Protein-Ligand Scoring with Convolutional Neural Networks

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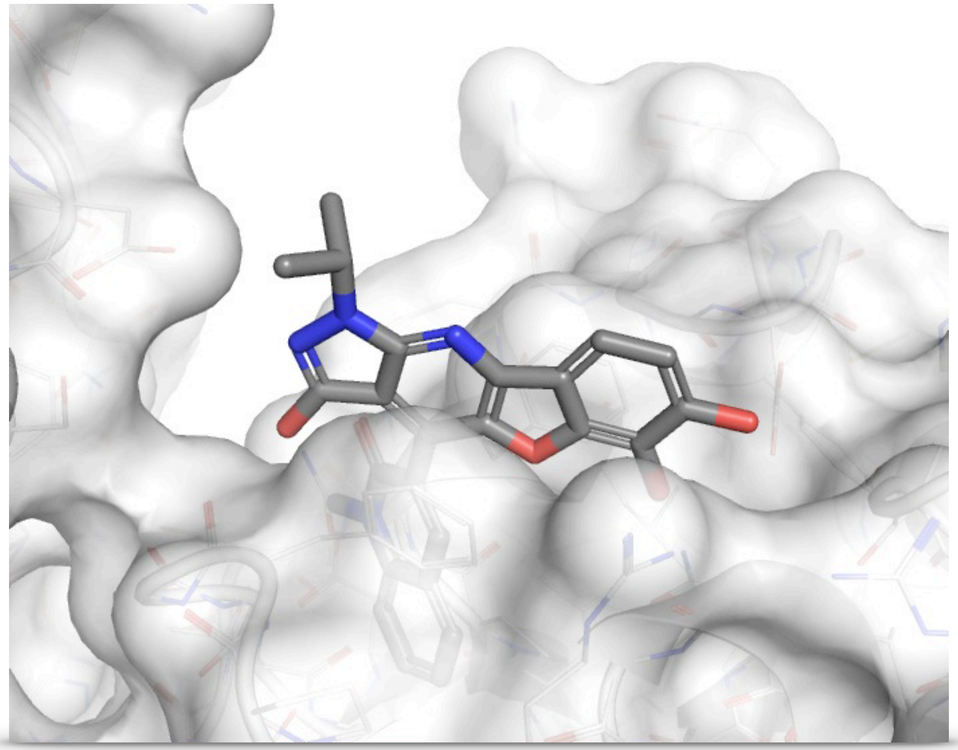
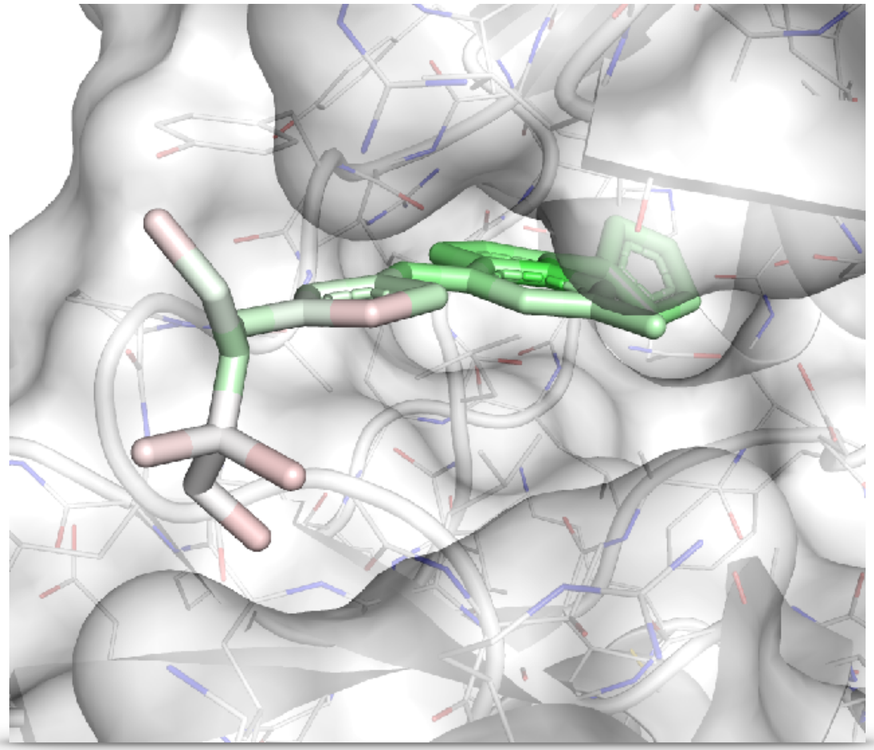
D3R Workshop
San Diego
February 22, 2018

Structure Based Drug Design

Virtual Screening



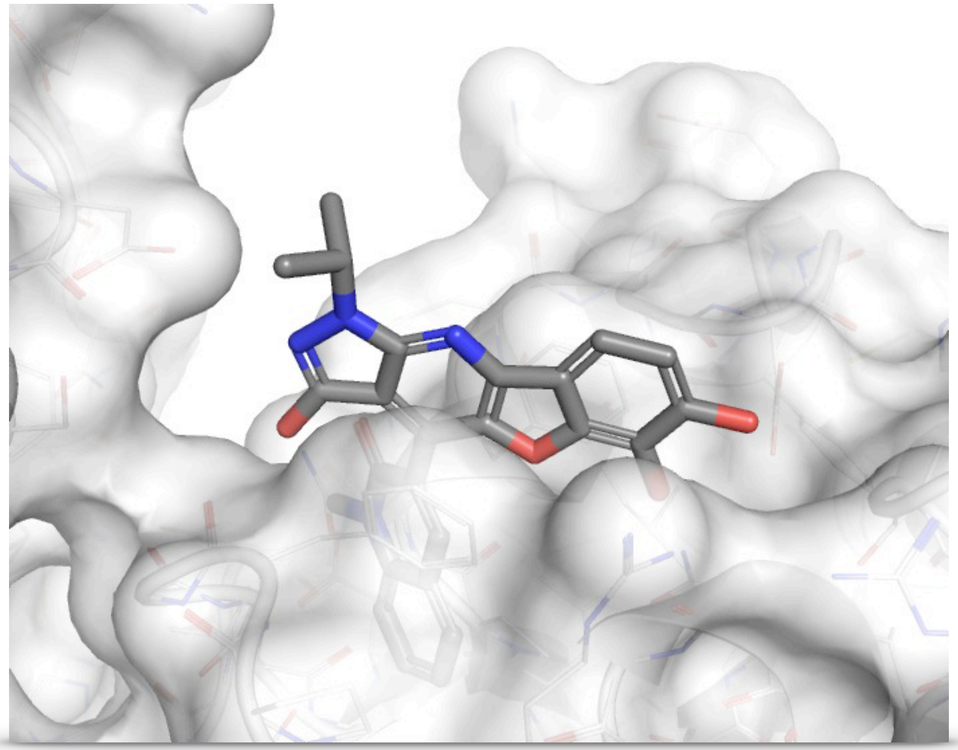
Lead Optimization



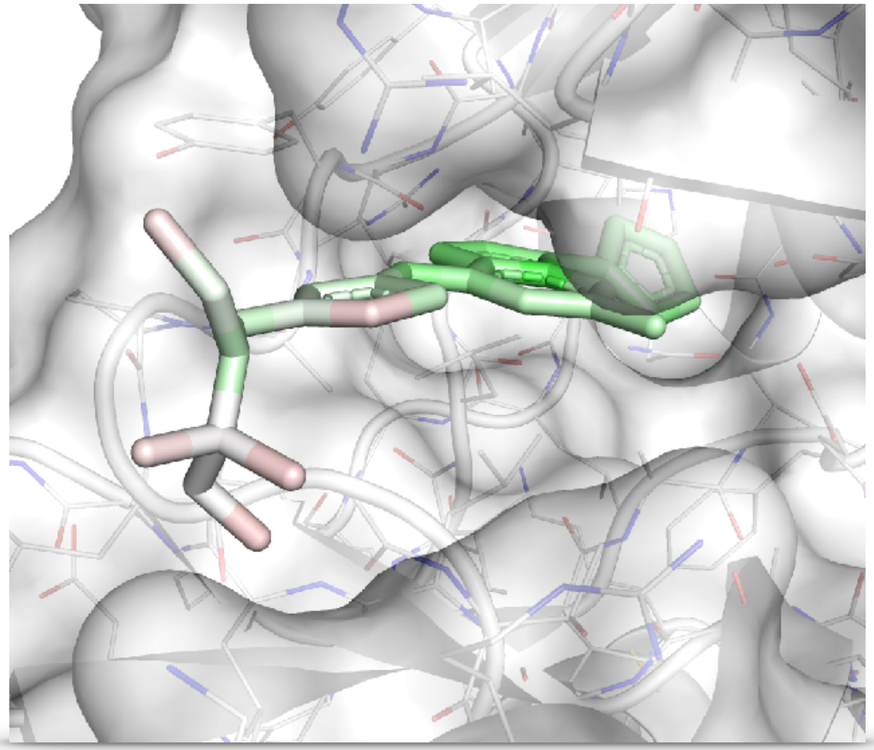
Pose Prediction Binding Discrimination **Affinity Prediction**

Structure Based Drug Design

Virtual Screening

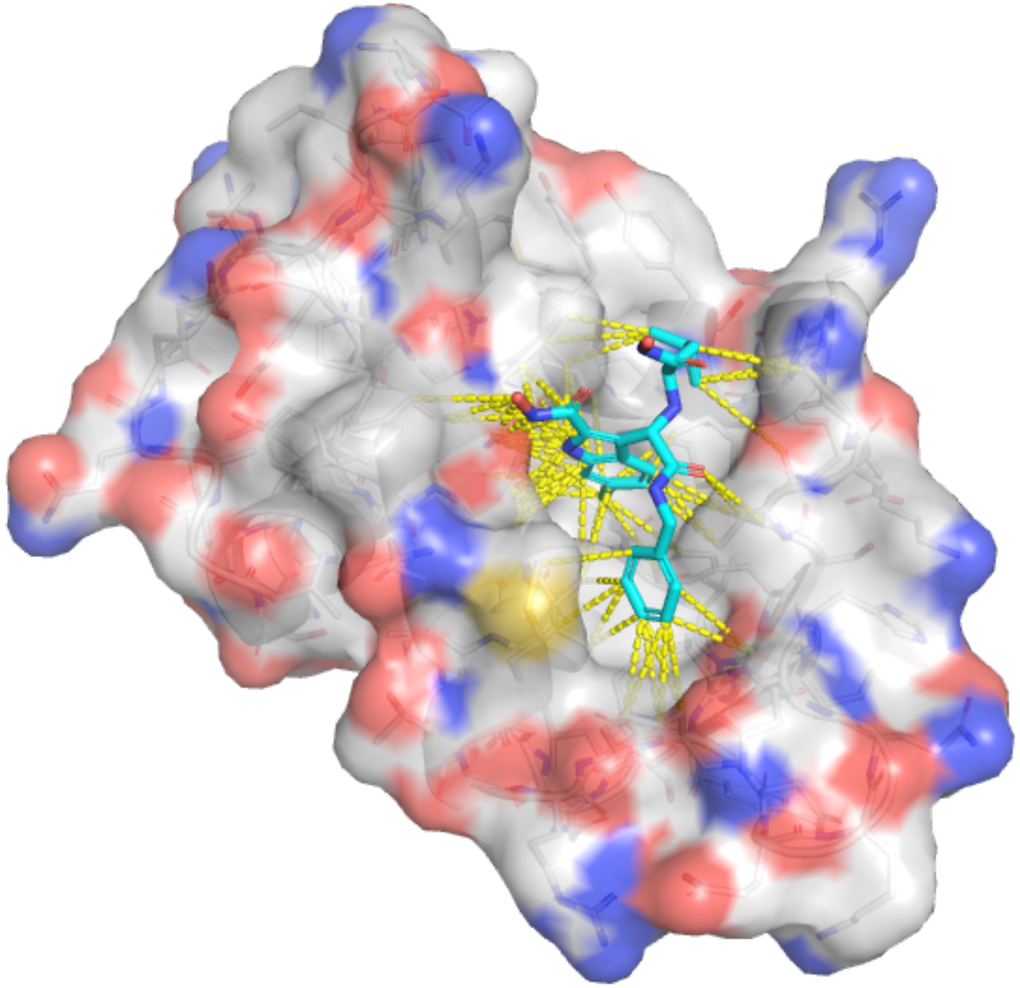


Lead Optimization



Pose Prediction Binding Discrimination **Affinity Prediction**

Protein-Ligand Scoring



AutoDock Vina

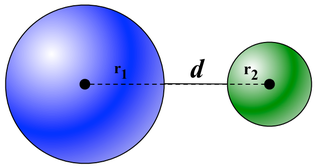
$$\text{gauss}_1(d) = w_{\text{guass}_1} e^{-(d/0.5)^2}$$

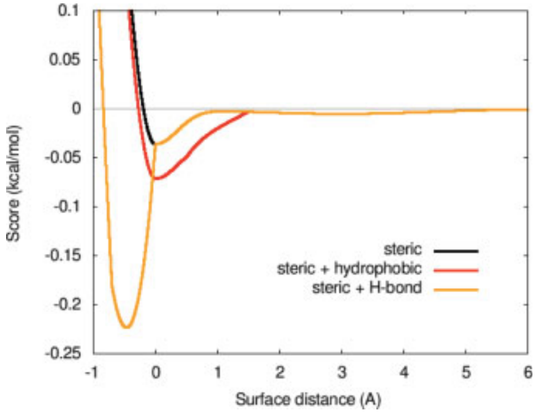
$$\text{gauss}_2(d) = w_{\text{guass}_2} e^{-((d-3)/2)^2}$$

$$\text{repulsion}(d) = \begin{cases} w_{\text{repulsion}} d^2 & d < 0 \\ 0 & d \geq 0 \end{cases}$$

$$\text{hydrophobic}(d) = \begin{cases} w_{\text{hydrophobic}} & d < 0.5 \\ 0 & d > 1.5 \\ w_{\text{hydrophobic}}(1.5 - d) & otherwise \end{cases}$$

$$\text{hbond}(d) = \begin{cases} w_{\text{hbond}} & d < -0.7 \\ 0 & d > 0 \\ w_{\text{hbond}}(-\frac{10}{7} d) & otherwise \end{cases}$$





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

Can we do better?

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

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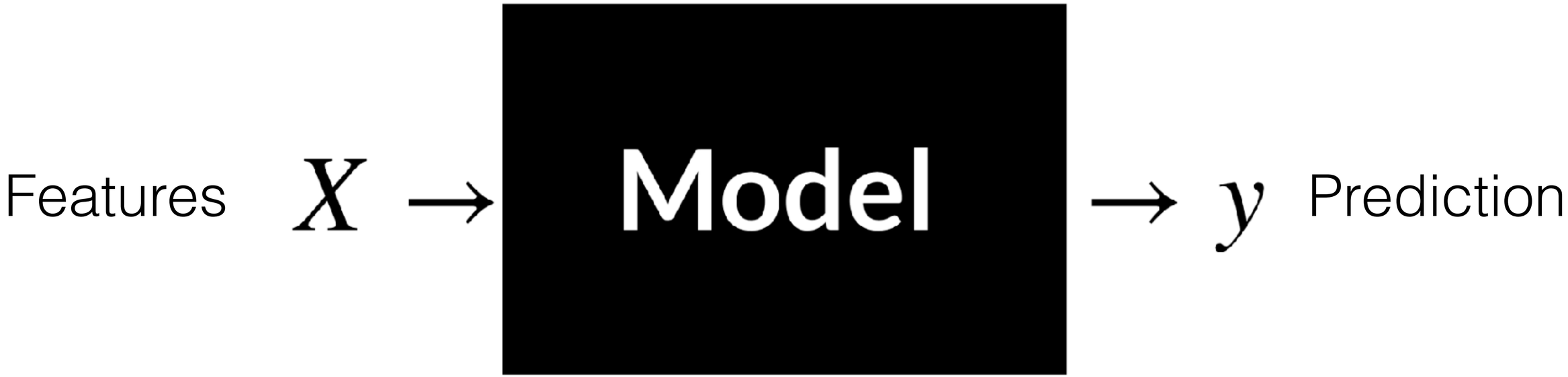
Accurate pose prediction, binding discrimination, **and** affinity prediction without sacrificing performance?

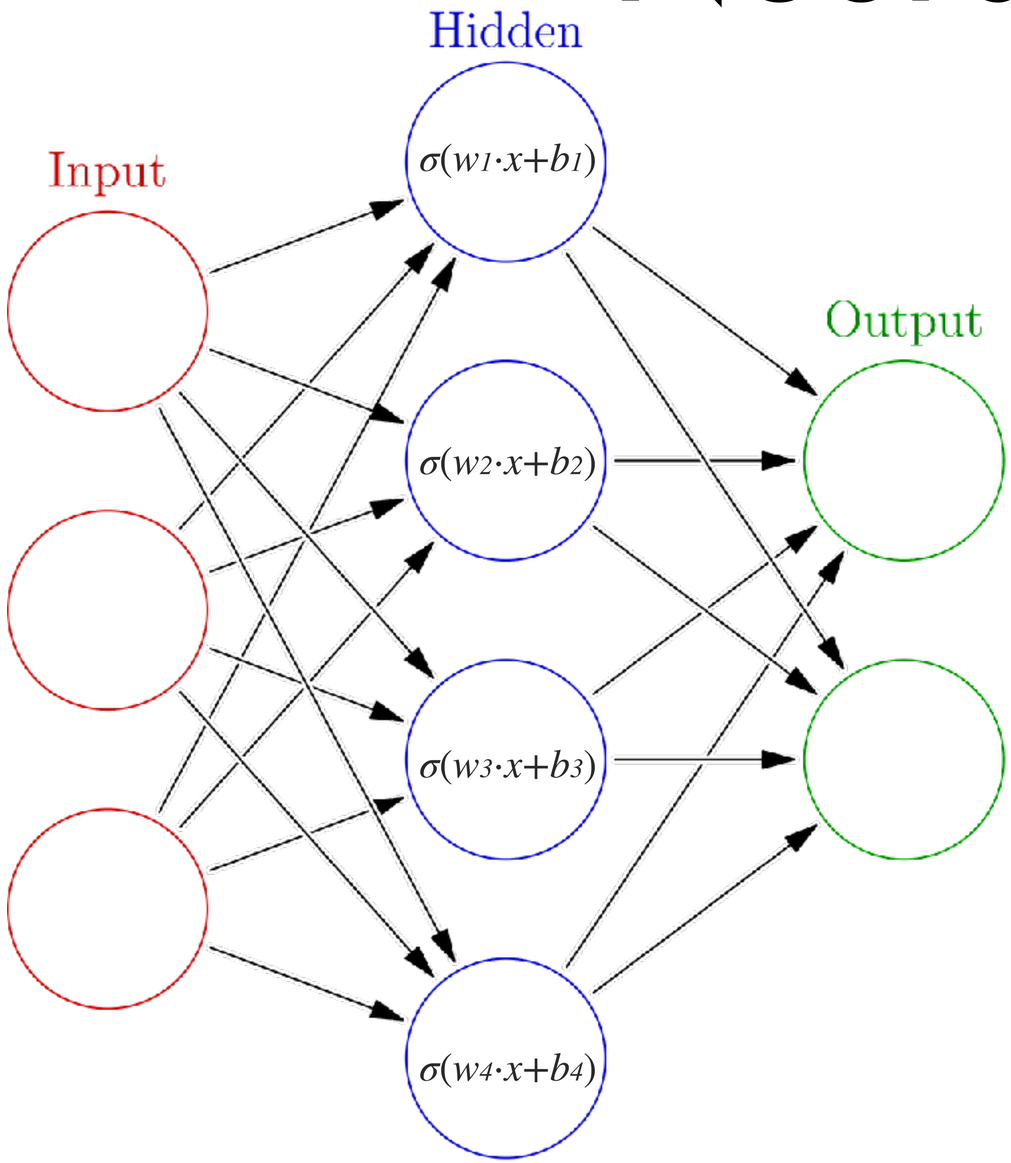
Key Idea: Leverage "big data"

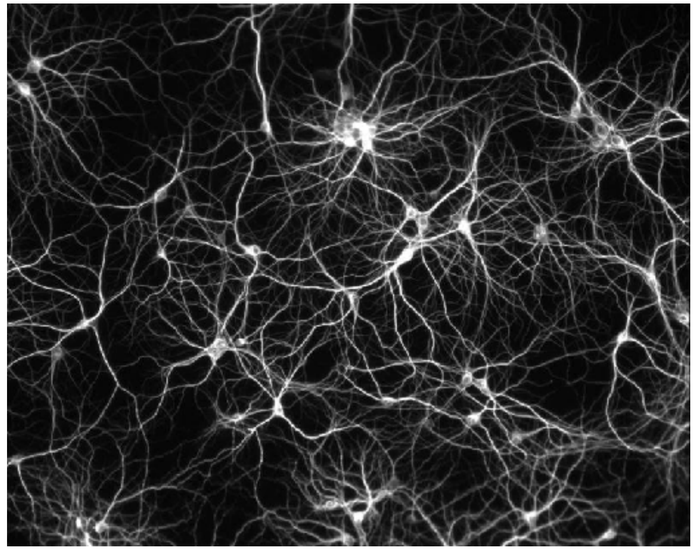
- 231,655,275 bioactivities in PubChem
- 125,526 structures in the PDB
- 16,179 annotated complexes in PDBbind

Machine Learning



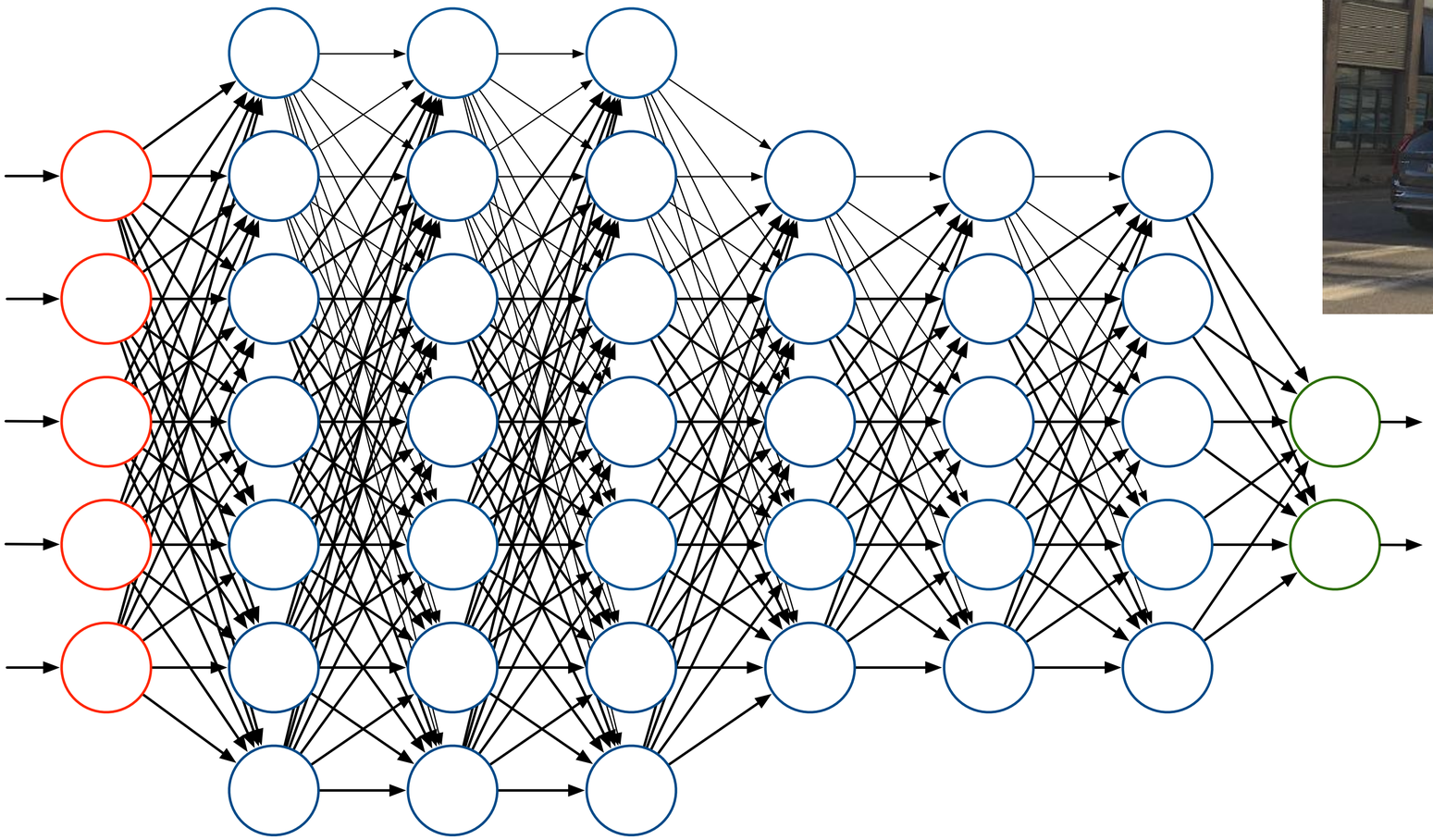
Neural Networks



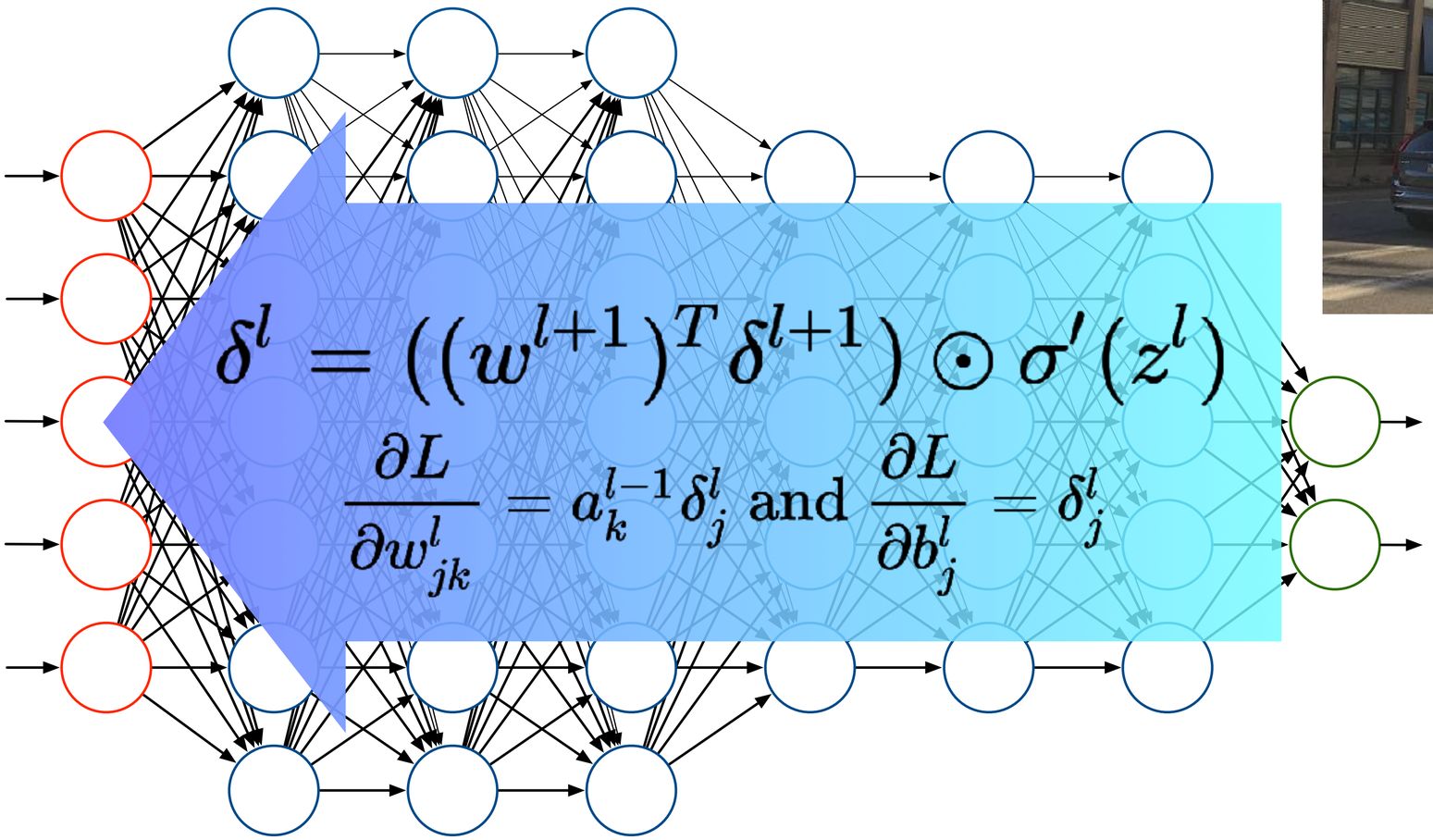


The **universal approximation theorem** states that, under reasonable assumptions, a feedforward **neural network** with a finite number of nodes **can approximate any continuous** function to within a given error over a bounded input domain.

Deep Learning



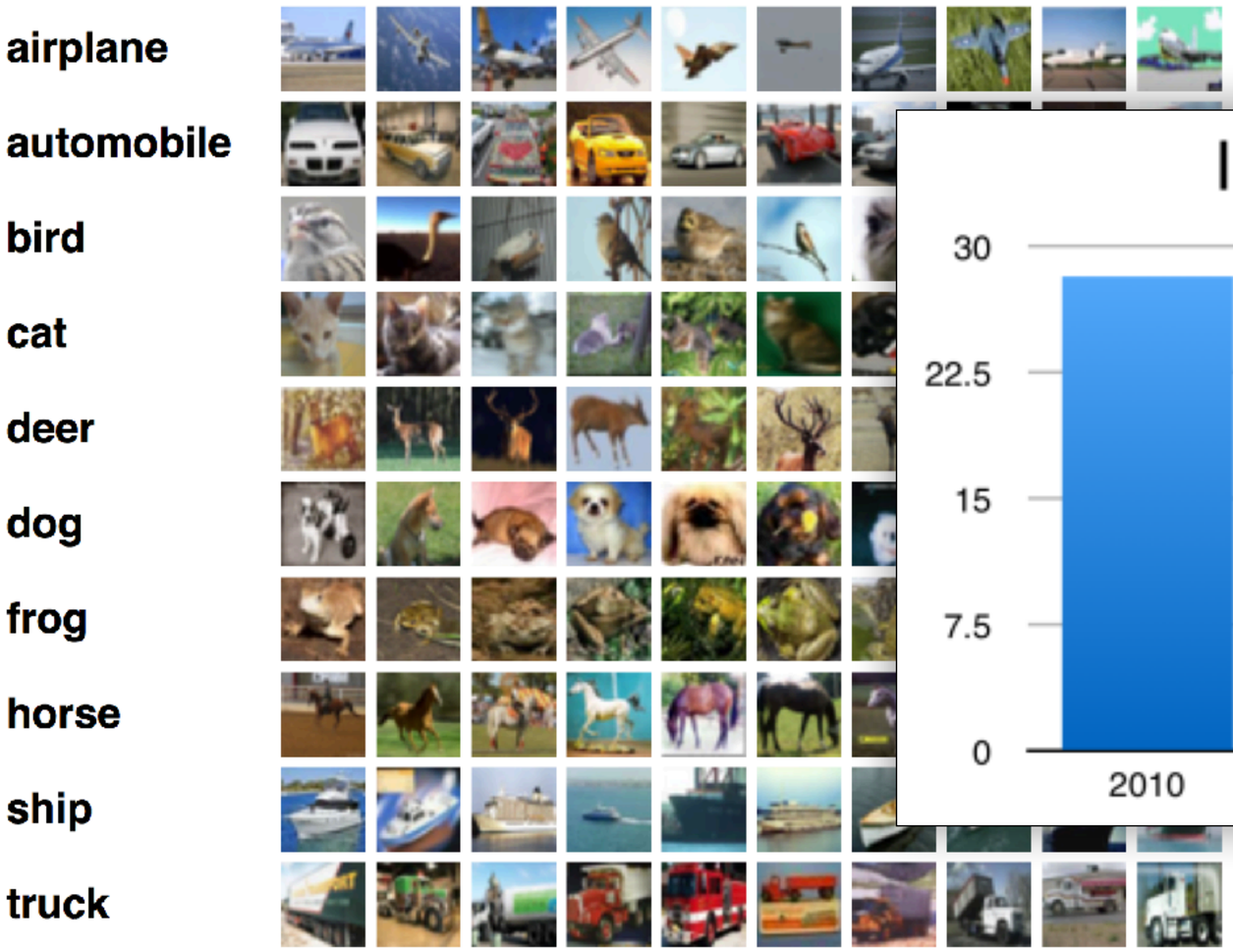
Deep Learning

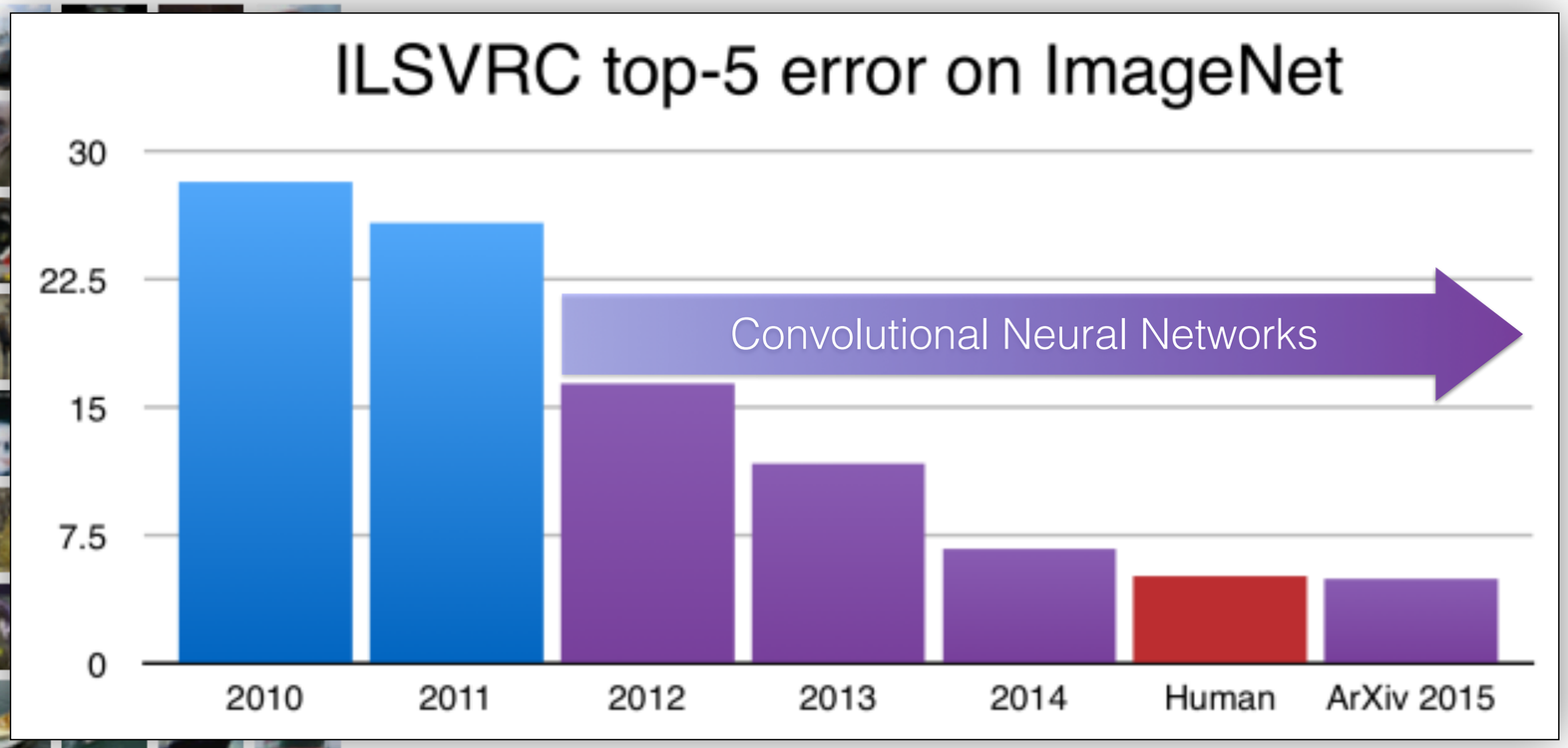


$$\delta^l = ((w^{l+1})^T \delta^{l+1}) \odot \sigma'(z^l)$$

$$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j \text{ and } \frac{\partial L}{\partial b^l_j} = \delta^l_j$$

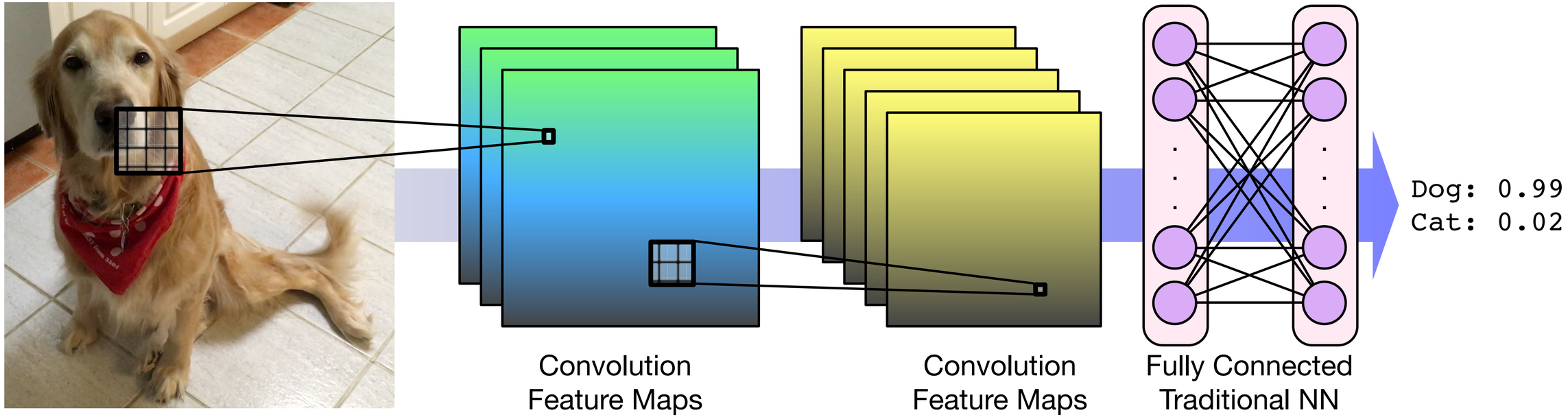
Image Recognition

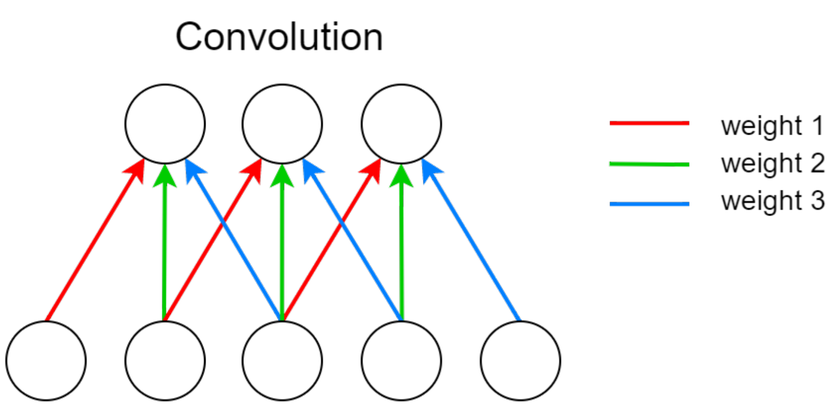


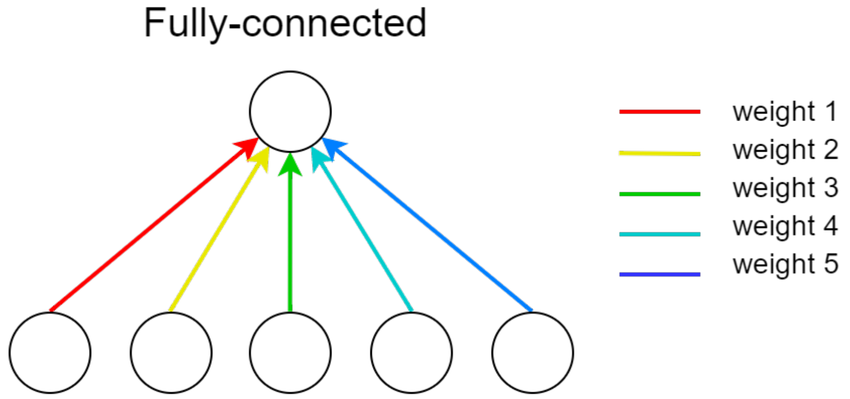


https://devblogs.nvidia.com

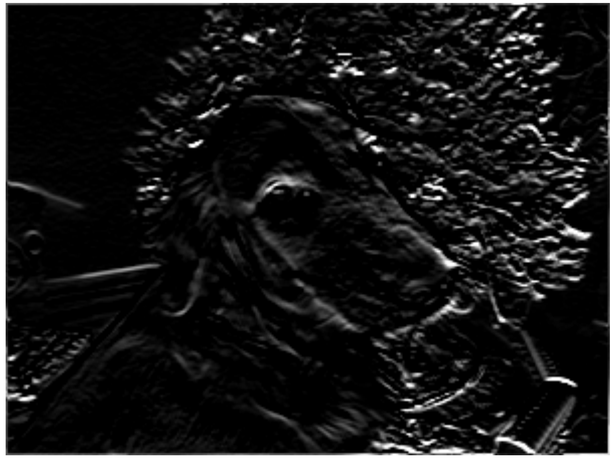
Convolutional Neural Networks







Convolutional Filters

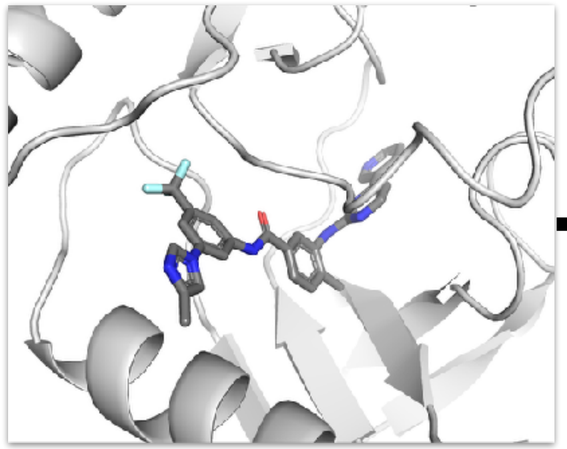


-1	-1	-1
0	0	0
1	1	1

-1	0	1
-1	0	1
-1	0	1

-1	-1	-1
-1	8	-1
-1	-1	-1

CNNs for Protein-Ligand Scoring



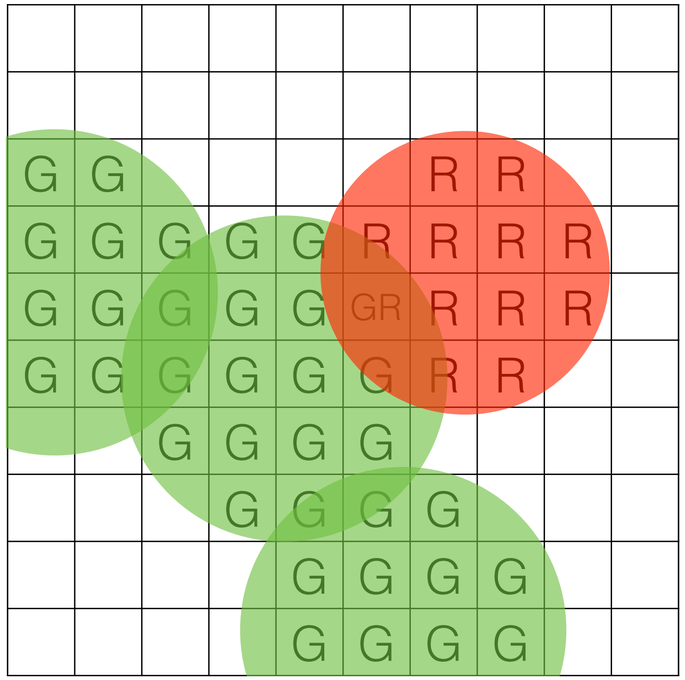
CNN

Pose Prediction

Binding Discrimination

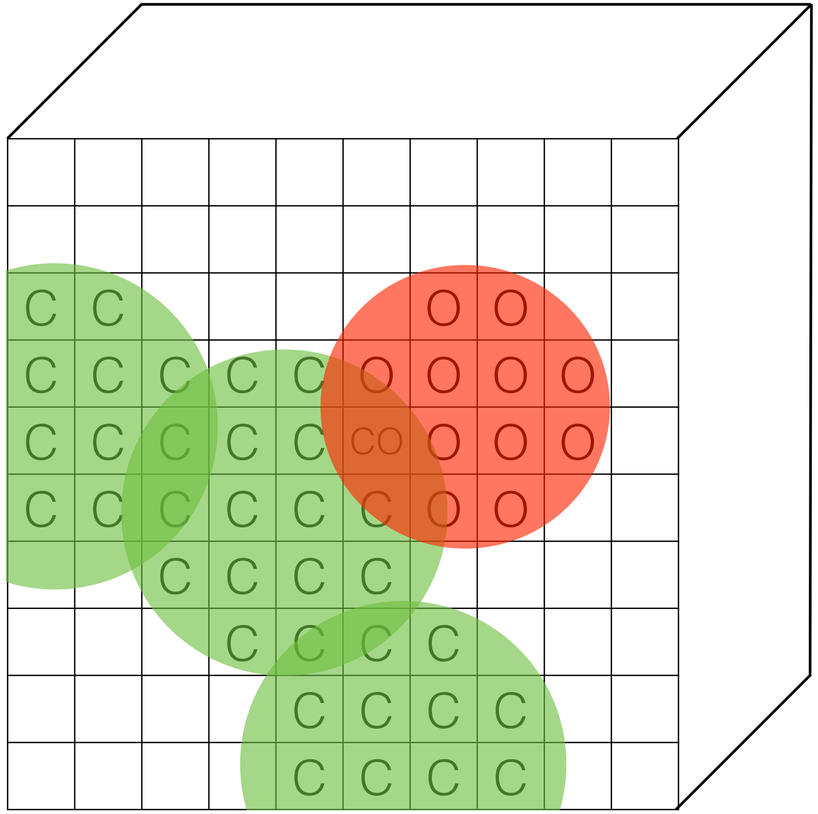
Affinity Prediction

Protein-Ligand Representation



(R,G,B) pixel

Protein-Ligand Representation



(R,G,B) pixel →

(Carbon, Nitrogen, Oxygen,…) **voxel**

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

Training Data

Pose Prediction

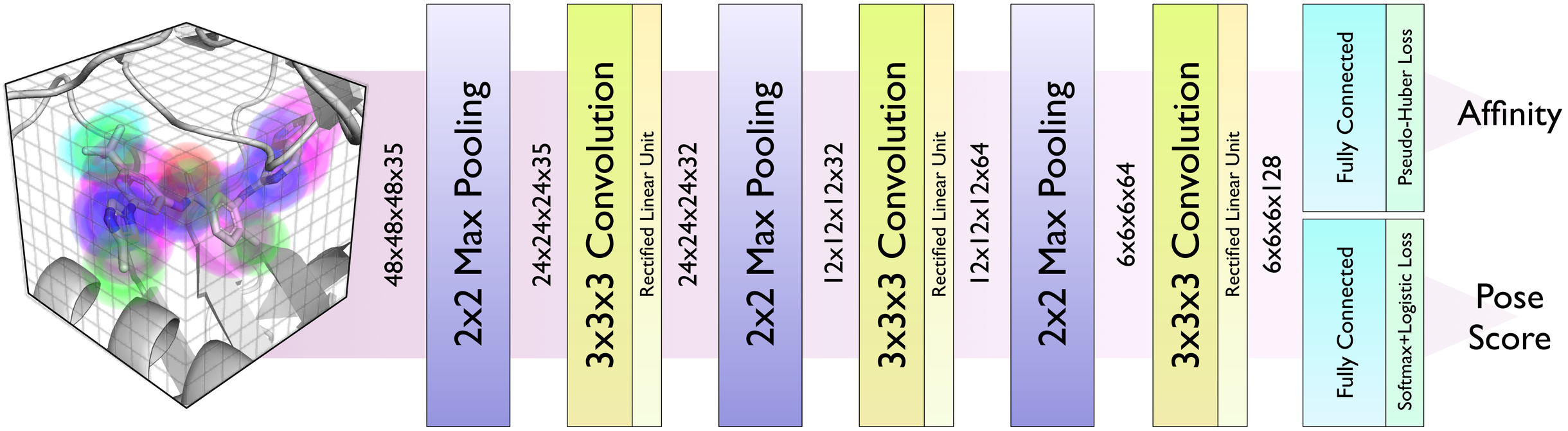
4056 protein-ligand complexes

- diverse targets
- wide range of affinities
- generate poses with AutoDock Vina
- include minimized crystal pose
  - 8,688 <2Å RMSD (actives)
  - 76,743 >4Å RMSD (decoys)

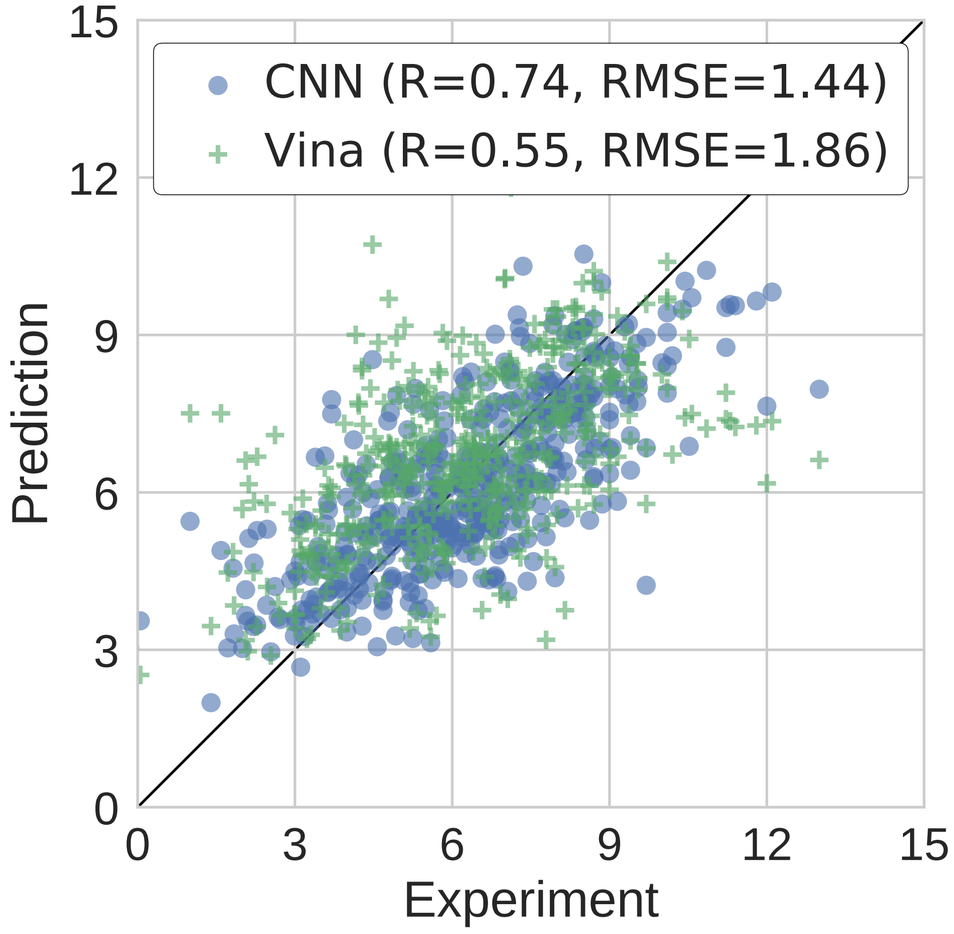
Affinity Prediction

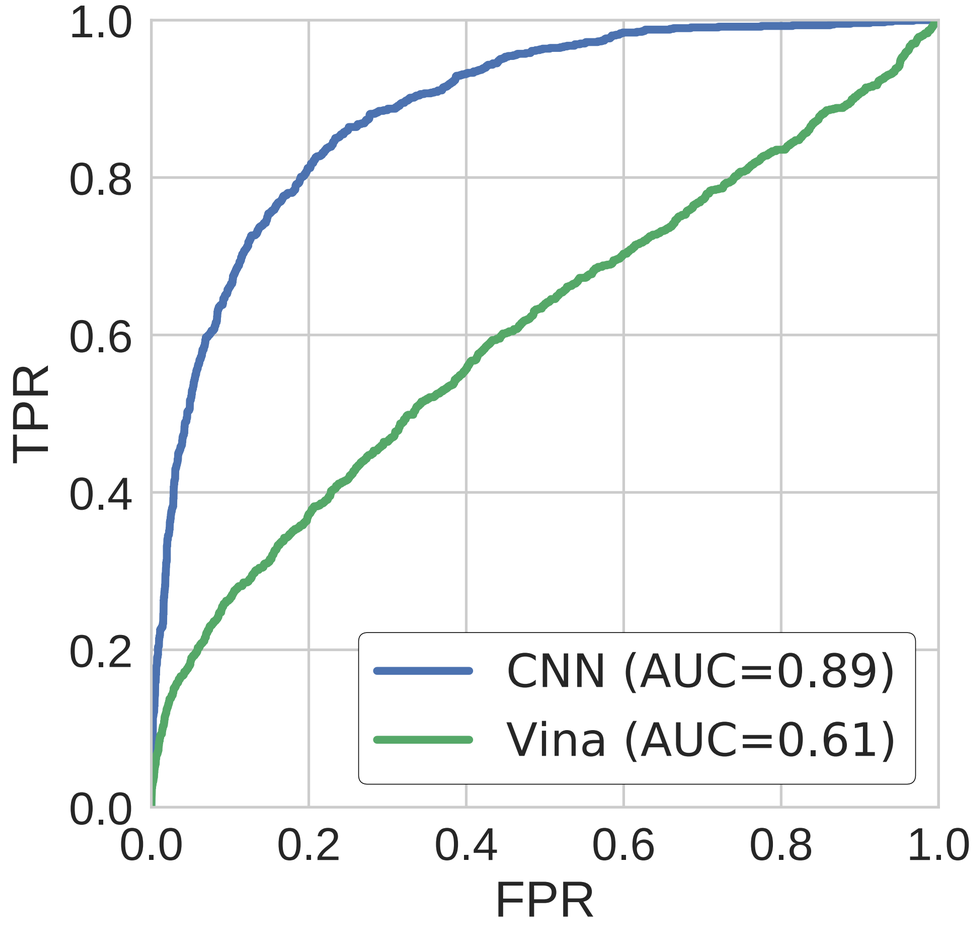
- 8,688 low RMSD poses
- assign known affinity
- **regression problem**

Model


48x48x48x35
2x2 Max Pooling
24x24x24x35
3x3x3 Convolution
Rectified Linear Unit
24x24x24x32
2x2 Max Pooling
12x12x12x32
3x3x3 Convolution
Rectified Linear Unit
12x12x12x64
2x2 Max Pooling
6x6x6x64
3x3x3 Convolution
Rectified Linear Unit
6x6x6x128
Fully Connected
Pseudo-Huber Loss
Affinity
Fully Connected
Softmax+Logistic Loss
Pose Score

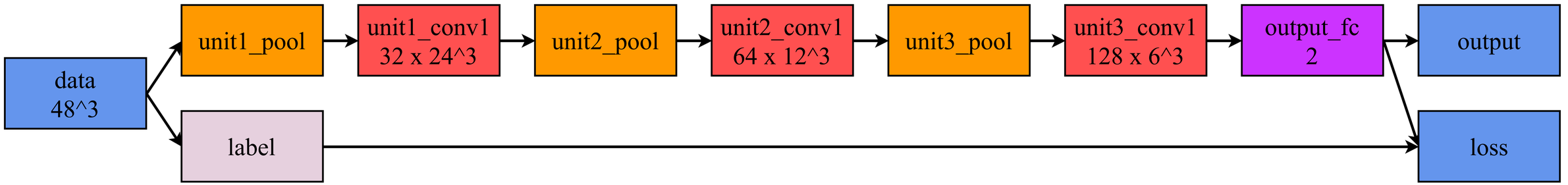
Results



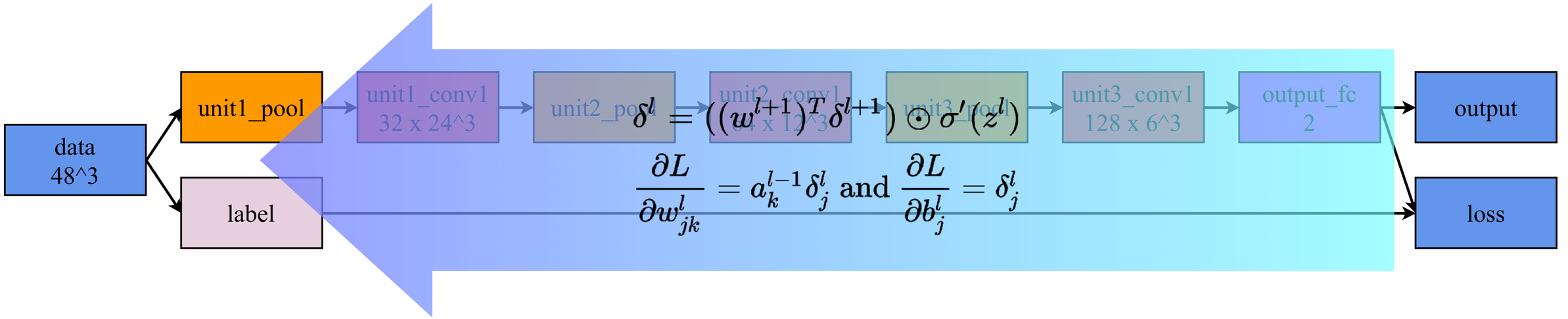


Trained on PDBbind refined; tested on CSAR

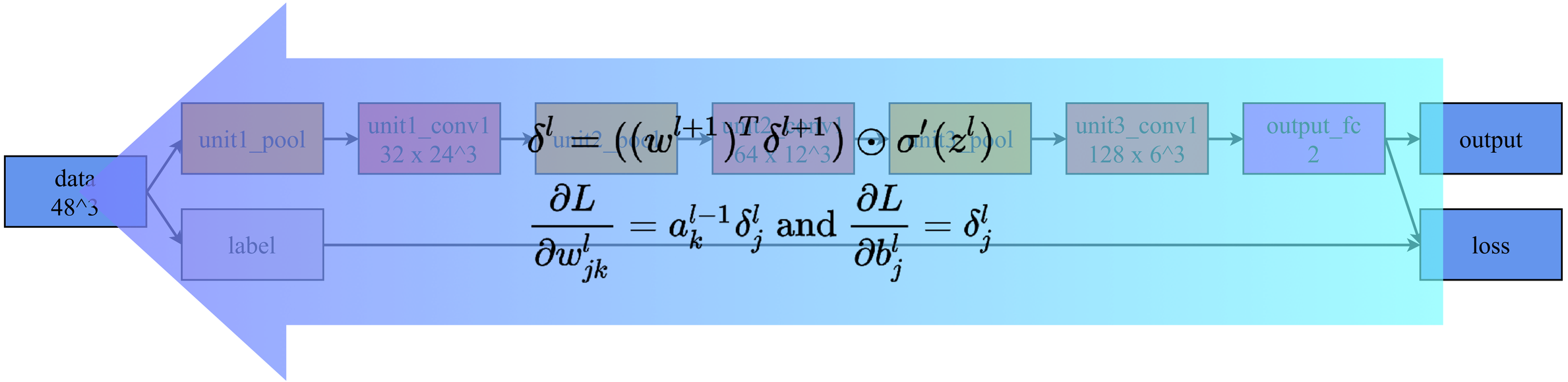
Beyond Scoring



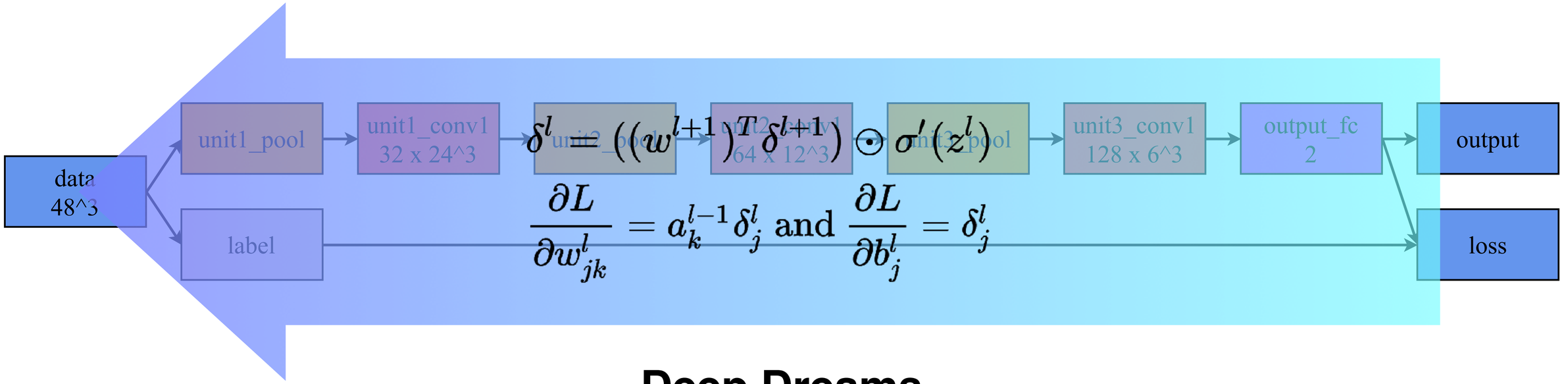
Beyond Scoring



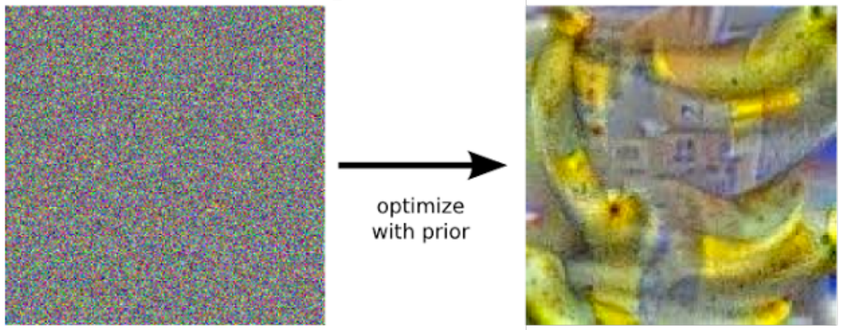
Beyond Scoring



Beyond Scoring

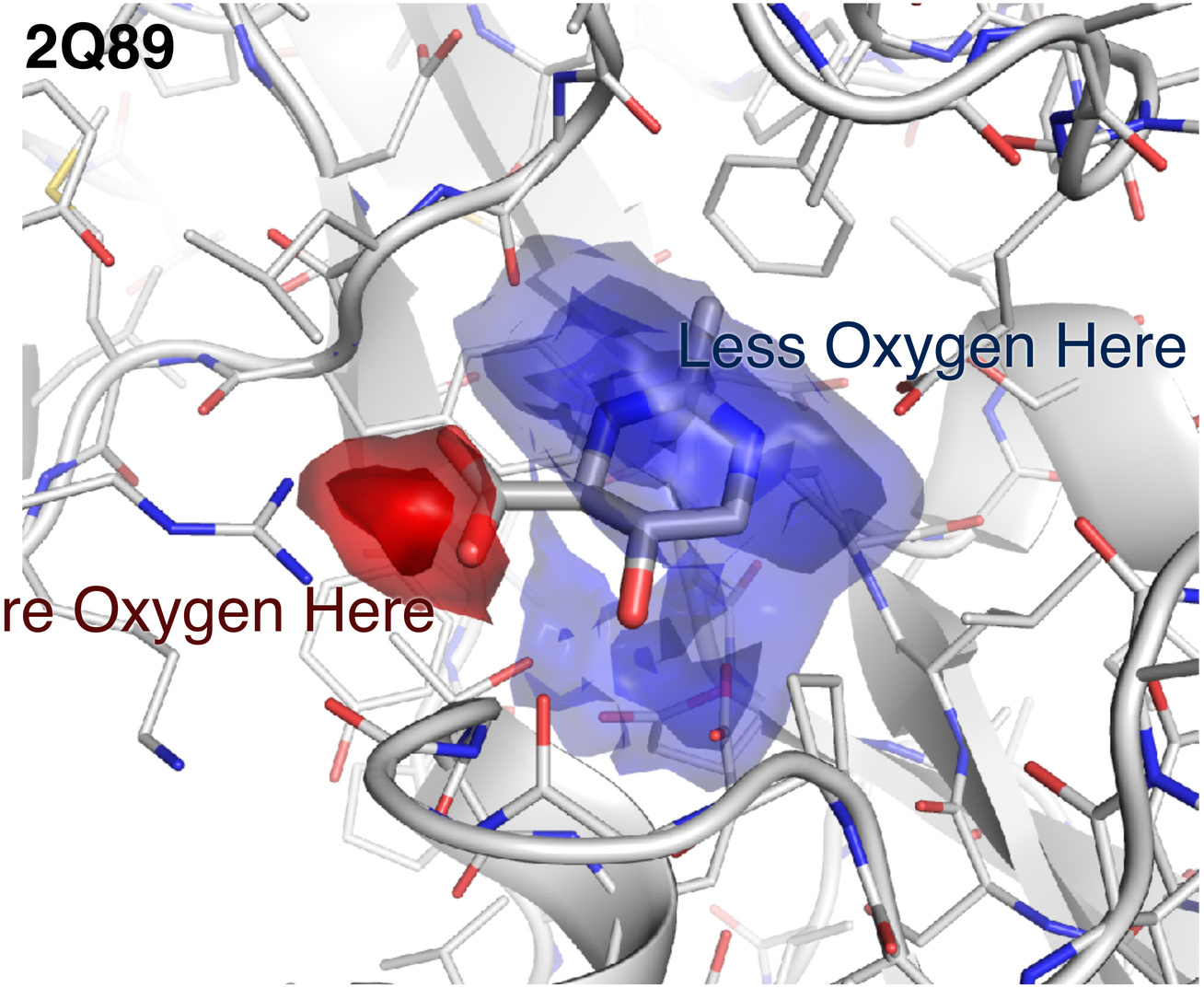


Deep Dreams

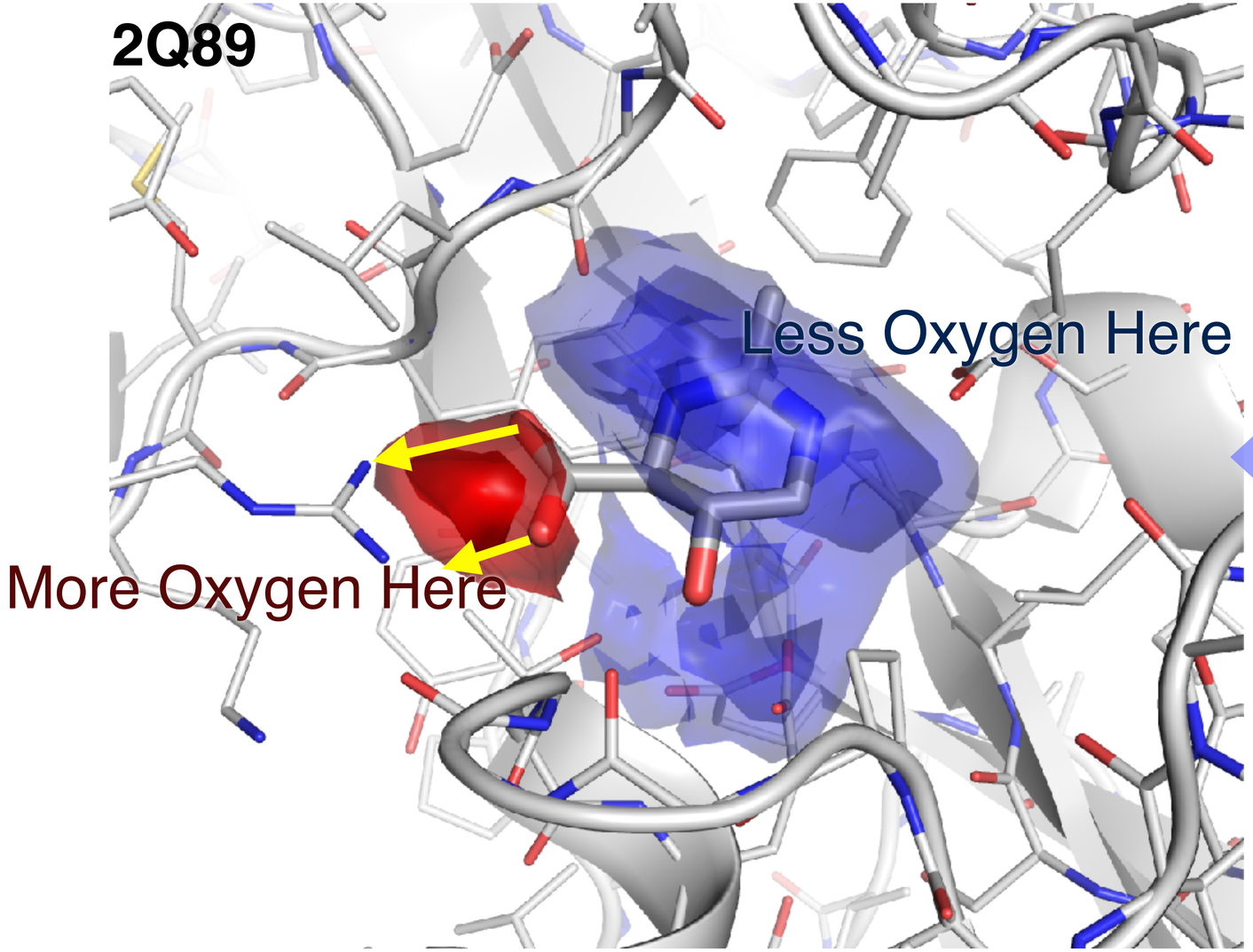


https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html

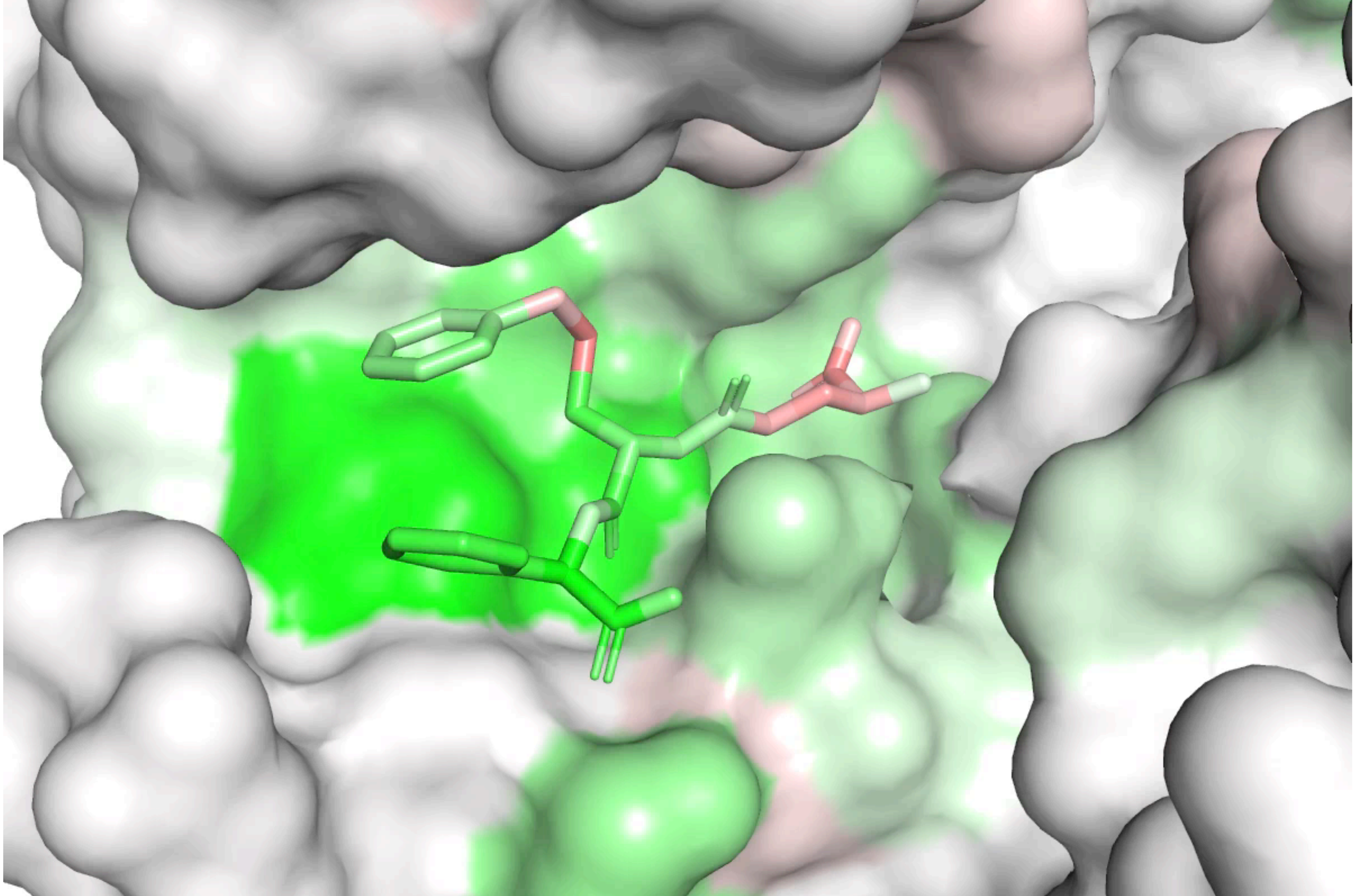
Beyond Scoring

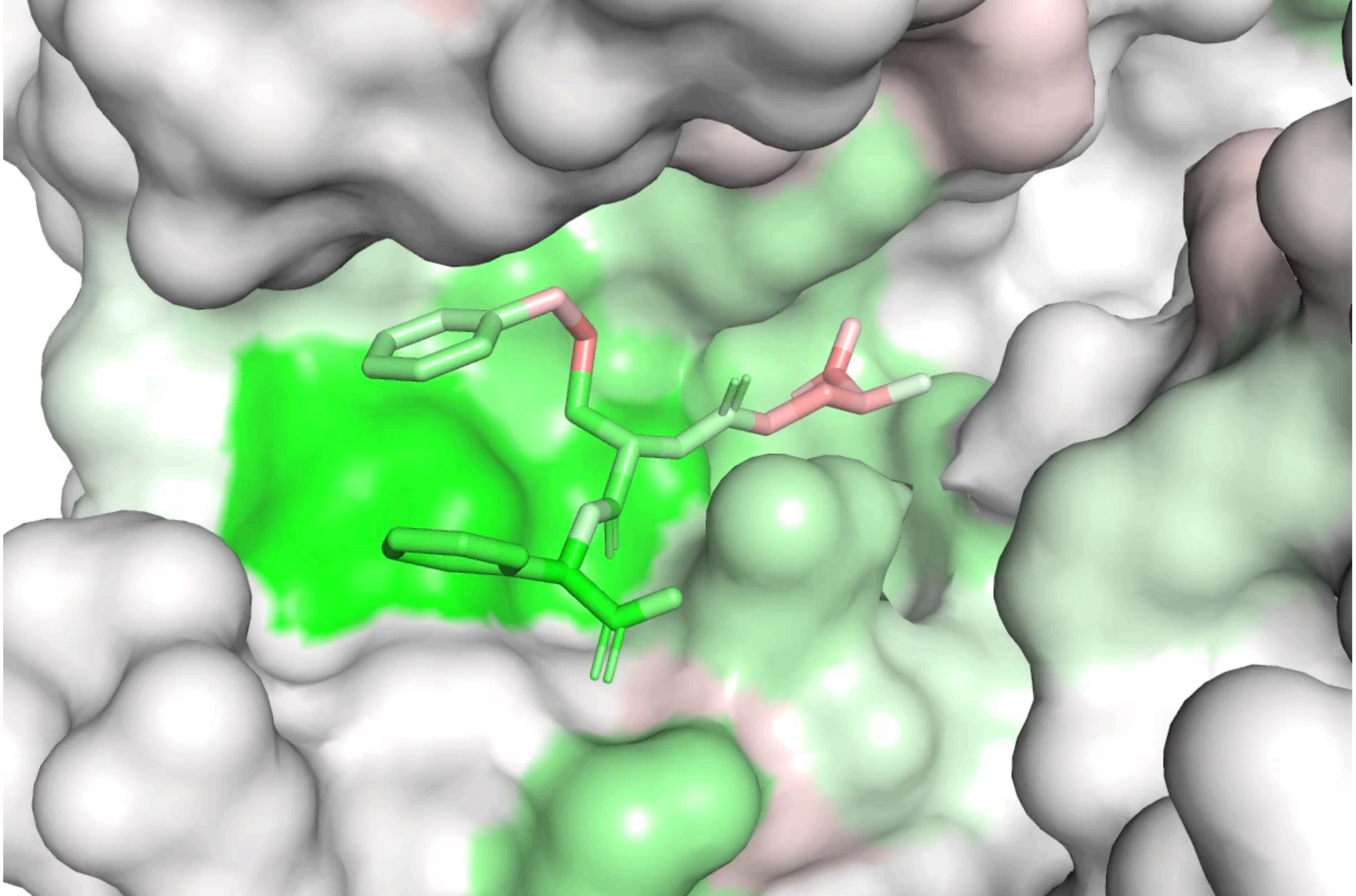


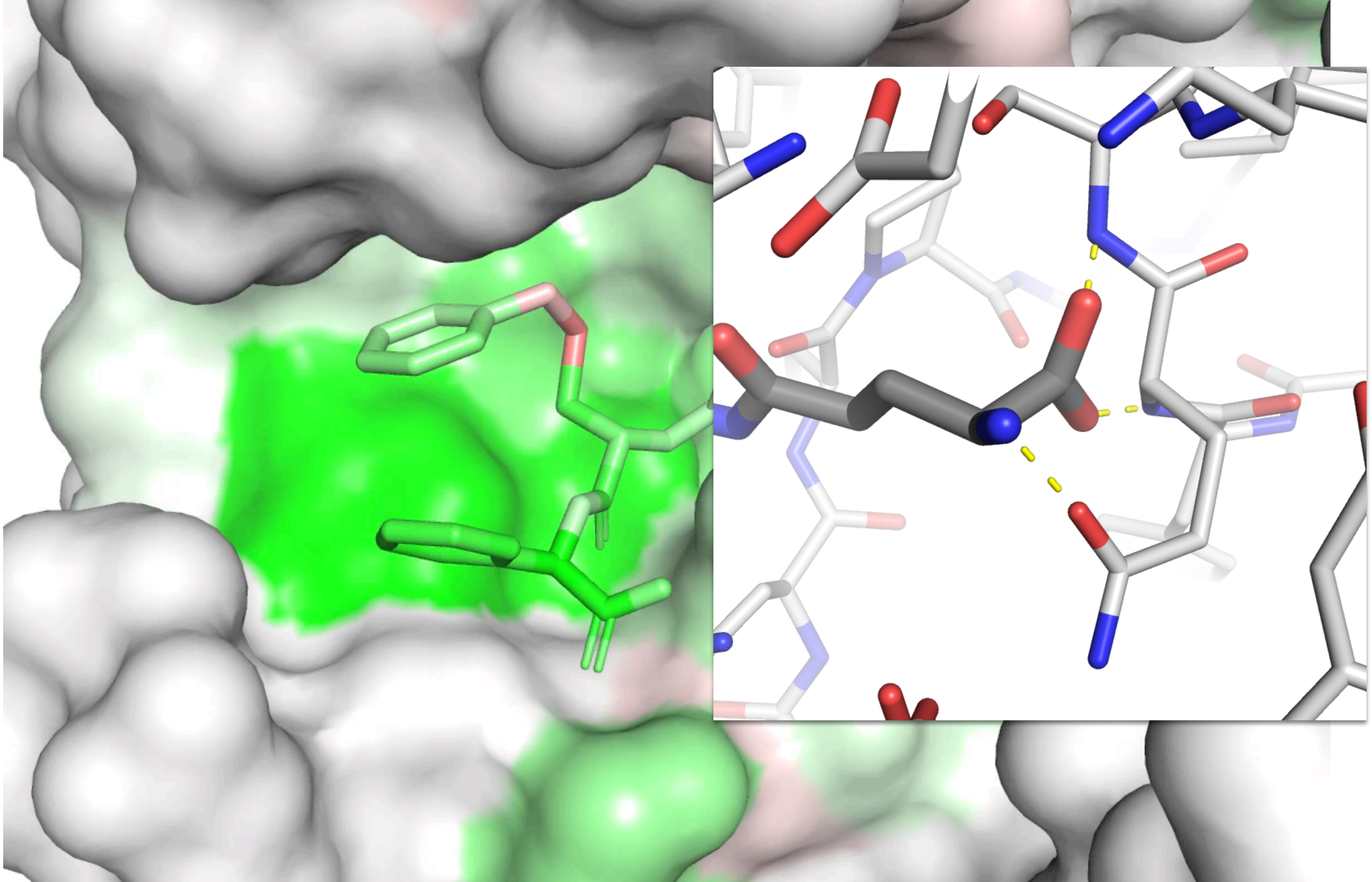
Beyond Scoring

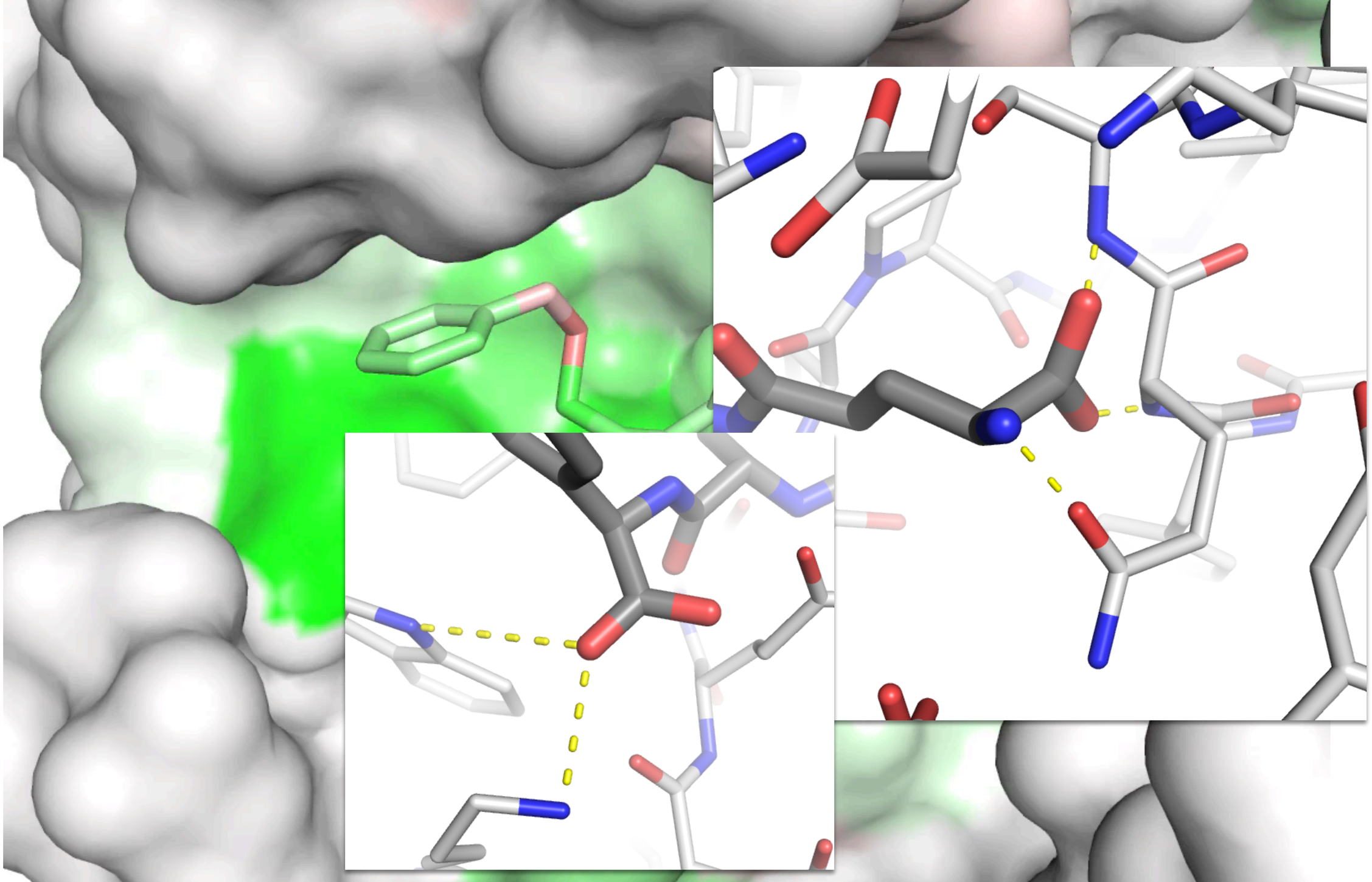


$$\frac{\partial L}{\partial A} = \sum_{i \in G_A} \frac{\partial L}{\partial G_i} \frac{\partial G_i}{\partial D} \frac{\partial D}{\partial A}$$

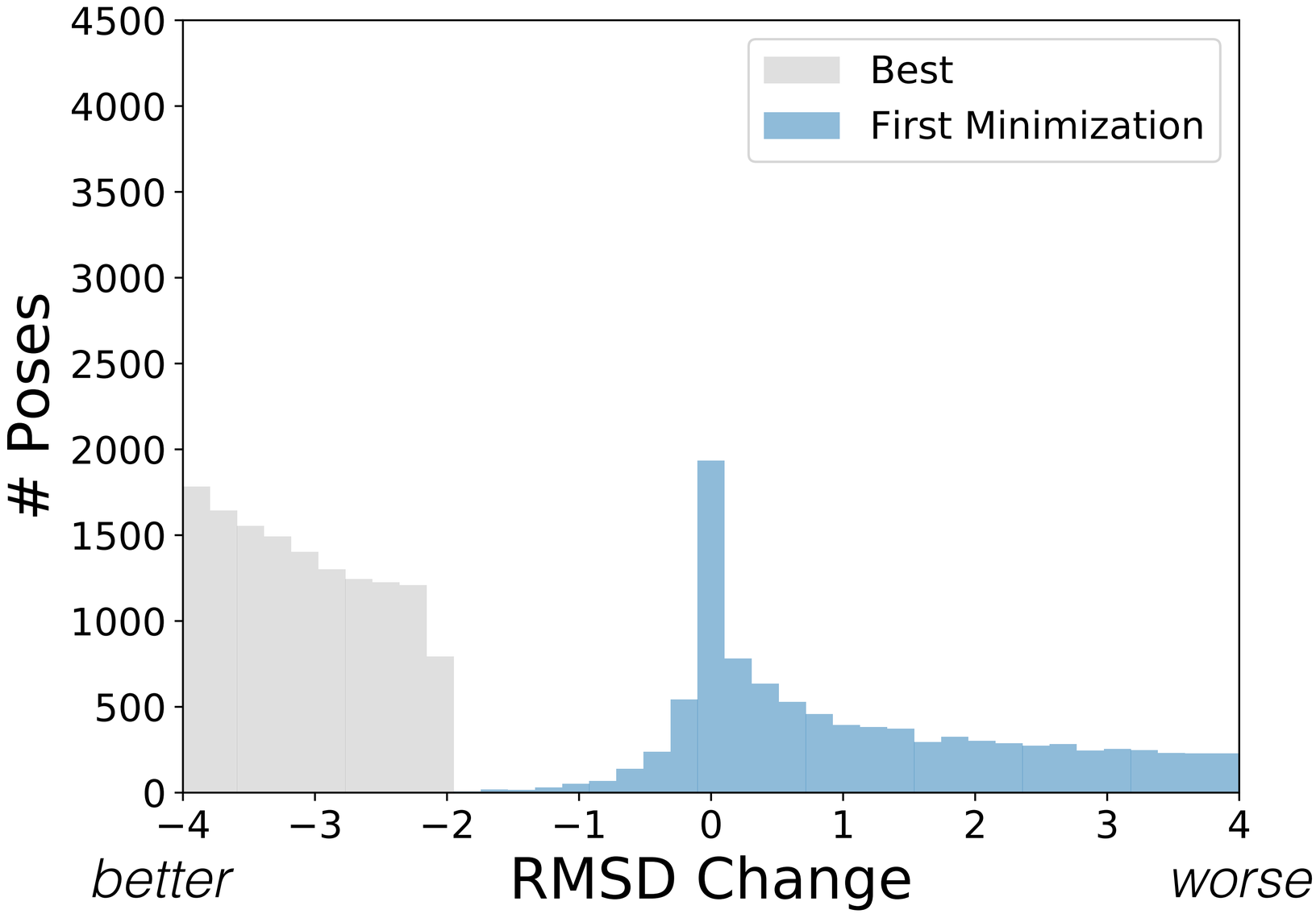


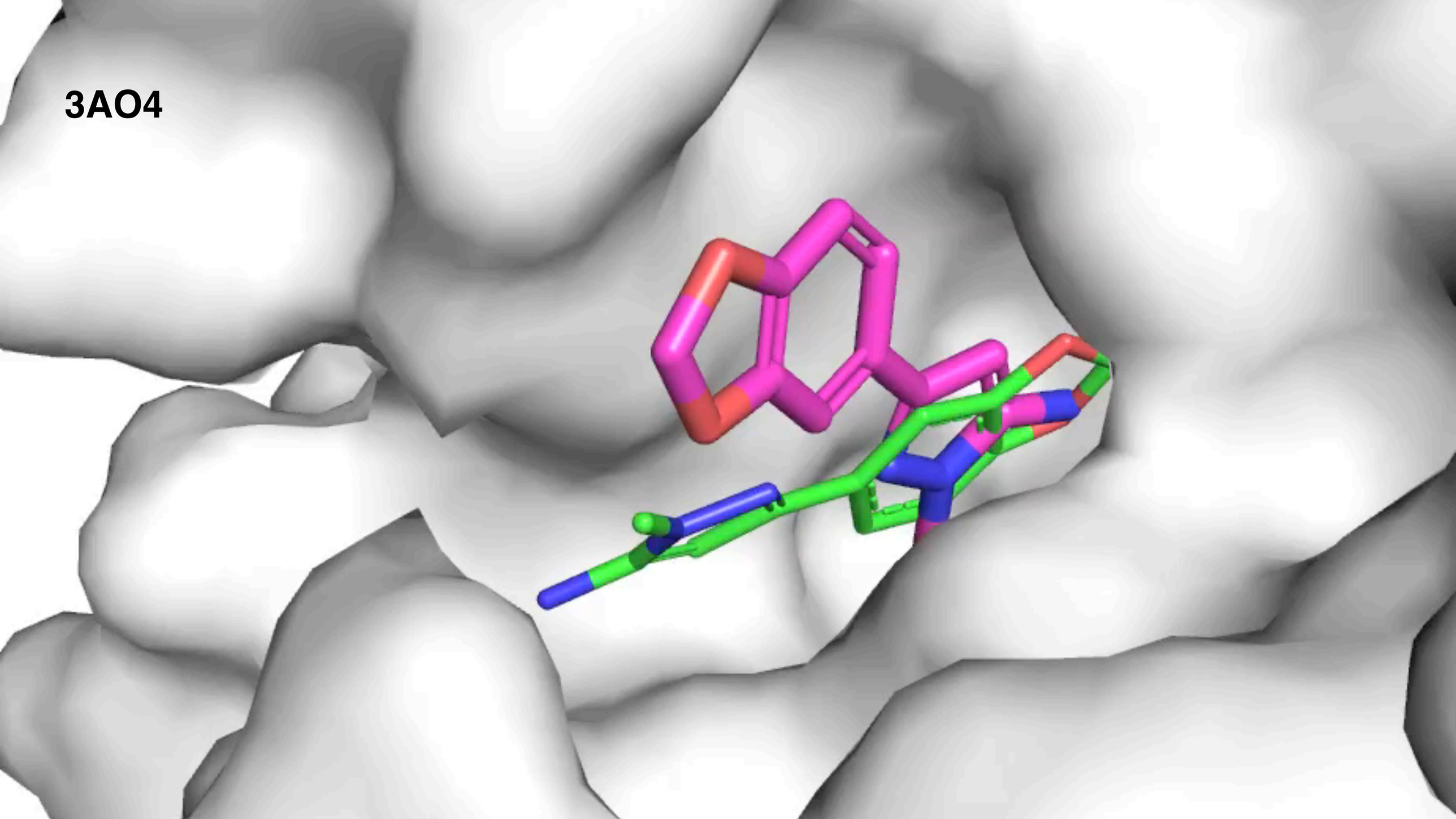


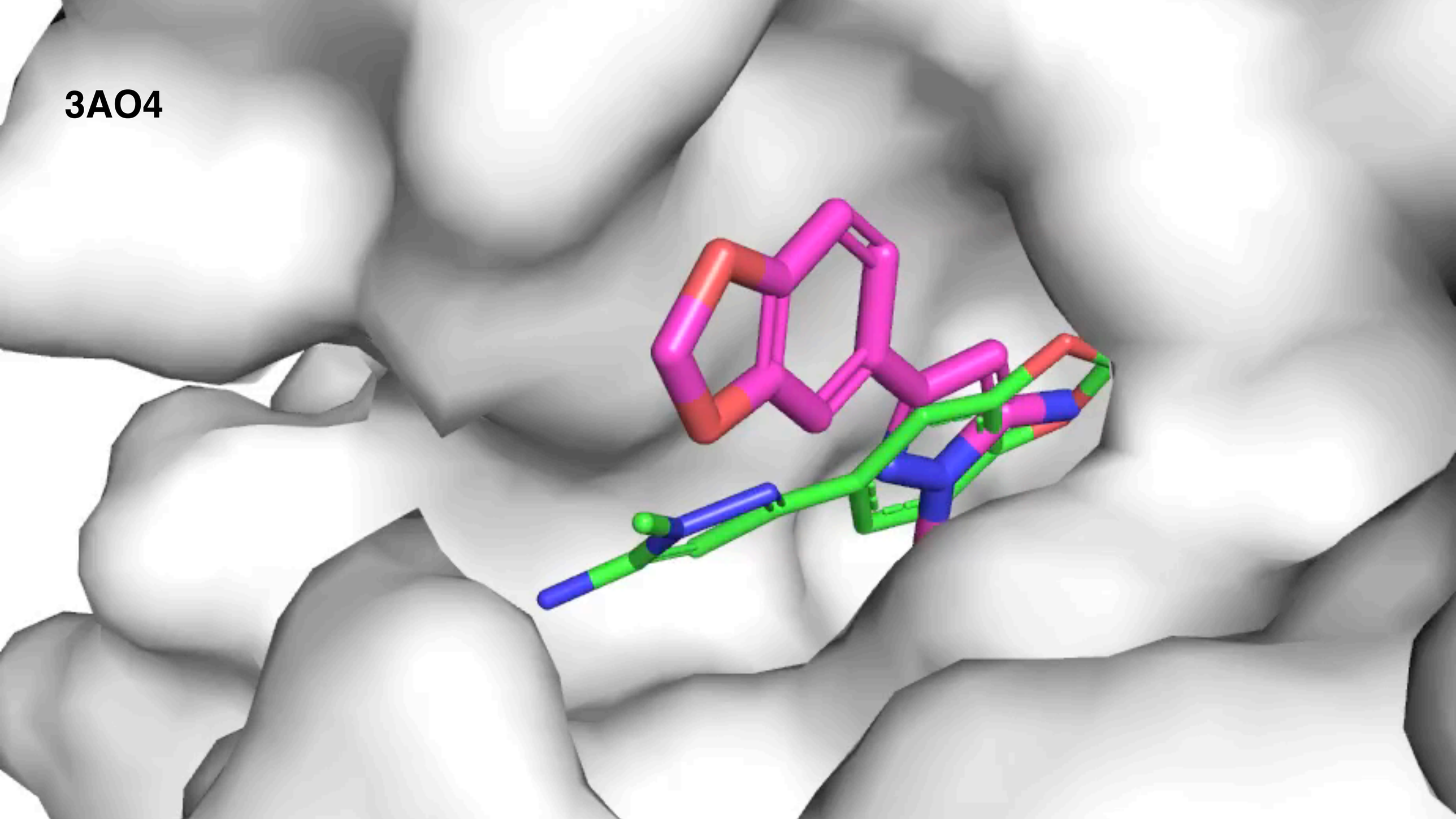




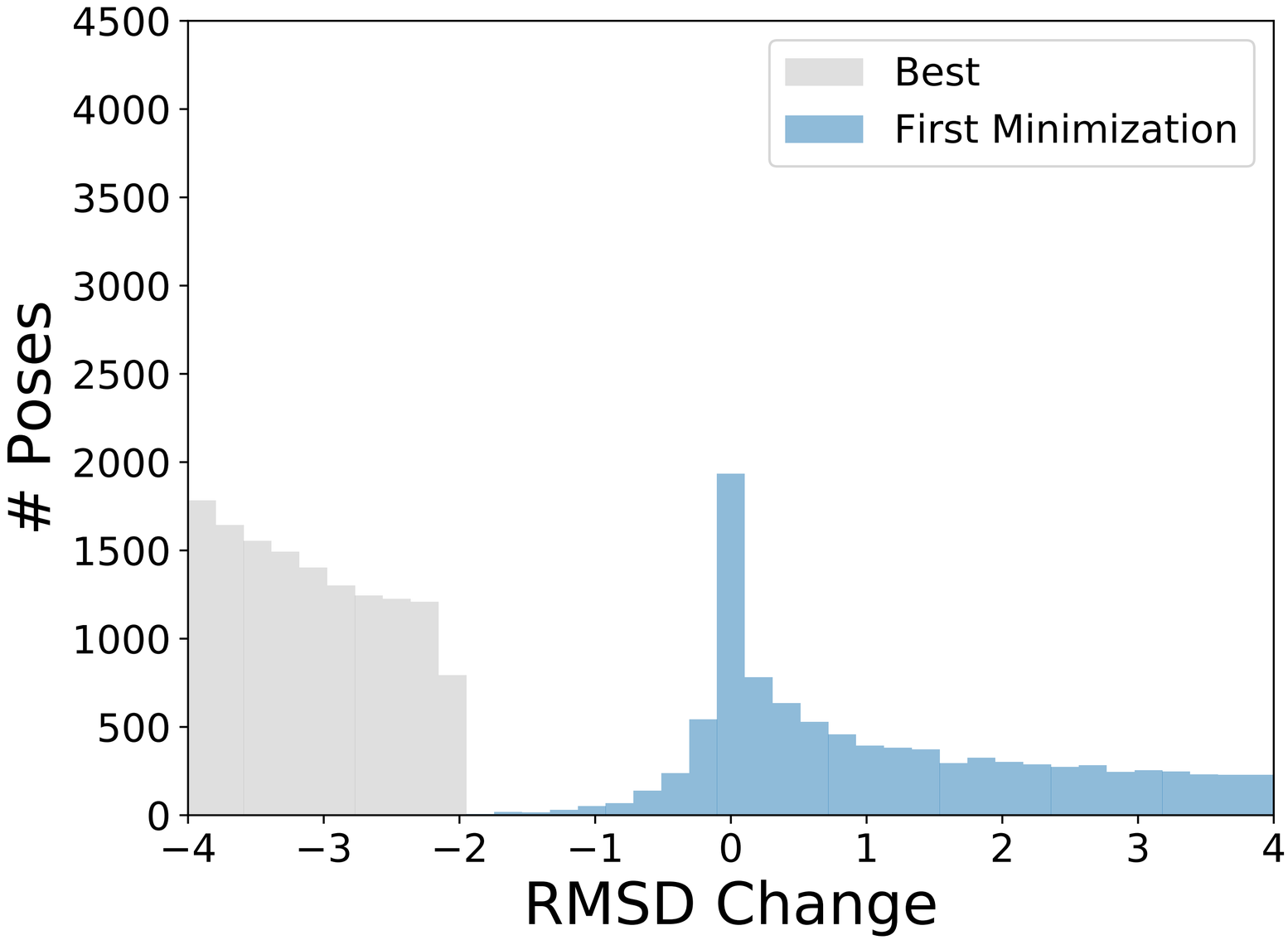
Minimizing Low RMSD Poses



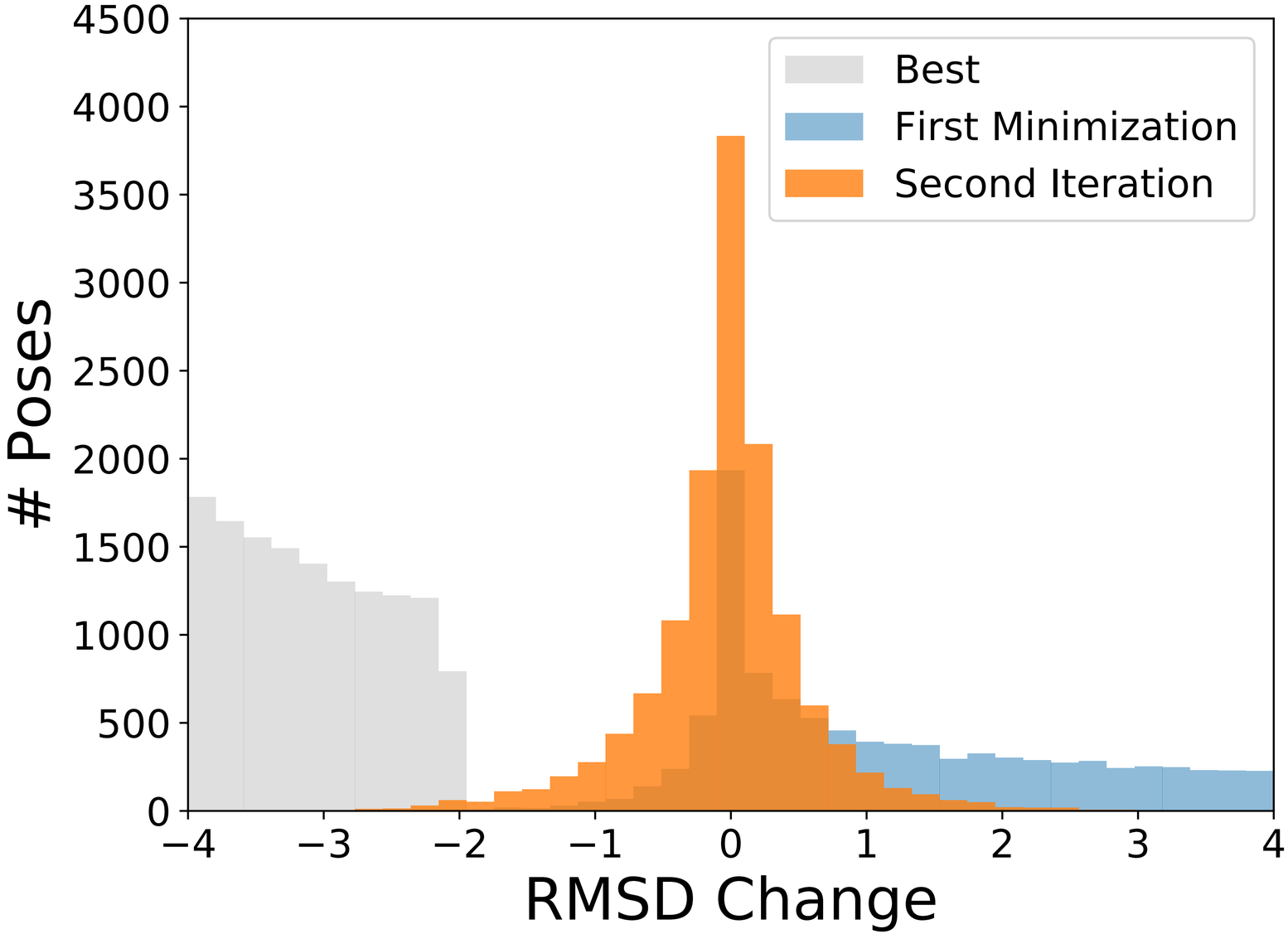

3AO4


3AO4

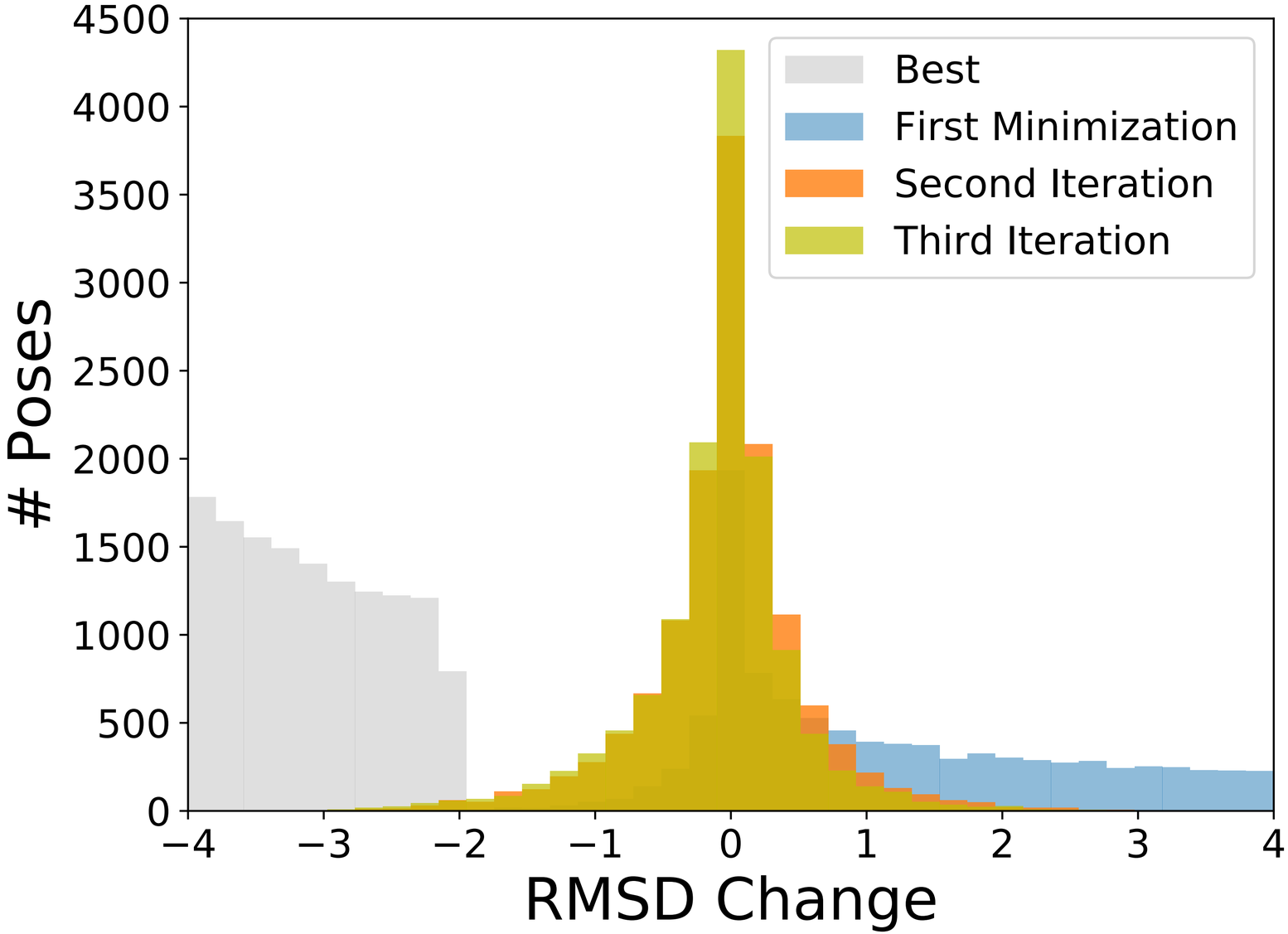
Iterative Refinement

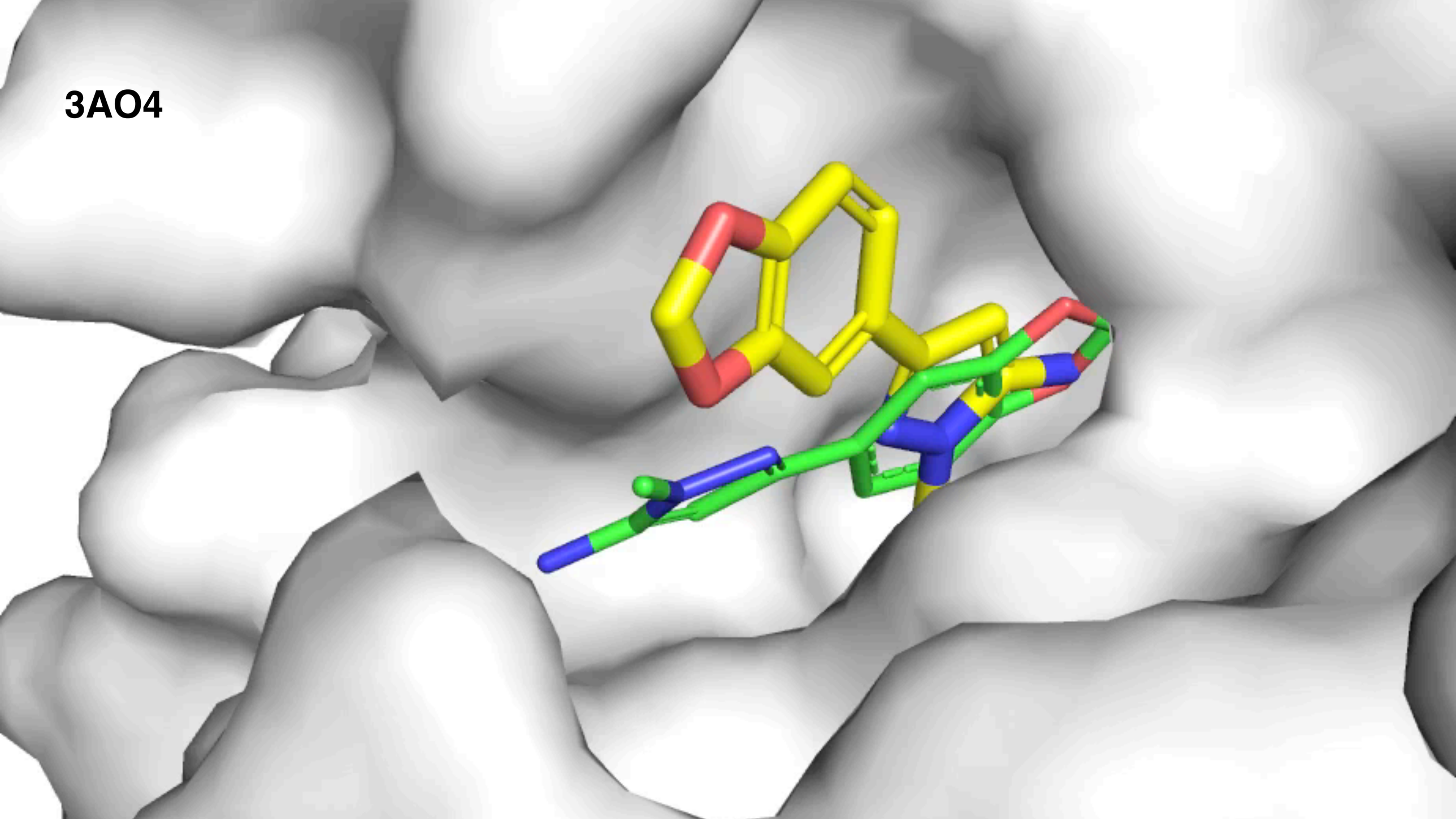


Iterative Refinement



Iterative Refinement

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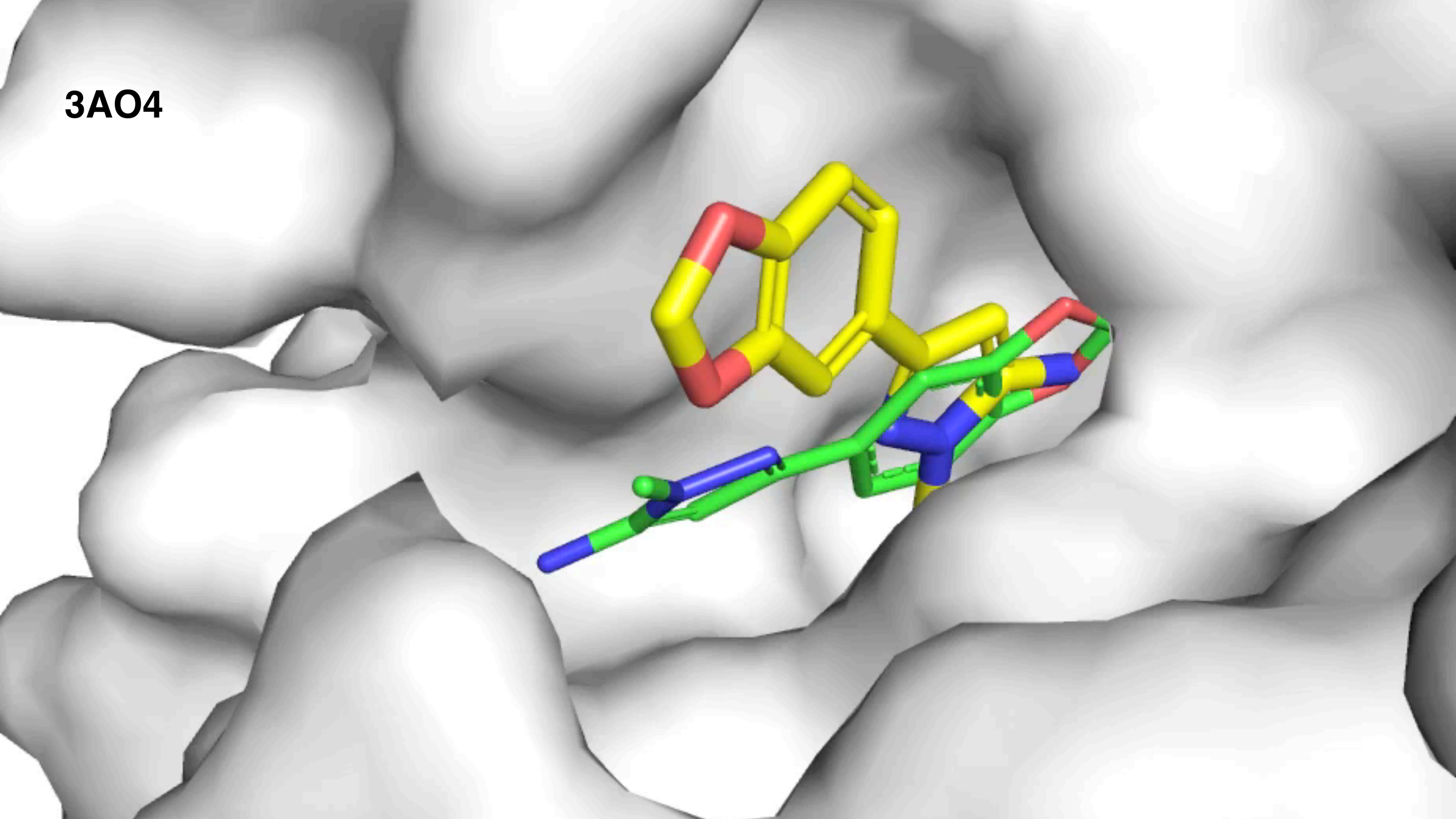

3AO4

Docking

vina/smina/gnina

Sampling

MCMC

MCMC

MCMC

MCMC

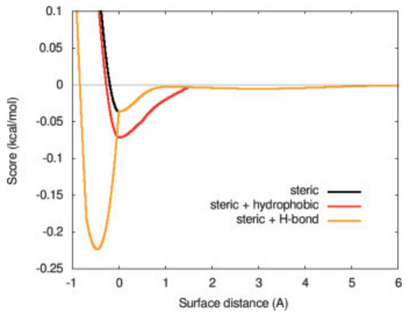
MCMC

⋮

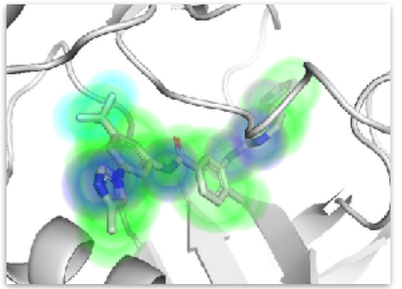
N (50) independent Monte Carlo chains
Scored with grid-accelerated Vina
Best identified pose retained

best poses

Refinement



Vina



CNN

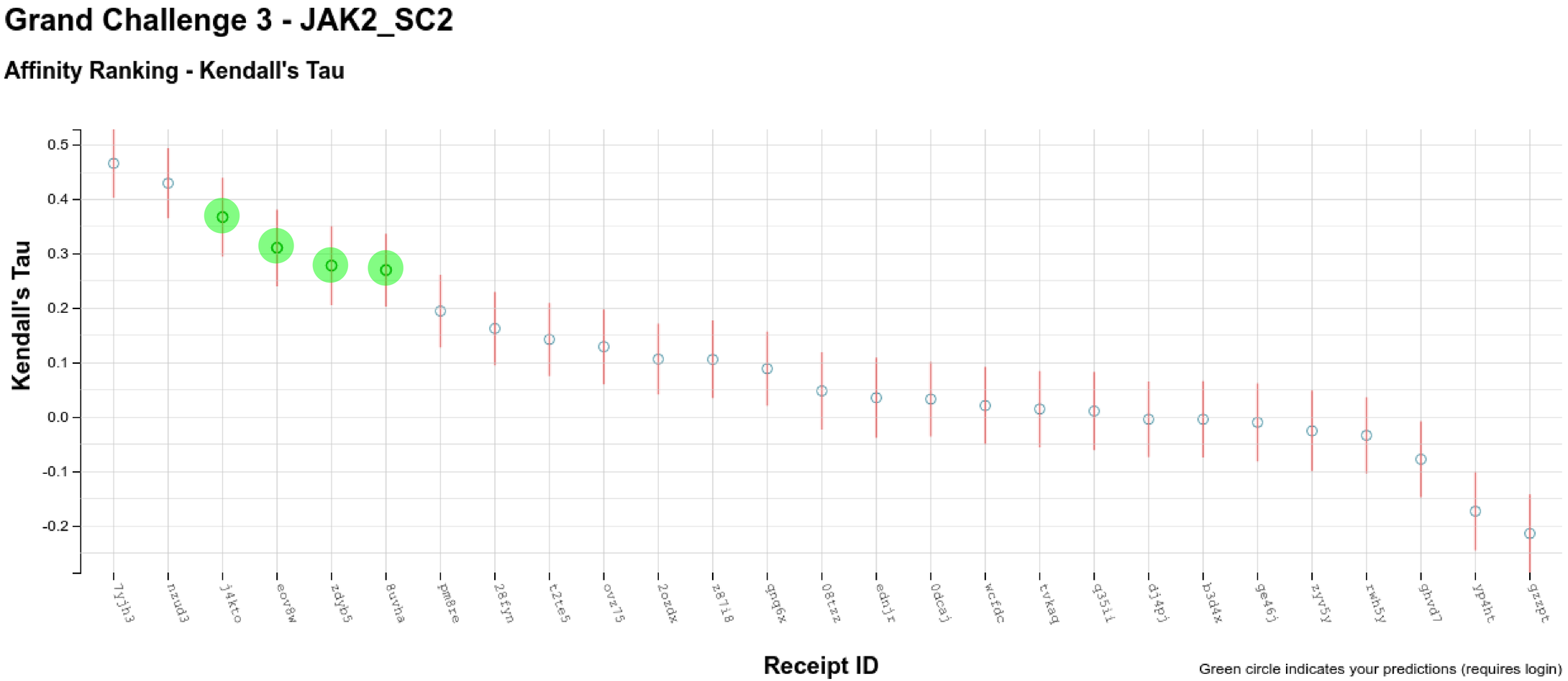
Rescoring

CNN
pose
affinity

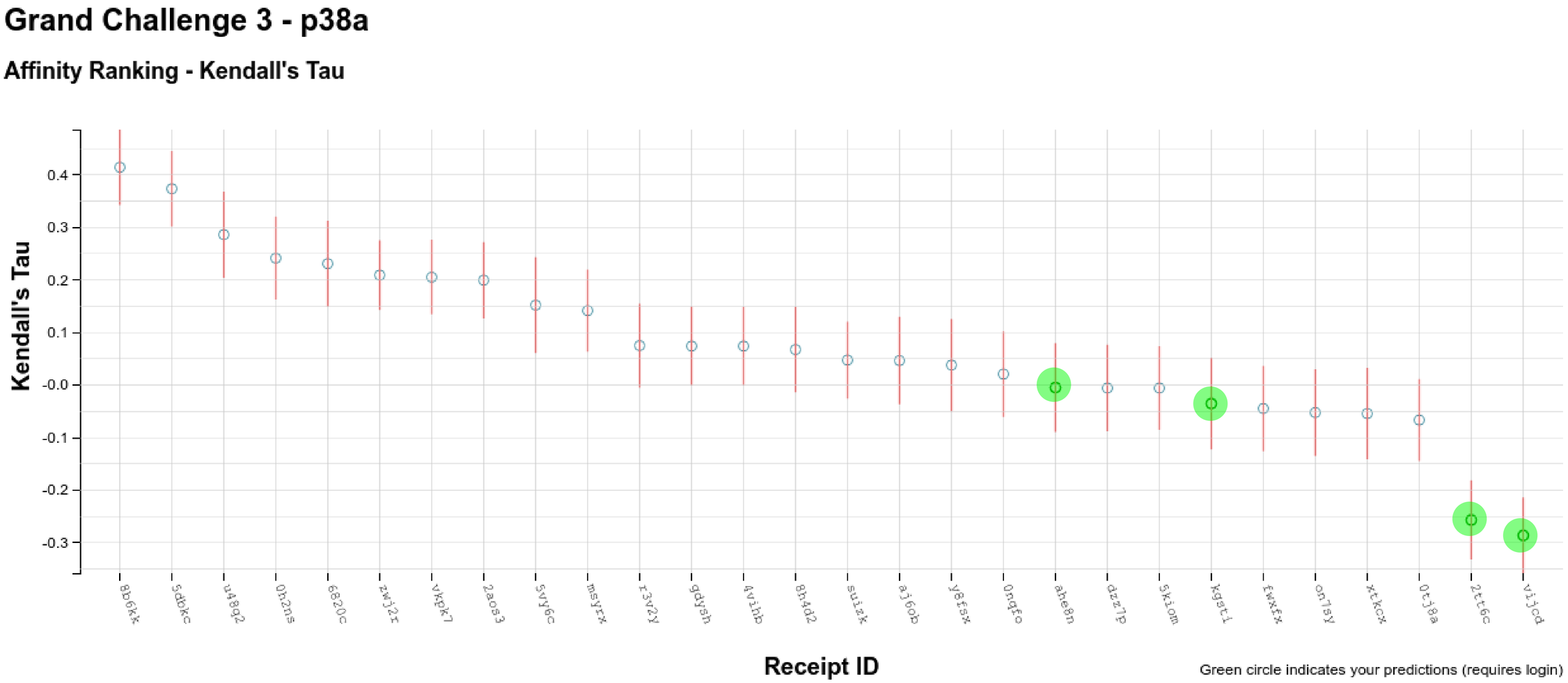
D3R Results

Grand Challenge 3

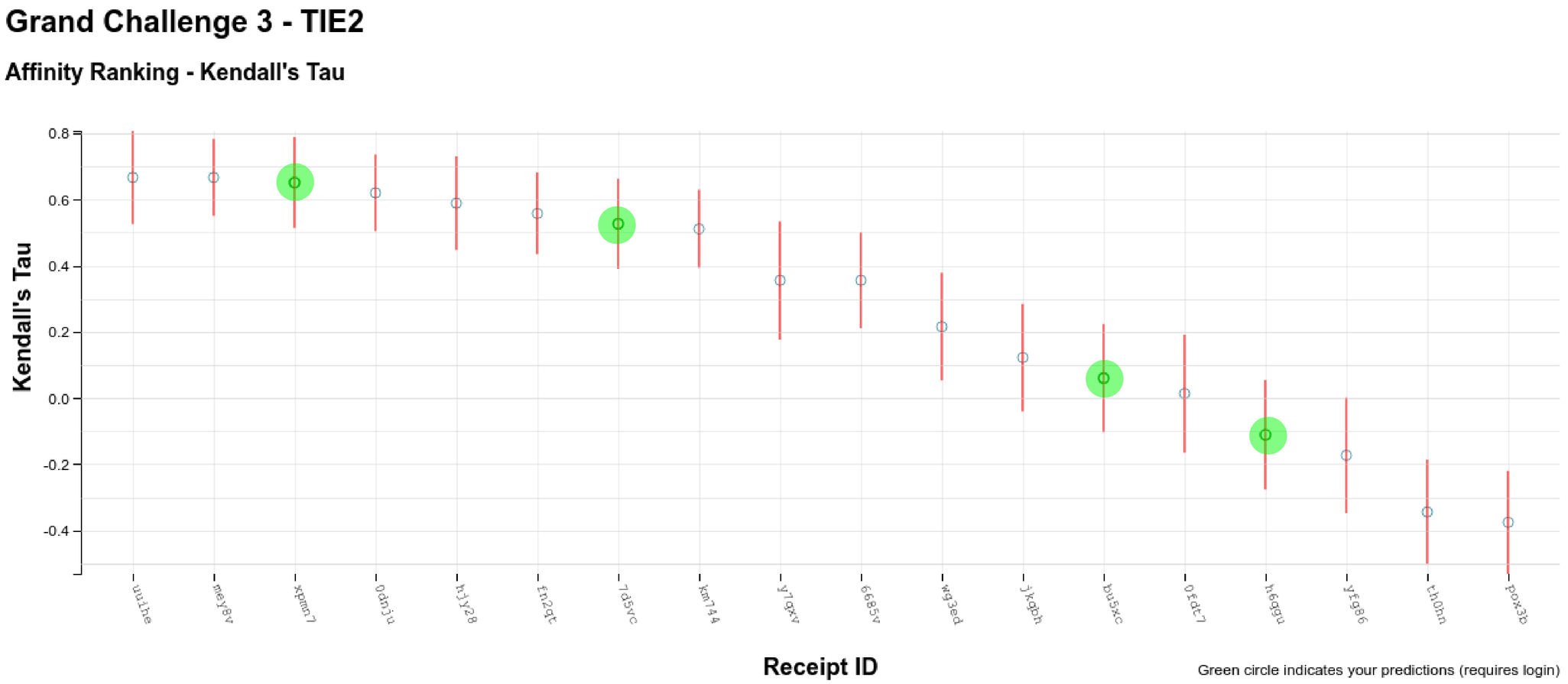
Grand Challenge 3



Grand Challenge 3



Grand Challenge 3



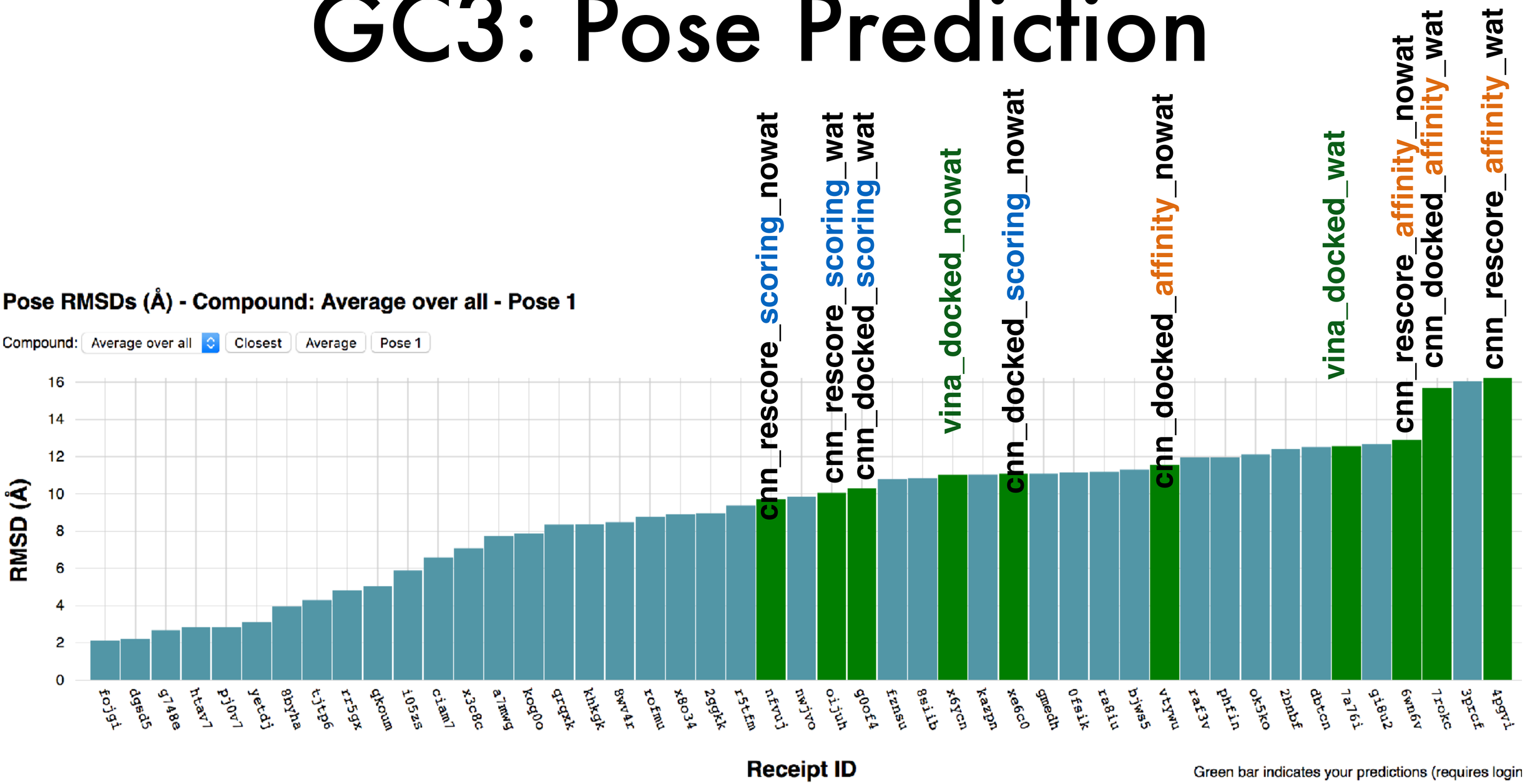
Grand Challenge 3

Grand Challenge 3

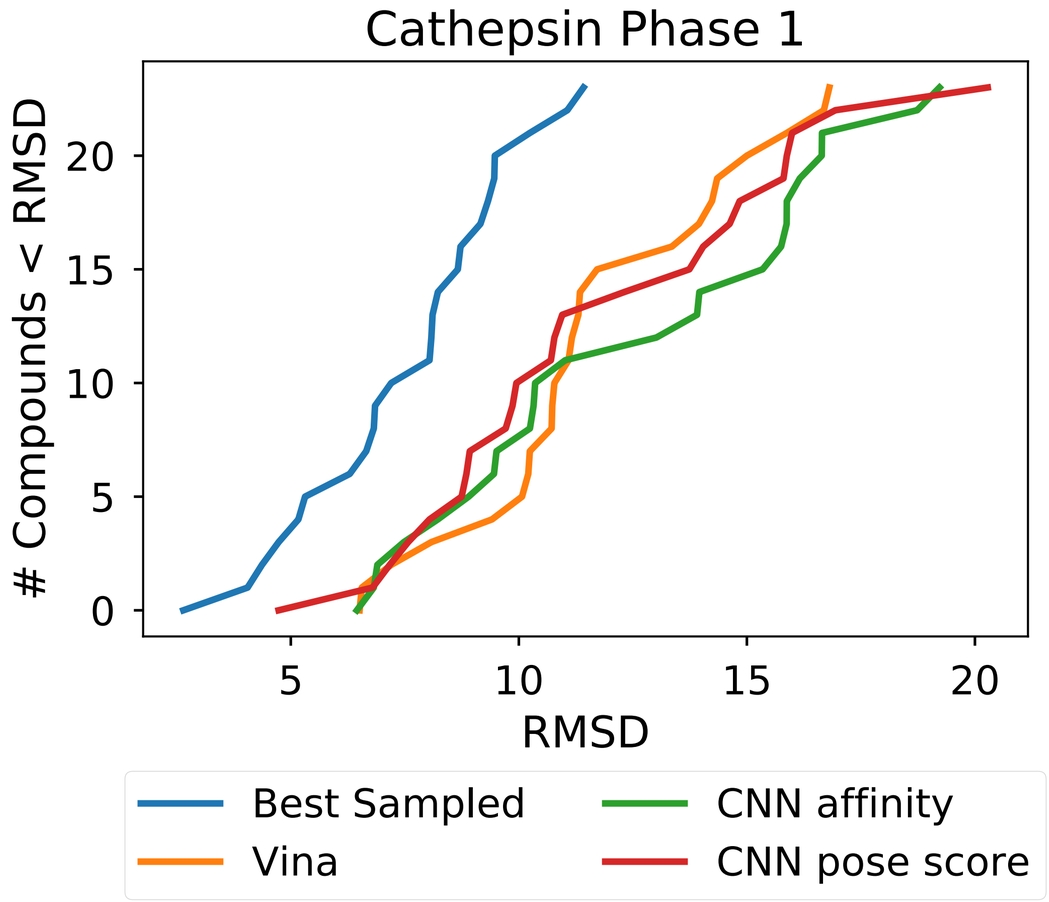
Spearman Correlation

	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

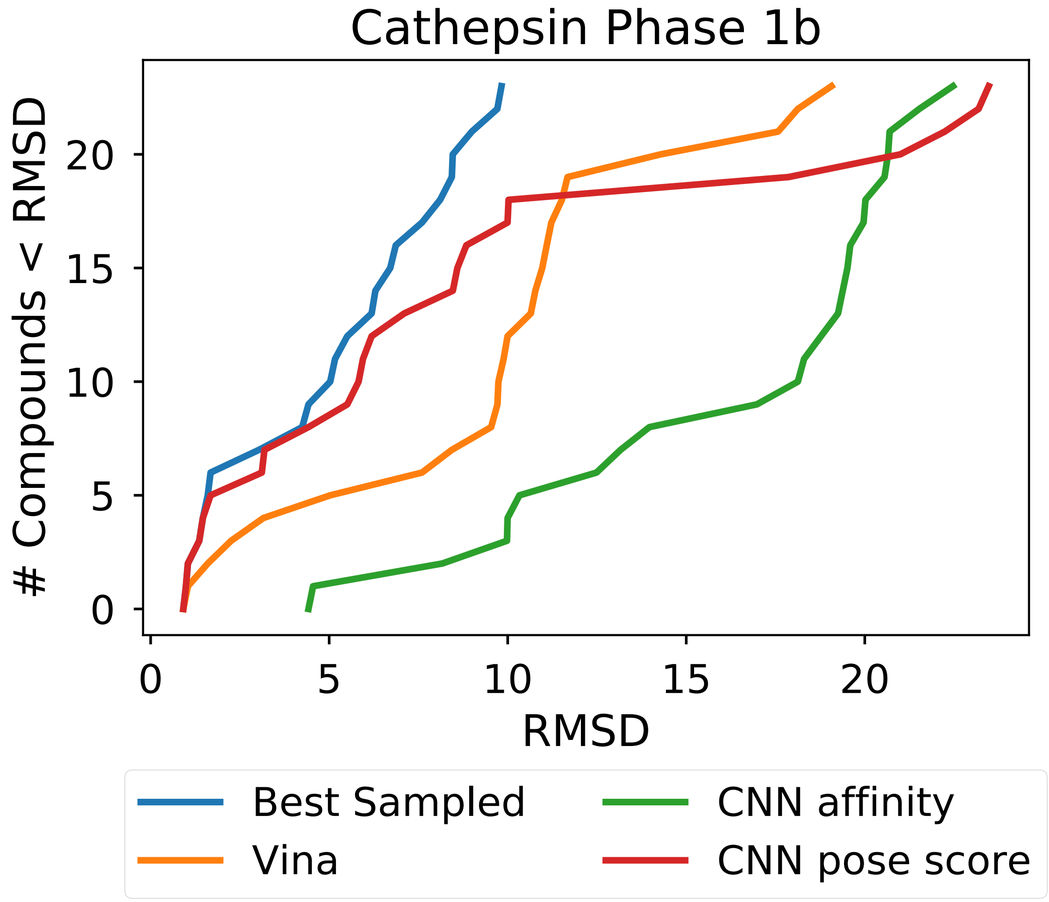
GC3: Pose Prediction



GC3: Pose Prediction

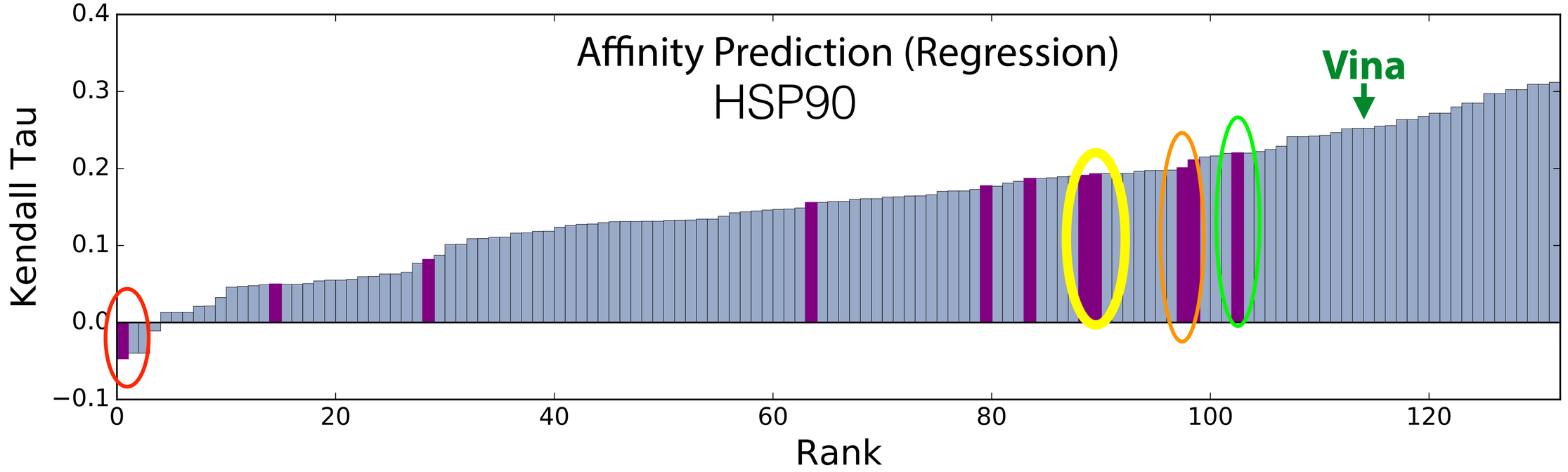


cross-docking



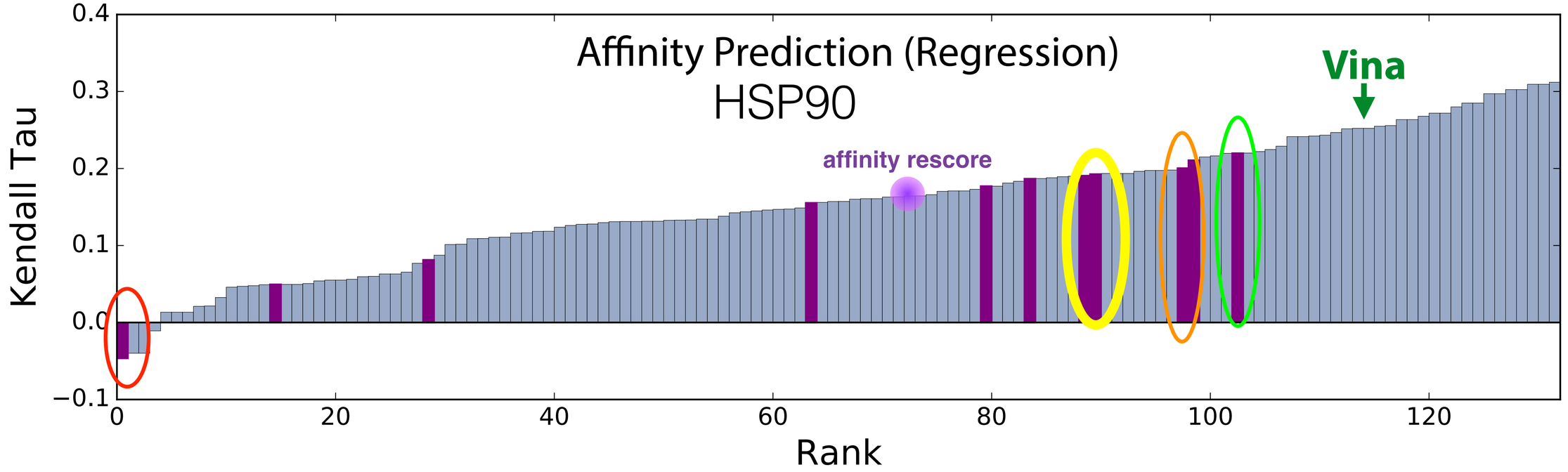
redocking

Grand Challenge 1



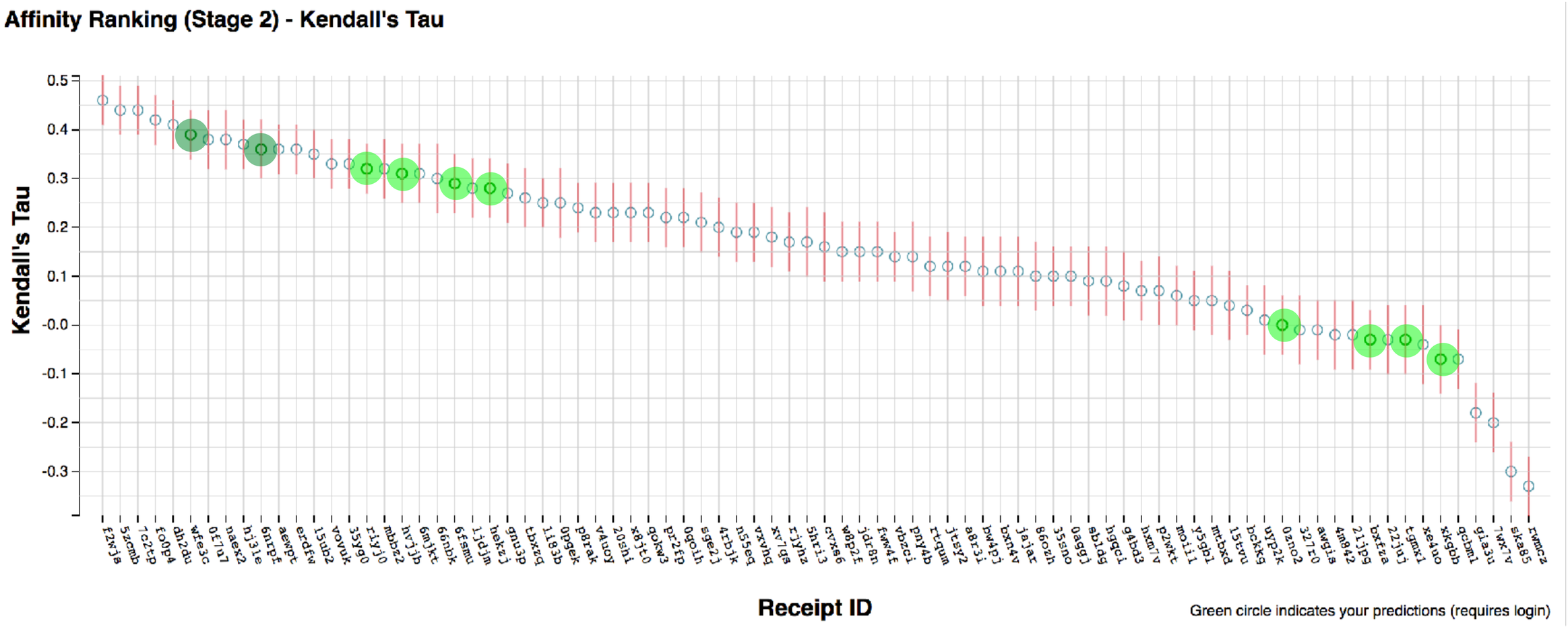
Target LASSO	QSAR SMARTS	Target Balanced NN	QSAR RDKit	Balanced CNN2	Reduced NN	Target Reduced NN	Balanced CNN1	QSAR ECFP6	Balanced NN	Balanced Linear

Grand Challenge 1

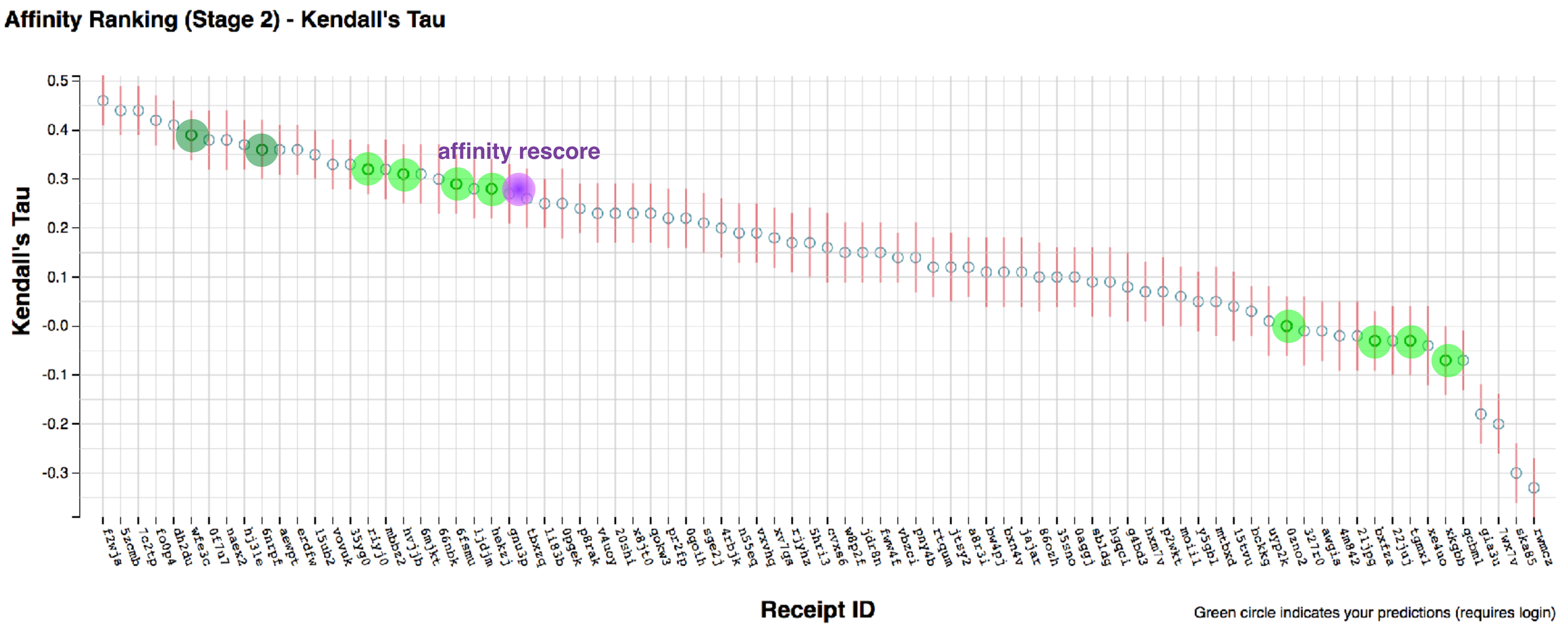


Target LASSO	QSAR SMARTS	Target Balanced NN	QSAR RDKit	Balanced CNN2	Reduced NN	Target Reduced NN	Balanced CNN1	QSAR ECFP6	Balanced NN	Balanced Linear

Grand Challenge 2



Grand Challenge 2



Future Plans

Train CNN for docking

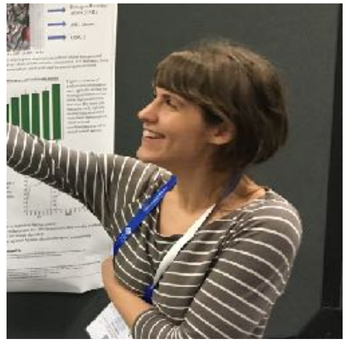
- iteratively train on docked poses
- train on cross-docked poses
- fully integrate CNN scoring into search

Continue to improve model/training parameters

Next Grand Challenge

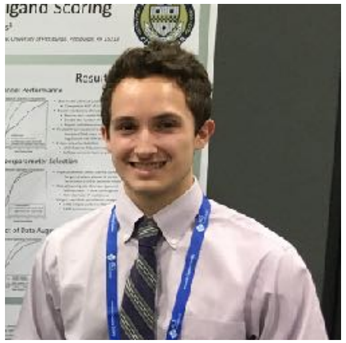
- Finish fully automated predictions early
- Make automated+human insight submission

Acknowledgements



Jocelyn Sunseri

Josh Hochuli



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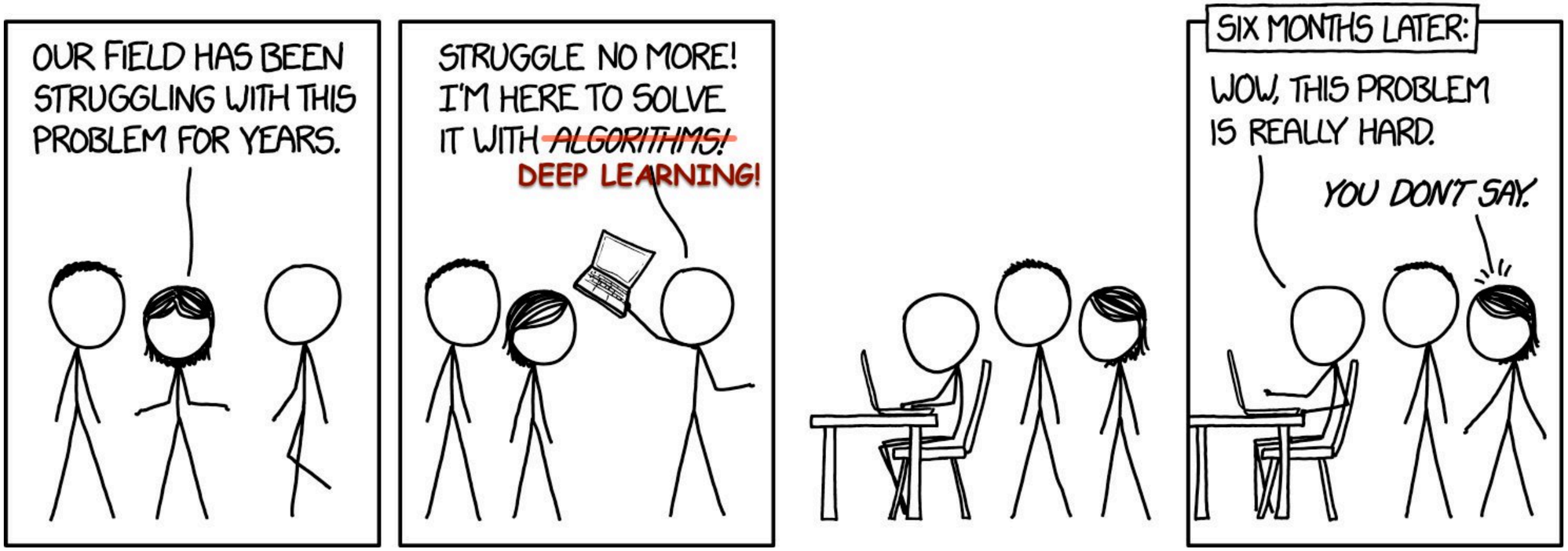
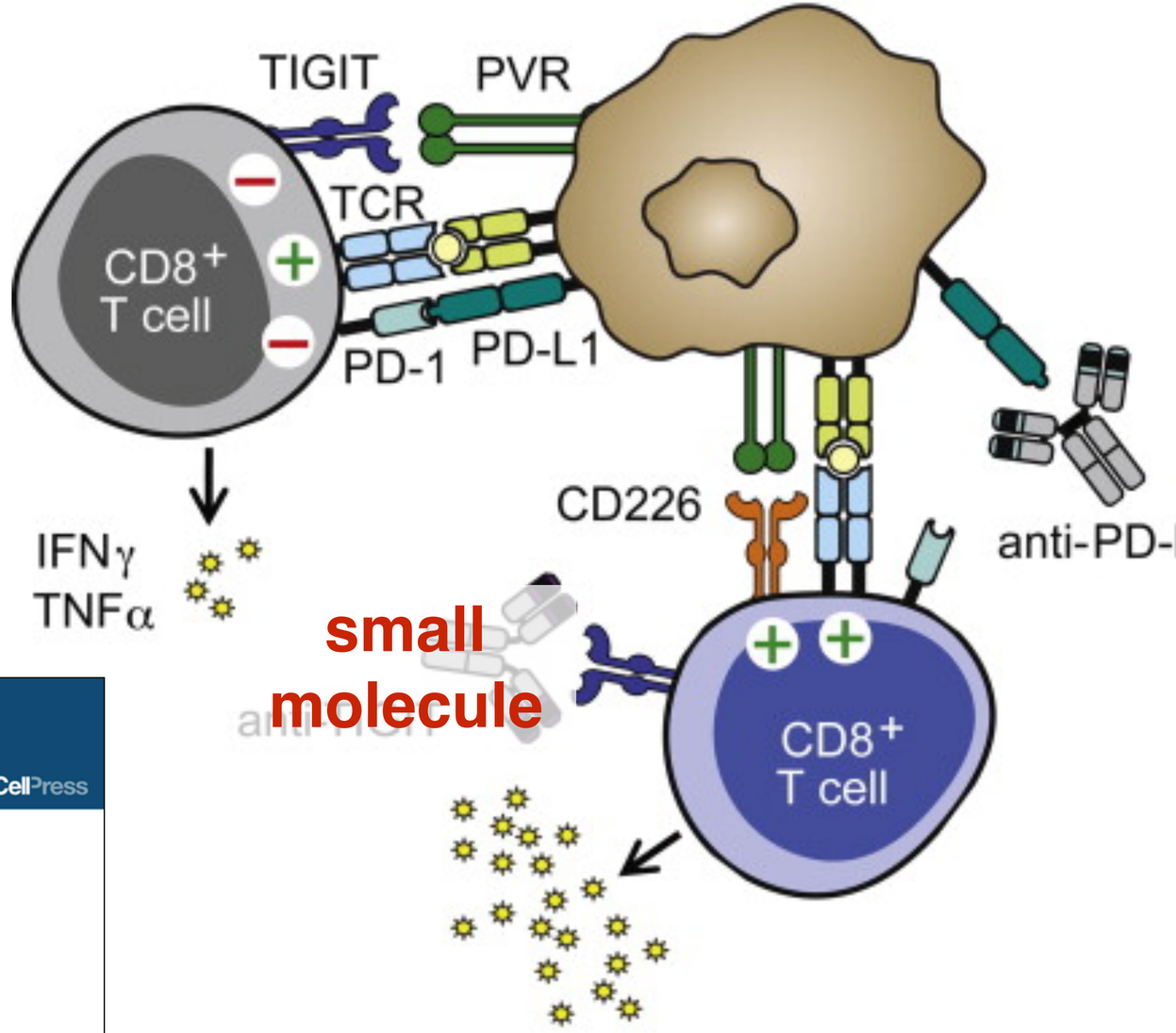


Prospective Case Study: TIGIT

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



Cancer Cell
Article

CellPress

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,*]
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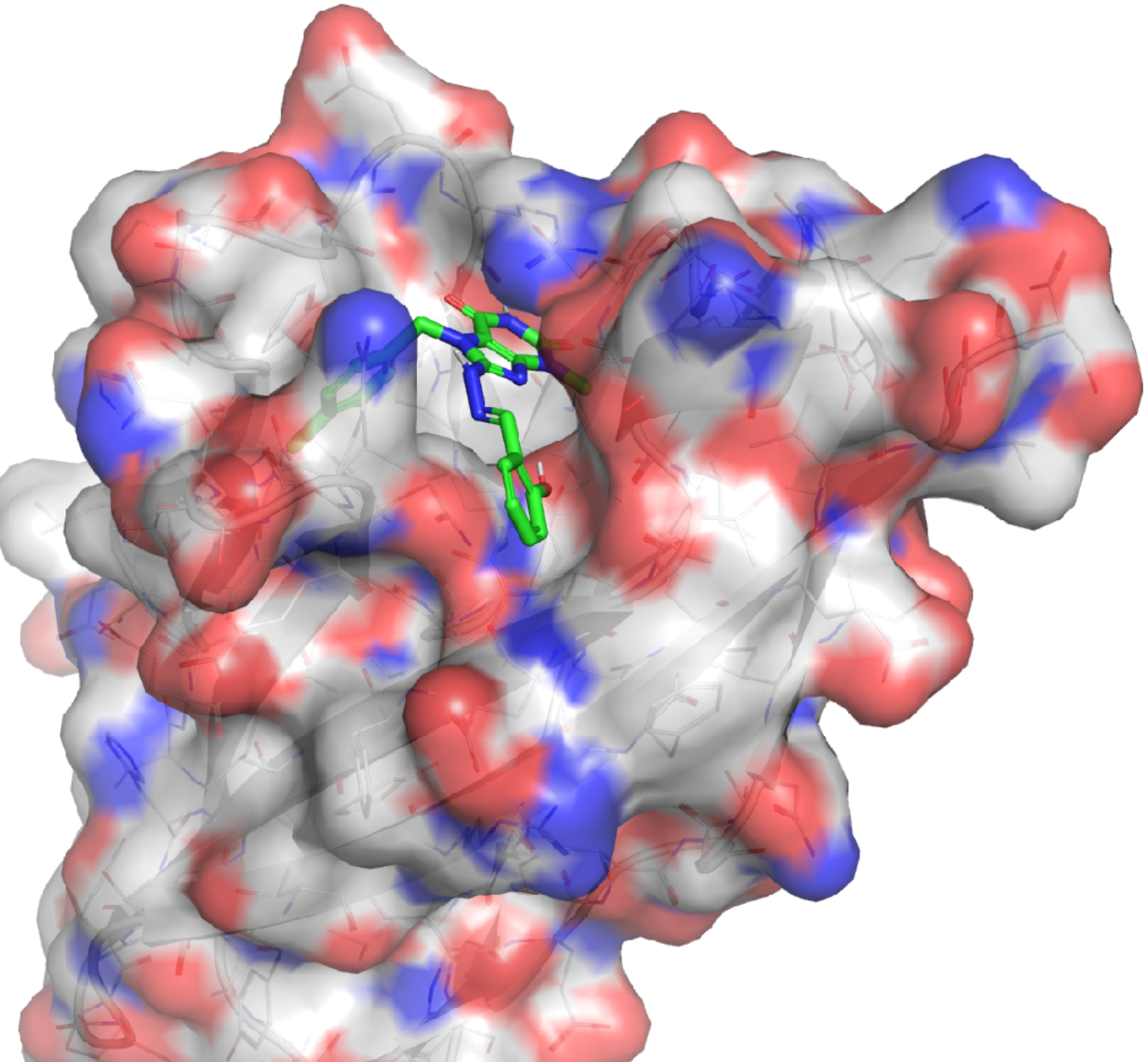
http://dx.doi.org/10.1016/j.ccell.2014.10.018

Screening

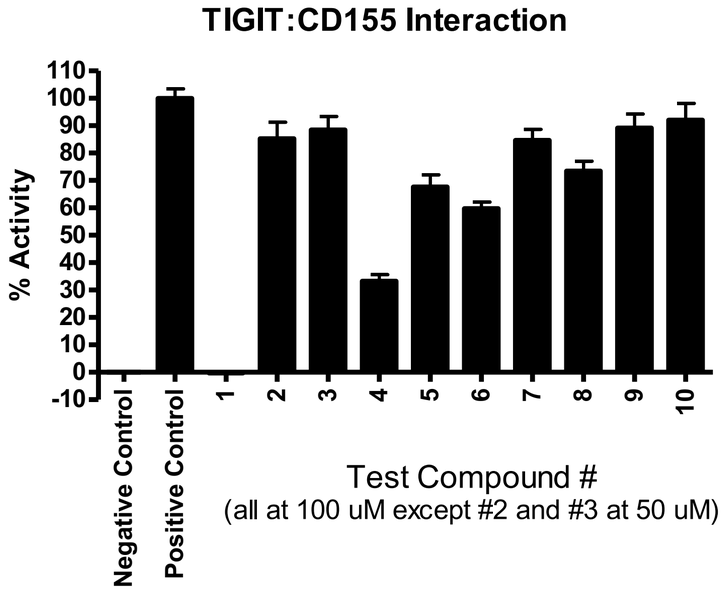


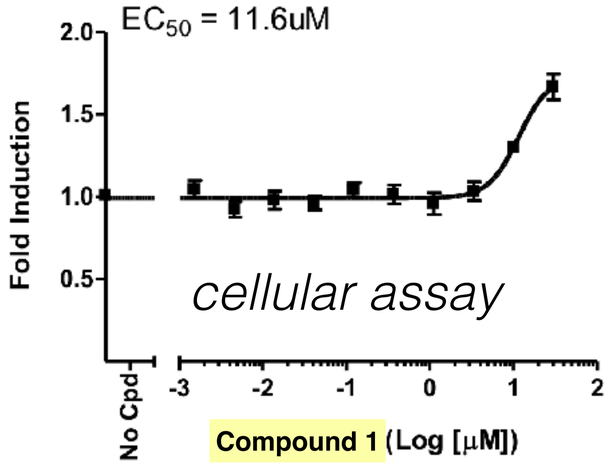
10 diverse compounds selected for screening

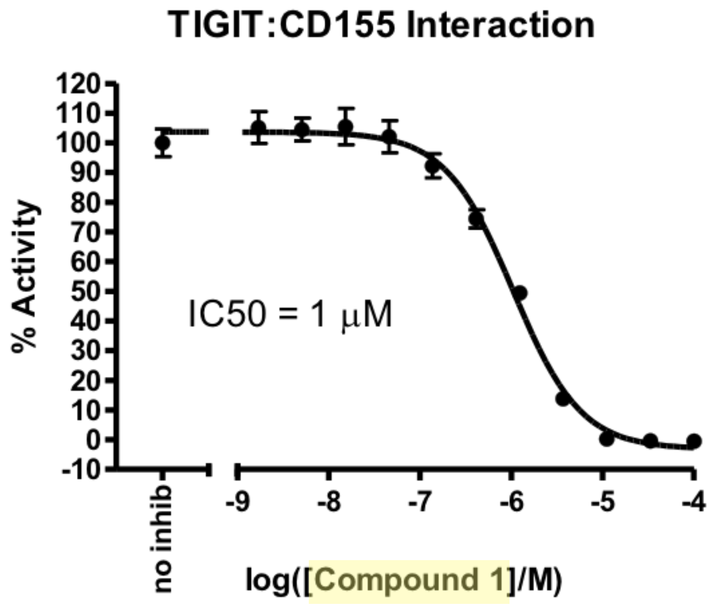
- **top ranked by Vina**
- **top ranked by CNN**

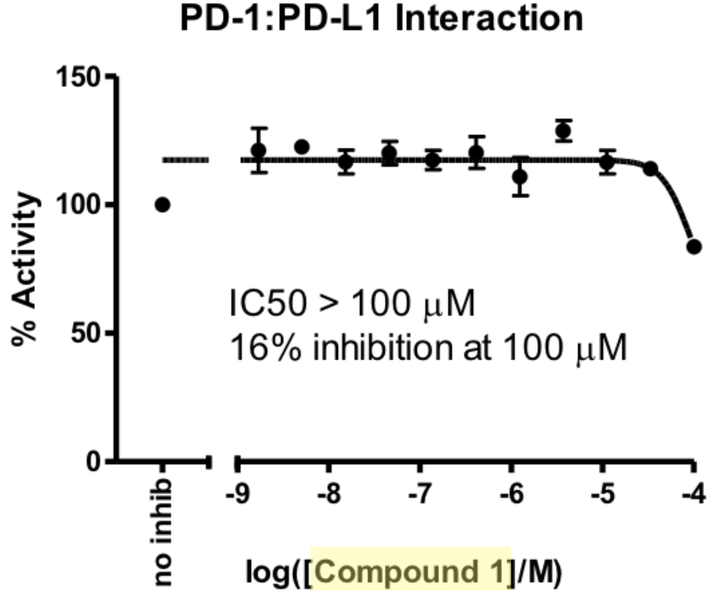
Name	CNN Affinity	CNN Score	Vina
Compound 1	7.69807	0.994763	85.95
Compound 2	5.57909	0.0180277	-8.12632
Compound 3	6.73692	0.0624742	-9.81935
Compound 4	6.87897	0.953488	-3.81378
Compound 5	6.32813	0.209807	-8.60293
Compound 6	5.689	0.0437	-8.991
Compound 7	4.368	0.022	-9.34722
Compound 8	4.81	0.072	-6.81787
Compound 9	5.22	0.032	-6.264
Compound 10	6.67	0.361	6.1053

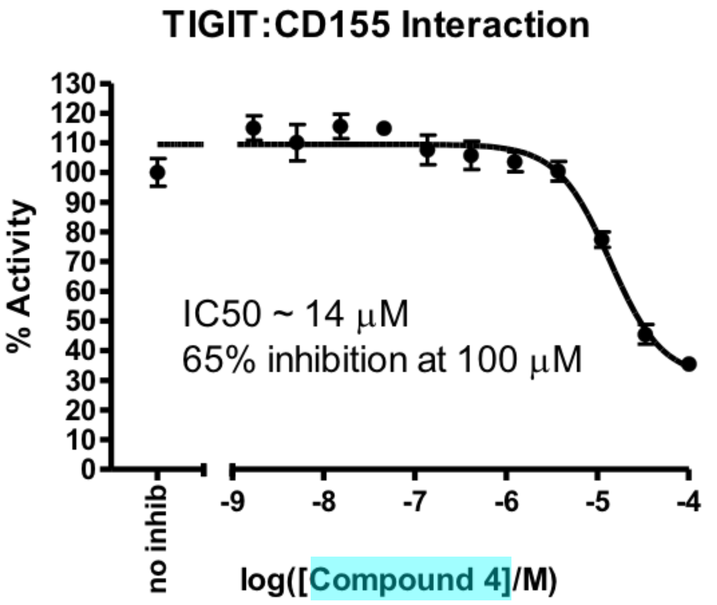
Results

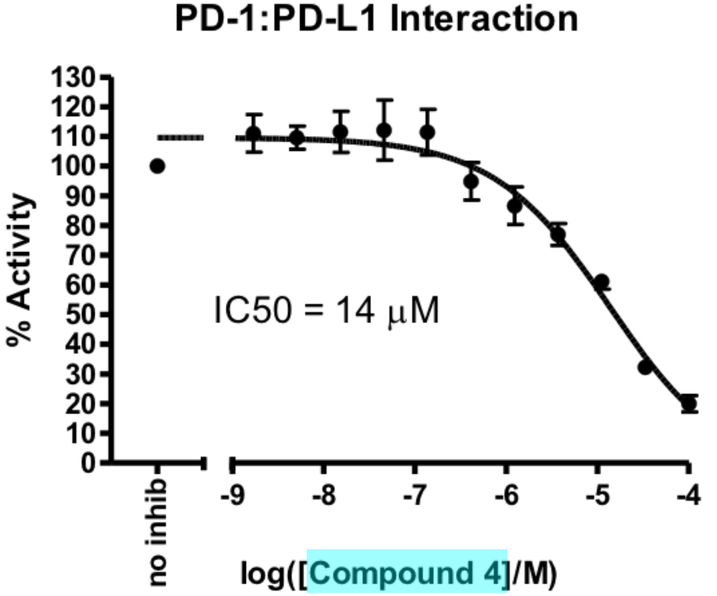

TIGIT:CD155 Interaction
% Activity
Negative Control
Positive Control
Test Compound #
(all at 100 uM except #2 and #3 at 50 uM)


EC50 = 11.6uM
Fold Induction
cellular assay
No Cpd
Compound 1 (Log [μM])

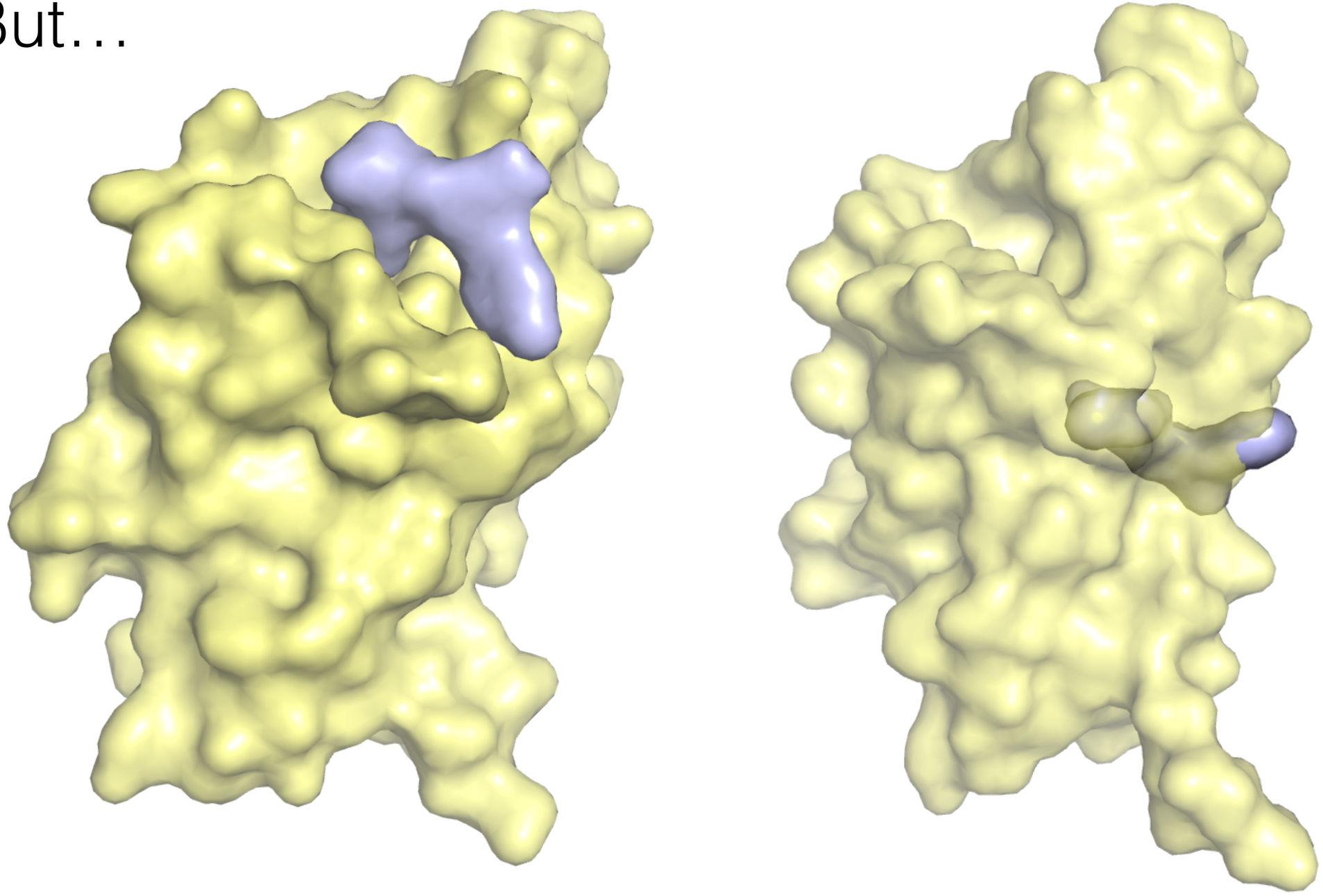

TIGIT:CD155 Interaction
% Activity
IC50 = 1 μM
no inhib
log([Compound 1]/M)


PD-1:PD-L1 Interaction
% Activity
IC50 > 100 μM
16% inhibition at 100 μM
no inhib
log([Compound 1]/M)

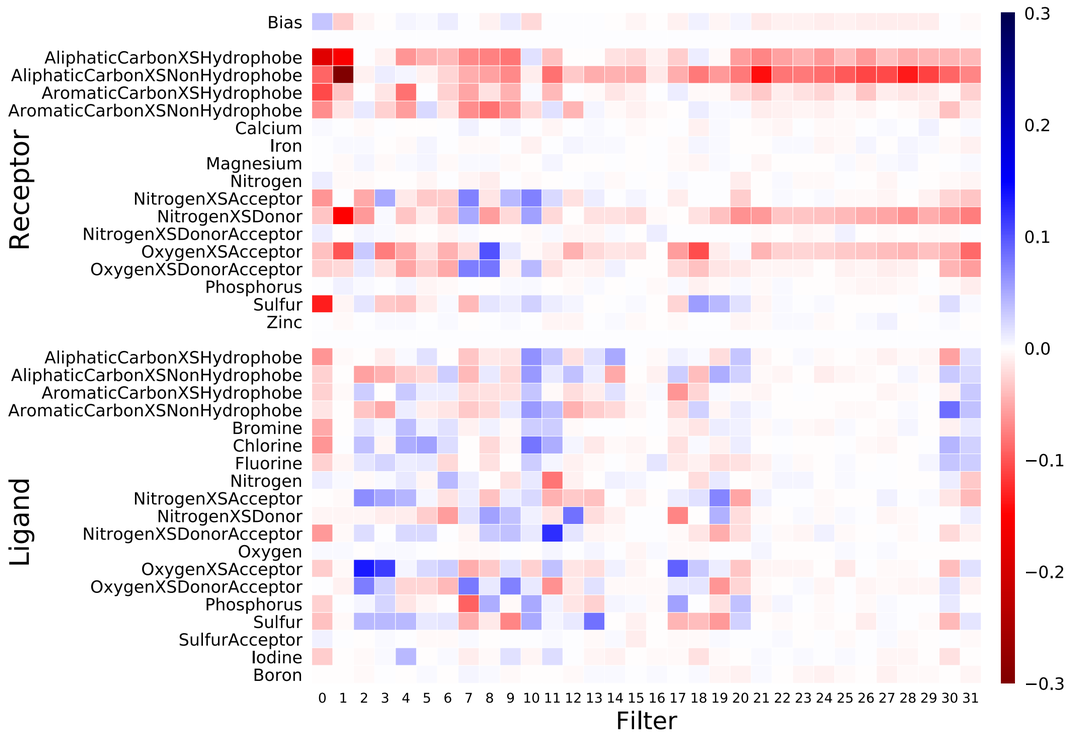

TIGIT:CD155 Interaction
% Activity
IC50 ~ 14 μM
65% inhibition at 100 μM
no inhib
log([Compound 4]/M)

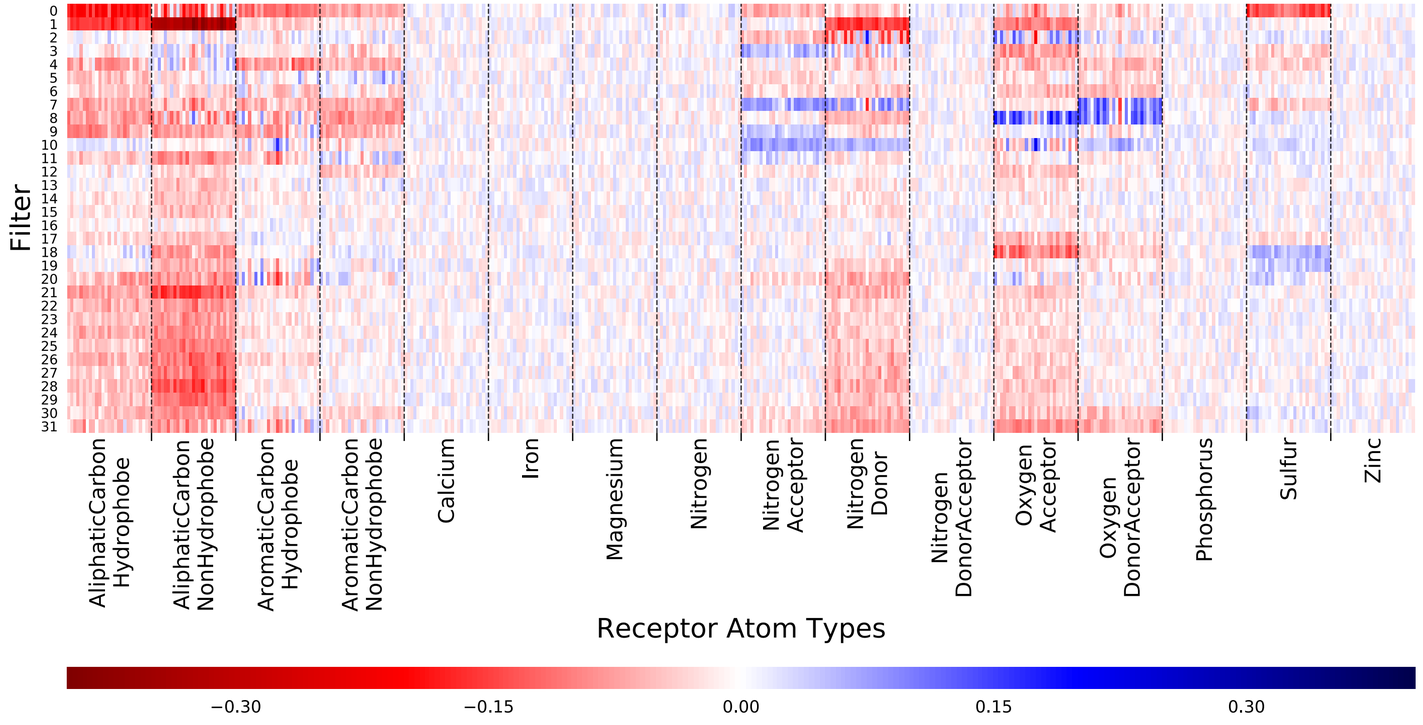

PD-1:PD-L1 Interaction
% Activity
IC50 = 14 μM
no inhib
log([Compound 4]/M)

But…



Filter Visualization


Bias
AliphaticCarbonXSHydrophobe
AliphaticCarbonXSNonHydrophobe
AromaticCarbonXSHydrophobe
AromaticCarbonXSNonHydrophobe
Calcium
Iron
Magnesium
Nitrogen
NitrogenXSAcceptor
NitrogenXSDonor
NitrogenXSDonorAcceptor
OxygenXSAcceptor
OxygenXSDonorAcceptor
Phosphorus
Sulfur
Zinc
Receptor
AliphaticCarbonXSHydrophobe
AliphaticCarbonXSNonHydrophobe
AromaticCarbonXSHydrophobe
AromaticCarbonXSNonHydrophobe
Bromine
Chlorine
Fluorine
Nitrogen
NitrogenXSAcceptor
NitrogenXSDonor
NitrogenXSDonorAcceptor
Oxygen
OxygenXSAcceptor
OxygenXSDonorAcceptor
Phosphorus
Sulfur
SulfurAcceptor
Iodine
Boron
Ligand
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
Filter
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3


Filter
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
AliphaticCarbon Hydrophobe
AliphaticCarbon NonHydrophobe
AromaticCarbon Hydrophobe
AromaticCarbon NonHydrophobe
Calcium
Iron
Magnesium
Nitrogen
Nitrogen Acceptor
Nitrogen Donor
Nitrogen DonorAcceptor
Oxygen Acceptor
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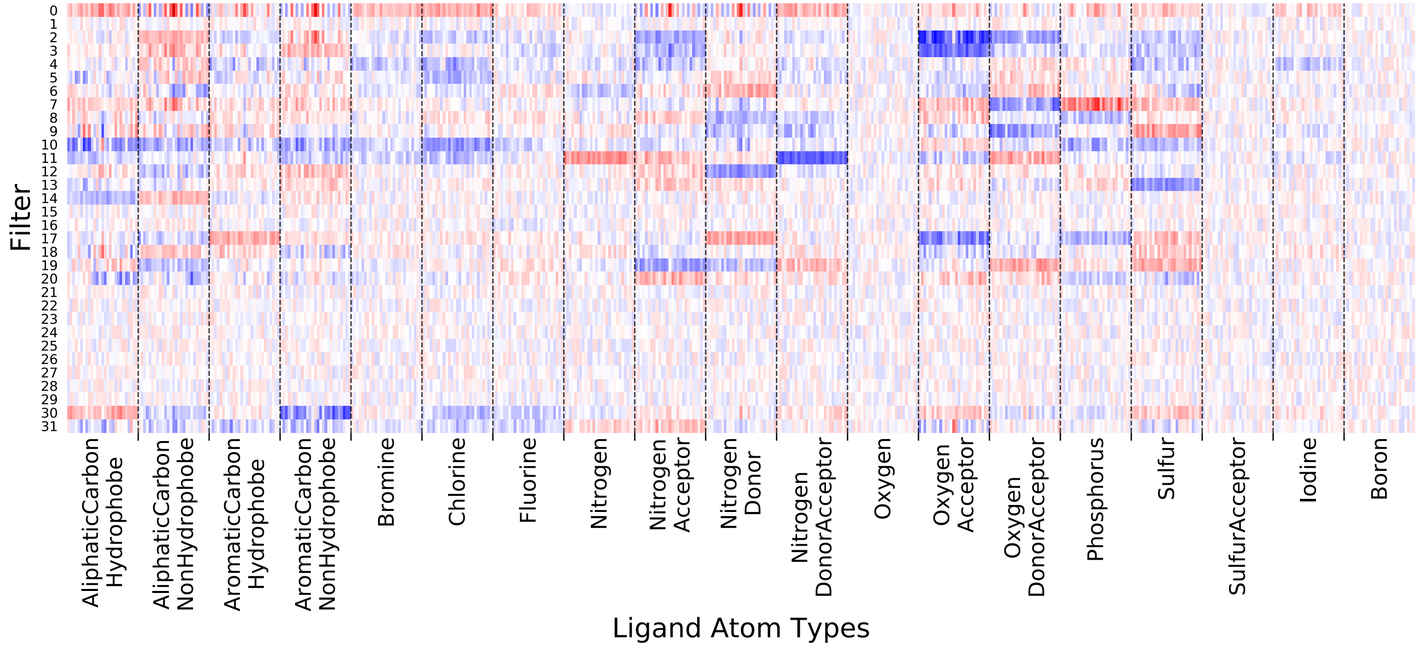
Phosphorus
Sulfur
Zinc
Receptor Atom Types


−0.30
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0.15
0.30
Filter
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
AliphaticCarbon Hydrophobe
AliphaticCarbon NonHydrophobe
AromaticCarbon Hydrophobe
AromaticCarbon NonHydrophobe
Bromine
Chlorine
Fluorine
Nitrogen
Nitrogen Acceptor
Nitrogen Donor
Nitrogen DonorAcceptor
Oxygen
Oxygen Acceptor
Oxygen DonorAcceptor
Phosphorus
Sulfur
SulfurAcceptor
Iodine
Boron
Ligand Atom Types