Vers les Pharmacophores Activity Deltas

Etienne LEHEMBRE

Équipe CODAG, GREYC

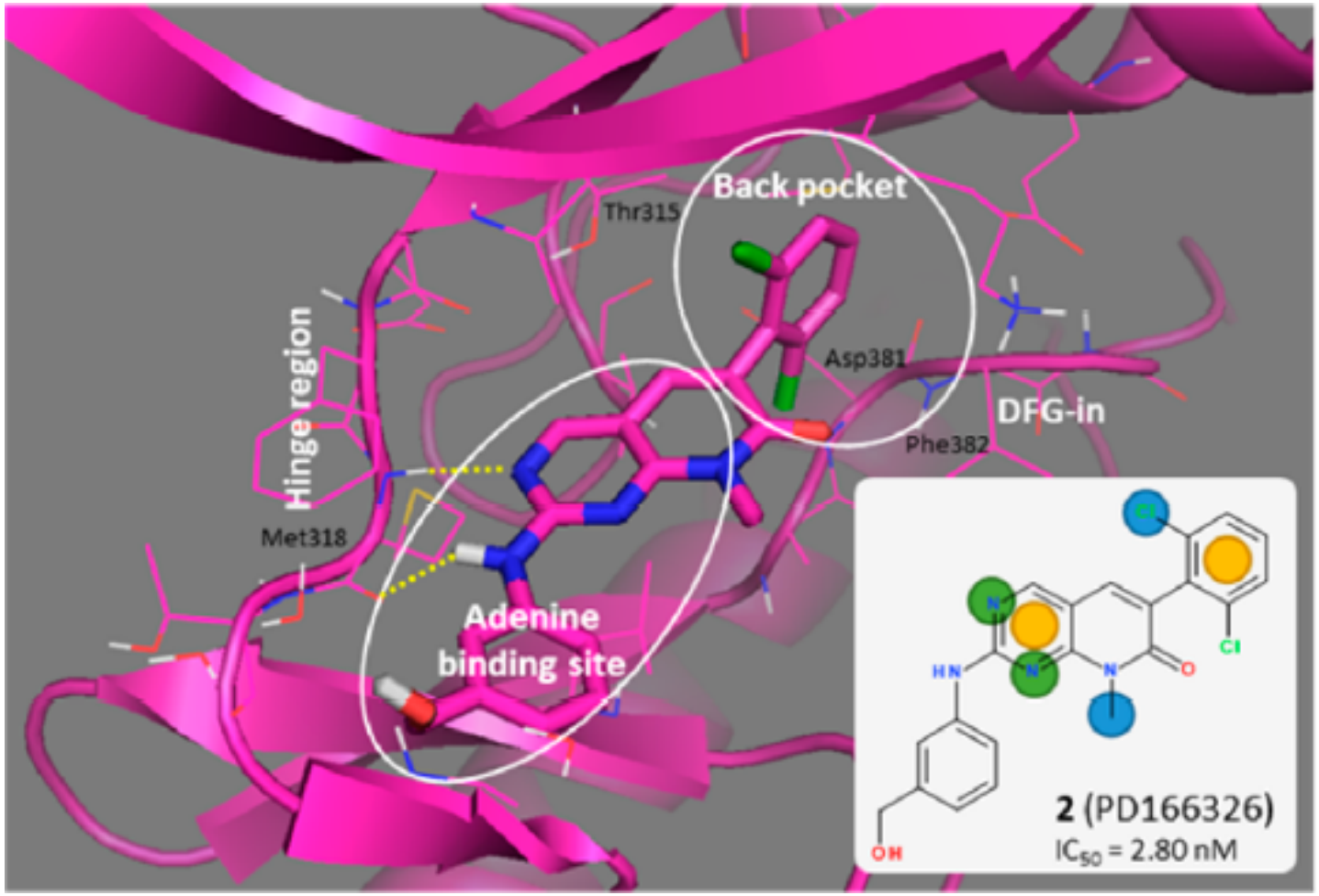
6 juillet 2021

UNIVERSITÉ
CAEN NORMANDIE

Plan de l'exposé

1. Notions fondamentales
   - Molécules et pharmacophores
   - Fouille de graphes
2. Applications
   - Les treillis
   - Classes d'équivalence
   - Pharmacophores Activity Delta
3. Expérimentation
   - Analyse statistique
   - Analyse visuelle
4. Conclusion

La chemoinformatique

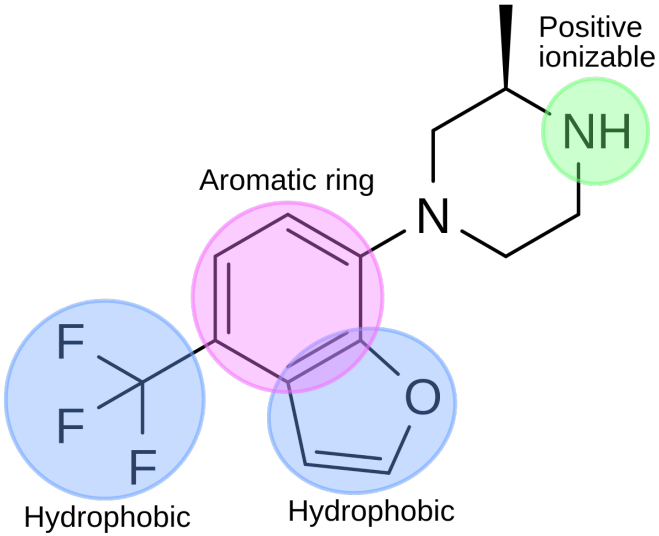


J.-P. METIVIER, B. CUISSART, R. BUREAU, and A. LEPAILLEUR.

Des molécules aux pharmacophores

Une molécule est :

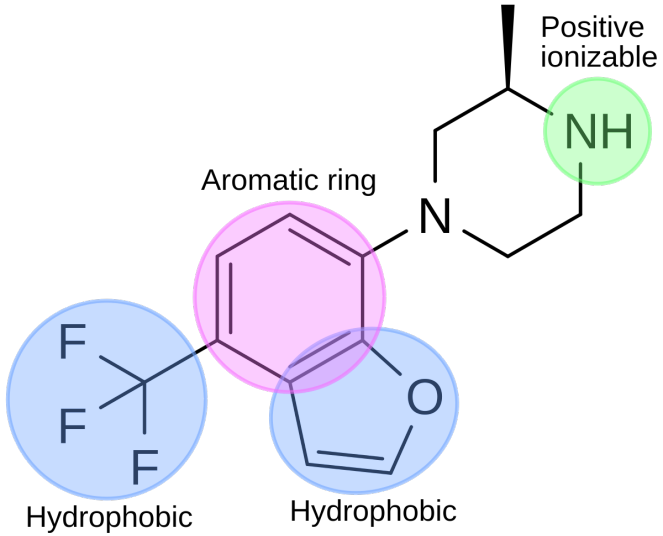
- Un ensemble d'atomes.
- Relié par des liaisons.



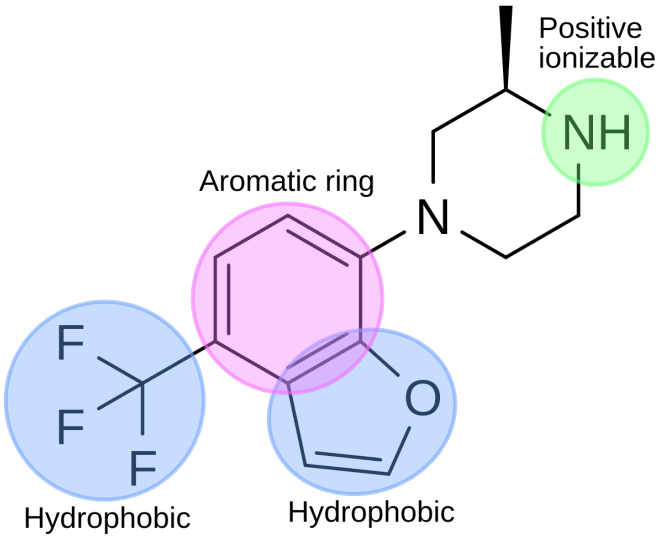
Des molécules aux pharmacophores

Graphe pharmacophorique :

- Une molécule.
- Marqueurs pharmacophoriques identifiés.



Des molécules aux pharmacophores



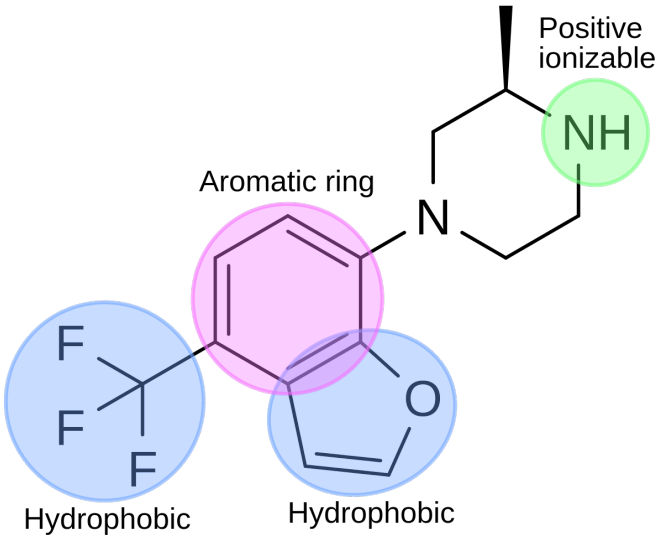
1

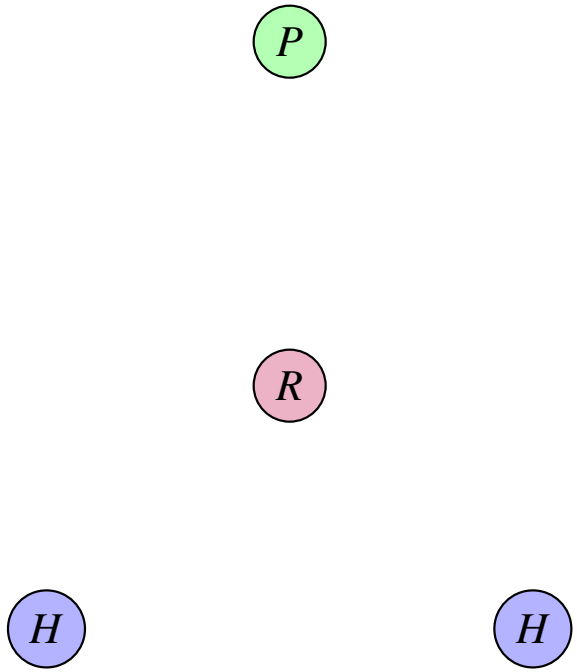
2

3

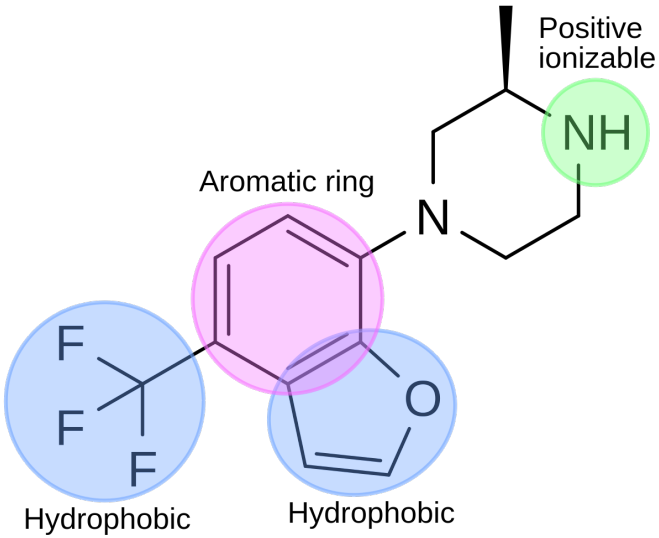
4

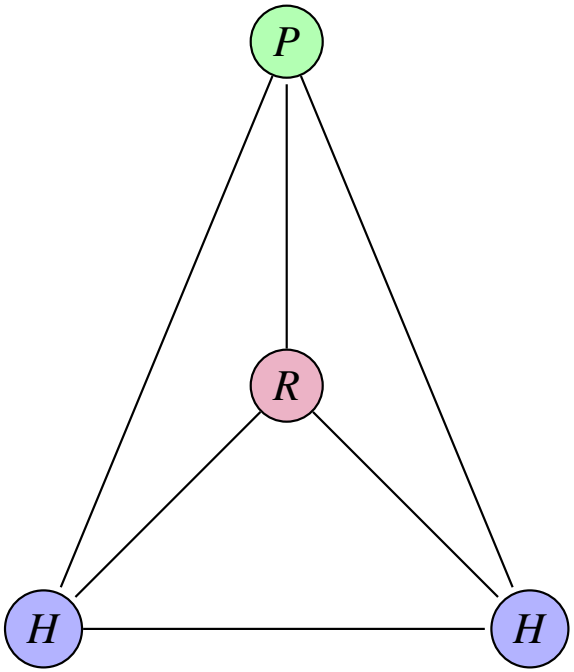
Des molécules aux pharmacophores



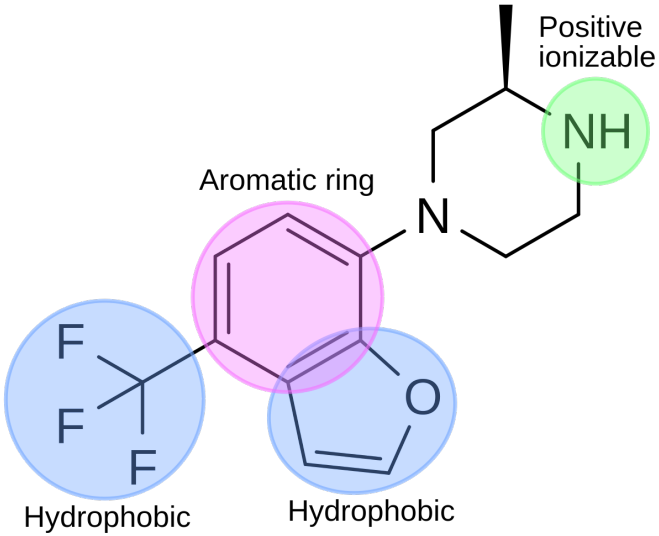


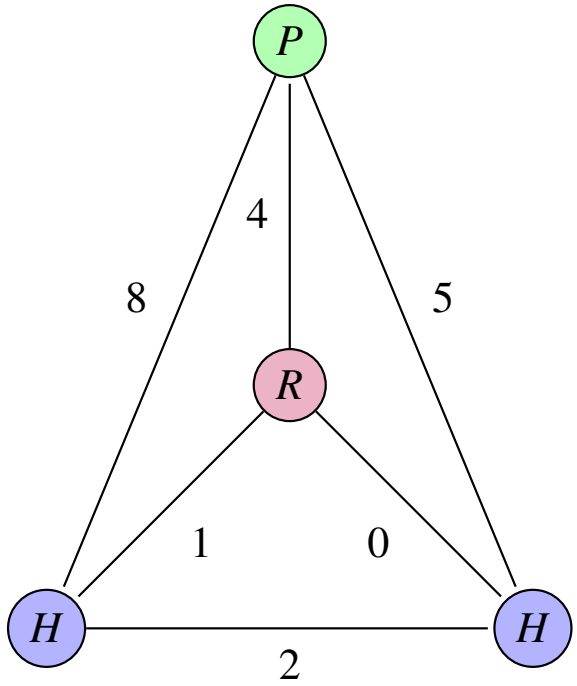
Des molécules aux pharmacophores





Des molécules aux pharmacophores

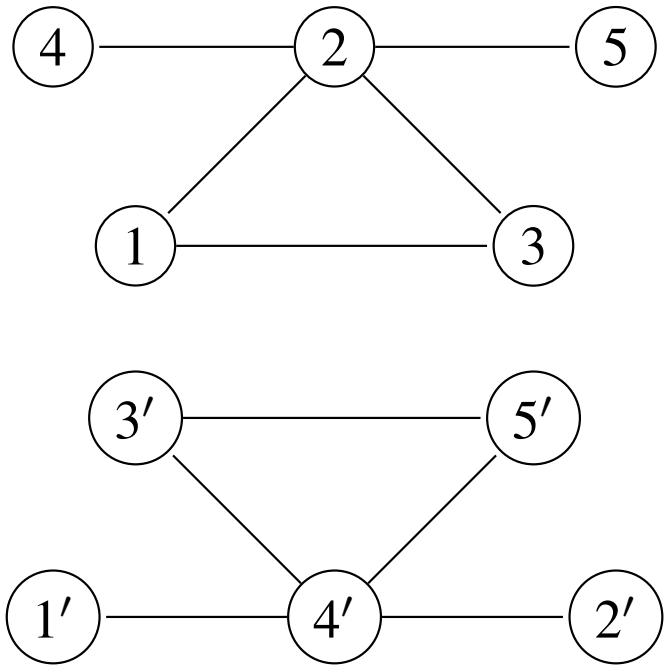




Isomorphisme de graphes

Fonction d'isomorphisme

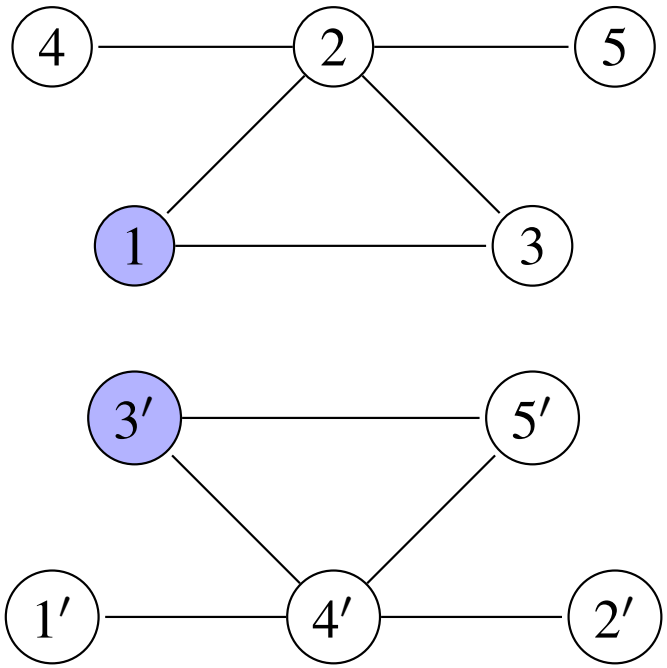
- $f(1) = -$
- $f(2) = -$
- $f(3) = -$
- $f(4) = -$
- $f(5) = -$



Isomorphisme de graphes

Fonction d'isomorphisme

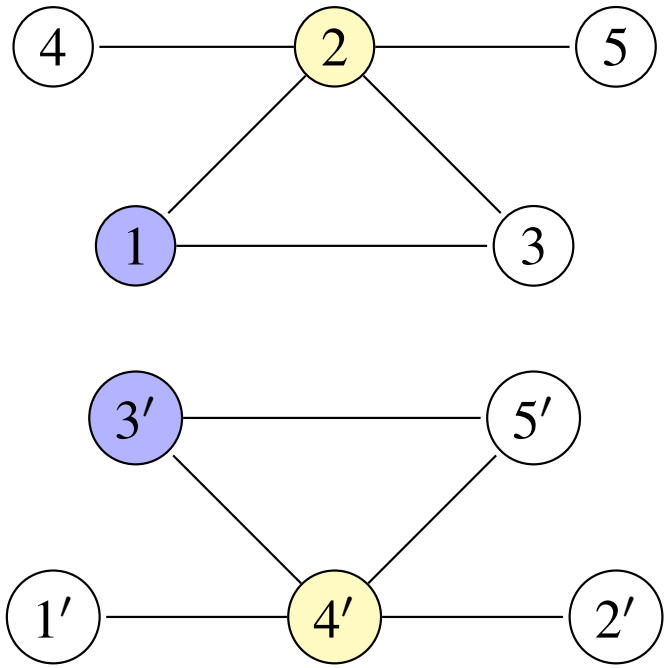
- $f(1) = 3'$
- $f(2) = -$
- $f(3) = -$
- $f(4) = -$
- $f(5) = -$



Isomorphisme de graphes

Fonction d'isomorphisme

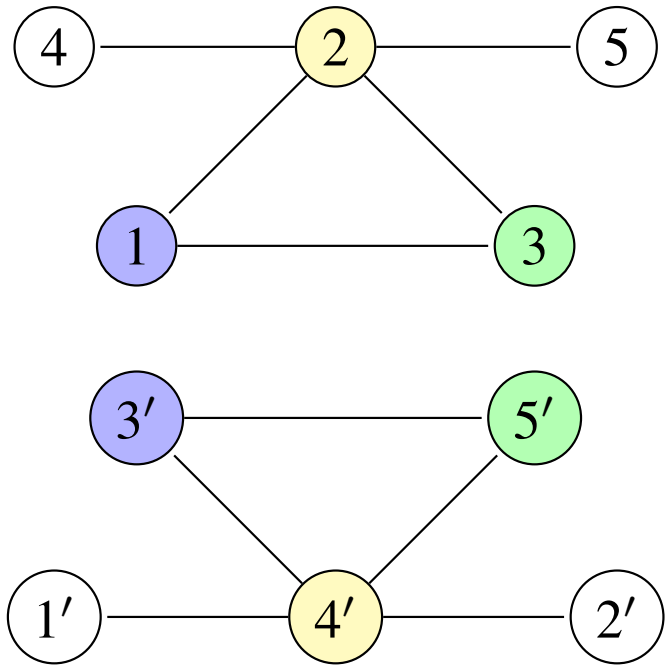
- $f(1) = 3'$
- $f(2) = 4'$
- $f(3) = -$
- $f(4) = -$
- $f(5) = -$



Isomorphisme de graphes

Fonction d'isomorphisme

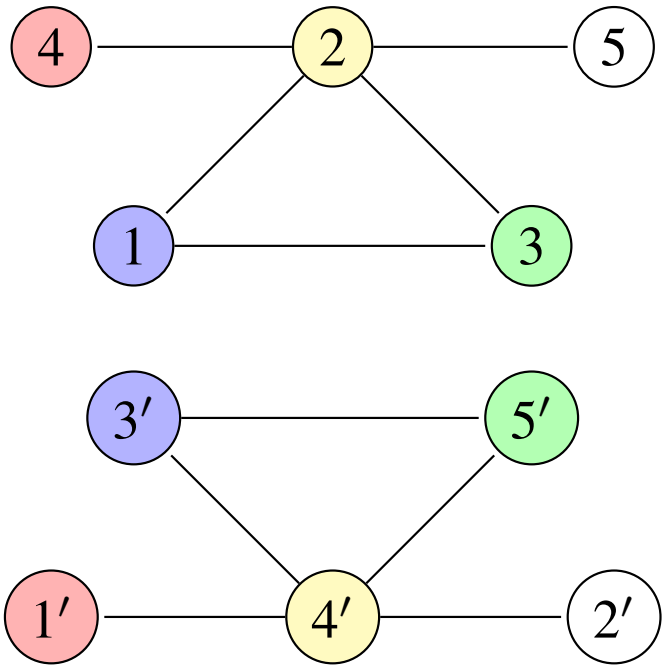
- $f(1) = 3'$
- $f(2) = 4'$
- $f(3) = 5'$
- $f(4) = -$
- $f(5) = -$



Isomorphisme de graphes

Fonction d'isomorphisme

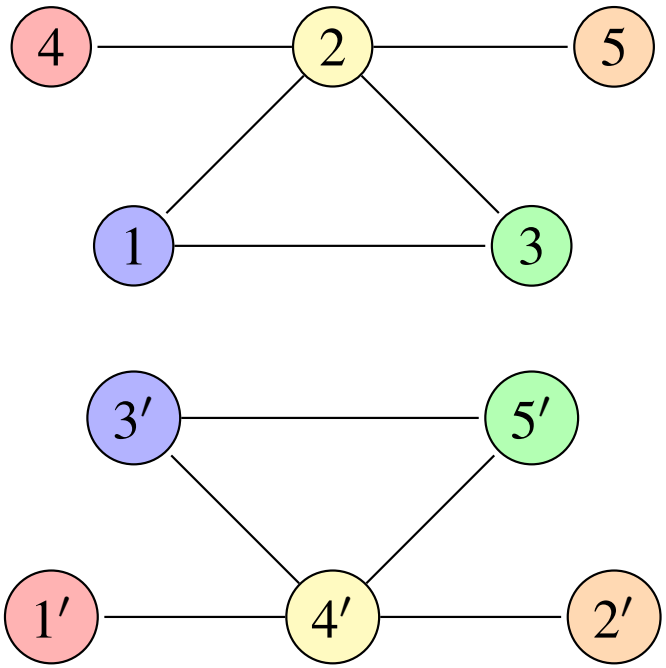
- $f(1) = 3'$
- $f(2) = 4'$
- $f(3) = 5'$
- $f(4) = 1'$
- $f(5) = -$



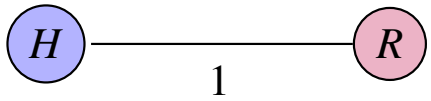
Isomorphisme de graphes

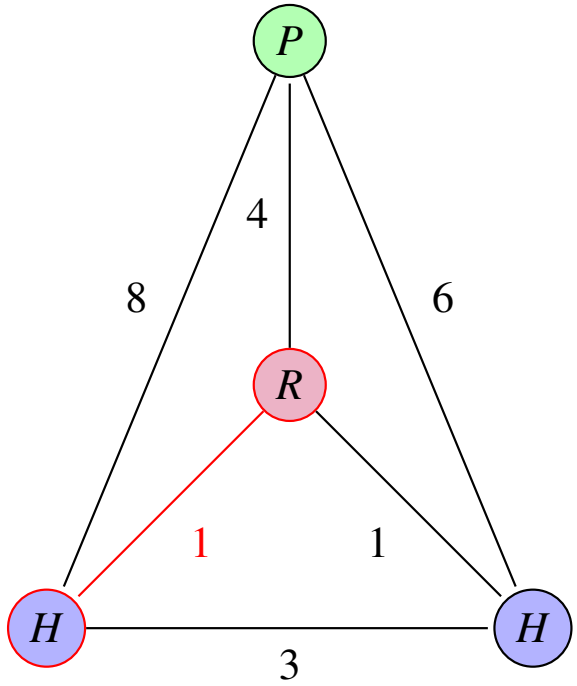
Fonction d'isomorphisme

- $f(1) = 3'$
- $f(2) = 4'$
- $f(3) = 5'$
- $f(4) = 1'$
- $f(5) = 2'$

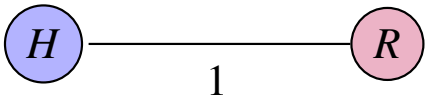


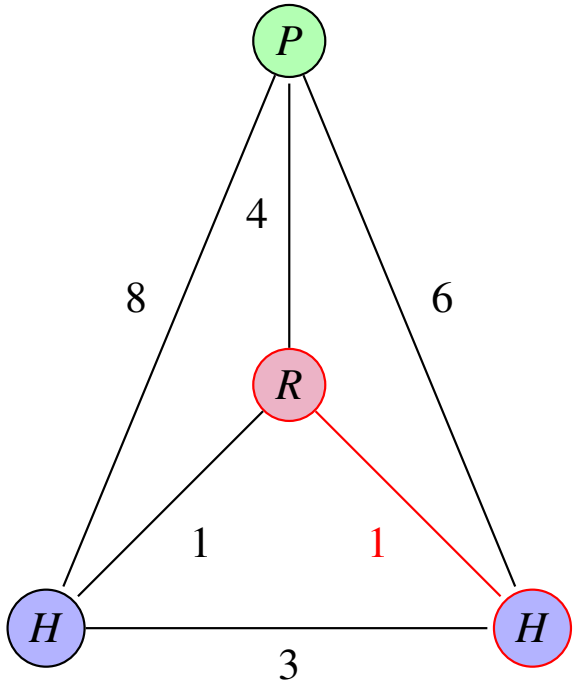
Motifs dans un graphe



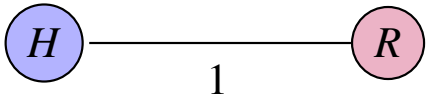


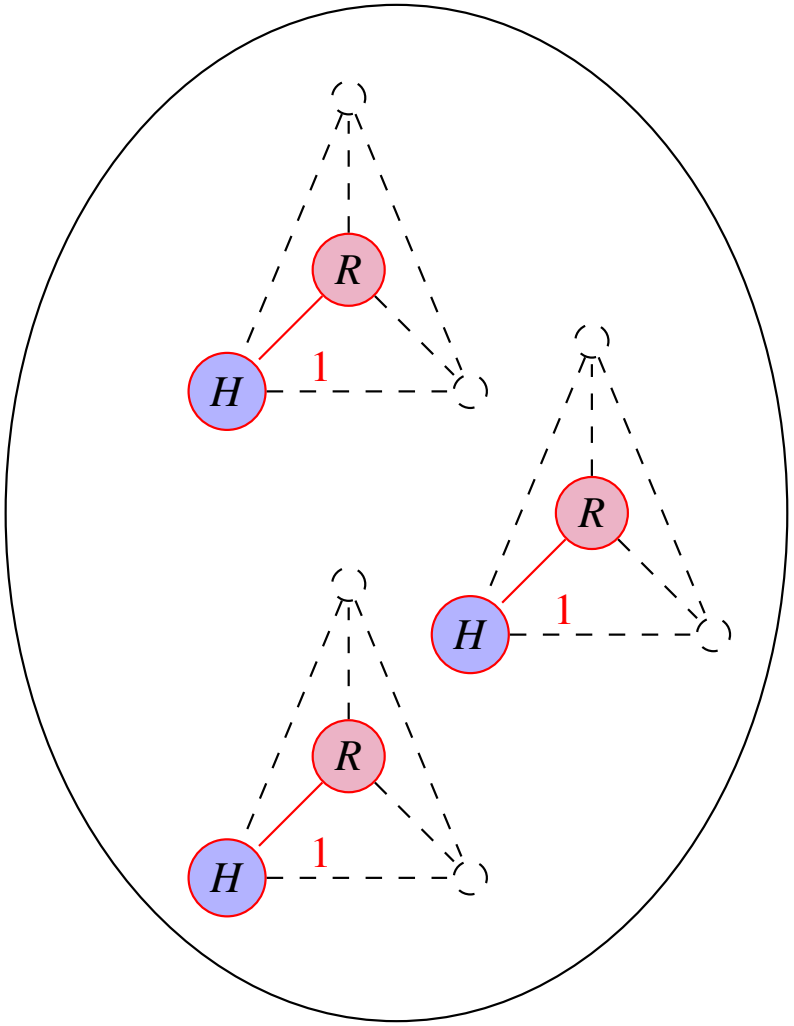
Motifs dans un graphe



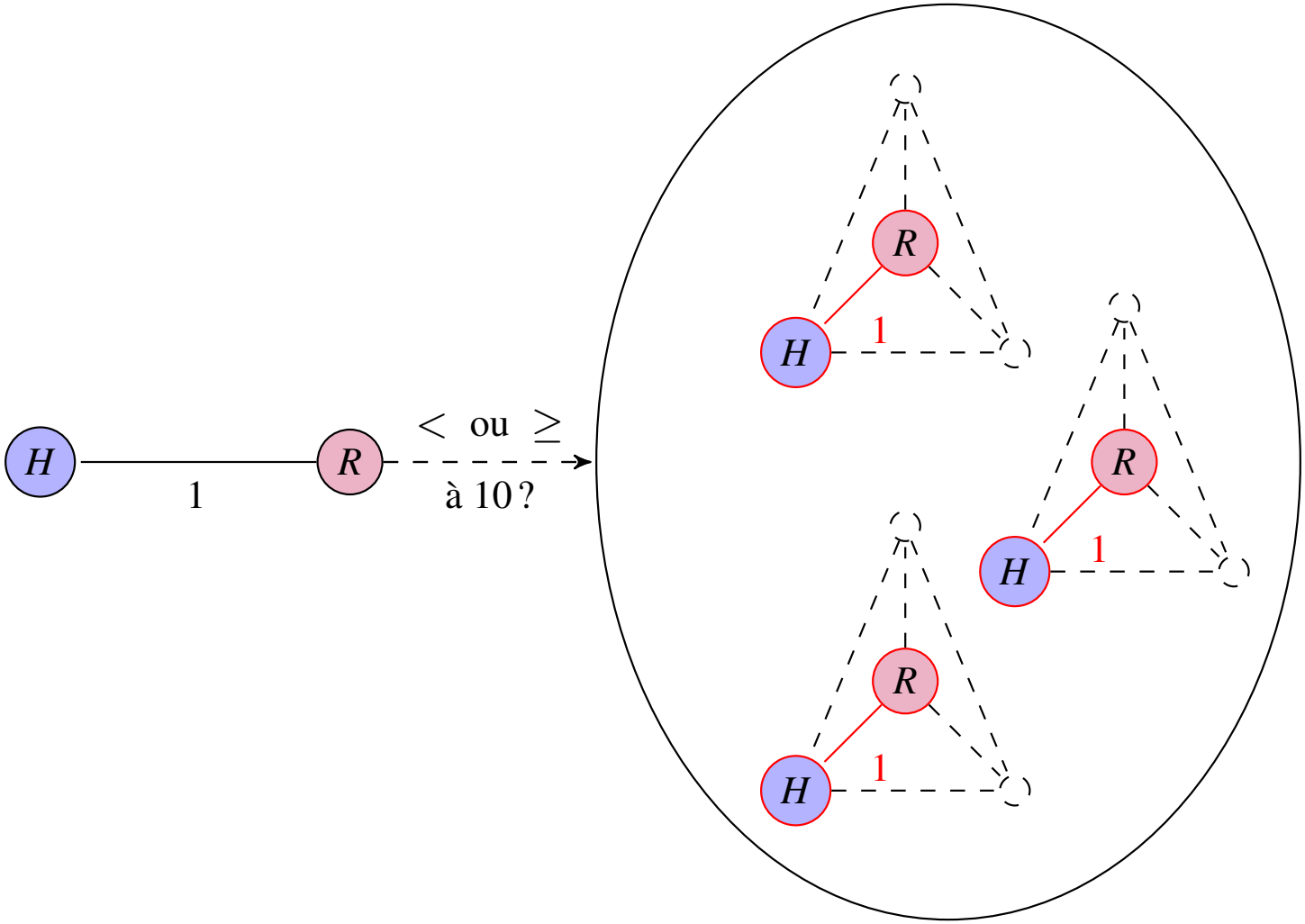


Motifs fréquents dans un ensemble de graphes

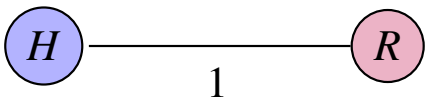




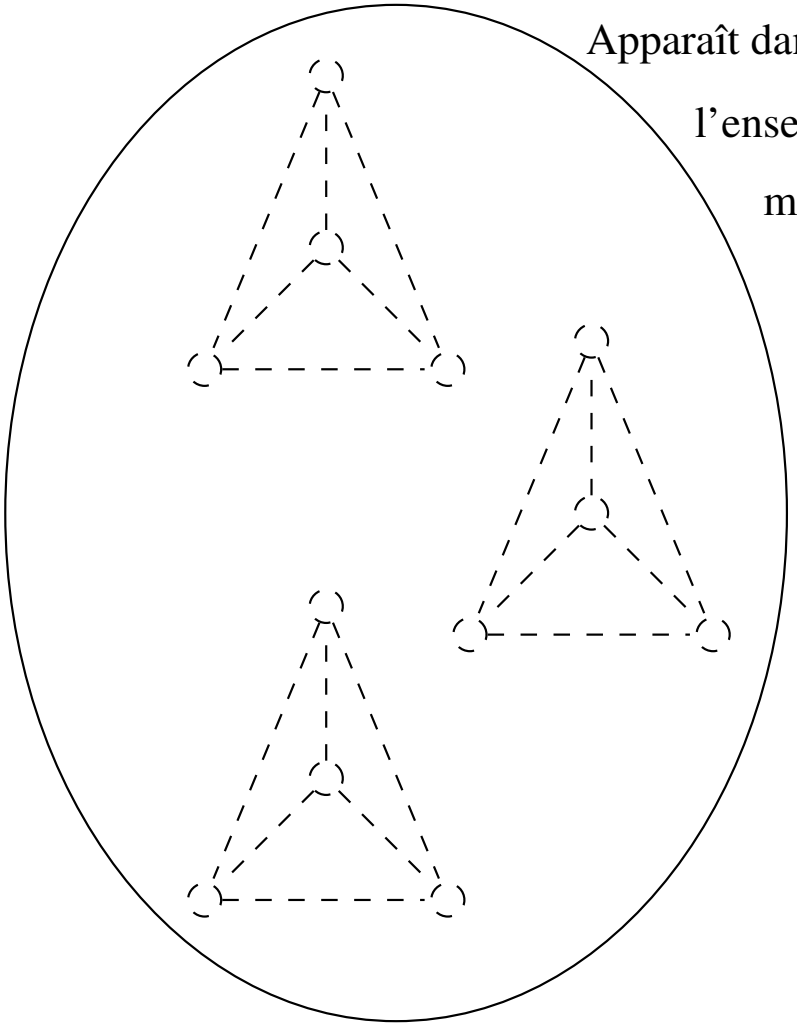
Motifs fréquents dans un ensemble de graphes



La fouille de pharmacophores dans un ensemble d'atome(s)

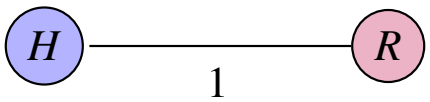


Pharmacophore

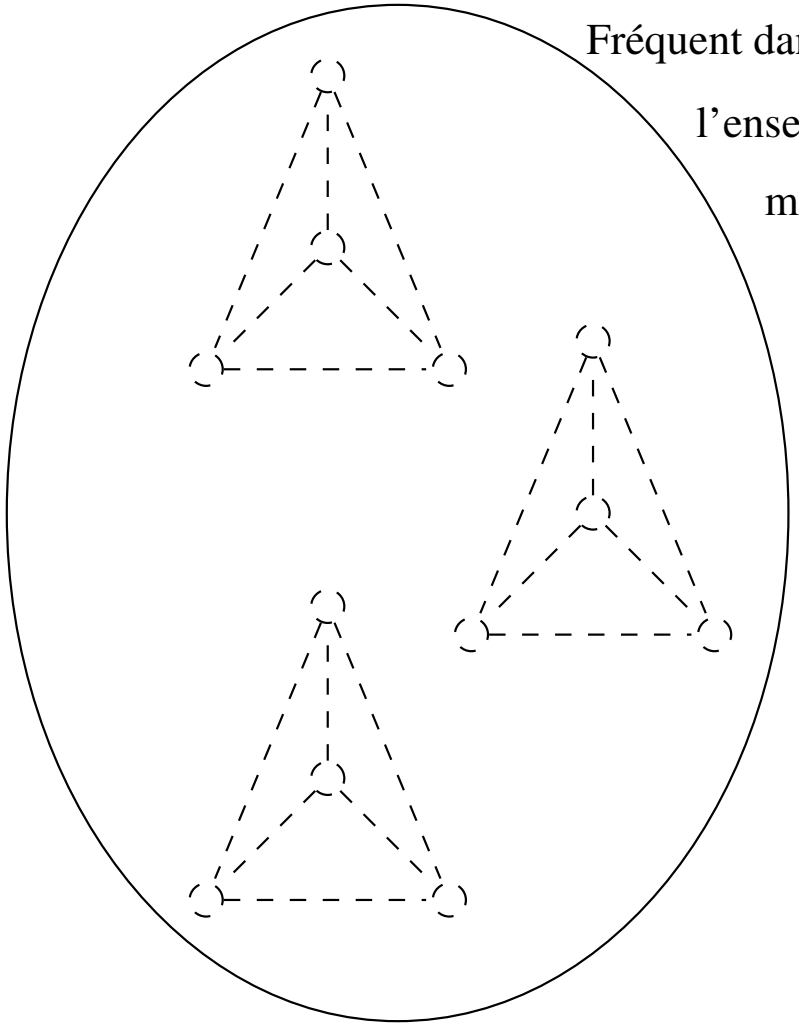


Apparaît dans l'ensemble des molécules ?

La fouille de pharmacophores dans un ensemble d'atome(s)



Pharmacophore



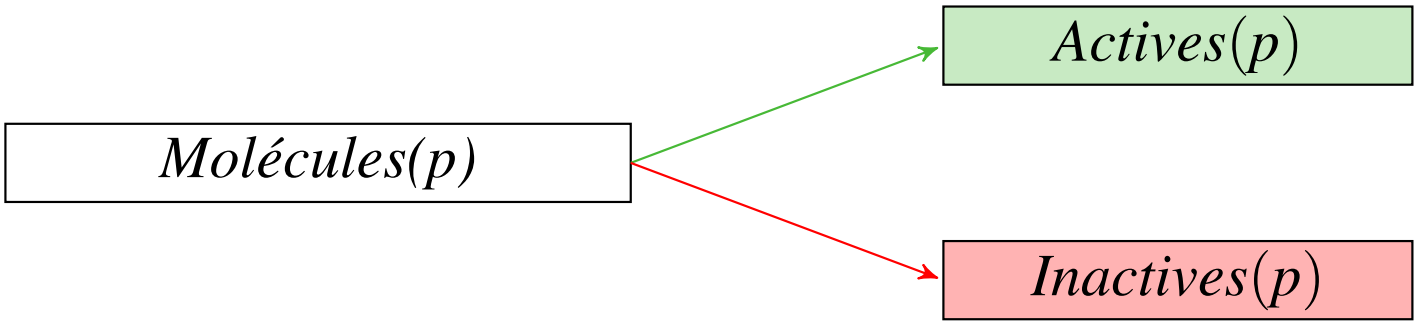
Fréquent dans l'ensemble des molécules ?

Les pharmacophores et qualité

$Molécules(p)$

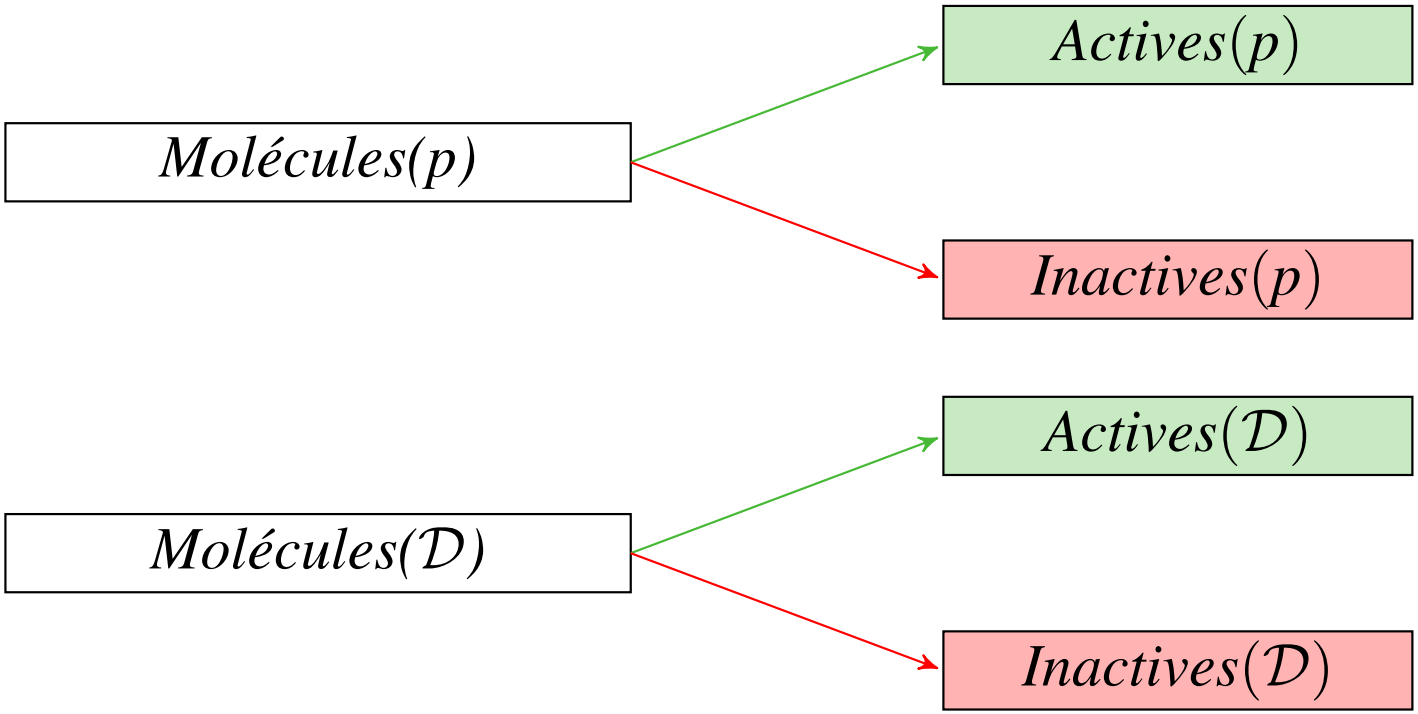
$Molécules(\mathcal{D})$

Les pharmacophores et qualité

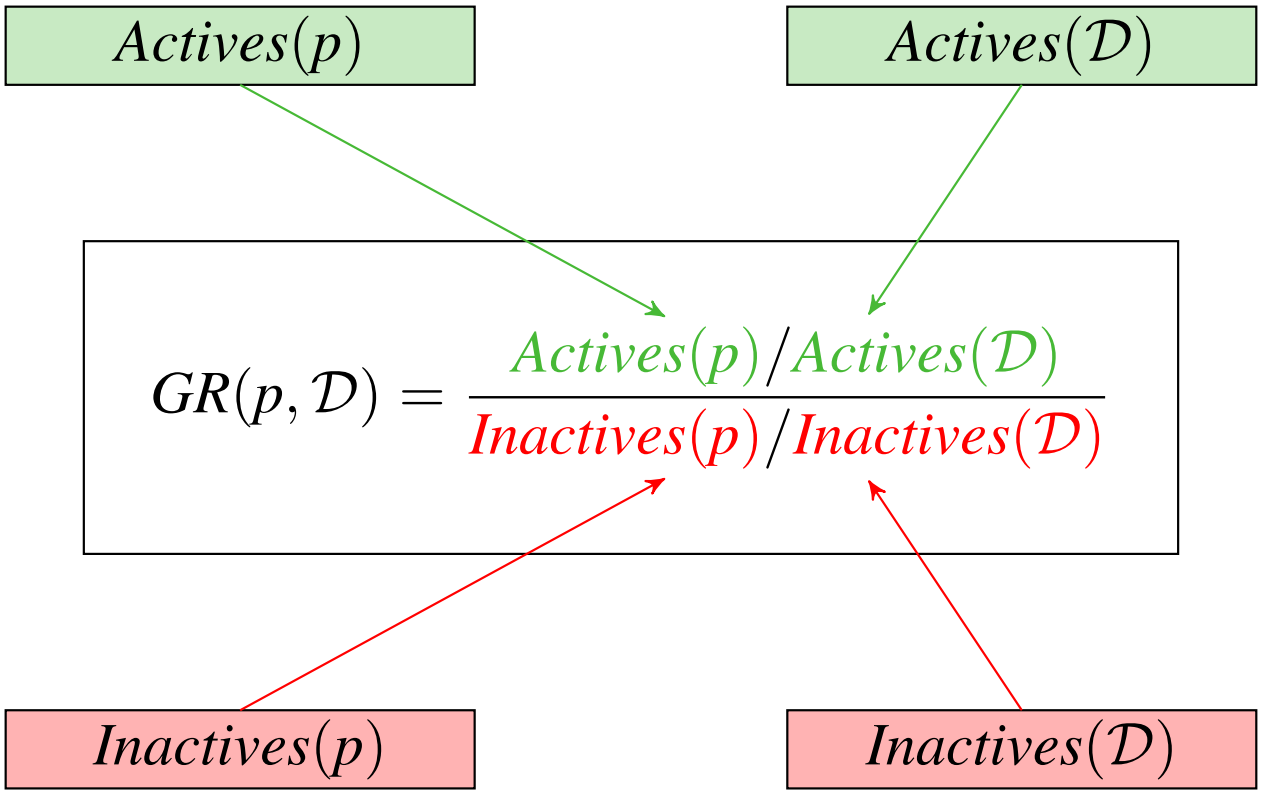


$Molécules(\mathcal{D})$

Les pharmacophores et qualité



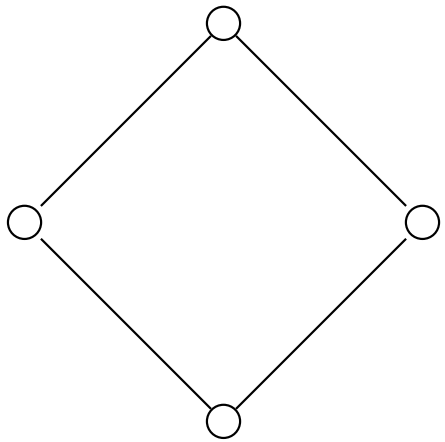
Les pharmacophores et qualité



Introduction aux treillis

Un treillis est :

- Ensemble de couples : $(objets, attributs)$.
- Avec un ordre sur l'ensemble : $<$.
- Chaque paire de couples admet une borne supérieure et une borne inférieure.

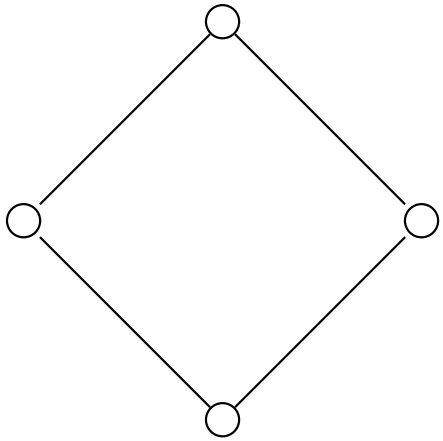


Introduction aux treillis

Correspondance des $(objets, attributs)$:

- *Objets* = pharmacophores
- *Attributs* = molécules

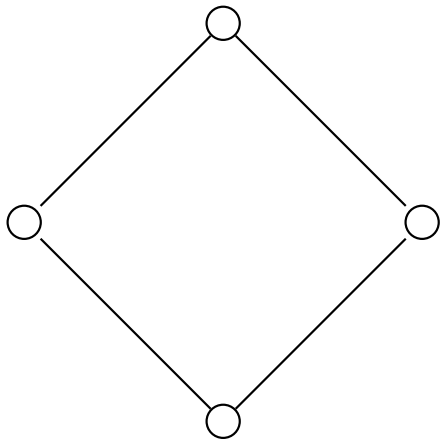
O/A	M_1	M_2
P_1	$\times$	$-$
P_2	$-$	$\times$



Introduction aux treillis

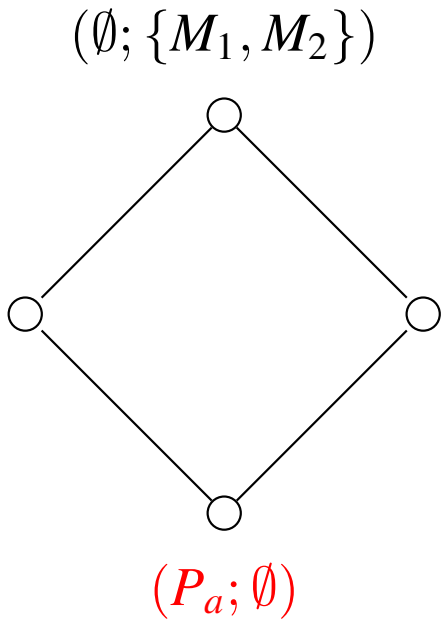
O/A	M_1	M_2
P_1	$\times$	$-$
P_2	$-$	$\times$

$(\emptyset; \{M_1, M_2\})$



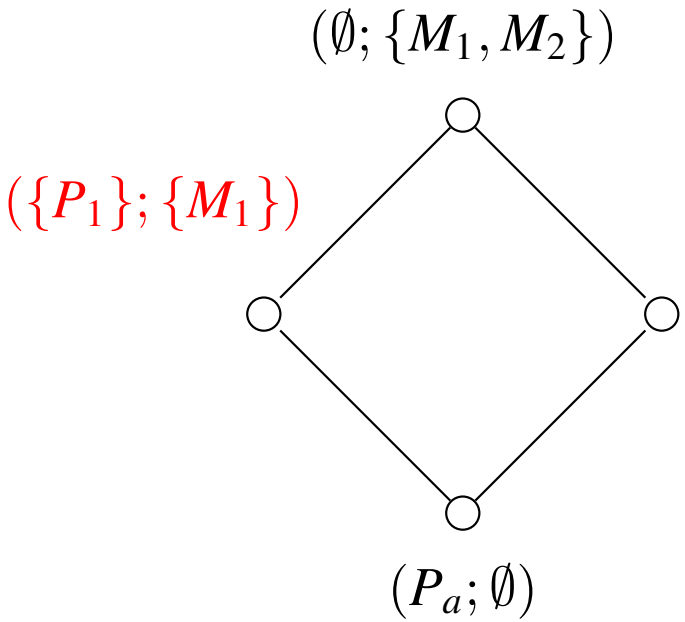
Introduction aux treillis

O/A	M_1	M_2
P_1	$\times$	$-$
P_2	$-$	$\times$



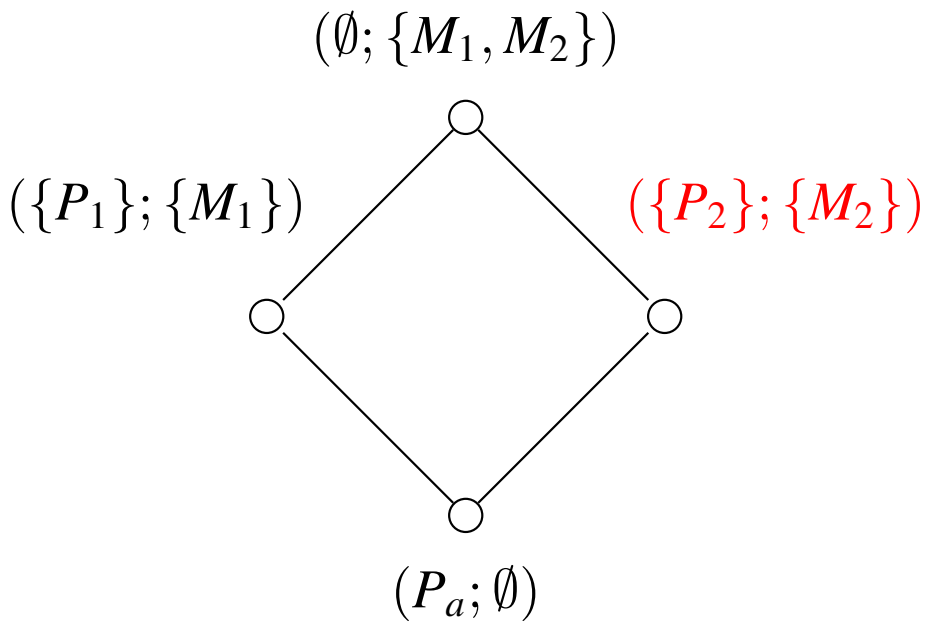
Introduction aux treillis

O/A	M_1	M_2
P_1	$\times$	$-$
P_2	$-$	$\times$



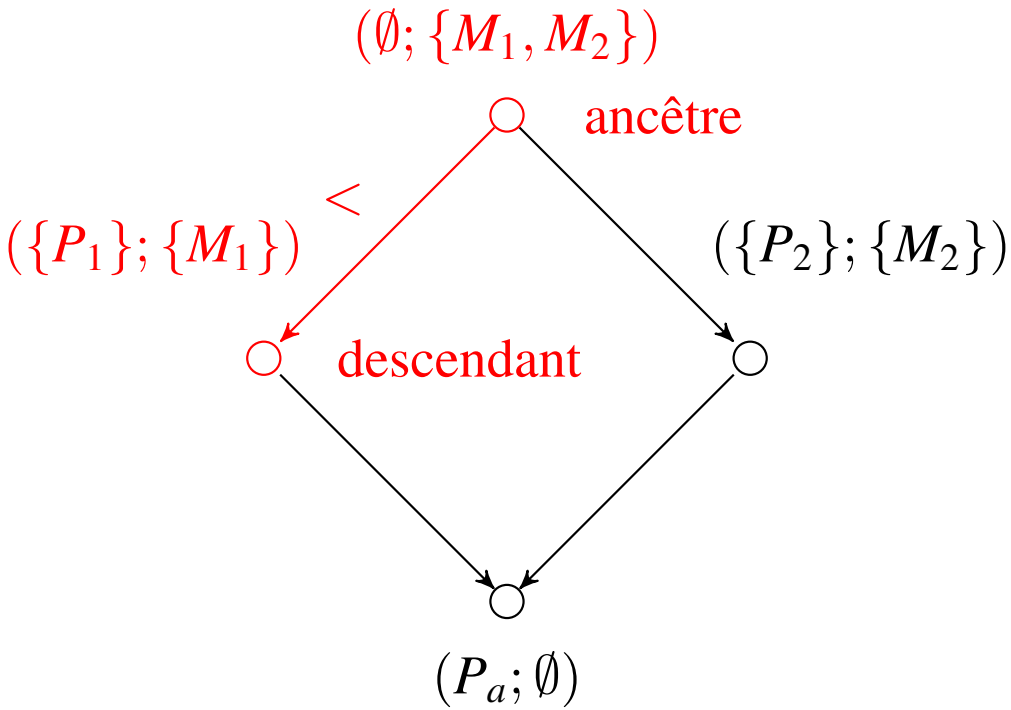
Introduction aux treillis

O/A	M_1	M_2
P_1	$\times$	$-$
P_2	$-$	$\times$

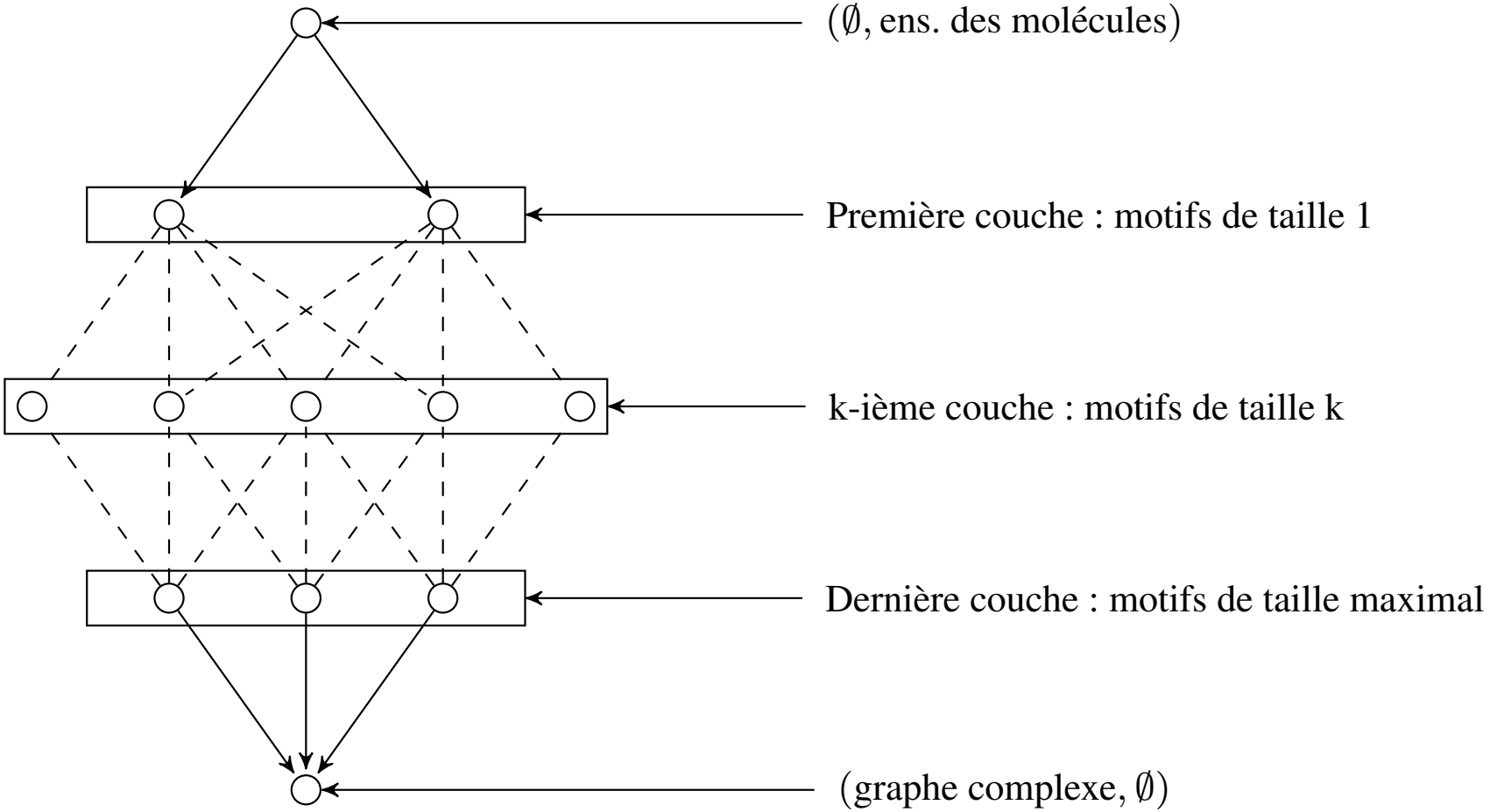


Introduction aux treillis

O/A	M_1	M_2
P_1	$\times$	$-$
P_2	$-$	$\times$



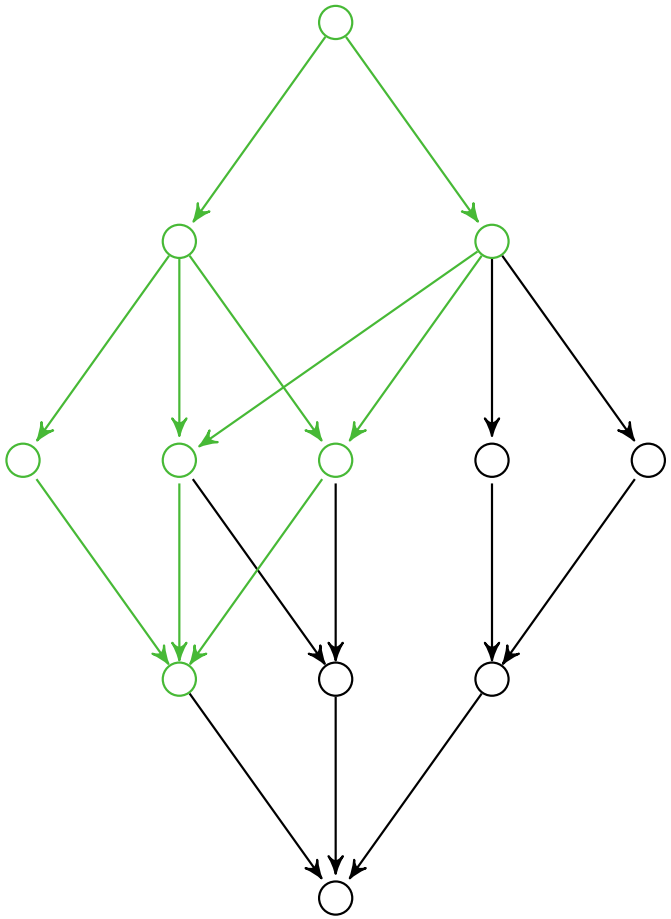
Norns_Lattice



Norns_Lattice

Avantages :

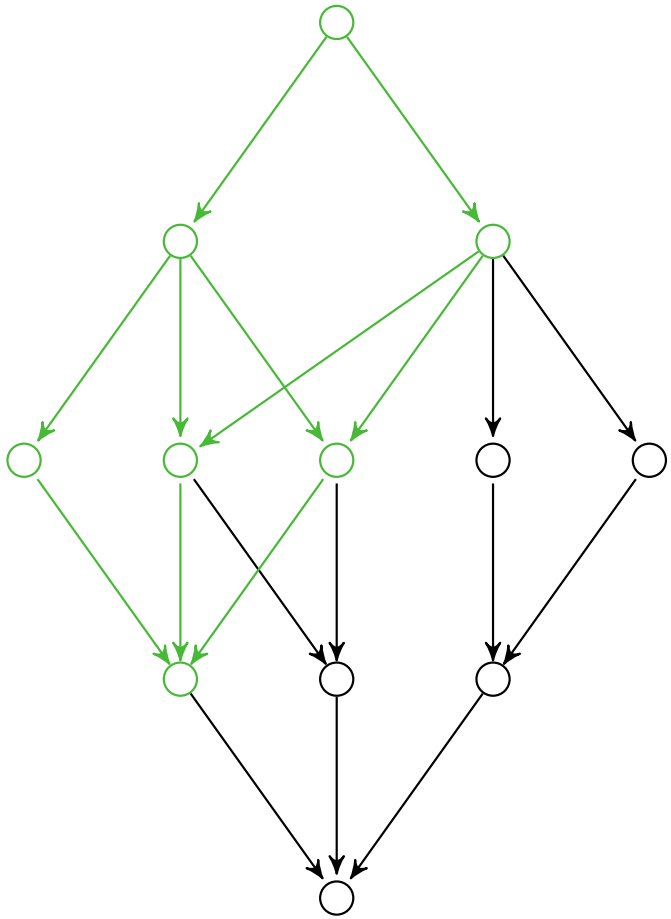
Mise en avant d'un chemin d'analyse pour l'utilisateur.



Norns_Lattice

Problèmes :

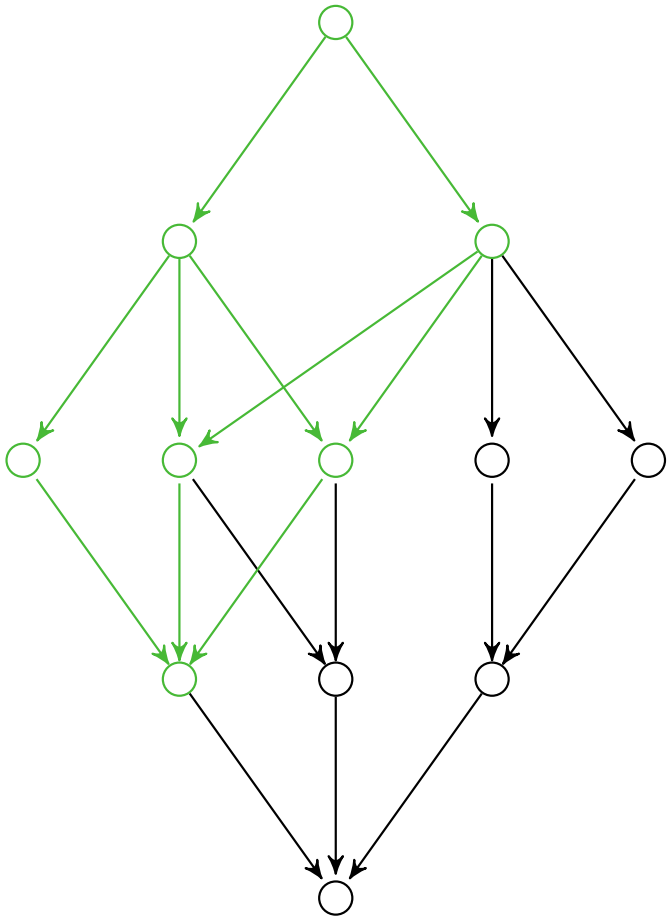
On a toujours trop de noeuds : 122, 343 pour notre jeu d'étude.



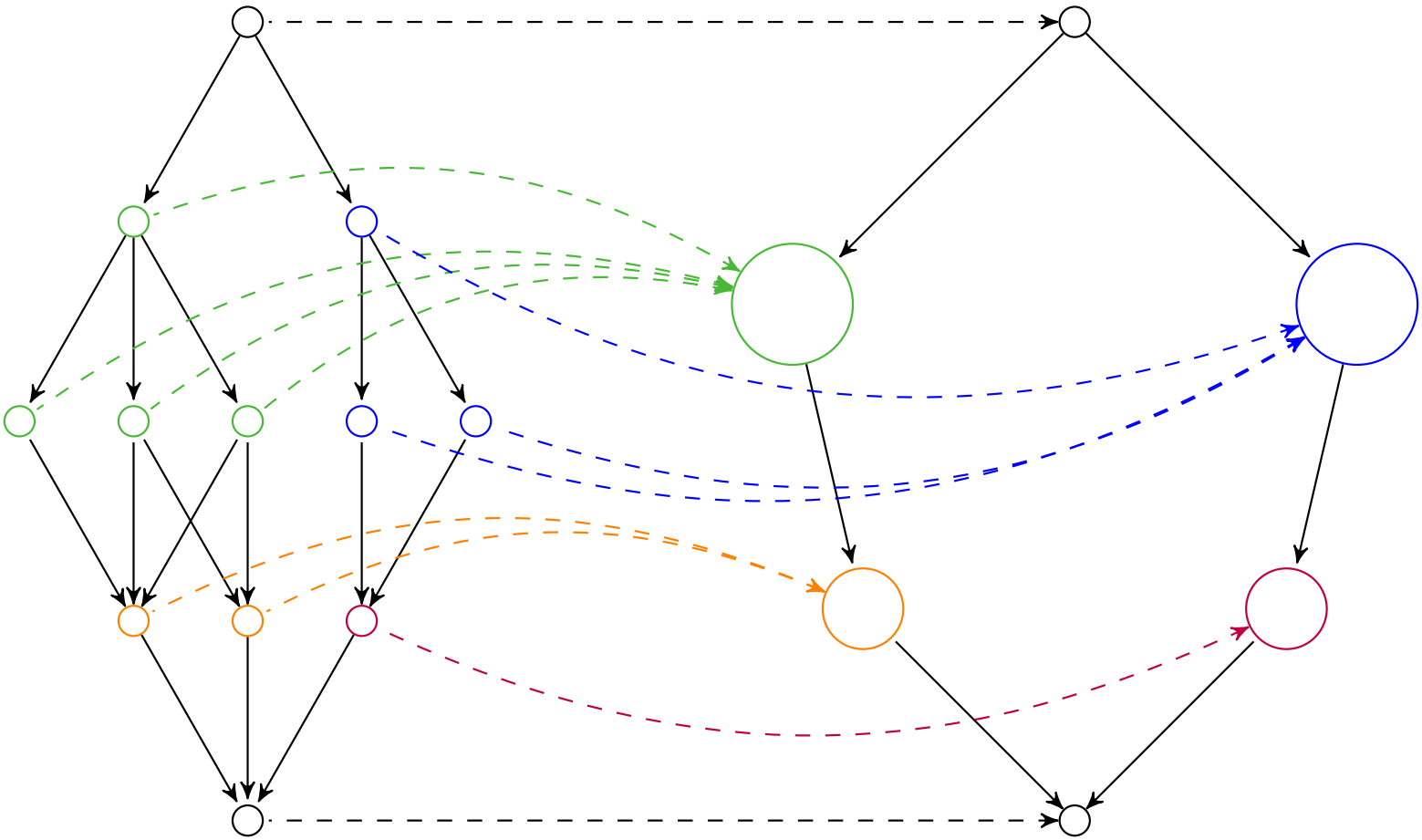
Norns_Lattice

Solutions :

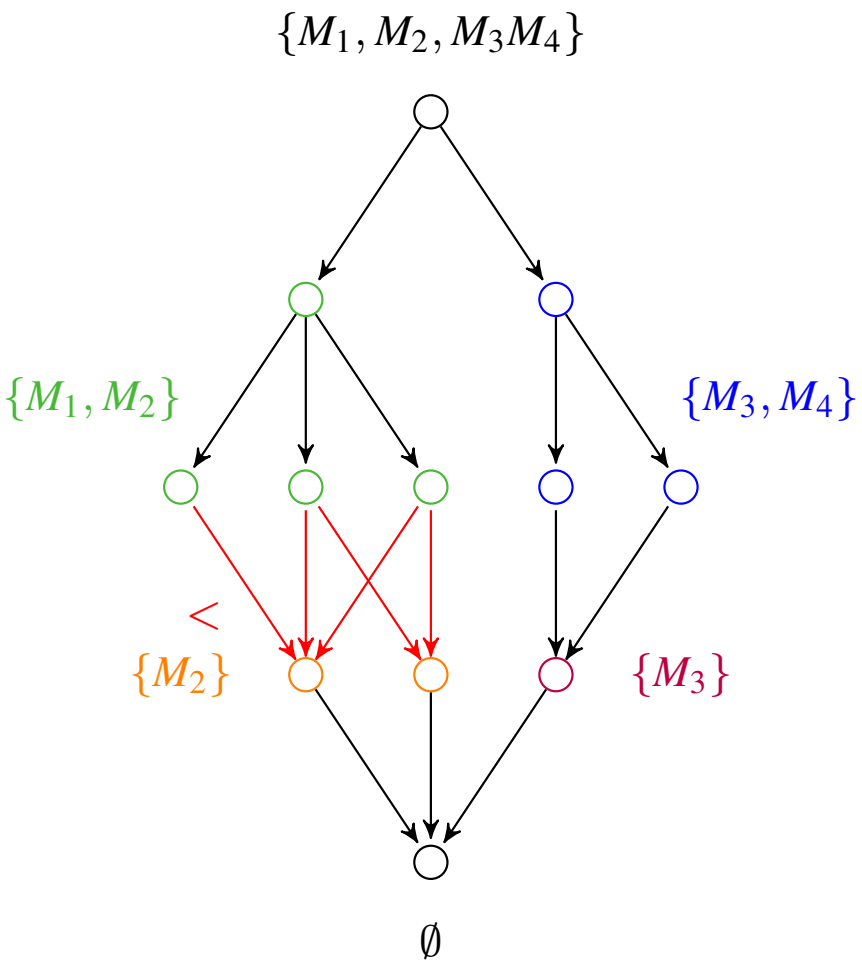
Rassembler les noeuds par attributs (molécules).

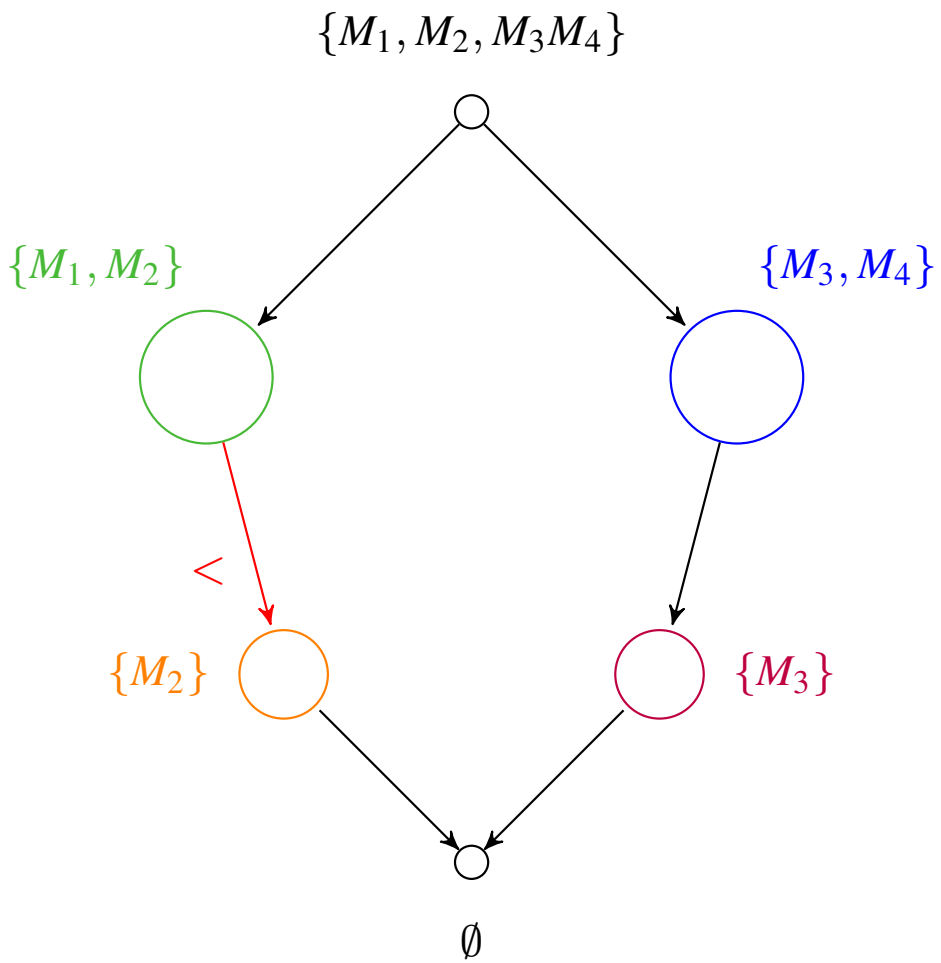


Définition des classes d'équivalence

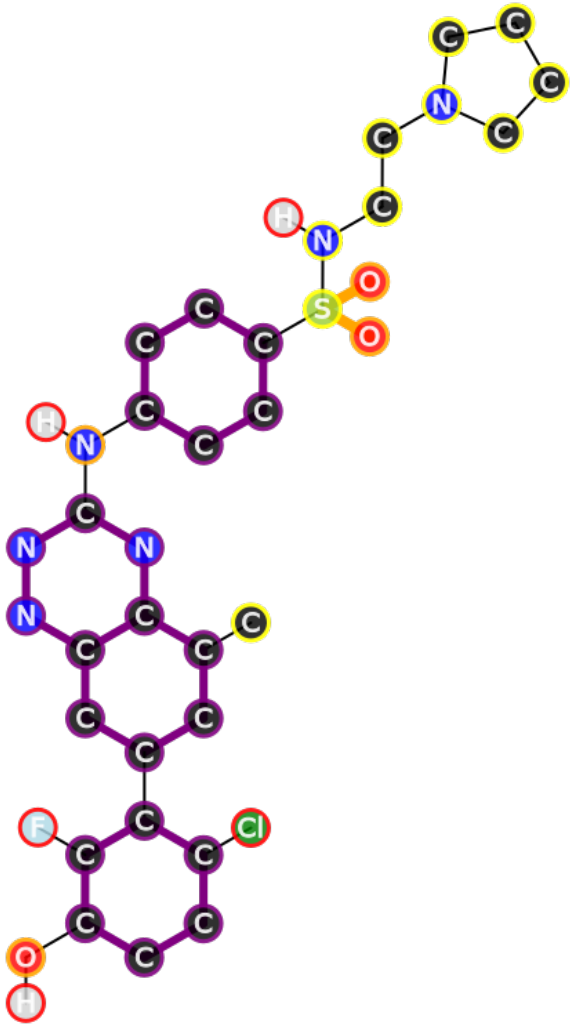


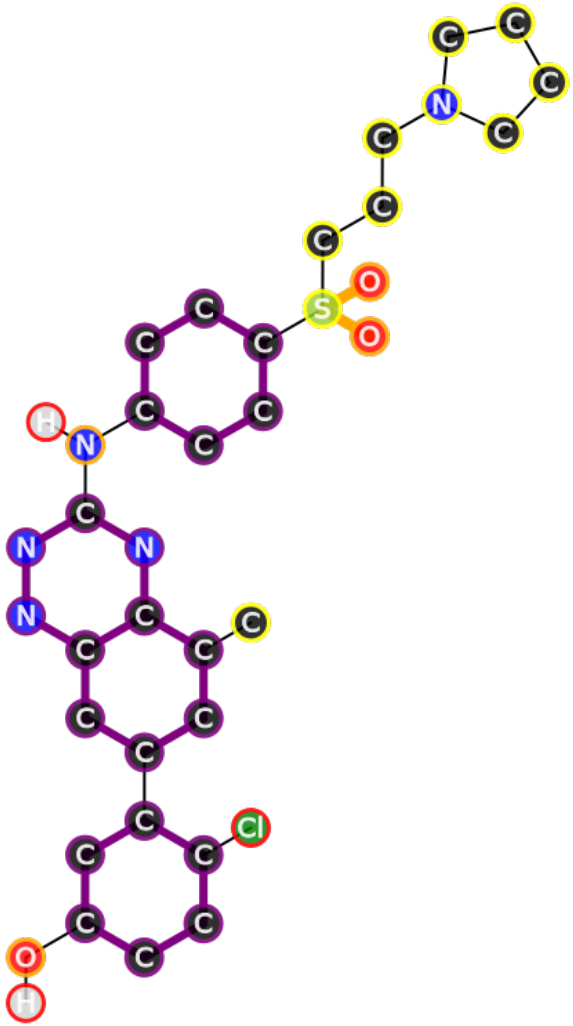
Définition des classes d'équivalence





Inspiration : Activity Cliffs

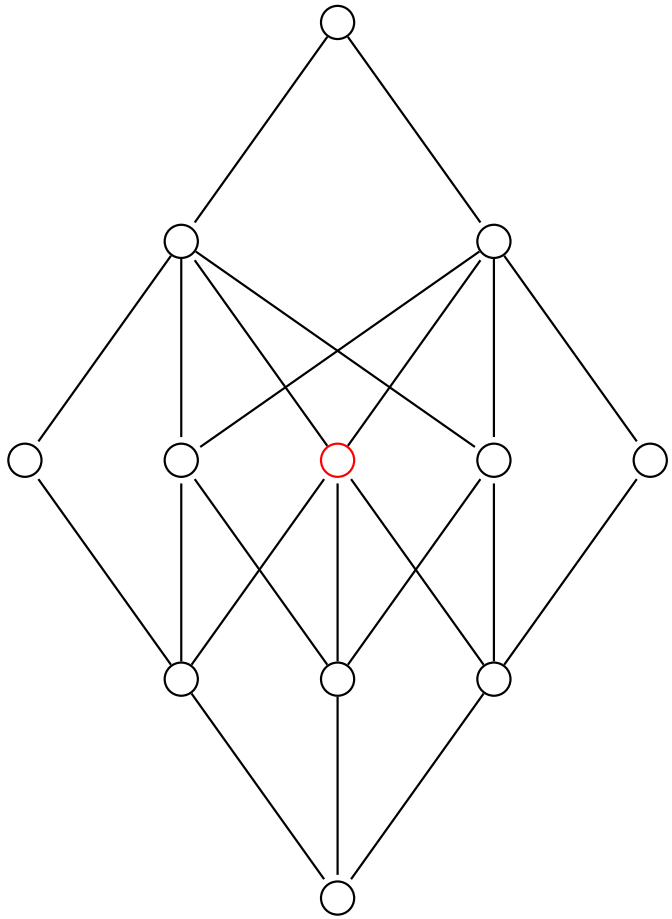




Définition des Pharmacophores Activity Deltas (PADs)

Étape 1 :

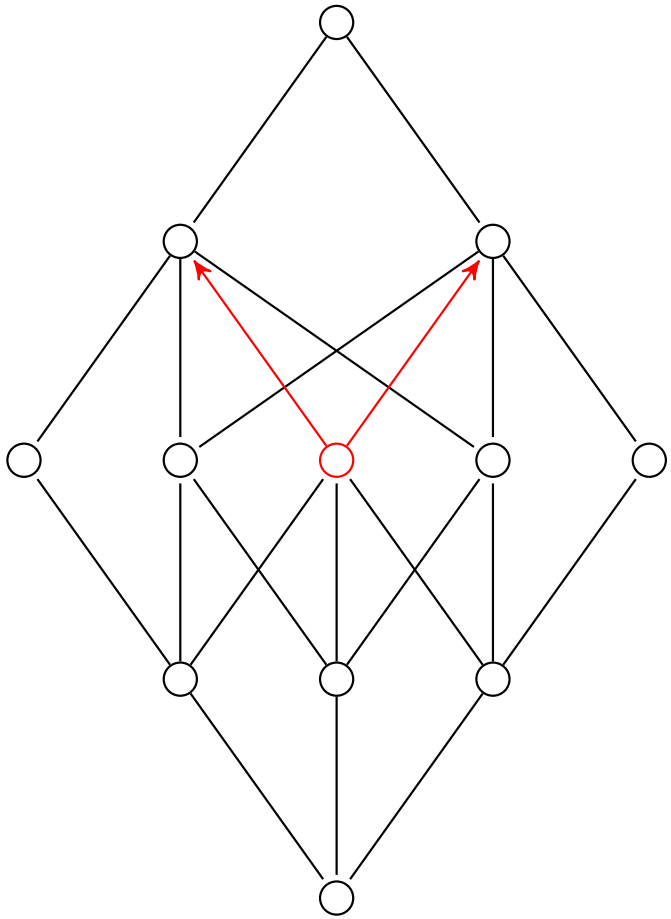
Choisir un noeuds de départ.



Définition des Pharmacophores Activity Deltas (PADs)

Étape 2 :

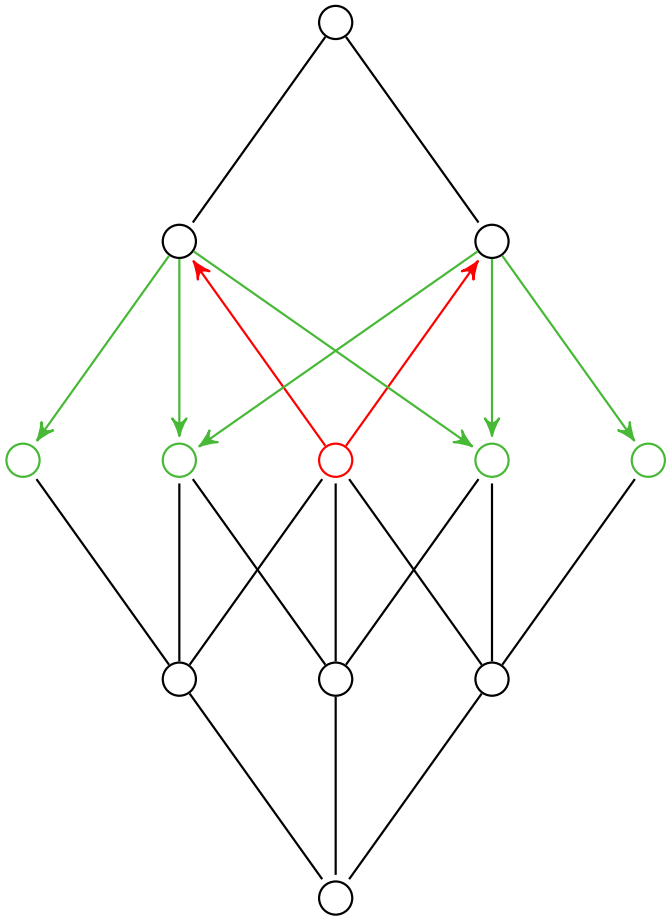
Remonter vers ses ancêtres au premier degré.



Définition des Pharmacophores Activity Deltas (PADs)

Étape 3 :

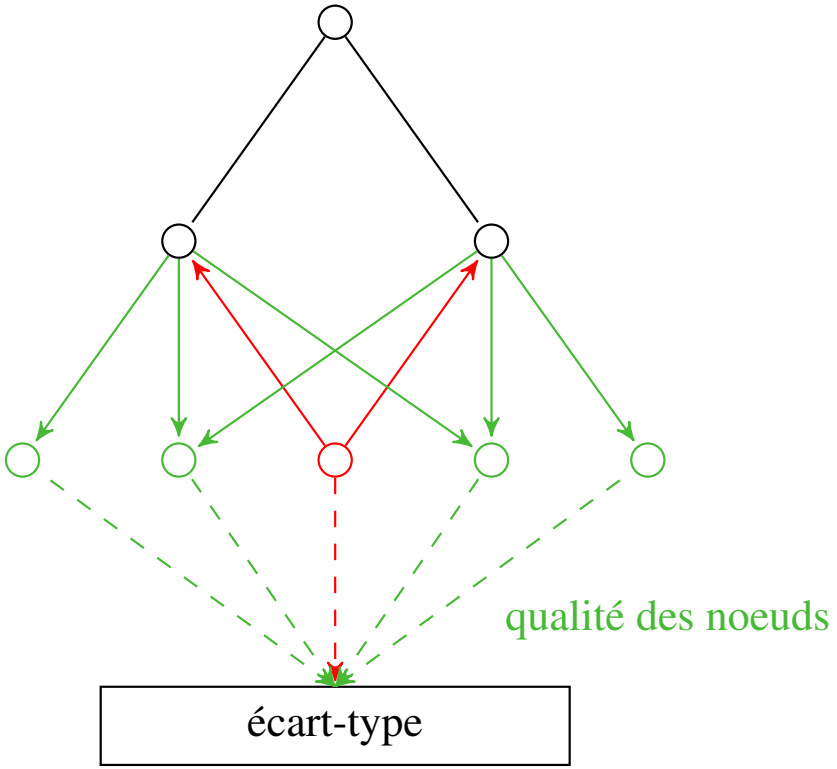
Récupérer tous les parents au premier degré.



Définition des Pharmacophores Activity Deltas (PADs)

Étape 4 :

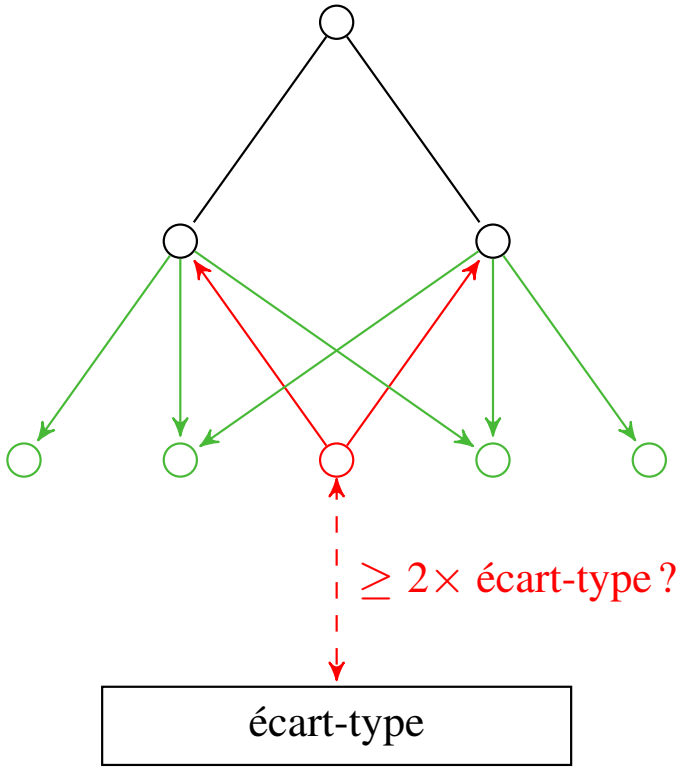
Calculer l'écart-type à partir des parents et du noeud de départ.



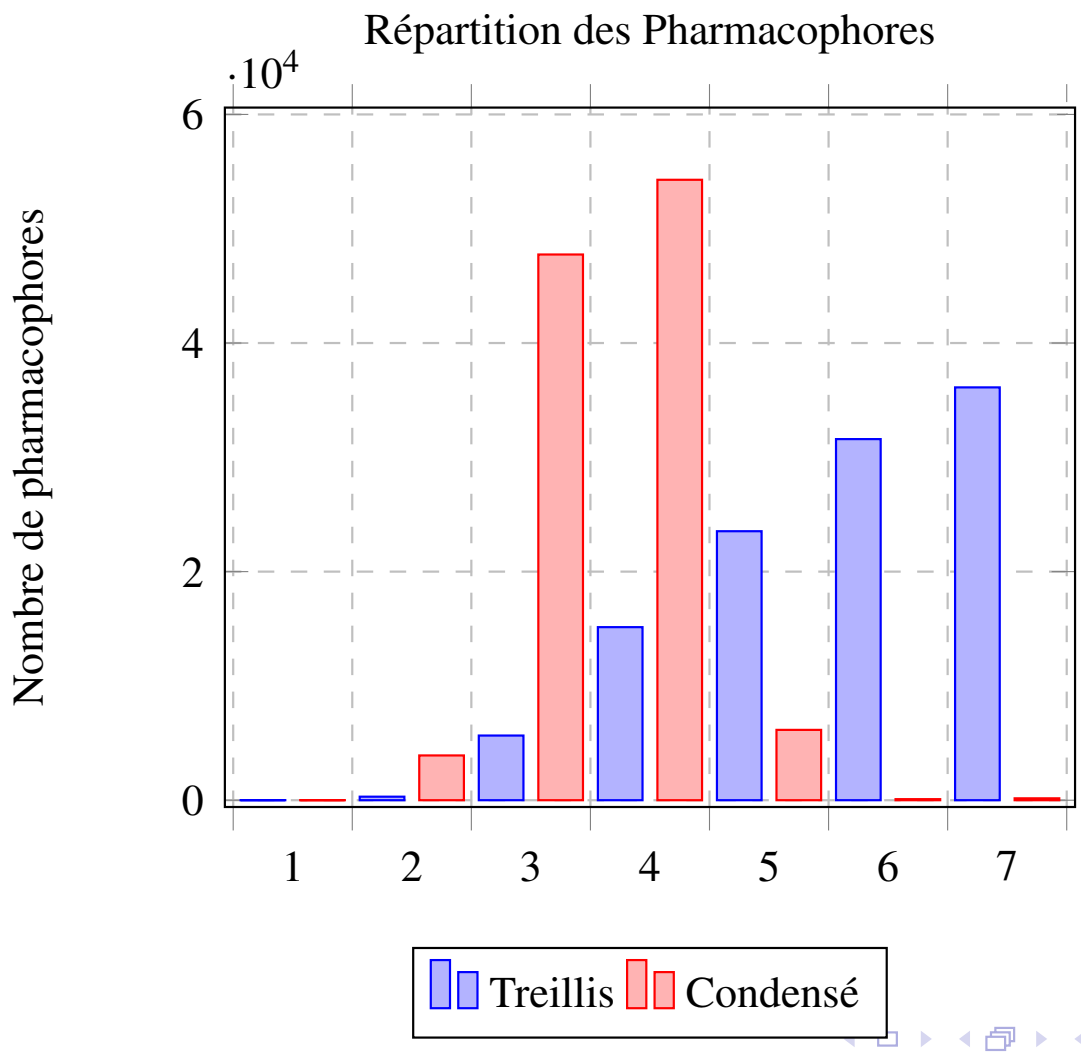
Définition des Pharmacophores Activity Deltas (PADs)

Étape 5 :

Vérifier si le noeud de départ est pertinent.

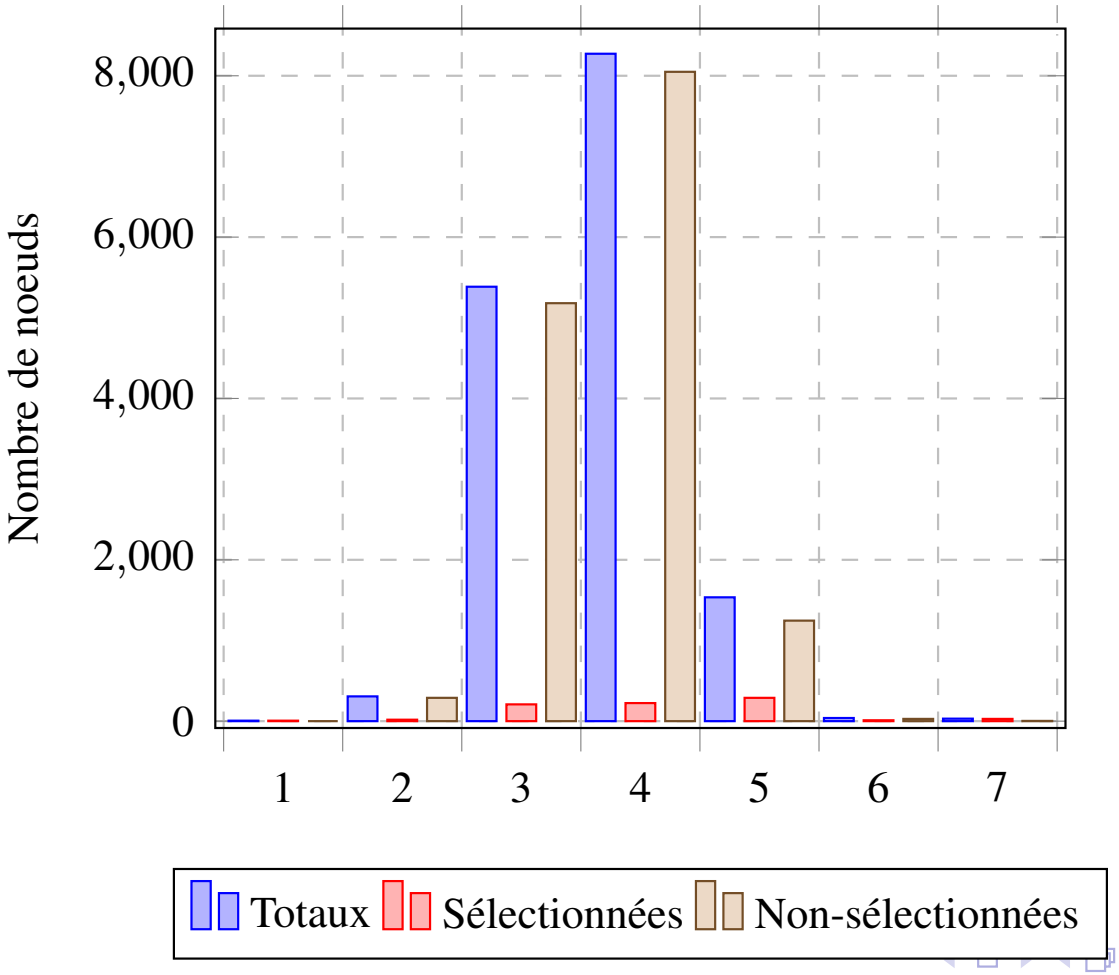


Application des PADs à un jeu de données

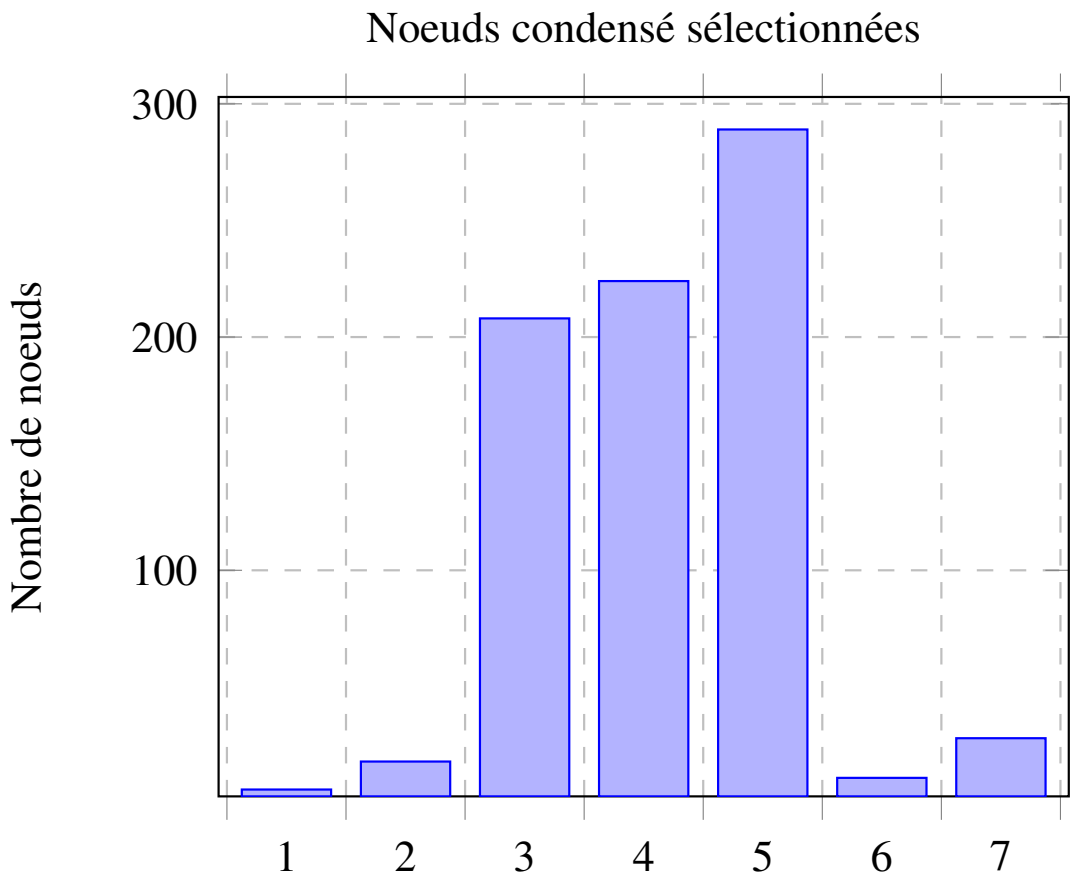


Application des PADs à un jeu de données

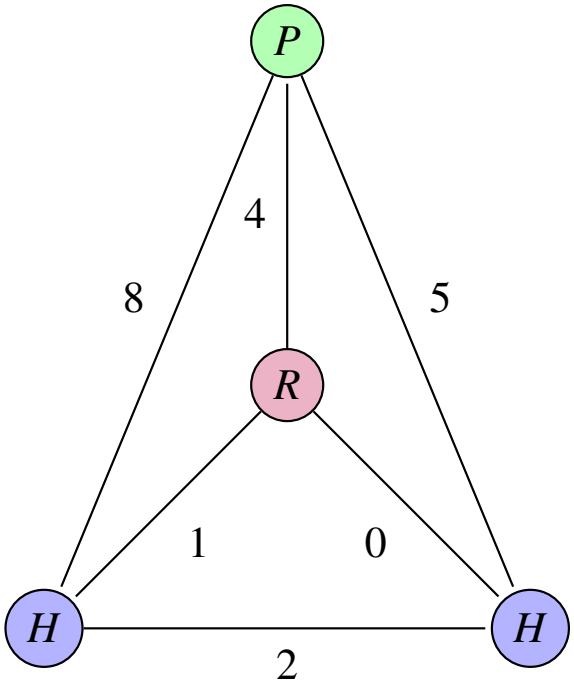
Rapport entre les noeuds condensés sélectionnées et non-sélectionnées



Application des PADs à un jeu de données



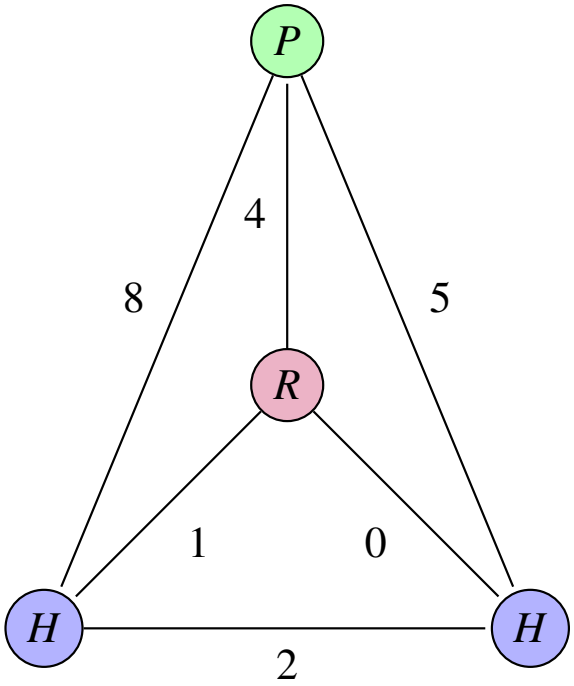
Syntaxe d'un pharmacophore



Pharmacophore

$|R|H|H|P|\ |1|0|4|2|8|5|$

Syntaxe d'un pharmacophore



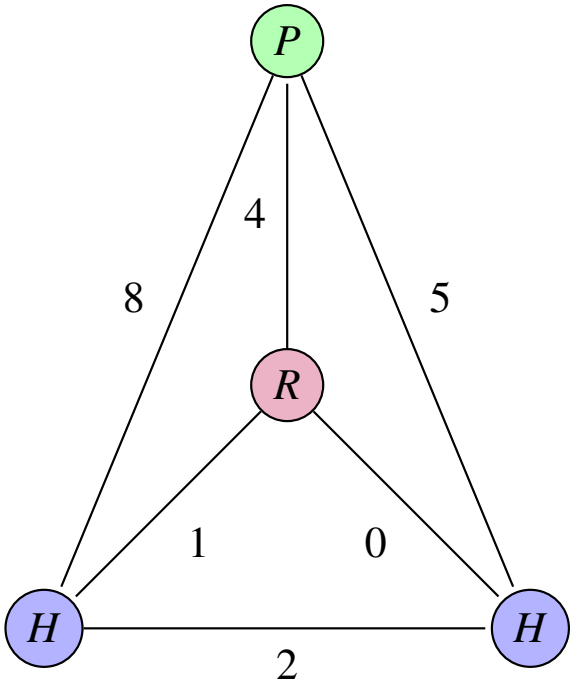
Pharmacophore

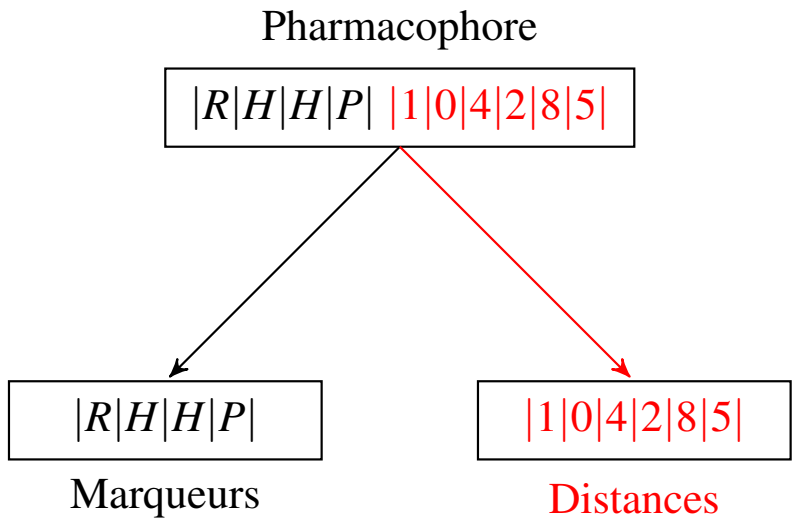
|R|H|H|P| |1|0|4|2|8|5|

|R|H|H|P|

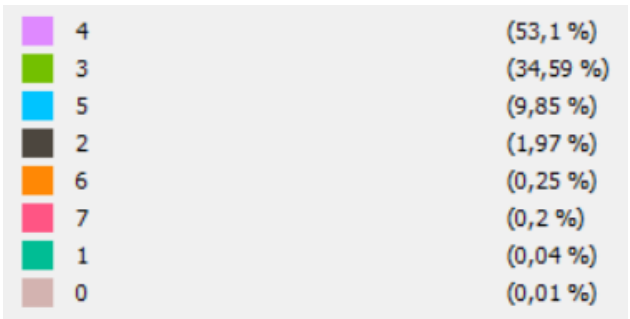
Marqueurs

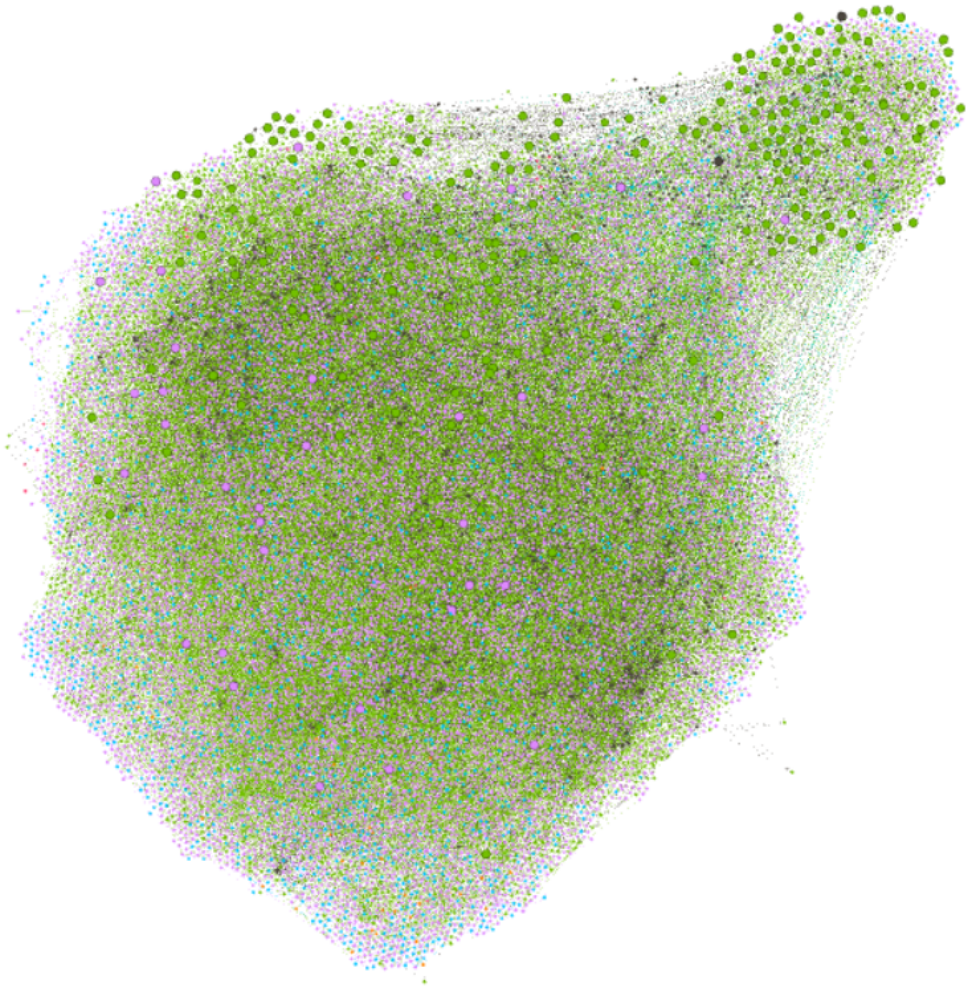
Syntaxe d'un pharmacophore



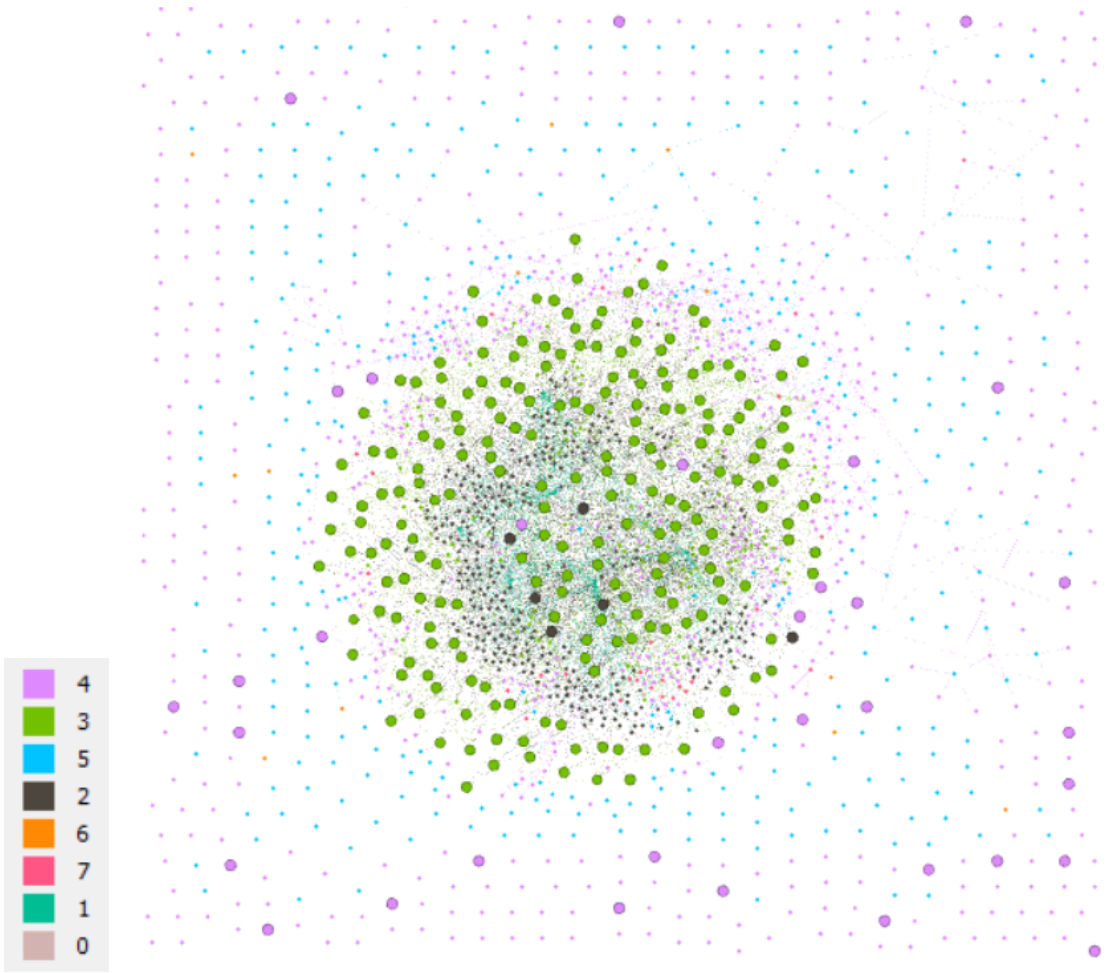


Présentation d'un exemple



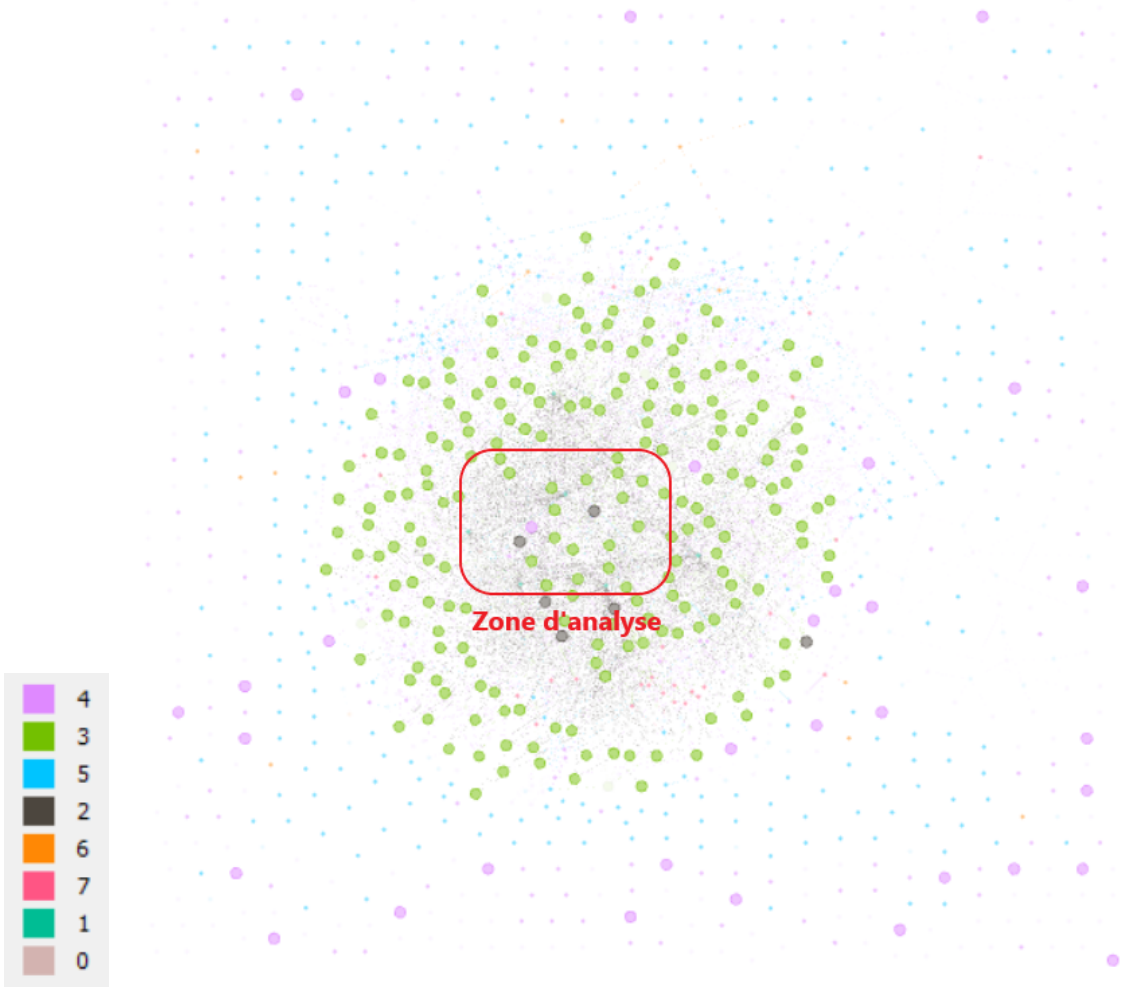


Présentation d'un exemple

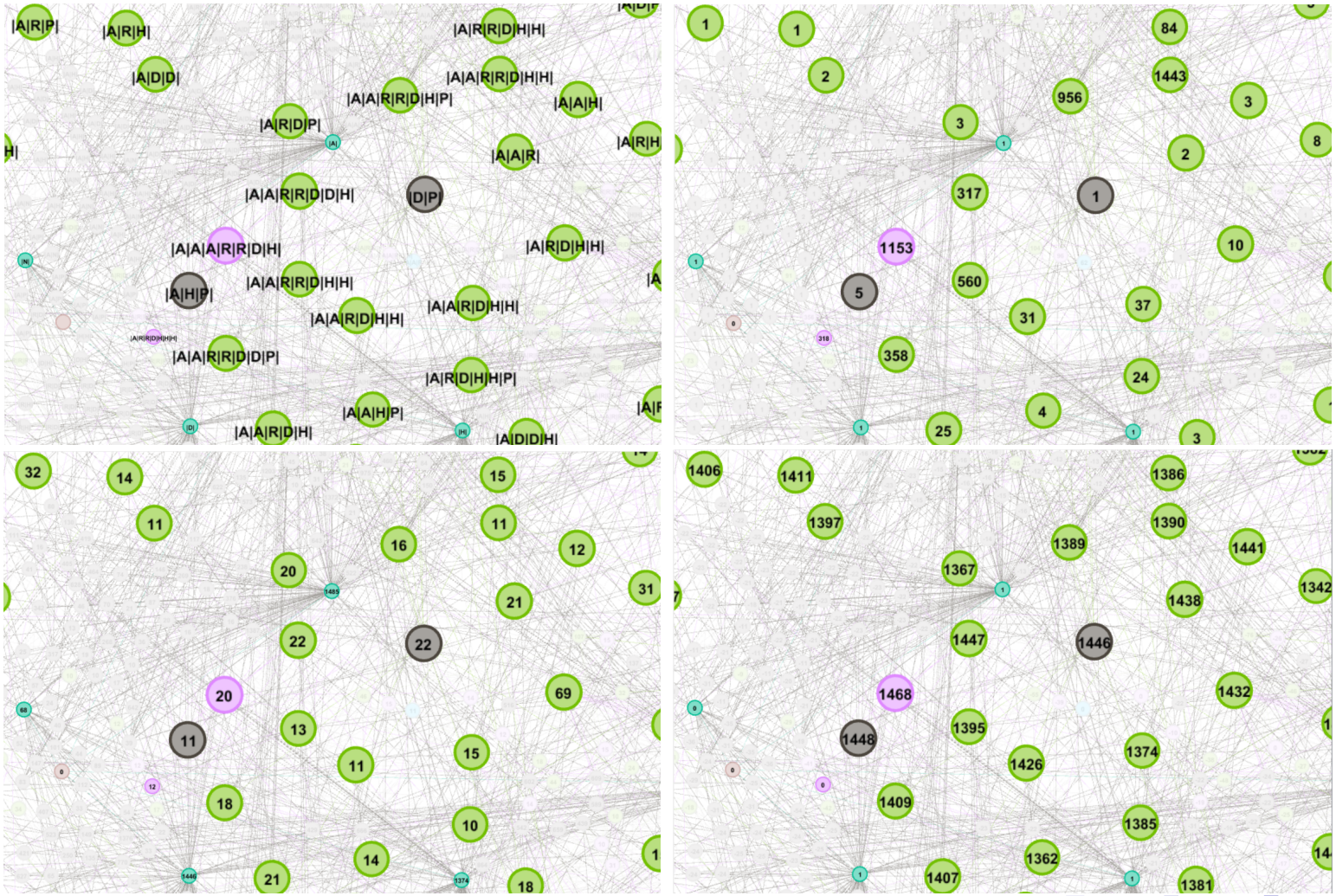


Présentation d'un exemple

Présentation d'un exemple



Présentation d'un exemple



Conclusion

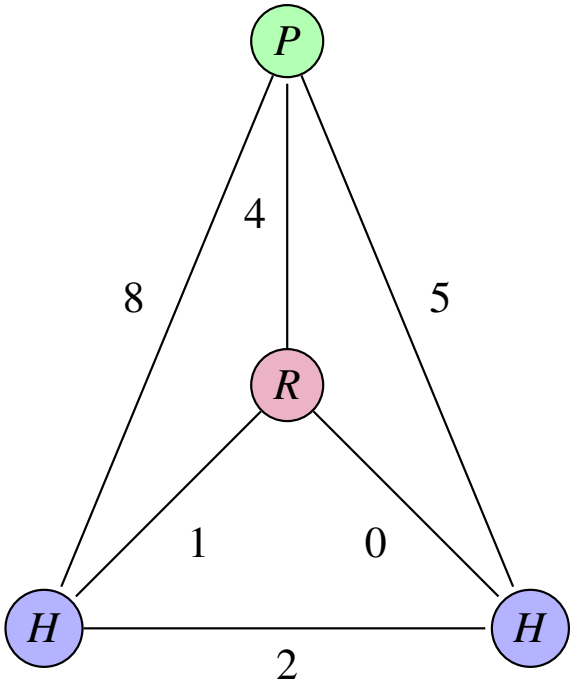
Résultats

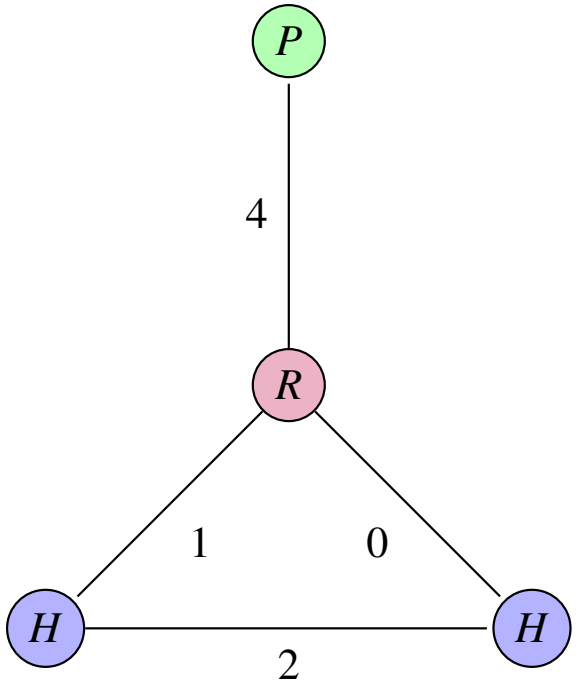
- Extension de l'API Norns.
- Treillis condensés pour la visualisation.
- Nouvelle mesure de pertinence.
- Soumission d'un résumé aux journées SFCI.

Ouvertures :

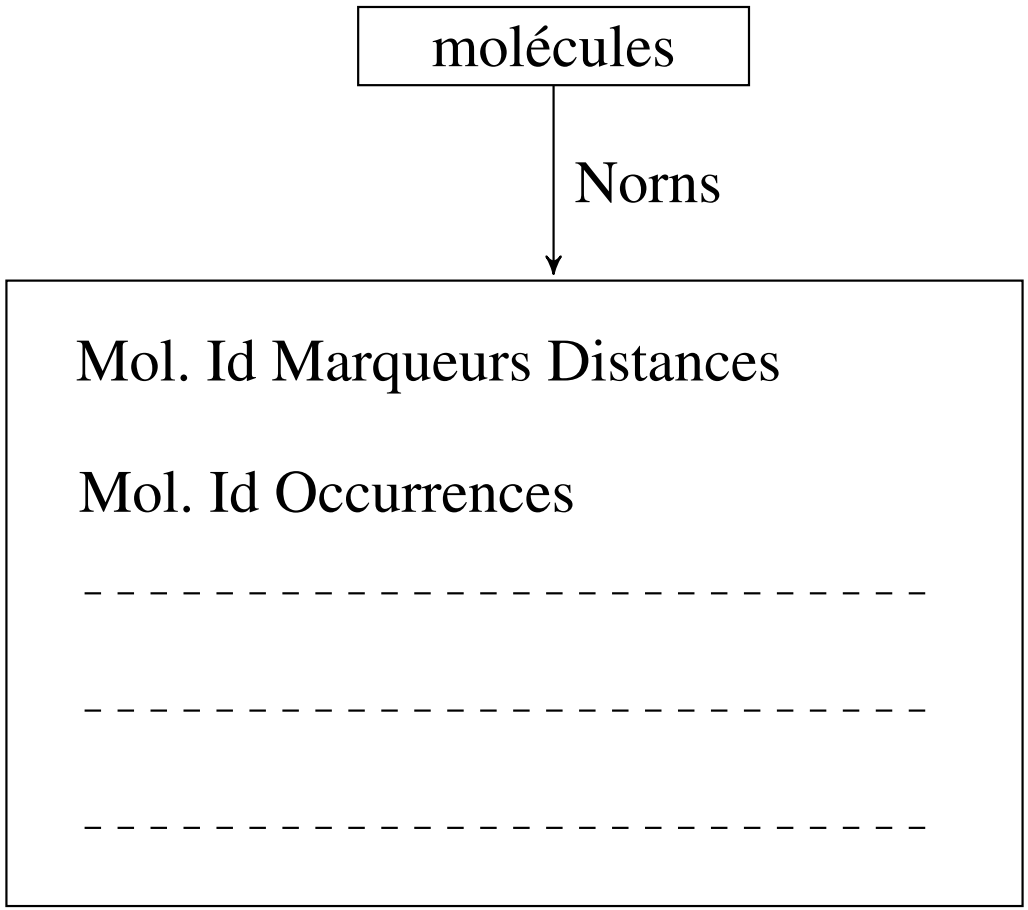
- Meilleur Visualisation de la structure des treillis (LABRI).
- Affichage des molécules.
- Visualisation des familles.
- Application des PADs à d'autres domaines.

Graphes complets et non-complets

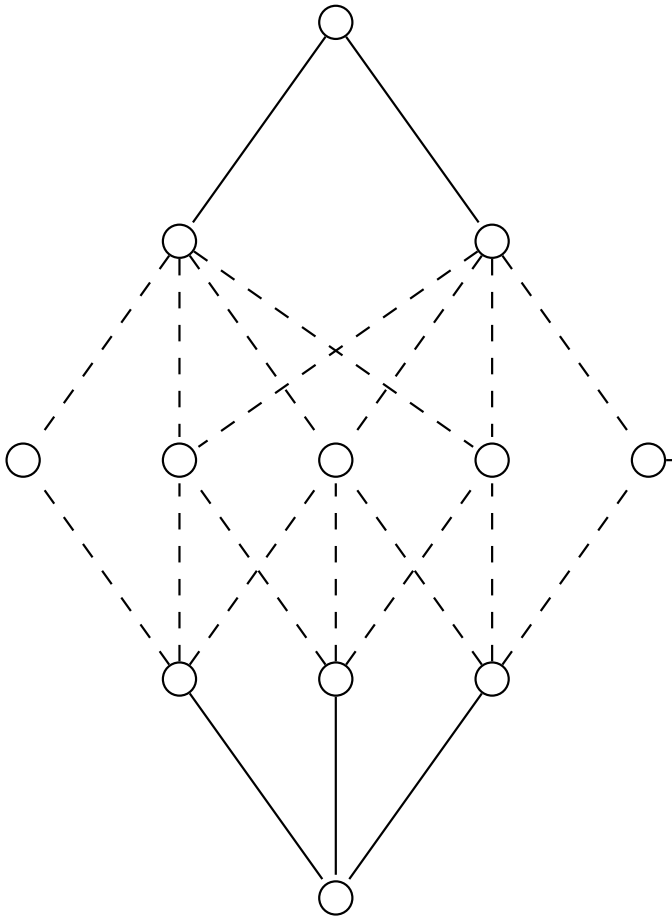


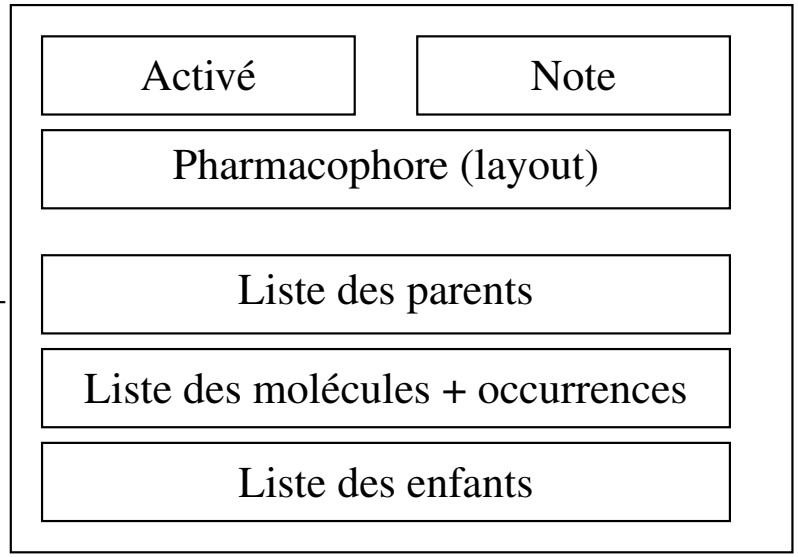


Norns : fouille de pharmacophores

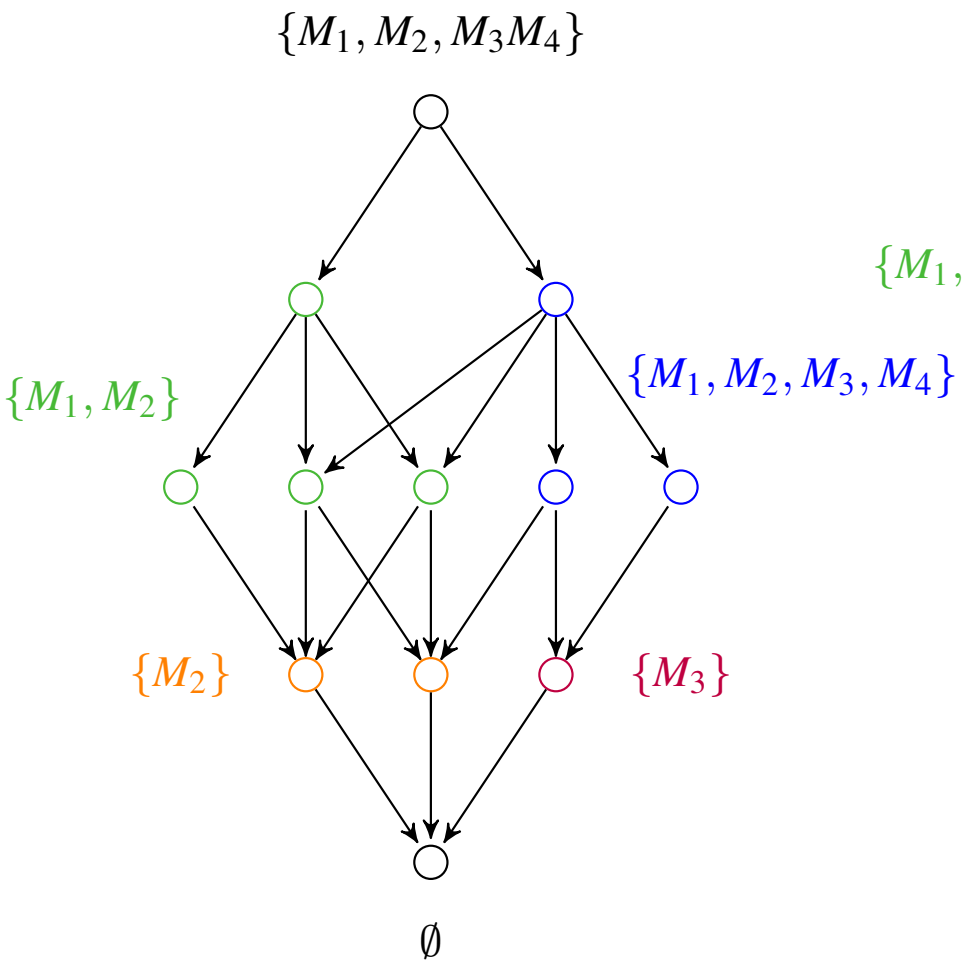


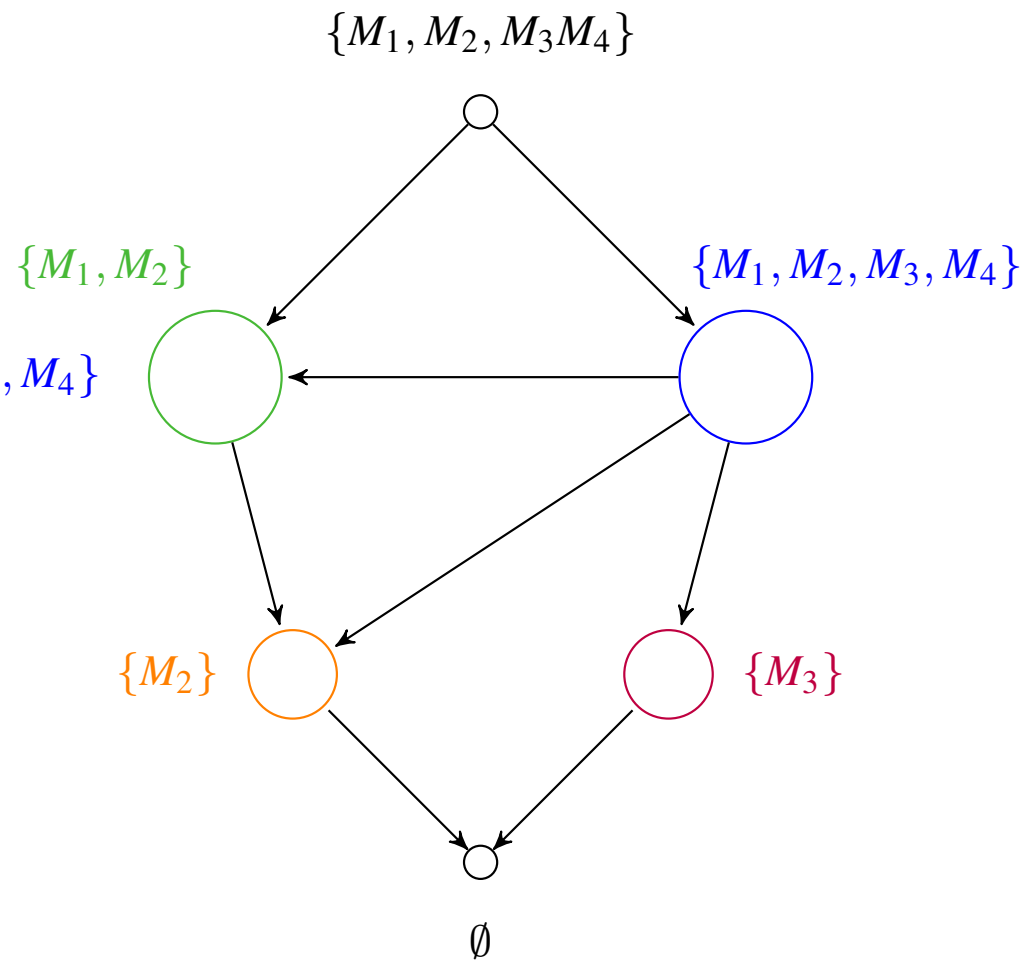
Norns_Lattice



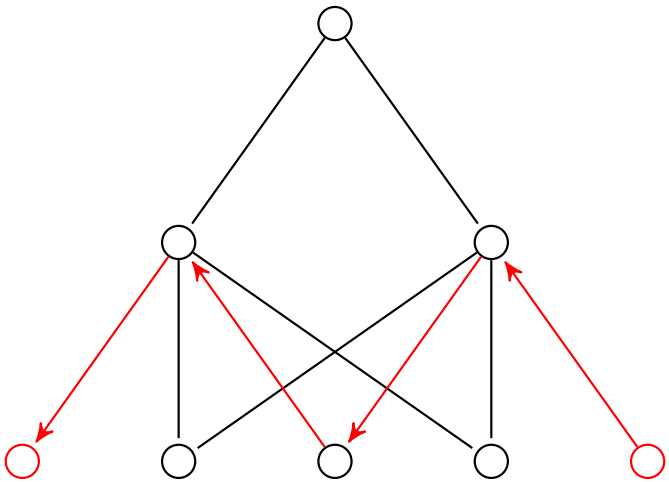


Détails sur les Structured Equivalence Classes(SEC)





Détails sur les Structured Equivalence Classes(SEC)

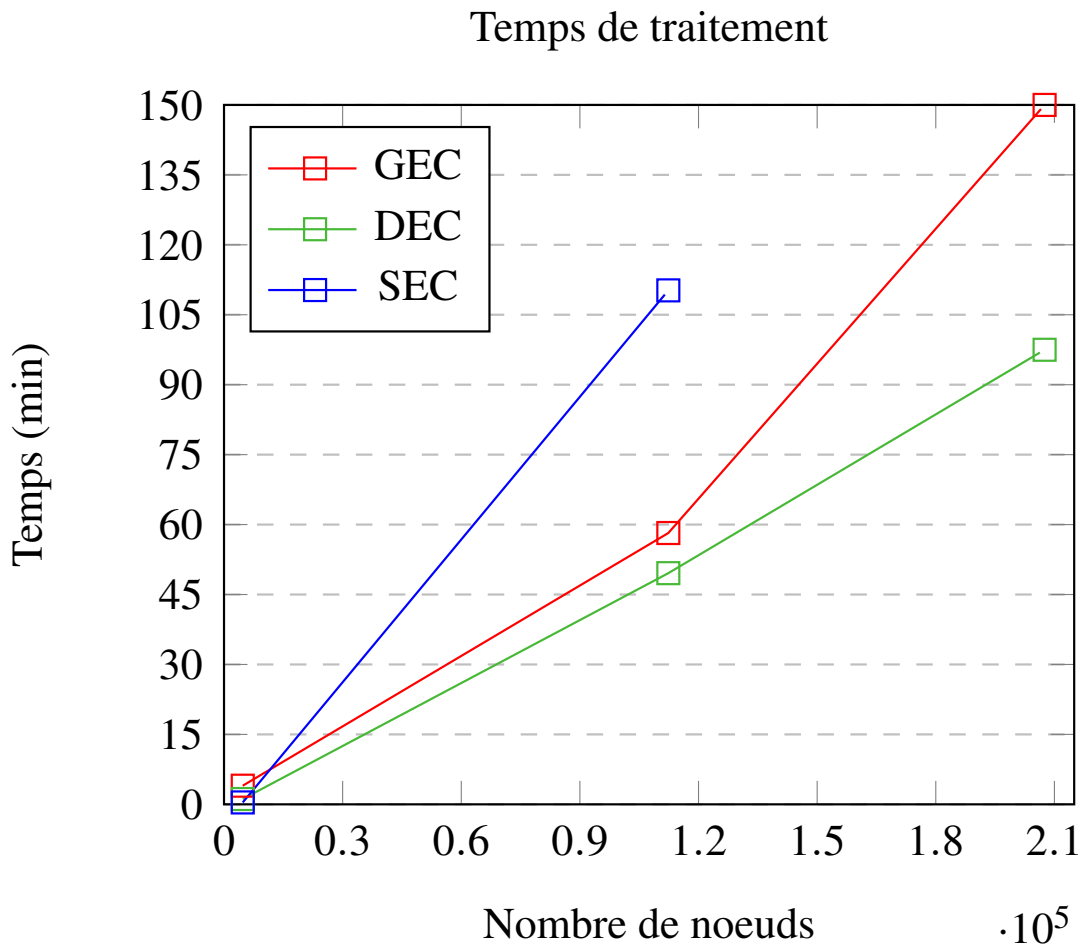


$\{M_1, M_2, M_3, M_4\}$

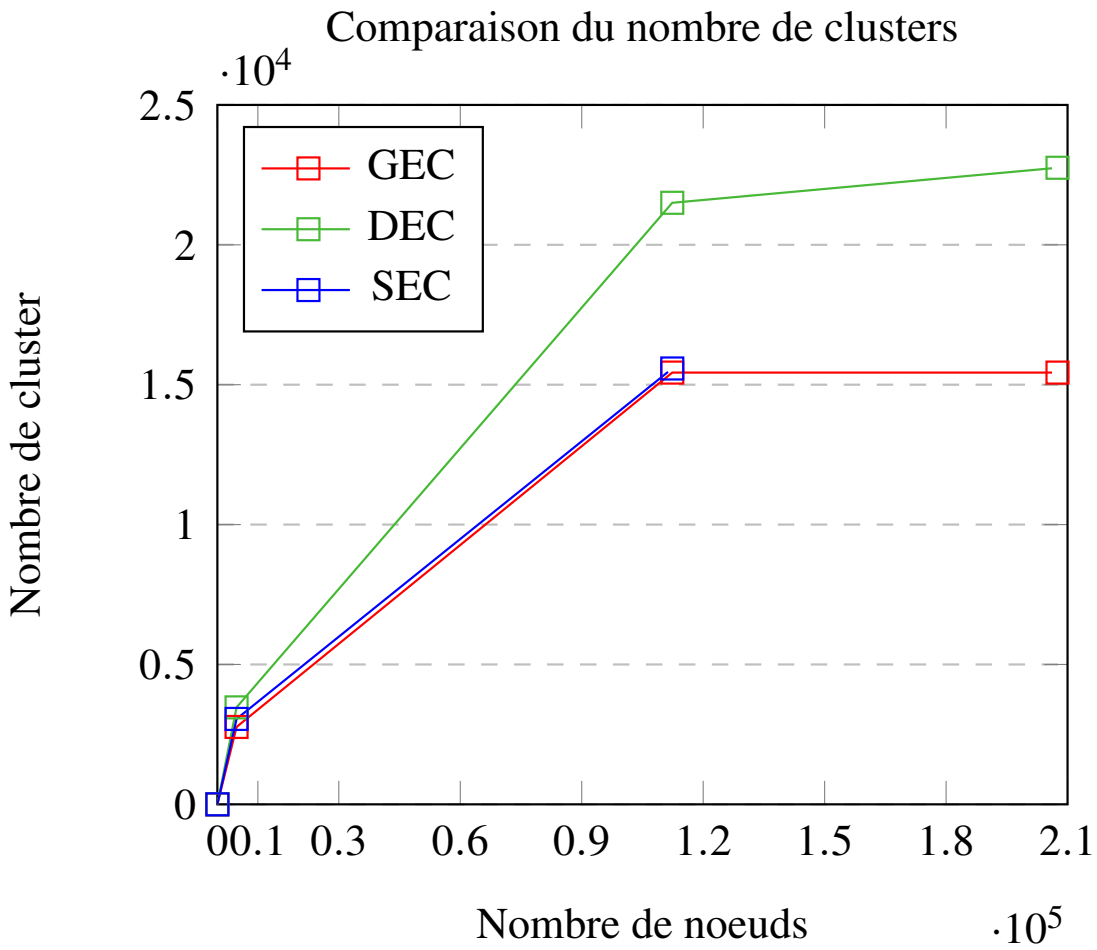
Les différentes classes d'équivalence

GEC	DEC	SEC
molécules communes	molécules communes	molécules communes
-	pharmacophores de mêmes ordres	structures communes

Performances des classes d'équivalences



Performances des classes d'équivalences



Analyse d'un exemple

N° molécule	Zone 1	Multiplicateur 1	Zone 2	Multiplicateur 2
106	✓	3	✓	4
132	✓	3	✓	4
244	✓	3	✓	4
254	✓	3	✓	4
266	✓	3	✓	4
327	✓	3	✓	4
331	✓	3	✓	4
345	✓	3	✓	4
355	✓	3	✓	4
406	✓	3	✓	4
583	✓	3	✓	4

Analyse d'un exemple

N° molécule	Zone 1	Multiplicateur 1	Zone 2	Multiplicateur 2
22	×	0	✓	2
165	✓	1	×	0
253	×	0	✓	2
378	×	0	✓	2
389	✓	1	×	0
437	×	0	✓	2