We would like to thank the reviewers for their evaluation of our manuscript and for providing valuable comments and suggestions. Below, please find our responses to the points raised by all reviewers. For convenience, we have displayed the referees comments in black and our responses in blue font.

Response to the First Referee

In this paper, the authors proposed two methods namely CMMC and CTMC for drug-target interaction prediction. Overall, the proposed methods are novel and the paper is well written. The experimental results also show that the proposed methods can achieve better performance than state-of-the-art matrix factorization methods with much reduced running time. However, I still have some comments as follows.

1. It is very good that the authors used a very large DTI network with 7385 drugs and 4765 targets for experimental evaluation. It will be even better if the authors can further evaluate the proposed methods with other DTI datasets. The four datasets in [1] are actually very small datasets and thus the authors may try this DTINet [2].

We thank the referee for the suggestion. In order to further evaluate the methods using other DTI datasets, we have created the DTI matrix using TTD. More details are provided in the data section and are marked in blue for your reference. Result section also changed accordingly.

2. The authors included 3 recent matrix factorization methods for comparison, namely, GRMF, L2,1-GRMF and NRLMF\beta. I still would like to suggest that the authors should include CMF and NRLMF into comparison.

We thank the referee for this suggestion. Agreeing with the referee, we have included NRLMF in the Related Work section as Section 2.3. It is marked in blue for your reference. The comparison between the newly added method, NRLMF, and the previously described methods is included in both Tables 2 and 3 and they are marked in blue for the convenience of the referee. We should also mention that since NRLMF\beta was already discussed in the manuscript, including NRLMF should with the logical flow

of the manuscript. The main reason in choosing the methods for the purpose of comparison yet lies in the fact that the information regarding these methods are publicly available and any interested individual may access the codes and conduct the comparison as we did in our manuscript. As the referee's suggestion in the following item, we have as well created a publicly available repository to share the codes and data we used in order to obtain the results reported in the manuscript.

3. Following the above two comments, the authors should make the datasets and source codes publicly available so that our fellow researchers can easily reproduce all the results reported in this paper.

We thank the referee for this suggestion. The datasets along with the source codes of the two proposed methods are made publicly available and can be found at:

https://umich.box.com/s/pgxh00op2sovhqvepq1kfcn8khi4mfwf

Please note that at this moment codes and data are uploaded and that they are documented and given full instruction. Additional edits, in terms of instruction and adding more details, might be done if needed.

4. Following the comment 2, the matrix factorization methods mentioned above have loss functions that are clear and easy to explain. However, the Equations (5) and (6) may be difficult for readers to understand. The authors may re-phase the method section or provide more explanations for these equations.

We thank the referee for this comment. Agreeing with the referee, we have added additional explanations, specially pertaining subjective functions, to the method section and we marked them in blue for your reference.

I also have some minor comments below.

1. The results in Tables 2 and 3 can be presented in a simpler way – the authors may present the comparison among different methods in terms of AUC and F-1 (probably the authors can also include AUPR for comparison). I don't think other values including the threshold, sensitivity, specificity or even accuracy are important in this evaluation.

We thank the referee for this suggestion. We have excluded some parameters from the tables while reformatting them in order to make them easier to follow, namely accuracy and threshold. However, since reporting extra values does no harm and some individuals may find them useful and informative, we kept the sensitivity and specificity values in remained in the tables.

2. Based on the results in Tables 2 and 3, WKNKN actually cannot improve CMMC's performance. I am wondering why the authors still include it.

We thank the referee for this comment. The reason we primarily kept the results of running CMMC with the pre-processing step WKNKN, even though there were the same, was to emphasize the fact that the proposed method does not depend on the pre-processing step. To this end and based on your suggestion, we excluded CMMC+WKNKN from all tables but table 2 which we made a point about it.

3. The running time of the proposed methods is a big advantage of this paper. I suggest that the authors should present this comparison for running time in a separate section.

We thank the referee for this suggestion. Agreeing with the referee, we have included more explanations regarding the run time we have marked the section in blue for your reference.

4. The authors should conduct sensitivity analysis for parameters and include these results in the paper.

We thank the referee for pointing out this comment. Sensitivity analysis for parameters are now included in the manuscript and are marked in blue for your references.

References

[1] Yamanishi, Y., Araki, M., Gutteridge, A., Honda, W., & Kanehisa, M. (2008). Prediction of drug–target interaction networks from the integration of chemical and genomic spaces. Bioinformatics, 24(13), i232-i240.

[2] Luo, Y., Zhao, X., Zhou, J., Yang, J., Zhang, Y., Kuang, W., Peng, J., Chen, L. and Zeng, J., 2017. A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. Nature communications, 8(1), p.573.

Response to the Second Referee

Drug-target interaction (DTI) prediction is a very hot research topic in recent years and lots of DTI prediction methods have been published. In this study, Bagherian et al. proposed two novel matrix-factorization methods, CMMC and CTMC, for DTI prediction. Comparing to three state-of-the-art matrix factorization methods, CMMC and CTMC showed obvious advantages. Moreover, CTMC outperforms CMMC in terms of average values of AUC, F1 score, sensitivity, specificity, and accuracy.

My comments about this paper are as follows.

1. There were many matrix factorization methods (e.g., Multiple Similarities one Class Factorizatioin, Variational Bayesian Multiple Kernel Logistic Matrix, Kernelized Bayesian Matrix Factorization, etc.) for DTI prediction. However, only three of them were compared. More matrix factorization methods should be compared if possible.

We thank the referee for this suggestion. Agreeing with the referee, we have included NRLMF in the Related Work section as Section 2.3. It is marked in blue for your reference. The comparison between the newly added method, NRLMF, and the previously described methods is included in both Tables 2 and 3 and they are marked in blue for the convenience of the referee. The main reason in choosing the methods for

the purpose of comparison yet lies in the fact that the information regarding these methods are publicly available and any interested individual may access the coeds and conduct the comparison as we did in our manuscript.

2. In the abstract, “Evaluation on two benchmark datasets shows that”. I don’t think the two types of matrixes (similarity matrix and interaction matrix) were datasets. As for me, only one dataset - DrugBank was used in this study. DrugBank contains lots of ambiguous drug targets, so only using the DrugBank maybe not accurately reflect the advantages of the two methods. Therefore, another dataset (e.g. TTD, ChEMBL, or KEGG, etc.) is essential to prove the advantages of CMMC and CTMC more accurately.

The two benchmark datasets mentioned in the abstract are in act referring to DrugBank and BioGrid. The two databases from which all the datasets were created.

Agreeing with the referee, we have created the additional dataset using TTD. More details are provided in the data section and are marked in blue for your reference..

3. This research proposed two novel methods (CMMC and CTMC), and then evaluated them respectively. However, the title “Coupled Tensor-Matrix Completion Method for Predicting Drug–Target Interactions” only mentioned CTMC. I think it would be better if the title contains both CMMC and CTMC.

We thank the referee for this comment. Agreeing with the referee, we have included both methods in the title of the manuscript as bellow:

“Coupled Matrix-Matrix and Coupled Tensor-Matrix Completion Methods for Predicting Drug-Target Interactions”

It is also marked in blue in the manuscript for your reference.

4. Two types of the dash were used in this article, “–” and “-”, such as “drug–target interactions” in the second sentence of abstract and “drug-target interaction” in the first line of introduction. I don’t know why.

5. Table 2 appears firstly after Table 3 in the 29th line of page 6. I suppose table 2 and table 3 should exchange the order.

6. The second sentence of the results section missed the right parenthesis.

We thank the referee for pointing out items 4,5 and 6 and for the attention. The typos have been fixed and so have the orders at which table 2 and 3 are appeared throughout the manuscript. The corrections are marked in blue for your reference.

Response to the Third Referee

Authors proposed Coupled Matrix–Matrix Completion (CMMC) to predict drug target interactions using drug-drug and target-target similarity/interaction tensors. This is very important topic. Following are some of my comments:

1) Currently it is ambiguous that how authors computed target-target similarity score. Can you explain it shortly?

We thank the referee for this comment. Agreeing with the referee, we added more details on how the similarity score of each target-target pair was calculated to the Data Section. For your reference, Jukes-Cantor which is a MatLab built-in function computes the maximum likelihood estimate of the number of substitutions between two sequences with the method p-distance which is proportion of sites at which the two sequences are different. p is close to 1 for poorly related sequences, and p is close to 0 for similar sequences. You may also check the following page for more information:

https://www.mathworks.com/help/bioinfo/ref/seqpdist.html

The similarity score was taken as an inverse of Jukes-Cantor distance based on the provided reference [12].

2) It's written in section 4 that "The algorithms are tested against common drug-target interaction databases", what are their names?

We agree with the referee about certain ambiguity in the language pertaining this sentence. The information about datasets and how they are created are provided in Section 3: Data, as well as Table 1. The drug-target interaction information is mainly obtained from Drugbank (being the most popular and commonly used by researchers) and BioGrid databases. We have edited the sentence in order to avoid any future ambiguity. You may find the changes in blue.

3) In methods sections, authors have mentioned mathematical formulations, but it is ambiguous how drug target interactions are predicted.

We thank the referee for this comment. Agreeing with the referee, we added more explanations to the methodology section. They are marked in blue for your reference.