Protein-Ligand Scoring with Convolutional Neural Networks

ACS Spring Meeting New Orleans, LA March 19, 2018

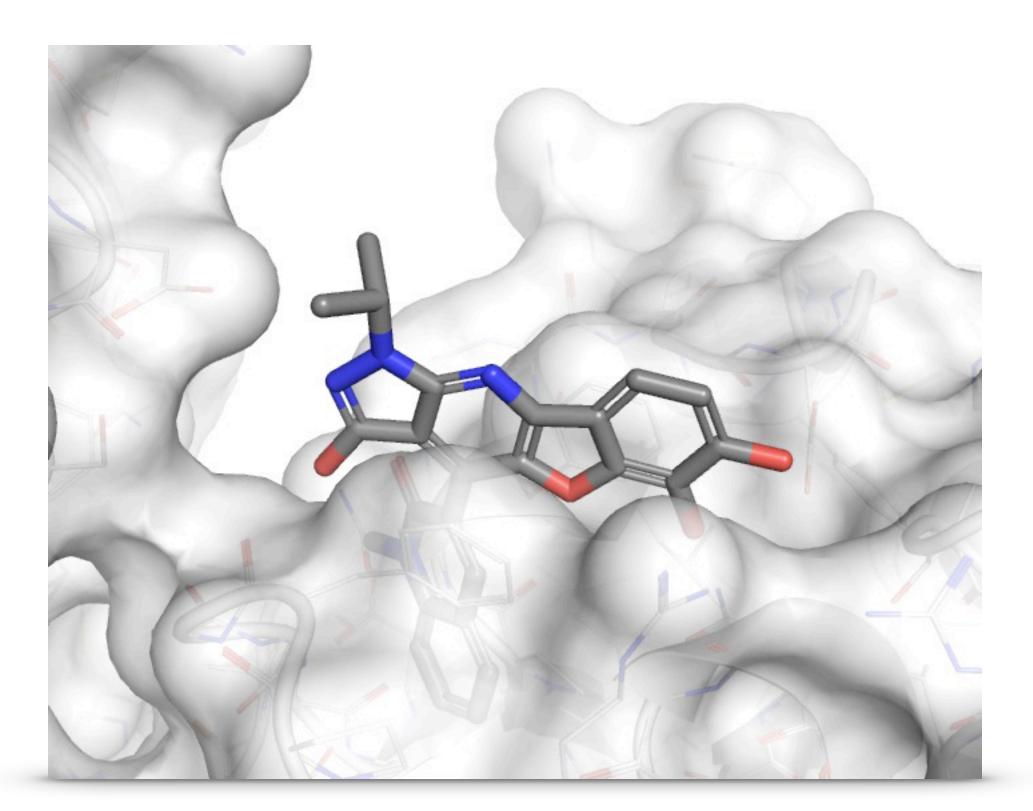
David Koes

@david_koes

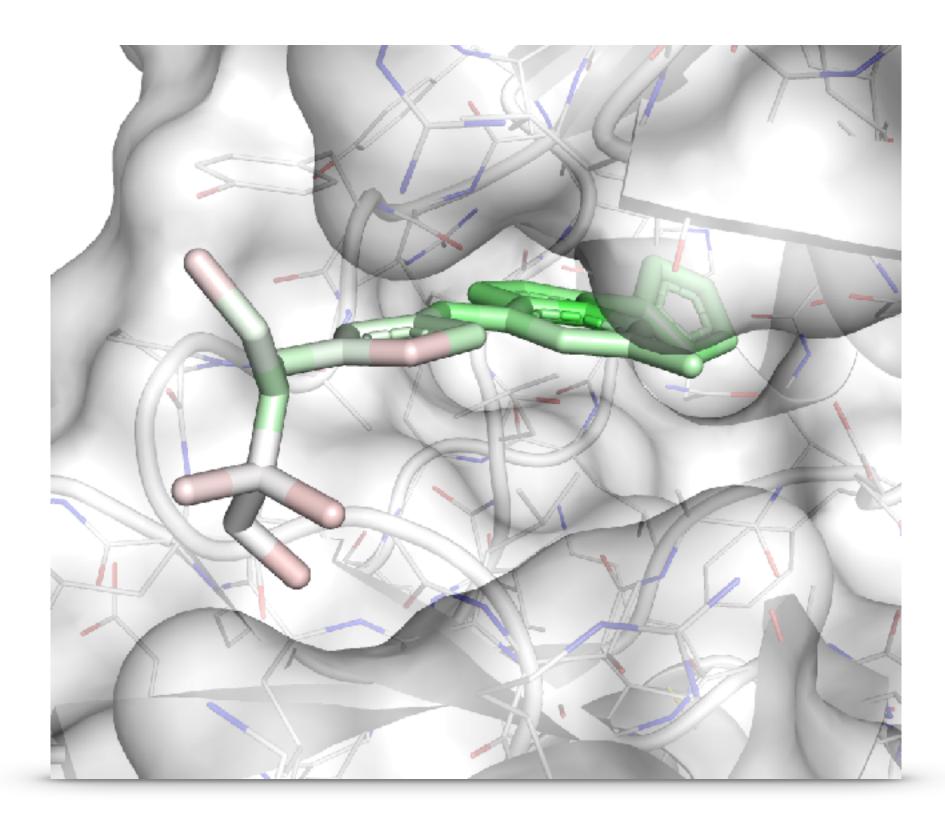




Structure Based Drug Design **Virtual Screening** Lead Optimization



Pose Prediction

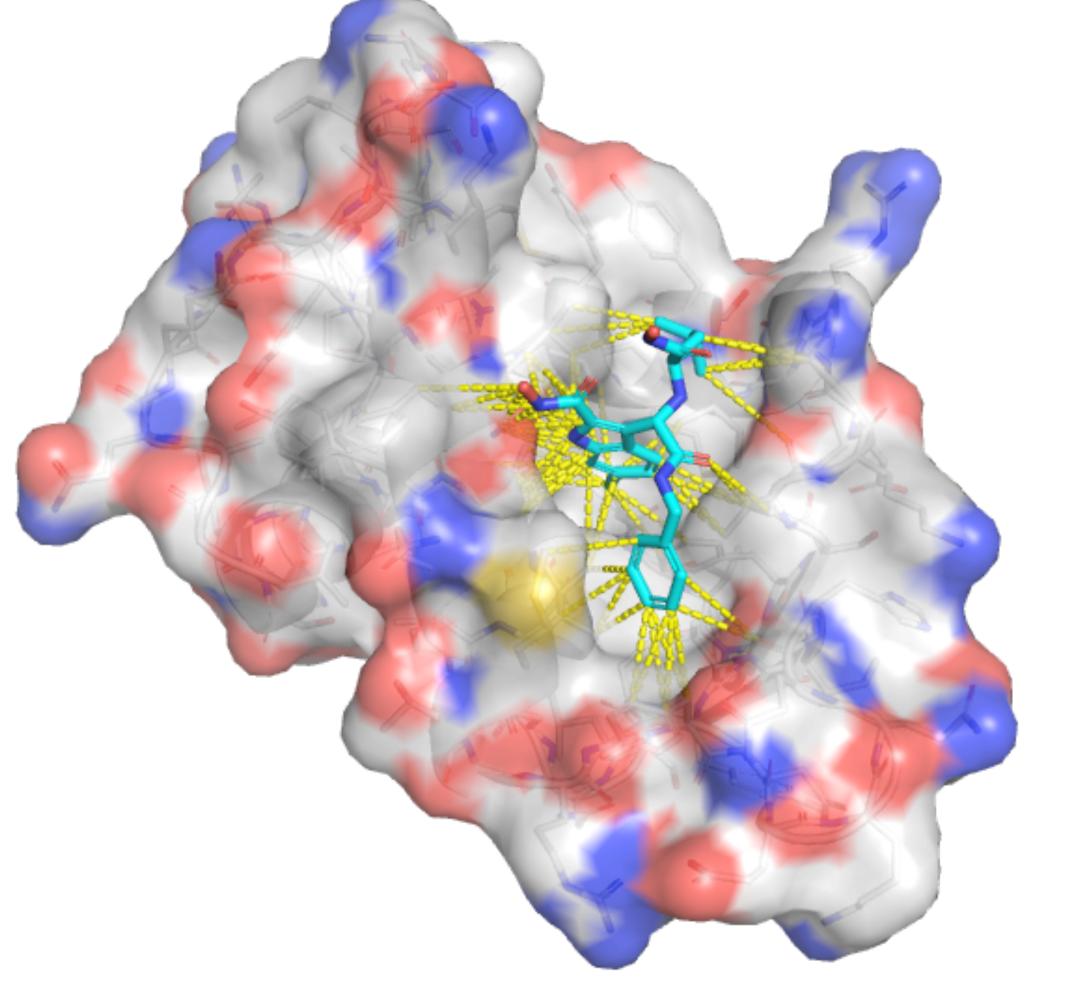


Binding Discrimination

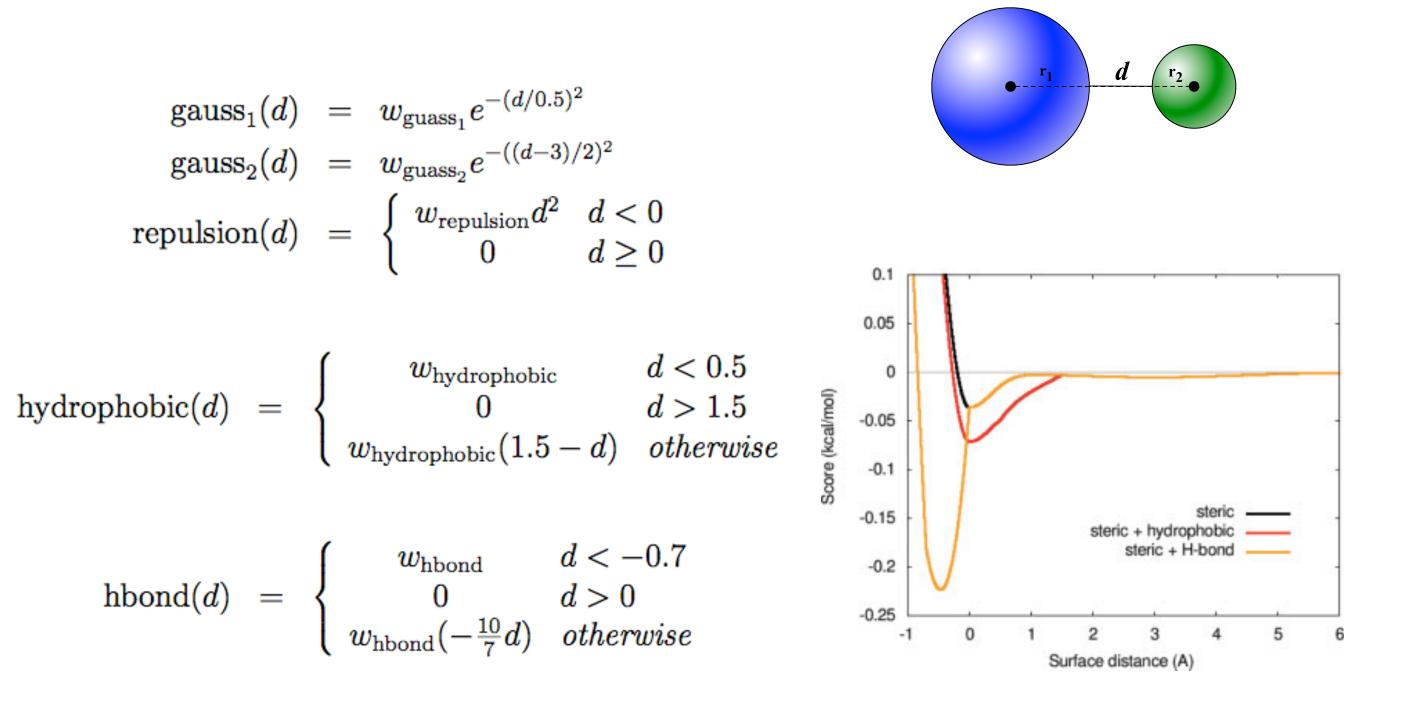
Affinity Prediction



Protein-Ligand Scoring



AutoDock Vina



O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry 31 (2010) 455-461





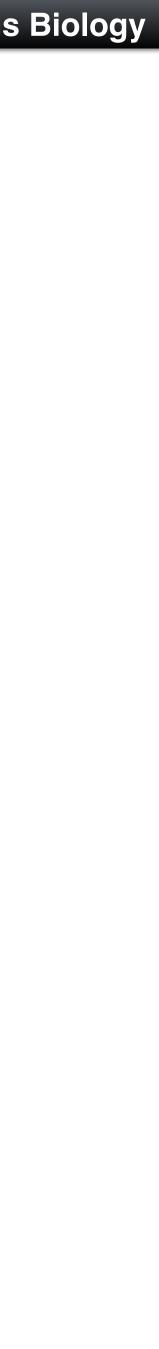
Accurate pose prediction, binding discrimination, and affinity prediction without sacrificing performance?

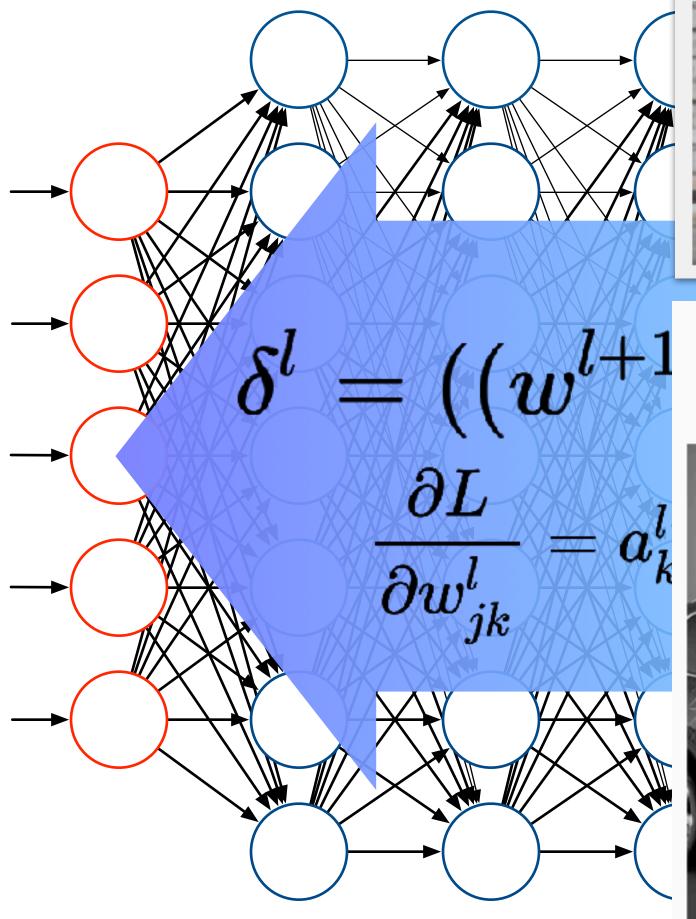
Key Idea: Leverage "big data"

- 231,655,275 bioactivities in PubChem
- 125,526 structures in the PDB
- 16,179 annotated complexes in PDBbind

Can we do better?









Pittsburgh



Deep Learning

Uber self-driving car crashes into another car in

Uber disputes a key element of the other driver's story.

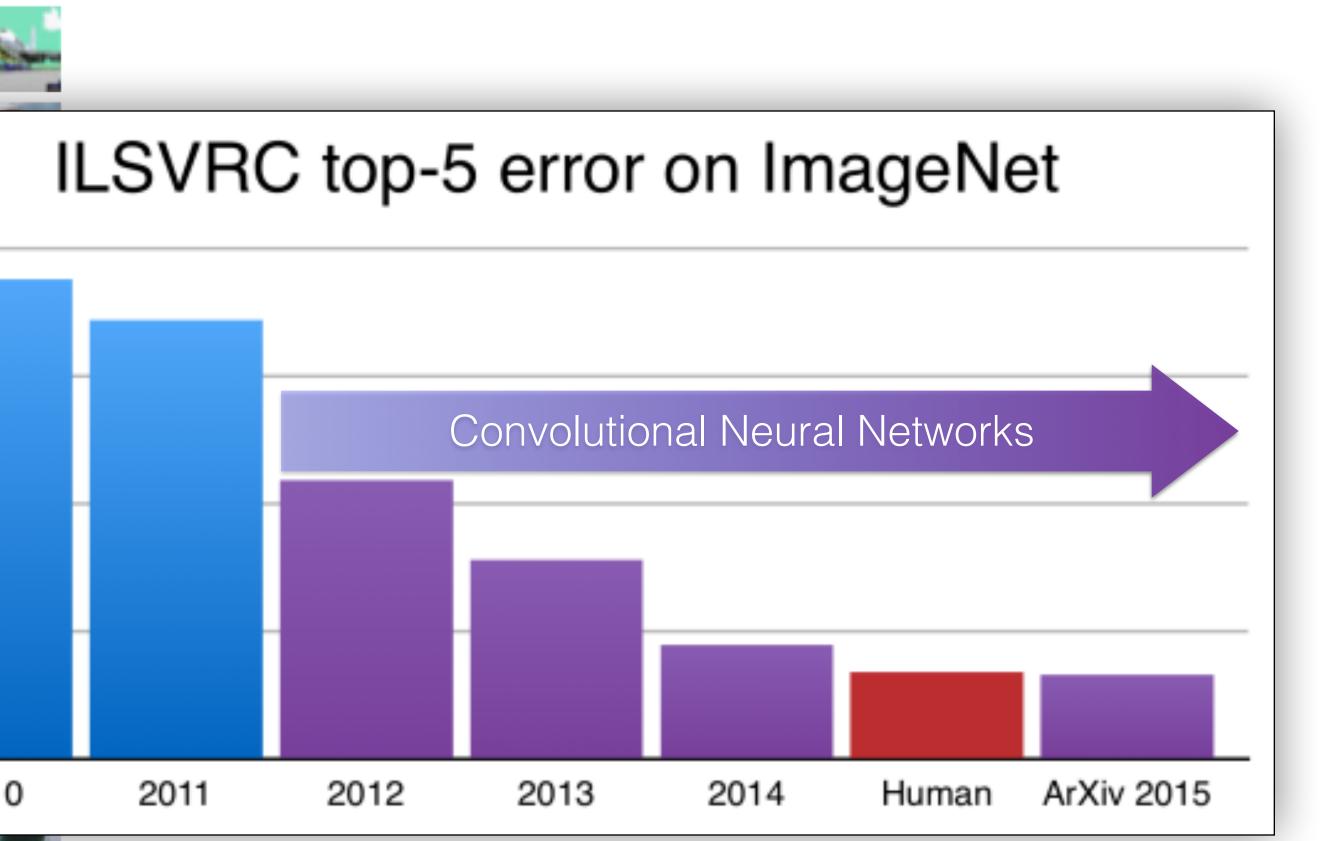
TIMOTHY B. LEE - 3/15/2018, 2:06 PM



Image Recognition

| | | | | | | | | | | _ |
|------------|--|------------|-----|----------|----|-----|----|------|---|------|
| airplane | 1 | H. | | X | * | * | 2 | -17 | - | |
| automobile | | | | | - | The | -U | | | |
| bird | S | ſ | 2 | | | 4 | N | 30 | _ | |
| cat | | | | aut. | | | | 22.5 | | |
| deer | 6 | 48 | X | RA | | Y | 1 | | | |
| dog | 376 | 1 | - | . | - | | - | 15 | | |
| frog | -7 | reg. | | | | | 1 | 7.5 | | |
| horse | - Ada | T. | P | 3 | m | 171 | - | 0 | | |
| ship | - | Carlos and | 100 | + | MA | | | Ŭ | ľ | 2010 |
| truck | Cont of the local division of the local divi | | - | | | | | | 0 | 1 |

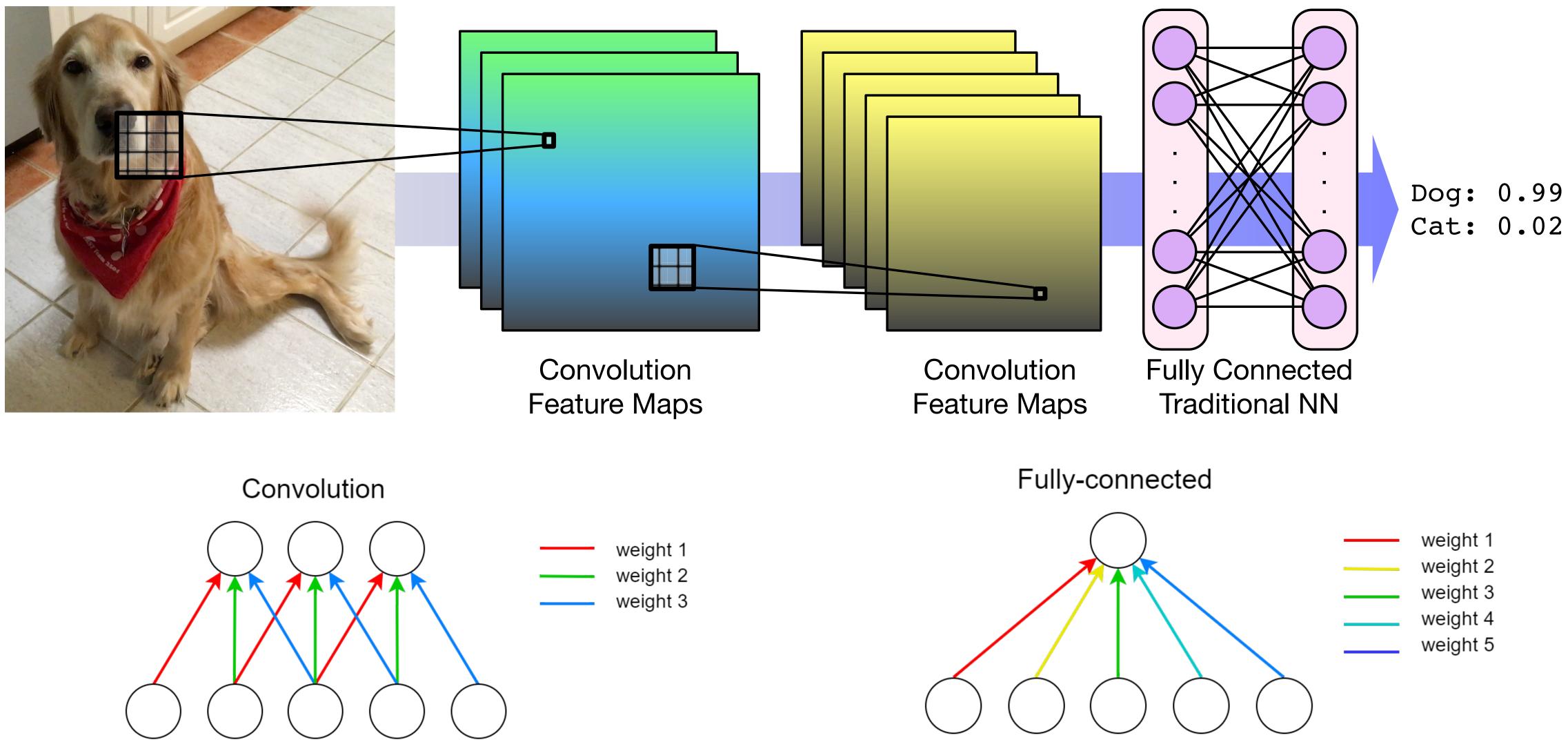


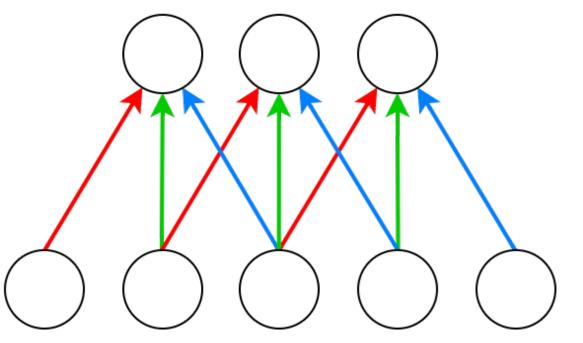




https://devblogs.nvidia.com

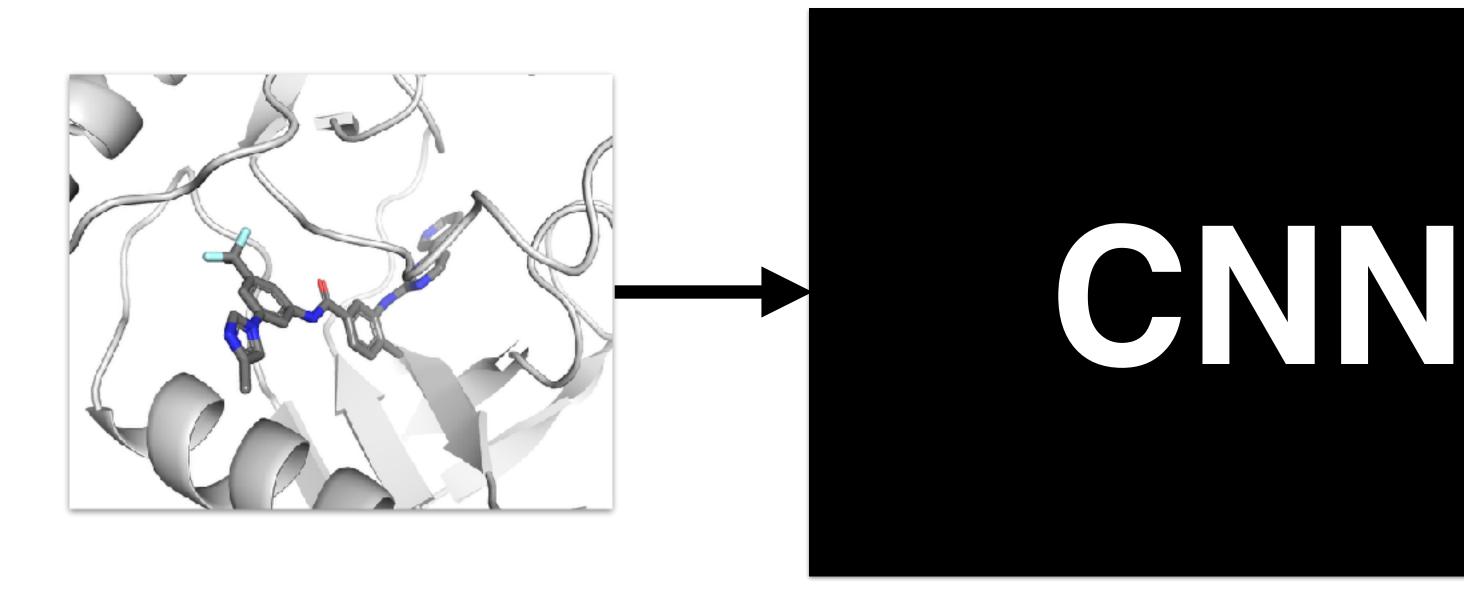






Convolutional Neural Networks

CNNs for Protein-Ligand Scoring



Pose Prediction

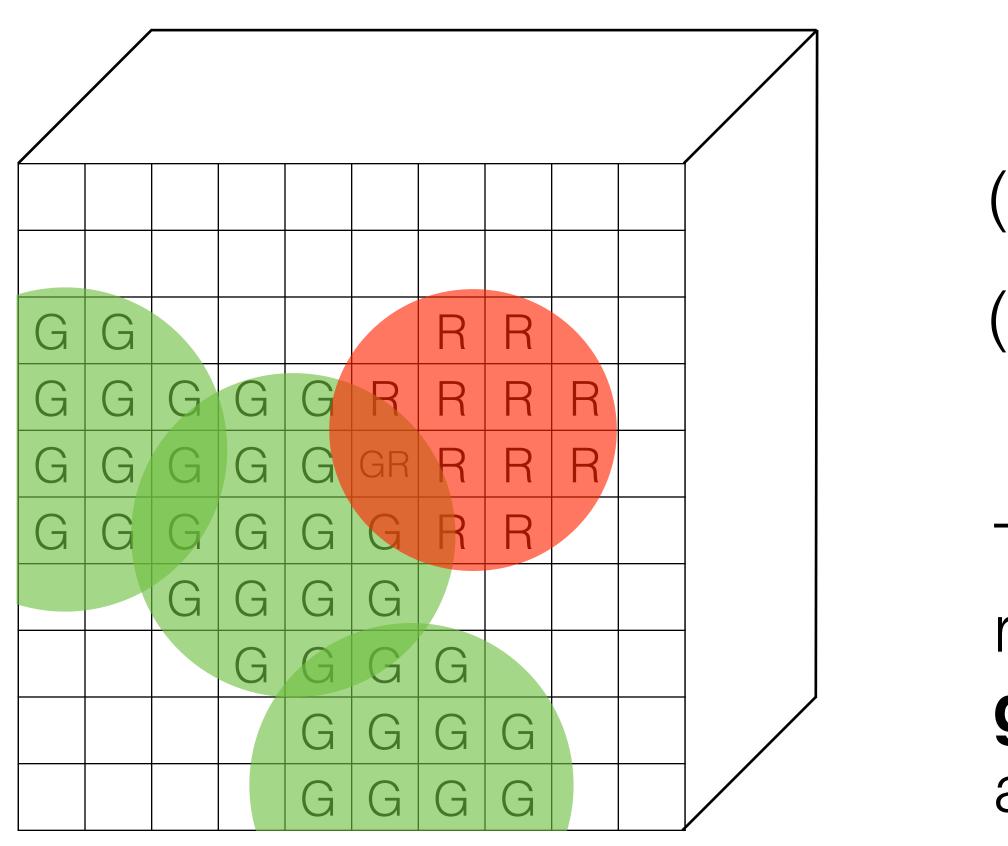
Binding Discrimination

Affinity Prediction





Protein-Ligand Representation



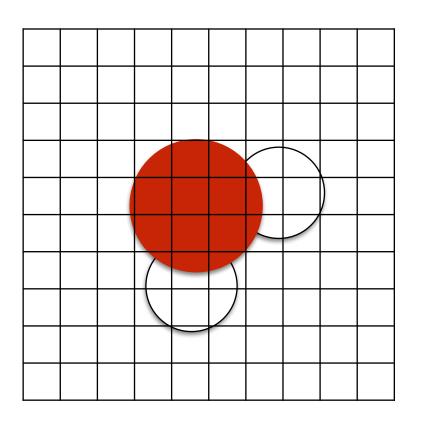
- (R,G,B) pixel \rightarrow
- (Carbon, Nitrogen, Oxygen,...) **voxel**

The only parameters for this representation are the choice of grid resolution, atom density, and atom types.



Pros

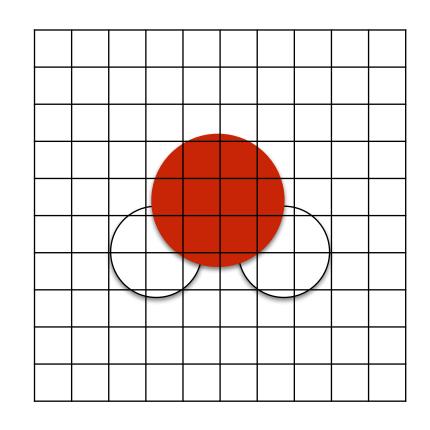
- clear spatial relationships
- amazingly parallel
- easy to interpret



Why Grids?

Cons

- coordinate frame dependent
- pairwise interactions not explicit





Pose Prediction

4056 protein-ligand complexes

- diverse targets
- wide range of affinities
- generate poses with AutoDock Vina
- include minimized crystal pose

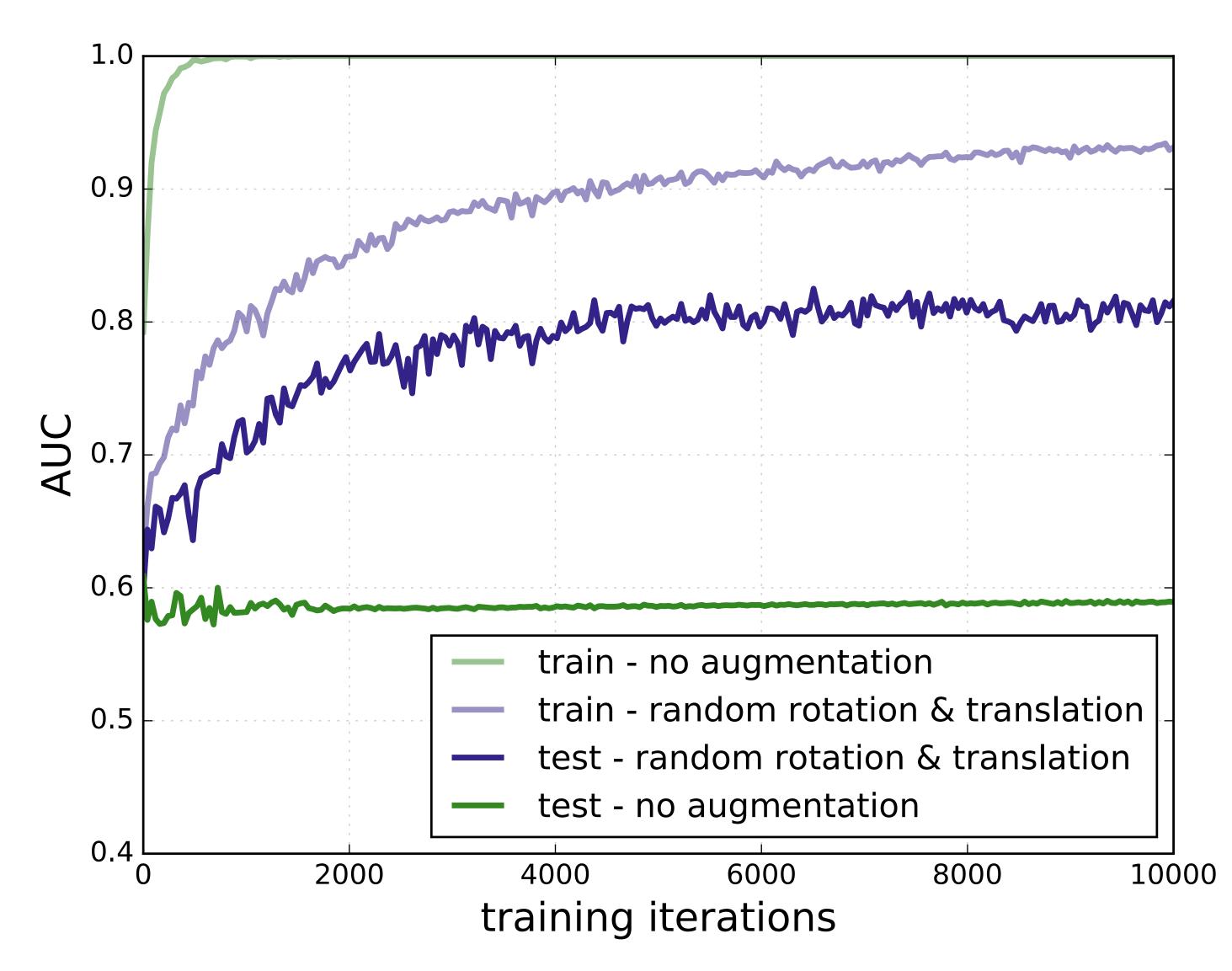


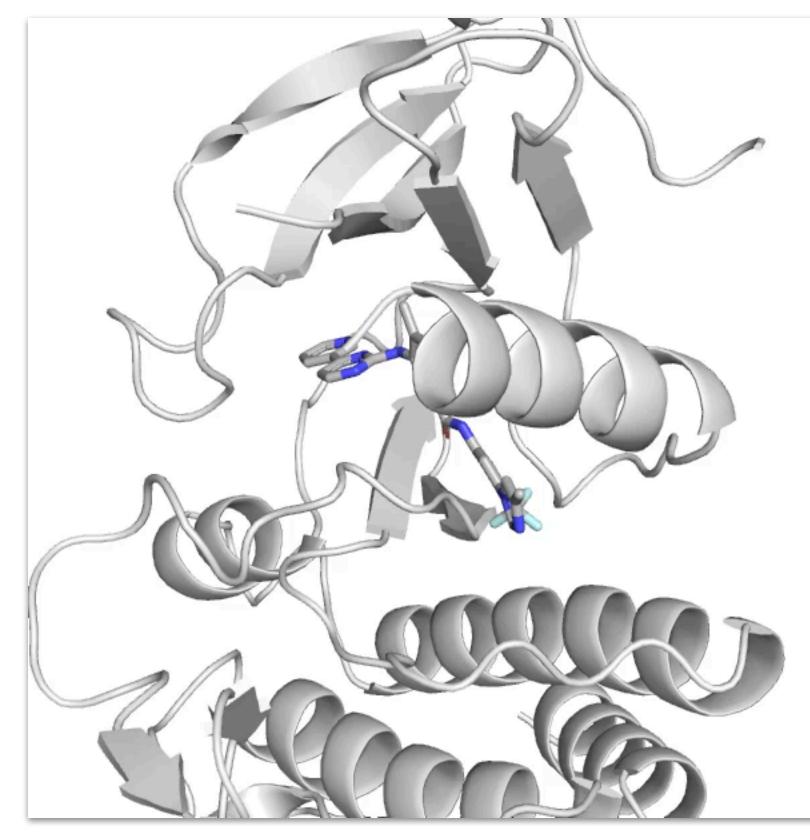
Affinity Prediction

- 8,688 low RMSD poses
- assign known affinity
- regression problem



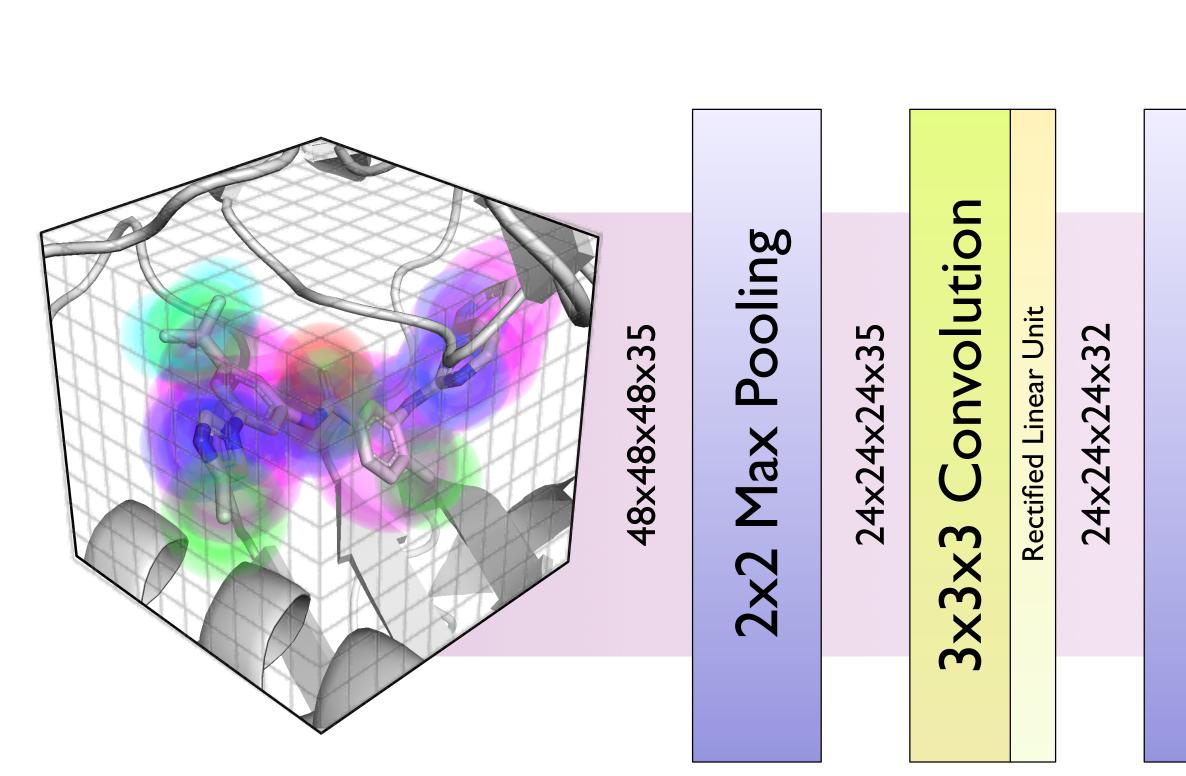
Data Augmentation













Pooling Max 2x2

| 2×| 2×| 2×32

Convolution 3×3×3

Rectified Linear Unit

| 2×| 2×| 2×64

Pooling Max 2×2

6×6×6×64

Convolution 3x3x3

Rectified Linear Unit

6×6×6×128

| Fully Connected | Pseudo-Huber Loss |
|-----------------|-----------------------|
| Fully Connected | Softmax+Logistic Loss |

Pose Score

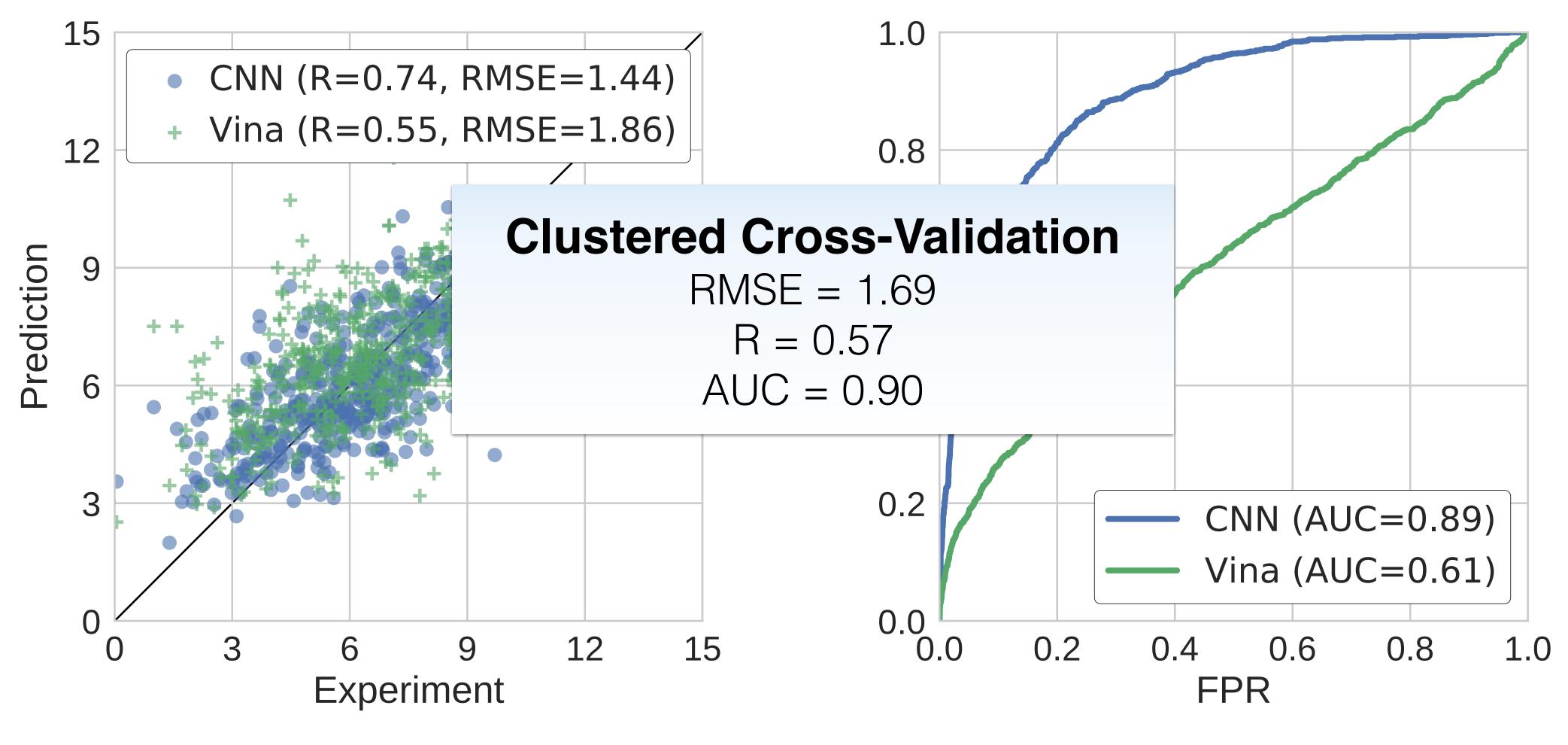
Model







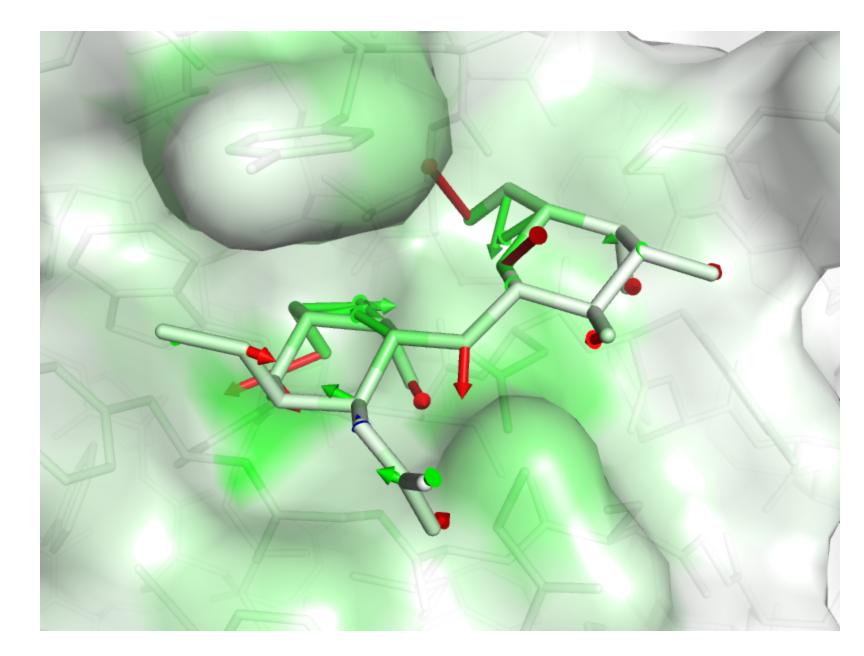
Results

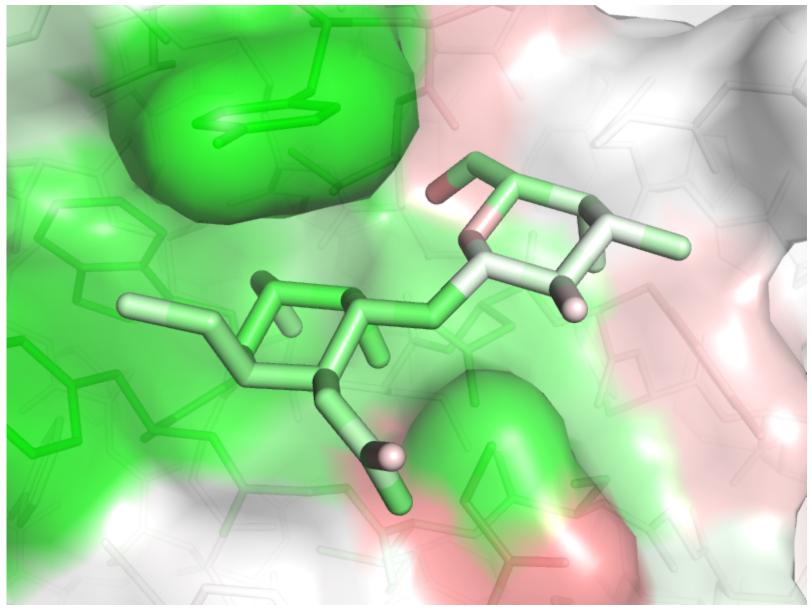


Trained on PDBbind refined; tested on CSAR

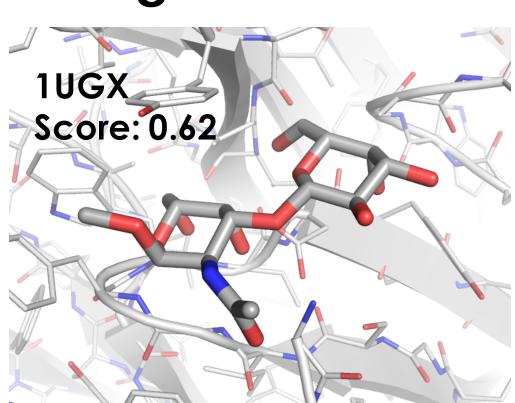


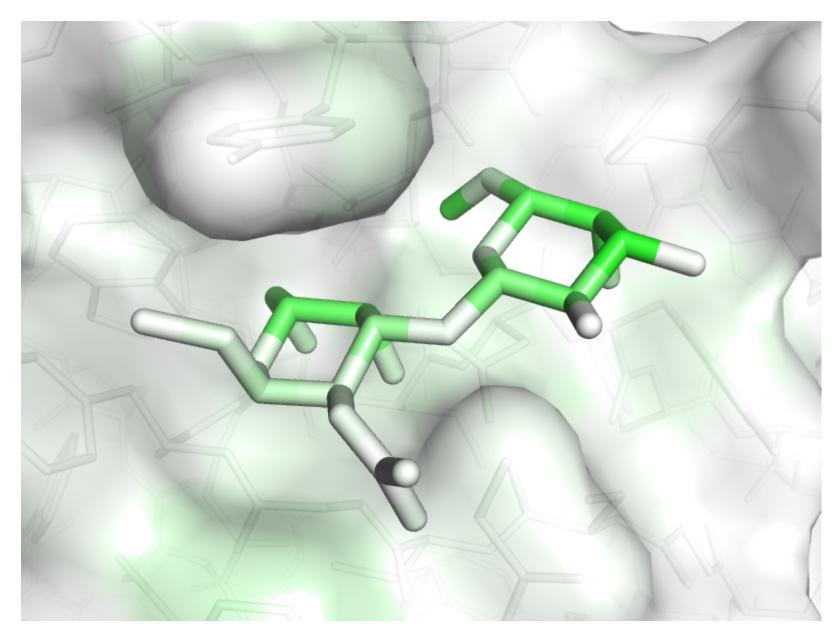
Visualization





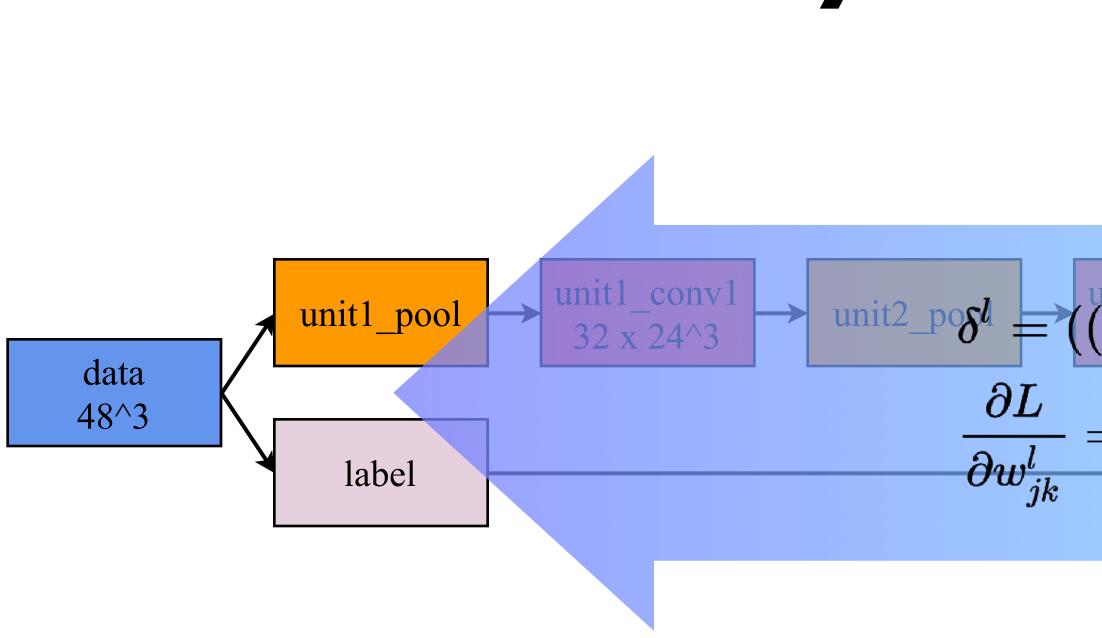
masking

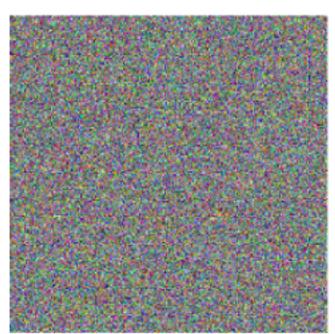




gradients

layer-wise relevance



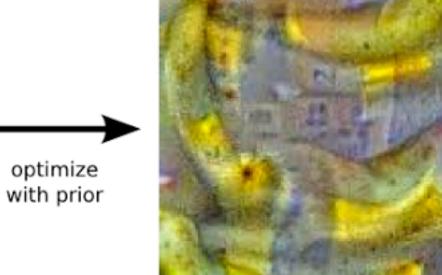


https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html

Beyond Scoring

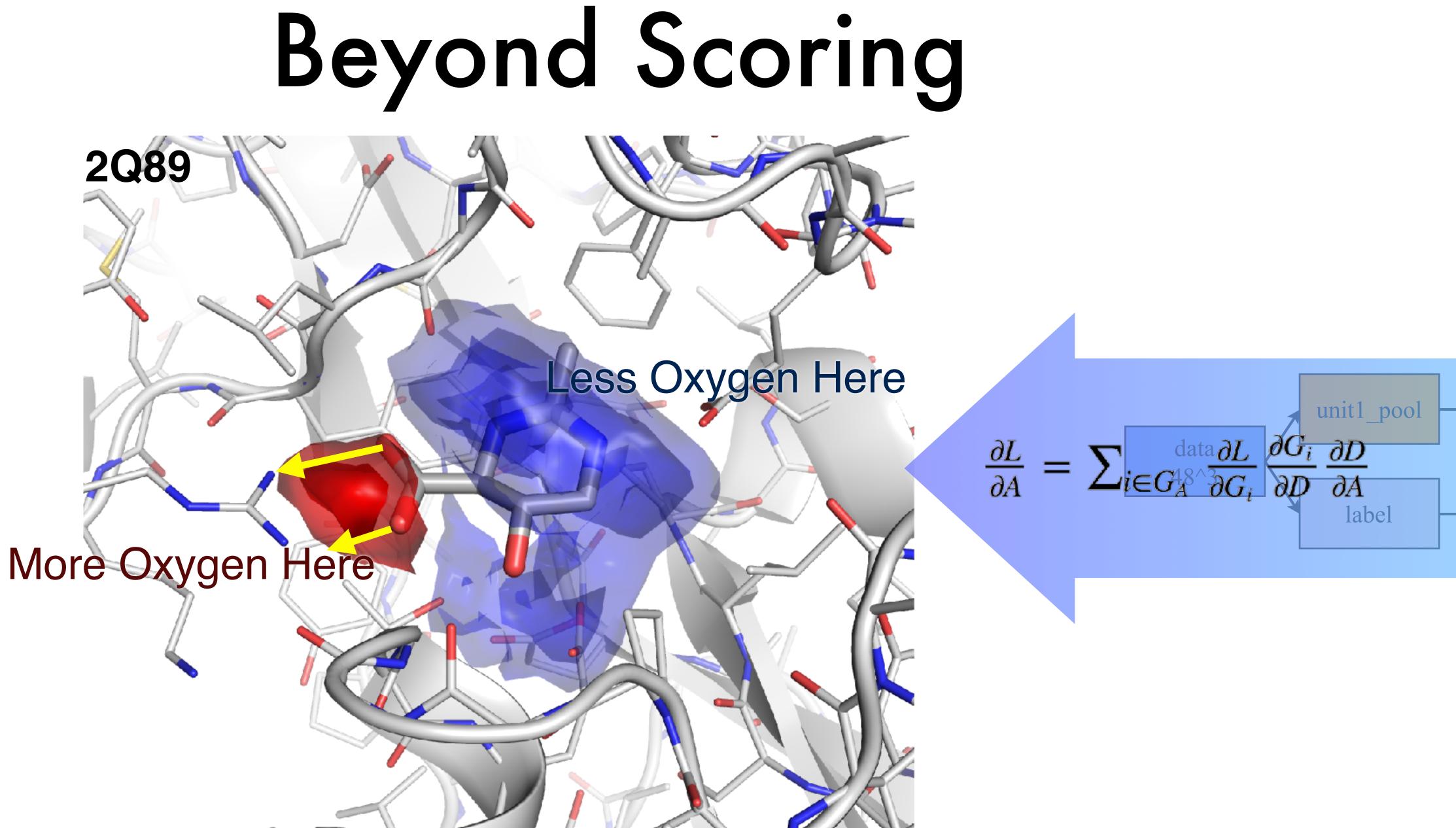
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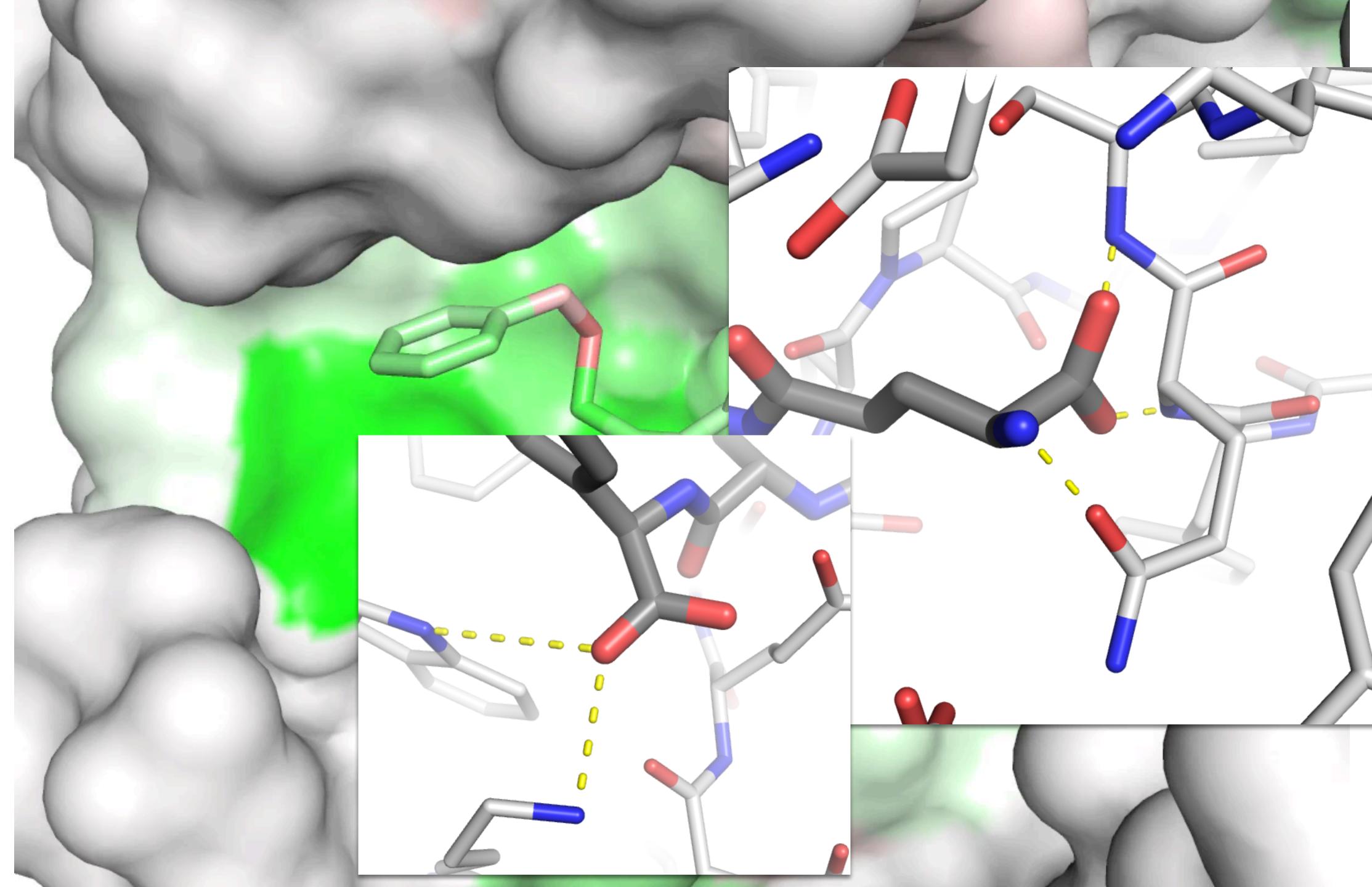
Deep Dreams



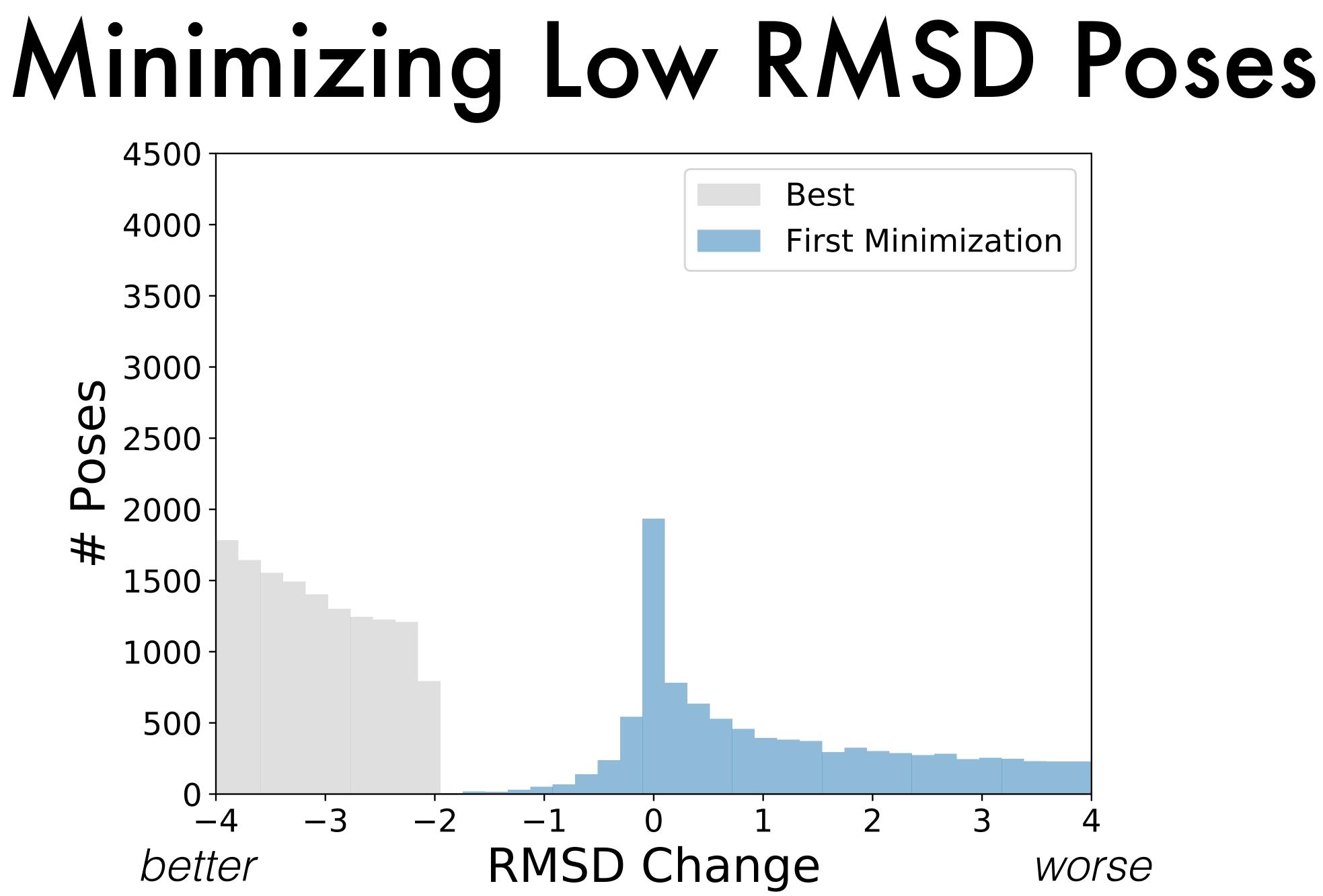




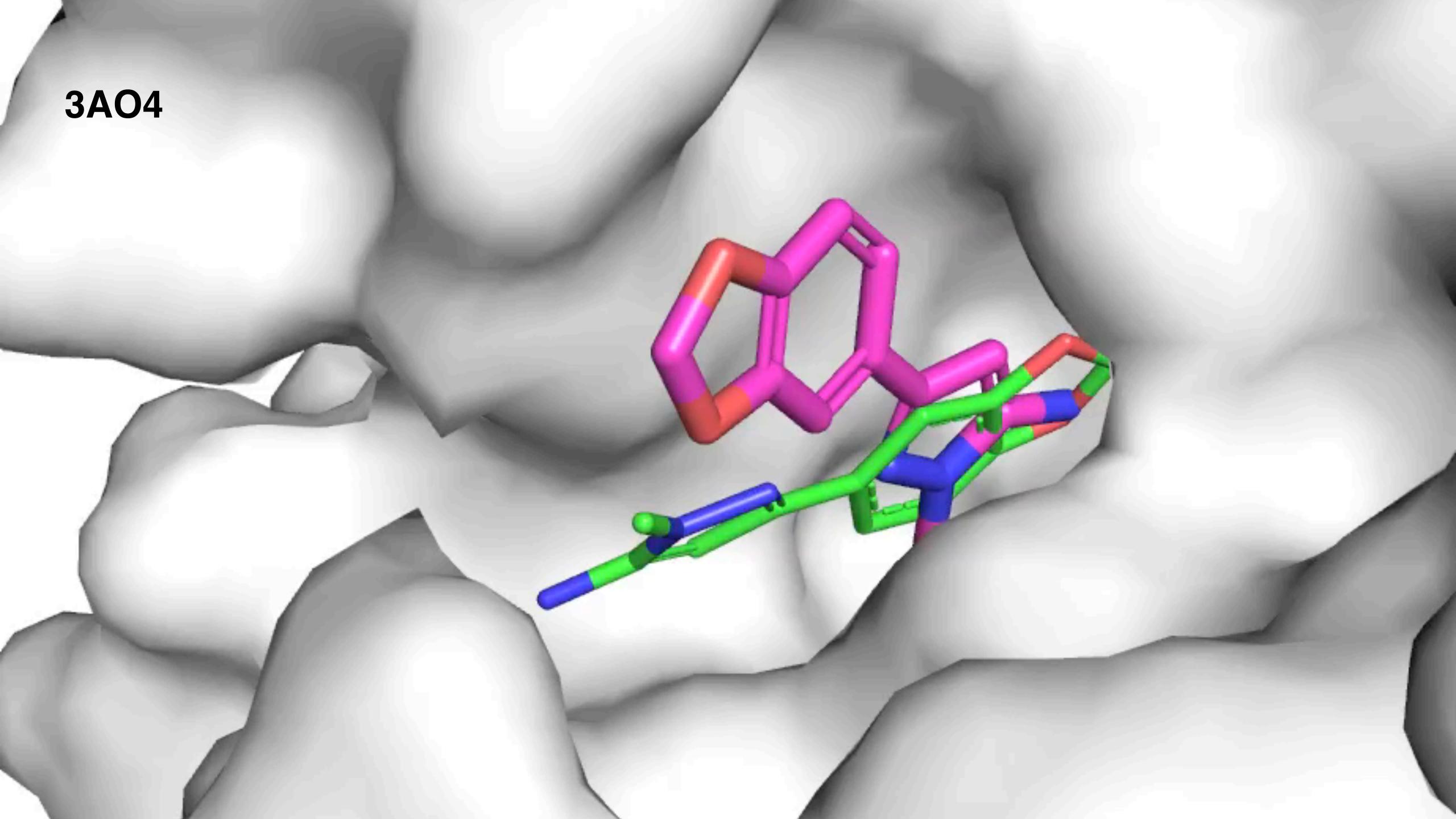


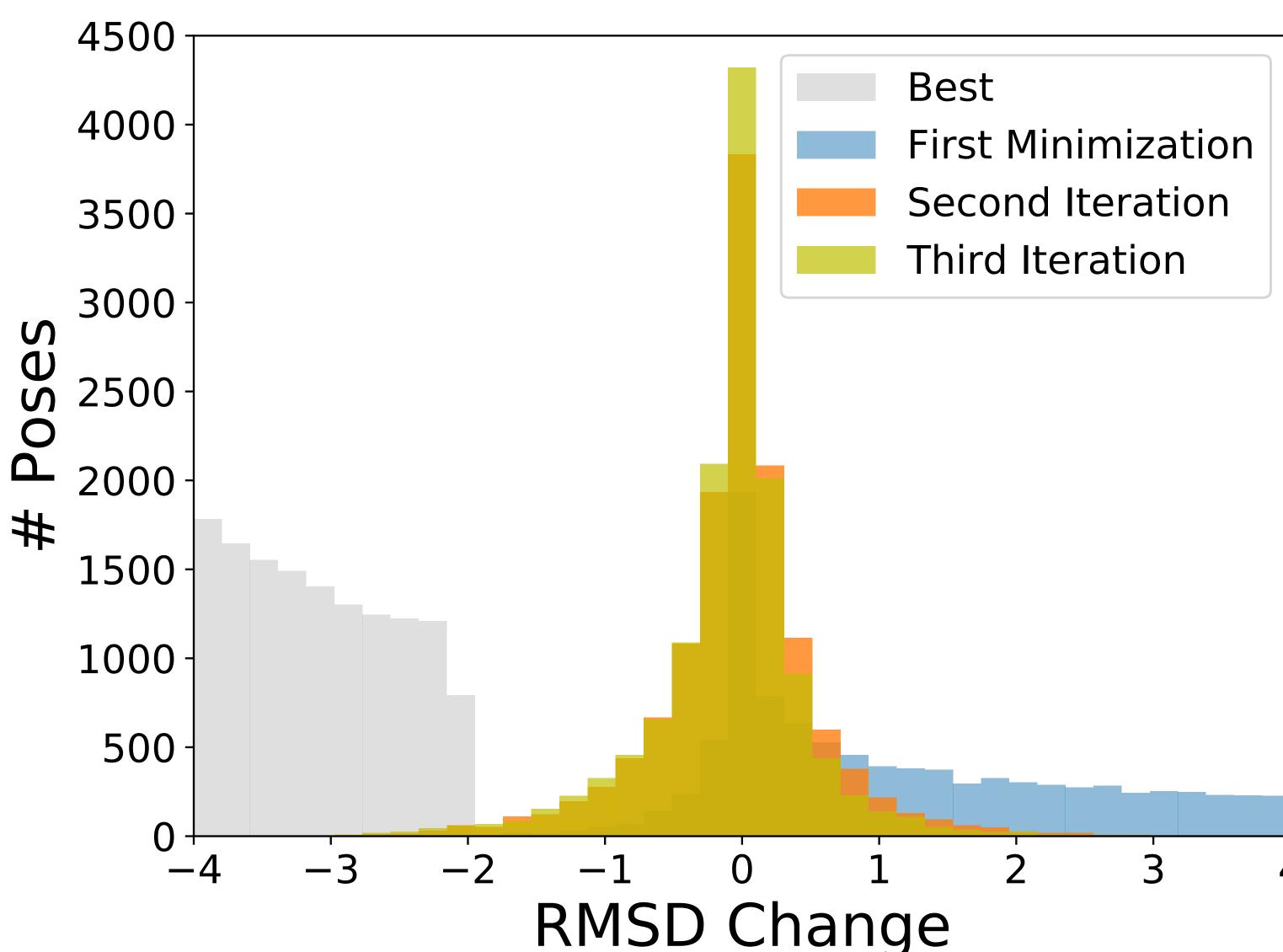




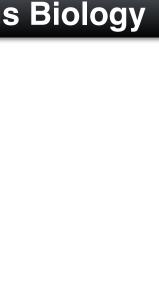


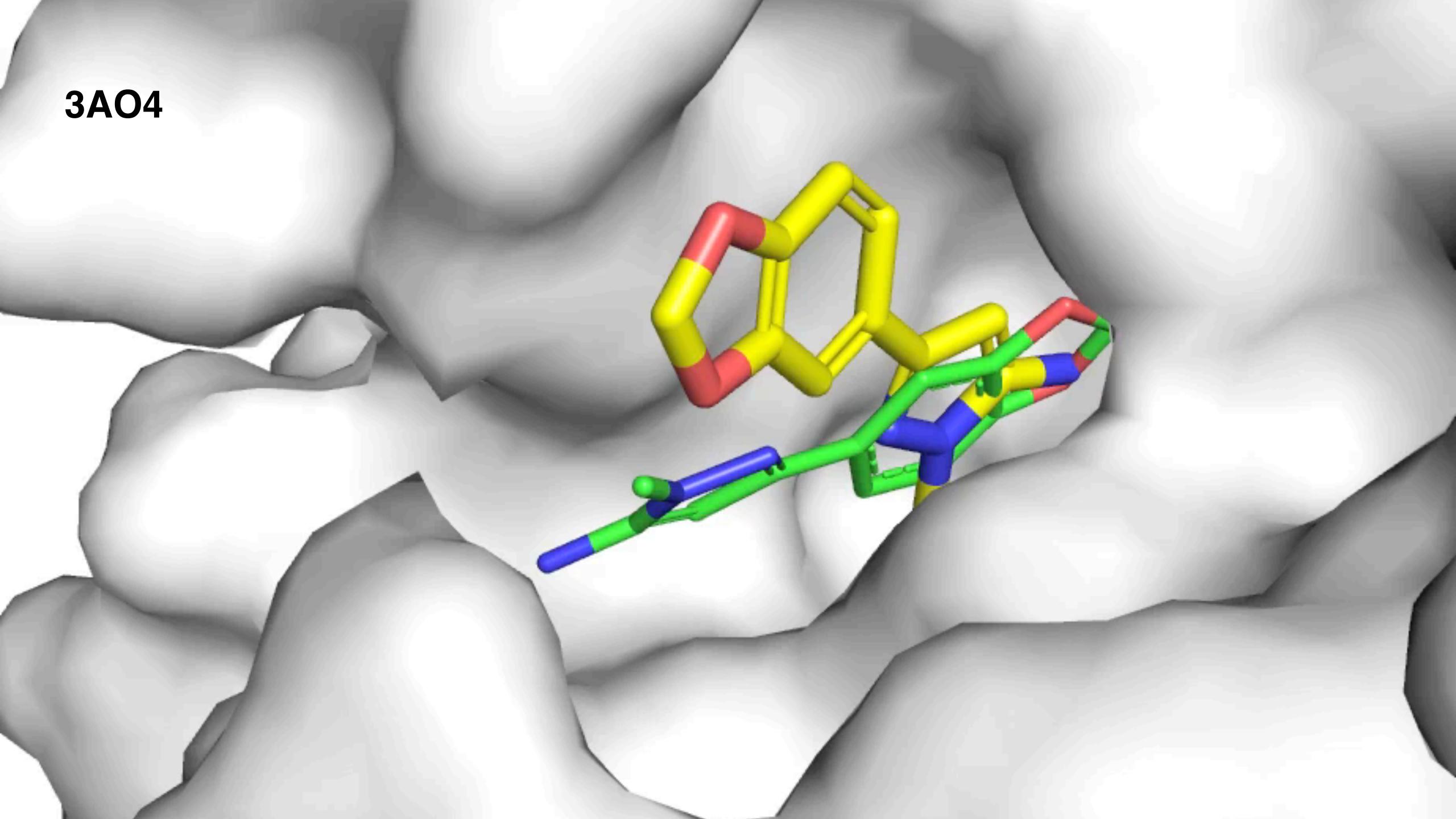






Iterative Refinement



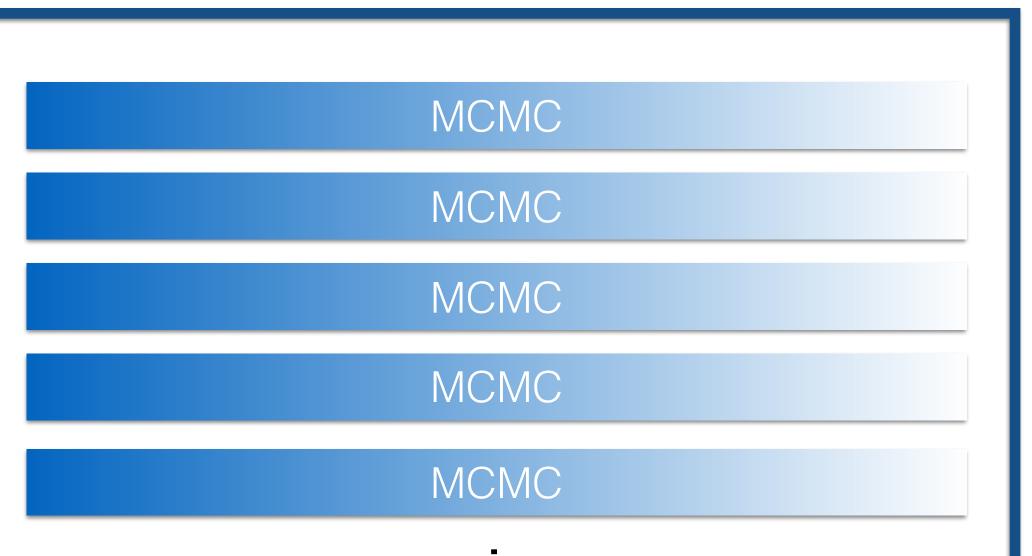


Docking vina/smina/gnina

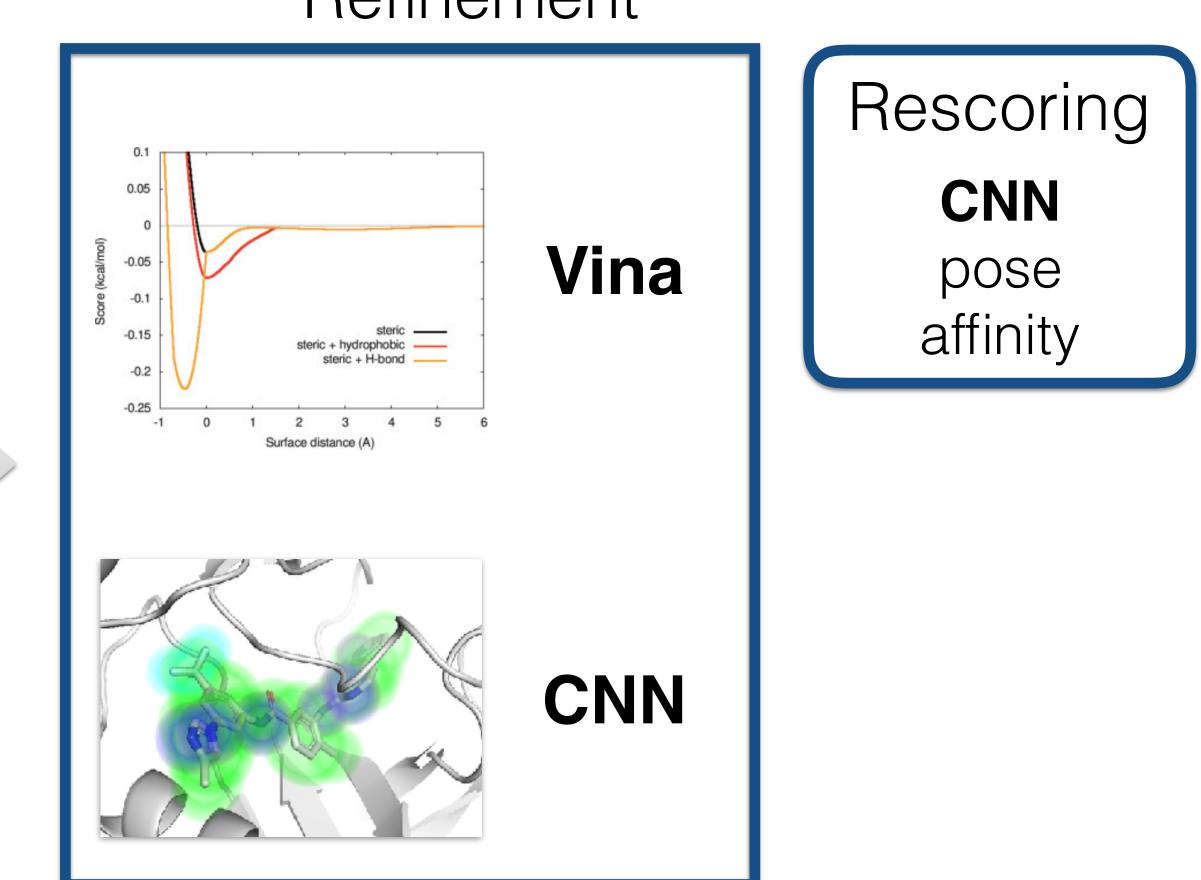
best

poses

Sampling



N (50) independent Monte Carlo chains Scored with grid-accelerated Vina Best identified pose retained



Refinement



Prospective Evaluation: D3R

Spearman Correlation

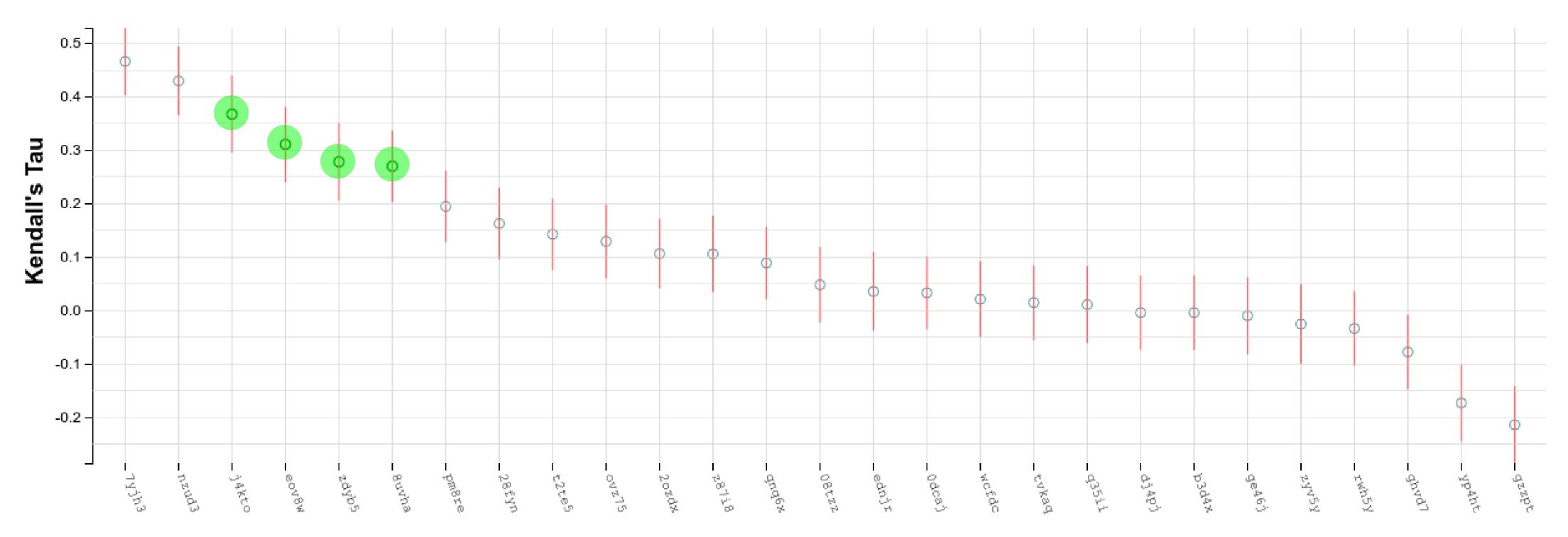
| | cnn_docked_affinity | cnn_rescore_affinity | cnn_docked_scoring | cnn_rescore_scoring | vina |
|-----------|---------------------|----------------------|--------------------|---------------------|---------|
| cat | 0.0701 | 0.154 | -0.0351 | 0.178 | 0.179 |
| p38a | -0.0784 | -0.116 | -0.329 | -0.305 | -0.0631 |
| vegfr2 | 0.366 | 0.484 | 0.434 | 0.448 | 0.414 |
| jak2 | 0.428 | 0.338 | 0.39 | 0.27 | 0.106 |
| jak2_sub3 | 0.68 | 0.369 | -0.372 | 0.159 | -0.633 |
| tie2 | 0.648 | 0.835 | 0.136 | -0.078 | 0.561 |
| | | | | | |
| abl1 | 0.634 | 0.745 | 0.005 | 0.182 | 0.713 |





Grand Challenge 3 - JAK2_SC2

Affinity Ranking - Kendall's Tau



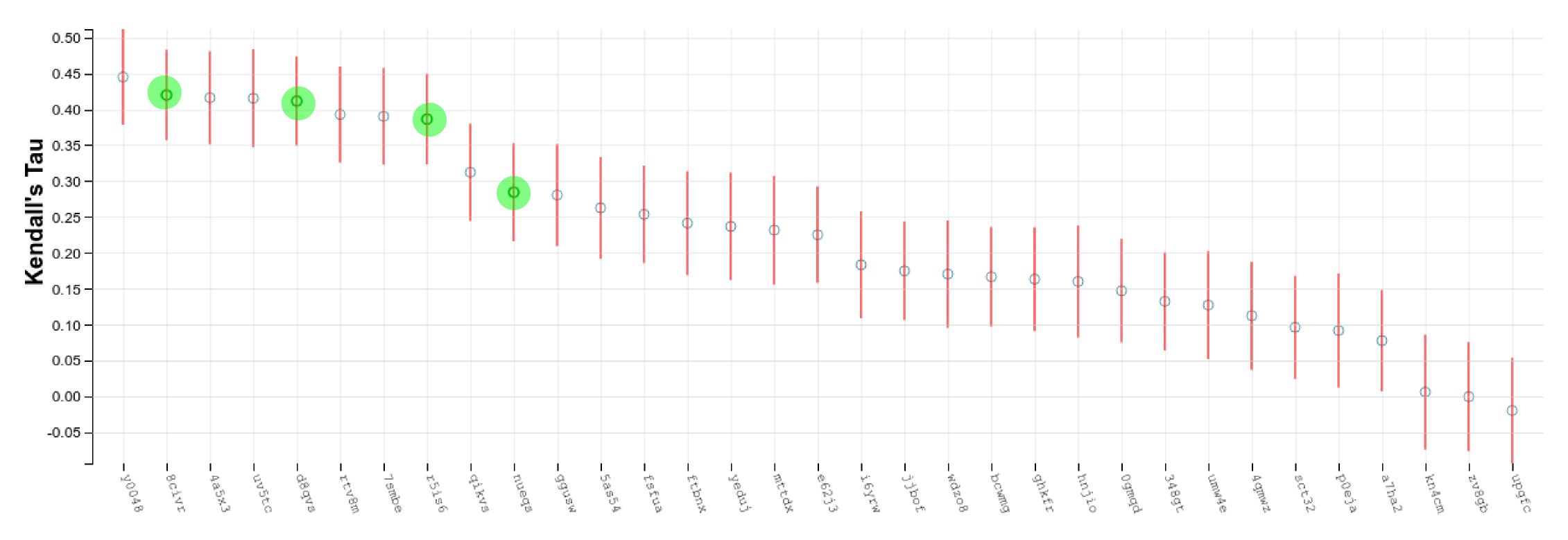
Receipt ID

Green circle indicates your predictions (requires login)



Grand Challenge 3 - VEGFR2

Affinity Ranking - Kendall's Tau



Receipt ID

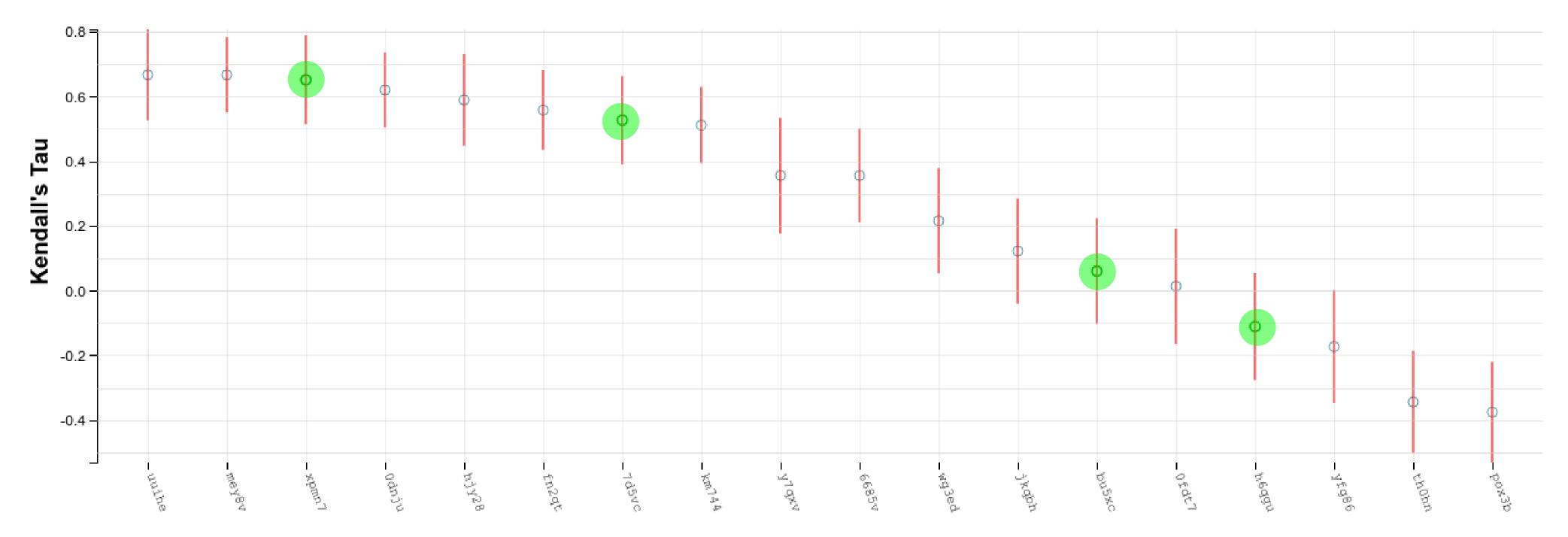
Green circle indicates your predictions (requires login)





Grand Challenge 3 - TIE2

Affinity Ranking - Kendall's Tau



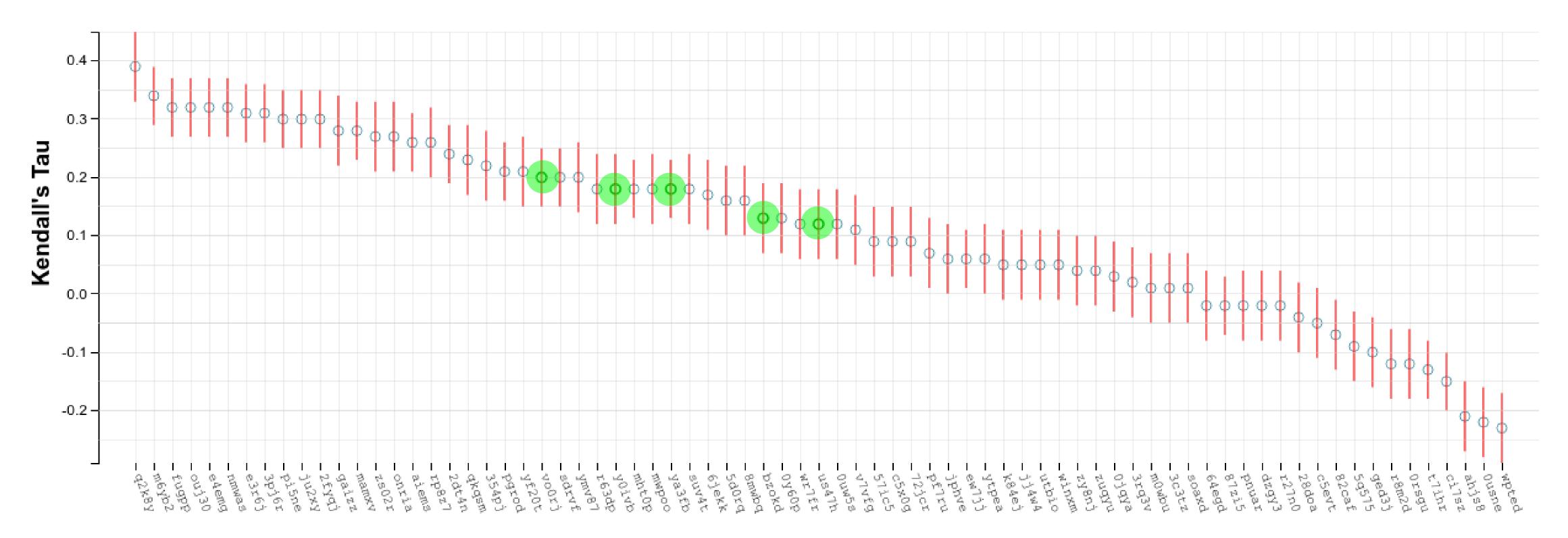
Receipt ID

Green circle indicates your predictions (requires login)



Grand Challenge 3 - CatS_stage2

Affinity Ranking - Kendall's Tau





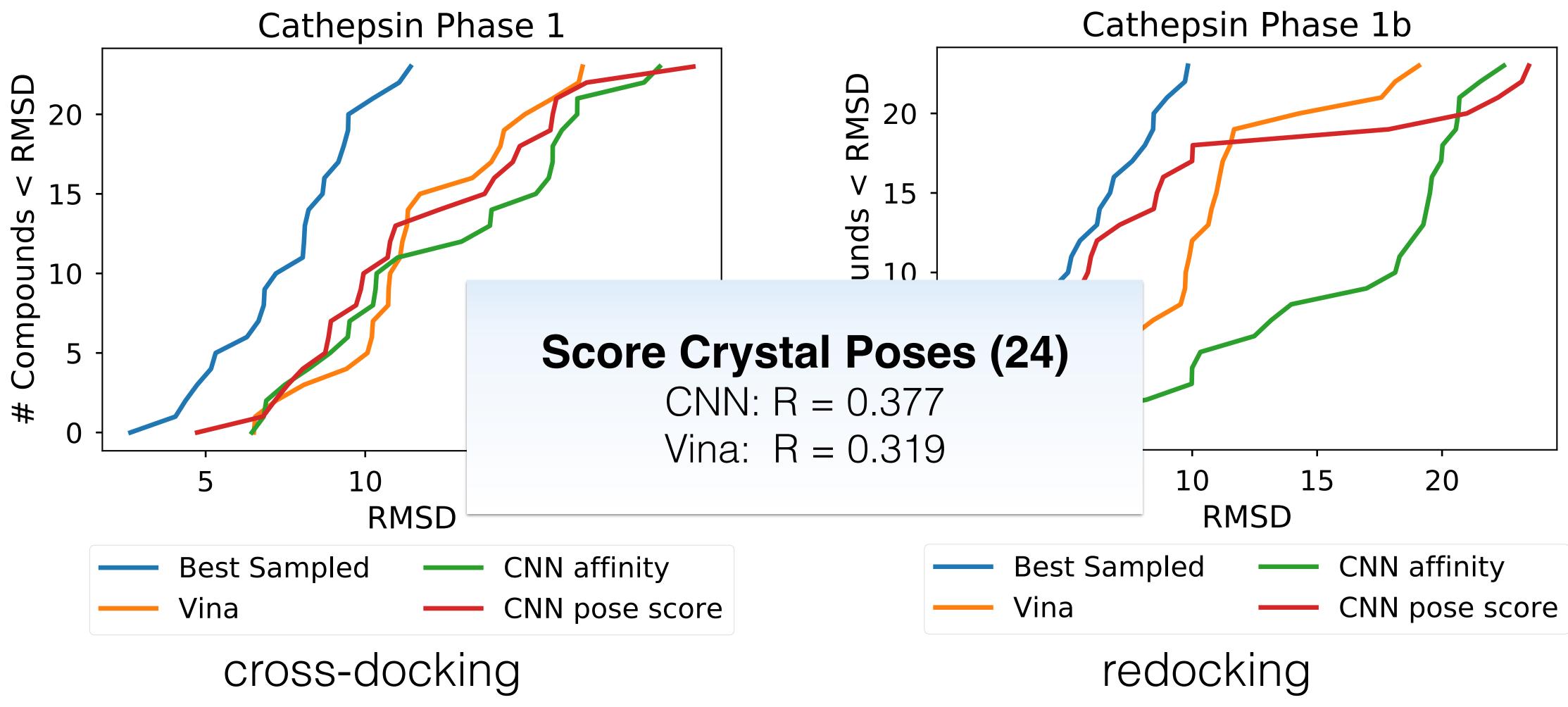
Receipt ID

Green circle indicates your predictions (requires login)



GC3: Pose Prediction

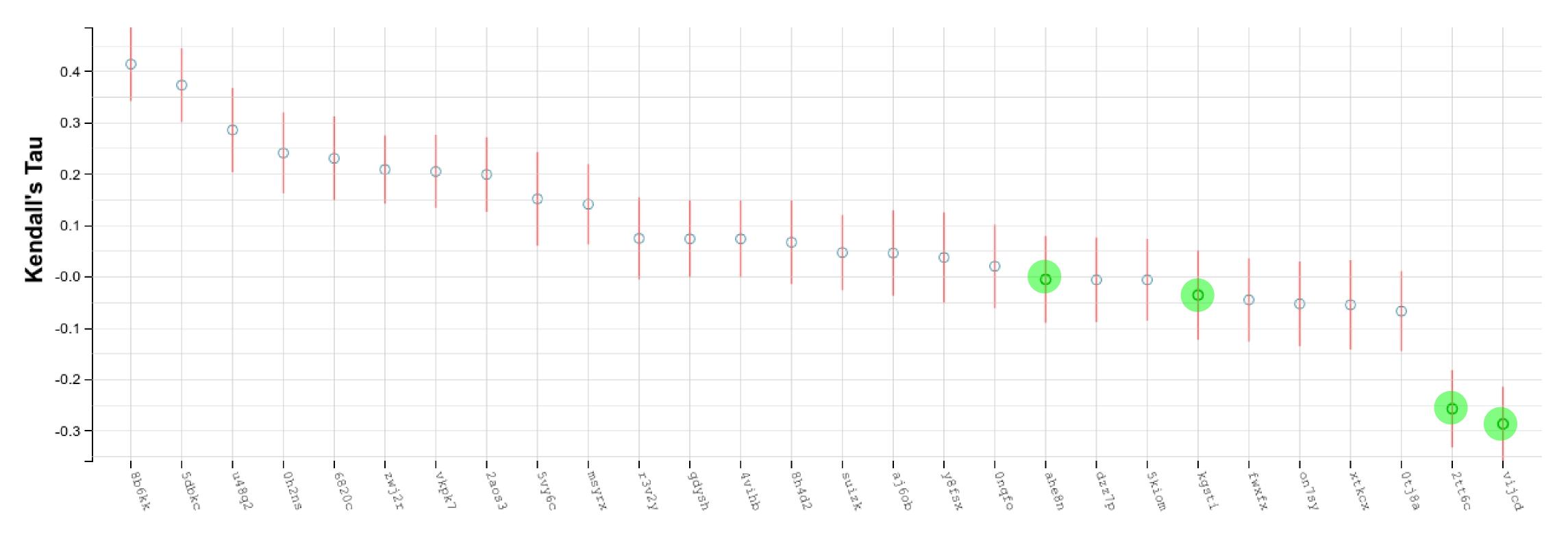
Cathepsin Phase 1





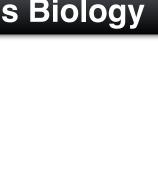
Grand Challenge 3 - p38a

Affinity Ranking - Kendall's Tau



Receipt ID

Green circle indicates your predictions (requires login)





Prospective Evalution: TIGIT



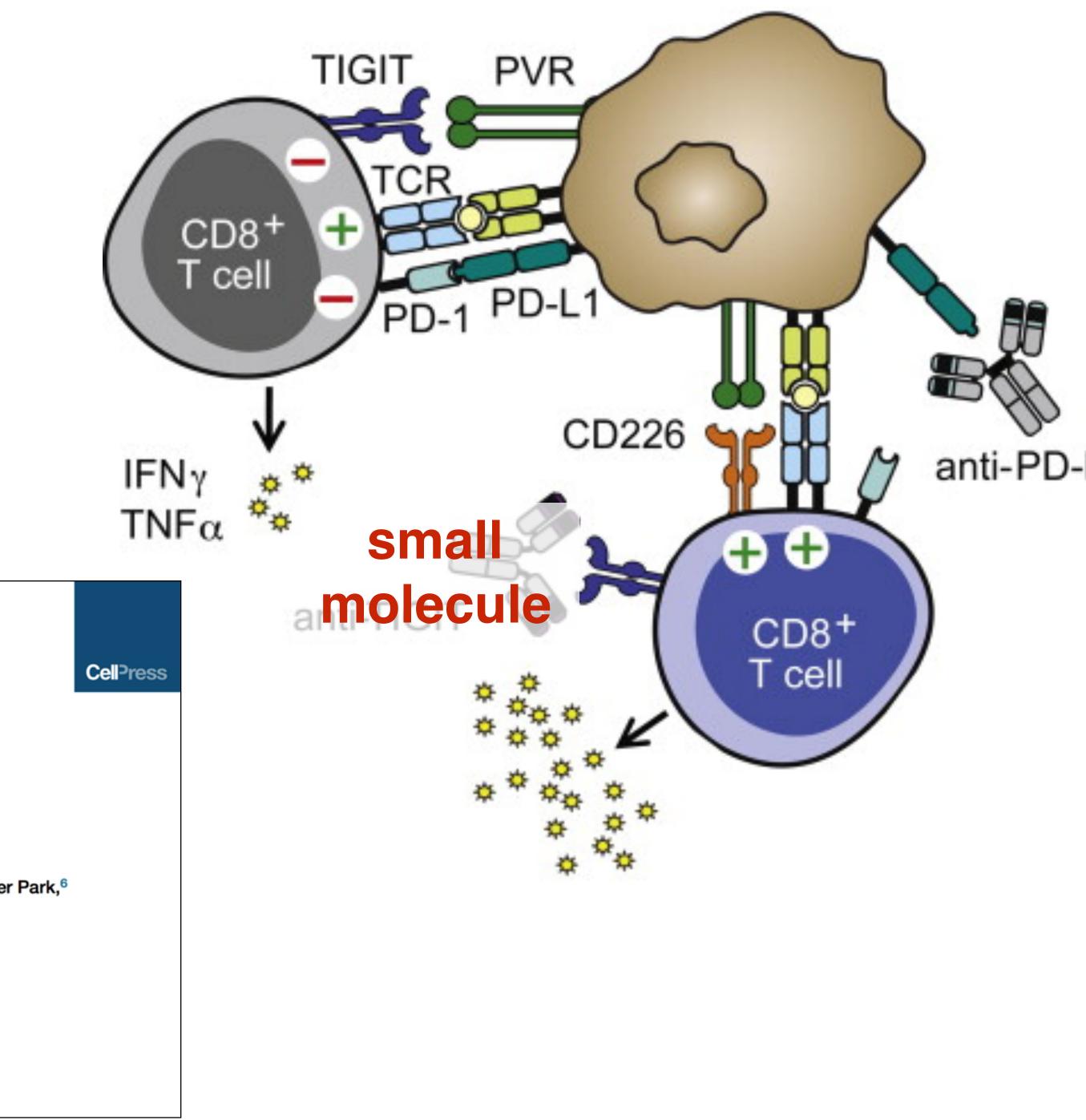


Can we block TIGIT/ PVR interaction with a small molecule?

Cancer Cell Article

The Immunoreceptor TIGIT Regulates Antitumor and Antiviral CD8⁺ T Cell Effector Function

Robert J. Johnston,¹ Laetitia Comps-Agrar,² Jason Hackney,³ Xin Yu,¹ Mahrukh Huseni,⁴ Yagai Yang,⁵ Summer Park,⁶ Vincent Javinal,⁵ Henry Chiu,⁷ Bryan Irving,¹ Dan L. Eaton,² and Jane L. Grogan^{1,*} ¹Department of Cancer Immunology ²Department of Protein Chemistry ³Department of Bioinformatics and Computational Biology ⁴Department of Oncology Biomarker Development ⁵Department of Translational Oncology ⁶Department of Translational Immunology ⁷Department of Biochemical and Cellular Pharmacology Genentech, 1 DNA Way, South San Francisco, CA 94080, USA *Correspondence: grogan.jane@gene.com http://dx.doi.org/10.1016/j.ccell.2014.10.018

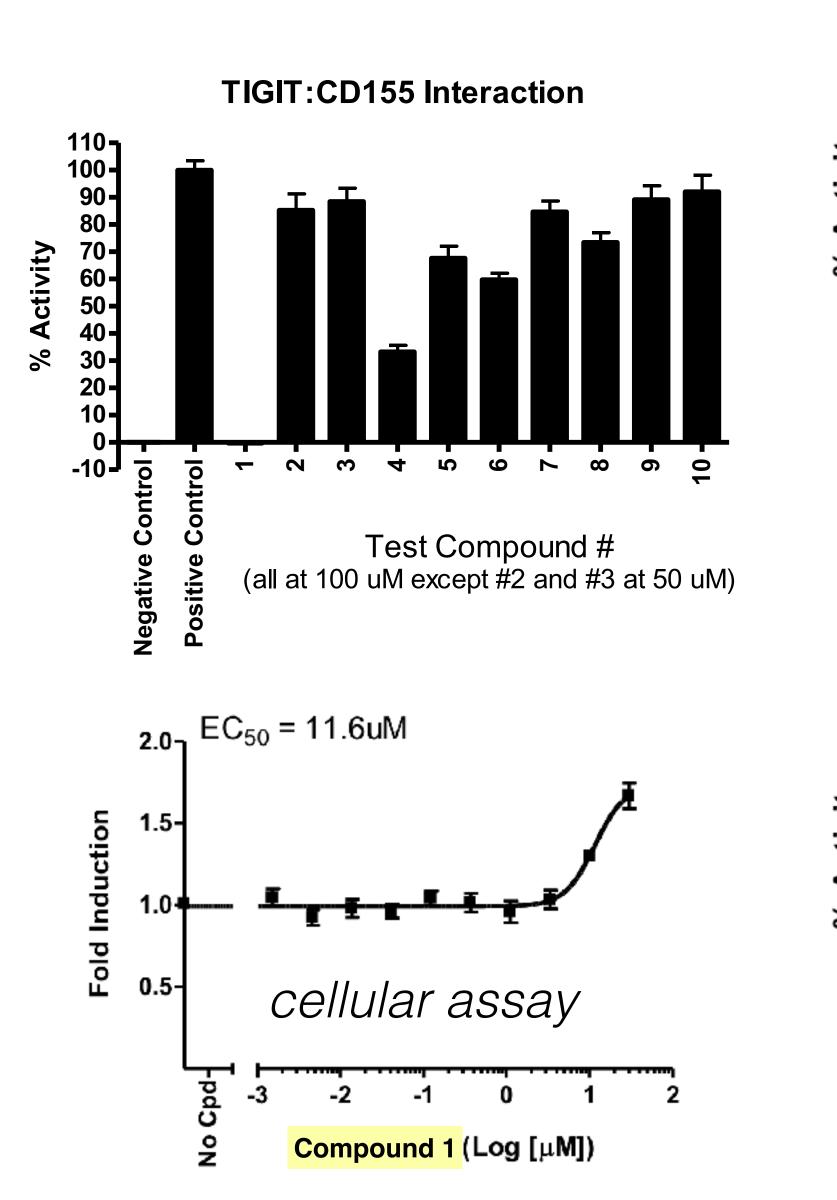


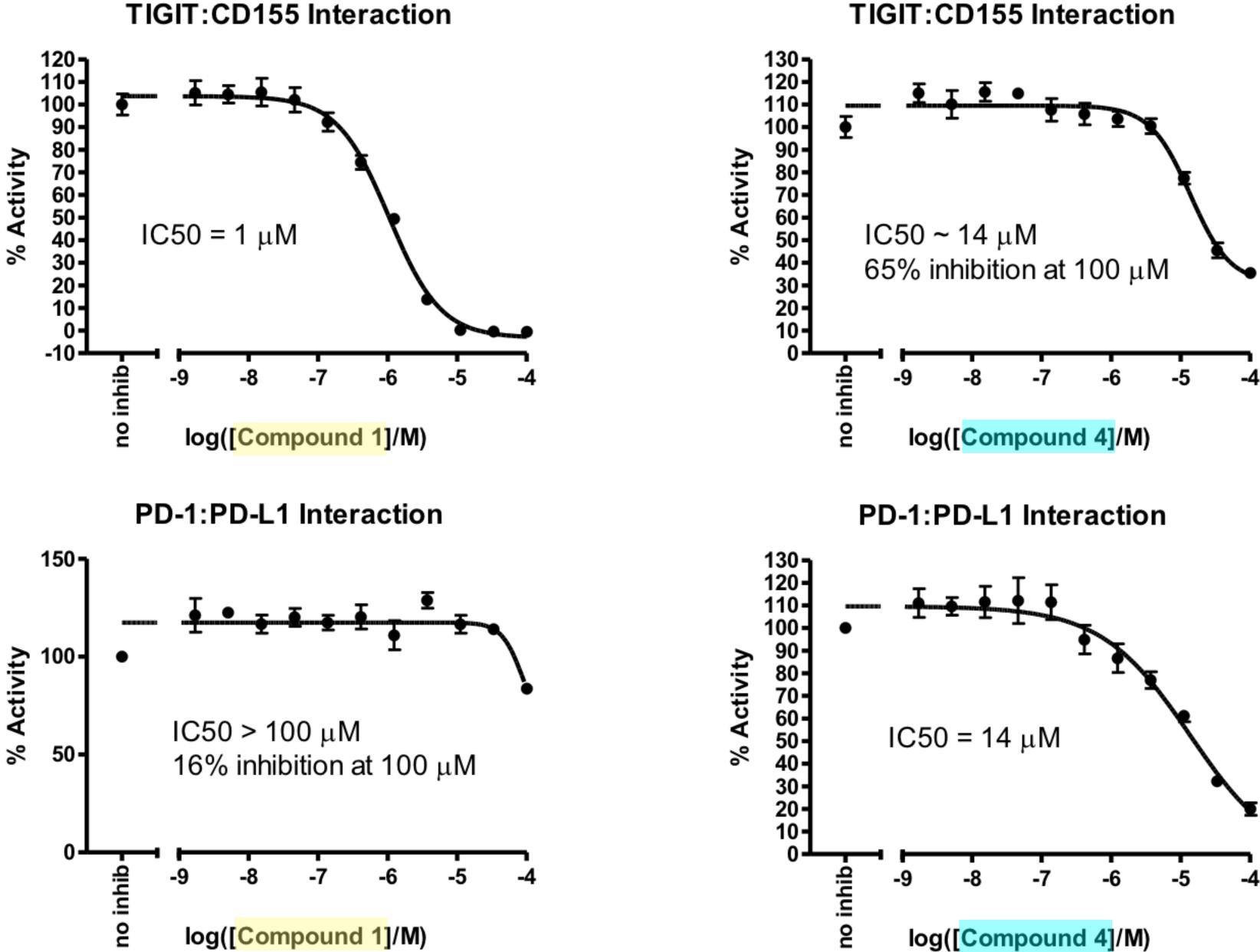
Screening

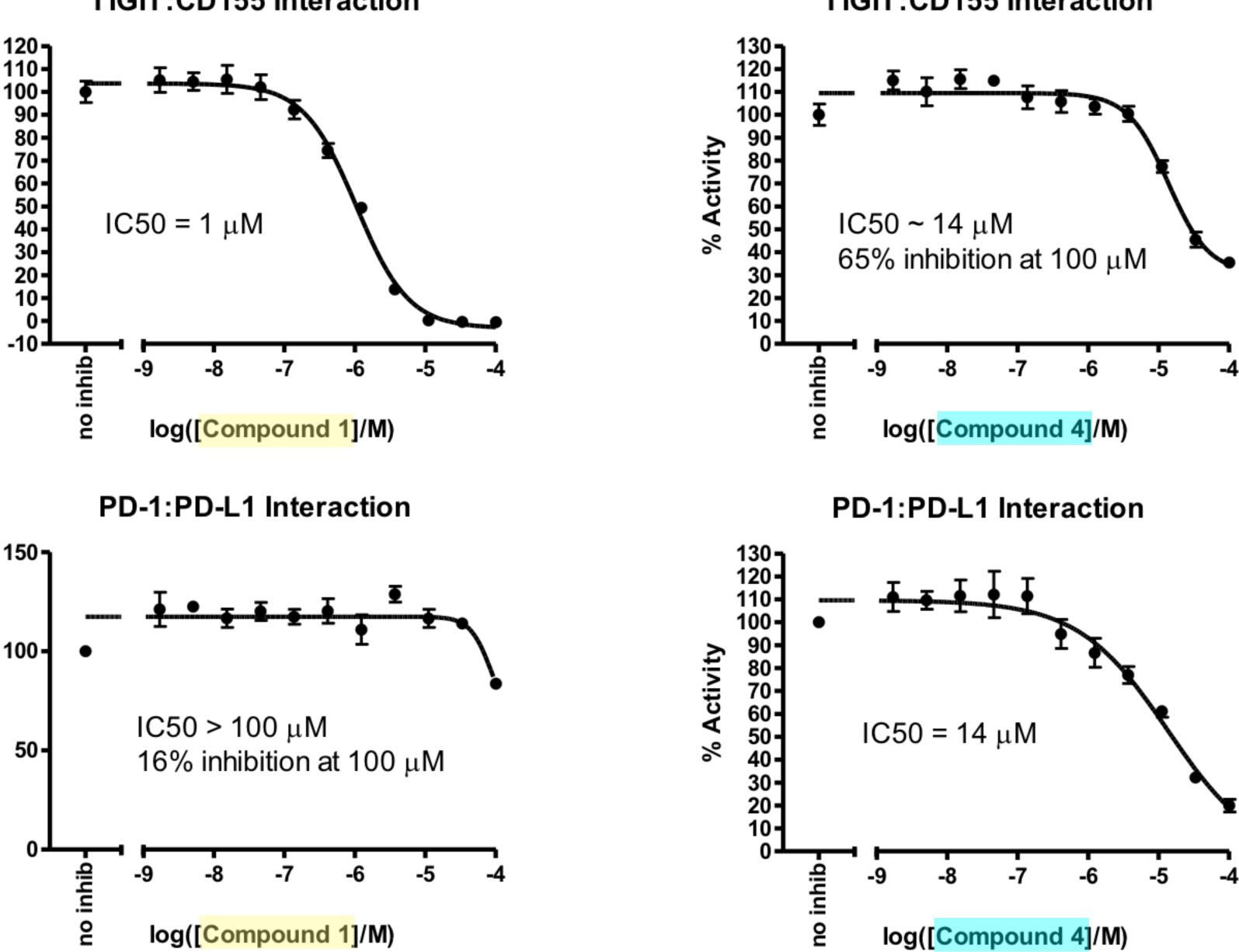
10 diverse compounds selected for screening top ranked by Vina top ranked by CNN

| Name | CNN Affinity | CNN Score | Vina |
|-------------|--------------|-----------|----------|
| Compound 1 | 7.69807 | 0.994763 | 85.95 |
| Compound 2 | 5.57909 | 0.0180277 | -8.12632 |
| Compound 3 | 6.73692 | 0.0624742 | -9.81935 |
| Compound 4 | 6.87897 | 0.953488 | -3.81378 |
| Compound 5 | 6.32813 | 0.209807 | -8.60293 |
| Compound 6 | 5.689 | 0.0437 | -8.991 |
| Compound 7 | 4.368 | 0.022 | -9.34722 |
| Compound 8 | 4.81 | 0.072 | -6.81787 |
| Compound 9 | 5.22 | 0.072 | -6.264 |
| Compound 10 | 6.67 | 0.361 | 6.1053 |

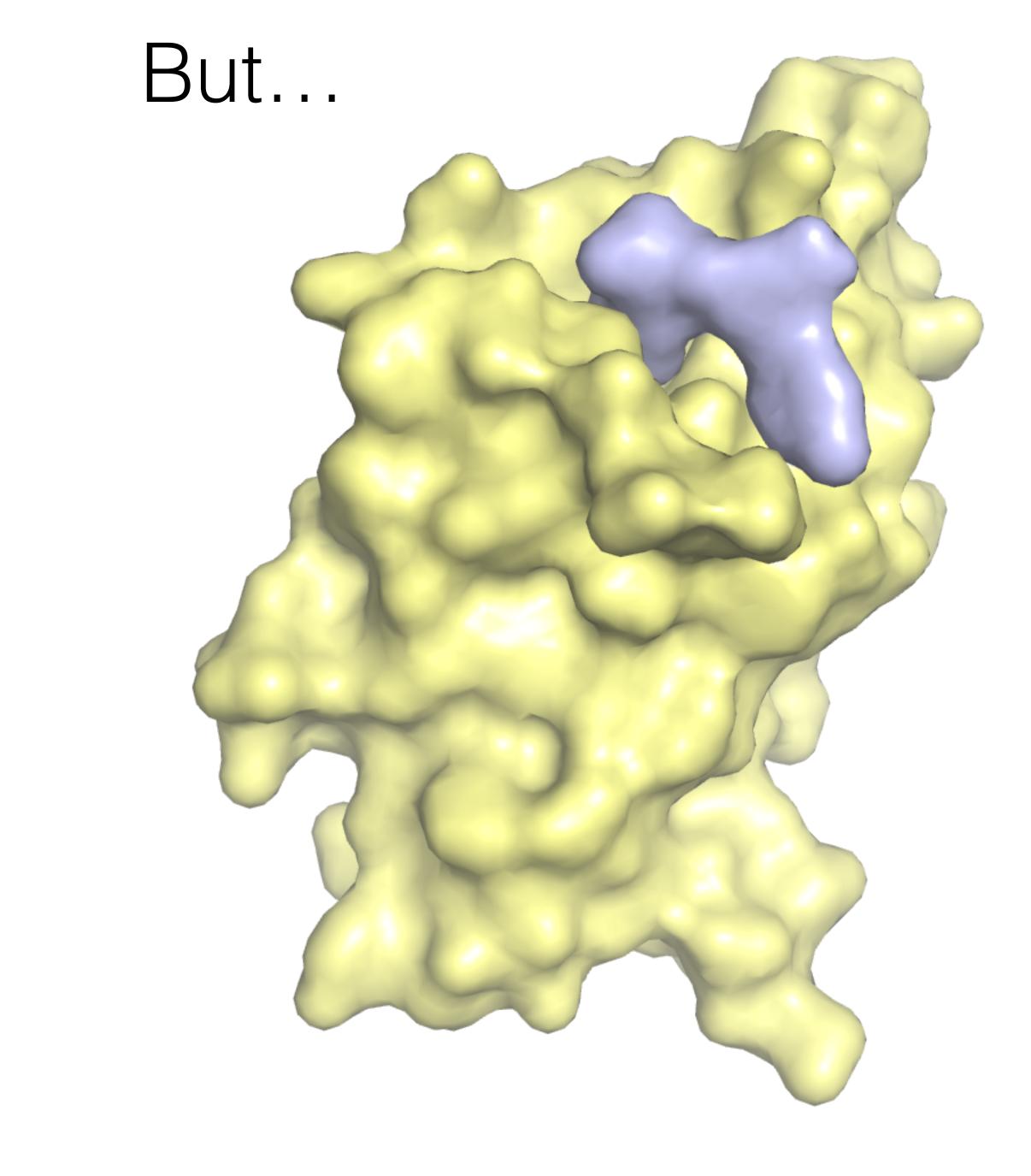
Results



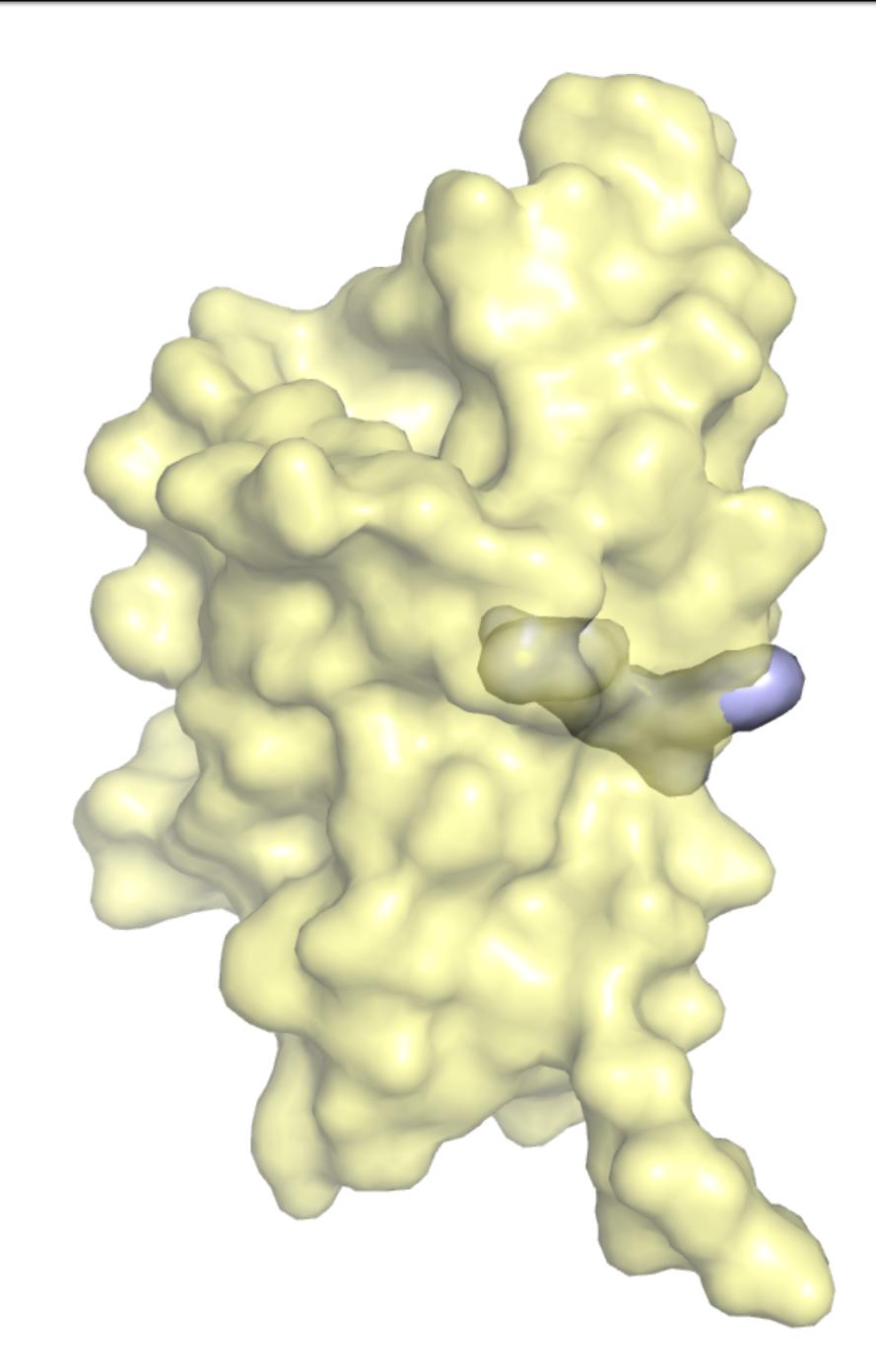




University of Pittsburgh

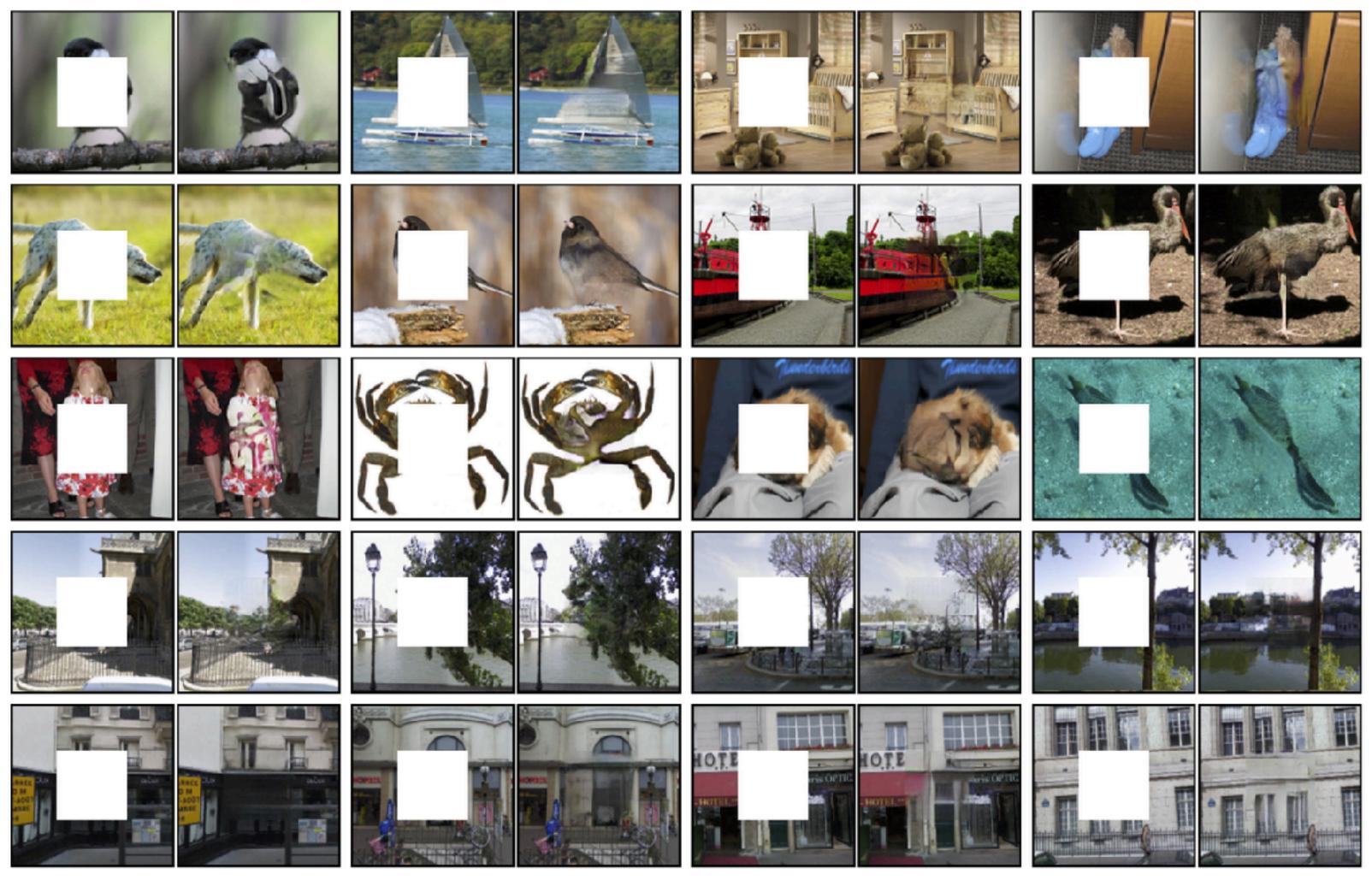


Computational and Systems Biology





and now for something completely different...

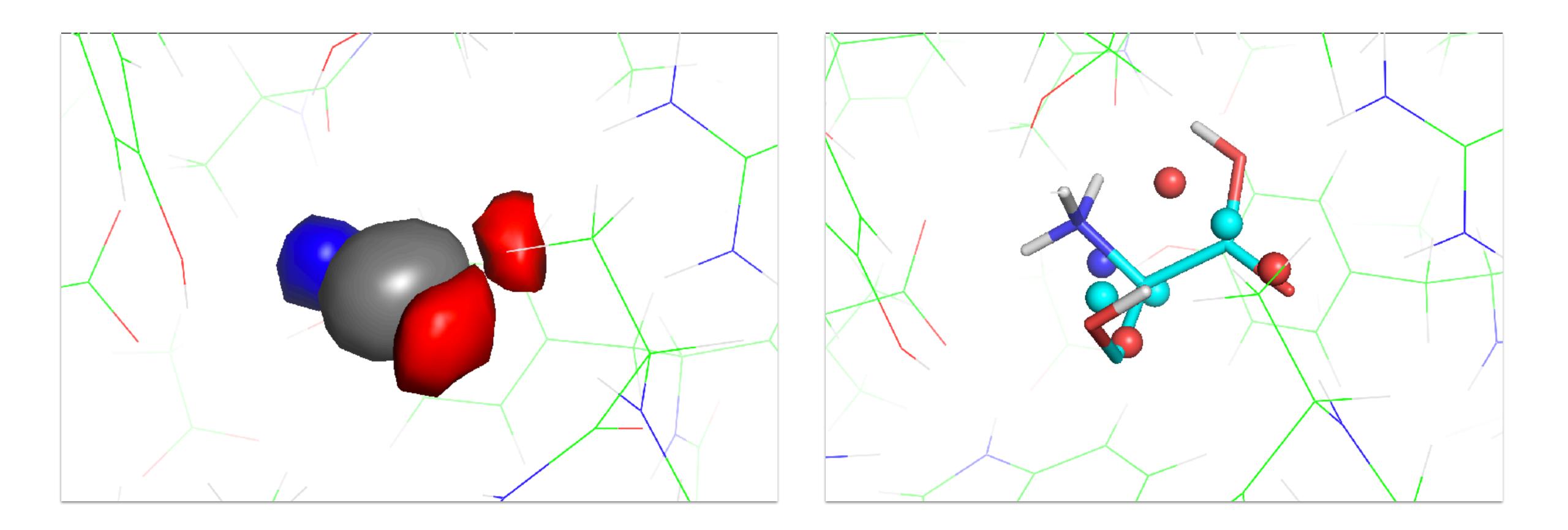


http://people.eecs.berkeley.edu/~pathak/context_encoder/

Context Encoding

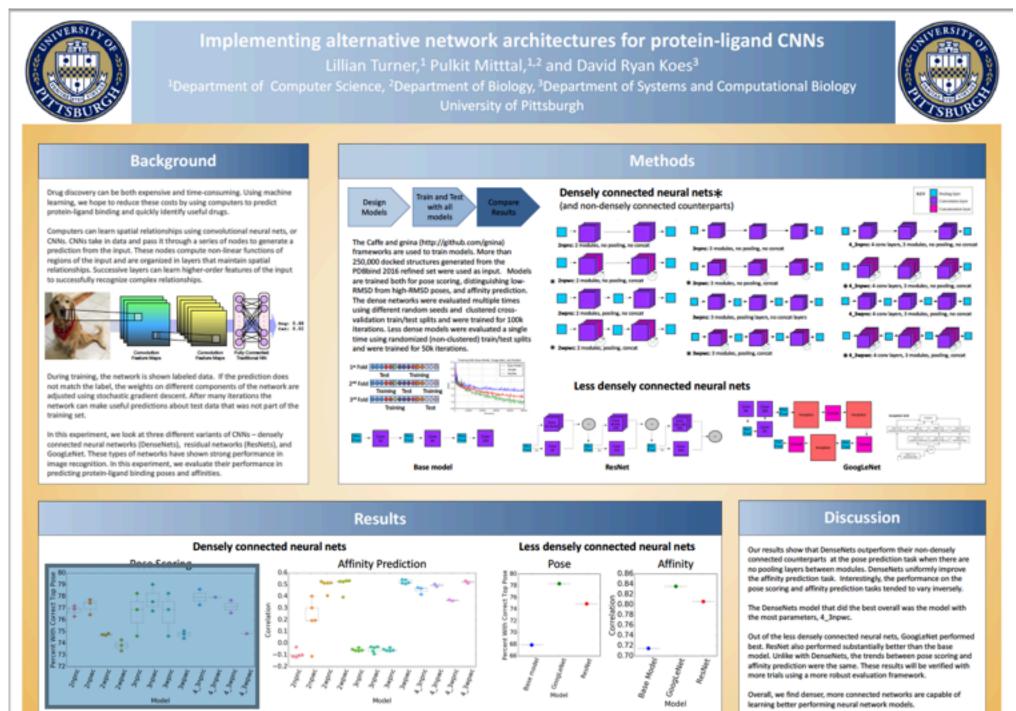


Molecular Context Encoding





Shameless Plug



Combined test performance on the pose scoring and affinity prediction tasks is shown. Pose scoring is evaluated by the percentage of targets where a low RMSD (<2Å) pose is top ranked Affinity prediction is evaluated using Pearson R correlation. Note that the performance of the DenseNet models and the ResNet and GoogLeNet models cannot be compared as they were not evaluated using the same procedure.

This work is supported by R01GM108340 from the National Institute

of General Medical Sciences.

COMP 191: Alternative network architectures for protein-ligand scoring



COMP 320: GPU molecular docking with convolutional neural network scoring functions

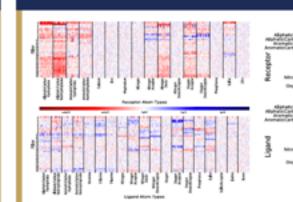
Visualization of Convolutional Neural Network Scoring of Protein-Ligand Binding

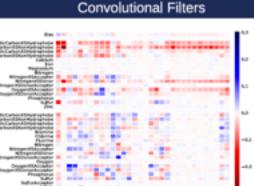
Joshua Hochuli,¹ Alec Helbling,² Matthew Ragoza,¹ and David Ryan Koes¹ ¹Department of Computational and Systems Biology, University of Pittsburgh, ²Pittsburgh Science and Technology Academy

Abstract

X

votein-ligand scoring functions rank and score molecular structures with the goals of accurately predicting binding affinity, selecting the correct binding pose, and distinguishing between binders and non-binders. Creating a function that can accurately do this has many positive implications pertaining to computational drug discovery. Convolutional neural networks are a specific style of neural networks that leverage translationally equivariant sets of weights that define filters. We developed a convolutional neural network model for protein-ligand scoring that takes a 4 D representation of a protein-ligand structure. Here we describe methods for visualizing the decision process of a trained network by projecting heatmaps onto the input structure using masking, layerwise-relevance propagation, and gradient-based approaches. Additionally, we provide direct visualizations of the first convolutional layer of the network, which reveal the ow-level features that maximally activate this this initia



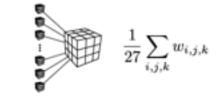


Weights of the first convolutional layer of the CNN are visualized in both figures. The first figure shows all filter weights for each filter and atom type, and the second figure shows average weights for each

U.V.

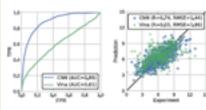
0.0

These visualizations help determine what atom types the CNN considers important for low-level feature



Background

Atom densities are vowelized to a grid that is the input to a 3D convolutional neural network. The network has two targets: pose scoring and affinity prediction, The targets share the same architecture and weights until the final fully connected layer, which is unique to each target. The network is trained on redocked ligands from the 2016 PDBbind refined set using AutoDock Vina. The pose scoring network is trained to distinguish between low (<2Å) and high (>4Å MSD poses, while the affinity prediction network is trained to predict the binding affinity in log units.



The trained network substantially outperforms AutoDock Vina at selecting and ranking poses and predicting binding attivity. Visualizations of the network provide insights into what the network has learned and how it processe specific features,

References

Hochuli, J., Helbling, A., Skaist, T., Ragoza, M., Koes, D.R., 2018. Visualizing Convolutional Neural Network Protein-Ligand Scoring, arXiv preprint arXiv: 1803.02398. Bach, S., Binder, A., Montavon, G., Klauschen, F., Müller, K.R. and Samek, W., 2015. On pixel-wise

explanations for non-linear classifier decisions by layer-wise relevance propagation. PloS one, 10(7), p.e0130140



score.

 ∂a

0.86

How the CNN scores the unchanged structure In order to address issues with propagating relevance through

decision back through the network to the input. At each layer, activation have their relevance summed and then distributed the sum of relevances on each node is equal to the score for the equally across the rest of the nodes in the layer,

 $f(x) = ... = \sum R_d^{(l+1)} = \sum R_d^{(l)} = ... = \sum R_d^{(l)}$



 $S_l = \sum_j \begin{cases} 0 & z_j \neq 0 \\ R_j & z_j = 0 \end{cases} \qquad R_j = \begin{cases} 0 & z_j = 0 \\ R_j + \frac{x_j}{Z_l} * S_l & z_j \neq 0 \end{cases}$

Gradient

 $\sum_{g \in G_a} \frac{\partial f}{\partial g} \frac{\partial g}{\partial d} \frac{\partial d}{\partial a}$

Masking

How the CNN scores changes to the structure

Atoms are removed from a complex, and the resulting difference in score is used to color the

- 0.84 = 0.02

GradientHow the CNN changes the structure to score betterThe loss gradient is propagated all the way back to
input atoms. We also produce a vector to visualize
where atoms should move in space to increase the
score.
$$\frac{\partial f}{\partial a} = \sum_{e=0}^{\infty} \frac{\partial f}{\partial g} \frac{\partial g}{\partial d} \frac{\partial d}{\partial a}$$

Alleby = 4,93

COMP 226: Visualizing convolutional neural network scoring of protein-ligand binding

Empty Space

CLRP provides an opportunity to visualize how the

network interprets empty space. This method helps

show how the network interprets implicit solvents and

also larger structural features like binding pocket size

After propagating relevance back to the first

convolutional layer, the relevance of nodes with zero

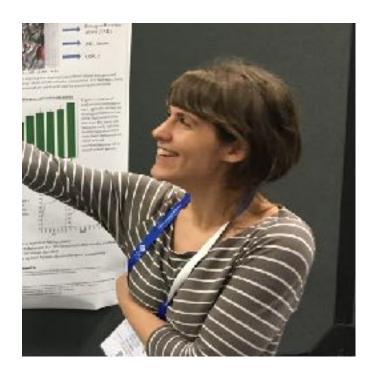
activation in the forward direction is directly mapped

and shape.

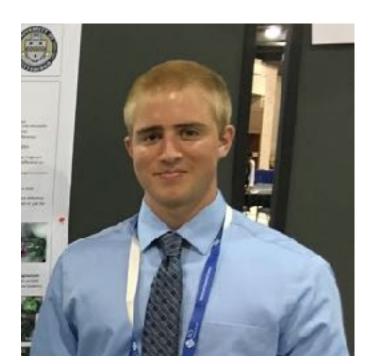
onto the input grid.



Acknowledgements



Jocelyn Sunseri



Result Person Perso

Matt Ragoza



Josh Hochuli

Lily Turner





National Institute of General Medical Sciences R01GM108340

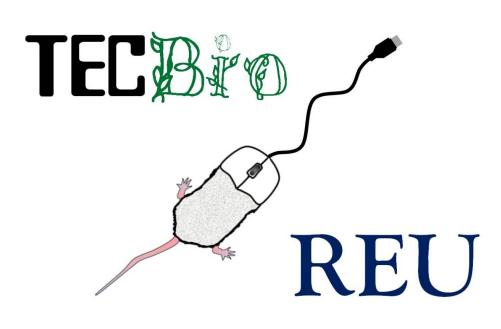
Group Members

Jocelyn Sunseri Jonathan King Paul Francoeur Matt Ragoza Josh Hochuli Lily Turner **Pulkit Mittal** Alec Helbling **Gibran Biswas** Sharanya Bandla Faiha Khan





Department of Computational and Systems Biology





O github.com/gnina http://bits.csb.pitt.edu @david_koes



Computer Facts (a) computer fact

concerned parent: if all your friends jumped off a bridge would you follow them? machine learning algorithm: yes.

2:20 PM · Mar 15, 2018



