I fully respect XXXX editorial decision to reject the manuscript ABCD, however, the review brought an issue frequently encountered by other researchers.

The problem is the crystallographic expertise of reviewer No.1 who applies wrong validation criteria of macromolecular crystal structure determination. The reviewer is not aware of developments in the field of X-ray diffraction data analysis and validation, and uses obsolete criteria that address problems encountered with previous generation of software and data collection methods. If this issue is not addressed, it is likely that in the future this reviewer may reject challenging, but important and fully valid structural results.

Three points of the review, which I strongly disagree with, are listed below. I provide a brief explanation with citations to the current literature.

1) "Technical details of crystallography. The R_{merge} for the data at the highest resolution shells are 70%, 80%, and 90% for the first three data sets. These reflect the instrument setting for the data collection rather than the acceptable resolution of the data for structural determination. The structures should be refined at appropriate resolution."

This is simply incorrect.
R_{merge} and related types of R statistics, e.g. R_{sym}, R_{pim}, R_{rim}, are either not weighted at all or weighted only by multiplicity of observations. For these reasons, they are insufficient to define the resolution limits of the diffraction data. This was discussed many times over past ten years, e.g. (Weiss, 2001, Diederichs & Karplus, 1997, Dauter, 1999, Evans, 1999). Instead, the weighted statistic $I/\sigma(I)$ should be used to define the resolution limit and the consensus in the field is that this value should be at least 2 (Dauter, 1999, Evans, 1999) in case of typical macromolecular structures. Even weaker criteria are sometimes acceptable but there is no need to be more stringent. The structures reported in our manuscript were refined to appropriate resolution based on the standard criterion.
The cutting resolution as the reviewer suggests would remove informative reflections and there is no reason to remove weak observations when they are properly weighted by experimental uncertainties. For this reason, removal of valid observations, as recommended by the reviewer, will decrease the quality of the final models.

2) "Since the data were collected using Se-Met crystals at the Se absorption edge, it should be possible to derive the experimental phases and show the electron density map of the very interesting ligand calculated from the experimental phases."

The request it easy to satisfy, but the reviewer asks for something that is not needed in the case of the structure solved by molecular replacement with the protein being the only component of the search model. The solution resulted in the clear difference electron density for the very interesting ligand. Obviously, the map for the very interesting ligand was unbiased as it was not part of the search model. Even if it also produced equally clear result, the Se-Met phasing did not provide any additional information, and for this reason was not discussed. There is no need to produce additional figures in the publication that do not add any value, but maybe there should be a mechanism to provide them for the reviewers. In case of any doubt, the readers can always download the experimental data from the PDB and calculate the map themselves, so there is no need for spurious figure.

3) "The Rwork and Rfree for the structure Y are 26.0% and 30.0% for the 2.5 Å resolution data, reflecting the refinement of the structure is not complete or the model needs to be improved."

The reviewer is using R_{work} and R_{free} to judge completeness of the refinement which is again simply wrong.

R_{work} and R_{free} describe only a global agreement of the molecular model with the experimental data. Their meaning cannot be separated from other indicators of data and model quality, e.g. overall temperature factors, Ramachandran plot statistics and Molprobity clash score (Davis *et al.*, 2007, Kleywegt, 2000). In this particular case, the model cannot be further improved with the existing methodology describing macromolecular thermal vibrations. The values of R_{work} and R_{free} higher than average result from a complex crystal packing, where some molecules are well-ordered, while the others are not. This is represented by differences in overall B-factor for each chain, which we listed in the table summarizing the refinement. We do not live in Lake Wobegon for all the crystal structures to be better ordered than average. In any case, the presence of such a limited disorder does not affect the conclusions and it was only present in one of the many data sets described.

The results of using obsolete knowledge to judge the quality of crystallographic studies are usually opposite to what was intended. The reviewer's hope was probably to improve the quality of the molecular models and the resulting biological interpretation. However, the models were already fully refined, with the diffraction data treated in the most optimal way. As a consequence, in the best situation, the less experienced crystallographers guided by such advices would remove useful data to fulfill the reviewer's wishes. In the worst situation, they would apply non-acceptable statistical procedures to improve the values of statistical indicators on which the reviewer focuses attention, e.g. by applying sigma cut-off on the intensity values (which would improve R_{merg}) or by adding non-existing or weakly-defined solvent molecules to the model (which would improve R_{work} and sometimes even R_{free}).

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