

Methods for Differential Evaluation of Gene Regulatory Networks

ASCA Hackaton



Association for Single Cell Analysis

GraphX Team

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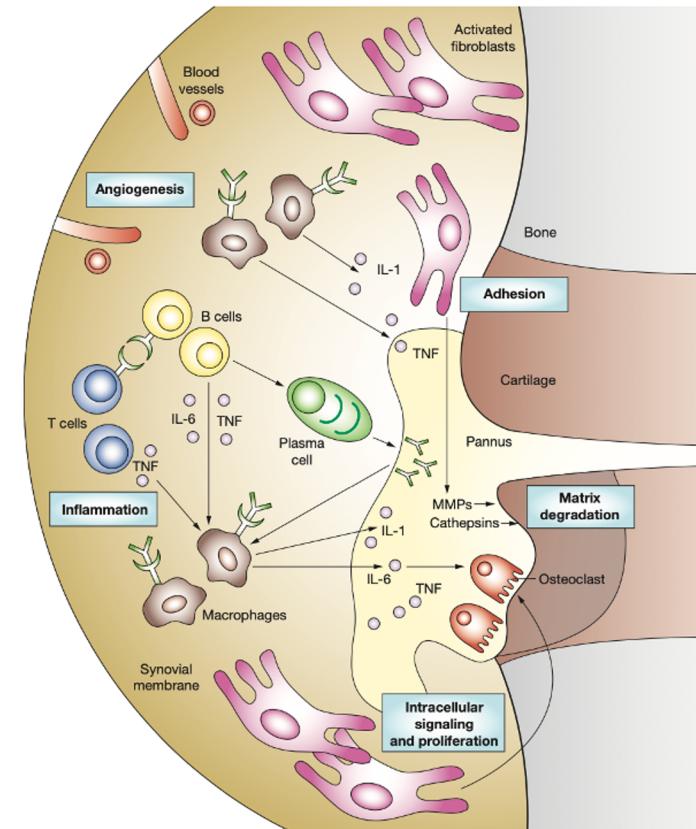
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Introduction

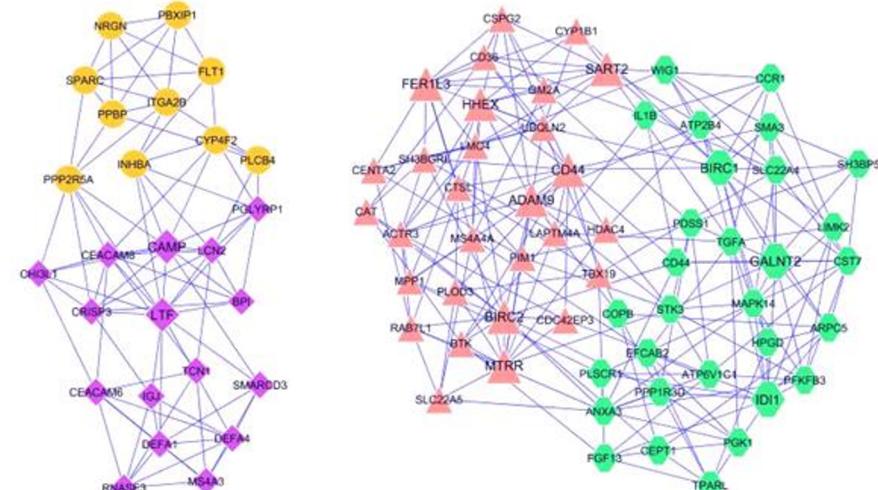
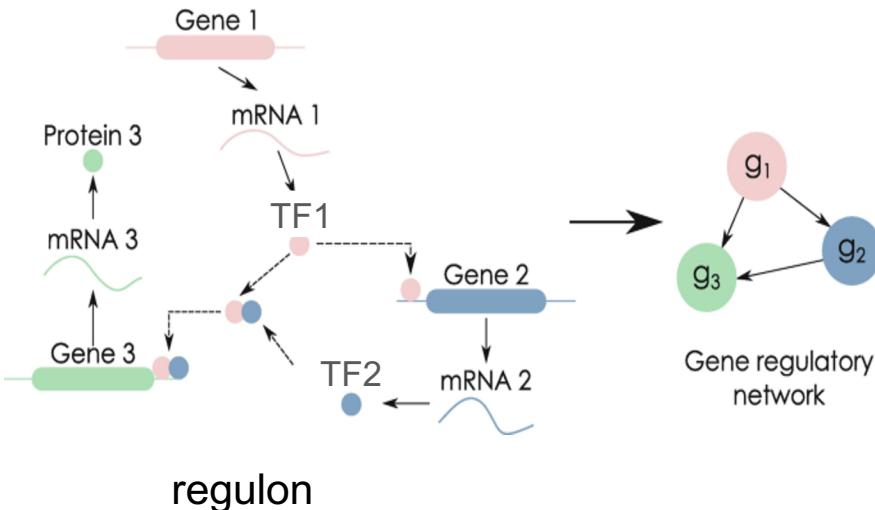
Disease – Juvenile Rheumatoid Arthritis (JRA).

The pathogenesis of rheumatoid arthritis involves multiple cell types, with a key role attributed to T cells, B cells, and resident macrophages.

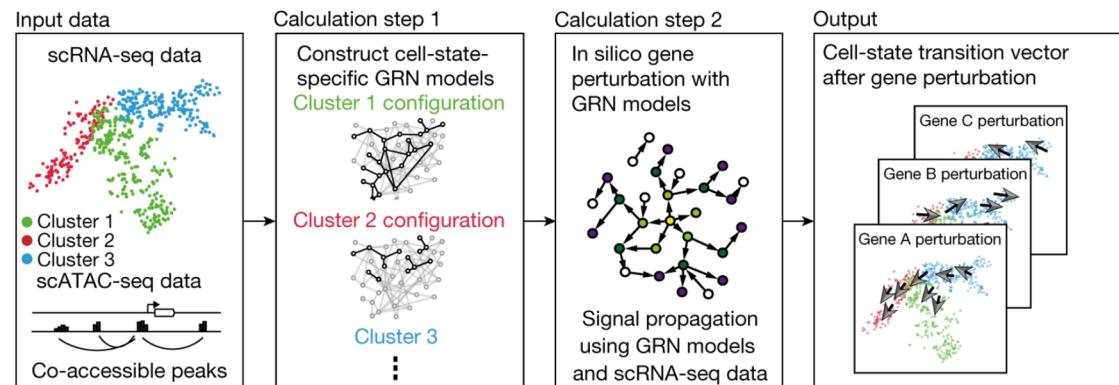
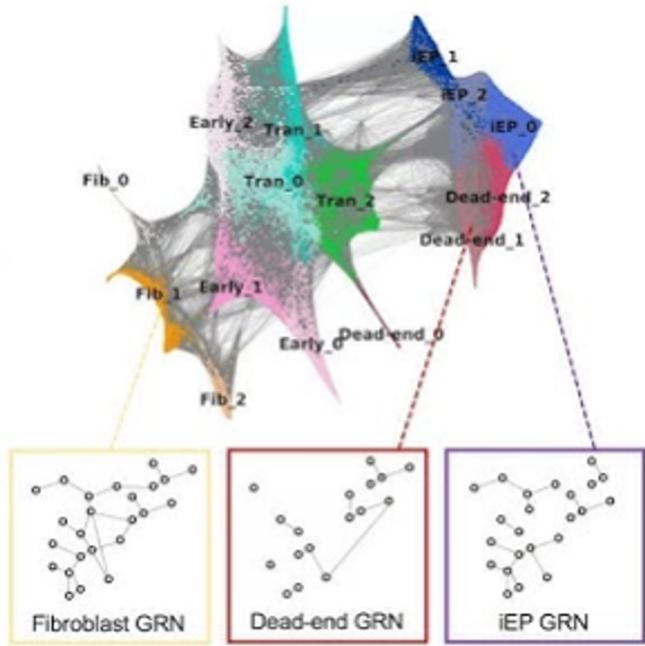
It is anticipated that the shift towards a pro-inflammatory phenotype leads to alterations in the transcriptional profile of immune cells.



Gene Regulatory Network (GRN)



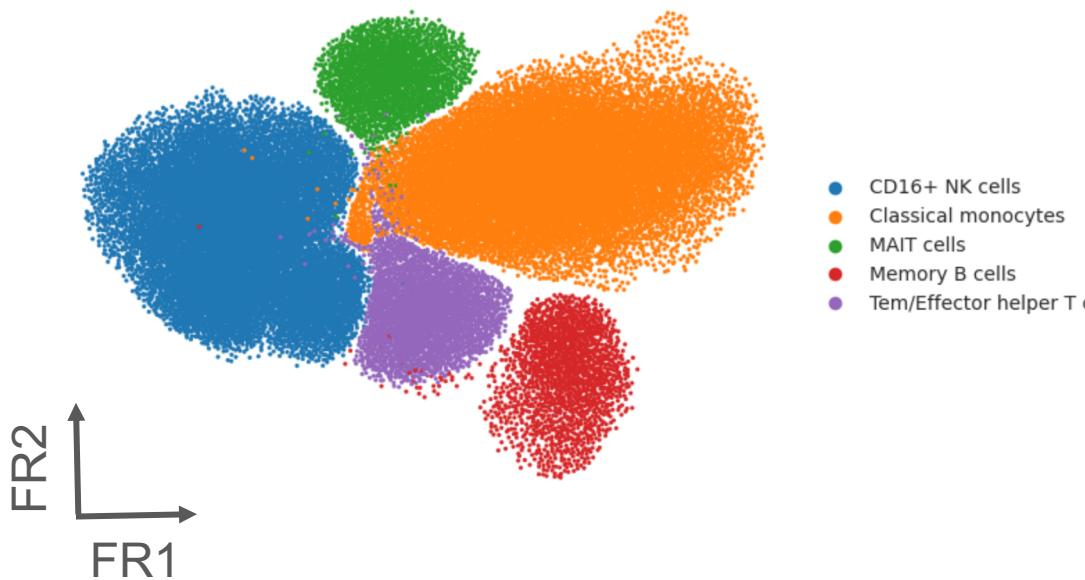
CellOracle



doi.org/10.1038/s41586-022-05688-9

Data

majority_voting

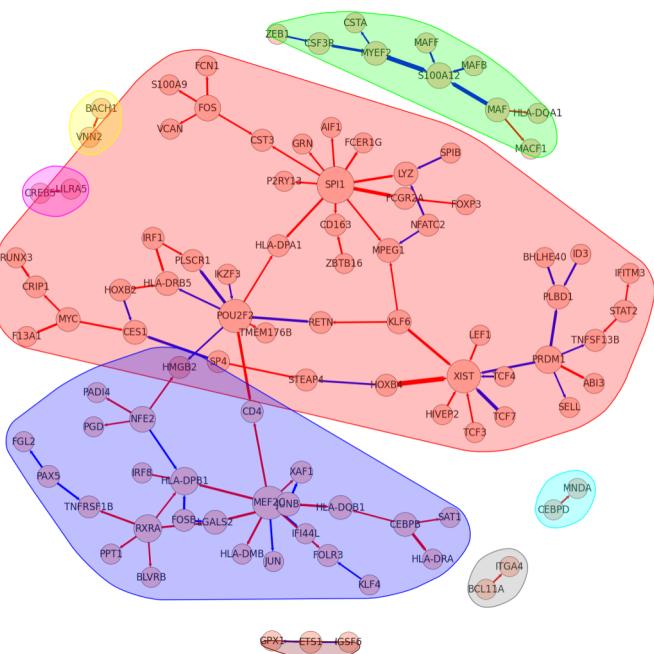


scRNA-seq samples

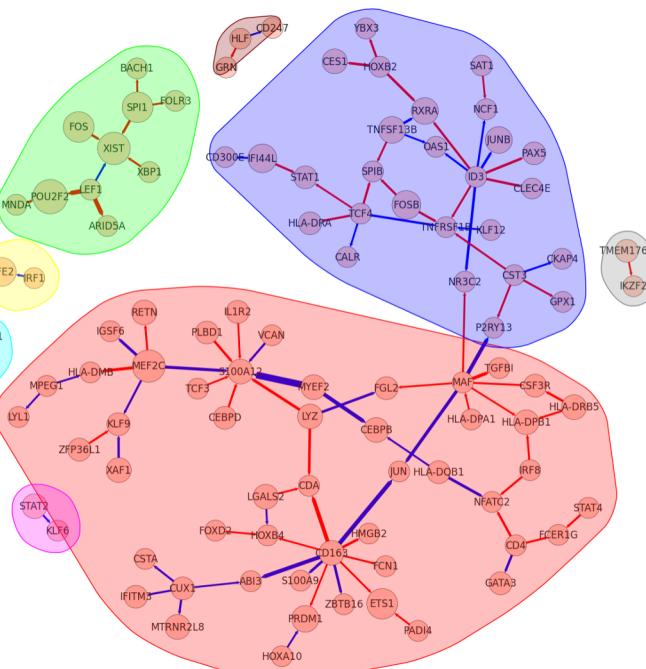
- Group of patients with juvenile rheumatoid arthritis with pulmonary manifestations (7 samples)
- Healthy control group (5 samples)
- Five cell types were selected based on standard evaluation methods, as these types were expected to exhibit the most significant differences.

Graph representation

Monocytes, control



Monocytes, disease

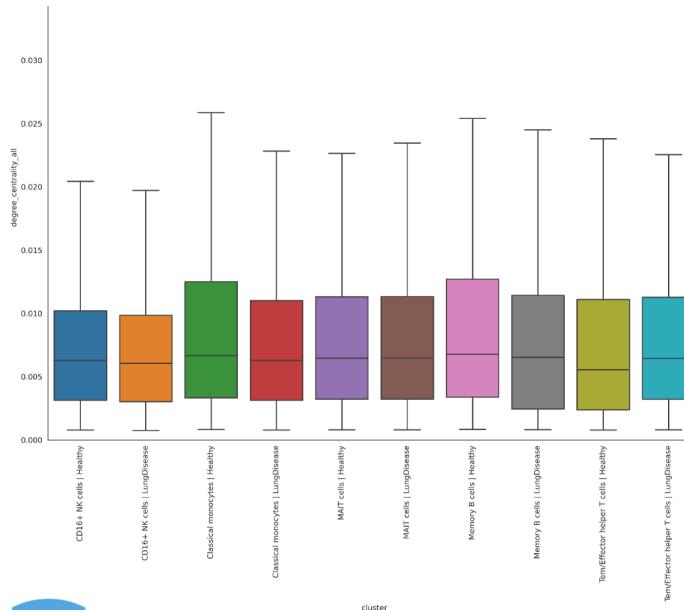


Tasks

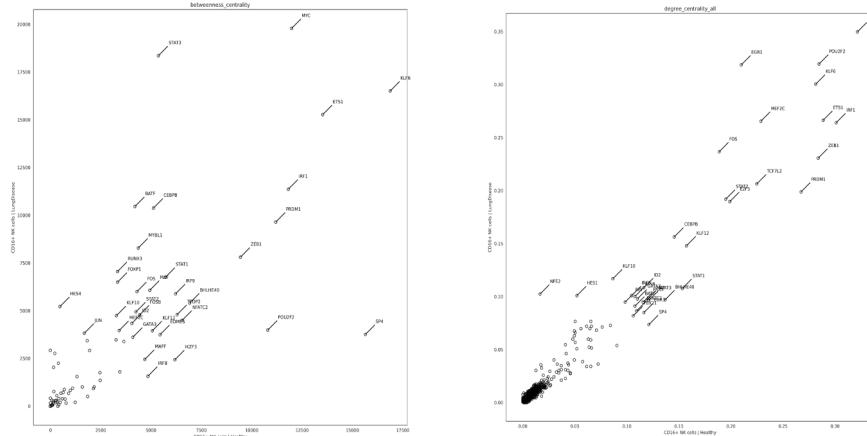
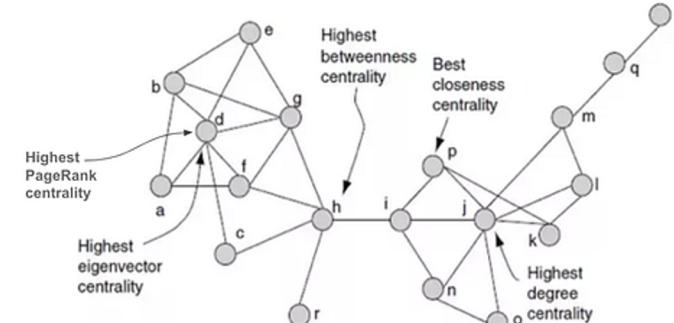
1. Literature review and study of the algorithm implemented in the CellOracle package
2. Filter the available input data
3. Perform basic differential evaluations of gene regulatory networks (GRNs) following the CellOracle tutorial
4. Develop custom heuristics and methods for differential GRN evaluation
5. Conduct biological interpretation of the obtained findings

CellOracle metrics

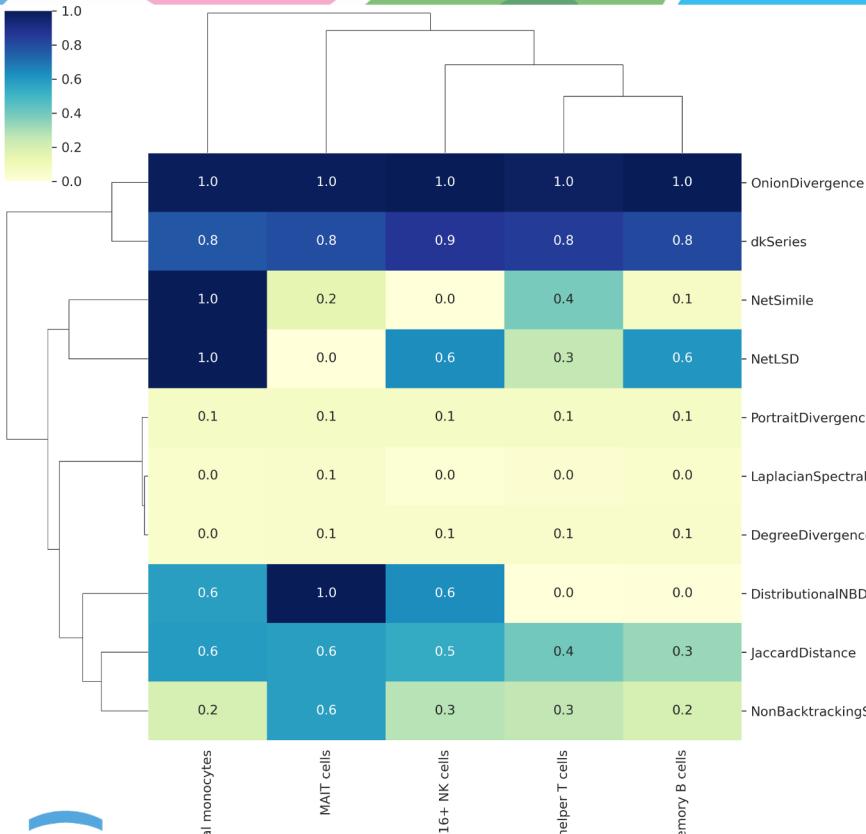
Centrality metrics in CellOracle



Association for Single Cell Analysis



Graph similarity metrics



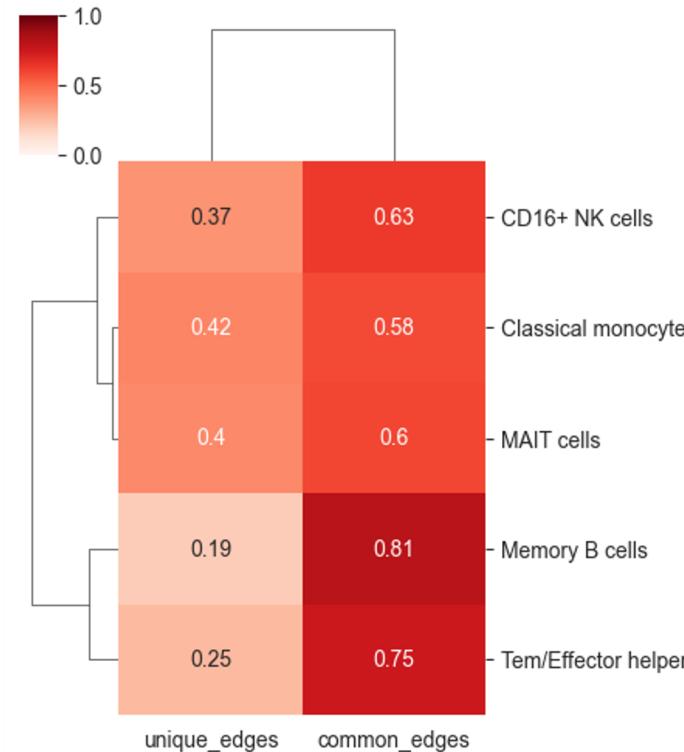
The metrics reflect the degree of similarity between gene regulatory networks in healthy conditions and juvenile rheumatoid arthritis for each cell type.

Jaccard distance

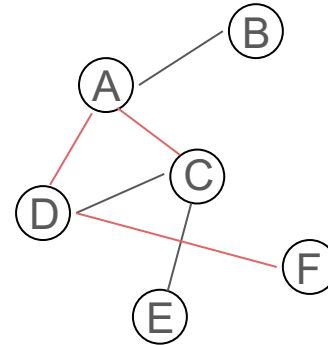
$$J(A, B) = \frac{|A \cap B|}{|A \cup B|}$$

$$d_J(A, B) = 1 - J(A, B)$$

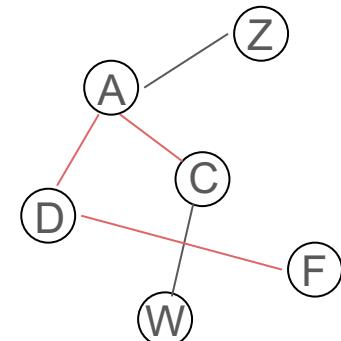
Frequency of unique and common edges in celltypes between conditions



Graph 1
(JRA)



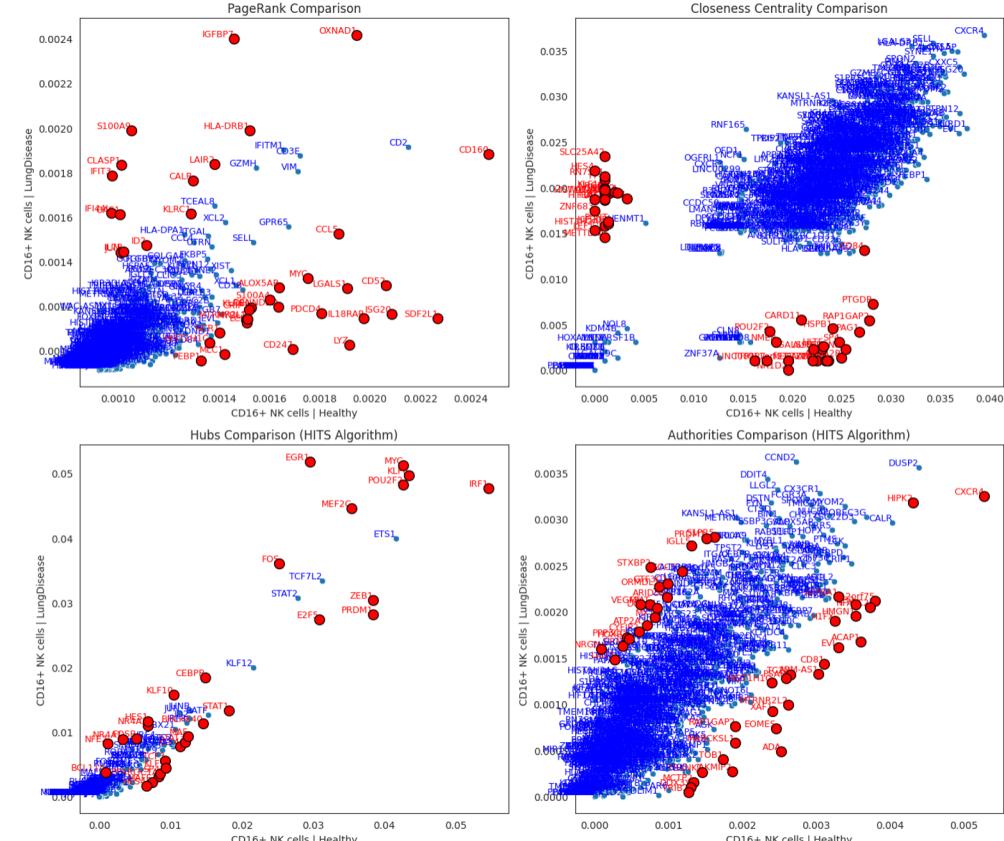
Graph 2
(Control)



Alternative metrics for identifying key nodes (genes) in GRNs

The following metrics were used to identify the most differential nodes between conditions:

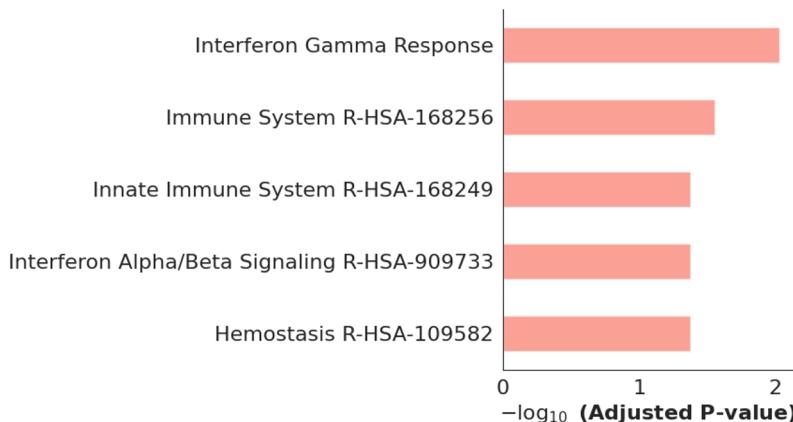
1. **PageRank**
2. **Closeness Centrality**
3. **Hubs Comparison (HITS Algorithm)**
4. **Authorities Comparison (HITS Algorithm)**



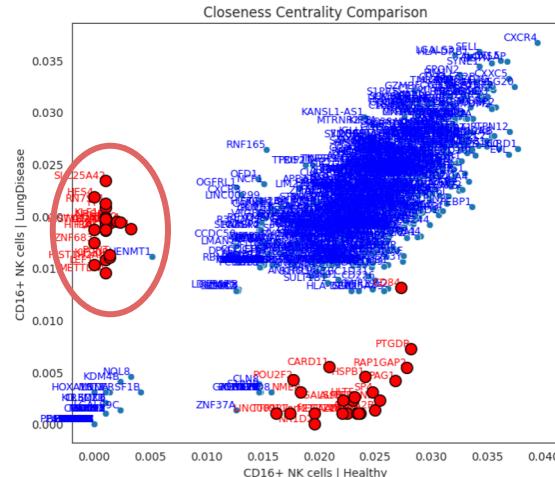
Альтернативные метрики для выявления ключевых узлов (генов)

Результаты ORA по узлам, характерным для CD16+ NK клеток группы ЮРА дополняют результаты анализа диф. экспрессии

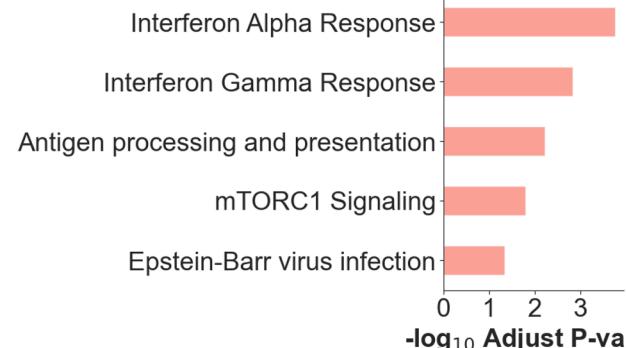
ЮРА (Closeness Centrality Outliers Nodes)



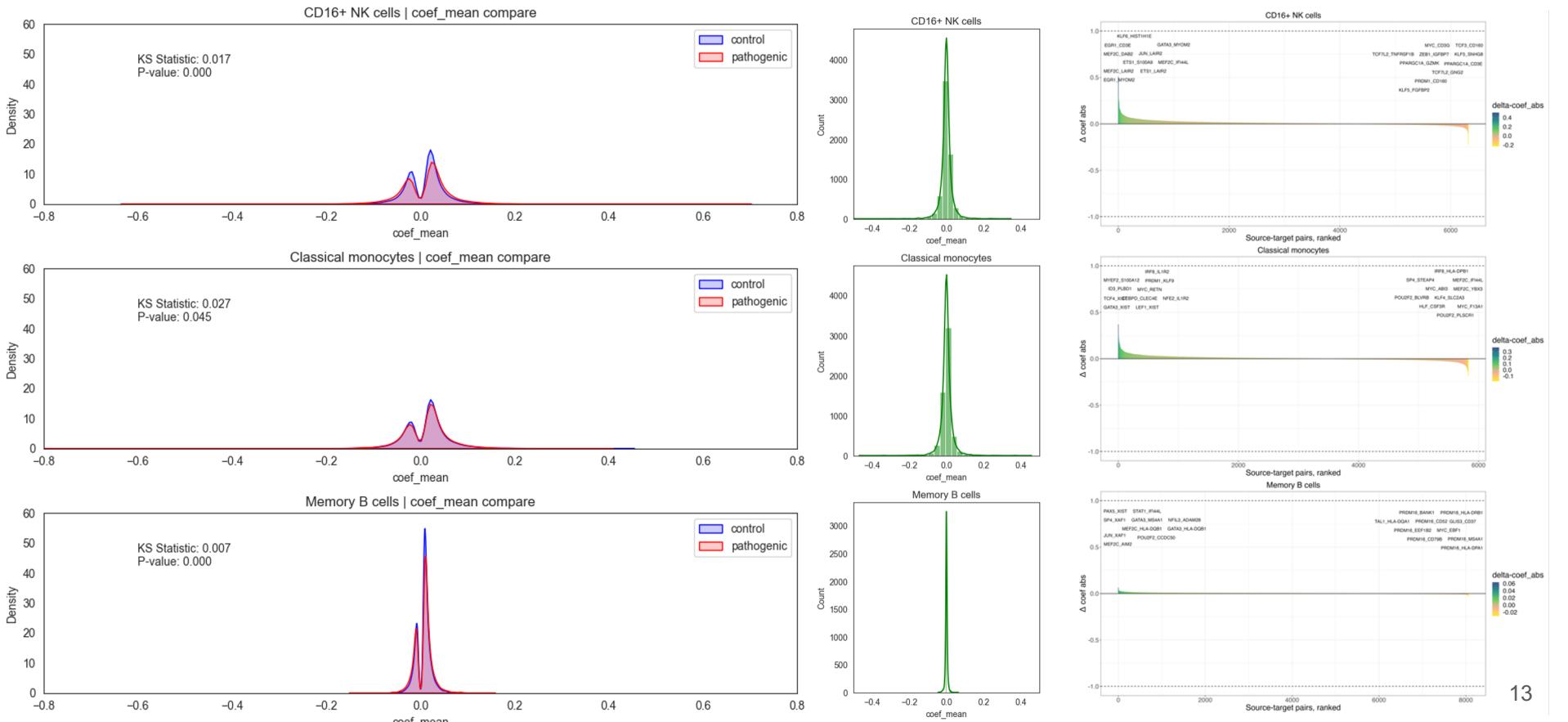
Association for Single Cell Analysis



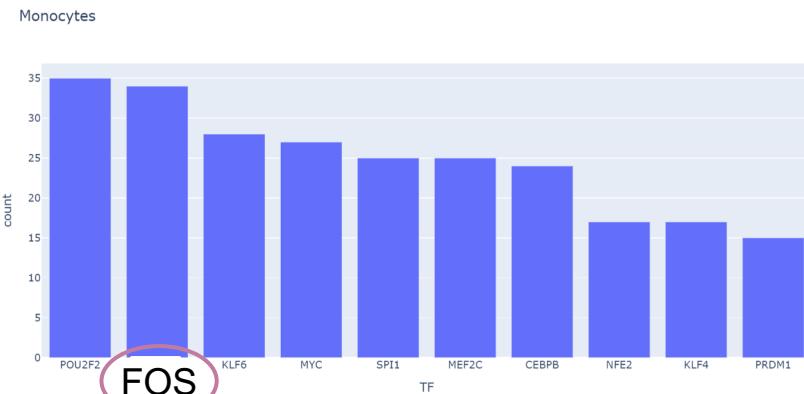
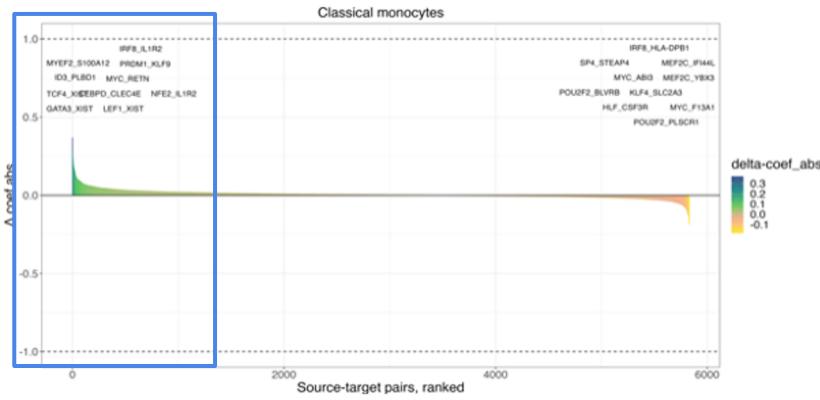
ЮРА (DEGs)



Distribution of Regression Coefficients Between States on an Isomorphic Graph. Kolmogorov-Smirnov Test.



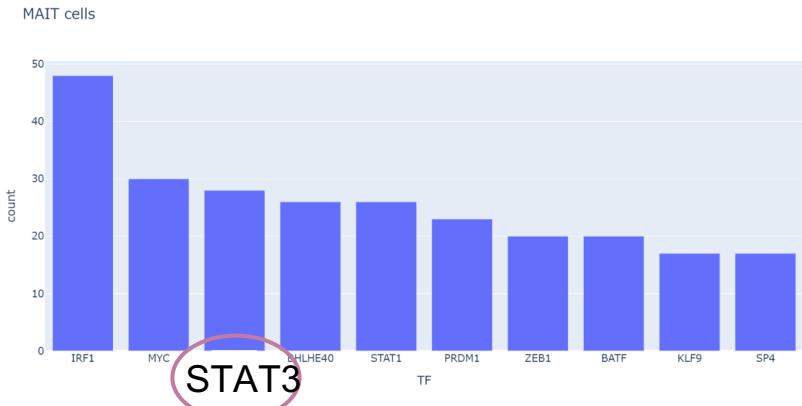
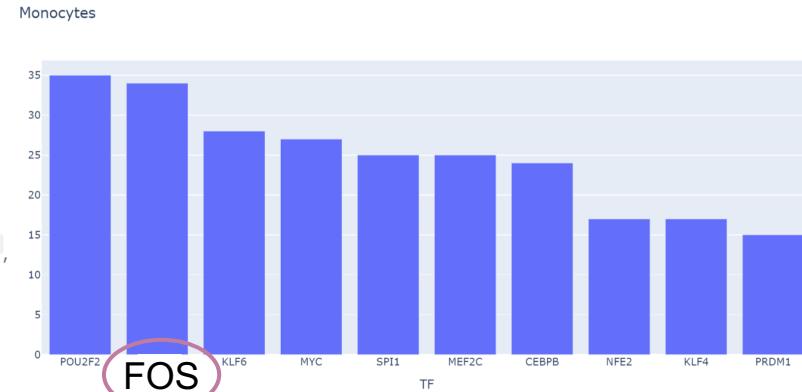
Transcription factors with the highest number of connections in JRA cells (among the top 500 most significant interactions)



Transcription factors with the highest number of connections in JRA cells (among the top 500 most significant interactions)

Metabolic rewiring controlled by c-Fos governs cartilage integrity in osteoarthritis

Kazuhiko Matsuoka ^{1 2}, Latifa Bakiri ³, Martin Bilban ^{4 5}, Stefan Toegel ^{6 7}, Arvand Haschemi ⁴,
Hao Yuan ⁸, Maria Kasper ⁸, Reinhard Windhager ⁶, Erwin F Wagner ^{9 3}



Conclusions

- 1) The metrics implemented in the current version of CellOracle for differential graph evaluation are based solely on node centrality assessment, which does not always capture the complete picture.
- 2) A set of heuristics and methods for differential graph evaluation has been developed, which can be applied to address biological questions using the CellOracle package.
- 3) Validation of the metrics and methods on other experimental datasets is required.