A STEP TOWARDS GPCRs POLYPHARMACOLOGY: AN ALGORITHM TO 5-HT$_7$/5-HT$_{1A}$ SELECTIVITY PREDICTION

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Methodology

- **Sets**
  - source: ChEMBL,
  - compounds with activity data to both 5-HT$_{1A}$R and 5-HT$_7$R,

ChEMBL

	Set Name	Description/Conditions used to generate the set	Amount
●	Selective	Selective ligands to 5-HT$_7$R: K_i(5-HT$_7$) < 100 nM & K_i(5-HT$_{1A}$)/K_i(5-HT$_7$) > 5	69
■	DUD	Decoy set generated for selective set using e-DUD service	5198
▲	Revsel	Reverse selective ligands (ligands selective to 5-HT$_{1A}$R): K_i(5-HT$_{1A}$) < 100 nM & K_i(5-HT$_7$)/K_i(5-HT$_{1A}$) > 5	124
★	Notsel	A set of ligands that do not meet the condition of selectivity: 0.20 < K_i(5-HT$_{1A}$)/K_i(5-HT$_7$) < 5	440
◆	Nselbact	The set of active ligands to both receptors simultaneously: K_i(5-HT$_7$) & K_i(5-HT$_{1A}$) < 100 nM	89

ML set preparation

The strategy of testing and training sets generation

Set ID	Class {+1}	Class {-1}
Dud	●	■
Revsel	●	▲
Notsel	●	★
Nselbact	●	◆

- **ML models**
  - two approaches (*structure-based* and *ligand-based*),
  - optimization of SVM RBF kernel parameters,
  - the 10 random training and testing sets were generated
  - diffrent size of training and testig sets,

structure-based approach

Sets

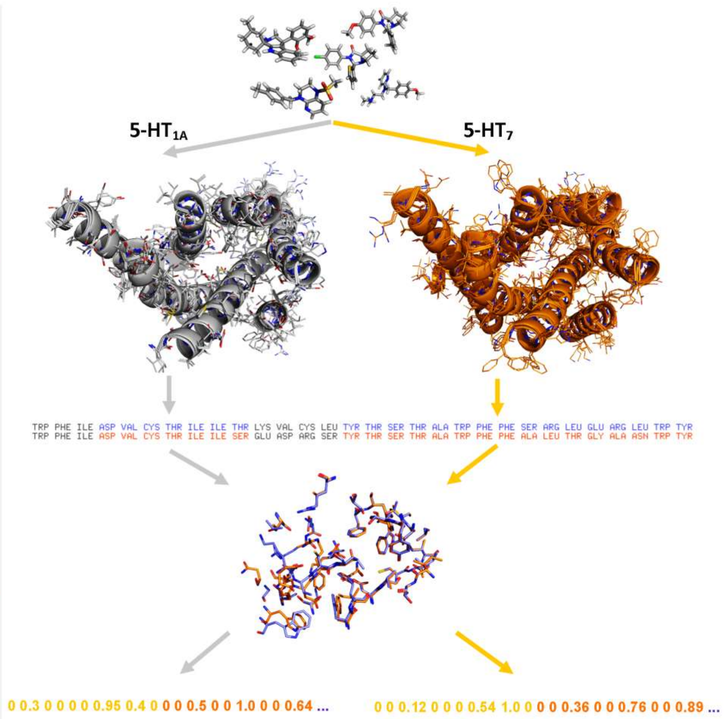
Docking (Glide SP)
- two templates: 5-HT$_{1B}$ and D$_3$ (with and without loops),
- three conformations per template,

Interaction analysis
- SIFt statistics

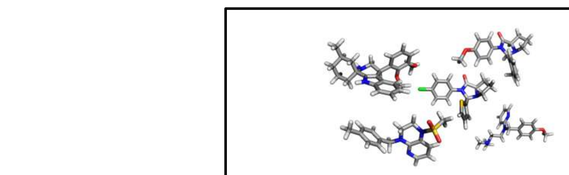
AA base setup
- selection the common set of amino acids,

SIFt profiles

SIFts Concatenation



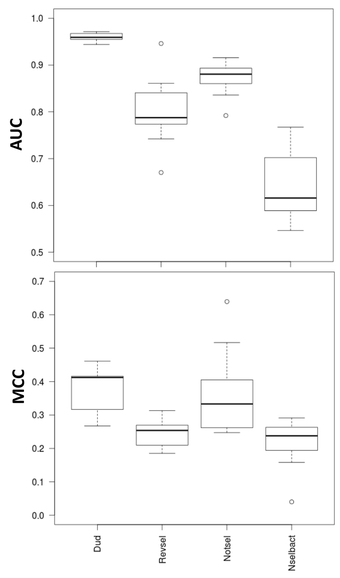
ligand-based approach



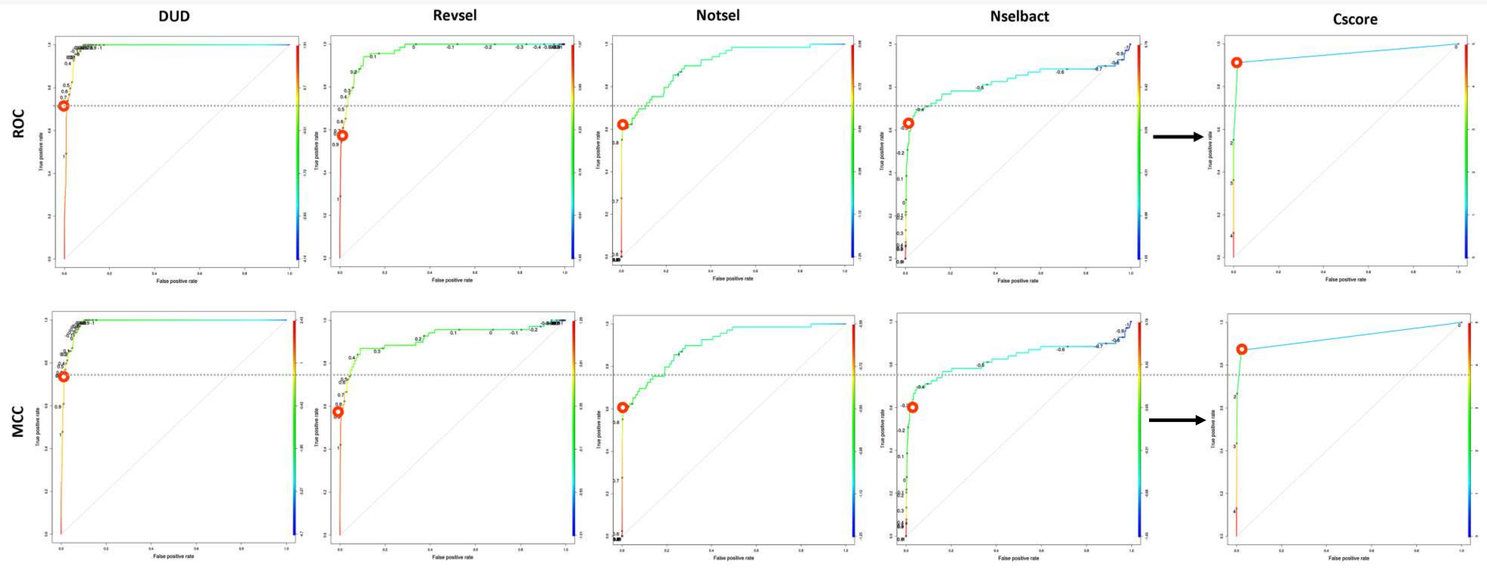
Molecular fingerprints

- MACCSFP 166 bits
- CDKFP 1024 bits
- Klekota-Roth FP 4068 bits

- **Cscore**
  - two optimization approaches (AUC and MCC),
  - only best models survived,
  - cutoff selection based on MCC maximization,
  - data fusion method (SUM rule) used to constuct final Cscore model,



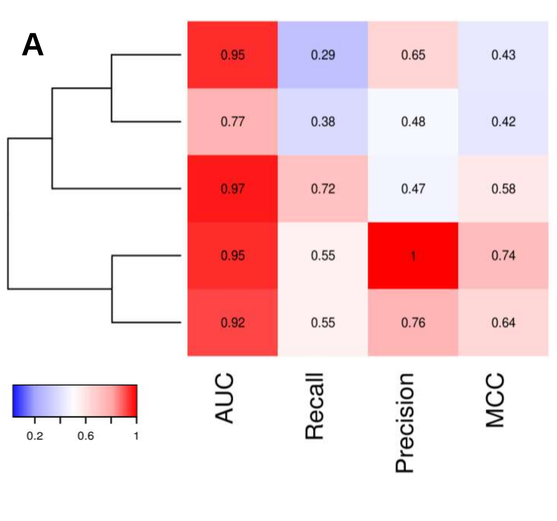
Selection of the best models



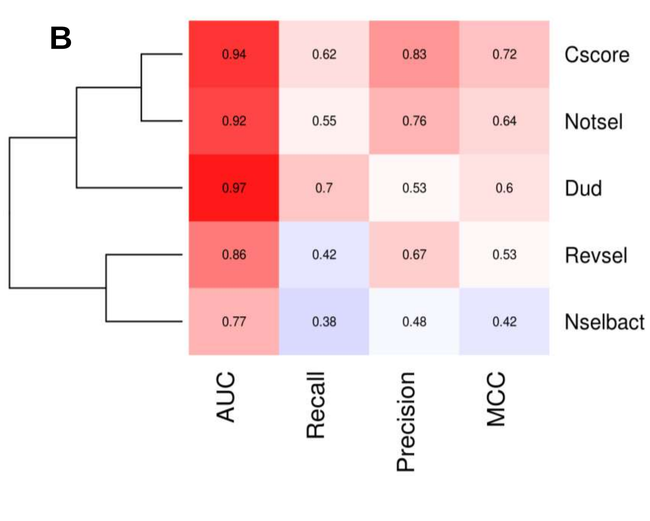
ROC curves of the best models selected to construct Cscore models.

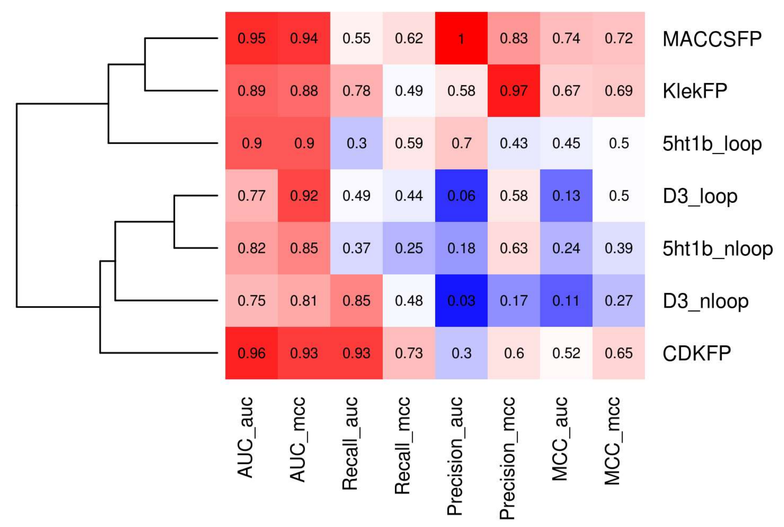
Results

- Cscore models performed globlally the best,
- ligand-based approach outperformed structure-based,
- larger training set do not significantly influenced on the models performance,



An example of performance for all models generated based on MACCSFP (*ligand-based* approach) with different distribution coefficients (A - 0.40, B – 0.60) of initial set of ligands.





The heat map comparing the performance of CScore models obtained for all studied cases (i.e. three molecular fingerprints and SIFt generated on four homology models).

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