Dr. Alison Cuff

Editor

BMC Bioinformatics Journal

Dear Editor,

First of all, thank you very much for the work you have carried out managing the reviews for our manuscript titled "*Supernoder: a tool to discover over-represented modular structures in networks*”, authored by Danilo Dessì, Jacopo Cirrone, Diego Reforgiato Recupero, and Dennis Shasha.

The article was under your review from February-09 2018 to June-02 2018 (BINF-D-18-00105) and you suggested to submit it again after addressing the reviewers’ comments.

In this article we present SuperNoder, a novel tool which implements new methods that, starting from all motifs of a given size in a given network, finds a subset of disjoint (i.e. non-overlapping) motifs in order to simplify the network. The article shows applications on real food-web and protein-protein interaction (PPI) networks.

We confirm that the manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

We would like also to thank you and the reviewers again for your useful suggestions that brought us to considerably improve the paper.

Reviewers' comments have been carefully considered and the manuscript has been revised accordingly as summarized in the point-to-point answers appended below.

Sincerely,

The Authors

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| REVIEWER #1 | |
| Comment #1 | The paper discussed pros and cons of the five methods based their experimental results. Their approach can reduce big complicate graphs into smaller/simpler ones, yet didn't shown how such reduction can improve the understandability of networks. I suggest the authors elaborate more on what insights (beyond graph compression) can be derived from the results. |
| Response  #1 | *We thank the reviewer for his/her suggestion. In order to address his/her point, we have now reported an analysis that shows how relations between proteins belonging to the same class play an important role into functionalities within PPI networks. The fact that SuperNoder uses labels in addition to structural elements of the networks may help to detect over-represented motifs where proteins belong to the same class. We show this by using an example on the PPI yeast network. The Use case section now thoroughly describes what SuperNoder can find and how it can be employed by biologists.* |
| REVIEWER #2 | |
| Comment #1 | The authors did not show the results of comparing their method with others, including finding overlapping motifs from a network, using a same dataset. |
| Response  #1 | *We understand the request of the reviewer and that helped us clarifying this point in the paper. We have not reported any comparisons in finding overlapping motifs with other tools because our work is built on top of an existing overlapping motif finding algorithm which is one of the state-of-the-art methods of the literature. Moreover, our tool targets networks whose nodes have labels: the subgraphs (for structures and labels) that meet a given threshold are considered over-represented. As we have reported in the background section, there are works that have similarities with ours, but there are differences such as the definition of disjointness and the employment of labels. Therefore, the innovation of our tool is not to present novel approaches to identify motifs, but rather to propose an approach to explore in a simple and effective way a huge number of motifs that are usually included in a given big network. Hence, we show in the manuscript how huge networks can be simplified and reduced by employing our approach and highlight some types of information that can be obtained.*  *The above comment has been properly included within the Background section of the paper.* |
| Comment #2 | It is not clear what improvements have been made by this approach and what are the advantages of using this approach over others. |
| Response  #2 | *Our response #1 to the reviewer partially answers this comment as well. To the best of our knowledge, there are no other tools that find disjoint motifs using the F3 disjoint definition and we would like remarking how in previous works labels have not been properly considered. In the Use case section, we have now aligned the results of SuperNoder on the yeast network with the real problem of finding relations between proteins belonging to the same class. We show how disjointness and high level labels help finding over-represented motifs with proteins that belong to the same class, suggesting how this can help biologists studying properties of different biological processes.* |
| Comment #3 | The authors made the program of SuperNoder at [https://github.com/danilo-dessi/SuperNoder](https://github.com/danilo-dessi/SuperNoder" \t "_blank) along with a test dataset. As for the test dataset, only yeast PPI data is available at the site and the other datasets are missing. |
| Response  #3 | *In the updated version on the Github repository all the used networks have been loaded (Arabidopsis, web-food, yeast). We have also included references of works where these networks have been generated. Last but not least, we have also prepared an online Graphical User Interface of our tool which is freely available at* <http://192.167.144.244:8080/> *and included in the paper as well.* |
| Comment #4 | Since SuperNoder is a common-line tool, it is a bit inconvenient to install Python and other networkX and use them. In particular, non-programmers, including biologists, would feel difficulty in using them. |
| Response  #4 | *We thank the reviewer for the heads up. As mentioned at the end of our comment #4, we have developed a simple web interface to allow anyone with no programming skills using the tool and we provide free access. Through the graphical interface, the user can easily load the network he/she wants and obtain results. In addition, if the server is overloaded or if the user is experiencing any difficulties with the network access, through the GitHub repository we have set up, the user can download the Docker virtualization of SuperNoder, easily install it and run it. This is explained in the readme file we prepared within the GitHub repository.* |