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▶ To cite this version:

Etienne Lehembre, Jean-Luc Lamotte, Abdelkader Ouali, Christophe Couronne, Bruno Crémilleux, et al.. Towards lattice-based interactive pharmacophore exploration. 10th SFCi, Sep 2021, Lille, France. hal-03764647

HAL Id: hal-03764647 https://hal.science/hal-03764647

Submitted on 30 Aug2022

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TOWARDS LATTICE-BASED INTERACTIVE PHARMACOPHORE EXPLORATION

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Computing key structural configurations from ligands is a major challenges in drug design. In the **InvolvD project**¹, we designed a **pharmacophore mining method** to discover structural layouts potentially linked to a biological activity.

Method overview

1) Defining **pharmacophoric features**.

3. PAD : a new quality measure



By using the **condensed lattice** and the Growth Rates of the pharmacophores, one computes the **Pharmacophore Acti**vity Delta :

1) Select a node in the lattice (red node).

4) Compute the family standard deviation.

5) Compute node delta from its quality and

2) Identify the ancestors (red arrows).

3) Identify the siblings (green nodes).

the standard deviation.

- 2) Representing molecular data-set as pharmacophore graphs.
- 3) Extracting **pharmacophores** by mining the pharmacophore graphs [3] via Norns^a.
- 4) Structuring pharmacophore set into a **concept lattice** [1].
- 5) Computing quality of each pharmacophore by applying the **Pharmacophore Ac**tivity Delta (PAD) measure, the latter being based on the Growth Rate. a. https://forge.greyc.fr/projects/norns

PAD has been inspired by the notion of **FIGURE 4:** Pharmacophore Activity Delta an Activity Cliff [2]

Results

Data-set : 1,485 ligands from CHEMBL-ABL. Lattice-set : 122,363 pharmacophores extracted from the data-set. Pharmacophores have been extracted with the following parameters :

1) Minimal frequency : 10.

2) Size : 1 to 7 features.

PAD have been computed on the condensed lattice with a minimum selecting threshold of 2 times the family standard deviation.

	Order 1	Order 2	Order 3	Order 4	Order 5	Order 6	Total
Selected	6	6	208	212	48	12	492



ric features

FIGURE 2: *Pharmacophore inclusions*

2. From a pharmacophore lattice to a condensed lattice

In order to structure the pharmacophores of interest composing our molecules, we use a **lattice structure**

- 1) Order relation : sub-graph inclusions.
- 2) Object / Attributes : pharmacophores / molecules.

Then, the lattice is condensed by building equivalence classes which group pharmacophores occurring in the same set of molecules as soon as they constitute a connected part.



FIGURE 3: Pharmacophore lattice (left) and its corresponding condensed lattice (right)

Discarded	0	301	5,181	8,064	1,487	28	15,061			
Total	6	307	5,389	8,276	1,535	40	15,553			
TABLE 1: Equivalence classes and PAD selection										



FIGURE 5: Equivalence classes network (left) and equivalence class connection (right)





Orange nodes from left figure have been separated because :



1) They are not connected by a common direct ancestor nor a common direct descendant.

2) One is not the ancestor nor the descendant of the other.

a. https://tulip.labri.fr/site/

Références



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