Imaging Methods for Hyperpolarized $^{13}\text{C}$ MR

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The signal enhancement for MR-visible compounds by multiple orders of magnitude afforded by dynamic nuclear polarization in combination with a dissolution process that preserves the magnetization has enabled new opportunities for MR imaging. In particular, the polarization of metabolically active substrates permits real-time imaging of metabolism in vivo. Although this new methodology still does not provide the sensitivity of positron emission tomography, the advantage is the ability to differentiate the metabolic products from the injected substrate based on their chemical shift (CS), i.e., the resonance frequency relative to a reference standard; the electronic structure in a molecule leads to small changes of the resonance frequency of a given nucleus. For example, the resonance frequency of the labeled carbonyl carbon in $[1^{-^{13}}\text{C}]$pyruvate and $[1^{-^{13}}\text{C}]$lactate differ by approximately 390 Hz at 3T. As the frequency difference is proportional to the field strength, the CS is commonly expressed in parts per million (ppm) of the spectrometer frequency. In this notation, the CS difference for $[1^{-^{13}}\text{C}]$pyruvate and $[1^{-^{13}}\text{C}]$lactate is about 12 ppm.

In comparison to conventional MRI, chemical shift imaging (CSI), also called MR spectroscopic imaging (MRSI), requires to encode one extra dimension that contains the frequency information in addition to the two or three spatial k-space dimensions. As the transverse magnetization linearly accrues phase proportional to the offset frequency of the respective resonance, the chemical shift information can simply be encoded by acquiring the data over a fixed duration without any spatial encoding gradients being present while using phase encoding (PE) for the spatial dimensions.

An important difference to imaging at thermal equilibrium polarization levels is the fact that the magnetization is not replenished between TR intervals, but instead decays with longitudinal relaxation constant $T_1$ (on the order of 30 s in vivo). Furthermore, as the imaging process itself reduces the available magnetization, efficient sampling strategies are required, in particular in the case of dynamic imaging. On the flip side, given that only a fixed amount of magnetization is available, the scan time reduction in fast imaging techniques does not necessarily lead to the usual reduction in signal-to-noise ratio (SNR).

Although PE-based CSI is considered the gold standard for conventional in vivo spectroscopic imaging, the use of this method is usually hampered by long acquisition times because the number of PE steps is in general equal to the number of voxels in the final metabolic image. Due to the large dispersion of the chemical shift in $^{13}\text{C}$-MRS, shortening the data acquisition window reduces the total scan time with minimal spectral overlap (1). Even when using circularly-reduced k-space sampling schemes the total acquisition time for a single-slice CSI experiment is on the order of 10 to 20 s (2). Blurring caused by the $T_1$ decay during this long acquisition can be reduced by using a variable flip angle scheme for the excitation pulse (3).

Larger reductions in total scan time are possible by simultaneously encoding spectral and spatial information during readout. Using echo planar-based spectroscopic imaging, which simultaneously encodes the data in the spectral and one spatial dimension, can speed up the acquisition by an order of magnitude (4,5). Even higher acceleration factors are achievable with spiral CSI, where data are encoded simultaneously in the spectral and two spatial dimensions (6). Therefore, this sequence permits single-shot 2D metabolic imaging (7). For both methods, the shorter acquisition time is achieved at the expense of decreased spectral width due to hardware constraints for maximum gradient amplitude and slew rate.

A different approach in reducing the scan time is by exploiting the sparsity of the $^{13}\text{C}$ spectrum using compressed sensing (8,9).
The amount of data to be acquired and, hence, scan time, can also be reduced by using prior knowledge of the resonance frequencies in the spectrum and generating metabolic images by least-squares estimation (10-12).

Another approach is to successively image each metabolite at a time by using spectral-spatial RF pulses that selectively excite a single resonance (13).

Further acceleration can be achieved by using receiver coil arrays combined with parallel imaging techniques (14,15).

While a lot of the fast imaging sequences apply a pulse-and-acquire scheme and detect the free induction decay (FID) signal, detection of the spin echo is advantageous, as it allows the acquisition of absorption mode spectra, i.e., no linear phase across the spectra as in the FID acquisition. Therefore, a double spin echo method using adiabatic refocusing pulses has been developed (4). However, if the animal/subject extends considerably past the edges of the transmit RF coil, this approach can potentially lead to a loss of hyperpolarized magnetization in dynamic imaging due to flow of spins through the fringe field of the coil, where the refocusing pulses fail to provide complete refocusing (16).

For dynamic imaging, multiband spectral-spatial excitations pulses have been developed that permit different flip angles for the products and the substrate (17). A low excitation flip angle for the injected substrate preserves its magnetization for subsequent conversion while a higher flip angle for the metabolic products increases their SNR. Using a 90°-excitation pulse on the metabolic products and saturating their resonances at each TR permits the quantitation of dynamic data using a Michaelis-Menten-type formulation that takes into account potential enzyme saturation effects (18). The resulting parameter estimates for maximum reaction velocity and apparent Michaelis-Menten constant are not biased with respect to experimental parameters such as substrate dose and bolus shape/duration. Although this quantitation scheme has so far only been applied to single-slice data, using multiband pulses with 90° excitation for the metabolic products (19,20) should allow the extension of this approach to multi-slice or volumetric data.

Also addressing the issue in order to differentiate locally generated metabolic products from metabolites that were carried into the imaging slice though blood flow, a stimulated echo acquisition mode (STEAM) based sequence was developed where phase sensitive acquisition distinguishes between metabolites previously present in the tissue and those generated in the tissue during a mixing interval (21).

To take advantage of the long transverse relaxation times of the $^{13}$C-labeled metabolites (in vivo $T_2$ are on the order of a 1 s), sequences have been developed that apply a series of refocusing pulses (22-24), either to increase SNR and/or estimate metabolite $T_2$s. However, the application of these methods in dynamic imaging is still under investigation.

References


