BITS :: Call for Abstracts 2024 - Oral communication

Type	Oral communication
Session	Bioinformatics AI, Models and Tools
Title	PACO: a Shiny app for comparing perturbed pathways associated with different phenotypes
All Authors	Giovanni Micale (1), Salvatore Alaimo (1), Alfredo Pulvirenti (1)
Affiliation	

(1) Department of Clinical and Experimental Medicine, University of Catania, Catania

Motivation

Pathways are biological networks describing interactions between genes and molecules that contribute to the development of a specific metabolic function or biological process. One of the goals of pathway analysis is to determine the alteration of functional processes in complex diseases by identifying perturbed pathways associated with a phenotype or condition. Metrics used to measure the degree of perturbation include the number of differentially expressed genes belonging to the pathway, the magnitude of their expression changes and their interaction type, direction, and strength. Recently, several algorithms have been developed to identify perturbed pathways associated with a phenotype, such as Pathway-Express, ClusterProfiler, SPIA, MITHrIL, and PHENSIM. These methods fully exploit the topology of pathways to calculate perturbation scores for each pathway and each pathway node. However, to the best of our knowledge, there are no tools available for comparing perturbed pathways associated with different phenotypes in the same or distinct species. Such a tool could be useful to get insights into the molecular mechanisms behind the functioning of specific biological processes in different organisms or classes of patients.

Methods

We developed a Shiny R web app called PACO (PAthway COmparator) to compare two or more sets of altered pathways associated with different phenotypes. Input data consists of text files containing lists of molecules (genes, miRNAs, drugs or compounds) with relative perturbation scores, with one list for each set of pathways the user wants to compare. To facilitate the integration of our app with the PHENSIM algorithm, the user can also directly upload simulation files returned by the PHENSIM simulator (https://phensim.tech/) after performing a new simulation. In the latter case, perturbation is given by the activity score of each molecule. By clicking on “Compare,” a multilayer network is shown, where each layer is a pathway associated with a specific phenotype, and inter-layer edges connect homologous genes. The user can choose the layers to be shown and which pathway (among those in common between the selected layers) should be compared. For ease of visualization, up to 3 layers at a time can be visualized. The user can also select one of the molecules present in the compared pathways to “zoom” into specific regions of the network and visualize the local neighborhoods of the molecule (and its homologous, if any).

Results

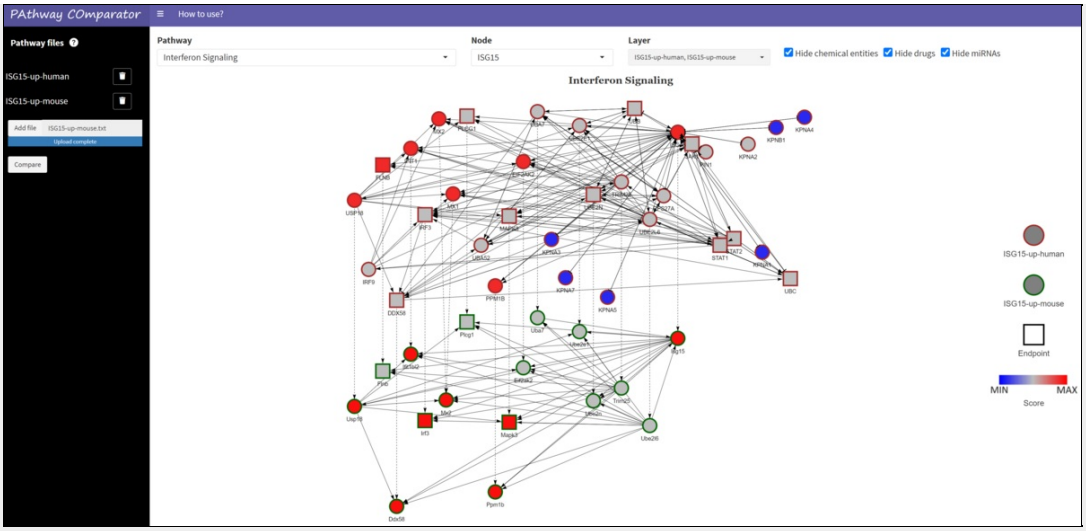
As a case study, we used PACO to compare perturbed pathways of the immune system in mice and humans after up-regulation of Interferon (IFN)-stimulated gene 15 (ISG15), a ubiquitin-like protein which acts both as an extracellular cytokine and as an intracellular protein modifier. Recently, the role of ISG15 in SARS-CoV-2 and other viral infections has been investigated, suggesting that ISG15 exerts anti- or pro-viral effects, acting as a post-translational modifier or 'cytokine-like' molecule during infection. We first ran two simulations in PHENSIM by upregulating ISG15 in humans and mice. After completion, we downloaded the simulation output files by clicking on “Download raw results,” then we uploaded the two files into PACO and clicked on “Compare.” For the visualization, we selected the “Interferon Signaling” pathway, which plays a critical role in the immune system response, and the “ISG15” gene. The resulting multilayer network shows some genes that are active in mice but not in humans (DDX58, EIF2AK2, and MAPK3) and a set of human importin genes (KPNA1, KPNA3, KPNA4, KPNA6, KPNA7, KPNB1) that are less active than normal condition and have no orthologs in the mouse. Inportin genes contribute to the formation of nuclear pore complex, facilitating selective membrane transport of various molecules across the nuclear envelope. These findings might suggest a different immune system response behavior in the two organisms, which can be further investigated.

Info

PACO is available at https://alpha.dmi.unict.it/shiny/users/gmicale/PathwayComparator/.
The app's source code and example input files are in a GitHub repo at https://github.com/GMicale/PathwayComparator.

filename	PathwayComparator.png

Figure



Availability	-

Dissemination Material

Social

-

Summary

-

Corresponding Author

Name, Surname	Giovanni, Micale
Email	giovanni.micale@unict.it
Submitted on	02.05.2024