Introduction

What is a high magnetic field? For horizontal in vivo MR systems using small animals like mice or rats, magnets of field-strengths as high as 11.7 T/31 cm (500 MHz) are available. Vertical microimaging systems operate up to 17.6 T/89 mm (750 MHz) and will reach in near future 21.2 T/105 mm (900 MHz). For research in humans the highest field currently available is 9.4 T/65 cm (400 MHz), while in the clinical environment the highest field is 3-4 T/95 cm (130-170 MHz).

MR spectroscopy (MRS) evolved rapidly over the last decades, and it is now an important tool in chemical and biological research focused on molecular composition, structure, and dynamics. Experiments initially conducted in cells and cell extracts, are now carried out in living animals and humans. Similarly, MRS applications in clinical diagnosis are growing steadily. The importance of field strength in such applications cannot be overemphasized: “increasing the magnetic field strength increases spectral resolution also for 1H NMR, which can lead to more than linear sensitivity gains”, Fig.1 (Gruetter et al., 1998b).

The several fold improved sensitivity at high fields enables the detailed quantitative study of both metabolic and neural signaling processes, as well as of their perturbations during disease.

Technical Issues

Significant improvements in signal-to-noise ratio are the most notable effects of the technical developments of in vivo MRS studies at high fields (Ugurbil et al., 2000).

SNR gains may be a linear (e.g. 1H) or even a quadratic function of field-strength, depending on several competing factors (Ugurbil et al., 2003).

In the human brain, SNR comparisons for 1H suggested an approximately 1.6 – 2-fold gain in sensitivity achievable at 7 T compared to 4 T (Vaughan et al., 2001).

SNR data at 4.7, 11 and 17.6 T of enriched 17O-water demonstrated a quadratic increase with field strength, see Fig. 2 (Thelwall et al., 2003). High fields will therefore allow improved spatial and/or temporal resolution in 17O-CSI of metabolically produced H217O.
MRS at high field benefits further from an improved spectral resolution due to increased chemical shift dispersion and reduced higher-order coupling effects. Sensitivity and resolution improvements were experimentally demonstrated comparing field strengths from 1.5T to 9.4T (Gruetter et al., 1998b).

In Fig. 3, the magnetic field dependence of glutamate (left) and glutamine (right) is shown in simulated $^1$H spectra from 50 to 400 MHz (top to bottom). These metabolites and similarly GABA, glucose, and taurine have large second-order effects, since the J coupling constants are similar to chemical shift differences (de Graaf et al., 1998).

Similarly, resonances of glutamine and glutamate $^1$H NMR spectra can be better separated at increasing magnetic field strengths; typically higher fields than 4 T are necessary for a separate quantification, see Fig. 4 (Tkac et al., 2001).
An important prerequisite for quality MRS is optimal, reproducible shimming to provide the narrowest possible \textit{in vivo} line-widths, clearest peak separation, and increased sensitivity. Automated algorithms like FASTMAP or FLATNESS are available for shimming 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd}-order contributions in a localized volume or a slice (z-shim), respectively (Gruetter, 1993; Gruetter \textit{et al.}, 2000; Glover, 1999; Chen \textit{et al.}, 2004).

\textbf{Selected high-field applications}

Excellent sensitivity of \textsuperscript{1}H MRS in the human brain was shown at 7 T even with single-shot spectra, see Fig. 5 (Tkac \textit{et al.}, 2001). At 9.4 T in the rat, up to 18 metabolites could be quantified, see Fig. 6 (Pfeuffer \textit{et al.}, 1999b).

Localized \textsuperscript{13}C MRS in the human visual cortex (4 T) and rat (9.4 T) has demonstrated its capacity to monitor glutaminergic neurotransmission, see Fig. 7 (Gruetter \textit{et al.}, 2000; Gruetter \textit{et al.}, 1998a; Pfeuffer \textit{et al.}, 1999a; Henry \textit{et al.}, 2003b; Henry \textit{et al.}, 2003a). Moreover, oxygen consumption rate can be calculated from \textsuperscript{13}C turnover. Spectacular spectra from multiple carbons of various amino acids and neurotransmitters reveal the power to obtain detailed metabolic information and study reaction-dynamics \textit{in vivo} (Gruetter, 2002; Gruetter \textit{et al.}, 2003).

Recent \textsuperscript{17}O chemical shift imaging represents a promising new high-field application: from \textsuperscript{17}O turnover of inhaled oxygen and injected water, the oxidative metabolism in the mitochondria (CMRO\textsubscript{2}) was measured directly, see Fig. 8 (Zhu \textit{et al.}, 2001; Zhu \textit{et al.}, 2002).

Further developments and applications of \textsuperscript{1}H chemical shift imaging (CSI) were steadily increasing in the last years, taking advantage of the sensitivity gains at higher magnetic field (Pan \textit{et al.}, 1998; Pan \textit{et al.}, 2000; van Dorsten \textit{et al.}, 2004; Scheenen \textit{et al.}, 2004; Dreher \textit{et al.}, 2002; Dreher \textit{et al.}, 2003; Mayer \textit{et al.}, 2004; Hiba \textit{et al.}, 2003; Hiba \textit{et al.}, 2004). High-resolution CSI in the monkey brain at 7 T with \textasciitilde1.5 mm in-plane resolution approached recently the spatial dimensions of the cortical thickness (1.5-1.7 mm in the monkey) - metabolite concentrations could be quantified separately in gray and white matter, see Fig. 9 (Juchem \textit{et al.}, 2004).
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**Figure 7.** LCModel fit of an *in vivo* $^{13}$C NMR spectrum. (bottom) $^1$H-localized $^{13}$C spectrum acquired in vivo from the rat brain 5 h after starting an infusion of [1,6-$^{13}$C2] glucose (2816 scans, TR 2.5 s). (middle) Fit obtained with LCModel using prior knowledge of chemical shifts and J-coupling values and (top) residuals. Only the expansion from 22 to 63 ppm is shown. From (Henry et al., 2003a).

**Figure 8 (left).** Cerebral $^1$H$_2^{17}$O spectra from one representative voxel (0.1 ml voxel size) as indicated by the circle in the anatomic image (left insert) acquired before (natural abundance), during and after a 2-min $^{17}$O inhalation. $^{17}$O spectrum of natural abundance $^1$H$_2^{17}$O in the rat carotid artery blood obtained using the implanted RF coil before inhalation of $^{17}$O$_2$ (B) and time course (C) of $^{17}$O MR signals during inhalation of $^{17}$O$_2$. (D) Plot of the calculated CMRO$_2$ values using the complete modeling as a function of inhalation time. Figure 8 (right). 3D $^{17}$O brain images of natural abundance $^1$H$_2^{17}$O from three adjacent slices (Left, color images) and corresponding anatomical images (Right, gray images) in the coronal orientation from a representative rat. (B) Chemical shift image of natural abundance $^1$H$_2^{17}$O from Middle as shown in A. From (Zhu et al., 2002).

**Figure 9.** High-resolution $^1$H CSI of metabolites from gray vs. white matter in the monkey visual cortex using a vertical 7 T / 60 cm MR system. Spatial in-plane resolution was below 1.5 mm. SNR and spectral/spatial resolution were high enough to distinguish GM and WM reliably via their metabolite concentrations.

(a)(b) Anatomical FLASH (axial, coronal) showing WM and GM areas; zoomed CSI FOV to the right.

(c) S/N map from LCModel fit. The WM (white contour) and vessel region (left horizontal black contour) show lower metabolite signals than the voxels in GM.

(d)(e) Map of NAA/NAAG and Glu/Gln concentrations (relative to 8 mM for Cr/PCr).

(f) CSI FOV with selected WM and GM tissue.

(g) Metabolite concentration histograms for Cr/PCr, NAA/NAAG and Glu/Gln in GM and WM. Metabolite concentrations were significantly higher in GM (p<1e-5). Ratios of NAA/NAAG vs. Cr/PCr and Glu/Gln vs. Cr/PCr were consistent with the literature.

Experimental parameters: STEAM: TE/TM 10ms, TR 3s, NA 42, VOI 17x17x2mm$^3$. CSI: 2D phase encoding, matrix size 13x13. Post-processing: smooth Gaussian filtering (62% at the edges), zero-filling to 27x27. Quantification: voxelwise with LCModel, Cramér-Rao lower bounds were (10.3 ± 3.3)% for NAA/NAAG and (16.4 ± 8.2)% for Glu/Gln. From (Juchem et al., 2004).
References


