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Reconstruction of randomly under-sampled spectra for *in vivo* ^{13}C magnetic resonance spectroscopy

Ningzhi Li, PhD^{1,*}, Shizhe Li, PhD², and Jun Shen, PhD^{1,2}

¹. Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

². Magnetic Resonance Spectroscopy Core Facility, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose: Over the past decade, many techniques have been developed to reduce radiofrequency (RF) power deposition associated with proton decoupling in *in vivo* Carbon-13 (^{13}C) magnetic resonance spectroscopy (MRS). In this work we propose a new strategy that uses data under-sampling to achieve reduction in RF power deposition.

Materials and Methods: Essentially, proton decoupling is required only during randomly selected segments of data acquisition. By taking advantage of the sparse spectral pattern of the carboxylic/amide region of *in vivo* ^{13}C spectra of brain, we developed an iterative algorithm to reconstruct spectra from randomly under-sampled data. Fully sampled data were used as references. Reconstructed spectra were compared with the fully sampled references and evaluated using residuals and relative signal intensity errors.

Results: Numerical simulations and *in vivo* experiments at 7 Tesla demonstrated that this novel decoupling and data processing strategy can effectively reduce decoupling power deposition by greater than 30%.

Conclusion: This study proposes and evaluates a novel approach to acquire ^{13}C data with reduced proton decoupling power deposition and reconstruct *in vivo* ^{13}C spectra of carboxylic/amide metabolite signals using randomly under-sampled data. Because proton decoupling is not needed over a significant portion of data acquisition, this novel approach can effectively reduce the required decoupling power and thus SAR. It opens the possibility of performing *in vivo* ^{13}C experiments of human brain at very high magnetic fields.

Keywords

in vivo ^{13}C ; proton decoupling; random under-sampling; high field

*Corresponding Author: Ningzhi Li, Ph.D., Molecular Imaging branch, National Institute of Mental Health, NIH, Address: 10 Center Dr., Room 3D46, Bethesda, MD, 20814, ningzhi.li@nih.gov, Telephone (O): (301)-594-0962, Fax: 301-480-5904.

1. Introduction

Carbon-13 (^{13}C) magnetic resonance spectroscopy (MRS) has evolved into a powerful tool for studying brain metabolism and neurotransmission [1–5]. One major limitation in the clinical applications of *in vivo* ^{13}C MRS is the required high RF power for decoupling the large one-bond ^1H - ^{13}C scalar couplings ($^1J_{\text{CH}}=125\text{--}145\text{ Hz}$). Specifically, the required RF strength for coherent decoupling has to be much greater than $^1J_{\text{CH}}$ [6]. The local and average specific absorption rate (SAR) accumulates linearly with the duration of decoupling and increases quadratically with field strength [6]. To prevent tissue overheating, *in vivo* ^{13}C MRS of human brain has been traditionally limited to relatively lower field strengths (≤ 4 Tesla).

To overcome the abovementioned problems, numerous strategies have been proposed to reduce RF power deposition associated with proton decoupling, such as using shaped or adiabatic RF pulses [7–10], shortening sampling time, or employing frequency-domain windowed stochastic decoupling [11]. In particular, Li et al. have developed carboxylic/amide ^{13}C MRS using low RF power broadband stochastic proton decoupling [12–14]. Recently, they have demonstrated that the low RF power carboxylic/amide ^{13}C MRS technique can be safely applied to occipital lobe human brain studies at 7 Tesla [14].

In contrast to the crowded short-TE proton spectra of brain, the corresponding ^{13}C spectra are sparsely populated. This is especially so in the carboxylic/amide region of *in vivo* ^{13}C spectrum of brain. Since the sparsity of the frequency domain translates into redundancy of information in the time domain, various time-domain under-sampling schemes for the indirect dimensions have been devised to accelerate multidimensional data acquisition in magnetic resonance imaging and high resolution nuclear magnetic resonance (NMR) spectroscopy [15, 16].

The purpose of the present study is to propose and demonstrate a new strategy for further reducing RF power deposition of proton decoupling by under-sampling during data acquisition of one-dimensional *in vivo* ^{13}C MRS. This new strategy uses a windowed decoupling scheme in the time domain in which decoupling is only required during randomly selected segments of data sampling. The spectra are iteratively reconstructed using those randomly selected segments of data only. Because the proton decoupling is not needed over a significant portion of data acquisition, this novel approach can effectively reduce the required decoupling power and thus SAR.

2. Materials and Methods

The carboxylic/amide region of ^{13}C spectrum are sparsely distributed and the spectral baseline in the carboxylic/amide region remains fairly constant. By taking advantage of this information, an iterative algorithm was developed to reconstruct spectra from random under-sampled datasets. The random under-sampling scheme begins with a fully sampled core followed by random sampled data segments throughout the dataset [17]. The under-sampling rate is defined as the percentage of under-sampled data over the full data length.

All frequency domain data points of *in vivo* ^{13}C spectrum are classified into two groups: 1) the signal group P where all data points are part of signal peaks; and 2) the empty frequency group Z where all data points have zero amplitude after baseline removal. In order to restore information from non-sampled data points, the reconstruction algorithm iteratively forces the under-sampled spectrum $f(k)$ to zero amplitude at known frequency intervals. The under-sampled spectrum $f(k)$ is the Fourier transformed of the under-sampled time domain data $x(s)$, where k refers to frequencies and s refers to under-sampled data locations.

In the first step, the initial $x_1(s)$ is the under-sampled FID obtained directly from the scanner. The algorithm first places zeros into the time intervals $\bar{s}$ when no decoupling is applied:

$$x_1(\bar{s}) = 0. \quad (1)$$

Starting from the second iteration, the algorithm reconstructs the frequency domain data by forward Fourier transform ($\mathcal{F}$) of the under-sampled data, and replaces the Z group data by zero in the frequency domain:

$$f_n(k) = \begin{cases} \mathcal{F}(x_n(s)) & k \in P \\ 0 & k \in Z. \end{cases} \quad (2)$$

Then, inverse Fourier transforms ($\mathcal{F}^{-1}$) were used to transform the updated frequency domain data back into time domain, and the algorithm computes the error term ϵ_n , which is defined as the absolute norm difference between the updated time domain data and the under-sampled-experimental data [17, 19].

$$x_n(s + \bar{s}) = \mathcal{F}^{-1}(f_n(k)); \quad (3)$$

$$\epsilon_n = \text{abs}|x_n(s + \bar{s}) - x_1(s)|. \quad (4)$$

If the error ϵ_n is larger than a manually set threshold, which is usually a very small number ($<10^{-6}$), the algorithm will replace the time domain data in the sampled segments by experimental data and continue to the next iteration:

$$x_{n+1}(s) = x_1(s); \quad (5)$$

$$f_{n+1}(k) = \begin{cases} \mathcal{F}(x_{n+1}(s + \bar{s})) & k \in P \\ 0 & k \in Z; \end{cases} \quad (6)$$

$$x_{n+1}(s + \bar{s}) = \mathcal{F}^{-1}(f_{n+1}(k)); \quad (7)$$

$$\varepsilon_{n+1} = \text{abs}|x_{n+1}(s + \bar{s}) - x_1(s)|. \quad (8)$$

The iteration continues until the error is less than the manually set threshold, which means the calculated time-domain data are consistent with the under-sampled experimental data. A maximum iteration number (>5000) is also set to stop the algorithm when it fails to converge. This occurs when the under-sampling rate is too high.

Numerical simulations were performed to verify and evaluate the iterative reconstruction of under-sampled data. Signals including γ -aminobutyric acid (GABA1 182.3 ppm), glutamate (Glu5 182 ppm), N-acetylaspartate (NAA1 179.7 ppm), NAA4 (179.5 ppm), glutamine (Gln5 178.5 ppm), aspartate (Asp4 178.4 ppm), Glul (175.3 ppm), Asp1 (175.1 ppm), Gln1 (174.8 ppm) and NAA5 (174.3 ppm) were simulated using a global linewidth and individual intensities obtained from fitting *in vivo* ^{13}C datasets [14]. Random noise was added to the simulated data to match the noise level observed *in vivo*. Two under-sampling strategies were compared: a random sampling pattern (A) and a coherent sampling pattern with gradually decreasing under-sampling rate (B). Both strategies began with a fully sampled core. Spectra were iteratively reconstructed using the under-sampled datasets based on Eqs. 2–8. Spectra from fully sampled data were also used to validate the proposed approach. To compare the signal-to-noise ratio (SNR) between full sampling and under-sampling, Monte Carlo simulations were performed with the same noise level but different realizations of random noise. Different core sizes and under-sampling rates were evaluated by comparing the residuals and signal intensity errors between the reconstructed spectra from under- and the corresponding fully sampled datasets. Signal intensities for simulated metabolites were computed using non-linear fitting with Lorentzian-Gaussian lineshape functions. The signal intensity errors were defined as the difference between fitted signal intensities from under- and fully sampled data divided by signal intensities from fully sampled data.

Four sets of *in vivo* ^{13}C human brain data [13, 14] acquired using a Siemens Magnetom 7T scanner (Siemens Healthcare, Erlangen, Germany) were analyzed to validate the iterative fitting technique. Detailed experiments settings could be found in refs. [13, 14] and are briefly summarized here. RF power in the proton channel and RF power of the ^{13}C coil were both calibrated before the experiments [13, 14]. Each subjects were infused with [2- ^{13}C] D-glucose and the *in vivo* data were acquired after 60–90 minutes of infusion, when the signal achieved a relative steady state. Product localizer and shimming sequence was first applied to properly position each subject and provided relatively homogeneous B_0 field within a $6 \times 6 \times 6 \text{ cm}^3$ selected cubical voxel from each subject. *In vivo* ^{13}C spectra were acquired from the selected voxel using a modified Siemens FID sequence that uses low power broadband stochastic proton decoupling. Specific acquisition parameters were: hard pulse length = 500 μs , spectral width (SW) = 5 kHz, data points = 1024 and TR = 6 s. A total of 48 averages were acquired with acquisition time = 205 ms for each average [13, 14]. Since the

carboxylic/amide ^{13}C spectral region is free from lipid contamination (the lipid carboxyls do not overlap with metabolite carboxyls), the experimentally observed spectral structures of ^{13}C baseline are fairly simple and remain unchanged in all datasets [14]. We used an in-house developed non-linear fitting algorithm [18] and generated a ^{13}C baseline model from all *in vivo* data sets. Different under-sampled data were generated by changing the sampling rate randomly but with a predetermined sampling density pattern. Different under-sampling rate were evaluated using the same criteria as in numerical simulations. The relatively small lipid signal appeared around 178 ppm from *in vivo* data was fitted using a group of Lorentzian-Gaussian functions. All algorithms were programmed in MATLAB (R2015b).

3. Results

Figure 1 shows the sampling pattern of two under-sampling strategies and the corresponding reconstructed spectra. Spectra from fully sampled dataset are also displayed for visual comparison and residual error calculation. The random sampling strategy A resulted in very small residuals. In comparison, the coherent under-sampling strategy B shows larger residuals for the same under-sampling rate. The mean signal intensity errors averaged from all metabolites for strategy A and strategy B is 1.28% and 2.50%, respectively. Similar results were obtained for all other under-sampling rates investigated in this study. Therefore, only results from the random under-sampling strategy A are reported below. A 20% fully sampled core size was chosen based on numerical simulations and was used in the following under-sampling rate evaluations. Figure 2 compares SNR from full sampling with under-sampling for the same total number of sampled data points (therefore, the same decoupling SAR). The corresponding T_2^* value is obtained by fitting an *in vivo* data [14]. Consistent with compressed sensing based data reconstruction algorithms [17, 19], Monte Carlo simulation shows that the noise variance ratio between the fully sampled and the under-sampled spectra is approximately 2.2:1, demonstrating that the SNR per unit power deposition by the random under-sampling strategy is significantly higher than full sampling. A systematic comparison of under-sampling rate verses signal intensity error of the three major signals in the carboxylic/amide spectral region (Glu5, Gln5 and Asp4) is displayed in Figure 3. The signal intensity errors increase significantly when the under-sampling rate reaches approximately 40%.

The reconstructed spectra from all four *in vivo* datasets with under-sampling rate of 30% are displayed in Figure 4. The baseline model described in the Method section was applied to all four datasets. With a 30% overall under-sampling rate, excellent reconstructed spectra were obtained as clearly seen by the small differences between the spectra reconstructed using the under-sampled data and those using the fully sampled data. Figure 5 shows the mean signal intensity error of Glu5, Gln5 and Asp4 averaged over 4 subjects as a function of under-sampling rate. As expected, the signal intensity errors are larger for weaker signals. When the under-sampling rate increases, generally up-trending signal intensity errors are also observed as expected.

4. Discussion and Conclusions

This study aims to evaluate a novel approach to acquiring ^{13}C data with further reduced proton decoupling power deposition and reconstruct *in vivo* ^{13}C spectra of carboxylic/amide metabolite signals using under-sampled data. Since no decoupling is needed for a significant portion of data acquisition, the accumulated SAR can be significantly reduced. This opens the possibility for *in vivo* ^{13}C experiments of human brain at even higher magnetic fields, especially for the frontal lobe studies where potential overheating of the poorly perfused eyes has been a safety concern.

Because the carboxylic/amide region of ^{13}C spectra has a relatively sparse distribution, random sampling allows cancellation of reconstruction errors originated from different metabolite signals in a manner bearing certain similarity to compressed sensing [17]. In comparison, coherent under-sampling patterns are prone to constructive addition of reconstruction errors due to well-documented Fourier aliasing effects [19]. Although random under-sampling has shown to be highly useful for accelerating high-resolution multidimensional NMR spectroscopy by reducing the time spent in sampling the indirect dimensions [15], this study represents the first application of random under-sampling in the directly observed dimension. Instead of attempting to accelerate data acquisition, we have shown that random under-sampling can lead to a significant reduction in proton decoupling RF power deposition.

The typical *in vivo* ^{13}C spectrum, either in the aliphatic region (10–65 ppm) or the carboxylic/amide region (170–185 ppm) is characterized by narrow peak linewidth and sparse signal distribution. In a previous work [10] we noted that the proton signals that are scalarly coupled to carboxylic/amide carbons are clustered in two bands of the proton spectrum: the alkyl protons resonating at 1.91 (GABA H₃)-3.90 (Asp H₂) ppm and the amide protons resonating at 6.83 (Gln H_Z)-7.60 (Gln H_E) ppm. We showed that a significant reduction in proton decoupling power deposition can be achieved by frequency-domain windowing, i.e., by avoiding RF irradiation in the empty spectral region between the alkyl and amide clusters in the proton channel while no time-domain windowing was used. In contrast, the current time-domain windowing method is more general and does not require a sparse signal distribution of the protons that are scalarly coupled to the carbons. As such, it is possible to combine both time domain and frequency domain windowing to further reduce RF power deposition due to proton decoupling. Since the protons that are scalarly coupled to the alkyl carbons are not well clustered, the frequency domain windowing method [11] is not expected to be useful there, while the current time-domain windowing or under-sampling strategy, in principle, should be applicable to acquisition of the sparsely populated alkyl ^{13}C MRS spectra (10–65 ppm) as well. We will investigate this interesting possibility in the near future. For the other ^{13}C regions where signal peaks are contaminated by lipid signal as in muscle tissue or not sparsely distributed, the usefulness of our method would be limited.

For simplicity, we did not use compressed sensing algorithms to reconstruct the under-sampled ^{13}C MRS spectra. In contrast to the computationally intensive compressed sensing algorithms [19], our MATLAB-based iterative procedure only requires less than one minute for a typical iteration of convergence on a desktop computer (Intel(R) Core (TM) i7-4770

CPU @3.40 GHz with 16 GB RAM). In addition, although compressed sensing has been shown to be successful in certain MRI and MRS reconstruction problems, the results of their general application to clinical studies have been mixed (for recent reports, see refs. [20, 21]). As demonstrated by this study, reconstruction of under-sampled *in vivo* ^{13}C MRS data can be accomplished reliably using computationally more efficient conventional iterative algorithms.

In MRS study, the data sampling duration is usually much longer than the T_2^* values of the sampled FID. Under-sampling in MRS does not necessarily lead to reduced SNR, because reducing data from the later part of the free induction decay, where noise dominates, contributes positively to SNR. For example, truncation of a FID and replacement of the noise-dominated later part of the FID with zeros can be considered as a special form of under-sampling. It is well known in MRS that if the signal has decayed significantly, such a procedure actually increases SNR by reducing the total noise power. In our under-sampling scheme, the sampling density decreases progressively as the FID becoming more and more noise-dominated. In addition to the above built-in mechanism for noise reduction, it is well-known that reconstruction from randomly under-sampled data by compressed sensing-like algorithms leads to denoising [17, 19]. Our numerical Monte Carlo simulations have demonstrated that SNR per unit power deposition by our random under-sampling and reconstruction strategy is significantly higher than full sampling (Figure 2).

In conclusion, a novel approach for decreasing decoupling power and thus SAR for the *in vivo* ^{13}C experiments is described. Because SAR increases quadratically with field strength and is linearly associated with the decoupling duration, it is always beneficial to use a decoupling/data sampling scheme that requires the lowest RF power deposition, especially for high field and/or frontal lobe ^{13}C studies of human subjects. Using the approach proposed in this paper, both simulations and *in vivo* experiments show that excellent spectra reconstruction can be achieved with > 30% under-sampling rate. This corresponds to 30% or more reduction in RF power deposition by proton decoupling, the major source of SAR in *in vivo* ^{13}C MRS. Since this method does not rely on sparse signal distribution in the proton channel, extension to alkyl ^{13}C MRS is also possible.

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Disclosures

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Figure 1. Data reconstruction using under-sampling strategies.

Examples of data reconstruction using the total random sampling pattern (A) and coherent sampling pattern with gradually decreasing under-sampling rate (B). The sampling patterns from top row display accumulated sampling rate over sampled data points. The last point of sampling pattern represents the overall under-sampling rate, which is 25%. Both methods began with a 20% fully sampled core. The corresponding reconstructed spectra are displayed below the sampling pattern.

Figure 2. Monte Carlo simulation results from fully and under-sampled data.

Fully sampled spectra (black) averaged from 70 Monte Carlo simulations and 30% under-sampled spectra (red) averaged from 100 Monte Carlo simulations. The total decoupling durations are the same for the fully sampled data and the under-sampled data. Zoomed in noise insets for each spectra are displayed at top. The ratio of noise variances between the fully sampled and the under-sampled spectra is 2.16:1.

Figure 3. Metabolite concentrations versus under-sampling rate from simulations.

The absolute value of signal intensity errors of Glu5 (red stars), Gln5 (blue triangle) and Asp4 (green cross) versus different under-sampling rates. The signal intensity errors are in general within 3% when the under-sampling rate is less than 40%.

Figure 4. In vivo under-sampling results.

Reconstructed spectra (red) from four different subjects with under-sampling rate of 30%. Spectra from fully sampled data (black) are displayed for comparison and used for signal intensity error calculation.

Figure 5. Metabolite concentrations versus under-sampling rate from *in vivo* studies. The absolute value of signal intensity errors averaged over 4 different subjects of Glu5 (left), Gln5 (middle) and Asp4 (right) verses different under-sampling rate. The signal intensity errors are within 5% when the under-sampling rate is less than 32% in general. Similar increase trends of signal intensity errors were observed across all three chemicals as the under-sampling rate increases.