Molecular hyperpolarization: the promise of the next technologies

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Clinical 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
Long-lived hyperpolarization will be clinically important

Many molecules with many-minute lifetimes

New methods robust and SAR friendly

Symmetry helps greatly - can get $^{13}\text{C}/^{15}\text{N}$ lifetimes with $^{1}\text{H}$ sensitivity and $^{1}\text{H}$-only sequences

Can screen for good targets at natural abundance

Many suitable architectures: AA’XX’, AA’X$_2$X$_2’$, AA’X$_3$X$_3’$, 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-$\text{H}_2$ polarization can be efficiently transferred to N

Pumping is simple, optimization straightforward
Methods for Molecular Hyperpolarization

\[ ^{13}C, T = 298K, B = 3\text{Tesla} : \frac{M}{M_0} = \tanh(h\nu / 2kT) = 2.5\text{ppm} \]

- Brute force (mK cooling): impractical
  
  \textit{Limited by very long } T_1 \textit{ times-can be years to thermal equilibrium}

- Spin exchange optical pumping: atoms only
  
  \textit{\textsuperscript{3}He, \textsuperscript{129}Xe, sometimes \textsuperscript{87}Kr: lung imaging}

- Dynamic nuclear polarization

- Para-H\textsubscript{2} addition across double bonds

- SABRE (catalytic transfer of para-H\textsubscript{2} order)
DNP proceeds by several different mechanisms, with different field dependence:

- Simplest mechanism: solid effect.
- Electrons polarized at low T:
  \[3 \text{ Tesla, 1K: } \frac{hv}{kT} = 1.3, P = 58\%
  \]
- Forbidden (gray) transitions slightly allowed because of spin-spin coupling.
- Glass with paramagnetic impurity: Pump (83 GHz) to slowly polarize nuclei
- Warm to 310 K 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

\[ J=1 \]
\[ S \equiv (\alpha\beta - \beta\alpha) / \sqrt{2} \]

\[ J=0 \]
\[ T_{-1} \equiv \beta\beta \]
\[ T_0 \equiv (\alpha\beta + \beta\alpha) / \sqrt{2} \]
\[ T_1 \equiv \alpha\alpha \]
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...

The two high-field SABRE approaches

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


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 \( (\omega_1 \approx 50000 \text{ rad/s}) \)

*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$_2$X$_2$’ ($^1$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
Introducing LIGHT-SABRE
(Low Intensity Generates High Tesla SABRE)

\[ \tau_{cw} = \frac{\pi}{2} \]

\[ CW_x \gamma B_1 = 2\pi J_{HH} \]

applied selectively on Ir-bound $^{15}$N-Pyridine

\[ \frac{\pi}{2} \times n \]

acquisition

para hydrogen

LIGHT-SABRE Pulses

orth hyperpolarized

\[ ^{1}H \]

\[ ^{1}H \]

\[ ^{16}N \]
First LIGHT-SABRE Data (Theis and W², Duke; Chekmenev and Truong, Vanderbilt)

- 9.4T; \( n=15, \ \tau_{cw}=0.5\text{s}, \ \omega_1 \approx 2\pi^* (15 \text{ Hz}) \)
- 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: $\text{SNR} \propto \gamma_{\text{prep}} \gamma_{\text{det}}^{7/4} B^{7/4}$
  
  Boltzmann equilibrium $\propto \gamma_{\text{prep}} B$; Magnetization $\propto \gamma_{\text{det}}$;
  Induced voltage $\propto \omega = \gamma_{\text{det}} B$; coil noise $\propto \omega^{1/4}$

- Conventional MRI: $\text{SNR} \propto \gamma_{\text{prep}} \gamma_{\text{det}} B^{1}$
  Coil noise $\propto \omega$, dominated by body

- Hyperpolarized MRI: $\text{SNR} \propto \gamma_{\text{det}}$
  Boltzmann factor eliminated!

- Relaxation times usually much longer at low field; power dissipation lower ($\text{SAR} \propto B^{2}$)
  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.

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