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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.

1. Method overview

- 1) Defining **pharmacophoric features**.
- 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 Activity Delta (PAD)** measure, the latter being based on the *Growth Rate*.

a. <https://forge.greyc.fr/projects/norns>

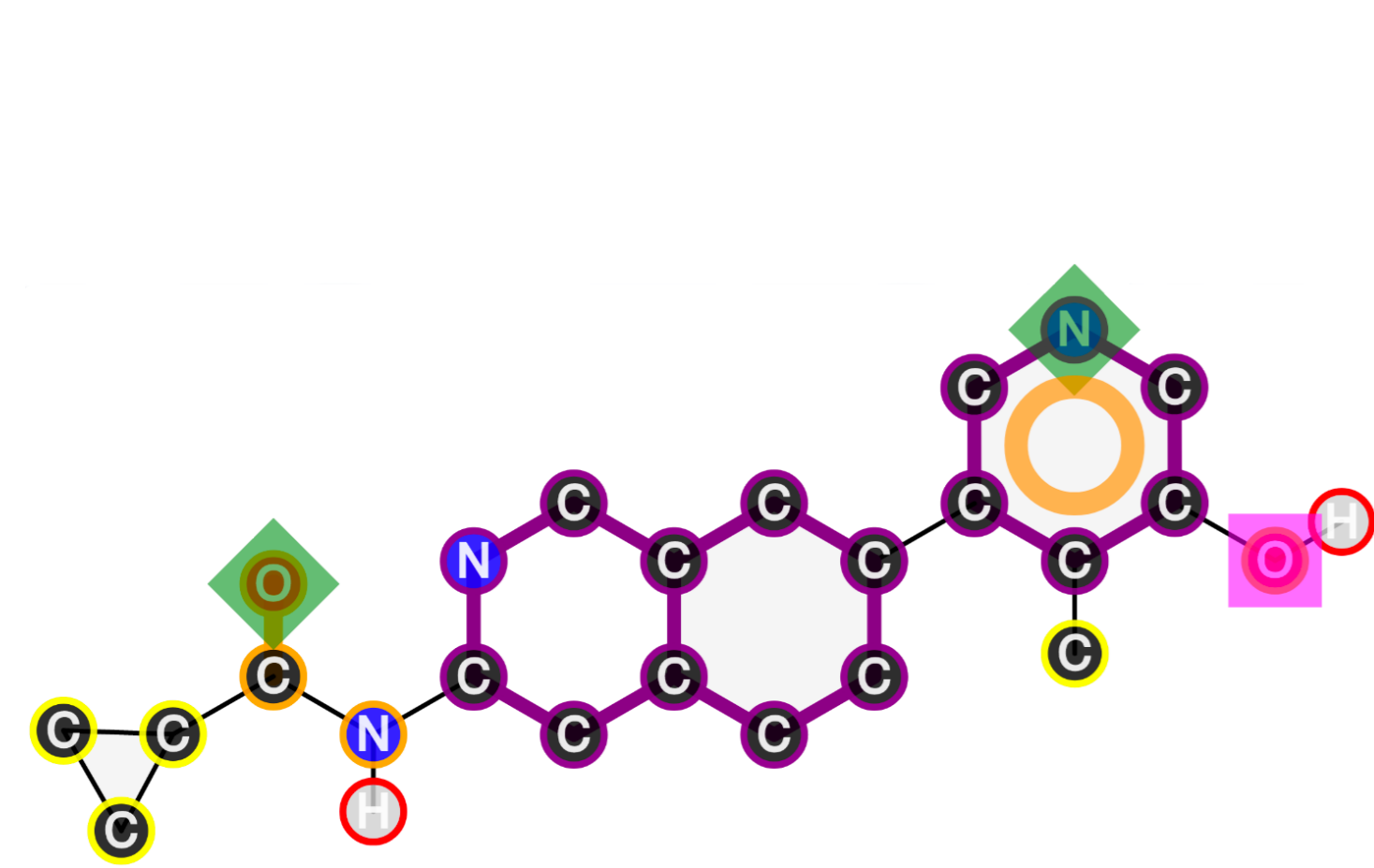


FIGURE 1: Molecule and its pharmacophoric features

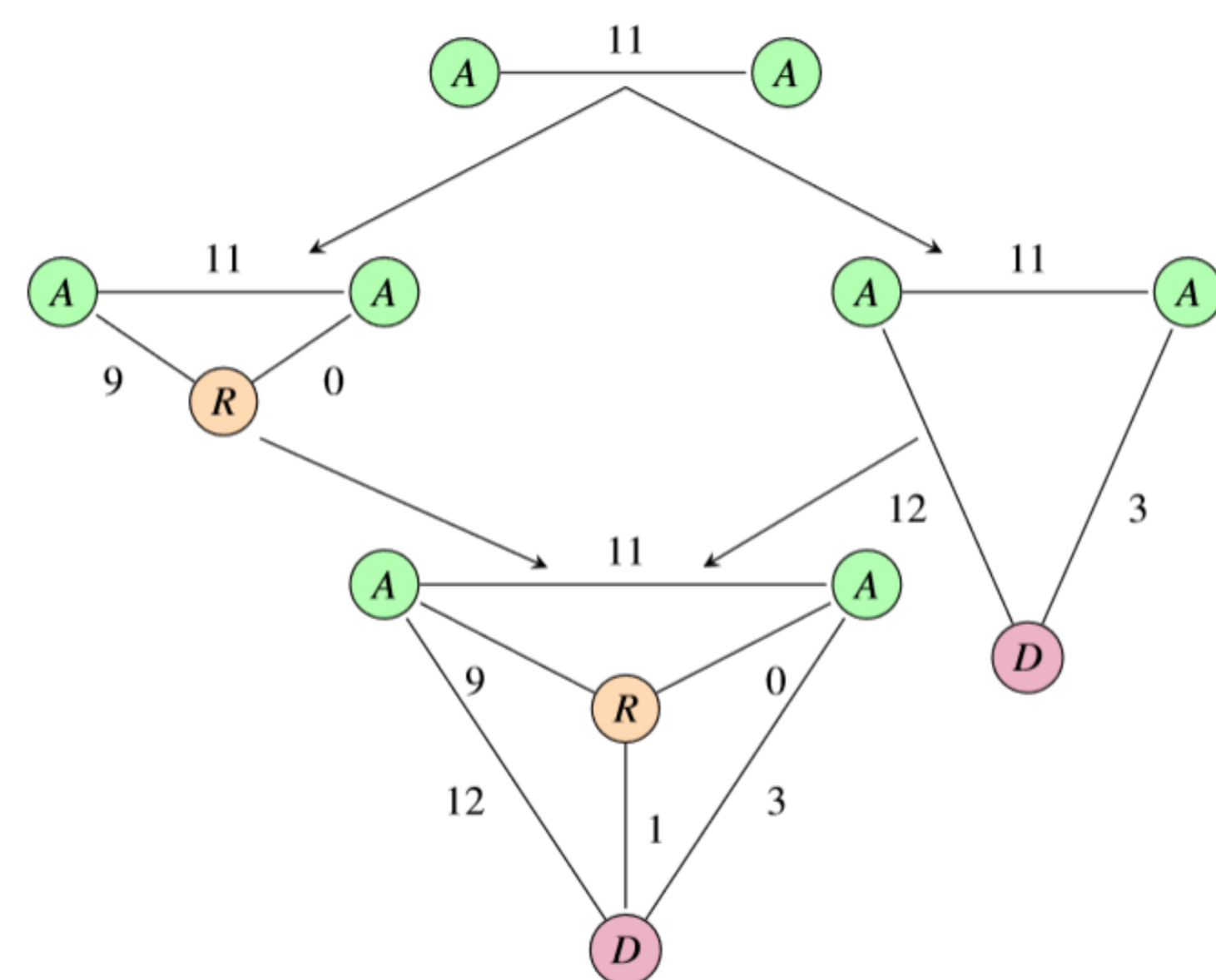


FIGURE 2: Pharmacophore inclusions

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.

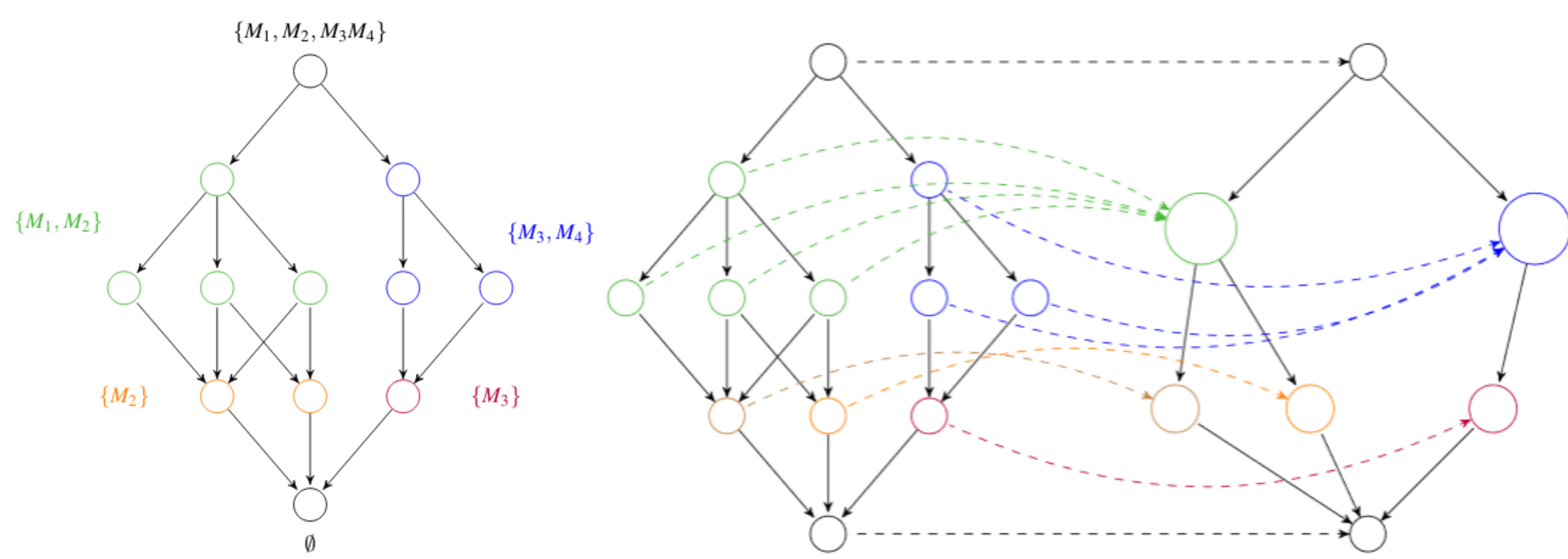
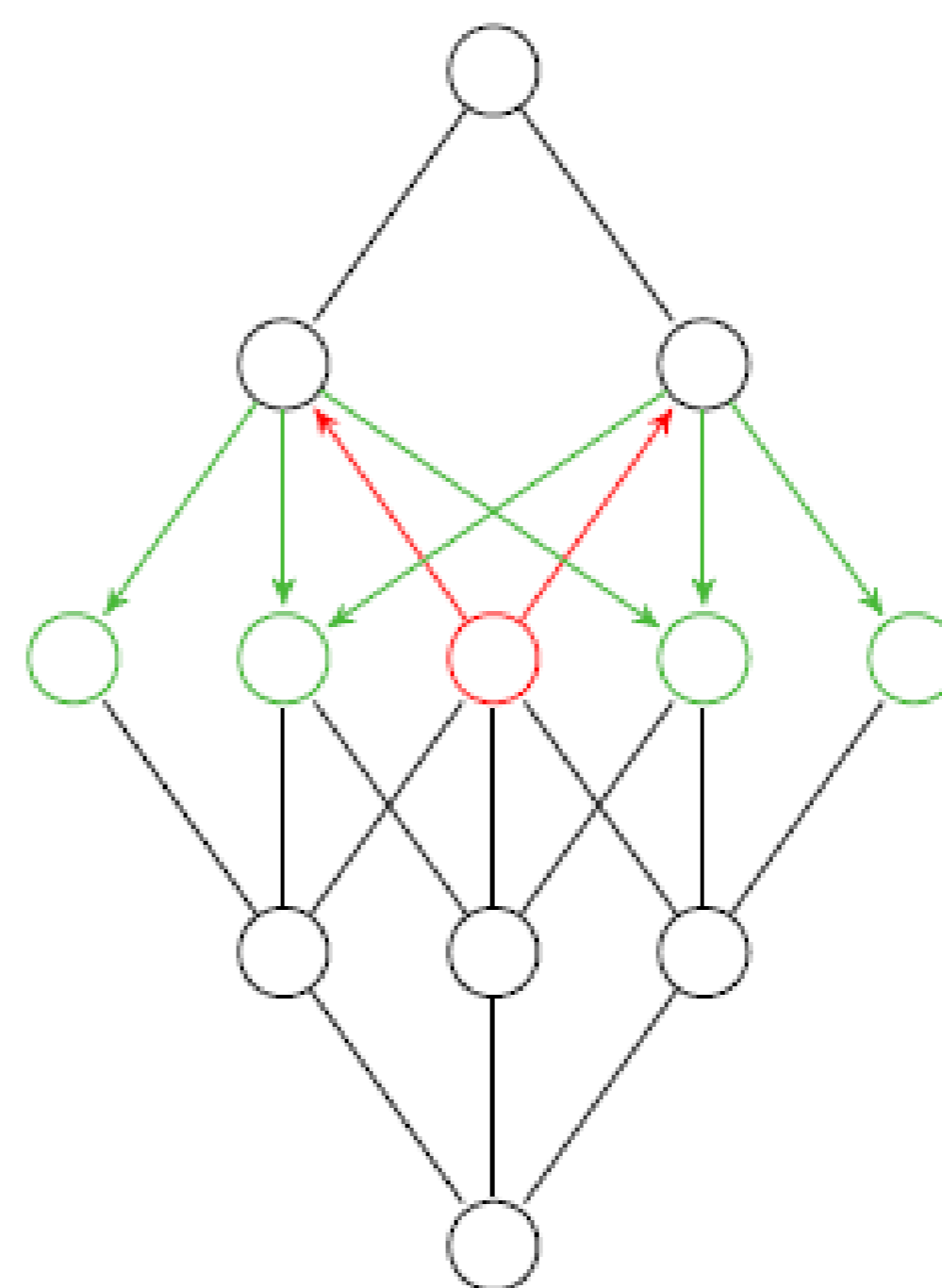


FIGURE 3: Pharmacophore lattice (left) and its corresponding condensed lattice (right)

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.

3. PAD : a new quality measure



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

- 1) Select a node in the lattice (red node).
- 2) Identify the ancestors (red arrows).
- 3) Identify the siblings (green nodes).
- 4) Compute the family standard deviation.
- 5) Compute node delta from its quality and the standard deviation.

PAD has been inspired by the notion of

an **Activity Cliff** [2]

4. 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
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

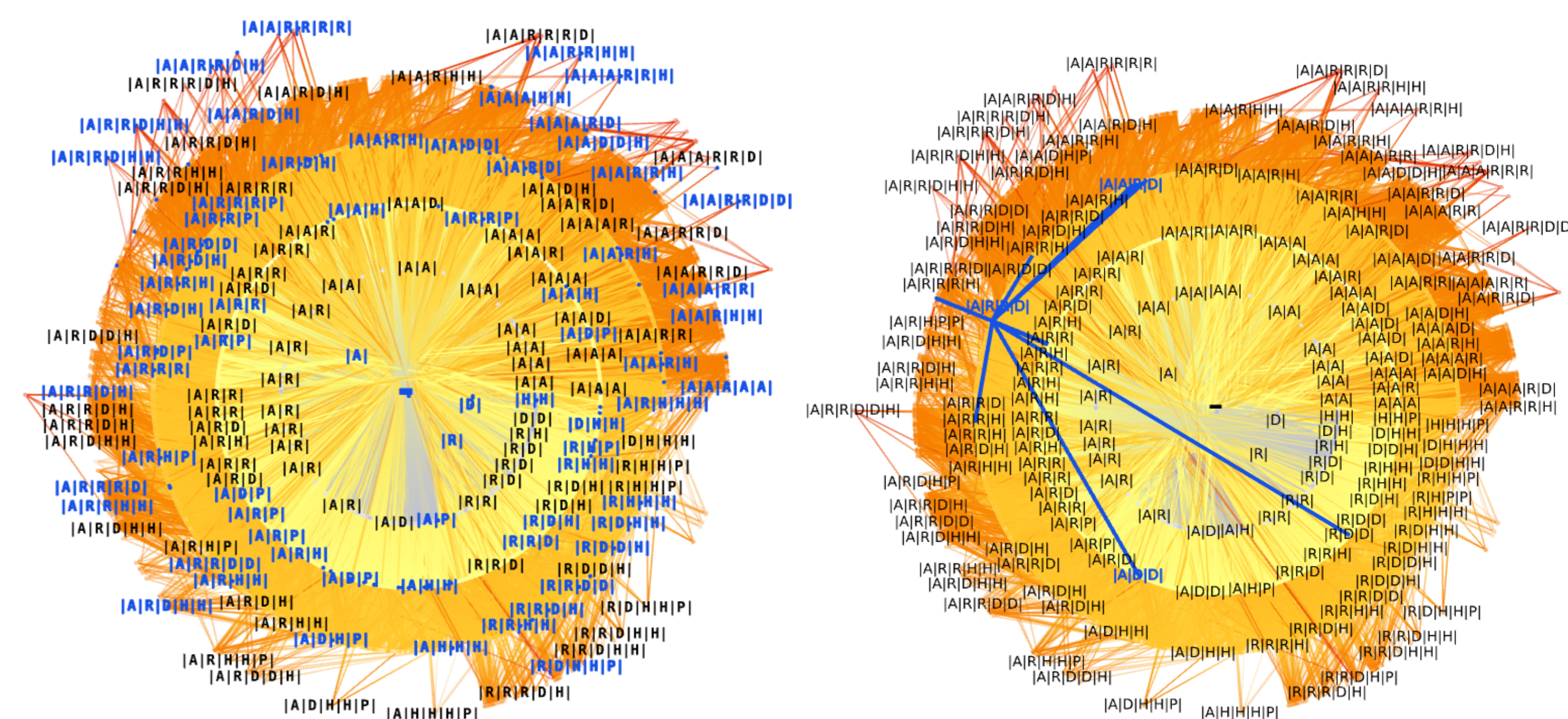


FIGURE 5: Equivalence classes network (left) and equivalence class connection (right)

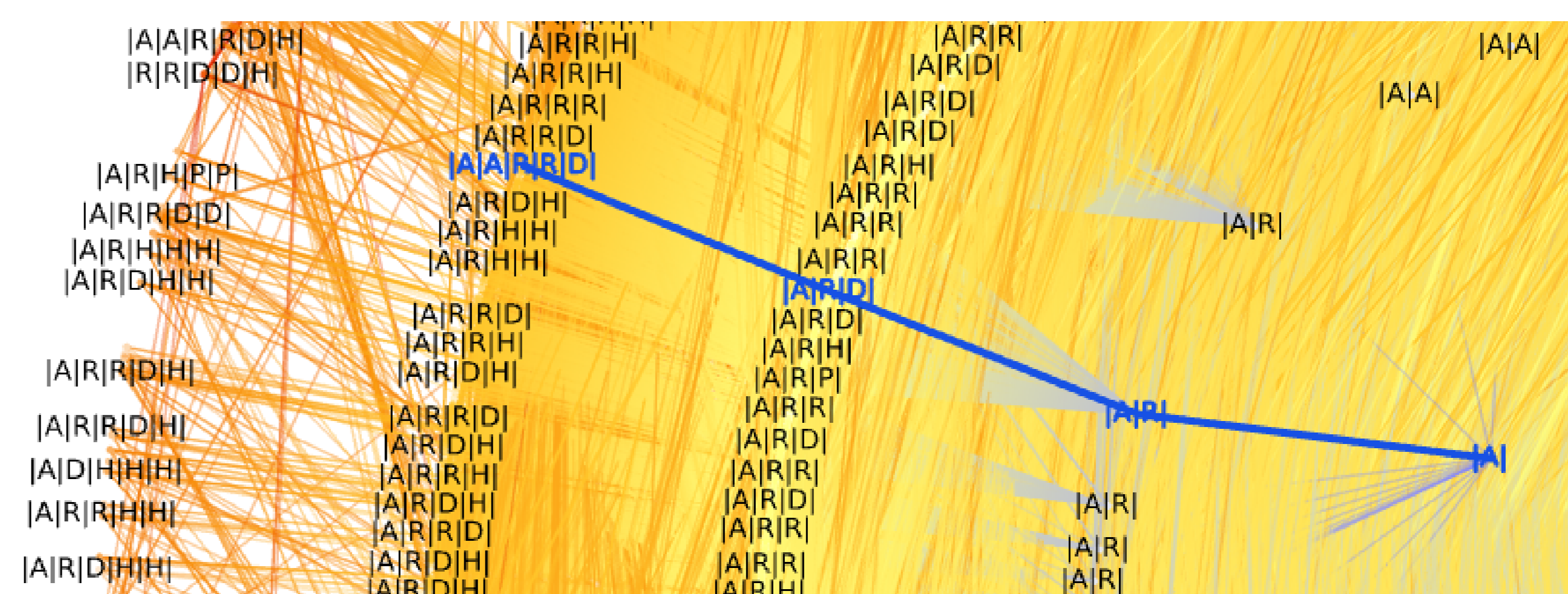


FIGURE 6: Path from a simple class to a complex selected class with Tulip^a

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

Références

- [1] Sergei O. KUZNETSOV et Sergei A. OBIEDKOV. "Algorithms for the Construction of Concept Lattices and Their Diagram Graphs". In : sous la dir. de Luc De RAEDT et Arno SIEBES.
- [2] Jose L. MEDINA-FRANCO et al. "Characterization of Activity Landscapes Using 2D and 3D Similarity Methods : Consensus Activity Cliffs". In : *Journal of Chemical Information and Modeling* 49.2 (2009), p. 477-491.
- [3] Jean-Philippe MÉTIVIER et al. "The Pharmacophore Network : A Computational Method for Exploring Structure–Activity Relationships from a Large Chemical Data Set". In : *Journal of Medicinal Chemistry* 61.8 (2018), p. 3551-3564.

1. <https://involv.d.greyc.fr/>