Review of: "A Novel Variable Neighborhood Search Approach for Cell Clustering for Spatial Transcriptomics"

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Potential competing interests: No potential competing interests to declare.

1) Could you elaborate on the specific characteristics or features of the gene expression and spatial coordinate data that your method leverages for cell clustering? Understanding these features can provide insights into the adaptability and robustness of your approach across different datasets.

2) How does the Variable Neighborhood Search (VNS) metaheuristic handle the inherent complexities of cell clustering, particularly when confronted with high-dimensional gene expression data and spatial coordinates? What are the advantages of using VNS over other optimization techniques in this context?

3) In what ways does your novel model based on VNS differ from traditional Integer Linear Programming (ILP) approaches for cell clustering? Could you discuss any trade-offs or computational efficiencies gained by adopting the VNS technique?

4) Regarding the extension of clustering beyond conventional cell-type clustering to spatial domain clustering, could you provide insights into how your method integrates spatial information into the clustering process? How does this integration enhance the interpretability and utility of the resulting clusters?

5) Can you elaborate on the validation methodology used to assess the performance of your approach compared to existing techniques? What specific metrics were employed, and how do the results demonstrate the superiority of your method? Additionally, are there any limitations or potential biases in the validation process that should be considered when interpreting the findings?

6) CPU times should be added, especially for the performance of the proposed method.