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Magn. Reson. Discuss., referee comment RC3
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Comment on mr-2021-9

Anonymous Referee #3

Referee comment on "Structural polymorphism and substrate promiscuity of a ribosome-associated molecular chaperone" by Chih-Ting Huang et al., Magn. Reson. Discuss., https://doi.org/10.5194/mr-2021-9-RC3, 2021

This work studies the chaperone trigger factor (TF) by NMR and EPR spectroscopy. The study addresses two topics. (1) What is the structure of the trigger factor dimer? (2) How do certain peptides interact with TF? Both these questions are of high biological / biophysical impact and have been previously addressed by other studies, as correctly cited by the authors. While the present study is following those previous works, it has nonetheless the potential to contribute valuable information on both topics and should therefore eventually be published. It requires however major revisions.

On the one hand, I support the technical issues raised by the other two referees, without wanting to rephrase them here. These should be addressed.

On the other hand, the authors should substantially strengthen the interpretation and discussion part of their data such that additional insights can be gained. Contrasts and communalities to prior work are to be spelled out explicitly.

Regarding topic 1, the structure of the TF dimer has been studied previously by two independent studies (Morgado et al. Nat Comm 2017 and Saio et al. eLife 2018). Interestingly, while both studies identified the same global arrangements of domains, they came to opposite results regarding the dynamics of the complex. The Morgado study comes up with the finding that the dimer forms a multi-conformational complex. The Saio study finds that TF dimer is a single conformer. The data presented here can contribute to distinguish between the two scenarios. The authors should revise their manuscript to introduce this question in detail and to come up with an analysis as to which scenario is better (or completely) supported by their data.

Regarding point 2, it seems that the peptides bind in a multi-conformational ensemble at multiple sites, as evidenced by the PRE data in Figures 4 and 5. This finding should be discussed with regard to the functionality of the chaperone and contrasted more clearly to the study Saio et al 2014, where other peptides bind in a single conformation.

Minor point:

- The first abstract of the discussion is essentially an introduction. It should be moved to and merged with the introduction.
- Figure 7 is unsystematic, mixing affinities and lifetimes. Also, the present study adds no new insight to this Figure. It should be removed.