Advanced NMR & Imaging

Lecture 2: Contrast in Magnetic Resonance Imaging

Objectives

- Understand different approaches to generating contrast in MR Images.

Bibliography for MRI

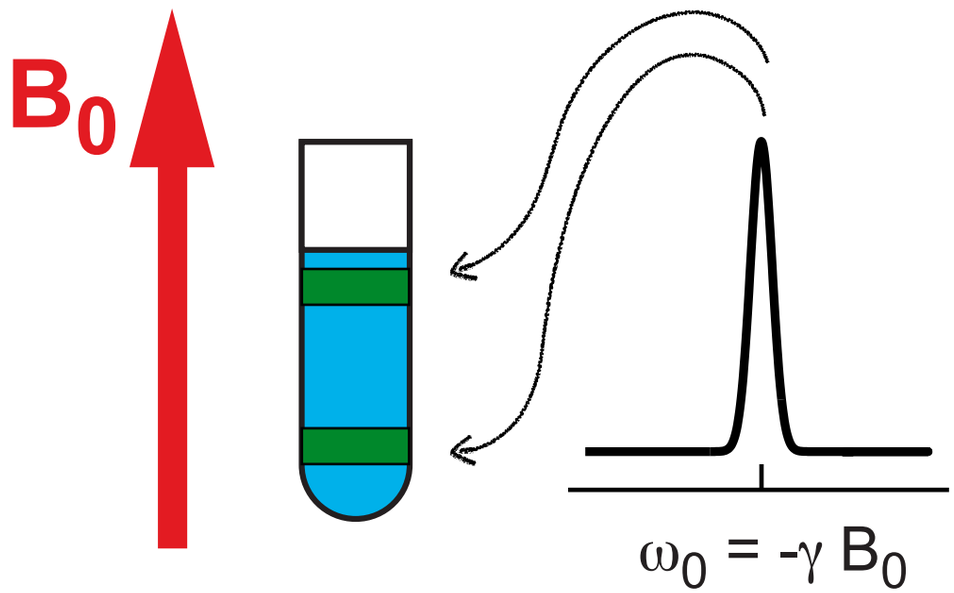
Many internet based resources and tutorials.

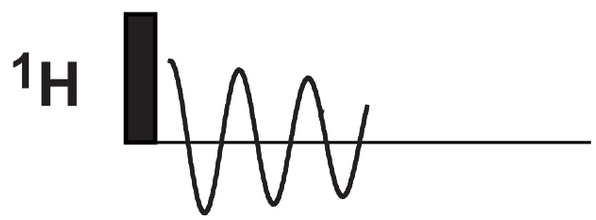
P. T. Callaghan. “Principles of nuclear magnetic resonance microscopy.” Oxford University Press, Oxford, 1993

many other books….

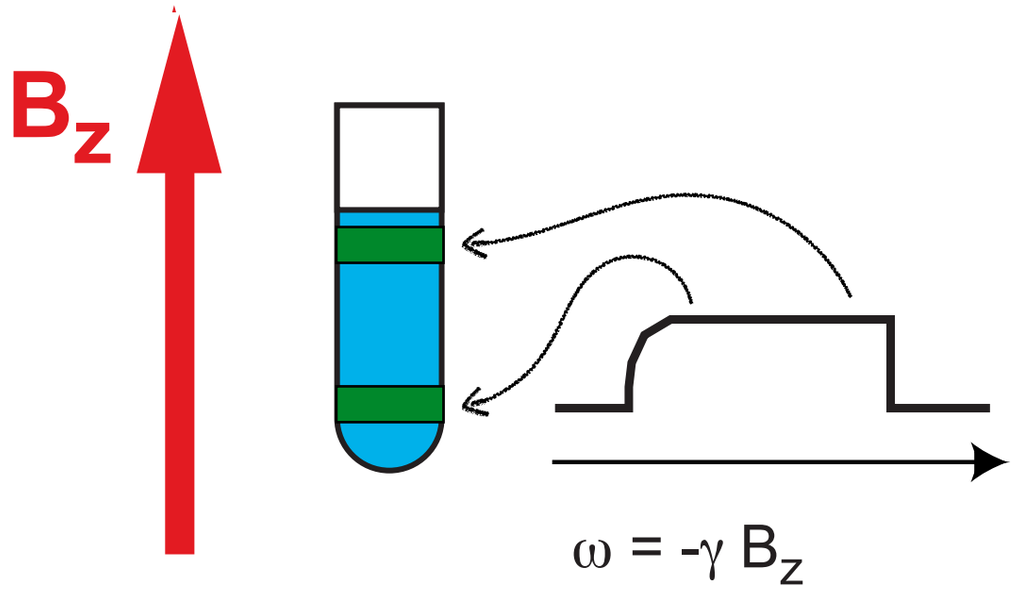
Principles of Magnetic Resonance Imaging

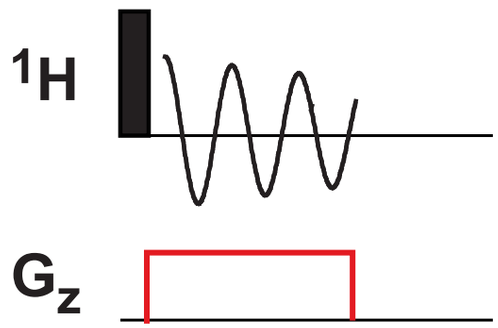
Spectroscopy





1D-Imaging (profile)



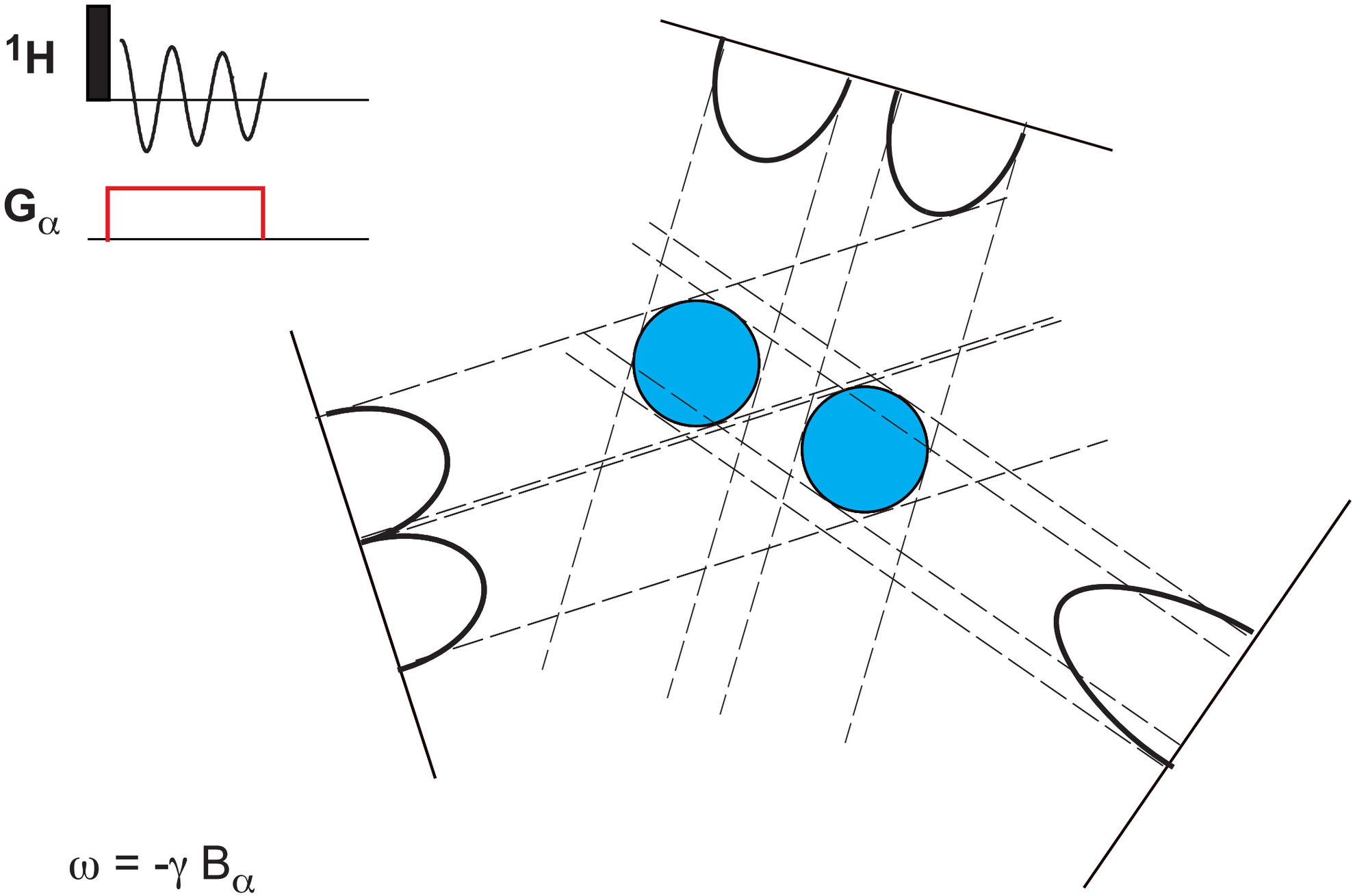


The spatial resolution in MRI depends on the gradient strength.

In imaging, we adjust the applied magnetic field to deliberately create a magnetic field gradient along a given spatial direction so that the molecules in the sample have a resonance frequency that is related to their position.

Multi-Dimensional Imaging?

change the gradient direction: (i) projection reconstruction

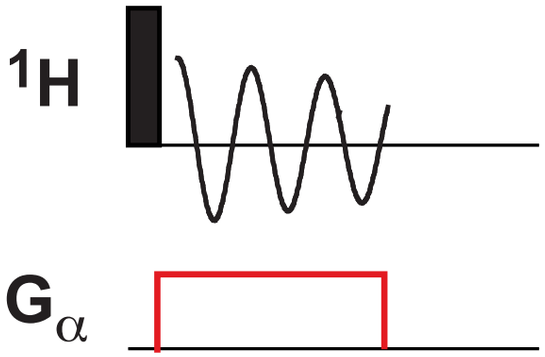


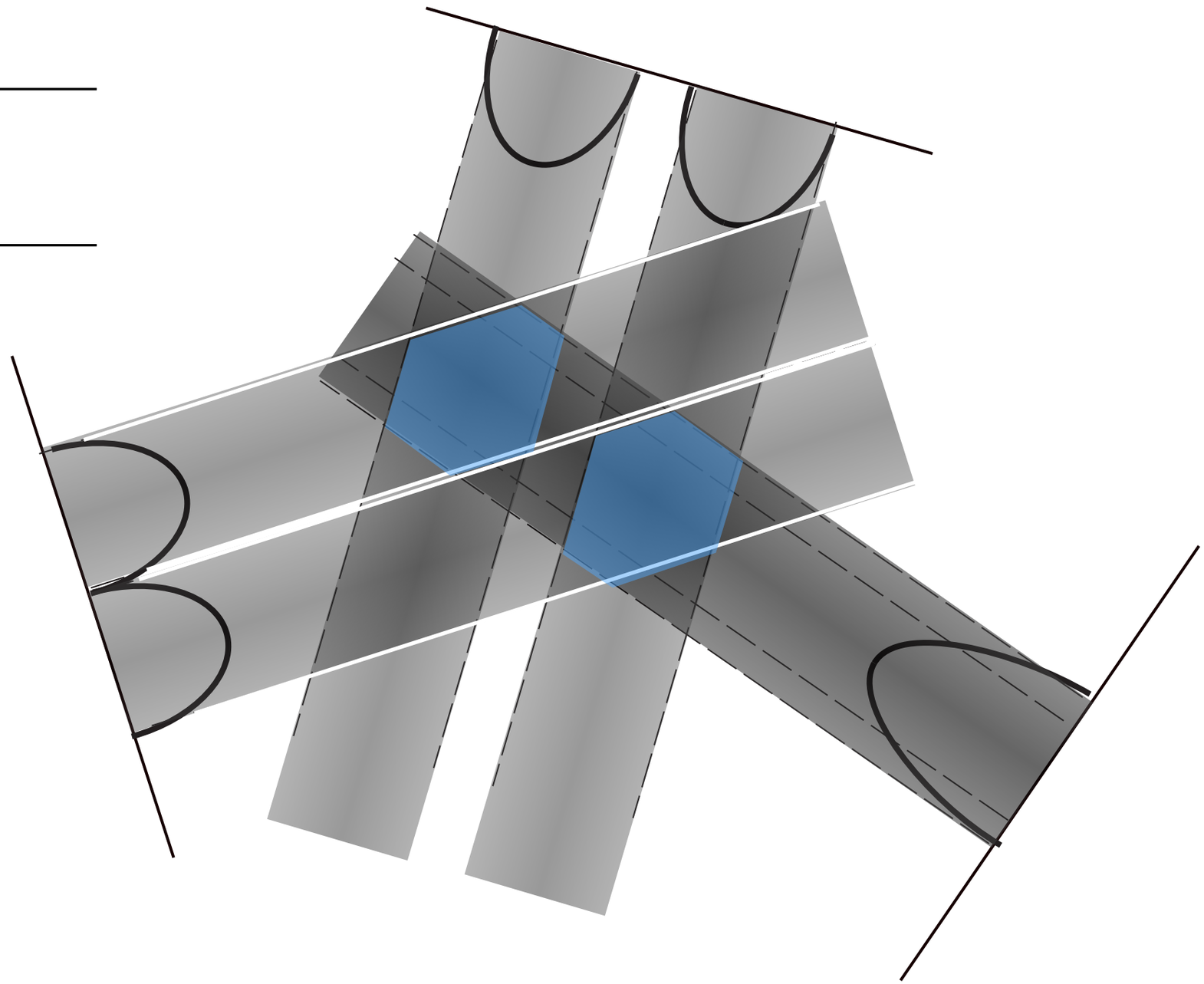
$$\omega = -\gamma B_\alpha$$

$$= -\gamma (B_0 + G_\alpha \alpha)$$

Multi-Dimensional Imaging?

change the gradient direction: (i) projection reconstruction

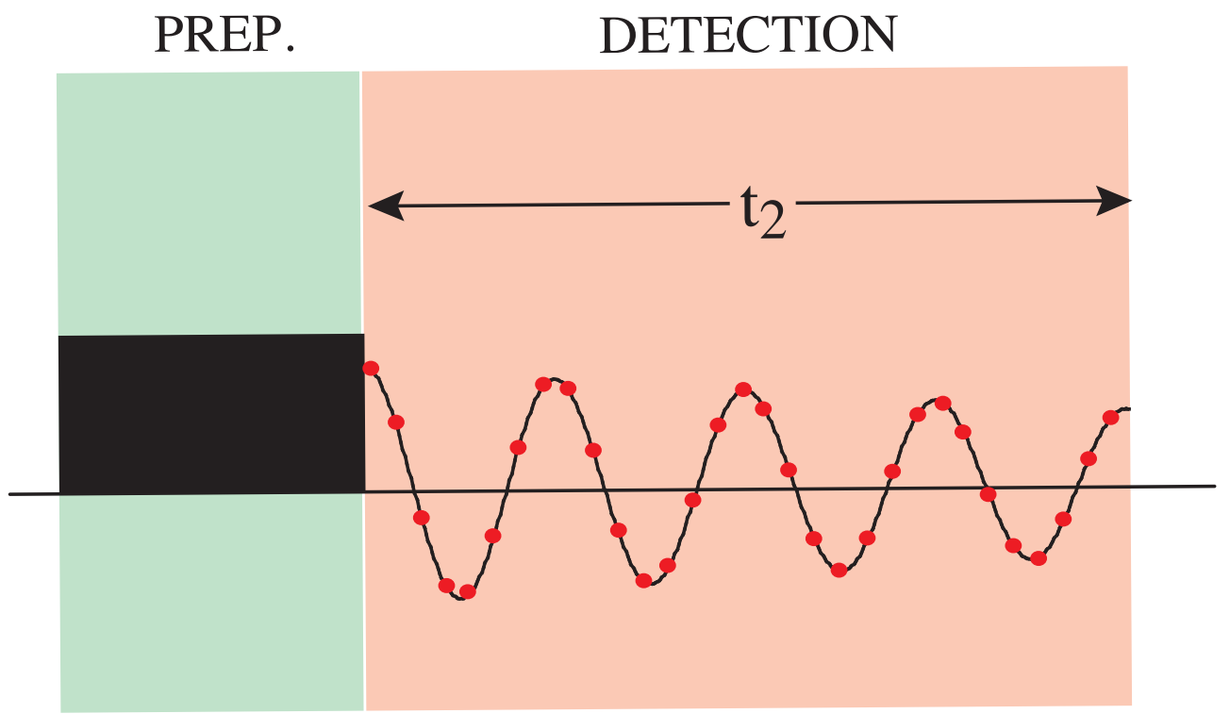




$$\omega = -\gamma B_\alpha$$

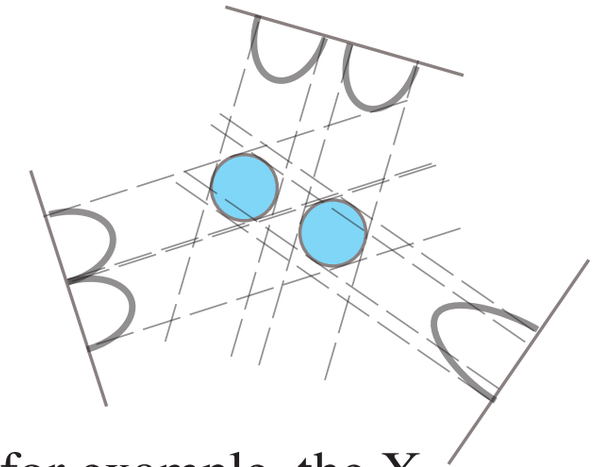
$$= -\gamma (B_0 + G_\alpha \alpha)$$

Recap: Time Domain Spectroscopy



Multi-Dimensional Imaging?

(i) Projection Reconstruction; k-space



The free induction decay during acquisition in presence of a gradient along, for example, the X direction, is given by

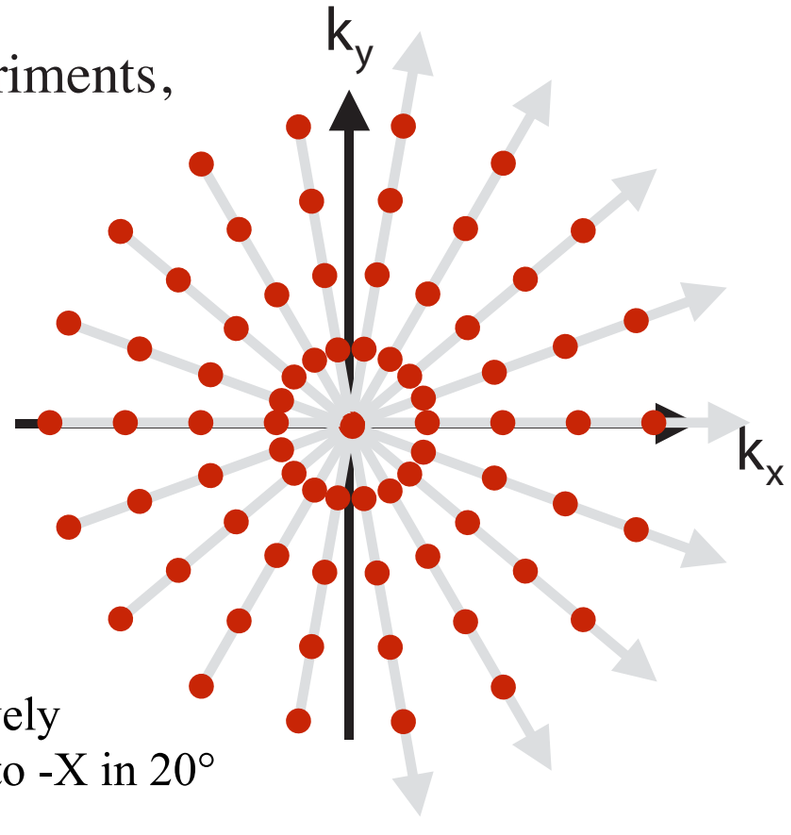
$$s(t_2) = \int \rho(X) \exp\{i\gamma X G_X t_2\} dX$$

where $G_X = dB_z/dX$ and we immediately see that the Fourier transform of the signal leads to a spectrum corresponding to a projection of the spin density onto the X axis.

We often talk about *k*-space (or reciprocal space) in imaging experiments, where the *k*-vector is given by $k_X = \gamma G_X t_2$. Then we have

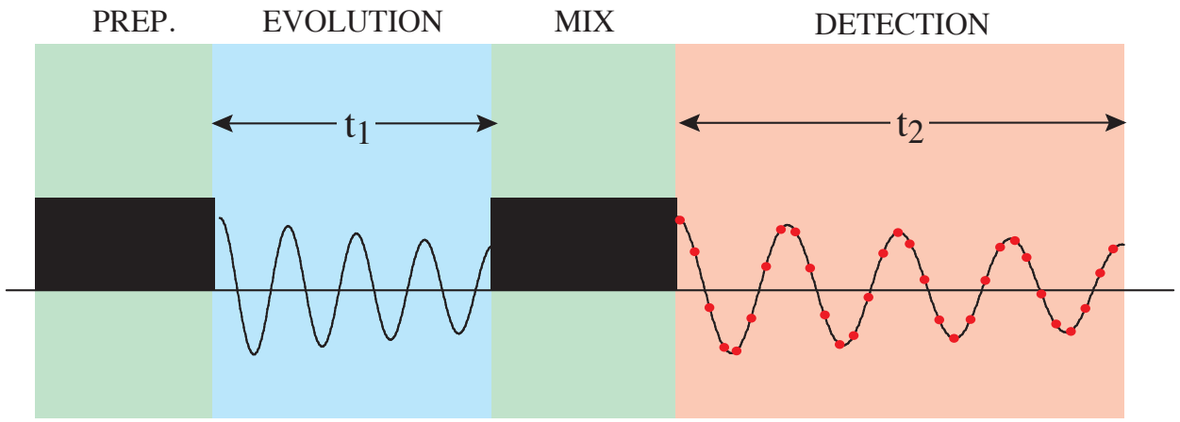
$$s(t_2) = \int \rho(X) \exp\{ik_X X\} dX \, .$$

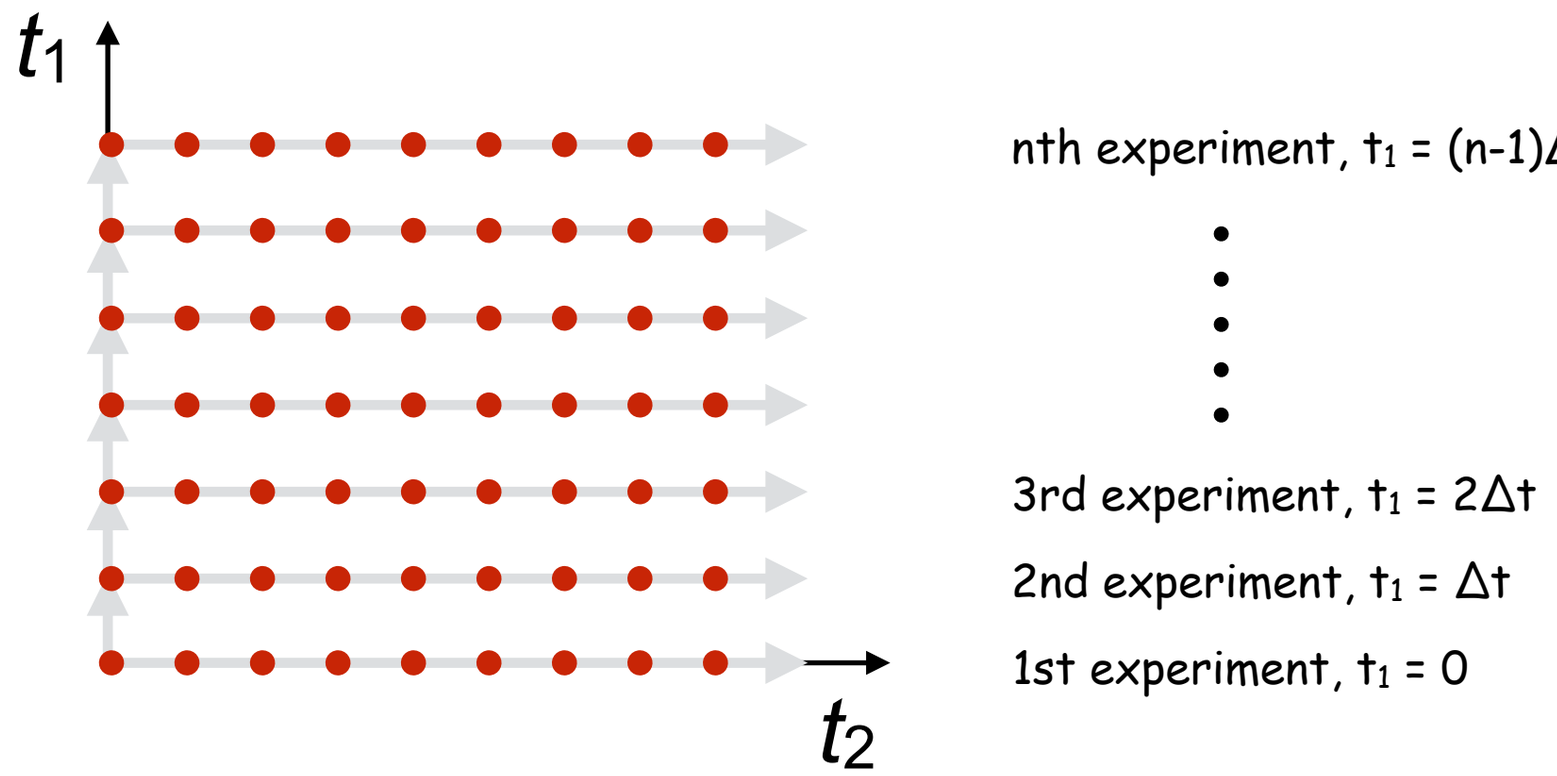
We can now look at the NMR signal in *k*-space. For projection reconstruction we find the following.



In this example, the experiment consists of acquiring 9 projections, progressively incrementing the gradient direction from being parallel to X to being parallel to -X in 20° steps

Principles of Multi-Dimensional Spectroscopy

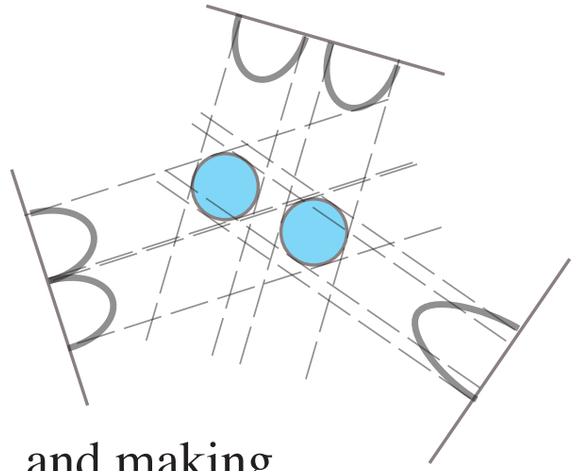




We can fill a two-dimensional time domain with data by repeating the experiment, with acquisition along t_2 in each experiment, and with t_1 being incremented progressively from one experiment to the next.

Multi-Dimensional Imaging?

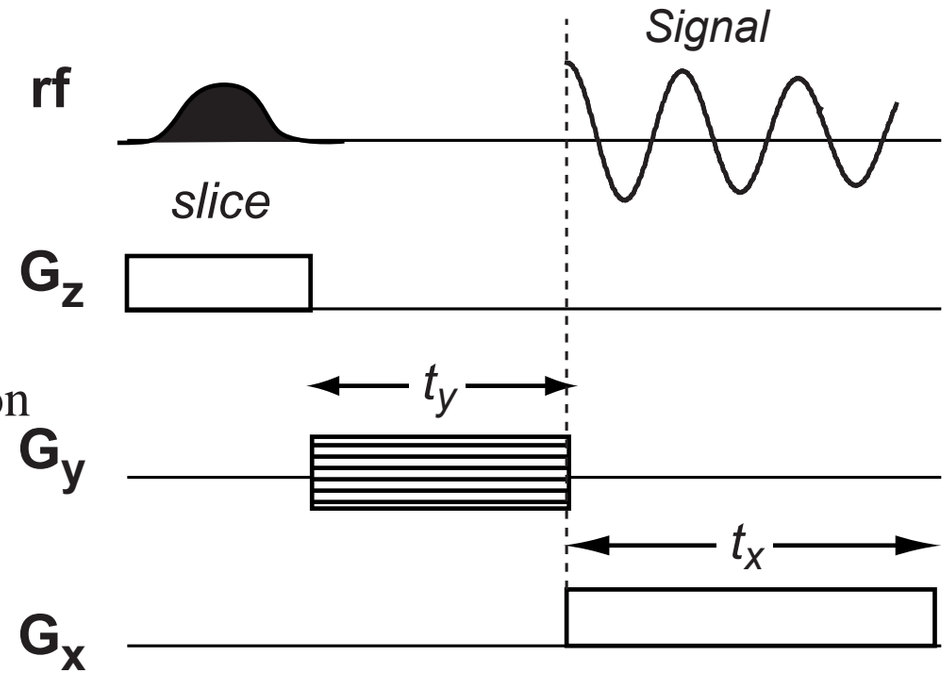
(ii) Fourier Imaging



Projection reconstruction over samples the center part of *k*-space, inducing artifacts, and making processing complicated. However, from our experience of multi-dimensional spectroscopy, we should see that there is a much more straightforward way to sample *k*-space, which yields the following signal, with $k_X = \gamma G_X t_X$ and $k_Y = \gamma G_Y t_Y$:

$$s(k_X,k_Y) = \int \rho(X,Y)\exp\{i(k_X X + k_Y Y)\}dXdY$$

Double Fourier transform yields a two dimensional image along the gradient directions X and Y.

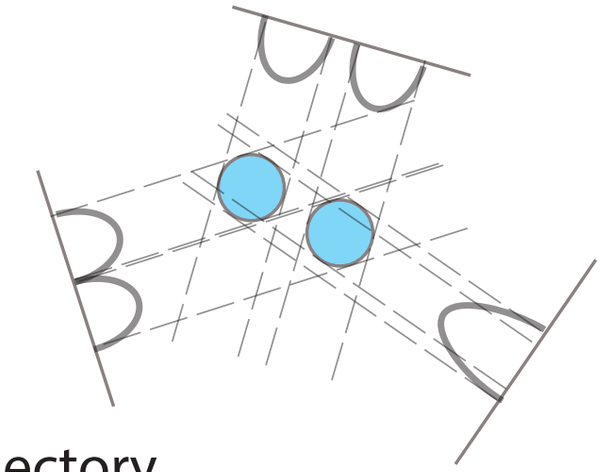


A full three-dimensional image could be obtained by acquisition along three gradient directions, X, Y, and Z, to yield a signal

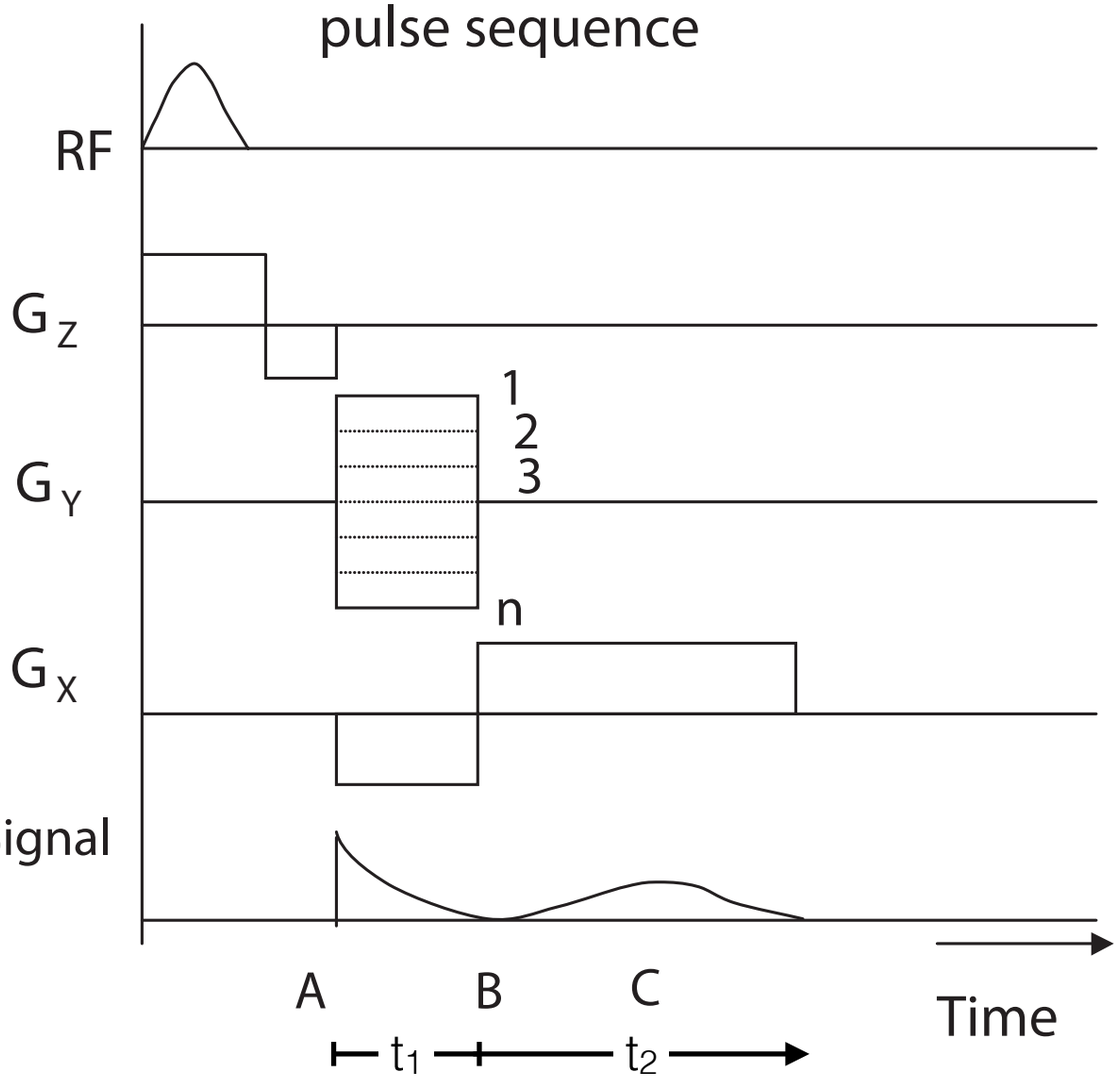
$$s(k_X,k_Y,k_Z) = \int \rho(X,Y,Z)\exp\{i(k_X X + k_Y Y + k_Z Z)\}dXdYdZ.$$

Multi-Dimensional Imaging?

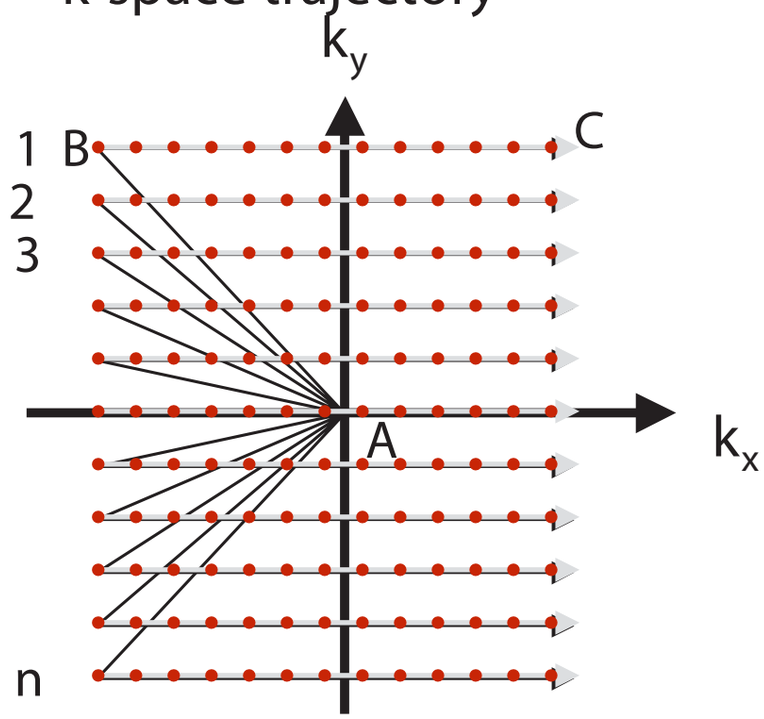
(ii) Fourier Imaging



Spin-warp
pulse sequence



Spin-warp
k-space trajectory



$k_x = \gamma(-G_X^{acq}\, t_1 + G_X^{acq}\, t_2)$

$k_y(n) = \gamma(G_Y^{n}\, t_1)$

In this example, the signal acquisition as a function of t_2 is always done with the gradient direction being parallel to X, and being constant in amplitude G_X^{acq}. Conversely, from one experiment to another the duration, t_1, of the gradient applied along the Y direction is kept constant, but the amplitude of the gradient along Y is incremented from G_Y^{max} to $-G_Y^{max}$ in 11 steps.

Multi-Dimensional Fourier Imaging

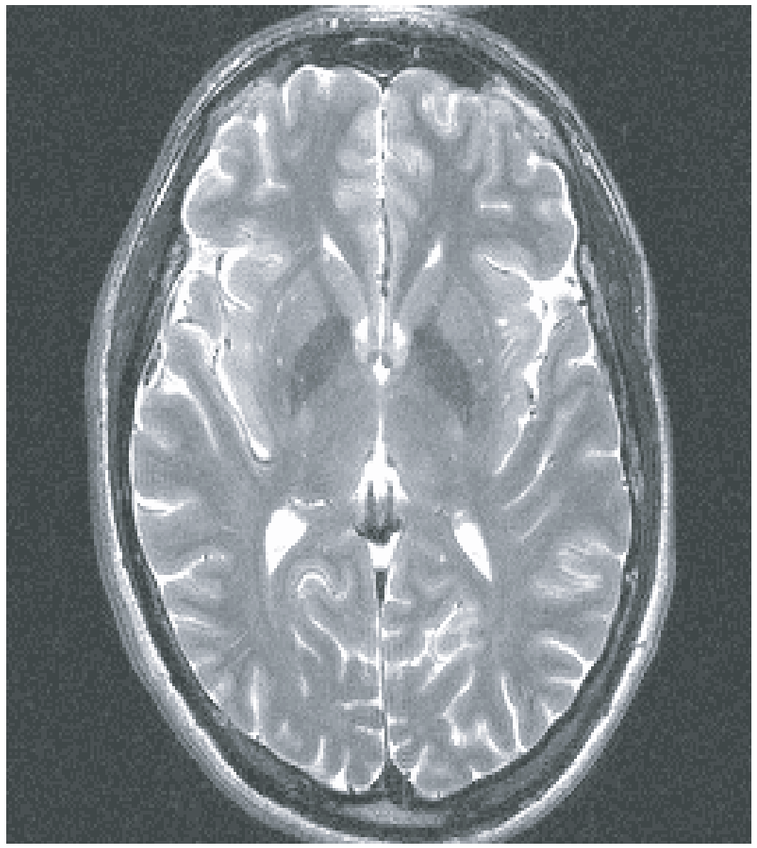
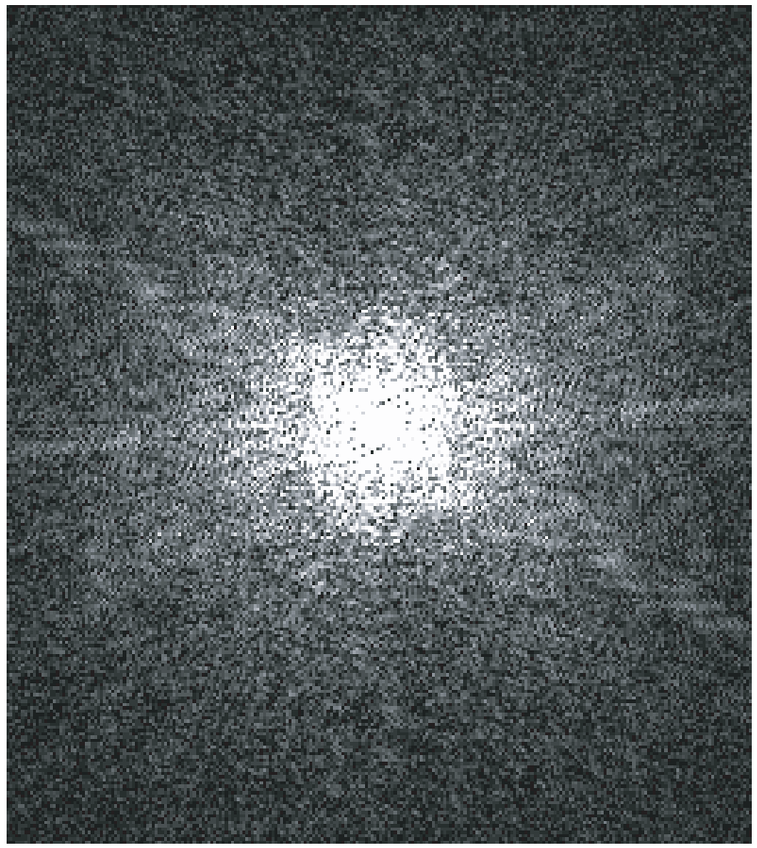


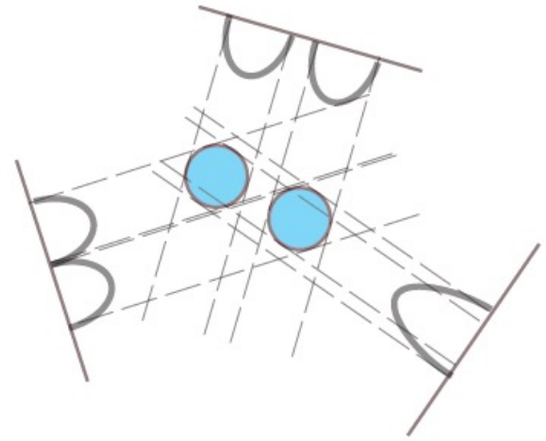
Image space

FT

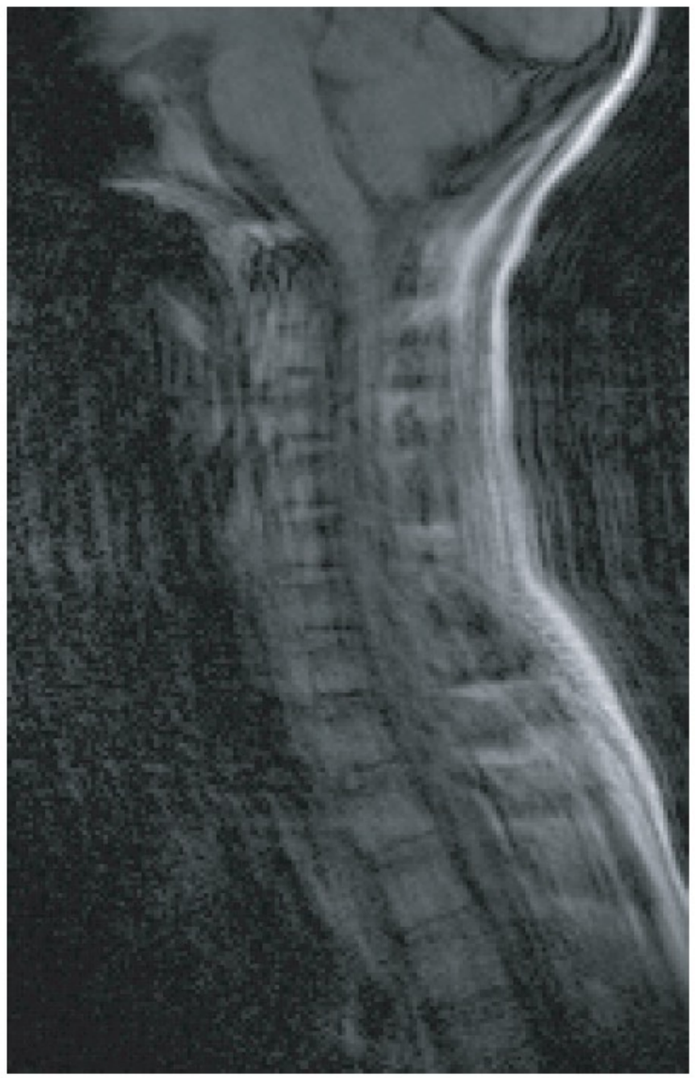


k space

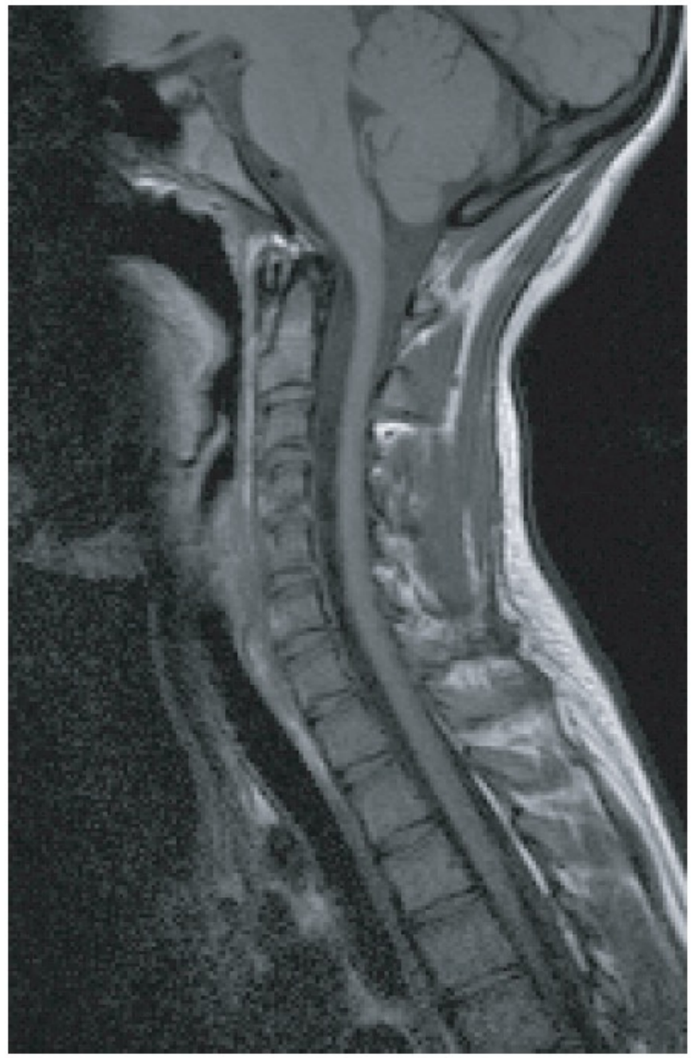
Problems due to Motion



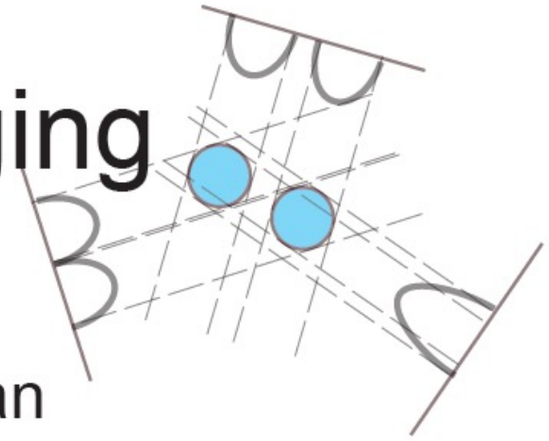
Macroscopic motion leads to image blurring....



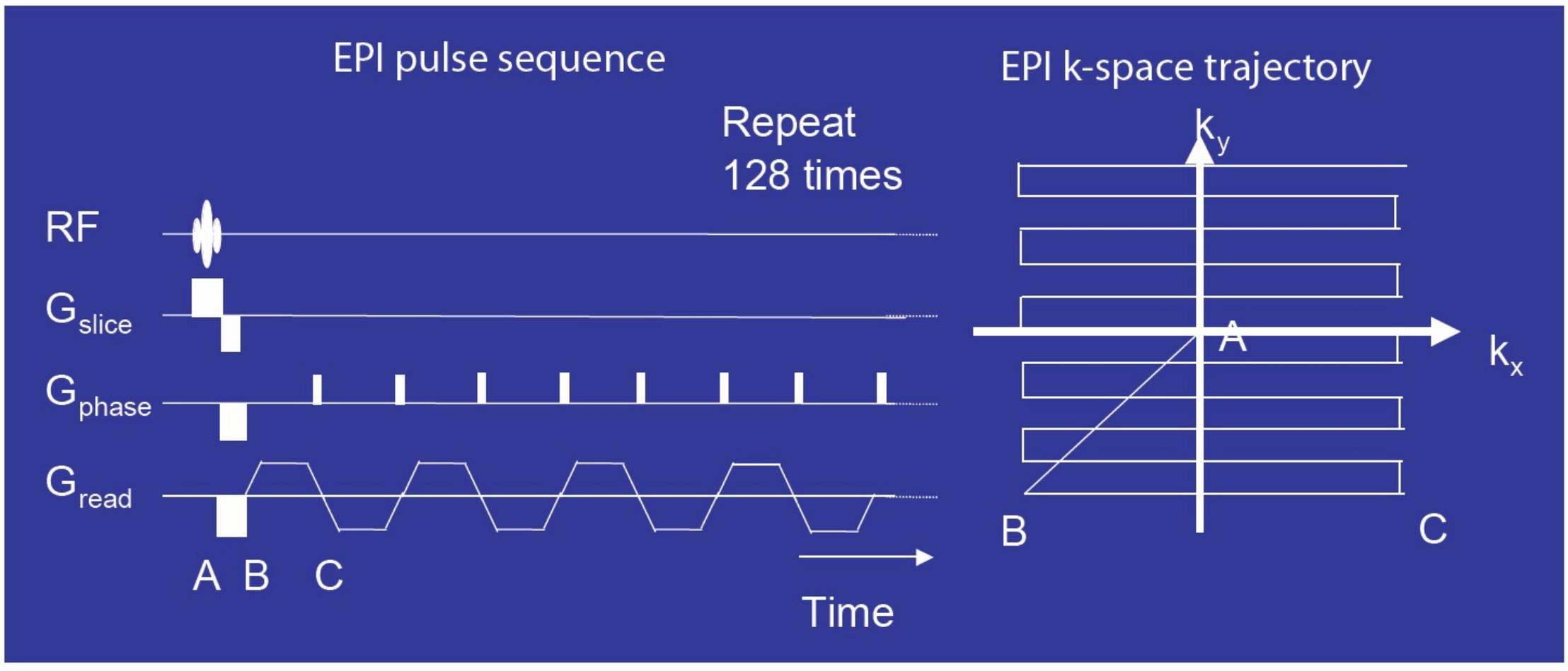
Anesthetic



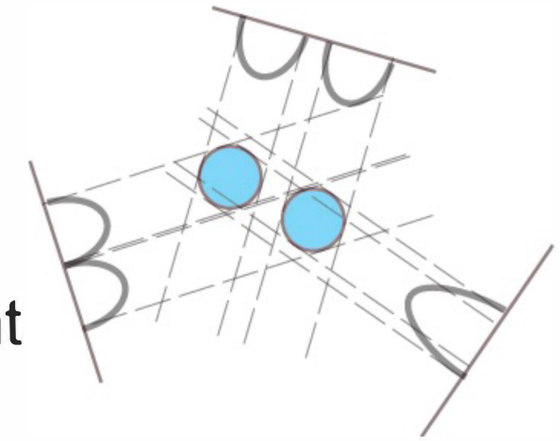
Fast Imaging: Echo Planar Imaging



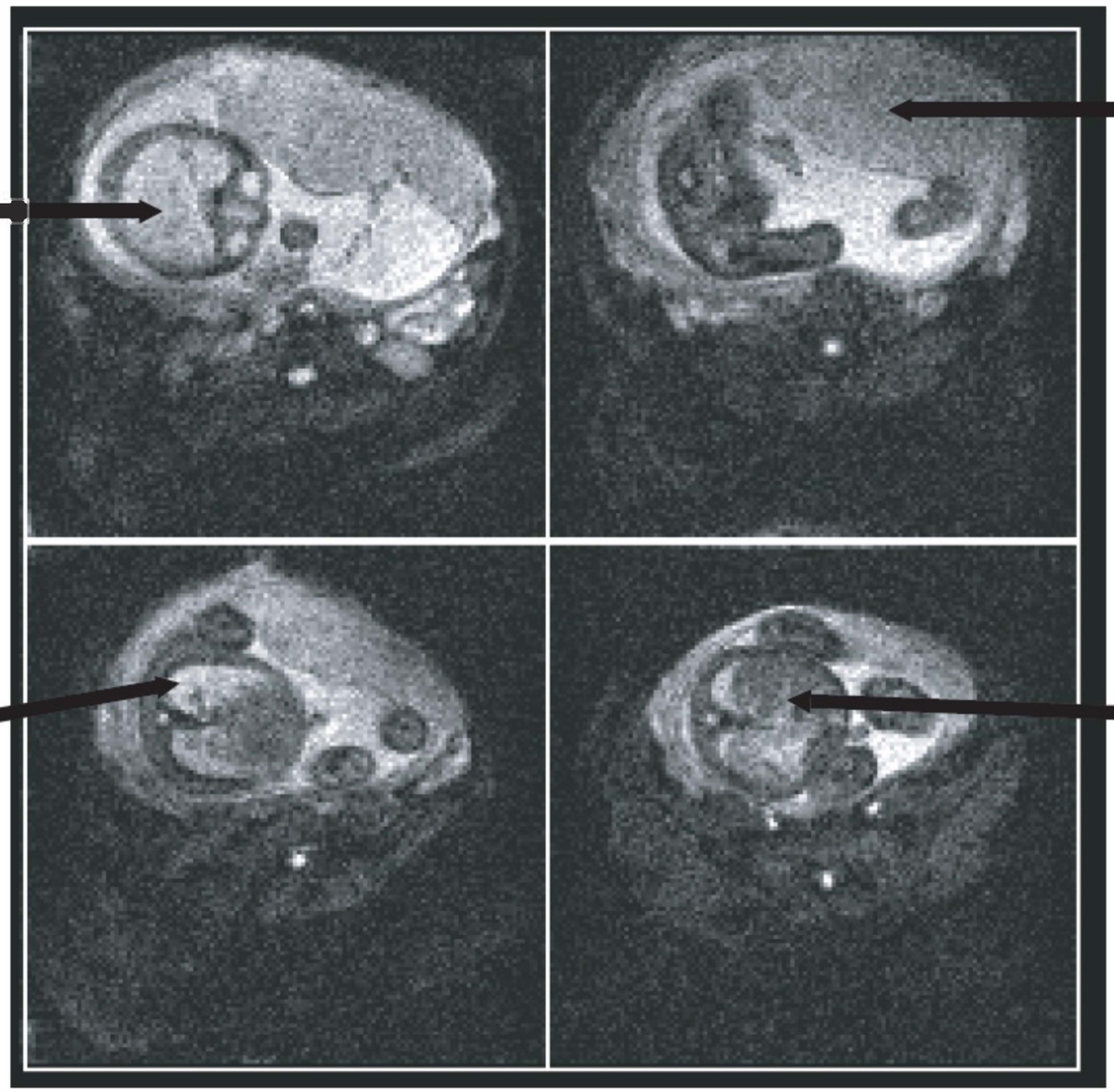
Once we understand the principles of imaging in *k* space,
we realise that a whole image can be acquired in a single scan
using "blipped" gradients (technically rather demading).....



Problems due to Motion

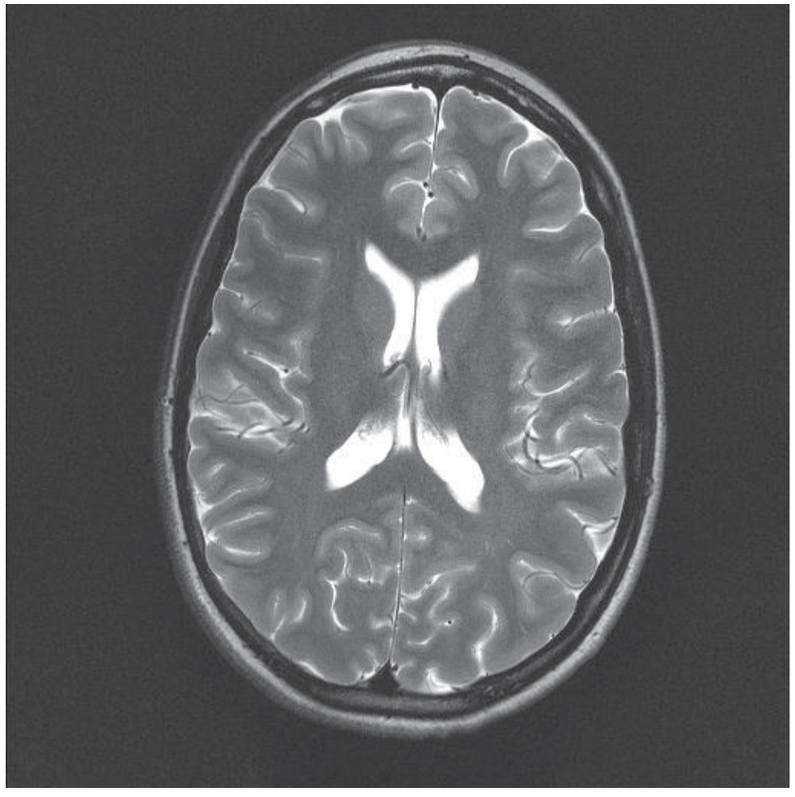


This is particularly important is cases where motion is present



EPI- fetus

Image contrast?

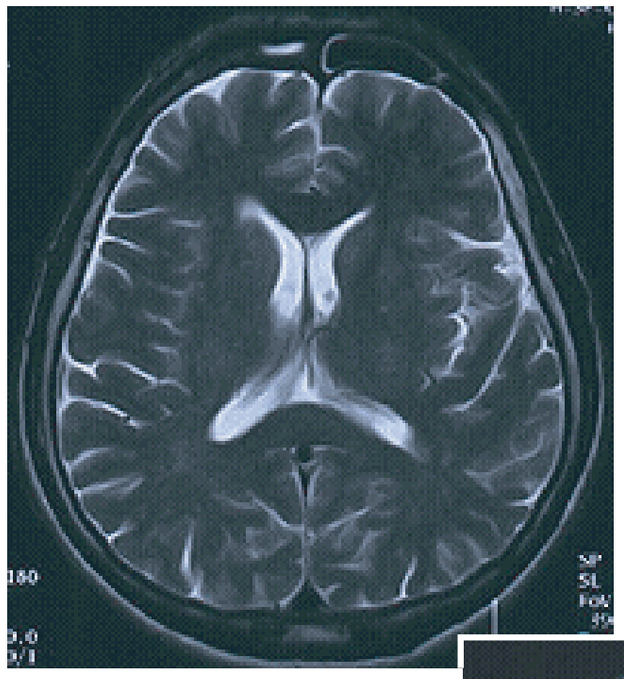


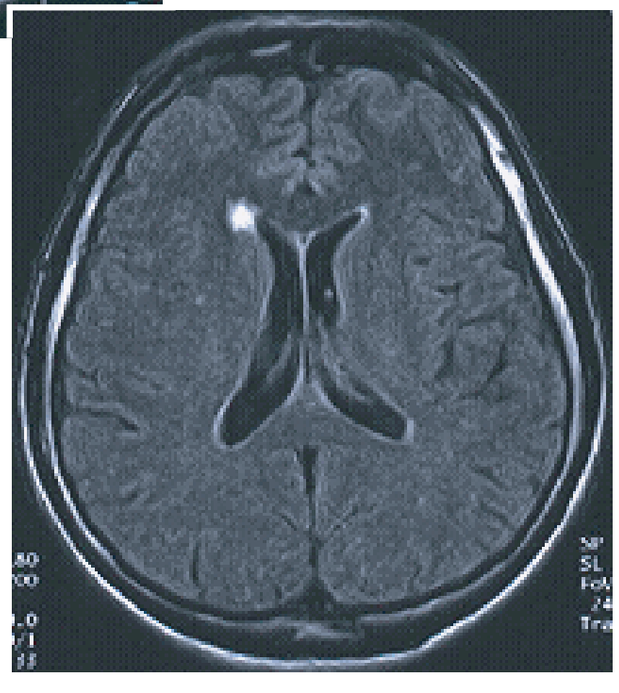
Where does the contrast in this image come from?

Spin (H_2O) density is more or less constant between white and grey matter....

tissue type	*water content*
grey matter	71 %
white matter	84 %
heart	80 %
blood	93 %
bone	12 %

Image contrast?





Worse (!?), these two images are of the same patient, at the same time. In one, CSF is bright. In the other CSF does not appear, and a MS plaque is bright.....

Image Contrast

- Can we enhance contrast further than just the natural T_1 and T_2 differences?

- Can we create contrast where there is no intrinsic difference in relaxation?

- Can we associate contrast to non-anatomical features?

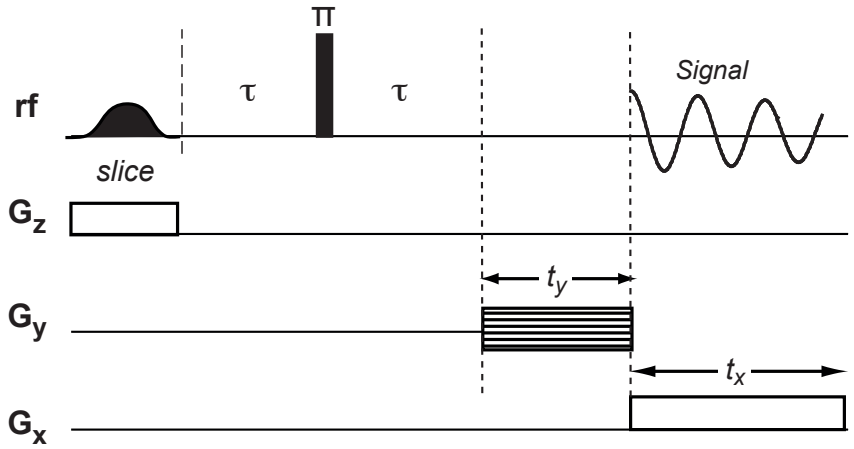
Image Contrast: T_1 & T_2 Weighting

Tissue	T1 (ms)	T2 (ms)
Grey Matter (GM)	950	100
White Matter (WM)	600	80
Muscle	900	50
Cerebrospinal Fluid (CSF)	4500	2200
Fat	250	60
Blood	1200	100-200

high contrast can be obtained for different tissue types by exploiting the considerable differences in relaxation times....

Image Contrast: T_2 Weighting

By introducing a spin echo period, this pulse sequence will weight the signal intensity by T_2.



Schematic signal intesities for two tissues having similar water content, but different T_2:

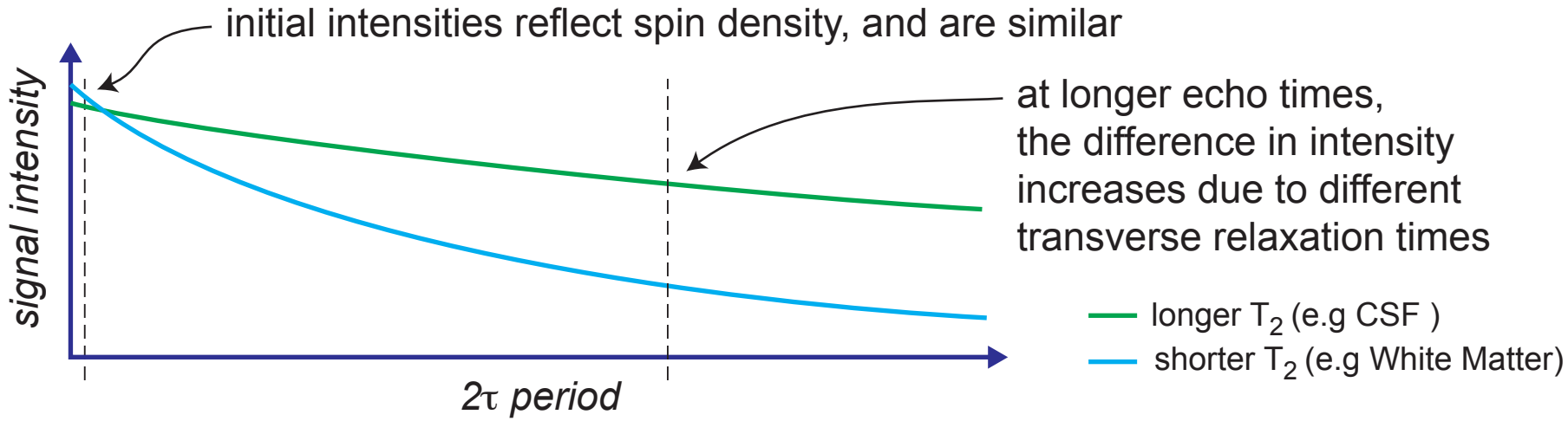
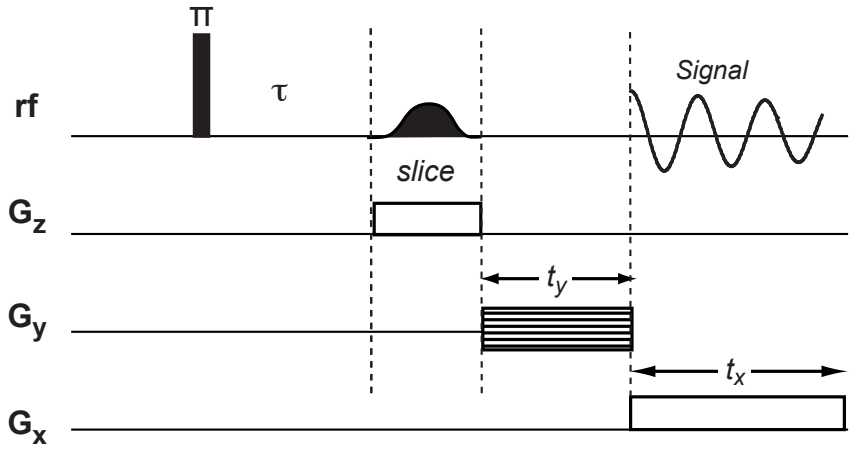
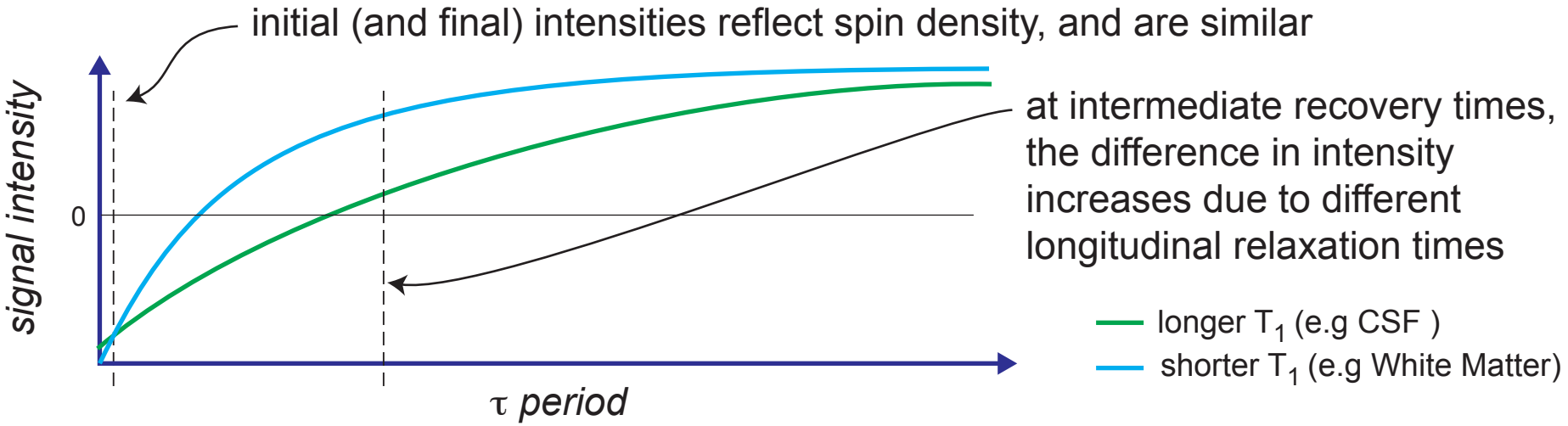


Image Contrast: T_1 Weighting

By introducing a inversion-recovery period, this pulse sequence will weight the singal intensity by T_1.



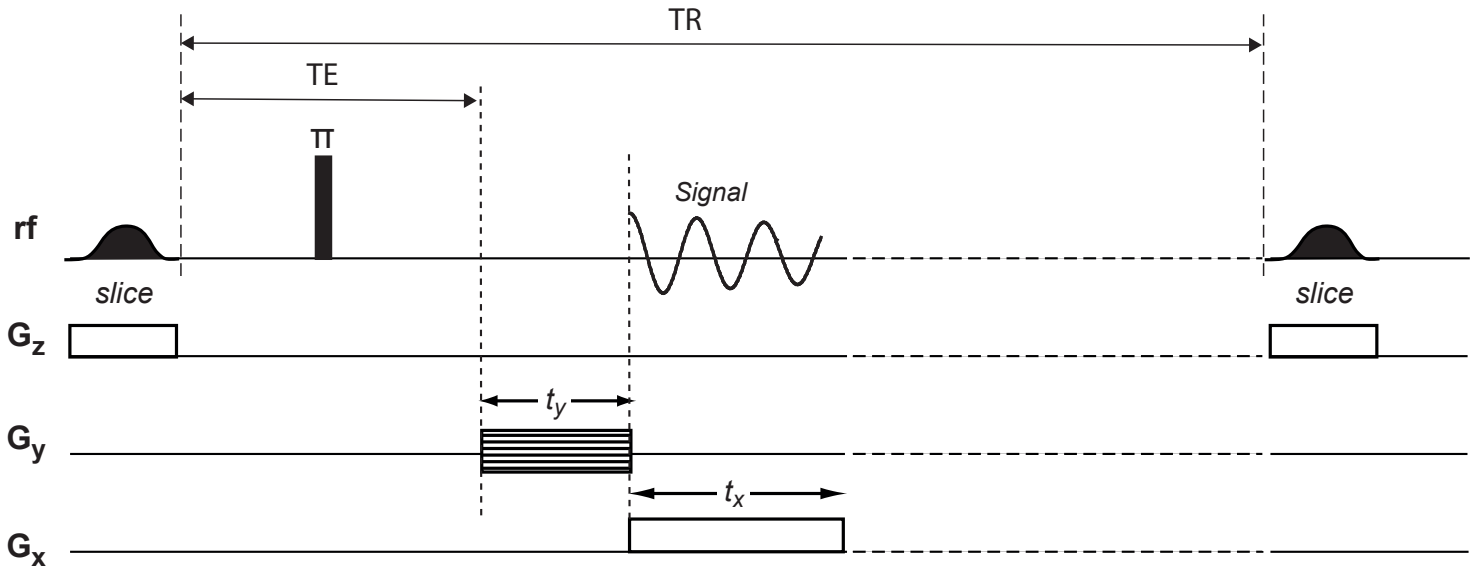
Schematic signal intesities for two tissues having similar water content, but different T_1:



Important reminder: the different periods in NMR pulse sequences are not uslly drawn to scale. e.g. typically non-selective (hard) pulses are micro-seconds long, selective (soft) pulses are milliseconds long, and the inversion recovery delay might be hundreds of milliseconds....

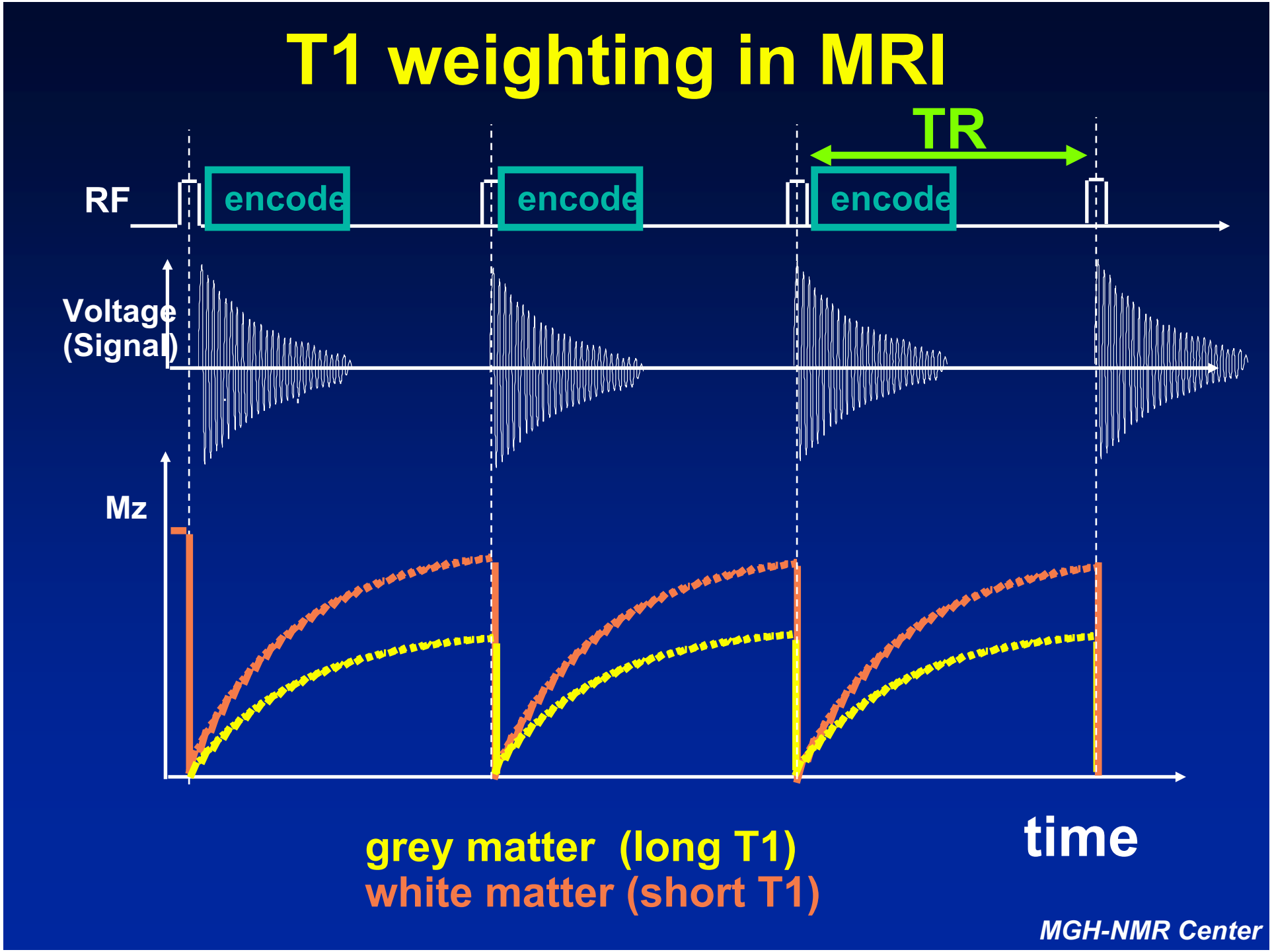
Image Contrast: T_1 Weighting

There is simpler way to weight the signal intensity by T_1 by simply repeating the experiment on a time scale faster than T_1

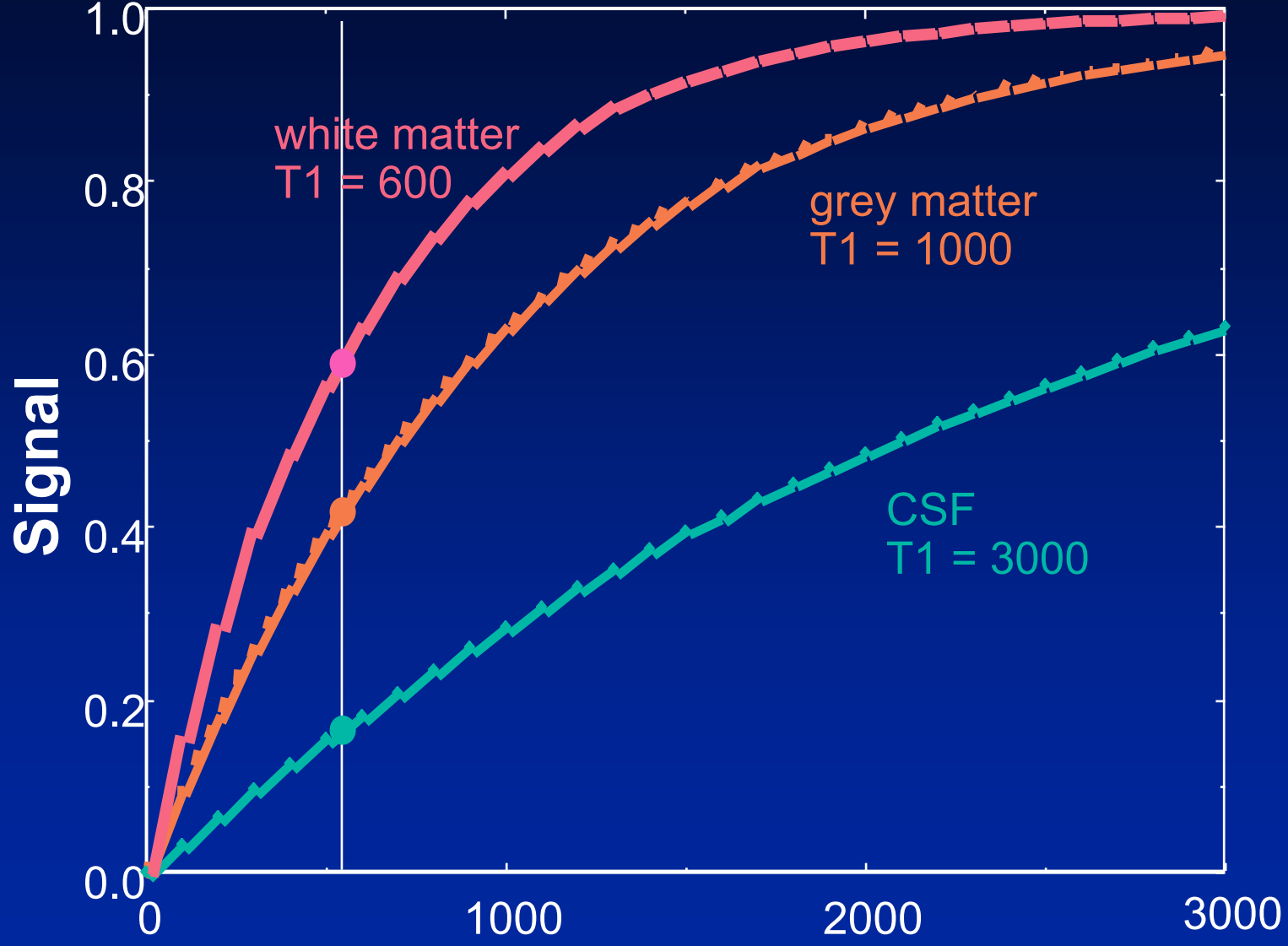


T_1 and T_2 weighting in MRI images is usually characterised by the echo-time (TE) and the repetition time (TR).

T1 weighting in MRI



T1-Weighting



MGH-NMR Center

Summarizing Contrast

Two knobs: TE and TR

Effects tend to compete, most tissue with long T1 also has long T2 and contrast goes opposite ways.

T1-weighting: short T1 is bright

T2-weighting: long T2 bright

Image Contrast: T_1 & T_2 Weighting

Relaxation parameters for various tissues. GM gray matter; WM white matter; CSF cerebrospinal fluid

Region	T1 (ms) 1.5 T	T1 (ms) 1.0 T	T2 (ms)
Brain			
GM	921	813	101
WM	787	683	92
CSF	2650	2650	280
Edema	1090	975	113
Meningioma	979	871	103
Glioma	957	931	111
Astrocytoma	1109	1055	141
Miscellaneous tumors	1073	963	121
Liver			
Normal tissue	493	423	43
Hepatomas	1077	951	84
Miscellaneous tumors	905	857	84
Spleen			
Normal tissue	782	683	62
Pancreas			
Normal tissue	513	455	
Miscellaneous tumors	1448	1235	
Kidney			
Normal tissue	652	589	58
Miscellaneous tumors	907	864	83
Muscle			
Normal tissue	868	732	47
Miscellaneous tumors	1083	946	87

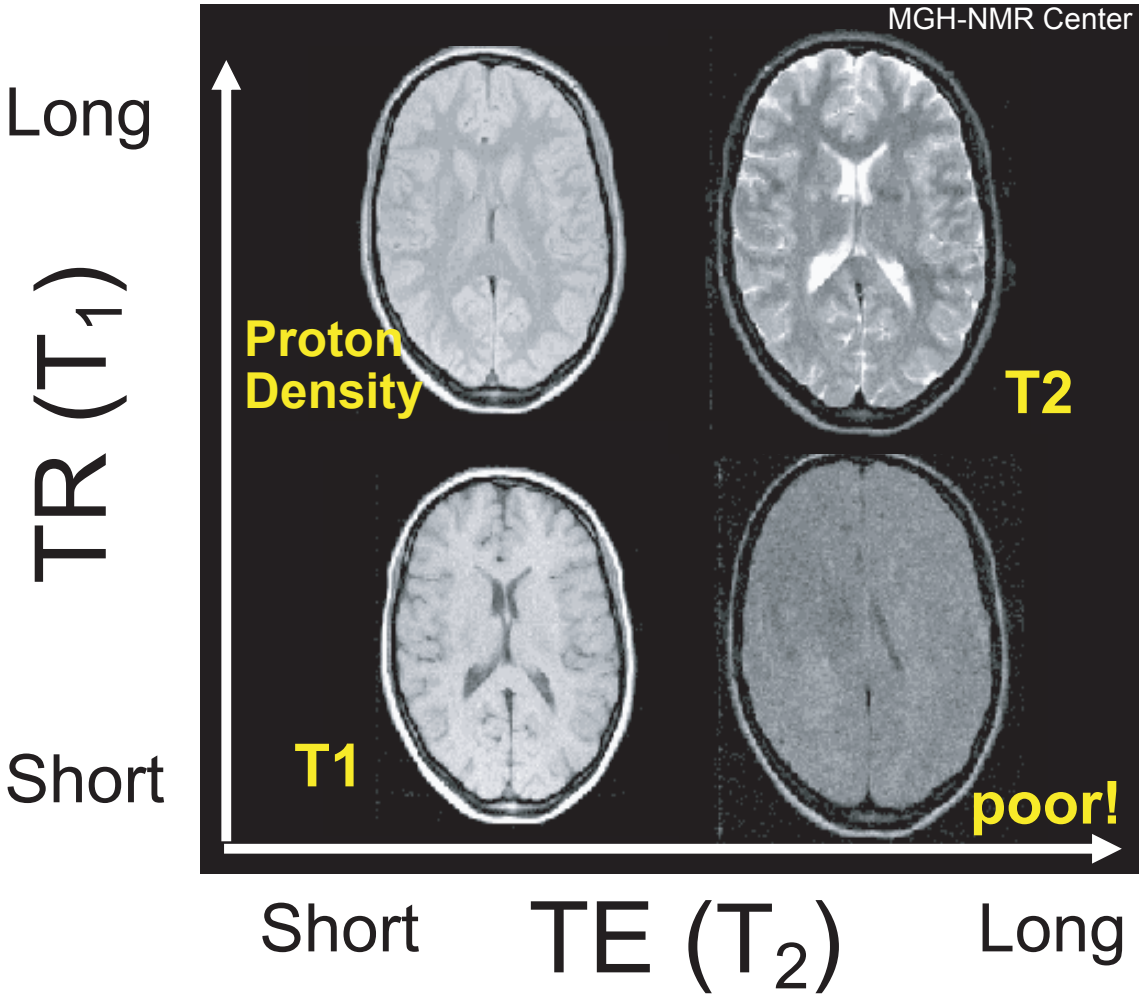


Image Contrast

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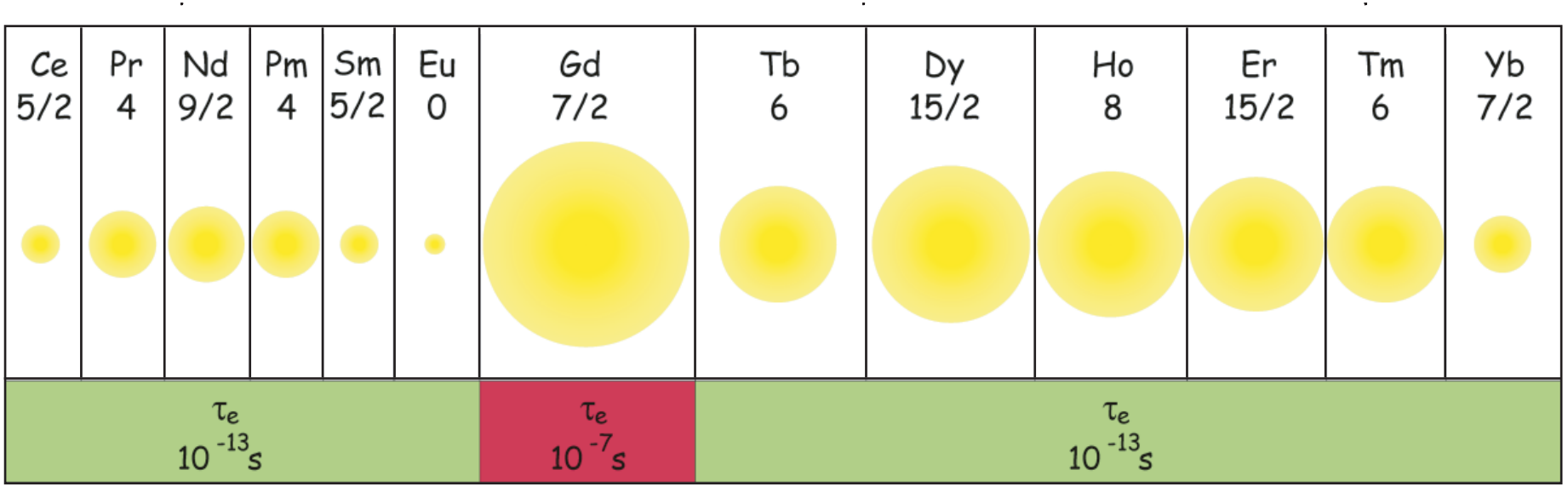
Paramagnetic Ions Provide Fast Relaxation

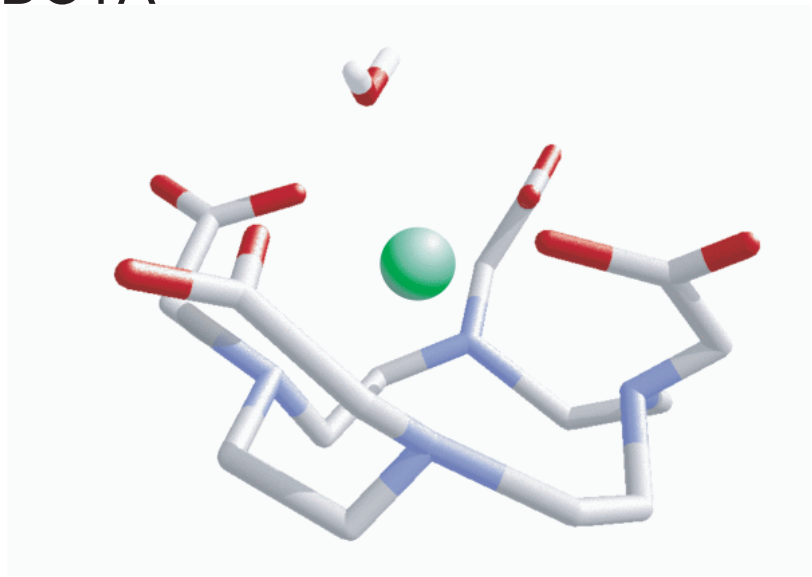


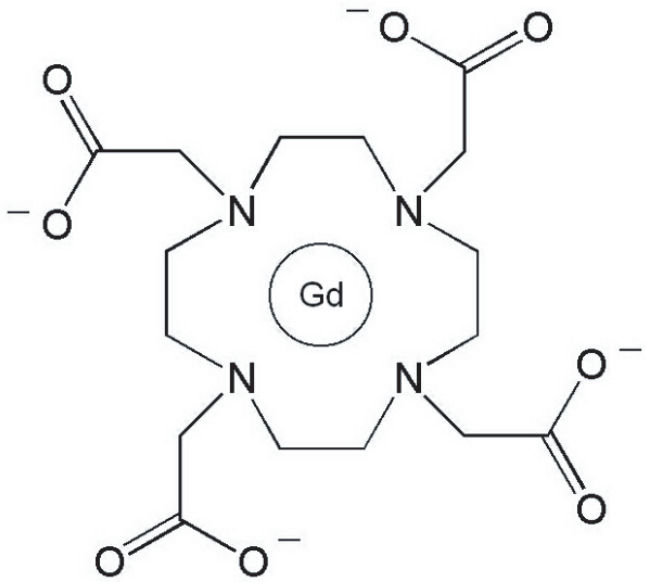
In paramagnetic ions, the unpaired electron fluctuates rapidly between its different spin states. This fluctuation in turn makes the electron-nuclear hyperfine coupling fluctuate, *and leads to an extremely efficient nuclear relaxation mechanism*.*

*we will learn more about the mechanism of how relaxation occurs later in the course.

Enhancing Image Contrast: Paramagnetic Contrast Agents

Gd-DOTA

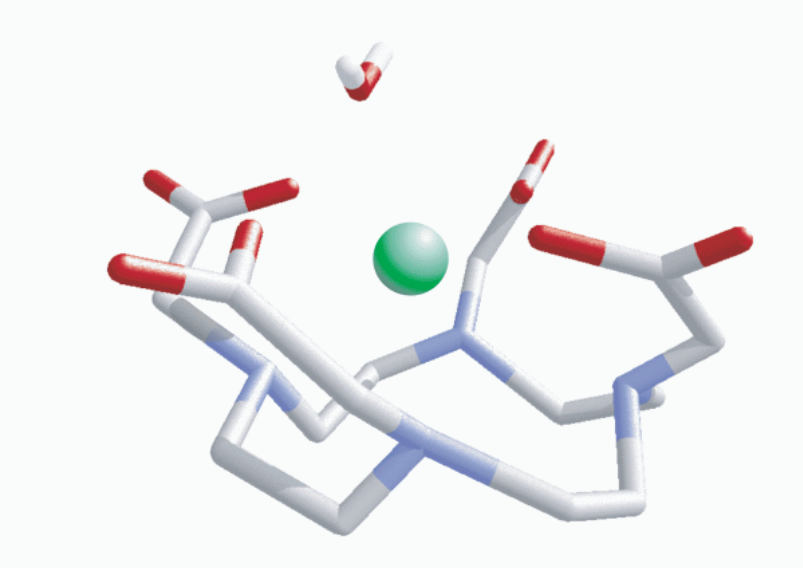




Paramagnetic contrast agents work on the principle of "relaxivity." That is the complex must have a binding site available for water molecules, but the water molecules must be in fast exchange with the solvent. In this way, the T1 of the bulk water is shortened by the Gd complex which acts as a relaxation sink....

Enhancing Image Contrast: Paramagnetic Contrast Agents

Gd-DOTA



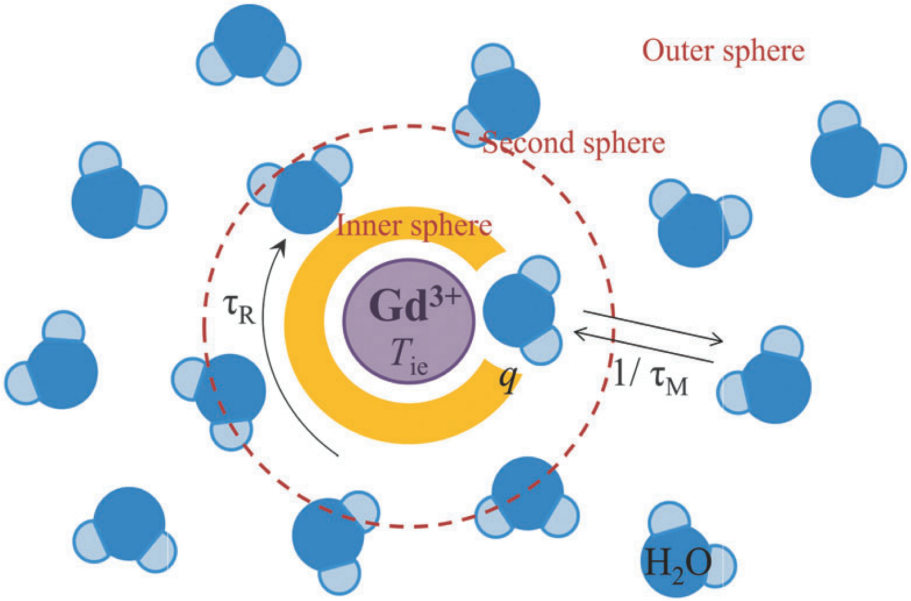


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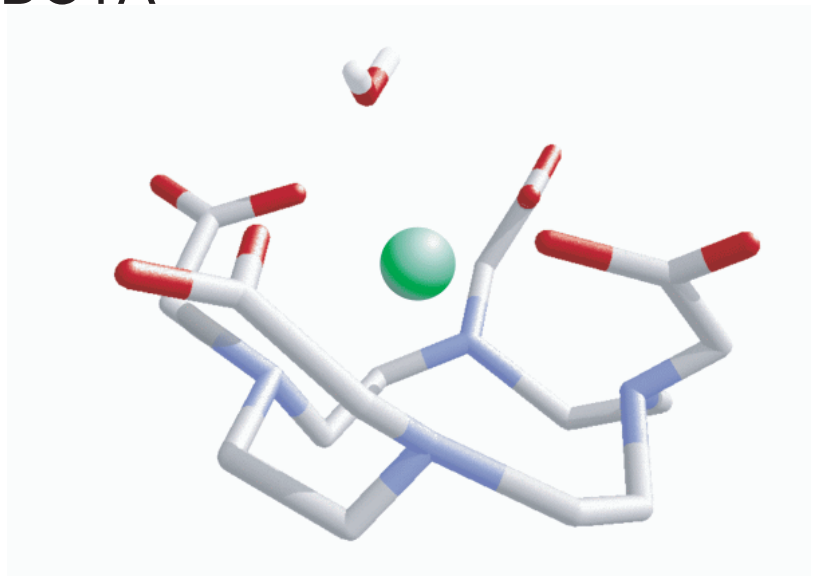
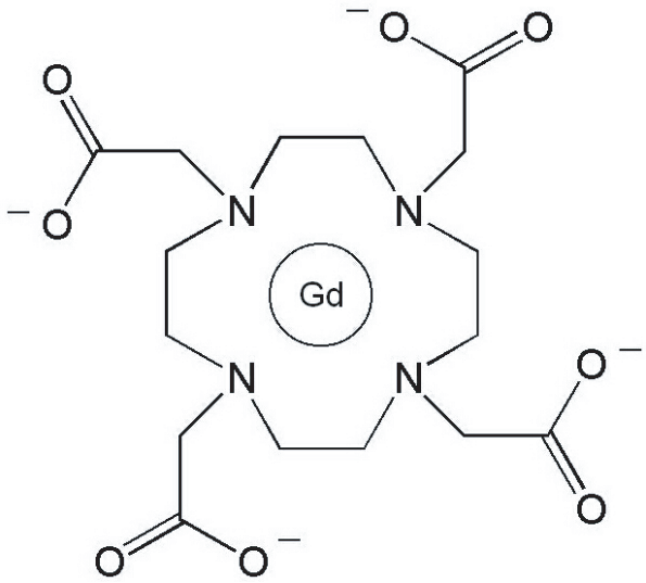
image from Debroye and Parac-Vogt, *Chem. Soc. Rev.*, 2014, **43**, 8178-8192

Enhancing Image Contrast: Paramagnetic Contrast Agents

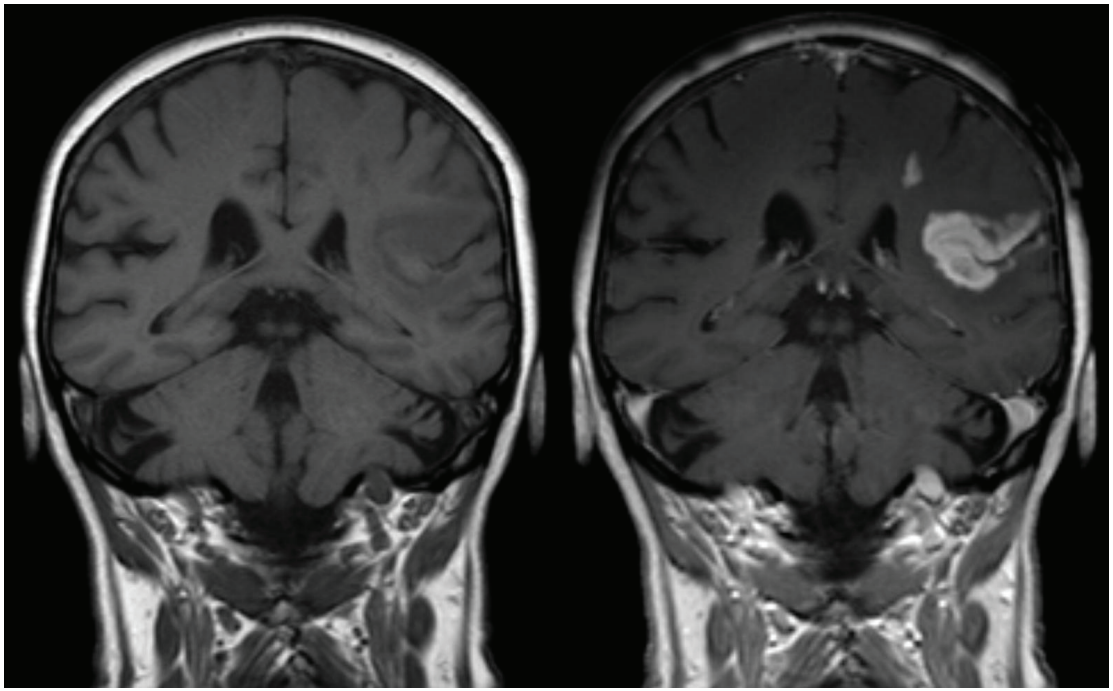
Gd-DOTA





After the injection of a contrast agent into a tissue, the concentration of the contrast agent increases, then starts to decrease as it is eliminated from the tissues. In general, a contrast enhancement is obtained by one tissue having a higher affinity or vascularity than another. Most tumors for example have a greater Gd uptake than the surrounding tissues, causing a shorter T1 and a larger signal.

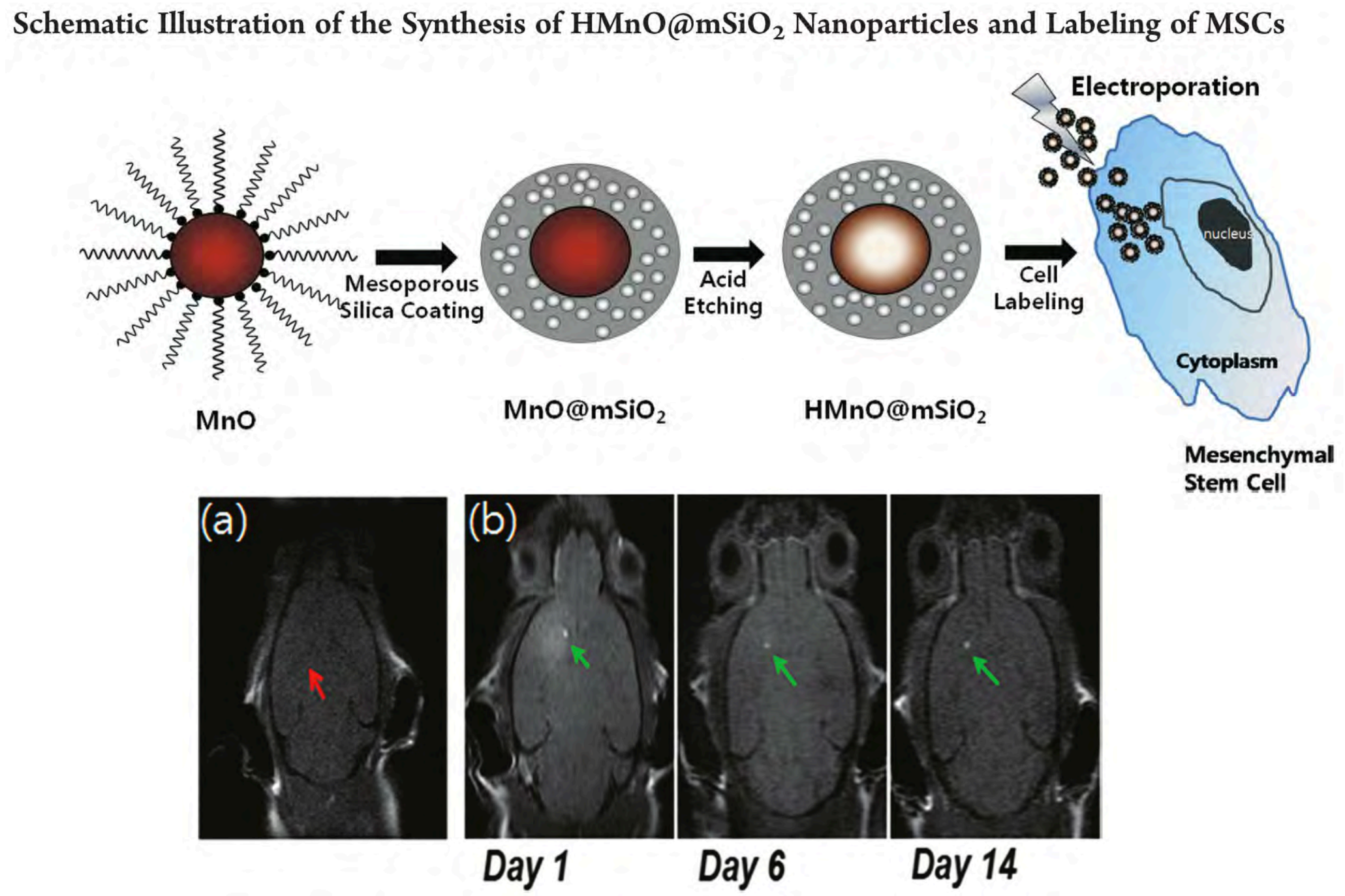
Enhancing Image Contrast: Paramagnetic Contrast Agents



Effect of Gd based contrast agent on images: Defect of the blood–brain barrier after stroke shown in MRI. T1-weighted images, left image without, right image with administration of a contrast agent.

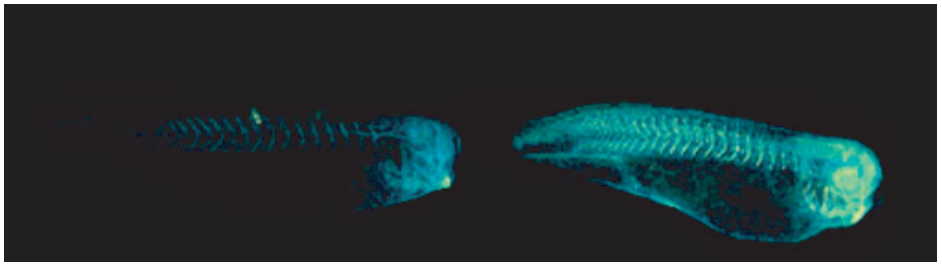
https://en.wikipedia.org/wiki/MRI_contrast_agent

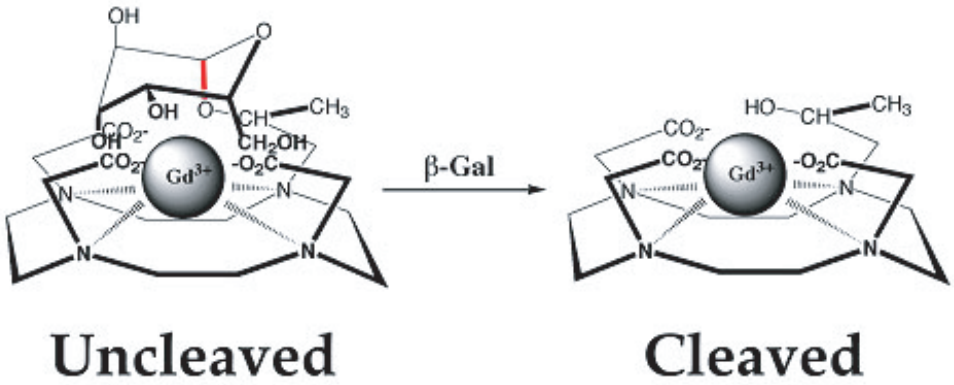
Contrast Agents



Hyeon, Gilad, and coworkers, "Mesoporous Silica-Coated Hollow Manganese Oxide Nanoparticles as Positive T1 Contrast Agents for Labeling and MRI Tracking of Adipose-Derived Mesenchymal Stem Cells"
J. Am. Chem. Soc. **2011**, 133, 2955.

Smart Contrast:
Biochemically Activated T1 Contrast Agents





Imaging enzymatic activity: Contrast agents with cleavable protection groups that largely prevent access of water to the paramagnetic center of the contrast agent permit an in vivo assay of enzymatic activities. By limiting access of water, the unprocessed agent will be an ineffective contrast agent. After cleavage of the protecting group by a reaction specific to an enzyme (here hydrolysis of the glycosidic bond by β-galactosidase), the coordination site for water molecules is now exposed, activating the contrast agent. The picture shows the detection of regions positive for β-galactosidase within a living Xenopus laevis.

https://www.meade-chemistry-northwestern.com/molecular-imaging-with-mri

Copper-Responsive Magnetic Resonance Imaging Contrast Agents

Emily L. Que,[†] Eliana Gianolio,[||] Suzanne L. Baker,[§] Audrey P. Wong,[†] Silvio Aime,[||] and Christopher J. Chang*[,†,‡]

Department of Chemistry and Howard Hughes Medical Institute, University of California, Berkeley, California 94720, Center for Functional Imaging, Lawrence Berkeley National Laboratory, Berkeley, California 94720, and Centro di Biotechnologie Molecolari, University of Torino, Torino I-10125, Italy

Received February 9, 2009; E-mail: chrischang@berkeley.edu

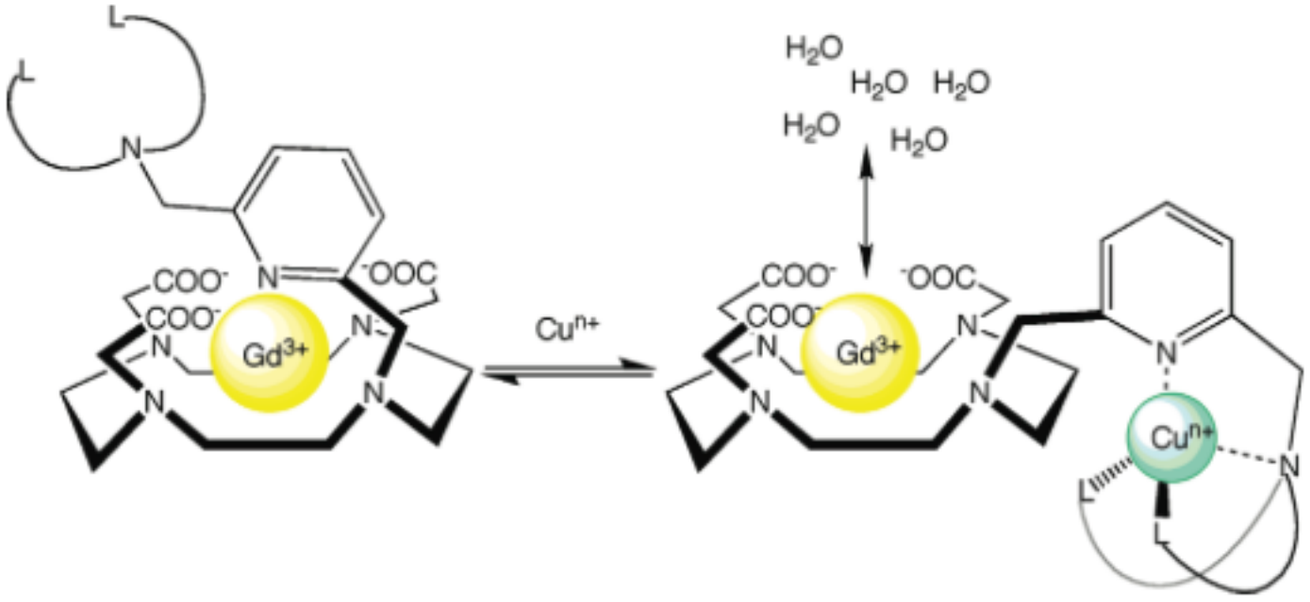


Figure 1. Design strategy for copper-activated MRI sensors.

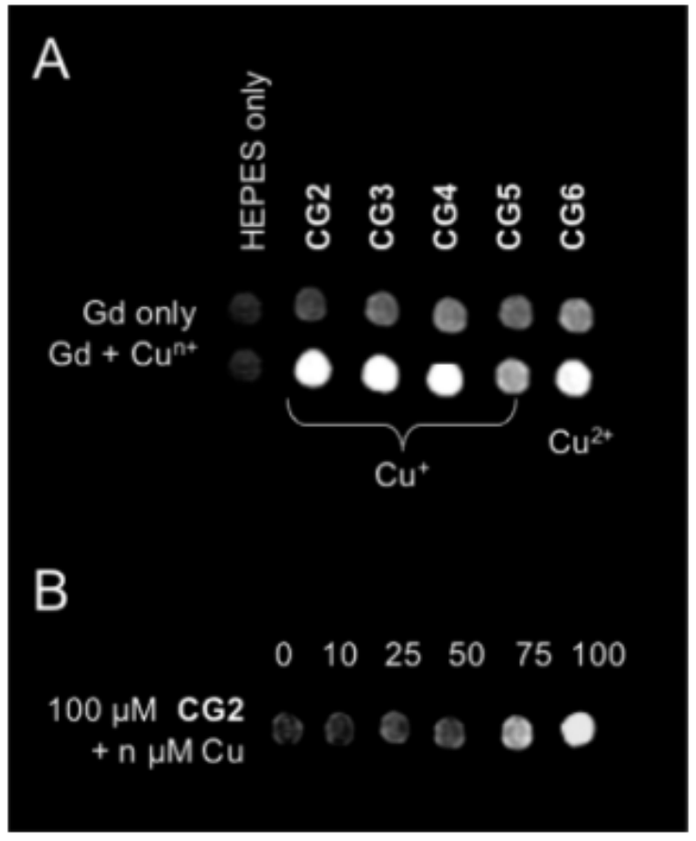


Figure 10. (A) T_1-weighted phantom images of 100 μM CG2−CG6 in 20 mM HEPES (pH 7) with and without 1 equiv of Cu^{n+}. (B) Phantom images of 100 μM CG2 with 0, 10, 25, 50, 75, and 100 μM $[Cu(NCCH_3)_4]PF_6$. Images were acquired at 25 °C at 1.5 T (~64 MHz proton Larmor frequency).

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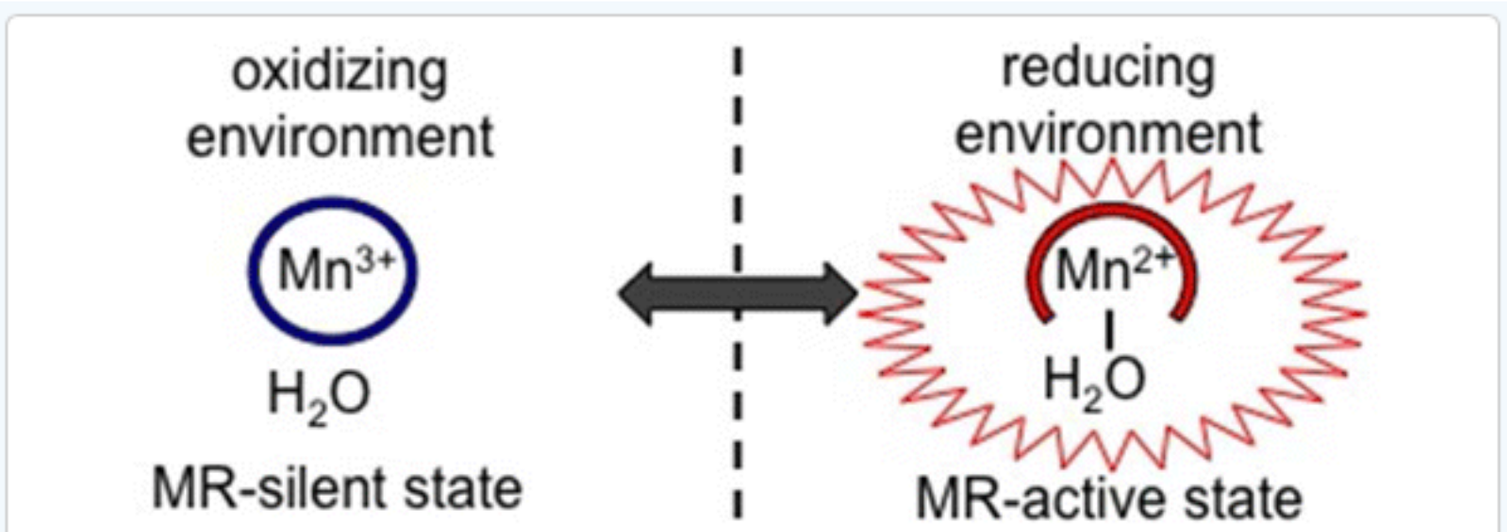
Communication

pubs.acs.org/JACS

Redox-Activated Manganese-Based MR Contrast Agent

Galen S. Loving,[‡] Shreya Mukherjee,[‡] and Peter Caravan*

A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Suite 2301, Charlestown, Massachusetts 02129, United States



Here we report a simple Mn coordination complex with utility as a redox-sensitive MR probe. The HBET ligand stabilizes both the Mn^{2+} and Mn^{3+} oxidation states. In the presence of glutathione (GSH), low relaxivity Mn^{III}-HBET is converted to high relaxivity Mn^{II}-HBET with a 3-fold increase in relaxivity, and concomitant increase in MR signal. Alternately, hydrogen peroxide can convert Mn^{II}-HBET to Mn^{III}-HBET with a reduction in MR signal.

dx.doi.org/10.1021/ja312610j | *J. Am. Chem. Soc.* 2013, 135, 4620−4623

J|A|C|S COMMUNICATIONS

Published on Web 09/20/2010

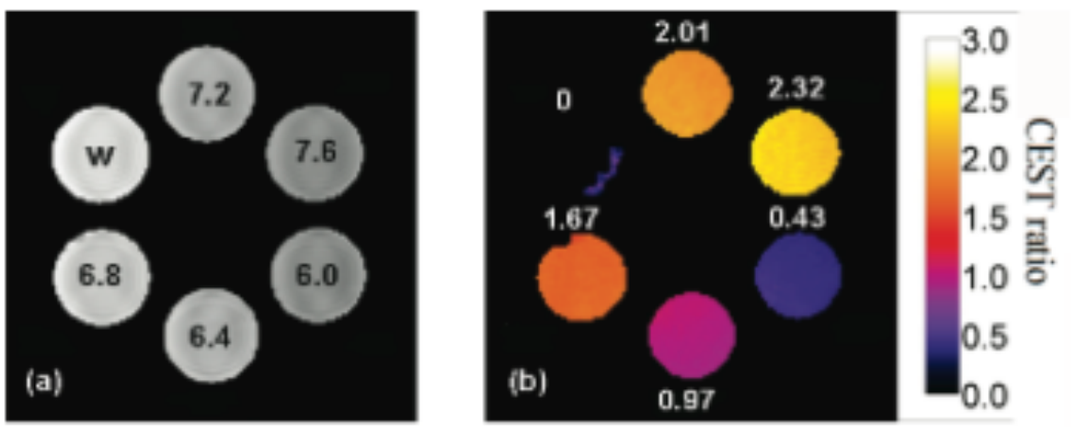
A Responsive Europium(III) Chelate That Provides a Direct Readout of pH by MRI

Yunkou Wu,[†] Todd C. Soesbe,[‡] Garry E. Kiefer,[†,§] Piyu Zhao,[†] and A. Dean Sherry*[,†,‡]

Department of Chemistry, University of Texas at Dallas, P.O. Box 830668, Richardson, Texas 75083, Advanced Imaging Research Center, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390, and Macrocyclics, Inc., 1309 Record Crossing, Dallas, Texas 75235

Received July 8, 2010; E-mail: sherry@utdallas.edu; dean.sherry@utsouthwestern.edu

Abstract: A europium(III) DO3A-tris(amide) complex is reported for imaging pH by MRI using ratiometric chemical exchange saturation transfer (CEST) principles. Deprotonation of a single phenolic proton between pH 6 and 7.6 results in an ~5 ppm shift in the water exchange CEST peak that is easily detected by MRI. Collection of two CEST images at two slightly different activation frequencies provides a direct readout of solution pH without the need of a concentration marker.



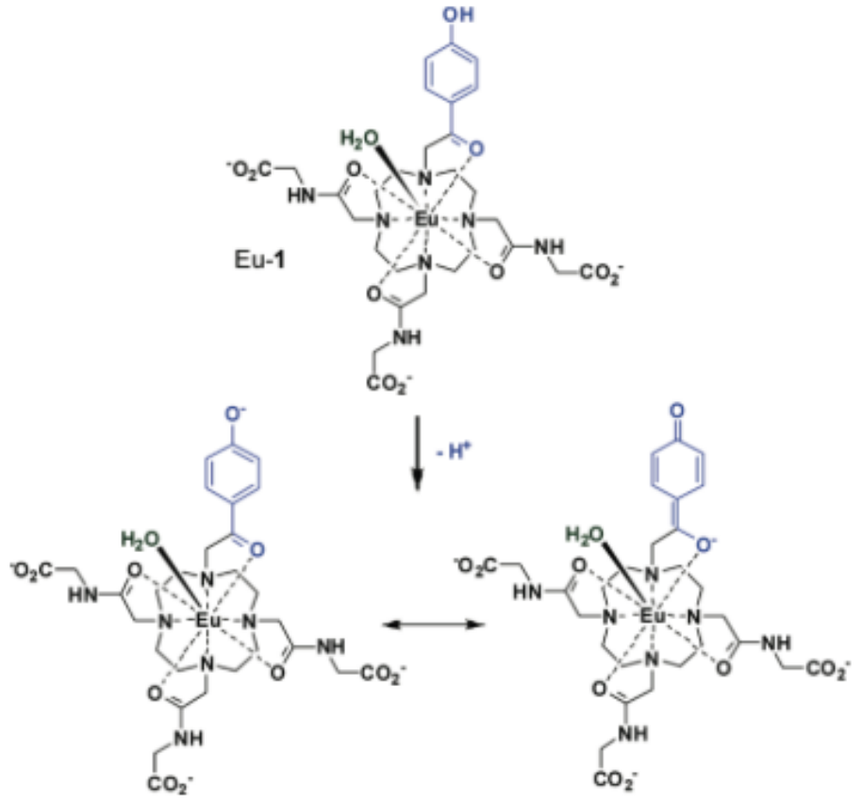
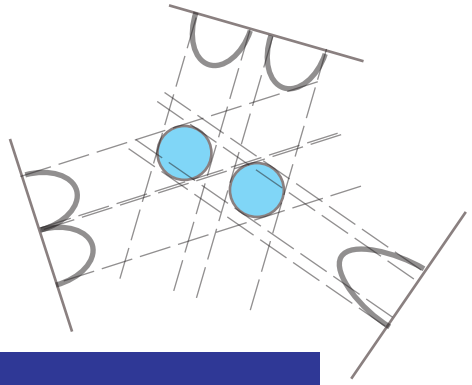


Figure 1. Structure of the pH-responsive PARACEST agent, Eu-**1**. Deprotonation of the phenolic proton results in conjugation of the resulting quinone-like structure with the acetyl oxygen atom coordinated to the Eu^{3+} ion (bottom).

Multi-Dimensional Imaging

(ii) Fourier Imaging



Spin-warp
pulse sequence

RF

G_Z

G_Y

G_X

Signal

1
2
3

n

A B C

Time

Spin-warp
k-space trajectory

k_y

1 B C
2
3

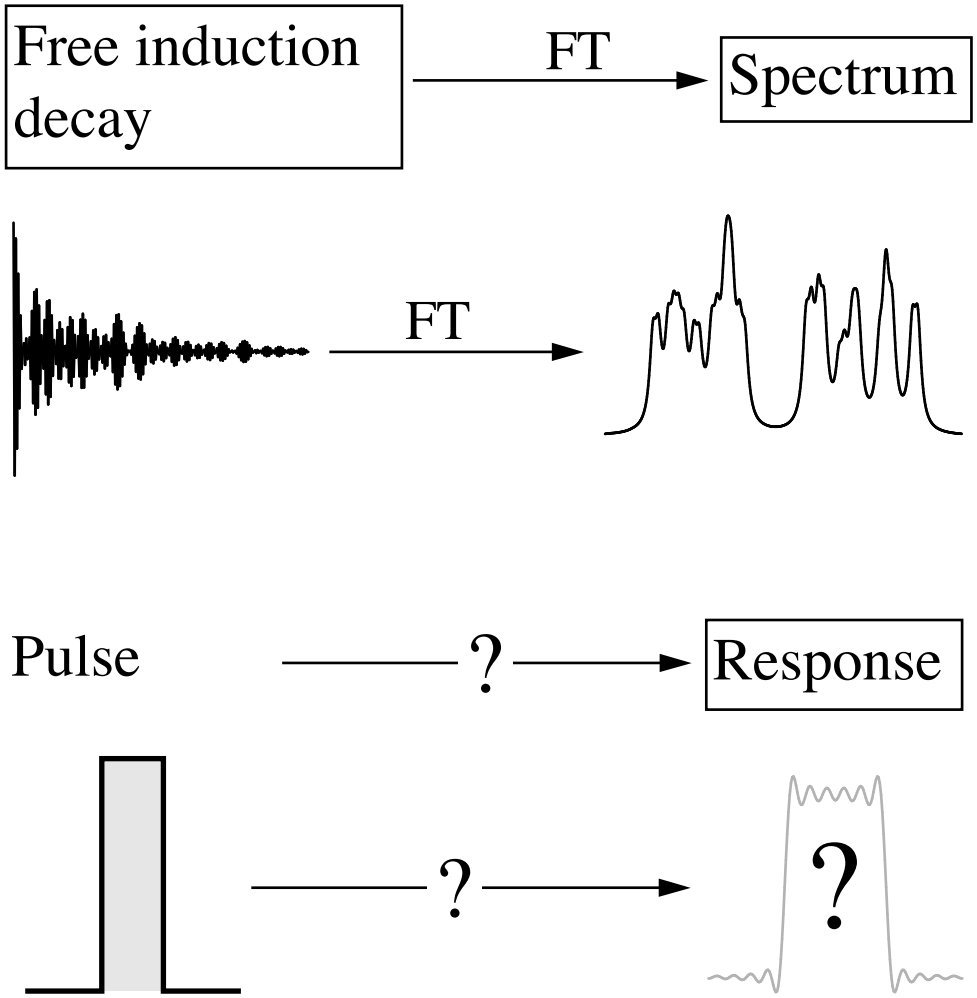
A

k_x

n

Slice Selection in 2D Imaging

What frequencies are contained in a pulse?



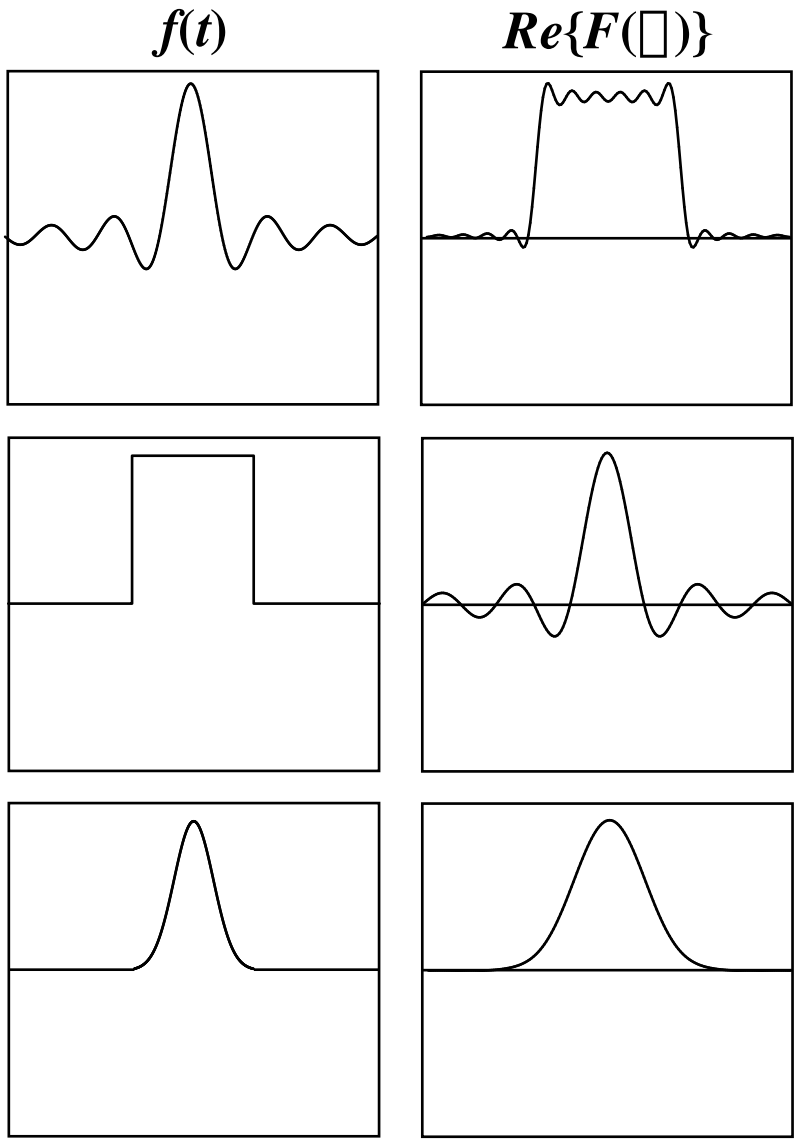
Slice Selection in 2D Imaging

What frequencies are contained in a pulse?

If the response is linear then the Fourier Transform of the time-domain pulse yields the frequency-domain response.

(Is the system linear?)

Shaped time-domain pulses yield selective frequency-domain responses.



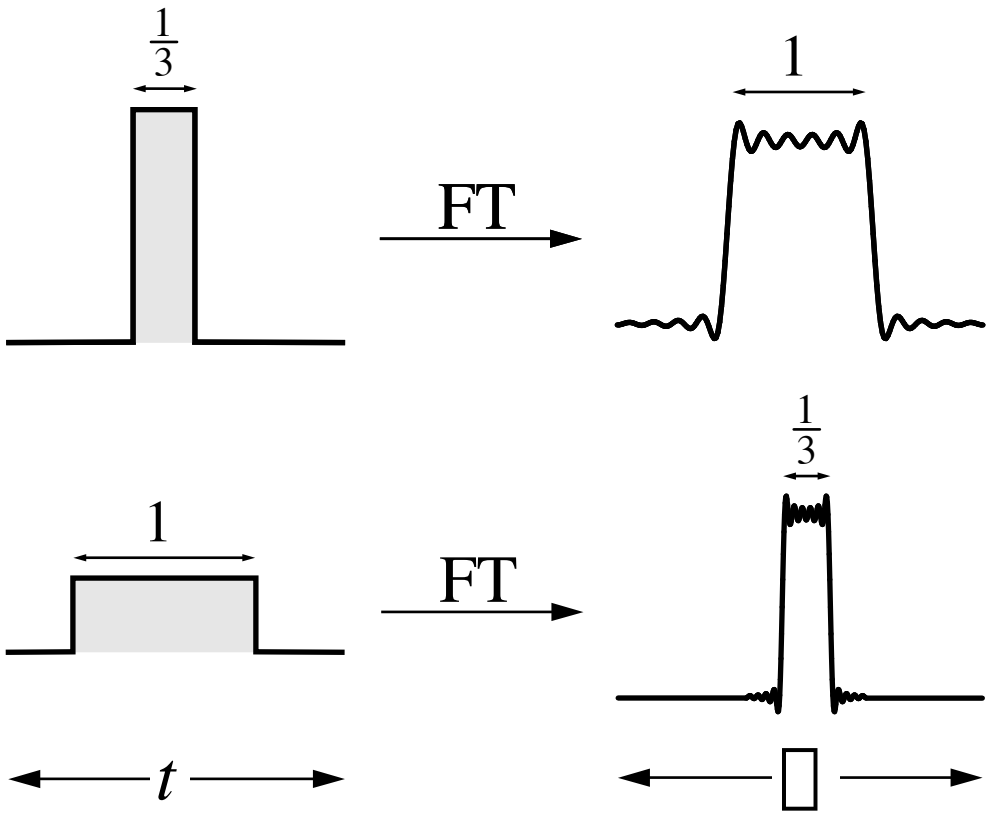
Slice Selection in 2D Imaging

What frequencies are contained in a pulse?

The bandwidth of the excitation is inversely proportional to the duration of the pulse, even outside the linear regime.

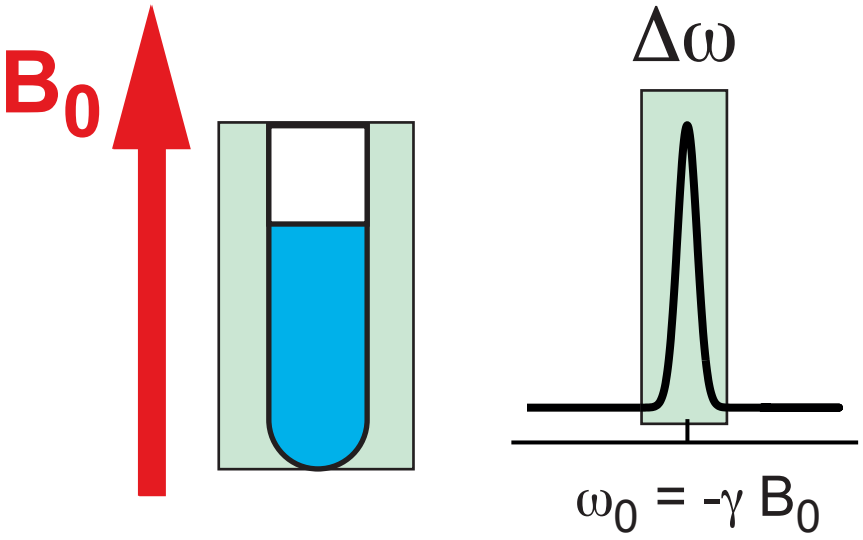
(This is a manifestation of the uncertainty principle.)

Long pulses give narrow band selective excitation.

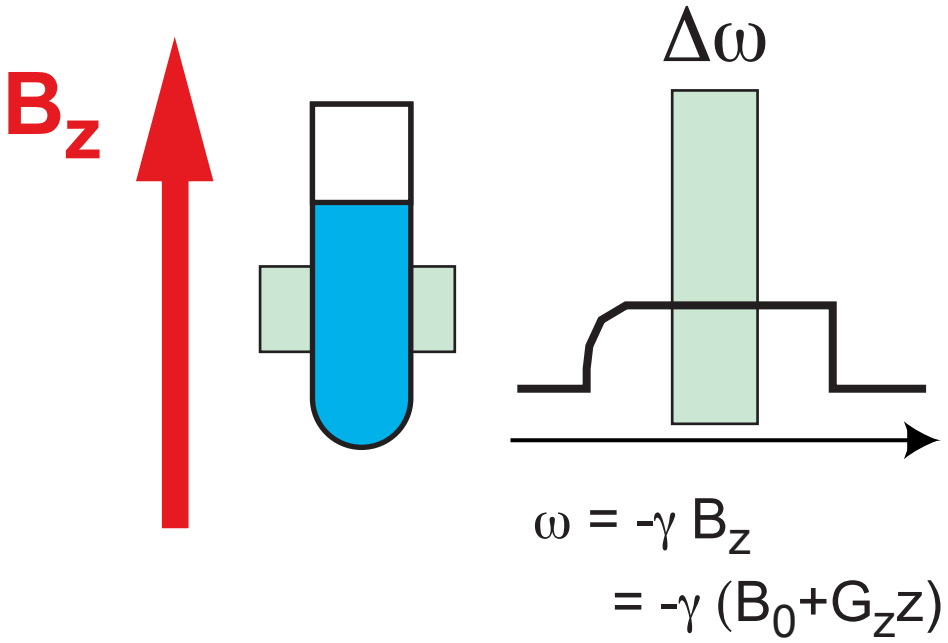


$$\Delta\Delta\Delta t = k$$

Slice Selection in 2D Imaging

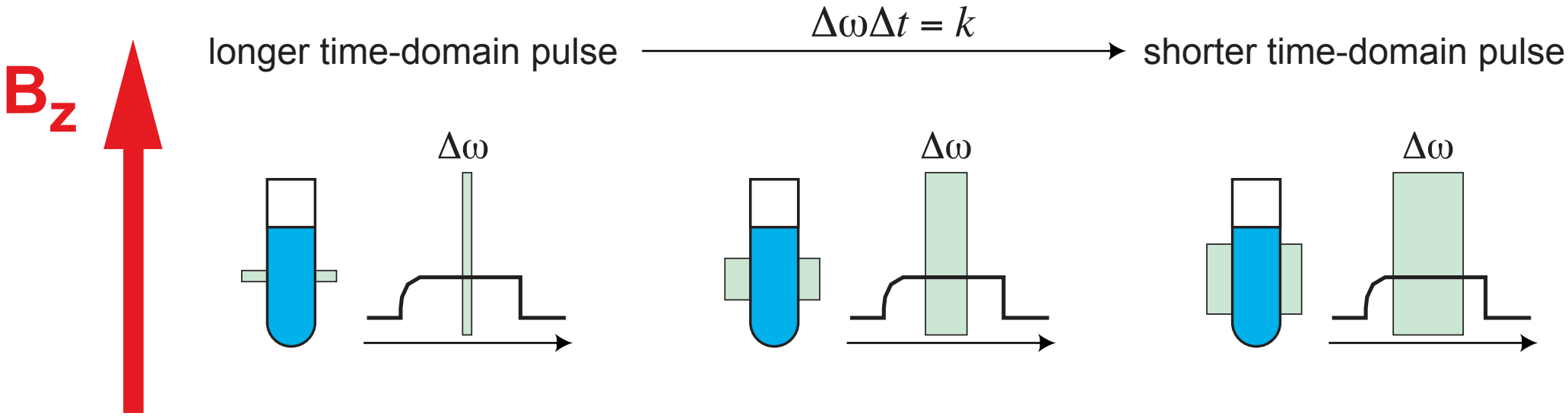


No gradient: narrow spectrum.
All pulses excite the whole sample.



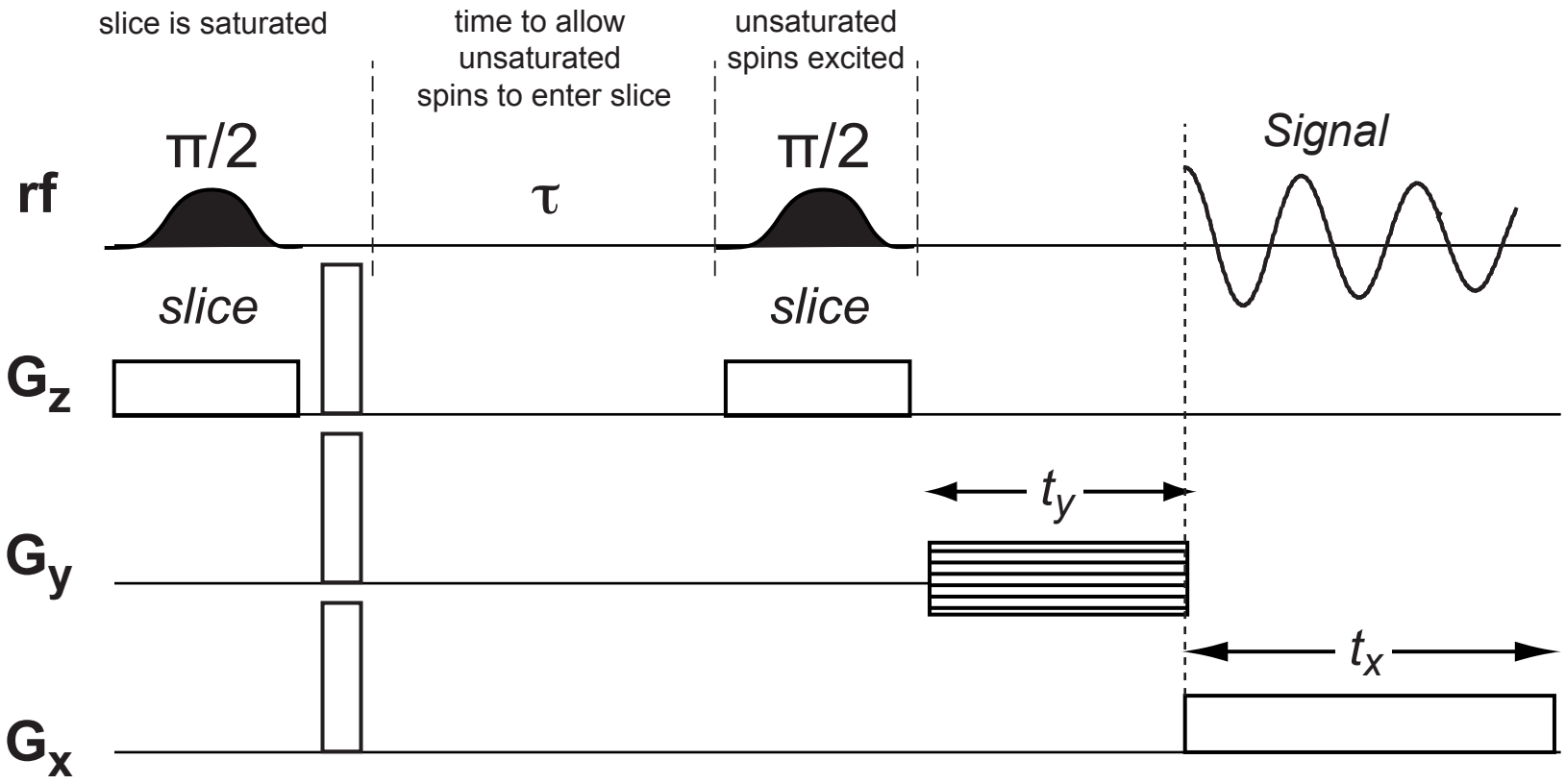
Gradient: broad spectrum.
Pulses excite only the part of the sample corresponding to the bandwidth of the pulse.

Slice Selection in 2D Imaging



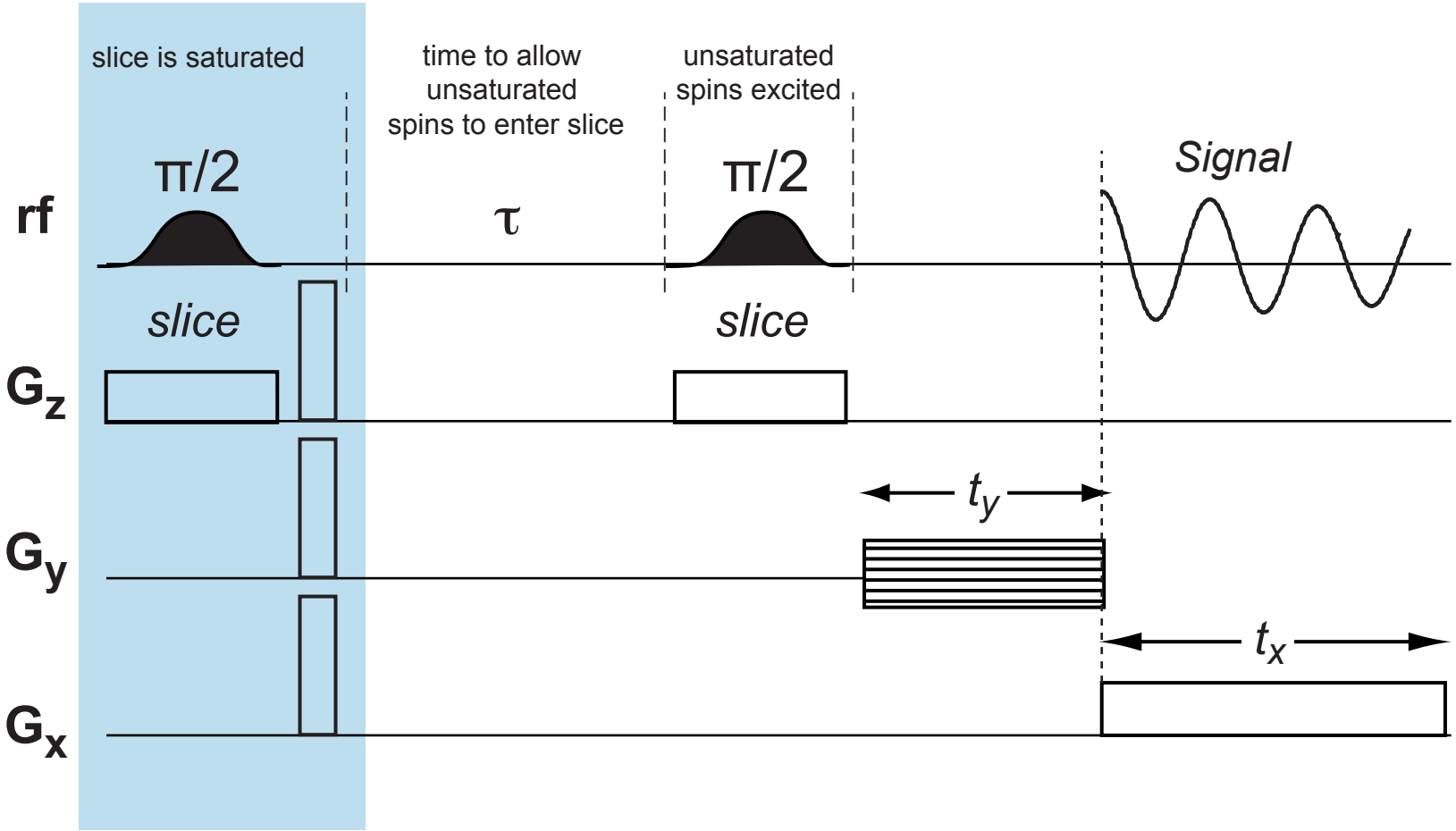
For slice selection: (i) **the shape of the time-domain pulse** controls the shape of the frequency-domain response. Typically (truncated) sinc-shaped pulses are use to obtain (nearly) square excitation profiles. (ii) **the duration of the time-domain pulse** controls the width of the frequency-domain response. In combination with the applied gradient strength this determines the thickness of the excited slice in the sample. (For a given pulse length, the stronger the applied gradient, the thinner the excited slice.)

Image Contrast: Motion



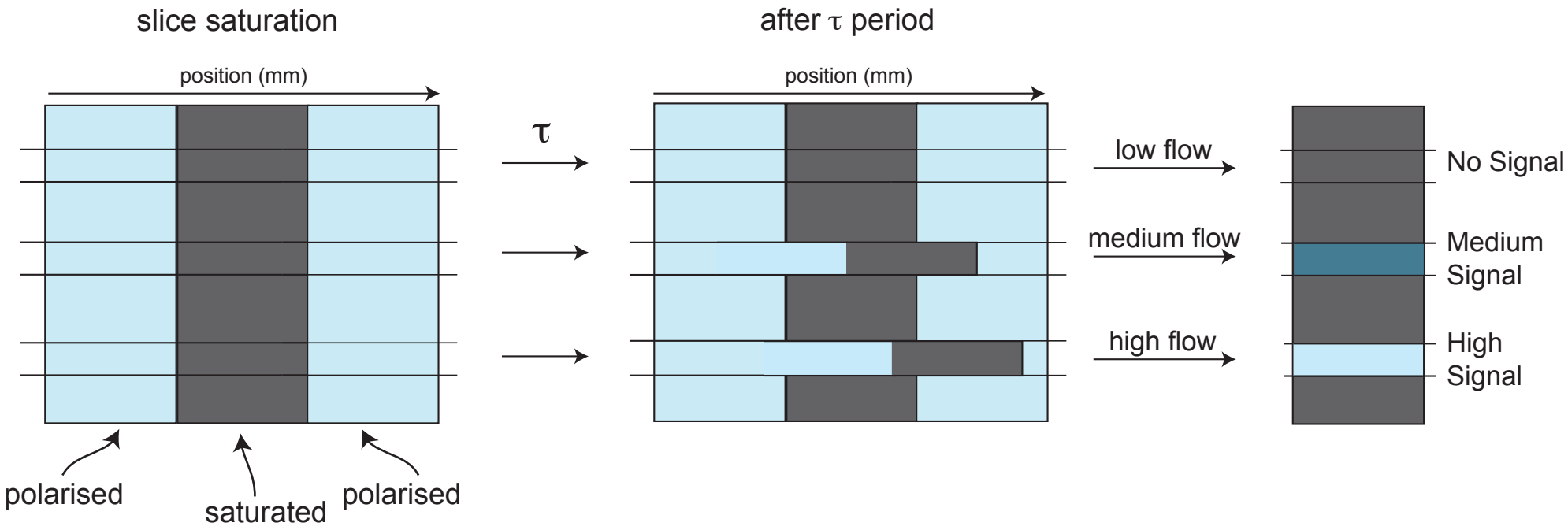
Contrast can be obtained for motion by "time of flight" saturation.

Image Contrast: Motion



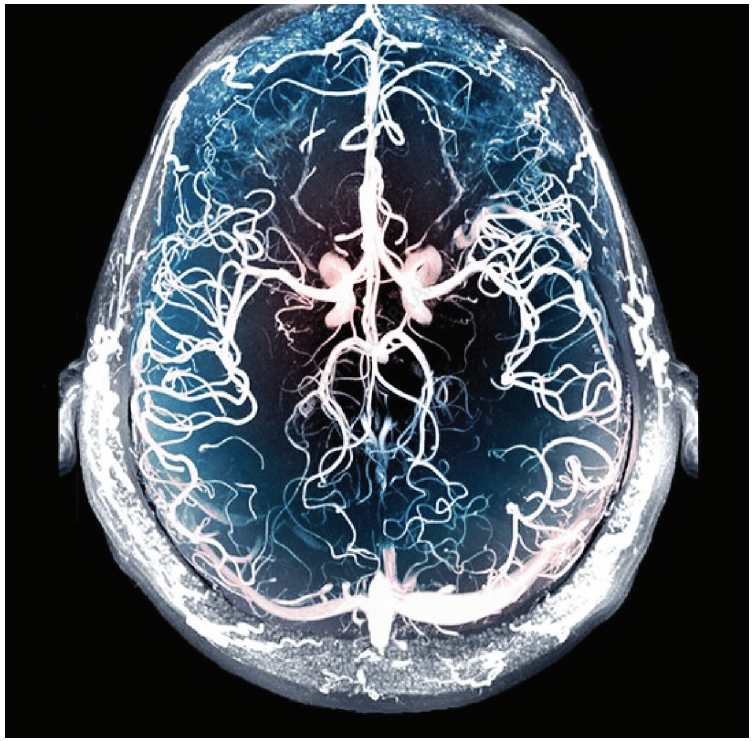
This block saturates (destroys) magnetization in a selected slice. The strong field gradients applied along all three directions just after selective excitation of magnetization in a slice, completely dephase the transverse magnetization, leading to **no net signal** once the gradients are removed.

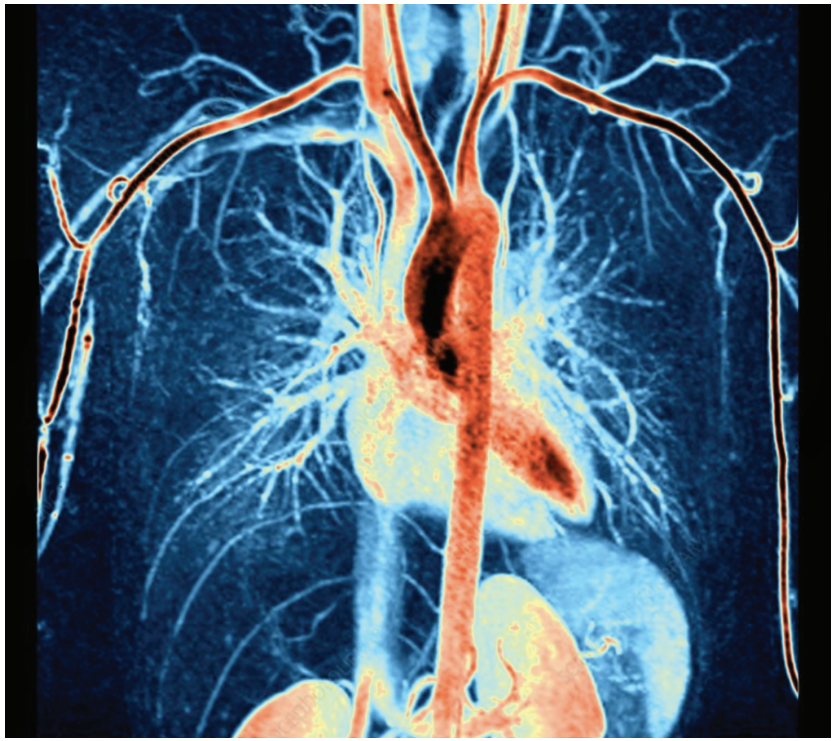
Image Contrast: Motion



Contrast can be obtained for motion by "time of flight" saturation.

Imaging Flow: MR Angiography



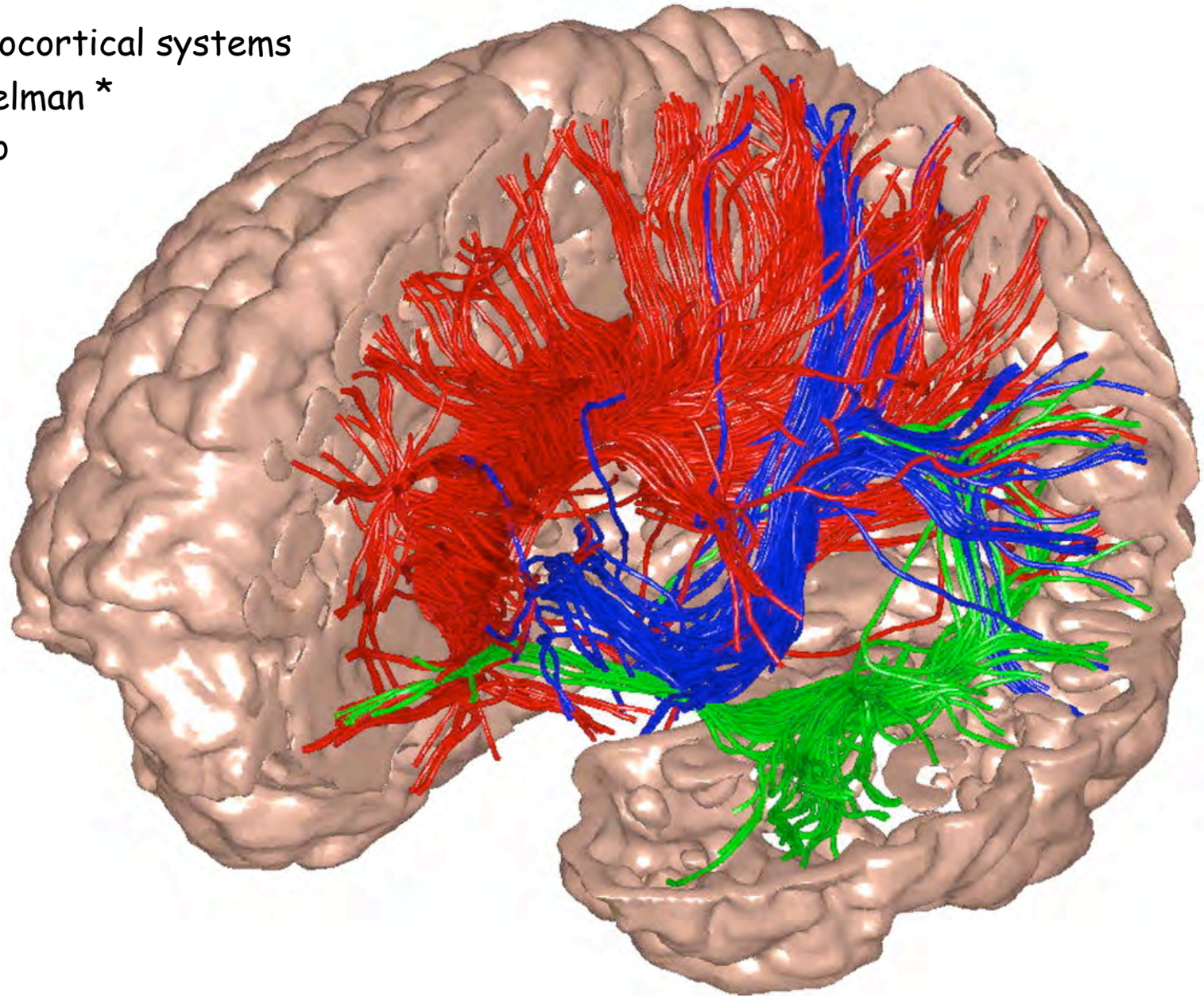


Left side: Magnetic resonance angiography (MRA) showing normal brain blood vessels imaged using 'time of flight' (TOF) technology with volumetric rendering in 3D using MRI angiography. The vertebral arteries and internal carotid arteries are seen meeting at the circle of Willis (centre).
Adapted from https://www.sciencephoto.com/media/1193528/view/blood-vessels-of-the-brain-mri-angiography

Right side: Heart and torso blood vessels. Coloured 3D frontal magnetic resonance angiography (MRA) scan of a healthy heart and blood vessels in the chest, neck, arms and upper abdomen of a 39-year-old woman. The heart is at centre, with its major blood vessels (including the aorta and vena cava) at bottom centre are the kidneys. The blood vessels of the neck and arms are at top centre and upper left and upper right.
Adapted from: https://www.sciencephoto.com/media/1077777/view/heart-and-torso-blood-vessels-mri-angiogram

Diffusion Tensor Imaging

Large-scale model of mammalian thalamocortical systems
Eugene M. Izhikevich and Gerald M. Edelman *
The Neurosciences Institute, San Diego
PNAS, 105, 3593–3598, 2007



The model's global thalamocortical geometry and white matter anatomy was obtained by means of diffusion tensor imaging (DTI) of a normal human brain. In the illustration, left frontal, parietal, and a part of temporal cortex have been cut to show a small fraction of white-matter fibers, color-coded according to their destination.

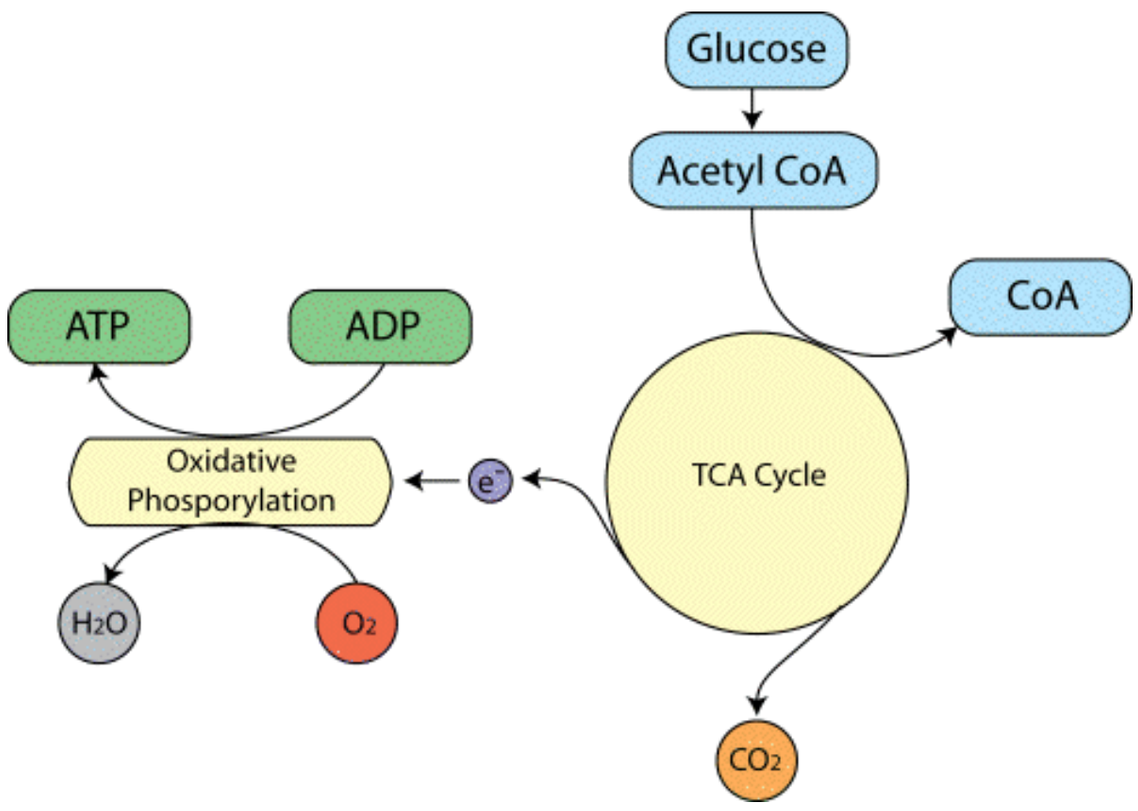
Smart Contrast

Could we image neural activity?

The biochemical reactions that transmit neural information all require energy.

This energy is provided in the form of ATP.

ATP is produced from glucose by oxidative phosphorylation and the Kreb's cycle.



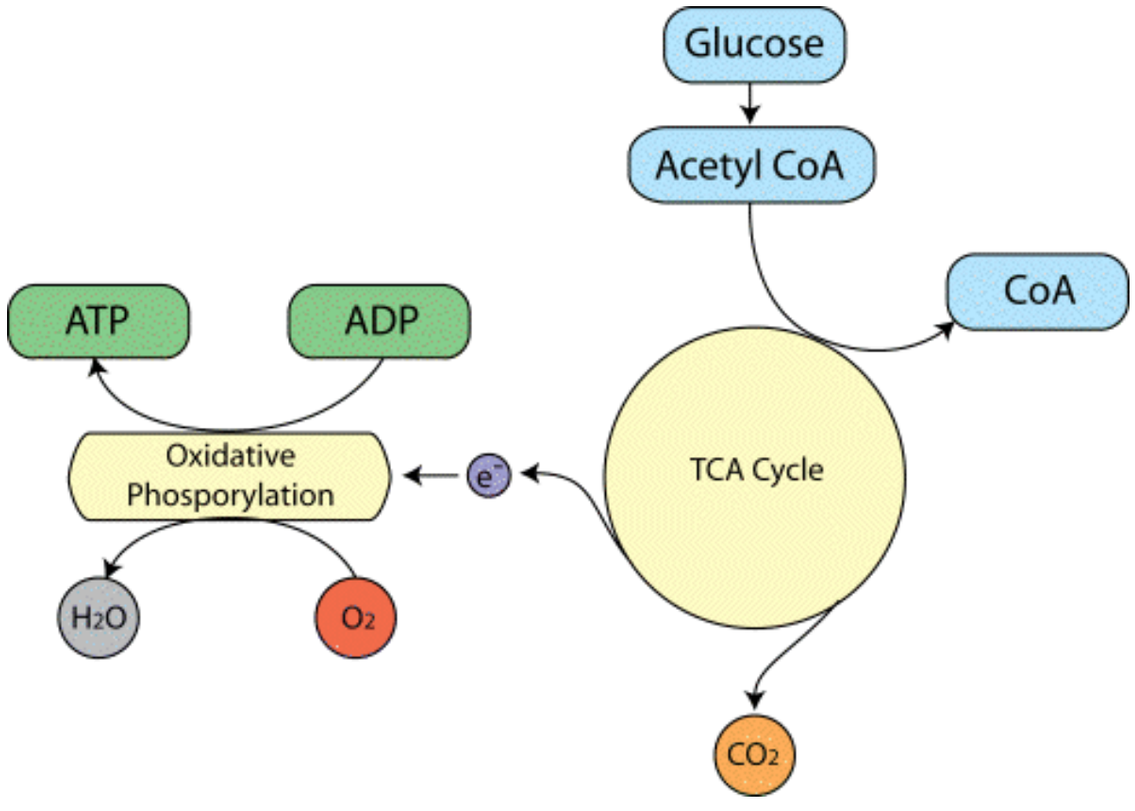
Smart Contrast

Could we image neural activity?

ATP is hydrolysed to ADP, giving up energy. The production of ADP from ATP is governed by demand.

The rate of oxygen consumption by oxidative phosphorylation is a good measure of neural activity.

Oxygen is supplied by haemoglobin in the blood.



Imaging Neural Activity

BOLD (Blood Oxygen Level Dependent Contrast)

There is thus an potential underlying contrast mechanism due to the fact that **a change in neuronal activity** – often termed activation – is accompanied by a rise in cerebral blood flow that at least transiently ‘uncouples’ from oxygen consumption and therefore

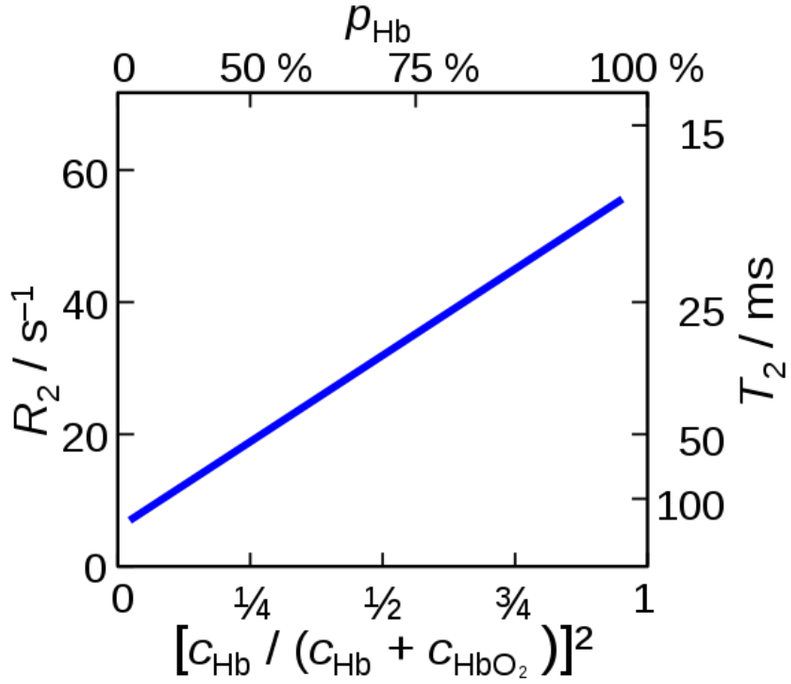
results in venous hyperoxygenation,

i.e. an increase in the ratio of hemoglobin/deoxyhemoglobin.

Since deoxyhemoglobin is paramagentic, **it acts as an endovascular contrast agent.**

Decreased deoxyhemoglobin leads to an increase in T_2 and an increase in signal intensity in a T_2 weighted image.

The effect is small, and is observed by acquiring very high sensitivity difference images.



Blood oxygenation level dependent (BOLD) relaxation: The transverse relaxation rate, R_2, of blood increases linear with the square of the concentration of deoxygenated hemoglobin

functional MRI (fMRI)

BOLD (Blood Oxygen Level Dependent Contrast)

There is thus an potential underlying contrast mechanism due to the fact that **a change in neuronal activity** – often termed activation – is accompanied by a rise in cerebral blood flow that at least transiently ‘uncouples’ from oxygen consumption and therefore

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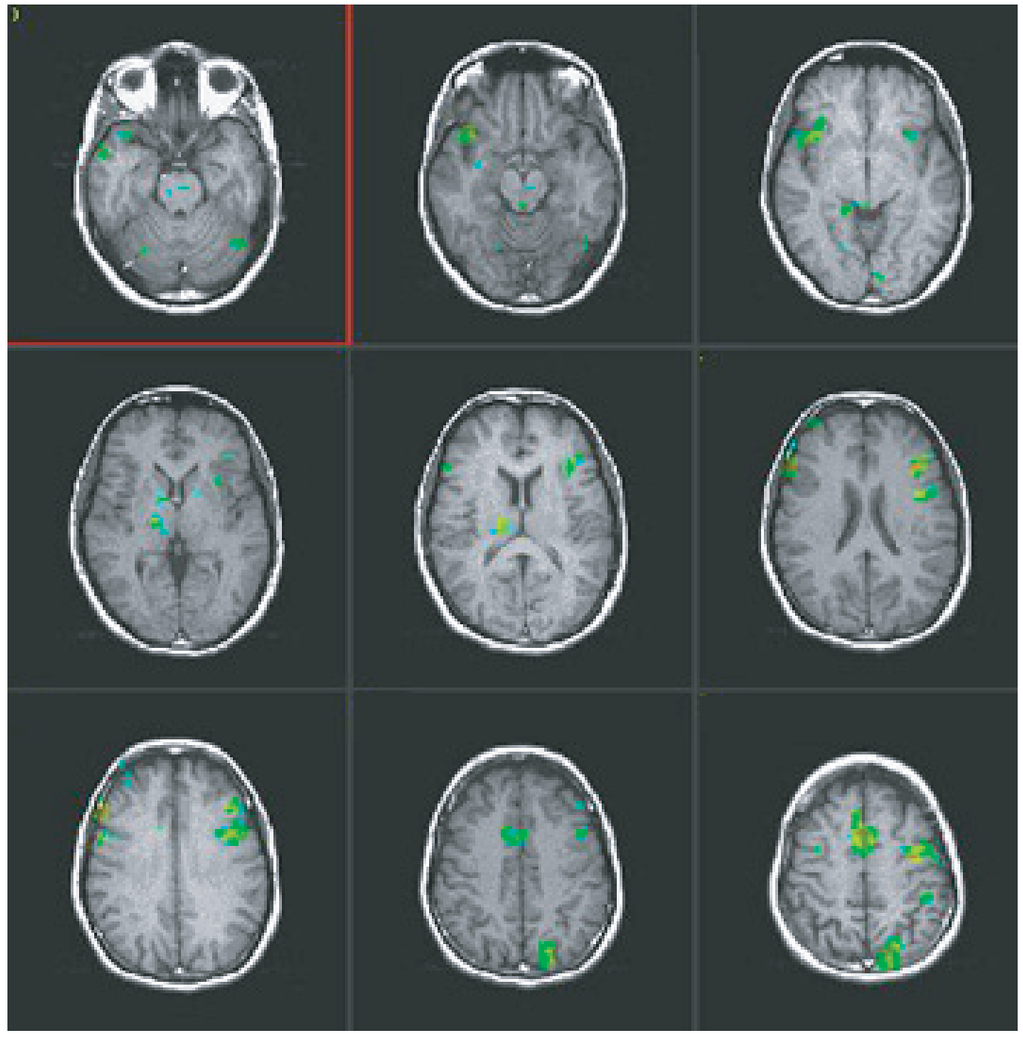

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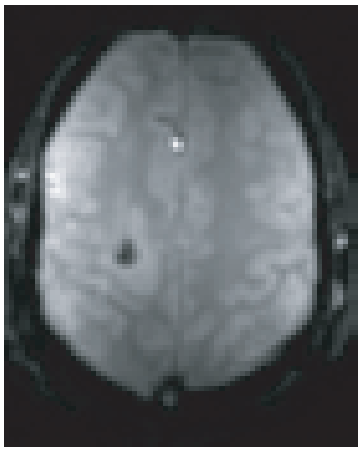
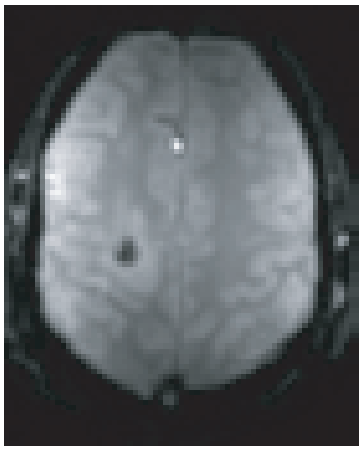
The effect is small, and is observed by acquiring very high sensitivity difference images.

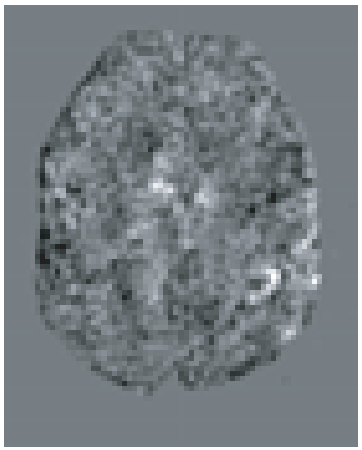
Imaging Neural Activity:
BOLD (Blood Oxygen Level Dependent)

Hand Clenching

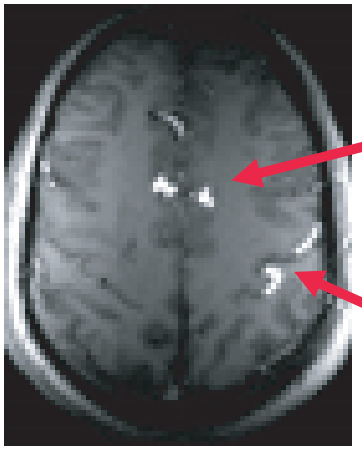


Rest





Statistical
Parameter Map



Overlay onto
Anatomical
Image

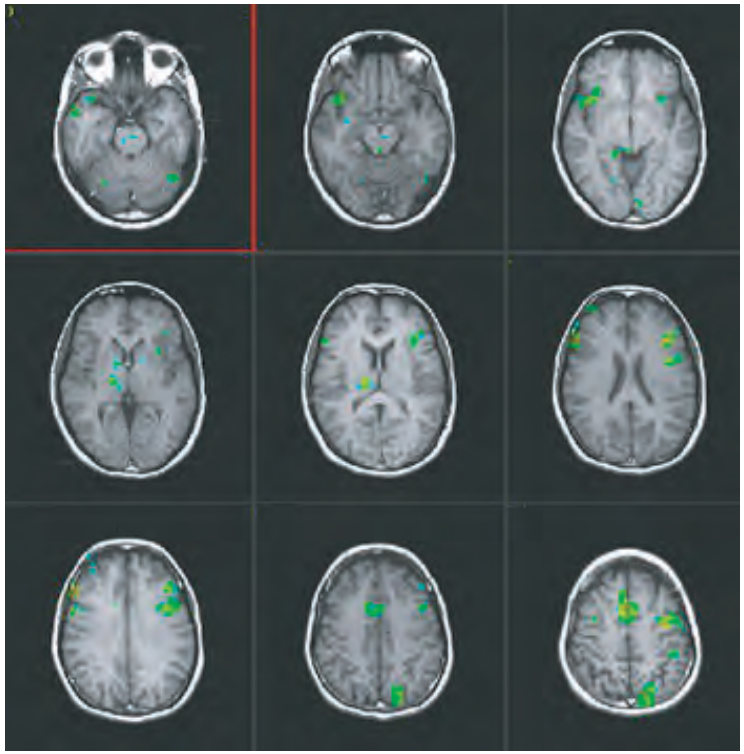
A typical fMRI study

Supplementary Motor Area

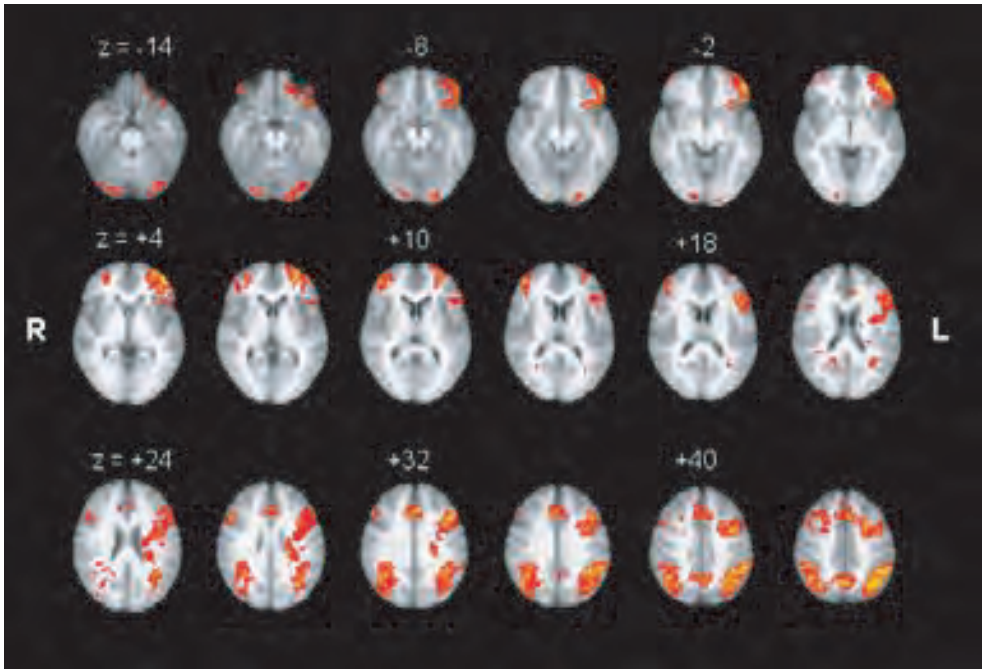
Primary Motor Area

Imaging Neural Activity:
BOLD (Blood Oxygen Level Dependent)

foreign language

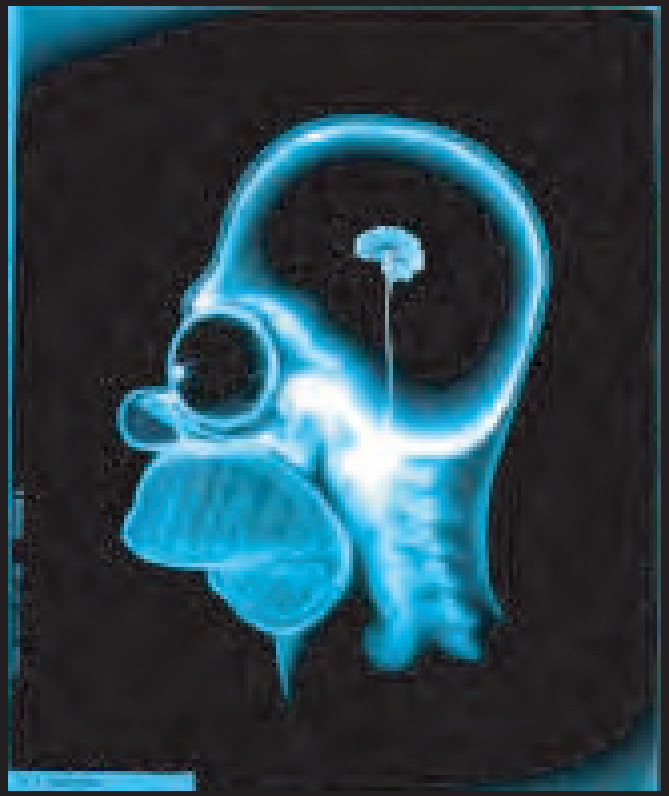


poetry.....



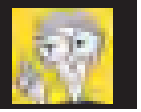
MRI vs. fMRI

MRI studies brain **anatomy**.



Functional MRI (fMRI) studies brain **function**.

Source: Jody Culham's fMRI for Dummies web site



Conclusions

- Contrast in the image can be obtained by weighting the intensity by parameters that have significant differences between, e.g., tissue types, such as T_1 or T_2.

- Differences in T_1 and T_2 can be accentuated by adding a chemical “contrast agent”, that can be systemic or specific.

- Smart contrast can be introduced by reactive molecules.

- Contrast can be introduced that is functional rather than anatomical: for example flow or brain function