NMR in rotating magnetic fields: Magic angle field spinning

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Abstract

Magic angle sample spinning has been one of the cornerstones in high-resolution solid state NMR. Spinning frequencies nowadays have increased by at least one order of magnitude over the ones used in the first experiments and the technique has gained tremendous popularity. It is currently a routine procedure in solid-state NMR, high-resolution liquid-state NMR and solid-state MRI. The technique enhances the spectral resolution by averaging away rank 2 anisotropic spin interactions thereby producing isotropic-like spectra with resolved chemical shifts and scalar couplings. Andrew proposed that it should be possible to induce similar effects in a static sample if the direction of the magnetic field is varied, e.g., magic-angle rotation of the B_0 field (B_0-MAS) and this has been recently demonstrated using electromagnetic field rotation. Here we discuss on the possibilities to perform field rotation using alternative hardware, together with spectroscopic methods to recover isotropic resolution even in cases where the field is not rotating at the magic angle. Extension to higher magnetic fields would be beneficial in situations where the physical manipulation of the sample is inconvenient or impossible. Such situations occur often in materials or biomedical samples where "ex-situ" NMR spectroscopy and imaging analysis is needed.

Introduction

Anisotropic interactions can provide a wealth of information for the characterization and the dynamics of a material. In solid-state NMR they are routinely measured to inform about internuclear distances, chemical shift and quadrupolar tensors and their relative orientation etc. Most of the times however, anisotropic interactions are synonymous to

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loss of spectral resolution, since the lines become broad because of their orientation dependence and the extraction of useful information directly from the spectrum is almost impossible. The way to proceed is by performing selective coherent averaging, using either the physical 3D space (sample reorientations, induced phase transitions) or the spin space (multiple pulse techniques), or a combination of both [1]. In solid-state NMR the combination of spinning the sample at the magic angle and applying multiple-pulse decoupling lead to tremendous resolution enhancement, allowing for the development of sophisticated analytical techniques, capable of addressing problems like the structure determination of amorphous biomolecular systems. In what traditionally is called "liquid-state" NMR the application of MAS to average magnetic susceptibility had spectacular success to the extend that the technique gained it own name "HR-MAS". Applications of HR-MAS in biological samples showed that the resolution enhancement was such that new medical problems could be tackled. Magic-angle spinning was also combined with field gradient manipulation allowing for Magnetic Resonance Imaging of solid objects.

The last years a significant effort has been made by many laboratories to extend traditional high-field NMR and MRI to portable magnetic resonance systems. The idea was first developed in the frame of well logging several years ago, and nowadays has reached the point were small permanent magnets can be used to record the NMR signal and perform relaxation measurements and imaging of various samples. Recently it was also demonstrated that spectroscopic information could be recovered even in the presence of inhomogeneous fields. Using the appropriate radio-frequency excitation, which has to be effectively spatially matched with the static field, chemical shift information can be recovered and used to perform spectroscopy and/or imaging. The technique was demonstrated even in the case of anisotropic samples where Magic angle sample spinning was used for 3D spatial averaging. However, in real "ex-situ" analysis the sample should remain static and other alternative methods for spatial averaging must be devised.

An elegant, though experimentally demanding, solution to the "ex-situ" magic angle-spinning problem comes from the pioneering idea of R. Andrew, who recognized that in the limit of adiabatic field rotation, the averaging effects should be identical. Here adiabatic means that the frequency of the field rotation is slower than the Larmor frequency of the nuclei, so that they follow the motion of the field at any time during their evolution. Even though theoretical descriptions of the technique were published, very slow experimental implementations of the technique were performed and only recently the power to perform high-resolution NMR of static solid samples was demonstrated. Even in this last case the power requirements to spin a strong magnetic field at the magic angle, limited the technique to fields of 20 Gauss and spinning frequencies of ~10 kHz at the magic angle, necessary to average only moderate dipolar couplings.

Along a different perspective, very slow sample rotation at the magic angle has been performed on small live animals giving an impressive enhancement in spectral resolution over the static NMR spectra. The main anisotropy in such cases is due to magnetic susceptibility, which is an inhomogeneous interaction and can be averaged very efficiently even at very low spinning frequencies. Indeed this sounds a very promising application for the field rotation since the power requirements can be drastically reduced. In addition to spinning frequency reduction, another experimental parameter could be in principle "relaxed". It has been demonstrated recently that if one combines evolution during spinning along two angles different from the magic angle, the 2D map contained the isotropic NMR spectrum. This projected-MAS experiment was also applied to tissue samples giving the expected resolution enhancement even in spinning angles between 0 and 20 degrees [10].

In this paper we propose a new method in order to relax further the power requirements is proposed and demonstrated in model high-field sample spinning experiments. This method is based on the acquisition of a series of 1D spectra for variable angles contained in a limited, non-magic region (limited-VACSY). The applicability of field rotation to averaging dipolar interactions, susceptibility and chemical shift anisotropy is discussed in the framework of various proposed experimental setups.

Limited VACSY

There are many problems associated with magnetic field rotation and its usage for high-resolution NMR. Geometrical constrains, power limitations and field stability are some of the potential issues. In this section we introduce a technique to recover isotropic spectral information while the rotation angle is restricted. Unlike projected-Magic Angle Spinning no fast angle switching is required, so the field can be stabilized before each data acquisition. The technique is based on the acquisition of independent 1D spectra for a range of rotation angles and was first introduced by Frydman *et al*. and applied to various solids in order to correlate the isotropic chemical shift with its anisotropic part. For the traditional high-field VACSY there is no such limitation and in the literature only data coming from regions of the grid containing the best signal to noise ratio were used (for example in Ref.{Frydman92} only data between 35 and 90 degrees were used). For electromagnetic and/or mechanical field rotation, small variations of the spinning angle around 0 degrees (or around 90 degrees), would facilitate tremendously the construction and the operation of such magnets.

Theory

In VACSY, independent spectra are recorded for different angles of the rotor or the field axis θ. If the system is characterized by an anisotropic inhomogeneous interaction, such as chemical shift anisotropy, susceptibility etc, the frequencies can be written as:

$$\omega(\theta) = \omega_i + P_2(\cos\theta)\omega_a \quad (1)$$

where $P_2(\cos\theta)$ is the rank two Legendre polynomial, ω_i is the isotropic frequency. The anisotropic frequency ω_a is a function of the relative orientation between the Principal Axis System of the interaction and the magnetic field. In Eq.(1) we neglected any time dependent terms coming from sample or field spinning, making the assumption that under fast spinning their presence on the spectrum is negligible. The accumulated phase $\phi(\theta)$ at time *t* is equal to:

$$\phi(\theta) = \omega(\theta)t = [\omega_i + P_2(\cos\theta)\omega_a]t \quad (2)$$

and if we define $t_i \equiv t$ and $t_a \equiv P_2(\cos\theta)t$, the signal:

$$S(\theta,t) = \int I(\omega_i,\omega_a)\exp(j\phi t)d\omega_i d\omega_a \quad (3)$$

can be written as :

$$S(t_i,t_a) = \int I(\omega_i,\omega_a)\exp(j\omega_a t_i)\exp(j\omega_a t_a)d\omega_i d\omega_a \quad (4)$$

One can then evaluate the 2D spectrum by performing standard 2D FFT:

$$I(\omega_i,\omega_a) = \int_0^{\infty} dt_i \int_{-t_i/2}^{t_i} dt_a S(t_i,t_a)\exp[-j(\omega_i t_i + \omega_a t_a)] \quad (5)$$

Note that $-t_i/2 \le t_a \le t_i$ because the spinning angles are bound between 0 and 90 degrees. This reflects on how the 2D data grid is filled in the VACSY experiment and is shown on Fig.1. One can see the similarities between the way the data filling in VACSY and in CT projection-reconstruction imaging experiments [11].

The data are sampled in equidistant time intervals DW_i for all angles. One defines a dwell time for the anisotropic dimension DW_a in such a way such that the spectrum is not aliased and that spectral resolution is preserved. We can then place the experimental data set onto a grid representing the *k* space of the 2D experiment, as is done in Fig.2(A). The point axis are defined as $n_i=t_i/DW_i$ and $n_a=t_a/DW_a$ and one can see that the points are equally sampled along the “natural” isotropic axis of the experiment. Data are then interpolated onto a cartesian grid and 2D Fourier transformed. The two-dimensional correlation spectrum contains correlations between the isotropic chemical shifts and the purely anisotropic interactions.

Reconstruction

In order to process the data using 2D FFT, one needs to interpolate them onto a Cartesian grid. In the literature linear interpolation has been arbitrarily applied [12]. In NMR usually one interpolates the spectrum by zero-filling the free induction decay signal. Here we need to interpolate the free induction decay without adding any extra frequency components. If one has sampled correctly the frequency range of the spectrum (ie. without aliasing) and knows that no other frequencies exist outside the spectral window, then adding zeros on the left and the right of the spectrum and applying inverse FT leads to arbitrarily faster sampling in the FID without any extra frequency artifacts. This corresponds to Fourier interpolation that has the advantage of oversampling without altering the spectrum.

Linear prediction with singular value decomposition allows us to calculate the frequencies, amplitudes, phases and damping factors for a given number of damped sinusoidal functions. Using more advanced techniques the number to functions can be estimated from the algorithm itself. In fact we have used the matrix pencil method described in [13], since it has lower noise bounds and seems to be the most appropriate for our problem. The reader is encouraged to find more information about the matrix-pencil method in the original literature, since only its application in the scope of this paper. Having this information a “noise-free” spectrum can be reconstructed only along the isotropic dimension.

Using this FID reconstruction, we can easily calculate the signal also at negative isotropic times t_i. This is useful since the symmetry relation for the second and forth quadrant:

$$S(-t_i,-t_a) = S^*(t_i,t_a) \quad (6)$$

allows to reconstruct the signal for negative anisotropic time t_a. This procedures allows then to obtain pure absorption lineshapes since the integration in the anisotropic dimension takes place over the two quadrants. After this symetrization standard 2D FT as described in [13] can be implemented and applied, along both dimensions.

In order to test the validity of our algorithm we applied it to a simulated set of data.
We generated numerical data that cover all the 2D *k* space. Of course such data are not accessible experimentally. Because all data in this data set are calculated on the cartesian grid, they can be used without the need of any interpolation scheme.

We used a model system consisting of 3 spins having chemical shift anisotropy. Their isotropic chemical shifts were: -2500 Hz, 0 Hz and 1000 Hz. Their anisotropic frequencies are 5000, 3000 and -4000 Hz and their asymmetry parameters are 0.8 0.35 and 0.5 respectively. The 2D VACSY spectrum of this spin system are presented on Fig. 2. The spectra were obtained by sampling 401 points every 100 μs, and the powder patterns were generated by summing signals from orientations having an equidistant grid of β and γ angles. The integration was numerically performed from 0 to π in 181 steps, generating thus 32761 crystal orientations. The spectra were apodized using a common damping factor for all resonances corresponding to an artificial relaxation time T_2 of 5 ms.

The previous algorithm was applied and the 2D reconstructed spectra are shown in Fig. 2. We observe that the high resolution in the 2D map is recovered even though the angle of rotation was restricted between 0 and XX degrees. The isotropic projection clearly resolves the three resonances, while the three anisotropic traces give a very good measure of the chemical shift anisotropy. Because of the limited size of this paper, reconstructed spectra from experimental data will be presented elsewhere.

Discussion about Field Rotation

In this paragraph we would like to discuss some issues about field rotation without whatsoever proposing optimal solutions to perform field rotation. Electromagnetic field rotation seems to be the most advantageous method. It offers a number of advantages, namely the possibility to fine-tune the angle, switch fast the angle of the field rotation or even perform any arbitrary field trajectories. It has been successfully implemented using one set of coils producing a static field and two sets of coils perpendicular to the static one producing 90 phase shifted alternative magnetic fields. A schematic diagram is represented in Fig. 1, and its generalization to three variable perpendicular magnetic fields is also possible. The homogeneity at the center of the setup is determined by the geometrical characteristic, can be easily calculated and it scales with the radius. The current that the system can dissipate with air-cooling corresponds to a power of several W while when extra cooling is present powers of the order of several kW could be possible. This shows that the field one can achieve for such system will always be of the order of 0.5 Tesla having a relatively large inhomogeneity at the center. The power that is needed for the rotation depends dramatically on the angle as shown in [9] and a decrease of 70 % can be easily performed by working between 0 and 20 degrees. Such projected-MAS experiments should be in principle possible using an electromagnetic field rotation, provided that the size of the field and it inhomogeneity are enough in order to see fine interactions (chemical shifts). In such experiments experience from fast field cycling techniques should help.

On the other hand, a primitive and naïve approach to obtain a strong rotating magnetic field would be the use of permanent magnets. Two cylindrical plates magnetized along a specific direction are mechanically around their axis. We have performed simple calculations using the numerical package Magnetica developed my XXX. Using N45 NeBFe cylindrical magnets of XX cm diameter a magnetic field of XXX Tesla at the center of the setup. A theoretical inhomogeneity of XXX ppm/mm3 is calculated, which in practice might not be achievable without the use of shims. Given the mass of the magnets (~XX kg) the rotating frequency of the system would be of the order of 50-100Hz. Another issue using permanent magnets would be the temperature dependence of the magnetic field, together with the mechanical stability of the rotation. A disadvantage of this setup might seem the impossibility to adjust the magic angle. Since most applications would have to deal with susceptibility broadening, such imperfection should be acceptable. The major difficulty in this magnet might be due to imperfect alignment between the axis of rotation and the magnetic center of the system. In this case passive shimming on the rotating magnets might be needed rendering the mechanical stability or the rotation at such high rotating frequencies quite demanding. Another disadvantage of that the angle of the rotation cannot be switched between two or more angles, making the application of projected-MAS impossible.

Finally, a hybrid solution can also be envisaged, where the main magnetic field is produced by a static solenoidal electromagnet and the oscillating components are produced by a mechanically rotating permanent magnet. The mass of the permanent magnets limits the achievable rotating frequencies to ~50 Hz. The only advantage with respect to electromagnetic oscillating components, is the size of the field. XXX Tesla can be easily achieved with a good inhomogeneity of XXX ppm/mm3 [16]. The static component can be made very homogeneous using external shims while the permanent components might need passive shimming. Temperature stability requirements will also be important since a permanent component is used. Fast field cycling techniques could also be used in order to switch the angle of the rotation. Another hybrid magnet alternative would also be to replace the solenoidal electromagnet by a superconducting solenoidal magnet providing a stronger and more stable static field component. In these hybrid magnets projected-MAS seems to be quite demanding since the size of the field is rather large and the switching might be quite slow.

Discussion

Here we discuss that it going to be difficult to make a strong field that spins fast
The choices are:

1) make a weak field that spins fast, then we use it for quadrupoles + dipoles
2) make a strong field (need to have chemical shift thus susceptibility) but then spin slowly.

The second option seems reasonable, and the way to go is by sacrificing the angle but even in this case limited VACSY or p-MAS should work.

We are working on demonstrating experimentally limited VACSY and we will give the details for the data reconstruction elsewhere.

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Figure Captions

Fig 1: Schematic diagram of *k* space data acquisition in standard 2D NMR and VACSY. (A) In standard 2D data are acquired during t_q for each value of the indirect evolution time t_i. A Cartesian two-dimensional FID signal grid is formed and processed using 2D FT. (B) In VACSY the data are acquired during time t for each value of the spinning angle. The acquired data have not an equidistant spacing in *k* space and interpolation onto a Cartesian grid is needed. In principle the data cover a large two-dimensional area since the angle can vary from 0 to 90 degrees. (C) In limited-VACSY only a small part of the 2D plane is covered and data prediction is needed in order to recover the lost information.

Fig 2: Simulated 2D VACSY spectrum. Three non-coupled nuclei having different chemical shift anisotropy tensors were simulated (see text for values). All angles (0 to 90) were included in the data processing. One can clearly distinguish the three isotropic resonances and measure their anisotropy from the broad lineshapes.

Fig 3: Anisotropic traces of the 2D reconstructed spectra for limited angle VACSY. (a) Traces at the values of the isotropic peaks for the three resonances from the reconstructed spectrum including data from 0 to XX degrees. (b) Identical to (a) but the spectrum included only data from 0 to XX degrees.

Fig 1

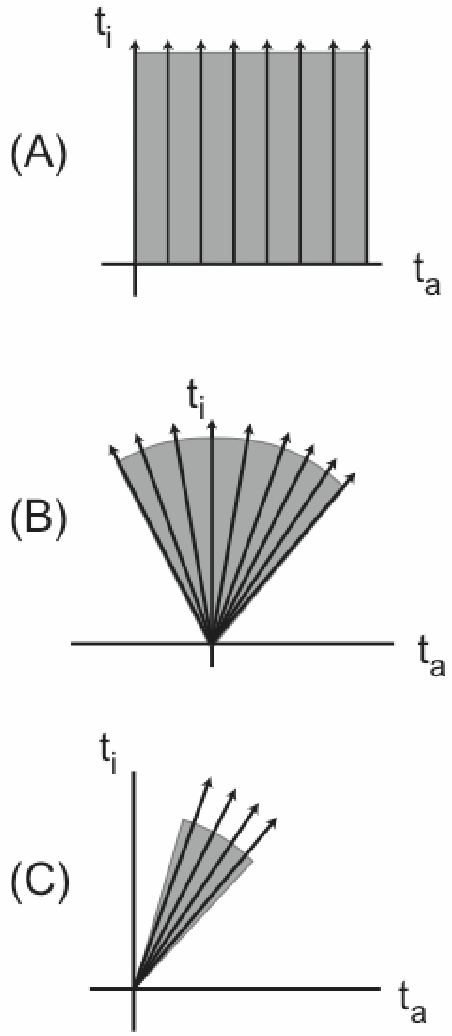

Fig. 2

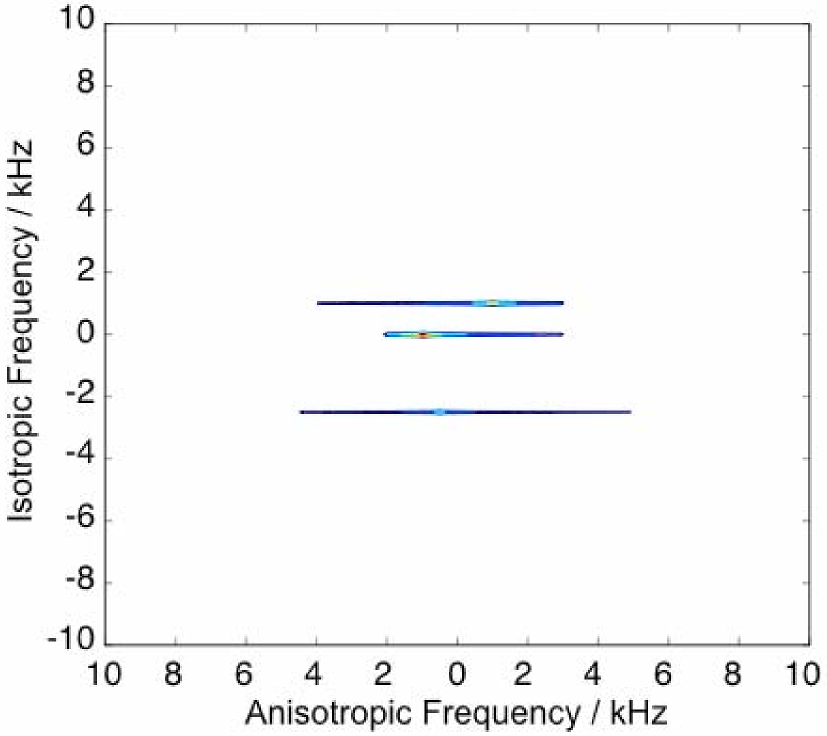
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Fig. 3