Supplemental Material

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Software and python libraries used for analysis

Scikit-learn, https://scikit-learn.org. Last accessed 04 Feb 2020

Statmodel, https://ww.statmodels.org/. Last accessed 04 Feb 2020

Orange, https://orange.biolab.si. Last accessed 04 Feb 2020

Matplotlib, https://matplotlib.org. Last accessed 04 Feb 2020

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UpSet usage

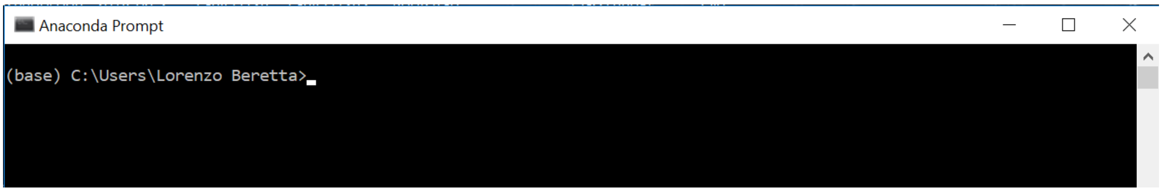
The UpSet tool (http://caleydo.org/tools/upset/) has been developed under different languages and environments. For explorative purposes on druggable pathways we found the web-based interface the most flexible and easy to use implementation but other implementations can be used as well. The interface can be accessed after local deployment; hereafter we provide step-by-step instructions to download all the necessary software and files to run the analysis on our data. All the provided examples are *for Windows*.

1. The Python environment should be installed on your computer (for convenience the open-source Anaconda software can be used: https://www.anaconda.com/distribution/#download-section).

2. Download the ZIP file containing the UpSet repository (https://github.com/VCG/upset/archive/master.zip) extract the file and place the extracted folder in your preferred location (in the example below on the Desktop). Rename the folder as “upset SSc”.

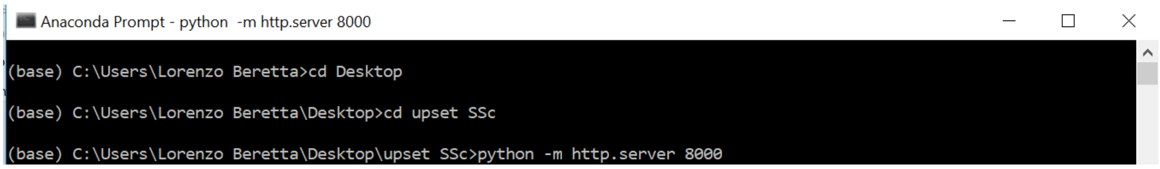
3. Create a folder named “FAIME SSc” in the “\upset SSc\data” folder. Copy in the newly created “\upset SSc\data\FAIME SSc” the “reactome.json” and the “Drug x reactome.csv” files downloaded from the supplemental materials.

4. Open the Anaconda Prompt:



```
(base) C:\Users\Lorenzo Beretta>_
```

5. locate the upset SSc folder on the Desktop and type in the code below to prepare the local host:

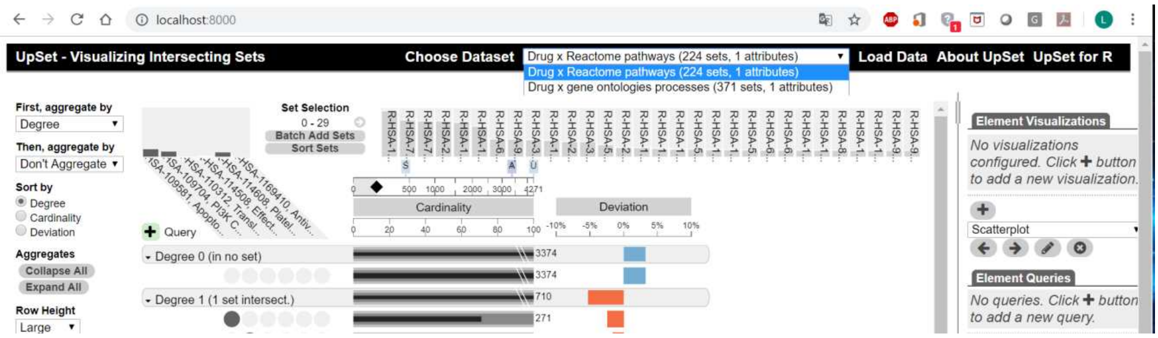


```
(base) C:\Users\Lorenzo Beretta>cd Desktop

(base) C:\Users\Lorenzo Beretta\Desktop>cd upset SSc

(base) C:\Users\Lorenzo Beretta\Desktop\upset SSc>python -m http.server 8000
```

6. Open a web browser and in the navigation tab type: *localhost:8000*



7. Choose the dataset to explore (Drug x Reactome). The other datasets available are those that comes with Upset.

Note that the Dataset made available in the *\upset SSc\data\FAIME SSc* pathway can be manually explored or used in the UpSetR shiny app (https://gehlenborglab.shinyapps.io/upsetr/)

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Legend to Supplementary Figures

Supplementary Figure 1 – Significant pathways in discovery and validation sets

Plot of individualized Functional Analysis of Individual Microarray Expression (FAIME) scores (left) and FDR-corrected pathways (right) in the discovery (blue line) or in the validation set (orange line). Nominal moderate robust effect size (dr) (> 0.62897 or < - 0.62897) and false-discovery adjusted p values (< 0.05) are depicted as dashed lines.

Supplementary Figure 2 – Heatmap of validated FAIME pathways

Heatmap representation of replicated pathways scored according to the Functional Analysis of Individual Microarray Expression (FAIME) method in the discovery (purple) or validation (pink) sets. Patients (in red) and controls (in green) are clustered column-wise via the k-means algorithm, genes are clustered row-wise via the hierarchical clustering Ward method. Patient-wise data standardization was applied before clustering. Due to magnification issues, labeling of hierarchical clustering is detailed in the Supplemental Figure 3.

Supplementary Figure 3 – Clusters of FAIME pathways from Supplementary Figure 2

Magnification of functionally annotated pathways from the heatmap representation in Supplemental Figure 2 (y-axis) and clustered according to the hierarchical clustering method.

Supplementary Figure 4 – Screenshot from Upset

Example of Upset representation of intersecting sets. Druggable pathways belonging to the immune system activation/IFN signalling are explored; the Drug Gene Interaction database (DGIdb) is used as reference.