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Highly polarized nuclear spin systems and dipolar interactions in NMR/Systèmes de spins nucléaires fortement polarisés et interactions dipolaires en RMN

Advances in ex-situ Nuclear Magnetic Resonance

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Abstract

Nuclear Magnetic Resonance has revolutionized modern science by its precision, selectivity and non-envasiveness. From complicated biomolecules to materials, from living organisms to nanometric particles, Magnetic Resonance Imaging and Spectroscopy have provided a wealth of invaluable information. Those studies take place in the laboratory, since they require strong and extremely homogeneous superconducting magnets and this represents a major limitation for the technique. Furthermore, the size of the object or subject to study is limited since it has to fit inside the bore of the magnet. Efforts to alleviate those problems lead to the recent development of portable magnetic resonance systems. Their use remained, however, mainly qualitative, since spectroscopic information could not be recovered. We have introduced recently an approach to regain this lost spectral information even in the presence of inhomogeneous magnetic fields. Our approach is based on the matching between the effect of the radio-frequency field and the effect of the static magnetic field. Several practical implementations will be reviewed and put in perspective for their applicability and efficiency in ex-situ NMR. ***To cite this article: D. Sakellariou et al., C. R. Physique 5 (2004).***

Résumé

Résonance Magnétique Nucléaire ex-situ. La Résonance Magnétique Nucléaire a révolutionné la science moderne par sa précision, par sa sélectivité et par son caractère non invasif. L'Imagerie par Résonance Magnétique et la Spectroscopie ont permis en effet l'obtention d'un grand nombre d'information pour des domaines aussi variés que les biomolécules, les matériaux, les organismes vivants ou les particules nanométriques. Une limitation majeure existe pourtant : toutes ces études ont lieu au laboratoire, car elles requièrent des aimants supraconducteurs très intenses et extrèmement homogènes. De plus, la taille maximale de l'object ou du sujet à étudier est limitée par les dimensions de l'aimant qui le contiendra. Les efforts pour contourner ces limitations ont conduit aux développements de systèmes de Résonance Magnétique portables. Leur utilisation est restée cependant principalement qualitative car l'information spectroscopique ne pouvait pas être obtenue. Nous avons introduit récemment une approche qui permet d'accéder à cette information spectrale même en présence de champ magnétique inhomogène. Elle est basée sur la corrélation entre le champ de radiofréquence effectif et le champs magnétique statique. Nous rapportons ici plusieurs implémentations pratiques de cette approche en discutant leurs perspectives en termes d'applicabilité et d'efficacité pour la RMN ex-situ. ***Pour citer cet article : D. Sakellariou et al., C. R. Physique 5 (2004).***

Keywords: Ex-situ NMR; Inhomogeneous fields; Z-rotations; Correlated fields; Adiabatic pulses; Composite pulses; NMR sensors; Open magnets; One-sided NMR systems

Mots-clés : RMN ex-situ ; Champs inhomogènes ; Rotations Z ; Champs corrélés ; Impulsions adiabatiques ; Impulsions composites ; Détecteurs de RMN ; Aimants ouverts ; Système RMN à un coté

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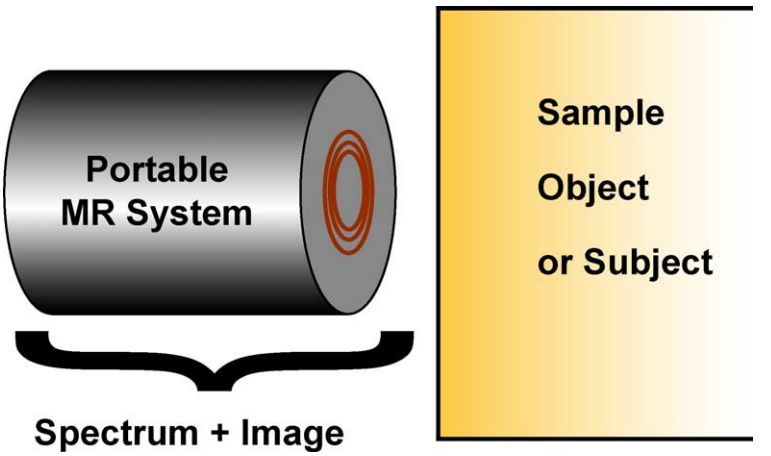

Fig. 1. The holy grail for portable Magnetic Resonance analysis. A one sided magnet could be the perfect industrial sensor because of its versatility, selectivity and portability. Large field inhomogeneities prevented until recently the idea of using such systems for NMR spectroscopy and imaging. Applications in localized medical imaging, industrial sensing, chemical and physical analysis would benefit tremendously from such portable and economically affordable MR systems.

1. Introduction

High resolution liquid and solid-state NMR is carried out in homogeneous static magnetic fields using homogeneous radiofrequency fields for the uniform excitation and detection of the nuclear magnetization [1]. The information we can obtain under these conditions is contained in the fine interactions, of the order of several parts per million of the main magnetic field, such as the chemical shift δ and the scalar J interactions. In fact, external shims are used to enhance the homogeneity of the static magnetic field, typically of the order of 1 ppb/cm^3. Along the same direction, a large variety of pulse schemes have been developed to compensate for radio-frequency (RF) inhomogeneities and provide robust sequences for excitation, inversion and decoupling [2]. On the other hand, Magnetic Resonance Imaging (MRI) makes use of large static magnetic field gradients, and thus of the spatial dependence of the chemical interaction, in order to map spin density [3]. The effect of the field inhomogeneity masks the chemical shift information and one is obliged to switch off or alternate the static field gradients in order to acquire images containing chemical shift information.

Magnetic resonance systems based upon those previous concepts have been largely become necessary for routine chemical and medical analysis. There are however many cases where the sample cannot be placed inside the bore of the magnet, or cannot be moved away from its natural environment, or one cannot extract a small piece of it in order to perform a laboratory analysis. In such circumstances *portable* magnetic resonance systems are needed. The idea of a high-resolution 'ex-situ' NMR portable sensor seems very promising. Even though portable magnetic resonance systems exist, they do not provide any spectroscopic information because their magnetic field is by definition inhomogeneous. Fig. 1 capitalizes on those ideas and shows an 'ideal' one sided magnetic resonance sensor.

Recently the problem of obtaining high resolution spectra containing chemical shift information as well as indirect J interactions, in the presence of inhomogeneous fields has been examined [4]. A novel approach based on the combined use of spatially correlated inhomogeneous radio-frequency and static magnetic fields, shows that high-resolution NMR is possible even under those unfavorable circumstances. All examples until today were proof of principle experiments. Here we review those recent advances in the area of ex-situ NMR, with respect to their physical principles and their potential towards realistic implementations of one-sided magnetic resonance devices.

2. Background

2.1. Existing techniques

Only a few examples of high resolution NMR in inhomogeneous fields are present in the literature [5–7]. A first approach was based upon the excitation of multiple quantum spin coherences [8]. Total spin coherence transfer echo spectroscopy [5] used the property of the transition between the two states having the maximum total coherence order ($+M_z \leftrightarrow -M_z$), to be insensitive to inhomogeneous broadening, while sensitive to chemical shift differences and J couplings. Intrinsically this

technique excites only lines which belong to the totally symmetric irreducible representation and thus some lines belonging to uncoupled subsystems are not excited. A second approach used coherence transfer echos [9,10]. Evolution of one nuclei species under the inhomogeneous field is refocused after a coherence transfer to a second species and evolution. The evolution frequencies are combinations of the isotropic chemical shifts of both nuclei. In this method the second nucleus behaves as a probe for the local environment of its neighbour and compensates for it. Recently this method has been applied successfully to amorphous solids in order to get resolution even in the presence of distributions of isotropic chemical shifts [11].

Another approach [6] is dealing with relatively small inhomogeneities (usually less than the chemical shift differences) that can be 'filtered out' using the NOE. The 2D HOESY experiment correlates the inhomogeneously broadened frequencies of the nuclei and looks similar to what we present in the following. It is important to note however that the underlying physical mechanism is completely different. The 1D hole-burning experiment yields a narrow spectrum only from the part of the sample having the "right" frequency, thus being a selective technique it suffers from low sensitivity. The main drawback for techniques using NOE, is the dependence on the relaxation mechanism, that can potentially lead to inequally excited spectra [6]. The latest approach [12–15,7] is making use of intermolecular zero-quantum coherences [16,17] which are almost static-field insensitive. The creation of zero-quantum coherences requires intramolecular couplings steming from the breaking of the spherical symmetry by static field gradients. The net distant dipolar field is proportional to the Boltzmann magnetization and thus scales with the static field. At room temperature these effects are too small at fields $\leqslant 2$ T as widely used in in vivo work or even lower in one-sided magnets used for process monitoring and material inspection. This constitutes a main drawback in the use of such techniques to ex-situ high resolution NMR spectroscopy and imaging.

2.2. Existing hardware

Since the pioneering work of one-sided magnetic resonance in well logging applications [18–20] a lot of effort has been put recently into the design of NMR systems with external small magnets and surface coils for the surface excitation and detection [21–23]. However, the large line-broadening caused by the intrinsic inhomogeneities of the external magnetic fields hides the chemical shift information. Thus, application of one-sided MR systems has been limited to relaxation measurements, imaging and lineshape analysis so far. Inhomogeneous broadening can be removed by a variety of techniques, but none is satisfactory for high-resolution spectroscopy. The Hahn spin-echo [24] and the Carr–Purcell sequences [25] both remove the inhomogeneous broadening, but they also completely refocus the chemical shift. Nevertheless, a variety of applications of the NMR-MOUSE to materials [26,27], imaging [28] and in vivo NMR [29] was possible. To our knowledge none of the techniques mentioned in Section 2.1 was successfully applied to one sided MR systems giving high-resolution spectra and this problem seemed impossible until recently.

We have introduced a novel approach towards high-resolution ex-situ NMR [4], which uses spatially correlated interactions, as the mechanism for the recovery of the chemical shift. Using a radio-frequency field that is spatially correlated with the inhomogeneous static magnetic field, one can compensate for their mutual dephasing. Evolution due to the isotropic chemical shift is not refocused since (one assumes) no chemical shift evolution is taking place during the rf irradiation. The effects of the inhomogeneities, have to be explicitly included in the pulse sequence since inhomogeneity in this framework is a tool to be used rather than a source of artifacts, spatial selectivity, or imperfections.

3. Correlated magnetic fields

3.1. Linear spatial correlation

Mapping the correlation between the static and the radio-frequency magnetic fields, proves to be useful in the beginning of the experiment. For the moment let us consider the case of linear correlation between $B_1(r)$ and $B_0(r)$ according to:

$$\frac{\mathrm{d}B_0(r)}{\mathrm{d}r} = k\frac{\mathrm{d}B_1(r)}{\mathrm{d}r}, \quad B_0(r)\cdot B_1(r) = 0, \tag{1}$$

in other words, the proportionality constant k is not a function of space. In practice, only the case of correlation along one dimension taken to be the longitudinal x axis of the rf-coil, has being treated.

The two-dimensional nutation sequence, presented in Fig. 2(a), yields the correlation between B_0 and the effective radio-frequency field B_{eff} during the pulse. The sequence consists of a single excitation pulse whose length is incremented in the indirect time t_1 domain. If $B_1(r)$ is the inhomogeneous rf field of the coil the effective field experienced by the sample located at the point r is simply:

$$B_{\mathrm{eff}}(r) = \sqrt{B_1^2(r) + \big(B_0(r) + \delta\big)^2}, \tag{2}$$

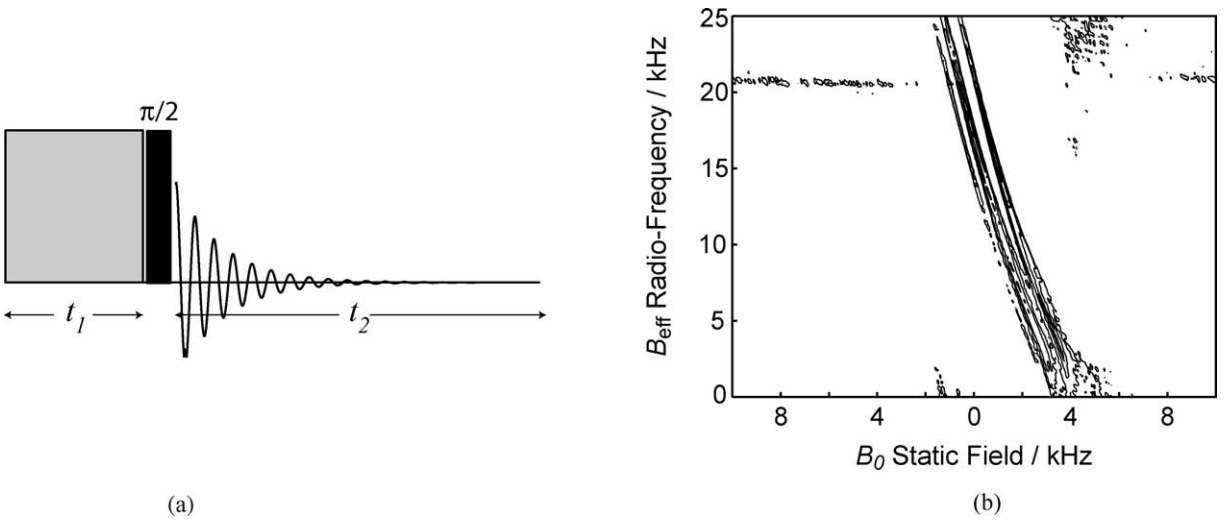

Fig. 2. 2D Nutation pulse sequence, used to map the correlation between the B_0 field the Calros effective radio-frequency field. 2D Fourier transform shows sharp ridges, if the correlation is good enough and allows one to recover spectral resolution. In cases of linear correlation, simple shearing leads to the high-resolution 1D NMR spectrum.

where δ is the chemical shift of each spin species.

The experiment yields a series of individual FIDs, where contributions of spins at different locations (and therefore with different Larmor-frequencies) are modulated with their individual rf frequency under the influence of the pulse. If the two $B_0(r)$ and $B_1(r)$ fields are spatially correlated, ridges in the 2D spectrum are observed as we can see in Fig. 2(b), and they correspond to the different resonance peaks. Chemical shifts are resolved in the F_2 domain, as nonequivalent spins experience the same B_1. The projection along the F_2 dimension gives us the broad spectrum that we obtain under only the static field gradient while the projection along th F_1 dimension gives the distribution of the rf frequencies produced by the coil and probed by the sample. While this experiment is well-suited for the direct determination of the B_0–B_1 correlation (a linear correlation according to Eq. (1) would result in straight lines), it suffers from low signal-to noise ratio, as only spins from small regions of the sample contribute to each slice in the F_2 domain. One way to unravel this problem is to add an extra dimension where the NMR signal is completely refocused (using a CPMG pulse train for example) and the bandwidth is very small. If the carrier frequency is placed at the Larmor frequency of the spins located far away from the coil, $B_{\mathrm{eff}}(r) = B_1(r)$, and for the spins located close to the coil $B_{\mathrm{eff}}(r) \approx B_1(r)$ provided that the amplitude of $B_1(r)$ is stronger than their offset. This choice of carrier frequency minimizes artifacts coming from the influence of offset during the pulse, throughout the sample volume. The offset dependance might be a serious problem in low field applications, and we will see in what follows that field correlations without artifacts can be also obtained using adiabatic pulses (see Section 4.2).

In the case where the correlation is linear throughout the sample, one-dimensional high-resolution spectra can be obtained either by shearing the 2D nutation spectra and taking the projections along F_1, or by a whole echo acquisition [30]. The residual linewidth in such spectra depends on the quality of the correlation or in other words on how unique the correspondence between B_0 and B_1 (B_{eff}) is throughout the sample.

3.2. Non-linear spatial correlation

In the case of a non-linear correlation the gradient of the static field is some function of the gradient of the radiofrequency field:

$$\frac{\mathrm{d}B_0(r)}{\mathrm{d}r} = f\left(\frac{\mathrm{d}B_{\mathrm{eff}}(r)}{\mathrm{d}r}\right). \tag{3}$$

The nutation experiment gives a 2D map containing narrow lines that cannot be easily deconvolved or sheared. High resolution in non-linearly correlated fields is synonymous with good correlation and can be easily, at least in principle, using a non-linear transformation (nonlinear projection). The extension thus to non-linearly correlated fields is straightforward [31]. In real life one-sided magnets one expects to find good correlations only in small parts of the sample. In order to gain sensitivity, one needs to work with the maximum sample size, which is equivalent to working with volumes where the fields are correlated in a linear or even non-linear way. Note that the development of pulses to 'linearize' this problem is of capital importance as will be shown

in the following sections. The appropriate design of the radio-frequency coil has to integrate the field profiles of the magnet (and vice versa) in order to optimize the volume of good correlation over the sample. The possibility of using more than one coil for to separate excitation from detection should not be underestimated in future hardware designs, since it would allow further degrees of optimization for the system.

4. Z-rotations and refocusing sequences

4.1. Composite pulses

In order to increase the sensitivity it would be advantageous to refocus the effect of different Larmor-frequencies in such a way that spins in identical chemical environment give rise to narrow signals while the chemical shifts are maintained. This can be achieved with the help of composite radiofrequency pulses which have the net effect of a negative sign rotation of magnetization in the xy-plane around the z-axis of the rotating frame. Such pulses are named 'z-rotation' pulses and are usually composite pulses [32]. The dephasing due to inhomogeneous B_0 and B_1 fields is illustrated on Fig. 3(a) and one can easily that in the case of spatial matching the dephasing effect is identical to all parts of the sample. If Eq. (1) is fulfilled for an extended region of a sample, the effect of the composite pulse compensates for the development of the magnetization under the influence of the inhomogeneous external magnetic field. The simplest z-rotation pulse can be achieved simply with the following composite pulse:

$$P_z(\beta) = P_y(\pi/2)P_x(\beta)P_{-y}(\pi/2). \tag{4}$$

In the presence of inhomogeneous B_0 and B_1 fields, the $P_y(\pi/2)$ pulses have to be replaced by appropriate constant-rotation [2] composite $\pi/2$ pulses which compensate for radio-frequency *and* magnetic field inhomogeneities, while the angle β depends on $B_1(r)$. The inhomogeneities refocus after some time τ forming a so-called 'nutation' echo [33–37], the amplitude of which is modulated by the chemical shifts. Stroboscopic acquisition at the nutation echo points and Fourier transformation leads to the high-resolution NMR spectrum. The resolution enhancement can be appreciated in the first simple use of z-rotation composite pulses in the context of ex-situ NMR shown on Fig. 3 (b) and (c).

The need for robustness and control over the correlation range of the pulse, lead to the development of other composite pulses. Some of them were presented in [38] and were shown to be performing well over a big range of static inhomogeneities. Frequency selectivity is a significant advantage of such pulses. Numerical studies showed the spatial selectivity of such pulses, emphasizing the importance of localization in future developments of pulses and ex-situ MR systems. In particular, such pulses can be used in order to limit the sample of interest only to the region where good spatial correlation takes place, enhancing this way the spectral resolution. Another advantage of such pulses, is the inherent efficiency in terms of rf power and thus their short length. In cases where large field gradients are present, molecular diffusion will be an issue and the refocusing of the inhomogeneous interactions should take place in a rate fast enough to avoid interference, or dephasing of the transverse coherences. Finally the same reason renders also such pulses less sentitive to effects due to scalar or dipolar couplings between spins.

4.2. Adiabatic pulses

In many cases spatially selective pulses might represent major disadvantages. In low field applications where signal to noise is crucial, spatial selectivity is synonymous to signal intensity loss. On the other hand, the behavior of the nonrefocused regions of the sample remains poorly understood and not fully controlled, and could be a potential resolution bottleneck in particular applications. There is the need thus for extremely robust and uniformly performing z-rotation pulse sequences. In MRI such pulses exist and are mainly inspired by the continuous passage magnetic resonance [39]. Since the change of the radio-frequency field is slow compared to its magnitude such pulses were named adiabatic pulses and offered a large range of good performance to applications such as excitation, inversion or decoupling [40,41]. Nevertheless, no z-rotation adiabatic pulses were present until recently and their preliminary application to ex-situ NMR seems very promising [42].

The trajectory of the magnetization under an adiabatic inversion can be easily understood from Fig. 4. In the rotating frame the effective field starts almost along the $+z$ axis and gradually passes through the xy place to finish at $-z$. Magnetization is dragged adiabatically and follows the effective field. If the same frequency sweeping is applied to transverse magnetization its trajectory is slightly different. The transverse magnetization will precess on a plane that remains perpendicular to the effective field during the duration of the pulse. Consequently, it will come back to the xy plane at the end of the passage, but it will have

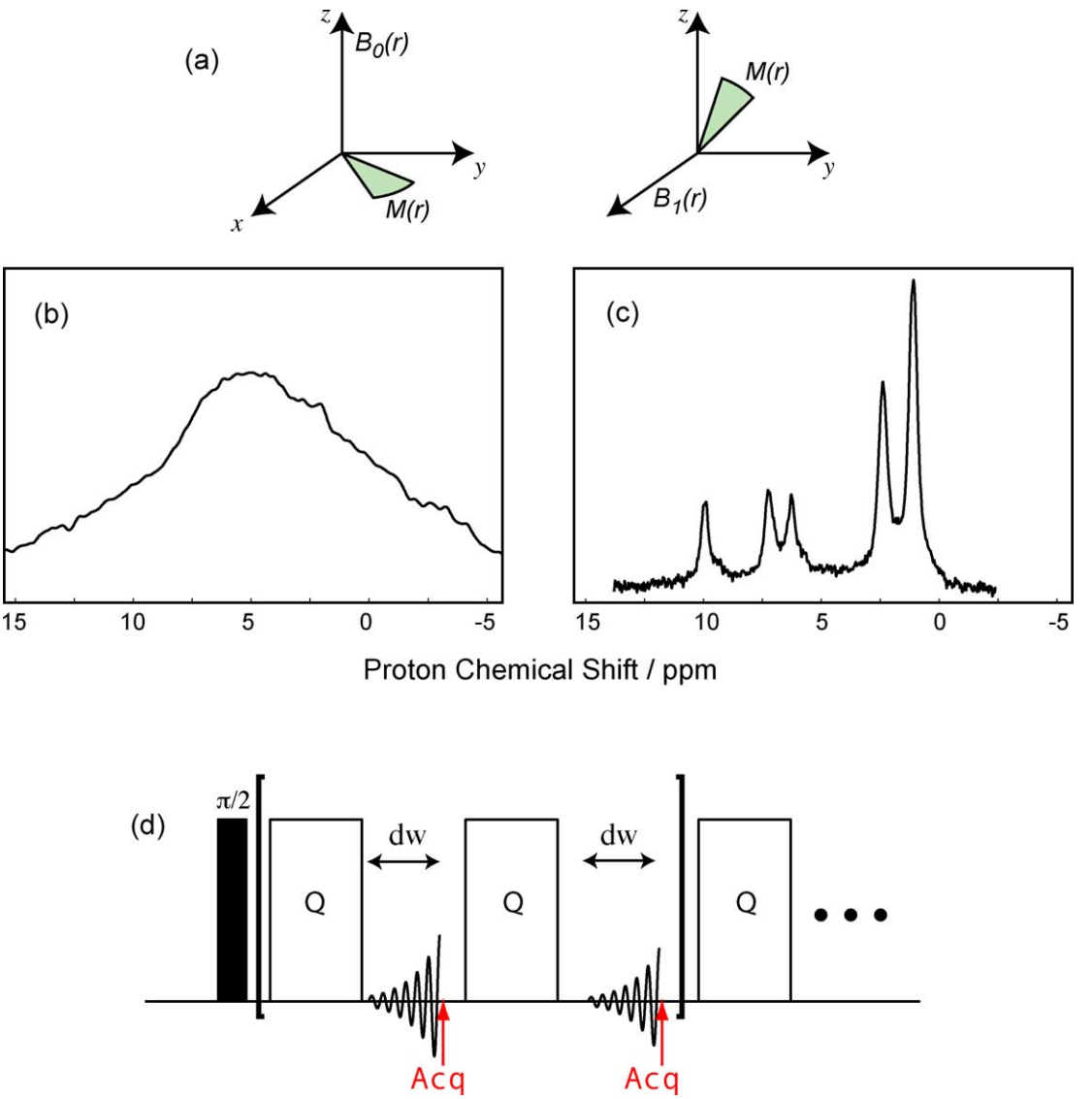

Fig. 3. (a) Schematic diagram of the dephasing caused by static B_0 and rf B_1 field inhomogeneities. If the fields are matched in space the dephasing is the same for all parts of the sample. (b) Proton NMR spectrum of a liquid sample of trans-2-pentenal in the presence of static field gradient of 0.12 mT/cm. (c) High-resolution spectrum acquired under the same gradient using a multiple pulse train of z-rotation pulses. (d) Stroboscopic acquisition using composite pulses. The effect of each block is to perform a B_1 dependent phase encoding on the transverse magnetization, over a large range of offset and rf inhomogeneities. Several combinations of pulses have such behavior. Robustness and spatial selectivity largely depends on the constituants of these blocks.

acquired a phase that depends on the characteristics of the pulse and the position in physical space of the spin. This phase can be written as:

$$\phi = \int_0^t \sqrt{B_1(t)^2 + \big(B_0(t) - (\omega_0 + \delta)\big)^2}\,\mathrm{d}t, \tag{5}$$

where $B_1(t)$ is the time dependent amplitude of the rf pulse, $B_0(t)$ is the time dependent frequency of the rf pulse, ω_0 is the central value of the frequency bandwidth and δ the position dependent frequency offset from this value for each spin. The dependance of the accumulated phase on the various parameters is non-linear and offers only little control. If one follows this encoding by an identical second passage, spins inside the adiabaticity region of the pulse (strong B_1 and frequency between

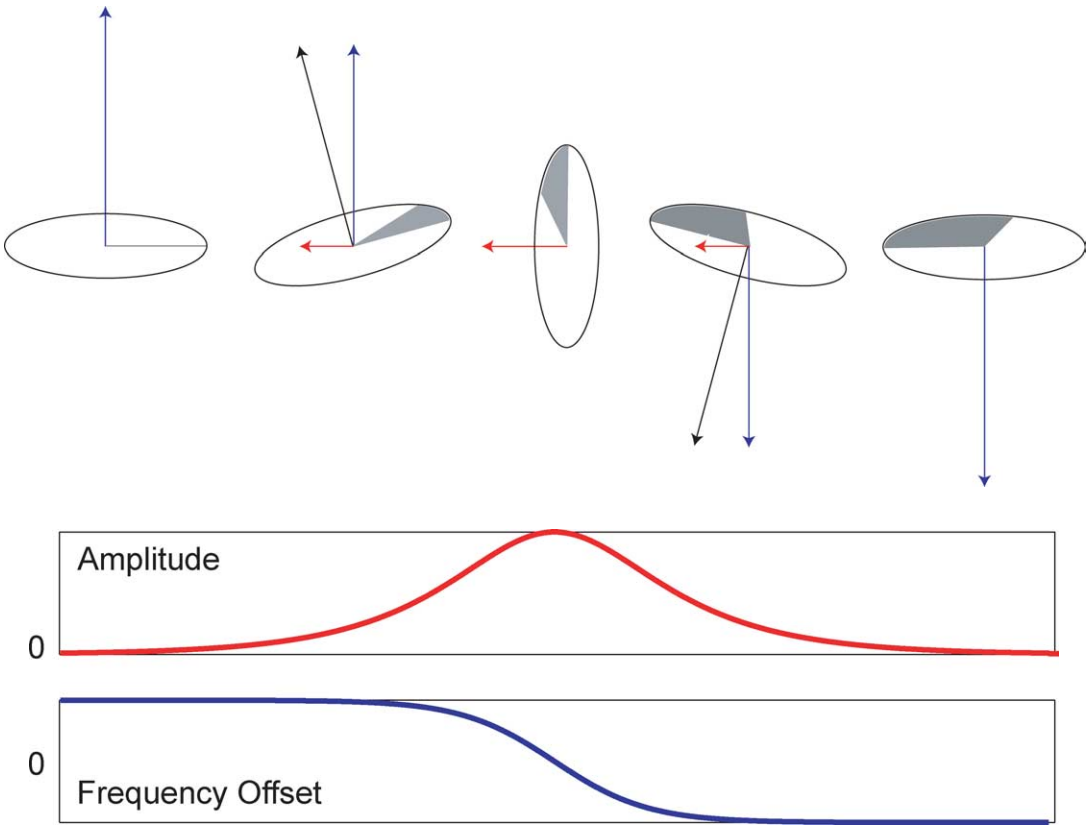

Fig. 4. Schematic diagram for a full adiabatic passage pulse. The amplitude and frequency (or phase) are modulated using a hyperbolic secant and hyperbolic tangent functions without loss of generality. Longitudinal magnetization follows the effective field inversion, while transverse magnetization precesses always on a plane perpendicular to it. At the end of the pulse an offset and B_1 dependent dephasing is accumulated. If a second identical full adiabatic passage is applied, the sense of the rotation for the transverse magnetization, is effectively inverted leading to a complete cancellation of this dephasing.

the limits of the passage), will experience the same phase with an opposite sign, thus will come back to their original position, along say the x axis. We are interested in a smooth linear phase encoding that is independent on the offset frequency and one way to achieve such performance, is by changing the characteristics of the pulse between the two passages. This way the second accumulated phase will not cancel identically the first and to first order the net accumulated phase will be roughly linear with the B_1 field. This has been shown in [42] and used to cancel inhomogeneities that are linearly correlated.

Of course such situations show the proof of principle of this methodology, and in real applications, the correlation might not be linear, and/or one might need pulses that are offset and B_1 dependent. Some simple modifications of the original adiabatic double passage are shown in Fig. 5. The frequency sweep is not symmetric anymore and induces an non-linear behavior on the phase encoding. In real applications the correlation between the rf coils and the magnet will dictate the pattern of the applied pulse, but already this simple double passage offers a lot of degrees of freedom for a so called ‘active matching’. One can see this as a tuning procedure for the pulse, that can be performed numerically or even experimentally. Currently one shims the magnet before an experiment and we project a similar interactive approach with active matching. On the other hand, completely general phase and amplitude modulations can also be implemented in order to provide even more broadband pulses. Such semi-continuous versions have been designed using computer models [43] and are not adiabatic. We believe that such non adiabatic schemes could easily be generalized to z-rotations and provide a much more adjustable performance.

5. Applications

Until today all of high-resolution ‘ex-situ’ experiments were carried out inside super-widebore imaging magnets and were proof of principle experiments. The inhomogeneity of the static field was simulated using gradient coils for imaging and the

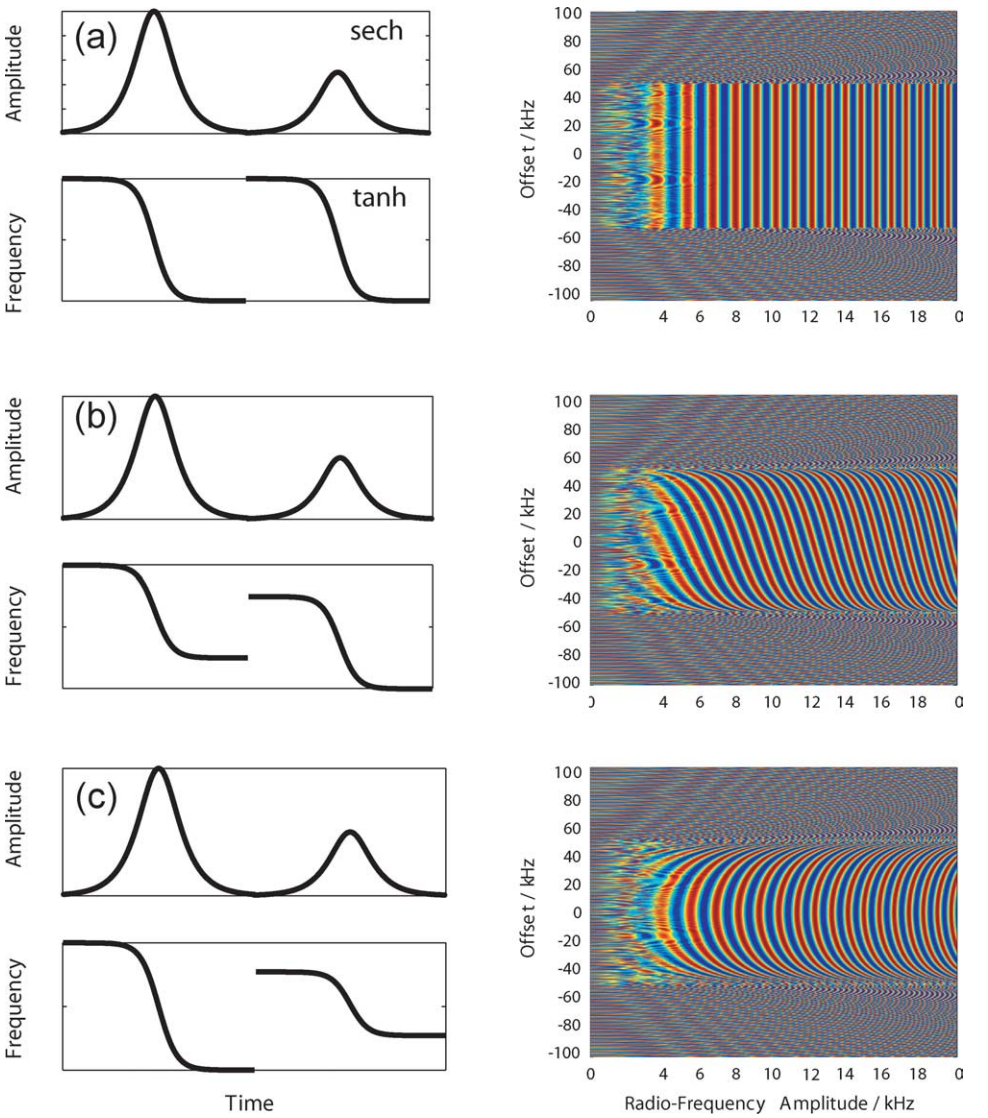

Fig. 5. Stroboscopic acquisition using adiabatic pulses. Robustness and selectivity is guaranteed by the frequency sweep of the pulse. Different modifications of the pulse characteristics lead to modified performance. Though adiabaticity might not be necessary for future pulse schemes, it sets a good initial guess for sequences actively matching non-linear correlation profiles.

inhomogeneity of the radio-frequency field using conical coils [38]. Various applications could be envisaged already using such primitive experimental setup. Homonuclear and heteronuclear multi-dimensional spectra were acquired using simple modifications of pulse sequences from liquid state NMR [4,30]. The inherent inhomogeneity of the field can be used to obtain depth sensitive spectra as well [30]. Additionally, phase encoded imaging has been explored using a combination of adiabatic pulses and gradient pulses [44]. An example of a chemically resolved three dimensional image is presented, without further details in Fig. 7. The main difference with previous methods being the non-slice selective excitation and detection, we believe that such pulse techniques could be translated to real ex-situ situations. Another direct application of the ex-situ methodology to diffusion measurements in inhomogeneous fields will provide direct chemical shift identification [45] and diffusion coefficient measurements. Finally, even in the case of anisotropic materials, such as porous media, solids, or oriented phases, the ex-situ methodology can be adapted to provide high resolution spectral information [42]. Magnetic susceptibility effects can be averaged out by magic angle sample spinning, or by magic angle field spinning for samples located outside the magnet.

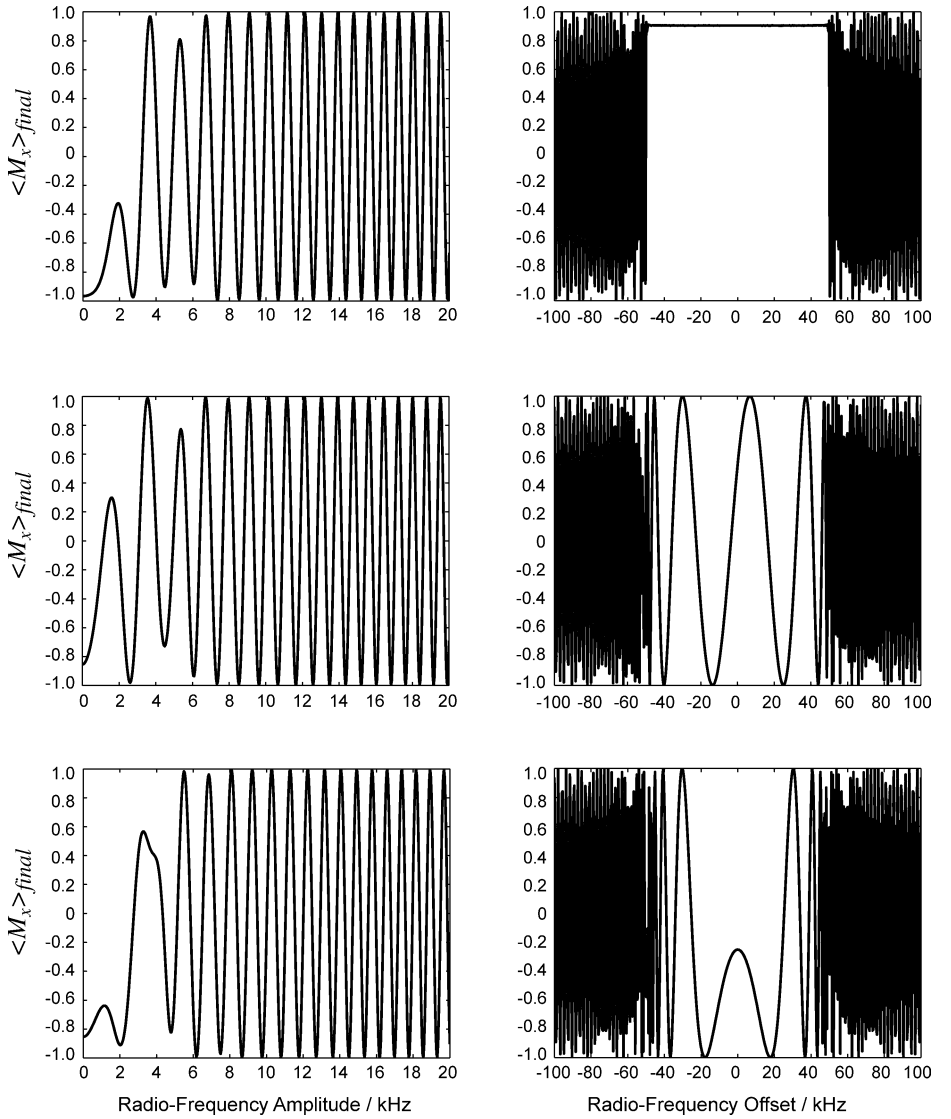

Fig. 6. Profiles of the transverse magnetization after different adiabatic double passages. (a) Symmetric frequency sweep between ± 50 kHz from the on-resonance condition. The functional form of the amplitude modulation was described by a hyperbolic secant shape, while the frequency sweep by a hyperbolic tangent shape [46,47]. The length of each pulse was set to 16 ms and each pulse was digitized into 1000 steps of constant amplitude and phase. The scaling in the second passage was set to 0.5 and the initial density operator was assumed to be I_x for all points in the graph. (b) The frequency range of the first passage was shifted by $+200$ Hz, while the frequency range of the second passage by -200 Hz. (c) The frequency range of the second passage was scaled by 0.98.

6. Conclusions

Portability is one missing quality in modern high-resolution NMR. The ex-situ methodology offers the possibility to recover spectral information in the presence of inhomogeneous magnetic fields and seems very promising in applications of one-sided portable magnetic resonance systems. Practical issues that have to do with the magnet and rf coil design are the most important reason for the time delay between the proof of principle experiments and their use in actual ex-situ situations. Large gradients and/or imperfect non-linear correlations are issues that should be taken into account during the initial stages of the design of high-resolution open NMR systems. The methods described here can provide a starting point for further development and better understanding of nuclear magnetic resonance in inhomogeneous fields. Applications from the field of industrial sensing,

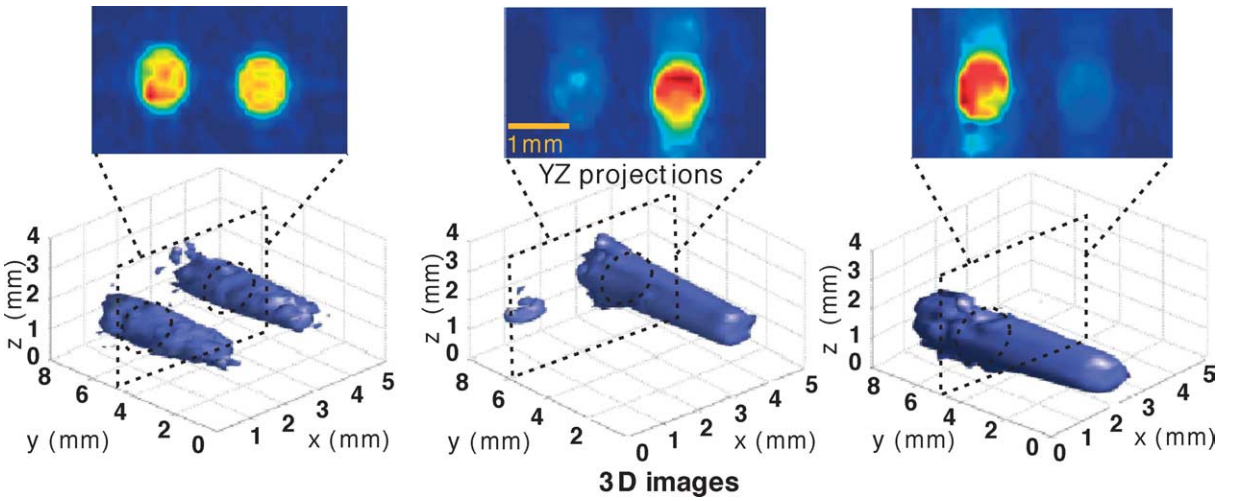

Fig. 7. Chemically resolved 3D imaging in the presence of a constant field gradient. The static field gradient along x is applied during all experiments in order to emulate the natural inhomogeneity of an ex-situ environment. Phase encoding is used to image the other two dimensions and the overall experiment is repeated for different scaling of the two adiabatic pulses. Two tubes (one filled with water and the other with oil) were placed inside a conical solenoidal coil producing a B_1 spatial profile that matched the linear magnetic field gradient along x. yz Projections and three-dimensional images of the sample (as a subset of the 4D data set) correlated with chemical shift. Either both tubes (trace at 4 ppm), or the water (trace at chemical shift of 4.8 ppm-water) and the oil (trace at chemical shift 3 ppm-oil) tubes are selectively displayed depending upon chemical shifts. From [44].

medical imaging and chemical analysis and detection would undoubtedly benefit from further developments in the technique. The door towards ex-situ NMR is wide open.

Acknowledgements

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