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On the Voxel Size and Magnetic Field Strength Dependence of Spectral Resolution in MR Spectroscopy

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Abstract

While the inherent low sensitivity of *in vivo* MR spectroscopy motivated a trend towards higher magnetic fields, B_0 , it since has become apparent that this increase does not seem to translate into the anticipated improvement in spectral resolution. This is attributed to the decrease of the transverse relaxation time, T_2^* , *in vivo* due to macro- and mesoscopic tissue susceptibility. Using spectral contrast to noise ratio arguments we show that if in biological systems the linewidth (on the frequency scale) increases linearly with the field, the spectral resolution (in ppm) improves approximately as the fifth-root of B_0 for chemically shifted lines and decreases as about $B_0^{4/5}$ (in Hz) for a structure of *J*-coupled multiplets. It is also shown that for any given B_0 there is a unique voxel size that is optimal in spectral resolution, linking the spectral and spatial resolutions. Since in practical applications the spatial resolution may be dictated by the target anatomy, nomograms to determine the B_0 required to achieve the desired spectral resolution at that voxel size are presented. More generally, the scaling of the nomograms to determine the achievable spectral and spatial resolutions at any given field is described.

Keywords

Contrast-to-noise-ratio (CNR); High-magnetic-field; MR spectroscopy (MRS); signal acquisition; spectral resolution; spatial resolution

Introduction

The increases in the magnetic field strength (B_0) of MR imagers and the proliferation of such systems is driven by expectation of improved sensitivity, spectral and spatial resolution (1-4). For *in vivo* MR spectroscopy (MRS), however, these efforts have been frustrated by commensurate line broadening (on frequency scale) from tissue-dependent susceptibility effects (1,5-7), which cannot be completely compensated with the first- and second-order shims of clinical MR instruments (8-10). As B_0 rises, the consequent increase in linewidths counteracts the chemical shift dispersion and leads to the overlap of the components of *J*-coupled multiplets (1). Experimentally, this linewidth increase (in frequency units) for peaks of several main metabolites was found to scale approximately as $B_0^{0.7}$ between 1.5 and 7 Tesla (11), almost proportionate to the chemical shift dispersion, $B_0^{1.0}$. The only way to allay such

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line broadening on standard systems is to reduce the voxel size in order to sample less macroscopic inhomogeneity (12). Since this can be done only if the signal-to-noise-ratio (SNR) is sufficiently high implies that for each $\mathbf{B}_0$ there should exist a voxel size that offers an optimal trade-off with the spectral resolution.

In this paper, we examine this dependence of the optimal voxel size on $\mathbf{B}_0$ and estimate the best spectral resolution that can be expected. For this purpose we consider a hypothetical experiment conducted at several field strengths where two otherwise identical spectral peaks are made to approach each other in the frequency domain until they can no longer be resolved. To distinguish technological from physical limitations, we assume that the duration of the experiments, sensitivity of radio frequency (RF) coils, shim quality *etc.* do not depend on $\mathbf{B}_0$. The experiment is hypothetical because we are not aware of a mechanism of either chemical shift or J -coupling alternations that could be utilized in a practical realization. Nevertheless, the results of this experiment are of practical importance. It is shown that $\mathbf{B}_0$ uniquely defines an optimal voxel size, which becomes smaller as the field is increased, interconnecting spatial and spectral resolutions. We find that if optimal acquisition settings are used at each field the spectral resolution of chemically shifted lines (in units of ppm) benefits only very slowly from higher fields – proportionally to $\mathbf{B}_0^{0.2}$ whereas the resolution of the structure of J -coupled multiplets (in units of frequency) is shown to *decrease* as $\mathbf{B}_0^{0.8}$. While higher order shim coils and better algorithms can improve the spectral resolution at any $\mathbf{B}_0$, inhomogeneities on mesoscopic and microscopic scales in biological tissue render the slow resolution gain with $\mathbf{B}_0$ intrinsic. Therefore, design of efficient RF coils, sequences, receivers, shim hardware and algorithms should remain the focus of development, especially for high field scanners (13).

Theory

I. Criterion for resolving adjacent lines

The ability to detect metabolites in a sample using MRS is determined by the degree of confidence that their “peaks” are real and not noise fluctuations. A preset acceptable level of confidence (the SNR threshold) defines the minimal detectable amount in a given experimental time – the sensitivity (14,15). Similarly, resolving adjacent lines depends on the presence of a “saddle” between them (16), which can be obscured or created by noise fluctuations, as shown in Fig. 1, the magnitude of which depends on the number of transients averaged, *i.e.* also on the experimental time. Therefore, akin to the sensitivity we define spectral resolution as the narrowest frequency interval between centroids of two equal-intensity test peaks that the saddle formed between them can still be distinguished from noise fluctuations. The goal is to find this narrowest separation at different field strengths and voxels sizes.

Clearly, the spectral resolution at a given $\mathbf{B}_0$ depends on the width of the peaks and not on their nature, *i.e.*, whether two adjacent lines arise from nuclei of different chemical shifts or from spin-spin coupling between adjacent nuclei. It may appear, therefore, that the behavior of the spectral resolution as a function of field strength does not depend on the nature of the lines as well. However, if one assumes for a moment that the spectral resolution degrades with $\mathbf{B}_0$ such that the narrowest spectral interval $\Delta\omega$ (in Hz) scales as $\mathbf{B}_0^\lambda$ with $0 < \lambda < 1$, then, it is evident that resolution in ppm units, $\Delta\gamma = \Delta\omega/\mathbf{B}_0$, will scale as $\mathbf{B}_0^{\lambda-1}$, and will be described as improving with $\mathbf{B}_0$. This possibility for spectral resolution to simultaneously improve for chemically shifted systems and to degrade for J -coupled ones is a simple consequence of the differences in the definitions of the frequency scales (ppm versus Hz) appropriate for the description of the corresponding systems.

To quantify these dependences, we propose to use the spectral contrast-to-noise ratio (SCNR) – the ratio of the saddle depth to its standard deviation as a metric of confidence that a pair of lines is real. In analogy with the SNR, a pair is said to be resolved if its SCNR exceeds a

predefined value. Although like the sensitivity the exact value of this threshold may depend on the particular application, the goal is to find the smallest frequency separation (in Hz or in ppm, as appropriate) that would, on average, make its SCNR exceed an *a priori* threshold. With this definition, the dependence of the resolution on $\mathbf{B}_0$ and voxel size can now be analyzed.

In the ensuing derivation, the depth of the saddle, d , and its variation, $\sigma(d)$, are determined first. Then, the dependence of the linewidth on $\mathbf{B}_0$ and voxel size, h , is modeled yielding an expression for the SCNR dependence on $\mathbf{B}_0$, h and $\Delta\omega$. Equating it to a threshold sets up the final equation whose numerical solution yields the desired resolution functions: $\Delta\omega(\mathbf{B}_0, h)$ for J -coupled multiplets and $\Delta\gamma(\mathbf{B}_0, h)$ for chemically-shifted systems.

II. The depth of the saddle

The spectrum in the frequency, ω , domain (in $\text{rad}\cdot\text{s}^{-1}$) is given by the Fourier transform of the N complex free induction decay (FID) data points, S_n , acquired at a sampling interval $-\Delta t$,

$$f(\omega) = \Re \Delta t \sum_{n=0}^{N-1} S_n e^{i\omega n \Delta t}, \quad [1]$$

where $\Re$ denotes the real-part operator. The shape of a peak centered at ω_1 , characterized by an exponential decay time T_2^* and acquired for $T_{acq} = N \cdot \Delta t$ at $\Delta f \ll T_2^*$, therefore, is expected to be:

$$f(\omega) = \Re T_2^* \frac{1 - e^{-T_{acq}/T_2^*} e^{i(\omega - \omega_1)T_{acq}}}{1 - i(\omega - \omega_1)T_2^*}. \quad [2]$$

Consequently, the spectrum of the two equal adjacent test lines, ω_1 and ω_2 , *i.e.*, $\Delta\omega = \omega_1 - \omega_2$ apart, is a superposition of the peaks forming a saddle with the depth, d . When the acquisition duration is long, $T_{acq} \gg T_2^*$, the exponents in the numerator vanish and the shapes of the underlying peaks become Lorentzian, as shown in Fig. 1a. The depth of the saddle can thus be estimated as:

$$\begin{aligned} d &= f(\omega_1) - f\left(\frac{\omega_1 + \omega_2}{2}\right) \\ &= \Re \left[\frac{1 - e^{-T_{acq}/T_2^*} e^{+i\Delta\omega T_{acq}}}{1 - i\Delta\omega T_2^*} \right] T_2^* + \left[1 - e^{-T_{acq}/T_2^*} \right] T_2^* \\ &\quad - 2\Re \left[\frac{1 - e^{-T_{acq}/T_2^*} e^{+i\Delta\omega T_{acq}/2}}{1 - i\Delta\omega T_2^*/2} \right] T_2^* \end{aligned} \quad [3]$$

III. The variability of the depth of the saddle

White noise in the measured data manifests itself as uniform variations of spectral amplitudes at all frequencies. The measured depth of the saddle in the presence of such noise is given by the difference of the amplitudes at the peaks and at the saddle, two random and possibly correlated quantities. To derive an estimate of the variability of depth, $\sigma(d)$, we first relate d directly to the measured signal, S_n , using Eq. [1]:

$$\begin{aligned}
d &= f(\omega_1) - f\left(\frac{\omega_1 + \omega_2}{2}\right) \\
&= \Re \Delta t \sum_{n=0}^{N-1} S_n e^{+i\frac{3\omega_1 + \omega_2}{4}n\Delta t} \left[e^{+i\frac{\omega_1 - \omega_2}{4}n\Delta t} - e^{-i\frac{\omega_1 - \omega_2}{4}n\Delta t} \right] \\
&= 2\mathfrak{I} \Delta t \sum_{n=0}^{N-1} S_n e^{+i\frac{3\omega_1 + \omega_2}{4}n\Delta t} \sin(\Delta\omega n\Delta t/4)
\end{aligned} \tag{4}$$

where $\Im$ is the imaginary-part operator. Since d is now expressed as a linear combination of the measured data points, we apply error propagation rules (see Appendix for a full derivation) to obtain $\sigma(d)$:

$$\sigma(d) = \sqrt{2RT_{\text{acq}} \left[1 - \text{sinc}(\Delta\omega T_{\text{acq}}/2) \right]} \tag{5}$$

Here, we used the fact that the standard deviation, σ_0 , of S_n in the real and imaginary receiver channels is proportional to $\sqrt{R/\Delta t}$ where R is an effective resistance of the loaded coil (17). (The temperature and physical constants irrelevant for this discussion are omitted.)

Note that $\Delta\omega$, T_2^* and T_{acq} appear in Eqs. [3] and [5] as dimensionless combinations of $x = \Delta\omega \cdot T_2^*$, and $T = T_{\text{acq}}/T_2^*$. Using these simplifying notations and dividing d (Eq. [3]) by σ (Eq. [5]), we obtain the estimate of the SCNR as a function of the new variables, x and T :

$$\text{SCNR}(x, T) = \sqrt{\frac{x}{2RT\Delta\omega [1 - \text{sinc}(xT/2)]}} \left[\Re \left[\frac{1 - e^{-T} e^{+ixT}}{1 - ix} \right] + 1 - e^{-T} - 2\Re \left[\frac{1 - e^{-T} e^{+ixT/2}}{1 - ix/2} \right] \right] \tag{6}$$

In this expression, the acquisition duration, T_{acq} , is a user selectable parameter whose influence will now be considered. Indeed, if T_{acq} is chosen to be long, then noise from the tail of the FID will dominate the spectrum lowering the SCNR and with it the ability to resolve the lines. If, on the other hand, T_{acq} is made short, the saddle will become shallow (for a fixed $\Delta\omega$) due to the line broadening caused by acquisition truncation, also reducing the SCNR. Therefore, the SCNR will experience its maximum at some intermediate T_{acq} , optimizing the ability to resolve the lines of the pair. If we re-write Eq. [6] to separate pure $\Delta\omega$ and R dependencies as:

$$\text{SCNR}(x, T) = \frac{1}{\sqrt{R\Delta\omega}} g(x, T) \tag{7}$$

where

$$g(x, T) = \sqrt{\frac{x}{2T [1 - \text{sinc}(xT/2)]}} \left[\Re \left[\frac{1 - e^{-T} e^{+ixT}}{1 - ix} \right] + 1 - e^{-T} - 2\Re \left[\frac{1 - e^{-T} e^{+ixT/2}}{1 - ix/2} \right] \right] \tag{8}$$

then the maximum SCNR at which the best spectral resolution is achieved is given by:

$$\text{SCNR}_{\max}(x) = \frac{1}{\sqrt{R\Delta\omega}} g_{\max}(x) = \frac{1}{\sqrt{R\Delta\omega}} \max_T g(x, T) \quad [9]$$

The function $g_{\max}(x)$ is presented in Fig. 2.

IV. The Linewidth

The half-width at half-maximum of spectral peaks in $\text{rad}\cdot\text{s}^{-1}$, $1/T_2^*$, (see Fig. 1a), is the sum of several contributions that can be grouped into three categories (18):

$$\frac{1}{T_2^*} = \frac{1}{T_2^{\text{micro}}} + \frac{1}{T_2^{\text{meso}}} + \frac{1}{T_2^{\text{macro}}} \quad [10]$$

Line broadening on microscopic and mesoscopic length scales due to dipole-dipole interactions, local magnetic field fluctuations caused by molecular vibrations and rotations, blood vessels, inter-tissue boundaries, ferritin deposits, *etc.* (19), as well as the magnet inhomogeneity itself, that cannot be shimmed out (20,21). Their contribution to the linewidth can be modeled by a linear function of $\mathbf{B}_0$ (14,19,22).

Contribution from the macroscopic susceptibility gradients that are induced by large (compared to voxel size) structures such as air-tissue interfaces (6) located outside the voxel also cannot be completely corrected for by the 1st and 2nd order shims found on most commercial imager (8-10). This residual field inhomogeneity can be assumed to be proportional to the voxel size, h (12,23). Since we presuppose that shim technology does not depend on the field strength, this component of the linewidth must, therefore, also be proportional to $\mathbf{B}_0$. Indeed, if we assume for a moment that this is the only contribution to the width and if after shimming we double both the currents within the main field and shim coils (necessarily retaining the shim quality), the linewidth (in $\text{rad}\cdot\text{s}^{-1}$) will also double. Thus, this contribution is proportional to $h\mathbf{B}_0$.

The overall half-width dependence on $\mathbf{B}_0$ and h , therefore, is:

$$\frac{1}{T_2^*} = \frac{1}{\tau} + \chi\mathbf{B}_0 + \kappa h\mathbf{B}_0 \quad [11]$$

which can be viewed as a Taylor expansion of $1/T_2^*$ to the first order in both the field strength, $\mathbf{B}_0$, and the macroscopic intravoxel inhomogeneity, $h\mathbf{B}_0$. The first parameter, τ , measured in seconds in essence represents the intrinsic line width. The second, χ , measured in $\text{s}^{-1}\text{T}^{-1}$ (in units of magnetic susceptibility multiplied by the gyromagnetic ratio) in essence represents the spread of frequencies within a voxel caused by inclusion of magnetically heterogeneous tissues each with its own magnetic susceptibility. The third, κ , measured in $\text{cm}^{-1}\text{s}^{-1}\text{T}^{-1}$ (in units of susceptibility gradient multiplied by the gyromagnetic ratio) in essence describes the shim quality, *i.e.*, the spatial spread of the frequencies due to the residual field gradient.

Since we wish to concentrate on the influence of the field strength and voxel size on the spectral resolution, we assume that τ, χ, κ are $\mathbf{B}_0$ - and h -independent constants of the Taylor expansion determined only by the sample (tissue type, voxel location, *etc.*) and the modern technology, independent of the details of the scanners' manufacturing. In other words, we assume that no

improvement in linewidth is possible for that sample and instrument. While sample and instrumentation contribute their share to these parameters, we are interested in the cumulative effect only described by them. The validity of such first order Taylor approximation can be demonstrated by plotting experimentally measured metabolite line widths versus $\mathbf{B}_0$ with $h=const$ (Fig. 3) and line width versus h with $\mathbf{B}_0=const$ (Fig. 4).

V. Bulk magnetization and partial saturation effects

Several coefficients ignored in the derivation of Eq. [9], will now be reinstated. First, the signal is proportional to the voxel volume, introducing a factor of h^3 . Second, the signal and the sample losses (the dominant noise source at high frequencies) described by the effective coil resistance, R , are both proportional to $\mathbf{B}_0^2$ (24), leading to a linear in $\mathbf{B}_0$ increase in the SCNR. We note that the additional noise produced by the coil electronics becomes increasingly important as the coil becomes smaller or the number of elements in the coil array rises, leading to slower than $\mathbf{B}_0^2$ noise growth. However, such coils do not yield the same SNR performance as the sample-noise dominated ones (25) and thus will not be considered. Third, due to repetitive excitations and signal averaging in MRS, the spin system is in a driven equilibrium. The most reasonable and fair approach, therefore, is to assume that the flip angle is always adjusted to the optimal, Ernst, condition and that repetition time is made as short as possible (15). When the repetition time is less than T_1 , the SNR is nearly a constant given by the duration of the experiment measured in multiples of T_1 (15). Since we wish to compare MRS sessions of the same duration regardless of the field strength or voxel size, a factor of $1/\sqrt{T_1(\mathbf{B}_0)}$ is introduced into the SCNR to account for the $\mathbf{B}_0$ -dependence of the longitudinal relaxation (15).

The T_1 depends on the chemical and physical environment of the spins which is known to vary with tissue type and pathology (14,26). Recent measurements of brain tissue water T_1 s between 0.2 and 7 Tesla indicate that it scales as $\mathbf{B}_0^\alpha$ with α between 0.34 and 0.38 for white matter, gray matter and blood (27). Combining with Eqs. [9] and [11] this yields the final expression for the SCNR per unit time:

$$\text{SCNR}_{\max}(\Delta\omega, \mathbf{B}_0, h) = \frac{h^3 \mathbf{B}_0^{1-\alpha/2}}{\sqrt{\Delta\omega}} g_{\max} \left(\frac{\Delta\omega}{\frac{1}{\tau} + \chi \mathbf{B}_0 + \kappa h \mathbf{B}_0} \right) \quad [12]$$

The signal and thus SCNR is also proportional to the spin density that should be included in Eq. [12] together with the omitted physical constants, sample temperature, transients averaged *etc.* Since we are not interested in the SCNR *per se*, but in setting up the equation for resolution:

$$\text{SCNR}_{\max}(\Delta\omega(\mathbf{B}_0, h), \mathbf{B}_0, h) = \text{threshold} \quad [13]$$

we incorporate these remaining constants into the threshold (another constant) and choose it equal to the $\text{SCNR}_{\max}$ of a chemically shifted pair 0.05 ppm apart at 3 T and $h=1$ cm voxel size. All $\Delta\omega$'s that yield the same or larger $\text{SCNR}_{\max}$ are then defined as “resolved.”

VI. Numerical solution

The final step in computing the resolution dependence on field strength and voxel size is substituting Eq. [12] into Eq. [13] and solving for $\Delta\omega$. In order to emphasize the universality of the solution we first re-write Eq. [12] in terms of dimensionless frequency - $\Delta\Omega = \Delta\omega\tau$, field - $\mathbf{b}_0 = \chi \tau \mathbf{B}_0$ and voxel size - $H = \kappa h/\chi$ as:

$$scnr_{\max}(\Delta\Omega, \mathbf{b}_0, H) = \frac{H^3 b_0^{1-\alpha/2}}{\sqrt{\Delta\Omega}} g_{\max} \left(\frac{\Delta\Omega}{1 + b_0 + H b_0} \right) \quad [14]$$

Then, instead of substituting Eq. [12] into Eq. [13] to obtain $\Delta\omega(\mathbf{B}_0, h)$ and $\Delta\gamma(\mathbf{B}_0, h)$ we insert Eq. [14] which does not contain the sample/hardware-dependent parameters τ, χ, κ , to obtain the corresponding sample/hardware independent resolution functions $\Delta\Omega(\mathbf{b}_0, H)$ for J -coupled doublets and $\Delta\Gamma(\mathbf{b}_0, H) = \Delta\Omega/\mathbf{b}_0 = \Delta\gamma/\chi$ for chemically-shifted systems in dimensionless units. (Note, we defined $scnr_{\max}$ as $scnr_{\max} = \tau^{(1-\beta)/2} \chi^{(4+\beta)/2} \kappa^3 SCNR_{\max}$.) Since the old and new variables differ only by field- and voxel size independent multipliers, the scaling of $\Delta\omega$ and $\Delta\gamma$ with $\mathbf{B}_0$ coincides with the sample/hardware independent scaling of $\Delta\Omega$ and $\Delta\Gamma$ with $\mathbf{b}_0$. The ballpark estimates of τ, χ , and κ are needed to translate the threshold defined by 0.05 ppm at $\mathbf{B}_0 = 3$ T and $h = 1$ cm to their dimensionless counterparts.

We obtain these estimates from published data describing the SNR dependence on magnetic field and voxel size (11,12). Since chemical solutions can be shimmed not worse than *in vivo* samples, we estimate κ using the NAA linewidth in a spherical phantom at 4 T for variable voxel sizes [Table 1 of Li *et al.* (12)] to find $\kappa \approx 2.3 \text{ s}^{-1} \cdot \text{T}^{-1} \cdot \text{cm}^{-1}$. To estimate χ we note (see Eq. [11]) that the slope of the linewidth dependence on the field strength at 1 cm voxels is given by $(\chi + \kappa \cdot 1 \text{ cm})$. Using the average slope of choline, creatine and NAA *in vivo* (see Fig. 3) leads to $(\chi + 2.3 \text{ s}^{-1} \cdot \text{T}^{-1} \cdot \text{cm}^{-1} \cdot 1 \text{ cm}) = 3.4 \text{ s}^{-1} \cdot \text{T}^{-1}$ and thus to $\chi = 1.1 \text{ s}^{-1} \cdot \text{T}^{-1}$. As noted above the data available in the literature suggest that κ may vary from almost zero (28,29) to about twice the value adopted here (30,31) depending on the sample, voxel location and shim quality. In a similar manner, the value of χ varies with the level of blood oxygenation and volume (22) placing its theoretical estimate around $1.45 \text{ s}^{-1} \cdot \text{T}^{-1}$. The estimates of τ , the inverse of the intercepts, are also not universal as evident for example from Figs. 3 and 4. Since, in essence, it reflects the pure line's width, we take $\tau = 0.3$ s. Knowing that the general behavior of spectral resolution does not depend on these choices, the exact values of the parameters become important only when rescaling $\Delta\Omega, \Delta\Gamma, \mathbf{b}_0$ and H to the physical $\Delta\omega, \Delta\gamma, \mathbf{B}_0$, and h in a given practical situation (see Discussion).

Analytic solution of Eq. [13] was not found. In obtaining the numerical one (Figs. 5 and 6) we adopted $\alpha = 1/3$, assuming that in our hypothetical experiment the spins are in an environment similar to that of brain tissue water (see above).

Discussion

Resolution has traditionally been interpreted as relating to the lines' width, $1/T_2^*$, and their separation, $\Delta\omega$ (16). Consequently, Lorentzians more than $2.0/T_2^* \text{ rad} \cdot \text{s}^{-1}$ apart are said to be "resolved," as shown in Fig. 1a. Experimentally, the width (in ppm) of ^1H peaks of the main brain metabolites at a fixed voxel size was found to decrease with increasing field strength from 1.5 to 7 Tesla and could be fit by a power law with an index of -0.28 (11). Within this definition, spectral resolution of chemically shifted systems is thus expected to improve slowly, as $\Delta\gamma \sim \mathbf{B}_0^{-0.28}$ while resolution of the individual peaks of J -coupled doublets is predicted to degrade as $\Delta\omega \sim \mathbf{B}_0^{0.72}$. This scenario, however, is incomplete since it does not take into account the abundance of noise in MRS experiments, as demonstrated in Fig. 1d, where two Lorentzians are irresolvable due entirely to noise. If several transients are averaged for SNR improvement, however, these peaks become progressively more distinct, as seen in Figs. 1c and 1b, even though their intrinsic linewidths or separation do not change, underscoring the important role the noise plays in spectral resolution.

In this report, we employ an operational criterion for resolvability - the spectral contrast to noise ratio. This criterion encompasses linewidth and separation, noise level, $\mathbf{B}_0$, voxel size, measurement duration and other acquisition parameters that influence the heights and widths of peaks. Although the SCNR is a frequency domain quantity, it translates to an equivalent, albeit more complicated, criterion in the time domain due to correspondence between the two made by the Fourier transform, Eq. [1]. In analogy to the SNR threshold in the definition of “sensitivity”, the choice of a SCNR threshold is a metric of confidence that an identified line-pair is not due to a chance fluctuation.

The advent of higher $\mathbf{B}_0$ imagers brought with it great expectation of spectral resolution improvements via two mechanisms (1,5). First, directly, through the increase of the chemical shift dispersion. Second, indirectly, due to increase of magnetization and thus peak heights, which benefit both chemically-shifted and J -coupled lines (28,32). Unfortunately, neither was fully realized, due to the commensurate decrease in T_2^* (2,3,7). This broadening, which is linear in $\mathbf{B}_0$ (in frequency units), can be only partially remedied by shimming due to three factors. First, clinical imagers rarely have higher than 2nd order user-controlled shims. Second, the available ones are of limited power. Third, some of the broadening is due to susceptibility gradients on meso- and microscopic length scales in the tissue, which cannot be shimmed.

Given the above three restrictions and the quantitative criterion for resolution we set out, in this paper, to analyze: (a) What spectral resolution improvement is reasonable to expect at higher fields; (b) given a field, what is the optimal voxel size to extract the most in terms of resolution; or alternatively, (c) given a desired spatial and spectral resolution, what is the best field to conduct the study. To answer these questions we proceeded with a set of hypothetical experiments conducted at different field strengths and voxel sizes: two otherwise identical peaks were made to approach one another in the frequency domain until they could no longer be resolved according to the SCNR criterion. This narrowest frequency separation (in Hz or ppm) represented the best achievable spectral resolution at that field and voxel size. Since we are not aware of a mechanism that can be used to alter either chemical shift or J -coupling for this purpose without affecting peak shape and keeping $\mathbf{B}_0$ and voxel size constant, the results of the experiments are calculated rather than observed. The calculation relies on three well established inputs: (i) the proportionality of the magnetization, induced voltage and noise to $\mathbf{B}_0$, (ii) the linear dependence of linewidth on $\mathbf{B}_0$ and voxel size; and (iii) the increase in longitudinal relaxation time with $\mathbf{B}_0$.

The results of the calculations are presented in Fig. 5 for J -coupled and in Fig. 6 for chemically shifted spin-systems. The full dependence of resolution on field strength and voxel size is shown in panels **a** of both figures. Panels **b** and **c** show sections of the resolution contour plots of Figs. 5a and 6a, made through $\mathbf{b}_0=1.01$ and $H=2.1$, the dimensionless field strength and voxel size. To transform the dimensionless frequency ($\Delta\Omega/2\pi$) to physical frequency in Hz, its value from Fig. 5 is to be divided by the value of τ , the tissue-specific parameter. The dimensionless analogue of the chemical shift distance, $\Delta\Gamma$, from Fig. 6, is transformed into $\Delta\gamma$ (in ppm) by multiplication with the tissue specific χ . The physical voxel size (in cm) is related to the dimensionless H through $h=\chi H/\kappa$ and the field strength (in Tesla) through $\mathbf{B}_0=\mathbf{b}_0/\chi\tau$.

I. The optimal field for a given voxel size

A fixed voxel size is frequently used to study the field dependence of the resolution (1,5,11). Spectral resolution of the components of J -coupled systems first improves and then degrades as $\mathbf{b}_0$ is increased, as shown in Fig. 5b. In the example considered, the optimal $\mathbf{b}_0$ for J -coupled systems is ~ 0.35 allowing to resolve splittings as narrow as ~ 1.2 (dimensionless analogue of Hz). Spectral resolution of chemically shifted systems, on the other hand, improves continuously, at first faster and then slower than the $\mathbf{b}_0^{-0.3}$, as shown in Fig. 6b. Using the plots

in the **b** panels of Figs. 5 and 6 as guides, it is easy to see that sections through the contour plots 5a and 6a at voxel size other than $H=2.1$ will yield new curves exhibiting the same qualitative behavior of the resolution (*i.e.* speed of improvement/degradation) as those presented in Figs. 5b and 6b.

II. The optimal voxel size for a given field

This most common scenario of MRS application is described in Figs. 5c and 6c. For both J -coupled and chemically shifted systems, the spectral resolution first improves and then degrades as the voxel size is increased. In the example considered, the optimal size is ~ 3.2 (dimensionless analogue of cm) for both J -coupled and chemically shifted systems. Using the plots in panels **c** as a guide, it is easy to see that sections of Figs. 5a and 6a at a different field will yield new curves exhibiting the same qualitative features (*i.e.* the existence of an optimal size) as those presented in Figs. 5c and 6c.

Based on these two scenarios, it is apparent that the spectral and spatial resolutions are inextricable. When $\mathbf{B}_0$ is raised, the MR signal increases and the optimal voxel size decreases to mitigate the susceptibility line broadening, as shown in Fig. 7a. Assuming that the voxel size is adjusted to its optimum, the spectral resolution of chemically shifted pairs is shown in Fig. 7b to improve at lower fields faster and at higher field slower than the fifth-root of $\mathbf{B}_0$. The spectral resolution of components of J -coupled doublets, whose splitting is not field dependent, deteriorates approximately as $\mathbf{B}_0^{4/5}$, *i.e.*, slower than linear in $\mathbf{B}_0$, as shown in Fig. 7c. This phenomenon of the spectral resolution to be simultaneously improving for chemically shifted and degrading for J -coupled systems is a simple consequence of the differences in the definitions of the frequency scales (ppm versus Hz) appropriate to describe them and is not specific to the proposed SCNR criterion.

In the calculations we had assumed T_1 to be a slow function of $\mathbf{B}_0$ which adversely affected resolution at higher fields. However, even if longitudinal relaxation is set to be field strength independent (best case scenario: $\alpha=0$ in Eq. [14]), the rate of improvement of the spectral resolution of chemically shifted pairs increases only slightly at the lower $\mathbf{B}_0$'s. The general behavior of the optimal voxel size and resolution with field strength is preserved (compare Figs. 7 and 8). This is probably due to the fact that replacing $\alpha=1/3$ with $\alpha=0$ in Eq. [14] leads to a minor change from $\mathbf{b}_0^{5/6}$ to $\mathbf{b}_0^1$. Thus, T_1 dependence is not a major contributor to the rate of spectral resolution improvement.

In practical applications voxel size and spectral resolution may be dictated by the target anatomy and task at hand, therefore, plots such as Figs. 5a and 6a can be used to assess the required field strength to realize both. To translate the dimensionless quantities of these figures to physical units one needs the values of τ , χ and κ describing the linewidth in the tissue of interest. Since we did not wish to consider improvement of resolution with advances in instrument manufacturing technology, we assumed that these parameters are field and scanner-hardware independent. In practice, κ which describes shim quality may appear to depend on the field strength through the scanner hardware, especially if shim coils of different (higher than 2nd) order are installed. Therefore, a practical approach of estimating the required parameters in a given sample and hardware configuration may proceed as follows:

1. Measure the half-width at half-max of peaks (in $\text{rad}\cdot\text{s}^{-1}$) as function of voxel size keeping the shim currents and thus κ constant. Obtain the values of κ (the slope) and $1/\tau + \chi\mathbf{B}_0$ (the intercept) by fitting the widths to Eq. [11].
2. Repeat step 1 at a different field strength with the same sample.
3. Use the intercepts obtained at the two different fields to calculate τ and χ .

Use the values of τ , χ and κ obtained to translate the dimensionless spectral resolution, field strength and voxel size to the physical units: $\Delta\omega = \Delta\Omega/\tau$, $\Delta\gamma = \chi\Delta\Gamma$, $\mathbf{B}_0 = \mathbf{b}_0/\chi\tau$ and $h = \chi H/\kappa$. Even if the κ 's obtained in the two scanners differ violating the assumption made, the results can still be used. For example, to find the optimal voxel size for one of the spectrometers using Fig. 7 the scaling from the dimensionless H to the physical h should be performed with the κ corresponding to the scanner in question.

The quest for the ultimate sensitivity and spectral resolution in a half an hour or less has been an ongoing struggle in *in vivo* MR spectroscopy. In recent years, the prevalent approach has been to increase $\mathbf{B}_0$ in order to enable the detection of metabolites of relatively low concentrations, whose signal would not exceed an acceptable SNR threshold at lower field strengths, and to resolve them from adjacent peaks. The sensitivity gain provided, however, does not translate into a corresponding increase in resolution even for chemically shifted systems, due to concomitant line broadening. Therefore, sensitivity and thus resolution enhancements achieved with non-line-broadening techniques such as efficient RF coils, sequence design, receivers, shim hardware and shim-algorithms should remain the focus of development even for very highest field scanners (13).

Conclusion

Using spectral contrast to noise ratio arguments we analyzed the dependence of the spectral resolution on magnetic field strength and voxel size. It was found that unlike the substantial increase in sensitivity associated with higher magnetic fields, the spectral resolution of chemically shifted spin systems in biological tissue is predicted to improve but only very slowly, as the fifth-root of $\mathbf{B}_0$. This is due to macro- meso- and microscopic susceptibilities that are intrinsic to heterogeneous tissue and, consequently, cannot be completely shimmed out with macroscopic shim coils, no-matter of what order. Furthermore, high magnetic fields also have a deleterious effect on the ability to resolve the individual components of J -coupled multiplets. Although sometimes graciously referred to in the literature as “spectral simplification” this “smearing” is shown to scale as $\mathbf{B}_0^{4/5}$. It is also shown that spectral resolution, voxel size and $\mathbf{B}_0$ are all interrelated, consequently, nomograms such as Figs. 5, 6 and 7, can be used at the planning stage of the MRS experiment to choose the best field for the spatial resolution, or the optimal voxel for a given field.

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Appendix

Error Propagation

The expression for standard deviation of the depth of the saddle, $\sigma(d)$, (Eq. [5]) is obtained using error propagation rules. Indeed, the depth d is related to the N measured statistically independent complex FID data points S_n through the sum (Eq. [4]),

$$d = \frac{1}{N} \sum_{n=0}^{N-1} S_n e^{+i\gamma n} w_n, \text{ where, } w_n = 2\Delta t \sin\left(\frac{\Delta\omega n \Delta t}{4}\right) \quad [\text{A1}]$$

Denoting $S_{n,re}$ and $S_{n,im}$ the real and imaginary parts of S_n , and since w_n 's are real, using error propagation rules we relate $\sigma(d)$ to the noise of the measured data points, σ_0 :

$$\begin{aligned}
 \sigma^2(d) &= \sigma^2 \left(\sum_{n=0}^{N-1} w_n [S_{n,re} \sin(\gamma n) + S_{n,im} \cos(\gamma n)] \right) \\
 &= \sum_{n=0}^{N-1} w_n^2 [\sigma^2(S_{n,re}) \sin^2(\gamma n) + \sigma^2(S_{n,im}) \cos^2(\gamma n)] \\
 &= \sum_{n=0}^{N-1} w_n^2 [\sigma_0^2 \sin^2(\gamma n) + \sigma_0^2 \cos^2(\gamma n)] \\
 &= \sigma_0^2 \sum_{n=0}^{N-1} w_n^2
 \end{aligned} \tag{A2}$$

This sum is converted to two sums of geometric series by noting that

$$w_n^2 = 4(\Delta t)^2 \sin^2 \left(\frac{\Delta \omega n \Delta t}{4} \right) = (\Delta t)^2 \left[2 - e^{+i \frac{\Delta \omega n \Delta t}{2}} - e^{-i \frac{\Delta \omega n \Delta t}{2}} \right] \tag{A3}$$

Then, execution of these sums for small sampling interval ($\Delta \omega \cdot \Delta t \ll 1$) yields:

$$\begin{aligned}
 \sigma^2(d) &= \sigma_0^2 \sum_{n=0}^{N-1} w_n^2 = \sigma_0^2 (\Delta t)^2 \sum_{n=0}^{N-1} \left[2 - e^{+i \frac{\Delta \omega n \Delta t}{2}} - e^{-i \frac{\Delta \omega n \Delta t}{2}} \right] \\
 &= \sigma_0^2 (\Delta t)^2 \left[2N - \frac{e^{+i \frac{\Delta \omega \Delta t N}{2}} - 1}{e^{+i \frac{\Delta \omega \Delta t}{2}} - 1} - \frac{e^{-i \frac{\Delta \omega \Delta t N}{2}} - 1}{e^{-i \frac{\Delta \omega \Delta t}{2}} - 1} \right] \\
 &\approx 2\sigma_0^2 (\Delta t)^2 \left[2N - 2 \frac{e^{+i \frac{\Delta \omega \Delta t N}{2}} - e^{-i \frac{\Delta \omega \Delta t N}{2}}}{i \Delta \omega \Delta t} \right] \\
 &= 2\sigma_0^2 (\Delta t)^2 N [1 - \text{sinc}(\Delta \omega \Delta t N / 2)] \\
 &= 2\sigma_0^2 \Delta t T_{\text{acq}} [1 - \text{sinc}(\Delta \omega T_{\text{acq}} / 2)]
 \end{aligned} \tag{A4}$$

The $\approx$ indicates where the $\Delta \omega \cdot \Delta t \ll 1$ approximation was made. The last expression leads directly to Eq. [5].

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Fig. 1.

Two underlying Lorentzian peaks (dashed lines) forming a saddle in the resultant spectrum (solid line) are resolved when the saddle can be distinguished from noise fluctuations. As the noise increases to 1, 4, and 9 in **b**, **c**, and **d**, the saddle gets obscured which diminishes the ability to resolve the individual lines of the pair demonstrating the linkage between resolution and the noise.

Fig. 2. The function $g_{\max}(x)$ of Eq. [9]. When the peak separation in units of half-width, x , is small, $g_{\max}(x)$ is negative indicating that no valley is formed. For comparison, the dashed line represents $\sqrt{x/4.5}$ dependence showing that at large separations $g_{\max}(x)$ approaches the square root.

Fig. 3.

In vivo full width at half maximum (in Hz) of ^1H peaks of the main brain metabolites versus field strength (in Tesla) measured using fixed, $h=1\text{cm}$, voxel size. (Adopted from (11), Fig. 9a.) The straight lines present linear fits with intercepts of 1.82, 2.07, 1.28 Hz and slopes of 1.02, 1.06, 1.17 Hz/T for NAA, creatine and choline respectively.

Fig. 4.

In vivo full width at half maximum (in Hz) of the creatine peak versus voxel size (in cm) at fixed, 3 Tesla, field strength. (Adopted from (30), Table 2.) The straight line presents a linear fit with the intercept of 0.74 Hz and the slope of 5.26 Hz/cm.

Fig. 5.

a: Contour plot of the spectral resolution $\Delta\Omega=\Delta\omega\tau$ (dimensionless analogue of frequency in Hz) as a function of static field, $b_0=\chi\tau\mathbf{B}_0$, and voxel size, $H=kh/\chi$, for components of J -coupled doublets in dimensionless units.

b: Dependence of the spectral resolution on magnetic field strength, for a fixed, $H=2.1$, voxel size (section through the contour plot **a** at $H=2.1$). For comparison, the dashed line represents the $b_0^{0.7}$ dependence.

c: Dependence of the spectral resolution on voxel size for a fixed $b_0=1.01$ (section of contour plot **a** at $b_0=1.01$). Note the presence of an optimal voxel size for the field (marked with the arrow).

Note, that to transform the dimensionless analogue of frequency $\Delta\Omega/2\pi$ to the physical frequency in Hz, the value of $\Delta\Omega/2\pi$ is to be divided by the value of the tissue specific parameter τ . The voxel size in cm is related to the dimensionless H through $h=\chi H/\kappa$ and the field strength in Tesla through $\mathbf{B}_0=b_0/\chi\tau$.

Fig. 6.

a: Contour plot of the spectral resolution $\Delta\Gamma = \Delta\gamma/\chi$ (the dimensionless analogue of the chemical shift in ppm) as a function of static field, $b_0 = \chi\tau B_0$, and voxel size, $H = \kappa h/\chi$, for chemically shifted spin systems in dimensionless units.

b: Dependence of the spectral resolution on magnetic field strength for a fixed, $H=2.1$, voxel size (section through the contour plot **a** at $H=2.1$). For comparison, the dashed line represents the $b_0^{-0.3}$ dependence.

c: Dependence of the spectral resolution on voxel size for a fixed $b_0=1.01$ (section of contour plot **a** at $b_0=1.01$). Note the presence of an optimal voxel size for the field (marked with the arrow).

Note, that the dimensionless analogue of chemical shift distance $\Delta\Gamma$ is transformed to $\Delta\gamma$ in ppm by multiplying it with a tissue specific χ . The voxel size in cm is related to the dimensionless H through $h = \chi H/\kappa$ and the field strength in Tesla through $B_0 = b_0/\tau$.

Fig. 7.

a: Optimal voxel size as a function of b_0 from 0.3 to 10.

b: Spectral resolution of chemically shifted spin systems as a function of b_0 assuming optimal voxel size, compared with $b_0^{-1/5}$ dependence (dashed line). Note that improvement in spectral resolution is *much* slower than linear in b_0 .

c: Spectral resolution of J -coupled spin systems as a function of b_0 for an optimal voxel size. For comparison, the dashed line represents a $b_0^{4/5}$ dependence. Note that resolution deteriorates slightly slower than linear in b_0 .

Fig. 8.

Same as Fig. 7 but assuming the most optimistic (for spectroscopic resolution) case when T_I does not depend on $\mathbf{B}_0$ ($\alpha=0$). The general behavior is the same as in Fig. 7.