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Cancer Center

Cancer Imaging – Advanced Contrast Mechanisms in MRI

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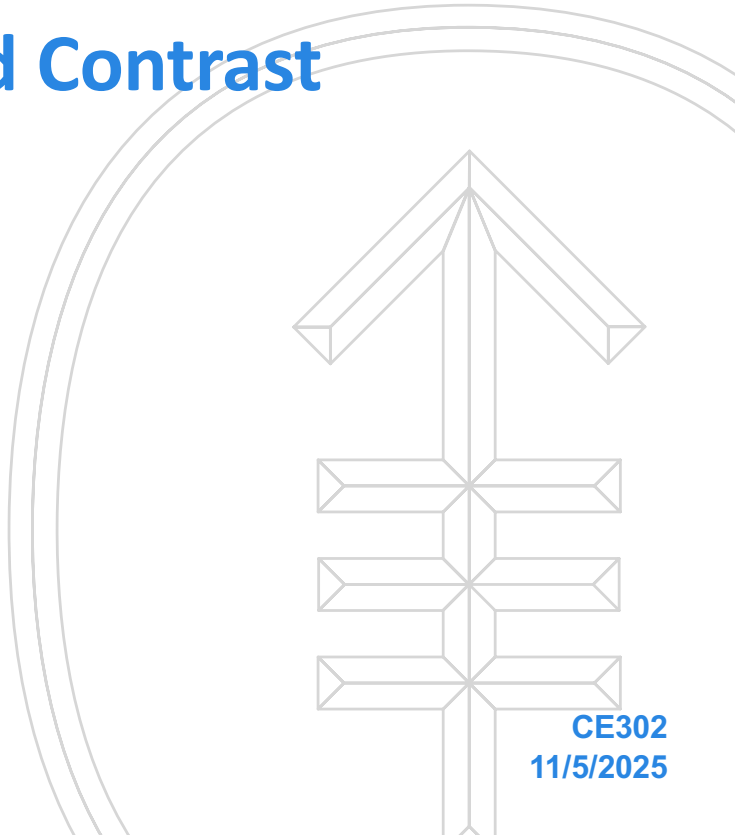


CE302
11/5/2025

The Plan

1. Revisiting Relaxation contrast (T_1, T_2 and T_2*)
   a. BOLD and ASL
2. Diffusion-weighted MRI
3. Contrast Mechanisms for MRI
   a. Relaxation based (small and large molecules)
   b. Chemical Exchange Saturation Transfer
   c. Magnetic Resonance Spectroscopy/Spectroscopic Imaging
   d. Multi-nuclear MRS/MRI
      - Isotope tracing
      - Hyperpolarization

Discussion Papers and Background

Background paper:

- James, M. L. & Gambhir, S. S. A molecular imaging primer: modalities, imaging agents, and applications. *Physiological reviews* **92**, 897-965 (2012).

2 Discussion Papers:

- Day, S. E. *et al.* Detecting tumor response to treatment using hyperpolarized 13C magnetic resonance imaging and spectroscopy. *Nat Med* **13,** 1382–1387 (2007).

- Choi, C. *et al.* 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. *Nat Med* **18,** 624–629 (2012).

Magnetic Resonance

- *Nuclear magnetic dipole* – charged particle spinning around an axis => small circular current…faster the nucleus spins => bigger the current

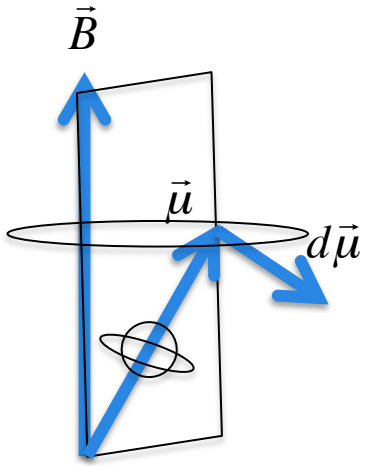
$$\vec{\mu} = \gamma \vec{I}$$

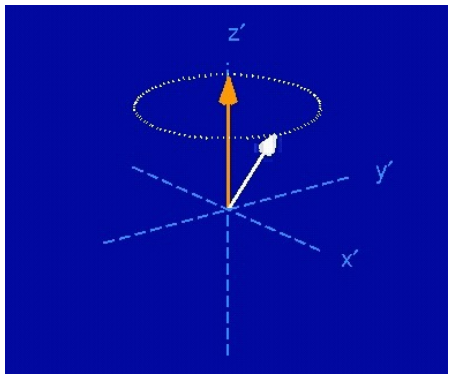
  - Magnetic moment μ, spin angular momentum I, gyromagnetic ratio γ
- When you put the nucleus in a field B, since the nucleus is spinning you have Larmor precession…
  - Spins precess perpendicular to the plane

$$\frac{d\vec{\mu}}{dt} = -\gamma \vec{B} \wedge \vec{\mu}$$

- Typically we have a static field B_0 and define angular velocity of the precession and frequency (*Larmor freq*)…

$$\omega_0 = \gamma B_0 \qquad \nu_0 = \frac{\omega_0}{2\pi}$$





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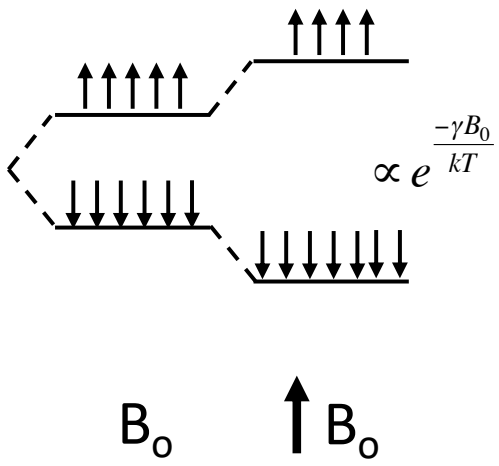
Magnetic Resonance

Signal depends on the Boltzmann Distribution (k), gamma, field, and temperature



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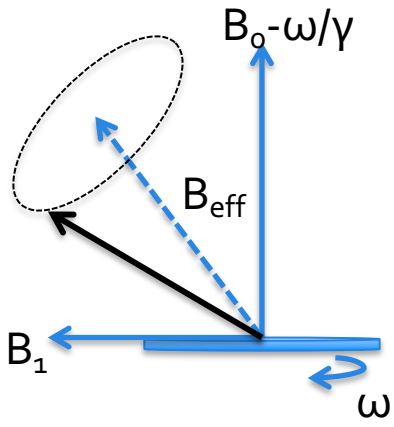
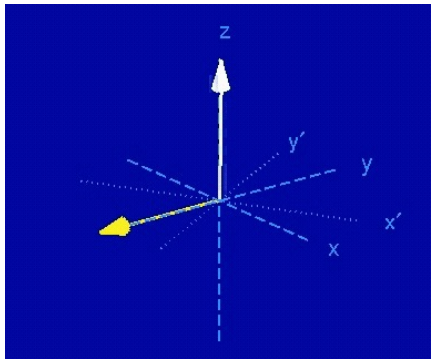
Revisiting Relaxation contrast (T_1, T_2 and T_2^*)

Magnetic Resonance

- Problem…if the magnetization is on Z (main field) we can't observe it…
- RF Excitation
  - Tip M away from Z with B_1
  - Then M precesses around the new field (B_0+B_1)
  - Since we would need a lot of power to generate a static B_1 that would actually influence the overall B field…
  - We let the B_1 field rotate around B_0 with the same frequency as M…=> we excite at the frequency of M
- Flip angle $\alpha = \gamma B_1 t_p$





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Magnetic Resonance

- Immediately after excitation, precession can't go on forever…
- Relaxation
  - T_1 – *spin-lattice*, restores Boltzmann => M_z regrows
  - T_2 – *spin-spin*, a result of an ensemble of different magnetic dipoles => M_{xy} decays
- Define the cross product in xyz.. And substitute our excitation scheme, B_0 and these relaxation coefficients…

$$\frac{d}{dt}M_x = -\gamma(B_y M_z - B_z M_y)$$
$$\frac{d}{dt}M_y = -\gamma(B_z M_x - B_x M_z)$$
$$\frac{d}{dt}M_z = -\gamma(B_x M_y - B_y M_x)$$

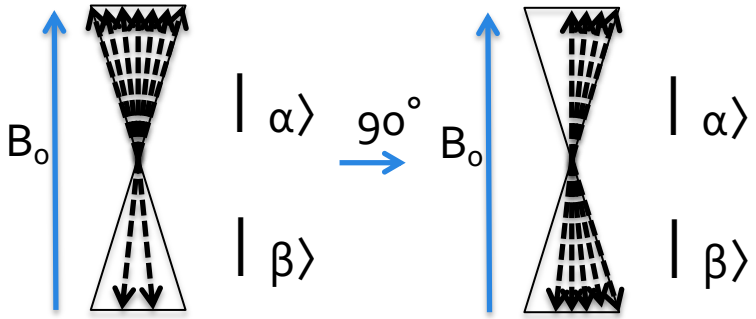
$$\vec{B} = \left[B_1, 0, B_0 - \frac{\omega}{\gamma}\right]$$

Bloch Equations

$$\frac{d}{dt}M_x = (\omega_0 - \omega)M_y - \frac{1}{T_2}M_x$$
$$\frac{d}{dt}M_y = -(\omega_0 - \omega)M_x - \frac{1}{T_2}M_y + \omega_1 M_z$$
$$\frac{d}{dt}M_z = -\omega_1 M_y - \frac{1}{T_1}(M_z - M_0)$$

Magnetic Resonance – T_1

- T_1 relaxation – spin-lattice
  - Spins exchange energy via "on resonance" fluctuations with the lattice
  - More fundamental…$|\alpha\rangle$ and $|\beta\rangle$ need to go through transitions to re-establish equilibrium

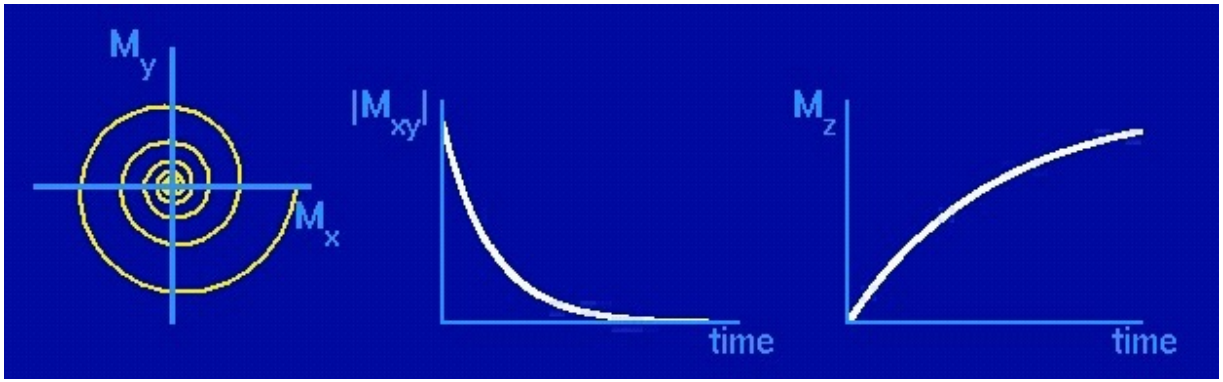


  - For this to happen, spins have exchange energy with the surroundings…*lattice*
  - This is dependent on the local field the spin experiences

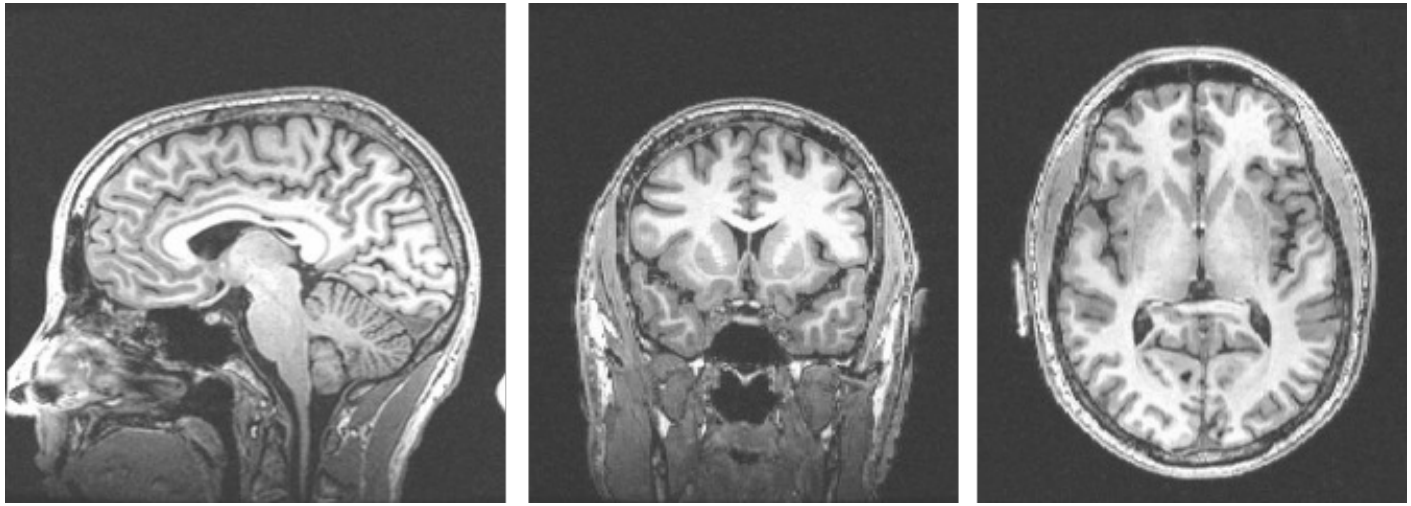
$$\frac{d}{dt}M_z = -\frac{1}{T_1}(M_z - M_0) \xrightarrow{\text{ode}} M_z(t) = M_0[1 - e^{-\frac{t}{T_1}}]$$

Magnetic Resonance - Relaxation

- Immediately after excitation, precession can't go on forever…
- Relaxation
  - T_1 – *spin-lattice*, restores Boltzmann => M_z regrows
    - Spins exchange energy via "on resonance" fluctuations with the lattice
  - T_2 – *spin-spin*, a result of an ensemble of different magnetic dipoles => M_{xy} decays
    - Spins "feel" magnetic fields from other molecules and become off frequency with respect to B_0 and other spins



T_1-weighted imaging



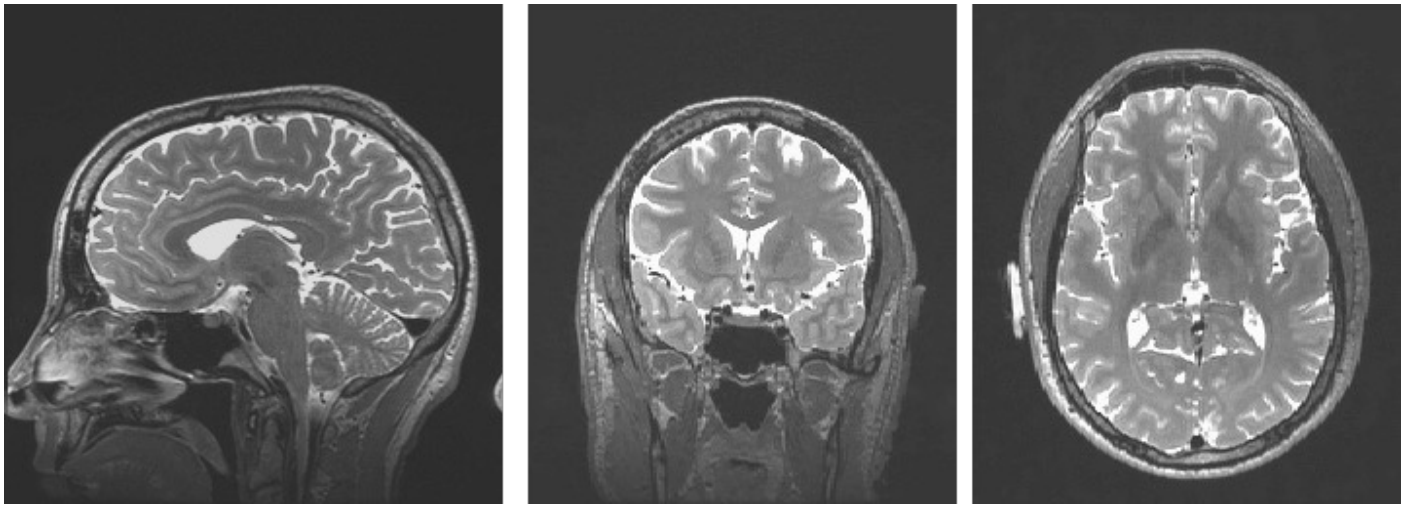
Dark on T_1-weighted image:

- increased water, as in edema, tumor, infarction, inflammation, infection, hemorrhage
- low proton density, calcification
- flow void

Bright on T_1-weighted image:

- **fat**
- subacute hemorrhage, protein-rich fluids
- paramagnetic substances: gadolinium, manganese, copper

T_2-weighted imaging



Bright on T_2-weighted image:

- increased water, as in edema, tumor, infarction, inflammation, infection, subdural collection
- methemoglobin (extracellular) in subacute hemorrhage

Dark on T_2-weighted image:

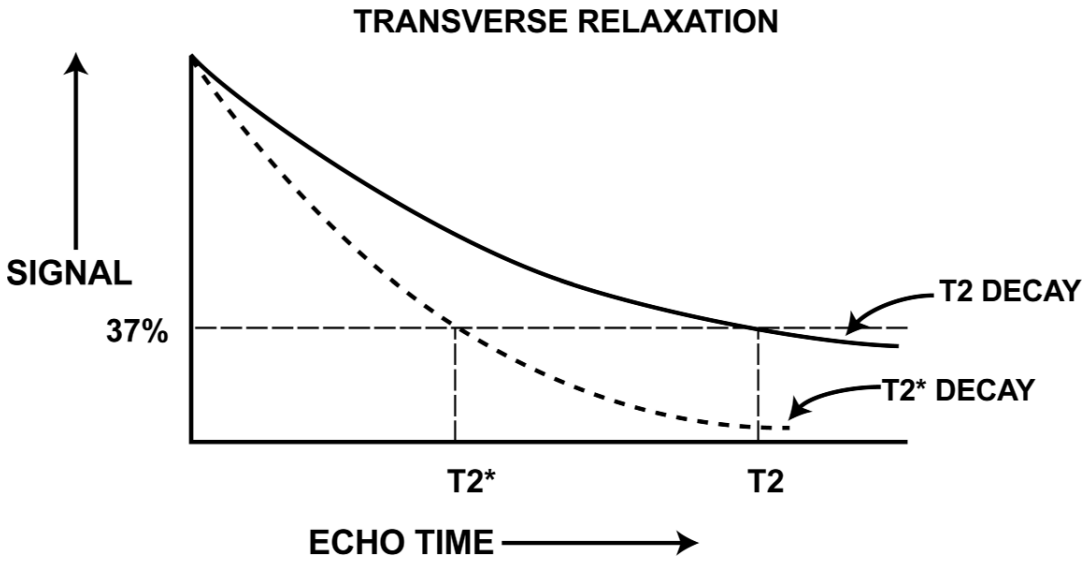
- low proton density, calcification, fibrous tissue
- paramagnetic substances: deoxyhemoglobin, methemoglobin (intracellular), iron
- protein-rich fluid
- flow void

So then what is T_2^*

The local magnetic field is actually not homogenous causing additional relaxation

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

$$\frac{1}{T_2'} = \gamma \Delta B_{inhom}$$



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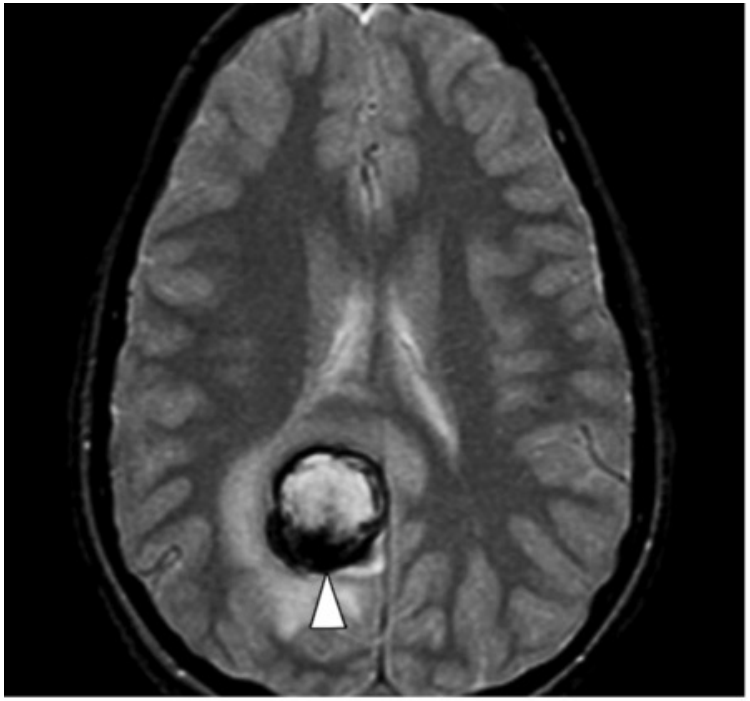
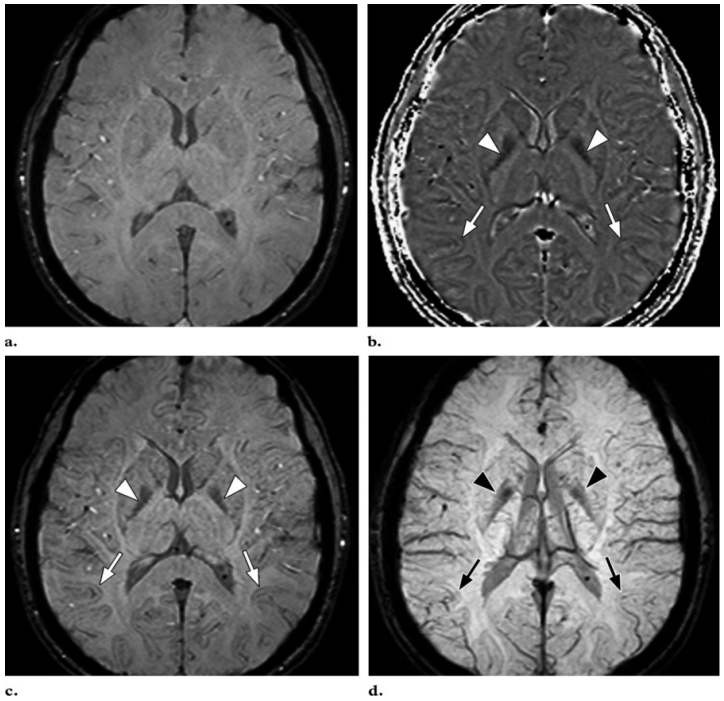
T_2*-weighted imaging



Blood causes local T_2*

Susceptibility weighted imaging (SWI)



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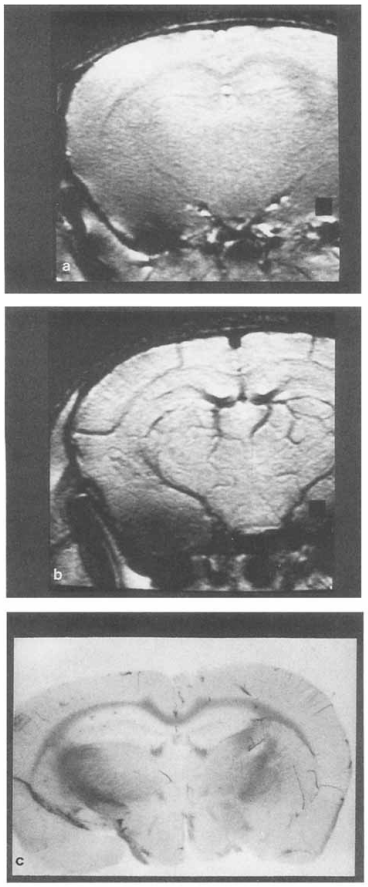
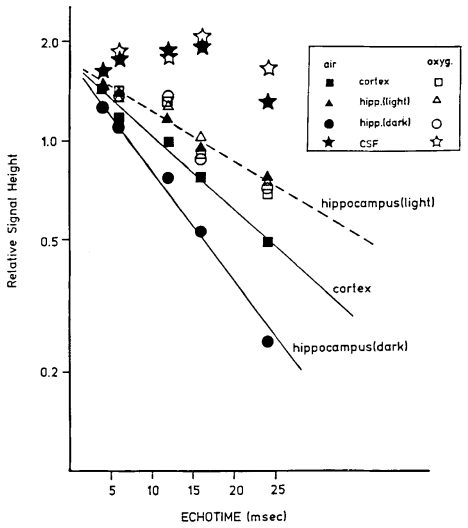
BOLD?

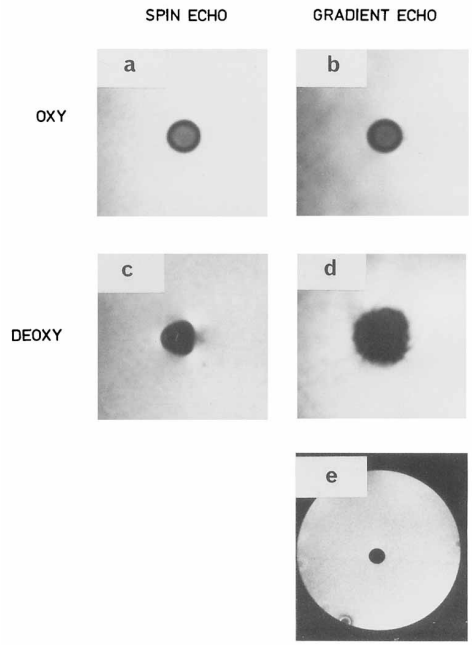
Breathing 100% oxygen

Breathing normal air





Signal decay as a function of echo time in gradient echo images



Ogawa et al. *MRM* 1990

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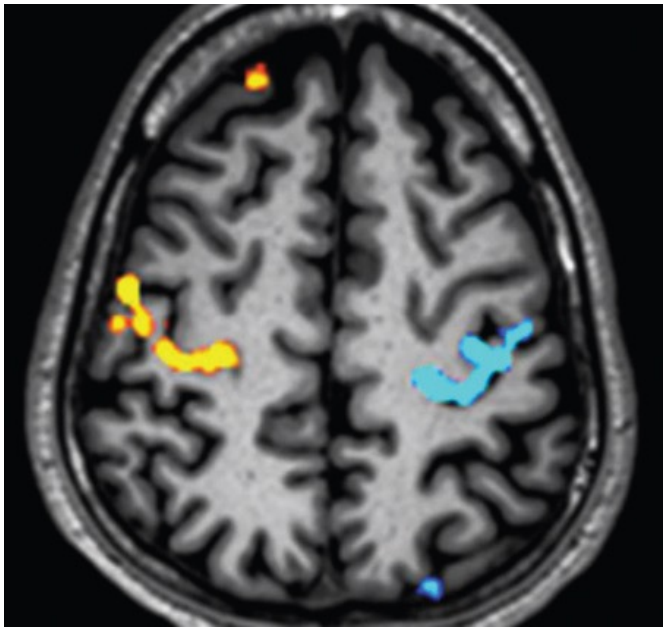
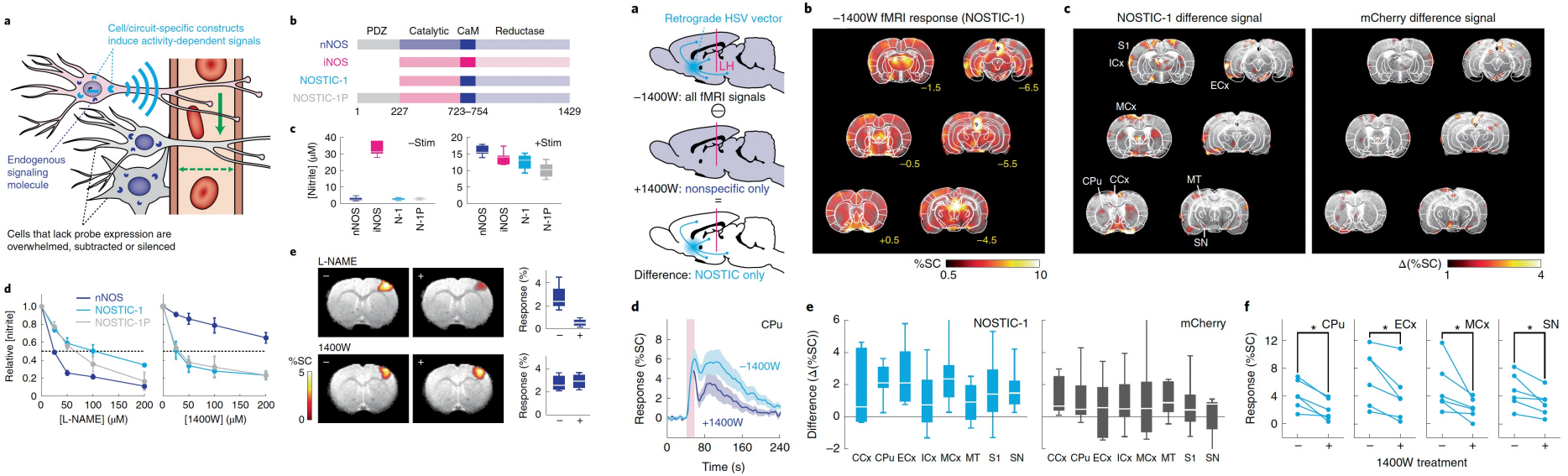
BOLD ➡ fMRI

- Oxyhemoglobin is diamagnetic while deoxyhemoglobin is paramagnetic relative to surrounding tissue
- Deoxyhemoglobin causes a reduction in signal by creating microscopic field gradients within and around the blood vessels
- Stimulation of a brain area cause increased cerebral blood flow to an area, increase in blood oxygen, decrease in deoxyhemoglobin and thus increase in local MR signal…we call this BOLD



Can you use BOLD to read out other mechanisms?



Ghosh et al. *Nature Neuro* 2022

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Arterial Spin Labeling (ASL)

- What happens if you invert a moving spin and then observe in a given FOV?
- Think of it as a “spin-tag”

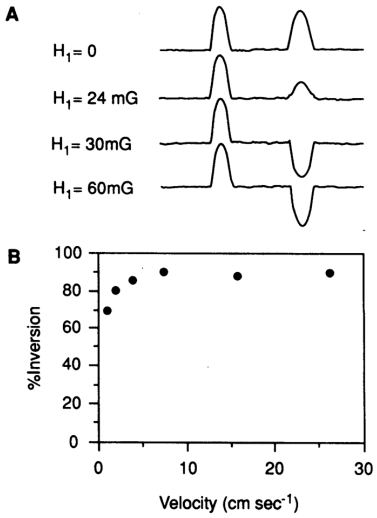

FIG. 1. Phantom studies on the effect of H_1 and velocity on spin inversion by adiabatic fast passage. (*A*) One-dimensional intensity profiles of a phantom consisting of stationary blood (left) and flowing blood (right), respectively, as a function of radiofrequency field strength, H_1, used for inversion. The blood is flowing through a gradient of 0.5 G·cm^{-1}. (*B*) Variation of degree of inversion in a phantom of flowing blood as a function of flow velocity. A gradient of 1.0 G·cm^{-1} and H_1 of 59 mG were used for all flow velocities.

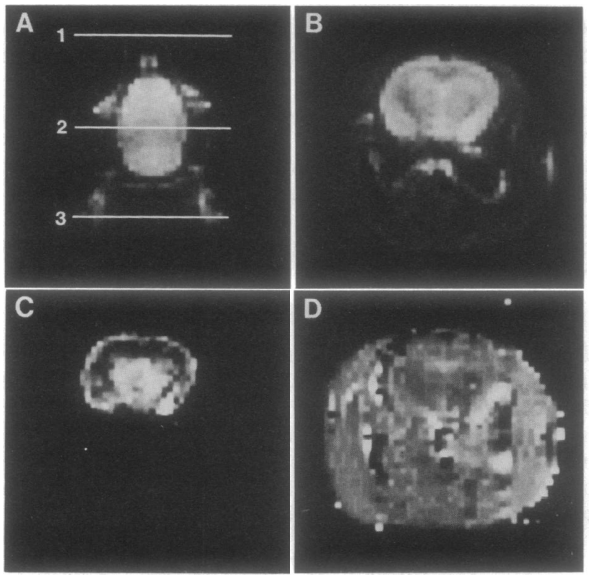

FIG. 2. (*A*) Coronal image of a rat head. The resonance planes for radiofrequency used for spin inversion by AFP for control and inversion images are indicated by 1 and 3, respectively, and plane 2 is the detection plane. (*B*) Control transverse image from the detection plane (plane 2 in *A*). (*C*) Difference image between control and inversion images. (*D*) T_{1app} image.

Williams et al. *PNAS* 1992

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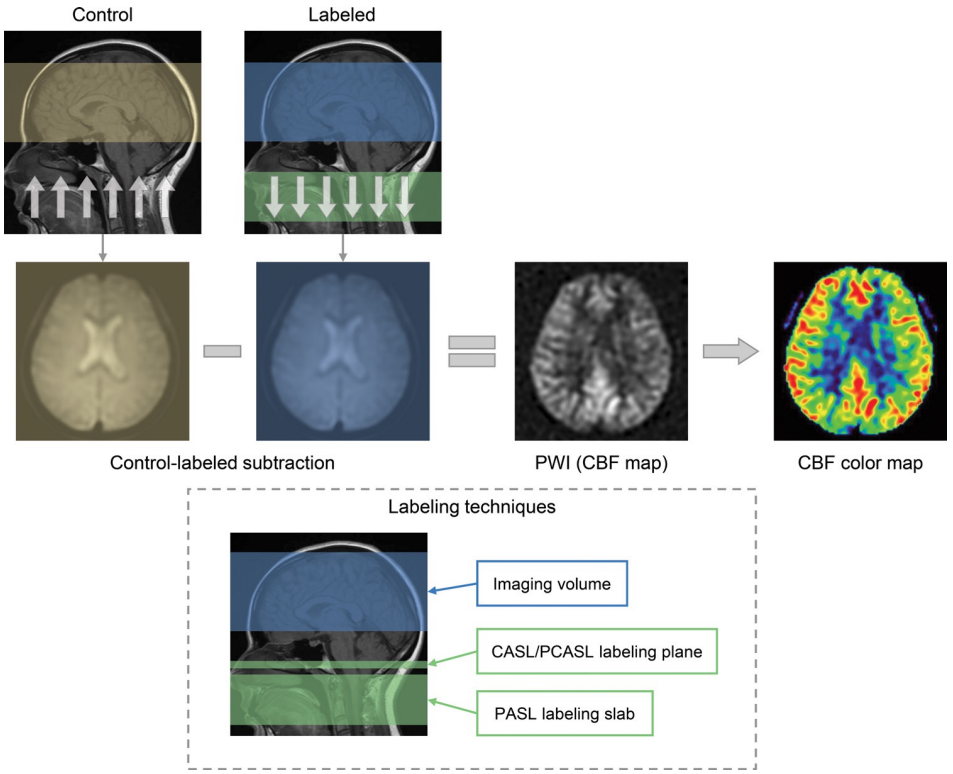
Arterial Spin Labeling (ASL)



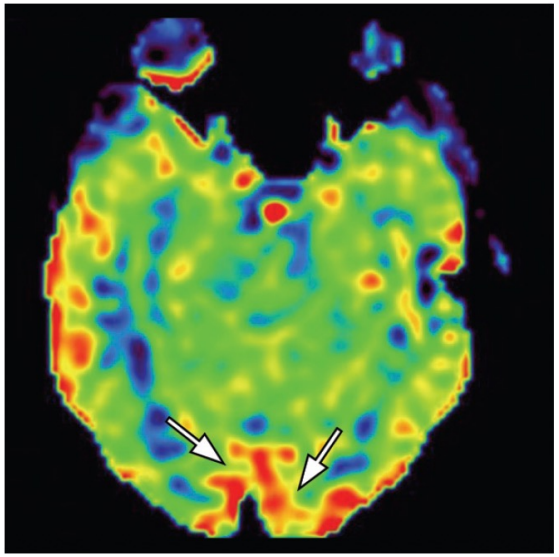


Figure 2. Occipital lobe hyperperfusion artifact in a healthy 32-year-old woman. ASL map shows bilateral and symmetric high signal intensity in the occipital lobes (arrows), which represents occipital lobe hyperperfusion artifacts that occurred because the patient opened her eyes during imaging.

Iutaka et al. *Radiographics* 2023

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Magnetic Resonance – Molecules tumbling

Rotational correlation time

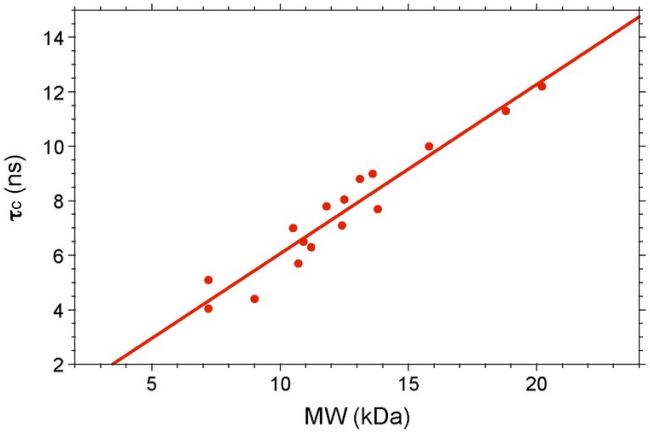
- Characteristic tumbling rate of a molecule, Brownian rotation diffusion of a particle
- Defined as time it takes a particle to rotate 1 radian
- Stoke's approx…

$$\tau_c = \frac{4\pi\eta r^3}{3kT} \qquad r \approx \sqrt[3]{\frac{3M}{4\pi\rho N_a}} + r_w$$

η is the viscosity, r eff hydrodynamic radius

M, mass in kDa, ρ density,

N_a avagadro, r_w = hydration (1-3A)



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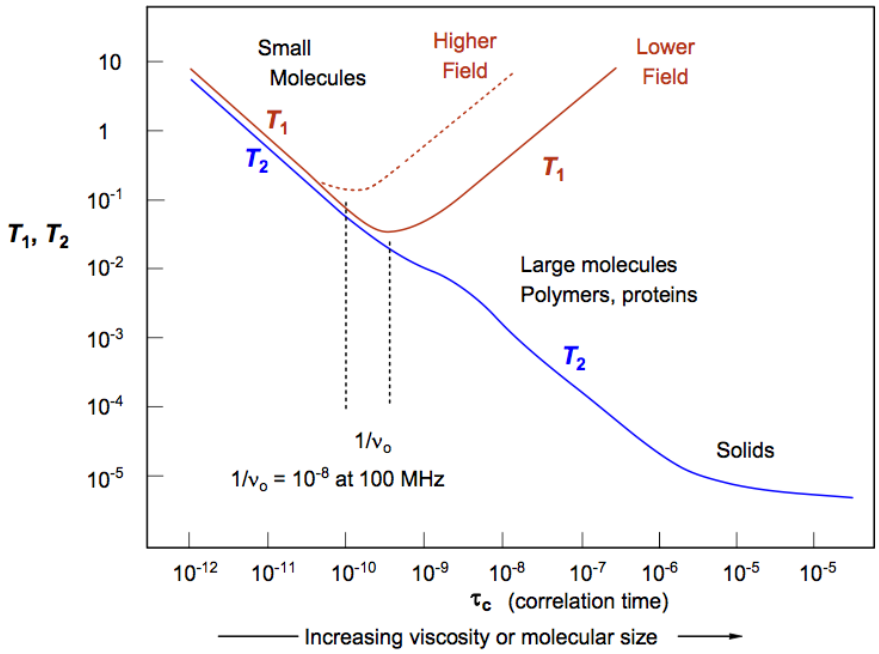
Magnetic Resonance – Correlation time

What does this have to do with NMR/MRI?

$$\frac{T_1}{T_2} = 1 + \frac{1}{2}\omega_0^2\tau_c^2$$



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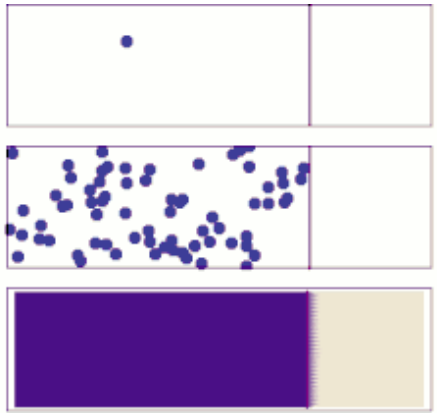
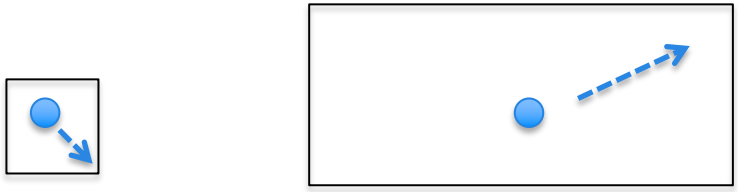
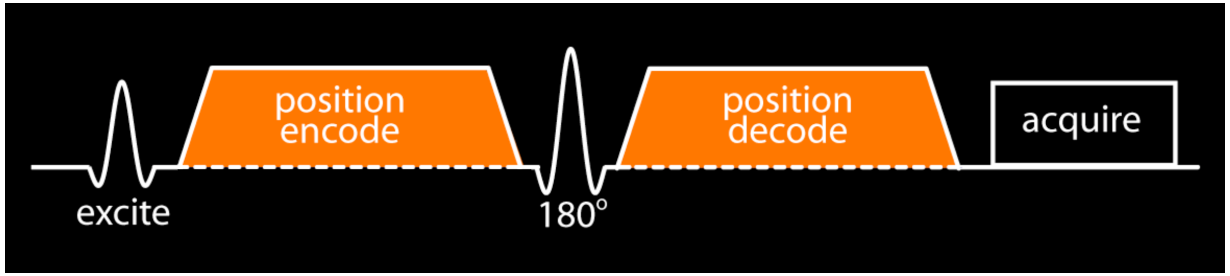
Diffusion-weighted MRI

Magnetic Resonance – Diffusion

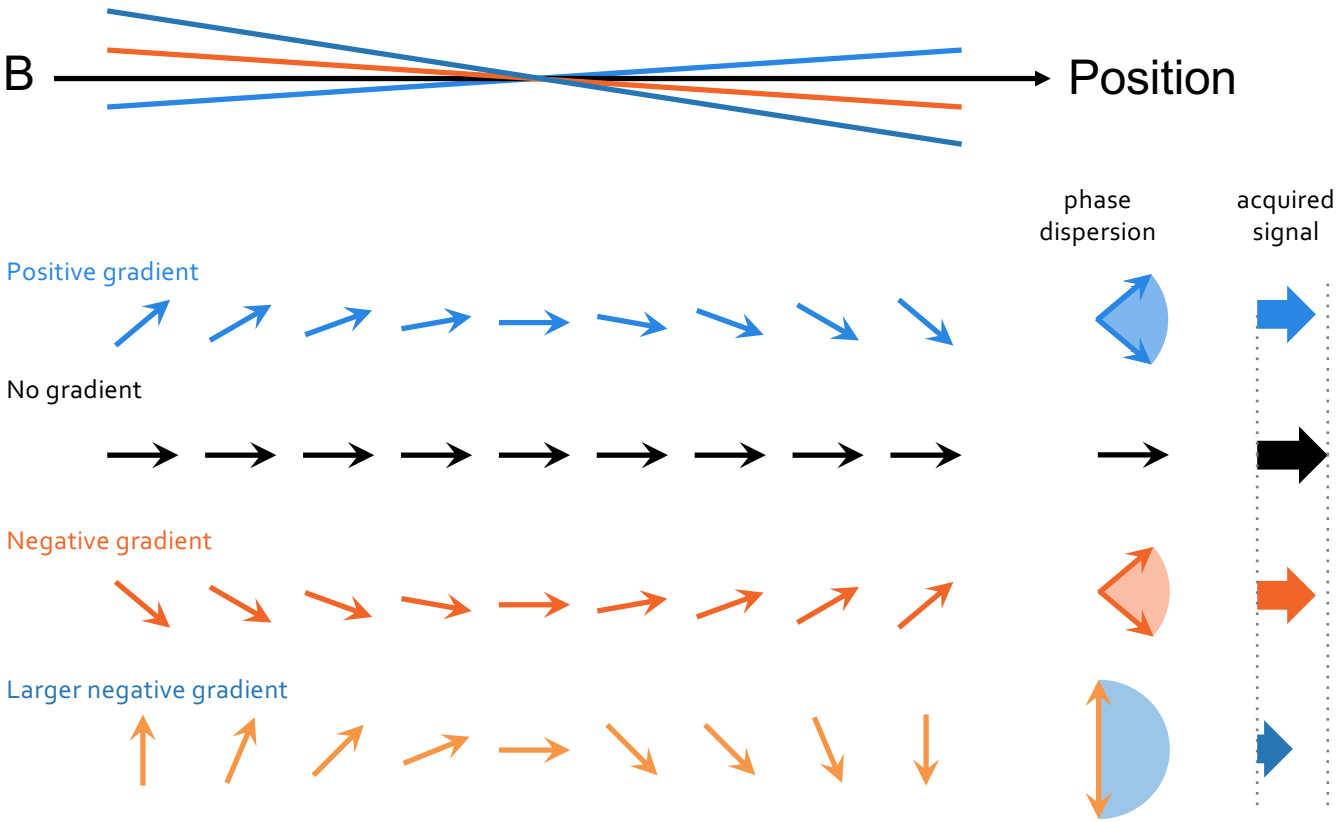
- Brownian motion – random movement of particles in a liquid
- What if they run into a wall?
- What if they travel a long distance?
- Can we encode that?



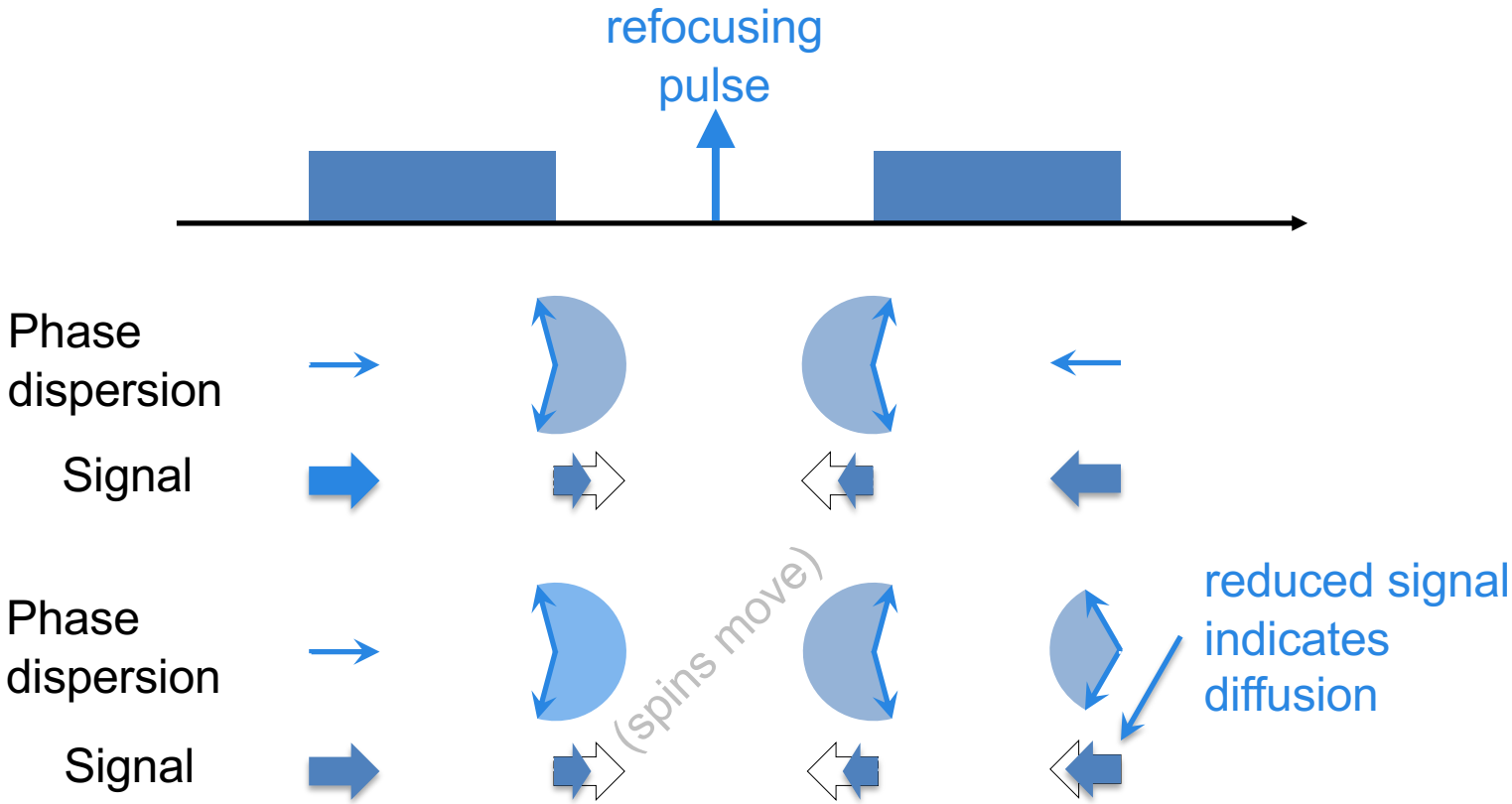




Gradients dephase spins within a voxel



Gradient pairs can be used to identify moving spins (spin echo sequence)



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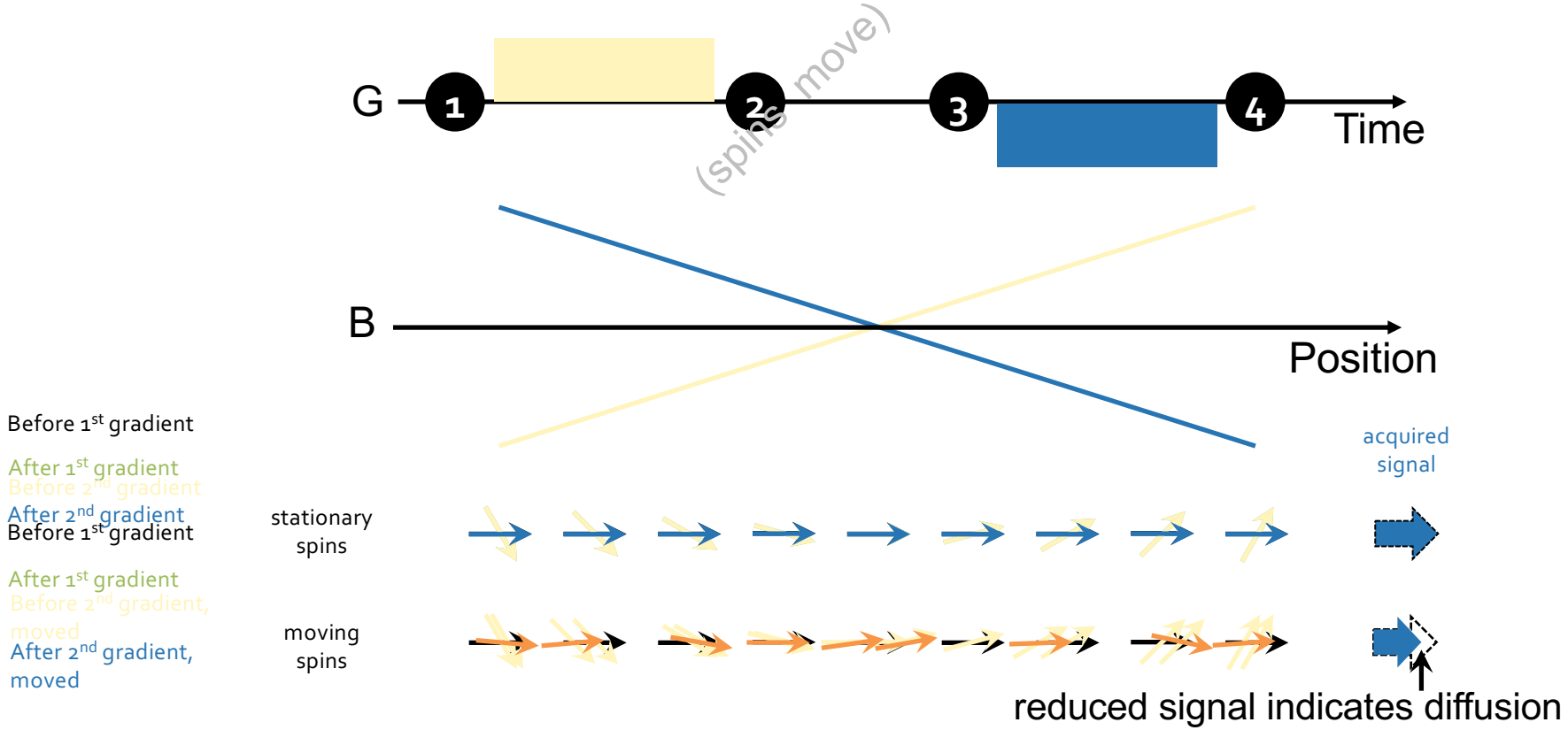


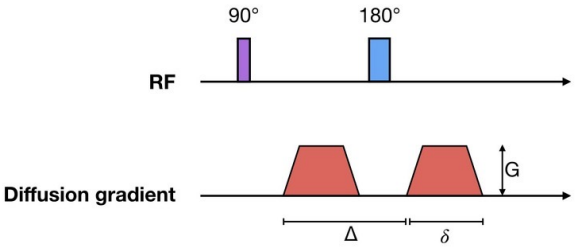
Basic DWI sequence

- Spin-echo EPI
  - Higher signal => restricted diffusion
  - *b* value describes the amount of diffusion-weighting for a given spin-echo sequence
  - Diffusion time (Δ) affects the range of diffusion differences

Quantification

b value

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



γ = gyromagnetic ratio

G = magnitude of the two balanced DW gradient pulses

δ = width of the two balanced DW gradient pulses

Δ = time between the two balanced DW gradient pulses

Relationship between signal of b = 0, DWI and ADC

$$S_{DWI} = S_{b=0} \times e^{(-b \times D)}$$

equivalent to...

$$D = -\frac{1}{b} \times \ln\left(\frac{S_{DWI}}{S_{b=0}}\right)$$

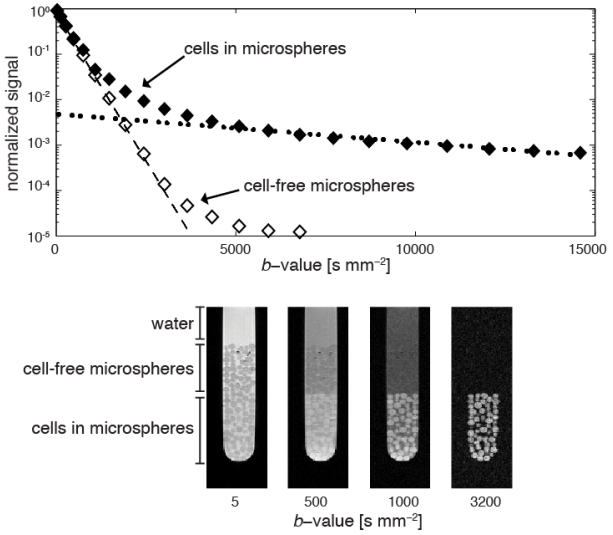
S_{DWI} = signal intensity of isotropic DWI

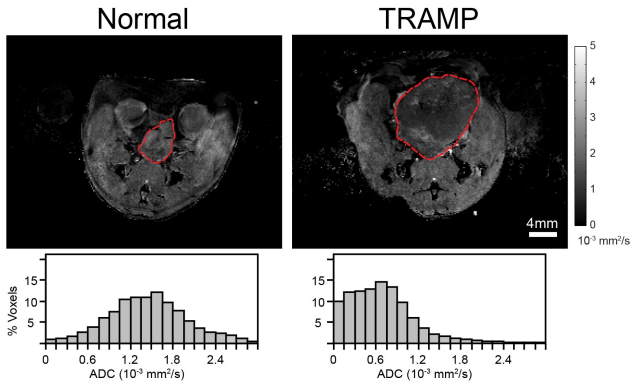
$S_{b=0}$ = signal intensity of b = 0

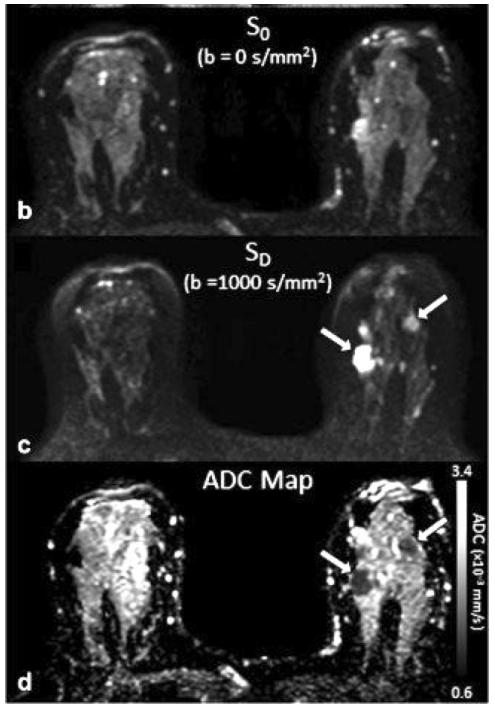
b = b value

D = apparent diffusion coefficient (ADC)

Magnetic Resonance – Diffusion *in vitro and in vivo*







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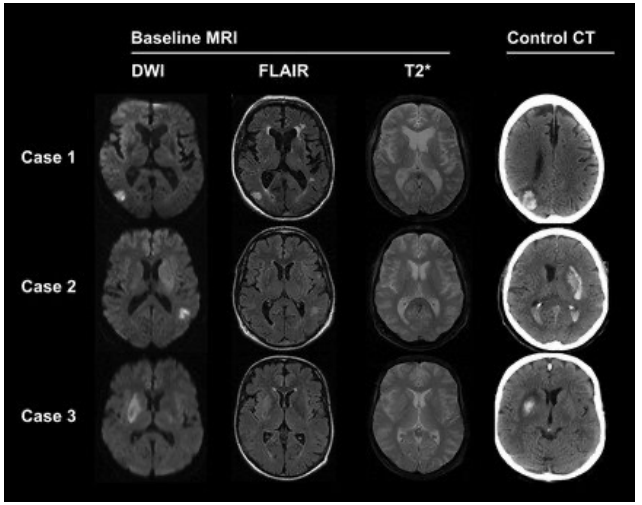
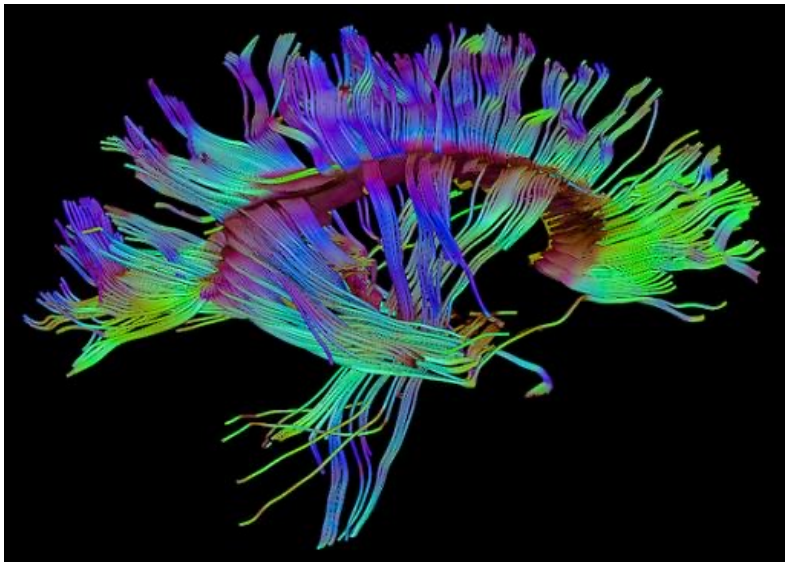
- Common applications
  - Ischemia
  - Edema
  - Cancer



- In vivo diffusion reflects
  - Cellularity
  - Structure (e.g., vessels, intracellular structures)
  - Presence of macromolecules and organelles

Advanced Applications

- Diffusion Tensor Imaging (DTI)
  - Multiple directions we calculate a tensor map…
  - measure diffusion anisotropy
- Intravoxel Incoherent Motion (IVIM) Imaging
  - separate perfusion and diffusion contributions
- Restriction Spectrum Imaging (RSI)
  - distinguish intra-cellular and extra-cellular components



Contrast Mechanisms for MRI

a. Relaxation based (small and large molecules)
b. Chemical Exchange Saturation Transfer
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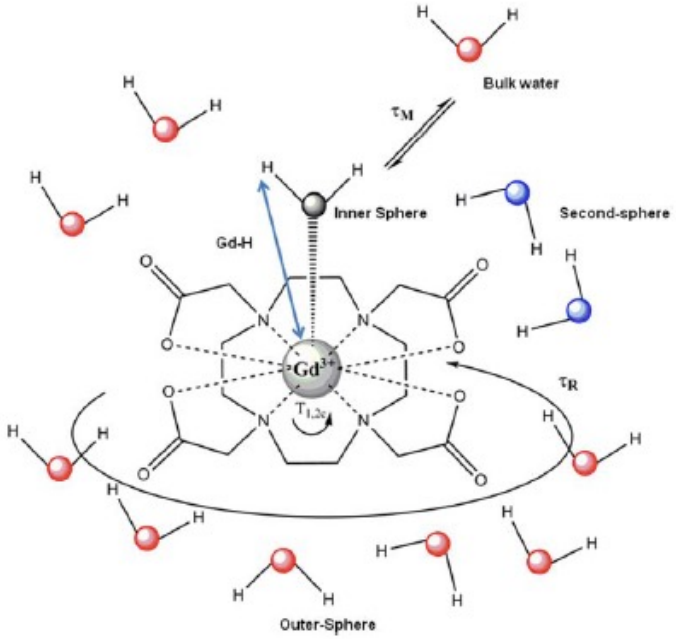
T_1-Based Contrast Agents

- Shortening longitudinal relaxation time of water
- “positive agent", brightening T_1-weighted image sequences
- Gd^{3+} in lanthanide(Ln) family of elements

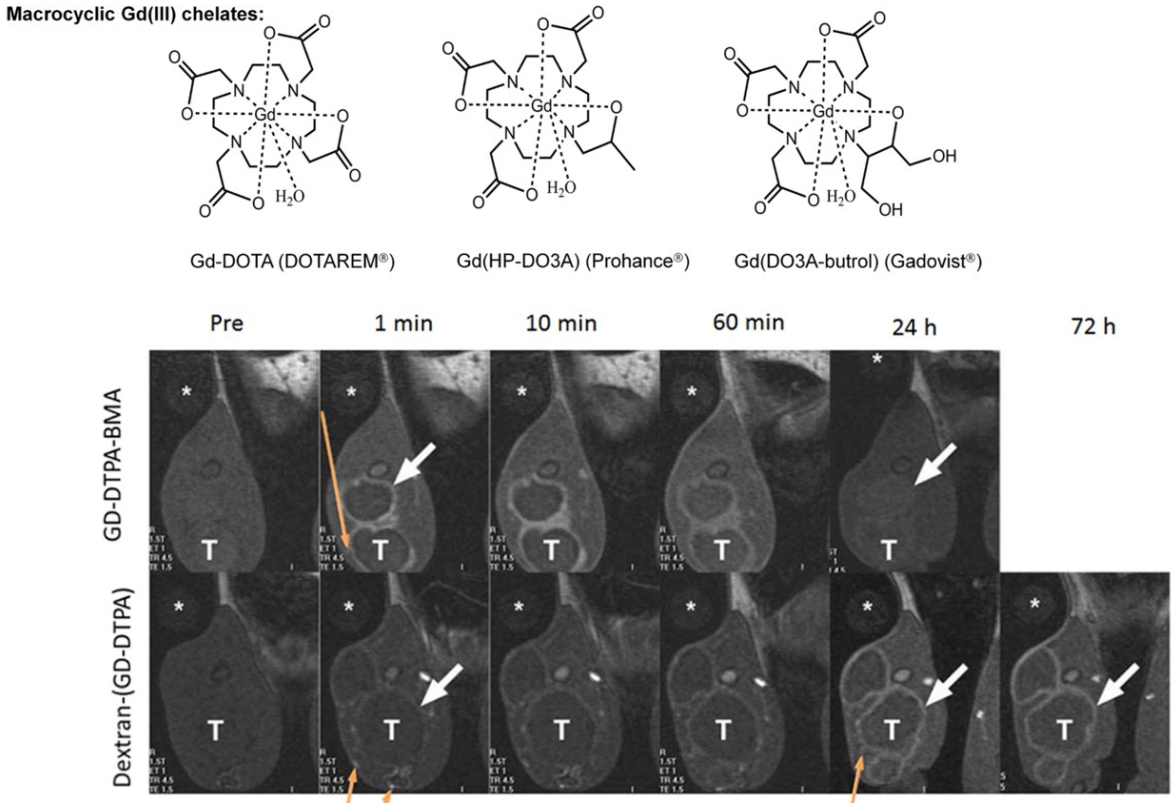
  - Seven unpaired electrons in 4f orbital
  - Very high magnetic moment
  - Unusual long electronic spin relaxation time



J Magn Reson Imaging. 2015 Sep;42(3):545-65

Perfusion – Gd^{3+} MRI

- Gd^{3+} chelates – change shorten T_1 relaxation



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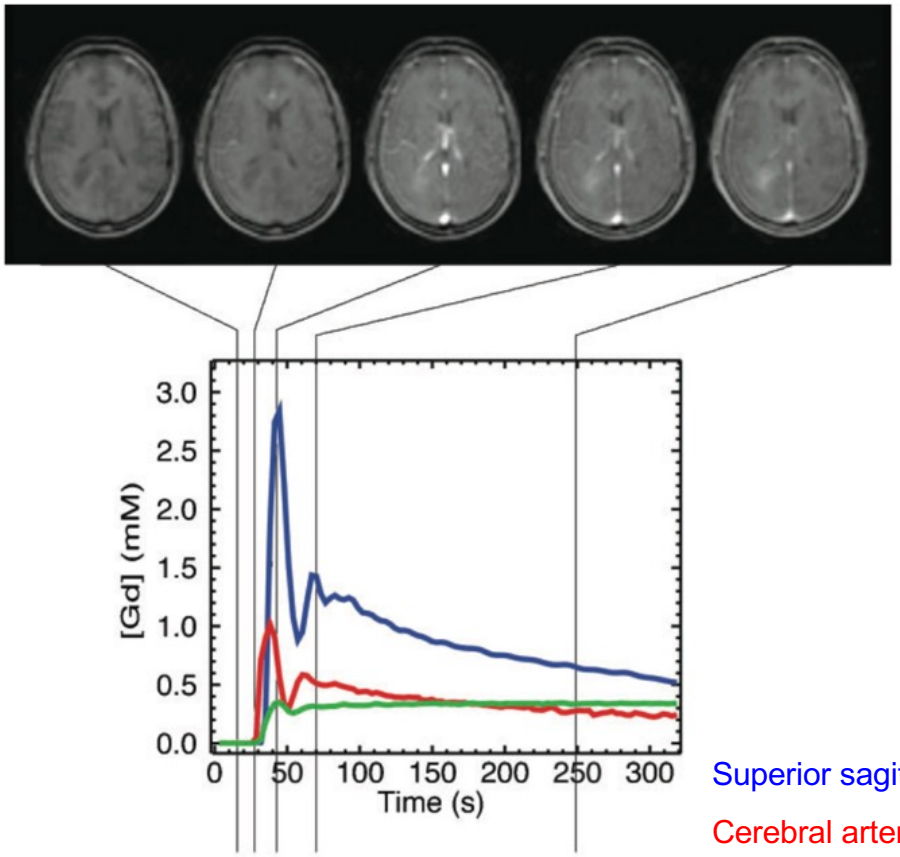
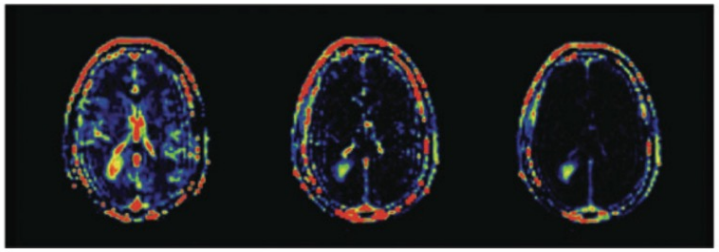
Perfusion – Gd^{3+} MRI



Superior sagittal sinus

Cerebral artery

Tumor



V_p
Blood pool volume

V_e
extracellular distribution space

K_{trans}
Perfusion "rate"

O'connor et al 2011

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Can we exploit T_2* - Super Paramagnetic Iron (SPIO)

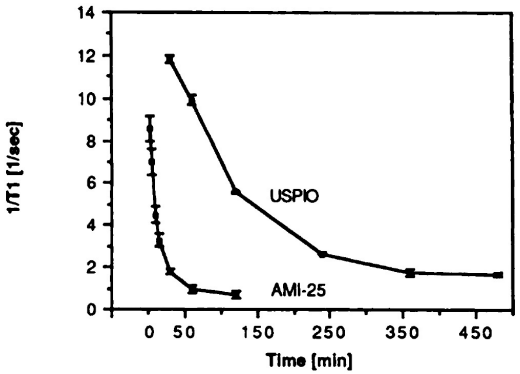
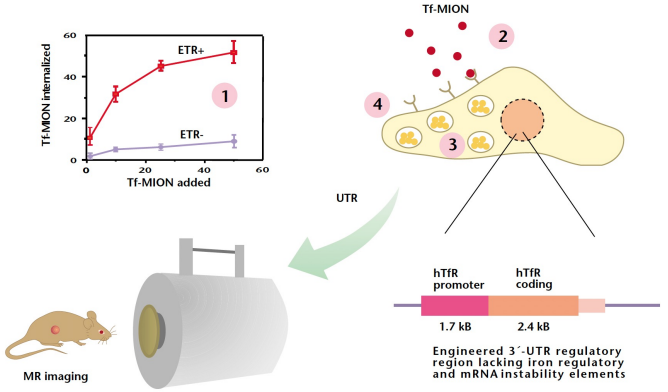
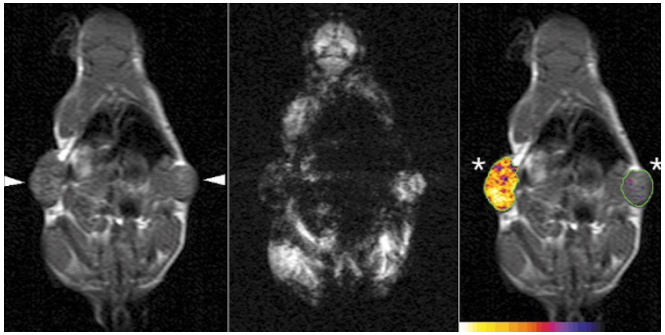


Figure 1. Blood clearance of USPIO and AMI-25. Means and SEMs of data from six animals are shown for each contrast medium. The calculated blood half-life of USPIO was 81 minutes, and that of AMI-25 was 6 minutes.





Weissleder et al. *Radiology* 1990
Weissleder et al *Nat Med* 2000

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Contrast Mechanisms for MRI

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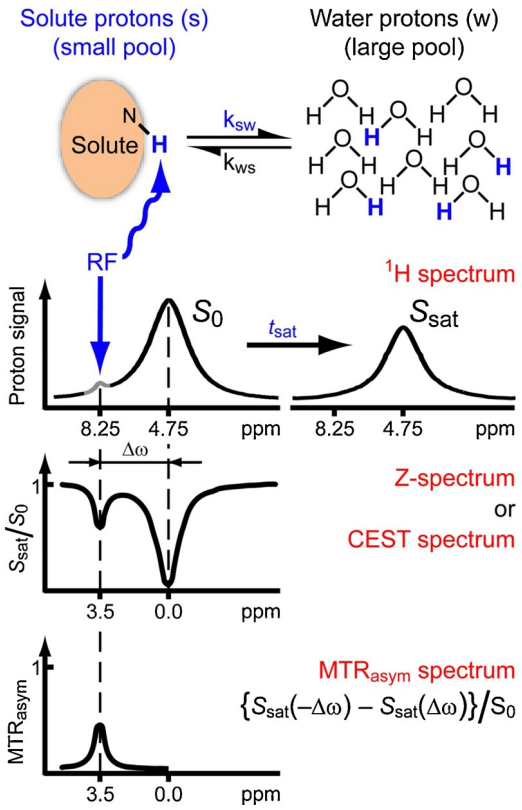
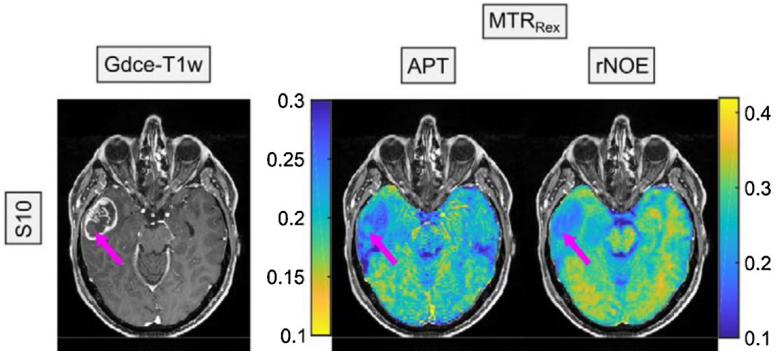
c. Magnetic Resonance Spectroscopy/Spectroscopic Imaging

d. Multi-nuclear MRS/MRI
   - Isotope tracing
   - Hyperpolarization

Chemical Exchange Saturation Transfer (CEST)



Technique	CEST agents	Chemical groups	Chemical Shift	Application
APT	Mobile proteins and peptides	Amide (N—H)	~3,5 ppm	Strokes (ischemic and hemorrhagic) Tumors Neurodegenerative diseases
GluCEST	Glutamate	Amine (N—H2)	~3 ppm	Neurodegenerative diseases, monitoring,
GlucoCEST	Glucose	—Hydroxyl (OH)	3 peaks [1.2 / 2.2/ 2.8 ppm]	Tumors
MICEST	Myo-inositol	Hydroxyl (O—H)	3 peaks [0.8 / 0.9 / 1.1 ppm]	Neurodegenerative diseases
CrCEST	Creatine	Amine (N—H2)	~1.8 ppm	Tumors, seizures



Mamoune et al. *J Chem Neuroanatomy* 2021
Goerke et al. *MRM* 2019

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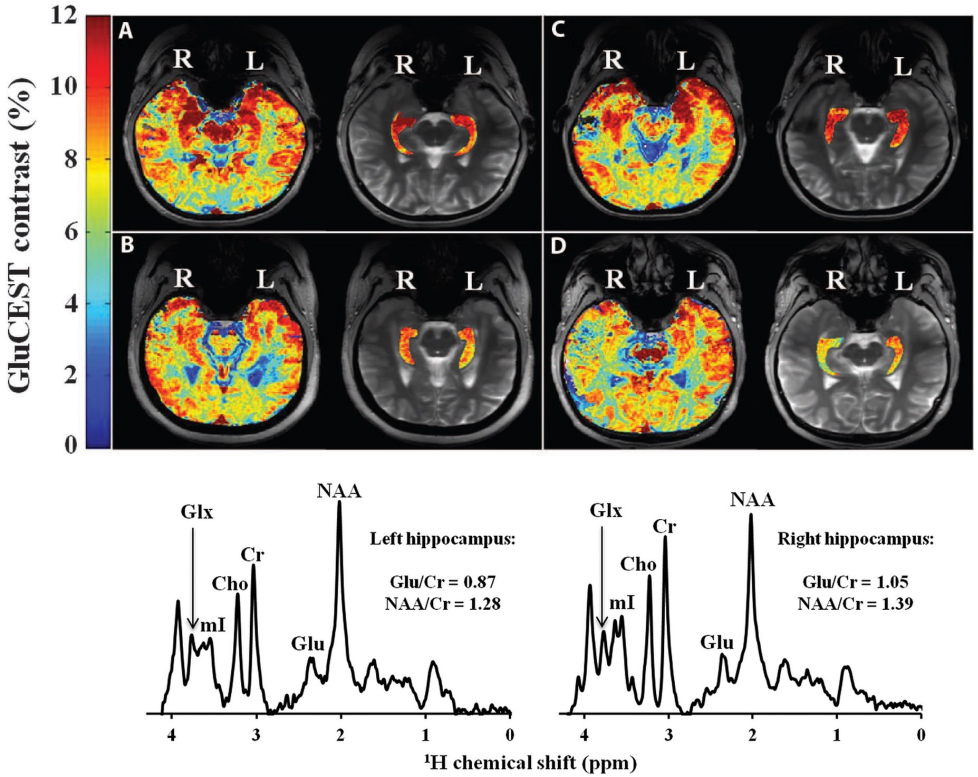
Endogenous Glutamate CEST



MRS confirmation for Right temporal lobe epilepsy (TLE)

Davis et al *Sci Trans Med* 2015

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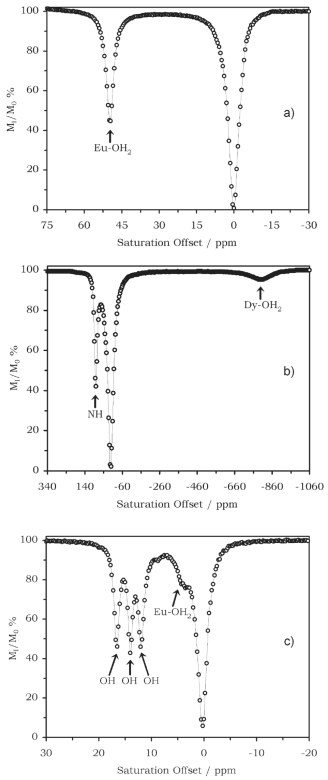
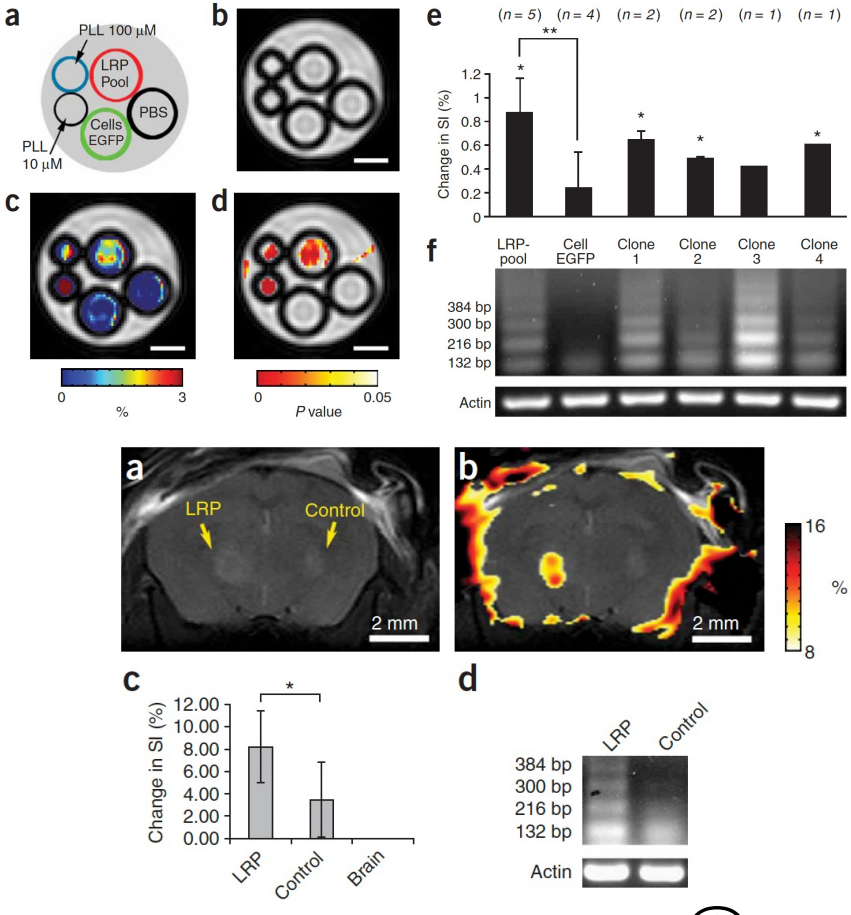
PARACEST





Woods et al *Chem Soc Rev* 2006
Gilad et al. *Nat Biotech* 2007

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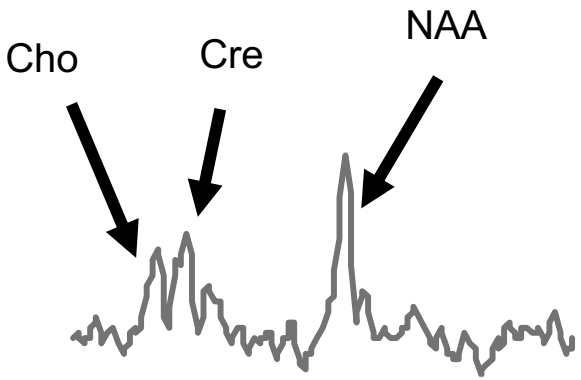
   - Hyperpolarization

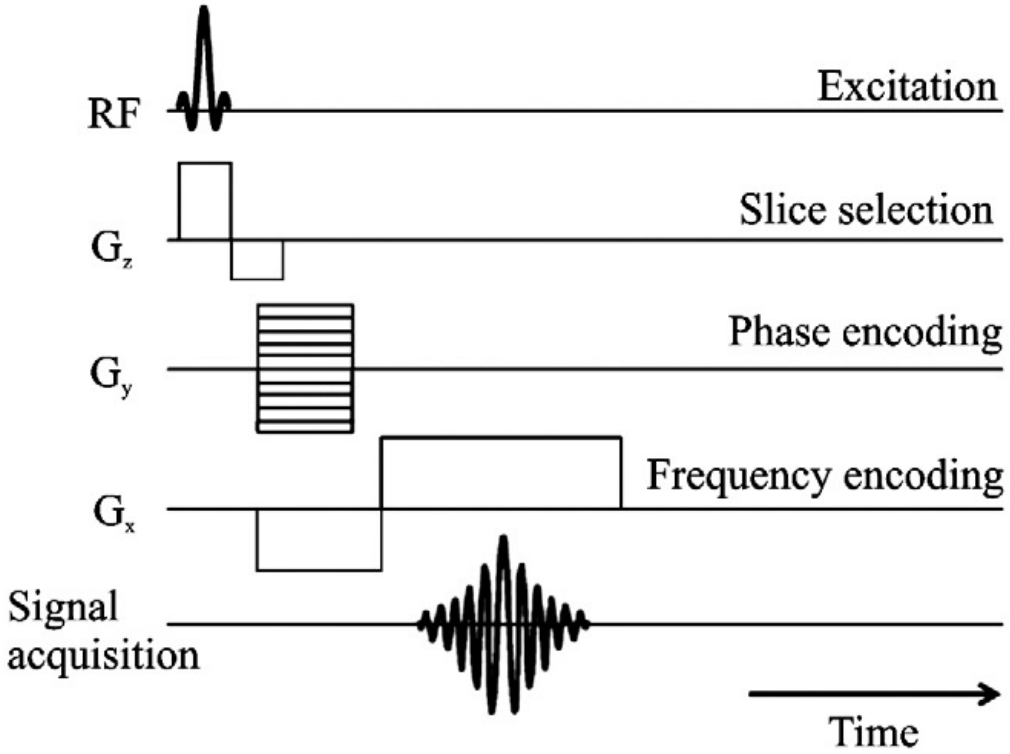
MR Spectroscopic Imaging (MRSI)

- What about detecting metabolites as opposed to structure?
  - MRI - mainly water 55 M, MRSI – metabolites ~5mM
    → Signal ~ 10,000x smaller!
  - End up w/ lower spatial resolution, longer scans but adds a new dimension



Healthy Brain

How do you localize MRS?



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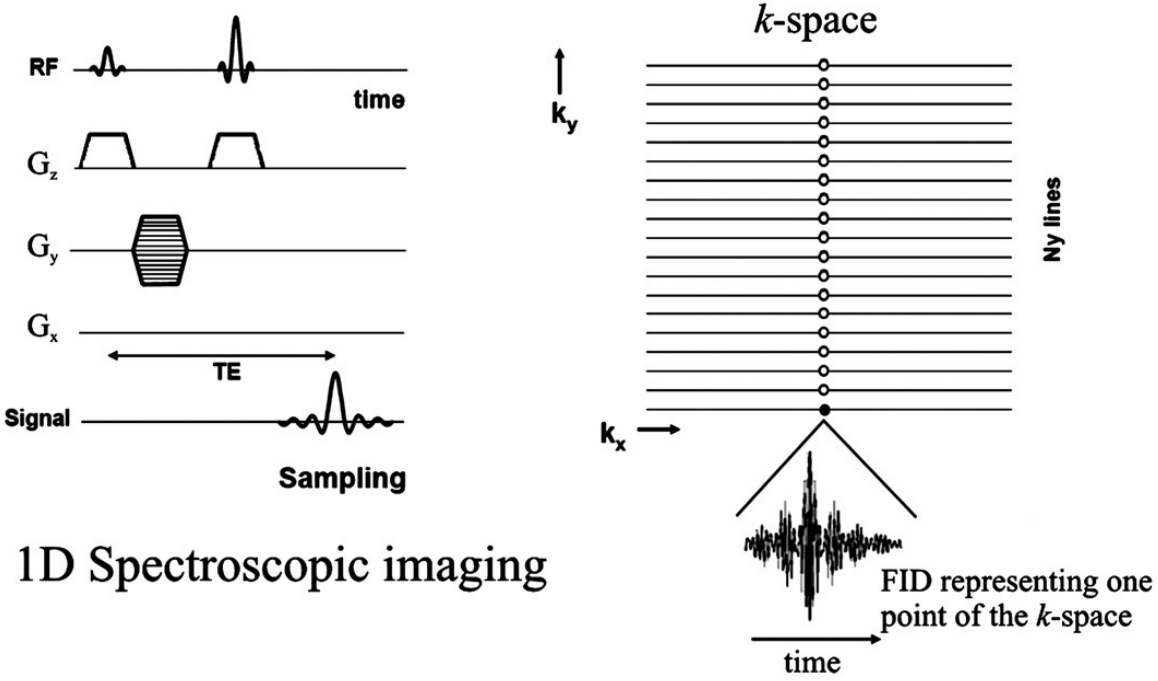
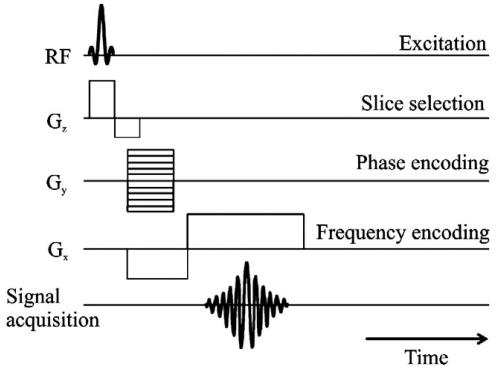
How do you localize MRS?



1D Spectroscopic imaging



Skoch et al. *Euro J of Rad* 2008

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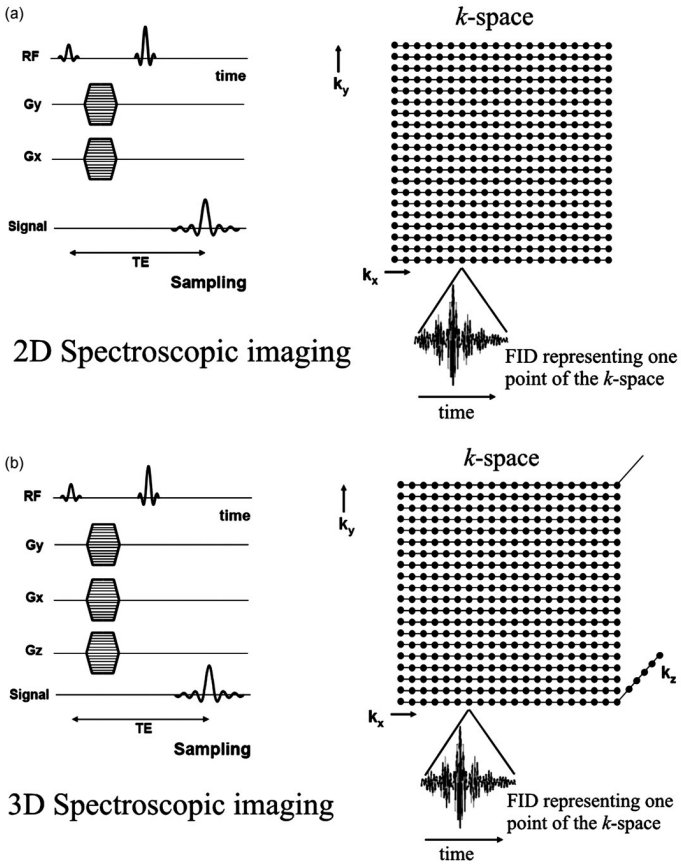
How do you localize MRS?



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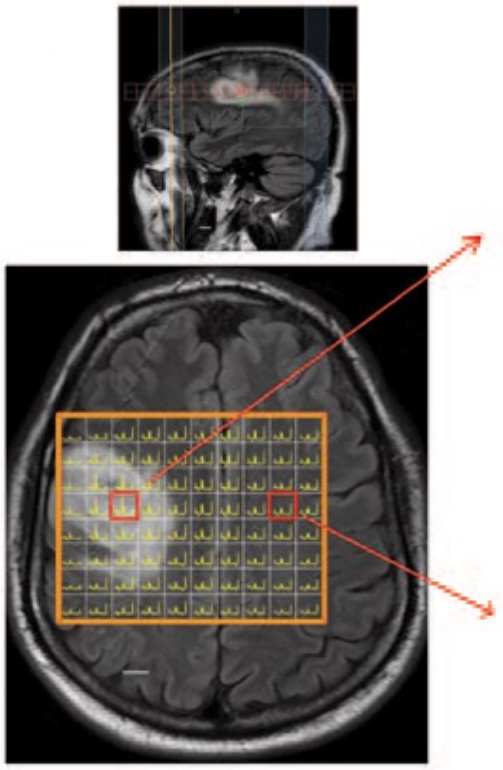
Steady state pool sizes ^{1}H MRSI



Choi et al *Nature Med* 2012

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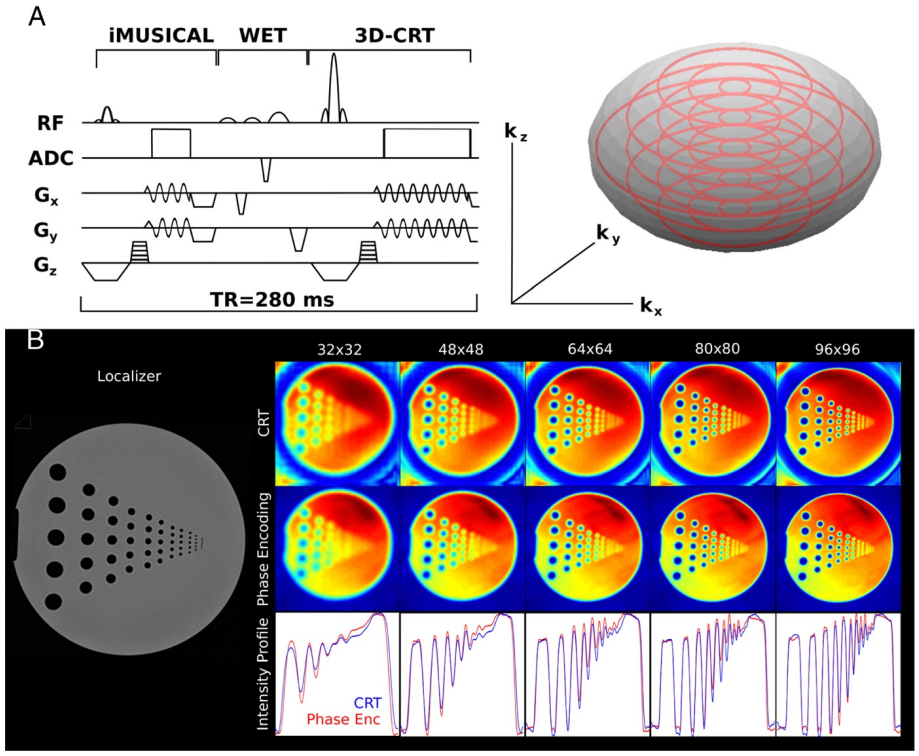
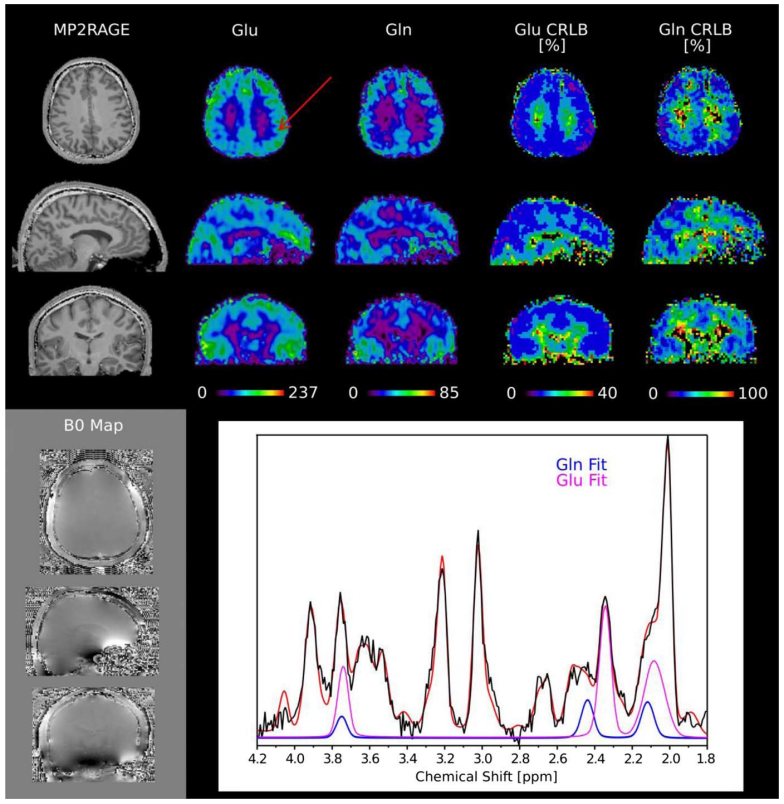
High-res 3D MRSI





Hingerl et al *Invest Rad* 2020

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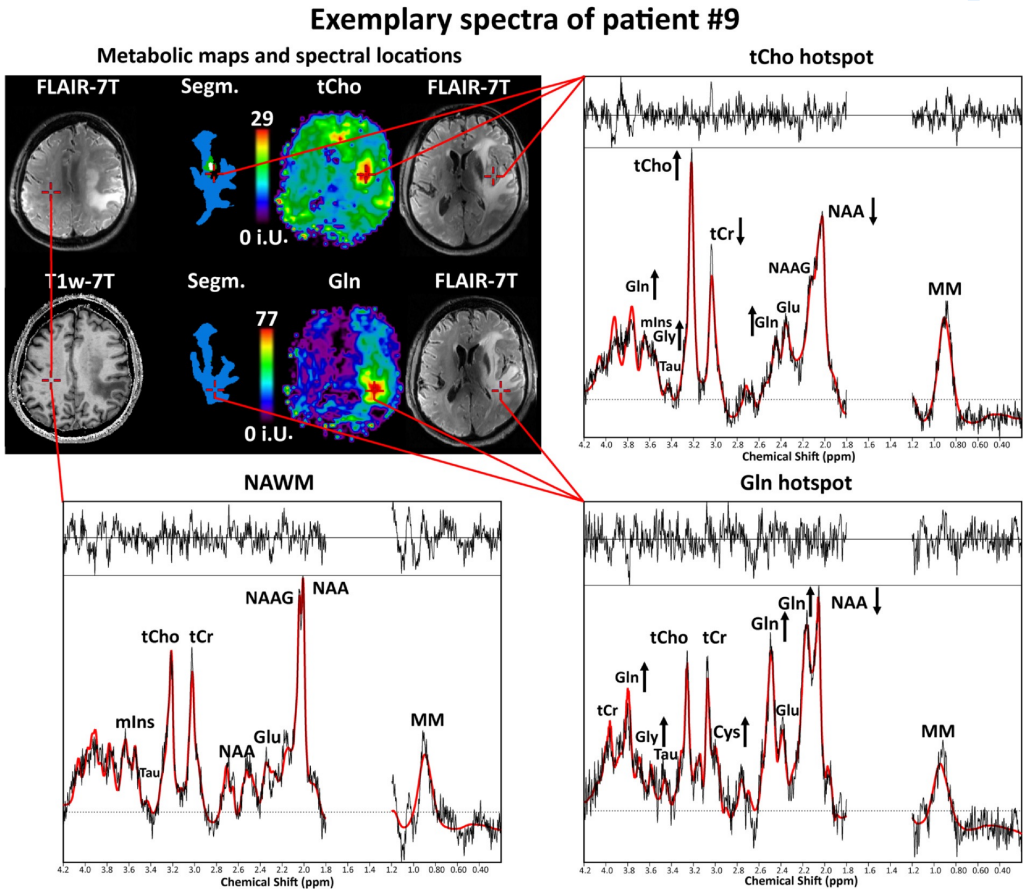
High-res 3D MRSI – brain tumor patient



Hangel et al *NeuroImage* 2020

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Contrast Mechanisms for MRI

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d. Multi-nuclear MRS/MRI
   - Isotope tracing
   - Hyperpolarization

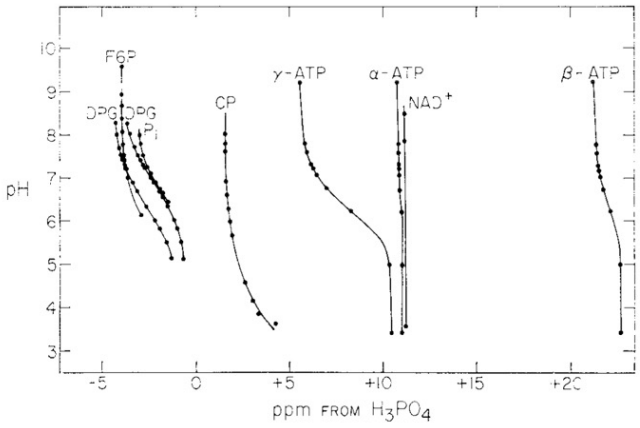
NMR/MRI active nuclei

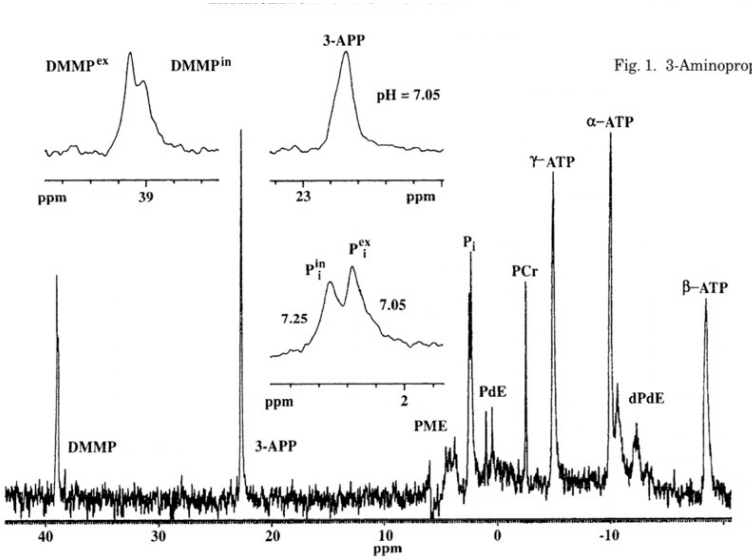
Nuclei	m (spin)	Natural abundance (%)	γ (rel to ^{1}H)	$\Delta\delta$ (ppm)	T_1 range	Example biomedical application
^{1}H	1/2	99.98	1	13	0.1–2 s	Total body MRI and MRSI
^{2}H	1	0.02	0.1535	13	<1 s	Metabolic tracer injection using MRSI
^{13}C	1/2	1.11	0.2515	200	0.1–100 s	Metabolic tracer injection using MRSI
^{15}N	1/2	0.37	0.1013	900	0.1–400 s	Metabolic tracer injection using MRSI
^{17}O	5/2	0.04	0.1355	1160	5–50 ms	Oxidative metabolism using MRSI
^{19}F	1/2	100.00	0.9409	700	0.1–1 s	Tracer injection of therapies using MRSI
^{23}Na	3/2	100.00	0.2645	72	10–50 ms	Neurodegeneration and cardiac using MRI
^{31}P	1/2	100.00	0.4048	430	0.05–2 s	Bioenergetics and pH using MRSI

MRI – magnetic resonance imaging, MRSI – magnetic resonance spectroscopic imaging, m – quantum spin number, γ – gyromagnetic ratio, $\Delta\delta$ – chemical shift.

pH – ^{31}P Spectroscopy

Intracellular pH (Moon and Richards 1973) and extracellular pH (Myer et al 1985) using chemical shift





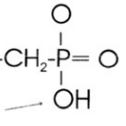


Fig. 1. 3-Aminopropylphosphonate (3-APP).

Gilles et al *MRM* 1994

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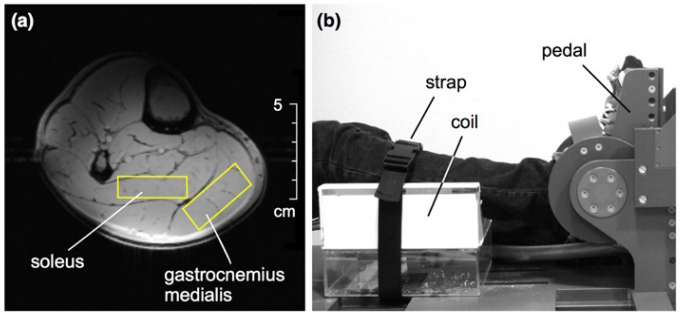
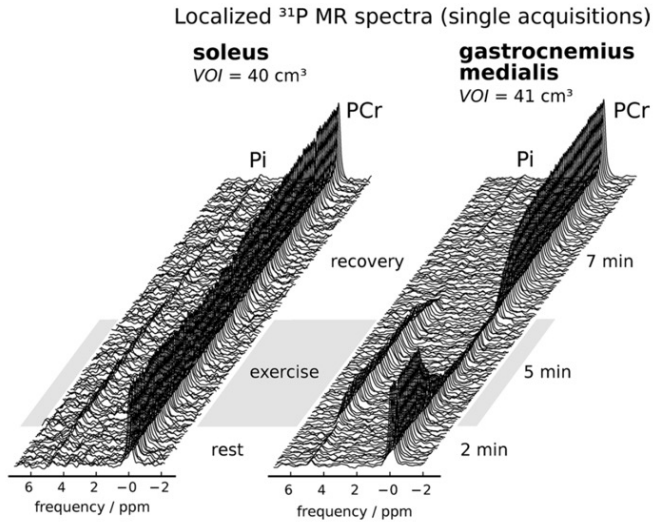
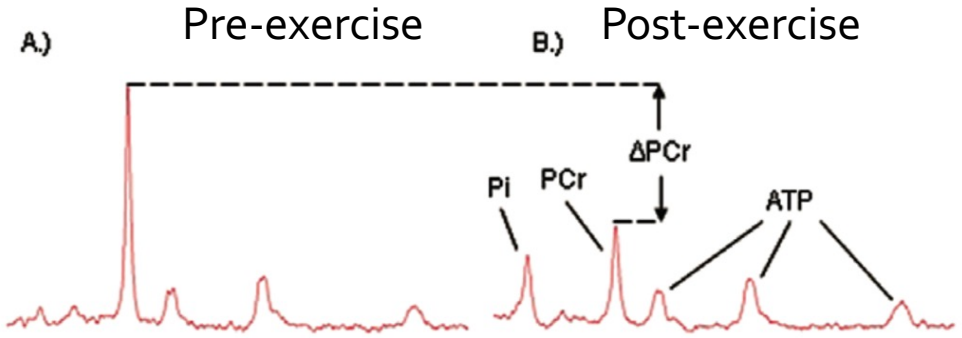
Bioenergetics – ^{31}P MR Spectroscopy







Fiedler et al 2015

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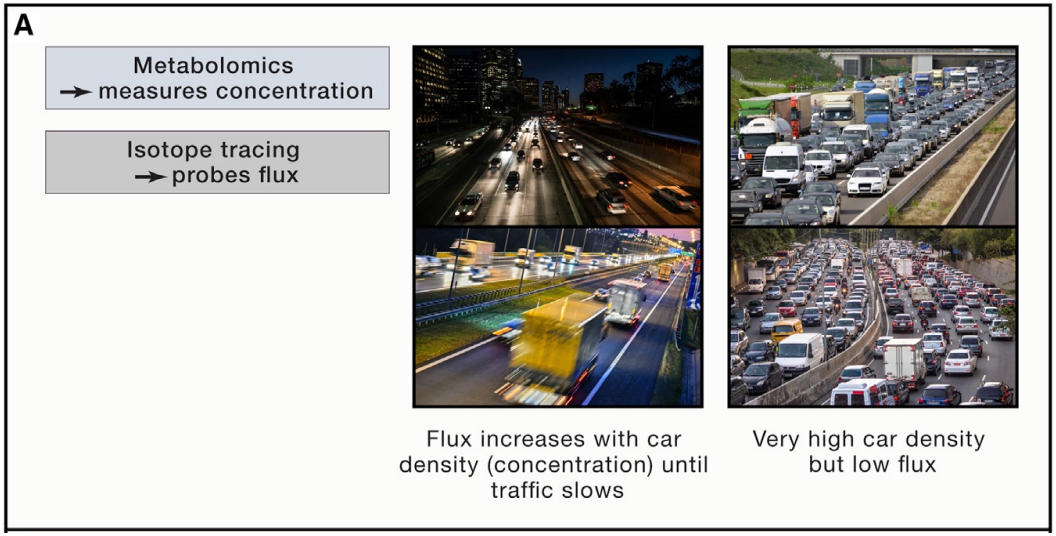
Isotope Tracing?

First isotope tracing studies

- Radioactive isotopes were first used in biological systems in the 1920s by George de Hevesy, who won the Nobel Prize in Chemistry in 1943 - Traced using ^{212}Pb into *Vicia faba* (horse-bean)[1]
- Later the first stable isotopes were used for tracing, including ^{2}H tracing by Schoenheimer[2]
- This lead to isolated organs, particularly the heart, and to translate isotopic labeling data into relative or absolute metabolic fluxes[3]
- Used in humans since 1934, when Hevesy and Hofer used deuterium oxide to estimate the size of the whole-body water pool and rate of water elimination[4]

[1]Hevesy Biochem J 1923
[2]Schoenheimer et al. *Science* 1935, *J Biochem* 1936
[3]Chance et al. 1983, Malloy et al. 1987, Russel et al 1997
[4]Hevesy and Hofer *Nature* 1934

Pool size versus Flux



Jang et al. *Cell* 2018

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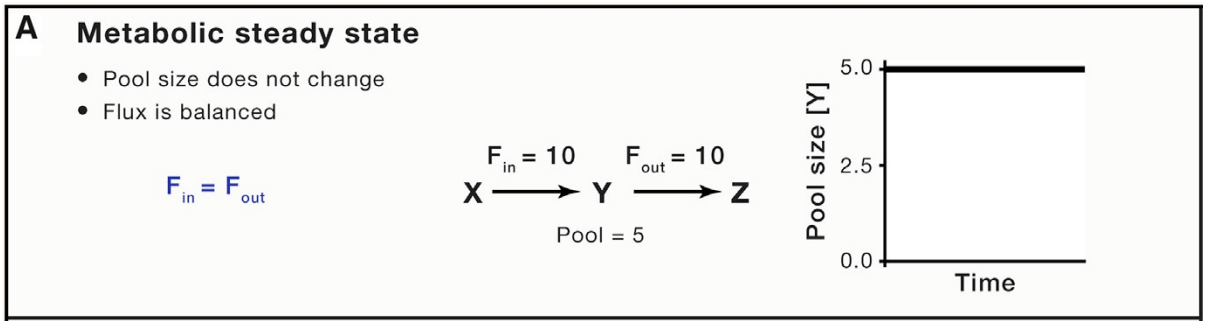

Jang et al. *Cell* 2018

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Early MRS leveraged isotope tracing and NMR

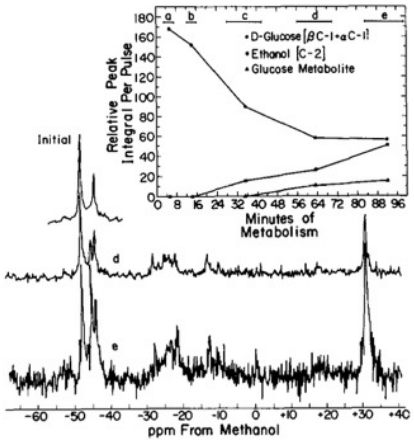

Fig. 3. Metabolism of [1-^{13}C] glucose. a) 500 pulses, 3–7 m after initiation of metabolism; b) 500 pulses, 12–16 min; c) 1500 pulses, 28–42 min; d) 1500 pulses, 56–70 min; e) 15(pulses, 83–99 min. The spectra obtained during the initial time periods show only the signals corresponding to the sub strate, [1-^{13}C] glucose. The C-1 region is illustrated. Spectra generated during the time periods (d) and (e) are illustrated for the region between 40 ppm and –65 ppm. Signals in the region between –12 ppm and –28 ppm are generated from the natural abundance ^{13}C in glucose carbon atoms other thai C-1.

Eakin et al. *FEBS Letters* 1972

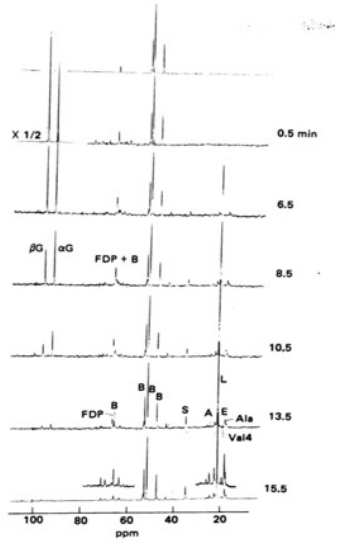

FIG. 1. The 90.52-MHz ^{13}C NMR spectra of anaerobic *E. coli* cells at 20°C as a function of time from ^{13}C-1 glucose addition. The cells were suspended in 10 mM Na_2HPO_4 10 mM KH_2PO_4 200 mM 1,4-piperazinediethanesulfonic acid (Pipes)/50 mM 2-(*N*-morpholino)ethanesulfonic acid (Mes), pH 7.5 (adjusted with NaOH), at a density of ~5 × 10^{11} cells per ml. [*1*-^{13}C]Glucose was added to a final concentration of 50 mM in the NMR sample, at time 0. Top spectrum (1600 scans) shows the natural-abundance ^{13}C peaks (assigned to the Pipes and Mes buffers) detectable in the suspension prior to glucose addition. All subsequent spectra, except the last one, represent 200 free induction decays accumulated in 1 min. The last spectrum consists of 1600 scans. The time given for each spectrum indicates the middle of the accumulation period, referred to glucose addition. FDP, Fru-1,6-P_2; see text for other abbreviations.

Ugurbil et al. *PNAS* 1978

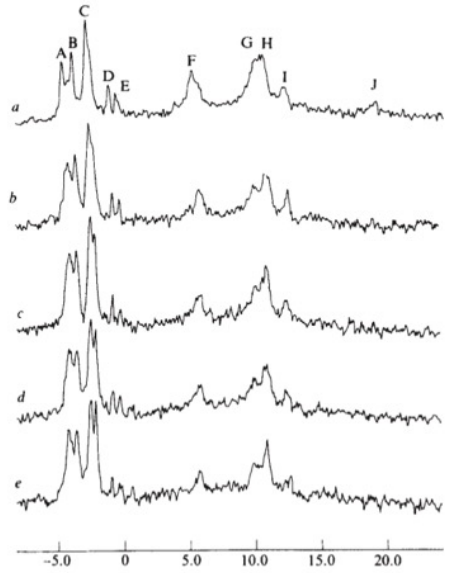

Fig. 1 NMR spectra at 145.7 MHz of ^{31}P nuclei in isolated rat liver cells. of 1,000 pulses of 60° free induction decays of 0.34s duration obtained with fasted for 24 h were used for the isolation of the liver cells. The cells were prep

Cohen et al. *Nature* 1978

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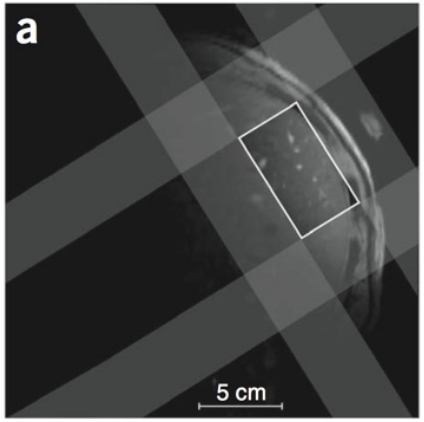
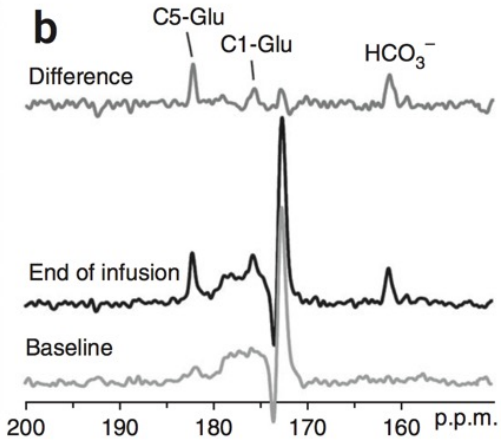
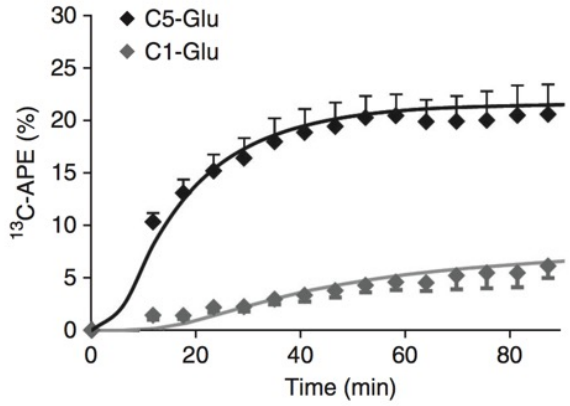
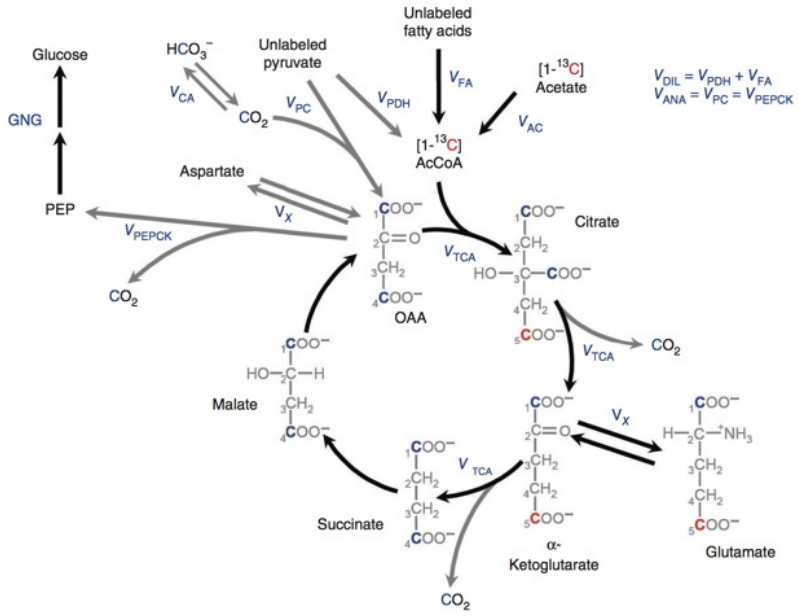
^{13}C-acetate MR Spectroscopy









Befroy et al *Nat Med* 2014

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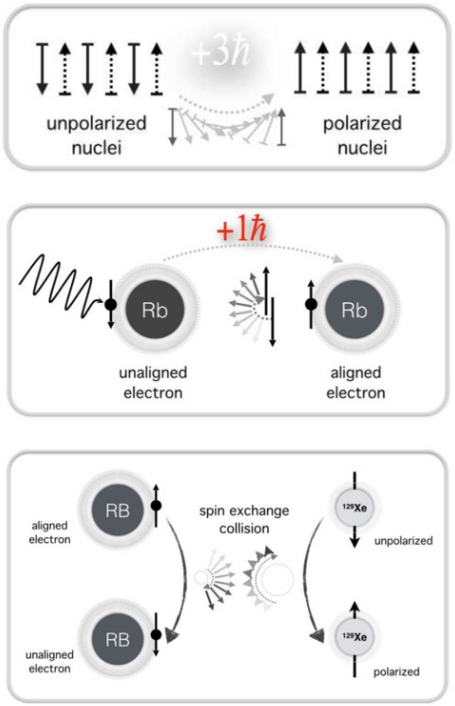
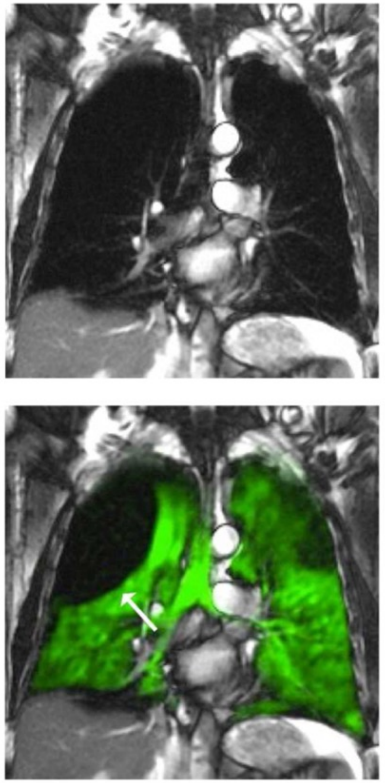
Hyperpolarized MRI

- Whats wrong with MRI? – Signal is weak!
- Multiple Methods to increase it for high SNR MRI:
  - **Optical pumping** (^{3}He, ^{129}Xe)
  - **Chemical reduction using Parahydrogen** (PHIP, SABRE)
  - **Dynamic nuclear polarization** (dissolution DNP, solid state DNP)

HP MRI of gases

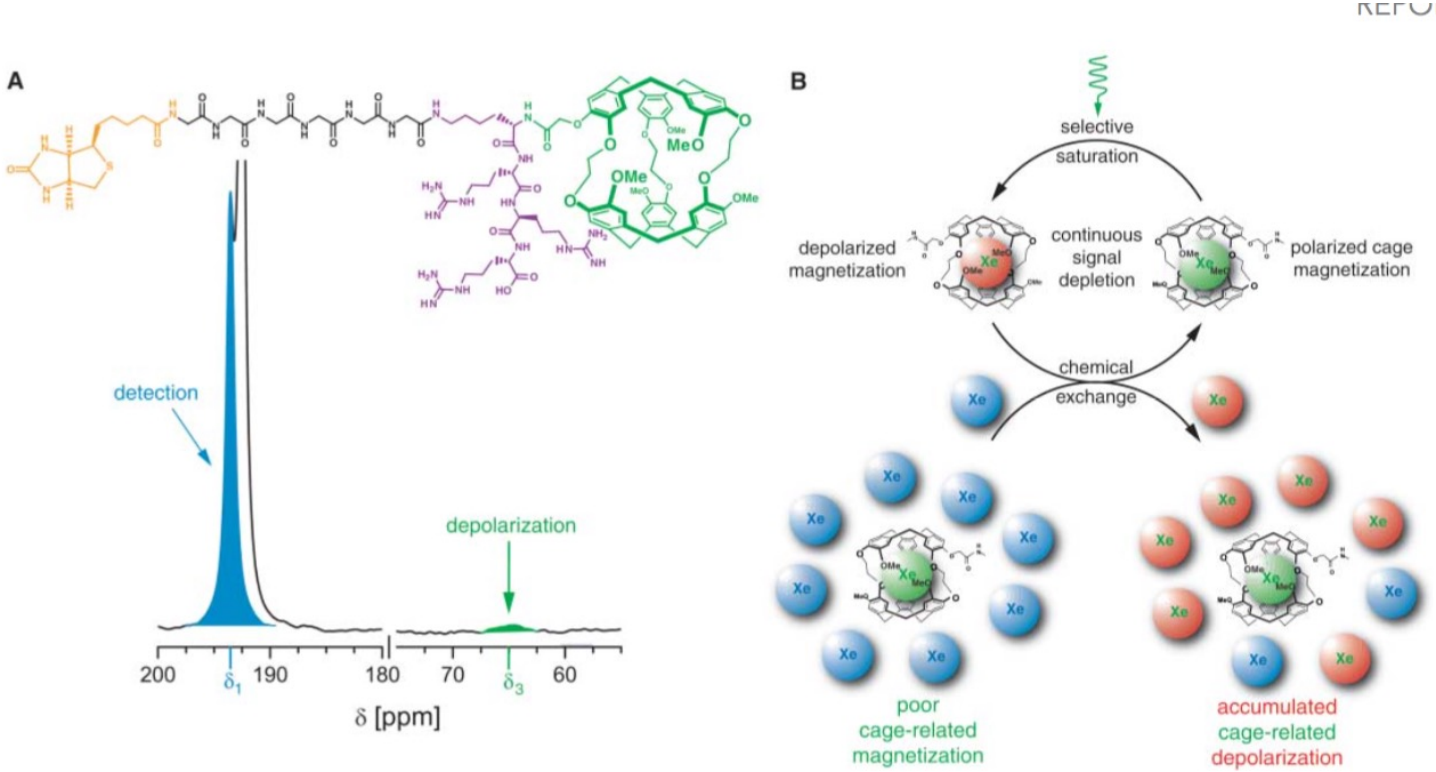




Roos et al. *Magn Reson Imaging Clin N Am* 2015

Memorial Sloan Kettering Cancer Center

HP MRI of gases (HyperCEST)



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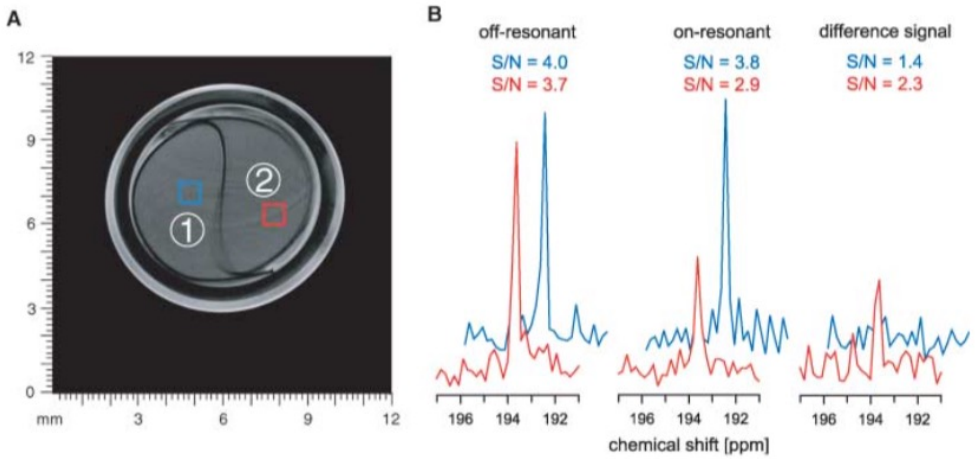
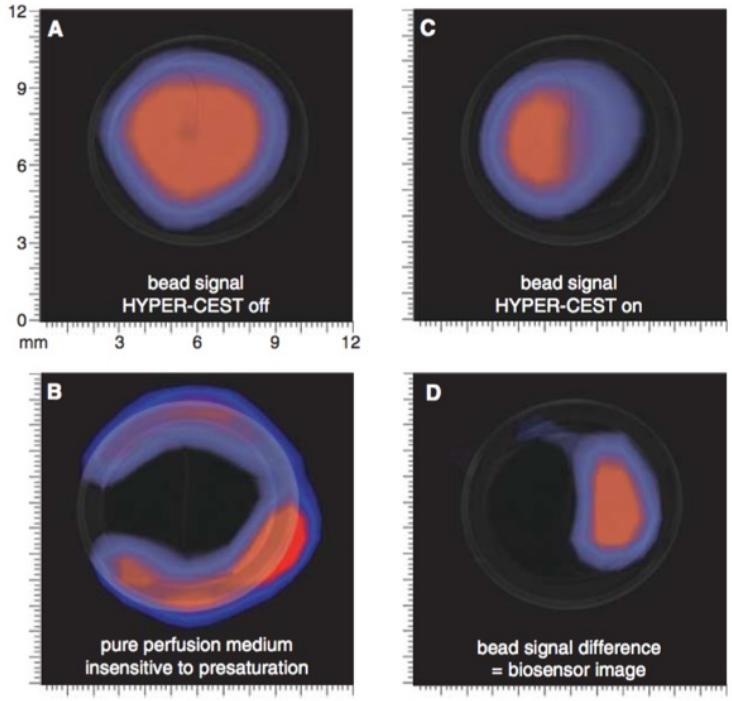
Schroeder et al. *Science* 2006

HP MRI of gases (HyperCEST)





Biosensor is only in volume 2

Schroeder et al. *Science* 2006

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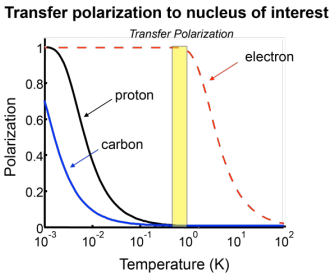
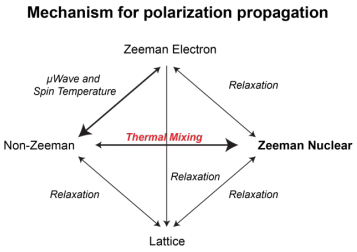
How do we overcome the limited sensitivity of magnetic resonance for isotope tracing in liquids?

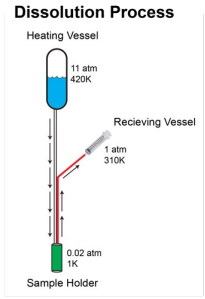
Dynamic Nuclear Polarization



Overhauser 1952



Abragam and Goldman 1955
Borghini 1968



Ardenkjaer-Larsen, Golman et al. 2003

Parahydrogen Induced Polarization

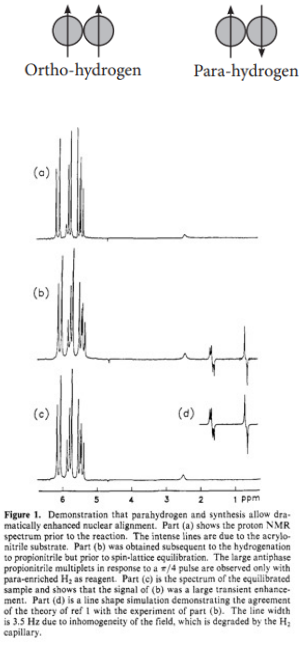


Figure 1. Demonstration that parahydrogen and synthesis allow dramatically enhanced nuclear alignment. Part (a) shows the proton NMR spectrum prior to the reaction. The intense lines are due to the acrylonitrile substrate. Part (b) was obtained subsequent to the hydrogenation to propionitrile but prior to spin-lattice equilibration. The large antiphase propionitrile multiplets in response to a $\pi/4$ pulse are observed only with para-enriched H_2 as reagent. Part (c) is the spectrum of the equilibrated sample and shows that the signal of (b) was a large transient enhancement. Part (d) is a line shape simulation demonstrating the agreement of the theory of ref 1 with the experiment of part (b). The line width is 3.5 Hz due to inhomogeneity of the field, which is degraded by the H_2 capillary.

Bowers and Weitekamp 1986,1987

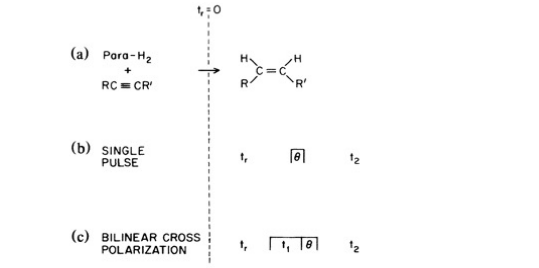
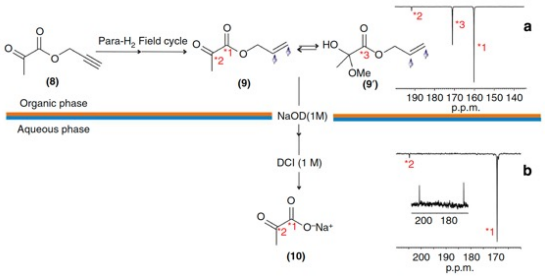


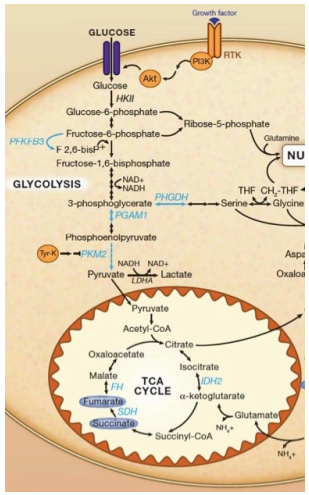
FIG. 1. Sequence of events for conversion of the spin order of parahydrogen to magnetization. The origin of time is the addition of molecular hydrogen to a suitable acceptor, as shown, for example, in (a). In (b) a brief mixing pulse of nutation angle θ at the proton Larmor frequency is delivered at a time t_r after the reaction to elicit development of transverse magnetization during t_2. In (c) the mixing pulse is preceded by a cross-polarization sequence of length t_1 to share the spin order with weakly coupled resonances.



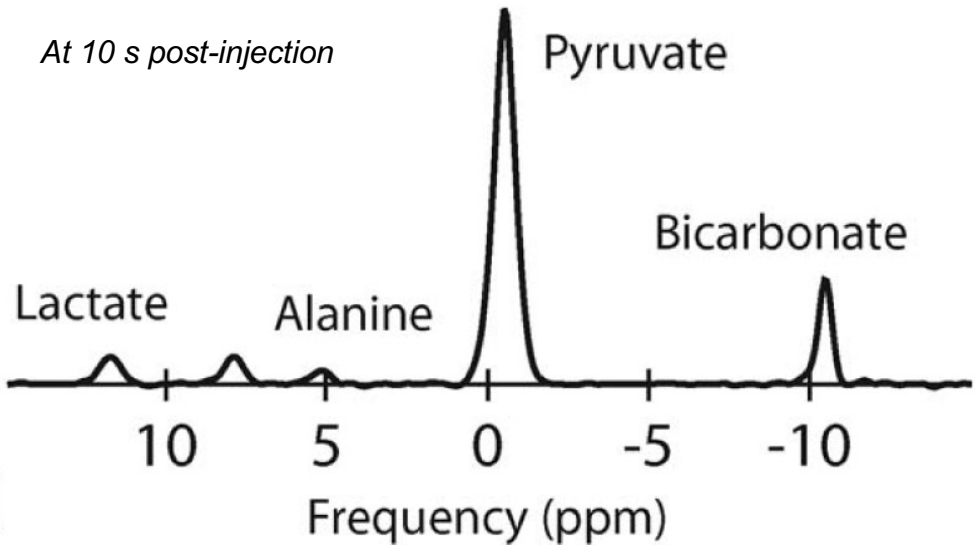
Reineri, Aime et al. 2015

Hyperpolarized ^{13}C Magnetic Resonance

- HP MRI provides a mechanism to overcome the sensitivity problem of MR by aligning spins outside of the magnet
- Follow the conversion of HP pyruvate through many pathways in seconds!
  - Reduction to HP Lactate
  - Transamination to HP Alanine
  - Decarboxylation to HP carbon dioxide and later bicarbonate (pH)



Keshari and Wilson *Chem Soc Rev* 2014



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Many probes and methods can be developed to interrogate metabolism

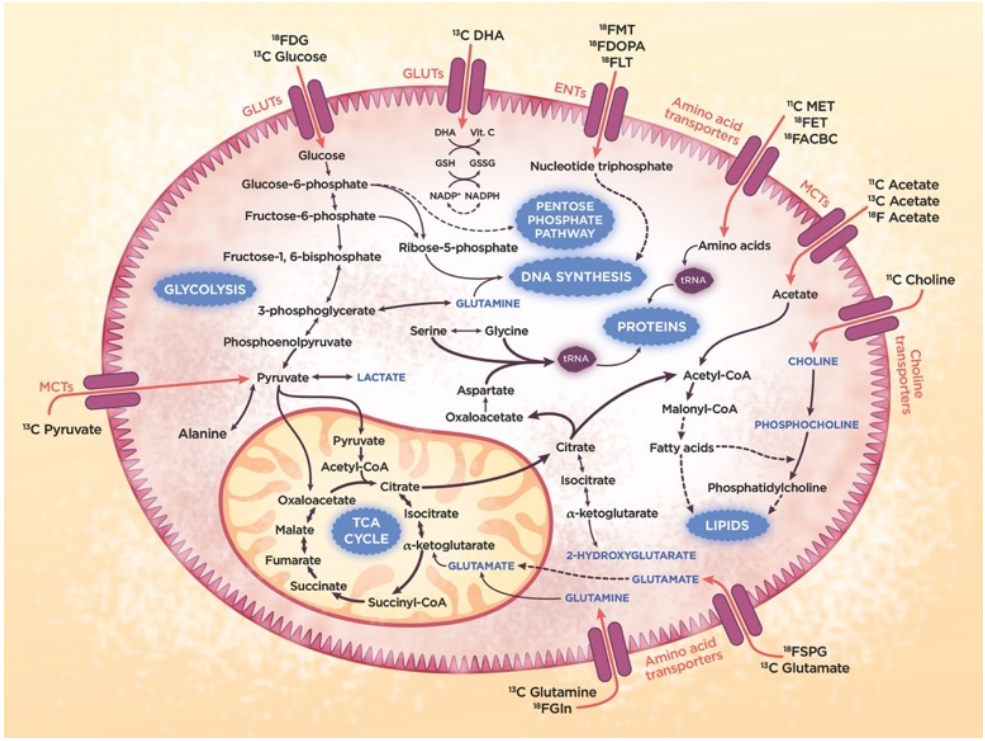

Table 3 Chemical structures of HP probes

Chemical structure	Index	HP agent	MW (Da)	Apparent T_1 (s)	Application	Ref.
carboxylic acid	1	^{13}C sodium formate	69	NR	C	222
	2	[1-^{13}C] glycine	76	50 (9.4 T)	C	78
	3	[1-^{13}C] sodium acetate	83	40 (9.4 T); 46 (14.1 T)	A, C	121, 223 and 224
	4	^{13}C-sodium bicarbonate	85	49 (11.7 T); 50 (3 T); 34 (3 T)	A, C	83 and 177
	5	[1-^{13}C, ^{2}H$_3$] sodium acetate	86	50 (14.1 T)	C	121
	6	[1-^{13}C] pyruvic acid	89	67 (3 T); 48 (11.7 T); 44 (14.1 T)	A, B, C	83 and 121
	6	C_1 of [1,2-^{13}C] pyruvic acid	90	56 (3 T)	A, C	177
	7	[1-^{13}C] alanine	90	42 (3 T); 29 (9.4 T)	A, C	78 and 225
	8	[1-^{13}C] sodium proprionate	97	NR	A, C	224
	9	[1-^{13}C] serine	106	23 (9.4 T)	C	78
	6	[1-^{13}C] sodium pyruvate	111	NR	C	80
	10	[1-^{13}C] sodium butyrate	111	43 (14.1 T)	C	226
	11	[1-^{13}C] sodium lactate	113	45, 50.6 (3 T); 32, 33.4 (14.1 T)	A, C	52 and 227
	12	[1,4-^{13}C$_2$] fumaric acid	118	24 (9.4 T); 29 (11.7 T)	A, B, C	83 and 196
	13	C_1 of benzoic acid	122	35 (11.7 T)	C	54
	14	[1-^{13}C] cysteine	122	30 (9.4 T)	C	78
	13	[1-^{13}C] benzoic acid	123	35 (11.7 T)	C	54
	15	[1-^{13}C] ketoisocaproic acid	131	55 (9.4 T)	A, C	169
	16	[1-^{13}C] leucine	132	24 (9.4 T)	C	78
	17	[1-^{13}C] aspartic acid	134	29 (9.4 T)	C	78
	18	C_1 of salicylic acid	138	NR	C	38
	19	[1-^{13}C] glutamine	147	25 (9.4 T)	C	78
	20	[1-^{13}C] lysine	147	26 (9.4 T)	C	78
	21	[1-^{13}C] glutamate	148	26 (9.4 T); 34 (9.4 T) FG	A, C	78
	22	[1-^{13}C] methionine	150	17 (9.4 T)	C	78
	23	[1-^{13}C] *N*-acetyl-methionine	192	28 (3 T)	A, B, C	188
	4	^{13}C-cesium bicarbonate	195	NR	A, C	37
	24	2-Napthaleneacetic acid-6-methoxy-α-methyl (NA)	230	15 (11.7 T)	C	54
ketone	25	[2,3-^{13}C$_2$] diacetyl	88	30 (7 T)	C	39
	6	[2-^{13}C] pyruvic acid	89	NR	B, C	84
	6	C2 of [1,2-^{13}C$_2$] pyruvic acid	90	44 (3 T)	A, C	177
	26	[2-^{13}C] benzoylformic acid	151	24 (11.7 T); 19 (14.1 T)	C	35
ester	27	[1-^{13}C] ethyl pyruvate	117	45 (3 T)	A, C	87
	28	Ethyl-2-cyanoacrylate (NA)	125	NR	C	132
	29	[1,1'-^{13}C$_2$] diethyl oxalate	148	22 (8.4 T)	C	126
	30	[1-^{13}C] dehydroascorbic acid	175	56 (3 T); 21 (9.4 T); 21 (11.7 T)	A, B, C	85 and 86
	31	C_1 of ascorbic acid (NA)	176	NR	C	38
	31	[1-^{13}C] ascorbic acid	177	29 (3 T); 16 (9.4 T); 16 (11.7 T)	A, B, C	85 and 86
	32	Methyl fusarate (NA)	193	NR	C	132
	33	Cyclohexyl-isopropyl-1,2-^{13}C$_2$-oxalate-^{2}H$_{18}$	234	54 (4.7 T)	C	128
	34	Nα-benzoyl-L-arginine-ethyl ester	306	NR	C	228
anhydride	35	[1,1'-^{13}C$_2$] acetic anhydride	104	34 (11.7 T); 45,50 (14.1 T)	C	40
	36	[1,1'-^{13}C$_2$, ^{2}H$_6$] acetic anhydride	110	NR	C	121
	37	[1,1'-^{13}C$_2$] butyric anhydride	160	39,40 (14.1 T)	C	226
amide	38	^{13}C-urea	61	44 (11.7 T); 35 (14.1 T)	A, C	83
	39	Dimethyl acetamide (NA)	87	NR	C	85
	40	*N*-[Acetyl-1-^{13}C] glycine	118	15 (11.7 T); 17 (14.1 T)	C	40
	41	*N*-[Acetyl-1-^{13}C] alanine	132	15 (11.7 T)	C	40
	19	[5-^{13}C] glutamine	145	16 (9.4 T)	B, C	118
	42	*N*-[Acetyl-1-^{13}C] serine	148	11 (11.7 T)	C	40
	43	[5-^{13}C, 4-^{2}H$_2$] glutamine	149	33 (9.4 T)	B, C	40

Tee and Keshari *Cancer J* 2015
Keshari and Wilson *Chem Soc Rev* 2014

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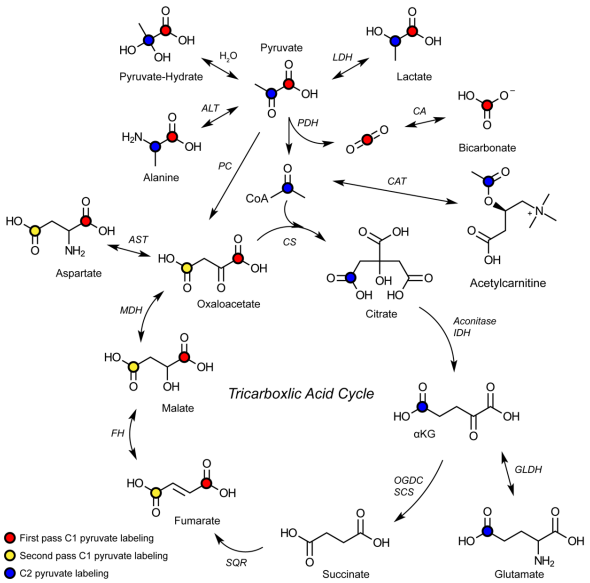
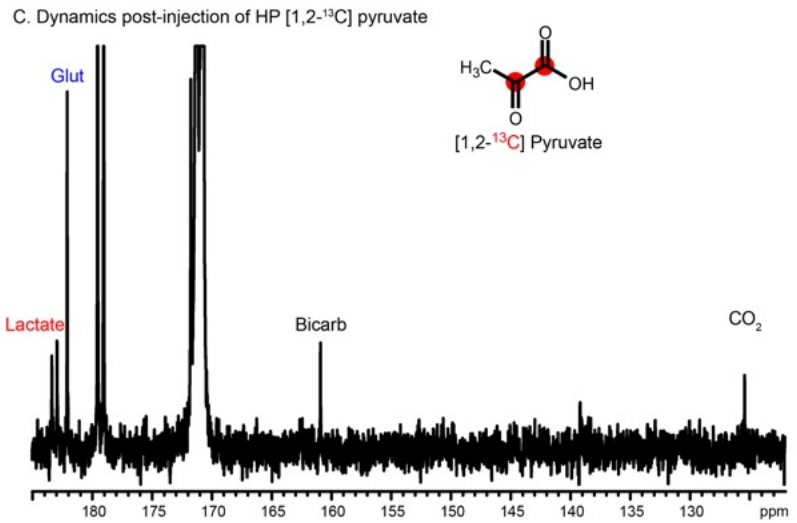
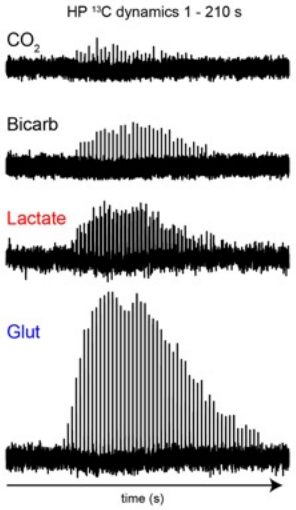
Hyperpolarized ^{13}C NMR/MRI







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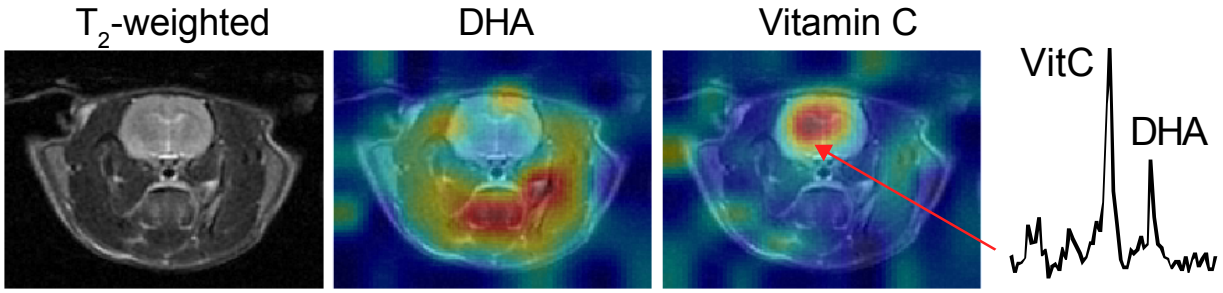
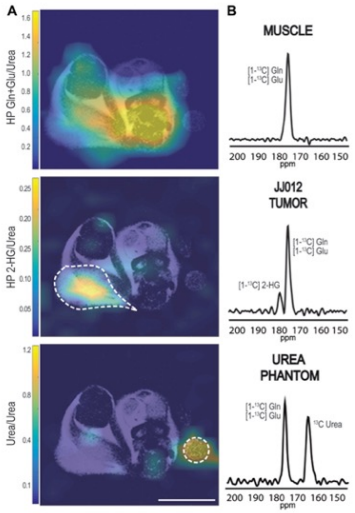
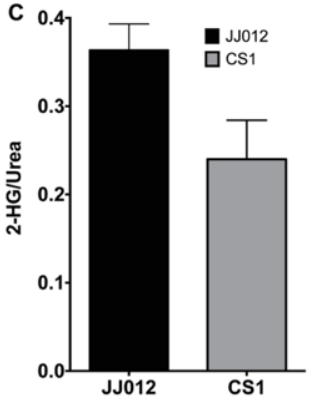
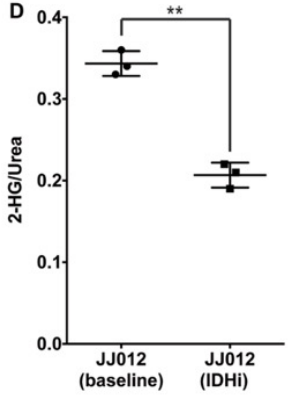
Hyperpolarized ^{13}C MRI









Keshari et al *PNAS* 2011
Salamanaca-Cardona et al. *Cell Metabolism* 2017

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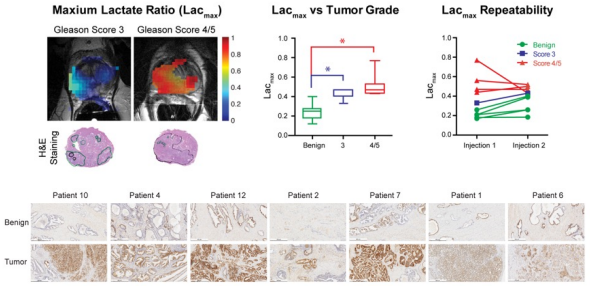
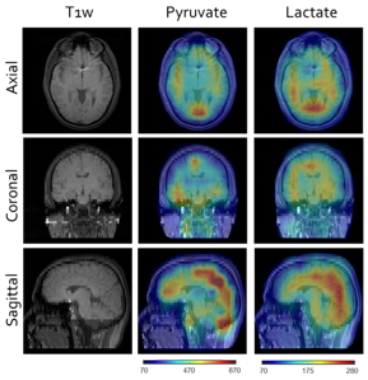
HP MRI in humans facilitates imaging isotope tracing

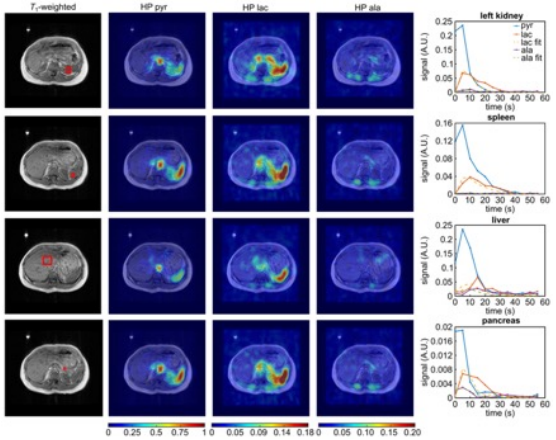
It turns out tumors make lactate…

and it might be rate limited by transport…

so do many organs (heart, brain etc)…







Miloushev et al. *Cancer Res* 2018
Granlund et al. *Cell Metabolism* 2020
Deh et al. *MRM* 2024
Zhang et al. *JMRI* 2024

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Lets take a break

Paper discussion

2 Discussion Papers:

- Day, S. E. *et al.* Detecting tumor response to treatment using hyperpolarized 13C magnetic resonance imaging and spectroscopy. *Nat Med* **13,** 1382–1387 (2007).
- Choi, C. *et al.* 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. *Nat Med* **18,** 624–629 (2012).