The 7th of February, 2022

Dear Editor,

We are pleased to submit our paper: Sam F. L. Windels, Noël Malod-Dognin and Nataša Pržulj, “Identifying cellular cancer mechanisms through pathway-driven data integration”, for consideration in Bioinformatics.

We observed in previous work that known cancer driver genes characteristically perform hub roles between pathways [1]. Therefore, contrary to current approaches, we hypothesise that cancer pathways should be identified by changes in their pathway-pathway relationships rather than their internal perturbation. Within this context, we propose pathway-driven non-negative matrix tri-factorisation (PNMTF) to learn an embedding space that captures the relationships between pathways in a healthy cell. In this space, we determine condition-specific (i.e. diseased and healthy) embeddings of pathways and genes. Based on these embeddings, we measure the functional importance of a pathway or gene in the cell and the disruption of their functional relationships in cancer.

We apply our method to predict 15 genes and pathways involved in four major cancers, predicting 60 gene-cancer associations in total, covering 28 unique genes. To further exploit driver genes’ tendency to perform hub roles, we model our network data using graphlet-adjacency, which considers nodes adjacent if their interaction patterns form specific shapes (e.g., paths or triangles). We find that the predicted genes rewire pathway-pathway interactions in the immune system and provide literary evidence that many are druggable (15/28) and implicated in the associated cancers (47/60). These results allow us to predict six druggable cancer-specific drug targets.

Thank you for considering our manuscript.

We look forward to hearing from you.

Sincerely yours,

Nataša Pržulj

References:

[1] Windels, S. F., Malod-Dognin, N., & Pržulj, N. (2022). Graphlet eigencentralities capture novel central roles of genes in pathways. *PloS one*, *17*(1), e0261676.