Weekend Educational Course: Molecular Imaging

How to Detect HP Agents: Pulse Sequences

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Highlights:

- The non-equilibrium nature of hyperpolarized magnetization, and the limited lifetime and amount of hyperpolarized agent, necessitate optimized imaging strategies to maximize information content from the acquisition.
- Excitation flip angles that increase as the acquisition proceeds, and RF pulses providing spatial localization in combination with different excitation flip angles at chemical-shift values of interest, are valuable for optimally managing the non-equilibrium magnetization.
- Balanced, steady-state free precession pulse sequences permit rapid acquisition of high signal-to-noise images for certain applications of hyperpolarized agents.
- Regional characterization of dynamic processes, such as metabolism, requires highly accelerated strategies for spatial (e.g., echo-planar or spiral trajectories) and spectral (e.g., optimized-Dixon [IDEAL] or sparse reconstruction from undersampled data) encoding.

Target audience: Researchers interested in pulse-sequence methods for molecular imaging using hyperpolarized agents.

Objective: Describe imaging strategies optimized for molecular imaging using hyperpolarized agents, particularly hyperpolarized ^{13}C compounds, with a focus on management of the non-equilibrium magnetization and acceleration of spatial/spectral encoding.

Introduction: *Hyperpolarization* -- generation of nuclear polarization orders of magnitude larger than the thermal equilibrium value in the static magnetic field strength of interest -- has yielded unprecedented opportunities for functional and metabolic MR-based studies in a wide range of application areas. Hyperpolarized noble gases yield new insights on the structure and function of the lung, while hyperpolarized ^{13}C compounds permit new approaches for characterization of organ function in health and disease throughout the body, including applications with high clinical potential such as fundamentally improved detection of cancer *in vivo*. Many additional opportunities are anticipated as methods continue to be developed and optimized for hyperpolarizing compounds containing a wider range of NMR-visible nuclei (e.g., ^{15}N).

While the benefits of substantially increased nuclear polarization are obvious, imaging strategies developed and optimized for MRI of thermally-polarized magnetization are often suboptimal for hyperpolarized agents, and thus new, or at least re-optimized, methods are required. For the large non-equilibrium magnetization of hyperpolarized agents, T1 relaxation results in loss of magnetization, instead of a regrowth of magnetization as occurs for the thermally-polarized case. In the context of many typical pulse sequences, this means that the longitudinal magnetization, not replenished through T1 relaxation, is irreversibly "consumed" as excitation RF pulses are applied. T1 relaxation times for currently available agents are generally

no more than tens of seconds, and, of practical importance, the amount of hyperpolarized agent is typically limited, particularly for *in-vivo* studies. Thus, barring repeated or continuous dosing of the agent, the timeframe for acquisition is fundamentally limited. These underlying characteristics and constraints lead to two driving themes for pulse-sequence design and optimization: management of the non-equilibrium magnetization and acceleration of spatial/spectral encoding.

Of the hyperpolarized agents developed to date, ^{13}C compounds have had, by far, the largest application to molecular imaging. Our discussion below will therefore be focused on pulse-sequence developments relevant to hyperpolarized ^{13}C.

Management of Non-equilibrium Magnetization: The simplest approach for dealing with the fixed amount of longitudinal magnetization available from a given dose (injection) of a hyperpolarized agent is to use a series of low-flip-angle RF excitations. For imaging a range of chemical shifts, it may be advantageous to acquire data in the form of a spin echo. For this purpose, a double-spin-echo implementation permits use of a low-flip-angle excitation RF pulse while returning the remaining longitudinal magnetization to the positive *z*-axis. The low-flip-angle, double-spin-echo concept was introduced many years ago for proton MRI [1, 2]. Optimization for ^{13}C imaging included use of a pair of adiabatic 180° pulses to greatly reduce sensitivity to B1 inhomogeneity [3]. The low-flip-angle, double-spin-echo method is naturally compatible with application of diffusion-sensitization gradients, and has been used to map diffusion coefficients of hyperpolarized ^{13}C metabolites [4].

While the constant, low-flip-angle approach may be sufficient for many applications, it results in gradually decreasing signal strength, which may complicate quantitation and yields decreasing signal-to-noise ratios in proportion to the decreasing signal. A straightforward, but effective, alternative is to incrementally increase the flip angle during the acquisition, with the goal of maintaining a constant signal level throughout while consuming all of the available magnetization. Assuming negligible contribution of transverse magnetization from a given excitation to subsequent repetitions, the recursive relationship $\theta_n = \tan^{-1}(\sin \theta_{n+1})$ permits calculation of the flip angles, for the condition that the last flip angle equals 90°. This relationship was given in an early paper by Mansfield [5], and subsequently applied for hyperpolarized gases [6] and hyperpolarized ^{13}C imaging [e.g., 4, 7, 8, 9]. An important practical aspect of this variable-flip-angle scheme is that the signal evolution may deviate substantially from the desired constant value if the applied flip angles deviate significantly from their intended values due to B1 inhomogeneity or inaccurate transmitter calibration. Robustness to these non-ideal factors can be achieved by reducing the target value of the last flip angle to less than 90°.

Molecular imaging applications of ^{13}C-containing compounds often involve signals at several chemical-shift values, deriving from one or a small number of input compounds (e.g., ^{13}C-pyruvate [input] and its metabolic products). Since the input compound is the source of magnetization for the downstream products, which have different resonant frequencies than the input, it is advantageous to use RF-excitation schemes that can provide specific flip angles corresponding to each frequency (compound) of interest, while potentially providing spatial localization at the same time [7, 10, 11]. For example, one may want to use a relatively low flip angle at the chemical shift associated with the source compound, so as not to deplete the magnetization pool for downstream products, a relatively high flip angle at the chemical shift associated with a downstream compound of interest, to obtain high signal-to-noise data, and no excitation (0° flip angle) at the chemical shift associated with a compound that is not of interest. These

requirements have led to the development of optimized spatial/spectral excitation RF pulses [12] that permit spatial localization in combination with different flip angles for specific chemical shifts (compounds) of interest and, as described in the previous paragraph, increasing flip angles as the acquisition proceeds [7, 13].

An important case of optimized spatial/spectral excitation RF pulses is when 90° (saturation) flip angles are used for downstream compounds of interest, thereby allowing direct and easy quantification of the amount of downstream compound formed during the time between successive excitations [10]. This approach is analogous to chemical shift saturation recovery (CSSR) spectroscopy [14, 15] used in hyperpolarized xenon-129 lung imaging, wherein xenon dissolved in the lung parenchyma and blood is periodically saturated to measure the rate of gas uptake from the lung airspaces.

A different approach to addressing the limitations imposed by the fixed amount of longitudinal magnetization associated with a hyperpolarized agent is to utilize a pulse sequence that inherently makes efficient use of the magnetization. For example, balanced steady-state free precession (SSFP) pulse sequences, as employed for a number of clinical MRI applications, are effective for obtaining high signal-to-noise data from substances having relatively long relaxation times. Balanced SSFP has been used for hyperpolarized ^{13}C angiography [16-18], as well as cerebral [19], renal [20] and pulmonary [21] perfusion studies. Note that, for these applications, there was only one chemical-shift value of interest. More recently, balanced SSFP has been used for vascular permeability and perfusion measurements using simultaneous acquisition of signals from three different hyperpolarized agents [22], and multi-echo balanced SSFP has been applied for fast volumetric spatial/spectral encoding [23]. Single-shot RARE (fast/turbo spin echo) can likewise be effective for obtaining signal-to-noise data from substances having relatively long relaxation times, as demonstrated in early ^{13}C angiography studies [24].

Acceleration of Spatial/Spectral Encoding: As noted above, molecular imaging applications commonly involve ^{13}C-containing compounds with a range of chemical-shift values, and thus imaging typically requires both spatial and spectral encoding. The straightforward approach for achieving this is conventional (fully phase-encoded) chemical-shift imaging (CSI) [25]. Although this method is relatively slow (acquisition times of seconds to tens of seconds per image set), because standard phase-encoding is used for all spatial dimensions of interest, it is perfectly adequate for some types of studies. Standard CSI was used for early metabolic studies [e.g., 26, 27], as well as for a number of more recent studies. Nonetheless, three-dimensional regional characterization of relatively fast dynamic processes, such as metabolism, requires much higher temporal resolution. This need has driven the development of accelerated methods for spatial/spectral encoding.

Acceleration has been attacked on two fronts: more efficient trajectories for spatial encoding, and spectral encoding using much less data (than sampling a full free induction decay) considering the relatively sparse nature (small number of well-defined peaks) and bandwidth limitations of the spectra. For example, echo-planar spectroscopic imaging (EPSI) [5, 28], as used for proton applications, combines spectral encoding with one-dimension of spatial encoding using an oscillating readout (symmetric or “flyback”) gradient to reduce acquisition time in proportion to the number of phase-encoding steps that would have been used along the respective spatial dimension [3, 8]. EPSI has been used with free induction decay, low-flip-angle

double-spin-echo and stimulated-echo pulse sequences [3, 8, 29]. A radial version of EPSI has also been described for hyperpolarized ^{13}C metabolic imaging [30].

As well-known from proton MRI, spiral *k*-space trajectories [32] offer a very efficient approach for spatial encoding. Spiral trajectories have been exploited with different spectral-encoding approaches, such as using repeated (multi-echo) spirals after a single excitation (essentially a spiral version of EPSI) with undersampling in the spectral domain and optimized reconstruction considering the sparse nature of the spectra [9, 32, 33], or using a small number (e.g., 7) of excitations, each including a single-shot spiral, with echo times incremented from excitation to excitation and reconstruction via an optimized-Dixon (IDEAL) scheme [13, 34]. (The IDEAL approach has also been applied to mutli-echo data acquired using an echo-planar type readout gradient with 7 echoes [11].)

More recently, a concentric-circles trajectory has been proposed for hyperpolarized ^{13}C spatial/spectral encoding [35]. This trajectory is faster than EPSI, and more robust to non-ideal gradient system performance than spiral-based methods. The spatiotemporal encoding approach has also been demonstrated for hyperpolarized ^{13}C spectroscopic imaging [36].

Since the number of distinct chemical species of interest is often small, a different way to obtain rapid, spectrally-resolved images is to use optimized spatial/spectral excitation RF pulses, as discussed in the previous section, to excite only a single compound at a time and interleave excitation among the compounds of interest [10, 37]. For example, if three metabolites are of interest, this approach would require only three excitations, as compared to seven excitations for the IDEAL spiral CSI method described above. It is also possible to excite a single compound while localizing a complex pattern in two spatial dimensions [38]. A compromise between excitation/spectral-encoding of all relevant chemical-shift values and one-by-one excitation is also possible, wherein a limited portion of the spectral bandwidth, containing a subset of the peaks of interest, is excited [39].

Low-flip-angle balanced-SSFP can be used to perform the spatial encoding analog of the single-compound-at-a-time method. A very low flip angle (e.g., ~2°) yields a narrow passband (on the order of 10 Hz for TR ~2 ms) for the SSFP pulse sequence, which can be positioned at the frequency corresponding to the compound of interest [40]. Another interesting approach is to use chemical shift differences to fully separate the signals associated with multiple compounds along the frequency-encoding direction of a standard gradient-echo based acquisition (analogous to the scheme used to separate signals from gaseous and dissolved-phase xenon-129 in the lung [41]), thereby allowing several chemically-shifted signals to be obtained without additional data acquisition dedicated to spectral separation. This approach has been demonstrated using both spoiled gradient-echo and balanced-SSFP pulse sequences [22, 42]. In addition, a radial version of this strategy has recently been demonstrated [30].

Lastly, generally-applicable techniques for acceleration (e.g., parallel imaging using multi-coil arrays, compressed sensing and related undersampling strategies) are of substantial value for accelerating spatial/spectral encoding of hyperpolarized agents [43-47], analogous to proton MRI.

Conclusion: The non-equilibrium nature of hyperpolarized magnetization, and the limited lifetime and amount of hyperpolarized agent, necessitate optimized imaging strategies. For molecular imaging using hyperpolarized ^{13}C compounds, these characteristics and constraints lead to two primary focuses for pulse-sequence optimization -- management of the non-equilibrium

magnetization and acceleration of spatial/spectral encoding. Optimized approaches for excitation and encoding have been demonstrated that permit dynamic characterization of ^{13}C metabolites with temporal resolution of less than 1 second (2D) to a few seconds (3D). Further improvements in speed and image quality are anticipated as a result of on-going development efforts.

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