Dear Rafal,

Thank you for reviewing our manuscript. We went through carefully your letter as well as the referees' reports. We are glad that referee 1 is happy with our revised manuscript, and we believe that referee 2 also has a positive impression with our revision in general, apart from a single point concerning the performance of our method in comparison with other methods. Nevertheless, this short comment is NOT a fair description of the complete picture, and by itself is even a bit misleading. As the editorial decision was hinged at this single point, we therefore feel that it is absolutely necessary to make a clarification.

We do not agree that our method is out-performed by current-state-of-art methods. As we have emphasized in the manuscript, OrthoClust performs cross-species clustering, which is a novel extension of single-species clustering widely used in every subfield of genomics. It is by NO mean merely an alternate approach of doing network alignment. We agree with referee 2 that a conserved module (a module consisting of genes from two species) is conceptually related to network alignment, and therefore we have performed a detailed comparison as requested by referee 2. In the first part of the comparison, we found that the network alignment algorithm (IsoRank) performs slightly better (88% to 81%) in terms of identifying the corresponding functional gene-pairs between two species. We honestly reported the observation in our manuscript and our response letter to referee 2 (point 2.1 in the letter). While referee 2 makes a bit deal out of this observation, it is not surprising because network alignment is a technique specially designed for identifying corresponding gene-pairs across two networks. However, unlike OrthoClust, current-state-of-art network alignment methods do NOT identify modules. If a worm gene does not have an aligned counterpart in fly but is co-expressed with many genes having aligned counterparts in fly, it will be captured in OrthoClust but not using the network alignment approach. In addition, OrthoClust detects species-specific modules in which network alignment tools do not capture by definition. These novel findings of OrthoClust were not represented in the 81% score we reported. We feel that referee 2 has probably exaggerated our observation a little.

We believe that referee 2 understands a direct comparison of our method to network alignment is not an apple-to-apple comparison. As suggested in the previous referee report (precisely quoted in point 2.1 of our response letter), essentially his/her argument is, output similar to OrthoClust can be obtained by combining network alignment and various ad-hoc procedures of filtering, gluing or clustering edges in individual networks. This might be true. Nevertheless, a slightly better performance in identifying corresponding gene-pairs does not guarantee a better performance in terms of identifying modules. Therefore saying our method performs worse than network alignment based merely on the numbers (81% vs 88%) is a bit misleading. As requested by referee 2, in the second part of the comparison in our revised manuscript, we compared our method with such an approach. We reported the results in our manuscript as well as our response letter. Because the lack of proper gold standard for this comparison, even though we found a certain level of discrepancy, we were not able to draw a conclusion. Nevertheless, such an ad-hoc approach requires lots of intermediate procedures and parameters tuning. Moreover, one can imagine that such an approach is especially hard to generalize for more than 2 species. On the contrary, what OrthoClust offers is a scalable and unified methodology with minimal number of parameters. We believe from a methodological standpoint this is already an important contribution.

We want to emphasis again our method can be readily applied to different types of network data. For instance, OrthoClust has been used to detect conserved as well as species-specific modules across worm, fly and human in the modENCODE comparative transcriptome paper. The analysis was well received by reviewers and the paper has already been accepted in a high profile journal. We agree that the original MATLAB code is not user

friendly. Since the submission of the manuscript, we have been working on improving the utility of the method. We have managed to speed up the optimization process by many orders of magnitude. Using the new code, clustering can be done in 10 minutes on a laptop. We would like to provide, in addition to the original code, the new code written in MATLAB as well as R. We believe it will greatly improve the utility of the method.

In conclusion, we greatly appreciate the comments of the editorial team and the two referees. These constructive comments have made our manuscript much stronger. With code accessibility been improved and the point concerning the performance of our method relative to others been clarified, we sincerely hope that you would reconsider the possibility of publication in Genome Biology

Best,
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