

Response to reviewers

We would like to express thanks for the comments and suggestions of the reviewers. Below is a listing of the concerns that were raised with an explanation of how we have addressed them.

Atom mapping in reaction databases

The editor states that surely reaction databases have atom-mapping and asks us to explain. Our lab has access to the SPRESI database and has attempted to mine the database for reaction prediction and retrosynthesis. Though SPRESI has several millions of reactions, we have found that only around 200,000 of these are completely "clean", meaning balanced and completely atom-mapped. As we don't wish to imply that the reaction databases completely lack atom mapping we have changed the line of text in question to:

While there are several commercially available reaction databases, such as CAS, Reaxys, and SPRESI, unfortunately the majority of the reactions in these databases are unbalanced, are incompletely atom-mapped, and lack mechanistic definition.

Precision of the arrow-pushing images.

The reviewer pointed out some imprecision in the mechanistic arrow-pushing diagrams of Figure 5 and Figure 9. These figures have been fixed such that the arrows are more precise.

Chemical name correctness and consistency.

The reviewer pointed out a mistake with chemical naming and hyphenation in the Generalization section of the Discussion and caption of Figure 11. These issues have been fixed.

Similarity of discussion examples to training examples.

The reviewer raises several issues about the triviality of output examples discussed. In particular, the reviewer raised issues about Figure 9 and Figure 10, wondering if the shown outputs are simply repeating examples from the database of training examples.

The output shown for Figure 9 (multi-step reaction) comes from a careful validation experiment in which all of the reactants (and thus all reactions over

these reactants) are held out as a separate testing set. However, the text in the original submission did not clearly articulate this. The section’s text and corresponding figure caption have been updated to properly convey this important information to the reader. All other examples shown in the Discussion come from cross-validation experiments. Again, the text has been updated to make this clearer.

Figure 13 interpretation.

The reviewer raises questions about the interpretability of the competing mechanisms shown in Figure 13. We show these reactions to exhibit subtle chemistry that we rank “incorrectly” based on Reaction Explorer labels, but that is mitigated by being intelligible and by returning all plausible reactions highly in the ranking. The figure caption and corresponding text have been expanded to discuss this point in more detail.

Reproducibility of the work.

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