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ABSTRACT

GENE NETWORK UNDERSTANDING AND ANALYSIS

by
Maria E. Somoza

Gene regulatory network (GRN) is a collection of regulators that interact with each other in the cell to govern the gene expression levels of mRNA and proteins. These regulators can either be DNA, RNA, protein and their complex. Transcriptional gene regulation is an important mechanisms in which an in-depth study can lead to various practical applications, and a greater understanding of how organisms control their cellular behavior. One of the most widely studied organisms in gene regulatory networks are the *Mycobacterium tuberculosis* and *Corynebacterium glutamicum* ATCC 13032.

Gene co-expression networks are of biological interests due to co-expressed genes which are controlled by the same transcriptional regulatory programs, as well as, studying the functionality of genes in a system-level. Correlation networks are increasingly being used in research applications, especially in the field of bioinformatics. It facilitates networks based on gene screening methods which can be used to identify biomarkers or therapeutic targets. Computational methods use for the development of network models, as well as, the analysis of their functionality proved to be of valuable resources.

GENE NETWORK UNDERSTANDING AND ANALYSIS

by
Maria E Somoza

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
In Partial Fulfillment of the Requirements for the Degree of
Master of Science in Bioinformatics

Department of Computer Science

May 2016

APPROVAL PAGE

GENE NETWORK UNDERSTANDING AND ANALYSIS

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I dedicate this thesis to my family, my husband and children.

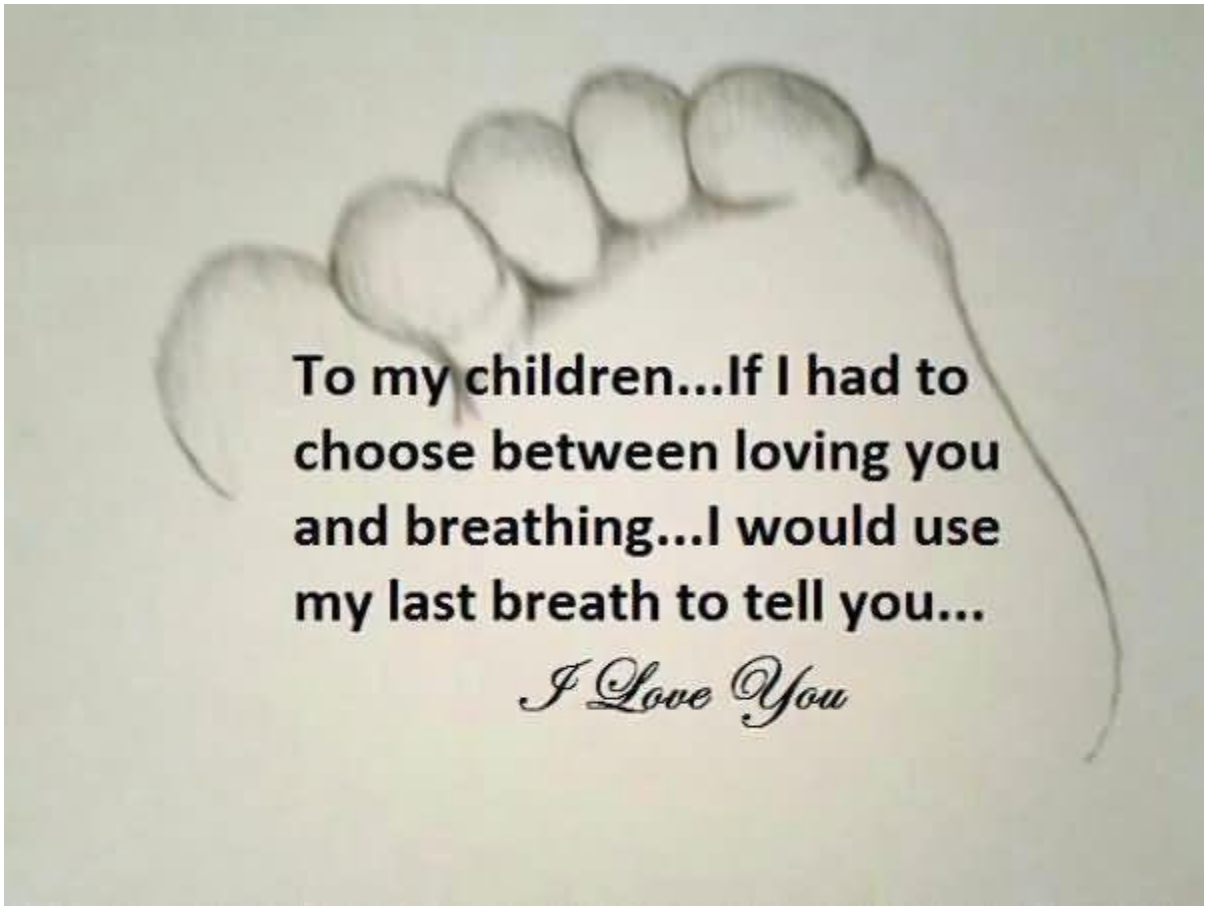

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TABLE OF CONTENTS

Chapters		Page
1	INTRODUCTION……..	1
	1.1 Objective……..	1
	1.2 Information about the CMNR Species…….	2
	1.3 Understanding Transcriptional Regulatory Networks……..	2
2	DATABASE AND SOFTWARES USED……	6
	2.1 Datasets and Normalization for M. Tuberculosis and C. Glutamicum ATCC 13032……	6
	2.2 Software for Visualization……	6
	2.3 Programming Tool……	6
3	IMPLEMENTATION……	12
	3.1 Methods for Gene Co-expression Networks……	12
	3.2 Measurements……..	14
	3.3 Results……..	15
4	CONCLUSIONS……	19
REFERENCES	……	42

LIST OF TABLES

Table		Page
1.1	Mycobacterium tuberculosis Transcription Regulatory Network……..	4
2.1	Participating Datasets…….	7
3.1	Q-value Scores for Each Organisms…….	15
1.2	Supplementary Table…….	20

LIST OF FIGURES

Figures		Page
1.1	Regulatory Networks Image of Corynebacterium glutamicum ATCC 13032……	5
2.1	Images of Yeast Sporulation (Aracne)……..	8
2.2	Images of Yeast Cell Cycle (Context Likelihood of Relatednesss)……..	8
2.3	Images of Yeast KY (Biweight Midcorrelation (Bicor))…….	9
2.4	Images of GDS825 (Human) (MINE)……..	9
2.5	Images of GDS958 (Mouse) (MRNET)……..	10
2.6	Images of GDS3702 (Rat) (Cor- Pearson Correlation)……	10
2.7	Images of Thaliana (WGCNA)…….	11
3.1	Bar graphs…….	16
3.2	Heatmap/clustering images……...	17
A.1	Images of Yeast Sporulation (Biweight Midcorrelation (Bicor))……	21
A.2	Images of Yeast Sporulation (Context Likelihood of Relatedness)…….	21
A.3	Images of Yeast Sporulation (Cor- Pearson Correlation Coefficient)…..	22
A.4	Images of Yeast Sporulation (MINE)……...	22
A.5	Images of Yeast Sporulation (MRNET)……...	23
A.6	Images of Yeast Sporulation (WGCNA)……..	23
B.1	Images of Yeast Cell LCycle (ARACNe)…….	24
B.2	Images of Yeast Cell Cycle (Biweight Midcorrelation (Bicor))……...	24
B.3	Images of Yeast Cell Cycle (Cor- Pearson Correlation)……...	25
B.4	Images of Yeast Cell Cycle (MINE)…….	25

LIST OF FIGURES
(Continued)

Figures		Page
B.5	Images of Yeast Cell Cycle (MRNET)…….	26
B.6	Images of Yeast Cell Cycle (WGCNA)……	26
C.1	Images of YeastKY (ARACNe)……...	27
C.2	Images of Yeast KY (Context Likelihood of Relatedness)……..	27
C.3	Images of Yeast KY (Cor- Pearson Correlation)…….	28
C.4	Images of Yeast KY (MINE)……...	28
C.5	Images of Yeast KY (MRNET)……...	29
C.6	Images of YeastKY (WGCNA)……	29
D.1	Images of GDS825 (Human) (ARACNe)…….	30
D.2	Images of GDS825 (Human) (Biweight Midcorrelation)…….	30
D.3	Images of GDS825 (Human) (Context Likelihood of Relatedness)…….	31
D.4	Images of GDS825 (Human) (Cor-Pearson Correlation)…….	31
D.5	Images of GDS825 (Human) (MRNET)……..	32
D.6	Images of GDS825 (Human) (WGCNA)…….	32
E.1	Images of GDS958 (Mouse) (ARACNe)…….	33
E.2	Images of GDS958 (Mouse) (Biweight Midcorrelation)…….	33
E.3	Images of GDS958 (Mouse) (Context Likelihood of Relatedness)…….	34
E.4	Images of GDS958 (Mouse) (Cor- Pearson Correlation)…….	34
E.5	Images of GDS958 (Mouse) (MINE)……...	35

LIST OF FIGURES
(Continued)

Figures		Page
E.6	Images of GDS958 (Mouse) (WGCNA)……..	35
F.1	Images of GDS3702 (Rat) (ARACNe)…….	36
F.2	Images of GDS3702 (Rat) (Biweight Midcorrelation)…….	36
F.3	Images of GDS3702 (Rat) (Context Likelihood of Relatedness)…….	37
F.4	Images of GDS3702 (Rat) (MINE)…….	37
F.5	Images of GDS3702 (Rat) **(**MRNET)……..	38
F.6	Images of GDS3702 (Rat) (WGCNA)……..	38
G.1	Images of Thaliana **(**ARACNe)……	39
G.2	Images of Thaliana **(**Biweight Midcorrelation)……	39
G.3	Images of Thaliana (Context Likelihood of Relatedness)……	40
G.4	Images of Thaliana (Cor- Pearson Correlation)……	40
G.5	Images of Thaliana **(**MINE)……..	41
G.6	Images of Thaliana **(**MRNET)……..	41

CHAPTER 1

INTRODUCTION

1.1 Objective

The objective of this thesis is to present an analysis in gene regulatory networks and gene co-expression networks. Gene regulatory networks is represented as a directed graph connecting two genes. These connections represent a biochemical process such as: reaction, transformation, interaction, inhibition, or activation.

As for gene co-expression networks, the graph is represented as undirected, and the edges represent a correlation or dependency relationship among genes. The datasets used for gene co-expression networks are generated by high-throughput gene expression database such as microarray and RNA-Seq. Gene co-expression measures are often used to describe the network results among genes. The most widely used is Mutual information (MI) for generalized correlation measure. Comparison of other co-expression measures were used to find the biologically meaningful modules (clusters of genes) [12]. The following network measures were used: CLR, MRNET, ARACNE, BICOR, COR, MINE and WGCNA .

1.2 Information about the CMNR Species

Mycobacterium tuberculosis are intracellular pathogens that have evolved strategies for coping with the pressures encountered inside host cells. Mycobacterium tuberculosis is a devastating virulence that affects roughly 9 million new cases and 2 million deaths yearly[1]. Unfortunately, there's not a lot is known about the dormant state of tuberculi bacilli in human infection. From published microarray data, researchers have assembled the largest *M. tuberculosis* transcriptional-regulatory network to date, and characterized the temporal response of this network during adaptation to stationary phase and hypoxia[2].

C. glutamicum ATCC 13032 belongs to the CMNR group of family which includes M*ycobacterium, Nocardia, and Rhodococcus*[9]. The members of this group are Gram-positive bacteria that exhibit many unusual features such as : high G + C content, and a specific organization of the cell wall composed of mycolic acid, peptidoglycan and arabinolactano [9]. Some species of the CMNR group are important for industrial and biotechnological applications, such as *Corynebacterium glutamicum* and *Corynebacterium efficiens* [9].These group of organisms consists of several bacterial species that are of medical, veterinary, and biotechnological interest.

1.3 Understanding Transcriptional Regulatory Networks

To further understand the complex structure of transcriptional regulatory networks, well known model organisms such as *E. coli*, have been studied extensively to analyse the conservation patterns of this network across 175 prokaryotic genomes, and predict components of the regulatory networks for these organisms[6]. The first step toward understanding the regulatory network of this pathogen is the prediction of operons in Mycobacterium tuberculosis (MTB)[7].

According to Roback et al, a gene regulatory network consisting of 222 links among 216 genes based on MtbRegList (http://mtbreglist.genap.ca/MtbRegList/www/index.php) was developed , a database that lists the binding sites of 21 TFs and sigma factors. Next, a network of 159 links among 164 genes was included, based on recent studies on the transcriptional regulatory activity of *mprA*, *dosR*, *Rv1395*, *Rv2358*, *furB*, *Rv0967*, *kstR*, *pknH*, *embR*, *trcR*, and *crp* . an *M. tuberculosis* TR network (223 links among 201 genes) inferred from gene orthology with 29 *E. coli* TFs and their targets were downloaded and included. Finally, the researchers completed the network based on the list of *Mycobacterium tuberculosis* operons [7], assuming that if a TF regulates a gene within an operon, it also regulates all other gene members of the operon. Following a similar procedure, a separate assembled network was created, purely literature derived network, with 581 links among 518 genes that should have higher confidence than those in the full network [2].

Table 1.1 Mycobacterium Tuberculosis Transcription Regulatory Network

Regulator			Target genes					*0= indicate whether a link is not orthology-based
GeneID	Rv #	Name	GeneID	Rv #	Name	Orthology*	Literature*	*1= indicate from the original orthology-based network
15607143	Rv0001	dnaA	15607143	Rv0001	dnaA	1	0	*2= inferred by operon-based extension of the original
15607143	Rv0001	dnaA	15607144	Rv0002	dnaN	1	0	orthology-based network
15607143	Rv0001	dnaA	15607145	Rv0003	recF	1	0	
15607143	Rv0001	dnaA	15610532	Rv3086c	gyrA	1	0	
15607143	Rv0001	dnaA	15610547	Rv3417c	gyrB2	1	0	
15607259	Rv0117	oxyS	15607259	Rv0117	oxyS	1	0	
15607259	Rv0117	oxyS	15609044	Rv1907c	Rv1907c	2	0	
15607259	Rv0117	oxyS	15609045	Rv1908c	katG	1	0	
15607259	Rv0117	oxyS	15609048	Rv1909c	furA	2	0	
15607259	Rv0117	oxyS	15609047	Rv1910c	Rv1910c	2	0	
15607259	Rv0117	oxyS	15609048	Rv1911c	ppsC	2	0	
15607259	Rv0117	oxyS	15609049	Rv1912c	fadB5	2	0	
15607259	Rv0117	oxyS	15609066	Rv2428	ahpC	1	0	
15607259	Rv0117	oxyS	15609068	Rv2429	ahpD	2	0	
15607259	Rv0117	oxyS	15611049	Rv3913	devB2	1	0	
15607259	Rv0117	oxyS	15611050	Rv3914	devC	2	0	
15607286	Rv0144	Rv0144	15607286	Rv0144	Rv0144	1	0	
15607303	Rv0212c	narR	15607713	Rv0573c	Rv0573c	1	0	
15607303	Rv0212c	narR	15607714	Rv0574c	Rv0574c	2	0	
15607303	Rv0212c	narR	15608732	Rv1584	narH	2	0	
15607303	Rv0212c	narR	15608733	Rv1585	narG	1	0	
15607303	Rv0212c	narR	15608734	Rv1586	narX	2	0	
15607443	Rv0302	Rv0302	15607403	Rv0262c	ssn	1	0	
15607443	Rv0302	Rv0302	15607404	Rv0263c	Rv0263c	2	0	
15607443	Rv0302	Rv0302	15607405	Rv0264c	Rv0264c	2	0	
15607443	Rv0302	Rv0302	15608662	Rv1522c	mmpL12	1	0	
15607494	Rv0353	nagR	15607391	Rv0250c	Rv0250c	0	2	
15607494	Rv0353	nagR	15607392	Rv0251c	hsp	0	1	
15607494	Rv0353	nagR	15607393	Rv0252	nrdB	0	1	
15607494	Rv0353	nagR	15607491	Rv0350	dnaK	0	1	
15607494	Rv0353	nagR	15607492	Rv0351	grpE	0	2	
15607494	Rv0353	nagR	15607493	Rv0352	dnaJ	0	2	
15607494	Rv0353	nagR	15607494	Rv0353	nagR	0	2	
15607494	Rv0353	nagR	15607525	Rv0384c	cpsB	0	1	
15607494	Rv0353	nagR	15607526	Rv0385	Rv0385	0	1	
15607626	Rv0485	Rv0485	15607626	Rv0485	Rv0485	1	0	
15607626	Rv0485	Rv0485	15608158	Rv1018c	glmU	1	0	
15607626	Rv0485	Rv0485	15608829	Rv1691	Rv1691	2	0	
15607626	Rv0485	Rv0485	15608830	Rv1692	Rv1692	1	0	

Source:Voskuil MI, Visconti KC, Schoolnik GK (2004) *Mycobacterium tuberculosis* gene expression during adaptation to stationary phase and low-oxygen dormancy. Tuberculosis (Edinb) 84: 218–227.

Table 1.1 shows the transcription regulatory network of M. tuberculosis where the numbers arerepresented as follows: 0 indicates whether a link is not orthology-based, but no gene to gene interaction, 1 indicate from the orthology-based network and gene to gene interaction, and 2 inferred by operon-based extension of the original orthology-based network.

Corynebacterium glutamicum ATCC 13032 is very well known in the industry in its production of the amino acids[8]. This is also use as a reference network to all other corynebacterium species, due to the fact that all experimental evidence was done on this particular species.

1.1 Regulatory Networks Image of Corynebacterium Glutamicum ATCC 13032

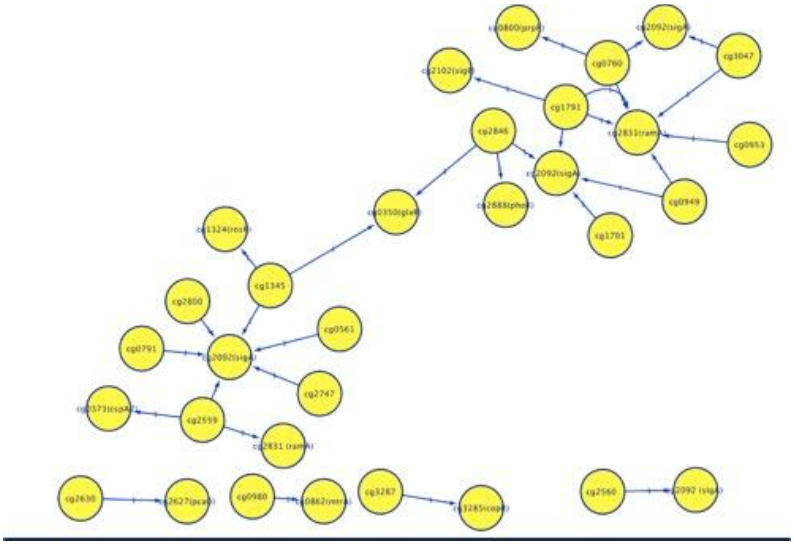


Figure 1.1 Is an image of a regulatory network of *Corynebacterium glutamicum* ATCC 13032 using Cytoscape. Genes with regulations and experimental evidence were specifically chosen for the network.

Source: Abreu VA, Almeida S, Tiwari S, Hassan SS, Mariano D, Silva A, Baumbach J, Azevedo V, Rottger R (2015) CMRegNet-An interspecies reference database for corynebacterial and mycobacterial regulatory networks. BMC Genomics 16:452. doi:10. 1186/ s12864-015-1631-0. http://www.lgcm.icb.ufmg.br/cmregnet/

The network shows gene to gene interactions as indicated by the arrow. In the experimental version, all transcriptional regulations are stored with experimental evidence[11].The interaction is represented by 1 means that genes are expressed when a gene is an activator , while a 0 (not shown on the image) means that genes are not expressed when a gene is a repressor.

CHAPTER 2

DATABASE AND SOFTWARES USED

2.1 Datasets and Normalization for M. Tuberculosis and C. Glutamicum ATCC 13032

The time course microarray data for *Mycobacterium tuberculosis* is the following GSE35362. This can be obtained from the database Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov)[6]. The transcriptional regulations in C. glutamicum ATCC 13032 which includes TFBS and regulation can be found in the following reference databases CMRegNet (http://lgcm.icb.ufmg.br/cmregnet) and CoryneRegNet (http://coryneregnet.compbio.sdu.dk/v6/index.html) [9,11]. After processing the raw data of microarray datasets, the normalization procedure was executed in order to avoid systematic biases due to the variation between different trials and samples. Robust multi-array average (RMA) was done using the justRMA function in the iffy package that is part of the BioConductor project in R [4].

2.2 Software for Visualization

Cytoscape is an open source software used for integrating biomolecular interaction networks using high-throughput data into a conceptual framework which can be downloaded in the following *http://www.cytoscape.org*[10].

2.3 Programming Tool

The R, or for an updated version, R Studio statistical programming language is an integrated suite of software facilities used for data manipulation, calculation, and graphical display. The software is freely available to download, www.r-project.org, it compile and runs on a wide variety of platforms such as UNIX, Windows, and MacOS.

The R language is similar to the S language which its environment was developed at the Bell Laboratories by John Chambers and colleagues.

Table 2.1 Participating Datasets

Datasets	Organisms	Sources
GDS958	Mouse	NCBI
GDS825	Human	NCBI
GDS3702	Rat	NCBI
Thaliana	Rice	http://anirbanmukhopadhyay.50webs.com/data.html
Yeast Sprorulation	Yeast	http://anirbanmukhopadhyay.50webs.com/data.html
Yeast KY	Yeast	http://anirbanmukhopadhyay.50webs.com/data.html
Yeast Cell Cycle	Yeast	http://anirbanmukhopadhyay.50webs.com/data.html

Table 2.1 shows the seven gene expression datasets that were included to compare the co-expression measures in order to define the networks among genes.

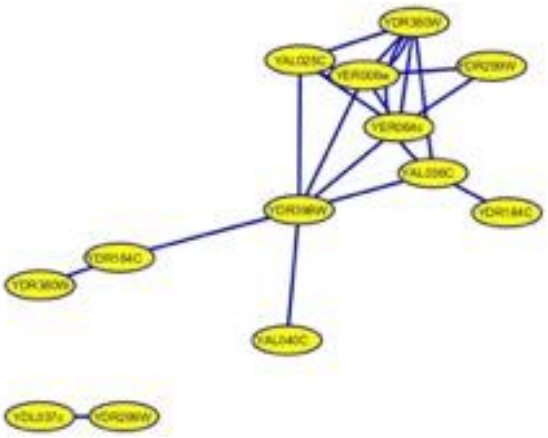


Figure 2.1 Images of Yeast Sporulation. **(**ARACNe**)**

Source: Cytoscape 3.2.1
http://www.cytoscape.org

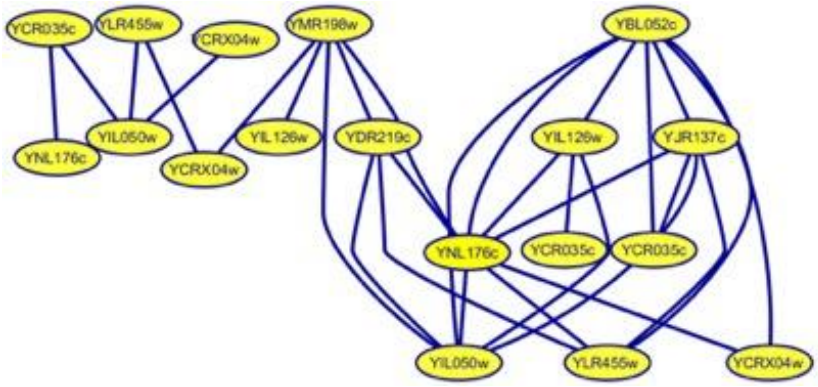


Figure 2.2 Images of Yeast Cell Cycle**.** (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

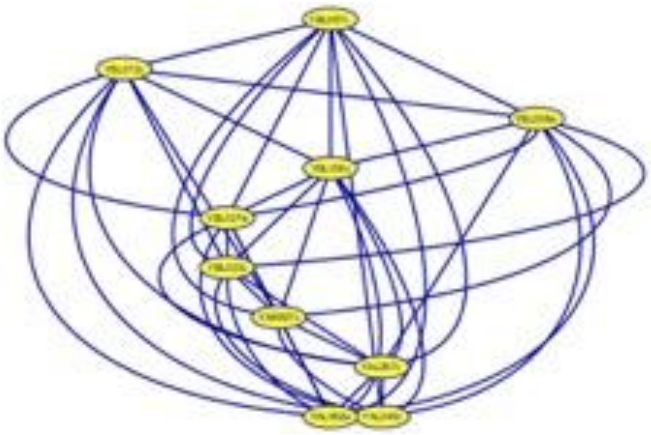


Figure 2.3 Images of Yeast KY. (Biweight Midcorrelation (Bicor))

Source: Cytoscape 3.2.1
http://www.cytoscape.org

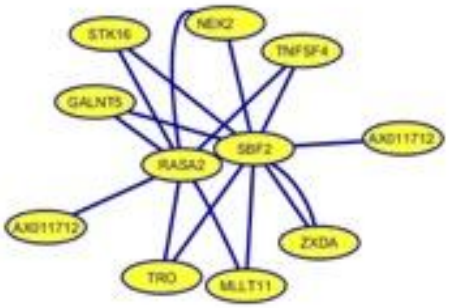


Figure 2.4 Images of GDS825 (Human). (MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

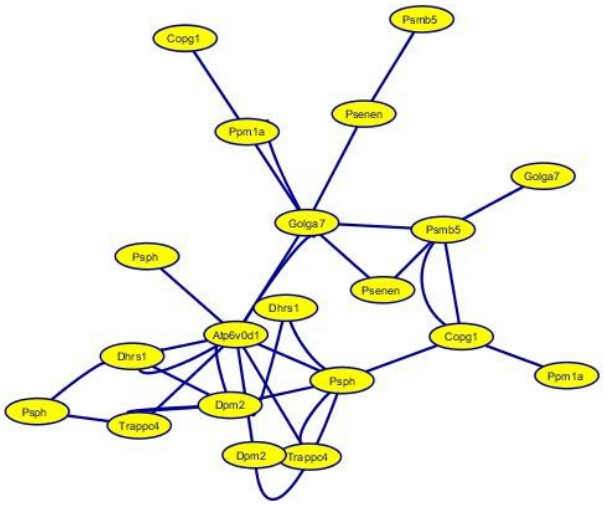


Figure 2.5 Images of GDS958 (Mouse). (MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

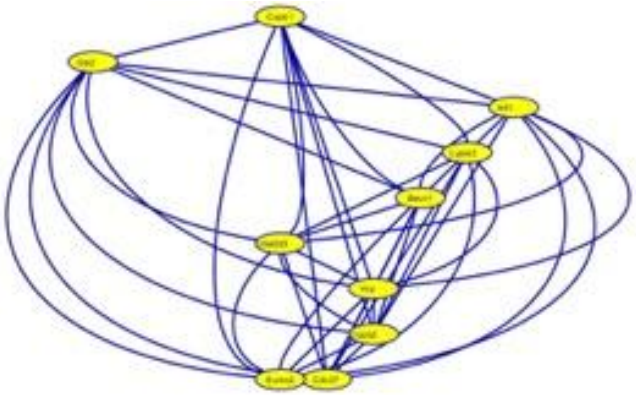


Figure 2.6 Images of GDS3702 (Rat). (Cor- Pearson Correlation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

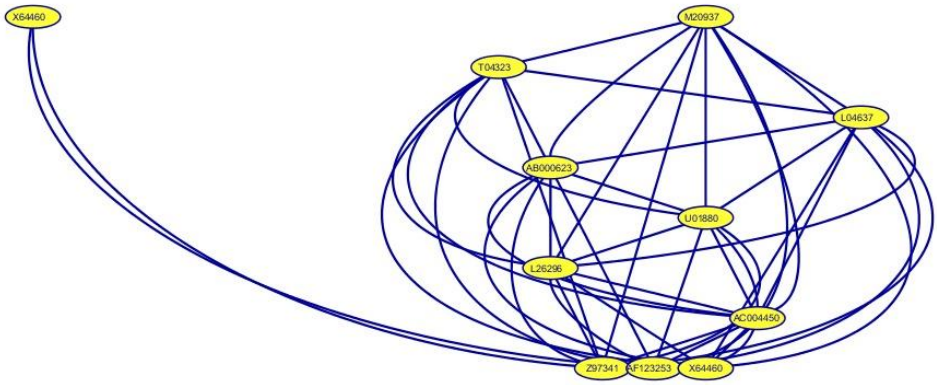


Figure 2.7 Images of Thaliana. (WGCNA)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

The network images of the seven gene expression datasets were done using the visual software Cytoscape. The images shows the comparison of the seven co-expression measures.

CHAPTER 3

IMPLEMENTATION

3.1 Methods for Gene Co-expression Networks

- Context Likelihood of Relatedness (CLR) is an algorithm that uses mutual information in order to infer networks from steady-state. It forms a matrix of mutual information scores by calculating between each pair of genes in the network. This algorithm output only undirected edges because of their bidirectional nature of mutual information [15].

- ARACNe (Algorithm for the Reconstruction of Accurate Cellular Networks) is a novel algorithm (information-theoretic) which is used for the reverse engineering of transcriptional networks from microarray data. In a biological context, the algorithm infers bona-fide transcriptional targets[3]. ARACNe begins by assigning to each pair of nodes a weight equal to the mutual information [14].

- MRNET is an inference method using the maximum relevance/minimum redundancy (MRMR), which performs a series of supervised MRMR gene selection procedures where each gene in turn plays the role of the target output [15].

- WGCNA (weighted gene correlation network analysis) is a method that can be used for finding clusters of highly correlated genes. By using the module eigengene or an intramodular hub gene in which clusters are summarized [13].

- Bicor (biweight midcorrelation) is an alternative to Pearson correlation. Bicor measures the ‘similarity’ between gene expression profiles which provides approach for gene differential coexpression analysis [16].

- MINE(maximal information-based nonparametric exploration) is a novel method which computes the MINE family measures between two variables. MIC (maximal information coefficient) is one of five statistics that is part of MINE, which identify important relationships in data sets and characterize them as well. The method can be downloaded, http://www.exploredata.net/, and is also available in R package ‘minerva’.

- Cor (Pearson Correlation Coefficient) functions implements a faster calculation of Pearson correlation. A measure of the linear correlation between two variables, giving a value between +1 and -1 inclusive, where +1 is total positive correlation, 0 is no correlation, and -1 is total negative correlation

3.2 Measurements

In order to determine the biological significance of the clusters which comprises of all the genes participating in the co-expression network, Q-values was used against statistically significant GO terms validated by using the GO annotation database [17].

Q-value is the minimum False Discovery Rate (FDR) in which genes appears significant. Q values from an FDR corrected hypergeometric test for enrichment can be obtained using GeneMania, a plugin, from Cytoscape. P-value is the probability of obtaining a result equal to or more in an observed sample results.

3.3 Results

As an example shown in Table 3.1, **c**luster 1 shown from the Yeast KY network is responsible for Protein-DNA complex with a Q value of 3.3e-12. While on cluster 1 shown from the Yeast Cell Cycle is responsible for chromosome segregation with a Q value of 3.9e-0 being the highly enriched one.

Table 3.1 Q-value Scores for Each Organisms

Dataset	Organism	Cluster No.	GO Annotation	Q-value
GDS958	Mouse	1	Vacuolar proton-transporting V-type ATPase complex	0.20
		2	Vacuolar membrane Vacuolar part	0.23
		3		0.25
GDS825	Human	1	Regulation of Mitosis Spindle Checkpoint	0.19 0.020
		2 3	Ubiquitin ligase complex	0.024
		4	Mitotic metaphase/ anaphase transition	0.026
GDS3702	Rat	1	Cell division	0.014
		2	Golgi-associated vesicle	0.021
		3	Regulation of cellular catabolic process	0.033
		4	Cytokinesis Golgi vesicle transport	0.058
		5	Intra-Golgi vesicle-mediated transport	0.072
		6	Cell leading edge	0.082
		7		0.093
Thaliana	Rice	1	Chitinase activity	9.0e-18
		2	Acting on paired donors	2.2e-05
		3	Fatty acid biosynthetic process	0.0060
		4	Lipid biosynthetic process	0.033
Yeast Sprorulation	Yeast	1	rRNA processing	1.2e-14
		2	Preribosome	1.2e-11
		3	Nuclear export	0.00041
		4	Nucleolus	3.5e-14
Yeast KY	Yeast	1	Protein-DNA complex	3.3e-12
		2	Replication fork DNA replication origin binding	3.0e-10
		3	Regulation of gene expression, epigenetic	2.4e-09
		4		0.0012
Yeast Cell Cycle	Yeast	1	Chromosome segregation	3.9e-05
		2	Spindle pole	0.0015
		3	Mitotic cell cycle Microtubule organizing center	0.014
		4		0.065

Source: http://www.cytoscape.org

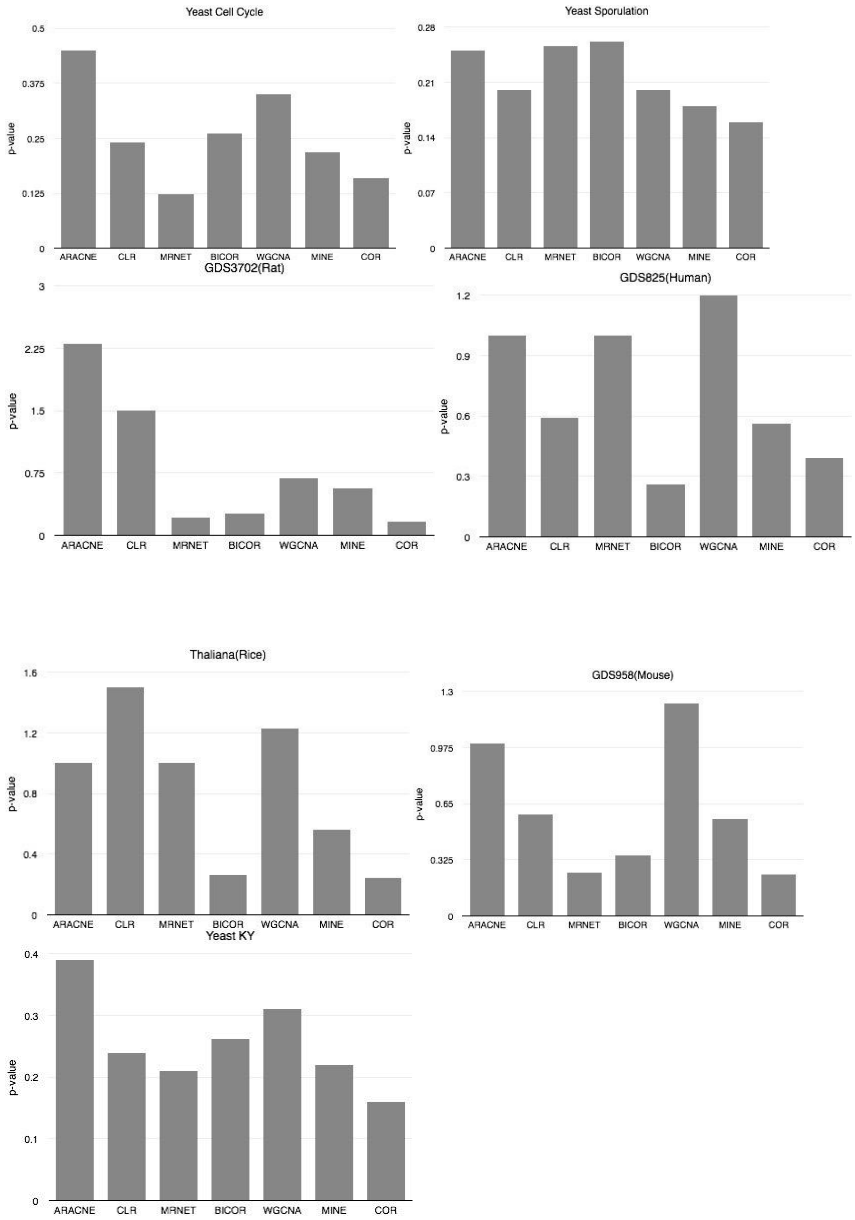


Figure 3.1 The bar graphs represent the p-value comparing the seven methods used on each seven datasets using the Pearson Correlation Coefficient measures in the minet Bioconductor package and WGCNA package. Aracne shows a better performance in most of the datasets.

Source: Meyer PE, Lafitte F, Bontempi G: minet: A R/Bioconductor Package for Inferring Large Transcriptional Networks Using Mutual Information, BMC Bioinformatics 2008, 9:461.

Figure 3.1 shows the Pearson Correlation Coefficient measures of the methods used. If the correlation coefficient is close to 1, it would indicates that the variables are positively linearly related. If the score is -1, it indicates that the variables are negatively linearly

related .A value of zero would indicate a weak linear relationship between the variables. This calculation was done using minet part of a bioconductor package in R[15] and WGCNA [13].

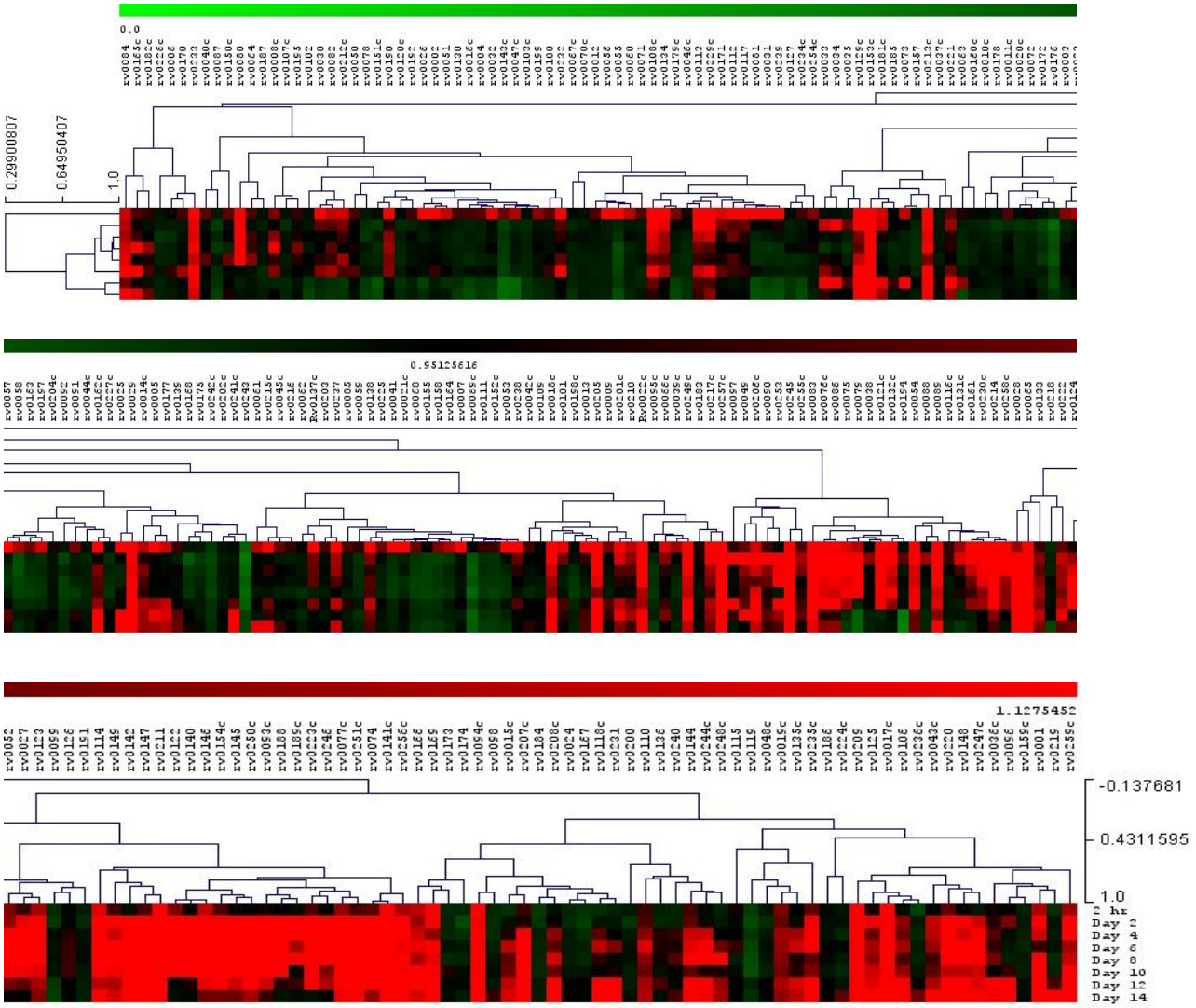


Figure 3.2 The images shows a heatmap/clustering of the gene expression of *Mycobacterium tuberculosis* using TM4:MeV.

Source: Rohde KH, Veiga DFT, Caldwell S., Balazsi G., Russell DG (2012) Linking the Transcriptional Profiles and the Physiological States of Mycobacterium tuberculosis during an Extended Intracellular Infection. PLoS Pathog 8(6): e1002769. doi:10.1371/journal.ppat.1002769.
www.tm4.org/mev.html

Figure 3.2 is a heatmap/clustering image of the *Mycobacterium tuberculosis* of the log scaled time series set in {2 hours, 2 days, 4 days, 6 days, 8 days, 10 days, 12 days, 14 days}[1].

CHAPTER 4

4. CONCLUSIONS

In summary, genetic network analysis are used and compared to better understand the important of assessing each co-expression measures in terms of how the genes are connected and its correlation. And in terms of gene regulatory network, to better understand the interaction of regulators among each other and other substances in the cell that governs the gene expression levels.

Table 1.2 is a supplementary table excel file of the transcriptional regulatory network of C. glutamicum ATCC 13032

cg2560	cg2909(sigA)	1
cg2559	cg0371(cspA2)	1
cg2559	cg2092(sigA)	1
cg2559	cg2831 (ramA)	1
cg3047	cg2092(sigA)	1
cg3047	cg2831(ramA)	1
cg0760	cg0800(prpR)	1
cg0760	cg2092(sigA)	1
cg0760	cg2831(ramA)	1
cg1701	cg2092(sigA)	1
cg3287	cg3285(copR)	1
cg0949	cg2092(sigA)	1
cg0949	cg2831(ramA)	1
cg2846	cg0350(glxR)	1
cg2846	cg2092(sigA)	1
cg2846	cg2888(phoR)	1
cg0791	cg2092(sigA)	1
cg0980	cg0862(mtrA)	1
cg0953	cg2831(ramA)	1
cg2630	cg2627(pcaO)	1
cg2747	cg2092(sigA)	1
cg1345	cg0350(glxR)	1
cg1345	cg1324(rosR)	1
cg1345	cg2092(sigA)	1
cg2800	cg2092(sigA)	1
cg0561	cg2092(sigA)	1
cg1791	cg2092(sigA)	1
cg1791	cg2102(sigB)	1
cg1791	cg2831(ramA)	1
cg1791	cg2831(ramA)	1

cg2560	cg0350 (glxR)	0
cg2560	cg0444(ramB)	0
cg2560	cg2831(ramA)	0
cg2559	cg0350(glxR)	0
cg2559	cg0444 (ramB)	0
cg3047	cg0350(glxR)	0
cg3047	cg0444(ramB)	0
cg3047	cg1120(ripA)	0
cg0760	cg0350(glxR)	0
cg1701	cg3253(mcbR)	0
cg0978	cg0979(-)	0
cg0949	cg0350(glxR)	0
cg0949	cg0444(ramB)	0
cg0791	cg0350(glxR)	0
cg0791	cg0444(ramB)	0
cg0953	cg0444(ramB)	0
cg2630	cg0350(glxR)	0
cg2630	cg2624(pcaR)	0
cg2747	cg0862(mtrA)	0
cg1345	cg1120(ripA)	0
cg1345	cg1340(arnR)	0
cg1746	cg2109(oxyR)	0
cg0469	cg2103(dtxR)	0
cg1791	cg0350(glxR)	0
cg1791	cg2115(sugR)	0

Source: Abreu VA, Almeida S, Tiwari S, Hassan SS, Mariano D, Silva A, Baumbach J, Azevedo V, Rottger R (2015) CMRegNet-An interspecies reference database for corynebacterial and mycobacterial regulatory networks. BMC Genomics 16:452. doi:10. 1186/ s12864-015-1631-0. http://www.lgcm.icb.ufmg.br/cmregnet/

APPENDIX A

CO-EXPRESSION NETWORK IMAGES

Figure A.1 to A.6 are network images of the Yeast Sporulation data.

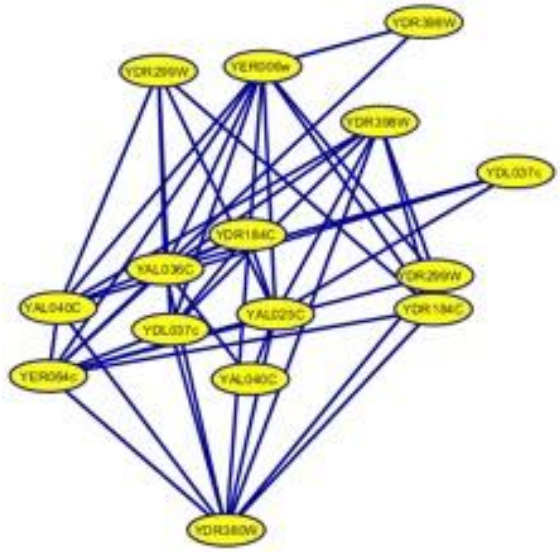


Figure A.1 Images of Yeast Sporulation. (Biweight Midcorrelation (Bicor))

Source: Cytoscape 3.2.1
http://www.cytoscape.org

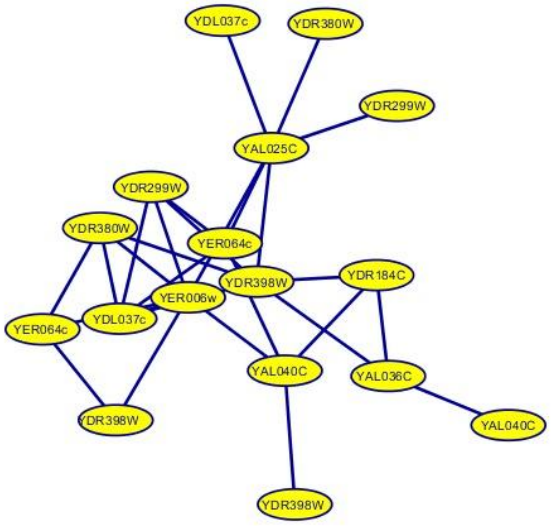


Figure A.2 Images of Yeast Sporulation. (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

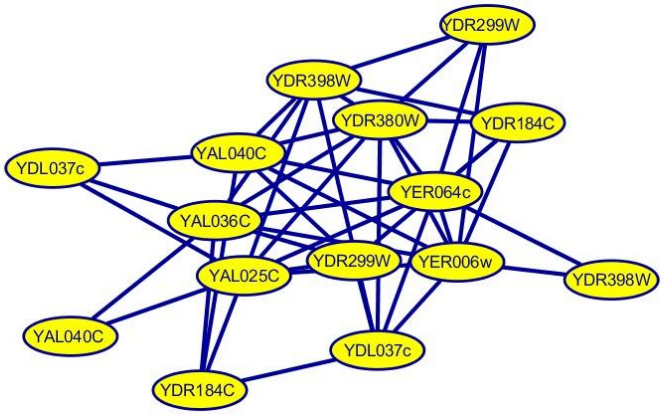


Figure A.3 Images of Yeast Sporulation. (Cor- Pearson Correlation Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

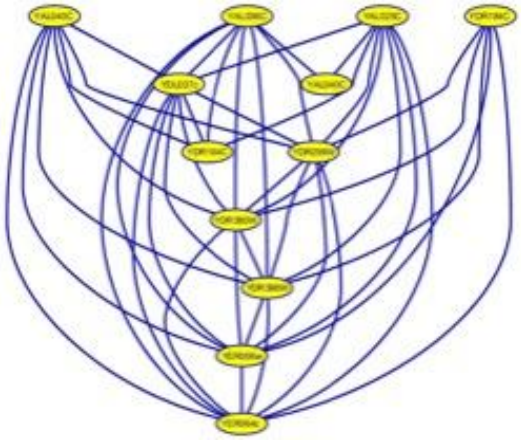


Figure A.4 Images of Yeast Sporulation. **(**MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

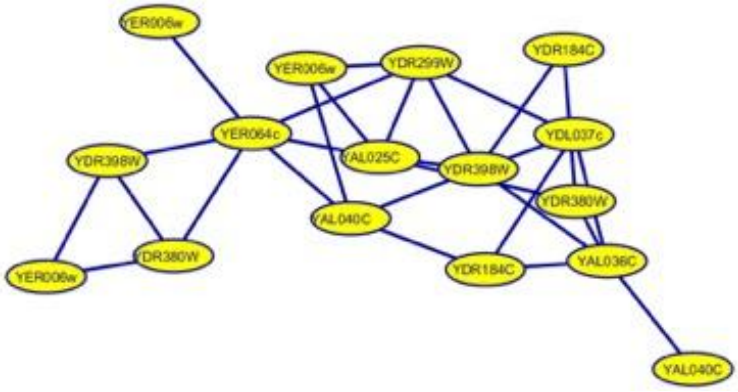


Figure A.5 Images of Yeast Sporulation. (MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

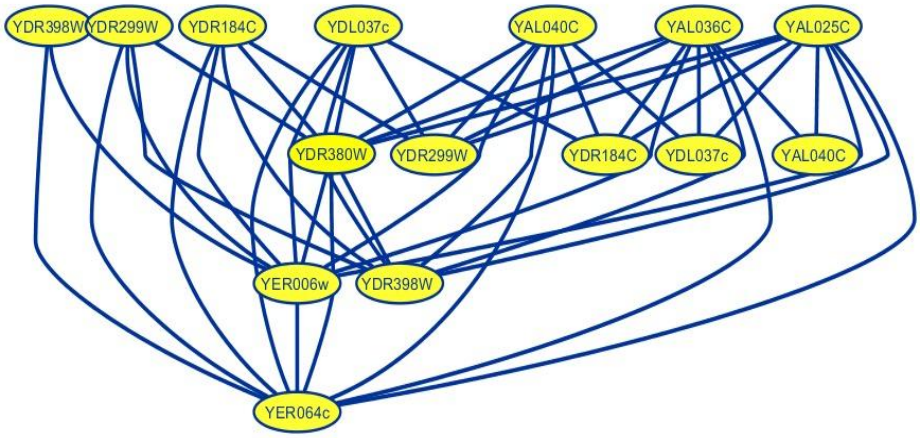


Figure A.6 Images of Yeast Sporulation. (WGCNA)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

APPENDIX B

Figure B.1 to B.6 are network images of Yeast Cell Cycle.

Figure B.1 Images of Yeast Cell LCycle**.** **(**ARACNe**)**

Source: Cytoscape 3.2.1
http://www.cytoscape.org

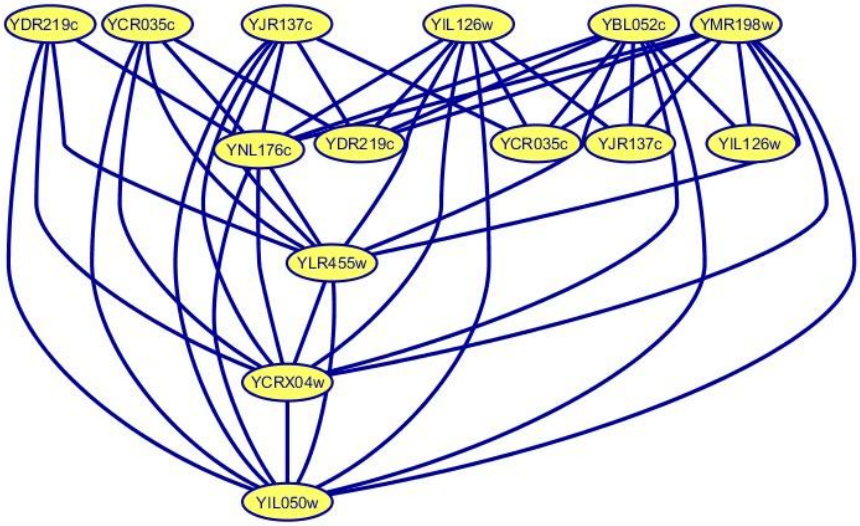


Figure B.2 Images of Yeast Cell Cycle. (Biweight Midcorrelation (Bicor))

Source: Cytoscape 3.2.1
http://www.cytoscape.org

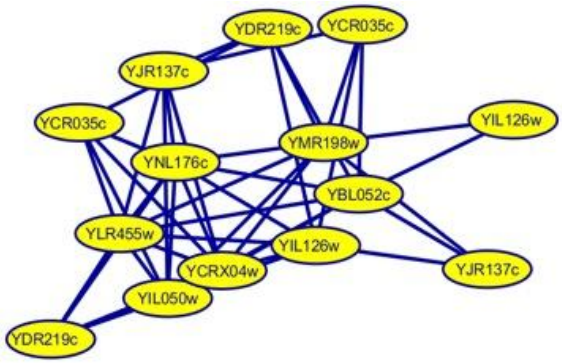


Figure B.3 Images of Yeast Cell Cycle**.** (Cor- Pearson Correlation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

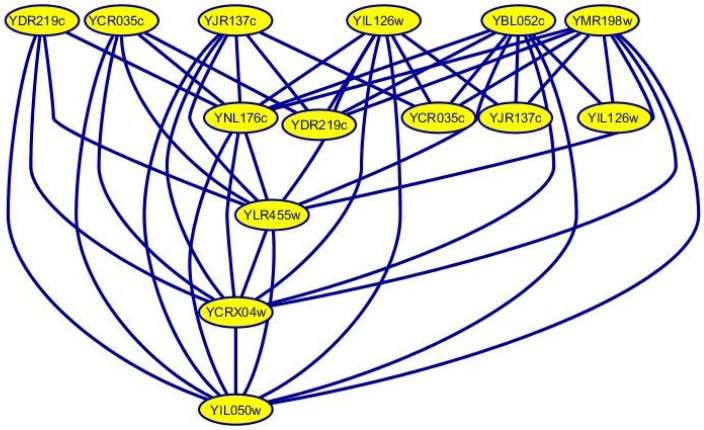


Figure B.4 Images of Yeast Cell Cycle**. (**MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

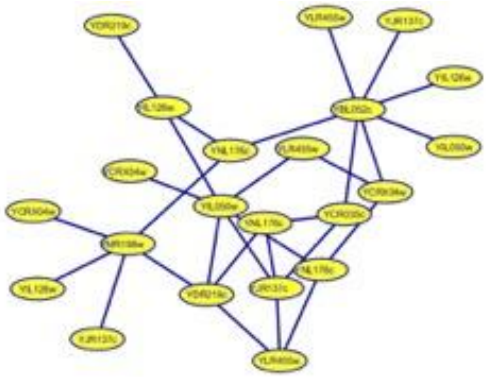


Figure B.5 Images of Yeast Cell Cycle. (MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

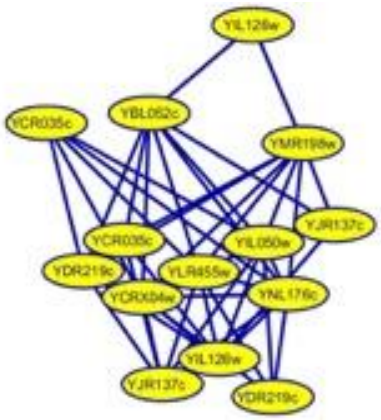


Figure B.6 Images of Yeast Cell Cycle**.** (WGCNA)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

APPENDIX C

Figure C.1 to C.6 are network images of Yeast KY.

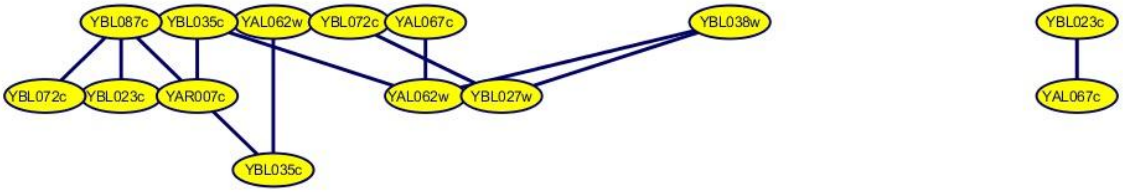


Figure C.1 Images of YeastKY**.** **(**ARACNe**)**

Source: Cytoscape 3.2.1
http://www.cytoscape.org

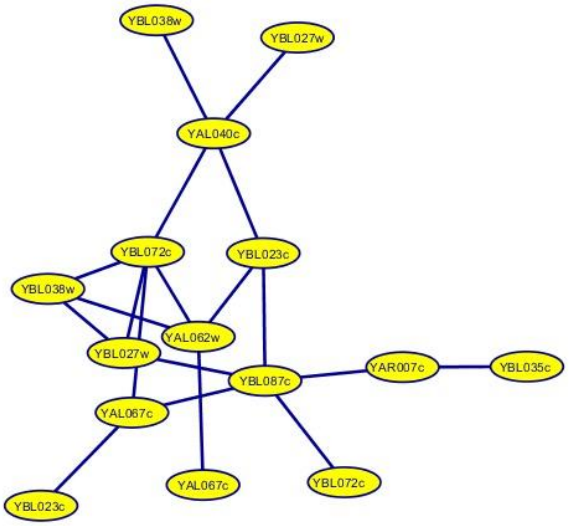


Figure C.2 Images of Yeast KY. (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

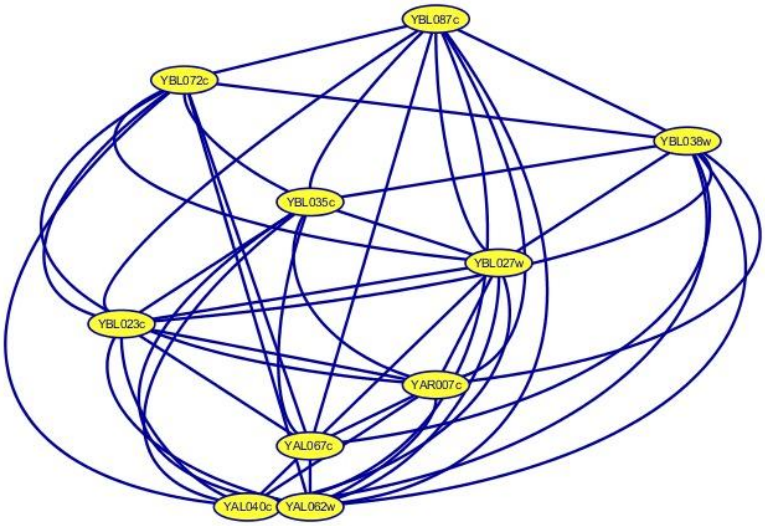


Figure C.3 Images of Yeast KY. (Cor- Pearson Correlation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

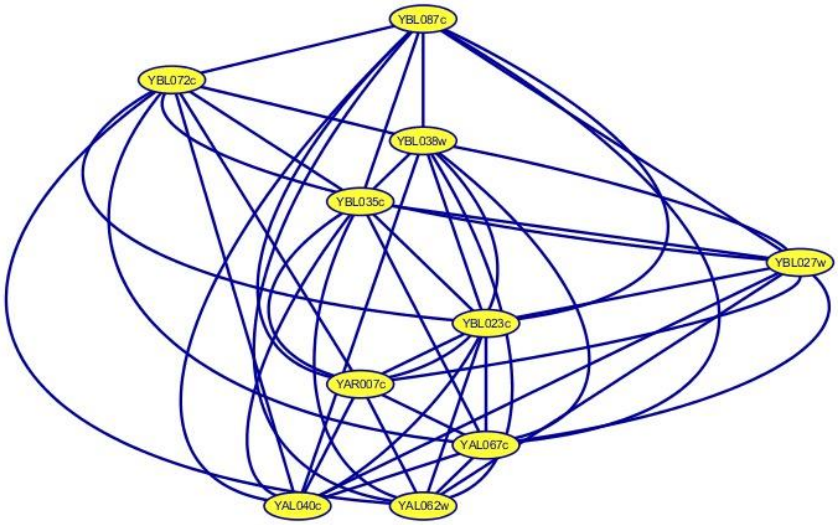


Figure C.4 Images of Yeast KY. (MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

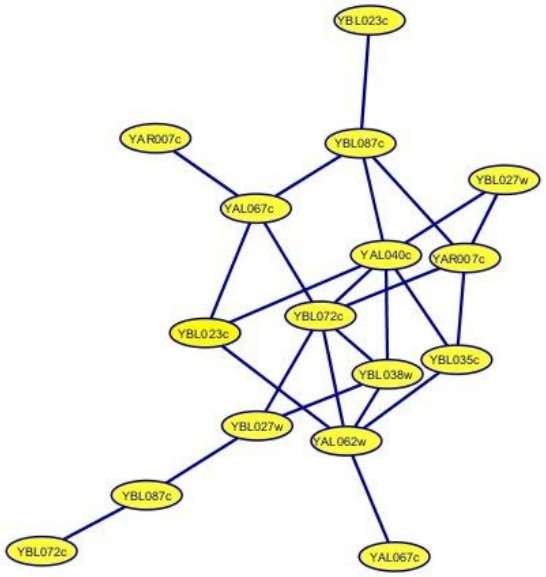


Figure C.5 Images of Yeast KY. (MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

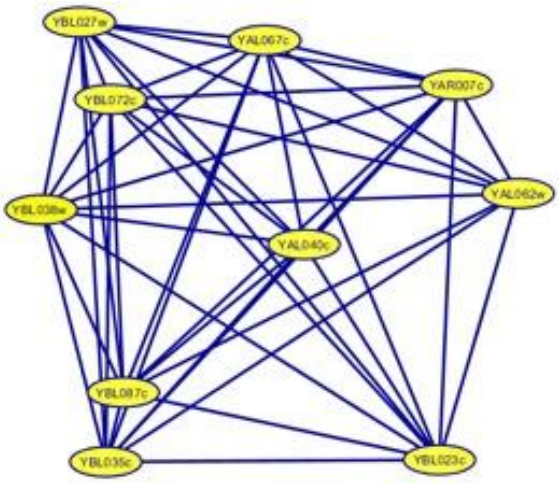


Figure C.6 Images of Yeast KY. (WGCNA)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

APPENDIX D

Figure D.1 to D.6 are network images of GDS825 (Human).

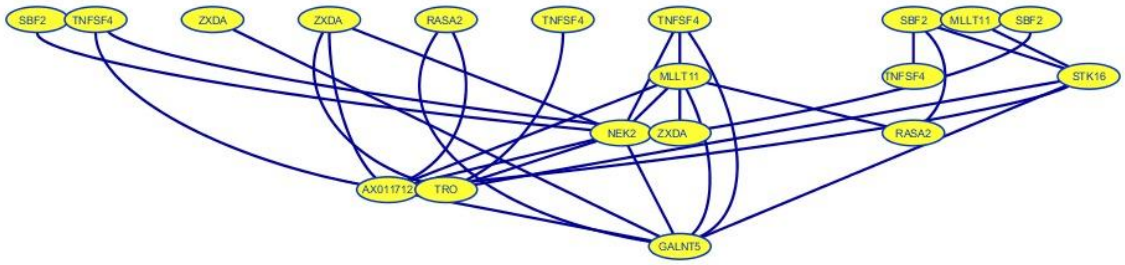


Figure D.1 Images of GDS825 (Human). (ARACNe)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

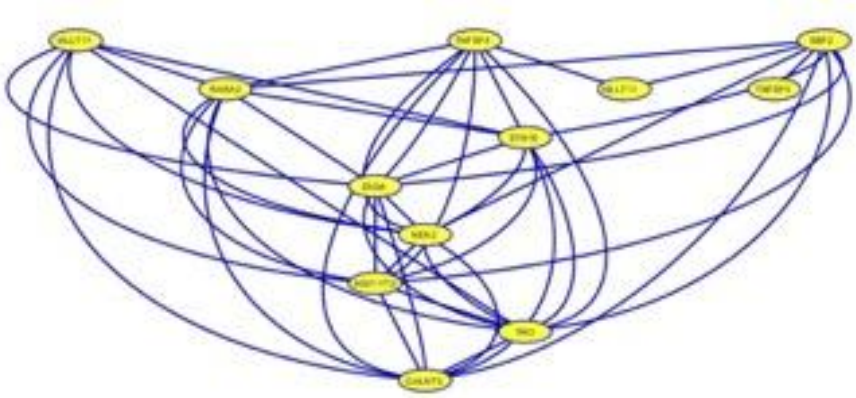


Figure D.2 Images of GDS825 (Human). (Biweight Midcorrelation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

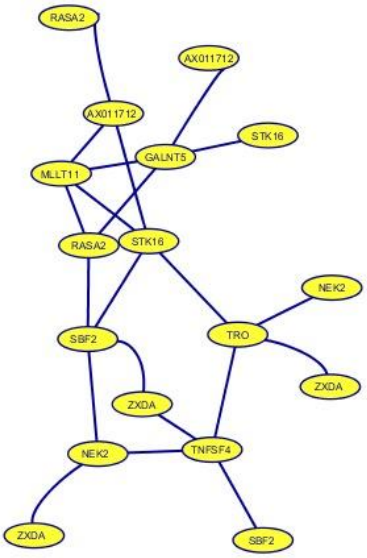


Figure D.3 Images of GDS825 (Human). (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

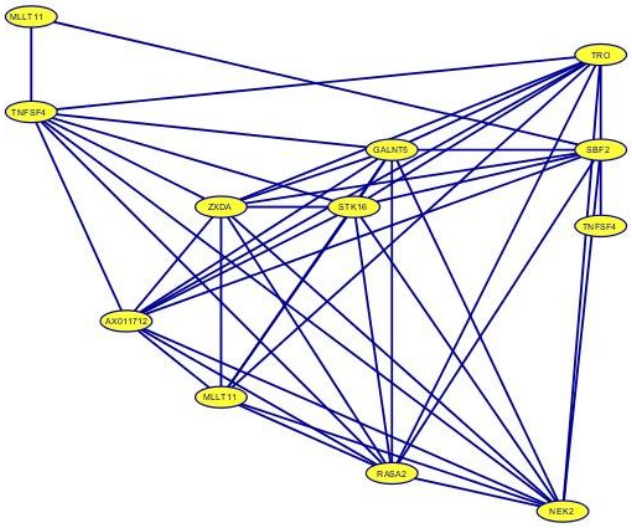


Figure D.4 Images of GDS825 (Human). (Cor-Pearson Correlation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

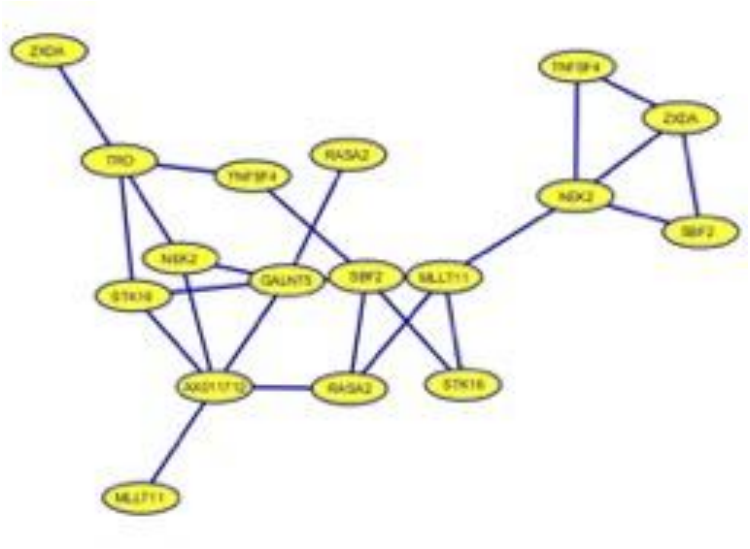


Figure D.5 Images of GDS825 (Human). **(**MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

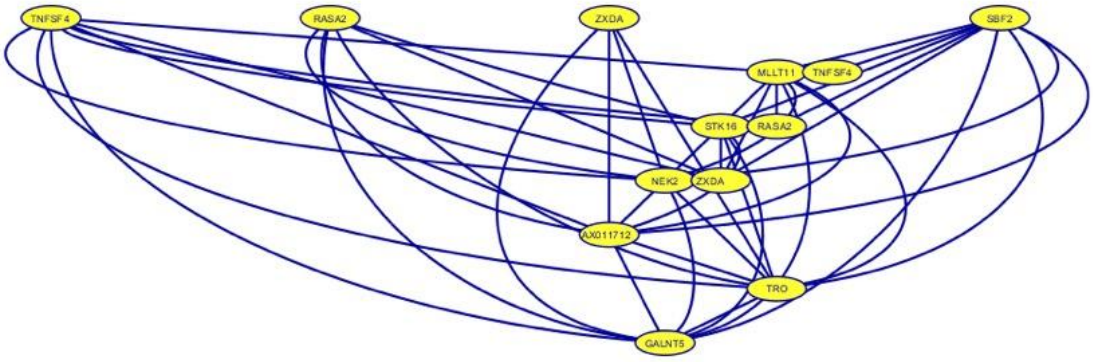


Figure D.6 Images of GDS825 (Human). (WGCNA)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

APPENDIX E

Figure E.1 to E.6 are network images of GDS958 (Mouse).

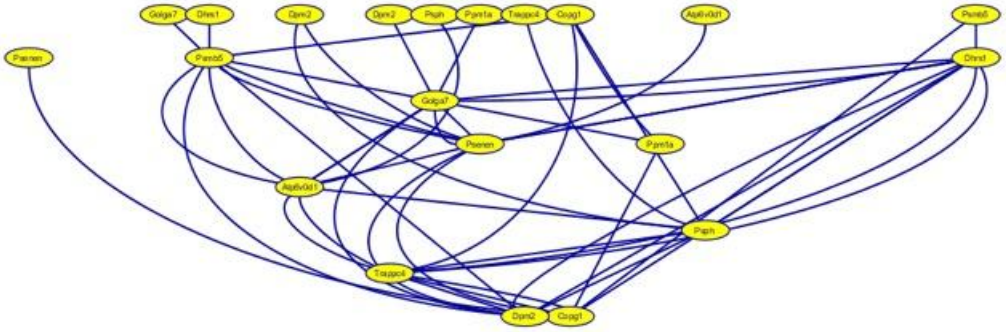


Figure E.1 Images of GDS958 (Mouse). (ARACNe)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

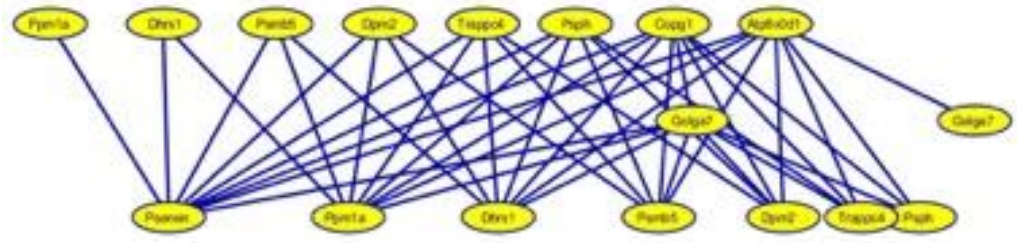


Figure E.2 Images of GDS958 (Mouse). (Biweight Midcorrelation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

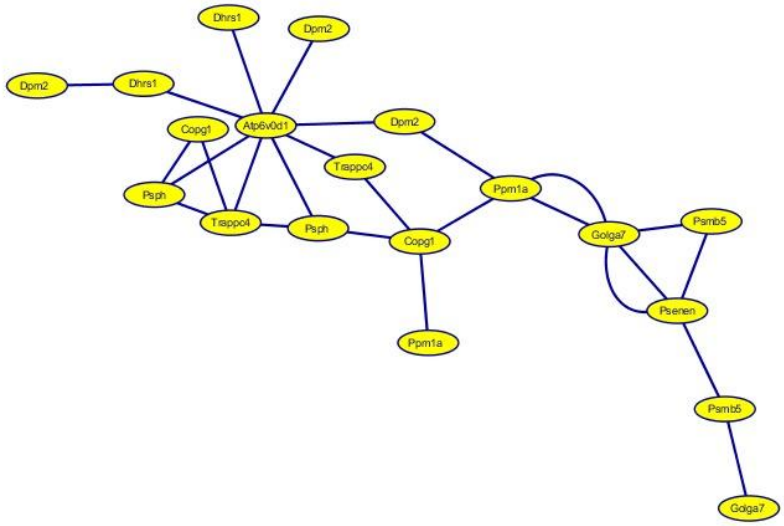


Figure E.3 Images of GDS958 (Mouse). (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

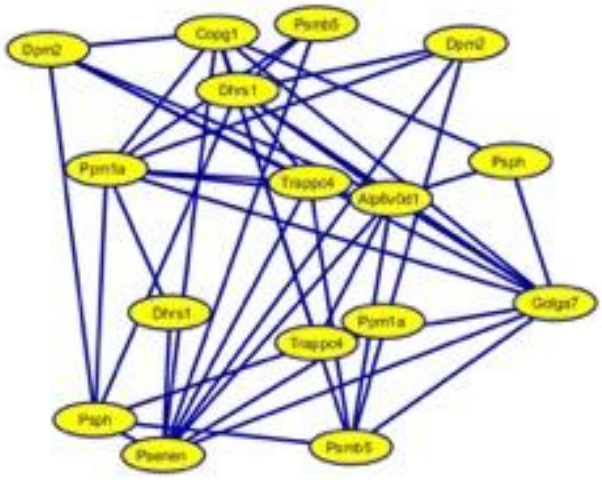


Figure E.4 Images of GDS958 (Mouse). (Cor- Pearson Correlation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

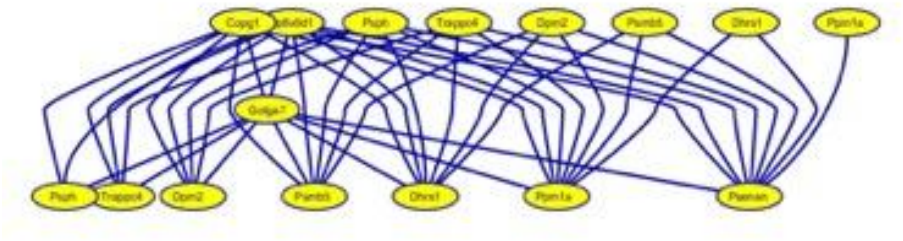


Figure E.5 Images of GDS958 (Mouse). (MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

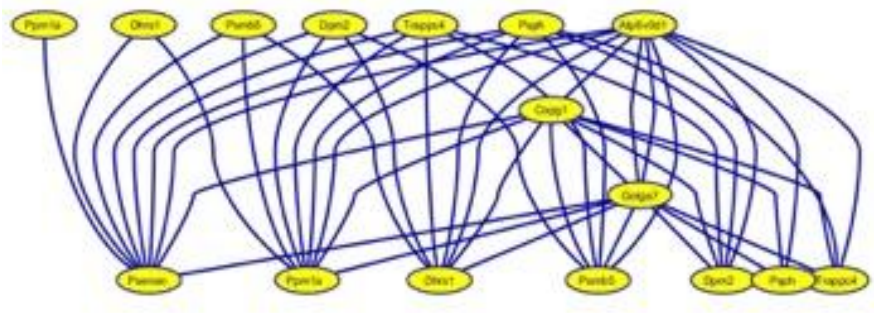


Figure E.6 Images of GDS958 (Mouse). (WGCNA)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

APPENDIX F

Figure F.1 to F.6 are network images of GDS3702 (Rat).

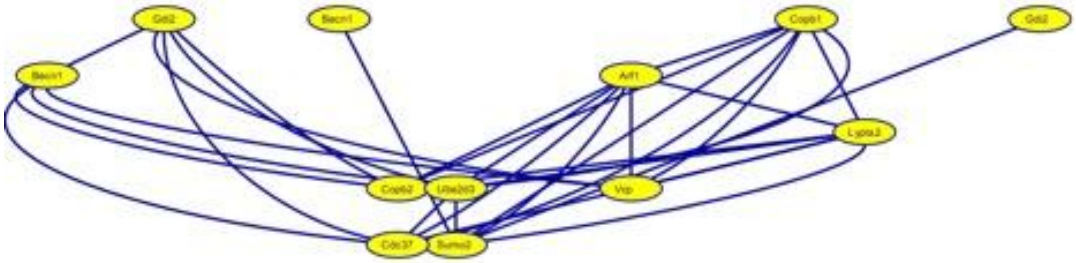


Figure F.1 Images of GDS3702 (Rat). (ARACNe)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

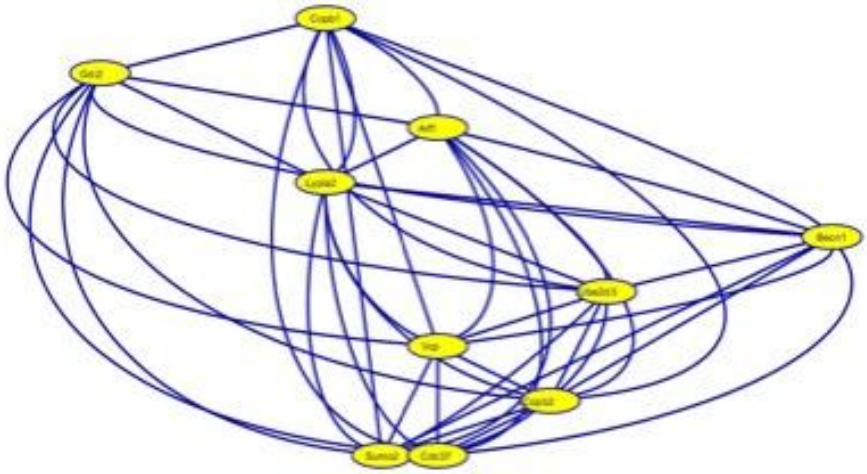


Figure F.2 Images of GDS3702 (Rat). (Biweight Midcorrelation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

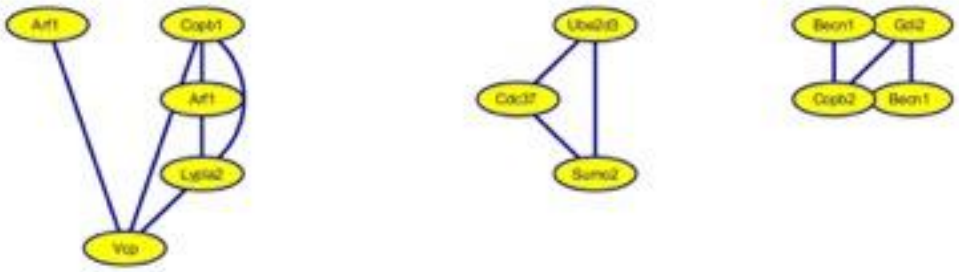


Figure F.3 Images of GDS3702 (Rat). (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

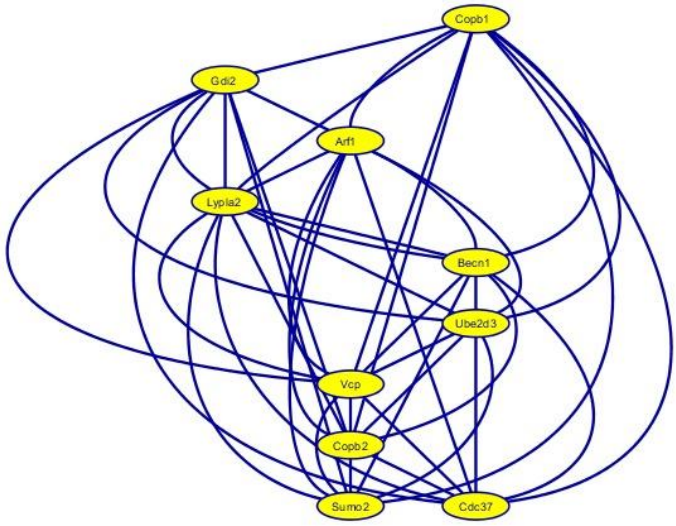


Figure F.4 Images of GDS3702 (Rat). (MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

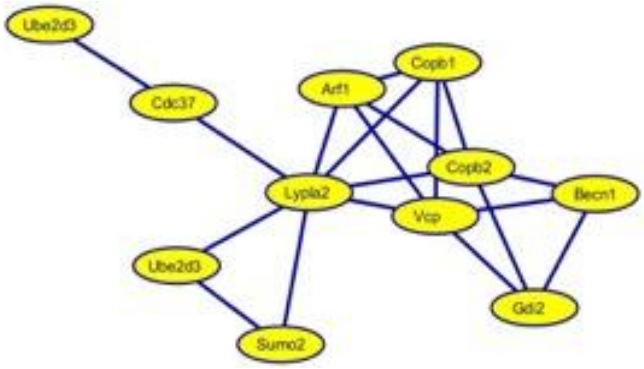


Figure F.5 Images of GDS3702 (Rat). **(**MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

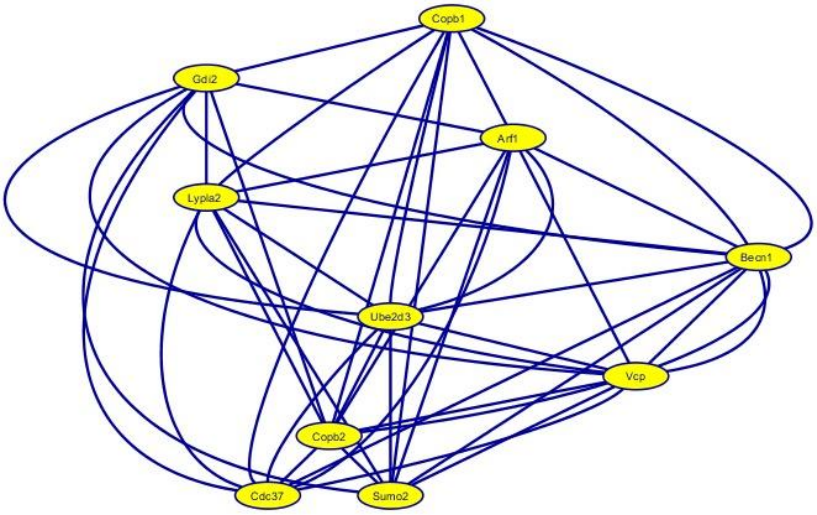


Figure F.6 Images of GDS3702 (Rat). (WGCNA)

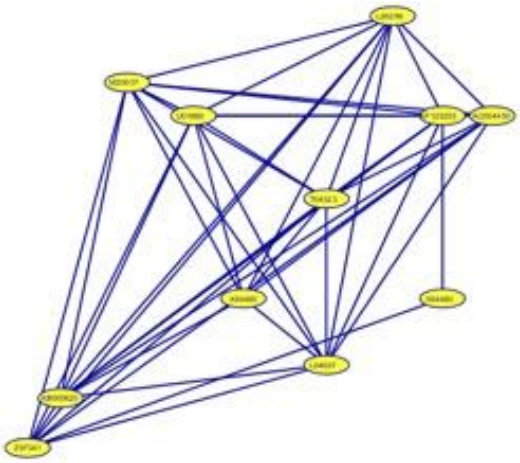
Source: Cytoscape 3.2.1
http://www.cytoscape.or

APPENDIX G

Figure G.1 to G.6 are network images of Thaliana.

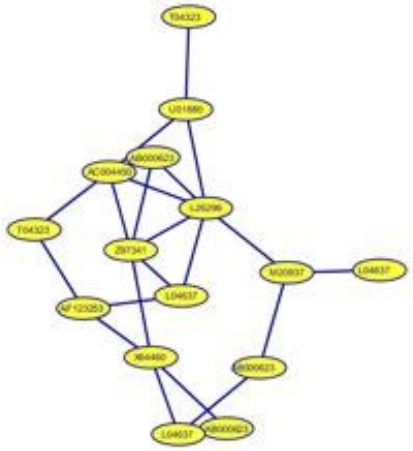
Figures G.1 Images of Thaliana. (ARACNe)

Source: Cytoscape 3.2.1
http://www.cytoscape.org



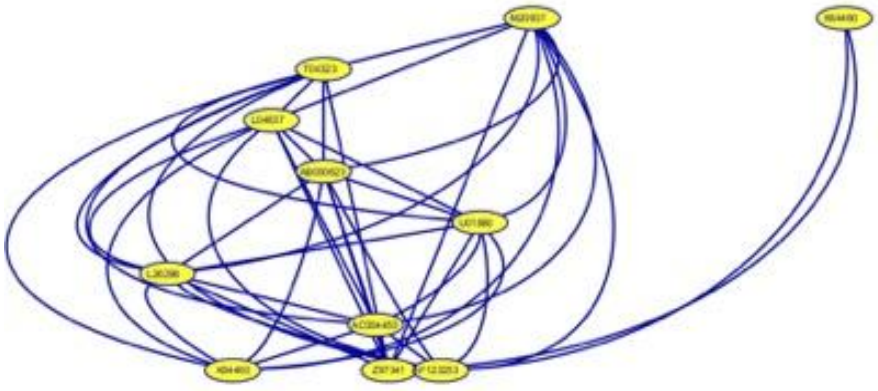
Figures G.2 Images of Thaliana. (Biweight Midcorrelation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org



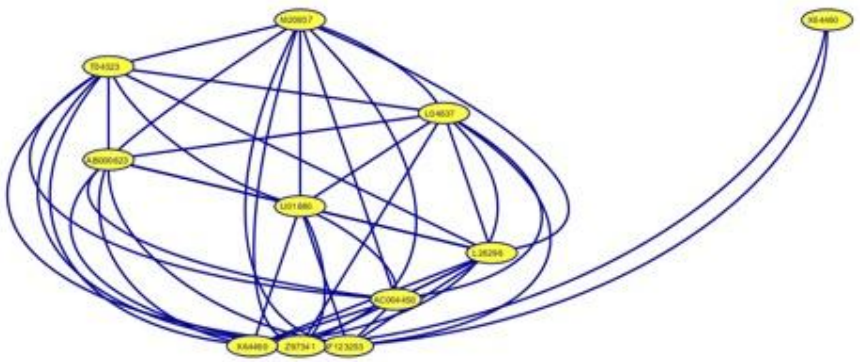
Figures G.3 Images of Thaliana**.** (Context Likelihood of Relatedness)

Source: Cytoscape 3.2.1
http://www.cytoscape.org



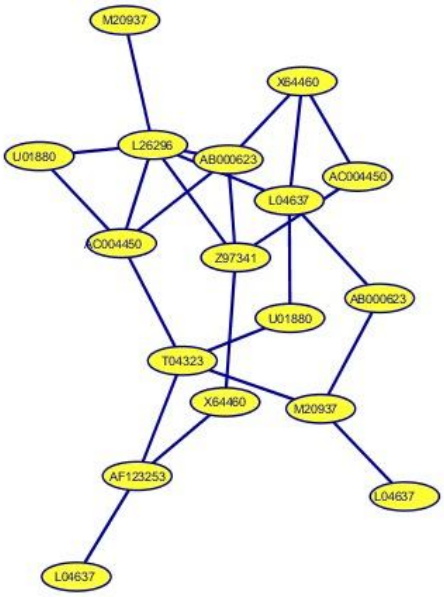
Figures G.4 Images of Thaliana. (Cor- Pearson Correlation)

Source: Cytoscape 3.2.1
http://www.cytoscape.org



Figures G.5 Images of Thaliana. **(**MINE- Maximal Information Coefficient)

Source: Cytoscape 3.2.1
http://www.cytoscape.org



Figures G.6 Images of Thaliana. **(**MRNET)

Source: Cytoscape 3.2.1
http://www.cytoscape.org

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