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Excitation of Delocalized Long-Lived States in Aliphatic Protons at Low and High Magnetic Fields - Sebastiaan Van Dyck, Coline Wiame, Kirill F. Sheberstov, and Geoffrey Bodenhausen

Replies to Reviewers.

Reply to Reviewer 1: Professor Danila A. Barskiy (Reviewer's comments are in black. Our reply in green)

Van Dyck, Wiame, Sheberstov, and Bodenhausen present an interesting study on monochromatic SLIC-based excitation of delocalized long-lived states in several molecules, with experiments performed at both low (1.4 T) and high (11.7 T) magnetic field. I found the manuscript valuable and timely, and in my opinion it is suitable for publication in Magnetic Resonance after the authors have considered the points below.

The manuscript focuses on monochromatic SLIC throughout. Since the optimization already involves varying v1, I wonder whether the authors could briefly comment on why adiabatic passage spin order conversion (APSOC) was not considered. APSOC may offer greater robustness with respect to B1 inhomogeneity, so even a short discussion of the rationale for choosing monochromatic SLIC would strengthen the presentation.

APSOC has been implemented and proven effective in the past at high magnetic fields for 2 spin systems. We added references to this approach in the revised manuscript and also mentioned its limitations. The main limitation of APSOC when applied to magnetically inequivalent geminal protons in aliphatic chains is that it cannot be performed in a polychromatic manner. Even though in this paper we restrict our considerations to monochromatic SLIC implementation, it is possible to apply SLIC to several CH_2 groups simultaneously, and by doing so, either increase the excitation yield (in molecules with 2 CH_2 groups) or, in the case of molecules with more than 2 CH_2 groups, it is possible to excite different long-lived states and coherences. Keeping these perspectives in mind, we have not yet explored using APSOC at low magnetic fields (such as 1.4 T).

I was also unsure how to interpret Fig. 5 quantitatively. It would be helpful if the authors stated explicitly whether the figure shows an absolute LLS conversion efficiency or a quantity normalized to a reference value. Related to this, what is the maximum achievable monochromatic SLIC efficiency under ideal conditions for spin systems containing more than two spins? In such systems the conversion efficiency is not necessarily expected to reach 100%, and I believe a short clarification would be useful for the reader.

We thank the reviewer for noticing this issue. Indeed, the normalization factor was not mentioned, and it might be confusing. The figure shows the LLS conversion efficiency normalized to 1 with respect to the high-field regime, which is achieved at the plateau on the right-hand side of the figure. Maximum conversion efficiency in the aliphatic spin networks for 4 spin systems for monochromatic SLIC applied to AA' spins is achieved when a full population of the $T_{+1}^{AA'}T_0^{XX'}$ or $T_{-1}^{AA'}T_0^{XX'}$ state is transferred to $S_0^{AA'}S_0^{XX'}$ state. This corresponds to ±5/72 ≈ 7% population imbalance between the 9 triplet-triplet states and a unique singlet-singlet state.

Regarding lines 96–100, I would suggest a more careful wording. Strictly speaking, the couplings themselves are not "strong" or "weak" in isolation; rather, the relevant distinction is whether the differences in precession frequencies are large or small compared with the corresponding couplings. This terminology is straightforward in homonuclear cases, but becomes less applicable in the presence of heteronuclei inequivalently coupled to nuclei of interest.

We suggest the following rephrasing:

As previously reported [Sonnefeld et al., 2022a, Sonnefeld et al., 2022b], the Hamiltonian of a 4-spin AA'XX' system at high magnetic fields (in this work at 11.7 T) only features strong couplings between the geminal pairs (e.g., H_A couples strongly to $H_{A'}$), but not between the vicinal protons (H_A couples weakly to H_X). Strong coupling is defined by $\Delta\delta < J$, whereas weak coupling holds when $\Delta\delta \gg J$. For a 4-spin system, $\Delta\delta$ is defined by the difference in chemical shift between the two adjacent CH_2 spin pairs (so AA' and XX').
The J-couplings are constant. However, $\Delta\delta$ scales with the magnetic field; therefore, as we move to a lower magnetic field, $\Delta\delta$ decreases, which results in a higher ratio of J with respect to $\Delta\delta$. Therefore, the couplings between geminal proton spin pairs become stronger. That is why the Hamiltonian, at low magnetic field (i.e., 1.4 T), may be represented by the topological diagram shown in Figure 3, where the geminal couplings $J_{AA'}$ and $J_{BB'}$ are approximately equal, while the vicinal couplings are pairwise degenerate $J_{AB} = J_{A'B'}$ and $J_{A'B} = J_{AB'}$.

For line 118, I would appreciate a more careful justification of the reference to a Bloch–Siegert shift. The observed shift of the non-irradiated spins under selective irradiation may instead reflect a more general AC-Zeeman-type effect. I think the manuscript would benefit from a brief clarification of the physical mechanism intended here, and why the term “Bloch–Siegert shift” is appropriate in this context. I am afraid it might not be since it involves the presence of a counter-rotating component presence of which should only be considered when B1 becomes comparable to B0.

We have come to realize that Bloch–Siegert effects are negligible in our case, as we apply very low amplitude RF pulses (the SLIC pulses have an amplitude of 23–30 Hz), and B_0 is 1.4 T, which corresponds to a Larmor frequency of 60 MHz for ^{1}H, which is far greater. Therefore, it is not necessary to include the Bloch–Siegert shift discussion in this case, which is why we chose to remove it from the revised paper.

Concerning line 127 and Eq. (3), I wondered whether other LLSs or LLCs are possible in principle for this class of systems?

For a 4-spin system, there are a total of 16 states. These states can be sorted according to symmetry. There are 10 symmetric states:

$|T_-T_-\rangle$, $|T_0T_-\rangle$, $|T_+T_-\rangle$, $|T_-T_0\rangle$, $|T_0T_0\rangle$, $|T_+T_0\rangle$, $|T_-T_+\rangle$, $|T_0T_+\rangle$, $|T_+T_+\rangle$, and $|S_0S_0\rangle$,

and 6 antisymmetric states:

$|S_0T_-\rangle$, $|S_0T_0\rangle$, $|S_0T_+\rangle$, $|T_-S_0\rangle$, $|T_0S_0\rangle$, $|T_+S_0\rangle$.

When we excite LLS, we restrict ourselves to the first 10 states that make up the symmetric subspace. However, it should be possible to also excite LLS in the 6 antisymmetric states. This LLS would correspond to the imbalance between the mean population of the first 3 antisymmetric states and the mean population of the last three antisymmetric states. A potential problem with this LLS is a strong mixing of the $|S_0T_0\rangle$ state with the $|T_0S_0\rangle$ state, so that to sustain such an LLS state, one might need to design an appropriate decoupling sequence.

In addition, lines 129–132 and several other places would benefit from a careful stylistic pass. For example, the formatting of "J"-s is not fully consistent throughout the manuscript.

We have improved the consistency of the notation.

Finally, in line 148, the sentence ending with “between spins A and X denoted as …” appears to be missing the corresponding symbol or definition.

We have removed this, as there is no need for this sentence there.

P.S. Figure 2 caption mention six molecules while I can see only 5!

The description of Fig. 2 has been updated, and it now mentions five molecules.

Reply to Reviewer 2: Dr. Mohammed Sabba (Reviewer’s comments are in black. Our reply in green)

I found this paper by Van Dyck and coworkers to be an enjoyable read. It is essentially the latest entry in a long line of exciting work employing variants of the popular SLIC sequence (initially introduced to singlet/LLS NMR by DeVience, Rosen, and Walsworth) to novel biomolecular applications, a "new genre" of spin choreography pioneered by Sheberstov and Bodenhausen.

It has already been shown by the present authors that SLIC may be used in AA'XX' spin systems to great effect to generate population imbalances involving the nuclear singlet state S0; e.g.|S0S0>-|T0T0> and |S0T0>-|T0S0> (see the previous work of Warren's group). It was common sense that this tends to work neatly provided that the chemical shifts/frequencies of the A and X spins are well-separated… but it was however not so clear how well this would work in the case of poorly-separated frequencies when secularization of the AX/AX' J-coupling Hamiltonian is no longer appropriate; i.e. the AA'BB' case that one would be forced to accept in lower magnetic fields. At the time of writing the world is entering the Fifth Helium Crisis, and exploring how pulse sequence methodology works at lower magnetic fields is a highly relevant research direction if you ask me!

This work publishable in standing form subject to some minor comments:

1. There is a typo in equation 3.

This has been rectified.

2. "This means there is a “blind spot” where excitation of LLS cannot be achieved, at least not starting with high-field SLIC parameters." It may be worth pointing out that this "blind spot" occurs at an offset of sqrt(3)*nu_{SLIC}, at least in the limit of a small Delta_J. This corresponds to a condition when the off-resonance spin pairs, which ideally shouldn't be touched at all, are oscillating at a Rabi frequency twice that of nu_{SLIC}.

Thank you for this wonderful suggestion! We have taken this comment into account by introducing the following paragraph: The blind spot can be understood from the dynamics of the off-resonant XX' spins in the rotating frame. Although these spins are not meant to be directly addressed by the SLIC irradiation applied to the AA' pair, they experience an effective field of magnitude $\nu_1^{eff} = \sqrt{\Delta\delta^2 + \nu_{SLIC}^2}$, where $\Delta\delta$ is the frequency offset between the two spin pairs. The dip in the LLS efficiency occurs when this effective nutation frequency matches $2\nu_{\mathrm{SLIC}}$, which gives the condition $\Delta\delta = \sqrt{3}\,\nu_{\mathrm{SLIC}}$.

Sincerely,
Kirill Sheberstov