NMR in Medicine:
From Simple Spin Mapping to Precision Medicine

Leif Schröder
Translational Molecular Imaging
DKFZ, Heidelberg
Molecular Systems in Diagnostic Magnetic Resonance
Heidelberg University

Quantum Technologies – Origins and Applications
841. WE-Heraeus-Seminar

Steinbach/Ts., 01.09.2025

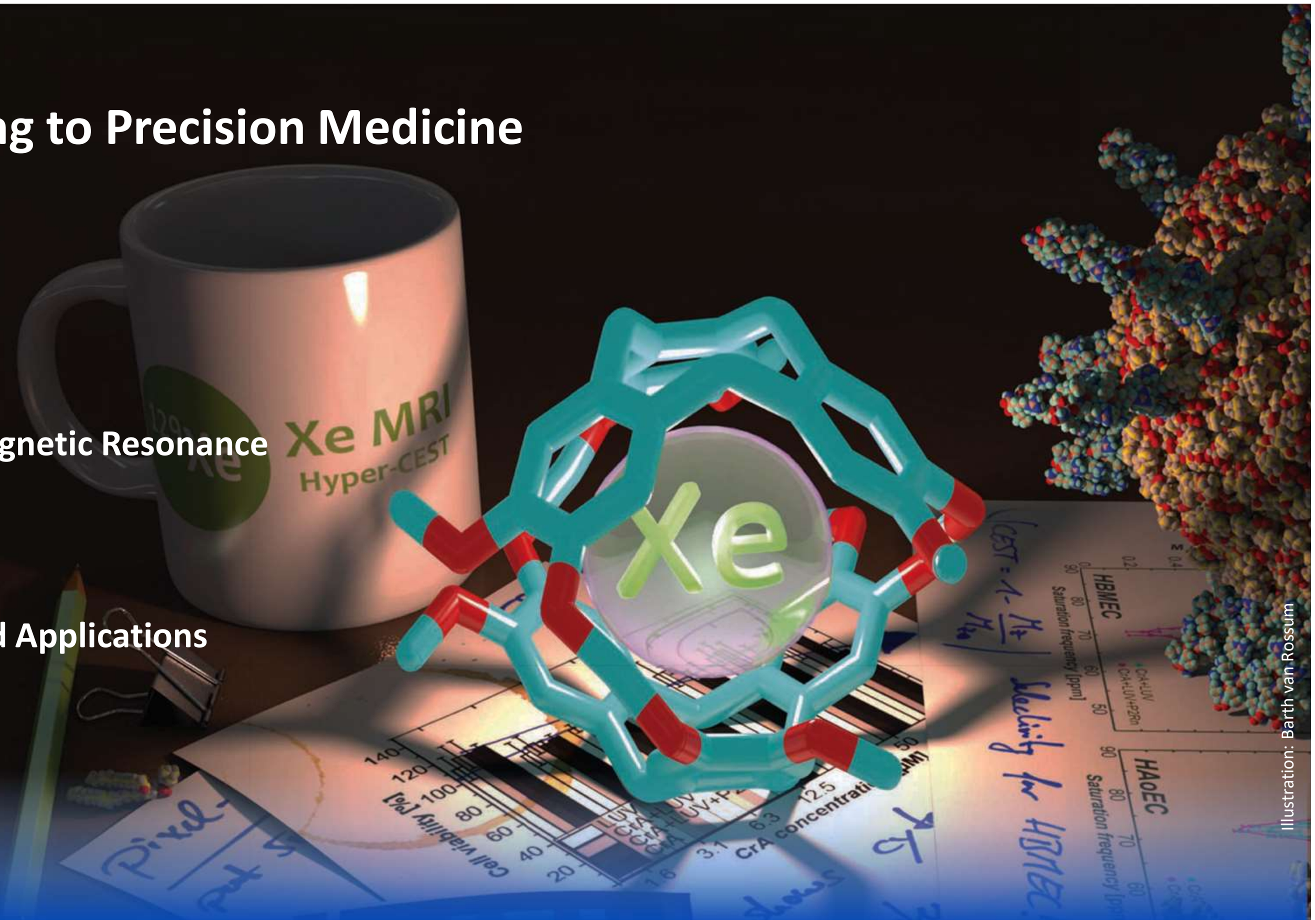

Illustration: Barth van Rossum

TRANSLATIONAL MOLECULAR IMAGING

UNIVERSITÄT HEIDELBERG ZUKUNFT SEIT 1386

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

NMR in Medicine: Past and Present Research

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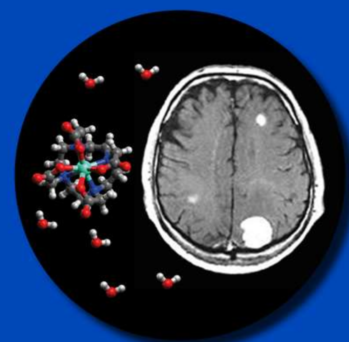
Research for a Life without Cancer

Historic Remarks:

“spin mapping“
and “zeugmatography“

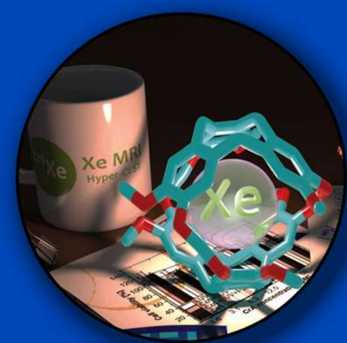


Unsolved Issues:

long term effects
and sensitivity

Mature Applications:

multi-parameter
image contrast



Hyperpolarized Reporters:

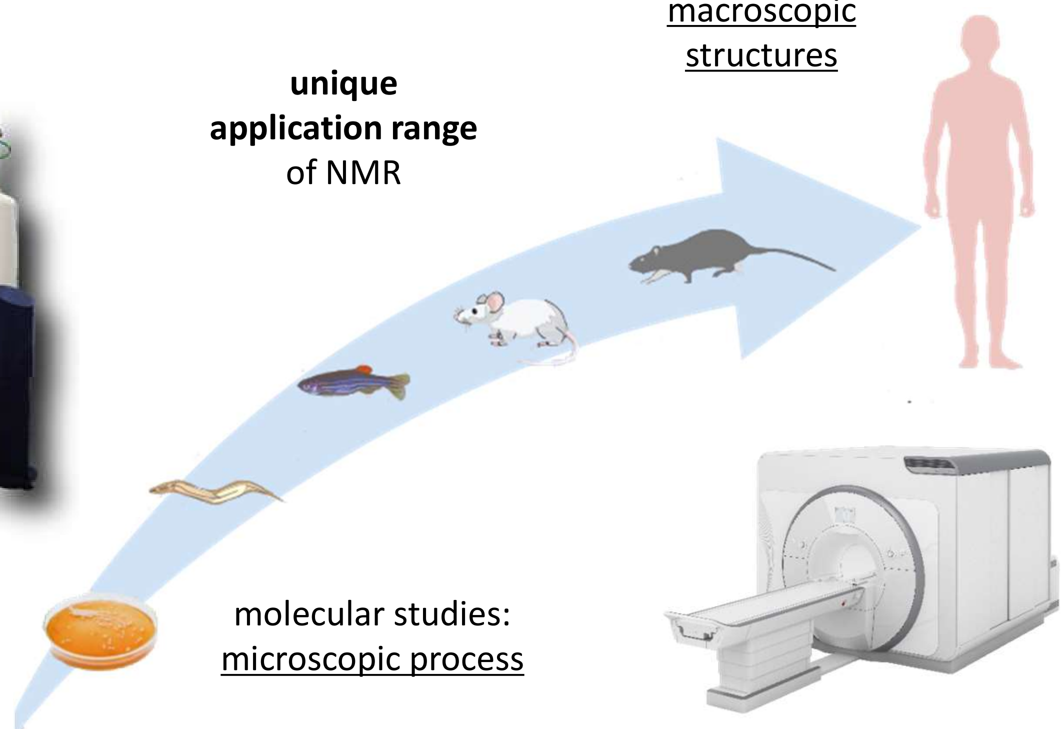
QM effects for
better sensitivity

Undiminished Research Interest in NMR / MRI

non-invasive method

retrieving molecular information from (opaque) samples

no limitations regarding penetration depth



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Historic Remarks

Perception of Scientific Progress

von Békésy, Nobel lecture 1961:

"Helmholtz, in a well-remembered talk, described the **two roads to research**:

- the shaky ladder that every scientist has to climb, and
- the smooth royal path on which the results are presented to an audience."

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Scientific Progress: The Spin Hypothesis

"It means that there is **a fourth degree of freedom for the electron**. It means that the electron has a spin, that it rotates."

G. Uhlenbeck & S. Goudsmit, 1925

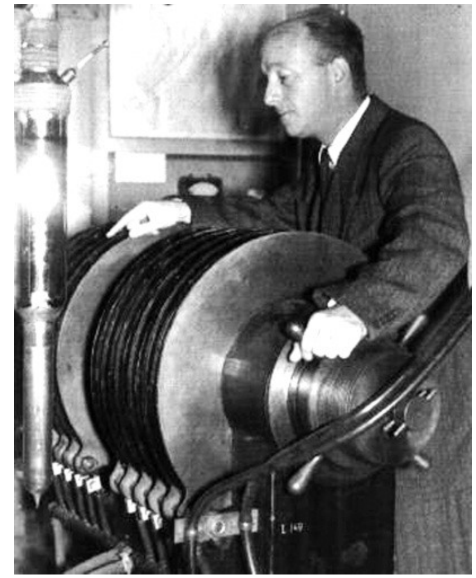
"Well, that is a nice idea, though it may be wrong. But you don't yet have a reputation, so **you have nothing to lose**."

P. Ehrenfest, 1925

Bad Luck in Scientific Discovery

continuous wave NMR:

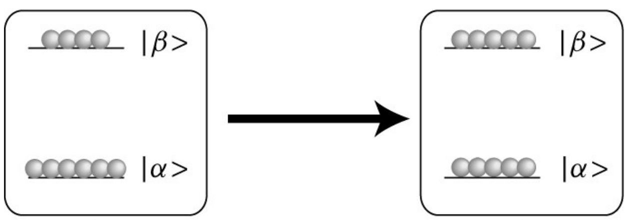
- constant RF signal
- sweeping H_0 to find a resonance condition



C. Gorter

problem:

one might '**saturate**' the system and fail to find the signal



equal population,
NO coherent superposition of $|\alpha\rangle$ and $|\beta\rangle$
(but in CEST: one option to "label" magnetization)

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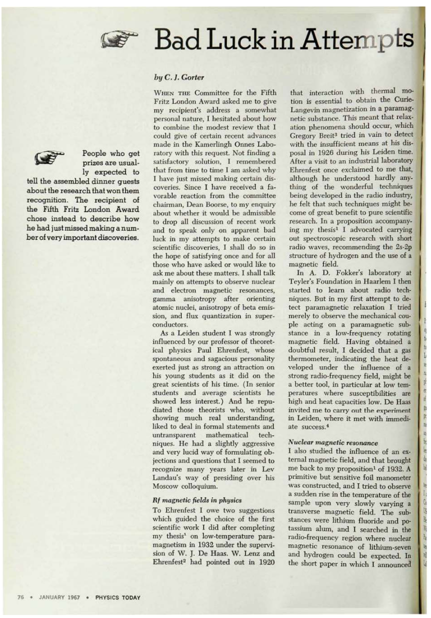
Bad Luck in Scientific Discovery

continuous wave NMR:

- constant RF signal
- sweeping H_0 to find a resonance condition



Bad Luck in Attempts

by C. J. Gorter

People who get prizes are usually expected to tell the assembled dinner guests about the research that won them recognition. The recipient of the Fifth Fritz London Award chose instead to describe how he had just missed making a number of very important discoveries.

When the Committee for the Fifth Fritz London Award asked me to give my recipient's address a somewhat personal nature, I hesitated about how to combine the modest review that I could give of certain recent advances made in the Kamerlingh Onnes Laboratory with this request. Not finding a satisfactory solution, I remembered that from time to time I am asked why I have just missed making certain discoveries. Since I have received a favorable reaction from the committee chairman, Dean Boorse, to my enquiry about whether it would be admissible to drop all discussion of recent work and to speak only on apparent bad luck in my attempts to make certain scientific discoveries, I shall do so in the hope of satisfying once and for all those who have asked or would like to ask me about these matters. I shall talk mainly on attempts to observe nuclear and electron magnetic resonances, gamma anisotropy after orienting atomic nuclei, anisotropy of beta emission, and flux quantization in superconductors.

As a Leiden student I was strongly influenced by our professor of theoretical physics Paul Ehrenfest, whose spontaneous and sagacious personality exerted just as strong an attraction on his young students as it did on the great scientists of his time. (In senior students and average scientists he showed less interest.) And he repudiated those theorists who, without showing much real understanding, liked to deal in formal statements and untransparent mathematical techniques. He had a slightly aggressive and very lucid way of formulating objections and questions that I seemed to recognize many years later in Lev Landau's way of presiding over his Moscow colloquium.

Rf magnetic fields in physics

To Ehrenfest I owe two suggestions which guided the choice of the first scientific work I did after completing my thesis[1] on low-temperature paramagnetism in 1932 under the supervision of W. J. De Haas. W. Lenz and Ehrenfest[2] had pointed out in 1920 that interaction with thermal motion is essential to obtain the Curie-Langevin magnetization in a paramagnetic substance. This meant that relaxation phenomena should occur, which Gregory Breit[3] tried in vain to detect with the insufficient means at his disposal in 1926 during his Leiden time. After a visit to an industrial laboratory Ehrenfest once exclaimed to me that, although he understood hardly anything of the wonderful techniques being developed in the radio industry, he felt that such techniques might become of great benefit to pure scientific research. In a proposition accompanying my thesis[1] I advocated carrying out spectroscopic research with short radio waves, recommending the 2s-2p structure of hydrogen and the use of a magnetic field.

In A. D. Fokker's laboratory at Teyler's Foundation in Haarlem I then started to learn about radio techniques. But in my first attempt to detect paramagnetic relaxation I tried merely to observe the mechanical couple acting on a paramagnetic substance in a low-frequency rotating magnetic field. Having obtained a doubtful result, I decided that a gas thermometer, indicating the heat developed under the influence of a strong radio-frequency field, might be a better tool, in particular at low temperatures where susceptibilities are high and heat capacities low. De Haas invited me to carry out the experiment in Leiden, where it met with immediate success.[4]

Nuclear magnetic resonance

I also studied the influence of an external magnetic field, and that brought me back to my proposition[1] of 1932. A primitive but sensitive foil manometer was constructed, and I tried to observe a sudden rise in the temperature of the sample upon very slowly varying a transverse magnetic field. The substances were lithium fluoride and potassium alum, and I searched in the radio-frequency region where nuclear magnetic resonance of lithium-seven and hydrogen could be expected. In the short paper in which I announced

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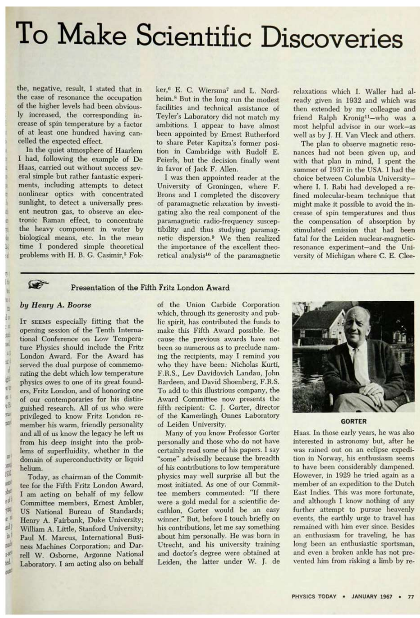


To Make Scientific Discoveries

the, negative, result, I stated that in the case of resonance the occupation of the higher levels had been obviously increased, the corresponding increase of spin temperature by a factor of at least one hundred having cancelled the expected effect.

In the quiet atmosphere of Haarlem I had, following the example of De Haas, carried out without success several simple but rather fantastic experiments, including attempts to detect nonlinear optics with concentrated sunlight, to detect a universally present neutron gas, to observe an electronic Raman effect, to concentrate the heavy component in water by biological means, etc. In the mean time I pondered simple theoretical problems with H. B. G. Casimir,[5] Fokker,[6] E. C. Wiersma[7] and L. Nordheim.[8] But in the long run the modest facilities and technical assistance of Teyler's Laboratory did not match my ambitions. I appear to have almost been appointed by Ernest Rutherford to share Peter Kapitza's former position in Cambridge with Rudolf E. Peierls, but the decision finally went in favor of Jack F. Allen.

I was then appointed reader at the University of Groningen, where F. Brons and I completed the discovery of paramagnetic relaxation by investigating also the real component of the paramagnetic radio-frequency susceptibility and thus studying paramagnetic dispersion.[9] We then realized the importance of the excellent theoretical analysis[10] of the paramagnetic relaxations which I. Waller had already given in 1932 and which was then extended by my colleague and friend Ralph Kronig[11]—who was a most helpful advisor in our work—as well as by J. H. Van Vleck and others.

The plan to observe magnetic resonances had not been given up, and with that plan in mind, I spent the summer of 1937 in the USA. I had the choice between Columbia University—where I. I. Rabi had developed a refined molecular-beam technique that might make it possible to avoid the increase of spin temperatures and thus the compensation of absorption by stimulated emission that had been fatal for the Leiden nuclear-magnetic-resonance experiment—and the University of Michigan where C. E. Clee-

Presentation of the Fifth Fritz London Award

by Henry A. Boorse

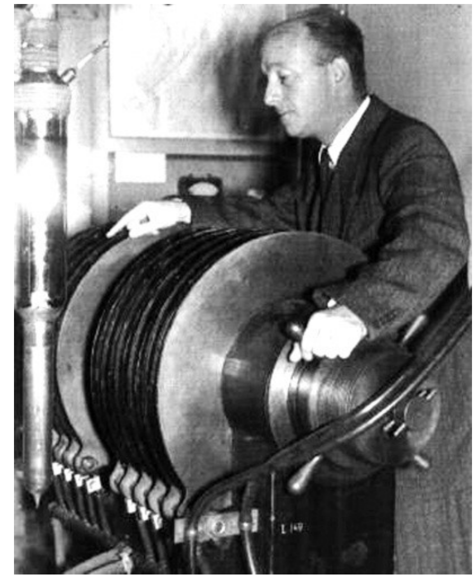
It seems especially fitting that the opening session of the Tenth International Conference on Low Temperature Physics should include the Fritz London Award. For the Award has served the dual purpose of commemorating the debt which low temperature physics owes to one of its great founders, Fritz London, and of honoring one of our contemporaries for his distinguished research. All of us who were privileged to know Fritz London remember his warm, friendly personality and all of us know the legacy he left us from his deep insight into the problems of superfluidity, whether in the domain of superconductivity or liquid helium.

Today, as chairman of the Committee for the Fifth Fritz London Award, I am acting on behalf of my fellow Committee members, Ernest Ambler, US National Bureau of Standards; Henry A. Fairbank, Duke University; William A. Little, Stanford University; Paul M. Marcus, International Business Machines Corporation; and Darrell W. Osborne, Argonne National Laboratory. I am acting also on behalf of the Union Carbide Corporation which, through its generosity and public spirit, has contributed the funds to make this Fifth Award possible. Because the previous awards have not been so numerous as to preclude naming the recipients, may I remind you who they have been: Nicholas Kurti, F.R.S., Lev Davidovich Landau, John Bardeen, and David Shoenberg, F.R.S. To add to this illustrious company, the Award Committee now presents the fifth recipient: C. J. Gorter, director of the Kamerlingh Onnes Laboratory of Leiden University.

Many of you know Professor Gorter personally and those who do not have certainly read some of his papers. I say "some" advisedly because the breadth of his contributions to low temperature physics may well surprise all but the most initiated. As one of our Committee members commented: "If there were a gold medal for a scientific decathlon, Gorter would be an easy winner." But, before I touch briefly on his contributions, let me say something about him personally. He was born in Utrecht, and his university training and doctor's degree were obtained at Leiden, the latter under W. J. de Haas. In those early years, he was also interested in astronomy but, after he was rained out on an eclipse expedition in Norway, his enthusiasm seems to have been considerably dampened. However, in 1929 he tried again as a member of an expedition to the Dutch East Indies. This was more fortunate, and although I know nothing of any further attempt to pursue heavenly events, the earthly urge to travel has remained with him ever since. Besides an enthusiasm for traveling, he has long been an enthusiastic sportsman, and even a broken ankle has not prevented him from risking a limb by re-

GORTER

PHYSICS TODAY • JANUARY 1967 • 77



C. Gorter

article on the occasion of 5th Fritz London Award

C. J. Gorter, H. A. Boorse, *Physics Today* **1967**, *20*, 76–81.

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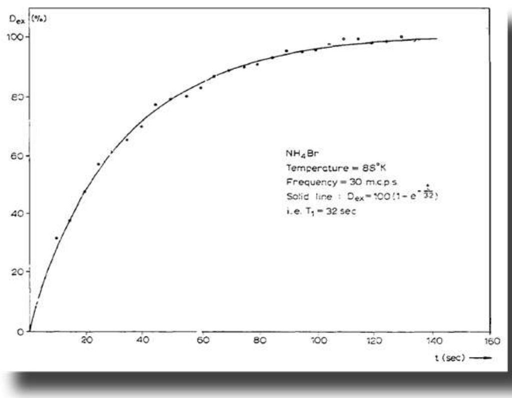
First Condensed Matter Applications

F. Bloch

Nobel Prize 1952 banquet speech

"I am sure my fellow-scientists will agree with me if I say that whatever we were able to achieve in our later years had its origin in the experiences of our youth and in the hopes and wishes which were formed before and during our time as students… **Free imagination** is the inestimable prerogative of youth and it must be cherished and **guarded as a treasure**."

E. Purcell



recovery of longitudinal magnetization in an external magnetic field – today's basis of the contrast of many MR images

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Scientific Progress in “Layers of Experimental Complexity“

SCIENCE ADVANCES | FOCUS

Alexander Pines and the end of an era

Warren S. Warren*

“To find the breakthroughs in medicine in 10 years, biomedical researchers looked to chemistry; to find the ones in 20 years, they looked to physics.“

→ NMR soon found applications outside physics

W. S. Warren, *Science Advances* 2025, **11**, eadw3504.

The Early Link of NMR to Biomedical Applications

… soon after making his discovery **Bloch poked his finger into the coil** of his spectrometer and got an NMR signal (1946). In 1948, **Purcell and a fellow scientist wrapped their heads with a coil** attached to a radio frequency generator and then stuck them in the field of the Harvard cyclotron.

"The only thing they sensed as they shoved their heads in and out of the magnet was the magnetic field that was generated in the metal filling of their teeth"

"I had more signal in my finger than Purcell in his whole head"

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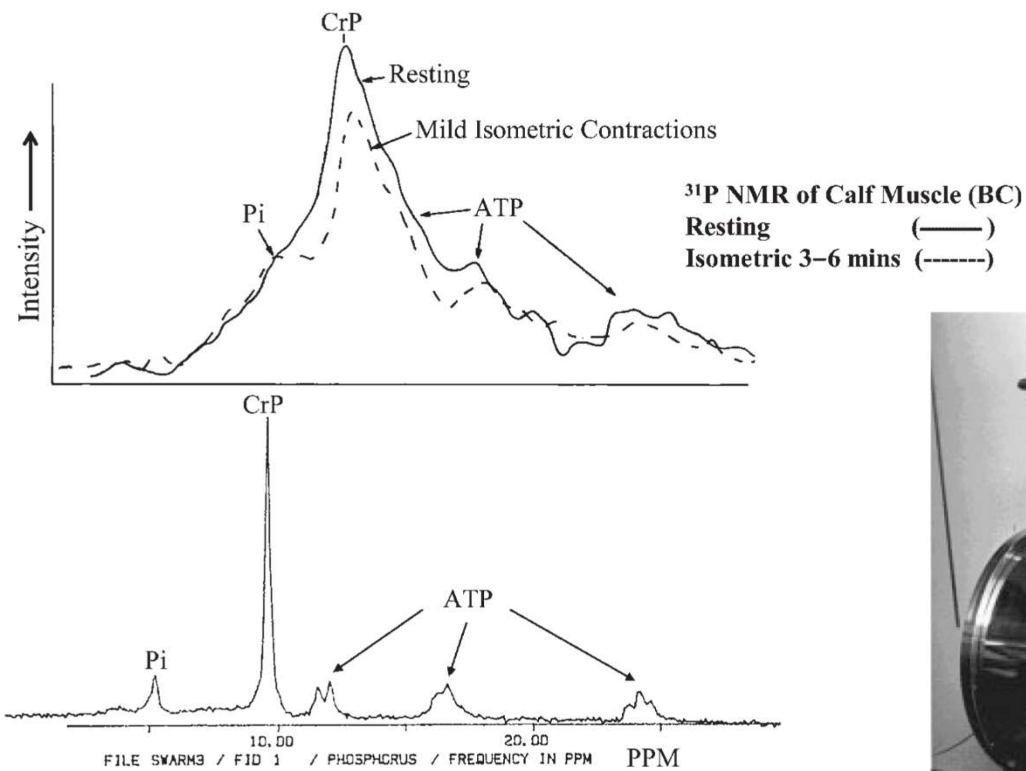
Early Biomedical Applications: A Glimpse into Biochemistry



NMR applications on living tissues started early

^{31}P muscle NMR in 1979 and 1982

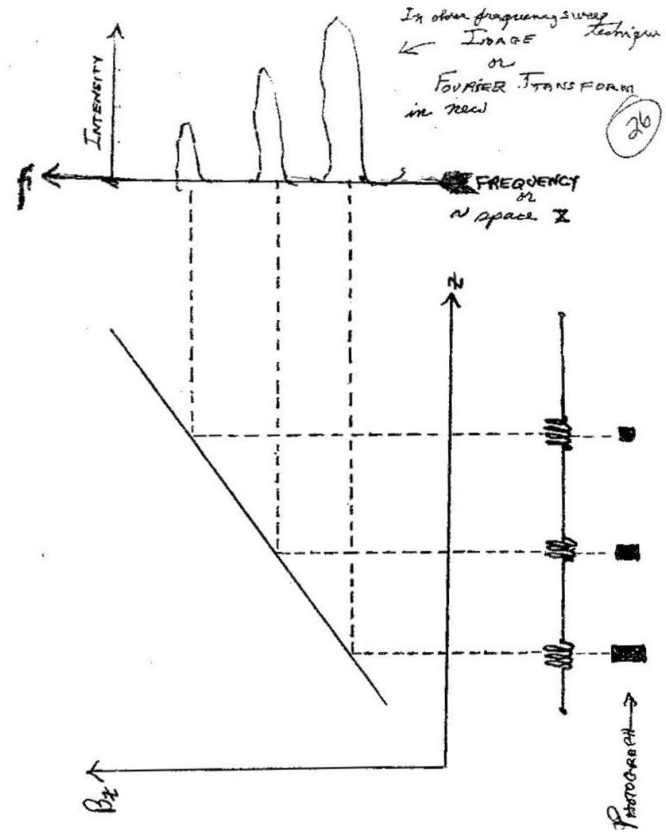
Chance et al. *NMR Biomed.* **19**: 904 (2006)

First Imaging Ideas

Carr proposes in the **1950s** gradients for ‘spin mapping’

nobody recognizes the potential for diagnostic imaging

imaging applications of NMR do not emerge until the 1970s



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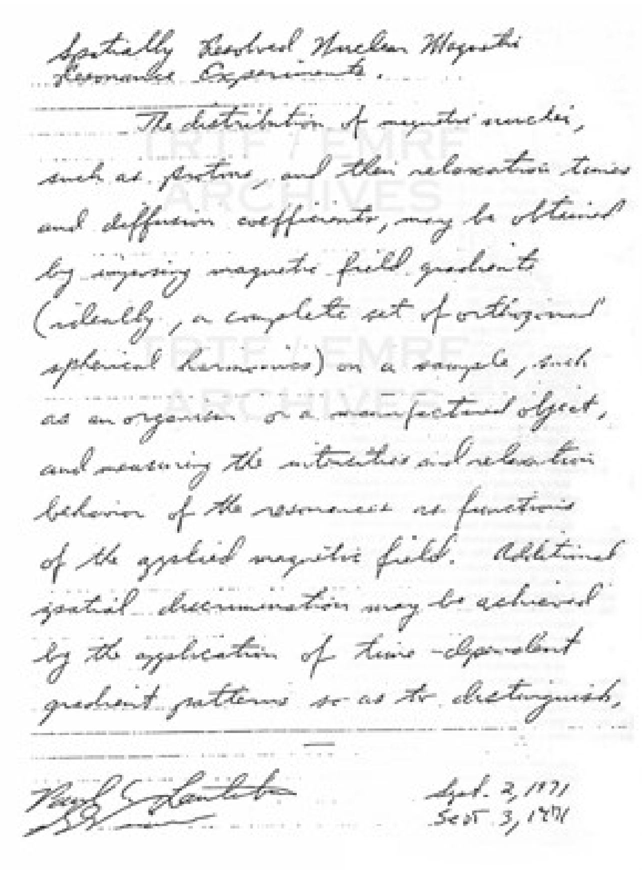
Zeugmatography Approach

Lauterbur’s lab notebook:

Spatially Resolved Nuclear Magnetic Resonance Experiments

The **distribution of magnetic nuclei**, such as protons, and their relocation times and diffusion coefficients, may be obtained by impairing **magnetic field gradients** (ideally, a complete set of orthogonal spherical harmonics) on a sample, such as an organism or a manufactured object, and **measuring the intensities and relaxation behavior** of the resonances as functions of the applied magnetic field. Additional **spatial discrimination may be achieved by the application of time-dependent gradient patterns** so as to distinguish, …


Spatially Resolved Nuclear Magnetic Resonance Experiments.
The distribution of magnetic nuclei, such as protons, and their relaxation times and diffusion coefficients, may be obtained by imposing magnetic field gradients (ideally, a complete set of orthogonal spherical harmonics) on a sample, such as an organism or a manufactured object, and measuring the intensities and relaxation behavior of the resonances as functions of the applied magnetic field. Additional spatial discrimination may be achieved by the application of time-dependent gradient patterns so as to distinguish,

Sept. 2, 1971
Sept. 3, 1971

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Zeugmatography Approach

1973: Lauterbur maps two water tubes reconstructed from four different projections by applying a gradient in four different directions

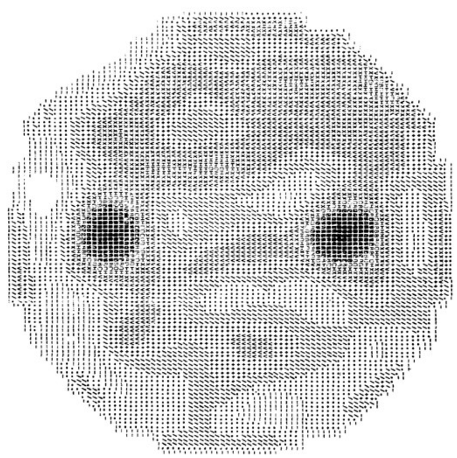

Figure 1. Proton n.m.r. zeugmatogram of two 1 mm capillaries of water in a 4.2 mm inside diameter tube containing a mixture of H_2O and D_2O.

NATURE VOL. 242 MARCH 16 1973

Image Formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance

AN image of an object may be defined as a graphical representation of the spatial distribution of one or more of its properties. Image formation usually requires that the object interact with a matter or radiation field characterized by a wavelength comparable to or smaller than the smallest features to be distinguished, so that the region of interaction may be restricted and a resolved image generated.

This limitation on the wavelength of the field may be removed, and a new class of image generated, by taking advantage of induced local interactions. In the presence of a second field that restricts the interaction of the object with the first field to a limited region, the resolution becomes independent of wavelength, and is instead a function of the ratio of the normal width of the interaction to the shift produced by a gradient in the second field. Because the interaction may be regarded as a coupling of the two fields by the object, I propose that image formation by this technique be known as zeugmatography, from the Greek ζευγμα, "that which is used for joining".

Lauterbur *et al. Nature* **242**: 190 (1973)

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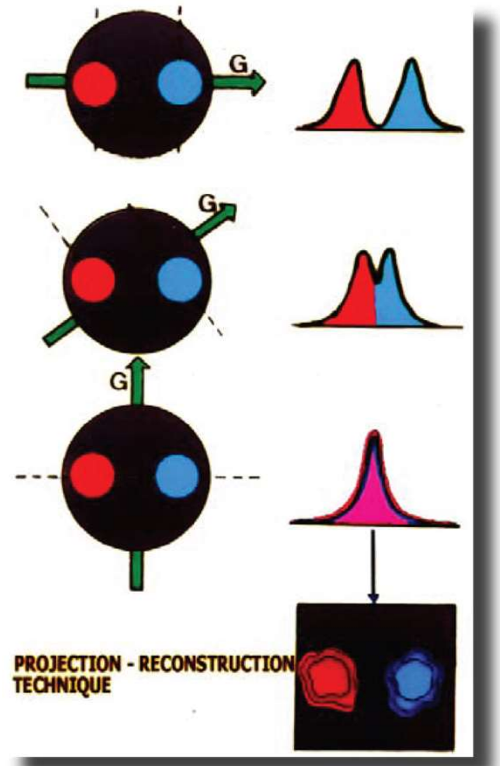
A Long Journey to Imaging Applications …

Imaging small objects with radiowaves?

„I congratulate you on **eventually giving in to my anguish**."

P. Lauterbur to the editor of *Nature*

projection imaging of water-filled tubes



Lauterbur *et al.* *Nature* **242**: 190 (1973)

… and their Scientific Recognition

Nobel Prize 2003 for modern techniques of MRI encoding

„I congratulate you on **eventually giving in to my anguish**."

P. Lauterbur to the editor of *Nature*

„… some people even dismissed it as being **improbable nonsense**."

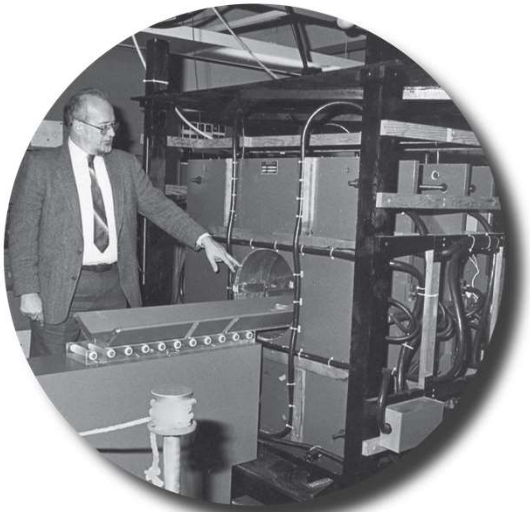
P. Mansfield

fast cardiac imaging

The Power of NMR

„There is nothing that nuclear spins will not do for you, as long as you **treat them as human beings.**"

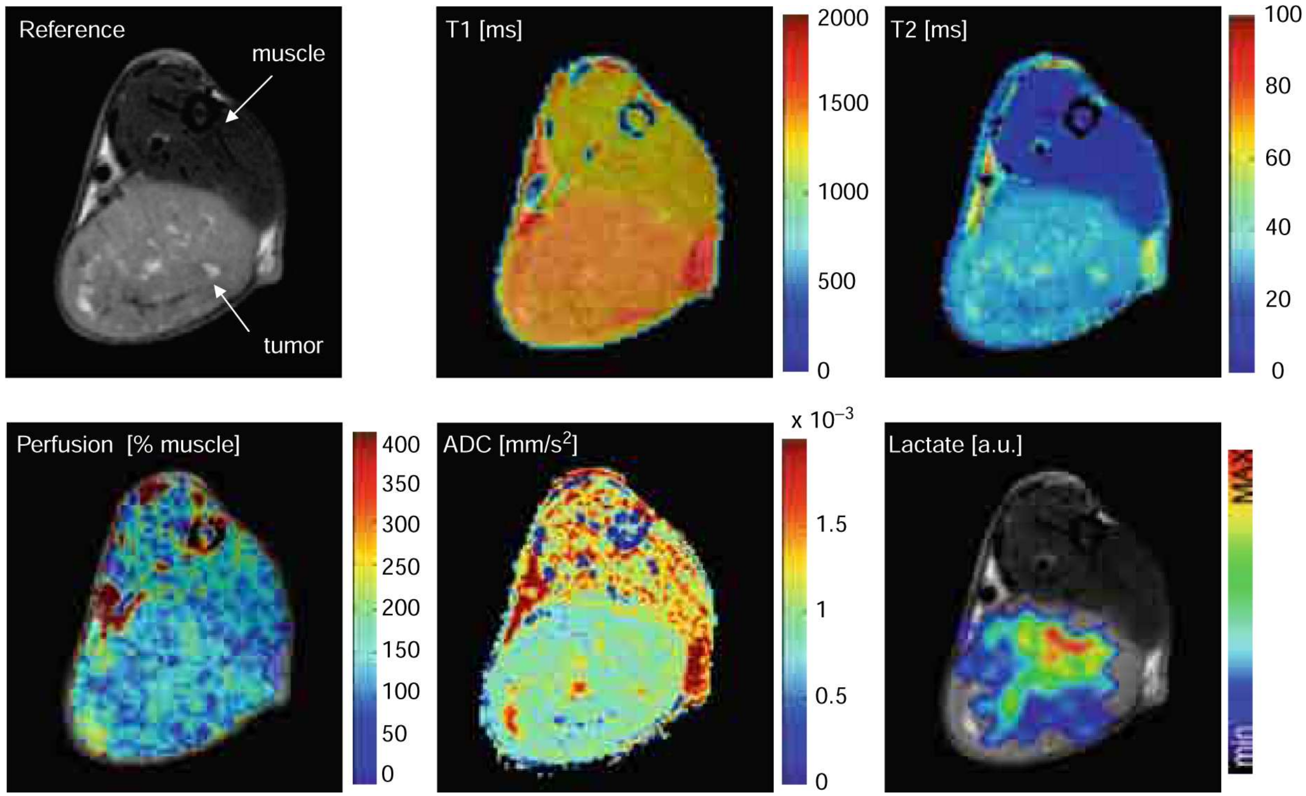
E. Hahn



Basic concept of (conventional) NMR / MRI measurements:

- Perturbation of thermal equilibrium
- Evolution under $\hat{H}_{int}$ and $\hat{H}_{ext}$
- Readout of the induction signal

MRI – The Classic Contrast Portfolio



visualization of various parameters by **careful manipulation of the magnetization**

wide range of morphological and functional contrast

Kiessling, Pichler (Editors), Small Animal Imaging, Springer

From (Doubted) Spin Physics to Real World Applications

- approx. 50,000 MR scanners in use worldwide (2022)
- estimated market volume: approx. 9 billion US$ by 2030
- 95 million images in 2022
- excellent soft tissue contrast allows incomparably good diagnostics for many issues

"You don't believe that the setting of atoms is something physically real, it's a **calculation rule**, the timetable of electrons."

P. Debye to W. Gerlach

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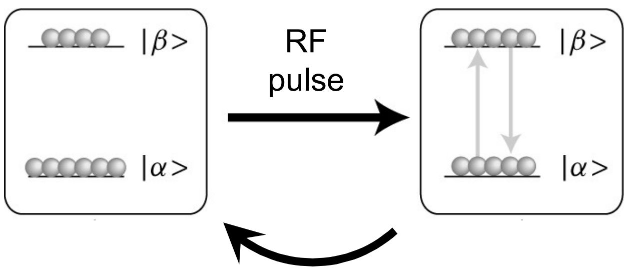
Mature Applications

Nuclear Spins as Spies for the Local Environment

$$\omega = \gamma \boldsymbol{B} = \gamma(\boldsymbol{B_0} + \boldsymbol{B_{loc}})$$

changes in state populations + coherences

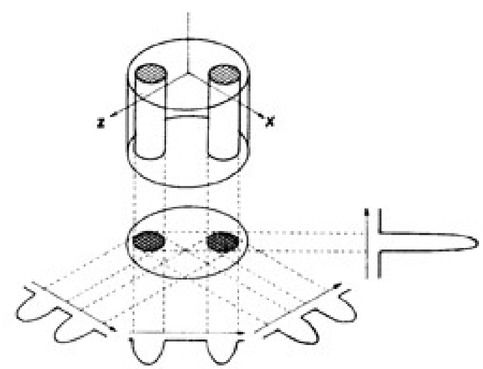
- external excitation → (selective) RF pulses
- internal relaxation → matching molecular dynamics
- dephasing, external → flow + diffusion encoding



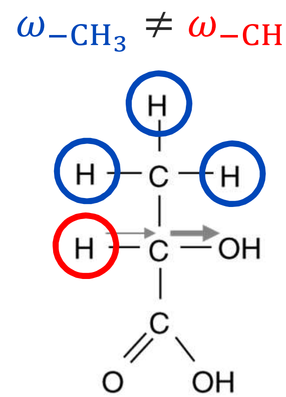
spontaneous/enforced relaxation
coherence decay, polarization recovery

changes in Larmor frequency

- external components → image encoding
- intrinsic components → chemical shift



external



intrinsic

MRI Based on Endogenous Water

destruction-free tomographic imaging of delicate samples based on ^1H_2O magnetization

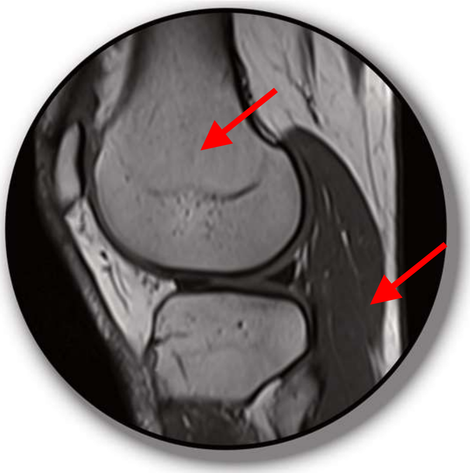
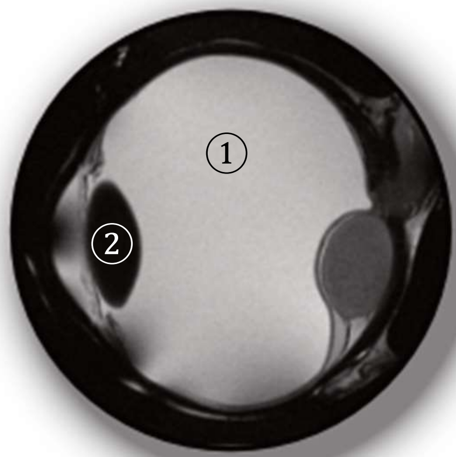


image contrast:

intrinsic differences in magnetization recovery

$$\frac{dM_{\text{muscle}}}{dt} \neq \frac{dM_{\text{bone}}}{dt}$$



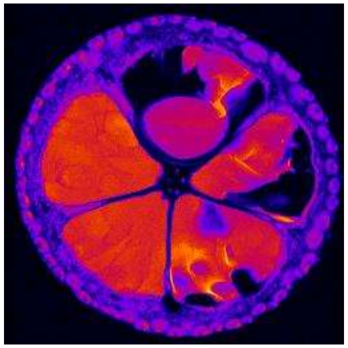
① liquid like
② solid like

oncology application:

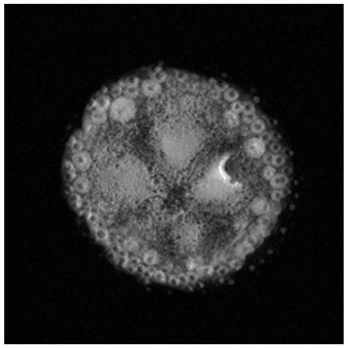
ex vivo tumour illustration of collapsible object

(coop. w/ O. Stachs, U Rostock)

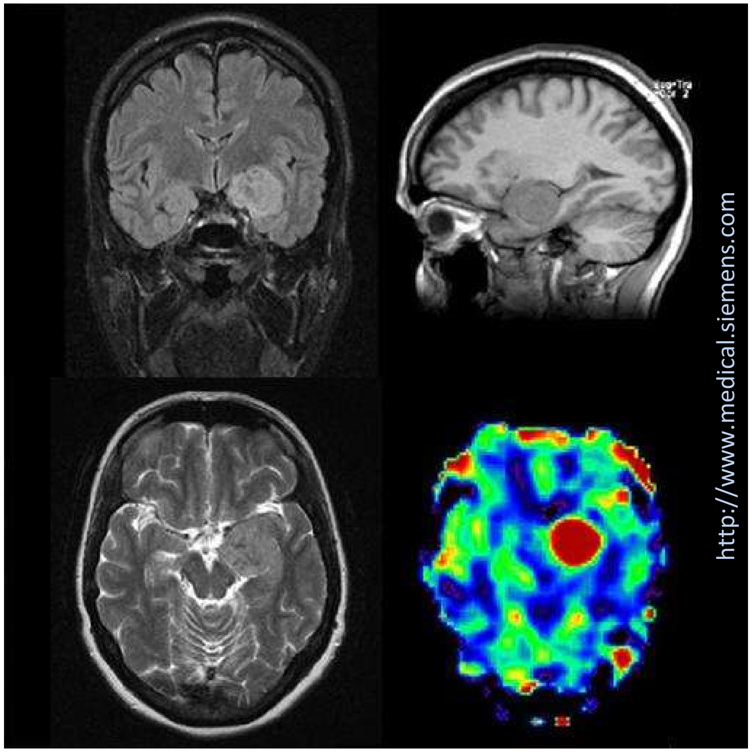
MRI Based on Endogenous Water



morphology

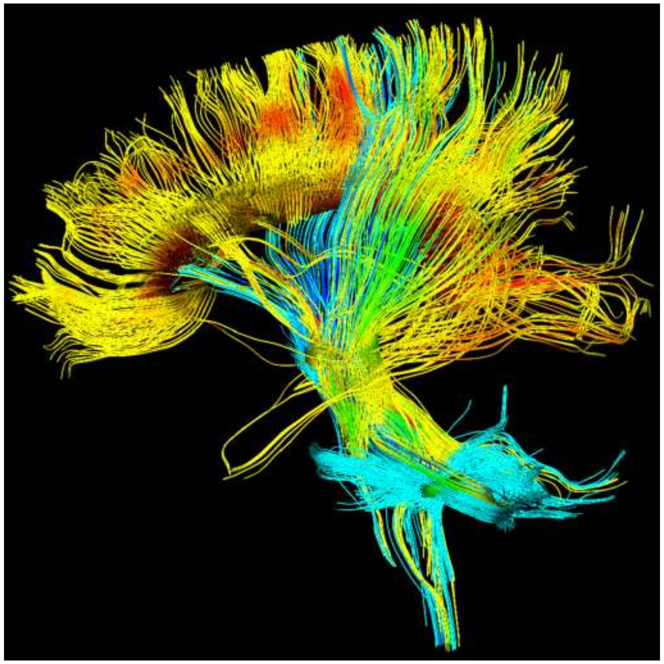


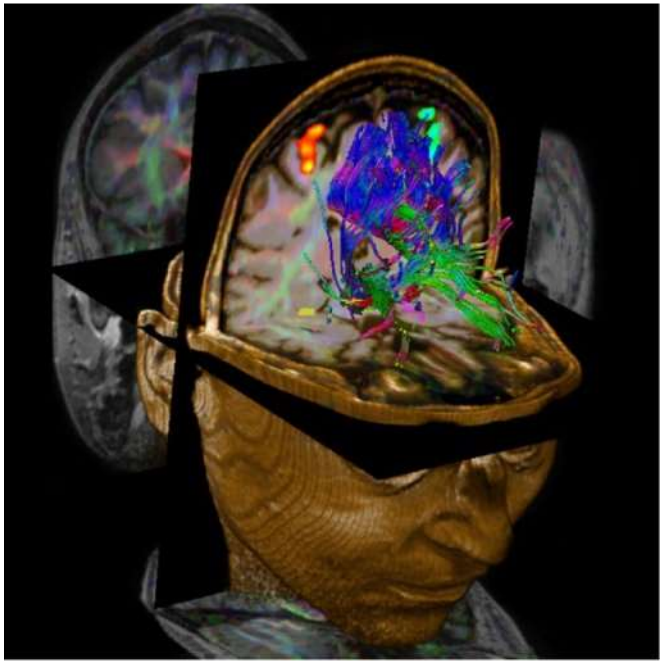
adjustable contrast



physiologic parameter: perfusion

MRI Based on Endogenous Water





physiologic parameter: diffusion

http://www.medical.siemens.com

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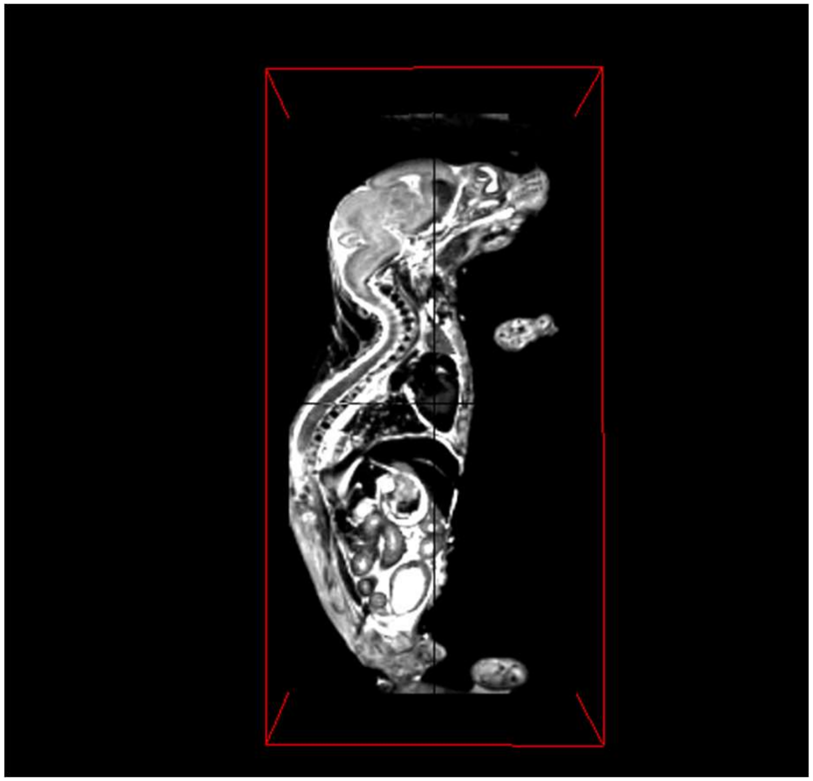
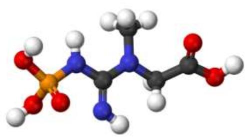
Pre-Clinical Micro-Imaging with Freedom of 3D Reconstruction

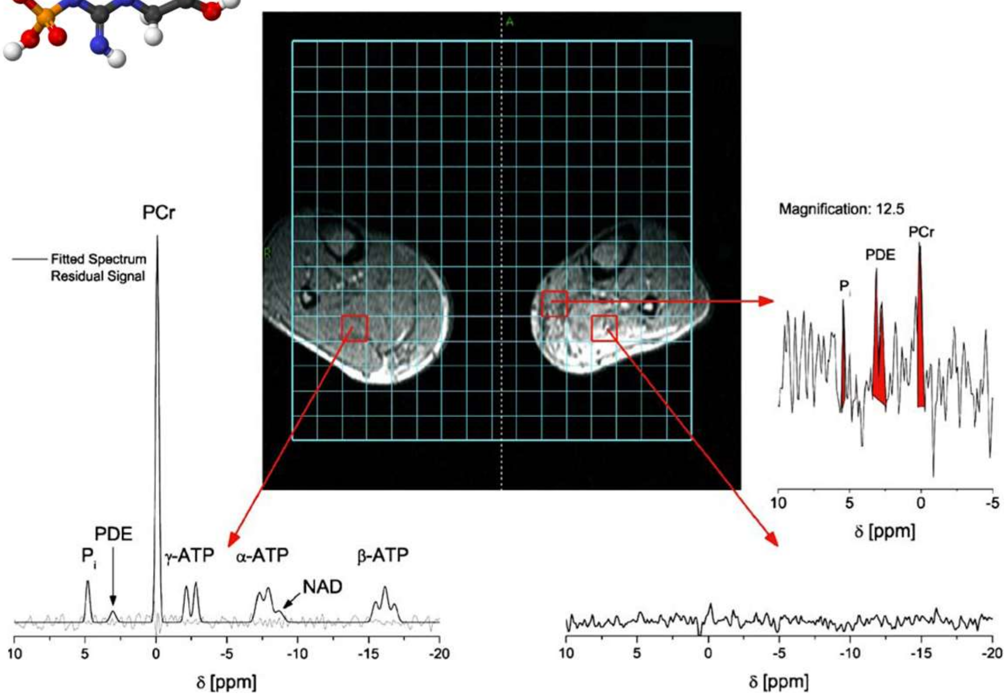


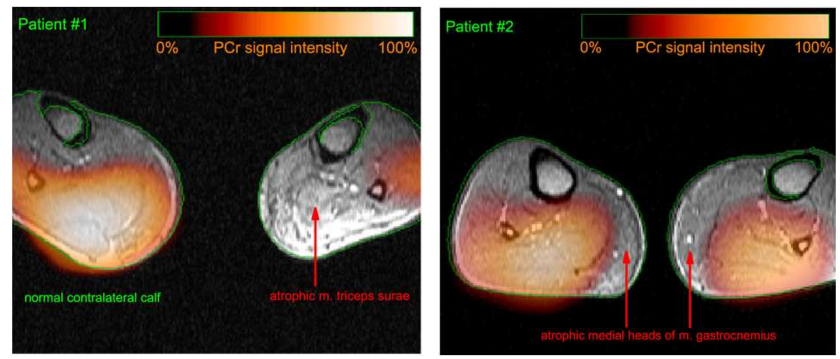
newborn mouse pup

50 µm isotropic resolution

^{31}P MRS in Clinical NMR Revealing Tissue Biochemistry







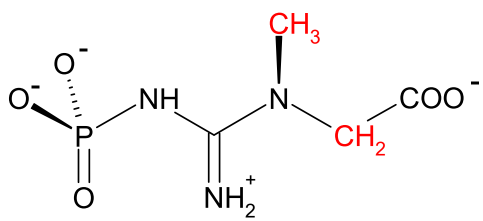
non-invasive mapping of metabolic state
can replace (painful) electrophysiology test

atrophic tissue:
breakdown of high energy
phosphorous metabolism

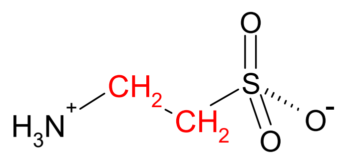
Schröder et al., *Neuroradiology* **48**: 809-816 (2006)

Residual Dipolar Couplings in ^{1}H NMR Spectra

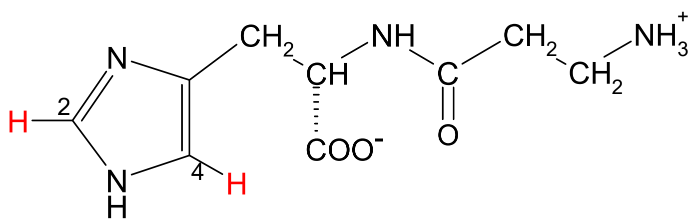
Phosphocreatine



Taurine



L-Carnosine



(phospho)creatine

- buffer for high-energy metabolism in terms of ADP → ATP synthesis

taurine

- stabilization of cell membrane (osmoregulation)
- regulation of Ca^{2+} ion binding to phospholipids of cell membrane

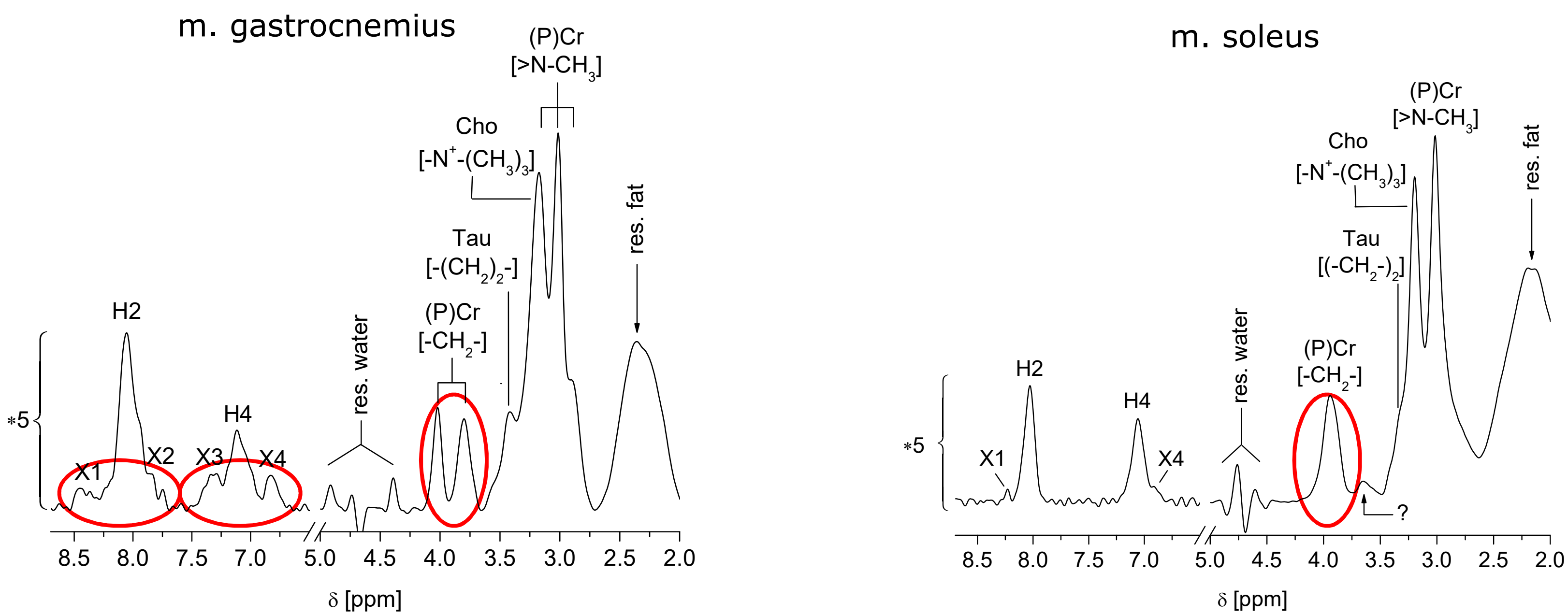
carnosine

- importand pH buffer during muscle contraction in certain species
- activation of Ryanodine receptors (Ca-release channels)

dkfz.

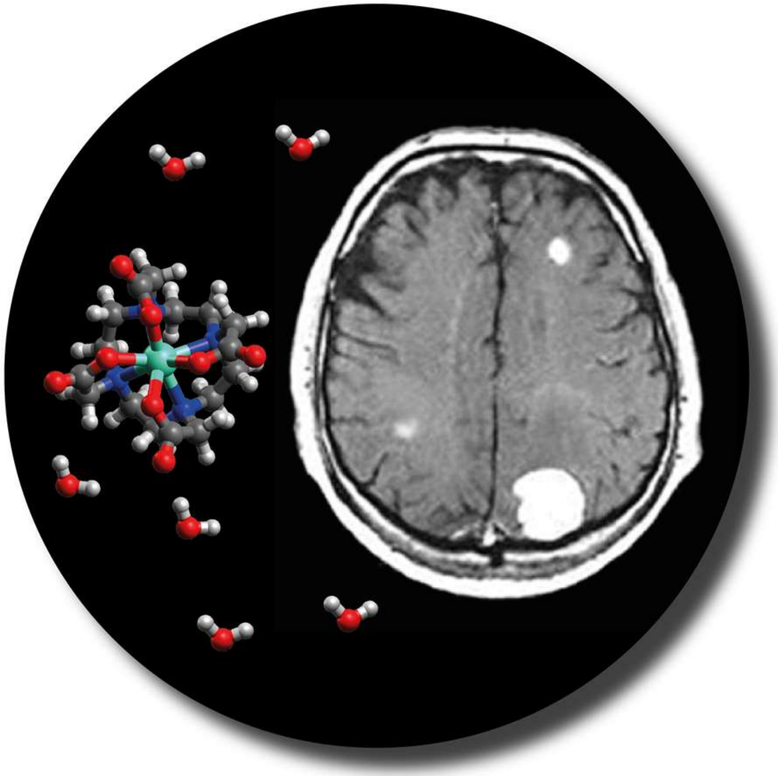
QM Fine Structure in Liquid Crystal-Like Tissue

residual dipolar spin-spin interactions due to restricted molecular mobility

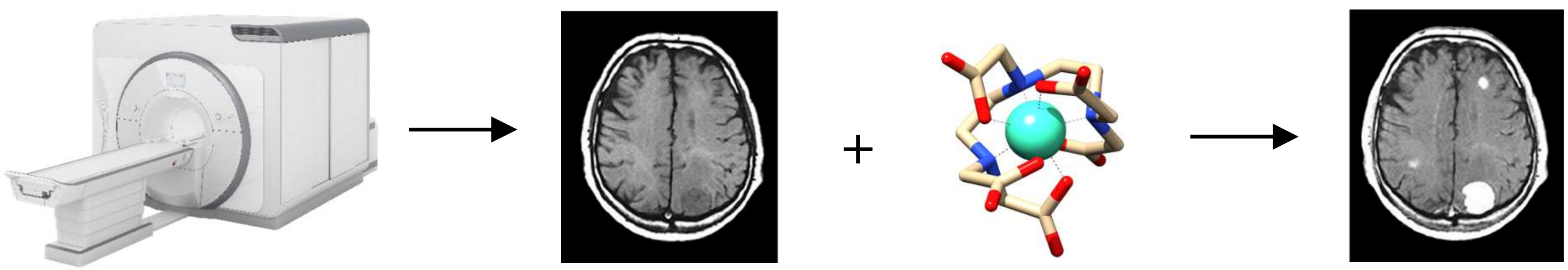


Schröder et al. *J. Magn. Reson.* **164**: 256-269 (2003)

Unsolved Issues



MRI with Gd-based Contrast Agents (GBCAs)



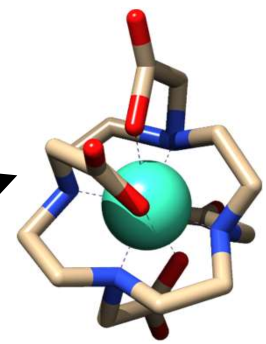
increased uptake in tumor tissue
vs. normal tissue

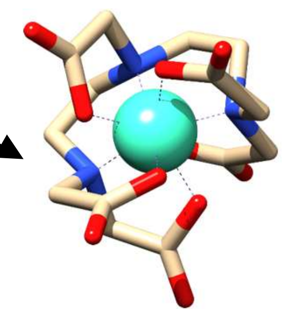
- global contrast agents market size:
  US$ 4.25 billion in 2016
- annual use: 50 t of Gd
- oligopolistic in nature, including:
  Bayer, GE Healthcare, Guerbet, Lantheus Medical Imaging, and Bracco Diagnostics
  (Σ > 60% share in the market)

Types of GBCAs

FDA-Approved GBCAs

Brand name	Generic name	Structure
Ablavar	gadofosveset trisodium	linear
Dotarem	gadoterate meglumine	macrocyclic
Eovist	gadoxetate disodium	linear
Gadavist	gadobutrol	macrocyclic
Magnevist	gadopentetate dimeglumine	linear
MultiHance	gadobenate dimeglumine	linear
Omniscan	gadodiamide	linear
OptiMARK	gadoversetamide	linear
ProHance	gadoteridol	macrocyclic



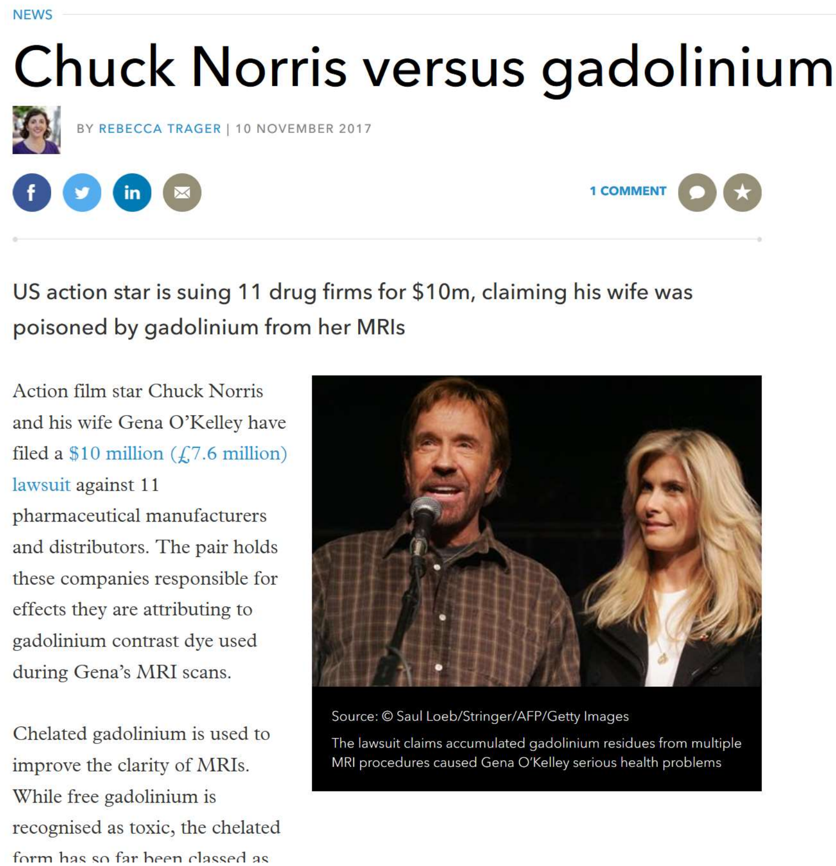


Routine MRI and the GBCA Market

typical relaxivity r_1:
~ 3.5 $mM^{-1}s^{-1}$ (20 MHz, 39°C)

clear contrast: minimum $\Delta R_1 = r_1 \times [GBCA] = 0.5\ s^{-1}$
→ ca. 140 µM required min. concentration

dosage up to 0.3 mmol/kg for angiography (multiple exams!)



NEWS

Chuck Norris versus gadolinium

BY REBECCA TRAGER | 10 NOVEMBER 2017

1 COMMENT

US action star is suing 11 drug firms for $10m, claiming his wife was poisoned by gadolinium from her MRIs

Action film star Chuck Norris and his wife Gena O'Kelley have filed a $10 million (£7.6 million) lawsuit against 11 pharmaceutical manufacturers and distributors. The pair holds these companies responsible for effects they are attributing to gadolinium contrast dye used during Gena's MRI scans.

Source: © Saul Loeb/Stringer/AFP/Getty Images
The lawsuit claims accumulated gadolinium residues from multiple MRI procedures caused Gena O'Kelley serious health problems

Chelated gadolinium is used to improve the clarity of MRIs. While free gadolinium is recognised as toxic, the chelated form has so far been classed as

dkfz.

Molecular Fate of GBCAs

However, it is now well established that **not all of the injected dose is eliminated**, and in some instances the presence of gadolinium can cause a delayed onset toxic effect.
Yet our **understanding of the fate of GBCAs in the human body remains limited**.


ROYAL SOCIETY OF CHEMISTRY

Metallomics

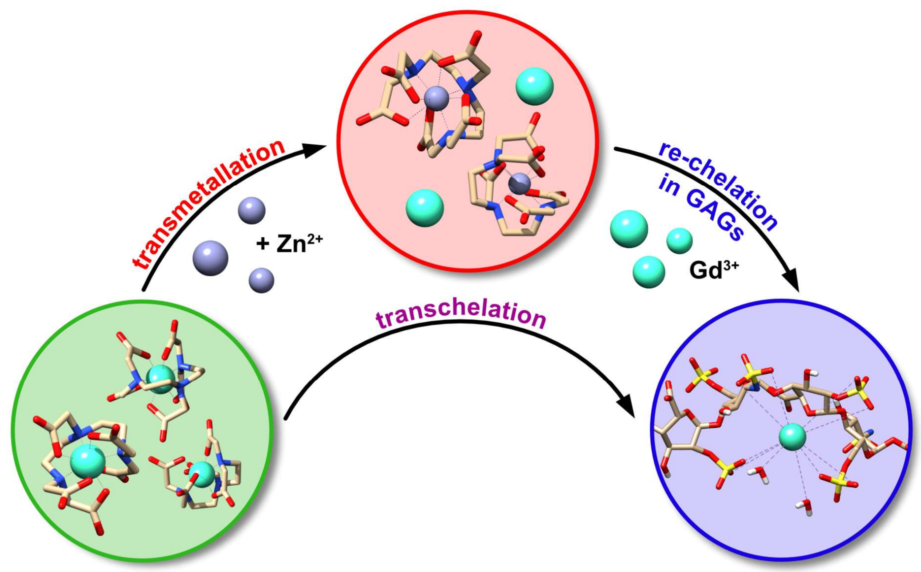
PERSPECTIVE — View Article Online / View Journal

Check for updates

Cite this: DOI: 10.1039/c8mt00302e

The biological fate of gadolinium-based MRI contrast agents: a call to action for bioinorganic chemists

Mariane Le Fur * and Peter Caravan *

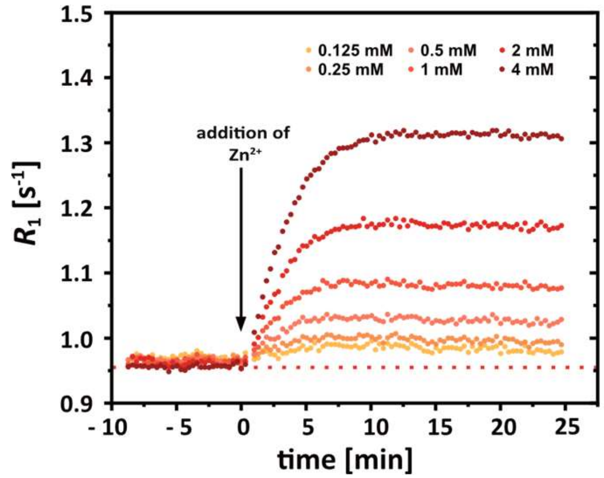


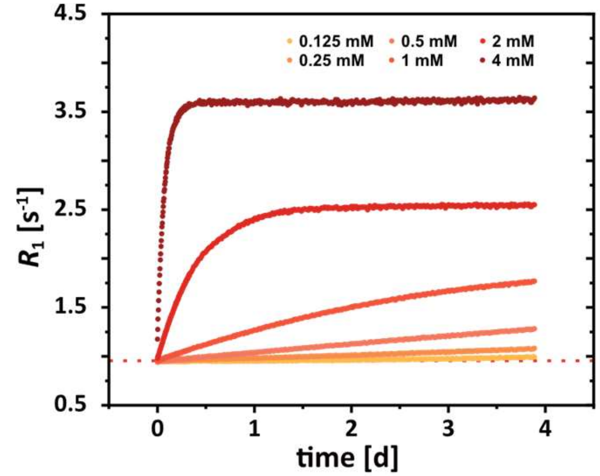
physics contribution:
quantify magnetization recovery of water protons

$$\left(\frac{dM}{dt}\right)_{\mathrm{GBCA}} < \left(\frac{dM}{dt}\right)_{\mathrm{Gd}^{3+}} < \left(\frac{dM}{dt}\right)_{\mathrm{Gd@GAGs}}$$

Werner *et al. Sci. Rep.* **11**(1): 21731 (2021)

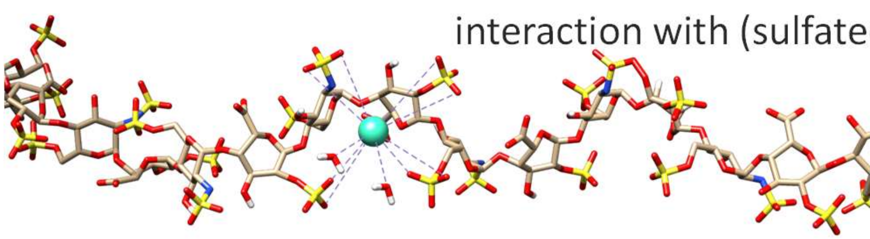
Relaxation Reveals Molecular Rearrangement



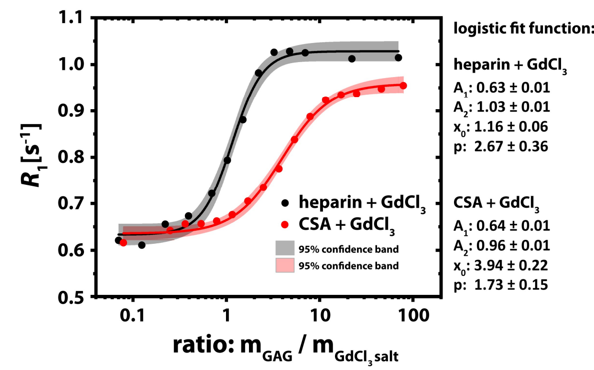


transchelation: slow chem. equilibrium

transmetallation: fast chem. equilibrium



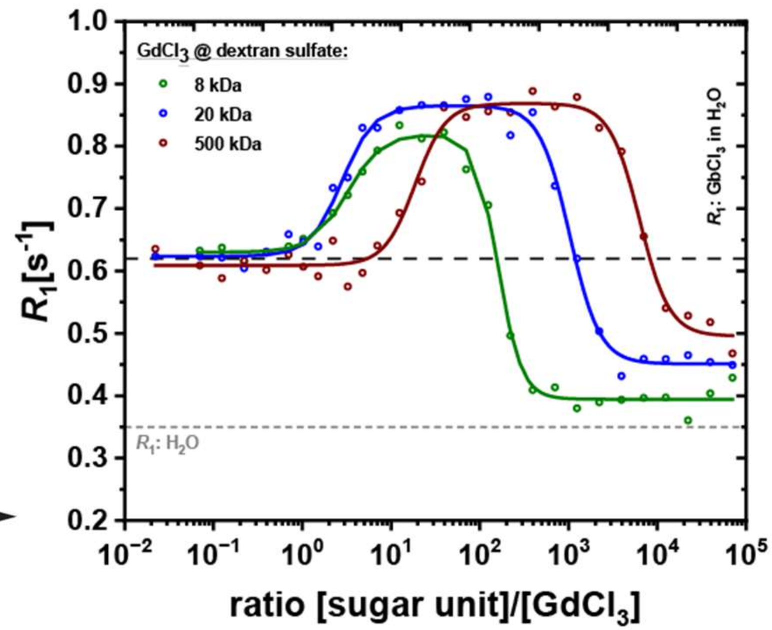
interaction with (sulfated) GAGs

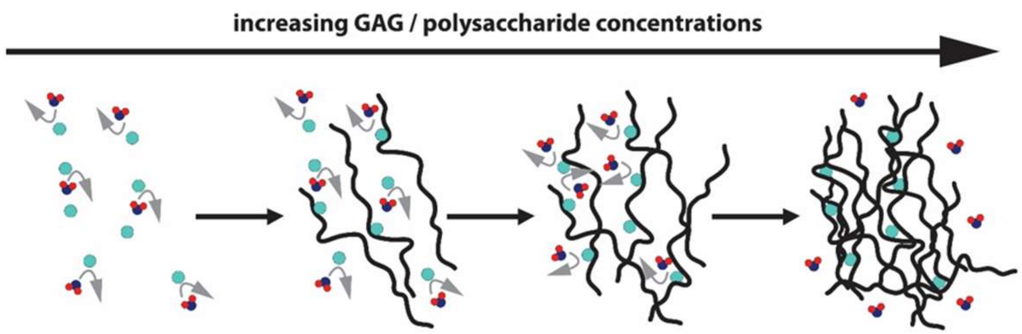


Werner *et al. Sci. Rep.* **11**(1): 21731 (2021)   Werner *et al. ChemMedChem.* **17**: e202100764 (2022)

Relaxivity Reveals Potential Shielding Effect of Gd-ions in Polysaccharides

- loss of relaxivity for Gd-ions presumably caused by reduced water accessibility
- easier achieved for smaller molecular weights → leads to earlier masking of the actual Gd-ion concentration





collaboration with Matrix in Vision CRC 1340

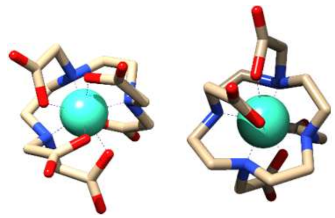
Werner *et al.* Proc. ISMRM (2023)

dkfz.

Limitations of Conventional MRI

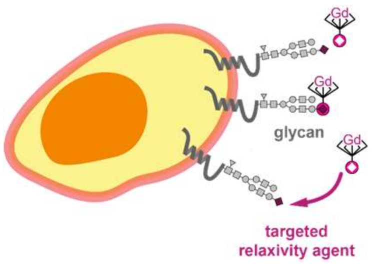
limitation without contrast agents:

- limited contrast / slow acquisition
- restricted choice of reporters



conventional agents:

- low sensitivity (~10 - 100 µM)
- not switchable
- safety concerns

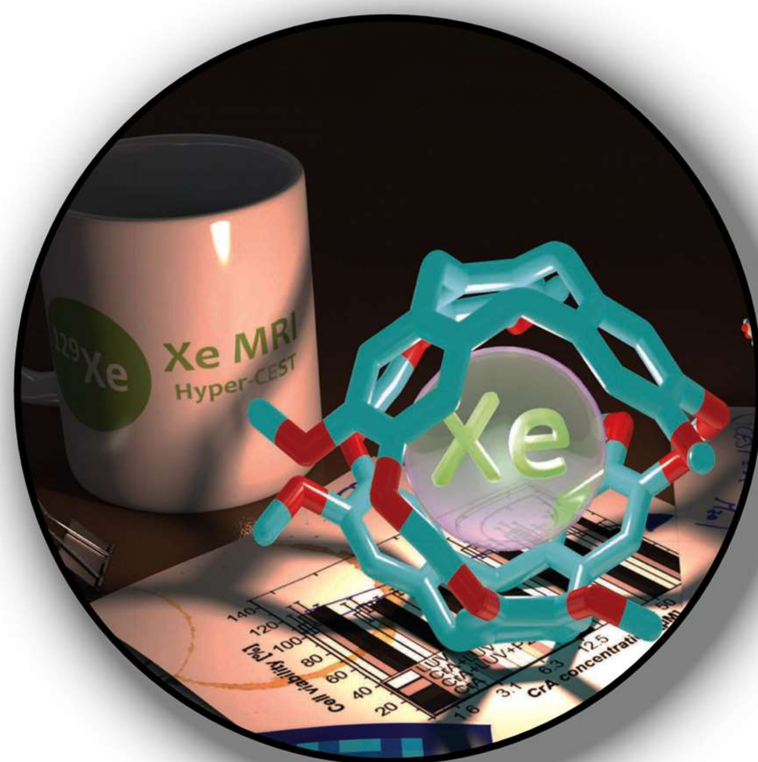


cell surface markers:
10^9 per cell,
10^5-10^6 cells/mL
10 µM Gd reporters

motivates further research:

- develop more sensitive contrast agents
- polarization transfer between coupled spin systems to improve sensitivity

Hyperpolarized MRI



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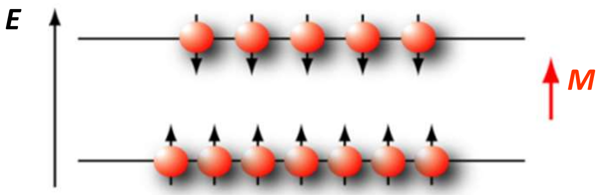
Limitations of Conventional Magnetic Resonance

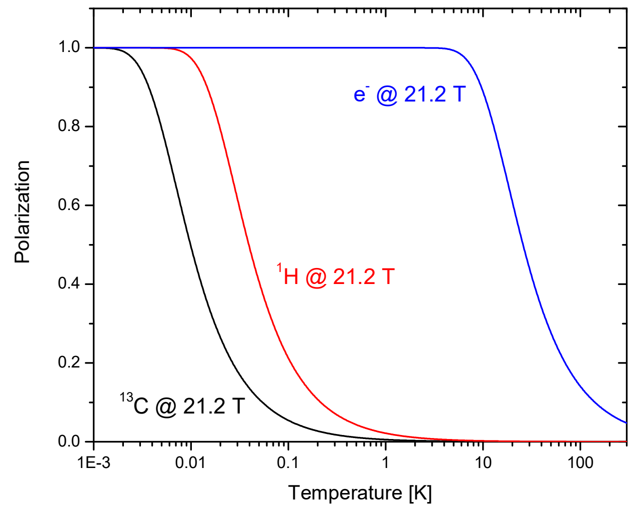
consider ensemble of spin-½ nuclei (e.g. ^{1}H, ^{129}Xe)
with magnetic moment *m* in external field *B*



$$M = N\langle\mu\rangle = N\mu \tanh\left(\frac{\mu B}{kT}\right)$$

spin polarization

$$P = \frac{N_\uparrow - N_\downarrow}{N_\uparrow + N_\downarrow} = \tanh\frac{\gamma\hbar B}{2kT}$$



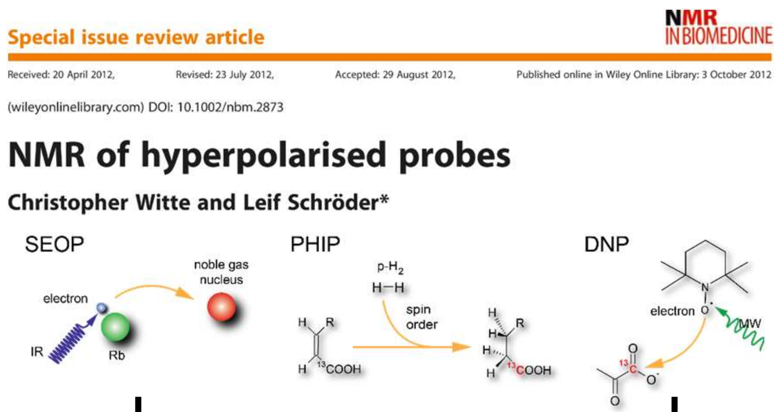
typically: ***P* ~ 10^{-8} ... 10^{-6}**

consequence: we live with

- **large samples**
- **high concentrations**
- **limited resolution**

NMR:
P ~ 10% requires *T* « 1K

Hyperpolarized NMR: A Versatile Toolbox



Special issue review article
NMR IN BIOMEDICINE
Received: 20 April 2012, Revised: 23 July 2012, Accepted: 29 August 2012, Published online in Wiley Online Library: 3 October 2012
(wileyonlinelibrary.com) DOI: 10.1002/nbm.2873

NMR of hyperpolarised probes

Christopher Witte and Leif Schröder*

oldest application

fast emerging application

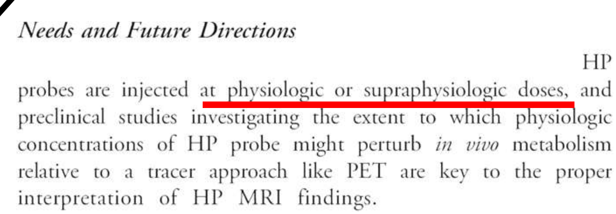
… MRI of hyperpolarized nuclei, …, provides information that is intrinsically not available using current molecular imaging methods.

Neoplasia, 2011

NEOPLASIA
www.neoplasia.com
Volume 21 Number 1 January 2019 pp. 1–16 1

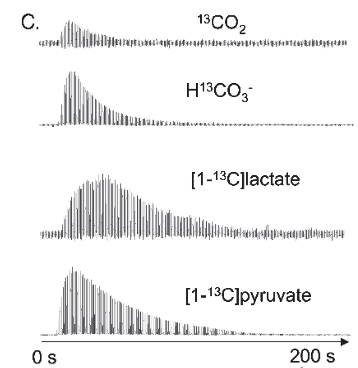
Hyperpolarized ^{13}C MRI: Path to Clinical Translation in Oncology

John Kurhanewicz, Daniel B. Vigneron, Jan Henrik Ardenkjaer-Larsen, James A. Bankson, Kevin Brindle, Charles H. Cunningham, Ferdia A. Gallagher, Kayvan R. Keshari, Andreas Kjaer, Christoffer Laustsen, David A. Mankoff, Matthew E. Merritt, Sarah J. Nelson, John M. Pauly, Philips Lee, Sabrina Ronen, Damian J. Tyler, Sunder S. Rajan, Daniel M. Spielman, Lawrence Wald, Xiaoliang Zhang, Craig R. Malloy and Rahim Rizi



Needs and Future Directions

HP probes are injected at physiologic or supraphysiologic doses, and preclinical studies investigating the extent to which physiologic concentrations of HP probe might perturb *in vivo* metabolism relative to a tracer approach like PET are key to the proper interpretation of HP MRI findings.



metabolic imaging at 10^{-4} … 10^{-3} M

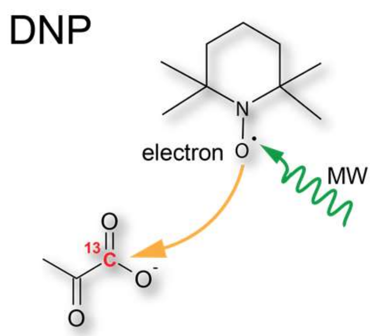
targeted imaging at 10^{-9} … 10^{-6} M

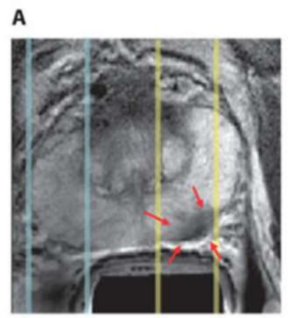
?

!

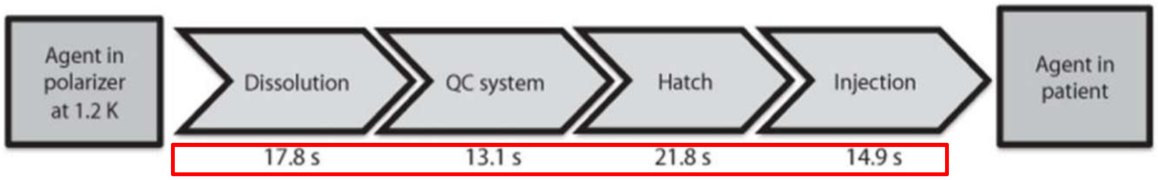
dkfz.

Clinical Hyperpolarized MRI Applications





	cancer progression	after therapy
levels of hyperpolarized [1-^{13}C]lactate	↑	↓
flux of [1-^{13}C]pyruvate to [1-^{13}C]lactate	↑	↓

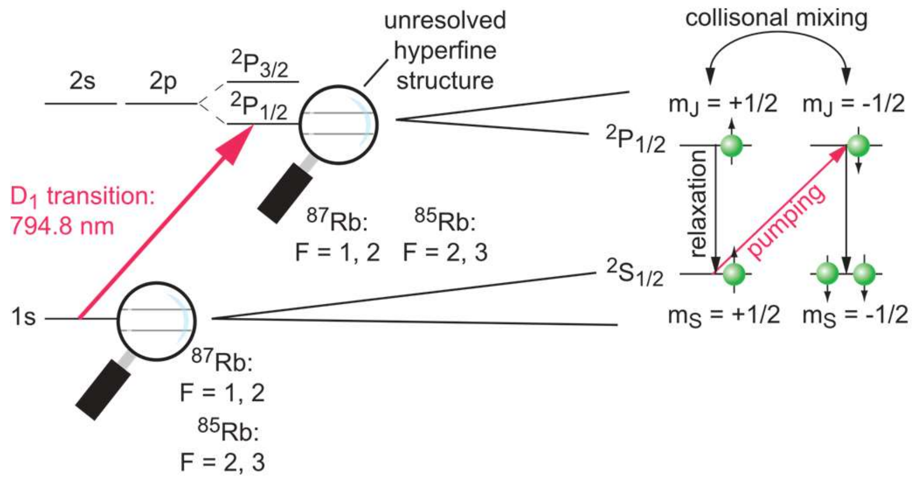


Nelson et al. *Science Transl. Med.* **5**: 198ra108 (2013)

Enhanced Spin Polarization of Laser-Polarized Noble Gases (SEOP)

setup for Spin Exchange
Optical Pumping
photon → electron → nucleus

driving the spin system
out of Boltzmann distribution

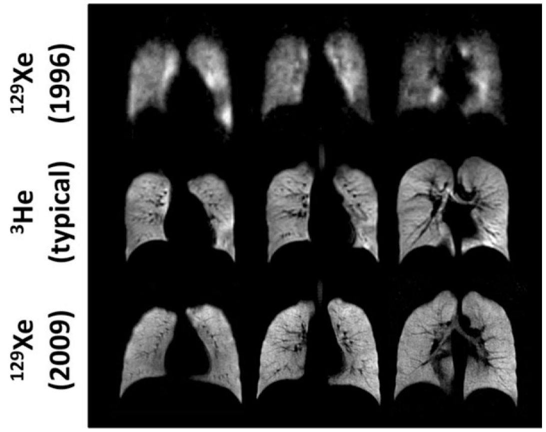


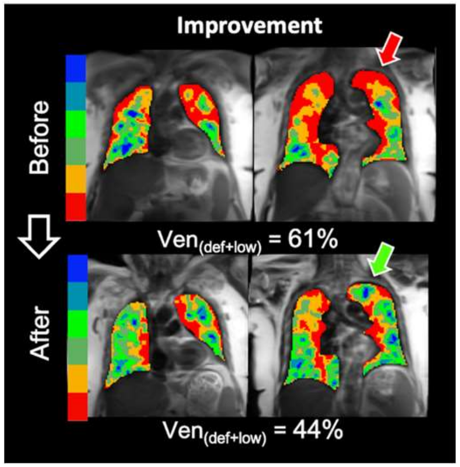
key components:

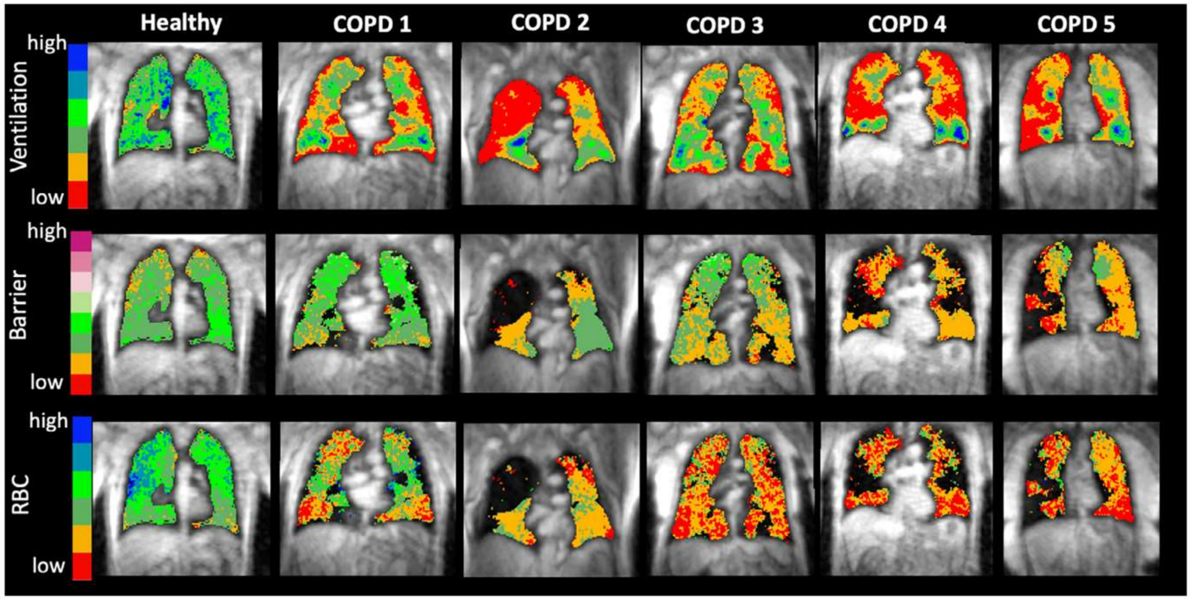
- alkali metal vapor providing single valence electron
- electron transitions driven by laser
- exposed to magnetic field (mT)

Jayapaul & Schröder; *Molecules*, **25**: 4627 (2020)

SEOP Application: Lung Imaging







increasing anatomical resolution + functional information

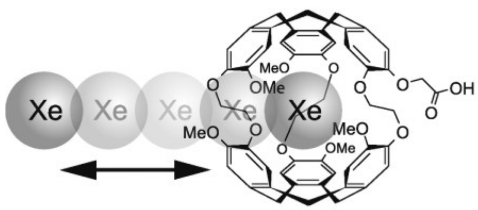
Mugler *et al.*, *J. Magn. Reson. Imag.* **37**: 313 (2013)

Mummy *et al.*, *J. Magn. Reson. Imag.* **54**: 964 (2021)

In situ Reversible Spin Loading of Targeted MRI Reporters

Xe host for functionalized biosensors:

CrA-ma



specific binding to molecular targets

reversible binding of hyperpolarized Xe

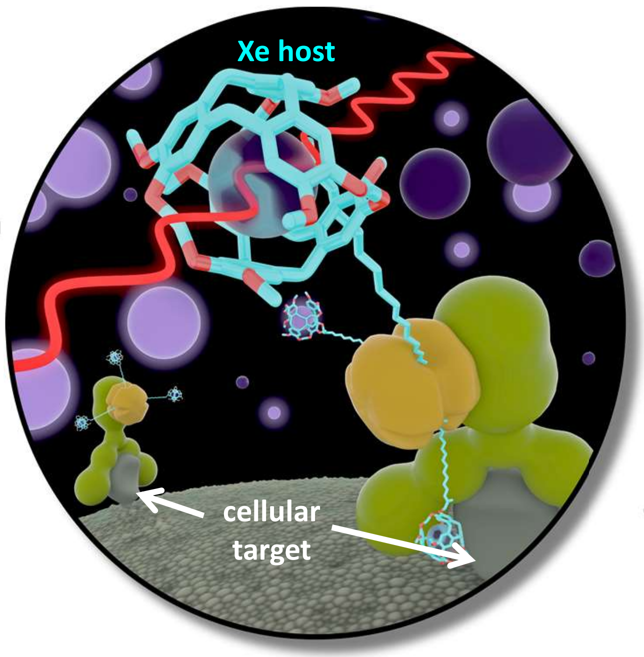
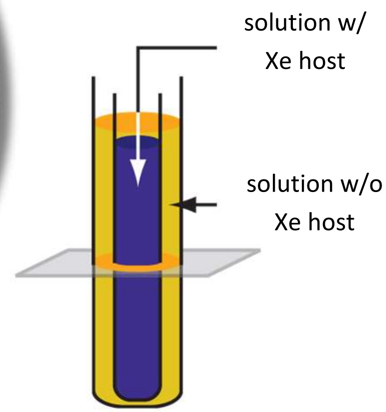
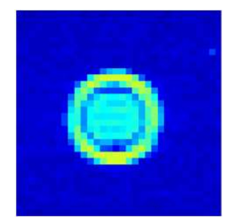


illustration: Barth van Rossum, FMP

combines high specificity + sensitivity
(10^4 from SEOP + 10^3 from CEST)

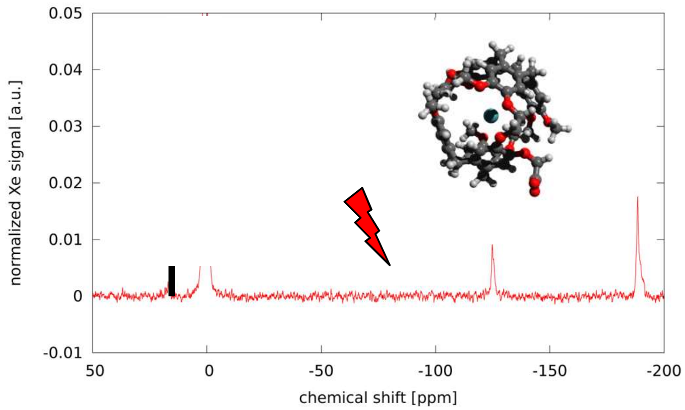
actively induced signal contrast





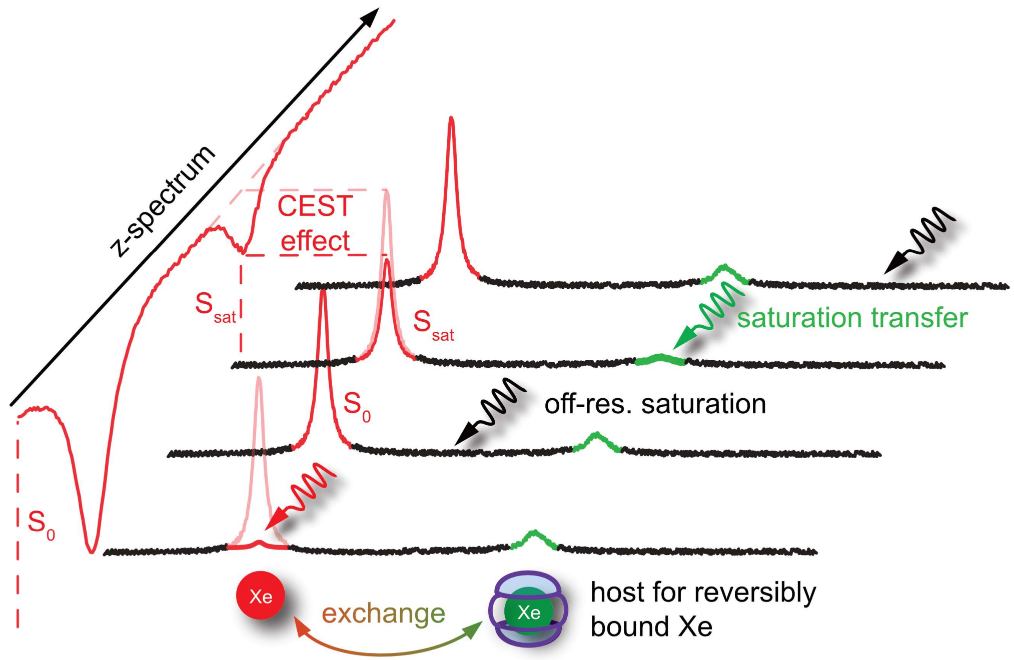
Witte & Schröder; *NMR Biomed.* **26**: 788 (2013)

Indirect Detection through Saturation Transfer (CEST)



CEST:
chemical exchange saturation transfer

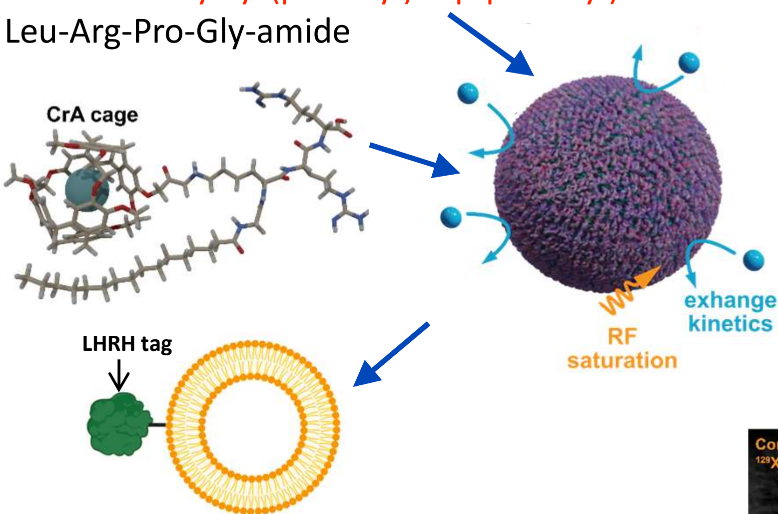
long (seconds) RF irradiation
- equilibrates the spin populations
- “saturates” the magnetization
- vanishing spin polarization: $M = P = 0$
- signal loss that propagates from small pool into large pool



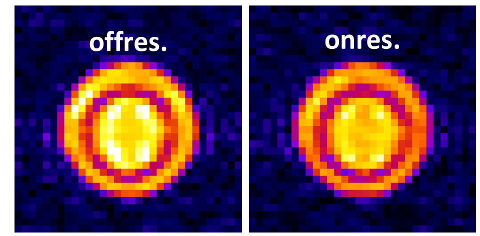
Jayapaul & Schröder; *Molecules* **25**: 4627 (2020)

Lung Metasteses Detection: LHRH1-directed Liposomes

LHRH1-Flu-LP:
pGlu-His-Trp-Ser-Tyr-DLys(Gly-Lys(Flu)Glu-Glu-Glu-O2Oc-Gly-Lys(palmityl)-Trp-palmityl)—Leu-Arg-Pro-Gly-amide

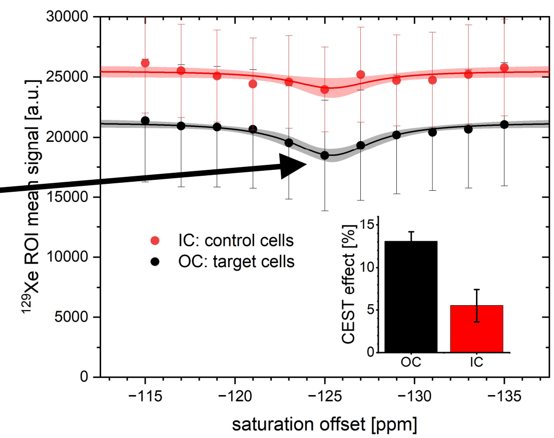


single-shot Xe MRI
1.8 million-fold spin dilution compared to ^{1}H MRI

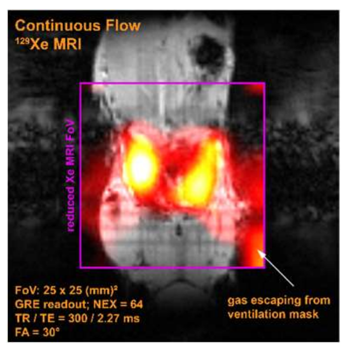


…

clear CEST response from MDA-MB-231 vs. UCI-107 cells



to be combined with continuous hp spin delivery through the lungs



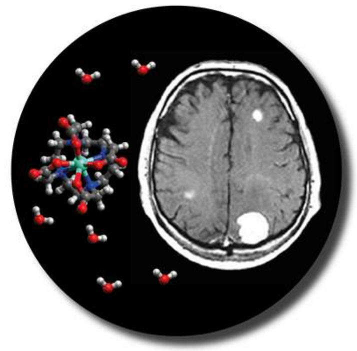
more details on posters
MR-2: Lehr MR-3: Kempny
MR-4: Gerbeth MR-5: Lee

Jayapaul *et al.*, unpublished results

dkfz.

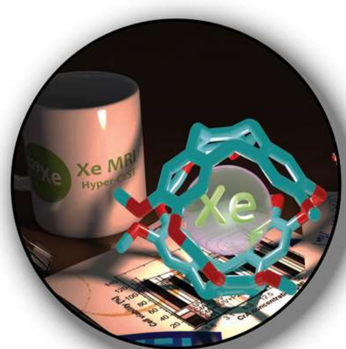
Summary

- medical applications of NMR were conceptualized early on
- MRI emerged in the 1970s and works outside wavelength limitations



- thermal magnetization is tiny
- contrast improves with paramagnetic substances
- many molecular markers are inaccessible with ^{1}H MRI

- most MRI scans rely on spin-1/2 systems
- excellent soft tissue contrast is based on different relaxation times
- QM effects like spin-spin couplings reveal tissue microstructure



- hp spin systems boost the signal but have limited lifetime
- applications focus on metabolic imaging
- synthetic hosts for hp Xe can be functionalized for molecular targets

Thank you for your attention!

DKFZ:
Viktoria Bayer
Leonard Bender
Sandra Casula
Hannah Gerbeth
David Hernandez
Jabadurai Jayapaul
Luca Kempny
Jason Lee
Samuel Lehr
Alexandra Lipka
Patrick Werner

Collaborators:
Amnon Bar-Shir (WIS)
Paul Beer (U of Oxford)
Yoram Cohen (Tel Aviv U)
Andreas Hennig (U Osnabrück)
André Martins (U Tübingen)
Mikhail Shapiro (Caltech)
Franz Schilling (TUM)
Ville Telkki (U of Oulu)

rendering: Barth van Rossum

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DKTK German Cancer Consortium