Gene expression signature for cancer classification

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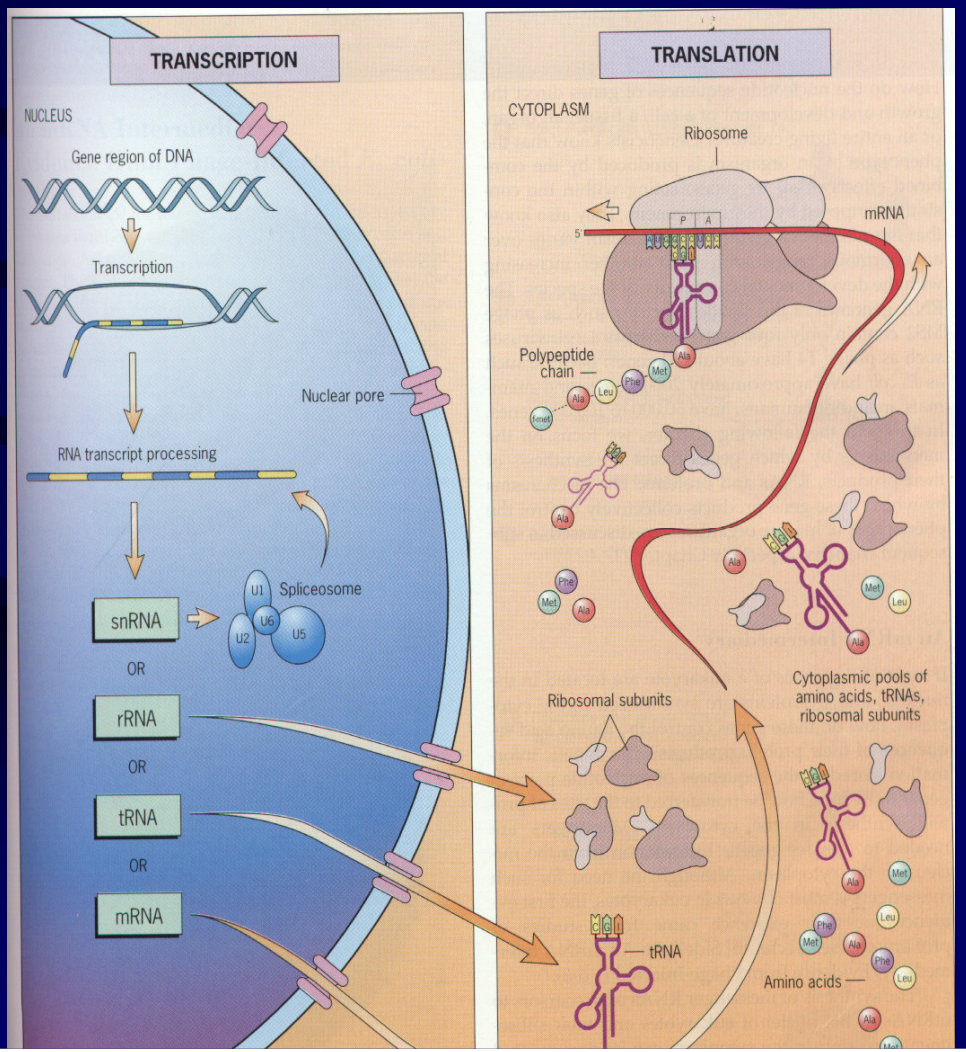
Layout

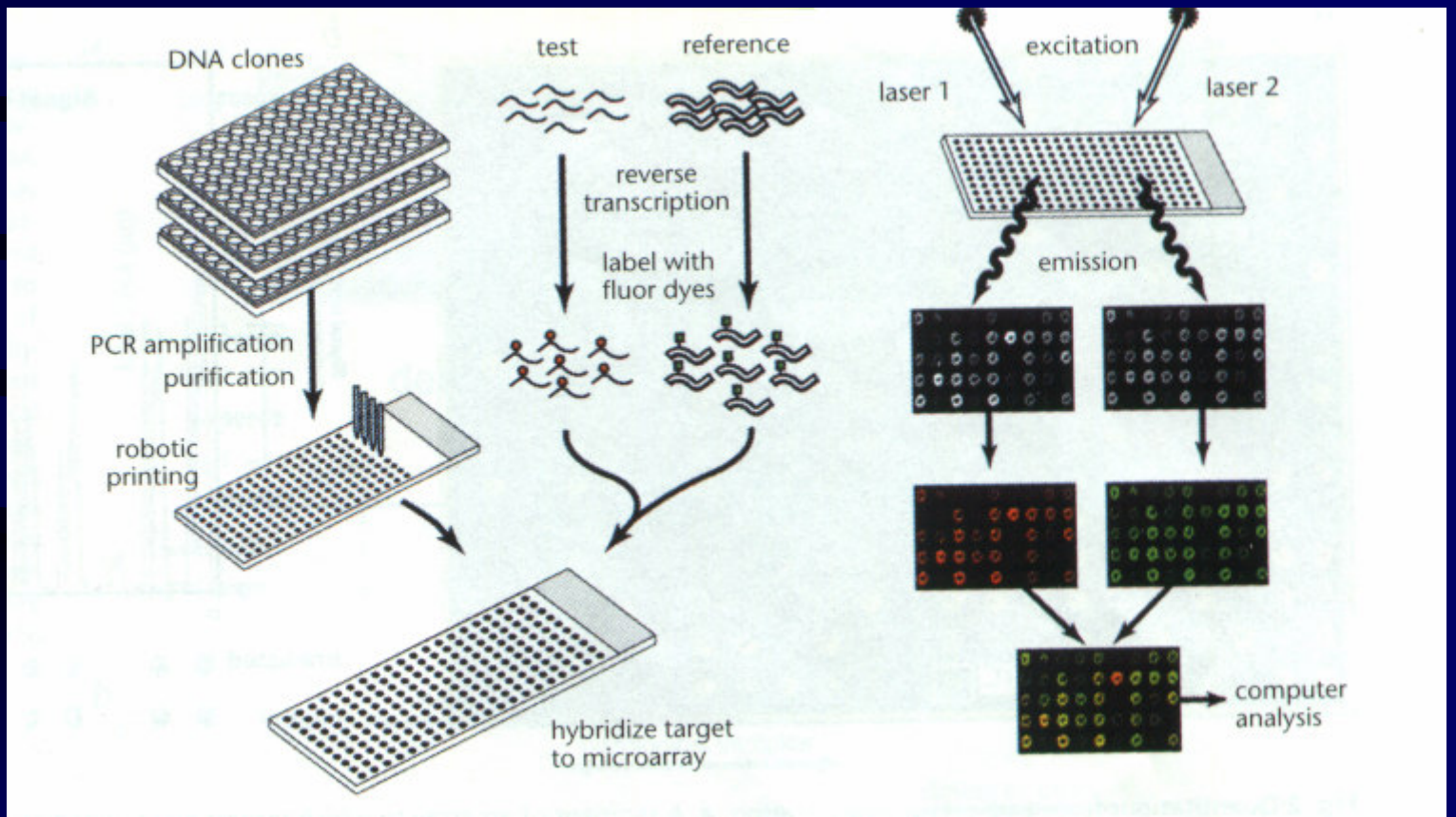
- Introduction
- Classifiers: concept and design
- Dimensionality reduction
- Mean conditional entropy
- Strong features : concept and algorithms
- Validation

Introduction

Gene Expression



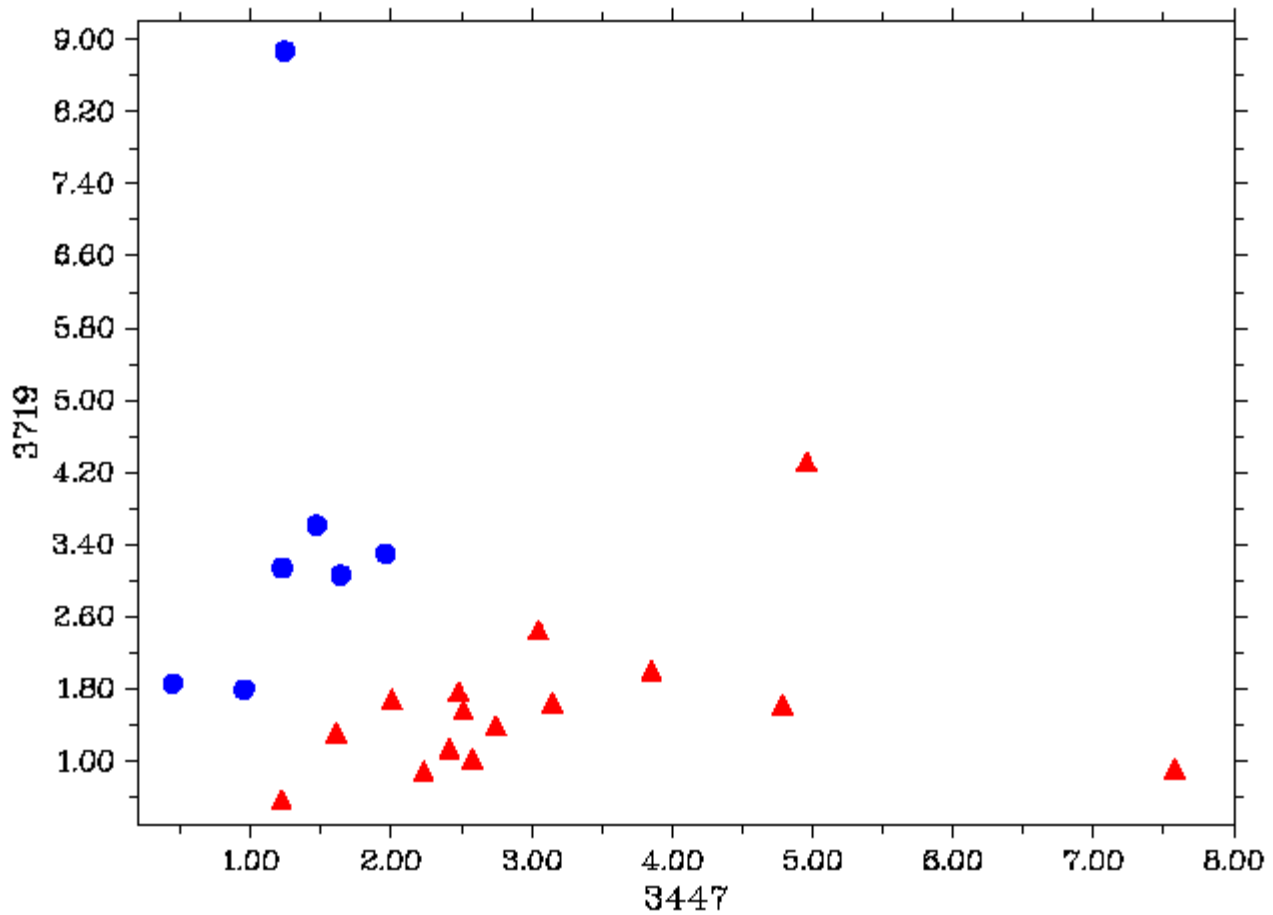
Expression measure



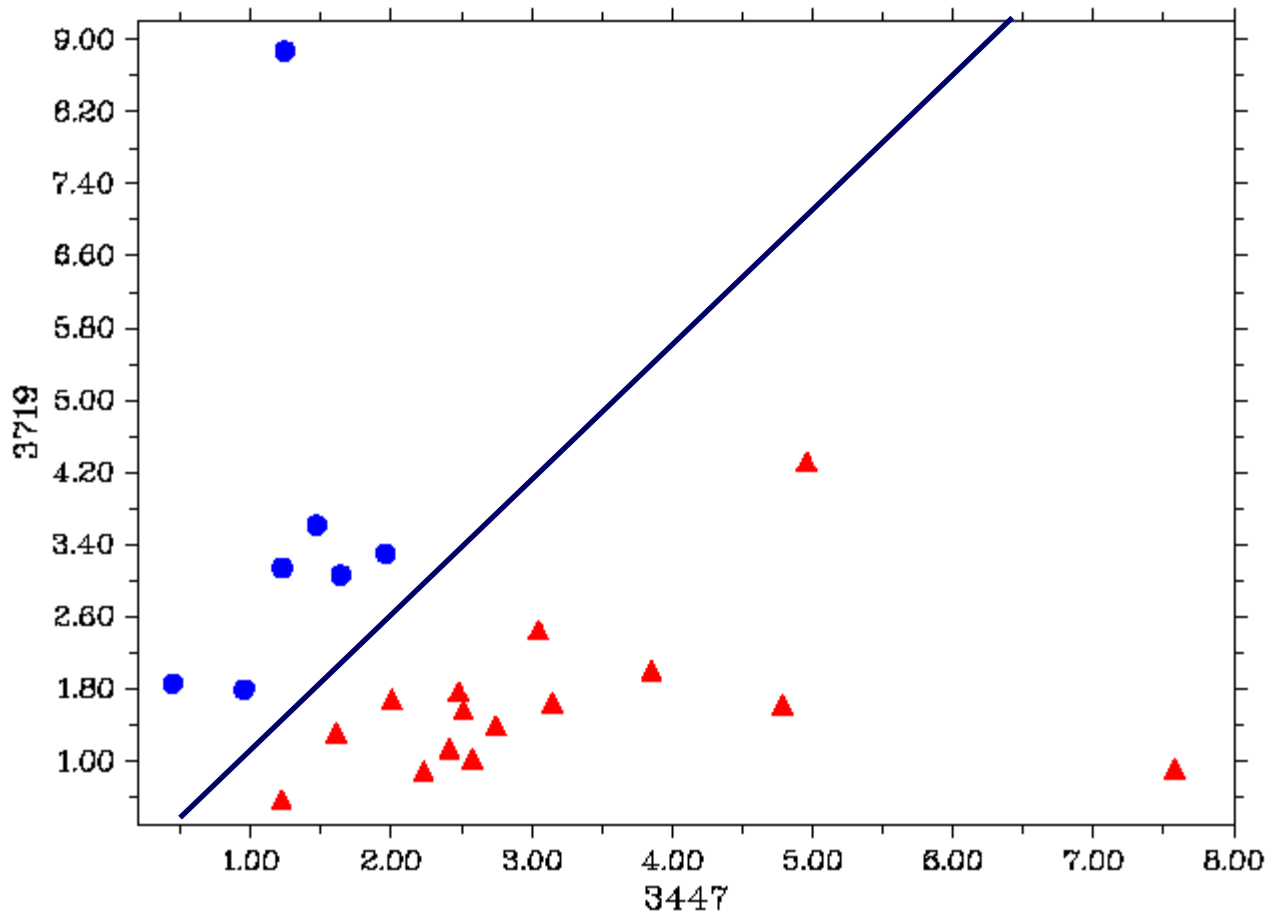
Goal: find a small subset of genes whose expression values are enough to recognize two or more cancer types.

Classifiers: concept and design

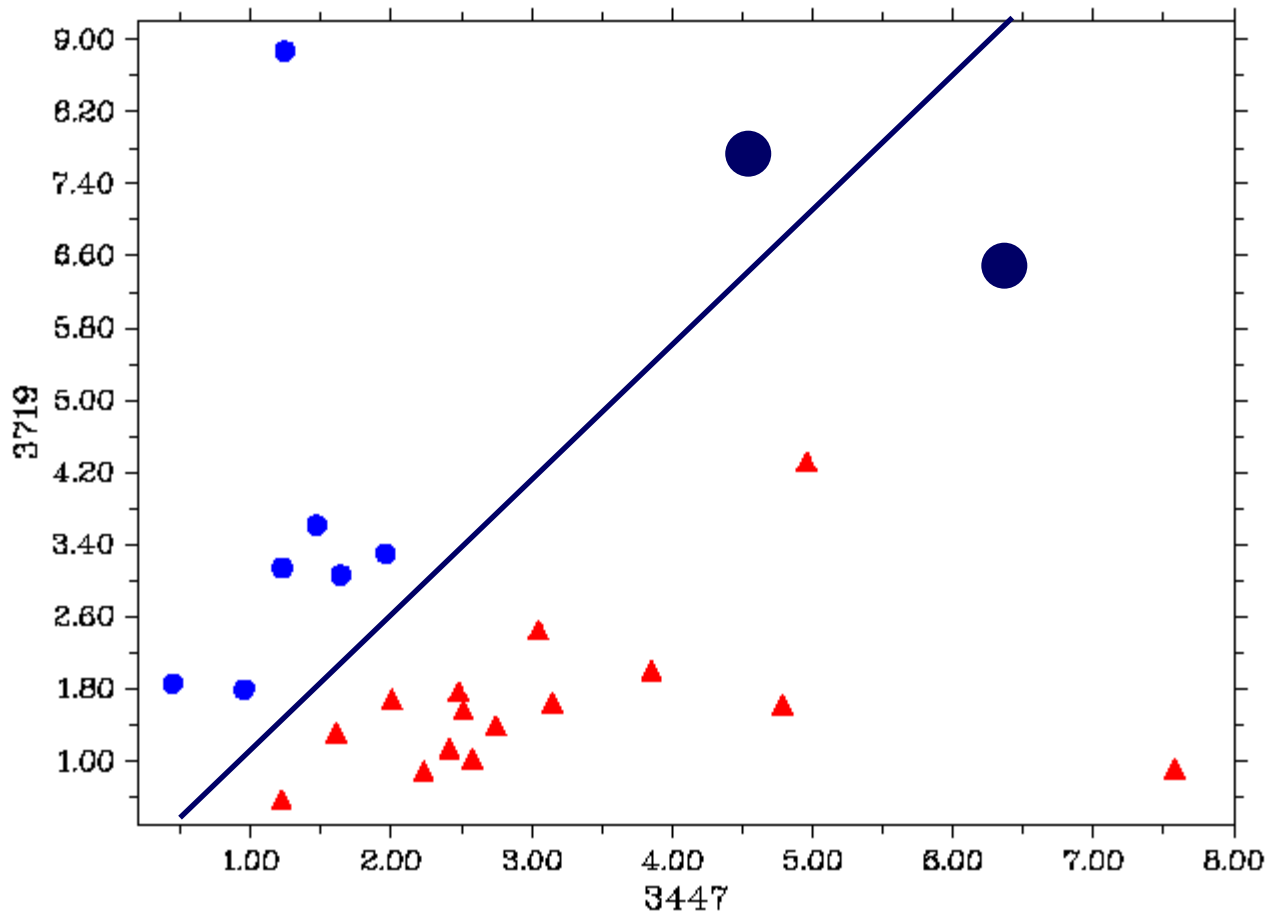
Classifiers



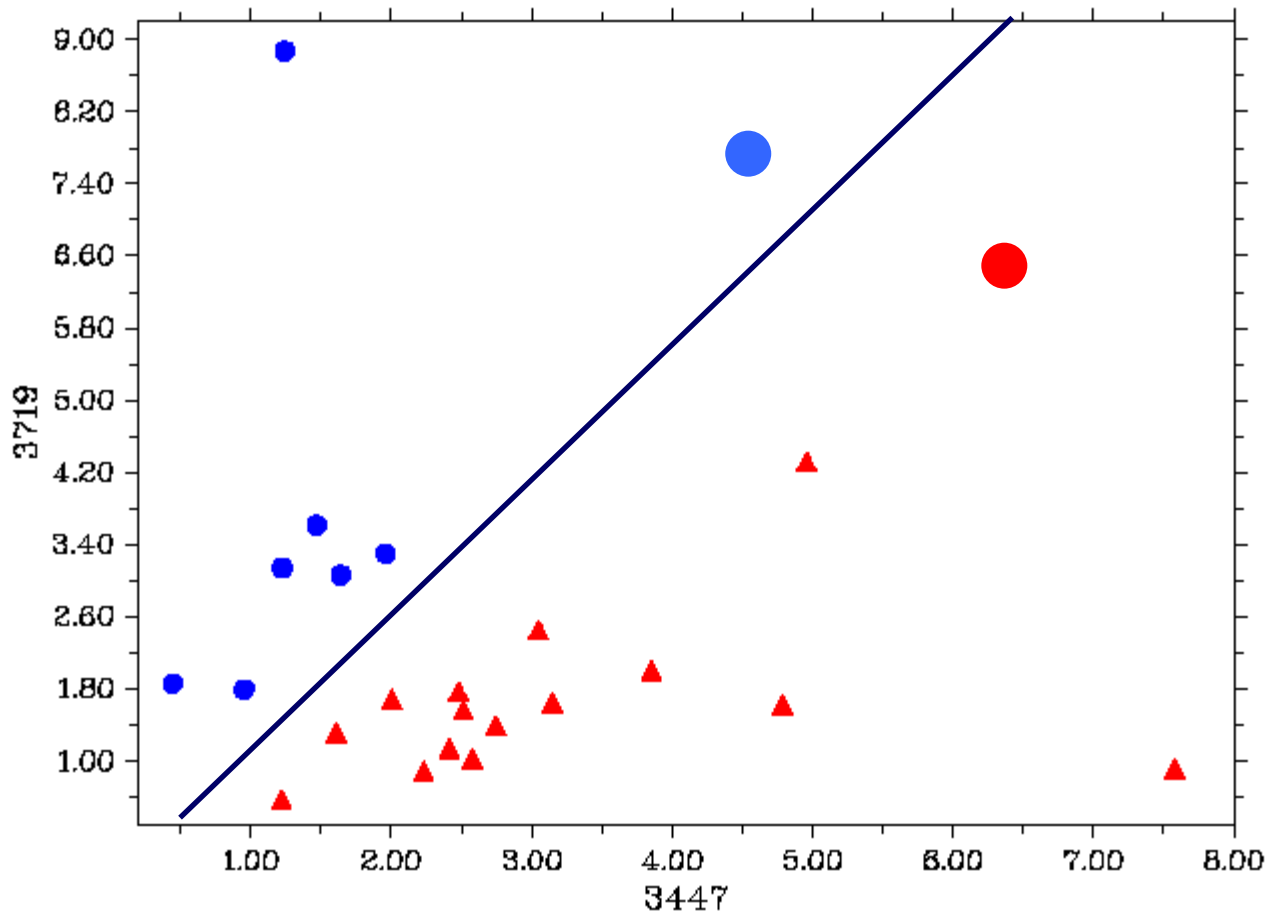
Classifiers



Classifiers



Classifiers



Classifier Design

- Design goal is to find a function with minimum risk.
- Risk (expected loss) of a function :

$$R(\psi) = E[l(\psi(X), Y)]$$

X is a random set
Y is a binary random variable

- Loss function

$$l : \{0,1\} \times \{0,1\} \rightarrow R^{+}$$

MAE example

- *Example* : MAE loss function

$$l_{MAE}(a,b) = |a-b| \qquad a,b \in \{0,1\}$$

$$MAE\langle\Psi\rangle = E[|\psi(X) - Y|]$$

- Optimal MAE function

$$\psi(X) = \begin{cases} 1 & p(1,X) > p(0,X) \\ 0 & p(1,X) \leq p(0,X) \end{cases}$$

PAC learning

L is Probably Approximately Correct (PAC)

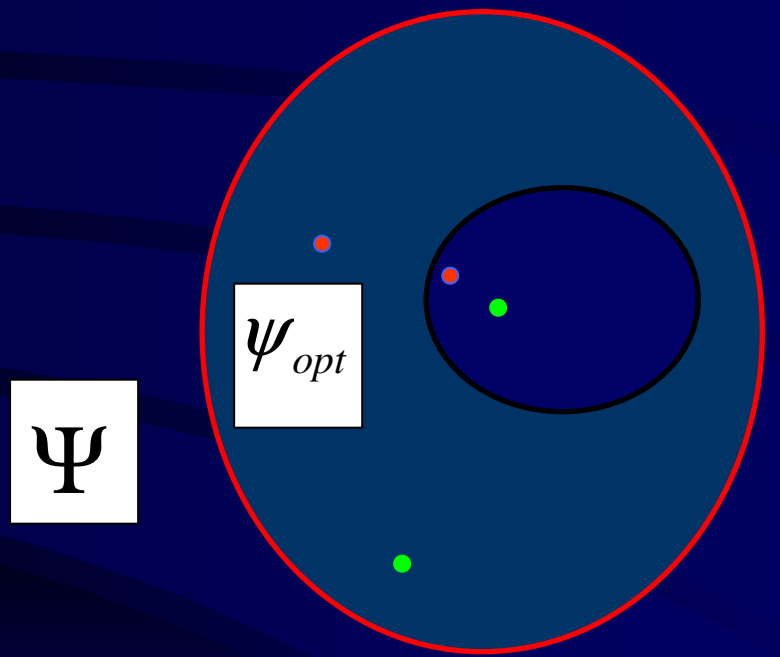
For $m > m(\varepsilon, \delta)$ examples

$$\Pr(|R(\psi) - R(\psi_{opt})| < \varepsilon) > 1 - \delta$$

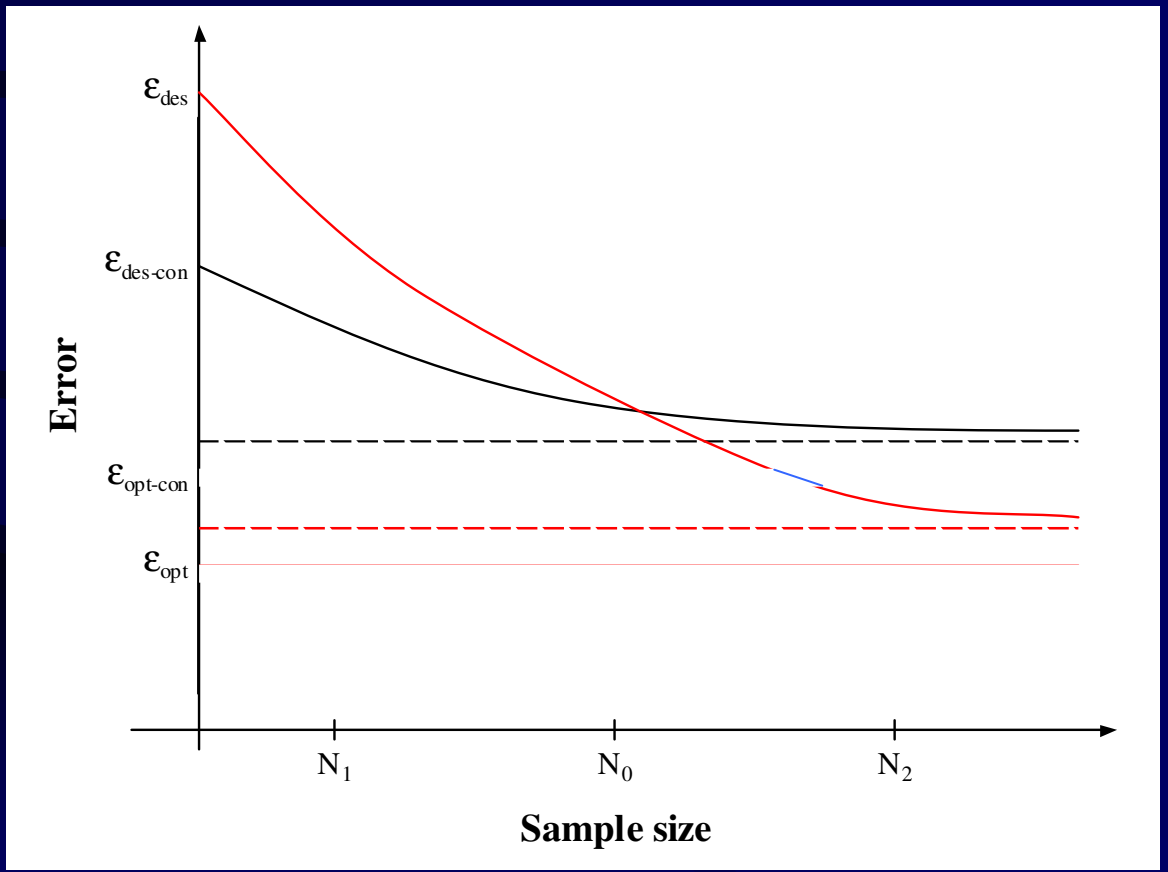
$$\varepsilon, \delta \in (0,1)$$

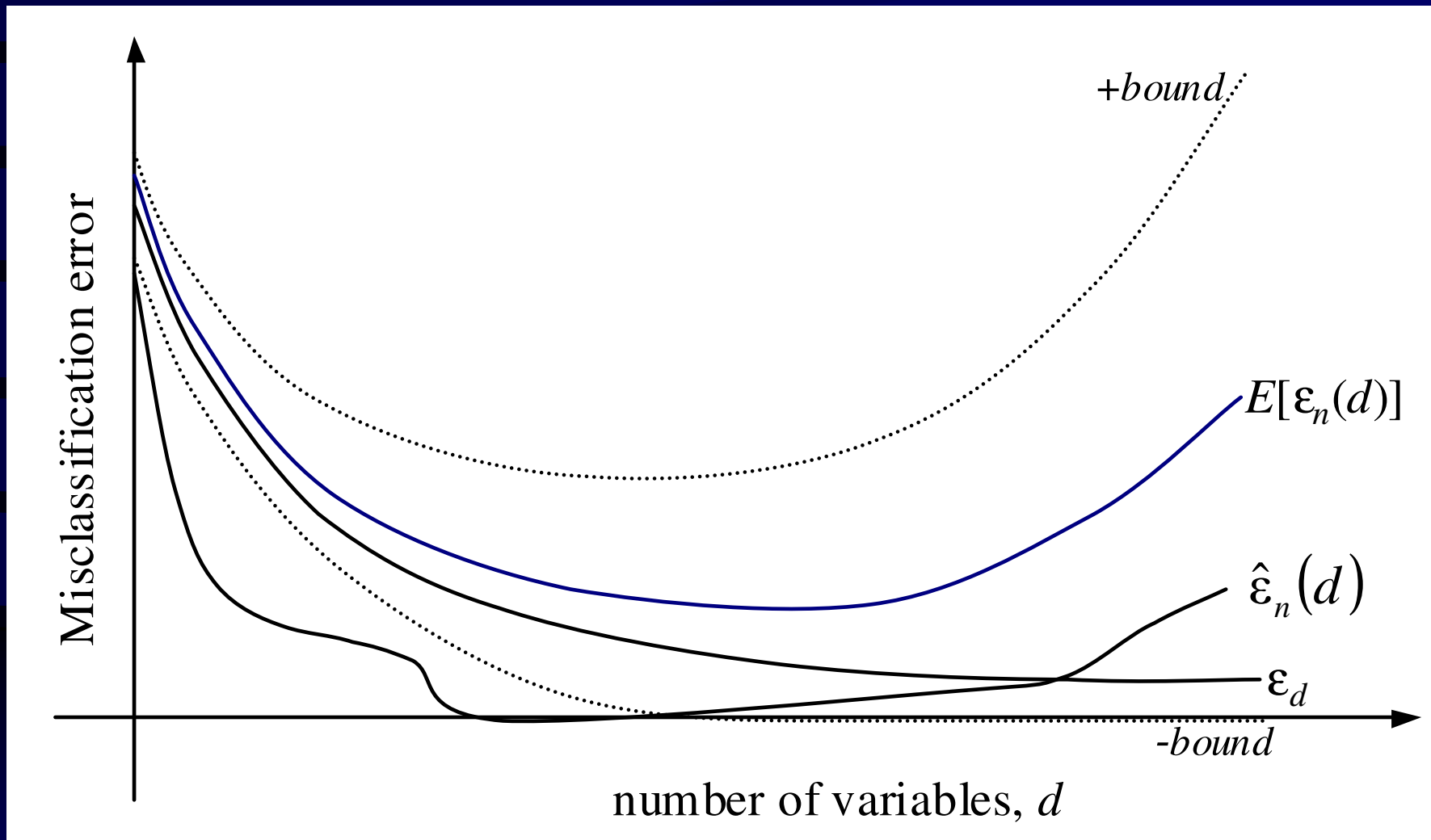
Dimensionality Reduction

Constraints



Constraints




+bound
Misclassification error
$E[\varepsilon_n(d)]$
$\hat{\varepsilon}_n(d)$
ε_d
-bound
number of variables, d

Mean conditional entropy

Entropy

- Distribution measure
- $H(X) = - \sum p(x) \log p(x)$
- decreases when the probability mass is more concentrated.
- Maximum for uniform distribution
- Invariant to redistribution of the probability mass, keeping the same proportion

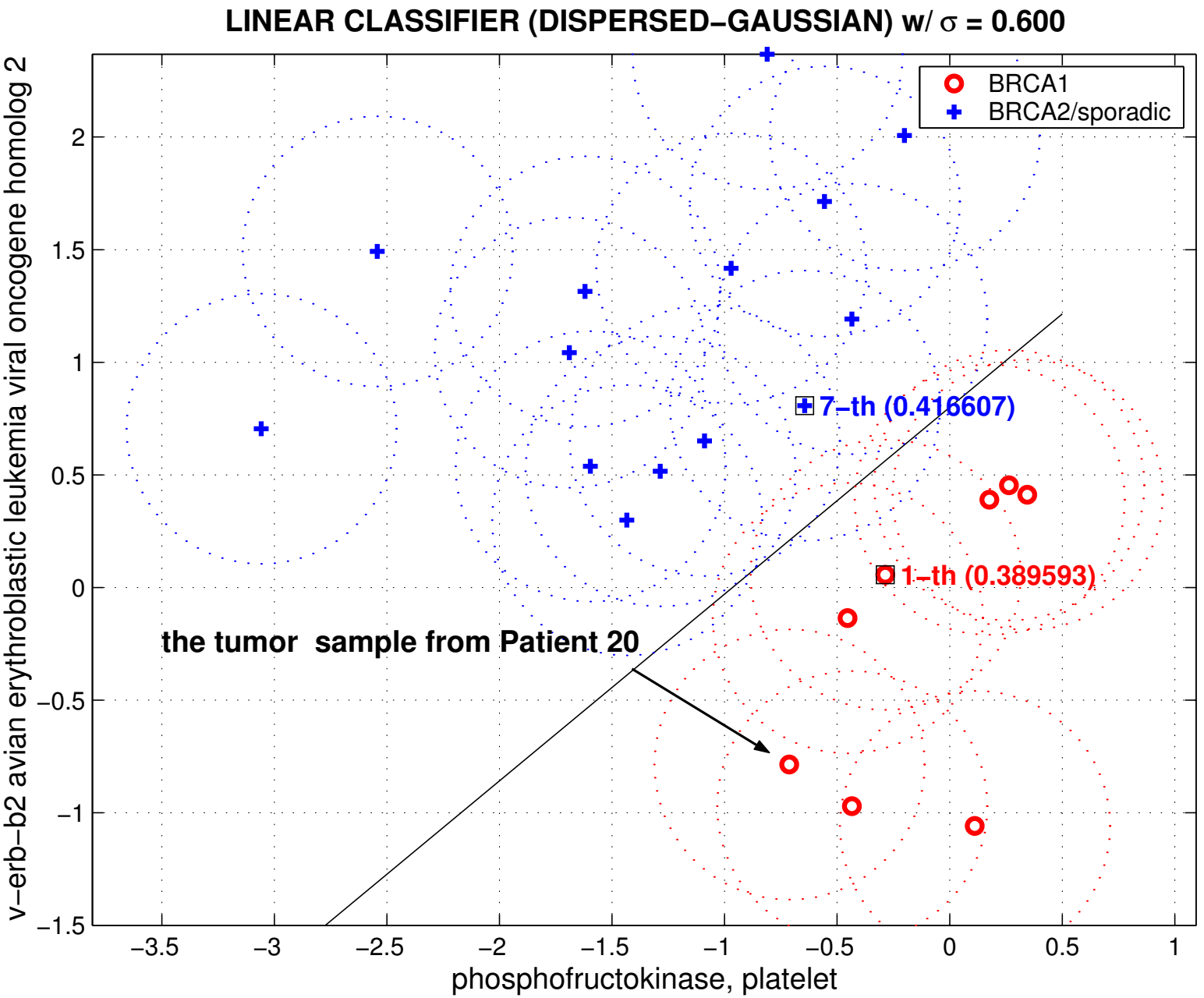
Expected Conditional Entropy

- $E[H(Y/X)] = \sum - p(x) \sum p(Y/x) \log p(Y/x)$
- When $E[H(Y/X)]$ is smaller, the pattern recognition problem is simpler

Finding the best features

- For each subset of features, p(x) and p(y/x) may be estimated from data. The best set of features has the smallest estimated conditional entropy.
- The feature space forms a Boolean lattice, that can be explored exhaustively or partially.

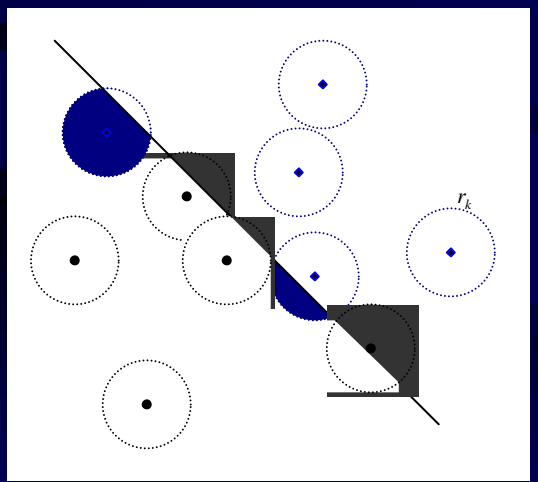
Strong features: concept and algorithms

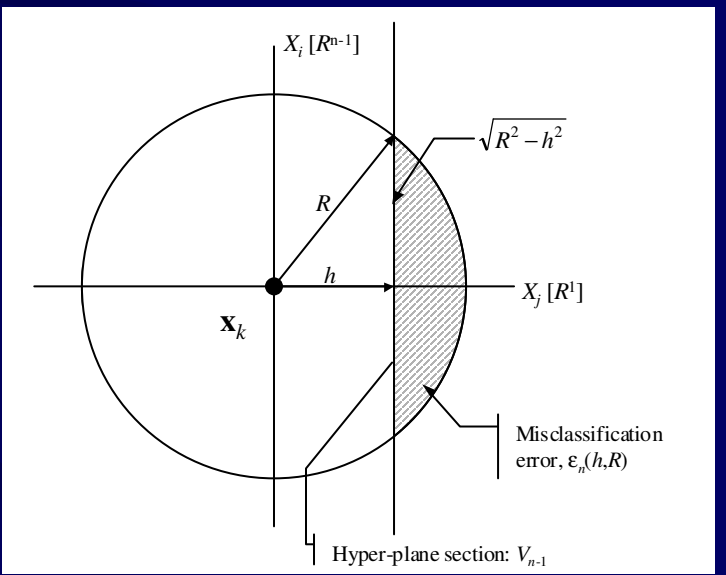

LINEAR CLASSIFIER (DISPERSED–GAUSSIAN) w/ σ = 0.600
BRCA1
BRCA2/sporadic
7–th (0.416607)
1–th (0.389593)
the tumor sample from Patient 20
v–erb–b2 avian erythroblastic leukemia viral oncogene homolog 2
phosphofructokinase, platelet
2
1.5
1
0.5
0
–0.5
–1
–1.5
–3.5
–3
–2.5
–2
–1.5
–1
–0.5
0
0.5
1

Approach

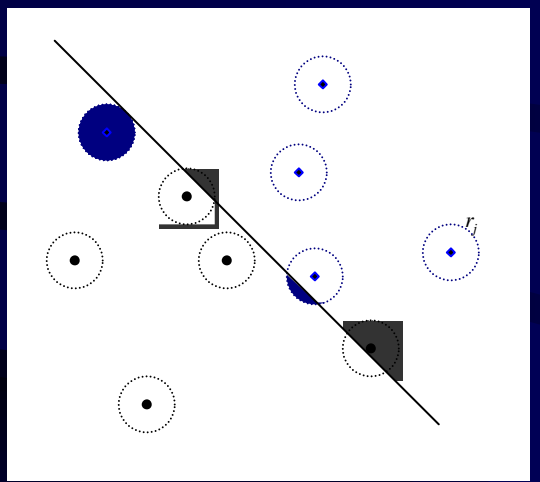
randomize data
compute classifier using genes subsets
measure error for different dispersions
choose the subset that balance small error and high dispersion.
A supercomputer is required.

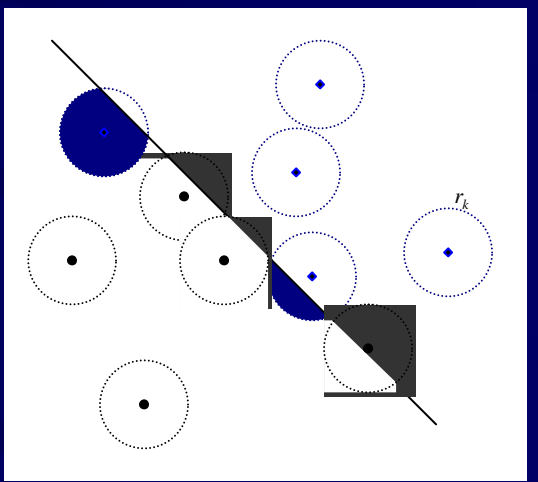
Linear classifier
Dispersion centered in the sample
Flat round dispersion model
Error computed analytically (faster)

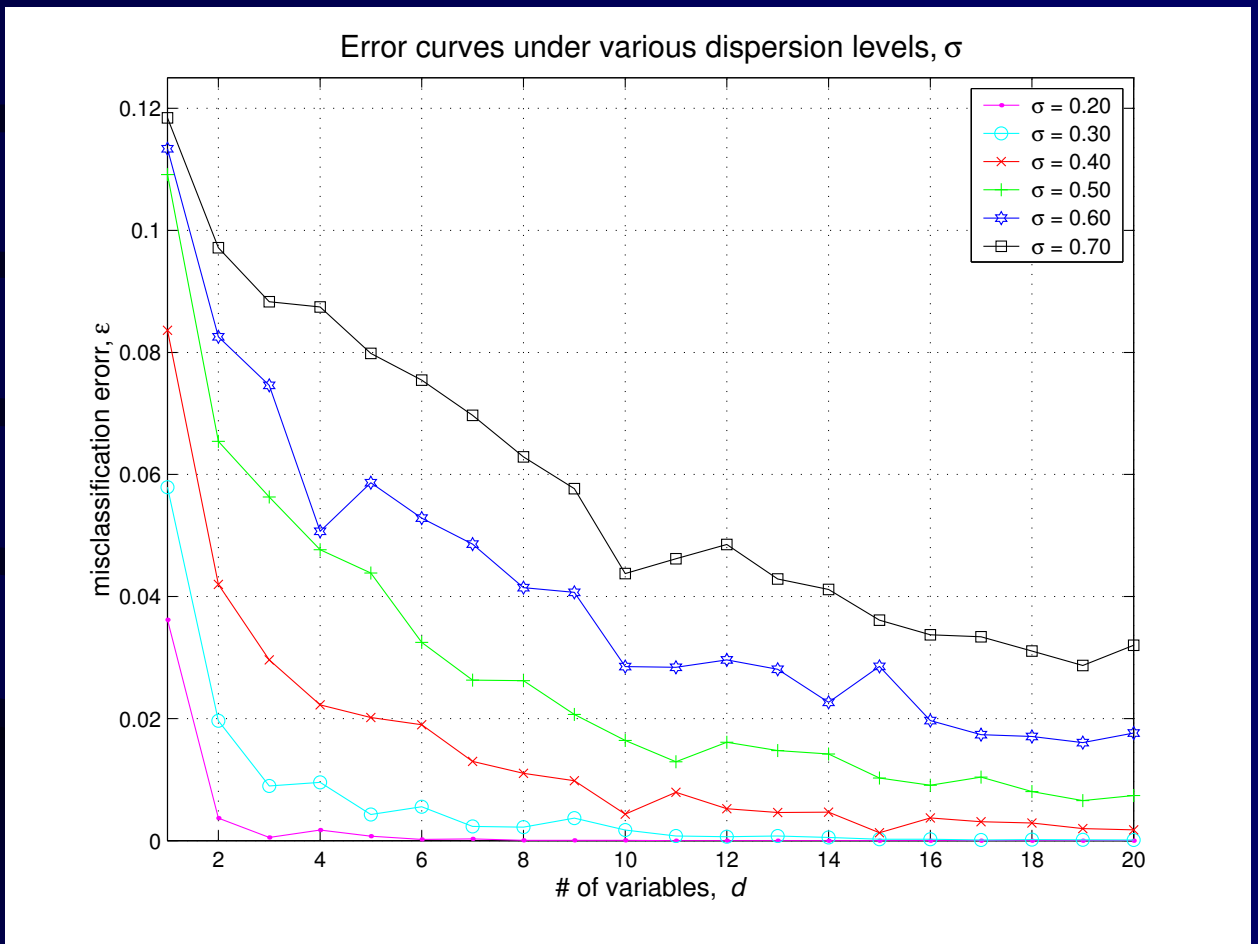




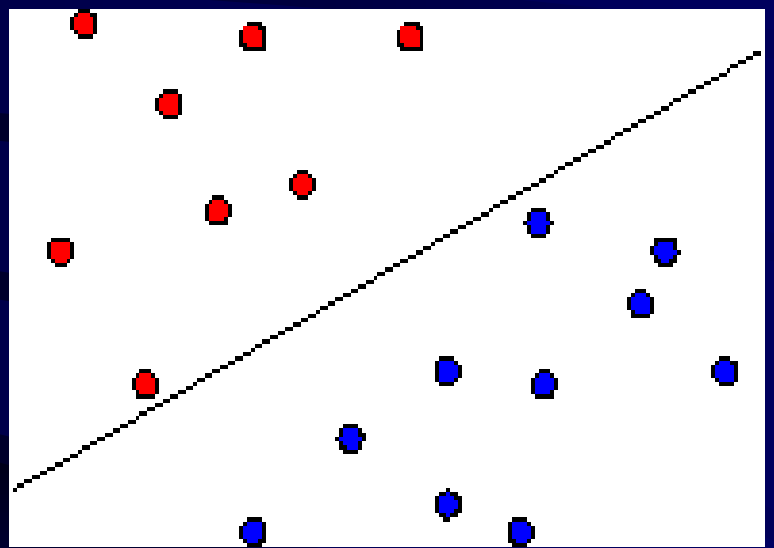
Robustness analysis

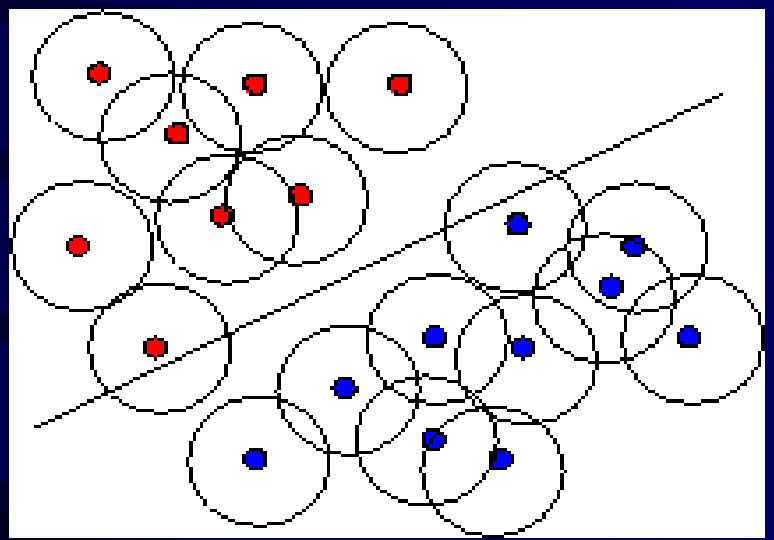


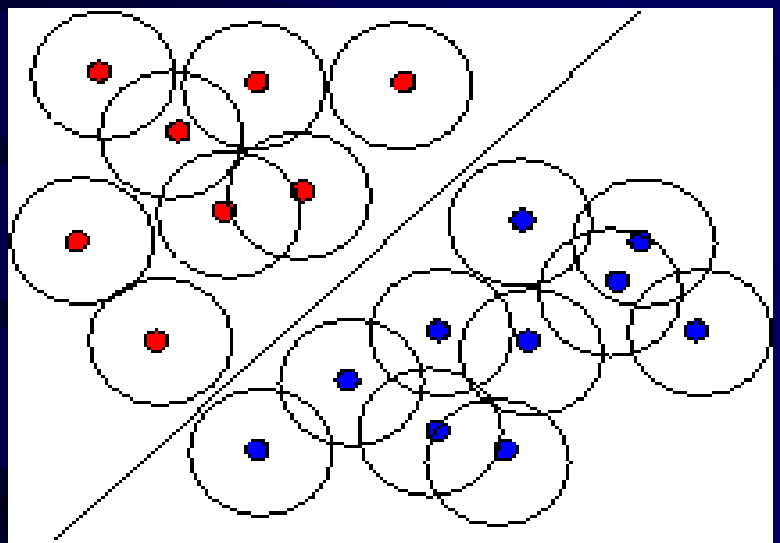



Error curves under various dispersion levels, σ
misclassification erorr, ε
# of variables, d
σ = 0.20
σ = 0.30
σ = 0.40
σ = 0.50
σ = 0.60
σ = 0.70
0
0.02
0.04
0.06
0.08
0.1
0.12
2
4
6
8
10
12
14
16
18
20

Algorithm based on linear programming







Steps

- The best linear classifier uses about 20-25 genes
- Genes used are eliminated and the best linear classifier is computed, more 20-25 genes are separated
- The procedure is repeated till having about 100 genes
- The full search is applied in the selected subset of genes

Validation

- Expression of chosen subsets of genes are measured several times in low cost experiments
- If the experiments reveal compact clusters the subset of genes chosen should be correct.

Classifiers