University of Pittsburgh

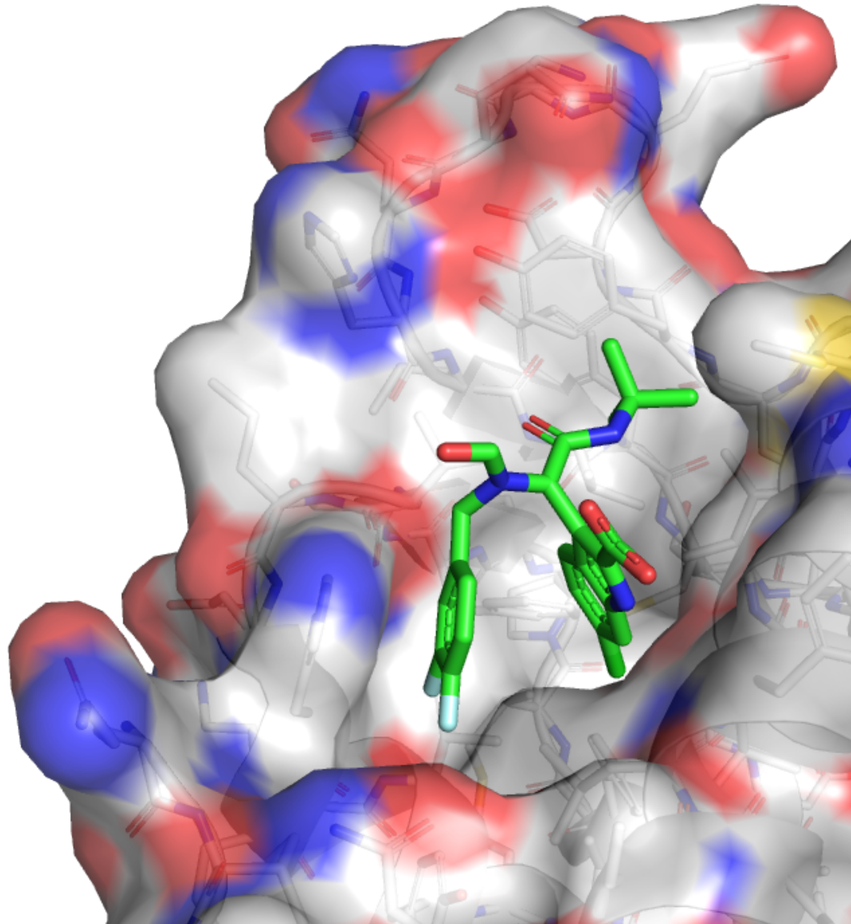
Deep Structure-Based Drug Design

David Ryan Koes

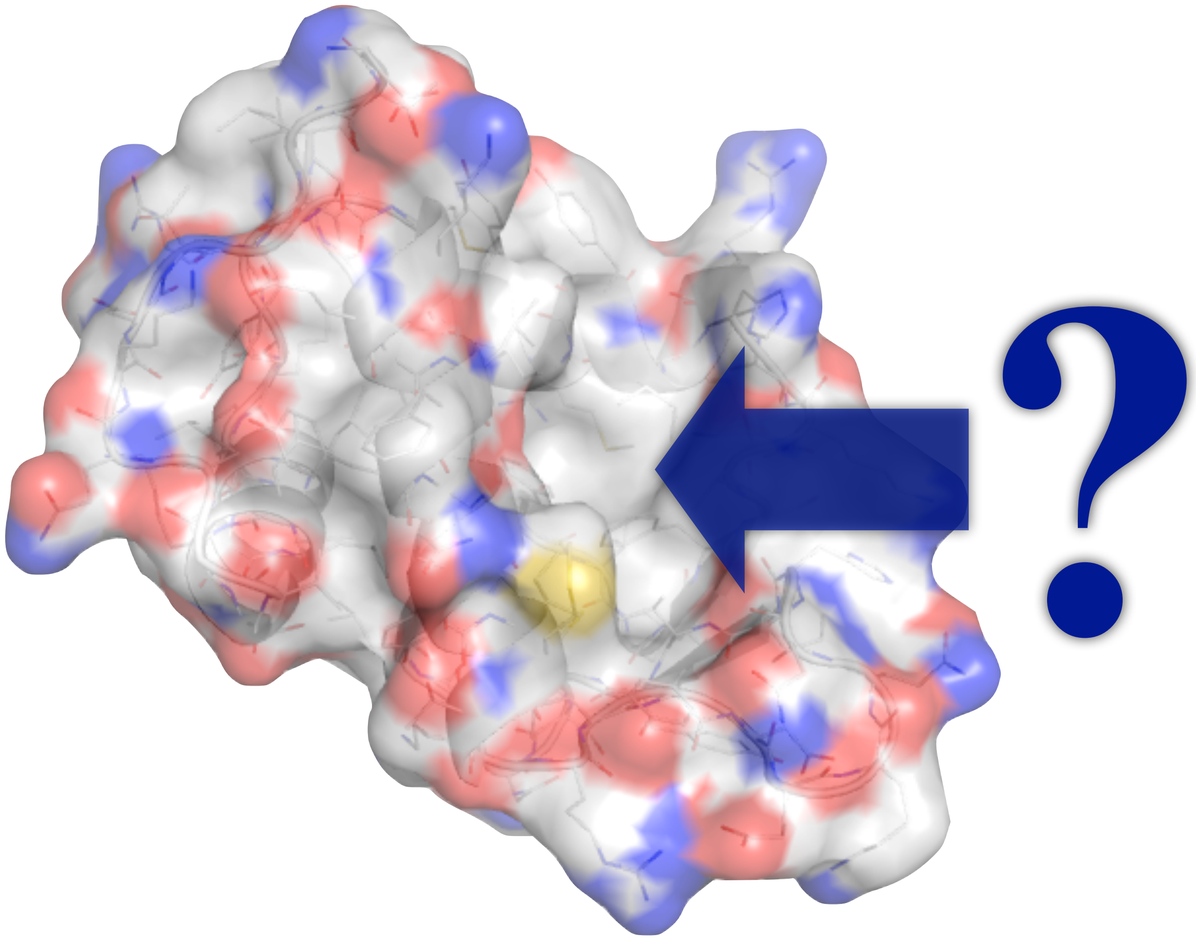
@david_koes

UCSD

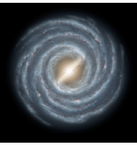
3/25/2022

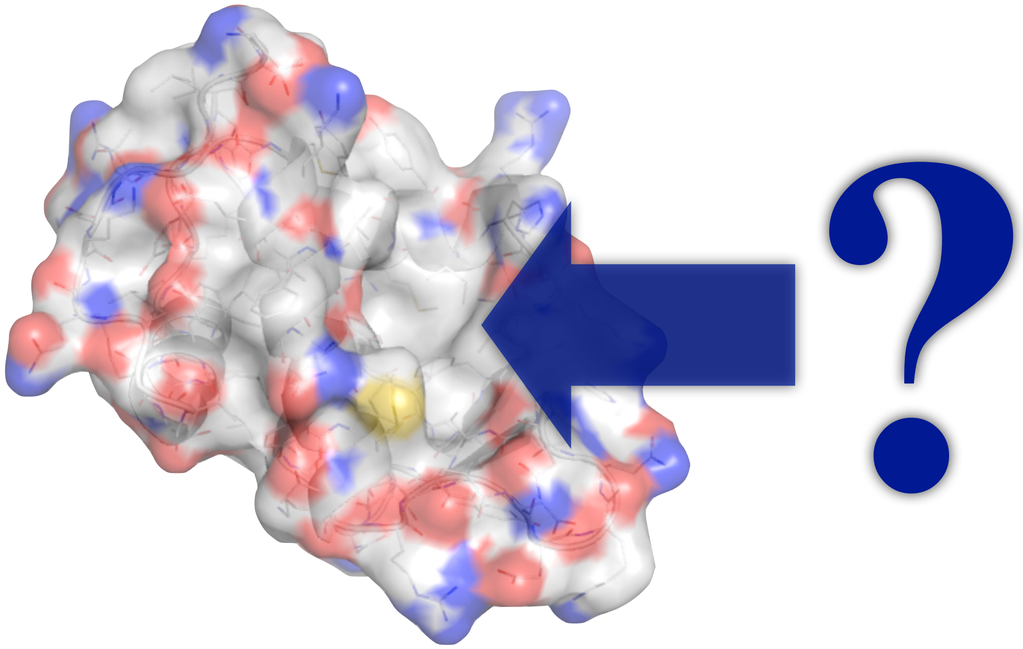


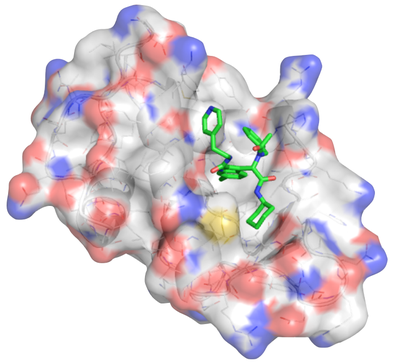
Structure Based Drug Design



Structure Based Drug Design Funnel

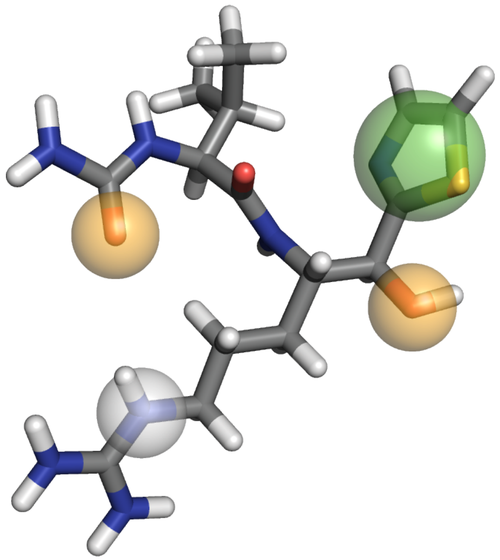
Purchasable  Accessible

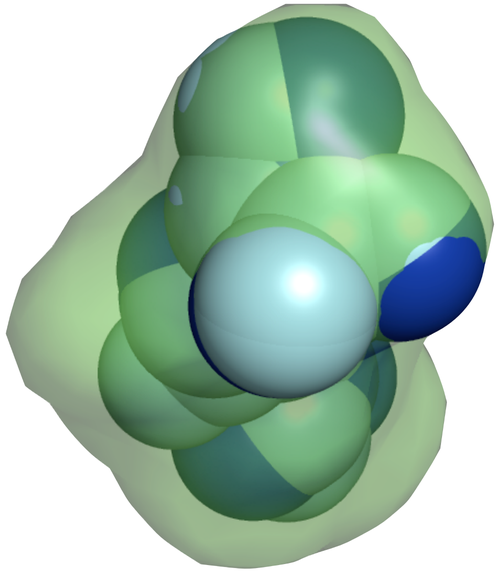


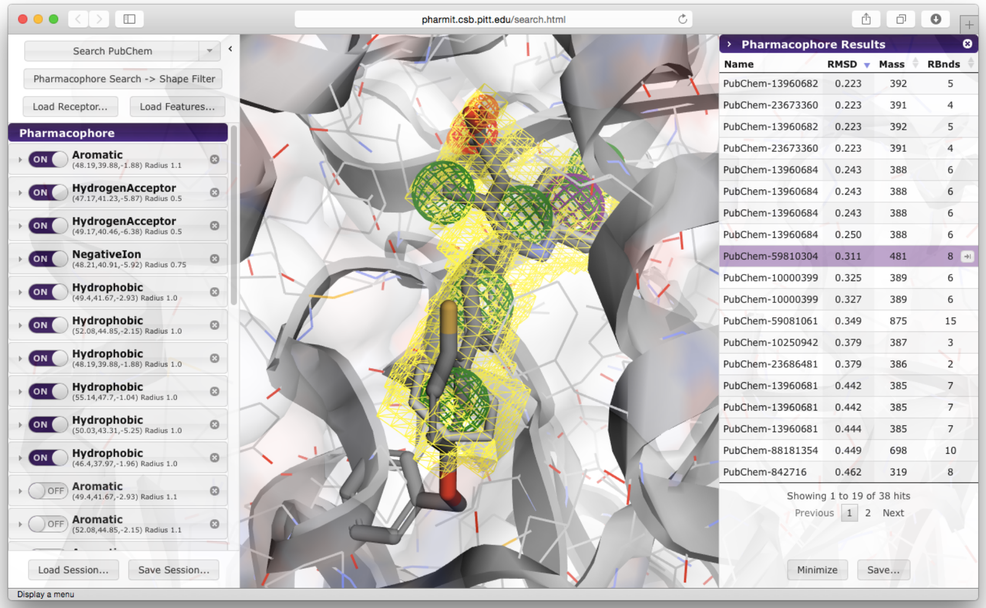


How does it bind? (pose prediction)
Does it bind? (virtual screening)
How well does it bind? (affinity prediction)

Matching







pharmer.sf.net

github.com/dkoes/shapedb

pharmit.csb.pitt.edu

Koes DR, Camacho CJ. Pharmer: efficient and exact pharmacophore search. J Chem Inf Model. 2011 Jun 27;51(6):1307-14.

Koes DR, Camacho CJ. Shape-based virtual screening with volumetric aligned molecular shapes. J Comput Chem. 2014 Sep 30;35(25):1824-34.

Hain E, Camacho CJ, Koes DR. Fragment oriented molecular shapes. J Mol Graph Model. 2016 May;66:143-54.

Koes DR, Camacho CJ. Indexing Volumetric Shapes with Matching and Packing. Knowl Inf Syst. 2015 Apr 1;43(1):157-180.

Rego N, Koes D. 3Dmol.js: molecular visualization with WebGL. Bioinformatics. 2015 Apr 15;31(8):1322-4.

Koes D. The Pharmit Backend: A Computer Systems Approach to Enabling Interactive Online Drug Discovery. IBM Journal of Research and Development. 2018 Nov 28.

Sunseri J, Koes DR. Pharmit: interactive exploration of chemical space. Nucleic Acids Res. 2016 Jul 8;44(W1):W442-8.

Protein-Ligand Scoring

AutoDock Vina

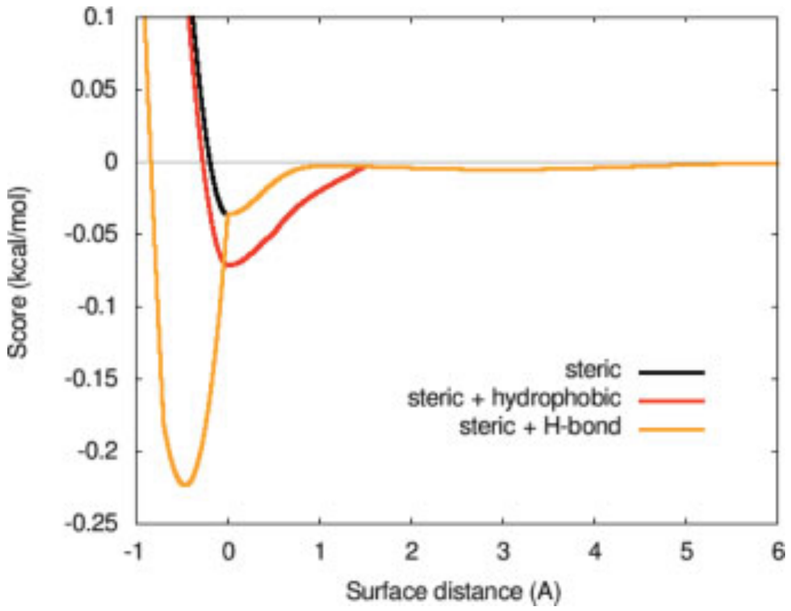
$$\text{gauss}_1(d) = w_{\text{guass}_1} e^{-(d/0.5)^2}$$

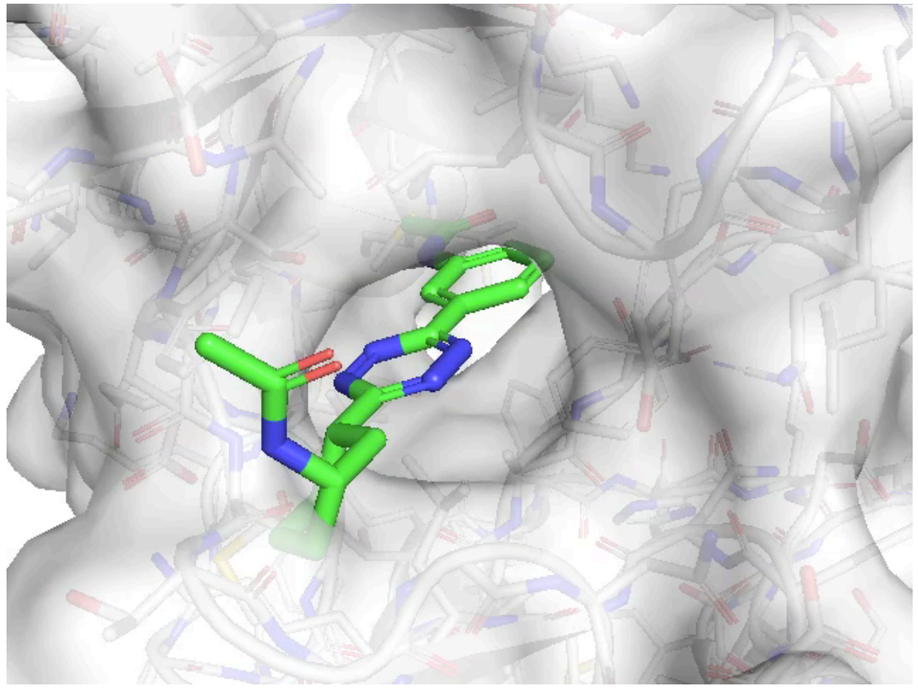
$$\text{gauss}_2(d) = w_{\text{guass}_2} e^{-((d-3)/2)^2}$$

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

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

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





Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*. 2010 Jan 30;31(2):455-61.

Protein-Ligand Scoring

AutoDock Vina

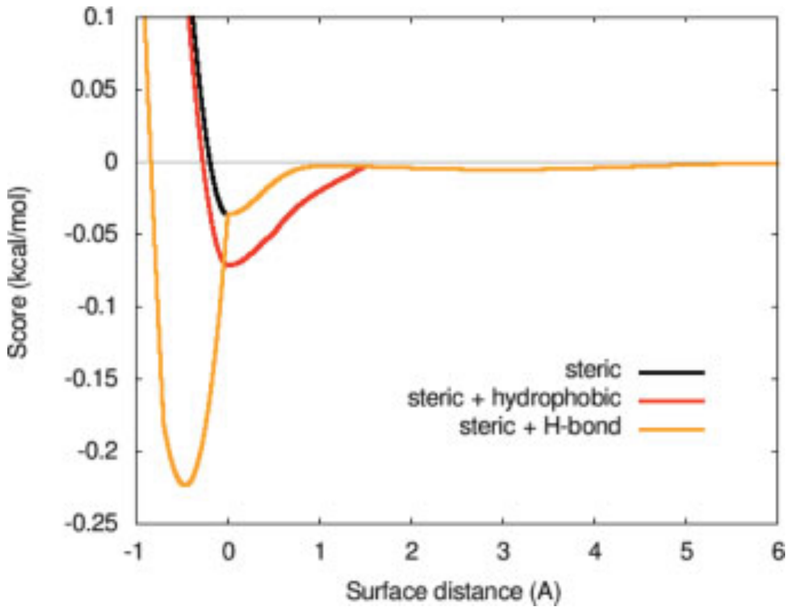
$$\text{gauss}_1(d) = w_{\text{guass}_1} e^{-(d/0.5)^2}$$

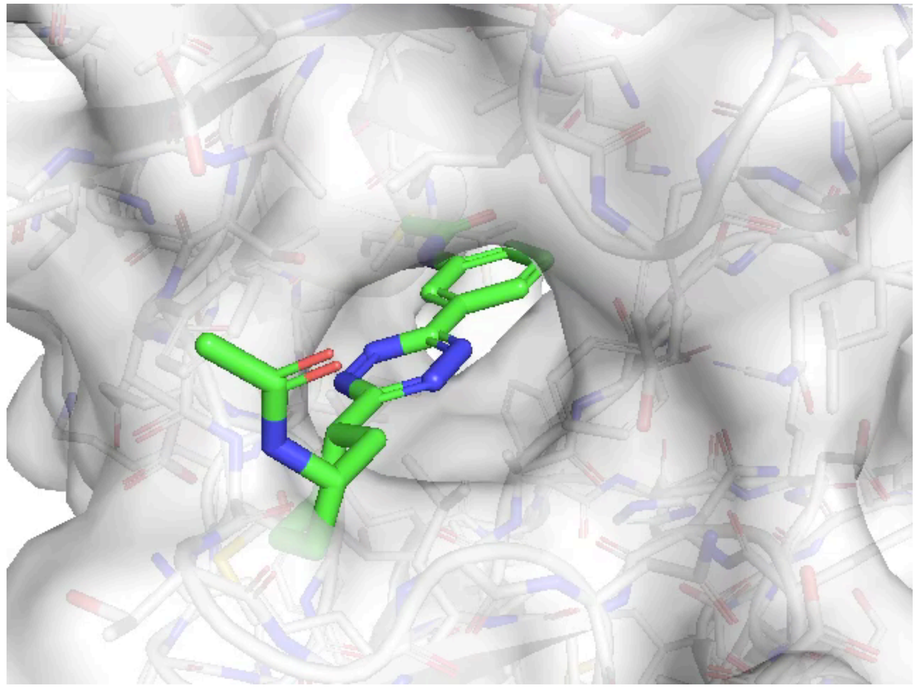
$$\text{gauss}_2(d) = w_{\text{guass}_2} e^{-((d-3)/2)^2}$$

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

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

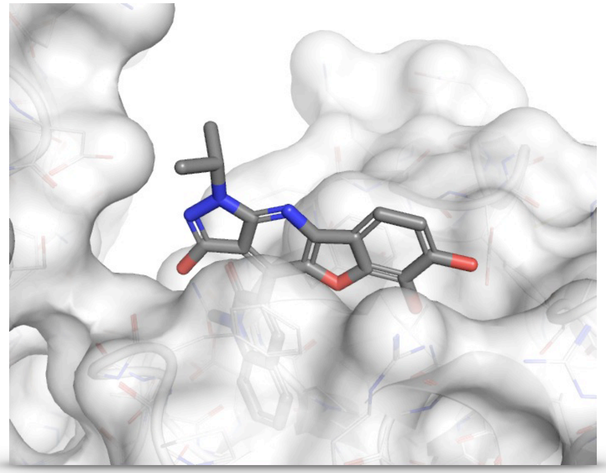
$$\text{hbond}(d) = \begin{cases} w_{\text{hbond}} & d < -0.7 \\ 0 & d > 0 \\ w_{\text{hbond}}(-\frac{10}{7} d) & otherwise \end{cases}$$





Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*. 2010 Jan 30;31(2):455-61.

Protein-Ligand Scoring



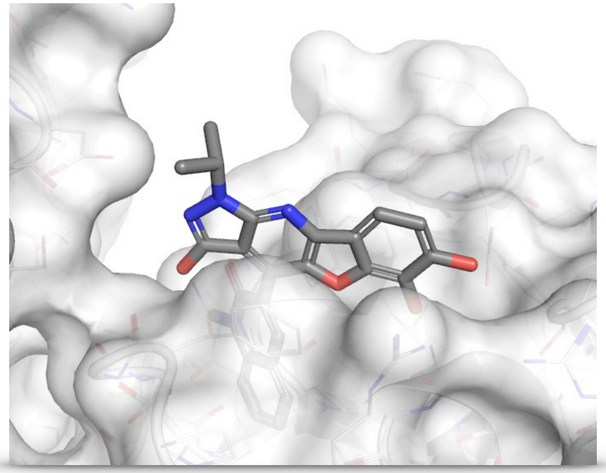
Model

Pose Prediction

Binding Discrimination

Affinity Prediction

Protein-Ligand Scoring



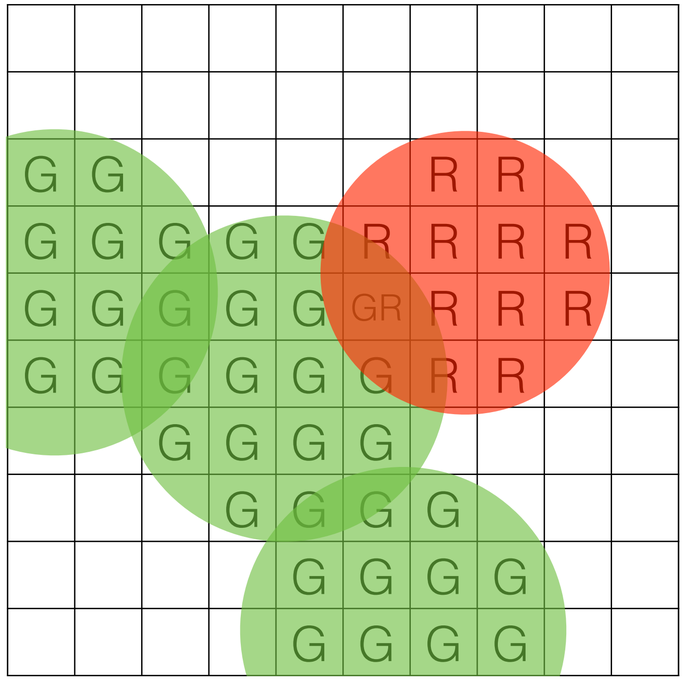
Model

Pose Prediction

Binding Discrimination

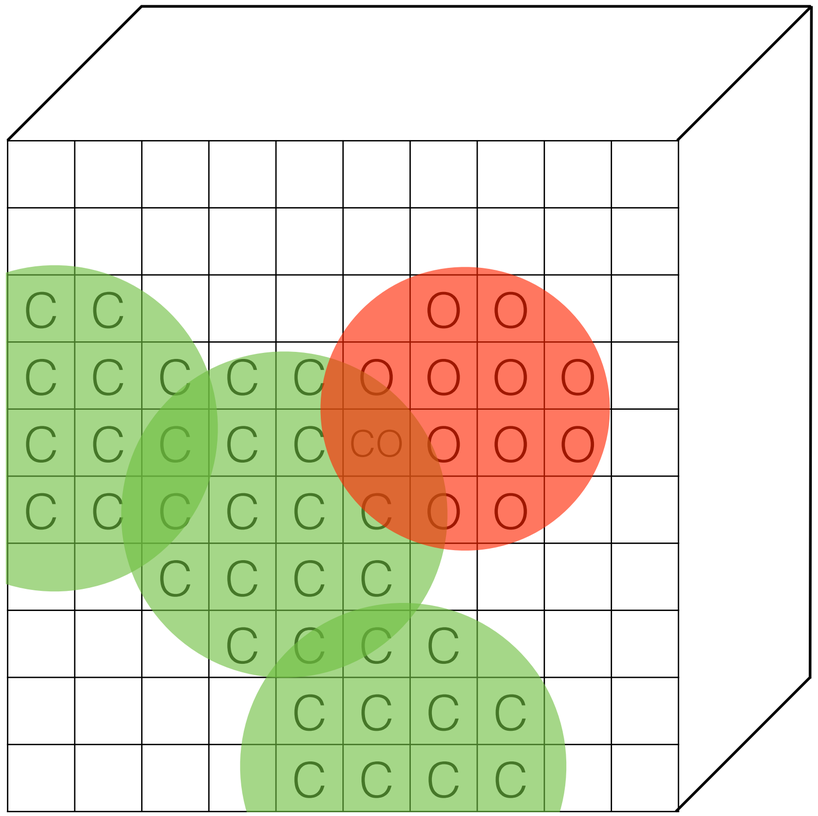
Affinity Prediction

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**.

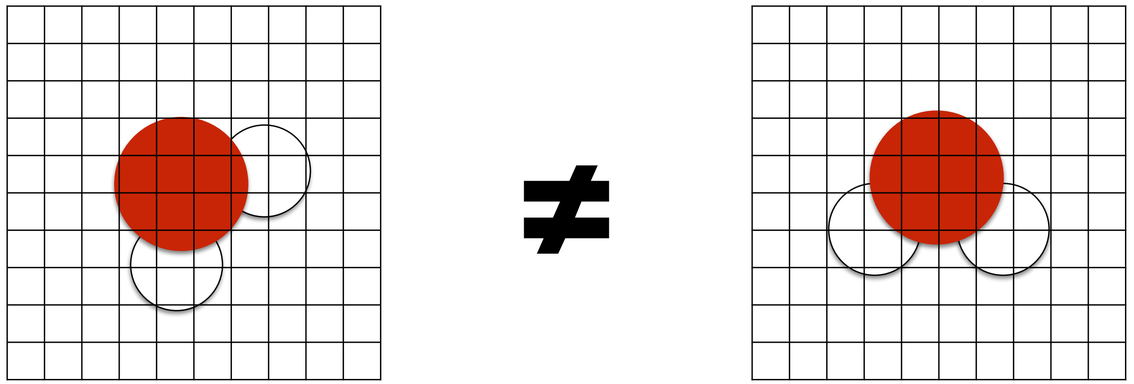
Why Grids?

Cons

- *coordinate frame dependent*
  - but can be input into equivariant networks
- pairwise interactions not explicit

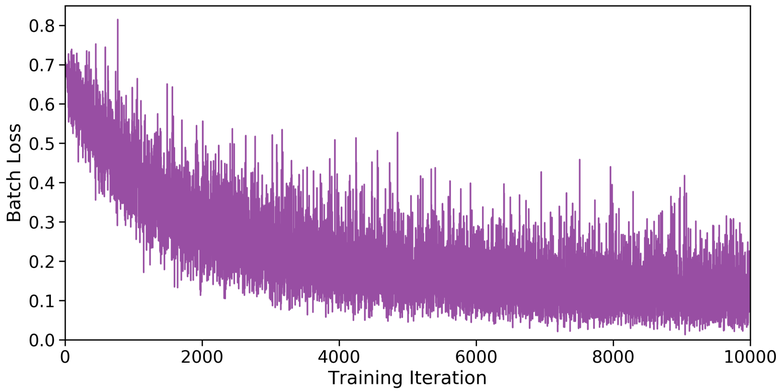
Pros

- clear spatial relationships
- amazingly parallel
- easy to interpret

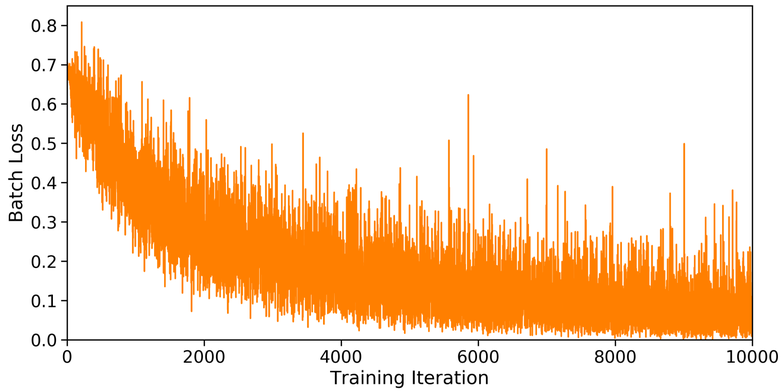


libmolgrid

Caffe Training



PyTorch Training



JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

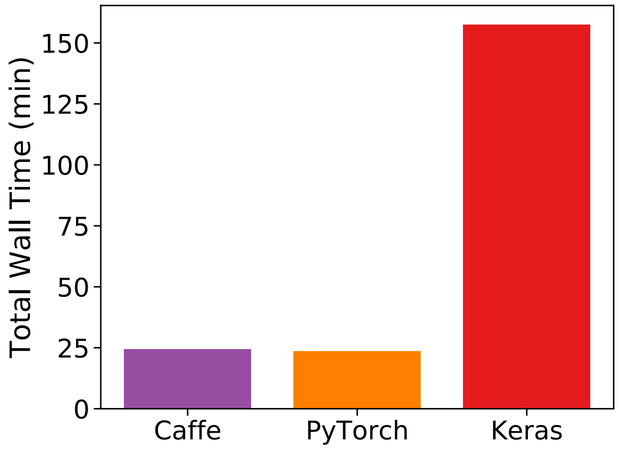
libmolgrid: Graphics Processing Unit Accelerated Molecular Gridding for Deep Learning Applications

Jocelyn Sunseri and David R. Koes*

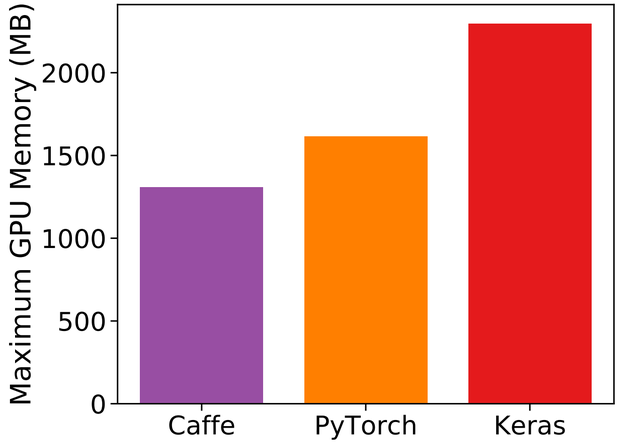
Cite this: *J. Chem. Inf. Model.* 2020, 60, 3, 1079–1084
Publication Date: February 12, 2020
https://doi.org/10.1021/acs.jcim.9b01145
Copyright © 2020 American Chemical Society

Article Views 4295 | Altmetric 15 | Citations 9
LEARN ABOUT THESE METRICS

GPU Performance



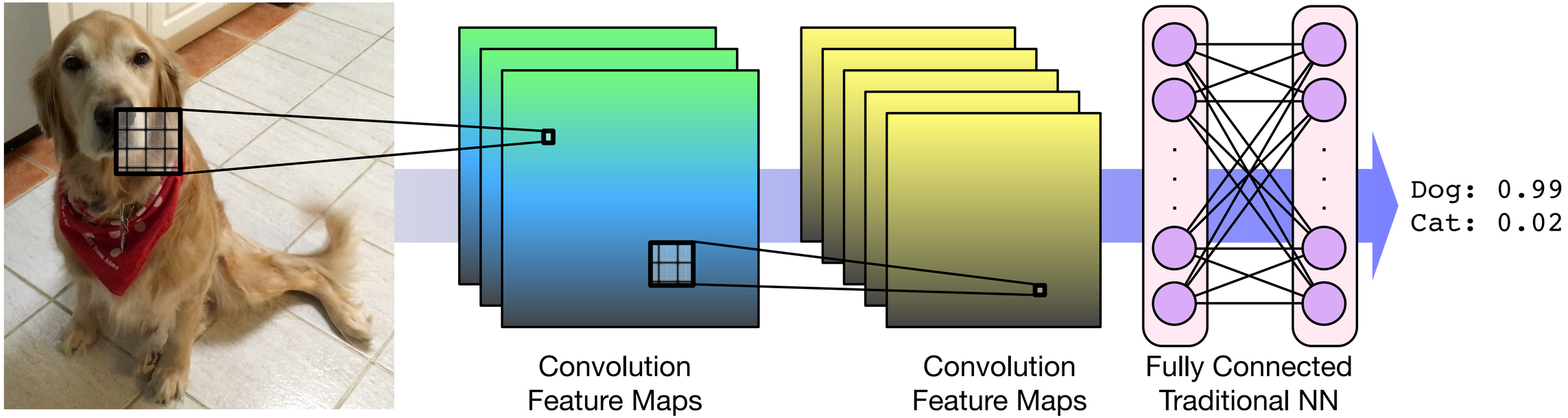
GPU Memory Utilization



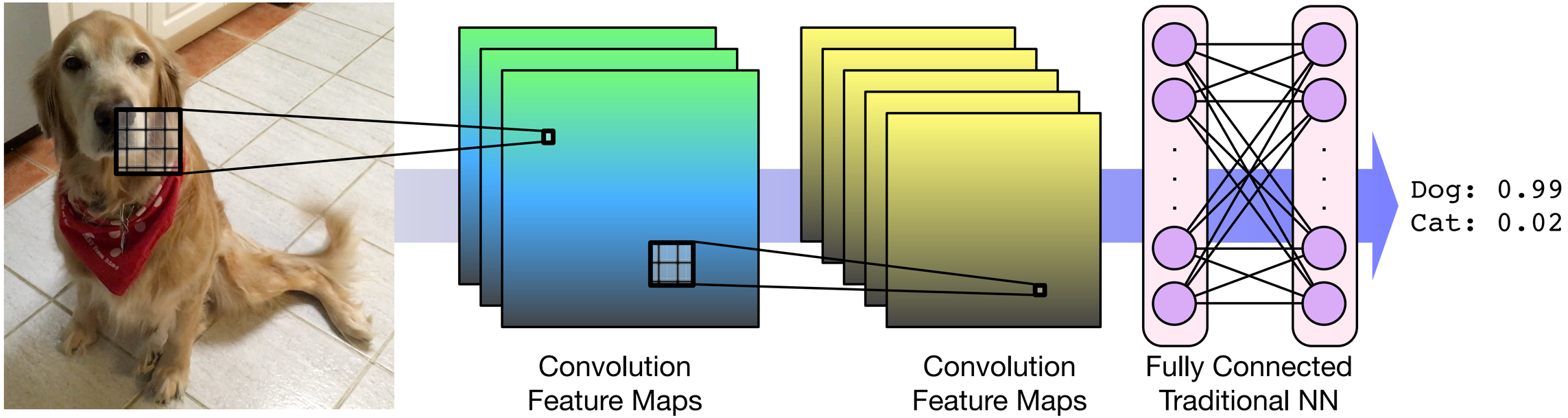

```
e = molgrid.ExampleProvider(balanced=True,shuffle=True)
e.populate('examples.txt')

gmaker = molgrid.GridMaker(resolution=0.5,
                           dimension=23.5)

batch = e.next_batch(batch_size)
gmaker.forward(batch, input_tensor,
          random_translation=0, random_rotation=True)
```

github.com/gnina/libmolgrid

Convolutional Neural Networks



Convolutional Neural Networks



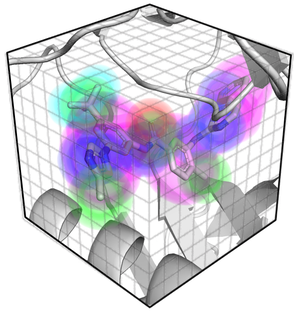
Ragoza M, Hochuli J, Idrobo E, Sunseri J, Koes DR. Protein–ligand scoring with convolutional neural networks. Journal of chemical information and modeling. 2017 Apr 11;57(4):942-57.

Sunseri J, King JE, Francoeur PG, Koes DR. Convolutional neural network scoring and minimization in the D3R 2017 community challenge. Journal of computer-aided molecular design. 2019 Jan 15;33(1):19-34.

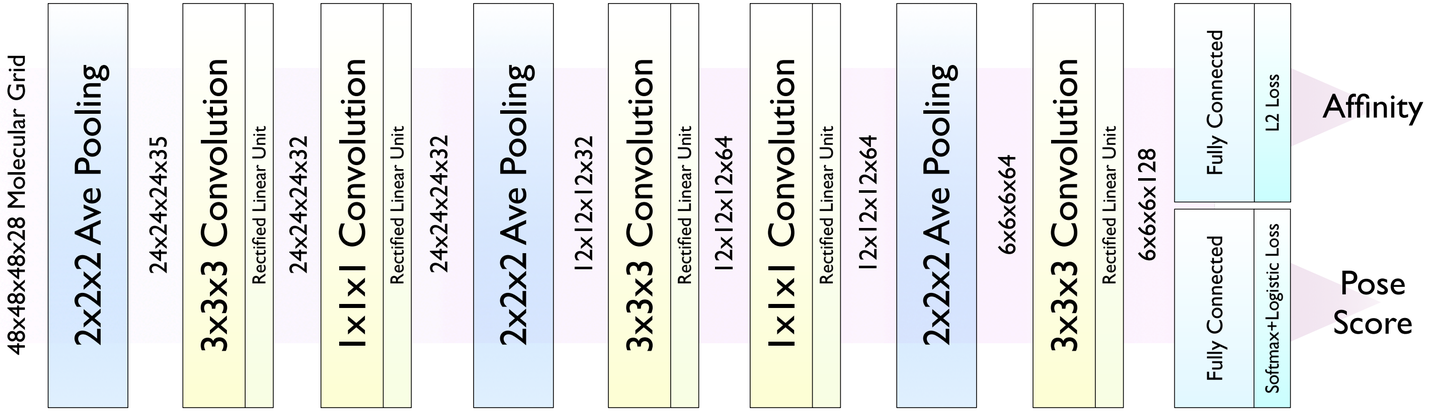
Hochuli J, Helbling A, Skaist T, Ragoza M, Koes DR. Visualizing convolutional neural network protein-ligand scoring. Journal of Molecular Graphics and Modelling. 2018 Sep 1;84:96-108.

Francoeur PG, Masuda T, Sunseri J, Jia A, Iovanisci RB, Snyder I, Koes DR. Three-Dimensional Convolutional Neural Networks and a Cross-Docked Data Set for Structure-Based Drug Design. Journal of Chemical Information and Modeling. 2020 Aug 31;60(9):4200-15.

Protein Ligand Scoring

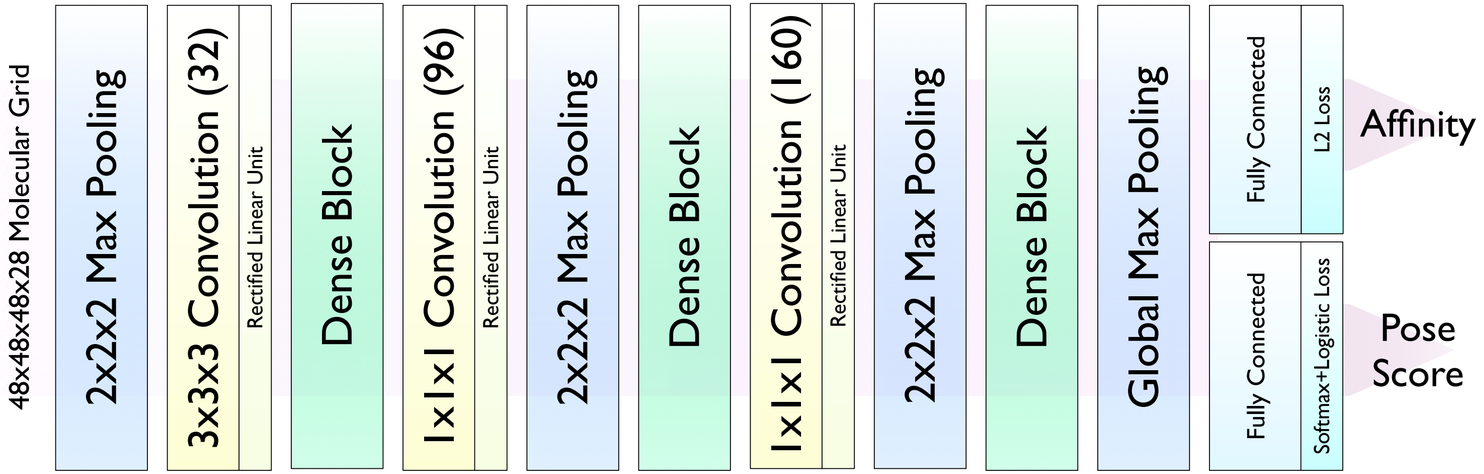


Def2018

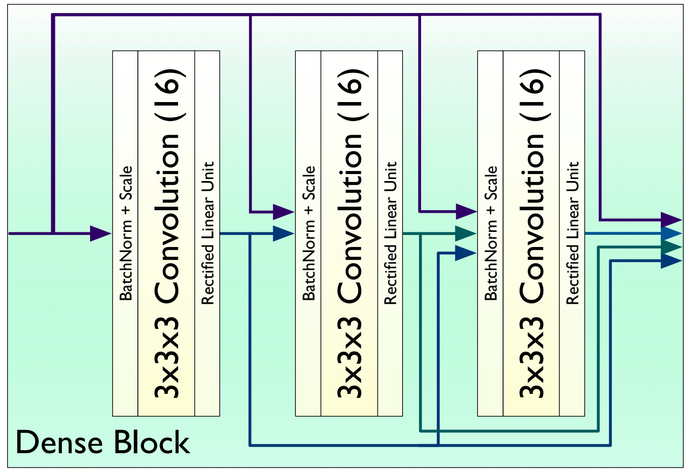


388,736 Parameters

Dense



684,640 Parameters



Cross-Docked Protein Ligand Scoring

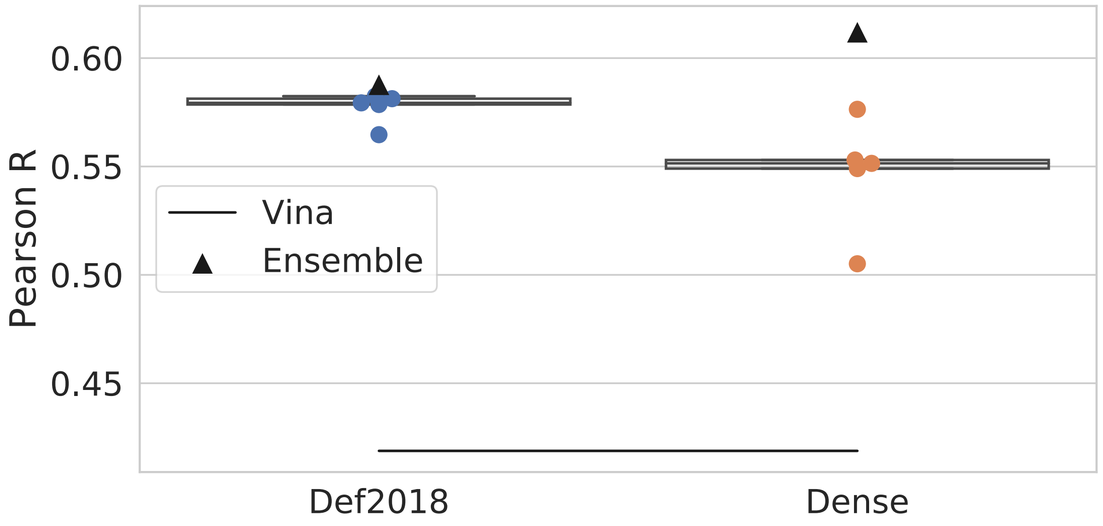
https://github.com/gnina/models/tree/master/data/CrossDocked2020

Three-Dimensional Convolutional Neural Networks and a Cross-Docked Data Set for Structure-Based Drug Design

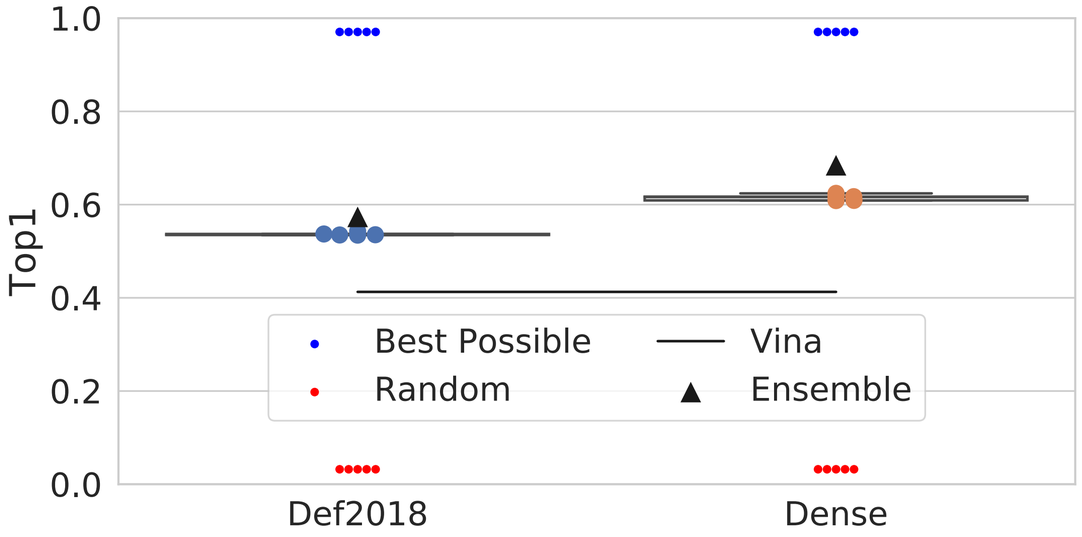
Paul G. Francoeur, Tomohide Masuda, Jocelyn Sunseri, Andrew Jia, Richard B. Iovanisci, Ian Snyder, and David R. Koes*

Cite this: *J. Chem. Inf. Model.* 2020, 60, 9, 4200–4215
Publication Date: August 31, 2020
https://doi.org/10.1021/acs.jcim.0c00411
Copyright © 2020 American Chemical Society
RIGHTS & PERMISSIONS

Article Views 1420 | Altmetric 17 | Citations 5
LEARN ABOUT THESE METRICS
Share Add to Export RIS



Affinity Prediction



Pose Selection

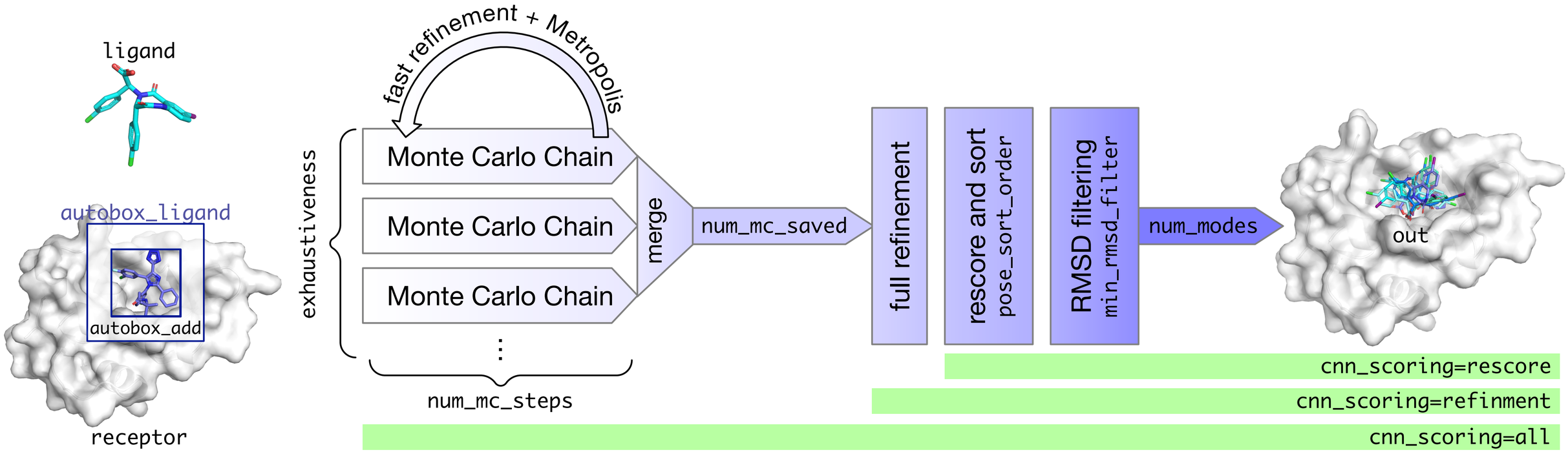
GNINA 1.0

https://github.com/gnina/gnina

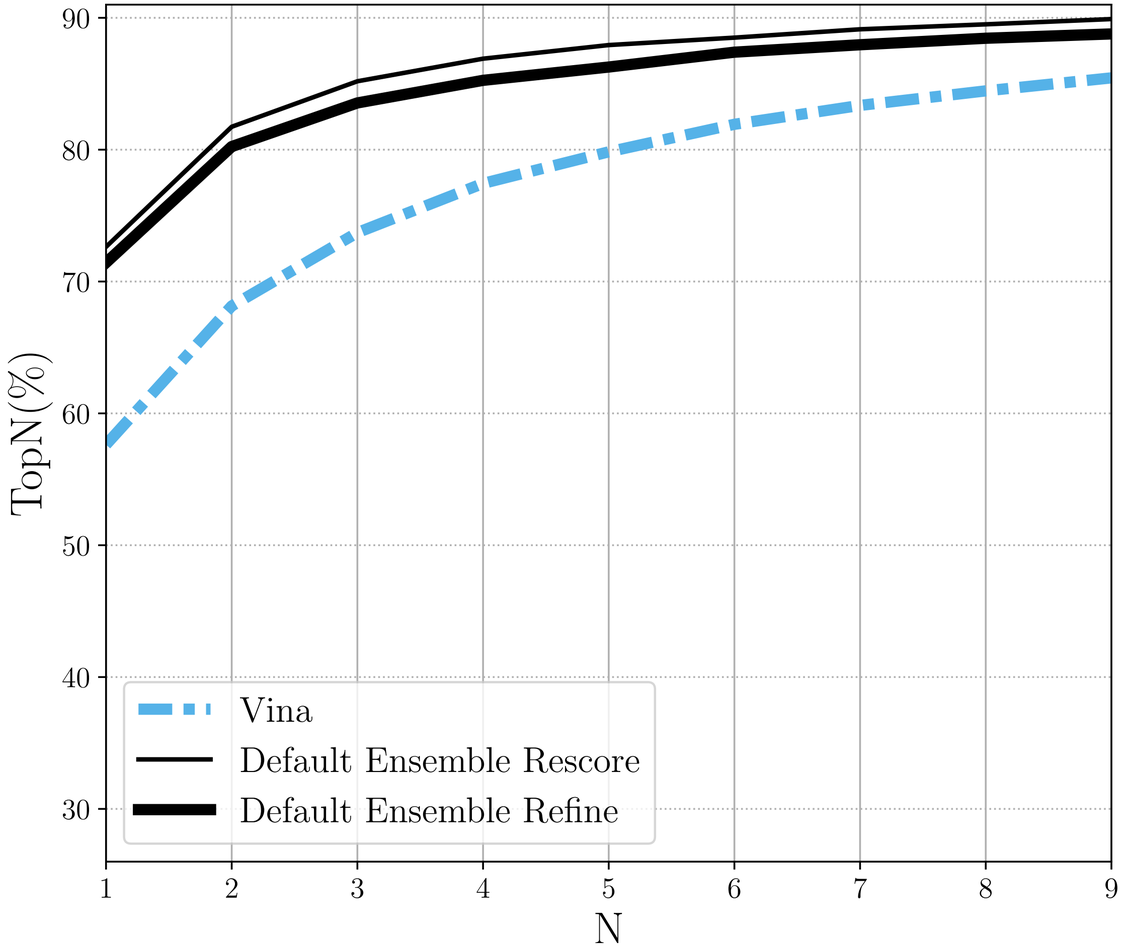
SOFTWARE Open Access

GNINA 1.0: molecular docking with deep learning

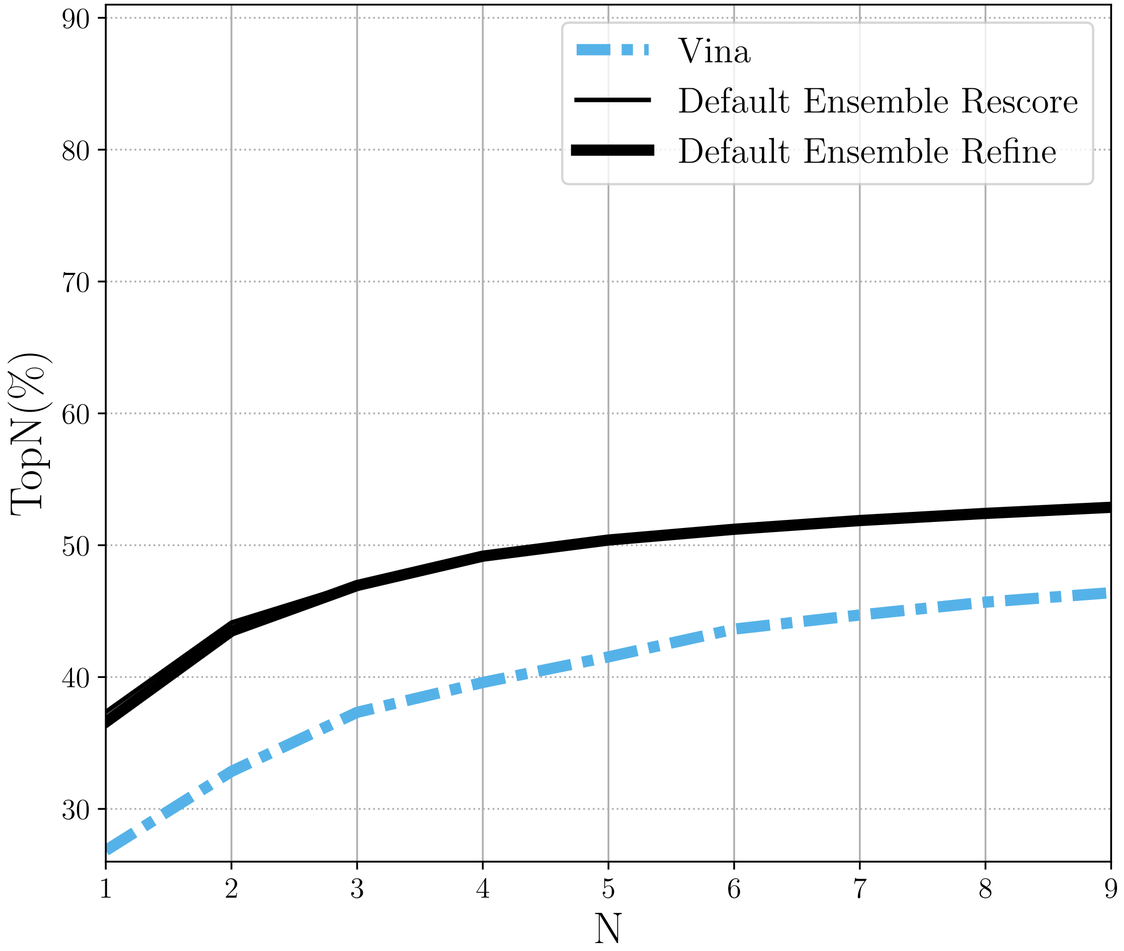
Andrew T. McNutt[1], Paul Francoeur[1], Rishal Aggarwal[2], Tomohide Masuda[1], Rocco Meli[3], Matthew Ragoza[1], Jocelyn Sunseri[1] and David Ryan Koes[1*]



Using the CNN

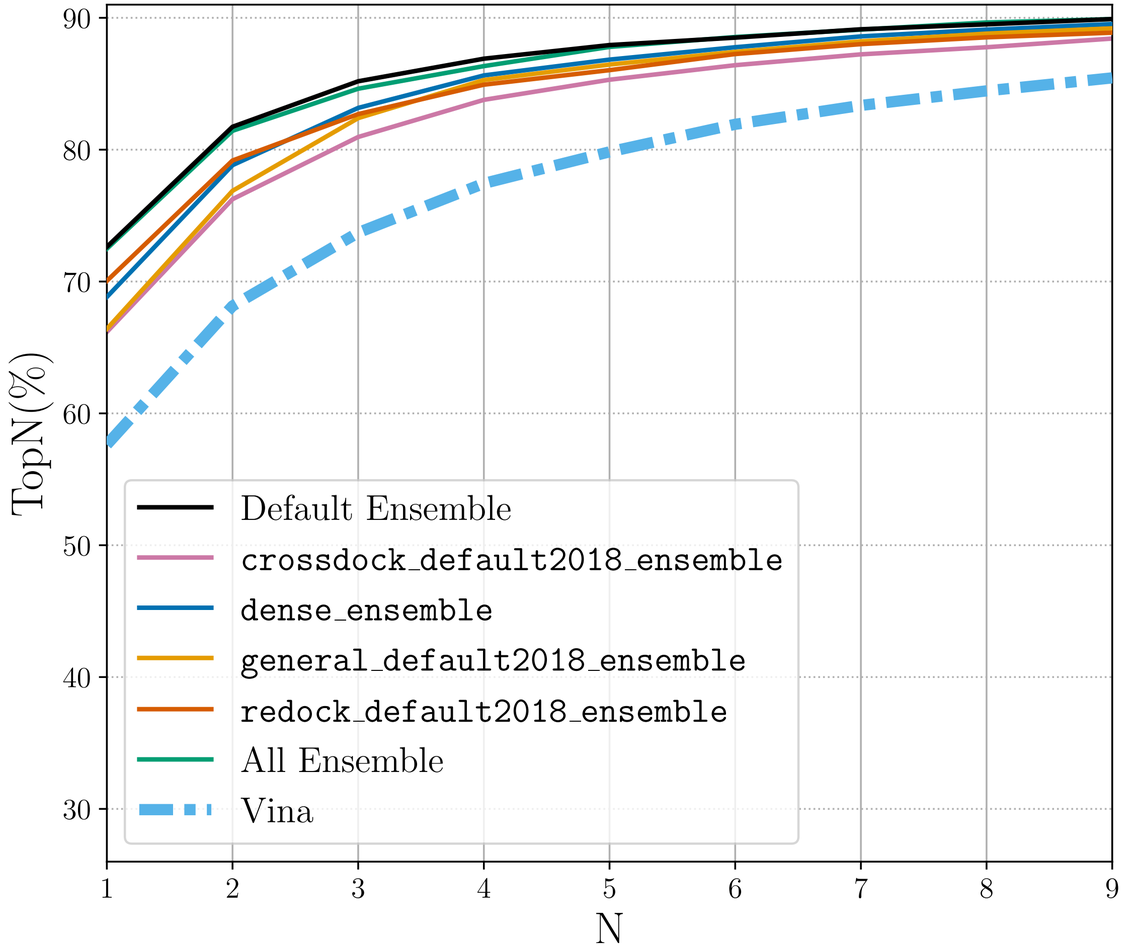


Redocking

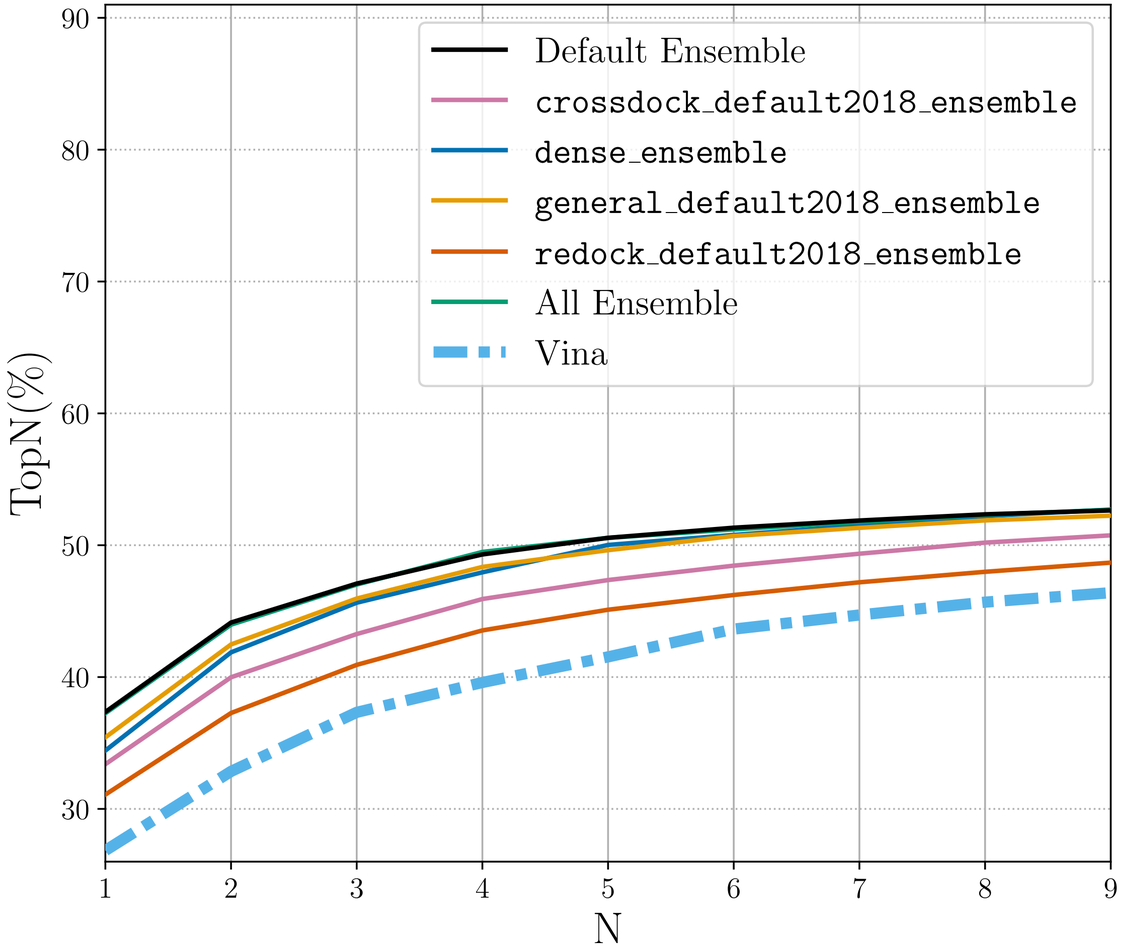


Crossdocking

Default CNN Ensemble



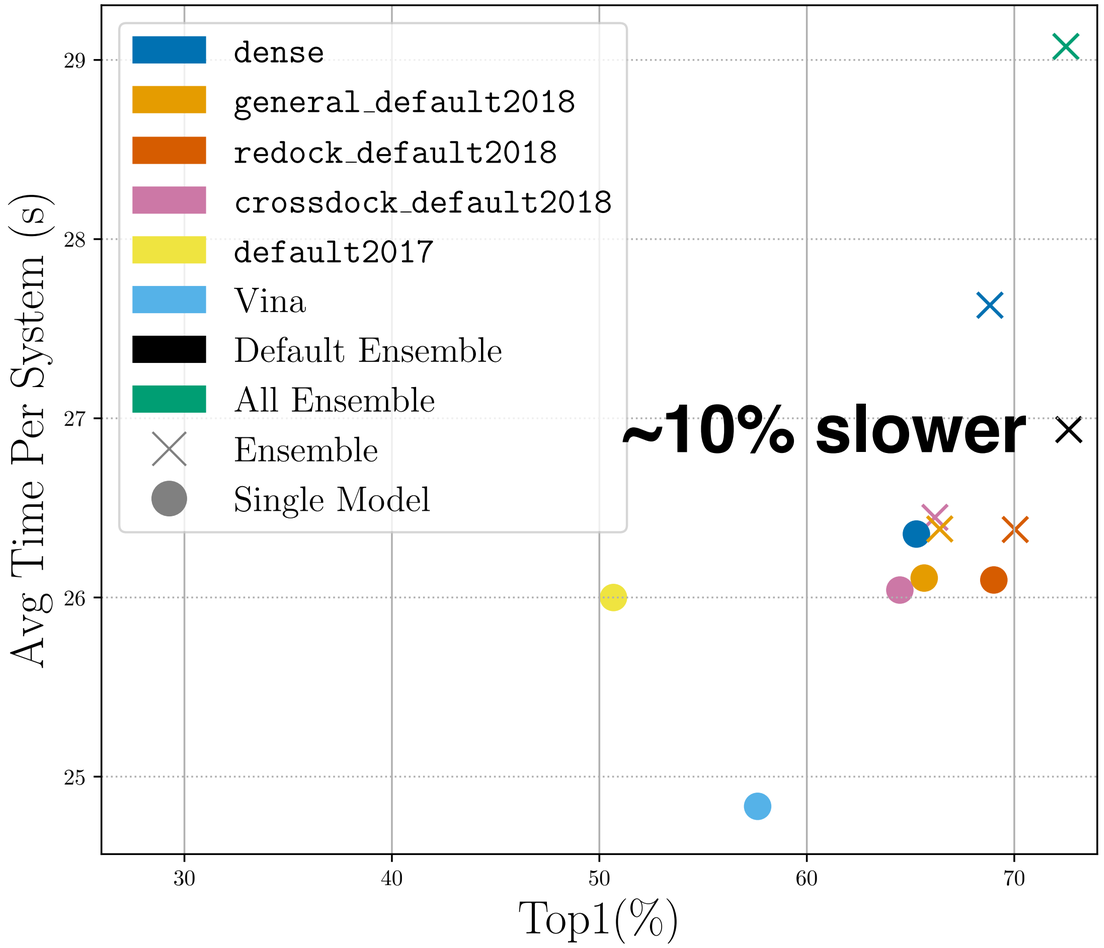
Redocking



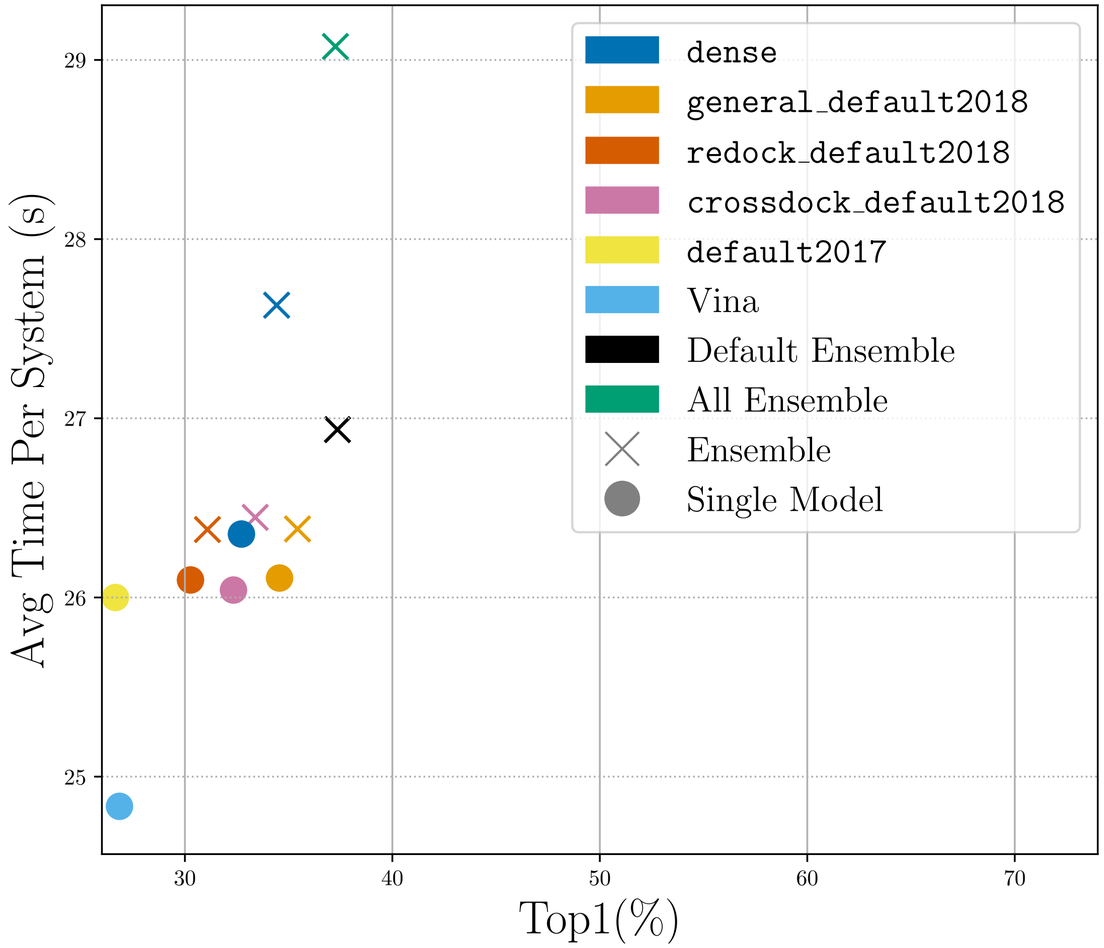
Crossdocking

Default CNN Ensemble

GPU Times



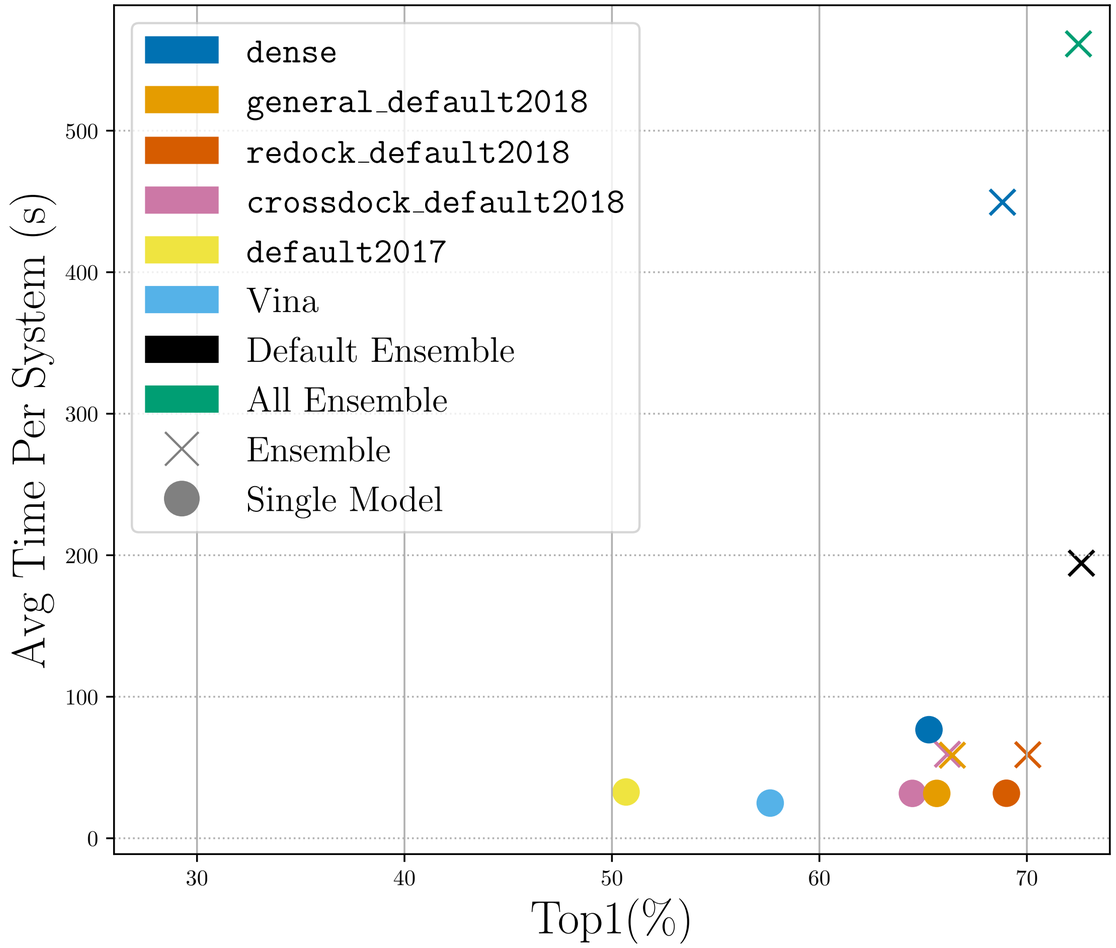
Redocking



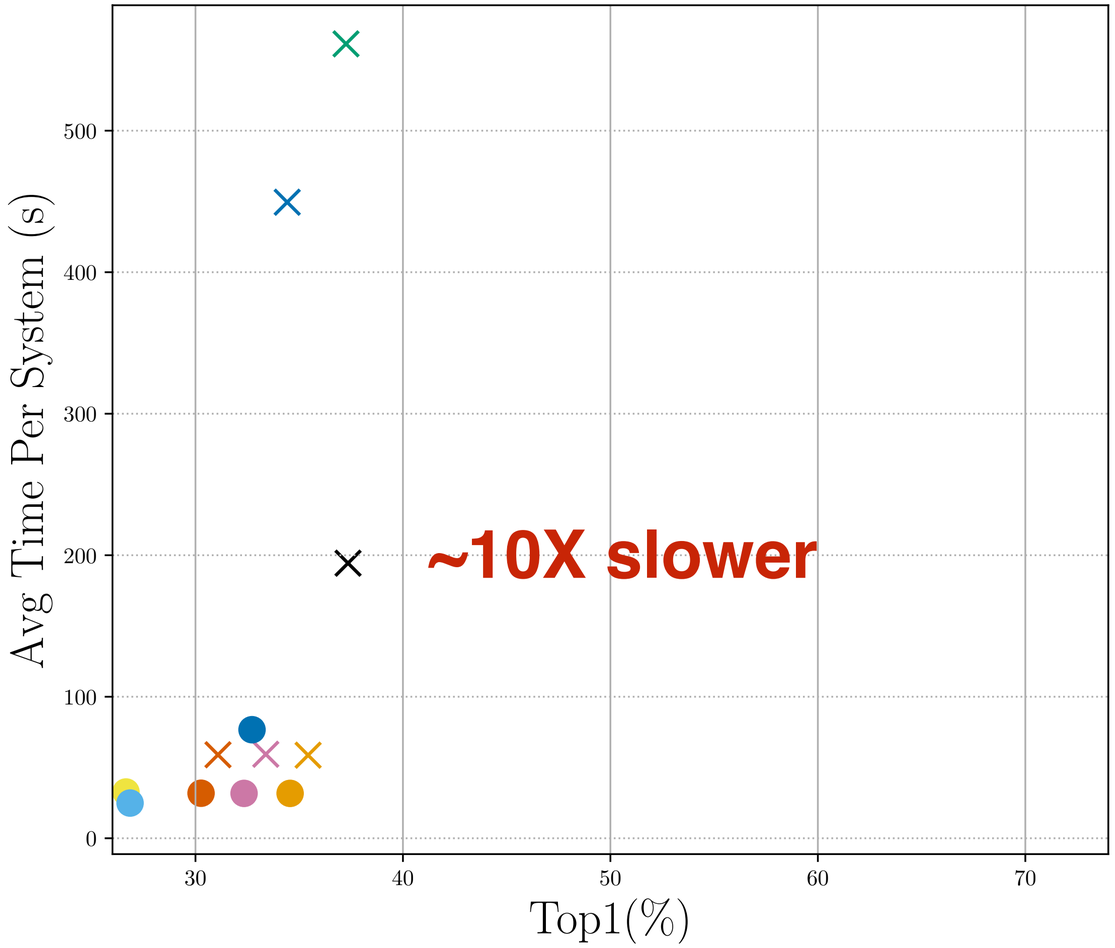
Crossdocking

Default CNN Ensemble

CPU Times

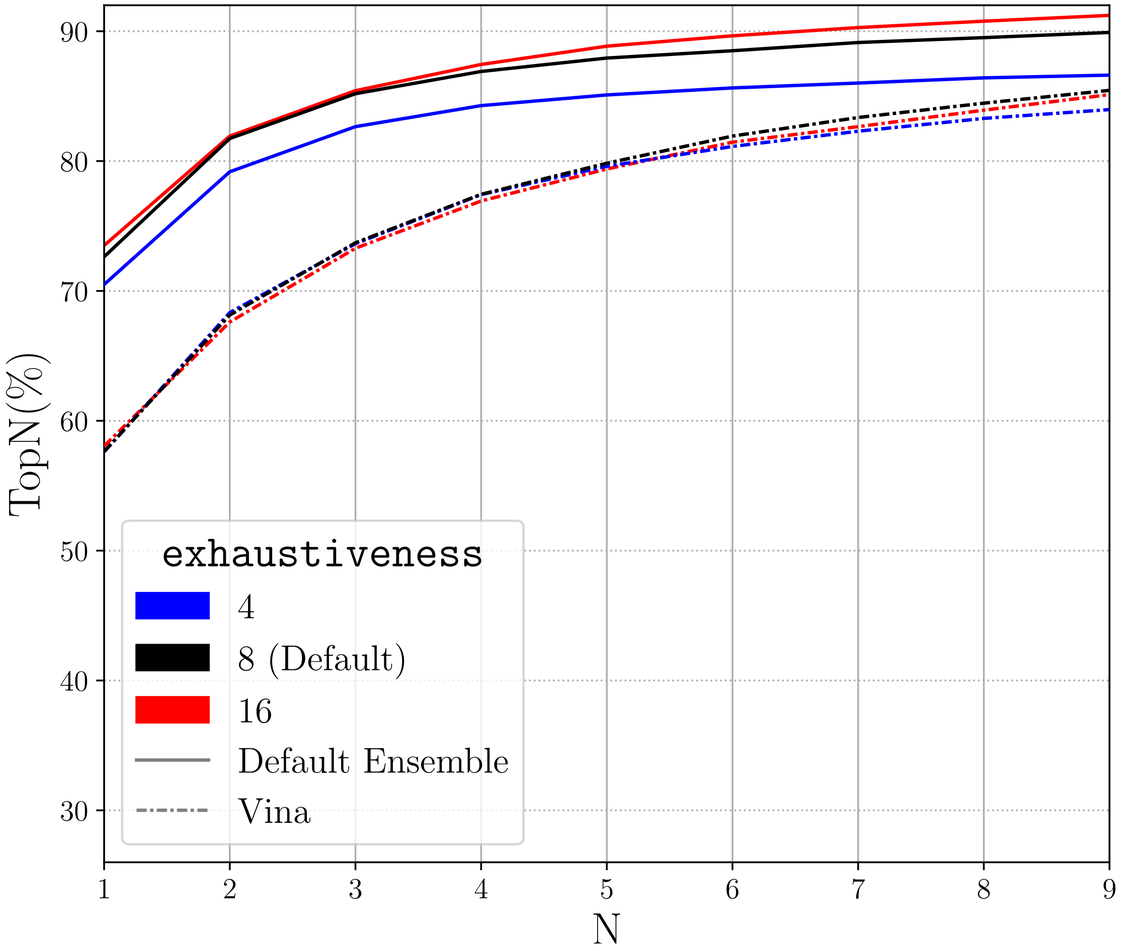


Redocking

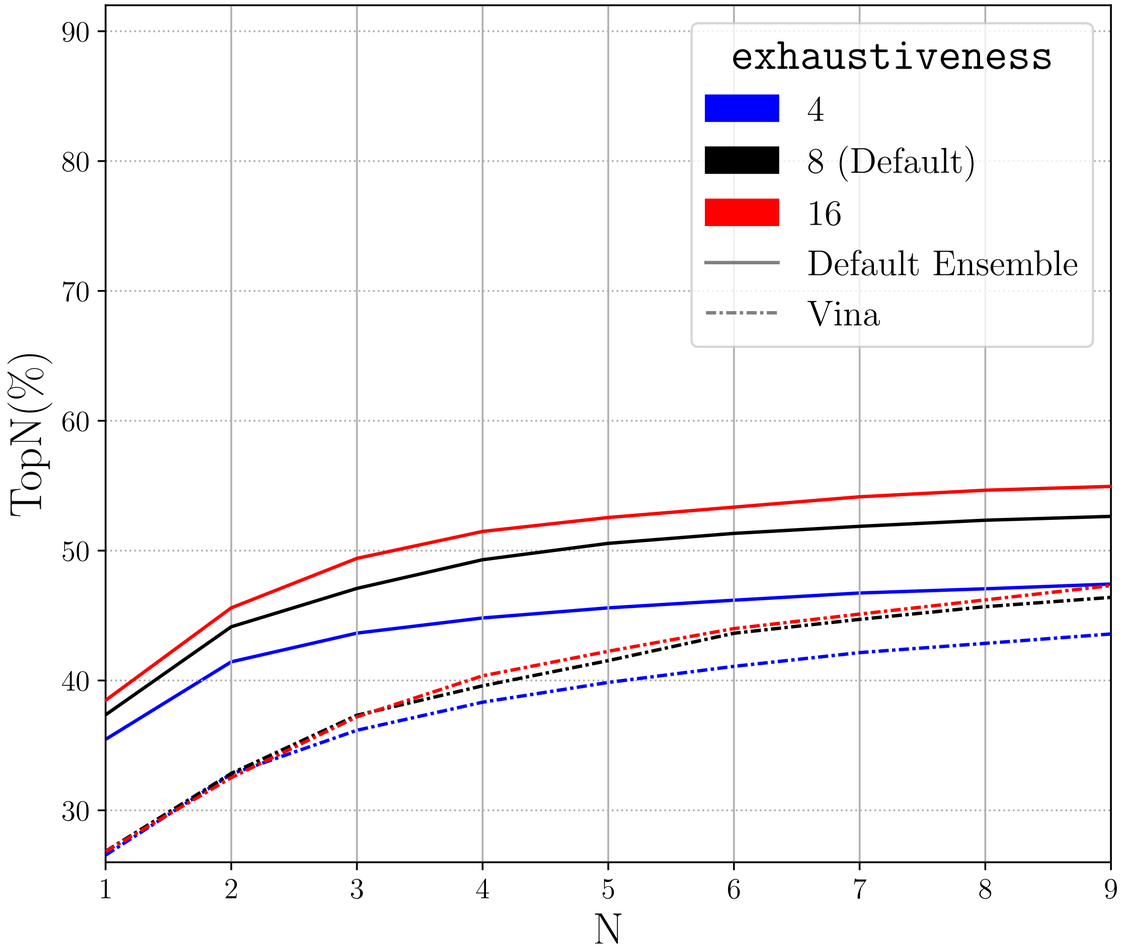


Crossdocking

Exhaustiveness



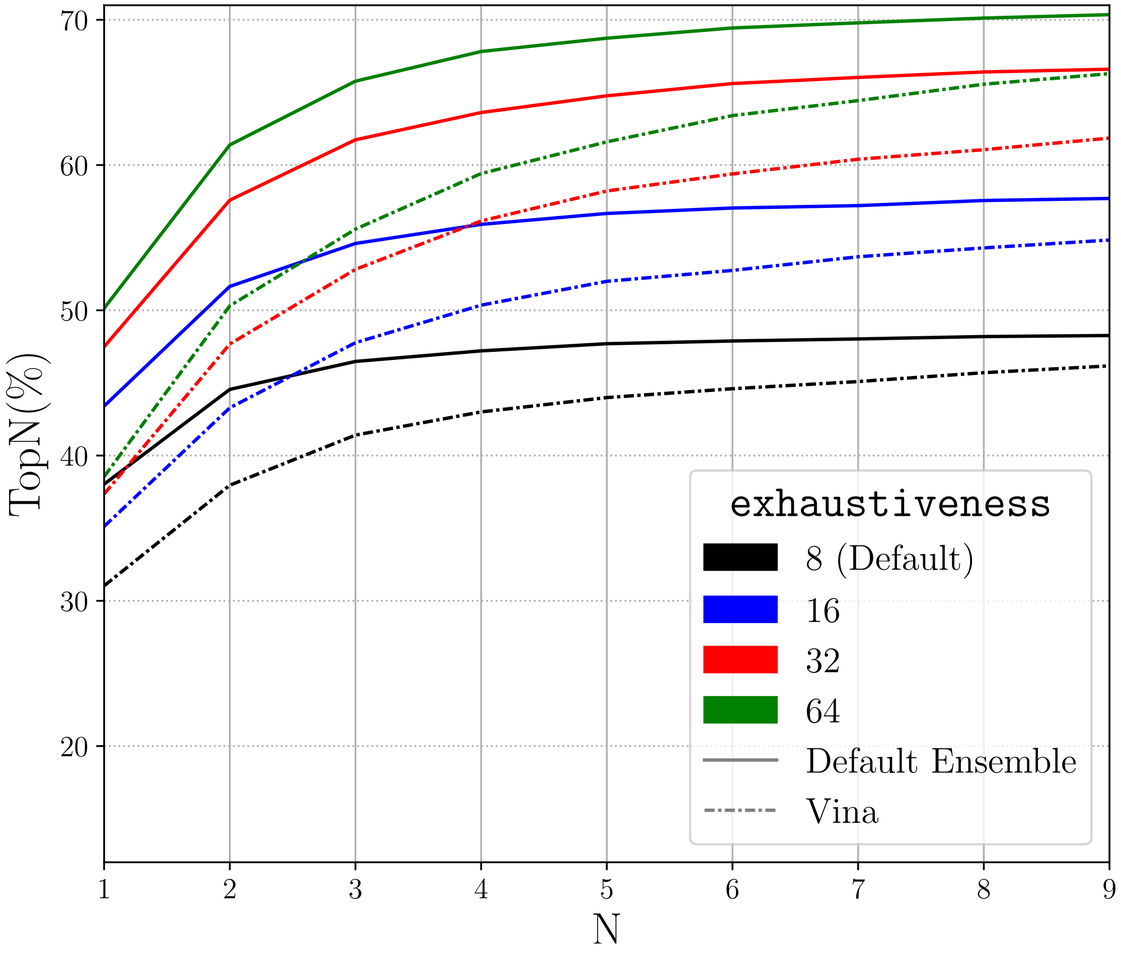
Redocking



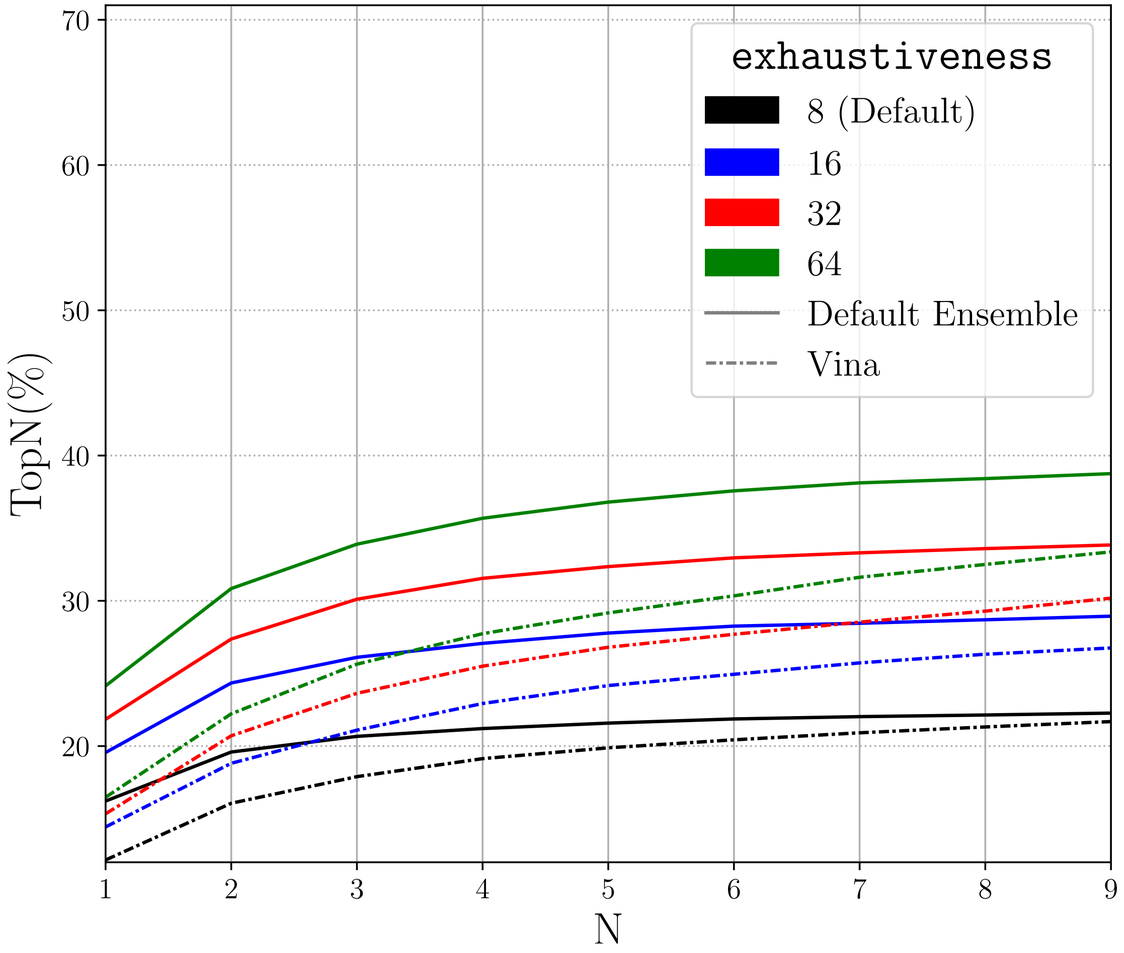
Crossdocking

Whole Protein Docking

```
gnina -r rec.pdb -l lig.pdb --autobox_ligand rec.pdb -o docked.sdf.gz
```



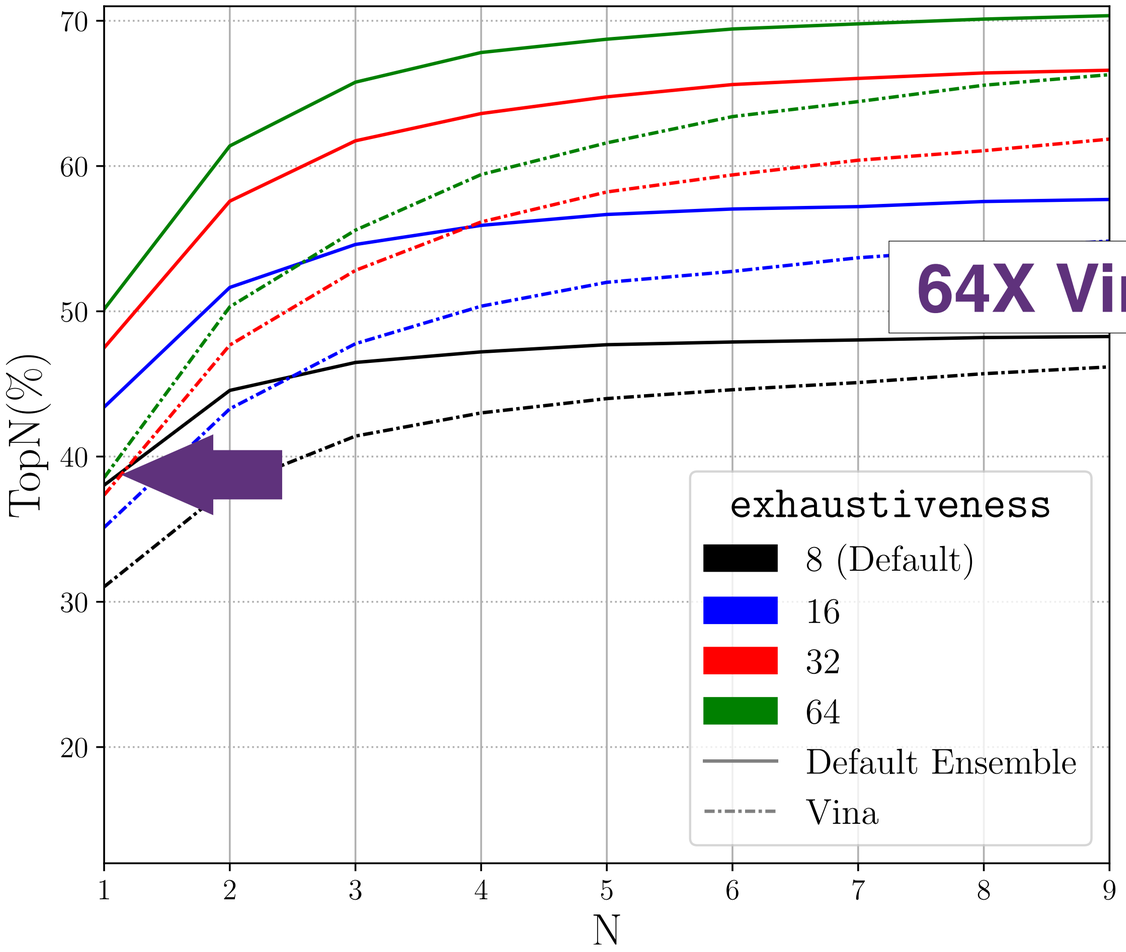
Redocking



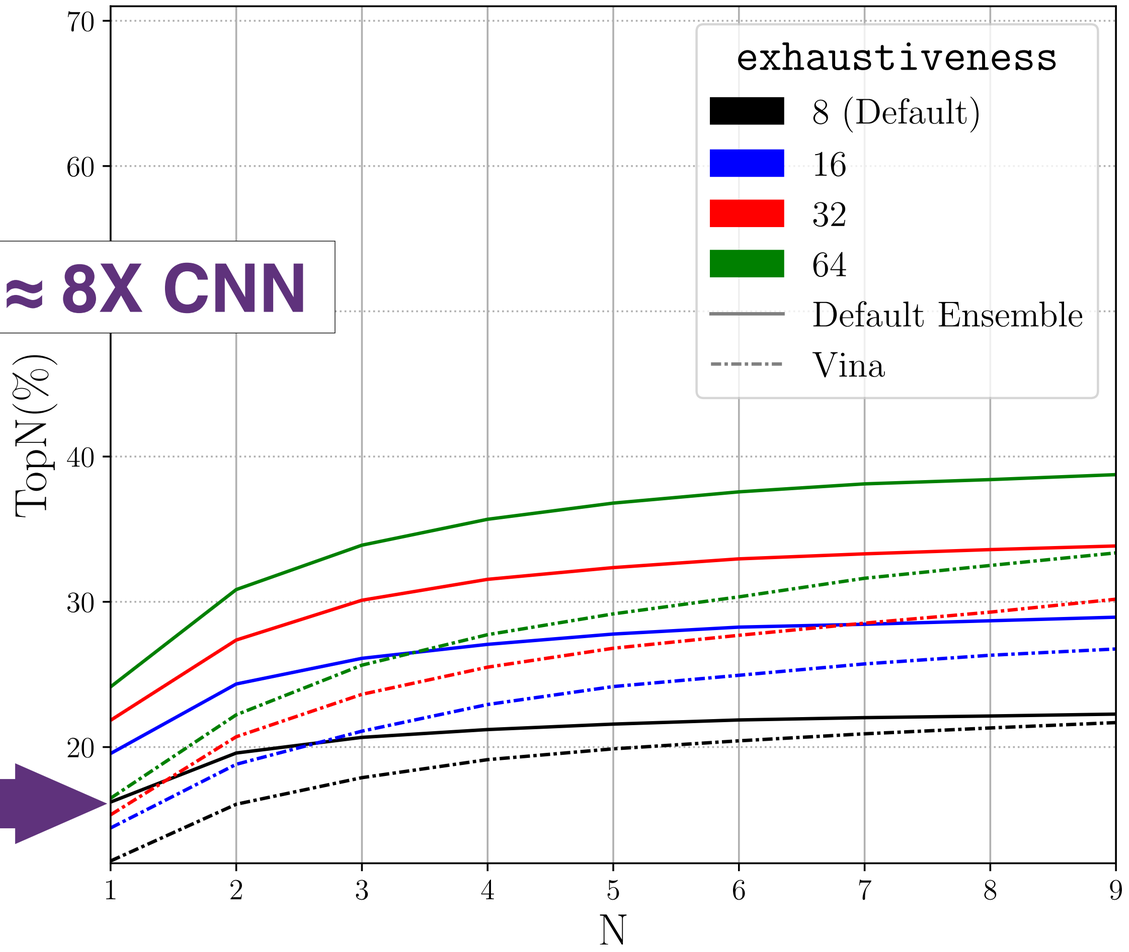
Crossdocking

Whole Protein Docking

```
gnina -r rec.pdb -l lig.pdb --autobox_ligand rec.pdb -o docked.sdf.gz
```



64X Vina ≈ 8X CNN

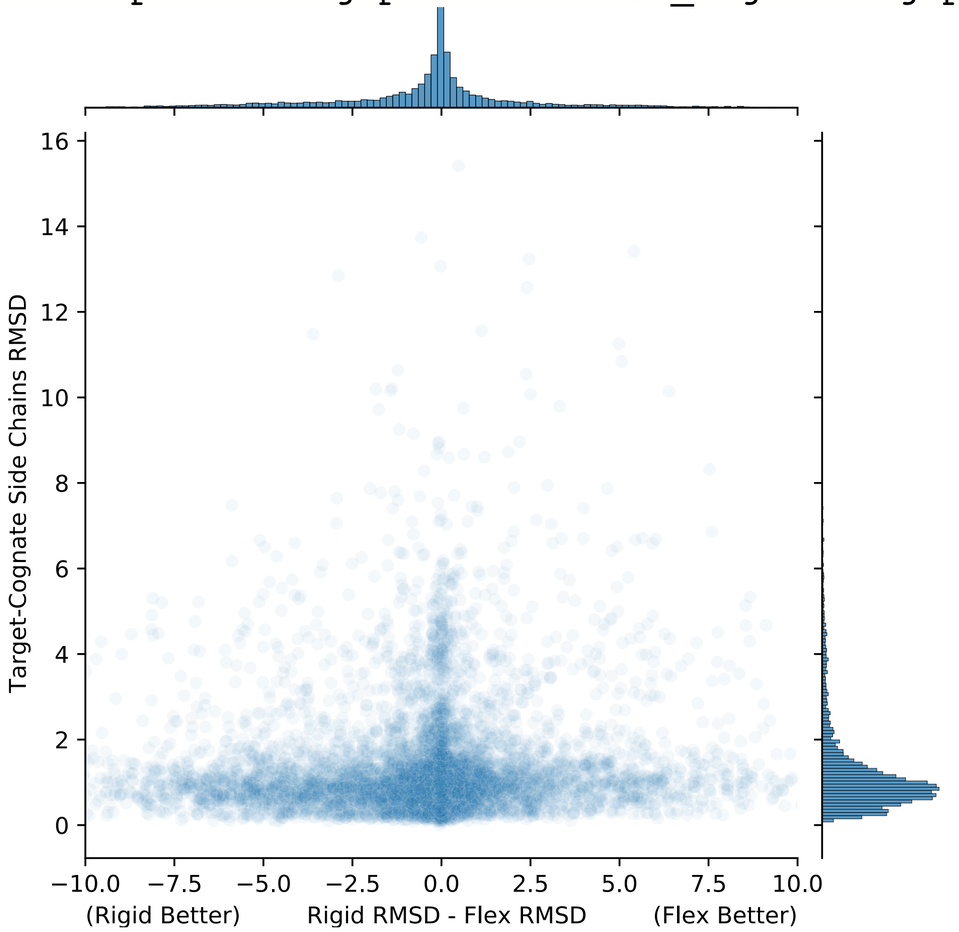


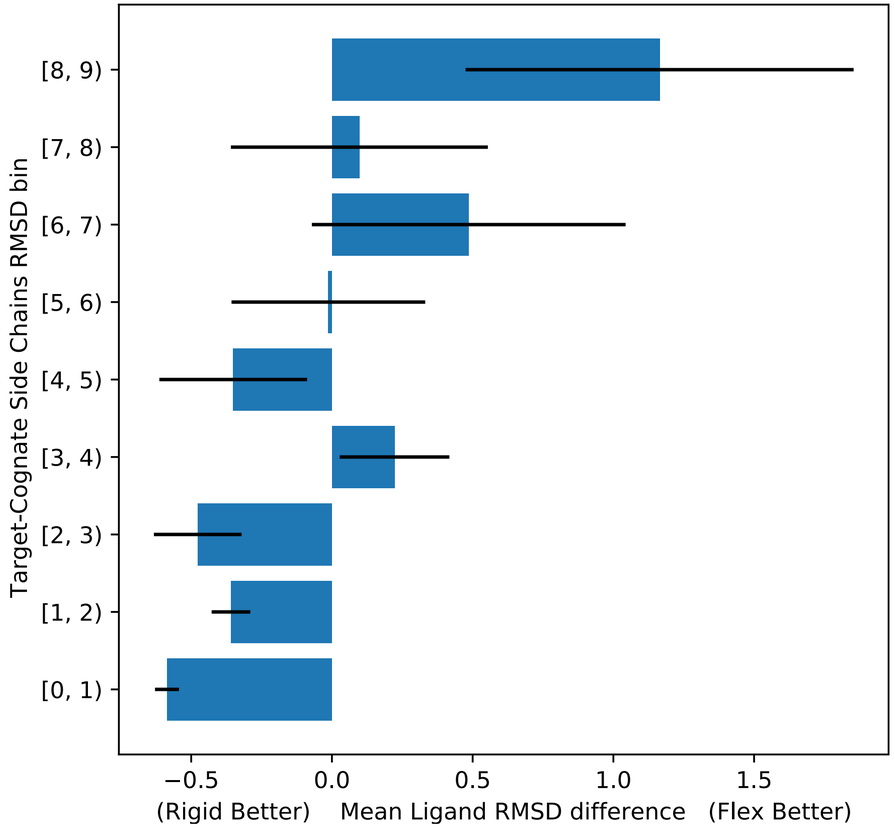
Redocking

Crossdocking

Flexible Docking

```
gnina -r rec.pdb -l lig.pdb --autobox_ligand lig.pdb -o docked.sdf.gz --flexdist 3.5 --flexdist_ligand lig.pdb
```

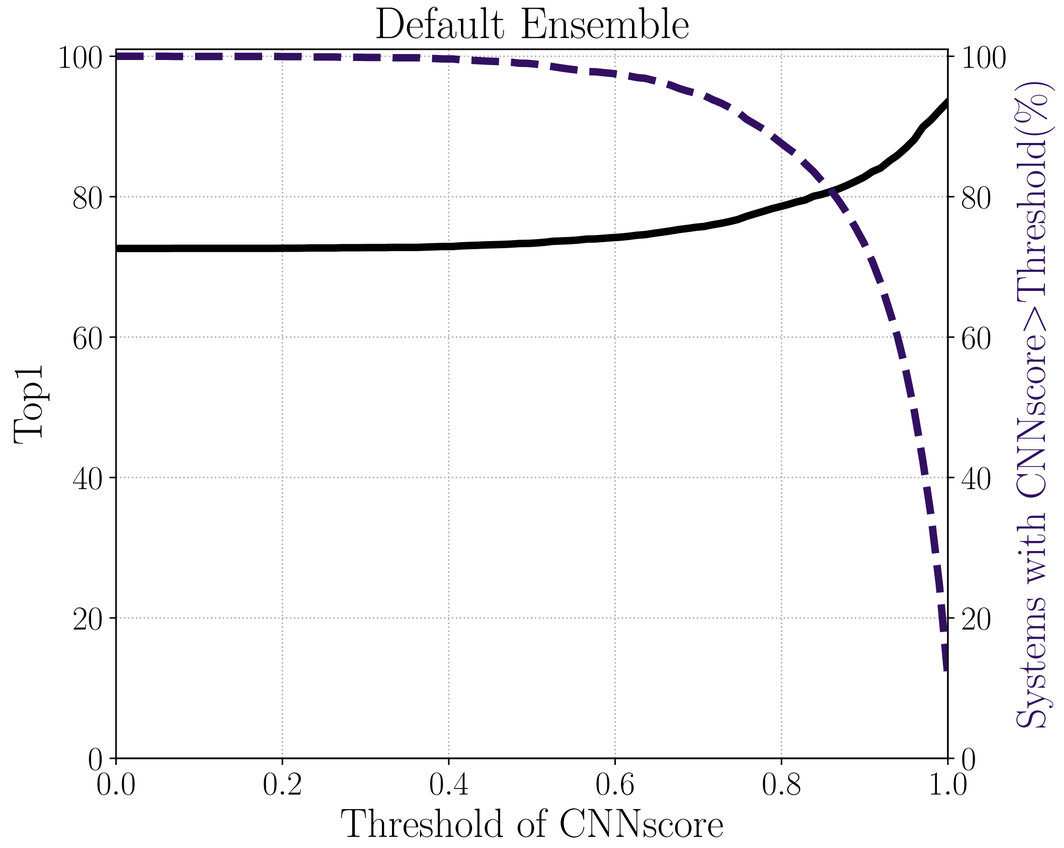




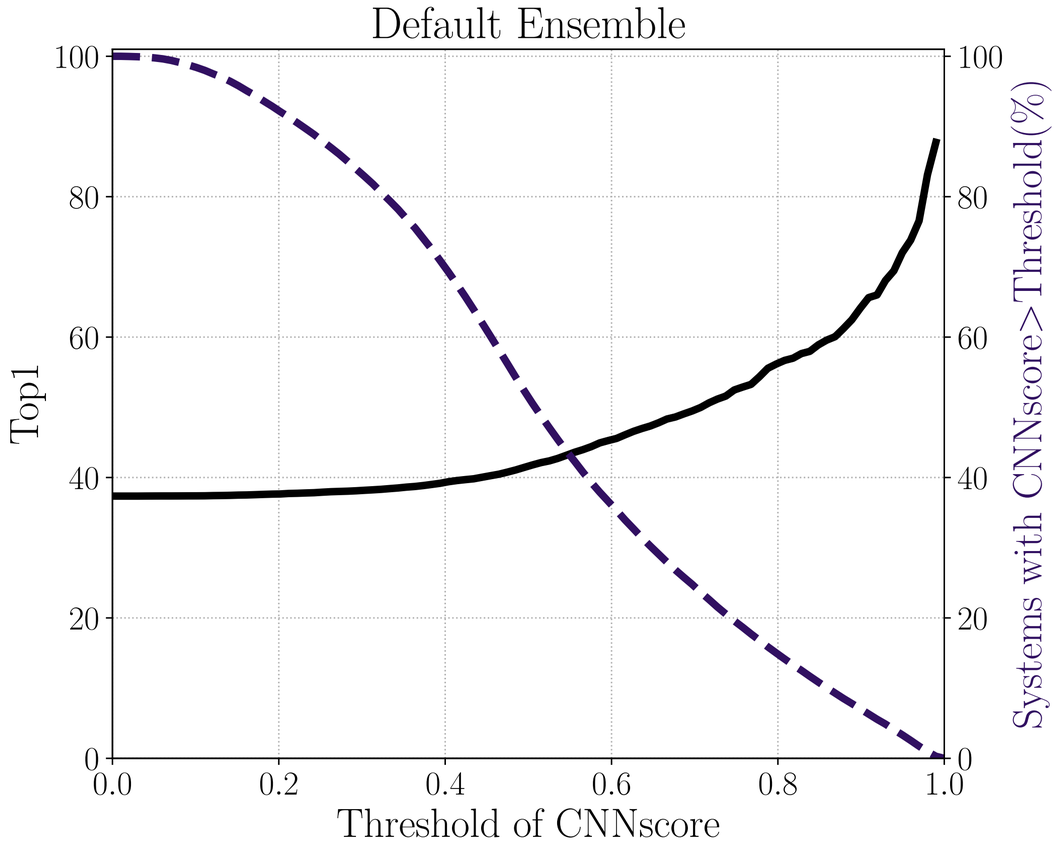
Recommendation: Use flexible docking for specific, intelligently selected residues

```
gnina -r rec.pdb -l lig.pdb --autobox_ligand lig.pdb -o docked.sdf --flexres A:84,A:88
```

CNN Scores



Redocking



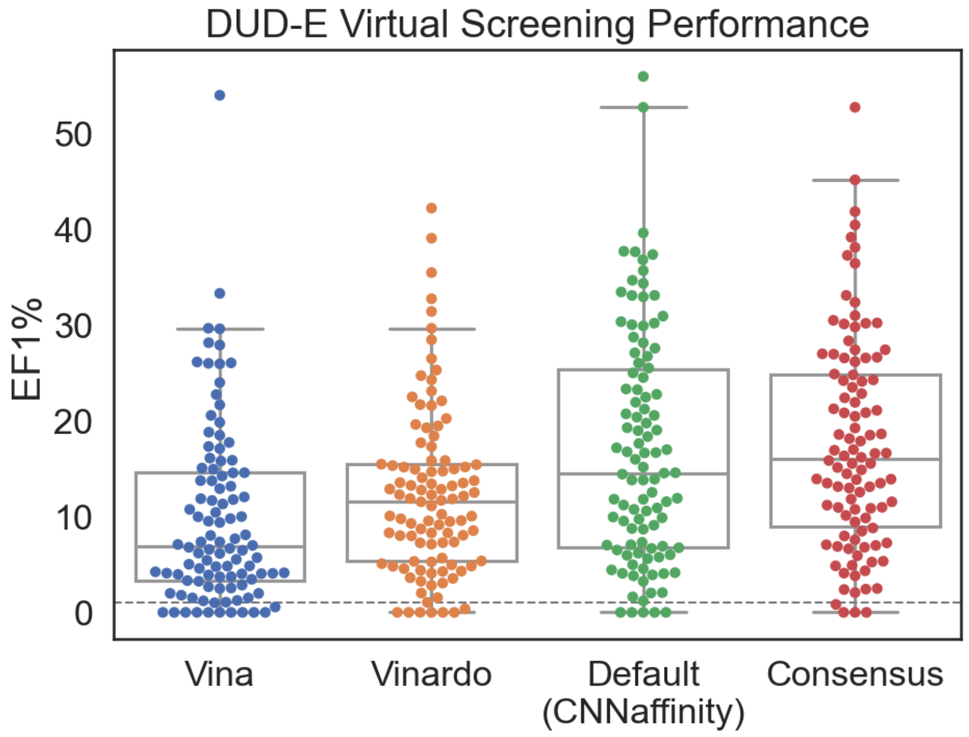
Crossdocking

molecules

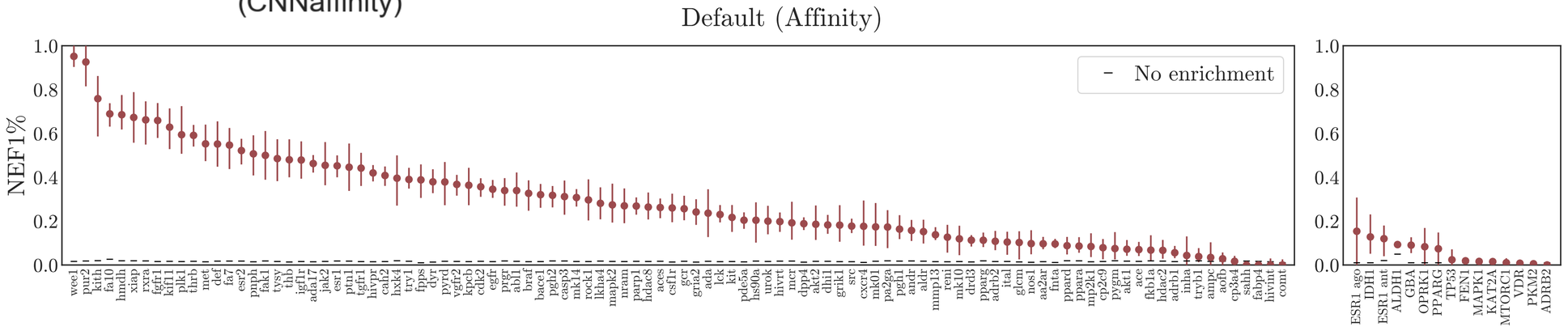
Open Access Article

Virtual Screening with GNINA 1.0

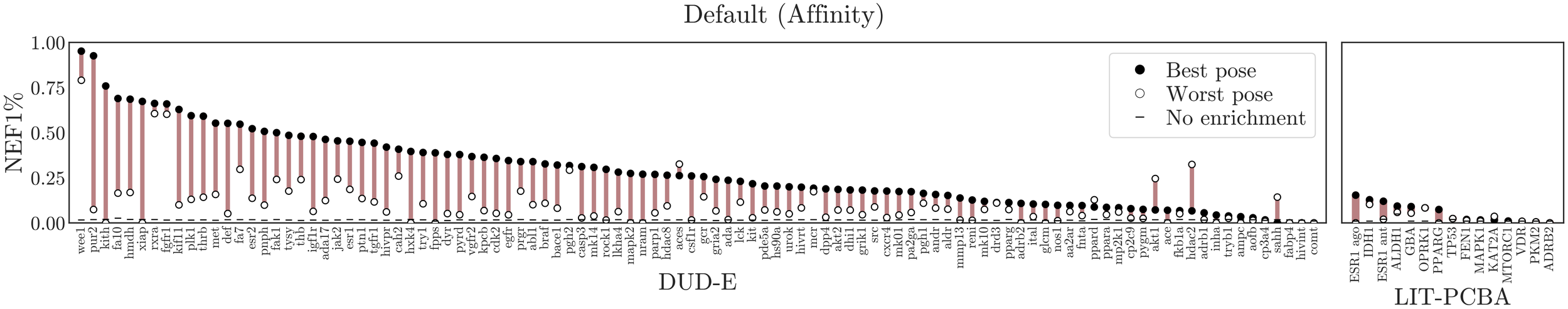
by Jocelyn Sunseri and David Ryan Koes *

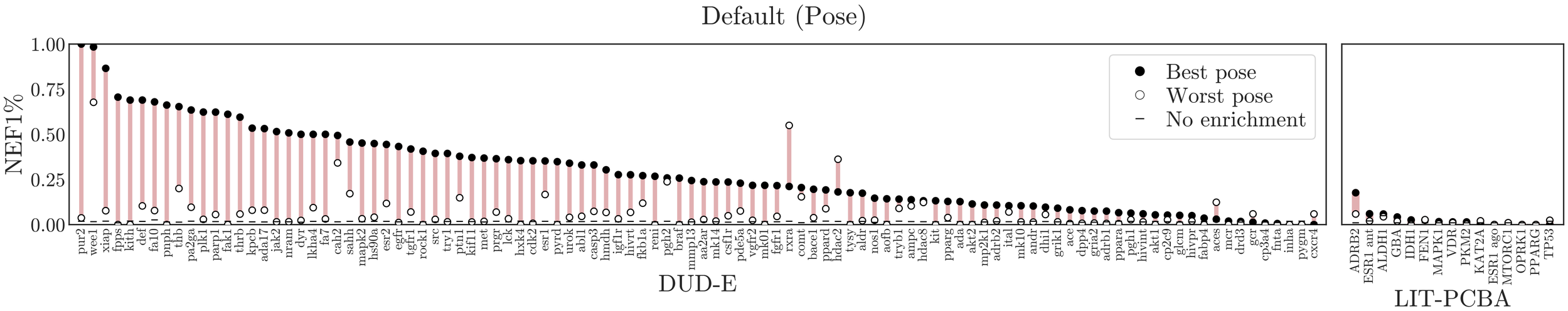


Model	DUD-E			LIT-PCBA		
	AUC	NEF1%	EF1%	AUC	NEF1%	EF1%
RFScore-4	0.683	0.0514	3.02	*0.6*	*0.013*	*1.28*
RFScore-VS	0.963	0.857	51.9	*0.542*	0.00733	0.733
Vina	0.745	0.118	7.05	*0.581*	*0.011*	1.1
Vinardo	0.764	0.187	11.4	*0.577*	0.0103	0.99
General (Affinity)	0.756	0.179	11.6	*0.579*	*0.037*	*2.06*
General (Pose)	0.702	0.156	10.3	0.498	*0.0147*	*1.3*
Dense (Affinity)	**0.795**	*0.27*	*17.7*	**0.616**	**0.037**	**2.58**
Dense (Pose)	*0.767*	**0.313**	**20.4**	0.514	*0.0238*	*1.81*
Default (Affinity)	*0.795*	*0.258*	*15.6*	*0.611*	*0.0238*	*1.88*
Default (Pose)	0.744	*0.241*	*15.8*	0.512	*0.0147*	*1.47*

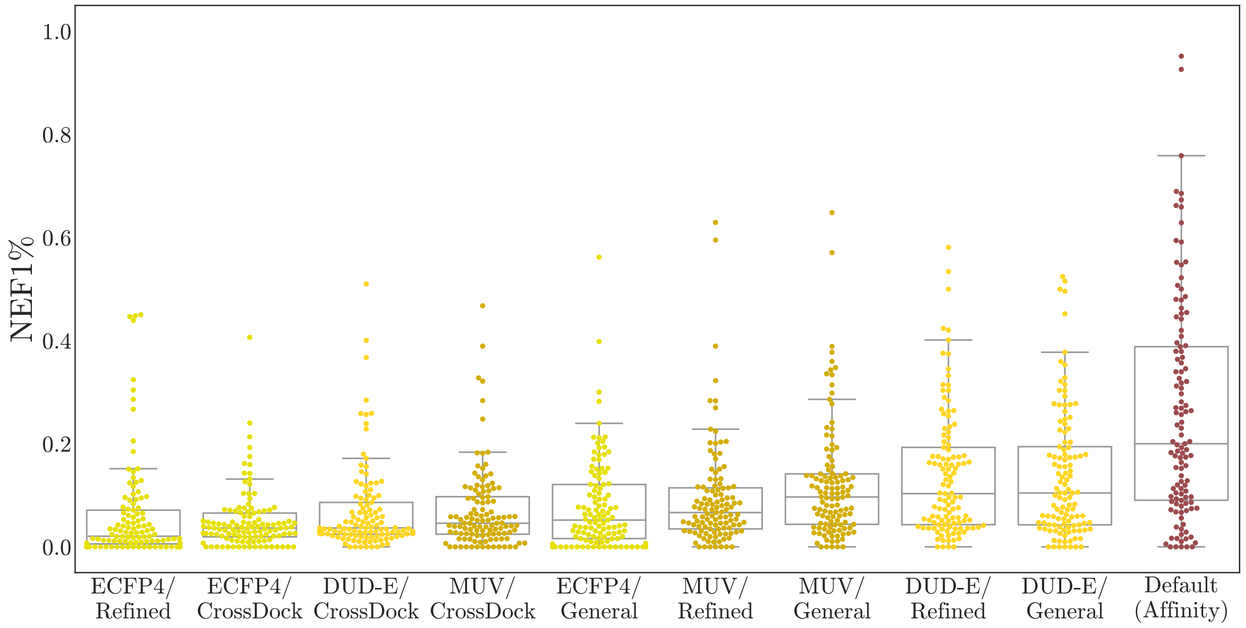


Pose Sensitivity

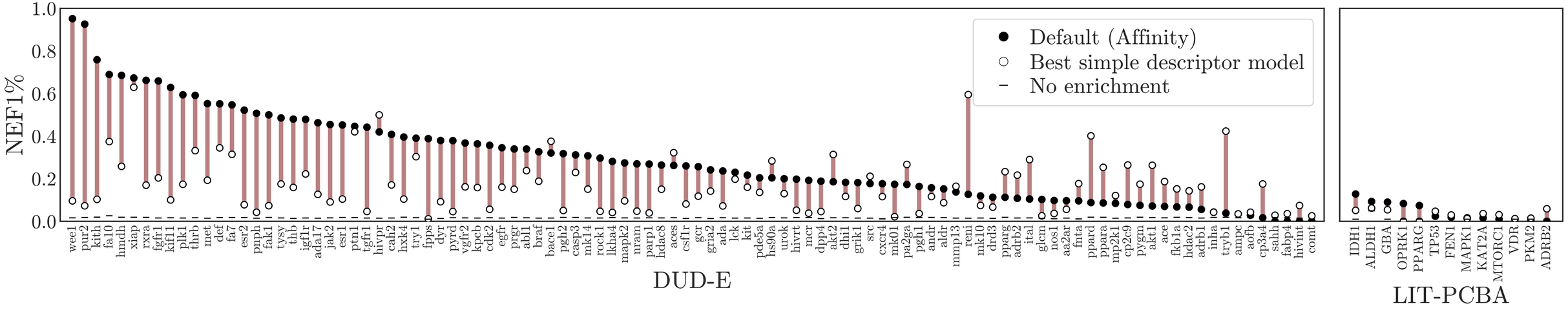




Simple Descriptors



DUD-E	MUV
molecular weight	
number of hydrogen bond acceptors	number of hydrogen bond acceptors
number of hydrogen bond donors	number of hydrogen bond donors
number of rotatable bonds	
logP	logP
net charge	
	number of all atoms
	number of heavy atoms
	number of boron atoms
	number of bromine atoms
	number of carbon atoms
	number of chlorine atoms
	number of fluorine atoms
	number of iodine atoms
	number of nitrogen atoms
	number of oxygen atoms
	number of phosphorus atoms
	number of sulfur atoms
	number of chiral centers
	number of ring systems
6 features	17 features



Using GNINA

Colab Notebook

gnina.ipynb - Colaboratory

colab.research.google.com/drive/1QYo5QLUE80N_G28PlpYs6OKGddhhd931?usp=sharing#scrollTo=sMTknhig...

gnina.ipynb

File Edit View Insert Runtime Tools Help All changes saved

Comment Share

+ Code + Text

RAM Disk

```
!./gnina -r rec.pdb -l lig.pdb --autobox_ligand lig.pdb -o docked.sdf --seed 0
```

```
                 _
                (_)
   __ _ _ __  _ _ __   __ _
  / _` | '_ \| | '_ \ / _` |
 | (_| | | | | | | | | (_| |
  \__, |_| |_|_|_| |_|\__,_|
   __/ |
  |___/

gnina v1.0.1 HEAD:aa41230   Built Mar 23 2021.
gnina is based on smina and AutoDock Vina.
Please cite appropriately.

Commandline: ./gnina -r rec.pdb -l lig.pdb --autobox_ligand lig.pdb -o docked.sdf --seed 0
================================
*** Open Babel Warning  in PerceiveBondOrders
  Failed to kekulize aromatic bonds in OBMol::PerceiveBondOrders

Using random seed: 0

0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |  affinity  |     CNN      |   CNN
     | (kcal/mol) | pose score | affinity
-----+------------+------------+----------
    1       -8.50       0.8963      6.783
    2       -8.08       0.6049      6.600
    3       -8.31       0.4536      6.456
    4       -6.59       0.2824      6.080
    5       -6.75       0.2072      5.836
```

48s completed at 12:16 AM

gnina.ipynb - Colaboratory

colab.research.google.com/drive/1QYo5QLUE80N_G28PlpYs6OKGddhhd931?usp=sharing#scrollTo=WctyMpd...

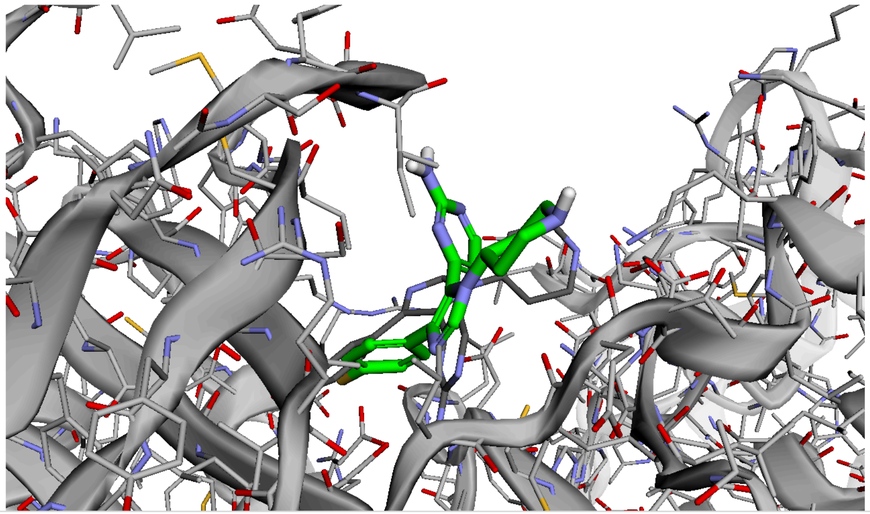
gnina.ipynb

File Edit View Insert Runtime Tools Help

+ Code + Text

RAM Disk

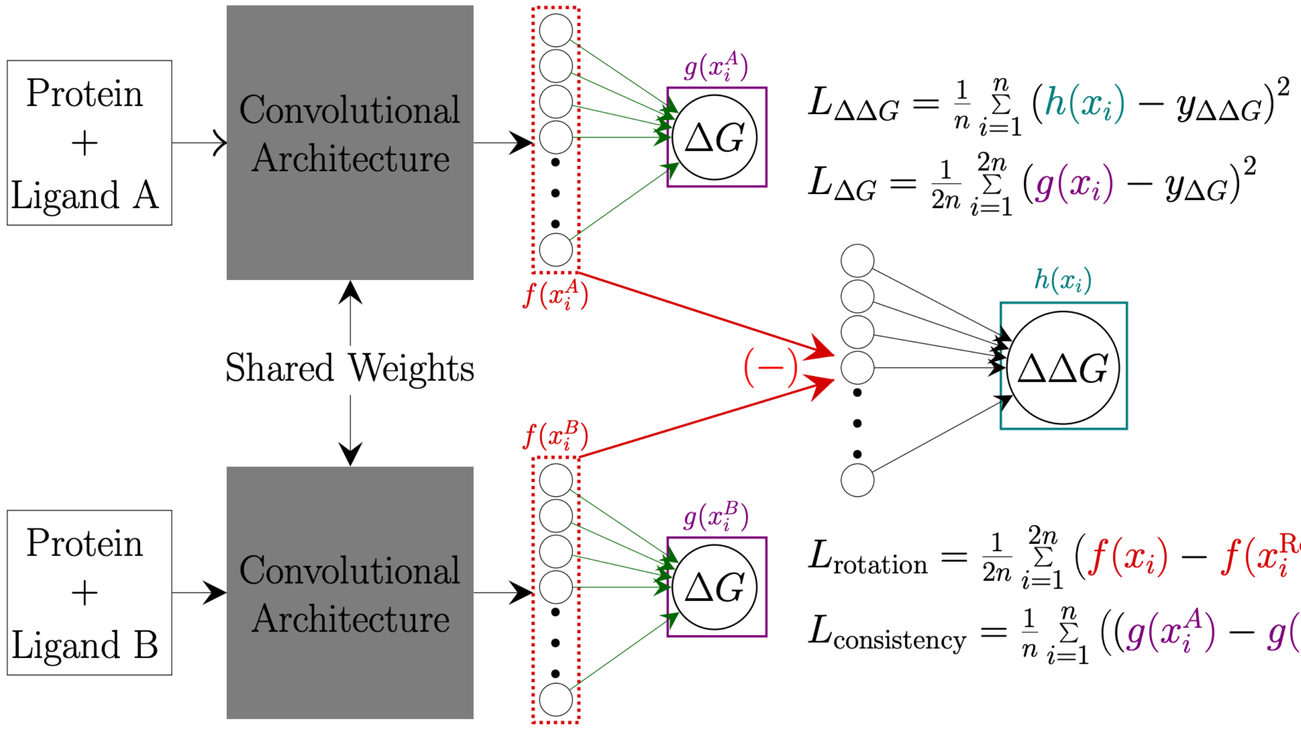
```
import py3Dmol
v = py3Dmol.view()
v.addModel(open('rec.pdb').read())
v.setStyle({'cartoon':{},'stick':{'radius':.1}})
v.addModel(open('lig.pdb').read())
v.setStyle({'model':1},{'stick':{'colorscheme':'dimgrayCarbon','radius':.125}})
v.addModelsAsFrames(open('docked.sdf').read())
v.setStyle({'model':2},{'stick':{'colorscheme':'greenCarbon'}})
v.animate({'interval':1000})
v.zoomTo({'model':1})
v.rotate(90)
```



48s completed at 12:16 AM

Improving $\Delta\Delta G$ predictions with a multi-task convolutional Siamese network

Andrew T. McNutt and David Ryan Koes*

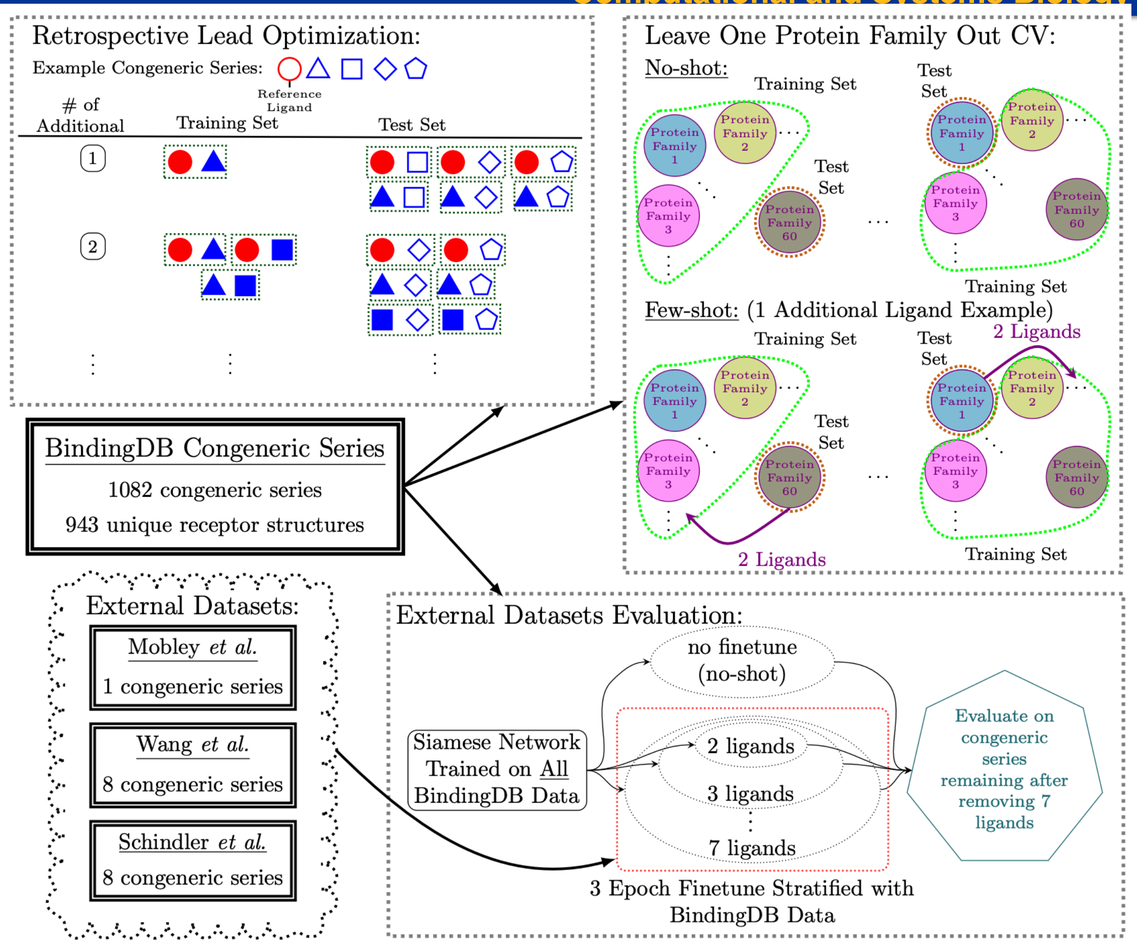


$$L_{\Delta\Delta G} = \frac{1}{n}\sum_{i=1}^{n}\left(h(x_i) - y_{\Delta\Delta G}\right)^2$$

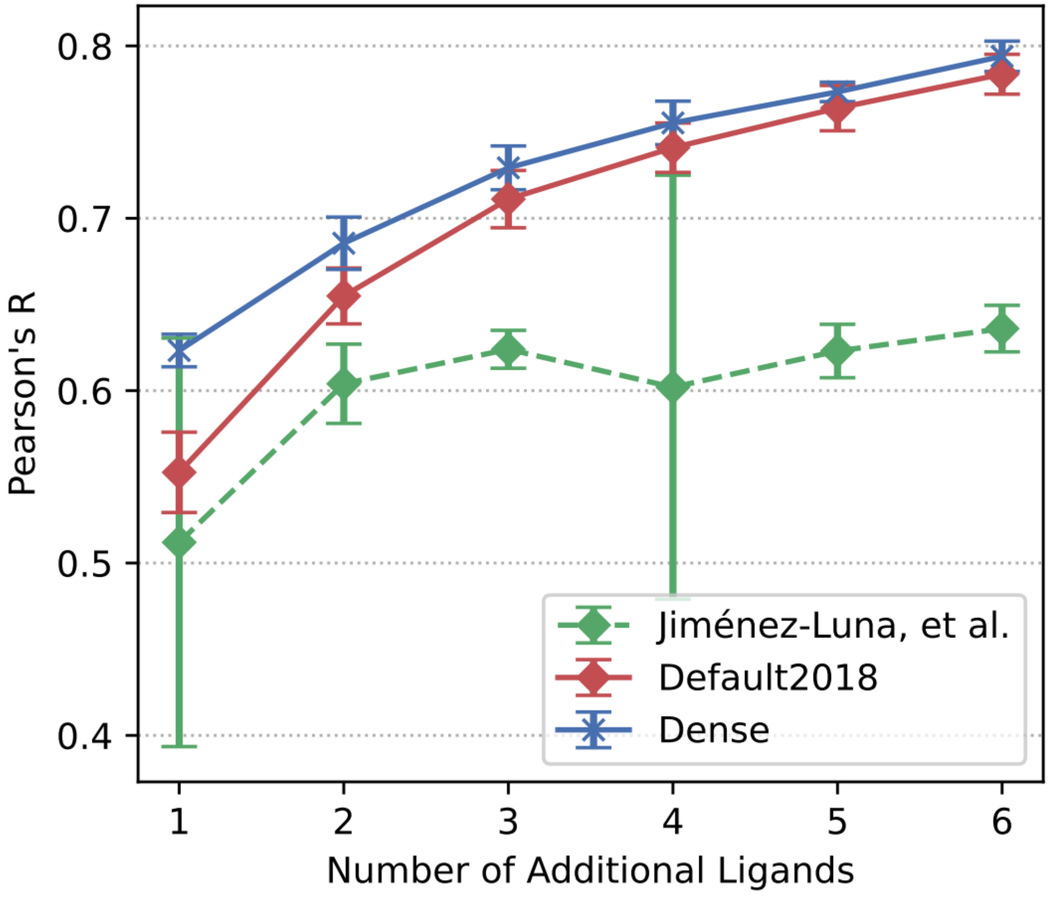
$$L_{\Delta G} = \frac{1}{2n}\sum_{i=1}^{2n}\left(g(x_i) - y_{\Delta G}\right)^2$$

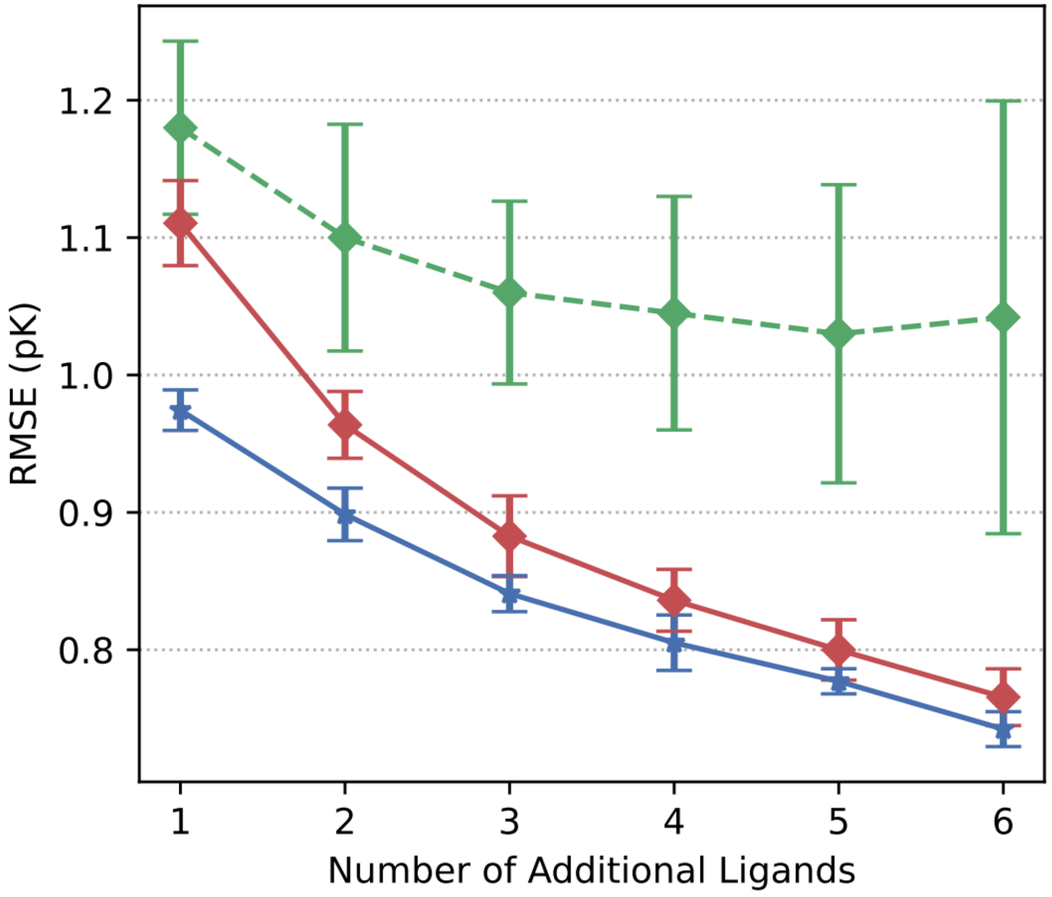
$$L_{\text{rotation}} = \frac{1}{2n}\sum_{i=1}^{2n}\left(f(x_i) - f(x_i^{\text{Rotated}})\right)^2$$

$$L_{\text{consistency}} = \frac{1}{n}\sum_{i=1}^{n}\left((g(x_i^A) - g(x_i^B)) - h(x_i)\right)^2$$

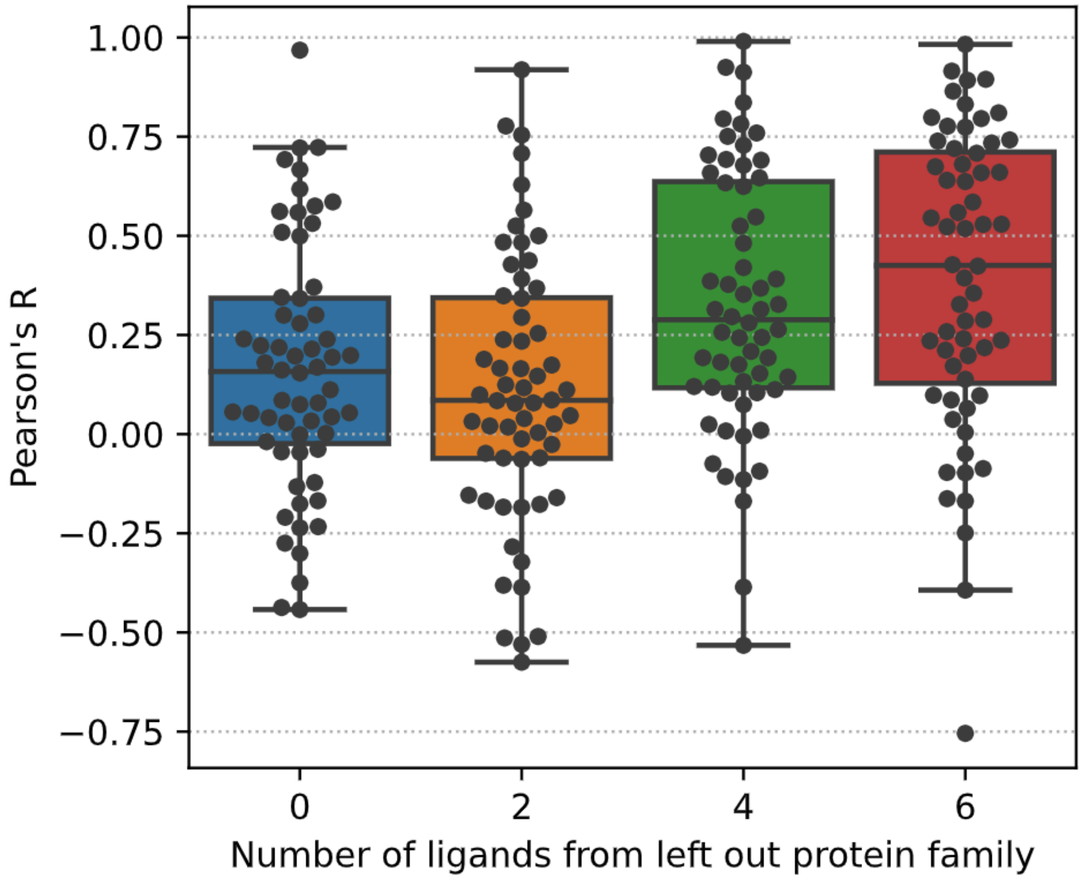


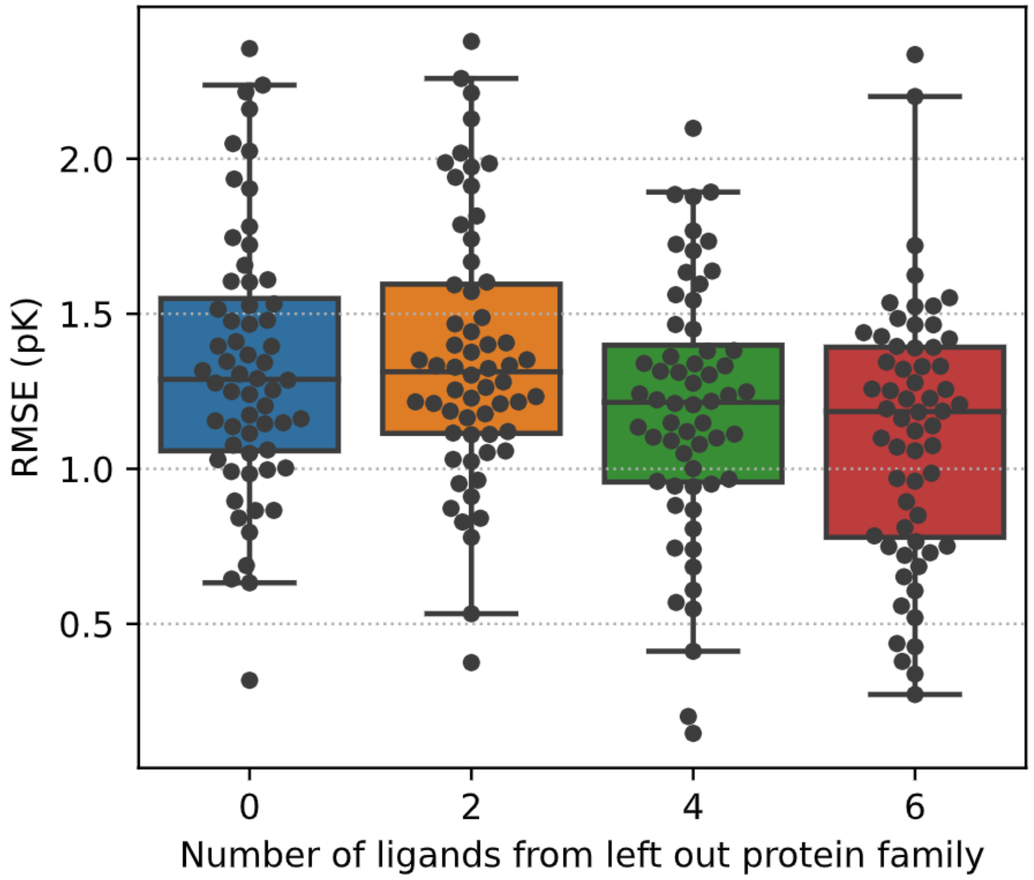
ΔΔG Results


0.8
0.7
0.6
0.5
0.4
Pearson's R
1
2
3
4
5
6
Number of Additional Ligands
Jiménez-Luna, et al.
Default2018
Dense


1.2
1.1
1.0
0.9
0.8
RMSE (pK)
1
2
3
4
5
6
Number of Additional Ligands

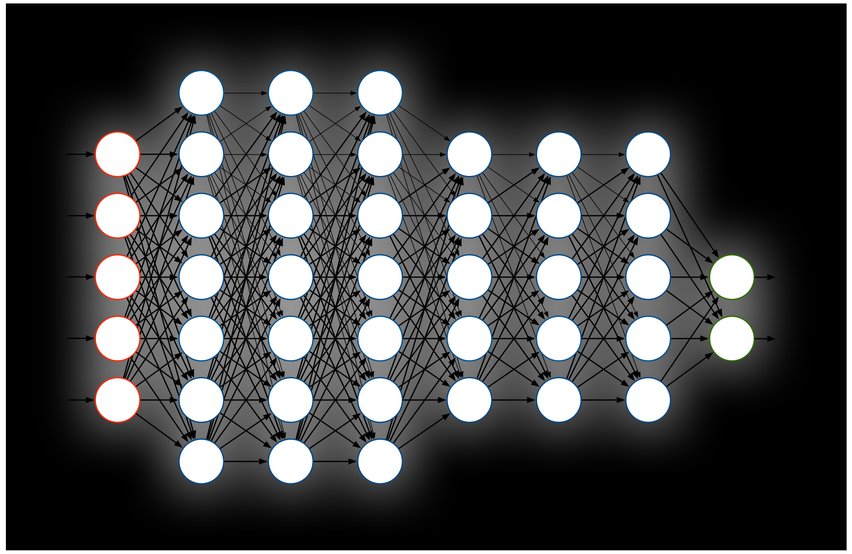
ΔΔG Results


Pearson's R
1.00
0.75
0.50
0.25
0.00
−0.25
−0.50
−0.75
0
2
4
6
Number of ligands from left out protein family

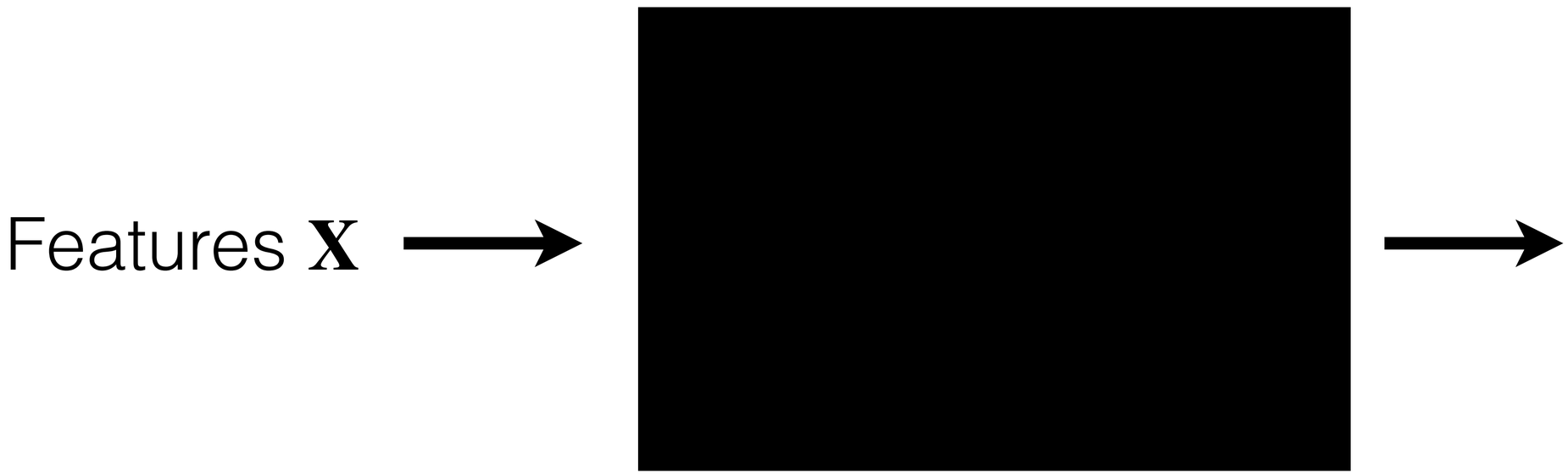

RMSE (pK)
2.0
1.5
1.0
0.5
0
2
4
6
Number of ligands from left out protein family

Generative Modeling

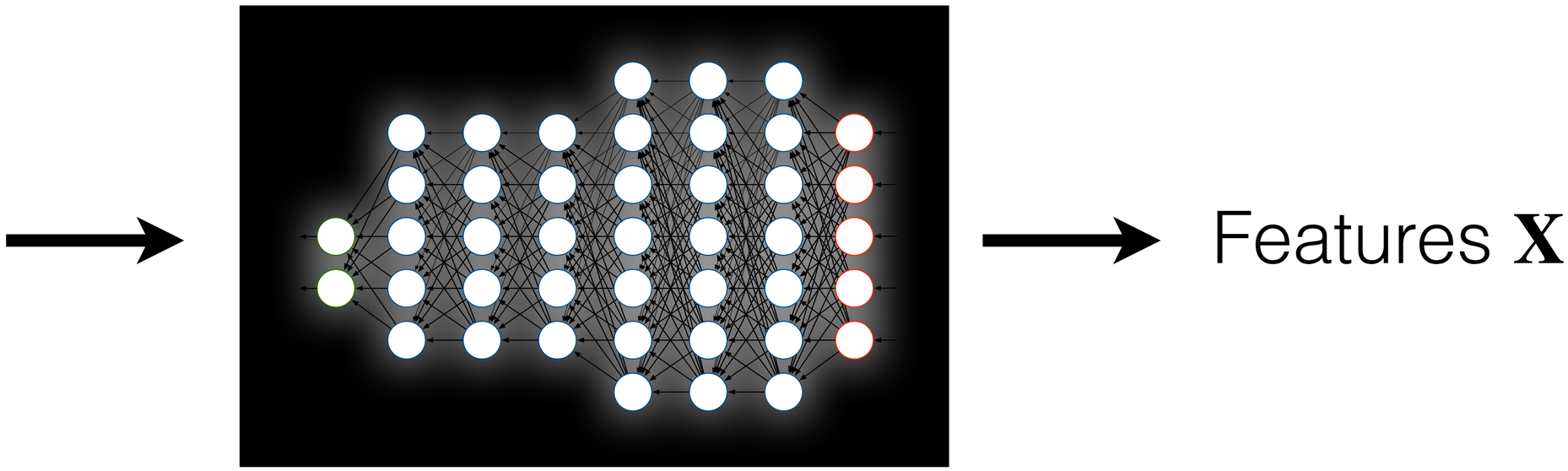
Discriminative Model

Features $\mathbf{X}$  Prediction $\mathbf{y}$

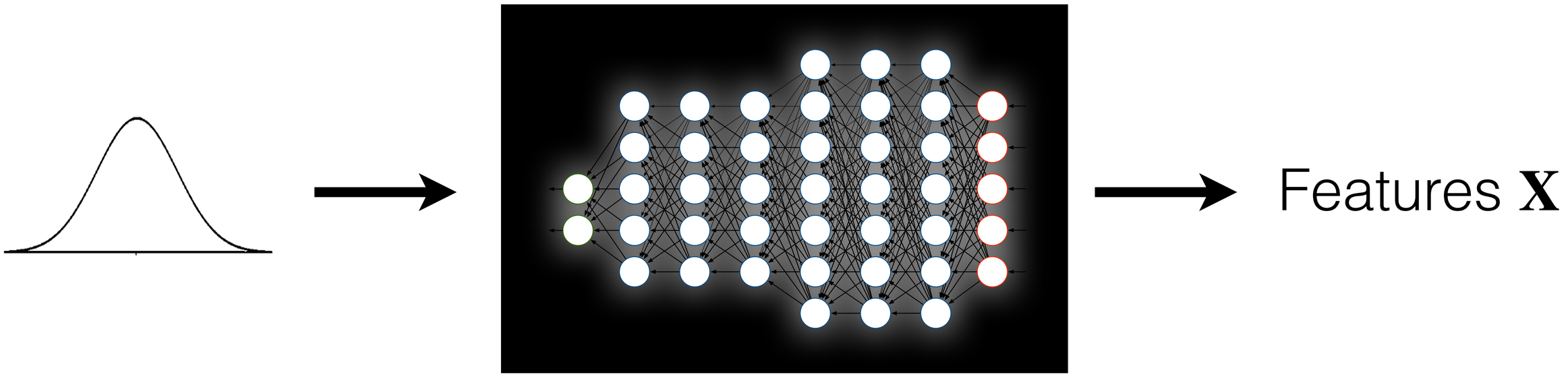
Generative Model



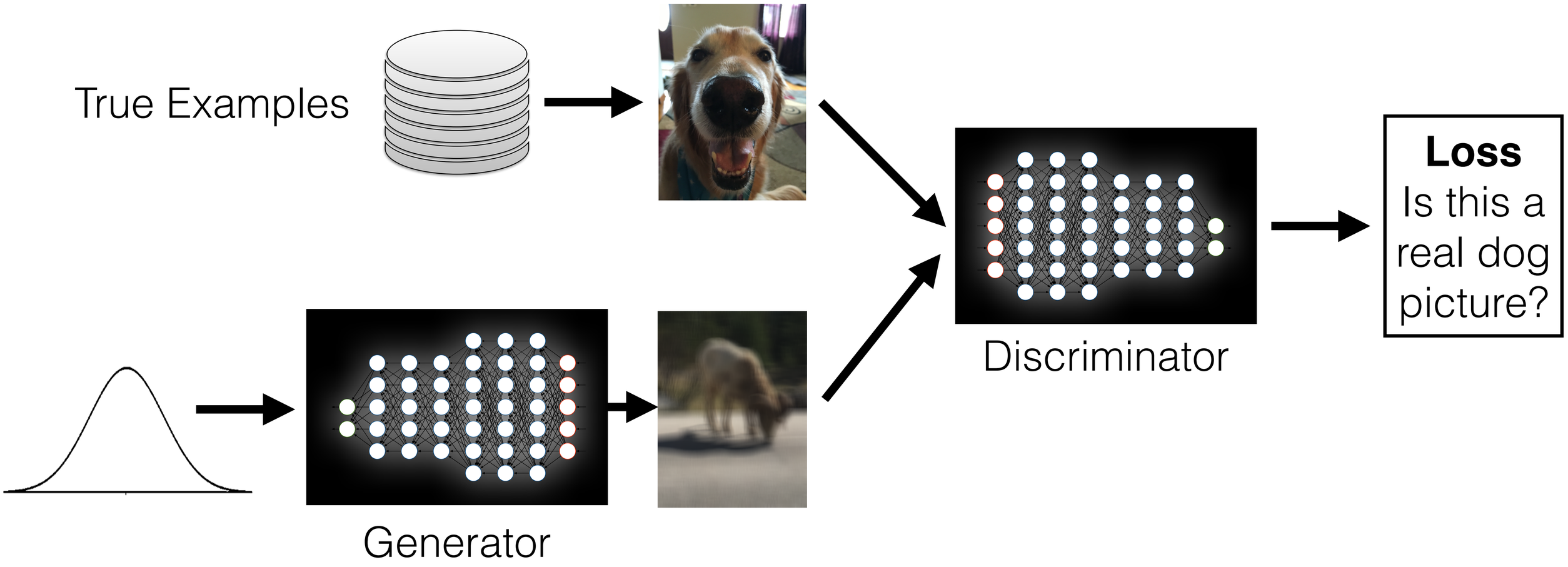
Generative Model



Generative Model



Generative Adversarial Networks



Generative Adversarial Networks

2014

2015

2016

2017

2018

Ian Goodfellow @goodfellow_ian · 2h
4.5 years of GAN progress on face generation. arxiv.org/abs/1406.2661 arxiv.org/abs/1511.06434 arxiv.org/abs/1606.07536 arxiv.org/abs/1710.10196 arxiv.org/abs/1812.04948

https://thispersondoesnotexist.com

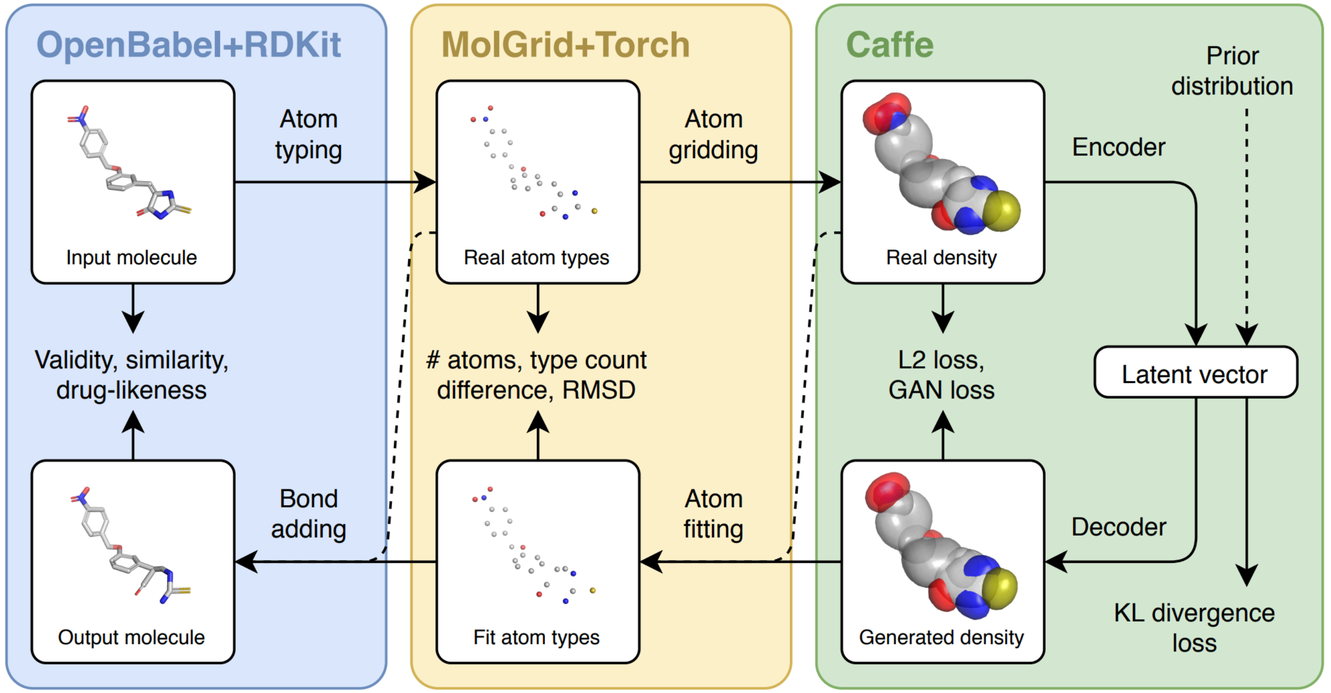
Learning a Continuous Representation of 3D Molecular Structures with Deep Generative Models

NeurIPS 2020 Workshop
Machine Learning for Structural Biology

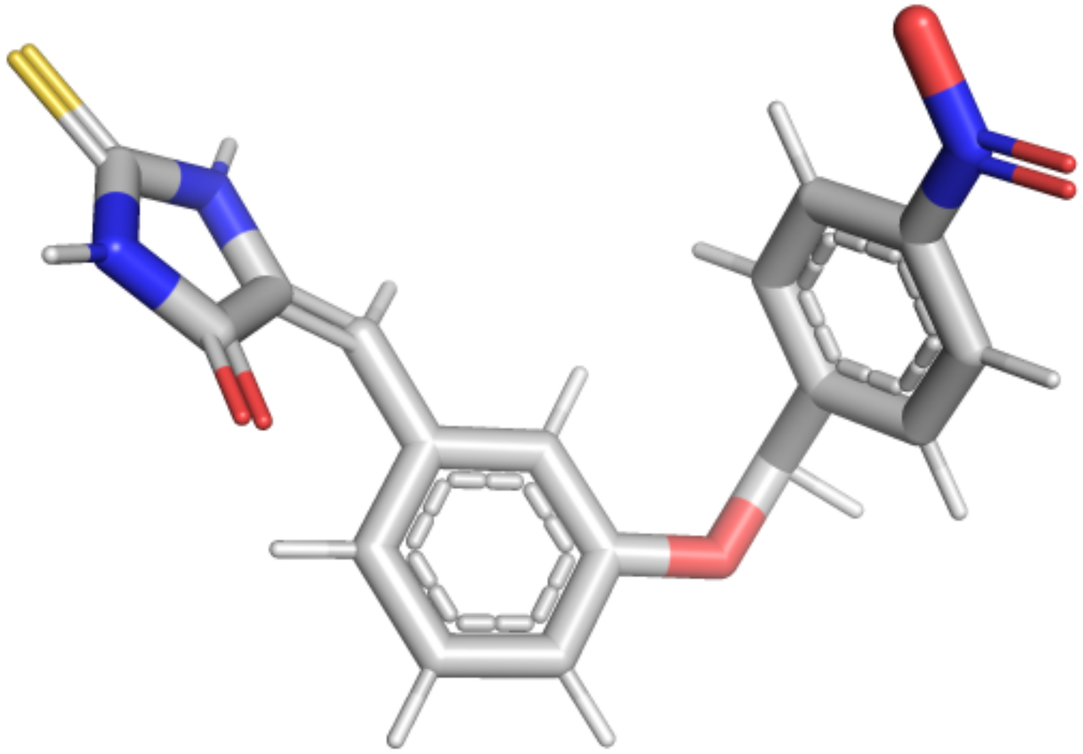
Matthew Ragoza*
Comp. & Systems Biology
University of Pittsburgh
Pittsburgh, PA 15213
mtr22@pitt.edu

Tomohide Masuda*
Comp. & Systems Biology
University of Pittsburgh
Pittsburgh, PA 15213
tmasuda@pitt.edu

David Ryan Koes
Comp. & Systems Biology
University of Pittsburgh
Pittsburgh, PA 15213
dkoes@pitt.edu

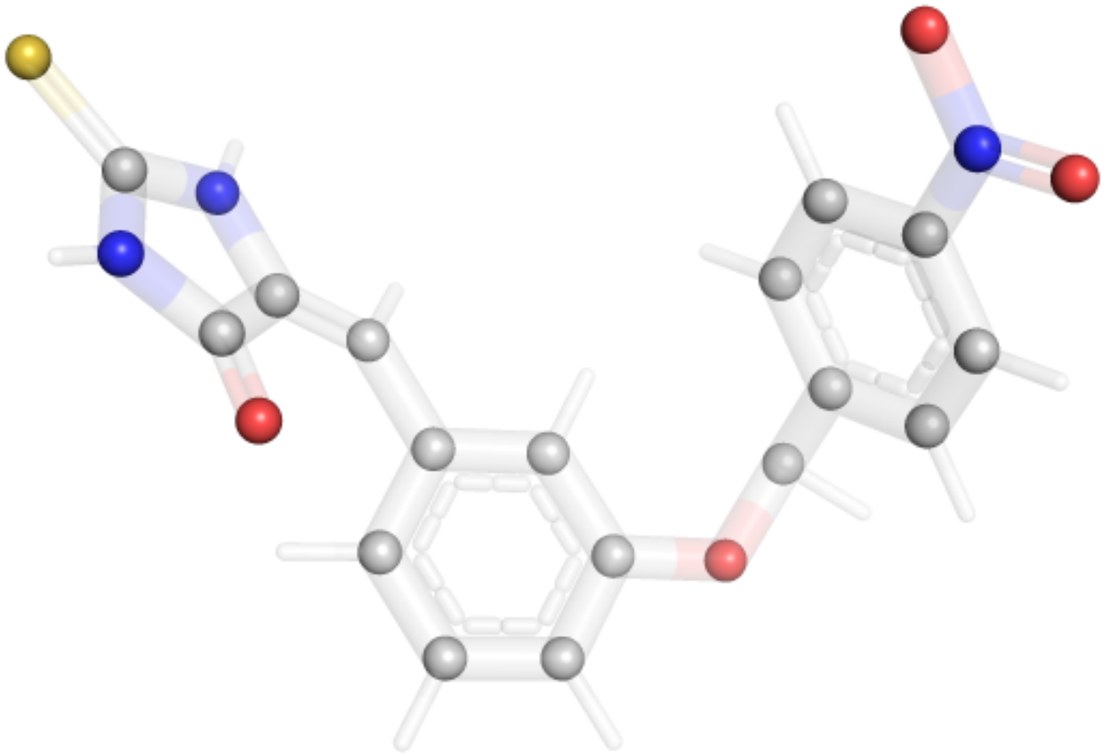


Goal: Create a generative model of 3D molecular structures

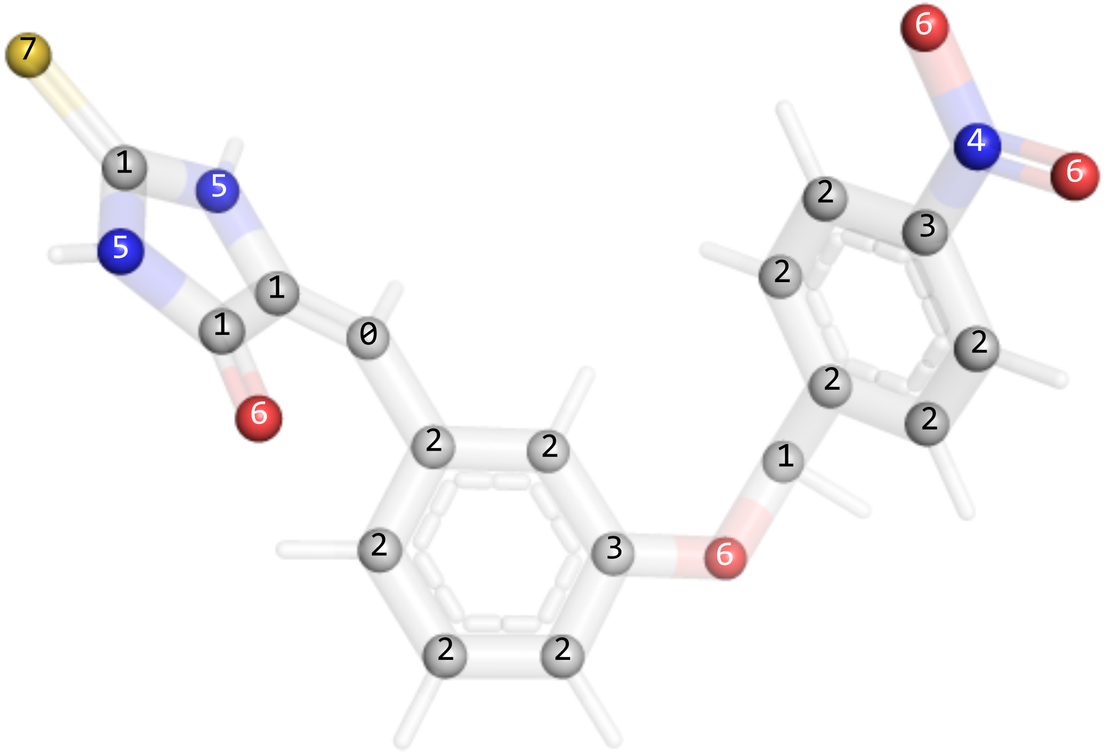


`O=C1NC(=S)N/C1=C/c1cccc(OCc2ccc([N+](=O)[O-])cc2)c1`

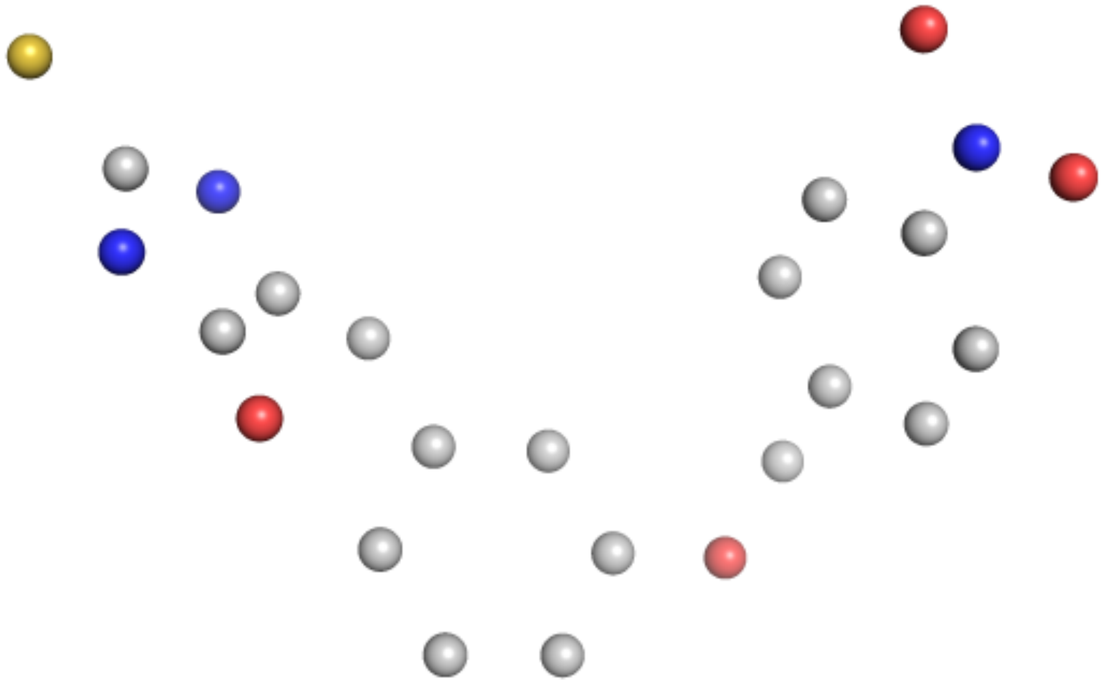
Assign **atom types** based on element, aromaticity, and neighbor atoms



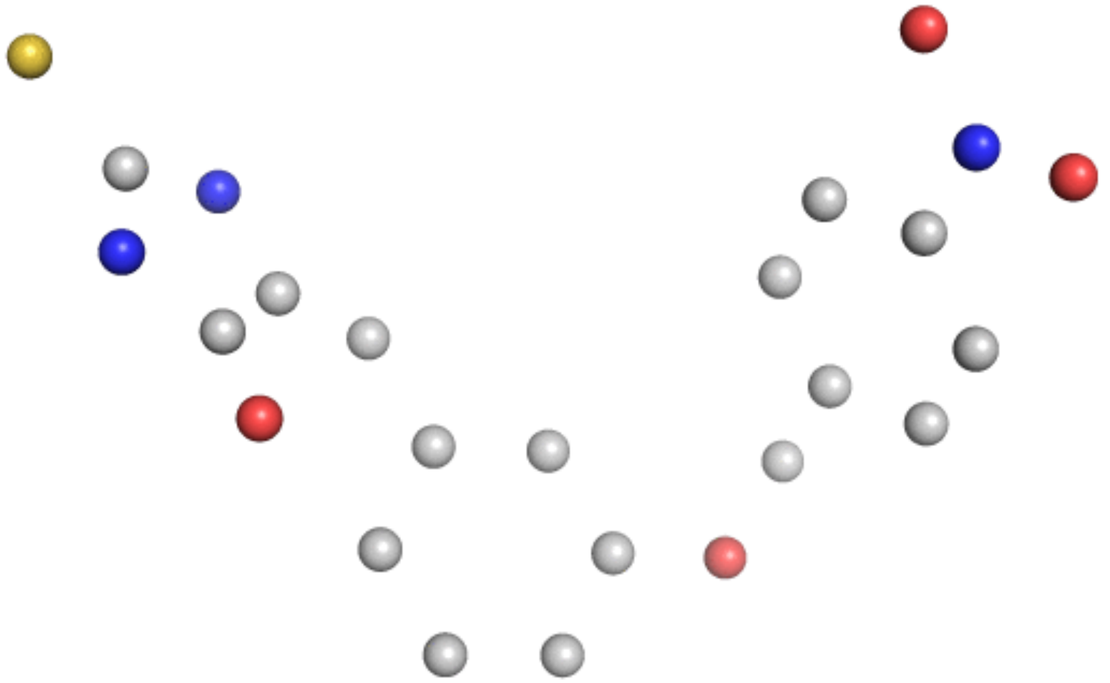
Assign **atom types** based on element, aromaticity, and neighbor atoms



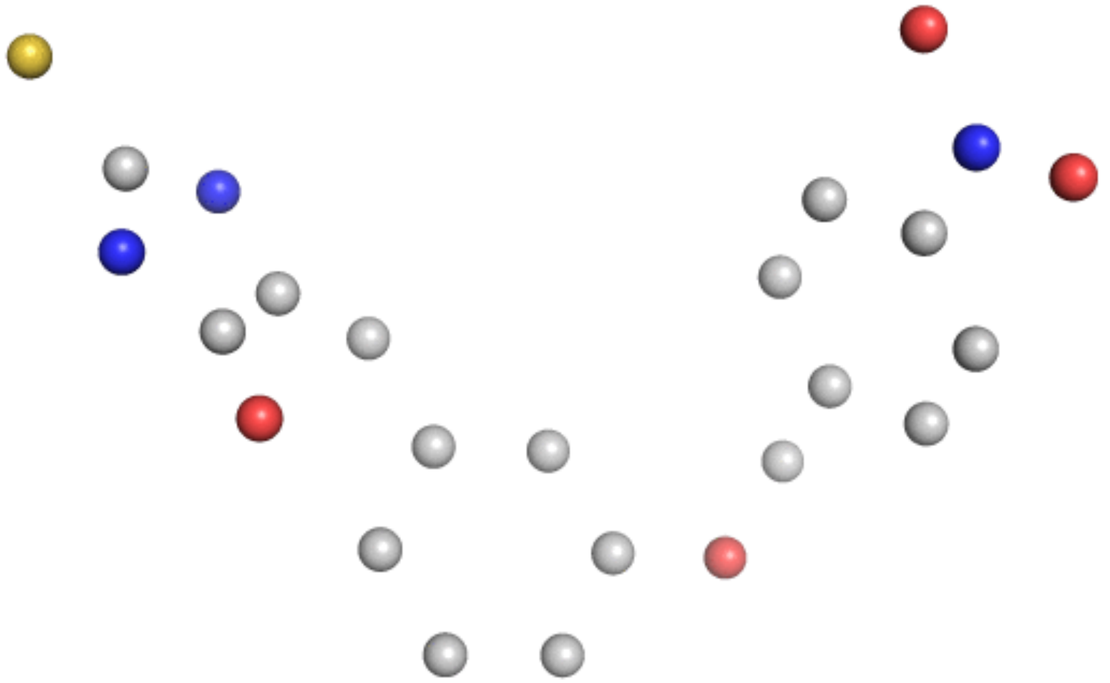
Represent atoms as Gaussian **densities** using their atomic radius



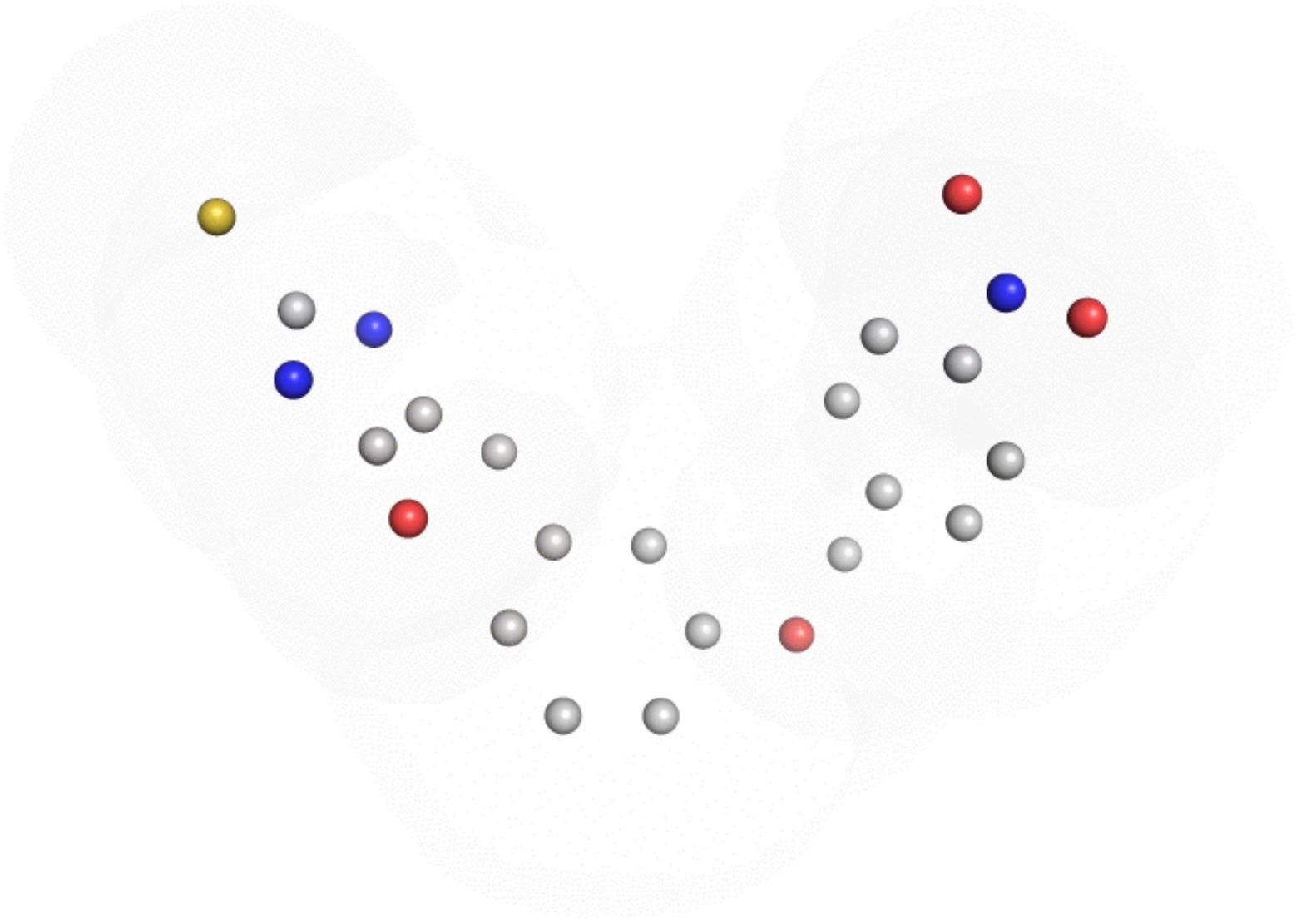
Represent atoms as Gaussian **densities** using their atomic radius



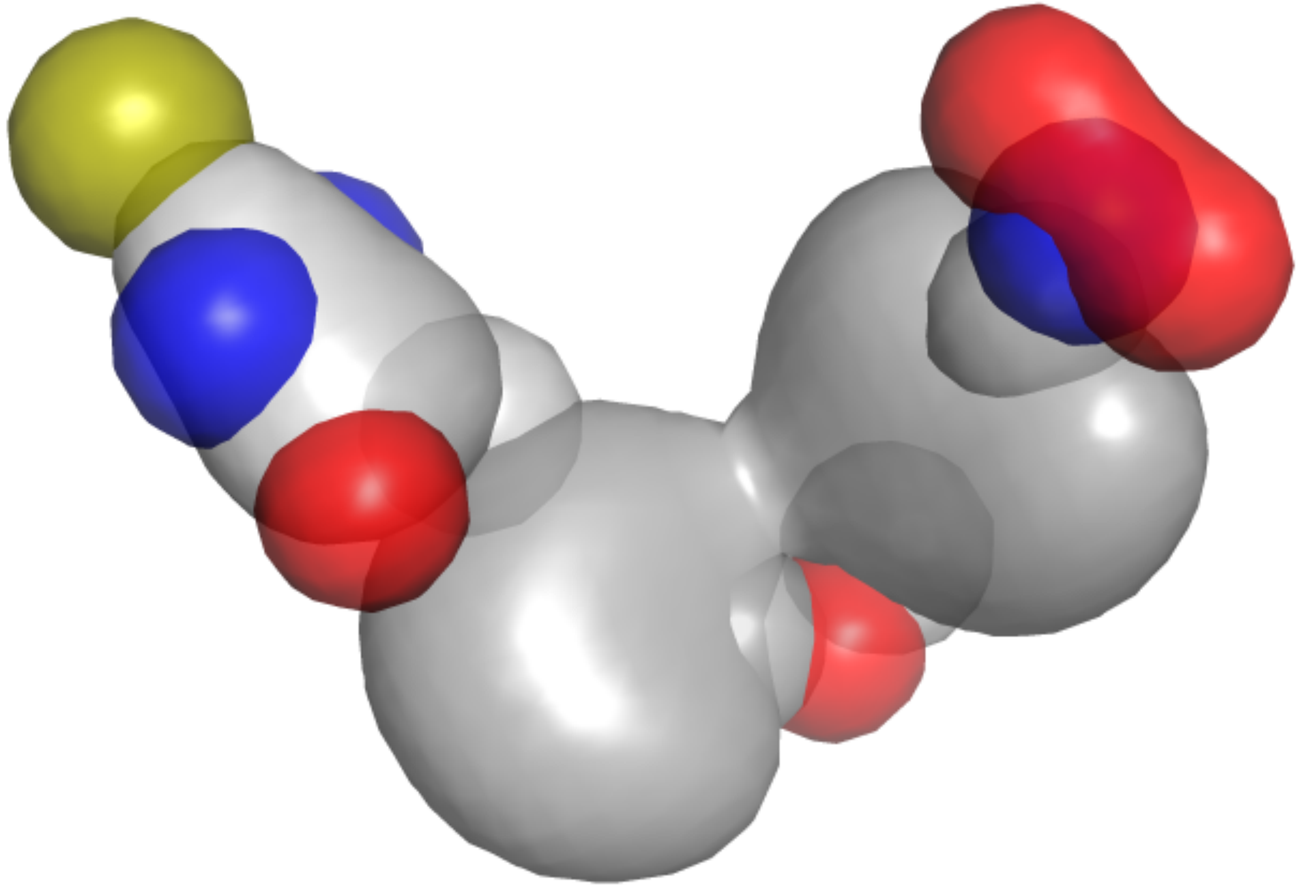
Sum atomic density on a **3D grid** with channels for each atom type

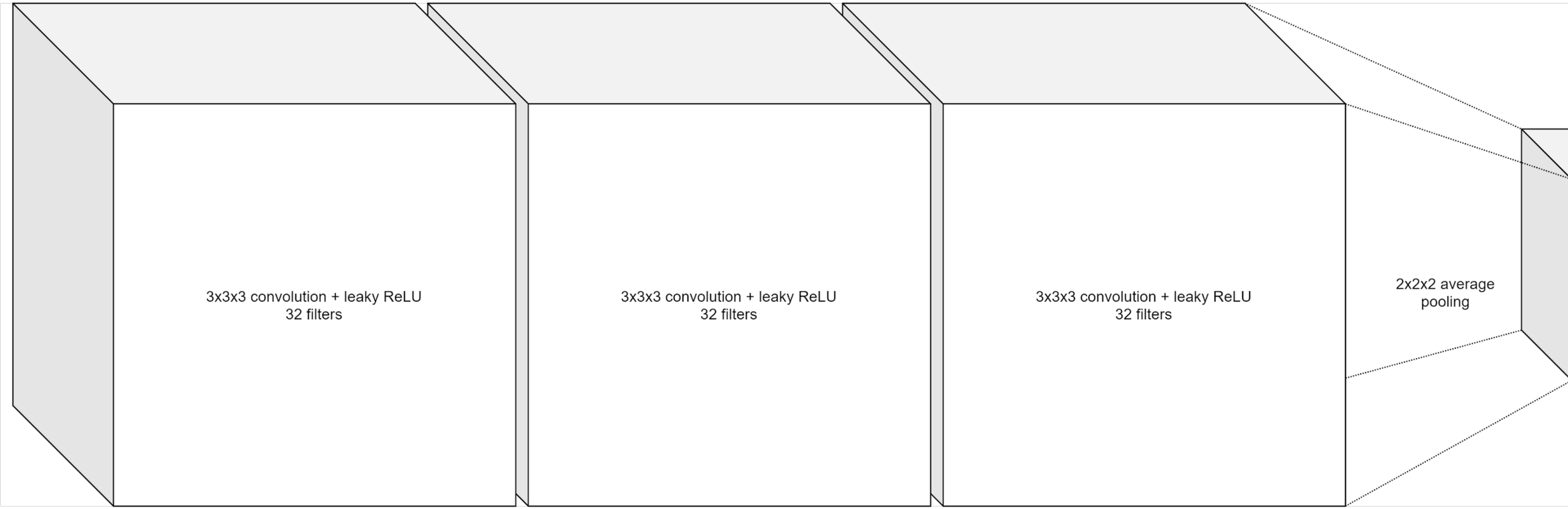


Sum atomic density on a **3D grid** with channels for each atom type

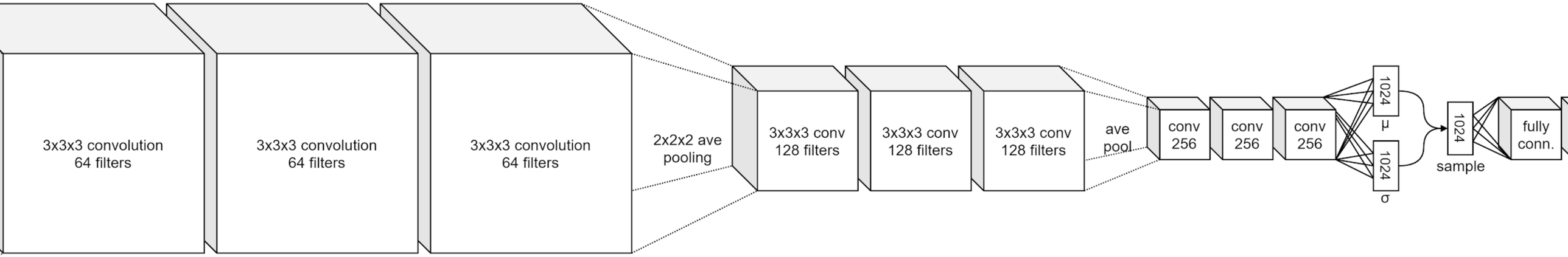


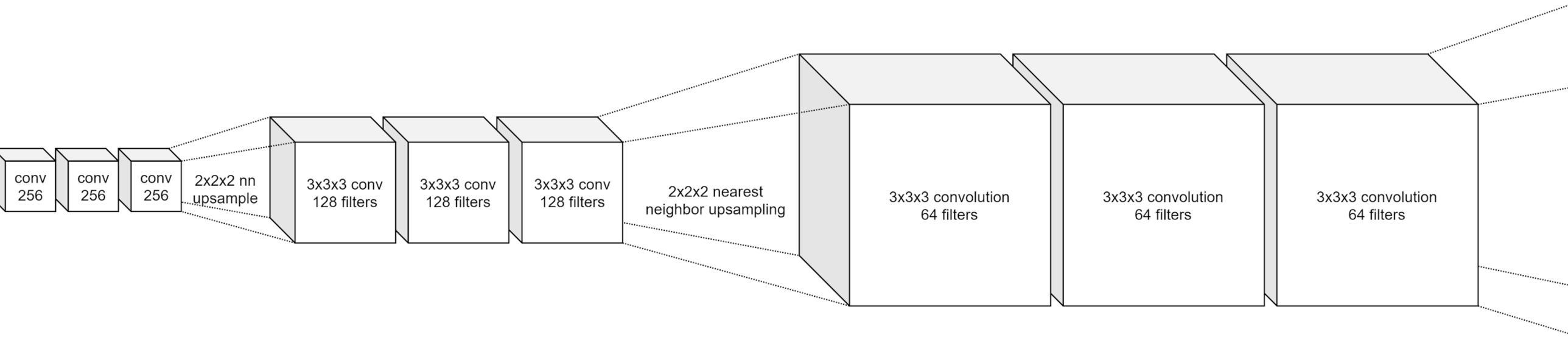
Provide density grids of real molecules to a **deep neural network**

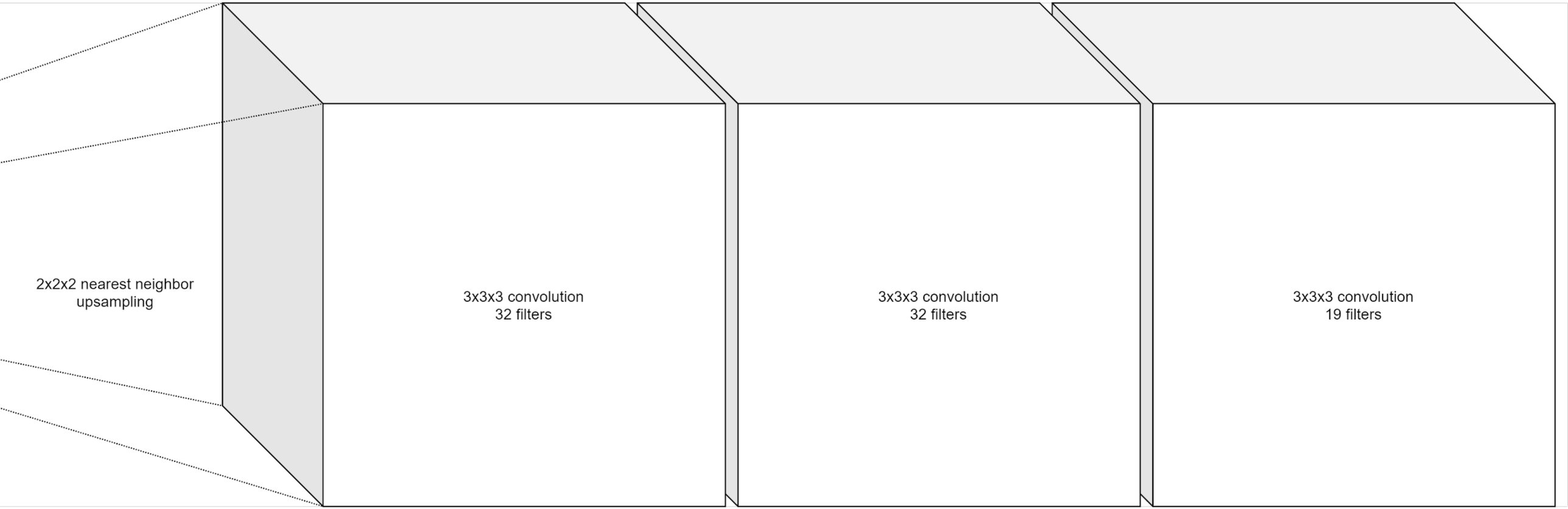



3x3x3 convolution + leaky ReLU
32 filters
3x3x3 convolution + leaky ReLU
32 filters
3x3x3 convolution + leaky ReLU
32 filters
2x2x2 average
pooling

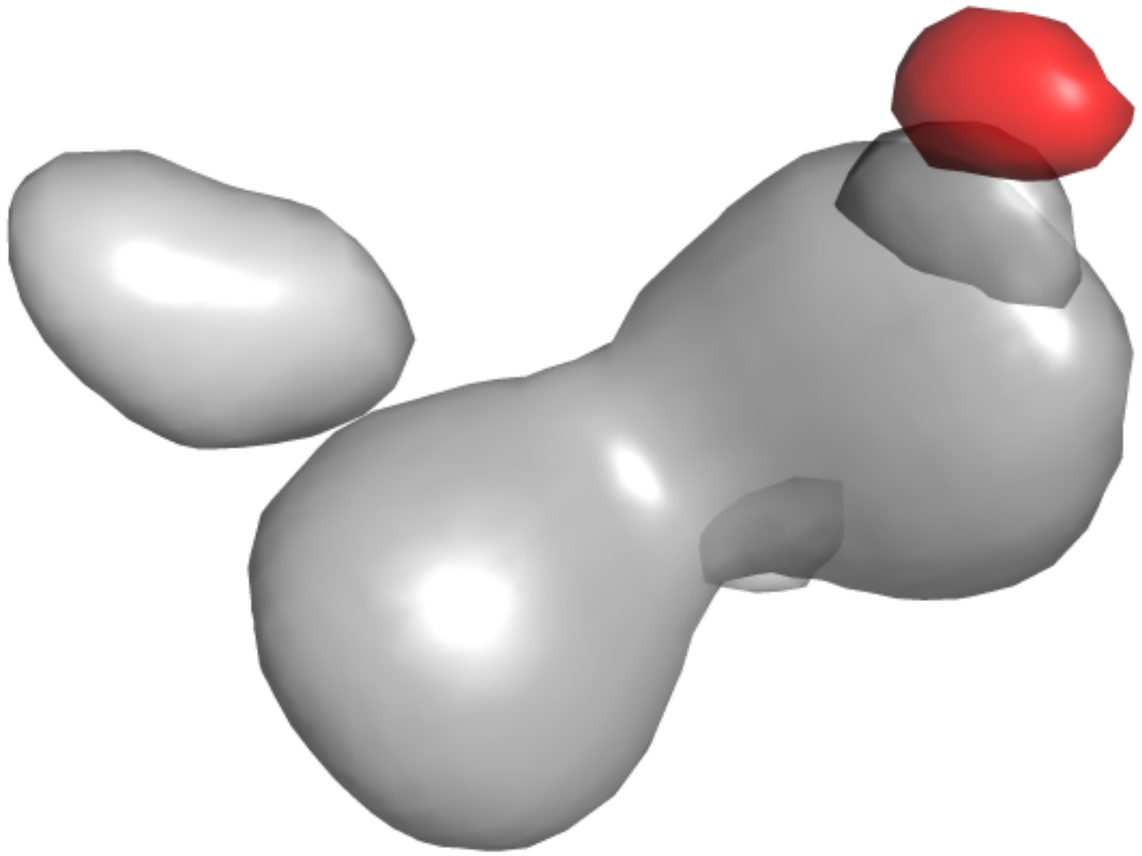
Map from input densities to normally distributed **latent variables**



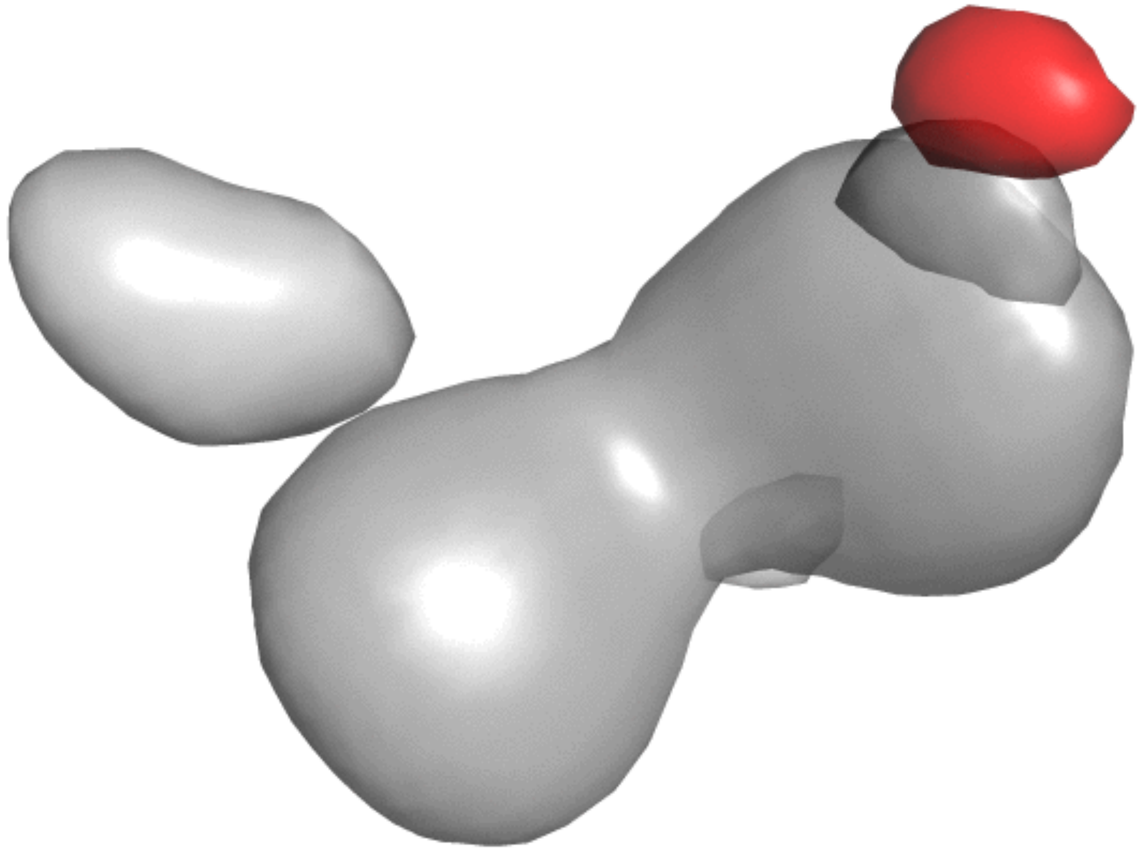

conv
256
conv
256
conv
256
2x2x2 nn
upsample
3x3x3 conv
128 filters
3x3x3 conv
128 filters
3x3x3 conv
128 filters
2x2x2 nearest
neighbor upsampling
3x3x3 convolution
64 filters
3x3x3 convolution
64 filters
3x3x3 convolution
64 filters


2x2x2 nearest neighbor upsampling
3x3x3 convolution 32 filters
3x3x3 convolution 32 filters
3x3x3 convolution 19 filters

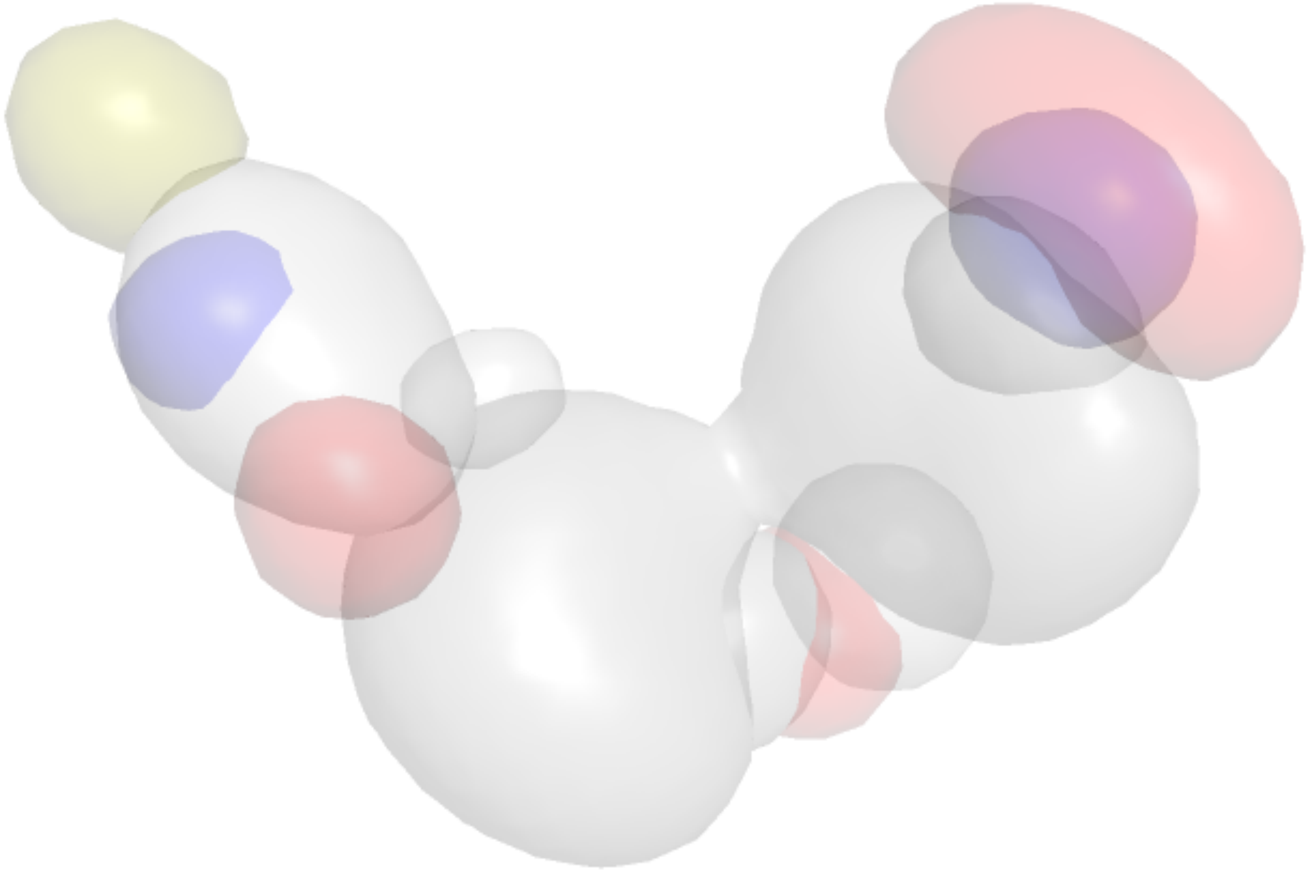
Train the model to reconstruct its input and generate realistic densities



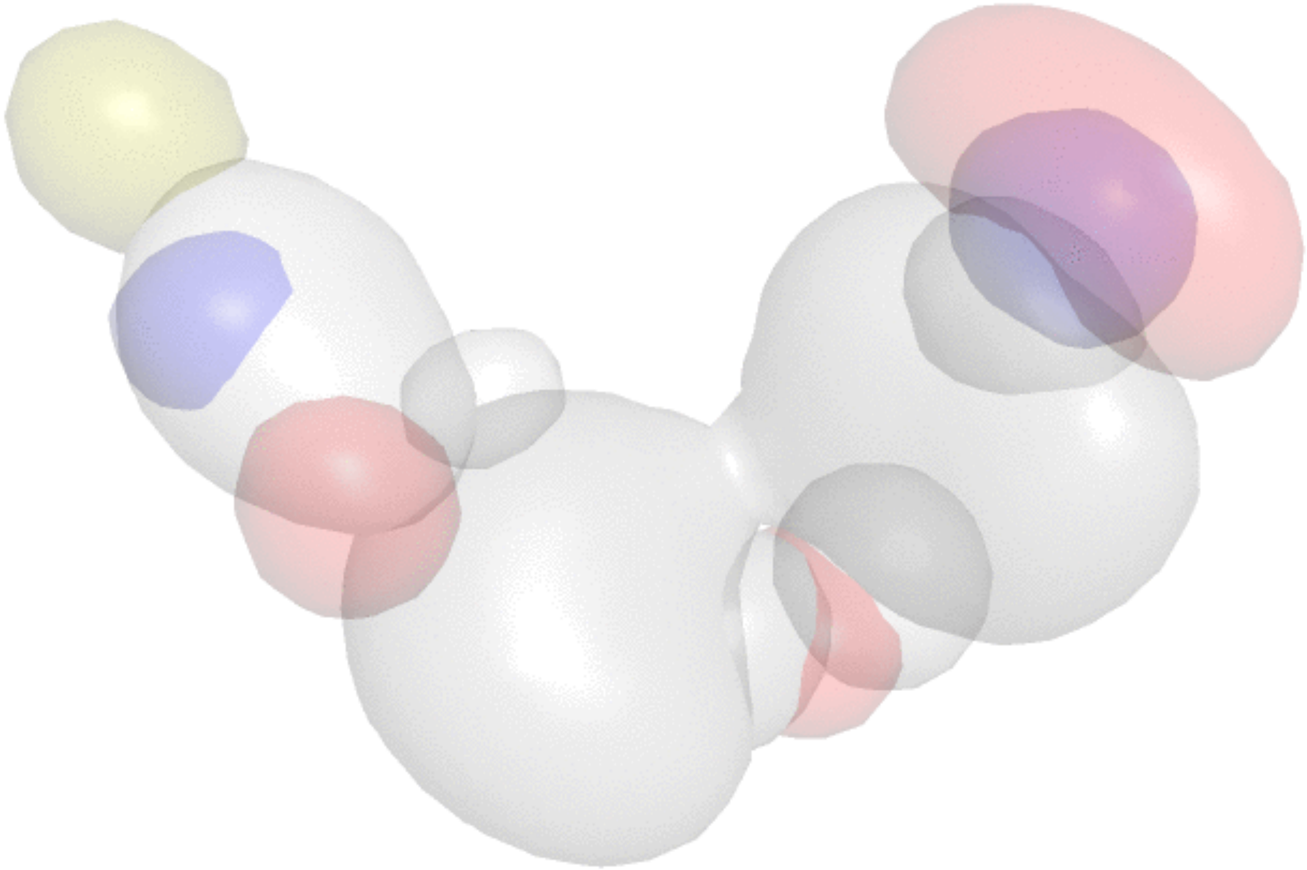
Train the model to reconstruct its input and generate realistic densities



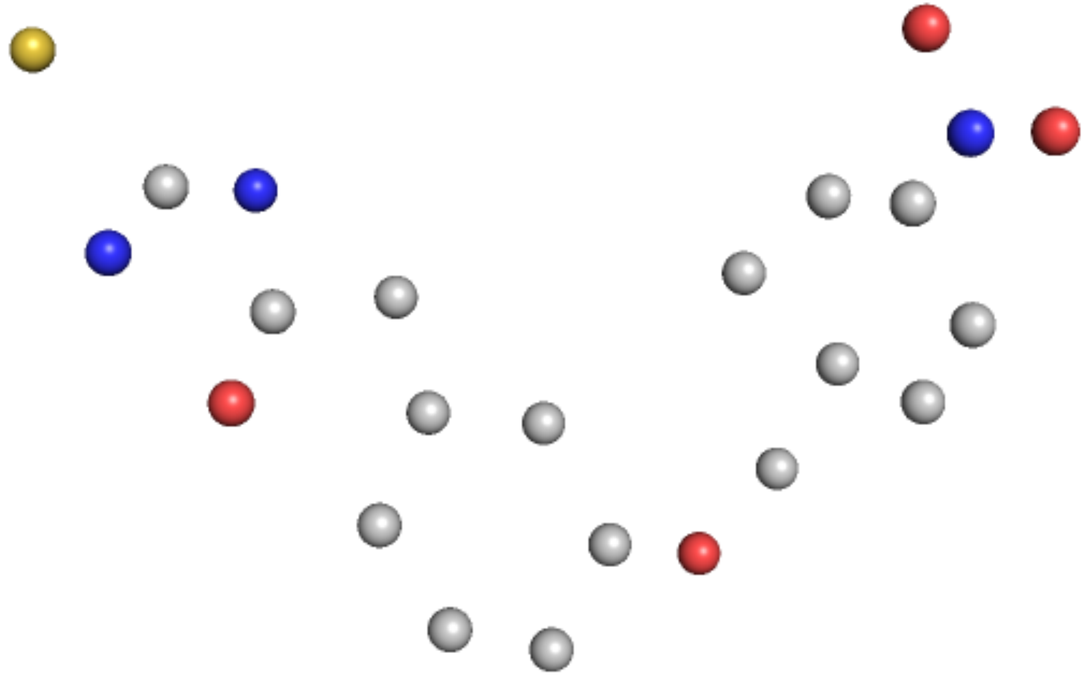
Detect and **fit atoms** to generated densities with gradient descent



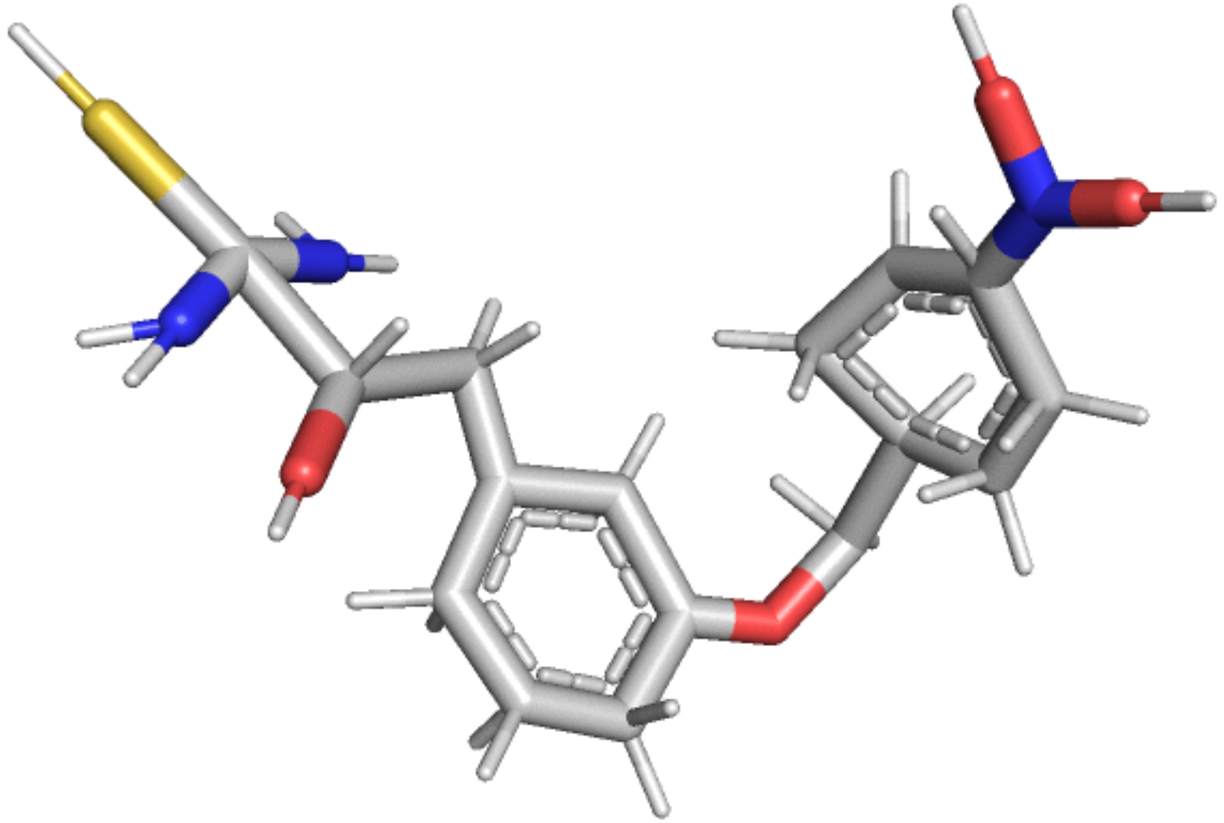
Detect and **fit atoms** to generated densities with gradient descent



Add bonds to fit atoms based on their atom types and geometry



Add bonds to fit atoms based on their atom types and geometry



Same input molecules

AE

VAE

Different input molecules

AE

VAE

Same input molecules

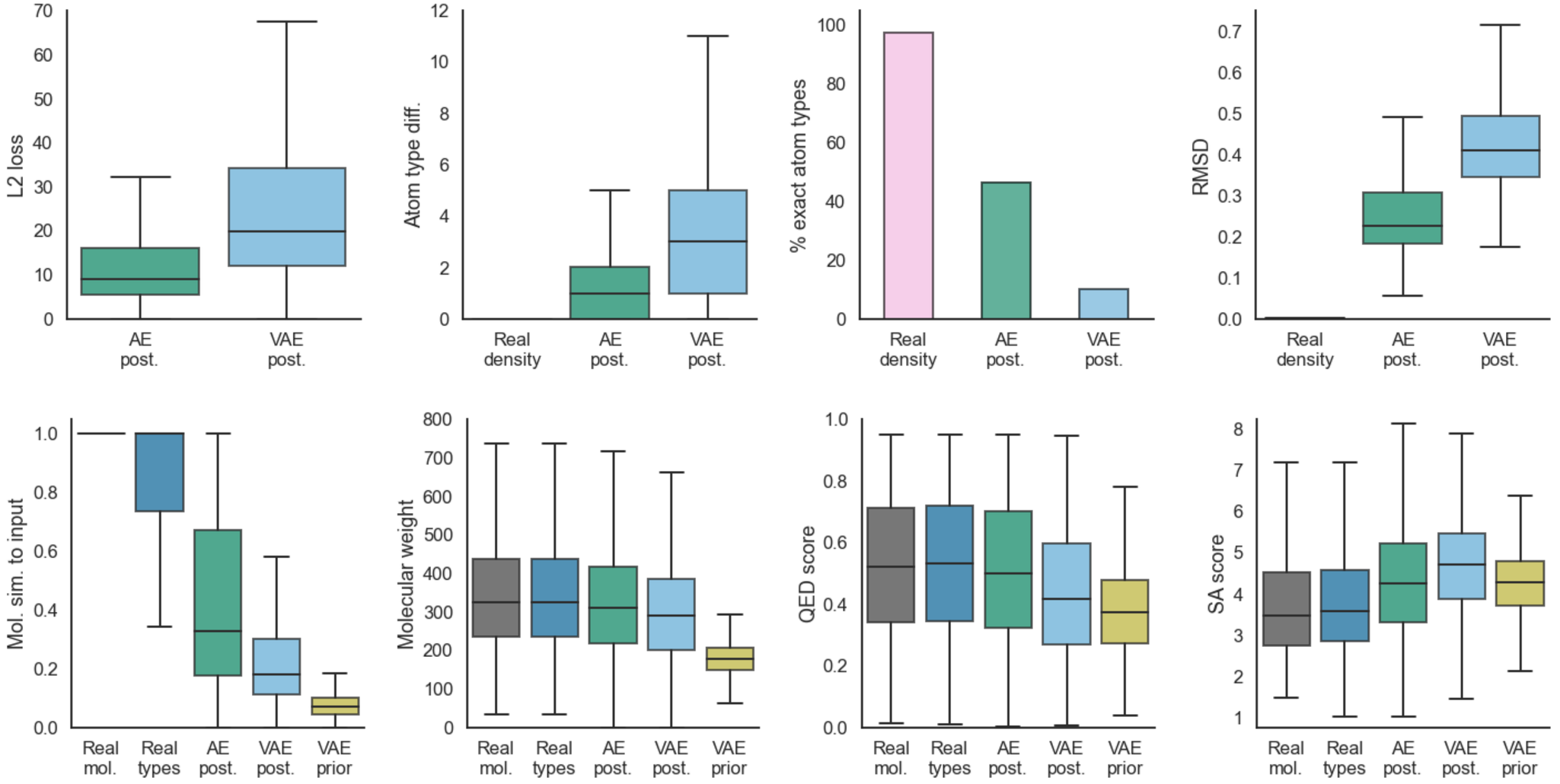
AE

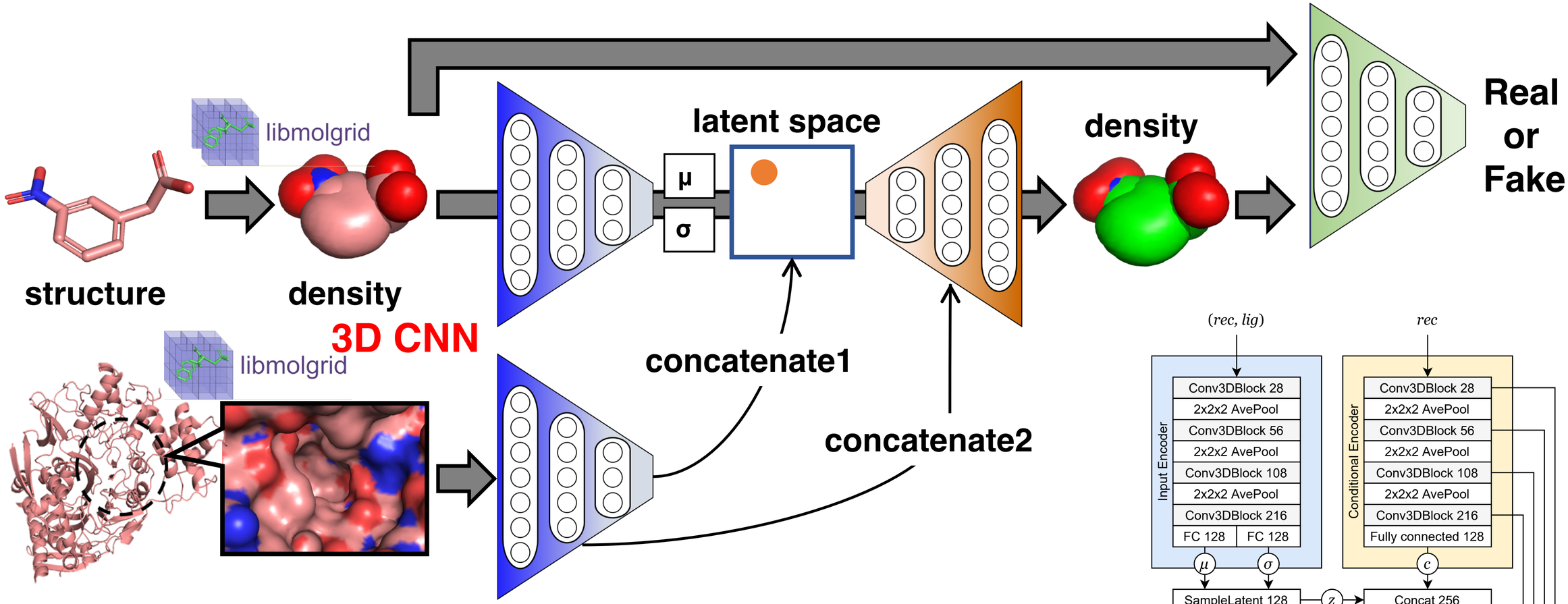
VAE

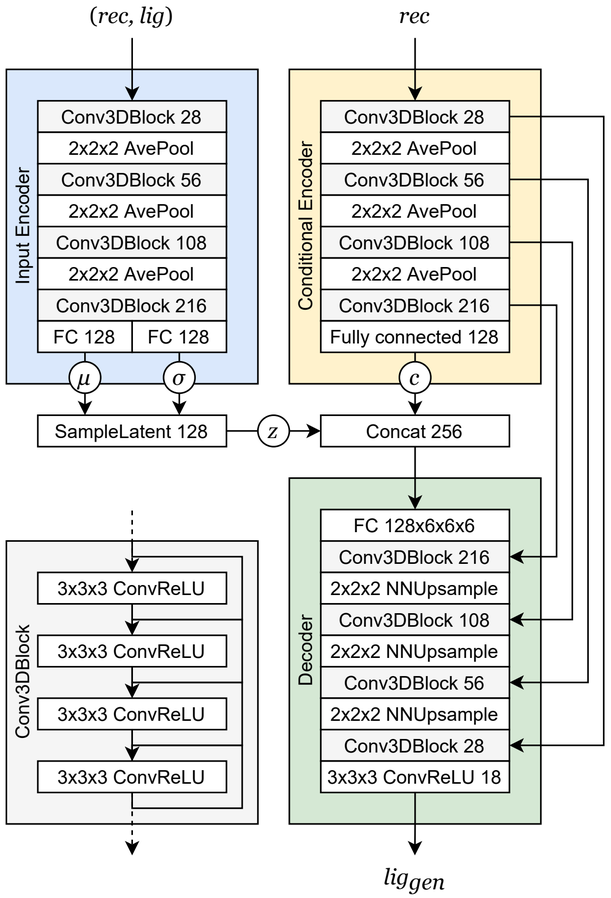
Different input molecules

AE

VAE


L2 loss
AE post.
VAE post.
Atom type diff.
Real density
AE post.
VAE post.
% exact atom types
Real density
AE post.
VAE post.
RMSD
Real density
AE post.
VAE post.
Mol. sim. to input
Real mol.
Real types
AE post.
VAE post.
VAE prior
Molecular weight
Real mol.
Real types
AE post.
VAE post.
VAE prior
QED score
Real mol.
Real types
AE post.
VAE post.
VAE prior
SA score
Real mol.
Real types
AE post.
VAE post.
VAE prior





Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

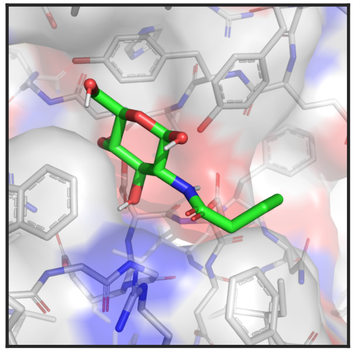
Check for updates

Cite this: *Chem. Sci.*, 2022, **13**, 2701

All publication charges for this article have been paid for by the Royal Society

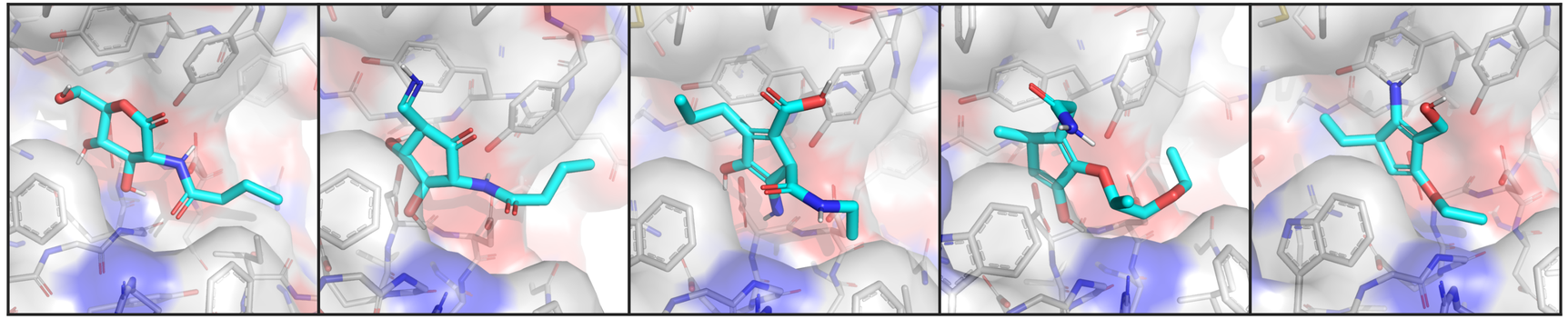
Generating 3D molecules conditional on receptor binding sites with deep generative models†

Matthew Ragoza, *[a] Tomohide Masuda[b] and David Ryan Koes[c]



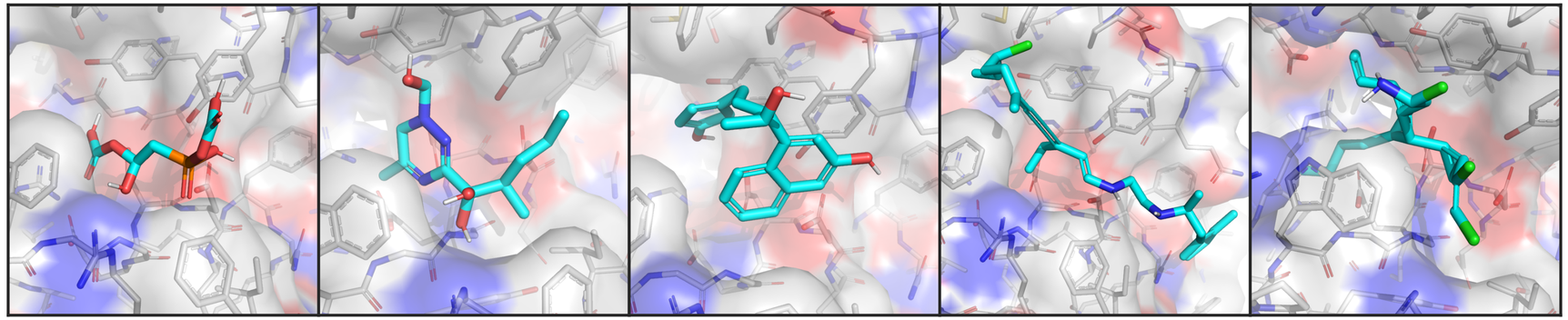
Reference molecule

Posterior



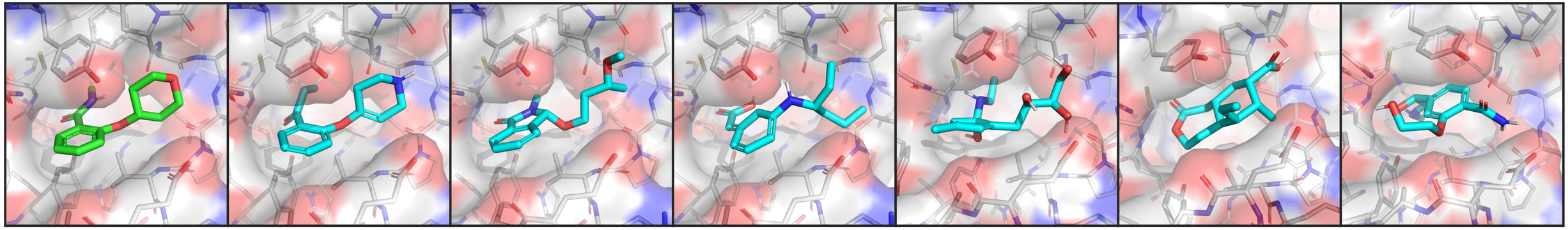
0.5 1.0 2.0 4.0 8.0

Prior



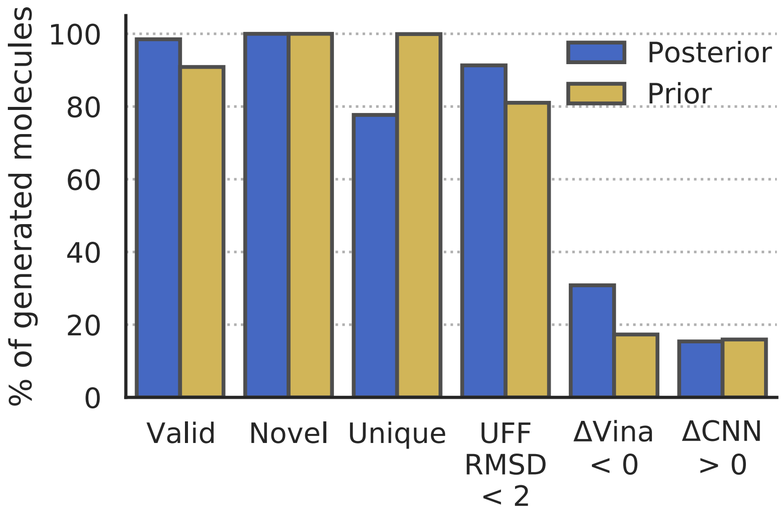
0.5 1.0 2.0 4.0 8.0

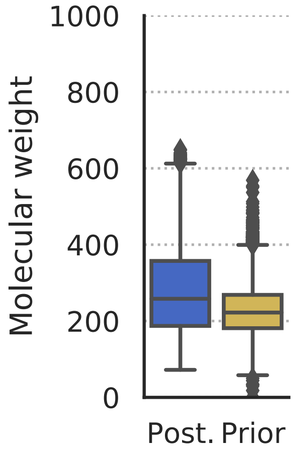
Variability factor

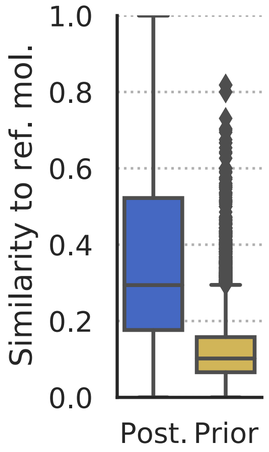


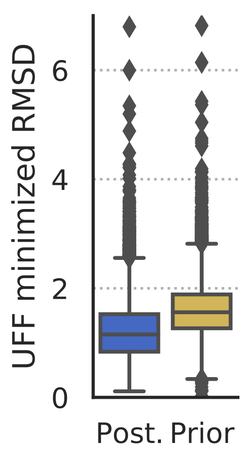
Reference molecule | 1.0 (Posterior) | 0.8 | 0.6 | 0.4 | 0.2 | 0.0 (Prior)

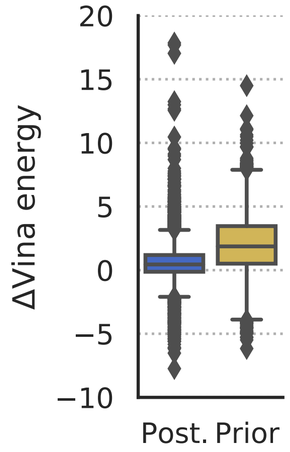
Bias factor

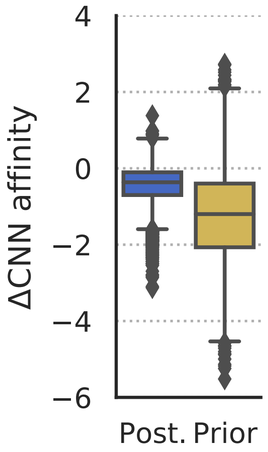




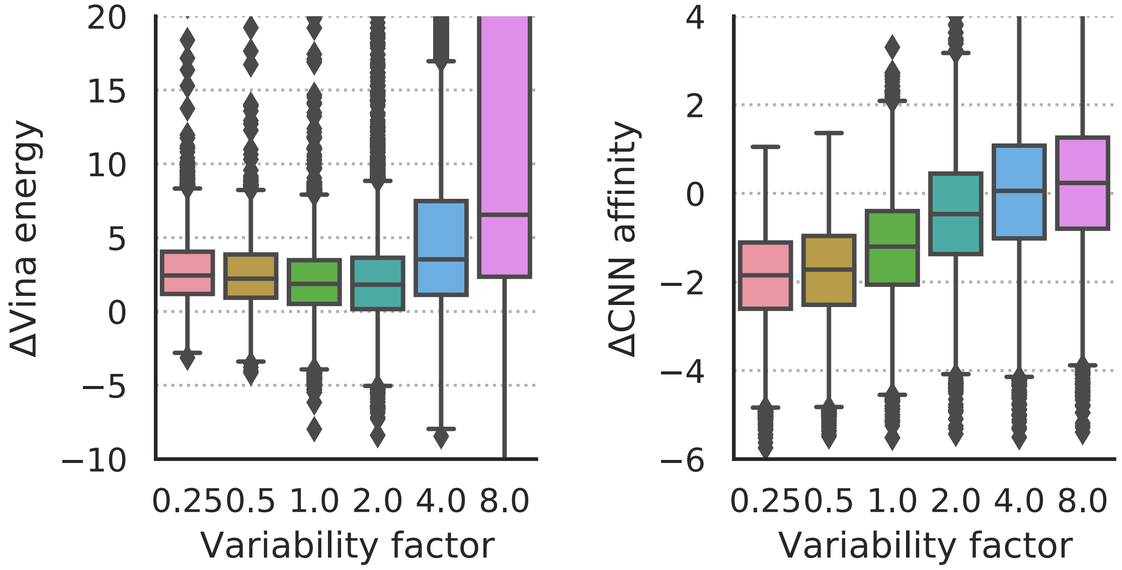




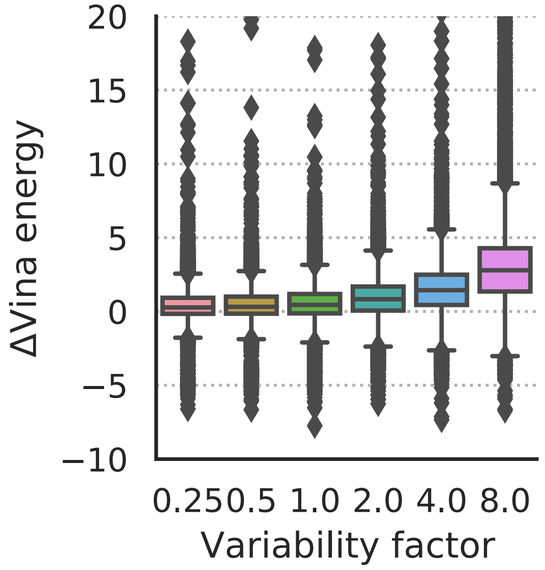


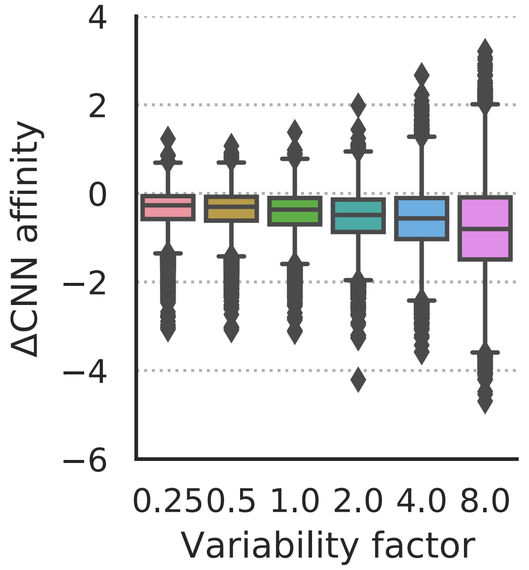


Prior



Posterior



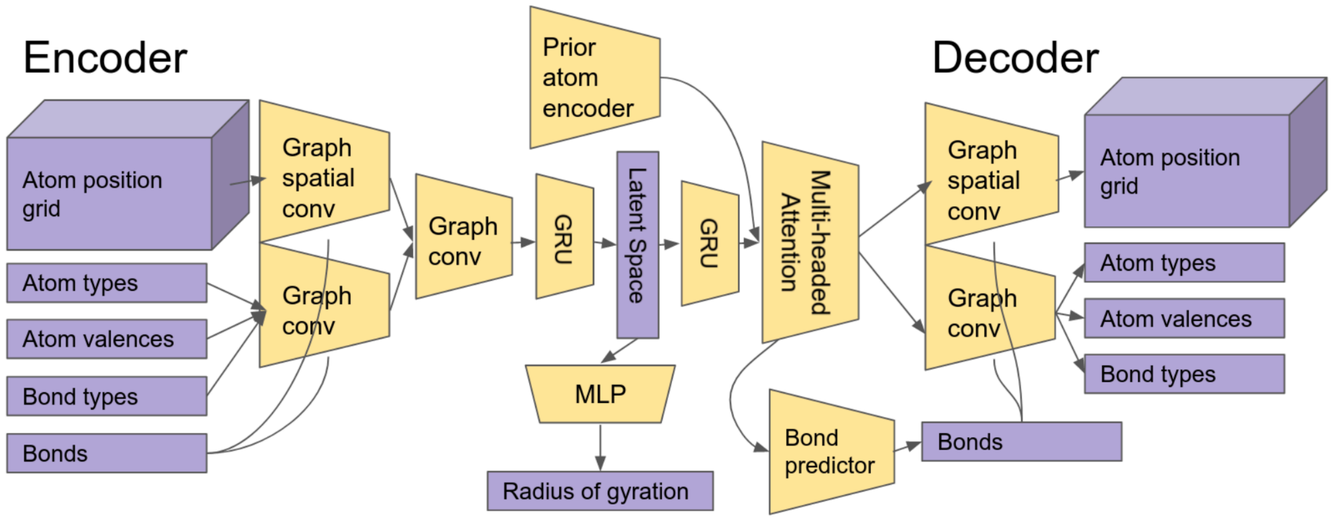


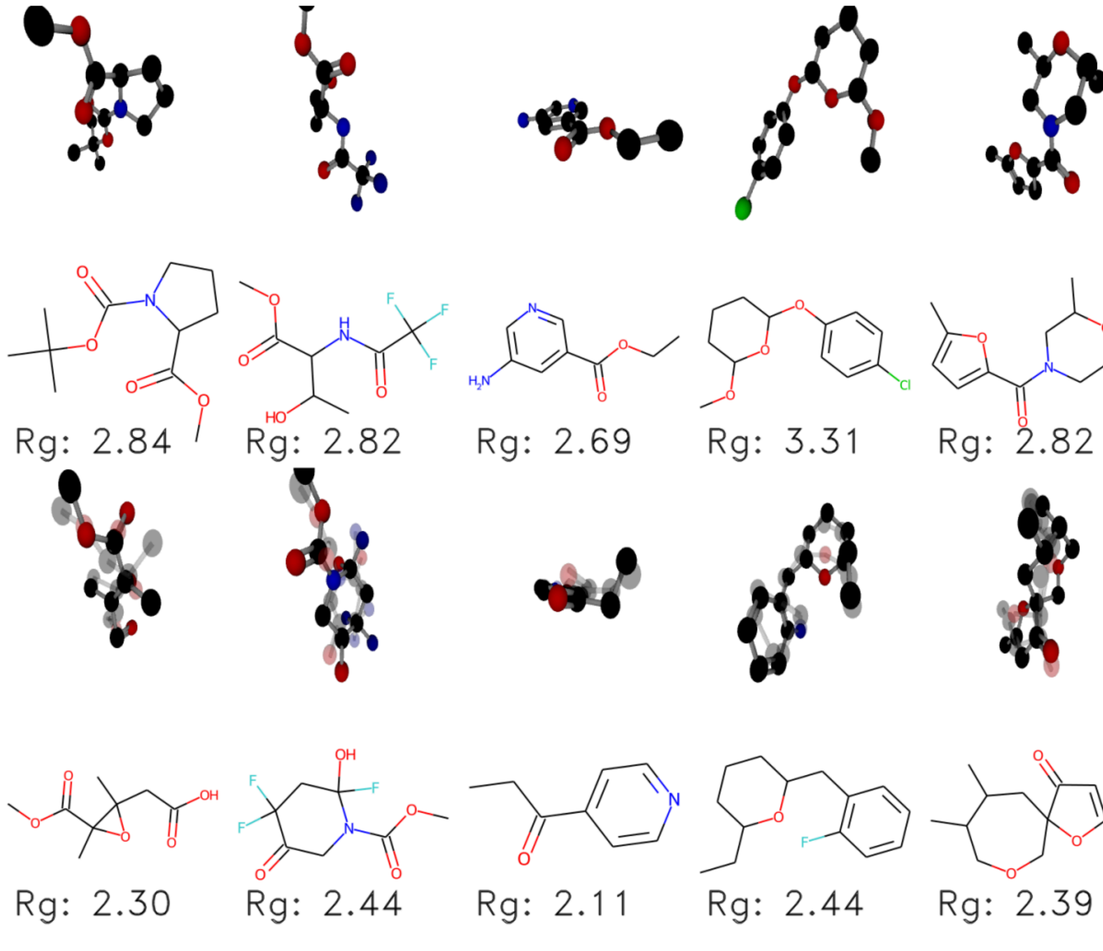
MOLUCINATE: A Generative Model for Molecules in 3D Space

Michael Arcidiacono
mixarcidiacono@gmail.com

David Ryan Koes
Comp. & Systems Biology
University of Pittsburgh
Pittsburgh, PA 15213
dkoes@pitt.edu

Machine Learning for Structural Biology Workshop, NeurIPS 2021

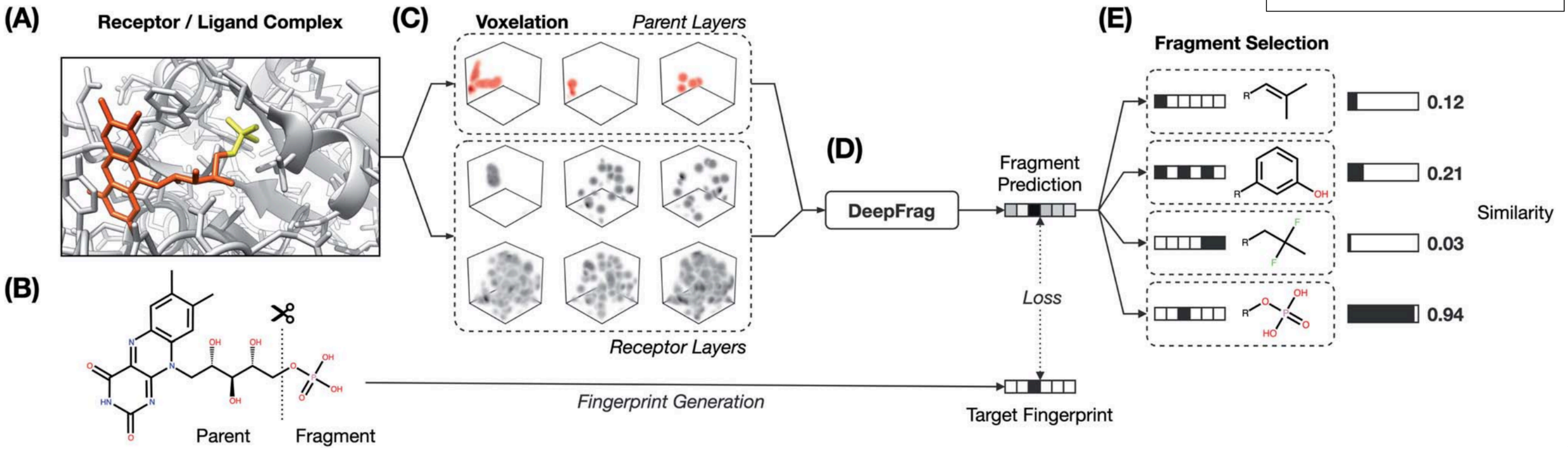




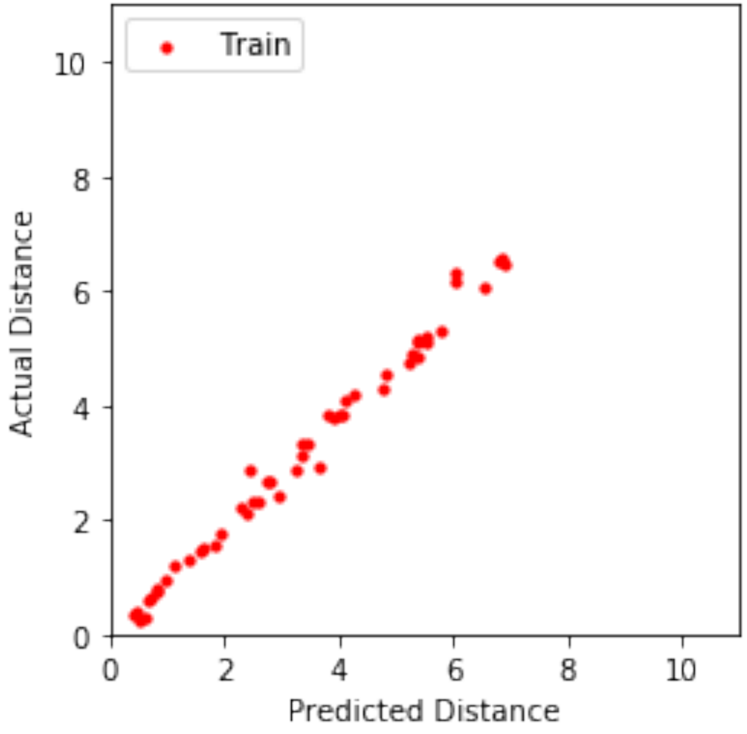
DeepFrag: a deep convolutional neural network for fragment-based lead optimization†

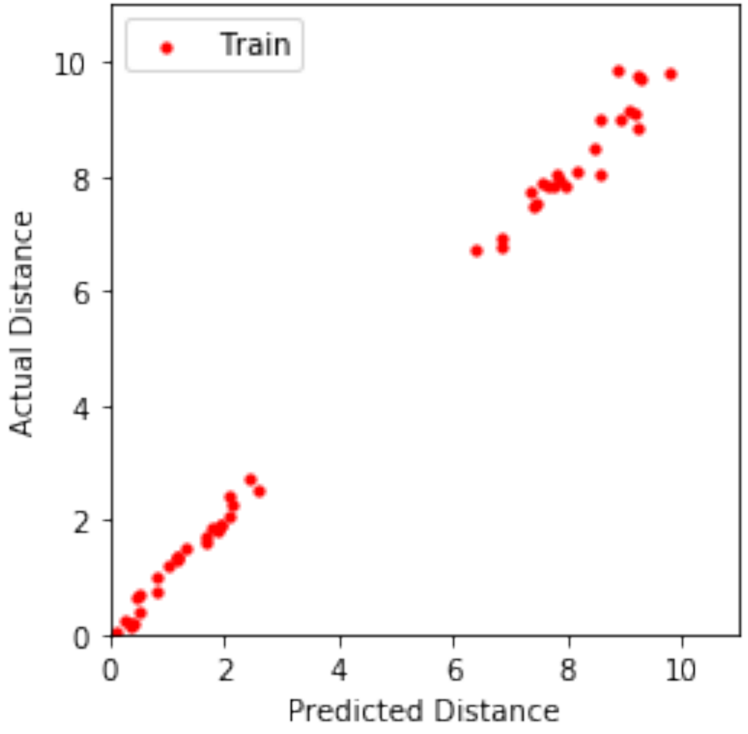
Harrison Green, [a] David R. Koes[b] and Jacob D. Durrant *[a]

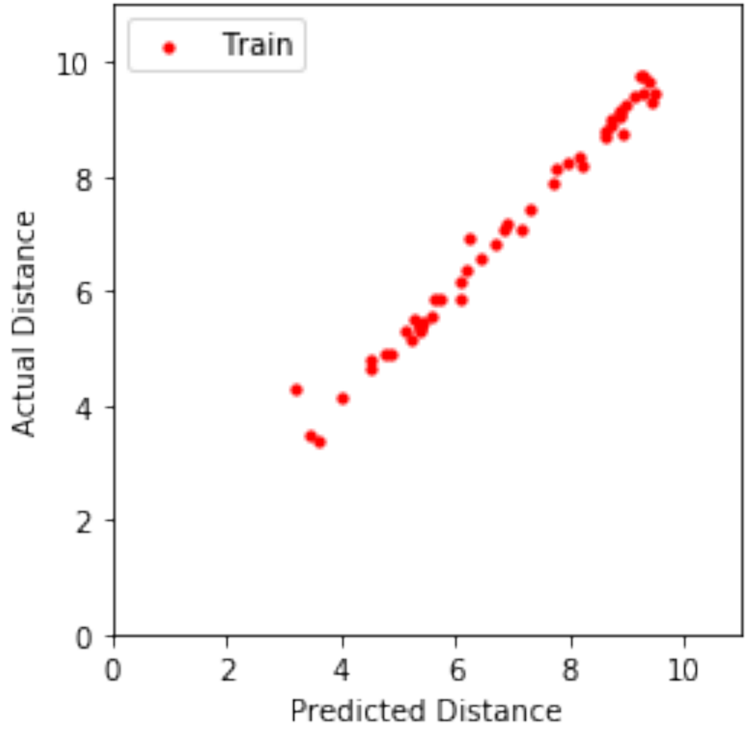
https://durrantlab.pitt.edu/deepfrag/

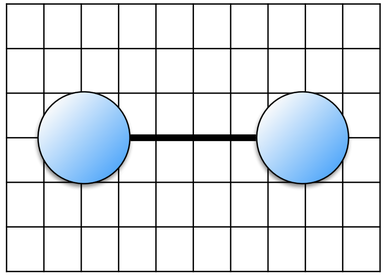


An Aside...



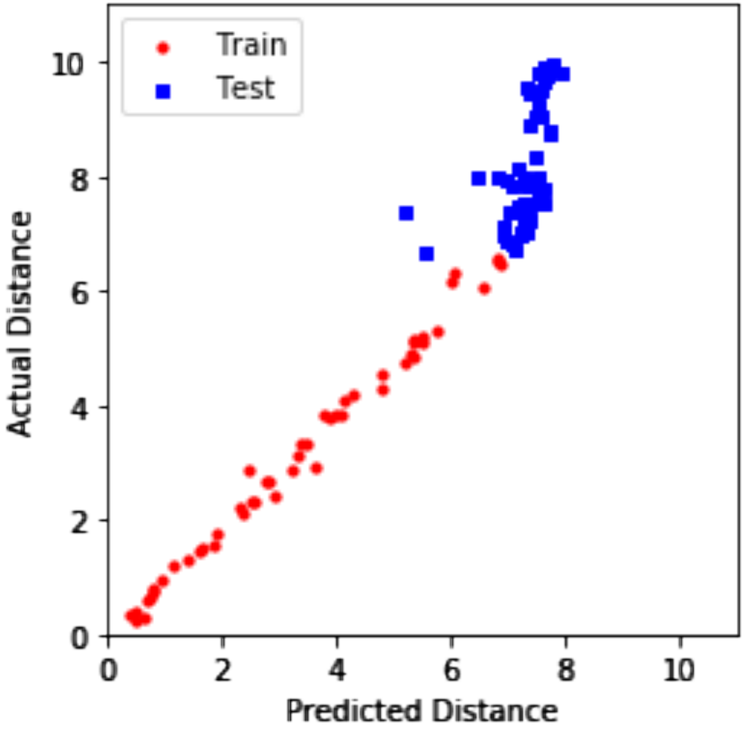


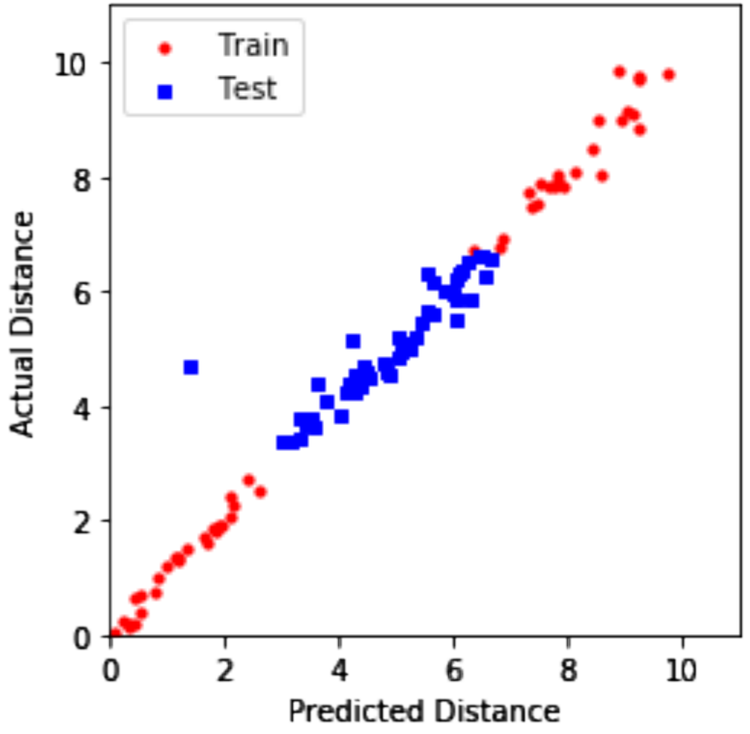


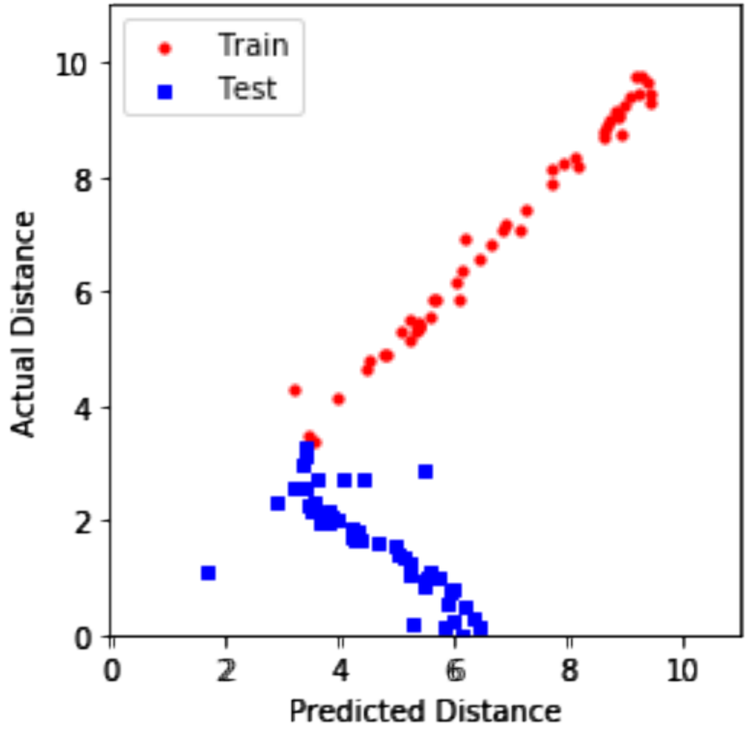


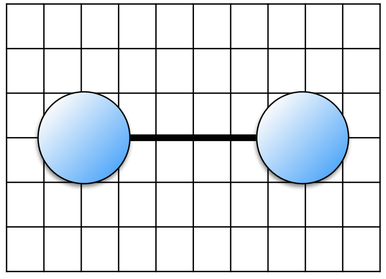
Distance

An Aside...



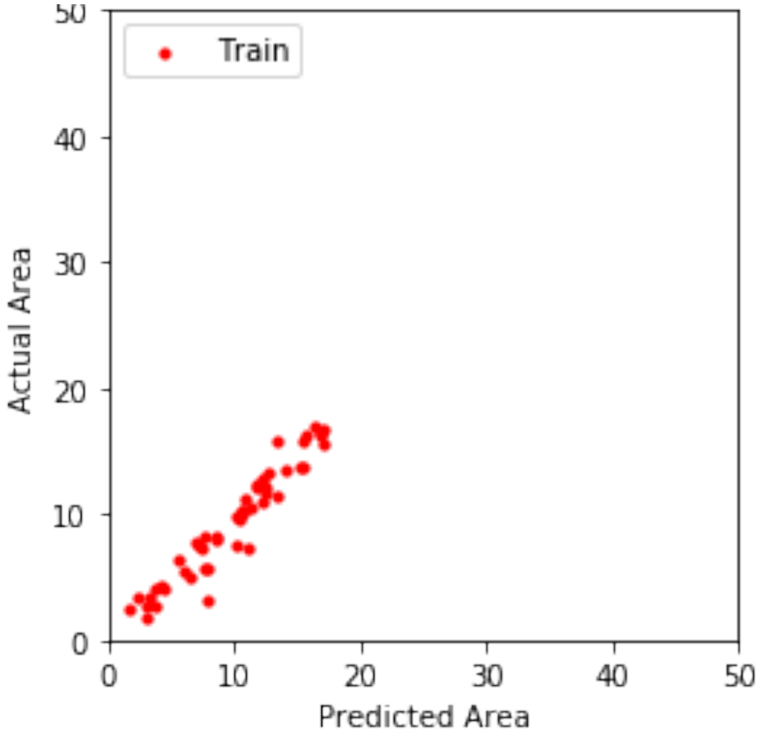


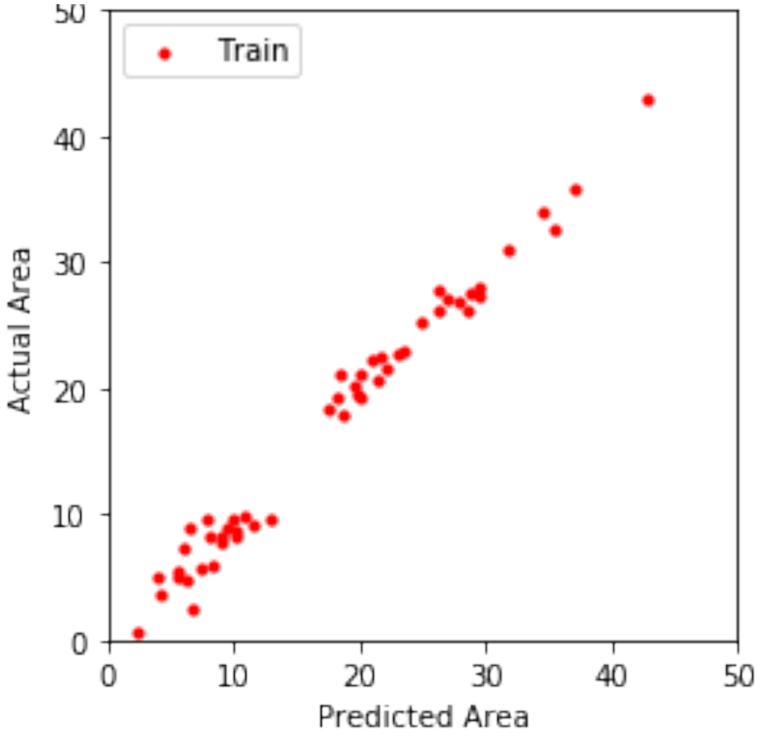


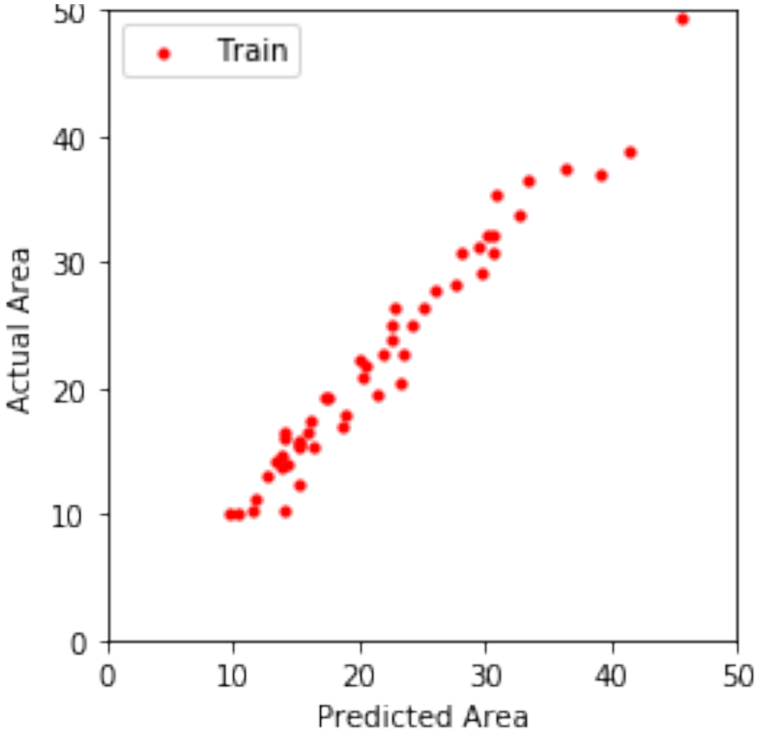


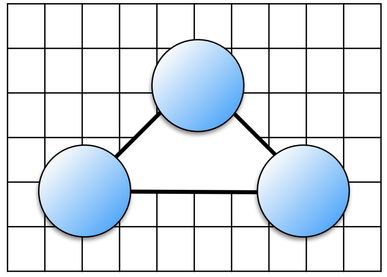
Distance

An Aside...



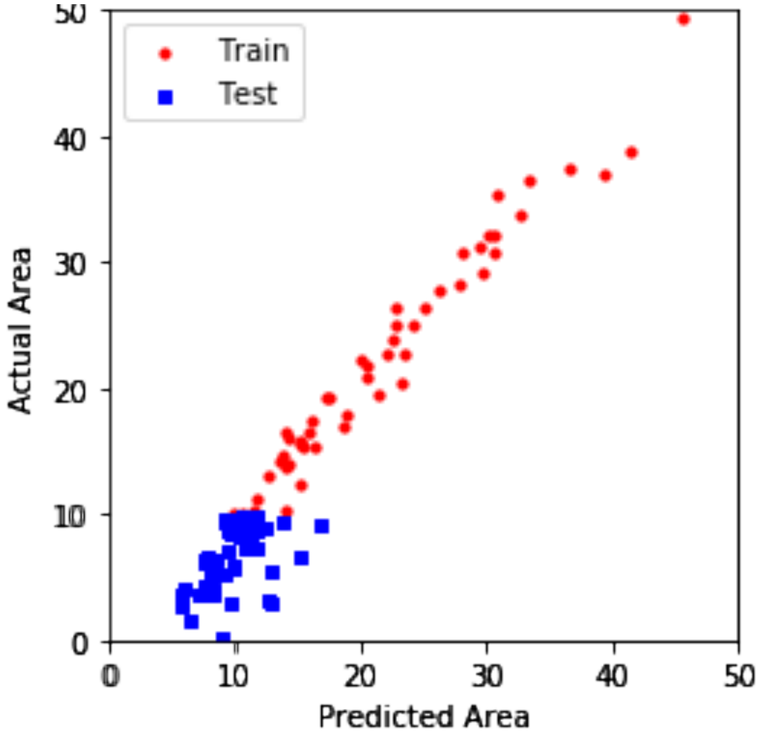


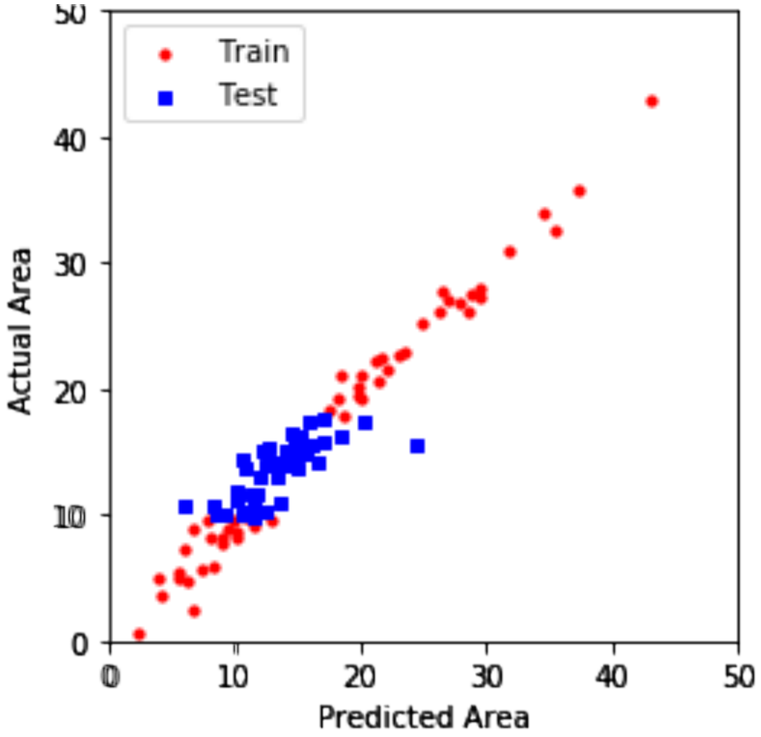


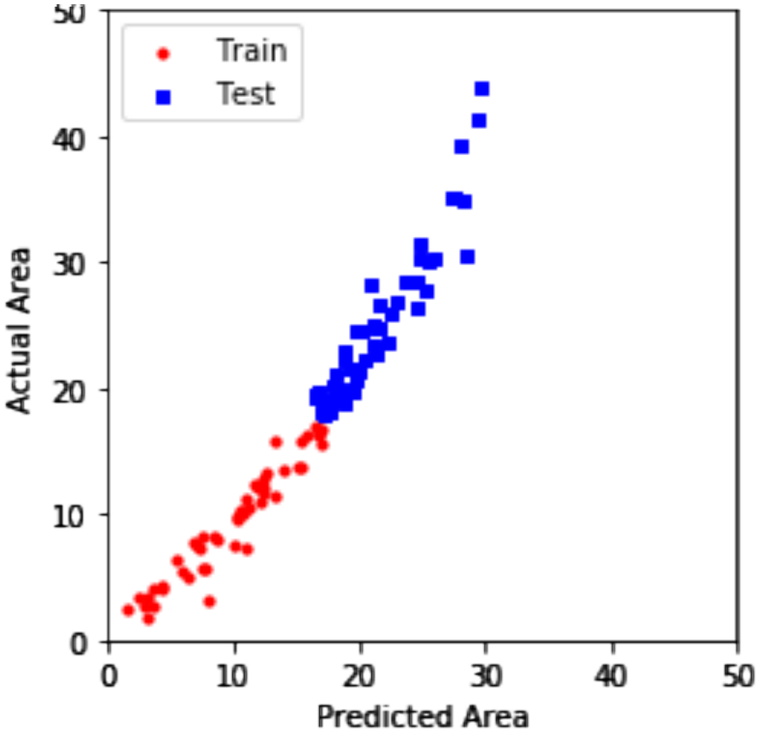


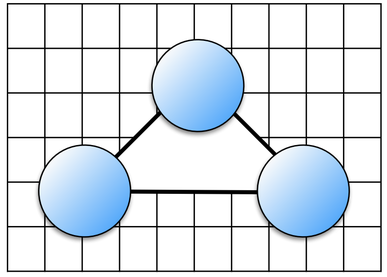
Area

An Aside...









Area

Acknowledgements

Drew McNutt
Jocelyn Sunseri
Matthew Ragoza
Paul Francoeur
Jonathan King
Tomohide Masuda

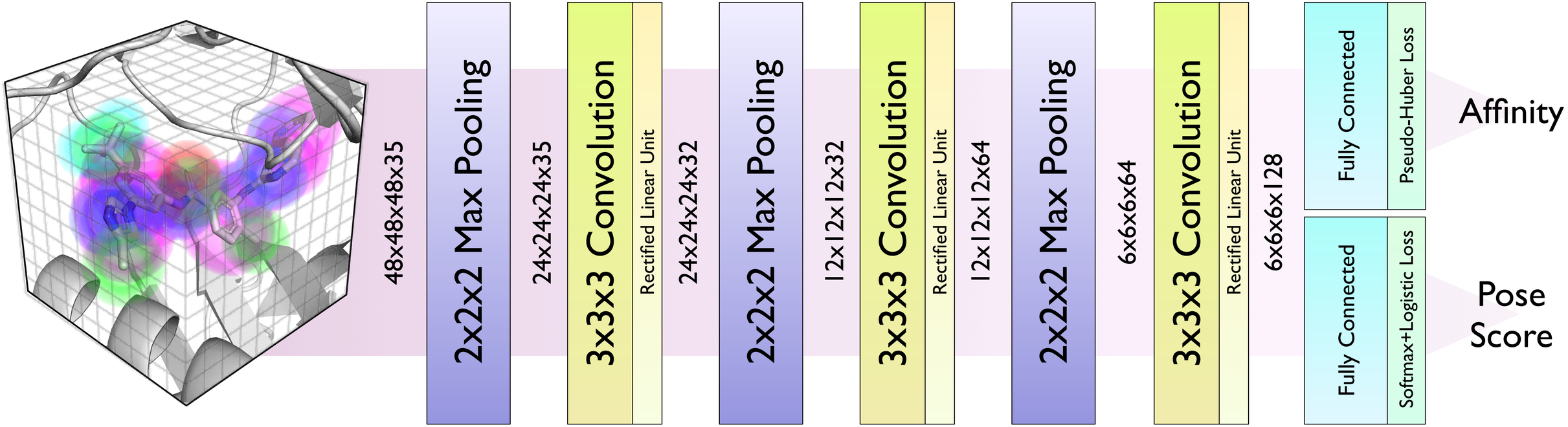
Rocco Meli
Rishal Aggarwal

Josh Hochuli
Elisa Idrobo
Lily Turner
Alec Helbling
Andrew Jia
Rich Iovanisci
Ian Snyder

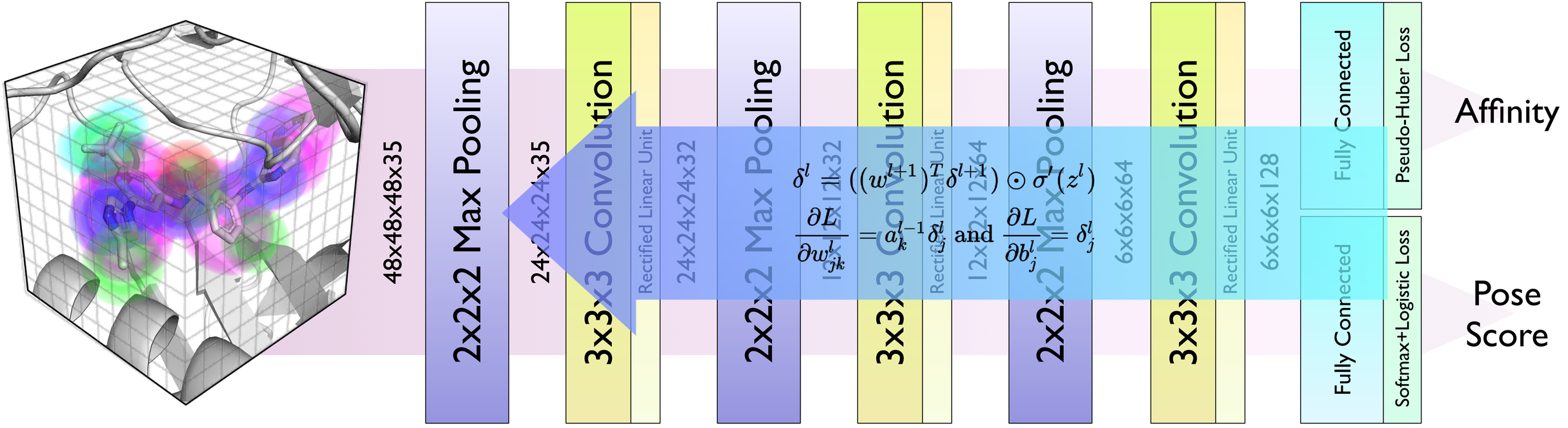
National Institute of General Medical Sciences
R01GM108340
R35GM140753

NSF
CHE-1800435

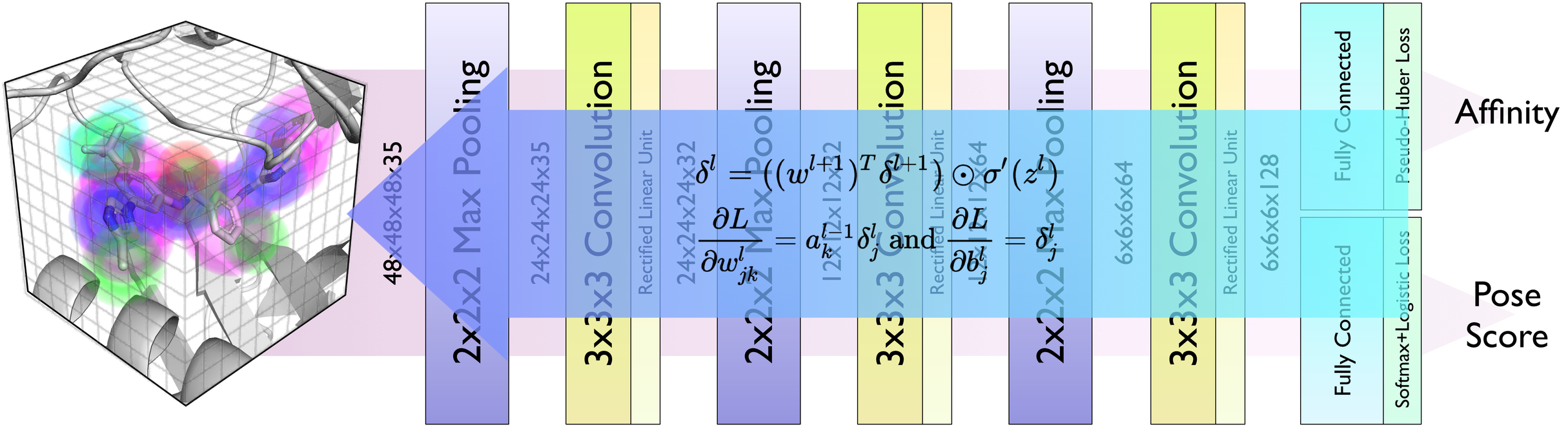
Gradients


48x48x48x35
2x2x2 Max Pooling
24x24x24x35
3x3x3 Convolution
Rectified Linear Unit
24x24x24x32
2x2x2 Max Pooling
12x12x12x32
3x3x3 Convolution
Rectified Linear Unit
12x12x12x64
2x2x2 Max Pooling
6x6x6x64
3x3x3 Convolution
Rectified Linear Unit
6x6x6x128
Fully Connected
Pseudo-Huber Loss
Affinity
Fully Connected
Softmax+Logistic Loss
Pose Score

Gradients


48x48x48x35
2x2x2 Max Pooling
24x24x24x35
3x3x3 Convolution
Rectified Linear Unit
24x24x24x32
2x2x2 Max Pooling
12x12x12x32
3x3x3 Convolution
Rectified Linear Unit
12x12x12x64
2x2x2 Max Pooling
6x6x6x64
3x3x3 Convolution
Rectified Linear Unit
6x6x6x128
Fully Connected
Pseudo-Huber Loss
Affinity
Fully Connected
Softmax+Logistic Loss
Pose Score
$\delta^l = ((w^{l+1})^T \delta^{l+1}) \odot \sigma'(z^l)$
$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j$ and $\frac{\partial L}{\partial b^l_j} = \delta^l_j$

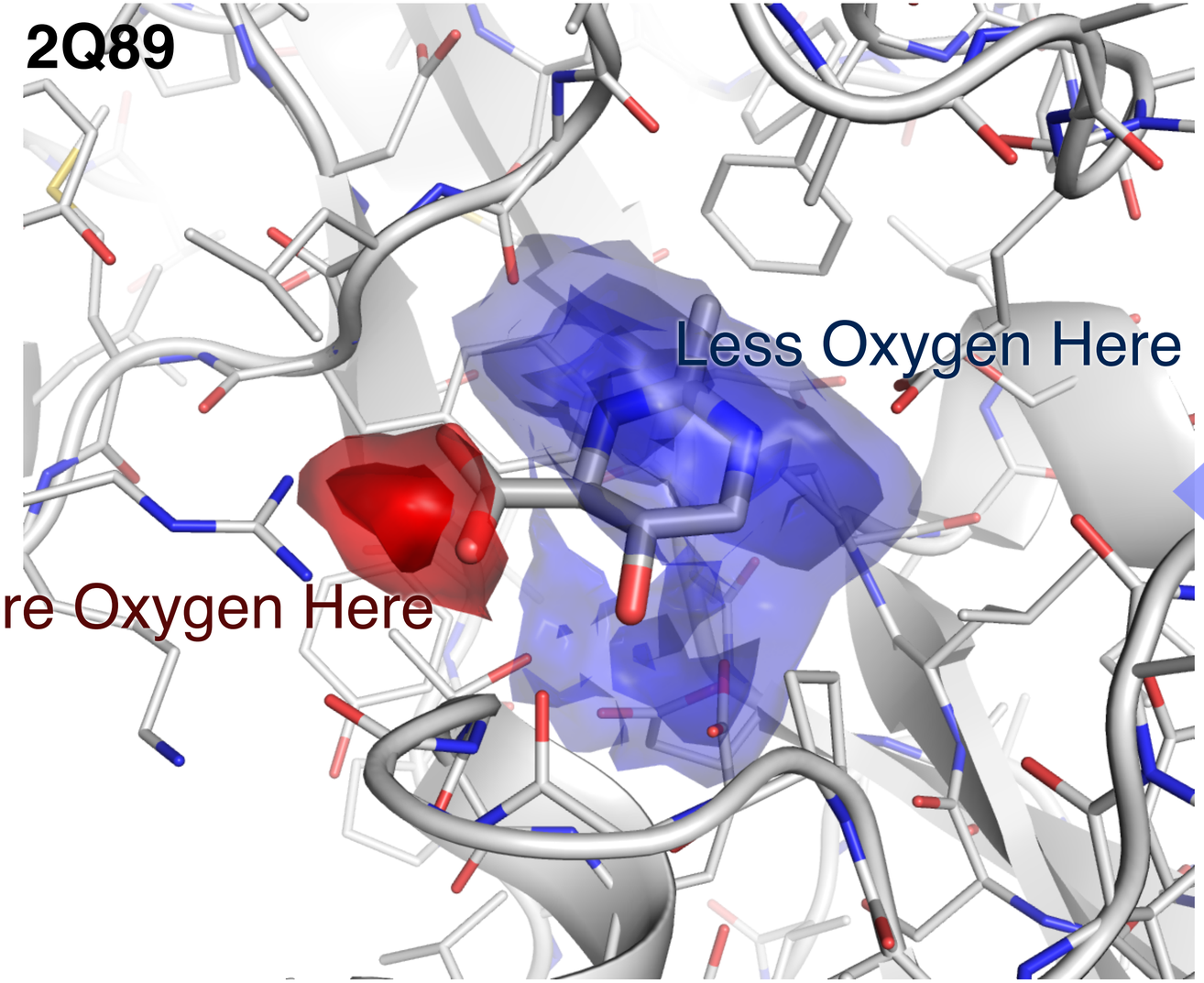
Gradients



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

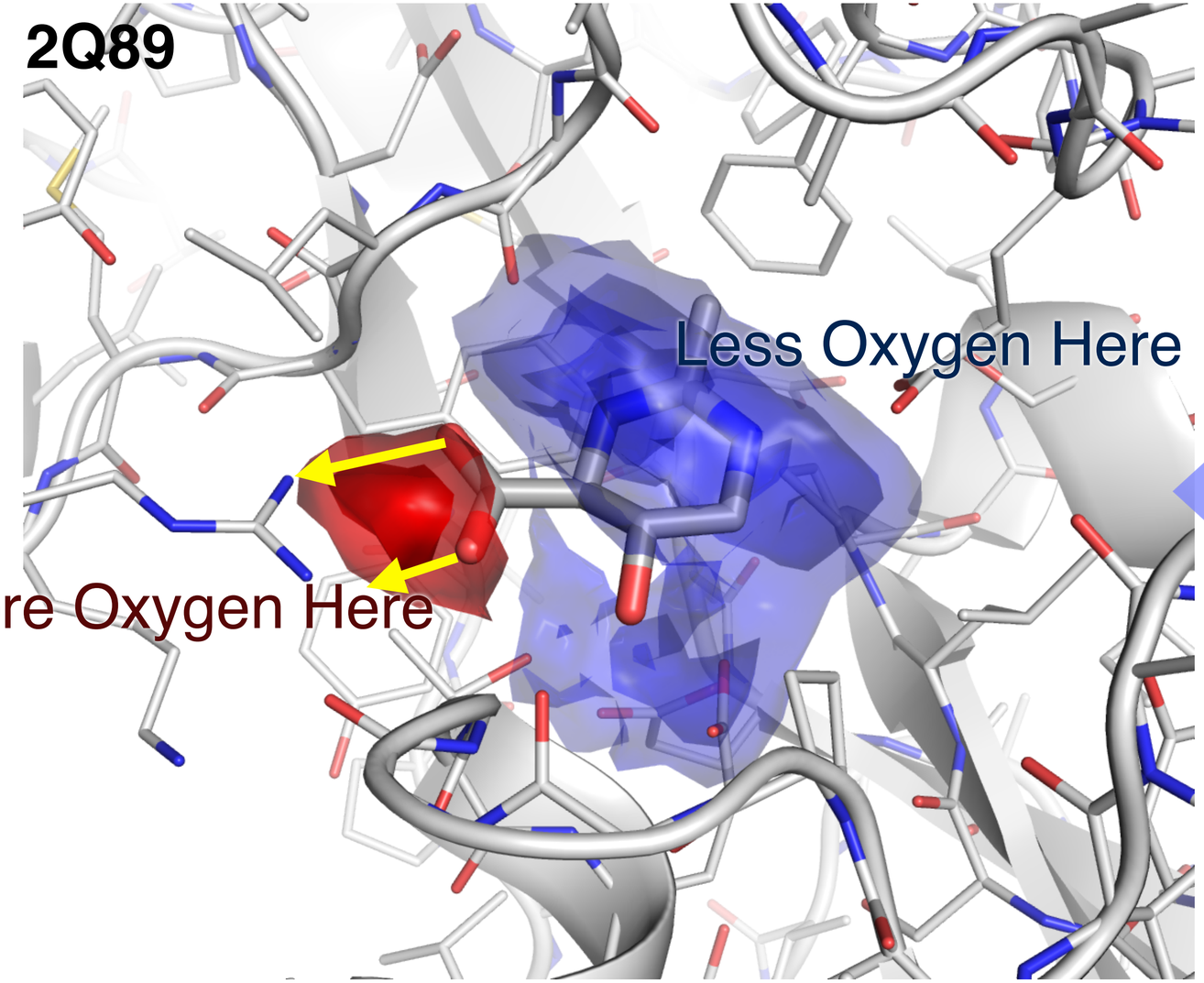
$$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j \text{ and } \frac{\partial L}{\partial b^l_j} = \delta^l_j$$

Gradients

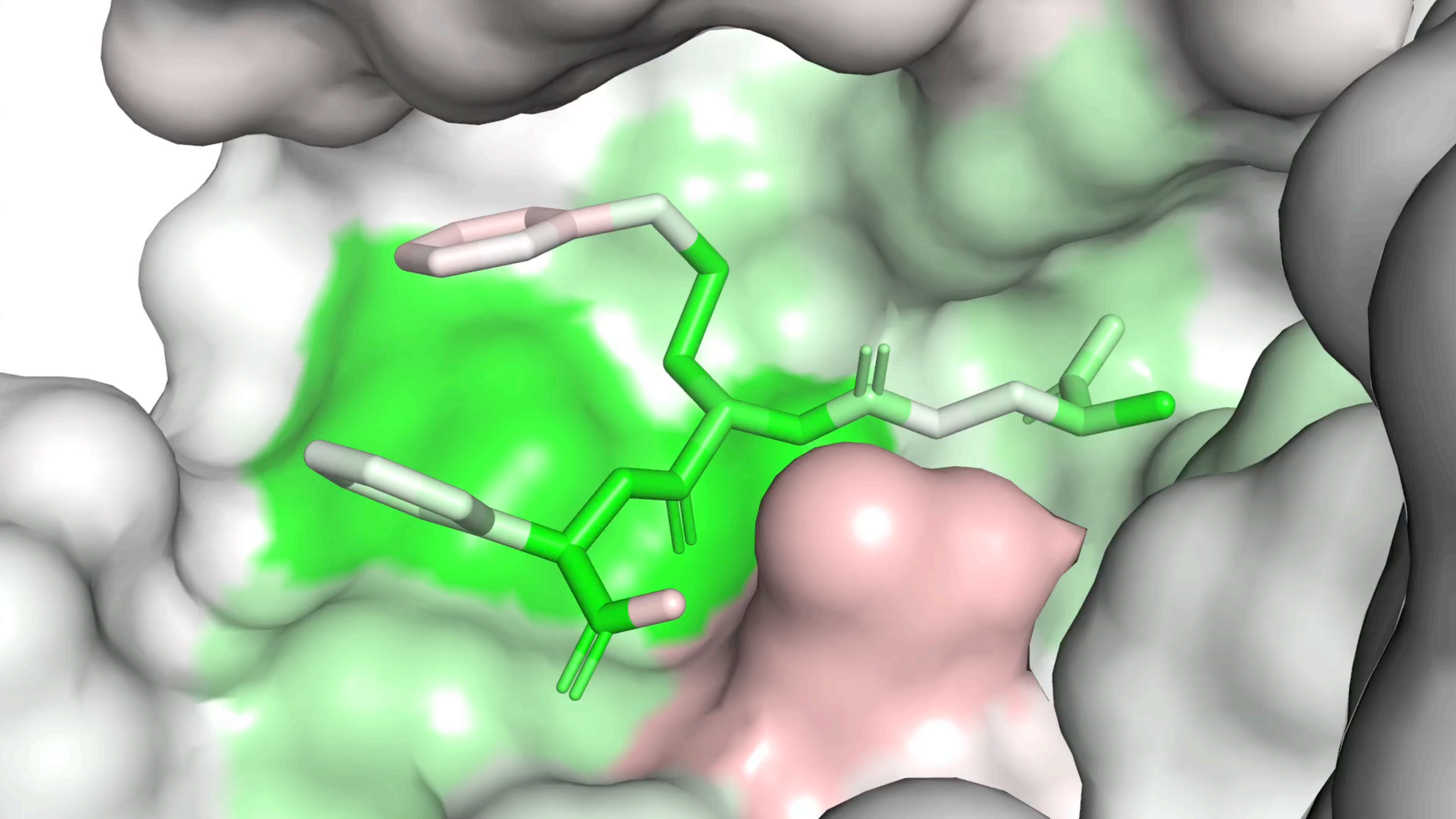


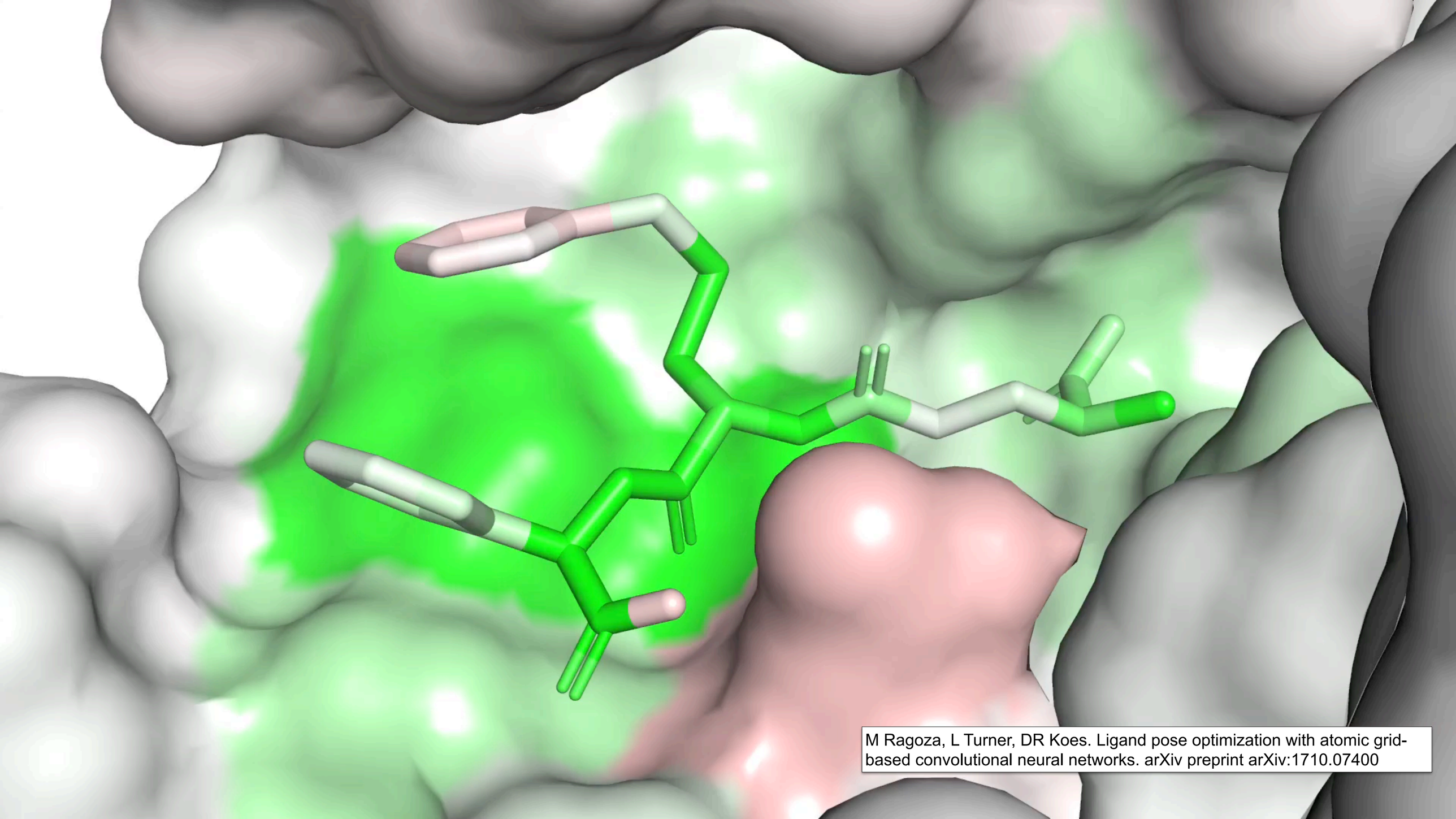
$$\frac{\partial L}{\partial A} = \sum_{i \in G_A} \frac{\partial L}{\partial G_i} \frac{\partial G_i}{\partial D} \frac{\partial D}{\partial A}$$

Gradients



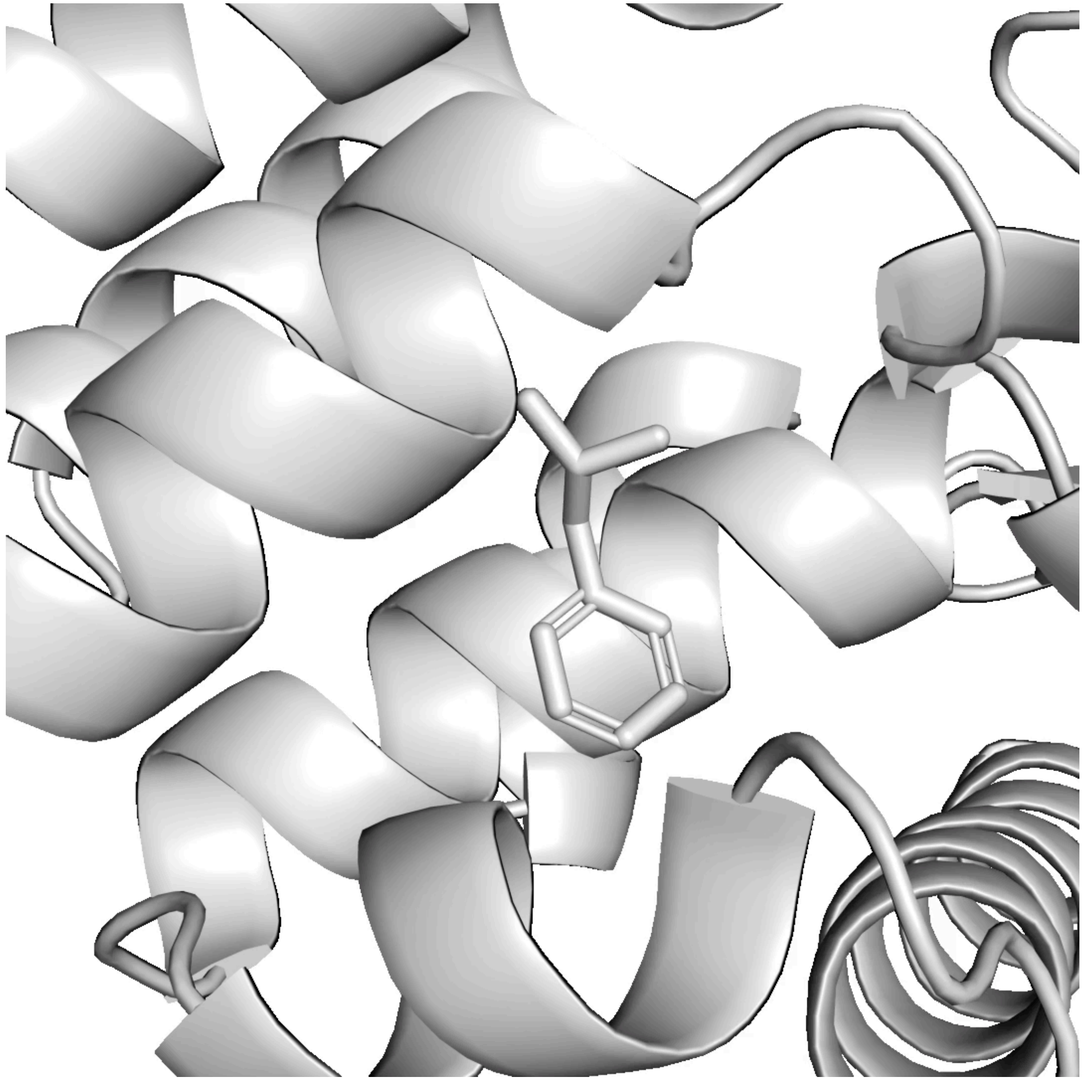
$$\frac{\partial L}{\partial A} = \sum_{i \in G_A} \frac{\partial L}{\partial G_i} \frac{\partial G_i}{\partial D} \frac{\partial D}{\partial A}$$

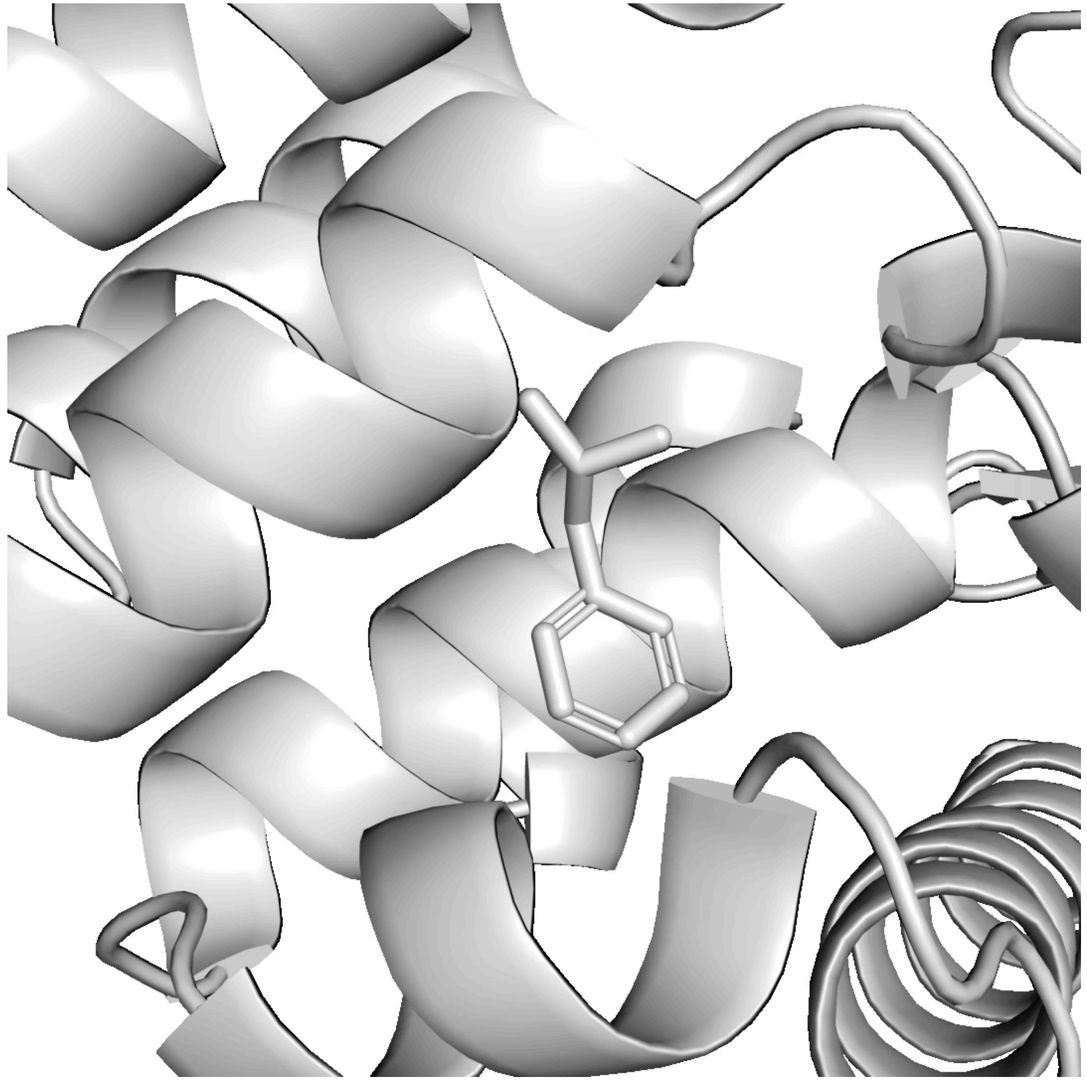




M Ragoza, L Turner, DR Koes. Ligand pose optimization with atomic grid-based convolutional neural networks. arXiv preprint arXiv:1710.07400

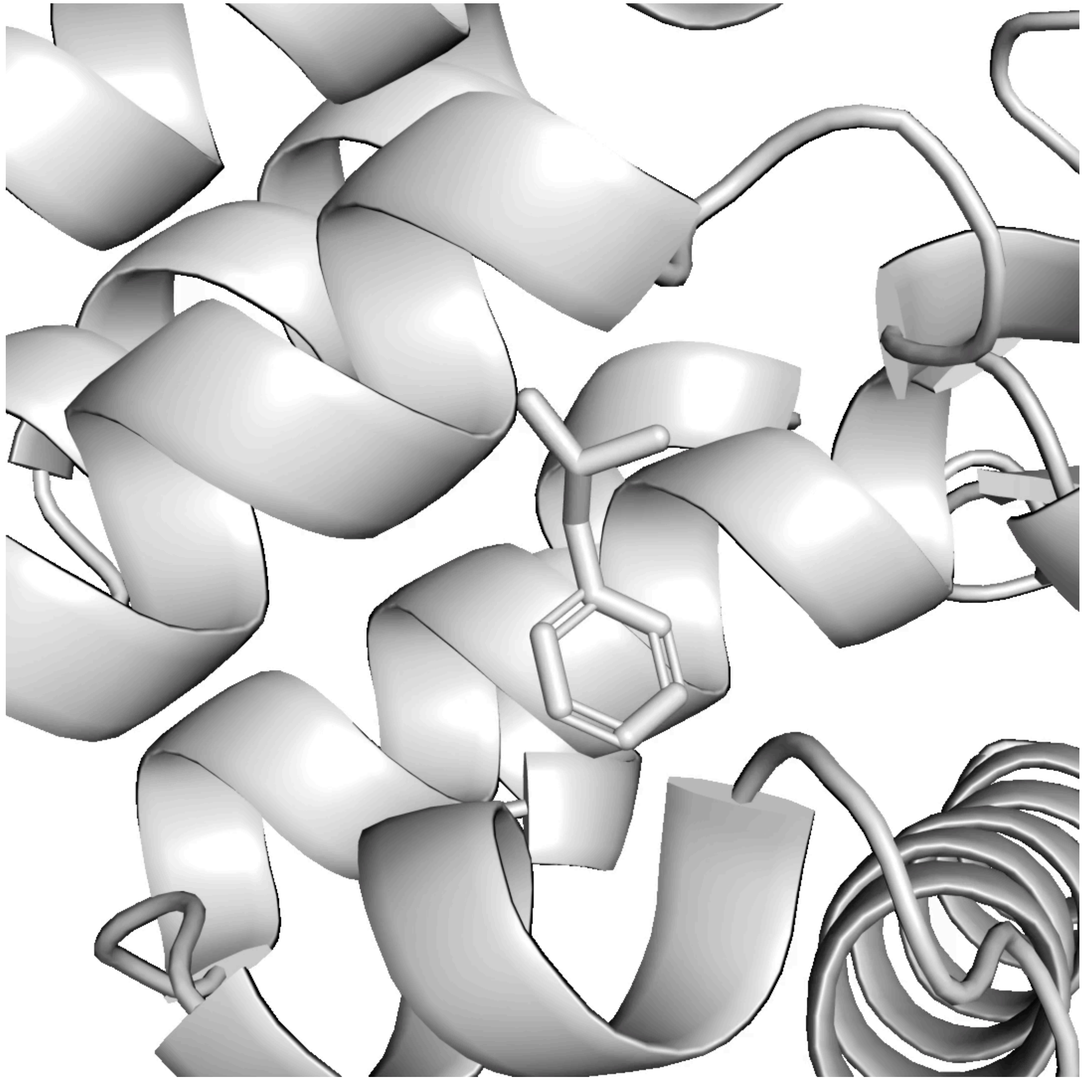
Deep Dreams of Molecules

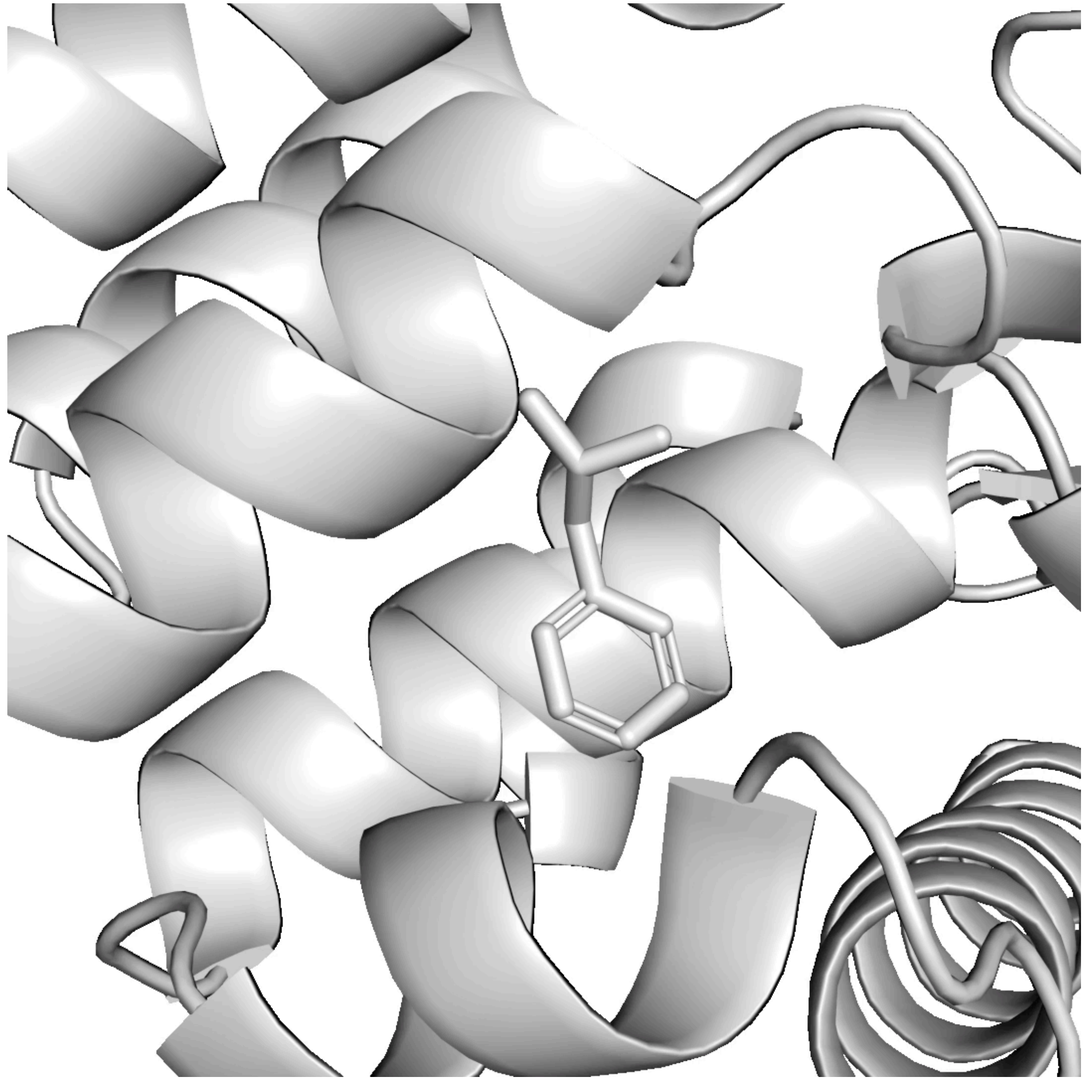




184l

Deep Dreams of Molecules

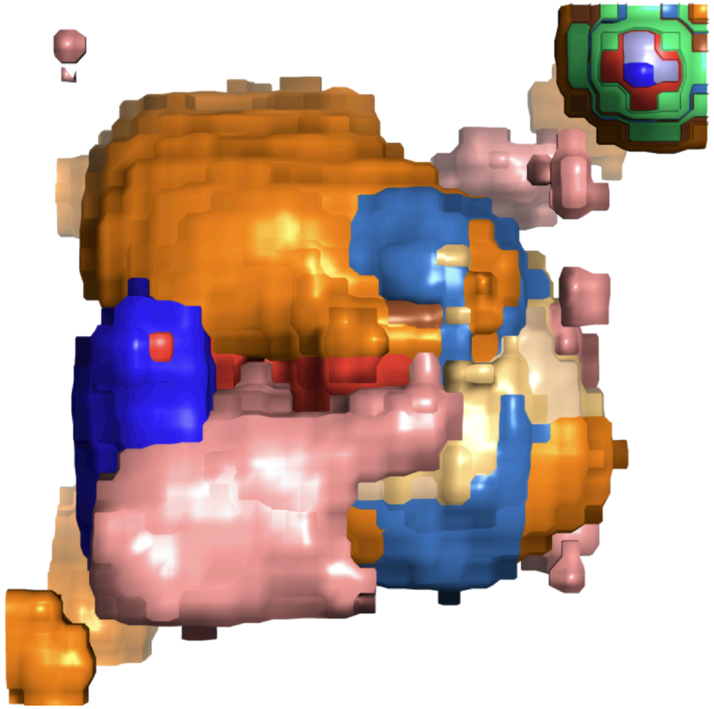


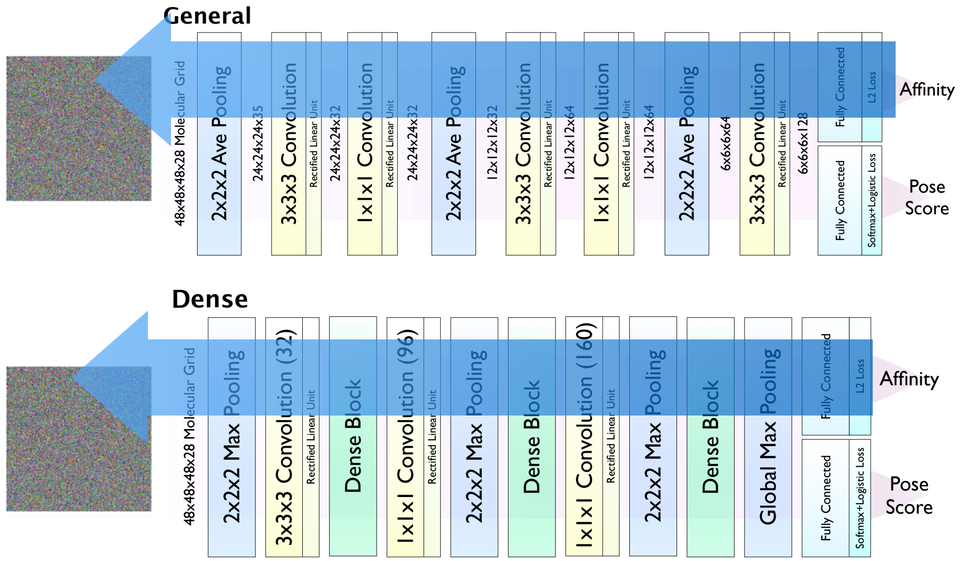


184l

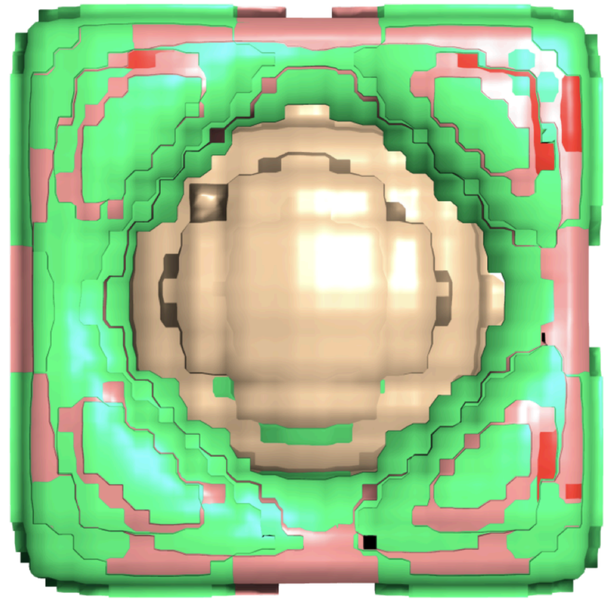
Visualizing

Dense





General



Ligand Aliphatic Carbon

Ligand Nitrogen

Receptor Aliphatic Carbon

Receptor Nitrogen

Ligand Aromatic Carbon

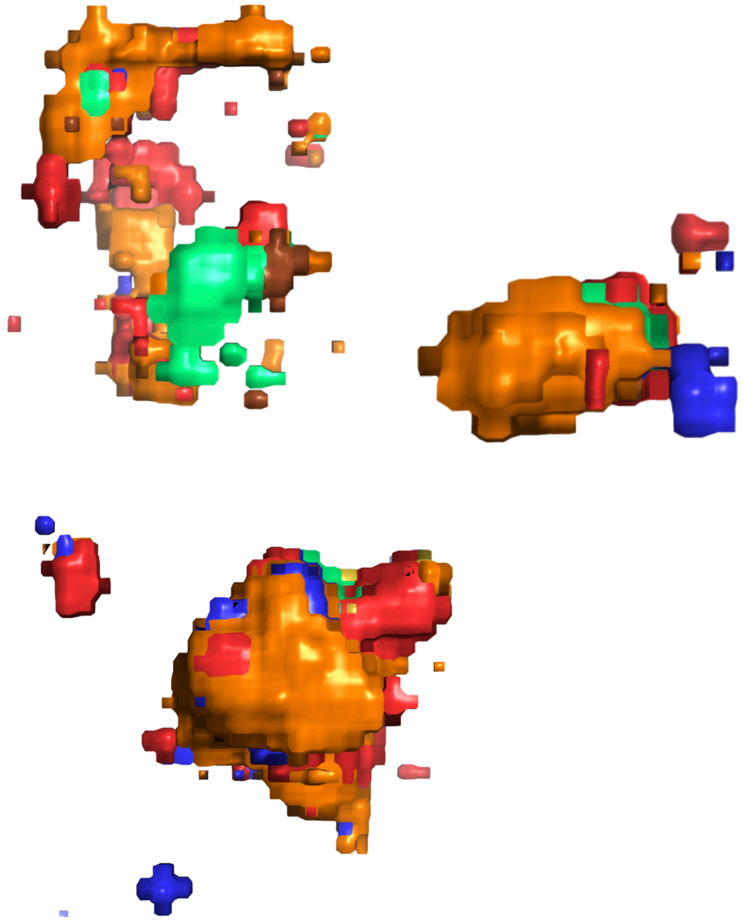
Ligand Oxygen

Receptor Aromatic Carbon

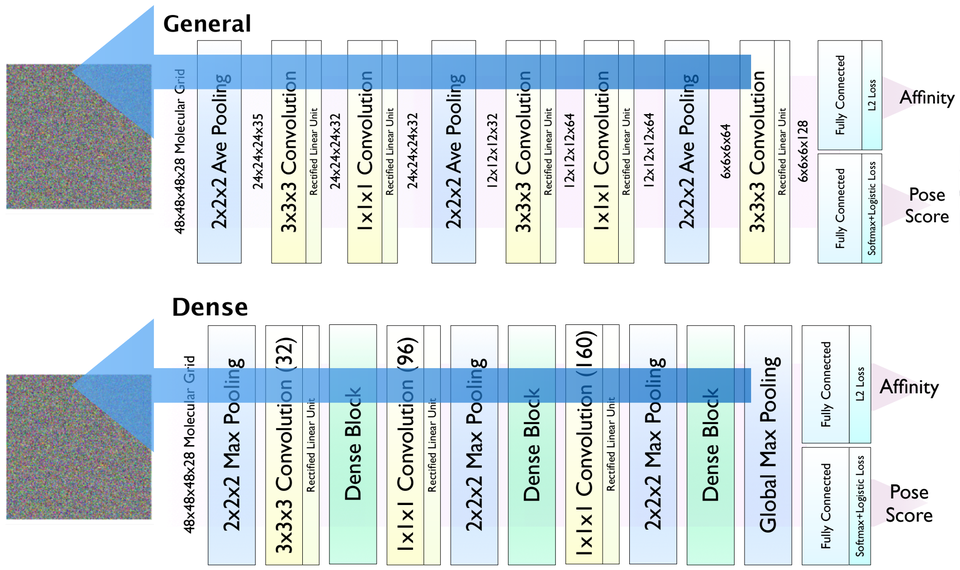
Receptor Oxygen

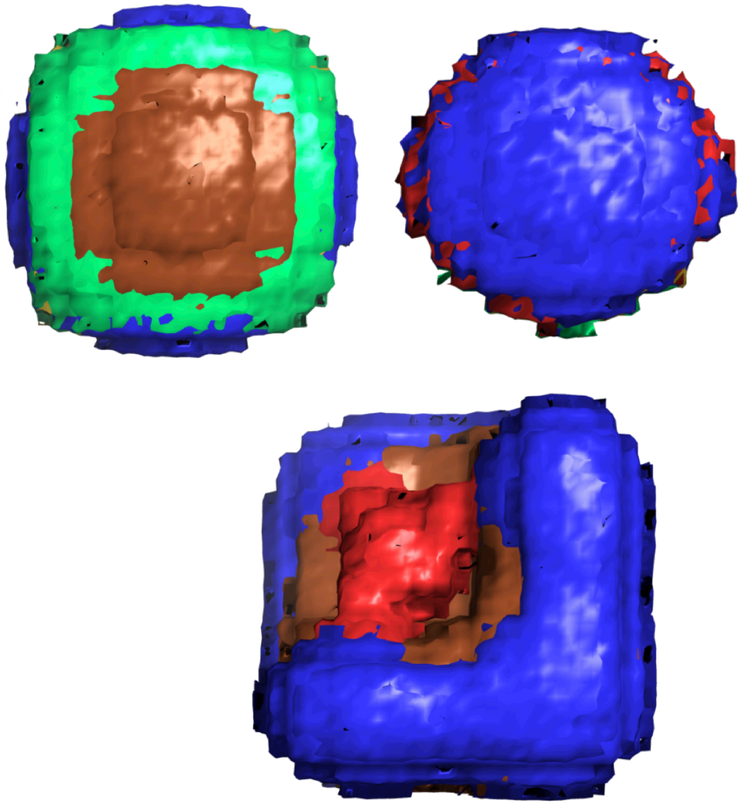
Visualizing

Dense



General

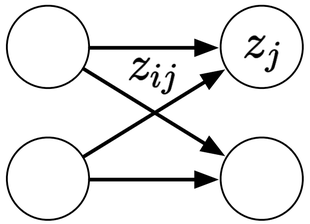




Layer-wise Relevance

$$f(x) = \ldots = \sum_{d \in l+1} R_d^{(l+1)} = \sum_{d \in l} R_d^{(l)} = \ldots = \sum_d R_d^{(1)}$$

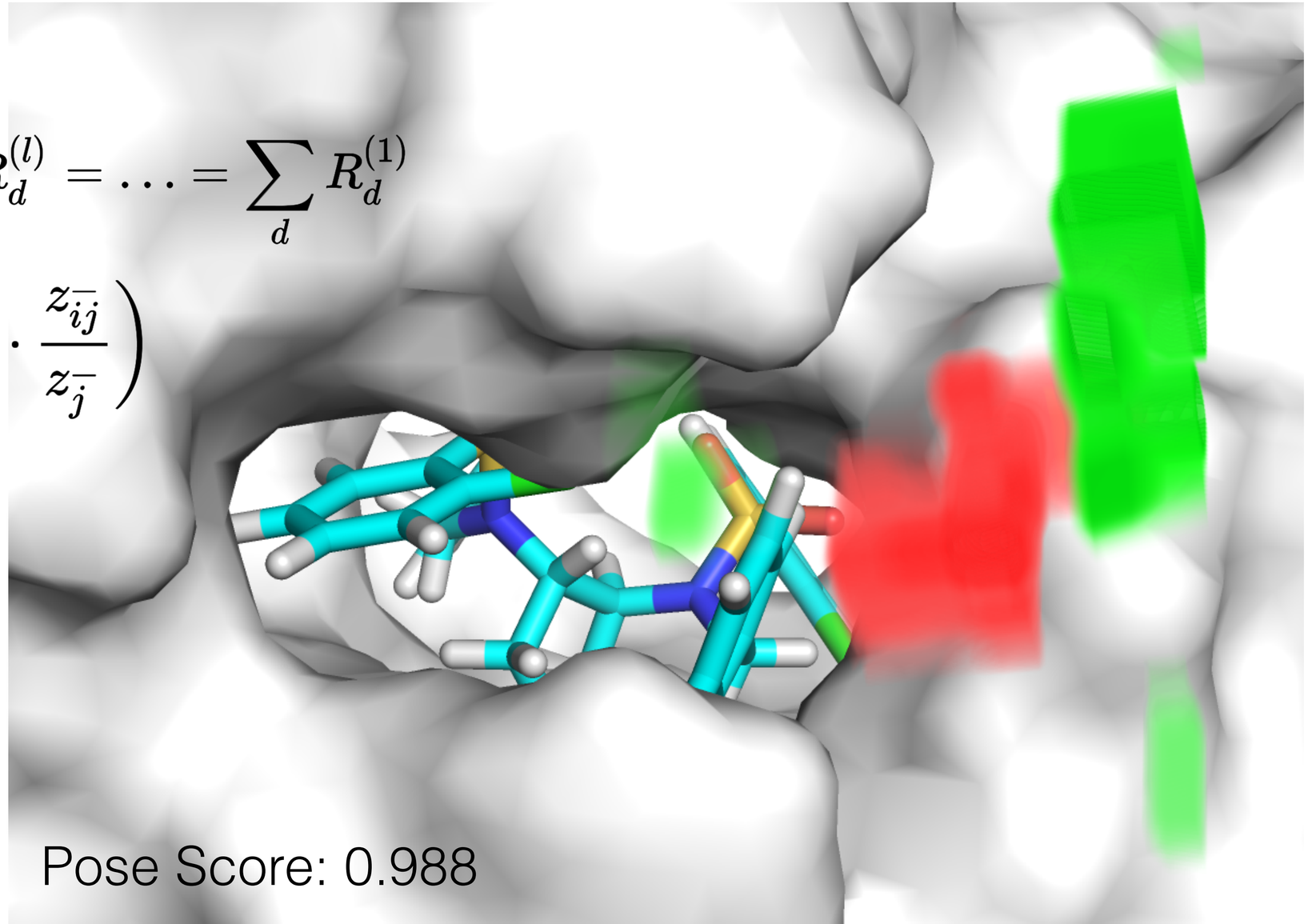
$$R_{i \leftarrow j}^{(l,l+1)} = R_j^{(l+1)} \cdot \left(\alpha \cdot \frac{z_{ij}^+}{z_j^+} + \beta \cdot \frac{z_{ij}^-}{z_j^-} \right)$$



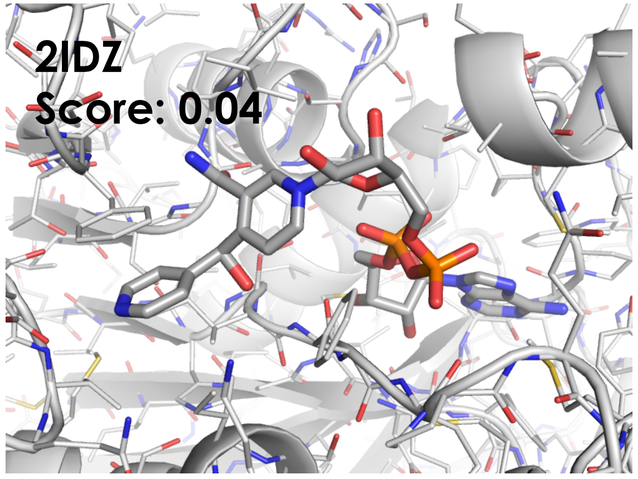
On Pixel-Wise Explanations for Non-Linear Classifier Decisions by Layer-Wise Relevance Propagation

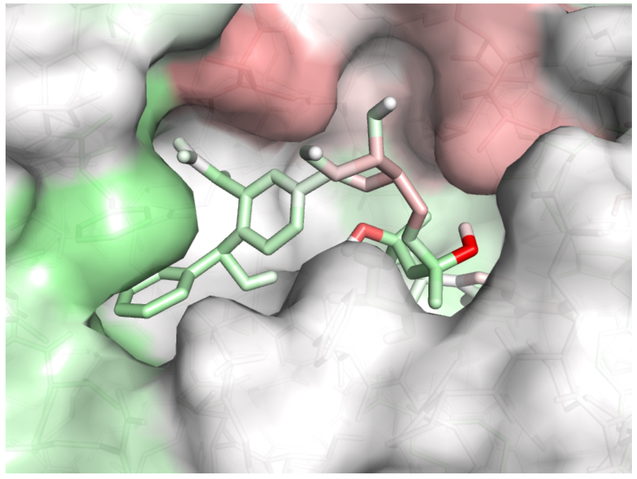
Sebastian Bach, Alexander Binder, Grégoire Montavon, Frederick Klauschen, Klaus-Robert Müller, Wojciech Samek

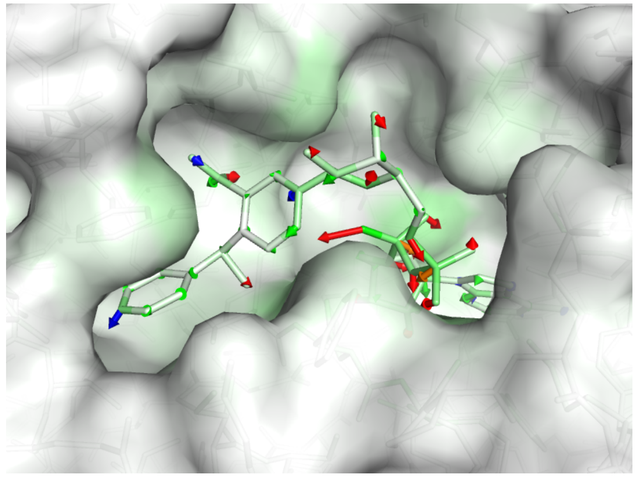
Published: July 10, 2015 • https://doi.org/10.1371/journal.pone.0130140

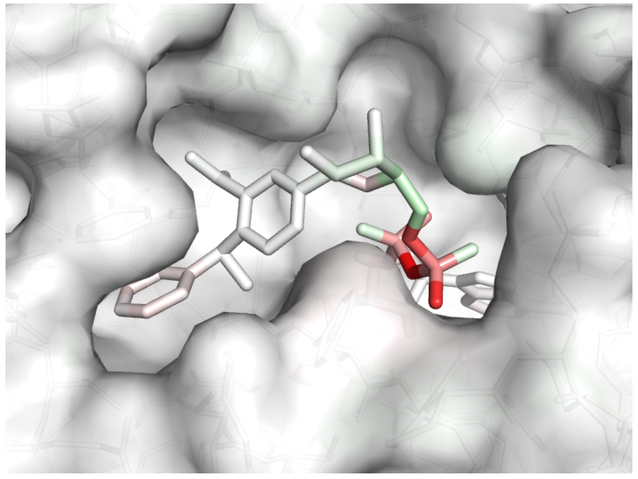


Visualizations





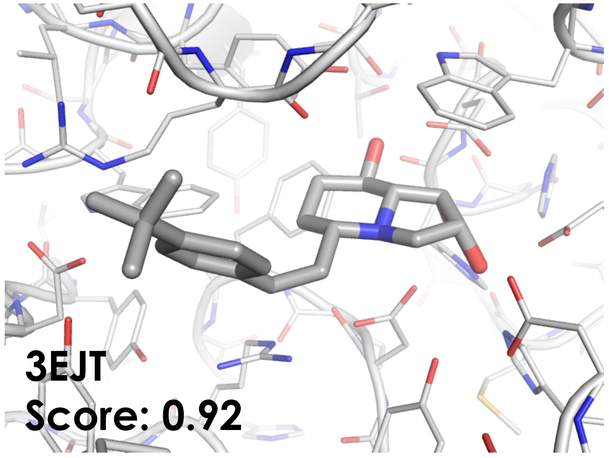


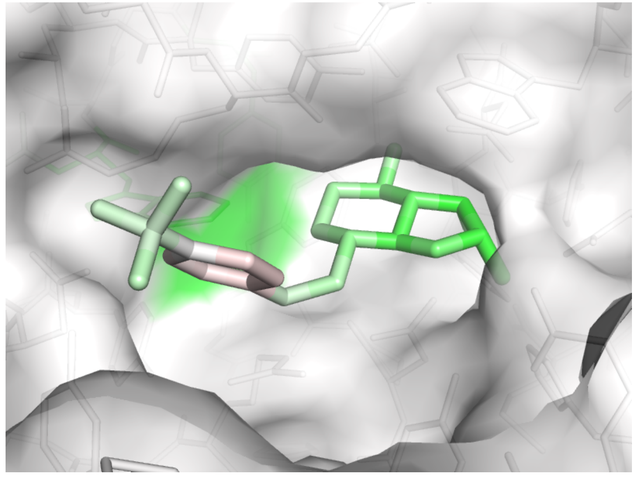


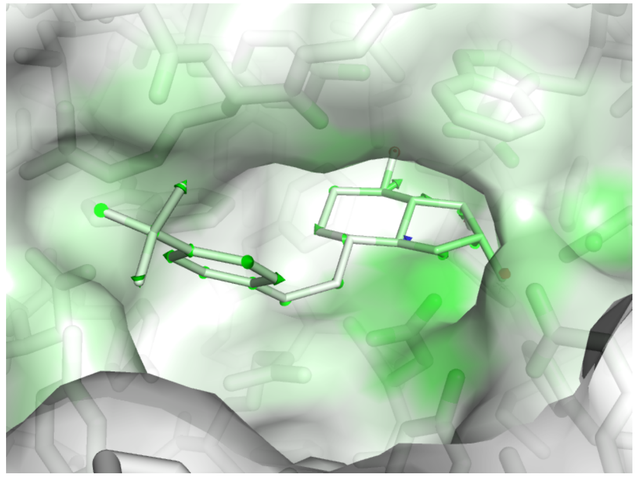
Masking

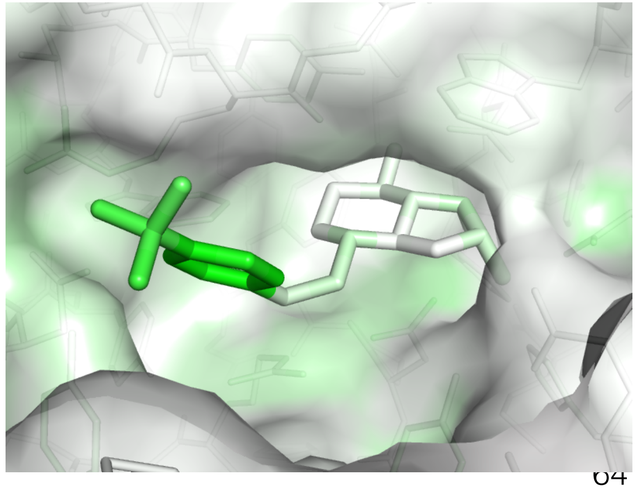
Gradients

LRP

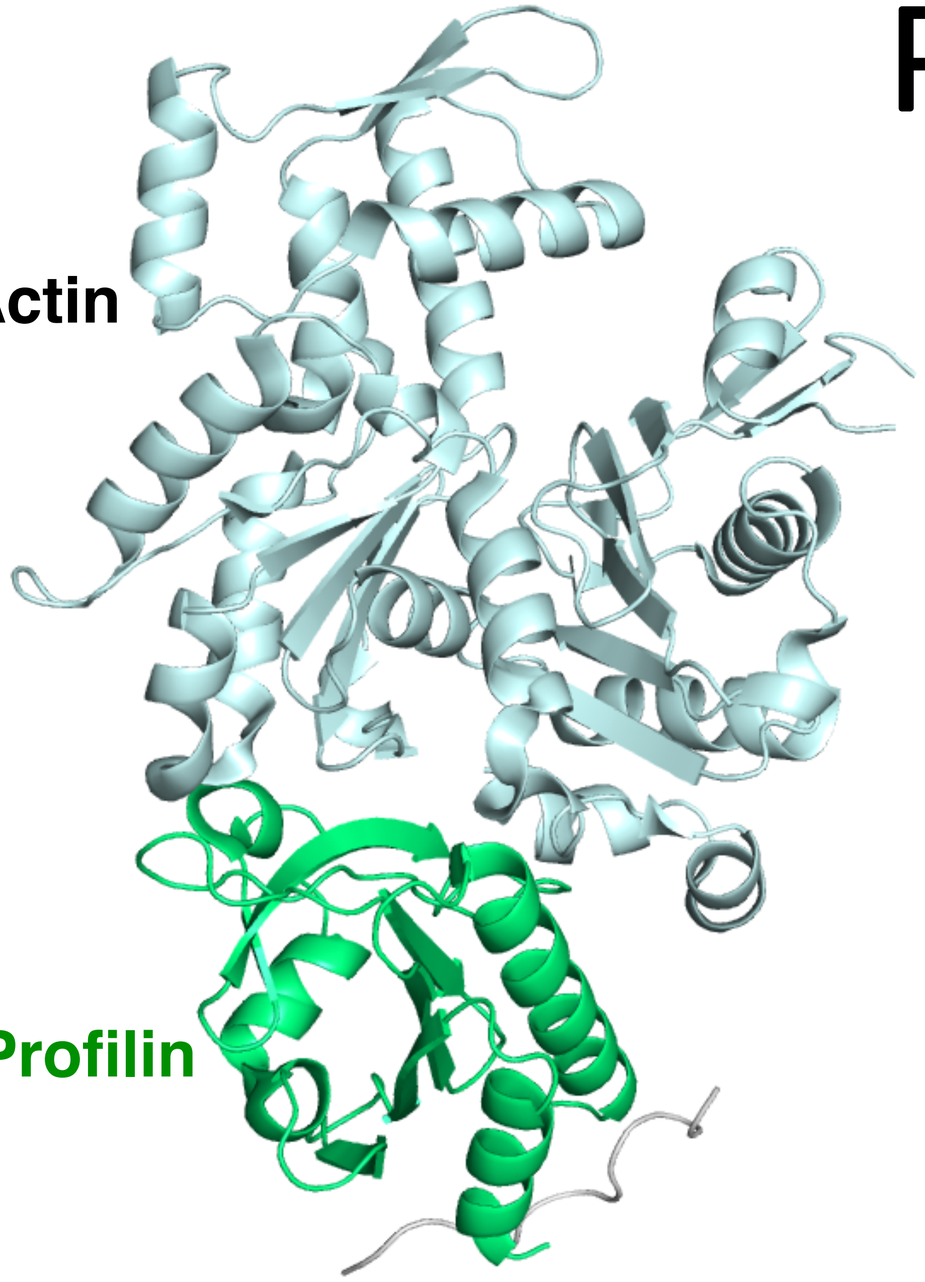








Profilin



- Actin-binding protein
- Accelerates actin polymerization in presence of proline-rich proteins (e.g. formin, WASP, VASP)
- Sequesters actin otherwise

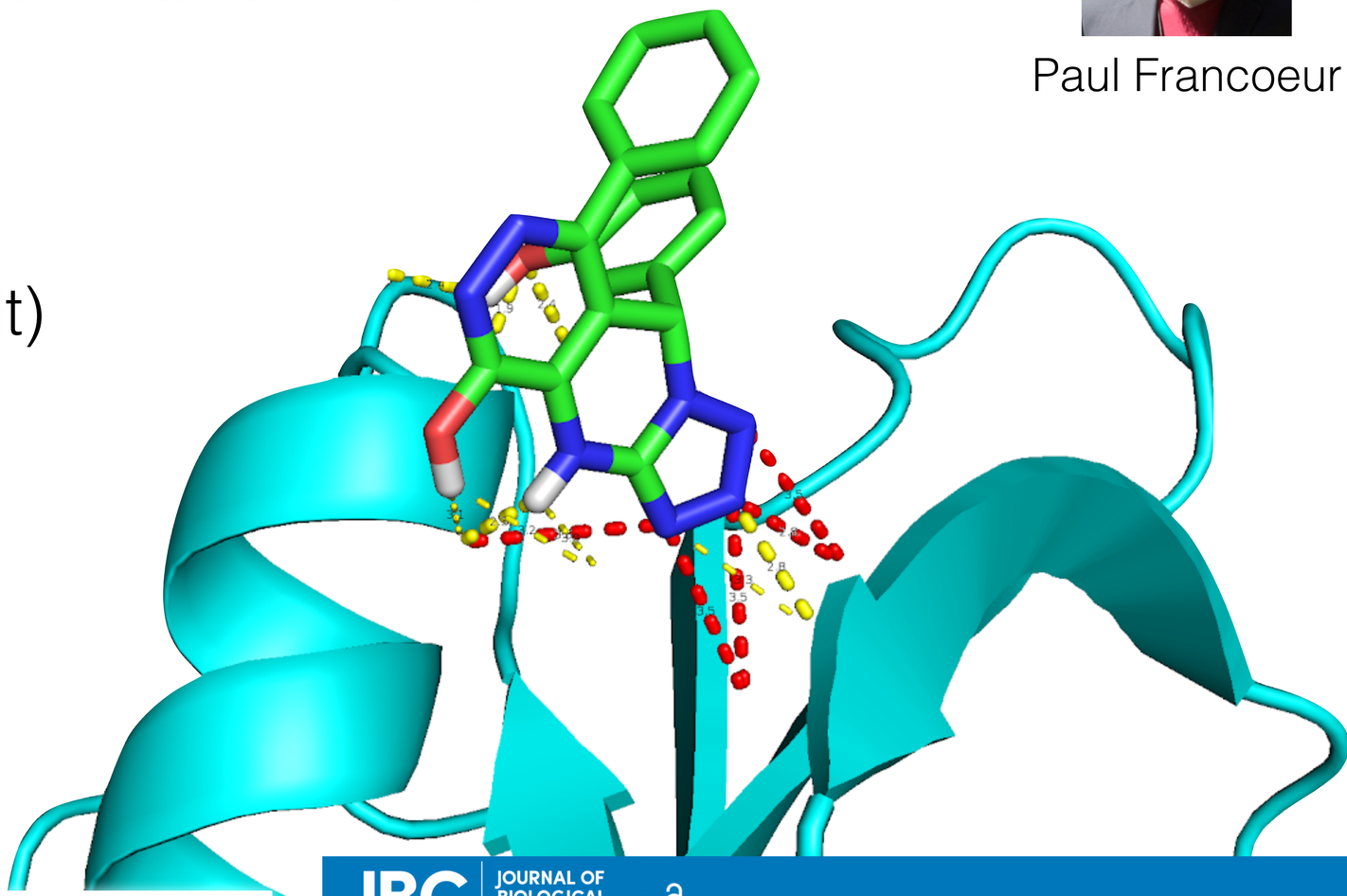
Dave Gau

Partha Roy

Virtual Screen

Paul Francoeur

- Scaffold Hop Early Hit
- Pharmacophore screen (Pharmit)
- Ranked with Vina and CNN



ELSEVIER

Experimental Eye Research
Volume 213, December 2021, 108861

Inhibition of ocular neovascularization by novel anti-angiogenic compound

David Gau [a], Lucile Vignaud [b], Paul Francoeur [c], David Koes [c], Xavier Guillonneau [b], Partha Roy [a, d]

JBC JOURNAL OF BIOLOGICAL CHEMISTRY

Structure-based virtual screening identifies a small-molecule inhibitor of the profilin 1–actin interaction

David Gau[‡1], Taber Lewis[§], Lee McDermott[¶], Peter Wipf[‡,§], David Koes[¶] and Partha Roy[‡,‖,**2]

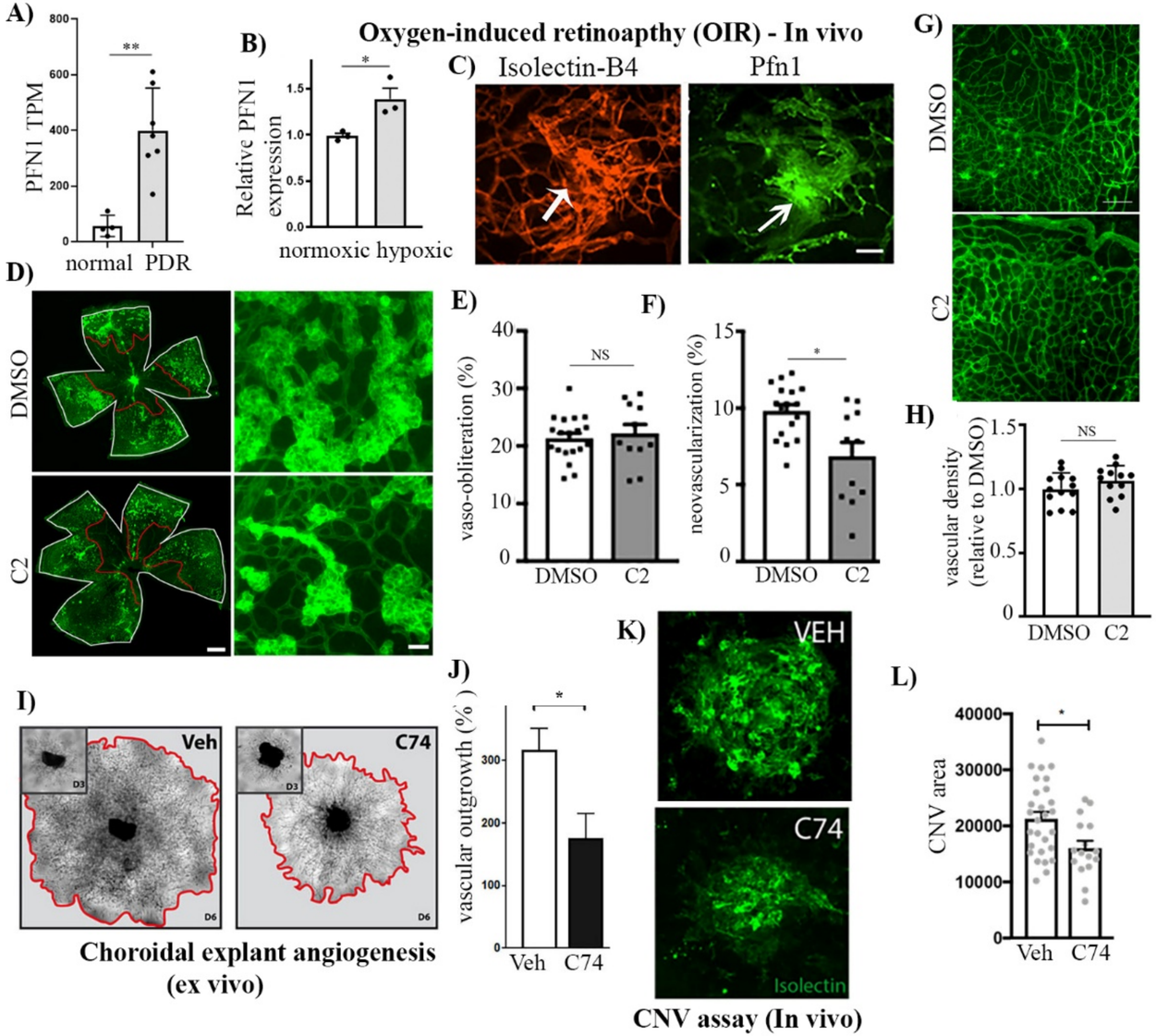
JBC JOURNAL OF BIOLOGICAL CHEMISTRY OPEN ACCESS

CELL BIOLOGY | VOLUME 295, ISSUE 46, P15636-15649, NOVEMBER 2020

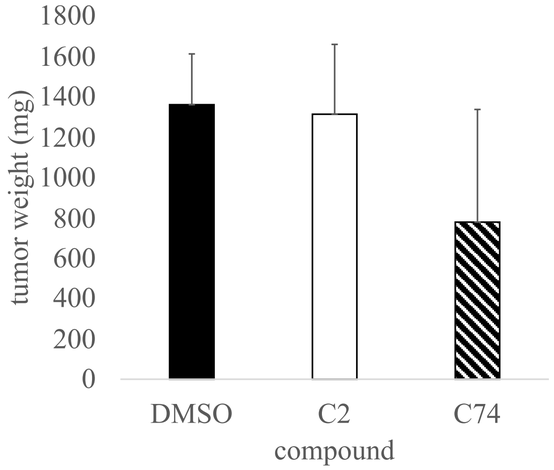
Actin-binding protein profilin1 promotes aggressiveness of clear-cell renal cell carcinoma cells

Abigail Allen • David Gau • Paul Francoeur • ... David Koes • Walter J. Storkus • Partha Roy • Show all authors

Results


A)
PFN1 TPM
normal PDR
B)
Relative PFN1 expression
normoxic hypoxic
Oxygen-induced retinoapthy (OIR) - In vivo
C) Isolectin-B4
Pfn1
G)
DMSO
C2
D)
DMSO
C2
E)
vaso-obliteration (%)
NS
DMSO C2
F)
neovascularization (%)
DMSO C2
H)
vascular density (relative to DMSO)
NS
DMSO C2
I)
Veh
C74
D3
D6
Choroidal explant angiogenesis (ex vivo)
J)
vascular outgrowth (%)
Veh C74
K)
VEH
C74
Isolectin
CNV assay (In vivo)
L)
CNV area
Veh C74

C74
DMSO
C2


tumor weight (mg)
DMSO
C2
C74
compound