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Classification with PAM and Random Forest

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Two roads to classification

- Given: patient profiles already diagnosed by an expert.
- Task: infer a general rule to diagnose new patients.
- Basically, there are two ways to solve this task

1. model class probabilities

   QDA, LDA, ...

2. model class boundaries directly

   Optimal Separating Hyperplanes, Random Forest

What‘s the problem?

In classification you have to trade off

- underfitting versus overfitting
- bias versus variance.

Curse of dimensionality! In 12’000 dimensions even linear methods are very complex! High variance!

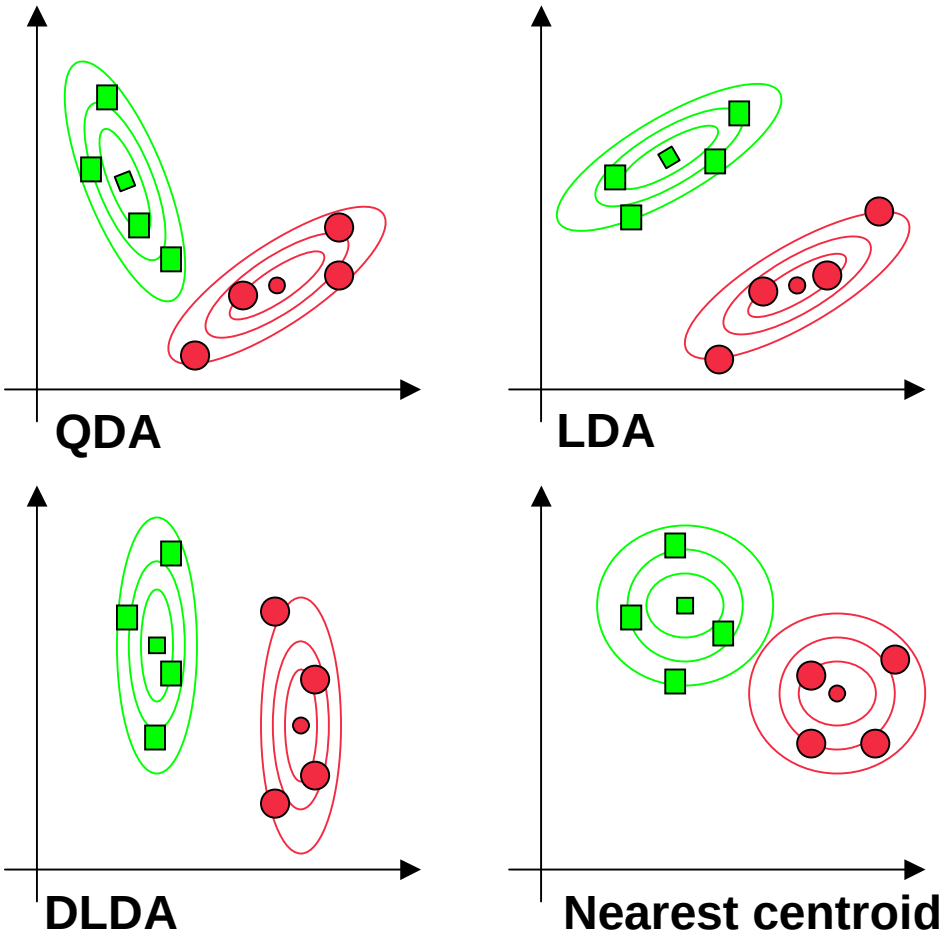
Simplify your models

Discriminant analysis and gene selection

Comparing Gaussian likelihoods

- Assumption: each group of patients is well described by a normal density.
- Training: estimate mean and covariance matrix for each group.
- Prediction: assign new patient to group with higher likelihood.
- Constraints on covariance structure lead to different forms of discriminant analysis.

Discriminant analysis in a nutshell



Characterize each class by mean and covariance structure.

1. Quadratic D.A.
   different COVs
2. Linear D.A.
   requires same COVs.
3. **Diagonal linear D.A.**
   same diagonal COVs.
4. Nearest centroids
   forces COVs to $\sigma^2 I$.

Discriminant analysis in a nutshell

Choose k that maximizes the linear discriminant function

$$\delta_k(x) = x^t \Sigma^{-1} \mu_k - \frac{1}{2} \mu_k^t \Sigma^{-1} \mu_k + \log \pi_k$$

The given data

Covariance matrix: same for all groups

Group centroid: one for each group

Prior class probability

For DLDA: Choose k that minimizes

$$\delta_k(x) = \sum_g \frac{(x_g - (\mu_k)_g)^2}{\sigma_g^{\,2}} - 2 \log \pi_k$$

variance of gene g

Feature selection

Next simplification:

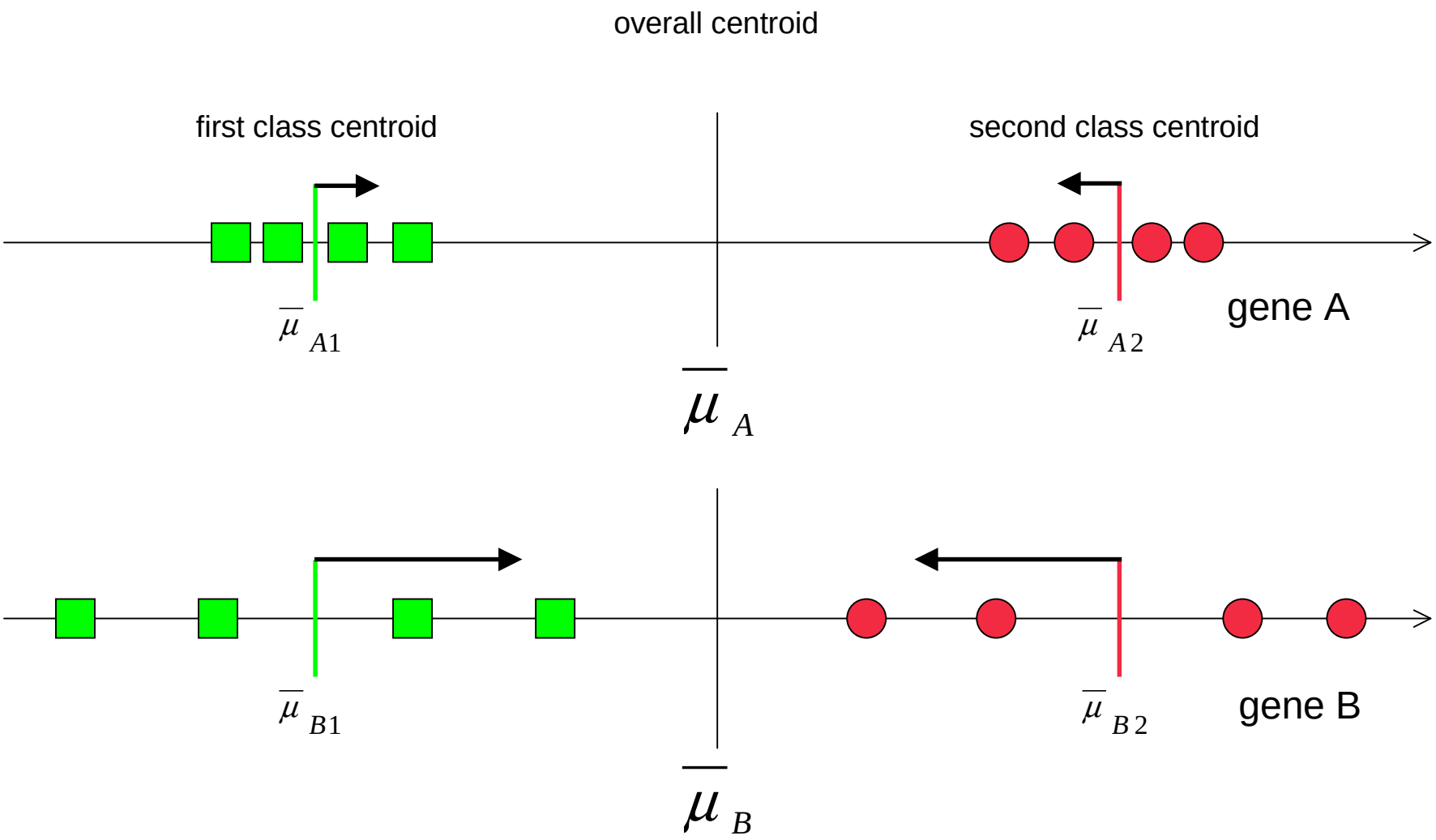
Base the classification only on a small number of genes.

Feature selection: Find the most discriminative genes.

1. Filter: Rank genes according to discriminative power
   by t-statistic, Wilcoxon, ...
   Use only the first k genes for classification. Discrete, hard thresholding.

2. Shrinkage: Continously shrink genes until only a few have influence on classification.
   Example: Nearest Shrunken Centroids.

Shrunken Centroids



Nearest Shrunken Centroids

The difference between the group centroid for gene i and class k and the overall centroid can be written as follows:

$$\overline{\mu}_{gk} - \overline{\mu}_{g} = \sqrt{1/n_k + 1/n} \cdot (s_g + s_0) \cdot d_{gk}$$

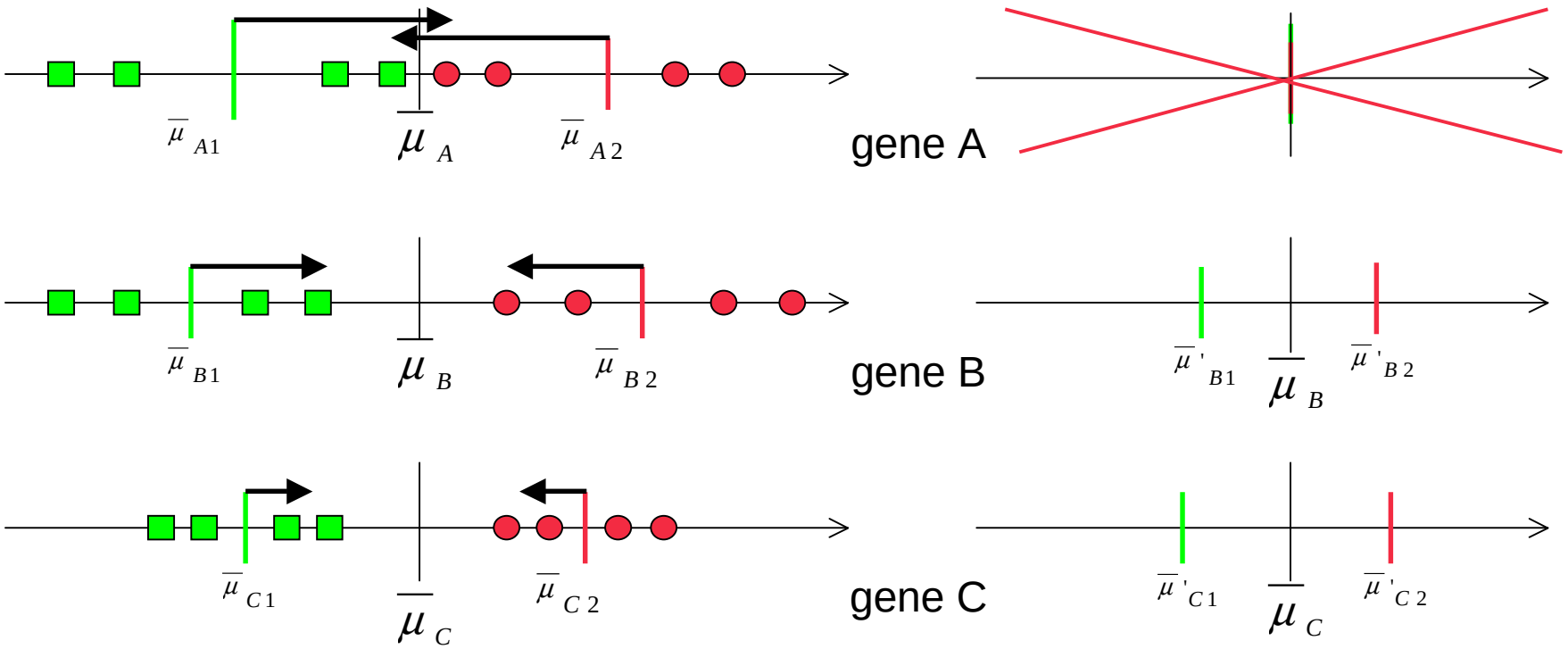
where s_i is the pooled within-class standard deviation of gene i and s_0 is an offset to guard against genes with low expression levels.

Shrinkage: Each d_{gk} is reduced by Δ in absolute value, until it reaches zero. Genes with $d_{gk}=0$ for all classes do not contribute to the classification.

$$\overline{\mu}'_{gk} - \overline{\mu}_{g} = \left(\overline{\mu}_{gk} - \overline{\mu}_{g}\right) - \Delta \cdot \sqrt{1/n_k + 1/n} \cdot (s_g + s_0)$$

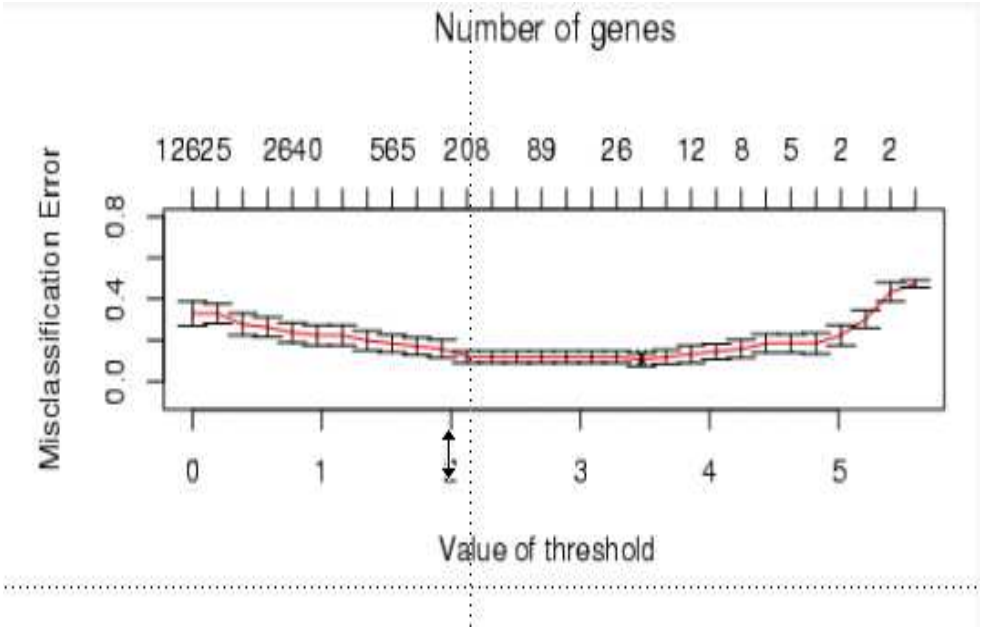
(Tibshirani et al., 2002)

Shrunken Centroids



$$\delta_k\left(\begin{pmatrix} x_B^* \\ x_C^* \end{pmatrix}\right) = \frac{(x_B^* - \bar{\mu}'_{Bk})^2}{(s_B + s_0)^2} + \frac{(x_C^* - \bar{\mu}'_{Ck})^2}{(s_C + s_0)^2} - 2\log \pi_k$$

Amount of shrinkage



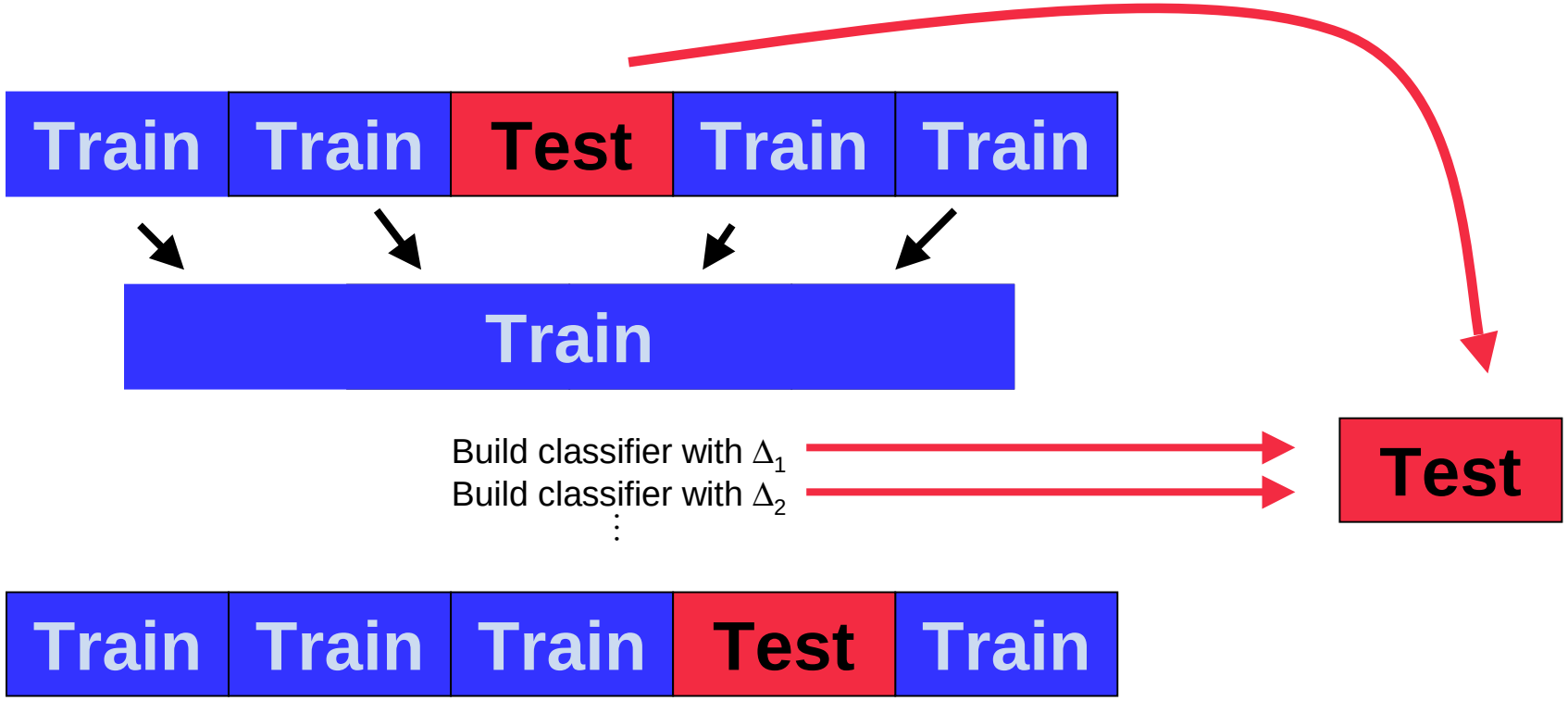
Small Δ, many genes, poor performance due to overfitting

High Δ, few genes, poor performance due to lack of information – *underfitting* -

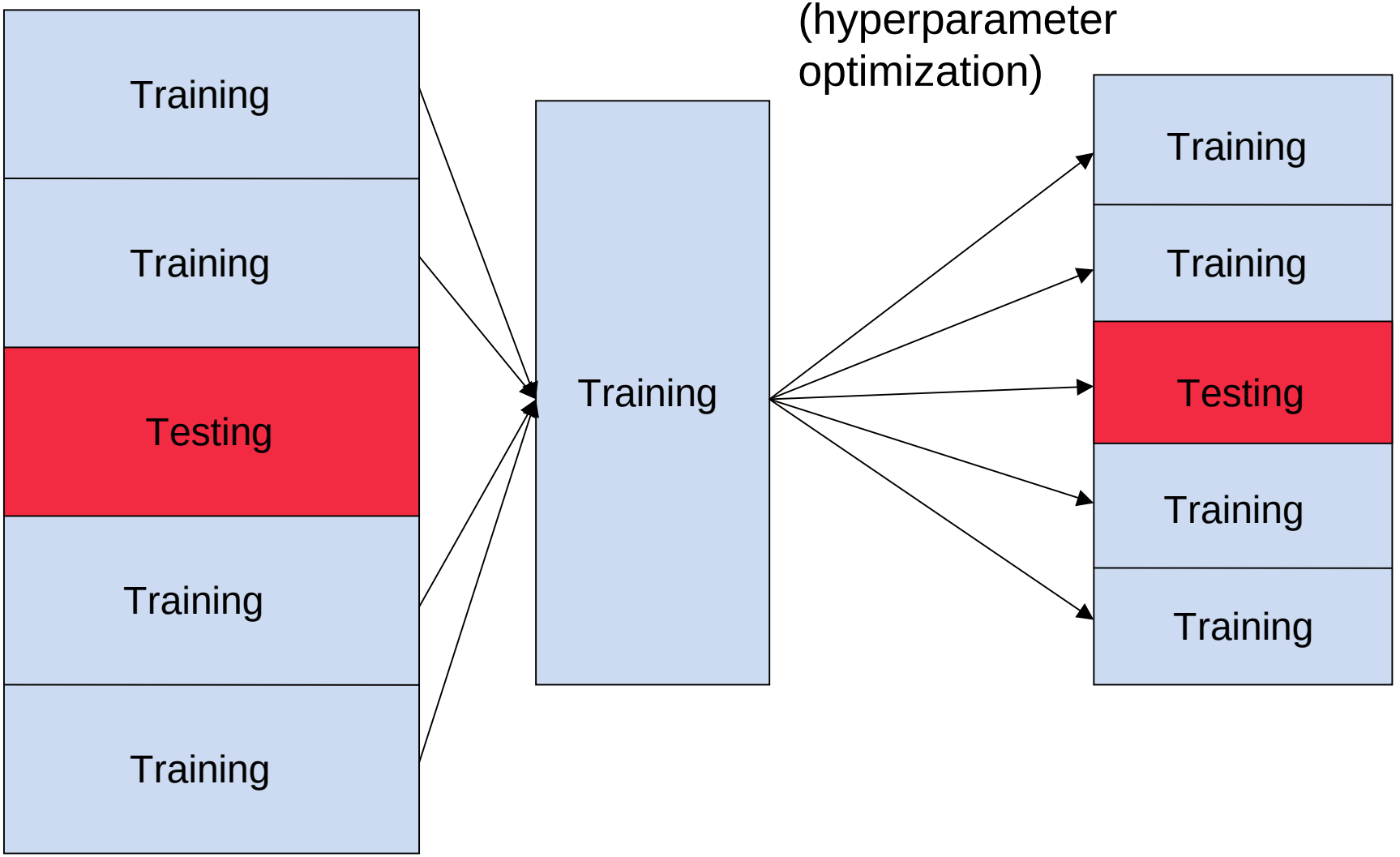
The optimal Δ is somewhere in the middle

Choosing Δ with cross-validation

•Idea: given a set of possible $\Delta=\{\Delta_1,..., \Delta_n\}$ we want to estimate the misclassification rate for each Δ and choose the ‚best'. Use cross-validation to estimate the misclassification rate.



Nested Cross-Validation



Shortcomings of filter and shrinkage methods

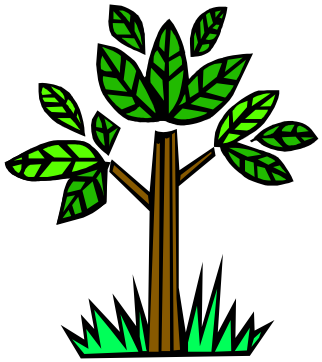
- Filter and Shrinkage work only on single genes.
  They don’t find interactions between groups of genes.

- Filter and Shrinkage methods are only heuristics.
  Search for best subset is infeasible for more than 30 genes.

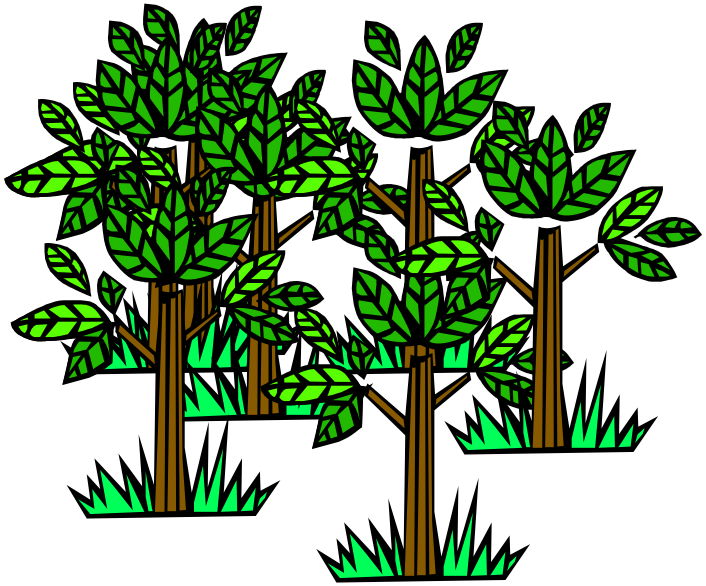
Random Forest

Random Forest

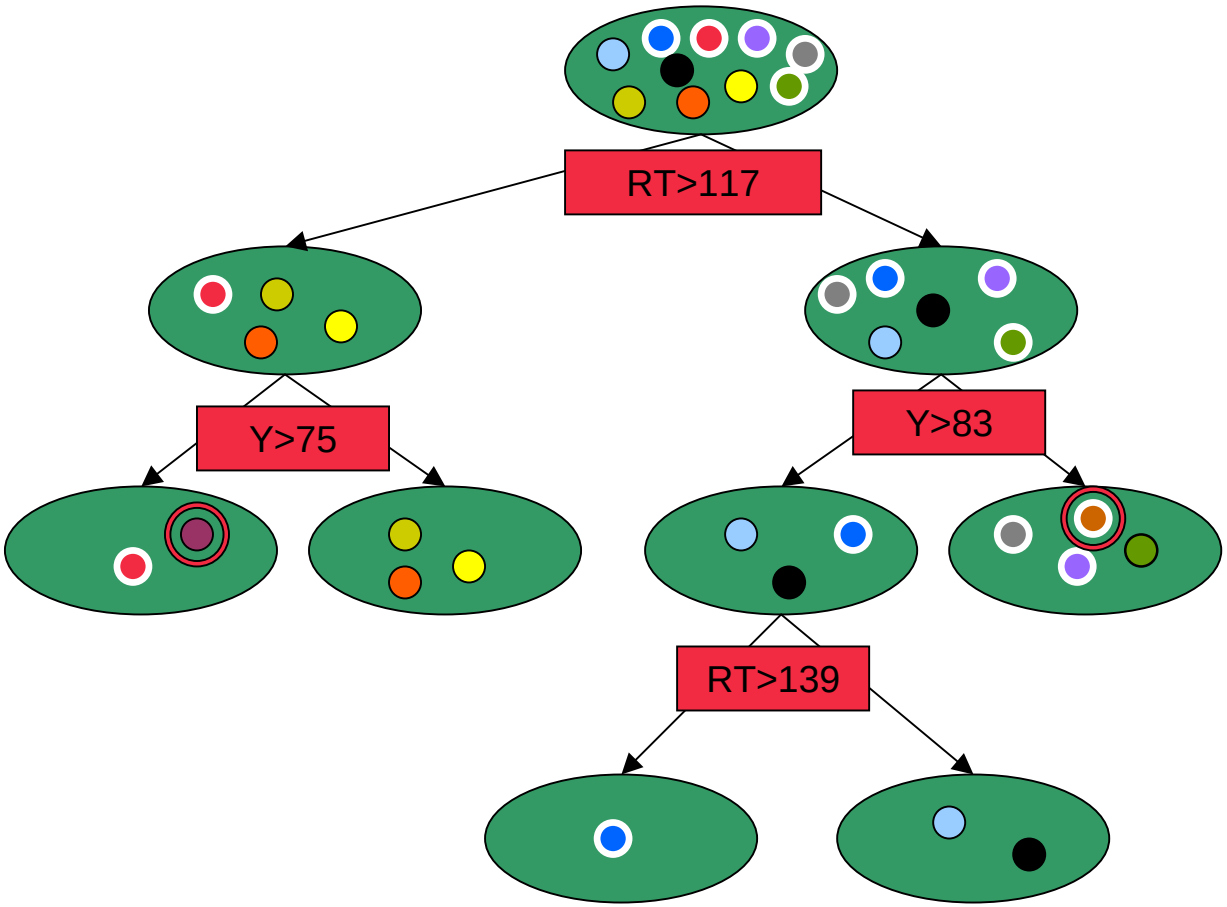
- Growing one tree



- Growing many trees (a forest)



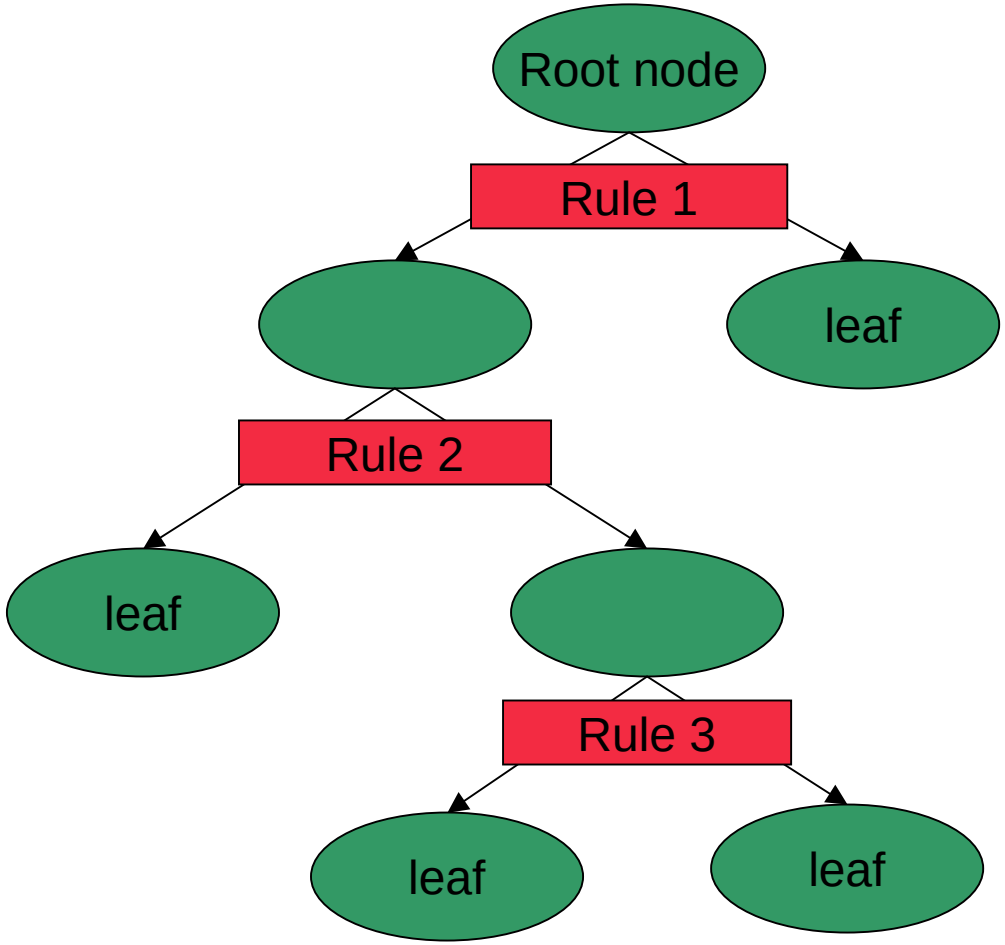
A binary tree – a classification example



Title		Year (Y)	Running time (RT)	Spielberg
Jaws		75	124	X
Duel		71	90	X
The Color Purple		85	154	X
Schindler‘s List		93	195	X
Jurassic Park		93	127	X
Back to the future		85	111	
The Godfather		72	175	
Das Boot		81	150	
Life of Brian		79	94	
Stand by me		86	89	

Hook		91	144	X
Harold and Maude		71	91	

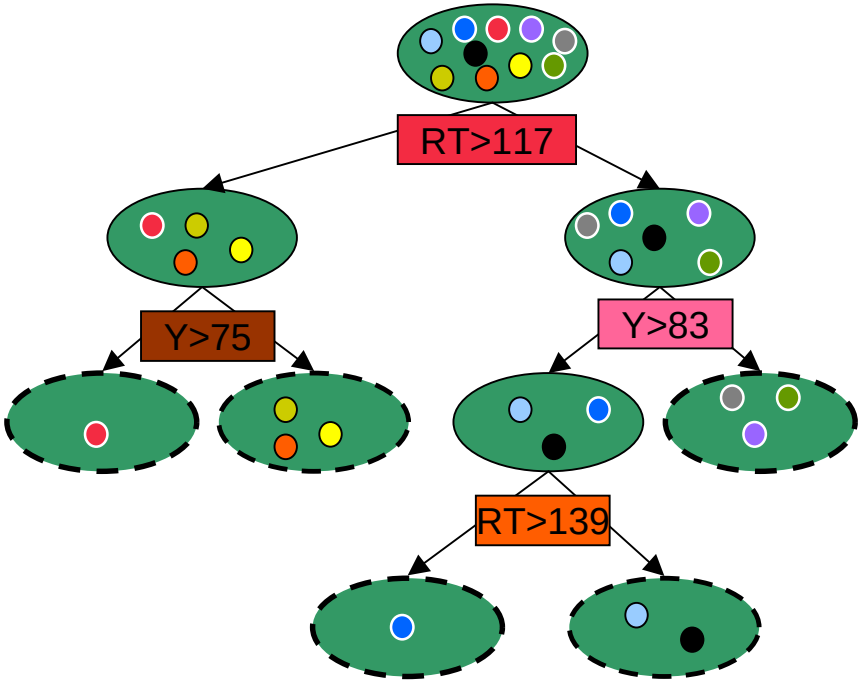
A binary tree for classification

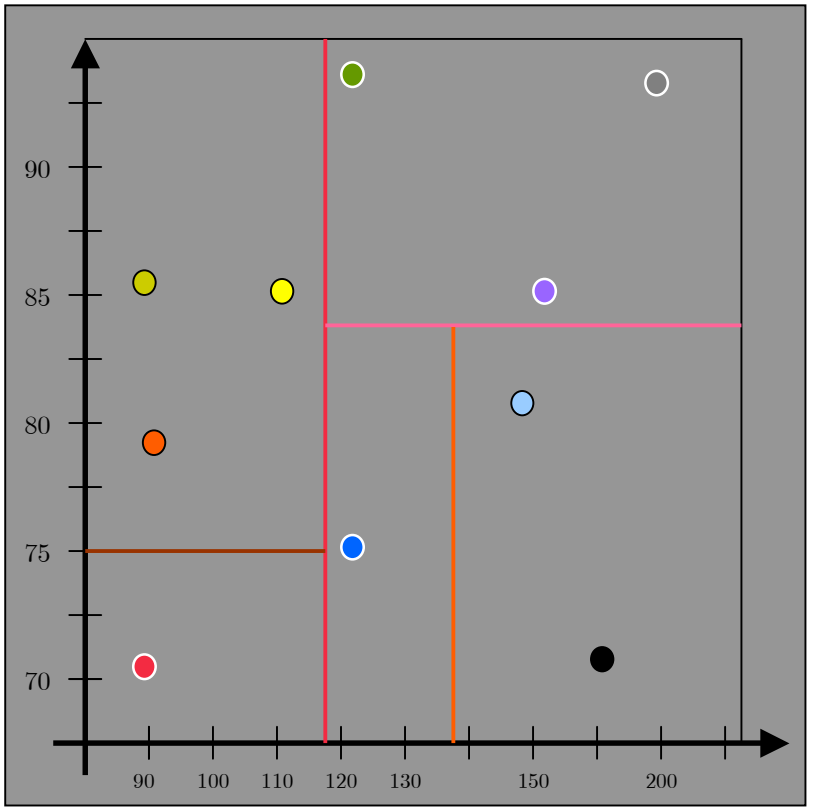


- The root node contains all samples.
- Each node contains a fraction of samples.
- Each rule splits up the samples into two groups.
- Every rule is of the form
  - $X > t$ for continuous X
  - $X \in A$ for categorial X

  Only one variable per rule.
- Each leaf should be more or less pure (contains only samples of one type).
- A new sample is run through the tree and one looks for the leaf it ends up.

A binary tree – a classification example





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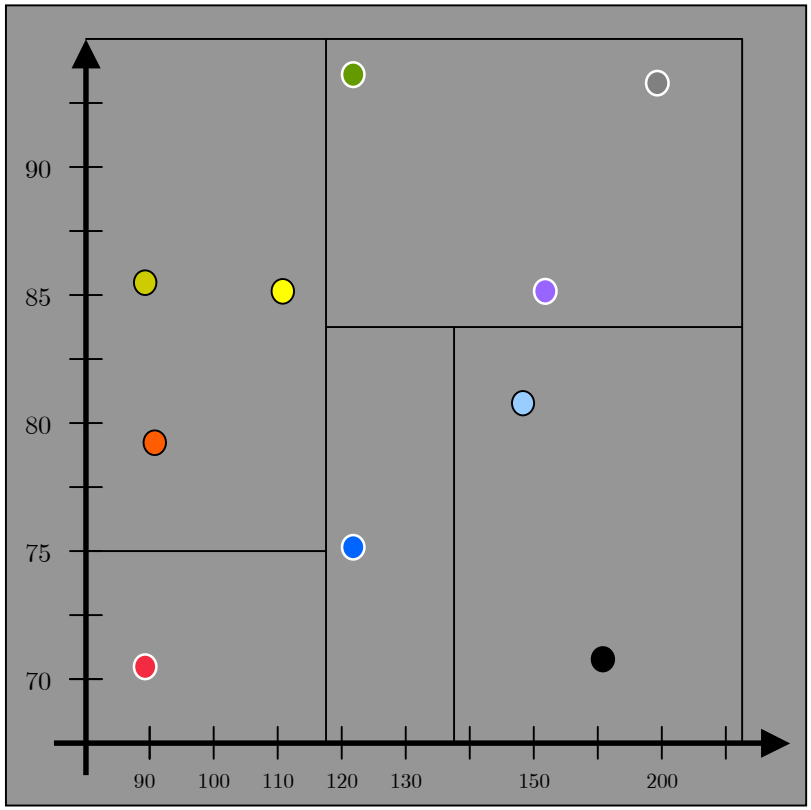
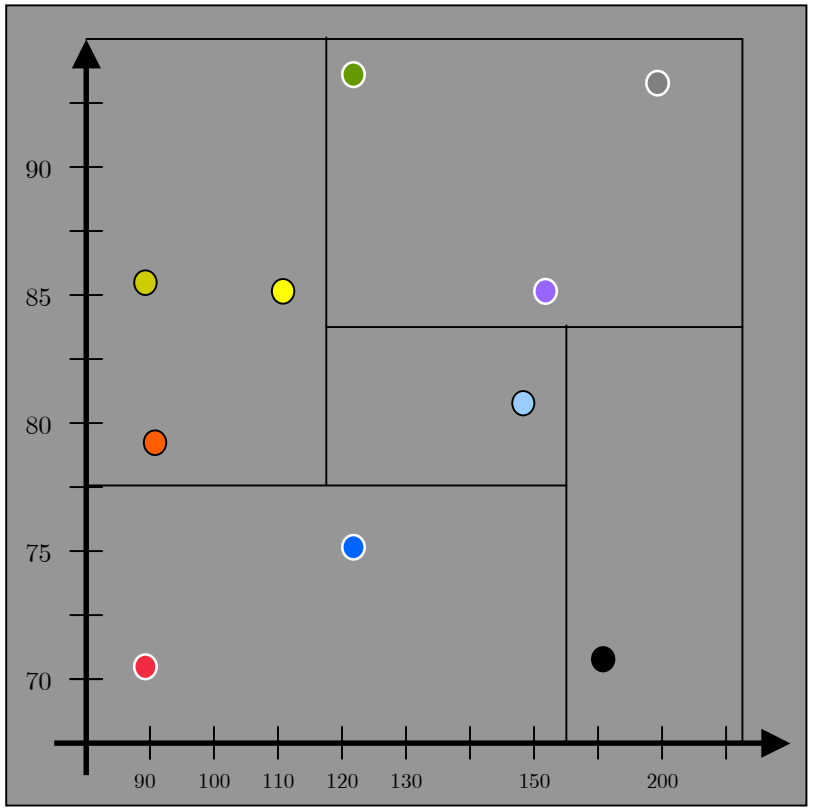
Not every partition can be achieved through a tree





Trees for microarray data

- Samples are microarray chips (containing many genes) divided into two or more classes, e.g. ER status +/- in breast cancer.

- Rules are based on the expression of one gene. Examples:
  - ERB2 is lower than 3.21
  - GAPDH is higher than 6.23

- You cannot base rules on more that one gene or two or more thresholds. Examples:
  - GAPDH is lower that ERB2
  - ERB2 is lower that 2.21 or higher than 5.32

How to construct a tree?

- Choose a good node and a good gene/threshold pair (x_i, t_i) for each split („Splitting rule“)
  - Which gene should we choose?
  - Which threshold should we use?

- Decide how many nodes your tree should have („Split-stopping rule“,”pruning”).

- Assign a class to each leaf („Class assignment rule“).

Splitting rule

Impurity function Φ: $[0,1]^k \rightarrow \Re$ (k: number of different classes)

A low impurity function is achievable.

Attributes:

- minimal for (1,0,0,....,0) and all permutations.
- maximal for (1/k,...,1/k)
- is symmetric function

  $\Phi(p_1,....p_n) = \Phi(\varphi(p_1),.. \varphi(p_n))$ for all permutations φ

There are various impurity functions: entropy, Gini index

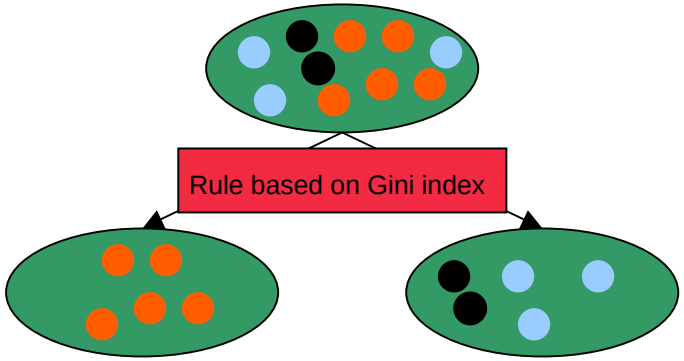
Gini index

Gini index $\Phi(p_1,\ldots,p_k)= 1 - \sum p_i^2=\sum p_i\,(1-p_i)= \sum\sum p_i\,p_j$

Minimum 0

Maximum 1- 1/k

Gini index tries to separate the largest class from the rest.



Gini index for two classes:

$$\Phi(p_1, p_2) = 2\,p_1 p_2$$

Using the impurity function

Define a function i(v) (v is a node of the tree)

$$i(v)=\Phi(P(1|v),...,P(k|v)).$$

P(j|v) := probability that you are member of class j if you are in node v

If the probabilities for all classes are equal one has

$$i(v)=\Phi(n_1(v)/n(v),...,n_k(v)/n(v)).$$

n (v) = all samples in node v

$n_j(v)$= all samples of class j in node v

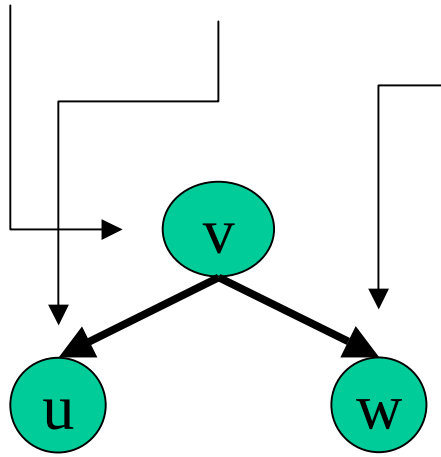
Two classes, Gini index, equal probability:

$$i(v) = \frac{2\, n_1(v)\, n_2(v)}{n(v)^2}$$

Goodness of fit – decrease of impurity

Determine gene x and threshold t that maximizes the following term:

$$G = i(v) - (p_u\, i(u) + p_w\, i(w))$$



p_u = fraction of samples in node u

p_w = fraction of samples in node w

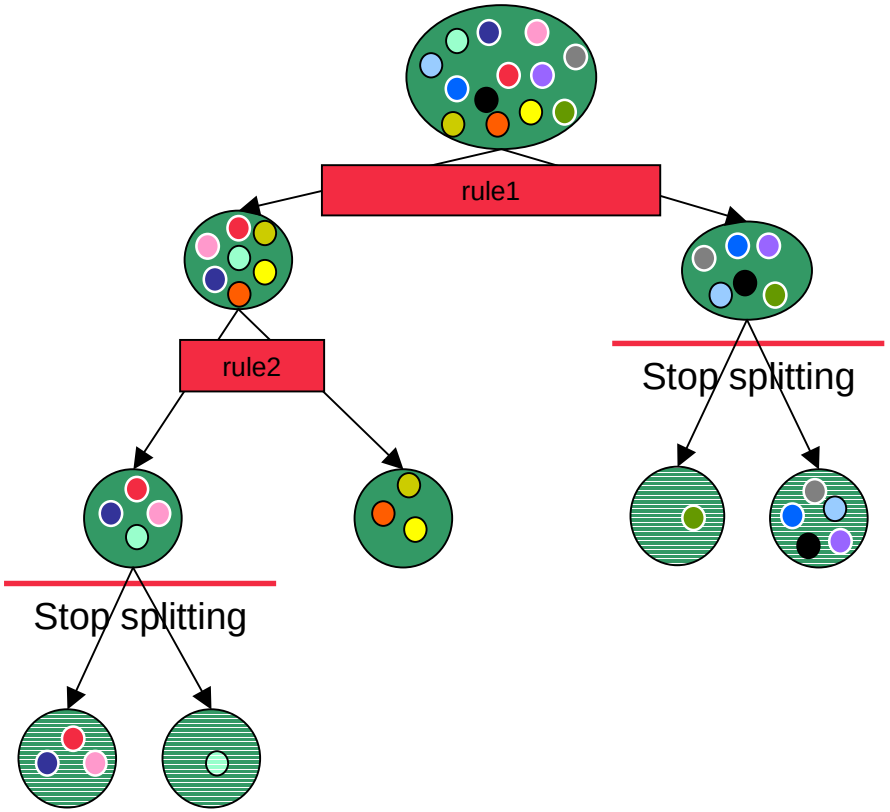
Because you have only a finite number of genes and a finite number of values, you have to test a finite number of pairs.

Two classes, Gini index, equal probability:

$$G = \frac{2}{n(v)} \cdot \left(\frac{n_1(v)\, n_2(v)}{n(v)} - \frac{n_1(u)\, n_2(u)}{n(u)} - \frac{n_1(w)\, n_2(w)}{n(w)} \right)$$

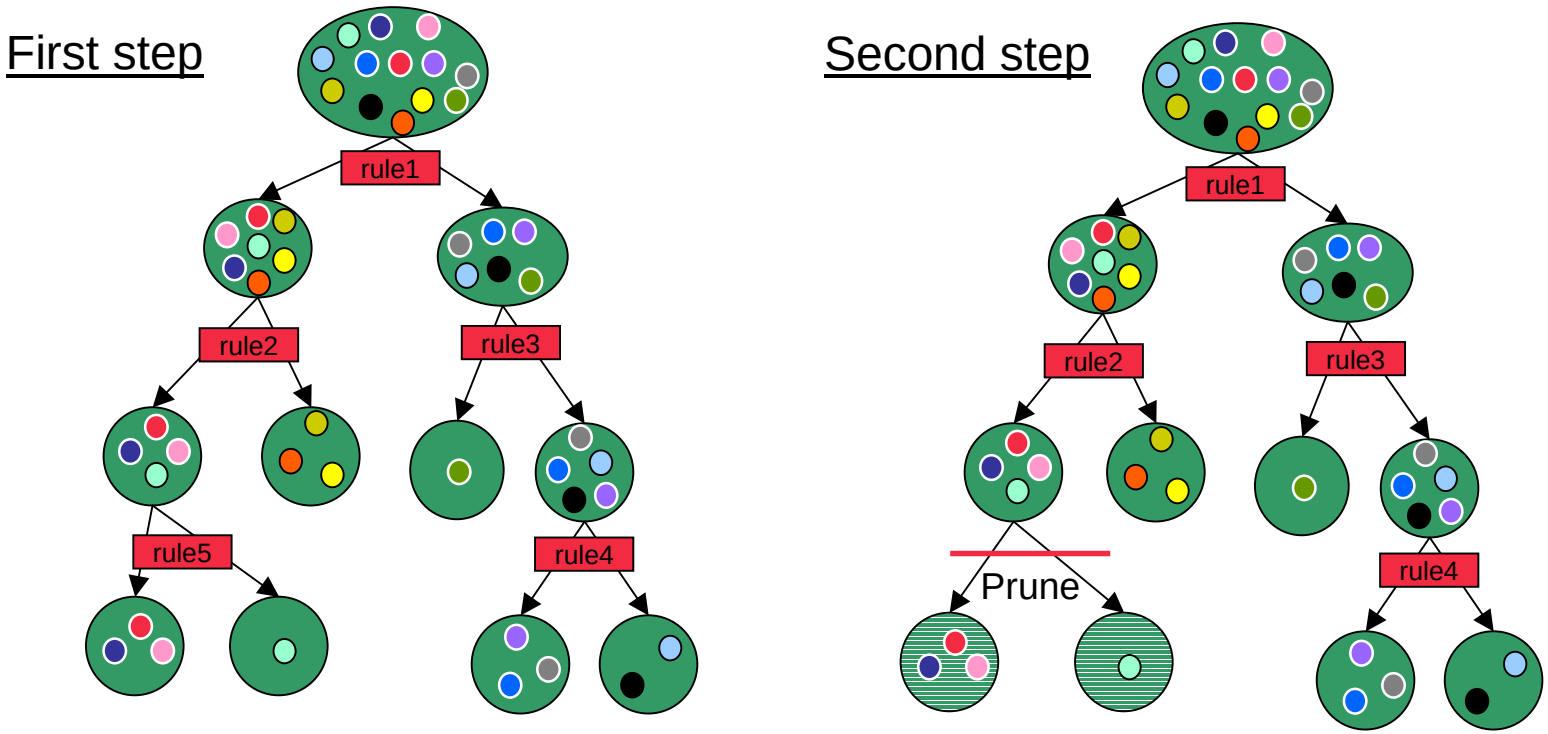
Stop splitting rules – stop decision

- Decide at each node if the node should be split further or not. Is there a high decrease in the Gini index?



Stop splitting rules - pruning

- First split until each node is pure or has a maximum number of elements, then prune the tree. Remove the splits with low decrease in the impurity function.



Advantages and Disadvantages for trees

- Advantages
  - At first sight good interpretation
  - Can cope with any data structure or type
  - Uses conditional information effectively
  - Invariant under transformations of the gene expressions

- Disadvantages
  - not robust
  - classification performance is not that good
  - Genes can be hidden due to other genes

From the tree to the forest

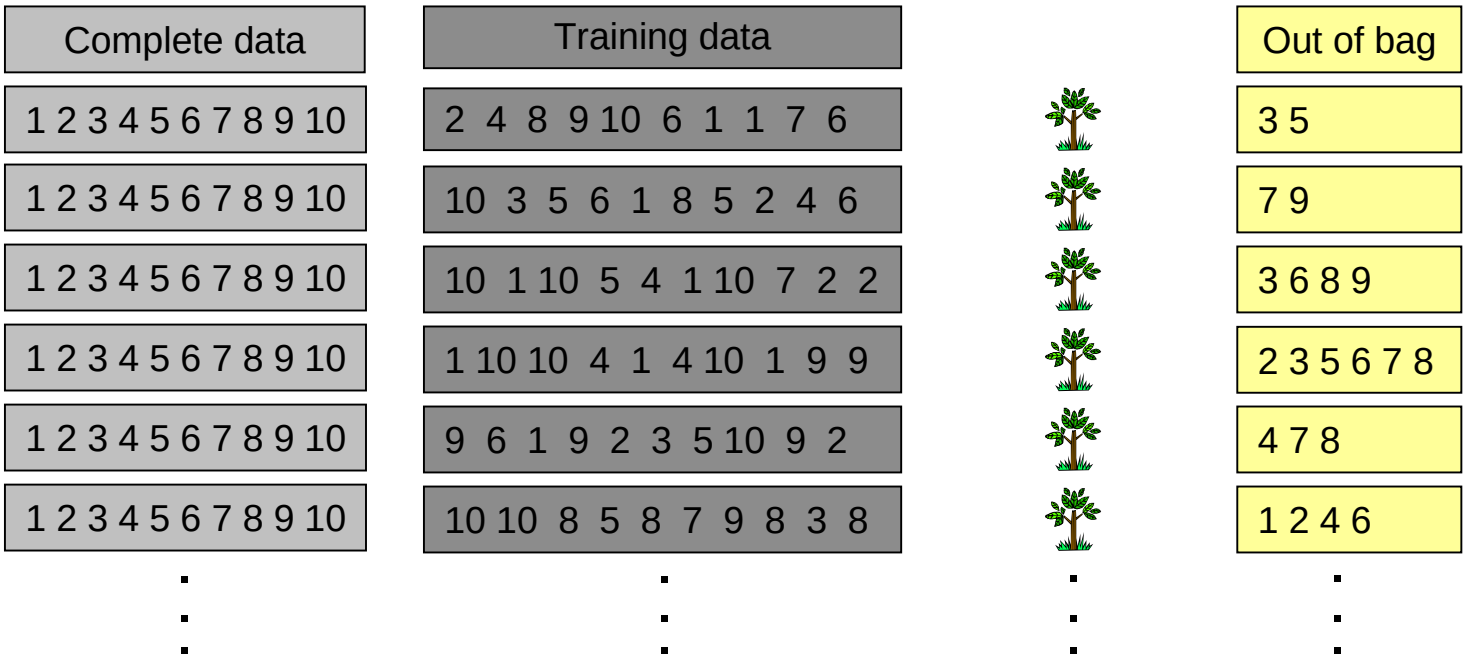
- General idea: combine collection of weak learners to construct a classification algorithm with better properties.
- Here: Construct a collection of trees and combine results of individual trees.

- Because the algorithm is deterministic, we have to introduce some kind of randomness. For each tree we will have two different sources of randomness:
  - random training set (bootstrap)
  - random gene selection

Bootstrap

- Complete data : K samples/patients
- Training data: draw K times with replacement from the data set
- Out of bag: sample that do not belong to the training set

Training data contains approximately 2/3 of the elements of the complete data set.



Random Forest – random variable selection

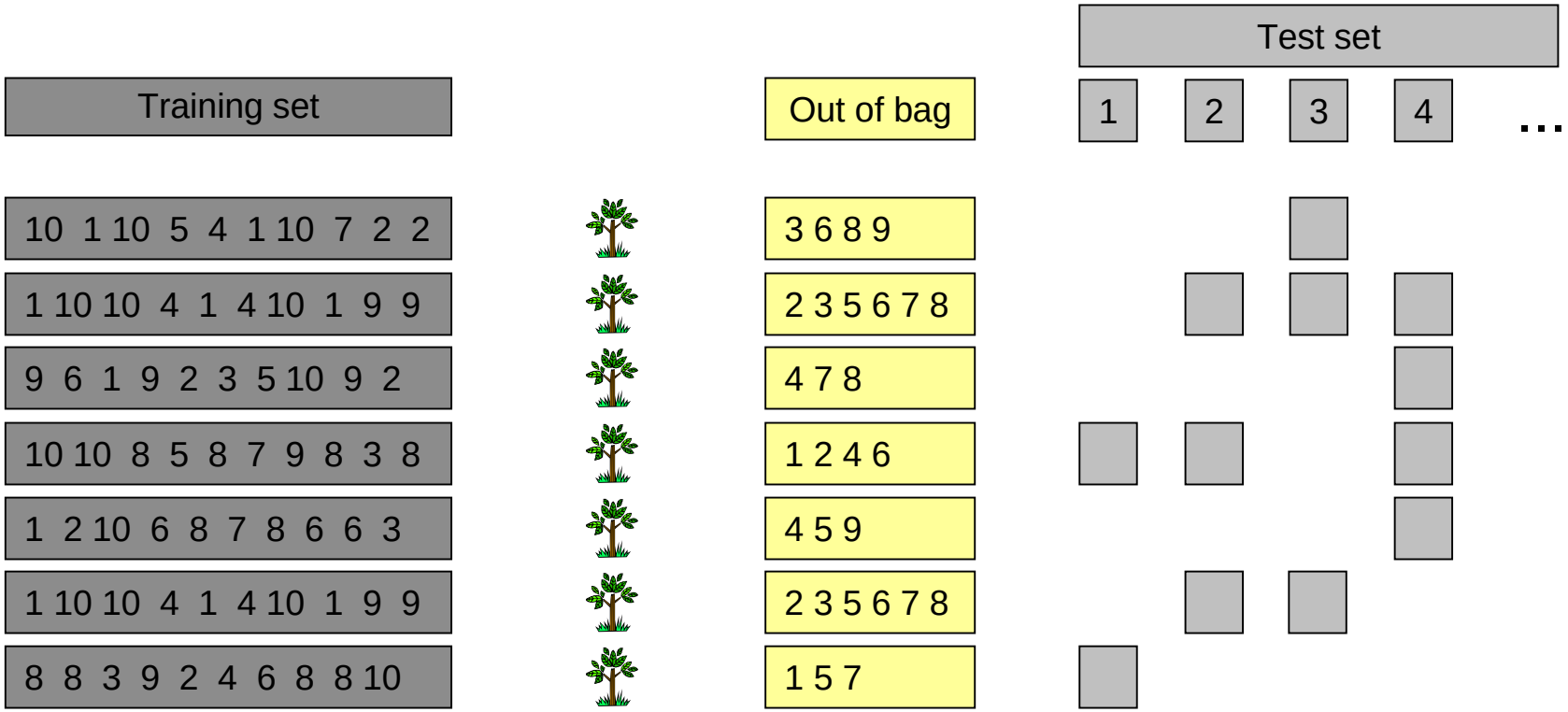
- Set the parameters **m** and **s**. These are the same for all nodes and all trees. Specify the number of trees you want to grow.
- For each tree:
  - Use bootstrap to get a training set T of samples. You use only data from this set to build the tree!
  - For each node, first choose **m** genes $x_1,...x_m$ at random.
  - Upon these genes choose the best pair (x_i,t_i).
  - Go on until each node contains elements of one class or consists of **s** elements.

Random Forest

- Classification rule: First classify a new sample with each tree. In the end form a major vote.

Estimating the test error

- For each sample x predict the class but use only the trees for which x belongs to the OOB set.
- Good estimate for the test error because the information provided by x was not used for building these trees.



Tradeoff correlation - prediction

The forest error rate depends on two things:

- The correlation between any two trees in the forest. Increasing the correlation increases the forest error rate.
- The strength of each individual tree in the forest. A tree with a low error rate is a strong classifier. Increasing the strength of the individual trees decreases the forest error rate.

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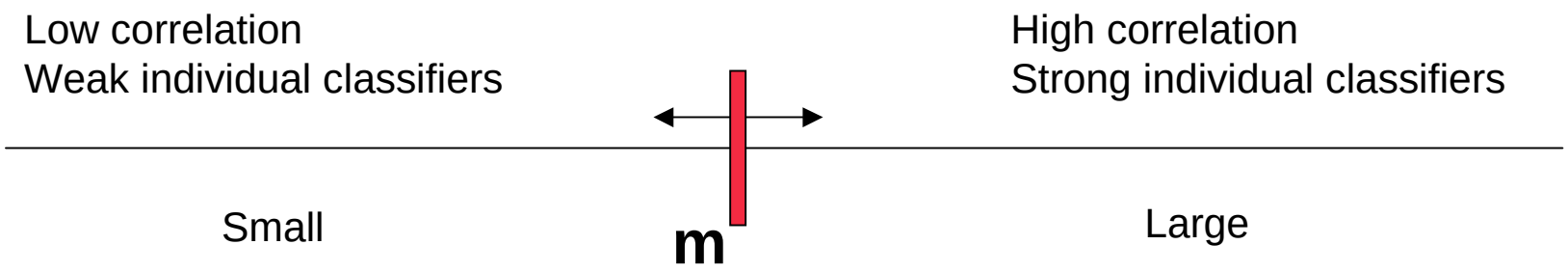

Use the OOB error estimate to find a good parameter m.

Variable importance

Idea: Change the values of a gene **x** and check whether the OOB error changes dramatically.

- For each gene **x** do the following:
  - For each tree t of a forest permute the values of x for the samples that belong to the out-of-bag set.
  - Estimate the OOB error as before (the samples have new values for the gene x).
  - Compare the OOB error of the samples with the original values to the OOB error of the samples with permuted values. This gives you an importance measure.

Literature

- S. Dudoit, J. Fridlyand: Classification in microarray experiments
- L. Breiman: Random Forests—Random Features
- L. Breiman: Statistical Modeling: The two Cultures
- J. Oh, M. Laubach, A. Luczak: Estimating Neuronal Variable Importance with Random Forest
- T. Hastie, R. Tibshirani, Jerome Friedman: The Elements of Statistical Learning. Springer 2001.
- R.Tibshirani, T. Hastie, B. Narasimhan, G. Chu: Diagnosis of multiple cancer types by shrunken centroids of gene expression, PNAS, 99(10), 6567–6572, 2002.

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Thank you