A Pose Prediction Approach based on Ligand 3D Shape Similarity: Lessons learned in D3R challenge

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Ligand 3D shape similarity has been routinely used as sole virtual screening approach or in combination with other structure based methods such as molecular docking.

Other utilities in drug discovery include use as ligand scoring approach.
PoPSS: Pose Prediction using Shape Similarity in D3R GC1

Ligand Conformations

Crystal Ligands

Shape similarity matching

Placement and Refinement

HSP90

MAP4K4

Protein Number of submissions Mean RMSD (Å) Median RMSD (Å) Mean RMSD Rank Median RMSD Rank

HSP90 42 Top 1.02 0.73 2 4

Best of 5 0.99 0.68 4 5

MAP4K4 27 Top 4.04 2.87 3 3

Best of 5 2.09 1.62 1 1

# ligands
HSP90 = 6
MAP4K4 = 30
What did we learn in D3R GC1

- Selection of right receptor conformation is very important in accurately predicting binding poses
- Receptor conformation suitable for one chemotype may not be suitable for others

Predicted pose scored using Chemgauss4 scoring function
- Scoring performance was very bad
- Random

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>HSP90</th>
<th>MAP4K4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson</td>
<td>0.16</td>
<td>0.05</td>
</tr>
<tr>
<td>Kendall Tau</td>
<td>0.10</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Available shape similarity correlates with pose prediction performance
- Poses can be reliably predicted if maximum available shape similarity is more than 1.4 TanimotoCombo

Crystal (green) v/s Predicted (magenta) v/s template (cyan)

- No ligand sampling after placing the conformation
- No rewards for forming good interactions
- No penalties for bad interactions
Cross-docking based virtual screening pipeline (CDVS)

- Evaluated in D3R Grand Challenge 2
- Involved prediction of poses and potency of farnesoid X receptor (FXR) ligands.
- Stage 1: Pose prediction for 36 ligands (FXR-1-FXR-36)
- Stage 1: Affinity prediction or ranking for 102 FXR ligands
- Stage 2: Affinity prediction or ranking for 102 FXR ligands utilizing crystal information from stage 1
Cross-docking based virtual screening pipeline (CDVS) in D3R

**Median RMSD**
- 1.19 Å
- 1.07 Å
- 1.00 Å

**Mean RMSD**
- Top pose: 2.92 Å
- Best of 5 pose: 2.09 Å

**Tanimoto Combo**
- 1.00
- 1.25
- 1.50
- 1.75
Cross-docking based virtual screening pipeline (CDVS): Virtual screening performance

<table>
<thead>
<tr>
<th>Scores</th>
<th>D3R GC2 Phase 1 value</th>
<th>D3R GC2 Phase 1 Rank/Participating groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95 % confidence interval) (%)</td>
<td>81.3 (72.3 – 90.4)</td>
<td>4/57</td>
</tr>
<tr>
<td>Spearman’s rho (ρ) (standard error)</td>
<td>0.59 (0.07)</td>
<td>8/57</td>
</tr>
<tr>
<td>Kendall’s tau (τ) (standard error)</td>
<td>0.40 (0.05)</td>
<td>8/57</td>
</tr>
</tbody>
</table>

(A) ROC curve showing sensitivity and specificity with AUC = 81.3 %

(B) Scatter plot of docking scores against pIC50 with Spearman’s ρ = 0.59
What did we learn in D3R Grand Challenge 2

Comparison with multiple receptor docking methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Median RMSD (Å)</th>
<th>AUC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDVS</td>
<td>1.19</td>
<td>81.3</td>
</tr>
<tr>
<td>Single-receptor docking</td>
<td>4.11</td>
<td>66.1</td>
</tr>
<tr>
<td>Multiple-receptor docking (subset of receptors)</td>
<td>3.54</td>
<td>68.4</td>
</tr>
<tr>
<td>Multiple-receptor docking (all receptors)</td>
<td>1.75</td>
<td>76.3</td>
</tr>
</tbody>
</table>

Receptor selection method

Median RMSD = 1.0
Mean RMSD = 2.09

FXR-18: Shape align (cyan) v/s template (green)

AUC ROCS sel. = 81.3 %
AUC Molprint2D sel. = 72.8 %
D3R Grand Challenge 3

➢ Mega challenge

➢ Five subchallenge
  • Cathepsin S: Subchallenge 1, Pose prediction, ranking, FEP
  • VEGFR2
  • JAK2 SC2
  • P38-α
  • JAK2 SC3: Subchallenge 3, Ranking, activity cliff
  • TIE2: Subchallenge 4, Ranking, activity cliff
  • ABL1: Subchallenge 5, Effect of mutation on binding affinities

➢ Subchallenge 1
  • Cathepsin S
  • Pose prediction, ranking and FEP
  • Dataset: 26 crystal structures, 136 compound affinities
  • Pose prediction of 24 compounds and affinity prediction or ranking of 136 compounds
Pose Prediction methods used in D3R Grand Challenge 3

Ligand Conformations

Crystal Ligands

Shape similarity matching

Receptor-ligand pair selection

Standard docking

Energy minimization

Sidechain repacking and MC minimization

PoPSS

PoPSS-Lite

CDVS

Placement and Refinement
Pose prediction performance (PoPSS)

- A maximum of 1000 conformations per ligand
- RefTverskyCombo coefficient
- Rest same as D3R GC1

CatS-24 predicted (magenta) v/s template (cyan)
CatS-24 predicted (magenta) v/s crystal (green)
Pose prediction performance (CDVS)

<table>
<thead>
<tr>
<th></th>
<th>Best</th>
<th>Best of 3</th>
<th>Best of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.14</td>
<td>3.13</td>
<td>3.13</td>
</tr>
<tr>
<td>Median</td>
<td>2.31</td>
<td>2.35</td>
<td>2.35</td>
</tr>
</tbody>
</table>

CatS-24 predicted (magenta) v/s crystal (green)

CatS-24 template (cyan) v/s crystal (green)

RefTverskyCombo: 1.1, 1.3, 1.5

RMSD (Å)

CatS-11 aligned (cyan) v/s crystal (green)

CatS-11 predicted (magenta) v/s crystal (green)
Pose prediction performance (PoPSS-Lite)

<table>
<thead>
<tr>
<th>Improved/Deteriotated</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>14/24</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>10/24</td>
</tr>
<tr>
<td>Improved by 0.5 Å RMSD</td>
<td>7/24</td>
</tr>
<tr>
<td>Deteriorated by 0.5 RMSD</td>
<td>3/24</td>
</tr>
</tbody>
</table>

PoPSS-Lite mean RMSD = 2.39 Å
PoPSS-Lite median RMSD = 2.05 Å
## Comparison of three methods in D3R GC3

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean RMSD (Å)</th>
<th>Median RMSD (Å)</th>
<th>Average number of atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PoPSS</td>
<td>2.60</td>
<td>2.61</td>
<td>89.25</td>
</tr>
<tr>
<td>CDVS</td>
<td>3.14</td>
<td>2.31</td>
<td></td>
</tr>
<tr>
<td>PoPSS-Lite</td>
<td>2.39</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>D3R 2015 (HSP90)</td>
<td>1.02</td>
<td>0.73</td>
<td>30.33</td>
</tr>
<tr>
<td>D3R 2015 (MAP4K4)</td>
<td>4.04</td>
<td>2.87</td>
<td>36.83</td>
</tr>
<tr>
<td>D3R 2016 (FXR)</td>
<td>2.92</td>
<td>1.19</td>
<td>63.97</td>
</tr>
</tbody>
</table>

**PoPSS**

- Poses can be predicted with relative accuracy
- Method generates several poses that are ranked by scoring function
- Occasionally, pose closest to native structure was not the top scoring one

**CDVS**

- Scoring/Ranking performance is better
- Ligand 3D shape similarity is only used in suitable receptor selection

**PoPSS-Lite**

- Poses can be predicted with relative accuracy
- Only one pose per ligand, so no scoring problem
Pose prediction comparison in D3R GC3

Mean RMSD (Å)

CDVS
PoPSS
PoPSS-Lite

Median RMSD (Å)

PoPSS
CDVS
PoPSS-Lite
Summary and lessons learned for future D3R

- Ligand 3D shape similarity can be successfully employed to improve pose prediction performance.
- Shape similarity based receptor selection has advantages over 2D similarity based receptor selection.
- Current implementation requires at least one suitable co-crystal ligand. Future development will explore the ligands from homologous proteins and homologous protein pockets to improve pose prediction.
- Generation of ligand conformations is critical for success and needs improvement as some bioactive conformation could not be generated.
- Scoring performance of PoPSS and PoPSS-Lite needs improvement.
Thank you for your attention

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