WAVE TOP-K RANDOM-D FAMILY SEARCH

Interactive exploration of a space of structured patterns

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Plan de l'exposé

Subgraph mining and chemoinformatics

Data :

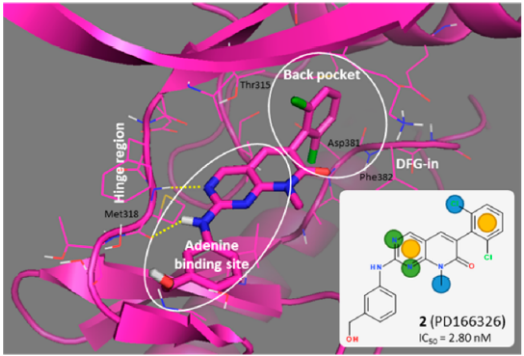
- 1 receptor : BCR-ABL
- 1485 molecules

Structured pattern :

- 112 363 pharmacophores
- 15 533 equivalence classes

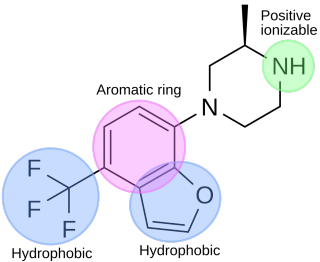
Method goal :

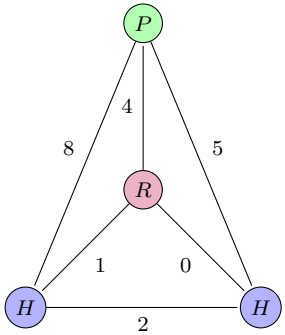
Guide an experts' exploration of the pharmacophores set.



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

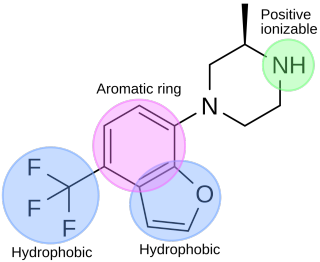
From molecules to pharmacophores (1)

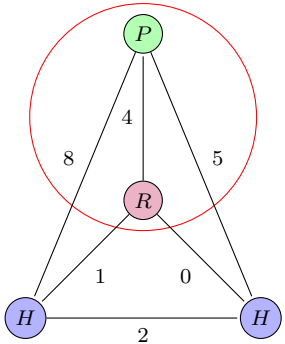




- Pharmacophoric features = pharmacophore vertices.
- Distances between features = labels of the pharmacophore edges.

From molecules to pharmacophores (2)





- The subgraph of a pharmacophore is a pharmacophore.
- We can build a partial ordered graph from the pharmacophore set.

Plan de l'exposé

1. Context and stakes

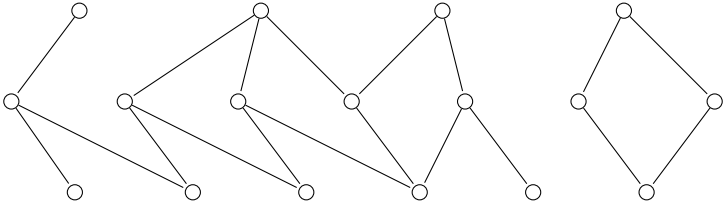
2. Method presentation

3. Experiences and evaluation

Proposed interactions

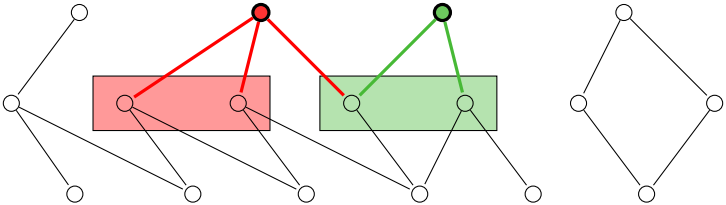
Interaction	Consequence·s	Color
Accepted	Prioritized area & Weights augmentation	Green
Interested	Weights augmentation	Blue
Uncertain	–	Purple
Not-interested	Weights diminution	Orange
Rejected	Exclusion area & Weights diminution	Red

Example on a partially ordered graph



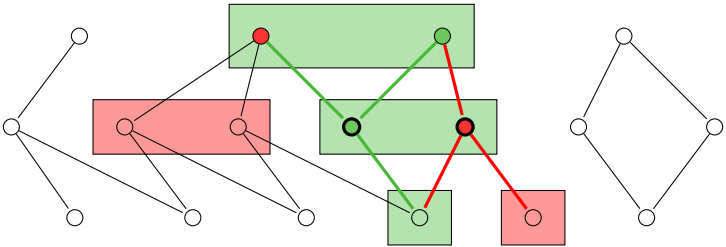
- Partially ordered graph as an input of the method.
- Each vertex is a pharmacophore.

Definition of the search areas (1)



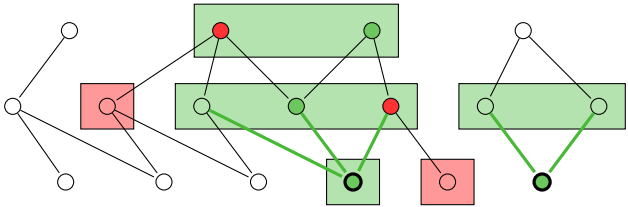
- **Interactions** : rejected (red) and accepted (green).
- Exclusion area in red, prioritized area in green.
- In case of **conflict**, the prioritized areas win.
- Areas are only defined on the **directs descendants**.

Definition of the search areas (2)



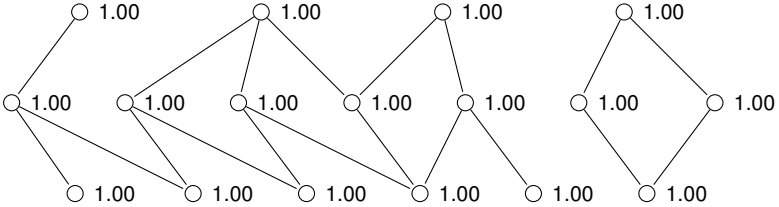
- Excluded and prioritized areas are defined on direct ancestors and descendants.
- There is not enough pharmacophores available in prioritized areas, we must offer a pharmacophore from an unbiased area.

Definition of the search areas (3)



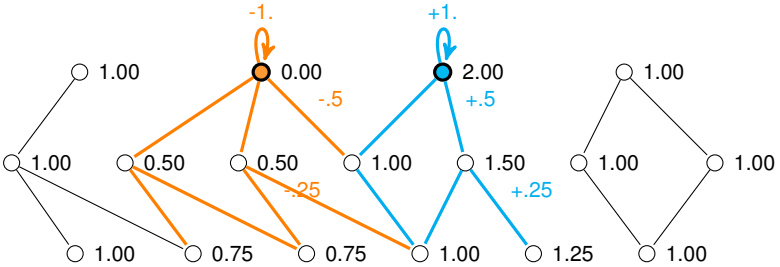
- Prioritized areas are defined on the direct ancestors.
- The search has reached the last layer. It goes up to the more generic patterns.
- **Question** : how to we choose the pharmacophores to propose ?

Weights diffusion (1)



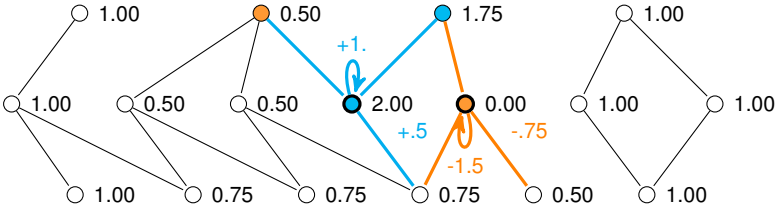
- The POG carries no interaction, every pharmacophores have the same weight.

Weight diffusion (2)



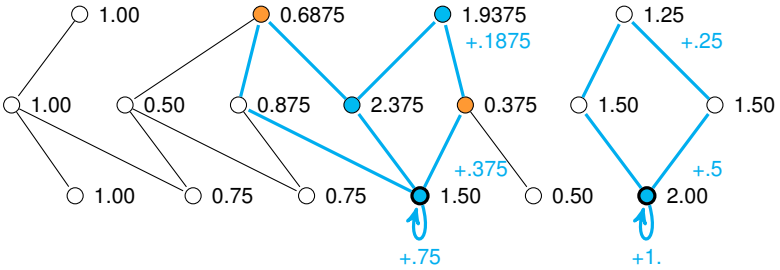
- **Interactions** : rejected or not-interested (orange) and accepted or interested (blue).
- Diffusing to the descendants : -1 for the negative interest and $+1$ for the positive interest.
- The raw interest diffused decreased with the increase of the distance from the origin of the interaction.

Weight diffusion (3)



- Diffusing interest to ancestors and descendants.
- Diffused interest is the **weight** of the pharmacophore carrying the interaction.

Weight diffusion (4)



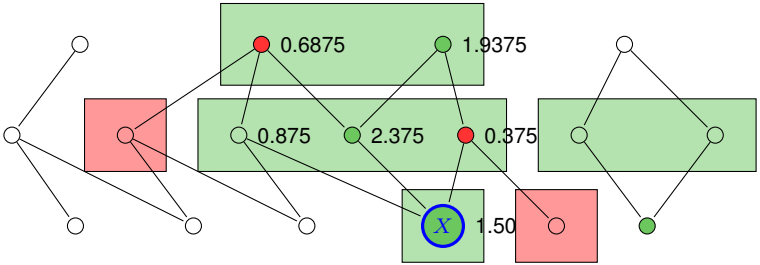
- Diffusing interest to the ancestors.
- The raw interest diffused decreased with the increase of the distance from the origin of the interaction.

Computing potential interest (1)

$$f_p(v,\mathbb{G}) = \sum_{i=0}^{k}(Weight(L_i^+(v,\mathbb{G})) + Weight(L_i^?(v,\mathbb{G}))+ \\ (Weight(L_i^\star(v,\mathbb{G})) - |Weight(L_i^+(v,\mathbb{G})) - Weight(L_i^-(v,\mathbb{G}))|)) * \frac{1}{2^i} \quad (1)$$

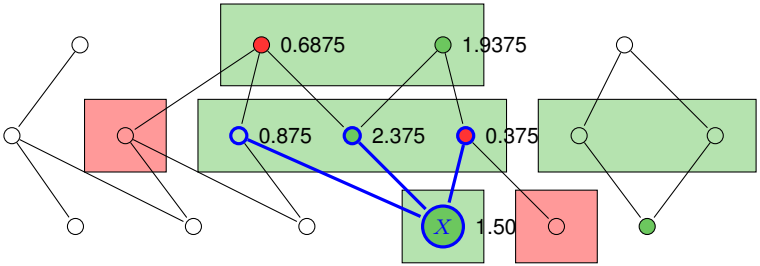
- $Weight(L_i^+(v,\mathbb{G}))$ is the **exploitation** heuristic.
- $Weight(L_i^?(v,\mathbb{G}))$ is the **exploration** heuristic.
- $(Weight(L_i^\star(v,\mathbb{G})) - |Weight(L_i^+(v,\mathbb{G})) - Weight(L_i^-(v,\mathbb{G}))|)$ is the **ambiguity** heuristic.
- $1/2^i$ is the distance modifier.

Computing potential interest (2)



$$f_p(X) = 1.50 \tag{2}$$

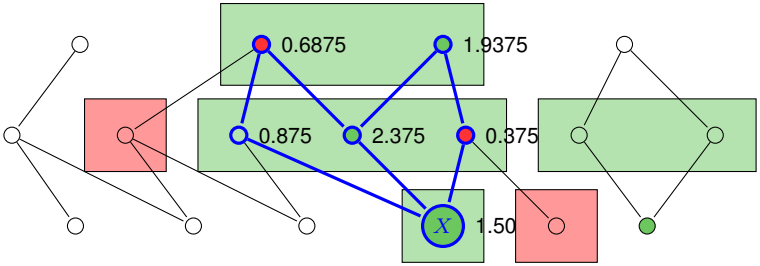
Computing potential interest (3)



$$f_p(X) = 1.50 \tag{3}$$

$$+ (2.375 + 0.875 + (2.375 + 0.375 - |2.375 - 0.375|)) * \frac{1}{2} \tag{4}$$

Computing potential interest (4)



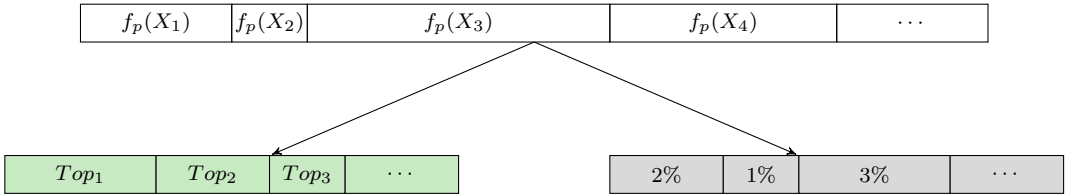
$$f_p(X) = 1.50 \tag{5}$$

$$+ (2.375 + 0.875 + (2.375 + 0.375 - |2.375 - 0.375|)) * \frac{1}{2} \tag{6}$$

$$+ (1.9375 + (1.9375 + 0.6875 - |1.9375 - 0.6875|)) * \frac{1}{4} \tag{7}$$

Potential interest and sampling

Unexplored layer of the partially ordered graph containing the pharmacophores.



Prioritized area (Drawing '$Top-k$' patterns)

Unbiaised area (Drawing '$Random-d$' pattern

- Prioritized area : we select patterns with the **highest potential interest**.
- Unbiased area : potential interest is converted into a **selection probability**.

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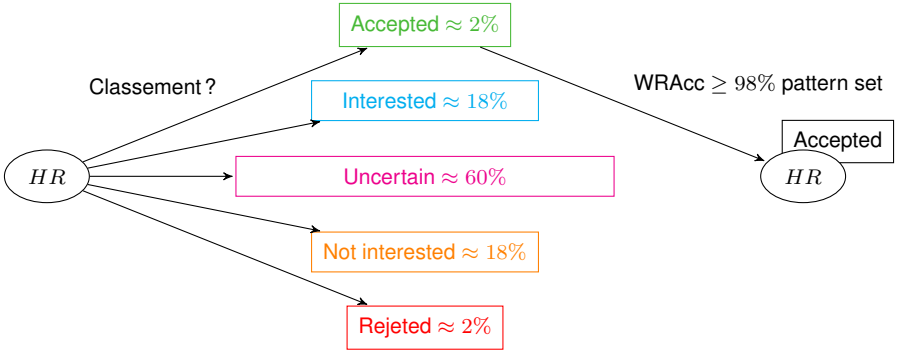
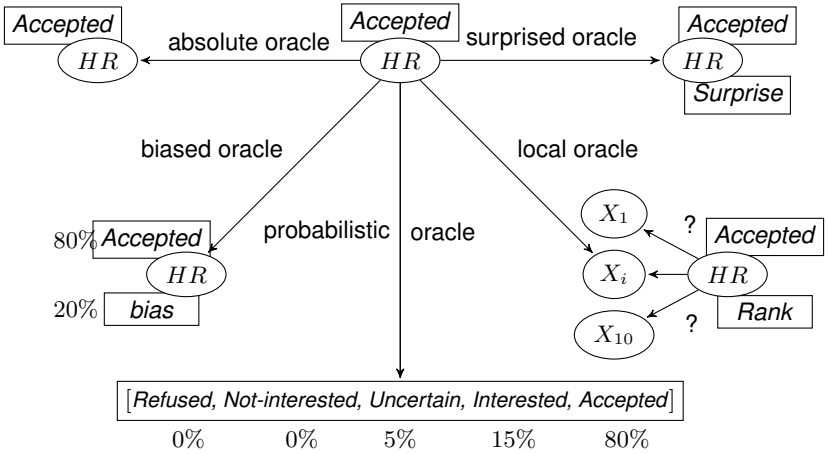
Oracles definition (1)



- The HR WRAcc is compared to the WRAcc of the studied pharmacophore set.

Oracles definition (2)



Recall graphs

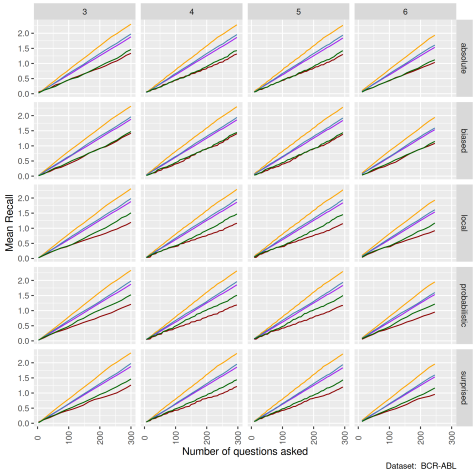


FIGURE – Random Sampling

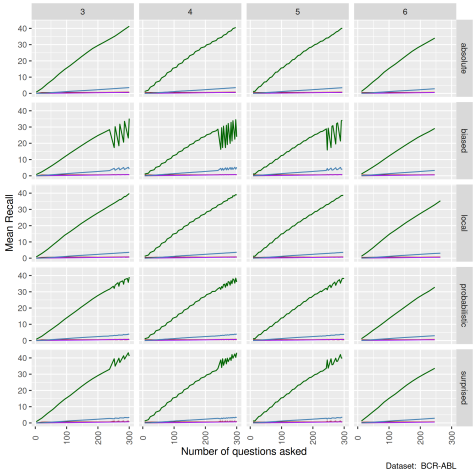
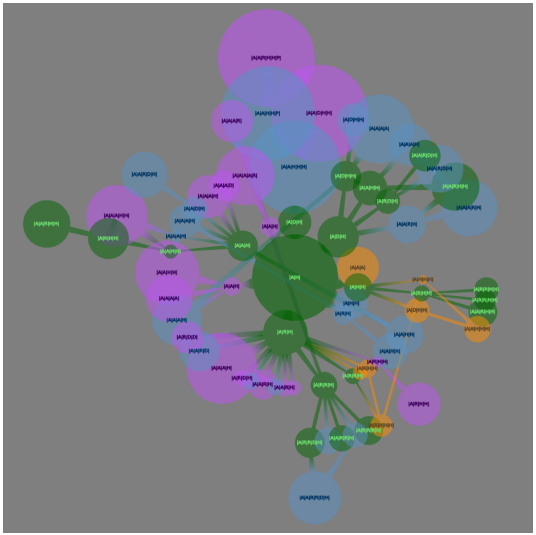


FIGURE – WTRFS

Interests' partially ordered graph



Conclusion and future works

Conclusion

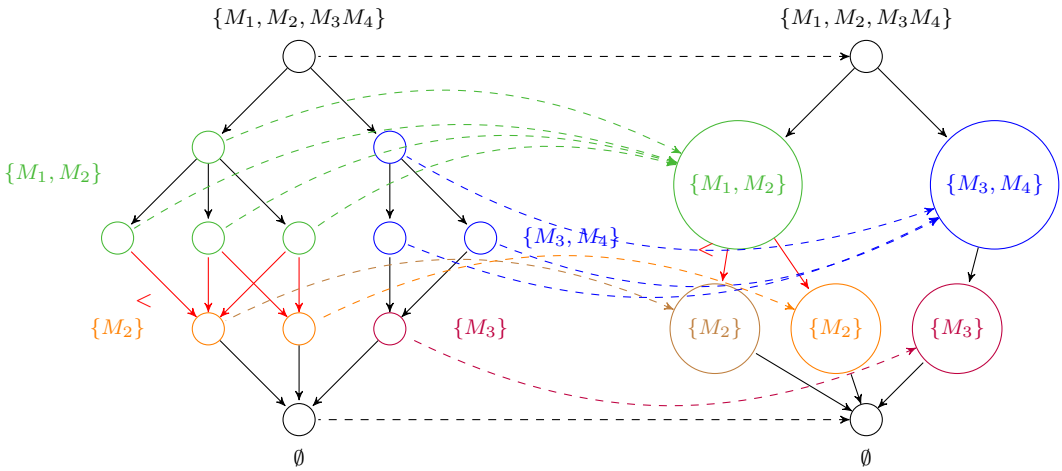
- Creation of the Interests' partial order graph.
- Interactive exploration without descriptor.
- New ideas for the evaluation process.

Future works

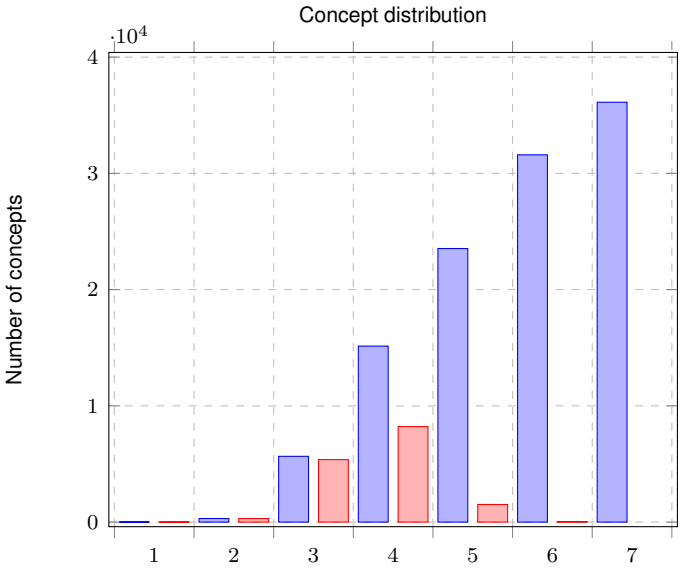
- Working on the visual representation (GUI and more).
- Adapting the algorithm to a mining task.
- Creation of new heuristics.

Annexes

Structured Equivalence Classes



BCR-ABL : patterns distribution by layers



Case study : selecting an outstanding pattern