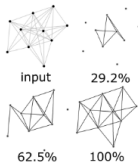
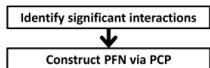


Multiscale Embedded Gene Co-expression Network Analysis (MEGENA)

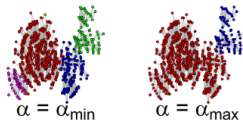
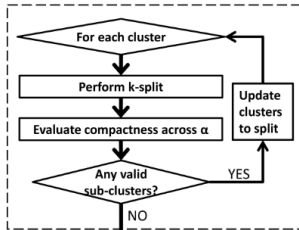
Brayan Gutierrez

MEGENA Flow Chart

A Fast PFN Construction



B Multi-scale Clustering Analysis



C Downstream Analyses

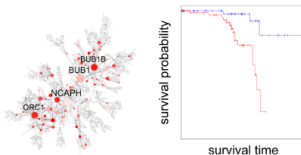
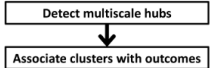


Fig 1. Flow chart of MEGENA. A) Fast planar filtered network construction. Significant interactions are first identified and then embedded on topological surface via a parallelized screening procedure described in the text. On the right, a toy example is illustrated to show construction of PFN from a thresholded network by FDR (top left), and gradual construction of PFN with number of included links and screened pairs shown on the top of each. B) Multi-scale clustering: Beginning from connected components of the initial PFN as the parent clusters, clustering is performed for each parent cluster and compactness of the sub-clusters are evaluated. These steps are described in the dotted box. The clustering is performed iteratively until there remains no further parent

Multiscale Embedded Gene Co-expression Network Analysis

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MEGENA vs. Other Methods

- Existing methods:
 - Require predefined parameters
 - Inability to reproduce scale-free properties
 - Lack support for multiscale organization
- MEGENA:
 - Developed to address issues above
 - Parallelized network construction
 - Efficiently handles large-scale genomic data
 - Novel clustering technique that can uncover hierarchy of co-expressed gene clusters

The MEGENA Framework

- Four-step methodology for inferring and analyzing gene co-expression networks
- Overcome computational and conceptual shortcomings of previous methods (Planar Maximally Filtered Graph (PMFG), Weighted Gene Co-expression Network Analysis (WGCNA), etc.)

Fast Planar Network Construction (FPFNC)

- First major step
- Takes in raw gene expression data → Compute pairwise similarities between genes
- Variety of similarity measures including:
 - Pearson's Correlation Coefficient (PCC)
 - Mutual Information (MI)
 - Euclidean Distance
- Includes optional step to remove insignificant interactions (False Discovery Rate)

FPFNC Cont.

- The core of FPFNC is the ability to construct a Planar Filtered Network (PFN)
 - Embeds gene pairs onto a topological sphere, ensuring no links cross each other
- To make the process scalable, parallelized screening procedure (PCP) is introduced
 - Efficiently identifies subset of gene pairs that are highly likely to be embedded
 - Reduces computational time required compared to existing serial algorithms

Multiscale Clustering Analysis (MCA)

- Can identify gene co-expression modules (aka “communities” or “clusters”)
- **Modules:** groups of genes whose expression profiles are tightly intertwined, suggesting they are involved in similar biological processes or disease states
- Clustering performed by the novel MCA procedure developed within MEGENA framework

MCA Cont. 1

- Uses hierarchical divisive approach to dissect complex interactions within PFN
- Turns this into coherent, multi-scale clusters
- Incorporates three distinct criteria to identify clusters:
 - **Shortest Path Distances (SPD)**: Optimizes for within-cluster compactness
 - **Local Path Index (LPI)**: Optimizes for local clustering structure, which is particularly effective in PFNs due to their abundance of 3- and 4-cliques
 - **Overall Modularity (Q)**: A measure used to identify an optimal partition of the network

MCA Cont. 2

- Uses a compactness measure, $v(\alpha)$, a function of resolution parameter α
- Used to identify clusters at different scales
- Smaller α value, the more compact the cluster
- Multiscale capability allows the framework to identify both coarse-grained and compact clusters that can coexist within a single network
- Addresses a key limitation of many other clustering methods

Hub Genes and Significance

- MEGENA provides a formal method for identifying most influential genes within modules: the hub genes
- **Hub Genes:** “highly connected members” of the co-expression network
- Identification of these hubs is performed by a dedicated procedure called Multiscale Hub Analysis (MHA)
- MHA works by:

Grouping the different scales that show similar connectivity patterns → Identify significant hubs within each scale → Identify multiscale hubs by combining significance scores for each node across all different scales

Innovations

| Method | Key Innovations | Purpose |
|--------------|--|---|
| FPFNC | Parallelized screening procedure (PCP); quality control of co-expression similarities | Construct a robust, scalable network efficiently |
| MCA | Hierarchical divisive clustering; uses SPD, LPI, and Q; compactness measure with a resolution parameter (α) | Identify multiscale clusters with varying degrees of compactness |
| MHA | Grouping of scales; combining significance scores across scales | Identify robust, highly connected hub genes at single and multiple scales |

Our Data

References

Song, W.-M., & Zhang, B. (2015). *Multiscale Embedded Gene Co-expression Network Analysis*. PLoS Computational Biology, 11(11), e1004574.