Application of linear combination of pharmacophore hypotheses into search for the dual 5-HT

Dawid Warszycki, Rafał Kafel, Andrzej J. Bojarski
Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, Kraków, Poland
e-mail: warszyc@if-pan.krakow.pl

Introduction
Pharmacophore modelling is one of the most basic concepts in medicinal chemistry, yet the current approaches face several limitations, such as partial coverage of chemical subspace of ligands of particular target, exploration of limited conformational space and, as a result, low-feature hypotheses with low selectivity potential. Recently published idea of using linear combination of pharmacophore hypotheses [1] allowed creation of an effective feature mapping protocol solving the aforementioned problems.

Methodology
In this study, the linear combination of hypotheses was applied to explore the space of dual 5-HT

For representative compounds selected from each cluster, separate pharmacophore hypotheses were generated and tested using Phase software [4]. All of them mapped at least half of the ligands used for their development. The best hypothesis for each cluster was selected on the basis of following criteria: maximal number of features, the highest number of matched representative compounds, and the highest value of selectivity score. Not all clusters returned pharmacophore hypothesis (27 hypotheses out of 33 clusters for 5-HT

Conclusions
Results (Figure 1) indicate that a combination for dual ligands is slightly more robust in active/inactive discrimination and less time-consuming (19 mapping procedures for combination of dual ligands vs 22 in total for individual targets), however, separate combinations for each target present a valid alternative in case of limited number of dual ligands available for training (e.g. only 7 dual ligands for 5-HT/SERT and 24 structures for 5-HT1A/SERT). Hypotheses for dual ligands are statistically more complex than hypotheses developed for individual targets (averagely 5.75 features per cluster vs 4.84) which influences on combination’s selectivity.

References

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Figure 1. The development of an optimal combinations of pharmacophore models.

Figure 2. An optimization MCC curve for the ligands of the investigated targets and dual ligands. Arrows indicate the maximum values of MCC reached a rate of 0.490 for SERT for 14 hypotheses, of 0.639 for 5-HT1A for 8 hypotheses and of 0.597 for 19 hypotheses for dual ligands.