

Dear Professor Levitt,

We are pleased to submit a revised version of our manuscript, “Scalable Modeling of Multi-Spin Ensembles in SABRE Hyperpolarization: A Symmetry-Based Framework for Zero and Ultralow Fields.” We sincerely thank the reviewers for their careful evaluation of our work and for their insightful suggestions, which have helped us improve the quality and clarity of the manuscript.

In response to the reviewers’ comments, we have made the following revisions:

1. We now explicitly discuss the cases in which the proposed symmetry-based reduction is not applicable and summarize the necessary conditions for the Hamiltonian, relaxation superoperator, and initial conditions (lines 350–365).
2. We clarify that, for large-scale high-field simulations, state-space reduction is implemented using the Spinach software package, and we have added the appropriate references (line 355).
3. Figure 2 has been revised to provide a more detailed and illustrative representation of the proposed symmetry-based reduction.
4. We have added a new subsection entitled “Benchmark and Scalability Analysis” to demonstrate the scalability of our approach in the worst-case scenario, namely systems composed entirely of non-equivalent spins. Correspondingly, Figure 10 has been included.
5. We have cited an important recent publication (DOI: [10.1039/D5CP01773D](https://doi.org/10.1039/D5CP01773D)), which first introduced Zero-Quantum reduction for SABRE. In addition, we have revised the wording in the Introduction to better define the scope of our work (lines 45 and 75).

We hope that the revised manuscript is now clearer and meets the high standards of Magnetic Resonance Discussions.

Sincerely,

Dr. Danil A. Markelov

## Reviewer #1

We thank the reviewer for their thorough and insightful feedback, which we greatly appreciate. Let us respond point by point.

- 1) The manuscript is carefully prepared and has no obvious errors. However, in its current detailed form, it is not always clear under which conditions the reduction of the Liouville space to a subspace is valid, and more importantly under which circumstances this approximation may break down. Clarifying these limits of applicability would strengthen the work.

We thank the reviewer for this remark. We agree that this point should indeed be clarified: the reduction is valid provided three conditions are met:

1. The Hamiltonian commutes with the z-projection of total spin, i.e.,  $[H, F_z] = 0$ ;
2. The initial density matrices of the free substrate (S) and the SABRE complex (C) commute with their respective  $F_z$  operators, i.e.,  $[\rho_C(0), F_{Cz}] = 0$  and  $[\rho_S(0), F_{Sz}] = 0$ ;
3. The relaxation superoperator conserves the coherence order.

Strictly speaking, these conditions can be satisfied at arbitrary magnetic field strengths, for example at 10 T or at 1  $\mu$ T. However, they are not met in the presence of transverse RF fields, in which case  $[H, F_z] \neq 0$  and our assumptions no longer hold. Our approach is particularly valuable for ZULF rather than for high-field applications, because under ZULF conditions, where microtesla fields enable strong coupling between heteronuclei and protons, nontrivial “spontaneous” dynamics (i.e., without RF pulses) can occur. This point will be clarified in the revised version of the manuscript.

- 2) Furthermore, the manuscript appears to focus primarily on ZULF NMR, although the authors suggest that the proposed methodology could be applied more broadly. It would therefore be beneficial to elaborate on how this approach could be extended to high-field NMR experiments, where, for example, the equivalence of methyl and methylene groups might also be exploited.

We thank the reviewer for this thoughtful comment. As noted in our previous response, our approach is not suitable for high-field applications because conventional high-field NMR experiments typically rely on RF pulses to induce nontrivial spin dynamics, which violates the conditions under which our reduction is valid. For high-field NMR simulations of multi-spin systems, the well-established SPINACH package (Kuprov, I. (2018). Large-scale NMR simulations in liquid state: A tutorial. *Magnetic Resonance in Chemistry*, 56(6), 415–437) provides an excellent framework. In the revised version of the manuscript, we will clarify that our approach is specifically intended for low-field regimes.

- 3) In this context, the authors should also reference prior efforts aimed at simplifying spin dynamics calculations through permutation symmetry. Relevant examples include, but are not limited to, the work of I. Kuprov (<https://doi.org/10.1016/j.jmr.2007.09.014>) and S. I. Doronin (<https://doi.org/10.1134/S1063776111130036>).

We thank the reviewer for bringing these important references to our attention. These are excellent works related to the SPINACH package, and we will certainly cite them in the revised version of the manuscript.

- 4) Finally, a minor point - line 410 appears to be missing an important reference and should be corrected.

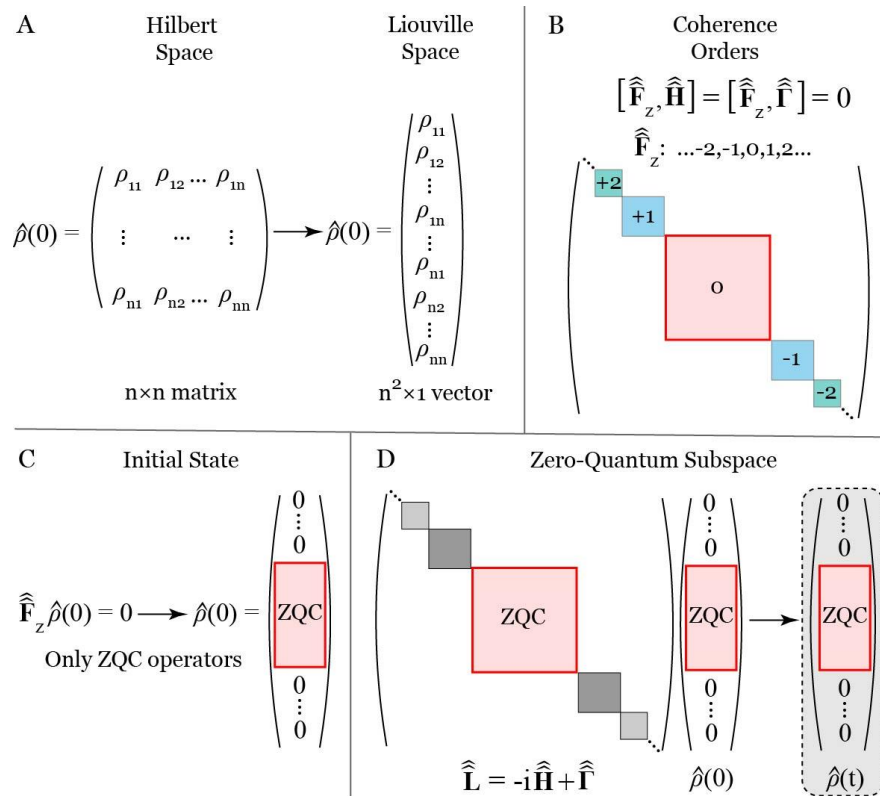
We thank the reviewer for pointing this out. Indeed, a relevant reference was inadvertently omitted, and this will be corrected in the revised version of the manuscript.

## Reviewer #2

We sincerely thank the reviewer for their thorough and thoughtful engagement with our work. The reviewer has clearly delved deeply into the manuscript, and we greatly appreciate the insightful comments and constructive suggestions, which we find very valuable for improving the quality of our paper. Below, we provide a point-by-point response.

- 1) In particular, additional schematic figures illustrating the structure of the basis states, the relevant coherence pathways, and how the dynamics evolve within the reduced Liouville space would significantly broaden the readability of the manuscript. Figure 2 goes in this direction, but in its current form it remains too minimal to effectively guide the reader through the underlying physics.

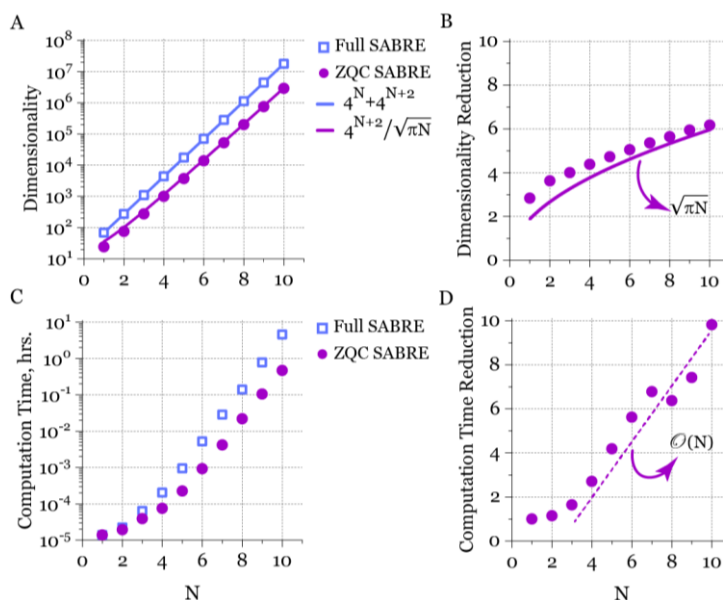
We thank the reviewer for this valuable suggestion. We agree that a more detailed graphical illustration would significantly improve the accessibility of the material. In the revised version of the manuscript, Figure 2 will be replaced by the figure shown below. We believe this enhancement will help guide the reader through the underlying physics and improve the overall clarity of the manuscript.



- 2) Another aspect, admittedly not straightforward to quantify in general, that would strengthen the manuscript is a more explicit discussion of computational scaling. Providing, where possible, estimates of computational cost as a function of the number of spins and of the relaxation model would enhance the practical relevance of the work and allow a clearer assessment of the advantages over full Liouville-space simulations.

We thank the reviewer for this very useful remark. Inspired by this comment, we decided to add a subsection presenting a direct benchmark between the full and reduced approaches. As noted

in line 340 of the original manuscript, the asymptotic reduction in matrix size scales with the number of spins as  $\sqrt{N}$  when  $\sqrt{N} \gg 1$ . Furthermore, we now demonstrate that while the reduction in memory scales as  $O(\sqrt{N})$ , the computational cost scales as  $O(N)$ . A corresponding figure illustrating this scaling will be added to the revised version of the manuscript. We believe this addition will significantly enhance the practical relevance of our work and provide a clearer assessment of the advantages offered by our approach over full Liouville-space simulations.



As for the dependence on the relaxation model, we note that our approach is compatible with most relaxation models relevant to NMR, with the exception of CSA relaxation in the absence of axial symmetry (as noted in line 255 of the manuscript). Consequently, the choice of relaxation model does not substantially affect the qualitative conclusions regarding computational scaling or the validity of the reduction. For the purposes of our benchmark, we consider the random fluctuating fields model to be representative, as it captures the essential features of relaxation while maintaining compatibility with our symmetry-based framework.

- 3) Finally, it would be important to better position the present work within the existing literature. A closely related numerical framework has recently been presented at Euromar 2025 in Oulu (FI) and published (DOI: 10.1039/D5CP01773D), where Liouville-space reduction is achieved not only through symmetry considerations of the Hamiltonian and superoperators, but also by explicitly exploiting molecular symmetry and incorporating a dipolar (non-random field) relaxation model. In that case, the reduction emerges naturally from both the spin system topology and the underlying physical relaxation mechanisms, rather than from symmetry arguments alone.

We thank the reviewer for bringing this excellent and closely related work to our attention. Indeed, the authors propose a very similar approach also based on zero-quantum (ZQ) reduction, and we will certainly cite it in the revised manuscript. We also note that molecular symmetry is already incorporated in our simulations, as we treat methyl and methylene groups in terms of total spin, which directly reflects the underlying molecular symmetry. This point will be clarified in the main text to improve readability and better position our work within the existing literature.

**The full list of changes is as follows:**

1. **Line 10, abstract** - the wording has been revised:  
*This symmetry-based reduction yields a scalable framework for efficient simulation of multi-spin SABRE systems, allowing the treatment of arbitrary spin ensembles, including those containing  $^{15}\text{N}$ ,  $^{13}\text{C}$ ,  $^1\text{H}$ , and other nuclei.*
2. **Line 45** — the wording has been revised:  
*Consequently, the development of a general and scalable framework for such multi-spin ensembles remains a significant challenge. Motivated by this, we present here a complementary approach to recent efforts (Mamone et al., 2025), leveraging symmetry to render the full Liouville-space treatment computationally tractable for complex SABRE systems.*
3. **Figure 1** — the font size has been increased and the graphical elements have been regrouped.
4. **Line 75** — the wording has been revised and the relevant reference has been added:  
*The relevance of the ZQC subspace for SABRE dynamics has recently been recognized (Mamone et al., 2025). Building on this insight, we develop a general and scalable computational framework based on a systematic reduction to the ZQC subspace, ...*
5. **Line 90** — it has been clarified that the model is not limited to ultralow fields:  
*However, the framework presented below is not restricted to this regime; chemical shifts can be incorporated straightforwardly without modifying the theoretical description.*
6. **Lines 100–105** — the role of molecular symmetry in the theoretical model has been emphasized:  
*We assume a group  $G_P$  of  $P$  equivalent spins, reflecting the underlying molecular symmetry, such as the three protons of a methyl ( $\text{CH}_3$ ) group or the two protons of a methylene ( $\text{CH}_2$ ) group.*
7. **Lines 165, 190, 200, 250, and 255** — references to Figure 2 have been added to illustrate the proposed symmetry-based reductions.
8. **Figure 2** — has been updated to better guide the reader through the theoretical framework.
9. **Lines 350–365** — now summarize the conditions necessary for the symmetry-based reduction.
10. **Line 420 (Eq. 58)** — a typo has been corrected.
11. **Line 425** — a missing reference has been added.
12. **Line 465** — benchmarking analysis has been introduced.
13. **Table 1** — a typo in the caption has been corrected.
14. **Figure 6** — a figure updated (horizontal lines  $y = 0$  are added to demonstrate the sign change of the polarization).
15. **Lines 560–570** — a new section entitled “Benchmark and Scalability Analysis” has been added.
16. **Figure 10** — a new figure has been included.
17. **Line 585** — the conclusions have been expanded to include results from the scalability analysis.
18. **Line 735** — a typo has been corrected.
19. **Lines 790, 840, and 855** — additional references have been added.