Hyperpolarized $^{13}$C MRI: A Pulse Sequence Perspective

Peder E. Z. Larson, Ph.D.

Surbeck Laboratory of Advanced Imaging, Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, United States
0. Basic principles of MRI with Hyperpolarized Agents
   – Unrecoverable signal decay
   – Metabolic conversion
   – Chemical shift

1. RF Pulse Strategies
   – Variable Flip Angles
   – Spectral selectivity

2. Data Acquisition Strategies
   – MR spectroscopic imaging
   – Spectral decomposition
   – MR imaging
   – Parallel imaging & compressed sensing

3. Experiment Strategies
   – Dynamic imaging
Spin Polarization

When a magnetic field is applied, it will be found to be either in the spin-up or spin-down state, no matter which mixed state it was in before. Furthermore, it will stay in that new state until the proton is subject to more interactions with the environment (e.g., another measurement). This so-called collapse into an eigenstate is a consequence of QM. It apparently implies that a measurement of the net magnetization (e.g., by MRI), will force each proton into either the spin-up or the spin-down state in agreement with myth 1. This is wrong, however.

The emphasized word \textit{individual} above is important in the present context, as we can only infer from QM that the protons are forced into single-spin eigenstates, if we measure their magnetization one-by-one as can be done with a Stern-Gerlach apparatus, for example (11). In contrast, that is never done in MR spectrometers or scanners: to get a measurable MR signal the total magnetization of many nuclei is always measured, and myth 1 does not follow. It could be true nevertheless, but in fact it is not, which is shown in appendix (proposition 1) by employing the QM formalism: A measurement of the net magnetization causes a perturbation of the system that is insufficient to affect the individual protons significantly. In particular, they are not brought into their eigenstates by the measurement process.

It is worth noting that even though the arguments mentioned above may occur complicated for the non-technical reader, they are what many students of MR more or less implicitly lay ears to, and for no good reason, as QM is not needed for understanding basic MR. Moreover, the students often hear the wrong version of the argument.

The lifetime of myth 1 may have been prolonged by an observation that many working with MR have made: when subject to a magnetic field, an oblong piece of magnetizable material have a strong tendency to align itself in one of two opposite directions parallel to the field (in contrast to permanently magnetized material that orient itself in one direction only). Despite a superficial resemblance, this well-known phenomenon has nothing to do with the effect expressed in myth 1. Rather it is a consequence of reorientation of magnetic constituents inside the metal. This gives rise to the existence of two low-energy states for the orientation of the metallic piece, parallel and antiparallel to the field. The magnetic constituents are in either case parallel to the field, because they have only one low-energy state. Similarly, the proton spin has only one low-energy state. Nothing but MR-irrelevant single-proton measurements give spins a tendency to align antiparallel to the field.

Consequently, spins can point in any direction and the energy eigenstates are not more relevant to MR than any other state (the eigenstates form a convenient basis for computations, but they are irrelevant for the understanding). Hence Fig. 1 that illustrates the nature of spin eigenstates, do not contribute much but confusion in an MR context. QM is later shown to imply that the spin-evolution of individual protons happens as expected classically unless perturbed, e.g., by a single-spin measurement.

Finally, replacements for Fig. 1 are discussed. According to both classical and QM, spins are expected to point in all directions in the absence of field as shown in Fig. 2. Except for precession, the situation does not change much when the polarizing $B_0$-field used for MR is applied as shown in Fig. 3. The energies associated with the orientation of the individual spins are much smaller than the thermal...
Polarization fraction:

0.0001-0.0005% at room temperature, depending on nucleus (γ) and field (B₀)
• Perturb spins from thermal equilibrium to increase fraction aligned parallel (or anti-parallel) to $B_0$

• Methods:
  – Optical pumping (for gasses, ie 3He, 129Xe)
  – Parahydrogen-induced Polarization (PHIP)
  – *Dynamic Nuclear Polarization (DNP)*
Hyperpolarization

Thermal Equilibrium Polarization and MR Signal

Hyperpolarization and MR Signal

Energy

Nuclear spins

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

Microwave Irradiation at
\( Y_{\text{electron}} B_0 \pm Y_{\text{C-13}} B_0 \)
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
Net magnetization behavior, hyperpolarized or at thermal equilibrium, is described by Bloch equation:

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

- **Precession**
- **RF Excitation**
- **Relaxation back to thermal equilibrium:**

\[
\vec{M} = \begin{bmatrix} 0 \\ 0 \\ M_0 \end{bmatrix}
\]
T₁ decay
(~40s in vivo for [1-¹³C]pyruvate at 3T)
1. Hyperpolarization of $^{13}$C-pyruvate (45-90 mins)

2. Rapidly dissolve 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)

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Only 1.1% of carbon molecules are $^{13}$C isotope, most are $^{12}$C, so isotopically enriched compounds are generally used.
HP [1-\(^{13}\)C]Pyruvate MR In Vivo

Unrecoverable Signal Decay

Chemical Shift

Lactate

Pyruvate

Bicarbonate

Metabolic Conversion

Fast decay: 96 sec shown
Dissolution DNP $^{13}$C Agents

**Requirements**
- Long $T_1$ relaxation time (polarization half-life)
- Water-soluble
- 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
- $[1-{^{13}}C]$-α-ketoglutarate: IDH mutation status
- and more

Simultaneous polarization of multiple agents


$\sim 2$ kHz (3T) chemical shift range of metabolites
1. Excite spins (RF)
2. Readout signal (spectral and/or spatial encoding)
3. Repeat
1. Excite spins (RF)
Polarization Usage

Magnetization Loss

RF

T₂ decay (~100ms-2s in vivo for pyruvate)

M₀

Mₓy

Signal

θ

time

M₀

Mₓy
Two key considerations:

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

2. Spectral selectivity
   - Spectral-spatial RF pulses
• 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

\[
\tan \theta_n = \frac{1}{\sqrt{N - n}}
\]

Nagashima, JMR 190 (2) (2008) 183–188.
Dynamic Imaging: Conventional Excitation

Lactate
Pyruvate

[Chemical structures]

Excess Pyruvate SNR

received signal

time

flip angle

20°
10°
5°
2.5°
Dynamic Imaging: Multiband Excitation

Smaller pyruvate flip leaves more magnetization that can then become lactate.

More lactate SNR for more time.

Pyruvate SNR is still sufficient.

Pyruvate

Lactate

\[ ^{13}C_1 \text{Pyruvate} \rightarrow ^{13}C_1 \text{Lactate} \]
Optimal Variable Flip Angle Schemes

- Choose flip angles based on best fitting of model parameters (e.g. $k_{PL}$) by maximizing “Fisher Information”
- Simulations validate improved $k_{PL}$ estimates compared to previous flip strategies

https://github.com/maidens/Flip-Angle-Design-Toolbox

![Optimized flip angle sequence](image-url)
Use spectrally selective RF pulses to control flip angles for different compounds.
• 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
Multiband Spectral-Spatial RF Excitation for \([2-^{13}\text{C}]\text{Dihydroxyacetone}\)

- Large spectral dispersion: 150 ppm = 4.7 kHz at 3T
- Chemical shift slice misregistration corrected across up to 6 spectral bands of interest
- Multiband flip angles

**Graphs and Images:**
- Graph showing RF and gradient waveforms over time.
- Graph illustrating chemical shifts and positions.
- Image showing magnitude and position with labels for G3P, DHAc-hydrate, and PEP.

**Citations:**
**Data Acquisition Strategies**

1. **Excite spins (RF)**
2. **Readout signal** (spectral and/or spatial encoding)

**Diagram:**
- RF pulse
- DAQ (Data Acquisition)
- Magnetization Vector
- $M_Z$, $M_{XY}$
- $T_1$, $T_2$
- Signal
- $x N_{TR}$
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

- No T\textsubscript{1} decay
- TR/T\textsubscript{1} = 1/200
- TR/T\textsubscript{1} = 1/50
Can be approximately grouped into three categories (from slowest to fastest)

1. MR spectroscopic imaging (MRSI)
2. Spectral decomposition with multiple Tes (Dixon/IDEAL)
3. MRI with spectrally-selective excitation
MRSI Readout

Phase Encoding

\[ G_z \]

DAQ

Echo-planar spectroscopic imaging (EPSI)

\[ G_z \]

DAQ

\[ k_z \]

\[ k_f \]
MRSI Readout

Phase Encoding

\[ k_z \]

\[ 1/\text{res}_z \]

\[ k_f \]

\[ 1/\text{FOV}_f = 1/\text{bandwidth} \]

Echo-planar spectroscopic imaging (EPSI)

\[ k_z \]

\[ 1/\text{res}_z \]

\[ k_f \]

\[ 1/\text{FOV}_f = 1/\text{bandwidth} \]

- Fast Acquisition
- Reduced SNR efficiency
- Tradeoff between spatial resolution and bandwidth
Flyback and Symmetric EPSI

**Flyback EPSI**

- Robust to system imperfections
- Simple reconstruction

**Symmetric EPSI (with ramp sampling)**

- Improved SNR efficiency
- Better resolution/bandwidth tradeoff
- Complex reconstruction
- Sensitive to delays and eddy currents
Other Accelerated MRSI Strategies


**Comparison of Accelerated MRSI Strategies**

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

**Acquisition Time**

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

**SNR Efficiency**

**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)

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Diagram:

- **TE1**: Fat → Water
  - Fat: Blue
  - Water: Green

- **TE2**: Fat → Water
  - Fat: Blue
  - Water: Green

- **TE3**: Fat → Water
  - Fat: Blue
  - Water: Green

- **TE4**: Fat → Water
  - Fat: Blue
  - Water: Green
Spectral Decomposition: Spiral CSI

Spectral K-space

Δf = 0 Hz

Δf = 614 Hz

Δf = 433 Hz

Δf = 272 Hz

**Single-shot Spiral MRI**

**Idea:** Excite only a single metabolite resonance, followed by any imaging-based readout

- **Methods:**
  1. Single-metabolite Spectral-spatial excitation
  2. Fast imaging readout (EPI, spiral)
- **Fast!**
- Requires chemical-shift separation of metabolites, sensitive to B0 inhomogeneities

**Metabolite-specific Imaging**

Spectral-spatial Excitation

Metabolite-specific Imaging with EPI

Key Features

- Spectral-spatial excitation of individual metabolites with variable flip angles
- Ramp sampled, symmetric EPI for on a clinical scanner (built off commercial 1H EPI sequence)
- Reference scan obtained directly on 1H channel and applied to 13C data
**Parallel Imaging**

**Idea:** Use coil arrays for acceleration-compatible with MRSI, MRI, & spectral decomposition

**Key Challenge:** Limited natural abundance $^{13}$C for coil sensitivity maps

**Solutions**
- Phantom calibration scans (Tropp et al. JMR 2011.)
- Calibrationless methods (Shin et al. MRM 2013)
- Biot-Savart law profile calculations

**Example: Autocalibrated partial Fourier parallel imaging**

- 6 x 6 Center Lines
- Outer Reduction Factor 2
- Partial Fourier
- 104 Total Phase Encodes
- Time 13.4 s
- Acceleration 2.9

Ohliger et al. JMRI 2013.
**Compressed Sensing**

**Idea:** Enforce sparsity in data for acceleration

Compatible with MRSI, MRI, & spectral decomposition

**Requirements**
1. Compressible signal: *sparse spectra, redundancy in space, redundancy in time*
2. Adequate SNR
3. Incoherent aliasing from sampling: *pseudo-random sampling*
4. Non-linear reconstruction

*Example: Dynamic HP [1-^{13}C]pyruvate MRSI is very sparse*

Compressed Sensing

- Human Prostate Imaging
## Technique Comparison

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<th>Technique</th>
<th>Pros</th>
<th>Cons</th>
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<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 Limits on sequence parameters (TE)</td>
</tr>
<tr>
<td>Metabolite-specific Imaging</td>
<td>Speed+SNR (max!)</td>
<td>Sensitive to off-resonance Requires spectrally separated metabolites</td>
</tr>
<tr>
<td>Parallel Imaging</td>
<td>Speed+SNR Compatibile with most methods</td>
<td>Requires $^{13}$C coil arrays</td>
</tr>
<tr>
<td>Compressed Sensing</td>
<td>Speed+SNR Compatibile with most methods</td>
<td>Non-linear reconstruction ➔ Artifacts difficult to detect &amp; non-linear denoising</td>
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</table>
Experiment Strategies

1. Excite spins (RF)
2. Readout signal (spectral and/or spatial encoding)
3. Repeat
## Dynamic vs. Single time-point Imaging

<table>
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<th>Single time-point</th>
<th>Dynamic</th>
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<td>One acquisition</td>
<td>Multiple acquisitions</td>
</tr>
<tr>
<td>Metabolite Ratio</td>
<td>Kinetic rates and perfusion</td>
</tr>
<tr>
<td>Assumes reproducible delivery</td>
<td>Invariant with delivery</td>
</tr>
<tr>
<td>Higher resolution &amp; SNR</td>
<td>Careful distribution of magnetization over time</td>
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### Simulated Metabolite Ratio

- **Curves have a 5 s difference in $^{13}$C-pyruvate delivery (was observed in Phase I Trial in Prostate Cancer)**
- **Large differences in $^{13}$C-lactate:$^{13}$C-pyruvate ratio**
- **High sensitivity to image acquisition timing**

### Prostate cancer voxel

- $k_{pyr-lac} = 0.016 \text{ s}^{-1}$

### Vascular voxel

- $k_{pyr-lac} = 0.005 \text{ s}^{-1}$
• Separation of overlapping $[5-^{13}C]\alpha$-ketoglutarate and $[1-^{13}C]2$-Hydroxyglutarate based on dynamic imaging
• Multiband variable flip angle for efficient magnetization usage
Summary

0. Basic principles of MRI with Hyperpolarized Agents
   – *Unrecoverable signal decay*: fast and efficient imaging
   – *Metabolic conversion*: preservation of hyperpolarized substrate
   – *Chemical shift*: spectrally sensitive imaging

1. RF Pulse Strategies
   – *Variable Flip Angles*: efficient use of HP magnetization
   – *Spectral selectivity*: control flip angles for individual compounds

2. Data Acquisition Strategies
   – *MR spectroscopic imaging*: robust, comprehensive, slow
   – *Spectral decomposition*: model-based multiple TE separation, faster ➔ SNR
   – *MR imaging*: single-compound excitation with EPI/Spiral/etc, fastest method
   – *Parallel imaging & compressed sensing*: accelerated imaging compatible with most acquisition strategies

3. Experiment Strategies
   – *Dynamic imaging*: robust, SNR spread across multiple images
Thank you!