Identification of Differentially Expressed Gene Modules in Heterogeneous Diseases

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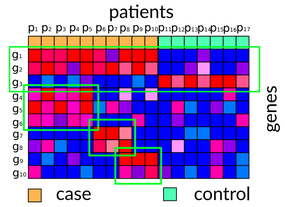
Novel network-constrained **biclustering method** reveals differentially expressed gene modules in **breast cancer**

BACKGROUND

Disease heterogeneity

- $g_{1\text{-}3}$ are up-regulated in case group compared to controls
- $g_{4\text{-}6}$, $g_{7\text{-}8}$ and $g_{9\text{-}10}$ are up-regulated only in **subgroups** of cases
- disease **subgroups** may be **unknown**

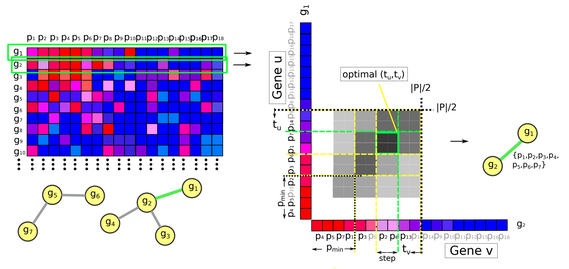


METHOD

DESMOND — a new method for identification of **D**ifferentially **E**xpre**S**sed gene **MO**dules i**N** **D**iseases

① Assigning patients on edges

Aim: find connected pairs of genes up- or down-regulated in subgroups of patients compared to the background



- for every pair of connected genes, identify optimal pair of thresholds, such that
  - number of patients with expression above both thresholds is maximal
  - this patient overlap is significant (hypergeometric test)
- the same approach is used to identify pairs of down-regulated genes and corresponding patients

② Probabilistic edge clustering

Aim: find connected subnetworks with similar patient sets on edges

- X_{mxn} for n edges and m patients is a matrix of patient module memberships obtained in step 1, where $x_{ij} = 1$, if sample i is assigned to edge j, or 0 otherwise
- The assignments of samples to the edges are modeled as a Bernoulli distribution with parameter θ_{ic} for each samples i and module c:

$$x_{ji}|\theta_{ic}, s_j \sim Bernoulli(x_{ji}|\theta_{ts_j}), \quad \theta_{ic}|\alpha \sim Beta(\theta_{ic}|\alpha/2, \alpha/2) \; for \; 1 \le c \le K$$

- s_j indicates the module membership of edge j and follows a categorical distribution with parameter π and a Dirichlet prior:

$$s_j|\pi \sim Categorical(s_j|\pi), \quad \pi|\beta \sim Dirichlet(\underbrace{\beta/K, ..., \beta/K}_{K \text{ of them}})$$

- conditional probability of edge j to join the module k:

$$P(s_j = k|X, s_{-j}, \alpha, \beta) \propto \prod_{i:x_{ji}=1} [\frac{\alpha/2 + \sum_{l:s_l=k, l\neq j} x_{li}}{\alpha + |\{l : s_l = k, l \neq j\}|}] \times \prod_{i:x_{ji}=0} [\frac{\alpha/2 + \sum_{l:s_l=k, l\neq j}(1 - x_{li})}{\alpha + |\{l : s_l = k, l \neq j\}|}] \times \frac{|\{l : s_l = k, l \neq j\}| + \beta/K}{m - 1 + \beta}$$

- Gibbs sampling is performed for parameter learning. After the model convergence, consensus module membership is taken.

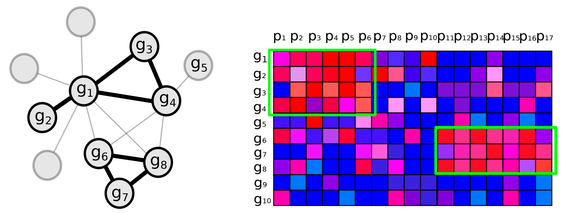
③ Postprocessing

- filtering out modules with low SNR
- merging modules with high overalp

PROBLEM DEFINITION

Find **groups of genes**

- **connected** on the PPI network
- **differentially expressed** in a **subgroup** of samples



Discovered **modules** are **reproducible**, enriched by **functionally related genes, and associated** with breast cancer **subtypes** and **survival**

This poster and code

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https://github.com/ozolotareva/DESMOND

EVALUATION

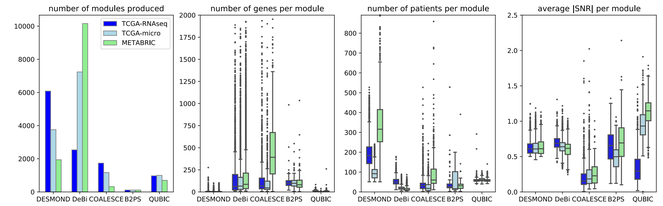
Datasets

- **TCGA-BRCA**
  - RNA-seq (1081)
  - microarrays (528)
- **METABRIC**
  - microarrays (1904)

Baseline Methods

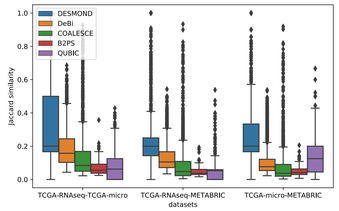
- DeBi
- QUBIC
- COALESCE
- B2PS

Characterization of modules produced by the five algorithms



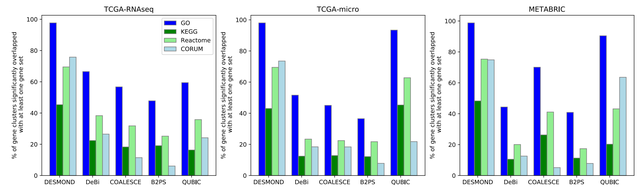
- DESMOND was the only method producing a number of large modules in terms of patients comprising nearly half of the whole cohort

Reproducibility



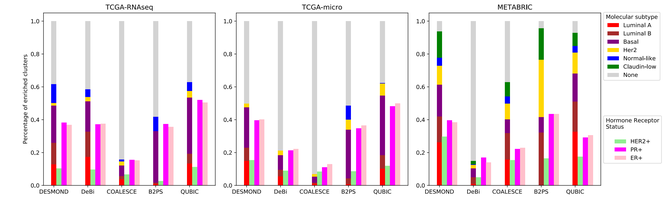
- Given clusterings $A=\{S_1,..,S_a\}$ and $B=\{S'_1,..,S'_b\}$, for every cluster $S_i \in A$ its best match $S'_j \in B$ is such that Jaccard similarity $J(S_i,S'_j)$ is maximal
- Similarly, all best matches of every $S'_j \in B$ are identified
- Distributions of Jaccard similarities of all matched pairs between the gene clusters found on datasets A and B are compared
- DESMOND produced more similar gene clusters in all three comparisons

GO and pathway enrichment



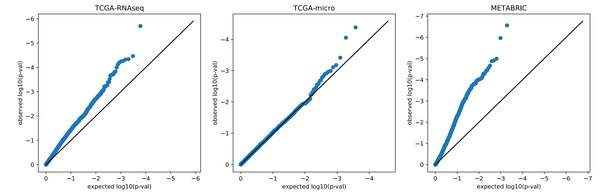
- DESMOND identified higher percentages of modules enriched by functionally related gene sets than the other methods

Association with known breast cancer subtypes



- DESMOND, QUBIC and B2PS identified similar proportions of sample clusters associated withknown molecular subtypes on all three datasets

Survival analysis



- Some modules identified by DESMOND are associated with overall survival