

We thank the editor for the insightful clarifications and comments to our submission. Please see responses to each point below. Editor comments are in bold.

1. Open data

Magnetic Resonance has quite a forward policy with respect to open data (https://www.magnetic-resonance-ampere.net/policies/data_policy.html). This aspect was key when MR was created and should be followed as much as possible. As a consequence, “available upon request” is not acceptable for MR.

The ideal case would be for you to post your matlab code, pulse sequence and parameters as well as raw NMR data in a well-managed open repository where these elements would be given DOIs. These DOIs would then be mentioned in the final version of your manuscript.

If this is not possible, the Matlab code and pulse sequence with parameters should be published alongside the article as supporting information.

We have deposited all of the NMR data (including acquisition parameters, processing scripts, and pulse sequences), Matlab codes used for simulations, and MALDI-TOF data into the open repository Zenodo where it was assigned a DOI (<http://doi.org/10.5281/zenodo.4730836>). We have updated the Code and Data Availability section of the paper:

“Code and Data Availability. All NMR data including acquisition parameters, pulse sequences, and NMRPipe processing scripts, Matlab codes, and MALDI-TOF data are available for download from Zenodo at <http://doi.org/10.5281/zenodo.4730836> (Marincin et al., 2021).”

A citation to the open-repository data has been included in the references:

“Marincin, K., Pal, I., and Frueh, D.: Using delayed decoupling to attenuate residual signals in editing filters [Data set], Zenodo, available at: <http://doi.org/10.5281/zenodo.4730836>, last access: 30 April 2021.”

We have removed both instances where we have mentioned that simulation codes or pulse sequences are available upon request.

2. Formatting

Equations are sometimes written in a surprising way: why is $2\pi J/2$ not written πJ ? Also, $1/2J$ is understandable but ambiguous, the ideal would be $1/|2J|$ but $1/(2J)$ would already be much better. This should be done in the text and in Figure 2c.

In Figure panels 2e and 2f, there should be units for Delta, for instance as 1 s / (2·150).

We thank the editor for clarifying this formatting issue. We have simplified the $2\pi J/2$ on page 5 to:

“i.e. for a two-spin system on resonance $\omega_0 = \pm \pi J$, and R is a transverse relaxation...”

and on page 8 to:

“...the simulation is only performed on resonance such that $\omega_{0\alpha} = \pi J$ and $\omega_{0\beta} = -\pi J$.”

To answer your question: the notation $2\pi J/2$ simply reflects that the P.I. did too much teaching, when he delineates the conversion to rad/s (2π) from the frequency offset for a 2-spin system ($\pm J/2$ when on resonance).

We have also implemented the suggested notation for every instance of fractions that involve scalar-coupling:

“...in which decoupling is applied after a time $\tau = 1/|2J|$ and assume...” (p. 5)

“...in the example we discussed, τ is set to $1/|2J|$, our objective is to...” (p. 7)

“...applying decoupling is kept at $\Delta = \Delta_{\text{prep}} + \tau = 1/|2J|$, where Δ_{prep} is...” (p. 7)

“... τ takes the values $1/|2J|$ (when Δ_{prep} is zero), $1/|4J|$, and $1/|8J|$.” (p. 7)

“...when decoupling is applied before reaching $1/|2J|$, a residual positive in-phase signal is detected, whereas a negative in-phase signal emerges passed $1/|2J|$.” (p. 7)

“...when Δ exceeds the optimal value of $1/|2J|$.” (p. 7)

“...on resonance for delays Δ slightly exceeding $1/|2J|$, ...” (p. 7)

“...the value of τ selected through visual inspection typically exceeds $1/|2J|$ as signal suppression appears more efficient at those values than at $1/|2J|$.” (p. 7)

“...that the length of each block in our pulse sequence is maintained to $1/|2J(NH)|$ so as to permit...” (p. 12)

The figure has been updated to include units in panels 2(e) and 2(f), as well as correcting the fractional J-coupling notation used on panel 2(c) (see updated figure in latest paper version). The caption to Figure 2 has been updated to:

Figure 2. Principles of editing through delayed decoupling. (a) Applying decoupling once coherences are antiphase truncates their FID and attenuates their signals (dashed line), as shown here for the isolated component of a doublet. (b) The two components

combine into a broadened and attenuated shape (dashed line). The analytical expressions of Eqs. (2) (solid grey line) and (4) (dashed black line) were used in (a) and (b). (c) Further attenuation is obtained when evolution into antiphase coherences is shared between a preparation period and detection as shown through simulations. The total evolution, Δ , was set to $1/2J$, with evolutions during detection $\tau = 1/2J$ (dashed line), $1/4J$ (dotted line), and $1/8J$ (solid line). In (a)-(c), spectra without delayed decoupling are shown in grey for reference. (d) Simulation where the duration Δ is arrayed for a fixed preparation period $\Delta_{\text{prep}} = 1/4J$, and τ ranges from zero to $3/4J$ leading to $\Delta = 1/J$ in ten increments $\Delta\tau$ of $3/40J$. This simulation predicts the results seen in Fig. 4(b). In (a)-(d), J is set to 120 Hz. (e) A delayed decoupling targeting 150 Hz leads to residual positive in-phase signals for spins with couplings at 120 Hz. (f) A delayed decoupling targeting 120 Hz leads to negative residual in-phase signals for couplings at 150 Hz. In (e) and (f), $\Delta_{\text{prep}} = 1/4J$ and τ is set to $1/4J$ for the targeted J , i.e. half of the total duration Δ .”

The caption to Figure 3 has been updated to include:

“The delays in the X_{J1} and X_{J2} filter blocks are: $\delta_3 = 1/4 J(\text{NH}) \approx 2.78 \text{ ms}$, $\delta_1 = 1/4 J1(\text{CH})$, $\delta_4 = 1/4 J2(\text{CH})$, $\delta_2 = 1/4 J(\text{NH}) - 1/4 J1(\text{CH})$, and $\delta_5 = 1/4 J(\text{NH}) - 1/4 J2(\text{CH})$.”

On line 233, I believe 10.008 Hz should be 10.008 kHz.

We thank the editor for catching this mistake. We have corrected this sentence to:

“The field strength of the DIPSI-2 TOCSY mixing sequence was 10.008 kHz and...”

3. Two points worthy of a discussion?

On page 9, you mention that 7 Hz line broadening was used. Given the expected line shape for IS pairs with scalar couplings above the target scalar coupling (i.e. Figure 2f), I wonder how much of an effect this can have by smoothing out these residual peaks.

You are right to highlight that 4(b) differs from 2(d) (and 2(e) or 2(f)) in part due to apodization, the other effect being overlap. Note that all signals report on CH systems with about the same scalar coupling, and hence optimal attenuation is obtained for the same value of τ , which leads to the spectrum in black in figure 4(b). At this value all residual signals appear as the orange curve in 2(f) (or the blue curve in 2(e)) and there are no residual sharp peaks. However, as you rightly pointed out, the appearance of the array is indeed different from that in 2(d) due to smoothing. We added a sentence to attract the attention of the reader to those aspects.

“The differences between the line shapes of Figs. 2(d) and 4(b) reflect signal overlap and apodization.”

We have also updated the text in Section 3.3 to expand on the use of line broadening:

“All 1D spectra were zero-filled to 4096 points before Fourier transform and subsequently apodized using exponential multiplication with 7 Hz broadening to reduce truncation artefacts from buffer signals.”

You present here the use of delayed decoupling in a fully filtered experiment, which is a perfectly legitimate and useful experiment. However, isotope filters are often run to detect intermolecular transient NOEs in experiments that are part isotope filtered and part isotope edited. In the common case where the isotope filter is performed before the NOE mixing time, I wonder if and how delayed decoupling could be used for an evolution in an indirect time dimension instead of detection.

We thank the editor for this insightful comment. Indeed, our immediate objective is to improve filtering methods in the detected dimension, notably to get 1D filtered spectra, and we focus exclusively on this objective in the current manuscript. We do have a solution to incorporate delayed decoupling in indirect dimensions. However, we have not yet tested this solution. Further, some methods already exploit evolutions during indirect dimensions to improve filtering, and we have not tested whether delayed decoupling would even be needed for these experiments.

We have included language to emphasize our focus on filtering in the detected dimension. For example:

“Many methodologies have been implemented to filter signals from labeled molecules in direct or indirect dimensions, reviewed in (Breeze, 2000; Robertson et al., 2009). As our immediate objective is to obtain 1D proton spectra of unlabeled moieties, we do not consider methods that exploit evolutions in indirect dimensions and here, we focus solely on filters for the detected dimension.” (p. 4)

“Here, we present a method to attenuate undesired signals in the detected dimension that escaped traditional filters with minimal increase in the length of the pulse sequence.”
(p. 4)

“Inclusion of delayed decoupling in the detected dimension of a sequential tuned filter removes spurious signals with minimal costs in sensitivity...” (p. 15)

“As an immediate application, we show enhanced suppression of undesired PCP1 signals when X_d is incorporated into the direct dimension of a sequential X-half-filtered 2D TOCSY experiment (Fig. 5).” (p. 15)