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High-Resolution Probing of Heterogeneous Samples by Spatially Selective Pure Shift NMR Spectroscopy

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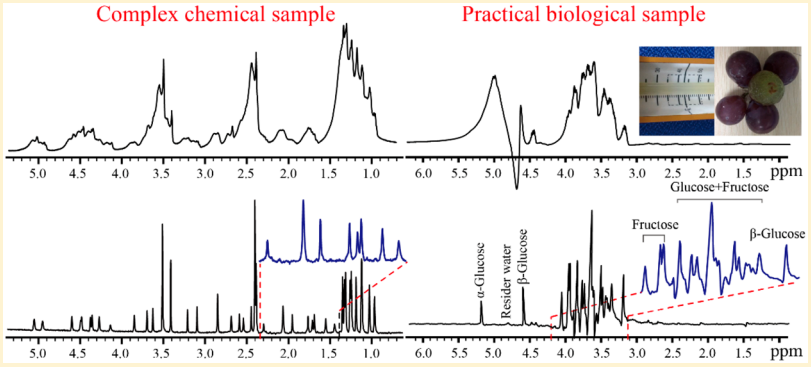
Supporting Information



ABSTRACT: Liquid NMR spectroscopy generally encounters two major challenges for high-resolution measurements of heterogeneous samples, namely, magnetic field inhomogeneity caused by spatial variations in magnetic susceptibility and spectral congestion induced by crowded NMR resonances. In this study, we demonstrate a spatially selective pure shift NMR approach for high-resolution probing of heterogeneous samples by suppressing effects of field inhomogeneity and *J* coupling simultaneously. A Fourier phase encoding strategy is proposed and implemented for spatially selective pure shift experiments to enhance signal intensity and further boost the applicability. The spatially selective pure shift method can serve as an effective tool for high-resolution probing of heterogeneous samples, thus presenting interesting prospects for extensive applications in the fields of chemistry, physics, biology, and food science.

Benefitting from the property of noninvasive detection, NMR spectroscopy presents a robust tool for furnishing molecular-level information including molecular structures,[1] chemical compositions,[2] and dynamic processes.[3] Measurements on heterogeneous samples, such as water−oil samples[4] or blended fuels[5] containing a spatially layered discontinuity at the sample interface, and biological tissues[6] or semisolid food[7] with intrinsic magnetic susceptibility variations, constitute a significant research topic in various fields throughout chemistry, food science, biology, and medicine.[8] Among the NMR spectroscopy family, 1D ^{1}H NMR is the most commonly used technique because of its rapid acquisition efficiency and robust detection performance. However, when probing heterogeneous samples, regular 1D ^{1}H NMR spectroscopy generally encounters two major challenges, namely, magnetic field inhomogeneity[9] caused by spatial variations in magnetic susceptibility and spectral congestion induced by crowded NMR resonances. First, field inhomogeneity caused by intrinsic magnetic susceptibility variations within heterogeneous samples leads to line-broadening effects, directly degrading spectral resolution and distorting spectral information in resulting NMR spectra. This field inhomogeneity is generally difficult to eliminate by routine field shimming approaches, although methods with advanced superconducting magnets[10] and optimized field shimming techniques[11] have been reported. Second, in practical NMR applications, heterogeneous samples, such as biological tissues and blended fuels, characteristically contain numerous chemical compositions along with crowded NMR resonances. This gives rise to spectral congestion in acquired ^{1}H NMR spectra resulting from the combined effect of narrow proton chemical shift ranges and extensive *J* coupling splittings, making the extraction of useful information from heterogeneous samples challenging.

Two mainstream techniques, magic-angle spinning (MAS)[12] and sample extraction,[13] are currently employed to eliminate intrinsic field inhomogeneity and record high-resolution spectral information from heterogeneous samples. The MAS NMR spectra directly acquired from heterogeneous samples show high spectral resolution similar to that of solution-state NMR spectra; however, this occurs at the cost of high requirements on NMR hardware facilities and potential risks of sample damage caused by high-speed sample spinning. The

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sample extraction approach generally requires complicated sample pretreatments following strict procedures, and it only indirectly reveals spectral information from original heterogeneous samples. The spatially selective NMR spectroscopy,[14,15] based on reduced sample volumes of spatially selective slices, provides an alternative to implement high-resolution NMR measurements on heterogeneous samples and thus is available for separating pyrolysis fuel samples[5] or diagnosing clinical diseases.[16] Nevertheless, the presence of spectral congestion generally hinders its further applications when probing complex samples that contain numerous chemical compositions and crowded NMR resonances. The spatially selective (or Zangger–Sterk) pure shift NMR spectroscopy,[17] stemming from a spatially selective scheme, provides a promising solution to spectral congestion in complex sample applications by eliminating homonuclear J couplings and collapsing complex multiplets into simplified singlets. Additionally, the spatially selective pure shift NMR method is also insensitive to field inhomogeneity primarily along the z direction.[17] However, to the best of our knowledge, there are no further reports regarding high-resolution measurements on heterogeneous samples.

In this study, we investigate the first applications of the spatially selective pure shift NMR spectroscopy to high-resolution probing of heterogeneous samples. Considering signal loss caused by reduced sample volumes of spatially selective slices, we propose and introduce a general multiband excitation strategy, termed Fourier phase encoding (FPE), into spatially selective pure shift experiments to enhance the detection sensitivity under inhomogeneous magnetic field conditions, further facilitating its applicability for heterogeneous samples. Pulse sequences of basic spatially selective pure shift spectroscopy originally proposed by Zangger and Sterk and a modified multiband FPE version are shown in Figure 1a,b. In Figure 1a, the spatially selective decoupling module, consisting of a nonselective inversion pulse and a selective inversion pulse in unison with a simultaneous weak gradient, introduces a spatial effect dependent on different slices of the sample tube. In a certain spatial slice, J coupling evolution is refocused while chemical shift evolution is undisturbed. The pulse sequence for multiband FPE spatially selective pure shift experiments is designed based on the combination of a Fourier phase encoding excitation module[18−20] and a spatially selective decoupling module. The Fourier phase encoding excitation module synchronously excites multiband resonances along with Fourier phase encoding, while the spatially selective decoupling module achieves J coupling elimination and retains chemical shift evolution for the multiband resonances. In this experiment, the resulting signals for a certain resonance are accumulated from N slices, after the designed data processing for the multiband FPE strategy (Figure 1c), thus theoretically improving the detection sensitivity by a factor of N. Because of the reduced sample volume per signal, both basic and multiband FPE spatially selective experiments are naturally tolerant to field inhomogeneity primarily along the z direction. Detailed theoretical deduction and data processing procedures are given in the Supporting Information.

Experiments on azithromycin, a clinical macrolide antibiotic, were performed under an inhomogeneous magnetic field to demonstrate the performance of the spatially selective pure shift spectroscopy on overcoming effects of field inhomogeneity and spectral congestion. In the inhomogeneous field, inhomogeneous line broadenings ruin all useful information in

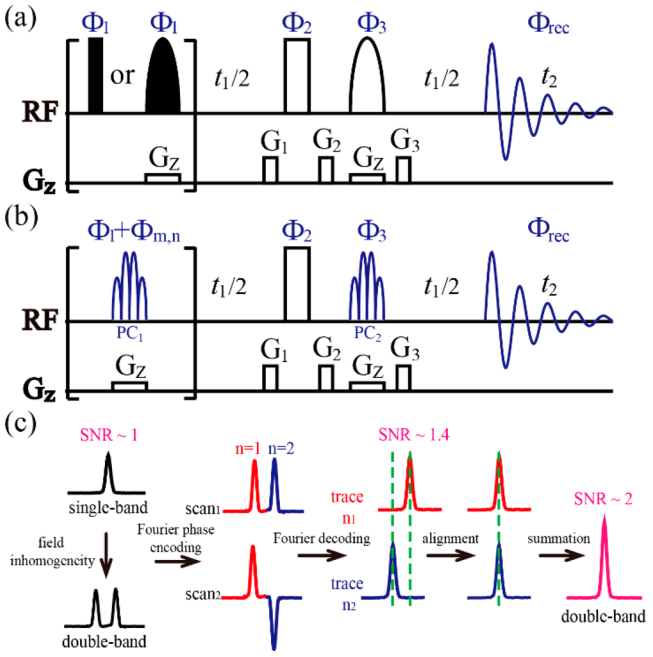

Figure 1. Pulse sequences for (a) basic and (b) multiband FPE spatially selective pure shift experiments. Filled and open bars denote $\pi/2$ and π nonselective pulses, respectively. Filled and open shaped pulses denote $\pi/2$ selective excitation and π selective inversion pulses, respectively. Pulsed field gradient G_z represents the slice-selection weak gradient; G_1, G_2, and G_3 are gradients for coherence selection. Shaped pulses PC_1 and PC_2 indicate polychromatic excitation and inversion pulses with and without Fourier phase encoding, respectively. (c) Detailed processing procedure of the multiband FPE strategy (taking double-band as an example), including performing two scans (scan 1 and scan 2) with Fourier phase encoding, 1D Fourier transformation with respect to the scan index to obtain decoded trace n_1 and trace n_2, spectral alignment, and summation. Phase cycling: $\Phi_1 = x, -x$; $\Phi_2 = x$; $\Phi_3 = x, x, y, y, -x, -x, -y, -y$; and $\Phi_{rec} = x, y, y, x$. $\Phi_{m,n}$ is the appended Fourier-encoding phase.

the standard 1D spectrum (Figure 2a). Benefiting from the ability of resistance against field inhomogeneity, the spatially selective pure shift method presents an effective way to yield high-resolution spectral information by suppressing influences of field inhomogeneity and spectral congestion. From the resulting spectrum (Figure 2b), it can be seen that inhomogeneous line broadenings are eliminated. Particularly, all overlapping resonances in the crowded spectral region are well-resolved because of the spatially selective decoupling (see the expanded region in Figure 2b), compared to the standard NMR acquired from a well-shimmed field (Figure 2c). As a result, the spatially selective pure shift method serves as a general tool for investigating complex samples with crowded even overlapped resonances under inhomogeneous magnetic fields.

The example of probing a heterogeneous sample is presented on intact grape tissue, characterized with intrinsic magnetic susceptibility variations and overlapped NMR resonances. The intrinsic field inhomogeneity resulting from magnetic susceptibility variations generally hinders direct measurements of heterogeneous biological samples. In standard water-presaturated 1D NMR (Figure 3a), line broadenings caused by intrinsic field inhomogeneity in grape tissues obscure useful spectral information. Fortunately, the high-

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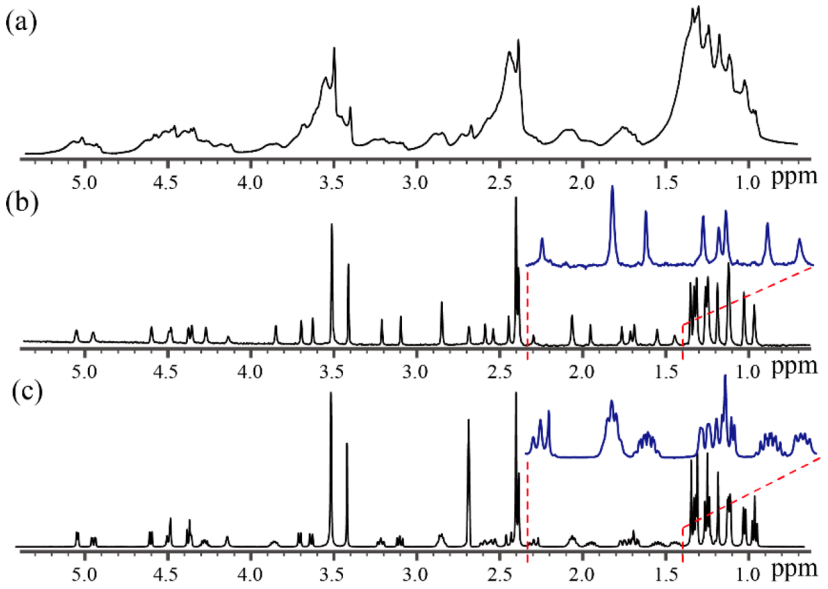

Figure 2. Experimental results on azithromycin. Spectra acquired by (a) standard 1D NMR and (b) spatially selective pure shift method acquired under a moderate inhomogeneous magnetic field. (c) Standard 1D NMR spectrum acquired under a well-shimmed magnetic field after careful field shimming for comparison. The crowded spectral region between 1.40 and to 2.35 ppm is expanded in panels b and c to exhibit the detailed resolution enhancement with the simultaneous suppression of field inhomogeneity and spectral congestion.

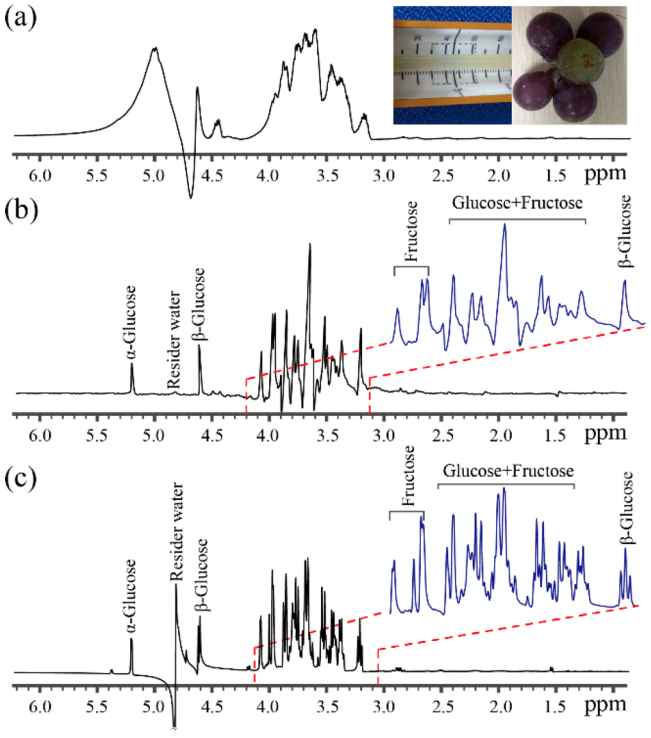

Figure 3. Experimental results on grape samples. (a) Standard 1D water-presaturated spectrum of grape sample and a photo of a piece of grape sarcocarp fitted into a 5 mm NMR tube. (b) High-resolution spatially selective pure shift spectrum of grape tissues. (c) Standard 1D water-presaturated spectrum of grape juice extracted from grape sarcocarp for comparison. The crowded spectral region between 3.0 and 4.2 ppm is expanded in panels b and c.

resolution 1D pure shift spectrum is recovered by the spatially selective pure shift experiment (Figure 3b) with enhanced spectral resolution, significantly facilitating metabolite assignments particularly for the overlapped region between 3.0 and 4.2 ppm. All well-resolved peaks are assigned according with previous reports.[21,22] For comparison, the standard water-presaturated 1D experiment on the grape juice extracted from the same grape tissues was performed on a well-shimmed sample. Although high-resolution spectral information is available in the resulting spectrum of grape juice (Figure 3c), spectral congestion induced by extensive J coupling splittings in the spectral regions of the glucose and fructose still impedes metabolite assignments. Benefiting from J coupling elimination and spectral simplification by the pure shift module, the spatially selective pure shift experiment yields the spectrum with only chemical shifts present (Figure 3b), thus facilitating metabolite analyses. To further verify the superiority of the spatially selective pure shift method in biological applications, experiments on pig brain tissues with lower metabolite concentrations were performed (Supporting Information, Figure S2). It should be noted that for spatially selective pure shift measurements on biological samples, the remaining field inhomogeneity along x and y directions may broaden spectral line width, and the employment of water-presaturated module may distort the spectral baselines, somewhat degenerating the high-resolution advantage. In spite of this, the spatially selective pure shift method still serves as a useful tool for direct biological detection and metabolite analyses without complicated NMR hardware requirements and specialized sample preparation.

Another illustration of probing a heterogeneous sample is performed on a spatially layered sample system composed of two naturally immiscible sample compositions of corn oil in $CDCl_3$ and γ-aminobutyric acid in D_2O. Experimental results (Supporting Information, Figure S3) demonstrate the applicability of the spatially selective pure shift method for high-resolution measurements on spatially layered samples with structural discontinuity at the sample interface, with potential for blended fuel detection and mixture constituent separation. In addition, the detailed comparison between spatially selective pure shift spectroscopy and other high-resolution methods, such as intermolecular multiple-quantum

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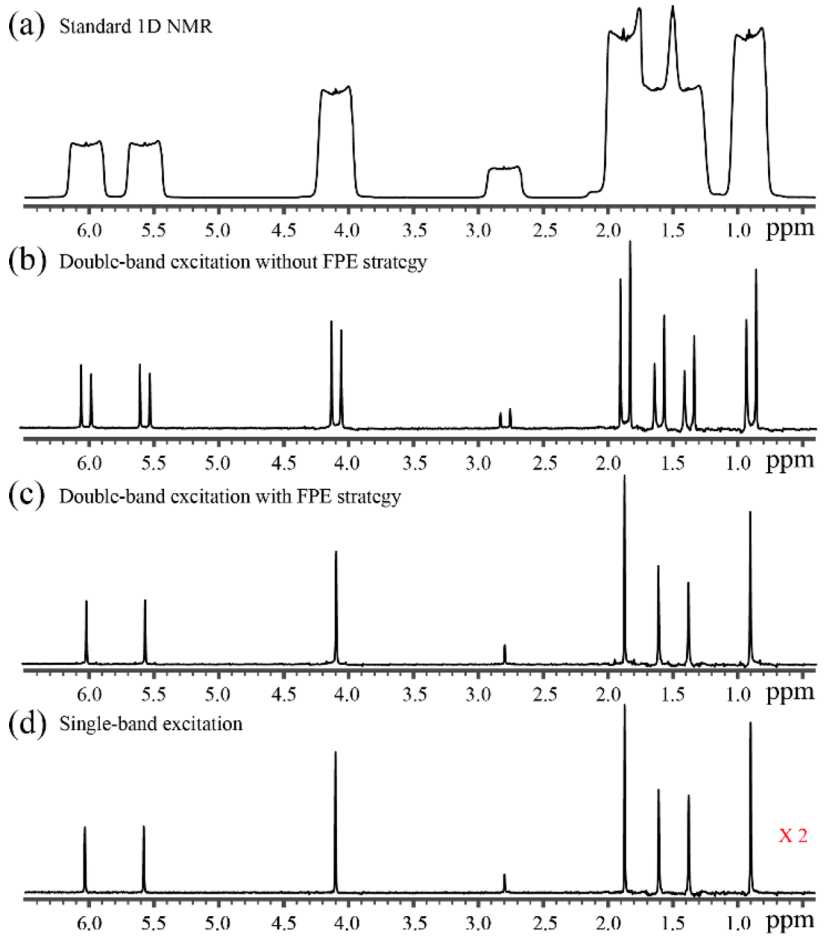

Figure 4. Experimental results on butyl methacrylate. Spectra acquired by (a) standard 1D NMR, (b) double-band excitation without the FPE strategy, (c) double-band excitation with the FPE strategy, and (d) referenced single-band excitation under an inhomogeneous field.

coherence (iMQC) scheme,[23,24] is also presented (Supporting Information, Figure S4).

Although the spatially selective pure shift spectroscopy provides an effective tool for high-resolution probing on heterogeneous sample systems, low sensitivity caused by the reduced sample volume constitutes a major limitation in practical applications. Herein, the multiband FPE excitation strategy (Figure 1b) is introduced into spatially selective pure shift experiments to compensate the signal loss and enhance the detection sensitivity under inhomogeneous magnetic fields. Experiments on butyl methacrylate were performed to demonstrate the performance of sensitivity enhancement by the multiband FPE strategy. The designed data processing for the multiband FPE strategy is applied to yield enhanced multiband signals (Figure 1c). In the double-band excitation experiments under an inhomogeneous field, signals from a certain resonance in two discrete bands (termed scan 1 and scan 2 in Figure 1c) are simultaneously excited. For the existing multiband proposal without the FPE strategy,[25] which is available for homogeneous magnetic conditions, double-band signals would interfere with each other (Figure 4b), rendering direct spectral analyses and sensitivity enhancement impossible. By contrast, for the double-band FPE experiments, an additional phase decoding by Fourier transformation over different scans succeeds in untangling the interfered signals into two different traces (termed trace n_1 and trace n_2 in Figure 1c). Then, a common spectral summation delivers the desired sensitivity enhancement after an accurate alignment for signals of two traces. Consequently, the double-band FPE excitation (Figure 4d) provides a two-fold sensitivity benefit over the single-band counterpart (Figure 4c) under the same field inhomogeneity. It should be noted that N scans should be performed for the N-band FPE experiments, and the N-band FPE excitation provides an additional sensitivity enhancement by $\sqrt{N}$ compared to simply averaged N-scan single-band experiments with the identical experimental durations. Further applications of multiband FPE excitation strategy are also verified by a viscous sample of corn oil (Figure S5). The multiband FPE excitation is a general sensitivity-enhanced strategy, thus suitable for spatially selective-based experiments under inhomogeneous magnetic fields. As a consequence, the multiband FPE strategy serves as a useful proposal for enhancing the sensitivity of spatially selective pure shift measurements on heterogeneous samples.

The spatially selective pure shift method is proven to be effective for high-resolution measurements on biological samples, but remaining field inhomogeneity along x and y directions still influences the resulting spectral resolution and degrades its performance. A possible protocol by extending the single-axis weak gradients used in this study to the orthogonal triple-axis gradients could potentially enhance the robust tolerance to triple-axis arbitrary field inhomogeneity.[26] Nevertheless, for heterogeneous biological tissues detected in standard NMR tubes, magnetic susceptibility variations along

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x and y directions are generally much smaller compared to those along the z direction, because the sample scales along x and y directions are over 4 times smaller than that along the z direction. Field inhomogeneity caused by magnetic susceptibility variations along x and y directions can be further eliminated by the sample spinning around the z axis. Multidimensional spatially selective pure shift experiments may be introduced into high-resolution probing on heterogeneous samples when more detailed structural information is required. Real-time pure shift techniques[27] also have potential for accelerating spatially selective pure shift experiments under inhomogeneous fields. With the aid of a higher magnetic field, cryo probe, and hyperpolarized NMR,[28] better performance on probing heterogeneous samples is predicted and available with spatially selective pure shift NMR experiments.

In conclusion, we investigate the first applications of spatially selective pure shift NMR spectroscopy to high-resolution measurements under inhomogeneous magnetic fields by simultaneously suppressing effects of field inhomogeneity and J couplings, particularly when probing heterogeneous samples. The feasibility and applicability of the spatially selective pure shift method are verified by a set of experiments on three typical heterogeneous samples, including complex chemical samples with crowded NMR resonances under externally inhomogeneous magnetic fields, biological tissues with intrinsic magnetic susceptibility variations, and spatially layered systems with intrinsic interface inhomogeneity. In addition, the FPE strategy, which is general for spatially selective-based experiments, is further proposed to enhance the detection sensitivity for practical applications. The spatially selective pure shift method serves as a useful tool for high-resolution probing of heterogeneous samples with extensive applications in the fields of chemistry, biology, and food science and may offer bright perspectives for analyzing in vivo biological systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpclett.9b03092.

Detailed theoretical analyses and signal evolutions for multiband FPE spatially selective method; experimental details; probing heterogeneous biological samples with lower metabolite concentrations; probing spatially layered samples with structural discontinuity at the sample interface; multiband FPE spatially selective pure shift experiments on a viscous sample (PDF)

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Notes

The authors declare no competing financial interest.

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