REVIEWER REPORT on "Radiation damping strongly perturbs remote resonances in presence of homo-nuclear mixing sequences"

GENERAL IMPRESSION: A very interesting paper, which should be revised somewhat to gain even more impact.

- *Does the paper address relevant scientific questions within the scope of MR?*

Yes, the paper addresses an interesting experimental effect of radiation damping on remote resonances in spin lock experiments. It may also offer a clue for the physical reason phasing problems often encountered in biomolecular NMR experiments in aqueous solution involving TOCSY-type coherence transfer, although the author does not mention this and is maybe not aware of it.

- *Does the paper present novel concepts, ideas, tools, or data? All submitted papers are assumed to report on new observations and/or new theory; there is no need to draw attention to the novelty in title, abstract, or conclusions.*

Yes the concept is new and has to my knowledge not been reported earlier.

- *Are substantial conclusions reached?*

Yes, but (as mentioned above) there may be even more to it than the author reveals.

- *Are the results sufficient to support the interpretations and conclusions? Is the description of experiments and calculations sufficiently complete and precise to allow their reproduction by fellow scientists with reasonable effort? Detailed technical and graphical explanations and documentation of limited file size can be provided as supporting information. Access to raw data, processed spectra, and other experimental data must be provided by depositing in a publicly accessible repository or archive as far as practically feasible, and the DOI provided in the article. Hardware developments need to be documented by photos or equivalent drawings (blueprints with precise dimensions if possible). New software must be accompanied by user instructions. New software should be open source and access to it provided through a software repository if possible.*

The experiments are clearly described. The formulae and symbols are clearly explained. However, it is not clear to me, how exactly the simulation was done. It appears that an "ideal spin lock" was simulated not the actual DIPSI pulse sequence used. But that is more from reading "between the lines". It would be beneficial to provide the simulation code in a Supplementary Information document.

Some questions remain open, which might at least be addressed in the discussion: Influence of relaxation times, e.g. a solvent with a long T2 like acetone, the importance of the type of the mixing pulse sequence (planar mixing vs isotropic).

What the effect be for a non-selective excitation pulse?

Does the imaginary component of RD, which causes tuning and polarization dependent phase shifts (Torchia(2009): DOI:10.1007/s10858-009-9363-6), have an influence on the effects observed under spin-lock conditions? What is the offset dependence, in theory and in practice.

- *Are numerical data accompanied by error estimates with a description of the methods used to obtain these estimates?*

There are no error estimates given, but in the pertinent context addition of error estimates would not add much to the impact and scientific value of the paper.

- *Do the authors give proper credit to related work and clearly indicate their own new/original contribution?*

The papers quoted are adequate. In my detailed comments below, I suggest a few additional references.

- *Does the title clearly reflect the contents of the paper?*

In principle yes. But, as only one mixing sequence is used in the paper I suggest to drop the last word of the title.

- *Does the abstract provide a concise and complete summary?*

The abstract is very short. It uses the term “inductive coupling”, which is not occurring anywhere else in the text (where the term “inductive backaction” is introduced). I’d suggest to use the term from the abstract also in the text. Again there is the plural “sequences” but only one sequence is used in the experiments.

- *Is the overall presentation well-structured and clear?*

Yes, except for the two problems mentioned above (what exactly was simulated; do the results also apply to other mixing sequences).

- *Is the language fluent and precise?*

Yes.

- *Should any parts of the paper (text, formulae, figures, tables) be clarified, reduced, combined, or eliminated?*

See my detailed comments to the figures. Figures 5 and 6 should be combined into one figure with four panels.

- *Are the number and quality of references appropriate?*

See detailed comments in the detailed comments.

- *Is the amount and quality of the supporting information and supplementary material appropriate?*

A supplementary file should be added, see comments in the detailed comments below.

DETAILED COMMENTS:

P.1
Title:
Actually only a single sequence is being used in this paper, so "sequences" should be dropped from the title

Abstract:
use “inductive coupling” also in the main text
avoid “sequences”, se above

Figures in general:
In most figures the light colors are too light, some lines too thin, please improve the presentation.

Figure 1:
the text label colors should match the graphical elements they refer to.

Figure Caption 1:
use the symbols from the figure in the caption:

RD field ω_R

water magnetization M^{H2O} ..

p.2 li17:
„if it is homogeneous in space, as with any RF field“
It is not clear to what this refers, RF-fields can be inhomogeneous

p.2 li18:
The importance of the quality factor Q should also be mentioned here

p.2 li19:
“partially- or non-deuterated solvents“
maybe better to use something like “highly protonated solvents (at thermal polarization levels)”; as there are solvents without any hydrogen which would also classify as non-deuterated

p.2 li20-25:
A more recent paper describes the interference of solvent RD with small partially overlapping peaks: Schlagnitweit et al. doi: 10.1002/cphc.201100724

p.2 li34: better use “variants of the TOCSY experiment” or similar

p.2 li39: a smaller pulse angle might help to reduce RD effects during the direct detection

p.2 li40: It would be interesting to know the influence of different types of mixing sequences (planar vs. isotropic)

p.3: Fig.2 needs to be improved, in particular the this lines in d and e

Figure 2, caption li.5:
The use of the word "tune" in this context is unusual, use "adjust" or "control"

Figure 2, caption li.10: T2 relaxation losses will also increase due to the additional delays; "Carrier frequency" applies to which pulses?

p.3 li 46: It is not clear to what extent the particular mixing sequence was simulated. The simulation code should be published in a Supplementary Information file or deposited.

p.2 li 48: I'd insert a "First," at the beginning of the section.

p.3 li 51: "relaxation-induced decay" → "decay owed to relaxation" (induce implies some „active" role)

p.4 Fig.3: Suggestion: name the two graphs two panels a and b instead of left and right

Showing the full range of n_M values could be instructive (maybe in the Supplementary Info)

p.4 li57: if → assuming
"water longitudinal" → "longitudinal water"

p.4 li66: The data should be shown in the Supplementary Info

p.4 li68: "…shows the result of an identical experiment, except that the carrier frequency has been moved to the solvent resonance…"

→

"…shows the result of an experiment, where the carrier frequency has been moved to the solvent resonance, and the amplitude of the selective Gaussian pulse has been increased in order to overcome RD effects during this pulse, so that the solvent magnetization is rotated in the xy-plane, while all other parameters wer unchanged." But maybe it would be better to split that long sentence.

Fig.4-6: Combining the three figures into one with 6 panels a,b,c,d,e,f is recommended.

p.5 Fig.4: the "black crosses" are hardly resolved

p.5 Fig.4 caption li.2: "varied" → "was varied"

p.5 Fig.4 caption li. 3: "complete saturation": As the state is reached by a 90° pulse, one should not call it saturation.

p.5. Fig. 5 caption: How was the RD rate "estimated"?

p.5 li. 70: …rotated to… → …rotated into…

It's not clear what the following sentence means: "Here, the z-component of the magnetization must be detected without changing the phase of the receiver for the different scans." Probably the phase cycle is different as the coherence pathway has been changed. More details should be discussed in that paragraph. "Clearly, effects of the RD field are also observed in the latter experiment." is not sufficient.

p.6: The theoretical approach is presented clearly, except for the fact that there is no explanation of how the particular spin lock pulse sequence was taken into account. One might also introduce definitions of eqs. 4 and 5 before eq.1.

p.7 li96ff: The estimation of the RD rate might be better via a small flip angle or a spin noise experiment. For short T2 a separate determination of T2 under non-RD conditions may be required for correction.

More recent papers elaborating on the differences in probe tuning under receive- and pulse-conditions by Pöschko et al., which might be relevant here: DOI:10.1002/cphc.201402236 (2014) and partially also relevant: DOI:10.1038/ncomms13914 (2017)

"The decay of the experimental curves is not only due to relaxation but also to RF inhomogeneities: the precession frequency of the DSS signal varies slightly with the ~~the~~ RF amplitude, while the evolution of the z component is even more sensitive (simulations not shown)."

Please show those simulations in the supplementary information.