Docking and virtual screening

- What is virtual screening?
- Pharmacophore searching
- Shape-based searching
- Docking
- Estimating model quality

What is virtual screening (VS)?

- Identification of interesting molecules out of a database of (virtual) molecules
- Ligand-based VS
  - Chemo-informatics
  - Pharmacophore searching
  - Shape-based searching
- Protein structure-based VS
  - Docking

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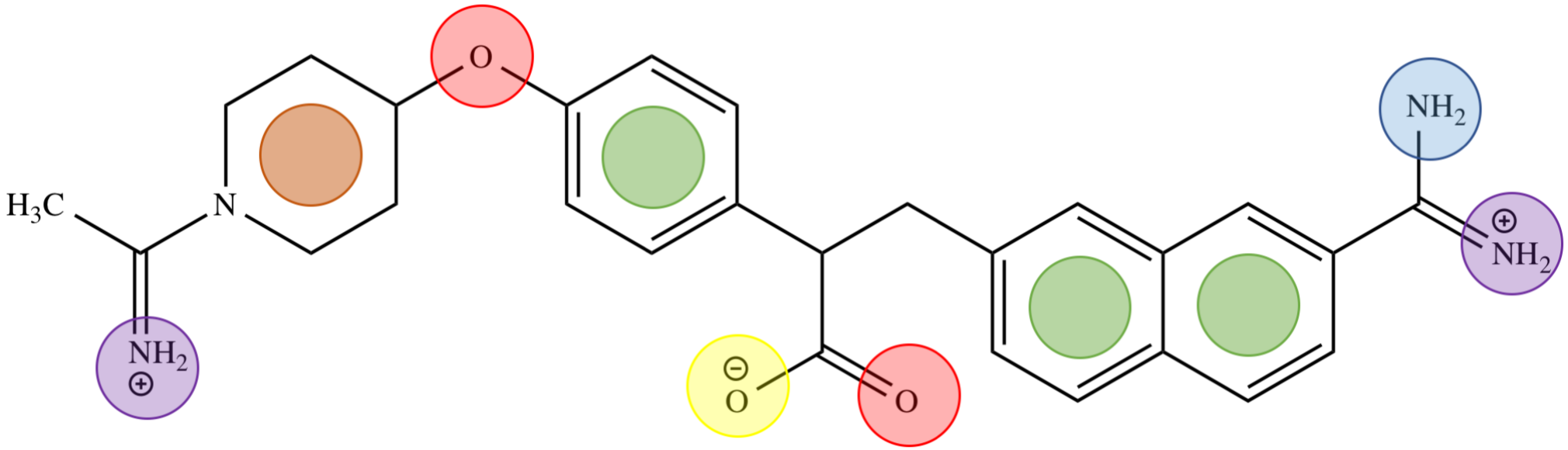
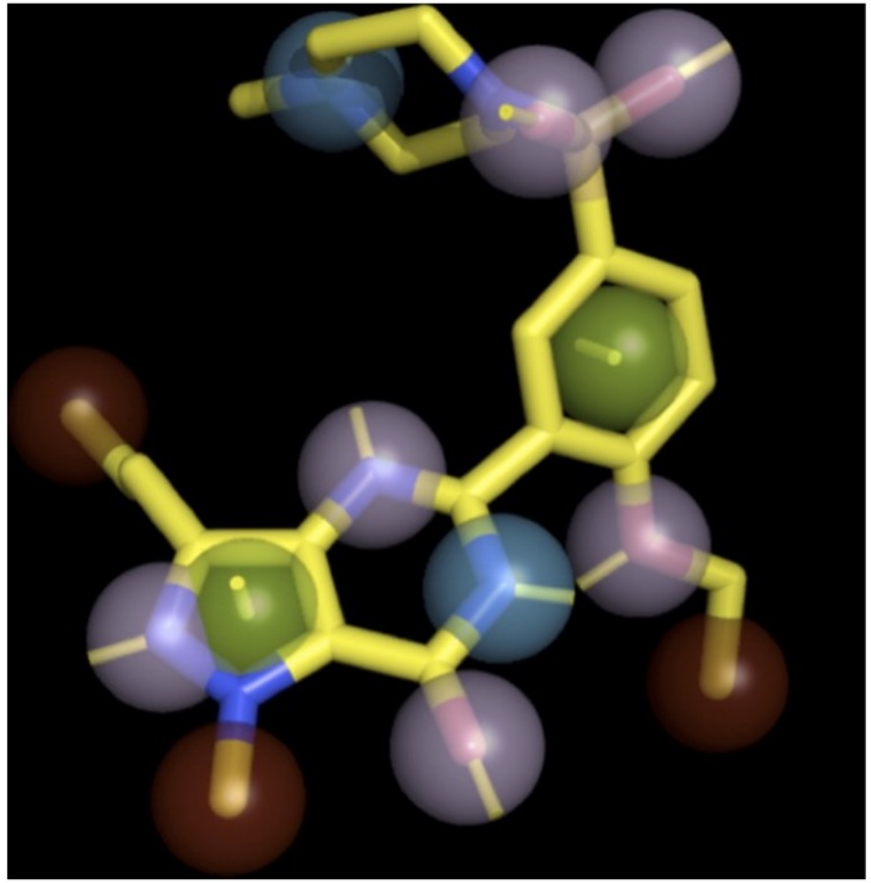
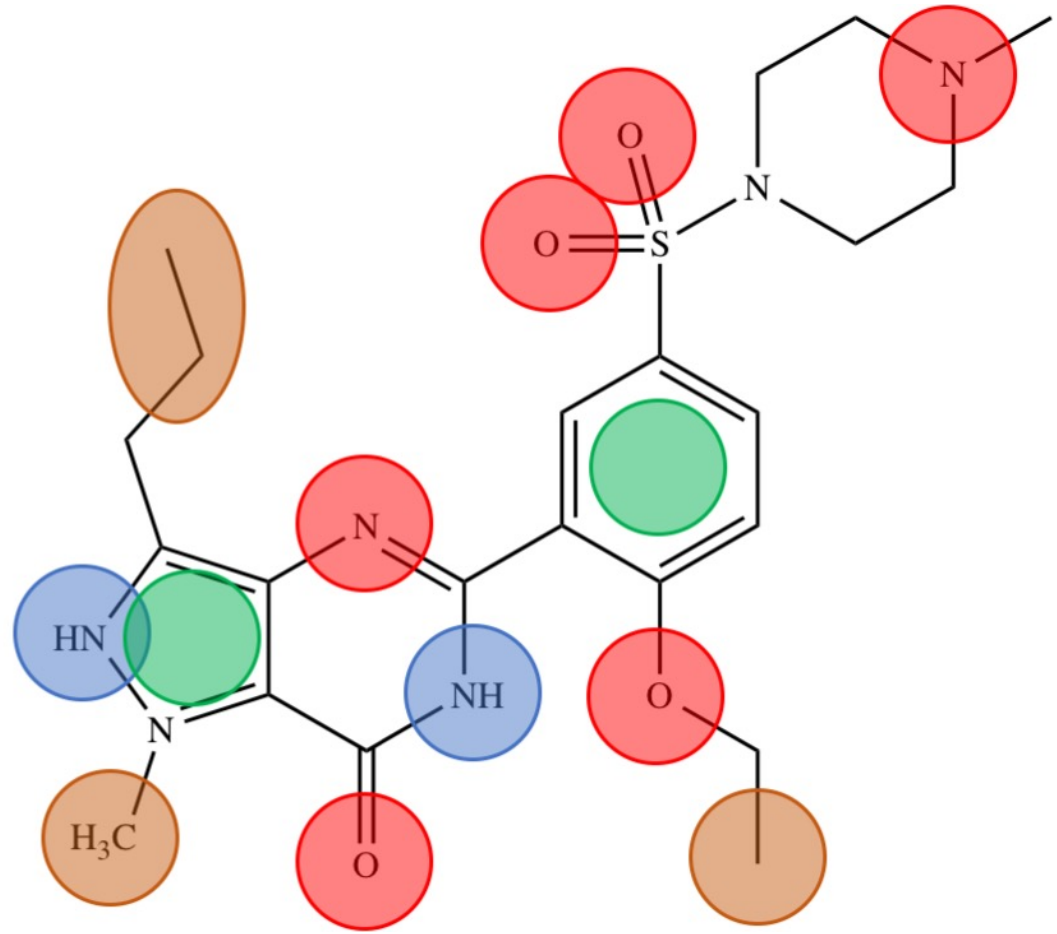
What is a pharmacophore?



Pharmacophore types

Code	Description	Normal
AROM	Aromatic ring	Yes
HDON	Hydrogen bond donor	Yes
HACC	Hydrogen bond acceptor	Yes
LIPO	Lipophilic (hydrophobic) region	No
POSC	Positive charge center	No
NEGC	Negative charge center	No
HYBH	Hydrogen bond donor and hydrogen bond acceptor	Yes
HYBL	Aromatic and lipophilic ring	Yes
EXCL	Exclusion sphere	No




O
O
S
N
N
N
HN
NH
O
N
H_3C
O

Gaussian representation of points

$$V = \int p\, e^{\left(-\frac{|m-r|^2}{\sigma}\right)} dr$$

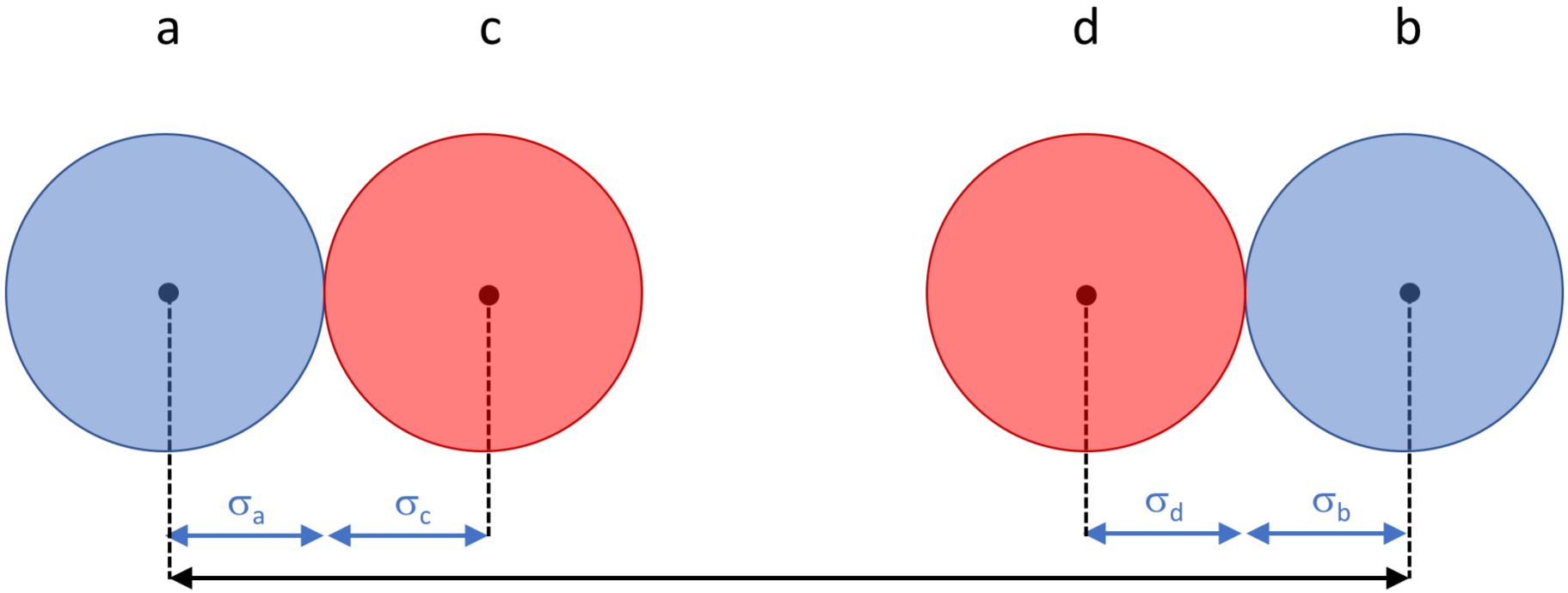
With:

p: scaling constant

m: position in space

σ: spread

Feature mapping



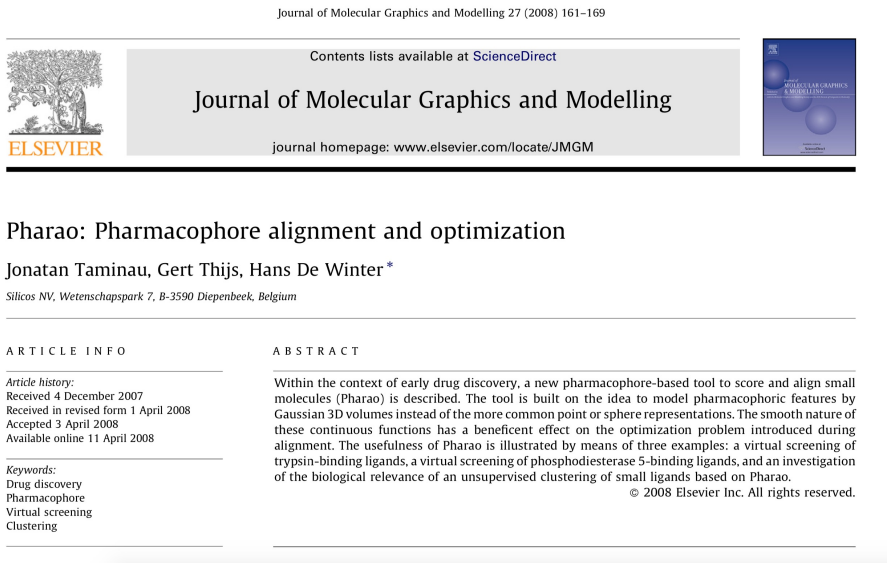
$$\varepsilon = \frac{|d_{ab} - d_{cd}|}{\sigma_a + \sigma_b + \sigma_c + \sigma_d}$$

Calculating the overlap

- The pharmacophore spheres are represented by Gaussian spheres, hence easy to calculate the overlap
- $TANIMOTO = \frac{V_{overlap}}{V_1 + V_2 - V_{overlap}}$
- $TVERSKY = \frac{V_{overlap}}{V_1}$

Popular pharmacophore searching programs

- Open source: Pharao



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Pharao: Pharmacophore alignment and optimization

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Virtual screening
Clustering

ABSTRACT

Within the context of early drug discovery, a new pharmacophore-based tool to score and align small molecules (Pharao) is described. The tool is built on the idea to model pharmacophoric features by Gaussian 3D volumes instead of the more common point or sphere representations. The smooth nature of these continuous functions has a beneficent effect on the optimization problem introduced during alignment. The usefulness of Pharao is illustrated by means of three examples: a virtual screening of trypsin-binding ligands, a virtual screening of phosphodiesterase 5-binding ligands, and an investigation of the biological relevance of an unsupervised clustering of small ligands based on Pharao.

- Commercial: Rocs

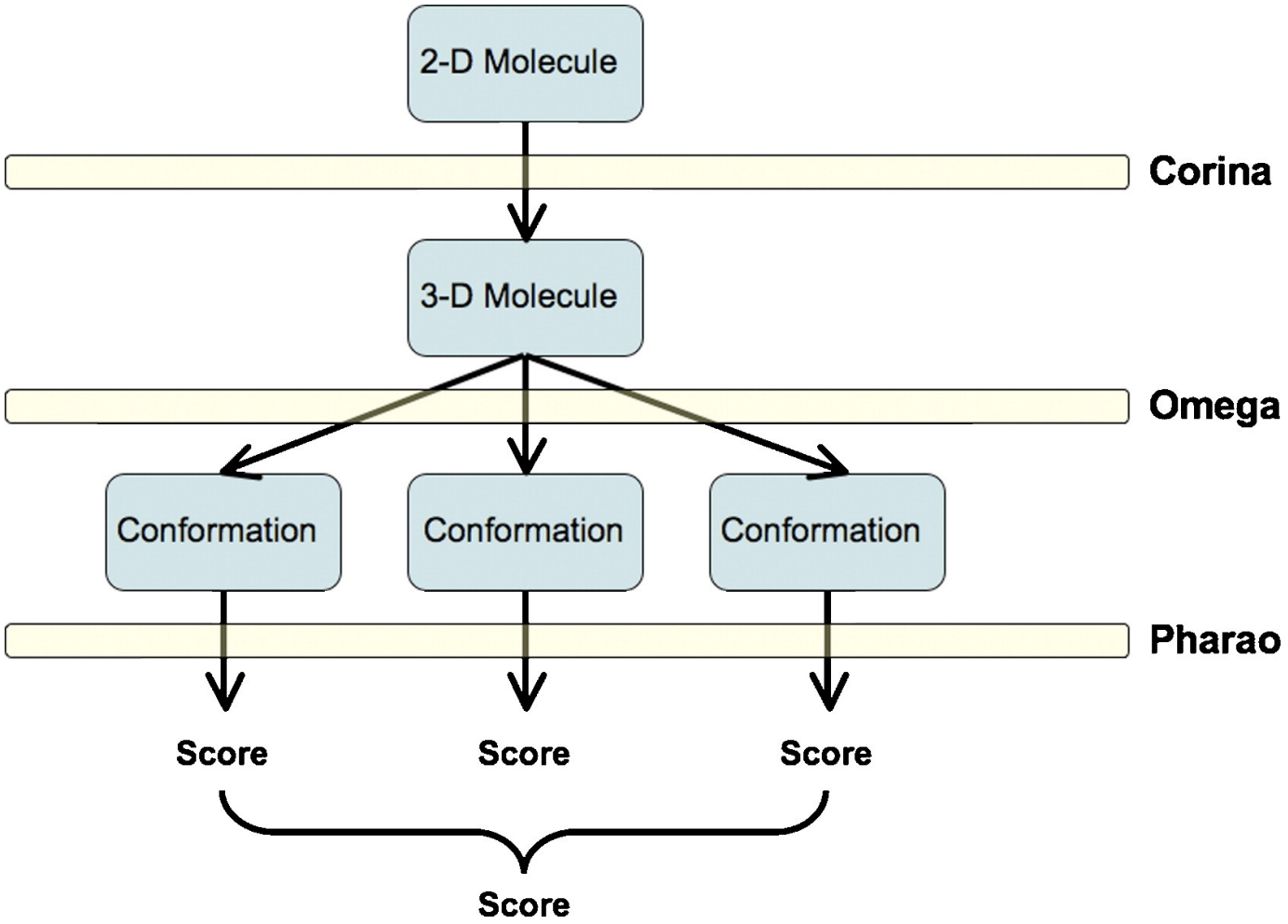
ROCS

Shape Similarity for Virtual Screening & Lead Hopping

ROCS is a powerful **virtual screening** tool which can rapidly

Taminau, J.; Thijs, G. & De Winter, H. (2008)
J. Mol. Graph. Model. **27**, 161-169.

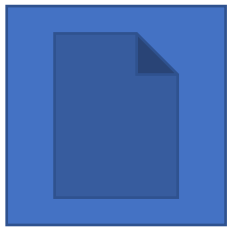
Pharao workflow

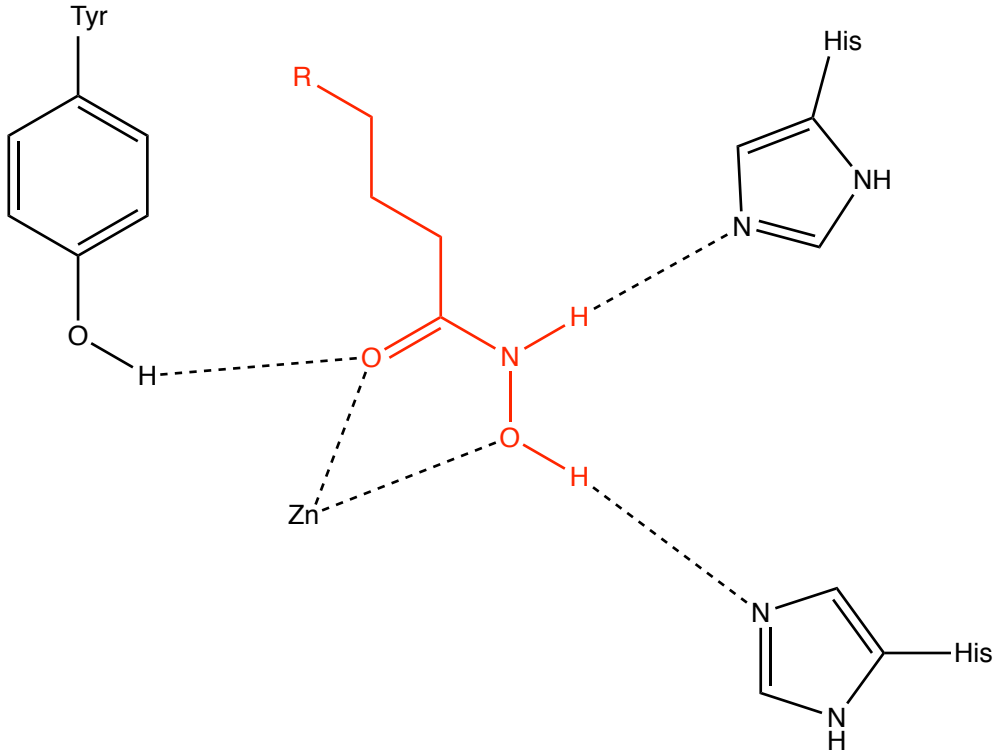


Case study

- HDAC inhibitors

Crystal structure with SAHA





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Gaussian representation of points

$$V = \int p\, e^{\left(-\frac{|m-r|^2}{\sigma}\right)} dr$$

With:

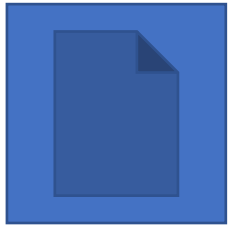
p: scaling constant

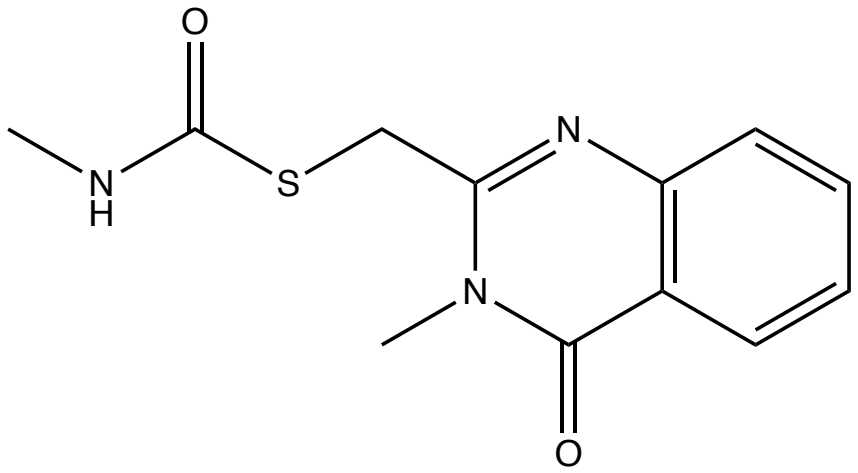
m: position in space

σ: spread

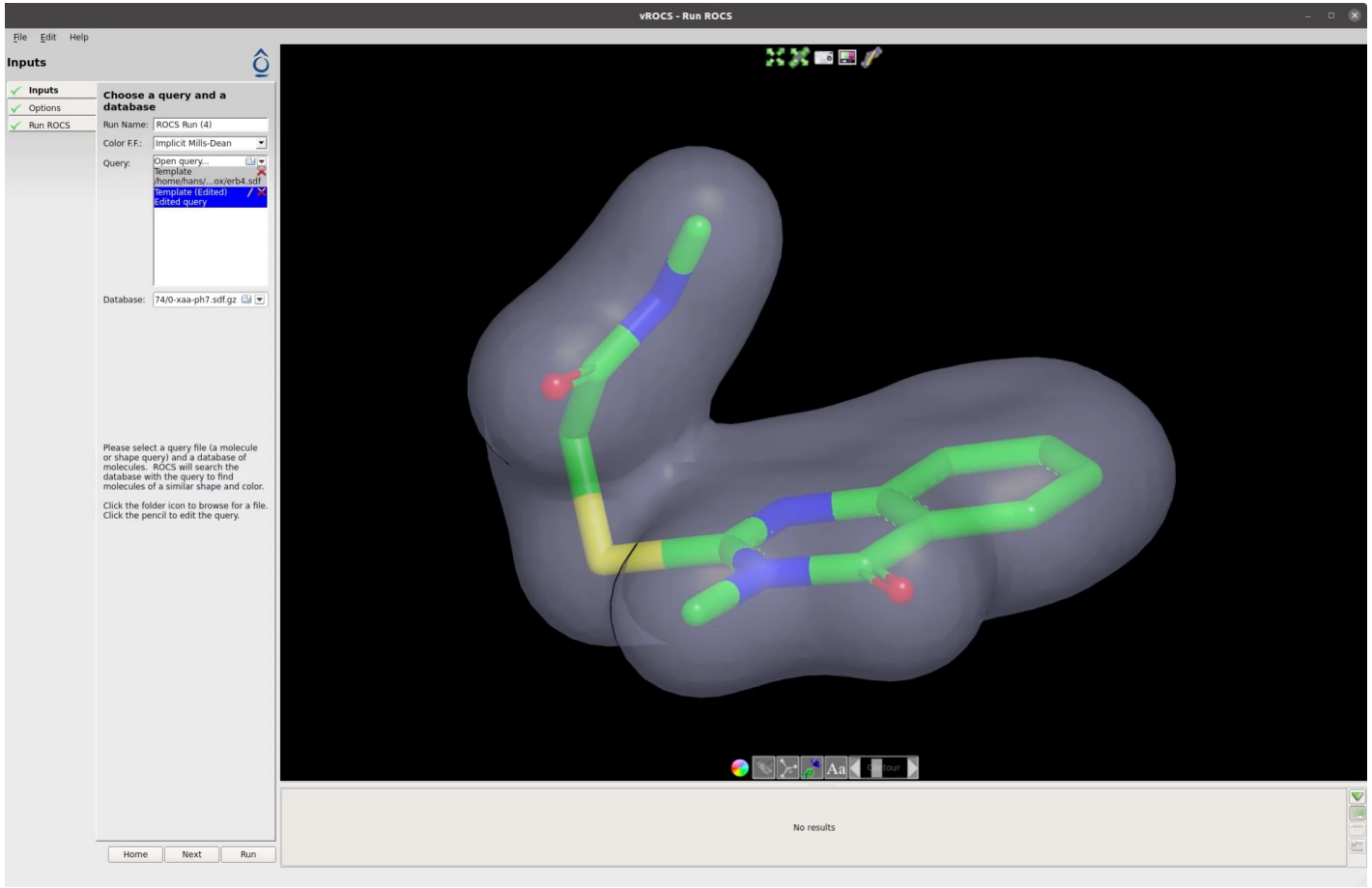
Case study

- Erb4 activators

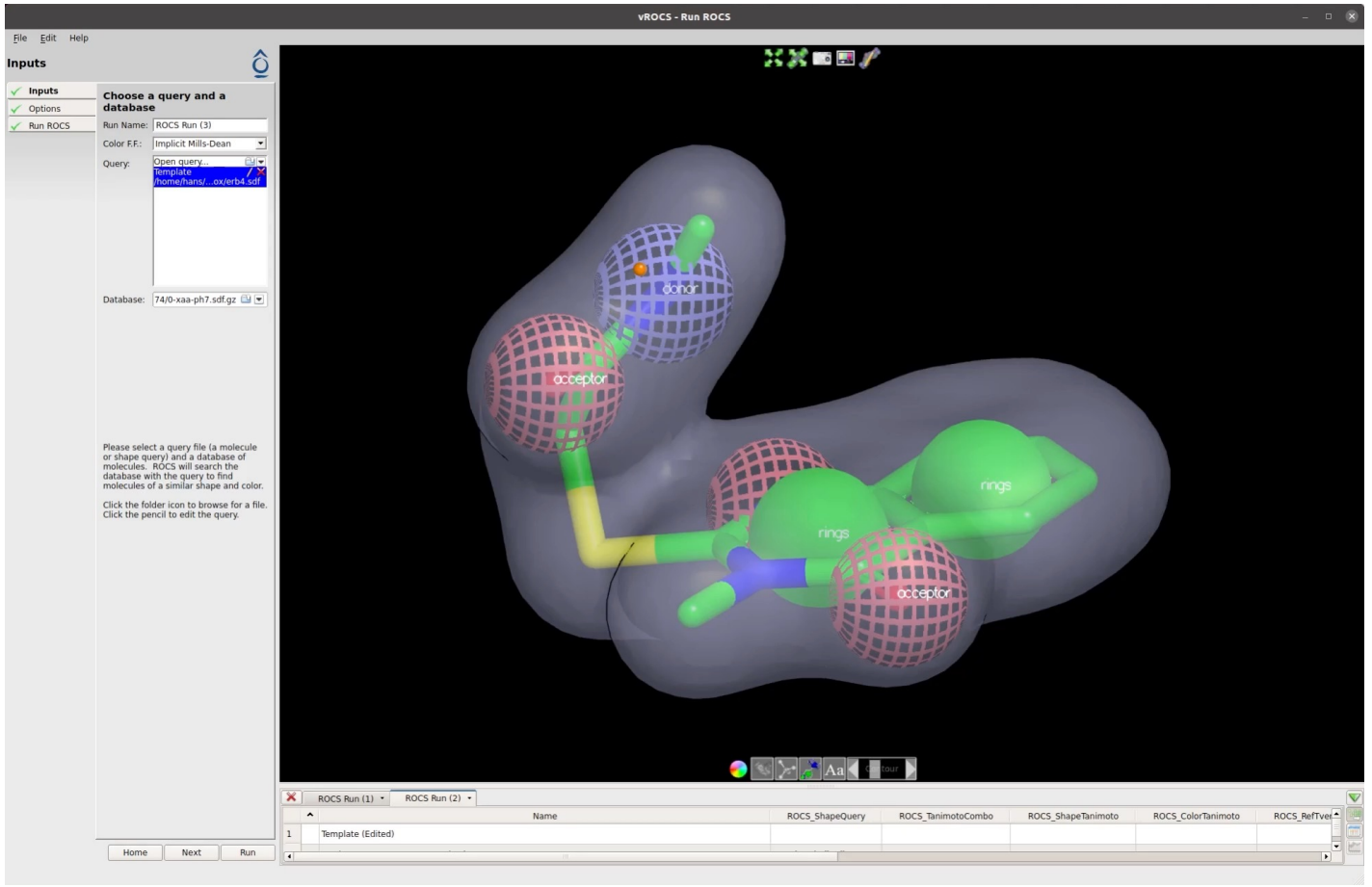




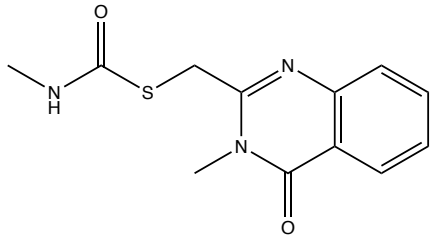
Using only the shape…



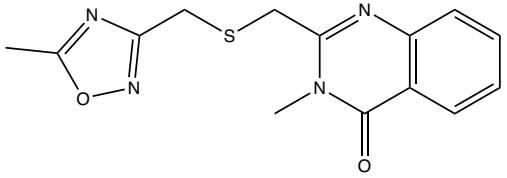
Or the shape with pharmacophoric points…

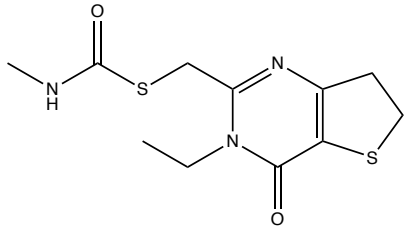


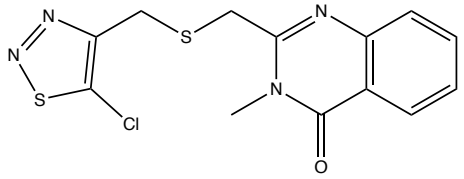
ROCS results



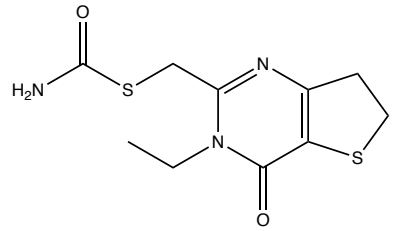
Using only the shape...

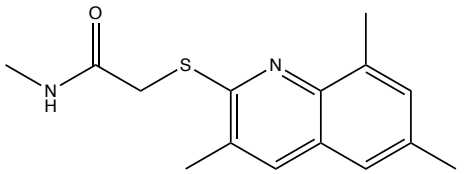


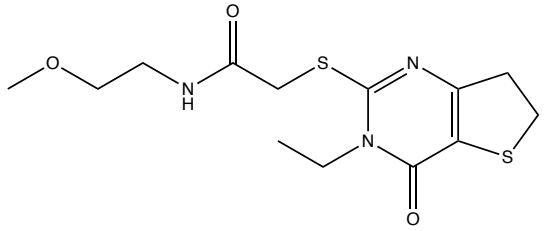




...or with pharmacophore info







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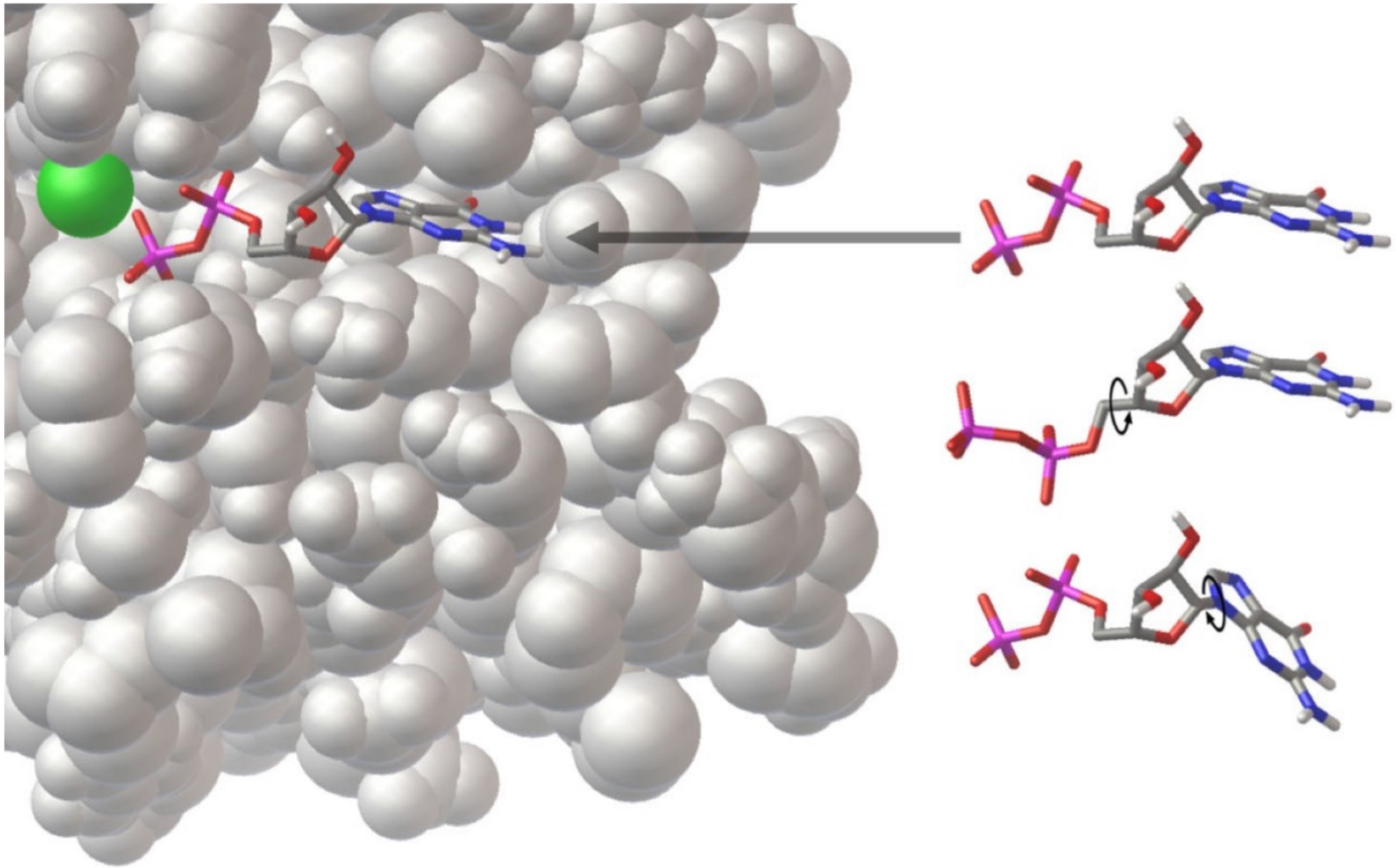
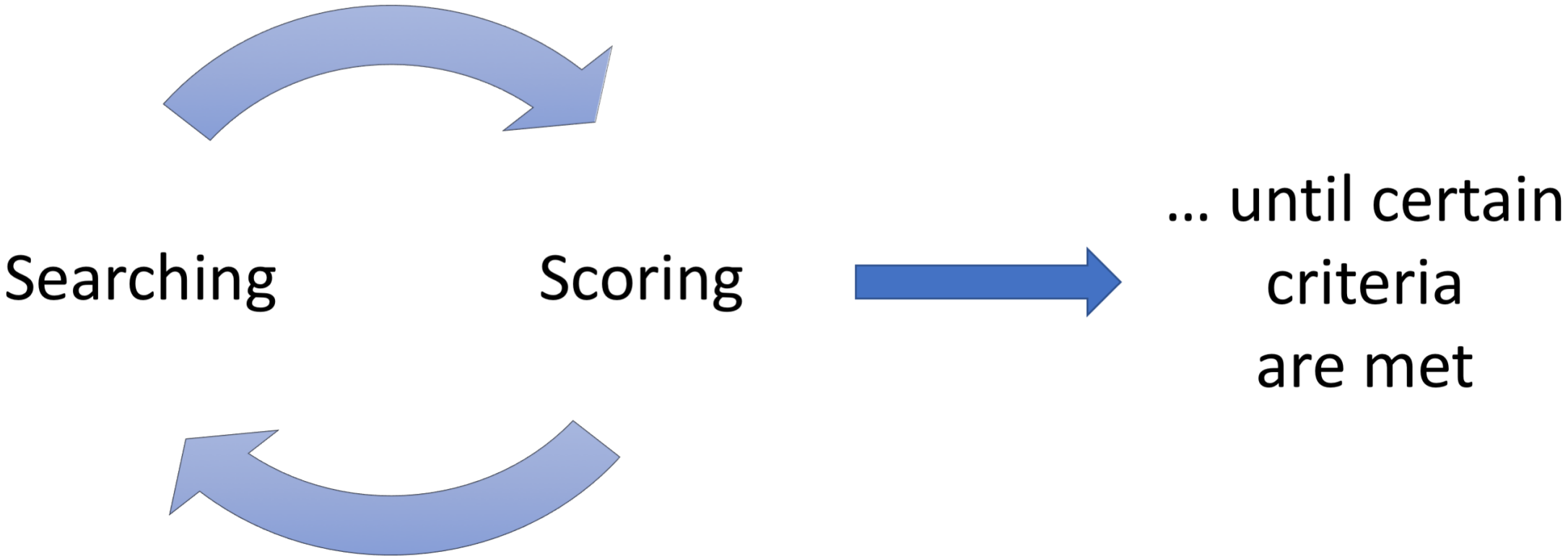
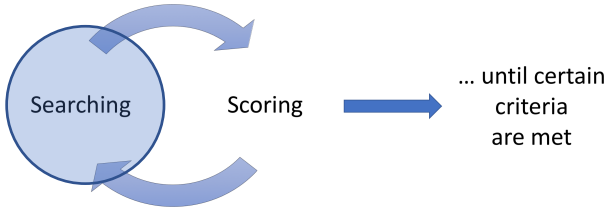
Docking



The repeated process of searching and scoring

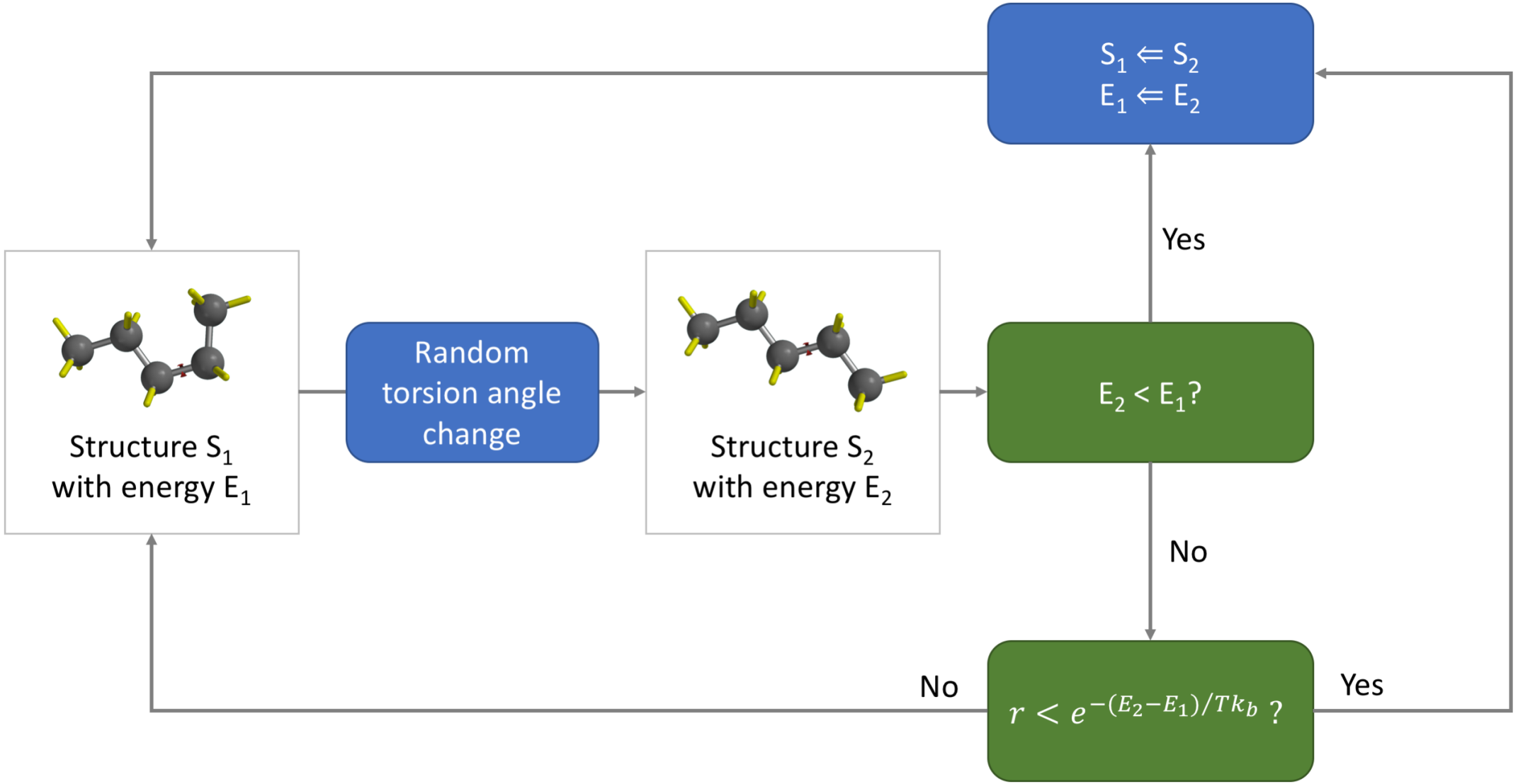


Searching methods

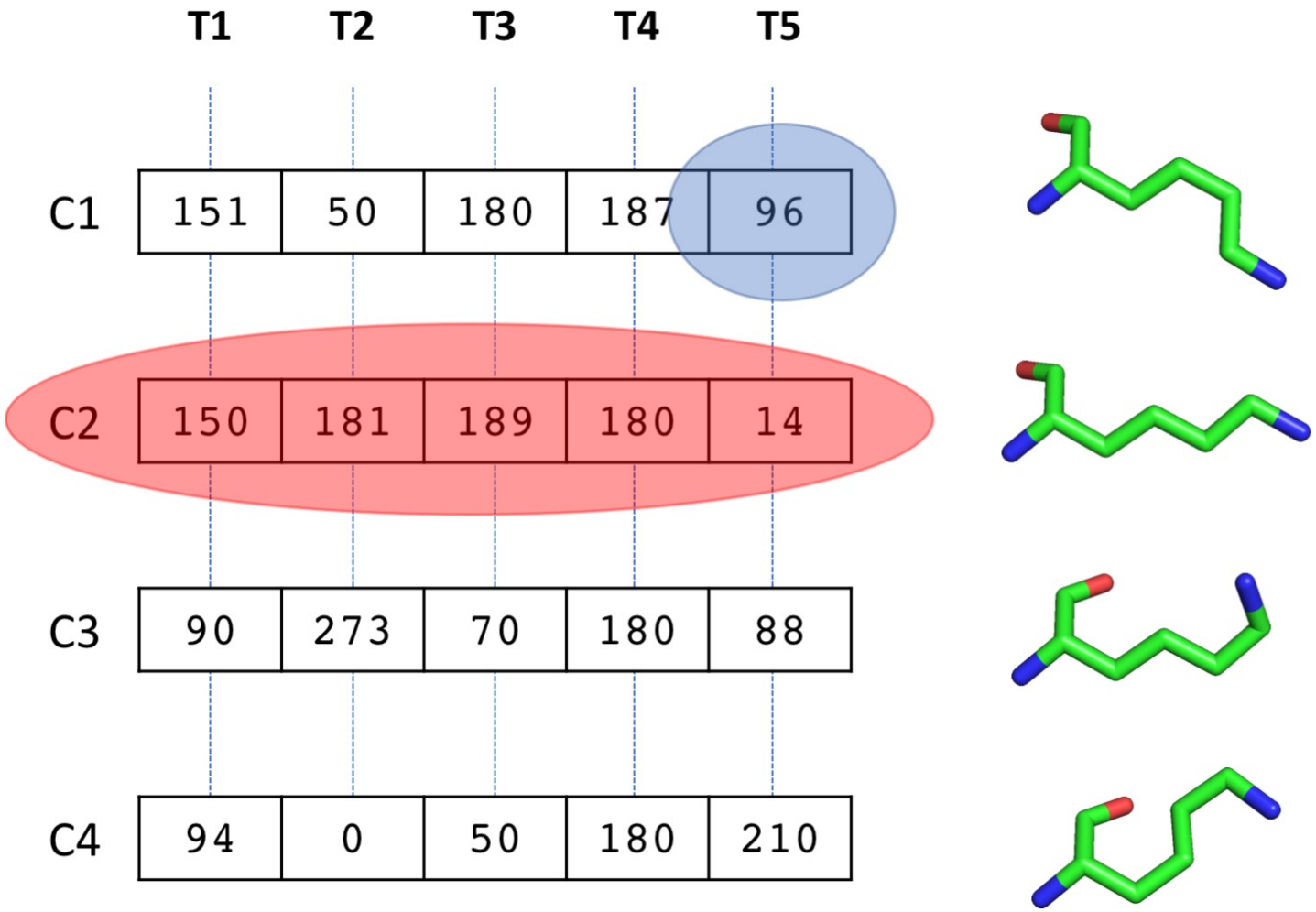


- Molecular dynamics or Monte Carlo simulations
  - $\boldsymbol{F} = m\,\boldsymbol{a}$
- Genetic algorithms
  - Gold
  - Autodock
- Shape-based methods
  - DOCK
  - FRED
  - Glide
  - SURFLEX

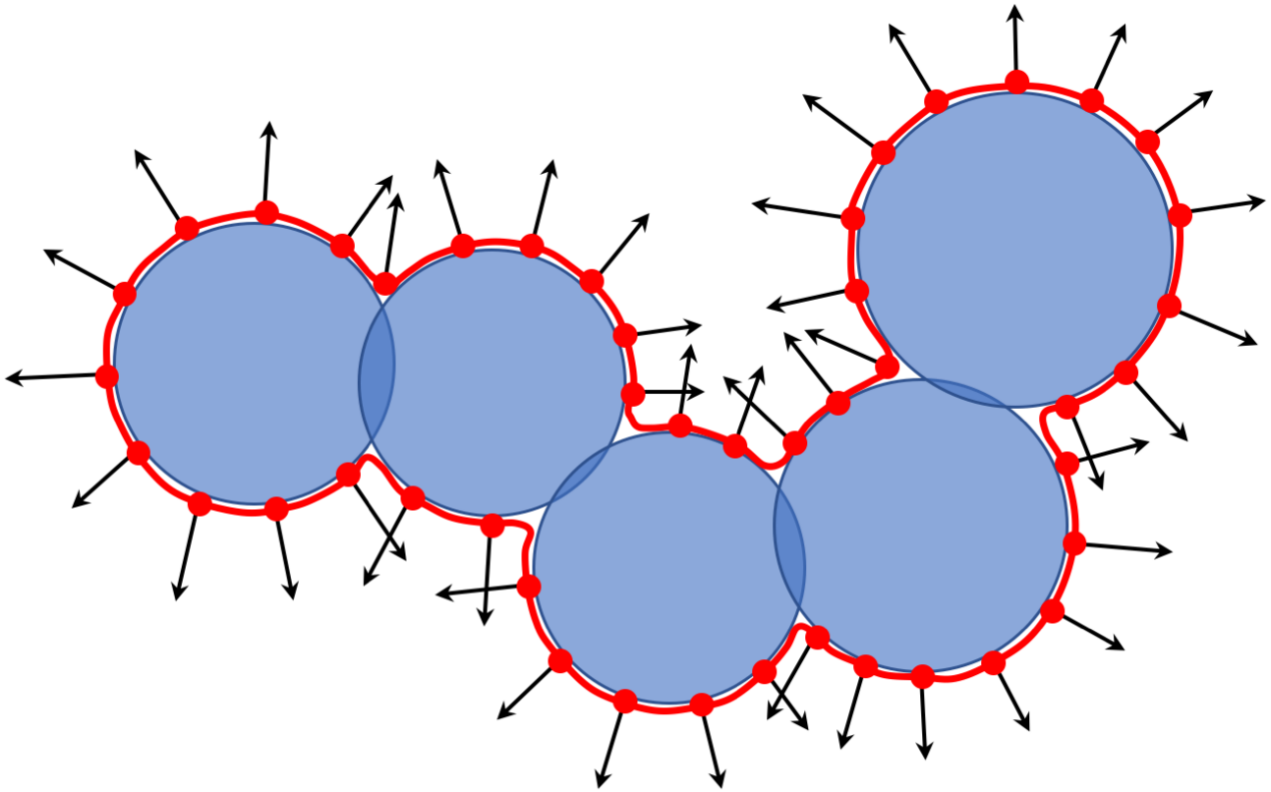
Monte Carlo searching

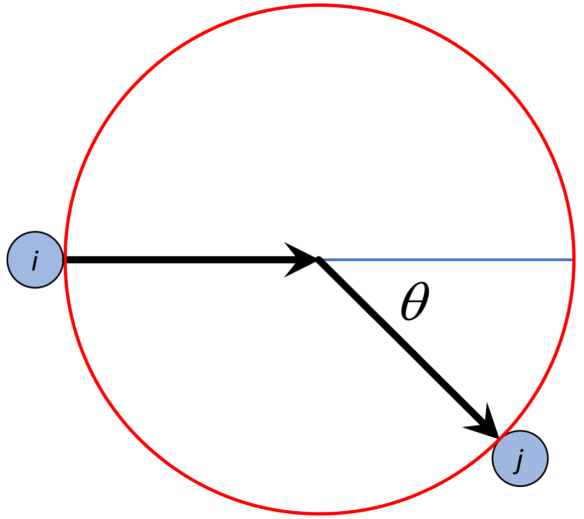


Genetic algorithms



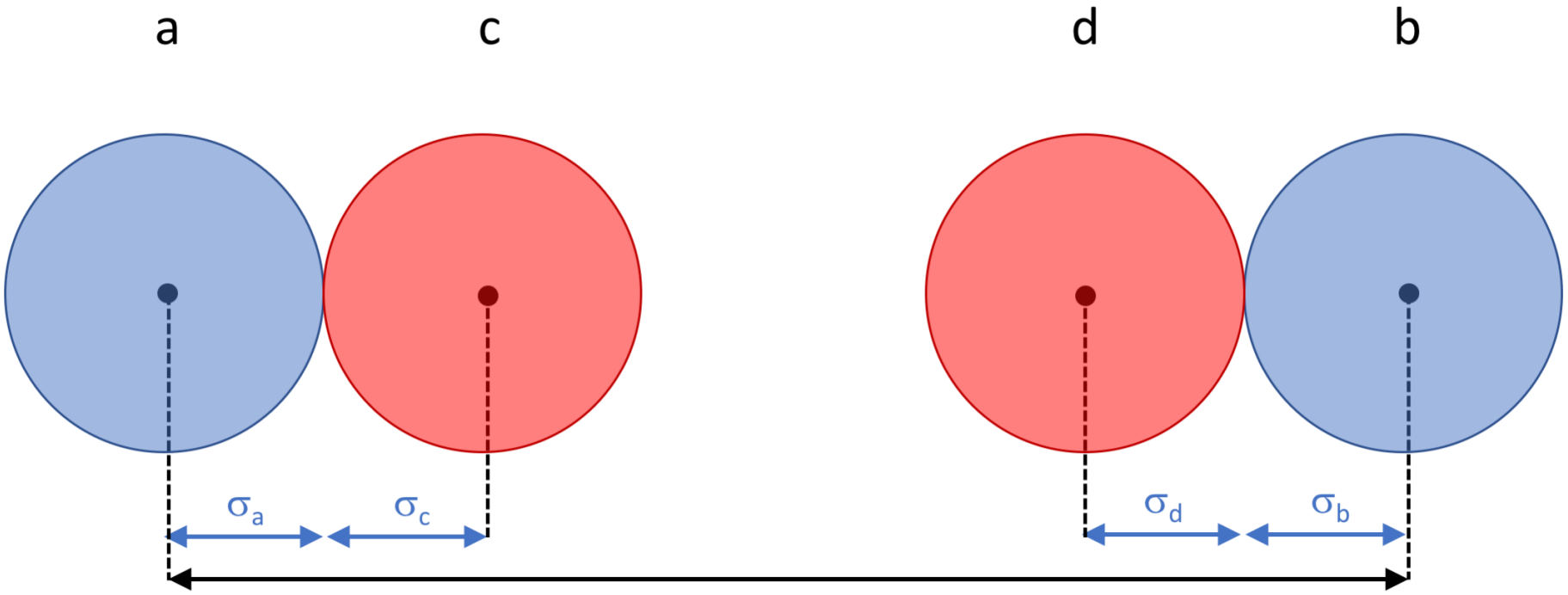
Shape-based searching:
- step 1: representation





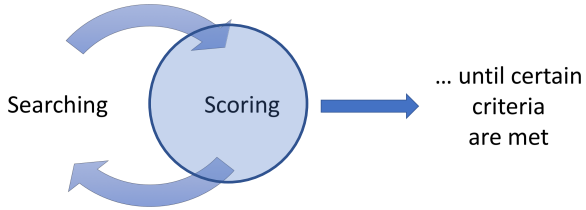
Kuntz et al. (1982) 'A geometric approach to macromolecule-ligand interactions', *J. Mol. Biol.* **161**, 269-288.

Shape-based searching:
- step 2: matching

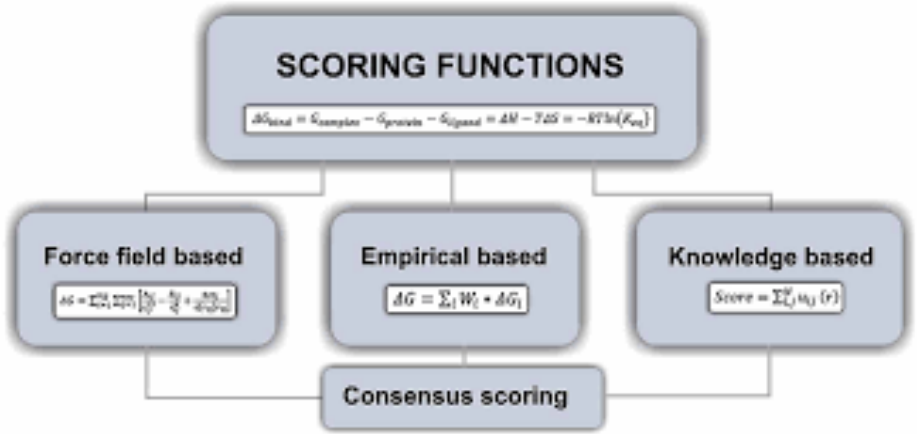


- step 3: optimisation

Scoring methods

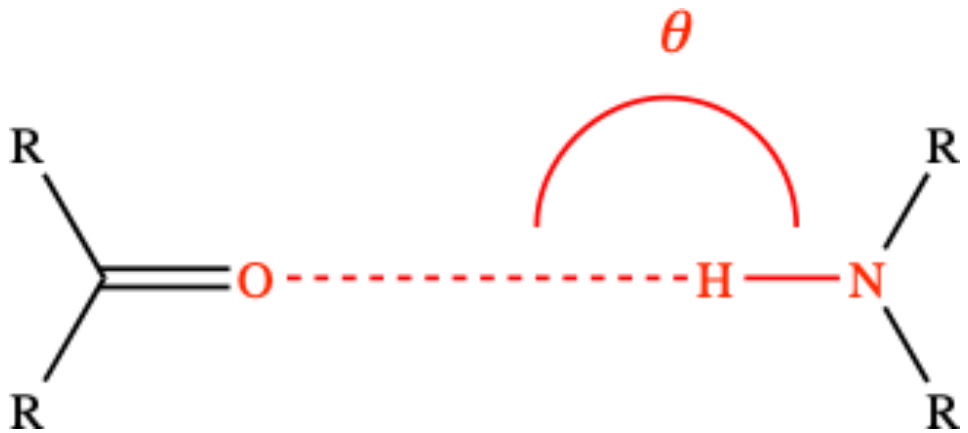


- Force-field based scoring functions
- Empirical scrong function
- Knowledge-based scoring function



Force-field based scoring

$$E = W_{VDW}\sum_{i,j}\left(\frac{A_{ij}}{r_{ij}^{12}}+\frac{B_{ij}}{r_{ij}^{6}}\right)+W_{hbond}\sum_{i,j}p(\theta)\left(\frac{C_{ij}}{r_{ij}^{12}}+\frac{D_{ij}}{r_{ij}^{6}}\right)+W_{elec}\sum_{i,j}\frac{q_i q_j}{r_{ij}}+W_{sol}\sum_{i,j}\left(S_i V_j + S_j V_i\right)e^{\left(-r_{ij}^2/2\sigma^2\right)}$$

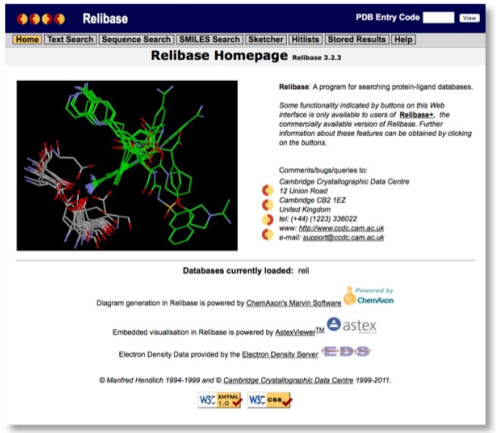


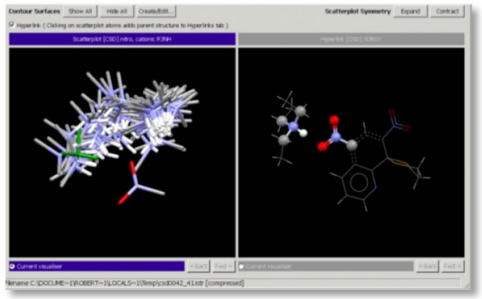
Empirical scoring functions

$$\Delta G = f_{hbonds}\Delta G_{hbonds} + f_{polar-apolar}\Delta G_{polar-apolar} + f_{nrot}\Delta G_{nrot} + f_{apolar-apolar}\Delta G_{apolar-apolar}$$

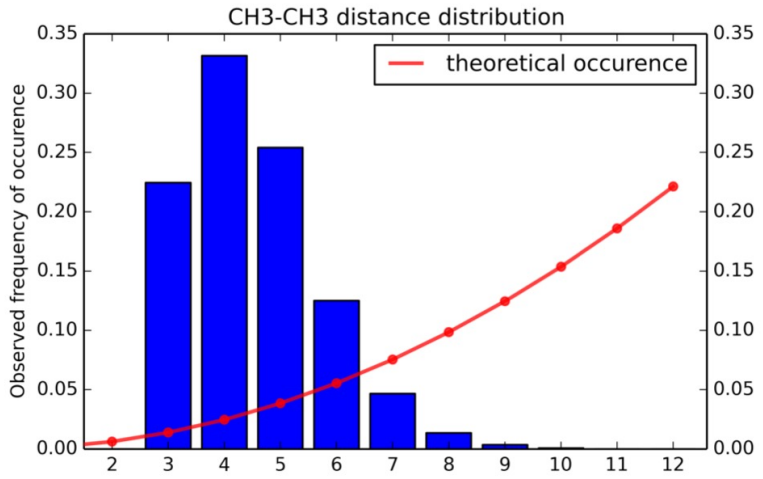
Knowledge-based scoring functions

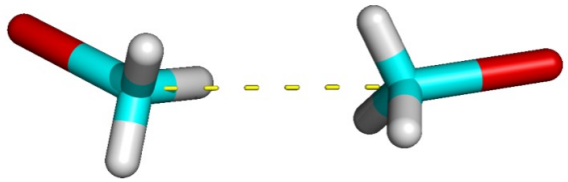
Experimental contact data from **X-ray structures**



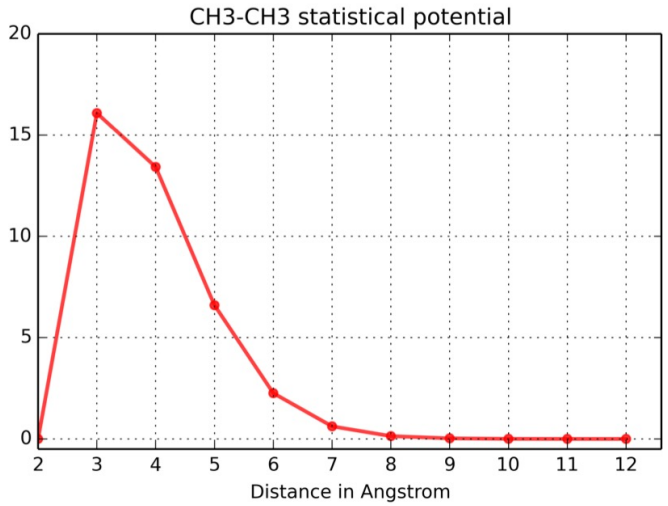


Extract **distance distributions** for each pair of atomtypes





Calculate **statistical potential** for each pair of atomtypes



$$P_{ij} = -\ln \frac{g_{ij}(r)}{g_{ref}}$$

Scope of the different scoring functions

	Pose prediction	Compound selection
Forcefield-based	✔	
Empirical		✔
Knowledge-based	✔	✔

Case studies

- BACE inhibitors
- Google Colab sessie: https://github.com/UAMCAntwerpen/2040FBDBIC/blob/main/11_Docking.ipynb

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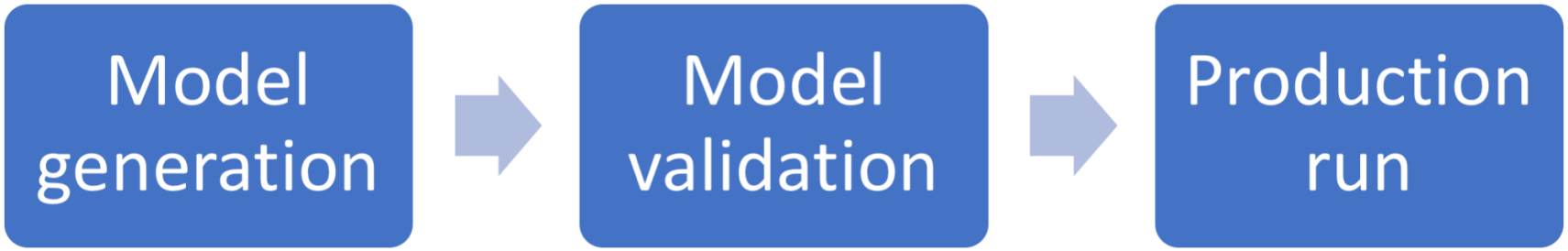
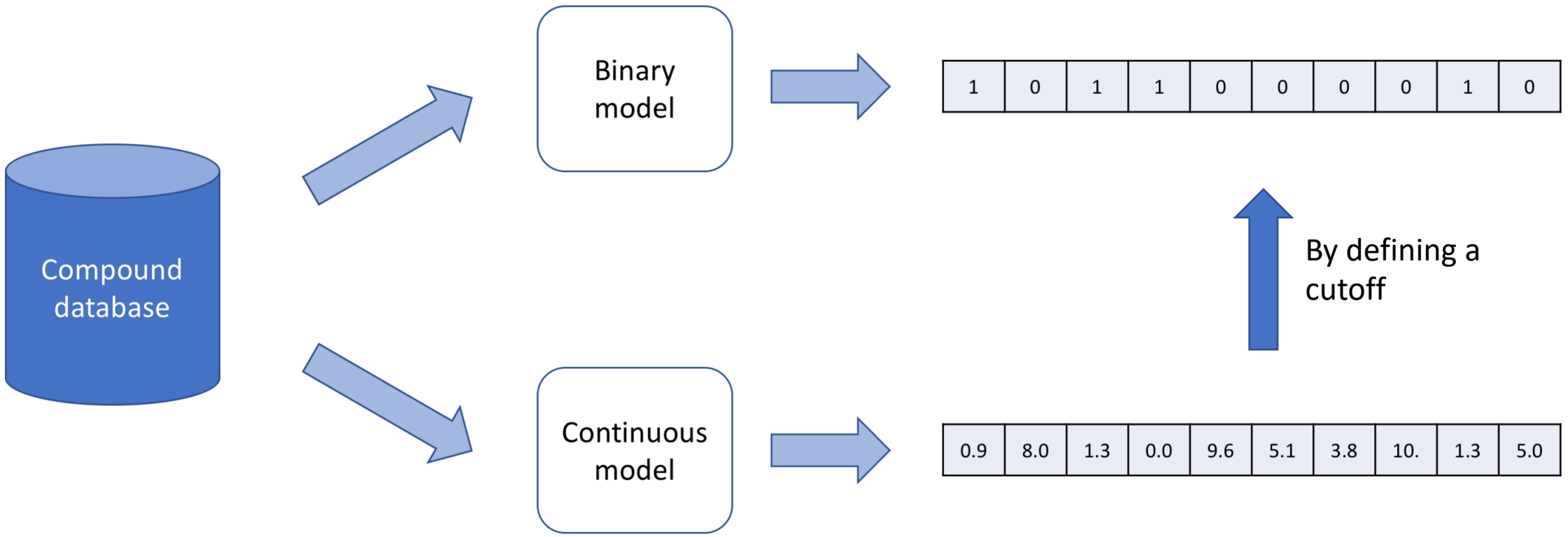
Estimating model quality

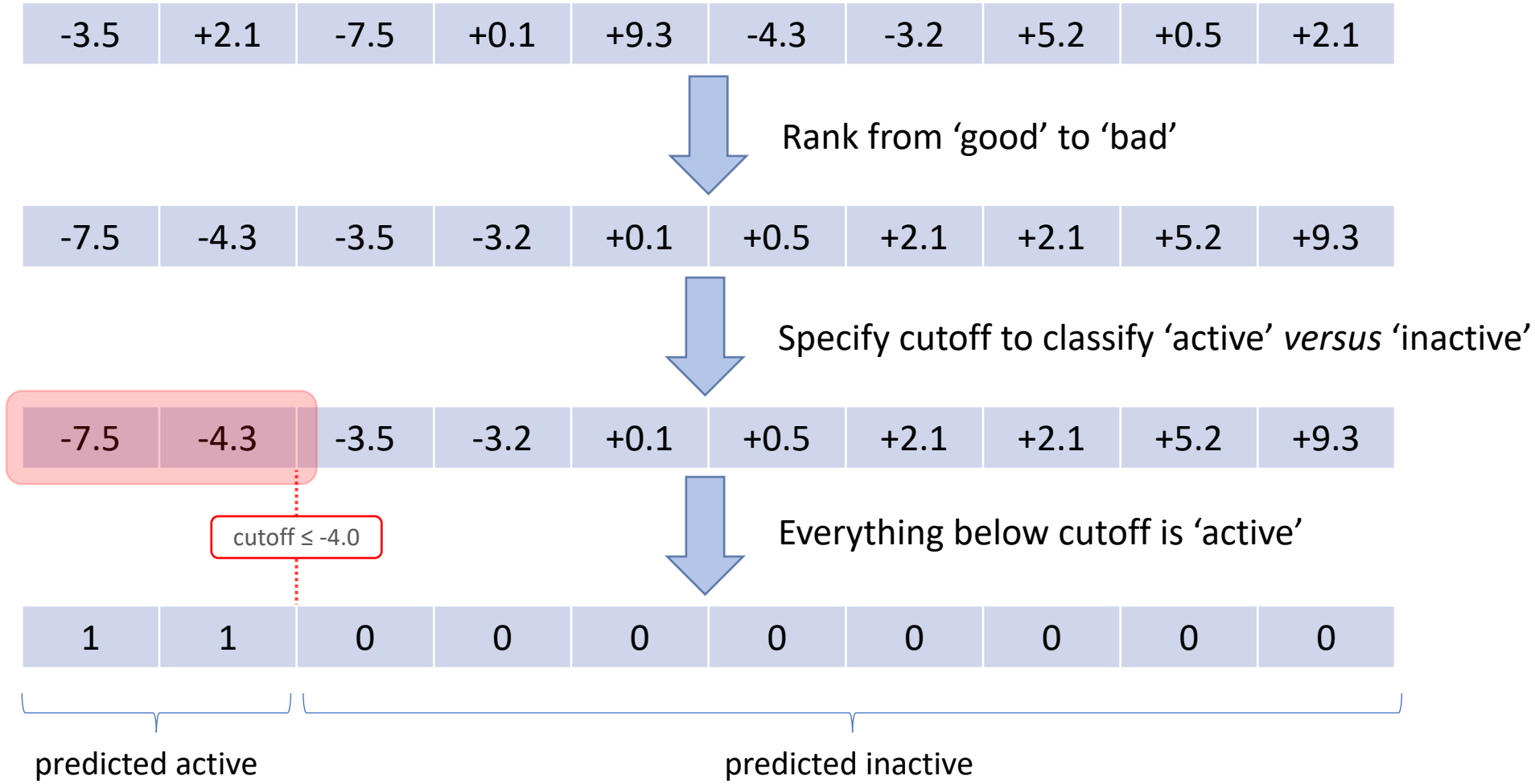
- Chemoinformatics-based screening
- Pharmacophore-based screening
- Docking



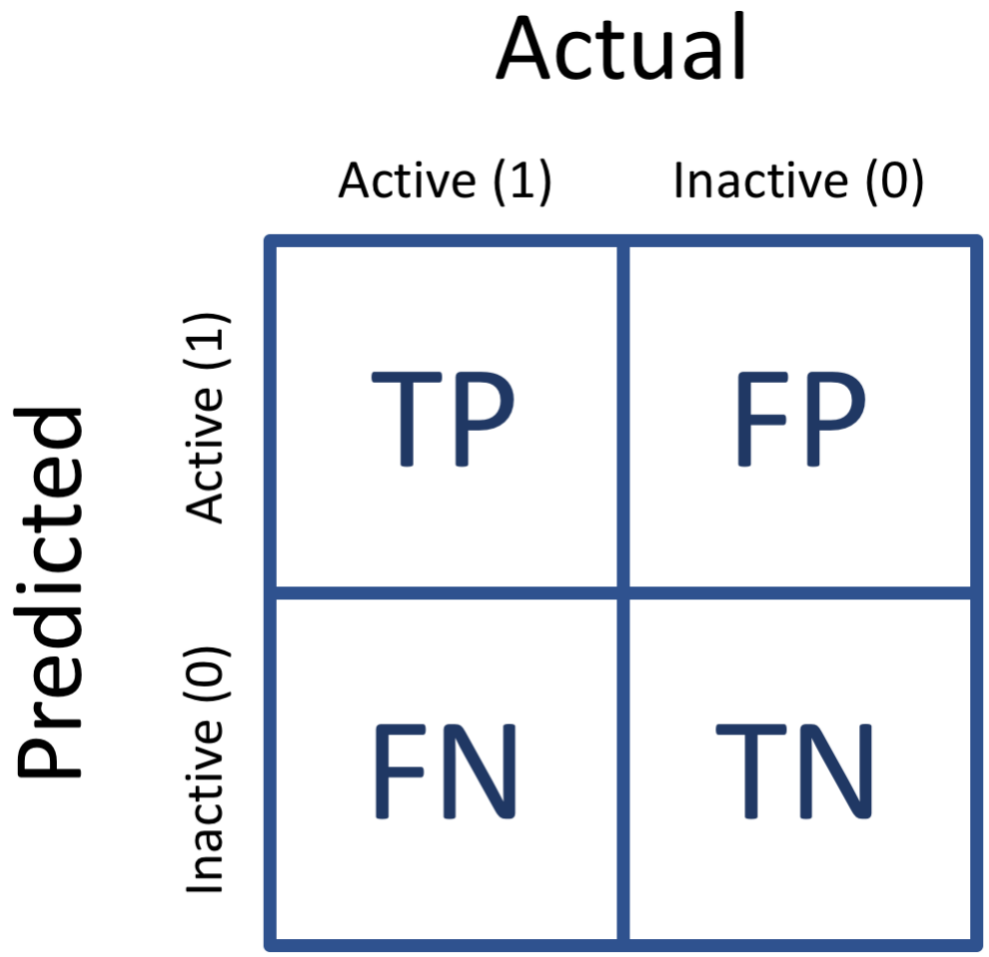
Ranking and classification



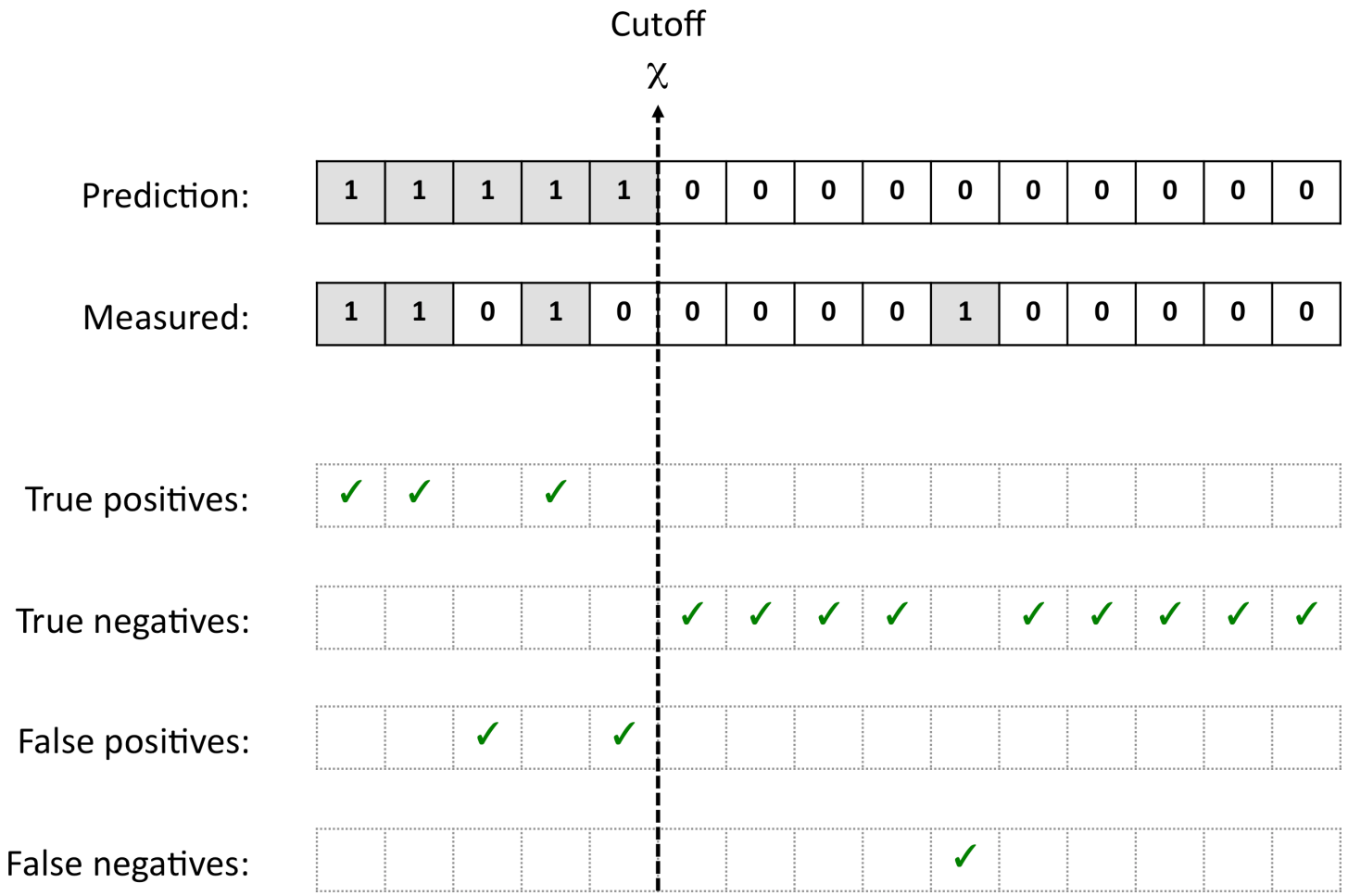
From continuous to binary



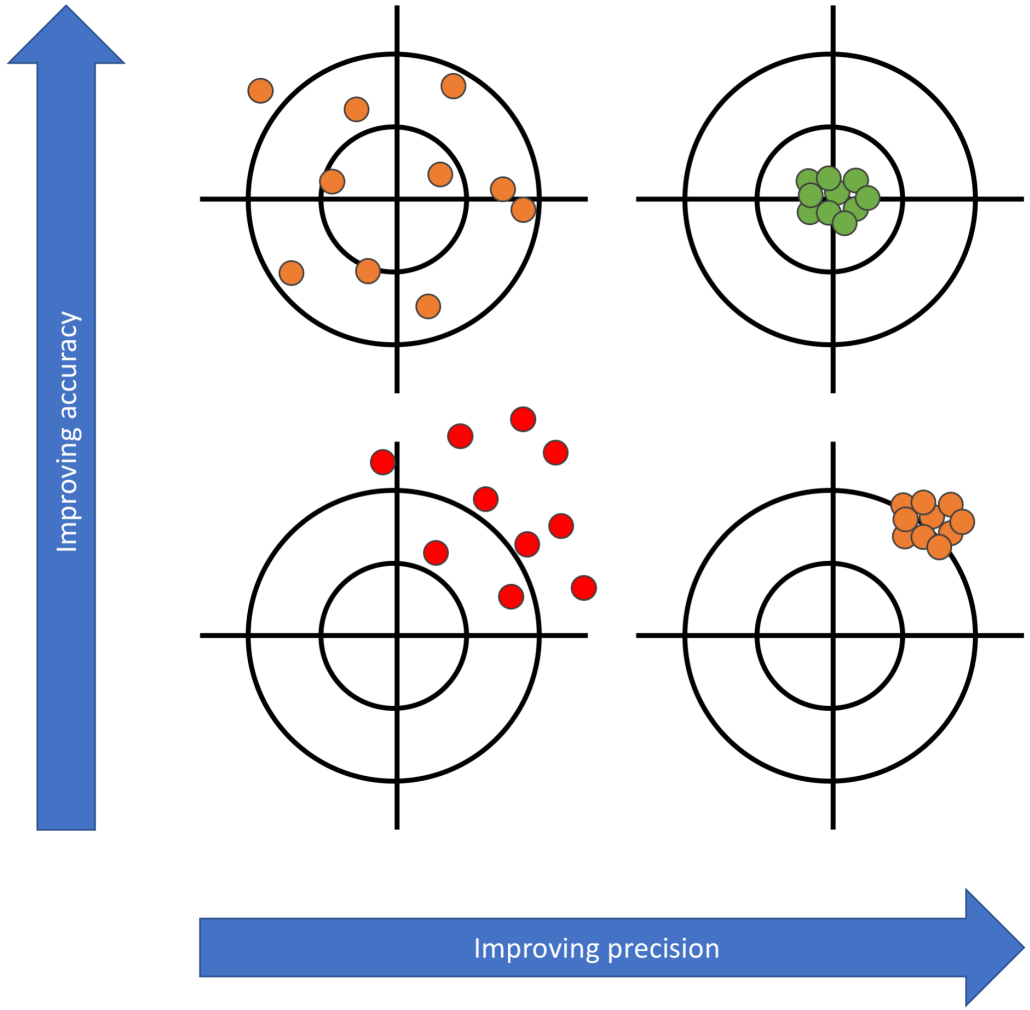
Confusion matrix



Confusion matrix and cutoff

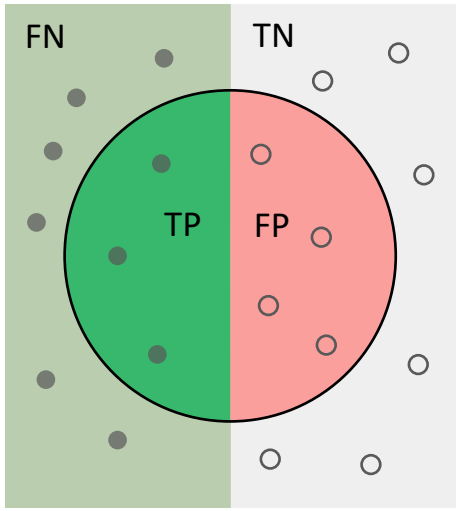


Performance metrics: accuracy & precision



Metrics and the confusion matrix

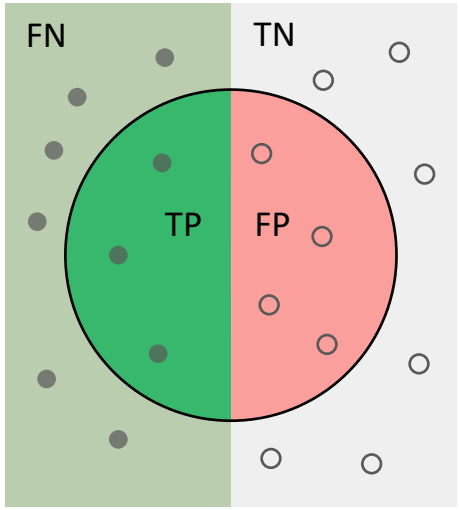
- $ACC = \frac{TP+TN}{P+N} = \frac{TP+TN}{TP+FN+TN+FP}$
- $PRE = \frac{TP}{TP+FP}$
- $SEN = \frac{TP}{P} = \frac{TP}{TP+FN}$

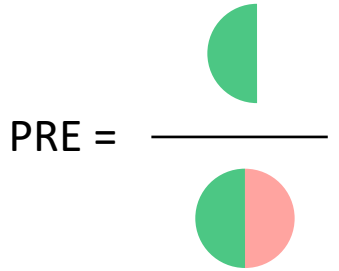


$$\text{Precision} = \frac{TP}{TP+FP}$$

- Useful if you have limited budget and you want to be sure that, if a compound is predicted to be ‘active’, changes are very likely that the compound is really active.

- A high precision comes at the cost of missing out real actives which are not selected by the method



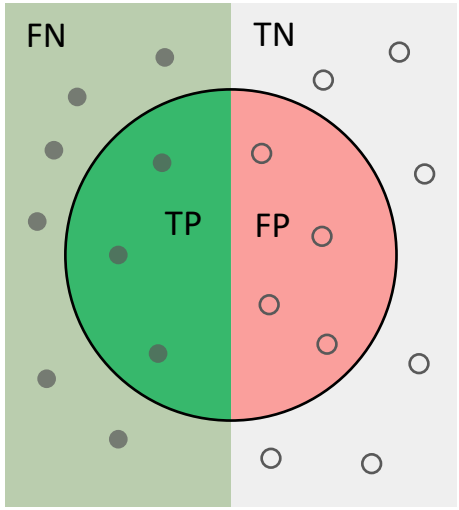


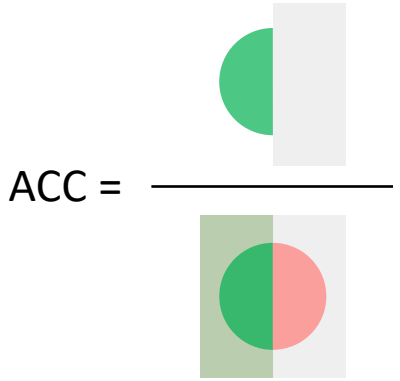
(only looks at the hitlist)

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN}$$

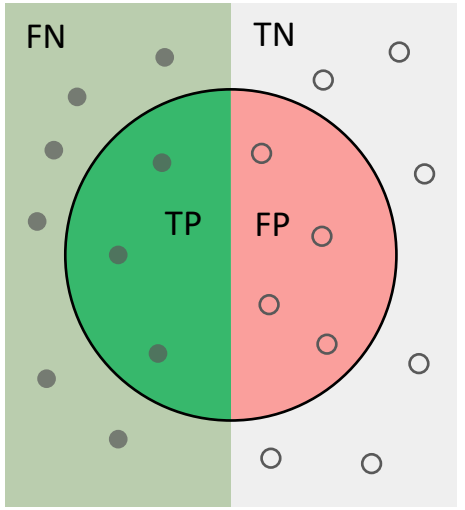
- Useful if you have a balanced dataset with balanced number of actives and inactives

- Should *never* be used when there are only a limited number of actives in the dataset.



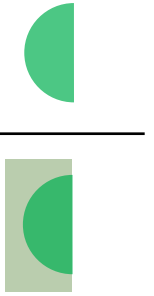


Recall = $\frac{TP}{TP+FN}$ = Sensitivity



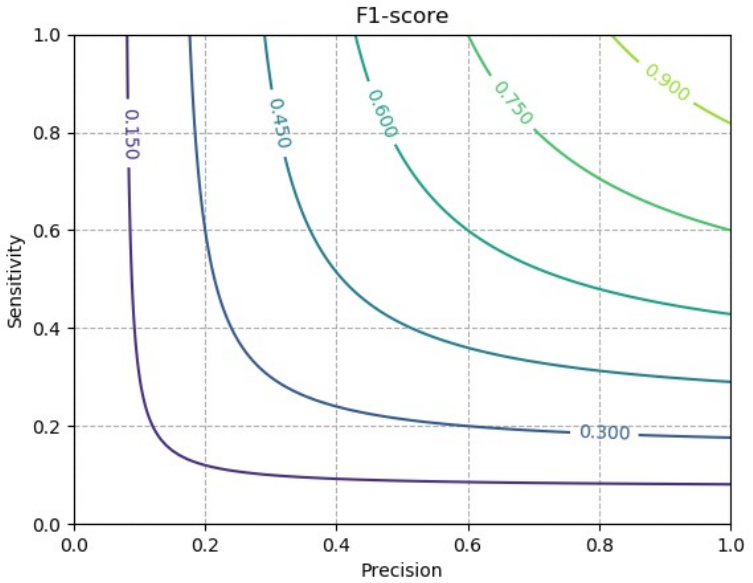
- Useful if you want to retrieve as many actives as possible from the database *("you don't want to miss actives"*)
- Comes at the risc of retrieving many false positives
- Optimising for recall is only useful if the precision is also taken into account:
  - When you screen the entire database you will always get 100% recall...

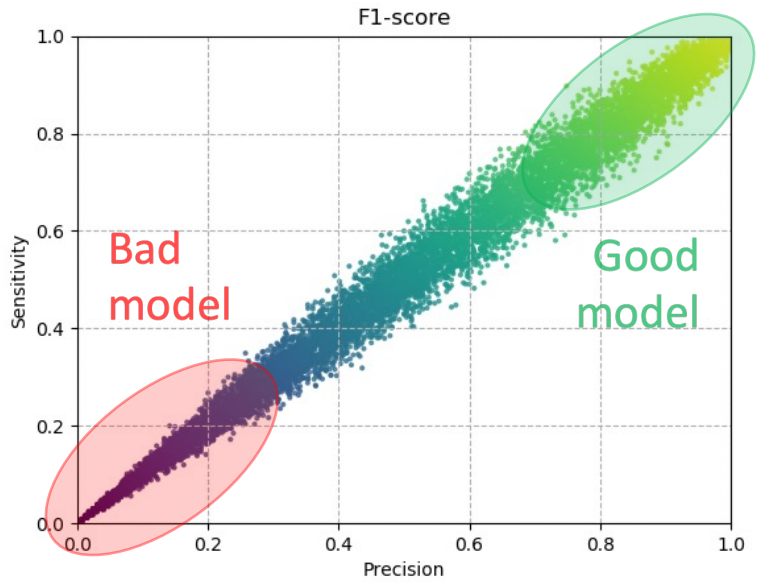
F1-score

SEN = 

$$\text{F1-score} = \frac{2\,TP}{2\,TP+FP+FN}$$

- The harmonic mean of precision and sensitivity:
  - $F1 = \frac{2 * PRE * SEN}{PRE + SEN}$
- Represents a good trade-off between identifying all actives versus a good likelihood of being truly active

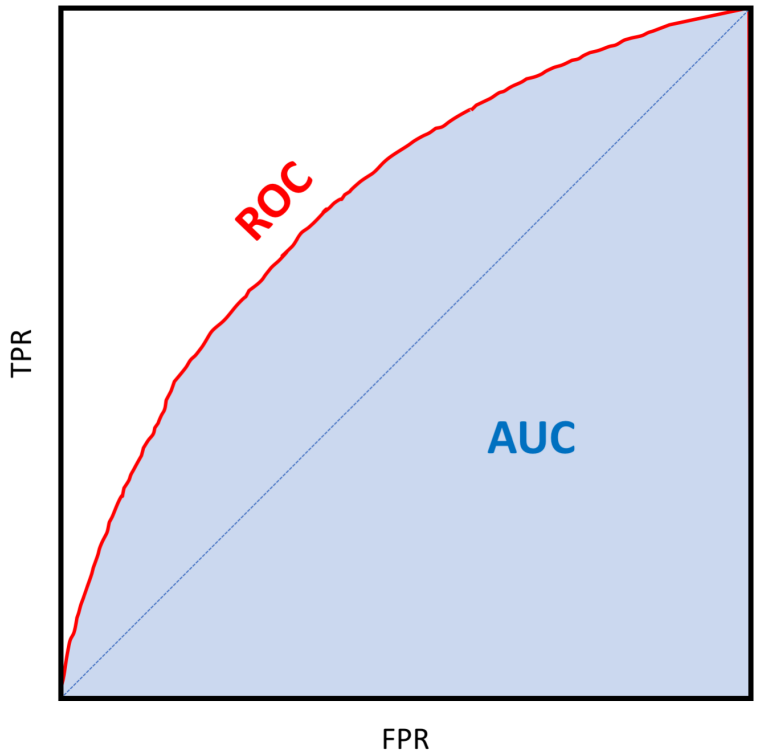


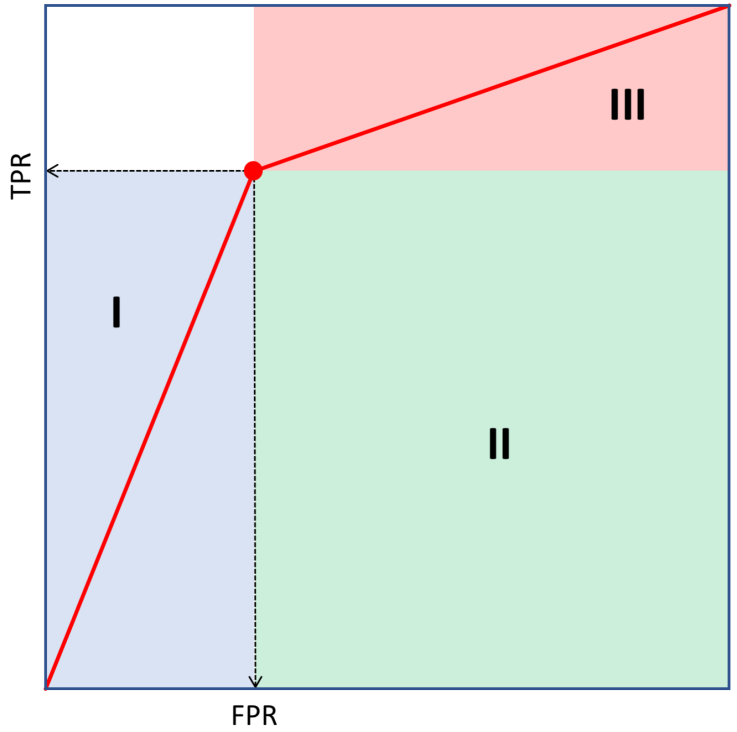


AUC-ROC curve

$$AUC = \frac{TPR - FPR + 1}{2}$$

$$TPR = \frac{TP}{P} = \frac{TP}{TP + FN}$$





$$FPR = \frac{FP}{N} = \frac{FP}{FP + TN}$$

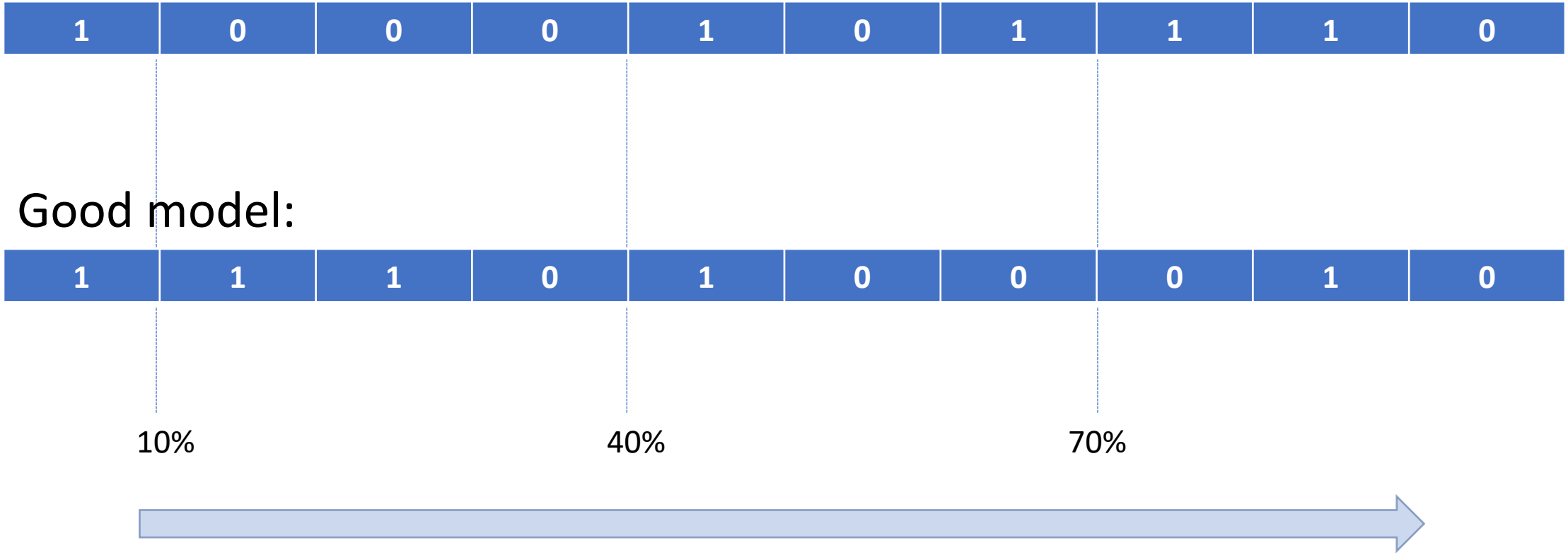
Metrics, model quality and cutoff

- The confusion matrix metrics are influenced by:
  - The quality of the *model*
  - Selection of the *cutoff* in case of a continuous model

- The quality of the model is influenced by:
  - The model itself:
    - Machine learning algorithm and parameters
    - Docking method and parameters
    - Pharmacophore selection and method
  - The quality of the training data

Good and bad models *versus* cutoff

Bad model:



Metrics:

Bad model:

	TP	TN	FP	FN	ACC	PRE
10% cutoff:						
50% cutoff:						
70% cutoff:						

Good model:

TP	TN	FP	FN	ACC	PRE

$$ACC = \frac{TP + TN}{P + N} = \frac{TP + TN}{TP + FN + TN + FP}$$

$$PRE = \frac{TP}{TP + FP}$$

Model validation: cross-fold approach

Step 1: Divide the dataset into *k* folds, here *k* is 10

Step 2: Use one fold for validating the model that has been built on all other folds

Step 3: Repeat the model building and validation for each of the data folds (10 times)

Step 4: Calculate the avarege of all of the *k* validation performance values