# Support vector machines, kernels, and applications in computational biology

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## Outline

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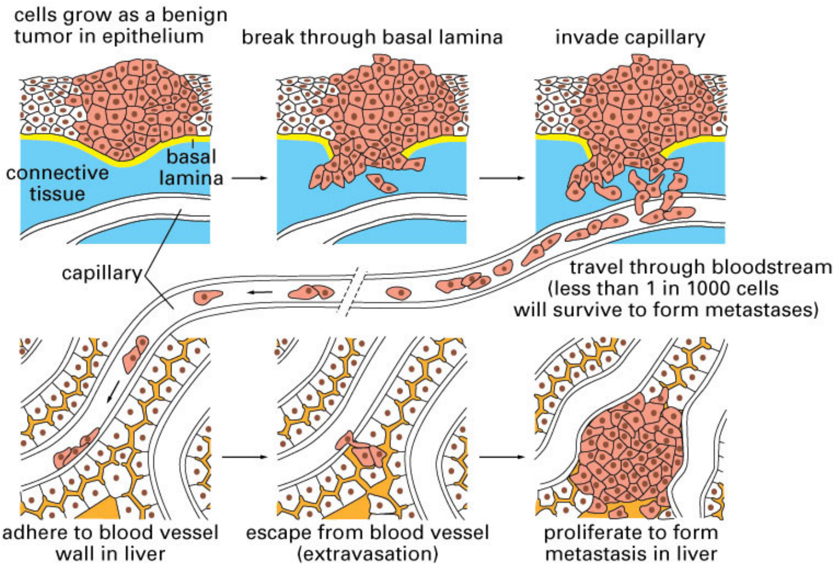
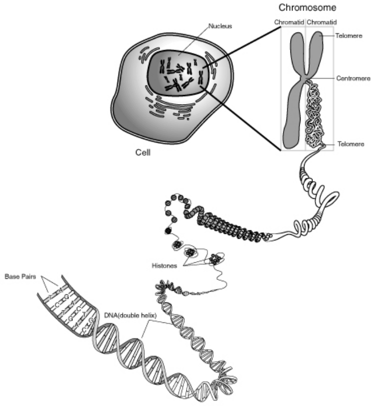
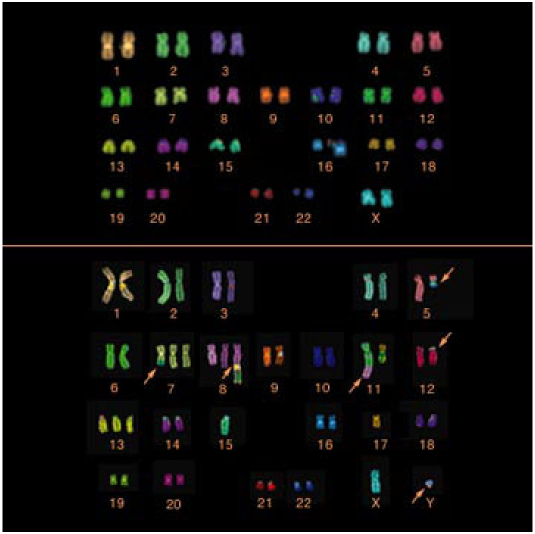
# A simple view of cancer progression


cells grow as a benign tumor in epithelium
break through basal lamina
invade capillary
basal lamina
connective tissue
capillary
travel through bloodstream (less than 1 in 1000 cells will survive to form metastases)
adhere to blood vessel wall in liver
escape from blood vessel (extravasation)
proliferate to form metastasis in liver

# Chromosomic aberrations in cancer

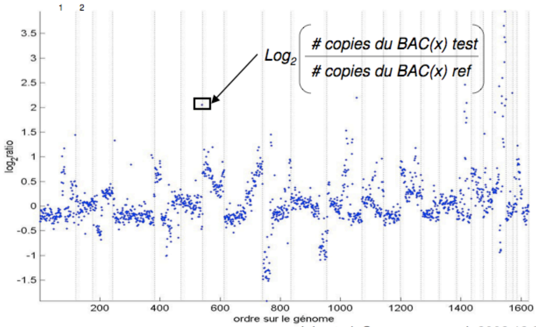




# Comparative Genomic Hybridization (CGH)

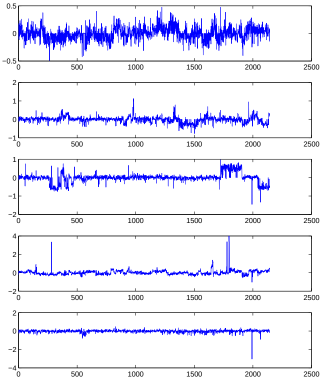
## Motivation

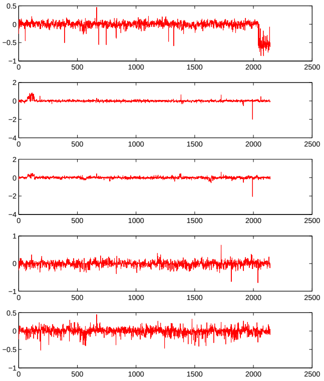
- Comparative genomic hybridization (CGH) data measure the DNA copy number along the genome
- Very useful, in particular in cancer research
- Can we classify CGH arrays for diagnosis or prognosis purpose?



Jain et al. Genome research 2002 12:325-332

# Aggressive vs non-aggressive melanoma

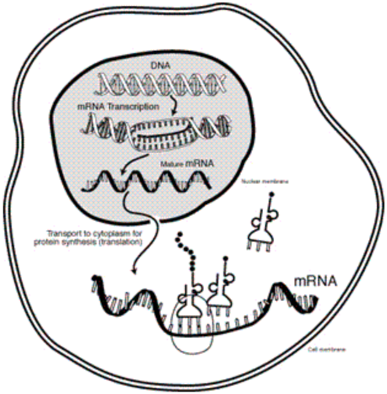




**Problem 1**

Given the CGH profile of a melanoma, is it aggressive or not?

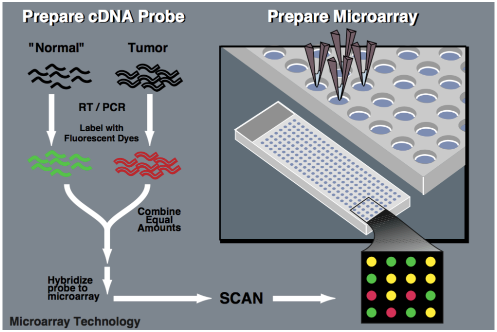
# DNA → RNA → protein

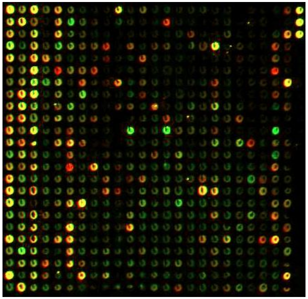


$$\begin{tikzcd}
\boxed{\text{DNA}} \arrow[d, "\text{transcription}"] \\
\boxed{\text{RNA}} \arrow[d, "\text{translation}"] \\
\boxed{\text{Protein}}
\end{tikzcd}$$

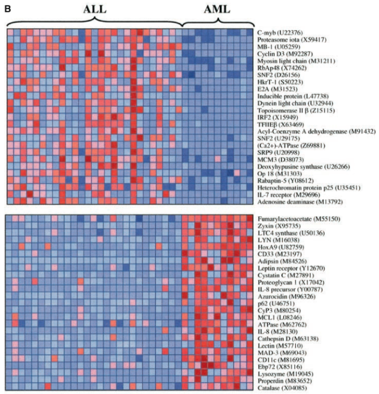
- CGH shows the (static) DNA
- Cancer cells have also abnormal (dynamic) gene expression (= transcription)

# Tissue profiling with DNA chips





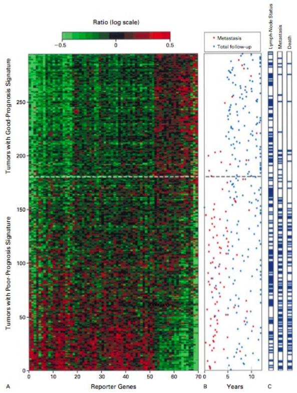
# Use in diagnosis

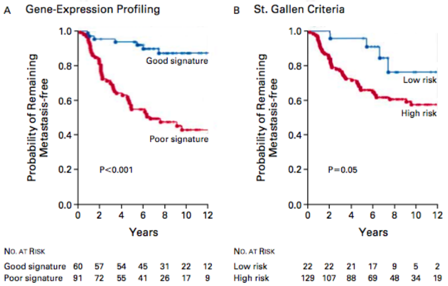


## Problem 2

Given the expression profile of a leukemia, is it an acute lymphocytic or myeloid leukemia (ALL or AML)?

## Use in prognosis

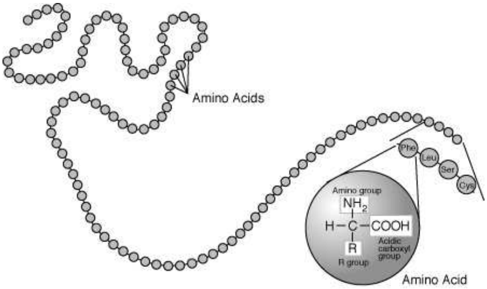




### Problem 3

Given the expression profile of a breast cancer, is the risk of relapse within 5 years high?

## Proteins



| | | |
|---|---|---|
| A : Alanine | V : Valine | L : Leucine |
| F : Phenylalanine | P : Proline | M : Methionine |
| E : Acide glutamique | K : Lysine | R : Arginine |
| T : Threonine | C : Cysteine | N : Asparagine |
| H : Histidine | V : Thyrosine | W : Tryptophane |
| I : Isoleucine | S : Serine | Q : Glutamine |
| D : Acide aspartique | G : Glycine | |

# Protein annotation

## Data available

- Secreted proteins:

```
MASKATLLLAFTLLFATCIARHQQRQQQQNQCQLQNIEA...
MARSSLFTFLCLAVFINGCLSQIEQQSPWEFQGSEVW...
MALHTVLIMLSLLPMLEAQNPEHANITIGEPITNETLGWL...
...
```

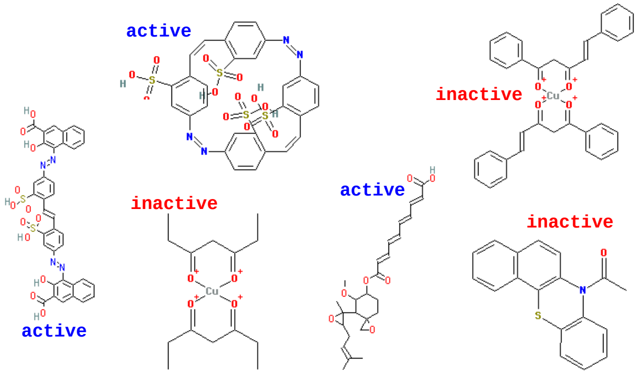
- Non-secreted proteins:

```
MAPPSVFAEVPQAQPVLVFKLIADFREDPDPRKVNLGVG...
MAHTLGLTQPNSTEPHKISFTAKEIDVIEWKGDILVVG...
MSISESYAKEIKTAFRQFTDFPIEGEQFEDFLPIIGNP..
...
```

## Problem 4

Given a newly sequenced protein, is it secreted or not?

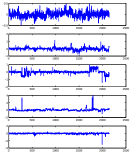
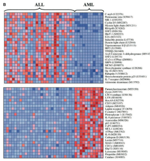
## Drug discovery

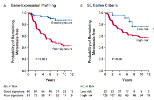


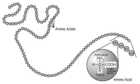
**Problem 4**

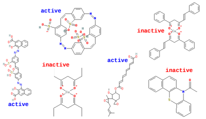
Given a new candidate molecule, is it likely to be active?

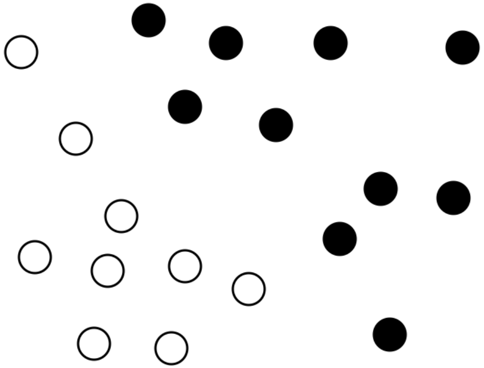
# Pattern recognition, *aka* supervised classification









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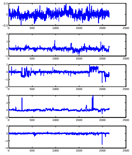

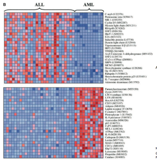

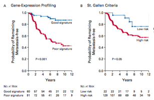

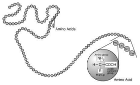

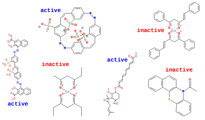

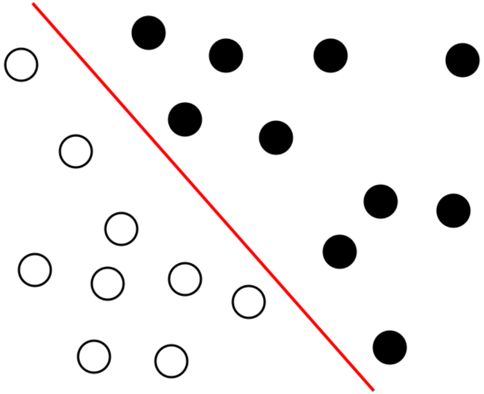

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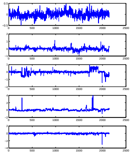
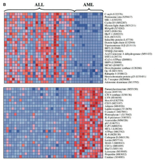

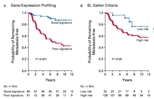

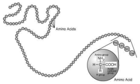

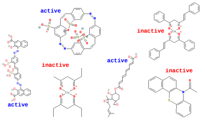

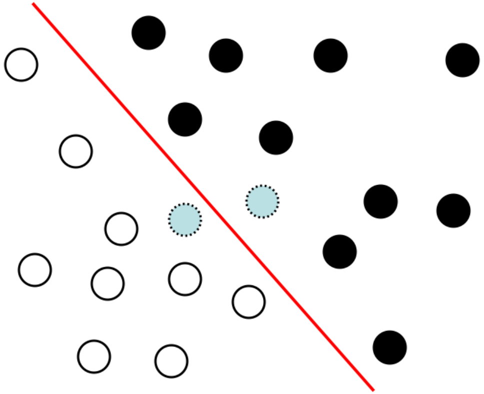

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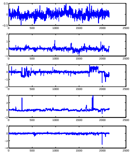
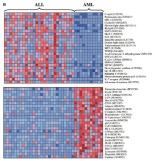
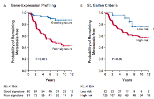
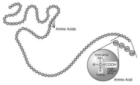
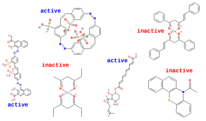
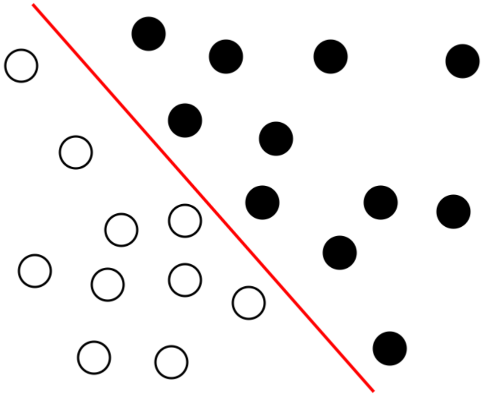



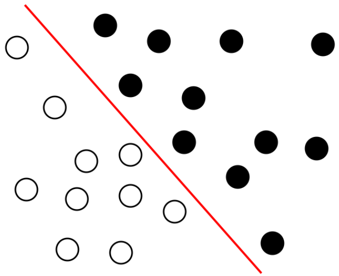








## Pattern recognition, *aka* supervised classification

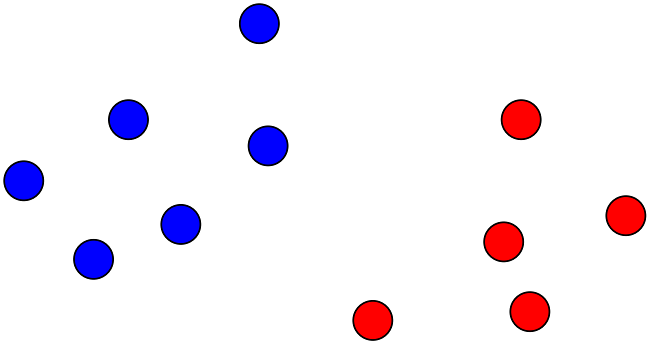


**Challenges**

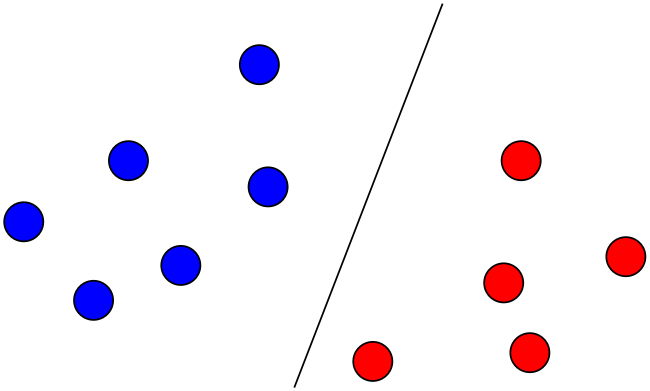
- High dimension
- Few samples
- Structured data
- Heterogeneous data
- Prior knowledge
- Fast and scalable implementations
- Interpretable models

## Outline

## Linear classifiers



## Linear classifiers



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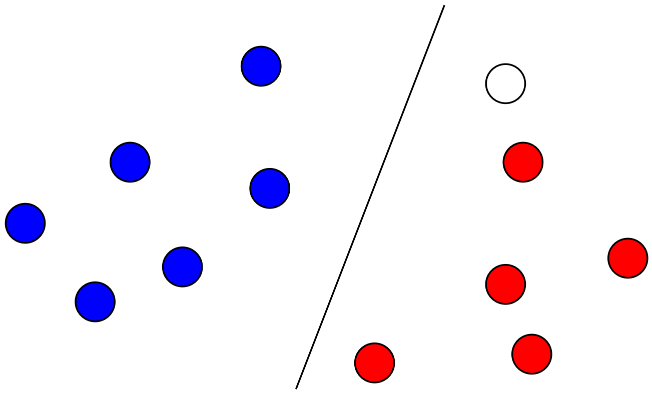

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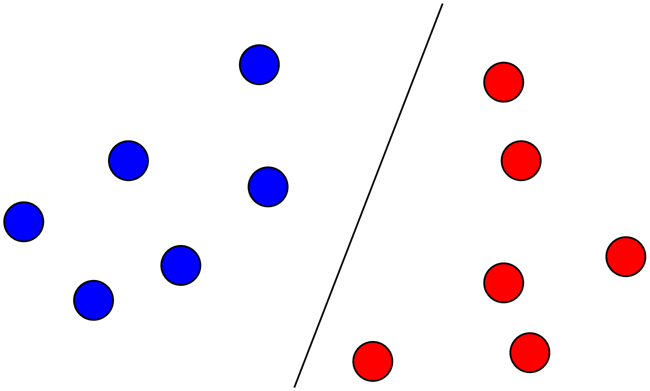

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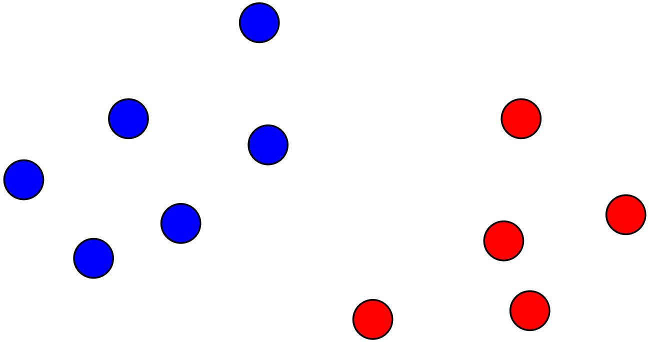

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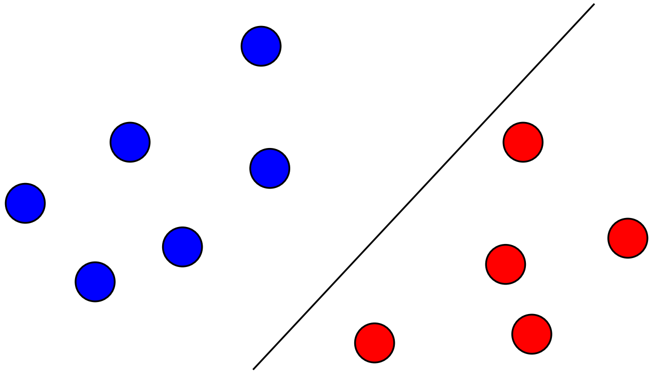

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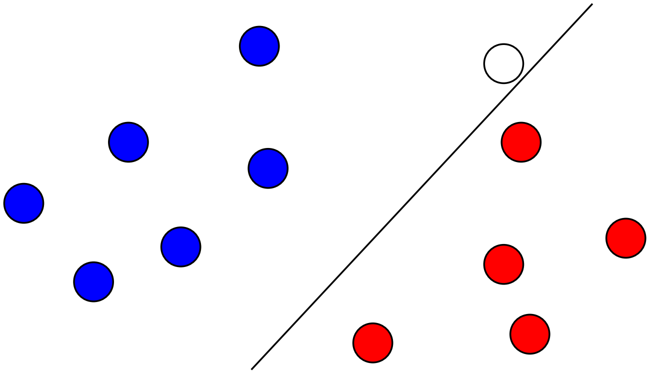

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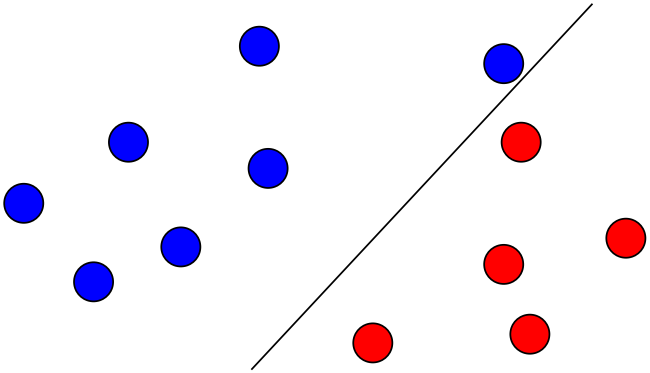
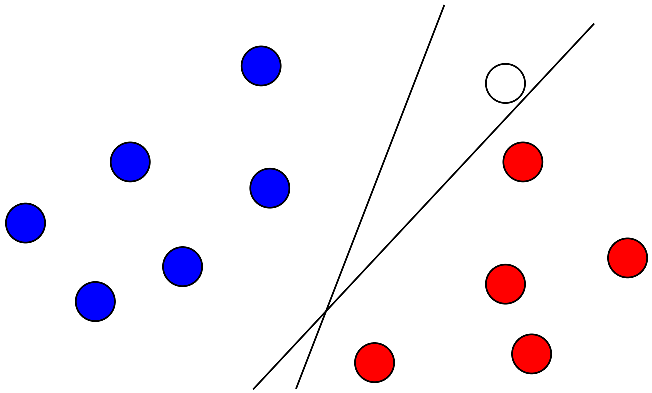
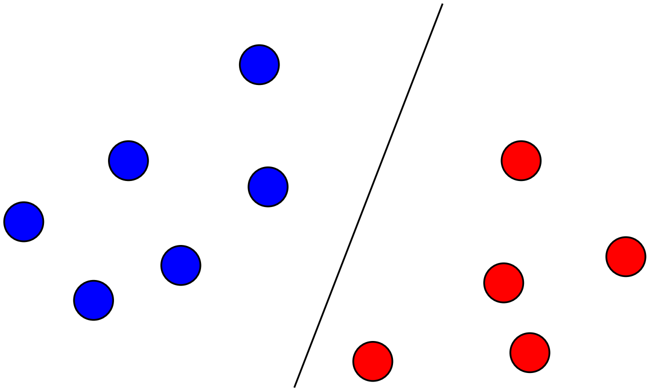


## Which one is better?



## The margin of a linear classifier



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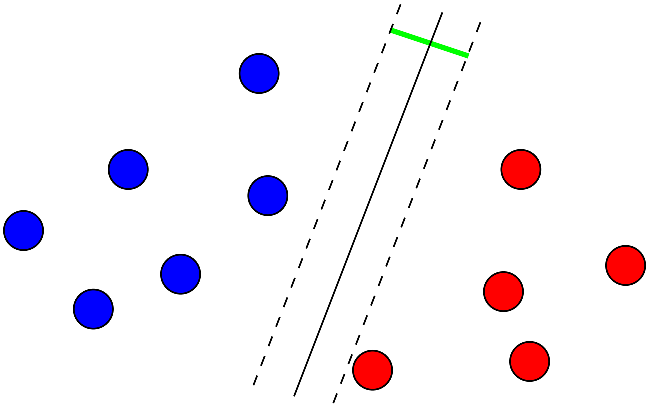

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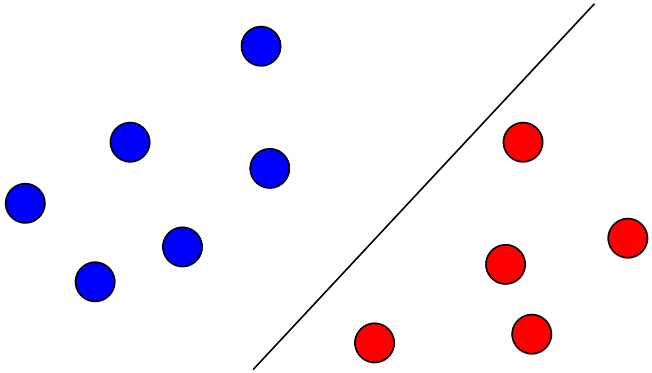

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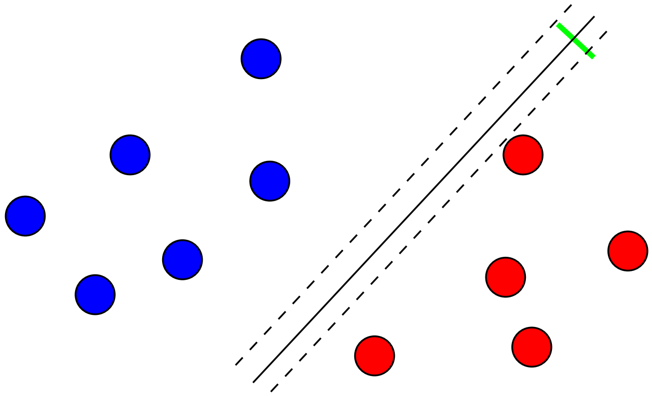
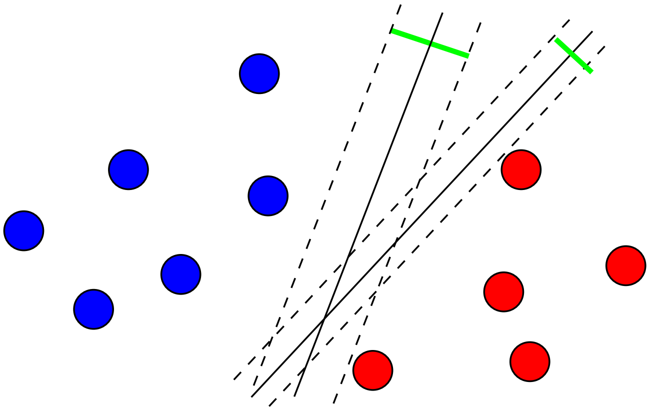
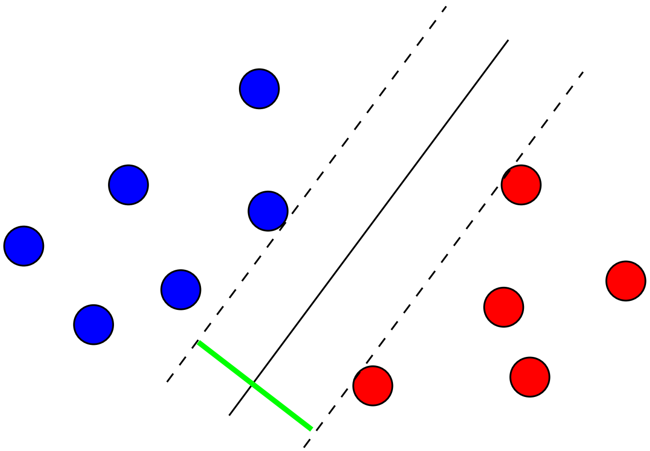


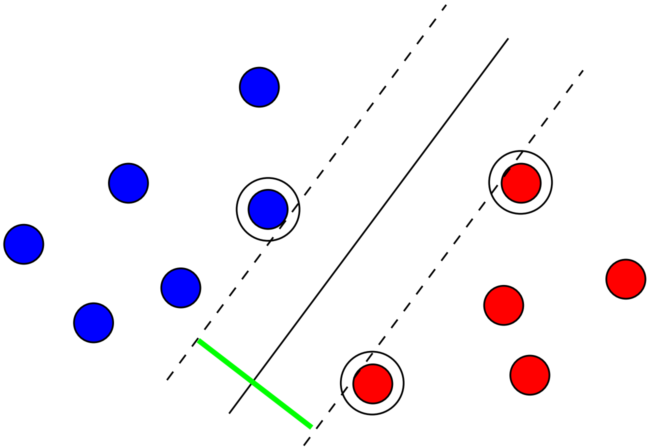
## The margin of a linear classifier



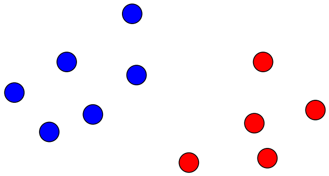
## Largest margin classifier (support vector machines)



## Support vectors



# More formally



- The training set is a finite set of $N$ data/class pairs:

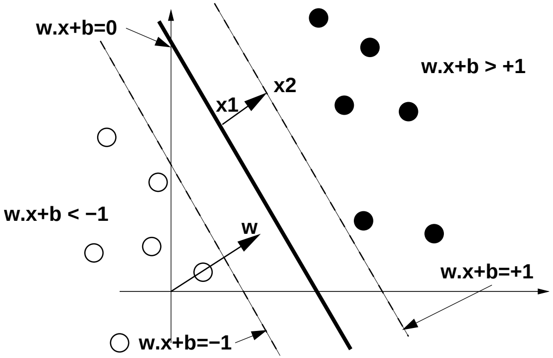
$$\mathcal{S} = \left\{ (\vec{x}_1, y_1), \ldots, (\vec{x}_N, y_N) \right\} ,$$

  where $\vec{x}_i \in \mathbb{R}^d$ and $y_i \in \{-1, 1\}$.
- We assume (for the moment) that the data are linearly separable, i.e., that there exists $(\vec{w}, b) \in \mathbb{R}^d \times \mathbb{R}$ such that:

$$\begin{cases} \vec{w}.\vec{x}_i + b > 0 & \text{if } y_i = 1 , \\ \vec{w}.\vec{x}_i + b < 0 & \text{if } y_i = -1 . \end{cases}$$

## How to find the largest separating hyperplane?

For a given linear classifier $f(x) = \vec{w}.\vec{x} + b$ consider the "tube" defined by the values $-1$ and $+1$ of the decision function:



## The margin is $2/||\vec{w}||$

Indeed, the points $\vec{x}_1$ and $\vec{x}_2$ satisfy:

$$\begin{cases} \vec{w}.\vec{x}_1 + b = 0, \\ \vec{w}.\vec{x}_2 + b = 1. \end{cases}$$

By subtracting we get $\vec{w}.(\vec{x}_2 - \vec{x}_1) = 1$, and therefore:

$$\gamma = 2||\vec{x}_2 - \vec{x}_1|| = \frac{2}{||\vec{w}||}.$$

## All training points should be on the right side of the dotted line

For positive examples ($y_i = 1$) this means:

$$\vec{w}.\vec{x}_i + b \geq 1$$

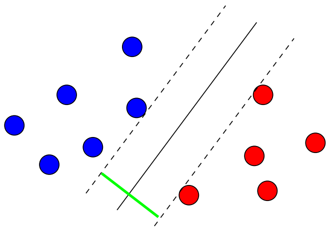
For negative examples ($y_i = -1$) this means:

$$\vec{w}.\vec{x}_i + b \leq -1$$

Both cases are summarized by:

$$\forall i = 1, \ldots, N, \qquad y_i \left(\vec{w}.\vec{x}_i + b\right) \geq 1$$

# Finding the optimal hyperplane



Find $(\vec{w}, b)$ which minimize:

$$||\vec{w}||^2$$

under the constraints:

$$\forall i = 1, \ldots, N, \qquad y_i \left(\vec{w}.\vec{x}_i + b\right) - 1 \geq 0.$$

*This is a classical quadratic program on* $\mathbb{R}^{d+1}$.

## Lagrangian

In order to minimize:

$$\frac{1}{2}||\vec{w}||^2$$

under the constraints:

$$\forall i = 1, \ldots, N, \qquad y_i \left(\vec{w}.\vec{x}_i + b\right) - 1 \geq 0.$$

we introduce one dual variable $\alpha_i$ for each constraint, i.e., for each training point. The Lagrangian is:

$$L(\vec{w}, b, \vec{\alpha}) = \frac{1}{2}||\vec{w}||^2 - \sum_{i=1}^{N} \alpha_i \left( y_i \left(\vec{w}.\vec{x}_i + b\right) - 1 \right).$$

## Dual problem

Find $\alpha^* \in \mathbb{R}^N$ which maximizes

$$L(\vec{\alpha}) = \sum_{i=1}^{N} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{N} \alpha_i \alpha_j y_i y_j \vec{x}_i . \vec{x}_j ,$$

under the (simple) constraints $\alpha_i \geq 0$ (for $i = 1, \ldots, N$), and

$$\sum_{i=1}^{N} \alpha_i y_i = 0.$$

*This is a quadratic program on $\mathbb{R}^N$, with "box constraints". $\vec{\alpha}^*$ can be found efficiently using dedicated optimization softwares.*

## Recovering the optimal hyperplane

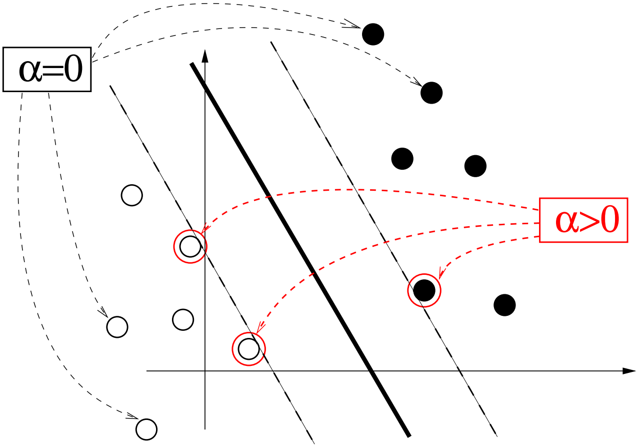
Once $\vec{\alpha}^*$ is found, we recover $(\vec{w}^*, b^*)$ corresponding to the optimal hyperplane. $w^*$ is given by:

$$\vec{w}^* = \sum_{i=1}^{N} \alpha_i \vec{x}_i,$$

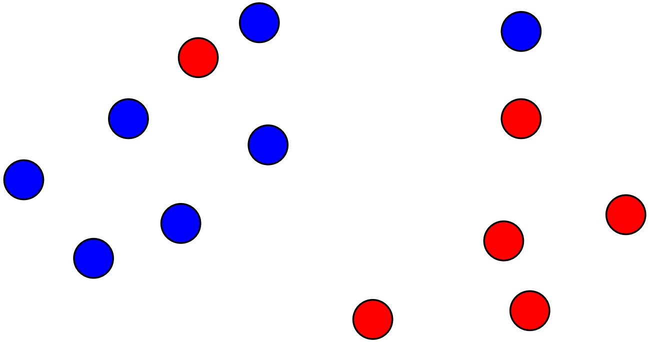
and the decision function is therefore:

$$\begin{aligned} f^*(\vec{x}) &= \vec{w}^*.\vec{x} + b^* \\ &= \sum_{i=1}^{N} \alpha_i \vec{x}_i.\vec{x} + b^*. \end{aligned} \tag{1}$$

## Interpretation: support vectors



## What if data are not linearly separable?



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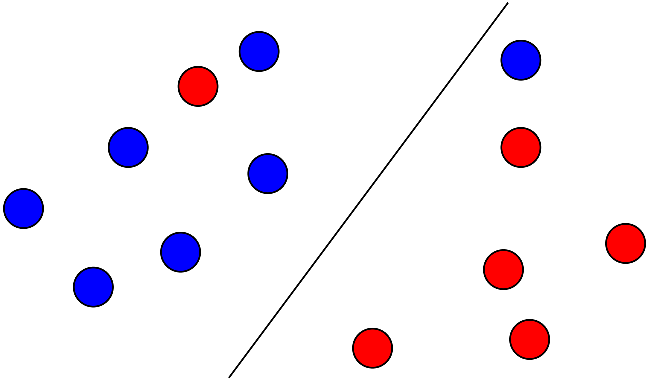

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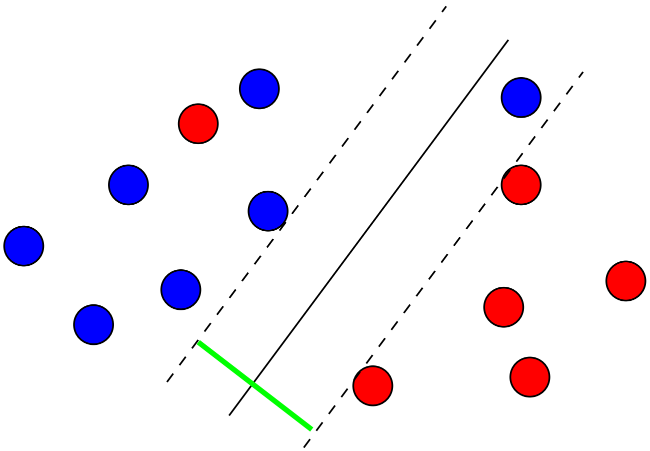

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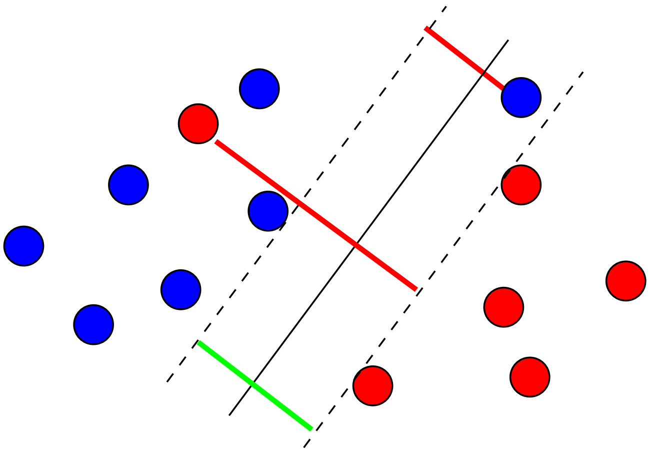
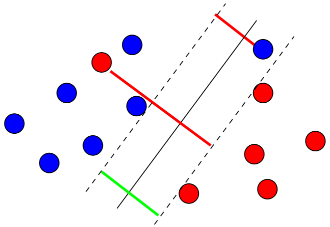


# Soft-margin SVM

- Find a trade-off between large margin and few errors.
- Mathematically:

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

- $C$ is a parameter



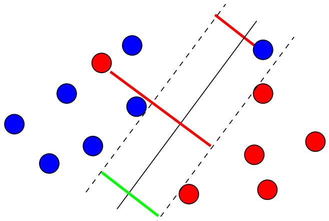
## Soft-margin SVM formulation

- The margin of a labeled point $(\vec{x}, y)$ is

$$margin(\vec{x}, y) = y\left(\vec{w}.\vec{x} + b\right)$$

- The error is
  - 0 if $margin(\vec{x}, y) > 1$,
  - $1 - margin(\vec{x}, y)$ otherwise.
- The soft margin SVM solves:

$$\min_{\vec{w},b}\left\{ ||\vec{w}||^2 + C\sum_{i=1}^{N}\max\left(0, 1 - y_i\left(\vec{w}.\vec{x}_i + b\right)\right)\right\}$$



## Dual formulation of soft-margin SVM

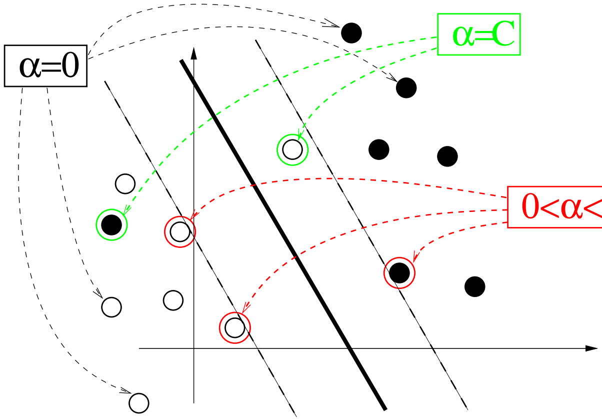
Maximize

$$L(\vec{\alpha}) = \sum_{i=1}^{N} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{N} \alpha_i \alpha_j y_i y_j \vec{x}_i . \vec{x}_j ,$$

under the constraints:

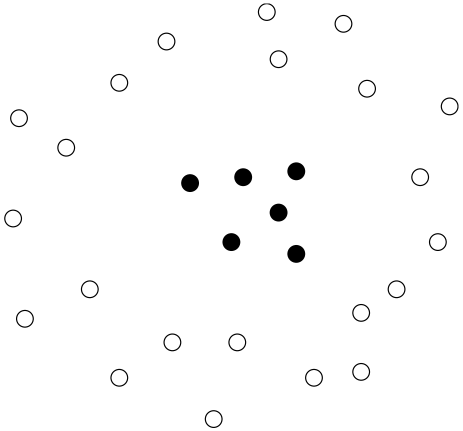
$$\begin{cases} 0 \leq \alpha_i \leq C, & \text{for } i = 1, \ldots, N \\ \sum_{i=1}^{N} \alpha_i y_i = 0. \end{cases}$$

## Interpretation: bounded and unbounded support vectors

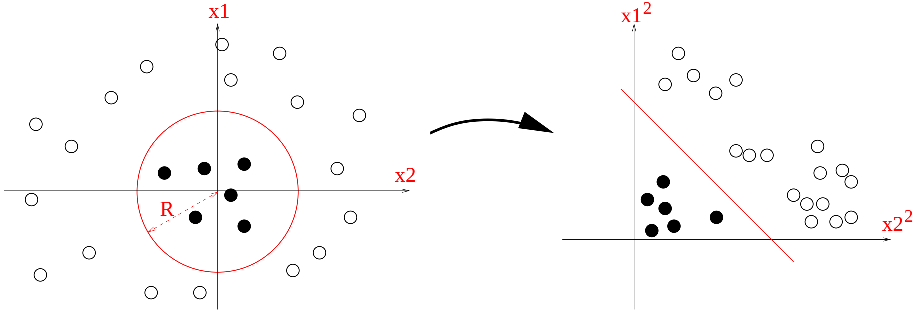


## Outline

## Sometimes linear classifiers are not interesting



## Solution: non-linear mapping to a feature space



Let $\vec{\Phi}(\vec{x}) = (x_1^2, x_2^2)'$, $\vec{w} = (1,1)'$ and $b = 1$. Then the decision function is:

$$f(\vec{x}) = x_1^2 + x_2^2 - R^2 = \vec{w}.\vec{\Phi}(\vec{x}) + b,$$

## Kernel (*simple but important*)

For a given mapping $\Phi$ from the space of objects $\mathcal{X}$ to some feature space, the kernel of two objects $x$ and $x'$ is the inner product of their images in the features space:

$$\forall x, x' \in \mathcal{X}, \quad \mathcal{K}(\S, \S') = \vec{\oplus}(\S).\vec{\oplus}(\S').$$

*Example: if* $\vec{\Phi}(\vec{x}) = (x_1^2, x_2^2)'$*, then*

$$K(\vec{x}, \vec{x}') = \vec{\Phi}(\vec{x}).\vec{\Phi}(\vec{x}') = (x_1)^2(x_1')^2 + (x_2)^2(x_2')^2.$$

## Training a SVM in the feature space

Replace each $\vec{x}.\vec{x}'$ in the SVM algorithm by $\vec{\Phi}(x).\vec{\Phi}(x') = K(x, x')$
The dual problem is to maximize

$$L(\vec{\alpha}) = \sum_{i=1}^{N} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{N} \alpha_i \alpha_j y_i y_j K(x_i, x_j),$$

under the constraints:

$$\begin{cases} 0 \leq \alpha_i \leq C, \quad \text{for } i = 1, \ldots, N \\ \sum_{i=1}^{N} \alpha_i y_i = 0. \end{cases}$$

## Predicting with a SVM in the feature space

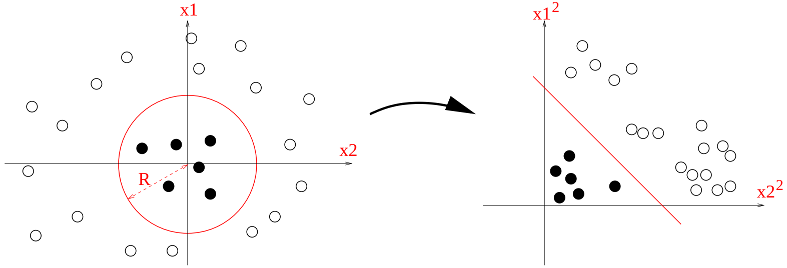
The decision function becomes:

$$
\begin{aligned}
f(x) &= \vec{w}^{*}.\vec{\Phi}(x) + b^{*} \\
&= \sum_{i=1}^{N} \alpha_i K(x_i, x) + b^{*}.
\end{aligned}
\tag{2}
$$

## The kernel trick

- The explicit computation of $\vec{\Phi}(x)$ is not necessary. The kernel $K(x, x')$ is enough. SVM work implicitly in the feature space.
- It is sometimes possible to easily compute kernels which correspond to complex large-dimensional feature spaces.

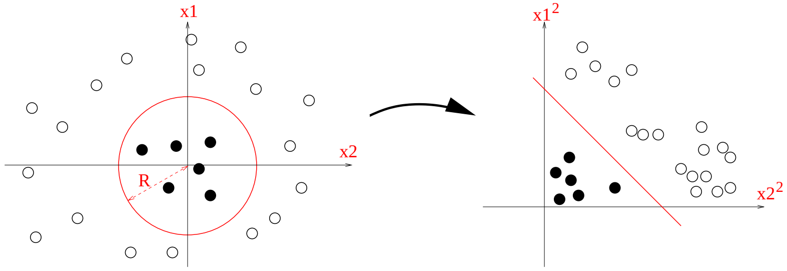
## Kernel example: polynomial kernel



For $\vec{x} = (x_1, x_2)^\top \in \mathbb{R}^2$, let $\vec{\Phi}(\vec{x}) = (x_1^2, \sqrt{2}x_1x_2, x_2^2) \in \mathbb{R}^3$:

$$\begin{aligned}
K(\vec{x}, \vec{x}') &= x_1^2 x_1'^2 + 2x_1x_2x_1'x_2' + x_2^2 x_2'^2 \\
&= \left(x_1x_1' + x_2x_2'\right)^2 \\
&= \left(\vec{x}.\vec{x}'\right)^2 .
\end{aligned}$$

# Kernel example: polynomial kernel



More generally,

$$K(\vec{x}, \vec{x}') = \left(\vec{x}.\vec{x}' + 1\right)^d$$

is an inner product in a feature space of all monomials of degree up to $d$ *(left as exercice.)*

## Which functions $K(x, x')$ are kernels?

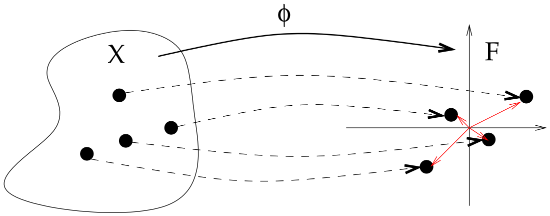
**Definition**

A function $K(x, x')$ defined on a set $\mathcal{X}$ is a kernel if and only if there exists a features space (Hilbert space) $\mathcal{H}$ and a mapping

$$\Phi : \mathcal{X} \mapsto \mathcal{H} \,,$$

such that, for any $\mathbf{x}, \mathbf{x}'$ in $\mathcal{X}$:

$$K\left(\mathbf{x}, \mathbf{x}'\right) = \left\langle \Phi\left(\mathbf{x}\right), \Phi\left(\mathbf{x}'\right)\right\rangle_{\mathcal{H}} \,.$$



## Positive Definite (p.d.) functions

### Definition

A positive definite (p.d.) function on the set $\mathcal{X}$ is a function $K : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$ symmetric:

$$\forall \left(\mathbf{x}, \mathbf{x}'\right) \in \mathcal{X}^2, \quad K\left(\mathbf{x}, \mathbf{x}'\right) = K\left(\mathbf{x}', \mathbf{x}\right),$$

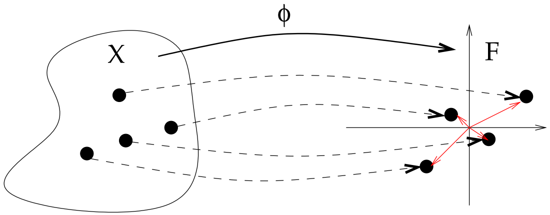
and which satisfies, for all $N \in \mathbb{N}$, $(\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_N) \in \mathcal{X}^N$ et $(a_1, a_2, \ldots, a_N) \in \mathbb{R}^N$:

$$\sum_{i=1}^{N} \sum_{j=1}^{N} a_i a_j K\left(\mathbf{x}_i, \mathbf{x}_j\right) \geq 0.$$

## Kernels are p.d. functions

**Theorem (Aronszajn, 1950)**

*$K$ is a kernel if and only if it is a positive definite function.*



## Proof?

- Kernel $\implies$ p.d. function:
    - $\left\langle \Phi\left(\mathbf{x}\right), \Phi\left(\mathbf{x}'\right)\right\rangle_{\mathbb{R}^d} = \left\langle \Phi\left(\mathbf{x}'\right), \Phi\left(\mathbf{x}\right)_{\mathbb{R}^d}\right\rangle$ ,
    - $\sum_{i=1}^{N}\sum_{j=1}^{N} a_i a_j \left\langle \Phi\left(\mathbf{x}_i\right), \Phi\left(\mathbf{x}_j\right)\right\rangle_{\mathbb{R}^d} = \| \sum_{i=1}^{N} a_i \Phi\left(\mathbf{x}_i\right) \|_{\mathbb{R}^d}^2 \geq 0$ .
- P.d. function $\implies$ kernel: more difficult...

## Kernel examples

- Polynomial (on $\mathbb{R}^d$):

$$K(x, x') = (x.x' + 1)^d$$

- Gaussian radial basis function (on $\mathbb{R}^d$)

$$K(x, x') = \exp\left(-\frac{||x - x'||^2}{2\sigma^2}\right)$$

- Laplace kernel (on $\mathbb{R}$)

$$K(x, x') = \exp\left(-\gamma|x - x'|\right)$$

- Min kernel (on $\mathbb{R}_+$)

$$K(x, x') = \min(x, x')$$

*Exercice: for each kernel, find a Hilbert space $\mathcal{H}$ and a mapping $\Phi : \mathcal{X} \to \mathcal{H}$ such that $K(x, x') = \langle \Phi(x), \Phi(x') \rangle$*

## Example: SVM with a Gaussian kernel

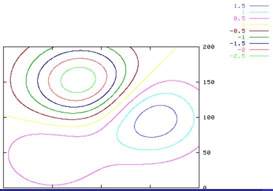
- Training:

$$\min_{\alpha\in\mathbb{R}^N} \sum_{i=1}^{N} \alpha_i - \frac{1}{2}\sum_{i,j=1}^{N} \alpha_i\alpha_j y_i y_j \exp\left(-\frac{||\vec{x}_i - \vec{x}_j||^2}{2\sigma^2}\right)$$

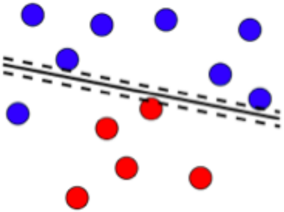
$$\text{s.t. } 0 \leq \alpha_i \leq C, \quad \text{and } \sum_{i=1}^{N} \alpha_i y_i = 0.$$

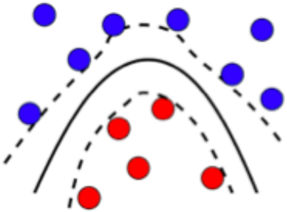
- Prediction

$$f(\vec{x}) = \sum_{i=1}^{N} \alpha_i \exp\left(-\frac{||\vec{x} - \vec{x}_i||^2}{2\sigma^2}\right)$$

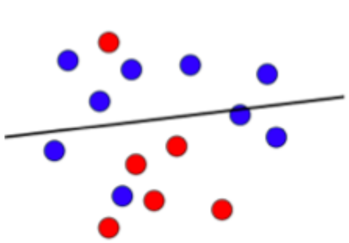


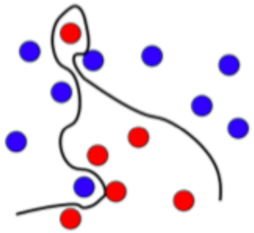
## Linear vs nonlinear SVM

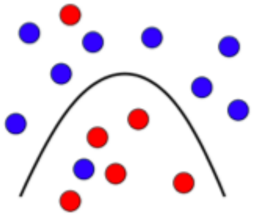




# Regularity vs data fitting trade-off



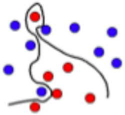




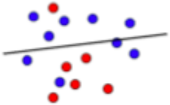
## $C$ controls the trade-off

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

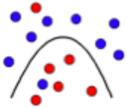
- Large C :
  - makes few errors



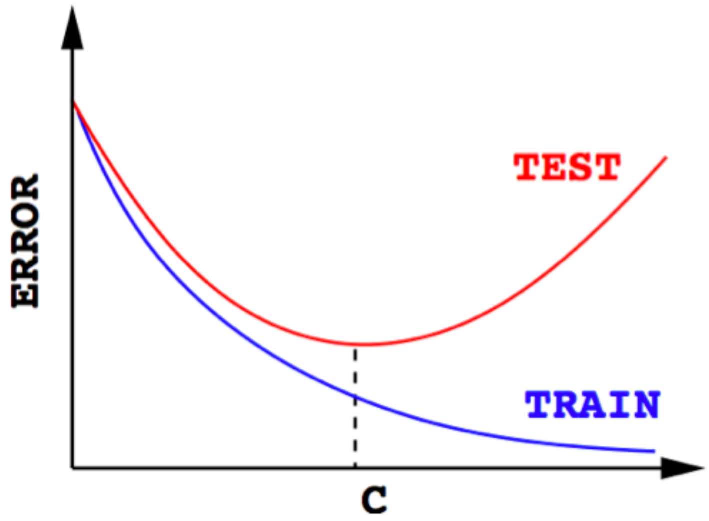
- Small C :
  - ensure a large margin



- Intermediate C:
  - finds a trade-off



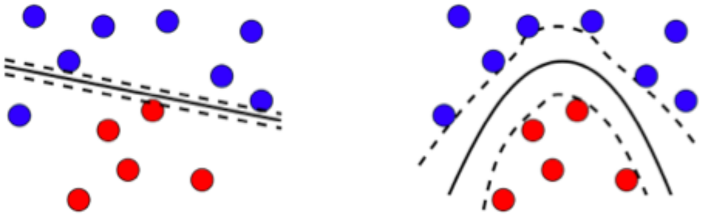
## Why it is important to control the trade-off



## How to choose $C$ in practice

- Split your dataset in two ("train" and "test")
- Train SVM with different $C$ on the "train" set
- Compute the accuracy of the SVM on the "test" set
- Choose the $C$ which minimizes the "test" error
- (you may repeat this several times = cross-validation)

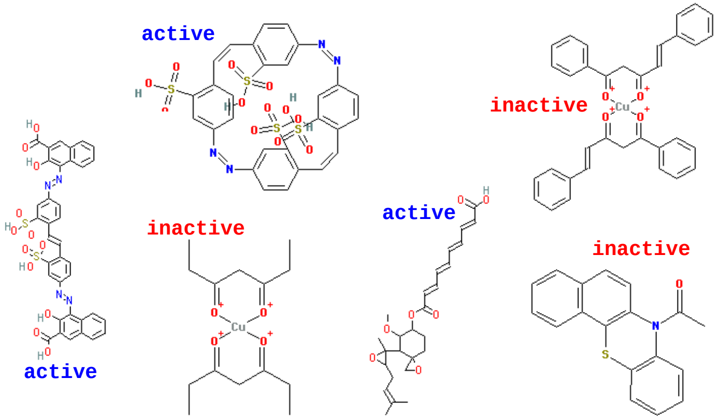
## SVM summary



- Large margin
- Linear or nonlinear (with the kernel trick)
- Control of the regularization / data fitting trade-off with $C$

## Outline

# Virtual screening for drug discovery



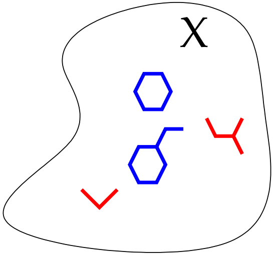
*NCI AIDS screen results (from http://cactus.nci.nih.gov).*

## Classification with SVM

1. Represent each graph $x$ by a vector $\Phi(x) \in \mathcal{H}$, either explicitly or implicitly through the kernel

$$K(x, x') = \Phi(x)^\top \Phi(x') .$$

2. Use a linear method for classification in $\mathcal{H}$.



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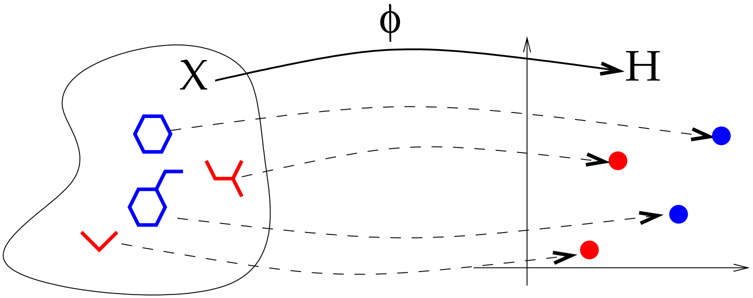

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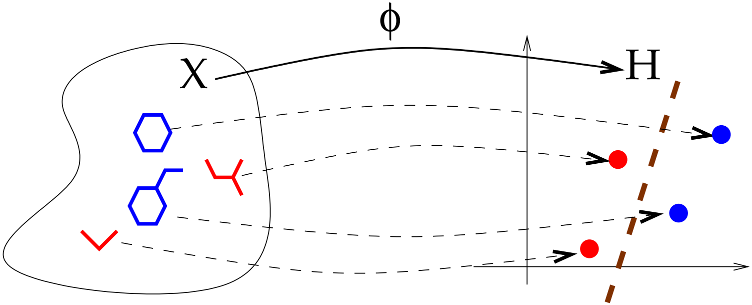
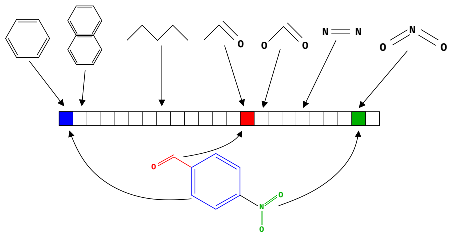


## Example: indexing by substructures

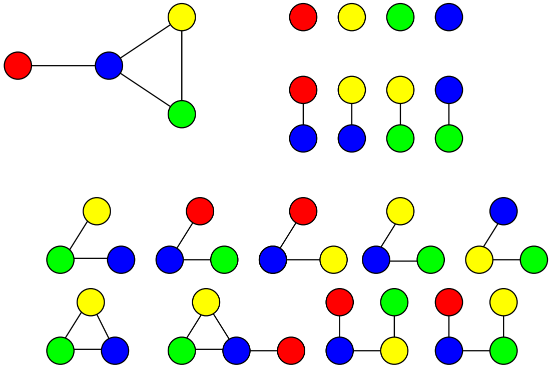


- Often we believe that the presence substructures are important predictive patterns
- Hence it makes sense to represent a graph by features that indicate the presence (or the number of occurrences) of particular substructures
- However, detecting the presence of particular substructures may be computationally challenging...

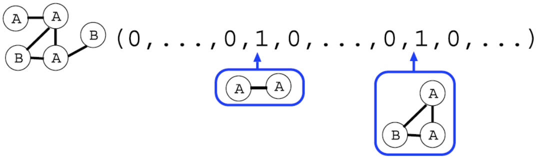
## Subgraphs

**Definition**

A subgraph of a graph $(V, E)$ is a connected graph $(V', E')$ with $V' \subset V$ and $E' \subset E$.



## Indexing by all subgraphs?



**Theorem**

1. *Computing all subgraph occurrences is NP-hard.*
2. *Computing the subgraph kernel is NP-hard.*

**Proof.**

1. Finding an occurrence of the linear path of size *n* is finding a Hamiltonian path, which is NP-complete.
2. Similarly, if we can compute the subgraph kernel then we can deduce the presence of a Hamiltonian path (left as exercice).

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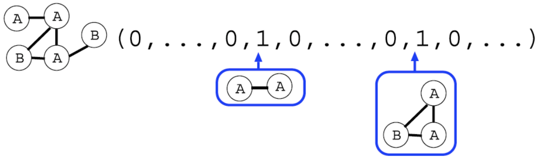

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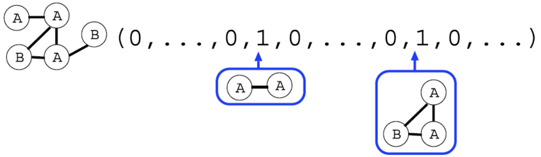

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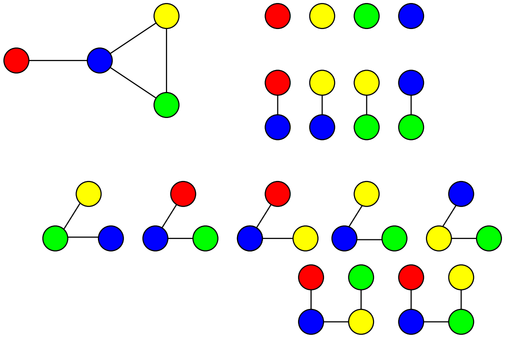
□

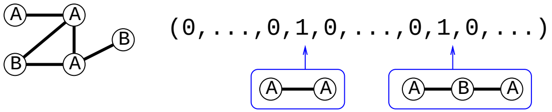
## Paths

### Definition

- A path of a graph $(V, E)$ is sequence of distinct vertices $v_1, \ldots, v_n \in V$ $(i \neq j \implies v_i \neq v_j)$ such that $(v_i, v_{i+1}) \in E$ for $i = 1, \ldots, n-1$.
- Equivalently the paths are the linear subgraphs.



# Indexing by all paths?



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2. *Computing the path kernel is NP-hard*

**Proof.**

Same as for subgraphs. □

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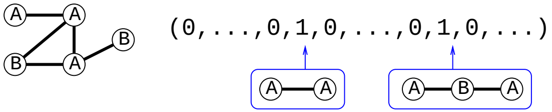

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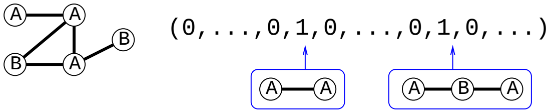

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2. *Computing the path kernel is NP-hard*

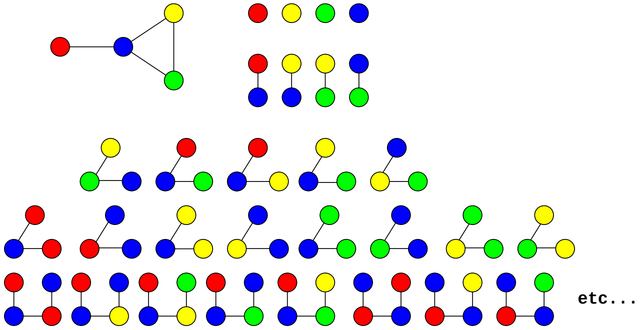
**Proof.**

Same as for subgraphs. □

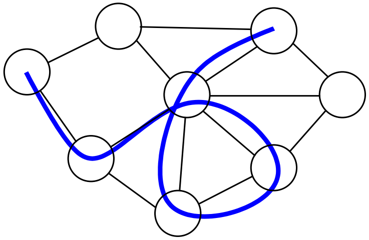
## Walks

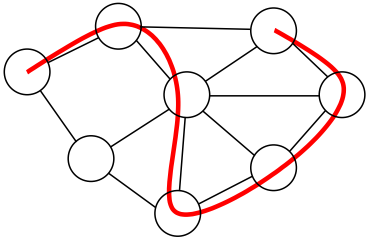
### Definition

- A walk of a graph $(V, E)$ is sequence of $v_1, \ldots, v_n \in V$ such that $(v_i, v_{i+1}) \in E$ for $i = 1, \ldots, n-1$.
- We note $\mathcal{W}_n(G)$ the set of walks with $n$ vertices of the graph $G$, and $\mathcal{W}(G)$ the set of all walks.



# Walks ≠ paths





# Walk kernel

## Definition

- Let $\mathcal{S}_n$ denote the set of all possible label sequences of walks of length $n$ (including vertices and edges labels), and $\mathcal{S} = \cup_{n \geq 1} \mathcal{S}_n$.
- For any graph $\mathcal{X}$ let a weight $\lambda_G(w)$ be associated to each walk $w \in \mathcal{W}(G)$.
- Let the feature vector $\Phi(G) = (\Phi_s(G))_{s \in \mathcal{S}}$ be defined by:

$$\Phi_s(G) = \sum_{w \in \mathcal{W}(G)} \lambda_G(w) \mathbf{1}\,(s \text{ is the label sequence of } w) \,.$$

- A walk kernel is a graph kernel defined by:

$$K_{walk}(G_1, G_2) = \sum_{s \in \mathcal{S}} \Phi_s(G_1)\Phi_s(G_2) \,.$$

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# Walk kernel examples

## Examples

- The *n*th-order walk kernel is the walk kernel with $\lambda_G(w) = 1$ if the length of $w$ is $n$, 0 otherwise. It compares two graphs through their common walks of length $n$.
- The random walk kernel is obtained with $\lambda_G(w) = P_G(w)$, where $P_G$ is a Markov random walk on $G$. In that case we have:

$$K(G_1, G_2) = P(label(W_1) = label(W_2)) \, ,$$

  where $W_1$ and $W_2$ are two independant random walks on $G_1$ and $G_2$, respectively (Kashima et al., 2003).
- The geometric walk kernel is obtained (when it converges) with $\lambda_G(w) = \beta^{length(w)}$, for $\beta > 0$. In that case the feature space is of infinite dimension (Gärtner et al., 2003).

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## Computation of walk kernels

**Proposition**

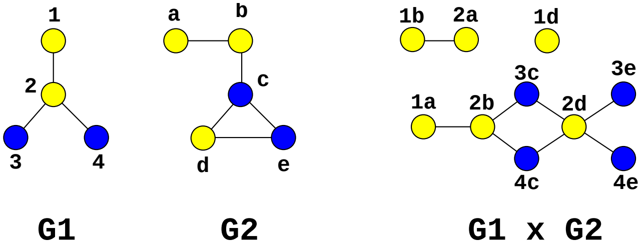
These three kernels (*n*th-order, random and geometric walk kernels) can be computed efficiently in polynomial time.

## Product graph

**Definition**

Let $G_1 = (V_1, E_1)$ and $G_2 = (V_2, E_2)$ be two graphs with labeled vertices. The product graph $G = G_1 \times G_2$ is the graph $G = (V, E)$ with:

1. $V = \{(v_1, v_2) \in V_1 \times V_2 \; : \; v_1 \text{ and } v_2 \text{ have the same label}\}$ ,
2. $E = \left\{ \left( (v_1, v_2), (v_1', v_2') \right) \in V \times V \; : \; (v_1, v_1') \in E_1 \text{ and } (v_2, v_2') \in E_2 \right\}$.



## Walk kernel and product graph

**Lemma**

There is a bijection between:

1. The pairs of walks $w_1 \in \mathcal{W}_n(G_1)$ and $w_2 \in \mathcal{W}_n(G_2)$ with the same label sequences,
2. The walks on the product graph $w \in \mathcal{W}_n(G_1 \times G_2)$.

**Corollary**

$$\begin{aligned}
K_{walk}(G_1, G_2) &= \sum_{s \in \mathcal{S}} \Phi_s(G_1)\Phi_s(G_2) \\
&= \sum_{(w_1, w_2) \in \mathcal{W}(G_1) \times \mathcal{W}(G_1)} \lambda_{G_1}(w_1)\lambda_{G_2}(w_2)\mathbf{1}(l(w_1) = l(w_2)) \\
&= \sum_{w \in \mathcal{W}(G_1 \times G_2)} \lambda_{G_1 \times G_2}(w) \, .
\end{aligned}$$

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### Corollary

$$\begin{aligned} K_{walk}(G_1, G_2) &= \sum_{s \in \mathcal{S}} \Phi_s(G_1)\Phi_s(G_2) \\ &= \sum_{(w_1,w_2)\in\mathcal{W}(G_1)\times\mathcal{W}(G_1)} \lambda_{G_1}(w_1)\lambda_{G_2}(w_2)\mathbf{1}(l(w_1) = l(w_2)) \\ &= \sum_{w\in\mathcal{W}(G_1\times G_2)} \lambda_{G_1\times G_2}(w)\,. \end{aligned}$$

## Computation of the *n*th-order walk kernel

- For the *n*th-order walk kernel we have $\lambda_{G_1 \times G_2}(w) = 1$ if the length of $w$ is $n$, 0 otherwise.
- Therefore:

$$K_{nth-order}(G_1, G_2) = \sum_{w \in \mathcal{W}_n(G_1 \times G_2)} 1 .$$

- Let $A$ be the adjacency matrix of $G_1 \times G_2$. Then we get:

$$K_{nth-order}(G_1, G_2) = \sum_{i,j} [A^n]_{i,j} = \mathbf{1}^\top A^n \mathbf{1} .$$

- Computation in $O(n|G_1||G_2|d_1 d_2)$, where $d_i$ is the maximum degree of $G_i$.

## Computation of random and geometric walk kernels

- In both cases $\lambda_G(w)$ for a walk $w = v_1 \dots v_n$ can be decomposed as:

$$\lambda_G(v_1 \dots v_n) = \lambda^i(v_1) \prod_{i=2}^{n} \lambda^t(v_{i-1}, v_i) .$$

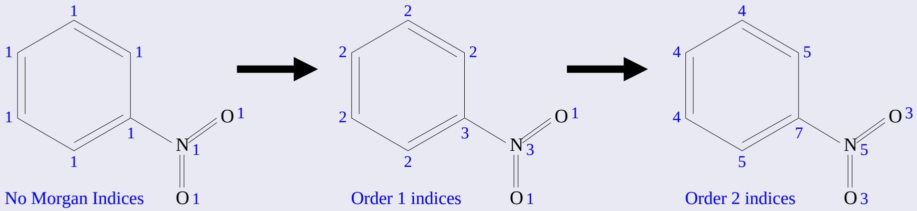
- Let $\Lambda_i$ be the vector of $\lambda^i(v)$ and $\Lambda_t$ be the matrix of $\lambda^t(v, v')$:

$$\begin{aligned} K_{walk}(G_1, G_2) &= \sum_{n=1}^{\infty} \sum_{w \in \mathcal{W}_n(G_1 \times G_2)} \lambda^i(v_1) \prod_{i=2}^{n} \lambda^t(v_{i-1}, v_i) \\ &= \sum_{n=0}^{\infty} \Lambda_i \Lambda_t^n \mathbf{1} \\ &= \Lambda_i \left(I - \Lambda_t\right)^{-1} \mathbf{1} \end{aligned}$$

- Computation in $O(|G_1|^3 |G_2|^3)$

## Extensions 1: label enrichment

### Atom relabebling with the Morgan index

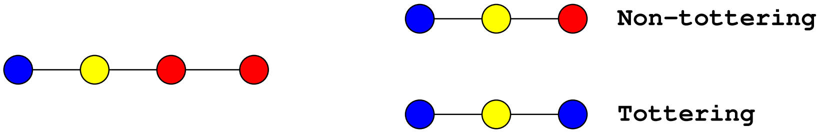


- Compromise between fingerprints and structural keys features.
- Other relabeling schemes are possible (graph coloring).
- Faster computation with more labels (less matches implies a smaller product graph).

## Extension 2: Non-tottering walk kernel

### Tottering walks

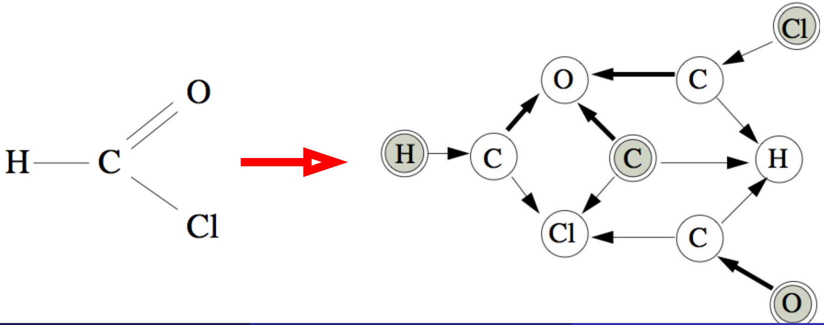
A tottering walk is a walk $w = v_1 \dots v_n$ with $v_i = v_{i+2}$ for some $i$.



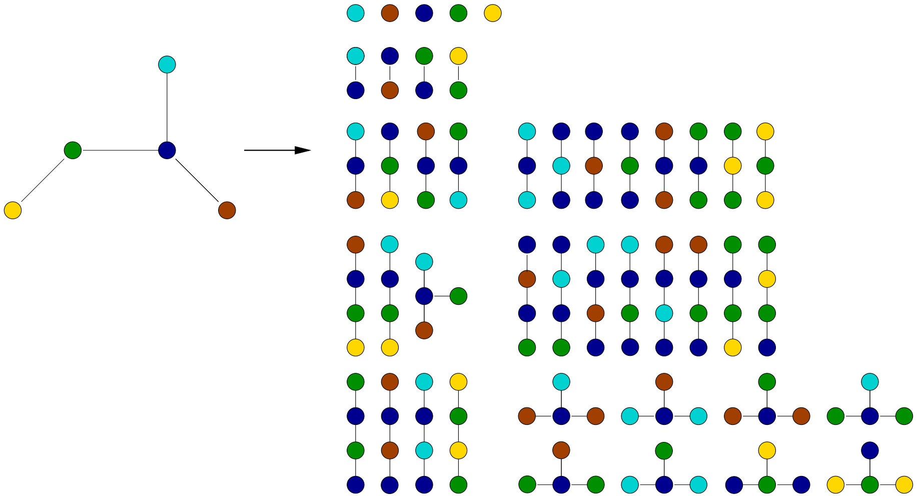
- Tottering walks seem irrelevant for many applications
- Focusing on non-tottering walks is a way to get closer to the path kernel (e.g., equivalent on trees).

## Computation of the non-tottering walk kernel (Mahé et al., 2005)

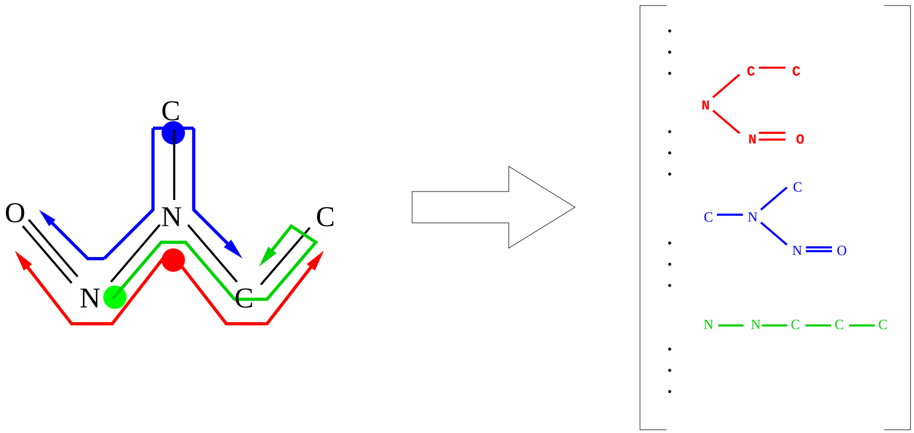
- Second-order Markov random walk to prevent tottering walks
- Written as a first-order Markov random walk on an augmented graph
- Normal walk kernel on the augmented graph (which is always a directed graph).



## Extension 3: Subtree kernels



## Example: Tree-like fragments of molecules



## Computation of the subtree kernel

- Like the walk kernel, amounts to compute the (weighted) number of subtrees in the product graph.
- Recursion: if $\mathcal{T}(v, n)$ denotes the weighted number of subtrees of depth $n$ rooted at the vertex $v$, then:

$$\mathcal{T}(v, n+1) = \sum_{R \subset \mathcal{N}(v)} \prod_{v' \in R} \lambda_t(v, v')\mathcal{T}(v', n)\,,$$

  where $\mathcal{N}(v)$ is the set of neighbors of $v$.
- Can be combined with the non-tottering graph transformation as preprocessing to obtain the non-tottering subtree kernel.

## Application in chemoinformatics (Mahé et al., 2004)

### MUTAG dataset

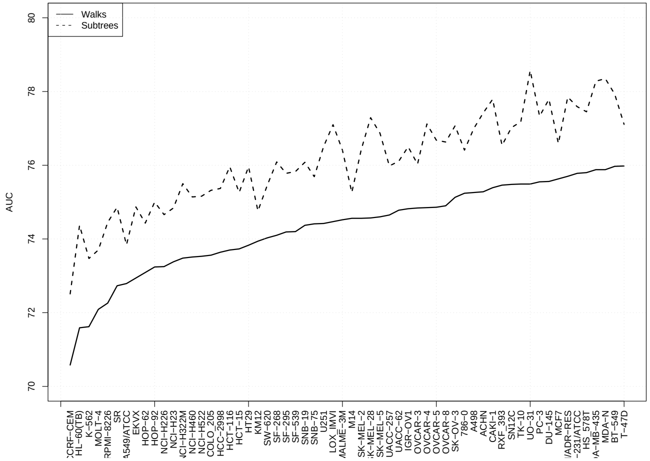
- aromatic/hetero-aromatic compounds
- high mutagenic activity /no mutagenic activity, assayed in *Salmonella typhimurium*.
- 188 compouunds: 125 + / 63 -

### Results

10-fold cross-validation accuracy

| Method | Accuracy |
|---|---|
| Progol1 | 81.4% |
| 2D kernel | 91.2% |

## 2D Subtree vs walk kernels (Mahé and V., 2009)



Screening of inhibitors for 60 cancer cell lines.

## Summary: graph kernels

### What we saw

- Kernels do not allow to overcome the NP-hardness of subgraph patterns
- They allow to work with approximate subgraphs (walks, subtrees), in infinite dimension, thanks to the kernel trick
- They give state-of-the-art results

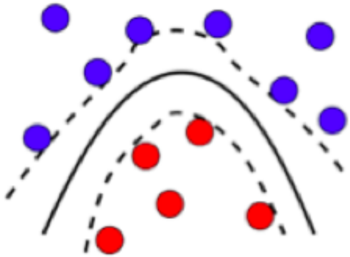
## Outline

## Machine learning in computational biology

- Biology faces a flood of data following the development of high-throughput technologies (sequencing, DNA chips, ...)
- Many problems can be formalized in the framework of machine learning, e.g.:
  - Diagnosis, prognosis
  - Protein annotation
  - Drug discovery, virtual screening
- These data have often complex structures (strings, graphs, high-dimensional vectors) and often require dedicated algorithms.

## Support vector machines (SVM)

- A general-purpose algorithm for pattern recognition
- Based on the principle of large margin *("séparateur à vaste marge")*
- Linear or nonlinear with the kernel trick
- Control of the regularization / data fitting trade-off with the $C$ parameter
- State-of-the-art performance on many applications



## Kernels

- A central ingredient of SVM
- Allows nonlinearity
- Allows to work implicitly in a high-dimensional feature space
- Allows to work with structured data (e.g., graphs)