A hypothesis-driven virtual screening methodology for structure-based inhibitor discovery

Sebastian Raschka*, Nan Liu, Santosh Gunturu, Anne M. Scott, Mar Huertas, Weiming Li, and Leslie A. Kuhn.

*Contact: raschkas@msu.edu. Michigan State University, East Lansing, MI 48824, U.S.A.

Introduction

- Sea lampreys are a non-native, ecologically disruptive parasitic fish in the Great Lakes.
- A sulfated steroid (3kPZS) in the male pheromone attracts ovulatory females towards nesting areas.
- Our goal is to control species-specific behavioral responses by identification of specific receptor antagonists.

Hypothesis and approach

- Sea lamprey reproduction can be halted by species-specific pheromone receptor antagonists.
- 3kPZS activity can be blocked by compounds that mimic its shape and functional groups.

Virtual screening

13,200 compounds

- Construction of a relational database with structural information from ZINC12 [1].
- Continuous addition of functional information for hypothesis-driven molecule filtering and analysis with structured query language.
- Selection of compounds that are commercially available.
- Removal of compounds with 7 or more rotatable bonds to minimize unfavorable entropy changes upon binding.
- Selection of compounds based on the presence of certain functional groups.

Functional group distance

- Sampling of low energy conformations [2].
- Selection of compounds based on functional-group distances.

Molecular docking

- Molecular docking of inhibitor candidates into receptor structural model to assess chemical fit [4].

Results and conclusions

- ~300 candidate antagonists from virtual screening were tested by EOG for their ability to block 3kPZS pheromone detection.

References and Acknowledgments


This research is supported by a grant from the Great Lakes Fishery Commission. We thank OpenEye Scientific Software for providing an academic software license for ROCS (v. 3.2.0.4), OMEEGA2 (v. 3.1.4), and MolCharg (v. 1.3.1).

We also thank Stacey Kneeshaw and Qinghua Yuan for their early contributions to this project.