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Type	Oral communication
Session	Multi-omics data analysis and integration
Title	A Nonparametric graphical approach for estimating differential networks between sex and age related chronic diseases.
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Motivation

Rewiring of gene interactions under different conditions is a fundamental cause of different phenotypic responses. In particular, there is a growing interest in elucidating different responses to drugs, disease outcomes, and comorbidities for many complex chronic diseases [1,2]. This is motivated by experimental observations, which demonstrate that both the incidence and progression of some diseases have remarkable differences considering sex and age as factors. For instance, there is evidence that patients affected by diabetes are more likely to develop comorbidities as they grow older. Furthermore, COVID-19 showed particular lethality in older males. Consequently, there is a need to introduce novel algorithms to explain the possible causes of such differences at the molecular level. The comprehension of these molecular mechanisms requires the analysis of large heterogeneous data at different scales as well as the integration of different data sources into network medicine models. Differential network analysis (DNA), among others, is an effective tool for investigating gene and protein network rewiring. Given two different datasets of experimental observations, which correspond to two different conditions (e.g. healthy/diseases, male/female, old/young), DNA algorithms try to infer association networks among entities that may discriminate the two conditions. These methods have been initially developed to analyse healthy vs diseased classes. More recently, some approaches have shown the possibility of using such methods to analyse age and sex [3]. There exist many computational methods to evaluate differential networks discriminating against these conditions. In particular, current methods explore the changes in the expression of genes as a cause of rewiring. Thus there is still room for identifying possible rewiring due to sex/tissue factors. Experimental observation shows that, in general, empirical observations of gene expression do not follow a Gaussian distribution, particularly NGS data which are count data.

Methods

We propose a novel differential network analysis method, namely NoPDNA (Non-Parametric Differential Network Analysis), that discovers differential edges and integrates differential expressions of nodes. Our approach does not impose any particular hypothesis over the distribution of experimental data, e.g. gaussian or Poisson distributed data. At the same time, we refer to data as extracted from multivariate count data. This is motivated by our experimental observation of publicly available NGS datasets. Consequently, starting from two experimental gene expression datasets corresponding to two different conditions, we derive the conditional dependence graph by employing pairwise Markov random fields. We build two conditional dependence graphs for the two tested conditions; then, we derive the final dependence graph from the previous two. Finally, we prune the resulting graph by admitting only edges incident to at least one differential expressed gene.

Results

We initially tested our method on a synthetic, simulated network to show the performances and compare it with state-of-the-art methods. Then, we applied our method to identify the differential networks between male and female patients, considering genes related to diabetes. Networks extracted by our method present high biological relevance, and we are currently validating our results with the help of biological and medical experts.

Info

References
[1] Tu, J. J., Ou-Yang, L., Zhu, Y., Yan, H., Qin, H., & Zhang, X. F. (2021). Differential network analysis by simultaneously considering changes in gene interactions and gene expression. Bioinformatics, 37(23), 4414-4423

[2] Rutledge, J., Oh, H., & Wyss-Coray, T. (2022). Measuring biological age using omics data. Nature Reviews Genetics, 1-13.
[3] [Mercatelli, D., Pedace, E., Veltri, P., Giorgi, F. M., & Guzzi, P. H. (2021). Exploiting the molecular basis of age and gender differences in outcomes of SARS-CoV-2 infections. Computational and Structural Biotechnology Journal, 19, 4092-4100.]

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Availability	-

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