Hyperpolarization - Description, Overview & Method

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Declaration of Financial Interests or Relationships

Speaker Name: Peder Larson

I have the following financial interest or relationship to disclose with regard to the subject matter of this presentation:

Company Name: GE Healthcare
Type of Relationship: Research Support
Outline

https://radiology.ucsf.edu/research/labs/larson/educational-materials

(Google: Peder Larson Lab, Educational Materials link on sidebar)

- Hyperpolarization
  - What does it mean?
  - Dissolution Dynamic Nuclear Polarization (dDNP)
  - Spin Exchange Optical pumping
  - Para-hydrogen induced polarization (PHIP, SABRE)

- Imaging Methods
  - RF pulse strategies
  - Acquisition strategies
  - Analysis – kinetic models
Spin Polarization

\[ B = 0 \]

\[ M_0 = 0 \]

Spins

Net Magnetization
Hyperpolarization Methods

Spin Polarization in a Magnetic Field

Spin polarization in a magnetic field

Polarization fraction:
\[ \tanh\left(\frac{-h\gamma B_0}{2\pi kT}\right) \]

0.0001-0.0005% at room temperature, depending on nucleus (\(\gamma\)) and field (B0)

Net Magnetization

\(M_0 \neq 0\)
Hyperpolarization

- Perturb spins from thermal equilibrium to increase fraction aligned parallel (or anti-parallel) to \( B_0 \)
- Polarizations of > 50%!!
- Methods:
  - Optical pumping (for gasses, ie \( ^3\)He, \( ^{129}\)Xe)
  - Parahydrogen-induced Polarization (PHIP)
  - Dynamic Nuclear Polarization (DNP)
Spin Exchange Optical Pumping

- Polarization of noble gases (e.g. $^3$He, $^{129}$Xe)
- Mixtures of alkali-metal vapors and noble gases irradiated with circularly polarized resonant light
- Major application is pulmonary imaging for lung disease


Hyperpolarized $^{129}$Xe MRI
Para-hydrogen Induced Polarization (PHIP)

- Parahydrogen is the Singlet State of Hydrogen gas, H₂

- MR invisible, can store magnetization

- Transfer the polarization from the singlet-state to other nuclei

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Singlet, $S_0$

$\frac{1}{\sqrt{2}} (|T\uparrow\downarrow - T\downarrow\uparrow\rangle)$

Triplet, $T_{+}$, $T_{0}$, $T_{-}$

- $T_{+}$: $|T\uparrow\uparrow\rangle$
- $T_{0}$: $\frac{1}{\sqrt{2}} (|T\uparrow\downarrow + T\downarrow\uparrow\rangle)$
- $T_{-}$: $|T\downarrow\downarrow\rangle$

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Para hydrogen

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Hyperpolarized substrate

SABRE
Adams, …, Duckett et al. 
*Science* 2009 323, 1708

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Para hydrogen

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Reversible exchange
Signal Amplification By Reversible Exchange (SABRE)

- At the appropriate magnetic field (e.g. 6.5 mT for hyperpolarization of protons), J-coupling interactions across the iridium catalyst drive hyperpolarization from parahydrogen to substrate.
- Reversible exchange of both, parahydrogen and substrate, leads to continuous hyperpolarization buildup.
- Heteronuclear SABRE greatly generalizes the substrate scope and enables long hyperpolarization lifetimes.

Theis et al. *JACS* 2015 137 (4), 1404
SABRE Discussion
Primarily limited to molecules containing sp or sp\(^2\) hybridized nitrogens

- **Pros**
  - Relatively Simple and Fast
  - Uses inexpensive equipment
  - Long-Lived States can be hyperpolarized directly

- **Cons**
  - Limitations on polarizable substrates
  - Reduced efficiency in water
  - Removal of the toxic hyperpolarization catalyst

Substrates:
Primarily limited to molecules containing sp or sp\(^2\) hybridized nitrogens

Colell et al. *JPCC* **2017** 121(12), 6626
Dynamic Nuclear Polarization (DNP)

- Microwaves at appropriate frequency transfer polarization from electrons to nuclei
- High magnetic field increases polarization of both nuclear and electron spins
- Very low temperature also used to increase polarization of both nuclear and electron spins

**Sample:** Amorphous solid material doped with unpaired electrons at a ratio ~ 1 free electron:1000 $^{13}$C

For $B_0 = 3.35$ T

At 1.2K,

$P_e = 94\%$ & $P_C = 0.086\%$
3.35 T and ~1.2°K
\( \gamma_{\text{electron}} B_0 = 94 \text{ GHz} \)
\( \gamma_{\text{C-13}} B_0 = 35 \text{ MHz} \)
Dissolution DNP Procedure

- The buffer is heated and pressurized
- The sample space is pressurized
- The sample is raised out of the liquid helium
- The dissolution stick is lowered, docking with the sample holder
- The solvent is injected, dissolving the sample, while preserving the enhanced polarization
SpinLab Clinical Polarizer

SpinLab Polarizer

5 T and ~0.8°K
γ_{electron} B_0 = 140 GHz
γ_{C-13} B_0 = 52 MHz

Automated Quality Control System

Ardenkjaer-Larsen et al. NMR Biomed 2011; 24:927
Dissolution DNP $^{13}$C Agents

Requirements

- Long $T_1$ relaxation time (polarization half-life)
- Water-soluble is best
- Mixture with free electron source, aka electron paramagnetic agent (EPA), free radical
- Low Toxicity
- In vivo interest

Agents

- $[1^{-13}C]$-pyruvate: metabolism, Warburg effect
- $^{13}$C-urea: inert, perfusion
- $bis$-$1,1$-(hydroxymethyl)[$1^{-13}$C]cyclopropane-$d_8$ (HMCP, HP001): long $T_1$ perfusion agent
- $[1,4^{-13}C_2]$-fumarate: necrosis
- $^{13}$C-bicarbonate: pH measurement
- $[2^{-13}C]$-fructose: metabolism
- $[5^{-13}C]$-glutamine: metabolism, cell proliferation
- $^{13}$C-dehydroascorbate (DHA): Reduction/oxidation potential
- $[1^{-13}C]$-$\alpha$-ketoglutarate: IDH mutation status
- $[U^{-2}H, U^{-13}C]$-glucose: metabolism
- and more

Hyperpolarized Carbon-13 Pyruvate

$^{13}$C-Pyruvate

- Most promising HP agent thus far
- Long $T_1$ ($\approx$ 40-60 s)
- Readily polarizable
- Endogenous
- Rapid uptake and conversion to lactate, alanine, and bicarbonate
- Directly probes the “Warburg Effect” in cancer
- (Safety and feasibility established in prostate cancer patients)
Net magnetization behavior, hyperpolarized or at thermal equilibrium, is described by Bloch equation:

\[
\frac{d}{dt} \vec{M} = \vec{M} \times \gamma \vec{B} + \begin{bmatrix}
-1/T_2 & 0 & 0 \\
0 & -1/T_2 & 0 \\
0 & 0 & -1/T_1 \\
\end{bmatrix} \vec{M} + \begin{bmatrix}
0 \\
0 \\
M_0/T_1 \\
\end{bmatrix}
\]
Relaxation to Equilibrium

$T_1$ decay of $M_z$ (~50 s in vivo for [1-13C]pyruvate)
Relaxation to Equilibrium

$T_2$ decay of $M_{xy}$
(~100ms-2s in vivo for pyruvate)
13C MR of Pyruvate Metabolism

Following injection of 13C-pyruvate, the dynamic MR spectrum shows the metabolic flux from pyruvate to lactate, alanine, bicarbonate, and pyruvate-hydrate.

- Pyruvate
- Lactate
- Alanine
- Bicarbonate

Dynamic MR Spectrum *in vivo*
Hyperpolarized $^{13}$C Imaging Procedure

1. Hyperpolarization of $^{13}$C-pyruvate (45-90 mins)
2. Rapid dissolution of frozen compound to create a hyperpolarized liquid agent (10 sec)
3. Agent is injected to the subject inside the MRI scanner (10 sec)
4. $^{13}$C MRI/MRSI is performed immediately (1-2 mins)
MR Pulse Sequence Components

1. Excite spins (RF)
2. Readout signal (spectral and/or spatial encoding)
3. Repeat
Hyperpolarized RF Pulses

Two key considerations:

1. Efficient use of hyperpolarization
   - Variable flip angles
   - “Multiband” excitation

2. Spectral selectivity
   - Spectral-spatial RF pulses
Constant Flip Angle

- Received signal varies between excitations (can cause blurring)
- Residual unused hyperpolarization after last excitation
Variable/Progressive Flip Angle

- Flip angle is strictly increasing
- Received signal constant when accounting for lost magnetization (Si = C)
- Efficient usage of all polarization

\[
\begin{align*}
\theta_1 = 45^\circ \\
\theta_5 = 90^\circ \\
\theta_2 = 45^\circ \\
\theta_3 = 90^\circ \\
\theta_4 = 45^\circ \\
\theta_6 = 90^\circ \\
\end{align*}
\]

\[
\tan \theta_n = \frac{1}{\sqrt{N - n}}
\]
Dynamic Imaging: Conventional Excitation

Flip angle

20°
10°
5°
2.5°

Received signal

Time

Excess Pyruvate SNR

Pyruvate
Lactate

Hyperpolarization Methods
Dynamic Imaging: Multiband Excitation

More lactate SNR for more time

Pyruvate SNR is still sufficient

Smaller pyruvate flip leaves more magnetization that can then become lactate

Pyruvate

Lactate
Combination of

- Variable flip angle across acquisitions for improved SNR
- Multiband pulse designs to account for metabolic conversion between acquisitions
Spectral Selectivity

Use spectrally selective RF pulses to control flip angles for different compounds.
Spectral Excitation Profile

- Design RF pulses for desired spectral profile
- Fourier Transform relationship between RF pulse shape and Magnetization profile: Valid for small tip angles, < 30° (pretty close up to 60°)
- Non-linear relationship for large tip angles: Use Shinnar-Le Roux transform or other tools for RF pulse design
Spectral-Spatial RF Pulses

- Add oscillating gradient for additional spatial selectivity
- Additional constraints on spectral and spatial selectivity
- Useful in vivo where spatial selectivity is important
Spectral-Spatial RF Pulse Design

**Features:**
- Simultaneous selectivity in frequency and position
- Customizable for different nuclei and MR hardware
- Multi-band specification
- Aliased bands are allowed
- Power minimization
- Time minimization
- Correction for non-uniform sampling
- VERSE for ramp sampling and peak B1 reduction

**MATLAB code available at:**
https://github.com/agentmess/Spectral-Spatial-RF-Pulse-Design
Hyperpolarized Acquisitions: Need for Speed

- Rapid signal decay
- Rapid metabolic conversion
- Single image SNR decreases with more excitations due to T1 decay
- Fast data acquisition is important for HP agents

Simulated Single-Image SNR with T1 decay and progressive flip angle
Readout Strategies

Can be approximately grouped into three categories (from slowest to fastest)

1. MR spectroscopic imaging (MRSI)
2. Model-based Spectral decomposition with multiple TEs (Dixon/IDEAL)
3. MRI with spectrally-selective excitation (“Metabolite-specific Imaging”)
Fast MR Spectroscopic Imaging

- **Methods**
  - Echo-planar spectroscopic imaging (EPSI)
  - Spiral spectroscopic imaging
  - Concentric Rings
  - Radial EPSI
  - Rosettes
  - And More

Simultaneous acquisition of spectral and spatial k-space data in ($k_x$, $k_y$, $k_z$, $t$) or ($k_x$, $k_y$, $k_z$, $k_f$) space
MRSI Readouts

Phase Encoding

Echo-planar spectroscopic imaging (EPSI)

DAQ

G_Z

k_z

k_f

DAQ

G_Z

k_z

k_f

Hyperpolarization Methods
Accelerated MRSI Strategies


Comparison of Accelerated MRSI Strategies

Tradeoffs

- Speed
- SNR efficiency
- Robustness to hardware imperfections
- Bandwidth
- Resolution

<table>
<thead>
<tr>
<th></th>
<th>Flyback EPSI</th>
<th>Symmetric EPSI</th>
<th>Concentric Rings</th>
<th>Spiral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>SNR</td>
<td>-</td>
<td>++</td>
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<td>++</td>
</tr>
<tr>
<td>Robustness</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>--</td>
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**Spectral Decomposition**

- **Dixon/IDEAL** (Iterative decomposition of water and fat with echo asymmetry and least-squares estimation) methods: *Originally developed for fat/water imaging*

- Reconstruct individual metabolite images based on known chemical shifts

- Multiple TEs: minimum # of TEs = Npeaks (*+1 if B0 field map estimated required*)
Spectral Decomposition: Spiral CSI

RF Spiral Readouts

TE_1

TE_2

TE_3

TE_4

Matrix Inversion

FFT

Spectral Images

Δf = 0 Hz

Δf = 614 Hz

Δf = 433 Hz

Δf = 272 Hz

Spectral Decomposition: Oversampled Spirals

Gordon et al., MRM 2013
Metabolite-specific Imaging

- Idea: Excite only a single metabolite resonance, followed by any imaging-based readout
- Methods:
  - Single-metabolite Spectral-spatial excitation
  - Fast imaging readout (EPI, spiral)
- Fast!
- Requires chemical-shift separation of metabolites, sensitive to $B_0$ inhomogeneities

*Spectral-spatial Excitation  Single-shot Spiral MRI*

*Cunningham JMR 2008, Lau MRM 2010 NMR Biomed 2011*
Metabolite-specific Imaging

- Spectral-spatial excitation of individual metabolites with variable flip angles
- Ramp sampled, symmetric EPI
- 16 slices of pyruvate and lactate images in 2 s

Cunningham et al. JMR 2008.
Clinical Metabolite-specific Imaging

Cardiac imaging with Spiral Readout

Brain imaging with EPI Readout


## Technique Comparison

<table>
<thead>
<tr>
<th>Technique</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSI</td>
<td>Robust to off-resonance</td>
<td>Slow</td>
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<tr>
<td></td>
<td>Flexible spectral content</td>
<td></td>
</tr>
<tr>
<td>Spectral Decomposition (IDEAL/Dixon)</td>
<td>Speed+SNR</td>
<td>Peak locations must be known</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limits on sequence parameters (TE)</td>
</tr>
<tr>
<td>Metabolite-specific Imaging</td>
<td>Speed+SNR (max!)</td>
<td>Sensitive to off-resonance</td>
</tr>
<tr>
<td></td>
<td>Works well with [1-13C]pyruvate spectrum</td>
<td>Requires spectrally separated metabolites</td>
</tr>
</tbody>
</table>
Parametrizations: Kinetic Modeling vs. alternatives

Numerous options

- Kinetic modeling (e.g. $k_{PL}$)
- Lactate/pyruvate

I advocate for unidirectional $k_{PL}$ model

- Insensitive to bolus delivery with any sampling strategy
- Incorporate effects of RF pulses
- Compare $k_{PL}$ (1/s) across sites, imaging protocols, and anatomy
- Simple (good for low SNR)

Choice of Model


- Models evaluated by Akaike Information Criteria (AIC) which balances fit quality with number of model parameters
  a. Pyr-lac (all lumped)
  b. Extravascular and intravascular compartments
  c. Extravascular/extracellular, intracellular, and intravascular compartments

- Assumptions
  - Neglect \( k_{LP} \), lactate transport. Gamma-variate pyruvate input
  - Pyruvate input estimated from heart voxels
  - \( T_{1P} = 45s, T_{1L} = 25s \)
“Input-less” Fitting

- Actual pyruvate signal as input, change in lactate as output
- No assumptions or fitting of pyruvate input
- **Pros**: Simple, insensitive to fitting errors in pyruvate (e.g. incorrect bolus shape), works with any sampling strategy
- **Cons**: No estimate of perfusion

\[
M_{Z,L}[n+1] = M_{Z,L}[n]S_{RF,L}[n] \exp(-R_{IL} \ast TR) + \\
M_{Z,P}[n]S_{RF,P}[n] \exp(-R_{1P} - k_{PL})TR + k_{PL} \exp(-R_{1L}TR) / R_{1P} - R_{1L} + k_{PL}
\]


https://github.com/agentmess/hyperpolarized-mri-toolbox
Hyperpolarized-MRI-Toolbox

https://github.com/agentmess/hyperpolarized-mri-toolbox

- MATLAB tools for designing and analyzing HP MRI
- Open-source, **contribute your coolest code!**

**Current Features**
- EPSI waveforms
- Spectral-spatial RF
- Variable flip angles
- Kinetic Modeling
- **Numerical phantom**

**Coming soon**: Datasets for standardized comparisons of analysis methods