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► **To cite this version:**

Maroua Lejmi, Damien Geslin, Bertrand Cuissart, Ilef Ben Slima, Nida Meddouri, et al.. Refinement of a ligand activity and representation of topological pharmacophores in a colored network. SFCI-11 : 11èmes Journées de la Société Française de Chémoinformatique, Oct 2023, Caen, France. hal-04236949

HAL Id: hal-04236949

<https://hal.science/hal-04236949>

Submitted on 11 Oct 2023

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Refinement of a ligand activity and representation of topological pharmacophores in a colored network

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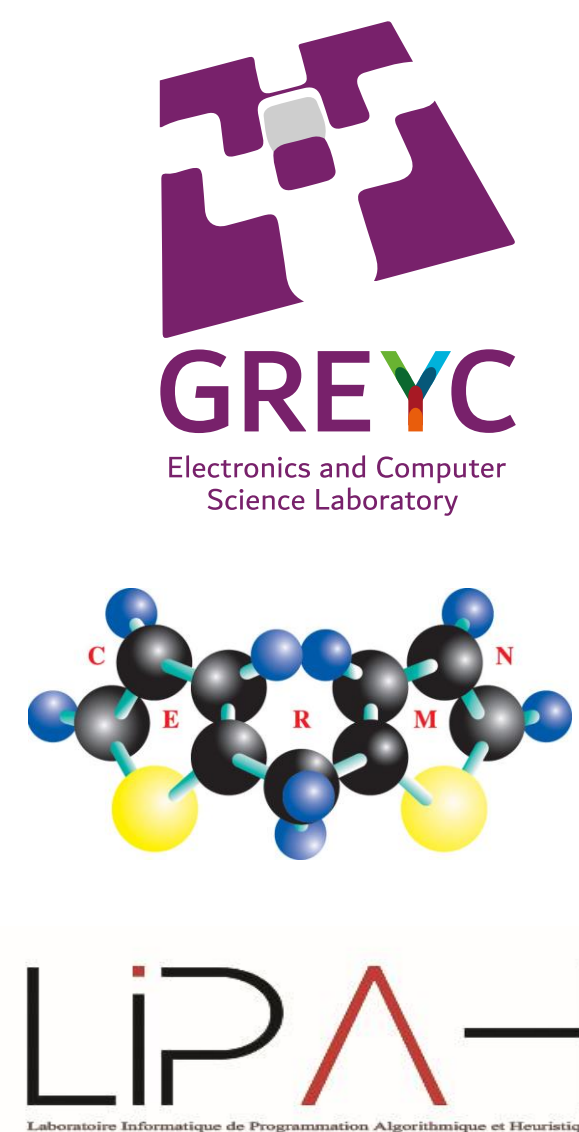
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Financial support : Campus France – PHC Utique – PAPRICA project

1. Context and Goal

SAR : better understanding of association between pharmacophores and ligand affinity.

• BCR-ABL dataset: 1517 ligands and their affinity (ChEMBL24)
Structure description: 309 representative pharmacophores of order 3 to 7 that support at least 10 molecules (extracted with Norns and selected using MMRFS) [1].

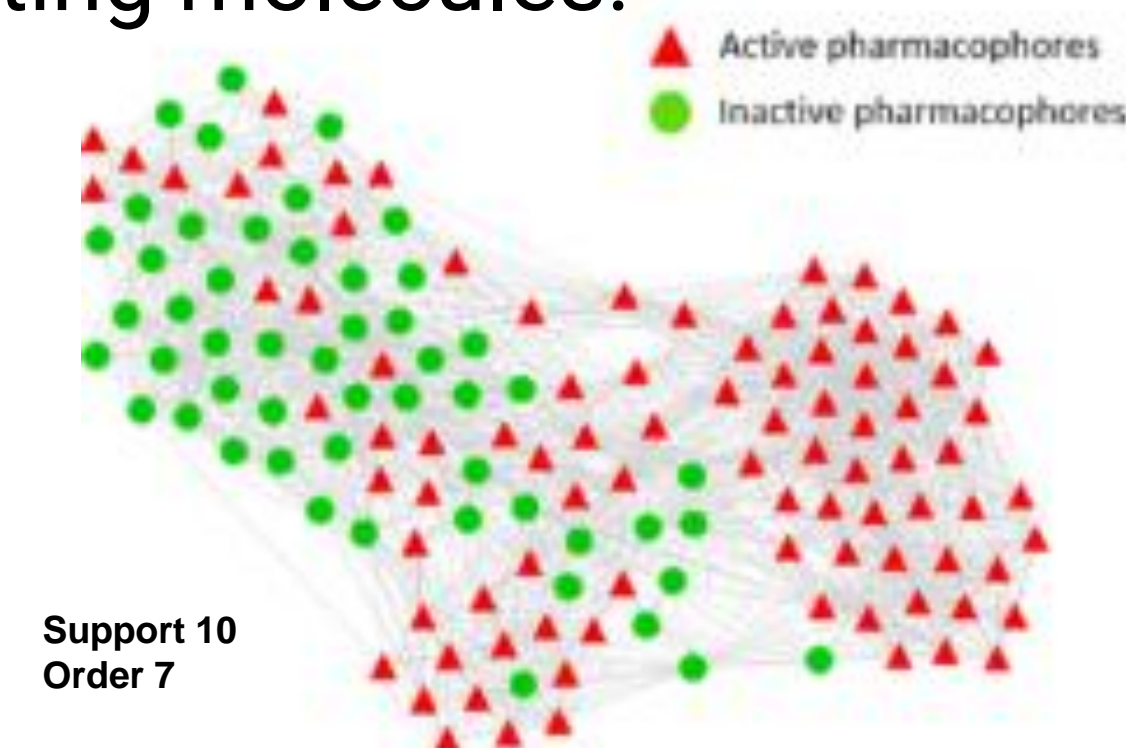
Method:

→ Refine the molecular affinity from 2 categories to 4 categories.

→ Construction of a colored "Pharmacophore Network" based on the similarity between the pharmacophores through the supporting molecules and an adapted Growth-Rate.

2. Previous work

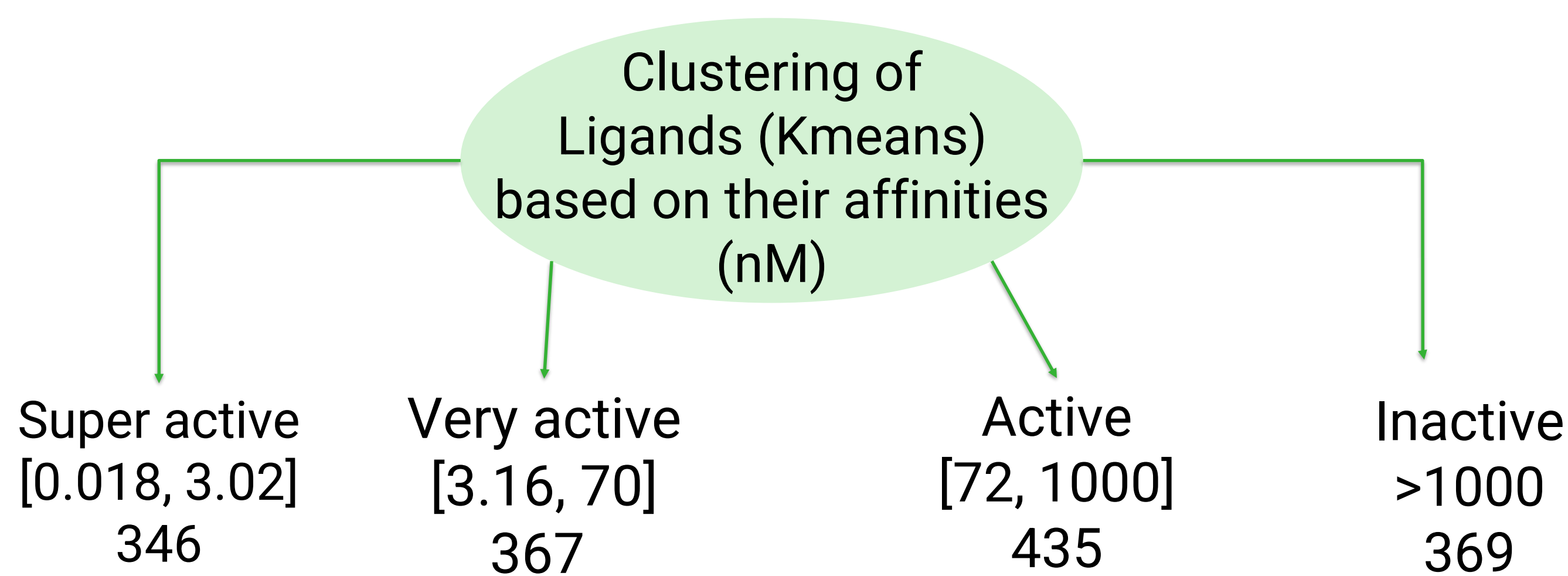
The Pharmacophore Network [2]: a graph of pharmacophores whose nodes represent the pharmacophores and edges represent the distance of similarity between them determined through similarities between the supporting molecules.



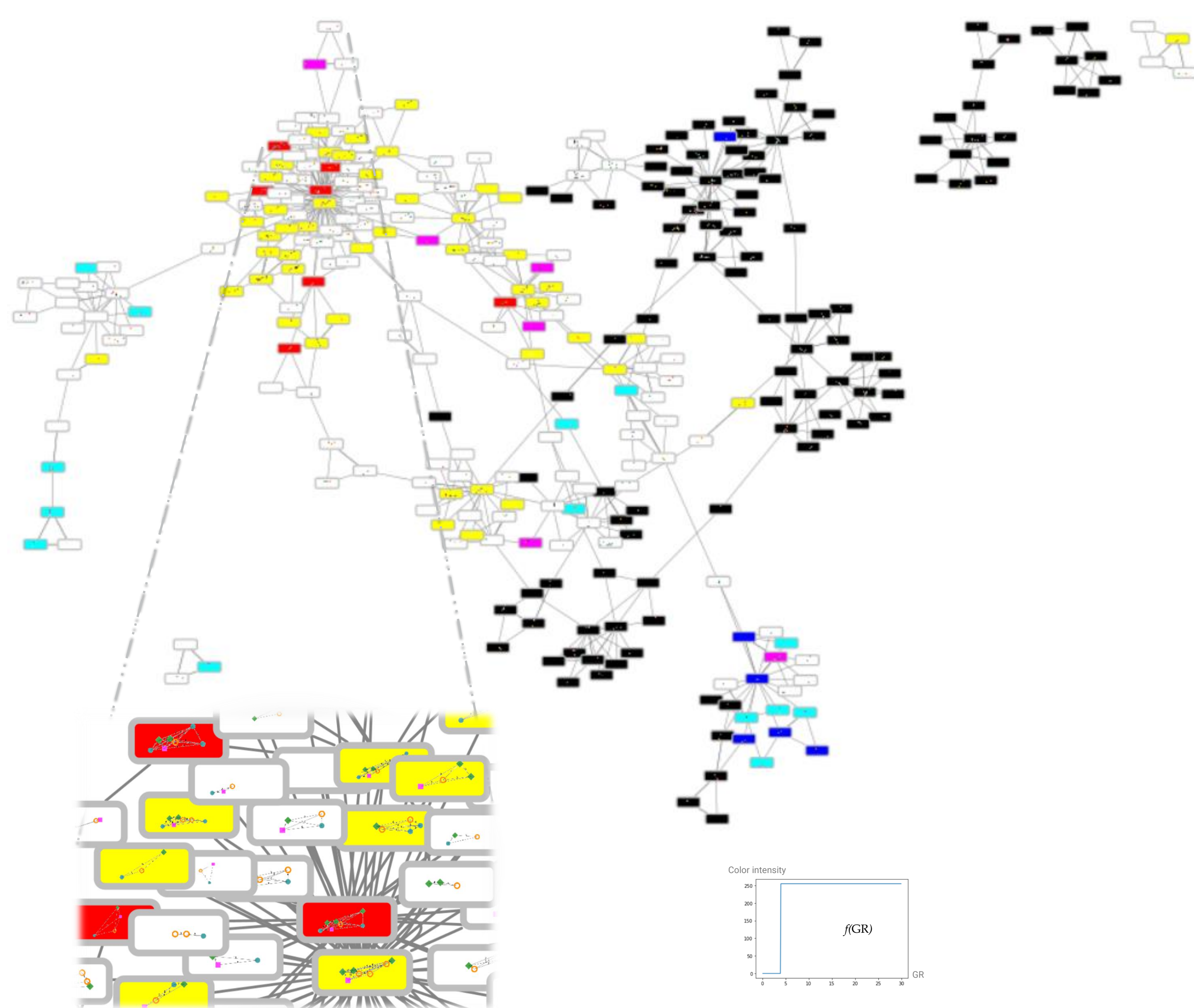
Pharmacophore evaluation: "Growth-Rate"

$$GR = \frac{\text{Frequency(Actives)}}{\text{Frequency(Inactives)}}$$

3. Contribution



Layout made with Cytoscape: 2 NNs - Force method.

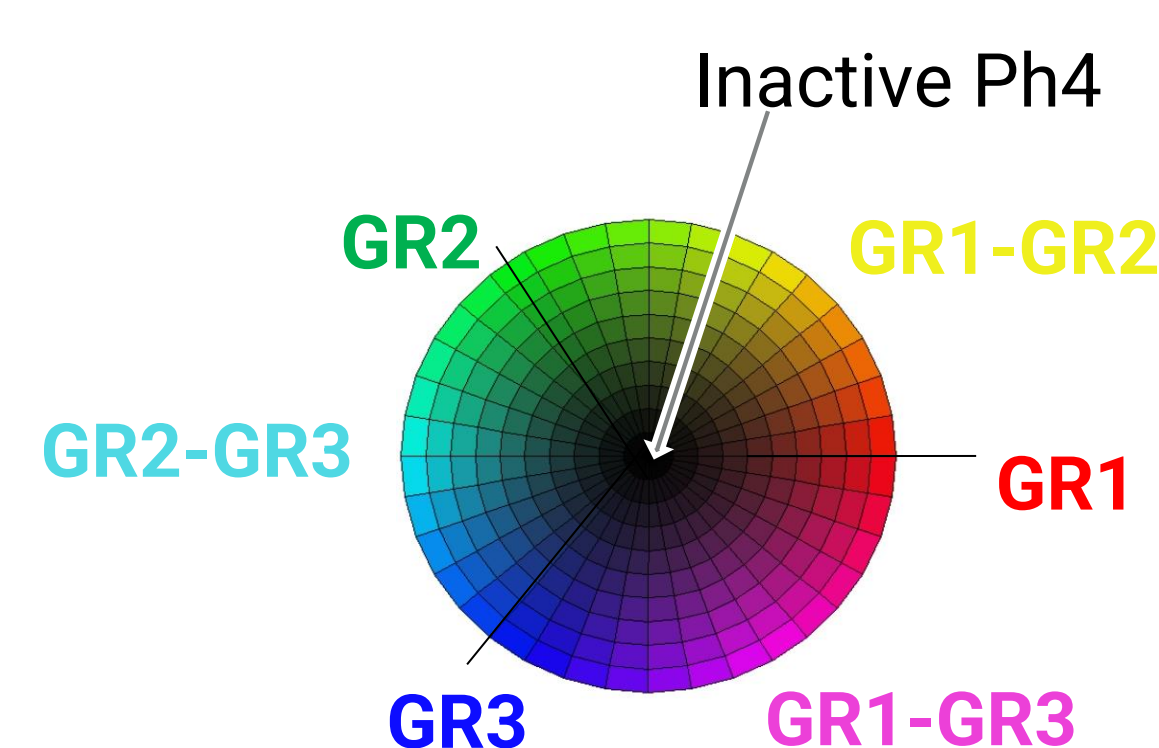


Pharmacophore evaluation: "Adapted Growth-Rate"

$$GR1 = \frac{\text{Frequency(Super actives)}}{\text{Frequency(Inactives)}}$$

$$GR2 = \frac{\text{Frequency(Very actives)}}{\text{Frequency(Inactives)}}$$

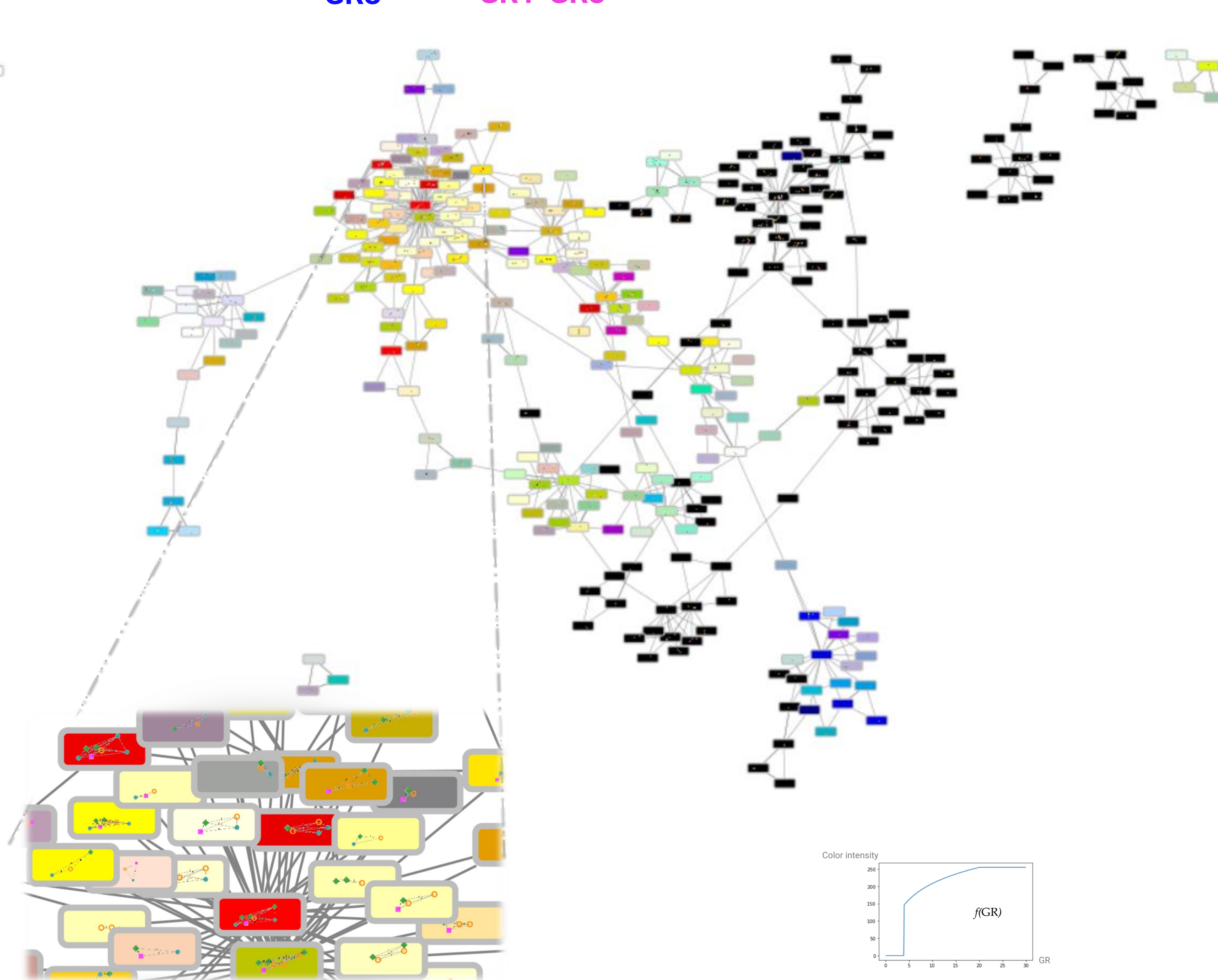
$$GR3 = \frac{\text{Frequency(Actives)}}{\text{Frequency(Inactives)}}$$



$$R = f(GR1)$$

$$V = f(GR2)$$

$$B = f(GR3)$$



Conclusion

- Definition of a space of representative pharmacophores of the activity of 1517 molecules.
- The pharmacophore space enables a visualization of the 4 activity classes and a clear differentiation between active groups and inactive ones.
- A zone analysis indicates activity graduations along close pharmacophores hence along close molecules and permit a better exploitation of GR values.

References

- [1] MÉTIVIER, Jean-Philippe, CUISSART, Bertrand, BUREAU, Ronan, et al. The pharmacophore network: a computational method for exploring structure–activity relationships from a large chemical data set. *Journal of medicinal chemistry*, 2018, vol. 61, no 8, p. 3551-3564.
- [2] Geslin, D., Lepailleur, A., Manguin, J.L., Vo, N.V., Lamotte, J.L., Cuissart, B., Bureau, R., 2022. Deciphering a pharmacophore network: A case study using bcr-abl data. *Journal of Chemical Information and Modeling* 62, 678–691.