

## Referee Comment Manuscript 10.5194.mr/mr-2025-6

The manuscript represents an interesting example of understanding to design and design for understanding related to the impact of the deuteration within the context of the relaxation processes. The message of the manuscript is clear and exhaustively delivered; however, for fulfilling the main ‘take-home’ message of the manuscript, some minor points can be revised:

- For the comparison of the values of  $1/T_{m,f}$  and  $\beta_f$  for different samples and temperatures (figure 7 C, F; please notice into the text at page 20 such figure has been referred as ‘5’), the authors refer to Figure 10 (page 22) for describing the contribution of the fast component. Besides the *fairly constant behaviour* for the PyMTA, it would be interesting to provide further elements to the discussion on the behaviour of TPMTA, exhibiting a completely different behaviour.
- The general approach proposed does not mention the effect of the pH, which may have an impact into the affinity of the two main ligands described; such an effect on the relaxation is probably beyond the scope of the manuscript, but it can be worth to mention also that tuneable parameter (i.e., pH).
- The assignment of dominating mechanism assigned for the two populations (*slow* and *fast*), as summarized on page 23 (lines 8-11) can eventually be reinforced by citing known structures where the  $T_1$  and tZFS are distinctively contributing to the relaxation paths. It may support the effect of the deuteration for ‘small’ molecules and validate the less pronounced effect on labelled proteins.
- Please notice that the authors refer to Figure 2D (page 10) but the capital letter on the figure 2 (page 11) is missing. A-B-C-D on the four panel must be revised.