Virtual Screening for Novel Ligands

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2007-09-04, Summer School “Roles of Eicosanoids in Biology and Medicine”, Aigen, Austria
Outline

Introduction  Context, problem setting
Virtual screening  Definition, ideas, techniques
Examples  Toxicity, COX-2 inhibition
Conclusions  Summary, collaborations
The drug development pipeline

*Discovery research* | *Hit identification* | *Lead identification*
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Target identification | *Assay tests* | *High-throughput screening* | *Virtual screening*

*Virtual screening* is the automatic testing of large compound libraries using computers
Virtual screening methods

Two basic approaches:

▶ Target structure is known $\Rightarrow$ structure-based methods
  Idea: Receptor-ligand interaction

▶ Target structure is unknown $\Rightarrow$ ligand-based methods
  Idea: Structural similarity implies functional similarity
Virtual screening methods

Two basic approaches:

- **Target structure is known ⇒ structure-based methods**
  Idea: Receptor-ligand interaction

  ![Structure-based method](image)

  PDB 121P, GCP

- **Target structure is unknown ⇒ ligand-based methods**
  Idea: Structural similarity implies functional similarity

  ![Ligand-based method](image)

  Aspirin (left)  Paracetamol (right)
Example 1: Toxicity mode of action

- 114 nonpolar (blue) and 76 polar (red) narcotic compounds
- 3 descriptors: $E_{\text{LUMO}}$, $E_{\text{HOMO}}$, $Q^-$

Example 2: Cyclooxygenase-2 inhibition

SC-558 (PDB 6COX)

Proschak, Rupp, Derksen, Schneider, J. Comp. Chem, accepted, 2007
Molecular similarity 1: Iterative graph similarity

- Representation: Annotated molecular graph
- Idea: Gradual graph similarity
- Pairwise atom similarities based on a recursion: “Two atoms are similar if their neighbours are similar”
- Overall score is based on best atom assignment

Example:
Molecular similarity 2: Steric distributions

- Representation: Steric probability distributions, based on e.g. atom-centered Gaussians or quantum-mechanics
- Idea: Surfaces without an arbitrary cutoff; electron densities
- Similarity of distributions, e.g. Kullback-Leibler related measures like the Hellinger integral

Example:

ZD 2138 (5-LO inhibitor). Left to right: Hard sphere model, iso-surfaces of mixture model at 75%, 63%, 50%, 32% probability mass.

Conclusions

Summary:
- Virtual screening can help find new inhibitors
- Right choice of representation and similarity measure are crucial
Thank you for your attention.