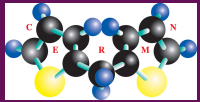
Computation of pharmacophores and subsequent analyse*s

Academic research carried out in Caen

Normandie Univ, UNICAEN, ENSICAEN, CNRS, GREYC, CERMN,Caen, FRANCE

https://www.greyc.fr/equipes/codag/, https://cermn.unicaen.fr/



GREYC
Laboratoire de recherche en sciences du numérique

Normandie Université

UNICAEN

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ÉCOLE PUBLIQUE D'INGÉNIEURS
CENTRE DE RECHERCHE

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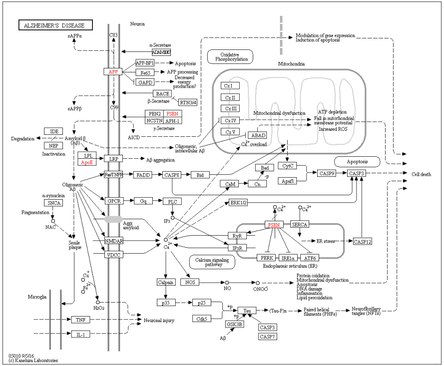
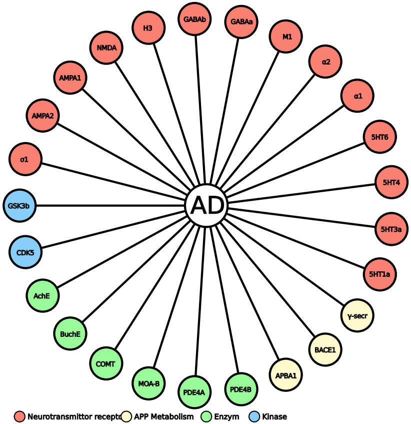
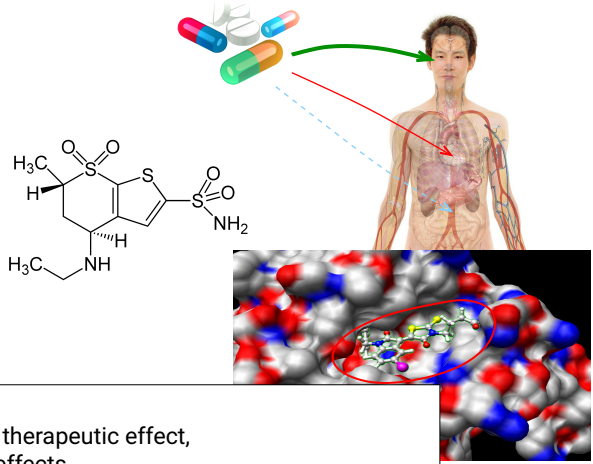
Rational drug design
Alzheimer disease





- KEGG PATHWAY Database, http://www.genome.jp/kegg/pathway.html

The search for a drug . . .
as an optimization problem

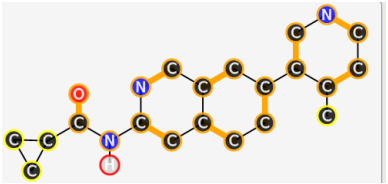


- Objective :
  - Maximize the therapeutic effect,
  - Limit all side effects,
  - Avoid any adverse effect.

The input: molecules (ligands) whose 2D structures are graphs

SDF file format: the atoms/the vertices

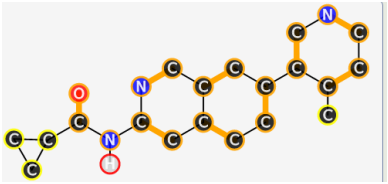
```
  24 27  0  0  0  0            999 V2000
    2.1456    0.2461    0.0000 C   0  0
    2.1446   -0.4139    0.0000 C   0  0
    2.8584   -0.8275    0.0000 C   0  0
    2.8570   -1.6525    0.0000 C   0  0
    2.1419   -2.0639    0.0000 N   0  0
    1.4281   -1.6503    0.0000 C   0  0
    1.4293   -0.8252    0.0000 C   0  0
    0.7145   -0.4125    0.0000 C   0  0
    0.7145    0.4125    0.0000 C   0  0
    0.0000    0.8250    0.0000 C   0  0
   -0.7145    0.4125    0.0000 C   0  0
   -1.4290    0.8250    0.0000 C   0  0
   -2.1435    0.4125    0.0000 C   0  0
   -2.8592    0.8238    0.0000 N   0  0
   -3.5735    0.4100    0.0000 C   0  0
   -3.5723   -0.2500    0.0000 O   0  0
   -4.2892    0.8213    0.0000 C   0  0
   -5.0707    0.7961    0.0000 C   0  0
   -4.6582    1.5106    0.0000 C   0  0
   -2.1435   -0.4125    0.0000 N   0  0
   -1.4290   -0.8250    0.0000 C   0  0
   -0.7145   -0.4125    0.0000 C   0  0
    0.0000   -0.8250    0.0000 C   0  0
   -2.8602    1.3738    0.0000 H   0  0
```



The input: molecules (ligands) whose 2D structures are graphs

SDF file format: the bonds/edges

1	2	1	0
2	3	2	0
3	4	1	0
4	5	2	0
5	6	1	0
6	7	2	0
7	2	1	0
7	8	1	0
8	9	2	0
9	10	1	0
10	11	2	0
11	12	1	0
12	13	2	0
13	14	1	0

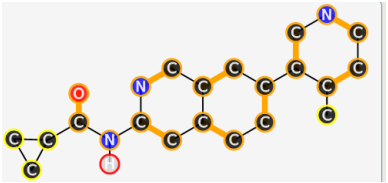


13	20	1	0
14	15	1	0
14	24	1	0
15	16	2	0
15	17	1	0
17	18	1	0
18	19	1	0
19	17	1	0
20	21	2	0
21	22	1	0
22	11	1	0
22	23	2	0
23	8	1	0

The input: molecules (ligands) whose 2D structures are graphs

SDF file format: the properties

```
> <CMPD_CHEMBLID>
CHEMBL3685020

> <STANDARD_TYPE>
Ki

> <RELATION>
=

> <STANDARD_VALUE>
0.03

> <STANDARD_UNITS>
nM

> <Molecular_Weight>
303.35778
```

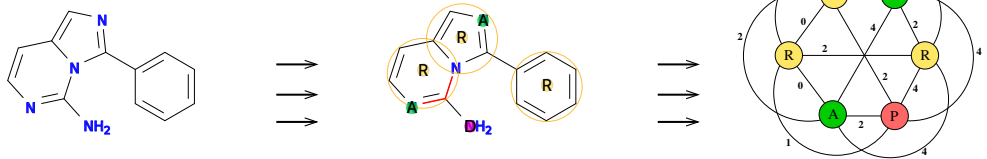


An abstracted representation of a molecule

Pharmacophoric features

- Hydrogen Bond **A**cceptor, Hydrogen Bond **D**onor, aromatic **R**ing, **H**ydrophobic area, **P**ositively ionizable group, **N**egatively ionizable group[a]
- an adjustable part of the input.

[a] OpenBabel. N. J. Cheminformatics 2011, 3, 33.

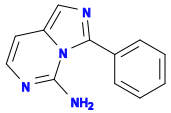


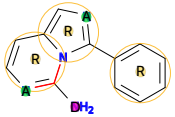
Skeletal formula | Feature occurrences | Pharmacophoric graph

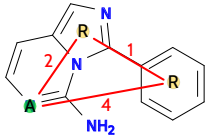
The Pharmacophoric graph (of a molecule)

- A vertex: an occurrence of a feature
- An edge: the distance between two features

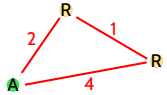
A pharmacophore







- An occurrence of a pharmacophore in a molecule $\iff$ an embedding that fits:
  - the labels of the features,
  - the distance constraints.



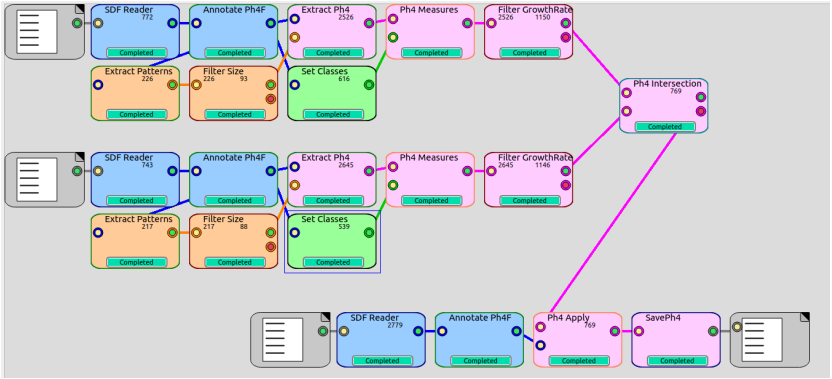
A pharmacophore:

Given a dataset of molecules,

- A graph of pharmacophoric features whose extent is:
  - sufficiently large,
  - discriminative enough.

Norns

A visual programming environment to implement a pharmacophore mining process



The Pharmacophore Network: A Computational Method for Exploring Structure-Activity Relationships from
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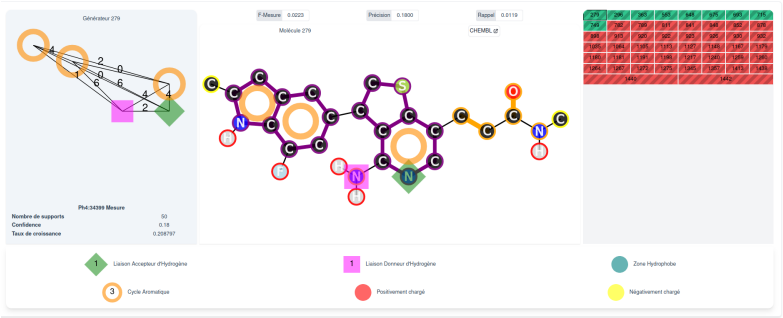

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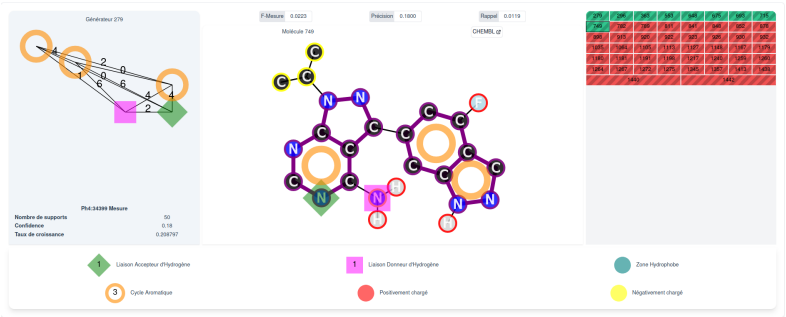

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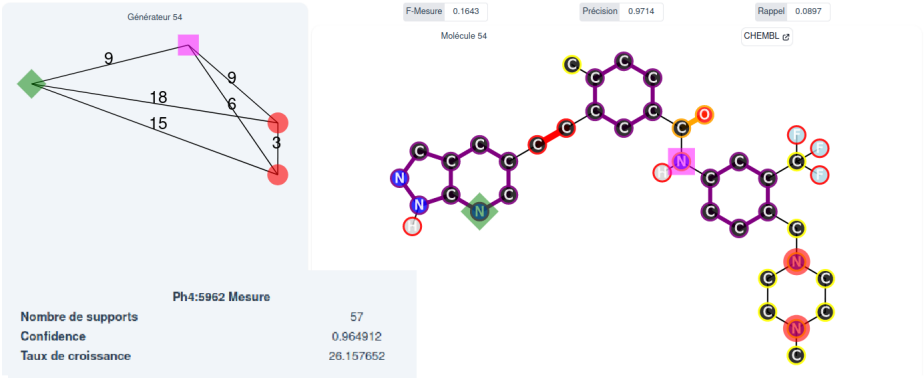

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Norns: a GUI to express workflows in chemoinformatics

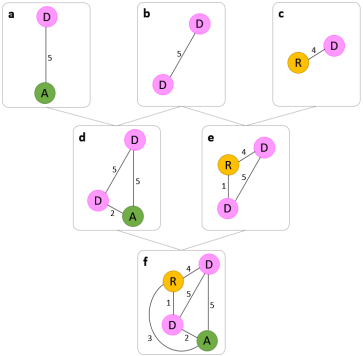
- implementation of complex processes by connecting boxes,
- 60 configurable boxes that include:
  - reading/writing of molecules from/into files,
  - molecular representations,
  - pharcophoric features mining,
  - pharmacophore selection,
  - **classifiers**

Towards a pharmacophore network

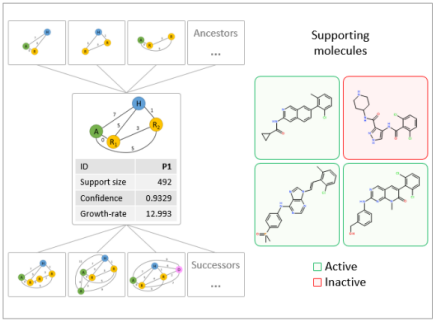
Exploration of Structure-Activity Relationships from a Large Chemical Data Set [?]

Relationship: the graph inclusion (being a subgraph of)

Hasse diagram

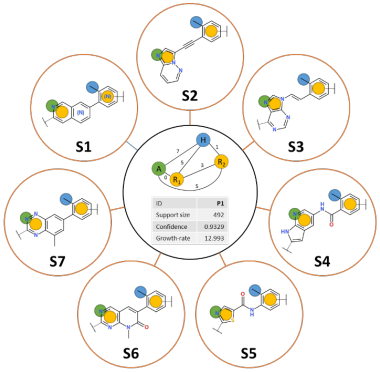


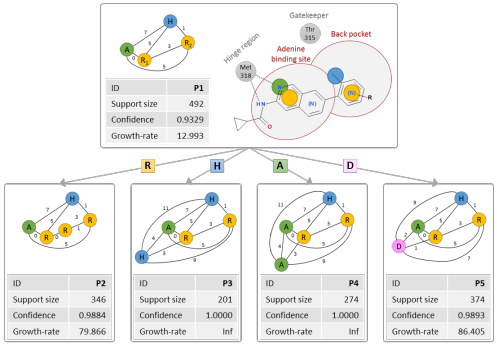
Navigation



A principal pharmacophore

Bcr-Abl





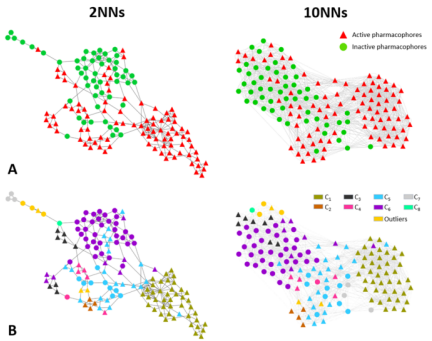
The addition of features on P1 improves its discriminative power.

The pharmacophores and the SAR principle [?] [1]

SAR principle

- Two “similar” chemical structures should be associated to a similar behaviour

- Relationship: a graph edit distance
- separation between the pharmacophores associated with active compounds and those associated with inactive ones,
- clustering $\longrightarrow$ pharmacophores that occurs in molecules with similar structures and biological activities



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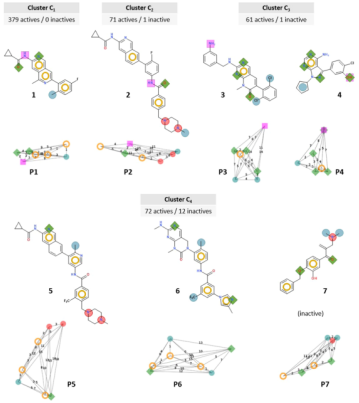

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Perspectives related to GNNs

- screening of a molecular bank to compute a large activity profile
- location/identification of the parts of the graph that are the most important
- (re)definition of the pharmacophoric features