Molecular hyperpolarization: the promise of the next technologies

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NIH/NIBIB, NSF

Clinicial applications of hyperpolarization: the potential and challenges

- Creating hyperpolarization: expensive
  - *Many different molecules hyperpolarized*
  - *DNP complex and slow (cooling to 1K needed; hour to polarize; >$20M for a clinical system)*
- Delivery in vivo: excellent progress
  - *GMP system demonstrated*
  - *Potentially important applications identified*
  - *Several clinically relevant molecules detected in vivo*
- General application: limited by spin physics
  - *Carbon signal lifetime ca. 1 min in favorable cases*
  - *Creates great demands on delivery systems*
  - *Limits accessible biochemical pathways*

The Big Picture

– Long-lived hyperpolarization will be clinically important

Many molecules with many-minute lifetimes
New methods robust and SAR friendly
Symmetry helps greatly- can get $^{13}C/^{15}N$ lifetimes with ^{1}H sensitivity and ^{1}H-only sequences
Can screen for good targets at natural abundance
Many suitable architectures: AA′XX′, $AA'X_2X_2'$, $AA'X_3X_3'$, AA′QQ′ (Q=spin>1/2)

–Efficient, High Field SABRE (LIGHT-SABRE) will produce inexpensive, scalable hyperpolarization

Long-lived states and high field SABRE closely related
Para-H_2 polarization can be efficiently transferred to N
Pumping is simple, optimization straightforward

Methods for Molecular Hyperpolarization

$$^{13}C, T = 298K, B = 3Tesla : \frac{M}{M_o} = \tanh(h\nu / 2kT) = 2.5ppm$$

- Brute force (mK cooling):impractical

  Limited by very long T_1 times-can be years to thermal equilibrium

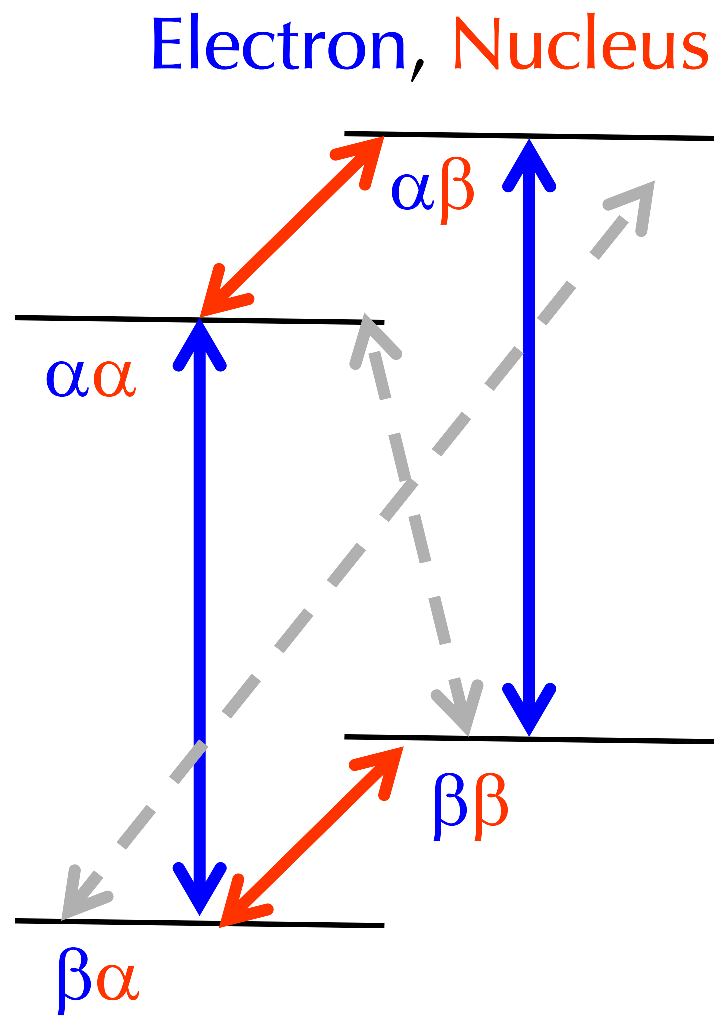
- Spin exchange optical pumping: atoms only

  ^{3}He, ^{129}Xe, sometimes ^{87}Kr: lung imaging
- Dynamic nuclear polarization
- Para-H_2 addition across double bonds
- SABRE (catalytic transfer of para-H_2 order)

DNP proceeds by several different mechanisms, with different field dependence

- Simplest mechanism: solid effect.
- Electrons polarized at low T:

  3 Tesla,1K: hν/kT=1.3,P=58%
- Forbidden (gray) transitions slightly allowed because of spin-spin coupling.
- Glass with paramagnetic impurity: Pump (83GHz) to slowly polarize nuclei
- Warm to 310K in <1 s

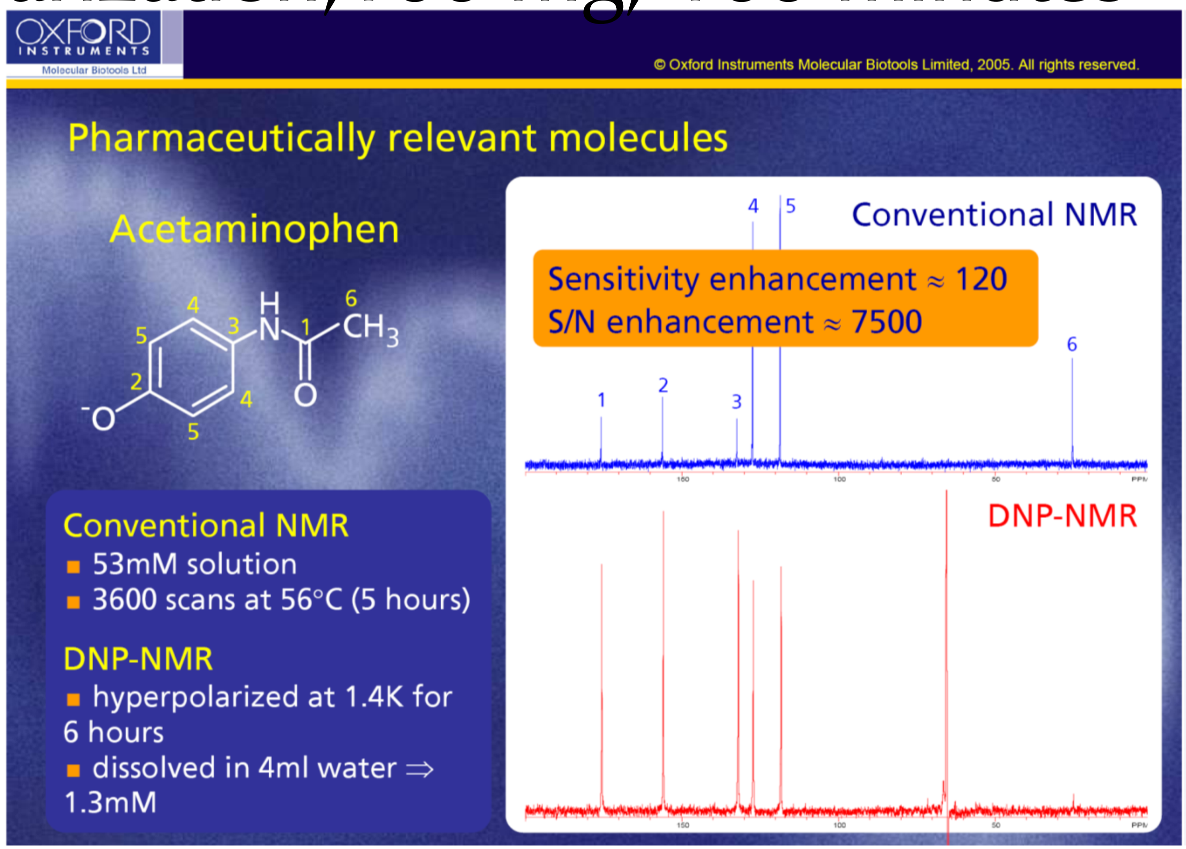


Typical commercial implementation: Hypersense™

- Cool sample to 1.4K, polarize with μwaves
- Rapidly (<1s) dissolve and heat
- Typical: 20% polarization,100 mg, 100 minutes
- Very bad scalability

  Cooling is slow and expensive

  Microwave penetration a major issue

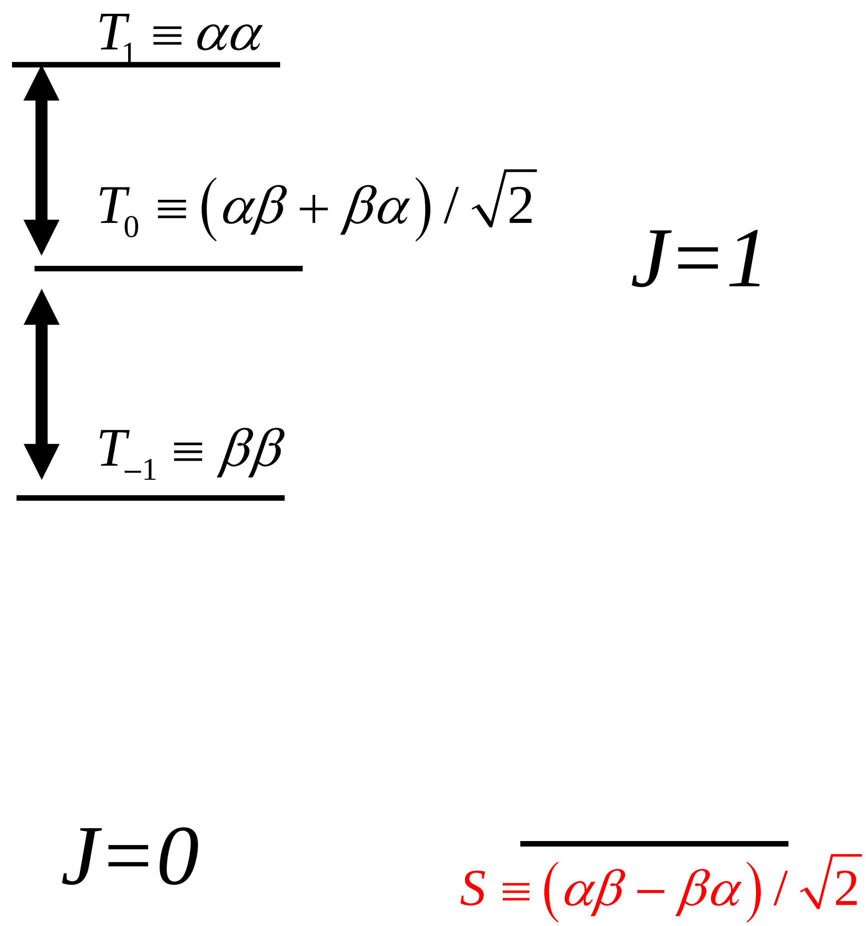


Addition of para-H_2 across double bonds

- Para-H_2 easy and cheap to make because wavefunction must be antisymmetric

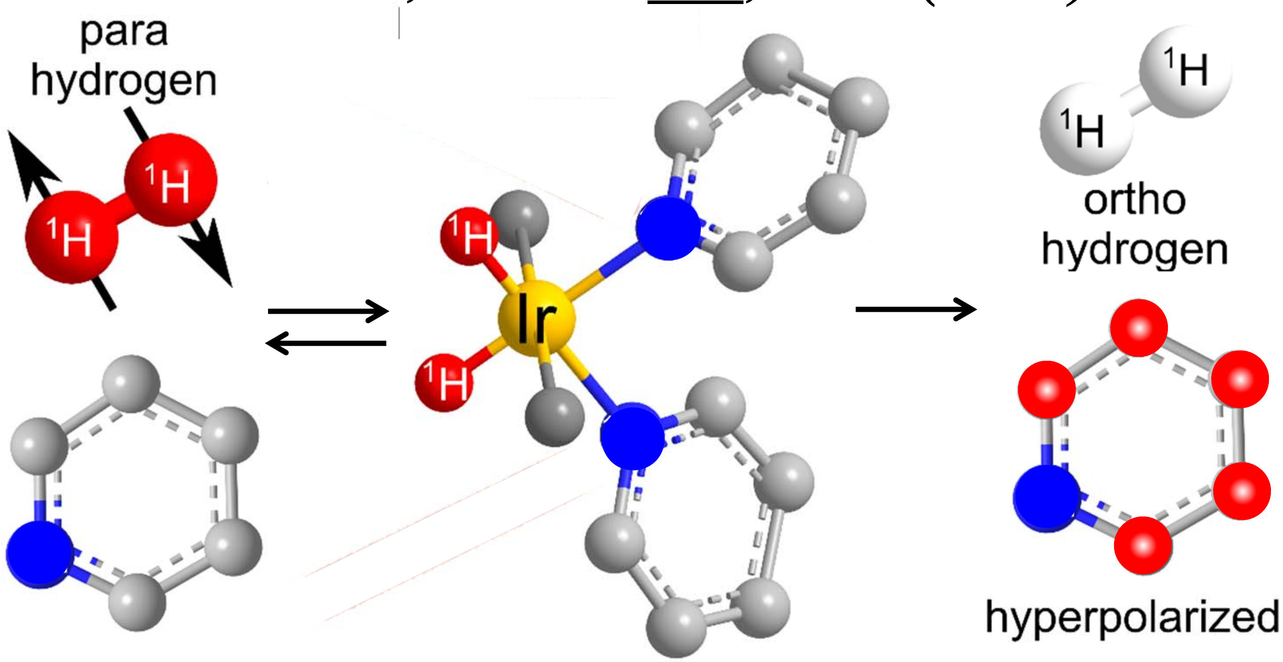
  T=40K, 85% para-H_2

- Weitekamp, 1985: add across double bond and convert to magnetization



SABRE (Signal Amplification By Reversible Exchange): para-H_2 and reversible binding polarizes bulk solution

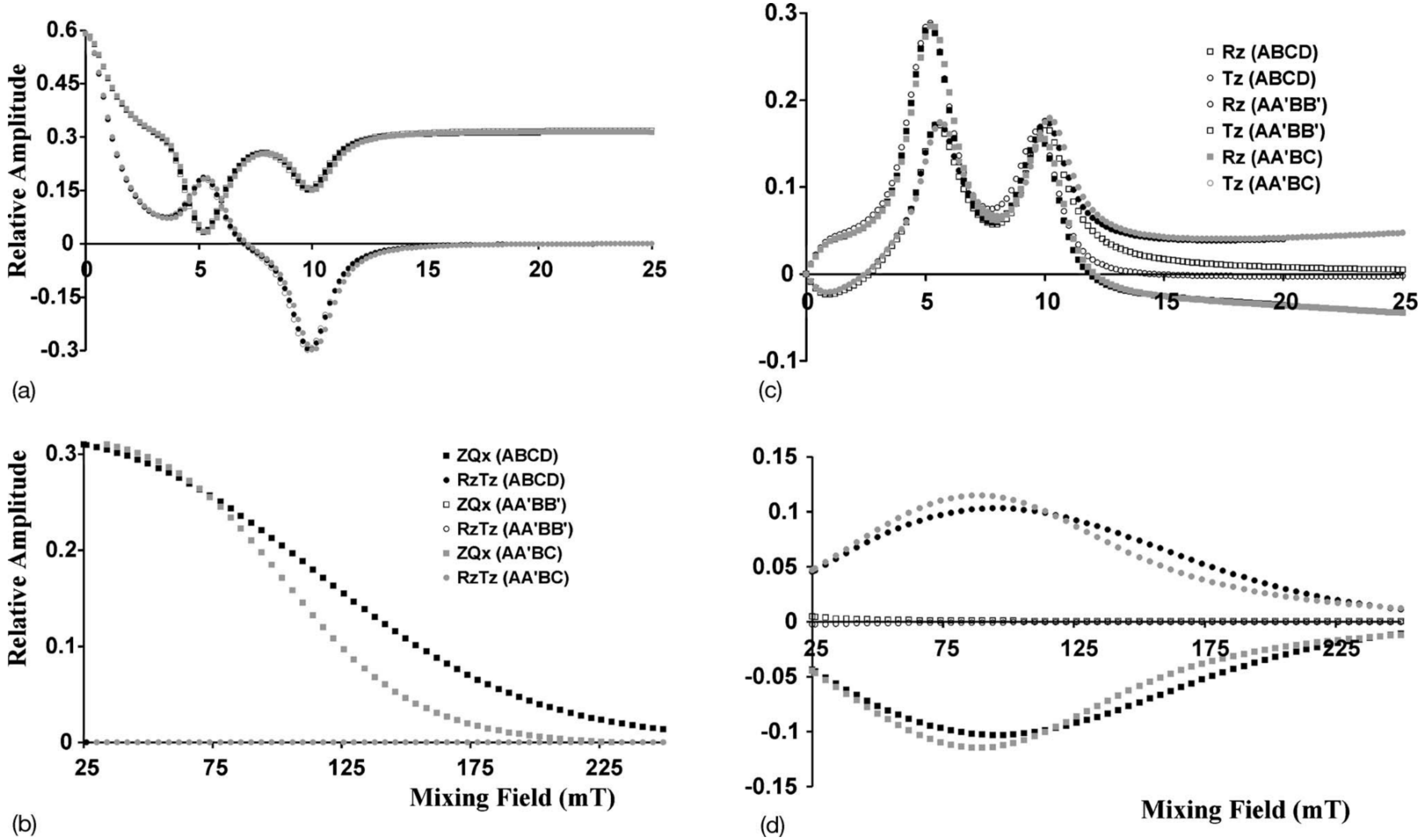
Duckett et. al., Science *__323__, 1708 (2009)*



- Since 2009: many molecules polarized, multiple catalysts (including heterogeneous)
- Hard part: creating bulk magnetization from singlet

  Working assumption (until this month): you need strong coupling

To get strong couplings between spins separated by several ppm, go to mT fields…

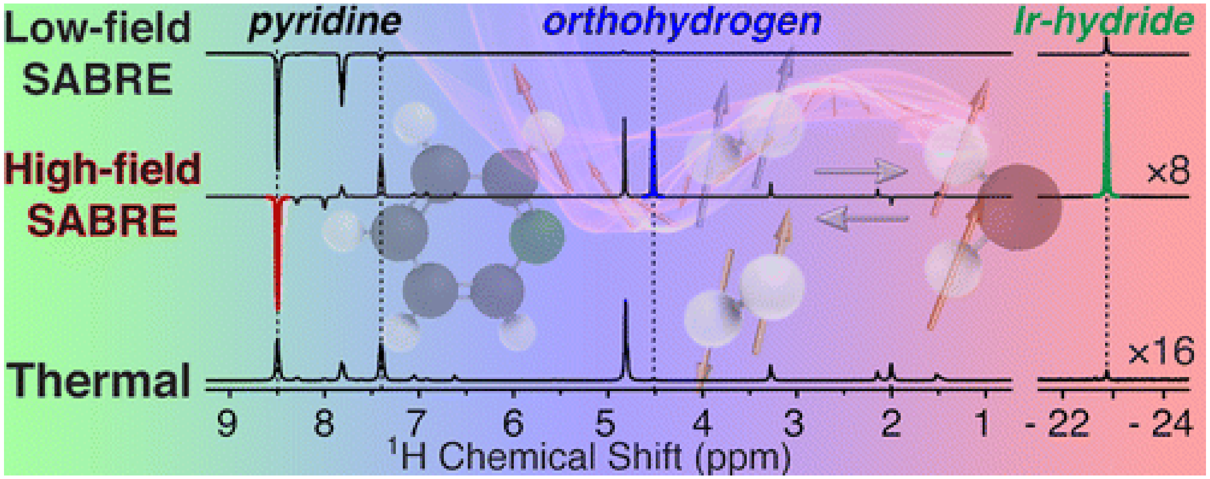


Ralph W. Adams, Simon B. Duckett, Richard A. Green, David C. Williamson, and Gary G. R. Green, The Journal of Chemical Physics **131**, 194505 (2009);

The two high-field SABRE approaches

– 1. Just try it and see if you get lucky..

The Feasibility of Formation and Kinetics of NMR Signal Amplification by Reversible Exchange (SABRE) at High Magnetic Field (9.4 T), Barskiy, Kovtunov, Koptyug, He, Groome, Best, Shi, Goodson, Shchepin, Coffey, Waddell, and Chekmenev, JACS ***2014****, 136,3322–3325*

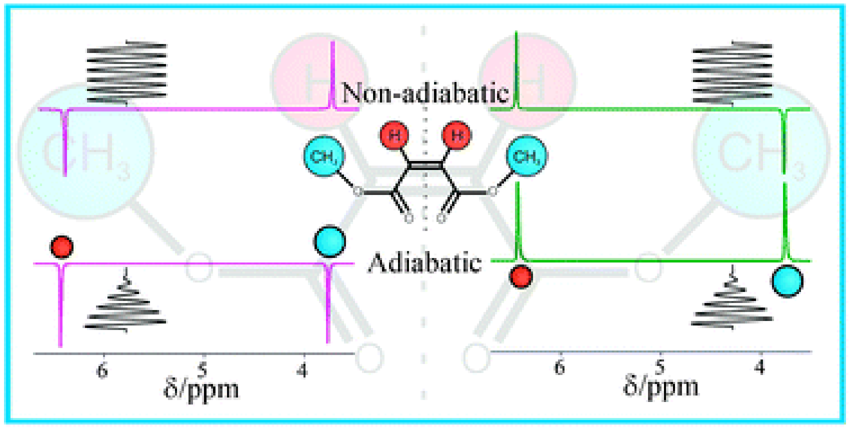


No irradiation here. Modest but nonzero gain.

The two high-field SABRE approaches

– 2. Spin lock one spin hard enough to shift and reintroduce strong couplings ($\omega_1 \approx 50000$ rad/s)

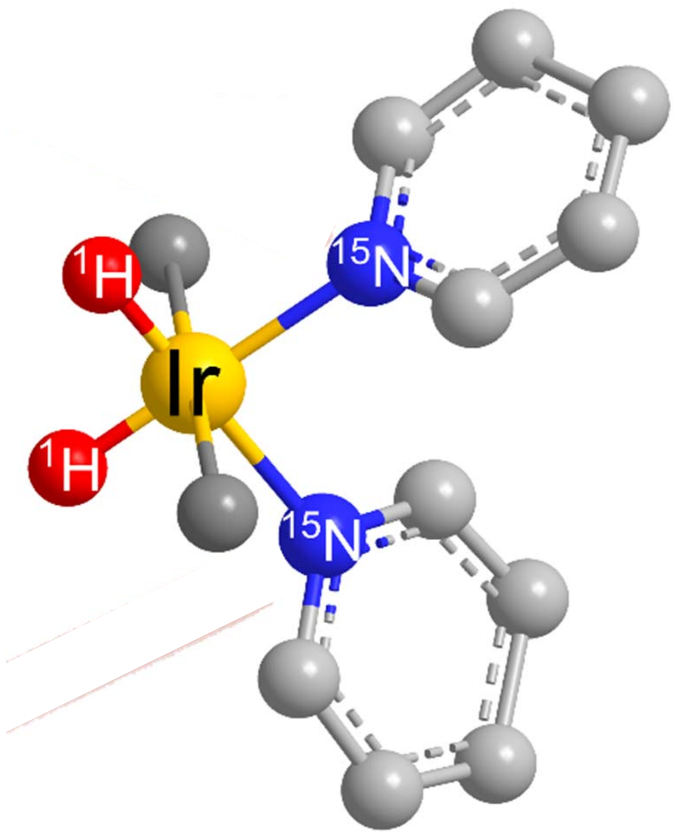
Exploiting level anti-crossings (LACs) in the rotating frame for transferring spin hyperpolarization; Pravdivtsev, Yurkovskaya, Lukzen, Vieth and Ivanov, Phys. Chem. Chem. Phys., 2014



Huge requirement for rf homogeneity to match well; Can't work for heteronuclear transfer

Take a step backwards: the SABRE system and our long-lived states are identical!

- Simplest case (with ^{15}N pyrazine): AA′XX′
- ^{14}N pyrazine: AA′QQ′ (^{14}N irradiation) or $AA'X_2X_2'$ (^{1}H irradiation)



These are exactly the spin systems I showed in the first half of the talk. What can we learn?

Moving population from bound para-H_2 to bound nitrogen is incredibly easy

$$S = (|\alpha\beta\rangle - |\beta\alpha\rangle)/\sqrt{2}; T_1 = |\alpha\alpha\rangle, T_0 = (|\alpha\beta\rangle + |\beta\alpha\rangle)/\sqrt{2}, T_{-1} = |\beta\beta\rangle;$$

$$X_1 = \frac{|\alpha\alpha\rangle + |\beta\beta\rangle + |\alpha\beta\rangle + |\beta\alpha\rangle}{2}, X_0 = \frac{|\alpha\alpha\rangle - |\beta\beta\rangle}{\sqrt{2}}, X_{-1} = \frac{|\alpha\alpha\rangle + |\beta\beta\rangle - |\alpha\beta\rangle - |\beta\alpha\rangle}{2}$$

Bound para-H_2 and thermal pyridine: red states 25% populated, all others empty

Irradiate ^{15}N:

$\omega_1 \approx 2\pi(J_{HH} \pm J_{NN})$

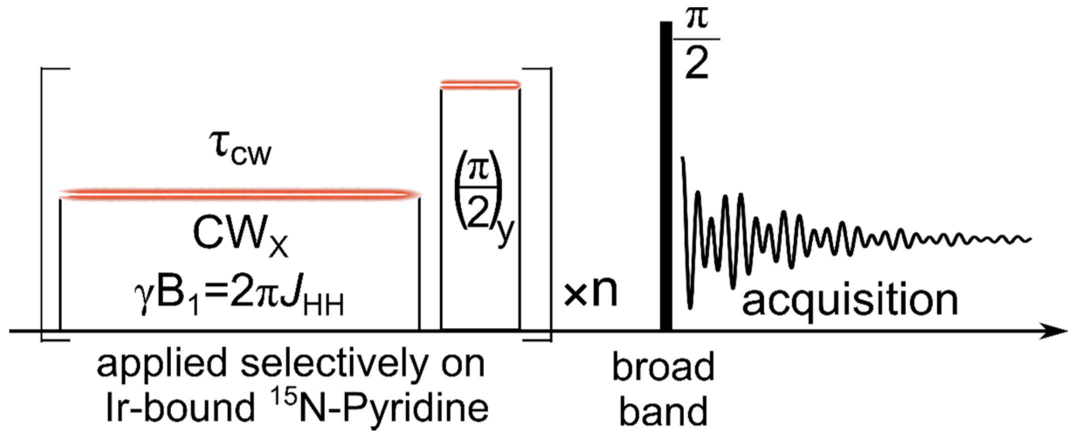
$t = \Delta J_{NH}/\sqrt{2}$

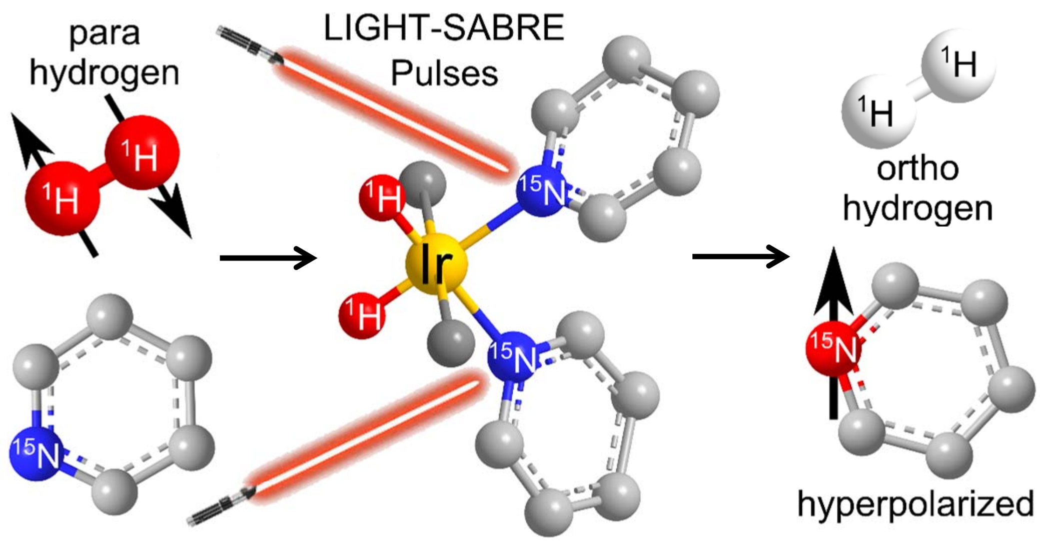
$\rightarrow$25% N transverse magnetization

$$\begin{array}{c|cccc} & S^N S^H & X_1^N T_0^H & X_0^N T_0^H & X_{-1}^N T_0^H \\ \hline S^N S^H & -2\pi(J_{HH}+J_{NN}) & \pi\Delta J_{NH}/\sqrt{2} & 0 & -\pi\Delta J_{NH}/\sqrt{2} \\ X_1^N T_0^H & \pi\Delta J_{NH}/\sqrt{2} & +\omega_1 & 0 & 0 \\ X_0^N T_0^H & 0 & 0 & 0 & 0 \\ X_{-1}^N T_0^H & -\pi\Delta J_{NH}/\sqrt{2} & 0 & 0 & -\omega_1 \end{array}$$

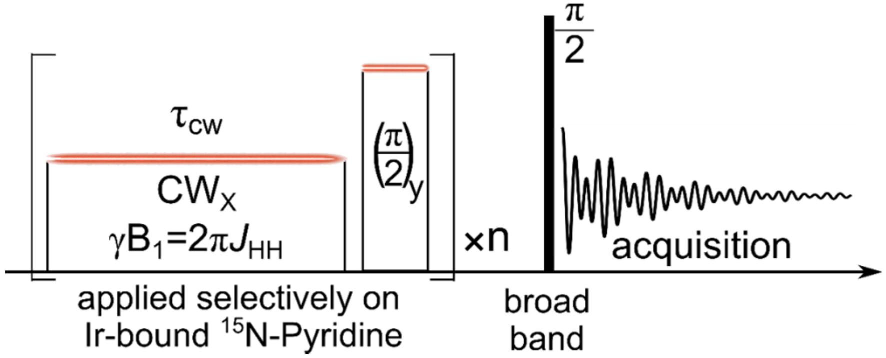
$$\begin{array}{c|cccc} & S^N T_0^H & X_1^N S^H & X_0^N S^H & X_{-1}^N S^H \\ \hline S^N T_0^H & 2\pi(J_{HH}-J_{NN}) & \pi\Delta J_{NH}/\sqrt{2} & 0 & -\pi\Delta J_{NH}/\sqrt{2} \\ X_1^N S^H & \pi\Delta J_{NH}/\sqrt{2} & +\omega_1 & 0 & 0 \\ X_0^N S^H & 0 & 0 & 0 & 0 \\ X_{-1}^N S^H & -\pi\Delta J_{NH}/\sqrt{2} & 0 & 0 & -\omega_1 \end{array}$$

Introducing LIGHT-SABRE
(Low Intensity Generates High Tesla SABRE)



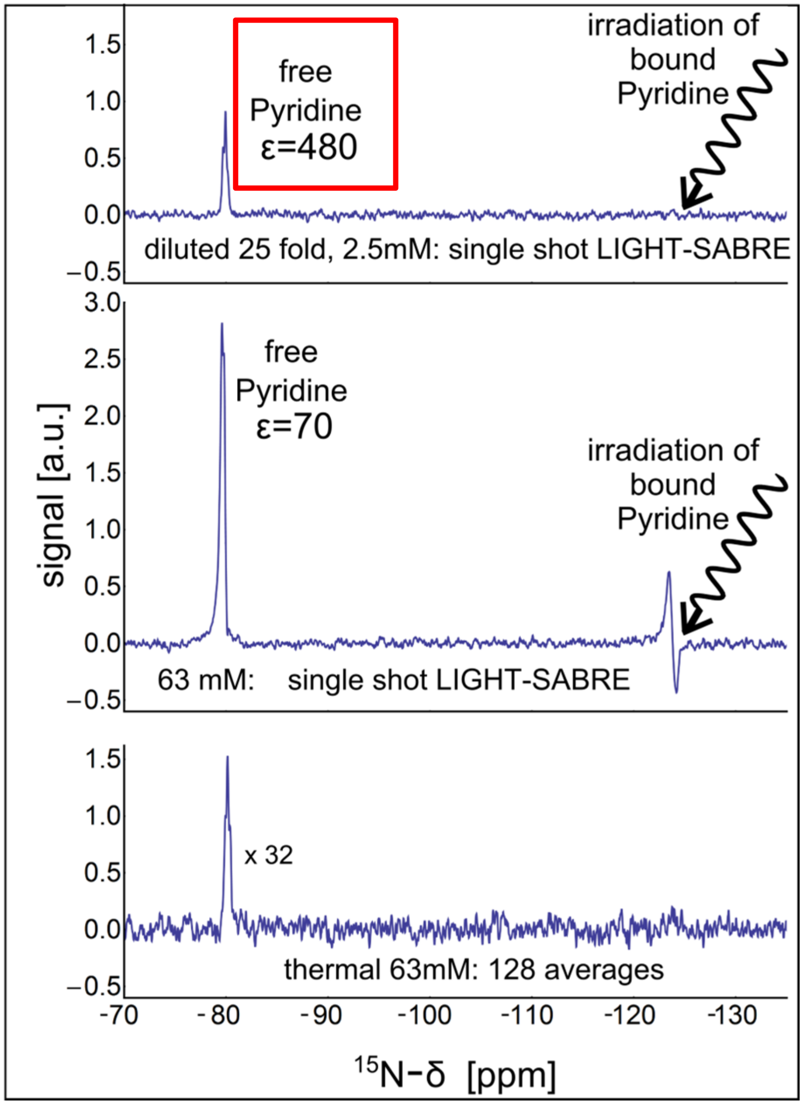


First LIGHT-SABRE Data (Theis and W^2, Duke; Chekmenev and Truong, Vanderbilt)



- 9.4T; n=15, τ_{cw}=0.5s, $\omega_1 \approx 2\pi$*(15 Hz)
- Pyridine 10:1 excess over catalyst

  Very far from optimized: coil much smaller than sample, no shaped pulses, …

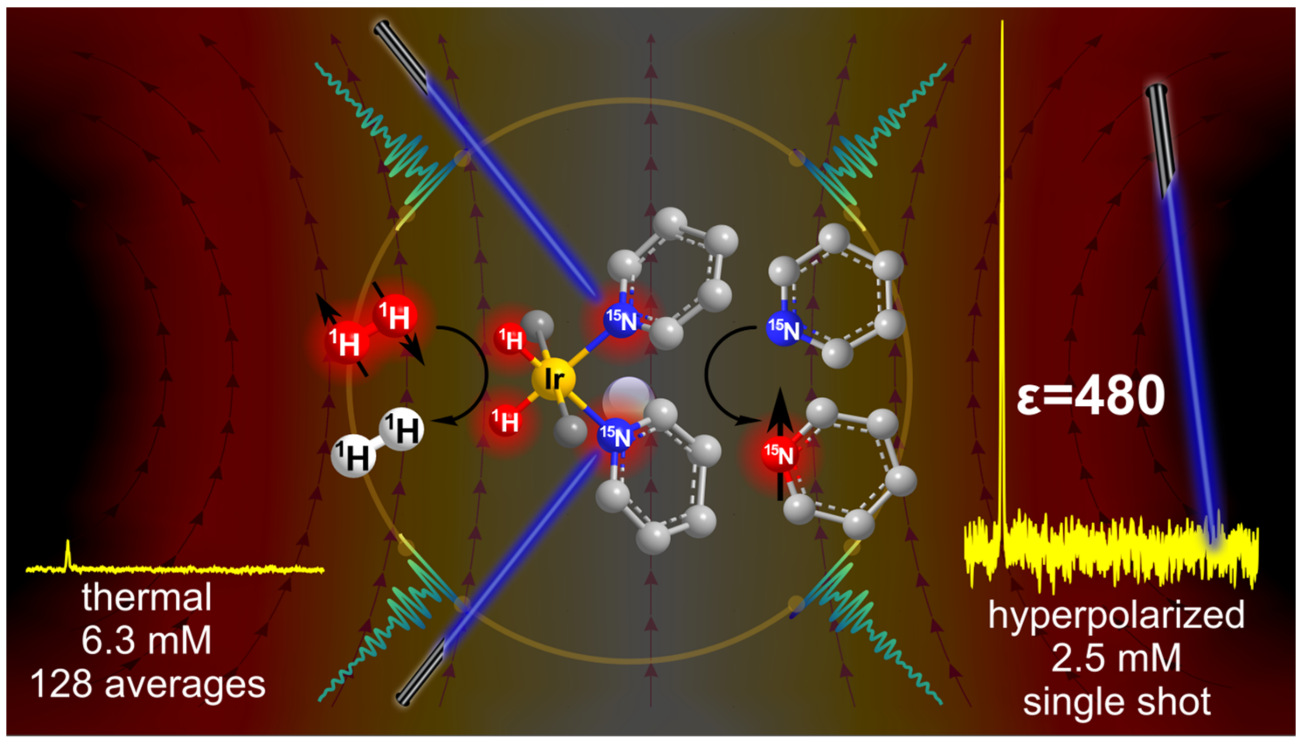


Opinion: HP MRI will have broadest impact at low fields with multimodality imaging

- Conventional NMR: SNR$\propto\gamma_{prep}\,\gamma_{det}^{7/4}\,B^{7/4}$
  Boltzmann equilibrium $\propto \gamma_{prep}B$; Magnetization $\propto \gamma_{det}$; Induced voltage $\propto \omega = \gamma_{det}B$; coil noise $\propto \omega^{1/4}$
- Conventional MRI: SNR$\propto\gamma_{prep}\,\gamma_{det}\,B^{1}$
  Coil noise $\propto \omega$, dominated by body
- Hyperpolarized MRI:SNR$\propto\gamma_{det}$
  Boltzmann factor eliminated!
- Relaxation times usually much longer at low field; power dissipation lower (SAR$\propto B^2$)
  Compromise (0.5-1.5T) to get a good anatomic and HP image, or marry with CT for even lower field

Conclusions

– High field SABRE is *very easy*. This makes SABRE a significant competitor to DNP with big advantages: scalable, no cryocooling, continuous hyper-polarization possible.



Cover article, Journal of Magnetic Resonance (Doi 10.1016/j.jmr.2014.09.005)