Support vector machines, kernels, and applications in computational biology

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1. Machine learning in bioinformatics
2. Linear support vector machines
3. Nonlinear SVM and kernels
4. SVM for complex data: the case of graphs
5. Conclusion
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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

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
Chromosomal 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
Problem 1

Given the CGH profile of a melanoma, is it aggressive or not?
CGH shows the (static) DNA
Cancer cells have also abnormal (dynamic) gene expression (= transcription)
Tissue profiling with DNA chips

1. Prepare cDNA Probe
   - "Normal"
   - Tumor
   - RT / PCR
   - Label with Fluorescent Dyes
   - Combine Equal Amounts

2. Prepare Microarray
   - Hybridize probe to microarray
   - SCAN

Microarray Technology

[Image of a DNA chip with different colors indicating the results of the assay.]
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

<table>
<thead>
<tr>
<th>A : Alanine</th>
<th>V : Valine</th>
<th>L : Leucine</th>
</tr>
</thead>
<tbody>
<tr>
<td>F : Phenylalanine</td>
<td>P : Proline</td>
<td>M : Methionine</td>
</tr>
<tr>
<td>E : Acide glutamique</td>
<td>K : Lysine</td>
<td>R : Arginine</td>
</tr>
<tr>
<td>T : Threonine</td>
<td>C : Cysteine</td>
<td>N : Asparagine</td>
</tr>
<tr>
<td>H : Histidin</td>
<td>V : Thyrosine</td>
<td>W : Tryptophane</td>
</tr>
<tr>
<td>I : Isoleucin</td>
<td>S : Serine</td>
<td>Q : Glutamine</td>
</tr>
<tr>
<td>D : Acide aspartique</td>
<td>G : Glycine</td>
<td></td>
</tr>
</tbody>
</table>
Protein annotation

Data available

- **Secreted proteins:**
  - MASKATLLLAFTLLFATCIARHQQRQQQONQCQLONIEA...
  - MARSSLFTFLCLAVFINGLSSEQIEQQSPWEFGSEVW...
  - MALHTVLIMLSLLPMLEAQNPEHANITIGEPITNETLGWL...
  - ...

- **Non-secreted proteins:**
  - MAPPSVFAEVPAQPVLVFKLIADEFREDPDPKRKNLGVG...
  - MAHTLGLTQPNSTEHKISFTAEIDVIEWKGDILVVG...
  - MSISESYAKEIKTAFQFTDFPIEGEQFEDFLPIIGNP...
  - ...

Problem 4

Given a newly sequenced protein, is it secreted or not?
Problem 4
Given a new candidate molecule, is it likely to be active?
Pattern recognition, *aka* supervised classification
Pattern recognition, *aka* supervised classification
Pattern recognition, *aka* supervised classification
Pattern recognition, *aka* supervised classification

**Challenges**
- High dimension
- Few samples
- Structured data
- Heterogeneous data
- Prior knowledge
- Fast and scalable implementations
- Interpretable models
1 Machine learning in bioinformatics
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5 Conclusion
Linear classifiers
Linear classifiers
Linear classifiers
Linear classifiers
Linear classifiers
Linear classifiers
Linear classifiers
Linear classifiers
Which one is better?
The margin of a linear classifier
The margin of a linear classifier
The margin of a linear classifier
The margin of a linear classifier
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:
  \[
  S = \{(\vec{x}_1, y_1), \ldots, (\vec{x}_N, y_N)\},
  \]
  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 \( f(x) = \vec{w} \cdot \vec{x} + b \) consider the "tube" defined by the values \(-1\) and \(+1\) of the decision function:

\[
\begin{align*}
\vec{w} \cdot \vec{x} + b > +1 \\
\vec{w} \cdot \vec{x} + b < -1 \\
\vec{w} \cdot \vec{x} + b = +1 \\
\vec{w} \cdot \vec{x} + b = -1
\end{align*}
\]
Indeed, the points $\vec{x}_1$ and $\vec{x}_2$ satisfy:

\[
\begin{align*}
\vec{w}.\vec{x}_1 + b &= 0, \\
\vec{w}.\vec{x}_2 + b &= 1.
\end{align*}
\]

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:

\[
\vec{w} \cdot \vec{x}_i + b \geq 1
\]

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

\[
\vec{w} \cdot \vec{x}_i + b \leq -1
\]

Both cases are summarized by:

\[
\forall i = 1, \ldots, N, \quad y_i (\vec{w} \cdot \vec{x}_i + b) \geq 1
\]
Finding the optimal hyperplane

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

\[
\|\mathbf{w}\|^2
\]

under the constraints:

\[
\forall i = 1, \ldots, N, \quad y_i (\mathbf{w} \cdot \mathbf{x}_i + b) - 1 \geq 0.
\]

This is a classical quadratic program on \(\mathbb{R}^{d+1}\).
In order to minimize:

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

under the constraints:

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

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

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

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

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

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". \( \alpha^* \) can be found efficiently using dedicated optimization softwares.
Once $\alpha^*$ is found, we recover $(\vec{w}^*, b^*)$ corresponding to the optimal hyperplane. $w^*$ is given by:

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

and the decision function is therefore:

$$f^*(\vec{x}) = \vec{w}^* . \vec{x} + b^*$$

$$= \sum_{i=1}^{N} \alpha_i \vec{x}_i . \vec{x} + b^*.$$  (1)
Interpretation: support vectors

\[ \alpha > 0 \quad \alpha = 0 \]
What if data are not linearly separable?
What if data are not linearly separable?
What if data are not linearly separable?
What if data are not linearly separable?
Soft-margin SVM

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

\[
\min_{f} \left\{ \frac{1}{\text{margin}(f)} + C \times \text{errors}(f) \right\}
\]

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

\[
\text{margin}(\vec{x}, y) = y (\vec{w} \cdot \vec{x} + b)
\]

The error is

- 0 if \(\text{margin}(\vec{x}, y) > 1\),
- \(1 - \text{margin}(\vec{x}, y)\) otherwise.

The soft margin SVM solves:

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

$\alpha = 0$

$0 < \alpha < C$

$\alpha = C$

$0 < \alpha < C$
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Sometimes linear classifiers are not interesting
Let $\Phi(\vec{x}) = (x_1^2, x_2^2)'$, $\vec{w} = (1, 1)'$ and $b = 1$. Then the decision function is:

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

$$\forall x, x' \in \mathcal{X}, \quad K(x, x') = \Phi(x) \cdot \Phi(x') = (x_1^2)(x'_1)^2 + (x_2^2)(x'_2)^2.$$ 

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

$$K(x, x') = \Phi(x) \cdot \Phi(x') = (x_1^2)(x'_1)^2 + (x_2^2)(x'_2)^2.$$
Replace each $\vec{x} \cdot \vec{x}'$ in the SVM algorithm by $\tilde{\Phi}(x) \cdot \tilde{\Phi}(x') = K(x, x')$

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:

\[ f(x) = \mathbf{w}^* \cdot \Phi(x) + b^* \]

\[ = \sum_{i=1}^{N} \alpha_i K(x_i, x) + b^*. \quad (2) \]
The explicit computation of $\Phi(x)$ 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.
For $\tilde{x} = (x_1, x_2)^\top \in \mathbb{R}^2$, let $\Phi(\tilde{x}) = (x_1^2, \sqrt{2}x_1x_2, x_2^2) \in \mathbb{R}^3$:

$$K(\tilde{x}, \tilde{x}') = x_1^2x_1'^2 + 2x_1x_2x_1'x_2' + x_2^2x_2'^2$$

$$= (x_1x_1' + x_2x_2')^2$$

$$= (\tilde{x}.\tilde{x}')^2.$$
More generally,

\[ K(\vec{x}, \vec{x}') = (\vec{x} \cdot \vec{x}' + 1)^d \]

is an inner product in a feature space of all monomials of degree up to \(d\) (left as exercise.)
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 $x, x'$ in $\mathcal{X}$:

$$
K(x, x') = \langle \Phi(x), \Phi(x') \rangle_{\mathcal{H}}.
$$
A positive definite (p.d.) function on the set \( \mathcal{X} \) is a function \( K : \mathcal{X} \times \mathcal{X} \rightarrow \mathbb{R} \) symmetric:
\[
\forall (x, x') \in \mathcal{X}^2, \quad K(x, x') = K(x', x),
\]
and which satisfies, for all \( N \in \mathbb{N} \), \( (x_1, x_2, \ldots, x_N) \in \mathcal{X}^N \) et \( (a_1, a_2, \ldots, a_N) \in \mathbb{R}^N \):
\[
\sum_{i=1}^{N} \sum_{j=1}^{N} a_i a_j K(x_i, x_j) \geq 0.
\]
Kernels are p.d. functions

Theorem (Aronszajn, 1950)

$K$ is a kernel if and only if it is a positive definite function.
Kernel $\Longrightarrow$ p.d. function:
\[
\langle \Phi(x), \Phi(x') \rangle_{\mathbb{R}^d} = \langle \Phi(x'), \Phi(x) \rangle_{\mathbb{R}^d},
\]
\[
\sum_{i=1}^{N} \sum_{j=1}^{N} a_i a_j \langle \Phi(x_i), \Phi(x_j) \rangle_{\mathbb{R}^d} = \| \sum_{i=1}^{N} a_i \Phi(x_i) \|^2_{\mathbb{R}^d} \geq 0.
\]

P.d. function $\Longrightarrow$ kernel: more difficult...
Kernel examples

- **Polynomial (on \( \mathbb{R}^d \))**:
  \[
  K(x, x') = (x \cdot x' + 1)^d
  \]

- **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 \( \Phi : \mathcal{X} \rightarrow \mathcal{H} \) such that \( K(x, x') = \langle \Phi(x), \Phi(x') \rangle \)
Example: SVM with a Gaussian kernel

- **Training:**

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

s.t. \(0 \leq \alpha_i \leq C\), 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
$$\min_f \left\{ \frac{1}{\text{margin}(f)} + C \times \text{errors}(f) \right\}$$

- **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 $C$
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Virtual screening for drug discovery

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

$$K(x, x') = \Phi(x) \transp \Phi(x').$$

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

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

   $$K(x, x') = \Phi(x)^T \Phi(x').$$

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

Jean-Philippe Vert (ParisTech)

Machine learning in bioinformatics

Mines ParisTech
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 $\mathcal{H}$. 

Jean-Philippe Vert (ParisTech) 

Machine learning in bioinformatics
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...
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 exercise).
Indexing by all subgraphs?

\[ (0, \ldots, 0, 1, 0, \ldots, 0, 1, 0, \ldots) \]

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**Definition**

- A path of a graph \((V, E)\) is a 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?

Theorem

1. Computing all path occurrences is \textit{NP-hard}.
2. Computing the path kernel is \textit{NP-hard}

Proof.

Same as for subgraphs.
Indexing by all paths?

Theorem

1. Computing all path occurrences is **NP-hard**.
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Indexing by all paths?

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1. Computing all path occurrences is **NP-hard**.
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**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 $\neq$ paths
Walk kernel

**Definition**

- Let \( S_n \) denote the set of all possible label sequences of walks of length \( n \) (including vertices and edges labels), and \( S = \bigcup_{n \geq 1} S_n \).
- 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 \( \Phi(G) = (\Phi_s(G))_{s \in S} \) 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:
  \[
  K_{walk}(G_1, G_2) = \sum_{s \in S} \Phi_s(G_1) \Phi_s(G_2).
  \]
Walk kernel

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  $$\Phi_s(G) = \sum_{w \in \mathcal{W}(G)} \lambda_G(w) \mathbf{1} (s \text{ is the label sequence of } w).$$
- A walk kernel is a graph kernel defined by:
  $$K_{\text{walk}}(G_1, G_2) = \sum_{s \in S} \Phi_s(G_1) \Phi_s(G_2).$$
Walk kernel examples

Examples

- The *nth-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 independent random walks on $G_1$ and $G_2$, respectively (Kashima et al., 2003).

- The *geometric walk kernel* is obtained (when it converges) with $\lambda_G(w) = \beta^{\text{length}(w)}$, for $\beta > 0$. In that case the feature space is of infinite dimension (Gärtner et al., 2003).
### Examples

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The geometric walk kernel is obtained (when it converges) with $\lambda_G(w) = \beta^{\text{length}(w)}$, for $\beta > 0$. In that case the feature space is of infinite dimension (Gärtner et al., 2003).
Computation of walk kernels

Proposition

These three kernels ($n$th-order, random and geometric walk kernels) can be computed efficiently in \textit{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. $V = \{(v_1, v_2) \in V_1 \times V_2 : v_1$ and $v_2$ have the same label\}$,
2. $E = \{((v_1, v_2), (v'_1, v'_2)) \in V \times V : (v_1, v'_1) \in E_1$ and $(v_2, v'_2) \in E_2\}$.
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

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

$$= \sum_{(w_1, w_2) \in \mathcal{W}(G_1) \times \mathcal{W}(G_1)} \lambda_{G_1}(w_1) \lambda_{G_2}(w_2) 1(l(w_1) = l(w_2))$$

$$= \sum_{w \in \mathcal{W}(G_1 \times G_2)} \lambda_{G_1 \times G_2}(w).$$
Walk kernel and product graph

Lemma

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\]

\[
= \sum_{w \in \mathcal{W}(G_1 \times G_2)} \lambda_{G_1 \times G_2}(w).
\]
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:

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

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

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

- Computation in $O(n|G_1| |G_2| d_1 d_2)$, where $d_i$ is the maximum degree of $G_i$. 
In both cases $\lambda_G(w)$ for a walk $w = v_1 \ldots v_n$ can be decomposed as:

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

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

$$K_{walk}(G_1, G_2) = \sum_{n=1}^{\infty} \sum_{w \in \mathcal{W}_n(G_1 \times G_2)} \lambda^i(v_1) \prod_{i=2}^{n} \lambda^t(v_{i-1}, v_i)$$

$$= \sum_{n=0}^{\infty} \Lambda_i \Lambda_t^n \mathbf{1}$$

$$= \Lambda_i (I - \Lambda_t)^{-1} \mathbf{1}$$

Computation in $O(|G_1|^3 |G_2|^3)$
Atom relabeling 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).
A tottering walk is a walk $w = v_1 \ldots v_n$ 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**).

![Diagram showing a chemical structure and its augmented graph representation.](image-url)
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 \textbf{product graph}.
- Recursion: if $I(v, n)$ denotes the weighted number of subtrees of depth $n$ rooted at the vertex $v$, then:

$$I(v, n + 1) = \sum_{R \subset \mathcal{N}(v)} \prod_{v' \in R} \lambda_t(v, v') I(v', n),$$

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 \textbf{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 compounds: 125 + / 63 -

Results

10-fold cross-validation accuracy

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progol1</td>
<td>81.4%</td>
</tr>
<tr>
<td>2D kernel</td>
<td>91.2%</td>
</tr>
</tbody>
</table>
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

1. Machine learning in bioinformatics
2. Linear support vector machines
3. Nonlinear SVM and kernels
4. SVM for complex data: the case of graphs
5. Conclusion
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)