Machine learning for cancer informatics and drug discovery

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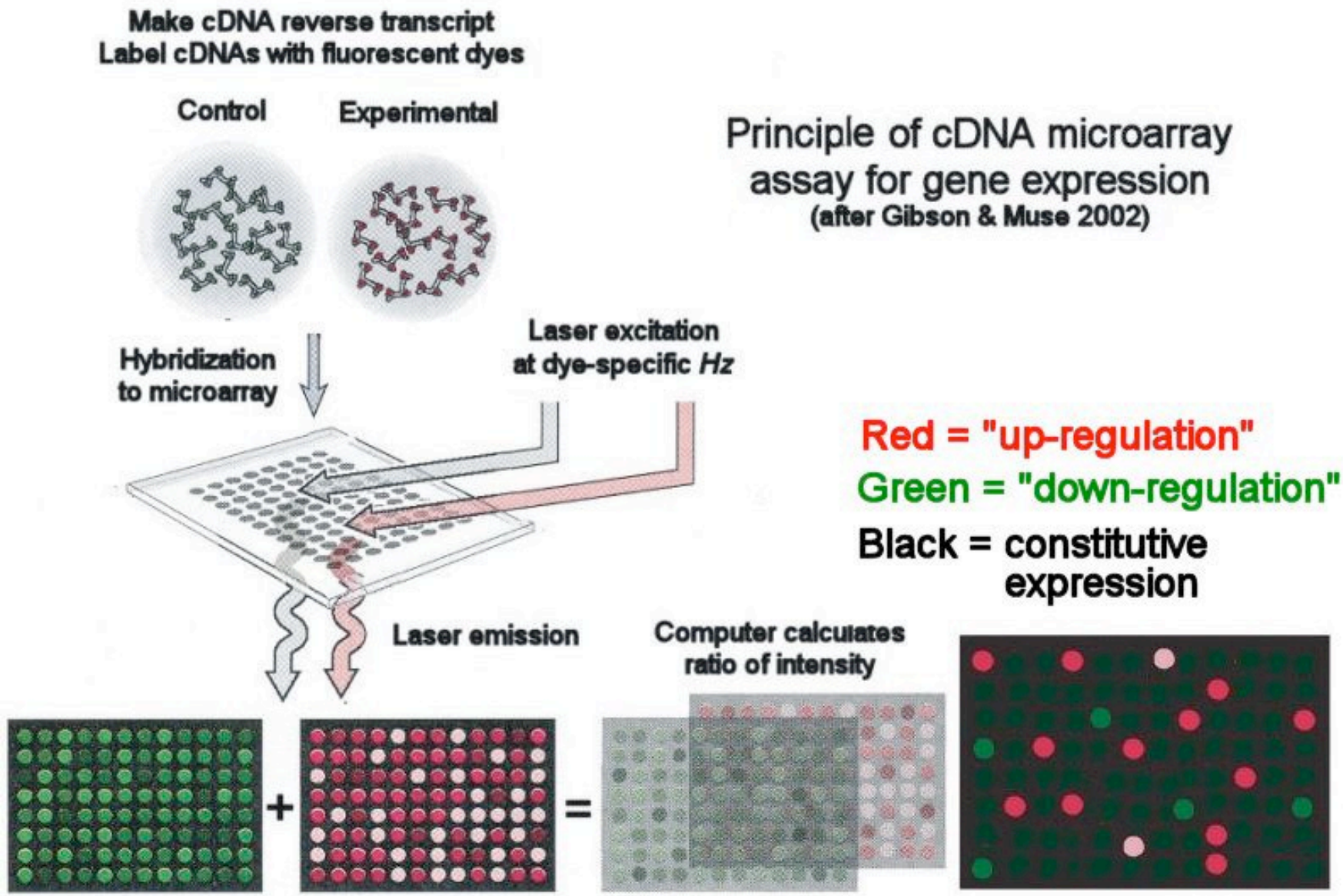
Inserm

Team's goal

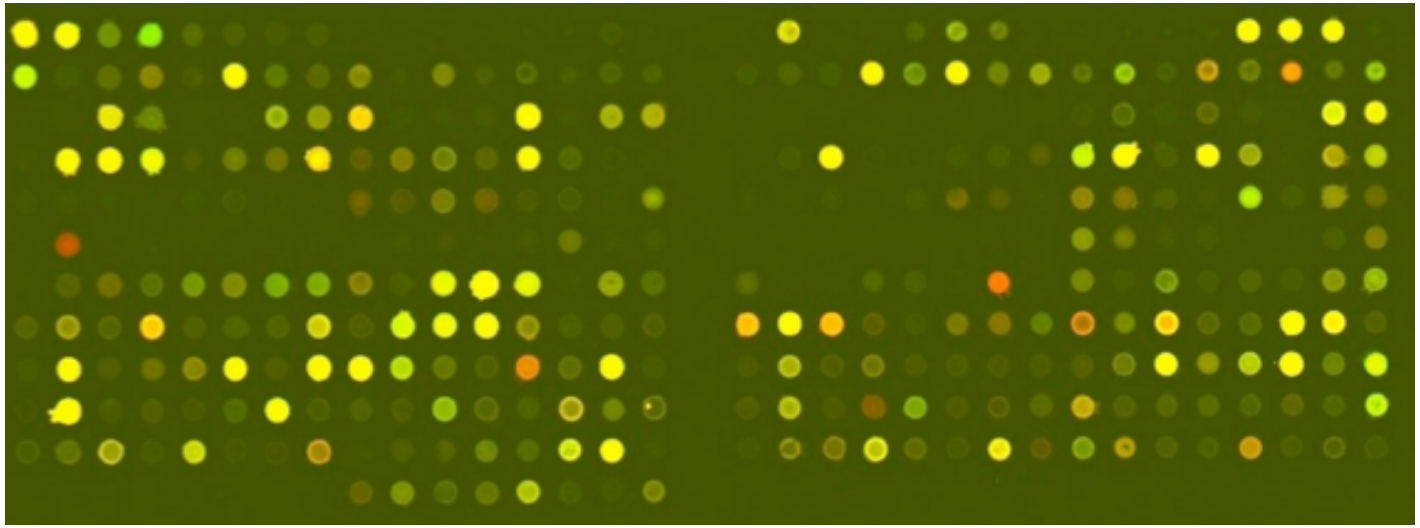
Develop new mathematical/computational models and tools, in particular machine learning, to contribute to:

1. Diagnosis, prognosis and predictive models
2. Identification of important pathways and new drug targets
3. Identification of new drugs

Example: DNA microarray to monitor the transcriptome

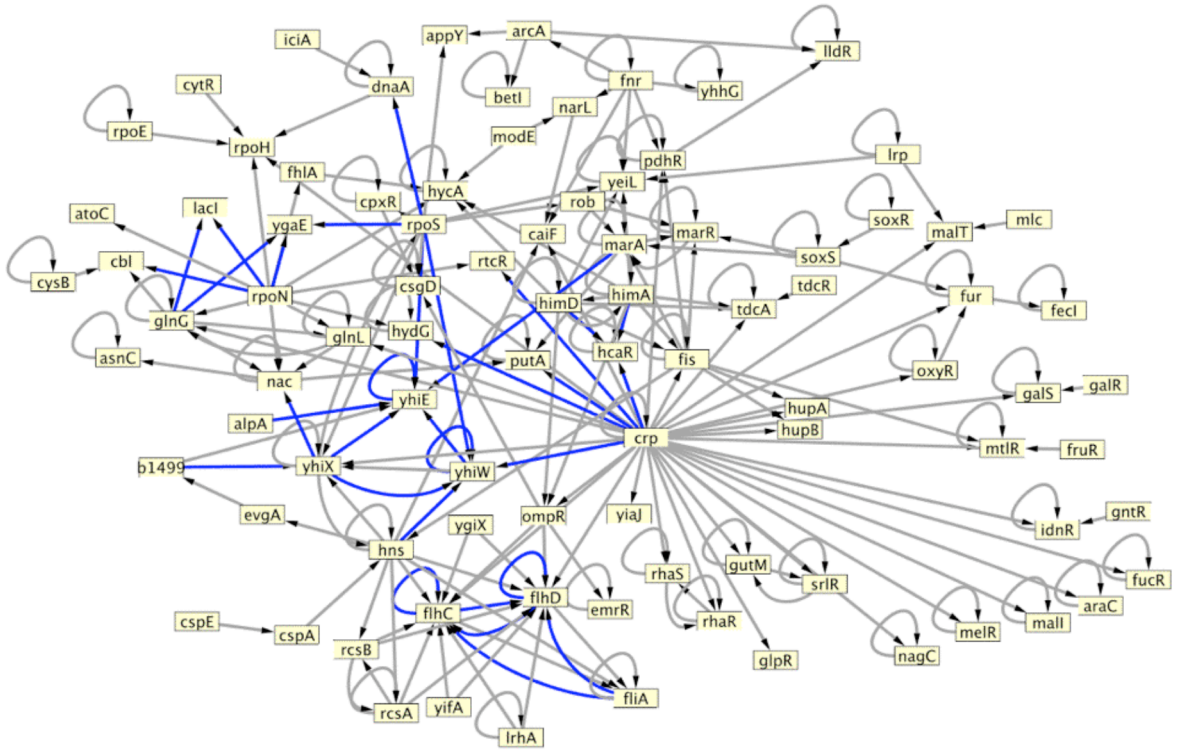


Question:
Diagnosis / Prognosis from genome / transcriptome



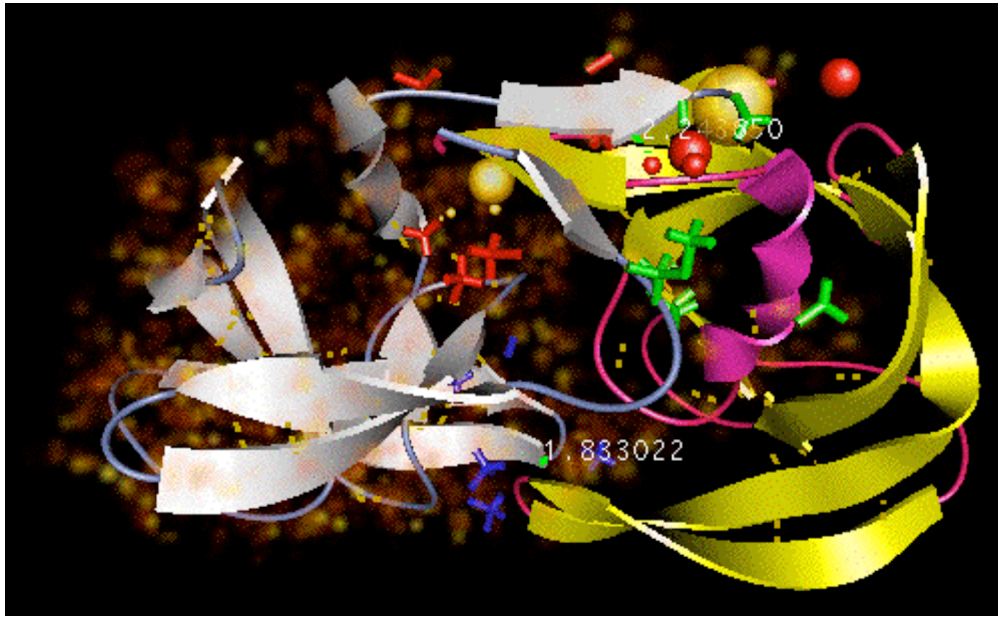
-What class of tumour is that?
-What is the risk of metastasis in 5 years?
-Will drug XXX have an effect?

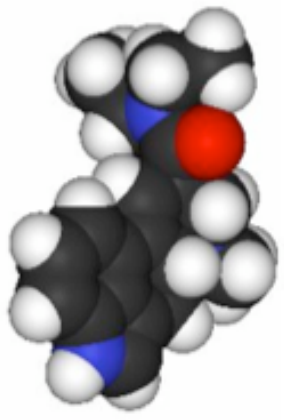
Question:
Identification of new regulations / therapeutic targets



-Which genes are regulated by XXX ?
-Which proteins interact with YYY?

Questions:
Virtual screening and QSAR





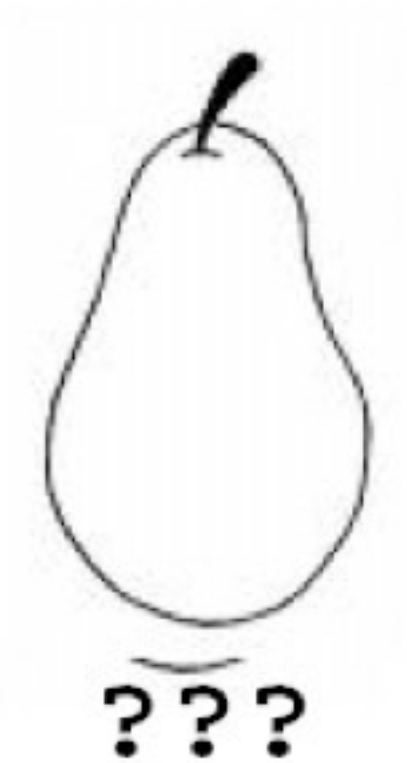
-Can this small molecule inhibit XXX ?
-Is it toxic? Is it drug-like?

Today's lectures

1. How to make an « intelligent » tool to predict biological properties? We will study the machine learning approach.
2. Then, we will survey several particular applications in bioinformatics and drug discovery

Part 1:
The machine learning approach

Apple or pear?



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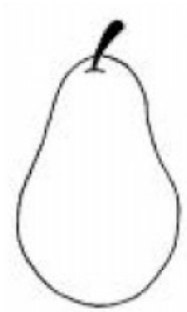
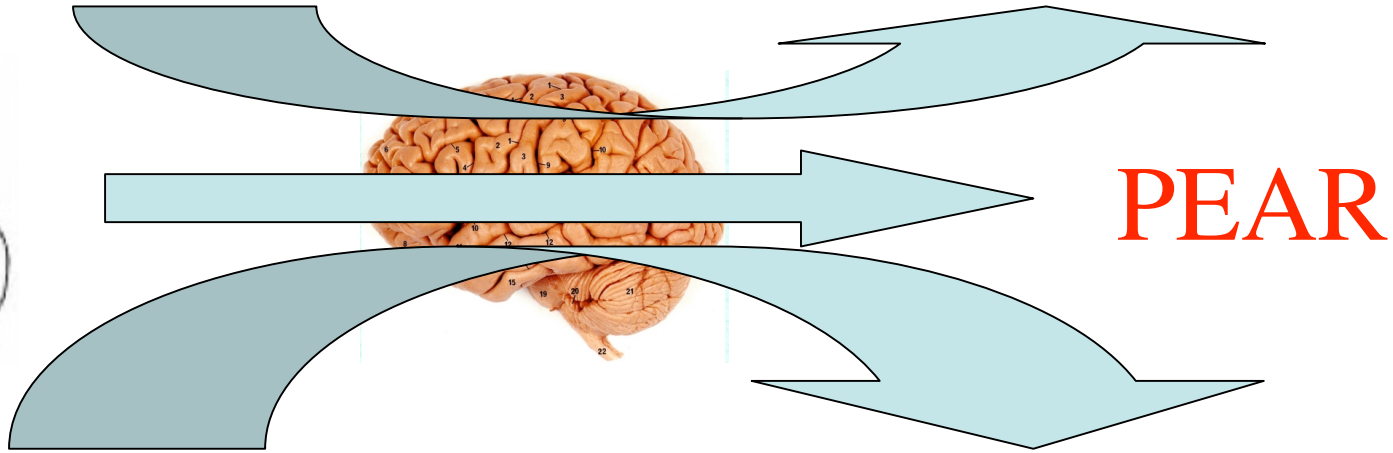
We need a classifier or predictor

APPLE

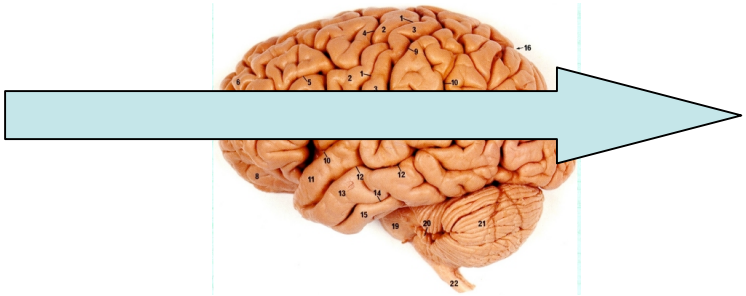




PEAR

PEAR

How to make a predictor?

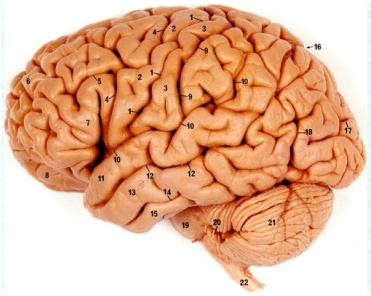
IMAGE  APPLE/PEAR

1. Experiment-based
2. Knowledge-based, « intelligent design »
3. Data-based, « machine learning »

Experiment-based classification

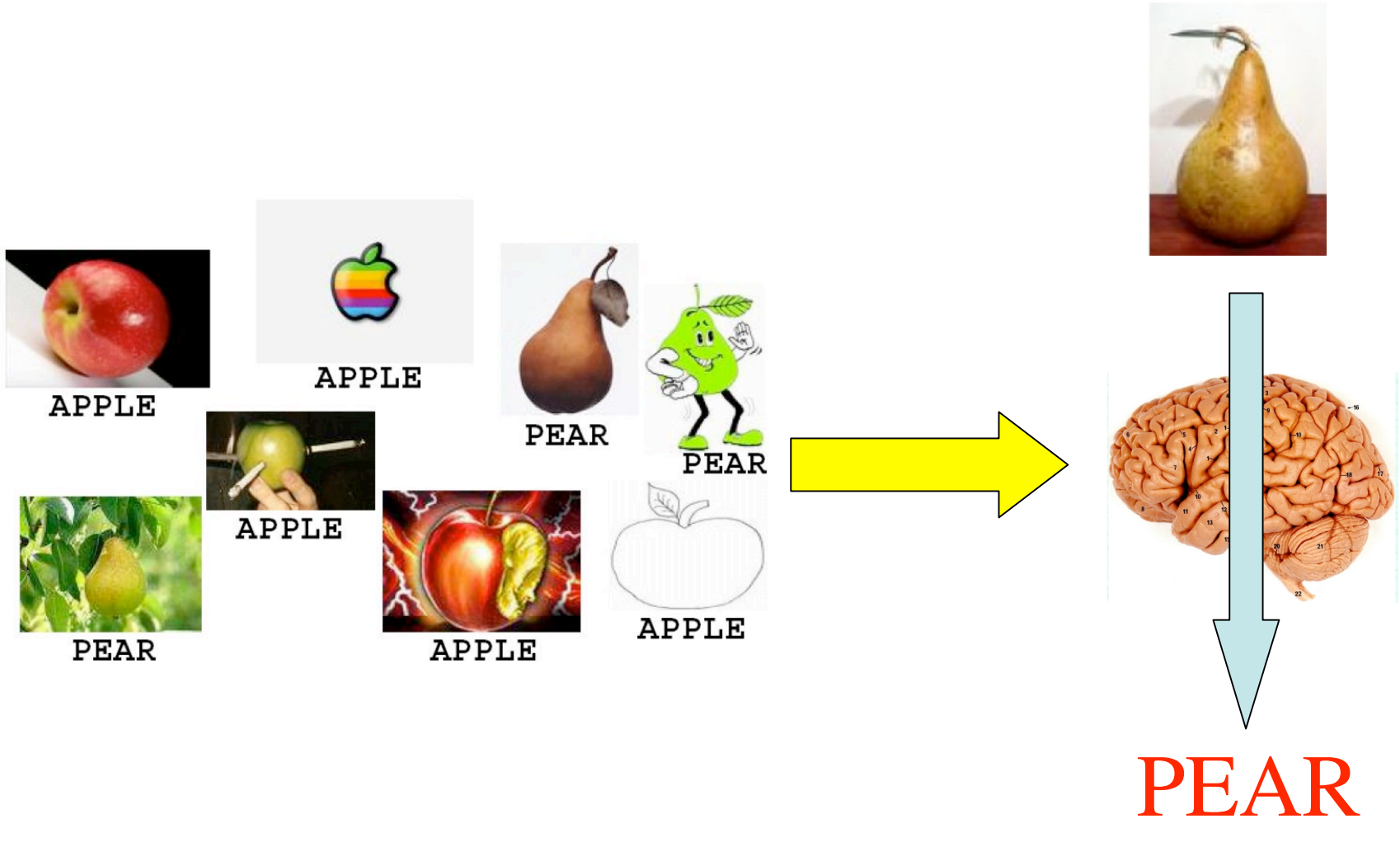
- Design experiments to answer the question
- Carry out the experiment
- The best approach if possible
- However: not always possible, takes time and money

Knowledge-based predictor

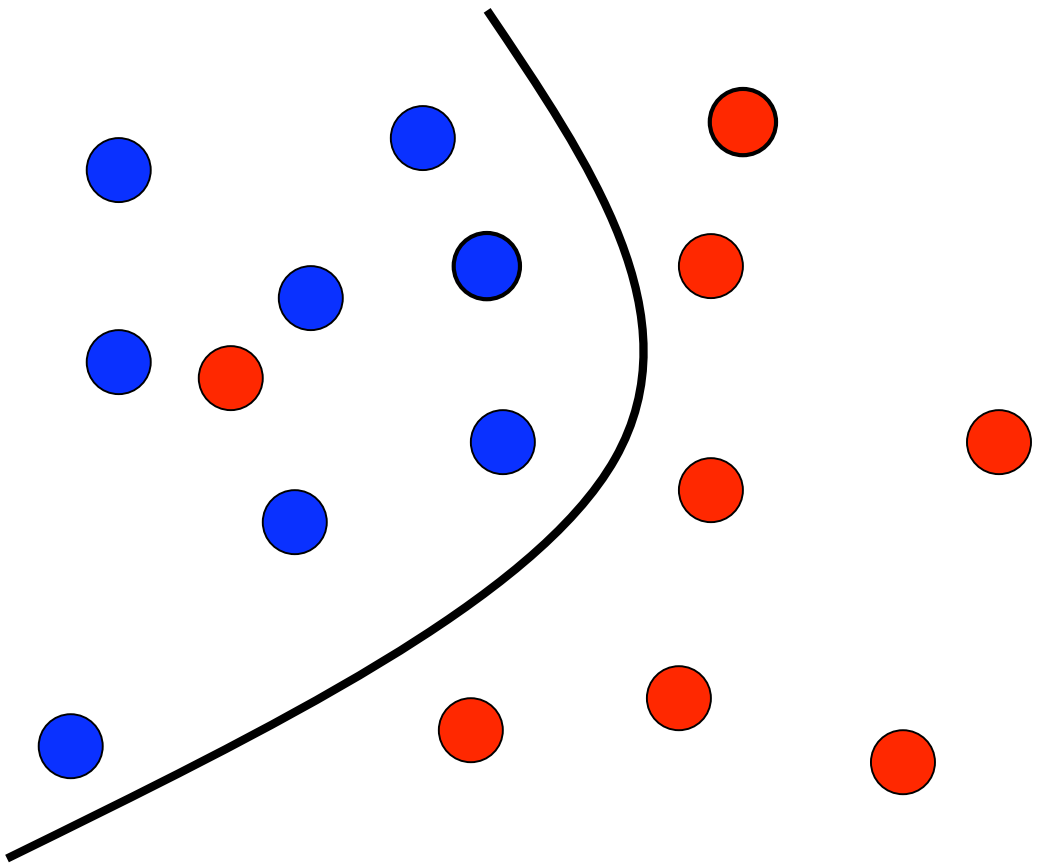


- Based on shape, texture, color, …
- Usually difficult to engineer
- Can not be used for other problems (eg, discriminate strawberries vs grapes)

Data-based predictor = learning

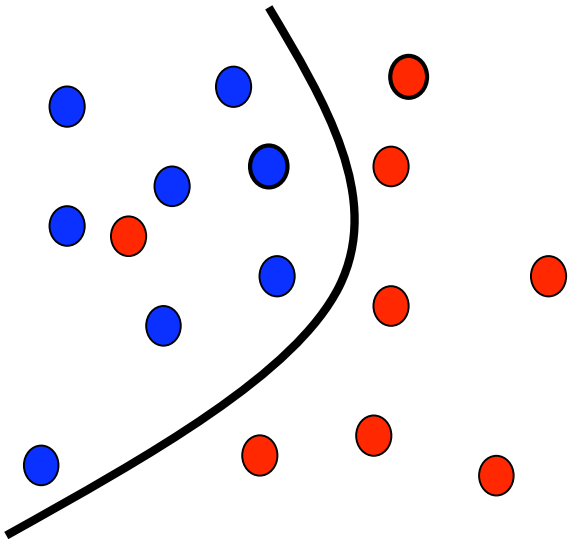


Another way to look at it



Some properties of data-based predictors

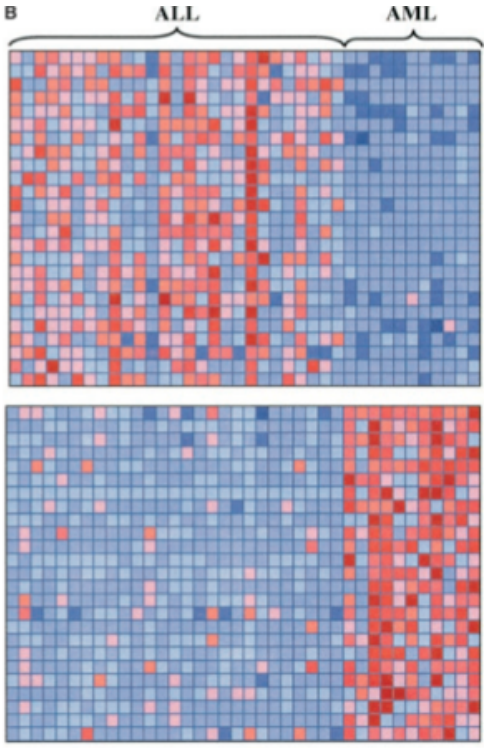
- Needs a database of labeled examples
- Does not always provide a simple rule (« black-box »)
- The more data the better!
- The algorithm can be quite generic

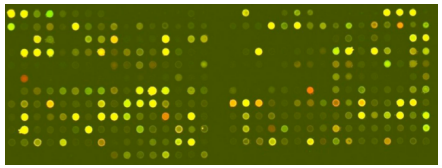


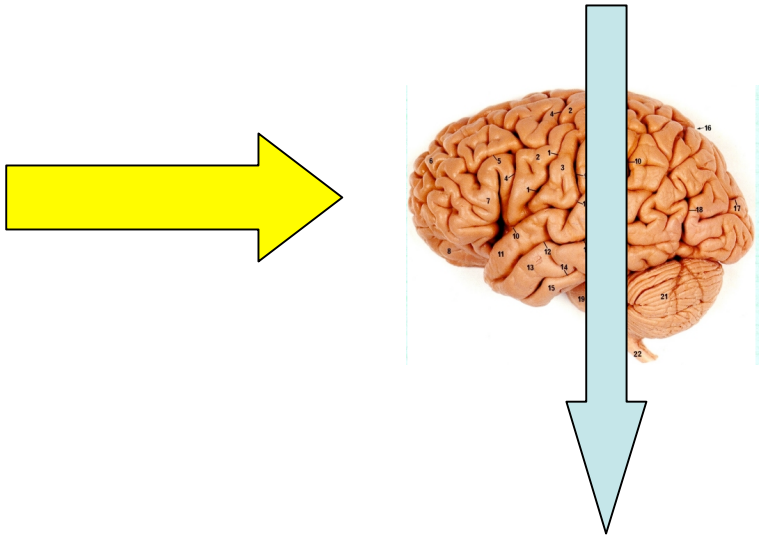
Ok, but there is no apple is bioinformatics!

- Sure, but:
  - There are many data
  - Many problems can be formulated as that of « learning a predictor from data »
  - It is often difficult to design knowledge-based predictors (no clear biological theory, noise, large number of features…)

Example: diagnosis/prognosis from microarray data

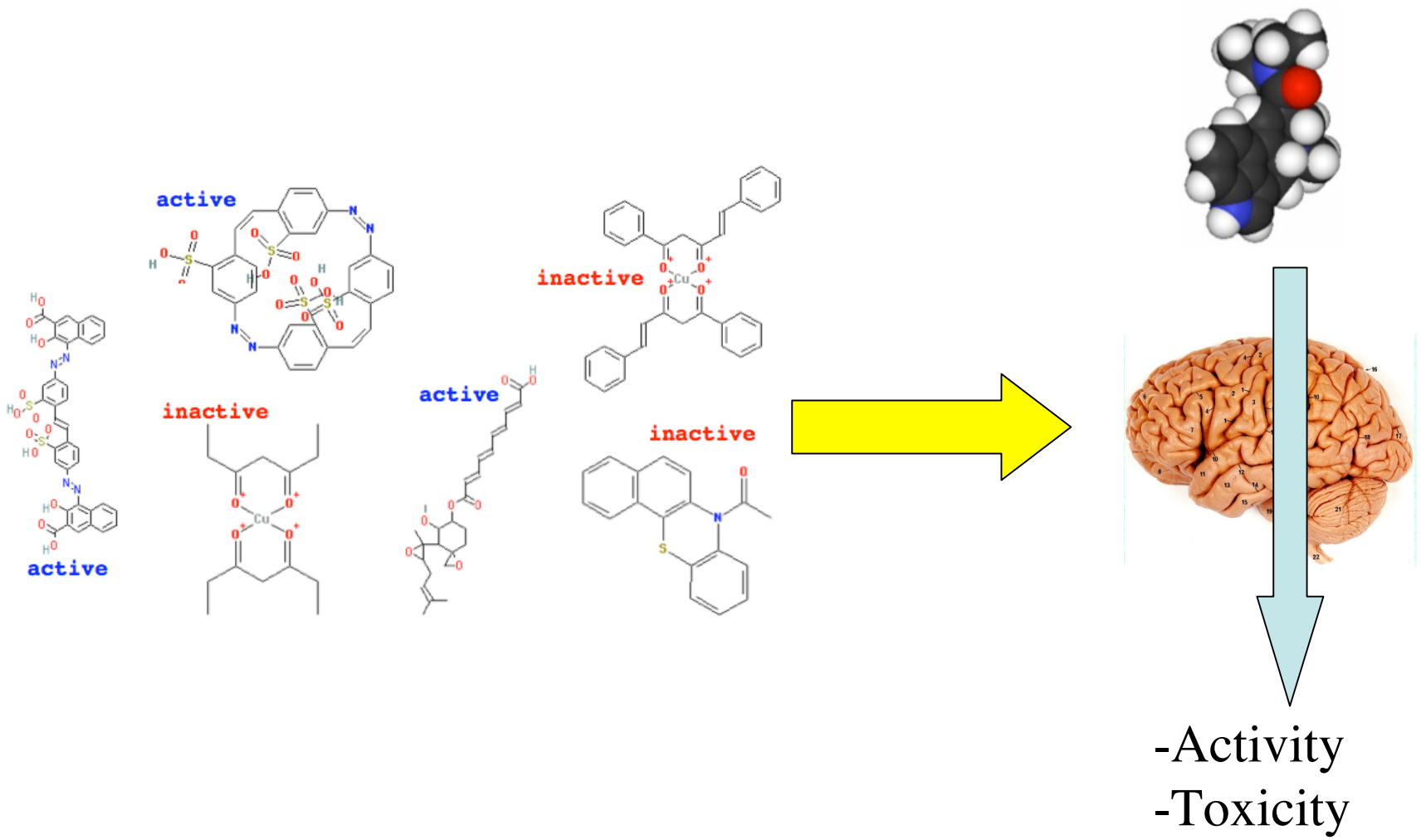






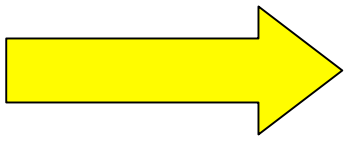
- Cancer type
- Future evolution

Example: virtual screening

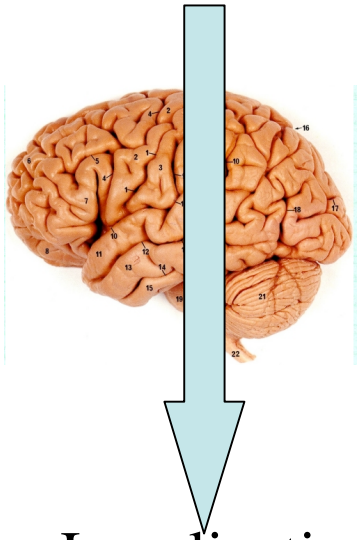


Example: gene annotation

- Secreted proteins:
  MASKATLLLAFTLLFATCIARHQQRQQQQNQCQLQNIEA...
  MARSSLFTFLCLAVFINGCLSQIEQQSPWEFQGSEVW...
  MALHTVLIMLSLLPMLEAQNPEHANITIGEPITNETLGWL...
  ...
- Non-secreted proteins:
  MAPPSVFAEVPQAQPVLVFKLIADFREDPDPRKVNLGVG...
  MAHTLGLTQPNSTEPHKISFTAKEIDVIEWKGDILVVG...
  MSISESYAKEIKTAFRQFTDFPIEGEQFEDFLPIIGNP..
  ...



MAHSKMQN…



-Localization
-Function
-Structure

Other examples

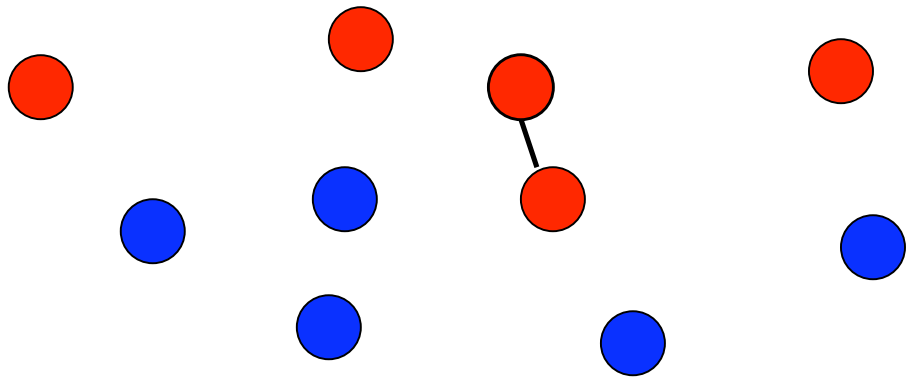
- Predict function from structure
- Predict splicing sites
- Predict binding sites
- Predict regulated genes
- …

Summary

- Patterns X (image/sequence/structure/…)
- Label Y (binary here, but can be more general)
- We want to build a predictor Y=f(X)
- For this we need a training set of (X,Y) pairs
- We need an algorithm that estimates the predictor f from the training set
- We can then use the predictor to make predictions on new patterns X by f(Y)

My first machine learning algorithm: nearest neighbour

- Define a similarity measure s(X,X’) between patterns
- For a new pattern X, predict as label f(X) the label of the most similar pattern in the training set



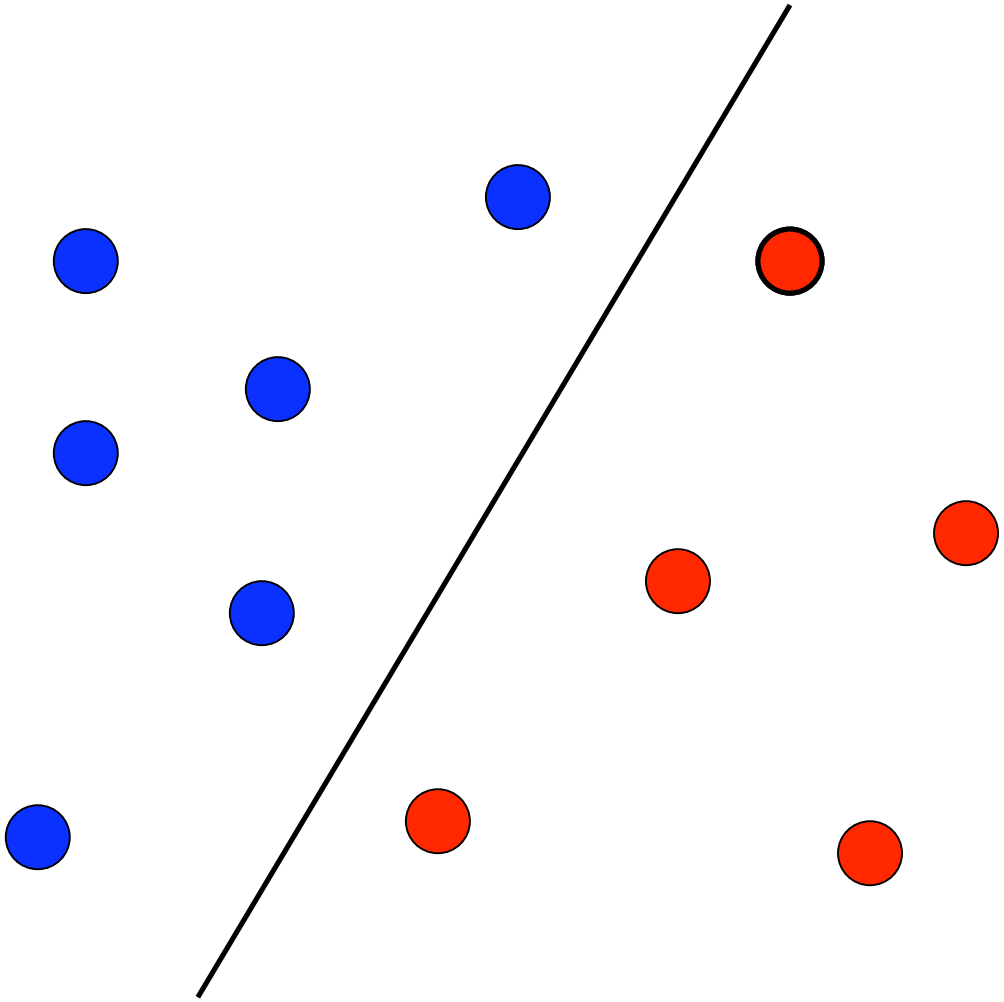
Nearest neighbours

- Very simple to implement
- Good baseline method
- Simple extension: make a majority vote of the k nearest neighbors (k-NN)

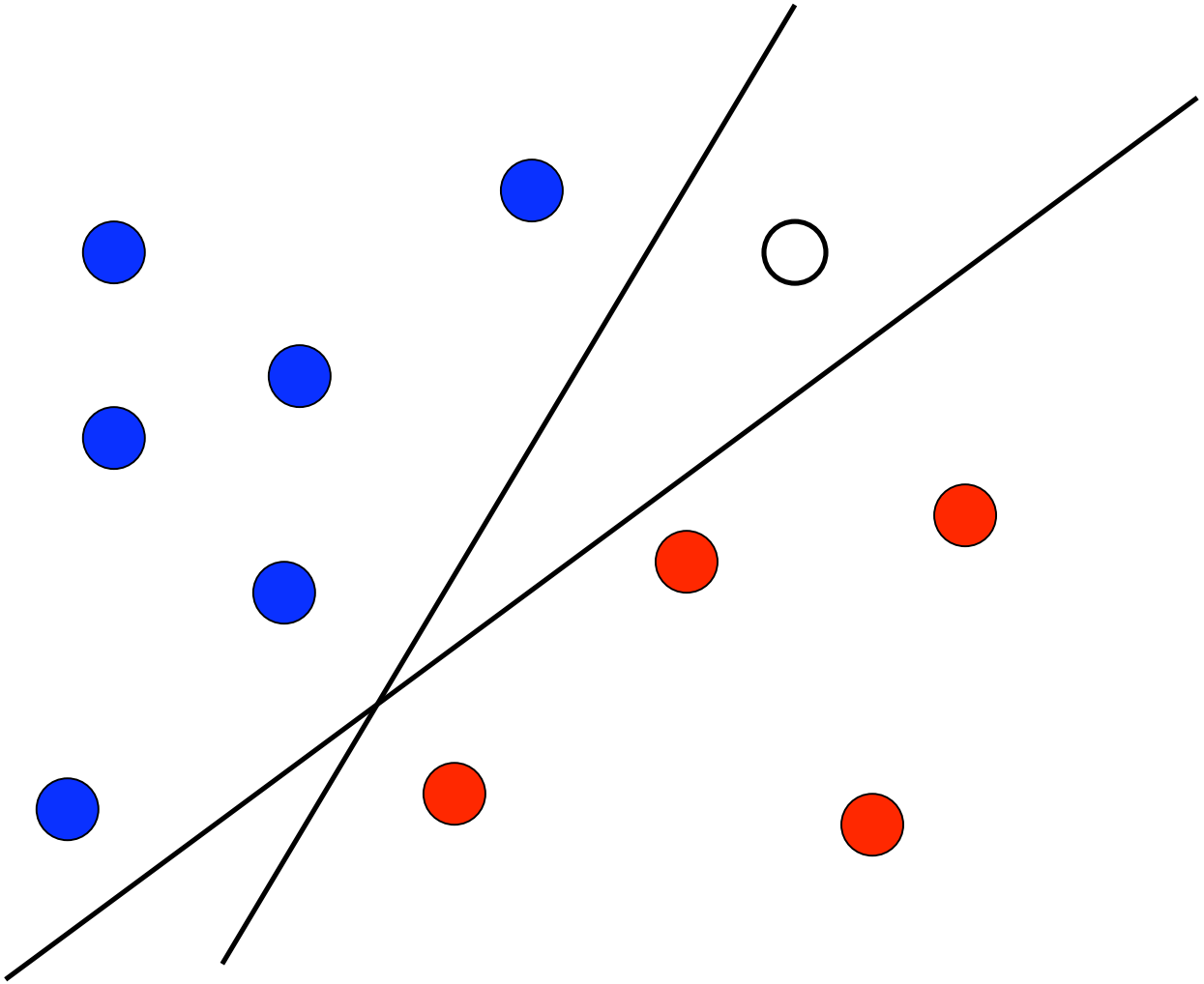
Other popular algorithms

- Decision trees, random forests
- Fisher linear discriminant
- Artificial neural networks (ANN)
- Logistic regression
- Boosting
- Support vector machines (SVM)

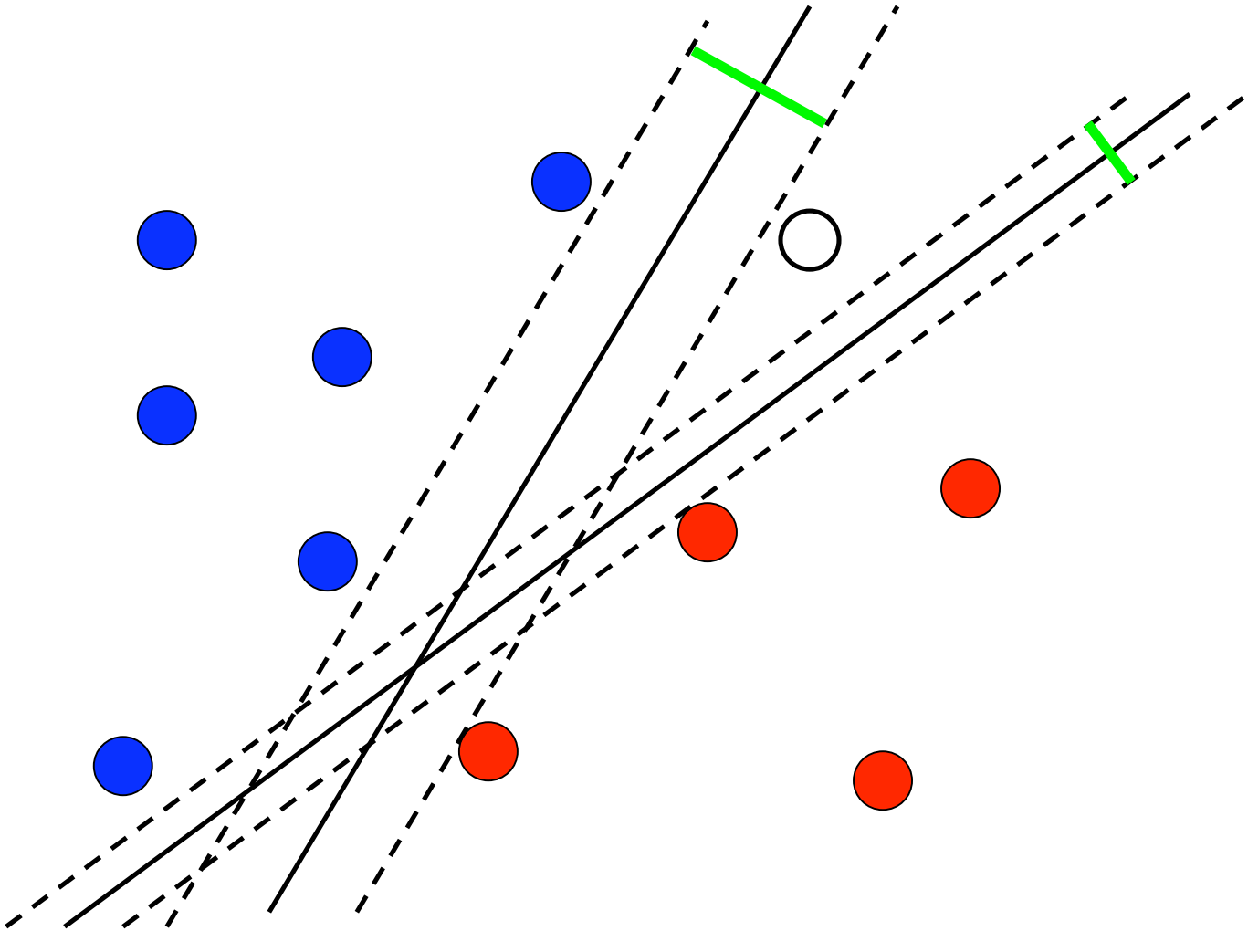
Linear classifier (simple case)



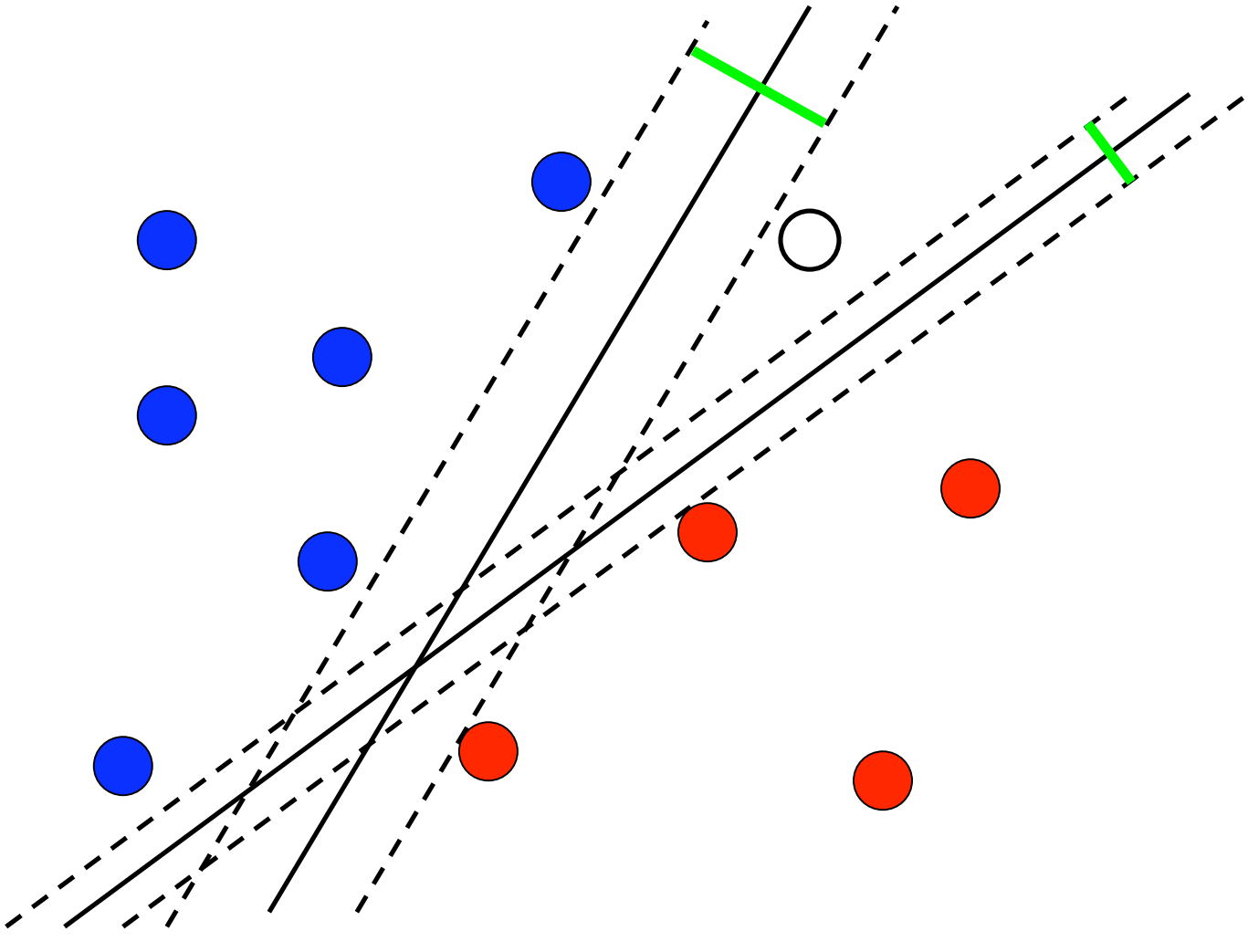
Which one is better?



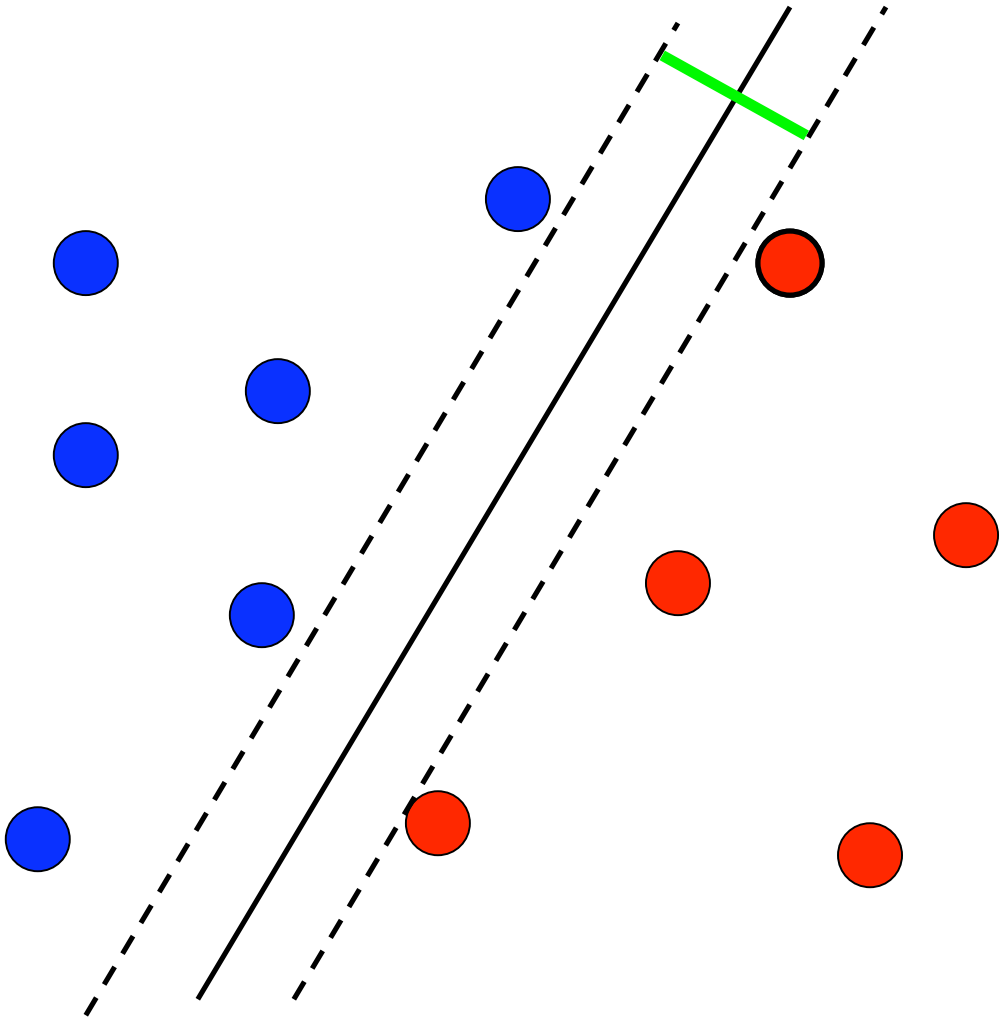
Vapnik's answer: margin



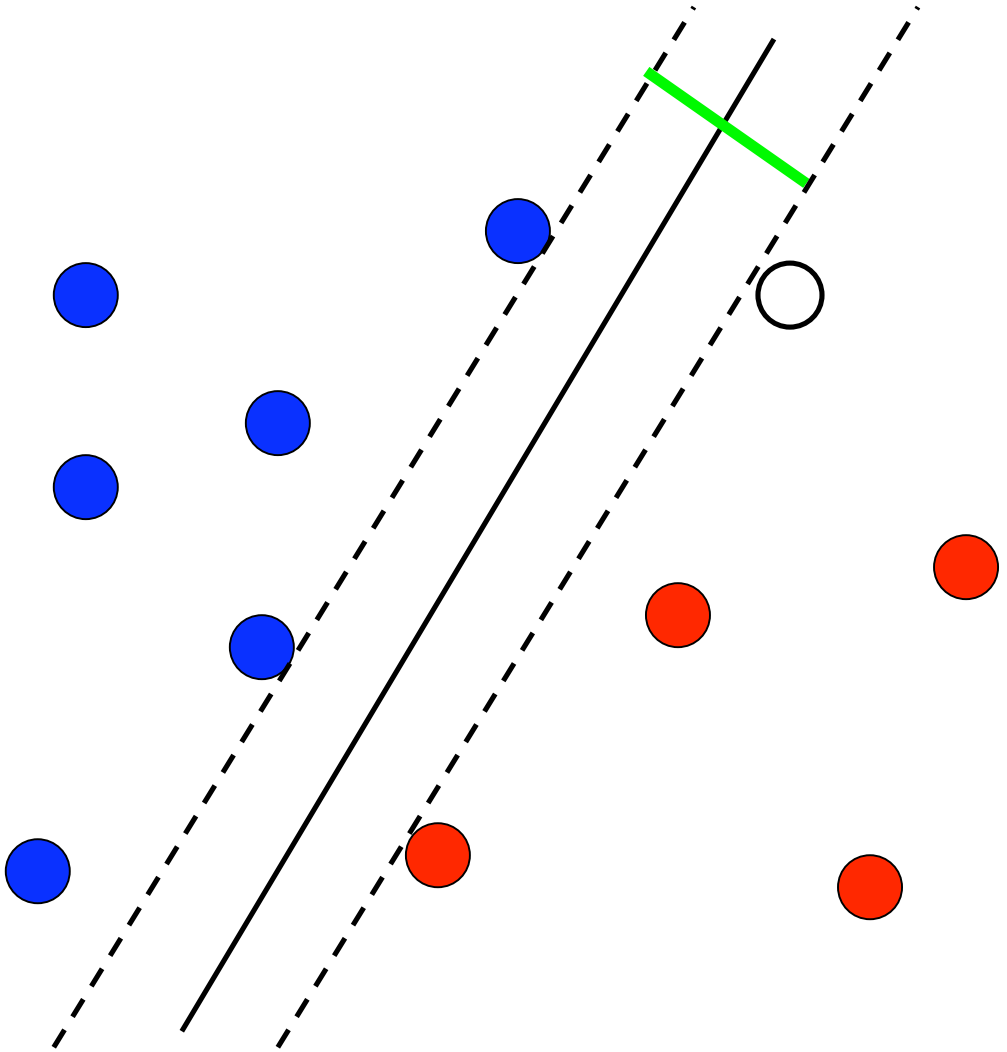
Vapnik's answer: margin



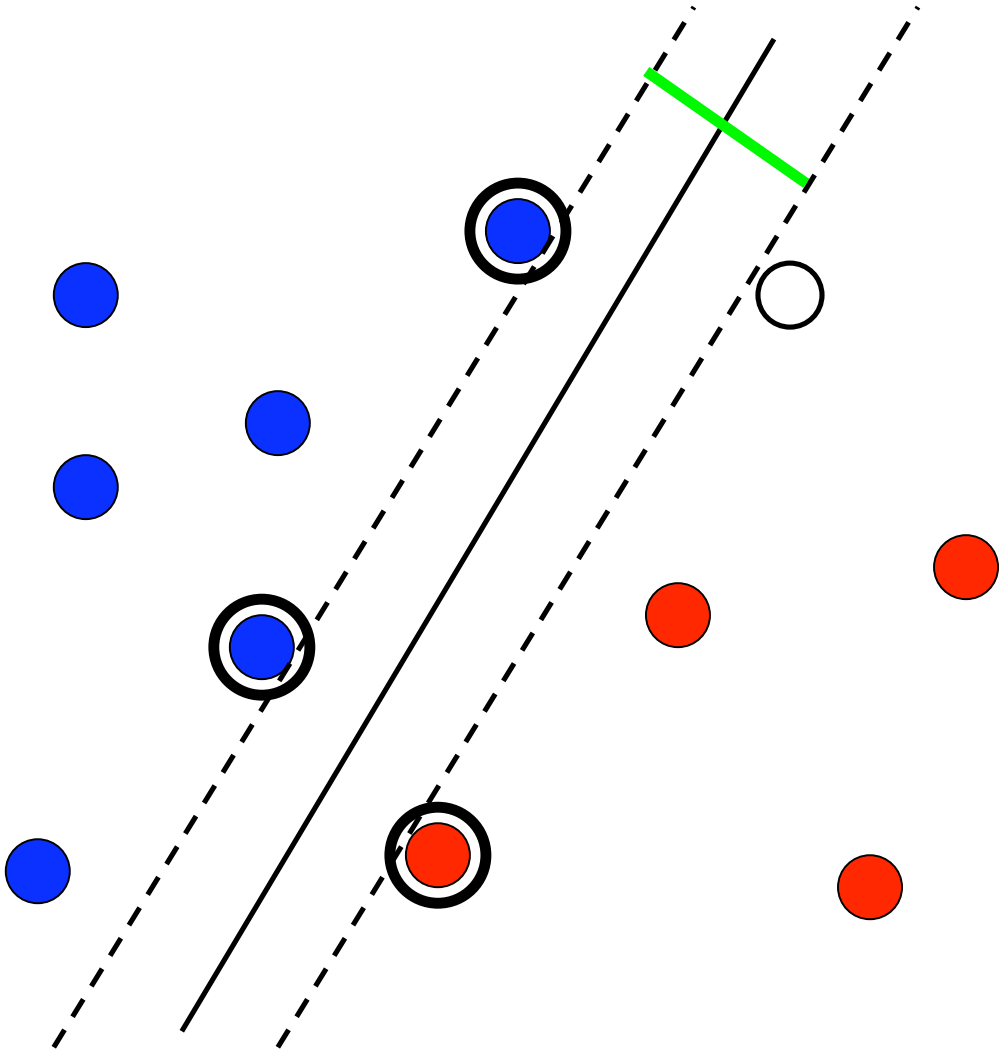
Vapnik's answer: margin



The best: largest margin



Support vectors

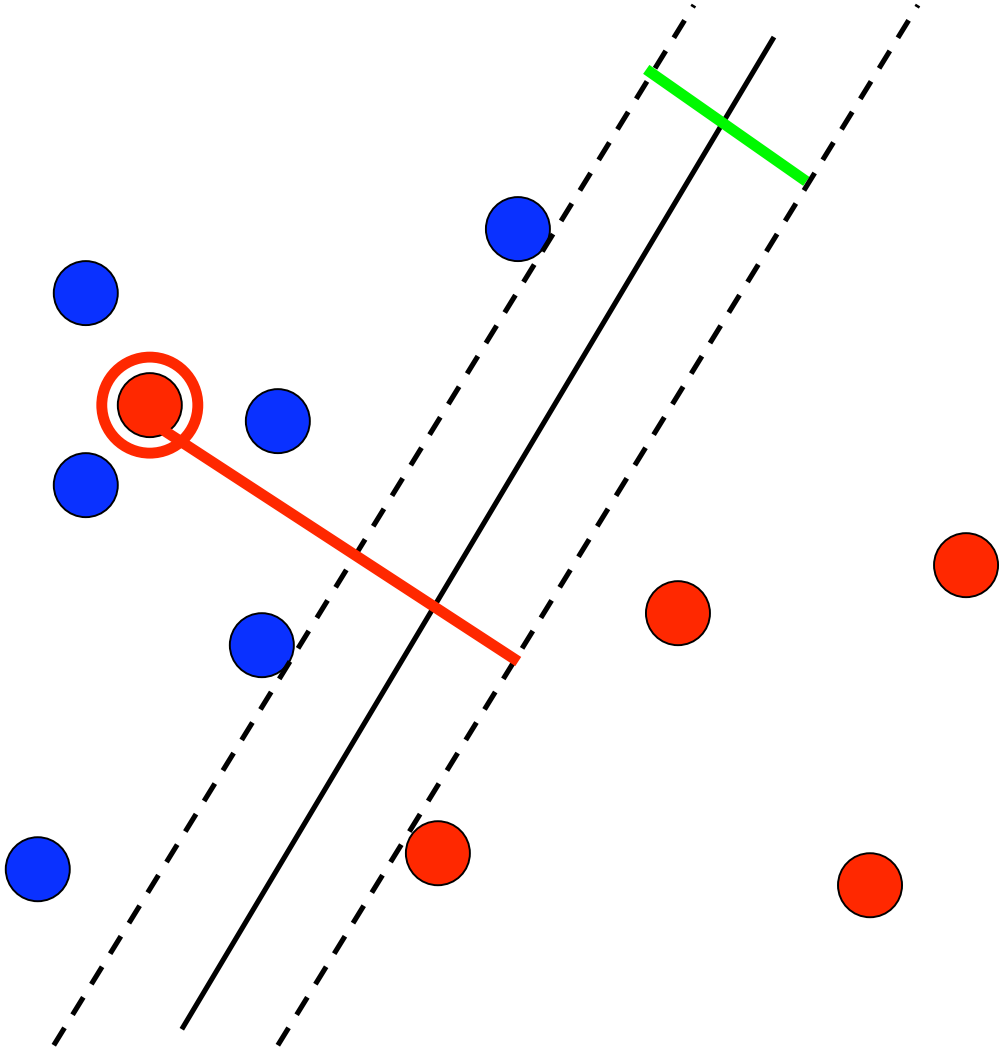


Implementation

$$\max_f \{margin(f)\} \Longleftrightarrow \min_f \left\{ \frac{1}{margin(f)} \right\}$$

- The problème of finding the largest margin hyperplane is easy to solve (but not by yourself!)
- Unique solution, no local optimum (convex optimization problem)
- Only depends on the support vectors

New problem



Soft-margin SVM

- Find a trade-off between:
  - Large margin
  - Few misclassification
- Mathematically:

$$\min_f \left\{ \frac{1}{margin(f)} + C \times error(f) \right\}$$

- Still easy to solve (for a good choice of « error »). C is a parameter.

Some limitations

- What if the data are not vectors?
- What if instead I have a way to measure a distance between patterns (e.g., alignment of sequences, stuctures, …)

An interesting property

- To train a SVM we just need the matrix of pairwise distances:

$$D_{i,j} = ||X_i - X_j||^2$$

- The predictor has the form:

$$f(X) = \sum_{i \in SV} w_i ||X_i - X||^2$$

An interesting generalization

- Take a distance d(X,X')
- Train a SVM from the matrix of pairwise distances:

$$D_{i,j} = d(X_i, X_j)^2$$

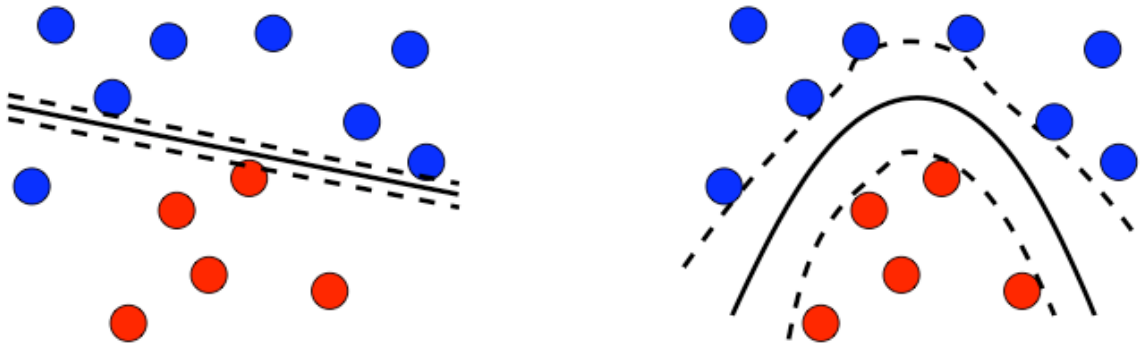
- The predictor now is:

$$f(X) = \sum_{i \in SV} w_i d(X_i, X)^2$$

Technical details

- This will work very well if the distance d(X,X') satisfies some mathematical conditions (« conditionally positive definiteness »)
- If not there still exist tricks to make it work

Example: nonlinear SVM



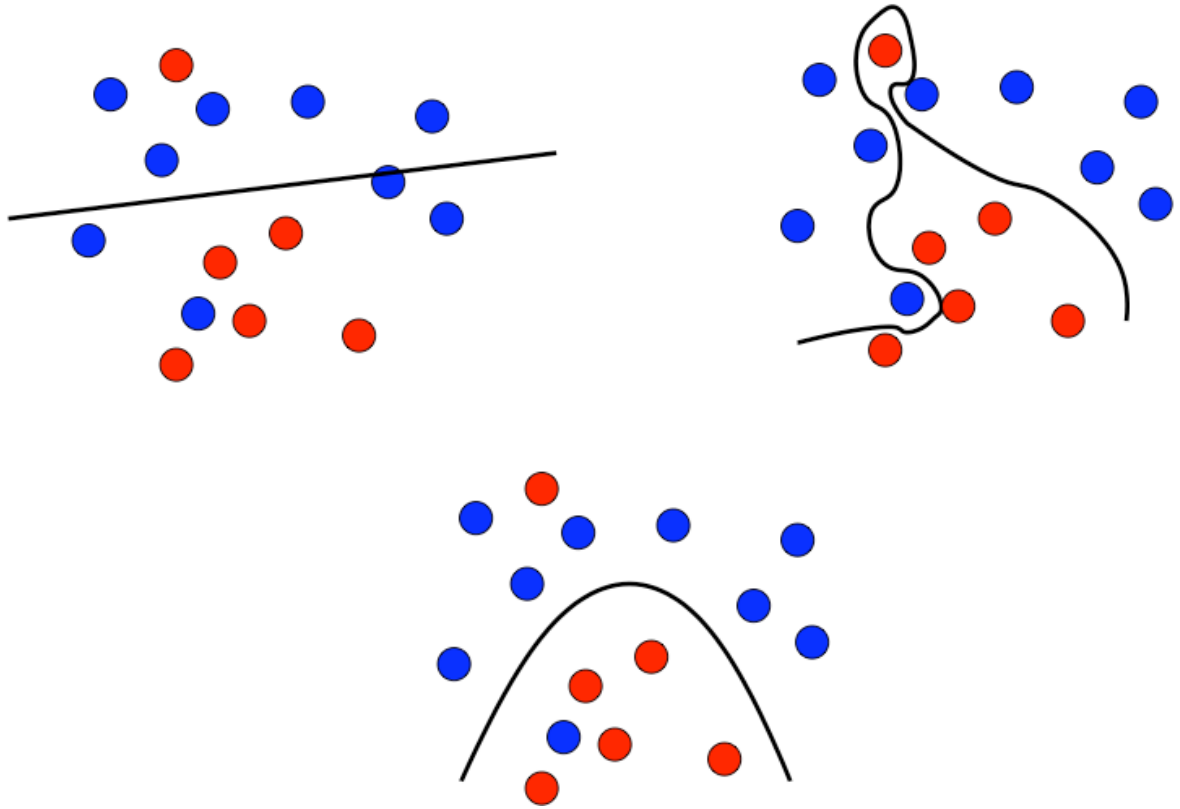
- Take a Gaussian distance:

$$d(X, X')^2 = 1 - \exp\left(-\frac{||X - X'||^2}{2\sigma^2}\right)$$

- We can then learn nonlinear predictors:

$$f(X) = \sum_{i \in SV} w_i \exp\left(-\frac{||X - X_i||^2}{2\sigma^2}\right) + cte$$

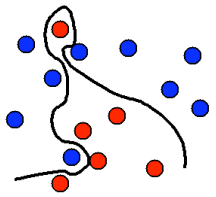
The fundamental trade-off: regularity (margin) vs error



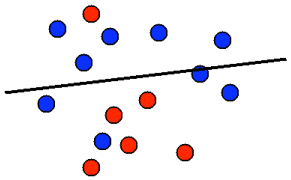
C controls the trade-off

$$\min_f \left\{ \frac{1}{margin(f)} + C \times error(f) \right\}$$

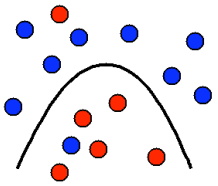
- Large C :
  - makes few errors



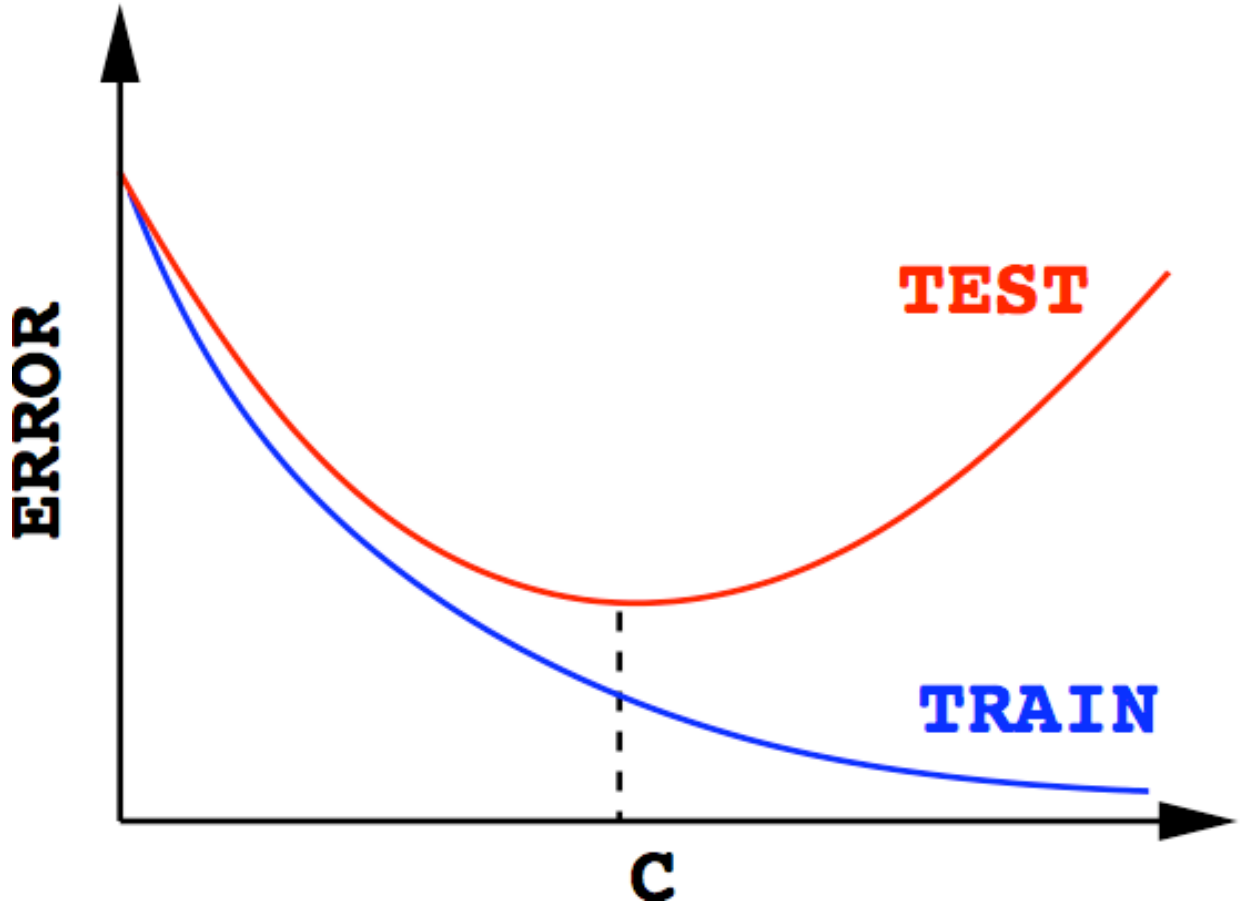
- Small C :
  - ensure a large margin



- Intermediate C:
  - finds a trade-off



Why it is important to care about the trade-off



Choosing C

- Split the annotated data in 2: training / validation
- Train a predictor on the training set
- Evaluate the performance on the validation set
- Choose C to minimize the validation error
- (you may repeat all this several times -> cross-validation)

SVM: summary

- You need a training set of labeled patterns, i.e., of (X,Y) pairs
- You need a distance d(X,X') between patterns
- You need to choose the parameter C (e.g., cross-validation)
- You plug this into any SVM implementation to train a predictor

SVM in practice
(eg: libsvm with Python)

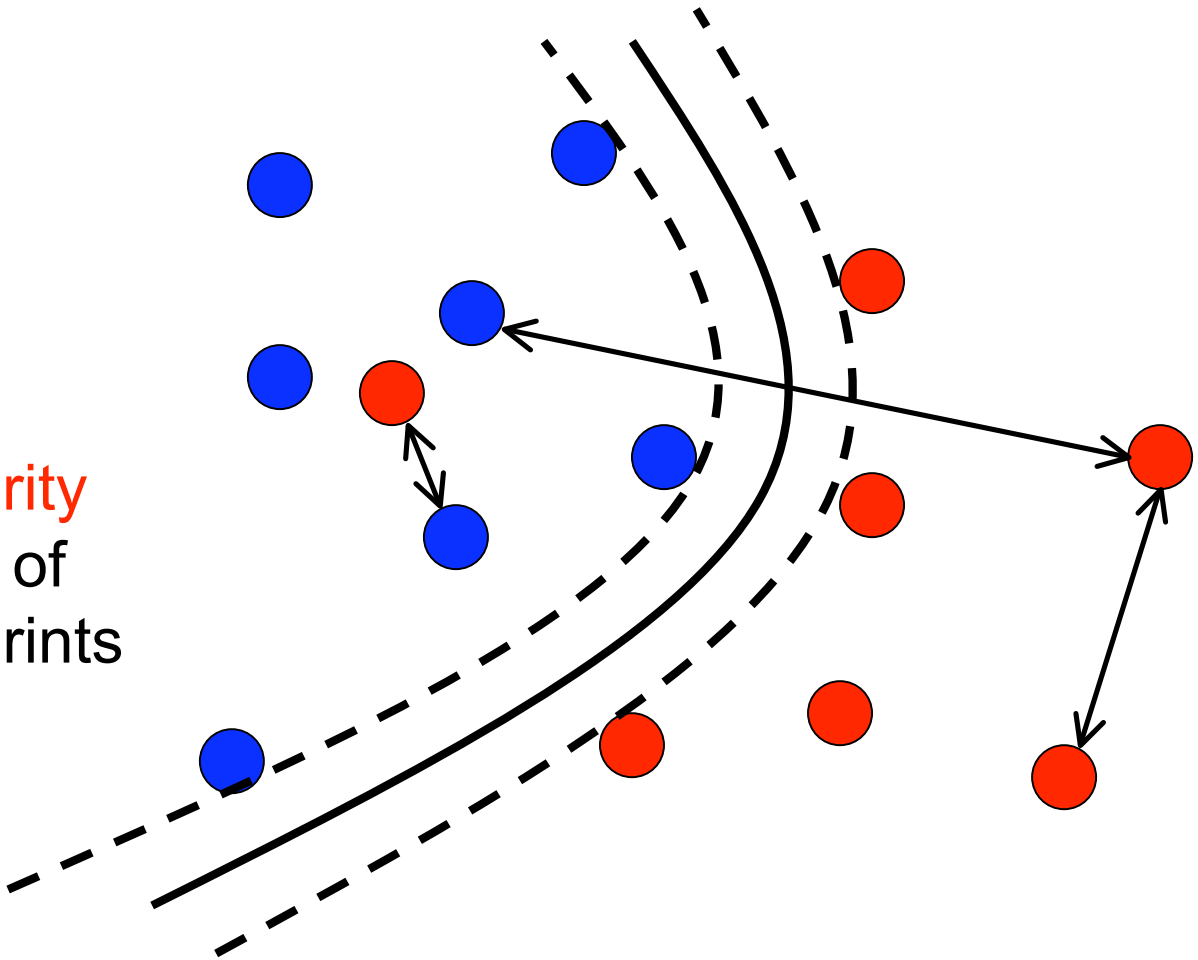
```
1> from svm import *
2> param = svm_parameter(kernel_type=LINEAR,C=10)
3> prob = svm_problem([1,-1],[[1,0,1],[-1,0,-1]])
4> m = svm_model(prob, param)
5> r = m.predict([1, 1, 1])
```

SVM summary

- Large margin

- Nonlinear

- Need pairwise distance / similarity as input instead of vectors / fingerprints



Part 2
Applications of machine learning in bioinformatics and drug discovery