MD Simulation in Pose Refinement and Scoring Using AMBER Workflows

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D3R Grand Challenge 2 Webinar
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Merck Research Laboratories, Merck & Co., Inc.
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Outline

► Overview of the D3R Predictions from Merck
  • Today just the Stage 1 results
  • Merck Team & Result Ranking

► Overall Pose Prediction and Scoring Approach
  • Structure Preparation & Docking
  • AMBER Workflows for Pose Refinement & Ranking

► Case Study & Lessons Learned
  • Ranking with Ensemble-based MD-MMGBSA
  • Pose Exploration with MD
Acknowledgement
Merck D3R Team

► Modeling
– Ying-Duo Gao
– Xavier Fradera
– Yuan Hu
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– Hongwu Wang
– James Fells
– Kira Armacost
– Alejandro Crespo
– Brad Sherborne

► Informatics
– Huijun Wang
– Zhengwei Peng
– Robert Sheridan

Motivation
➢ To refine and share our best practices
➢ To be engaged in the scientific community
➢ To better understand the capability of sciences in industry & academia
Overall Approach for Stage 1

Step 1: preparation as a team

102 D3R dataset

Literature search
Data mining from PDB and CHEMBL

Structure Preparation
Schrodinger’s ligprep/prepwizard
(Protomer/Tautomer, fill missing loop)
Overall Approach for Stage 1

Step 1: preparation as a team

- Literature search
  - Data mining from PDB and CHEMBL

Step 2: docking experiments

- Glide Ensemble Docking
  - Submission A
- Colony Entropy Docking
  - Submission B
- Glide+Gold Docking
  - Submission C
- Visual Inspection (A+C)
  - Submission E

Structure Preparation
- Schrodinger’s ligprep/prepwizard
  - (Protomer/Tautomer, fill missing loop)

102 D3R dataset
Overall Approach for Stage 1

Step 1: preparation as a team
- 102 D3R dataset

Step 2: docking experiments
- Glide Ensemble Docking Submission A
- Colony Entropy Docking Submission B
- Glide+Gold Docking Submission C
- Visual Inspection (A+C) Submission E

Step 3: MD-MMGBSA
- MD simulations using multiple replicates
- MD pose refinement Submission D
- Ensemble-based MMGBSA ranking
Overall Approach for Stage 1

Step 1: preparation as a team

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- Glide Ensemble Docking Submission A
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Step 3: MD-MMGBSA

- Can MD be used to refine docking pose?
- How does MD-MMGBSA perform in ranking?

- MD simulations using multiple replicates
- MD pose refinement Submission D
- Ensemble-based MMGBSA ranking
Overall conclusion: MD improves pose prediction and ranking

Mean RMSD of Top Scoring Poses

Kendalls Tau (Stage 1-Ligand Scoring)

* n=36
Overall conclusion: MD improves pose prediction and ranking

Mean RMSD of Top Scoring Poses

Kendalls Tau (Stage 1-Ligand Scoring)

* n=36
Glide Ensemble Docking & AMBER workflows
Completely automated

Ensemble Docking

Ligand/Protein Structure Preparation
- Glide XP Ensemble Docking
  36 ligands x 40 templates = 1,440

Glide Ensemble Docking

Pose selection
- Rank by score
- rmsd >= 1.0 Å to previously selected pose to ensure diversity

Top Scoring Pose

*Workflow was validated before on 40 native ligands

AMBER MD-MMGBSA workflows

Docking Pose
- Equilibration
- Replicates
  - rep1
  - rep2
  - rep3
  - rep4
  - ...

Equilibration
- MMGBSA

Pose selection
- Rank by score
- rmsd >= 1.0 Å to previously selected pose to ensure diversity

Top Scoring Pose

*Workflow was validated in large data sets.

Glide Ensemble Docking & AMBER workflows
Completely automated

**Ensemble Docking**

- Ligand/Protein Structure Preparation
- Glide XP Ensemble Docking 36 ligands x 40 templates = 1,440
- Pose selection
  - Rank by score
  - rmsd >= 1.0 Å to previously selected pose to ensure diversity
- Top Scoring Pose

**AMBER MD-MMGBSA workflows**

- Docking Pose
- Equilibration
- rep1, rep2, rep3, rep4, ...
- Equil
- Prod
- MMGBSA

**Molecular Mechanics/Generalized Born Surface Area (MM/GBSA)**
Free Energy Workflow with Replicates

- Model System
- Protein Structure (pdb)
- Ligand Structures (mol2)
- Prep
  - Protein Preparation
  - Force Field
  - Ligand Preparation
- Process
  - Equilibration Time (ns)
- Replica Equilibration Time (ns)
- Replica Production Time (ns)
- MMGBSA Setting
- AMBER 14
- Job Name
- Email Job Notification

**CRAY:** 7h
**GPU:** 3h
10-15 cmpds/day

*Workflow was validated before on 40 native ligands*

*Workflow was validated in large data sets.*

Y. Hu, B. Sherborne, Z. Guo. “How to Obtain Reliable and Reproducible MMGBSA Results?” manuscript in preparation.
Glide Ensemble Docking & AMBER workflows
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**Ensemble Docking**

- Ligand/Protein Structure Preparation
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- Pose selection
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- Top Scoring Pose

**AMBER MD-MMGBSA workflows**

- Docking Pose
- Equilibration
  - rep1
  - rep2
  - rep3
  - rep4
  - ...
  - Equi
  - Equi
  - Equi
  - Equi
  - ...
  - Prod
  - Prod
  - Prod
  - Prod
  - ...
  - MMGBSA
  - MMGBSA
  - MMGBSA
  - MMGBSA
  - ...

**Pose Selection**

- Structure of the lowest free energy snapshot
- Average structure of the lowest 10% free energy snapshots scored by MMGBSA
- Average structure of the lowest 10% VDW snapshots scored by MMGBSA
- Average structure of the highest 10% ELEC snapshots scored by MMGBSA
- Highest population cluster generated by using structural similarity

*Workflow was validated before on 40 native ligands
Y. Hu, B. Sherborne, Z. Guo. “How to Obtain Reliable and Reproducible MMGBSA Results?” manuscript in preparation.
Good template is important for docking...

Similarity matters

2D Similarity of closest template ligand in ensemble of complexes
(descriptor: ECFP6)
Good template is important for docking…

Similarity matters

Docking Pose RMSD to X-ray Crystal (Å)

Size by activity
Red: Activity > 1 μM
Green: Activity <= 1 μM

2D Similarity of closest template ligand in ensemble of complexes
(descriptor: ECFP6)
Good template is important for docking…

Similarity matters

Docking Pose RMSD to X-ray Crystal (Å)

Similarity < 0.5
Less templates
More inactive

Similarity <= 0.5
More templates
More active

Similarity > 0.5
More templates
More active

2D Similarity of closest template ligand in ensemble of complexes
(descriptor: ECFP6)
Question 1

Can MD be used to refine docking pose?
**Pose refinement with MD**

- **Pose maintained**
- **Pose improved**
- **Pose no help**

<table>
<thead>
<tr>
<th>RMSD to X-ray Crystal (Å)</th>
<th>ΔRMSD &gt; 0.5 Å</th>
<th>ΔRMSD &lt; -0.5 Å</th>
<th>-0.5 &lt; ΔRMSD &lt; 0.5 Å</th>
</tr>
</thead>
</table>

**Docking Pose RMSD to X-ray Crystal (Å)**
Case Study-success: FXR_3
Ligand interactions optimized through MD

- Ligand moves to create stable H-bond

Crystal Structure  Docking Pose  MD refinement
RMSD 2.00 Å  RMSD 0.92 Å
Case Study-success: FXR_3
Ligand interactions optimized through MD
Case Study-success: FXR_10
Protein optimized through MD

- MD reorients the Asn to make H-bond contact

Crystal Structure
Docking Pose
RMSD 2.26 Å

MD refinement
RMSD 1.41 Å
Case Study-success: FXR_10
Protein optimized through MD

- MD reorients the Asn to make H-bond contact

Crystal Structure
Docking Pose
RMSD 2.26 Å

MD refinement
RMSD 1.41 Å
Case Study-success: FXR_10
Protein optimized through MD
Case Study-failure: FXR_15
MD workflow can’t rescue reversed pose

- The docked pose has a reverse direction comparing to x-ray
- Hard to refine the structure with MD…

Crystal Structure
Docking Pose
RMSD 8.83 Å
MD refinement
RMSD 9.37 Å
Case Study-failure: FXR_15
MD workflow can’t rescue reversed pose
Case Study-failure: FXR_18
MD workflow can’t address very large protein movements

► Protein conformation change

Crystal Structure
Docking Template
Protein RMSD 2.59 Å

Ligand RMSD to X-ray
Docking: 9.36 Å
MD: 10.32 Å

Chain opened up in template

MD refinement
Case Study-failure: FXR_18
MD workflow can’t address very large protein movements
Lesson learned from previous D3R challenge:
“Explicit solvent free energy methods have not yet outperformed faster scoring methods in blinded protein-ligand affinity predictions.”
-D3R website (Posted October 11, 2016)
https://drugdesigndata.org/about/what-we-have-learned

Question 2
How does MD-MMGBSA perform in ligand scoring?
**MD-MMGBSA improves on docking scores**

### Docking Methods

<table>
<thead>
<tr>
<th>Docking Method</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glide Ensemble Docking</td>
<td>0.324</td>
</tr>
<tr>
<td>A: Glide Ensemble Docking</td>
<td>0.324</td>
</tr>
<tr>
<td>C: X-score Docking</td>
<td>0.243</td>
</tr>
<tr>
<td>B: Gold ChemScore</td>
<td>0.126</td>
</tr>
<tr>
<td>D: MD-MMGBSA</td>
<td>0.361</td>
</tr>
</tbody>
</table>

**Stage 1: 36 cmpds**

**binding pocket is deep inside challenge data set for implicit model (MMGBSA)**
Summary

▶ Lessons
- Ensemble docking performs well in pose prediction & ranking, if there are suitably close protein complexes available
- MD maintains or refines docking poses (protein and ligand) and extends the limit of prediction
  - MD can’t refine challenging poses
- Ensemble-based MD-MMGBSA ranking improves on docking scores
- Teamwork broke the challenge down to manageable portions

▶ Next
- AMBER MD-MMGBSA to AMBER TI
- CPU to GPU

Thank You!
Pose exploration with MD

Multiple studies show that the low energy snapshots correlate with best pose prediction.

*average energy of the 10 lowest energy snapshots for each trajectory of 22 MD simulations differed by the initial position.
