An introduction to NMR Hyperpolarization

The struggle towards higher NMR sensitivity

Dr. Sören Lehmkuhl soeren.lehmkuhl@kit.edu
Dr. Mazin Jouda, Dr. Vlad Badilita, Dr. Sören Lehmkuhl, Prof. Jürgen Brandner

It’s always about sensitivity

How to increase sensitivity?

Physics

Chemistry

Engineering

NMR sensitivity

Most important: signal to noise ratio (SNR)

Other factors:
- high homogeneity (e.g. for spectral or spatial resolution)
  high gradient strenghts (e.g in MRI)
- Noise reduction: (e.g. Johnsson noise)
- sensitive coils (B_1 field)

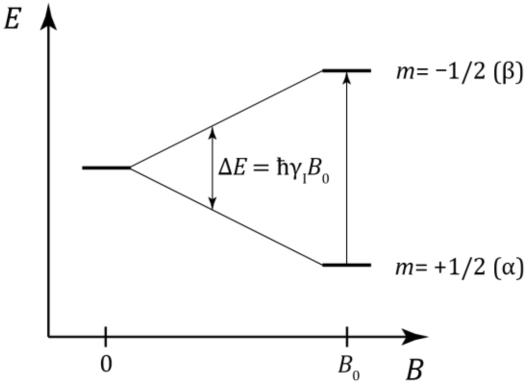
Time

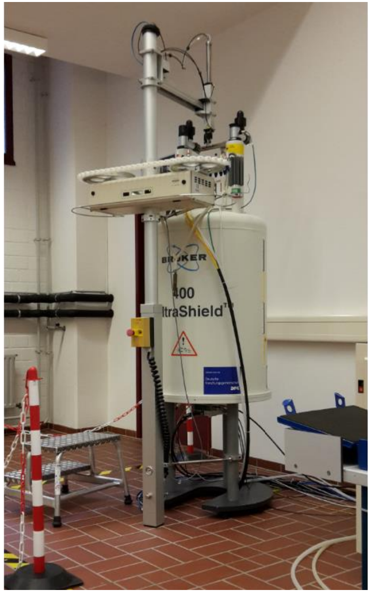
$$SNR = \frac{S}{N} \sim \sqrt{t}$$

Is there another way to get more signal?

How to increase an NMR signal:

Spin density	Polarization	Hyperpolarization
Concentration Abundance	Gyromagnetic ratio Temperature Magnetic field	DNP SEOP PHIP





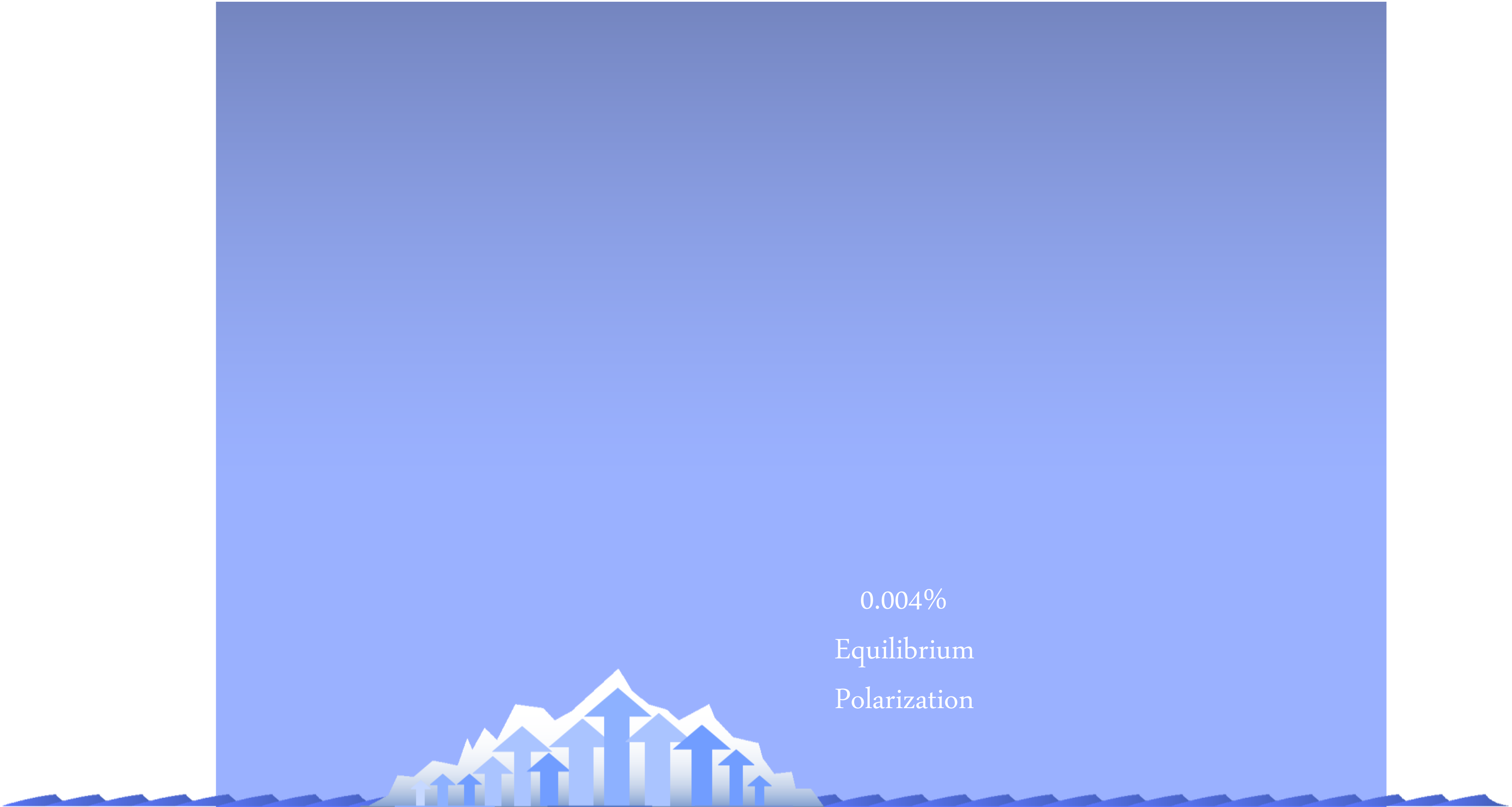
Zeeman splitting

at thermal equilibrium Boltzmann distribution

Energy difference between the two spin states: 1.6×10^{-4} kJ mol^{-1}

→ population difference of 1 : 31000 for 9.4 T at 300K

The NMR signal



NMR signal

- In the simple case of I=½ the resulting magnetization is

$$M = \frac{\hbar}{2} N \gamma P \qquad P = \frac{N_+ - N_-}{N_+ + N_-}$$

- Ratios between populations of successive magnetic energy levels

$$\frac{N_m}{N_{m+1}} = \exp\left(\frac{\gamma \hbar B_0}{kT}\right)$$

- At high temperatures (T > 1K) and average fields (1-10 Tesla):

$$M = \frac{N\gamma\hbar}{2}\left(\frac{1+\frac{\gamma\hbar B_0}{2kT} - 1 + \frac{\gamma\hbar B_0}{2kT}}{1+\frac{\gamma\hbar B_0}{2kT} + 1 - \frac{\gamma\hbar B_0}{2kT}}\right) = \frac{N}{4}\gamma^2\hbar^2\frac{B_0}{kT}$$

NMR signal

- In the simple case of I=½ the resulting magnetization is

$$M = \frac{\hbar}{2} N\gamma \boldsymbol{P} \qquad \boldsymbol{P} = \frac{\boldsymbol{N_+ - N_-}}{\boldsymbol{N_+ + N_-}}$$

- Ratios between populations of successive magnetic energy levels

$$\frac{N_m}{N_{m+1}} = \exp\left(\frac{\gamma\hbar B_0}{kT}\right)$$

- At high temperatures (T > 1K) and average fields (1-10 Tesla):

$$M = \frac{N\gamma\hbar}{2}\left(\frac{1+\frac{\gamma\hbar B_0}{2kT} - 1 + \frac{\gamma\hbar B_0}{2kT}}{1+\frac{\gamma\hbar B_0}{2kT} + 1 - \frac{\gamma\hbar B_0}{2kT}}\right) = \frac{N}{4}\gamma^2\hbar^2\frac{B_0}{kT}$$

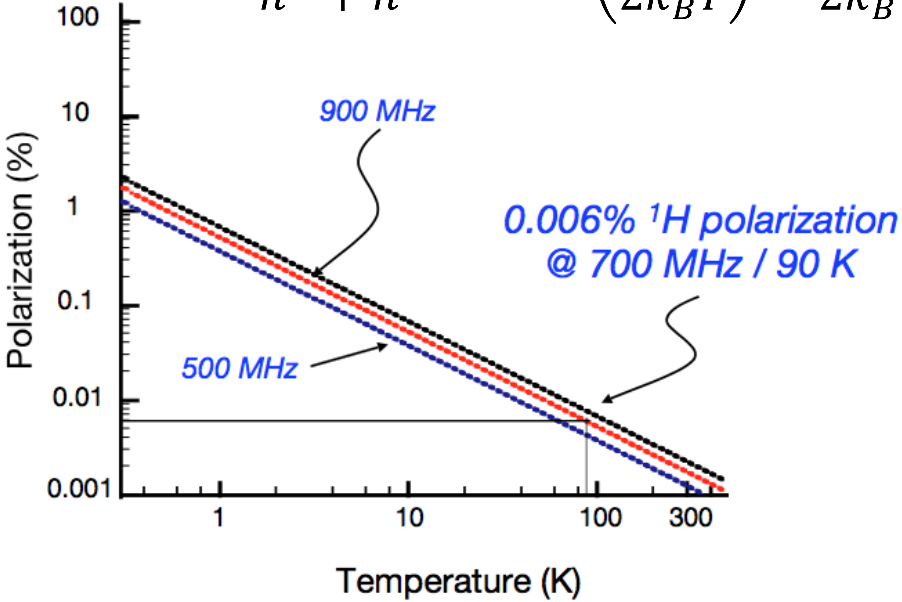
NMR Hyperpolarization

- Brute Force NMR
  - Very low temperatures
  - Very high fields
- Dynamic nuclear polarisation (DNP)
- Spin-exchange optical pumping (SEOP)
- Parahydrogen induced polarisation (PHIP)

Nuclear Spin Polarization

Temperature and Field Dependence

$$P = \frac{n^+ - n^-}{n^+ + n^-} = \tanh\left(\frac{\gamma\hbar B_0}{2k_B T}\right) \simeq \frac{\gamma\hbar B_0}{2k_B T}$$



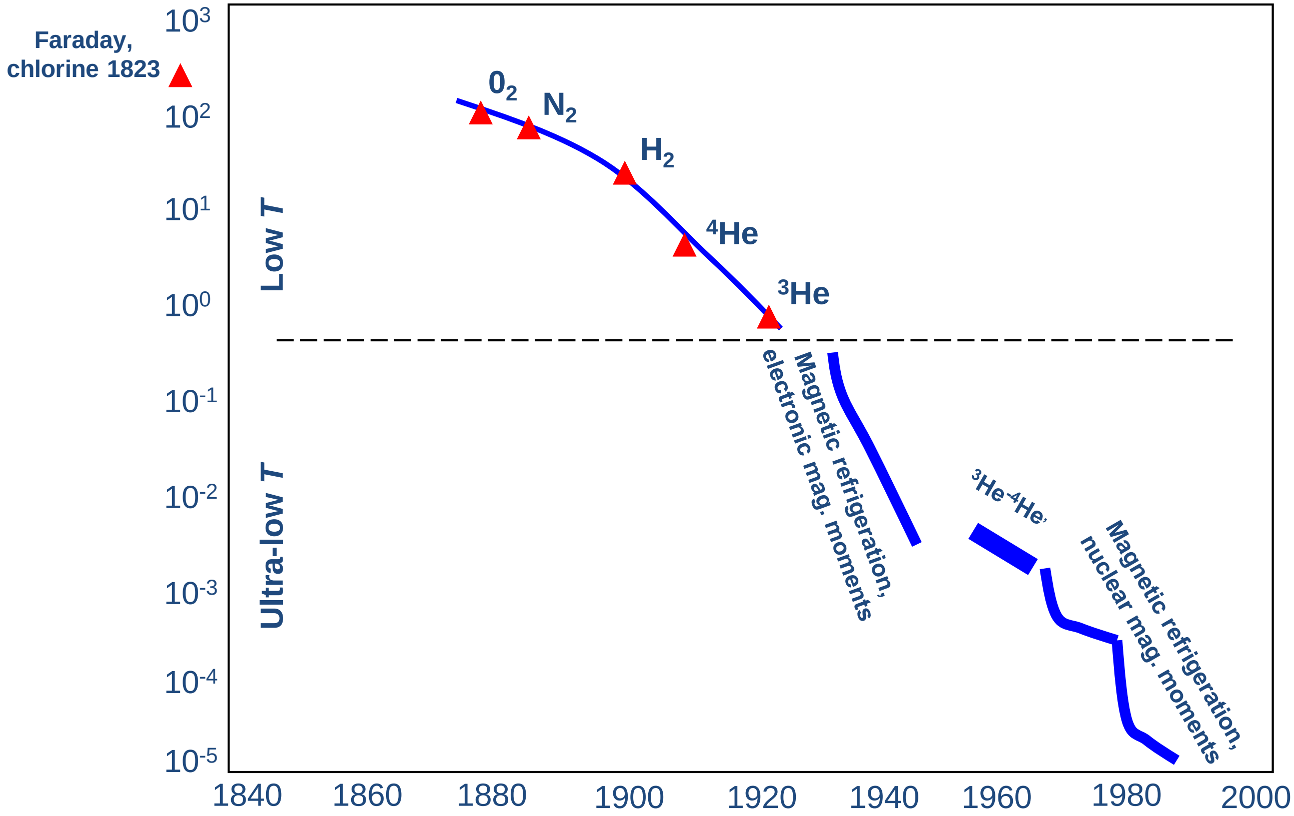
Evaporation of Liquified Gases (T > 1K)

Substance	boiling T (P=1 bar)	melting T (P=1 bar)	Latent heat kJ/liter	Price $ / liter
H_2O	373.15	273.15	2252	
Xe	165.1	161.3	303	
O_2	90.2	54.4	245	
N_2	77.4	63.3	160	0.3
H_2	20.3	14.0	31.8	
^4He	4.21	--	2.56	4
^3He	3.19	--	0.48	$5x10^4$

the cooling power diminishes rapidly with decreasing ***T***

P , torr	10^{-4}	10^{-3}	10^{-2}	10^{-1}	1	10	100
T(^{4}He), K	0.56	0.66	0.79	0.98	1.27	1.74	2.64
T(^{3}He), K	0.23	0.28	0.36	0.47	0.66	1.03	1.79

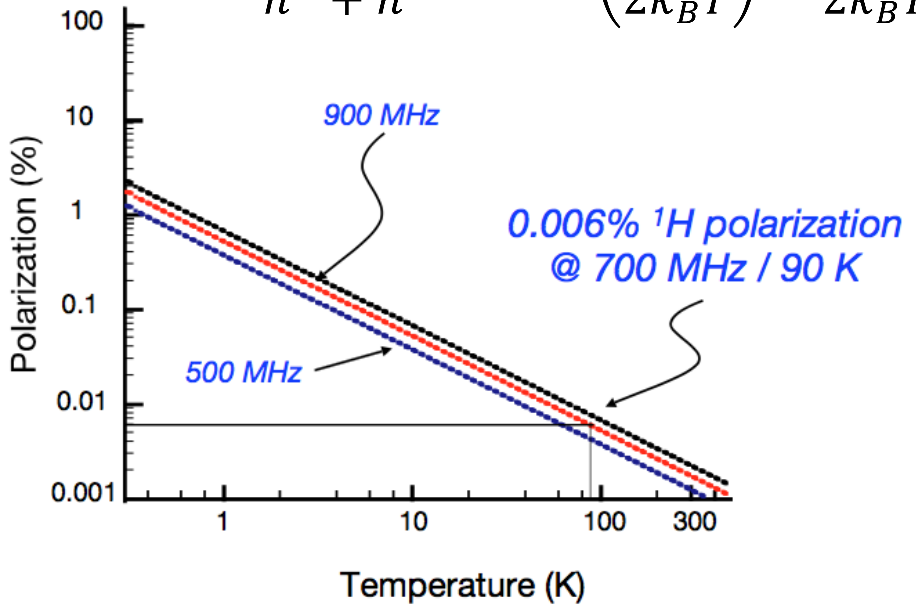
Historical Development of Refrigeration



Nuclear Spin Polarization

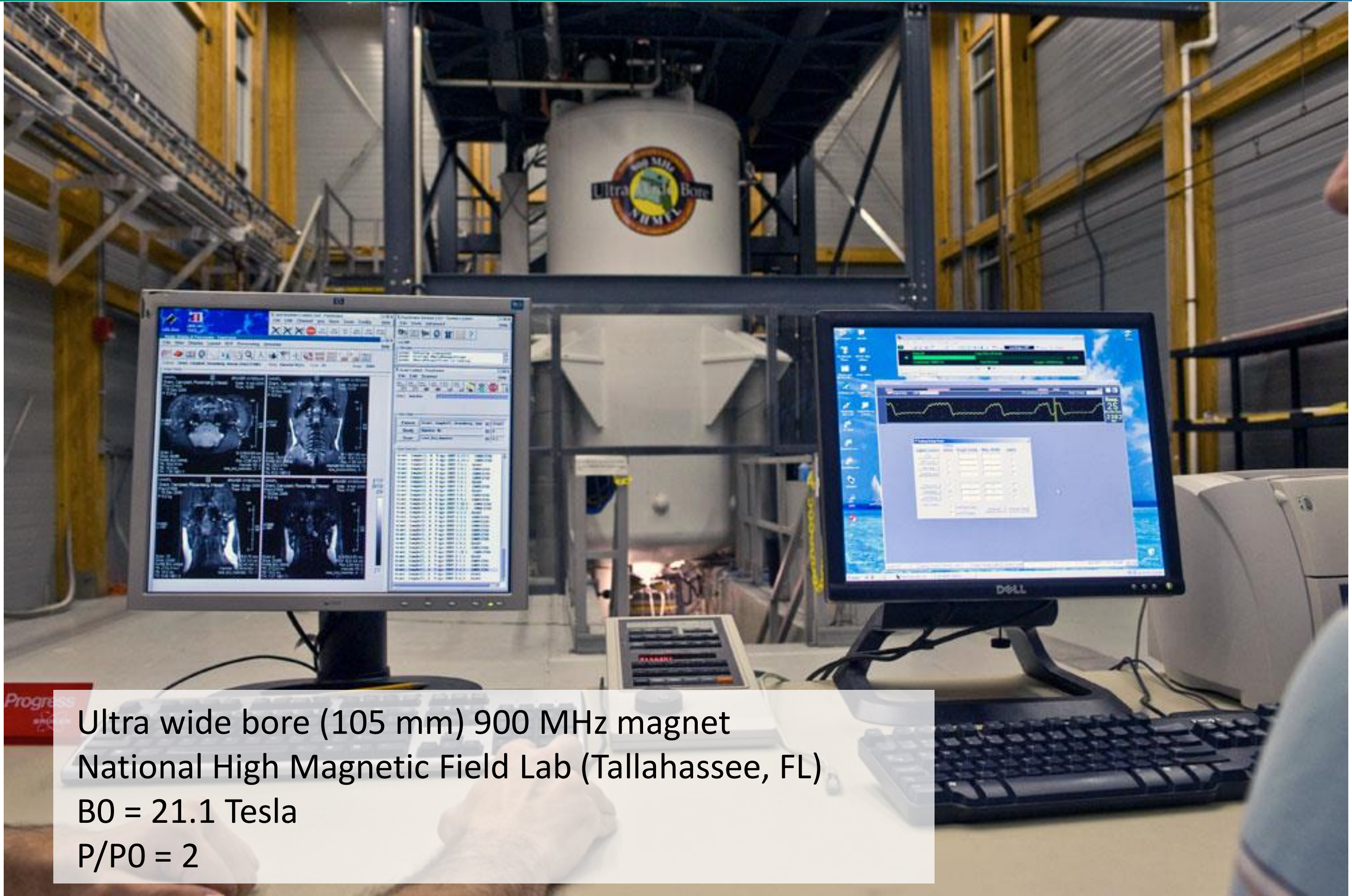
Temperature and Field Dependence

$$P = \frac{n^+ - n^-}{n^+ + n^-} = \tanh\left(\frac{\gamma\hbar B_0}{2k_B T}\right) \simeq \frac{\gamma\hbar B_0}{2k_B T}$$



Bruker Aeon 1 GHz magnet

Bruker Aeon 1 GHz magnet
Installed at the University of Bayreuth
B0 = 23.5 Tesla
P/P0 = 2



Ultra wide bore (105 mm) 900 MHz magnet
National High Magnetic Field Lab (Tallahassee, FL)
B0 = 21.1 Tesla
P/P0 = 2

MagLab Magnets

	Series Connected Hybrid Magnet	45 Tesla Hybrid Magnet	900 MHz Ultra-Wide Bore NMR Magnet
Frequency	1.5 GHz	n/a	900 MHz
Field strength	36 tesla	45 tesla	21.1 tesla
Bore size	40 mm	32 mm	105 mm
Field Homogeneity	1 part per million	150 part per million	0.001 part per million
Year completed	2016	1999	2004
Cost	$18.7 million	$14.4 million	$16 million

MagLab Magnets

	Series Connected Hybrid Magnet	45 Tesla Hybrid Magnet	900 MHz Ultra-Wide Bore NMR Magnet
Height	3.6 meters (11.8 feet)	6.7 meters (22 feet)	About 5 meters (16 feet)
Weight	30,000 kg (33 tons)	31,752 kg (35 tons)	13,600 kg (15 tons)
Type of magnet	Resistive-superconducting hybrid (coils connected in series)	Resistive-superconducting hybrid (coils connected in parallel)	Superconducting
Cost to operate at full field	$678 /hour	$1,452 /hour	$33 /hour
Power required to operate	14 Megawatts	30 Megawatts	0 Megawatts

nali

Pulsed fields at HLD

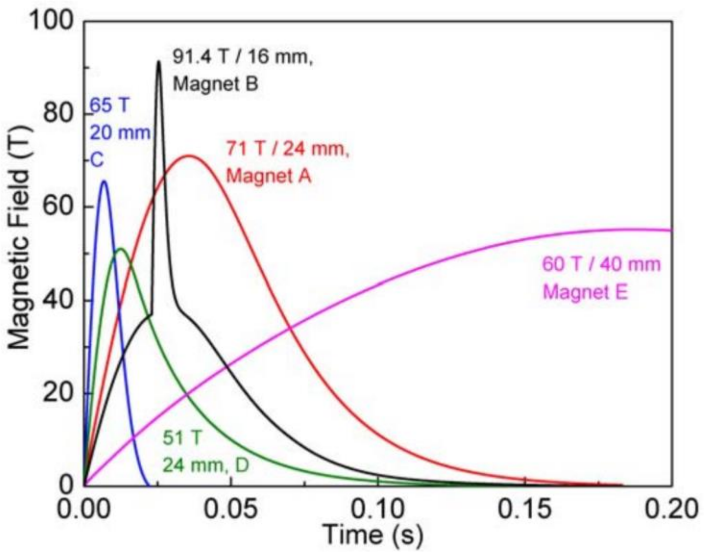
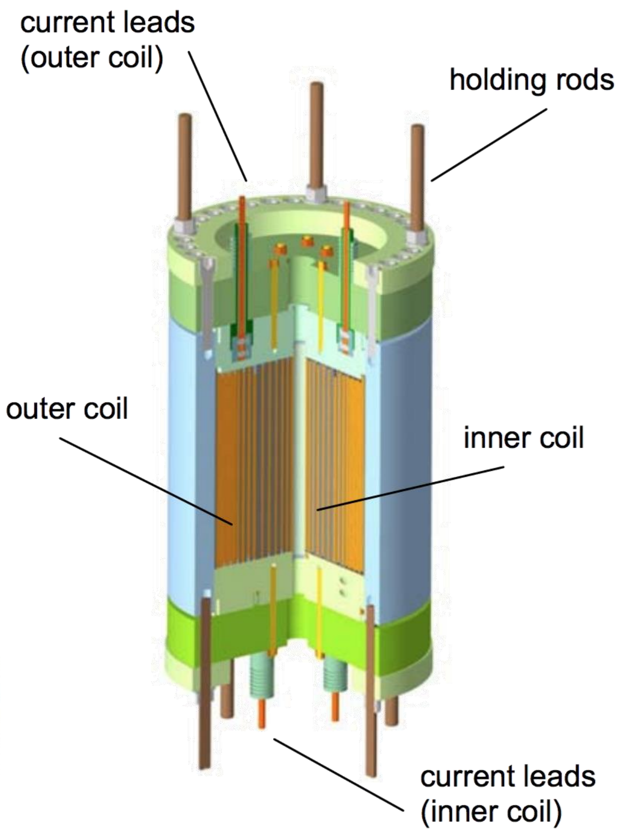
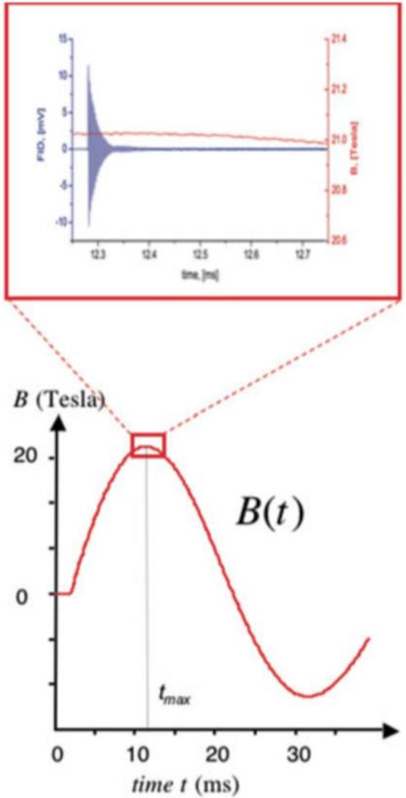
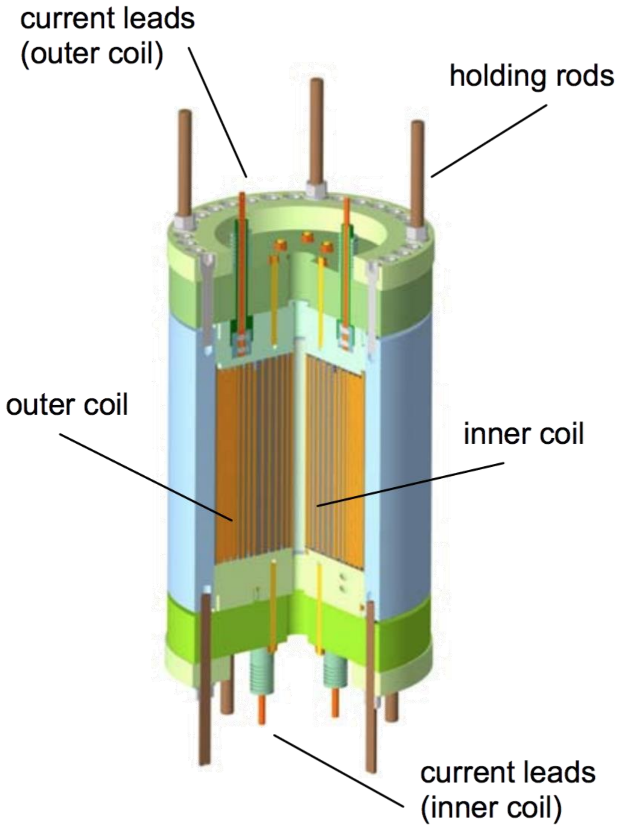


Fig. 2. (Color online) Measured time dependences of the magnetic fields obtained with various pulsed magnets operational at the HLD. Magnets A and D are 8.5 and 1.5 MJ magnets, respectively. Both of them have bores of 24 mm. Magnet B is a dual-coil 9.5 MJ magnet with a 16 mm bore. Magnet C is a 1 MJ pulsed magnet with a 20 mm bore. Magnet E is a 43 MJ long-pulse magnet with a 40 mm bore.



Pulsed fields at HLD





Brute Force is a lot of effort

Is Brute Force Convenient?

Average enhancements (ref: H = 11.7 Tesla, T =300 K) :

High fields (100 T), room temp: $P/P_0 = 10$
Standard fields and low temp (10 mK): $P/P_0 = 10^4 - 10^5$
High fields, low temp: $P/P_0 = 10^5$

Pros:
High enhancements at extremely low temperatures
In situ polarization, independent from sample preparation
Sample is not contaminated by foreign agents

Cons:
Technically demanding
Slow relaxation times at low temperatures / high fields
Long measurement times
Not necessarily safe for the sample

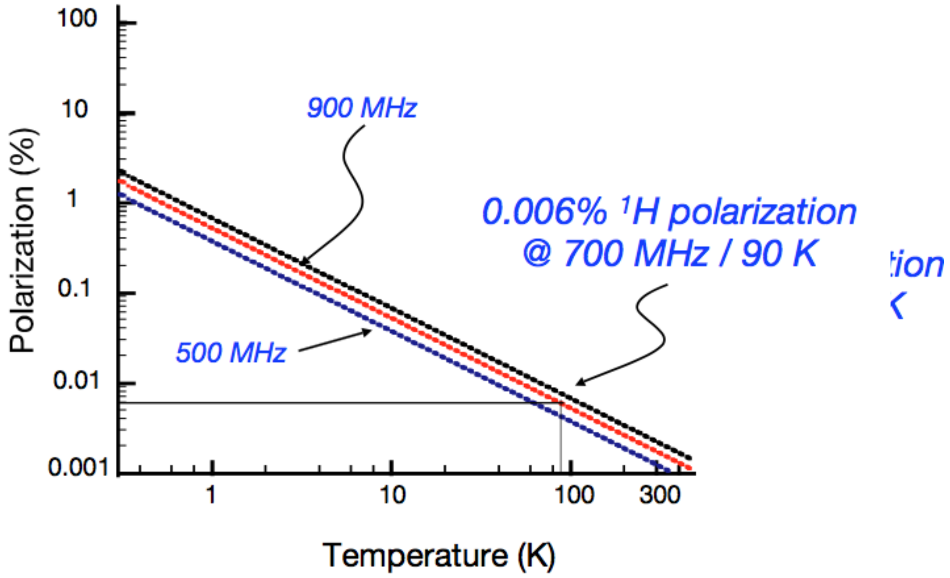
NMR Hyperpolarisation

- Brute Force NMR
  - Very low temperatures
  - Very high fields
- Dynamic nuclear polarisation (DNP)
- Spin-exchange optical pumping (SEOP)
- Parahydrogen induced polarisation (PHIP)

Electron and Nuclear Spin Polarization

Temperature and Field Dependence

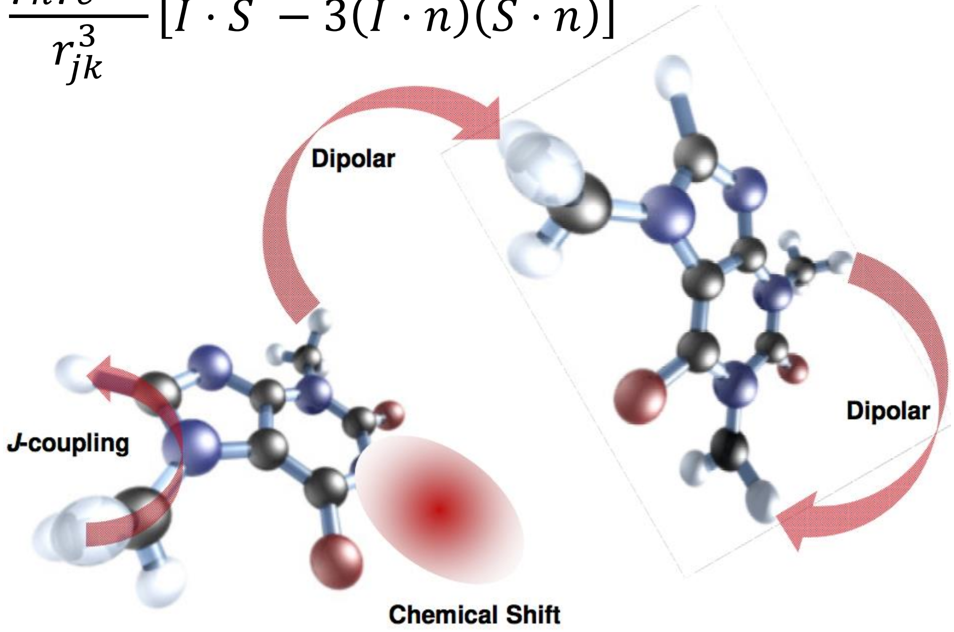
$$P = \frac{n^+ - n^-}{n^+ + n^-} = \tanh\left(\frac{\gamma \hbar B_0}{2k_B T}\right) \simeq \frac{\boldsymbol{\gamma} \hbar B_0}{2k_B T} \qquad \frac{\gamma_e}{\gamma_{^1H}} \sim 660$$



Dipolar couplings

$$H = \omega_e S_Z - \omega_n I_Z + H_{ee} + H_{en} + H_{nn}$$

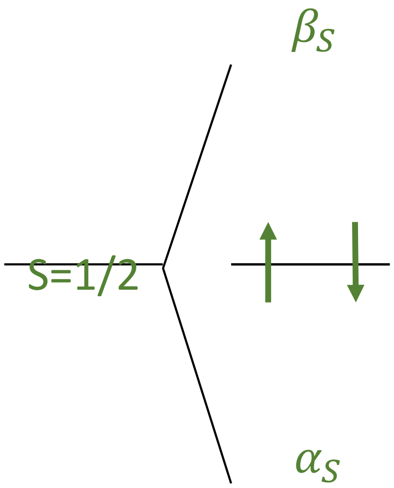
$$H_{en}^{D} = \frac{\gamma_n \gamma_e \hbar^2}{r_{jk}^3}\left[I \cdot S - 3(I \cdot n)(S \cdot n)\right]$$



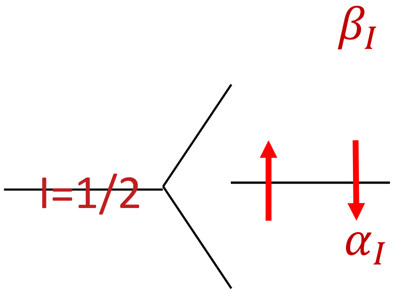
In liquids we don’t see an effect on the spectrum
due to tumbling motions
BUT it affects relaxation

2-spin system: magnetic energy levels

Electron

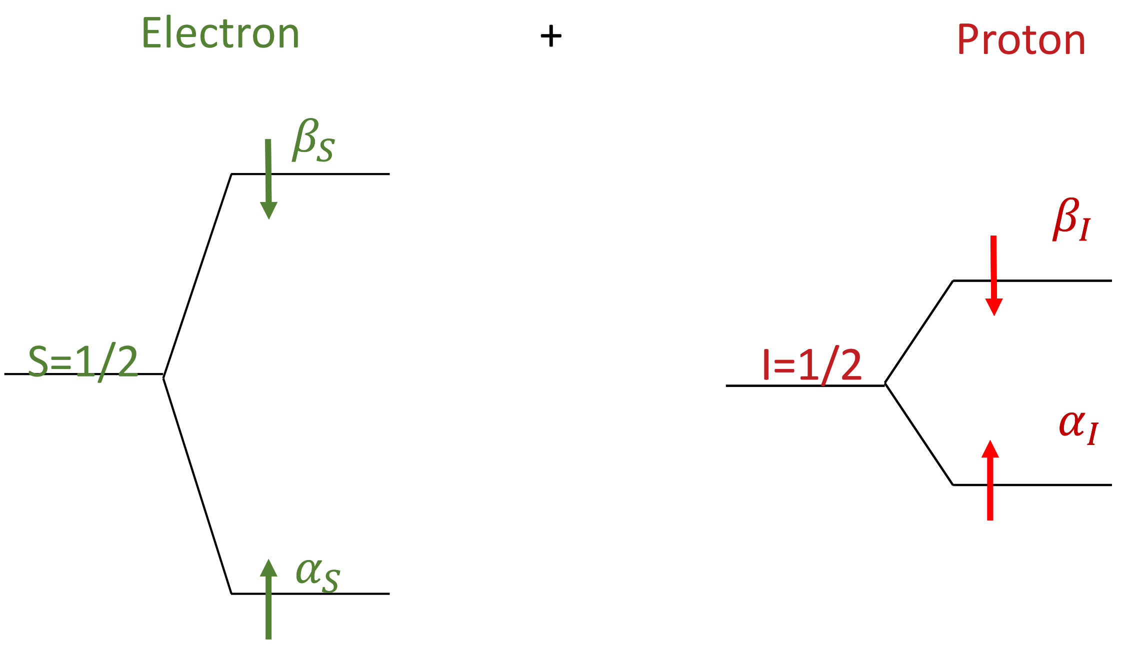


Proton



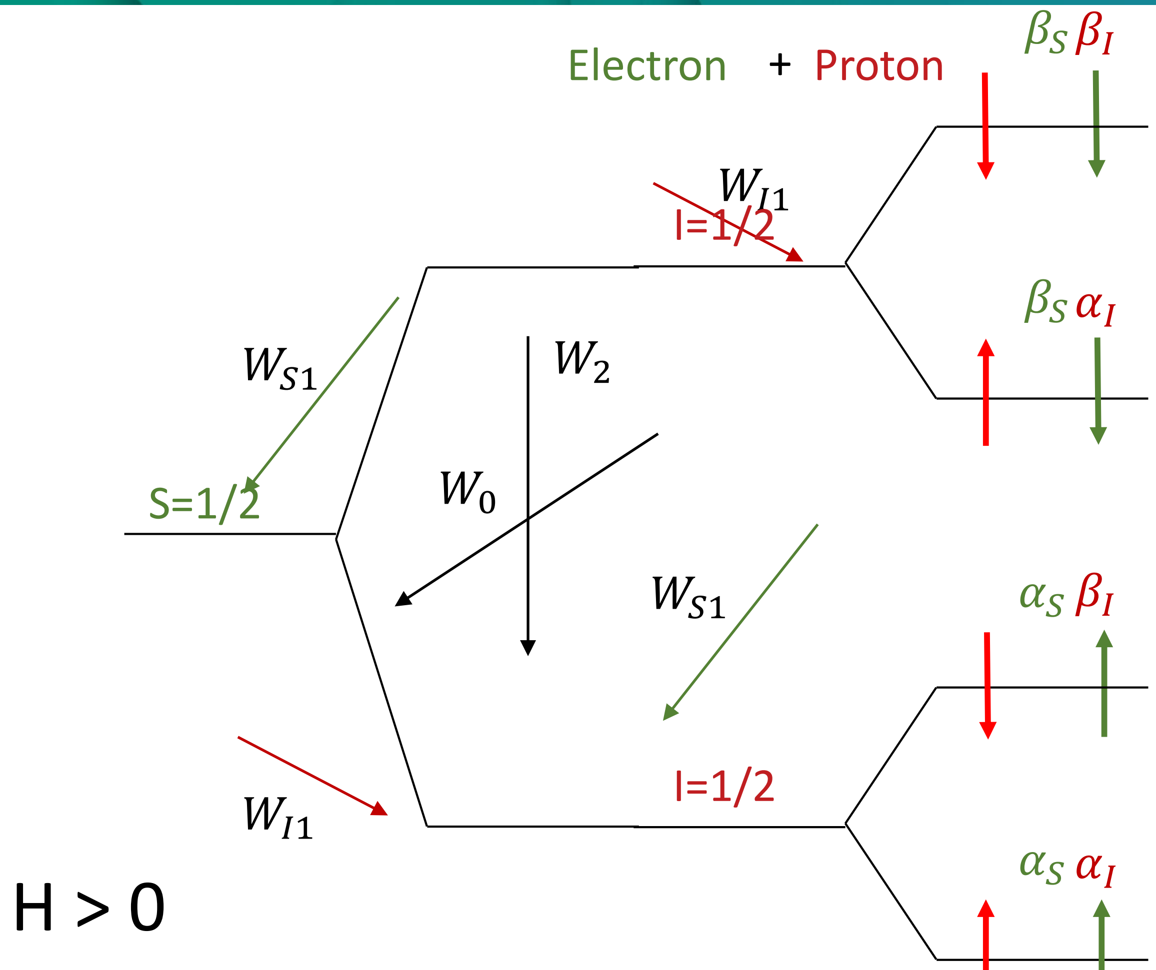
$H \geq 0$

2-spin system: magnetic energy levels

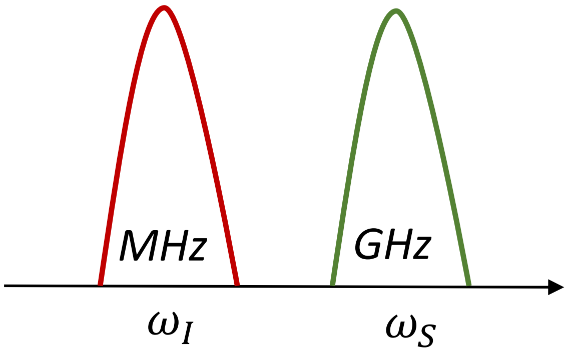


H > 0

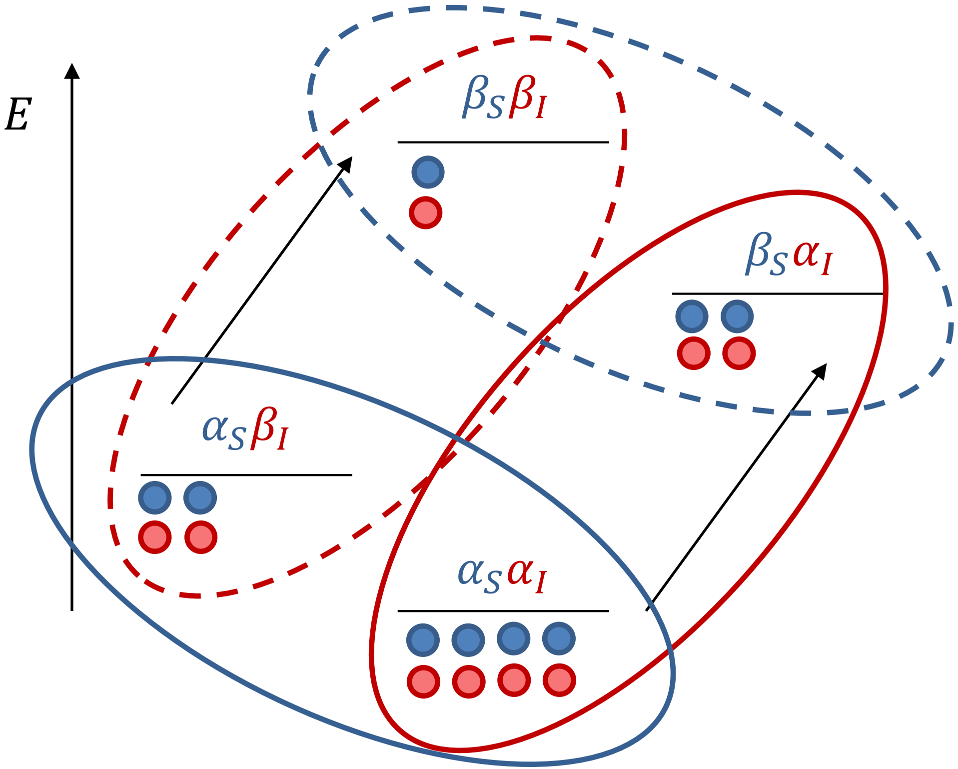
2-spin system: magnetic energy levels



W_0 and W_2 are allowed by the presence of e-H dipolar couplings but they don't show up in the NMR spectrum



Overhauser effect

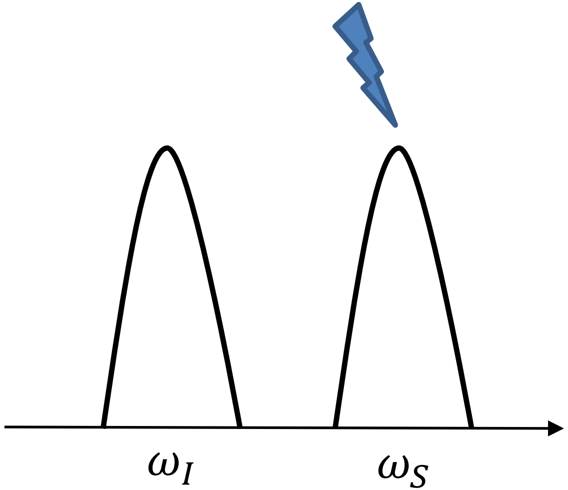


Populations

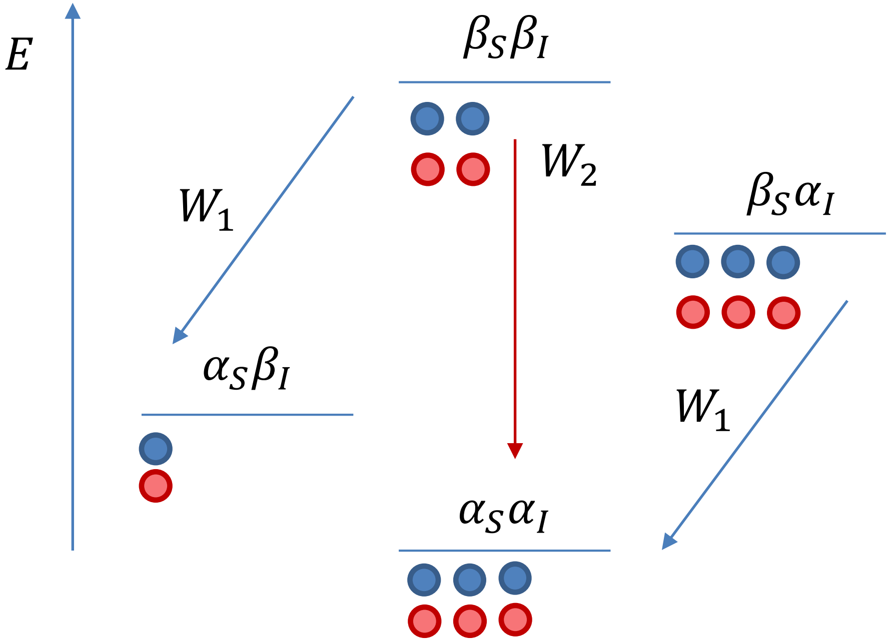
$N_i = N_{i\alpha} - N_{i\beta}$

$N_S = \not{3}\ 1$

$N_I = 3$



Overhauser effect

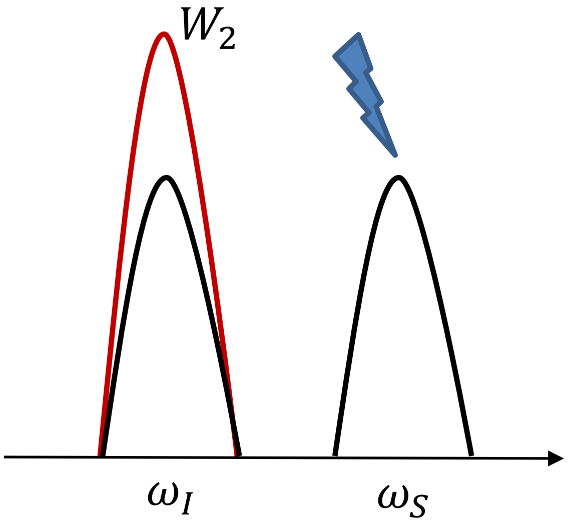


Populations

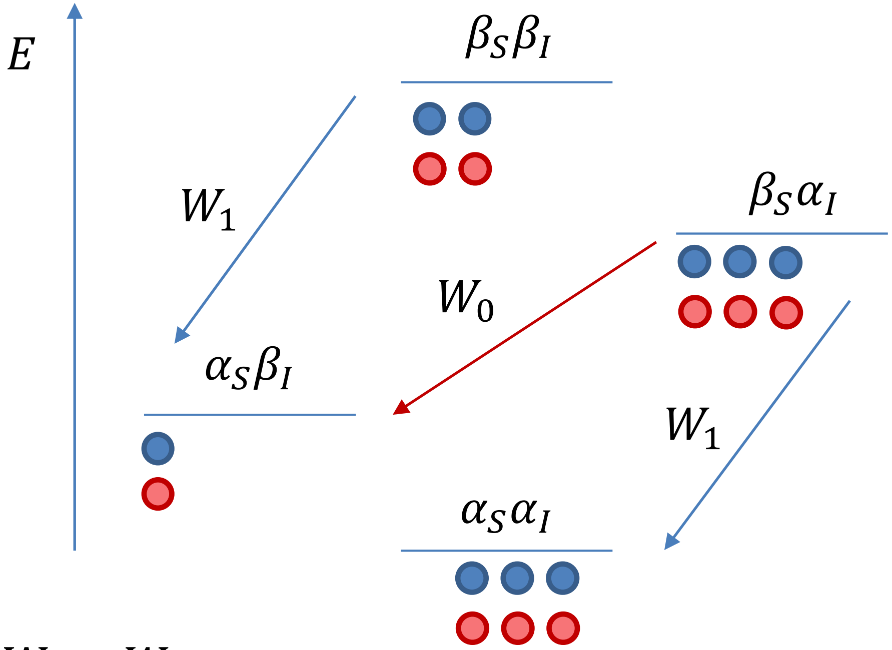
$N_i = N_{i\alpha} - N_{i\beta}$

$N_S = 1\!\!\!-\!1$

$N_I = 5$ / 3



W_2 dominates for fast tumbling molecules

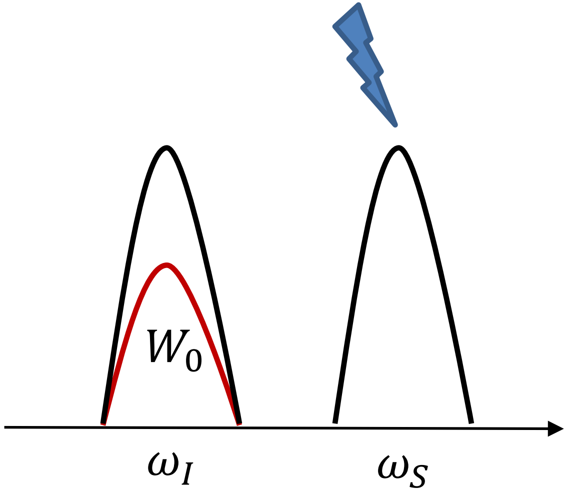


Populations

$$N_i = N_{i\alpha} - N_{i\beta}$$

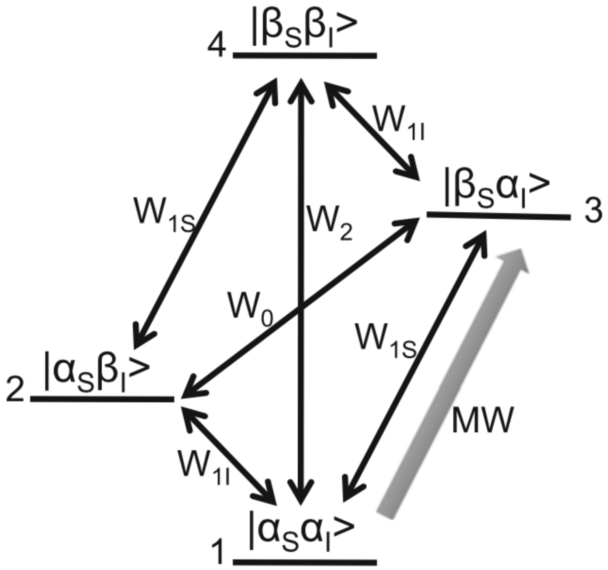
$$N_S = 1\ 1$$

$$N_I = 3$$

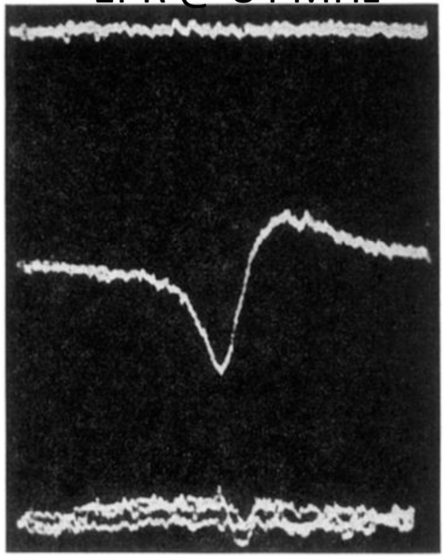


$$\frac{P_I}{P_{I0}} = 1 + \frac{W_2 - W_0}{2W_1 + W_2 + W_0} \cdot \frac{\gamma_S}{\gamma_I} \cdot \chi_{DD}$$

Overhauser effect



^{7}Li NMR @ 50kHz
EPR @ 84 MHz



^{7}Li w/o DNP

^{7}Li with DNP
@ 84 MHz

^{1}H glycerol

Carver and Slichter, Phys. Rev. 92, 212-213 (1953)
Phys. Rev. 102, 975-980 (1956)

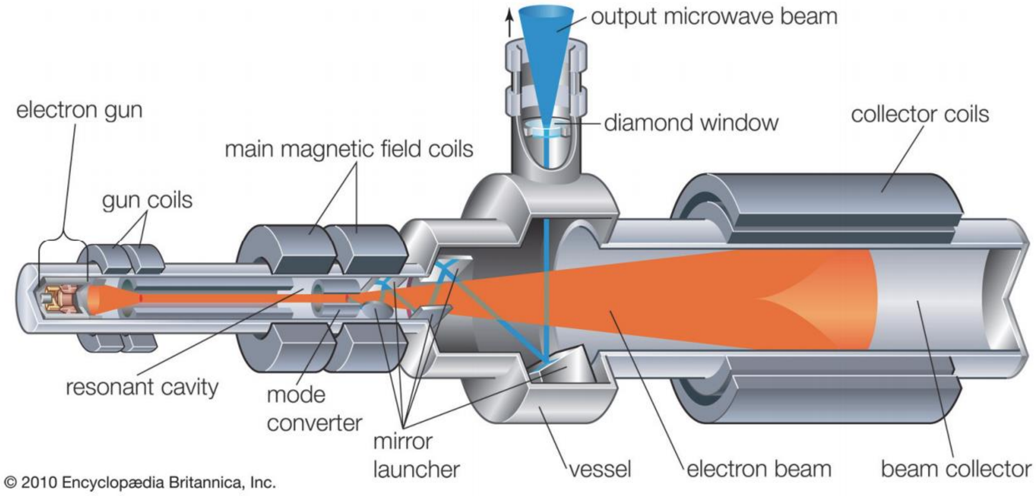
$\epsilon \sim 100$

The many flavors of DNP

DNP can be classified by the experimental arrangement that is used to carry out the experiment.

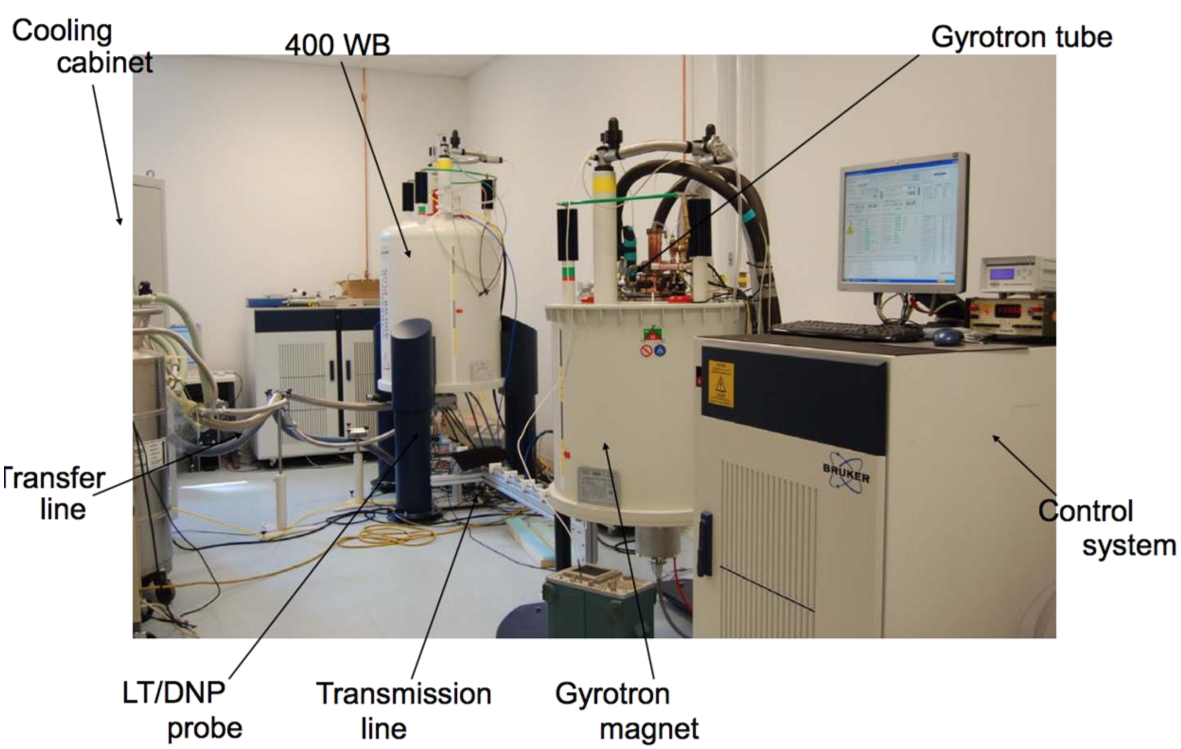
Overhauser DNP (O-DNP)	Solid-state DNP (SS-DNP)	Dissolution DNP (D-DNP)
Room temperature	Low temperatures (typically 90 K)	Low temperatures <1.5 K
Driven by the Overhauser effect (OE), where the entire process is carried out in the liquid state.	Driven by the cross effect (CE), using high-power microwave sources in conjunction with MAS for solid-state NMR.	Driven by thermal mixing (TM) or the solid effect (SE).

Microwave sources: Gyrotrons

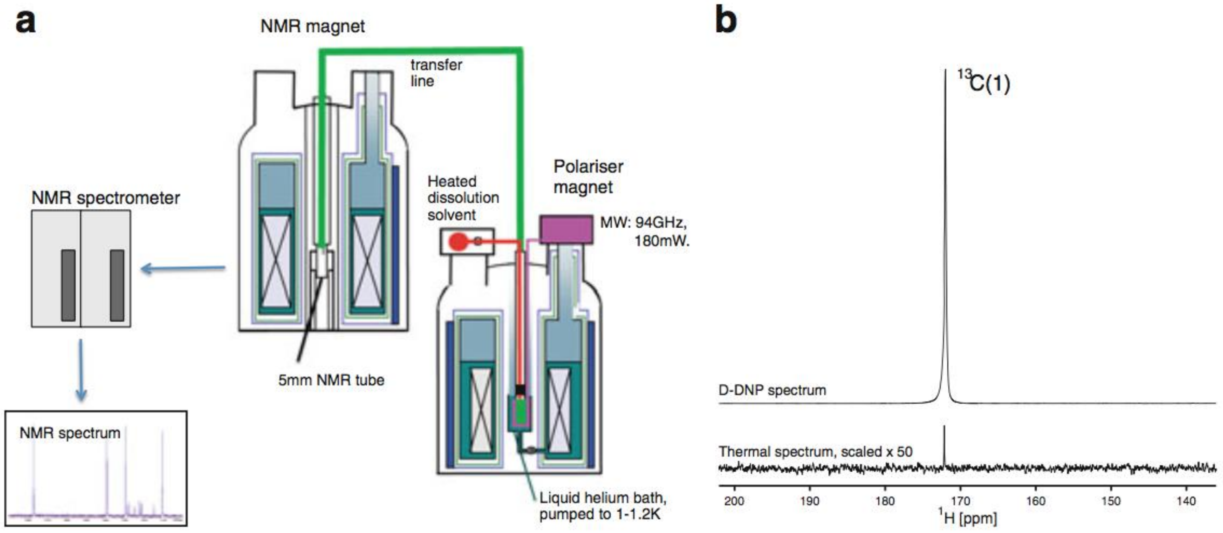


A *gyrotron*, also known as *cyclotron resonance maser*, is a type of free electron maser. The device creates a strong beam of electrons with spiral trajectories moving in a strong magnetic field and passing through a resonant cavity. The bunching in this case occurs along the trajectory spiral. Gyrotron output power can reach many megawatts. The output frequency is easily tuned by changing the magnet field and the resonance frequency of the cavity.

263 GHz gyrotron in Bruker Billerica (MA) DNP Lab



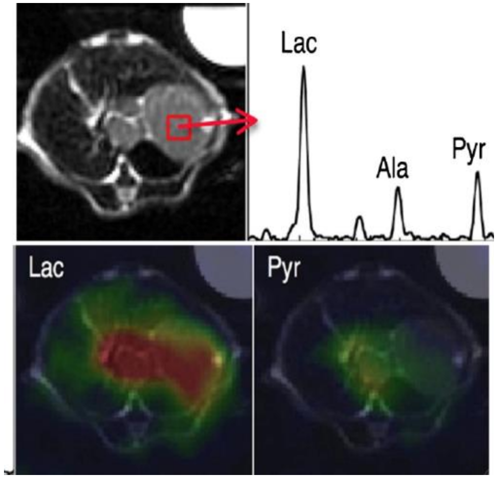
Dissolution DNP



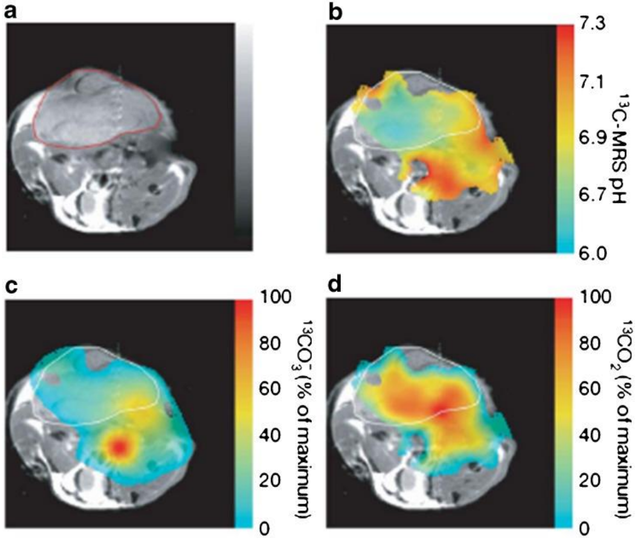
Dissolution DNP (also ex-situ DNP), pioneered by Ardenkjær-Larsen, yields by far the largest overall enhancements of all implementations of DNP.

$$\epsilon' = \epsilon \frac{B_{DNP}}{B_{NMR}} \cdot \frac{T_{NMR}}{T_{DNP}} \sim 10^5$$

Applications of DNP



^{13}C MRS of hyperpolarized pyruvate
To observe tumor metabolites



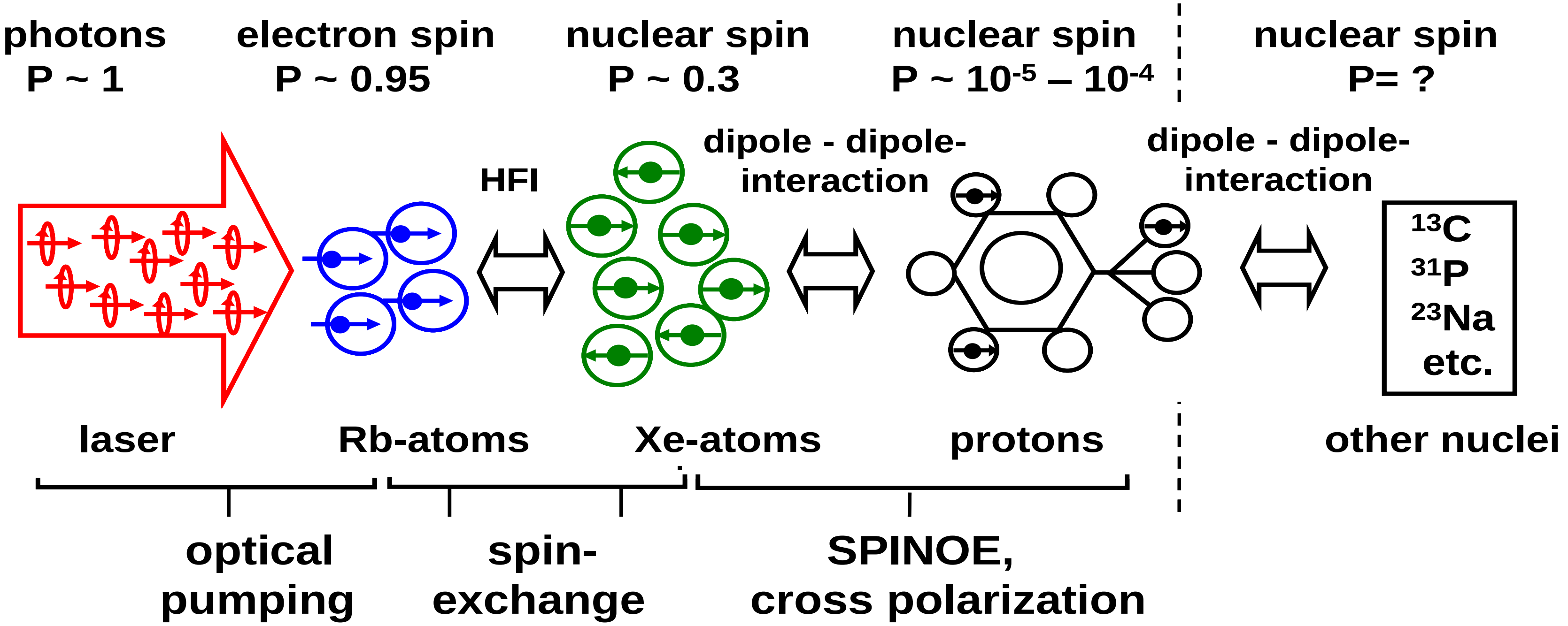
Imaging of tumor ph in-vivo
with hyperpolarized ^{13}C bicarbonate

P. Dutta, G. Martinez, and R. J. Gillies , *Biophys Rev.* **2013**; 5(3): 271–281.

NMR Hyperpolarisation

- Brute Force NMR
  - Very low temperatures
  - Very high fields
- Dynamic nuclear polarisation (DNP)
- Spin-exchange optical pumping (SEOP)
- Parahydrogen induced polarisation (PHIP)

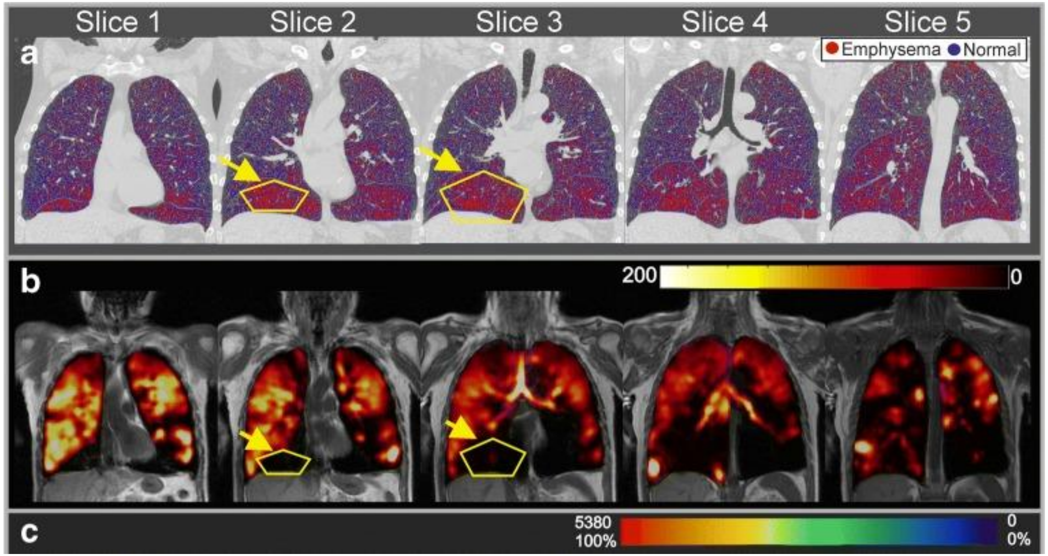
Spin Exchange Optical Pumping (SEOP)



Why hyperpolarized ^{129}Xe?

- ^{129}Xe is an excellent probe for non-invasive NMR measurements on materials
  - Zero chemical reactivity
  - Favourable absorption properties
  - Relatively high isotopic abundance (~26%)
  - Spin ½
  - High electronic polarizability, which means high chemical shifts dependent on shape, size and nature of occupied cavities.
  - High enchanced polarization (~85-90%).
  - Lack of NMR backround

Spin Exchange Optical Pumping (SEOP)



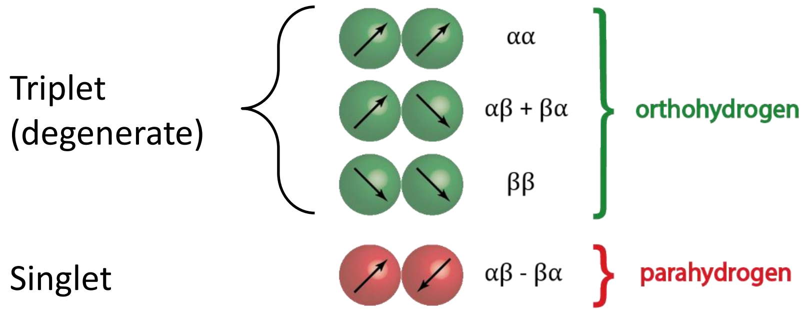
a) CT and
b) combined ^{1}H and hyperpolarized ^{129}Xe MRI
in a stage IV COPD patient

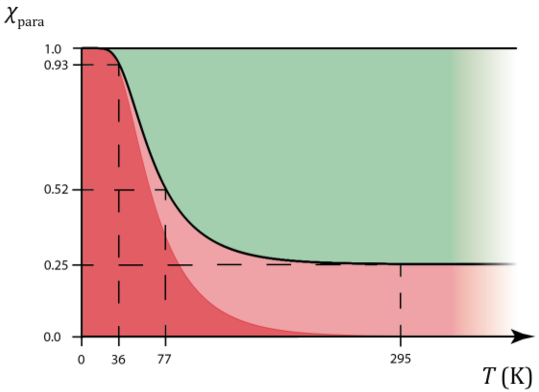
O. Doganay *et. al* , *Eur. Radiol.* **2019**, 29(8):4058-4067.

NMR Hyperpolarisation

- Brute Force NMR
  - Very low temperatures
  - Very high fields
- Dynamic nuclear polarisation (DNP)
- Spin-exchange optical pumping (SEOP)
- Parahydrogen induced polarisation (PHIP)

What is parahydrogen?



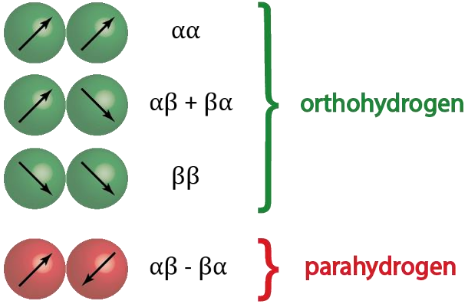


Energy difference: 1.5 kJ/mol (175 K or ~10^{12} Hz)

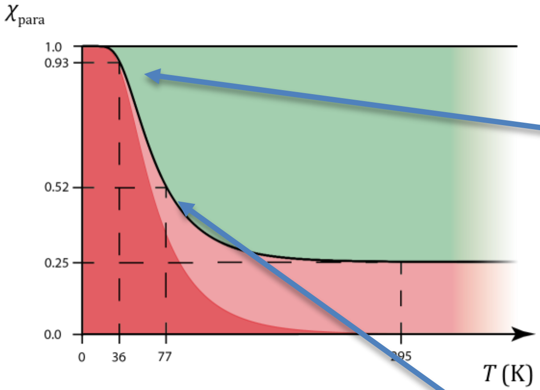
$$\Psi = \Psi_{elec}\,\Psi_{vib}\,\Psi_{rot}\,\Psi_{trans}\,\Psi_{nuclearspin}$$

But: Symmetry has to be broken to yield NMR signals

Generating parahydrogen

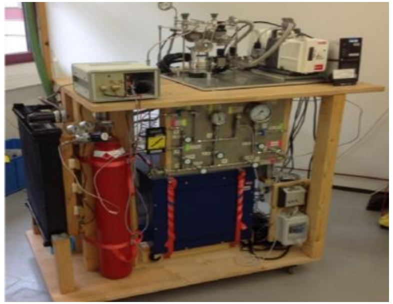


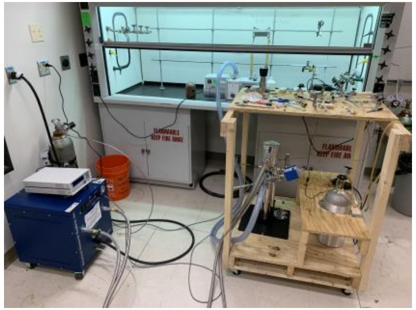
$$\Psi = \Psi_{elec}\,\Psi_{vib}\,\Psi_{rot}\,\Psi_{trans}\,\Psi_{nuclearspin}$$

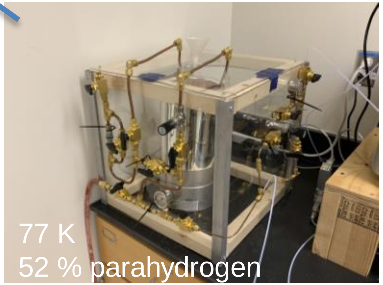


Commercial Bruker generator

IMT @ KIT



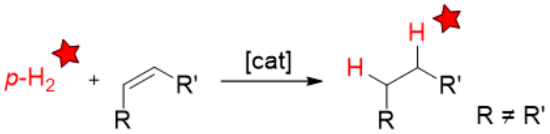




Custom made generators to achieve over 95% parahydrogen

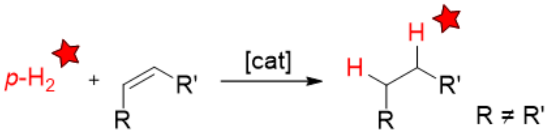
There are different mechanisms for PHIP

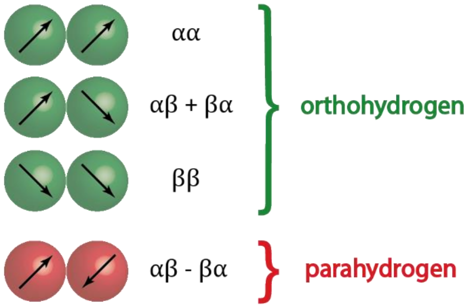
a) Hydrogenation with p-H_2

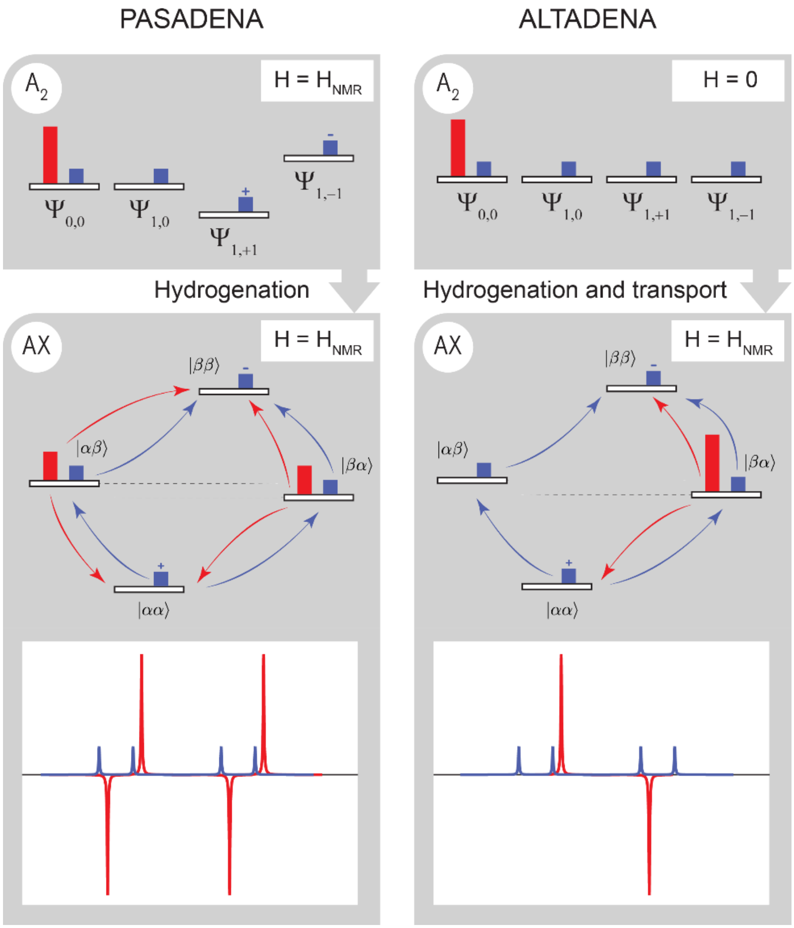


There are different mechanisms for PHIP

a) Hydrogenation with p-H_2

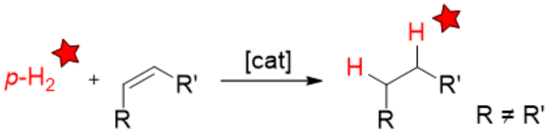




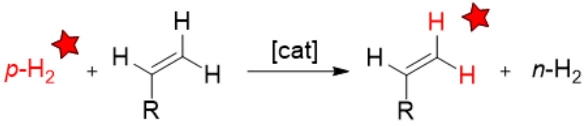


There are different mechanisms for PHIP

a) Hydrogenation with p-H_2



b) Pairwise replacement with p-H_2

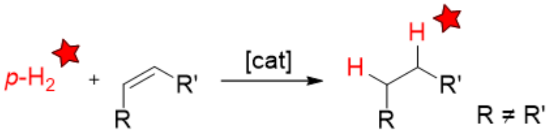


[a] C. R. Bowers and D. P. Weitekamp, *J. Am. Chem. Soc.* **1987**, 109, 5541-5542.

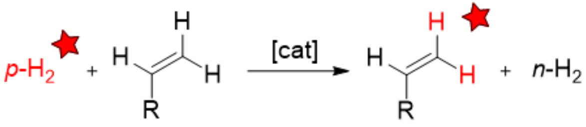
[b] A. Harthun, R. Giernoth, C. J. Elsevier and J. Bargon, *Chem. Commun.* **1996**, 2483.

There are different mechanisms for PHIP

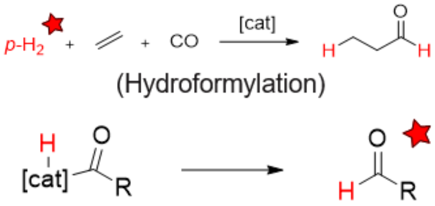
a) Hydrogenation with p-H_2



b) Pairwise replacement with p-H_2



c) Single proton transfer



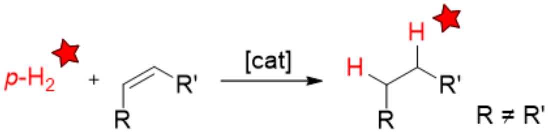
[a] C. R. Bowers and D. P. Weitekamp, *J. Am. Chem. Soc.* **1987**, 109, 5541-5542.

[b] A. Harthun, R. Giernoth, C. J. Elsevier and J. Bargon, *Chem. Commun.* **1996**, 2483.

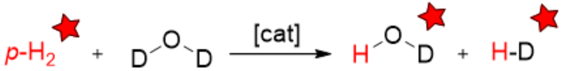
[c] A. B. Permin and R. Eisenberg, *J. Am. Chem. Soc.*, **2002**, 124, 12406-12407.

1) There are different mechanisms for PHIP

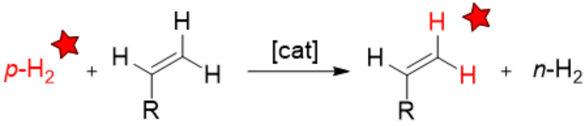
a) Hydrogenation with p-H_2



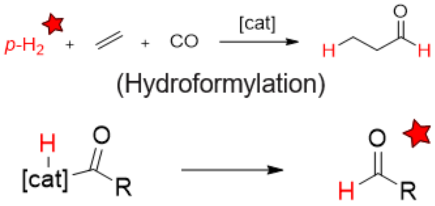
d) Single proton exchange



b) Pairwise replacement with p-H_2



c) Single proton transfer



[a] C. R. Bowers and D. P. Weitekamp, *J. Am. Chem. Soc.* **1987**, 109, 5541-5542.

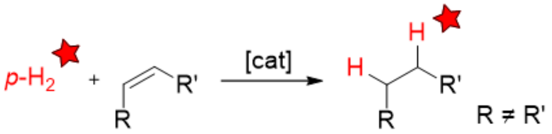
[b] A. Harthun, R. Giernoth, C. J. Elsevier and J. Bargon, *Chem. Commun.* **1996**, 2483.

[c] A. B. Permin and R. Eisenberg, *J. Am. Chem. Soc.*, **2002**, 124, 12406-12407.

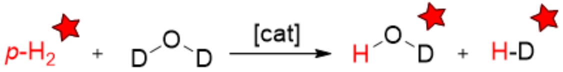
[d] S. Lehmkuhl, M. Emondts, L. Schubert, P. Spannring, J. Klankermayer, B. Blümich and P. P. M. Schleker, *ChemPhysChem* **2017**, 18, 2426-2429.

There are different mechanisms for PHIP

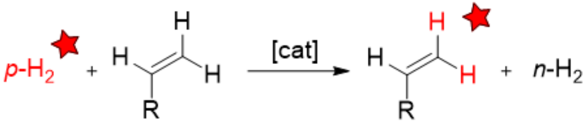
a) Hydrogenation with p-H_2



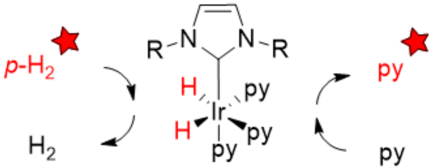
d) Single proton exchange



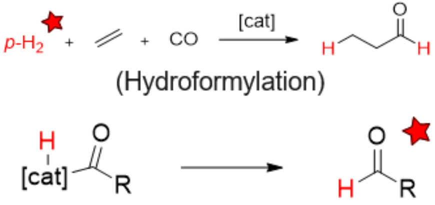
b) Pairwise replacement with p-H_2



e) SABRE: J-coupling transfer

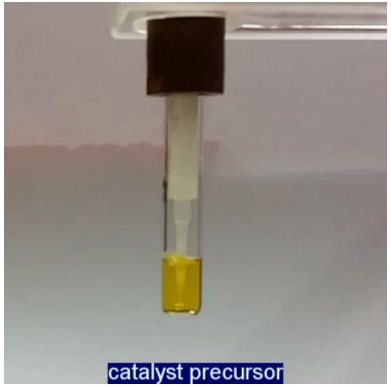


c) Single proton transfer



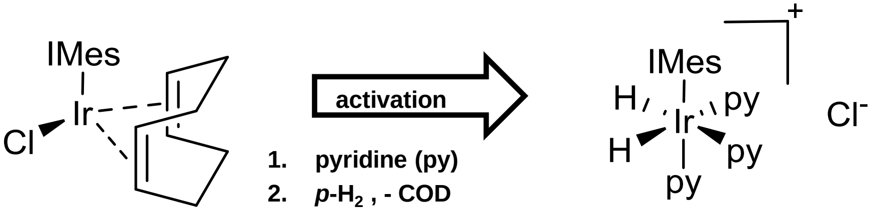
[a] C. R. Bowers and D. P. Weitekamp, *J. Am. Chem. Soc.* **1987**, 109, 5541-5542.
[b] A. Harthun, R. Giernoth, C. J. Elsevier and J. Bargon, *Chem. Commun.* **1996**, 2483.
[c] A. B. Permin and R. Eisenberg, *J. Am. Chem. Soc.*, **2002**, 124, 12406-12407.
[d] S. Lehmkuhl, M. Emondts, L. Schubert, P. Spannring, J. Klankermayer, B. Blümich and P. P. M. Schleker, *ChemPhysChem* **2017**, 18, 2426-2429.
[e] R. Adams, J. Aguilar, K. Atkinson, M. Cowley, P. Elliott, S. Duckett, G. Green, I. Khazal, J. Lopez- Serrano and D. Williamson, *Science* **2009**, 323, 1708.

SABRE Catalyst activation



after 15 min

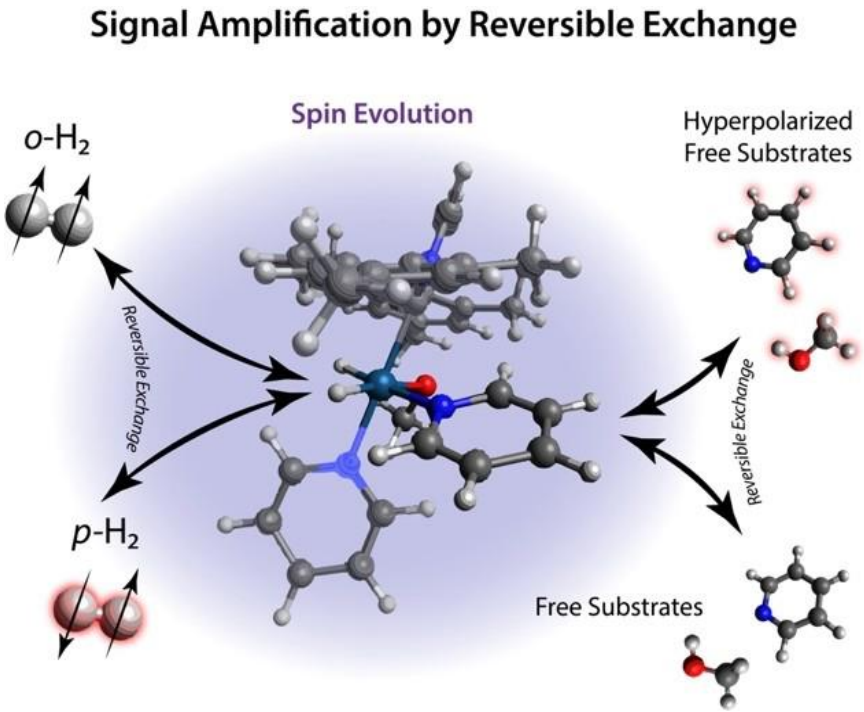
activation

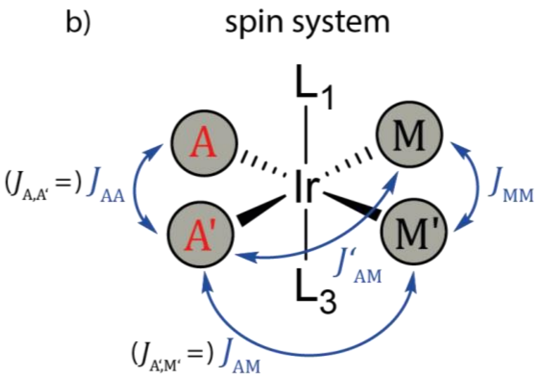


COD

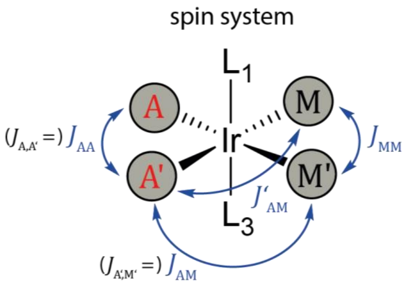
COD: cyclooctadiene

IMes: 1,3-bis(2,4,6-trimethylphenyl) imidazole-2-ylidene

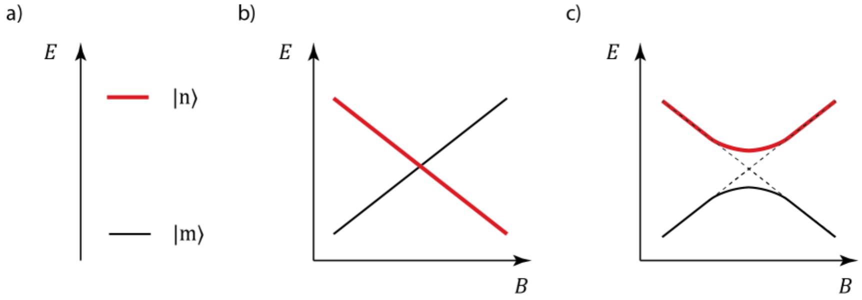

Signal Amplification by Reversible Exchange
Spin Evolution
o-H2
p-H2
Reversible Exchange
Hyperpolarized Free Substrates
Reversible Exchange
Free Substrates

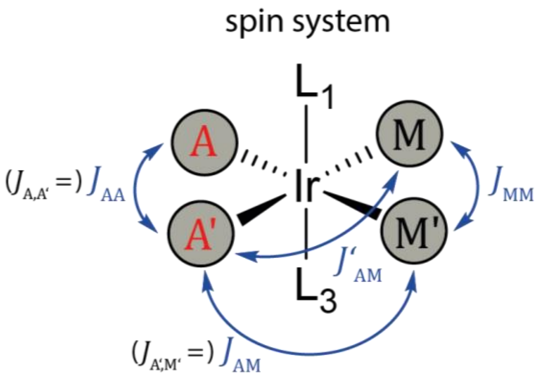

b)
spin system
L1
L3
Ir
A
A'
M
M'
(JA,A' =) JAA
JMM
J'AM
(JA',M' =) JAM

Level anti crossings (LACs) and SABRE



$$x = \frac{J}{\Delta\nu}$$



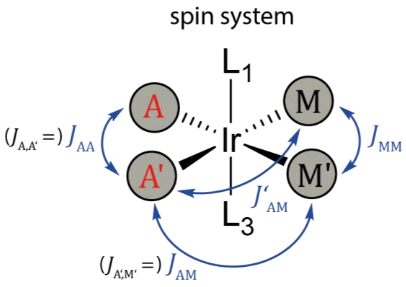


$$x = \frac{J}{\Delta\nu}$$

For pyridine SABRE:

~ 6 mT (60 G) for ^{1}H

~ 0.6 µT for ^{15}N



$$B_{\text{evo}} = \frac{\pm(J_{\text{AA}} - J_{\text{MM}})}{\gamma_{\text{A}}(1-\delta_{\text{A}}) - \gamma_{\text{M}}(1-\delta_{\text{M}})}$$

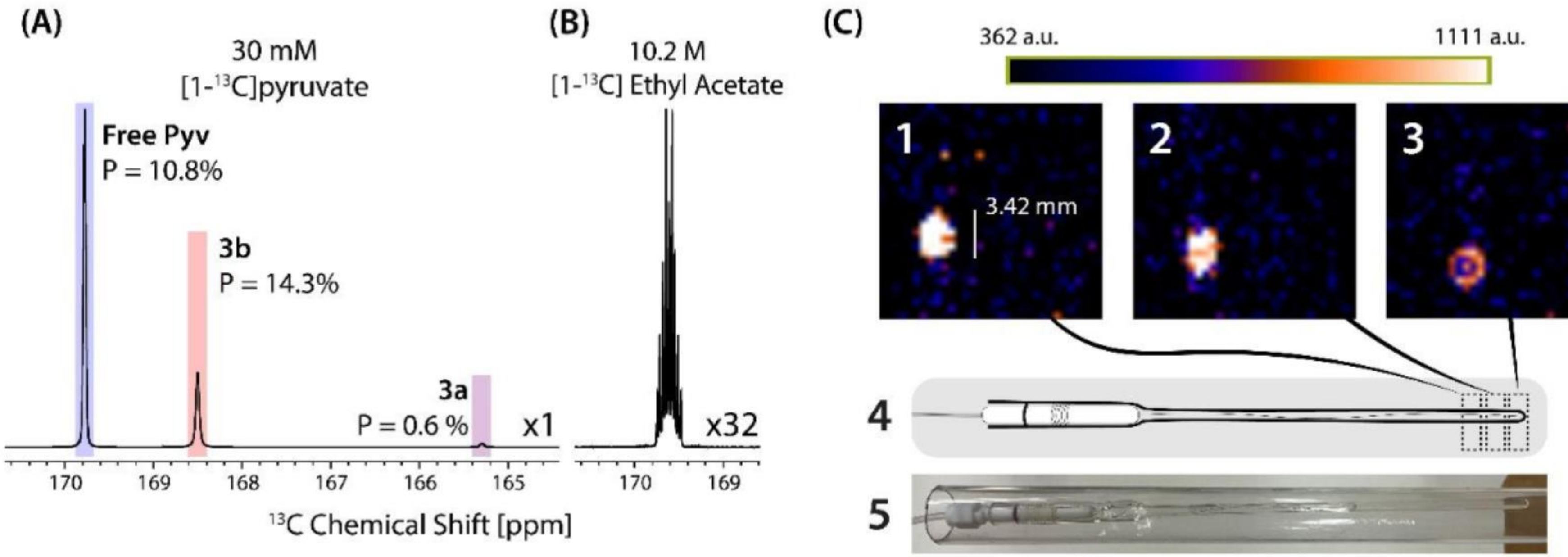
$$B_{\text{evo}} = \frac{\pm(J_{\text{AA}} + J_{\text{MM}}) \mp \frac{1}{2}(J_{\text{AM}} + J'_{\text{AM}})}{\gamma_{\text{A}}(1-\delta_{\text{A}}) - \gamma_{\text{M}}(1-\delta_{\text{M}})}$$

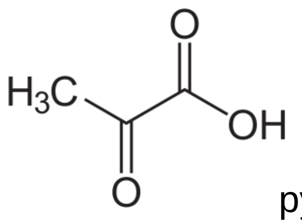
SABRE-SHEATH

(SHield Enables Alignment Transfer to Heteronuclei)

A. N. Pravdivtsev, A. V. Yurkovskaya, H. M. Vieth and K. L. Ivanov, *J. Phys. Chem. B*, 2015, **119**, 13619-13629.

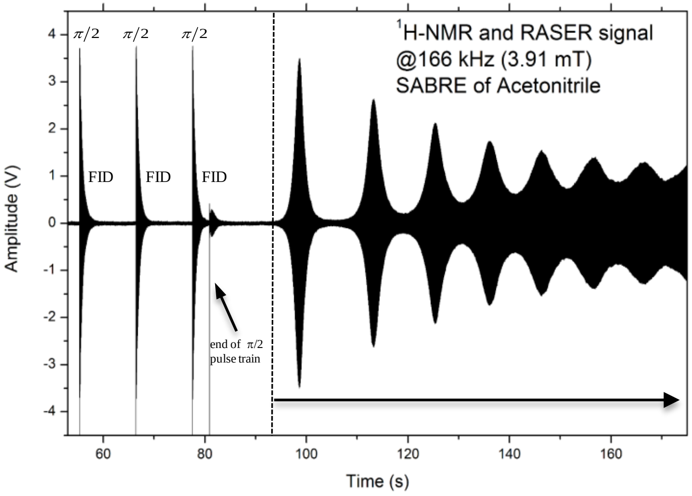
10% polarization on pyruvate





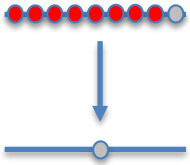
pyruvate

P. TomHon*, M. Abdulmojeed, I. Adelabu, S. Nantogma, M. S. Hafez Kabir, S. Lehmkuhl, E. Y. Chekmenev, and T. Theis, Temperature Cycling Enables Efficient 13C SABRESHEATH Hyperpolarization and Imaging of [1-13C]Pyruvate, *accepted JACS* 2021.



Unpublished data

Population inversion by hyperpolarization:



$$P_{threshold} = \frac{-4}{\mu_0 \eta \hbar \gamma^2 T_2{}^* Q n_s}$$

Need enough Polarization to surpass the RASER threshold

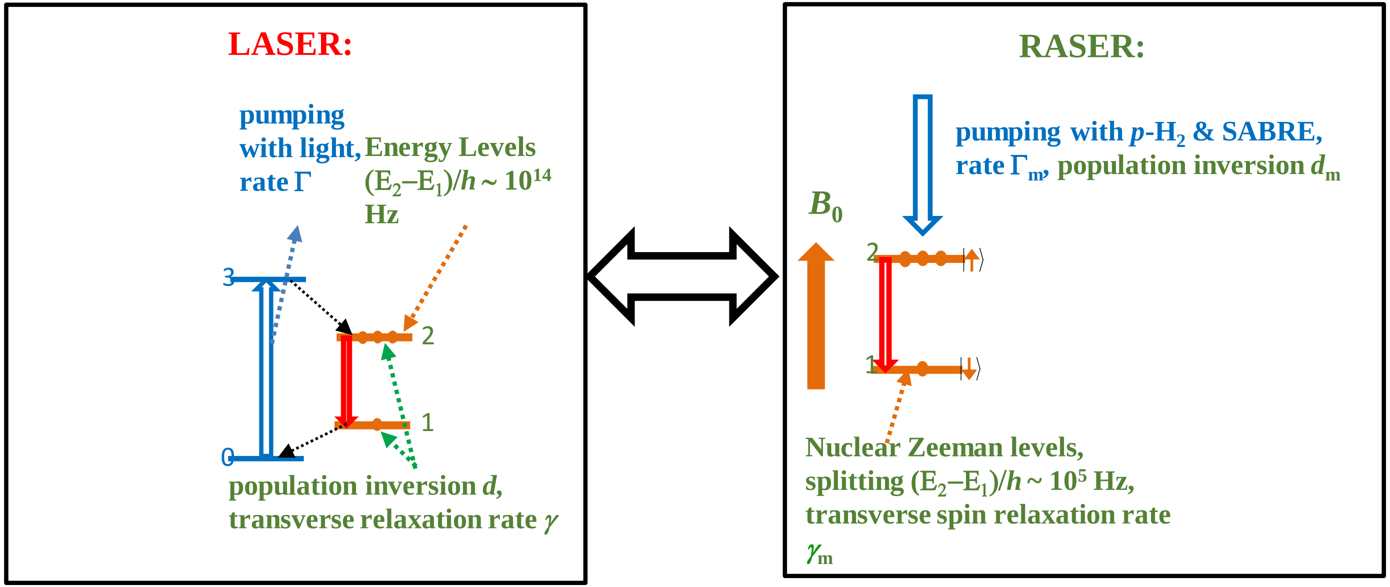
γ: gyromagnatic ratio of the spin species

T_2: effective transverse relaxation time

Q: Quality factor of the resonant circuit

n_s Spin number density

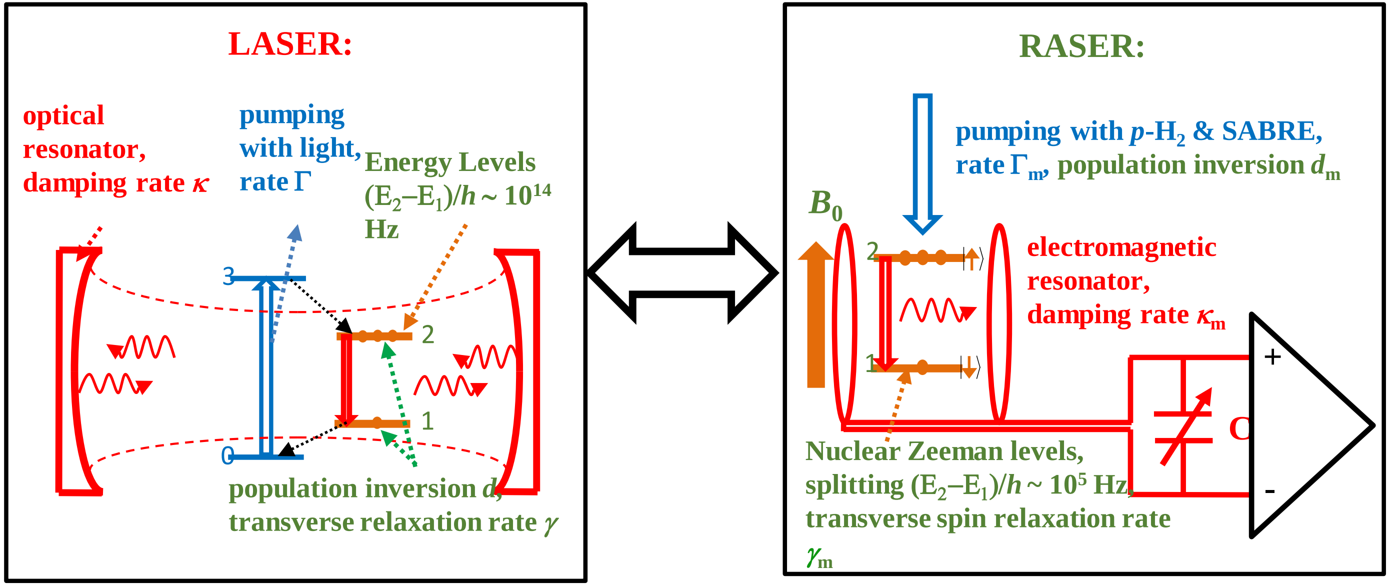
Laser vs Raser



- **Pumping with light or electrons with Γ**
- **Atoms or molecules as LASER medium**

- **Pumping with para-H_2 (spin zero) with Γ_m**
- **Nuclear spins as RASER medium**

Laser vs Raser



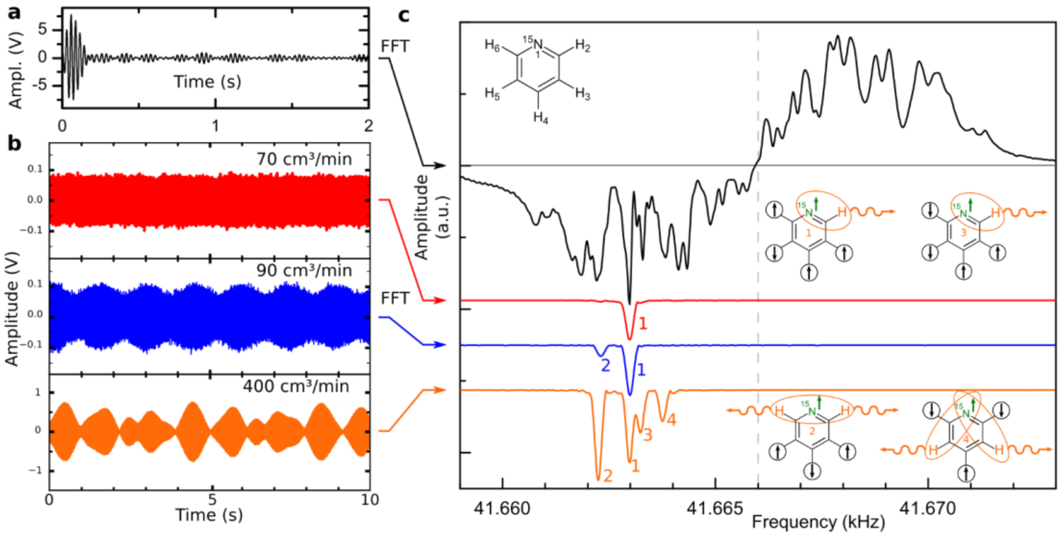
- Pumping with light or electrons with Γ
- Atoms or molecules as LASER medium
- Optical resonator with damping rate κ
- LASER emission starts at threshold d_0

Frequency: ~10^{14} Hz, $\Delta\nu_L/\nu_L \sim 10^{-14}$

- Pumping with para-H_2 (spin zero) with Γ_m
- Nuclear spins as RASER medium
- LC-resonator with damping rate κ_m
- RASER emission starts at threshold $d_{0,m}$

Frequency: ~10^5 Hz, $\Delta\nu/\nu < 10^{-10}$

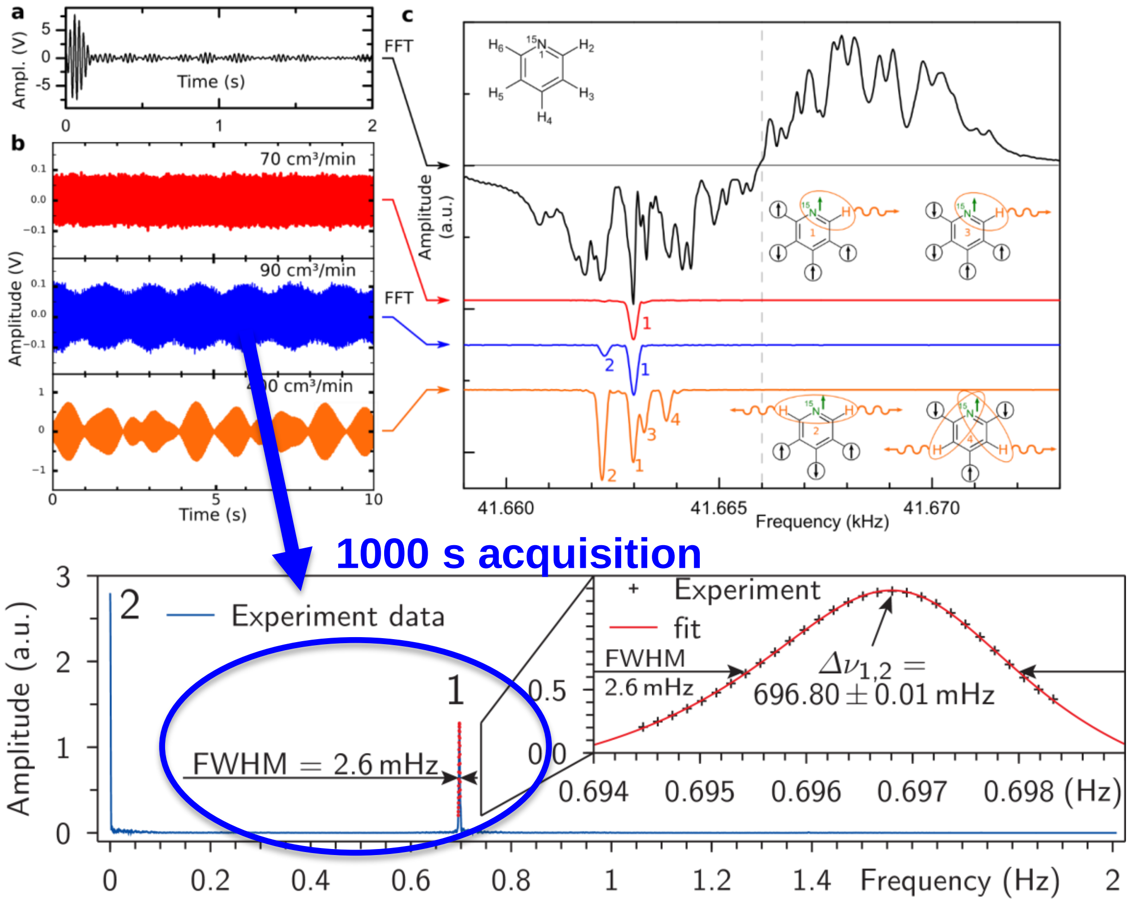
Multimode RASER delivers unprecedented precision



Multimode RASER of molecular states!

M. Süfke, S. Lehmkuhl, A. Liebisch, B. Blümich & S Appelt: Nature Physics **13**, 568–572 (2017)

Multimode RASER delivers unprecedented precision



MULTIMODE RASER OF MOLECULAR STATES!

UNPRECEDENTED RESOLUTION

M. Süfke, S. Lehmkuhl, A. Liebisch, B. Blümich & S Appelt: Nature Physics **13**, 568–572 (2017)

How to increase an NMR signal:

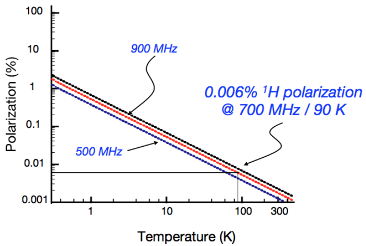
Spin density

Concentration
Abundance

$$M = \frac{\hbar}{2} N \gamma P$$

Polarization

Temperature
Magnetic field



Hyperpolarization

DNP
SEOP
PHIP