Reviewer 1

The paper by Taleanu and Vasos is a historical overview of some of the early methodology developments and associated theory, in the field of long-lived states. Personally I find it interesting to learn of the chain of reasoning which led to some of these sequences, in particular the sequence introduced in the JACS 2007 paper, as well as others leading to singlet-triplet coherences. The operation of this very clever sequence is far from obvious but it has proved very useful in the study of long-lived states in the far-from-equivalence regime ("weak coupling"). However I doubt that my personally finding an article interesting is sufficient to justify publication in Magnetic Resonance, whose stated aim is to publish "significant innovation regarding new insights into magnetic resonance methodology". In my opinion the new insights described here are modest. At the same time I have to acknowledge that the very wordy exposition might have obscured some original aspects that I failed to notice. I therefore suggest that the authors revise the article to accentuate with far more clarity and directness the original aspects of their work. The journal editors can determine whether I have misjudged the case, but I expect that a historical review of some old pulse sequences, however interesting, is not a suitable topic for an original research paper. Perhaps it could be part of a more extensive review article, which should, however, in that case, cover more than the methods described here.

Thank you for reading the paper and for the kind observations. Our intention was to provide an example of NMR pulse sequence design rationale, taken from the history of LLS development. As we stated in the Letter to the Editor accompanying the Ms, as well as in the Introduction (line 41, page 2), the Ms does not aim to communicate new research results, thereby belonging, as the editors explain to us, in the 'review' area. The scope is to revisit contributions to LLS pulse sequences with a hindsight of 15 years *circa*.

Though we initially intended to revisit spin systems in the weak *J*-coupling regime and sequences that perform well in terms of translating longitudinal magnetisation to singlet in such systems, the reviewer's comments (and the fact that such systems guarantee the longest spin memory) prompted us to address these sequences that over-populate singlet states in challenging systems containing nuclei near magnetic equivalence (figure 3 of the revised Ms and paragraph starting with line 229). The construction of these sequences contains useful information for the reader. Density operators are used to describe conversions of coherences in the singlet-triplet operator basis, highlighting the dynamics of the singlet state population.

Following the reviewer's suggestion, we have added a numerical simulation using SpinDynamica to show the efficiency of singlet excitation using M2S, SLIC and $\mathrm{ZZ+ZQ}_x$ pulse sequences in both the strongly- and weakly-coupled regimes. Moreover, we have added results concerning the relaxation rate constant of the operator, i.e., the time-dependence of the auto-relaxation rate constants of the density operator corresponding to LLS, but in the absence of radio-frequency fields, in the revised manuscript (lines 188-205 pages 7-8).

We have also analysed in the Ms the similarities and differences between LLCs and zero-quantum coherences, between which comparisons are often drawn, and discussed their distinct nature and properties.

Other comments:

- *An abstract should be a brief and clear summary of the article contents. The current abstract does not fit that description and contains many digressions and pieces of exposition which do not enlighten. It should be cut down by a large factor.*

- We addressed this issue and abridged the manuscript's abstract, as well as the introduction.

- *The article concerns itself exclusively with systems in the weakly coupled limit, which was the main focus of singlet-state research in the 2000's but has since been somewhat displaced by interest in strongly coupled and near-equivalent systems. I was rather disappointed that the article included so little discussion or review of methodology in that regime, which perhaps holds more current interest.*

- We have added (*vide supra*) a paragraph about pulse-sequences that were developed for the nearly-equivalent spin systems, which are the most promising in terms of magnetisation lifetime conservation. M2S and SLIC pulse sequences are discussed at lines 228-237 of the revised Ms as well as in Figure 3 and the corresponding caption; several other pulse sequences, fit for both the strong- and weak-coupling situations, are also mentioned.

- *page 4 includes the phrase "provided the two spins are rendered identical". I know what the authors mean, but this phrase is misleading. Two nuclei of the same isotopic species are, of course, always identical.*

- We have changed the expression to *"provided the chemical shift difference between the two spins is eclipsed by ample radio-frequency radiation or by cycling the main field"* in the paragraph starting at line 85 in the revised Ms.

- *page 6 includes the phrase "changing the chirality of the magnetic system". The issue of chirality and in general, the symmetries of molecules and associated fields, is a very complex and deep issue, and I am not sure the authors are able to underpin this rather casual statement by rigorous theory. If so, they should do so. If not, they should steer clear.*

- The Greek term was aimed to evoke the hands-like reciprocal orientation of the (I_zS_z,ZQ_x) vector pairs prior to and after ZQ_x rotation by 180 degrees (clarified in Figure 2 and caption in the revised Ms) triggered by the chemical-shift difference. When locked by radio-frequency, the two configurations have marked differences in relaxation behaviour.

- *the term "pulsation" is used in several places where "precession" is probably intended.*

- Indeed, we have corrected accordingly, thank you.

Reviewer 2

The work by Florin Teleanu and Paul Vasos gives an overview of the pulse sequences developed for the excitation and manipulation of long-lived spin order in solution state NMR. Particular reference is made to previous work describing broad band excitation sequences developed for excitation of singlet state magnetization and previously reported in J Am Chem Soc 129, 328-334 (2007). I agree that aspects of basic science and methodological development can sometimes be obscured by 'utilitarian perspective' and that the latter should never be an impediment to the former. Unfortunately, no funding would follow, my feeling is the two need to go hand in hand. The current work gives an interesting overview of some of the thinking that underscored this work. However, it does not appear to give much additional analysis or insight that is not already contained either within the original JACS paper or in the Supplemental Info to that paper. In this context the current work reads partway between a review article and a personal reflection, rather than a novel research work per se. If the purpose is a review article then the scope should be expanded to include other works, and maybe include some areas of application. If it is intended as a novel work in its own right, then this needs to be spelled out much more clearly.

Thank you for the comments and for agreeing that perspective is sometimes important. We did not comment on other implications, indeed. This article was written to provide additional insight into several papers on the singlet-development route (notably Sarkar et al., JACS 2007, Sarkar et al., Chemphyschem 2007, Ahuja et al., JACS 2009) and to comment on the difference between long-lived coherences and zero-quantum coherences. By no means did we intend it to be a comprehensive review of the available literature, as there are already such papers describing extensively, notably from Malcolm Levitt's group (M.H. Levitt JMR 2019, G. Pileio, PNMRS, 2017). However, we did expand the scope, as described above, to comment on recent sequences designed for weakly-coupled spin systems (M2S) and discuss them in parallel with the ZZ+ZQx sequence mentioned above.

Other comments:

- *I personally find it very difficult to see the equivalence between operators in the singlet-triplet basis and Cartesian operators. The latter are much more intuitive for understanding the response to pulse sequences. I had to refer to the SI to the JACS paper to follow the interconversions here. In the absence of this SI and the transformations required, it is very difficult to follow the current manuscript, switching from one basis set to another.*

- We performed all conversion from Cartesian product operators to Singlet-Triplet Operator using SpinDynamica. We will upload the notebook as SI. The conversion can be easily reproduced.

- *The figures generated in SpinDynamica are confusing. For example in Figure 1, the LLS would be a vector located in the ZQx/2IzSz plane given by Eq (3) and that interconversion between ZQx and ZQy takes place at the difference in chemical shifts under the Hamiltonian $H = \Omega 1Iz + \Omega 2Sz$. However, as it is drawn it looks like the evolution of zero quantum coherence is under the influence of the scalar coupling 2IzSz* *which interconverts ZQx and ZQy at a frequency ΔΩ. This can't be what is intended as ZQ is invariant under the active coupling which means it shouldn't rotate about 2IzSz? Similarly, in Figure 2. Maybe something else is being portrayed in these figures? In which case it could be better explained.*

- We saw the issue of how figures may have been misleading and corrected accordingly, thank you for pointing this out. We meant to show the evolution of the density operator projected on its three different components (ZQx, ZQy and IzSz), thus rendering a visual 3D dynamics during the pulse sequence. We never intended to state that the zero-quantum coherences evolve due to the scalar coupling.

- *In Eq. (8) should the Hamiltonian just be Ω1Iz + Ω2Sz since ZQx commutes with 2IzSz the latter term is not needed?*

- We agree, this was corrected accordingly

- *Please clarify what is meant by Eq (10)? The expression on the RHS is not a LLS? Isn't it SQ evolution of the in phase and antiphase components of the doublet under the scalar coupling? Which means it's not long lived?*

- In Eq (10), now equation 13, we showed the expression for long-lived coherences (the counterparts of long-lived states) in terms of product operators. Even though they are a combination of singlet-quantum coherences, they do display a long lifetime under CW irradiation much greater than the one corresponding to transverse magnetization (see Sarkar, Ahuja, Vasos, Bodenhausen, PRL, 2010), though not as big as the one corresponding to long-lived states.

- *Figure 5 needs better explaining for the same reason as point 2) above. Should the left-hand evolution of ZQx and ZQy at a frequency ΔΩ be under the Zeeman Hamiltonian Ω1Iz + Ω2Sz. While the evolution in the right-hand diagram at a frequency J should be under the active coupling Hamiltonian 2IzSz?*

- We modified Figure 5 to avoid any misunderstanding. The evolution of ZQ and LLC is displayed under the Zeeman Hamiltonian for a pair of magnetically unequivalent and scalar coupled spins.

- *In the pulse sequence in Figure 1, it looks like the density operator at time point C should contain more terms than described? Should there not be some IxSz or IzSx type terms which are also destroyed by the gradient g1?*

- After the spin-echo (point B) only the anti-phase terms are present which will be completely converted by a 45 ° pulse with phase y into a sum of zero- and double-quantum coherences as well as zz-order magnetization.

- *Please define all parameters in the pulse sequences in the figure captions. There is a great deal of detail missing. How are all the delays defined? Label all pulse phases? Does the phase of the spin lock matter? There is no mention of any phase cycling. The pulse sequence in Figure 1 looks like it needs a phase cycle? Otherwise would Zeeman terms be excited by the final pulse and contribute to the spectrum?*

- We modified Figure 1 accordingly and add a full description of the pulse sequence and comment on the above. The phase of the lock is of no consequence, as the locked operator has spherical symmetry. We made this clear in the revised Ms.

- *In figure 2, should* Q_{LLS} *be in the opposite quadrant if it is given by* $-4/3(ZQ_x + I_zS_z)$*?*

- We have deleted the minus sign (thus reversing the population difference we refer to).

- *Is there a typo on the RHS of Eq (8), second term should be ZQy?*

- *Figure 1, timepoint A should be after the 90° pulse?*

- Corrected, thank you.