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MODA: MOdule Differential Analysis for weighted gene co-expression network

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Abstract

Summary: Gene co-expression network differential analysis is designed to help biologists understand gene expression patterns under different condition. By comparing different gene co-expression networks we may find conserved part as well as condition specific set of genes. Taking the network as a collection as modules, we use a sample-saving method to construct condition-specific gene co-expression network, and identify differentially expressed subnetworks as conserved or condition specific modules which may be associated with biological processes. We have implemented the method as an R package which establishes a pipeline from expression profile to biological explanations. The usefulness of the method is also demonstrated by synthetic data as well as Daphnia magna gene expression data under different environmental stresses.
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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Gene co-expression network attracts much attention nowadays. In such a network, nodes represent genes and each edge connecting two genes stands for how much degree may this pair of genes are co-expressed across several samples. The presence of these edges is commonly based on the correlation coefficients between each gene pairs. The higher of correlation between a pair of genes, the higher probability that there exists a co-functionality relationship between them. With proper choice of minimal correlation value as a threshold, we can generate an unweighted and undirected network for given gene expression profile. But the optimal cut-off threshold is difficult to determine. And throwing away relatively large proportion of correlation coefficients will lead to information loss. In contrast, weighted correlation network analysis (WGCNA) overcomes this drawback by keeping all possible edges but shows how significant is the co-expression relationship using edge weights [1, 2].

A module in a biological network is defined as a subnetwork which may involves a common function in biological processes. The module detection in WGCNA is based on hierarchical clustering, which groups similar genes into one cluster. The similarity was defined by topological overlap measure [2]. Following the logic of WGCNA, here we mainly improve it from the following three aspects: 1) How to determine the cutting height of hierarchical clustering tree roughly depends on self-definition in WGCNA. Here we give an option to choose the height based on the quality of partition. 2) Edge weights in gene co-expression networks are defined by correlation coefficients of gene pairs. And it is well known that the accurate correlation coefficient is approximated by $1/sqrt(n)$ where n is the number of samples, which makes it impossible to get reliable correlation coefficients with only several replicates under each experimental condition in practice. We use a sample-saving way to analyze condition-specific co-expression network for each single condition. 3) Taking a network as a collection of modules, we generalize the differential

analysis from individual genes to modules, which may find condition specific and conserved subnetworks.

2 Methods

Inspired by the concept of partition density of link communities [3] where the modules were defined based on the link similarity, we propose a cutting method to make the average density of resulting modules to be maximal. Here we simply define the module density as the average edge weights in one module (equation (1) in supplementary file) which keeps the same in [2], and then find the cutting height of hierarchical clustering that leads to maximal average density. We also provide other criterion such as average modularity for weighted network [4] of resulting clusters to determine the cutting height.

General gene differential analysis has covered identification of important individual genes which shows significant changes across multiple conditions [5]. However, based on the fact that genes interact with each other to exert some biological function instead of acting alone, it is more informative to identify a subnetwork (module) of genes which are conserved across multiple conditions or just active in certain conditions. DICER [6] also goes beyond individual gene differential analysis, using a probabilistic framework to detect differentially co-expressed gene sets. DINA [7] can identify condition-specific modules from a collection of condition-specific gene expression profiles which differs from our sample-saving method. Based on a set of condition-specific networks, we use WGCNA to identify modules for different networks. Then, we use the Jaccard index, which essentially measures the similarity between two sets of elements, to measure the similarity between modules from two different networks.

By comparing all module pairs of two networks, we can get a similarity matrix A,where each entry A_{ij} means the Jaccard similarity coefficient between the i-th module from the network N_1 and j-th module from the network N_2. Assume the N_1 is background, normally containing samples from all conditions, and the N_2 is constructed from all samples minus samples belong to certain condition D [8]. Then the elements in row sum of A (vector denoted by $\mathbf{s}$) indicate how much degree that modules in N_1 can be affected by condition D. The higher $\mathbf{s}_i$ means the module i in N_1 may just be responsible for general stress. Especially when some $\mathbf{s}_i$ in N_1 keeps relatively high row sum of A compared with all other N_2 (remove one condition each time), showing these modules have little association with any specific conditions. While lower $\mathbf{s}_i$ means module i in N_1 is very different from the modules in N_2, which may indicate the module has some connection with condition D. The rationale behind this simple criteria is based on the mechanism of correlation, i.e. which samples can make impact on the correlation coefficient while others may not? More details can be found in supplementary file part 1.

After determine which module may be condition specific, we can associate biological process with module by functional annotation enrichment analysis. The input can be gene list from the module, or overlapping just part much with others. Here we use DAVID [9] to conduct integrative functional annotation enrichment analysis of gene list based on an R Webservice interface [10]. We implemented a module differential analysis pipeline, from gene expression profile of multiple conditions to enrichment analysis results. Figure shows the general process of each step mentioned above.

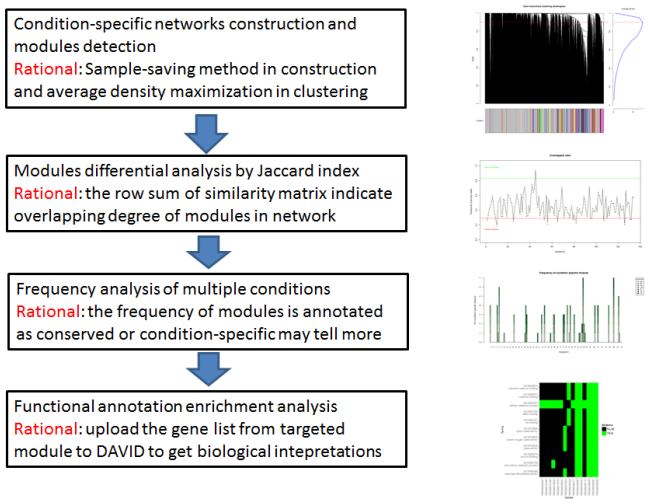

Fig. 1. Overview of MODA.

3 Result

We evaluated the effectiveness of proposed methods on both synthetic data and real-world data. By comparing two gene expression profiles generated by different desired correlation matrices of the same set of genes, we can determine the genes affected by a groups definition, which is consistent with the generator. The details for simulation as well as the usage of package can be found in supplementary file part 2. The method is also used on a comprehensive RNA-Seq data set obtained from two natural genotypes fo D. magna, to detect condition-specific as well as conserved responsive genes and biological functions. Several biological meaningful results show the capability of the algorithm, and more details can be found in [stressflea draft].

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