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Docking and scoring of protein-ligand complexes: *What is possible and what is not?*

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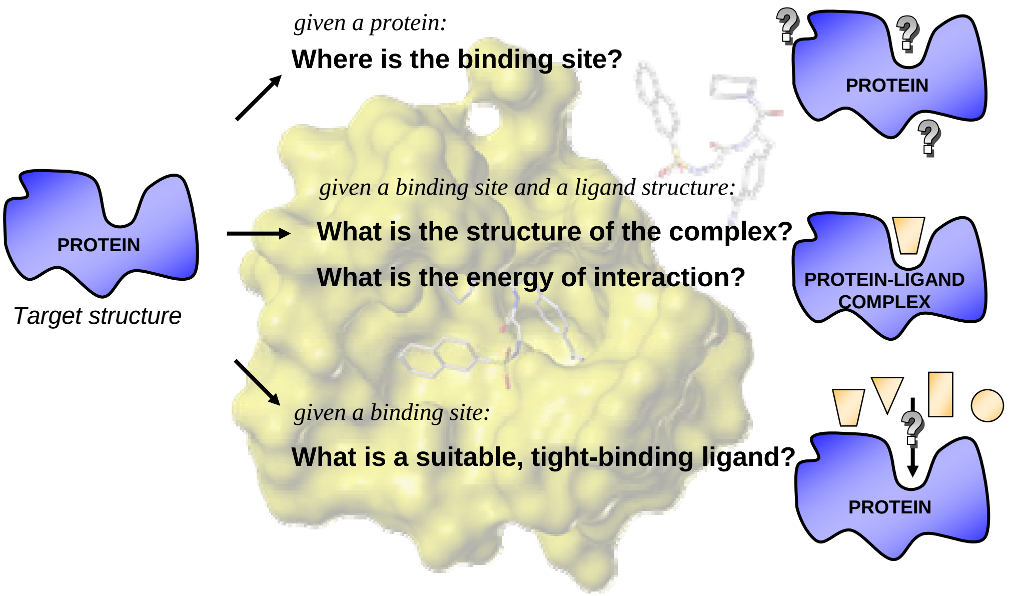
Key questions in structure-based drug design



given a protein:

Where is the binding site?

given a binding site and a ligand structure:

What is the structure of the complex?

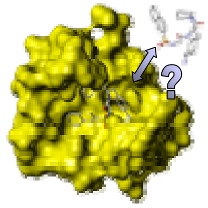
What is the energy of interaction?

given a binding site:

What is a suitable, tight-binding ligand?

Required: **ligand placement** and **affinity prediction**

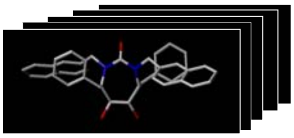
Docking problems & scoring tasks



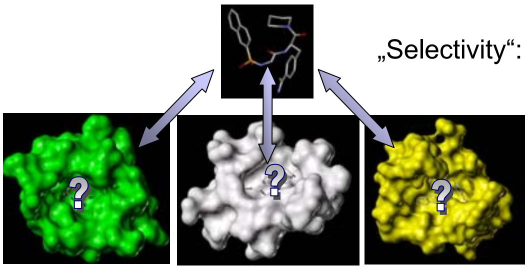
„Single Docking“: *1 protein – 1 ligand*

looking for: binding mode (and affinity) of the ligand

„Virtual Screening“: *1 protein – many (potential) ligands*



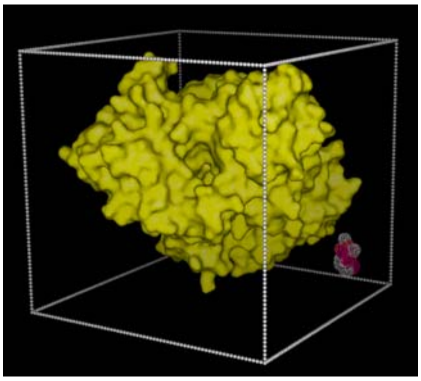
looking for: ligands with high affinity for target protein



„Selectivity“: *many proteins – one or more ligands*

looking for: ligands with high selectivity for one target

Why is docking a „problem“?

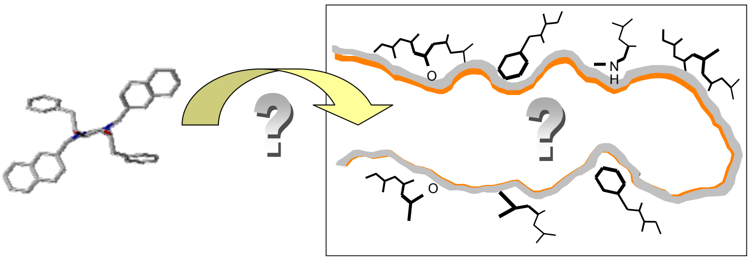


- complex 3D jigsaw puzzle
- conformational flexibility
- mutual adaptations („induced fit“)
- solvation in aqueous media
- complexity of thermodynamic contributions
- no easy route to ΔG evaluation for scoring

⇨ Simplifications und heuristic approaches necessary

Modelling and computer-aided drug design are frequently a quest for suitable simplifications

Approaches to solve the docking problem



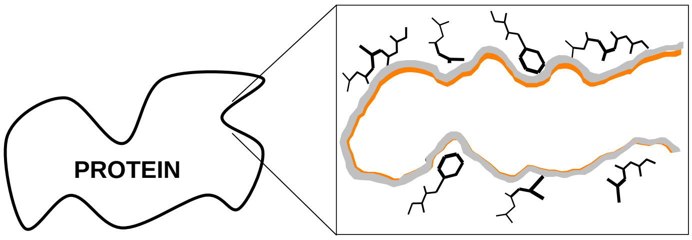
„Representing“ — „Searching“ — „Evaluating“

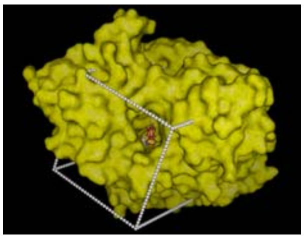
• Surface representations • Physicochemical descriptors • Grid-based approaches	• Rule-based • Energy-driven	• Force fields • Regression functions • Knowledge-based potentials

„Representing“: Molecular representations for docking

A.) Protein

0. Restricting the search space to the binding pocket

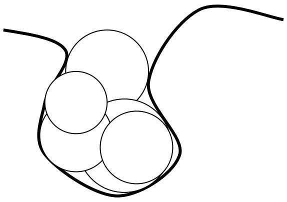




1. Geometric surface descriptors

e.g., sphere representation of binding pockets

(→ program DOCK)

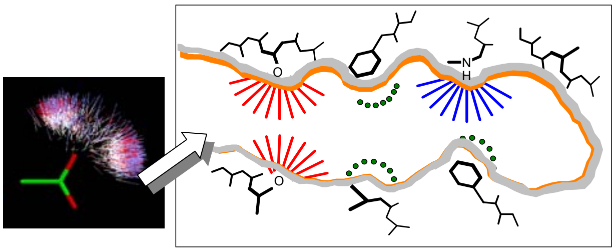


„Representing“: Molecular representations for docking

2. Physicochemical descriptors

Interaction points and vectors

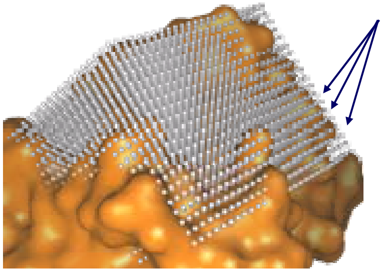
(→ Programs LUDI, FlexX)



3. Grid representations

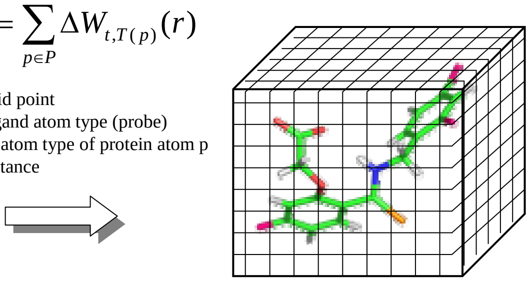
Interaction potentials of probe atoms are mapped to grid points

(→ Program AutoDock)



$$\Delta P_{g,t} = \sum_{p\in P} \Delta W_{t,T(p)}(r)$$

g: grid point
t: ligand atom type (probe)
T(p): atom type of protein atom p
r: distance



„Representing“: Molecular representations for docking

B.) Ligand

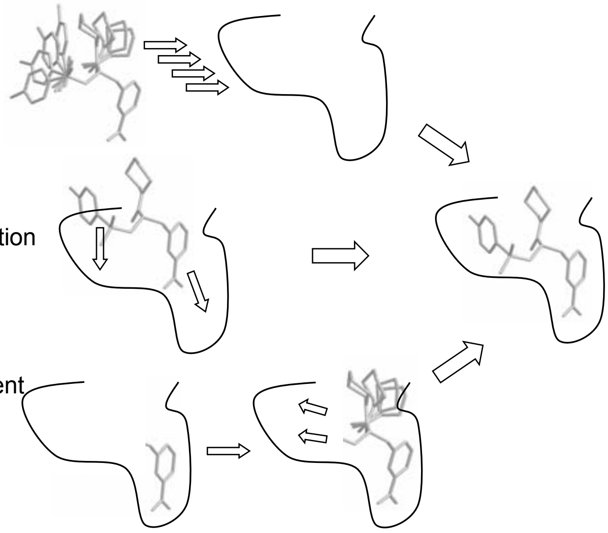
major problem: conformational flexibility

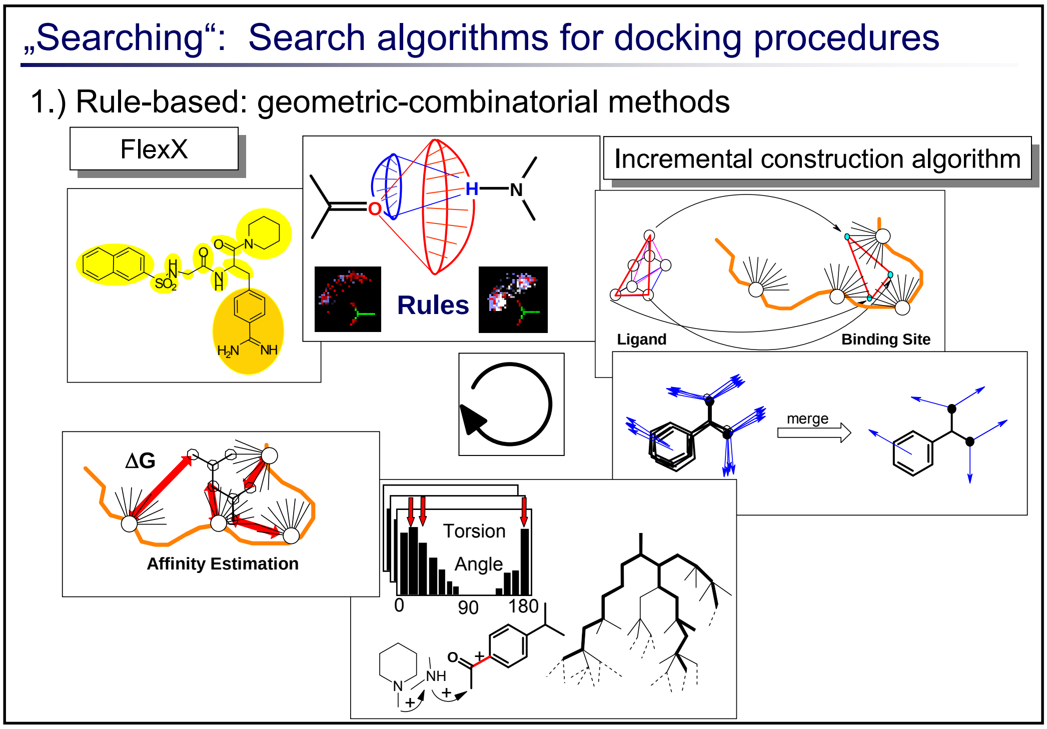
⇨ strategies for flexible ligand docking

1.) rigid docking of conformers

2.) simultaneous optimization of orientation and conformation

3.) placement of a base fragment followed by incremental construction



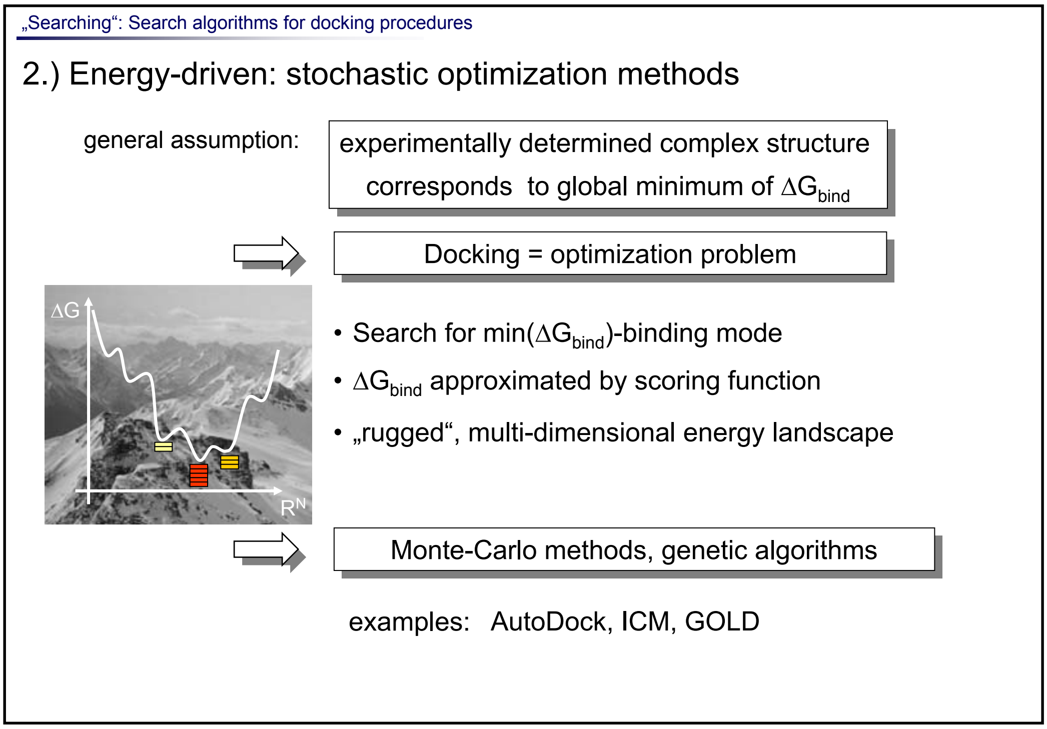


„Searching“: Search algorithms for docking procedures

1.) Rule-based: geometric-combinatorial methods

FlexX

Incremental construction algorithm



„Searching“: Search algorithms for docking procedures

2.) Energy-driven: stochastic optimization methods

general assumption: experimentally determined complex structure corresponds to global minimum of ΔG_{bind}

Docking = optimization problem

- Search for min(ΔG_{bind})-binding mode
- ΔG_{bind} approximated by scoring function
- „rugged“, multi-dimensional energy landscape

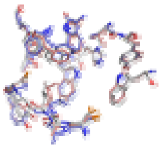
Monte-Carlo methods, genetic algorithms

examples: AutoDock, ICM, GOLD

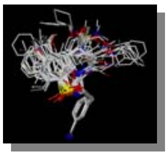
Before docking ...

... take care of the setup!

- Protein structures:
  - Protonation states and H-bonding networks
  - Quality and completeness of structural data
  - Location of binding site
  - Experimental data about water molecules and flexible regions



- Ligand structures:
  - Protonation states (influenced by protein!)
  - Tautomers
  - Conformers



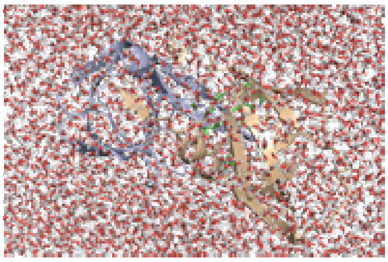
- Docking program:
  - Choose suitable parameters
  - Validate, validate, validate (in particular for your system)!
- Know you program!
- Check structures and setup visually!
- Critically assess the quality of automated setup routines!

„Evaluating“ / Scoring: Why is affinity prediction a challenge?

1.) Protein-ligand complexes are dynamic systems in aqueous solution

- huge number of particles
- simultaneous, unperiodic, continuously changing interactions

⇨ Simulation methods required!



Statistical thermodynamics: Calculation of ΔG° needs integration over entire phase space!

⇨ Computationally very expensive!

2.) The prediction methods need to be fast

Database screens: ~ 10^3 – 10^6 molecules need to be compared

Docking runs: ~ 10^7 – 10^9 configurations need to be evaluated

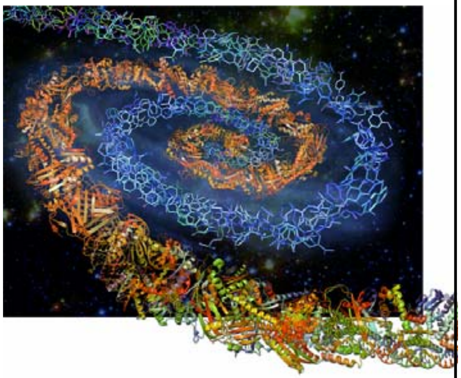
⇨ „Scoring functions“ required:

Fast, simplified, heuristic methods for prediction of binding strength

Scoring functions: Goals

The ultimate goals of an ideal function:

- accurate within less than 1 pK_D unit (<1.4 kcal/mol)
- generally valid (not system specific; large affinity range)
- robust (tolerant with respect to structural uncertainties)
- widely applicable (docking, virtual screening)
- physically meaningful (interpretable)
- fast and easy to compute



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Scoring functions: Tasks and types

Application tasks:

A) Identification of the correct binding mode for a given ligand

Pose prediction in docking

B) Identification of new active ligands

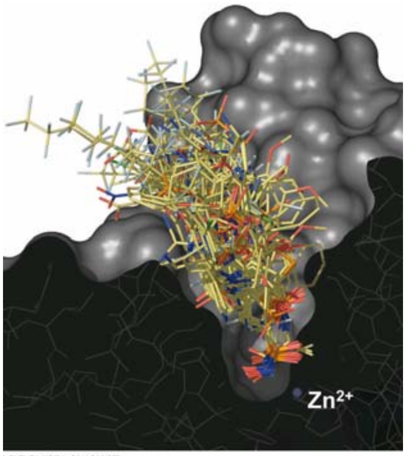
Virtual screening

C) Affinity ranking for compound series

Ligand design, lead optimization

Available approaches:

- Force field-based methods
- Knowledge-based scoring functions
- Empirical scoring functions



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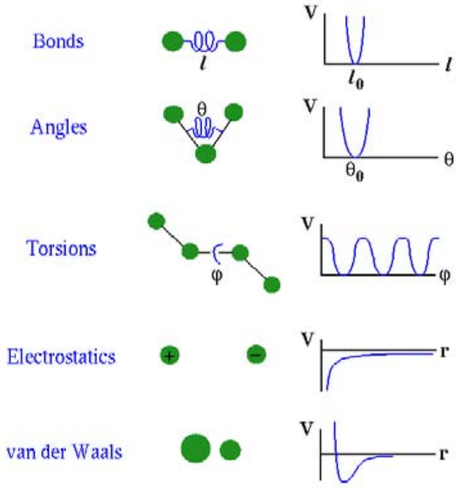
Force field-based methods

Molecular Mechanics (MM):

- atoms → charged spheres
- bonds → springs
- classical potentials
- no electrons → no bond formation / cleavage
- typically parameterized to reproduce molecular potential energy surface (→ conformational ΔH in the gas phase!)



⇨ Scoring protein-ligand complexes:

+ for pose prediction in docking

− for ligand ranking by affinity

⇨ Terms accounting for (de)solvation & entropic factors required (cf. MM-PBSA)

Knowledge-based scoring functions

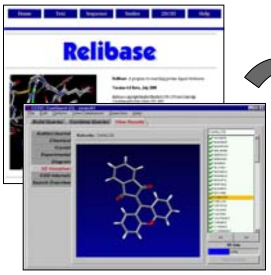
Derivation from crystal-structure data

$$P_{ij}(r) = -\ln \frac{g_{ij}(r)}{g_{ref}}$$

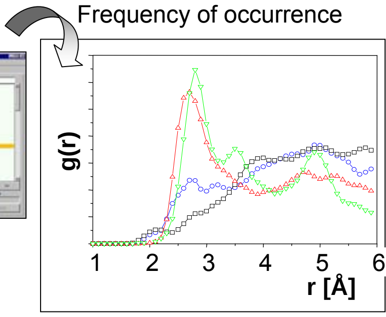
P_{ij}: distance-dependent pair potential

g_{ij}: frequency distribution of atom-atom contacts

g_{ref}: reference distribution

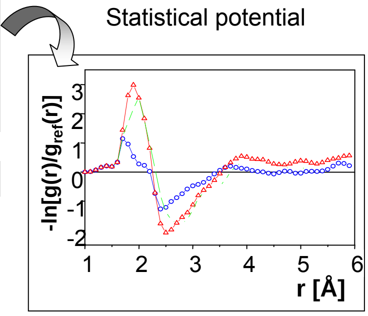


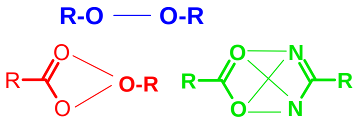
Frequency of occurrence



No experimental affinities used!

Statistical potential





Empirical scoring functions

Regression-based: $pKi = \Sigma\, pKi_n\, f_n(\text{structure})$

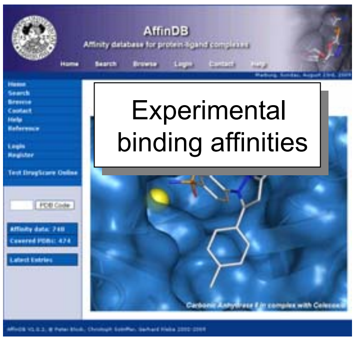
affinity

weighting factors

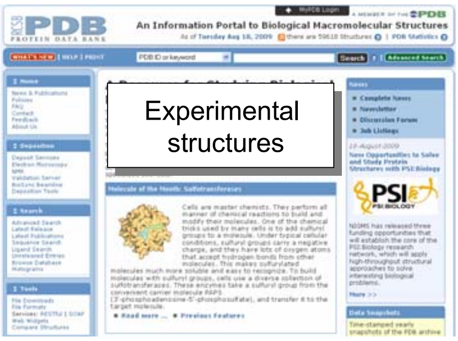
structure descriptors

determined via regression analysis (MLR, PLS)

Data:



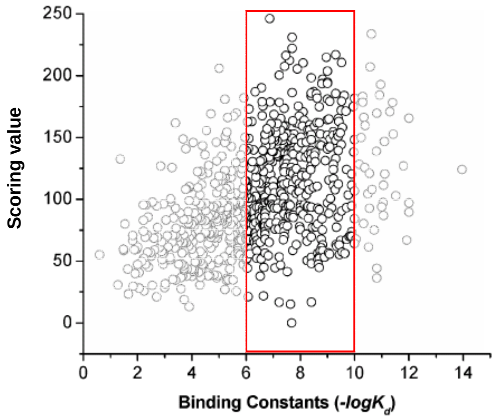
Experimental binding affinities


PDB
PROTEIN DATA BANK
An Information Portal to Biological Macromolecular Structures

Experimental structures

Where do we stand with docking & scoring?

A not too unusual result ...



Correlation with affinity for a test set of 800 known complexes:

in general,
$r < 0.55$ ($r^2 < 0.3$)

Wang et al., *J. Chem. Inf. Comp. Sci.* 44 (2004), 2114

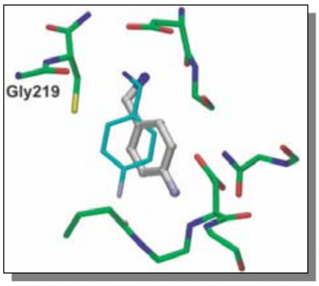
So, what is possible and what is not?

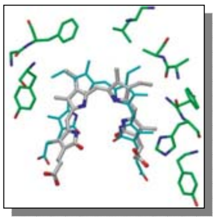
I. Docking

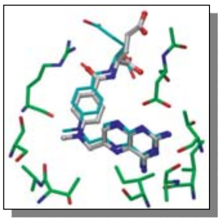
Preface: „Comparing protein-ligand docking programs is difficult“

Cole et al., *Proteins* 60 (2005), 325

- Test sets needs to be carefully selected to
  - ensure sufficient diversity
  - provide good experimental reliability
  - avoide crystal packing effects
- Consider search complexity and timings
- RMSD values can be misleading
- Tests may cover different aspects, e.g.
  - redocking
  - crossdocking
  - blind docking
  - blind predictions

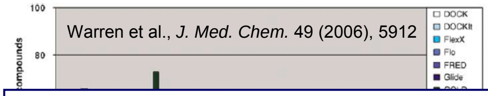






I. Docking

Comparative evaluations of docking programs



Warren et al., *J. Med. Chem.* 49 (2006), 5912

Success rate for reproducing exp. binding mode on top rank with RMSD < 2Å

Compiled by Moitessier et al., *Br. J. Pharmacol.* 153 (2008), S7

- best approaches typically around 60%
- individual success rates up to 90%
- no approach consistently best
- highly target-dependent

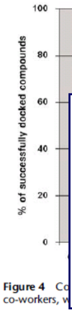


Figure 4 Co
co-workers, w

Similar general conclusions by recent studies:

- Cross et al., *J. Chem. Inf. Model.* 49 (2009), 1455 (68 complexes; DOCK, FlexX, Glide, ICM, PhDOCK, Surflex)
- Li et al., *J. Comput. Chem.* 31 (2010), 2109 (195 complexes; Glide, GOLD, LigandFit, Surflex)

I. Docking

A critical issue: Conformational flexibility!

- Complex reconstruction from **rigid binding partners**: Essentially a solved problem!

e.g.: RosettaLigand, 85 complexes (Astex diverse): 99% success rate; av. RMSD <1Å

Davis et al., *J.Mol.Biol.* 385 *(*2009), 381

- **Flexible ligand** – rigid protein docking: Standard, but not without problems

  - docking success rate drops for more flexible ligands (>7-8 rotatable bonds)
  - danger of insufficient sampling (correct conformation and pose is not generated)

- Flexible ligand – **flexible protein** docking: Active field of development

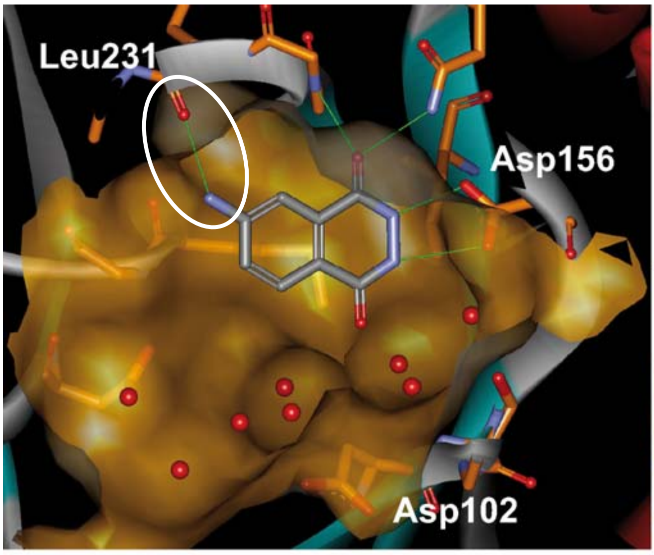
Modeling of protein flexibility:

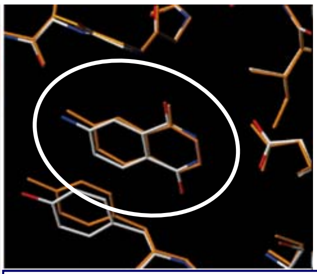
- *before* ligand placement (e.g., ensemble docking)
- *after* ligand placement (e.g., complex refinement)
- *during* ligand placement (e.g., MC/MD techniques)

⇨ But: even „simple“ conformational changes can be out of reach!

I. Docking: What is possible and what is not?

Example 1: TGT - Successful docking and ...



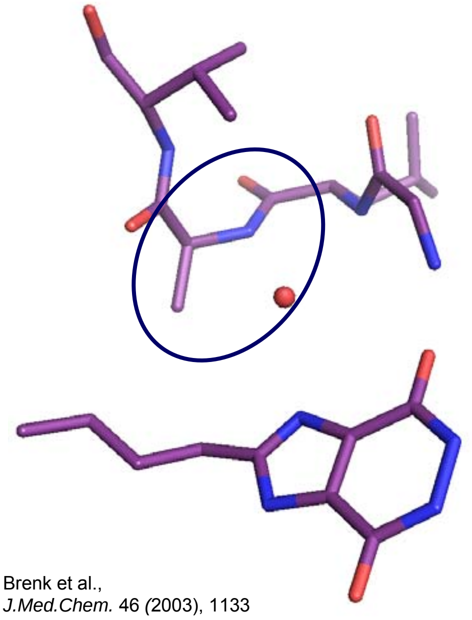


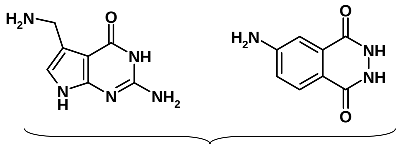
X-ray confirmed a perfect binding-mode-prediction for a new virtual-screening hit!

aus: Klebe, Wirkstoffdesign, 2. Aufl. © Spektrum Akademischer Verlag GmbH, 2009

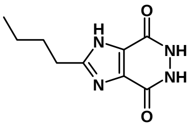
I. Docking: What is possible and what is not?

... surprises out of reach for any docking program





form H-bond with Leu231



?

Backbone flip at Leu231

and water molecule

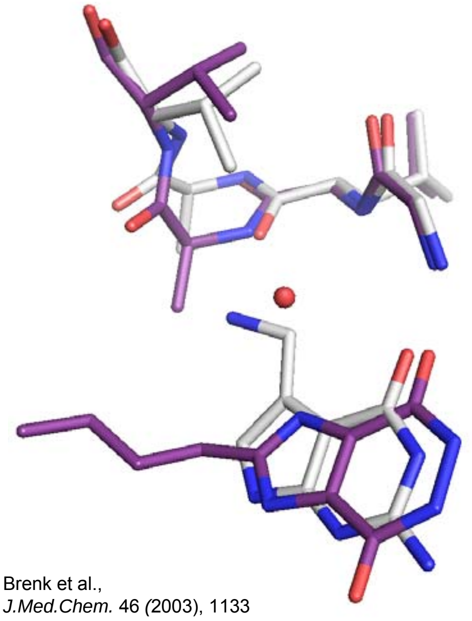
mediate formation of new

H-bond interaction!

Brenk et al.,
J.Med.Chem. 46 (2003), 1133

I. Docking: What is possible and what is not?

... surprises out of reach for any docking program



Virtually impossible to predict
with current protein-flexibility
docking approaches
(unless alternative conformation
is experimentally known in advance)

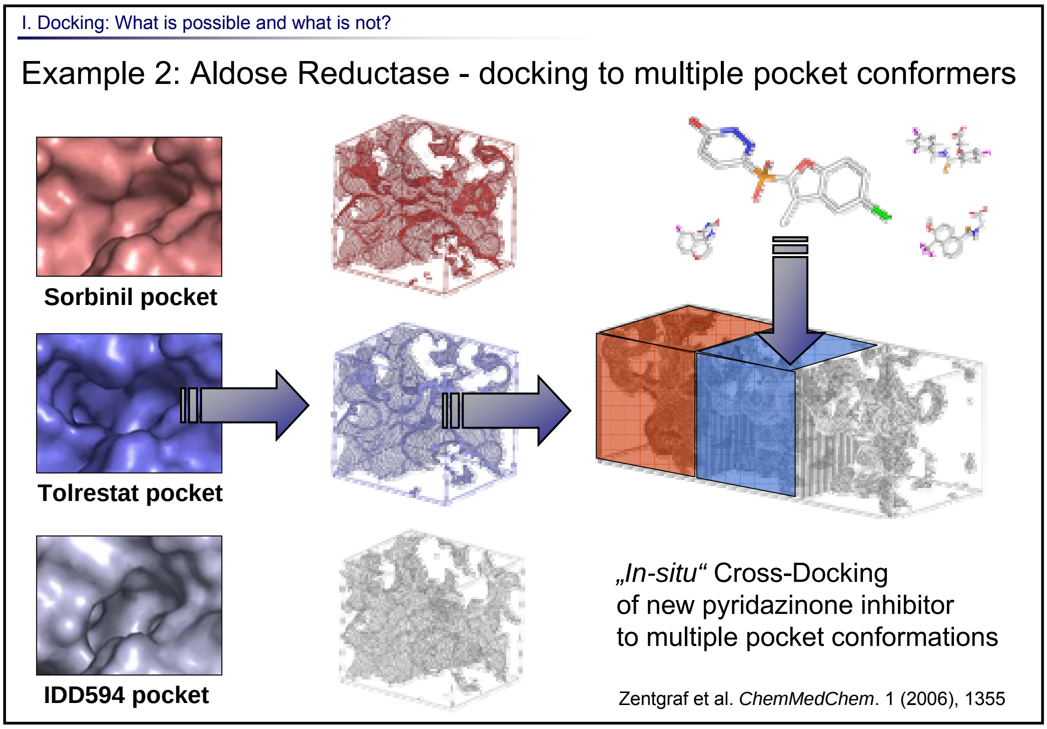
Backbone flip at Leu231

and water molecule

mediate formation of new

H-bond interaction!

Brenk et al.,
J.Med.Chem. 46 (2003), 1133



I. Docking: What is possible and what is not?

Example 2: Aldose Reductase - docking to multiple pocket conformers

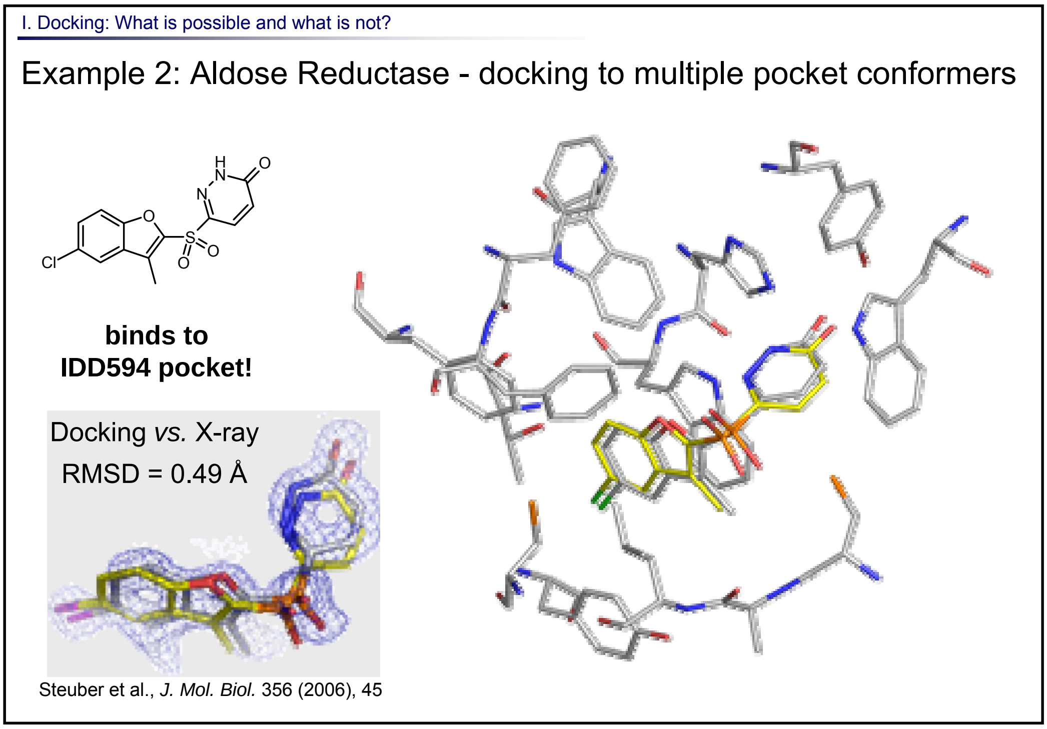
Sorbinil pocket

Tolrestat pocket

IDD594 pocket

„In-situ“ Cross-Docking
of new pyridazinone inhibitor
to multiple pocket conformations

Zentgraf et al. *ChemMedChem*. 1 (2006), 1355



I. Docking: What is possible and what is not?

Example 2: Aldose Reductase - docking to multiple pocket conformers

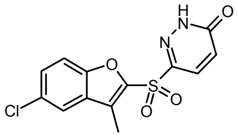
**binds to
IDD594 pocket!**

Docking *vs.* X-ray
RMSD = 0.49 Å

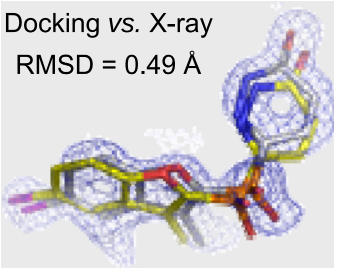
Steuber et al., *J. Mol. Biol.* 356 (2006), 45

I. Docking: What is possible and what is not?

Example 2: Aldose Reductase - docking to multiple pocket conformers



binds to IDD594 pocket!



Steuber et al., *J. Mol. Biol.* 356 (2006), 45

Reason for successful prediction:

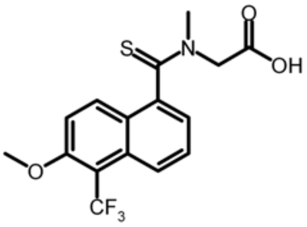
- ligand binds to protein conformer known from previous X-ray structures
- scoring function correctly scores the true binding mode much better than binding modes in alternative protein conformers

⇒ despite protein flexibility:

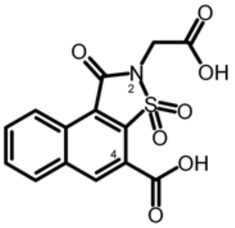
„easy task“ for common docking tools

I. Docking – Example 2: Aldose Reductase

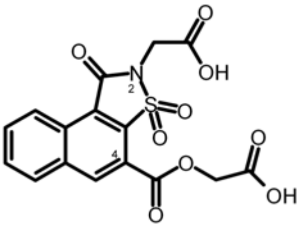
Design of new inhibitors: Tolrestat analogues



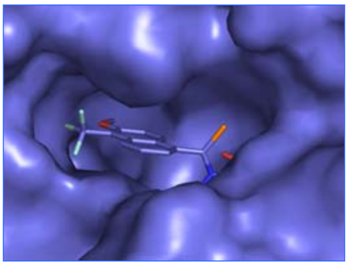
tolrestat



1

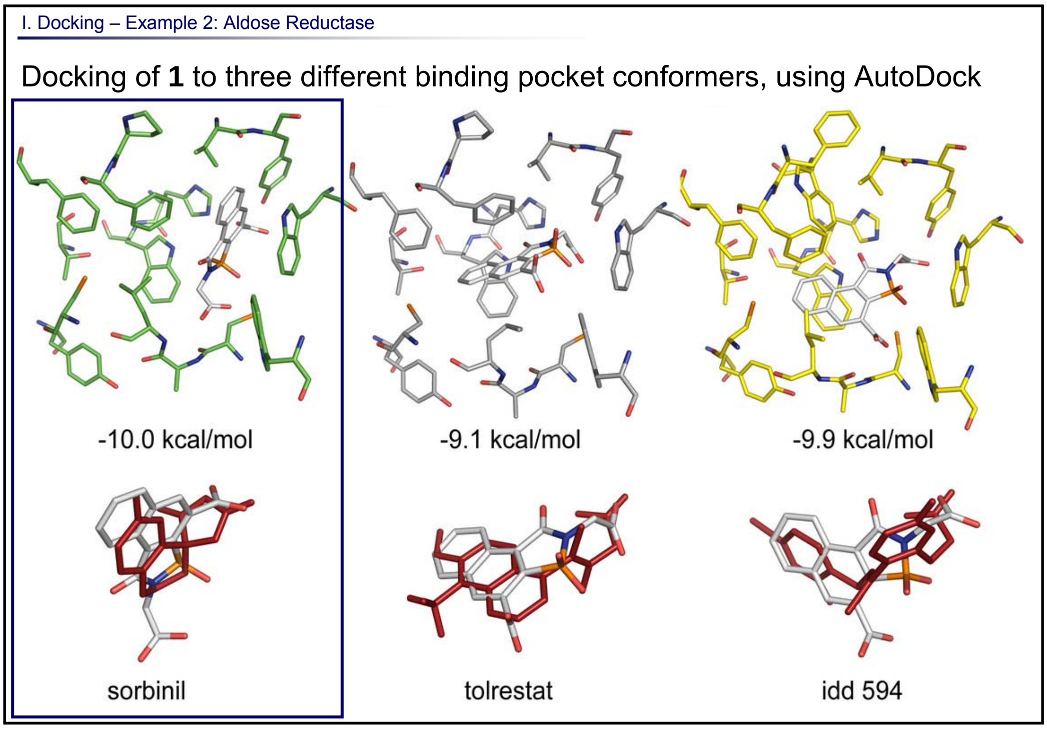


2



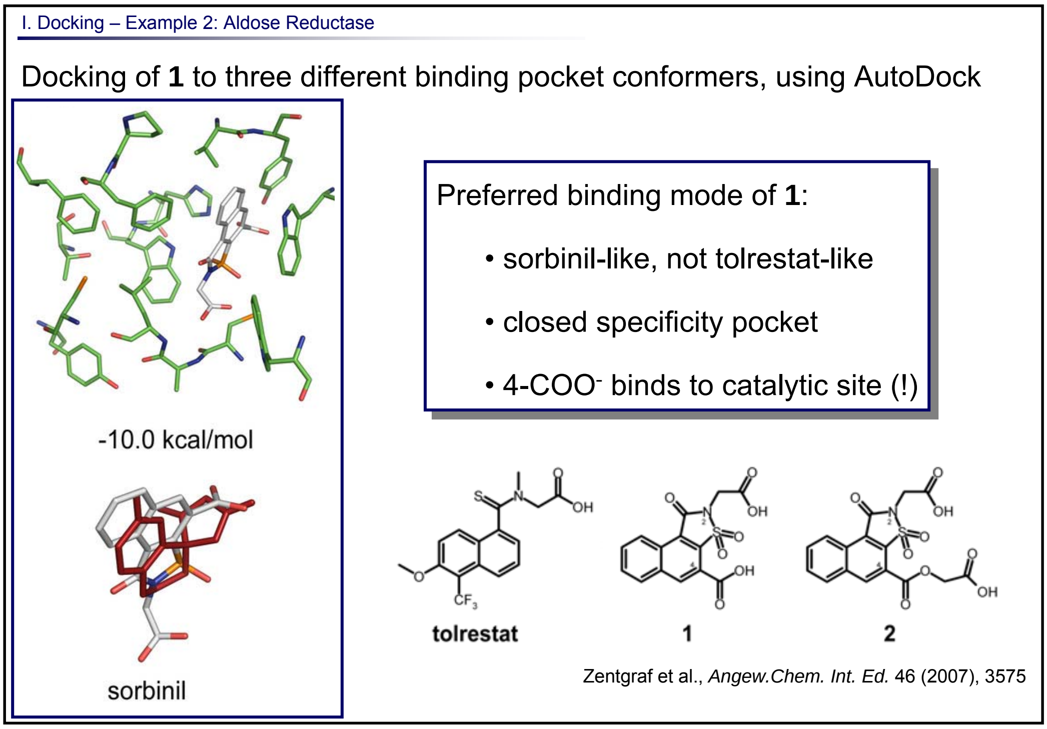
Da Settimo et al., *J. Med. Chem.* 48 (2005), 6897.
Naphtho[1,2-d]isothiazole acetic acid derivatives as a novel class of selective aldose reductase inhibitors.

Do the new compounds adopt the same binding mode as tolrestat?



I. Docking – Example 2: Aldose Reductase

Docking of **1** to three different binding pocket conformers, using AutoDock



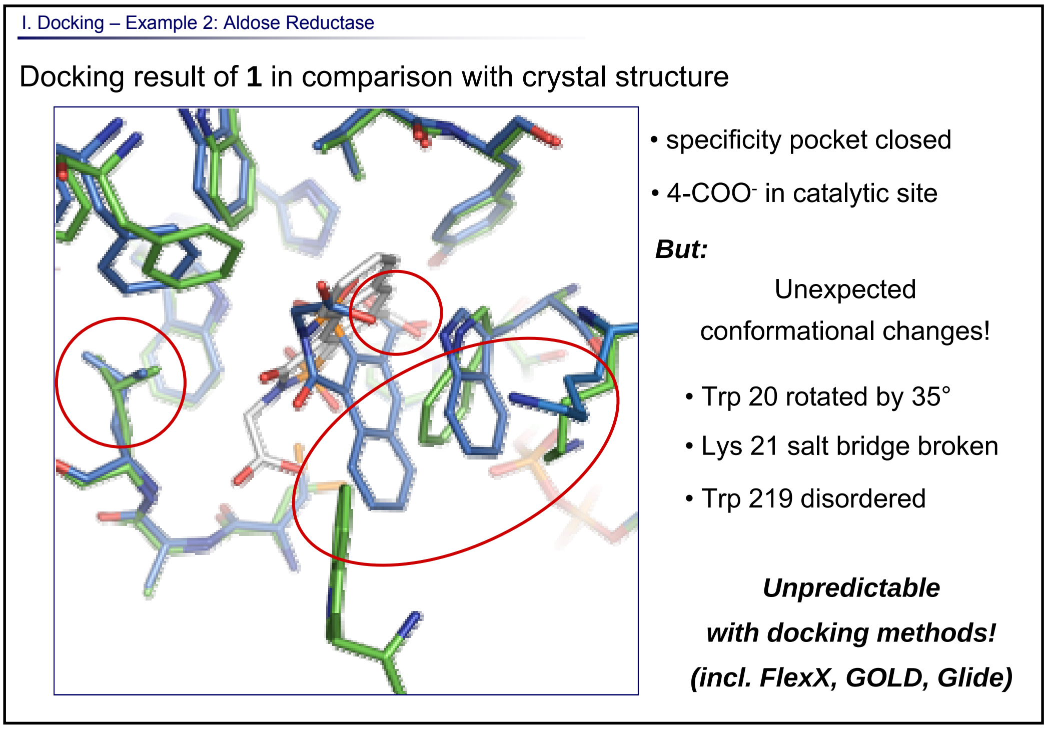
I. Docking – Example 2: Aldose Reductase

Docking of **1** to three different binding pocket conformers, using AutoDock

Preferred binding mode of **1**:

- sorbinil-like, not tolrestat-like
- closed specificity pocket
- 4-COO$^-$ binds to catalytic site (!)

Zentgraf et al., *Angew.Chem. Int. Ed.* 46 (2007), 3575



I. Docking – Example 2: Aldose Reductase

Docking result of **1** in comparison with crystal structure

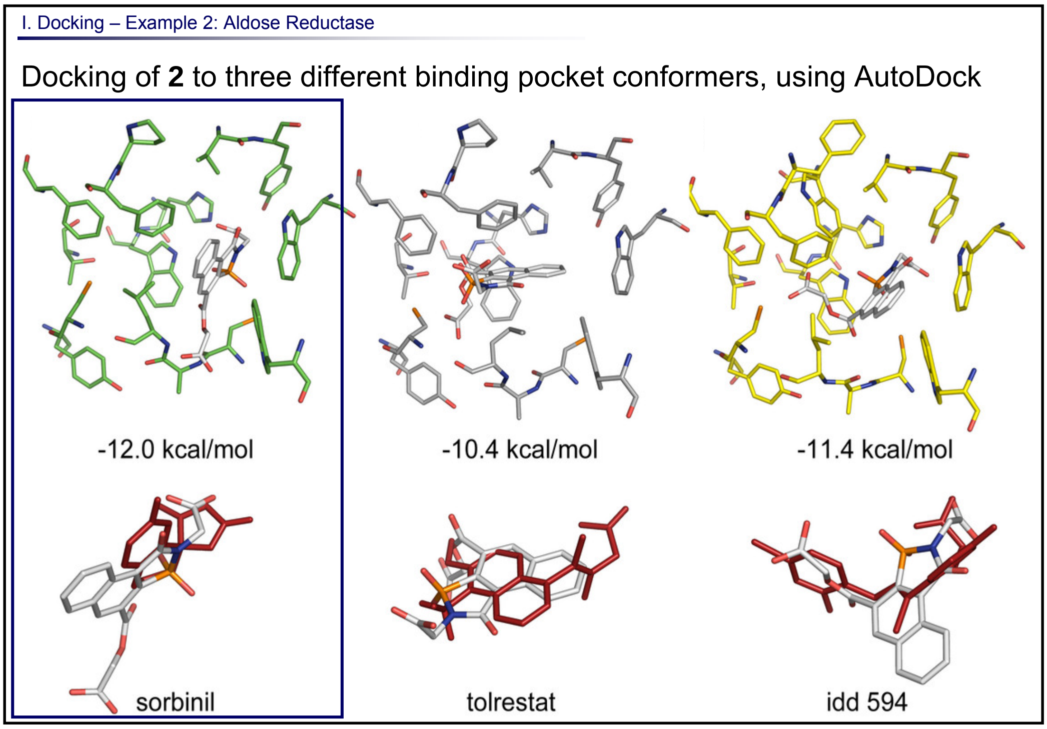
- specificity pocket closed
- 4-COO^- in catalytic site

But:

Unexpected conformational changes!

- Trp 20 rotated by 35°
- Lys 21 salt bridge broken
- Trp 219 disordered

Unpredictable with docking methods! (incl. FlexX, GOLD, Glide)



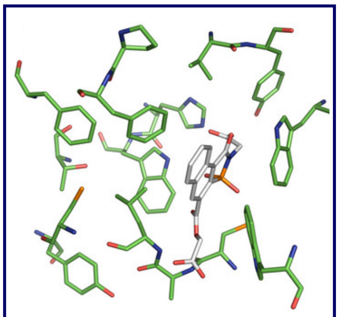
I. Docking – Example 2: Aldose Reductase

Docking of **2** to three different binding pocket conformers, using AutoDock

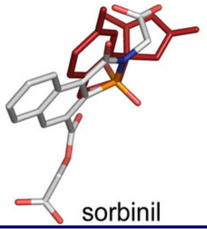
-12.0 kcal/mol	-10.4 kcal/mol	-11.4 kcal/mol
sorbinil	tolrestat	idd 594

I. Docking – Example 2: Aldose Reductase

Docking of **2** to three different binding pocket conformers, using AutoDock



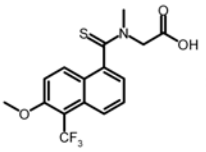
-12.0 kcal/mol



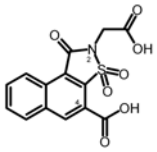
sorbinil

Preferred binding mode of **2**:

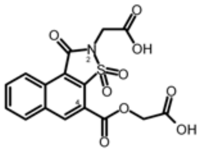
- sorbinil-like, not tolrestat-like
- closed specificity pocket
- 2-COO$^-$ binds to catalytic site



tolrestat



1

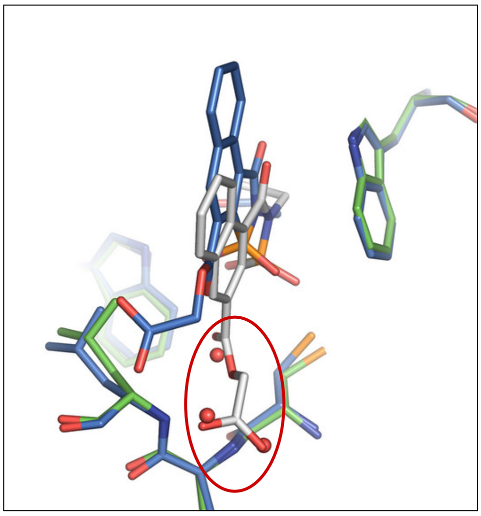


2

Zentgraf et al., *Angew.Chem. Int. Ed.* 46 (2007), 3575

I. Docking – Example 2: Aldose Reductase

Docking result of **2** in comparison with crystal structure



- specificity pocket closed
- 2-COO$^-$ in catalytic site
- no conformational changes!

But:

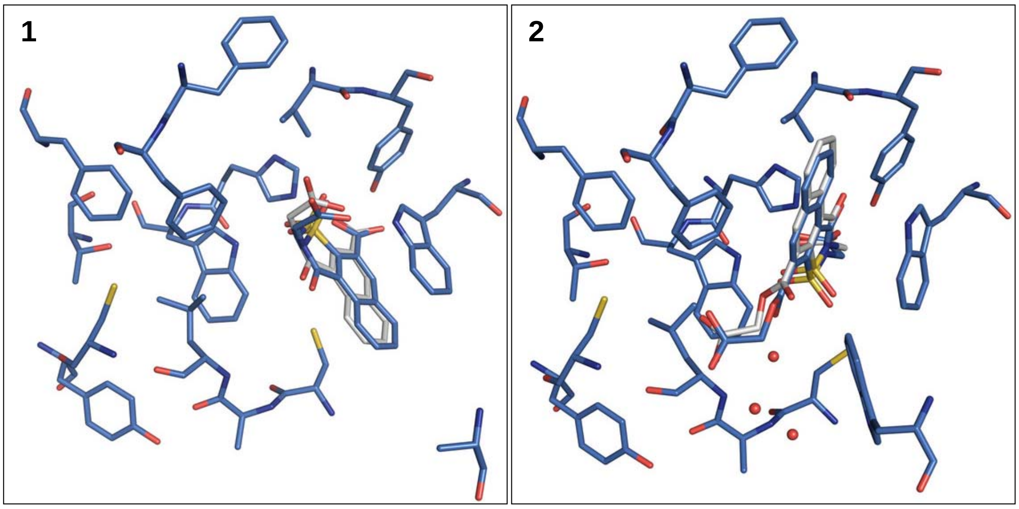
Water molecules

immobilized in binding pocket!

3 very „similar“ ligands
lead to
3 very different binding modes!

I. Docking – Example 2: Aldose Reductase

AutoDock results obtained when using the „correct“ binding-site conformer



Bindung mode exactly reproduced in both cases!

I. Docking: What is possible and what is not?

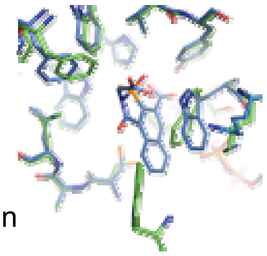
Protein flexibility and docking

<u>What´s already possible:</u>

- simultaneous docking to multiple protein conformers of arbitrary difference
- correct predictions if multiple protein conformers are known
- support by MD: generation of relevant conformers
- docking with explicit side-chain flexibility

<u>What remains a problem:</u>

- predicting: - the details
  - backbone mobility
  - large conformational changes
- fast estimate of energetic contributions from protein
- explicit consideration of full protein dynamics upon ligand binding



II. Scoring

Application tasks:

A) Identification of the correct binding mode for a given ligand

Pose prediction in docking

B) Identification of new active ligands

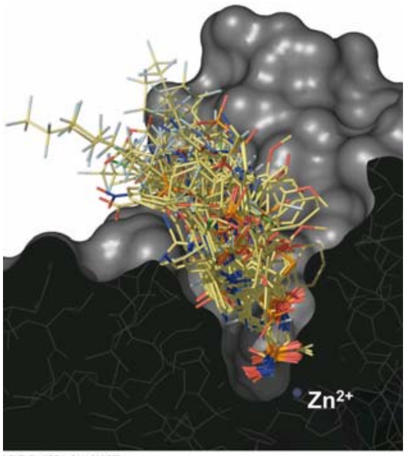
Virtual screening

C) Affinity ranking for compound series

Ligand design, lead optimization

Available approaches:

- Force field-based methods
- Knowledge-based scoring functions
- Empirical scoring functions



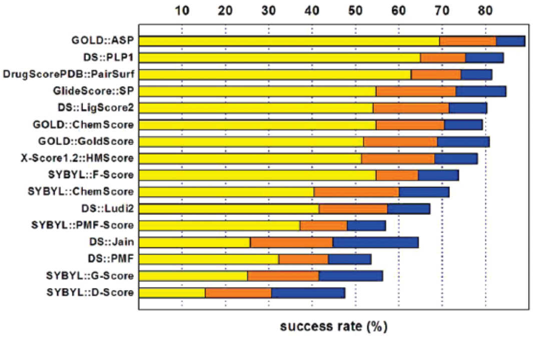
[illegible]

A) Pose prediction in docking

Identification of near-native binding pose
among a set of geometric decoys

- Test set of 195 complexes of 65 different targets
- 100 low-energy poses per complex (0-10 Å rmsd)
- 29 scoring functions tested

- **native poses can be detected fairly well**
- **success rates of up to ~80%**
- **knowledge-based approaches work best**

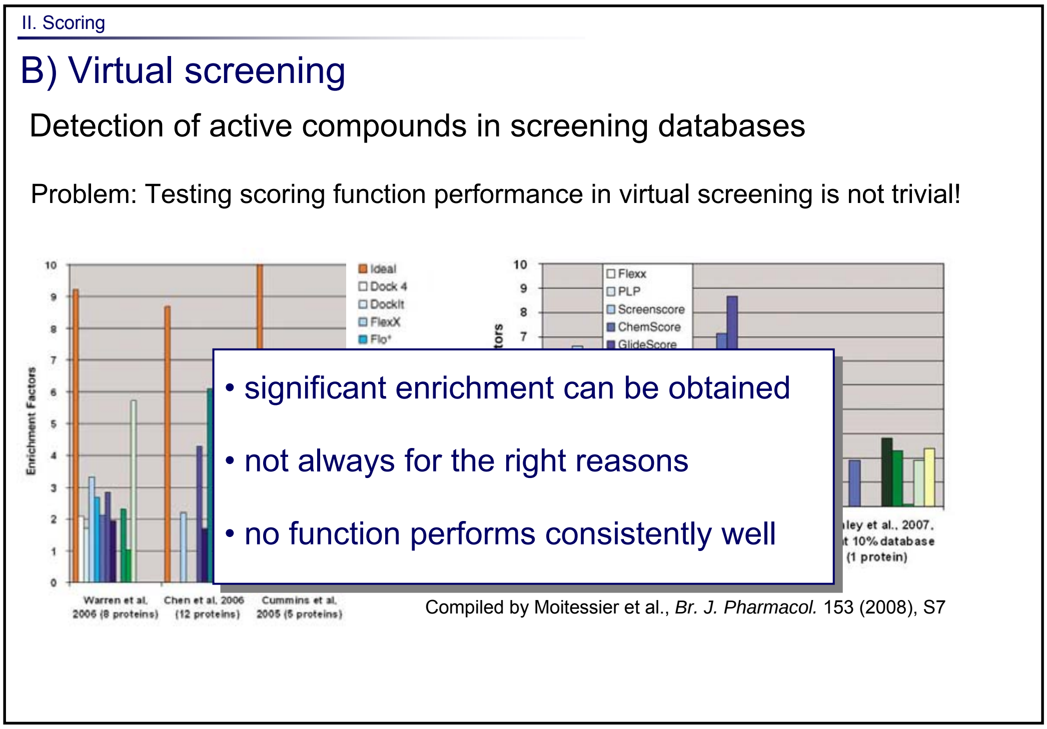


DrugScoreX^{CSD} 93%

Success rate for identifying best-scored ligand binding pose with

🟨	rmsd < 1.0 Å
🟧	rmsd < 2.0 Å
🟦	rmsd < 3.0 Å

Cheng et al., *J. Chem. Inf. Model.* 49 (2009), 1079



II. Scoring

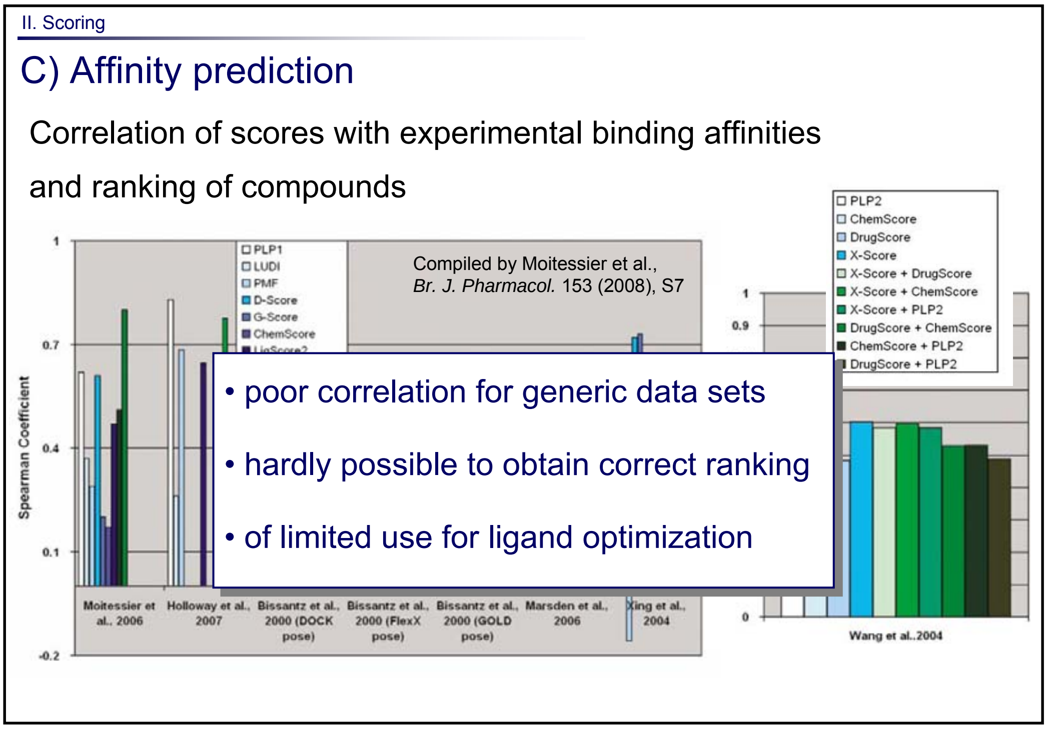
B) Virtual screening

Detection of active compounds in screening databases

Problem: Testing scoring function performance in virtual screening is not trivial!

- significant enrichment can be obtained
- not always for the right reasons
- no function performs consistently well

Compiled by Moitessier et al., *Br. J. Pharmacol.* 153 (2008), S7



II. Scoring

C) Affinity prediction

Correlation of scores with experimental binding affinities and ranking of compounds

Compiled by Moitessier et al., *Br. J. Pharmacol.* 153 (2008), S7

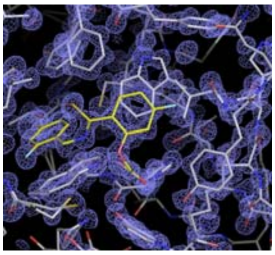
- poor correlation for generic data sets
- hardly possible to obtain correct ranking
- of limited use for ligand optimization

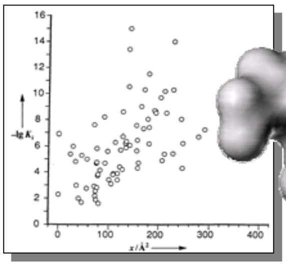
II. Scoring: What is possible and what is not?

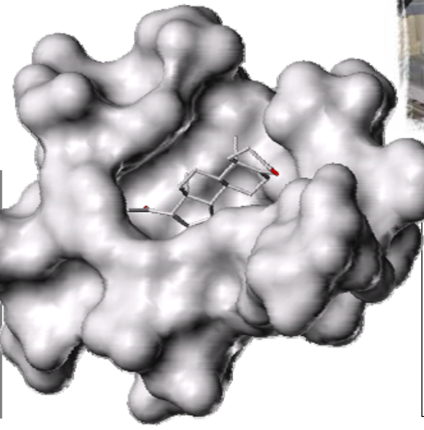
Since all methods are of empirical nature:

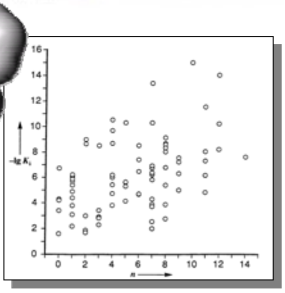
Do more and „better" experimental data

lead to better functions?









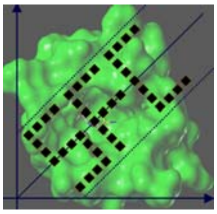
II. Scoring: What is possible and what is not?

SFCscore empirical scoring functions

SFC: Scoring Function Consortium

⇨ Data collection from public & industry sources

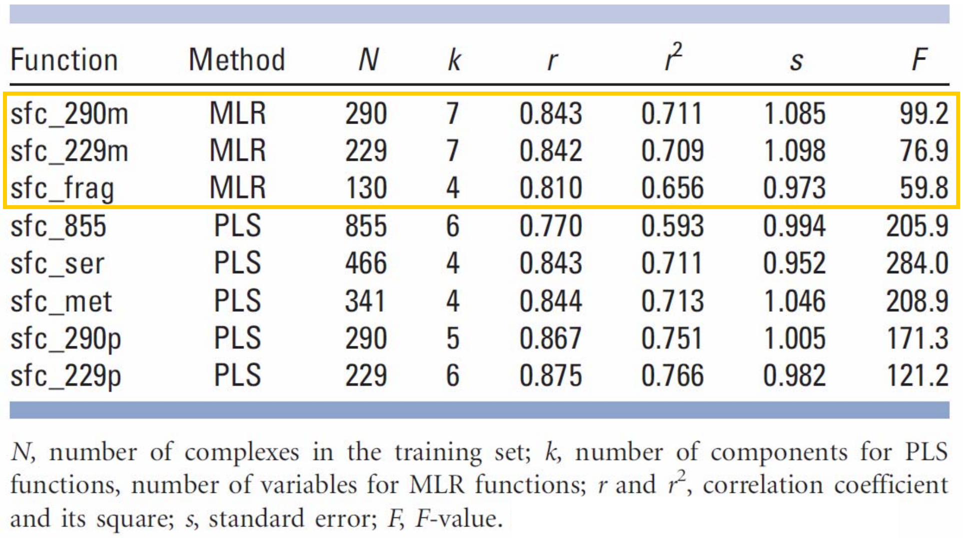
- affinity data from literature for PDB complexes
- „diversity" from PDB, SAR series from industry
- unique data format and encoding for industry data
- up to 58 complexes per target, 28 series, mostly IC_{50} (!)



⇨ Raw data in total (public + industrial):

complexes from PDB:	440	filtered: 290
complexes from industry:	618	filtered: 565
total:	1058	855

SFCscore Training sets: Regression statistics

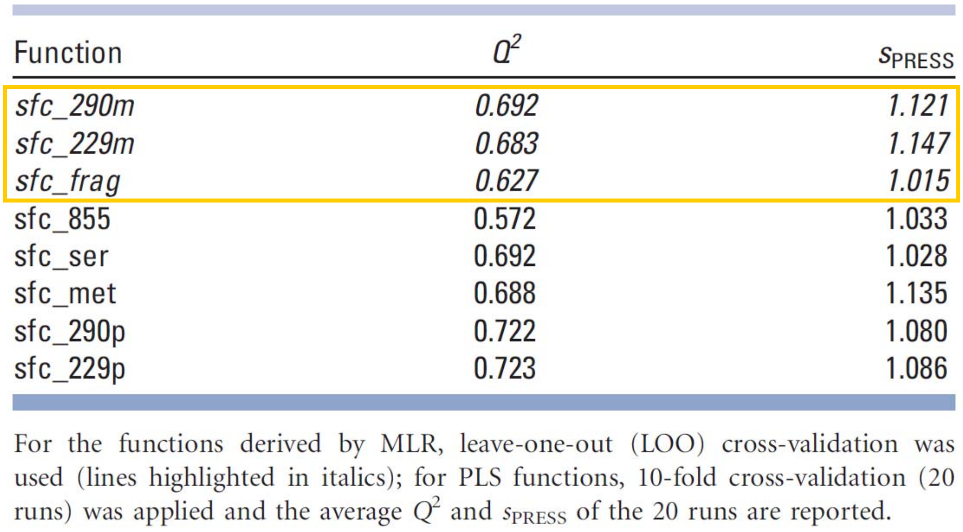


Function	Method	N	k	r	r^2	s	F
sfc_290m	MLR	290	7	0.843	0.711	1.085	99.2
sfc_229m	MLR	229	7	0.842	0.709	1.098	76.9
sfc_frag	MLR	130	4	0.810	0.656	0.973	59.8
sfc_855	PLS	855	6	0.770	0.593	0.994	205.9
sfc_ser	PLS	466	4	0.843	0.711	0.952	284.0
sfc_met	PLS	341	4	0.844	0.713	1.046	208.9
sfc_290p	PLS	290	5	0.867	0.751	1.005	171.3
sfc_229p	PLS	229	6	0.875	0.766	0.982	121.2

N, number of complexes in the training set; *k*, number of components for PLS functions, number of variables for MLR functions; *r* and r^2, correlation coefficient and its square; *s*, standard error; *F*, *F*-value.

Sotriffer et al., *Proteins* 73 (2008), 395

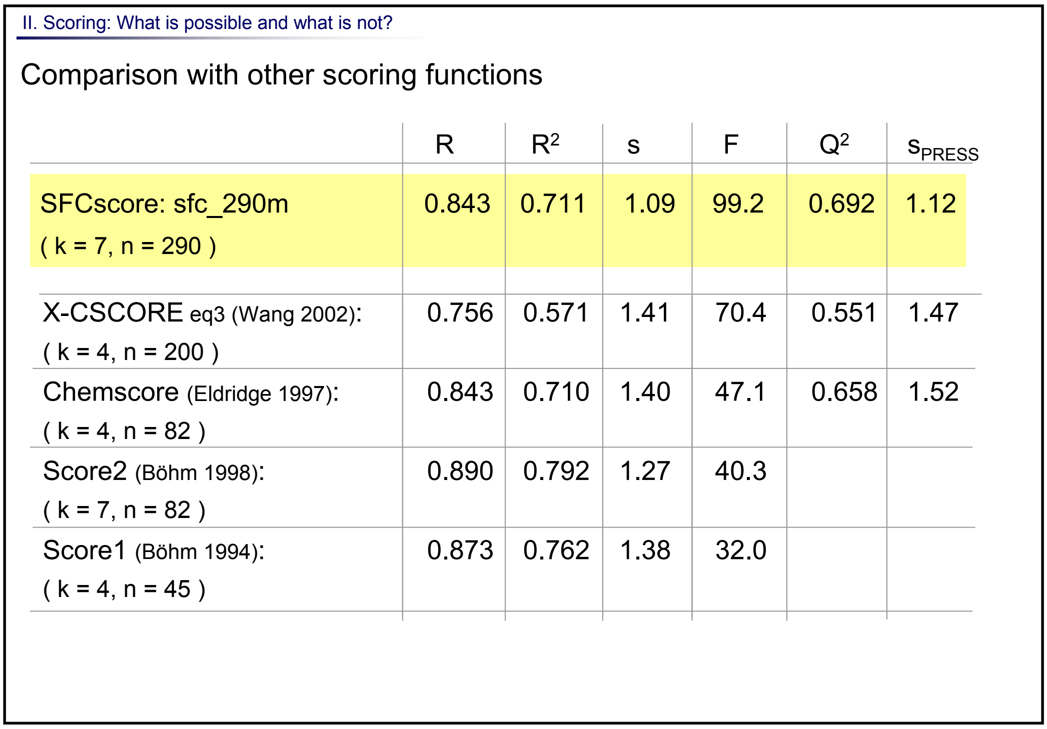
SFCscore Training sets: Internal cross validation



Function	Q^2	s_{PRESS}
sfc_290m	*0.692*	*1.121*
sfc_229m	*0.683*	*1.147*
sfc_frag	*0.627*	*1.015*
sfc_855	0.572	1.033
sfc_ser	0.692	1.028
sfc_met	0.688	1.135
sfc_290p	0.722	1.080
sfc_229p	0.723	1.086

For the functions derived by MLR, leave-one-out (LOO) cross-validation was used (lines highlighted in italics); for PLS functions, 10-fold cross-validation (20 runs) was applied and the average Q^2 and s_{PRESS} of the 20 runs are reported.

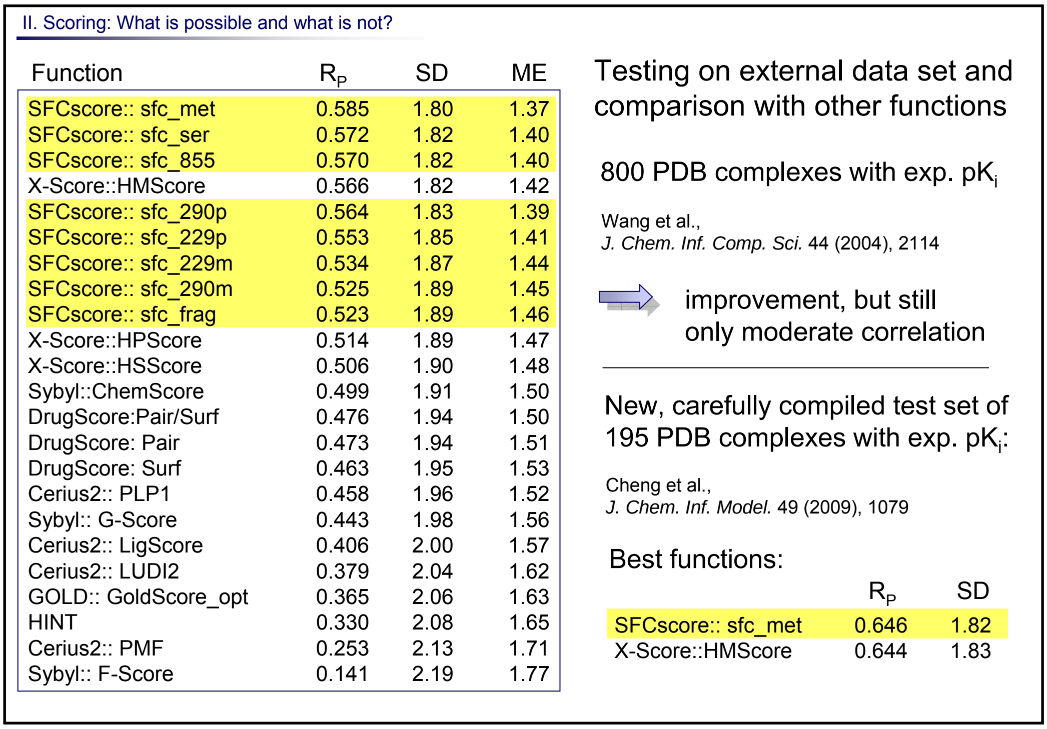
Sotriffer et al., *Proteins* 73 (2008), 395



II. Scoring: What is possible and what is not?

Comparison with other scoring functions

	R	R^2	s	F	Q^2	s_{PRESS}
SFCscore: sfc_290m (k = 7, n = 290)	0.843	0.711	1.09	99.2	0.692	1.12
X-CSCORE eq3 (Wang 2002): (k = 4, n = 200)	0.756	0.571	1.41	70.4	0.551	1.47
Chemscore (Eldridge 1997): (k = 4, n = 82)	0.843	0.710	1.40	47.1	0.658	1.52
Score2 (Böhm 1998): (k = 7, n = 82)	0.890	0.792	1.27	40.3		
Score1 (Böhm 1994): (k = 4, n = 45)	0.873	0.762	1.38	32.0		



II. Scoring: What is possible and what is not?

Function	R_P	SD	ME
SFCscore:: sfc_met	0.585	1.80	1.37
SFCscore:: sfc_ser	0.572	1.82	1.40
SFCscore:: sfc_855	0.570	1.82	1.40
X-Score::HMScore	0.566	1.82	1.42
SFCscore:: sfc_290p	0.564	1.83	1.39
SFCscore:: sfc_229p	0.553	1.85	1.41
SFCscore:: sfc_229m	0.534	1.87	1.44
SFCscore:: sfc_290m	0.525	1.89	1.45
SFCscore:: sfc_frag	0.523	1.89	1.46
X-Score::HPScore	0.514	1.89	1.47
X-Score::HSScore	0.506	1.90	1.48
Sybyl::ChemScore	0.499	1.91	1.50
DrugScore:Pair/Surf	0.476	1.94	1.50
DrugScore: Pair	0.473	1.94	1.51
DrugScore: Surf	0.463	1.95	1.53
Cerius2:: PLP1	0.458	1.96	1.52
Sybyl:: G-Score	0.443	1.98	1.56
Cerius2:: LigScore	0.406	2.00	1.57
Cerius2:: LUDI2	0.379	2.04	1.62
GOLD:: GoldScore_opt	0.365	2.06	1.63
HINT	0.330	2.08	1.65
Cerius2:: PMF	0.253	2.13	1.71
Sybyl:: F-Score	0.141	2.19	1.77

Testing on external data set and comparison with other functions

800 PDB complexes with exp. pK_i

Wang et al.,
J. Chem. Inf. Comp. Sci. 44 (2004), 2114

⇨ improvement, but still only moderate correlation

New, carefully compiled test set of 195 PDB complexes with exp. pK_i:

Cheng et al.,
J. Chem. Inf. Model. 49 (2009), 1079

Best functions:

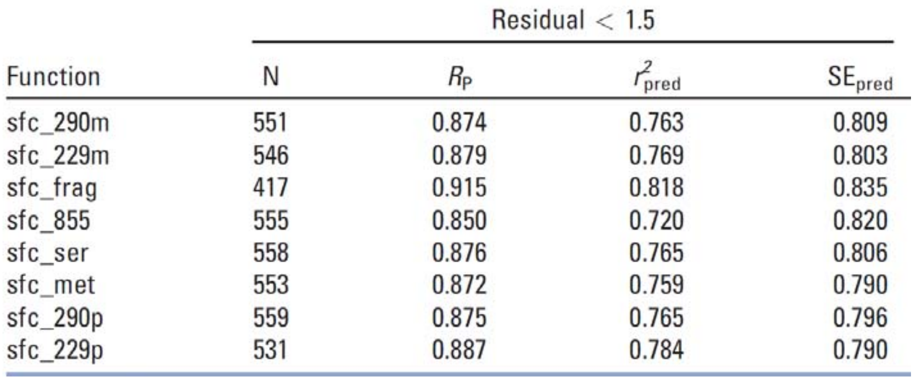
	R_P	SD
SFCscore:: sfc_met	0.646	1.82
X-Score::HMScore	0.644	1.83

II. Scoring: What is possible and what is not?

Why did many functions in the past appear more successful than they are?

⇨ Very small external test sets of limited diversity

cf. how many of the now available complexes are well predicted by SFCscore!



	Residual < 1.5			
Function	N	R_P	r^2_{pred}	SE_{pred}
sfc_290m	551	0.874	0.763	0.809
sfc_229m	546	0.879	0.769	0.803
sfc_frag	417	0.915	0.818	0.835
sfc_855	555	0.850	0.720	0.820
sfc_ser	558	0.876	0.765	0.806
sfc_met	553	0.872	0.759	0.790
sfc_290p	559	0.875	0.765	0.796
sfc_229p	531	0.887	0.784	0.790

⇨ CAVE with any conclusions derived from too small test sets!

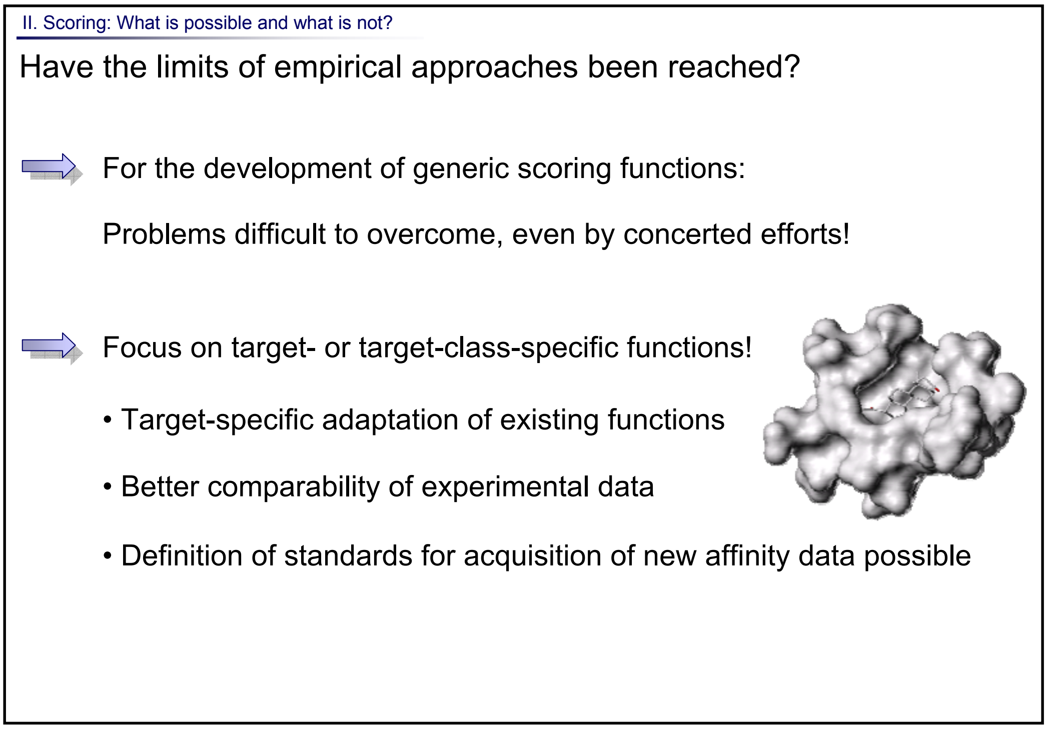
II. Scoring: What is possible and what is not?

Have the limits of empirical approaches been reached?

⇨ Consider quality and comparability of experimental data!

- Structural data (mainly X-ray) of protein-ligand complexes
  - multiple conformations (highly dynamic systems)
  - hydrogen atom positions (protonation states) not observable
  - side-chain orientation may be ambiguous (Asn, Gln, His)
  - water molecules are only partially observable
  - binding modes may depend on crystallization conditions and crystal packing
- Affinity data of protein-ligand complexes
  - may highly depend on pH, buffer, salt concentration, temperature
  - enyzme kinetics: inhibition mechanism must be known
  - $IC_{50} \leftrightarrow K_i \leftrightarrow K_d$

Knowledge-based and empirical scoring methods cannot be better than the exp. data they are based on!



II. Scoring: What is possible and what is not?

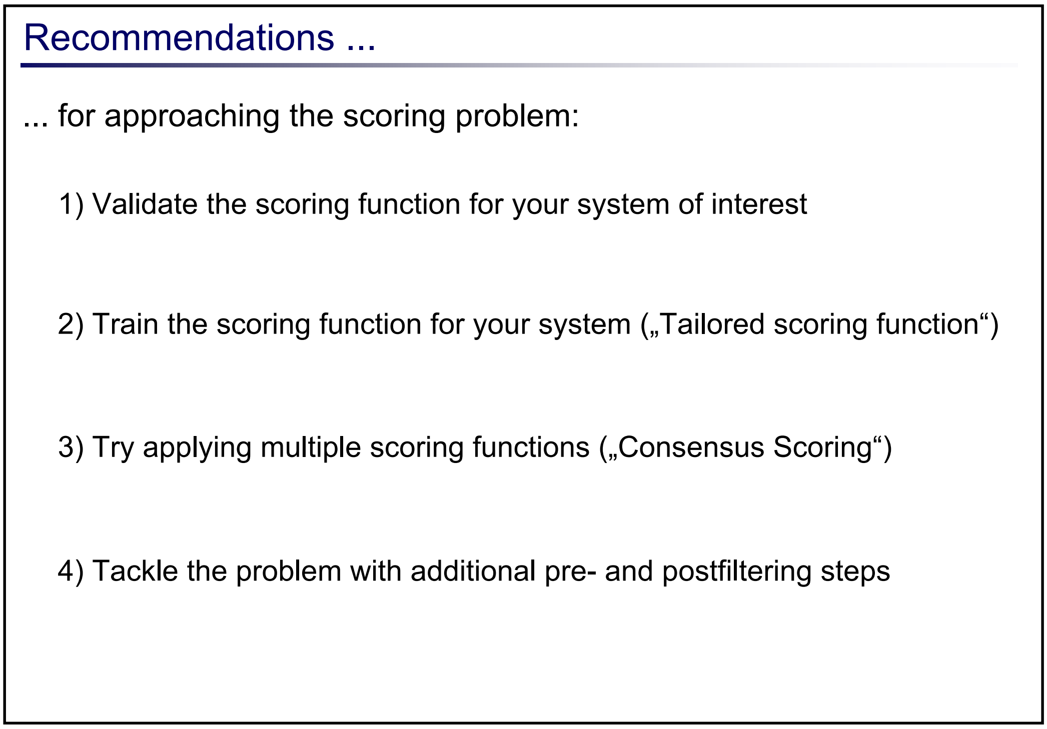
Have the limits of empirical approaches been reached?

⇨ For the development of generic scoring functions:

Problems difficult to overcome, even by concerted efforts!

⇨ Focus on target- or target-class-specific functions!

- Target-specific adaptation of existing functions
- Better comparability of experimental data
- Definition of standards for acquisition of new affinity data possible



Recommendations ...

... for approaching the scoring problem:

1) Validate the scoring function for your system of interest

2) Train the scoring function for your system („Tailored scoring function“)

3) Try applying multiple scoring functions („Consensus Scoring“)

4) Tackle the problem with additional pre- and postfiltering steps

Further developments required ...

... to overcome the most serious simplifications in scoring functions:

„Flexibility – Water – Entropy“

- single configuration of the binding partners in the complex
- no consideration of the unbound state
- no or simplified consideration of the solvent
- focused on enthalpic contributions and interaction descriptors
- additivity of interaction terms

A single model may not be sufficient to capture
the complex interplay of
residual mobility, desolvation, and interaction quality in protein-ligand complexes!

The wrong conclusion ...

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Scoring
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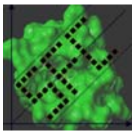

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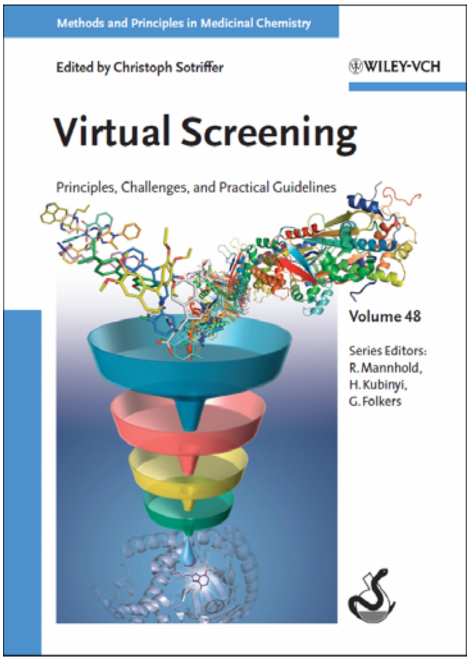

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Principles, Challenges, and Practical Guidelines

Volume 48

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