Protein-Ligand Scoring with Convolutional Neural Networks

David Koes

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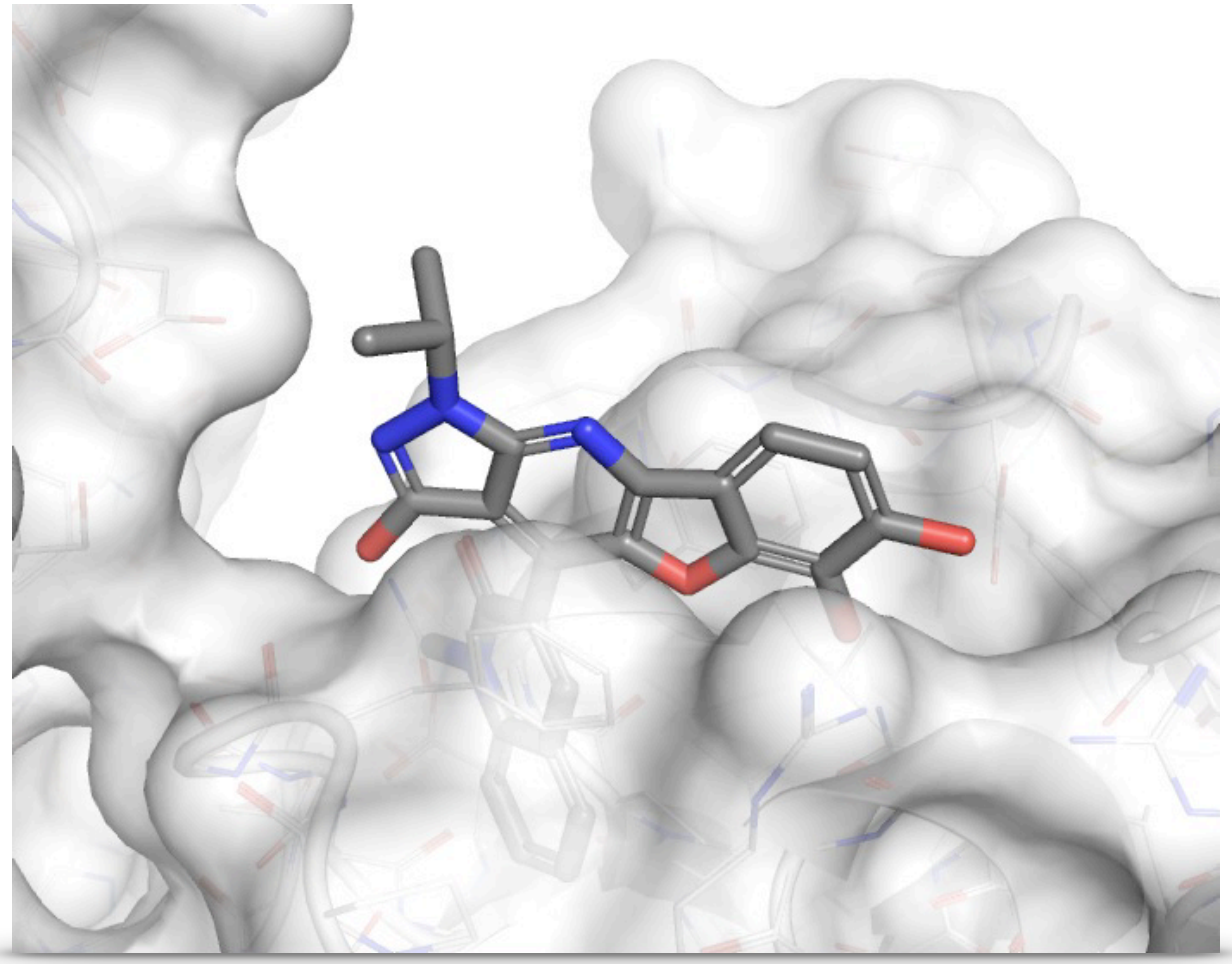
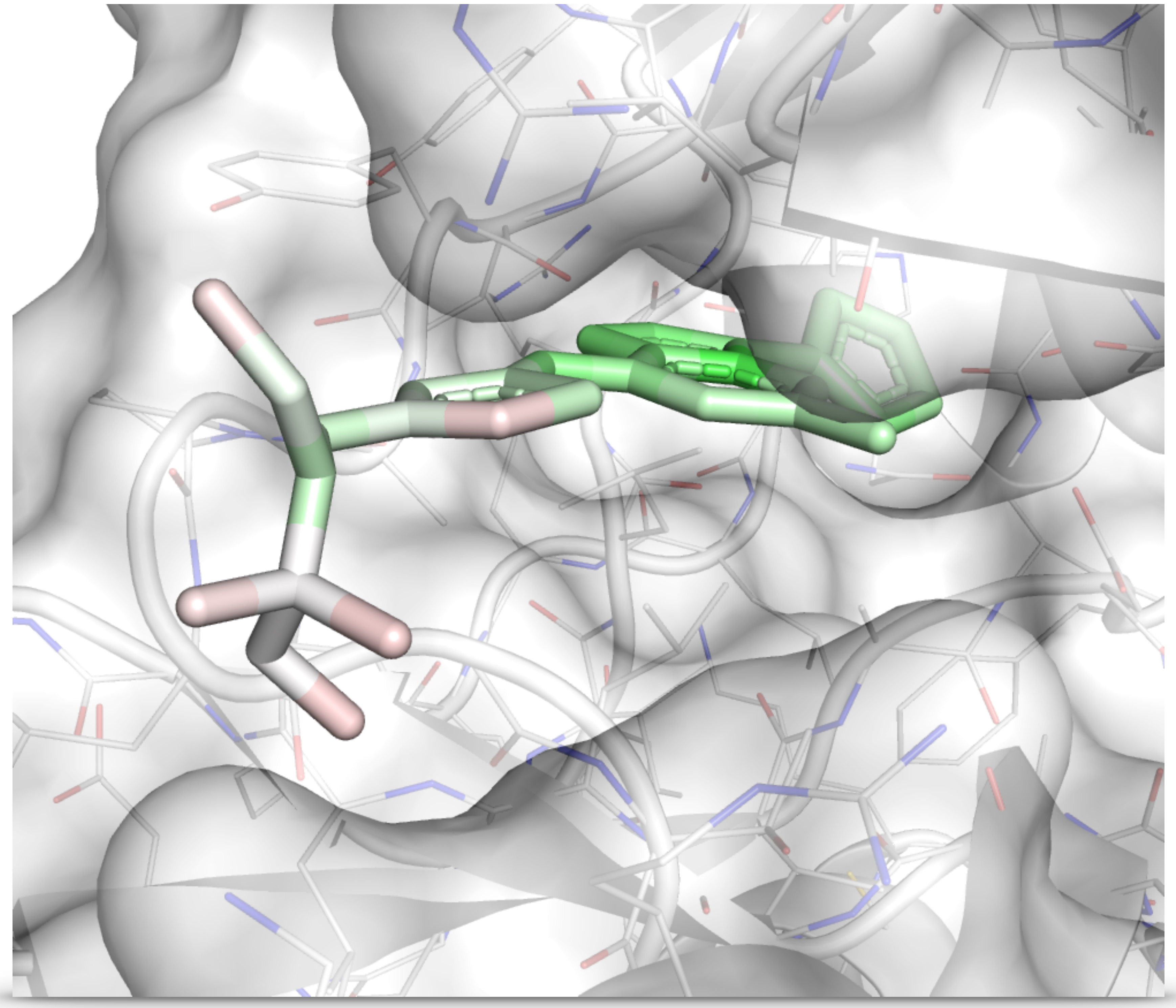
D3R Workshop
San Diego
February 22, 2018

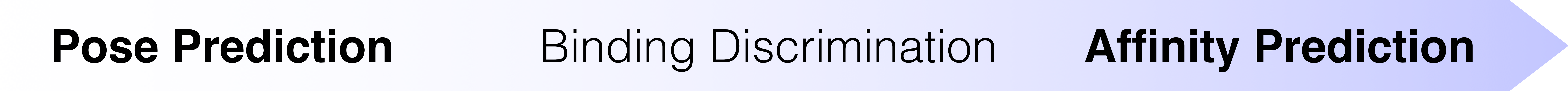
Structure Based Drug Design

Virtual Screening

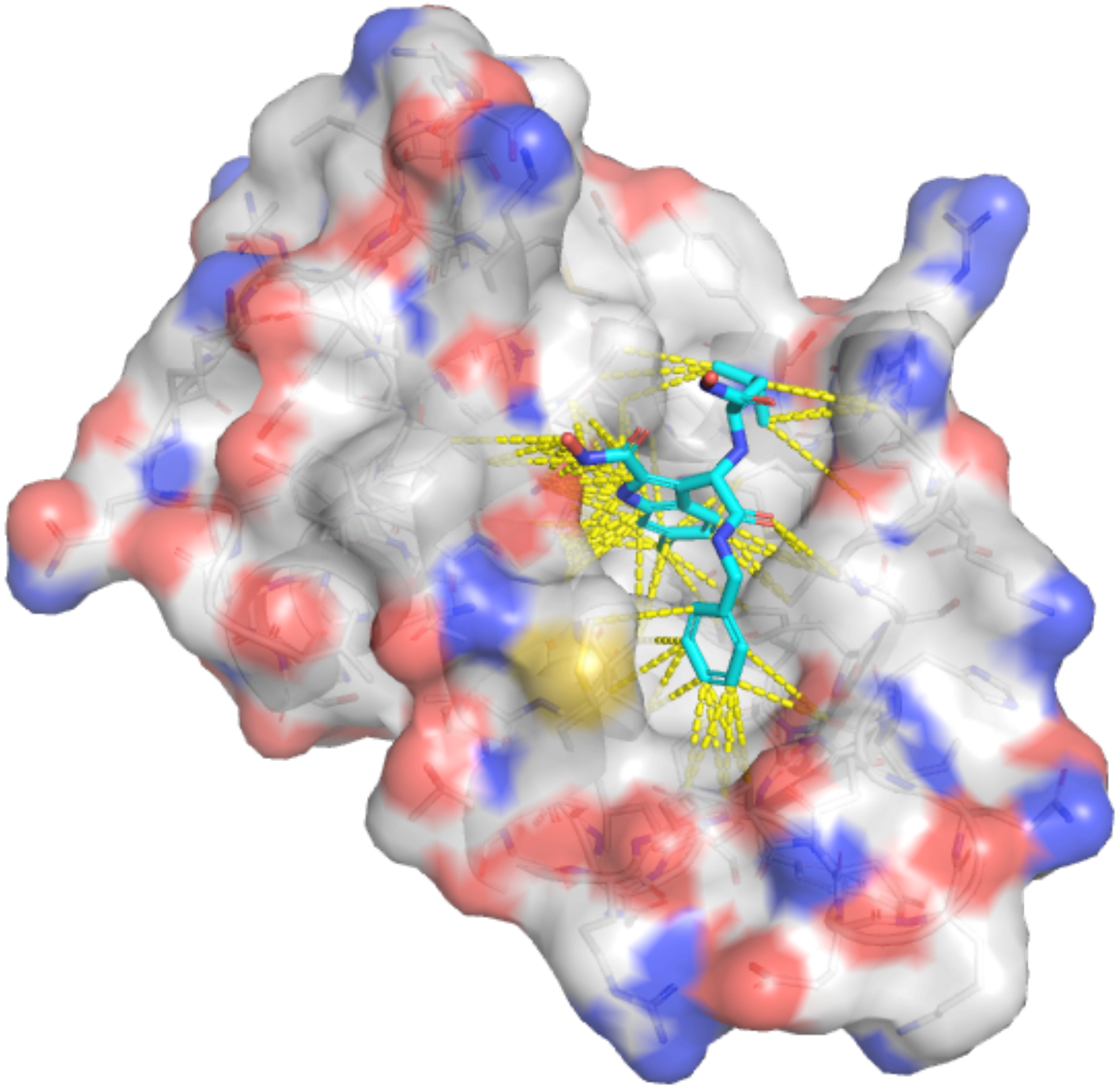
Lead Optimization



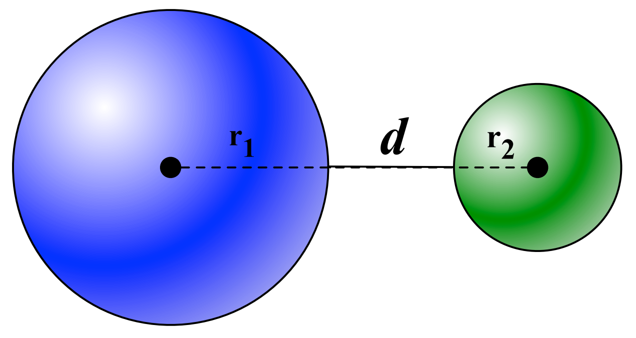




Protein-Ligand Scoring



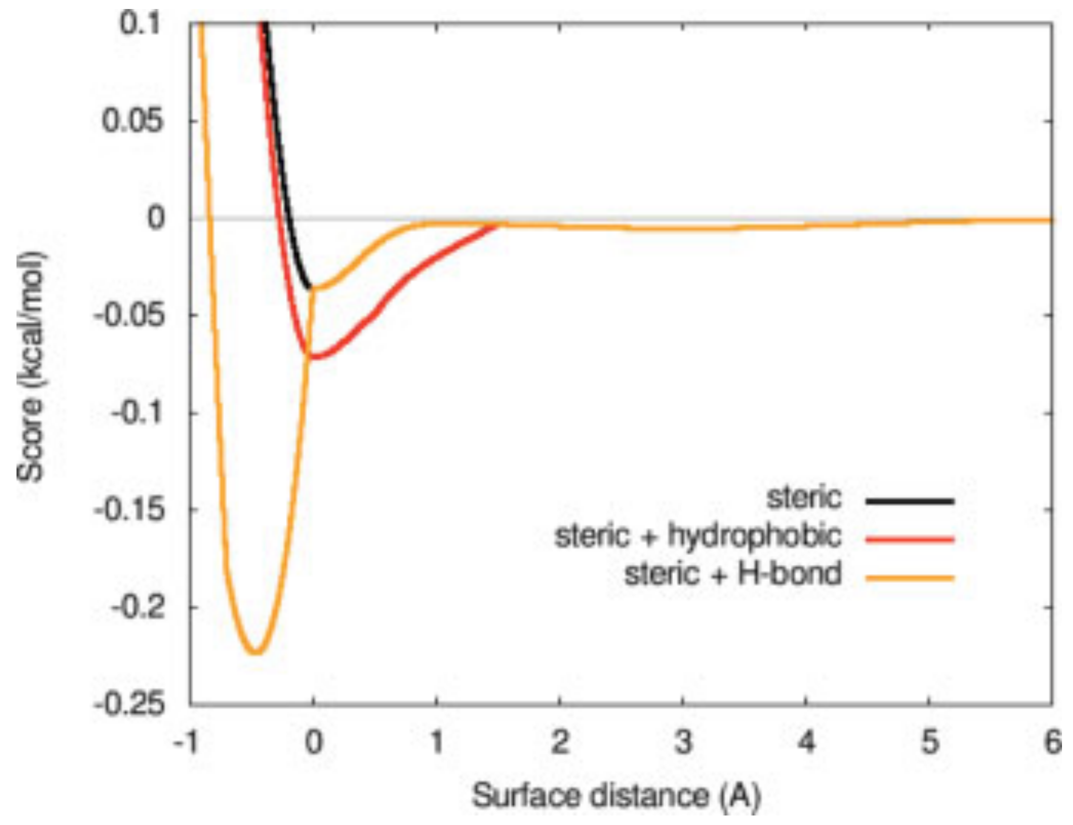
AutoDock Vina



$$
\begin{aligned}
\mathrm{gauss}_1(d) &= w_{\mathrm{guass}_1} e^{-(d/0.5)^2} \\
\mathrm{gauss}_2(d) &= w_{\mathrm{guass}_2} e^{-((d-3)/2)^2} \\
\mathrm{repulsion}(d) &= \begin{cases} w_{\mathrm{repulsion}} d^2 & d < 0 \\ 0 & d \geq 0 \end{cases}
\end{aligned}
$$

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

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



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

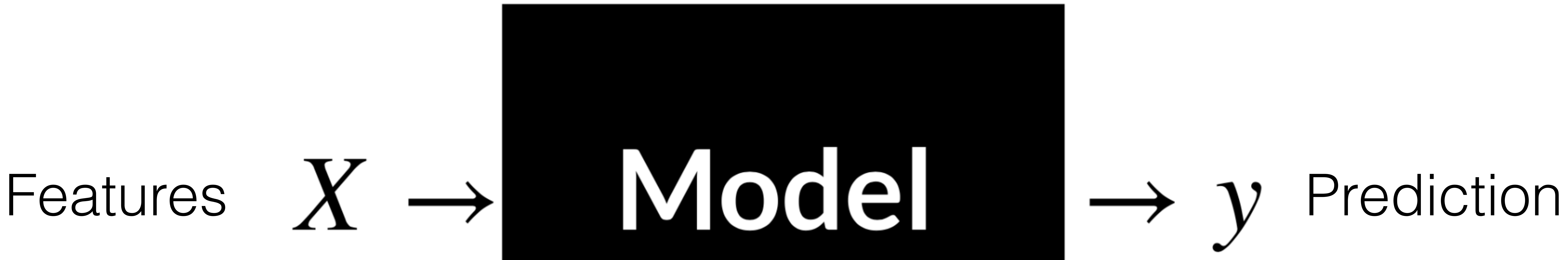
Can we do better?

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

Key Idea: Leverage "big data"

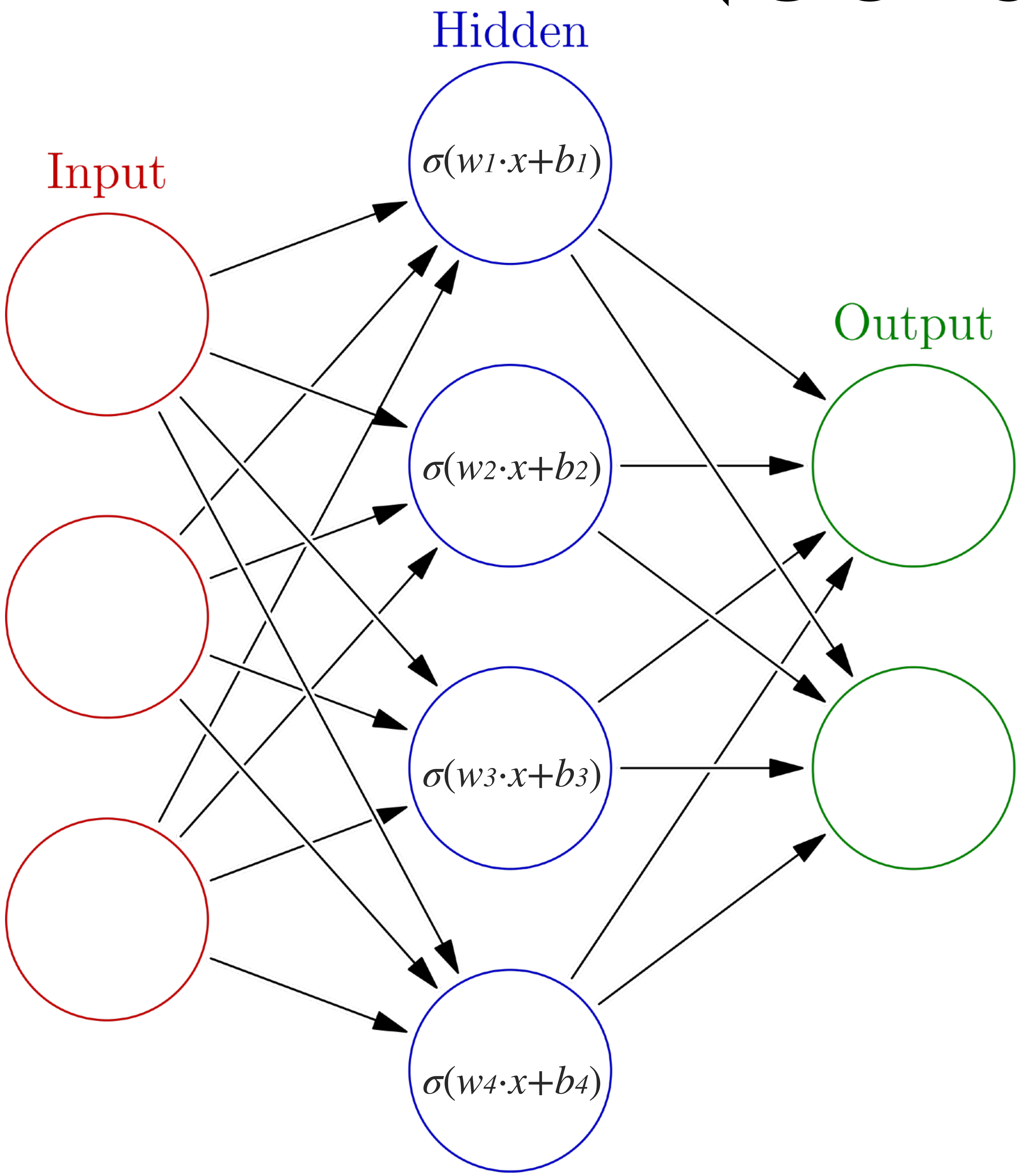
- 231,655,275 bioactivities in PubChem
- 125,526 structures in the PDB
- 16,179 annotated complexes in PDBbind

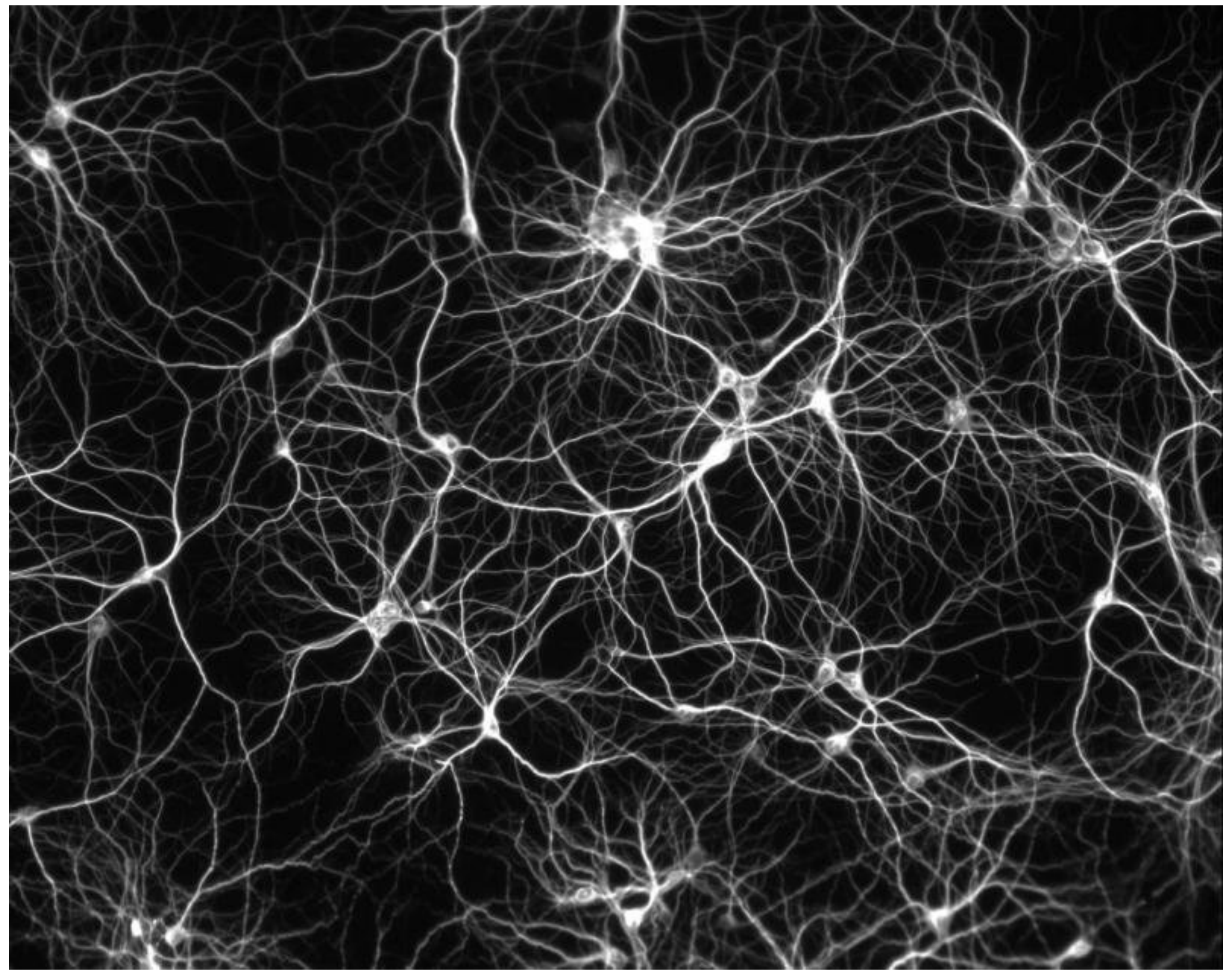
Machine Learning



Features $X \rightarrow$ **Model** $\rightarrow y$ Prediction

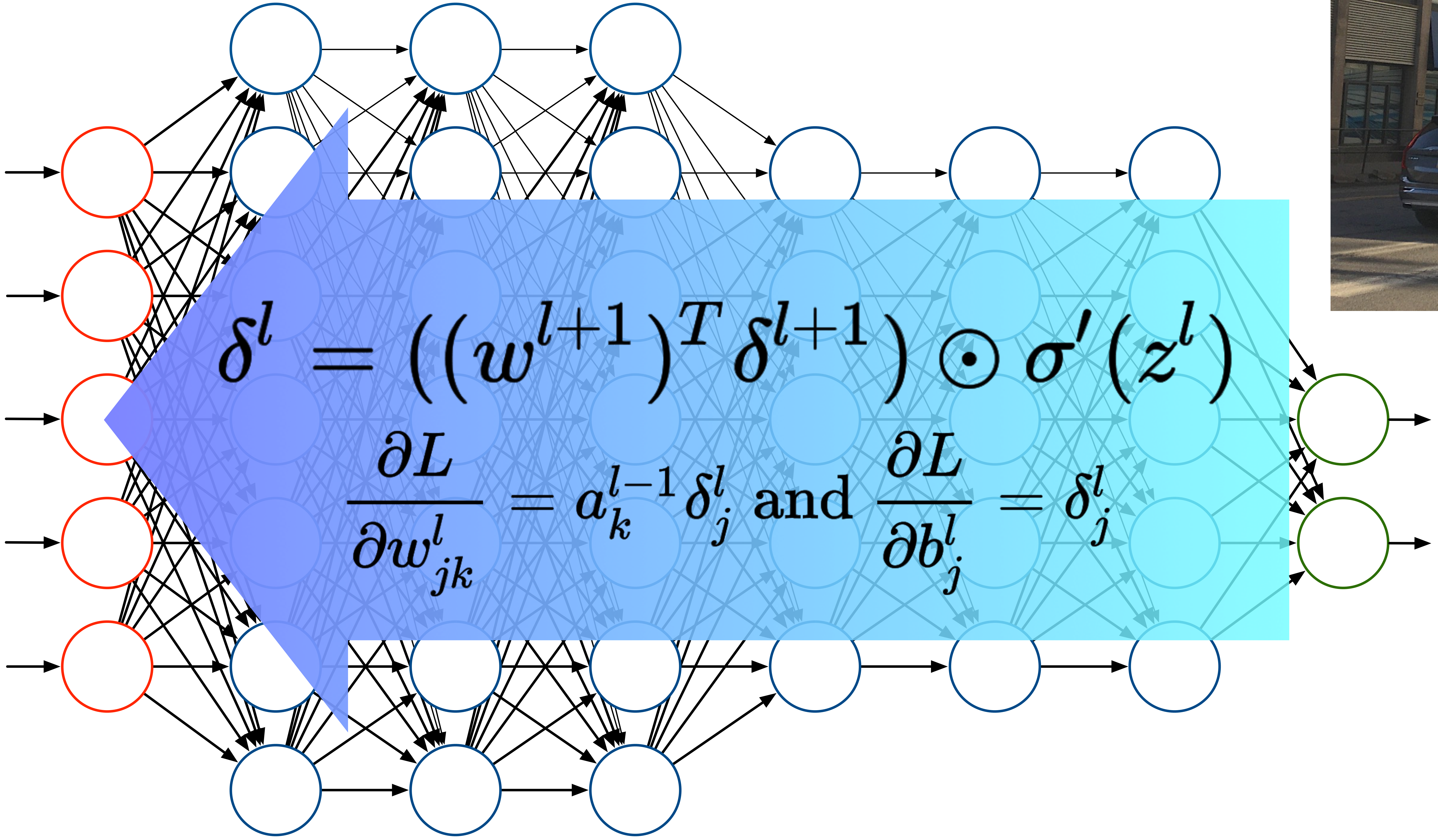
Neural Networks





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



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

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

nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
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Illegal harvest of millions of Mediterranean birds
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SAFEGUARD TRANSPARENCY
Don't let openness backfire on individuals
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POPULAR SCIENCE
WHEN GENES GOT 'SELFISH'
Dawkins's calling card forty years on
PAGE 462
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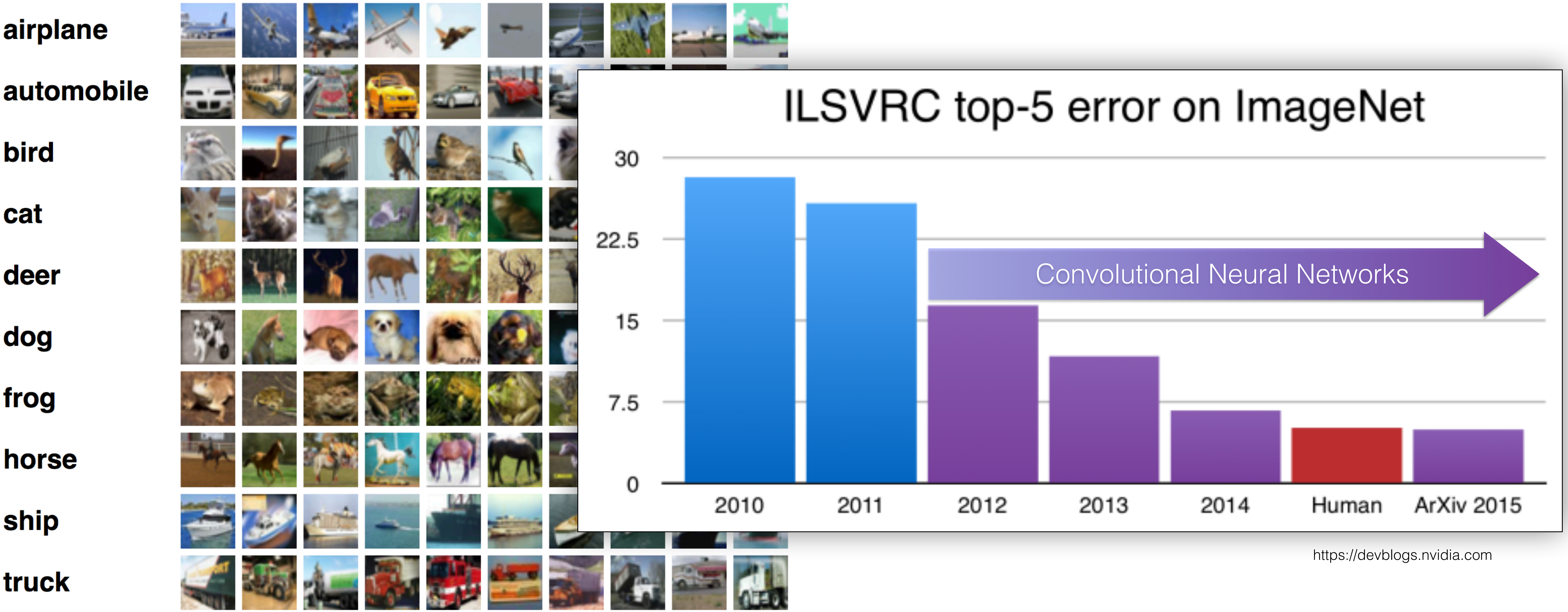
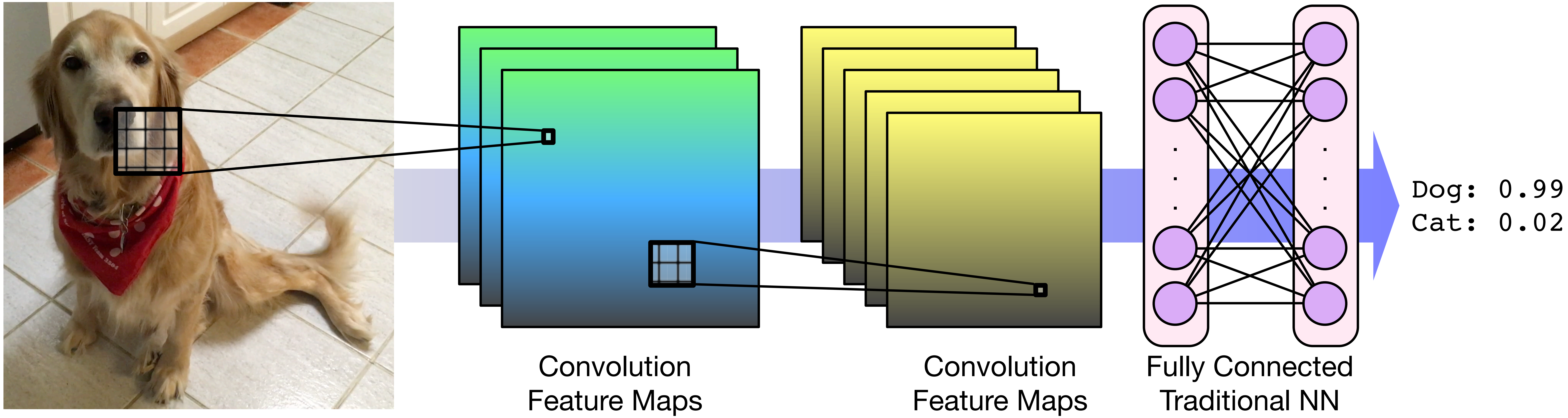
Image Recognition



https://devblogs.nvidia.com

Convolutional Neural Networks

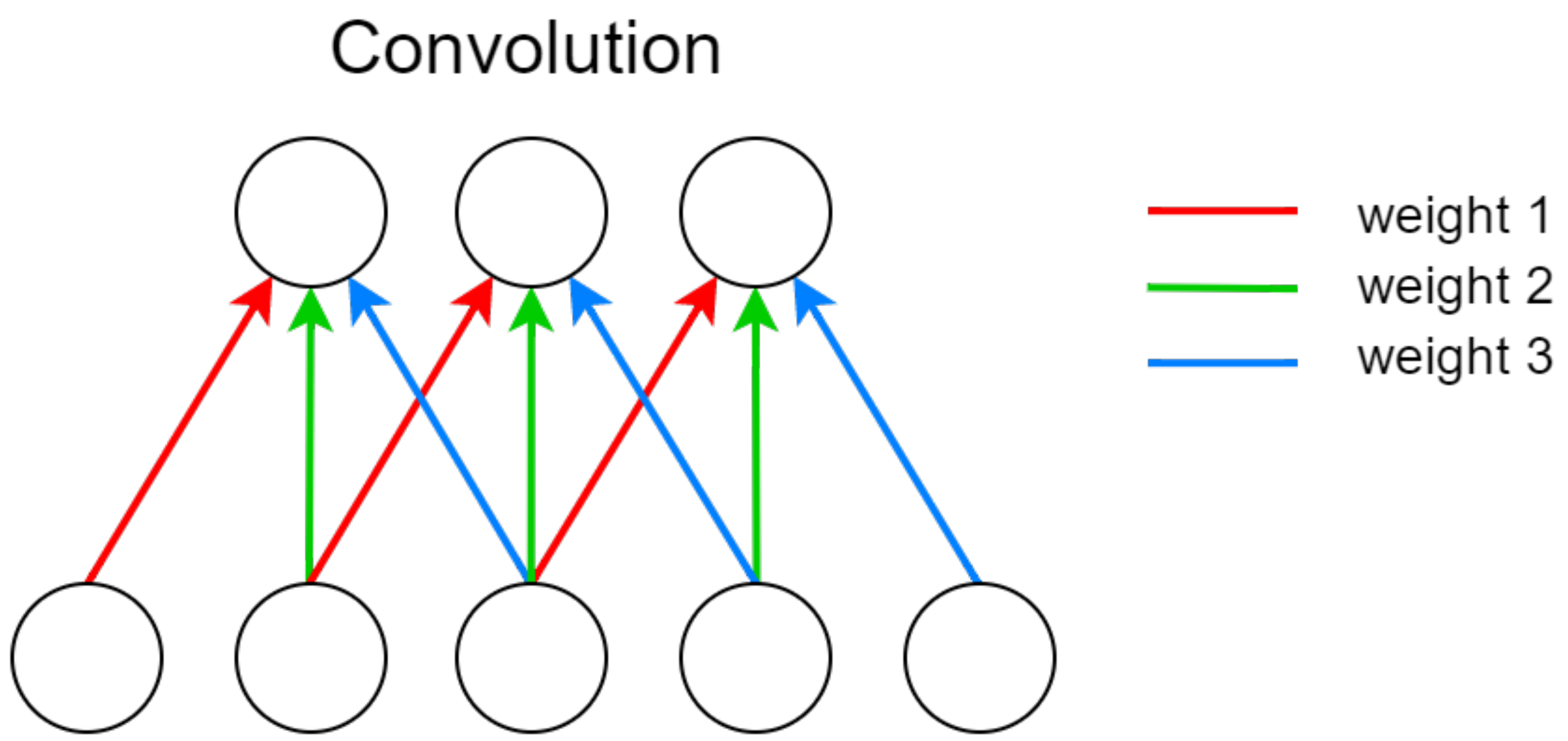


Convolution
Feature Maps

Convolution
Feature Maps

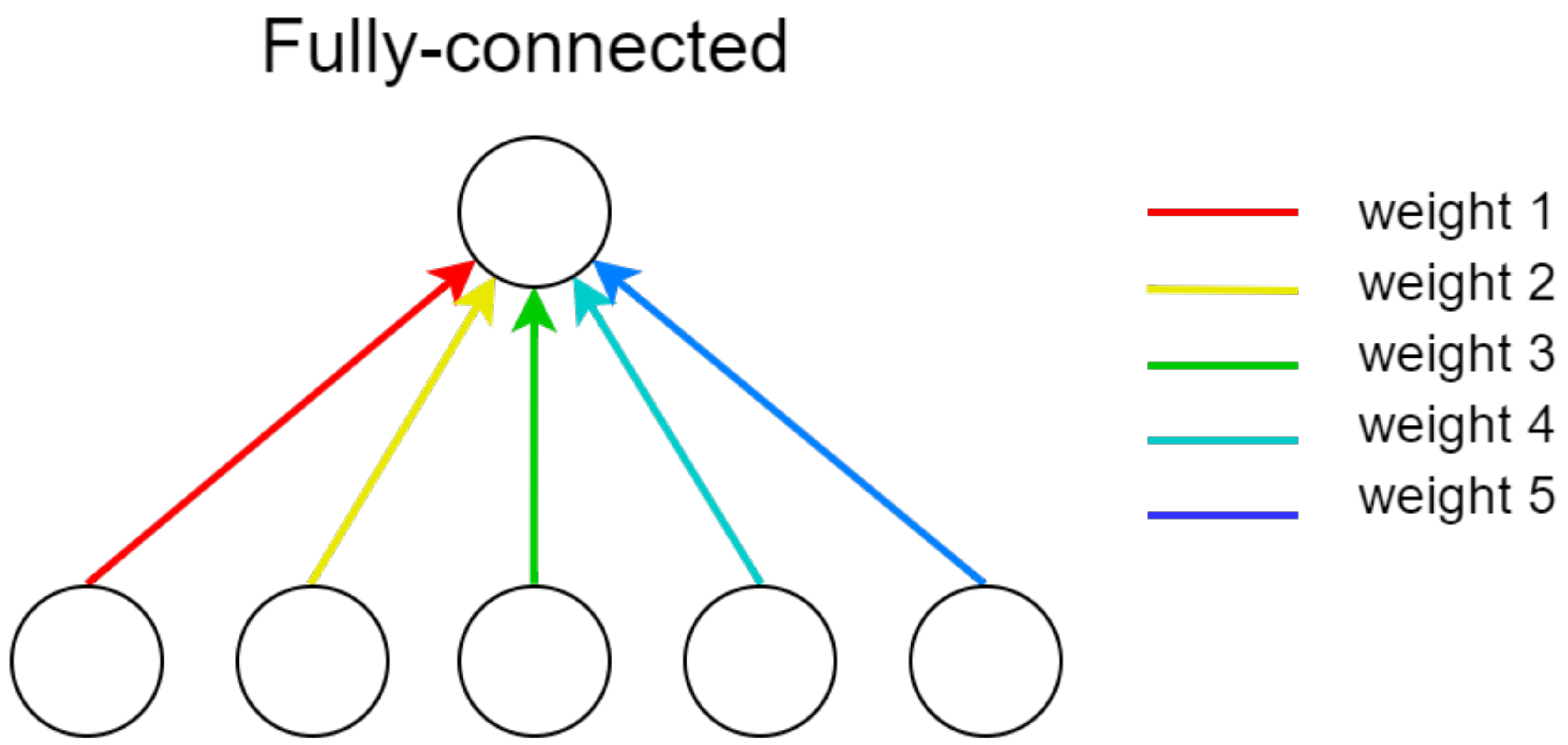
Fully Connected
Traditional NN

Dog: 0.99
Cat: 0.02



Convolution

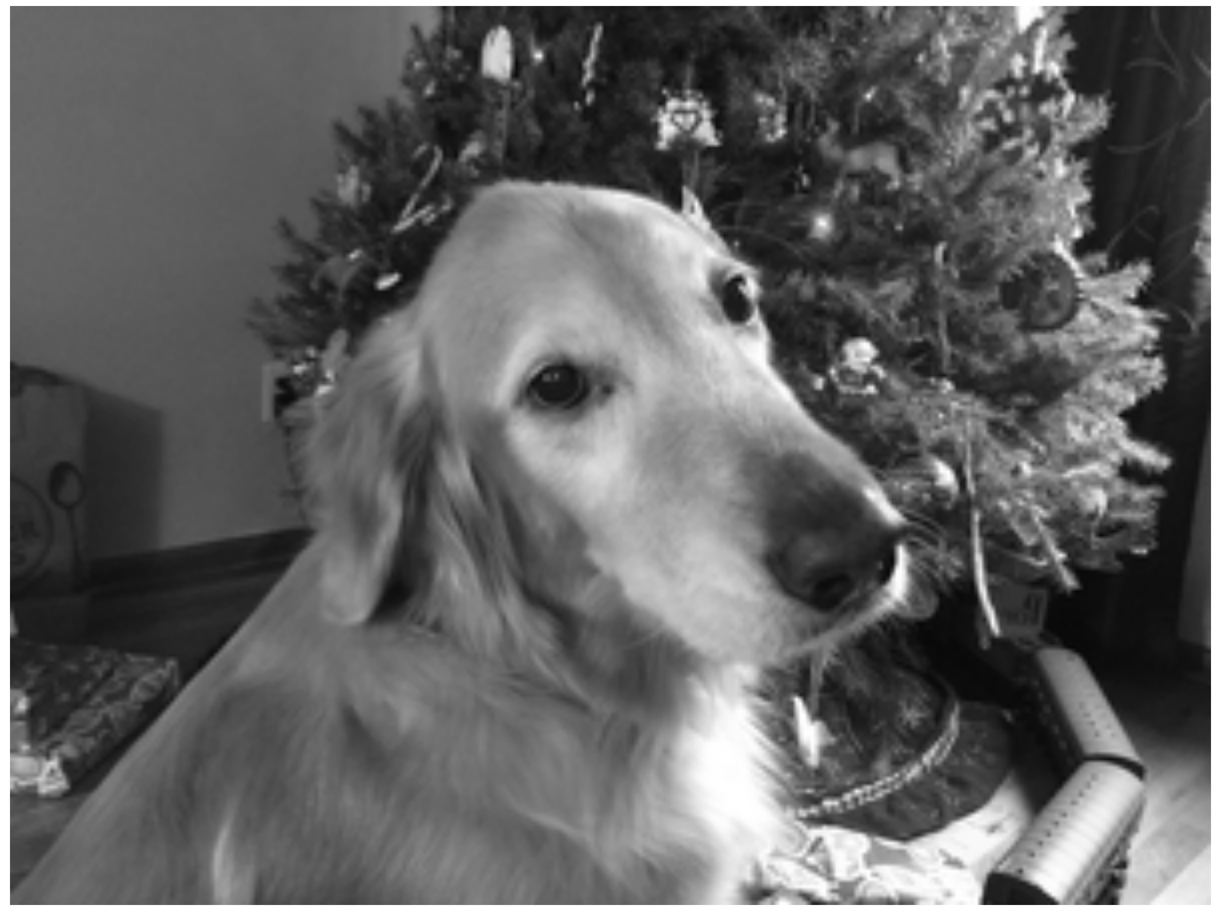
weight 1
weight 2
weight 3

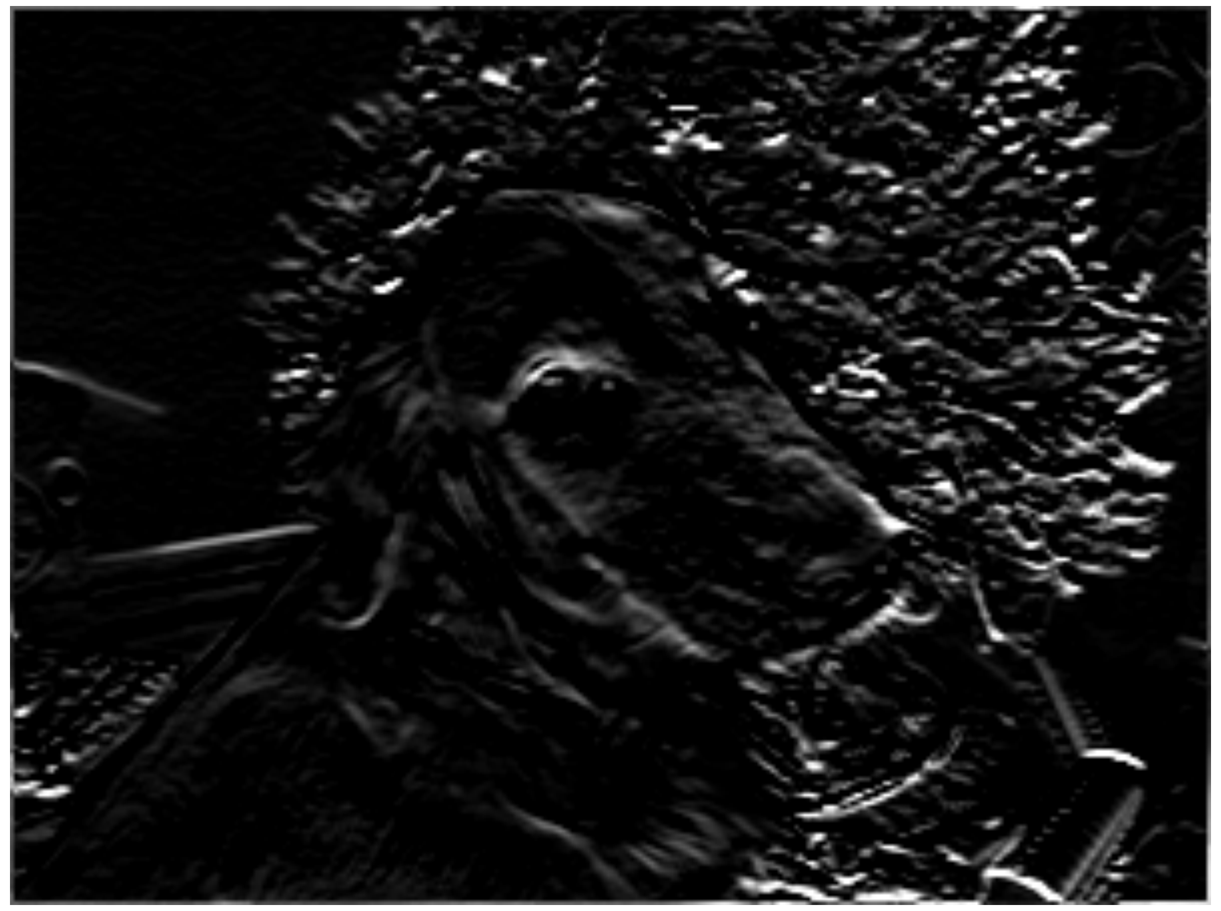


Fully-connected

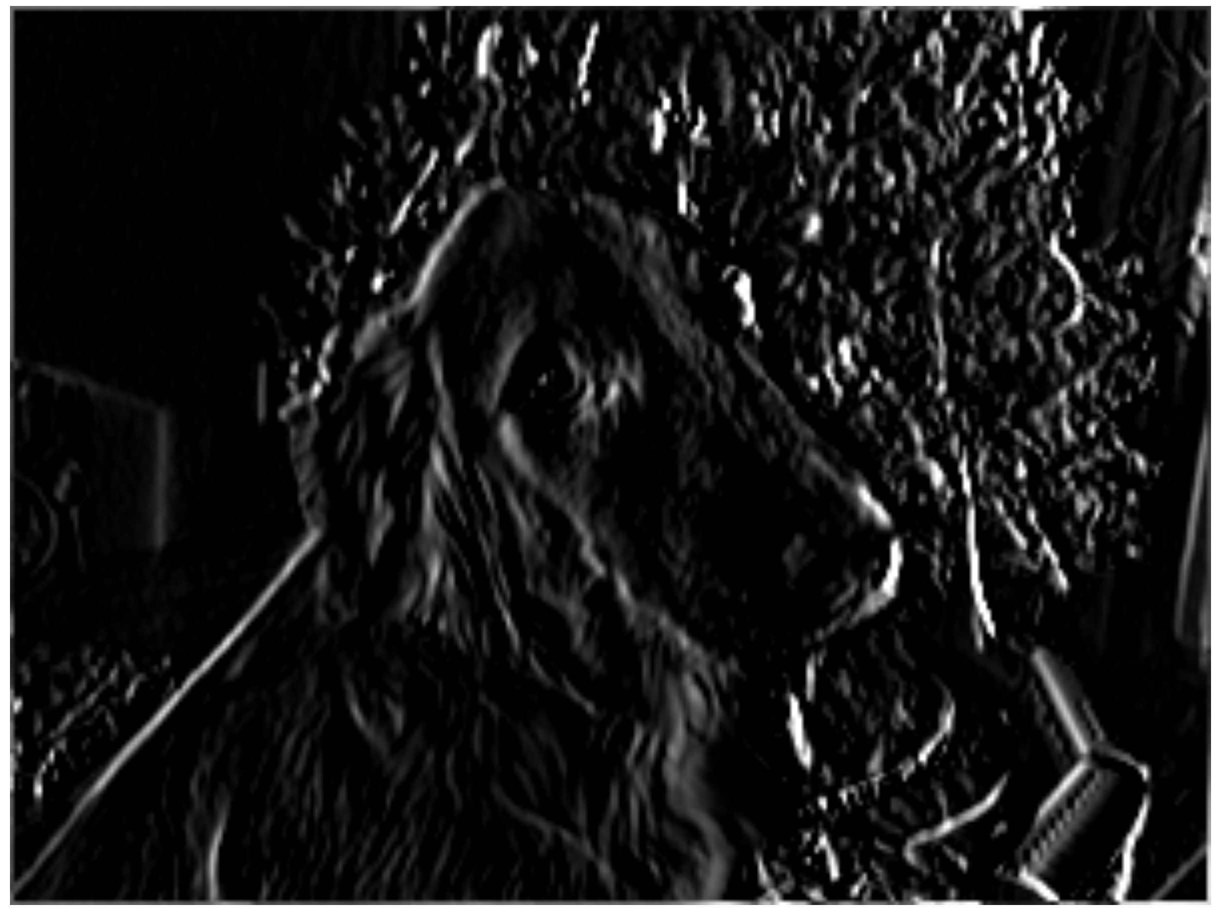
weight 1
weight 2
weight 3
weight 4
weight 5

Convolutional Filters

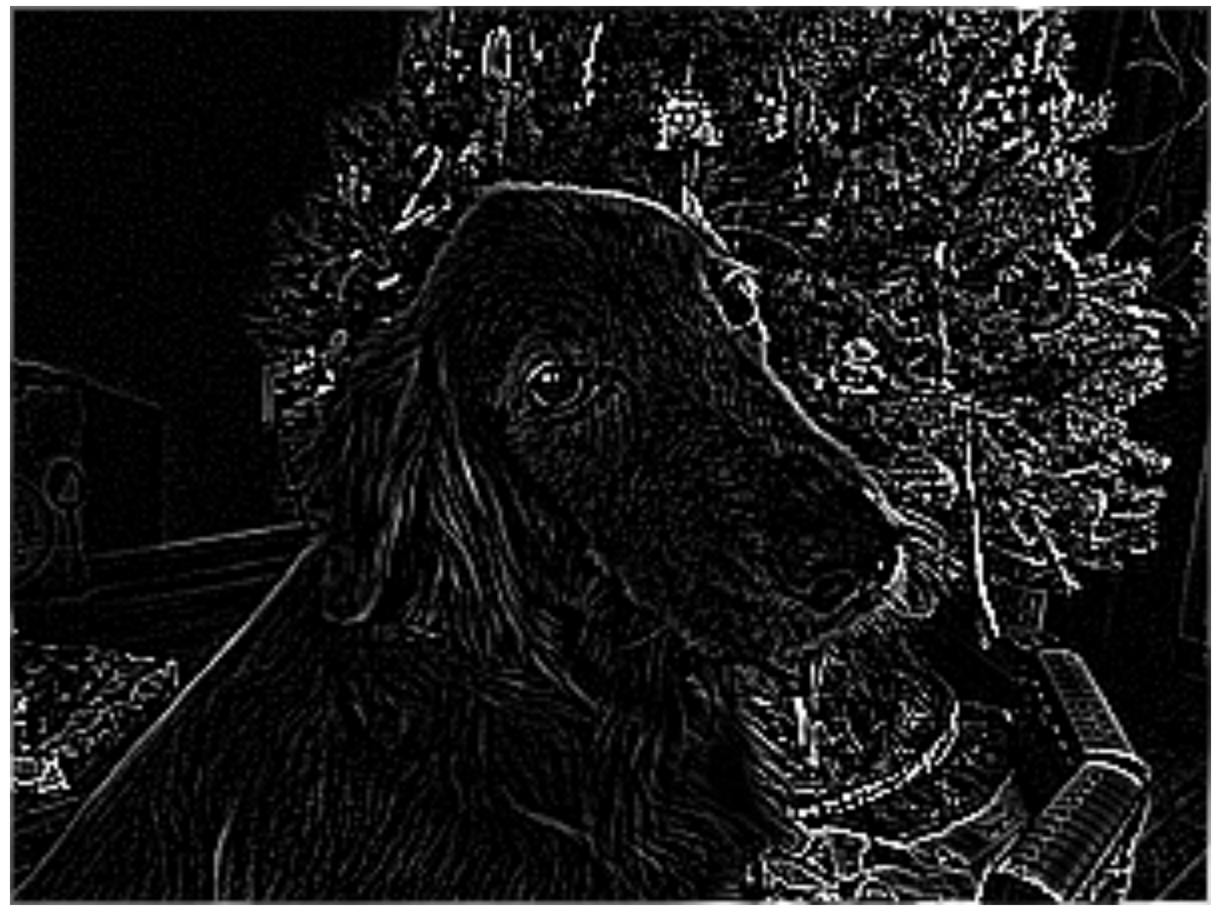




-1	-1	-1
0	0	0
1	1	1

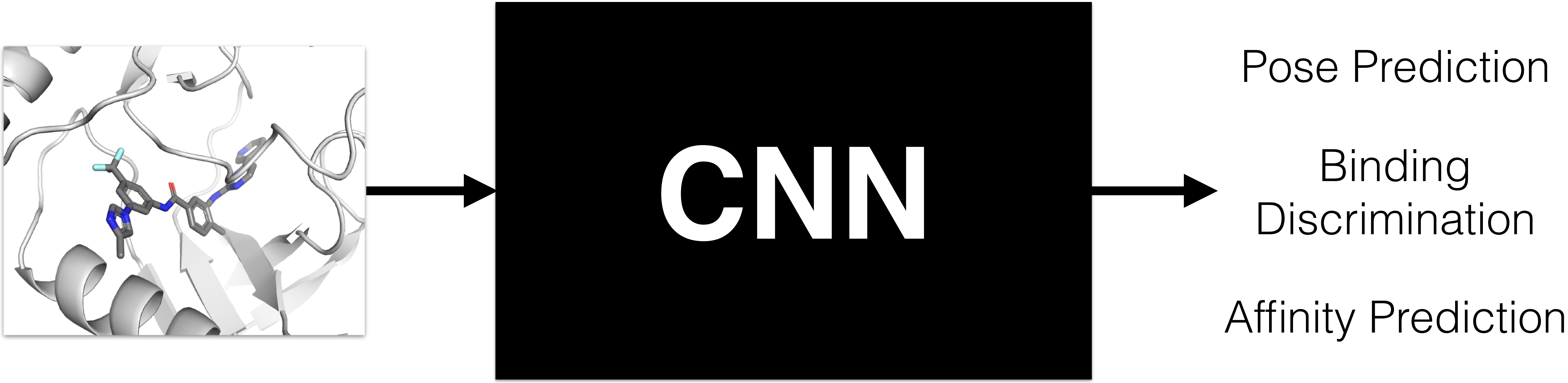


-1	0	1
-1	0	1
-1	0	1



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

CNNs for Protein-Ligand Scoring



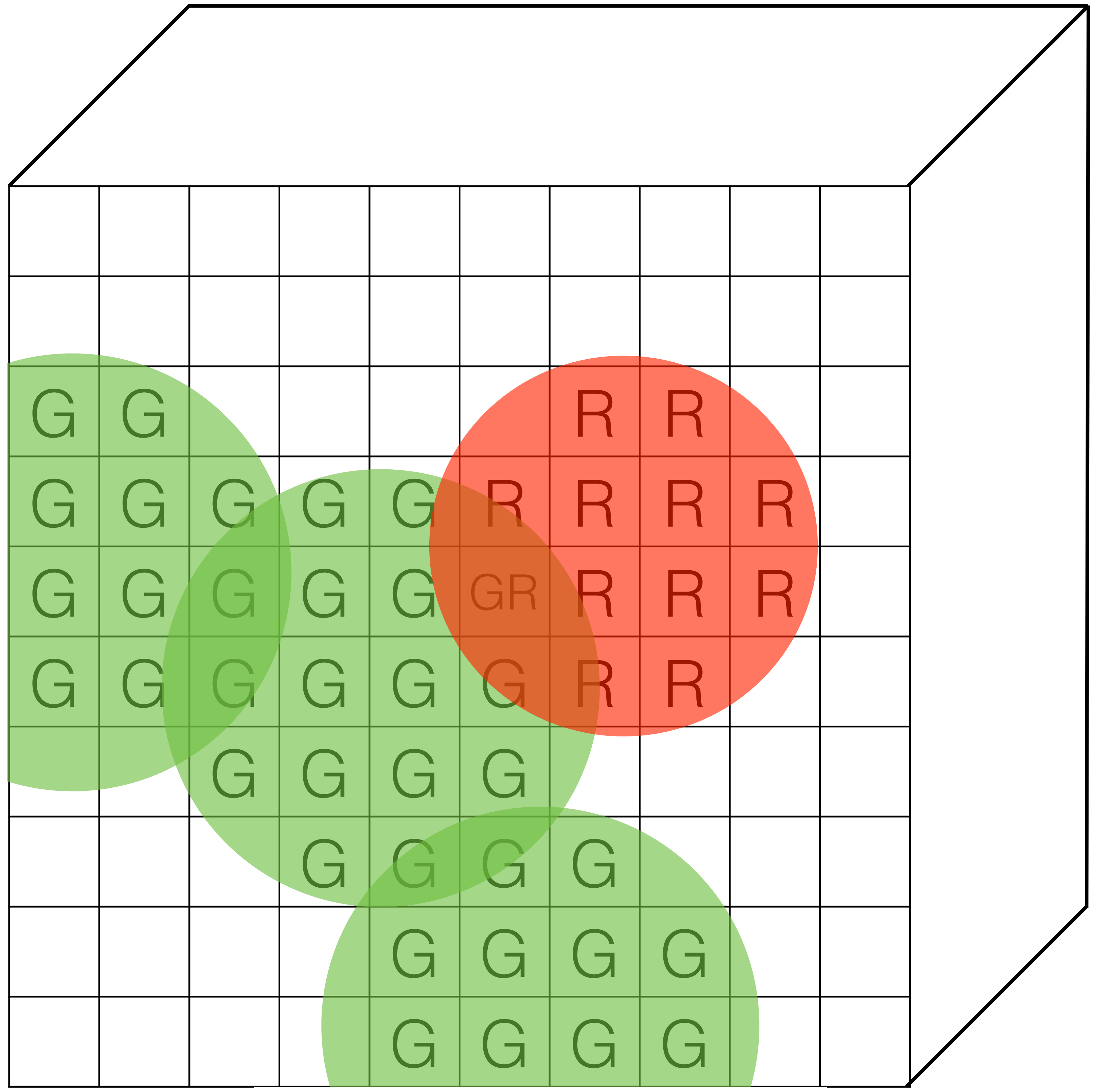
CNN

Pose Prediction

Binding Discrimination

Affinity Prediction

Protein-Ligand Representation



(R,G,B) pixel →

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

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

Training Data

PDBbind

Pose Prediction

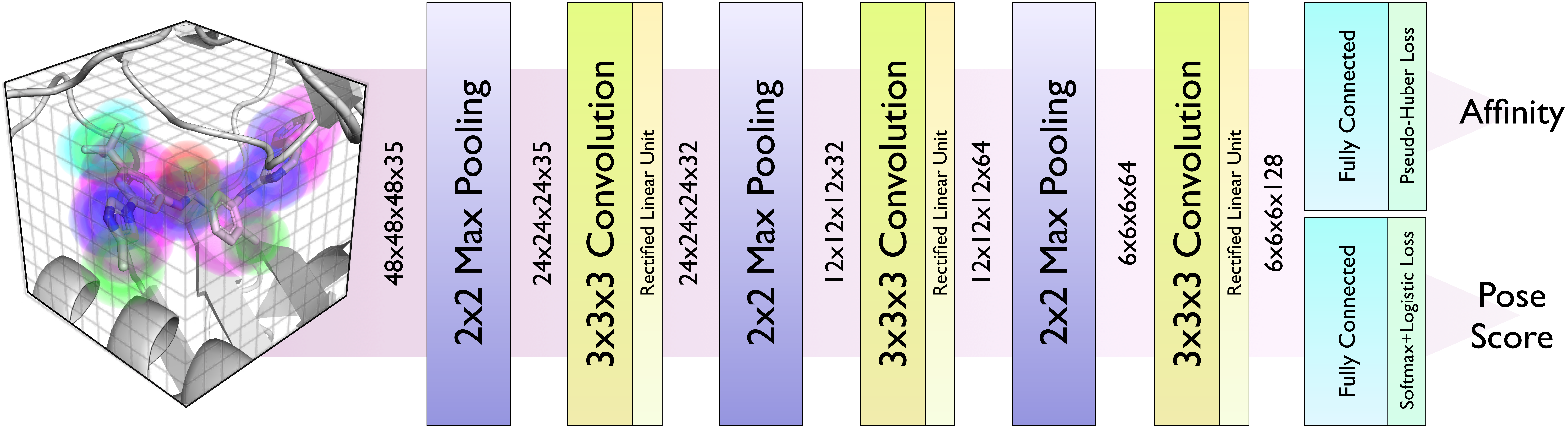
4056 protein-ligand complexes

- 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

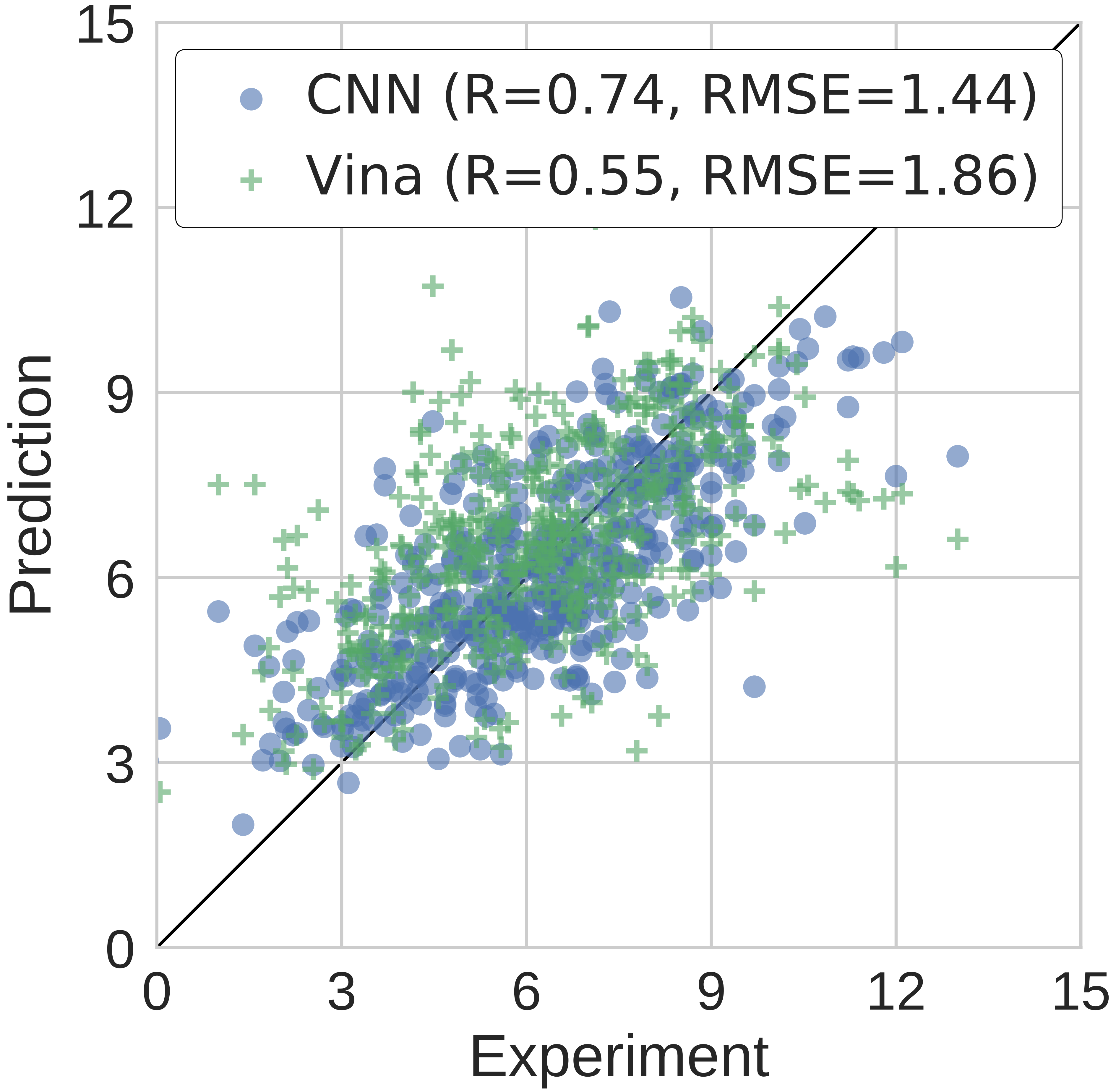
Affinity

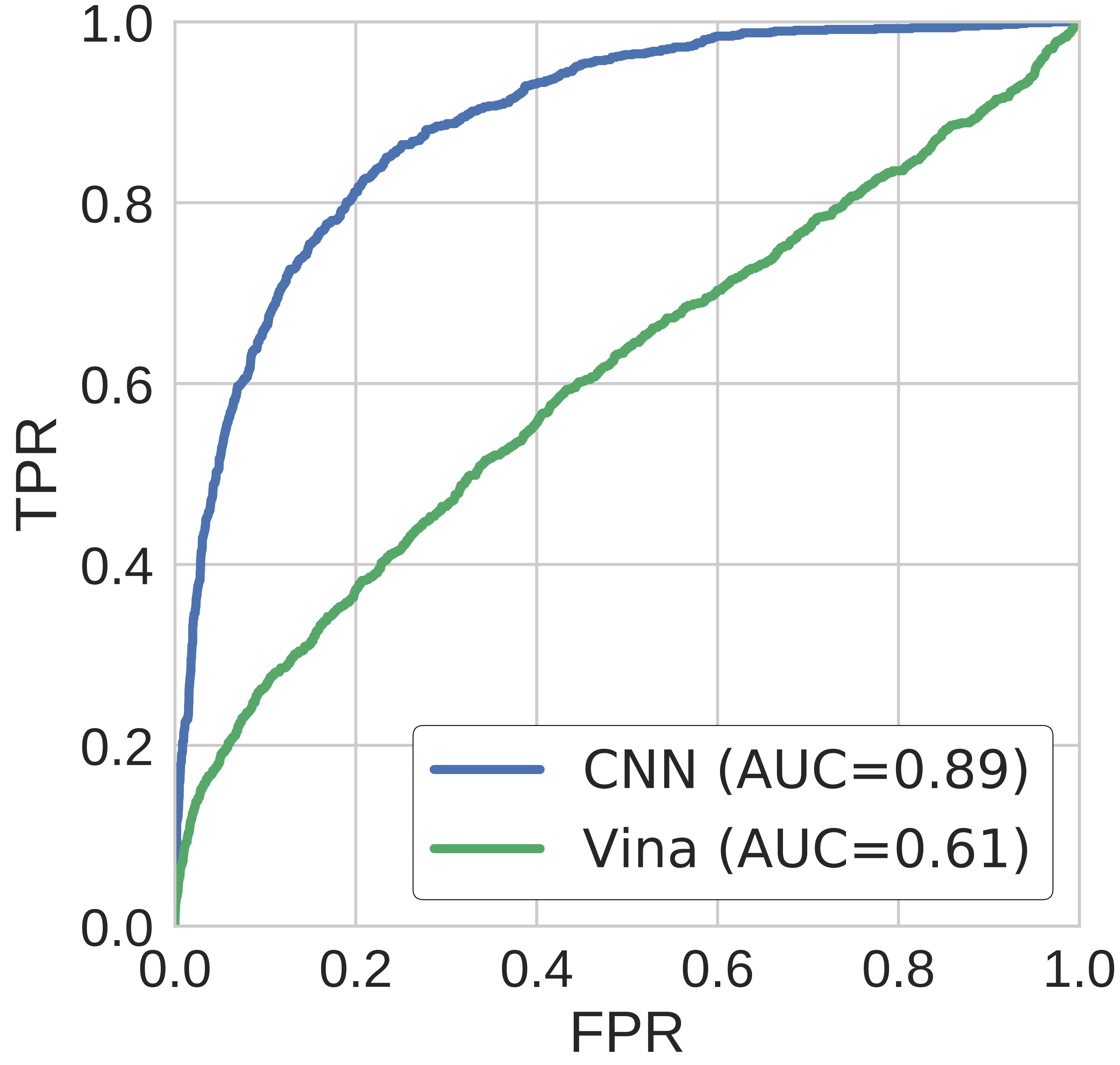
Fully Connected

Softmax+Logistic Loss

Pose Score

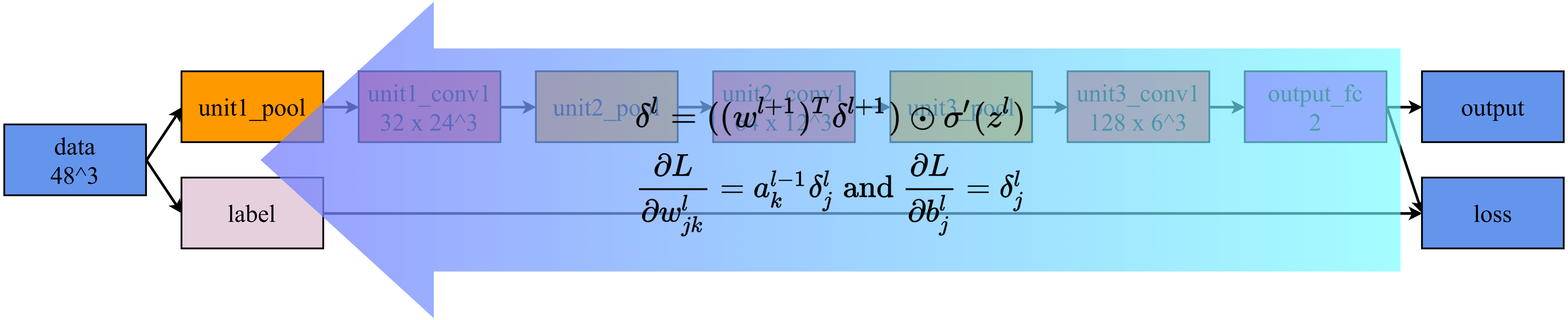
Results





Trained on PDBbind refined; tested on CSAR

Beyond Scoring



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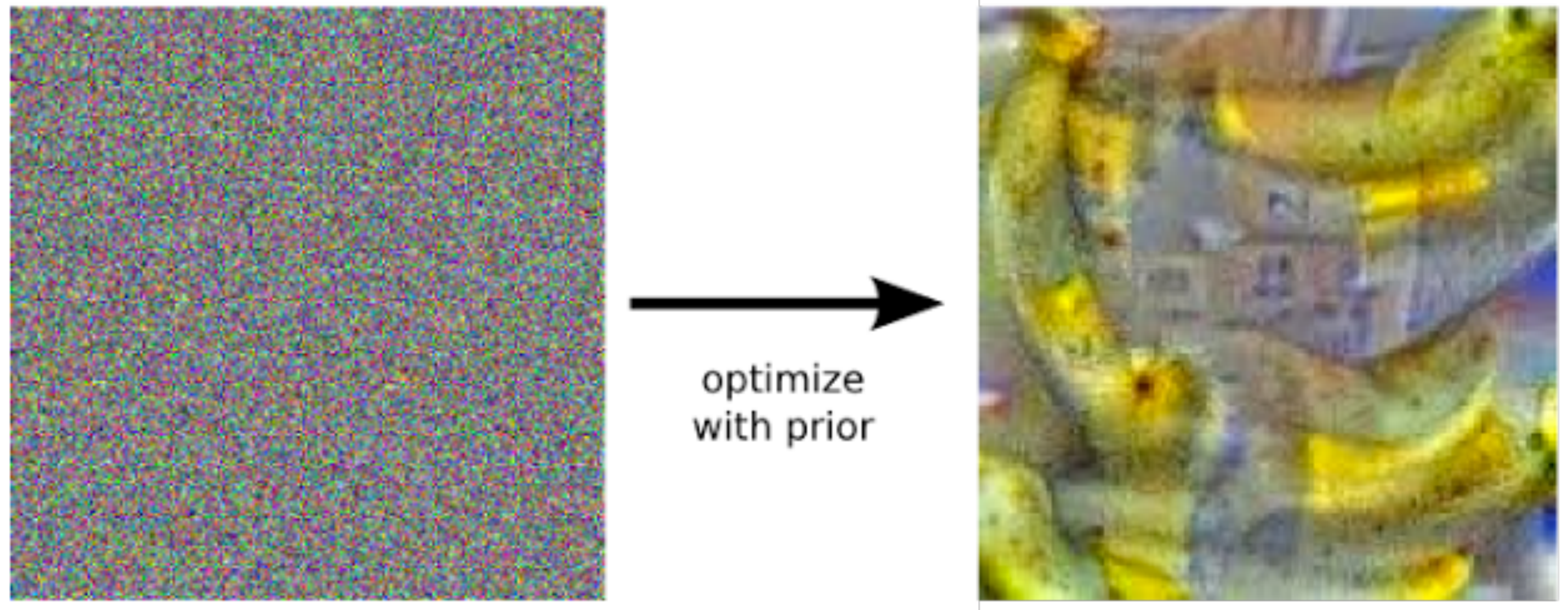
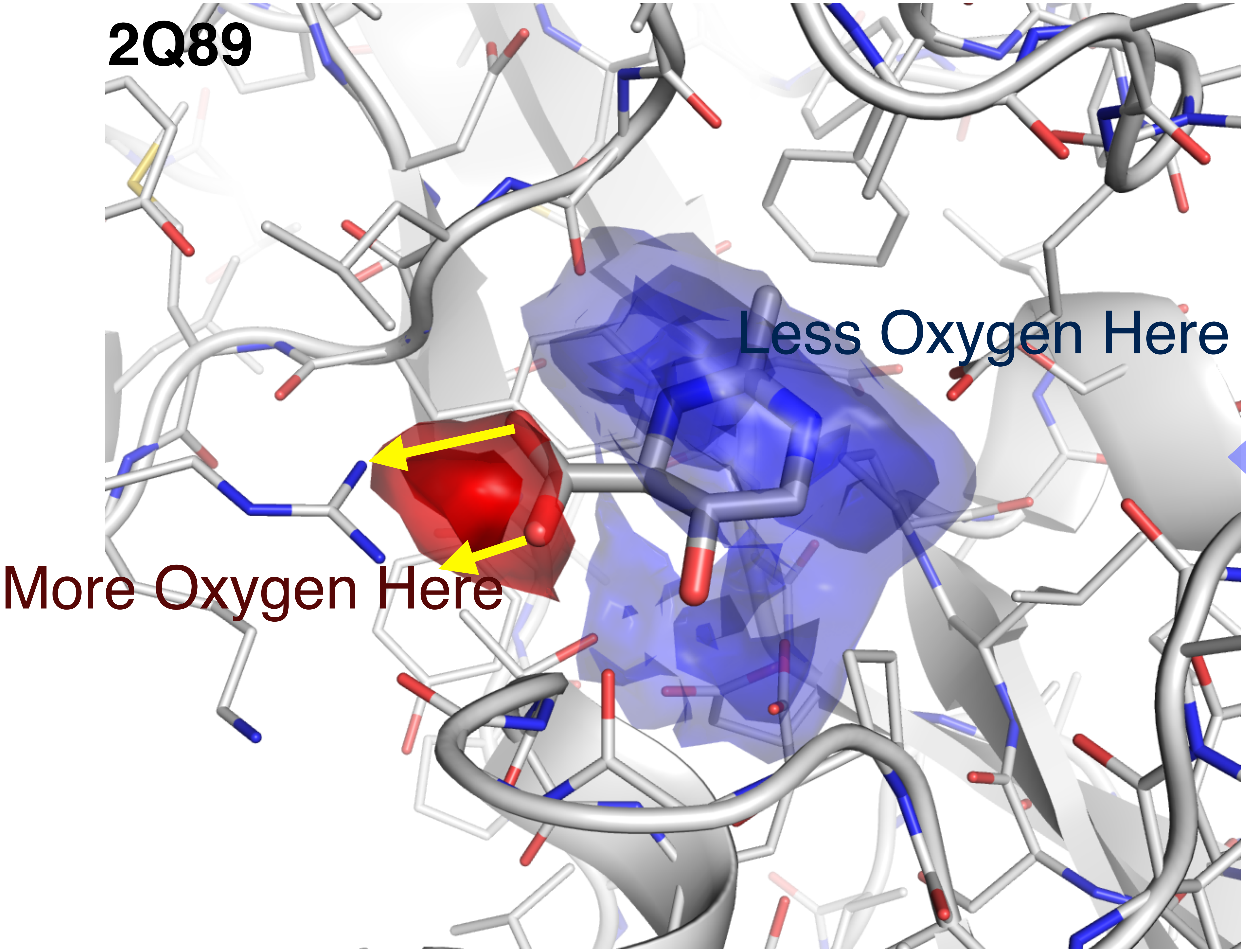
$$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j \text{ and } \frac{\partial L}{\partial b^l_j} = \delta^l_j$$

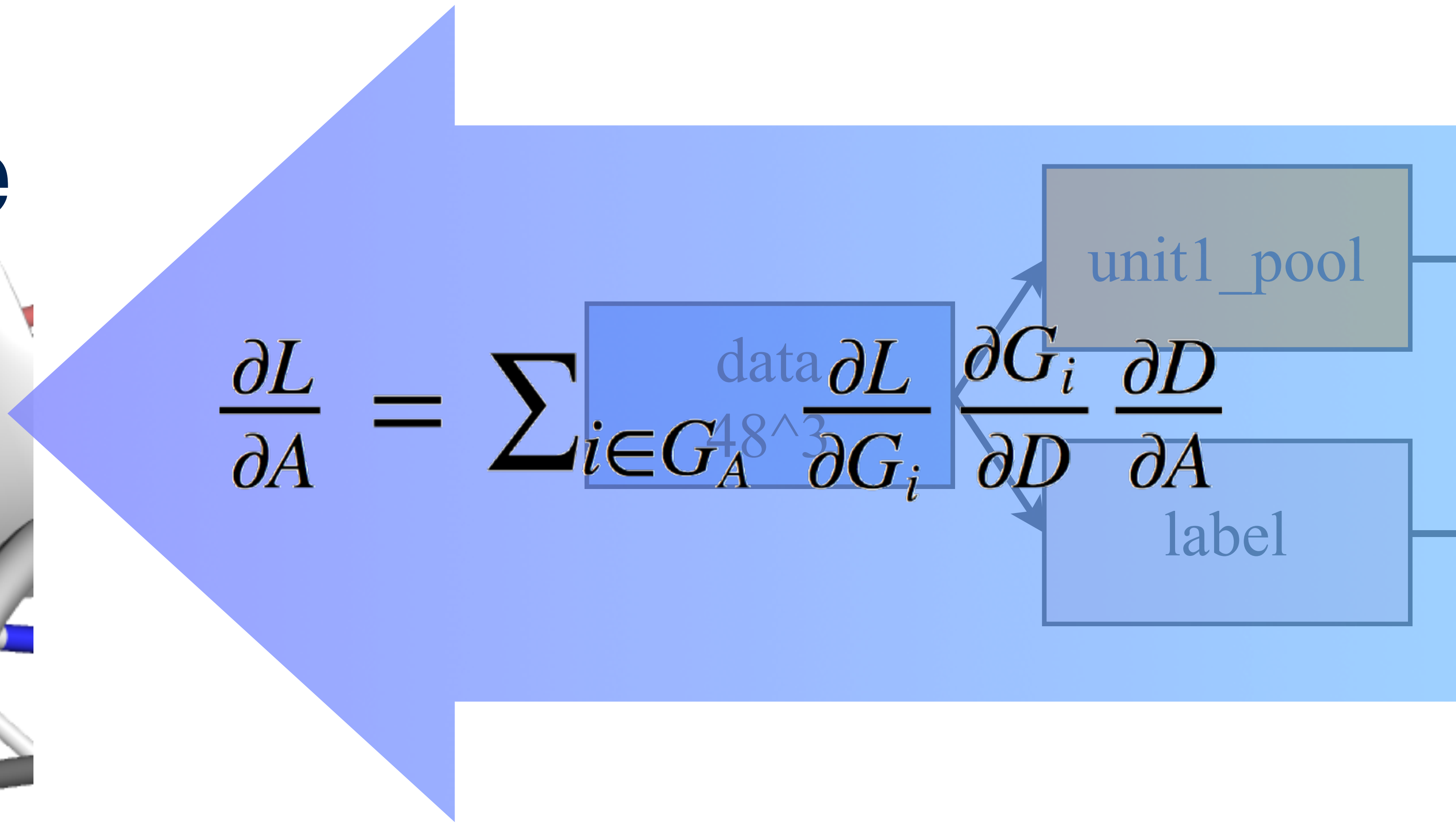
Deep Dreams



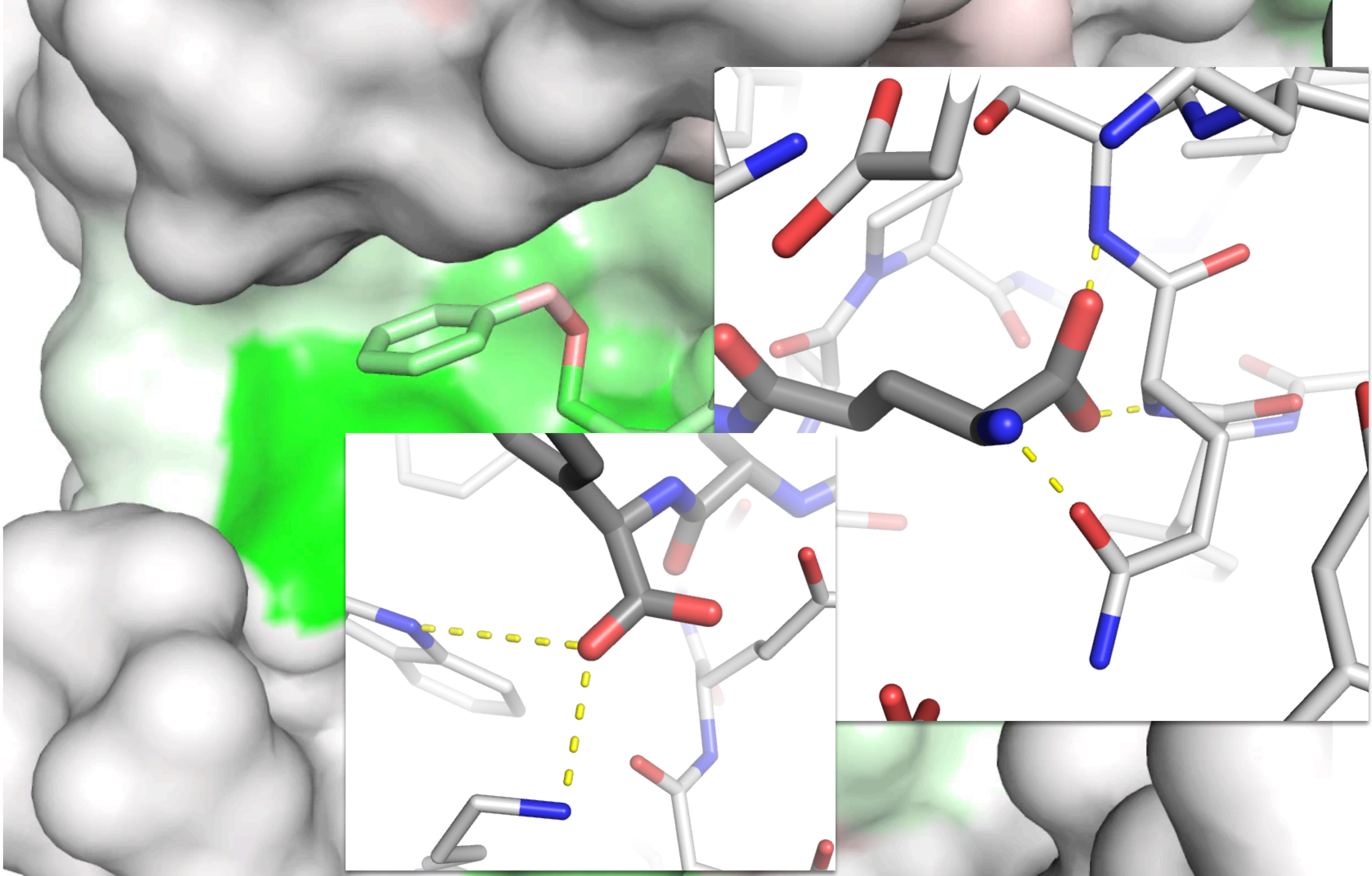
https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html

Beyond Scoring

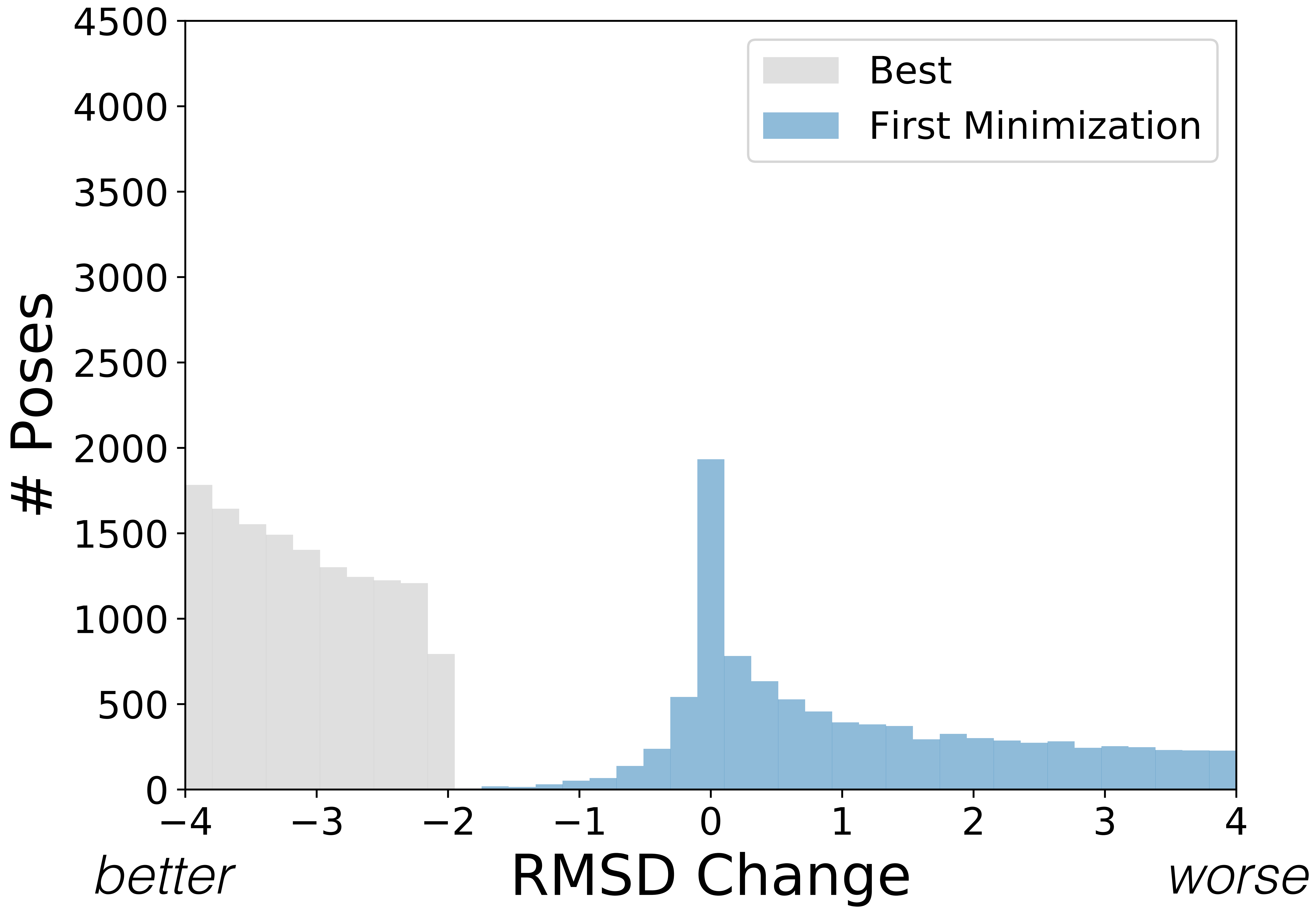




$$\frac{\partial L}{\partial A} = \sum_{i \in G_A} \frac{\partial L}{\partial G_i} \frac{\partial G_i}{\partial D} \frac{\partial D}{\partial A}$$

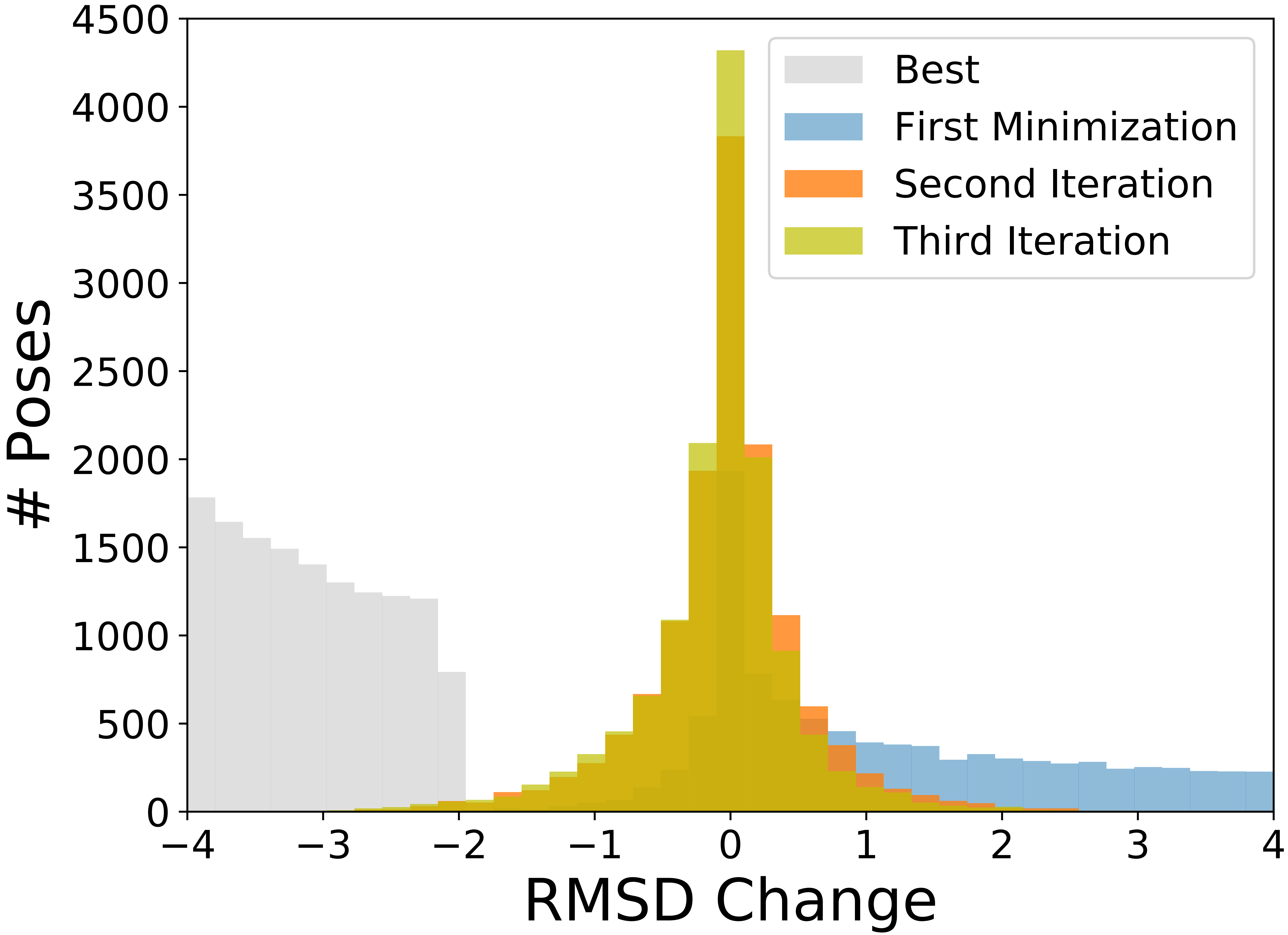


Minimizing Low RMSD Poses



3AO4

Iterative Refinement



3AO4

Docking

vina/smina/gnina

Sampling

MCMC

MCMC

MCMC

MCMC

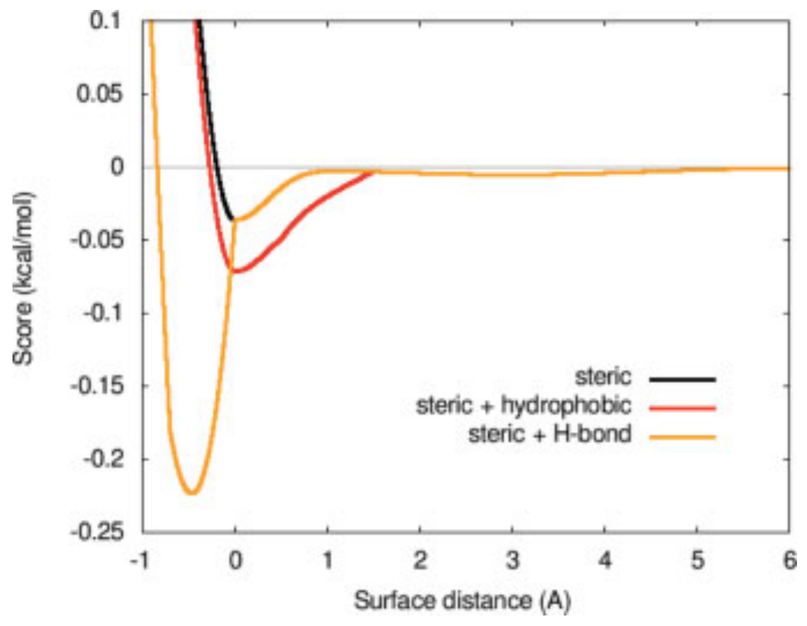
MCMC

⋮

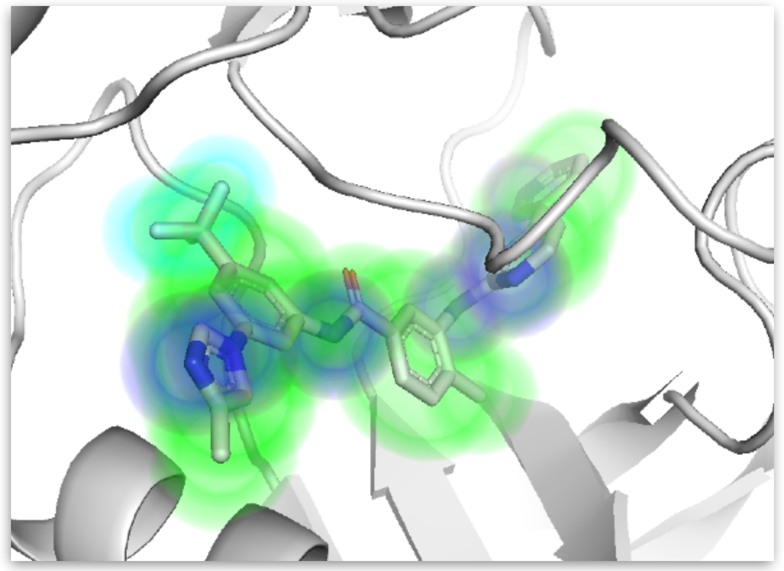
N (50) independent Monte Carlo chains
Scored with grid-accelerated Vina
Best identified pose retained

best poses

Refinement



Vina



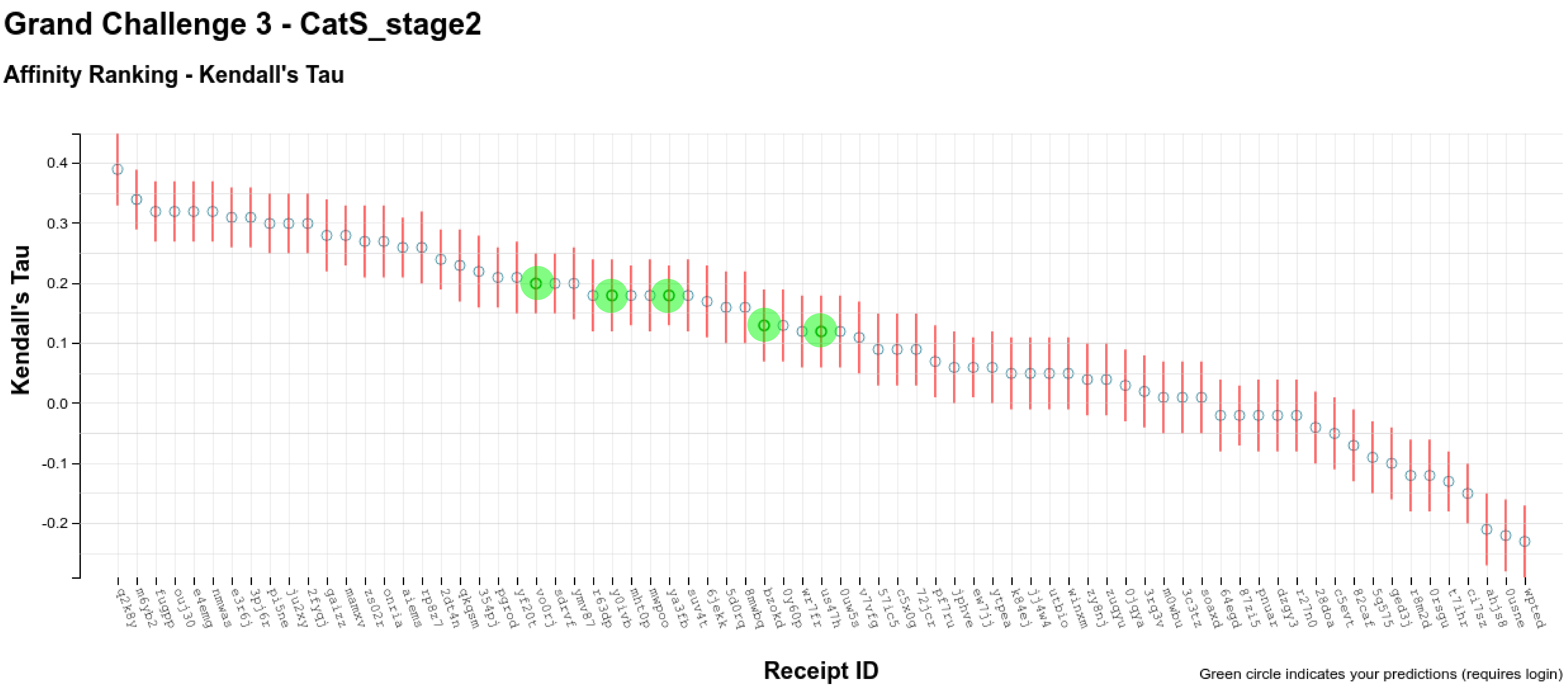
CNN

Rescoring

CNN
pose
affinity

D3R Results

Grand Challenge 3



Grand Challenge 3 - CatS_stage2

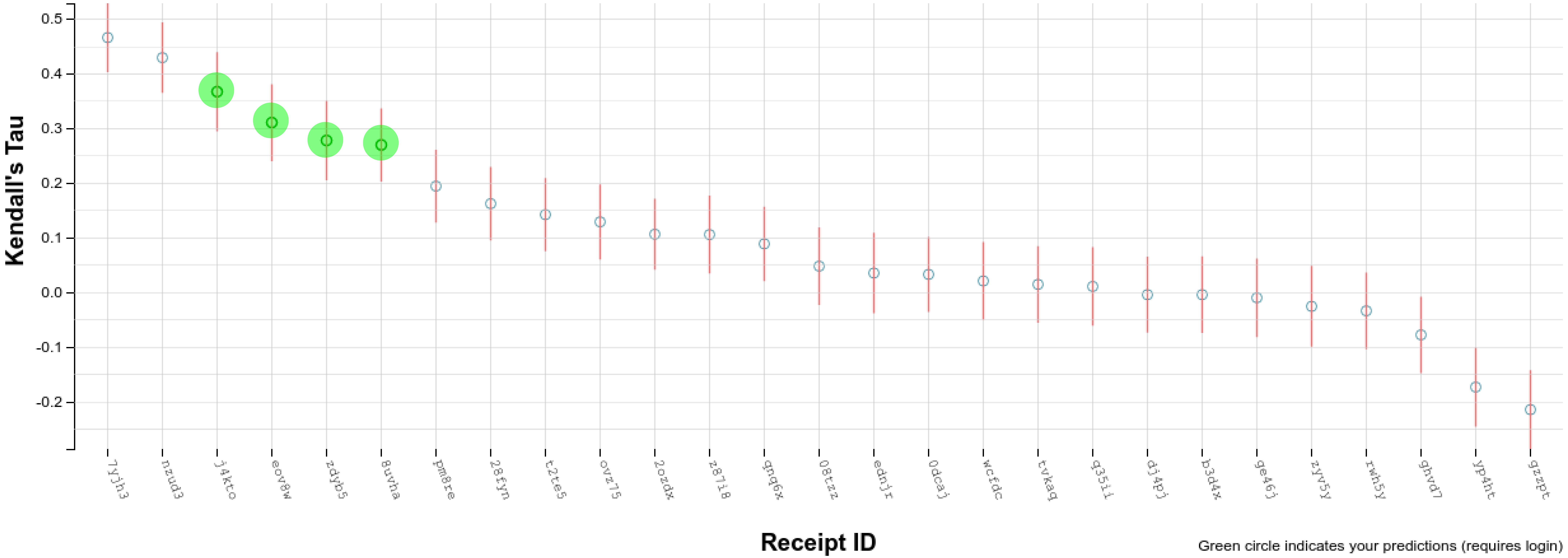
Affinity Ranking - Kendall's Tau

Green circle indicates your predictions (requires login)

Grand Challenge 3

Grand Challenge 3 - JAK2_SC2

Affinity Ranking - Kendall's Tau

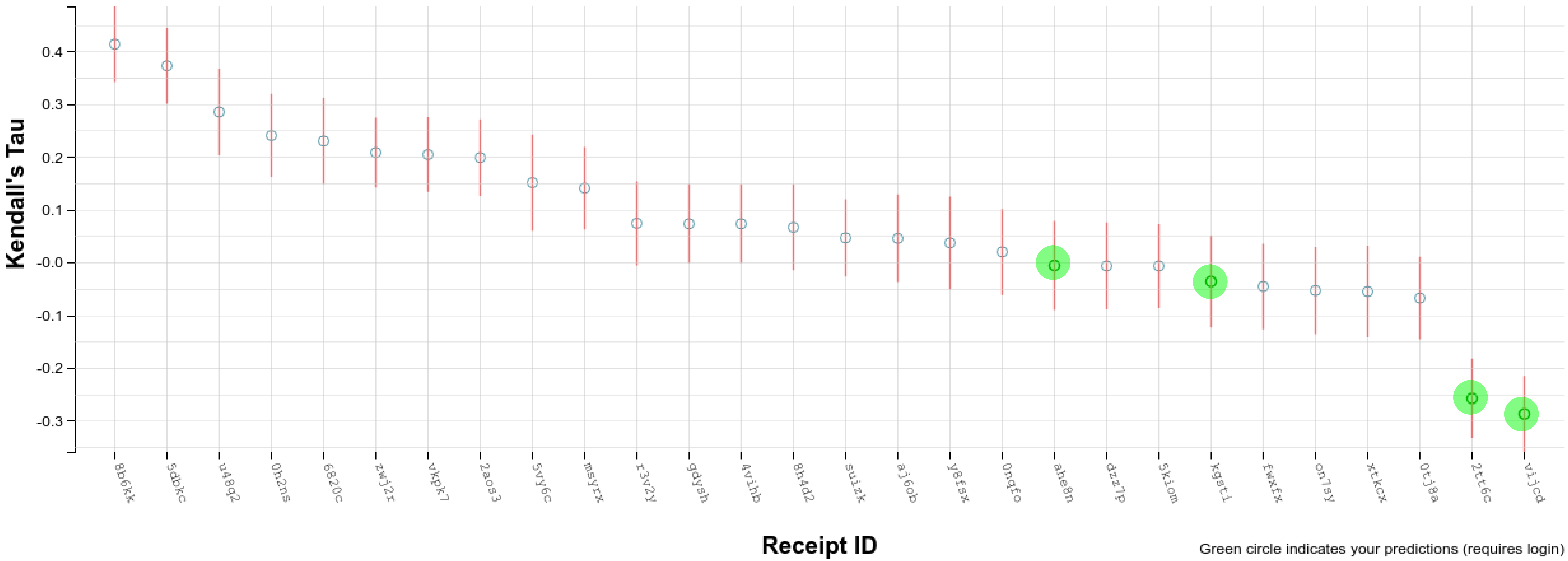


Green circle indicates your predictions (requires login)

Grand Challenge 3

Grand Challenge 3 - p38a

Affinity Ranking - Kendall's Tau

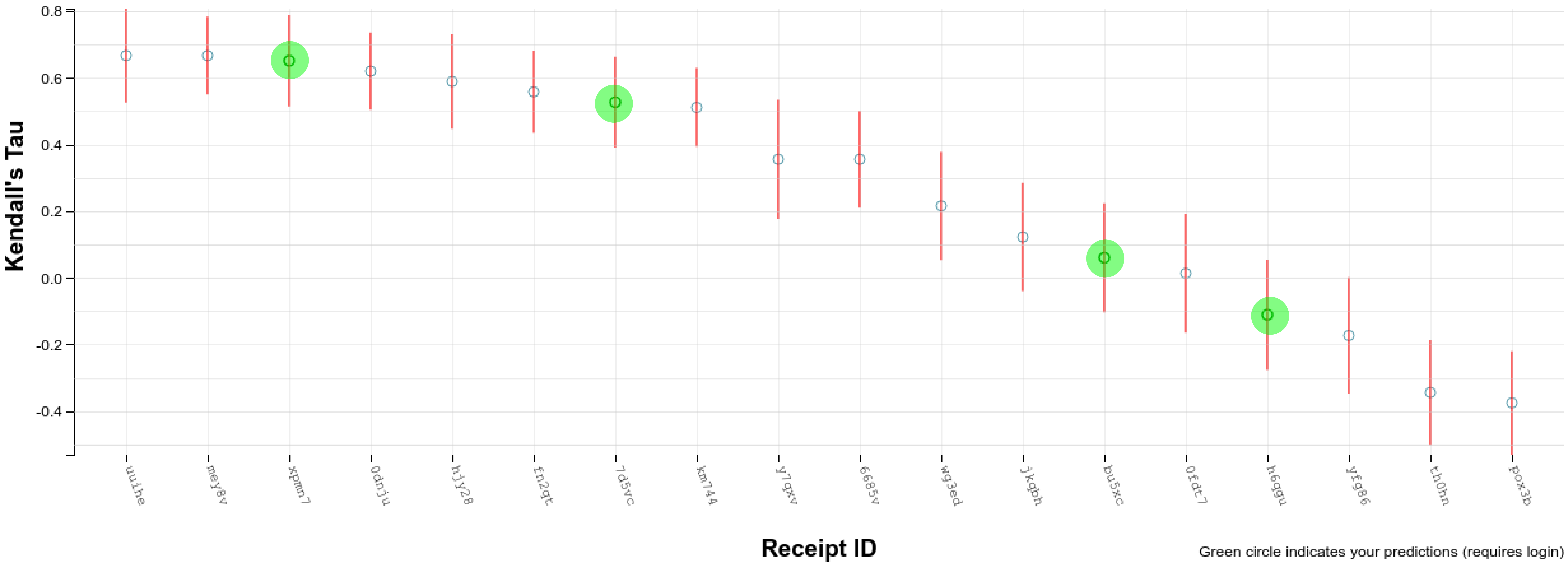


Green circle indicates your predictions (requires login)

Grand Challenge 3

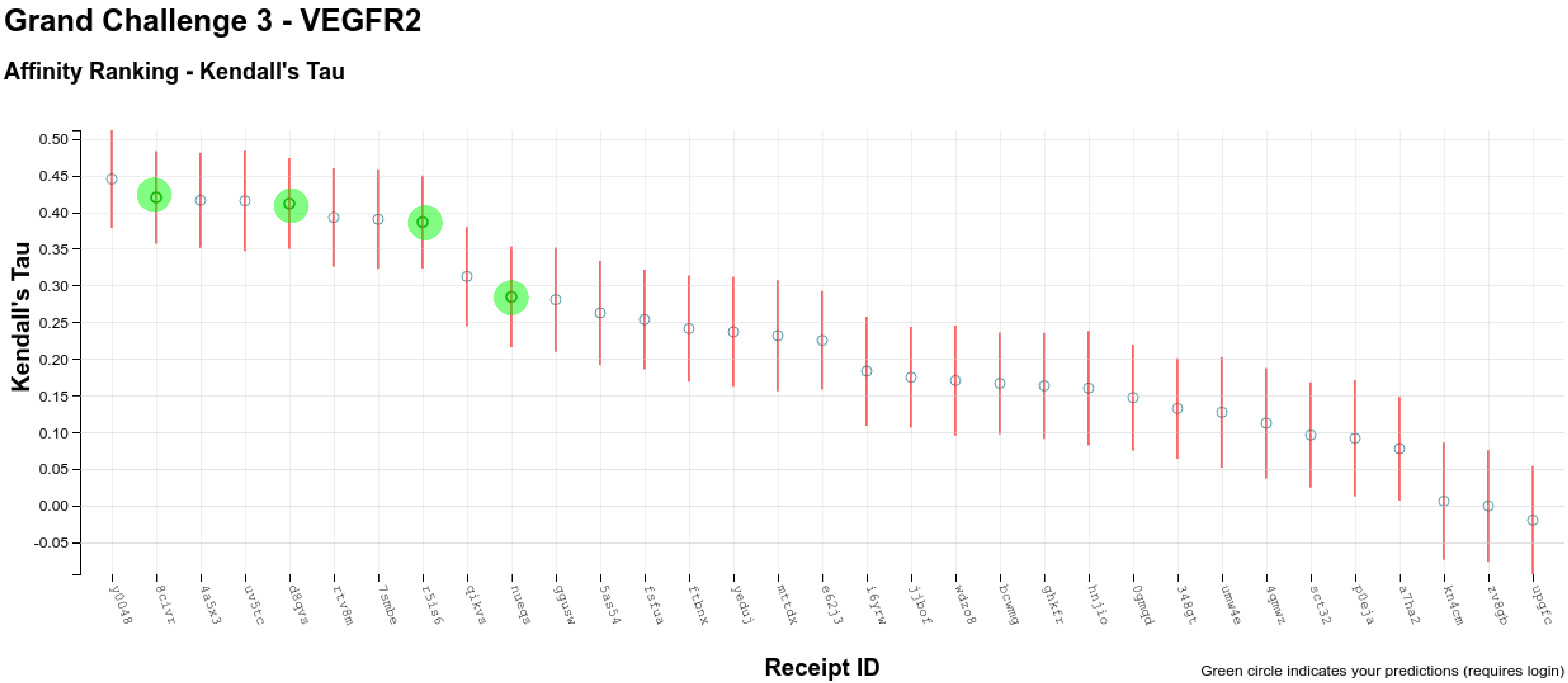
Grand Challenge 3 - TIE2

Affinity Ranking - Kendall's Tau



Green circle indicates your predictions (requires login)

Grand Challenge 3



Grand Challenge 3 - VEGFR2

Affinity Ranking - Kendall's Tau

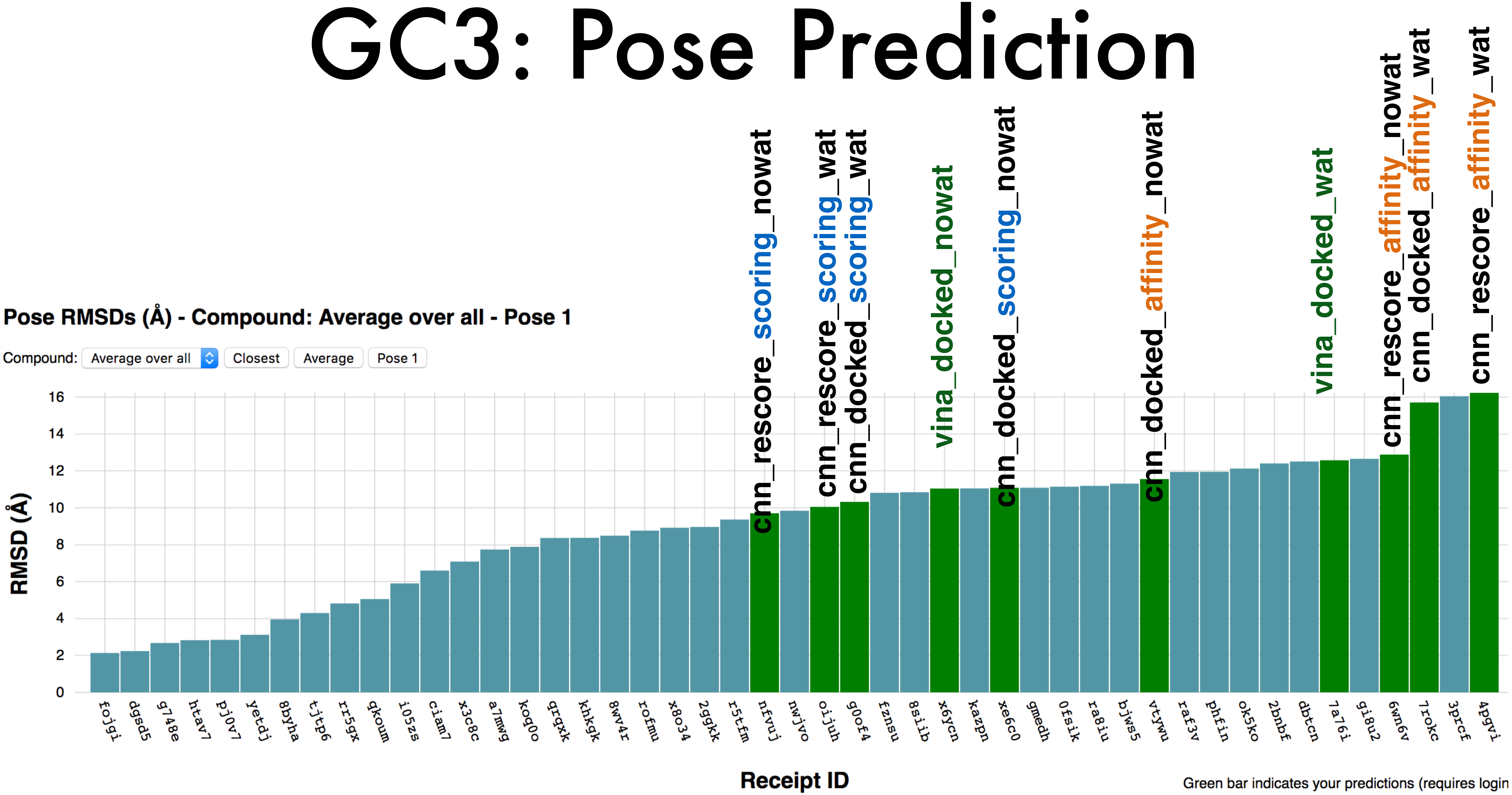
Green circle indicates your predictions (requires login)

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



Pose RMSDs (Å) - Compound: Average over all - Pose 1

Compound: Average over all Closest Average Pose 1

cnn_rescore_scoring_nowat

cnn_rescore_scoring_wat

cnn_docked_scoring_wat

vina_docked_nowat

cnn_docked_scoring_nowat

cnn_docked_affinity_nowat

vina_docked_wat

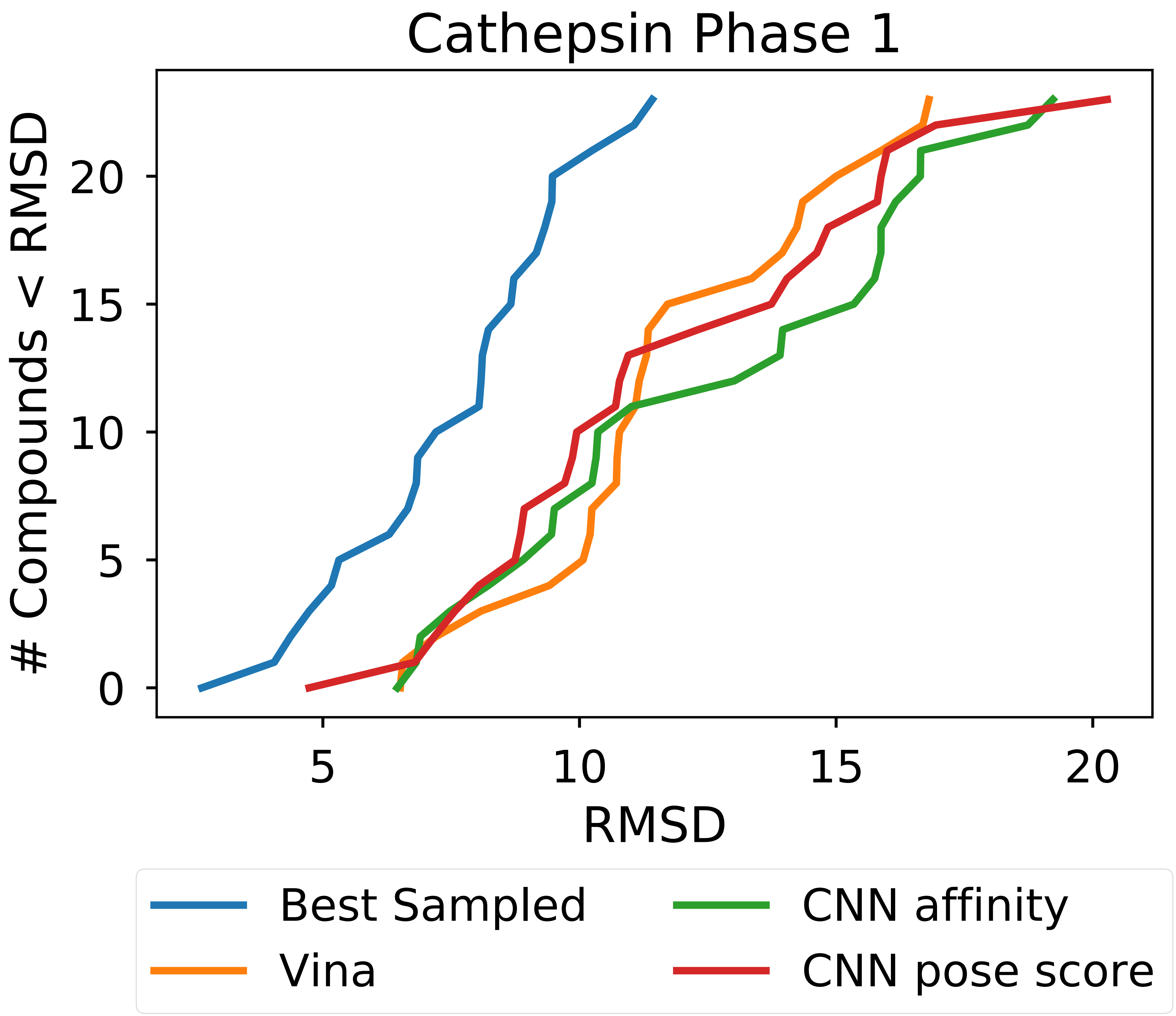
cnn_rescore_affinity_nowat

cnn_docked_affinity_wat

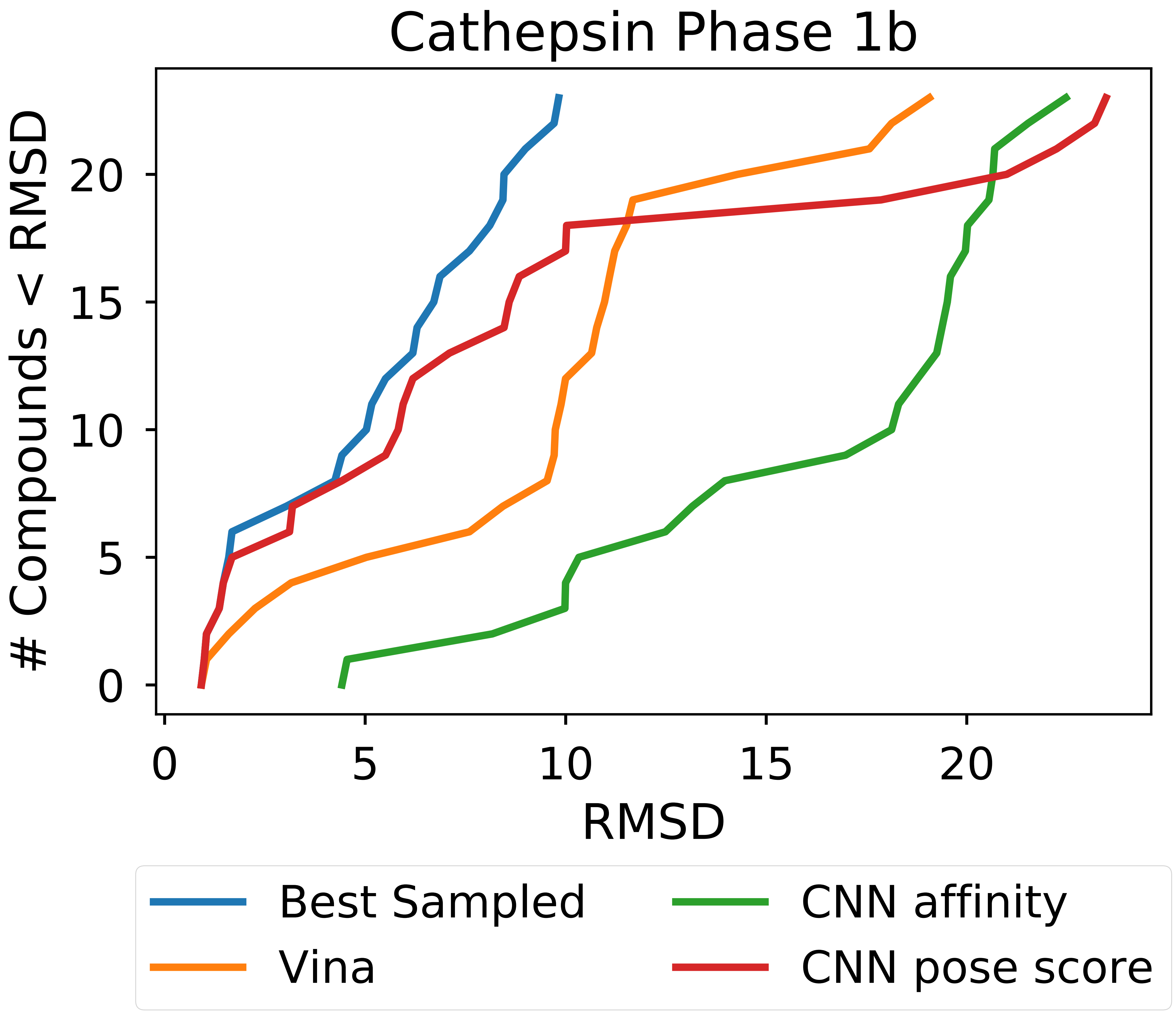
cnn_rescore_affinity_wat

Green bar indicates your predictions (requires login

GC3: Pose Prediction

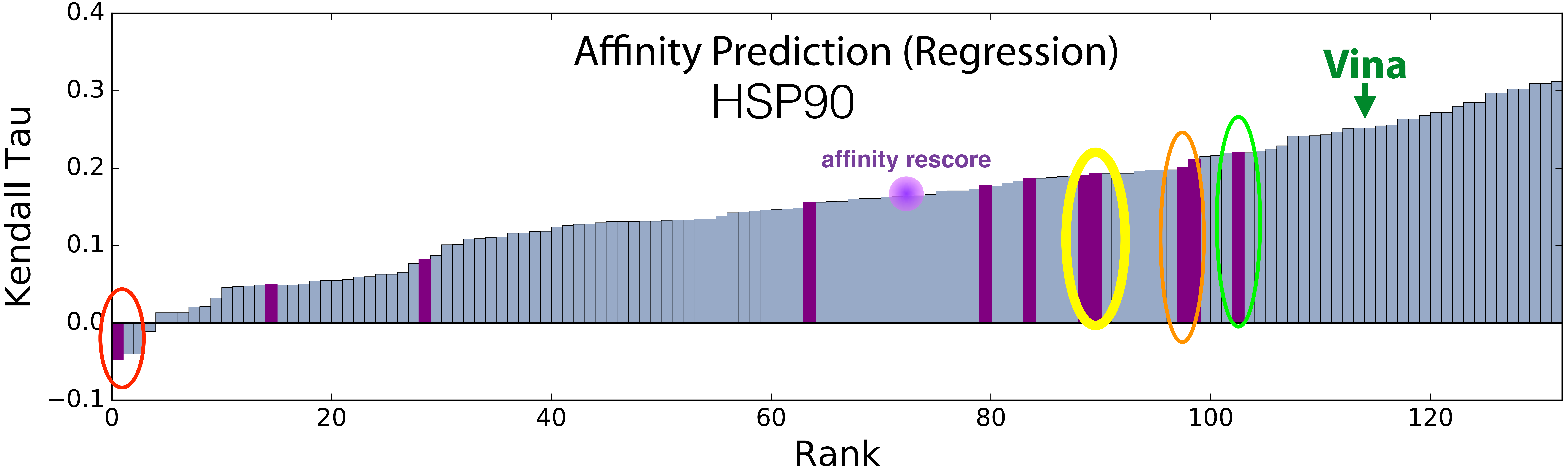


cross-docking



redocking

Grand Challenge 1



Target LASSO

QSAR SMARTS

Target Balanced NN

QSAR RDKit

Balanced CNN2

Reduced NN

Target Reduced NN

Balanced CNN1

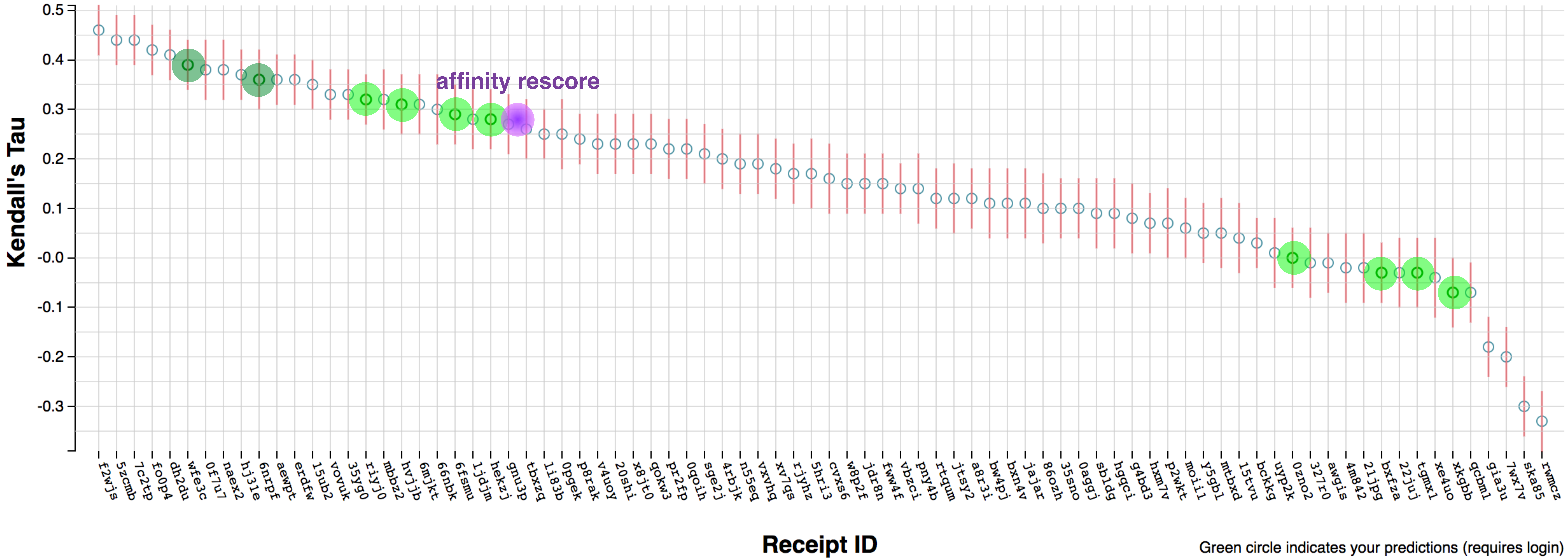
QSAR ECFP6

Balanced NN

Balanced Linear

Grand Challenge 2

Affinity Ranking (Stage 2) - Kendall's Tau



affinity rescore

Green circle indicates your predictions (requires login)

Future Plans

Train CNN for docking

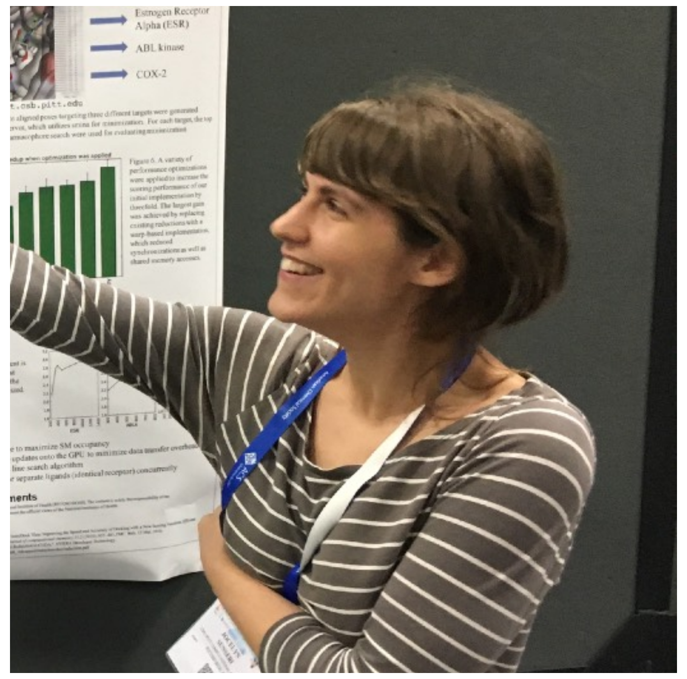
- iteratively train on docked poses
- train on cross-docked poses
- fully integrate CNN scoring into search

Continue to improve model/training parameters

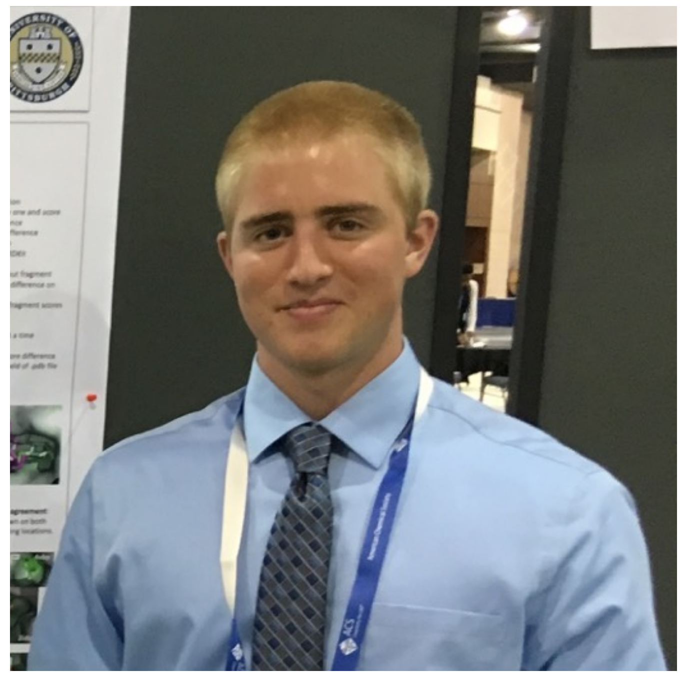
Next Grand Challenge

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

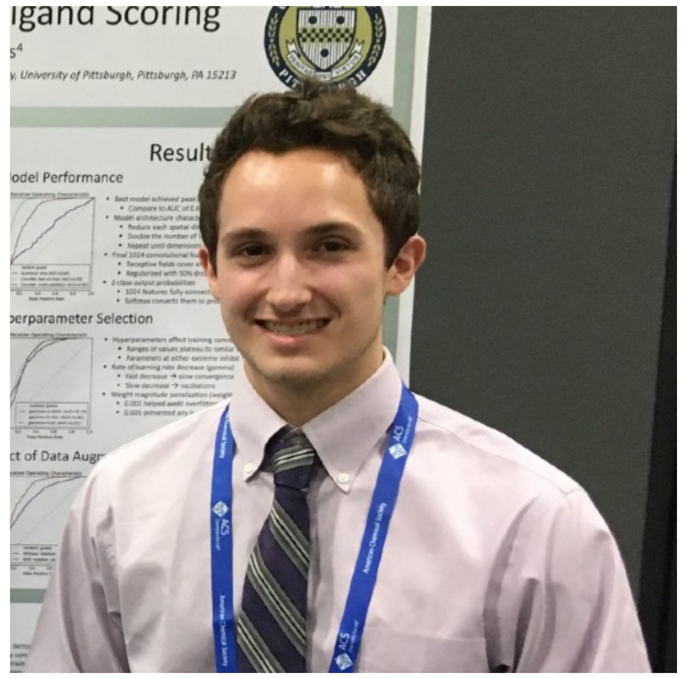
Acknowledgements



Jocelyn Sunseri



Josh Hochuli



Matt Ragoza

Group Members

Jocelyn Sunseri
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github.com/gnina

http://bits.csb.pitt.edu

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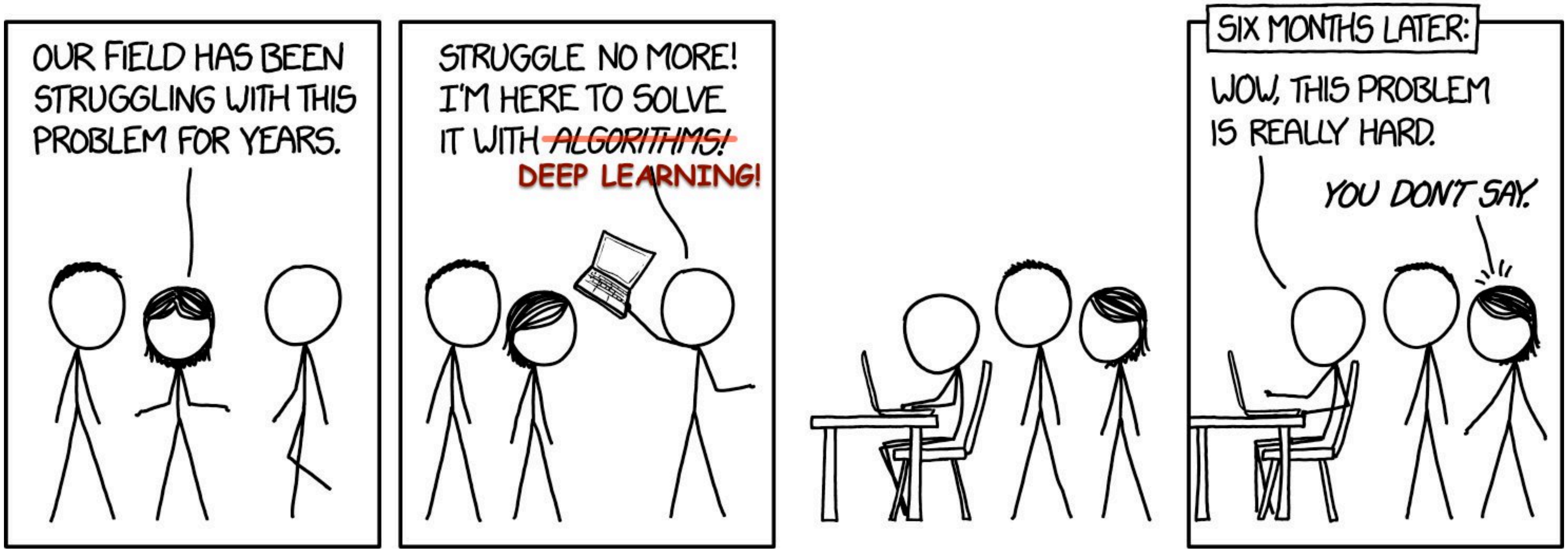
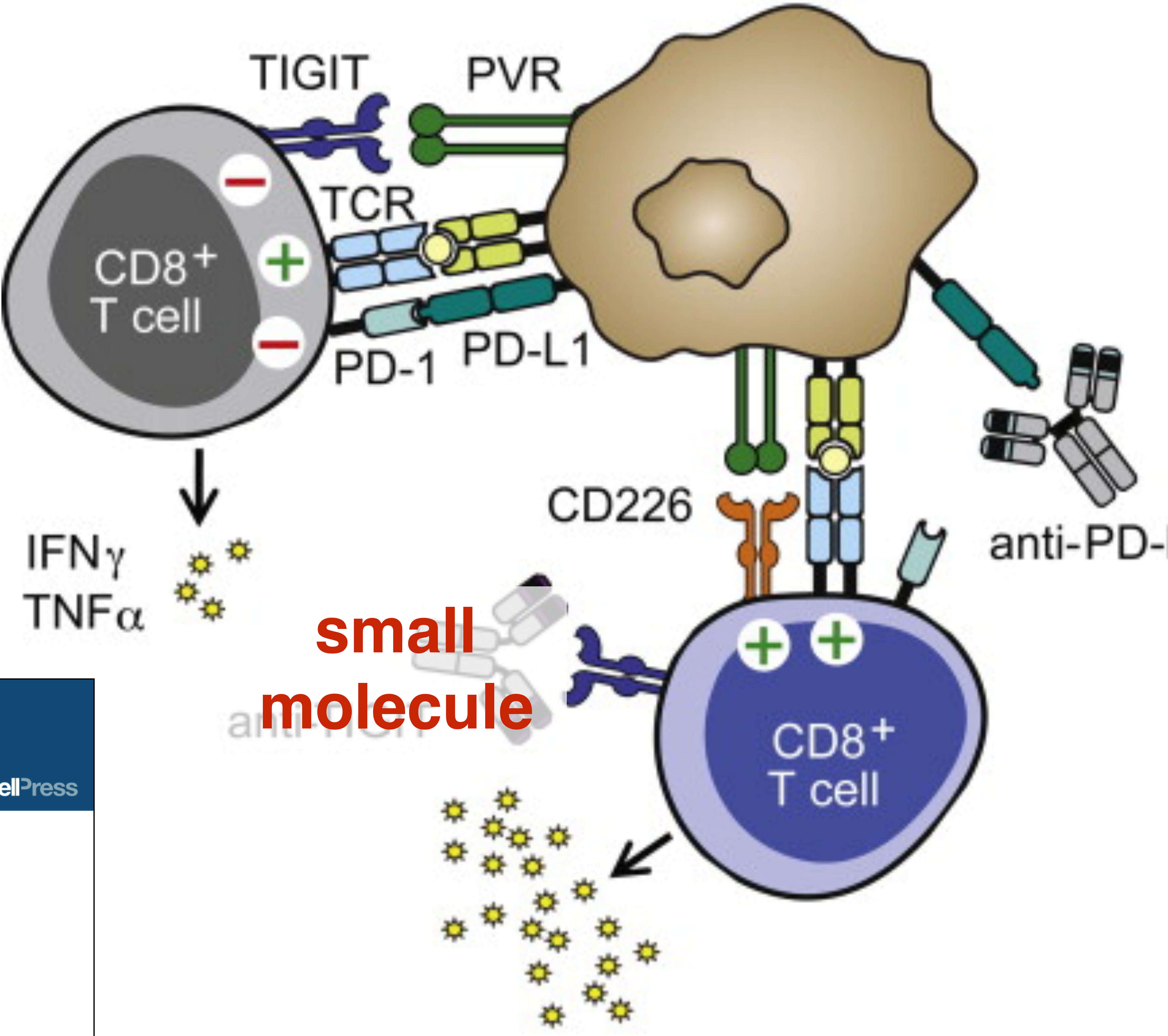
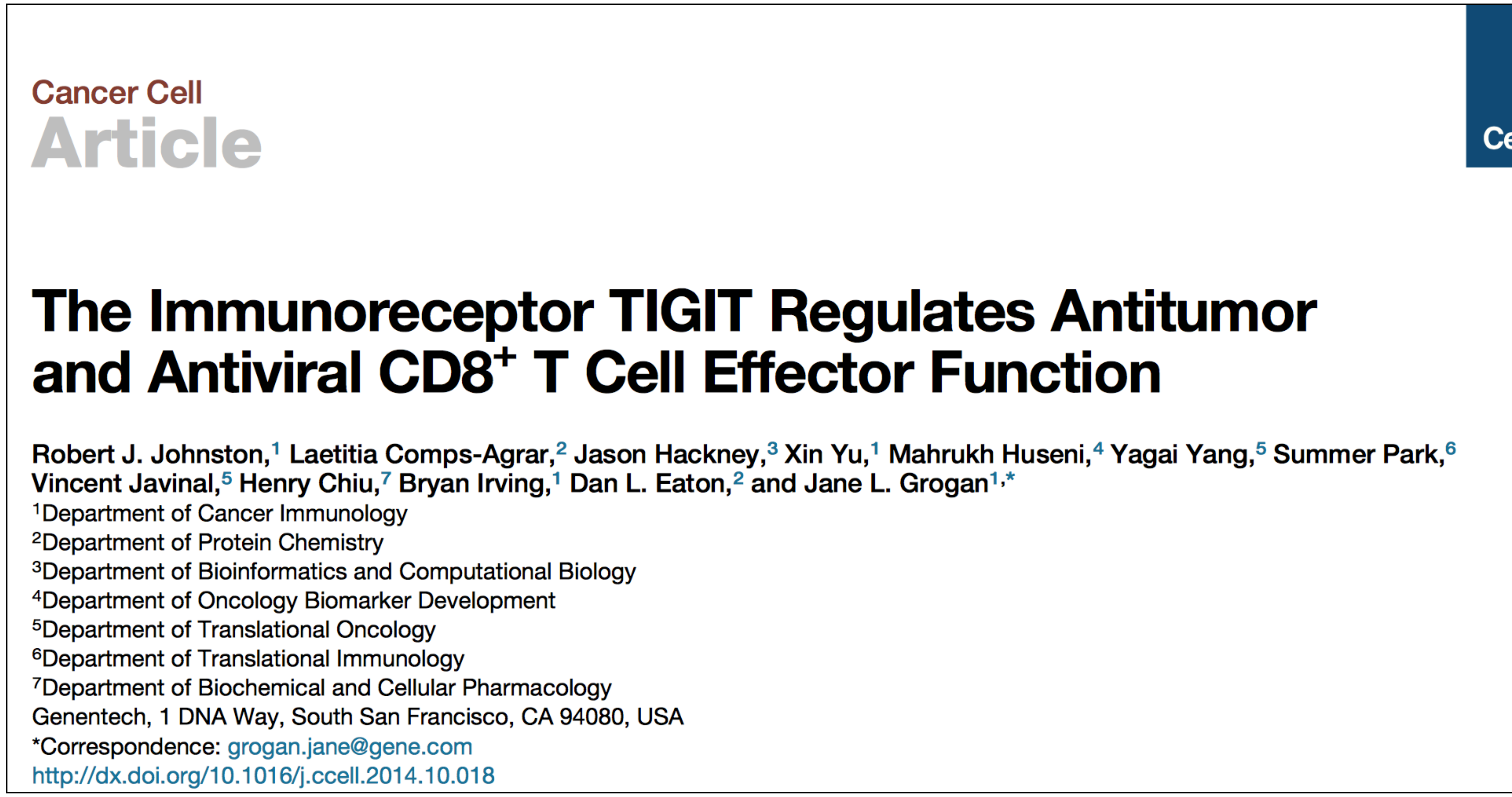

OUR FIELD HAS BEEN STRUGGLING WITH THIS PROBLEM FOR YEARS.
STRUGGLE NO MORE! I'M HERE TO SOLVE IT WITH ~~ALGORITHMS!~~ DEEP LEARNING!
SIX MONTHS LATER:
WOW, THIS PROBLEM IS REALLY HARD.
YOU DON'T SAY.

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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[3]Department of Bioinformatics and Computational Biology
[4]Department of Oncology Biomarker Development
[5]Department of Translational Oncology
[6]Department of Translational Immunology
[7]Department of Biochemical and Cellular Pharmacology
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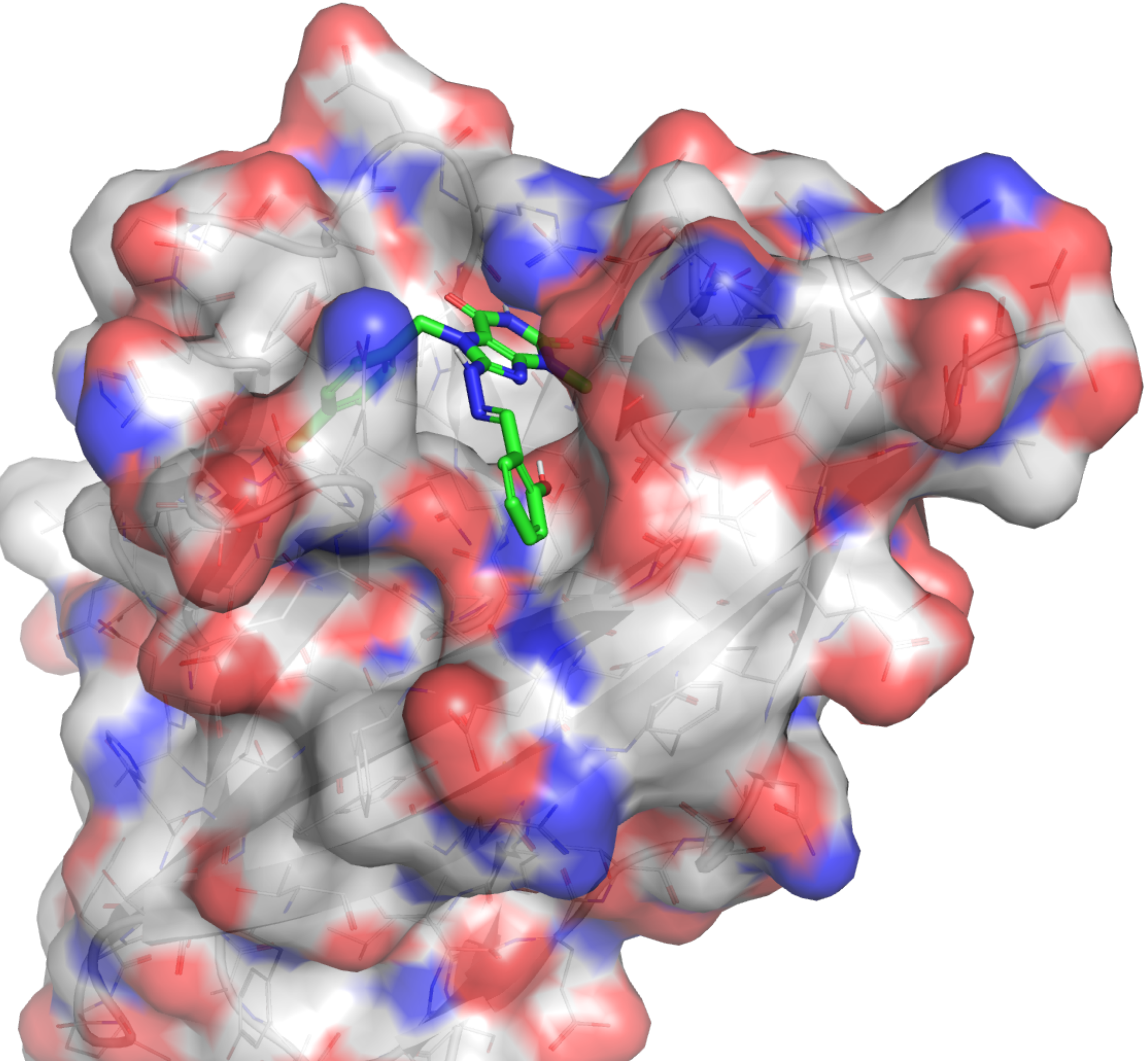
*Correspondence: grogan.jane@gene.com

http://dx.doi.org/10.1016/j.ccell.2014.10.018

Screening



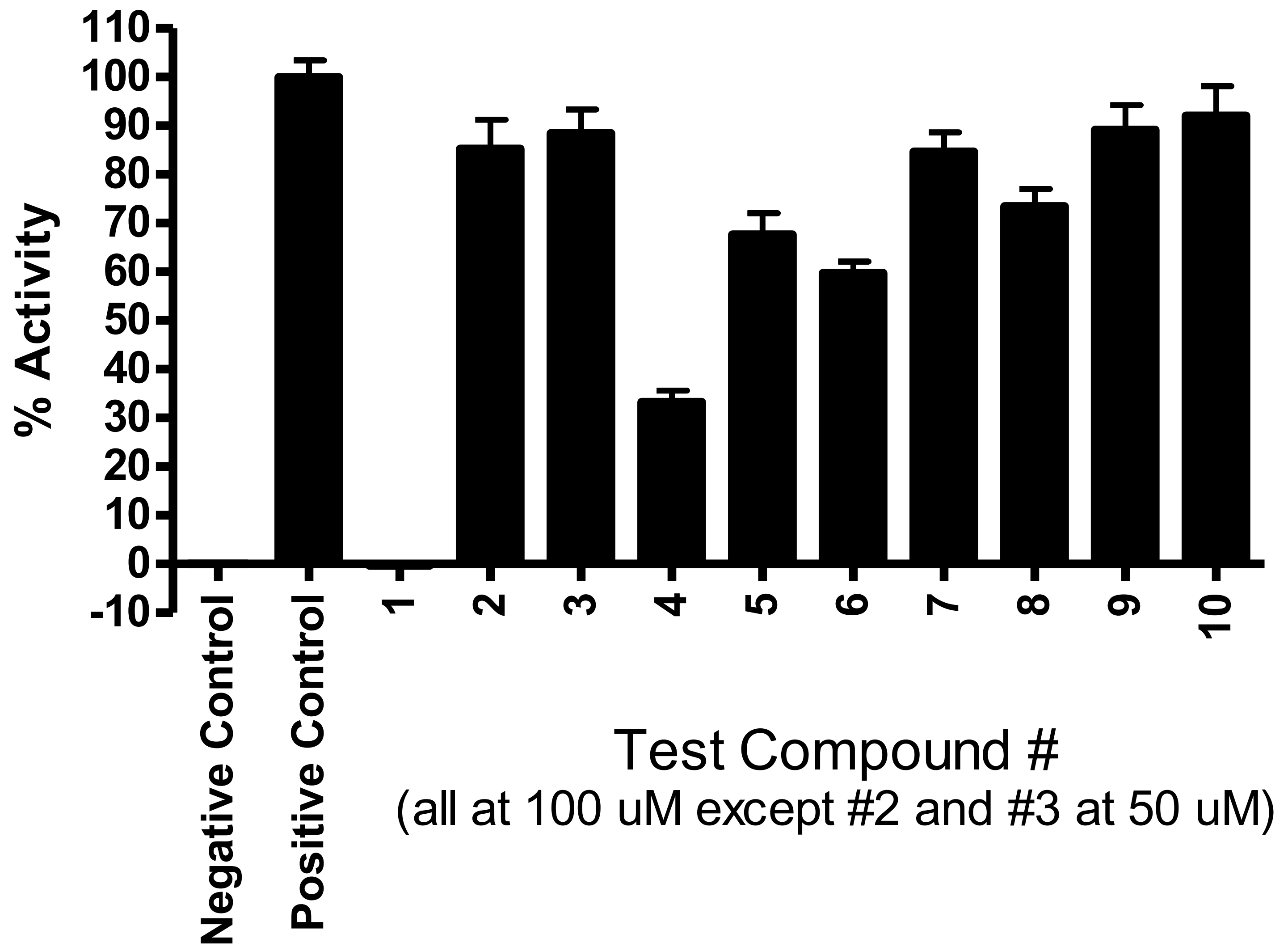
10 diverse compounds selected for screening

- **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	0.032	-6.264
Compound 10	6.67	0.361	6.1053

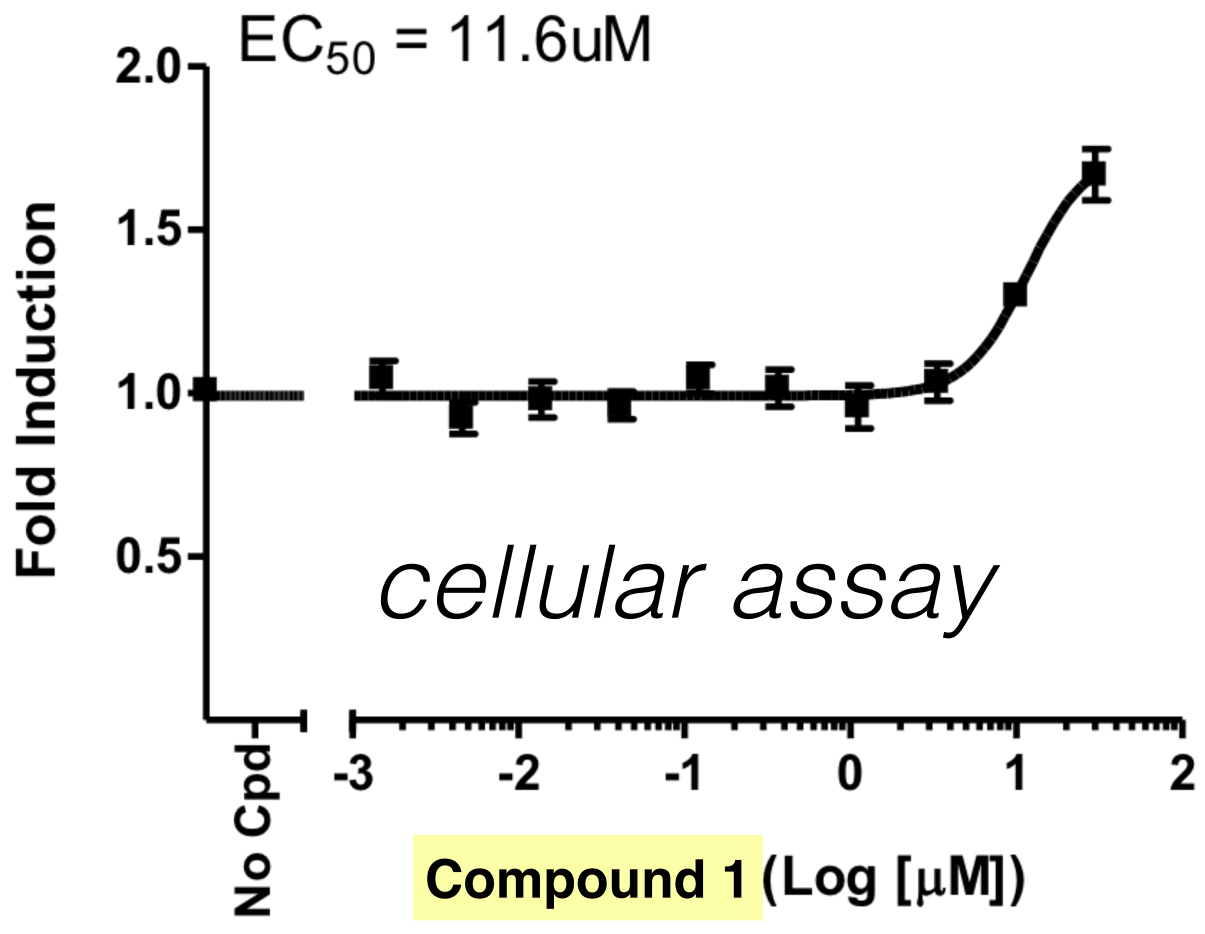
Results

TIGIT:CD155 Interaction



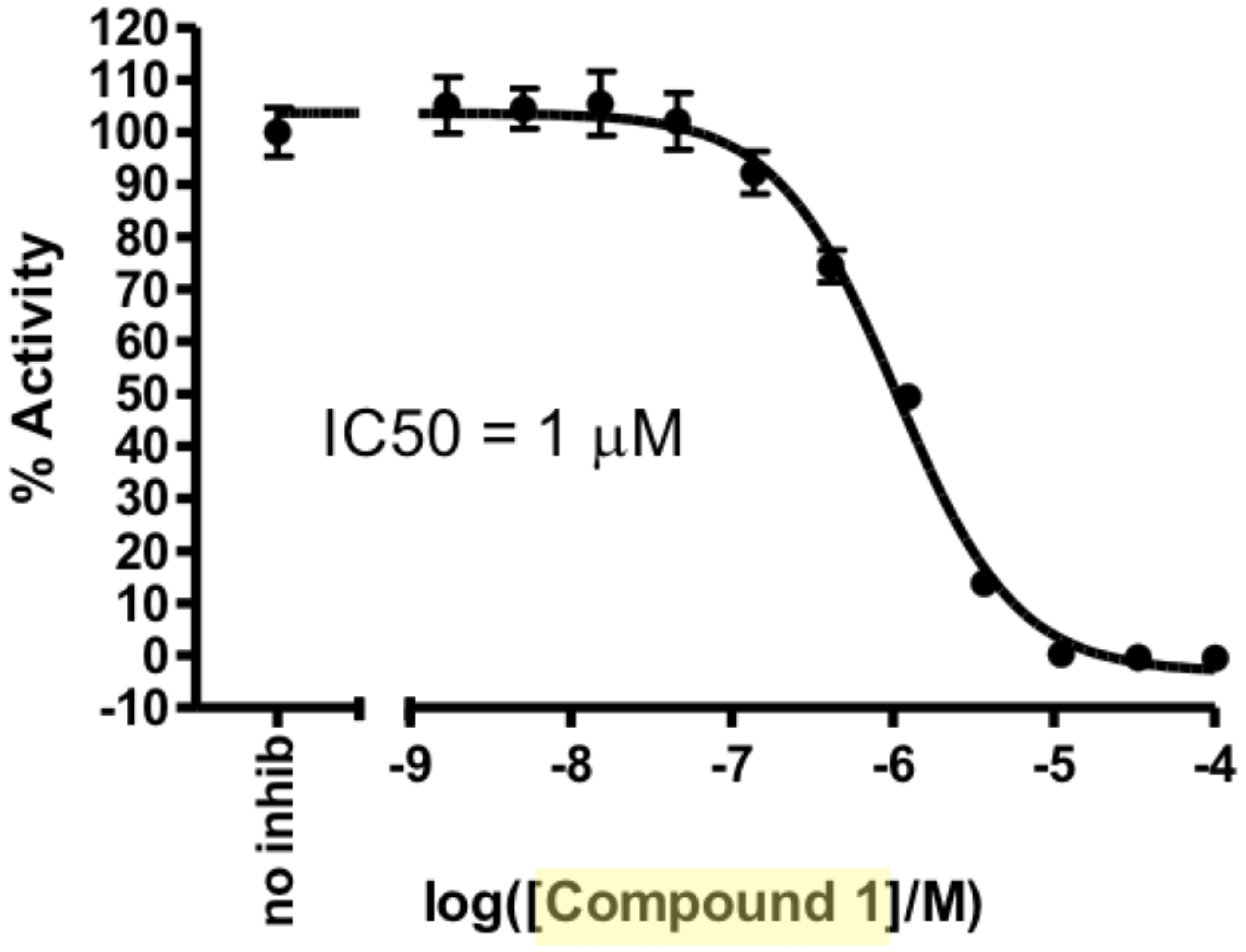
(all at 100 uM except #2 and #3 at 50 uM)

EC$_{50}$ = 11.6uM



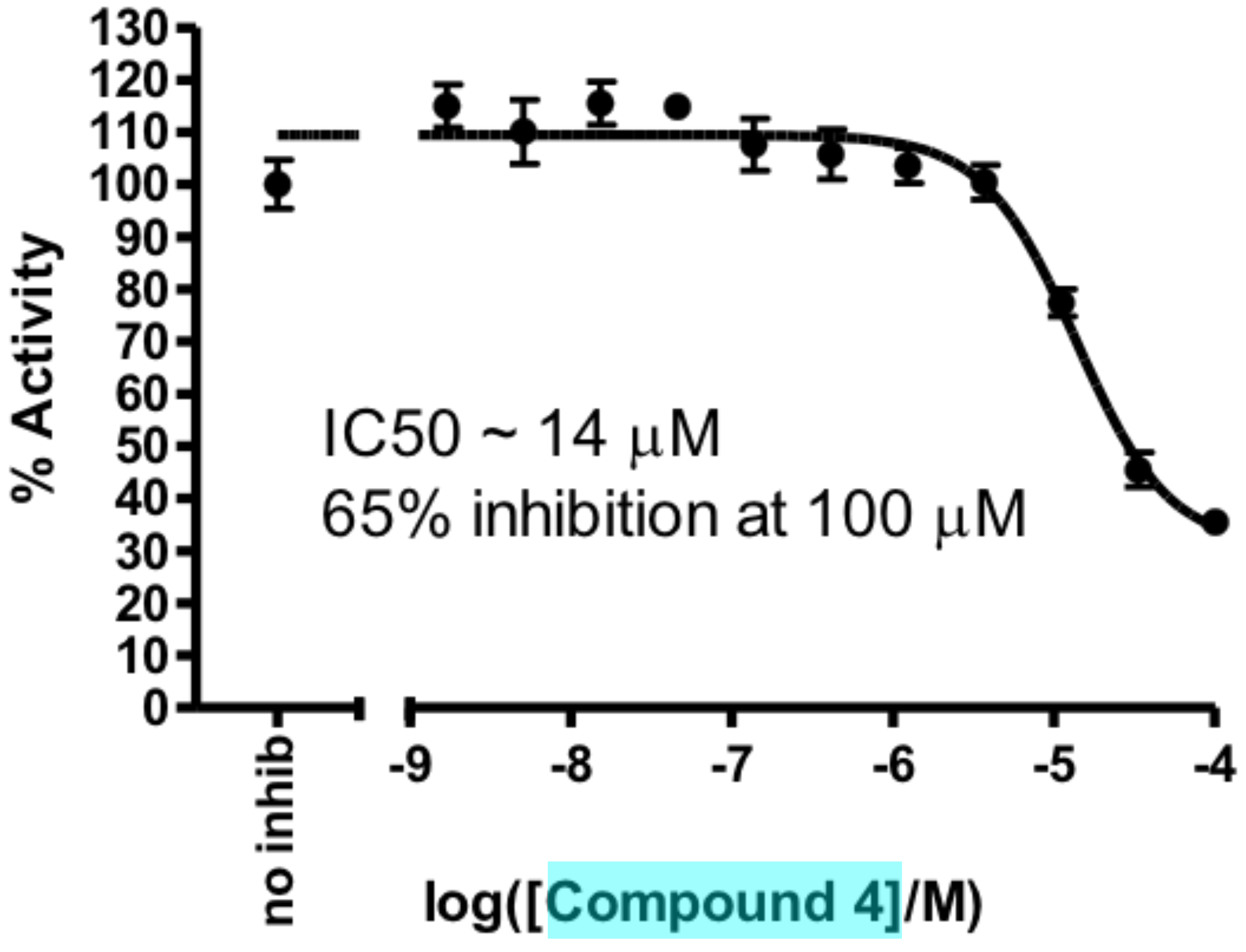
cellular assay

TIGIT:CD155 Interaction



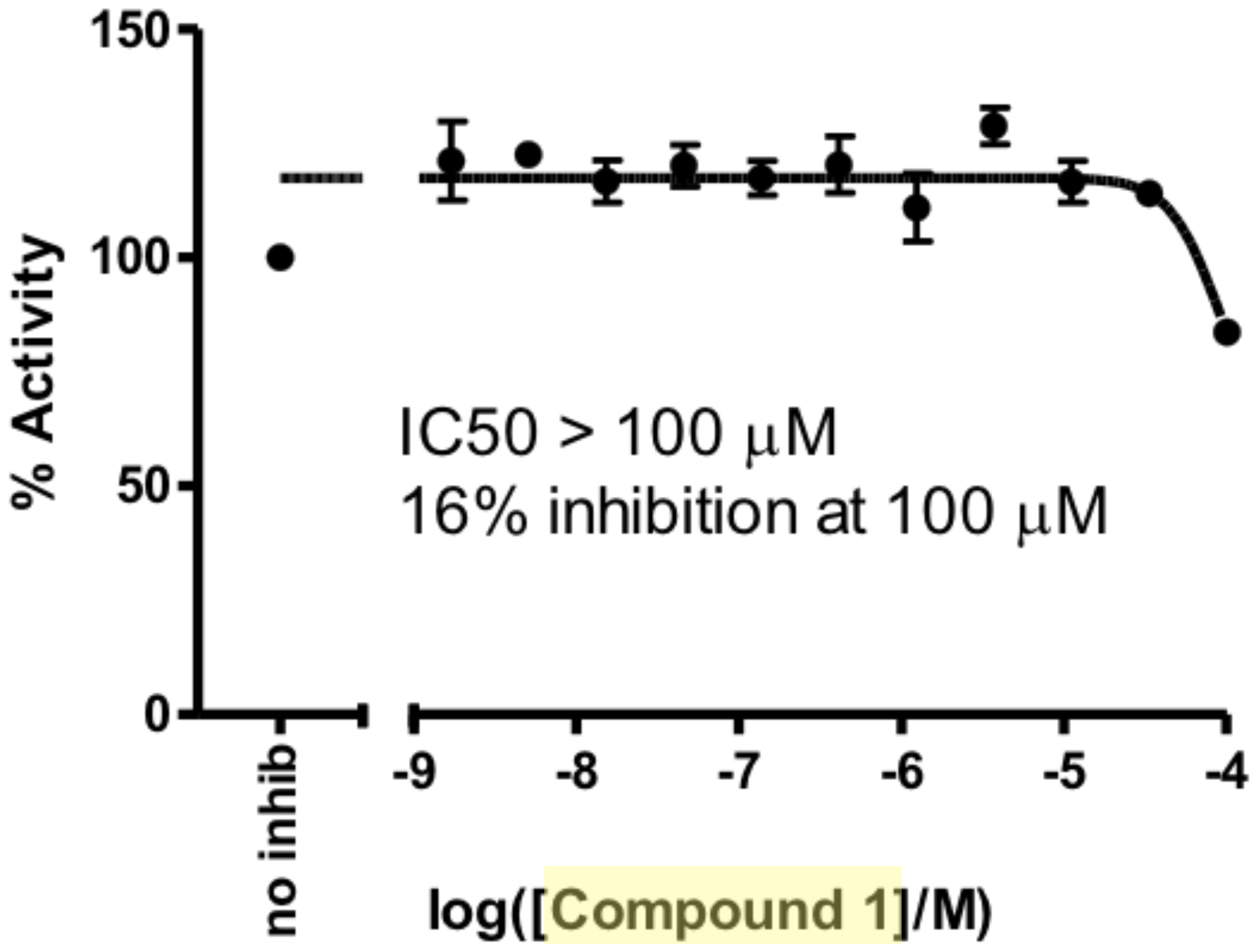
IC50 = 1 μM

TIGIT:CD155 Interaction



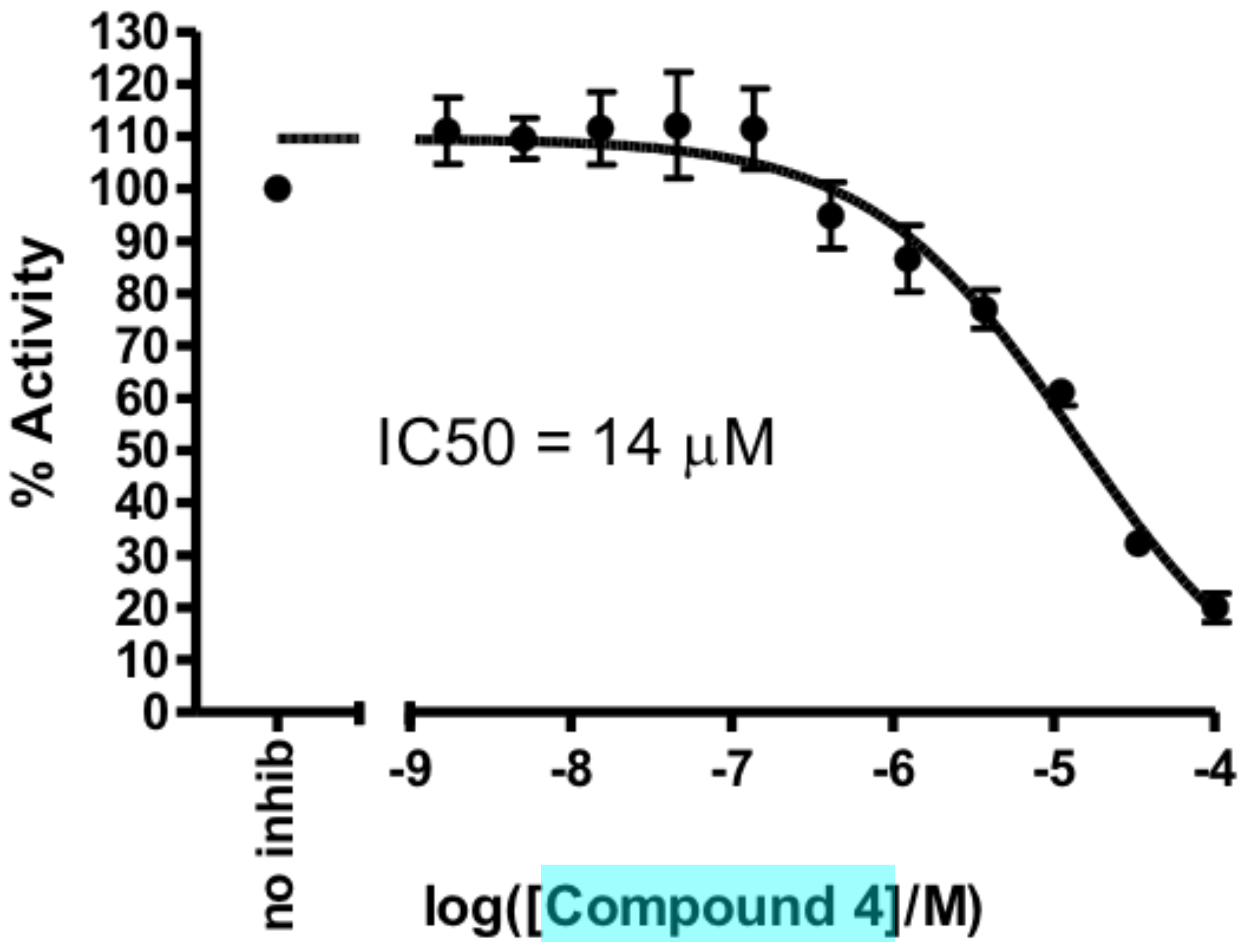
IC50 ~ 14 μM
65% inhibition at 100 μM

PD-1:PD-L1 Interaction



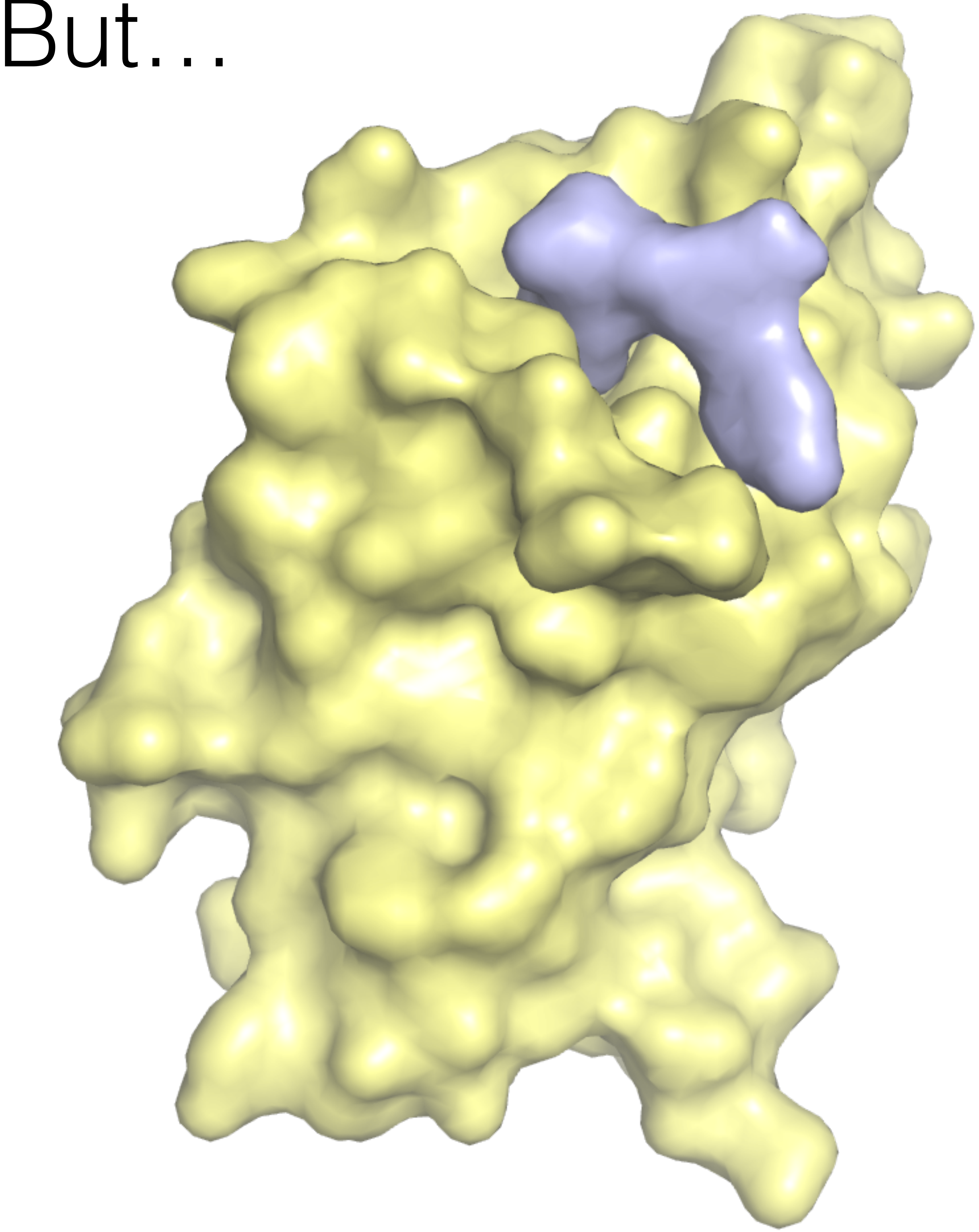
IC50 > 100 μM
16% inhibition at 100 μM

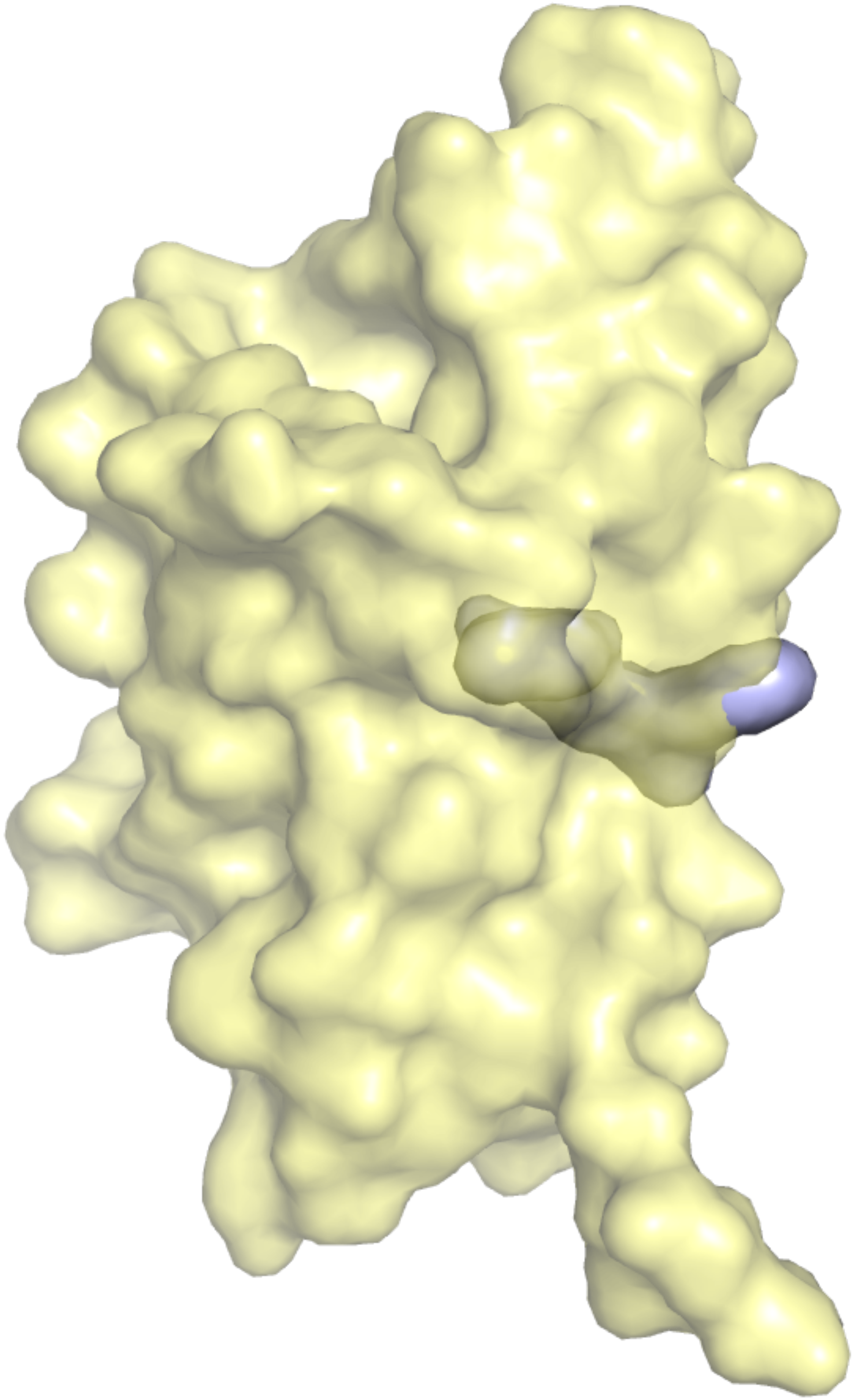
PD-1:PD-L1 Interaction



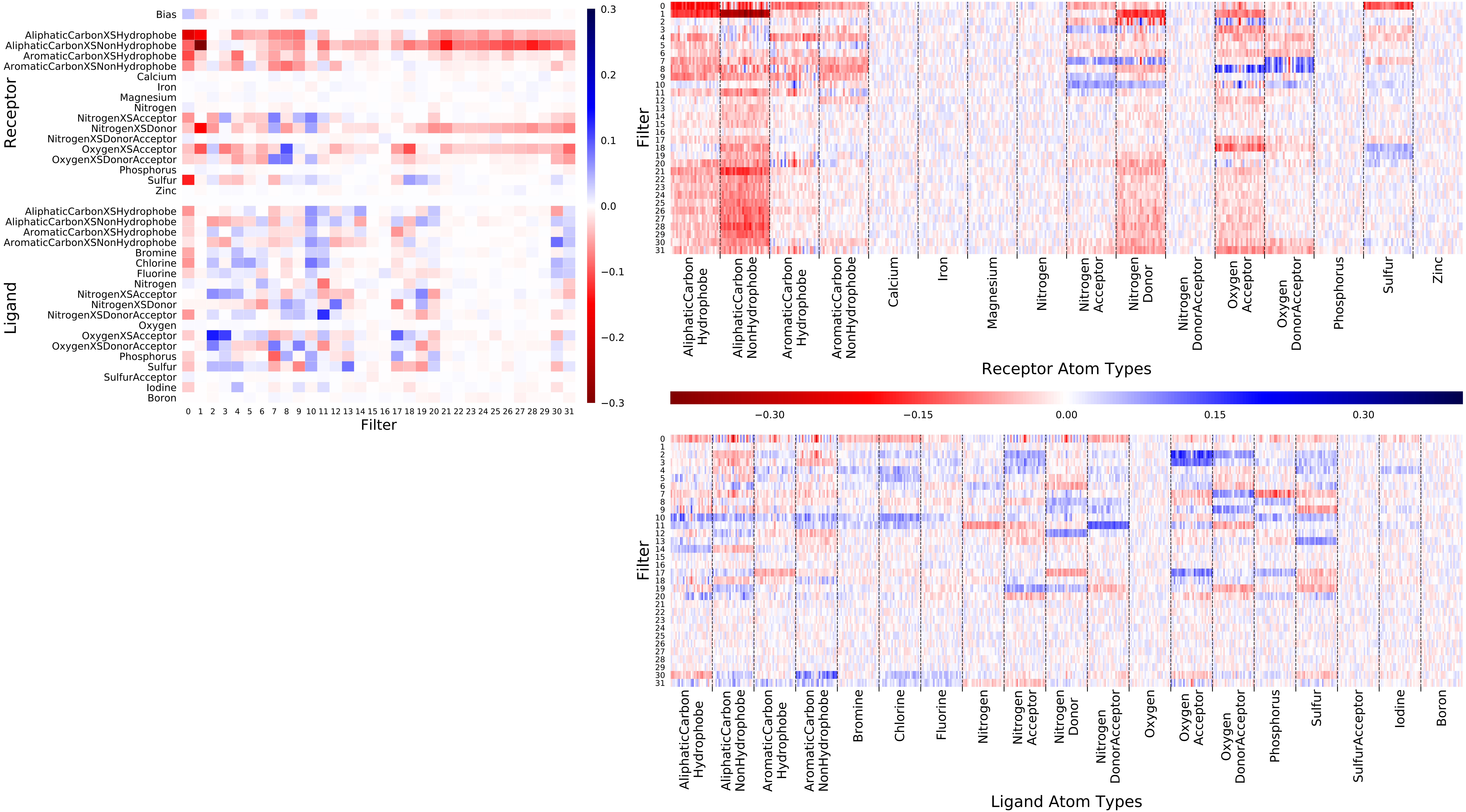
IC50 = 14 μM

But…





Filter Visualization


Bias
Receptor
AliphaticCarbonXSHydrophobe
AliphaticCarbonXSNonHydrophobe
AromaticCarbonXSHydrophobe
AromaticCarbonXSNonHydrophobe
Calcium
Iron
Magnesium
Nitrogen
NitrogenXSAcceptor
NitrogenXSDonor
NitrogenXSDonorAcceptor
OxygenXSAcceptor
OxygenXSDonorAcceptor
Phosphorus
Sulfur
Zinc
Ligand
AliphaticCarbonXSHydrophobe
AliphaticCarbonXSNonHydrophobe
AromaticCarbonXSHydrophobe
AromaticCarbonXSNonHydrophobe
Bromine
Chlorine
Fluorine
Nitrogen
NitrogenXSAcceptor
NitrogenXSDonor
NitrogenXSDonorAcceptor
Oxygen
OxygenXSAcceptor
OxygenXSDonorAcceptor
Phosphorus
Sulfur
SulfurAcceptor
Iodine
Boron
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
Oxygen DonorAcceptor
Phosphorus
Sulfur
Zinc
Receptor Atom Types
−0.30
−0.15
0.00
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