Potentials of High-Field Spectroscopy

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Localized in vivo NMR spectroscopy allows to characterize the metabolic status of tissue and to study metabolic changes and metabolic pathways. Thus it is possible to improve the basic biochemical and biomedical understanding and to support diagnostic decisions. The current advances in high-field NMR spectroscopy, both for single voxel magnetic resonance spectroscopy (MRS) and MR spectroscopic imaging (MRSI) could only be achieved by combining the progress made in different areas:

1. the availability of modern high-field MR systems with improved hardware components,
2. a large number of advances in MR methodology,
3. improved and accelerated adjustments applied prior to measurements,
4. optimized data processing and quantification methods.

It is the aim of this contribution to outline briefly the potentials of high-field NMR spectroscopy, the current major problems and challenges, and future improvements required. While there are several general aspects of high-field NMR spectroscopy, it is necessary to consider specific problems for animal or human high-field systems, and for different nuclei. Since the majority of spectroscopic high-field measurements are ^{1}H studies, this contribution will primarily focus on proton MRS and MRSI, although many consideration are also valid for other nuclei such as ^{31}P or ^{13}C.

Although the increasing values of the maximum B_0 field strength of MR scanners for animals (11.7 T, 14.1 T, 16.4 T, 17.6 T, …) and humans (7 T, 8 T, 9.4 T, …) may be most impressive, the increasing number of implemented „standard“ high-field systems (7-11.7 T for animals, 3-7 T for humans) will probably be even more important to fully exploit the potentials and to solve the numerous experimental and methodological problems of high-field NMR spectroscopy. The large number of high-field installations does not only lead to increasing interest of the manufacturers and thus improved hardware and software (and vice versa), but will allow to establish large networks of MR groups which may exchange their solutions developed for specific problems. The enormous progress made to build compact high-field magnets with reduced fringe fields makes the installation of high-field systems much easier, whether in existing laboratories or within a clinical environment.

For NMR spectroscopy, the major benefits of increasing B_0 fields are (a) the improved spectral resolution and signal separation and (b) the higher signal-to-noise ratio ($SNR \sim B_0$) [1, 2]. The higher SNR can be exploited in different ways. Either the total measurement time T_{meas} can be reduced or a smaller voxel size can be used (for a given SNR), or the quantification accuracy can be improved and the number of detectable metabolites can be increased (using constant T_{meas} and constant voxel size). Short T_{meas} values are essential for many applications, e.g. to achieve better temporal resolution in time-resolved metabolic studies, or to allow to incorporate spectroscopic measurements into clinical protocols.

While the performance of B_0 gradients, particularly the slew rate, is rather limited for human systems to avoid peripheral nerve stimulations, the gradient performance of high-field systems for animals has considerably improved, so that 400 mT/m and 4000 mT/m/ms are already „standard“ values for the maximum gradient strength and slew rate, respectively. This progress is essential for developing and implementing optimized pulse sequences for high-field systems, particularly in the field of fast MRSI.

Furthermore, high field NMR spectroscopy benefits from the availability of RF array coils. Although array coils are certainly more important for human high field systems, both regarding RF reception and RF transmission, their use increases the quality of high-field animal studies, too. A multifrequency and multichannel architecture has been used for most animal scanners for many years allowing non-proton studies using ^{31}P, ^{13}C, ^{15}N or other nuclei, decoupling, inverse experiments etc.. However, the number of high-field human systems, which allow comparable spectroscopic experiments, is increasing, thus fostering non-proton MRS and MRSI.

The high quality of high-field spectra is not an automatic result of applying known spectroscopic techniques at an increased B_0 field [1, 3-5]. Most pulse sequences have to be adapted, optimized or even completely changed for high-field systems. These modified sequences have to take into account that with increasing B_0 (i) the relaxation time T_1 increases [6] and T_2 and particularly T_2^* decreases [7], (ii) the chemical shift range (in Hz) increases ($\sim B_0$), and (iii) the required RF power and the specific absorption rate (SAR) increases ($\sim B_0^2$) for an RF pulse with given duration and flip angle. While the moderate increase in T_1 is not a severe drawback, the other changes require modifications of the pulse sequences and/or lead to increased hardware requirements. To limit chemical shift artifacts of spatially selective RF excitation or refocusing, RF pulses with increased bandwidth are required. This could be achieved by shortened RF pulses, but would cause a further SAR increase and problems with the maximum B_1 amplitude available. Therefore, optimized or novel RF pulses are better

alternatives, e.g. using the concepts of VERSE [8], multidimensional RF pulses (9], spectral-spatial pulses [10], or transmit SENSE [11].

A large number of optimized pulse sequences is available for single voxel MRS measurements and for spectroscopic imaging of slices or 3D volumes. For proton MRS, optimized STEAM [3,5], PRESS [12], or SPECIAL [13] pulses sequences with efficient water suppression and outer volume suppression have been described. Data evaluation using prior knowledge and modern numerical algorithms allows to quantify about 20 metabolites in rat or mouse brain [4,14] and 17 metabolites in human brain [15] . During the last decade, only a small number of NMR detectable metabolites have been added to the neurochemical profile described in the original papers on ^{1}H measurements at 9.4T animal and 7T human scanners [3-5]. However, e.g., it was shown that ascorbate can be quantified both in animal and human brain [16, 17]. The main advantage of increased B_0 fields is the improved accuracy of quantification, as shown in animals (9.4 T vs. 14.1 T) [14] and humans (4 T vs. 7 T) [15]. For human high-field systems, the LASER sequence [18] is of particular importance, because adiabatic pulses are used to reduce problems cause by spatial inhomogeneities of the B_1 field.

Various MRSI pulse sequences, each with different advantages and drawbacks, have been proposed and modified for high-field application. However, despite the obvious potentials of high-field MRSI, only recently convincing applications have been published for human systems (e.g., [19-21]). For standard spectroscopic imaging, where spatial localization is only achieved by incrementing phase encoding gradients in a series of measurements, B_0 shimming and, particularly for studies on humans, B_1 inhomogeneities are the major problems. Different approaches have been developed to reduce these problems, e.g. by using optimized hard- and software for B_0 shimming [22], LASER/pseudo-LASER/semi-LASER sequences [18,19,23-25] or transmit-SENSE to avoid spatially inhomogeneous RF pulses.

The numerous approaches towards fast MRSI with reduced minimum total measurement time T_{min} require modifications for high-field applications, too. If oscillating read gradients are used as in echo planar MRSI (EPSI) or spiral MRSI, faster gradient switching is required (to avoid more interleaves) because of the increased chemical shift range. However, successful implementations of EPSI and spiral MRSI have been shown on animal and human high-field scanners without or with additional acceleration by parallel imaging approaches [26-29]. Fast MRSI methods that use trains of RF refocusing pulses, such as spectroscopic U-FLARE [30] or spectroscopic RARE [31] suffer from increasing B_1 inhomgeneities, high SAR values and reduced sampling efficiency, and are currently only of interest for high-field studies on animals. Steady-state free precession (SSFP) based fast MRSI sequences have been used for high-field measurements on animals [32] and humans [33,34], although severe methodological changes are required for each scanner type and field strength. Fast MRSI sequences with very short T_{min} are also of great interest for time resolved studies with hyperpolarized ^{13}C MRSI measurements [35,36].

The simultaneous measurement of all detectable metabolite signals by MRS or MRSI with 1D spectral resolution is an efficient way to acquire a maximum of information with high SNR and within a reasonable T_{min}. However, in those cases when metabolite signals cannot be separated by measurements with 1D spectral resolution, even if all available prior knowledge is used for data evaluation and despite the improved spectral resolution with increasing B_0, 2D NMR spectroscopy or specific editing sequences for metabolites of interest may be a remedy. It is still an open question, when, i.e. for which combinations of application, metabolite of interest, and available hardware, optimized measurements with 1D spectral resolution will not be sufficient.

It is important to note that the full potentials of high-field MRS and MRSI can only be exploited after appropriate adjustments, in particular optimized B_0 shimming, and by applying optimized quantification algorithms. However, these aspects as well as typical and cutting-edge applications of high-field NMR spectroscopy will be discussed in separate contributions.

In the future, the excellent spectral resolution and the increased SNR achieved at high B_0 fields will allow to reconsider spectroscopic studies that do not only focus on the quantification of metabolites, but also on other effects such as metabolite diffusion [37-40], magnetization transfer effects [41-43] or absolute temperature measurements. Because the accuracy and reproducibility of MRS and MRSI measurements can be improved at high B_0, it is even more important than at lower B_0 to avoid any systematic quantification errors. Such errors can be caused by magnetization transfer effects, which may result from water suppression techniques [42]. Therefore, ^{1}H MRS and MRSI measurements without water suppression are interesting options to avoid systematic quantification errors.

There is still a large amount of work to be done to exploit the full potentials of high-field NMR spectroscopy. While some problems are still unsolved, there are already many different approaches, sequences or sequence modules for high-field MRS and MRSI. However, their simultaneous availability and the option to combine different sequence modules, which are the prerequisite to perform an optimized experiment for a given task, are still a critical issue. This problem can only be solved by consequent modular programming, a close cooperation

between costumers and manufacturers, and by extensive cooperation between the numerous groups working in the field of high-field NMR spectroscopy.

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