X-Nuclei Imaging

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X-Nuclei

Spin > 0

imaging of native nuclei

tracking of injected cells/tracers

stable

- As opposed to positron emission tomography (PET)

$^{3}H^{i}$	—
^{3}He	1.37×10^{-4}
^{13}C	1.07
^{15}N	0.368
^{19}F	100
^{29}Si	4.6832
^{31}P	100
^{57}Fe	2.119
^{77}Se	7.63
^{89}Y	100
^{103}Rh	100
(^{107}Ag)	51.839
^{109}Ag	48.161
(^{111}Cd)	12.80
$^{113}Cd^{q}$	12.22
(^{115}Sn)	0.34
(^{117}Sn)	7.68
^{119}Sn	8.59
(^{123}Te)	0.89
^{125}Te	7.07
^{129}Xe	26.44
^{183}W	14.31
^{187}Os	1.96
^{195}Pt	33.832
^{199}Hg	16.87
(^{203}Tl)	29.524
^{205}Tl	70.476
^{207}Pb	22.1

$^{2}H^{j}$	1
^{6}Li	1
^{7}Li	3/2
^{9}Be	3/2
^{10}B	3
^{11}B	3/2
$^{14}N^{j}$	1
^{17}O	5/2
^{21}Ne	3/2
^{23}Na	3/2
^{25}Mg	5/2
^{27}Al	5/2
^{33}S	3/2
^{35}Cl	3/2
^{37}Cl	3/2
^{39}K	3/2
(^{40}K)	4
(^{41}K)	3/2
^{43}Ca	7/2
^{45}Sc	7/2
^{47}Ti	5/2
^{49}Ti	7/2
$(^{50}V)^{q}$	6
^{51}V	7/2
^{53}Cr	3/2
^{55}Mn	5/2
^{59}Co	7/2
^{61}Ni	3/2
^{63}Cu	3/2
^{65}Cu	3/2
^{67}Zn	5/2
(^{69}Ga)	3/2
^{71}Ga	3/2
^{73}Ge	9/2

^{75}As	3/2
(^{79}Br)	3/2
^{81}Br	3/2
^{83}Kr	9/2
(^{85}Rb)	5/2
$^{87}Rb^{q}$	3/2
^{87}Sr	9/2
^{91}Zr	5/2
^{93}Nb	9/2
^{95}Mo	5/2
(^{97}Mo)	5/2
$^{99}Tc^{q}$	9/2
^{99}Ru	5/2
^{101}Ru	5/2
^{105}Pd	5/2
(^{113}In)	9/2
$^{115}In^{q}$	9/2
^{121}Sb	5/2
(^{123}Sb)	7/2
^{127}I	5/2
$^{131}Xe^{j}$	3/2
^{133}Cs	7/2
(^{135}Ba)	3/2
^{137}Ba	3/2
$^{138}La^{q}$	5
^{139}La	7/2
^{177}Hf	7/2
^{179}Hf	9/2
^{181}Ta	7/2
(^{185}Re)	5/2
$^{187}Re^{q}$	5/2
$^{189}Os^{j}$	3/2
(^{191}Ir)	3/2
^{193}Ir	3/2
^{197}Au	3/2
$^{201}Hg^{j}$	3/2
^{209}Bi	9/2

Harris R. et al., Solid State Nuclear Magnetic Resonance 22, 458–483 (2002)

Nuclei most relevant for *in vivo* MRI

Nucleus	I	$\gamma/2\pi$ [MHz/T]	NA [%]	Rel. Sensitivity
^{1}H	$1/2$	42.577	99.985	1.00
^{2}H	1	6.536	0.015	$1.45*10^{-6}$
^{3}He	$1/2$	-32.434	$1.4*10^{-4}$	$5.75*10^{-7}$
^{13}C	$1/2$	10.708	1.108	$1.76*10^{-4}$
^{17}O	$5/2$	-5.772	0.037	$1.08*10^{-5}$
^{19}F	$1/2$	40.087	100	0.834
^{23}Na	$3/2$	11.262	100	$9.27*10^{-2}$
^{31}P	$1/2$	17.235	100	$6.65*10^{-2}$
^{129}Xe	$1/2$	-11.777	26.44	$5.71*10^{-3}$

$$\gamma^3 I(I+1)\mathrm{NA}$$

Harris R. et al., Solid State Nuclear Magnetic Resonance 22, 458–483 (2002)

Oxygen

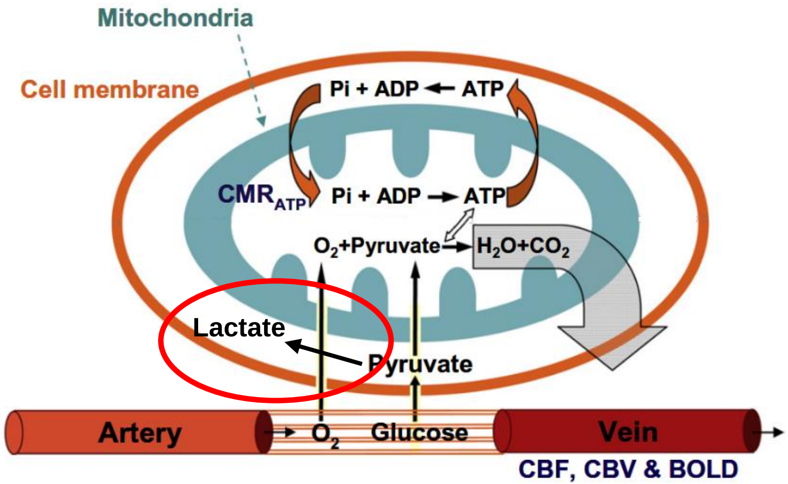
In the human body

Normal cells

- Low rate of glycolysis
- Oxidation of pyruvate in mitochondria

Tumor cells (Warburg effect)

- high rate of glycolysis
- anaeorbic gycolysis from pyruvate to lactate



Zhu et al, Magn Reson Sprectroscopy 59 (2011)

$^{17}O_2$ is paramagnetic -> MR-invisible

$H_2{}^{17}O$ is MR-visible -> only sensitive to metabolic products

Oxygen-17

properties

only MR-detectable oxygen isotope

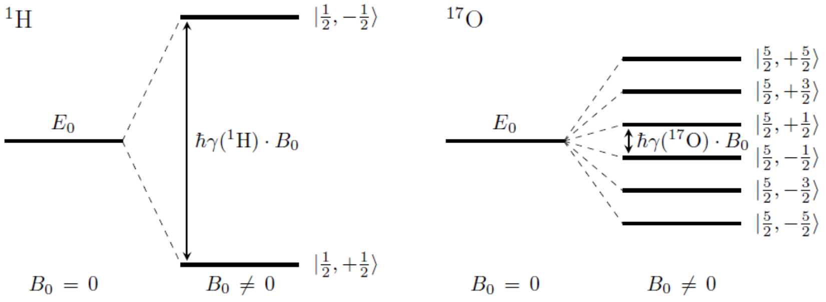
nuclear spin I: 5/2

- quadrupolar moment
- $T_1 \approx T_2 \approx 5\mathrm{ms}$ (independent of B_0)

gyromagnetic ratio $\frac{\gamma}{2\pi}$: -5.772 MHz/T

Natural abundance: 0.037%

Body mass 80kg (65% H_2O) -> ~19ml $H_2{}^{17}O$



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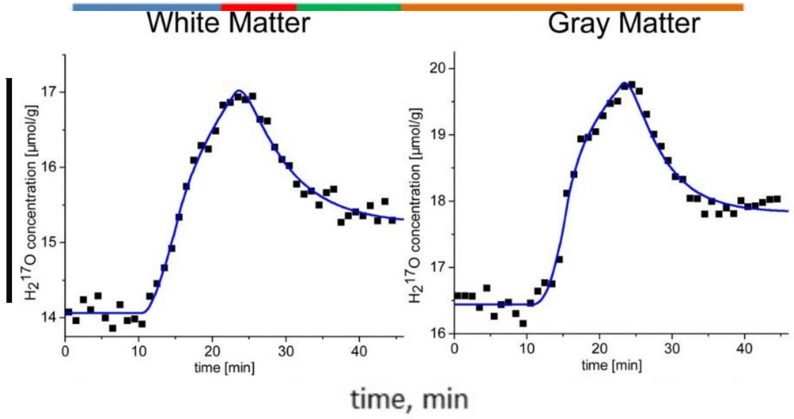
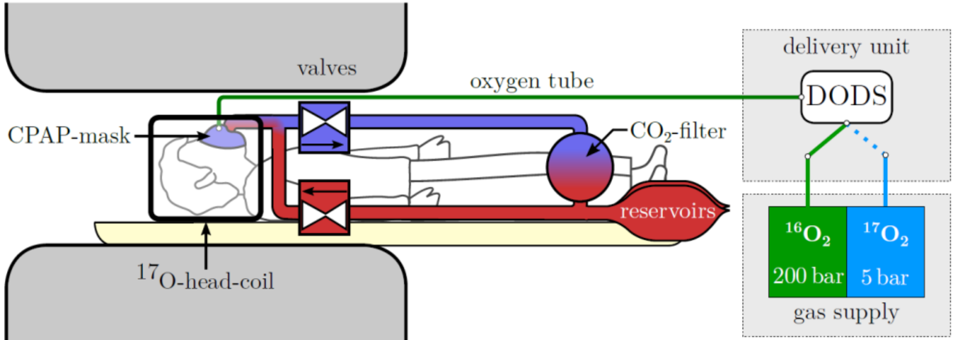
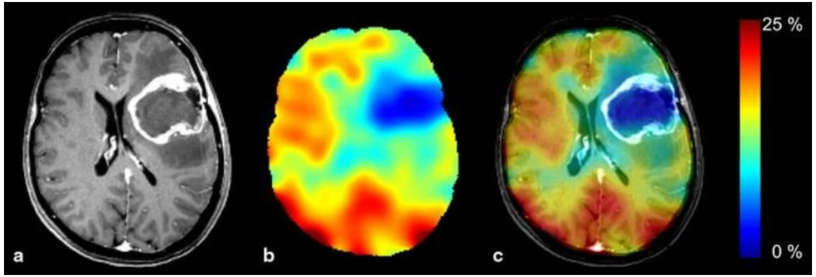
Measurement of $CMRO_2$

Cerebral Metabolic Rate of Oxygen





Yanis Taege



Hoffmann et al., MAGMA 27(6) 2014

Tissue	CMRO2 mmol/(g_{tissue}*min) 3 Tesla	CMRO2 mmol/(g_{tissue}*min) 7 Tesla	CMRO2 mmol/(g_{tissue}*min) ^{15}O PET
Gray matter (GM)	**1.65±0.15**	**1.65±0.29**	**1.59±0.23**
White matter (WM)	**1.35±0.08**	**0.83±0.14**	**0.65±0.10**

Kurzhunov D., et al., Magn Reson Med, 78(3), 2017

Fluor

non-essential nutrient[1]

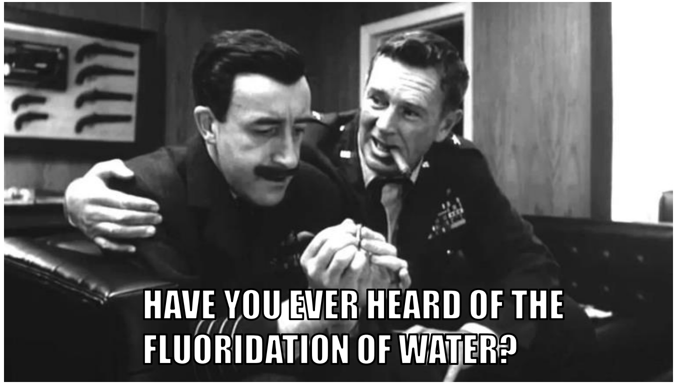
beneficial effect in prevention of dental caries
- Forms protective layer

absorbed in bone
- Skeletal fluorosisis

total mass ~2.6g in adults[2]
tightly bound -> MR-invisible

no background signal!

gyromagnetic ratio $\frac{\gamma}{2\pi}$: 40.087 MHz/T   Spin I: 1/2



Columbia Pictures

[1] Scientific Opinion on Dietary Reference Values for fluoride, EFSA 2013
[2] Cerklewski F., Nutirtion Research 17(5), 1997

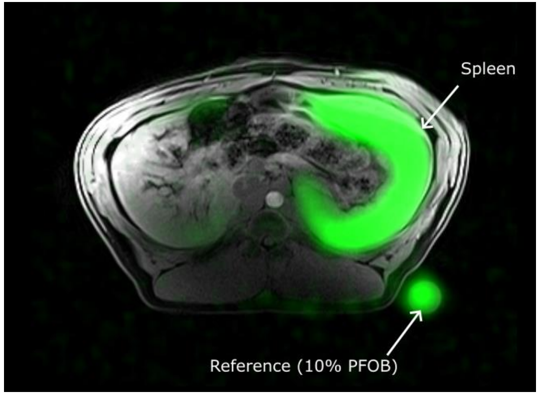
Cell tracking with 19F

WYSIWYG (What you see is what you give)

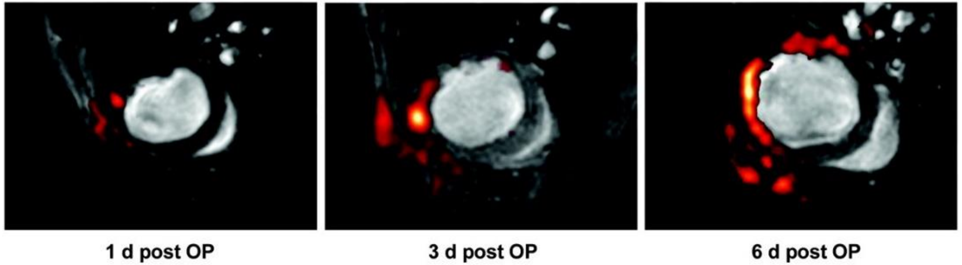
In vitro cell labeling and injection

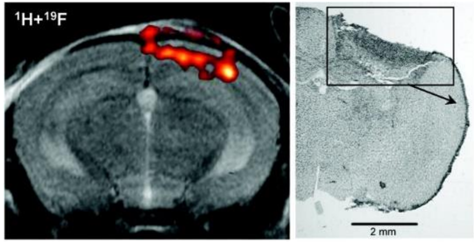
In vivo labeling by injection of perfluorcarbon (PFC) compounds

- PFCs are taken up by monocytes and stored in the spleen
- Monocytes respond to inflammation, illuminating the site in 19F images



Kian Tadjalli Mehr, ISMRM 2024





Flögel et al., Circulation 118 (2008)

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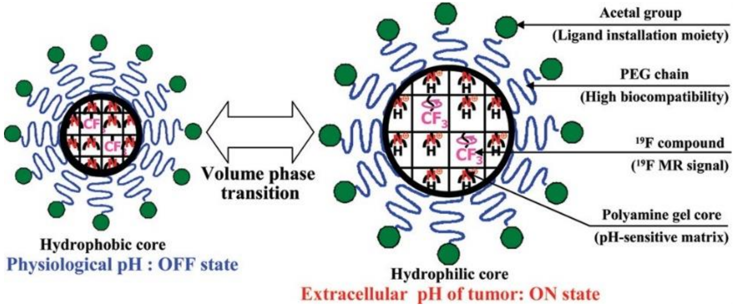
Fluor-19

pH-sensitive On/Off switch (in-vitro)

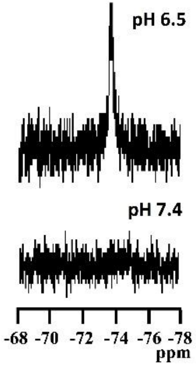


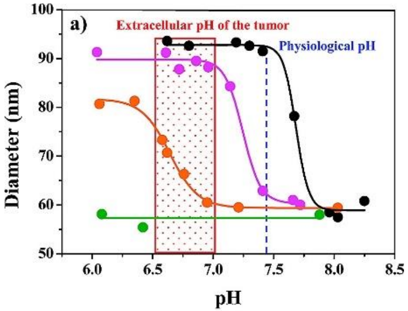
pH in tumor 0.4-1.0 units below physiological pH (~7.4)

PEG-based gel swells in lower pH environment

- increased mobility of incorporated ^{19}F
- increased T_2^*

pH-dependent swelling can be tuned via amount of trifluoroethyl methacrylate (TFEMA)





Oishi M., et al. *Bioconjugate Chem.* 2007, 18, 5, 1379–1382

Carbon-13

Carbon is the main component of organic chemistry

nuclear spin: 1/2

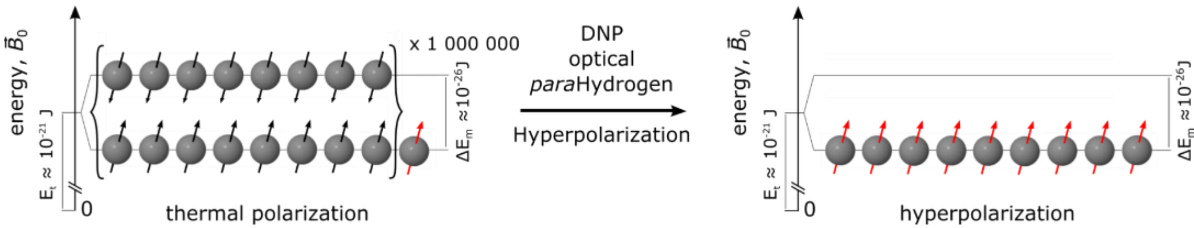
gyromagnetic ratio $\frac{\gamma}{2\pi}$: 10.708 MHz/T

natural abundance 1.1%

relative sensitivity: $1.76*10^{-4}$

Long T_1, up to 1 min

Excellent choice for labeling of endogeneous compounds



10^4-10^5 signal enhancement [1-2]

[1] Kovtunov et *al*. J. of Phys. Chem. (2018), [2] Adams et *al*. AAAS (2009)

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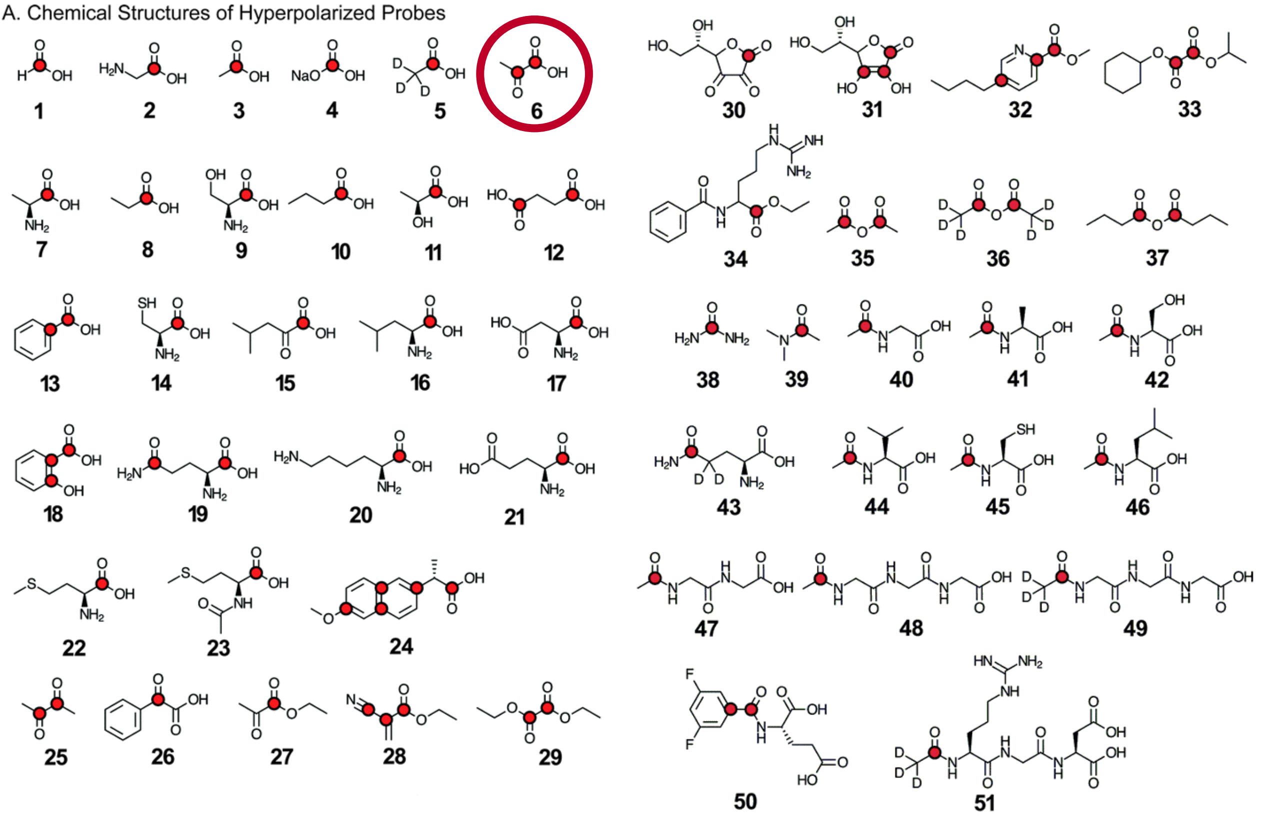
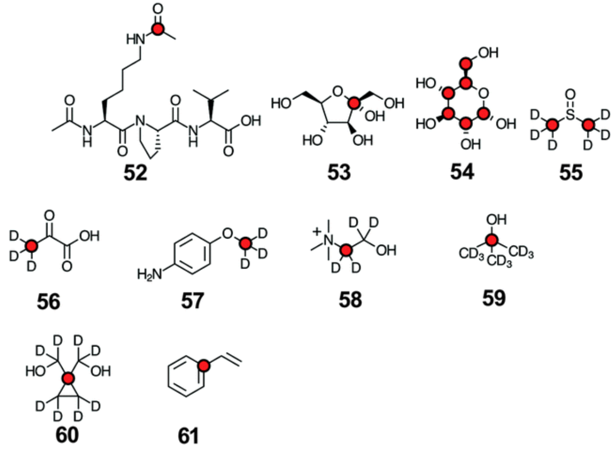
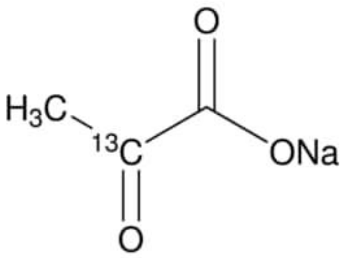




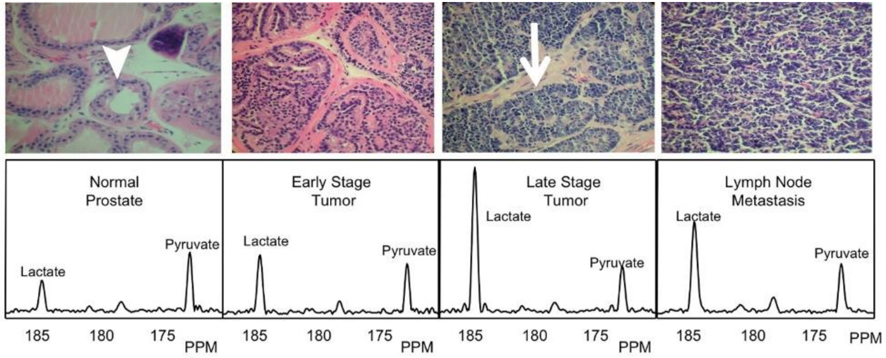


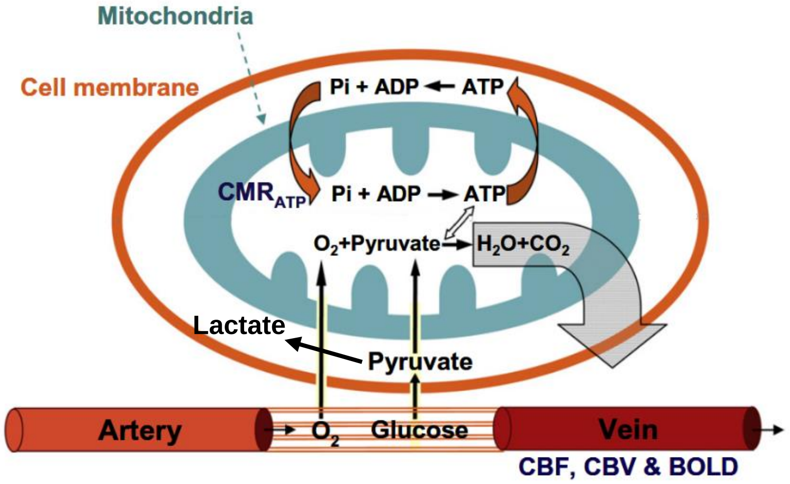
Pyruvate

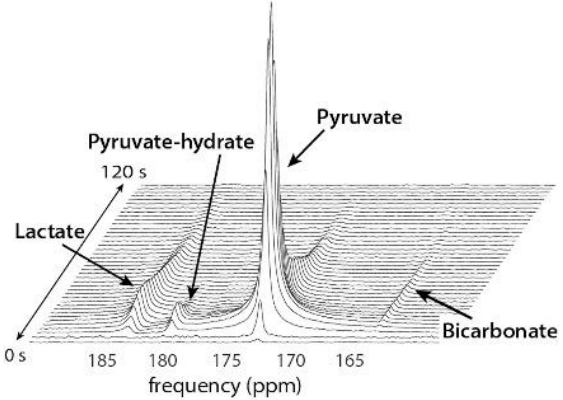
Keshari et *al.*, Chem. Soc. Rev. (2014)

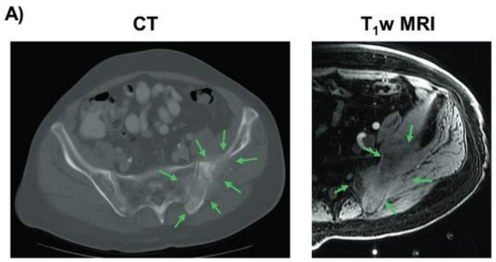
Carbon-13

Imaging the Warburg effect









Albers M., et *al.*, Cancer Research (2008)
Aggarwal et al., Eur Urol. (2017)
Chen et al, Prostate Cancer and Prostatic Diseases (2020)

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Challenges

Where does a low γ affect imaging?

Larmor Frequency: $\omega_0 = \gamma B_0$

RF-excitation: $\omega_1 = \gamma \int B_1(t)\mathrm{d}t$

Spatial encoding: $k = \gamma \int G(t)\mathrm{d}t$

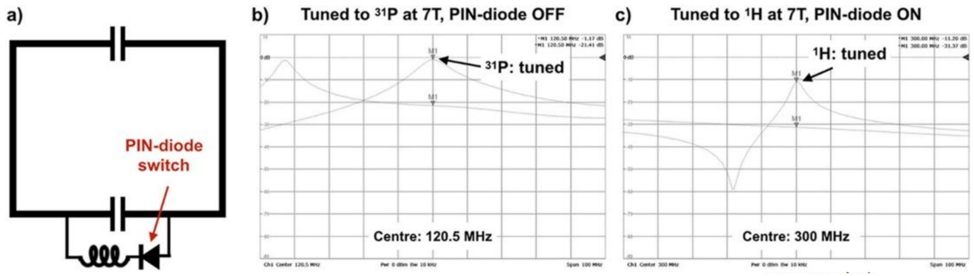
$$\dot{k}(t) = \gamma G(t)$$

Challenges

Coils

High SNR for X-nucleus

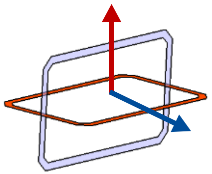
^{1}H coil for anatomy and shimming

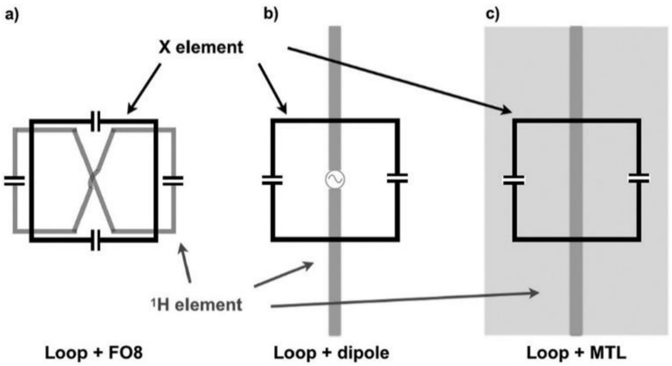


Dual tuned coils

Single structure

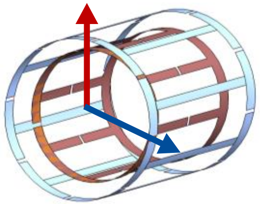
- Frequency trap, frequency blocking
- Same imaging region is scanned





Multi structure

- Geometric B_1 decoupling
- Indiviual tuning, better SNR



Choi C., et al., Magn Reson Imag 72 (2020)

Challenges

Setting up the scanner

1. make sure the machine supports multiple nuclei
   - boradband, low-power RF-amplifier for x-nuclei

2. manually adjust the frequency

3. calibrate the reference voltage for RF-excitation
   - U_{ref} is the voltage needed for a rectangluar, 1ms long, 180° pulse

Challenges

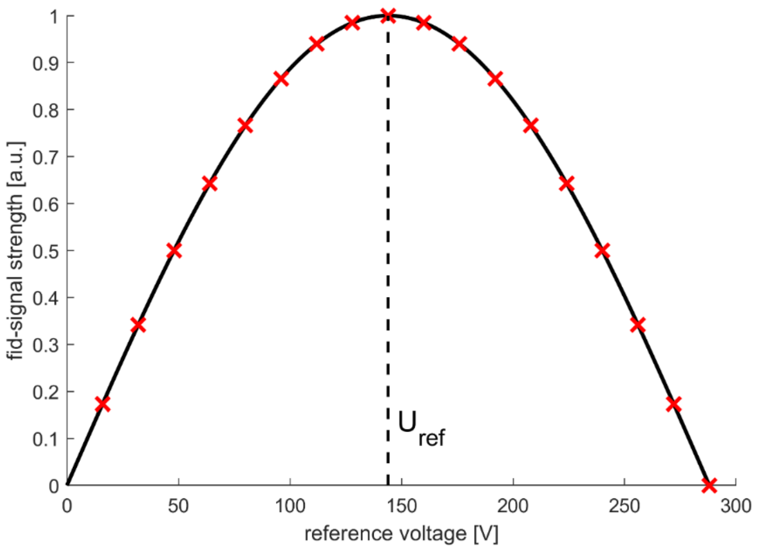
calibration of U_{ref}

Create fid sequence with 1ms rect pulse and set FA to 90°

$$S \sim M_\perp \sim \sin(\gamma B_1)$$

Repeat measurement for different U_{ref}

When signal is maximized, U_{ref} is correctly calibrated



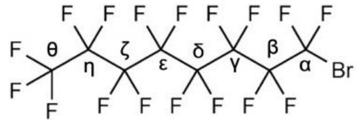
Challenges

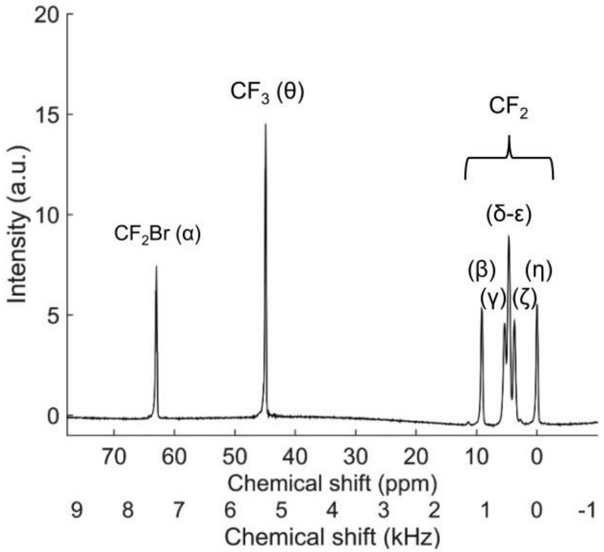
Multiple resonances

Complex molecular structures lead to chemical shift

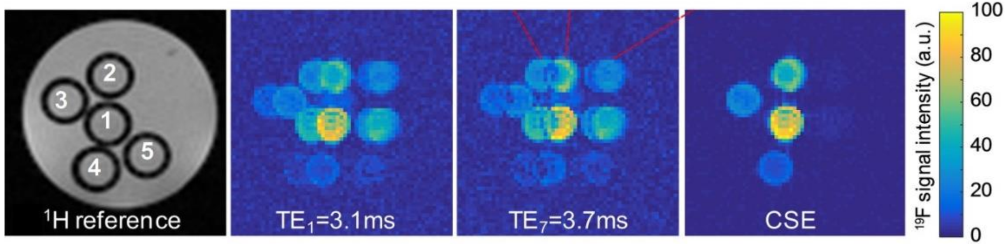
- Spectrally selective pulses
- Saturation pulses (think Fat-Sat.)[1]
- Model based reconstruction from multi-echo data[2, 3]

Perfluorooctyl bromide (PFOB)





$$s_{TE}\left(k_x, k_y(t), t\right) = \int\int_{x,y} \rho(x,y)\left[\sum_{m=1}^{M} A_m \exp\left(i2\pi\cdot(TE+t)f_m\right)C_m\right]\exp(i2\pi x k_x)\exp\left(i2\pi y k_y(t)\right)dx\ dy$$



[1] Nöth et al., Magn Reson Imag 12 (1994)
[2] van Heesweijk et al., MRM 79(5) (2018)
[3] Brodsky et al. MRM 59(5) (2008)

Challenges

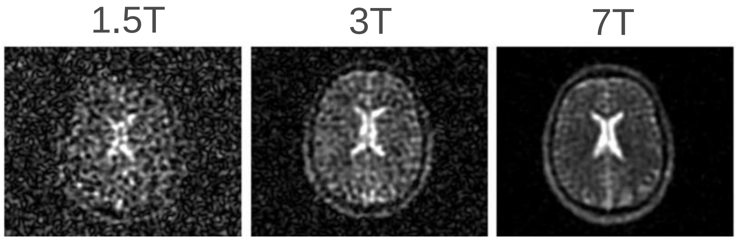
Low signal amplitude

$$\frac{\mathrm{SNR}}{\mathrm{voxel}} \sim \Delta x \Delta y \Delta z \sqrt{N_{\mathrm{Acq}} N_{\mathrm{Avg}} T_{\mathrm{Ro}}} * B_0 \sin(\alpha) \frac{1-e^{-\mathrm{TR}/T_1}}{1-\cos(\alpha) e^{-\mathrm{TR}/T_1}} e^{-\mathrm{T}E/T_2^*}$$

Average

Increase B_0

$^{23}\mathrm{Na}$



Huhn K., et al., Front. Neurol. 10:84

Increase voxel size

Increase readout time T_{RO} (lower BW)

Reduce TE

Challenges

Short T_2 relaxation times

signal: $S(t) \sim e^{-\mathrm{T}E/T_2^*}$

short, non-selective excitation pulse

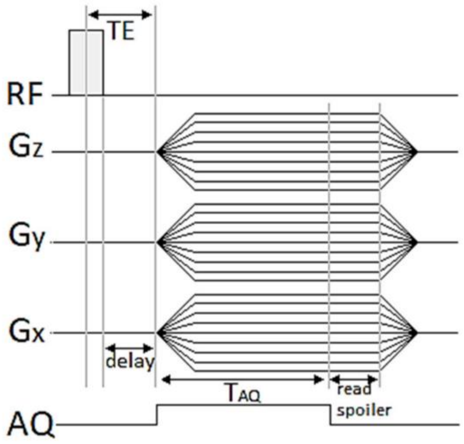
3-dimensional encoding of k-Space using radial spokes

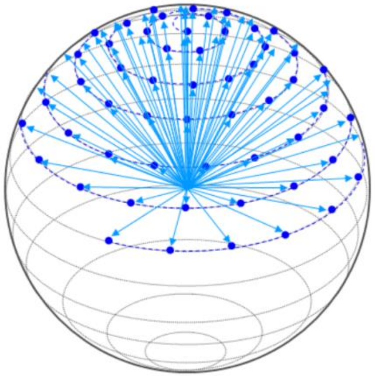
- archimedian spiral[1]

$$z(n) = \frac{2n - N - 1}{N},$$

$$x(n) = \cos(\sqrt{N\pi}\sin^{-1}z(n))\sqrt{1 - z^2(n)},$$

$$y(n) = \sin(\sqrt{N\pi}\sin^{-1}z(n))\sqrt{1 - z^2(n)},$$

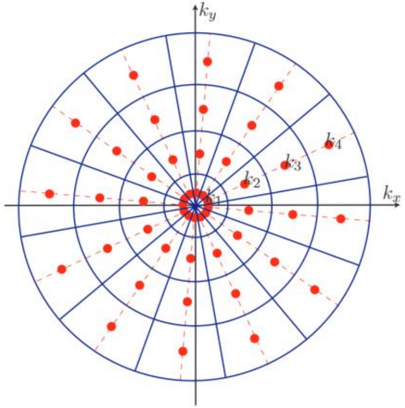




[1] Wong S., et al. *Magn Res Med.* 1994, 32, 6

Challenges

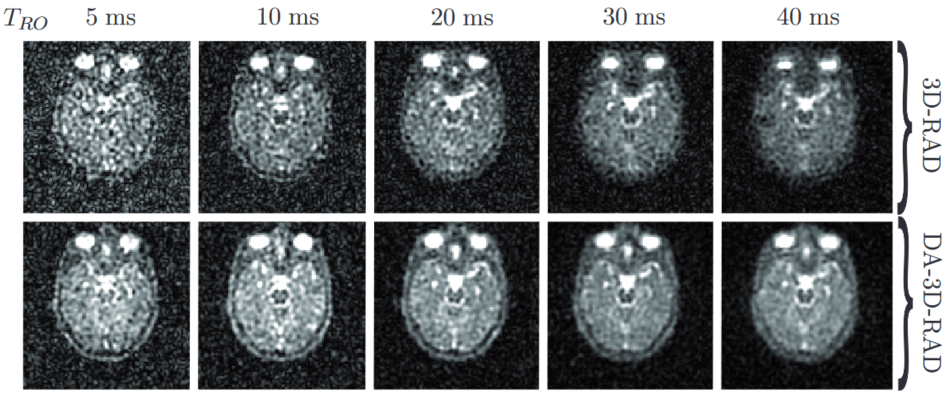
Inhomogeneous sampling density

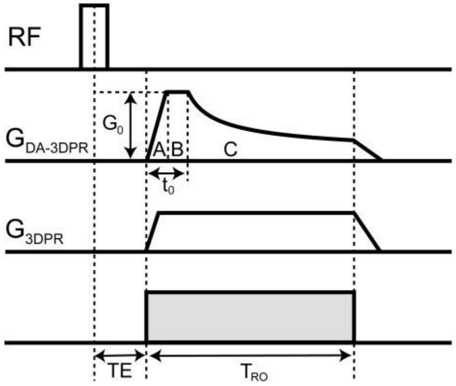


Uniform sampling density improves SNR[1]

Adapt gradient-shape such that density is constant for $k > k_0$

$$G(t) = k_0^2 G_0 \left(3 \frac{\gamma}{2\pi} k_0^2 G_0 (t - t_0) + k_0^3\right)^{-\frac{2}{3}}$$





SNR improvement	1,7x	1,6x	1,5x	1,7x	1,8x

Nagel et al., MRM 62(6) (2009)

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[1] Liao et al., Magn Reson Imag 37 (1997)

Pulseq sequence

Gradient amplitudes in pulseq

Sequence design is independent of γ

Gradient amplitudes in pulseq are defined in $A = \frac{\gamma}{2\pi} G$

$$k(t) = \int \frac{\gamma}{2\pi} G(t)\mathrm{d}t = \int A(t)\mathrm{d}t$$

Pulseq provides functions to calculate between Hz/m and mT/m

How to run an X-nuclei sequence with pulseq?

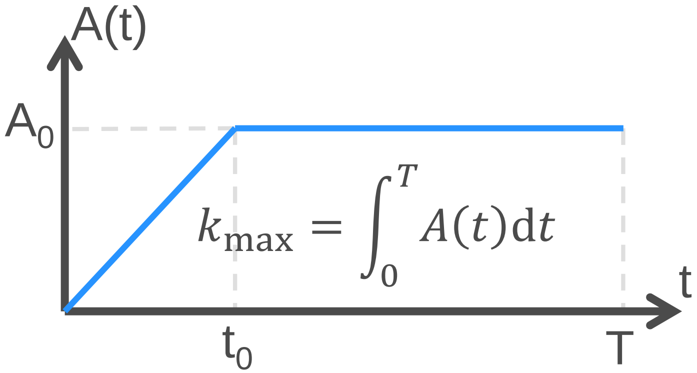
```
system = pp.opts(…, gamma=-5.772e6)
```

Pulseq sequence

design a center out readout

Use `pypulseq.make_extended_trapezoid`, which requires a numpy array of times and amplitudes.

- Find: t_0, T, A_0
- t_0, T must lie on `opts.gradient_raster_time` (10μs)



Calculate the gradient amplitude: $\mathrm{BW} = \frac{\mathrm{FOV} * A_0}{N} \rightarrow A_0 = \frac{\mathrm{BW} * N}{\mathrm{FOV}}$

Choose a high slew rate, SR: $t_0 = \frac{A_0}{\mathrm{SR}} \rightarrow t_{0\mathrm{grt}} = \lceil t_0 \rceil$

$$k_{\max} = \frac{t_{0\mathrm{grt}} A_0}{2} + A_0 \left(T - t_{0\mathrm{grt}} \right)$$

$$T = \frac{k_{\max}}{A_0} + \frac{t_{\mathrm{grt}}}{2} \rightarrow T_{\mathrm{grt}} = \lceil T \rceil$$

Pulseq sequence

design a center out readout

Use `pypulseq.make_adc`, which requires a dwell time, τ, and a duration TADC

- τ must lie on `opts.adc_raster_time` (100ns)
- Nyquist must be fulfilled: $\tau A_0 = \Delta k = {}^{1}/_{\mathrm{FOV}}$
- Chose an oversampling of 2

$$\tau = \frac{1}{\mathrm{OS}}\frac{1}{\mathrm{FOV}A_0} = \frac{1}{2\mathrm{BW}N} \rightarrow \tau_{\mathrm{art}} = \lfloor \tau \rfloor$$

- Number of ADC samples (multiple of 2)

$$N_{\mathrm{ADC}} = \left\lceil \frac{T}{\tau_{\mathrm{art}}} \right\rceil$$

$$T_{\mathrm{grt}} = \lceil N_{\mathrm{ADC}} \tau_{\mathrm{art}} \rceil$$