Combined interactive and automated adaptive search for molecular design

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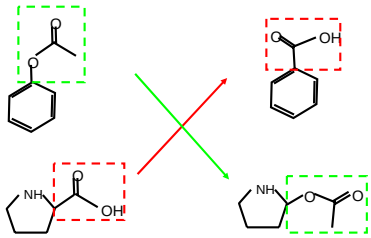
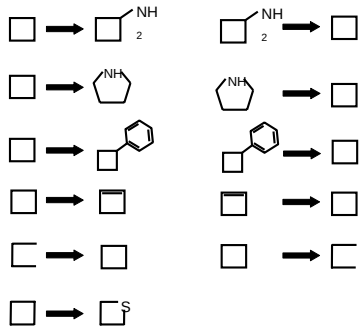
The Molecule Evoluator™

The Molecule Evoluator is a software tool for the interactive design of drug molecules. It implements an interactive evolutionary algorithm to support the expert in pharmacology to explore the huge space of molecular structures.

Recombination

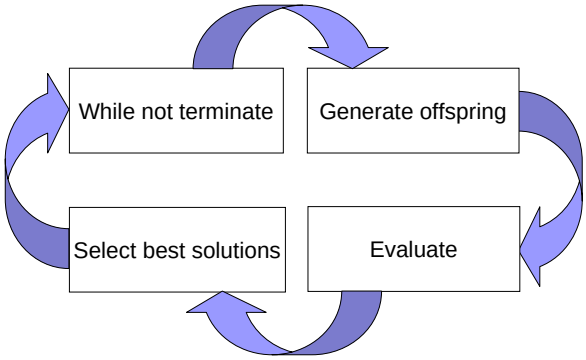


Mutation



An Automated Evolutionary Algorithm as extension to the Molecule Evoluator

- The interactive evolutionary algorithm is very powerful as a design tool, but has limitations as it is biased and limited when it comes to the number of evaluations.
- Automated methods are unbiased and can explore a larger part of the search space.
- We have developed an automated multi-objective evolutionary algorithm that can be used for molecular design.
- The automated search is based on targets for a number of molecule properties.
- The advantages of automated evolution and interactive evolution can be combined in one molecule design tool.



Constraints - chemical filters

Constraints set for:

- Follow Bredt's rule
- Allow Acetals
- Allow CH_2-Imines
- Min size ortho paracyclophane
- Min size meta paracyclophane
- Min size paracyclophane
- Only common ring system
  - Also consider atoms

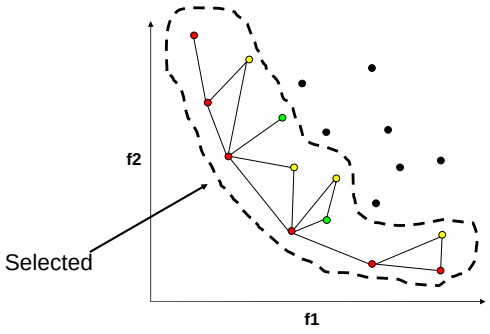
Experiments

- Inverse design of 6 well known molecules
- Goal: find molecules with similar properties

Results

- 53 out of 60 test-run managed to find 5 solutions within 1000 generations (between 10 minutes and 1 hour)
- All runs found at least one solution
- Only one run found the original molecule

Selection using Pareto Domination



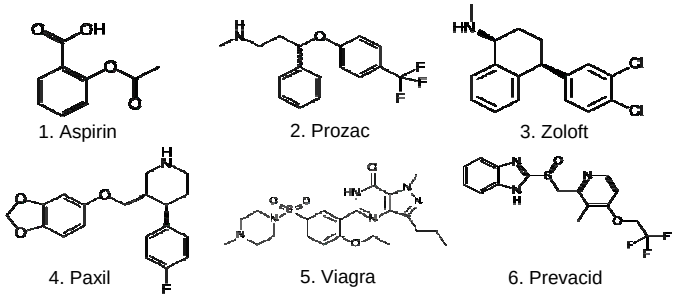
Objectives - targets for physical filters

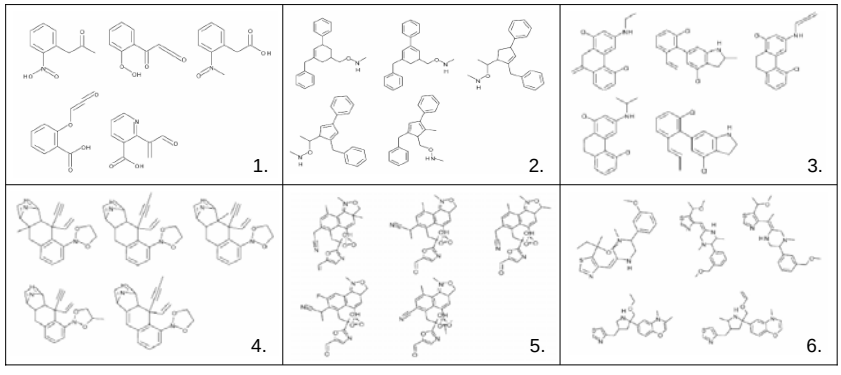
Optimization towards targets for:

- Polar Surface Area (PSA)
- Log of octanol/wate partition coefficient
- Log of aqueous solubility
- Molecular Weight (MW)
- Hydrogen Donors (HD)
- Hydrogen Acceptors (HA)
- Rotatable Bonds (RTB)
- Number of aromatic systems
- Number of aromatic substituents

Experiments: search for molecules with similar properties as the test molecules

Test molecules





- Automated Evolutionary Algorithms can indeed be applied to find molecules with pre-defined properties
- Extending the Molecule Evoluator with an automated Evolutionary Algorithm makes it a very powerful design tool
- Future research will focus on niching, landscape analysis, molecule stability, molecule synthesizability, and application in real-world problems