Identifying Differentially Connected Genes of Breast Invasive Carcinoma in Co-expression Networks

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***Abstract*—Topological changes of a gene network across different conditions such as normal versus cancer can provide hints regarding the disrupted regulatory relationships or affected regulatory sub-networks specific to a phenotype of interest. This work aims to identify differentially connected genes (DCGs) that cause significant topological changes between two gene co-expression networks: breast invasive carcinoma versus normal samples.**

I. Introduction

Breast cancer is the most common malignancy in women worldwide with high mortality from the cancer. [1] Breast cancer accounts for 5-10% of hereditary of all cases. [2] Since $BRCA1$ and $BRCA2$ the first two breast cancer susceptibility genes identified, [3], [4], more and more causal genes such as $TP53$, $PTEN$, $STK11$, $CHEK2$, ATM, $PALB2$, $BRIP1$, and $CASP8$ were identified to be highly related to Breast cancer. [5] Therefore, identification of breast cancer susceptibility genes holds promise in providing potential therapeutic targets.

Gene expression profiling has been widely used for cancer research, one popular way to identify susceptibility genes is to figure out the differentially connected genes among cancer and normal gene co-expression networks. [6], [7] Most of them picked out differentially connected genes focused on the hub genes of the networks, however, it is highly possible that some differentially connected genes are not included in hub genes for a specific cancer. In this work, we plan to integrate multiple measures to identify differentially connected genes (DCGs), for the purpose of seeking new genes that can provide hints regarding the disrupted regulatory relationships or affected regulatory sub-networks specific to a phenotype of interest.

The gene expression dataset we use is Breast invasive carcinoma dataset from The Cancer Genome Atlas (TCGA, https://tcga-data.nci.nih.gov/tcga), which contains expression profiles of 17,614 genes for 531 tumor and 62 normal samples. We would construct gene co-expression networks for the cancer and the normal group by simply calculating correlation coefficients between pairs of genes for each group. In order to figure out the important topological changes and corresponding genes between two networks, we will first compute the Euelidean Commute Time Distance (ECTD) [8] of each pair of genes by letting a random walker walks on each gene network. Then we calculate several graphical measures such as the clustering coefficient and the three types of node centrality measures from ECTD. We will propose several DCG measures to identify differential connectivity of each gene between two networks. We will pick out the top ranked DCGs based on those DCG measures individually, and identify overlapped genes among the DCG measures. The enriched biological GO terms and KEGG pathways will be evaluated based on selected interesting genes for further biological evaluation as well as literature reviews on those genes.

II. Method

In this section, we illustrate each procedure of the Differentially Connected Gene (DCG) analysis along with the Figure II. In section II-A, a weighted, undirected gene co-expression network for each group is constructed using gene expression profiles. In section II-B, a Euclidean Commute Time Distance (ECTD) matrix for each group is computed which will be used to calculate the differential network measures for each gene within each network in section II-C. In section II-D, we propose several DCG statistics to evaluate connectivity difference of each gene between two networks using the differential network measures.

A. Preliminaries

Given gene expression profiles for each group A and B, where n_A and n_B is the number of samples for group A and B respectively. Two sample t-test is performed on each genes to select differentially expressed genes between the two groups. The selected genes are used to construct a $p \times p$ gene co-expression matrix $\mathbf{N}_A$ for group A and $\mathbf{N}_B$ for group B such that:

$$\mathbf{N}_A = [|r_{A,ij}|]_{p\times p}$$
$$\mathbf{N}_B = [|r_{B,ij}|]_{p\times p}$$

where $r_{A,ij}$ and $r_{B,ij}$ are sample Pearson correlation coefficients between gene i and j for group A and B respectively; and p is the number of selected genes. Each co-expression matrix represents each gene network $\mathcal{G}_A(\mathcal{V}, \mathcal{E}_A)$ and $\mathcal{G}_B(\mathcal{V}, \mathcal{E}_B)$ where $\mathcal{V}$ is the set of p nodes (genes); $\mathcal{E}_A$ and $\mathcal{E}_B$ are the set of edges in $\mathcal{G}_A$ and $\mathcal{G}_B$ respectively; an edge between a pair of genes are weighted with $|r_{A,ij}|$ and $|r_{B,ij}|$ respectively. Each weight represents the intensity of relationship between pairs of genes are non-negative and symmetric.

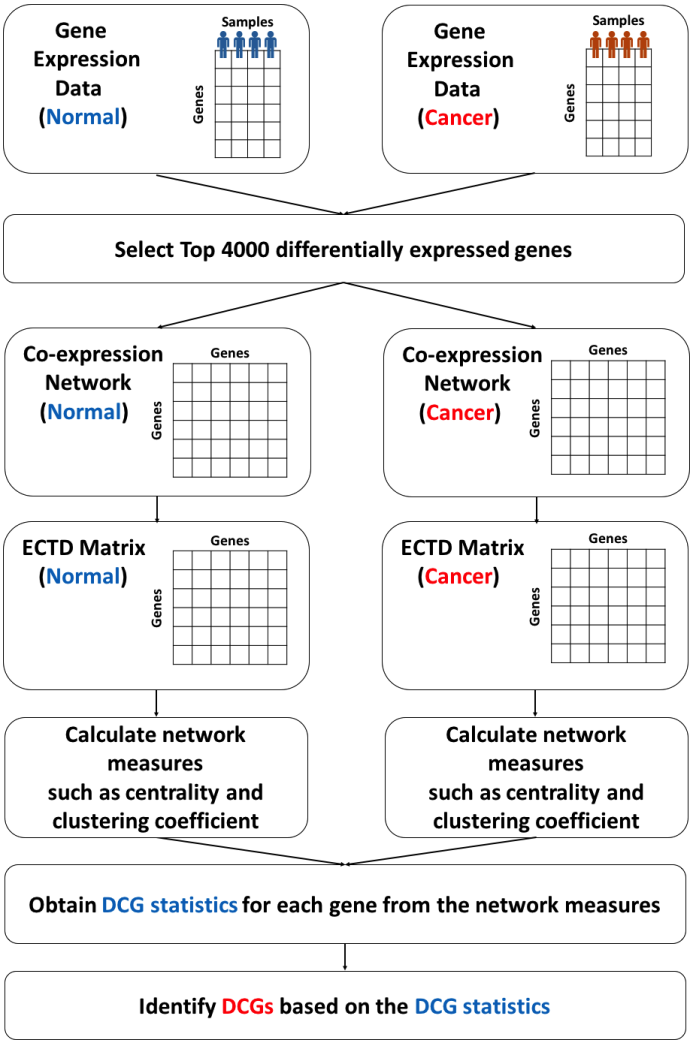

Fig. 1. Flowchart of DCG analysis

B. Euclidean Commute Time Distance

Euclidean Commute Time Distance (ECTD, [8]) is a distance metric between nodes of a weighted, undirected graph. ECTD matrix for each group is computed based on a random walk Markov chain model which transition probability is obtained from a Laplacian matrix of the gene co-expression network.

1) Laplacian Matrix of a Weighted Gene Network: An adjacency matrix $\mathbf{A}$ of each group is defined in a standard way as:

$$\mathbf{A_A} = [a_{A,ij}]_{p\times p} \begin{cases} |r_{A,ij}| & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases}$$

$$\mathbf{A_B} = [a_{B,ij}]_{p\times p} \begin{cases} |r_{B,ij}| & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases}$$

which is both positive and symmetric. The Laplacian matrix $\mathbf{L}$ of each group is defined as $\mathbf{L} = \mathbf{D} - \mathbf{A}$ where $\mathbf{D} = diag(d_{ii})_{p\times p} = diag(\sum_{j=1}^{p} a_{ij})_{p\times p}$.

2) Random Walk Markov Chain Model: We define a random walk Markov chain model [9] along with each node in the gene co-expression network. Every gene is associated with a state of the Markov chain. The Laplacian matrix $\mathbf{L}$ is used to define a transition probability matrix $\mathbf{P}$ which is assigned to each edge. A random walker starts from node i at time t jumps from gene to gene with a single-step transition probability such that:

$$\mathbf{P}[s(t+1) = j | s(t) = i] = a_{ij}/d_{ii} = p_{ij}$$

where $s(t)$ is a random variable representing the state of the Markov chain at time t. Therefore, we define $\mathbf{P} = \mathbf{D^{-1}A}$.

3) Expected Commute Time: Under the random walk Markov chain model, two basic quantities can be computed: the expected first-passage time and the expected commute time. [9] The expected first-passage time $m(k|i)$ is defined as the expected number of steps a random walker, starting in state i, will get to state k for the first time:

$$m(k|i) = \mathbf{E}[T_{ik}|s(0) = i]m(k|k) = 0$$

where T_{ik} it the minimum time until hitting state k such that $\min(t \geq 0 | s(t) = k$ and $s(0) = i)$. The expected commute time is defined as a related quantity of the expected first-passage time:

$$n(i,j) = m(j|i) + m(i|j)$$

Note that $n(i,j)$ is symmetric and non-negative measures by definition. Moreover, it has been shown that the expected commute time $n(i,j)$ is a distance metric. [8], [10], [11]

4) Computation of Euclidean Commute Time Distance: The Euclidean Commute Time Distance (ECTD) can easily be computed as a function of pseudo-inverse of the Laplacian matrix $\mathbf{L}$ and volume of the graph V_A and V_B. [8]

$$\begin{aligned} \mathbf{ECTD_A} &= [n_{A,ij}]_{p\times p} \\ &= [V_A(e_i - e_j)^T \mathbf{L}_A^-(e_i - e_j)]_{p\times p} \\ \mathbf{ECTD_B} &= [n_{B,ij}]_{p\times p} \\ &= [V_B(e_i - e_j)^T \mathbf{L}_B^-(e_i - e_j)]_{p\times p} \end{aligned}$$

where $V_A = \sum_{i,j} a_{A,ij}$ and $V_B = \sum_{i,j} a_{B,ij}$; e_i is a unit basis vector for each node i; $\mathbf{L}_A^-$ and $\mathbf{L}_B^-$ are a Moore-Penrose pseudo-inverse of the Laplacian matrix for each group. [12] Since $\mathbf{L}^-$ is a positive semi-definite matrix, n_{ij} is a distance metric in the Euclidean space of the gene network.

C. Differential Network Measures

Each node within a network can be characterized via several differential network measures. The measures attempts to quantify the 'importance' of a node within a network, however there is no unique interpretation of the 'importance'. For example, the 'importance' can be represented by potential for autonomy, control, risk, exposure, influence, belongingness, and so on. [13] Here we introduce three type of centrality measures and clustering coefficient based on ECTD matrix. Since the expected commute time represents dissimilarity between pairs of genes, the inverse of it used as a weight of the edges in each gene network. Those measures will be utilized to define DCG statistics in section II-D.

1) Centrality Measures:

- Degree Centrality
  In a binary graph, the degree centrality for node i is defined as the number of its neighbors. In general, degree centrality $c_d(i)$ is simply the sum of weight of edges including the gene i. [14], [15]

$$c_d(i) = \sum_{j=1}^{p} \frac{1}{n(i,j)}$$

  By the definition, the degree centrality represents how each gene is involved in the weighted gene network along with its neighbors.
- Betweenness Centrality
  Betweenness centrality [16] is defined by the number of shortest paths going through a gene. In a binary network, it is defined as:

$$c_b(i) = \sum_{u \neq v \neq i} \frac{\sigma_{uv}(i)}{\sigma_{uv}}$$

  where σ_{uv} is the total number of shortest paths from gene u to gene v and $\sigma_{uv}(i)$ is the number of those paths that pass through the gene i. We use a fast algorithm to calculate betweenness centrality proposed by Brandes (2001). [17] which allow to calculate the betweenness centrality on weighted networks.
- Closeness Centrality
  Closeness centrality [16] quantifies how many steps is required to access every other genes from a given gene. (i.e. the sum of distances to all other gene from a given gene) The closeness centrality has been generalized to weighted networks by Newman [18]. Therefore it is defined as:

$$c_c(i) = \frac{1}{\sum_j dist(i,j)}$$

  where $dist(i,j)$ is the shortest distance between gene i and j. Note that the closeness centrality and degree centrality using ECTD matrix are very similar to each other since the expected commute time is a distance metric.

2) Clustering Coefficient: Clustering coefficient [19], [20] refers a fraction of neighbors of given gene that are interconnected each other, which is also called as transitivity. It quantifies how its neighbors are clustered together given a gene. Note that there are essentially two types of clustering coefficients: one for each gene and the other for a whole network. The clustering coefficient here refers the gene-level measurement. Also we use the generalized clustering coefficient suggested by Barrat [21] which can be calculated on a weighted network:

$$CC(i) = \frac{1}{s_i(c_d(i)-1)} \sum_{j,h} \frac{w_{ij}+w_{ih}}{2} a_{ij}a_{ih}a_{jh}$$

where s_i is the strength of gene i; a_{ij} are elements of the adjacency matrix; $c_d(i)$ is the vertex degree; w_{ij} are the weights. Note that we use the inverse of expected commute time as a weight on each edge, so s_i, a_{ij}, and w_{ij} will be obtained from the ETCD.

D. Measures for Differentially Connected Gene

Based on the differential network measures introduced in section II-C, we propose four measures to quantify connectivity difference of a gene between two different networks: degree differences, betweenness differences, closeness differences, and clustering coefficient differences. Note that the differential network measures are defined for each gene within a network. By comparing the measures from two different networks, we will identify differentially connected genes (DCGs).

1) Degree Differences: Degree differences is defined as an absolute difference between the degree centrality measures of group A and B, normalized by those sum:

$$DCG_{degree}(i) = \frac{|c_{A,d}(i) - c_{B,d}(i)|}{|c_{A,d}(i) + c_{B,d}(i)|}$$

where $c_{A,d}(i)$ and $c_{B,d}(i)$ are the degree centrality of gene i in group A and B respectively. Genes that have large difference in the degree centrality between two groups while overall degree centrality are small will be highly ranked based on the degree differences.

2) Betweenness Differences: Betweenness differences is defined as an absolute difference between the betweenness centrality measures of group A and B.

$$DCG_{betweenness}(i) = |c_{A,b}(i) - c_{B,d}(i)|$$

where $c_{A,b}(i)$ and $c_{B,b}(i)$ are the betweenness centrality of gene i in group A and B respectively. The betweenness difference ranks genes that has large difference in the betweenness centrality between two groups.

3) Closeness Differences: Closenness differences is defined as an absolute difference between the centralized closeness centrality of group A and B.

$$\begin{aligned} DCG_{closenness}(i) = |&(c_{A,c}(i) - median(c_{A,c}(i))) \\ &-(c_{B,c}(i) - median(c_{B,c}(i)))| \end{aligned}$$

where $c_{A,c}(i)$ and $c_{B,c}(i)$ are the closeness centrality of gene i in group A and B respectively; $median(c_{A,c}(i))$ and $median(c_{B,c}(i))$ are median of the closeness centrality of all genes in group A and B respectively. Genes which derivation of closenness centrality from its median is changed a lot between two groups will be highly ranked based on the closeness differences.

4) Clustering Coefficient Differences:

$$DCG_{CC}(i) = \left| \log \frac{CC_A(i) \times c_{A,d}(i)}{CC_B(i) \times c_{B,d}(i)} \right|$$

where $CC_A(i)$ and $CC_B(i)$ are the clustering coefficient of gene i in group A and B respectively; $c_{A,d}(i)$ and $c_{B,d}(i)$ are the degree centrality of gene i in group A and B respectively. By the definition, clustering coefficient is inversely proportional to degree of genes. Therefore, effect of degree centrality of genes is controlled by multiplying the degree centrality to the clustering coefficient. The clustering coefficient differences is log ratio of those between two groups. As it increases, genes will be highly ranked.

III. Experimental Results

A. Data

The gene expression dataset we use is Breast invasive carcinoma dataset from The Cancer Genome Atlas (TCGA, https://tcga-data.nci.nih.gov/tcga), which contains expression profiles of 17,814 genes for 531 tumor and 62 normal samples. Missing values are imputed via K-nearest neighborhood (KNN, [22], [23]) method with $K = 10$. For each samples, it finds the 10 nearest neighbors using a Euclidean metric, then imputes the missing values by averaging values of its neighbors.

B. Experiment on Real Dataset

The DCG analysis is conducted to the TCGA Breast invasive carcinoma dataset. The 531 tumor samples are consist of a *Cancer* group, and 62 normal samples are consist of a *Normal* group. Two sample T-test is performed on each gene to find significant genes showing differential expression levels between two groups. Top 4000 DEGs are selected as significant genes, and used to construct co-expression matrix for each group. (Although it can be any numbers where the p-values are smaller than a significant level α, we choose the largest number possible to run in a computer.) ETCD matrix for each group is then constructed. The differential network measures are calculated via R-package called igraph. [24] Each DCG measures are calculated by comparing the network measures from two groups.

C. Result

The DCG measures are used to identify DCGs. Top k ranked genes having large values of the DCG measures are selected. The number of overlapped genes are examined in Figure 2. ($k = 20, 50$) Unlike other measures, the betweenness differences are obtained from the gene co-expression matrix but not from the ECTD matrix because most of the values from ECTD matrix is zero. Majority of genes are selected from all four measures, indicating that topological difference of those genes are very obvious in any measures. The completely overlapped genes among all DCG measures are listed in Table I. Note that the p-value from DEG analysis represents differential expression level between two groups while the DCG measures identify differential connectivity. Therefore, DCG measures can identify DCGs that have not been considered significant as much as other highly ranked genes in DEG analysis. Table II is a list of partially overlapped genes that are ranked high at least one DCG measure but not all DCG measures. Note that the partially overlapped genes are identified because at least one of differences in betweenness, closeness, or clustering coefficient, not because of the degree differences. Therefore, we consider those genes very interesting because it had been hard to be detected when you only consider the module centrality to evaluate its connectivity status. That is, the partially overlapped genes are not easy to be identified by previous approaches on gene co-expression network that has only focused on hub genes connected with large number of neighbors, while the completely overlapped genes might

Fig. 2. Overlapped genes between the DCG measures. Top 20 genes (left) are selected for each method. Total 27 genes are selected from at least one criteria. Total 50 genes (right) are selected for each method. Total 70 genes are selected from at least one criteria.

be identified. Moreover, there are few more interesting genes identified based on the betweenness difference measure. Figure 3 represent the betweenness difference measures obtained from the ECTD matrix and the gene co-expression matrix. Majority of genes has zero values for the betweenness difference measure because the betweenness centralities from both the cancer and the normal ECTD matrix are zero. Unlike the majority of genes, three genes ($NSMCE4A$, $ATE1$, $APBB$) show large changes in the betweenness difference measures. Especially, $ATE1$ and $NSMCE4A$ show large difference even though there are almost no difference in the betweenness difference measures obtained from the gene co-expression matrix. Those two genes are also highly ranked from other measures: density differences, closeness differences, and clustering coefficient.

Detailed evaluation of all of those selected genes will be examined in section III-D.

D. Biological Evaluation

Among the top overlapped differentially connected genes as shown in Table I, gene $CKAP2$ is a newly identified a prognostic indicator for Breast cancer. [26] Gene $KIAA0859$

TABLE I
LIST OF COMPLETELY OVERLAPPED GENES BETWEEN THE DCG MEASURES. TOP 20 GENES ARE SELECTED FOR EACH METHOD. P-VALUES OBTAINED FROM DEG ANALYSIS ARE ADJUSTED USING A METHOD PROPOSED BY BENJAMINI AND HOCHBERG (2005). [25] GENES ARE RANKED BASED ON THE P-VALUES.

Gene	P-value (BH)	Rank in DEG Analysis
$APBB1$	$2.23E-20$	2069
$ATAD1$	$1.40E-14$	3881
$C2orf37$	$1.68E-27$	647
$CAPRIN1$	$1.02E-13$	3790
$CKAP2$	$2.48E-39$	205
$KIAA0859$	$4.29E-27$	1609
$LOC388284$	$8.14E-17$	2405
$LRFN3$	$3.09E-13$	3751
$NUP155$	$2.10E-27$	1151
$PCGF5$	$7.41E-23$	1611
RBJ	$5.86E-21$	1685
$RFWD3$	$1.16E-27$	1040
$STAU1$	$3.77E-16$	2889
$TBRG4$	$6.74E-17$	2780

TABLE II
LIST OF PARTIALLY OVERLAPPED GENES BETWEEN THE DCG MEASURES. TOP 20 GENES ARE SELECTED FOR EACH METHOD. P-VALUES OBTAINED FROM DEG ANALYSIS ARE ADJUSTED USING A METHOD PROPOSED BY BENJAMINI AND HOCHBERG (2005). [25] GENES ARE RANKED BASED ON THE P-VALUES.

Gene	P-value (BH)	Rank in DEG Analysis
$ATE1$	$8.22E-16$	3139
$GSTP1$	$3.84E-38$	1049
$NSMCE4A$	$2.45E-13$	4030
$ATP13A1$	$2.10E-18$	1895
$FAM10A5$	$6.71E-16$	2953
$GGPS1$	$1.58E-18$	2571
$RXFP4$	$3.39E-14$	3592
$WDR8$	$5.54E-17$	2787
$BRMS1$	$7.01E-20$	1777
$C20orf121$	$1.03E-18$	2425
$FKSG24$	$6.88E-22$	1559
$GON4L$	$2.13E-14$	3543
$WSB1$	$4.73E-24$	1235

is a tumor promoter in most of human cancers including Breast Ductal Carcinoma. [27] In addition, for the less overlapped genes as shown in Table II, gene $ATE1$ is an important gene that could affect the pathway of susceptibility gene $BRCA1$. [28] Gene $BRMS1$ encodes the protein $BRMS1L$ that could suppress Breast cancer metastasis by inducing epigenetic silence of $FZD10$. [29] These confirmations led us to do further biological evaluation on enriched GO terms and KEGG pathways on the DCGs.

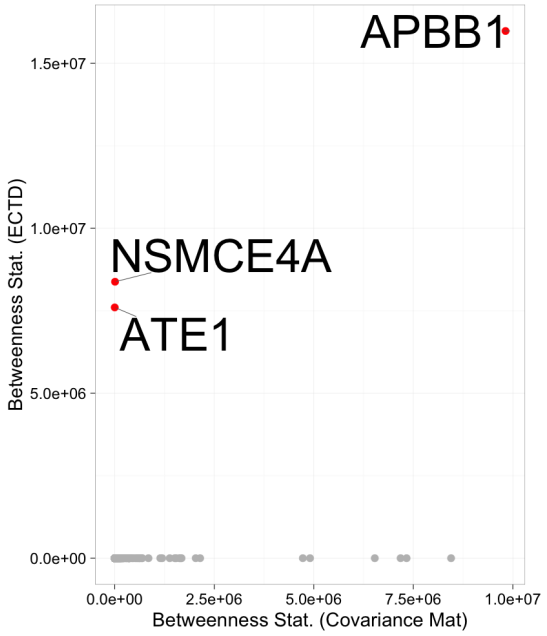

Fig. 3. The betweenness difference measures obtained from the ECTD matrix (y-axis) versus from the gene co-expression matrix (x-axis).

For the enriched biological GO terms and pathways of the DCGs, Top 200 genes out of 17,814 genes obtained from each DCG measures are used to perform the pathway analysis. Table III shows the odd ratio and its p-value for two pathways related to Breast invasive carcinoma. The ErbB is an oncogene that have been reported to play an early role in spradic Breast cancer. [30], [31] In the top 200 list of genes from DCG analysis we have three genes ($PRKCA$, $SHC1$, $PAK4$) included in *ErbB signaling pathway* (KEGG ID: 04012). As we can see in Table III, the pathway have an odd ratio close to 1, which means that previous approaches based on differential expression could not identify those pathway. Other interesting pathway is *Progesterone-mediated oocyte maturation* ($CDC25B$, $PLK1$, $MAPK13$), which the DCG approach has identified. However, it also higher odds ratio in DEG analysis so that it could be found from previous approaches based on differential expression of genes.

TABLE III
LIST OF PATHWAYS THAT IS RELATED TO BREAST INVASIVE CARCINOMA ON THE KEGG PATHWAY ANALYSIS

KEGG ID	Pathway	Odd Ratio (P-value)	Odd Ratio (P-value) in DEG
04012	ErbB signaling pathway	1.817 (0.241)	1.105 (0.902)
04914	Progesterone-mediated oocyte maturation	1.840 (0.245)	2.893 (0.095)

IV. CONCLUSIONS

In this paper, we proposed a new approach to identify differentially connected genes (DCGs) between two gene co-expression network. The gene co-expression networks are

converted to Euelidean Commute Time Distance (ECTD) Matrix composed of distance metrics between two genes within each network. Several graphical network measures such as degree centrality, betweenness centrality, closeness centrality and clustering coefficient are calculated for each genes within each network. Based on those network measures, we propose four DCG measures to identify DCGs.

Based on the four DCG measure, the completely overlapped genes among the four measures are identified as well as the partially overlapped genes. Majority of genes listed in Table I and II are not easy to be identified by focusing on differential expression profiles for each genes. Moreover, the partially overlapped genes are not easy to be identified by previous approaches on gene co-expression network that has only focused on hub genes connected with large number of neighbors, while the completely overlapped genes might be identified. Also by comparing the betweenness difference measure between ECTD and co-expression network, we could find three interesting genes that show very different patterns from other genes.

Among the DCG that we identified based on the DCG measures, 4 out of 27 genes were confirmed to be typical breast cancer related genes. It is highly possible that other top ranked genes might play potential role in breast cancer. In addition, KEGG Pathway enrichment analysis helps identify potential breast cancer related pathway ($ErbB$ signaling pathway), which could not be identified by methods based on differentially expressed genes alone.

All those analysis can contribute to the understanding breast cancer and its causal genes, and will provide hints regarding the disrupted regulatory relationships or affected regulatory sub-networks specific to breast cancer.

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