Graph Kernels in Chemoinformatics

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Bordeaux,
November, 20 2014

Plan

Plan

Motivation

Structural Pattern Recognition

- ✚ Rich description of objects
- ▬ Poor properties of graph's space does not allow to readily generalize/combine sets of graphs

Statistical Pattern Recognition

- ▬ Global description of objects
- ✚ Numerical spaces with many mathematical properties (metric, vector space, ...).

Motivation

Analyse large famillies of structural and numerical objects using a **unified** framework based on pairwise similarity.

Chemoinformatics

- Usages of computer science for chemistry
- **Prediction of molecular properties**
- Prediction of biological activities
  - Toxicity, cancerous ...
- Prediction of physico-chemical properties.
  - Boiling point, LogP, ability to capture CO_2...

Screening :

- Synthesis of molecule,
- Test and validation of the synthesized molecules

Virtual Screening :

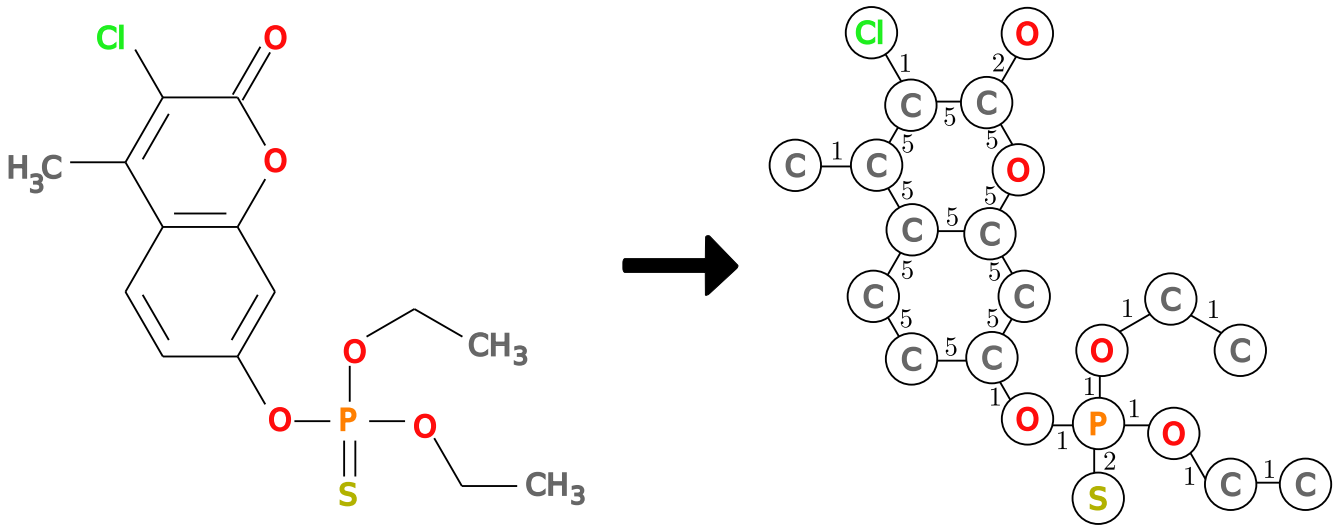
- Selection of a limited set of candidate molecules,
- Synthesis and test of the selected molecules,

→ Gain of Time and Money

Molecular representation

Molecular Graph:

- Vertice ⟶ atoms.
- Edges ⟶ Atomic bonds.



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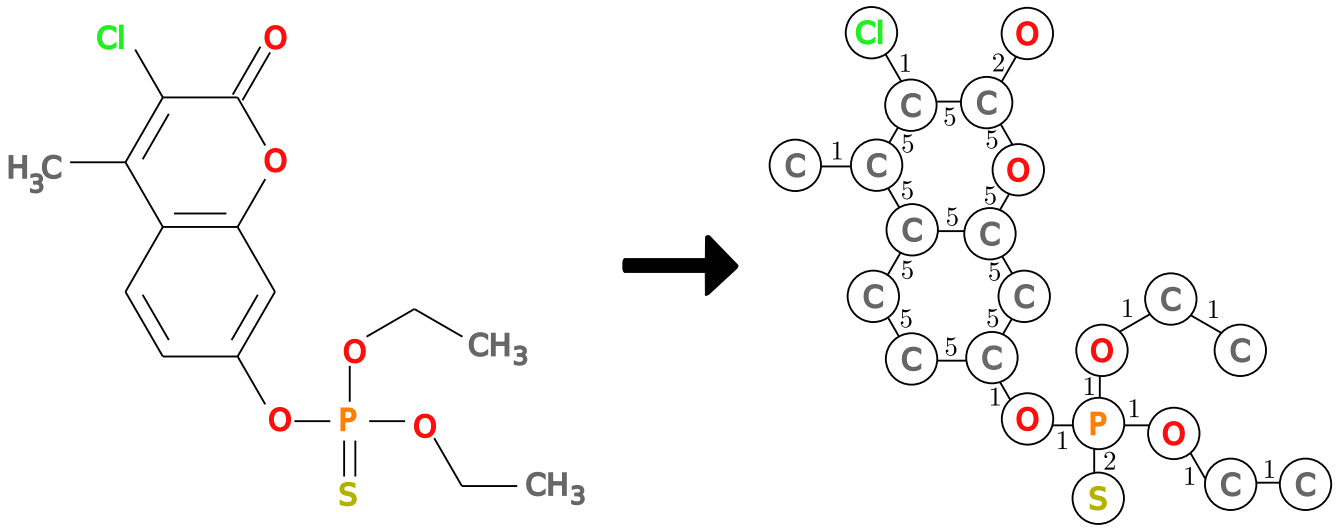

Similarity principle [Johnson and Maggiora, 1990]

- *"Similar molecules have similar properties."*

⟶ Design of similarity measures between molecular graphs.

Plan

Kernel Theory

Kernel $k : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$

- Symmetric: $k(x_i, x_j) = k(x_j, x_i)$,
- For any dataset $D = \{x_1, \ldots, x_n\}$, Gram's matrix $K \in \mathbb{R}^{n \times n}$ is defined by $K_{i,j} = k(x_i, x_j)$.
- Semi-definite positive: $\forall \alpha \in \mathbb{R}^n, \alpha^T K \alpha \geq 0$

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Connection with Hilbert spaces, reproducing kernel Hilbert Spaces [Aronszajn, 1950]:

- Relationship scalar product $\Leftrightarrow$ kernel :

$$k(x, x') = \langle \Phi(x), \Phi(x') \rangle_{\mathcal{H}}.$$

Graph Kernels

Graph kernels in chemoinformatics

- Graph kernel $k : \mathcal{G} \times \mathcal{G} \to \mathbb{R}$.
- Similarity measure between molecular graphs
- ✚ Natural encoding of a molecule
- ✚ Implicit embedding in $\mathcal{H}$,
- ✚ Machine learning methods (SVM, KRR, ...).

Graph Kernels

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- Similarity measure between molecular graphs
- ✚ Natural encoding of a molecule
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- ✚ Machine learning methods (SVM, KRR, ...).

→ Natural connection between molecular graphs and machine learning methods

→ Definition of a similarity measure as a kernel

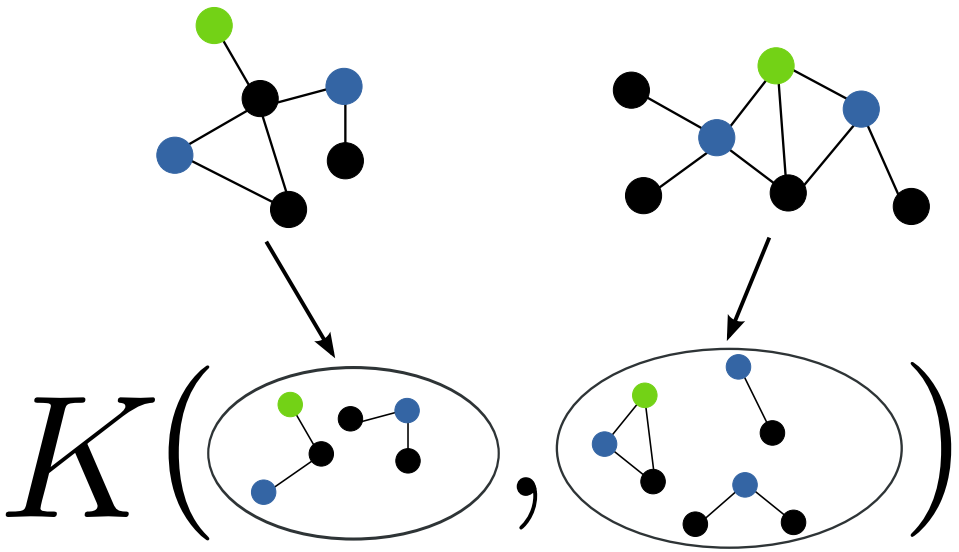
Kernels based on bags of patterns

Graph kernels based on bags of patterns

(1) Extraction of a set of patterns from graphs,

(2) Comparison between patterns,

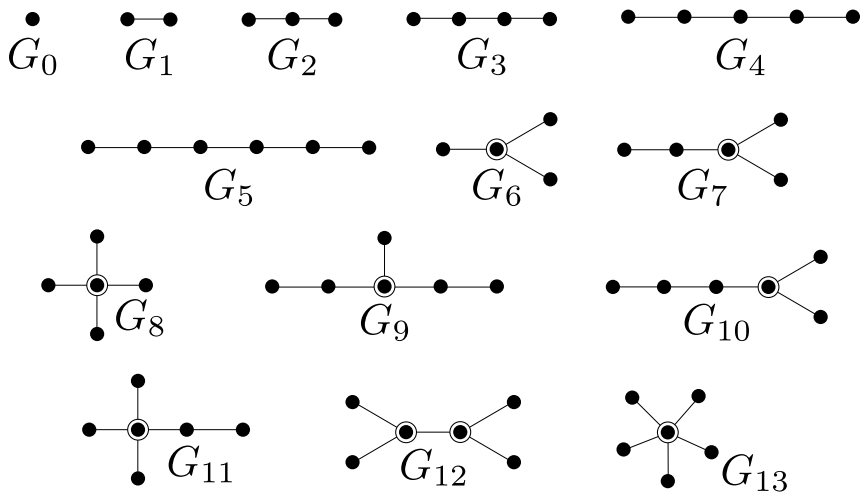
(3) Comparison between bags of patterns.



Plan

Treelets

Set of labeled subtrees with at most 6 nodes :

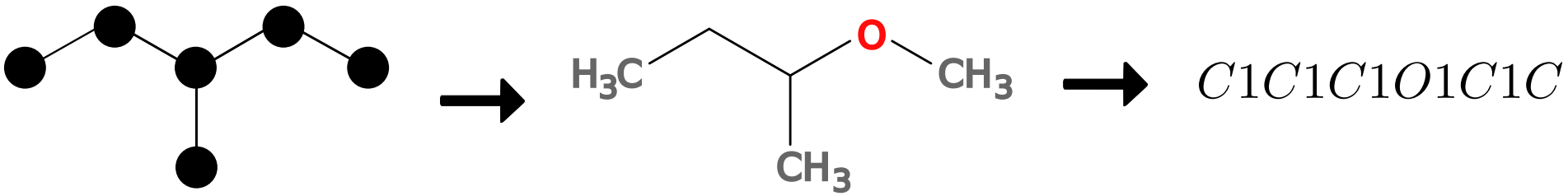


- Encode branching points
- Take labels into account.
- Pertinent from a chemical point of view
- limited set of substructures
- Linear complexity (in $\mathcal{O}(nd^5)$).

enumaration

Labelling

- Code encoding the labels,
- Defined on each of the 14 structure of treelet,
- ✚ Computation in constant time.



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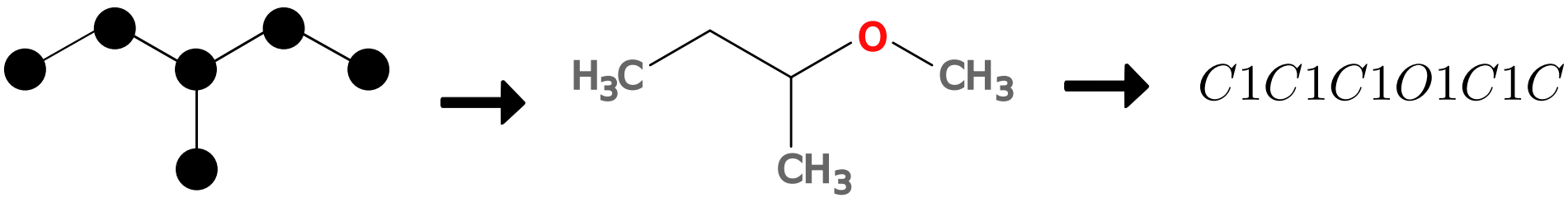

Canonical code :

- type of treelet,
- Labels.

} canonical code : G_9-$C1C1C1O1C1C$

$$t \simeq t' \Leftrightarrow \text{code}(t) = \text{code}(t')$$

Definition of the Treelet kernel

Counting treelet's occurences

- $f_t(G)$: Number of occurences of treelet t in G.

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Treelet kernel

$$k_{\mathcal{T}}(G, G') = \sum_{t \in \mathcal{T}(G) \cap \mathcal{T}(G')} k(f_t(G), f_t(G'))$$

- $\mathcal{T}(G)$: Set of treelets of G.
- $k(.,.)$: Kernel between real numbers.

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Treelet kernel

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- $\mathcal{T}(G)$: Set of treelets of G.
- $k_t(G, G') = k(f_t(G), f_t(G')$.
- $k_t(.,.)$: Similarity according to t.

Pattern selection

Prediction problems:

- Different properties ⟶ Different causes.

Pattern selection

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Chemist approach:

- Pattern relevant for a precise property
- A priori selection by a chemical expert

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- Different properties ⟶ Different causes.

Chemist approach:

- Pattern relevant for a precise property
- A priori selection by a chemical expert

Machine learning approach:

- Parcimonious set of relevant treelets
- Selection *a posteriori* induced by data.

Multiple kernel learning

Combination of kernels [Rakotomamonjy et al., 2008] :

$$k(G, G') = \sum_{t \in \mathcal{T}} k_t(G, G')$$

Multiple kernel learning

Optimal Combination of kernels [Rakotomamonjy et al., 2008] :

$$k_W(G, G') = \sum_{t \in \mathcal{T}} w_t \, k_t(G, G')$$

- $\mathcal{T}$: Set of treelets extracted from the learning dataset.
- $w_t \in [0, 1]$: Measure the influence of t

✚ Weighing of each sub kernel

→ Selection of relevant treelets

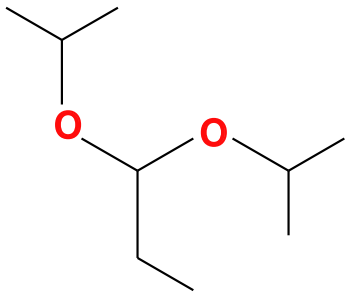
✚ Weighs computed for a given property.

Experiments

Prediction of the boiling point of acyclic molecules:

- 183 acyclic molecules :
  - Learning set: 80 %
  - Validation set: 10 %
  - Test set: 10 %

  } $10\times$
- Selection of optimal parameters using a grid search
- RMSE obtained on the 10 test sets.



Experiments

Prediction of the boiling point of acyclic molecules:

Méthode	**RMSE ($^\circ C$)**
Descriptor based approach [Cherqaoui et al., 1994]*	5,10
Empirical embedding [Riesen, 2009]	10,15
Gaussian kernel based on the graph edit distance [Neuhaus and Bunke, 2007]	10,27
Kernel on paths [Ralaivola et al., 2005]	12,24
Kernel on random walks [Kashima et al., 2003]	18,72
Kernel on tree patterns [Mahé and Vert, 2009]	11,02
Weisfeiler-Lehman Kernel[Shervaszide, 2012]	14,98
Treelet kernel	6,45
Treelet kernel with MKL	**4,22**

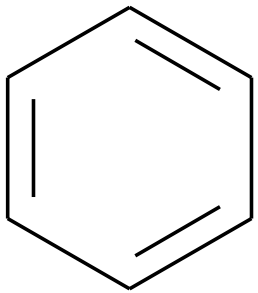
* leave-one-out

Plan

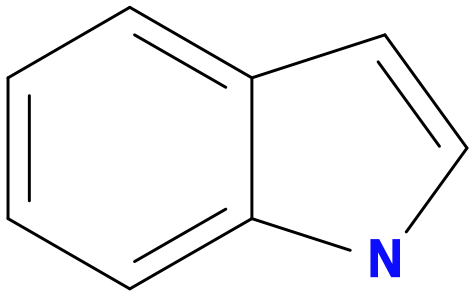
Cyclic molecular information

Cycles of a molecule

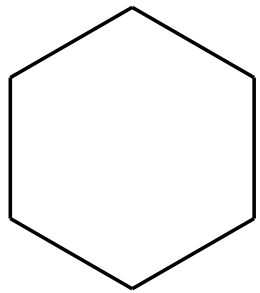
- Have a large influence on molecular properties.
- Identifies some molecular's families.



(a) Benzène



(b) Indole

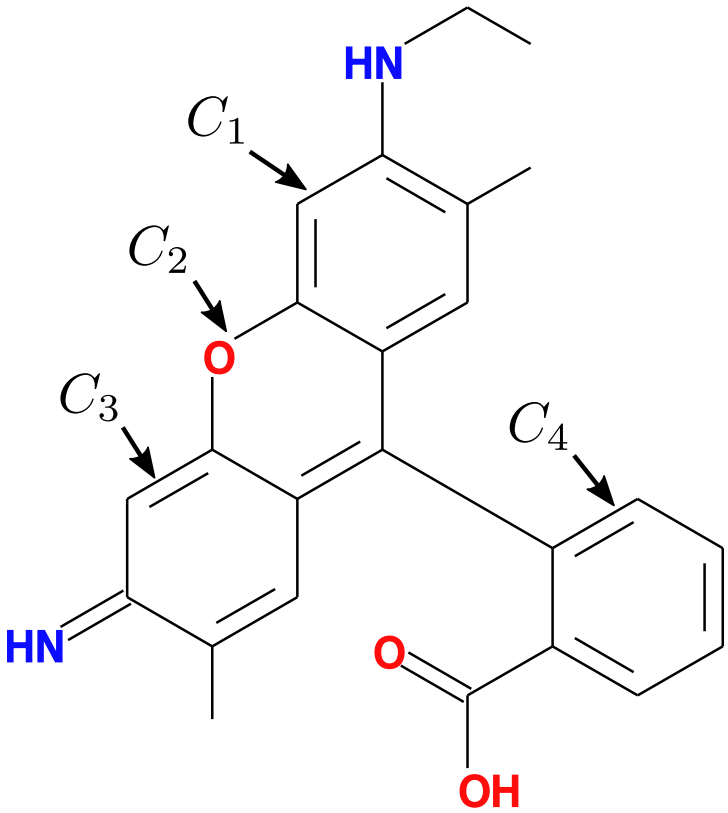


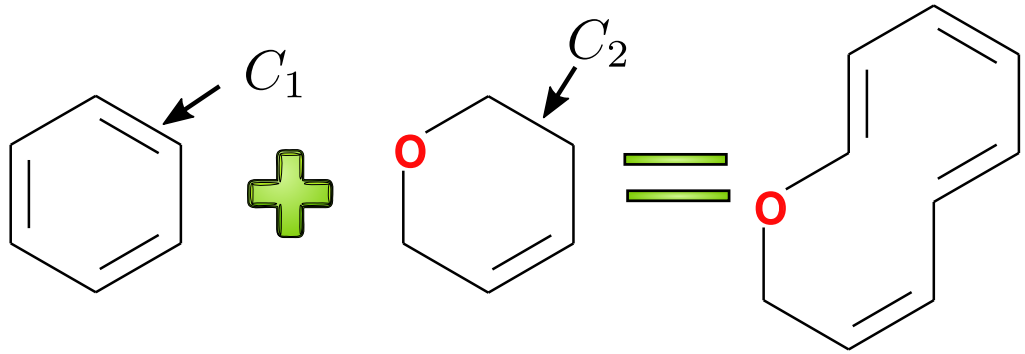
(c) Cyclohexane

→ **Cyclic information must be taken into account.**

Relevant Cycles

- Enumeration of all cycles is NP complete
- Cycles of a graph form a vector space on $\frac{\mathbb{Z}}{2\mathbb{Z}}$.

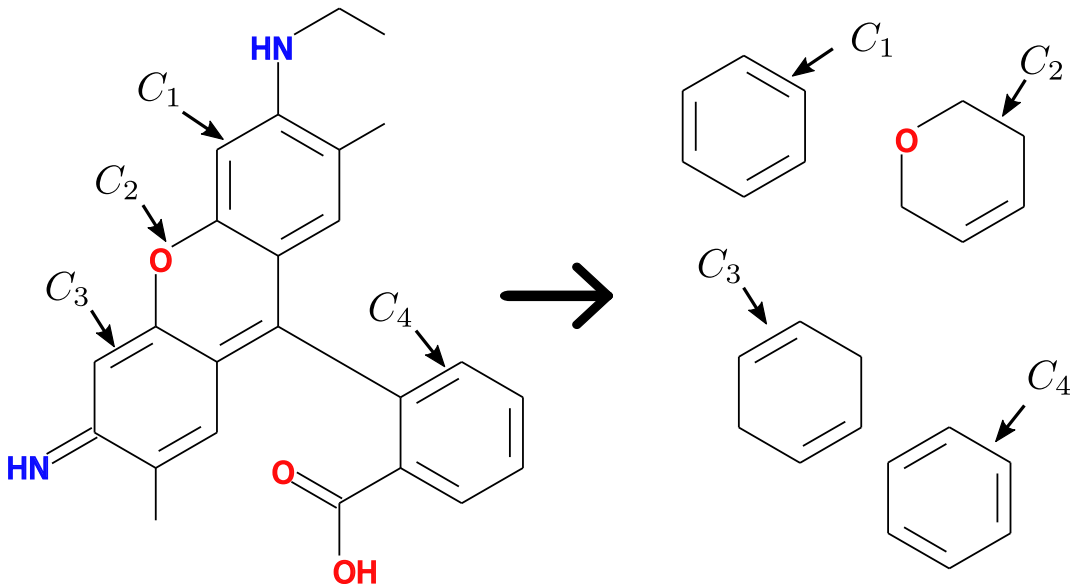




Relevant Cycles

Enumeration of relevant cycles [Vismara, 1995]:

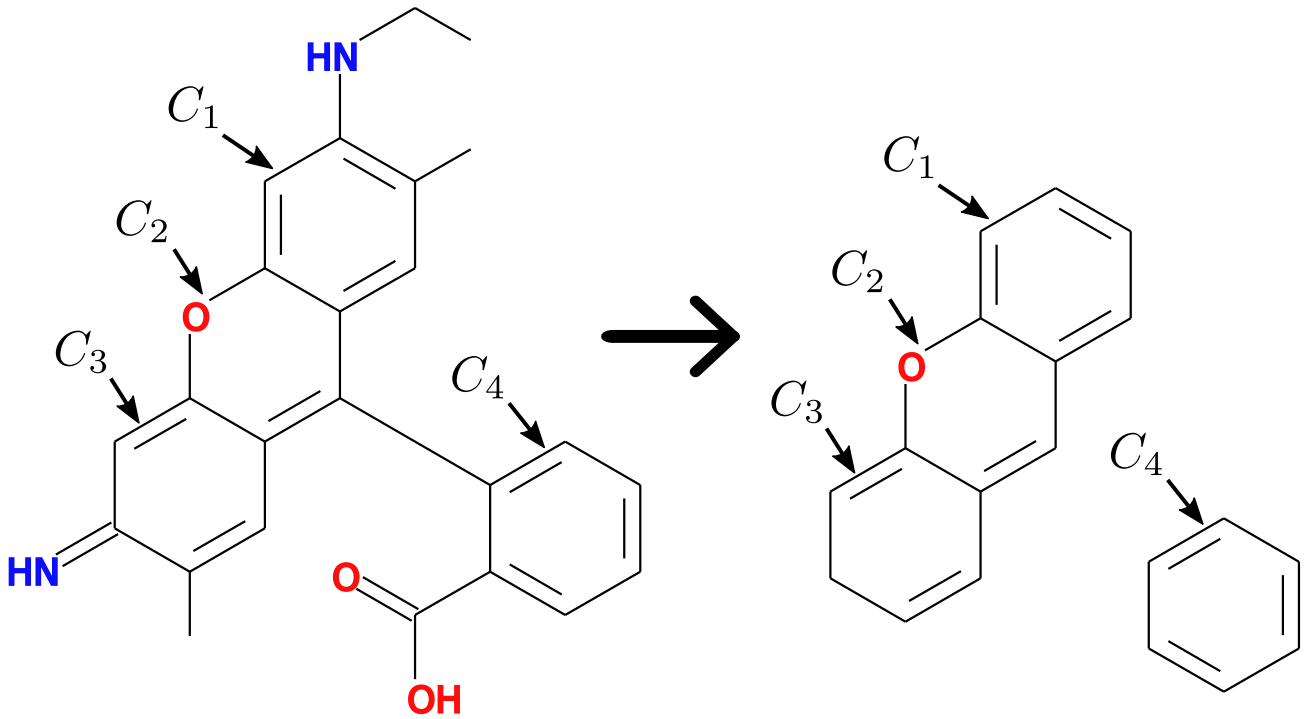
- Union of all cyclic bases with a minimal size,
- ✚ Unique for each graph,
- ✚ Enumeration in polynomial time,
- Kernel on relevant cycles [Horváth, 2005].



Relevant cycles Graph

Graph of relevant cycles $G_{\mathcal{C}}(G)$ [Vismara, 1995] :

- Representation of the cyclic system,
- Vertices: Relevant cycles,
- Edges: intersection between relevant cycles.



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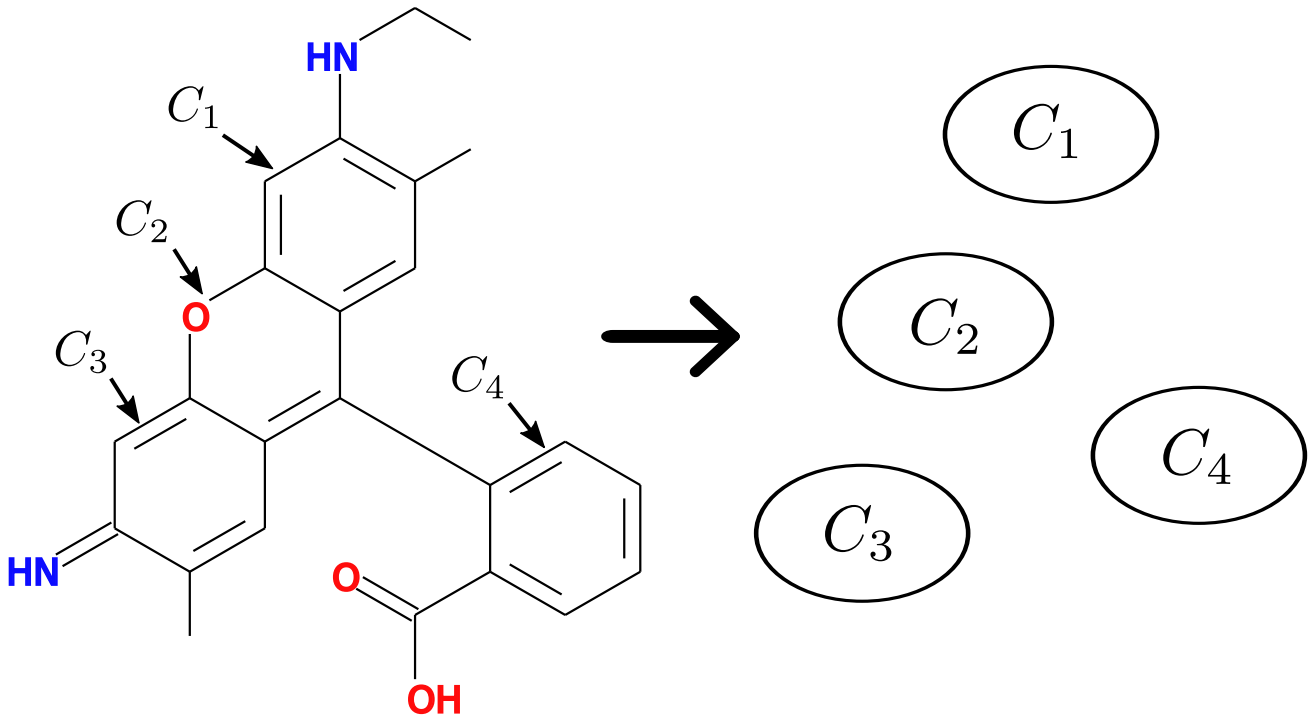

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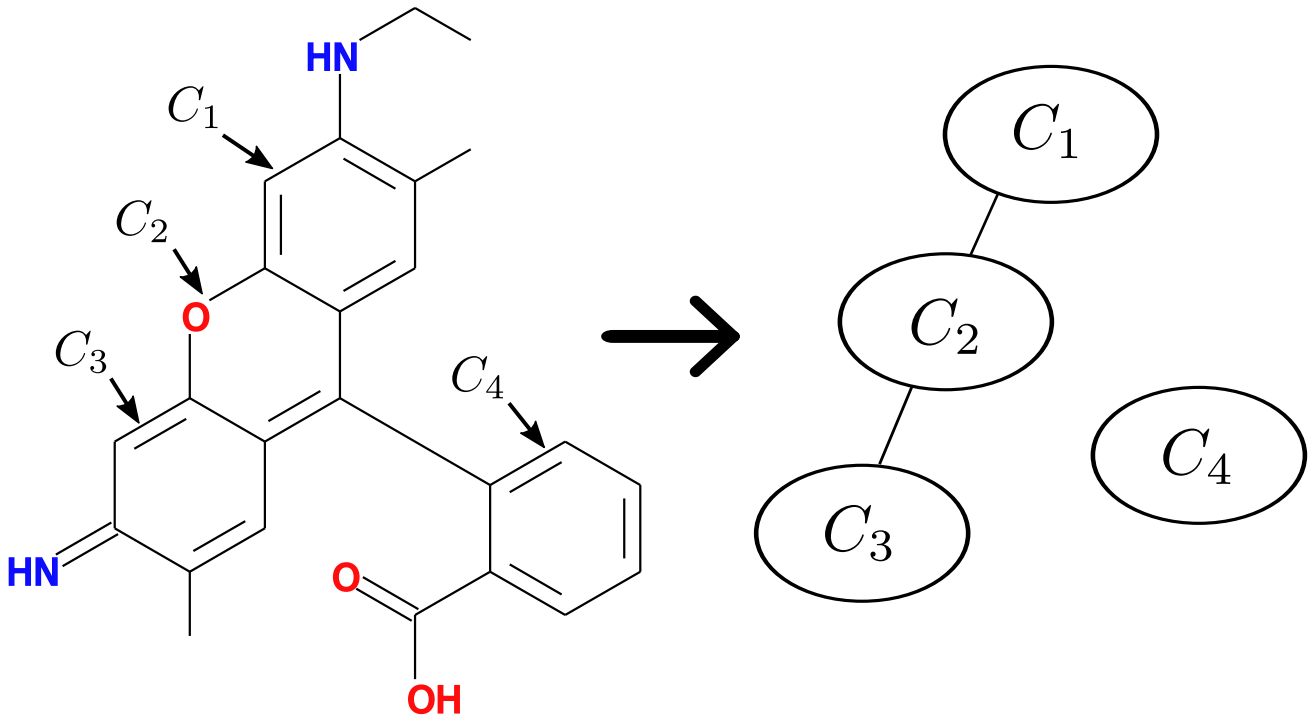
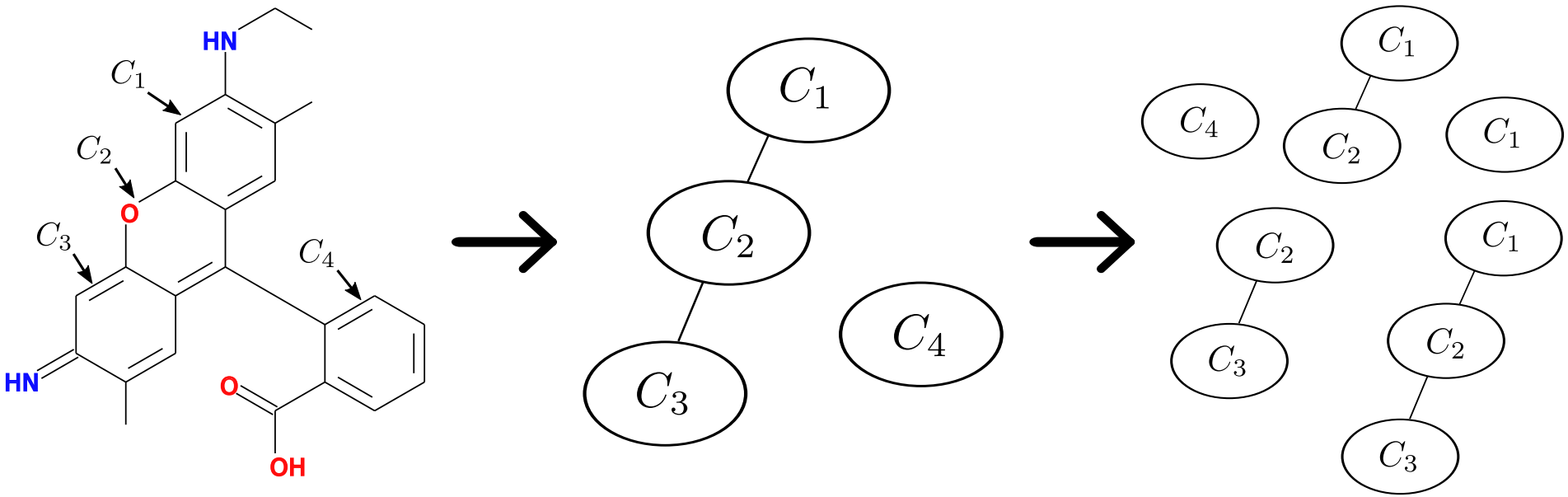


Relevant cycles Graph

Similarity between relevant cycle graphs

- Enumeration of relevant cycle graph's treelets.
- ✚ Adjacency relationship between relevant cycles.

Extracted Patterns :



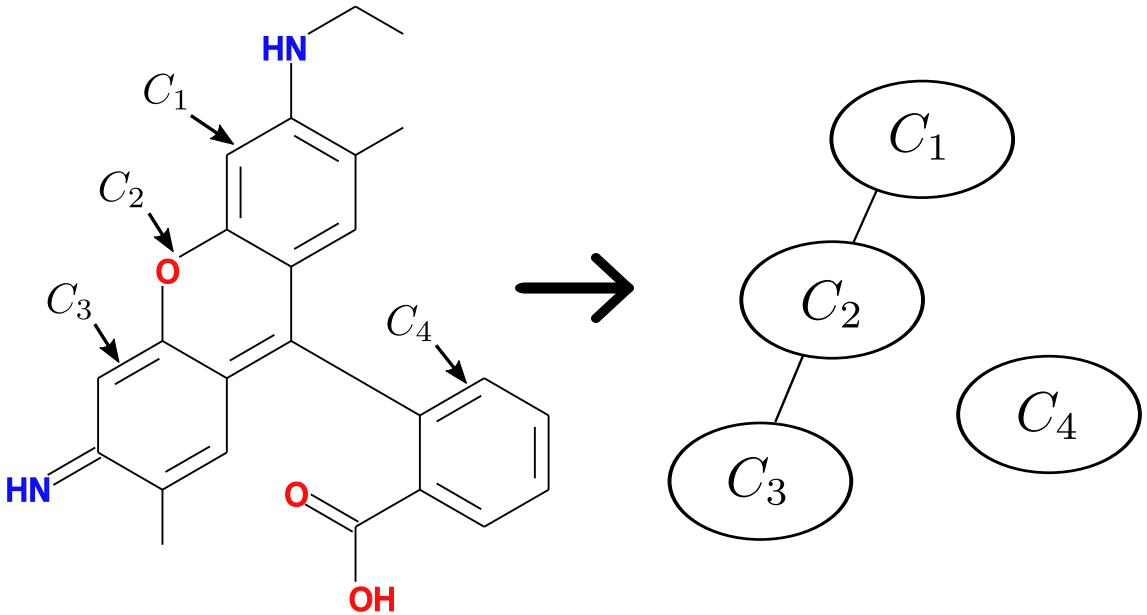
- Solely cyclic information.

Relevant cycle Hypergraph

Connexion between cycles and acyclic parts

- **Idea** : Molecular Representation:
  - Global,
  - Explicit cyclic Information

→ Addition of acyclic parts to the relevant cycle graph.



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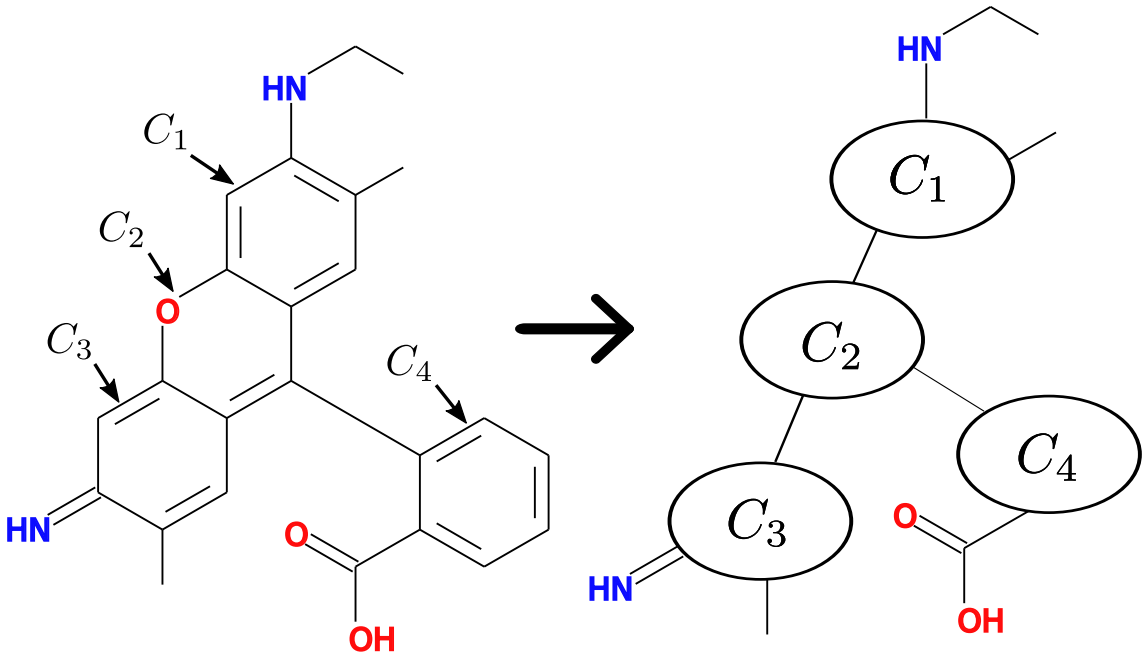
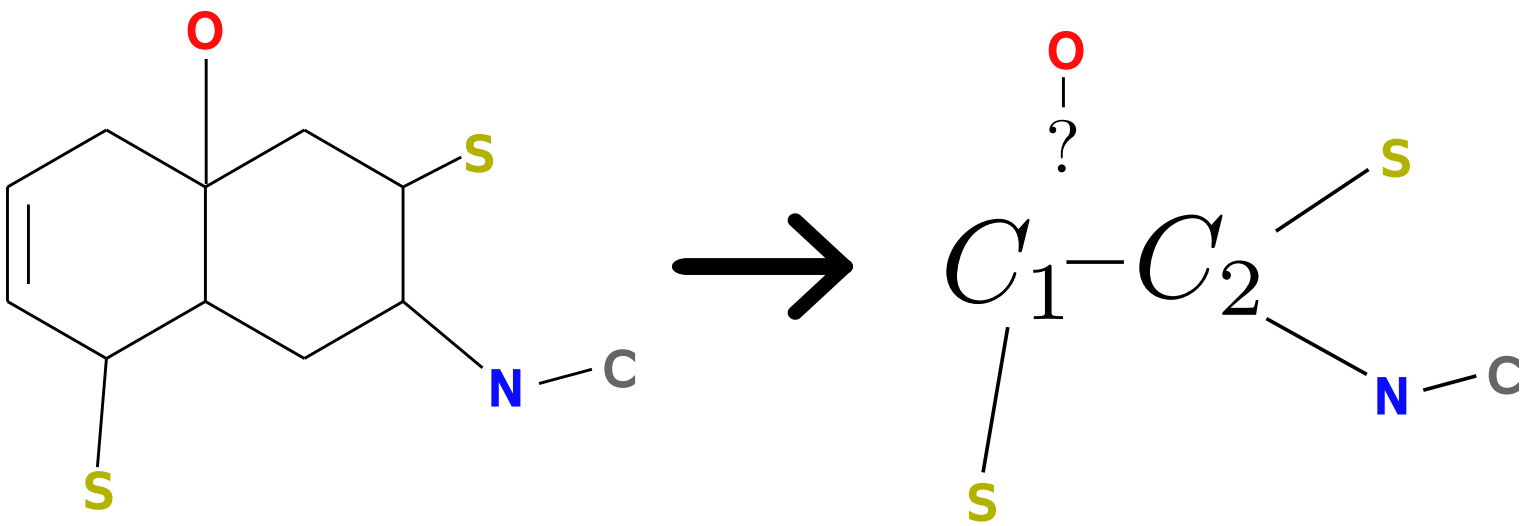


Relevant cycle Hypergraph

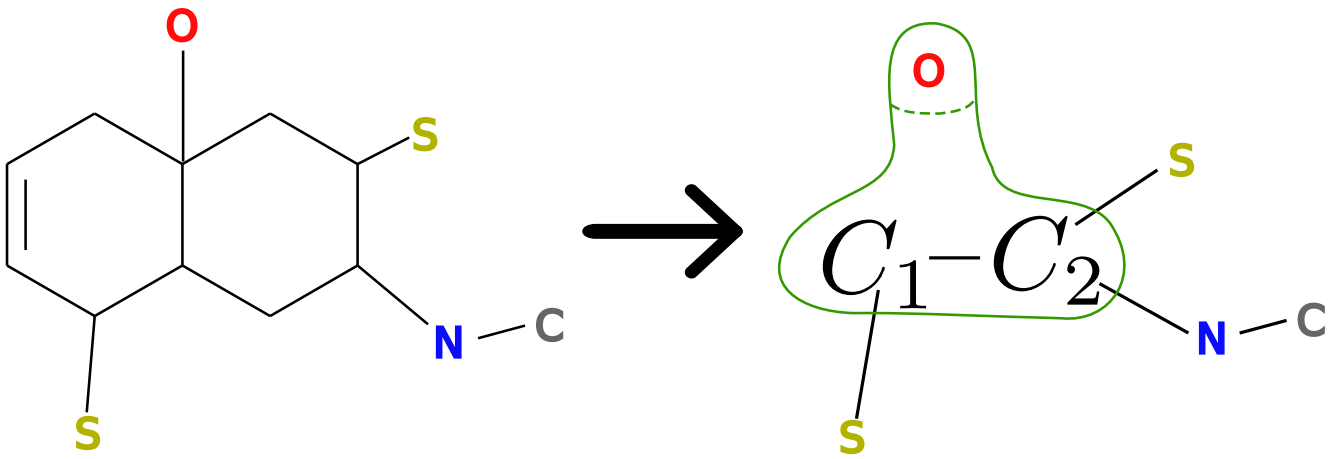
Problem : An atomic bound can connect an atom to two cycles.



Relevant cycle Hypergraph

Connexion between cycles and acyclic parts

- hypergraph representation of the molecule.
- Adjacency relationship: oriented hyper-edges.



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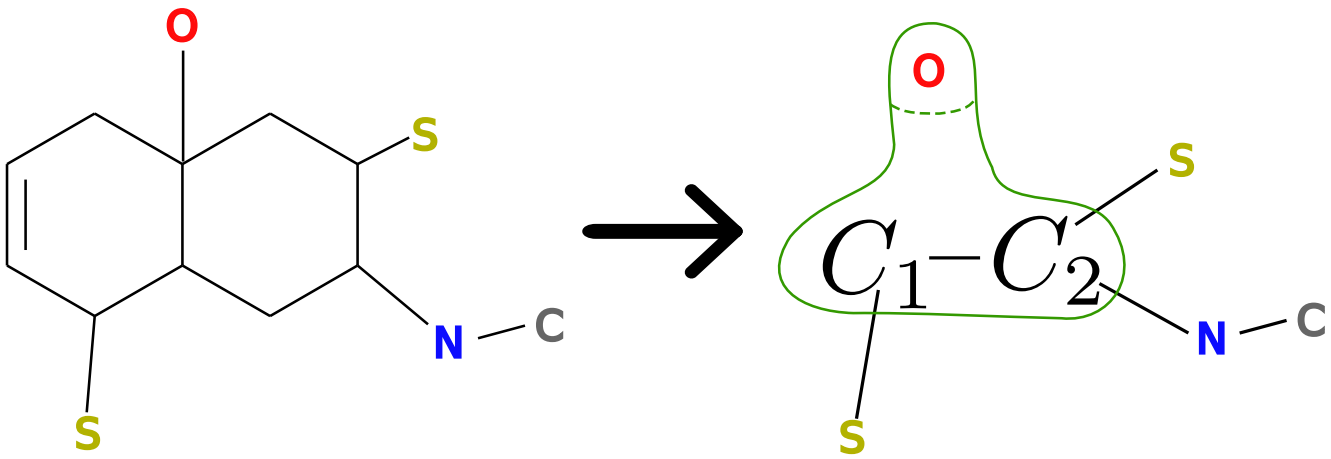
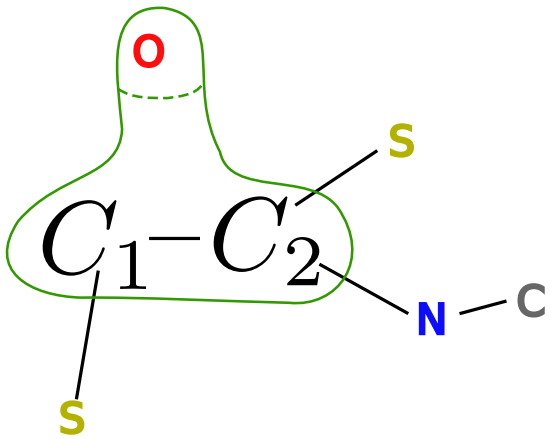


→ Hypergraph comparison.

Treelets on relevant cycle hypergraphs

Adaptation of the treelet kernel:

(1) enumeration of the relevant cycle hypergraph's treelets without hyper-edges.



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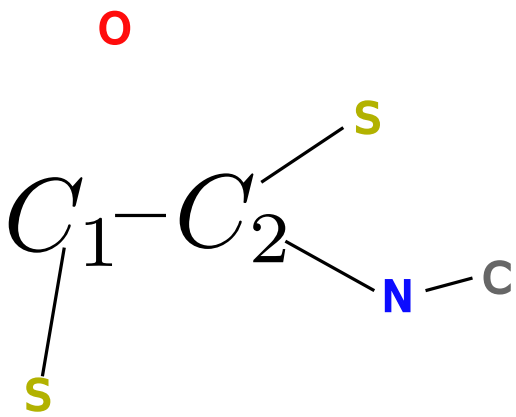

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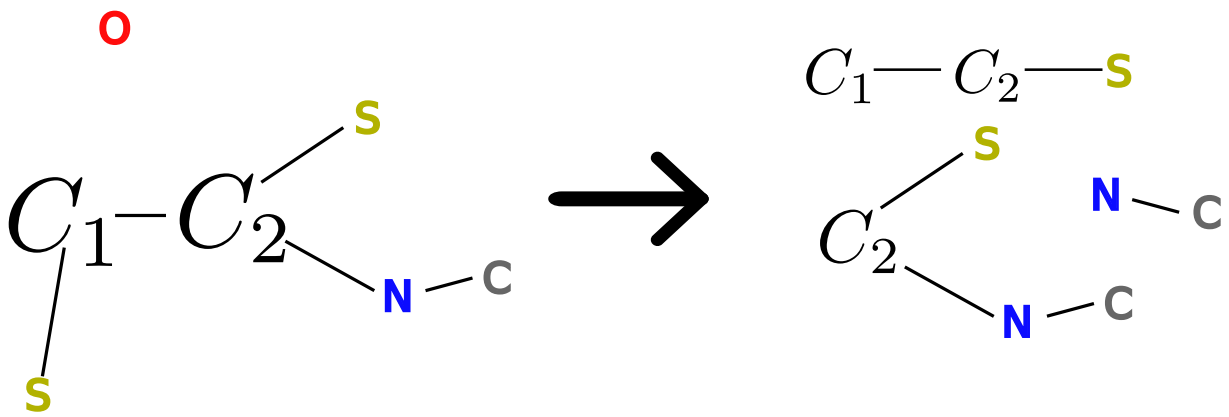

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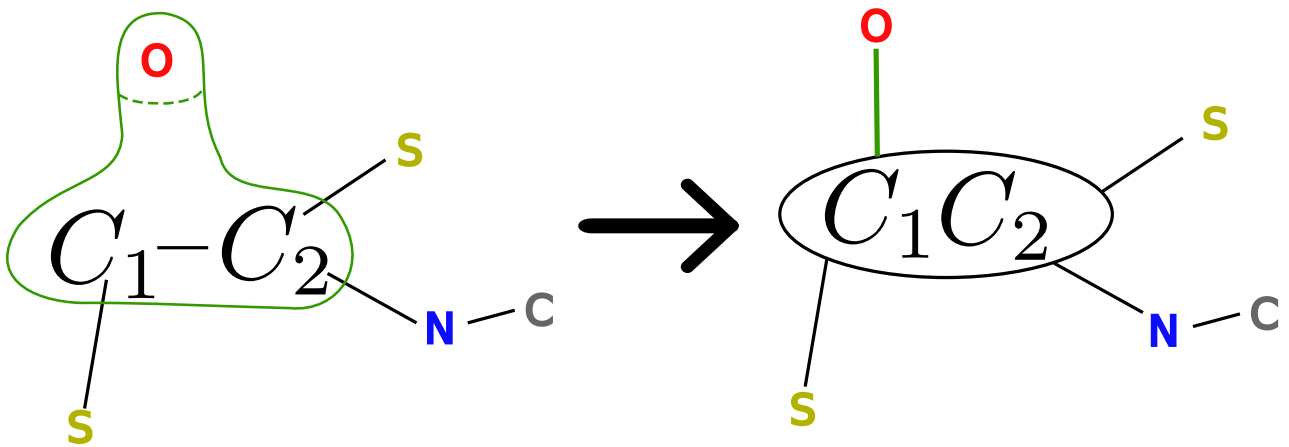
(2) Contraction of cycles incident to each hyper-edge.

→ Construction of the reduced relevant cycle hypergraph $G_{RC}(G)$.



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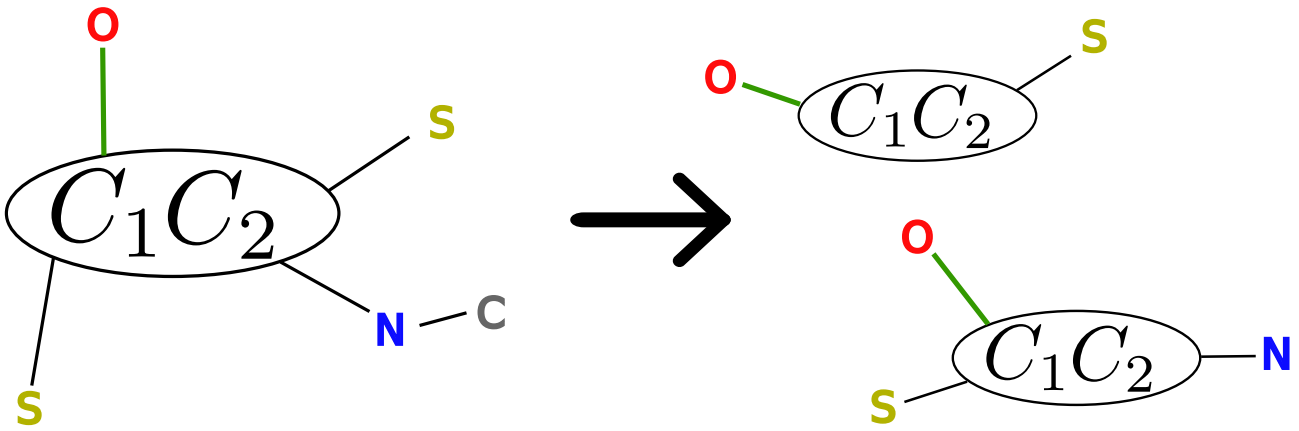
(3) Extraction of treelets containing an initial hyper-edge



Kernel on relevant cycle hypergraphs

Bag of patterns: $\mathcal{T}_{CR}(G) = \mathcal{T}_1 \cup \mathcal{T}_2$

- $\mathcal{T}_1$: Set of treelets obtained from the hypergraph without hyper-edges.
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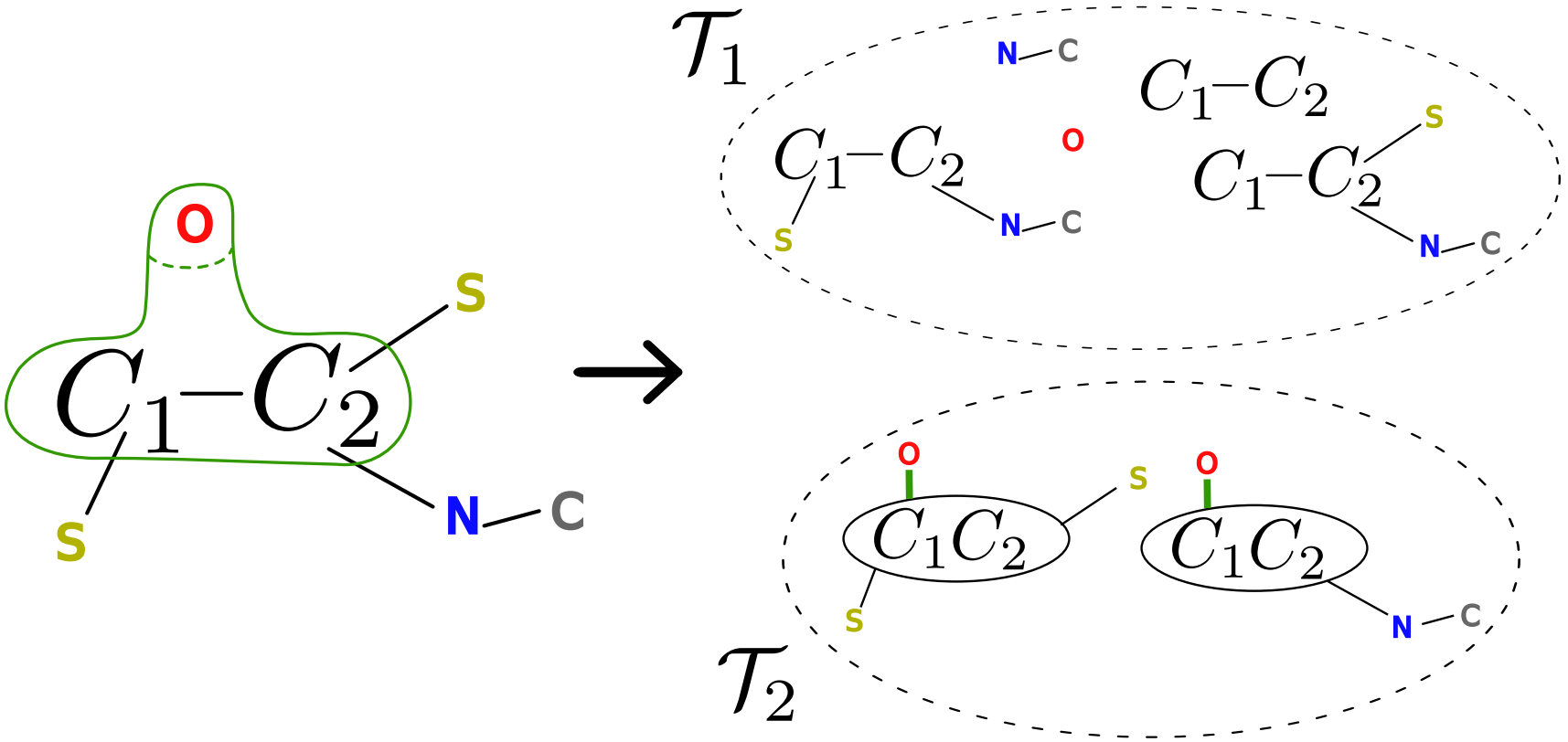

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Kernel design:

$$k_{\mathcal{T}}(G, G') = \sum_{t \in \mathcal{T}_{CR}(G) \cap \mathcal{T}_{CR}(G')} w_t \; k_t(f_t(G), f_t(G'))$$

Experiments

Predictive Toxicity Challenge

- Molecular graph labelled and composed of cycles.
- $\simeq$ 340 molecules for each dataset
- 4 classes of animals (MM, FM, MR, FR) :
  - Learning set $\simeq$ 310 molécules,
  - Test set $\simeq$ 34 molecules,

  $\Big\}\ 10\times$
  - Number of molecules correctly classified on the 10 test sets.

Méthode	**MM**	**FM**	**MR**	**FR**
Treelet kernel (TK)	208	205	**209**	212
Relevant cycle kernel	209	207	202	228
TK on relevant cycle graph (TC)	211	210	203	232
TK on relevant cycle hypergraph (TCH)	**217**	**224**	207	**233**

Experiments

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TK + MKL	218	224	**224**	**250**
TC + MKL	216	213	212	237
TCH + MKL	**225**	**229**	215	239

Experiments

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TK + MKL	218	224	224	250
TCH + MKL	**225**	229	215	239
Combo TK - TCH	**225**	**230**	224	**252**
Gaussian kernel on graph edit distance [Neuhaus and Bunke, 2007]	223	212	194	234
Laplacien kernel	207	186	209	203
Kernel on paths [Ralaivola et al., 2005]*	223	225	**226**	234
Weisfeiler-Lehman Kernel [Shervaszide, 2012]	138	154	221	242

* leave-one-out

Plan

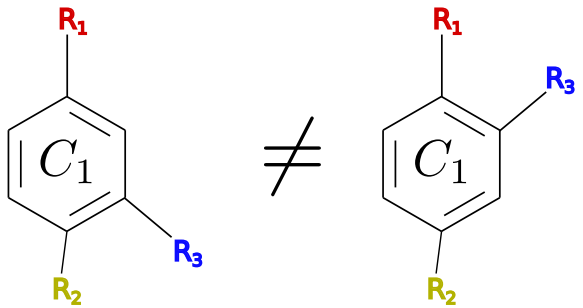
Conclusion

General problem:

Kernel between molecular graphs including cyclic and acyclic patterns in order to predict molecular properties.

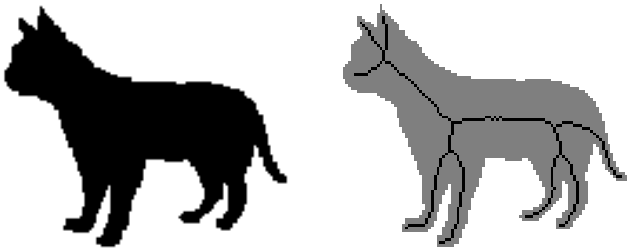
Extensions :

- Cyclic Information:
  - Encoding the relative positioning of atoms
- Taking into account stereoisometry.

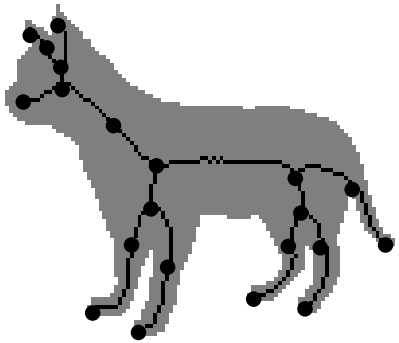


Plan

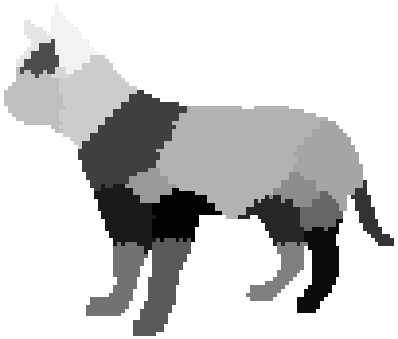
Kernel between shapes



- Compute skeletons
- Encode skeletons by graphs,
- Kernel between bags of treelets.

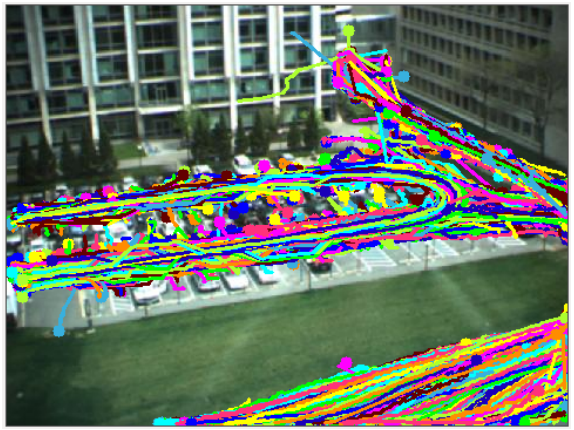


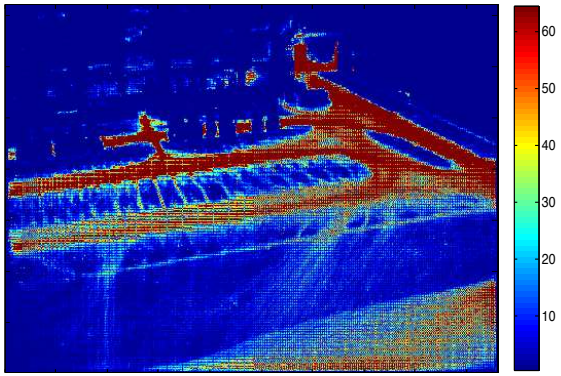
a) le graphe

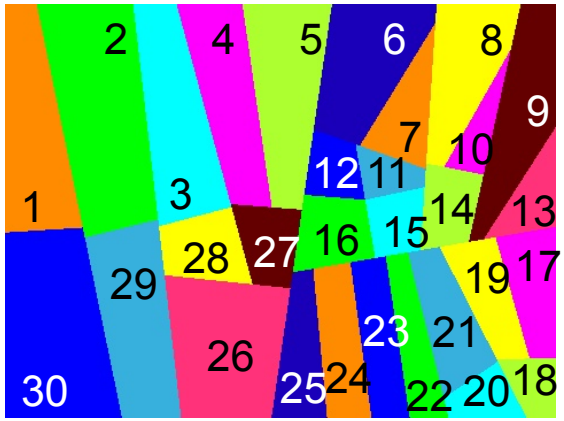


b) la segmentation induite

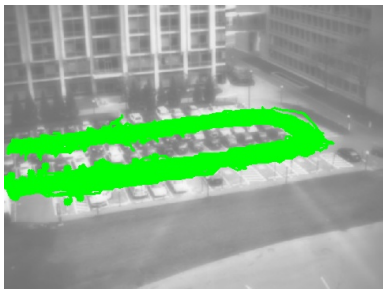
Kernel on strings

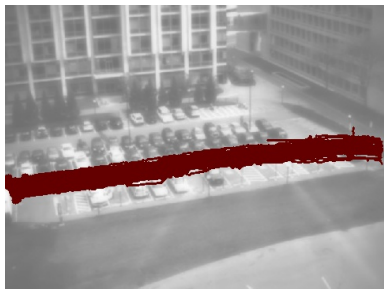






- Decompose the scene into zones,
- Compute a string encoding the sequence of traversed zones,
- Define a kernel between strings,
- Cluster strings.





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