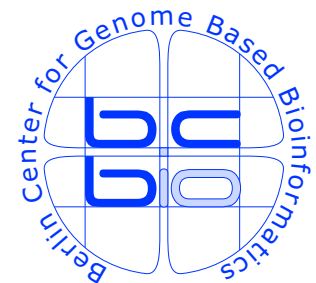
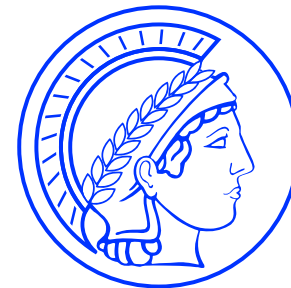


# Classification by Nearest Shrunken Centroids and Support Vector Machines

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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 the task

1. model **class probabilities**

→ QDA, LDA, ...

2. model **class boundaries** directly

→ Optimal Separating Hyperplanes, SVM



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## What's the problem?

In classification you have to trade off

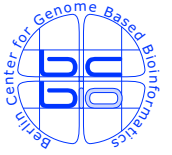
- **overfitting** versus **underfitting**
- **bias** versus **variance**.

**Curse of dimensionality!** In 12'000 dimensions even linear methods are very complex → high variance!

# Simplify your models



# Discriminant analysis and gene selection



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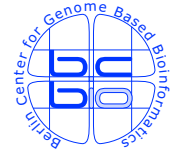
# Comparing Gaussian likelihoods

**Assumption:** each group of patients is well described by a Normal density.

**Training:** estimate **mean** and **covariance matrix** for each group.

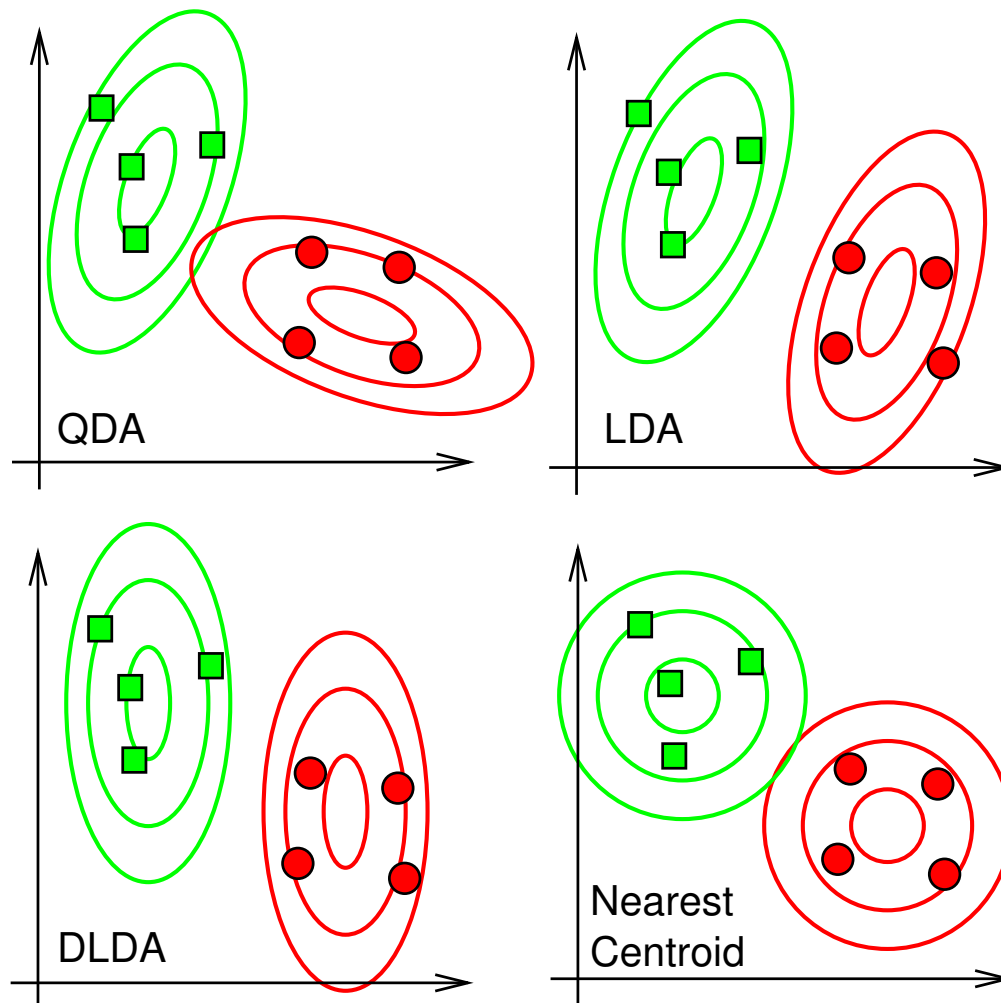
**Prediction:** assign new patient to group with higher likelihood.

**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  $\sigma^2 \mathbf{I}$ .



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# Feature selection

## Next simplification:

Base the classification only on a small number of genes.

Feature selection: Find the **most discriminative genes**.

*This task is different from testing for differential expression. Genes can be significantly differential expressed, but still useless for classification.*



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# Feature selection

## 1. Filter:

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

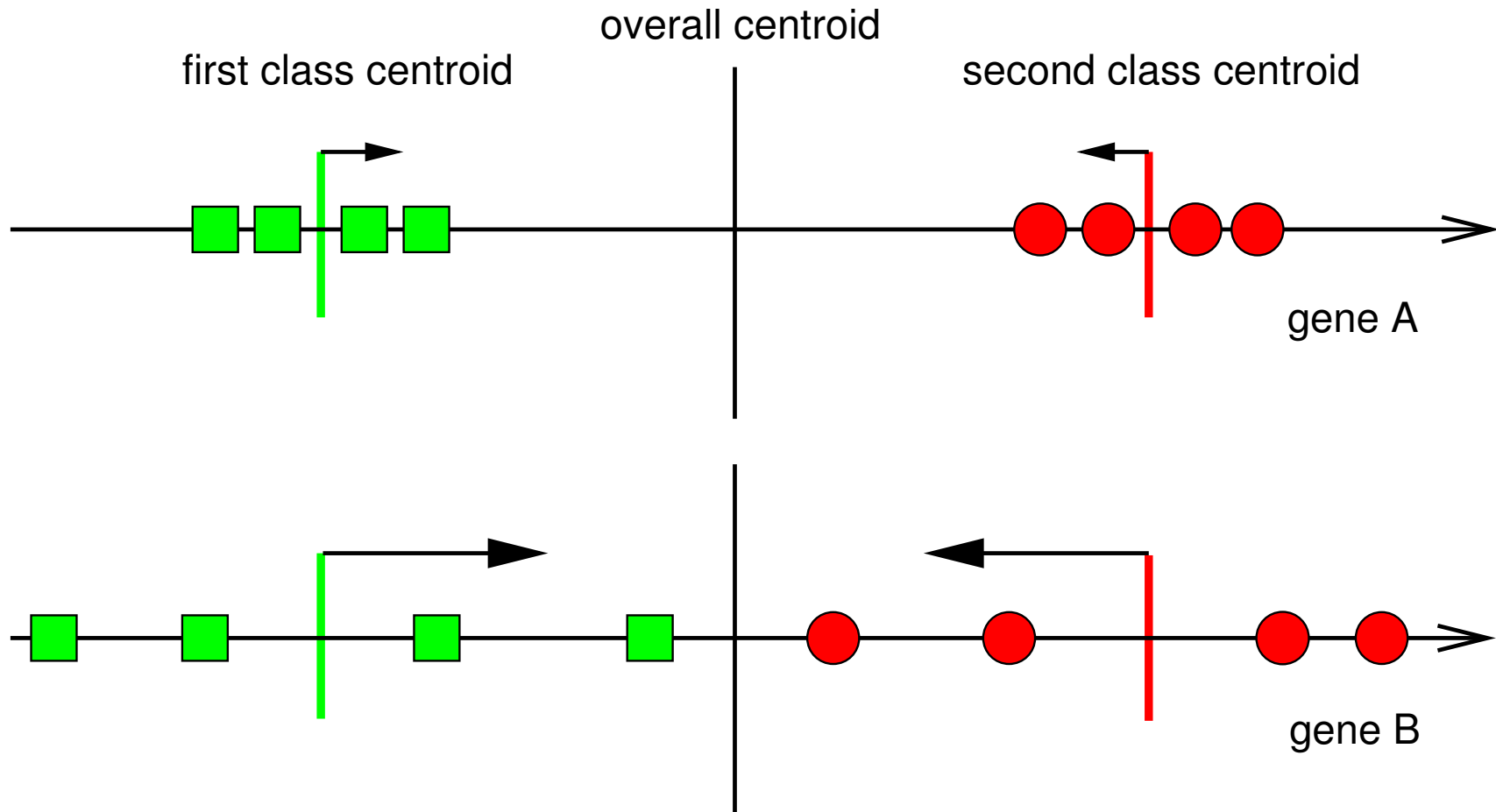
## 2. Shrinkage:

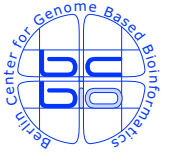
- Continuously shrink genes until only a few have influence on classification.
- Example: [Nearest Shrunken Centroids](#).





# Shrunken Centroids





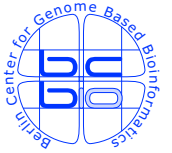
## Nearest Shrunken Centroids *cont'd*

The **group centroid**  $\bar{x}_{gk}$  for gene  $g$  and class  $k$  is compared to the **overall centroid**  $\bar{x}_g$  by

$$\bar{x}_{gk} = \bar{x}_g + m_k(s_g + s_0) d_{gk} ,$$

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

**Shrinkage:** Each  $d_{gk}$  is reduced by  $\Delta$  in absolute value, until it reaches zero. Genes with  $d_{gk} = 0$  for all classes do not contribute to the classification. (Tibshirani *et al.*, 2002)



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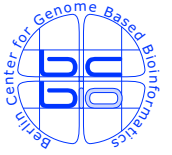
# Shortcomings of filter and shrinkage methods

1. Highly **correlated genes** get similar score but offer no new information.  
But see (Jaeger *et al.*, 2003) for a cure.
2. Filter and Shrinkage work only on **single genes**.  
They don't find interactions between groups of genes.
3. Filter and Shrinkage methods are only **heuristics**.  
Search for *best subset* is infeasible for more than 30 genes.

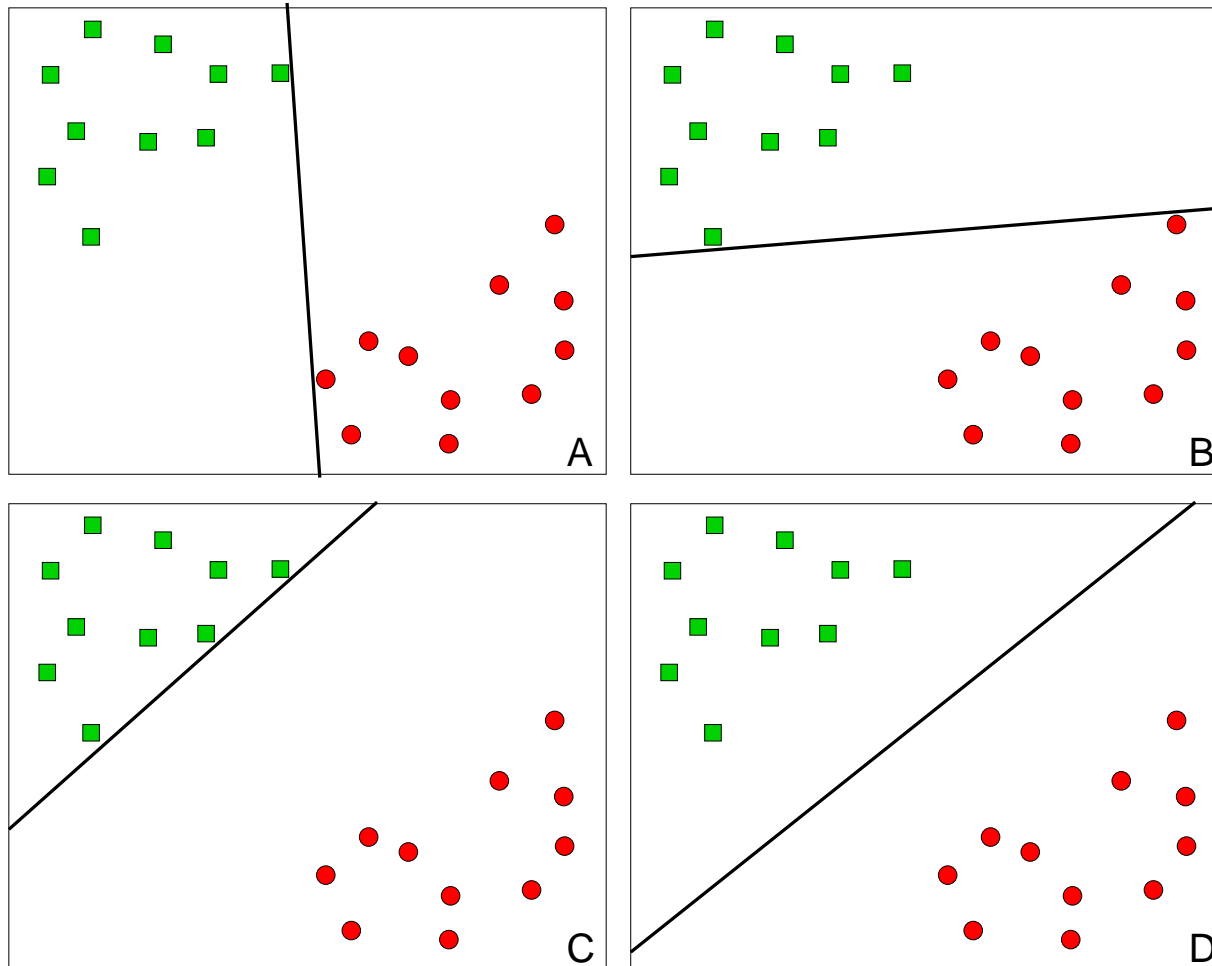


# Support Vector Machines

## — SVM —

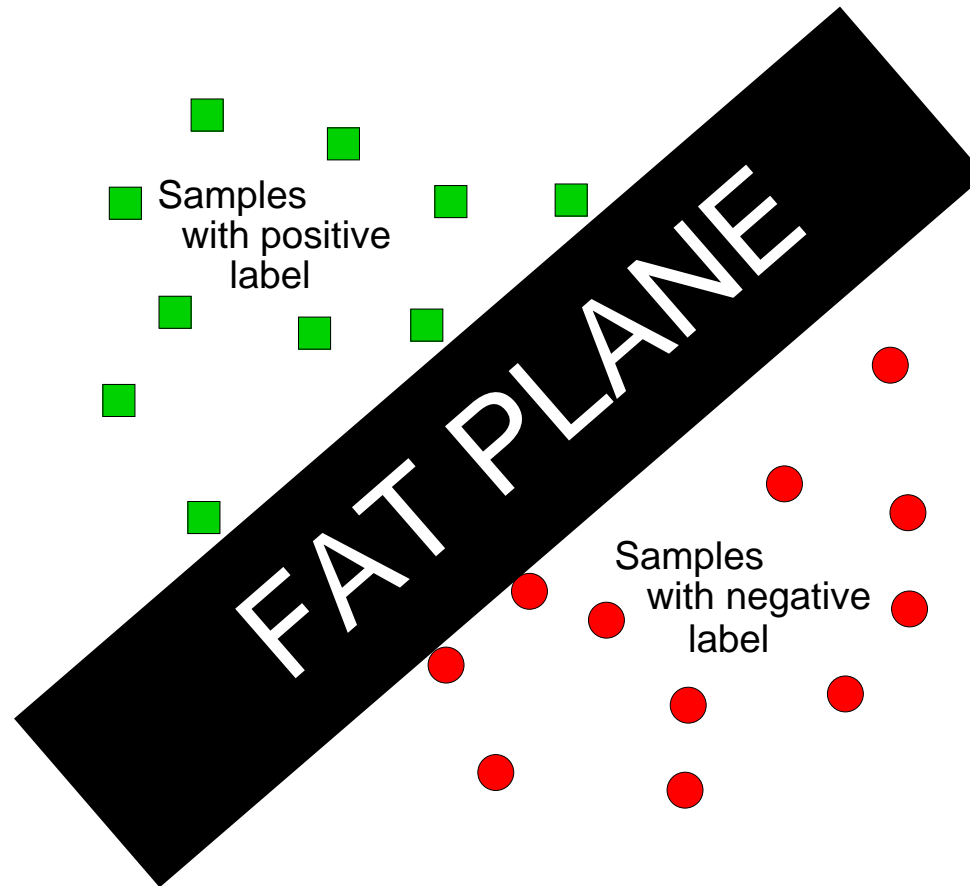


# Which hyperplane is the best?



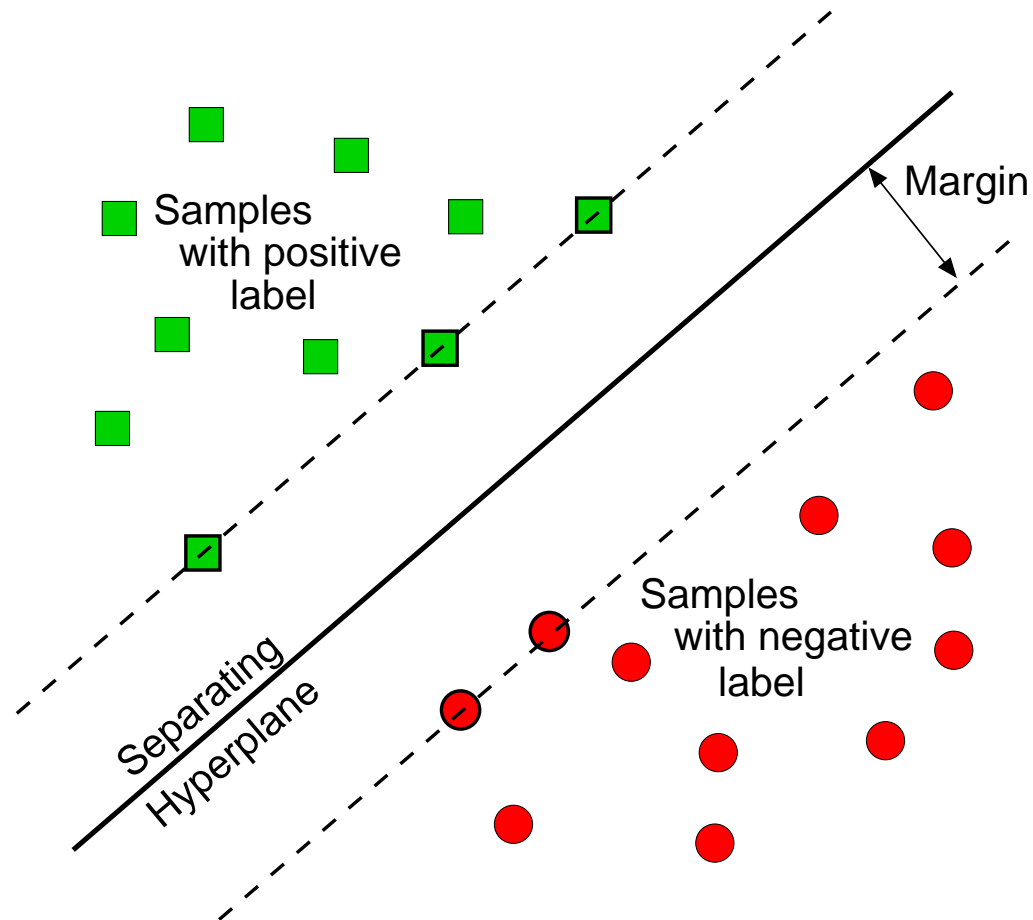


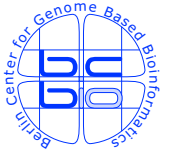
# No sharp knife, but a fat plane





# Separate the training set with maximal margin



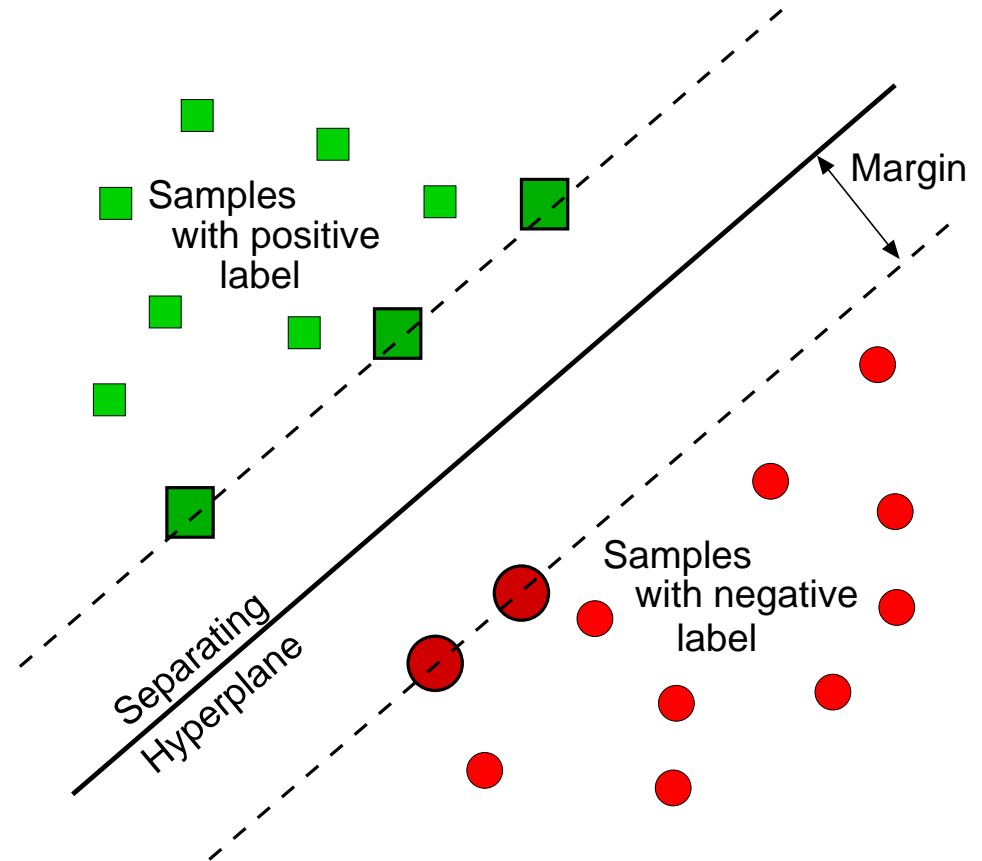


# What are Support Vectors?

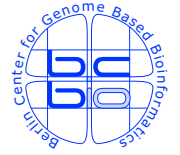
The points nearest to the separating hyperplane are called **Support Vectors**.

Only they determine the position of the hyperplane. **All other points have no influence!**

**Mathematically:** the weighted sum of the Support Vectors is the normal vector of the hyperplane.

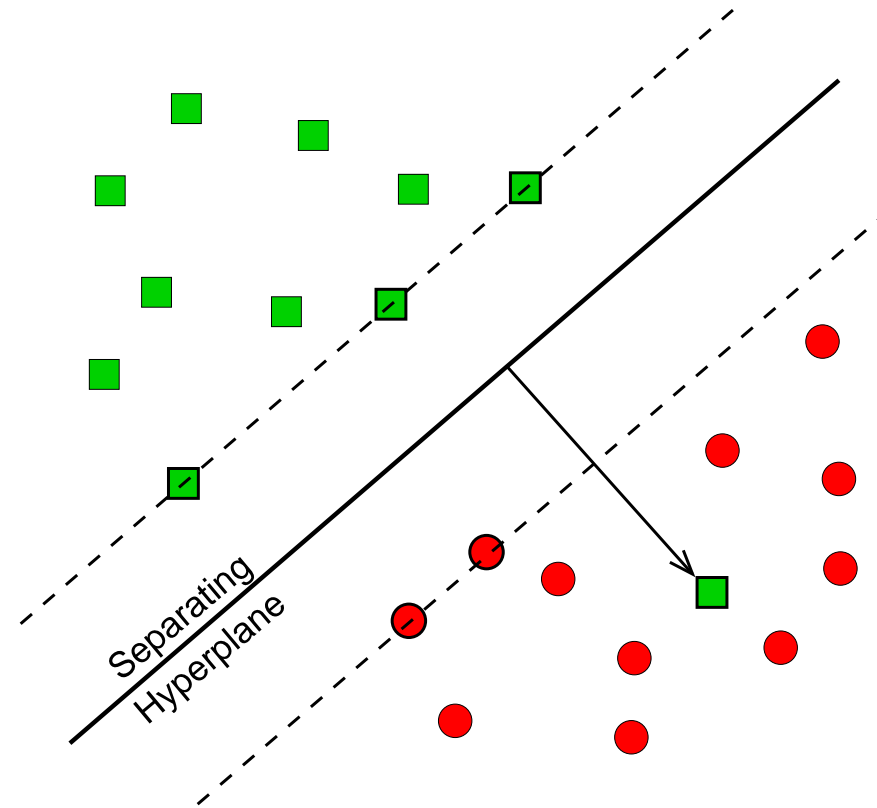






# Non-separable training sets

Use linear separation, but admit training errors.



Penalty of error: distance to hyperplane times *error cost*  $C$ .



# The end?

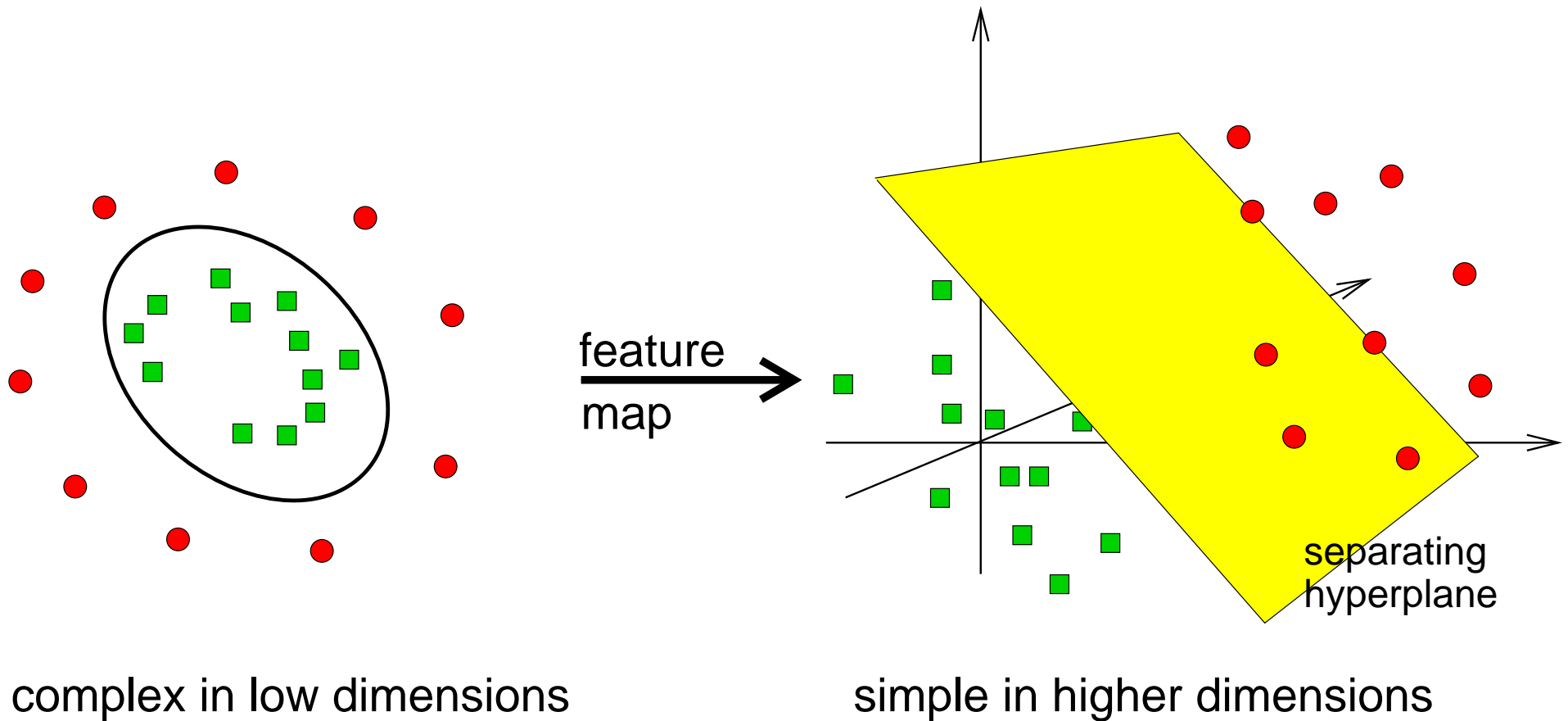
**The story of how to simplify your models is finished.**

But for the sake of completeness:

How do we get from the simple linear Optimal Separating Hyperplane to a full-grown Support Vector Machine?

It's a trick, a **kernel trick**.

# Separation may be easier in higher dimensions





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# The kernel trick

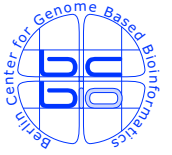
## Maximal margin hyperplanes in feature space

If classification is easier in a high-dimensional feature space, we would like to build a maximal margin hyperplane there.

The construction depends on inner products  $\Rightarrow$  we will have to evaluate inner products in the feature space.

This can be computationally intractable, if the dimensions become too large!

**Loophole** Use a kernel function that lives in low dimensions, but behaves like an inner product in high dimensions.



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# Kernel functions

Expression profiles  $p = (p_1, p_2, \dots, p_g) \in \mathbb{R}^g$   
and  $q = (q_1, q_2, \dots, q_g) \in \mathbb{R}^g$ .

## Similarity in gene space: INNER PRODUCT

$$\langle p, q \rangle = p_1q_1 + p_2q_2 + \dots + p_gq_g$$

## Similarity in feature space: KERNEL FUNCTION

$$\mathcal{K}(p, q) = \text{polynomial, radial basis, ...}$$



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# Examples of Kernels

**linear**  $\mathcal{K}(p, q) = \langle p, q \rangle$

**polynomial**  $\mathcal{K}(p, q) = (\gamma \langle p, q \rangle + c_0)^d$

**radial basis function**  $\mathcal{K}(p, q) = \exp(-\gamma \|p - q\|^2)$



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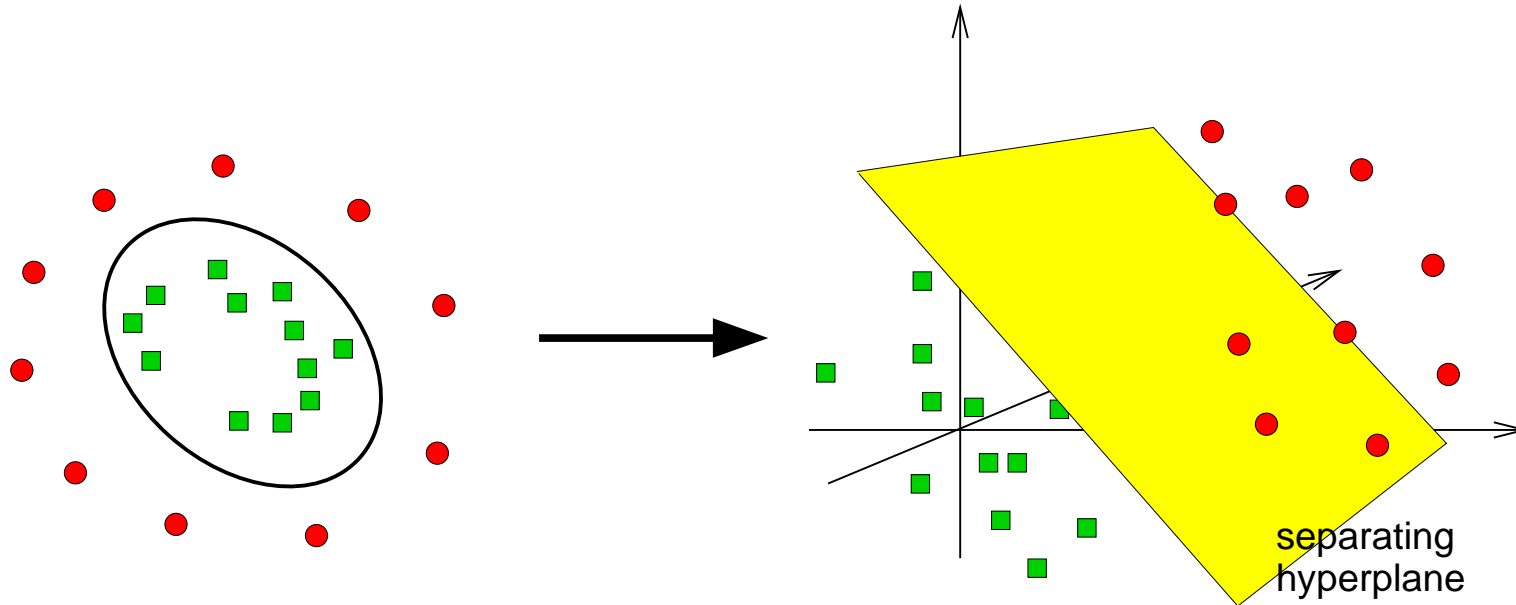
## Why is it a trick?

**We do not need to know,  
how the feature space really looks like,  
we just need the kernel function as a measure of similarity.**

This is kind of **black magic**: we do not know what happens inside the kernel, we just get the output.

Still, we have the **geometric interpretation** of the maximal margin hyperplane, so SVMs are more transparent than e. g. Artificial Neural Networks.

## The kernel trick: summary



Non-linear separation  
between vectors  
**in gene space**  
using kernel functions

=

Linear separation  
between vectors  
**in feature space**  
using inner product





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# Support Vector Machines

A Support Vector Machine is  
a **maximal margin hyperplane** in feature space  
built by using a **kernel function** in gene space.



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## Parameters of SVM

Kernel Parameters	$\gamma$ :	width of rbf coeff. in polynomial ( = 1)
	$d$ :	degree of polynomial
	$c_0$	additive constant in polynomial (= 0)
Error weight	$C$ :	influence of training errors



# SVM@work: low complexity

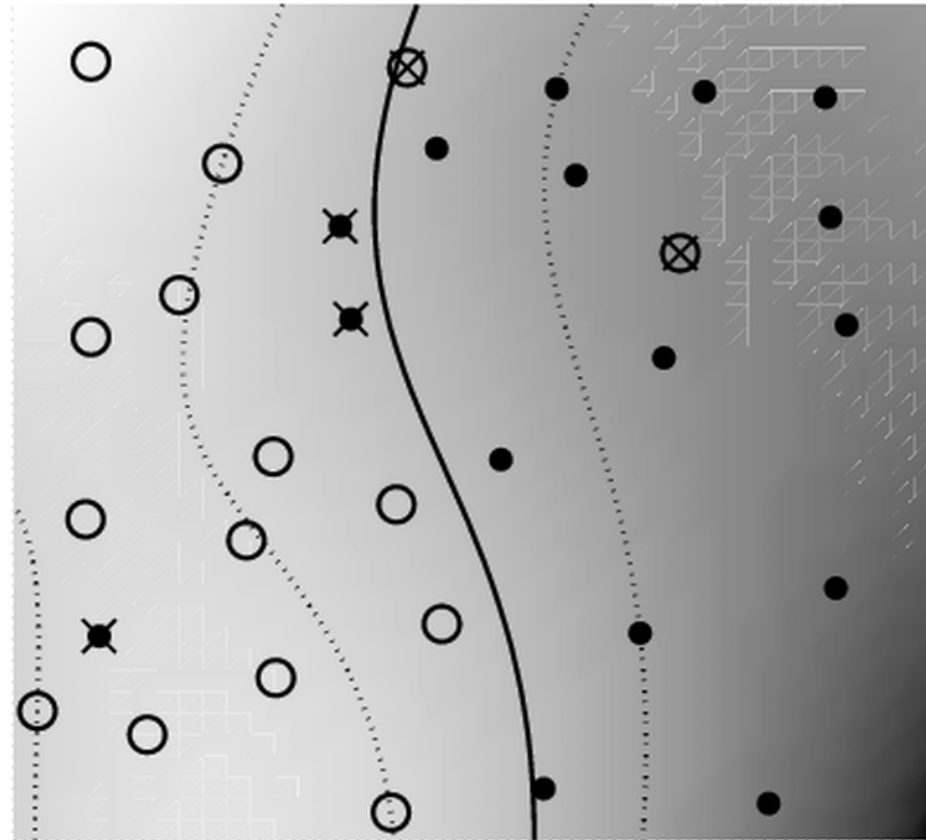


Figure taken from SCHÖLKOPF and SMOLA, *Learning with Kernels*, MIT Press 2002, p217



# SVM@work: medium complexity

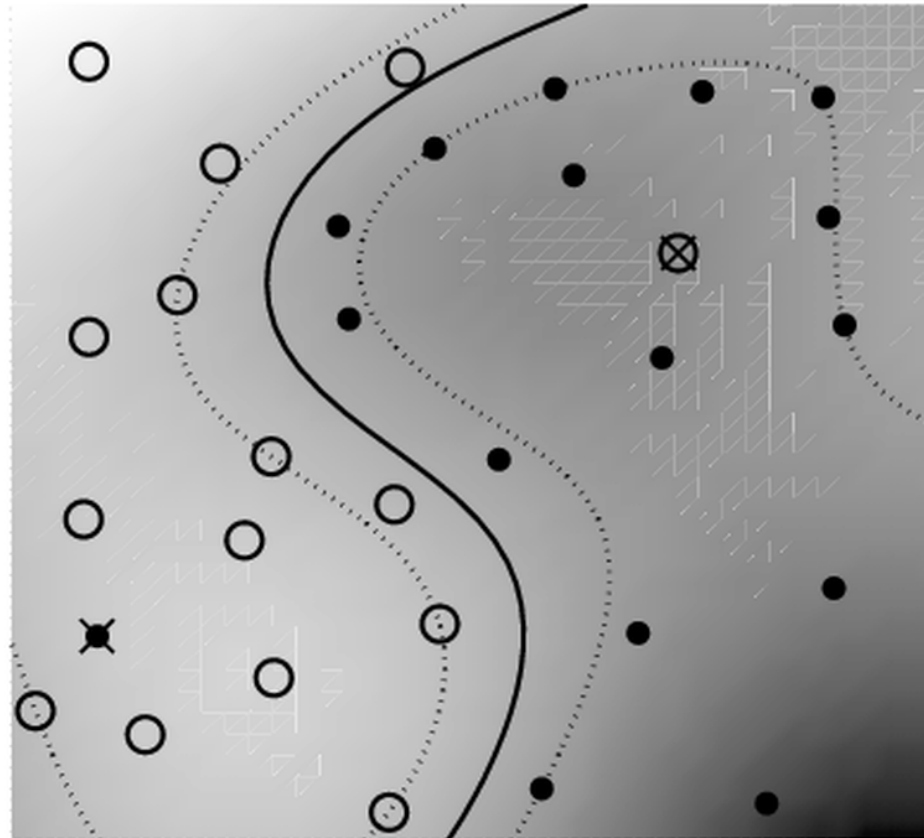
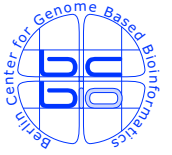


Figure taken from SCHÖLKOPF and SMOLA, *Learning with Kernels*, MIT Press 2002, p217



# SVM@work: high complexity

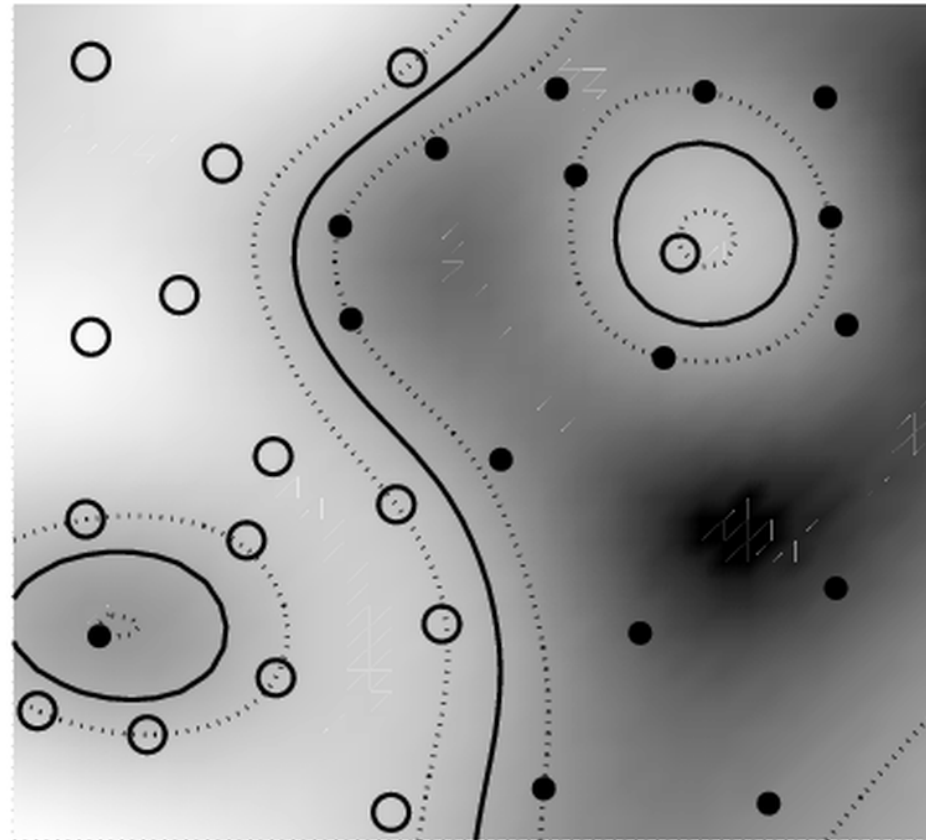


Figure taken from SCHÖLKOPF and SMOLA, *Learning with Kernels*, MIT Press 2002, p217



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**The Elements of Statistical Learning.** Springer 2001.
2. Bernhard Schölkopf and Alex Smola.  
**Learning with Kernels.** MIT Press, Cambridge, MA, 2002.
3. Robert Tibshirani, Trevor Hastie, Balasubramanian Narasimhan, Gilbert Chu  
**Diagnosis of multiple cancer types by shrunken centroids of gene expression,** PNAS, 99(10), 6567–6572, 2002.
4. Jochen Jäger, R. Sengupta and W.L. Ruzzo  
**Improved Gene Selection for Classification of Microarrays,** Proc. PSB 2003



# Intro into practical session



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# Computational Diagnosis

## TASK:

For 3 new patients in your hospital, decide whether they have a chromosomal translocation resulting in a BCR/ABL fusion gene or not.

## IDEA:

Learn the difference between the cancer types from an archive of 76 expression profiles, which were analyzed and classified by an expert.





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## Training ... tuning ... testing

### TRAINING:

```
model <- svm(data = "76 profiles",  
             labels = "by an expert",  
             kernel = "..",  
             parameters = "..")
```

### TUNING:

```
svm.doctor <- tune.svm( data, labels,  
                       all.parameter.values )
```

### TESTING:

```
diagnosis <- predict(svm.doctor, new.patients)
```



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## Training ... tuning ... testing

### TRAINING:

```
model <- pamr.train( data , labels )
```

### TUNING:

```
pamr.cv( data, labels )
```

### TESTING:

```
diagnosis <- pamr.predict(new.patients,  
                          best.treshhold)
```