Induced-Fit Posing in Orion®

CUP XXII | March 14th, 2023

Hyesu Jang

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Drug Discovery Process before Pre-clinical Studies

Target Validation	Lead ID	Lead Optimization

orion®

All Floes / Packages / OpenEye MD Affinity Floes

Generative modeling

Filtering, Clustering Force Field Refinement

Short Trajectory MD with Analysis [MDPrep] [MDRun] [MDAnalysis]

Perform MD simulations given a prepared protein and a set of posed and prepared ligands, running both bound and unbound simulations of each ligand, then analyze the trajectory for pose stability.

Light, Fast MD Screening: MMPBSA; BintScore
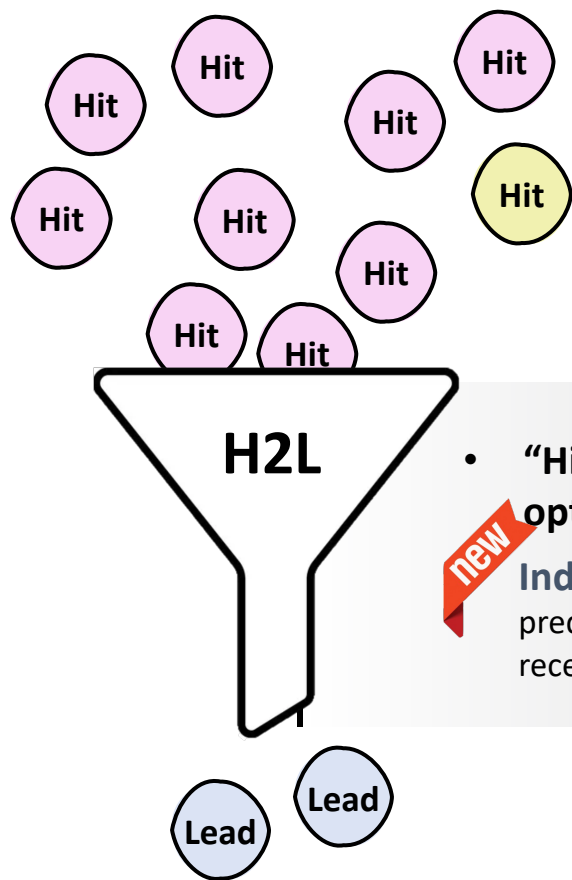
RBFE: Nonequilibrium Switching

Non-Equilibrium Switching [MDRun] [FECalc]

Perform relative binding free energy (RBFE) calculations using the nonequilibrium switching (NES) method.

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Hit to Lead (H2L) and Induced-Fit Posing
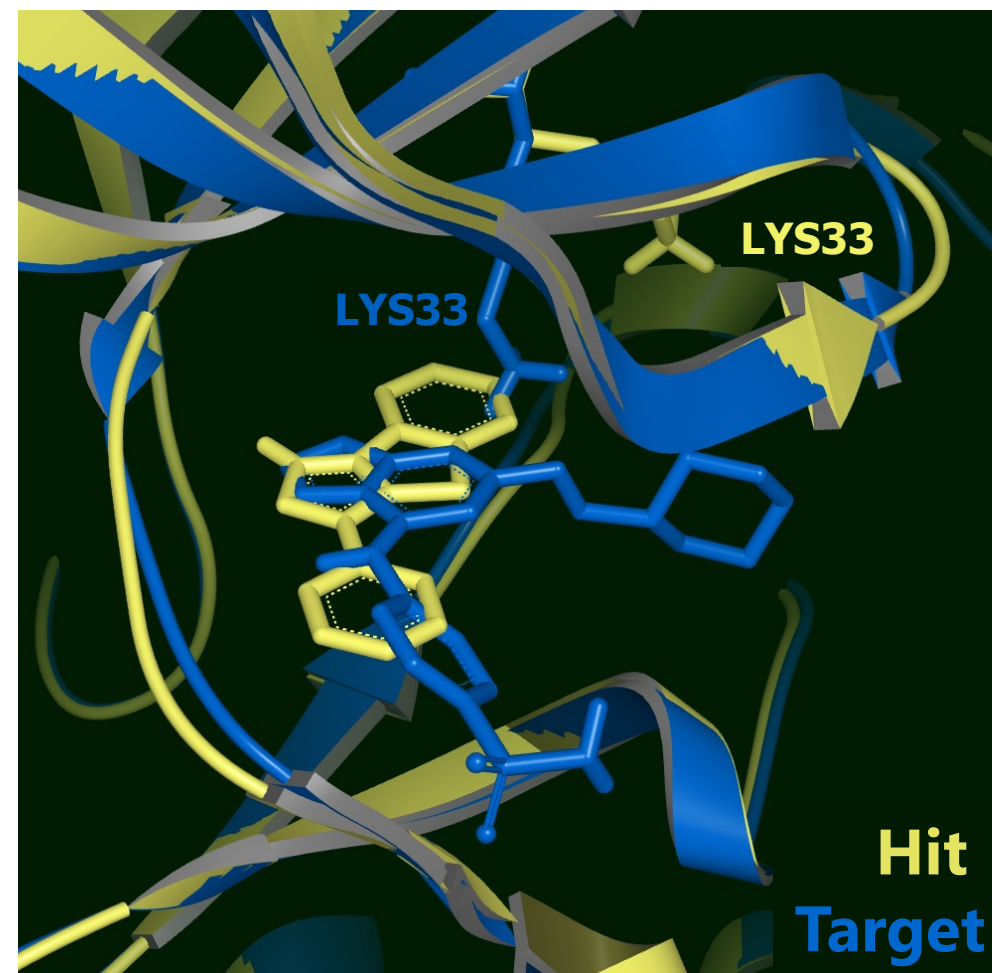
| Target Validation | Lead ID | Lead Optimization |

H2L

- "Hits are evaluated and undergo limited optimization to identify promising leads."

new **Induced-Fit Posing:** 3-step protocol for the correct prediction of the binding pose of a ligand which requires receptor conformation change

LYS33

LYS33

Hit
Target

Induced-Fit Docking (IFD)

Docking software applications developed to account for protein flexibility

JCTC Journal of Chemical Theory and Computation

pubs.acs.org/JC

Article

Prediction of Protein−Ligand Binding Poses via a Combination of Induced Fit Docking and Metadynamics Simulations

Anthony J. Clark,[†] Pratyush Tiwary,*,[†] Ken Borrelli,[‡] Shulu Feng,[‡] Edward B. Miller,[‡] Robert Abel,[‡] Richard A. Friesner,[†] and B. J. Berne[†]

[†]Department of Chemistry, Columbia University, New York, New York 10027, United States
[‡]Schrödinger, Inc., 120 West 45th Street, New York, New York 10036, United States

PLOS COMPUTATIONAL BIOLOGY

🔓 OPEN ACCESS   📄 PEER-REVIEWED

RESEARCH ARTICLE

AutoDockFR: Advances in Protein-Ligand Docking with Explicitly Specified Binding Site Flexibility

Pradeep Anand Ravindranath, Stefano Forli, David S. Goodsell, Arthur J. Olson, Michel F. Sanner ✉

JCTC Journal of Chemical Theory and Computation

pubs.acs.org/JCTC

Article

Reliable and Accurate Solution to the Induced Fit Docking Problem for Protein−Ligand Binding

Edward B. Miller, Robert B. Murphy, Daniel Sindhikara, Kenneth W. Borrelli, Matthew J. Grisewood, Fabio Ranalli, Steven L. Dixon, Steven Jerome, Nicholas A. Boyles, Tyler Day, Phani Ghanakota, Sayan Mondal, Salma B. Rafi, Dawn M. Troast, Robert Abel, and Richard A. Friesner*

Journal of COMPUTATIONAL CHEMISTRY

WWW.C-CHEM.ORG

FULL PAPER

Flexible CDOCKER: Development and Application of a Pseudo-Explicit Structure-Based Docking Method Within CHARMM

Jessica K. Gagnon, Sean M. Law, and Charles L. Brooks III*

1. *J. Chem. Theory Comput.* 2016, 12, 6, 2990–2998
2. Ravindranath, P. A.; Forli, S.; Goodsell, D. S.; Olson, A. J.; Sanner, M. F. PLoS Comput. Biol. 2015, 11, e1004586–e1004614
3. Gagnon, J. K.; Law, S. M.; Brooks, I.; Charles, L. J. Comput. Chem. 2016, 37, 753–762
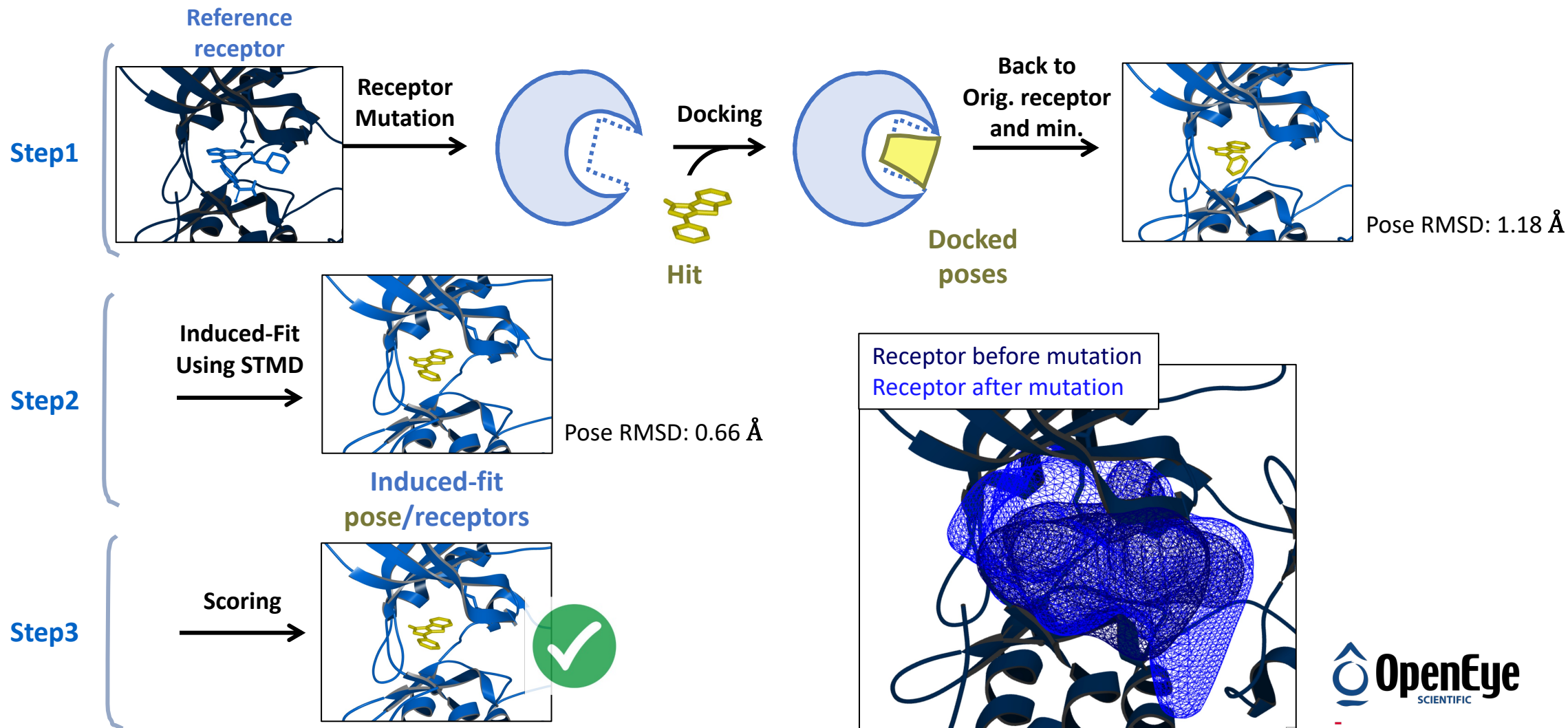4. J. Chem. Theory Comput. 2021, 17, 2630–2639

Induced-Fit Posing (IFP) in Orion

3-step protocol for the correct prediction of the binding pose of a ligand which requires receptor conformation change
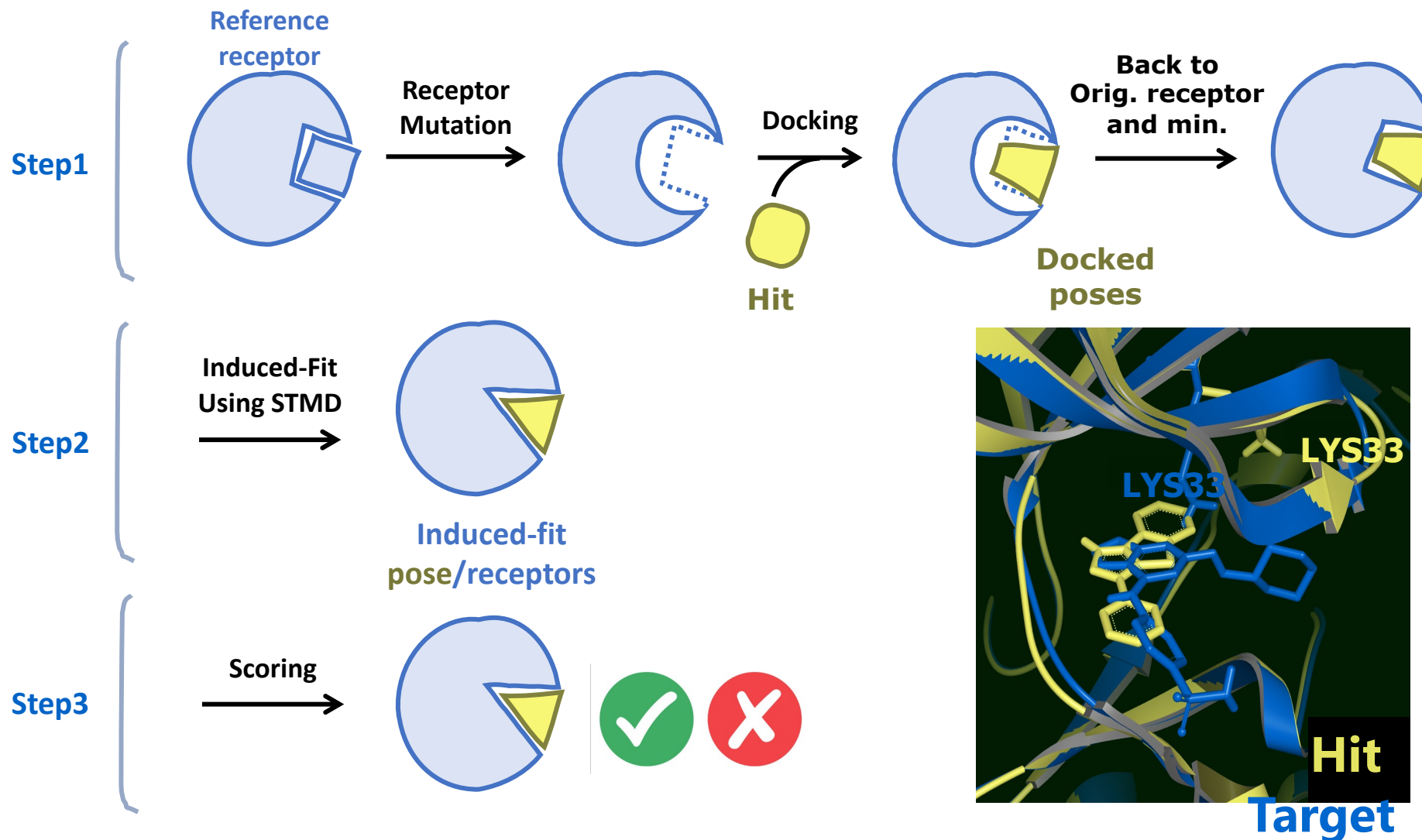
Induced-Fit Posing (IFP) in Orion

3-step protocol for the correct prediction of the binding pose of a ligand which requires receptor conformation change
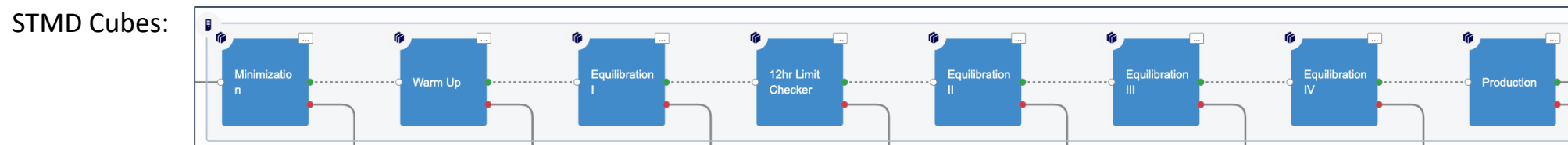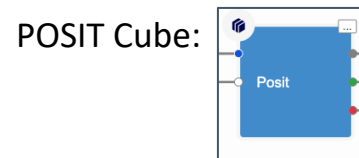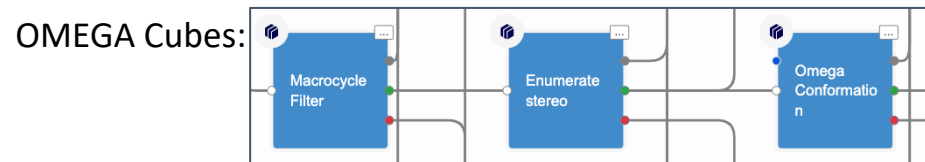
Orion platform allowed the fast implementation of IFP

- In the Orion platform, workflows (Orion Floes) are comprised of individual compute units (Orion Cubes): Highly reusable, easy to modify and create
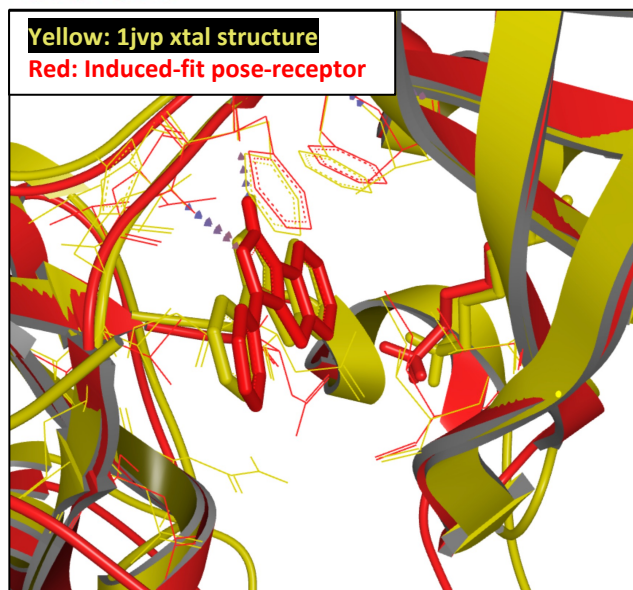
- IFP Floe Diagram

Step 1:
OEDocking and Initial Processing

Step 2:
Induced-fit using STMD

Step 3:
Scoring

o ~ 82 % of existing Cubes

OMEGA Cubes:

Macrocycle Filter | Enumerate stereo | Omega Conformation

POSIT Cube:

Posit

STMD Cubes:

Minimization | Warm Up | Equilibration I | 12hr Limit Checker | Equilibration II | Equilibration III | Equilibration IV | Production

Preliminary Results of IFP

The Good, the Bad and the Ugly
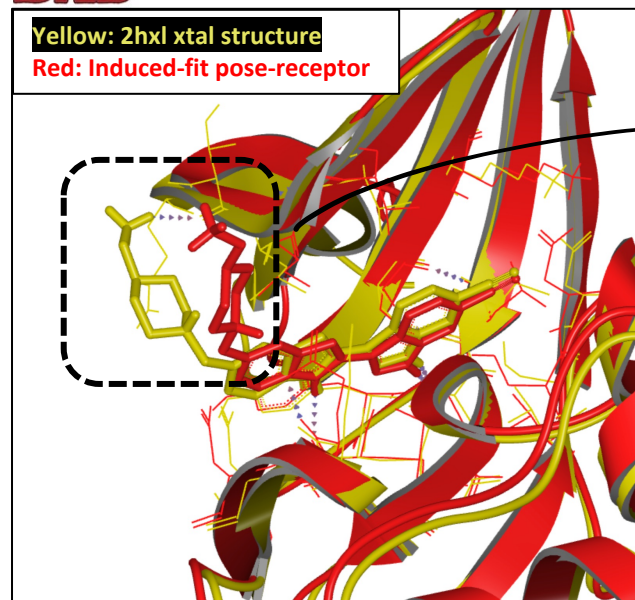

Pose RMSD: 0.66 Å

Pose RMSD: 2.47 Å
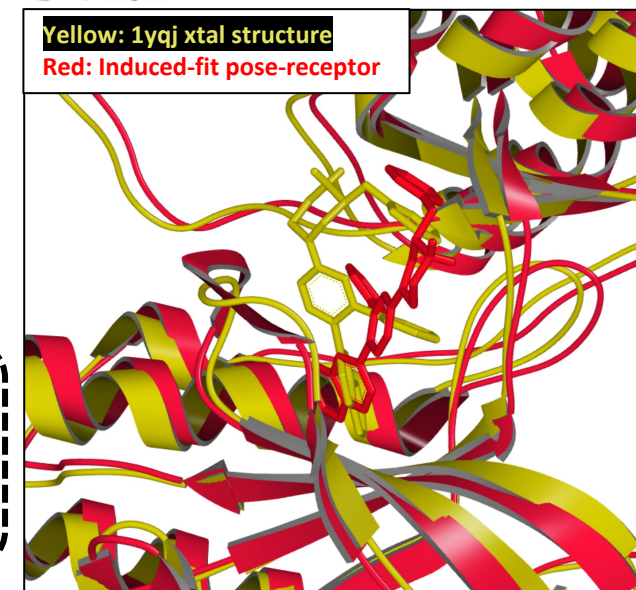
Pose RMSD: 4.18 Å
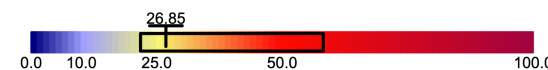
B-factor depiction

The Good, the Bad and the Ugly

- Test set: 10 targets, 36 cross-docks

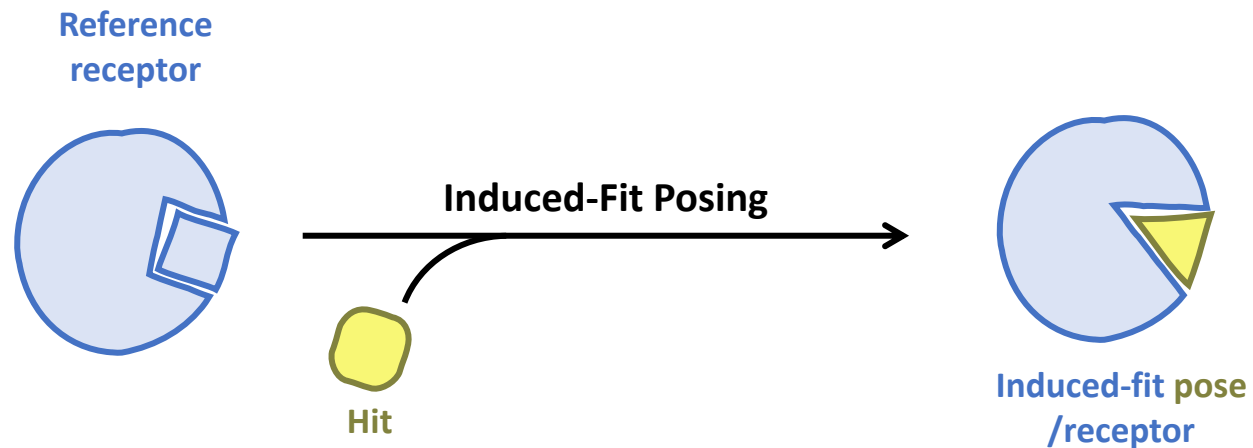| Target	# cross-docks
CDK2	6
FXa	6
PTP1B	5
BACE1	2
Chk1	2
p38	5
hsp70	1
rpa	2
afaB	2
Thrombin	5
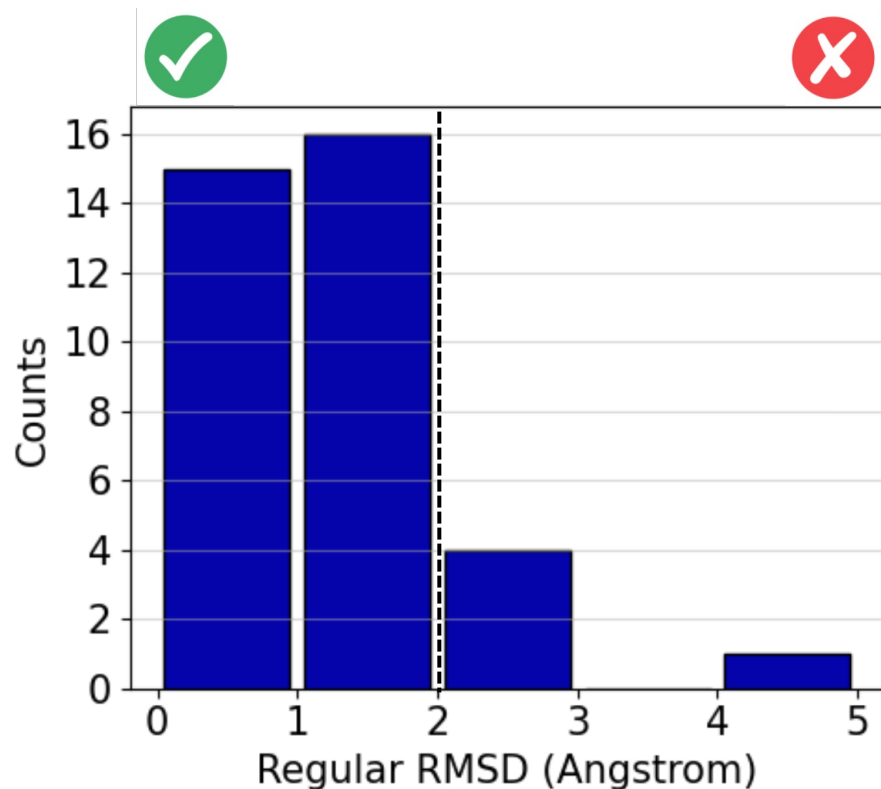
o Histogram of pose RMSDs of the best poses (lowest pose RMSD)
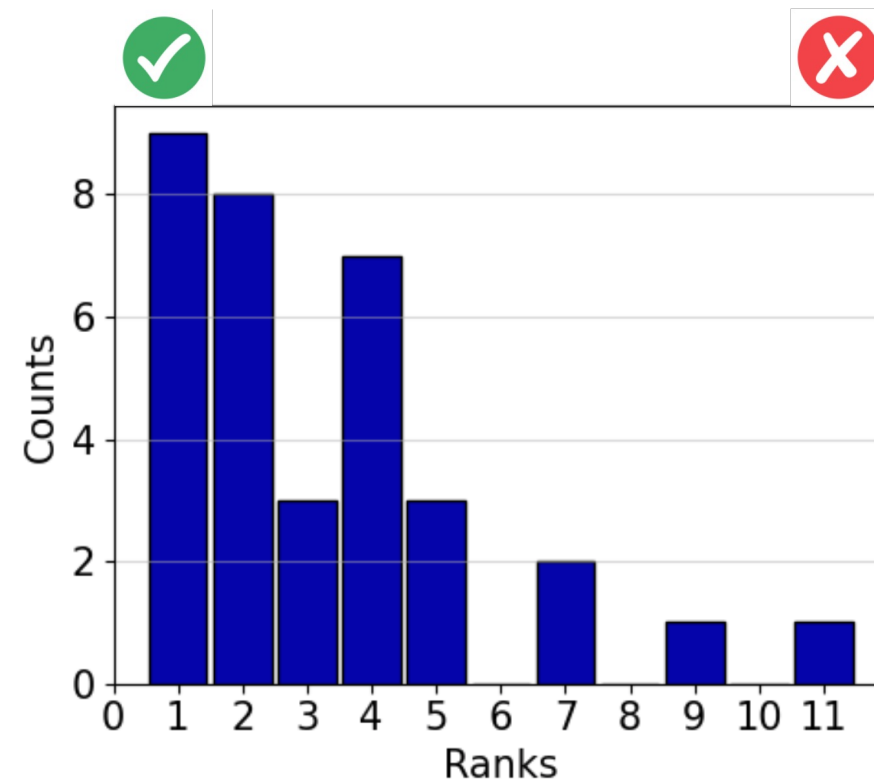
o Histogram of the ranks of the best poses

Conclusions and Acknowledgments

Conclusions

Reference receptor → **Induced-Fit Posing** → **Induced-fit pose /receptor**
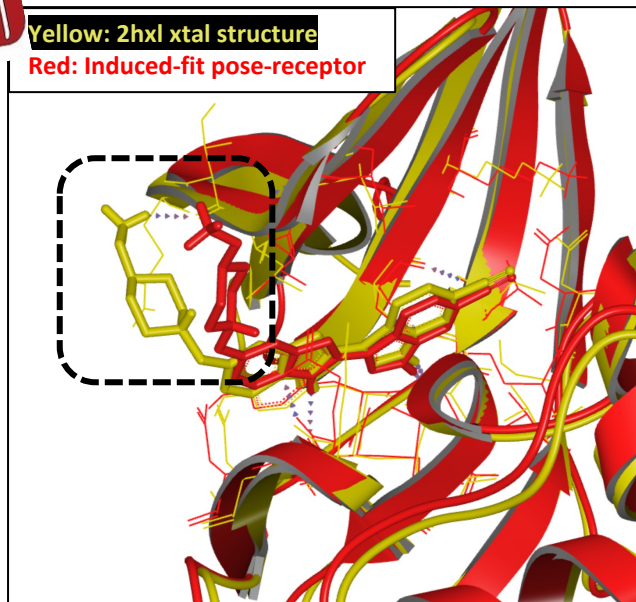
Hit

- The performance of the early version of IFP is promising

- Many directions for the performance improvement of IFP
  - Proper comparison with the reference xtal structures with high B-factor for retrospective study

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...But, is it worth comparing the high b-factor region?

THE **BAD**

Yellow: 2hxl xtal structure
Red: Induced-fit pose-receptor

Pose RMSD: 2.47 Å > 0.59 Å

o   Pose RMSD histogram

o   Partial pose RMSD histogram (RMSD of ligand atoms with b-factor < 35)

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Conclusions

- The performance of the early version of IFP is promising

- Many directions for the performance improvement of IFP
  - Proper comparison with the reference xtal structures with high B-factor for retrospective study
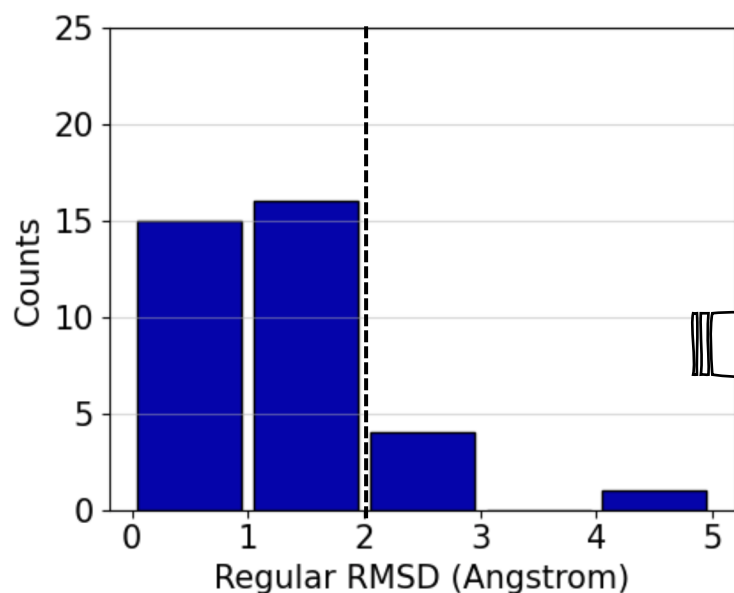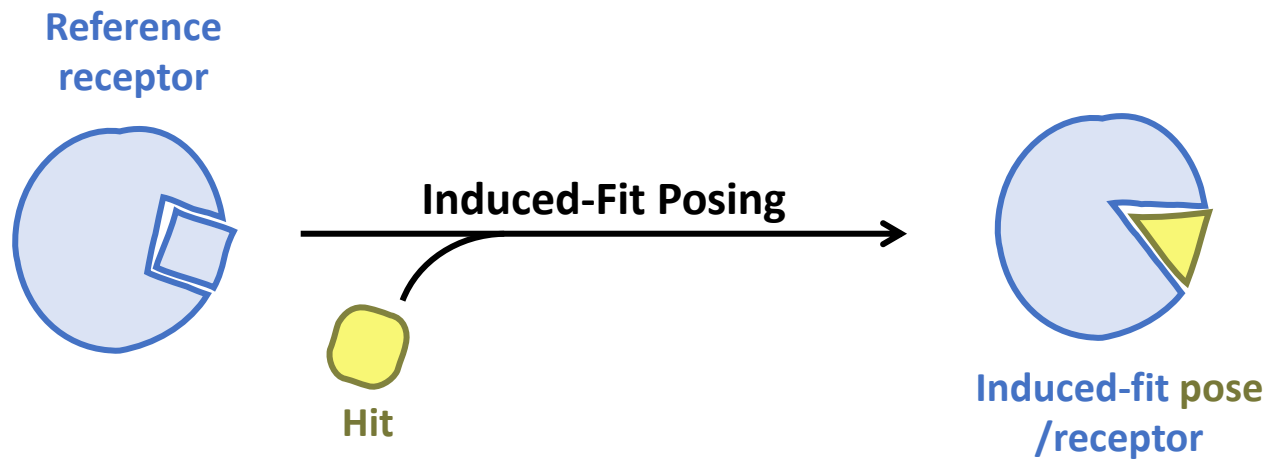 - Further refinement of stage 2 (MD): Enhanced Sampling
  - Optimizing step 3 scoring function to identify the correct IFP solution
  - Account for tautomeric and ionization state in the active site
- Aiming for a general release in 2023

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Acknowledgments

INTERLINE
therapeutics

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- **Itai Leven**, Mario Cardozo (Interline Therapeutics)

- **Suhani Nagpal**, **Bing Xie**, Christopher Bayly (OpenEye)

- Cloud Ops team @ OpenEye

Thank you for listening!

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