**Response to the Reviewers’ Comments and Summary of Changes**

**Submission ID:** CIBM-D-24-02656 (Computers in Biology and Medicine)

**Title**: "Drivergene.net: A Cytoscape app for the identification of driver nodes of large-scale complex networks and case studies in discovery of drug target genes"

**Authors**: Duc-Tinh Pham, Tien-Dzung Tran\*

First, we would like to appreciate the valuable comments of reviewers. We have revised the manuscript to accommodate or respond to all the points raised. Overall, our revised manuscript has main changes as follows:

* Added description network datasets for experiments into section 2.1
* Added description the algorithm into section 2.2
* Added text for comparison with other methods into section 3.4
* Removed Fig 2 to UserManual file.
* Added limitations of the study into section Discussion.
* Added open-source code into <https://github.com/tinhpd/Drivergene.git>
* Added relationship between driver nodes and hub protein into section Discussion.
* Removed duplication in the manuscript.
* Checked the grammar sentences in the manuscript
* Added text as the suggestion of the reviewers. The texts were highlighted in red.

We highlighted the changes by red color in our manuscript. What follows is a detailed account of the changes made.

**[No Reviewer #1]**

**[Reviewer #2]**

The authors developed Drivergene.net, a novel Cytoscape plug-in application, aimed at identifying driver nodes within large-scale complex networks, with a particular focus on uncovering potential anticancer drug target genes. Utilizing a competition-based controllability method, they showcased the tool's effectiveness through its high computing power and speed in analyzing large biomolecular networks. Their analysis indicated that a significant number of the top driver nodes identified correspond to known anticancer drug target genes, underscoring Drivergene.net's potential role in expediting the drug discovery process and contributing to precision medicine in the field of oncology. The authors' work is highly appreciated; however, the reviewer offers the following recommendations for consideration:

**Comment 1**: Figure 2 could be moved to the supplementary materials to streamline the main text.

**Response:** Yes, we moved Fig. 2 to UserManual file.

**Comment 2**: The GitHub repository currently contains only the .jar file for the plugin. Given that this plugin is designed for an open-source software, it is recommended to provide the source code in detail to facilitate transparency and reproducibility.

**Response 2**: Yes, the open-source code has been uploaded at <https://github.com/tinhpd/Drivergene.git> on directory of “Source code” that contains source codes in sub-directories.

**Comment 3**: The graphical abstract primarily mentions other methods without specifying them. It is advised to detail which methods have been compared, providing clarity on the comparative analysis conducted.

**Response 3**: We updated specific methods into graphical abstract and Section 3.4 as your suggestion. Thank you for the valuable comments.

**[Reviewer #3]**

**Comment 1**. The authors should provide more details on the algorithmic approach used in this study for better understanding.

**Response 1**: Yes, we updated section 2.3 by adding the specific description for Algorithm 1.

**Comment 2**: The authors should evaluate the computational performance of Drivergene.net using various sizes of networks to assess its effectiveness.

**Response 2**: We have presented Table 1 for computational performance of real networks with various sizes. Next, we clarify the computational performance of Drivergene.net by adding a graph with x-axis is time and y-axis is geomean of node and edge into User-manual file. This graph will help the users to know the effectiveness of our software. Thank you for this suggestion.

**Comment 3**: Why is published evidence for some candidate genes missing in Table 2?

**Response 3**: In Table 2, 26 out of 30 genes have evidence whereas the remaining 4 genes have no evidence found. These evidence-missing genes are found and reported only by us at the present, so they are considered the potential candidate genes for further studies. We added “For further studies” in Table2 for readers to understand the reason.

**Comment 4**: Provide a more detailed discussion on the specific metrics used for comparison and how Drivergene.net outperforms these methods to enrich the analysis.

**Response 4**: Yes, our method outperforms the other methods because it has the largest consensus with the other methods while having statistically similar size of sample to the other (to make makes sure that the comparison is not bias due to the difference in sample sizes). We have added description of methods in details in Section 3.4 and clarified how it outperforms the other.

**Comment 5**. It is suggested to provide the limitations of the study in the discussion.

**Response 5**: Yes, we provided the limitations into Discussion.

**Comment 6**: Explore the relationship between the identified driver nodes and hub proteins within the network and discuss it.

**Response 6**: Yes, we made a discussion and updated section 4 for the relationship between driver nodes and hub nodes in undirected (like protein nets) and directed networks (like signaling pathways).

**Comment 7**: The authors should avoid repetitions in the manuscript.

**Response 7**: The duplication in the manuscript has been removed.

**Comment 8**: Please check the grammar and revise the sentences in the manuscript.

**Response 8**: The sentences has been revised and checked the grammar. Thank you so much.

**[Reviewer #4]** The novelty of these manuscript is clear. The figures are with good resolution.

**Comment 1**: The written is well but it is better to rewrite it with ignoring words " We" and " our"

**Response 1**: The words “We” and “our” has been limited in the manuscript.

**Comment 2**: Add the limitation of the study

**Response 2**: Limitations was added into section Discussion.

**Comment 3**: Add the environment you developed the software on it .

**Response 3**: The environment for developed the software has been introduced in Section 3.1. Thank you for the comments.

**[Reviewer #5]**

The manuscript "Drivergene.net: A Cytoscape app for the identification of driver nodes of large-scale complex networks and case studies in discovery of drug target genes" presents a network-based method for identifying driver nodes in biological complex networks that enables the discovery of drug target genes.

Since the authors proposed the identification of driver gene nodes in complex biomolecular networks:

**Comment 1**: They should provide more details in the Materials and Methods section about the relevance of the selected networks in terms of the gene data they contain,

**Response 1**: Yes, description of usage datasets has been added into Section 2.1.

**Comment 2**: How these networks are built (who are the nodes, what represent the edges, other relevant network properties), and their dynamic/temporal features.

**Response 2**: The description of network datasets for network construction has been added in Section 2.1.

**Comment 3**: Unfortunately, tables S1-S5 were not available.

**Response 3**: Besides provided as supplementary, tables S1-S5 were uploaded on Github for easier downloading at <https://github.com/tinhpd/Drivergene.git>

**Comment 4**: The authors claim their tool can identify driver nodes in other biological networks.

**Response 4:** Yes, we made investigation on various networks in Table 1 with evidence found in the Pubmed database.

**Comment 5**: What characteristics should the networks have to obtain reliable results by applying the Drivergene tool?

**Response 5**: To get the reliable result, it requires the input networks are interconnected. We updated this sentence in Discussion section. Thank you for the special comments.