

Magn. Reson. Discuss., author comment AC1
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Reply on RC1

Jamie Guest et al.

Author comment on "Signal-to-noise ratio in diffusion-ordered spectroscopy: how good is good enough?" by Jamie Guest et al., Magn. Reson. Discuss.,
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We are grateful to both referees for their helpful comments and for noting several errors.

An important problem in DOSY is how well differences in diffusion coefficient can be resolved. In older literature, a "rule of thumb" can be found stating that (in case of nonoverlapping signals and good signal-to-noise ratios) the diffusion coefficients have to differ by at least 30% to be distinguished, but the reality is of course more complex.

This statement is a little confused. In the limit of good SNR and no overlap, differences in D as small as 1% can be distinguished in practice. The 30% figure is commonly quoted as the resolution limit for biexponential fitting where signals are overlapped, although at very high SNR signals of comparable intensity can be resolved with somewhat smaller differences (Anal Chem 78, 3040).

This work presents a very welcome quantitative assessment of how the signal to noise and sampling of gradient strengths affect the diffusion resolution. These new insights can indeed help practitioners to assess beforehand whether it will at all be feasible to resolve different molecules in the diffusion dimension, using for instance also tools to predict diffusion coefficients (based on molecular weight, by the same research group).

I do have some questions that the authors may wish to clarify or consider commenting on.

The final equation (13) illustrates that in practice improving the diffusion resolution by increasing the signal-to-noise ratio has its limits. The same equation seems to suggest that an increase in the number of gradient values N , rather than increasing the number of transients, could indefinitely improve the diffusion resolution. Figure 2 indeed shows no deviation from the linear behaviour of RD as a function of $\sqrt{(N-1)}$. Do the authors think that in reality there is also here a limit to be reached, for instance due to gradient hardware limitations, or environmental changes as a function of time or gradient strength?

There are two points at issue here. First, the analysis in this manuscript specifically excludes the influence of such systematic errors, which will indeed impose limits on diffusion resolution. Second, Fig. 2 only describes the effect of spectral noise on diffusion resolution. As is explained later in the manuscript, random and pseudorandom perturbations of the measured signal intensity from other sources, for example pulse irreproducibility, do indeed also limit diffusion resolution. The effect of these random and pseudorandom perturbations averages out with increasing N just as the effect of noise averages out with increasing time averaging. What is left in the limit of infinite numbers of scans and of gradient values is the effect of systematic error. In this unattainable limit, and with no complications such as peak overlap, conventional DOSY processing would lead to diffusion peaks with finite widths, determined by the systematic deviation of the measured data from the Stejskal-Tanner equation used, but always at the same apparent D .

The value of SNR_{lim} in equation (13) appears to be determined by systematic errors in signal intensity, which, besides hardware and environment fluctuations, will probably depend on the pulse sequence used. The authors rightly mention that in general more rfpulses

in the sequence or additional unwanted coherence transfer pathways will result in

more systematic 'noise'. I wonder if SNR_{lim} , which can be determined experimentally in the

way described in the paper, could serve as a means to compare the performance of

various DOSY pulse sequences, comparing it to, for instance, the value measured for the oneshot sequence on the same spectrometer and sample?

It is important to distinguish here between systematic and experimentally reproducible sources of error (e.g. gradient non-uniformity) and irreproducible random or pseudorandom sources of error (e.g. gradient noise, pulse irreproducibility). This manuscript deals with the latter: the former is a different can of worms, and has been addressed elsewhere (including the references by Connell et al and Damberg et al.). The limit imposed by SNR_{lim} derives from random/pseudorandom variations in signal intensity; it could be used in comparing pulse sequences, but the choice of what sequence to use in a given context also depends on a range of other factors.

Figure 2 shows that the data points obtained for low values of N (10 (black) and 17 (grey)) deviate somewhat more from the fitted curve than all the other data points. Does this imply that equation (13), combined with equation (11) and Table 1, approximates reality less well for lower values of N?

That is correct.

Some further technical comments that should be fixed:

In equation (3), the gradient shape factor for half-sine shapes, $(2/\pi)^2$, has been forgotten.

To be clarified on revision. [Bruker's Topspin software, which is used for almost all acquisitions using half-sine pulses, defines an effective gradient $G_i = G_{max}(2/\pi)$]

Equation (5), expression for B, shows t_i before the exponent. I guess this should be ϵ_i .?

To be corrected on revision.

There are problems with the references. Some citations in the main text do not feature in the reference list (I spotted Brihuega-Moreno 2003, Franconi 2018, Reci 2020 and Power 2016 to be lacking). The reference to Mehlkopf et al. lacks the title.

To be corrected on revision.