Some contributions of machine learning to bioinformatics

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Where I come from

institutCurie

MINES PARIS ParisTech

Inserm

- A joint lab about “Cancer computational genomics, bioinformatics, biostatistics and epidemiology”
- Located in th Institut Curie, a major hospital and cancer research institute in Europe

”Statistical machine learning for cancer informatics” team

Main topics

- Towards better diagnosis, prognosis, and personalized medicine
  - Supervised classification of genomic, transcriptomic, proteomic data; heterogeneous data integration
- Towards new drug targets
  - Systems biology, reconstruction of gene networks, pathway enrichment analysis, multidimensional phenotyping of cell populations.
- Towards new drugs
  - Ligand-based virtual screening, *in silico* chemogenomics.

Outline

Outline

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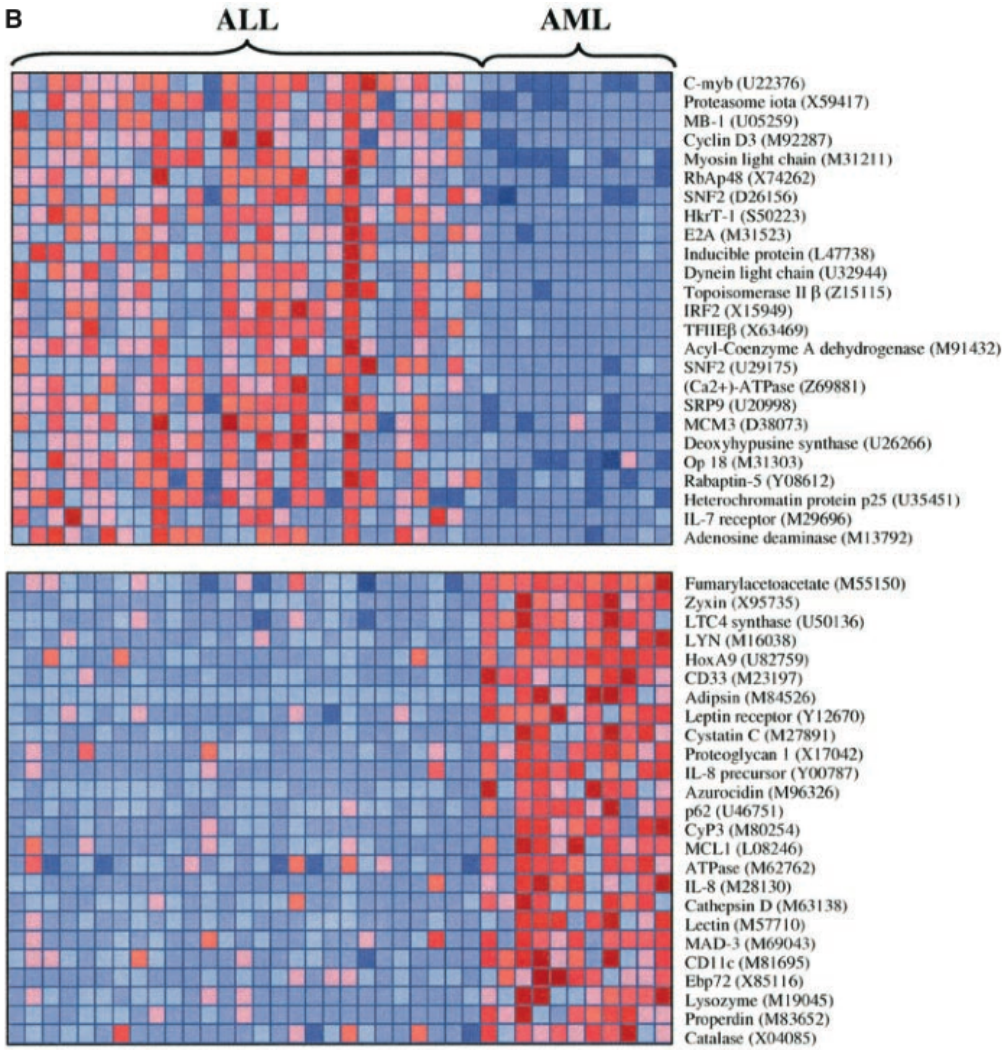
Motivation



Goal

- Design a classifier to automatically assign a class to future samples from their expression profile
- Interpret biologically the differences between the classes

Difficulty

- Large dimension
- Few samples

Linear classifiers

The model

- Each sample is represented by a vector $x = (x_1, \ldots, x_p)$
- Goal: estimate a linear function:

$$f_\beta(x) = \sum_{i=1}^{p} \beta_i x_i + \beta_0 \ .$$

- Interpretability: the weight β_i quantifies the influence of feature i (but...)

Training the model

$$f_\beta(x) = \sum_{i=1}^{p} \beta_i x_i + \beta_0 \ .$$

- Minimize an empirical risk on the training samples:

$$\min_{\beta \in \mathbb{R}^{p+1}} R_{emp}(\beta) = \frac{1}{n} \sum_{i=1}^{n} l(f_\beta(x_i), y_i) \ ,$$

- ... subject to some constraint on β, e.g.:

$$\Omega(\beta) \leq C \ .$$

Example : Norm Constraints

The approach

A common method in statistics to learn with few samples in high dimension is to constrain the Euclidean norm of β

$$\Omega_{ridge}(\beta) = \| \beta \|_2^2 = \sum_{i=1}^{p} \beta_i^2 \, ,$$

(ridge regression, support vector machines...)

Pros

- Good performance in classification

Cons

- Limited interpretation (small weights)
- No prior biological knowledge

Example : Feature Selection

The approach

Constrain most weights to be 0, i.e., select a few genes (< 100) whose expression are sufficient for classification.

- Greedy feature selection (T-tests, ...)
- Contrain the norm of β: LASSO penalty ($\| \beta \|_1 = \sum_{i=1}^{p} | \beta_i |$), elastic net penalty ($\| \beta \|_1 + \| \beta \|_2$), ...)

Pros

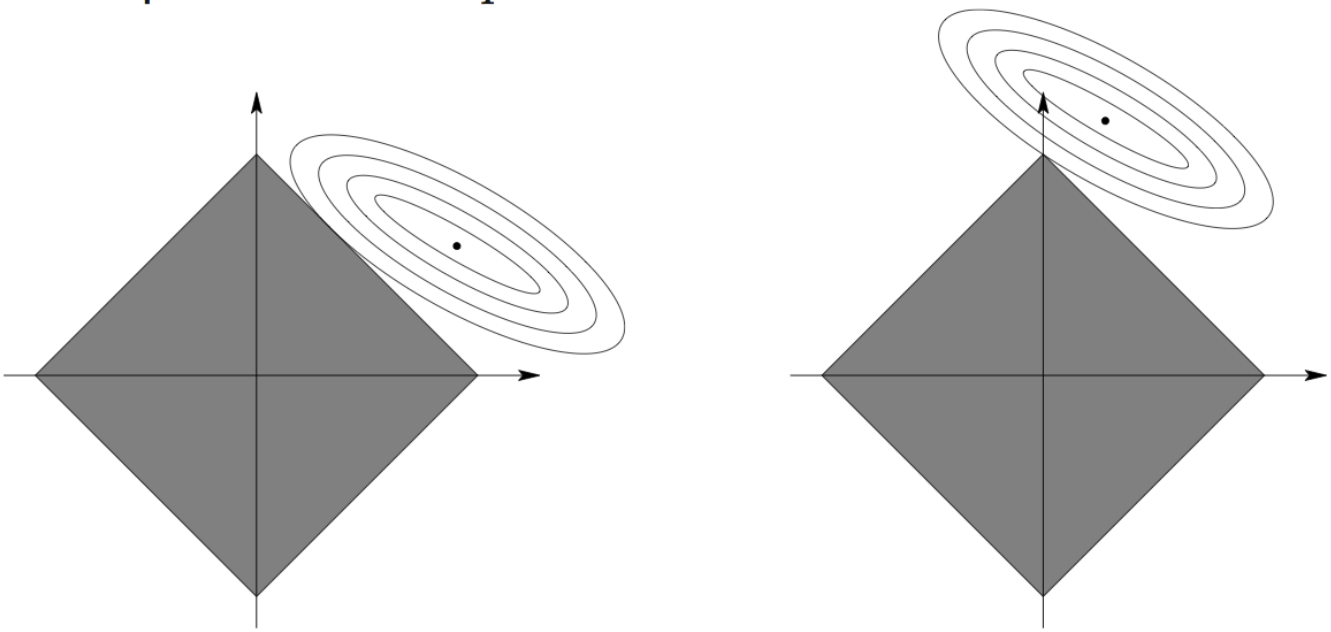
- Good performance in classification
- Biomarker selection
- Interpretability

Cons

- The gene selection process is usually not robust
- No use of prior biological knowledge

Why LASSO leads to sparse solutions

Geometric interpretation with $p = 2$



Incorporating prior knowledge

The idea

- If we have a specific prior knowledge about the "correct" weights, it can be included in Ω in the contraint:

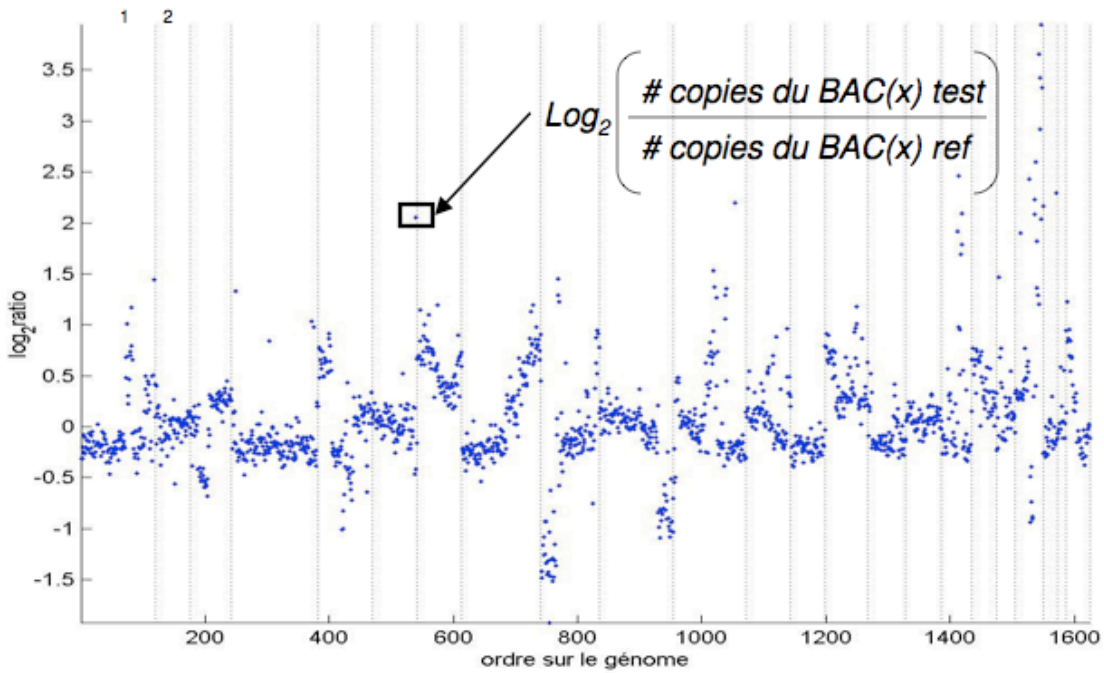
$$\text{Minimize } R_{emp}(\beta) \text{ subject to } \Omega(\beta) \leq C\,.$$

- If we design a convex function Ω, then the algorithm boils down to a convex optimization problem (usually easy to solve).
- Similar to priors in Bayesian statistics

Example: CGH array classification

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

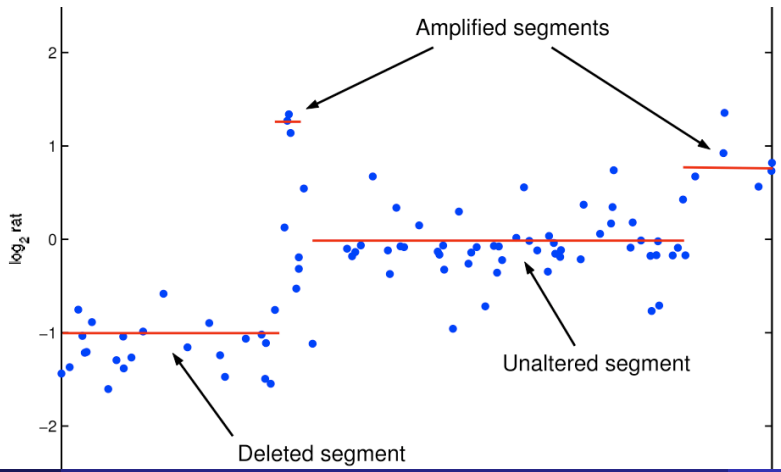
Example: CGH array classification

Prior knowledge

- Let **x** be a CGH profile
- We focus on linear classifiers, i.e., the sign of :

$$f(\mathbf{x}) = \mathbf{x}^\top \beta \,.$$

- We expect β to be
  - sparse : only a few positions should be discriminative
  - piecewise constant : within a region, all probes should contribute equally

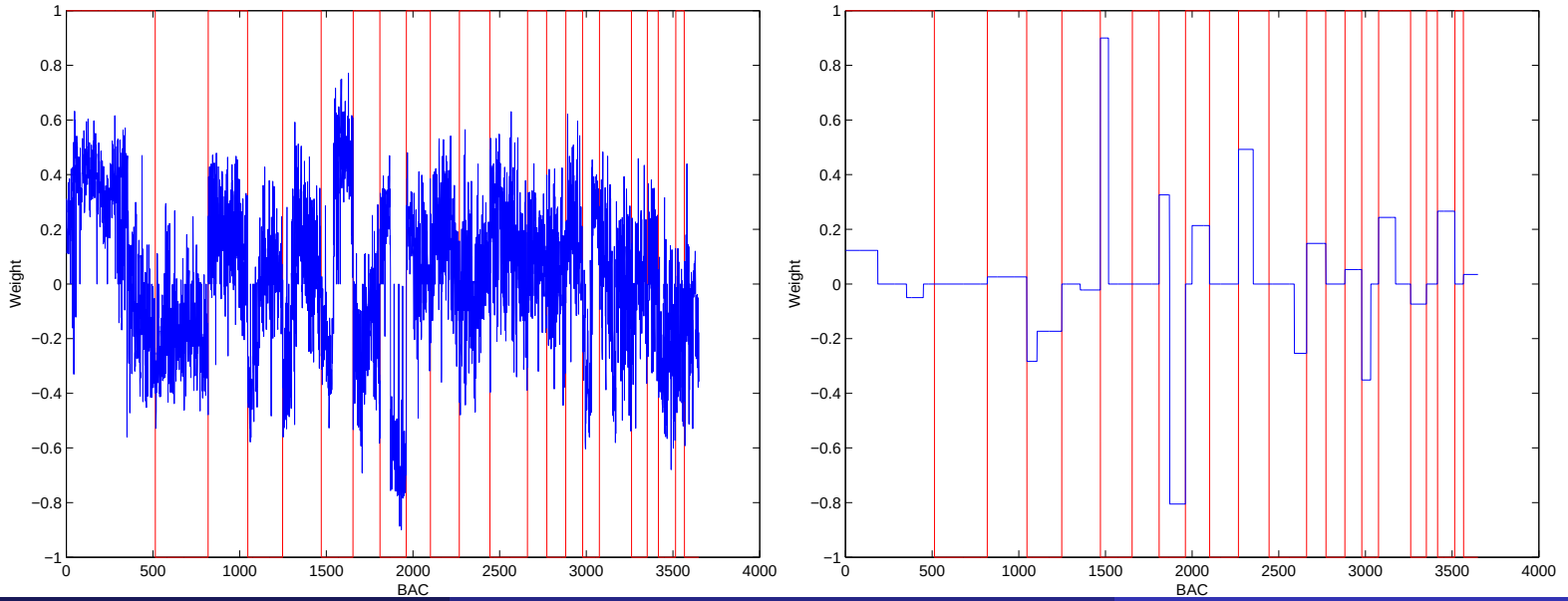


Example: CGH array classification

A solution (Rapaport et al., 2008)

$$\Omega_{fusedlasso}(\beta) = \sum_i |\beta_i| + \sum_{i \sim j} |\beta_i - \beta_j| \,.$$

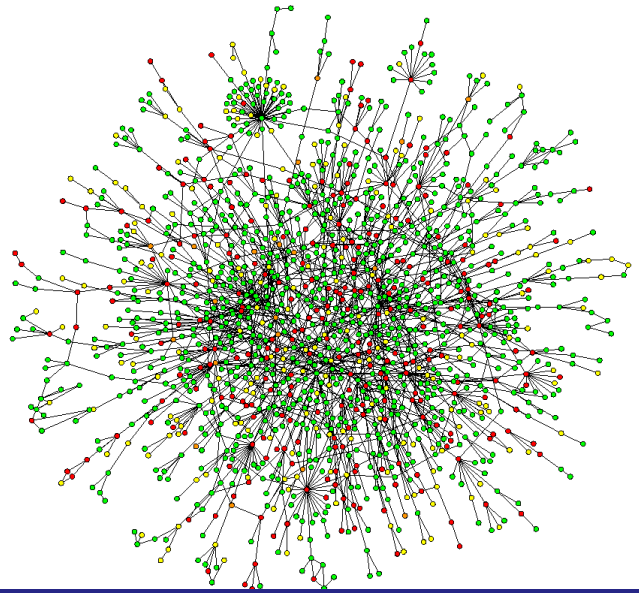
- Good performance on diagnosis for bladder cancer, and prognosis for melanoma.
- More interpretable classifiers



Example: finding discriminant modules in gene networks

The problem

- Classification of gene expression: too many genes
- A gene network is given (PPI, metabolic, regulatory, signaling, co-expression...)
- We expect that “clusters of genes” (modules) in the network contribute similarly to the classification



Example: finding discriminant modules in gene networks

Prior hypothesis

Genes near each other on the graph should have similar weigths.

Two solutions (Rapaport et al., 2007, 2008)

$$\Omega_{spectral}(\beta) = \sum_{i \sim j} (\beta_i - \beta_j)^2 \,,$$

$$\Omega_{graphfusion}(\beta) = \sum_{i \sim j} |\beta_i - \beta_j| + \sum_i |\beta_i| \,.$$

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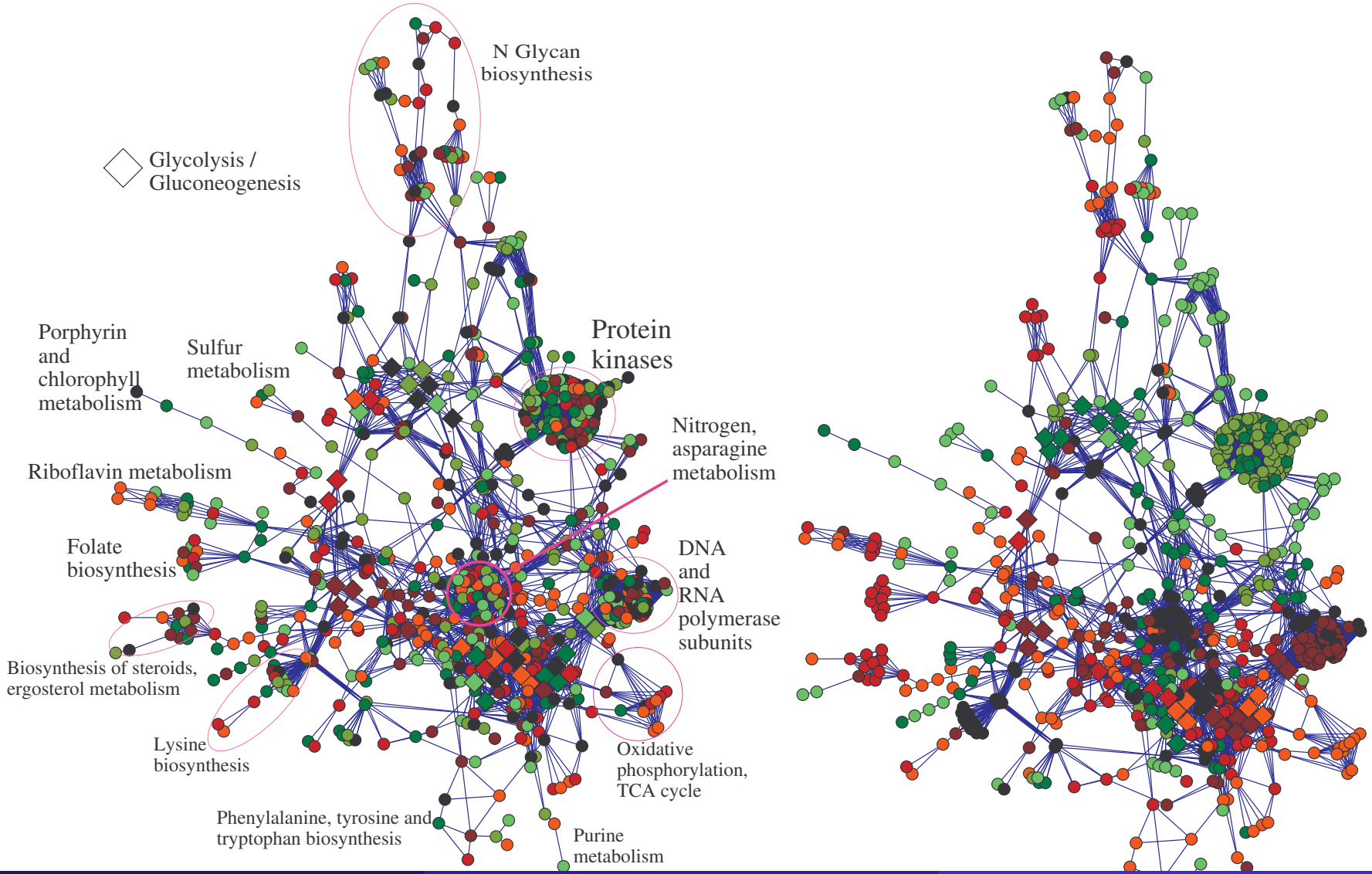

Example: finding discriminant modules in gene networks

Prior hypothesis

Genes near each other on the graph should have non-zero weigths (i.e., the support of β should be made of a few connected components).

Two solutions?

$$\Omega_{intersection}(\beta) = \sum_{i \sim j} \sqrt{\beta_i^2 + \beta_j^2}\,,$$

$$\Omega_{union}(\beta) = \sup_{\alpha \in \mathbb{R}^p : \forall i \sim j, \|\alpha_i^2 + \alpha_j^2\| \leq 1} \alpha^\top \beta\,.$$

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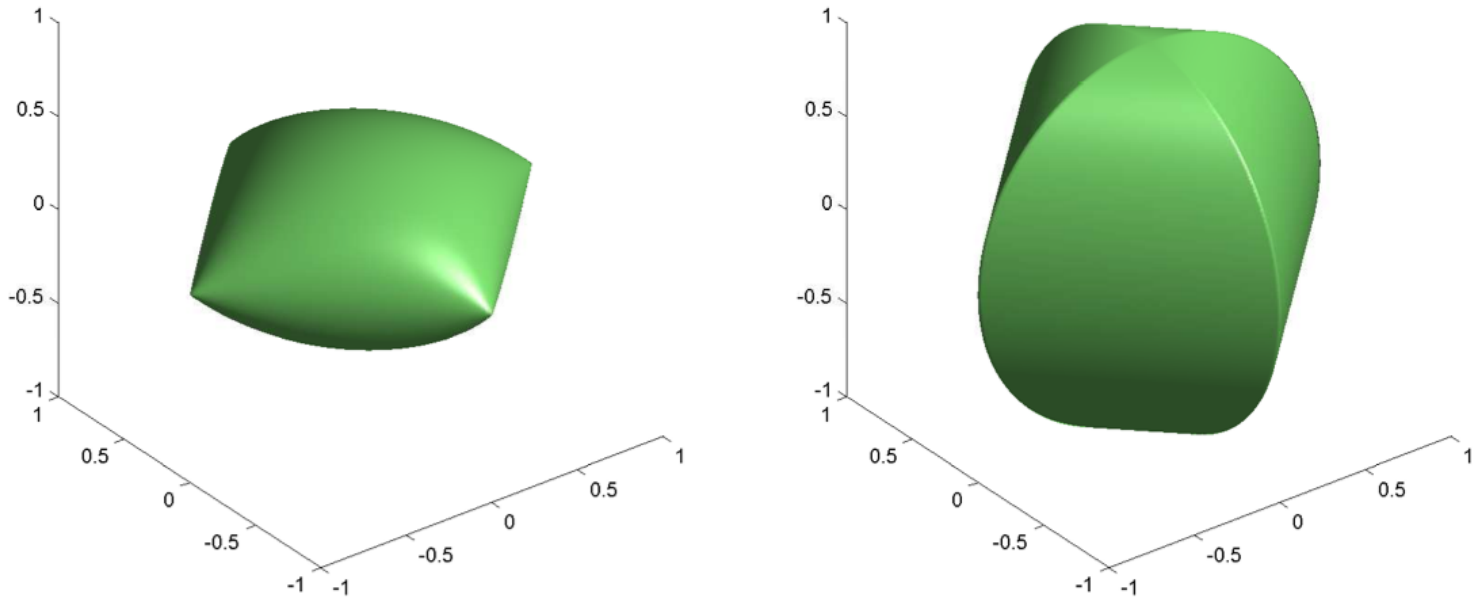


Groups $(1,2)$ *and* $(2,3)$. *Left:* $\Omega_{intersection}(\beta)$. *Right:* $\Omega_{union}(\beta)$. *Vertical axis is* β_2.

Outline

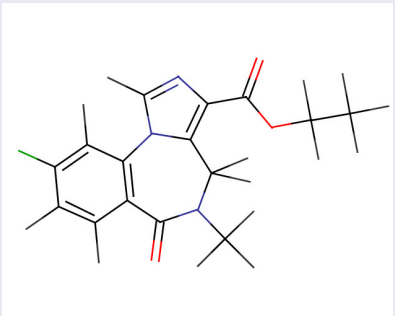
Ligand-Based Virtual Screening

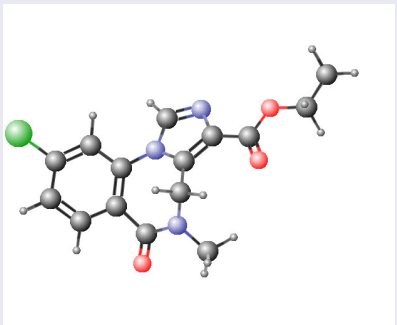
Objective

Build models to predict biochemical properties of small molecules from their structures.

Structures

$C_{15}H_{14}ClN_3O_3$

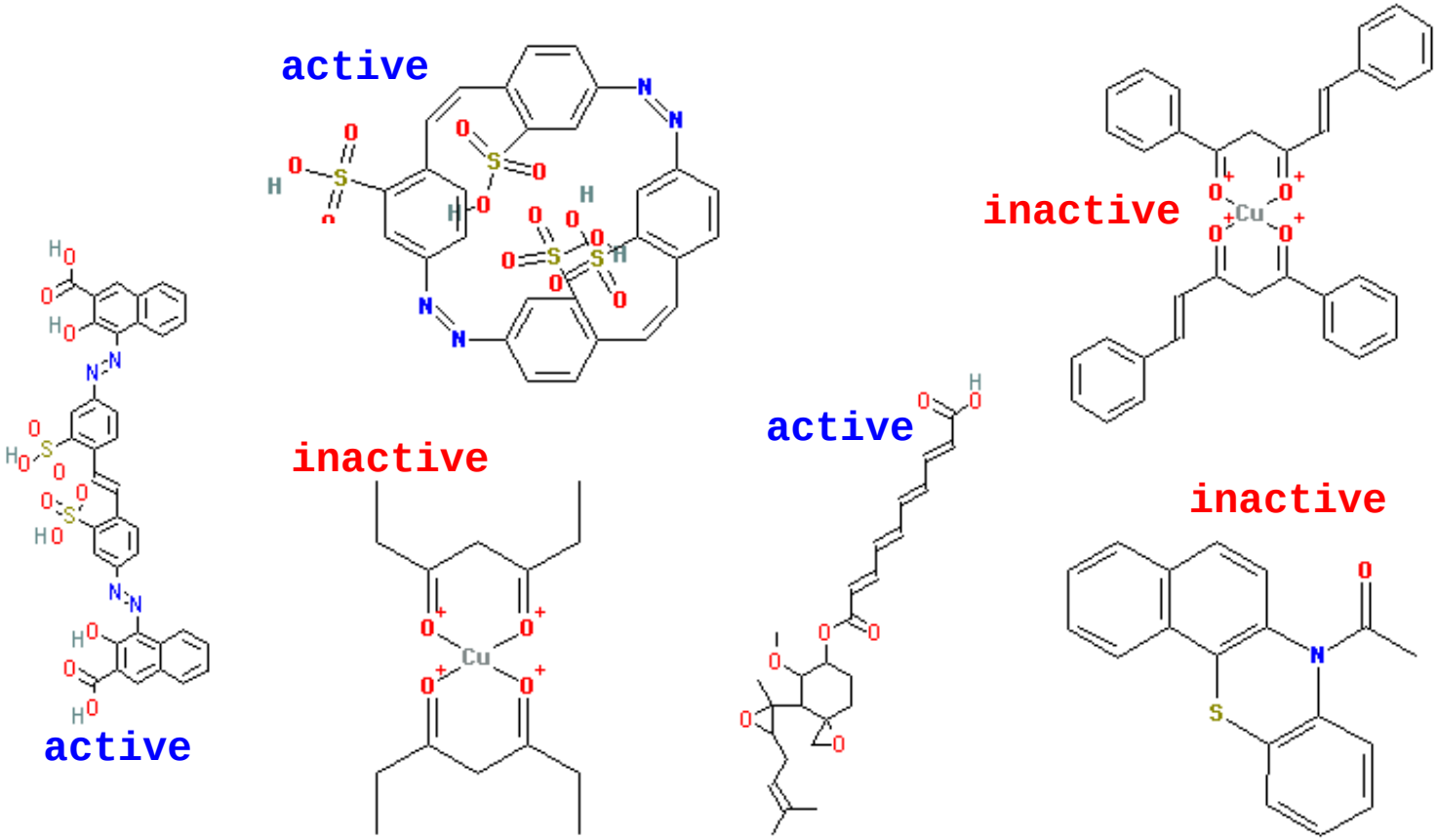




Properties

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

Ligand-Based Virtual Screening and QSAR



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

Formalization

The problem

- Given a set of training instances $(x_1, y_1), \ldots, (x_n, y_n)$, where x_i's are graphs and y_i's are continuous or discrete variables of interest,
- Estimate a function

$$y = f(x)$$

where x is any graph to be labeled.

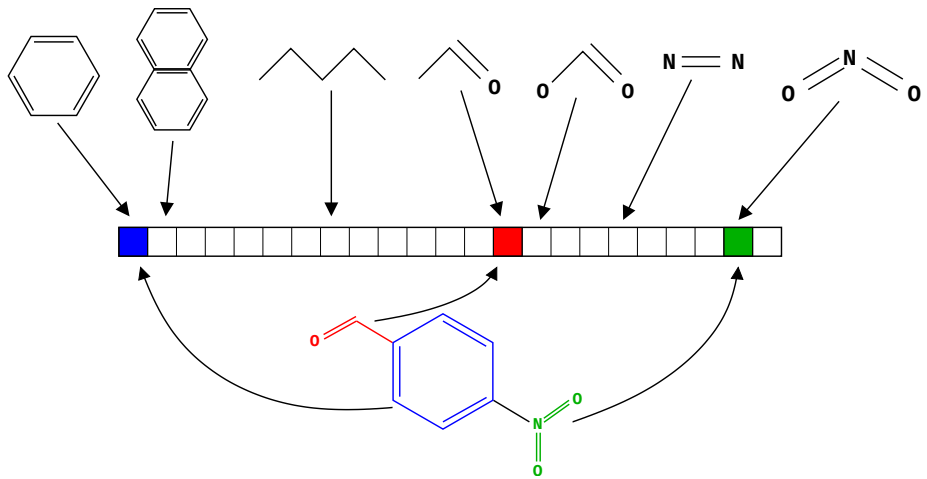
- This is a classical regression or pattern recognition problem over the set of graphs.

Classical approaches

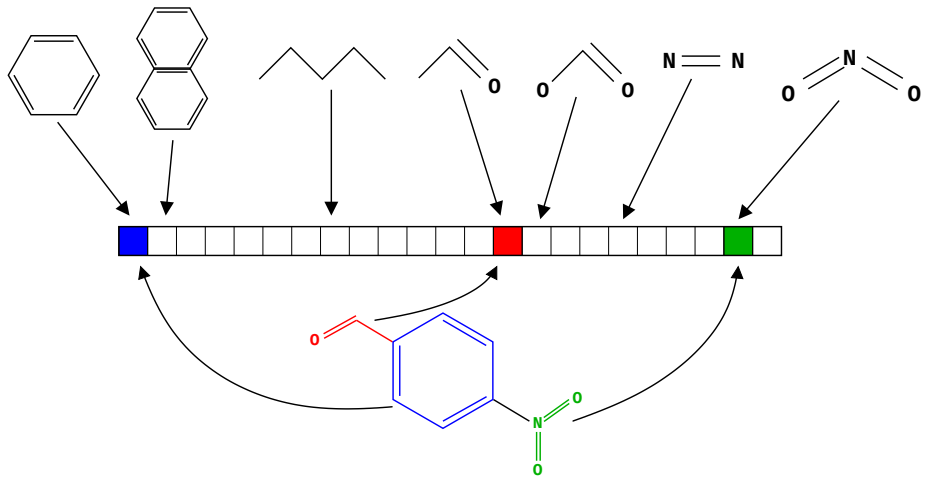
Two steps

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

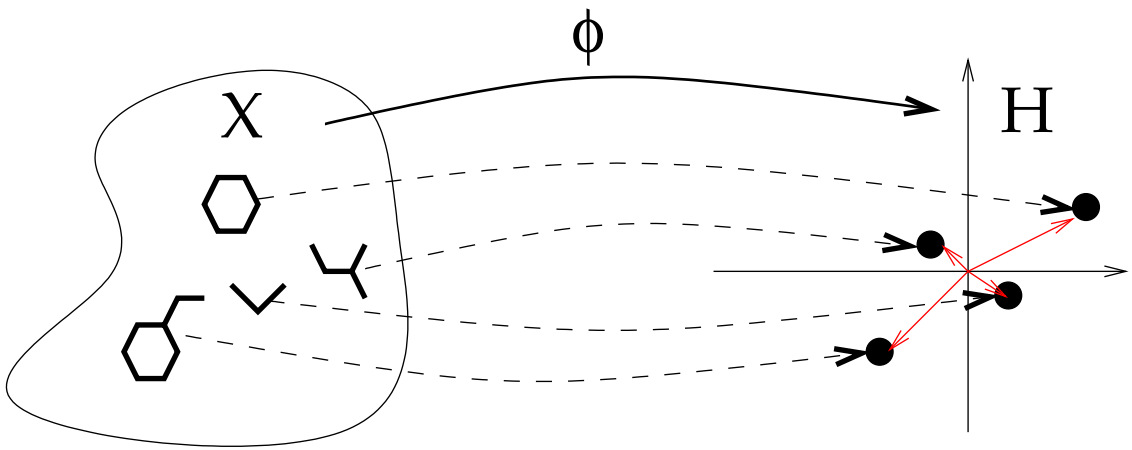
- Many descriptors are needed to characterize various features (in particular for 2D and 3D descriptors)
- But too many descriptors are harmful for memory storage, computation speed, statistical estimation

Kernels

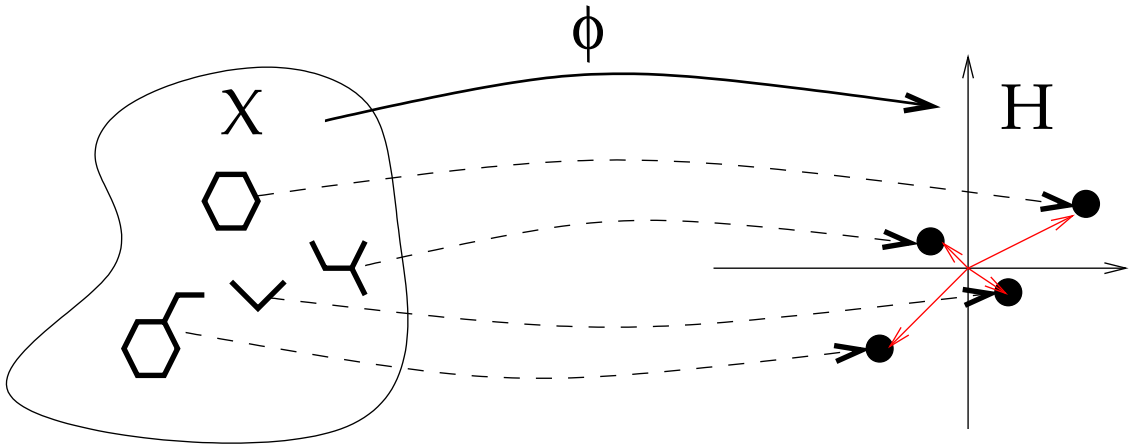
Definition

- 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



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

The trick

- Many linear algorithms for regression or pattern recognition can be expressed only in terms of inner products between vectors
- Computing the kernel is often more efficient than computing $\Phi(x)$, especially in high or infinite dimensions!

Expressiveness vs Complexity of graph kernels

Definition: Complete graph kernels

A graph kernel is complete if it separates non-isomorphic graphs, i.e.:

$$\forall G_1, G_2 \in \mathcal{X}, \quad d_K(G_1, G_2) = 0 \implies G_1 \simeq G_2 \,.$$

Equivalently, $\Phi(G_1) \neq \Phi(G_1)$ if G_1 and G_2 are not isomorphic.

Proposition (Gärtner et al., 2003)

Computing any complete graph kernel is at least as hard as the graph isomorphism problem.

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Subgraph kernel

Definition

- Let $\mathcal{X}$ be a set of graphs, and $(\lambda_G)_{G \in \mathcal{X}}$ a set or nonnegative real-valued weights
- For any graph G, let

$$\forall H \in \mathcal{X}, \quad \Phi_H(G) = \left| \left\{ G' \text{ is a subgraph of } G \,:\, G' \simeq H \right\} \right| .$$

- The subgraph kernel between any two graphs G_1 and G_2 is defined by:

$$K_{subgraph}(G_1, G_2) = \sum_{H \in \mathcal{X}} \lambda_H \Phi_H(G_1) \Phi_H(G_2) .$$

Subgraph kernel complexity

Proposition (Gärtner et al., 2003)

Computing the subgraph kernel is NP-hard when:

- $\mathcal{X}$ is the set of all graphs (all subgraph kernel)
- $\mathcal{X}$ is the set of all linear graphs (path kernel)

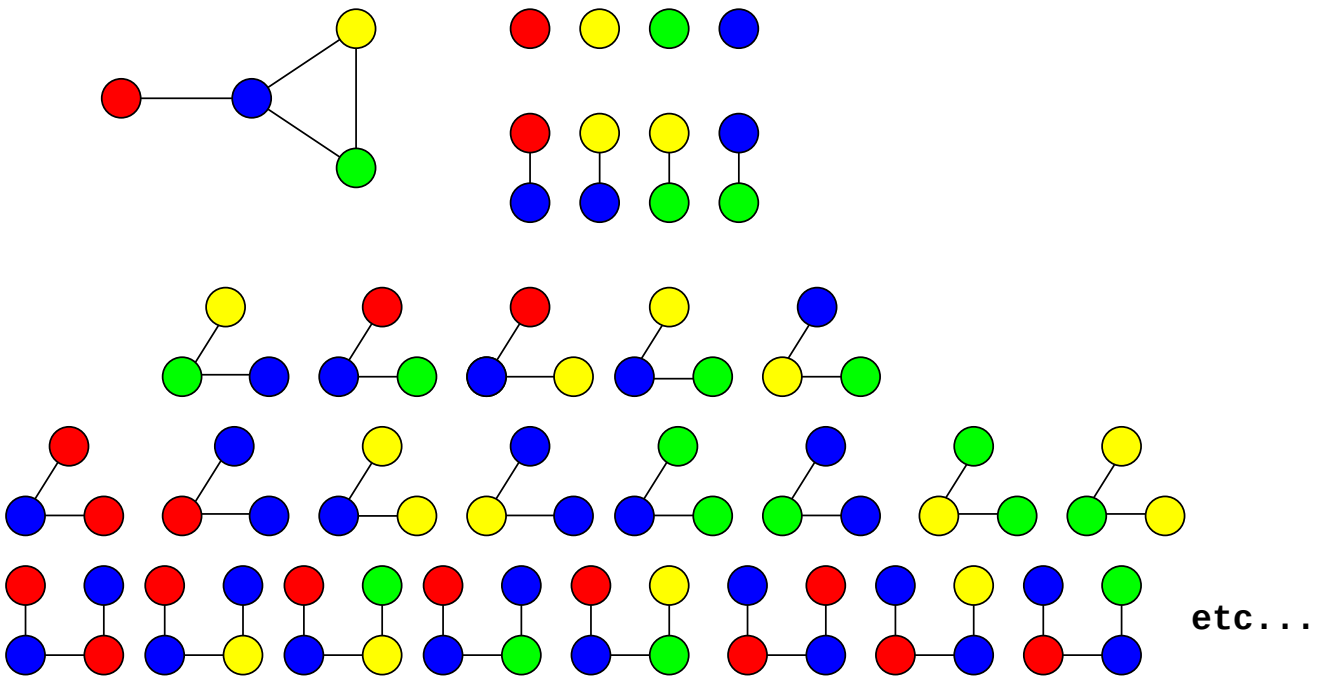
Proof (sketch)

Computing these kernels allows to decide whether a graph has a Hamiltonian path, which a NP-complete.

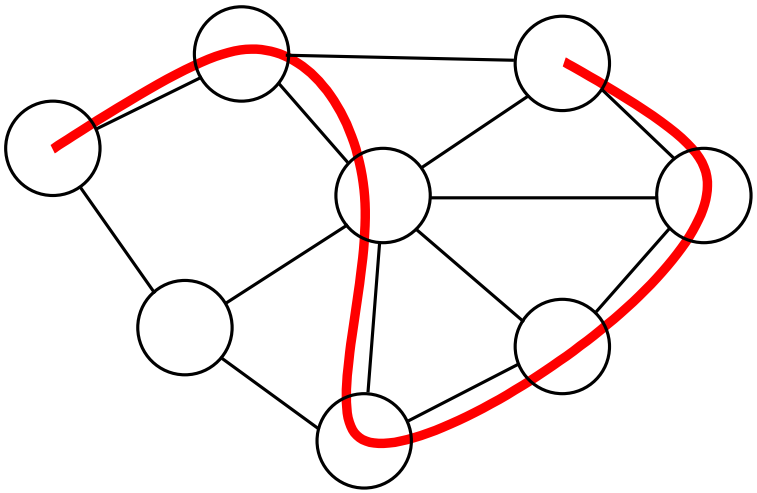
Walks

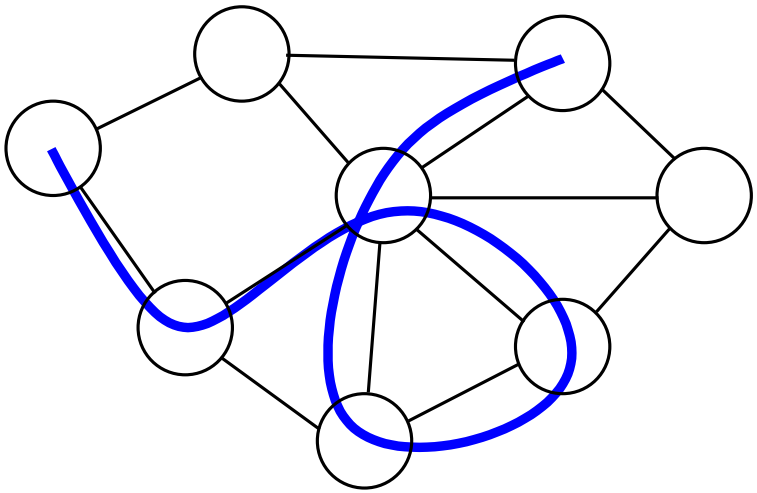
Definition

- 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.



Paths and walks





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:

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

- 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

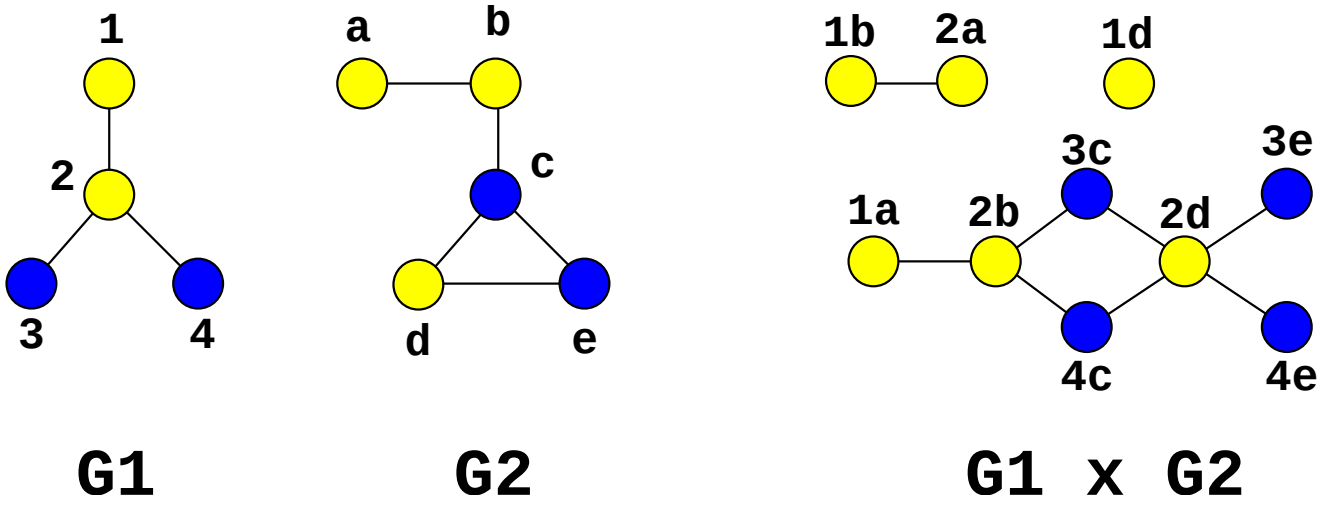
These three kernels (*n*th-order, random and geometric walk kernels) can be computed efficiently in polynomial time.

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

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

Computation of the nth-order walk kernel

- For the nth-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:

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

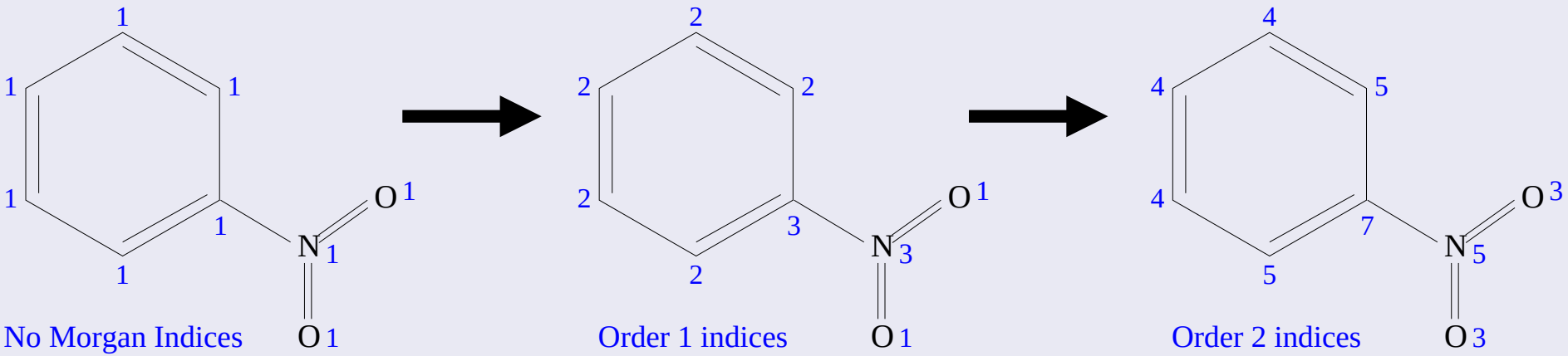
- Let Λ_i be the vector of $\lambda^i(v)$ and Λ_t be the matrix of $\lambda^t(v, v')$:

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

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

Extensions 1: label enrichment

Atom relabebling with the Morgan index

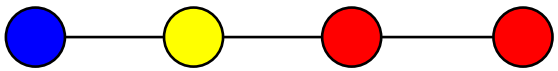


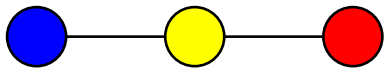
- Compromise between fingerprints and structural keys features.
- Other relabeling schemes are possible (graph coloring).
- Faster computation with more labels (less matches implies a smaller product graph).

Extension 2: Non-tottering walk kernel

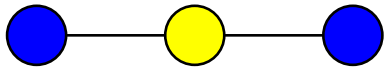
Tottering walks

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





Non-tottering

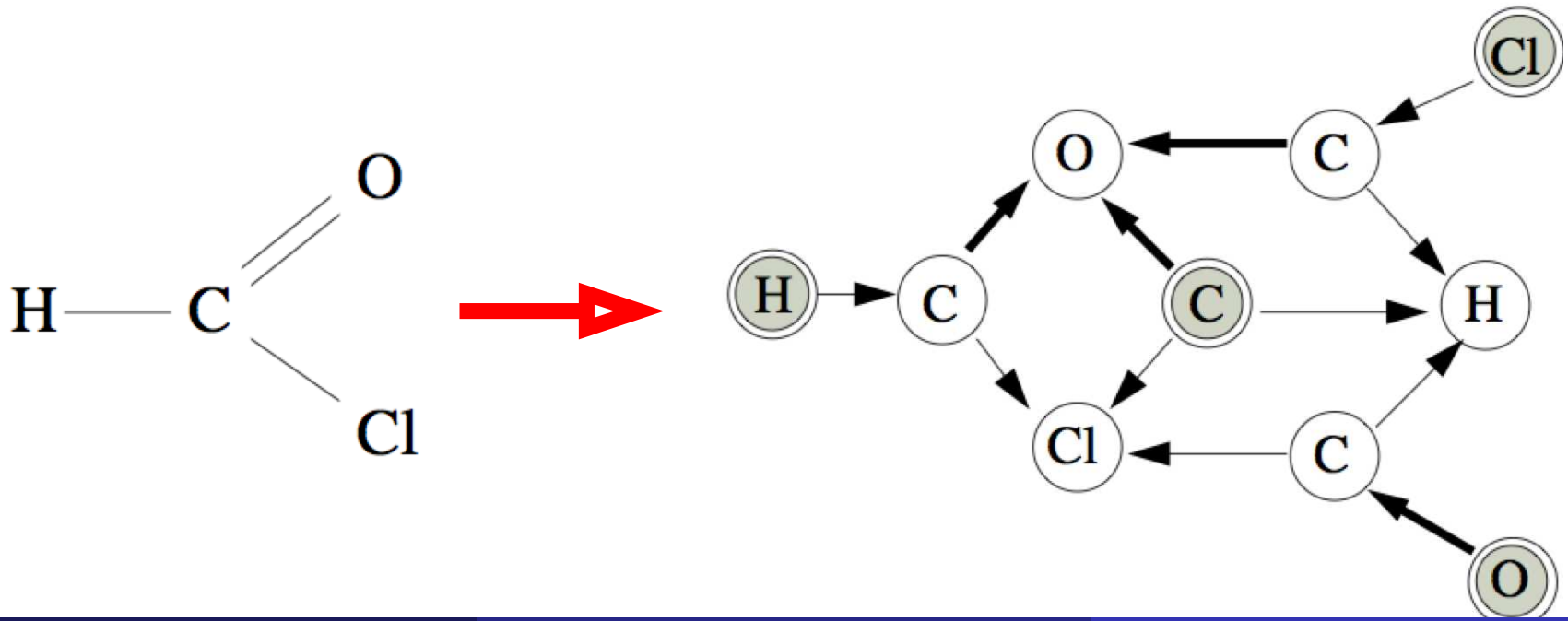


Tottering

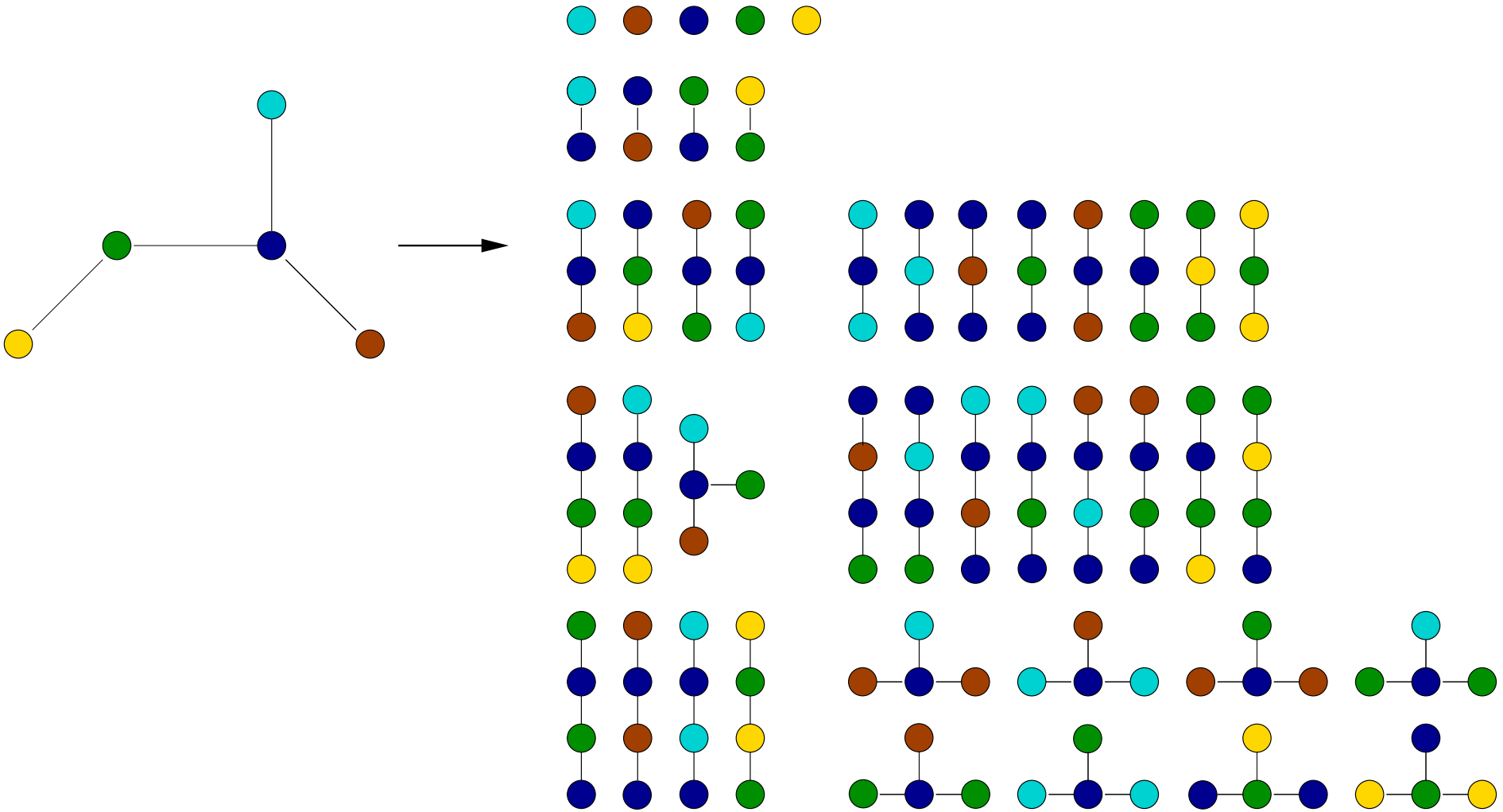
- Tottering walks seem irrelevant for many applications
- Focusing on non-tottering walks is a way to get closer to the path kernel (e.g., equivalent on trees).

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

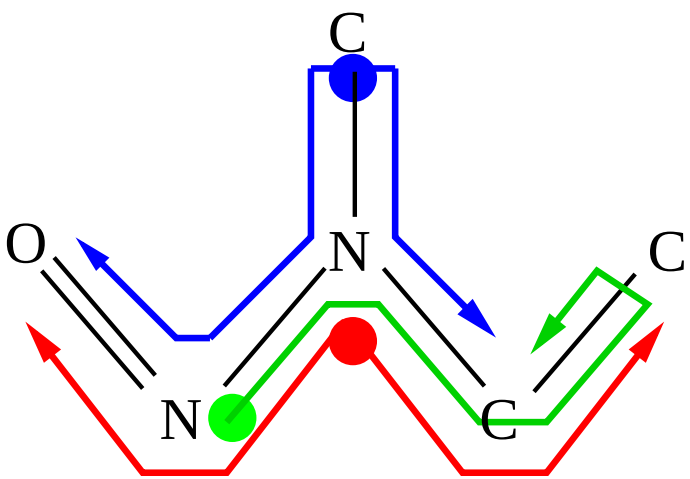
- Second-order Markov random walk to prevent tottering walks
- Written as a first-order Markov random walk on an augmented graph
- Normal walk kernel on the augmented graph (which is always a directed graph).

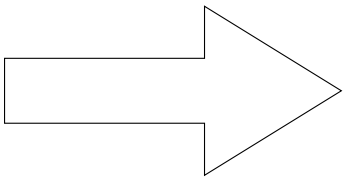


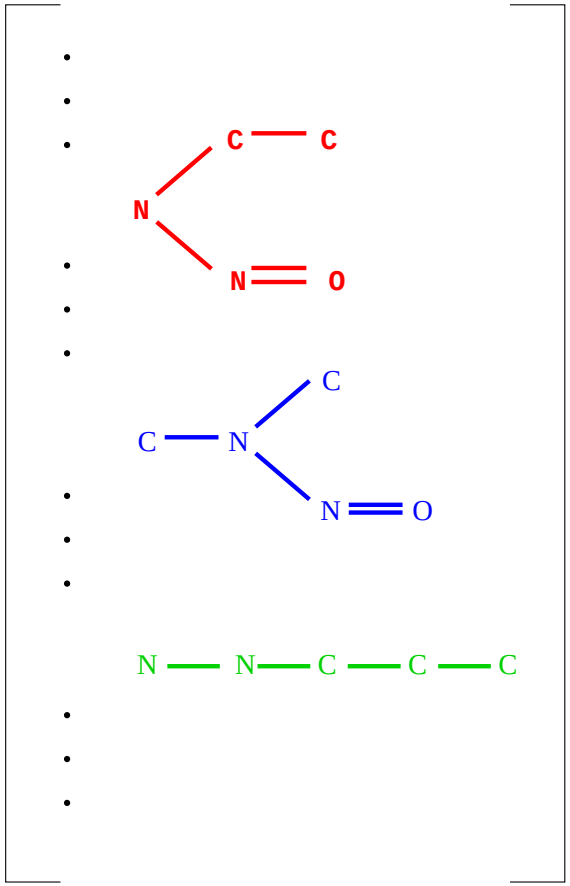
Extension 2: Subtree kernels



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 (Mahé et al., 2004)

MUTAG dataset

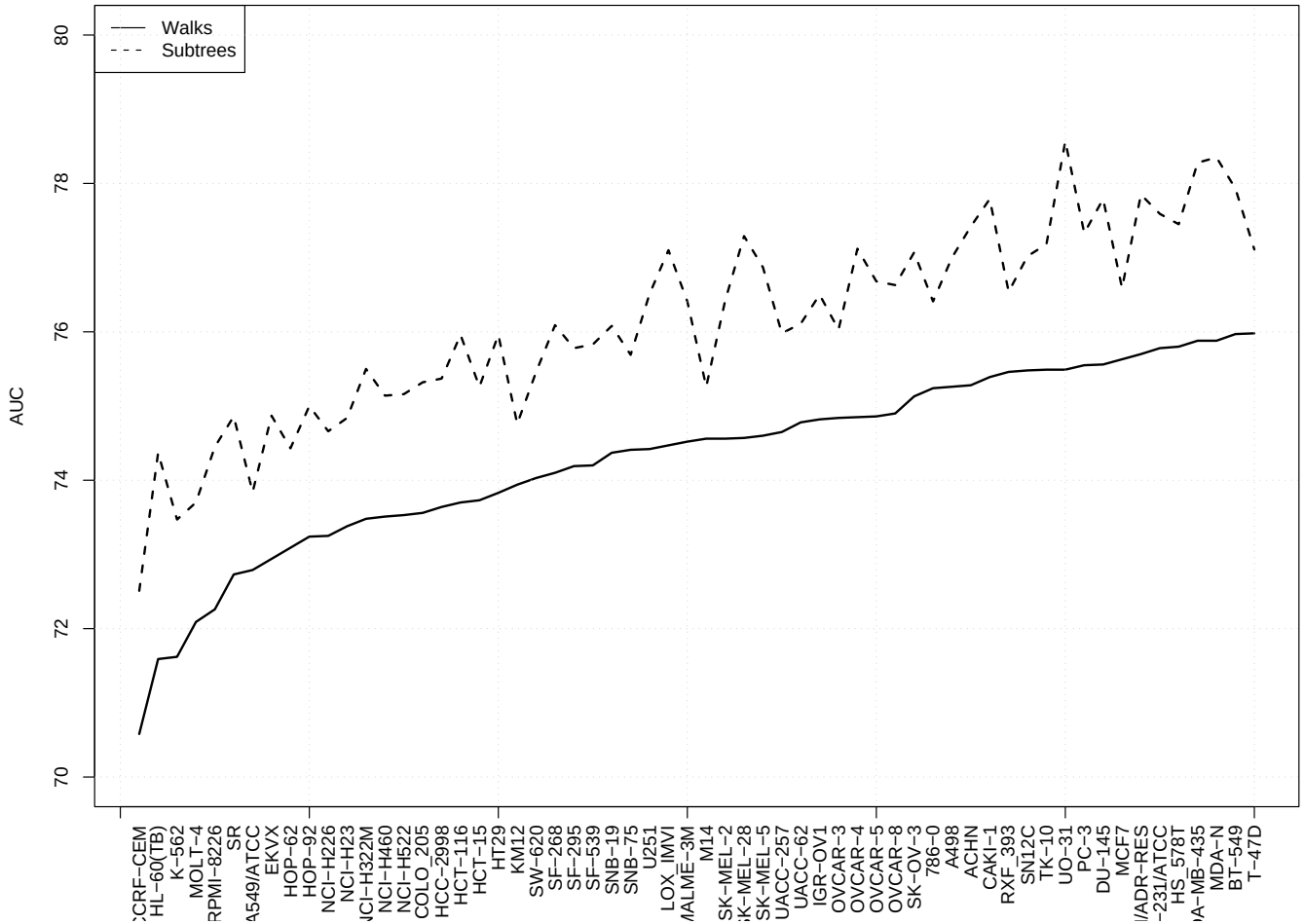
- aromatic/hetero-aromatic compounds
- high mutagenic activity /no mutagenic activity, assayed in *Salmonella typhimurium*.
- 188 compouunds: 125 + / 63 -

Results

10-fold cross-validation accuracy

Method	Accuracy
Progol1	81.4%
2D kernel	91.2%

2D Subtree vs fragment kernels (Mahé and V, 2007)



Screening of inhibitors for 60 cancer cell lines (from Mahé and V., 2008)

Outline

Conclusion

- Modern machine learning methods for regression / classification lend themselves well to the integration of prior knowledge in the penalization / regularization function.
- Kernel methods (eg SVM) allow to manipulate complex objects (eg molecules, biological sequences) as soon as kernels can be defined and computed.

People I need to thank

Including prior knowledge in penalization

Franck Rapaport, Emmanuel Barillot, Andrei Zynoviev, Laurent Jacob, Kevin Bleakley...

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