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Deciphering functional annotation of multiple gene sets with MOTVIS

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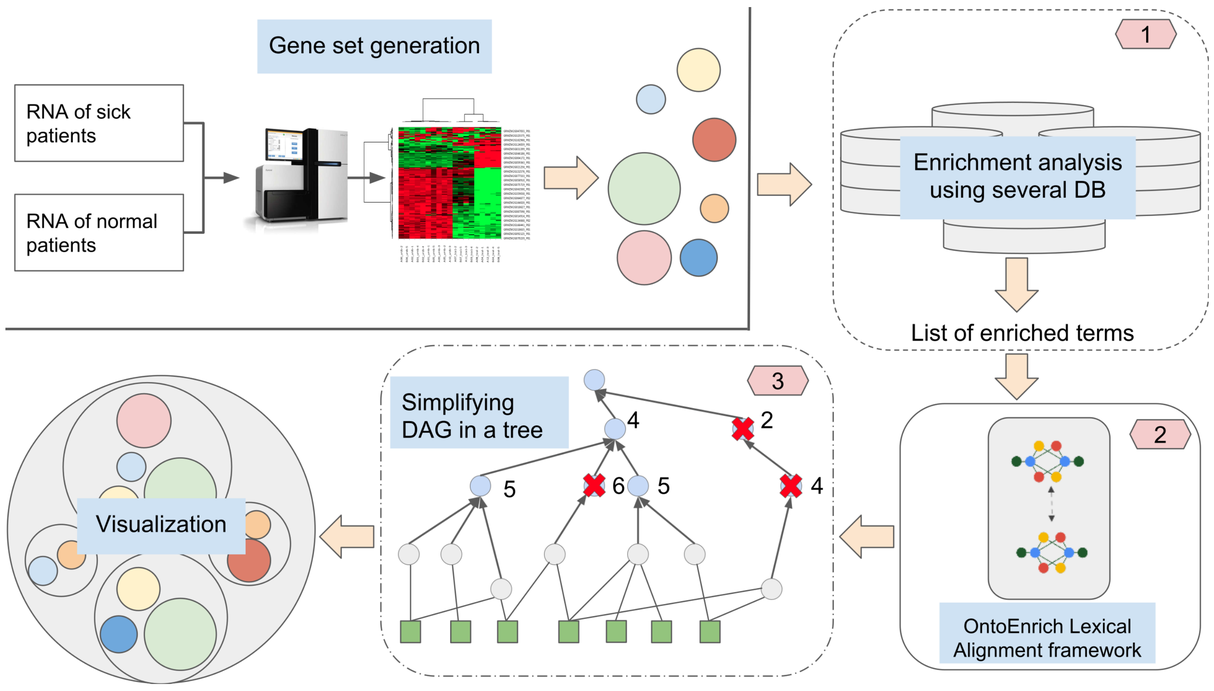


1 - Context

- The advances in **omics technologies**, such as single-cell, RNA-SEQ or microarray facilitate **understanding the link between expression profiling and phenotype**.
- Statistical approaches or clustering aim at grouping genes according to their expression levels [1] to detect **gene signatures** and **understand the biological processes**.

For that, **annotating gene sets** will be crucial to:

- Elucidate the biological role of these specific cells.
- Highlight their specificity.

Problem:

- Managing a **large number of annotation terms** associated with a gene set is **very difficult**.
- **Enrichment methods** have been proposed [1] but they show an important pitfall related to **redundancy** in the results [2] due to the **lack or under-exploitation of semantic relations** between terms.

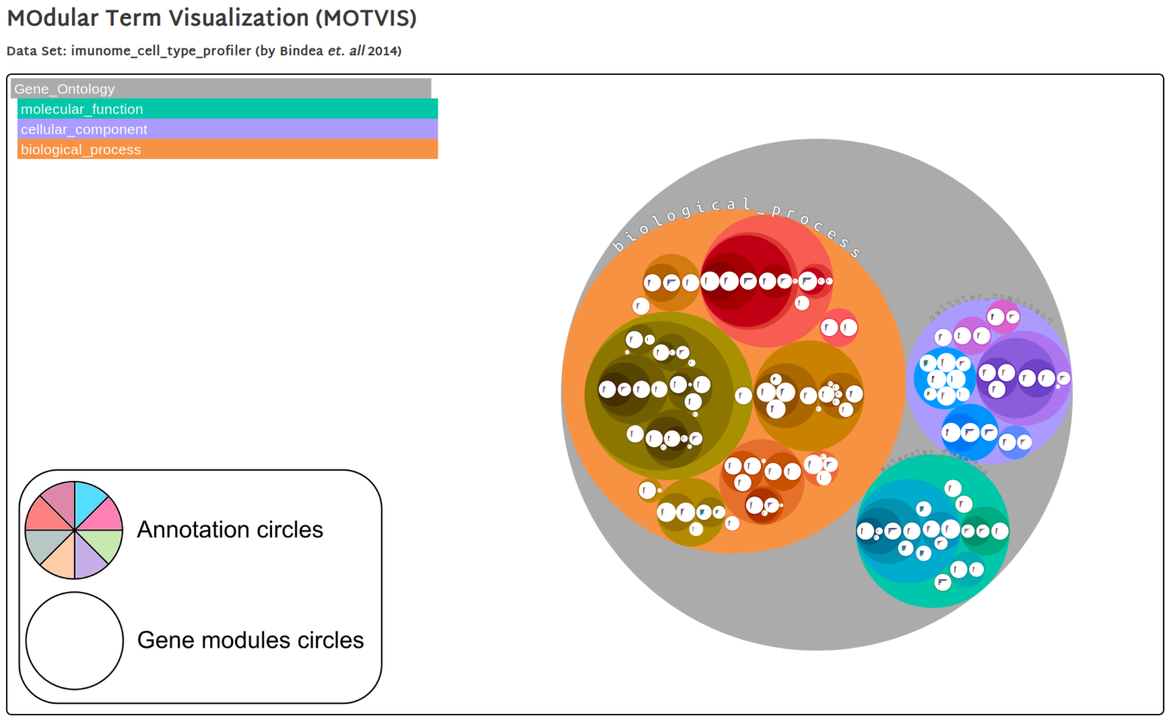
Objective

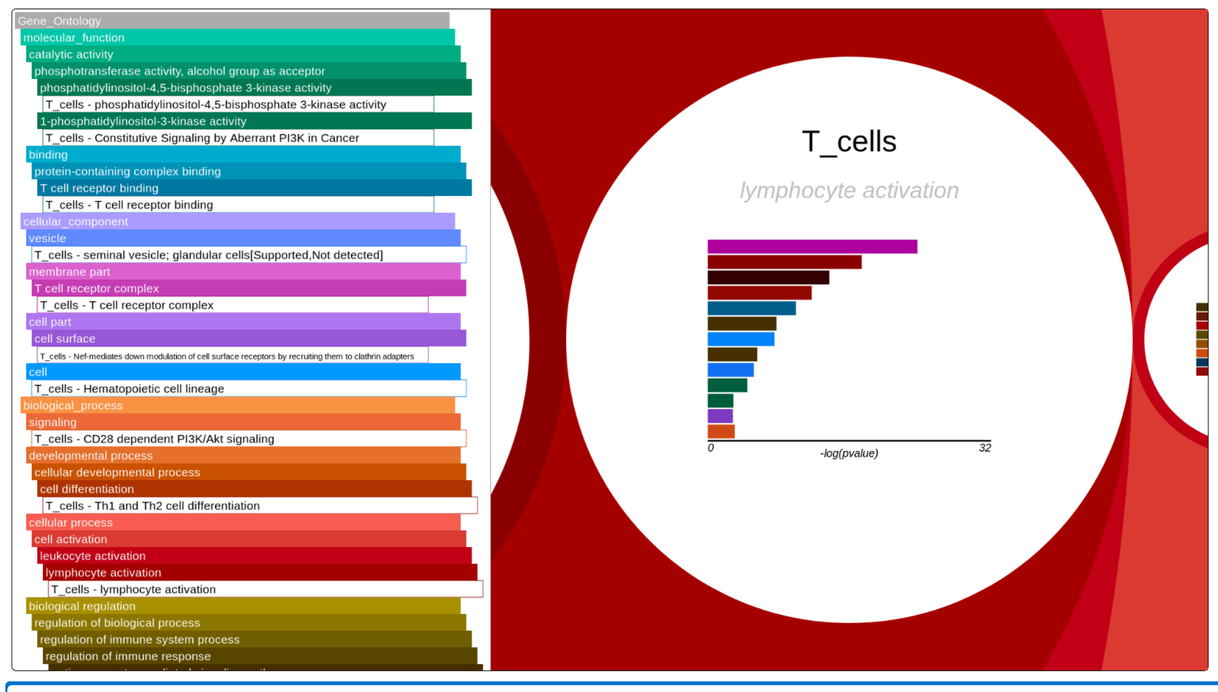
To illustrate the usefulness of the MOTVIS workflow to decipher the main roles in immune cell signatures

2 - Workflow

We proposed **three main steps** to compute gene sets annotations before presenting the visualization system [3]:

1. Gene sets are annotated using an enrichment approach. **g:Profiler** has been chosen because it uses **several annotation databases.** This enables to combine complementary knowledge for enriching functional information about gene sets.
2. **Lexical analysis** is done to infer relations between terms coming from different sources to **eliminate redundant terms**. The **OntoEnrich framework** [4] has been integrated for associating annotation terms with GO terms according to the following strategy:
   - Decomposing annotations into words
   - Searching groups of consecutive words that correspond to a GO term or its synonyms
   - Removing words included in other ones.
3. Because of the **large size of GO**, we selected only the most **relevant terms** that **synthesize the functional information** of the input gene sets. The most informative parent terms of each GO term found at the previous step are recursively processed until the root term is reached.





3 - Case study

To **demonstrate the efficiency and reproducibility** of the pipeline, the signature profiling of different types of cells has been analyzed using the data from **The immunome compendium of immune cell** subpopulations [5]. They isolated **28 subpopulations of innate and adaptive immune cells**, including normal mucosa and colon cancer cell lines. Each cell type presents different transcriptional profiles that can be considered as gene sets.

- **323 annotations for 24 gene sets** using a hierarchical filter proposed in the tool.
- **98 annotations** would have been obtained for only **16 gene sets**.
- After using the lexical mapping, **264 out of the 323 annotations were kept**.
- **5 out of the 24 gene sets were ignored** by our pipeline.
- Hierarchy simplification **decreased the number of annotations from 264 to 119.**

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