Review of: "Interpretable and Generalizable Attention-Based Model for Predicting Drug-Target Interaction Using 3D Structure of Protein Binding Sites: SARS-CoV-2 Case Study and in-Lab Validation"

Cong Shen[1]

1 Tianjin University

Potential competing interests: The author(s) declared that no potential competing interests exist.

- **1. Overall comment.**
  - Major Revision
- **2. Summary.**
  - This paper introduces a computational prediction framework of drug-target interaction (DTI), referred as AttentionSiteDTI, which is a graph-based deep learning architecture along with self-attention, to learn which protein binding sites interact with a given ligand. Results on three benchmark datasets show improved performance compared to previous graph-based models. They also have experimentally validated the predicted binding interactions between seven candidate compounds and spike (or ACE2) protein.
- **3. Strengths.**
  - 1) I find the overall idea of this work to be noteworthy. The authors attempted to leverage the power of both attention and graph-based networks, within a single framework, for the task of DTI prediction. This end-to-end model has the advantage that the user do not need to intervene manually.

    2) The paper attempts to validate its algorithm effectiveness and demonstrate its generalizability on three characteristic datasets from different sources. This indeed requires much effort for experiments. Furthermore, the results looks fine, although there exists some issues with the evaluations metrics that need to be more fully addressed.

    3) The paper is well organized. It is easy to follow with nice visualized representations which facilitate reader's understanding. What's more, the authors have released the source codes and dataset files, which makes the work more persuasive.
- **4. Weaknesses and suggestions.**
  - The novelty of the methodology is not enough remarkable. Although the story that “treating the drug-target complex as a sentence” is interesting, the components introduced in this work, such as GCN or attention mechanism have been proposed before. More important, the description of the work still needs more refinement. I also suggest that the proposed methodologies need to be validated more effectively such as tested on more datasets. I further expand

upon these details:

- 1) I appreciate that the authors provide a graphical representation of their framework in Fig. 1. However, the “MSE Loss” and “CE Loss” marked in the figure are not mentioned in the text.
- 2) The formal descriptions among the components in the methodology lack coherence. If supplementing an algorithm list, the manuscript written could be more professional.
- 3) The authors adopted the Harvard citation style to cite the references. Nevertheless, they did not notice the smoothness of text reading, even overlapping statements of the authors. The whole paper is full of this problem.
- 4) The spelling of the words in the manuscript is necessary to be checked carefully. For example, I am not sure the word “generalizablity” is the correct spelling in the abstract.
- 5) In the DTI prediction field, SOTA efforts always exploit golden datasets used by Yamanishi et al., including enzyme, ion channels, GPCR, and nuclear receptors, to evaluate the performance and scalability. If the authors can give another comparison of these four datasets, the generalizability of their method should be more persuasive. The pertain reference is:
- Yamanishi, Y.; Araki, M.; Gutteridge, A.; Honda, W.; Kanehisa, M. Prediction of drug-target interaction networks from the integration of chemical and genomic spaces. Bioinformatics 2008, 24, i232–i240.
- 6) The comparison given in the current edition of the manuscript could be more plentiful. For instance, more SOTA methods can be considered in adding to the corresponding comparison. More criteria can be adopted in illustrating the effectiveness, such as AUPR, which can more effectively show the performance of the methods on the unbalanced dataset.
- 7) Some criteria need to be listed and kept consistent statement. For example, the authors used "AUC" in Tab. 3 but typed "AUROC" in Tab. 4. Moreover, the declaration of AUC also lacks a formula in the main text.