Kernel Methods for QSAR and Virtual Screening

Jean-Philippe Vert
Jean-Philippe.Vert@ensmp.fr

Center for Computational Biology
Ecole des Mines de Paris, ParisTech

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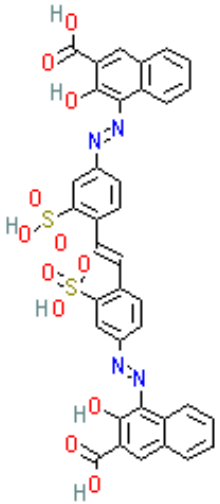
Ligand-Based Virtual Screening and QSAR



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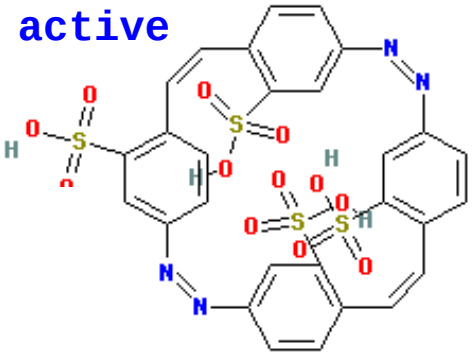

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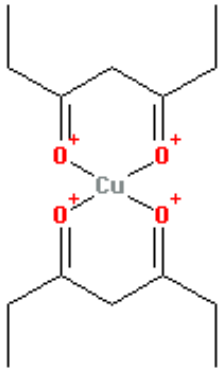

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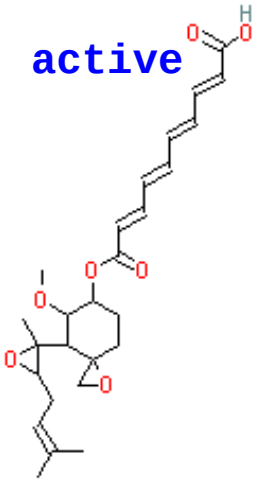

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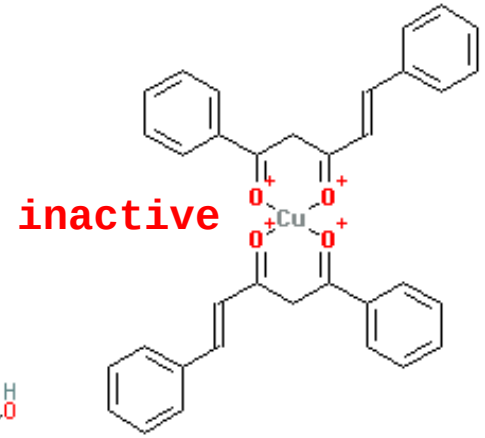

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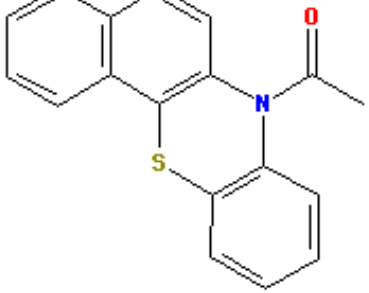


NCI AIDS screen results (from http://cactus.nci.nih.gov).

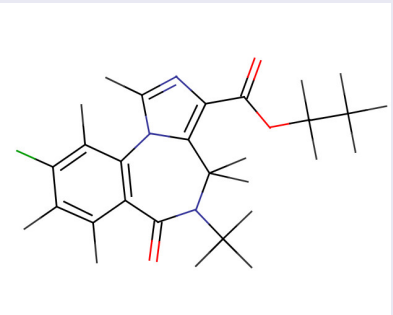
More formally...

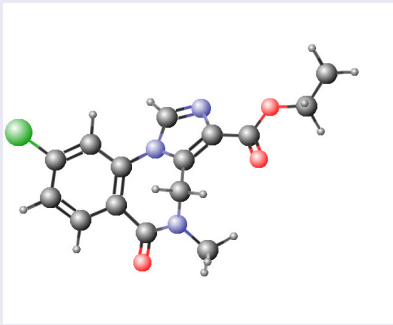
Objective

Build models to predict biochemical properties Y of small molecules from their structures X, using a training set of (X, Y) pairs.

Structures X

$C_{15}H_{14}ClN_3O_3$





Properties Y

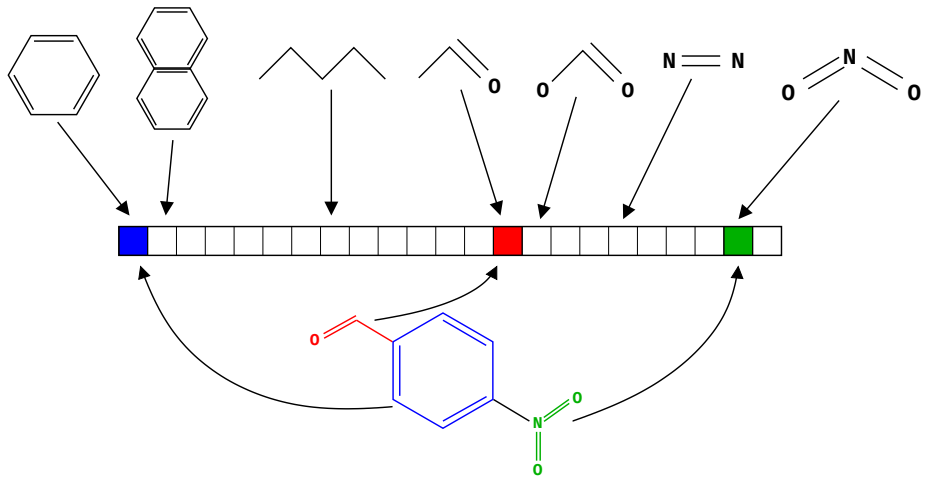
- binding to a therapeutic target,
- pharmacokinetics (ADME),
- toxicity...

Classical approaches

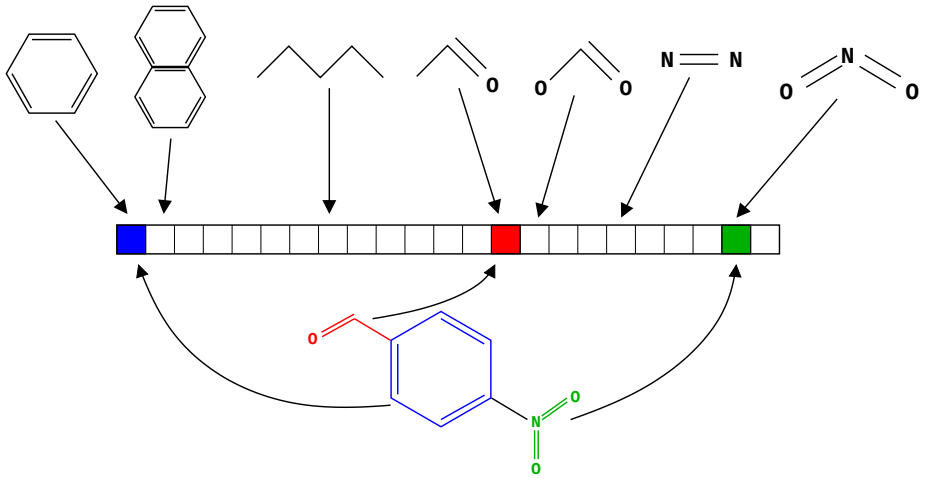
Two steps

1. Map each molecule to a vector of fixed dimension using molecular descriptors
   - Global properties of the molecules (mass, logP...)
   - 2D and 3D descriptors (substructures, fragments, ...)
2. Apply an algorithm for regression or pattern recognition.
   - PLS, ANN, ...

Example: 2D structural keys



Which descriptors?



Difficulties

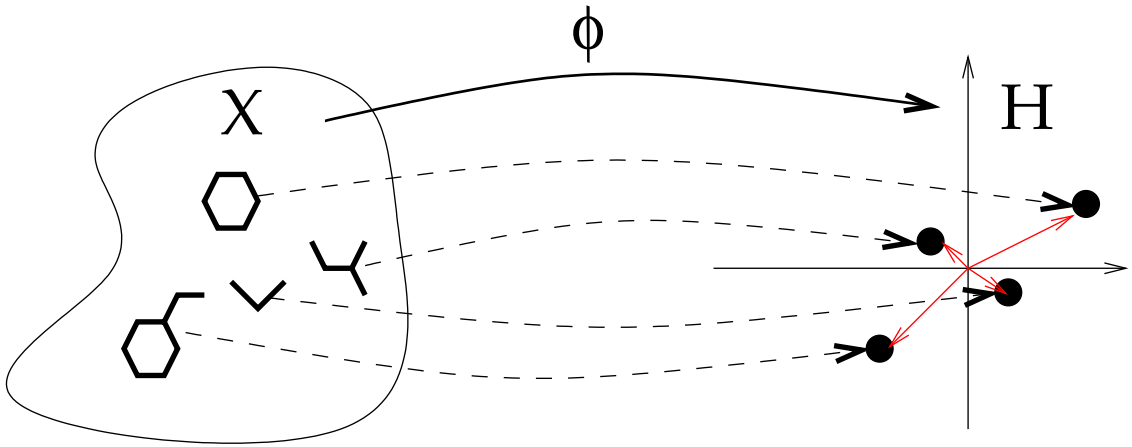
- Many descriptors are needed to characterize various features (in particular for 2D and 3D descriptors)
- But too many descriptors are harmful for memory storage, computation speed, statistical estimation

Kernels

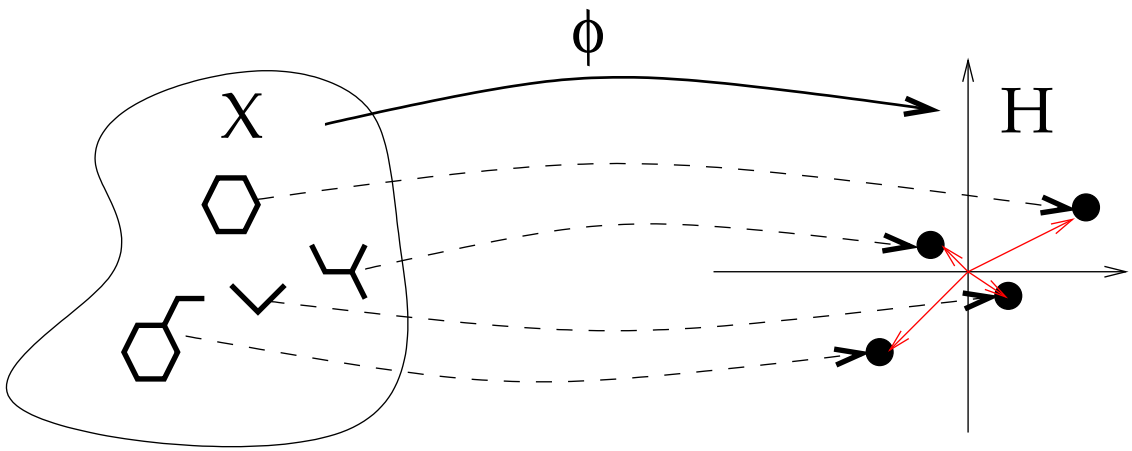
Definition

- Let $\Phi(x) = (\Phi_1(x), \ldots, \Phi_p(x))$ be a vector representation of the molecule x
- The kernel between two molecules is defined by:

$$K(x, x') = \Phi(x)^\top \Phi(x') = \sum_{i=1}^{p} \Phi_i(x) \Phi_i(x') \,.$$



The kernel trick



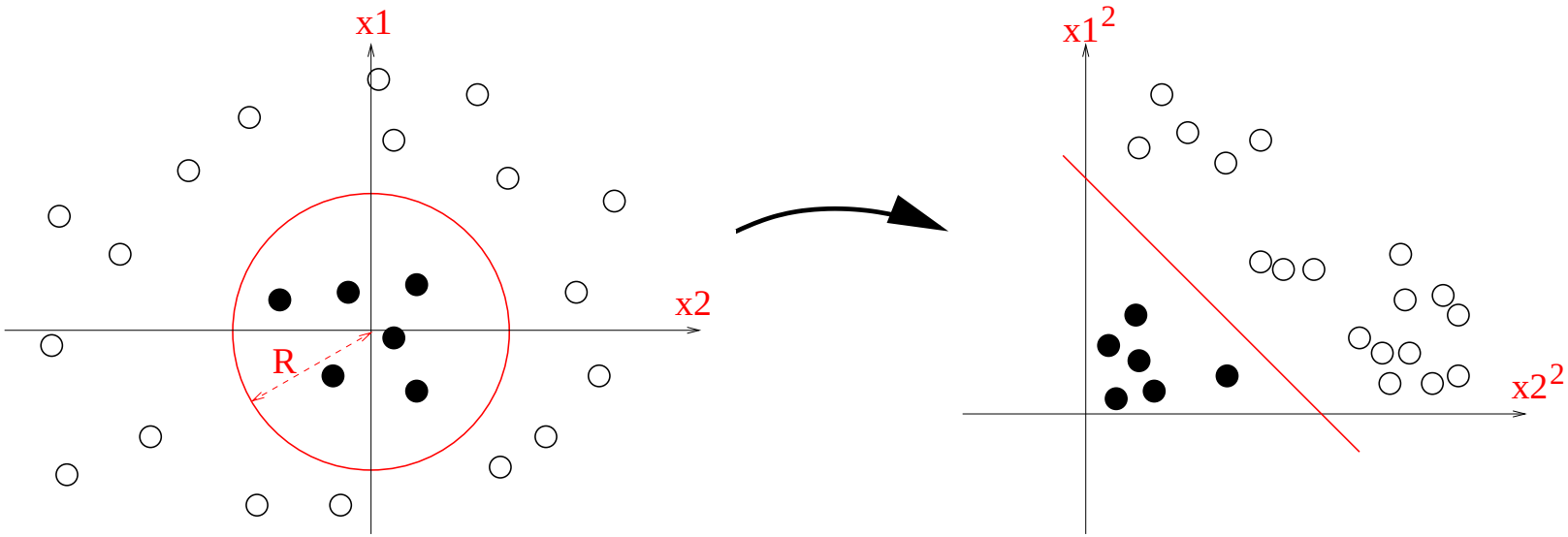
The trick

1. Computing the kernel $K(x, x')$ is often more efficient than computing $\Phi(x)$, especially in high or infinite dimensions! Ex:

$$K(x, x') = \exp\left(-\gamma \| x - x' \|^2\right) .$$

2. Many linear algorithms for regression or pattern recognition can be expressed only in terms of kernels.

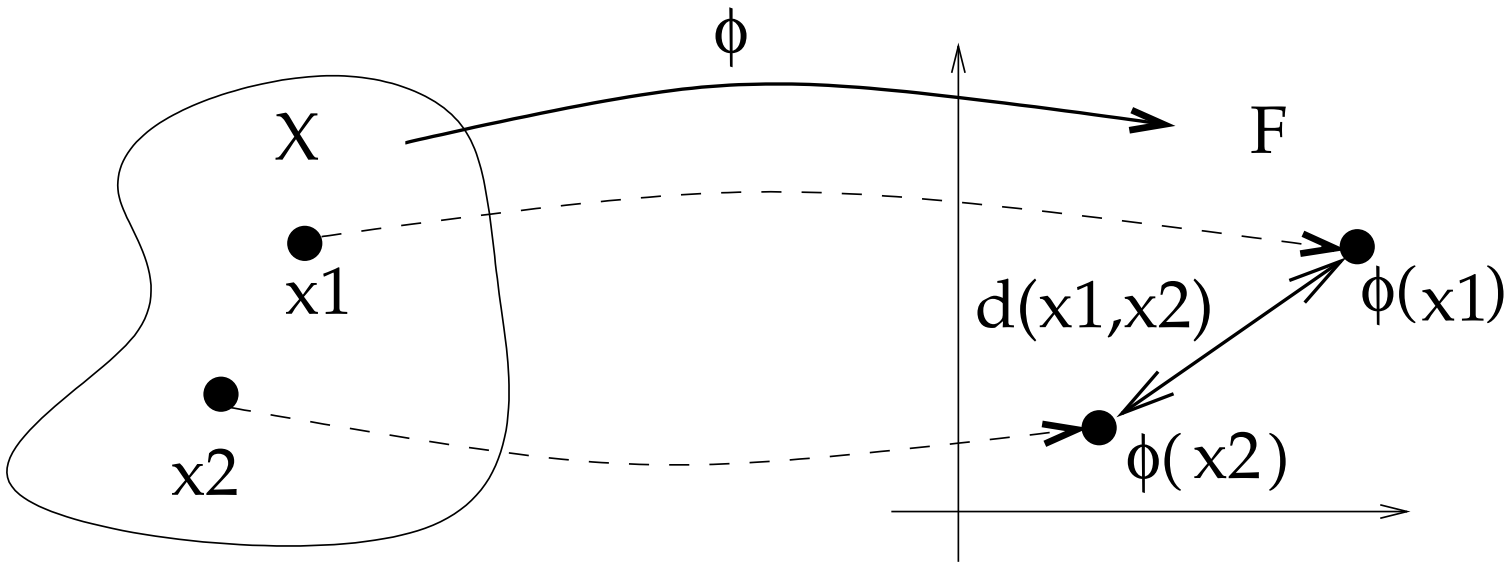
Kernel example: polynomial kernel



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

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

Kernel trick example: computing distances in the feature space



$$
\begin{aligned}
d_K(\mathbf{x}_1, \mathbf{x}_2)^2 &= \| \Phi(\mathbf{x}_1) - \Phi(\mathbf{x}_2) \|_{\mathcal{H}}^2 \\
&= \langle \Phi(\mathbf{x}_1) - \Phi(\mathbf{x}_2), \Phi(\mathbf{x}_1) - \Phi(\mathbf{x}_2) \rangle_{\mathcal{H}} \\
&= \langle \Phi(\mathbf{x}_1), \Phi(\mathbf{x}_1) \rangle_{\mathcal{H}} + \langle \Phi(\mathbf{x}_2), \Phi(\mathbf{x}_2) \rangle_{\mathcal{H}} - 2 \langle \Phi(\mathbf{x}_1), \Phi(\mathbf{x}_2) \rangle_{\mathcal{H}}
\end{aligned}
$$

$$
d_K(\mathbf{x}_1, \mathbf{x}_2)^2 = K(\mathbf{x}_1, \mathbf{x}_1) + K(\mathbf{x}_2, \mathbf{x}_2) - 2K(\mathbf{x}_1, \mathbf{x}_2)
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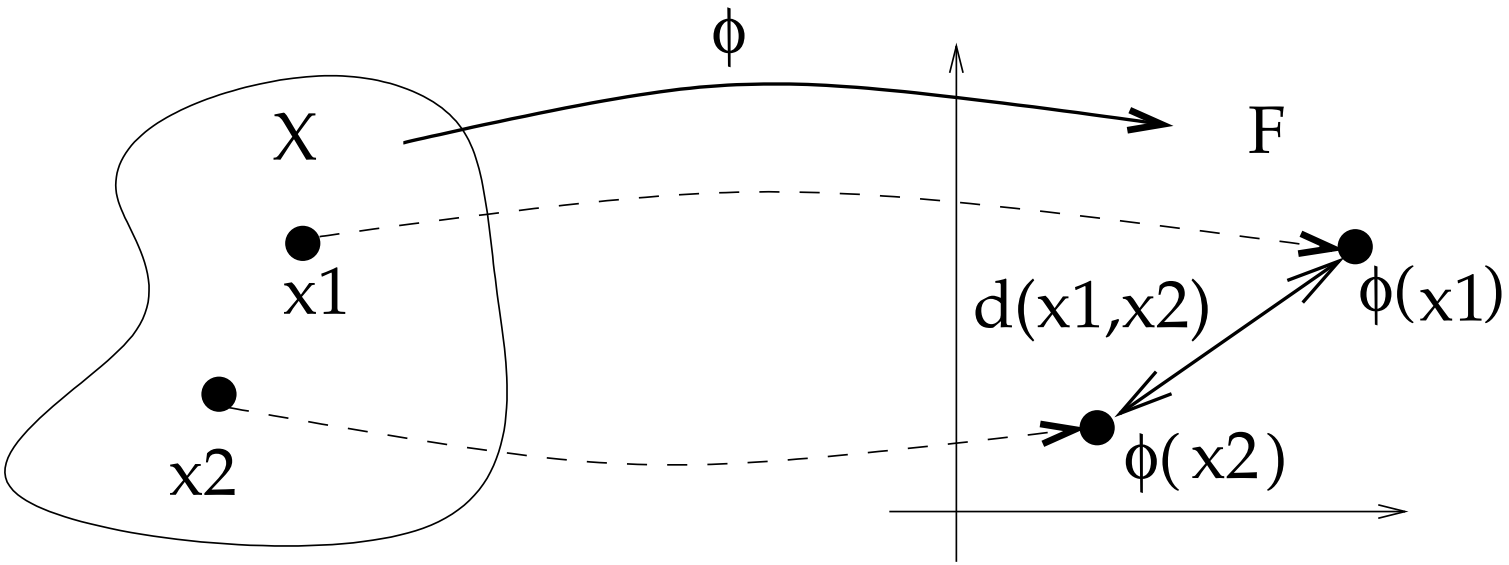
Kernel trick example: computing distances in the feature space



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$$

Other algorithms

Kernel methods

You don't like nearest-neighbor classification, or your problem is not binary classification, but you would like to benefit from the kernel trick (nonlinearity, structured data etc...)? Try other kernel methods that extend your favorite algorithm to handle kernels:

- Support Vector Machines,
- kernel PLS,
- kernel PCA,
- kriging,
- kernel perceptron,
- kernel logistic regression,
- and many more!

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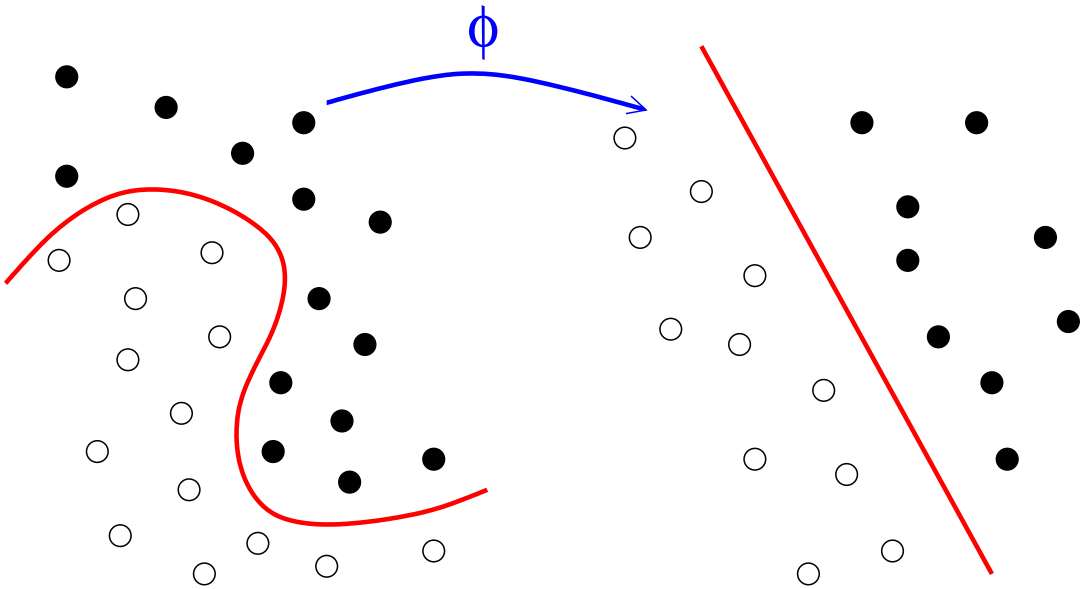
Example: Support Vector Machine



$$\text{minimize} \quad \sum_{i=1}^{n}\sum_{j=1}^{n} \alpha_i \alpha_j K(x_i, x_j) - \sum_{i=1}^{n} \alpha_i$$

$$\text{subject to} \quad 0 \leq \alpha_i \leq C, \quad i = 1, \ldots, n \,,$$

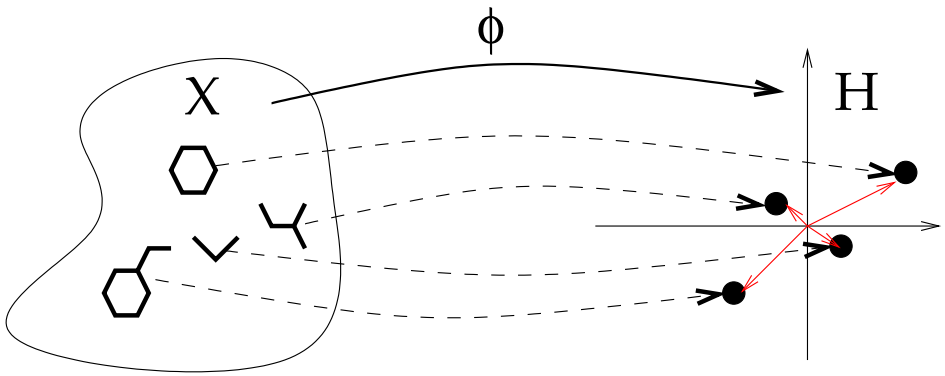
$$\sum_{i=1}^{n} \alpha_i y_i = 0 \,.$$

Making kernels for molecules

- Strategy 1: use well-known molecular descriptors to represent molecules m as vectors $\Phi(m)$, and then use kernels for vectors, e.g.:

$$K(m_1, m_2) = \Phi(m_1)^\top \Phi(m_2).$$

- Strategy 2: invent new kernels to do things you can not do with strategy 1, such as using an infinite number of descriptors. We will now see two examples of this strategy, extending 2D and 3D molecular descriptors.



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Summary

The problem

- Regression and pattern recognition over molecules
- Classical vector representation is both statistically and computationally challenging

The kernel approach

By defining a kernel for molecules we can work implicitly in large (potentially infinite!) dimensions:

- Allows to consider a large number of potentially important features.
- No need to store explicitly the vectors (no problem of memory storage or hash clashes) thanks to the kernel trick
- Use of regularized statistical algorithm (SVM, kernel PLS, kernel perceptron...)to handle the statistical problem of large dimension

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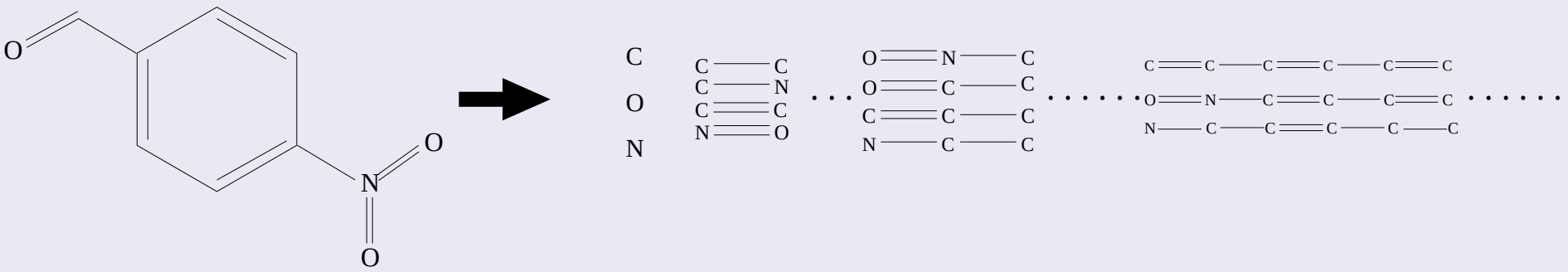
Outline

Motivation: 2D Fingerprints

Features

A vector indexed by a large set of molecular fragments



Pros

- Many features
- Easy to detect

Cons

- Too many features?
- Hashing $\Longrightarrow$ clashes

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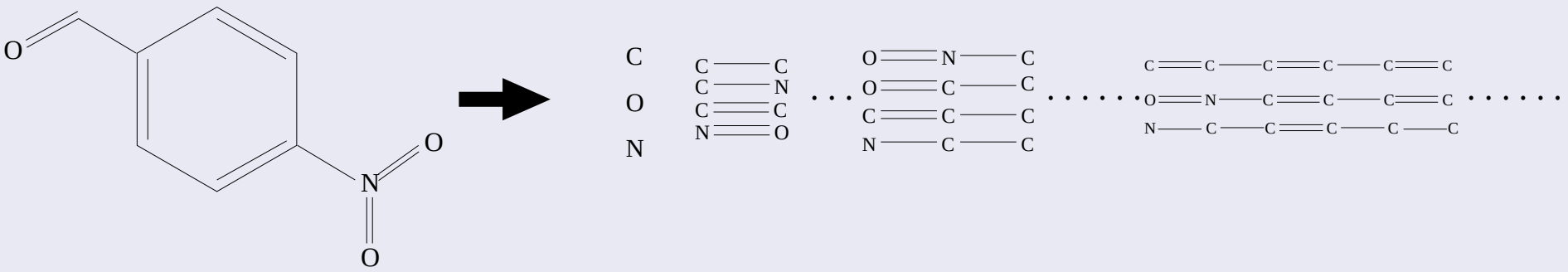

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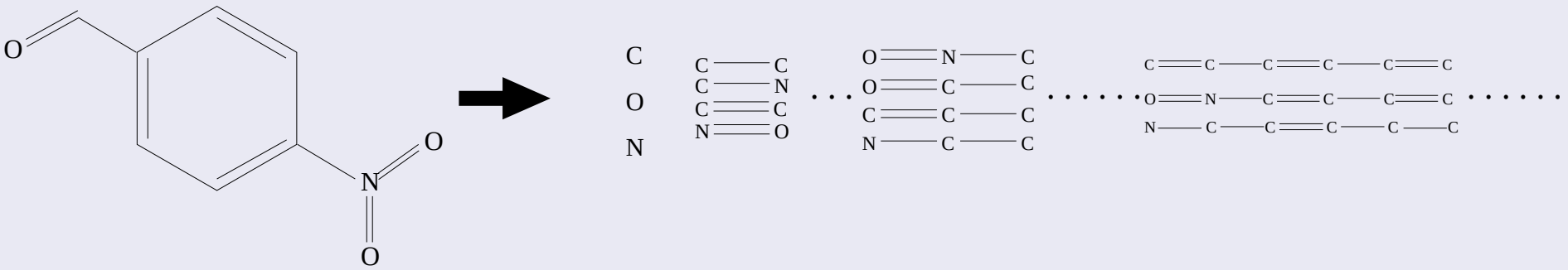
SVM approach



Let $\Phi(x)$ the vector of fragment counts:

- Long fragments lead to large dimensions :
  SVM can learn in high dimension
- $\Phi(x)$ is too long to be stored, and hashes induce clashes:
  SVM do not need $\Phi(x)$, they just need the kernel

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

2D fingerprint kernel

Definition

- For any $d > 0$ let $\phi_d(x)$ be the vector of counts of all fragments of length d:

$$\phi_1(x) = (\quad \#(\mathtt{C}), \#(\mathtt{O}), \#(\mathtt{N}), \quad \ldots)^\top$$
$$\phi_2(x) = (\quad \#(\mathtt{C\text{-}C}), \#(\mathtt{C{=}O}), \#(\mathtt{C\text{-}N}), \quad \ldots)^\top \quad \text{etc...}$$

- The 2D fingerprint kernel is defined, for $\lambda < 1$, by

$$K_{2D}(x, x') = \sum_{d=1}^{\infty} \lambda^d \phi_d(x)^\top \phi_d(x') \; .$$

- This is an inner product in the space of 2D fingerprints of infinite length.

2D kernel computation

Theorem

The 2D fingerprint kernel between two molecules x and x' can be computed with a worst-case complexity $O\left((|x| \times |x'|)^3\right)$ (much faster in practice).

Remarks

- The complexity is not related to the length of the fragments considered (although faster computations are possible if the length is limited).
- Solves the problem of clashes and memory storage.
- Allows to work with infinite-length fingerprints without computing them!

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Theorem

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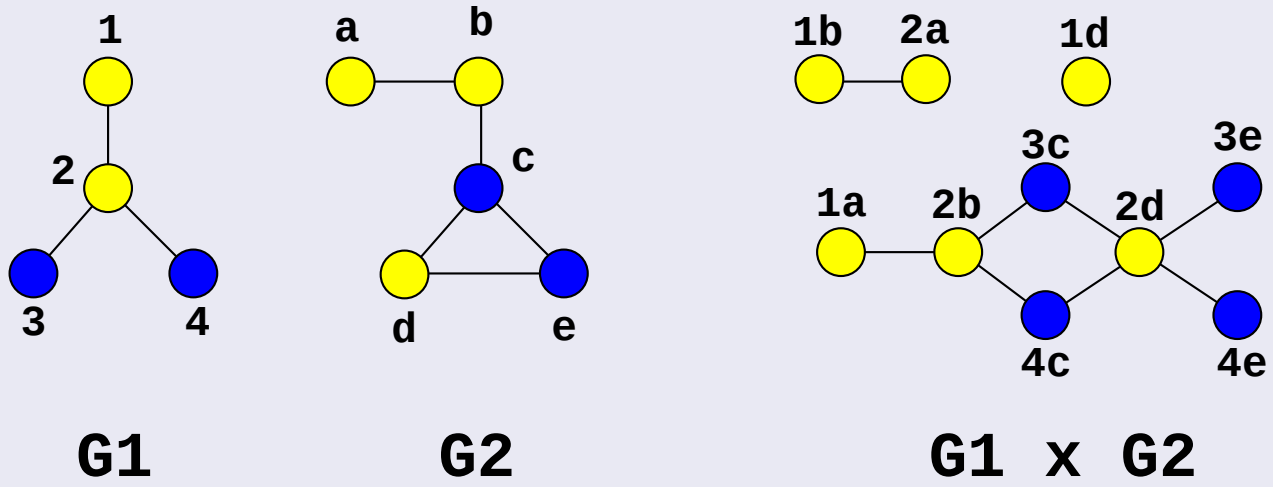
2D kernel computation trick

- Rephrase the kernel computation as that as counting the number of walks on a graph (the product graph)

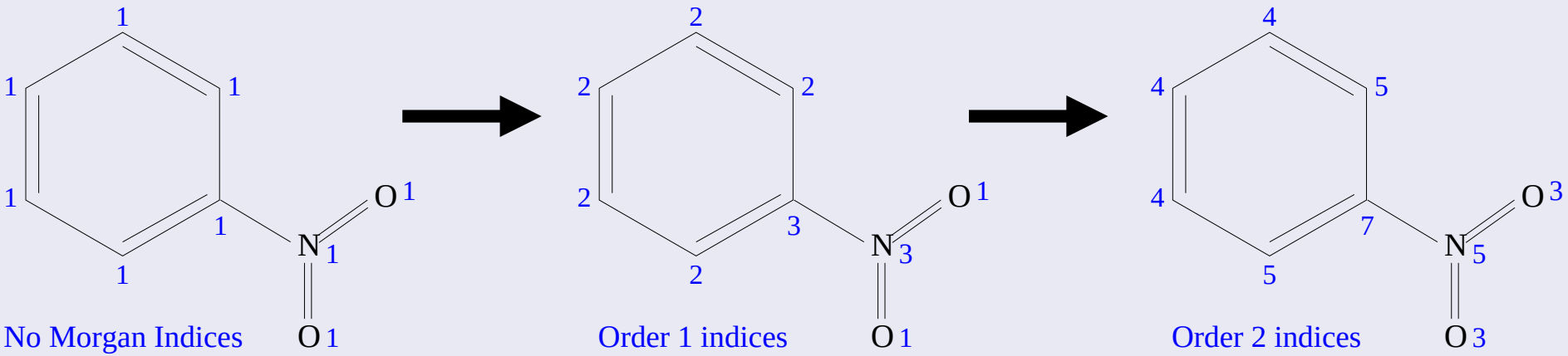


- The infinite counting can be factorized

$$\lambda A + \lambda^2 A^2 + \lambda^3 A^3 + \ldots = (I - \lambda A)^{-1} - I .$$

Extensions 1: label enrichment

Atom relabebling with the Morgan index

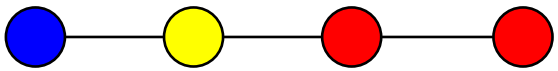


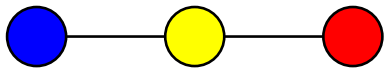
- Compromise between fingerprints and structural keys features.
- Other relabeling schemes are possible.
- Faster computation with more labels (less matches implies a smaller product graph).

Extension 2: Non-tottering walk kernel

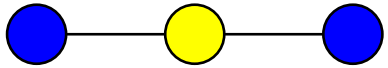
Tottering walks

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





Non-tottering

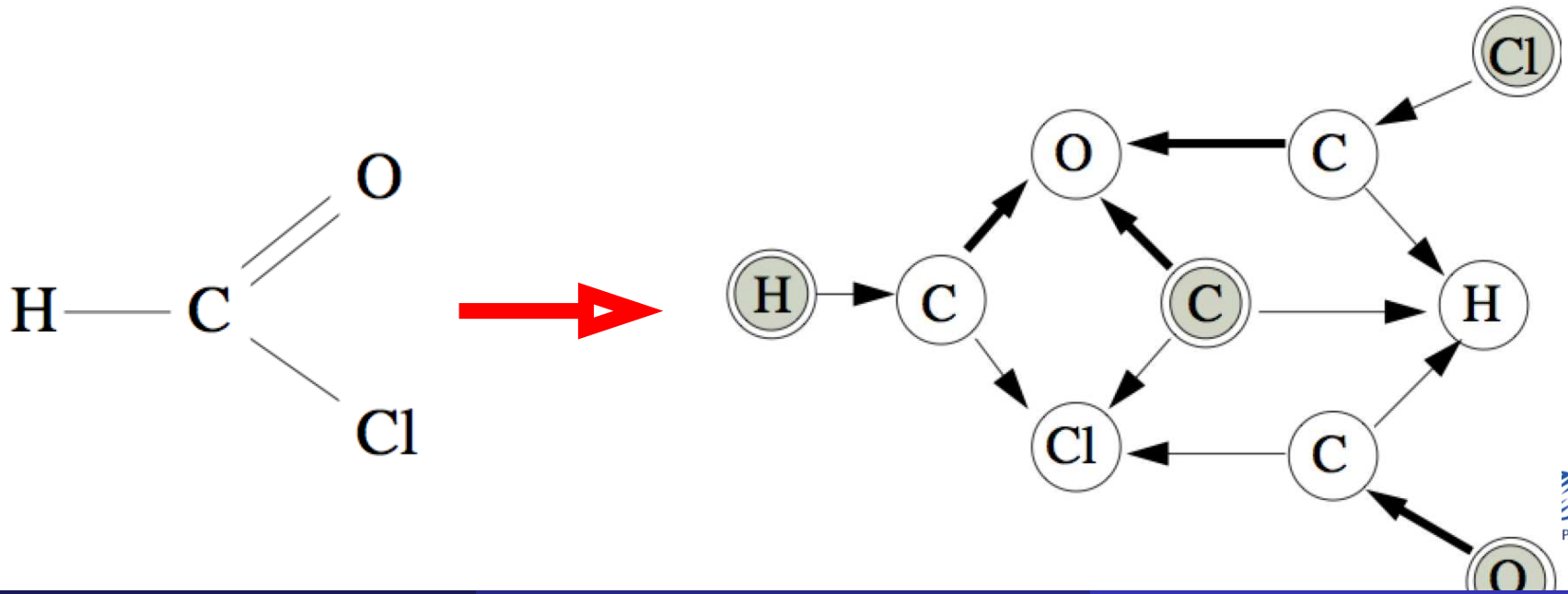


Tottering

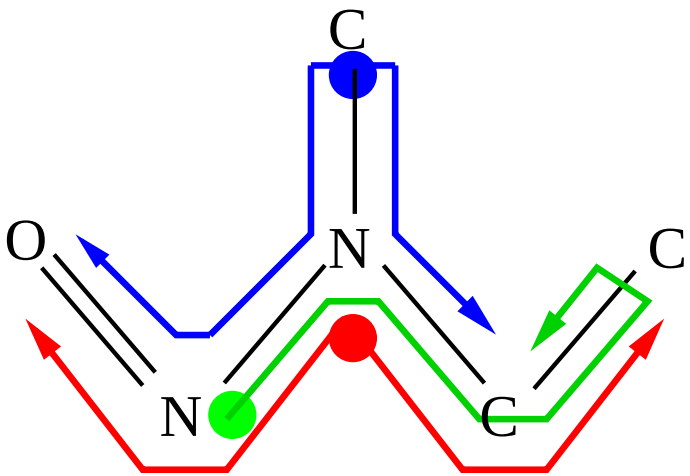
- Tottering walks seem irrelevant for many applications
- Focusing on non-tottering walks is a way to get closer to the path kernel (e.g., equivalent on trees).

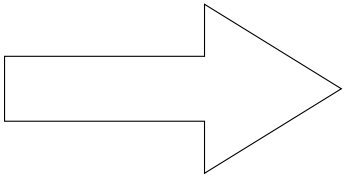
Computation of the non-tottering walk kernel (Mahé et al., 2005)

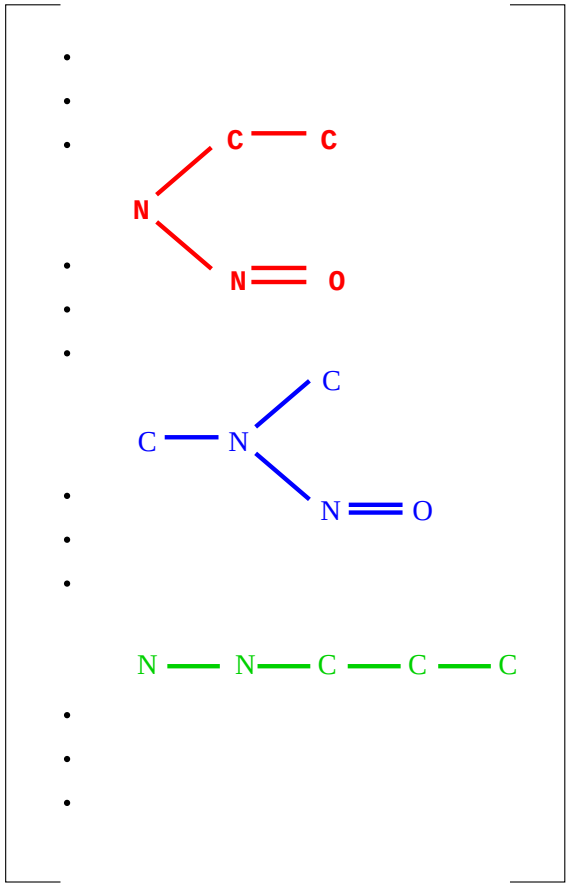
- Second-order Markov random walk to prevent tottering walks
- Written as a first-order Markov random walk on an augmented graph
- Normal walk kernel on the augmented graph (which is always a directed graph).



Extensions 3: tree-like fragments







Experiments

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%

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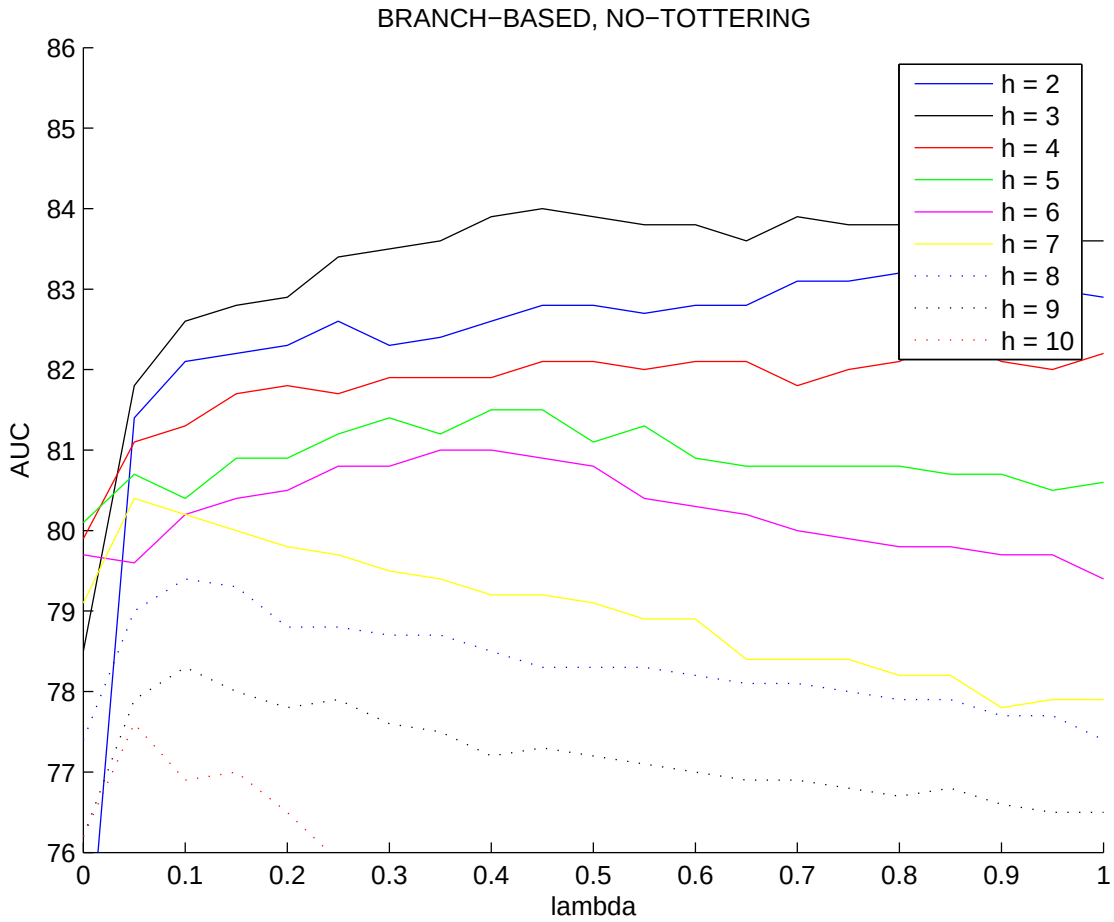
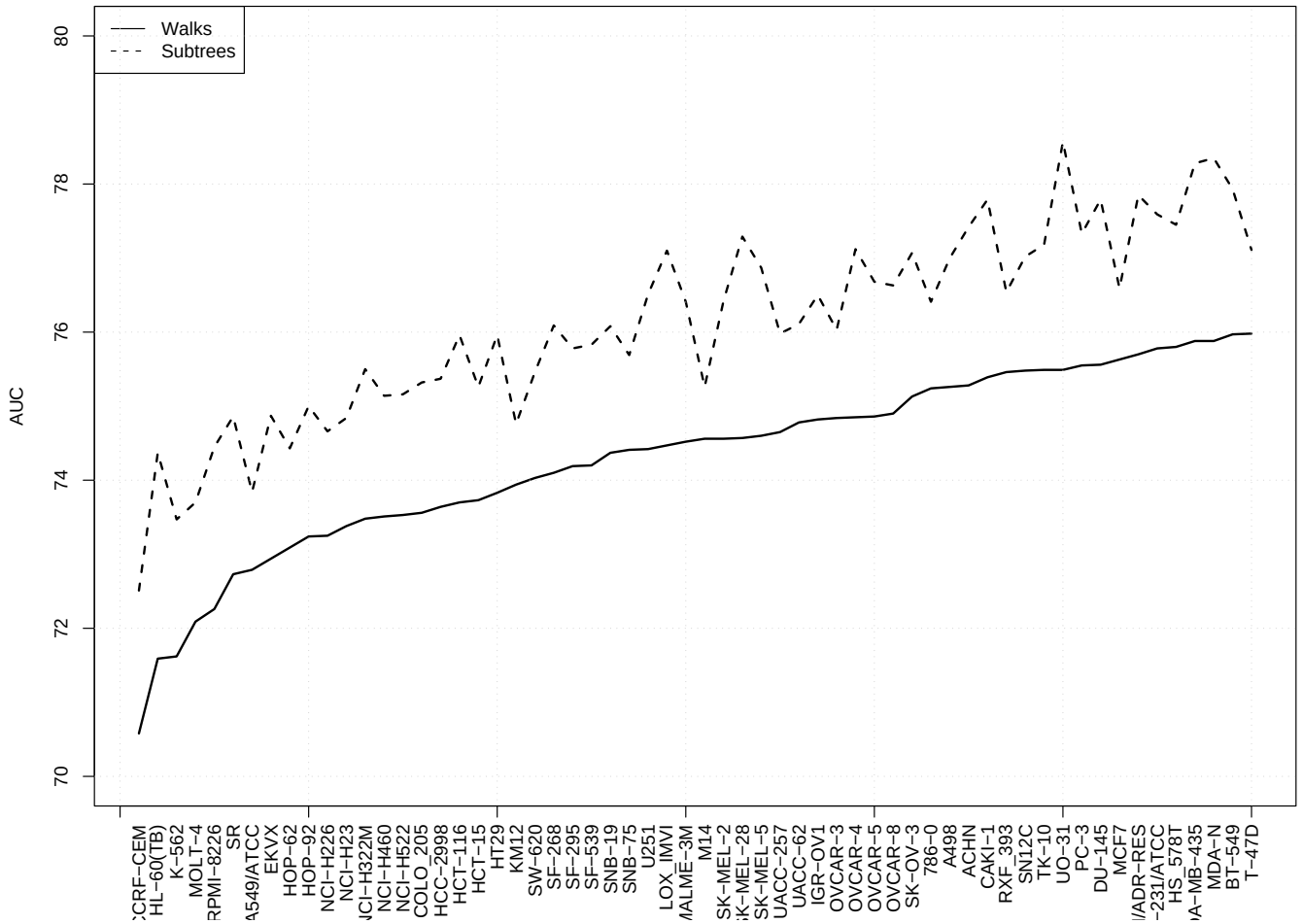
Subtree kernels



AUC as a function of the branching factors for different tree depths (from Mahé et al., 2007).

2D Subtree vs walk kernels

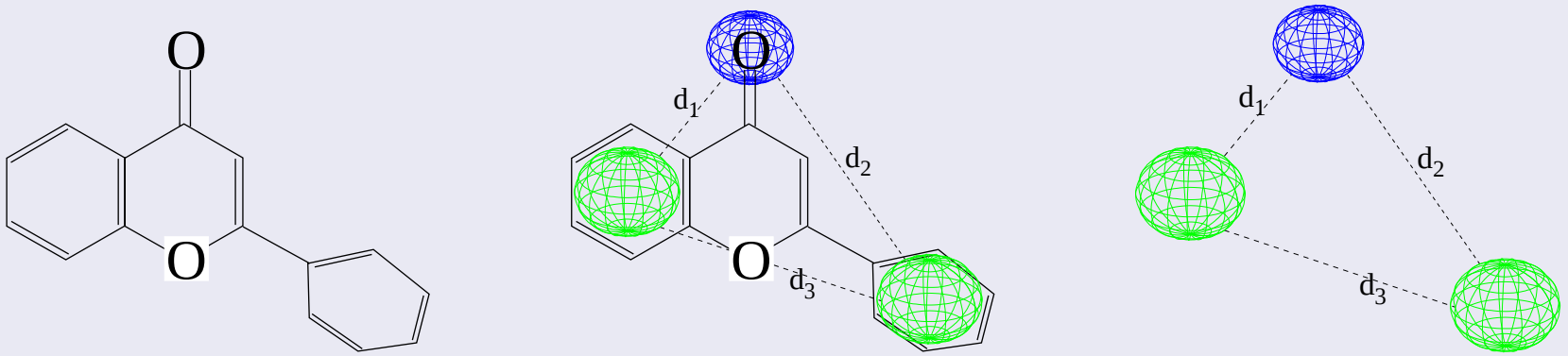


Screening of inhibitors for 60 cancer cell lines.

Outline

Space of pharmacophore

3-points pharmacophores



A set of 3 atoms, and 3 inter-atom distances:

$$\mathcal{T} = \{((x_1, x_2, x_3), (d_1, d_2, d_3)), x_i \in \{\text{atom types}\}; d_i \in \mathbb{R}\}$$

3D fingerprint kernel

Pharmacophore fingerprint

1. Discretize the space of pharmacophores $\mathcal{T}$ (e.g., 6 atoms or groups of atoms, 6-7 distance bins) into a finite set $\mathcal{T}_d$
2. Count the number of occurrences $\phi_t(x)$ of each pharmacophore bin t in a given molecule x, to form a pharmacophore fingerprint.

3D kernel

A simple 3D kernel is the inner product of pharmacophore fingerprints:

$$K(x, x') = \sum_{t \in \mathcal{T}_d} \phi_t(x) \phi_t(x') \ .$$

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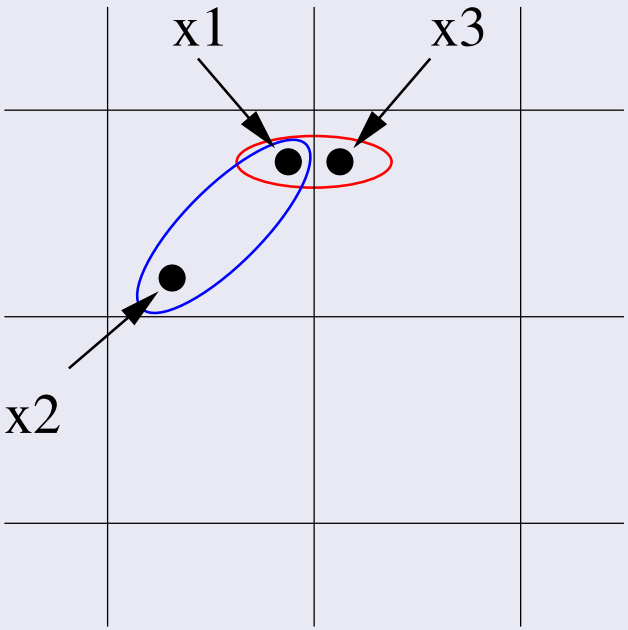
Discretization of the pharmacophore space

Common issues

1. If the bins are too large, then they are not specific enough
2. If the bins are too large, then they are too specific

In all cases, the arbitrary position of boundaries between bins affects the comparison:



$$\rightarrow d(x_1, x_3) < d(x_1, x_2)$$
$$\text{BUT} \quad \text{bin}(x_1) = \text{bin}(x_2) \neq \text{bin}(x_3)$$

Kernels between pharmacophores

A small trick

$$
\begin{aligned}
K(x,y) &= \sum_{t \in \mathcal{T}_d} \phi_t(x)\phi_t(y) \\
&= \sum_{t \in \mathcal{T}_d} \Big(\sum_{p_x \in \mathcal{P}(x)} \mathbf{1}(\text{bin}(\mathbf{p_x}) = \mathbf{t}) \Big) \Big(\sum_{p_y \in \mathcal{P}(y)} \mathbf{1}(\text{bin}(\mathbf{p_y}) = \mathbf{t}) \Big) \\
&= \sum_{p_x \in \mathcal{P}(x)} \sum_{p_y \in \mathcal{P}(y)} \mathbf{1}(\text{bin}(\mathbf{p_x}) = \text{bin}(\mathbf{p_y}))
\end{aligned}
$$

General pharmacophore kernel

$$
K(x,y) = \sum_{p_x \in \mathcal{P}(x)} \sum_{p_y \in \mathcal{P}(y)} K_P(p_x, p_y)
$$

New pharmacophore kernels

- Discretizing the pharmacophore space is equivalent to taking the following kernel between individual pharmacophores:

$$K_P(p_1, p_2) = \mathbf{1}\left(\text{bin}(\mathbf{p_x}) = \text{bin}(\mathbf{p_y})\right)$$

- For general kernels, there is no need for discretization!
- For example, is $d(p_1, p_2)$ is a Euclidean distance between pharmacophores, take:

$$K_P\left(p_1, p_2\right) = \exp\left(-\gamma d\left(p_1, p_2\right)\right) \ .$$

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Experiments

4 public datasets

- BZR: ligands for the benzodiazepine receptor
- COX: cyclooxygenase-2 inhibitors
- DHFR: dihydrofolate reductase inhibitors
- ER: estrogen receptor ligands

	TRAIN		TEST	
	Pos	Neg	Pos	Neg
BZR	94	87	63	62
COX	87	91	61	64
DHFR	84	149	42	118
ER	110	156	70	110

Experiments

Results (accuracy)

Kernel	BZR	COX	DHFR	ER
2D (Tanimoto)	71.2	63.0	76.9	77.1
3D fingerprint	75.4	67.0	76.9	78.6
3D not discretized	**76.4**	**69.8**	**81.9**	**79.8**

Outline

Summary

- SVM is a powerful and flexible machine learning algorithm. The kernel trick allows the manipulation of non-vectorial objects at the cost of defining a kernel function.
- The 2D kernel for molecule extends classical fingerprint-based approches. It solves the problem of bit clashes, allows infinite fingerprints and various extensions.
- The 3D kernel for molecule extends classical pharmacophore fingerprint-based approaches. It solves the problems of bit clashes and of discretization.
- Both kernels improve upon their classical counterparts, and provide competitive results on benchmark datasets.

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- Open-source kernels for chemoinformatics: `http://chemcpp.sourceforge.net/`

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