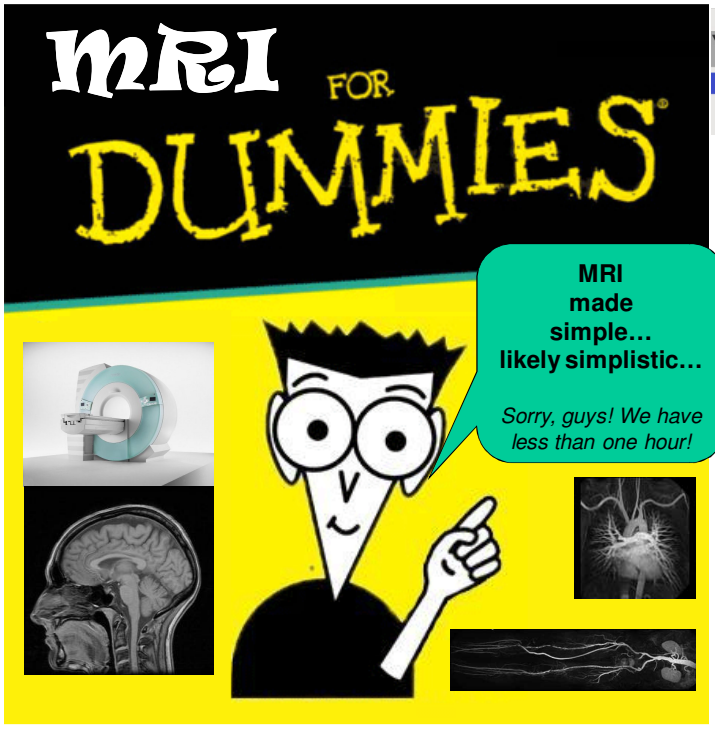
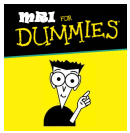



Young Belgian Magnetic Resonance Scientist 2011
YBMRS 2011
21st - 23rd NOVEMBER
BLANKENBERGE

*U. Himmelreich*
*K.U.Leuven*

*B. Gallez*
*U.C.Louvain*

*B. Jordan*
*U.C.Louvain*



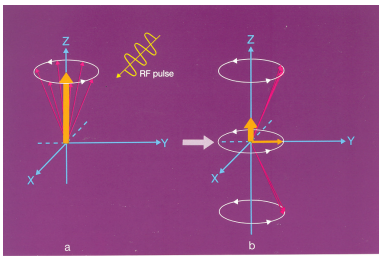

# Part 2: Sources of contrast

- Endogenous (tissue) contrast
  - Relaxation times
  - Proton density
  - Mobility of protons
- Exogenous contrast (contrast agents)
  - Paramagnetic agents
  - Superparamagnetic agents

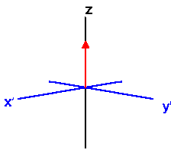
# Relaxation as the main source of contrast

Blankenberge
November 2011

# NMR relaxation times: $T_1$

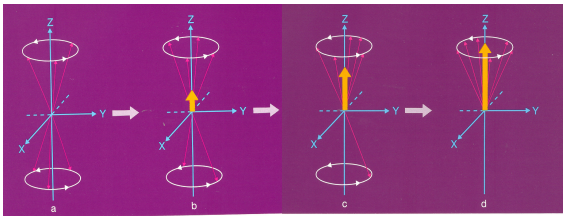


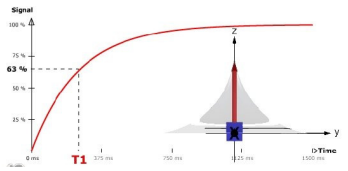

Consequences of the application of a RF pulse:
- decrease in longitudinal magnetization
- protons start to precess in phase: establishment of a transversal magnetization




**$T_1$ (spin-lattice) relaxation time**

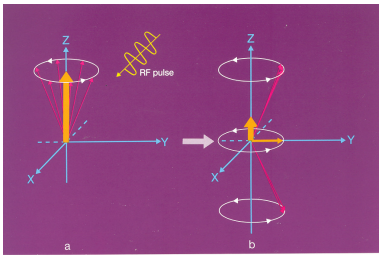
Return
of the longitudinal magnetization
to its original value




Source: H. Schild, MRI made easy
http://www.imaios.com/en/e-Courses/e-MRI

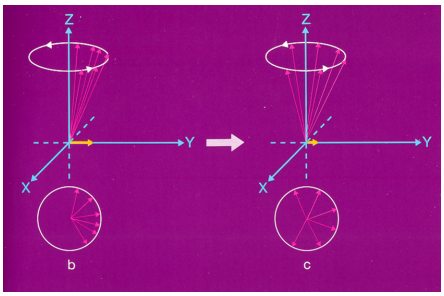
# NMR relaxation times: $T_2$

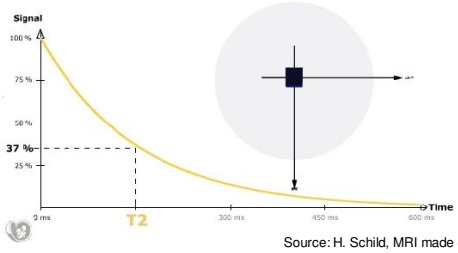



Consequences of the application of a RF pulse:
- decrease in longitudinal magnetization
- protons start to precess in phase: establishment of a transversal magnetization

**$T_2$ (spin-spin) relaxation time**

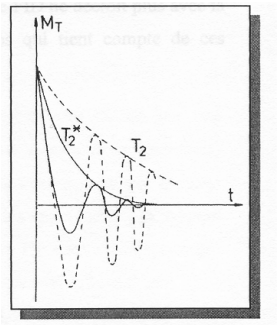
Loss of phase coherence




Source: H. Schild, MRI made easy
http://www.imaios.com/en/e-Courses/e-MRI

# NMR relaxation times: $T_2$*

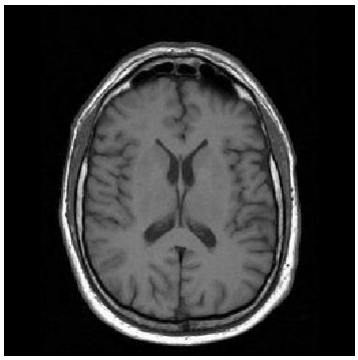



- FID signal decays faster than $T_2$ would predict and decreases exponentially at a time constant $T_2$*
- $T_2$* takes into account :

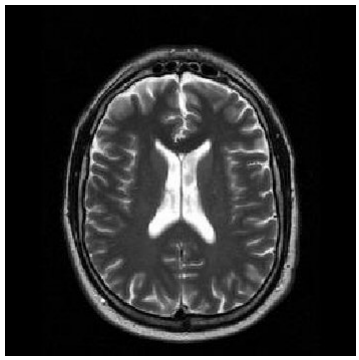
  - tissue specific spin-spin relaxation (random interactions between spins) responsible for pure $T_2$ decay

  - static inhomogeneities in magnetic fields which accelerate spins dephasing

# How to weight the contrast in a MR image?



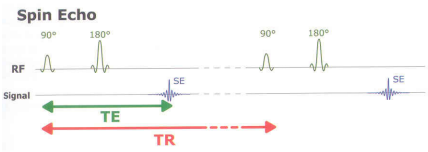
$T_1$-weigthed image

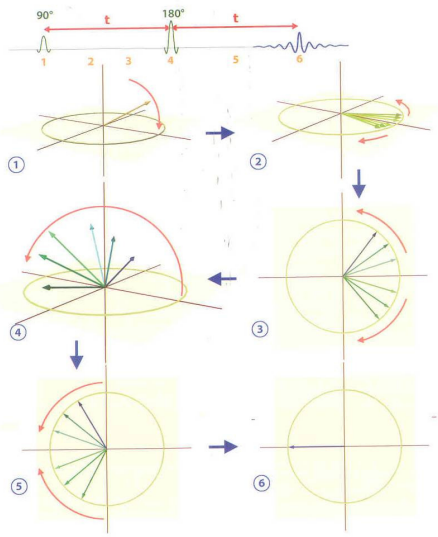


$T_2$-weighted image

## Spin - echo

SE is composed of a 90° excitation pulse followed by one or more 180° pulses

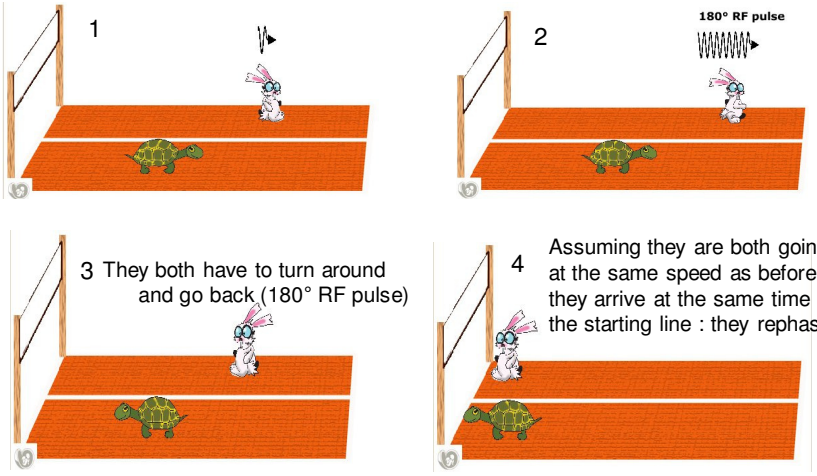



http://www.imaios.com/en/e-Courses/e-MRI

# How a 180° RF pulse can refocus spins?

Once the race starts (the relaxation begins), the turtle and the rabbit are at the same place (the starting line): they are in phase. As the rabbit runs faster, there is a distance between him and the turtle: they dephase.




http://www.imaios.com/en/e-Courses/e-MRI

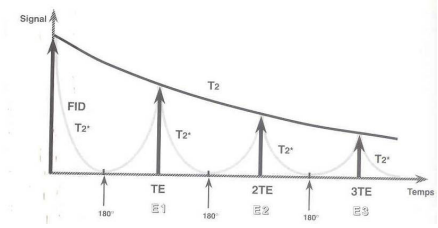
# Spin - echo

**Role of 90° pulse and repetition time**:

- 90° RF pulse tips the magnetization in the transversal plane for signal recording
- The size of the signal will depend on the TR and the possible recovery of the magnetization between two 90° RF pulses

**Role of 180° pulse and echo time**:

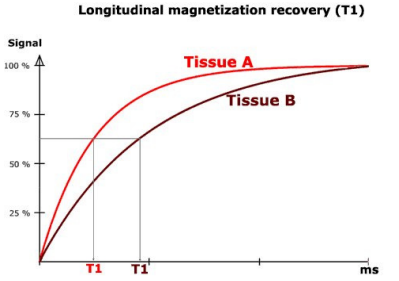
- refocus the spins
- depending on the echo time, the signal will depend on $T_2$

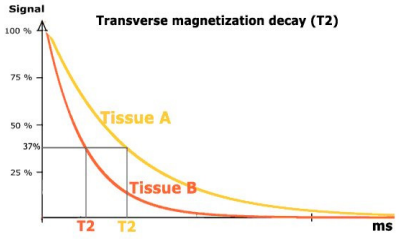



B. Kastler, Comprendre l'IRM, Masson

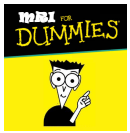

# Signal weighting

- Each tissue has a specific proton density, $T_1$ and $T_2$ relaxation time
- The NMR signal depends on these 3 factors
- To distinguish different tissues, we need to obtain contrast between them



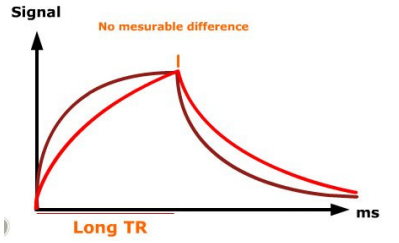



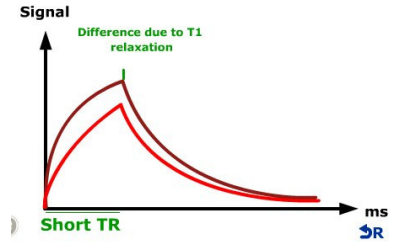

http://www.imaios.com/en/e-Courses/e-MRI




# Signal weighting

- 2 tissues A and B with **different $T_1$s** :
  - Long TR: the longitudinal magnetization of both tissues will recover completely before the next excitation
  - If TR is short and if tissue A has a longer $T_1$ than tissue B, the longitudinal magnetization of tissue A will recover less than the longitudinal magnetization of tissue B

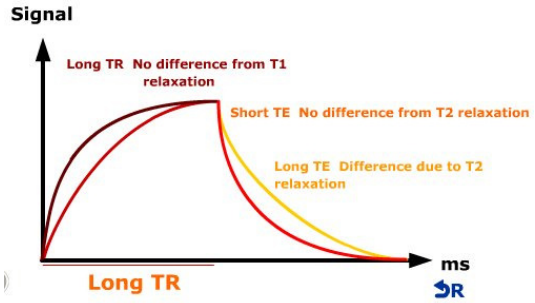



http://www.imaios.com/en/e-Courses/e-MRI

# Signal weighting

- By setting the TR to long values, the T1 effect on tissue contrast will be reduced
- If TE is long enough, differences in transverse relaxation will alter tissue contrast (the T2 effect)

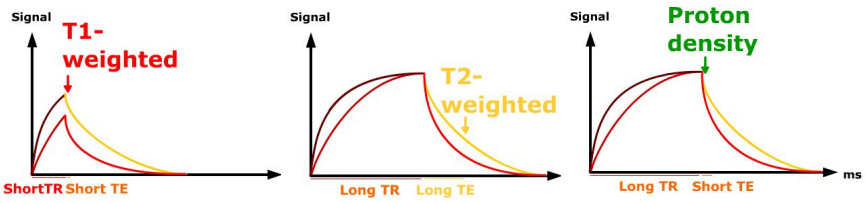



http://www.imaios.com/en/e-Courses/e-MRI

# Signal weighting

With a spin echo sequence :

- TR modifies T1-weighting : the shorter is the TR, the more T1-weigthed the image is
- TE modifies T2-weighting : the shorter is the TE, the less T2-weigthed the image is
- A short TR and a short TE give a T1-weighted image.
- A long TR and a long TE give a T2-weighted image.
- A long TR and a short TE give a PD-weighted image.




http://www.imaios.com/en/e-Courses/e-MRI


# Why $T_1/T_2$ is changing from one tissue to another?

- **$T_1$ depends on tissue composition, structure and surroundings: possibility to exchange the thermal energy to the lattice.**
  - In pure liquid (like water), it is difficult to exchange the energy because the protons move too rapidly: protons of water have long $T_1$.
  - In tissues (that contain small, medium and large molecules), because there are fluctuating magnetic fields that are closed to the Larmor frequency, the energy is transferred effectively: $T_1$ is short.

- **$T_2$ depends on inhomogeneities of the local magnetic field within the tissues**
  - In pure water, molecules move around very fast, no big differences in magnetic field strength: $T_2$ is long
  - In tissues, large variations in the local magnetic fields due to differences in movements of large and small molecules: $T_2$ is short

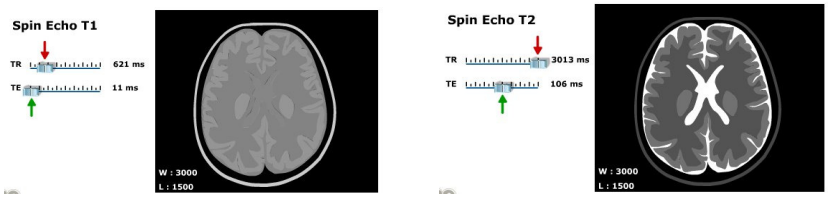

# Why $T_1/T_2$ is changing from one tissue to another?

At 1.5 Tesla:

| | T1 (ms) | T2 (ms) |
|---|---|---|
| Water | 3000 | 3000 |
| Gray matter | 810 | 100 |
| White matter | 680 | 90 |
| Liver | 420 | 45 |
| Fat | 240 | 85 |
| Gadolinium | Reduces T1 | Reduces T2 |

$T_1$ and $T_2$ are strongly dependent on the magnetic field

# Signal weighting

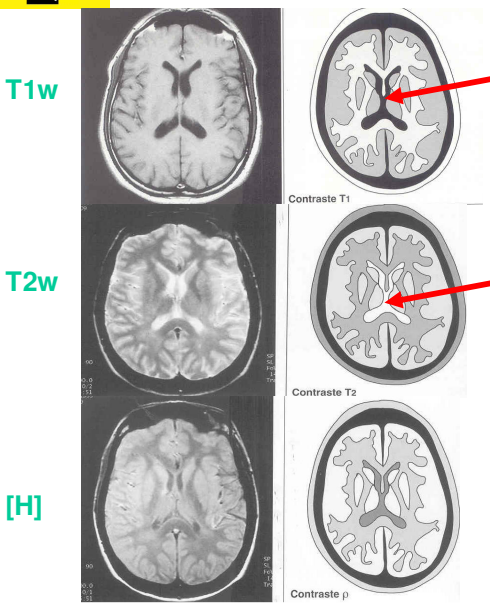



- A tissue with a long $T_1$ and $T_2$ (like water) is dark in the $T_1$-weighted image and bright in the $T_2$-weighted image
- A tissue with a short $T_1$ and a long $T_2$ (like fat) is bright in the $T_1$-weighted image and gray in the $T_2$-weighted image

http://www.imaios.com/en/e-Courses/e-MRI

# Signal weighting

At 1.5 Tesla




| | |
|---|---|
| CSF: | black |
| Grey matter: | gray |
| White matter: | white |

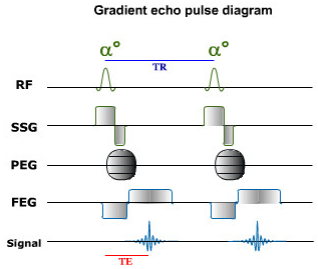
| | |
|---|---|
| CSF: | white |
| Grey matter: | light gray |
| White matter: | gray |

| | |
|---|---|
| CSF: | dark gray |
| Grey matter: | white |
| White matter: | gray |

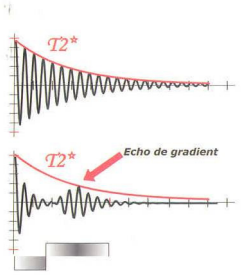
B. Kastler, Comprendre l'IRM, Masson

# $T_2$* as a source of contrast
## Use of Gradient Echo sequences

- Two major differences distinguish the gradient echo technique from the spin echo technique :
  - An excitation pulse with a flip angle lower than 90°
  - No 180° rephasing pulse



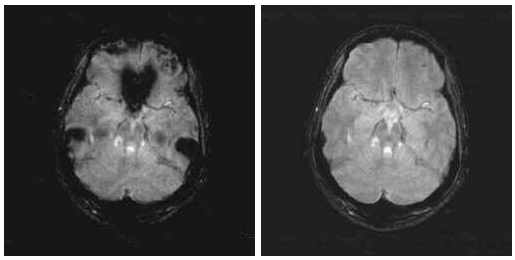

- As GE techniques use a single RF pulse and no 180° rephasing pulse, the relaxation due to fixed causes is not reversed and the loss of signal results from $T_2$* effects (pure $T_2$ + static field inhomogeneities)



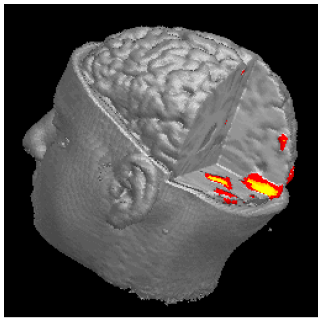

http://www.imaios.com/en/e-Courses/e-MRI

# $T_2$* - Field inhomogeneities as a source of contrast

Magnetic susceptibility artifacts



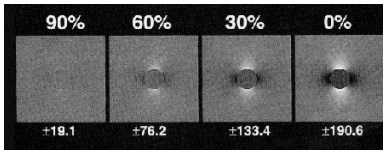
Physiological information: fMRI




# fMRI: endogenous contrast

- The phenomenon is due to the field inhomogeneities induced by the endogenous MRI contrast agent dHb.
- In dHb, the iron ($Fe^{2+}$) is in a paramagnetic high spin state, as four out of six outer electrons are unpaired.
- The paramagnetic nature of dHb can modify the strength of the magnetic field passing through it. It decreases T2* in the tissue surrounding the blood vessels.
- « **BOLD** » contrast:

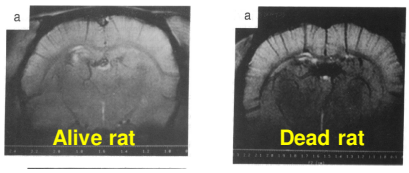
  « **B**lood **O**xygen **L**evel **D**ependent »




Blood samples at different concentrations of oxygen

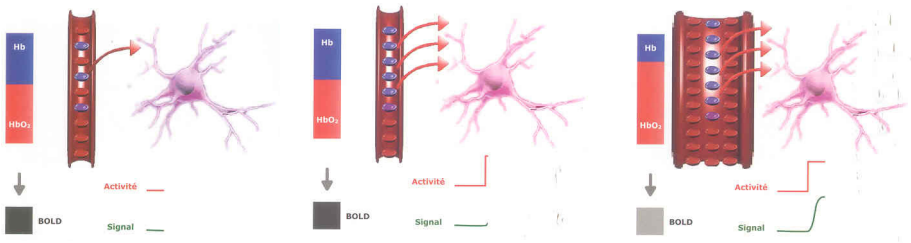
**Oxy-Hemoglobin: diamagnetic**

**Deoxy-Hemoglobin: Paramagnetic**




*S. Ogawa et al, PNAS 1990, 87, 9868*


# Principle of fMRI



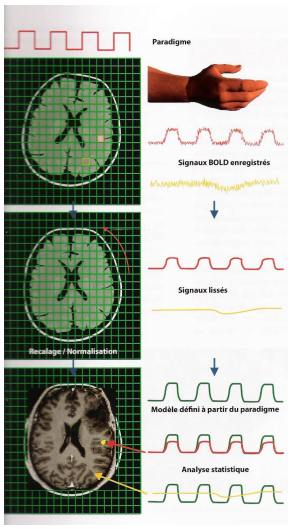

Neuronal activity provokes an increase in oxygen consumption and an even higher **increase in local blood flow** (**neurovascular coupling**).

As the increase in flow exceeds the increase in oxygen consumption, neuronal activity leads to a **relative increase in oxyhemoglobin compared to deoxyhemoglobin in the activated zones**. The relative decrease in deoxyhemoglobin concentration, which has a paramagnetic effect, can be detected by MRI as a weak transient rise in the T2* weighted signal.

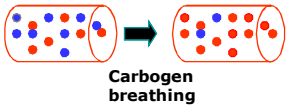
http://www.imaios.com/en/e-Courses/e-MRI

# Applications of fMRI

## Neurophysiology

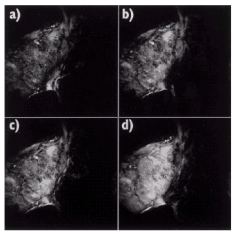


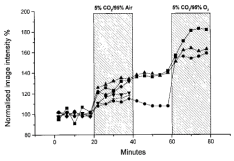

## Oncology



**Carbogen breathing**

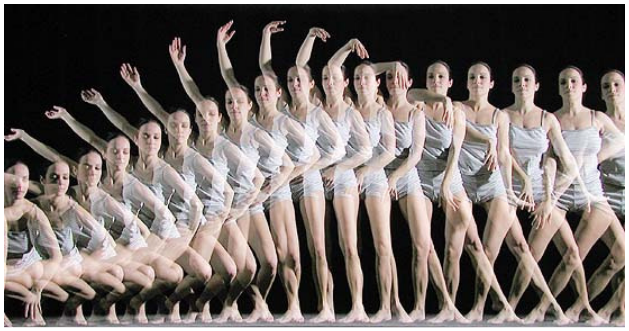
Level of blood oxygenation ↑
DeoxyHb ● /OxyHb ● blood content ↓
} ↑ SI



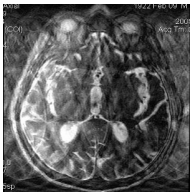

*GS Karczmar, NMR Biomed 1994, 12, 881*
*SP Robinson, IJROBP 1995, 33, 855*
*C. Baudelet, MRM 2002, 48, 980*

# Motion as a source of contrast




# Motion as a source of contrast

- **Motion artifacts…**



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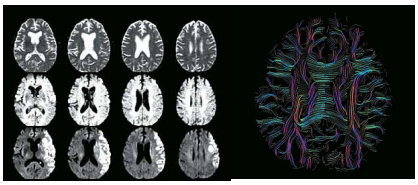
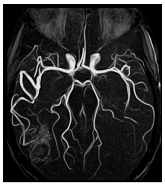
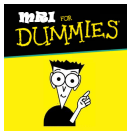
- **Microscopic movements (diffusion)**



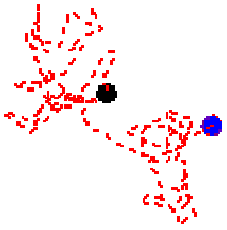
- **Macroscopic movements (angiography)**



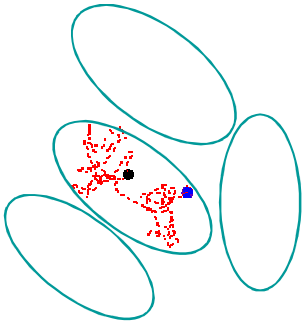



# Diffusion-weighted MR imaging

**Diffusion imaging** focuses on the micromovements (random, brownian) of the **water molecules** inside voxels



True diffusion

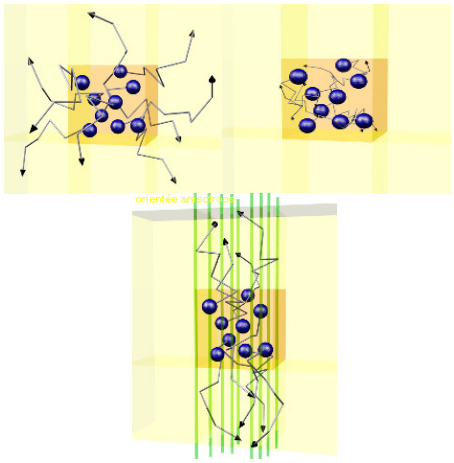


Apparent diffusion
ADCw

# Diffusion-weighted MR imaging

The displacement of water molecules can be summarized into three different types of freedom of movement:

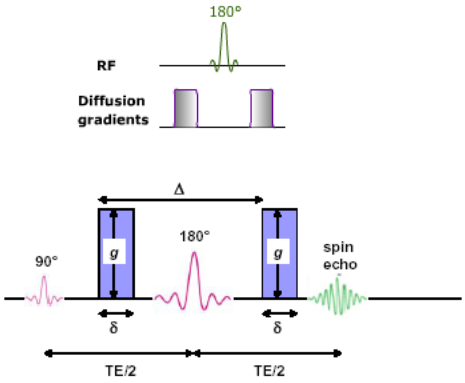
- **Free diffusion**: all spatial directions
- **Restricted isotropic diffusion** displacement is restricted, in whatever spatial direction, by numerous obstacles (proteins, cells)
- **Restricted anisotropic diffusion** certain structured tissues create obstacles that orientate the motion of the water molecules (tendency to displace themselves in one or several particular directions)



http://www.imaios.com/en/e-Courses/e-MRI

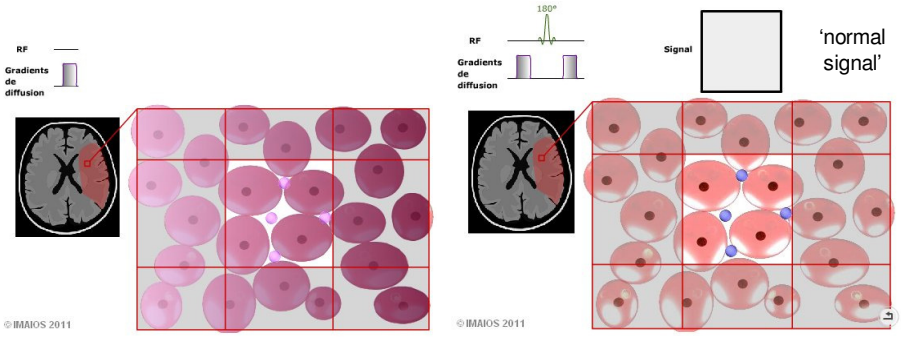
# Diffusion gradients

- The aim of these diffusion-weighted sequences is to obtain images whose contrast is influenced by the differences in water molecule mobility
- This is done by adding diffusion gradients during the preparatory phase of an imaging sequence
- The diffusion gradients are strong and symmetrical in relation to the 180° rephasing pulse



# Diffusion-weighted MR imaging

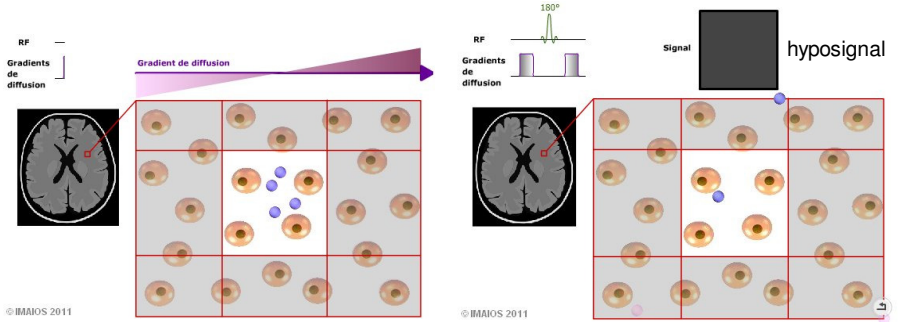
The spins of the immobile water molecules between the applications of the two gradients are dephased by the first gradient and rephased by the second




http://www.imaios.com/en/e-Courses/e-MRI

# Diffusion-weighted MR imaging

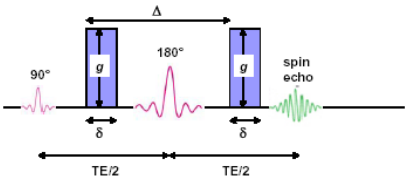
The spins of the water molecules that move in the direction of the gradients, during the interval between the two gradient applications, will not be rephased by the second gradient: they dephase in relation to the hydrogen nuclei of the immobile water molecules (hyposignal)




http://www.imaios.com/en/e-Courses/e-MRI

# Diffusion weighting, ADC

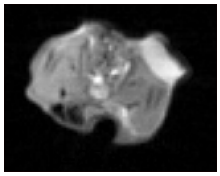
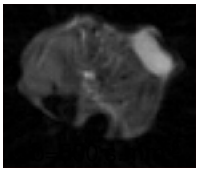
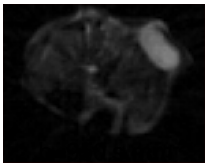
- **The attenuation of the MR signal** results from the dephasing of the nuclear spins due to the combined effect of the translational motion and the gradients
- The degree of diffusion weighting of the sequence, expressed as the **b-factor** (in s/mm$^2$), depends on the characteristics of the diffusion gradients:
  - gradient amplitude
  - application time
  - time between the two gradients



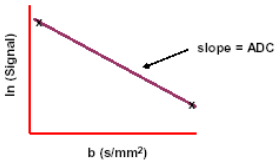

$$b = \gamma^2 \delta^2 g^2 \left( \Delta - \frac{\delta}{3} \right)$$

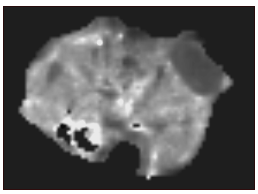
# Diffusion weighting, ADC

Two (or more) diffusion sequences with different b-factors can be used to quantitatively measure the degree of molecular mobility, by calculating the apparent diffusion coefficient (ADC)

$$S = S_0 \exp(-b \cdot ADC)$$



The ADC map is not dependent on the $T_2$, contrarily to the simple DW-Image

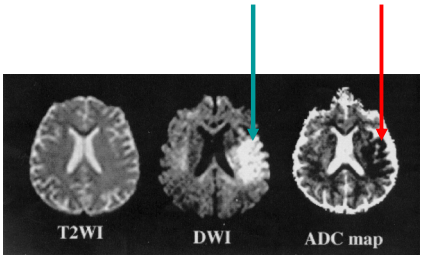
## Diffusion weighting / ADC
## Examples of application

### Cerebral stroke

**Acute stroke → cytotoxic oedema**

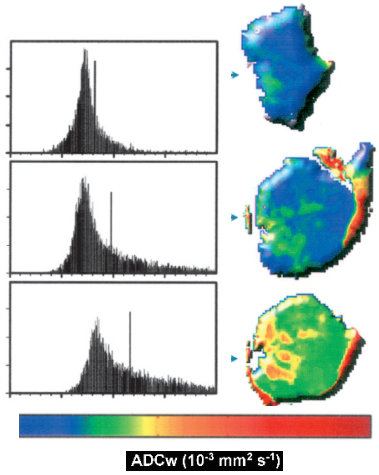
**↑intracellular water → restricted diffusion**

**Hyperintensity in DWI, ↓ ADC**




### Marker of tumor response

**Cytotoxic effect → ↑ ADC**



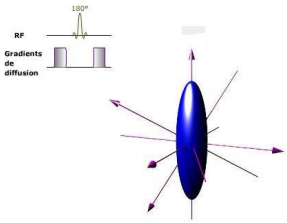

## DW-MRI - DTI

- **DW-MRI** aims at highlighting the differences in water molecule mobility, irrespective of their direction of displacement

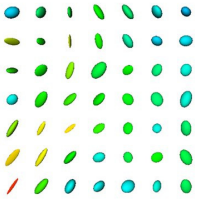
- **Diffusion Tensor Imaging (DTI)** studies the directions of water molecule motion to determine, for example, whether or not they diffuse in all directions (fractional anisotropy), or attempts to render the direction of a particular diffusion (which can be applied to indirectly reconstituting the nerve fiber trajectory)


# Diffusion tensor and anisotropy

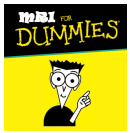
- The microarchitecture specific to nerve tissues causes diffusion anisotropy in the white matter of the brain: water molecule diffusion preferably follows the direction of the fibers and is restricted perpendicularly to the fibers
- By performing diffusion-weighted acquisitions in at least 6 directions (and far more in angular high resolution imaging), it is possible to extract the diffusion tensor which synthesizes all the data




Diffusion tensor



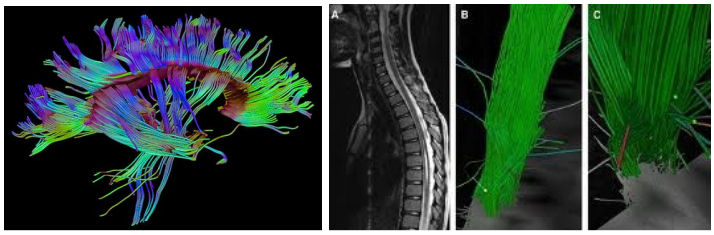
DTI




# Diffusion tensor and anisotropy

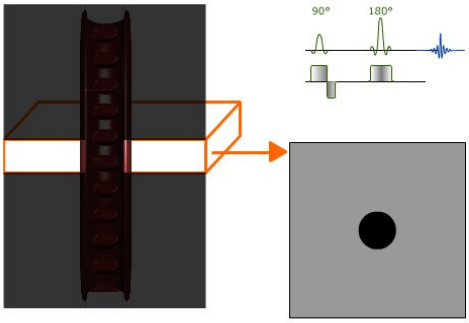
The **diffusion tensor** characterizes diffusion: anisotropic coefficient, preferred directions and restrictions in space. Different images will be obtained depending on the complexity of the post-processing of this data

- Fractional anisotropy (null when diffusion is isotropic, of increasing value when diffusion becomes anisotropic)
- Main diffusion direction
- Fiber tracking



# Sensitivity of MR signal to flow

- The spins in the blood are excited during the slice selection pulse
- At time TE/2 some of these spins move out of the slice and so are not subjected to the 180° pulse: therefore there is a reduction in the signal from their initial region.
- Vessels appear as hyposignals in Spin-Echo due to the outflow effect






http://www.imaios.com/en/e-Courses/e-MRI

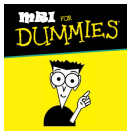
# Basic Principles of MR Angiography (MRA)

- These sequences implement a strategy to suppress the background signal represented by the stationary tissue.
- All these techniques can be adapted to 3D
- One illustrative example of MRA vascular contrast:

  **Time-of-flight**: uses modifications linked to blood volume displacement, which will not be subjected to all the RF pulses, unlike the stationary tissue.


# Time-of-flight angiography

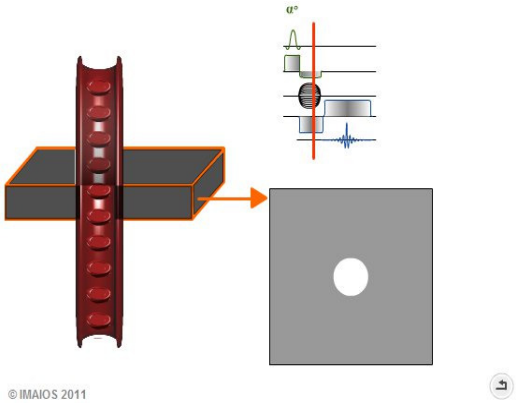
- Saturation of the stationary tissue signal with very short TR => the longitudinal magnetization of these tissues does not have time to regrow and their signal weakens
- Exploitation of the Inflow effect in GE: because the blood flowing into the explored zone has not been saturated, its longitudinal magnetization is maximal. The signal from the blood flow is thus stronger than that of the saturated tissues (no use of SE to avoid outflow effects)




# Time-of-flight angiography

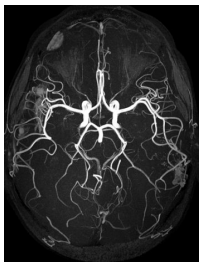
Signal depends on:

- Flow velocity
- Vessels length
- Vessels orientation
- TR, TE
- Slice thickness

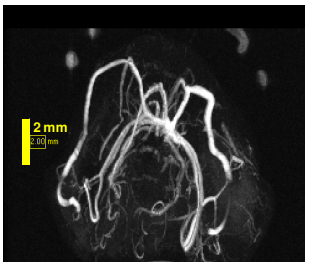



http://www.imaios.com/en/e-Courses/e-MRI

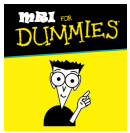

# Examples of MR Angiography (MRA)



TOF – Human Brain
3T




TOF – Mouse tumor
UCL, 11.7T




Exogenous sources of contrast

Contrast agents

www.uniklinik-freiburg.de


# Contrast in tissues

**The endogenous contrast between tissues depends on**:

- Water content
- Proton mobility
- **Relaxation times**

Example: the signal intensity I (in the spin-echo sequence)

$$I = N(H).v.(1-e^{-TR/T1}).e^{-TE/T2}$$

The **MRI contrast agents** (magnetopharmaceuticals) will act by changing the **relaxation times** of the protons


# Classes of MRI contrast agents

- **Paramagnetic agents (gadolinium)**
  - Gd produces a decrease in $T_1$
  - Shorter $T_1$ produces bright $T_1$ images
  - Gd is a $T_1$ « positive » contrast agent
- **Superparamagnetic agents (iron oxide)**
  - Iron oxides produce a decrease in $T_2$ and $T_2^*$
  - Shorter $T_2$ produces dark $T_2$ images
  - Iron oxides are $T_2$ « negative » contrast agents

*At least, in most cases !...*

# Relaxivity $r_1$ and $r_2$

- **Relaxation rates**: $R_1 = 1/T_1$ and $R_2=1/T_2$ $(s^{-1})$
- **Relaxivity ($r_i$, $s^{-1}$ $mM^{-1}$)**: Contribution to the observed water proton relaxation rate that a contrast agent (CA) complex gives to a solution in which it is solved in 1 mM concentration
- **Influence of CA on relaxation rates**:

  $R_{i\ observed} = R_{i\ tissue} + r_i \cdot [CA]$

- ***Relaxometric property indicator $r_2/r_1$***
  - **Paramagnetic** (Gd): $r_2/r_1$ between 1 and 2

    As $T_{2\ tissues} << T_{1\ tissues}$ (or $R_{2\ tissues} >> R_{1\ tissues}$) and $r_2 \approx r_1$,

    **the major effect observed is the decrease in $T_1$**

    Liver $T_1$= 500 ms $R_1$=2 $s^{-1}$ Gd-DTPA: $r_1$= 4.5 $s^{-1}$ $mM^{-1}$

    $T_2$= 50 ms $R_2$=20 $s^{-1}$ $r_2$= 6 $s^{-1}$ $mM^{-1}$

    If [Gd-DTPA]= 0.1 mM

    $R_1$ post = 2.45 s-1 $T_1$ post = 408 ms $\Delta T_1$ : ~ 20%

    $R_2$ post = 20.6 s-1 $T_2$ post = 48.5 ms $\Delta T_2$ : ~ 3%
  - **Superparamagnetic** (iron oxide): $r_2/r_1$ as higher as 50

    **the major effect observed is the decrease in $T_2$**

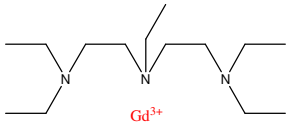
    (the change in signal decrease can not be compensated by the decrease in T1: signal disappears!)

# Gadolinium complexes

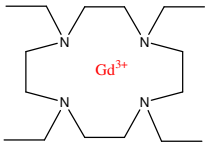
**Free $Gd^{3+}$ ion is highly toxic even at low doses (10-20 µmol/kg)**

⇨ **Need to use tight chelates to prevent the toxicity**

**Linear complexes : DTPA-like**



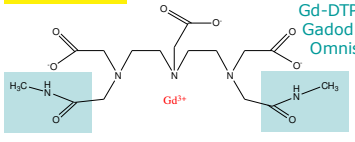

**Macrocyclic complexes: DOTA-like**



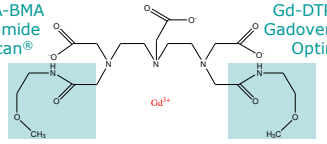

**Important to have at least one water molecule coordinated to the metal ion: the « inner sphere » relaxation process is more efficient.**

**The charge and the substitution on the backbone will influence:**
- **the stability of the complex**
- **the pharmacokinetics of the complex**

# Linear Gd complexes



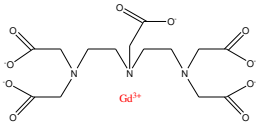
Gd-DTPA-BMA
Gadodiamide
Omniscan®



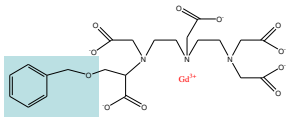
Gd-DTPA-BMEA
Gadoversetamide
Optimark®

**Hydrophilic**
**Extracellular**

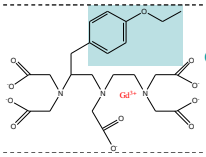
**Non Ionic**
**Lower stability**



Gd-DTPA
Gadopentetate
Magnevist®



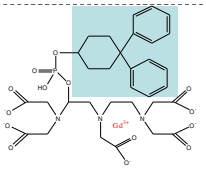
Gd-BOPTA
Gadobenate
MultiHance®



Gd-EOB-DTPA
Gadoxetate
Primovist®

**More lipophilic**
**Hepatobiliary**

**Substitution**
**Higher stability**



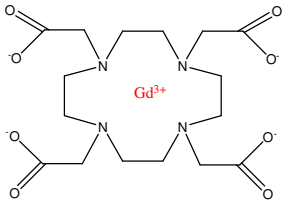
MS-325
Gadofosveset
Vasovist®

**Affinity for Albumin**
**Vascular**

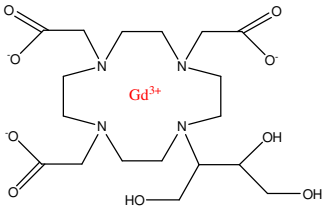
**Substitution**
**Higher stability**

# Macrocyclic Gd complexes

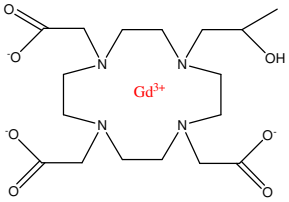
Gd-DOTA
Gadoterate
Dotarem®



Gd-BT-DO3A
Gadobutrol
Gadovist®



Gd-HP-DO3A
Gadoteridol
ProHance®

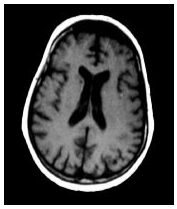


**All commercial macrocyclic compounds are extracellular**

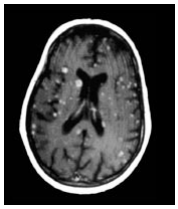
**Very high kinetic stability**


# Added value of contrast-enhanced MRI

**Qualitative information**



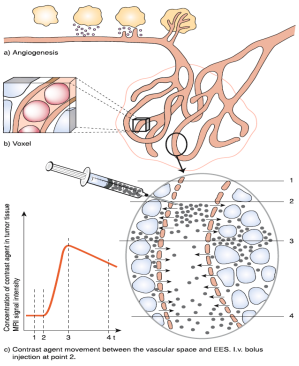
Before Gd-DTPA

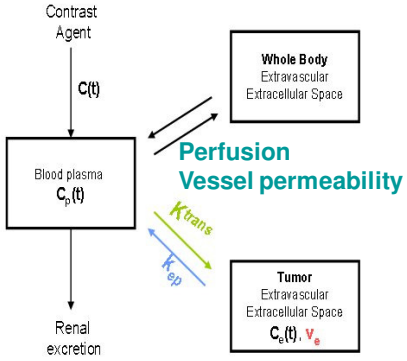


After Gd-DTPA

**Quantative information**

**DCE-MRI**

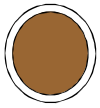




# Superparamagnetic agents

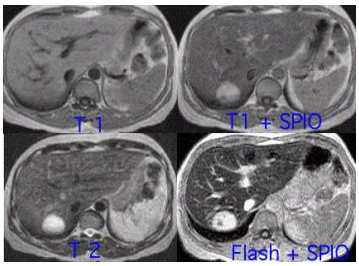
- **Composition**:
  - Magnetic iron oxide core (magnetic properties)
    - Magnetite $Fe_3O_4$
    - And/or Maghemite $Fe_2O_3$
  - Exterior coating material (biocompatibility, avoid agregation, possible targeting)



- **Size**:
  - Oral SPIOs: 300 nm-3.5 µm
  - Parenteral SPIOs: 60-150 nm
  - USPIOs: 5-40 nm

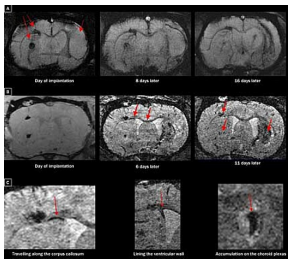
# Superparamagnetic agents
# Example of application

**Passive targeting**
**Uptake by RES**



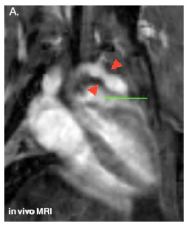

Depending on the size:
Kuppfer cells
Lymph nodes

**Cell labeling**



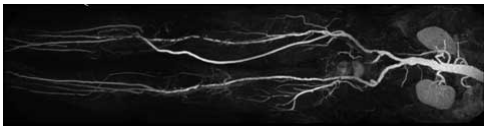
Labeling
of stem cells

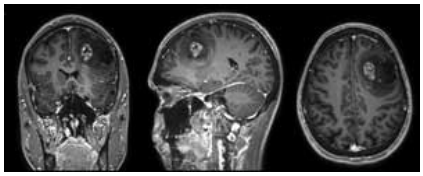
**Active targeting**

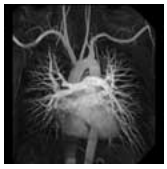


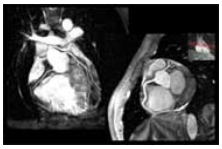

VCAM-targeting
Atherosclerotic plaques

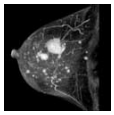
**MRI**
**A unique world to discover**

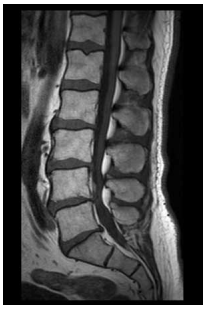


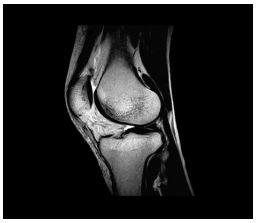


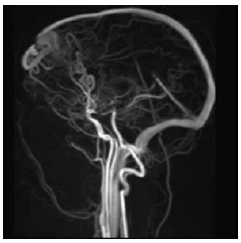


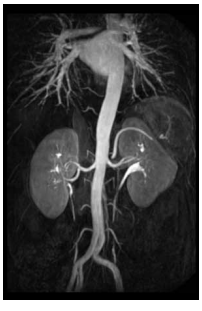


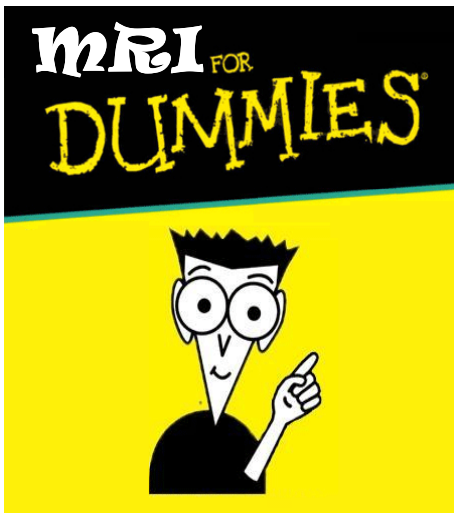











MRI FOR
DUMMIES


"That's all Folks!"