“Emerging contrasts at ultrahigh fields"

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ADVANCED IMAGING
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"Emerging contrasts at ultrahigh fields"

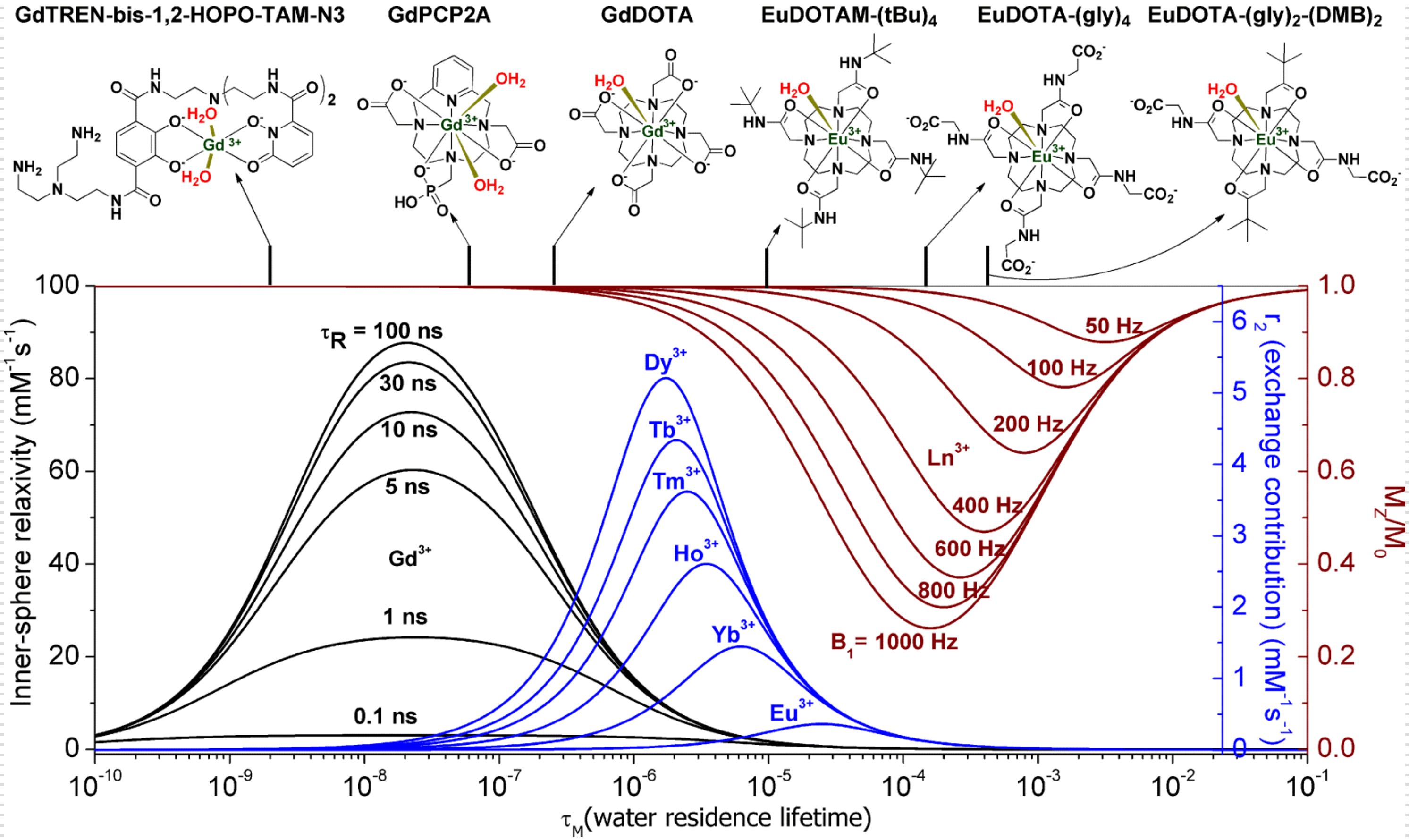
- T_1 and T_2 contrast agents
  a) Will they remain widely used clinically at high magnetic fields?

- Newer types of contrast agents: CEST
  a) Opportunities to detect specific cellular metabolites, physiology, and biochemical processes

- Spectroscopy of other nuclei
  a) ^{31}P, ^{13}C and ^{23}Na should gain traction as clinical diagnostic tools

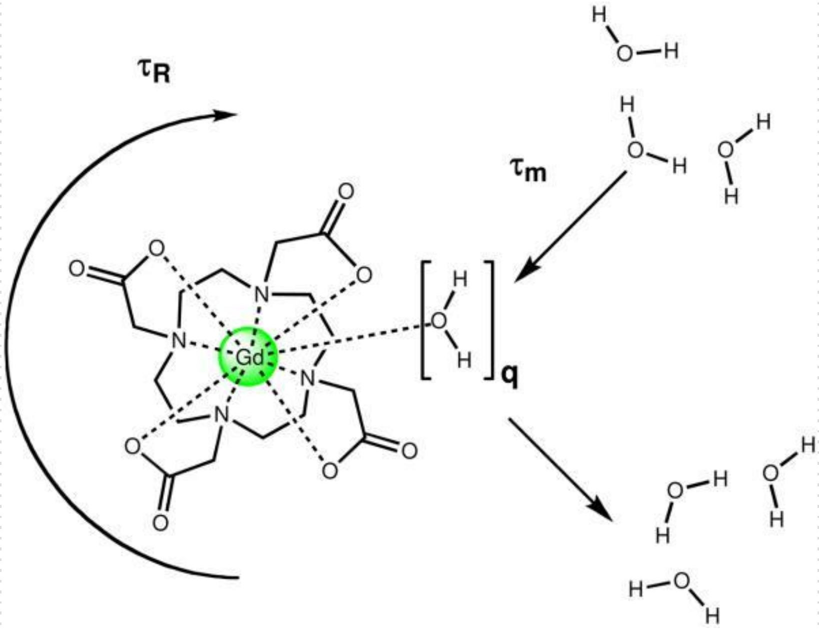
The importance of water exchange in the design of MRI contrast agents

AD Sherry & Y Wu, Curr Opin Chem Biol, 17: 167-174 (2013).



T1 agents   T2exch agents   PARACEST agents

Factors to consider in the design of a responsive probe for MRI

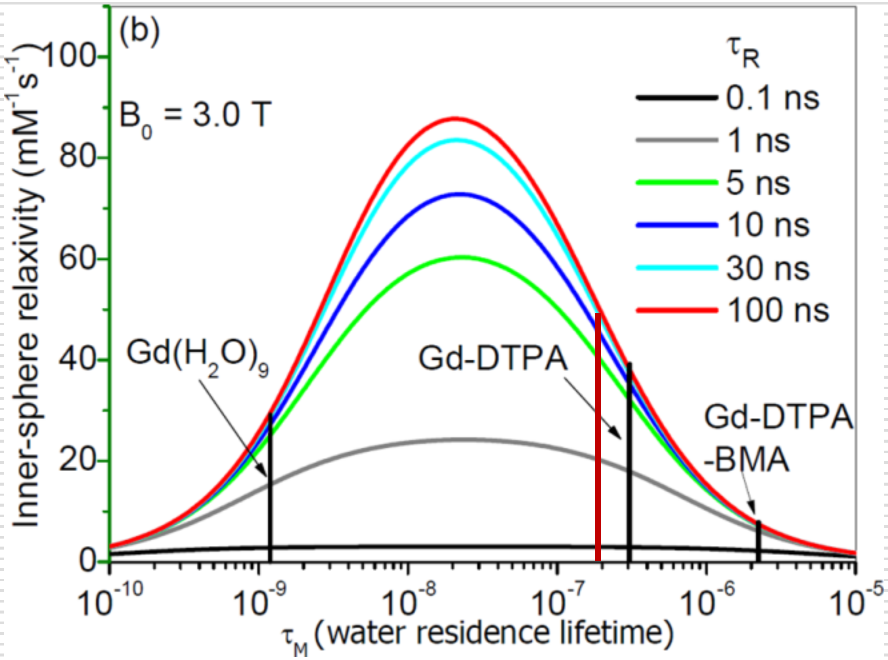


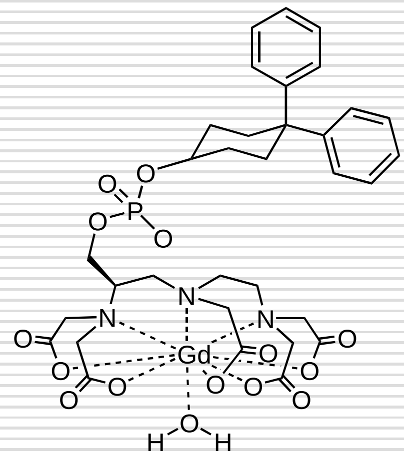
Relaxivity also heavily depends upon the Gd-OH_2 distance (r^{-6}) but this is not easily modified.

One of three parameters can be modified:

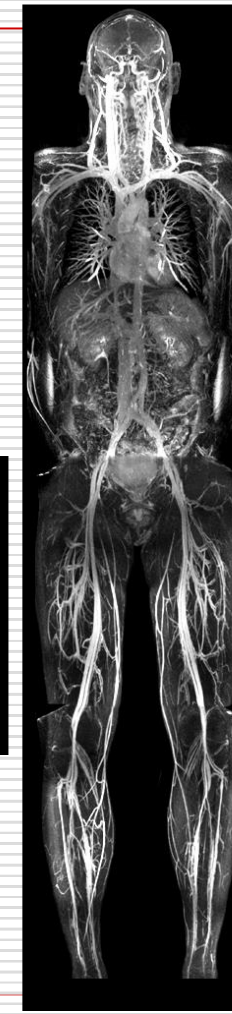
1. Rotational motion (τ_R)
2. Number of inner-sphere water molecules (q)
3. Water exchange lifetime (τ_M)

The importance of water exchange in the design of MRI contrast agents





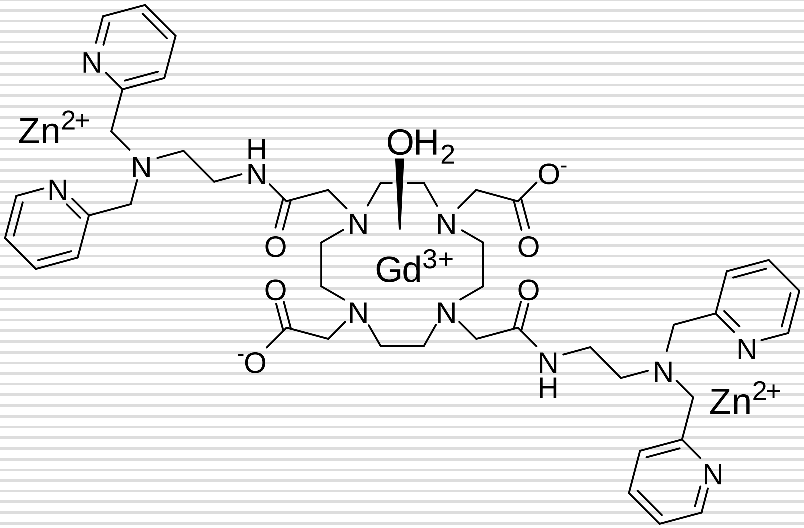
MS-325, Ablavar

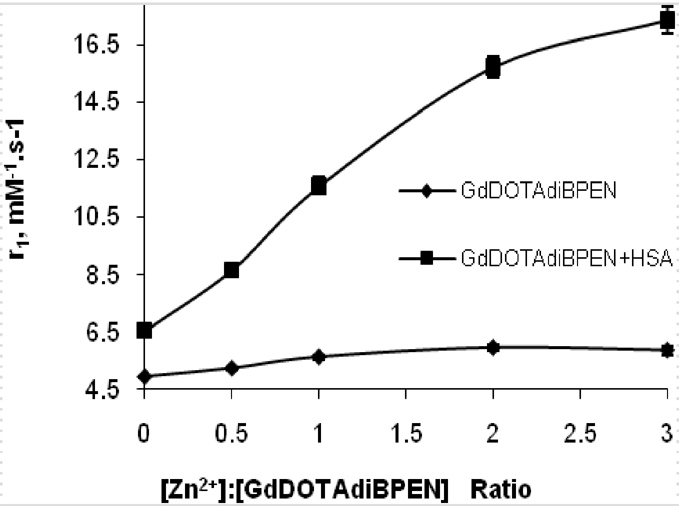


MS-325 (τ_M = 172 ns when bound to HSA)

AD Sherry & Y Wu, Curr. Opin. Chem. Biol., 17: 167-174 (2013)

Previously reported MRI Zn^{2+} sensors





In the absence of albumin, r_1 increases from 5 to 6 $mM^{-1}s^{-1}$ upon addition of Zn^{2+}

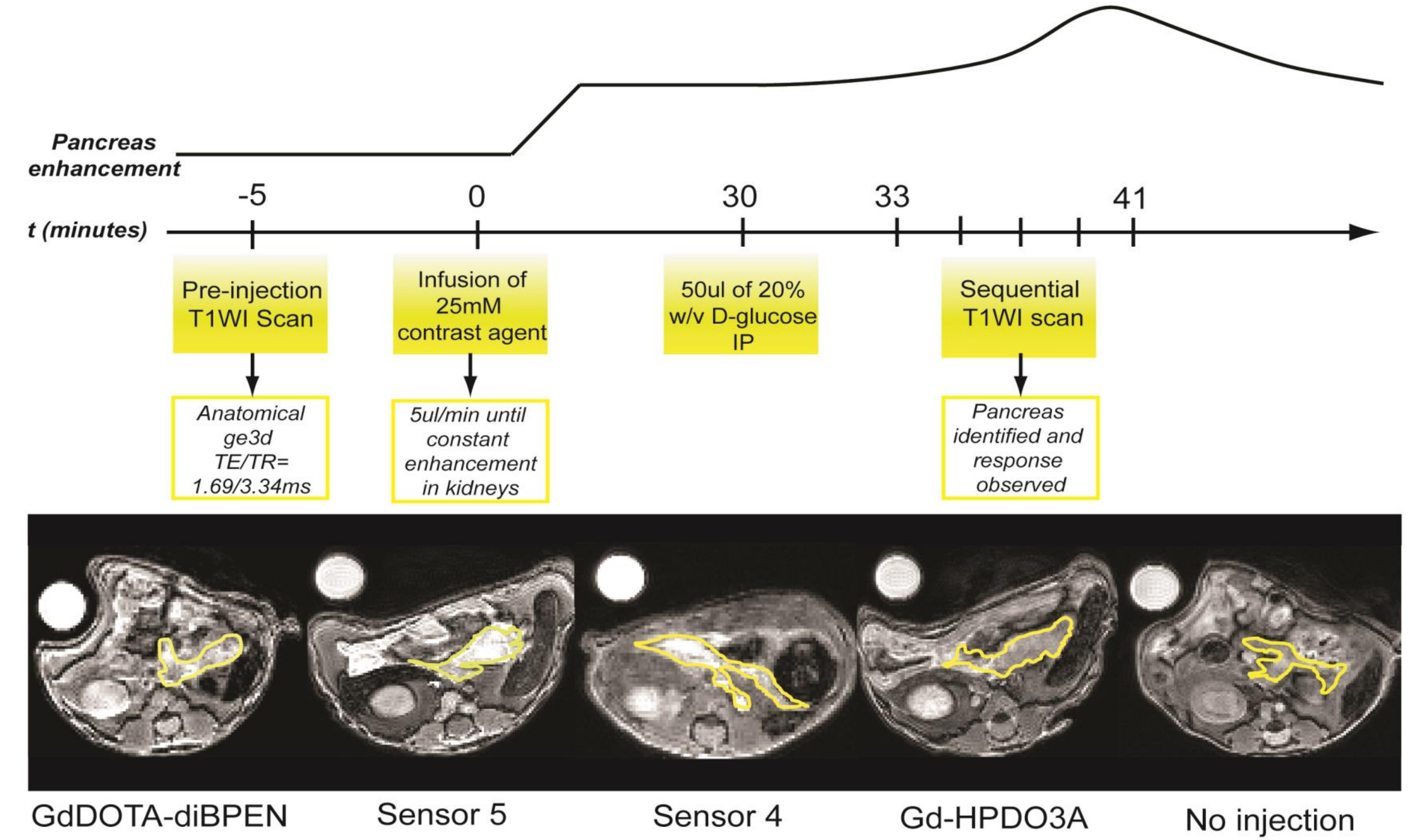
In the presence of albumin, r_1 increases from 6.6 to 17.5 $mM^{-1}s^{-1}$ upon addition of Zn^{2+}

K_d = 5 nM   Positive contrast!

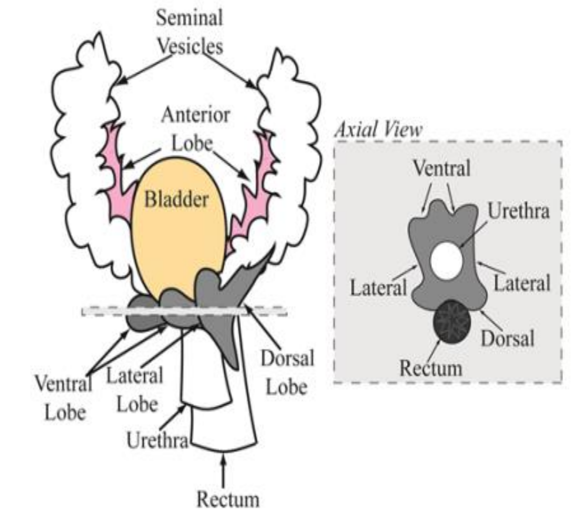
Esqueda, et al., JACS, 131: 11387-11391 (2009)

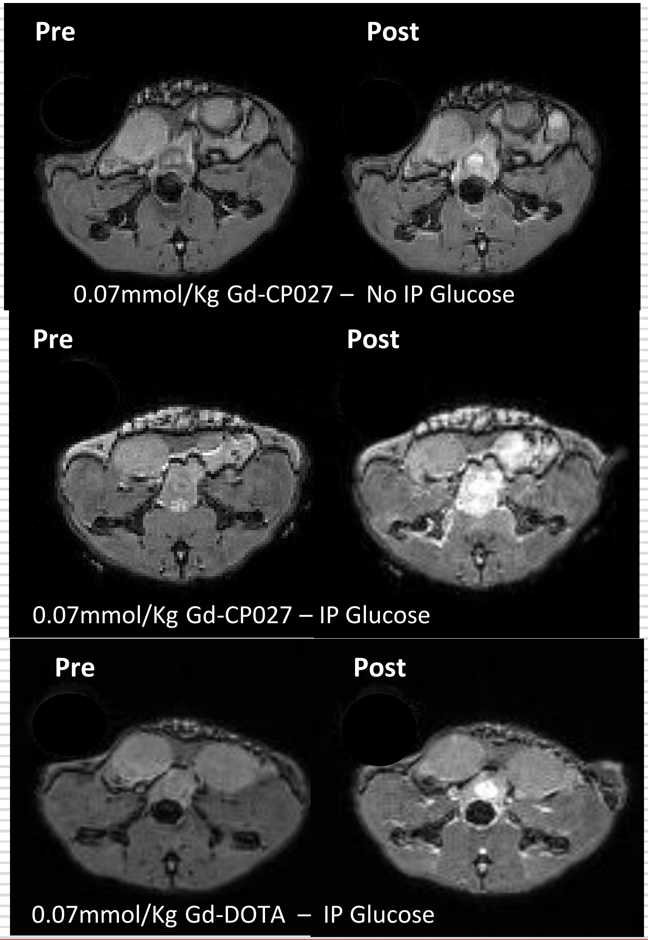
The new high relaxivity Zn^{2+} sensors provide much greater image contrast in vivo!

J. Yu, et al., J. Am. Chem. Soc., 2015, 137 (44), pp 14173–14179



Zn^{2+} release from the healthy prostate is also stimulated by glucose





“Emerging contrasts at ultrahigh fields"

- Will responsive T_1 agents such as this be useful at higher magnetic fields?

High Magnetic Field Water and Metabolite Proton T_1 and T_2 Relaxation in Rat Brain In Vivo

deGraaf, et al., MRM, 56: 386-394 (2006)

Table 1
Water T_1 and T_2 Relaxation Time Constants for Rat Brain at 4.0, 9.4, and 11.7 T

	Structure								
	cc	cx	ob	hc	cw	cg	st	th	mb
4.0 T									
T_1 (ms)	1096.8	1285.8	1640.6	1334.1	1046.9	1352.6	1288.2	1169.4	1064.4
SD (ms)	49.3	77.0	20.8	97.4	53.3	82.6	87.3	69.5	17.3
9.4 T									
T_1 (ms)	1752.1	1948.4	2129.1	2059.7	1660.3	2097.2	1927.0	1793.1	1786.5
SD (ms)	52.1	51.9	63.7	66.1	79.3	68.2	54.7	64.3	81.9
11.7 T									
T_1 (ms)	1861.3	2073.4	2304.3	2222.8	1745.1	2109.4	2046.5	1903.2	1893.2
SD (ms)	73.5	100.7	63.4	63.2	36.0	95.0	55.3	61.2	44.3
4.0 T									
T_2 (ms)	57.9	65.2	80.2	72.0	58.8	65.3	69.7	61.7	60.6
SD (ms)	1.6	2.4	2.0	1.3	1.5	2.0	2.0	2.1	1.9
9.4 T									
T_2 (ms)	35.8	42.1	48.1	45.4	37.2	41.7	43.5	40.6	40.3
SD (ms)	1.2	1.2	1.9	1.8	2.0	1.6	2.4	1.2	1.4
11.7 T									
T_2 (ms)	30.7	36.2	38.9	38.9	27.1	37.3	36.4	33.8	33.8
SD (ms)	1.0	1.0	1.1	1.3	1.3	2.3	2.2	1.6	1.9

cc = corpus callosum, cx = cerebral cortex, ob = olfactory bulb, hc = hippocampus, cw = cerebellar white matter, cg = cerebellar gray matter, st = striatum, th = thalamus, mb = mid-brain.

T_1 ~70-80% longer

T_2 ~50% shorter

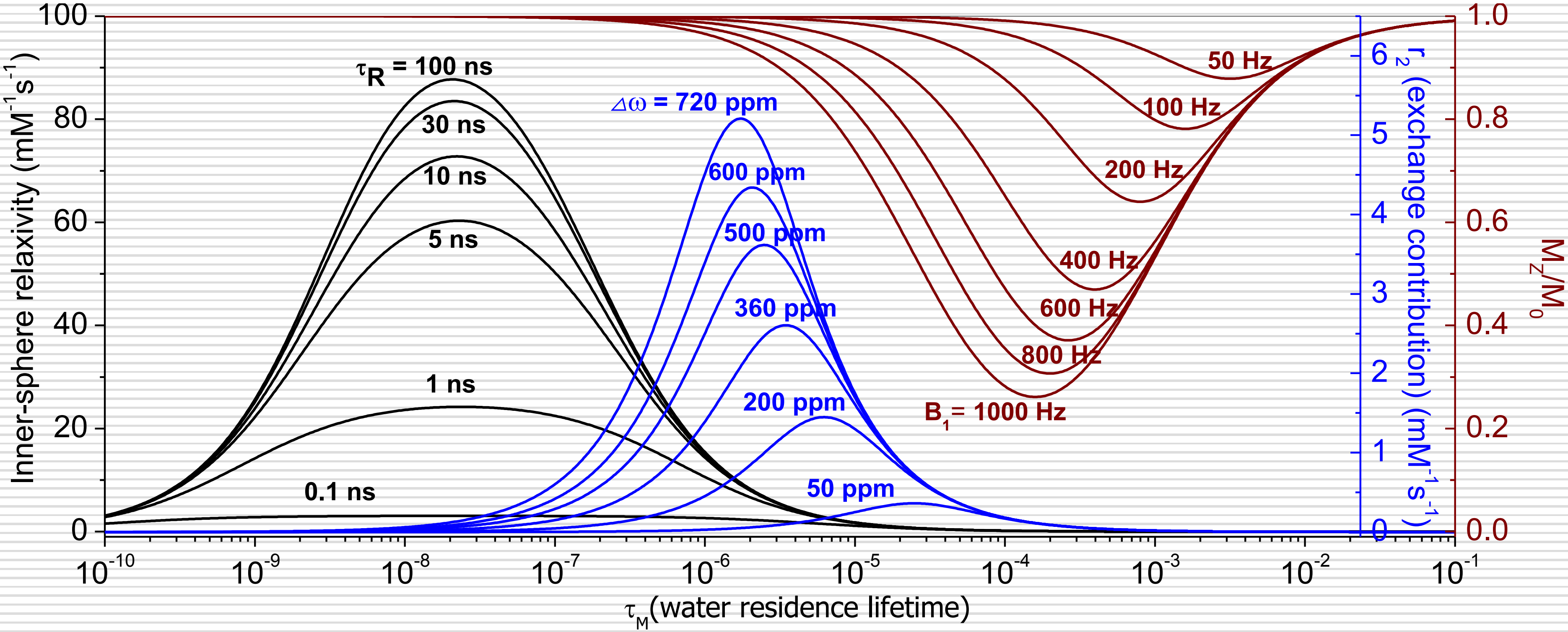
Relaxation times measured on the same subjects in human brain (Philips scanners)

Masaya Takahashi, UTSW, unpublished data

Tissue	T_1 (ms)			T_2 (ms)		
	1.5T	3T	7T	1.5T	3T	7T
Gray Matter						
Frontal cortex	1362	1599	1756	99	91	77
Putamen	1096	1230	1378	80	71	51
Caudate nucleus	1275	1359	1548	87	77	57
Thalamus	1186	1255	1473	82	71	49
Globus pallidus	801	914	1060	71	65	42
White Matter						
Frontal	721	800	914	77	72	61
Corpus Callosum	702	791	965	78	69	54

Impact of water exchange rates on CA sensitivity as one transitions to higher magnetic fields for imaging

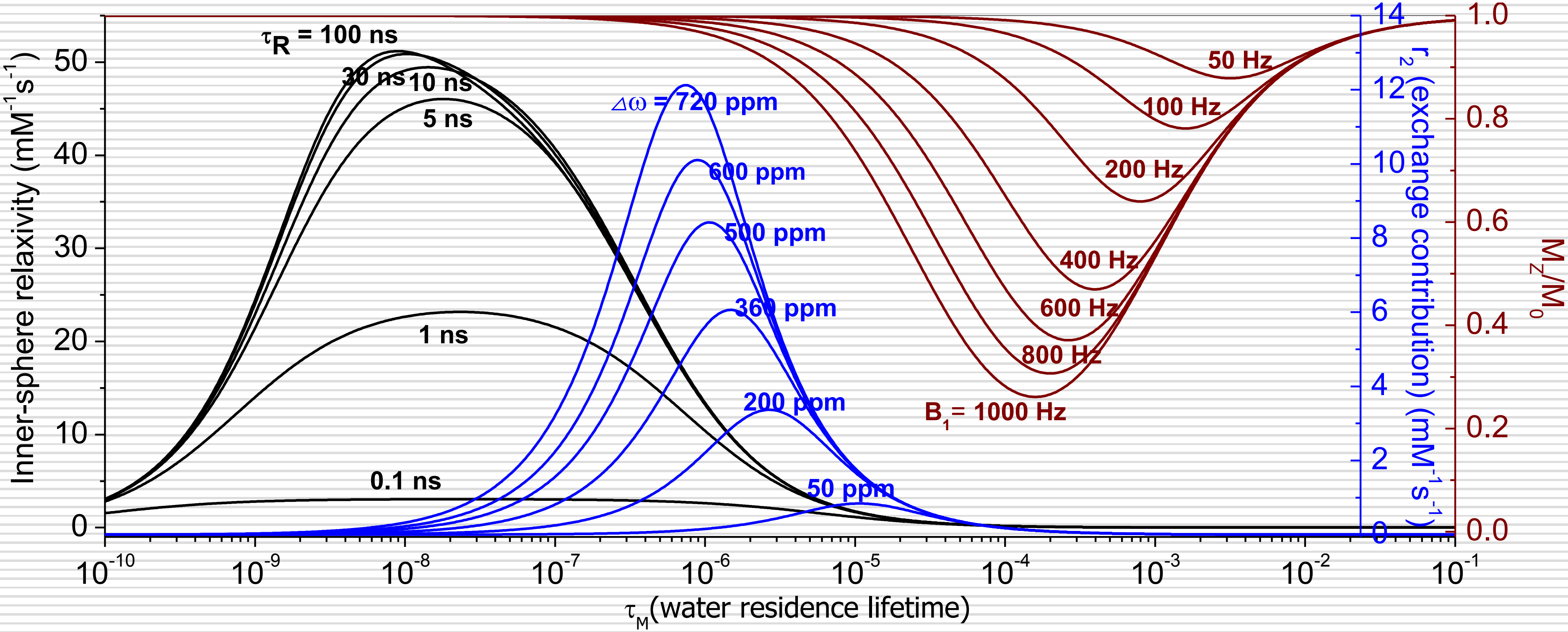
3T



Gd-based T_1 T_{2exch} paraCEST

Impact of water exchange rates on CA sensitivity as one transitions to higher magnetic fields for imaging

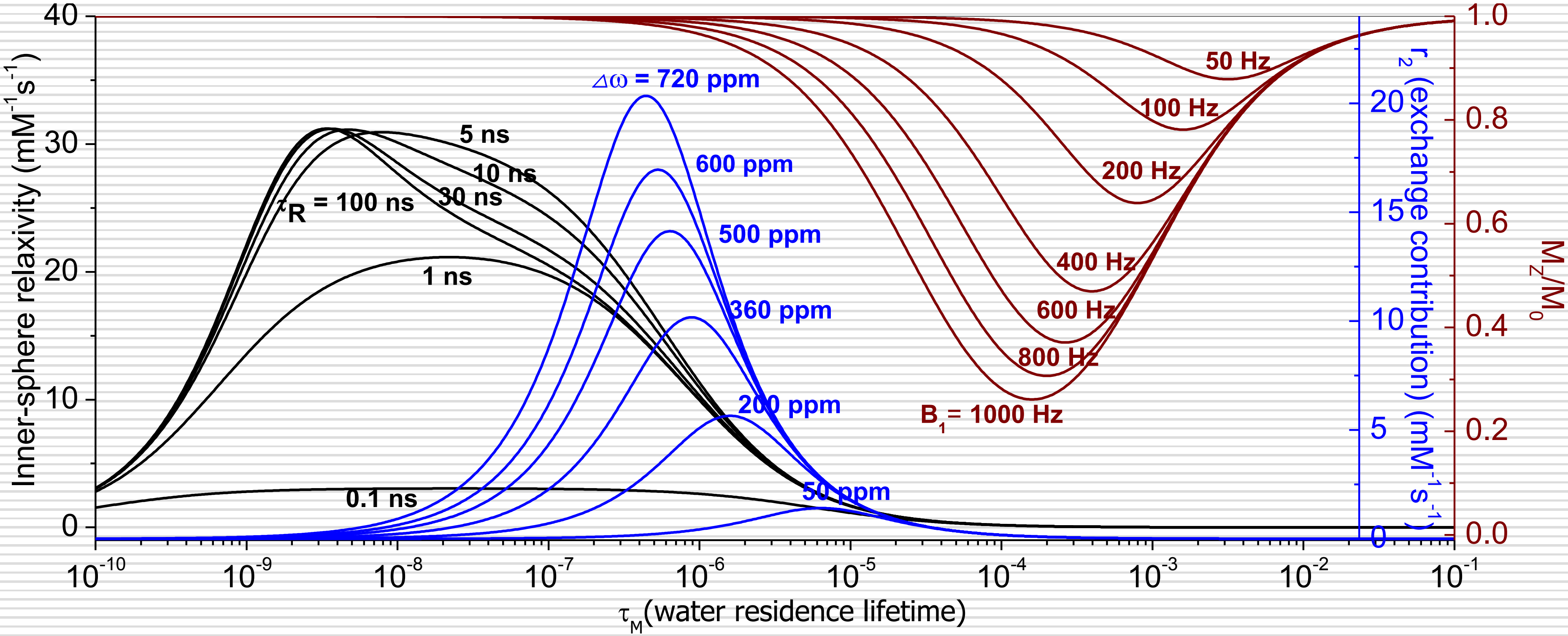
7T



Gd-based T_1 T_{2exch} paraCEST

Impact of water exchange rates on CA sensitivity as one transitions to higher magnetic fields for imaging

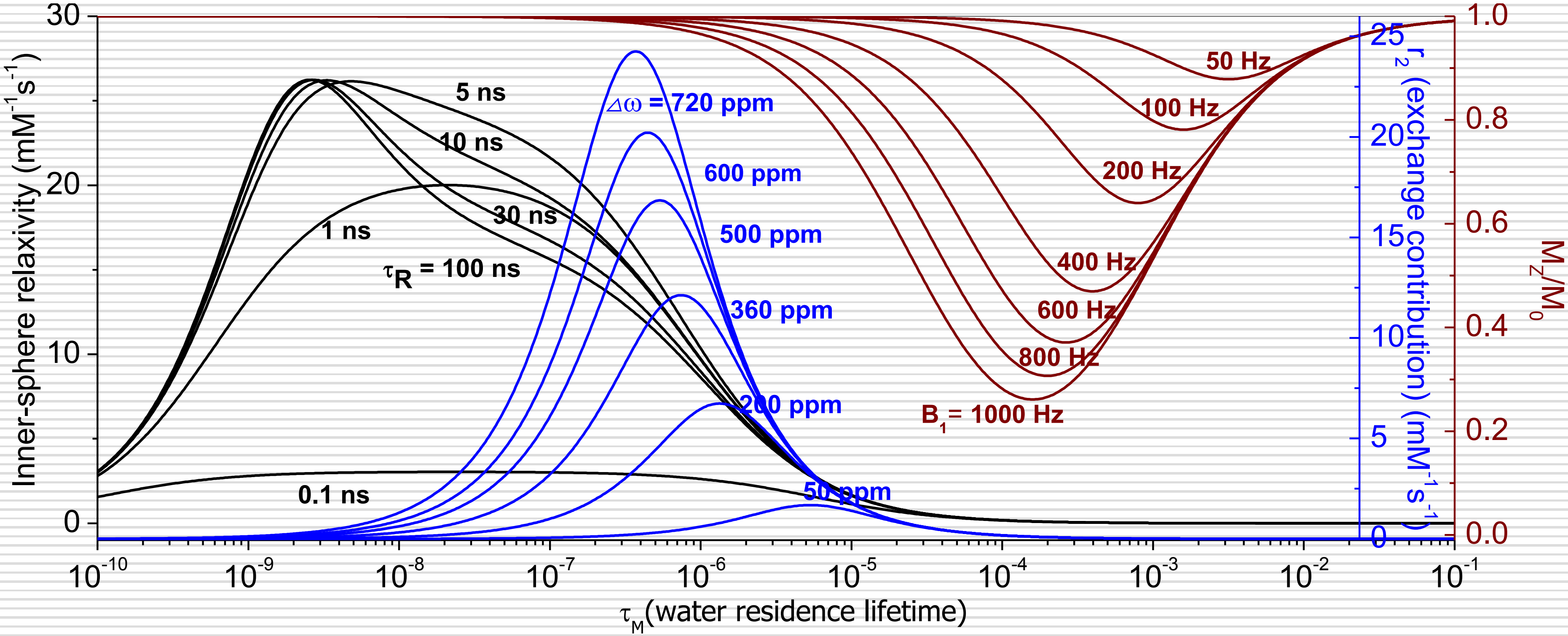
11.75T



Gd-based T_1 T_{2exch} paraCEST

Impact of water exchange rates on CA sensitivity as one transitions to higher magnetic fields for imaging

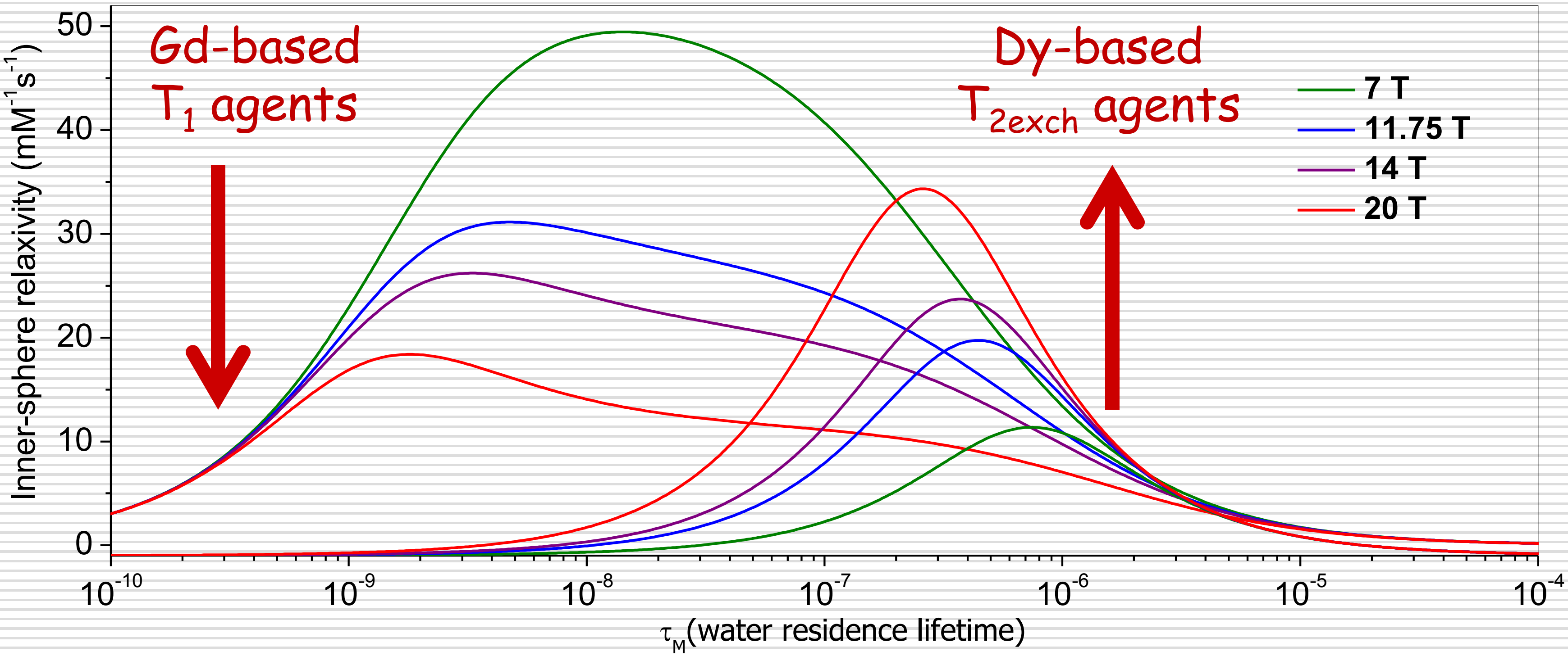
14T



Gd-based T_1 T_{2exch} paraCEST

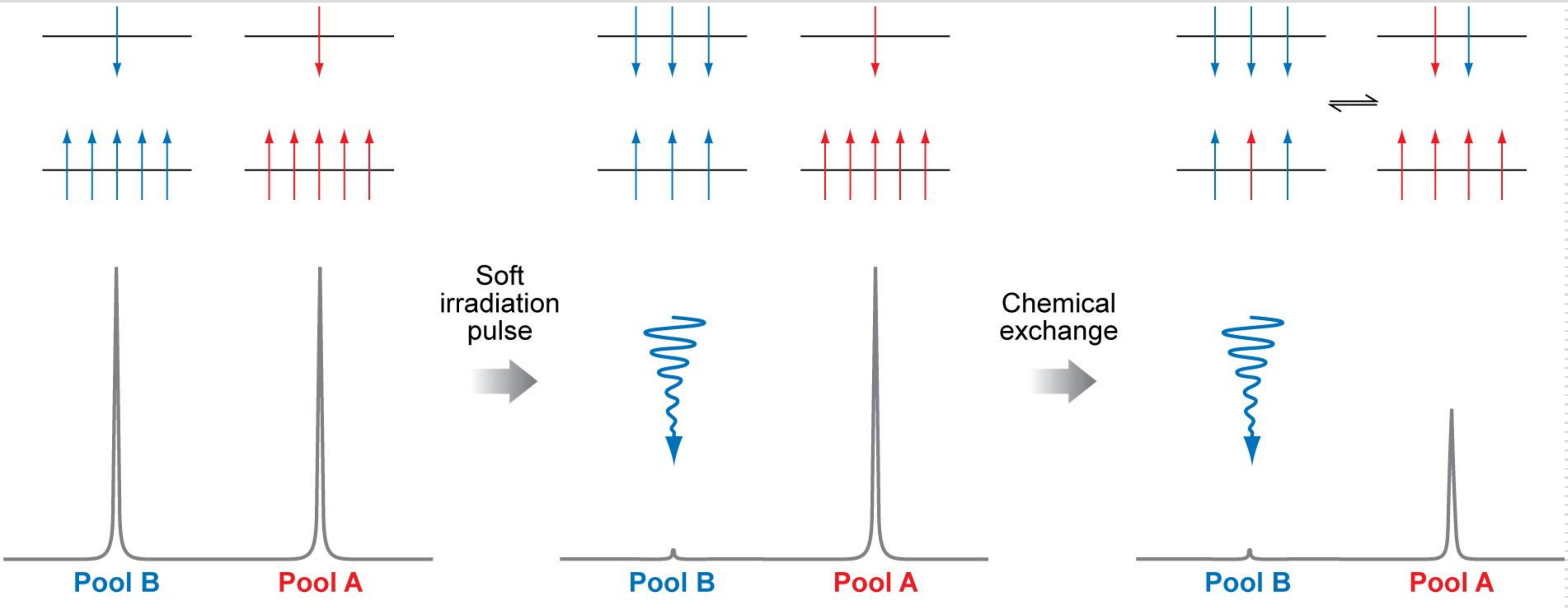
Impact of water exchange rates on CA sensitivity as one transitions to higher magnetic fields for imaging

plotted on the same $r_{1,2}$ relaxivity scale



- Newer types of contrast agents: CEST
  a) Opportunities to detect specific cellular metabolites, physiology, and biochemical processes

Basic principles of chemical exchange saturation transfer (CEST) imaging

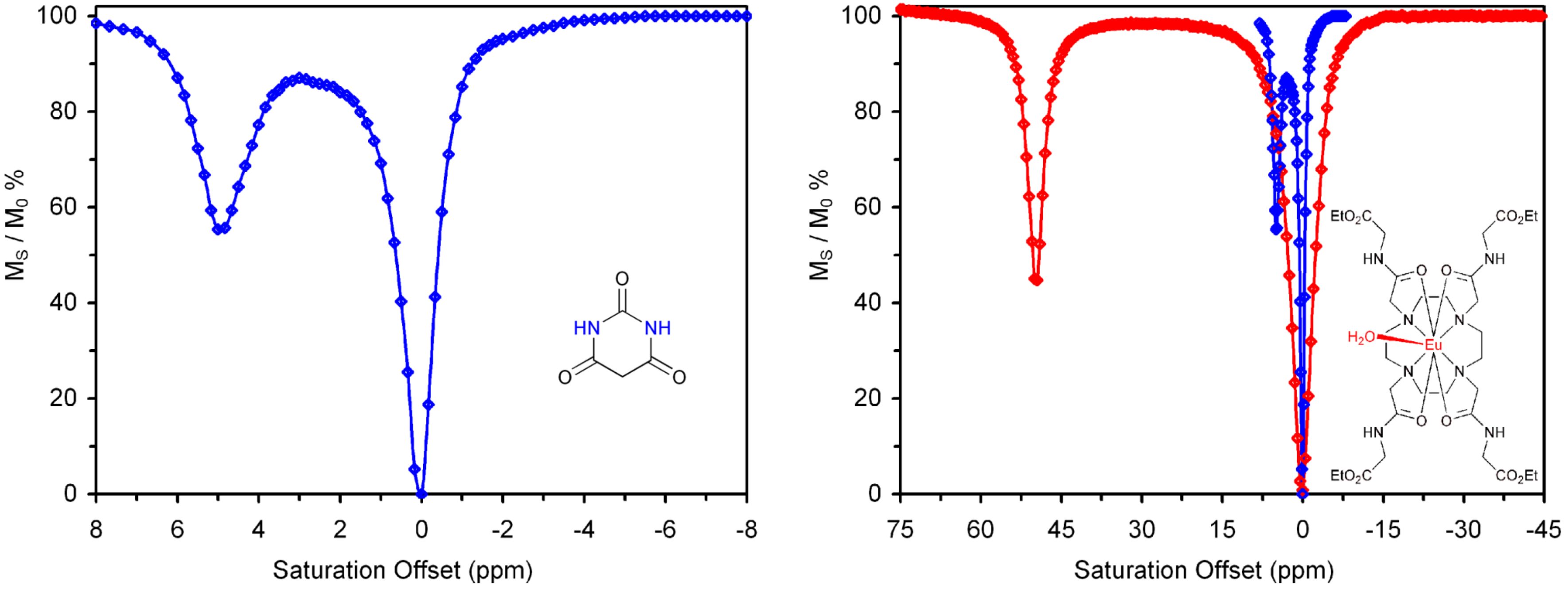


Chemical shift, $\Delta\omega$, must differ

RF saturation must be selective

Intermediate exchange rate, $k_{ex} < \Delta\omega$,

One clear advantage of PARACEST agents for CEST imaging ⇒ large $\Delta\omega$



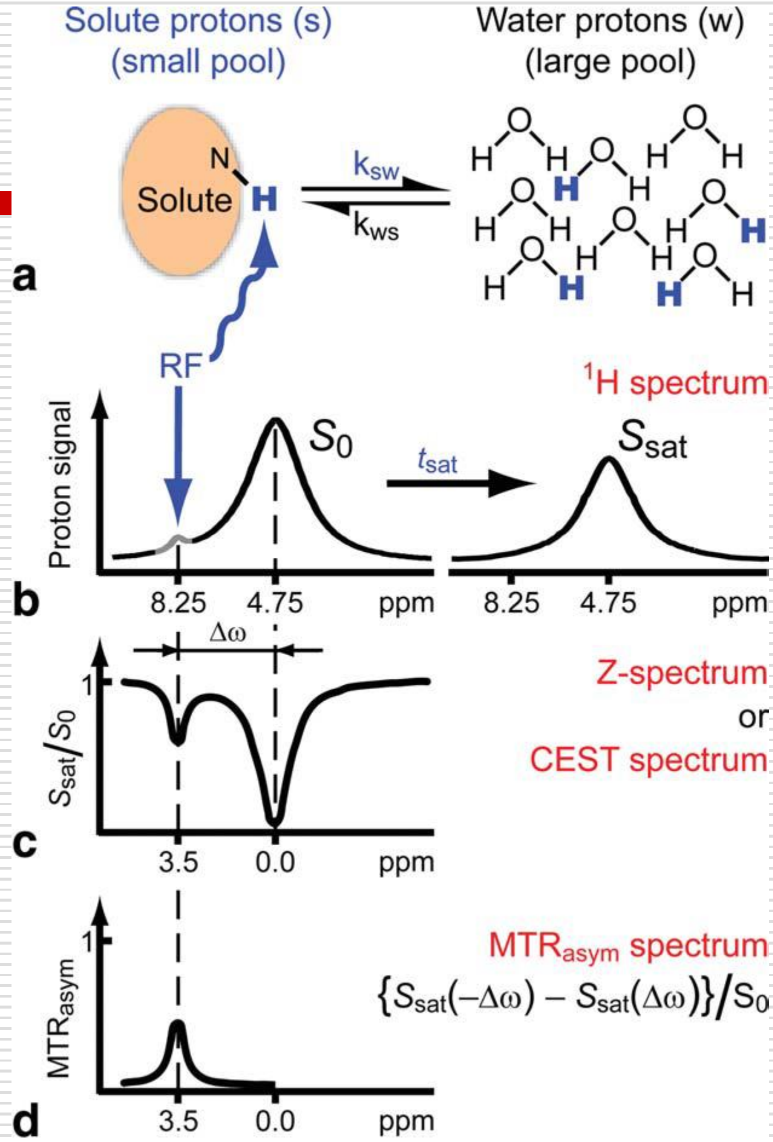
Reproduced from Ward, Aletras & Balaban. *J. Magn. Reson*. **143**: 79 (2000)

CEST and paraCEST agents

propects for clinical translation

There are many chemical types of exchanging protons in tissue:

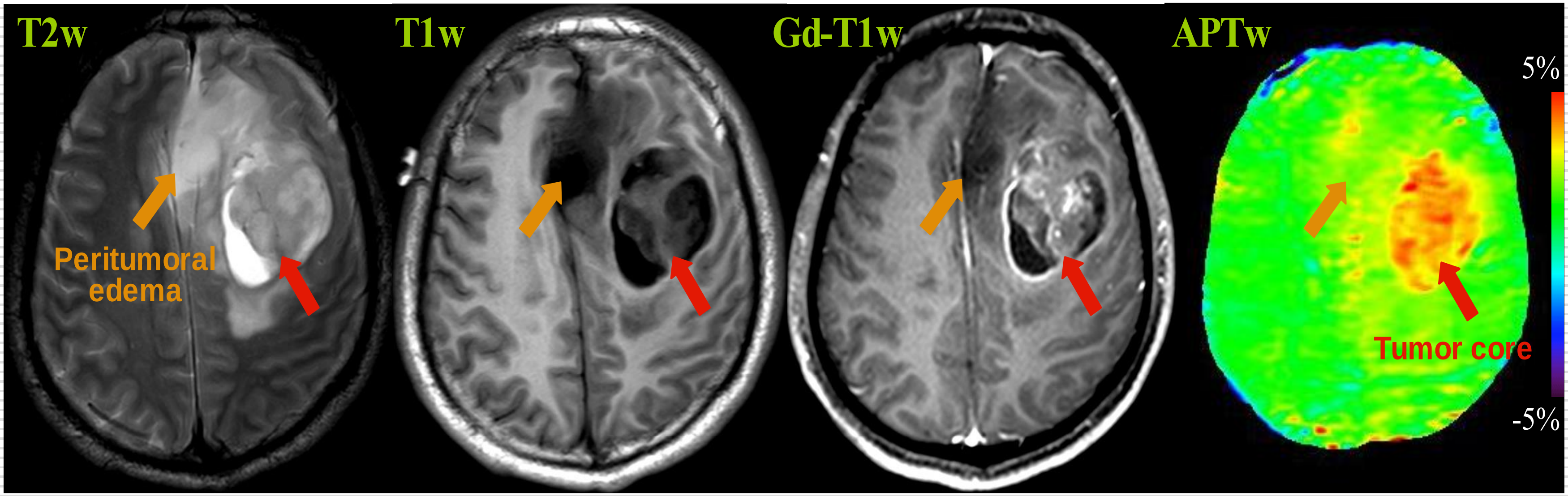
- N-H from proteins & amino acids, nucleic acids
- O-H from sugars, polysaccharides
- S-H from cysteine & glutathione
- many others



From "Chemical Exchange Saturation Transfer (CEST): What is in a Name and What Isn't?"
P. van Zijl & N. N. Yadav, Magn. Reson. Med. 65: 927-948 (2011)

Amide Proton Transfer (APT) signal of tumors reflects enhanced -NH proton exchange

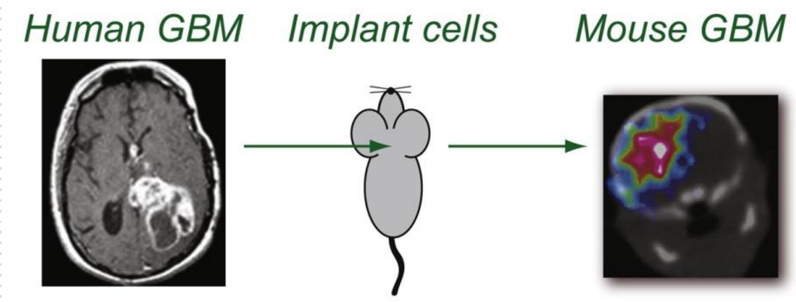
Wen, et al., NeuroImage, 51: 616-622 (2010)

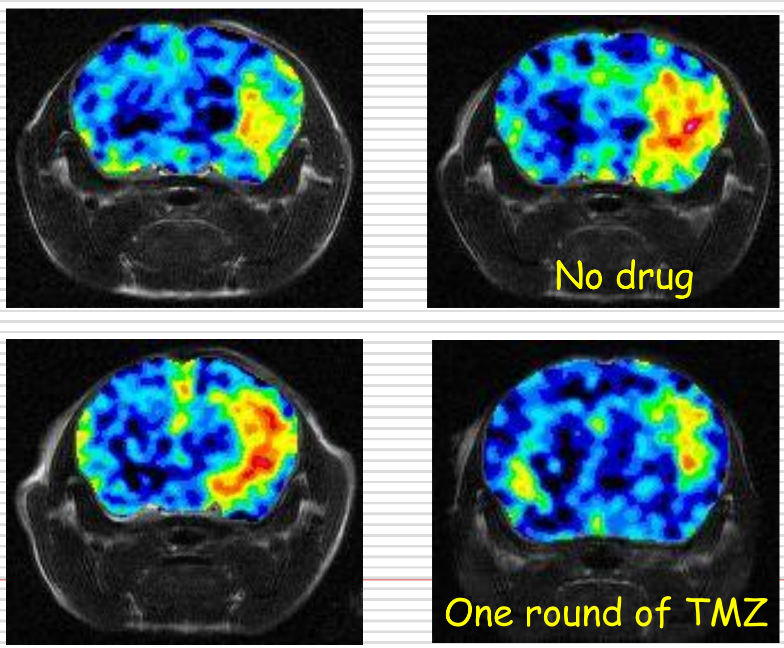


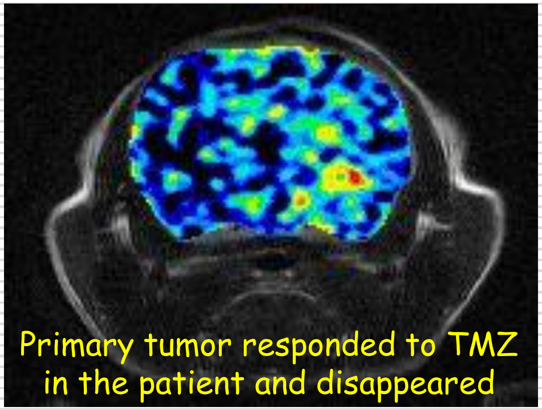
Note: limited contrast in edema region (orange arrow); high APT contrast in tumor

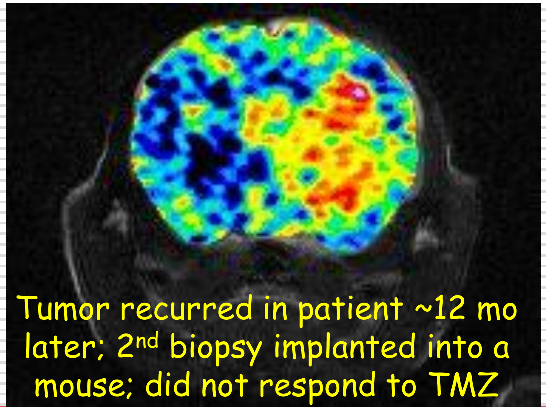
APT imaging detects early response in glioblastoma (GBM) to temozolomide

K. Sagiyama, et al., PNAS, 111: 4542-4547 (2014)





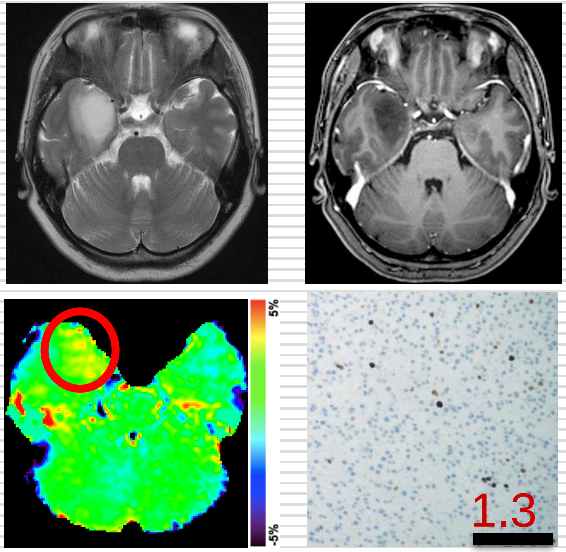




Amide proton transfer imaging of adult diffuse gliomas: correlation with histopathological grades

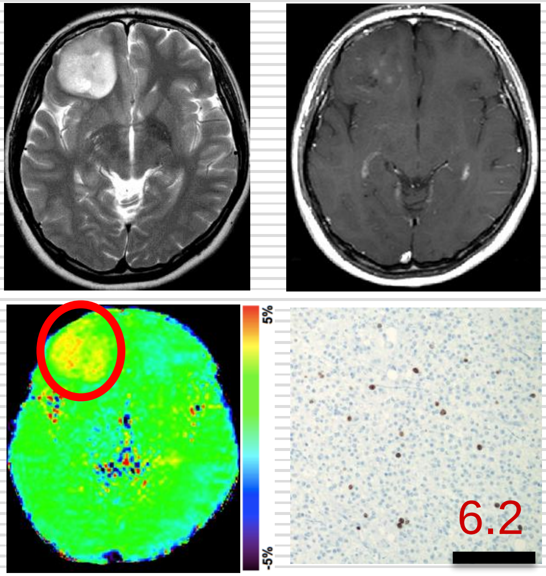
Togao, et al., Neuro-Oncology, 16: 441-448 (2014)

Astrocytoma (Grade II)



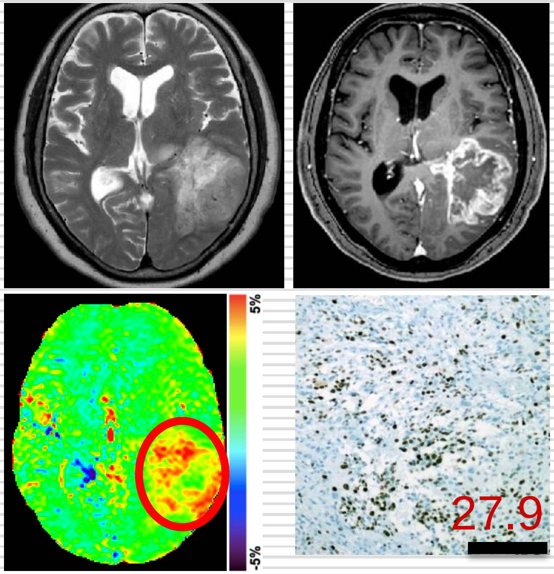
1.4

Anaplastic oligodendroglioma (Grade III)



2.8

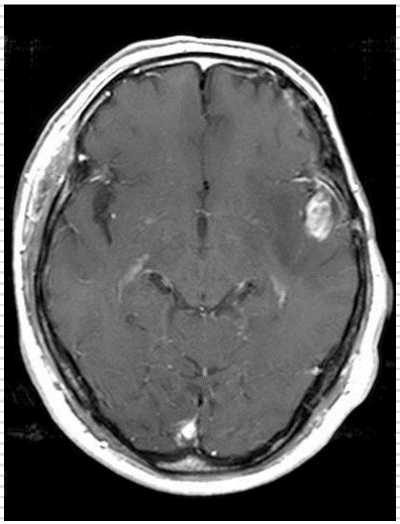
Glioblastoma multiforme (Grade IV)

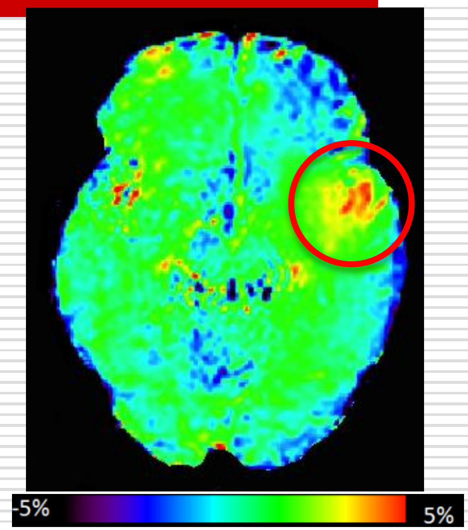


4.0

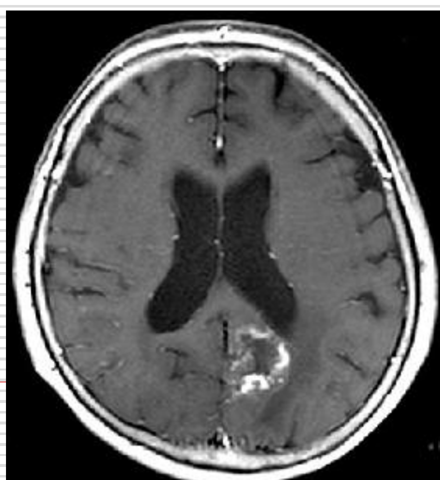
APT imaging differentiates between tumor recurrence versus radiation necrosis

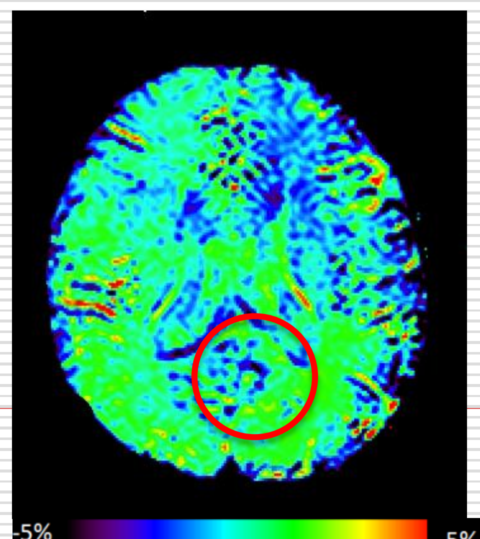
By courtesy of Dr. Osamu Togao, Kyushu University





Recurrence

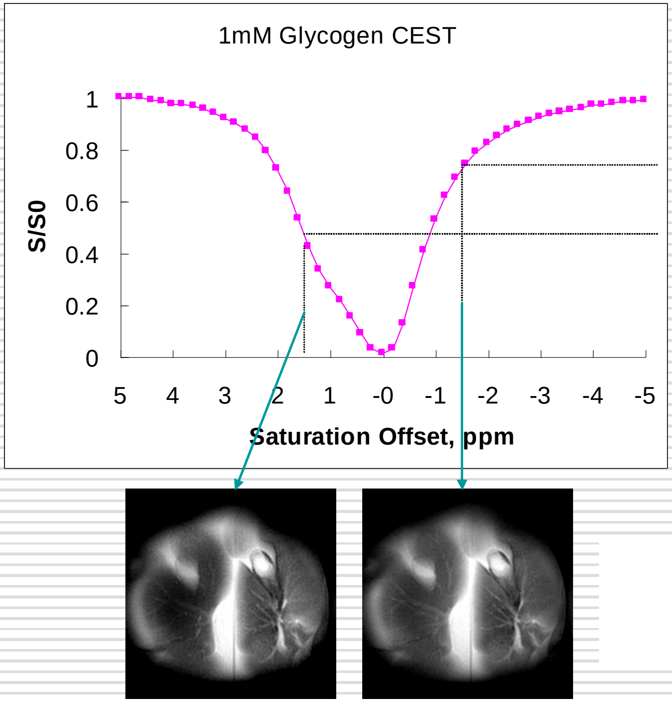


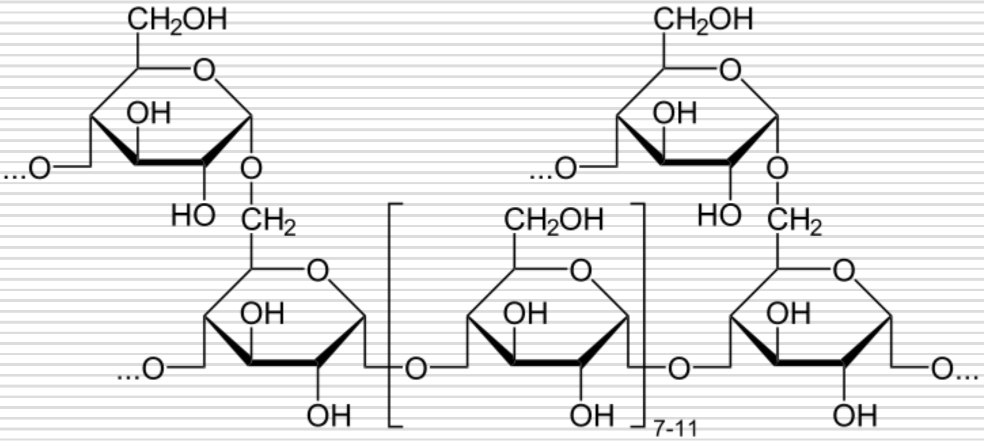


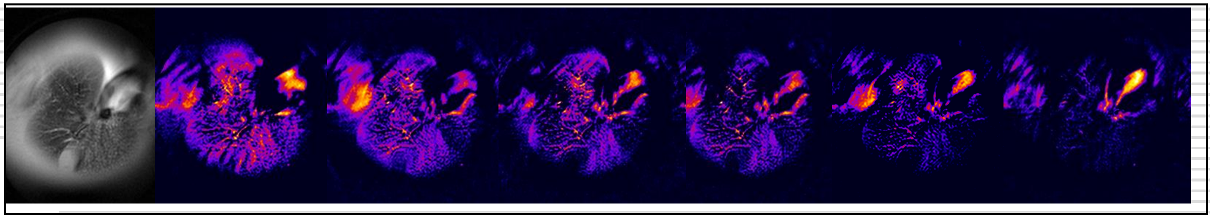
Radiation Necrosis

glycoCEST

imaging the distribution of glycogen in liver



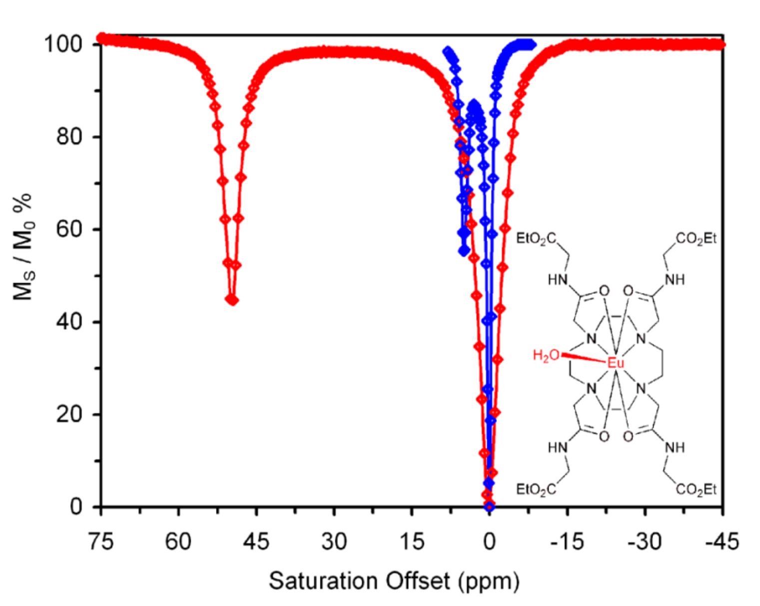


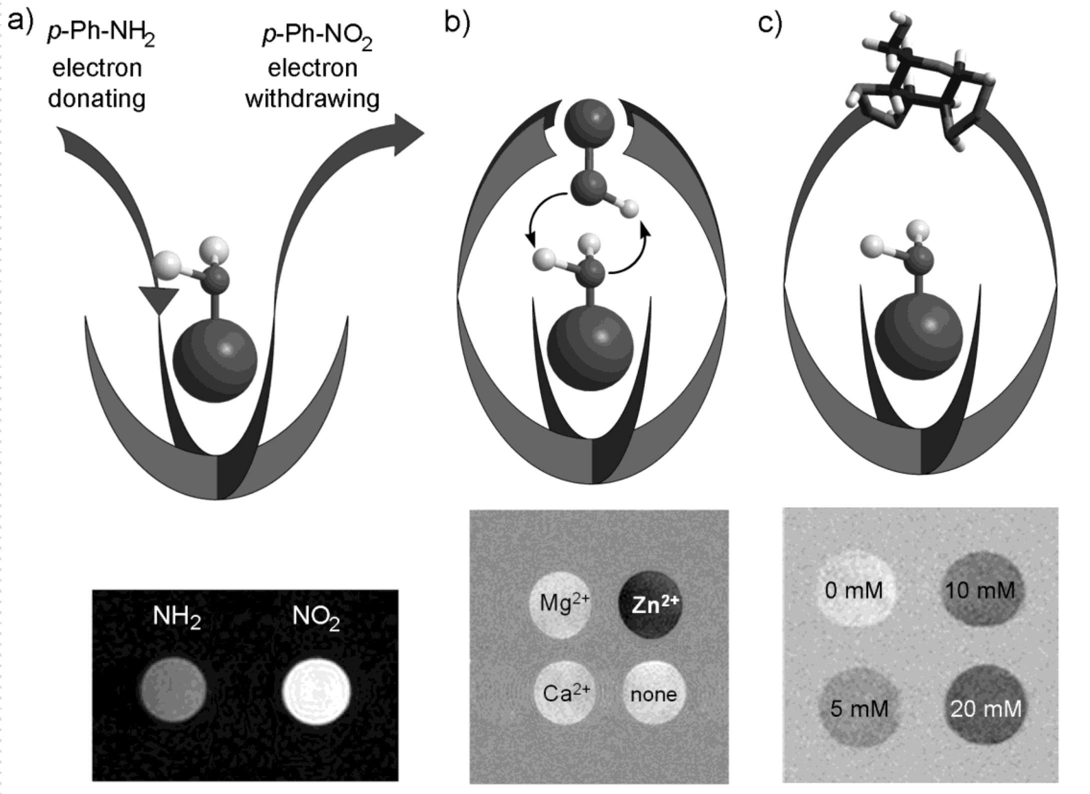


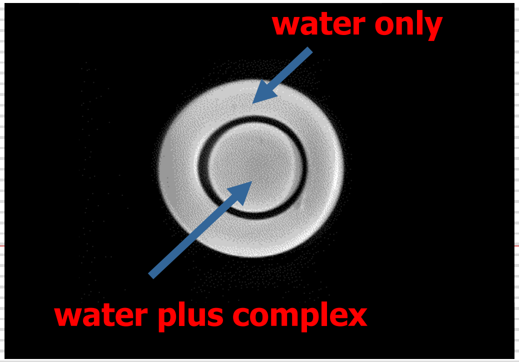
CEST images showing depletion of glycogen in liver after exposure to glucagon

van Zijl, et al., PNAS, 104, 4359-4364 (2007)

PARACEST agents can be turned "on" and "off" using frequency-selective RF pulses





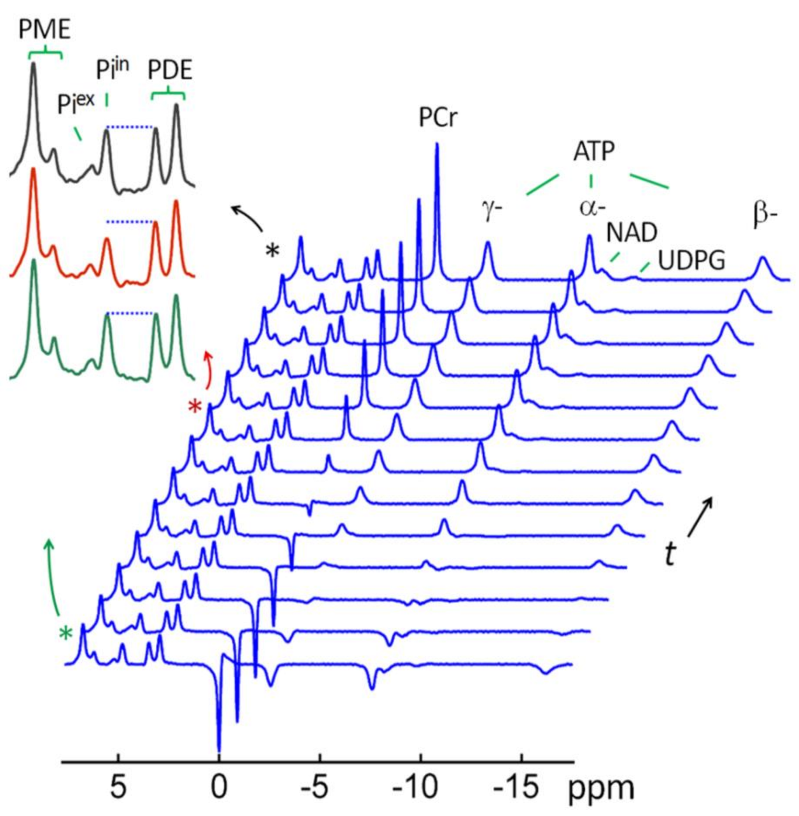


The CEST intensity is highly sensitive to water exchange rates ⇒ relatively easy to design responsive agents

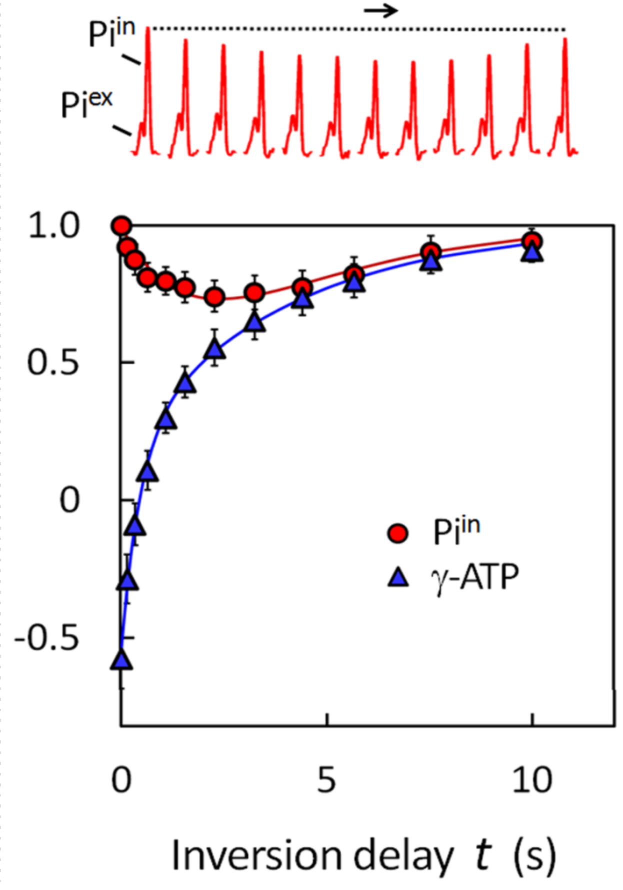
Other lower γ nuclei: ^{31}P, ^{13}C and ^{23}Na

^{31}P MRS of healthy human brain at 7T

J. Ren, et al., NMR Biomed, 2015, DOI: 10.1002/nbm.3384



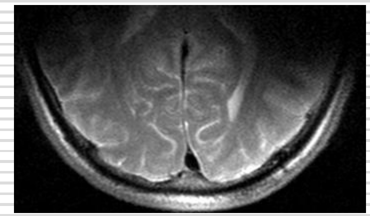
EBIT (Exchange Kinetics by Band Inversion Transfer)

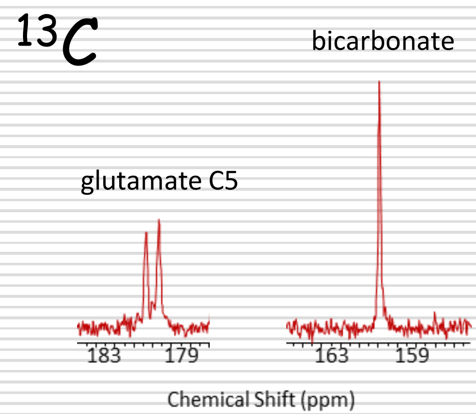


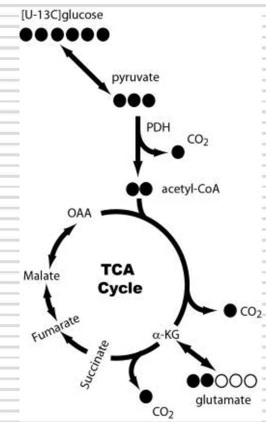
ATP synthesis rate : 9.9 ± 2.1 mmol/min/kg

^{13}C is a unique NMR nucleus for probing intermediary metabolism

Nucleus	Spin	Natural abundance	Rel. NMR sensitivity
^{1}H	1/2	99.9%	100
^{31}P	1/2	100%	6.6
^{23}Na	3/2	100%	9.3
^{13}C	1/2	1.1%	1.7×10^{-2}





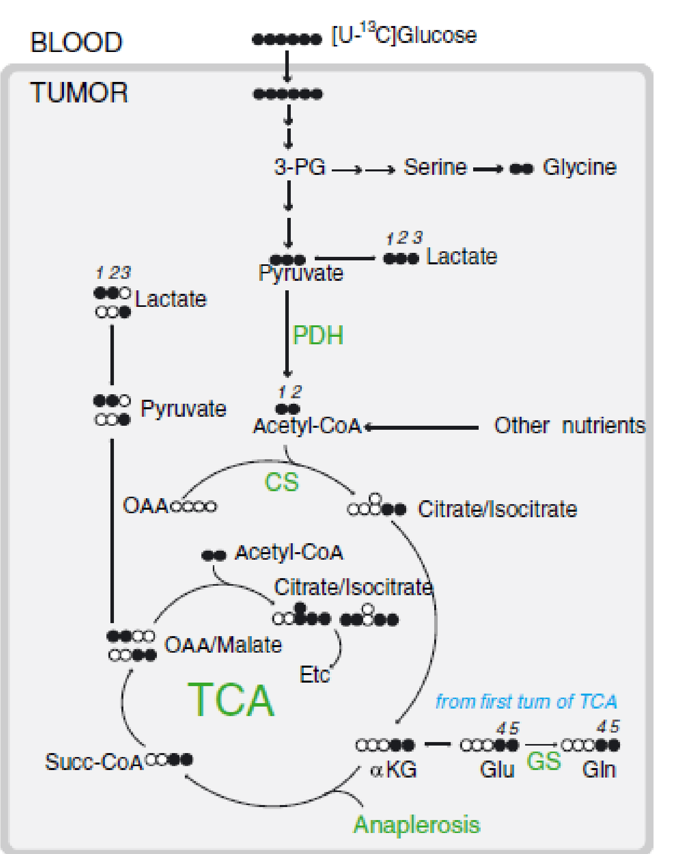


^{13}C can be used as a tracer of metabolism

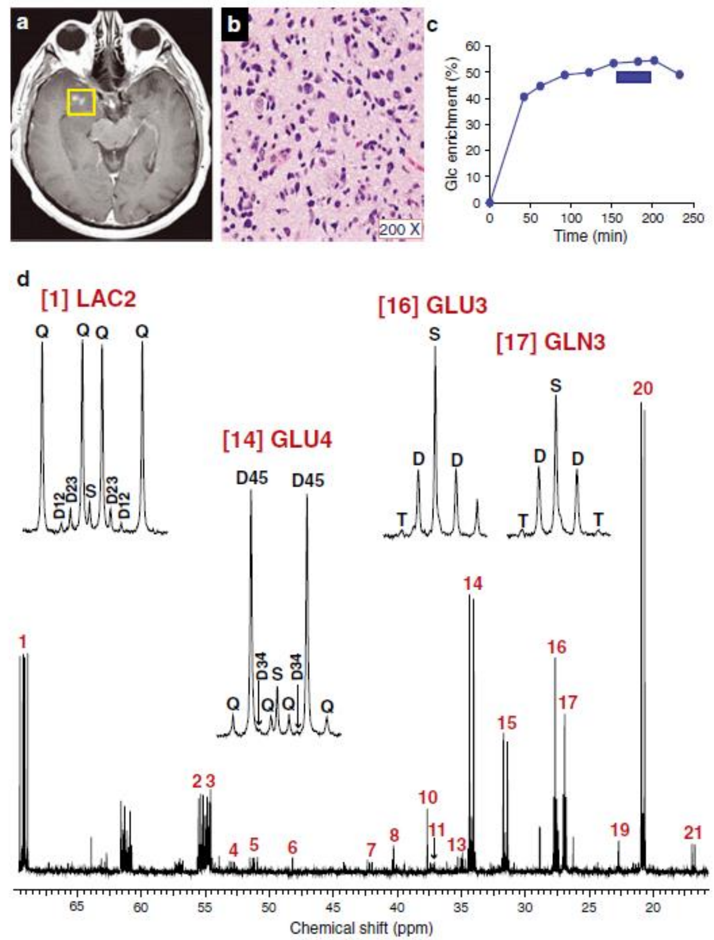
- Steady-state ^{13}C isotopomer methods
- Hyperpolarized ^{13}C tracers

Metabolism of [U-$^{13}C_6$]glucose in human brain tumors *in vivo*

EA Maher, et al., NMR in Biomed. 25: 1234-1244 (2012)



Summary of glucose metabolism in tumors. Filled circles represent a carbon with enriched ^{13}C; open circles reflect ^{12}C



^{13}C NMR spectrum of tumor tissue removed from a patient with a WHO grade II astrocytoma after infusion of [U-^{13}C]glucose for 2 hr prior to surgical resection and during removal (8 g/h)

Summary

- MR contrast agents will continue to be useful at higher magnetic fields. Dy-based T_{2exch} agents may play a bigger role in imaging biological function at high magnetic fields.
- Responsive MRI contrast agents with high sensitivity can be developed for *in vivo* use, provided that water exchange rates are optimized. Zn^{2+} sensitive MRI agents may prove useful for monitoring β-cell function and in detecting prostate tumors.
- CEST & NOE signals from tissues will be greatly magnified at higher magnetic fields. These endogenous contrast mechanisms are sensitive to tissue structures and metabolite contents.
- MRS of lower gamma nuclei will become more important. ^{13}P NMR will provide ATP synthesis rates from local tissue regions. ^{13}C NMR will provide metabolic flux details.