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Magn. Reson. Discuss., referee comment RC1
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Comment on mr-2022-5

Anonymous Referee #1

Referee comment on "An improved, time-efficient approach to extract accurate distance restraints for *N*MR^2 structure calculation" by Aditya Pokharna et al., Magn. Reson. Discuss., https://doi.org/10.5194/mr-2022-5-RC1, 2022

The manuscript entilted "An improved, time-efficient approach to extract accurate distance restraints for NMR2 structure calculation" by
Pokharna, Torres, Kadavath, Orts, and Riek describes a new approach for improving the precision of distances measured by NMR and used to calculate the position of ligand in protein pocket. The proposed method which consist to normalize the measured NOEs with the intensities of the corresponding diagonal element, has been proposed in the past, but is validated here in the frame of the NMR2 approach, used to determine poses of ligands in a protein pocket using NMR measurements. The normalisation with the diagonal intensity is shown to improve the precision of the determination of a ligand pose.

The content of the manuscript is significant and deserves publication. Nevertheless, at several places, the manuscript text should be worked
out to clarify the presentation of the work:

a) the last abstract sentence is very complicated and fuzzy.
b) line 90: the expression "(0%)" is a bit strange, as no experimental measure can be obtained at a infinite precision.
c) in Figure A2, results of simulations are described. It is not clear on which system the simulations were performed.
d) caption of Figure 2: it is not clear that the colors purple and brown concern the ligand. The correspondance between the ligands shown in
Figure 2 and the lines of Table 1 should be given. In addition, to which pose corresponds the ligands in which all atoms are colored?
In lines 130-147, the description of Figure 2 is not clear, the ligand colors should be quoted.
e) What is the meaning of Total number of degenerate lowest energy conformers in Table 1?

In addition, there is a more basic question about the method NMR2. The manuscript presents the use of NMR2 for the determination of very
precise position of ligand, which should correspond to an high affinity interaction? But,

NMR is used for studying the interaction of low
affinity ligands for which the poses may much less precise. It would be interesting to insert comments about these points.