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Reply to RC2

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., https://doi.org/10.5194/mr-2021-52-AC2, 2021

We are grateful to both referees for their helpful comments and for noting several errors.

In this article, Guest et al. analyse the effect of the signal to noise ratio in diffusion-ordered

NMR spectroscopy (DOSY), and provide guidelines on a choice of sampling

strategy (number of gradient increment, maximum attenuation, SNR) that provides good

accuracy. The paper is very well written and contains a number of interesting and useful

explanations on DOSY. The main message is enlightening and important for users of the

method. I recommend publication in Magnetic Resonance, after the following minor points

have been addressed.

It would be useful to clarify what is meant by “accuracy” in the text. Sometimes the word

refers to systematic errors only, sometimes to a combination of systematic and random

errors (https://en.wikipedia.org/wiki/Accuracy_and_precision). Here the latter seems to

be used, but this would need to be explicit.

This is not straightforward. The diffusion dimension of a DOSY spectrum plots an estimated probability distribution of values of D: each resonance has a Gaussian peak centred on the estimated diffusion coefficient with a width determined by the estimated standard error obtained in the fitting process. Viewed simply, the width of the diffusion peak is thus a measure of its experimental precision, and the difference between the peak

position and the true D is a measure of its accuracy - just as is illustrated in the figure on the Wikipedia page. On a strict view, however, the difference between the peak position and the true D in the absence of systematic error is purely a reflection of the precision of the estimate of D obtained by fitting: if a large number of DOSY experiments were performed, all perfect apart from the effect of noise, the accuracy would be infinite (the average of the estimated D values would converge on the correct value). The ambiguity arises because of the nature of the DOSY display. We took the pragmatic view that while it is a loose usage, accuracy, in the ISO sense of trueness, is the more helpful word for readers. To be clarified on revision.

The conclusion reads "a trivial calculation will show both whether or not such experiments are worth attempting in the first place, and what limiting diffusion resolution is achievable". Does this calculation require knowledge of SNR_lim? How can this quantity be determined?

SNR_lim is not needed to determine, using Eq. (11), whether it is possible for a given experiment under otherwise ideal conditions to achieve sufficient SNR in the time available to give the diffusion resolution required. A more sophisticated calculation, using Eq. (13), would show whether instrumental limitations would impose a more restrictive limit, but this would require experimental characterisation of the effects of instrumental irreproducibility.

To be clarified on revision.

It would be useful to have guidelines on what to do in a fixed total experimental time. Is it better to increase the number of gradient increments, or the number of averaged scans? In which cases? The answer lies in the proposed equations, but this is so frequent a question that it may deserve a specific discussion. For example, it seems from Eq. 13, that increasing N will always increase accuracy, while increasing SNR is only useful up to a certain limit. Is it the case that one should increase N only as soon as the number of scans is sufficient for phase cycling purposes and peak detectability ?

The short answer is that in the case analysed in this manuscript (no systematic errors), increasing SNR will only be useful up to a limit set by N, and increasing N will only be useful up to a limit set by SNR, but that there is no limit to the accuracy obtainable by increasing both N and SNR. The long answer is that of course systematic errors play a crucial role in limiting DOSY, and that in choosing experimental parameters there are many other factors to be taken into account (expected range of D, the desirability of being able to detect multiexponential decay, the variation of signal irreproducibility with signal

amplitude, the effect of B_1 inhomogeneity, the effects of electrical nonlinearity of the gradient circuitry and spatial nonlinearity of the gradients applied, …). The question of optimum sampling strategy is beyond the scope of this manuscript, which deals purely with the effect of SNR. (See also the reply to the first point raised by Referee 1).

Overall, while all the tools are provided to guide readers in the choice of appropriate parameters, the usefulness of the paper would be increased by the addition of a practical example.

Figures 3 and 4 provide this.

The "inverse of the coefficient of variation" is introduced as "a convenient measure of resolution". This choice should be justified. In spectroscopy, resolution or dispersion is usually quoted on an absolute, not a relative scale. Why use a relative scale here ?

This is straightforward. In the diffusion dimension, unlike the spectral dimension, linewidths scale with D. A 1% error in a D of 1 x 10–10 m2/s has a tenth the impact of a 1% error in a D of 10 x 10–10 m2/s. This is (partly) why when DOSY spectra are conventionally plotted, with D increasing from top to bottom, the linewidths in the diffusion dimension also tend to increase from top to bottom.

In Eq. 4, the half sine shape seems to be accounted for in Deltaprime, but not in the gradient area.

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

In Eq. 5, shouldn't a sum symbol be used instead of an integral symbol?

It certainly should! To be corrected on revision..

Also in Eq. 5: what is the variable t_i ? From Franconi et al., it should be espilon_i ?

To be corrected on revision.

I could not find the reference to Reci et al. and Franconi et al. in the manuscript

To be corrected on revision.