Subject Section

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

Dong Li¹, James B. Brown², Luisa Osini³, Zhisong Pan⁴, Guyu Hu⁴ and Shan He¹

¹School of Computer Science, University of Birmingham, Birmingham, B15 2TT, UK,
²Department of Genome Dynamics, Lawrence Berkeley National Laboratory, University of California Berkeley, Berkeley, California, 94720 USA,
³School of Biosciences, University of Birmingham, Birmingham, B15 2TT, UK,
⁴College of Command Information System, PLA University of Science and Technology, Nanjing, 210007, China

∗To whom correspondence should be addressed.

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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.

Availability: Available at https://www.cs.bham.ac.uk/ szh/software.xhtml

Contact: s.he@cs.bham.ac.uk

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 pair. 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 $a$) indicate how much degree that modules in $N_1$ can be affected by condition $D$. The higher $s_i$ means the module $i$ in $N_1$ may just be resistant for general stress. Especially when some $s_i$ 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 $s_i$ 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 Web service 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.

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 [stresslea draft].

References


