Response to Reviewers for "Optimally controlled NMR in electrochemistry: Larmor and nutation frequency selective spin excitation for locally selective NMR experiments"

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Note for the Editor

We thank the Editor for considering our manuscript for publication in the journal *Magnetic Resonance Copernicus*, and the reviewers for their valuable comments that they have provided us with. In the current revision, we have addressed the comments made by the reviewers.

We were especially pleased that the reviewers appreciated our writing and presentation of the work, and that they recommended it for publication after revisions. Therefore, we believe that the revised version of the manuscript meets the criteria for publication in the journal *Magnetic Resonance Copernicus*.

We report below a detailed point-by-point answer to the reviewers' comments. As a convention, text in *italic black* is original text written by the reviewers. The text quoted from the article is:

- normal text if unchanged compared to the original version,
- green if added in the revised version,
- ~~strikethrough red if deleted (no longer in the revised article)~~.

We also attach a LatexDiff version, titled 'main-diff.pdf' of the manuscript with modifications with respect to the previous version marked.

1 Reviewer 1

The paper describes the use of OC generated selective pulses in frequency and nutation space for use in electrochemical cells. It demonstrates the performance of such pulses on a phantom sample containing two different liquids between copper plates and PEEK plates. The two lines are clearly shifted in frequency space and also in the nutation space. I think the paper is suitable for MR but the presentation is sometimes confusing and should be improved.

Response: We thank the reviewer for their concise summary of our work and in particular for their extensive review of the draft as well as their detailed and productive comments. We worked actively to improve the presentation, to make the text easier to read, and to highlight the key messages more clearly (see following responses for details).

1. I am not an expert on OC pulses so I cannot judge how demanding the generation of such pulses is. My impression is that this is quite standard and that the application to electrochemical problems is the new part. My expectation from the title and the first reading och Chapter 2.1, I expected the pulses to be simultaneously selective in frequency and nutation space. The title says "Larmor and nutation frequency selective pulses". After a more careful reading, I think now that these are frequency selective pulses that are tolerant to deviations in the nutation frequency and nutation selective pulses that are insensitive to changes in the resonance frequency. If this is correct, I think this should be made clearer in phrasing of the title and the text. Later on, the paper always talks about B_0 selective or nutation-frequency selective pulses. I just realized that the phrasing in the SI is much clearer: B1-robust selective excitation within ±500 Hz in a ±2000 Hz suppression band" and "Larmor frequency-robust selective excitation for 0% artificial nutation frequency increase". It would be nice if the phrasing in the main text and title would reflect that precision of the SI. By the way, I think the use of the term "B_0 selective" pulses is not a good choice since B_0 by definition is the same everywhere. I think it would be good to use a different term here like resonance frequency selective pulses.

Response:

The reviewer is correct. Neither ν_0-, nor ν_1-tailored pulses, nor the combination are new in the NMR optimal control community as we detailed in the Introduction. So far, B_0 and B_1 field distortions due to metallic components have mostly been considered in order to minimize and compensate for them. The new aspect presented in our work, is exploiting the B_1 distortions near electric conductors to achieve spatial and ultimately surface selectivity for in operando electrochemical catalysis applications while accounting for B_0 distortions, too.

We agree that the phrasing in places was not clear about which frequency (or field inhomogeneity) the respective pulses are robust or sensitive to. We revised the text (and title) with respect to this point. In particular, we included an additional paragraph at the beginning of the Results and Discussion section and rephrased the subtitles.

We consistently replaced B_0-selective/-robust with ν_0-selective/-robust, and analogously for B_1 and ν_1, to characterize the pulses.

Action:

We revised the title and sections of the text.

Revised Paragraph:

New title: Optimally controlled NMR in electrochemistry: Larmor ~~and~~ versus nutation frequency selective spin excitation for locally selective NMR experiments

Results and Discussion

QOC pattern pulse design is capable of providing either selectivity or robustness with respect to both ν_0 and ν_1 independently. Each variation is useful for certain applications. Selectivity with respect to the Larmor frequency allows for selective measurement of specific spin species, which enables solvent suppression or the suppression of other dominating bulk signals to increase sensitivity with respect to minority spin species. In contrast, ν_0 robustness facilitates quantitative, phase-stable measurements despite B_0 inhomogeneities. Robustness with respect to the nutation frequency ν_1 allows for the uniform, quantitative excitation within an electrochemical cell despite B_1-distorting metallic components. On the other hand, ν_1 selectivity potentially promises to enable spatial selectivity to B_1-distorting metallic surfaces.

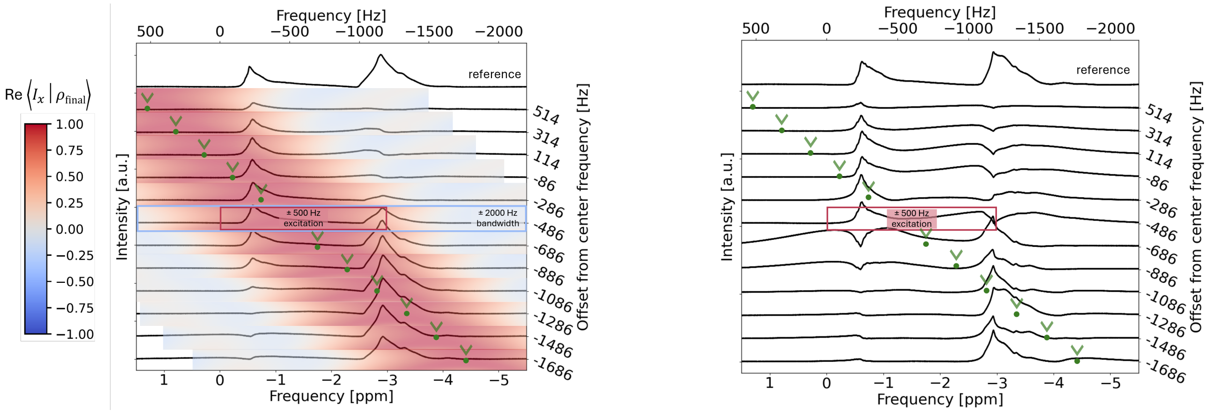
With electrochemical applications in mind, we discuss in the following ν_1-robust, ν_0-selective pulses, which will enable efficient solvent suppression even in the presence of B_1-distorting electrical conductors. Secondly, we demonstrate ν_0-robust, ν_1-selective excitation in order to achieve spatial selectivity in proximity to electrical conductors independent of their B_0-distorting effects.

2. I was wondering how much the improvement of these pulses are compared to "standard" frequency band selective pulses like BURP pulses (H. Geen, R. Freeman, J. Magn. Reson. 93 (1991) 93–141) or nutation-frequency selective pulses in the rotating frame (K. Aebischer, N. Wili, Z. Tosner, M. Ernst, Magn. Reson. 1 (2020) 187–195) that also have some inherent nutation or frequency frequency bandwidth. Can the authors comment, please, how important the simultaneous optimization for both parameters is for this application?

Response:

The results based on GRAPE-optimized QOC pulses were compared against E-BURP pulses on a freshly constructed model setup. The superior performance of the QOC approach is illustrated in a comparison of two waterfall spectra (analogously to

Figure 3 and 4), detailing the application of QOC (a) versus E-BURP (b) pulses. Figure (a) shows again an efficient excitation within the selective bandwidth of the QOC pulse and a suppression of resonances outside of this bandwidth. While the E-BURP pulses in Figure (b) also manage to provide decently selective excitation of *n*-dodecane, its suppression when selectively exciting H_2O is less efficient. Additionally whenever selectively exciting *n*-dodecane, its peak shape seems to be affected uncontrollably, while E-BURP pulses never affect the peak shape of H_2O. Finally, the application of E-BURP pulses heavily distorts the baseline for some resonance frequency offsets. The most important individual spectra of the experiments (on-resonance pulses for *n*-dodecane and H_2O) were summarized in Figure S28 and added to the SI.



(a)

(b)

We assume that the poorer performance of E-BURP lies indeed in the lack of robustness against nutation frequency deviations, as strong residuals appear predominantly when attempting suppression of the signal associated with the Cu cavity. The BURP excitation pulses as originally published by Geen and Freeman (1991), therefore, seem to be only suited for Larmor-frequency selective measurements with unperturbed B_1, since suppression of the signal associated with the PEEK cavity was still satisfactory. In summary, the robustness against nutation frequency deviations enabled with QOC pulses provides a drastic improvement in selectivity for measurements in the vicinity of conductive surfaces.

Further reasons for using GRAPE over BURP regard pulse length. Pulses optimized in a Fourier basis tend to require longer pulse durations τ due to less flexibility in the pulse shape. For example, an excitation band of ±500 Hz around the irradiation frequency, as used in our paper, corresponds to a BURP-1 pulse length of 4 ms according to the BURP-1 design rule $0 \leq \nu_{\text{exc}} \leq 2/\tau$. Since GRAPE can optimize pulses with arbitrary shape within the piecewise-constant treatment, a shorter pulse duration of 1 ms was sufficient, while providing robustness against nutation frequency deviations on top. Shorter pulse durations are crucial for future applications in the electrochemical context. In particular, in operando applications and their temporal resolution depend critically on the duration of the individual pulse sequence as well as the selectivity and efficiency of the excitation (and suppression), as the latter one impacts how many repetitions have to be conducted to achieve a reasonable signal-to-noise. Furthermore, relaxation or dephasing may be enhanced in the vicinity of electrodes, which leads to broad lines. Having excitation pulses that are as short as possible to achieve a required selectivity is crucial to minimize the T_2 or $T_2^\star$ weighting effects. In addition, GRAPE-optimized pulses can have multiple excitation bands, which might find applications for CO_2 reduction producing various different solvated products in low concentrations, such as CO, methanol, ethanol, formic acid, etc.

Nutation-frequency selective inversion pulses in the spin-lock frame as published by Aebischer et al. (2020) can be adapted for excitation experiments. Again, we chose GRAPE due to its flexibility. For example, the nutation frequency band targeted by the pulses in the spin-lock frame is defined by the pulse length. In GRAPE, the parameters can be tuned more freely. Furthermore, GRAPE-optimized pattern pulses can excite multiple nutation frequency bands, which may be required in future experiments, as both increases and decreases in B_1 intensity have been observed in the proximity of conductive surfaces.

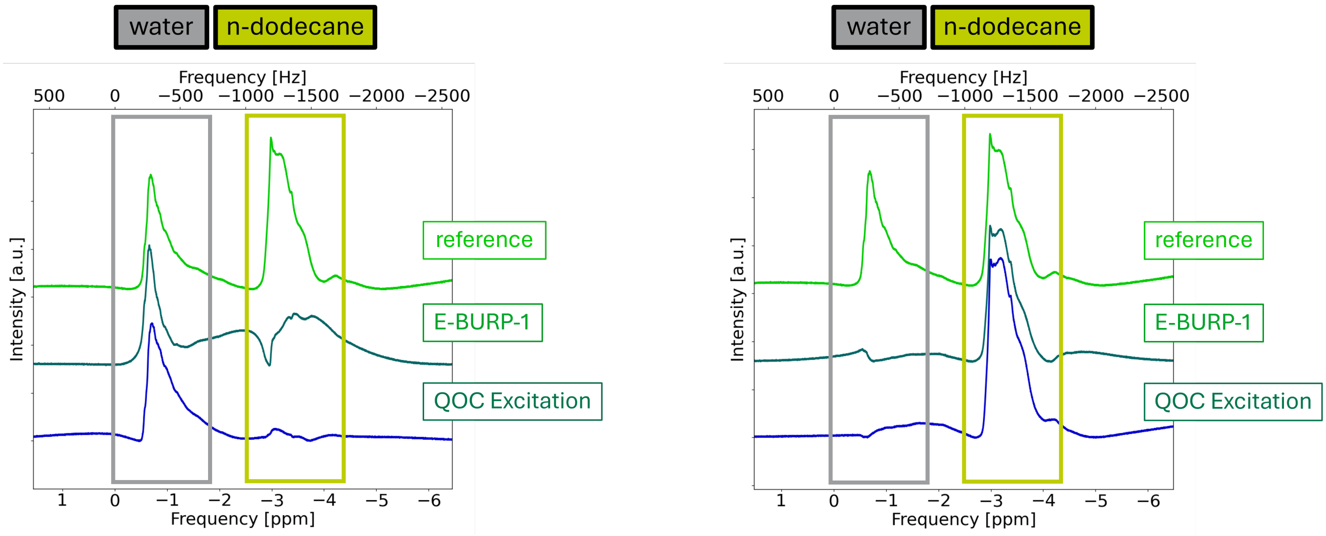
Simultaneous optimization for both Larmor frequency and nutation frequency might become relevant for future spectroelectrochemical experiments with more complex sample mixtures, as well as more sophisticated electrochemical cells or conductive interface properties. Combinability of both parameters has been shown in the original work on pattern pulses (Kobzar et al., 2005).

Action:

Testing of E-BURP pulses and additions in introduction, conclusion as well as in the SI.

Revised Paragraph:

New figure:



(a)

(b)

Figure S28: ^{1}H spectra recorded utilizing a ν_0-selective QOC excitation pulse (1 ms) versus an E-BURP-1 pulse (4 ms) with a selective excitation range of 2.5 ppm (±500 Hz). The top spectrum depicts the reference ^{1}H spectrum recorded using a hard pulse. Hereby, the resonance at approx. -3.3 ppm is assigned to *n*-dodecane and the resonance at approx. -0.8 ppm to H_2O. The pulses were applied on-resonance for either H_2O (a) or *n*-dodecane (b). The selective excitation of *n*-dodecane is achieved to a similar degree with both pulses, while the selective excitation of water is less efficient when using the E-BURP-1 pulse. The E-BURP-1 pulse is observed to distort the spectrum baseline and excites the *n*-dodecane resonance to a significant degree. The shift in frequencies with respect to previous measurements (other figures) originates from a severe drift of the magnet in the meantime.

Introduction

The rf modulation impedes the effectiveness of established selective pulse sequences such as BURP, which are not optimized for systems with inherently distorted B_1 fields Geen and Freeman (1991).

Conclusion

To support this claim, a comparison of QOC excitation pulses and E-BURP pulses on the herein presented model setup was undertaken (SI Fig. S28). The comparison evidently visualized, that when using literature-known ν_0-selective pulses without ν_1 robustness for electrochemical setups, baseline distortions and unsatisfactory selectivity may occur due to strong B_1 field distortions near conductive cell components. Furthermore, the B_1 field distortions ~~near conductive electrochemical cell components~~ in the model setup were accurately predicted by FEM and integrated into a QOC workflow to tailor pattern pulses which exploit the simulated sharp B_1 enhancement near conductive interfaces.

3. A second more general point is the use of the term "quantum optimal control" for the generation of the pulses. What is "quantum" about the optimal control methods used to generate pulses on a classical computer? I realize that "quantum" is very trendy and sells well but I really think that "optimal control" would be sufficient here.

Response: The term “quantum optimal control” indicates that the equations of motion which are integrated during the optimization process are quantum mechanical. The method of “optimal control” is not bound to quantum mechanical problems, but is also applied in engineering and economics. Thus, the specification of “quantum optimal control” is not trivial and the term has been in use in the quantum control scientific community since at least the 90s (Zhu and Rabitz, 1999). It is true that within the magnetic resonance literature mainly the term “optimal control” has been used. But we argue that even within the field of magnetic resonance, this distinction is warranted, considering that optimal control can be applied to both the classical Bloch equations and quantum master equations.

4. The presentation of the results in Figs. 3 and 4 using double color coding of the spectra and the background is not easy to understand and interpret. Would it not be much simpler to plot the theoretical excitation profile over the spectra with a little arrow or dot indicating the irradiation frequency. What is especially grating is the fact that the color coding on the right goes to -1 but is in reality never smaller than 0.

Response:

We replaced the double color coding with an additional y-axis specifying the accurate frequency offset. Furthermore, a green dot and arrow now mark the irradiation frequency of each measurement. We decided against removing or changing the color gradient for the excitation profile. First, it depicts clearly that the transition from excitation to suppression is not instantaneous but continuous in behavior, despite the distinct transition from excitation to suppression specified for the QOC optimization. Second, we did not change the limits of the color bar. The light blue coloring of certain areas show, that the theoretical x-magnetization does go into the negative range (about -0.1). Furthermore, the physical limits of the theoretical x-magnetization are given by $[-1, 1]$ defining the limits of our color bar.

Action:

We revised the figures in question.

Revised Paragraph:

Results and Discussion

The revised Figure 3 and the corresponding text excerpt are shown as an example. The other figures and excerpts were revised accordingly.

Here, $\Delta\nu_0$ was varied with a step size of 200 Hz between 2975 Hz and 775 Hz (marked with a green dot and arrow), with the excitation centered on either the resonance of H_2O at $\Delta\nu_0 = 2375$ Hz or on the resonance of *n*-dodecane at $\Delta\nu_0 = 1375$ Hz.

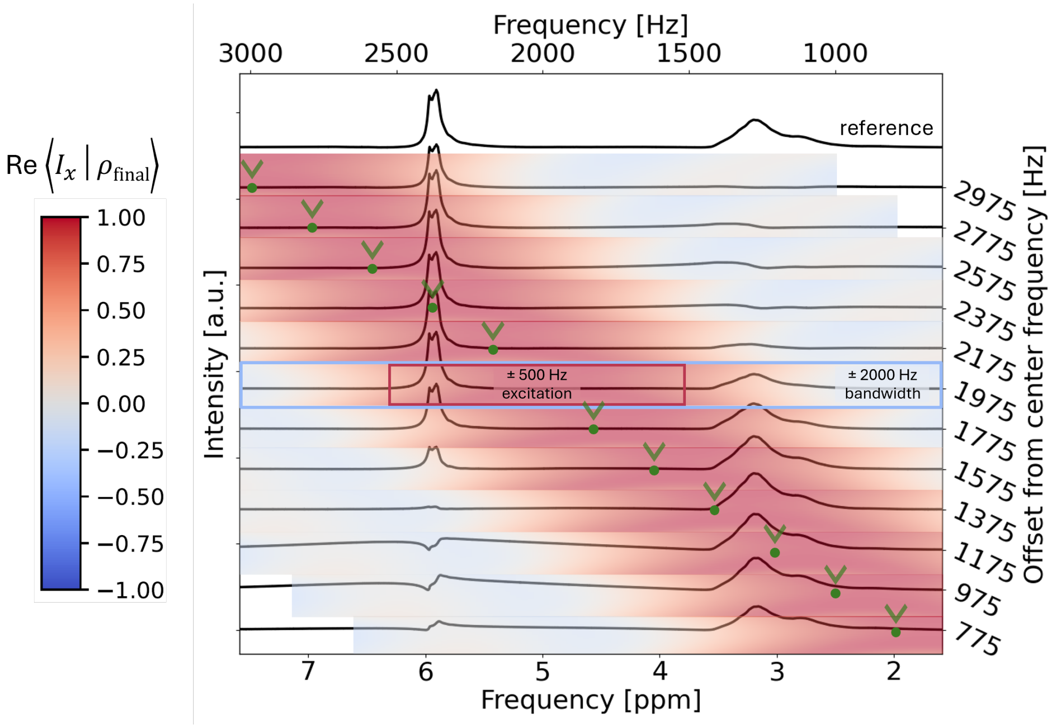


Figure 2: ^{1}H spectra recorded utilizing a ν_0-selective excitation pulse with a selective excitation range of 2.5 ppm (±500 Hz), $1\ \mathrm{ms}$ duration, and a total frequency range of $4000\ \mathrm{Hz}$ applied at different $\Delta\nu_0$ (marked with green dot and arrow). The top spectrum depicts the reference ^{1}H spectrum recorded using a hard pulse. Hereby, the resonance at approx. 3 ppm is assigned to *n*-dodecane and the resonance at approx. 6 ppm to H_2O. The spectra recorded with QOC pulses are underlaid with colour gradients representing the theoretical x-magnetization $\mathrm{Re}\langle I_x|\rho_{\text{final}}\rangle$, normalized to a range $[-1,1]$, after applying the QOC pulse at each particular $\Delta\nu_0$. Selective excitation is achieved for the on-resonance pulses with $\Delta\nu_0 = 2375$ Hz for H_2O and $\Delta\nu_0 = 1375$ Hz for *n*-dodecane.

5. Fig. 2 and text: Why use ppm for the frequency axis if the ppm are meaningless. I think here a Hz scale would be much more meaningful since also the selectivity of the pulses was specified in Hz. (applies also to Figs. 3,4 and 7)

Response:

We added a second x-axis, too, for simultaneous ppm and Hz labeling. The unit ppm is the standard, relative unit for NMR spectra and Hz is more in focus here, since the pulses are optimized for specific absolute frequencies in Hz.

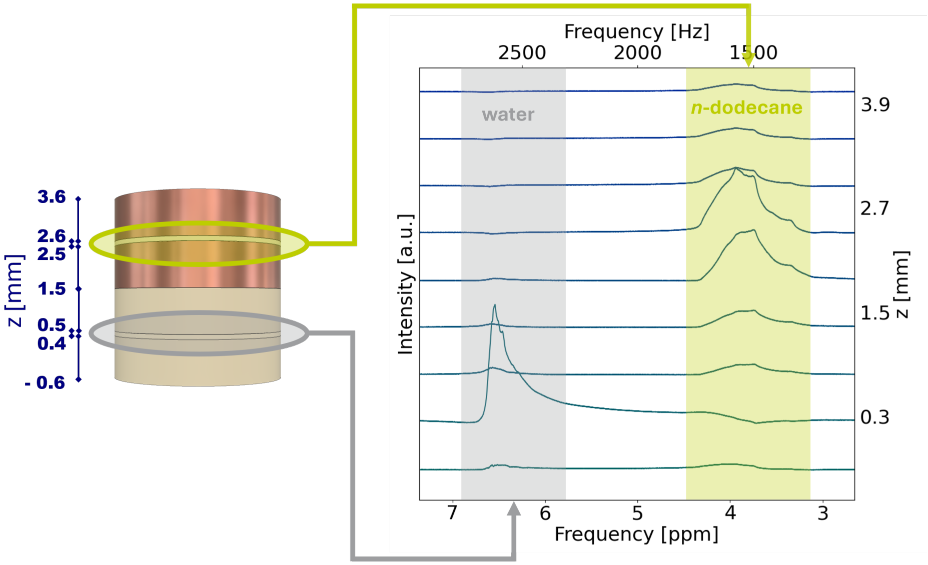
Action:

We revised the figures in question.

Revised Paragraph:

Experimental Methods and Simulations

The revised Figure 2 is shown as an example. The other figures were revised accordingly (see question 4).



6. Fig. 2: Add a z scale to the drawing on the left to make the mapping from the drawing to the plot of the spectra clearer. Maybe even scale the drawing and the spectral plot such that the scale is the same.

Response:

Thanks for pointing out the shortcomings of the figure. We have revised it.

It becomes obvious when comparing the z-axis of the phantom setup and the spatially encoded chemical shift imaging, that the signals of n-dodecane and H_2O are not restricted to the 0.1 mm corresponding to the copper and PEEK cavities respectively. We hypothesize, that the presence of the solvent signals outside of the z-coordinates associated with the cavities might originate from one of the following reasons. First, the solvents could obviously leak out of their cavities despite their immiscibility. Second, the magnetic field distortions due to the copper do not only impact B_0 and B_1, but naturally also the applied gradients for spatial resolution, hence corrupting the mapping of resonance frequency to spatial coordinate.

Action: We revised the figure in question.

Revised Paragraph:

See question 5.

7. Maybe Figures 1 and 2 could be combined in a single figure that contains all the details.

Response:

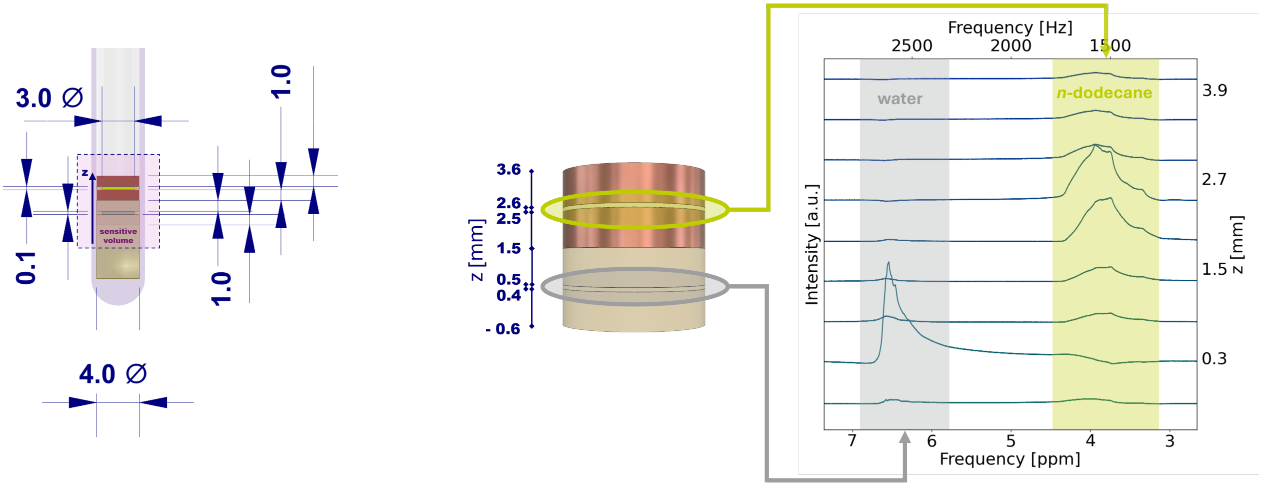
We agree with the reviewer that Figure 1 and 2 could be combined. We merged the figures and added some details that help with the clarity of the figure.

Action:

We combined the figures in question by omitting the old figure 1b and adding a few details to the new figure 1. All later figure descriptions were adjusted accordingly

Revised Paragraph:

Experimental Methods and Simulations



(a)

(b)

Figure 1: Sectional side view of experimental setup inside a shortened standard 5 mm NMR tube with cell dimensions given in mm (a) and 3D illustration of setup ~~inside a shortened standard 5 mm NMR tube~~ with a spatially-encoded chemical shift imaging of H_2O and *n*-dodecane in between the double coins (b). The cavities each have a diameter of 3 mm and a height of 0.1 mm. The coins each have a diameter of 4 mm and a height of 1 mm. The NMR-sensitive volume for homogeneous excitation is marked by a pink hue. The spatial position of the liquids can be differentiated on a scale of about half a mm.

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