

STRUCTURAL EQUATION MODELING ASSESSING MICRO ARRAY DATA

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ABSTRACT

Micro arrays are part of a new class of biotechnologies that allow the monitoring of expression levels for thousands of genes simultaneously. We will discuss a novel method to investigate gene marker data by classifying several genes into a homogenous group so that similar genes will be classified together. Gene markers are often studied through micro array analysis where a chip containing identified genes is treated with a specific drug and then examined. We will compare several genes by all treatments of interest and determine whether there are any differences among the genes.

[1]

Structural equation modeling, or SEM, is a very general, chiefly linear, chiefly cross-sectional statistical modeling technique. Factor analysis, path analysis and regression all represent special cases of SEM. In building the structural equation model, the key variables of interest are latent constructs. The model contains two types of variables, namely exogenous and endogenous variables. Exogenous constructs are independent variables in all equations in which they appear. While endogenous constructs are dependent variables in at least one equation; although they may be independent variables in other equations in the system. In this paper we demonstrate how structural equation modeling can be used to extract biologically significant insights from DNA micro array gene expression data and find which of the genes can be predicted by the performance of other genes. It is a good method to build the interaction network of gene activity.

INTRODUCTION

Although the application of structural equation modeling (SEM) has been widely used for the social and behavioral sciences to model human interactions, it has not been developed to use to analyze micro array data. In this paper we will demonstrate how this method can be used to model gene interactions. The primary task of this process is to locate the predictors of gene activity.

Structural equation models are sets of linear equations used to specify phenomena in terms of their presumed cause-and-effect variables [2]. Once the model's parameters have been estimated, the resulting model-implied covariance matrix can be compared to an empirical covariance matrix. If the two matrices are consistent with each other, then the structural equation model can be considered a plausible explanation for relations between the measures.

BACKGROUND

DNA micro array technology can measure the expression of thousands of genes in a biological sample. DNA micro arrays have been increasingly used in the last few years and have the potential to help advance our biological knowledge at a genomic scale [3,4]. In analyzing DNA micro array gene-expression data, a major role has been played by various cluster-analysis techniques, most notably by hierarchical clustering [5], K-means clustering [6] and self-organizing maps [7]. K-means clustering will be used to classify the same genes together. Those homogeneous genes will be classified in one cluster. If we have a new gene, we can classify the gene by assigning it to the group with which it is homogenous. Then the gene is classified with the gene clusters.

The dataset, yeast, was obtained from Amada software [8]. The data set of yeast genome consists of 200 genes measured at 17 time levels. In this data set of yeast, we will analyze how the genes react when biological samples taken from the same subject at different time points are used to measure the gene expression levels. It has been observed that the gene expression patterns of samples of a given yeast gene measured at different time points are likely to be much more similar to each other than are the expression patterns of yeast samples of the same type taken from different subjects. In statistics, this phenomenon is called the within-subject correlation of repeated measurements on the same subject.

STRUCTURAL EQUATION MODELING

The structural equation model is of the form:

$$\text{Effect Variable} = \text{Sum} \left(\text{Structural Coefficient} \times \text{Casual Variable} \right) + \text{Disturbance}$$

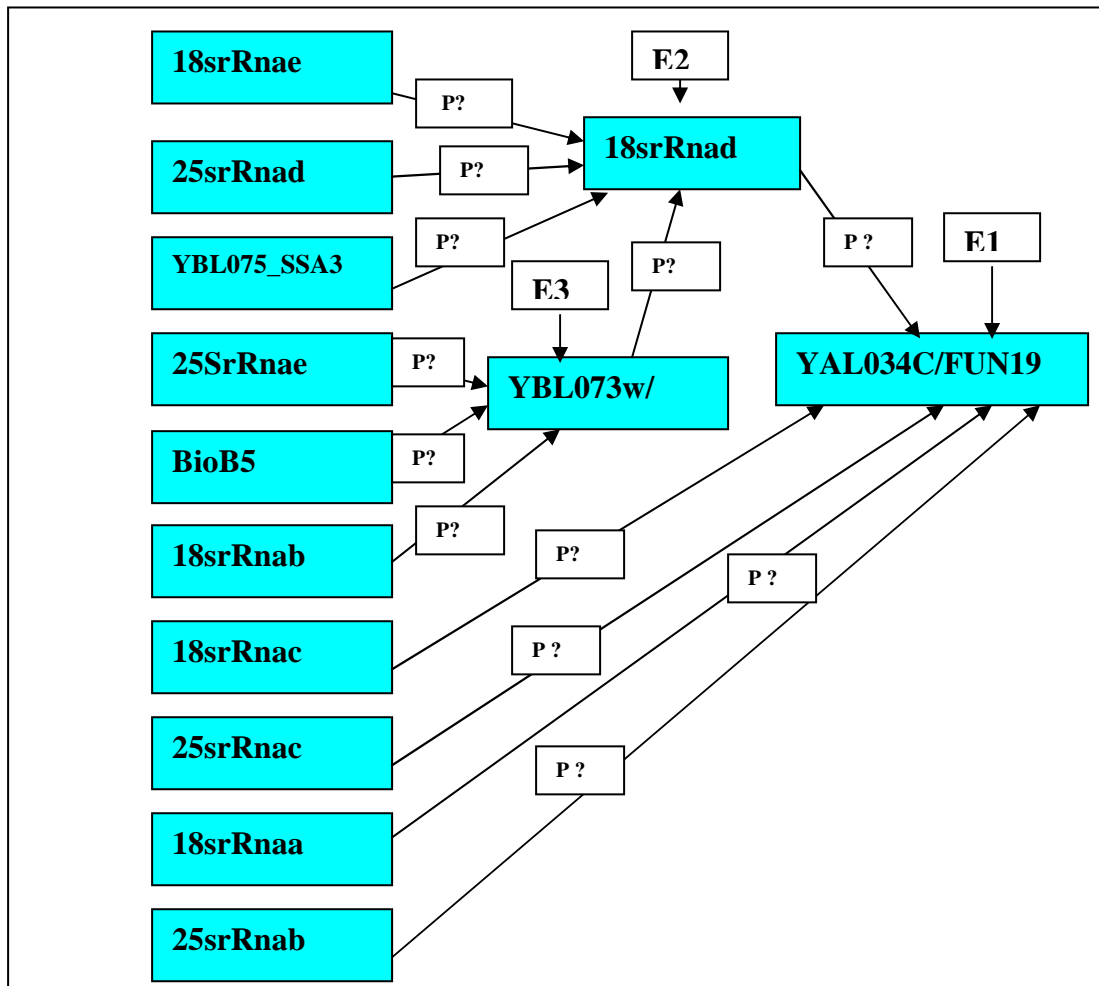
such that

$$Y_i = \Lambda_{i1} X_1 + \Lambda_{i2} X_2 + \dots + \Lambda_{ip} X_p + \epsilon_i$$

$(p \times 1)$ $(p \times m)$ $(m \times 1)$ $(p \times m)$ $(m \times 1)$ $(p \times m)$ $(m \times 1)$ $(p \times 1)$

Where the Y_i and the X_i 's are the names of the gene expressions. The Λ_{ij} 's are the estimated paths for the genes and the ϵ_i are the error term (Disturbance). Figure 1.1 demonstrates how a structural equation model is formulated [1].

Figure 1.1 Graphical representation of structural equation model for Gene Markers



The **P** values listed in Figure 1.1 represent coefficients that relate the gene markers, and **E** represents residuals. Other equations are defined similarly. The correlations are computed and entered in a data statement. The variable on which an arrow is pointed towards is an endogenous variable.

```
DATA MICROARRAY13(TYPE=CORR) ;
```

```
INPUT _TYPE_ $ _NAME_ $ V1-V13 ;  
      LABEL
```

```
V1 ='YALO34C/FUN19'  
V2 ='18srRnad'  
V3 ='YBL073w/'  
V4 ='18srRnae'  
V5 ='25srRnad'  
V6 ='YBL075_SSA3'  
V7 ='25srRnae'  
V8 ='BioB5'  
V9 ='18srRnac'
```

```
V10 ='25srRnac'
V11 ='18srRnaa'
V12 ='18srRnab'
V13 ='25srRnab';
```

```
CARDS;
N . 17 . 17 . 17 . 17 . 17 . 17 . 17 . 17 . 17
17 . 17 . 17 . 17
STD . 17.92017 19.52901 23.11989 35.08404 32.78865 15.95398 121.11950 4.45649 44.13190
37.01311 64.09317 40.29587 20.04664
CORR V1 1.00000.
CORR V2 -0.74381 1.00000.
CORR V3 0.65353 -0.94693 1.00000.
CORR V4 -0.72820 0.97229 -0.90787 1.00000.
CORR V5 -0.65810 0.93810 -0.90945 0.97347 1.00000.
CORR V6 0.43454 -0.28069 0.08922 -0.34117 -0.29536 1.00000.
CORR V7 -0.70571 0.95579 -0.90427 0.98635 0.98176 -0.30038 1.00000
CORR V8 -0.61499 0.72688 -0.52995 0.79071 0.71455 -0.40644 0.76330 1.00000
CORR V9 -0.65262 0.97015 -0.96722 0.97375 0.96811 -0.23124 0.97039 0.66385 1.00000.
CORR V10 -0.71717 0.94291 -0.90783 0.95236 0.95050 -0.23519 0.97578 0.72583 0.95346
1.00000.
CORR V11 -0.70162 0.97317 -0.94981 0.98360 0.98178 -0.29313 0.98312 0.69476 0.99161
0.96301 1.00000.
CORR V12 -0.64690 0.88626 -0.97042 0.85603 0.88027 -0.05646 0.87613 0.42663 0.92769
0.88754 0.91817 1.00000.
CORR V13 -0.64067 0.91581 -0.85225 0.95469 0.96957 -0.27380 0.97315 0.77815 0.93146
0.95207 0.95728 0.82705 1.00000
;
```

The above data are input as a correlation matrix obtained among the thirteen genes.

The data statement is followed by PROC CALIS.

```
PROC CALIS COVARIANCE CORR RESIDUAL MODIFICATION ;
LINEQS
```

```
V1 = PV1V2 V2 + PV1V9 V9 + PV1V10 V10 + PV1V11 V11 + PV1V13 V13 + E1,
V2 = PV2V3 V3 + PV2V4 V4 + PV2V5 V5 + E2,
V3 = PV3V7 V7 + PV3V8 V8 + PV3V9 V9 + PV3V12 V12 + E3;
```

```
STD
```

```
E1 = VARE1,
E2 = VARE2,
E3 = VARE3,
V4 = VARV4,
V5 = VARV5,
V6 = VARV6,
V7 = VARV7,
V8 = VARV8,
V9 = VARV9,
V10 = VARV10,
V11 = VARV11,
V12 = VARV12,
V13 = VARV13;
```

```
COV
```

```
V4 V5 = CV4V5,
V4 V6 = CV4V6,
V4 V7 = CV4V7,
V4 V8 = CV4V8,
V4 V9 = CV4V9,
V4 V10 = CV4V10,
V4 V11 = CV4V11,
V4 V12 = CV4V12,
```

The **LINEQS** statement makes the equations that determine the analysis of gene marker for the data being studied; each line consists of the variables, the path coefficients and the error term.

STD statement determines the variance of the endogenous variables (Independent) and the error term of the exogenous variables (independent). The **COV** statement determines the covariance among each pair of endogenous variables (dependent).

```

V4 V13 = CV4V13,
V5 V6 = CV5V6,
V5 V7 = CV5V7,
V5 V8 = CV5V8,
V5 V9 = CV5V9,
V5 V10 = CV5V10,
V5 V11 = CV5V11,
V5 V12 = CV5V12,
V5 V13 = CV5V13,
V6 V7 = CV6V7,
V6 V8 = CV6V8,
V6 V9 = CV6V9,
V6 V10 = CV6V10,
V6 V11 = CV6V11,
V6 V12 = CV6V12,
V6 V13 = CV6V13,
V7 V8 = CV7V8,
V7 V9 = CV7V9,
V7 V10 = CV7V10,
V7 V11 = CV7V11,
V7 V12 = CV7V12,
V7 V13 = CV7V13,
V8 V9 = CV8V9,
V8 V10 = CV8V10,
V8 V11 = CV8V11,
V8 V12 = CV8V12,
V8 V13 = CV8V13,
V9 V10 = CV9V10,
V9 V11 = CV9V11,
V9 V12 = CV9V12,
V9 V13 = CV9V13,
V10 V11 = CV10V11,
V10 V12 = CV10V12,
V10 V13 = CV10V13,
V11 V12 = CV11V12,
V11 V13 = CV11V13,
V12 V13 = CV12V13;
VAR V1 V2 V3 V4 V5 V6 V7 V8 V9 V10 V11 V12 V13;
RUN;

```

RESULTS

The initial model given in output 1.1 reveals a significant model with chi-square value equal to 44.1293, $p = 0.0022$. The SAS/STAT Users Guide says that the chi-square test statistics provides a “test of the specified model vs. the alternative that the data are from a multivariate normal distribution with unconstrained covariance normal distribution with unconstrained covariance matrix” (SAS/STAT Users guide 1989, *volume 1*, p. 139). The chi-square statistics provides a test of the null hypothesis that the theoretical model fits the data. Comparative fit index (CFI), Normed fit index (NFI) and Non-normed fit index (NNFI) compare the fit of an independence model (a model which asserts no relationships between variables) to the fit of the estimated model [9]. The result of this comparison is usually a number between 0 and 1, with 0.90 or greater accepted as values that indicate good fit. Although the value on the NFI and CFI exceeds 0.9, the NNFI value for this model was only 0.8456, indicating that the fit between the model and data needs improvement.

The correlation matrix was used on the data statement, the standardized path coefficients are tested whether the path is significant or not. The null hypothesis to be tested in SEM is the path coefficient is zero, meaning that there is no relationship between the exogenous variables and endogenous variables. The standardized path coefficients, given in output 1.1 tells us that the path connecting gene 25srRnae (V7) to YBL073w/ (V3) with a p- value of 0.0246 and YBL075_SSA3 (V6) to 18srRnad (V2) with a p- value of -0.0462 are not significant ($p < 0.05$); in other word the path coefficients are zero. The model was re-computed with those paths eliminated. The Lagrange Multipliers test identifies paths or covariance that possibly should be added to the model. The GAMMA matrix result reveals that the path connecting gene YBL073w/ (V3) to 18srRnac (V9) is statistically significant 6.22761 ($p = 0.0126$). This would suggest that adding a path from gene 18srRnac to YBL073w/ could result in a significant improvement in the model's fit.

Output 1.1 Model summary fit statistics for the initial model

**The CALIS Procedure
Covariance Structure Analysis: Maximum Likelihood Estimation**

Fit Function	2.7581
Goodness of Fit Index (GFI)	0.8021
GFI Adjusted for Degrees of Freedom (AGFI)	0.1426
Root Mean Square Residual (RMR)	7.1868
Parsimonious GFI (Mulaik, 1989)	0.2160
Chi-Square	44.1293
Chi-Square DF	21
Pr > Chi-Square	0.0022
Independence Model Chi-Square	634.52
Independence Model Chi-Square DF	78
RMSEA Estimate	0.2624
RMSEA 90% Lower Confidence Limit	0.1524
RMSEA 90% Upper Confidence Limit	0.3708
ECVI Estimate	72.7581
ECVI 90% Lower Confidence Limit	.
ECVI 90% Upper Confidence Limit	.
Probability of Close Fit	0.0037
Bentler's Comparative Fit Index	0.9584
Normal Theory Reweighted LS Chi-Square	25.6548
Akaike's Information Criterion	2.1293
Bozdogan's (1987) CAIC	-36.3682
Schwarz's Bayesian Criterion	-15.3682
McDonald's (1989) Centrality	0.5065
Bentler & Bonett's (1980) Non-normed Index	0.8456
Bentler & Bonett's (1980) NFI	0.9305
James, Mulaik, & Brett (1982) Parsimonious NFI	0.2505
Z-Test of Wilson & Hilferty (1931)	2.8332
Bollen (1986) Normed Index Rho1	0.7417
Bollen (1988) Non-normed Index Delta2	0.9623
Hoelter's (1983) Critical N	13

**The CALIS Procedure
Covariance Structure Analysis: Maximum Likelihood Estimation**

Manifest Variable Equations with Standardized Estimates

$$\begin{aligned} V1 &= -1.0209*V2 + 4.3691*V9 + -1.0130*V10 + -4.4668*V11 \\ &\quad PV1V2 \quad PV1V9 \quad PV1V10 \quad PV1V11 \\ &\quad + 1.4714*V13 + 0.4098 E1 \\ &\quad PV1V13 \\ V2 &= -0.4784*V3 + 0.8813*V4 + -0.3633*V5 + -0.0462*V6 \\ &\quad PV2V3 \quad PV2V4 \quad PV2V5 \quad PV2V6 \\ &\quad + 0.1539 E2 \\ V3 &= 0.0246*V7 + -0.1534*V8 + -0.9265*V12 + 0.2045 E3 \\ &\quad PV3V7 \quad PV3V8 \quad PV3V12 \end{aligned}$$

By comparing the chi-square statistics for the initial model (output 1.1) to the chi-square for the revised model (output 1.2), it was possible to perform a chi-square difference test to determine whether the addition of the new path resulted in a significant improvement in the model's fit. This difference test was computed as $44.9923 - 37.1039 = 7.8884$. With $df = 1$, the chi-square difference statistics was equal to 7.8884 and since this value is greater than the table chi-square with 1 df (3.841), this difference is clearly significant. So the model still needs some improvement, but provided a better fit than the original model.

Output 1.2 Model summary fit statistics for the revised model 1

The CALIS Procedure
Covariance Structure Analysis: Maximum Likelihood Estimation

Fit Function	2.3190
Goodness of Fit Index (GFI)	0.8140
GFI Adjusted for Degrees of Freedom (AGFI)	0.2307
Root Mean Square Residual (RMR)	7.1595
Parsimonious GFI (Mulaik, 1989)	0.2296
Chi-Square	37.1039
Chi-Square DF	22
Pr > Chi-Square	0.0230
Independence Model Chi-Square	634.52
Independence Model Chi-Square DF	78
RMSEA Estimate	0.2071
RMSEA 90% Lower Confidence Limit	0.0772
RMSEA 90% Upper Confidence Limit	0.3197
ECVI Estimate	71.3190
ECVI 90% Lower Confidence Limit	.
ECVI 90% Upper Confidence Limit	.
Probability of Close Fit	0.0328
Bentler's Comparative Fit Index	0.9729
Normal Theory Reweighted LS Chi-Square	23.7608
Akaike's Information Criterion	-6.8961
Bozdogan's (1987) CAIC	-47.2268
Schwarz's Bayesian Criterion	-25.2268
McDonald's (1989) Centrality	0.6413
Bentler & Bonett's (1980) Non-normed Index	0.9038
Bentler & Bonett's (1980) NFI	0.9415
James, Mulaik, & Brett (1982) Parsimonious NFI	0.2656
Z-Test of Wilson & Hilferty (1931)	1.9942
Bollen (1986) Normed Index Rho1	0.7927
Bollen (1988) Non-normed Index Delta2	0.9753
Hoelter's (1983) Critical N	16

Manifest Variable Equations with Standardized Estimates

V1	=	-1.0487*V2	+	4.4636*V9	+	-1.0349*V10	+	-4.5634*V11
		PV1V2		PV1V9		PV1V10		PV1V11
		+	1.5032*V13	+	0.4187 E1			
		PV1V13						
V2	=	-0.4188*V3	+	0.9482*V4	+	-0.3657*V5	+	0.1572 E2
		PV2V3		PV2V4		PV2V5		
V3	=	0.0425*V8	+	-0.5622*V9	+	-0.4670*V12	+	0.1599 E3
		PV3V8		PV3V9		PV3V12		

Standardized path coefficients for the revised model 1 are presented in Output 1.2. Since the path coefficient for gene BIOB5 (V8) – YBLO73w/ (V3) (0.0425) is less than 0.05; this path has to be eliminated. As the Lagrange Multipliers in _GAMMA matrix result reveals that the path connecting gene YBLO73w/ (V3) to 25SrRnae (V7), which was eliminated earlier, must now be added, since the chi-square value 6.87344 (p = 0.0087) is significant. This significance might suggest the model is a poor fit of the data adding a path from gene 25SrRnae to YBLO73w/ could result in a significant improvement in the model's fit. On the other hand, the NFI, NNFI and CFI for the revised model 1 all exceed 0.9, indicative of an acceptable fit. So we have to look for ways to improve revised model 1 to be a good fit of the data. The normalized residuals for gene 25SrRnae and YBLO73w/ is 2.62172, and the residual for gene 25srRnab and YBL073 is 2.13587 from model 1 exceed 2 indicating that the model needs some improvement so that these residuals will be less

than 2. Even though the revised model 1 has all values NFI, NNFI and CFI values all exceed 0.9 but still since the chi-square value of the study is significant, there fore the model needs improvement.

Output 1.3 Model summaries fit statistics for the revised model 2

The CALIS Procedure
Covariance Structure Analysis: Maximum Likelihood Estimation

Fit Function	1.9367
Goodness of Fit Index (GFI)	0.8229
GFI Adjusted for Degrees of Freedom (AGFI)	0.2676
Root Mean Square Residual (RMR)	5.3579
Parsimonious GFI (Mulaik, 1989)	0.2321
Chi-Square	30.9876
Chi-Square DF	22
Pr > Chi-Square	0.0964
Independence Model Chi-Square	634.52
Independence Model Chi-Square DF	78
RMSEA Estimate	0.1598
RMSEA 90% Lower Confidence Limit	.
RMSEA 90% Upper Confidence Limit	0.2812
ECVI Estimate	70.9367
ECVI 90% Lower Confidence Limit	.
ECVI 90% Upper Confidence Limit	.
Probability of Close Fit	0.1234
Bentler's Comparative Fit Index	0.9839
Normal Theory Reweighted LS Chi-Square	22.3755
Akaike's Information Criterion	-13.0124
Bozdogan's (1987) CAIC	-53.3431
Schwarz's Bayesian Criterion	-31.3431
McDonald's (1989) Centrality	0.7677
Bentler & Bonett's (1980) Non-normed Index	0.9427
Bentler & Bonett's (1980) NFI	0.9512
James, Mulaik, & Brett (1982) Parsimonious NFI	0.2683
Z-Test of Wilson & Hilferty (1931)	1.3040
Bollen (1986) Normed Index Rho1	0.8269
Bollen (1988) Non-normed Index Delta2	0.9853
Hoelter's (1983) Critical N	19

Manifest Variable Equations with Standardized Estimates for revised model 2

$$\begin{aligned}
 V1 &= -1.0569*V2 & + & 4.5066*V9 & + & -1.0448*V10 & + & -4.6074*V11 \\
 & \quad PV1V2 & & PV1V9 & & PV1V10 & & PV1V11 \\
 & + & 1.5177*V13 & + & 0.4227 E1 \\
 & \quad PV1V13 \\
 V2 &= -0.4195*V3 & + & 0.9499*V4 & + & -0.3663*V5 & + & 0.1574 E2 \\
 & \quad PV2V3 & & PV2V4 & & PV2V5 \\
 V3 &= 0.4000*V7 & + & -0.9327*V9 & + & -0.4556*V12 & + & 0.1321 E3 \\
 & \quad PV3V7 & & PV3V9 & & PV3V12
 \end{aligned}$$

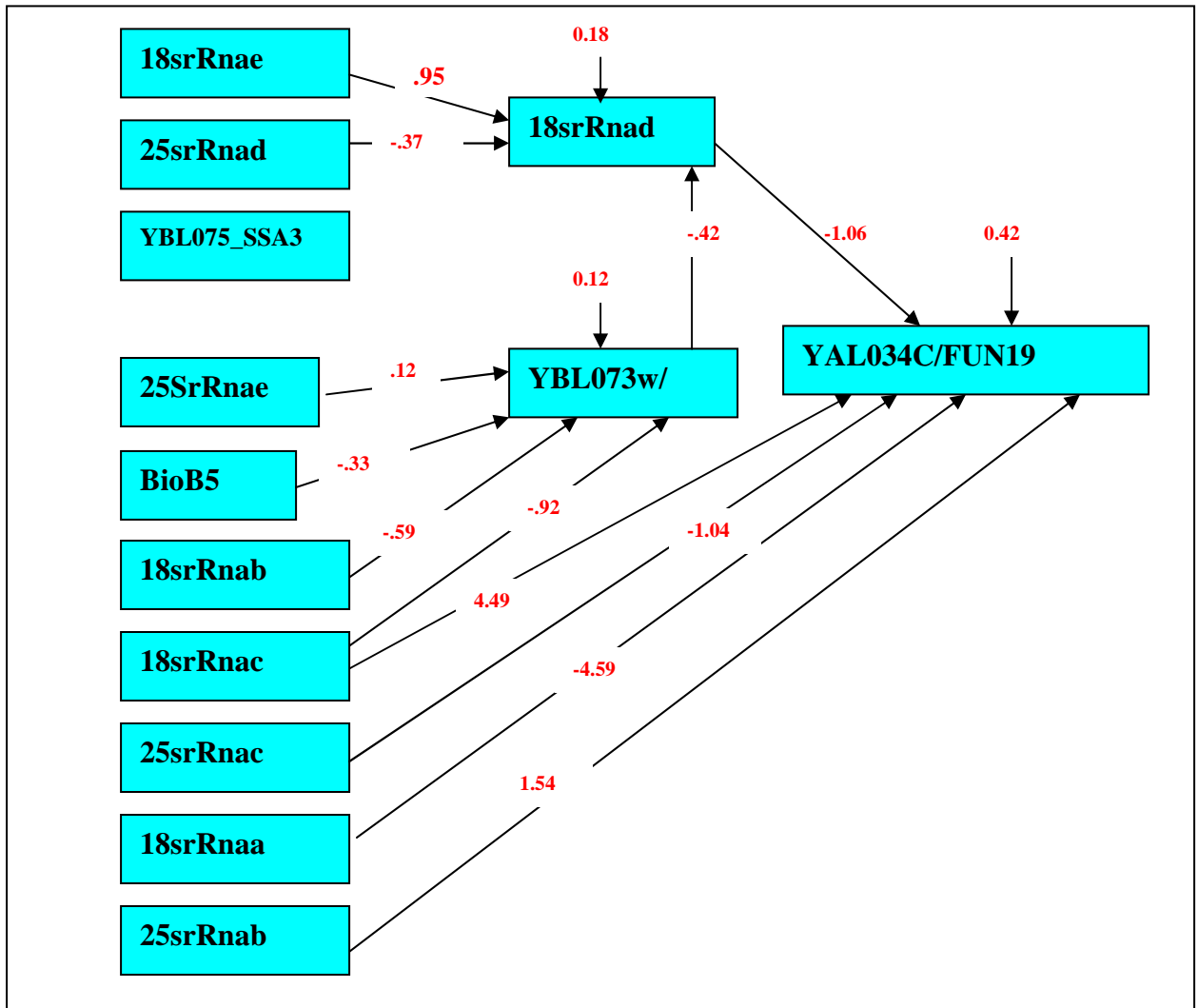
Table 1.1**Goodness of Fit Indices for Various Models, Genes Model study**

Model	Chi-square	df	p	NFI	NNFI	CFI
Null model	634.52	78	0.0040	0.000	-	-
Initial model	44.9923	23	0.0040	0.9291	0.8660	0.9605
Revised model 1	37.1039	22	0.0230	0.9415	0.9038	0.9729
Revised model 2	30.9876	21	0.1367	0.9557	0.9525	0.9872

Output 1.3 reveals that the revised model 2 chi-square statistics were non-significant, chi-square = 30.9876, $p = 0.0964$, and the NFI, NNFI, and CFI all exceed 0.95. In addition, the chi-square difference test revealed that connecting the path from gene 25SrRnae (V7) to YBL073w/ (V3) resulted in a significant improvement in the model's fit, chi-square $37.1039 - 30.9876 = 6.1163$, $p < 0.05$.

The standardized path coefficients for the revised model 2 are presented in Output 1.3. All of these coefficients are statistically significant; t tests revealed that all coefficients are significant at $p < 0.05$. In the revised model 2, gene YALO34C/FUN19 (V1) was directly determined by genes 18srRnad (V2), 18srRnac (V9), 25srRnac (V10), 18srRnaa (V11) and 25srRnab (V13) but indirectly determined by gene YBL073w/ (V3). Output 1.3 shows that these six genes 18srRnad (V2), YBL073w/ (V3), 18srRnac (V9), 25srRnac (V10), 18srRnaa (V11) and 25srRnab (V13) accounted for 82.2% of the variance in V1 (YALO34C/FUN19). Also gene 18srRnad (V2) was said to be determined by YBL073w/ (V3), 18srRnae (V4) and 25srRnad (V5), and these three genes YBL073w/ (V3), 18srRnae (V4) and 25srRnad (V5) account for 97.5% of the variance in 18srRnad (V2). The gene YBL073w/ (V3) is determined by genes 25srRnae (V7), BIOB5 (V8), 18srRnac (V9) and 18srRnab (V12) and these four genes accounted for 98.5% of the variance in YBL073w/ (V3).

Figure 1.2 Path diagram for the Gene Marker modeled by using LINEQS procedure in Proc Calis.



CONCLUSION

Analyzing gene marker data using structural equation modeling (SEM) shows that the model that we first used to predict a casual relationship had to be revised. Structural equation modeling predicts the paths for predicting the endogenous variables. In this paper we have demonstrated that structural equation modeling can be used to analyze micro array data. As the output 1.3 shows, we have determined the predictor variables and the output variables. Those genes that are homogenous are classified on the same cluster under the equation on the left side. Gene 25SrRnae (V7), BioB5 (V8), 18srRnab (V12) are classified under gene YBL0732/ (V3) and genes 18srRnae (V4) and 25srRnad (V5) are classified under gene 18srRnad (V2). Genes 18srRnad (V2), 18srRnac (V9), 25srRnac (V10), 18srRnaa (V11) and 25srRnab (V13) are classified under gene YAL034c/FUN (V1), which is the output variable. So using structural equation modeling we are predicting the output genes from several independent genes. So this task can be repeated for additional genes to create a network that relates process to genes. Table 1.1 reveals the goodness of fit indices for various models of genes. And we can observe that the revised model 2 gives a better decrease in chi-square value and the NNFI, NFI and CFI values all exceed 0.95, and a the normalized residuals for the genes is reduced to a value less than 2, hence at this stage we have chosen revised model 2 as a final model for prediction of the gene marker of the yeast data.

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