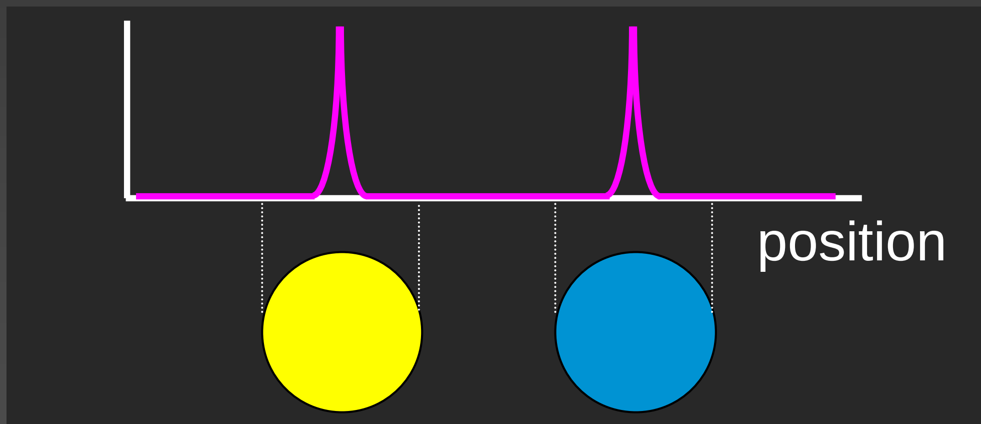
Simple "imaging" experiment (1D)

Signal



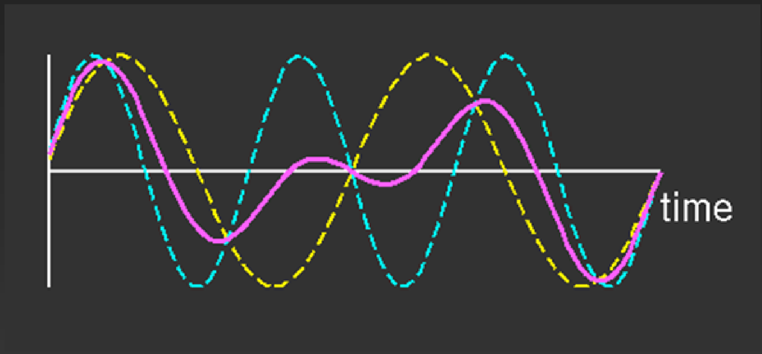
Fourier transform

"Image"



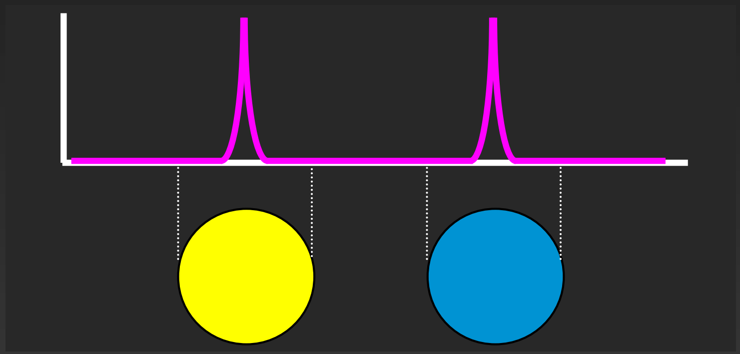
Fourier Transform: determines amount of material at a given location by selectively "listening" to the corresponding frequency

2D Imaging via 2D Fourier Transform

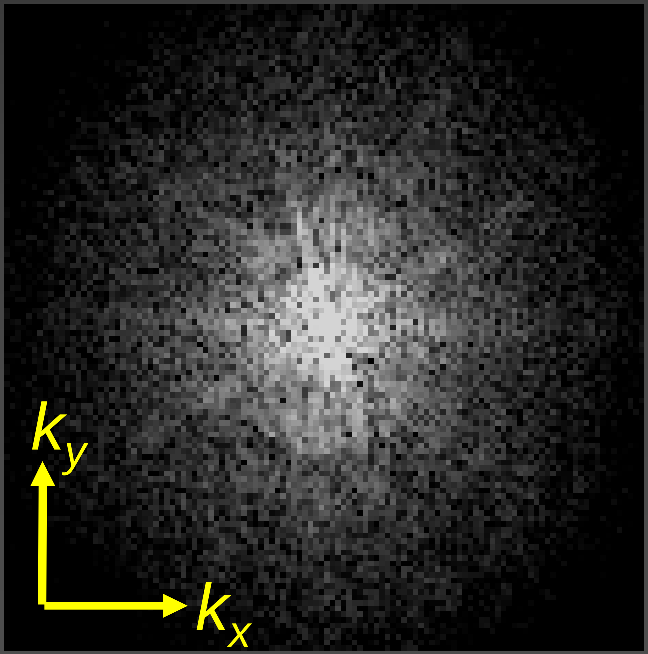


1D Signal

1DFT

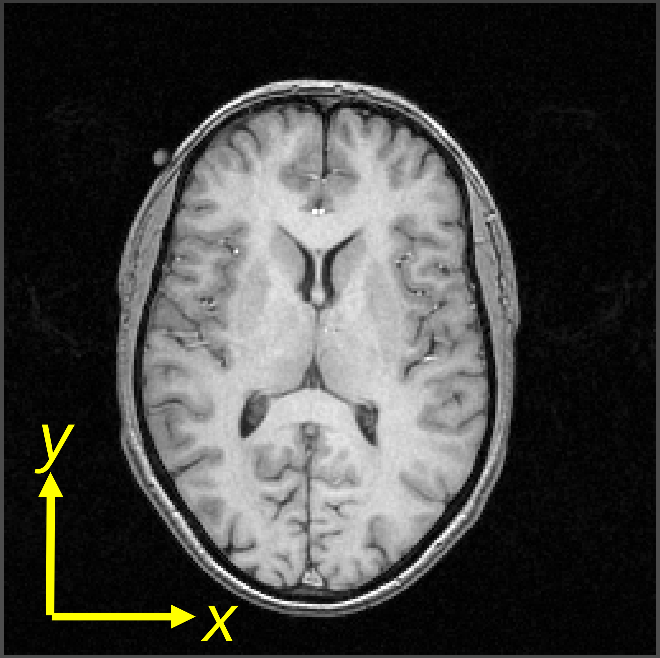


1D "Image"



2D Signal

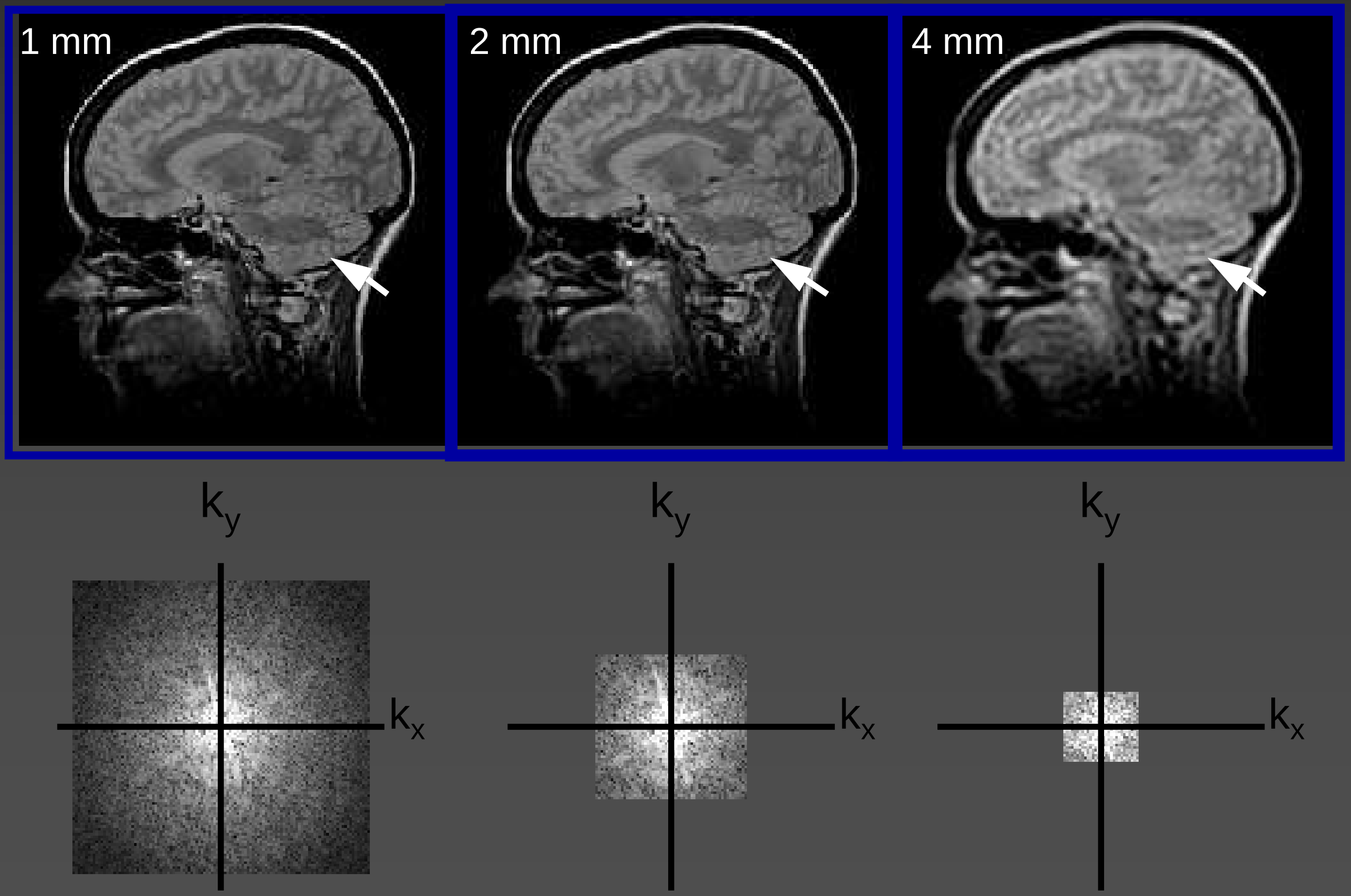
2DFT



2D Image

Resolution

- Image resolution increases as higher spatial frequencies are acquired.



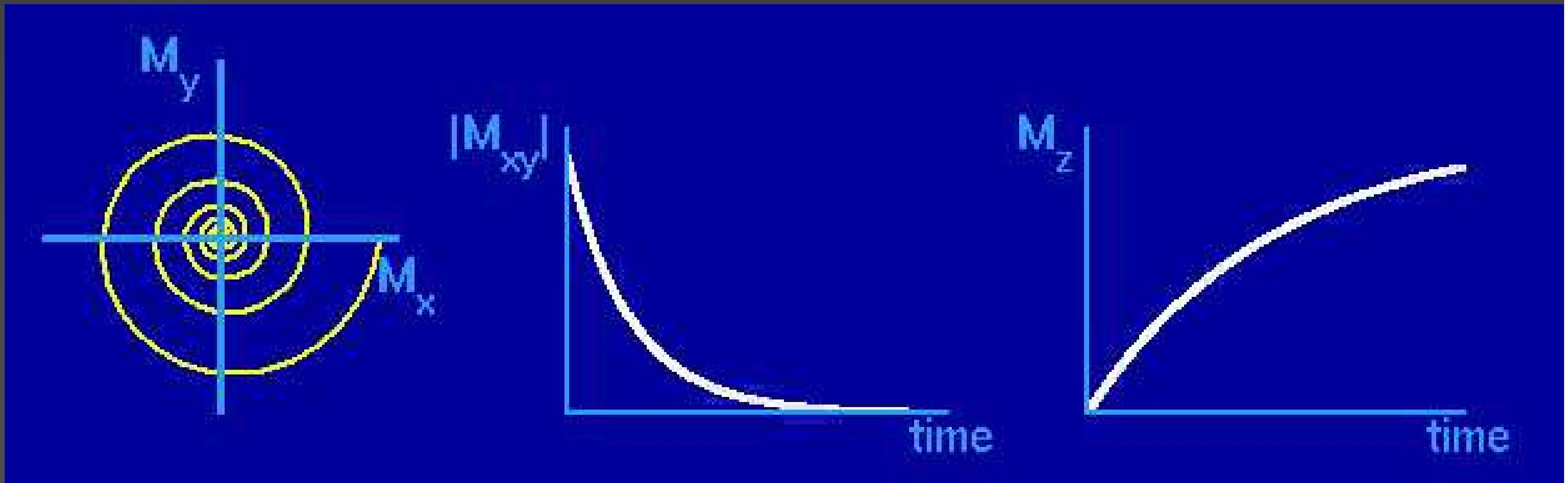
Contrast

- Contrast is the difference in appearance of different tissues in an image.

X-ray contrast is based on transmission.

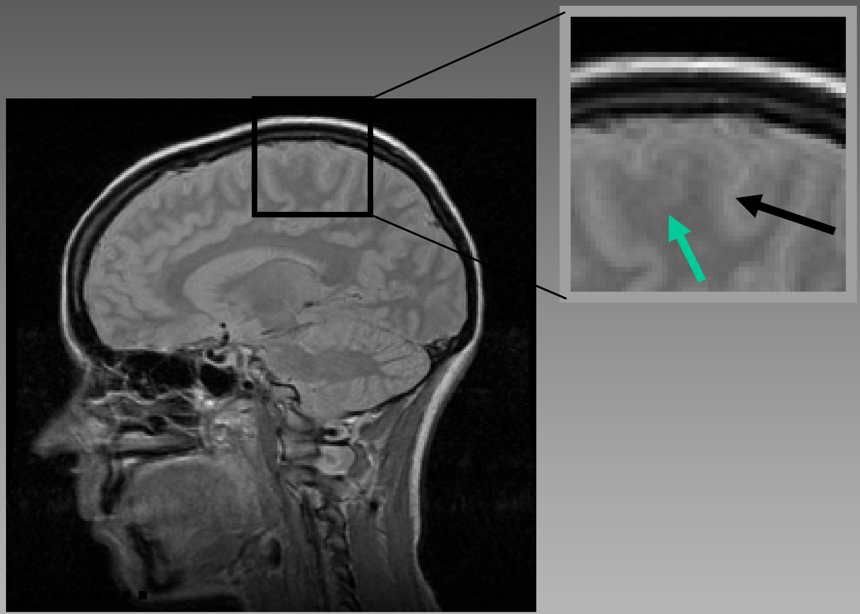
Contrast in MRI

- Hydrogen (water) density results in contrast between tissues.
- Many other mechanisms, some based on relaxation.

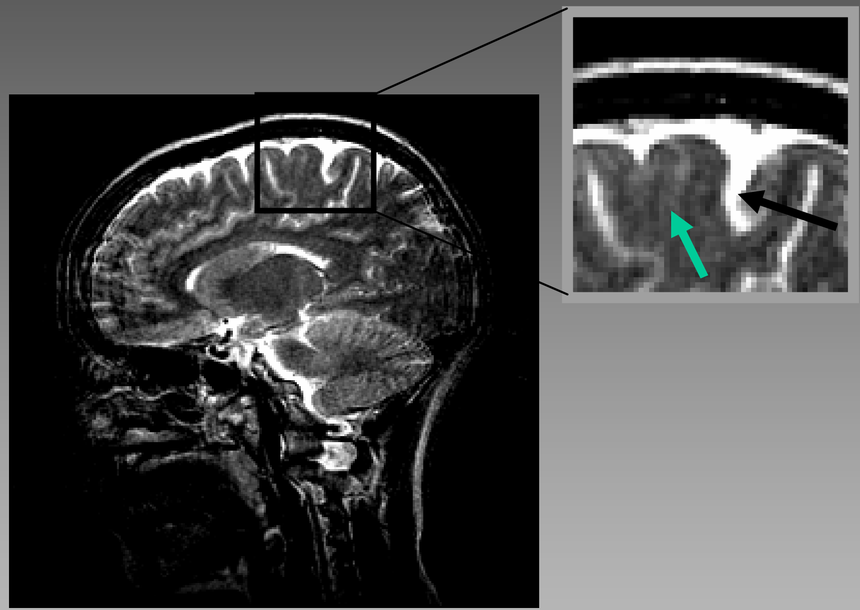


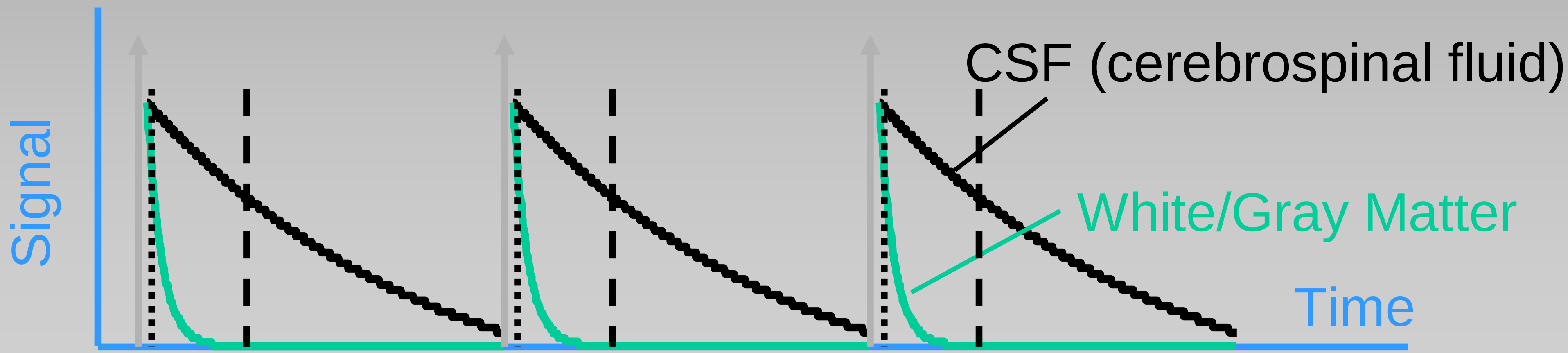
T_2 Contrast

Short Echo-Time



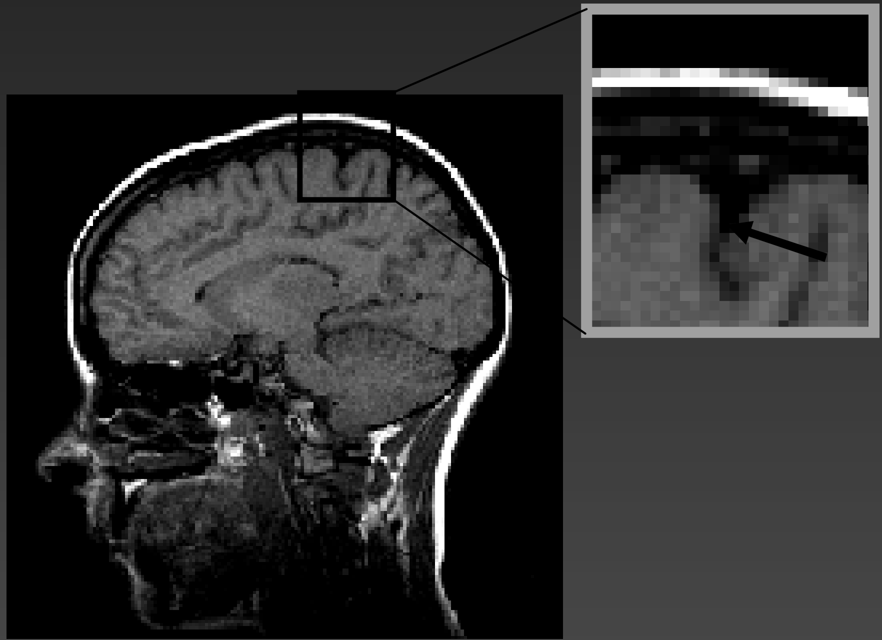
Long Echo-Time

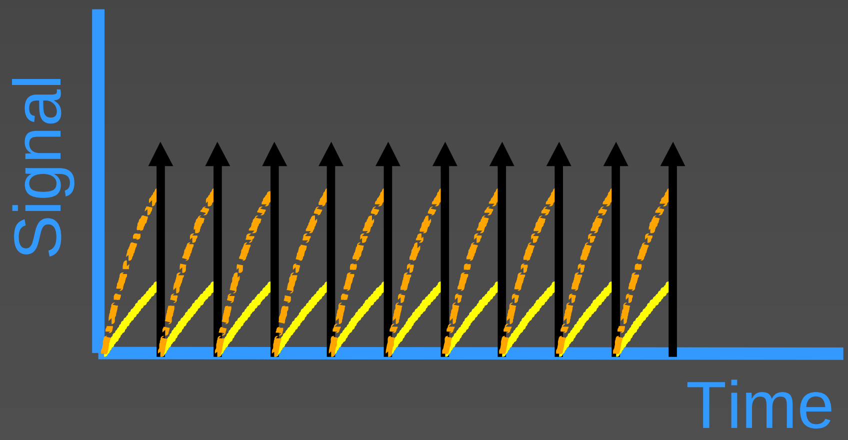




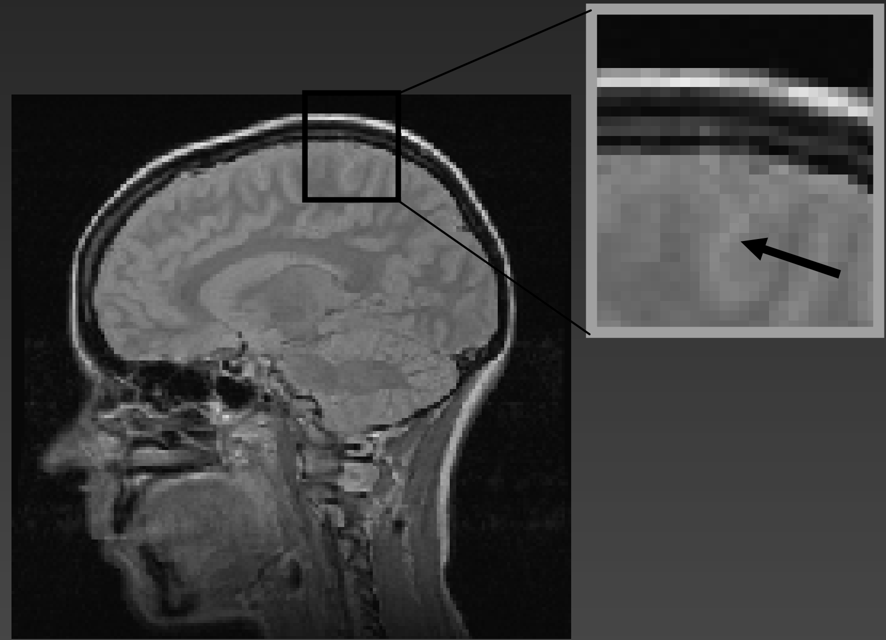
T_1 Contrast

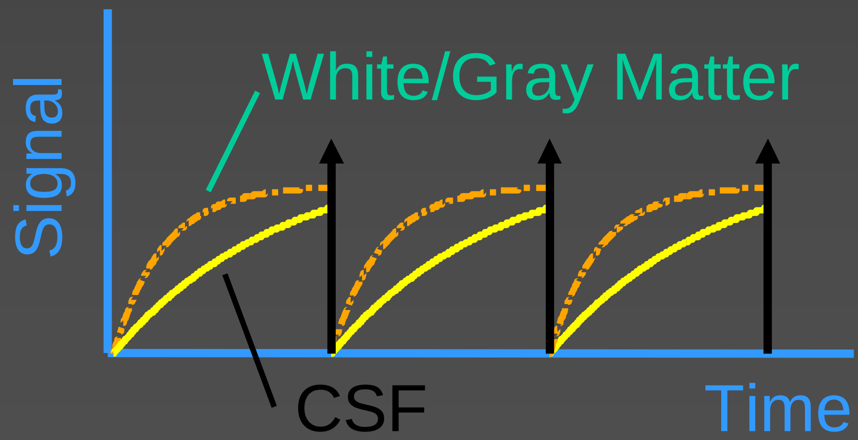
Short Repetition





Long Repetition

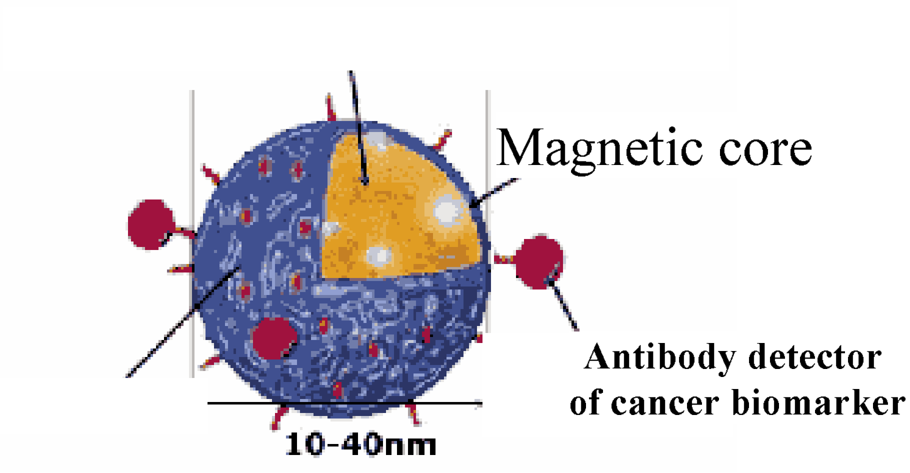


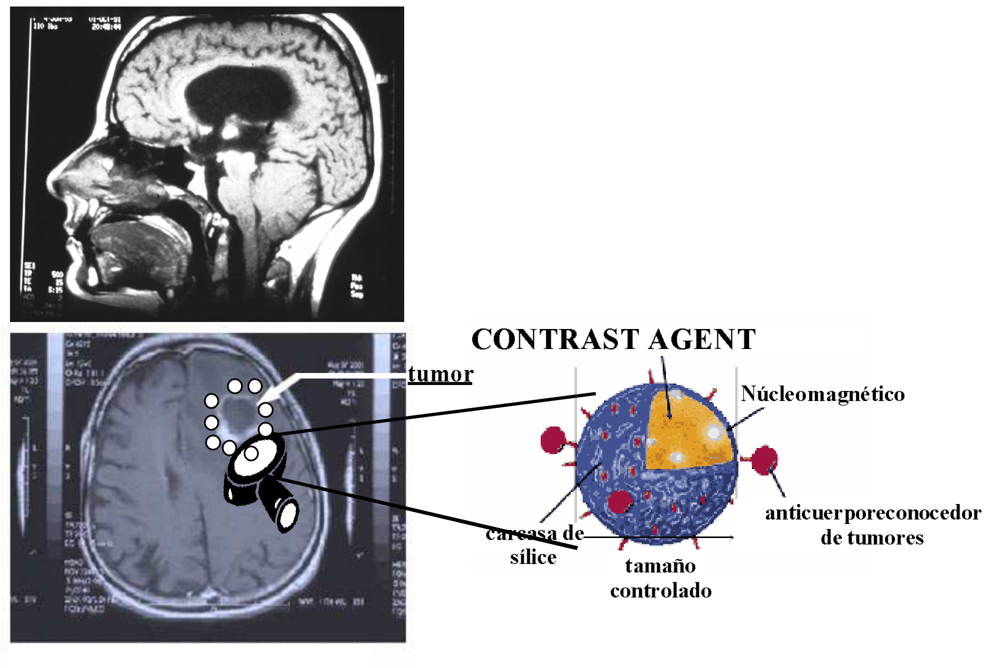


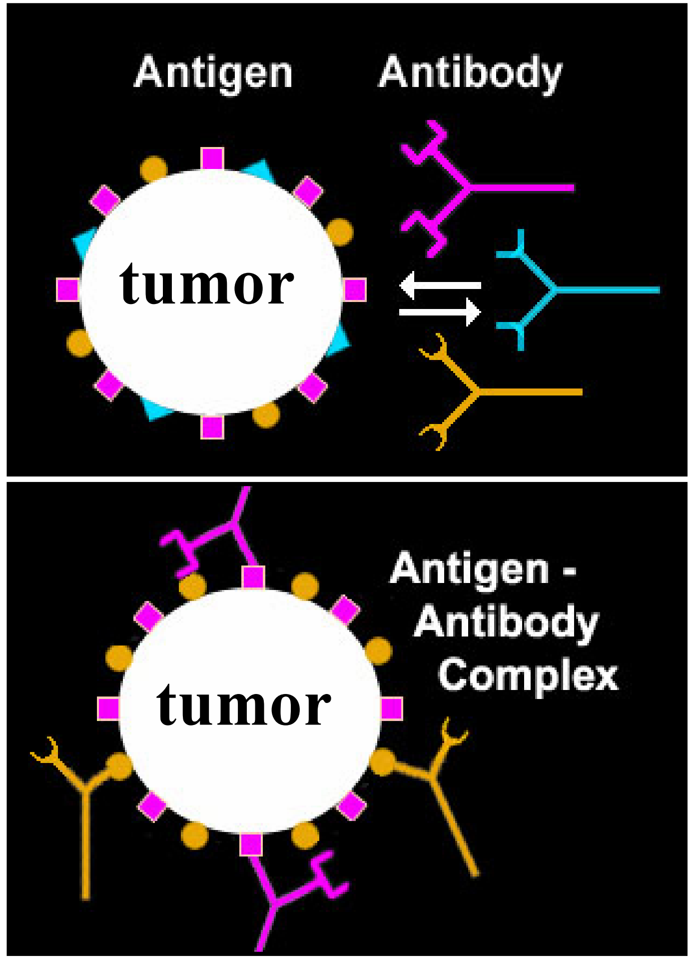
Knee Imaging - Menisci

- MRI is the best non-invasive method of diagnosing meniscal tears

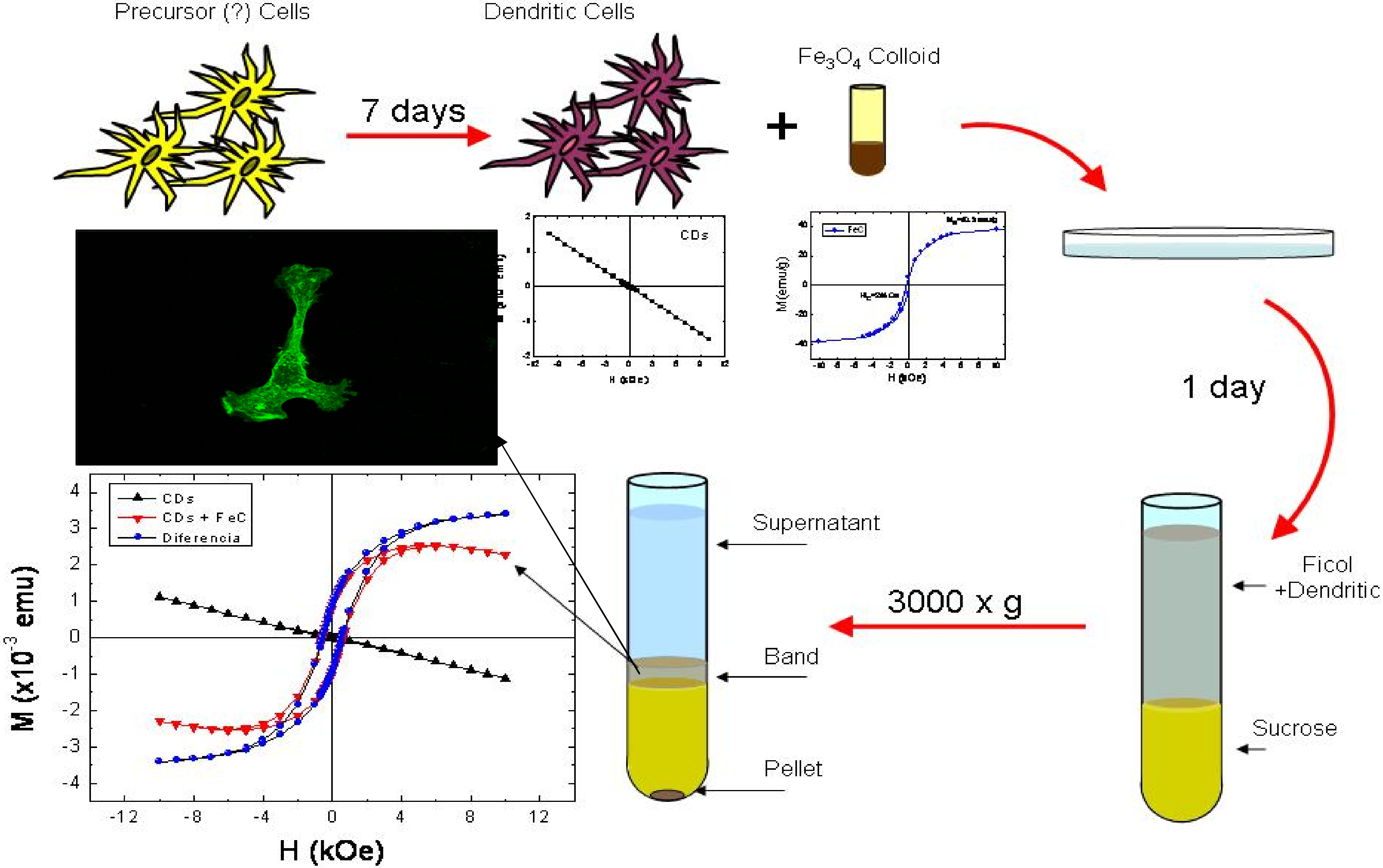
Enhance MRI contrast by molecular recognition







Dendritic cells as MRI contrast agent

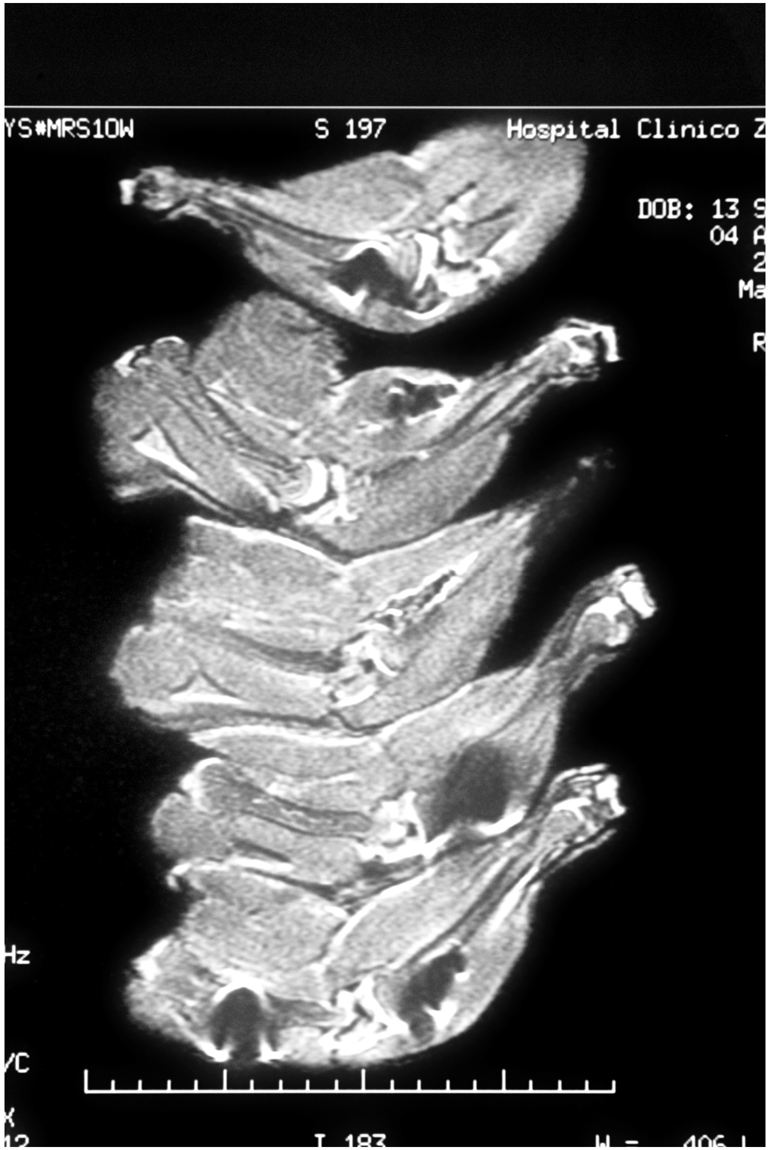


G. Goya et al. INA (2006)

Superparamagnetic Iron Oxide Nanoparticles (SPION)

"Ex-vivo" studies show a enhanced MRI contrast using a 2 Tesla scanner

Iron encapsultaed nanoparticles in PEG and other inorganics covers give a good contrast




I HOPE YOU UNDERSTOOD
EVERY THING

Energy Conveyed (typical)

Method	Frequency Range (Hz) from	to	Forwarded Energy (Watts) from	to
Galvano-treatment	0	10^2	1	5
Inductive heating	10^3	10^6	50	500
Capacitive heating	10^6	4.5×10^7	50	800
Antenna	6×10^7	2×10^8	150	2000
Microwave radiation	7×10^7	2.4×10^9	50	2000

What is hyperthermia?

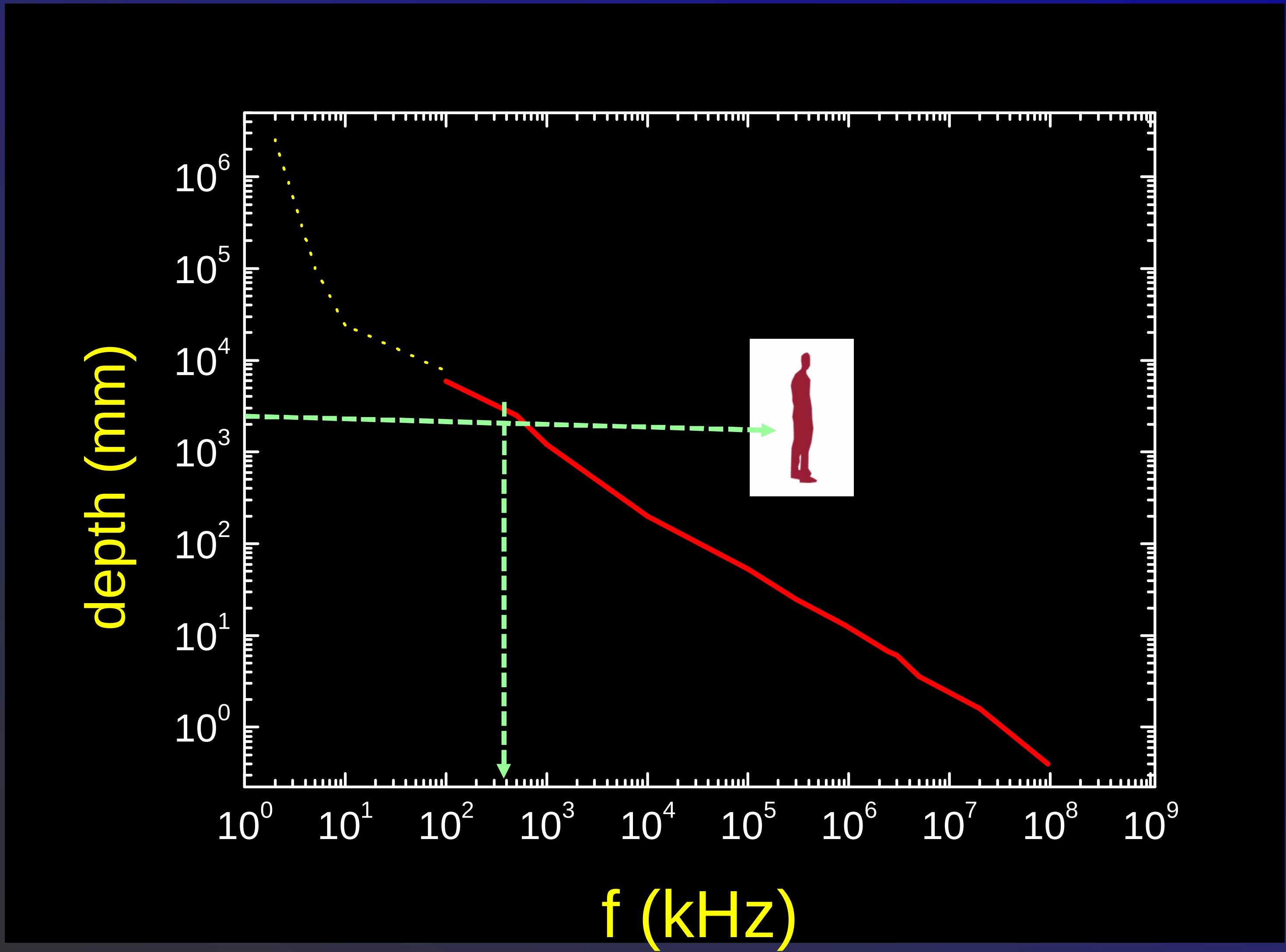
“Hyperthermia” is the general name given to a variety of heat-related illnesses. The two most common forms of hyperthermia are heat exhaustion and heat stroke. Of the two, heat stroke is especially dangerous and requires immediate medical attention.

National Institute of Aging

QUE ES LA HIPERTERMIA MALIGNA? La Hipertermia Maligna (HM) es un desorden hereditario y silente del musculo. Afecta a individuos en apariencia perfectamente normales y que no tienen ninguna limitacion funcional en su vida diaria. Sin embargo, cuando a estos individuos se les administra algun anestesico gatillante, este desorden silencioso puede transformarse en fatal.

MHAUS
Malignant Hyperthermia Association of the United States

Penetration Depth



Hypertermia Methods

Delivery kind: Conduction, Convection, Radiation, Bioactive

Energy Production: Contac methods, chemical, biological, mechanical, electromagnetic.

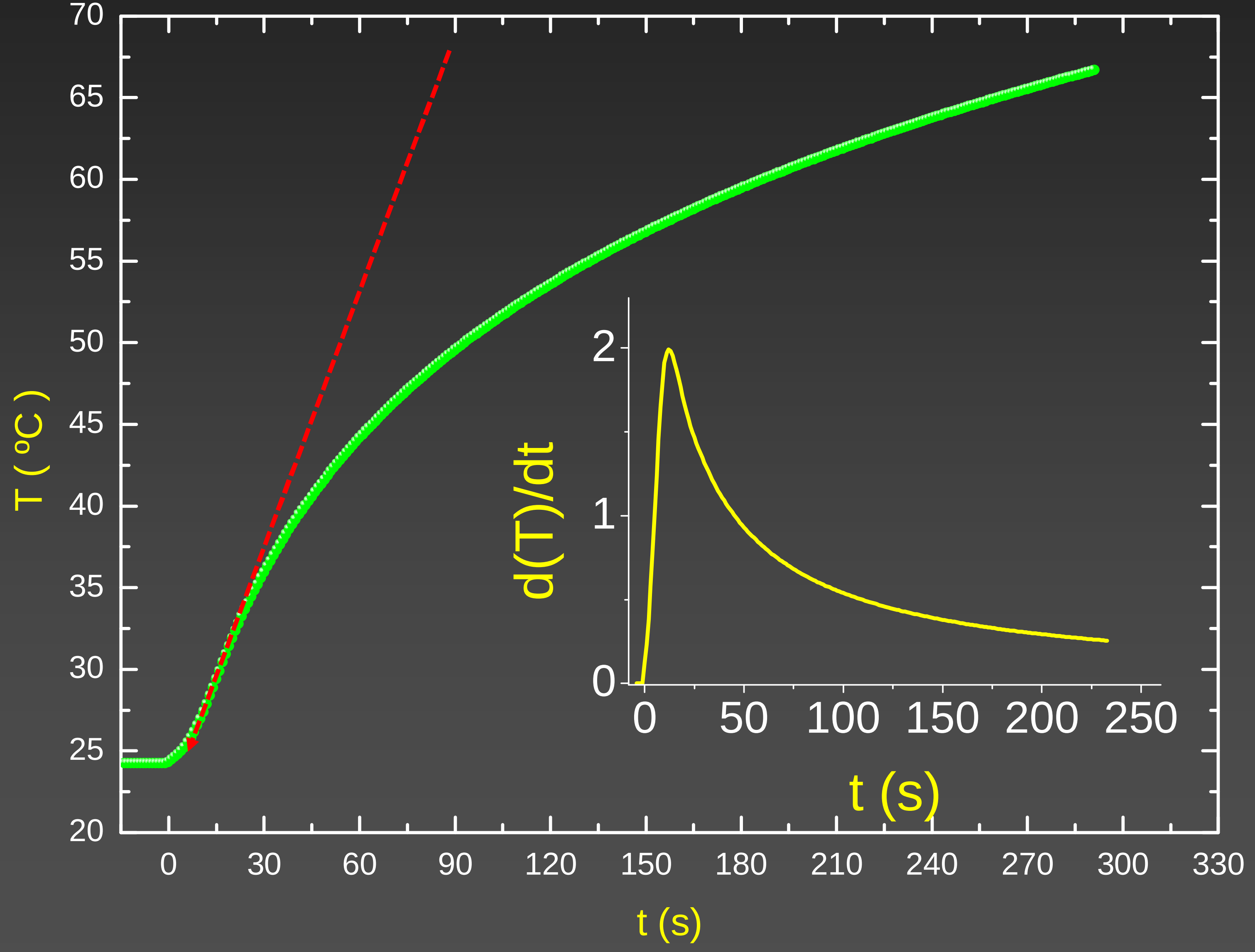
Locality: Local, Regional, systemic

Clinical applications: superficial, intracavitational, deep-seated, whole-body.

Combination with: Chemo-therapy, radiotherapy, surgery, gene-therapy, hormone therapy

What we actually measure

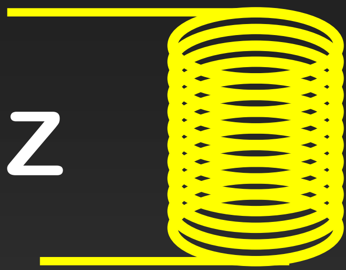
$P \propto dT/dt$



Material				Hysteresis Loss/Cycle (J/m^3)	Resistivity ρ (Ω.m)
Commercial Fe ingot	99.95Fe	150	21400	270	1.0×10^{-7}
Si-Fe (oriented)	97Fe, 3Si	1400	20100	40	4.7×10^{-7}
45 Permalloy	55Fe, 45Ni	2500	16000	120	4.5×10^{-7}
Supermalloy	79Ni, 15Fe, 5Mo, 0.5Mn	75000	8000	--	6.0×10^{-7}
Ferroxcube A	48$MnFe_2O_4$, 52 $ZnFe_2O_4$	1400	3300	~ 40	2000
Ferroxcube B	36 $NiFe_2O_4$, 64 $ZnFe_2O_4$	650	3600	~ 35	10^7

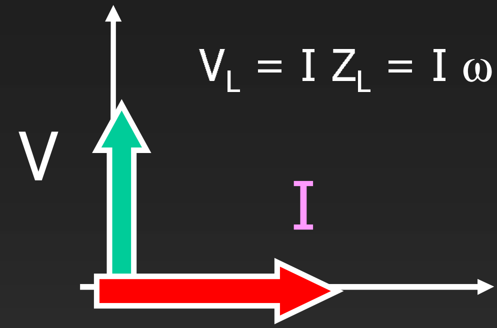
Adapted from Metals Handbook : Properties and Selection: Stainless Steels, Tool Materials and Special-Purpose Metals, Vol.3, 9th Edition. D. Benjamin (Senior Editor), American Society for Metals, 1980.

$$V = I\,Z$$



$$V(t) = L\,\frac{di(t)}{dt}$$

$$V_L = I\,Z_L = I\,\omega\,L$$



$$Z_L = \omega\,L$$

$$L = \frac{\mu\,N^2 A}{l} \qquad B = \frac{\mu\,N}{l} I$$

L = 6.8 cm, Diam= 4 cm

N = 9,

B = 300 Oe

I = 200 Amp

a 250 kHz

$$V = I\,\omega\,L = \mathbf{630\ V}$$

Es decir… ~ 120 kVA

Magnetic Gradients

Gradient: Additional magnetic field which varies over space

- Gradient adds to B_0, so field depends on position
- Precessional frequency varies with position!
- "Pulse sequence" modulates size of gradient

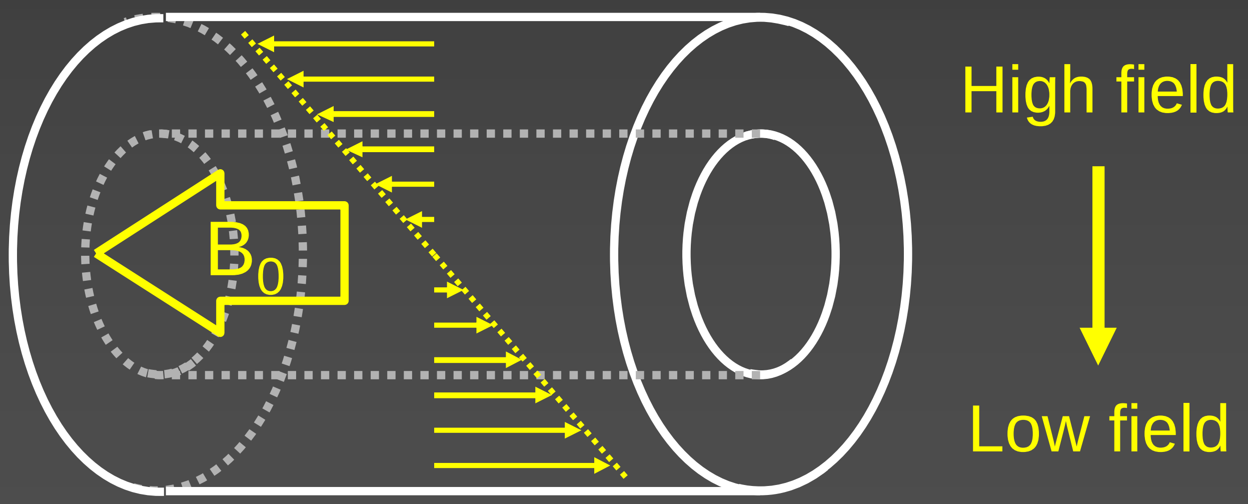
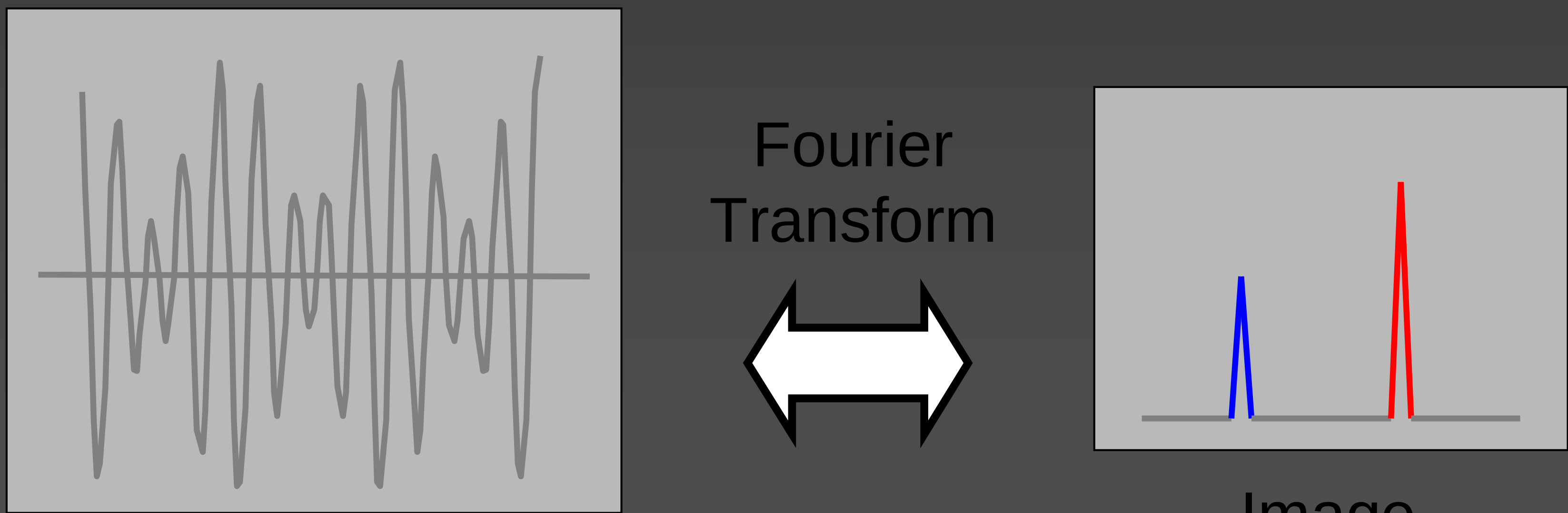


Image Reconstruction

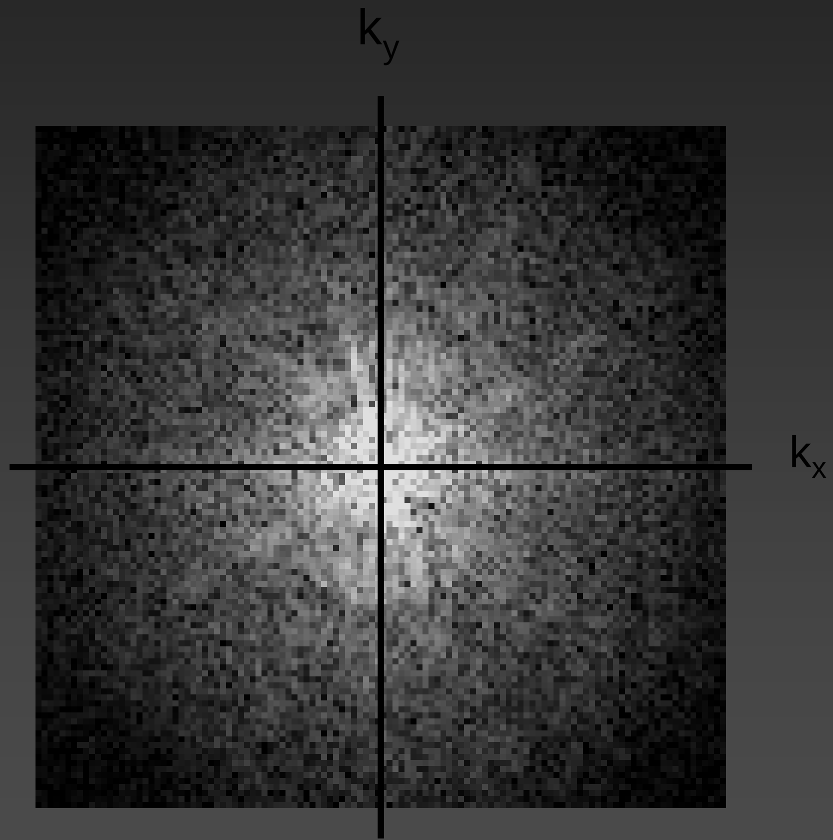
- Received signal is a sum of “tones.”
- The “tones” of the signal are the image.
- This also applies to 2D and 3D images.



Received Signal

Image

2D Image Reconstruction



Frequency-space
(k-space)

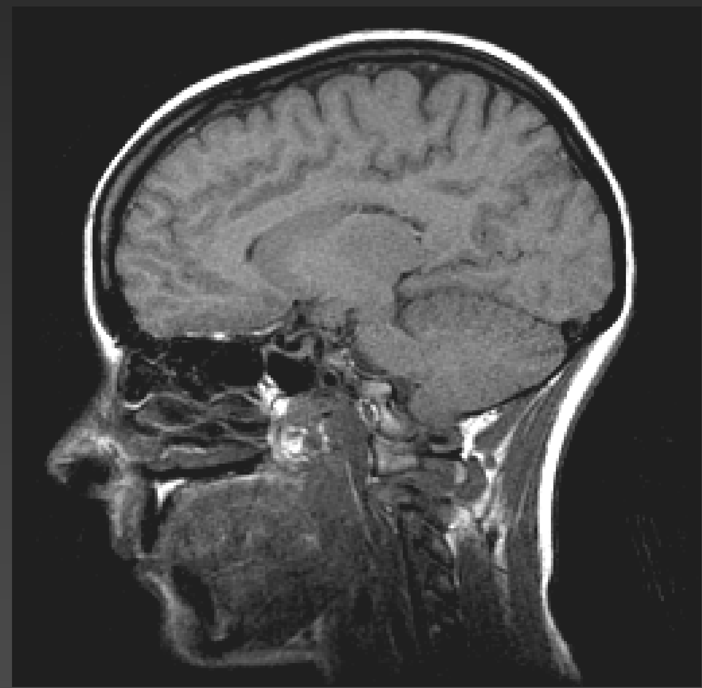
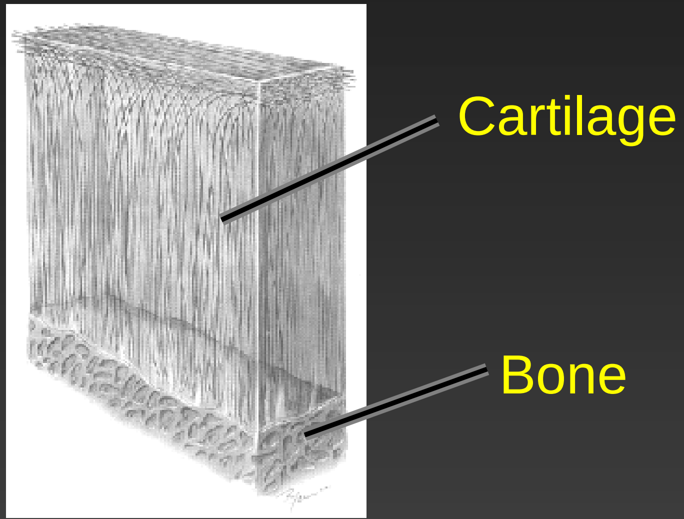


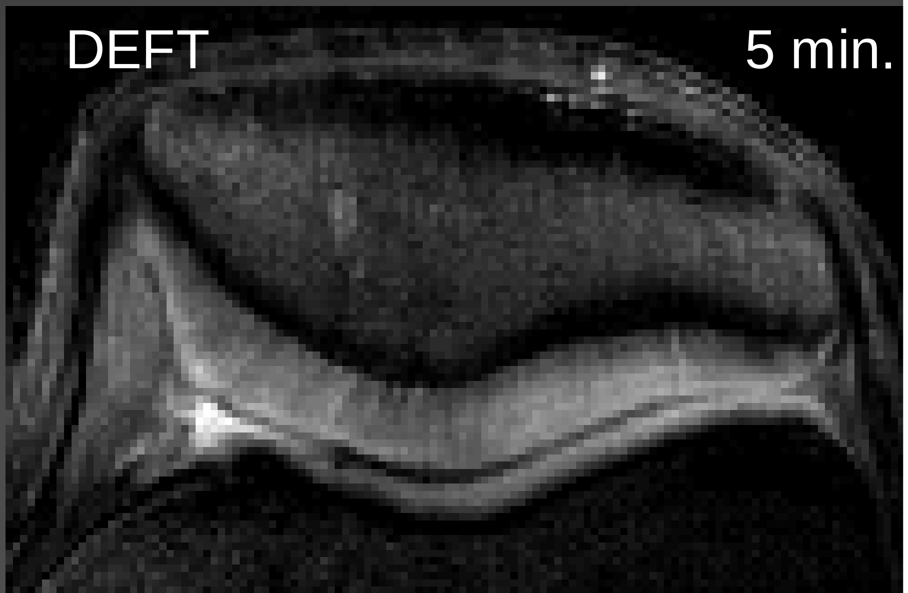
Image space

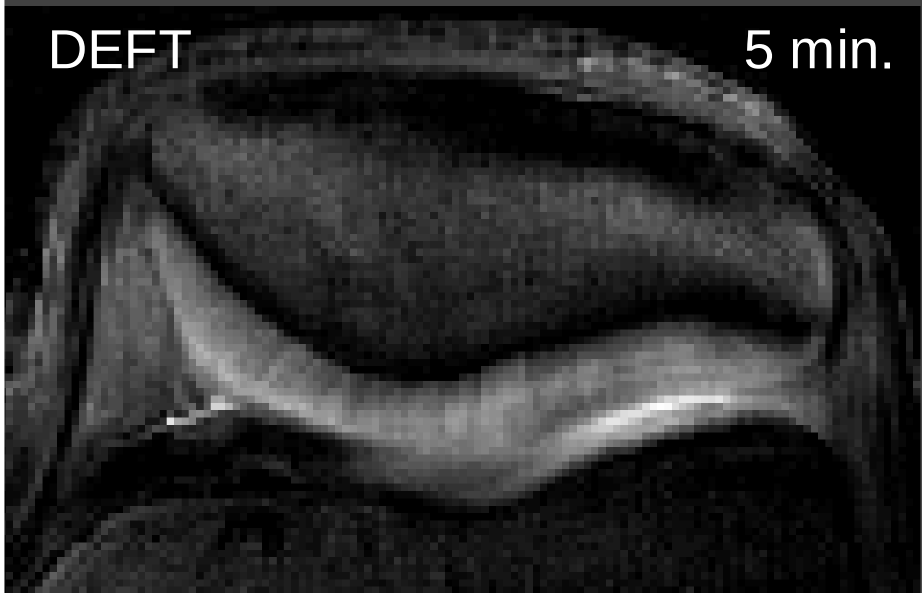
Knee Imaging - Cartilage

- High resolution images begin to show cartilage structure:
  - 0.4 x 0.4 x 2 mm^3 resolution
  - 5 minute scan time



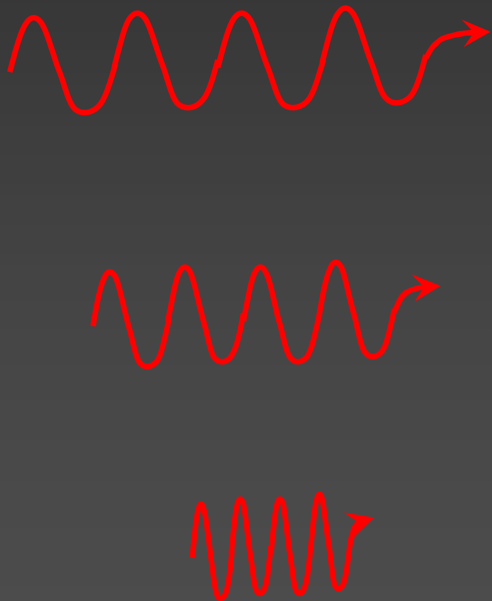
(from Erickson– 1997)

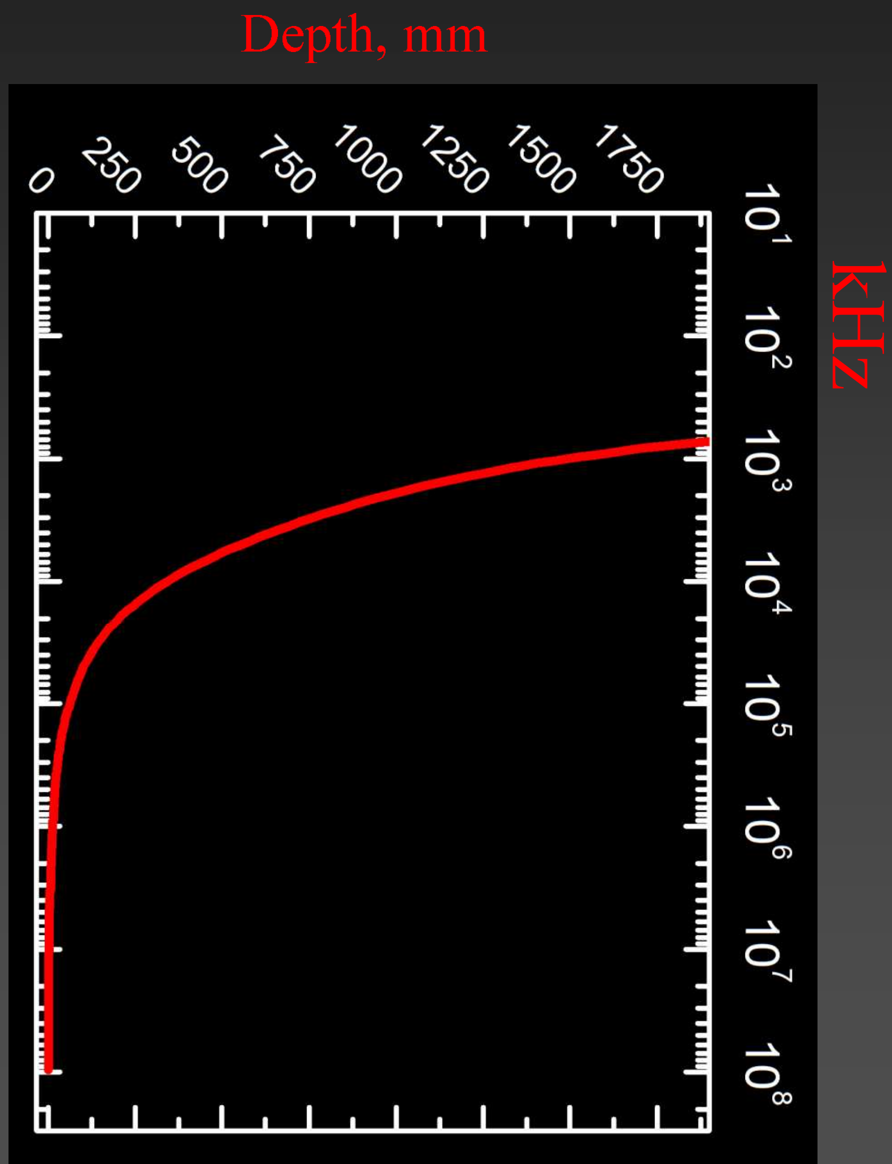




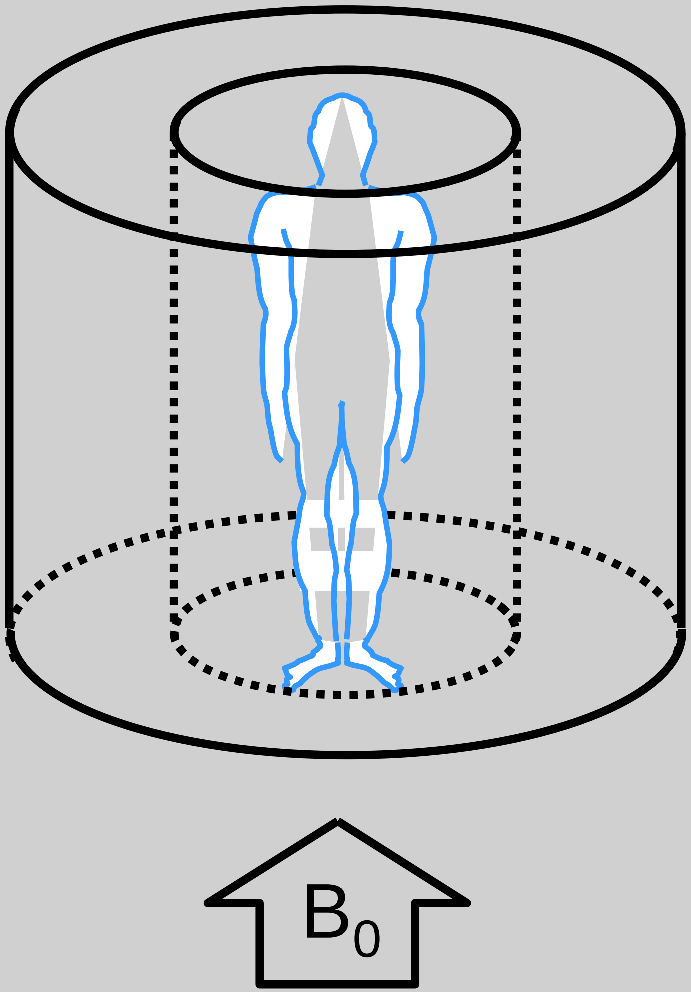
Penetration Depth

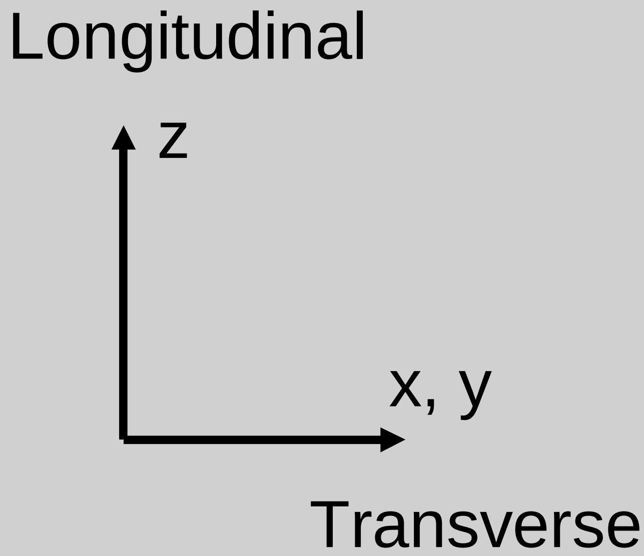
RF





Static Magnetic Field





$\Delta E = g_N \mu_N B_o = h\omega$

B_o = 1 Tesla, ω = 10 MHz