Modeling of Flexible Side Chains for Protein-Ligand Docking

Promotionskolloquium von
Christoph Hartmann
Overview

- Background
- Publications
- ROTA scoring function
  - Derivation procedure
  - Results
- Side-chain prediction tool IRECS
  - Model and Algorithm
  - Results
- Applications
  - Virtual Screening with Side-Chain Flexibility
  - Mutation Analysis
- Conclusions
Example: HCV NS3 protease
- Essential for viral reproduction
- Important drug target
- PDB IDs and ligands (drugs):
  - 1RTL, Pyrrolidine-5,5-translactam
  - 2FM2, SCH5446211
  - 2OC8, SCH505034

Structural comparison shows
- rigid backbone
- same active site
- similar binding mode of similar groups
- flexible side chains

Similar observations:
- Aldose reductase
- Neuraminidase
- Glutocorticoid receptor
- ...
Background: Structural Biology
Relevance of side-chain flexibility for ligand binding

- Example: HCV NS3 protease
  - Essential for viral reproduction
  - Important drug target
  - PDB IDs and ligands (drugs):
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  - ...

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Other reasons for limitation on side-chain flexibility

- Real life examples of wrong homology models are hard to retrieve
- Discrete side-chain conformations can be enumerated and systematically sampled => enables representative simulation
- About every 6\textsuperscript{th} side chain has a wrong conformation in a homology model\textsuperscript{1,2} => insufficient for docking
- FlexE is more capable of handling side-chain flexibility than of handling backbone flexibility\textsuperscript{3}

Publications

- 1st Poster Price at the *Drug Discovery Workshop in Marburg*, 2007


The ROTA Scoring Function

- Tasks of ROTA\textsuperscript{1,2}:
  - Identify wrong side-chain rotamers
  - Predict binding affinity
  - Filter false ligand poses

- Features:
  - Knowledge-based scoring function
  - Soft potentials of mean force\textsuperscript{3}
  - Trained to tolerate modelled side chains

- Derivation procedure:
  - Define atom types
  - Generate representative structure set
  - Generate native-like models
  - Generate decoy models
  - Count all distances between atoms pairs
  - Derive potentials of mean force

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Proteins
- amino acid type + atom name

Ligands
- mol2 atom types
- hybridization state
- # connected hydrogen atoms

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40,000 X-ray structures of proteins

4,778 X-ray structures of protein-ligand complexes
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  - Define atom types
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  - Generate *native-like* models
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  - Derive potentials of mean force
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- Identify wrong side-chain rotamers
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Features:
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Derivation procedure:
- Define atom types
- Generate representative structure set
- Generate native-like models
- Generate decoy models
- Count all distances between atom pairs
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Probability density function of Glu-OE1 and Lys-NZ in native and decoy models
The ROTA Scoring Function

- **Tasks of ROTA:**
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- **Inverse Boltzmann law applied to both probability functions**

\[ S_{ab}^{ROTA}(d) = -kT \ln \frac{P_{ab}^{\text{native}}(d)}{P_{ab}^{\text{decoy}}(d)} \]

- **Constant penalty (4 kJ/mol) if one probability gets zero**

ROTA score

ROTA potential for Glu-OE1 and Lys-NZ
Rota Results: Ranking docking solutions

![Bar chart showing the number of complexes where a native-like ligand was ranked on top for various scoring methods. The methods include DrugScore CSD, ITScore, Cerius2/PLP, SYBYL/F-Score, Cerius2/LigScore, DrugScorePDB, Lennard Jones 12-6, Cerius2/LUDI, ROTA, X-score, AutoDock, DFIRE, Cerius2/PMF, SYBYLG-Score, SYBYL/ChemScore, SYBYL/D-Score.]

Rota Results: Prediction of binding affinity

Rank correlation coefficient

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8

ROTA
X-score
ITScore
DFIRE
DrugScoreCSD
Cerius2/PLP
DrugScorePD B
SYBYL/G-Score
SYBYL/D-Score
SYBYL/ChemScore
Cerius2/LUDI
DOCK/FF
Cerius2/PMF
Cerius2/LigScore
SYBYL/F-Score
AutoDock
The Side-Chain Prediction Tool IRECS

- Tasks of IRECS¹:
  - Predict conformations of side chains
  - Predict side chain flexibility
  - Generate point mutations

- Features:
  - Uses ROTA, BBDep² rotamer library
  - Fast heuristic algorithm
  - Was motivated by the mean field approach³
  - Interface to FlexE⁴
  - Interface to Dynacell

Download IRECS and ROTA at http://irecs.bioinf.mpi-inf.mpg.de/

The IRECS Algorithm

Example: Human cycline-dependent kinase, 1CKP
The IRECS Algorithm

- Full Conformational Space
- Update Probability
- Update Effective Energy
- Find Most Determined Side chain
- Remove Worst Rotamer

Backbone Dependent Rotamer Library

Lysine
Tyrosine
The IRECS Algorithm

- Full Conformational Space
- Update Probability
- Update Effective Energy
- Find Most Determined Side chain
- Remove Worst Rotamer
The IRECS Algorithm

\[ E_{\text{eff}}(x_i) = U_{\text{self}}(x_i) + U_{\text{inter}}(x_i, b) + \sum_{j=1, j \neq i}^{S} \sum_{y_j}^{C_j} p(y_j) U_{\text{inter}}(x_i, y_j) \]
The IRECS Algorithm

Full Conformational Space
Update Probability
Update Effective Energy
Find Most Determined Side chain
Remove Worst Rotamer

Range: 0.8
-1.1
-1.3
-1.1
-0.8
-0.7
-0.5

Range: 5.3
-3.2
-2.8
+2.1

Range: 5.3
-3.2
-2.8
+2.1

Range: 0.8
-1.1
-1.3
-1.1
-0.8
-0.7
-0.5
The IRECS Algorithm

Full Conformational Space
Update Probability
Update Effective Energy
Find Most Determined Side chain
Remove Worst Rotamer
The IRECS Algorithm

- Full Conformational Space
- Update Probability
- Update Effective Energy
- Find Most Determined Side chain
- Remove Worst Rotamer

Iteration until user interrupt or one rotamer per side chain is left
Results: Prediction of rigid side chains

<table>
<thead>
<tr>
<th></th>
<th>$\chi_1$ [%]</th>
<th>$\chi_{1+2}$ [%]</th>
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<tbody>
<tr>
<td></td>
<td>all</td>
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<tr>
<td>SCWRL¹</td>
<td>82.3</td>
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<tr>
<td>SCA P²</td>
<td>84.0</td>
<td>91.0</td>
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<tr>
<td>IRECS³</td>
<td>84.7</td>
<td>92.6</td>
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# Results: Prediction of flexible side chains

<table>
<thead>
<tr>
<th>X-ray structure:</th>
<th>![Image 1]</th>
<th>![Image 2]</th>
<th>![Image 3]</th>
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<tbody>
<tr>
<td>2 rotamers</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>2 rotamers on average</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 rotamer</td>
<td>![Image 7]</td>
<td>![Image 8]</td>
<td>![Image 9]</td>
</tr>
<tr>
<td>2 rotamers</td>
<td>![Image 10]</td>
<td>![Image 11]</td>
<td>![Image 12]</td>
</tr>
<tr>
<td>more than 2 rotamers</td>
<td>![Image 13]</td>
<td>![Image 14]</td>
<td>![Image 15]</td>
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<table>
<thead>
<tr>
<th>hit rate $\chi_{1+2}$ [%]</th>
<th>1 hit: 85.1%</th>
<th>1 hit: 93.4%</th>
<th>1 hit: 93.2%</th>
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<tr>
<td></td>
<td>2 hits: 54.7%</td>
<td>2 hits: 64.5%</td>
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Application: Docking with Side-Chain Flexibility

X-ray structures
- backbone & ligands

IRECS
- build full rotamer ensembles
- reduce rotamers ensembles

protein models with rotamer density
- 1, 2 or 3

FlexX^2/FlexE^3
- base fragment placement
- complex construction
- scoring: F-Score or ROTA

compounds (ligand/decoys)

active/inactive classification

binding free energy estimations

Screening
- ranking

enrichment factors


Virtual Screening with Flexible Side Chains

$$EF_{\text{subset}} = \frac{|\text{ligands} \cap \text{subset}|}{|\text{subset}|} \times \frac{|\text{ligands}|}{|\text{compounds}|}$$

<table>
<thead>
<tr>
<th>Model source</th>
<th>Rotamer density</th>
<th>$\varnothing$ Side-chain RMSD [Å]</th>
<th>Program</th>
<th>Scoring Function</th>
<th>Enrichment Factor $&gt;$</th>
<th>Runtime per ligand [s]</th>
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<tr>
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<td>F-Score</td>
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<td>187.0</td>
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Virtual Screening with Flexible Side Chains

ROTA does not improve docking much when using X-ray structures …

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<td>ROTA</td>
<td>48</td>
<td>41</td>
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Virtual Screening with Flexible Side Chains

... but ROTA performs much better than F-Score on IRECS models ...

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<td>29</td>
<td>157.0</td>
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... docking into flexible IRECS models is as good as docking into X-ray structures ...

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<td>23 27 25 10 4 2 2</td>
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Promotionskolloquium Christoph Hartmann
Virtual Screening with Flexible Side Chains

...an average number of two rotamers per side chain is usually sufficient for docking

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</table>
Clinical trial revealed resistance mutations during treatment with telepravir\textsuperscript{1}

Observed resistance mutations of HCV protease NS3-4A: $V_{36}$ to G, M, A and L


Conclusions

- ROTA is less useful for ranking docking solutions
- ... but is especially useful for predicting binding affinity

- Usage of IRECS is unnecessary if a high quality X-ray structure of the target protein is available AND the binding pocket is rigid
- IRECS is not capable of modeling induced fit-effects that also affect the backbone
- ... but IRECS can support virtual screening if side chains are
  - flexible (surface areas, binding pocket) or
  - their conformation is unknown (e.g. mutations)

- Accuracy of side-chain prediction and binding affinity estimation is still low and there is much room for improvement
- Conformational ensembles for side-chains are still rarely used

„Essentially, all models are wrong, but some are useful.“
by Georg E. P. Box, Professor of Statistics at the University of Wisconsin
Acknowledgement

Max-Planck-Institut für Informatik
- Thomas Lengauer
- Iris Antes
- Joachim Büch
- Ruth Schneppen-Christmann
- my group

Universität des Saarlandes
- Hans-Peter Lenhof
- Thorsten Herfet

BioSolveIT
- Christian Lemmen
- Holger Claußen
- Markus Gastreich

University of California, San Francisco
- Brian Shoichet
- John Irwin
Acknowledgement

Thank you for your attention