Symbolic Discriminant Analysis for Mining Gene Expression Patterns

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Introduction

- Questions
  - Can we classify and/or predict biological and clinical endpoints using gene expression data? Which genes are important? What is the pattern or statistical relationship among the genes?
- Statistical Challenges
  - Modeling
    - What statistical method do you use? How do you select a statistical model?
  - Variable Selection
    - > 5,000 gene expression variables
    - How do you select a subset of variables?
    - 100 variables ~ $1.27 * 10^{30}$ subsets
- Objectives
  - Develop a computational or statistical methodology that is able to handle the model and variable selection challenges.
  - Use this methodology to identify patterns of gene expression that classify and predict clinical endpoints.

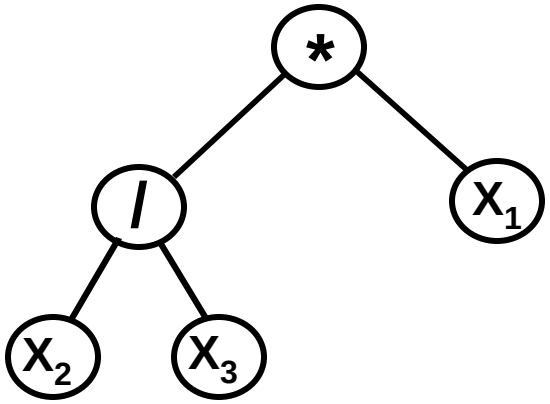
Symbolic Discriminant Analysis

- Supply list of gene expression variables
  - $X_1, X_2, \ldots X_{10,000}$
- Supply list of mathematical functions
  - +, -, *, /, abs, log, exp, sqrt
- Use variables and functions as building blocks

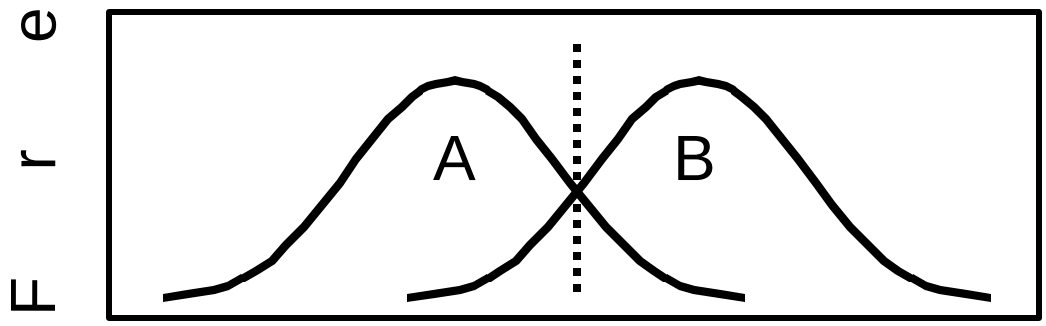
$$S_j = X_{1ij} * X_{2ij} / X_{3ij}$$

Symbolic Discriminant Analysis

- Supervised classification approach
- Use parallel genetic programming (GP) to build symbolic discriminant functions
- Misclassification rate is fitness function



$S = X_1 * X_2 / X_3$



Symbolic Discriminant Scores

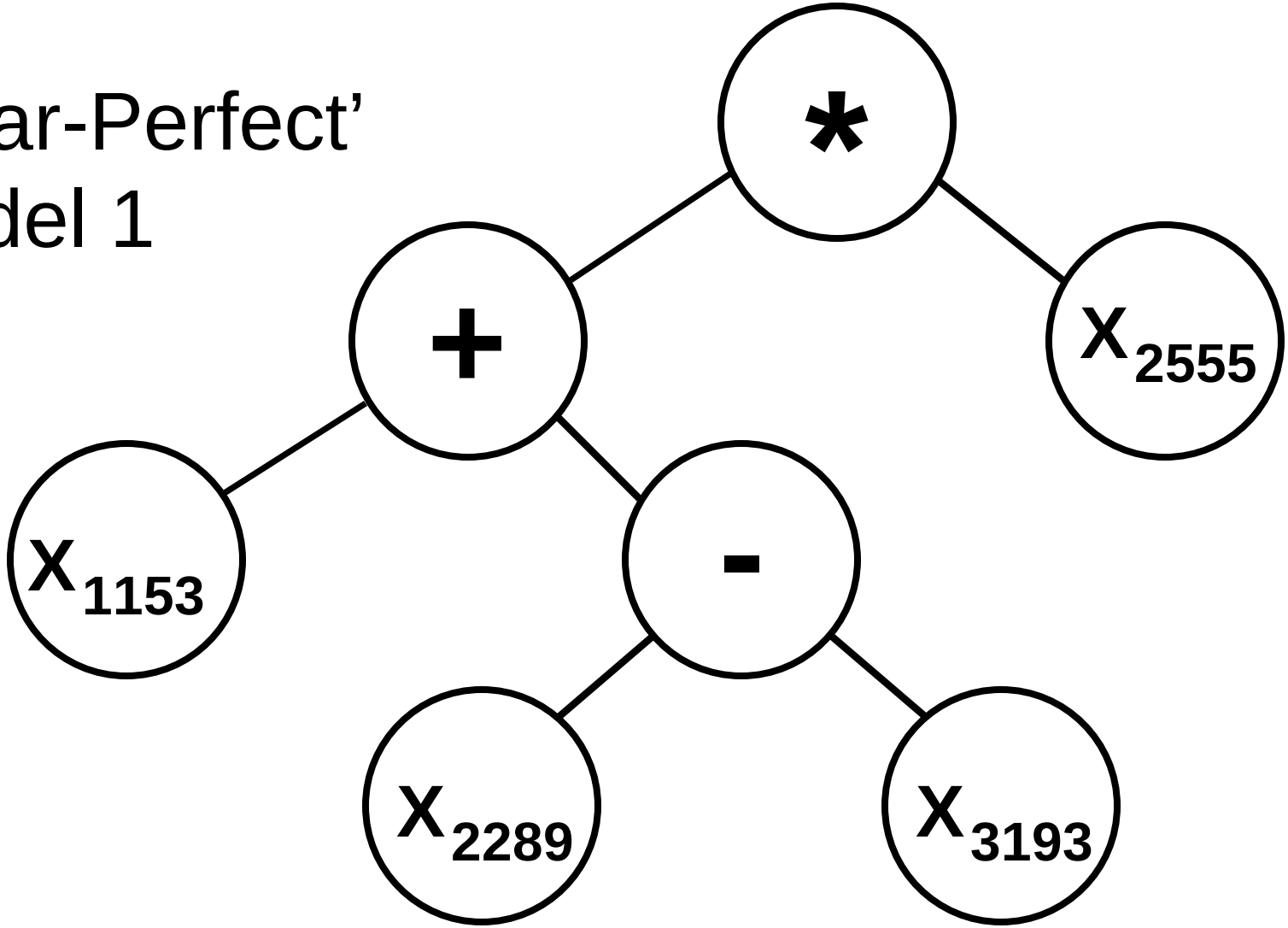
Application to Leukemia Data

- Leukemia Data (Golub et al. 1999)
  - Dataset 1 (n=38, training)
  - Dataset 2 (n=34, testing)
  - ~7100 expressed genes measured using Affymetrix oligonucleotide chips
- Cross Validation Strategy
  - Divide the training dataset into 38 equal parts.
  - Optimize SDA with each 37/38 of data.
  - Select SDA models that minimize the classification error and correctly predict the 1/38 of the data left out.
  - Estimate the prediction error using the testing dataset (n=34).
- Genetic Programming Settings
  - Population Size: 500
  - Iterations: 100
  - Populations: 4
  - Migration of best solutions every 25 iterations
  - Crossover probability: 0.6
  - Maximum depth: 6

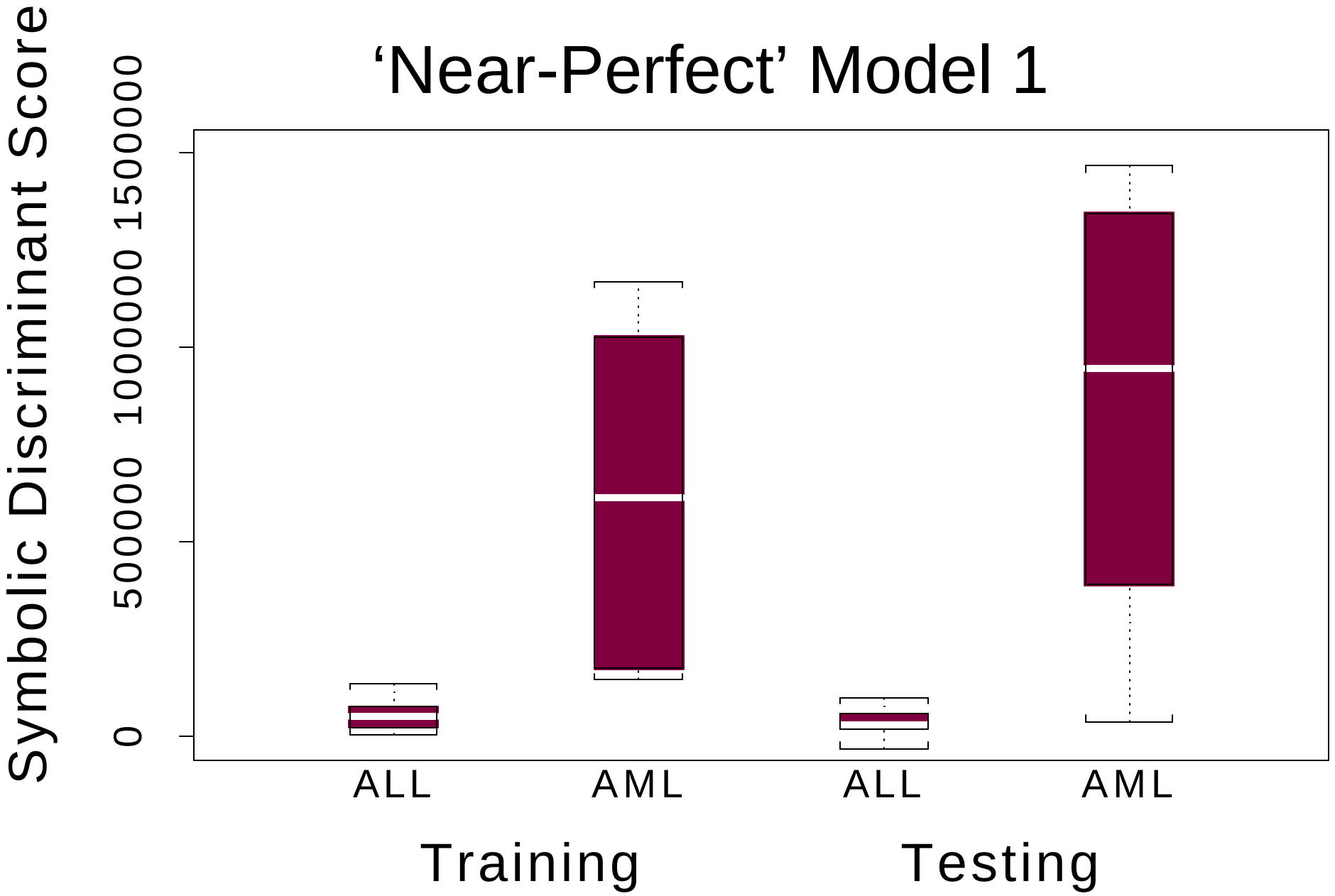
Results

- Identified 2 ‘near-perfect’ models
  - Classified 38/38 correctly
  - Predicted 33/34 correctly
- Identified 16 ‘very good’ models
  - Classified 38/38 correctly
  - Predicted 32/34 correctly
- Identified 36 ‘good’ models
  - Classified 38/38 correctly
  - Predicted 31/34 correctly

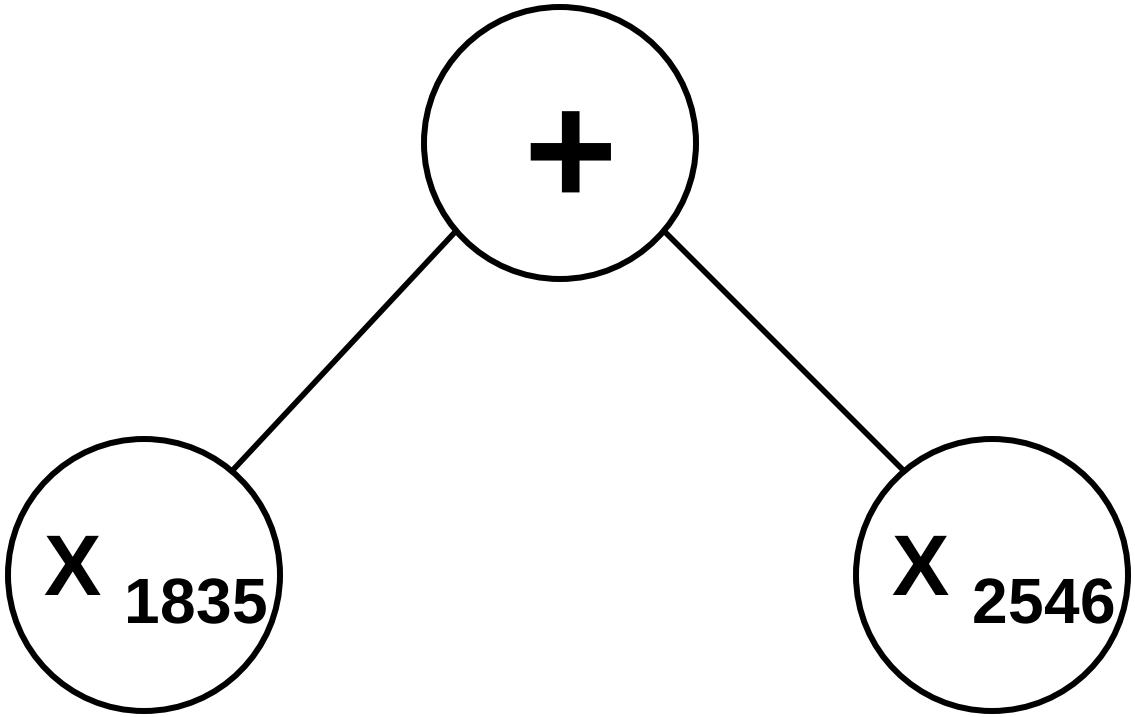
‘Near-Perfect’
Model 1



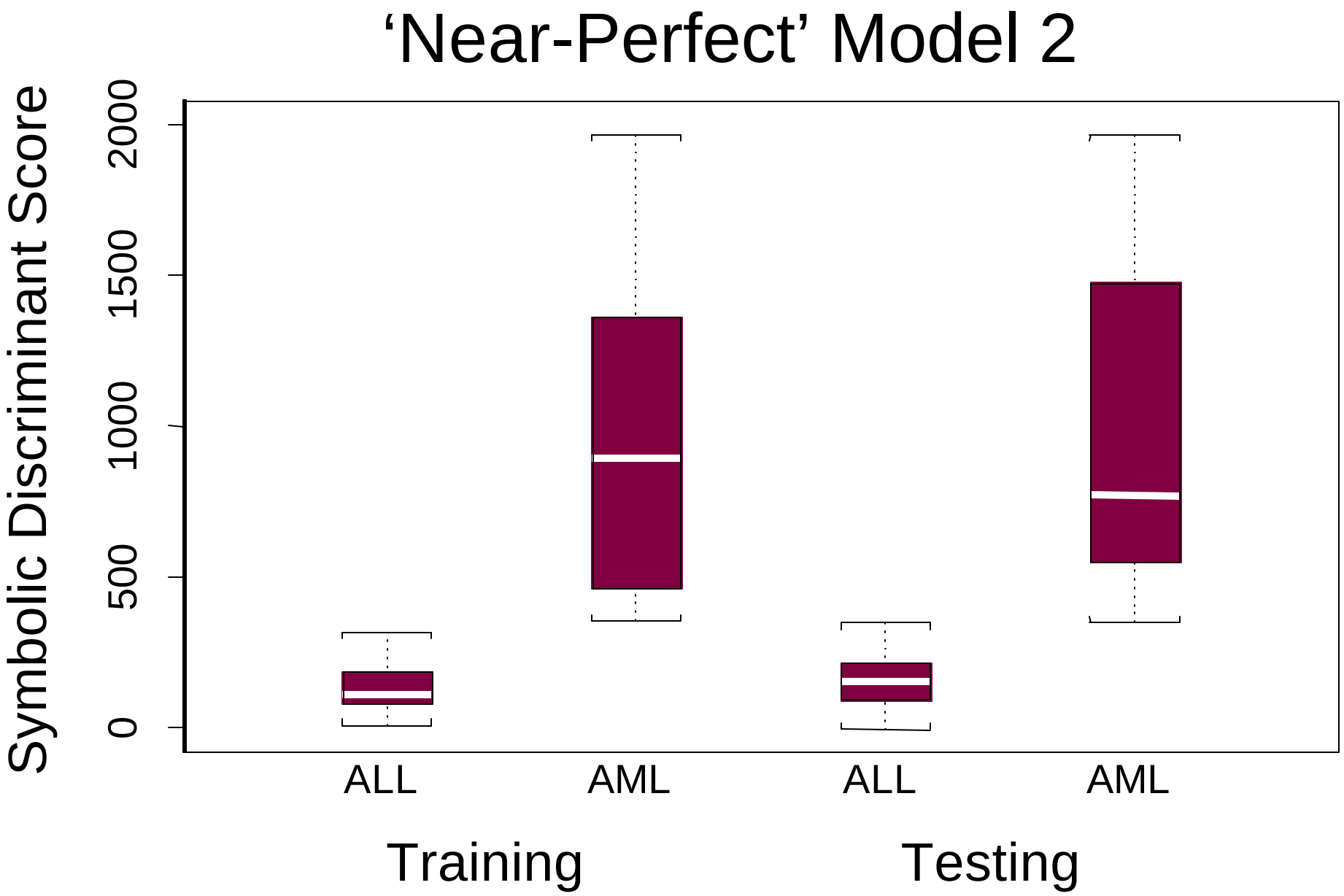
$$Y = X_{2555} * (X_{1153} + X_{2289} - X_{3193})$$


‘Near-Perfect’ Model 1
Symbolic Discriminant Score
0
5000000
10000000
15000000
ALL
AML
ALL
AML
Training
Testing

‘Near-Perfect’
Model 2



$$Y = X_{1835} + X_{2546}$$


‘Near-Perfect’ Model 2
Symbolic Discriminant Score
0
500
1000
1500
2000
ALL
AML
ALL
AML
Training
Testing

Which Genes Were Identified?

- Model 1: $Y = X_{2555} * (X_{1153} + X_{2289} - X_{3193})$
  - X_{2555}: Testis-specific cDNA on 17q
    - Cloned from a translocation, t(12;17), in a campomelic dysplasia patient.
  - X_{1153}: Erythroid beta-spectrin
    - Major component of red cell membrane, expressed during normal erythropoiesis
  - X_{2289}: Adipsin
    - Part of a gene cluster expressed during myeloid cell differentiation.
  - X_{3193}: Nucleoporin 98
    - Fuses with HOXA9 during an AML associated translocation, t(7;11)(p15;p15).
- Model 2: $Y = X_{1835} + X_{2546}$
  - X_{1835}: CD33
    - Differentiation antigen of AML progenitor cells.
  - X_{2546}: Rho E
    - Part of Rho family of signal transduction proteins
    - Lacks GTPase activity

Conclusions

- Symbolic discriminant analysis is a powerful alternative to traditional multivariate statistical methods.

- We anticipate this will be an important methodology to add to the repertoire approaches for mining gene expression patterns.