Dissolution DNP

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Disclosure: Owner of Polarize that manufactures instrumentation for hyperpolarization

In 1953 Albert Overhauser presented his idea of polarizing nuclear spins by saturation of conduction electrons at an APS meeting

PHYSICAL REVIEW VOLUME 92, NUMBER 2 OCTOBER 15, 1953

Polarization of Nuclei in Metals

ALBERT W. OVERHAUSER*
Department of Physics, University of Illinois, Urbana, Illinois
(Received June 25, 1953)

A new method for polarizing nuclei, applicable only to metals, is proposed. It is shown that if the electron spin resonance of the conduction electrons is saturated, the nuclei will be polarized to the same degree they would be if their gyromagnetic ratio were that of the electron spin. This action results from the paramagnetic relaxation processes that occur by means of the hyperfine structure interaction between electron and nuclear spins. A shift of the electron spin resonance due to the same interaction will occur for large amounts of polarization and should provide a direct indication of the degree of polarization.

I. INTRODUCTION

A NUMBER of methods[1] have been proposed for producing polarization or alignment of nuclear spins. A new method, applicable to the nuclei of atoms of a metallic solid, is made possible by the existence[2] of the electronic spin resonance from electrons in the conduction band. The interaction b spin magnetic moment β_e and the nu moment β_n that is responsible for t is that of the hyperfine coupling of

$$H = -(8\pi/3)\beta_e\cdot\beta_n\delta$$

Here, $\delta(\mathbf{r})$ is a delta function of the of the electron and nucleus under polarization is produced when the n constant magnetic field $\mathcal{H}_0$, is irradi dicular microwave magnetic field,

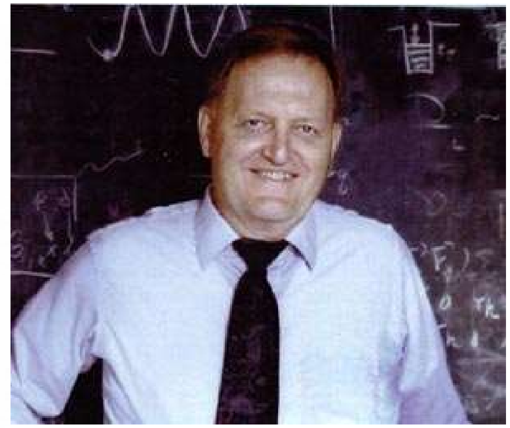
direction, with a resulting steady state nuclear polarization. This action cannot be attributed to a large Boltzmann factor for the energy separations of adjacent nuclear magnetic states, and the spin-temperature concepts, familiar in the literature of magnetic resonance, do not apply.

PHYSICAL REVIEW VOLUME 89, NUMBER 4 FEBRUARY 15, 1953

Paramagnetic Relaxation in Metals*

ALBERT W. OVERHAUSER†
Department of Physics, University of California, Berkeley, California
(Received August 11, 1952)

The paramagnetic relaxation time of electron spins in a metal is calculated. Relaxation processes due to interaction with lattice vibrations, nuclear spins, other electrons, and impurity atoms are treated. It is found that the most important process of those considered is due to the interaction between electron magnetic moments and the fields caused by the translational motion of other electrons.



The idea that the heating of one spin system could lead to the cooling of another was not well received by prominent physicists of the time

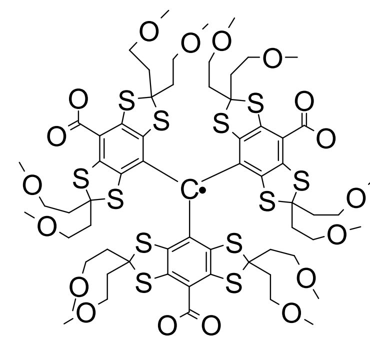
Overhauser MRI (OMRI)

263 MHz EPR (9 mT)

600 kHz ^{1}H MRI (15 mT)

With RF saturation

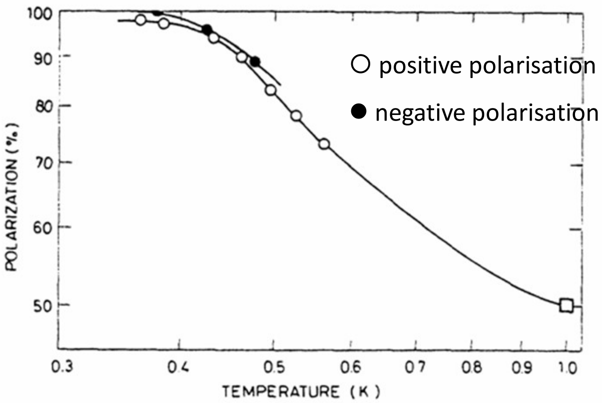
Without RF saturation



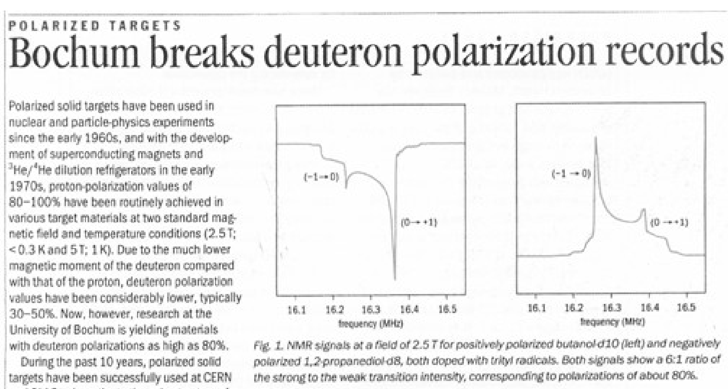
Trityl radical

Polarized targets; the nuclear physics community

Dynamic nuclear polarisation of protons in 1,2-ethanediol
doped with complexes of Cr(V) at 2.5T



de Boer et al, Nucl.Instrum.Meth. 114, 495 (1974).



POLARIZED TARGETS

Bochum breaks deuteron polarization records

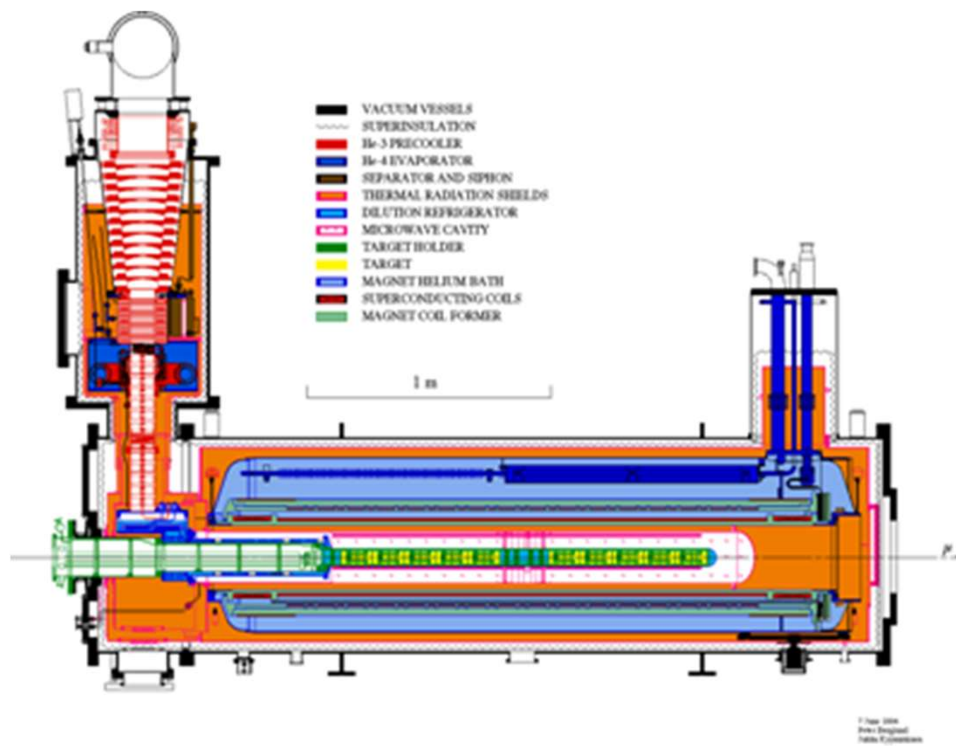
Polarized solid targets have been used in nuclear and particle-physics experiments since the early 1960s, and with the development of superconducting magnets and $^{3}He/^{4}He$ dilution refrigerators in the early 1970s, proton-polarization values of 80–100% have been routinely achieved in various target materials at two standard magnetic field and temperature conditions (2.5 T; < 0.3 K and 5 T; 1 K). Due to the much lower magnetic moment of the deuteron compared with that of the proton, deuteron polarization values have been considerably lower, typically 30–50%. Now, however, research at the University of Bochum is yielding materials with deuteron polarizations as high as 80%.

During the past 10 years, polarized solid targets have been successfully used at CERN

Fig. 1. NMR signals at a field of 2.5 T for positively polarized butanol-d10 (left) and negatively polarized 1,2-propanediol-d8, both doped with trityl radicals. Both signals show a 6:1 ratio of the strong to the weak transition intensity, corresponding to polarizations of about 80%.

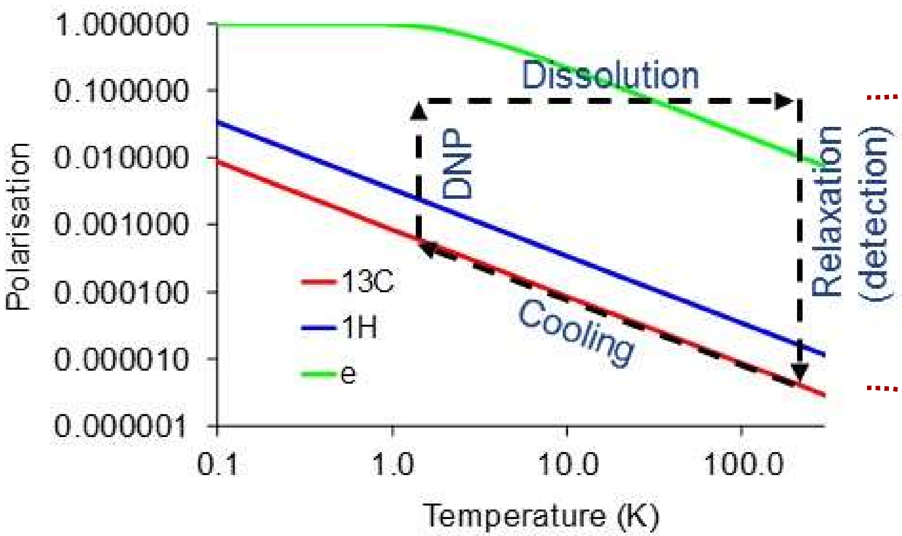
CERN courier, Sep 2003

SMC target: several liters of target volume

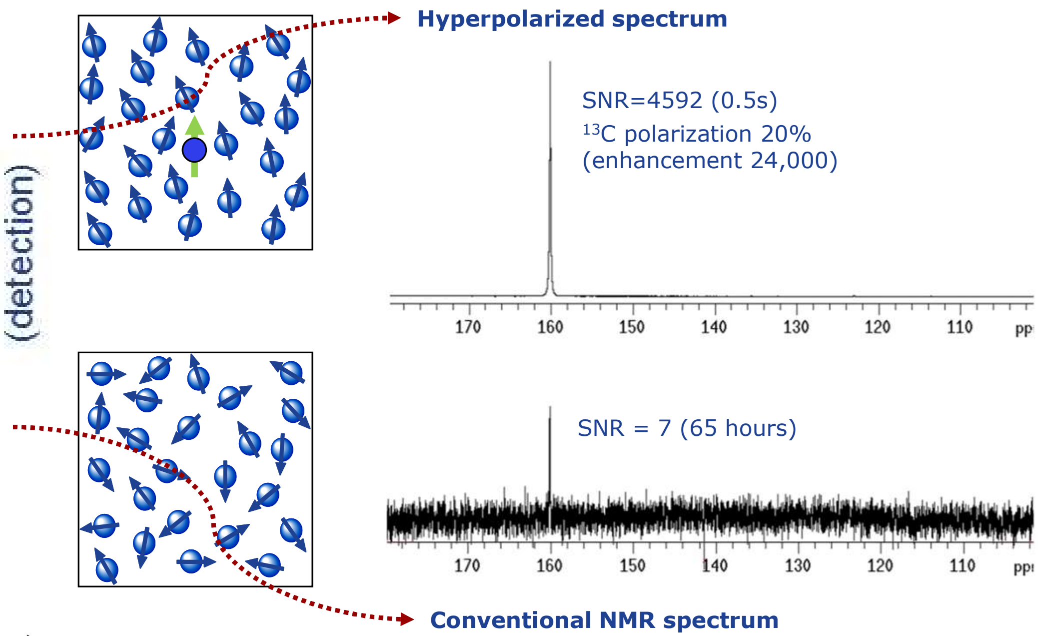


Hyperpolarized MR

dissolution Dynamic Nuclear Polarization

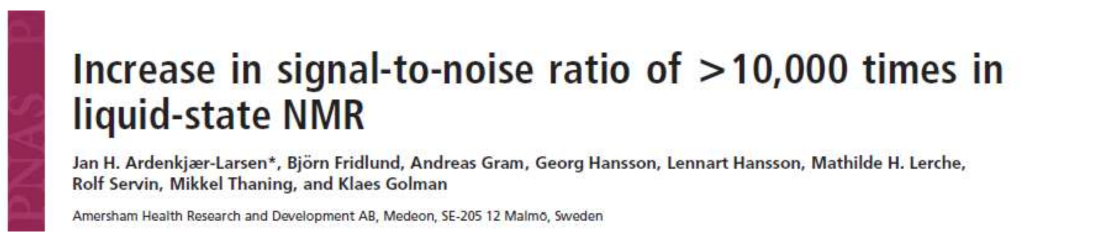


Hyperpolarization



^{1}H:	42.5 MHz/T
^{13}C:	10.7 MHz/T
e:	28.0 GHz/T
$k_B T$ = 25.2 meV =	6.1 THz @ RT

$$P_{thermal} = \tanh\left(\frac{\mu B_0}{k_B T}\right)$$


PNAS

Increase in signal-to-noise ratio of >10,000 times in liquid-state NMR

Jan H. Ardenkjær-Larsen*, Björn Fridlund, Andreas Gram, Georg Hansson, Lennart Hansson, Mathilde H. Lerche, Rolf Servin, Mikkel Thaning, and Klaus Golman

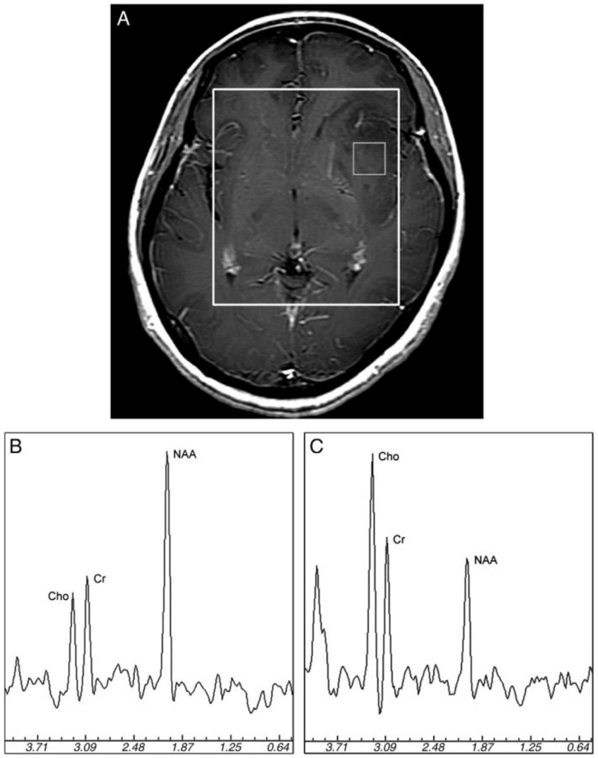
Amersham Health Research and Development AB, Medeon, SE-205 12 Malmö, Sweden

Charles Slichter,
Principles of Magnetic Resonance

"… . We emphasize that an arbitrary orientation can be specified, since sometimes the belief is erroneously held that spins may only be found pointing either parallel or antiparallel to the quantizing field. One of the beauties of quantum theory is that it contains features of both discreteness and continuity. In terms of the two quantum states with $m=\pm\frac{1}{2}$ we can describe an expectation value of the magnetization which goes all the way from parallel to antiparallel, including all values in between. …"

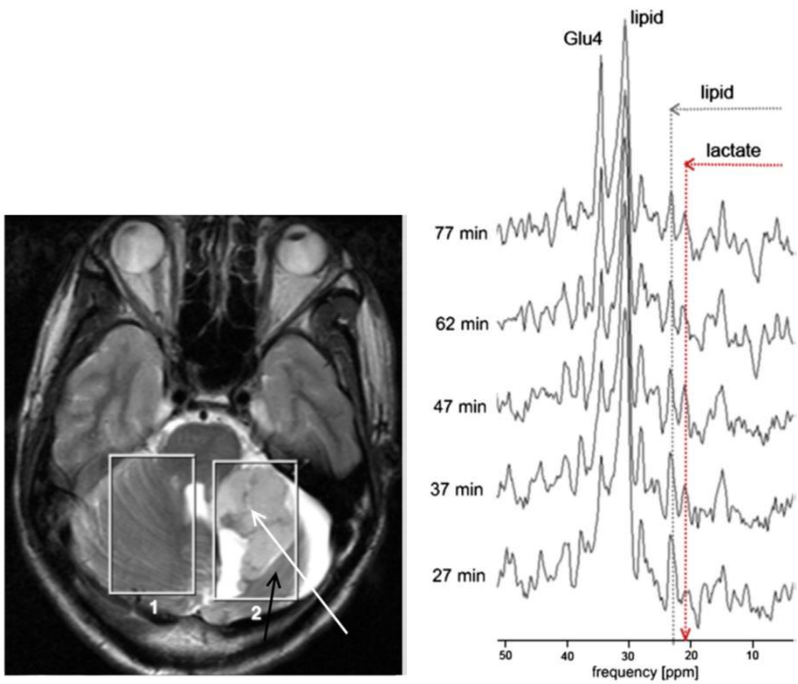
MR is a never ending quest for signal

And has led to increased magnetic field strength, optimized pulse sequences and detection coils



~9 min acquisition with 10 cm³ voxel size

Zeng et al, Magnetic Resonance Imaging 29 (2011) 25–31

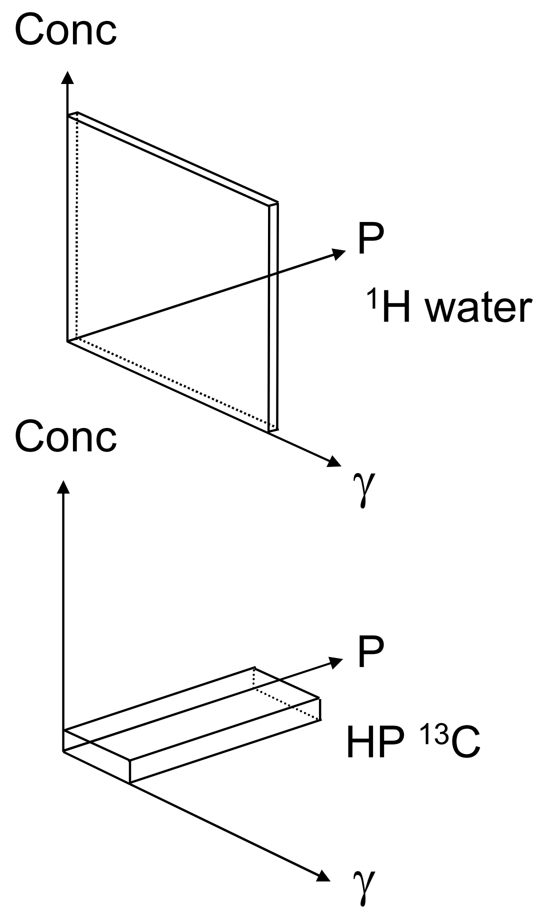


>12 g of [1-^{13}C]glucose infused during examination. 10 min acquisition time and ~50 cm³ voxel size

Wijnen et al, Magnetic Resonance Imaging 28 (2010) 690–697

Why is hyperpolarization interesting?

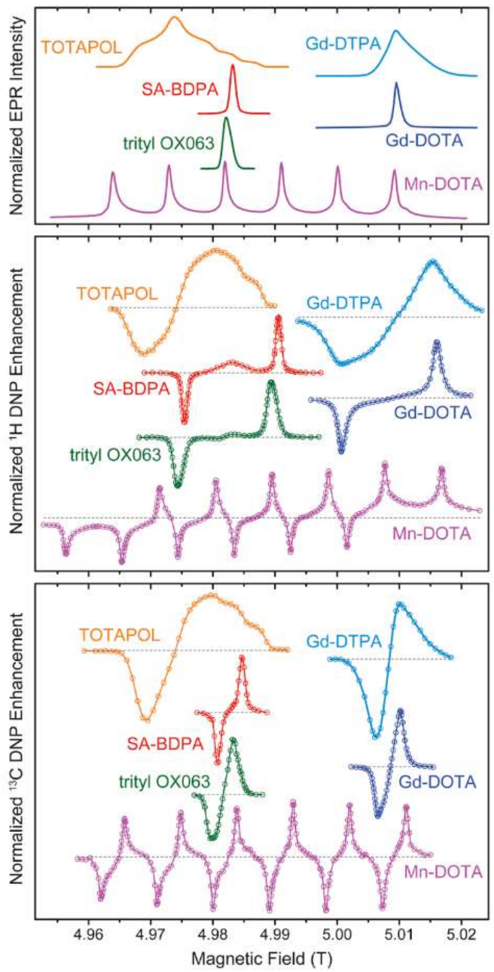
- Sensitivity in MRI is proportional to concentration and polarization and gyromagnetic ratio (γ).
- Higher sensitivity allows higher resolution or better contrast or detection of lower concentrations.

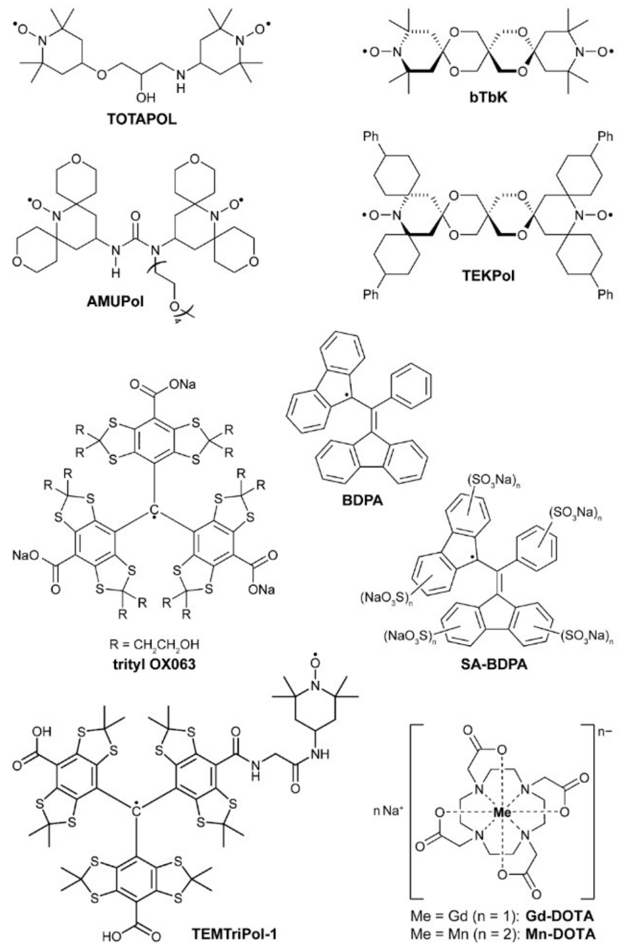


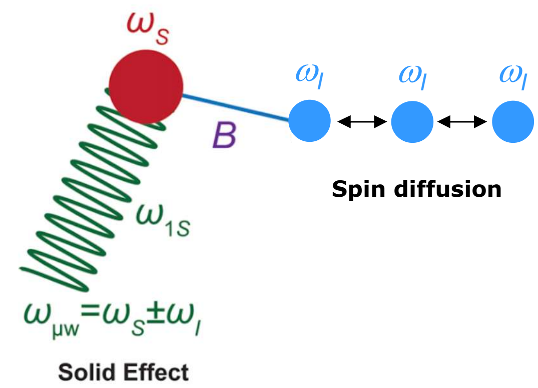
$$SNR \propto \frac{f_o B_{1xy} M_o}{F\sqrt{4k_B T R}}$$

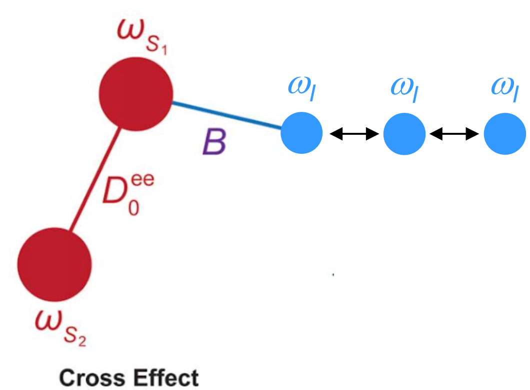
$$M_0 = N\mu P$$

Dynamic Nuclear Polarization and polarizing agents







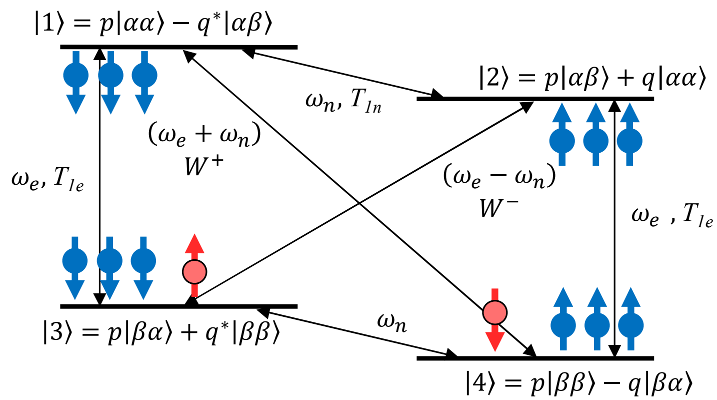


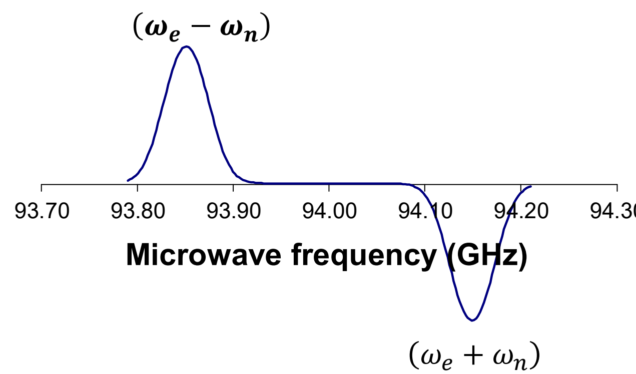
Corziliius, "Dynamic Nuclear Polarization" in Paramagnetism in Experimental Biomolecular NMR

Dynamic Nuclear Polarization – solid effect

Thermal equilibrium:

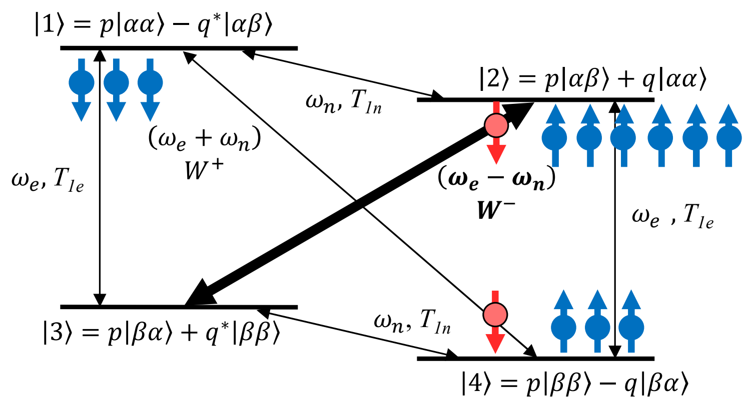
$P_n \approx 0$, $P_e \approx 1$



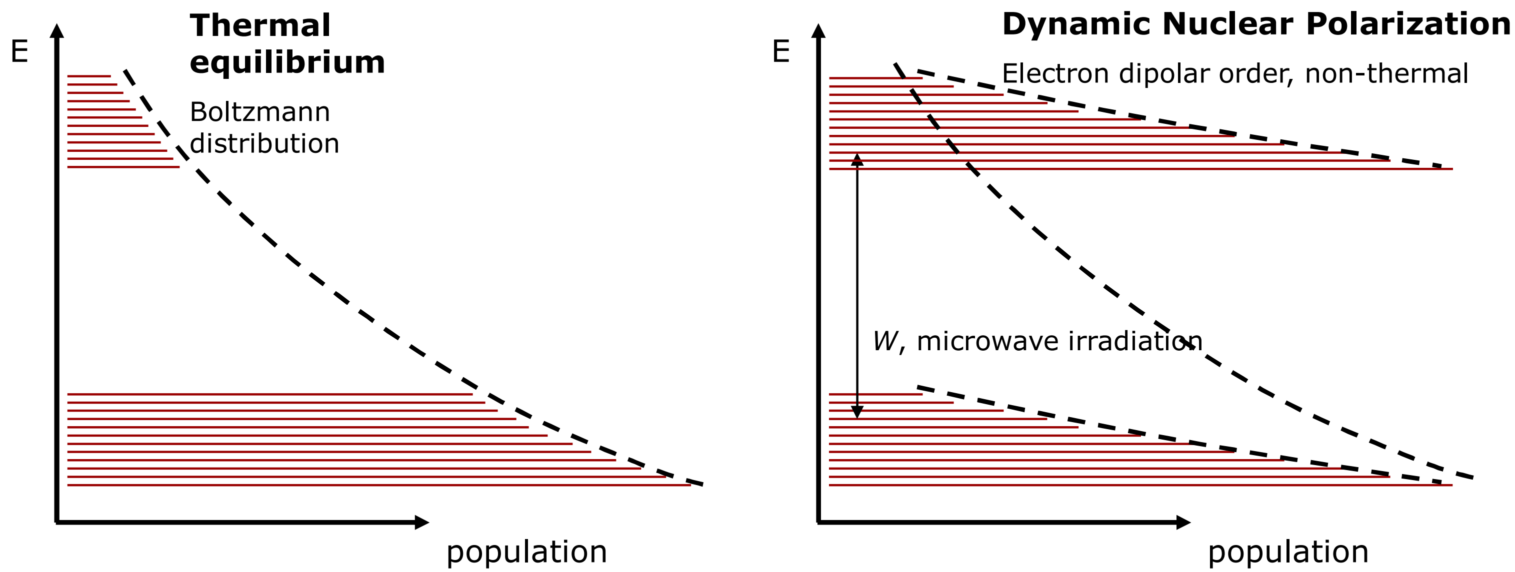


DNP:

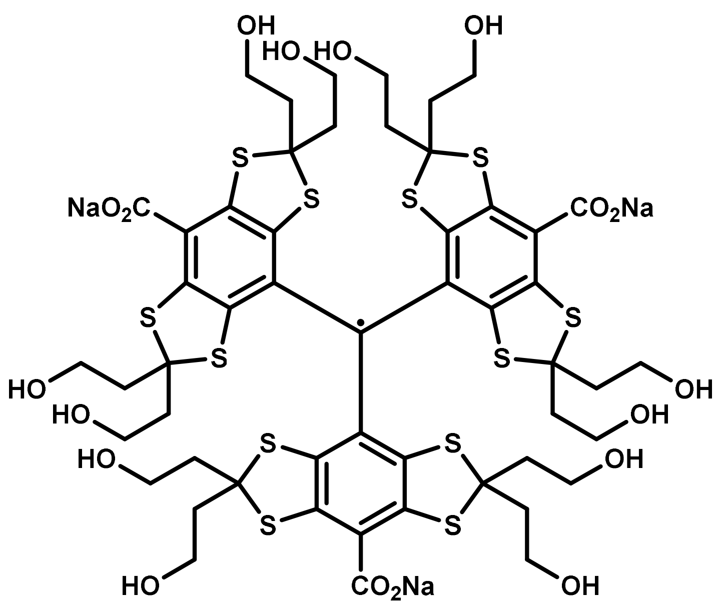
$P_n \approx 1$, $P_e \approx 1$



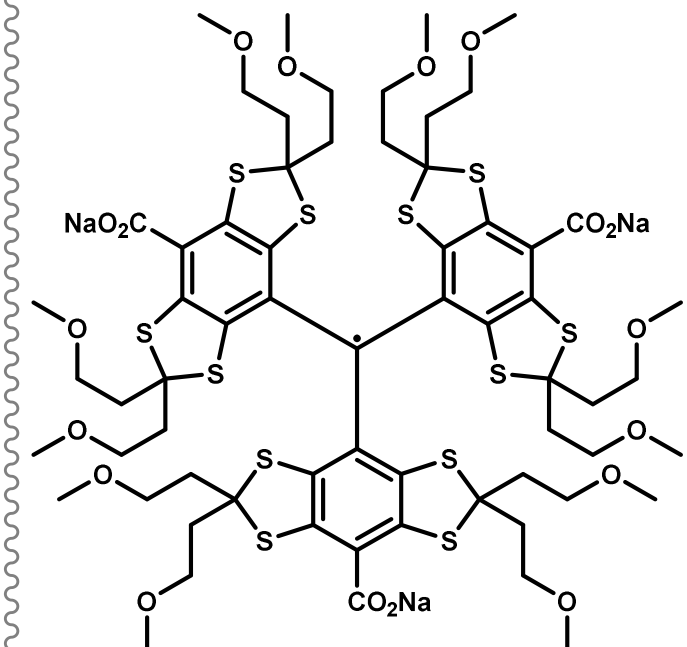
Dynamic Nuclear Polarization – thermal mixing



DNP with two trityls at 6.7 T



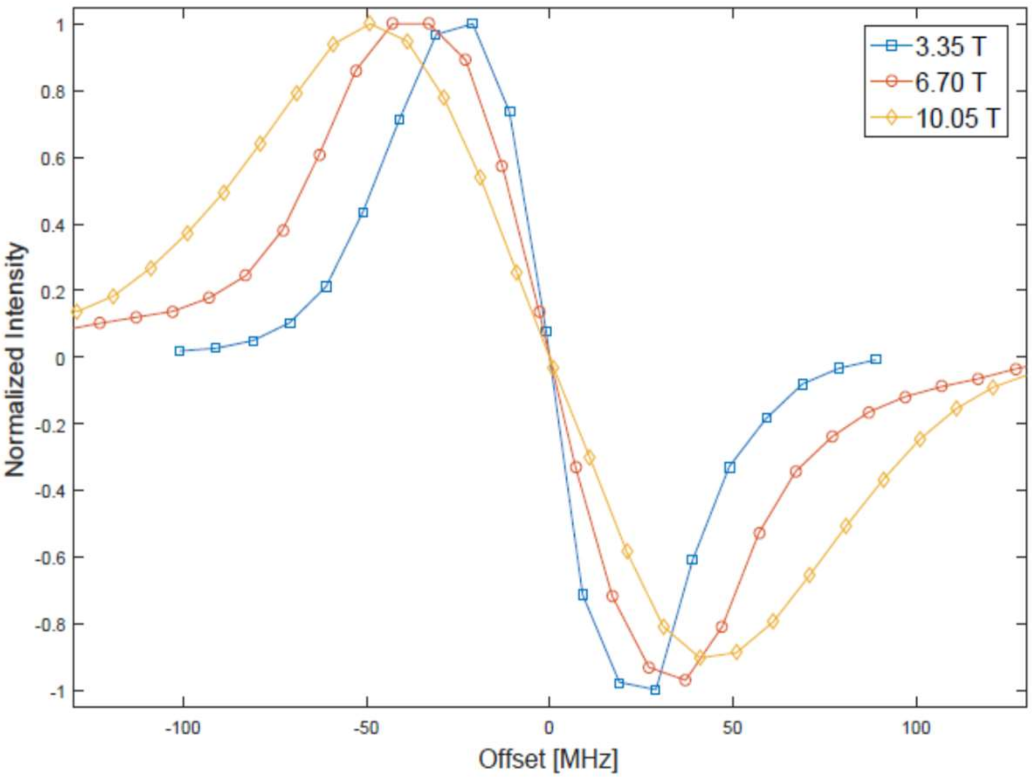
(OX063)



(AH111501)

DNP profile at 3.35 T, 6.70 T and 10.1 T

[1-^{13}C]Pyruvic acid with 15 mM AH111501



Ardenkjær-Larsen et al, MRM 2019

Field	^{13}C NMR freq	DNP peak separation
3.35 T	35.9 MHz	50 MHz
6.70 T	71.8 MHz	72 MHz
10.1 T	108 MHz	93 MHz

$\langle DD_{ee} \rangle$ = 1.74 MHz for 15 mM trityl mono-radical

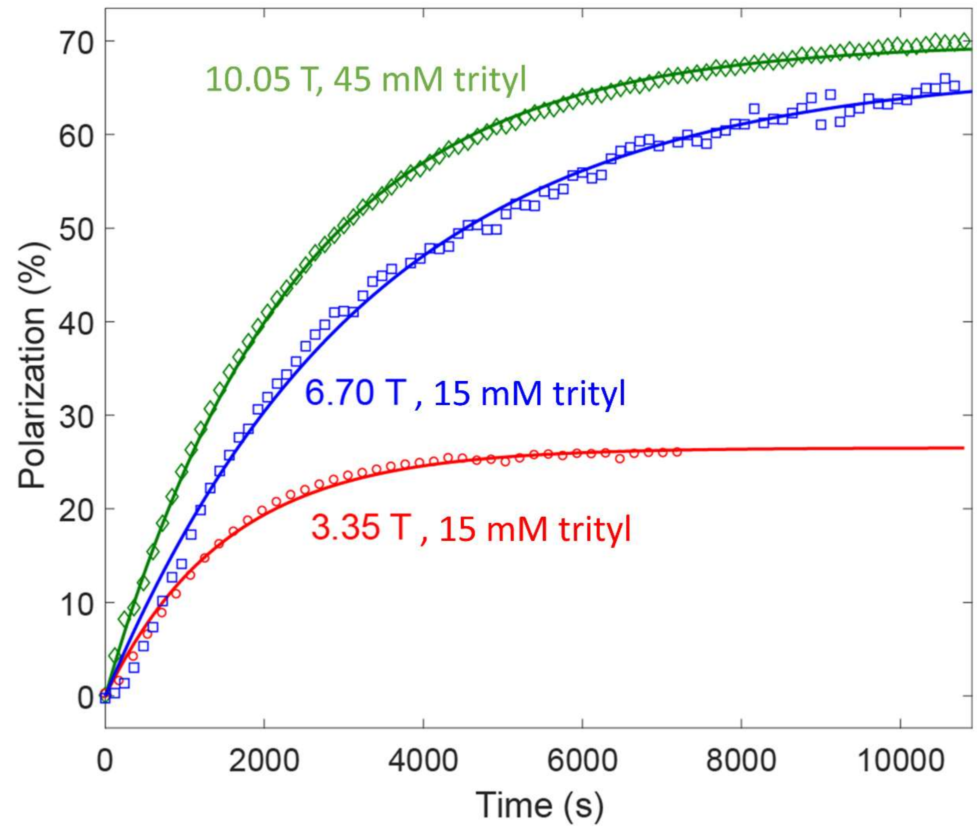
D_z = 18 MHz for trityl biradical

Macholl et al, PCCP 2010

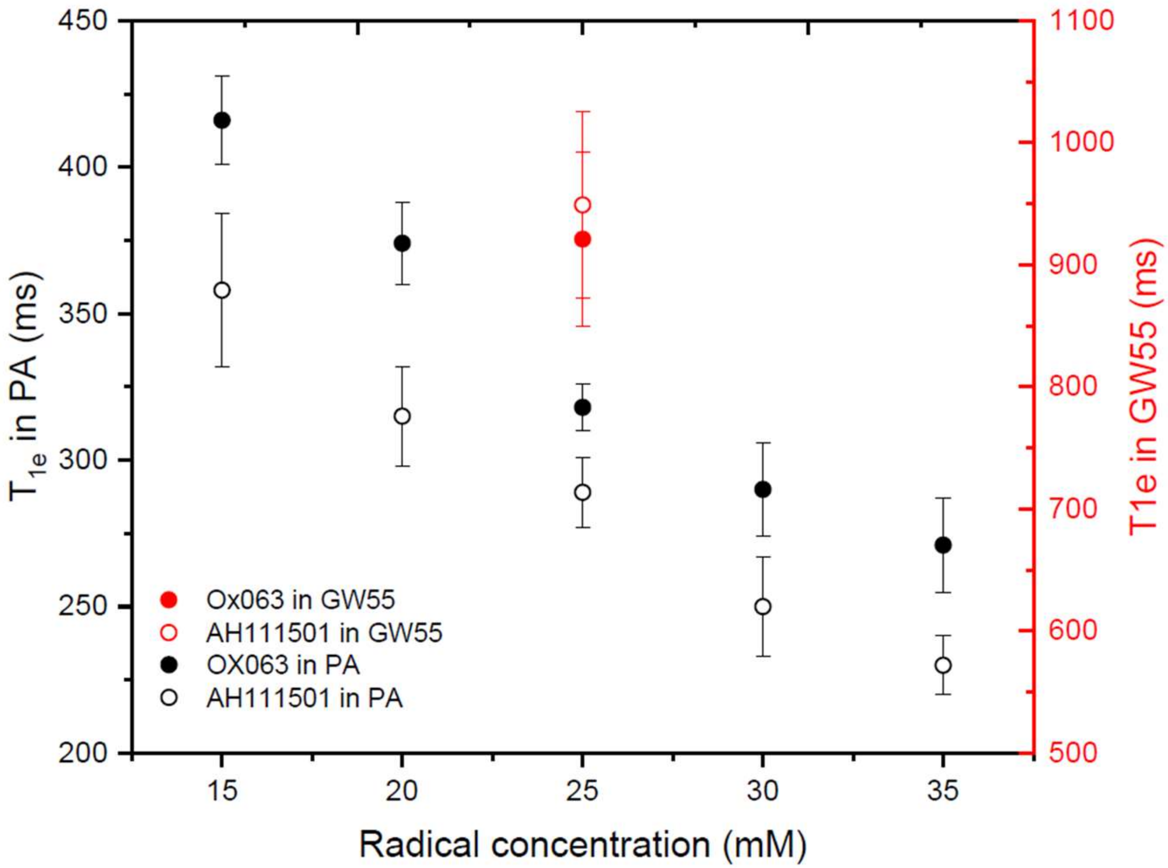
DNP solid state build-up

[1-^{13}C]pyruvic acid with trityl

Field strength (T)	T_{1n} (s)	DNP time constant (s)
3.35	6,400	900
6.70	33,000 (9 h)	1,200 (20 min) (MW modulation)
10.1	90,000 (25 h)	2,200 (36 min) (MW modulation)



T_{1e} measured by LOD-ESR

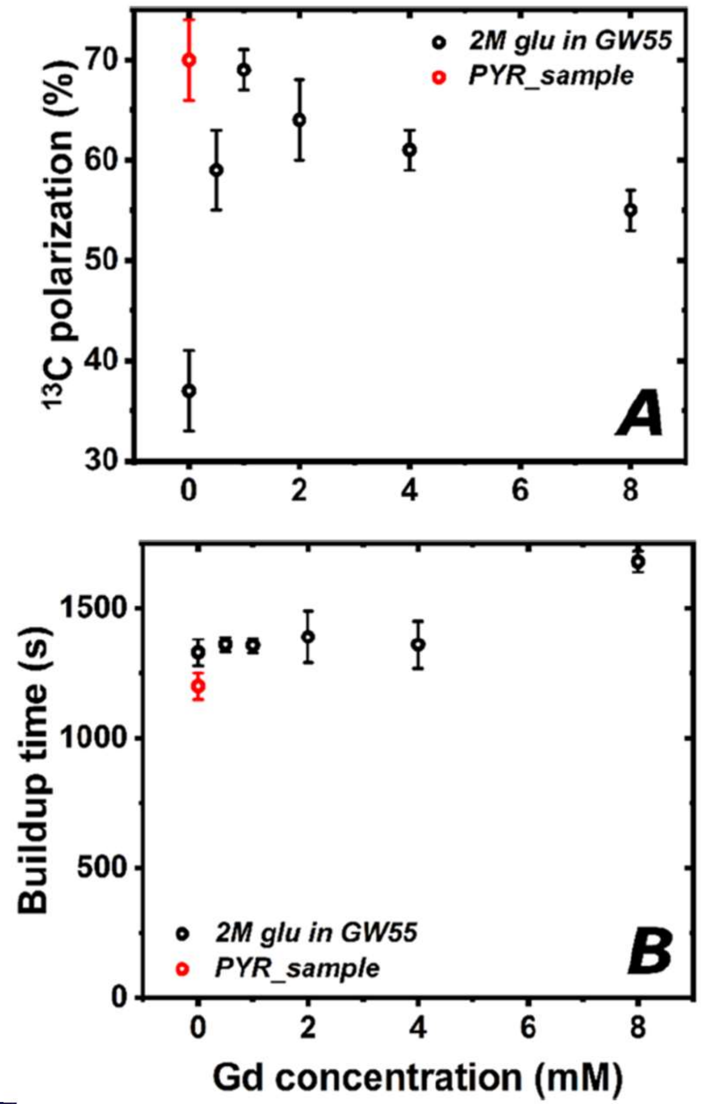


U-^{13}C-Glucose and AH111501/Gd^{3+}

Table 1. ^{13}C Spin Polarization of [U-$^{13}C_6$-d_7]-D-Glucose at Increasi

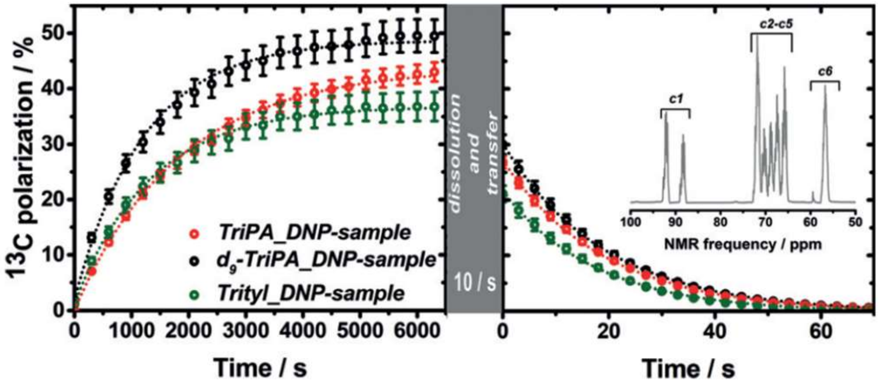
$[Gd^{3+}]$ (mM)	T_{1e} (ms)	ESR fwhm (MHz)	DNP maxima delta (MHz)
0	925 ± 4	108 ± 2	120 ± 5
0.5	538 ± 19	85 ± 2	110 ± 5
1	279 ± 11	79 ± 2	90 ± 5
2	205 ± 6	74 ± 2	90 ± 5
4	112 ± 3	69 ± 2	70 ± 5
8	80 ± 2	65 ± 2	70 ± 5

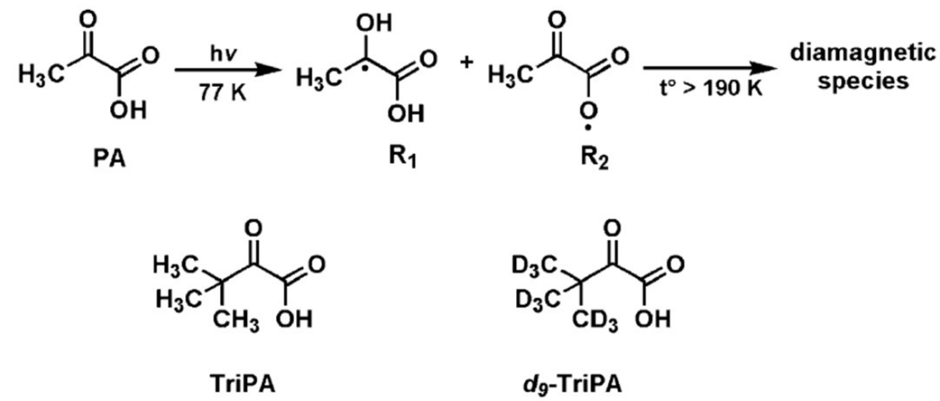
[a]In solid state at 6.7 T and 1.1 K (SS pol) and 10 s after dissolution in 40 mM state polarization buildup time constant; LS T_1, liquid-state relaxation constant; after dissolution; SS pol, solid-state polarization, back-calculated given the li polarizer to NMR magnet.



Capozzi et al, J. Phys. Chem Letter. 2019

U-13C-glucose with UV radicals





DNP Sample	Radical conc [mM]	ESR linewidth [MHz]	SS T_b [s]	SS pol [%]
TriPA	20 ± 1	142	1836 ± 28	49.5 ± 3.0
d9-TriPA	40 ± 1	131	1230 ± 30	42.9 ± 2.8
Trityl_DNP	30	108	1330 ± 28	35.7 ± 2.5

Capozzi et al, Angew.Chem. Int. Ed. 2019,

Dissolution-DNP: Sample preparation requirements

A human dose is ~0.1 mmol/kg-BW → 10 mmol is needed

That means 600 mg to 1200 mg of the imaging agent depending on MW

Maximum 60 mL can be injected into a patient at 5 mL/s, i.e. >100 mM concentration of agent.

Dissolution efficiency has to be retained for large sample to solvent ratios.

Thus, additives have to be kept low:

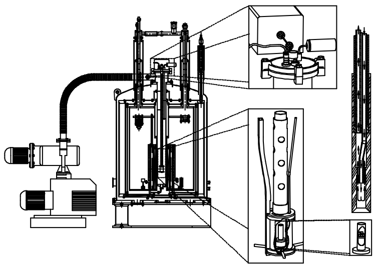
- Safety; have to be well tolerated (e.g. glycerol and DMSO)
- Dissolution; full recovery in dissolution

New agents: Formulation

- Neat (e.g. pyruvic acid, ethyl-pyruvic acid, KIC, HP001)
- Cs-salt (e.g. bicarbonate)
- Tris-salt (e.g. acetate)
- Saturated DMSO, glycerol or aqueous solution (e.g. fumaric acid)
- Acidic or caustic preparation (e.g. amino acids)

Enables formulation of all classes of compounds in high concentration and with good polarization

DNP Polarizer generations



Ardenkjær-Larsen et al, PNAS 2003

HyperSense™
Oxford Instruments

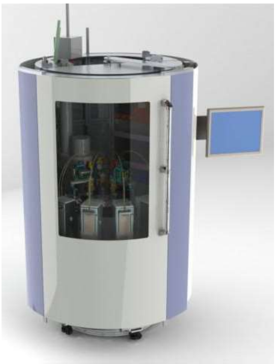
In vitro only;
Discontinued

SpinAligner
Polarize (www.polarize.dk)

Ardenkjær-Larsen et al, MRM 2018

UCSF clean room installation for 1st human study

SPINlab
GE Healthcare



Ardenkjær-Larsen et al,
NMR in Biomedicine 2011

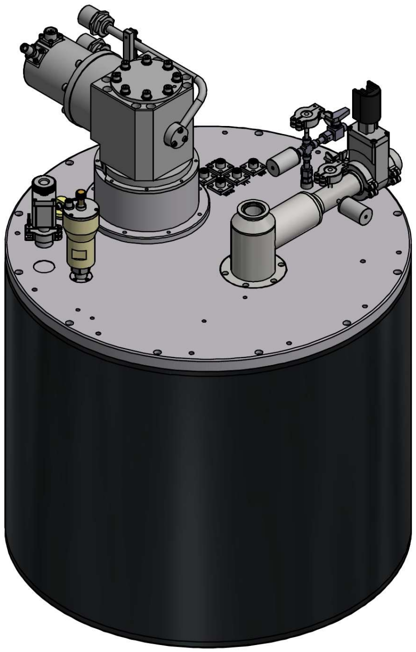
SpinAligner

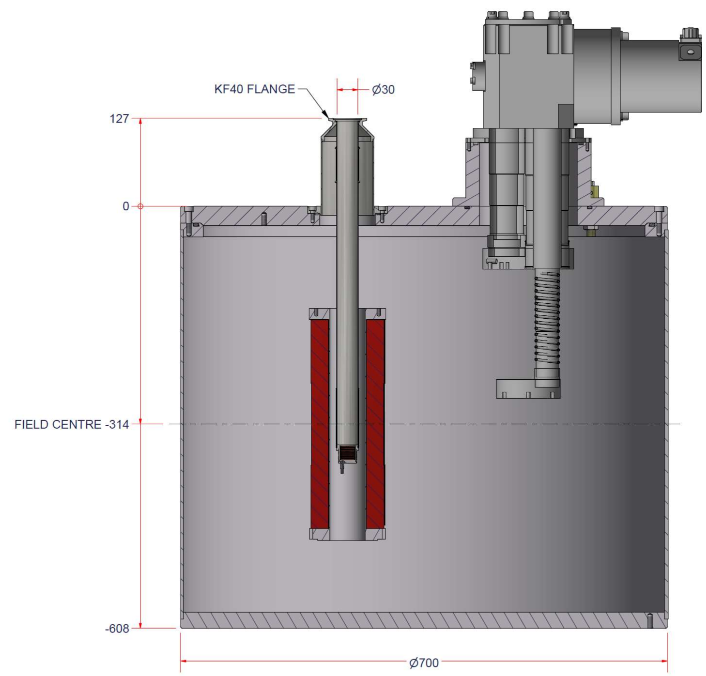
- Compact, dry magnet (no liquid cryogens)
- Closed-cycle, continuous, pumped helium cooling
- 6.7 T (188 GHz) / 1.4 K
- Broad band NMR console and tuneable probe
- Highly efficient, integral fluid path for dissolution
- Automated processing

Ardenkjær-Larsen et al, MRM 2019

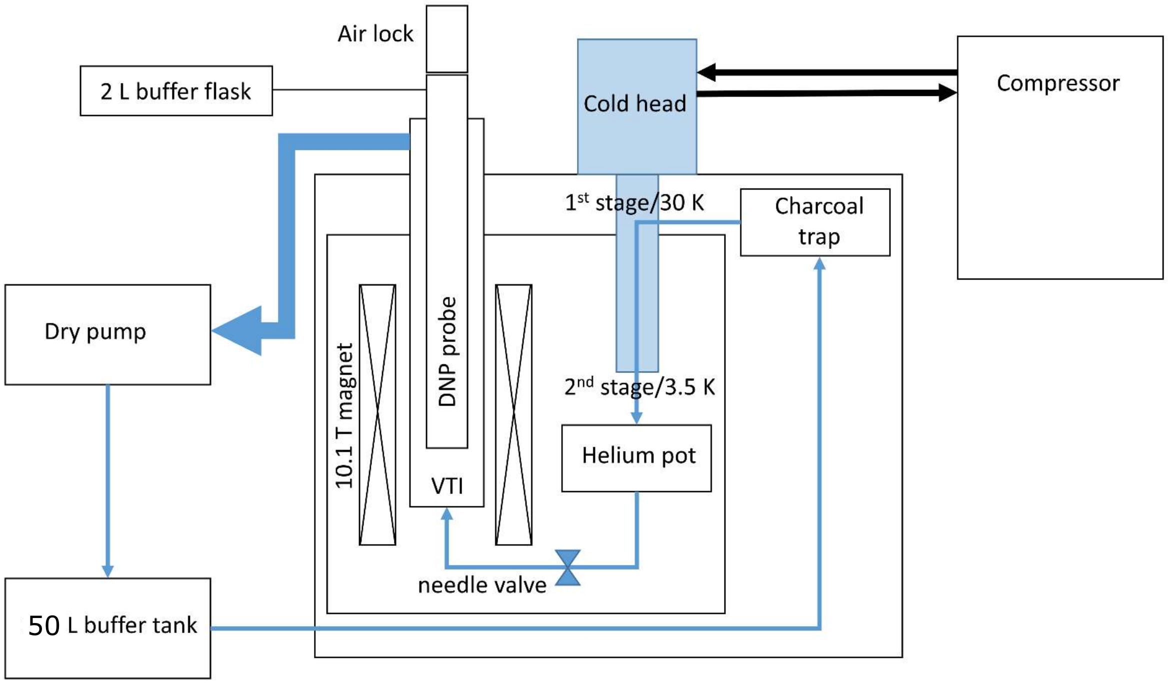
Polarizer magnet

- 6.7 T magnet (dry), 50 ppm in 25 mm diameter cylinder, <0.1 ppm/h drift rate
- Variable Temperature Insert (VTI), 30 mm diameter and 440 mm length
- Unshielded, 5 G line at 1.5 m
- Cools down in 24 hours from room temperature (from quench in ca 2 hours)
- Always connected to power supply





Helium cooling system

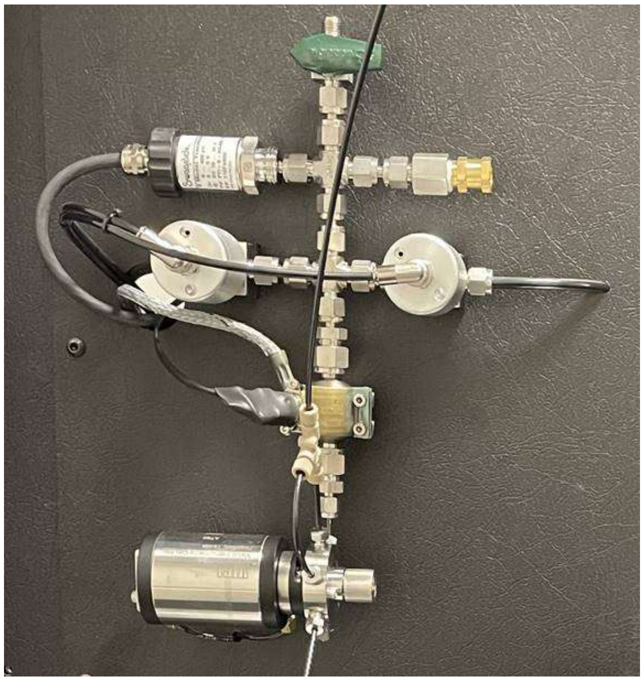


Base temperature (without heat loads): <1.4 K (range: 1.4 K – 300 K)

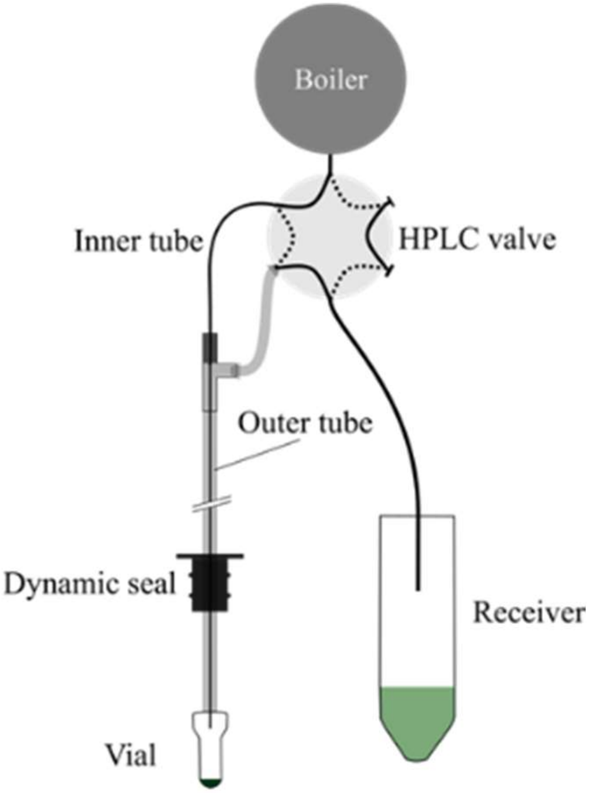
Buffer tank is charged with 50 L helium gas (ca 65 mL of liquid Helium).
Leybold Ecodry Plus (dry pump) has a pumping speed of 50-60 m^3/h

Dissolution module and fluid path

Filling of solvent into boiler



Fluid Path



Screw-on-vial

dDNP probe and microwave source

3.35 T

94.0 ± 1.0 GHz

400 mW

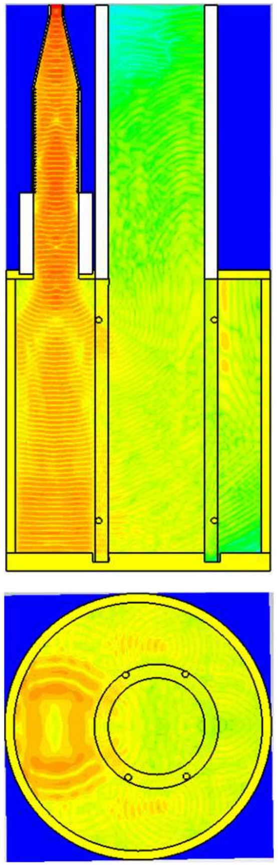
FM and PM

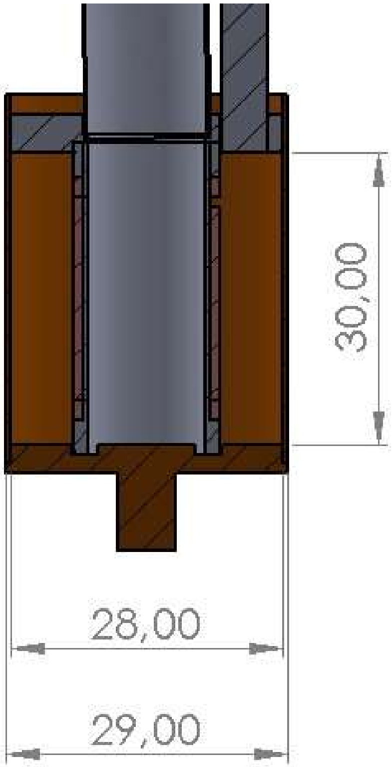
6.70 T

x 2

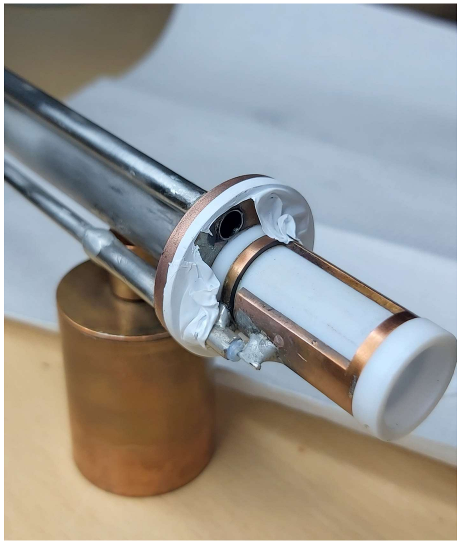
188.0 ± 2.0 GHz

100 mW



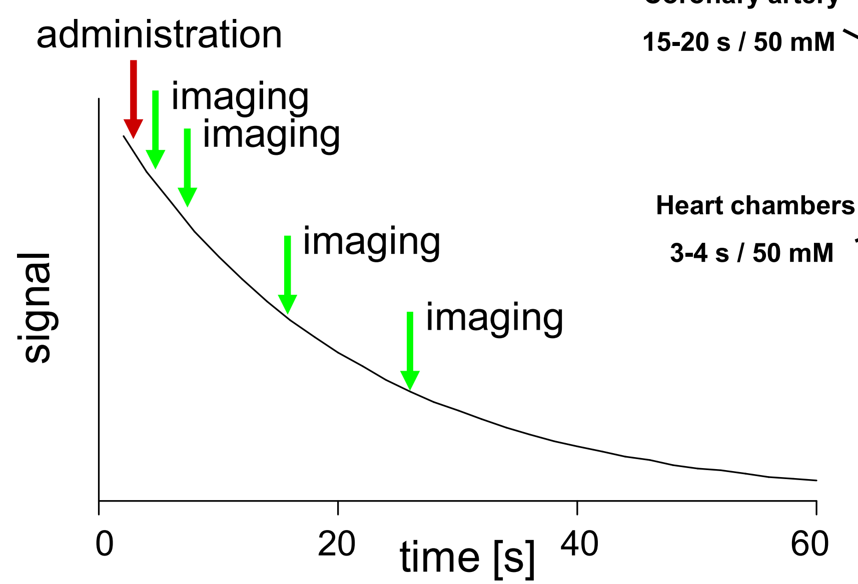


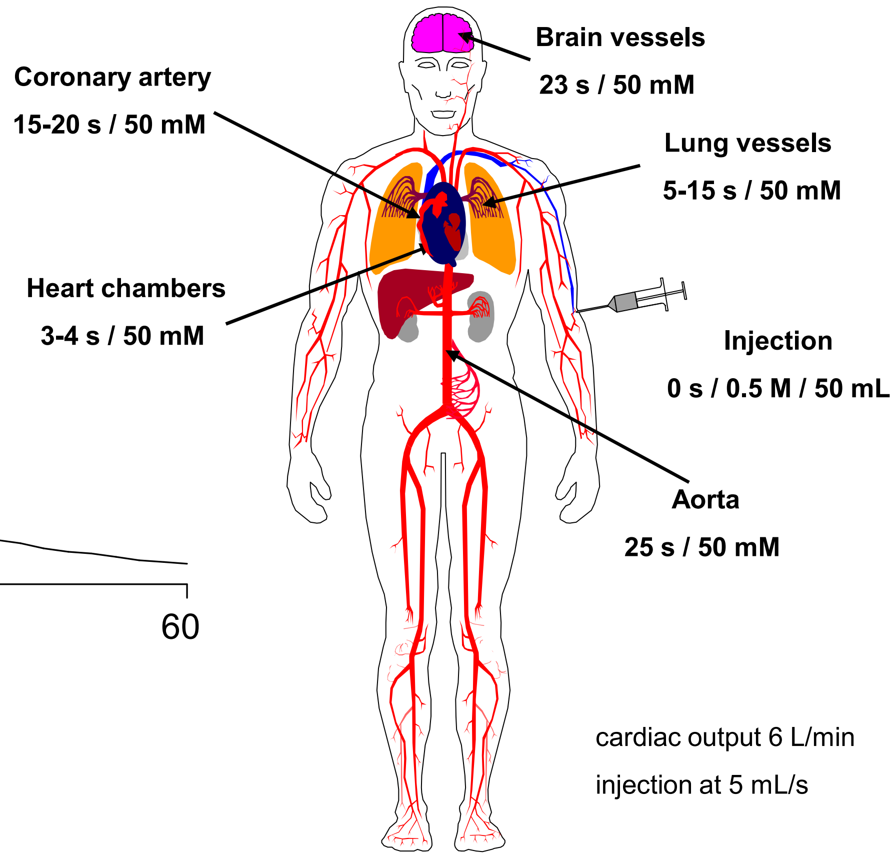
dDNP probe and NMR spectrometer



NMR spectrometer (Gecho)
2 channels
5 us dead time (active TR switch)
300 W Tomco RF amplifier (5-310 MHz)

The signal decays due to relaxation and dilution

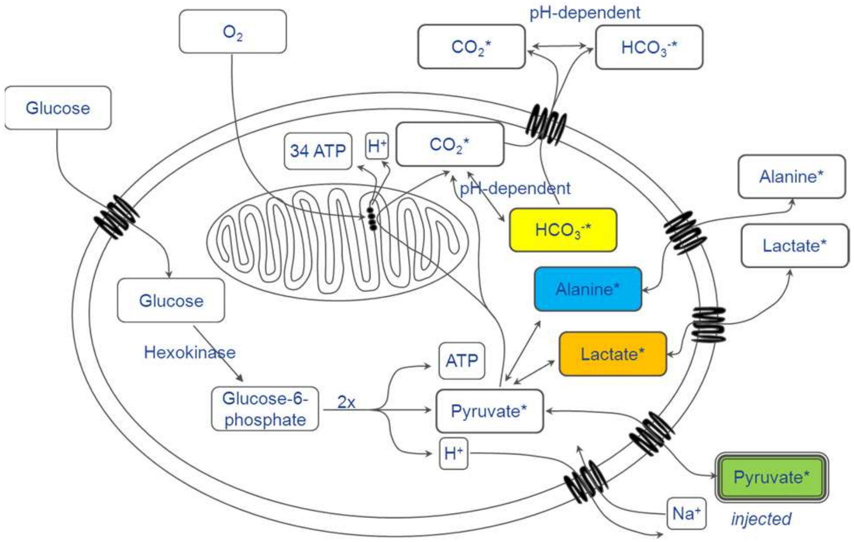


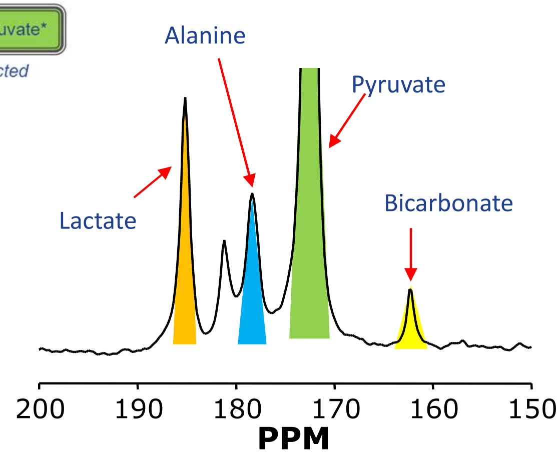


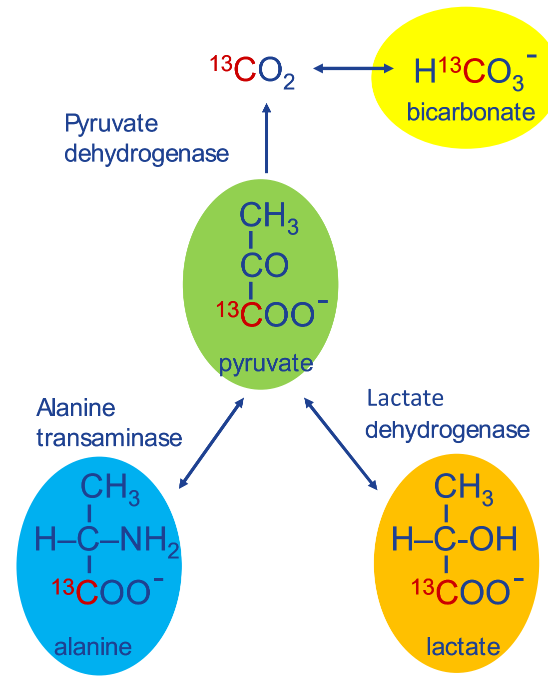
cardiac output 6 L/min

injection at 5 mL/s

Hyperpolarized Metabolic MR with [1-^{13}C]pyruvate







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Danmarks Grundforskningsfond Danish National Research Foundation

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LUNDBECKFONDEN

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POLARIZE

Peter Bodin, Joachim Vinther, Axel Morgenstjerne, Søren Jakobsen, David Gaurin