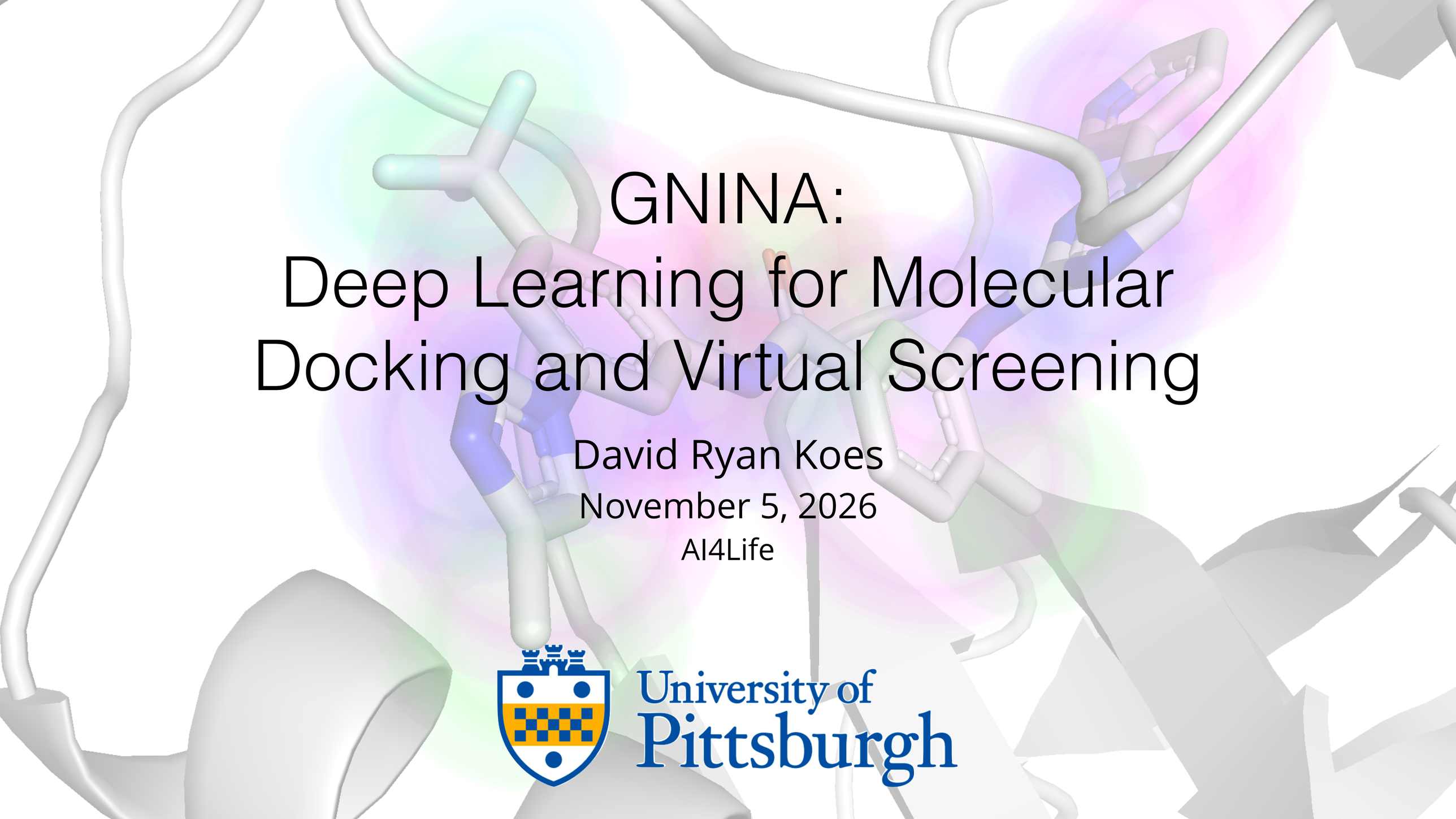


GNINA: Deep Learning for Molecular Docking and Virtual Screening

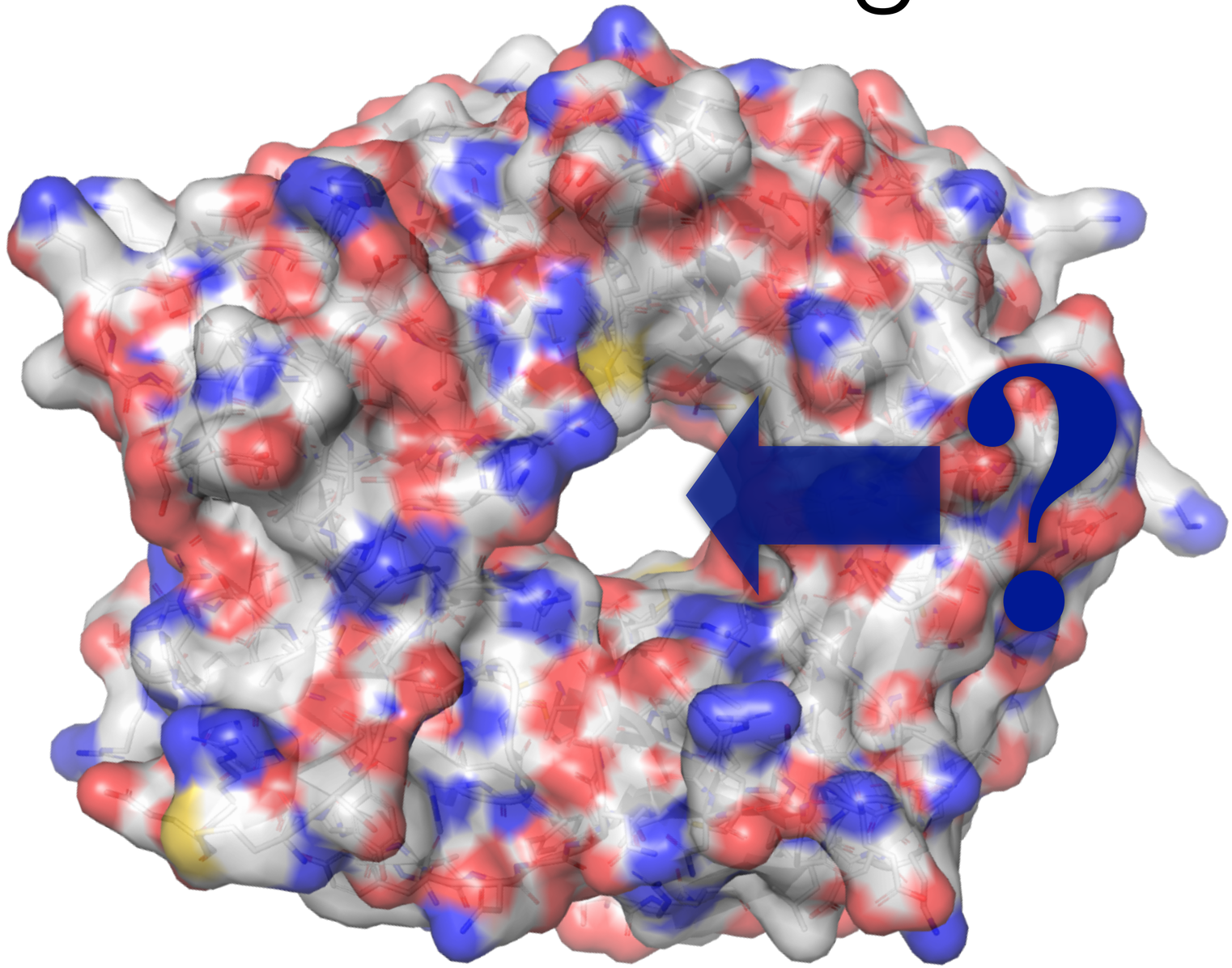
David Ryan Koes

November 5, 2026

AI4Life

University of Pittsburgh

Structure Based Drug Discovery



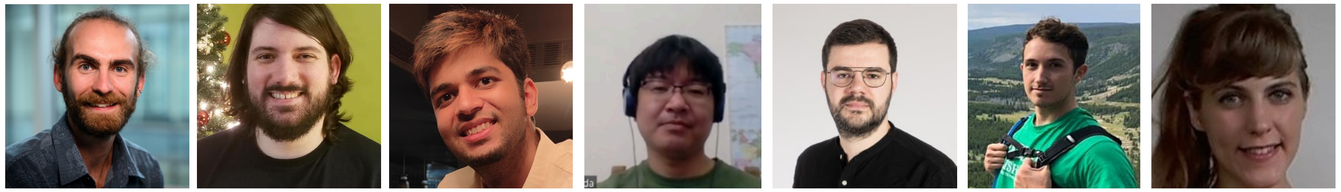
GNINA 1.0

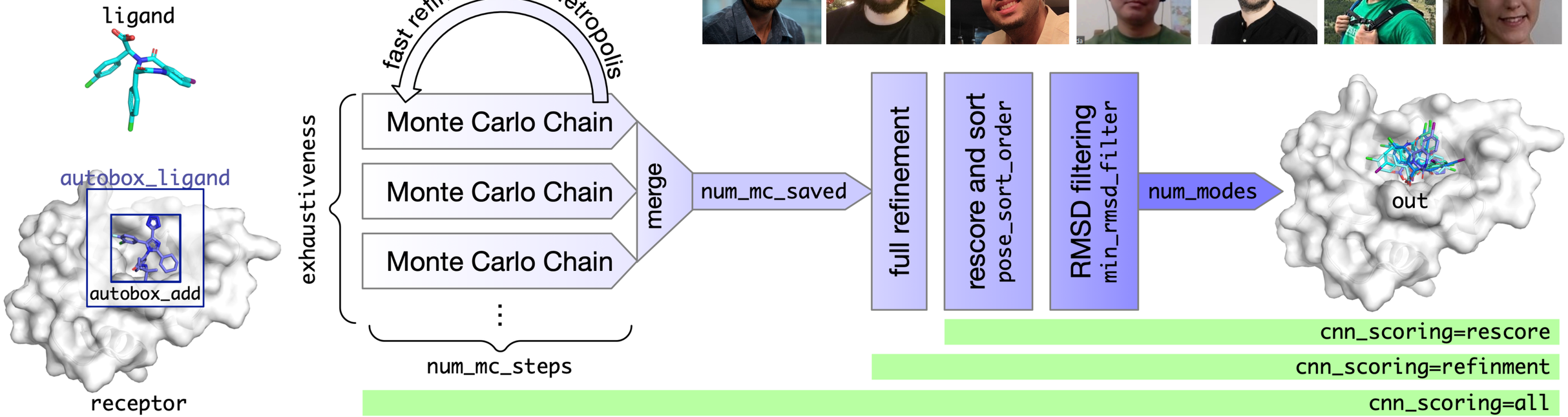
https://github.com/gnina/gnina

SOFTWARE Open Access

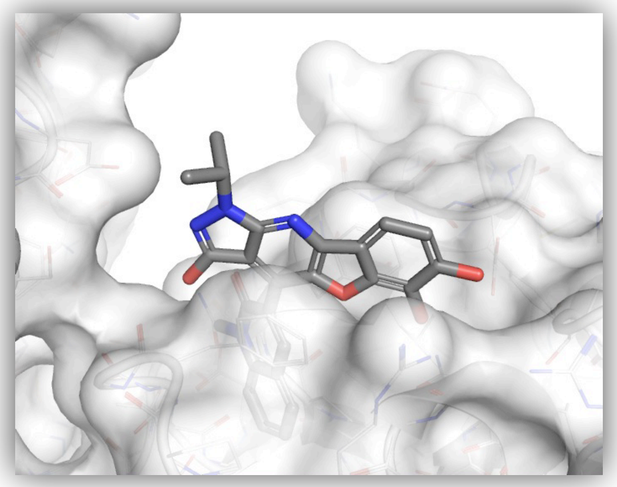
GNINA 1.0: molecular docking with deep learning

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*]





Protein-Ligand Scoring



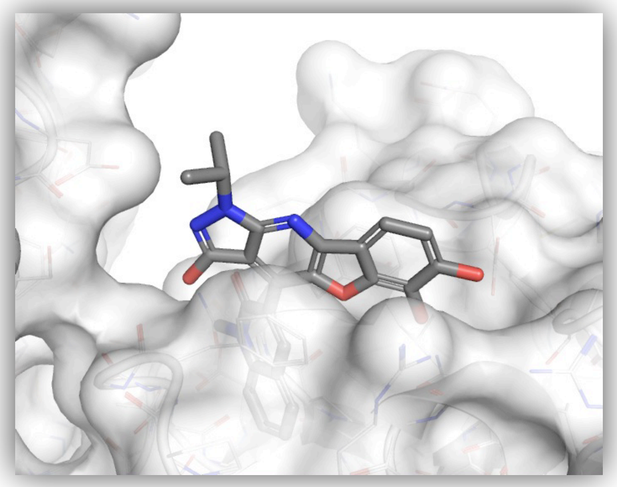
Model

Pose Prediction

Binding Discrimination

Affinity Prediction

Protein-Ligand Scoring



Model

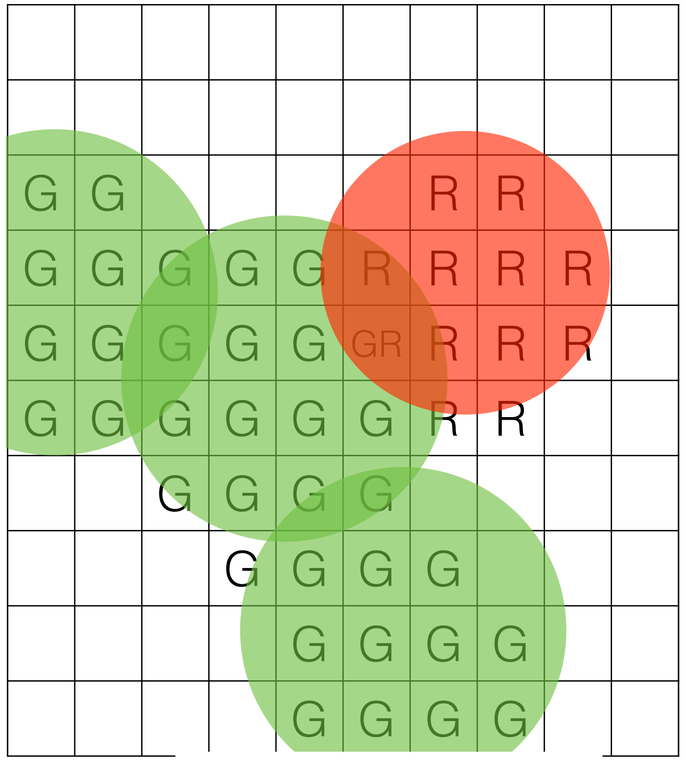
Pose Prediction

Binding Discrimination

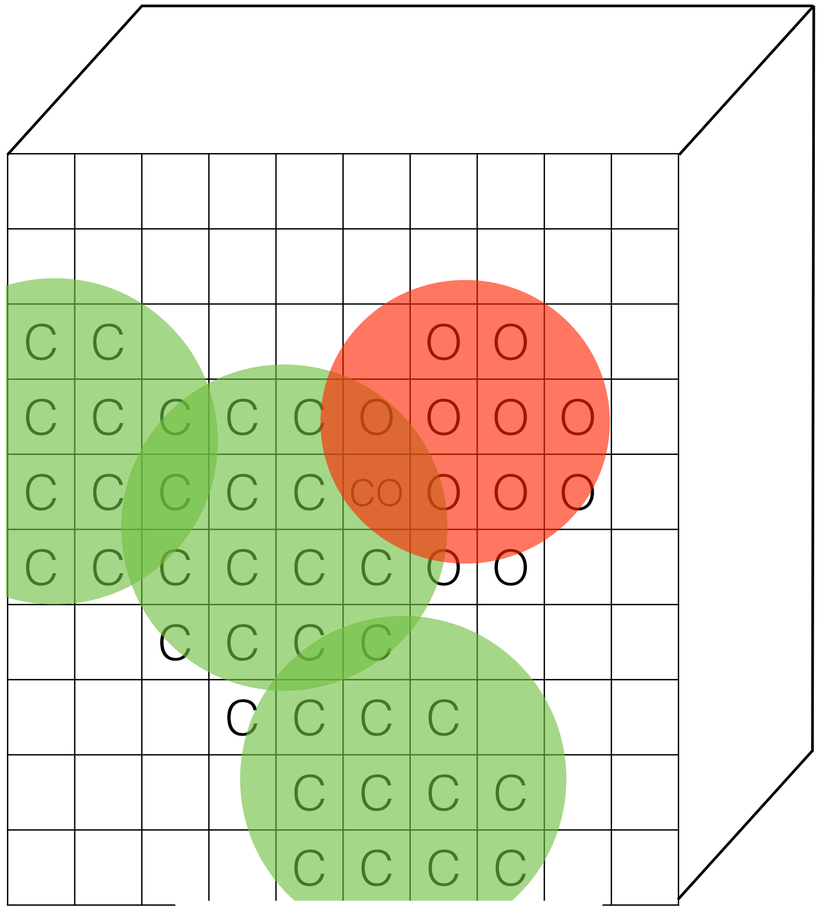
Affinity Prediction

Protein-Ligand Representation

(R,G,B) pixel



Protein-Ligand Representation



(R,G,B) pixel →

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

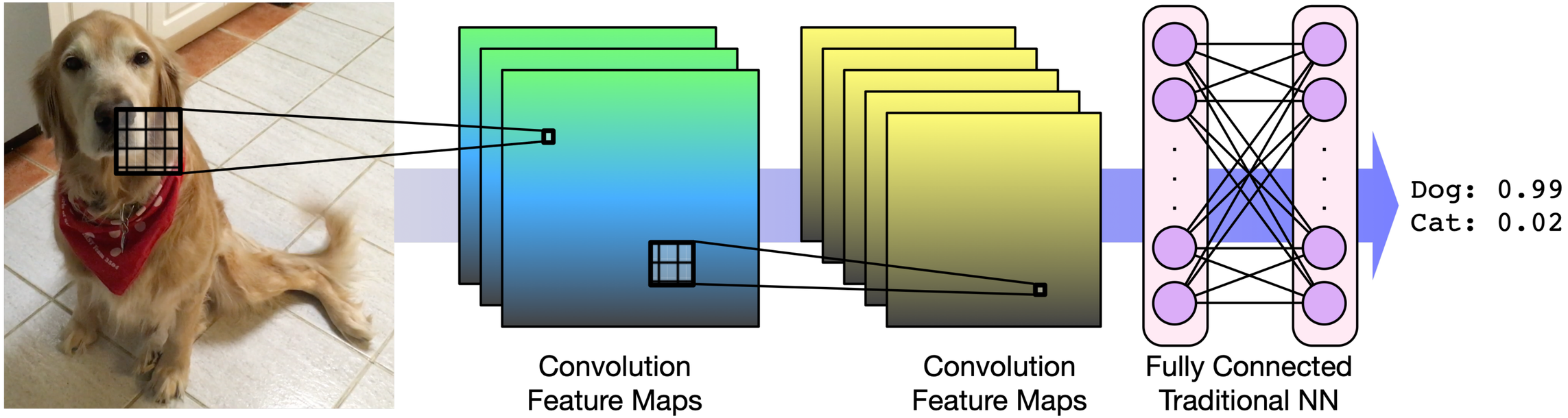
The only parameters for this representation are the choice of **grid resolution**, **atom density**, and **atom types**.

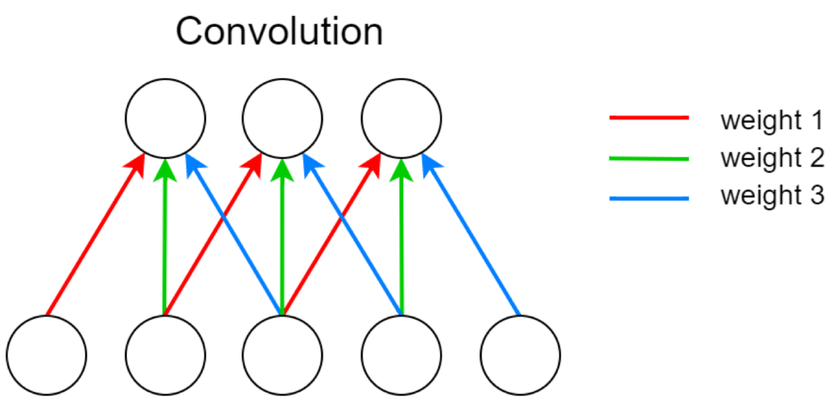
JOURNAL OF CHEMICAL INFORMATION AND MODELING
Article
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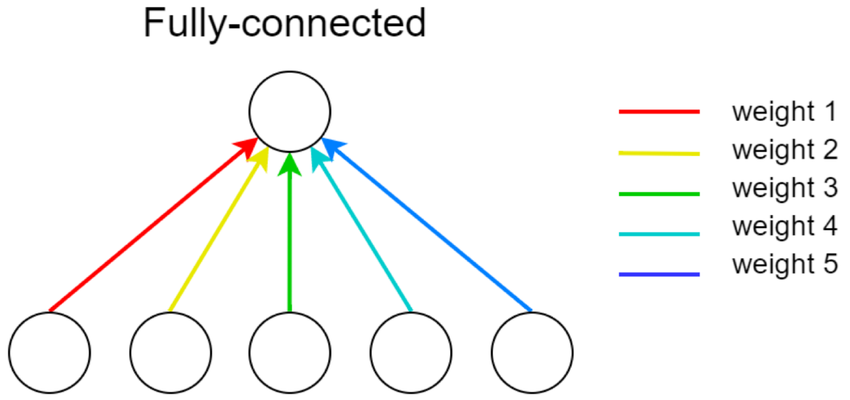
Protein–Ligand Scoring with Convolutional Neural Networks

Matthew Ragoza,[†,‡] Joshua Hochuli,[‡,¶] Elisa Idrobo,[§] Jocelyn Sunseri,[∥] and David Ryan Koes*[,∥]

Convolutional Neural Networks

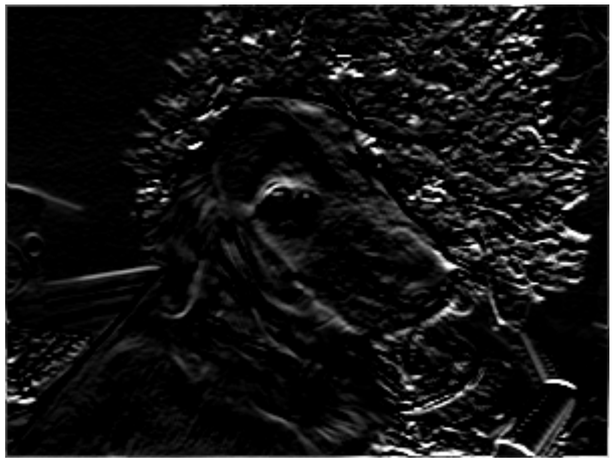






Convolutional Filters





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

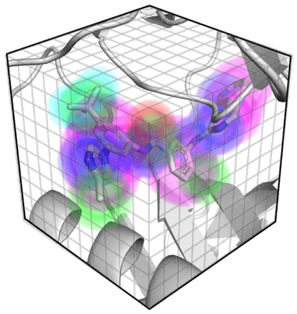


-1	0	1
-1	0	1
-1	0	1

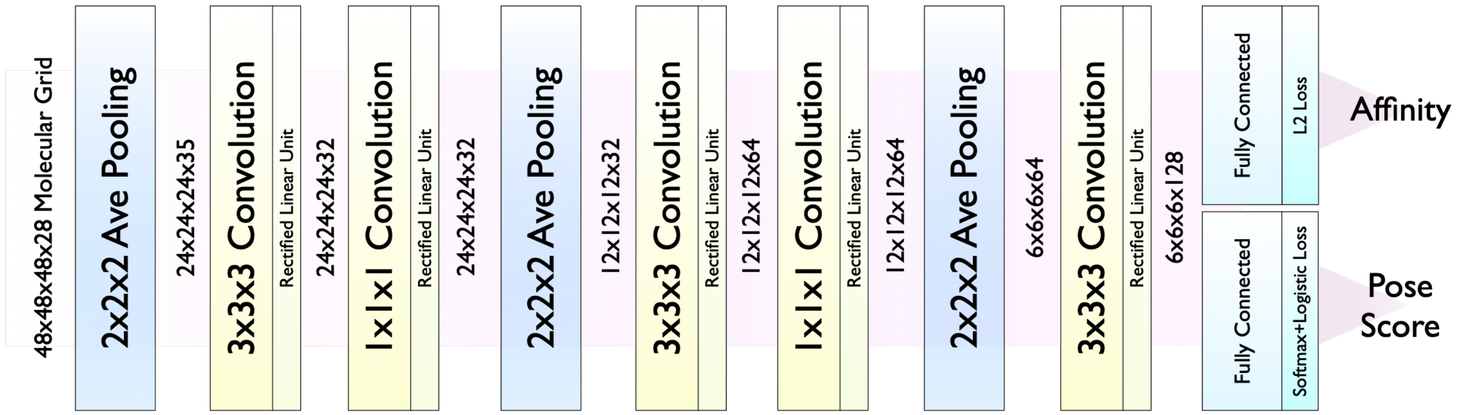


-1	-1	-1
-1	8	-1
-1	-1	-1

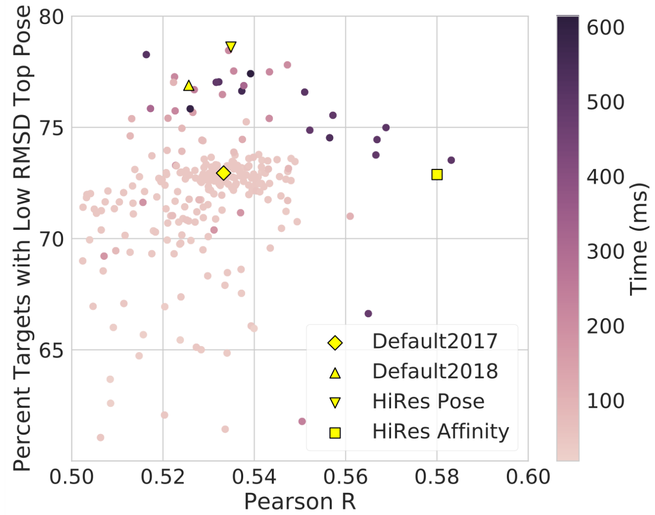
Protein Ligand Scoring



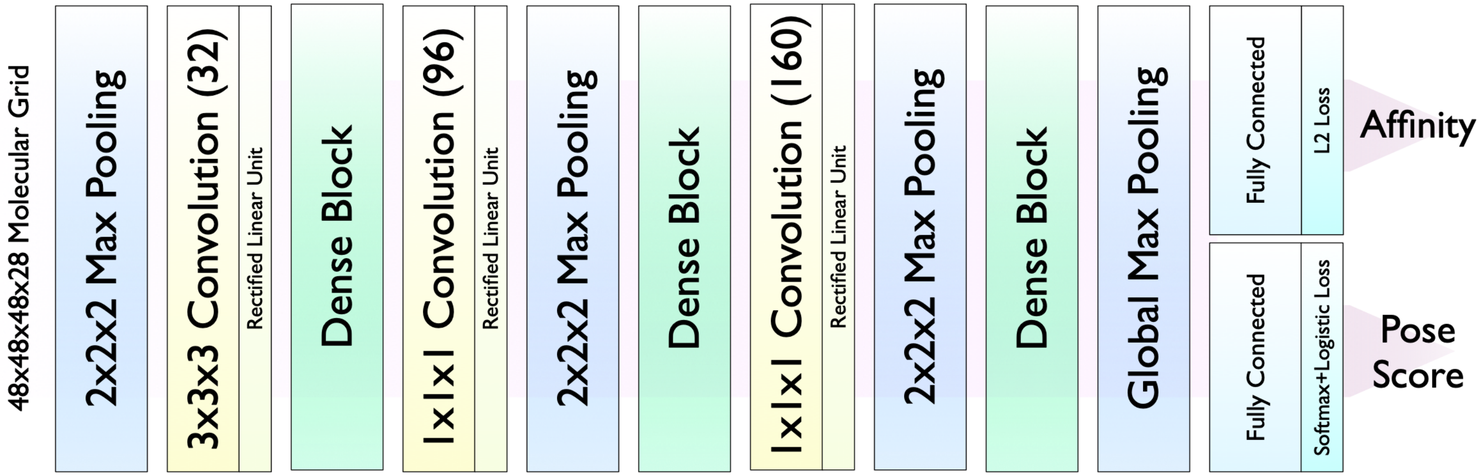
Def2018



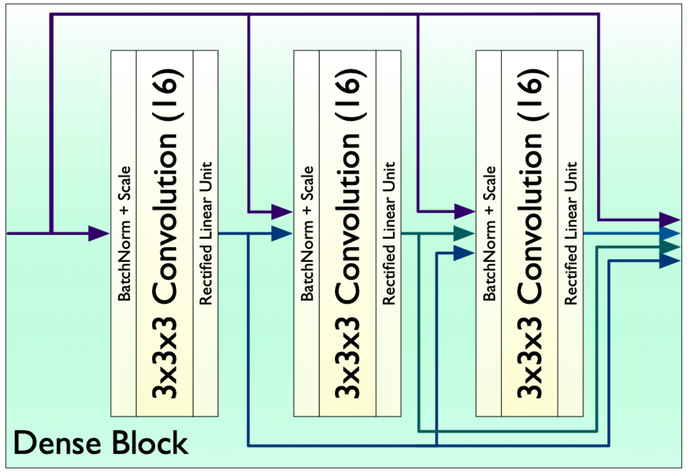
388,736 Parameters



Dense



684,640 Parameters



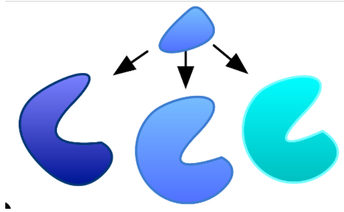
Cross-Docked Protein Ligand Scoring

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

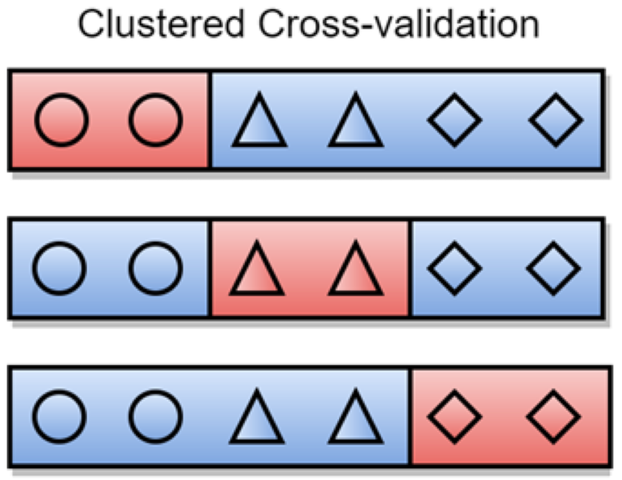
Paul G. Francoeur, Tomohide Masuda, Jocelyn Sunseri, Andrew Jia, Richard B. Iovanisci, Ian Snyder, and David R. Koes*

Cite this: *J. Chem. Inf. Model.* 2020, 60, 9, 4200–4215
Publication Date: August 31, 2020
https://doi.org/10.1021/acs.jcim.0c00411
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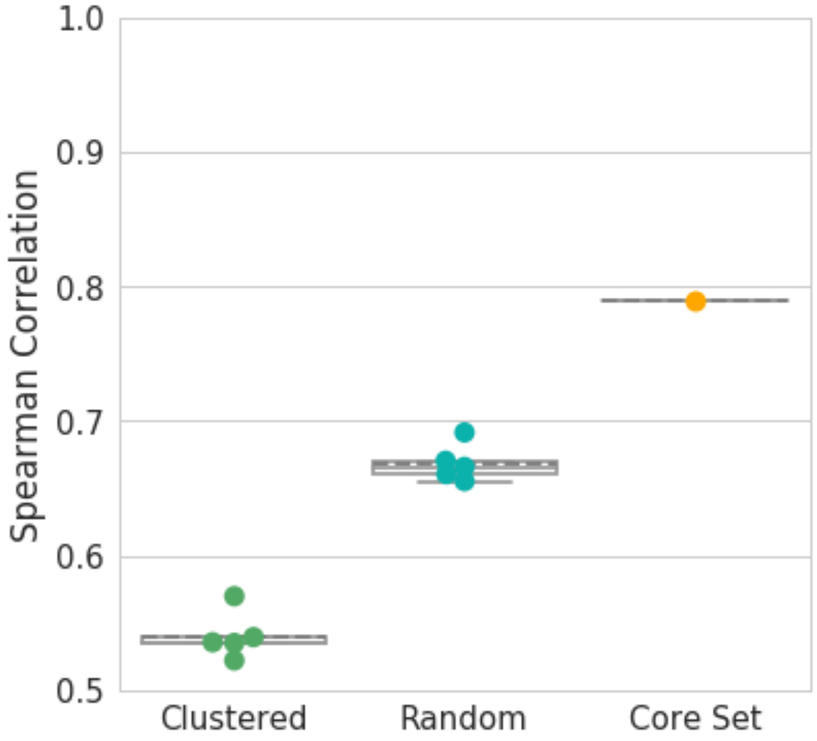
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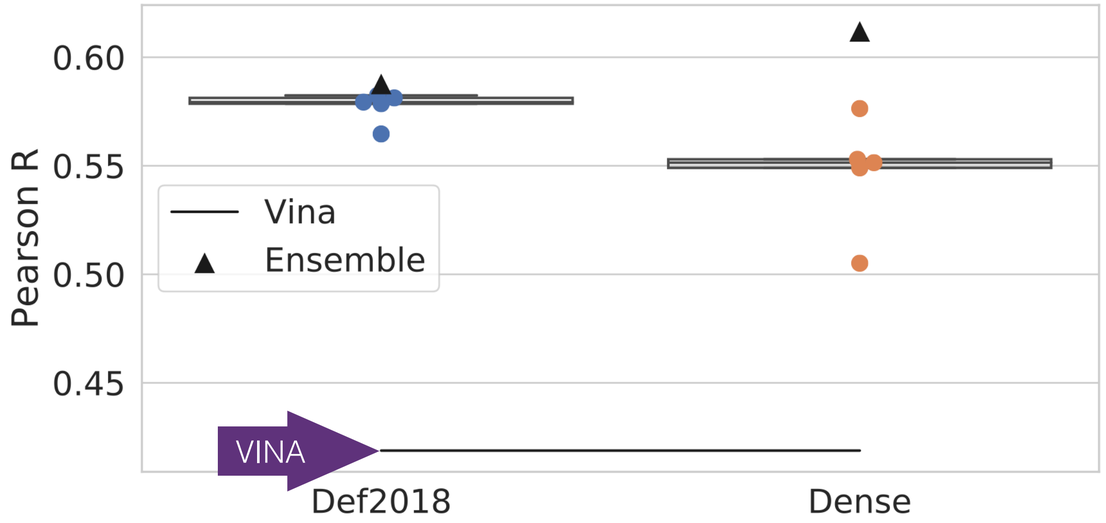


18,450 complexes
22.6 million poses

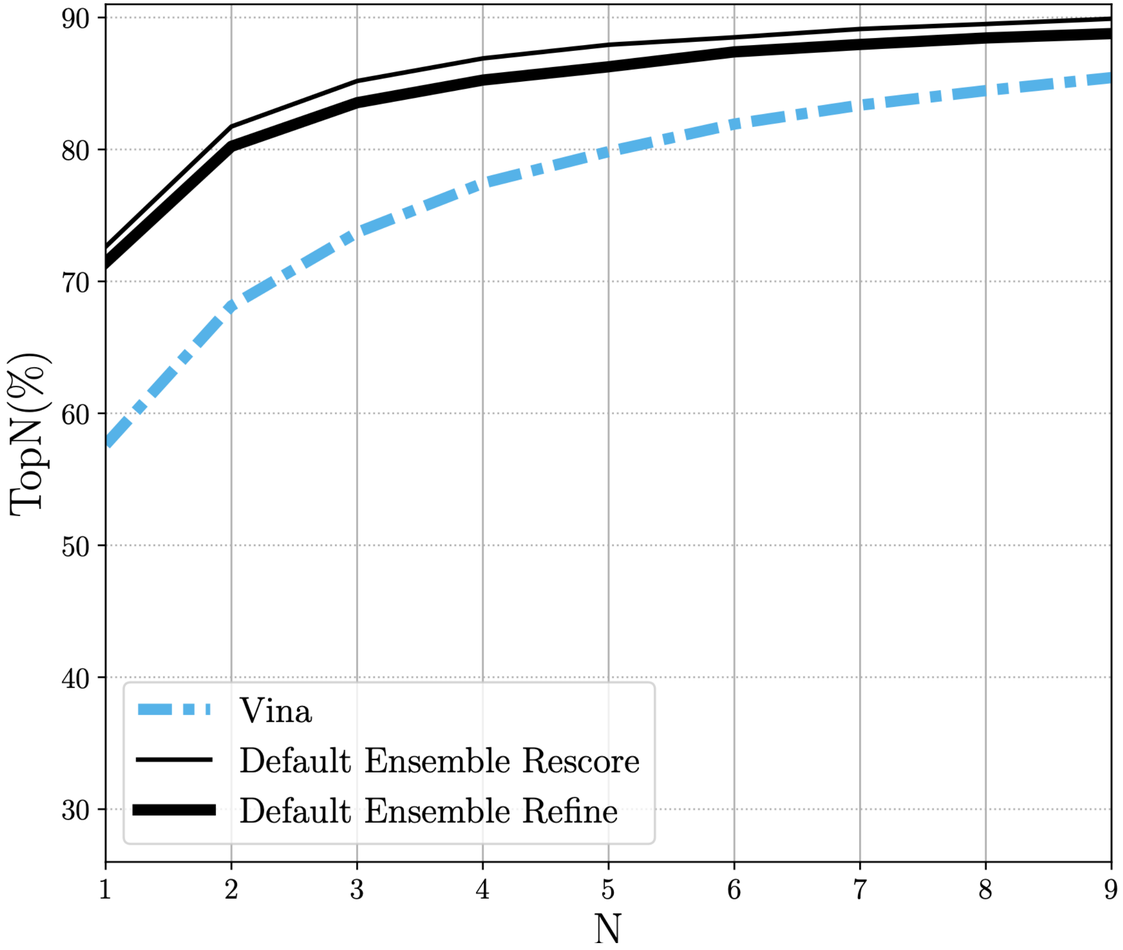


Affinity Prediction

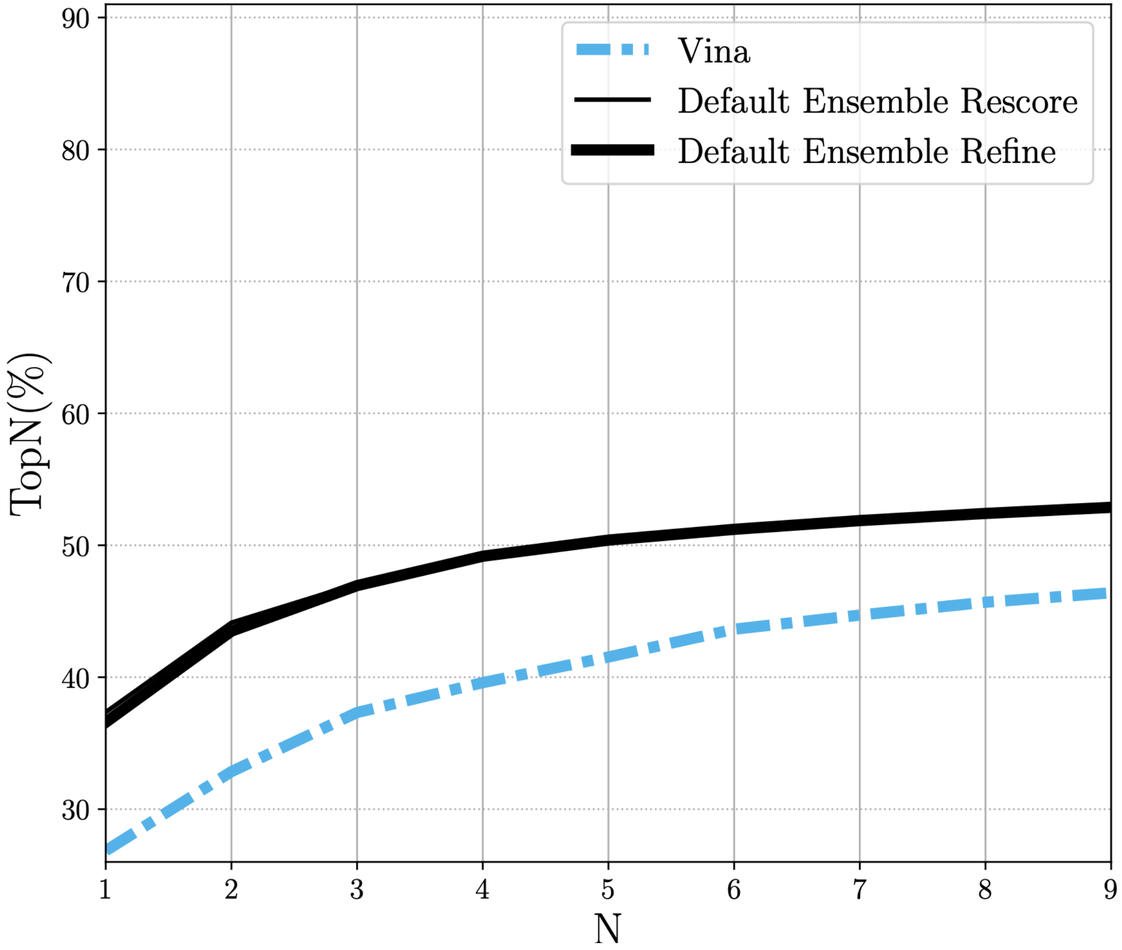




Docking Performance



Redocking



Crossdocking

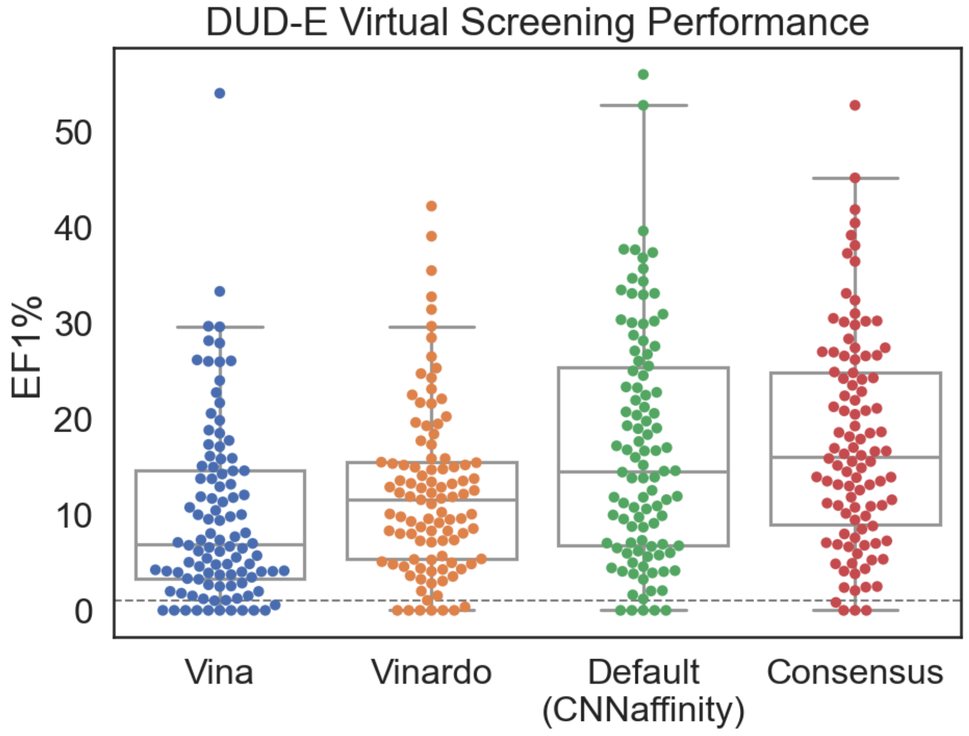
molecules

Open Access Article

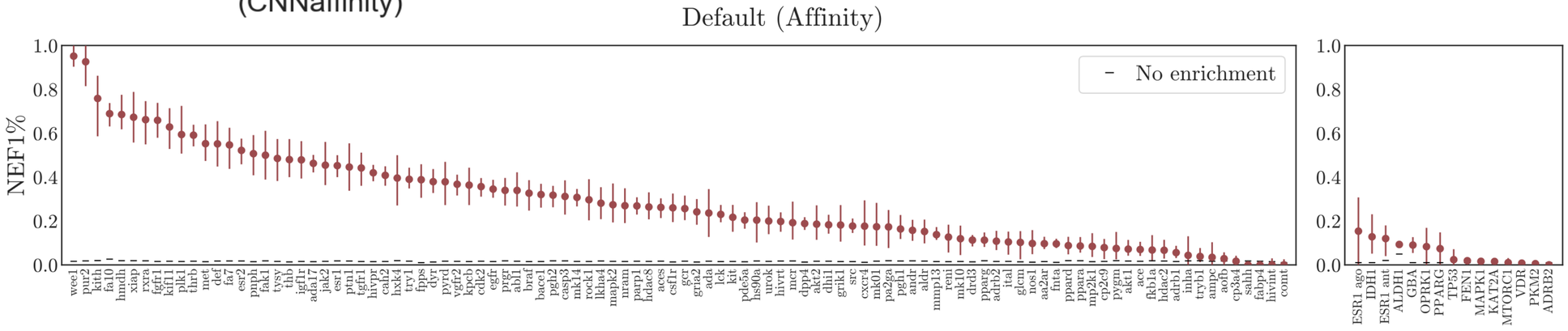
Virtual Screening with GNINA 1.0



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*



GNINA 1.3

https://github.com/gnina/gnina

GNINA 1.3: the next increment in molecular docking with deep learning

Andrew T. McNutt, Yanjing Li, Rocco Meli, Rishal Aggarwal & David Ryan Koes

Journal of Cheminformatics **17**, Article number: 28 (2025) | Cite this article



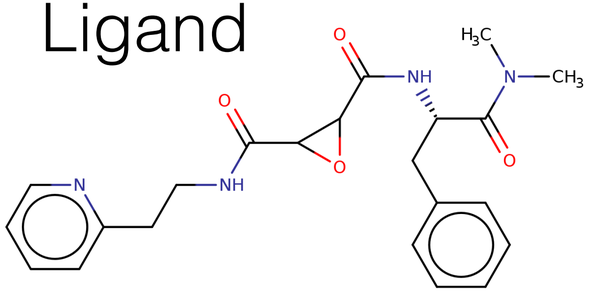
Caffe → Torch

easy covalent docking

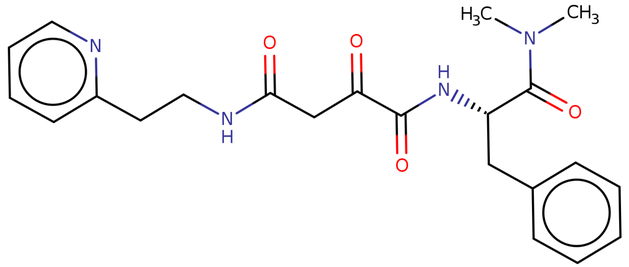
retrained models

Covalent Docking

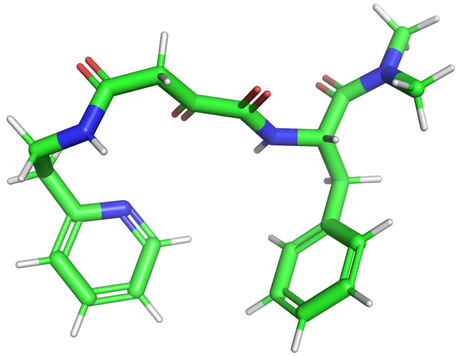
Prepare Ligand



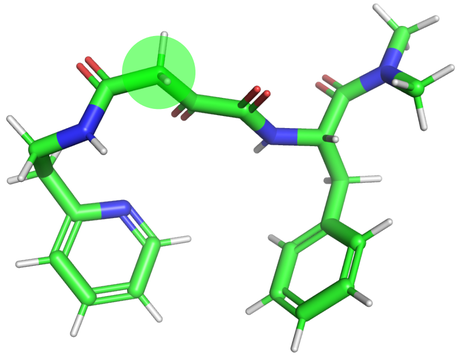
apply chemical transformations

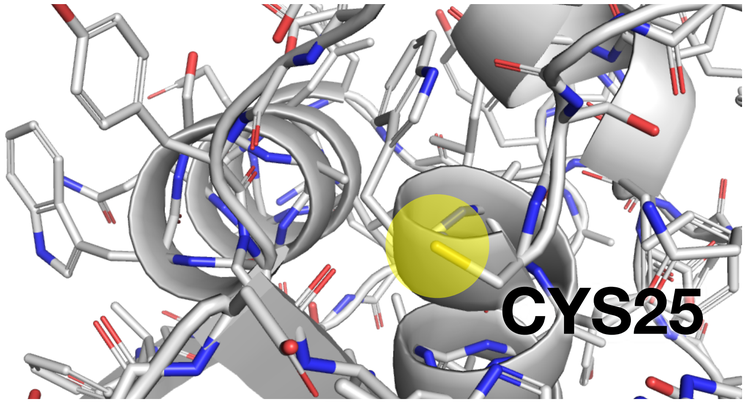


generate conformer



Specify Covalent Bond






```
--covalent_lig_atom_pattern '[$(C(C=O)C(=O)C=O)]'   --covalent_rec_atom 'A:25:SG'
```

Optional Arguments

`--covalent_lig_atom_position`

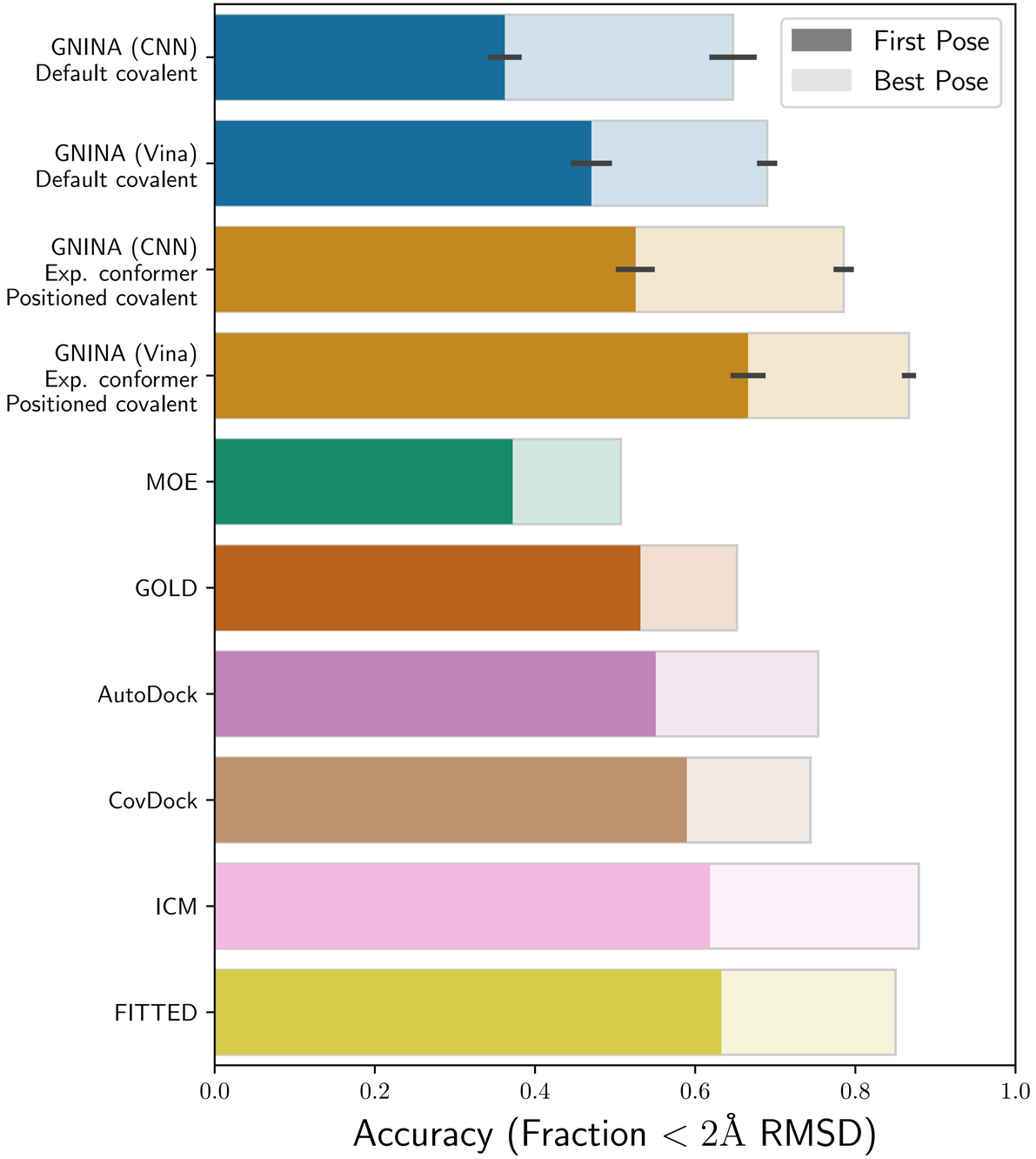
If not specified, OpenBabel's GetNewBondVector function will be used to position ligand atom.

`--covalent_bond_order`

Bond order of covalent bond (default 1).

`--covalent_optimize_lig`

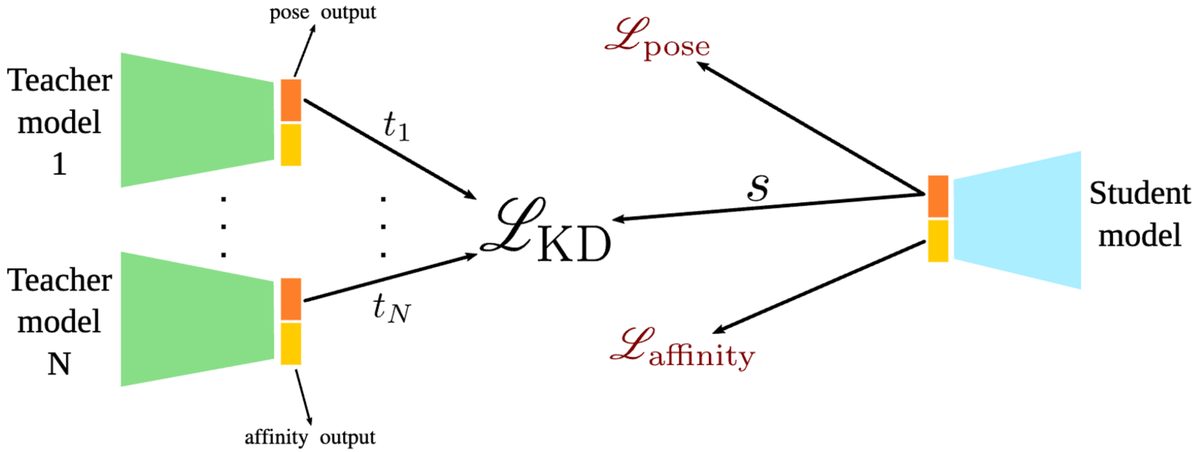
Optimize the covalent complex of ligand and residue using UFF to refine bond angles/lengths.

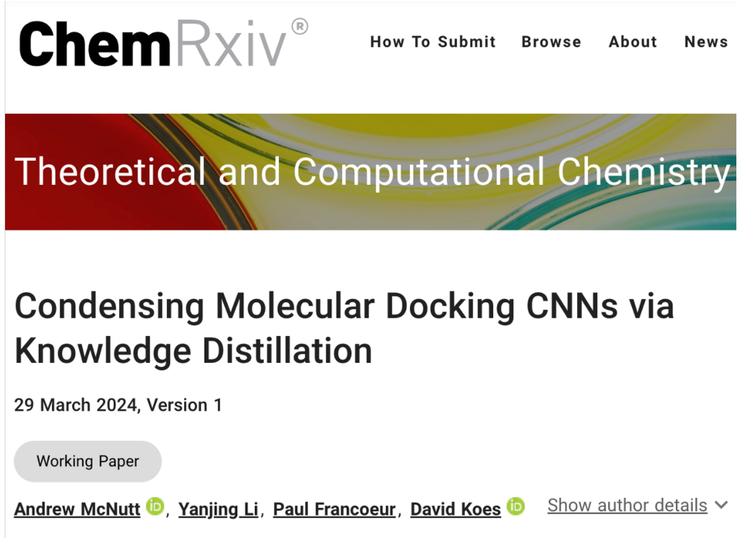


Results

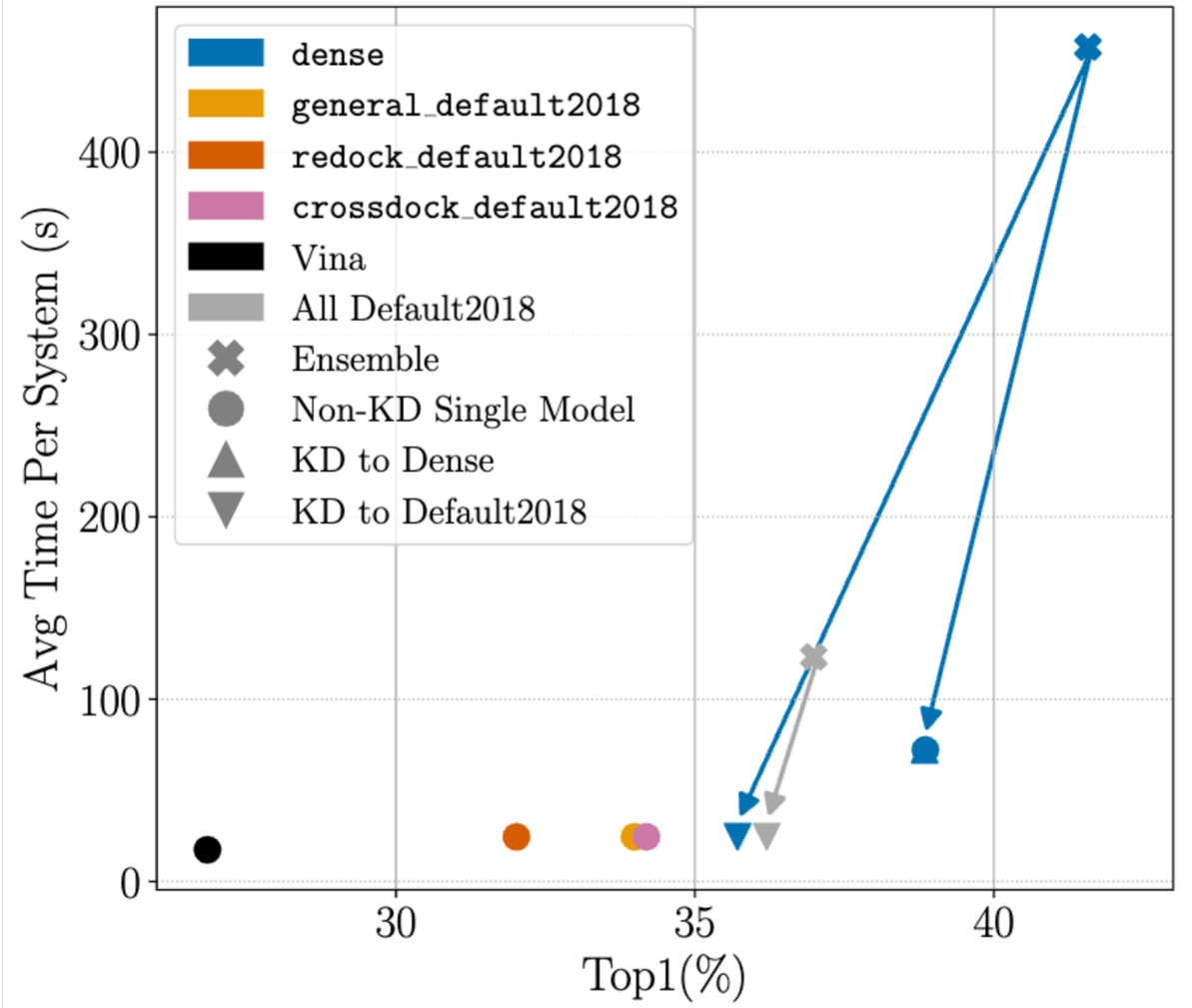
- Not the best, not the worst
- CNN needs to be trained for this task
- Input conformer important

Knowledge Distillation

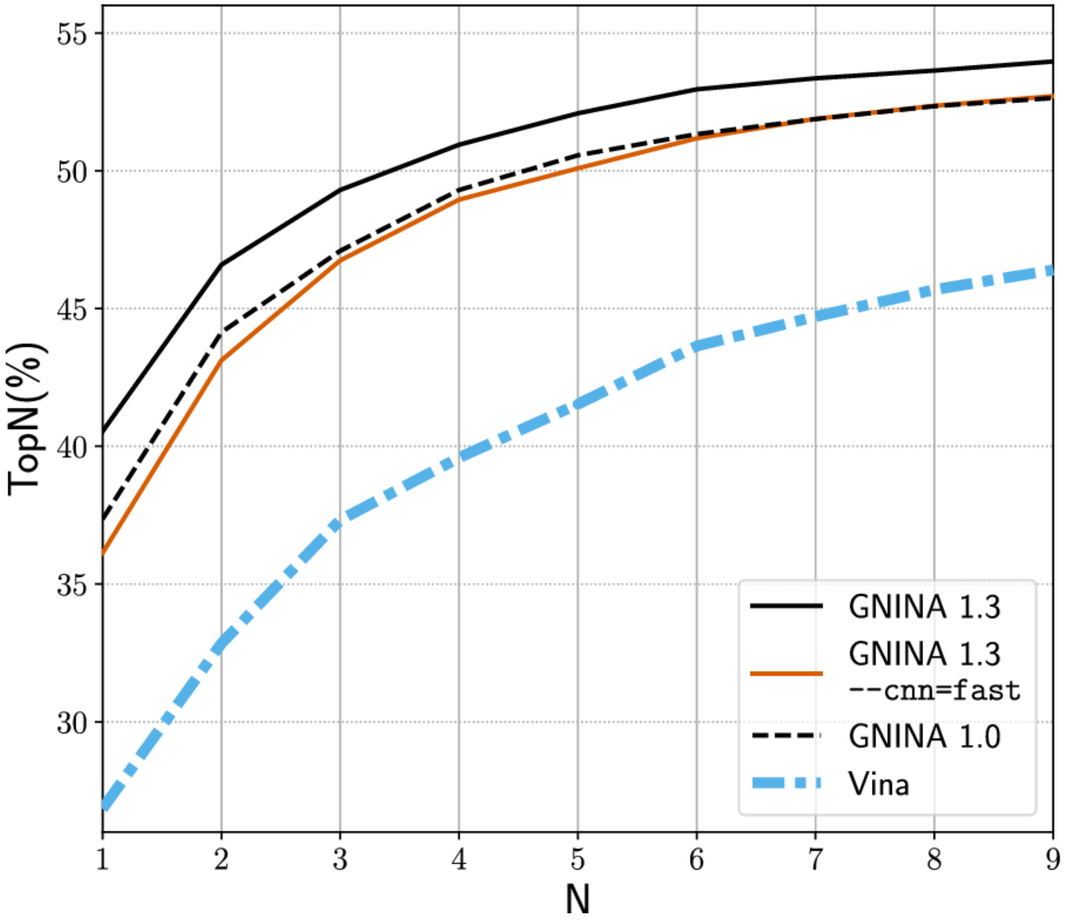




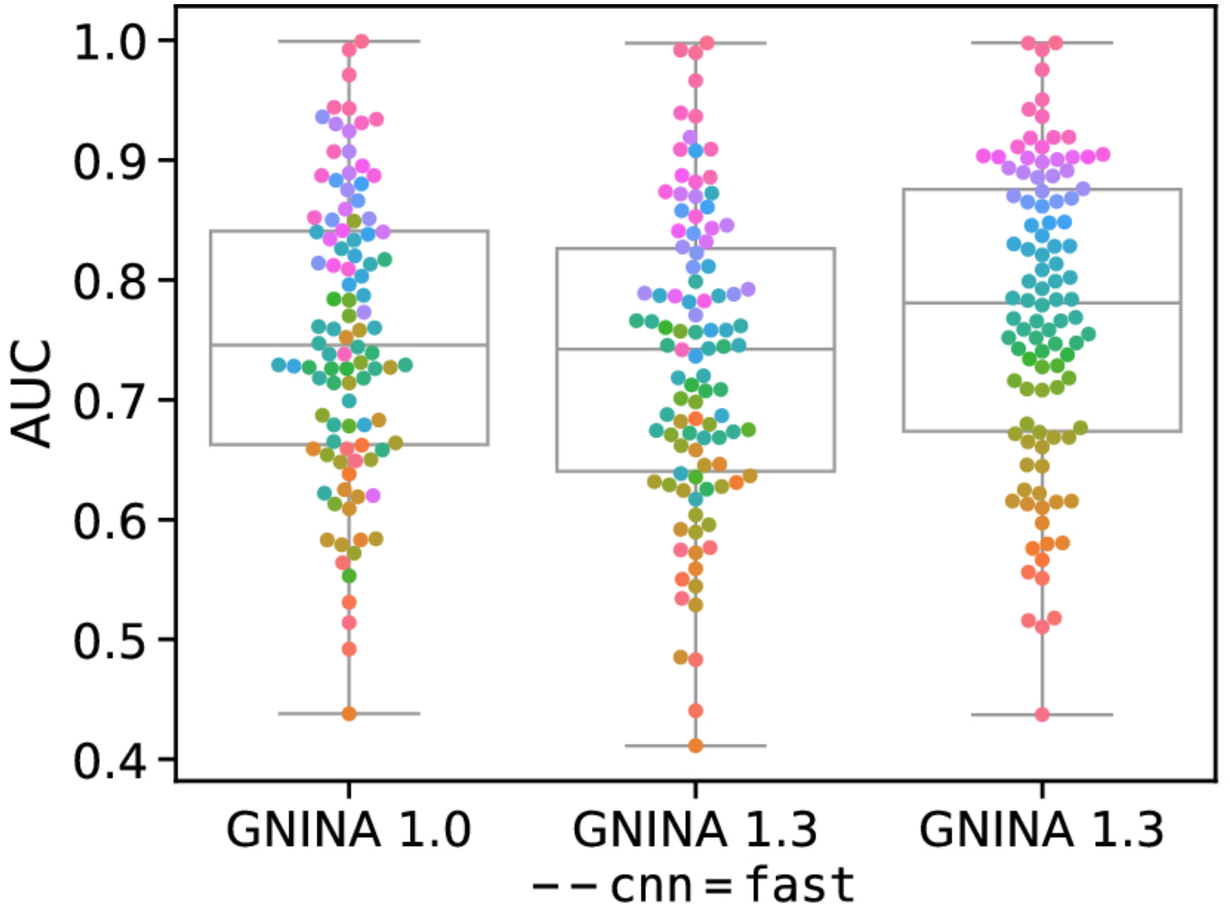




GNINA 1.3 Performance

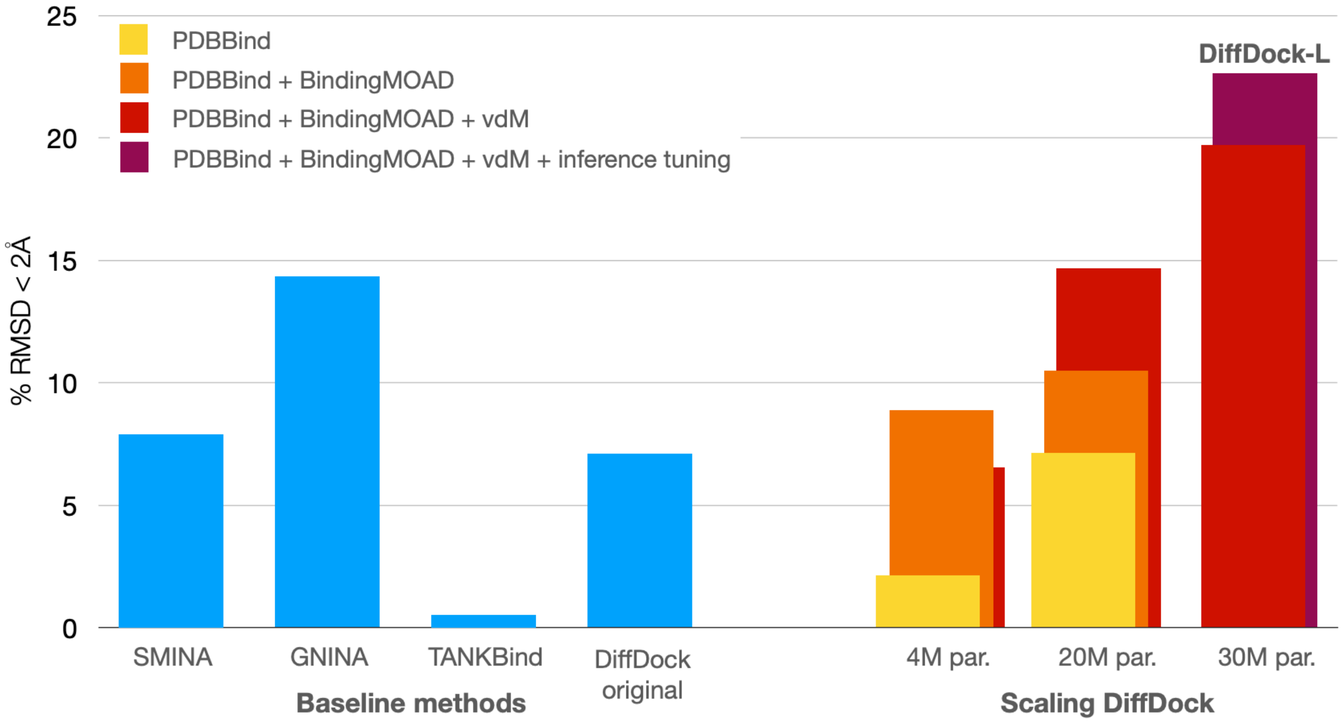


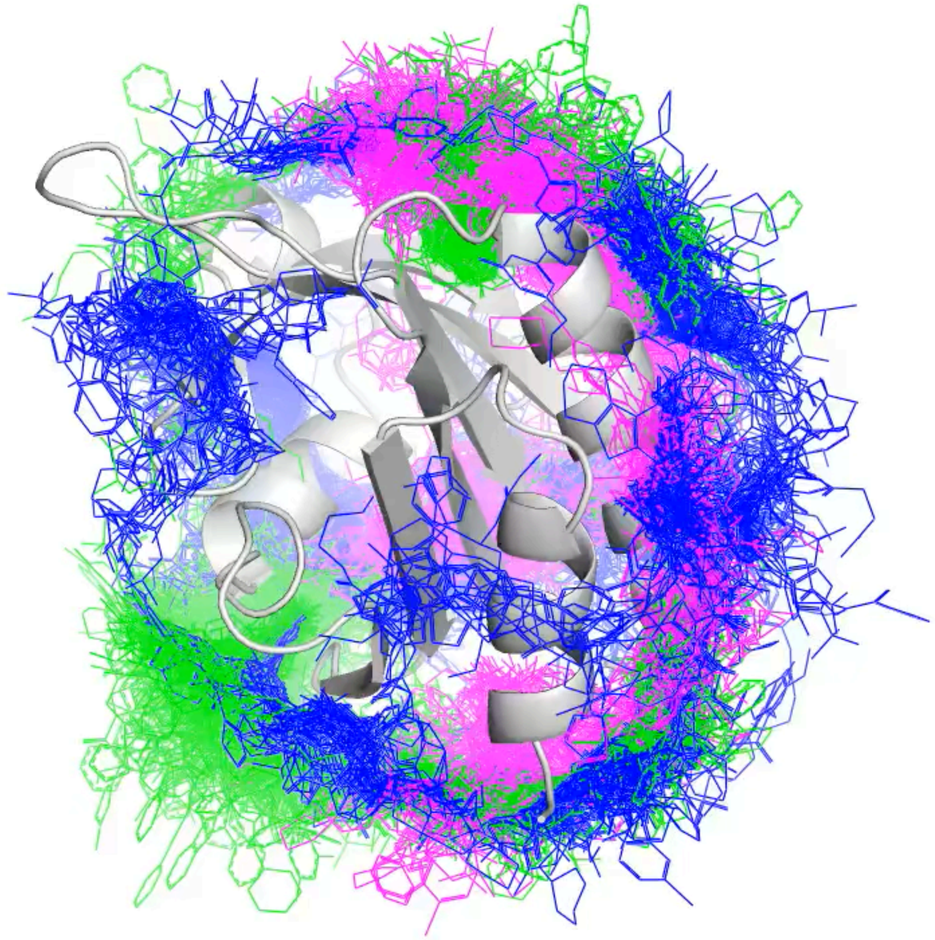
Crossdocking



Virtual Screening (DUD-E)

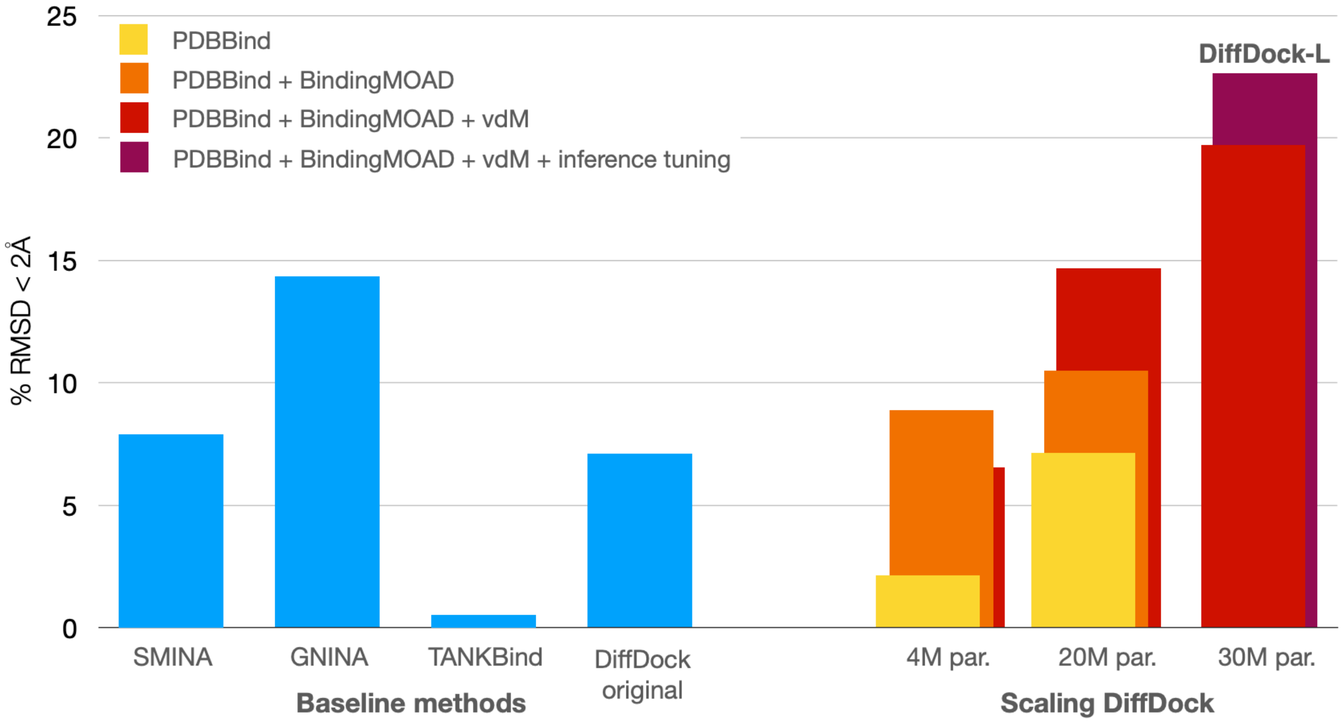
GNINA vs End-to-end Deep Docking

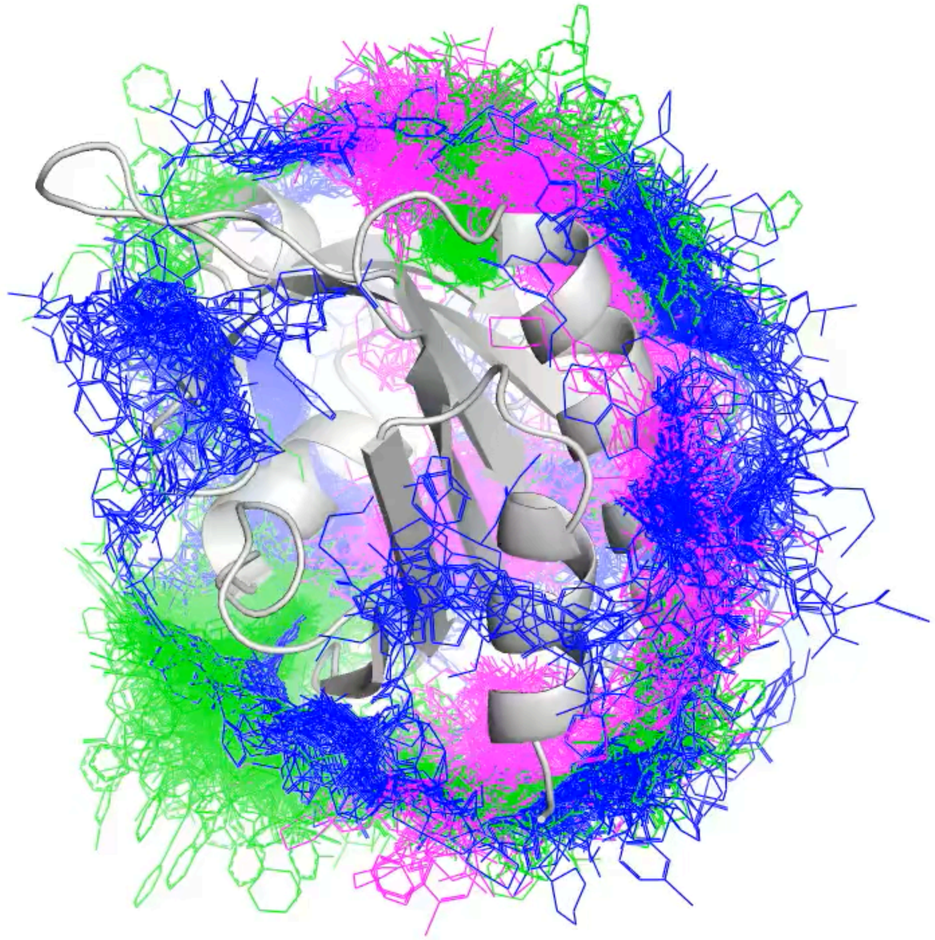




GNINA DynamicBind Boltz1

GNINA vs End-to-end Deep Docking

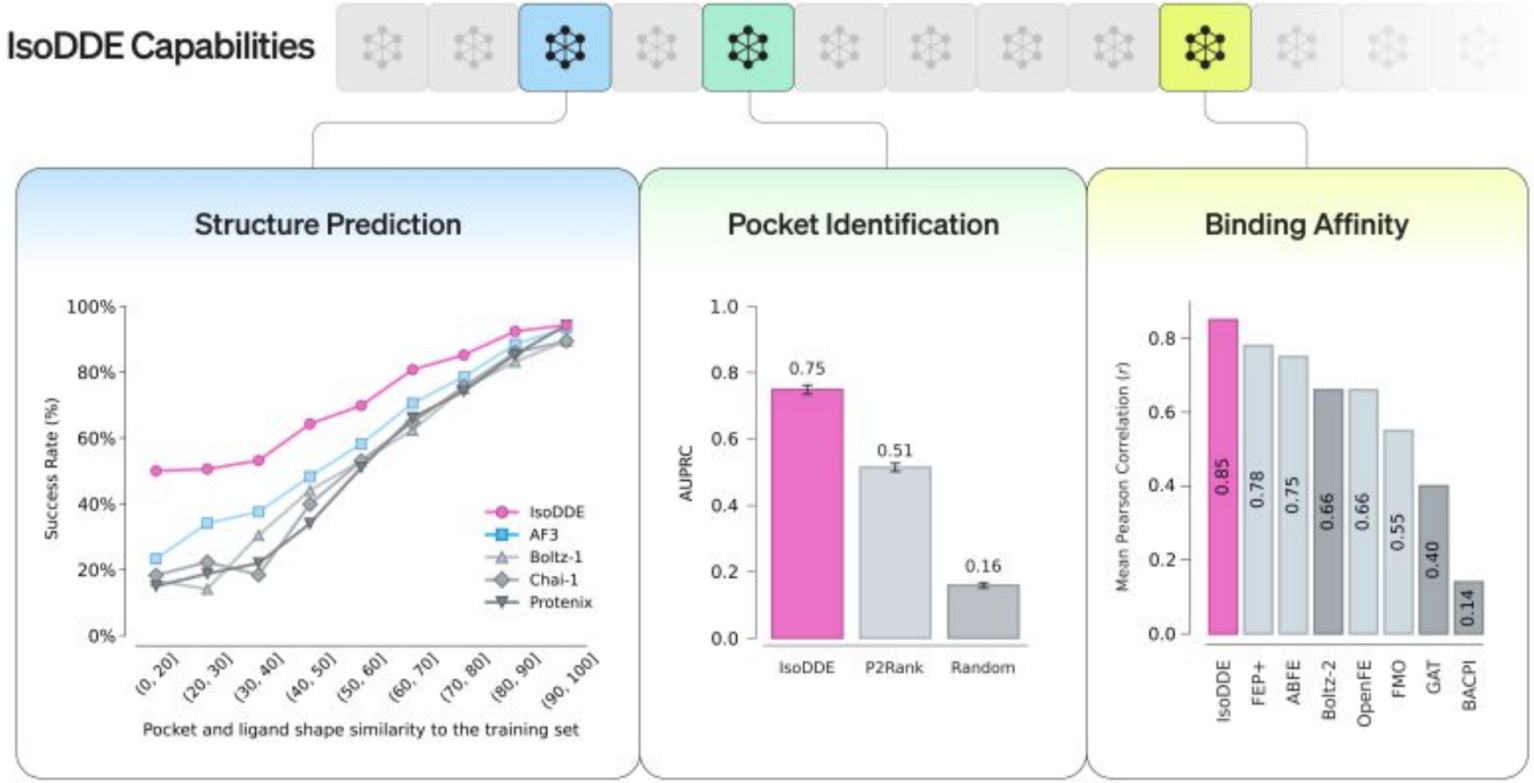




GNINA DynamicBind Boltz1

Isomorphic Labs
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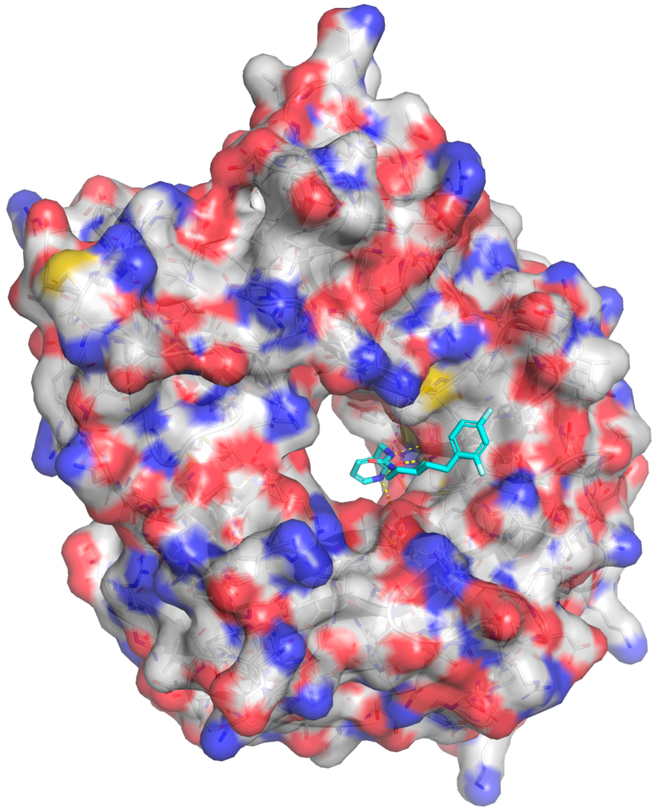
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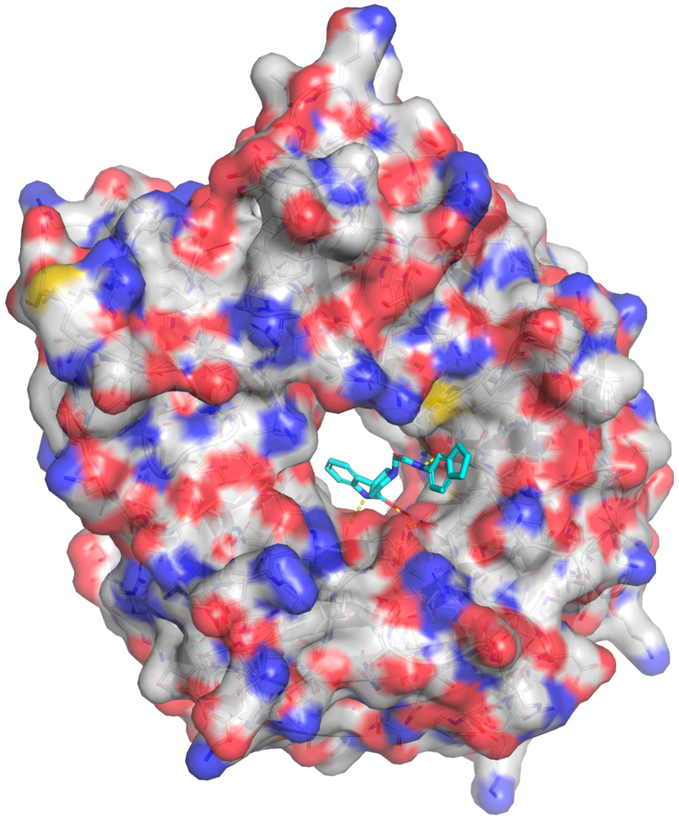
Prospective Evaluation

CACHE CHALLENGE

CRITICAL ASSESSMENT OF COMPUTATIONAL HIT-FINDING EXPERIMENTS

CACHE Challenge #1



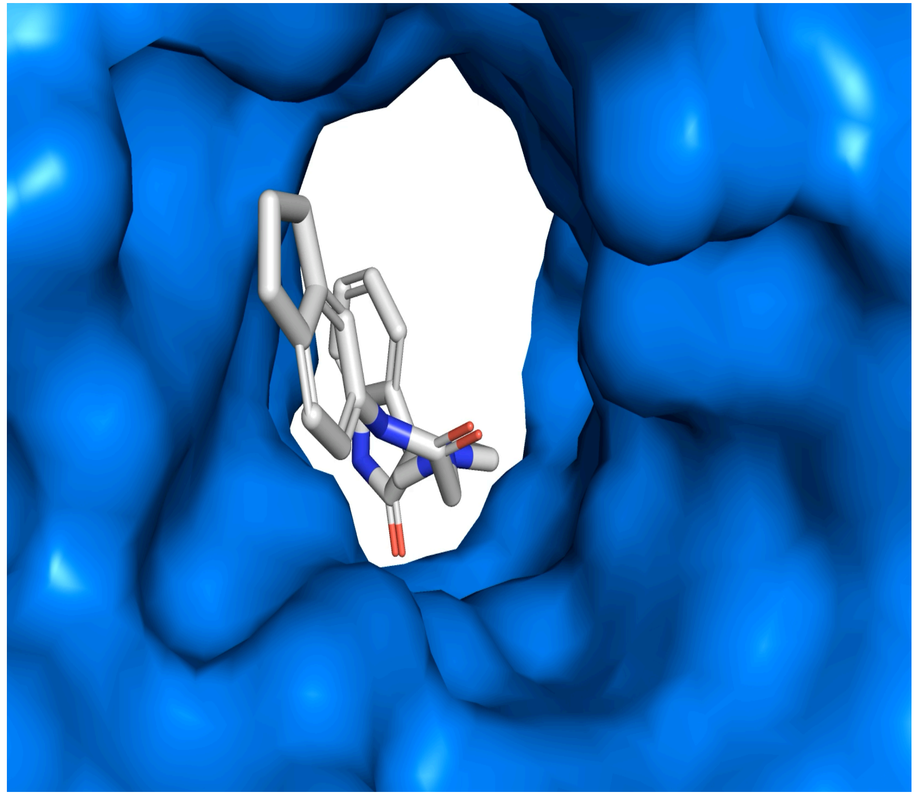




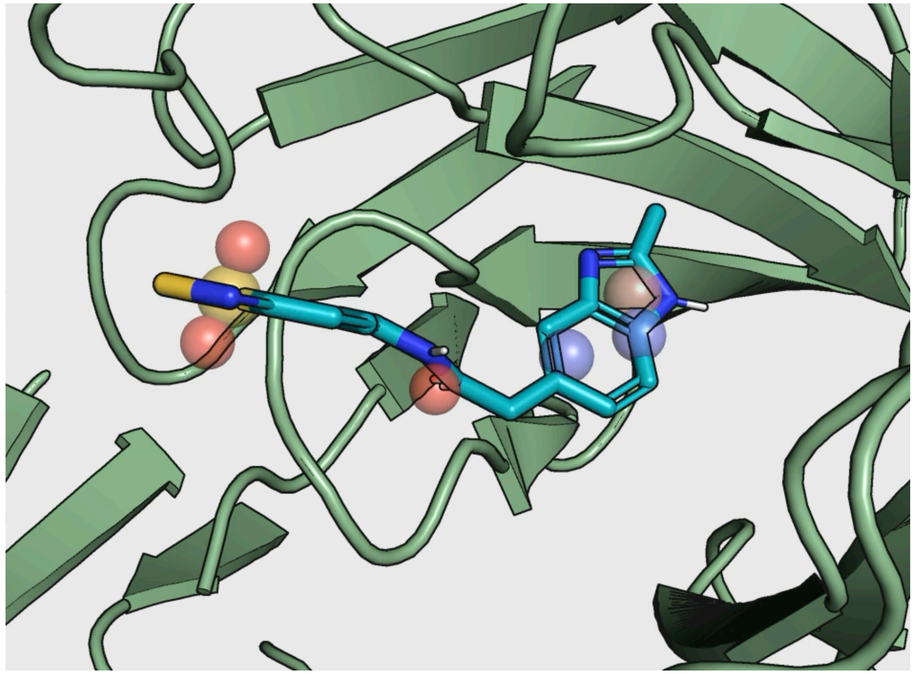
Ian Dunn

A Tale of Two Methods

Large-Scale Docking with GNINA

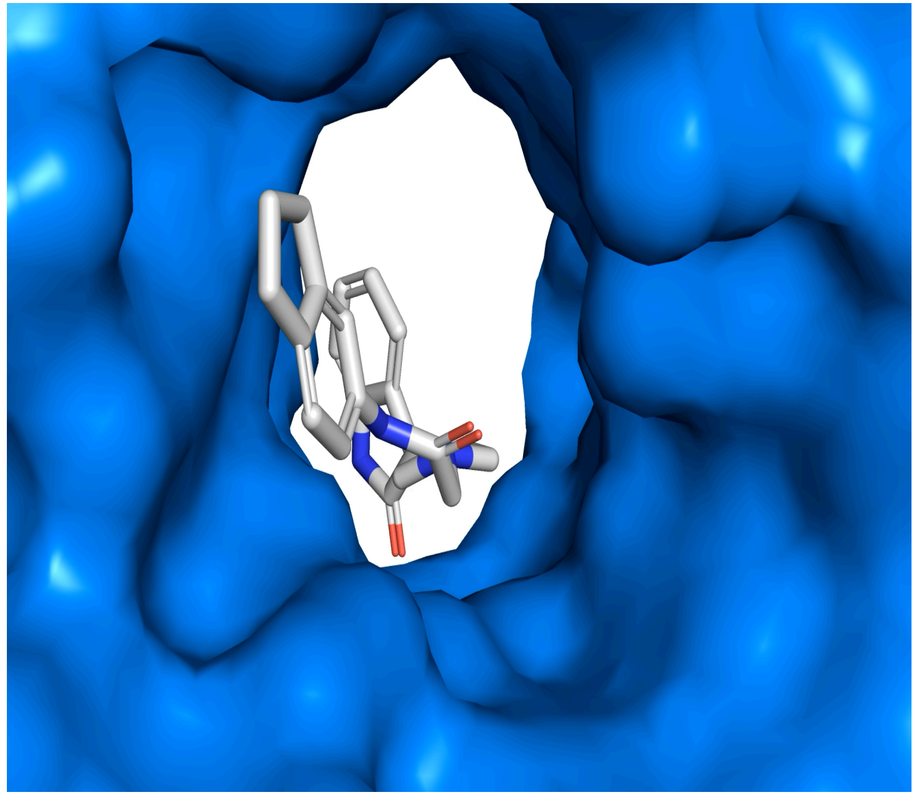


Pharmacophore Screening with Pharmit

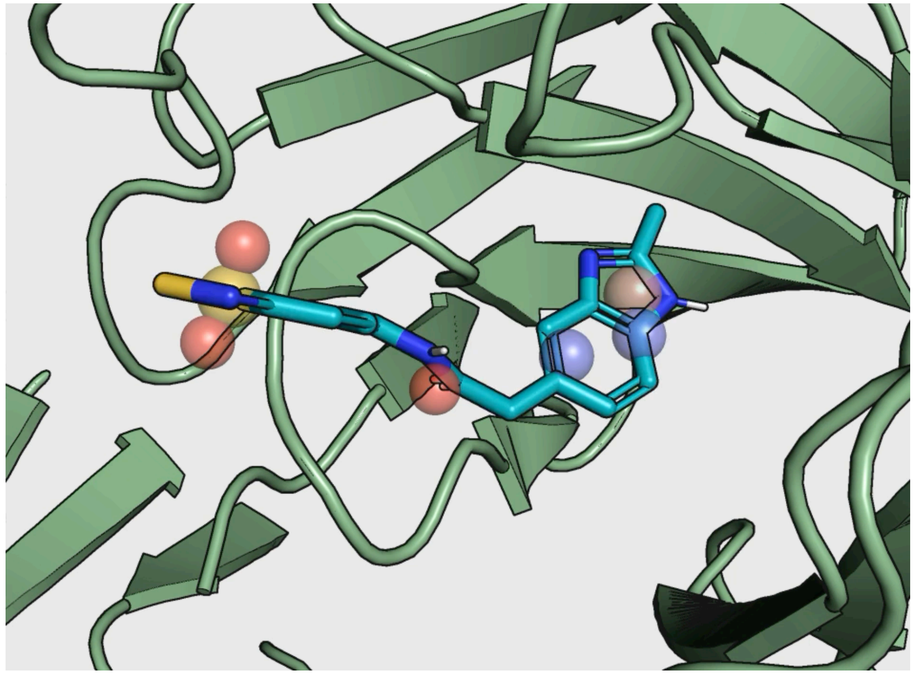


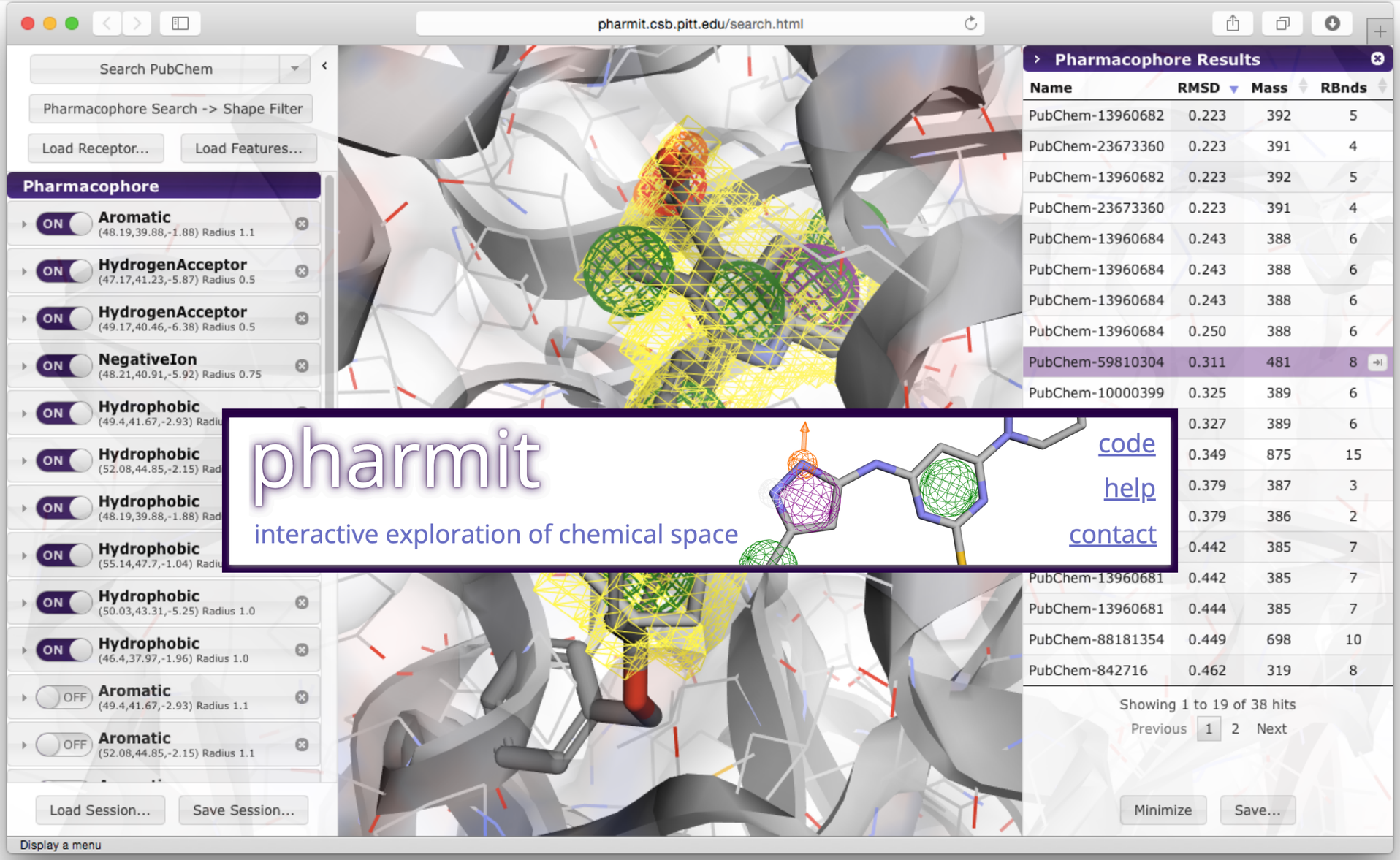
A Tale of Two Methods

Large-Scale Docking with GNINA



Pharmacophore Screening with Pharmit



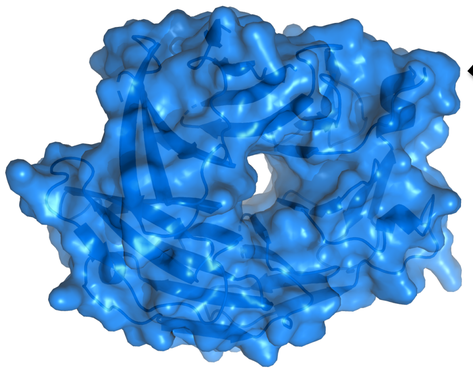


http://pharmit.csb.pitt.edu/

High-throughput Docking Pipeline

molport

~7 million molecules

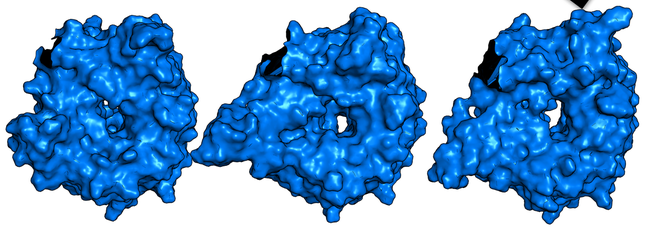


Crystal Structure

Docking with GNINA



Top 1k Molecules by GNINA score

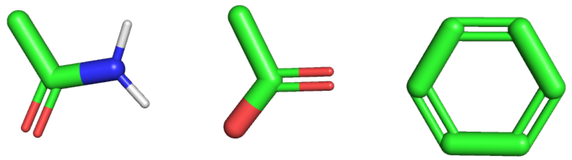


MD Ensemble Structures

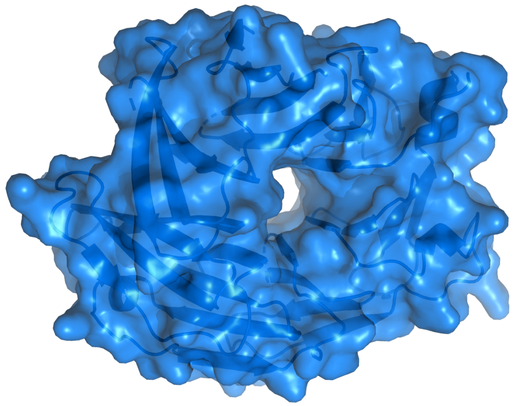
Docking with GNINA

1000 molecules, + GNINA Scores

Pharmacophore Generation via Fragment Docking

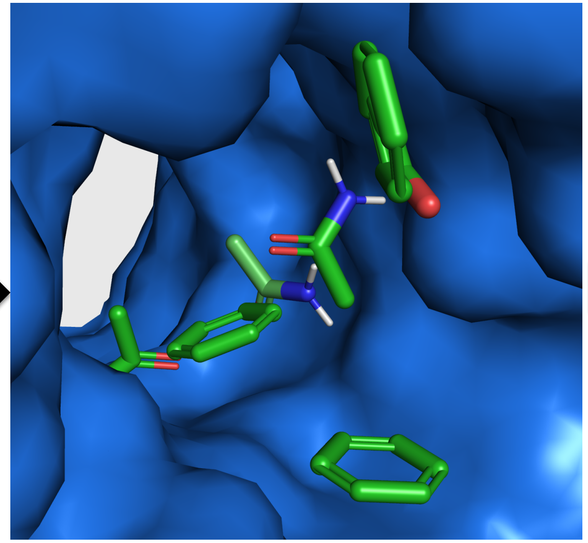


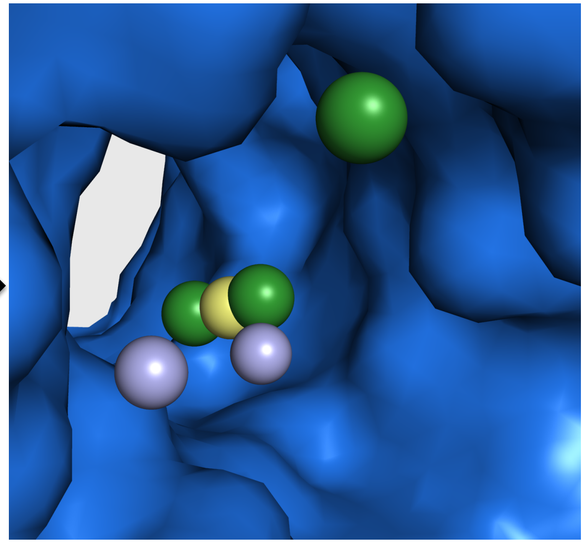
Molecule Fragments



Crystal Structure

Docking with GNINA

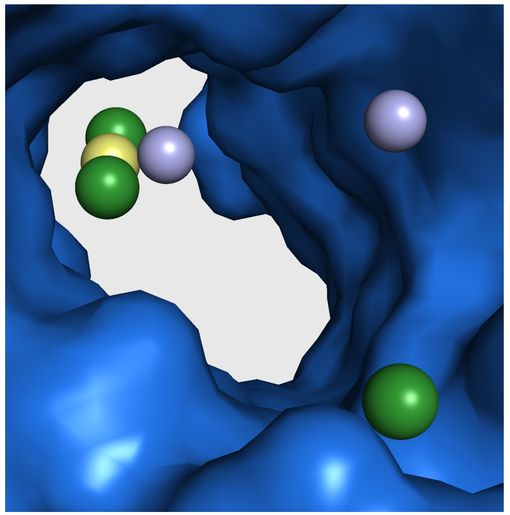




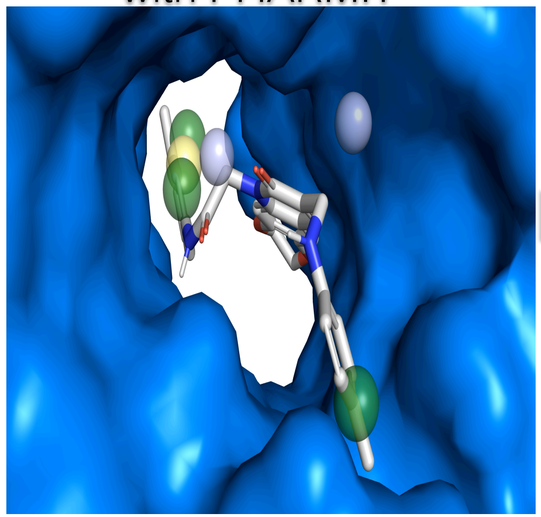
Pharmacophore Generation

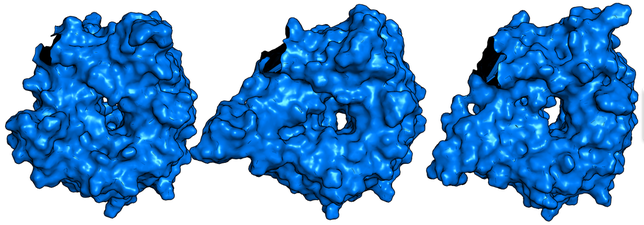
Pharmacophore Pipeline

Pharmacophore Generation



Pharmacophore Screening with PHARMIT





MD Ensemble Docking with GNINA

3572 molecules
+
GNINA scores

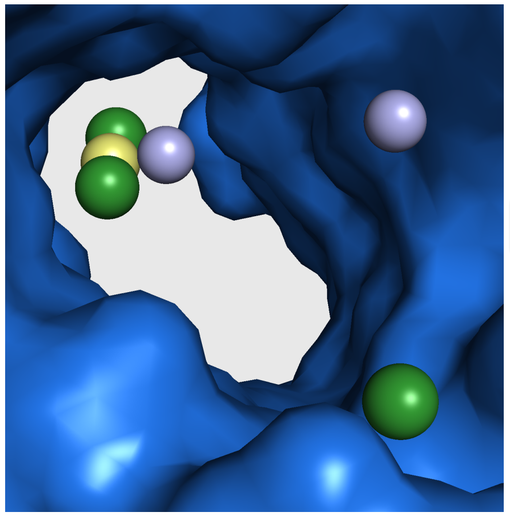


- ZINC20: 20 mil molecules
- MCULE: 45 mil molecules
- MCULE-ULTIMATE: 126 mil molecules

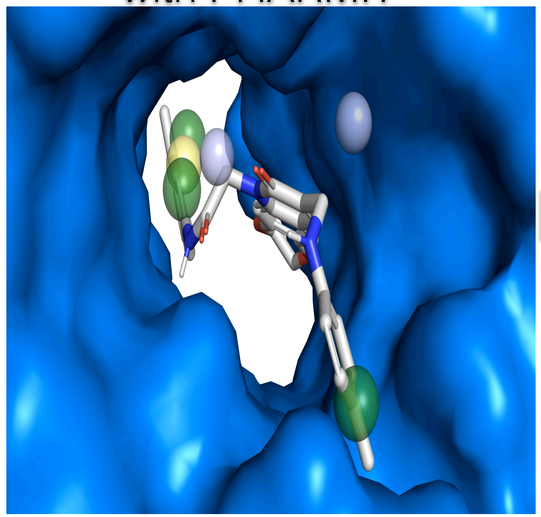
Molecule Libraries

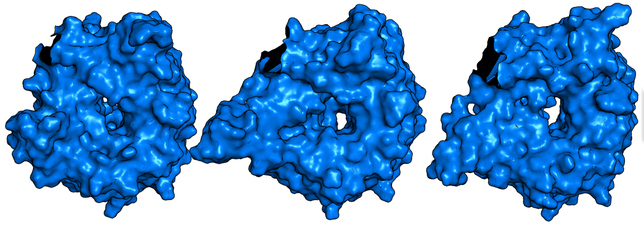
Pharmacophore Pipeline

Pharmacophore Generation



Pharmacophore Screening with PHARMIT





MD Ensemble Docking with GNINA

3572 molecules
+
GNINA scores

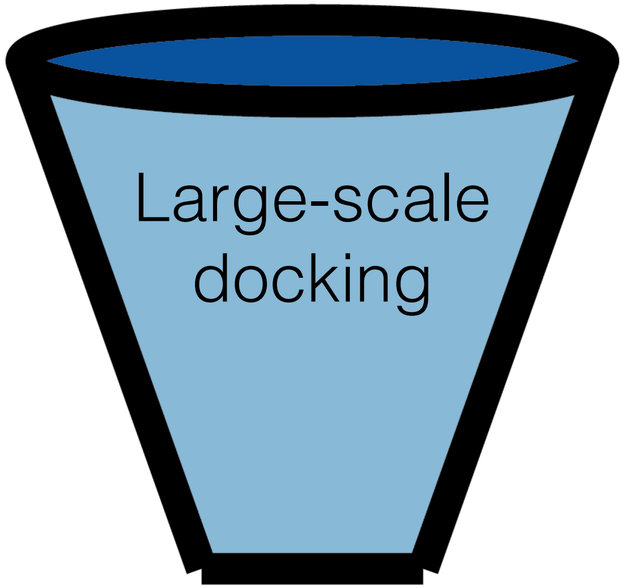


- ZINC20: 20 mil molecules
- MCULE: 45 mil molecules
- MCULE-ULTIMATE: 126 mil molecules

Molecule Libraries

Round 1 Submission

molport



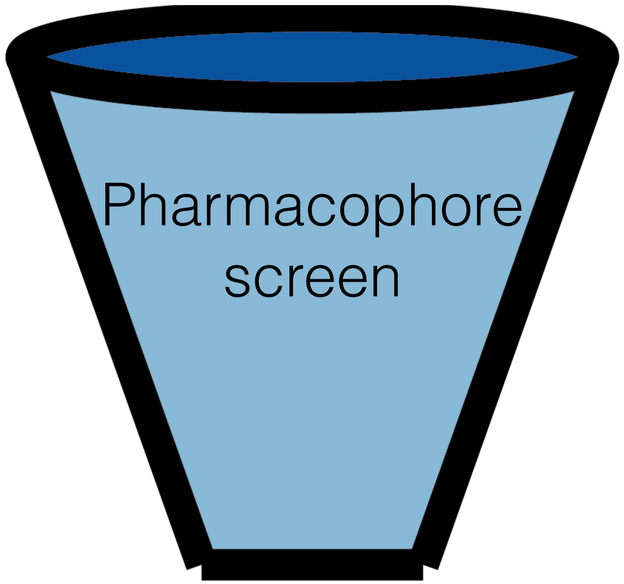
1k ligands
gnina scores
vina scores

2 screening methods
2 scoring methods



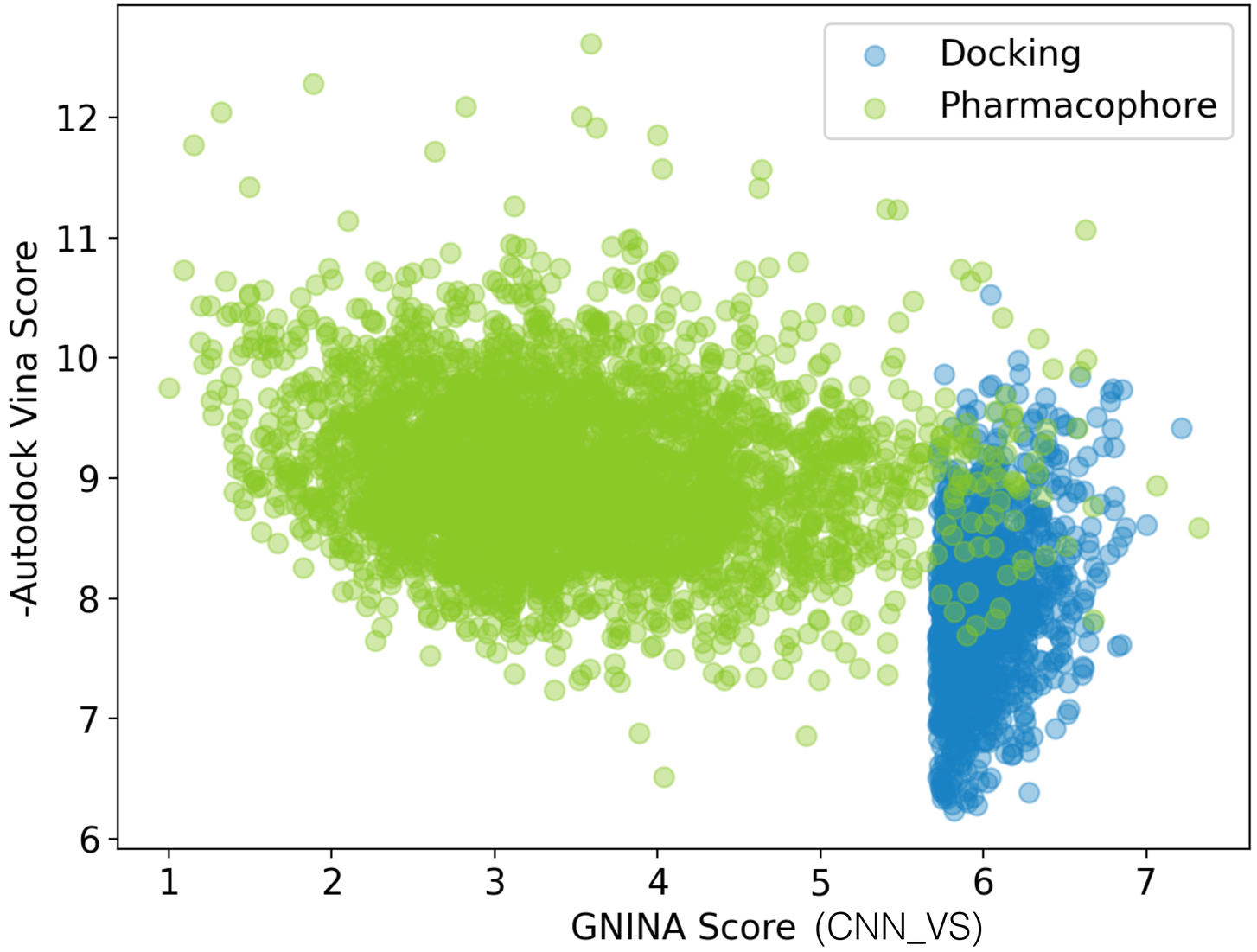
- ZINC20: 20 mil molecules
- MCULE: 45 mil molecules
- MCULE-ULTIMATE: 126 mil molecules

Molecule Libraries



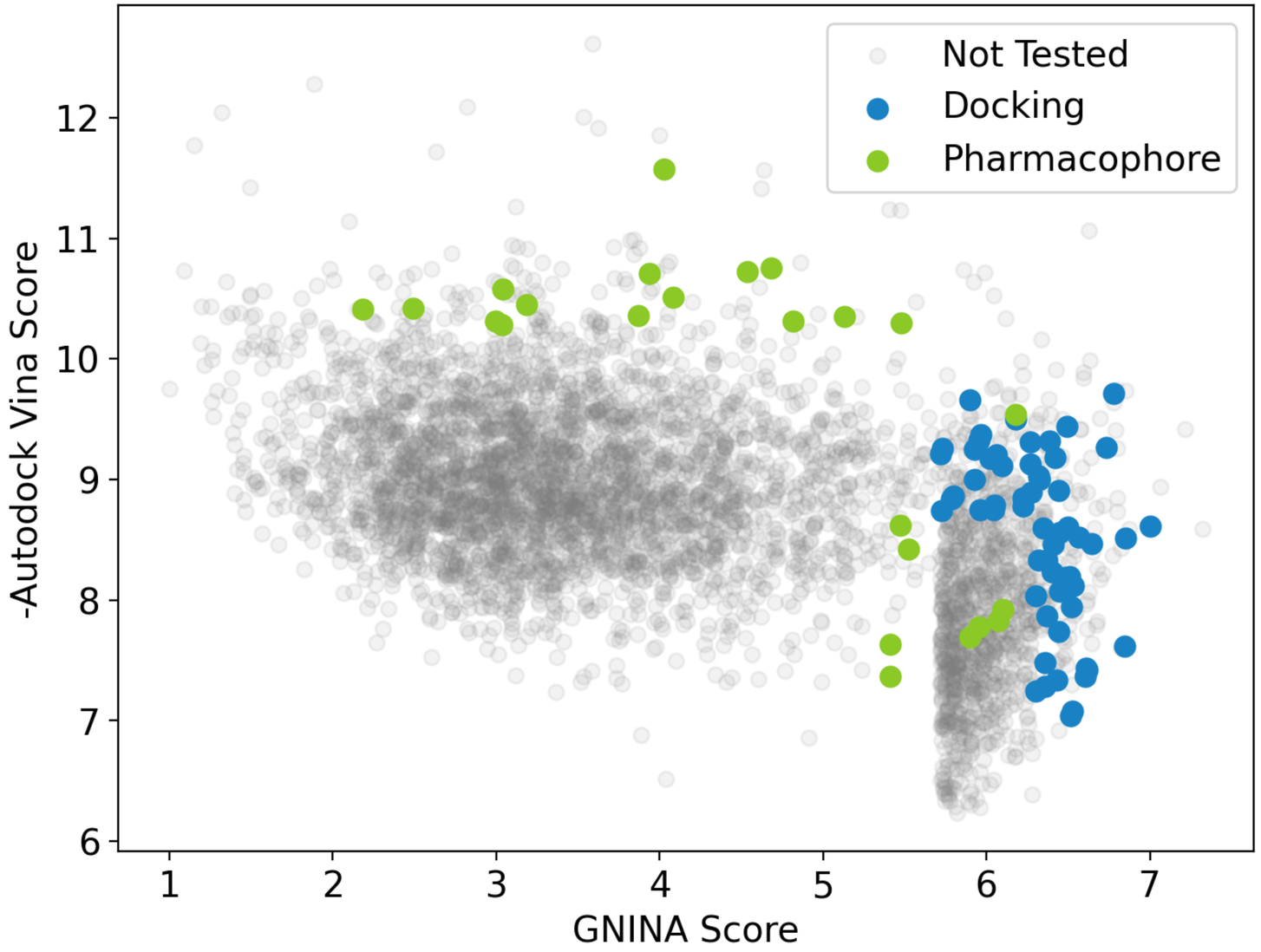
3.5k ligands
gnina scores
vina scores

Round 1 Results



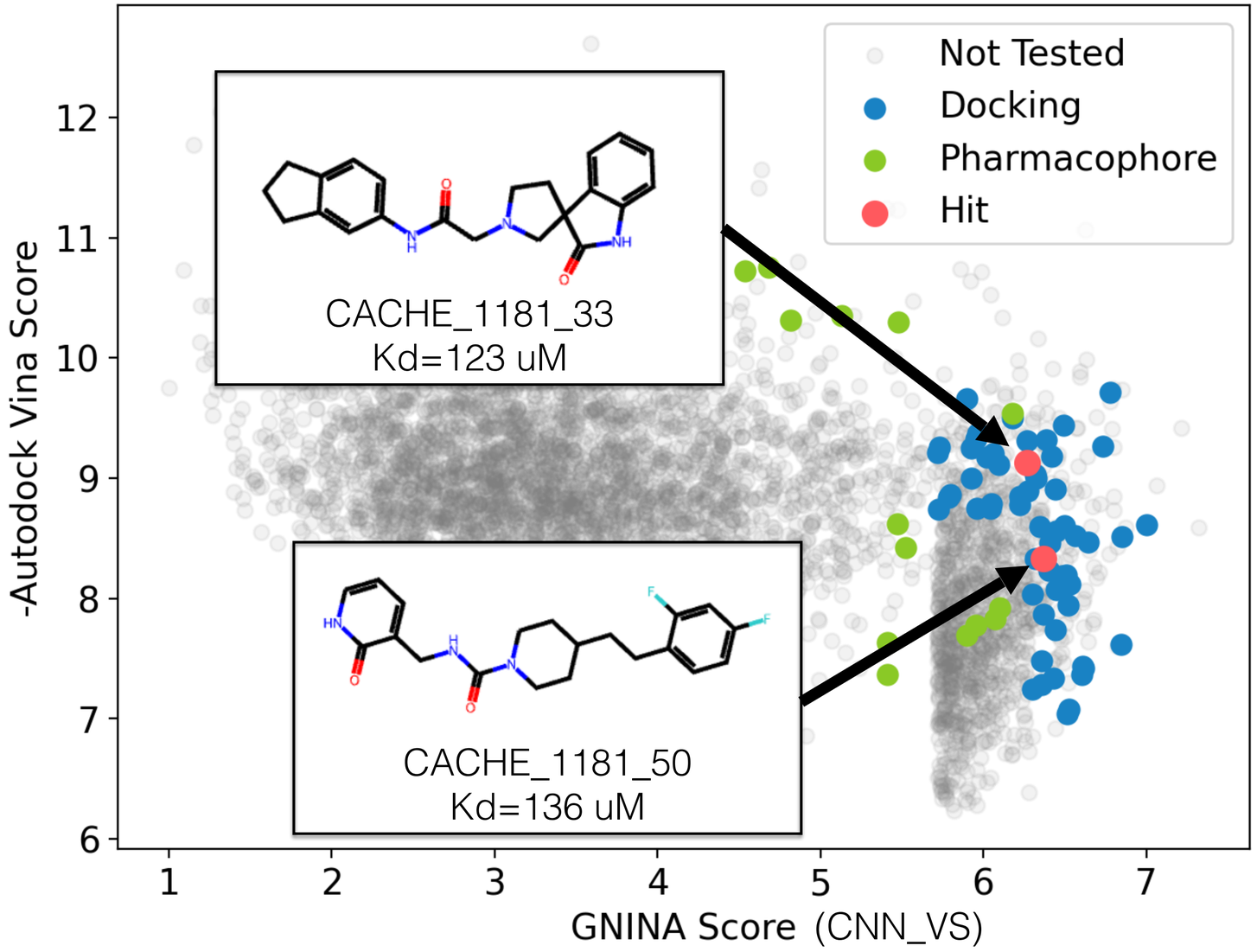
- Selection limited/ skewed by database availability
- 84 ligands tested
  - 59 from docking
  - 24 from pharm screen

Round 1 Results



- Selection limited/ skewed by database availability
- 84 ligands tested
  - 59 from docking
  - 24 from pharm screen

Round 1 Results

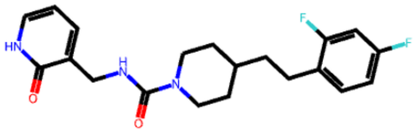


- 2/84 were hits
  - Both from docking

Round 2: Hit Optimization

Hit Optimization Pipeline

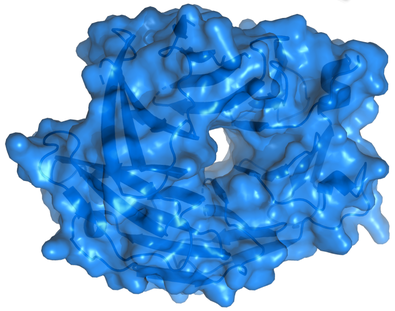
Parent Compound



Similarity screen against
Enamine REAL
Return 5000 most similar
ligands by tanimoto score

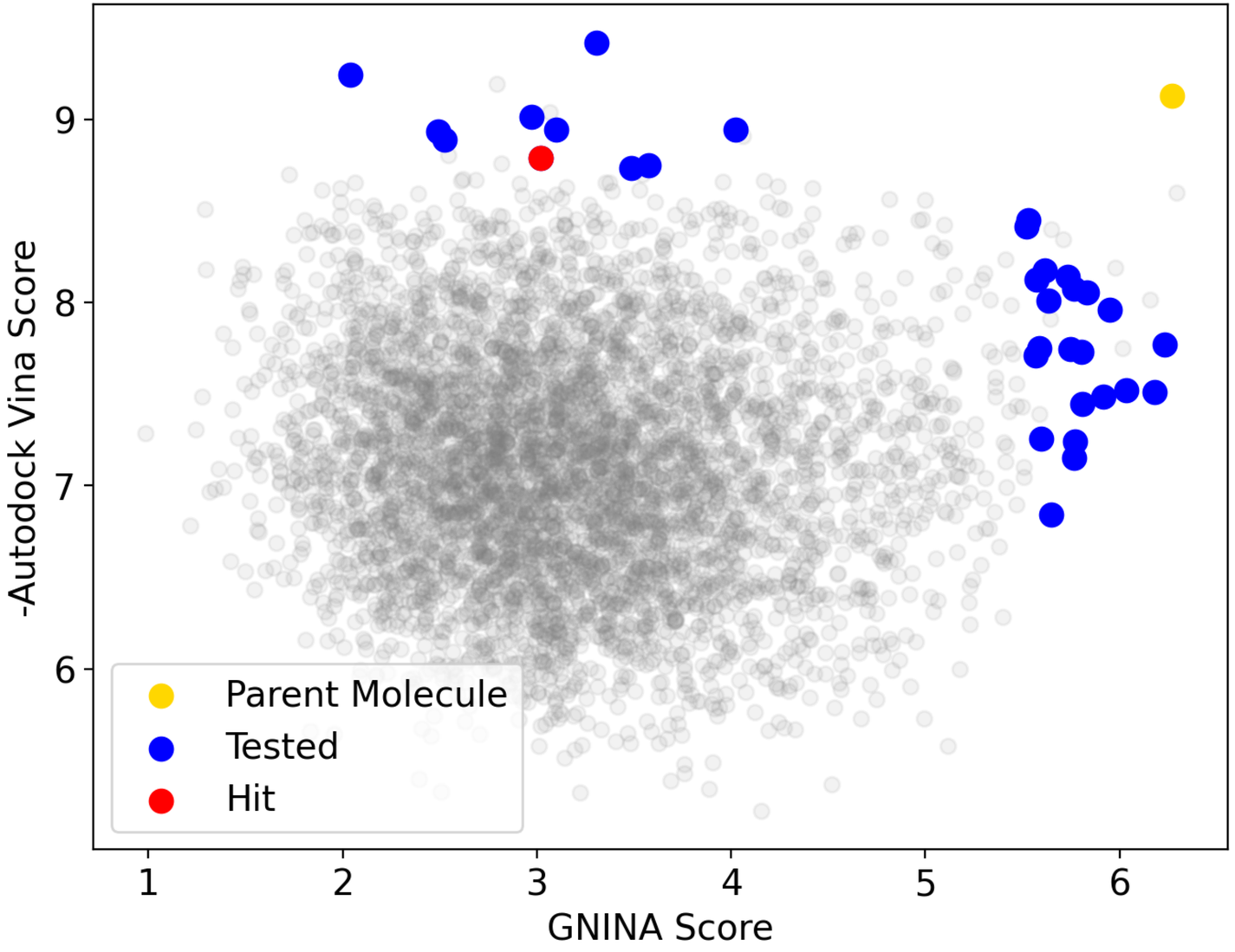
Docking with
GNINA

5000 molecules
+
GNINA scores

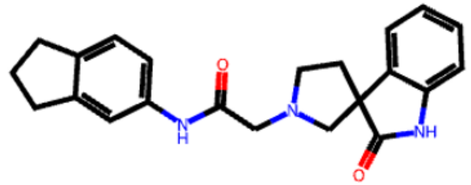


Crystal Structure

Hit Optimization Results

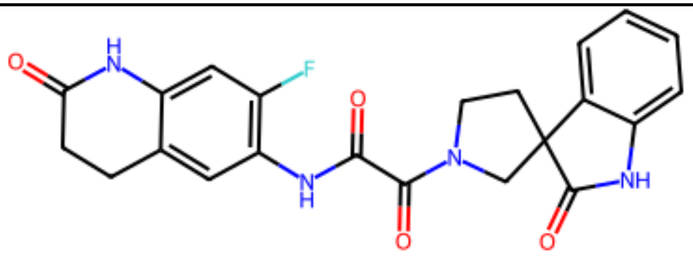


Parent Compound



CACHE_1181_33
Kd=123 uM

Hit Compound



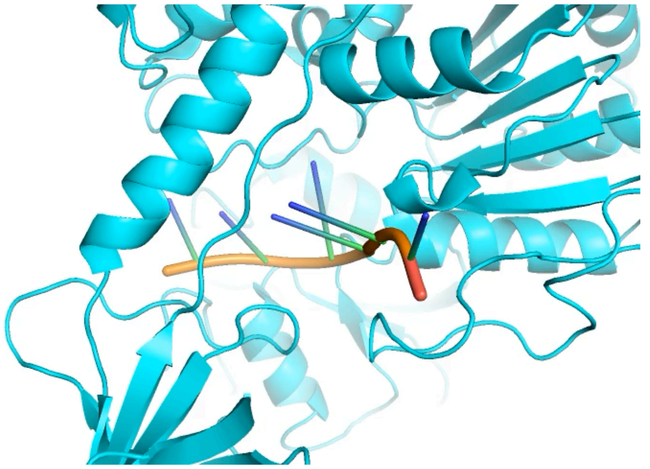
CACHE-HO_1181_24
Kd=56 uM

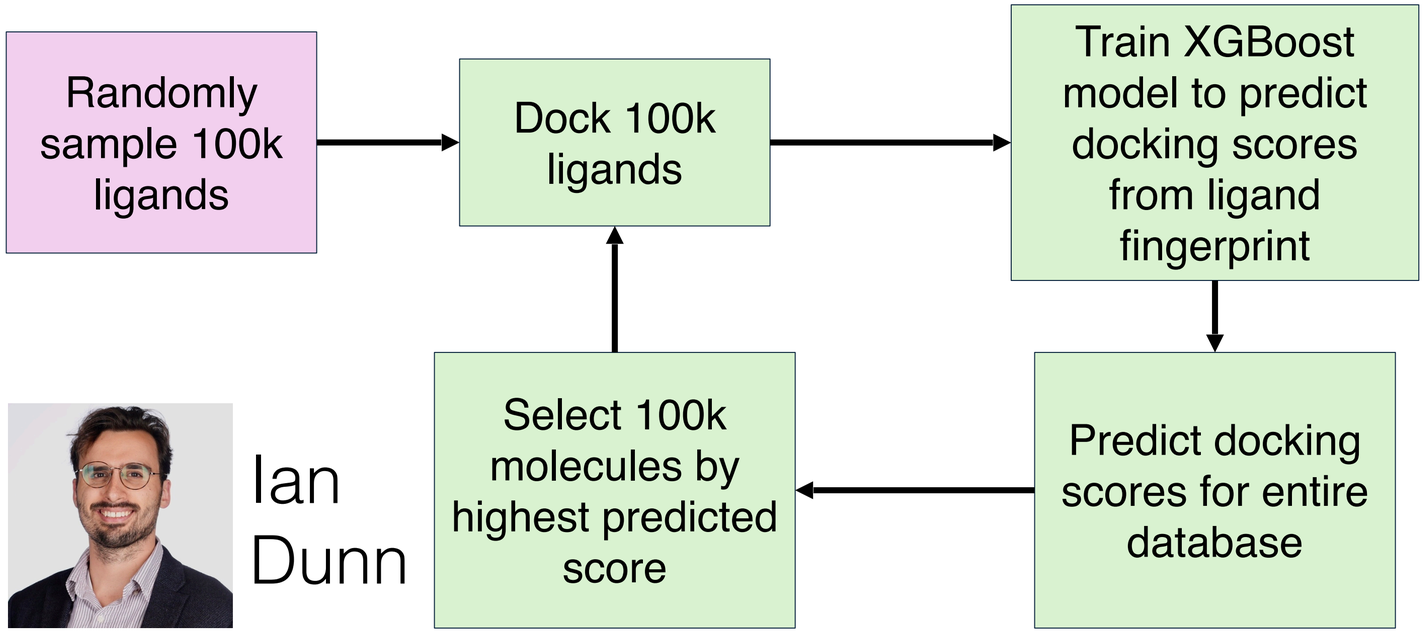
Final Results

Participant	Participant ID	Aggregated score
David Koes, University of Pittsburgh	1181	18
Olexandr Isayev & Maria Kurnikova, Carnegie Mellon University & Artem Cherkasov, University of British Columbia	1209	18
Christina Schindler, Merck KGaA	1193	17
Dmitri Kireev, University of Missouri	1183	16
Christoph Gorgulla, St. Jude Children's Research Hospital and Harvard University	1195	16
Didier Rognan, Université Strasbourg	1202	16
Pavel Polishchuk, Palacky University	1210	16
Kam Zhang, Centre for Biosystems Dynamic Research, RIKEN	1188	15
Shuangjia Zheng, Shanghai Jiao Tong University (previously Galixir)	1187	14
Carlos Zepeda, Treventis/UHN	1200	14
Fabian Liessmann, Leipzig University	1201	14
	1179	13

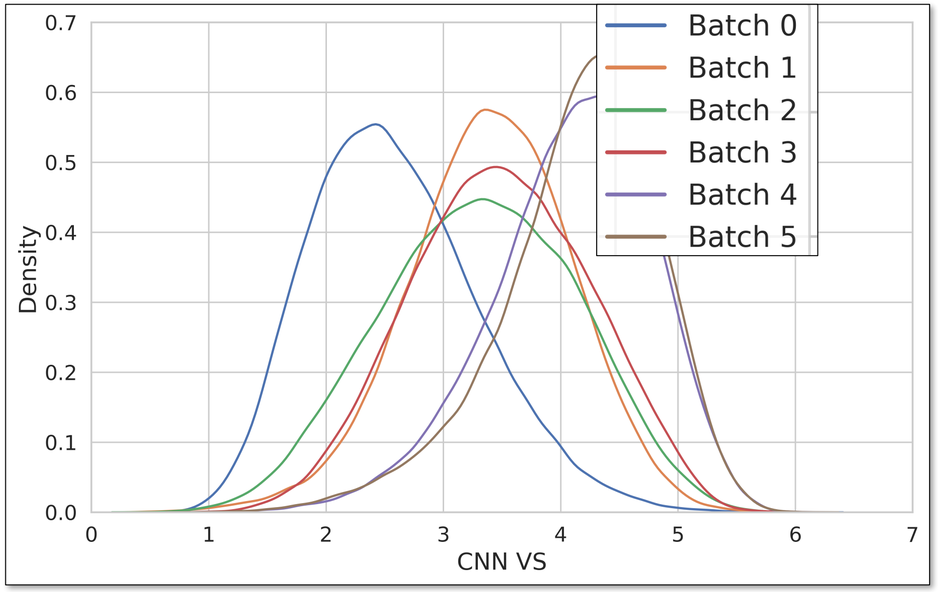
CACHE Challenge #2

- RNA binding site of SARS-COV2 NSP13
- “Deep Docking” of Enamine (4B)



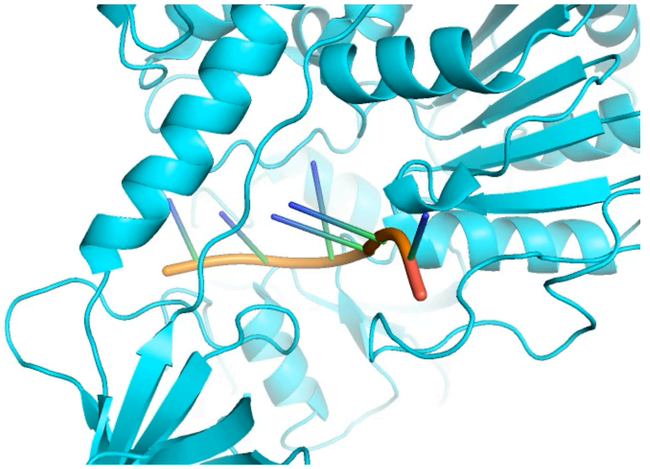


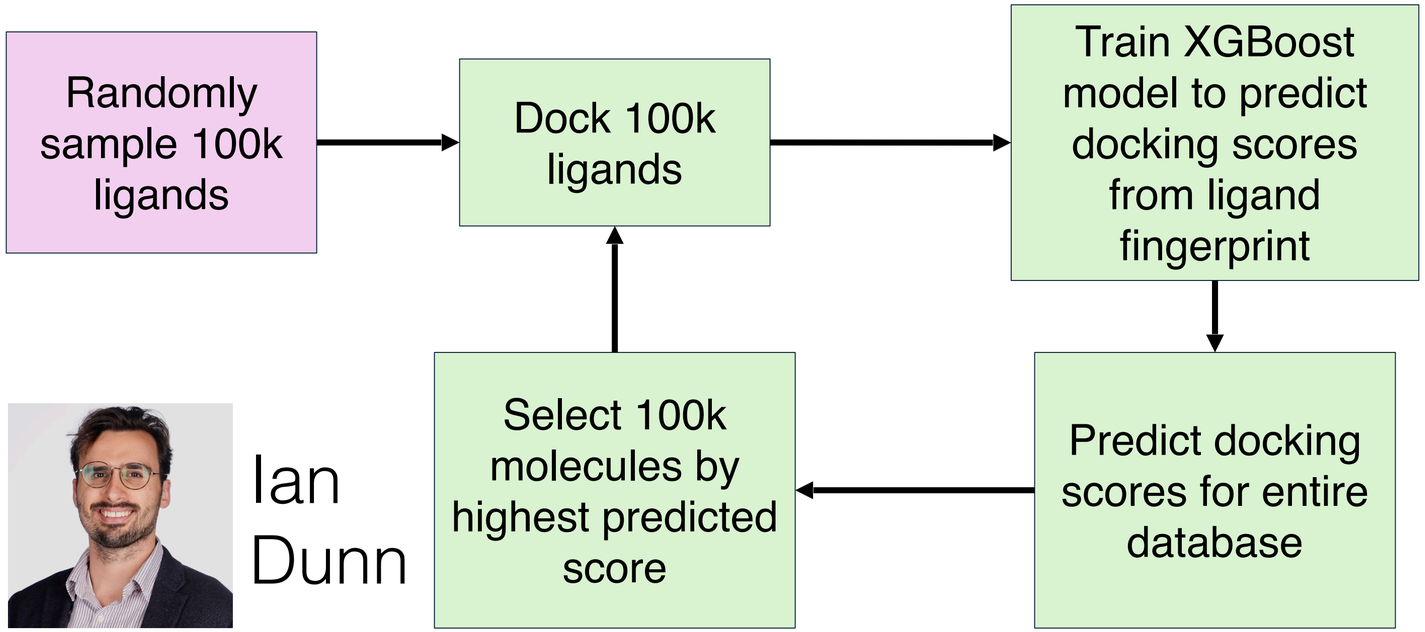
Ian Dunn



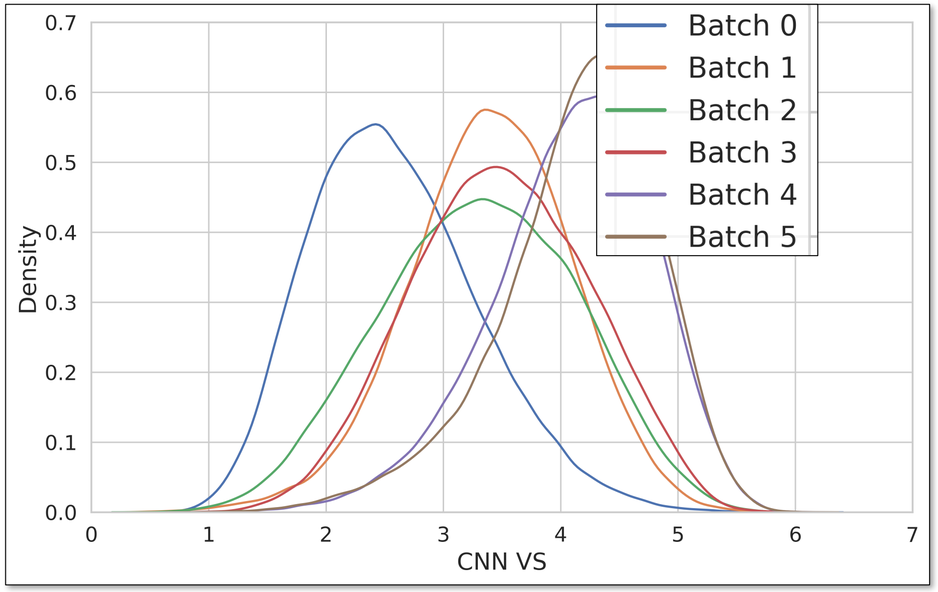
CACHE Challenge #2

- RNA binding site of SARS-COV2 NSP13
- “Deep Docking” of Enamine (4B)





Ian Dunn



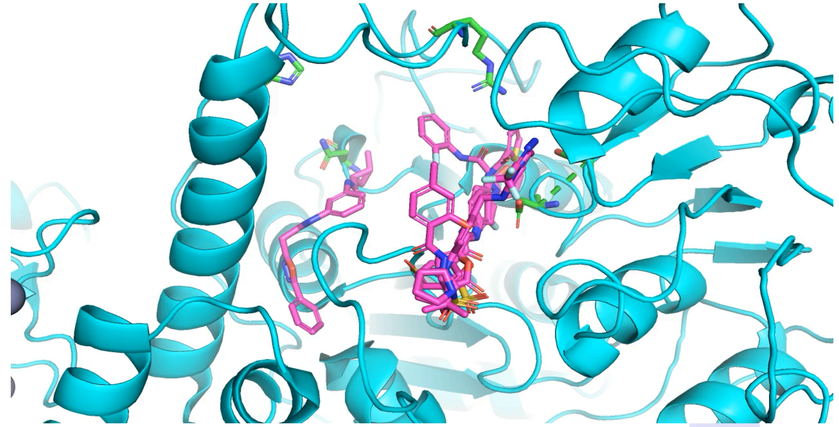
CACHE #2 Results

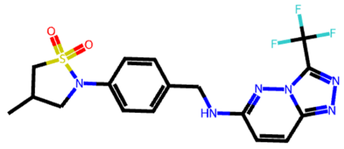
5/50 compounds identified as potential hits

>2x the average hit rate

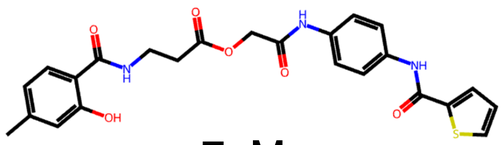
4/5 hits from last round of active learning

Highest affinity round 1 hit in the competition

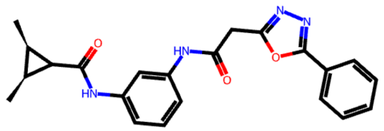




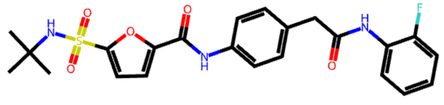
43μM



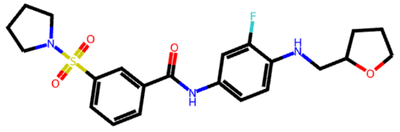
7μM



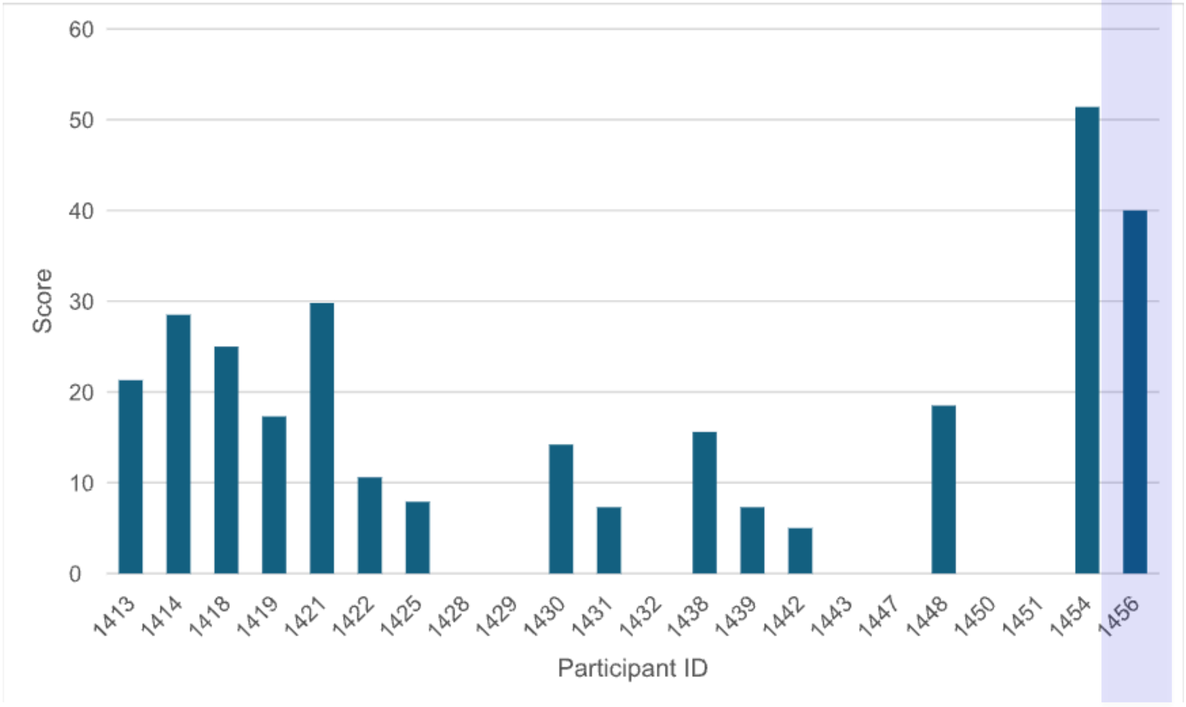
5μM



45μM



96μM



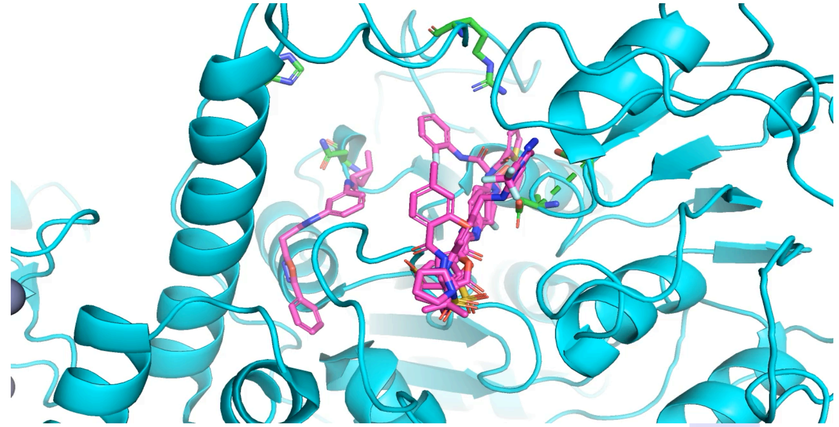
CACHE #2 Results

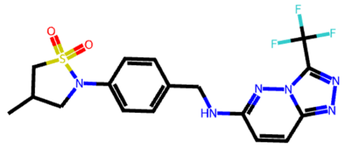
5/50 compounds identified as potential hits

>2x the average hit rate

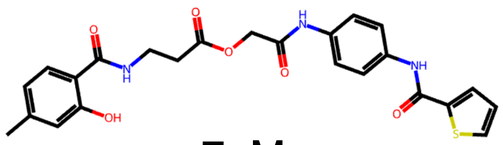
4/5 hits from last round of active learning

Highest affinity round 1 hit in the competition

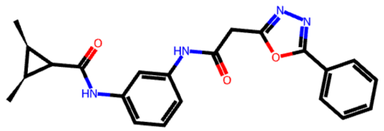




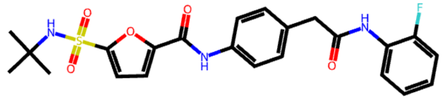
43μM



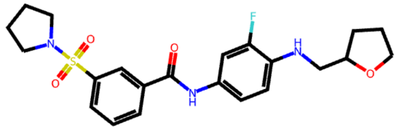
7μM



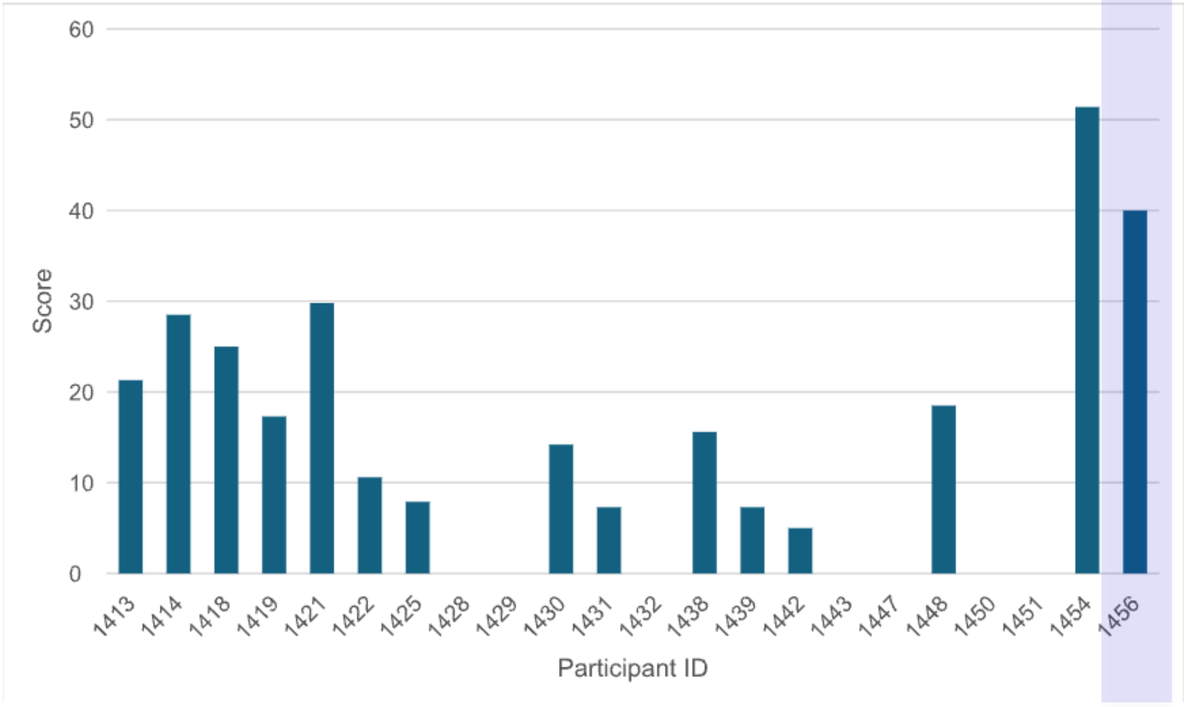
5μM



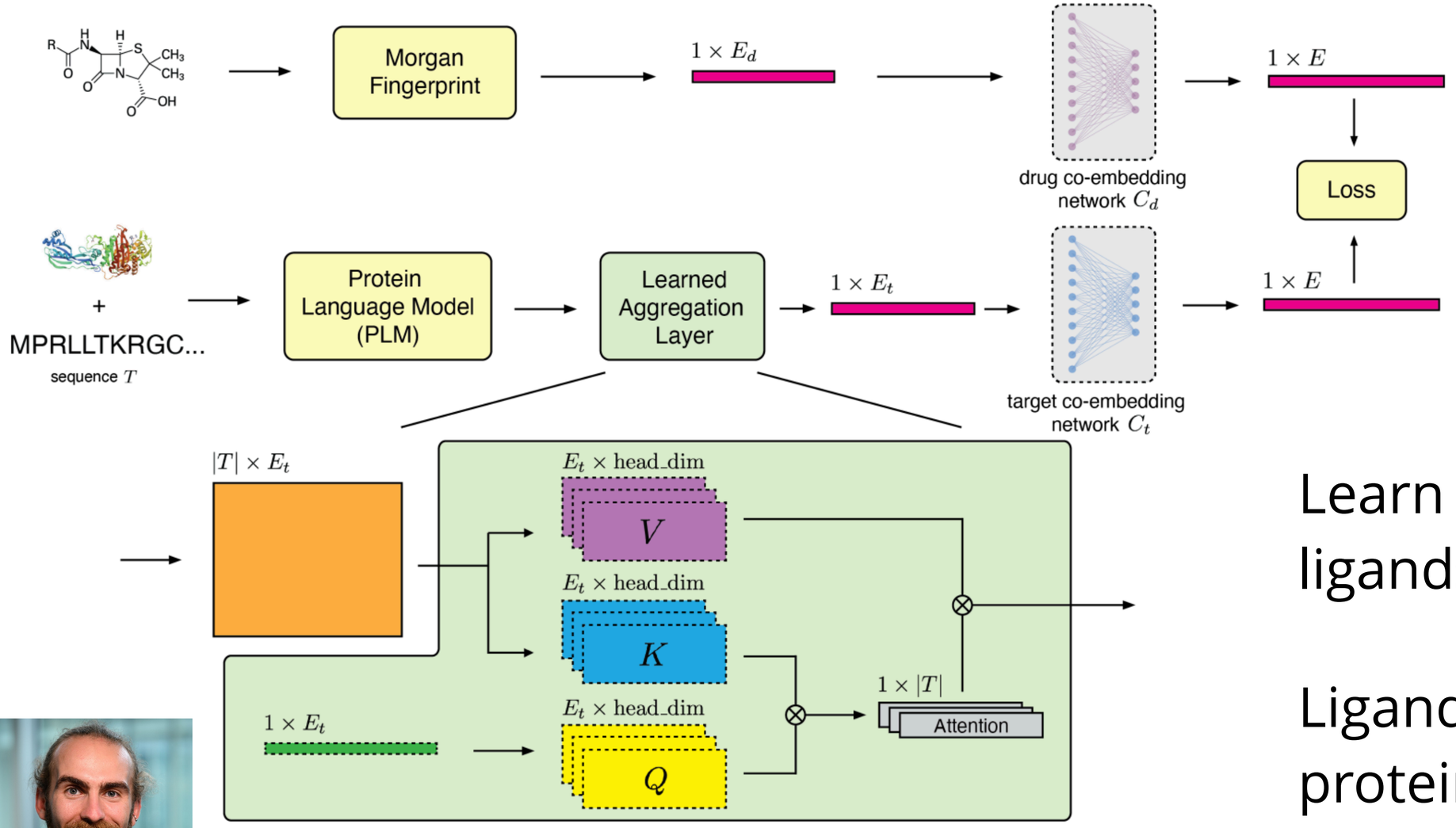
45μM



96μM



Scalable Screening of Ultra Large Libraries



$$P(Y = 1|Z_d, Z_t) = \sigma\left(\alpha \frac{Z_d}{||Z_d||} \cdot \frac{Z_t}{||Z_t||}\right)$$

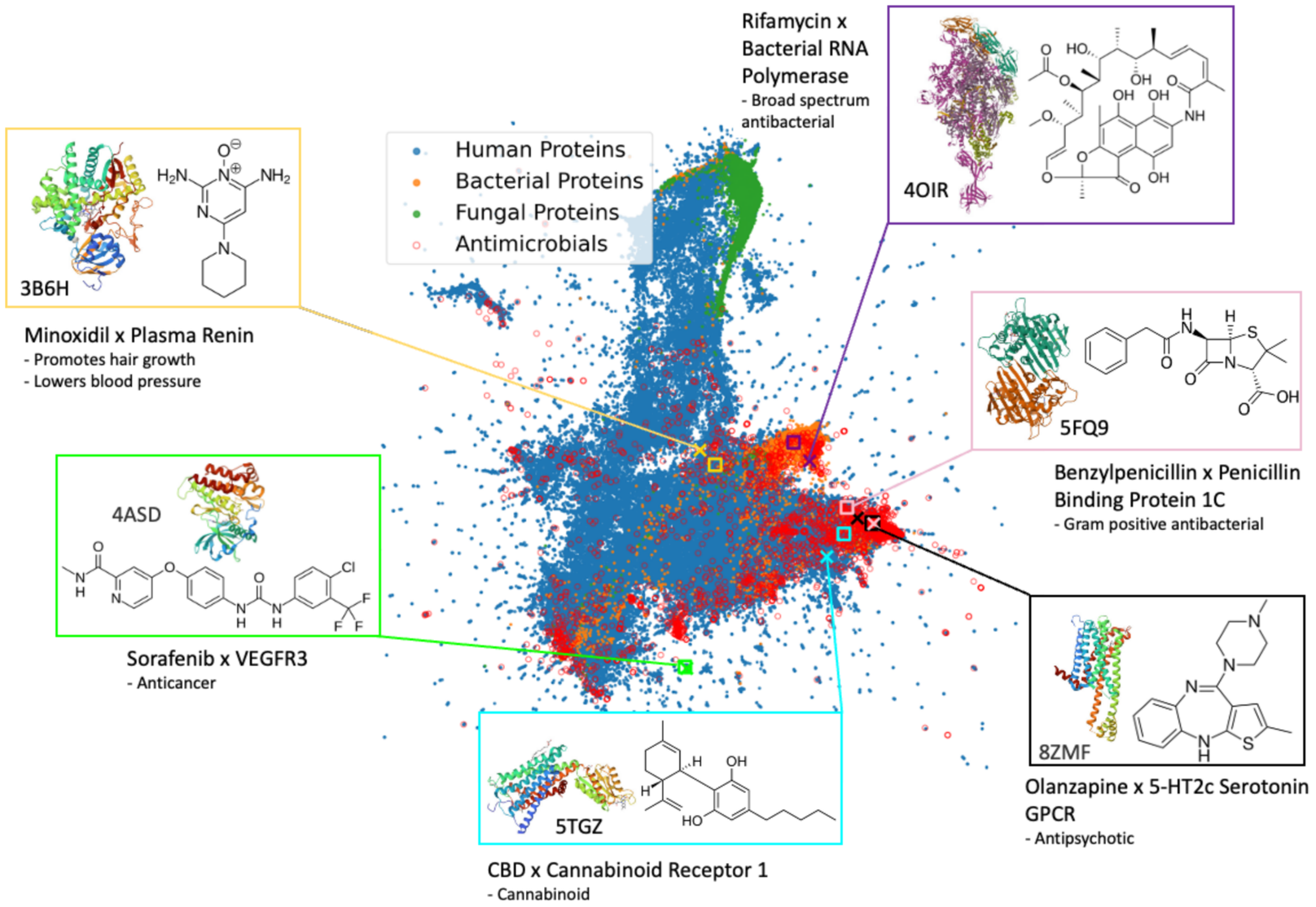
Learn *co-embedding* of ligands and proteins

Ligands are "close" to proteins they bind to



McNutt AT, Adduri AK, Ellington CN, Dayao MT, Xing EP, Mohimani H, Koes DR. *Scaling structure aware virtual screening to billions of molecules with SPRINT.* ArXiv. 2025 Jan 20:arXiv-2411.

SPRINT Co-embeddings



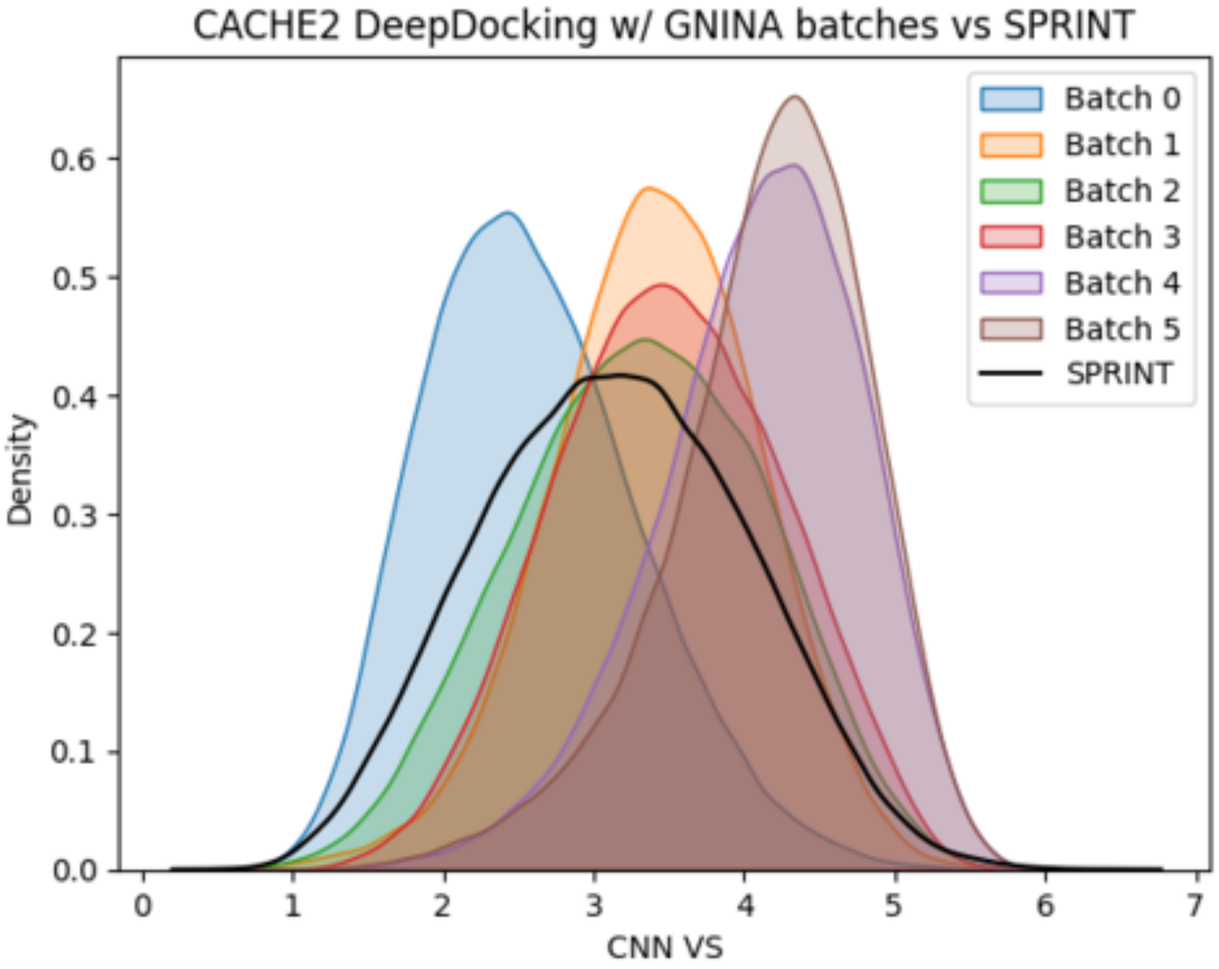
Suspiciously Good Retrospective Virtual Screening

Table 2: Virtual Screening results on LIT-PCBA. SPRINT-ProtBert replaces SaProt with the ProtBert model, and SPRINT-Average replaces learned aggregation with average pooling and additional MLP layers. Parameter counts are shown in parentheses.

	AUROC (%)	BEDROC (%)	EF		
			0.5%	1%	5%
Surflex [20]	51.47	-	-	2.50	-
Glide-SP [21]	53.15	4.00	3.17	3.41	2.01
Planet [22]	57.31	-	4.64	3.87	2.43
GNINA [23]	60.93	5.40	-	4.63	-
DeepDTA [24]	56.27	2.53	-	1.47	-
BigBind [25]	60.80	-	-	3.82	-
DrugCLIP [9]	57.17	6.23	8.56	5.51	2.27
SPRINT-Average (15.7M)	67.49	7.80	7.23	6.26	3.71
SPRINT-ProtBert (15.9M)	**73.4**	11.9	11.68	10.19	5.27
SPRINT (16M)	**73.4**	**12.3**	**15.90**	**10.78**	**5.29**

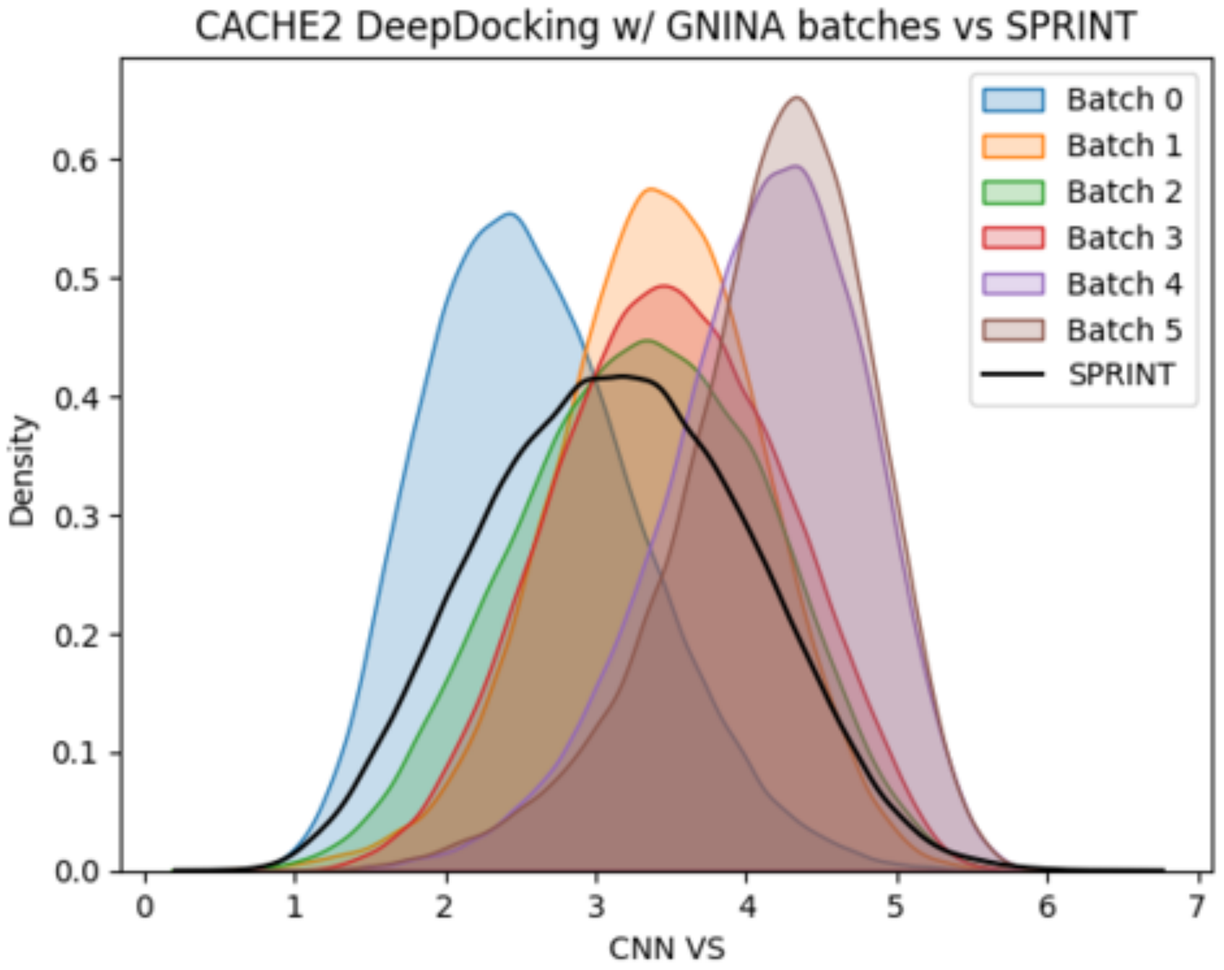
Enhanced Deep Docking with SPRINT

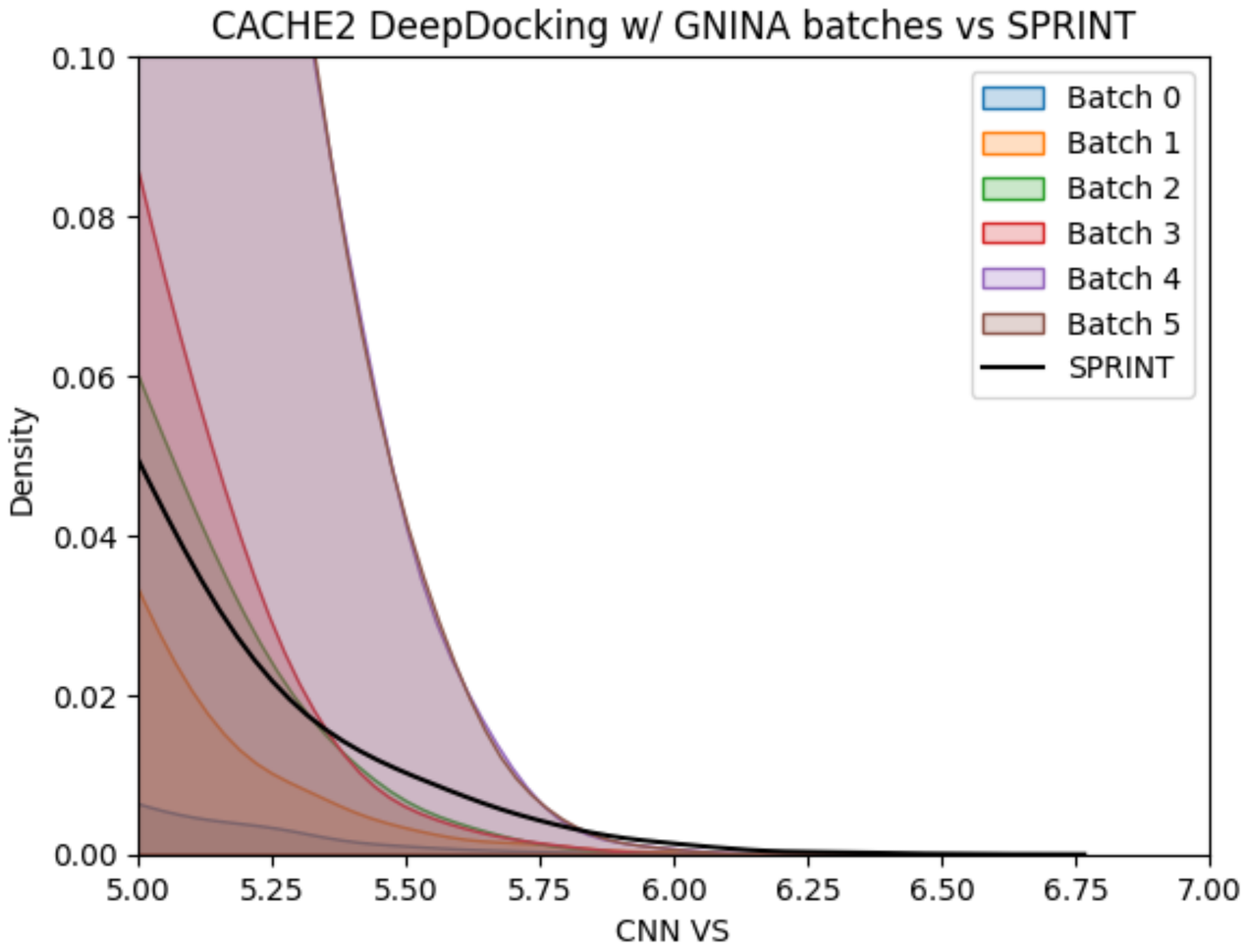
Retrospective CACHE2 Deep Docking



Enhanced Deep Docking with SPRINT

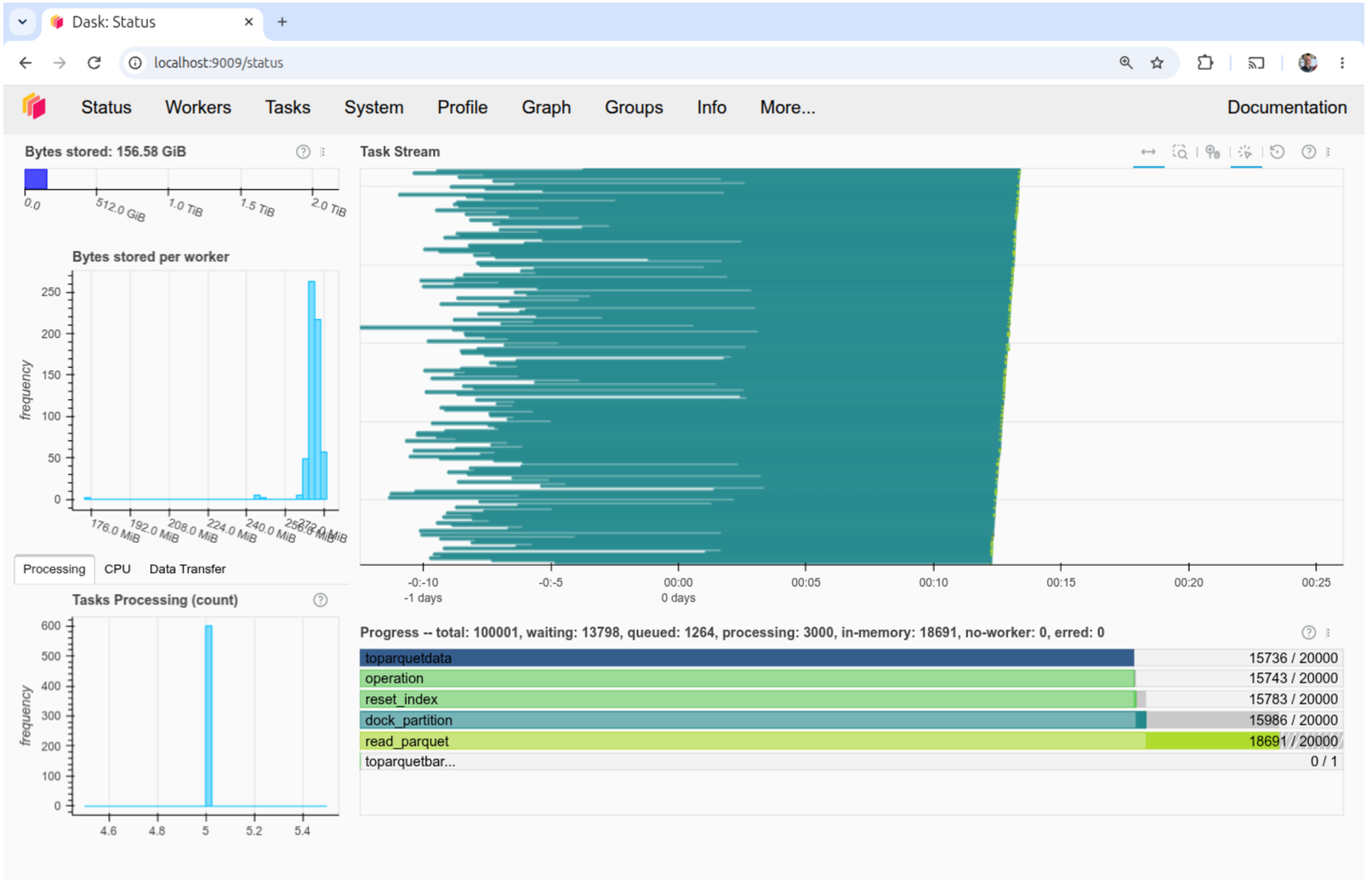
Retrospective CACHE2 Deep Docking

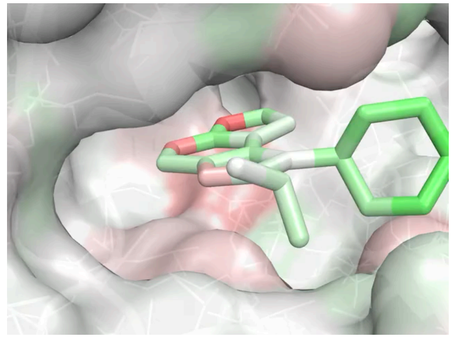




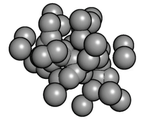
Deep Docking with GNINA

master gnina / scripts / deepdock.py

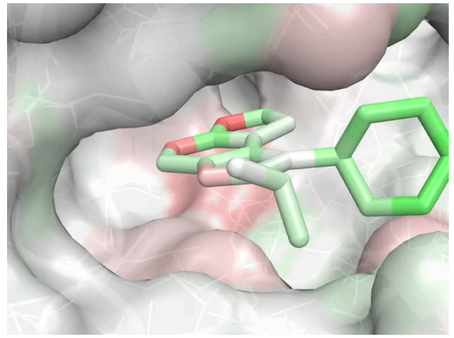




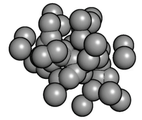
Takeaways



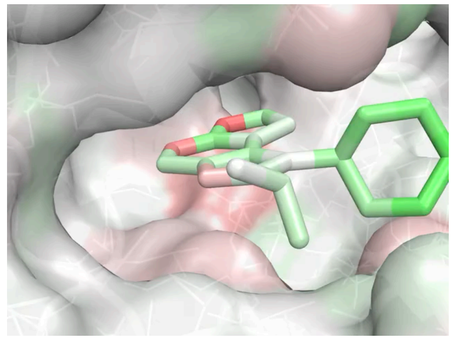
Deep learning works for molecules!



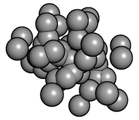
Takeaways



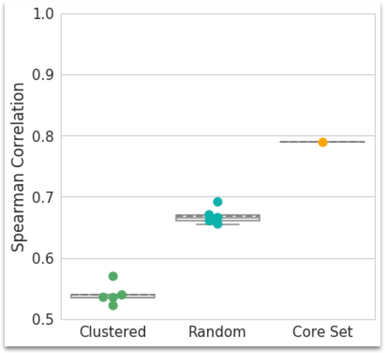
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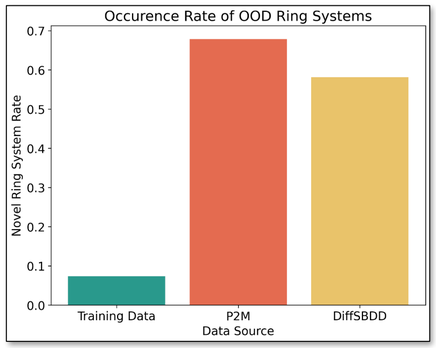


Takeaways

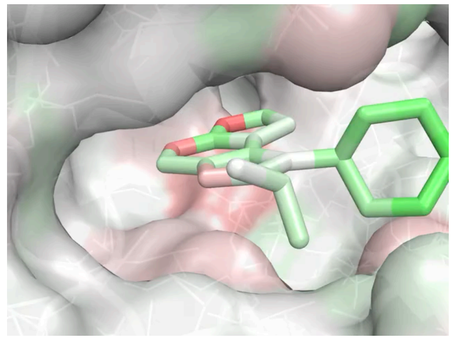


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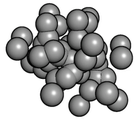




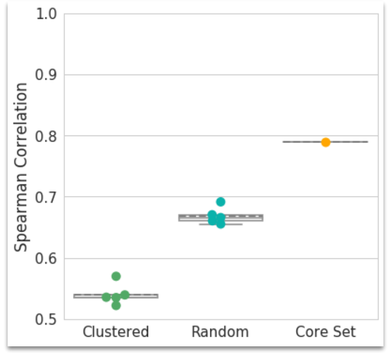
Rigorous evaluation is essential

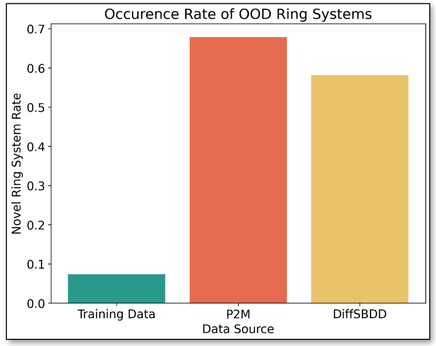


Takeaways



Deep learning works for molecules!

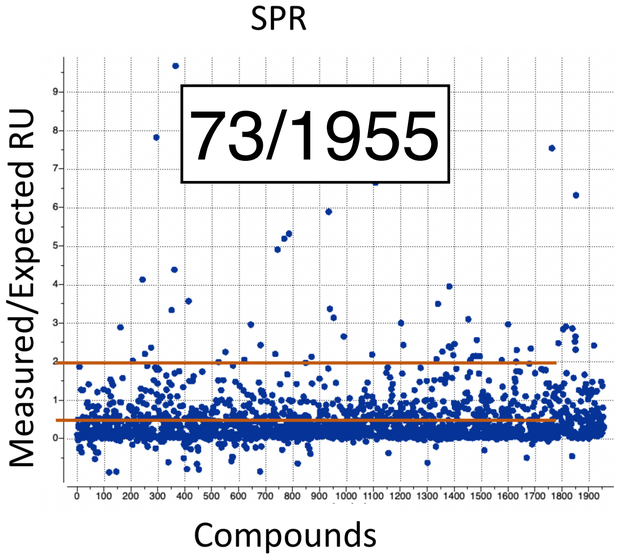


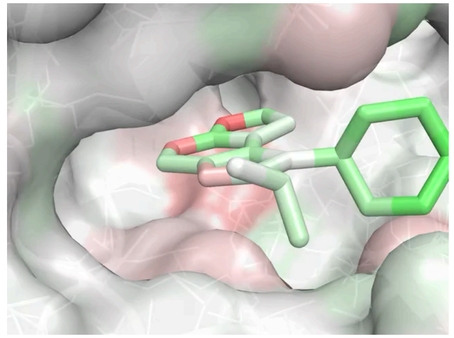


Rigorous evaluation is essential

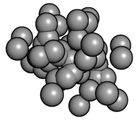
No replacement for prospective evaluation

Still pretty bad





Takeaways



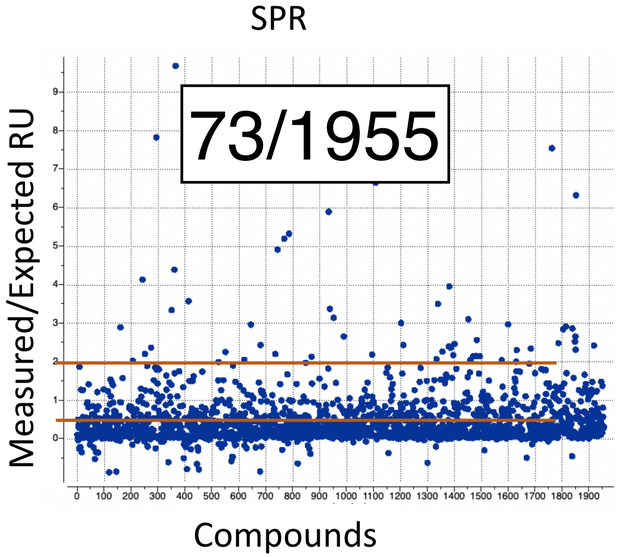
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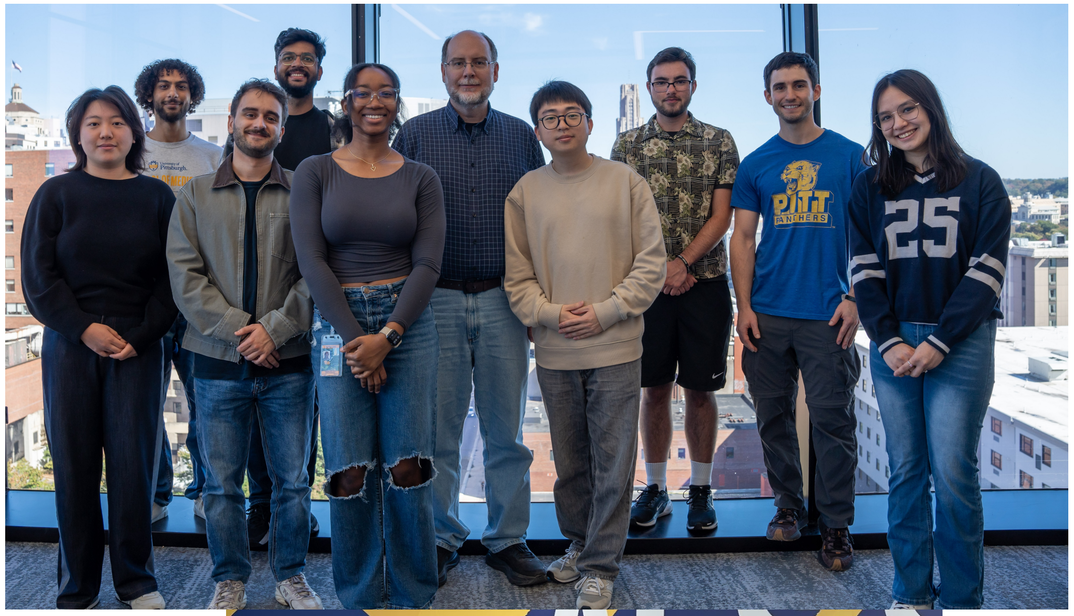
It is pronounced NEE-na

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Still pretty bad



Acknowledgements





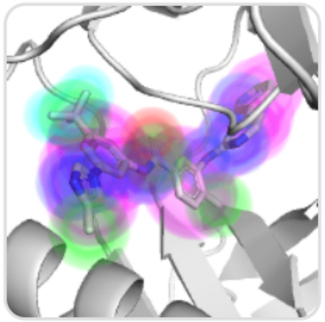
Current
Emma Flynn
Riya Shah
Rishal Aggarwal
Daniel Penaherrera
Jacky Chen
Fareeda Abu-Juam
Ben Krummenacher
Marios Gavrielatos

Previous
Ian Dunn
Drew McNutt
Jocelyn Sunseri
Matthew Ragoza
Tomohide Masuda
Paul Francoeur
Jonathan King
Rocco Meli
Josh Hochuli
Elisa Idrobo
Lily Turner
Alec Helbling
Andrew Jia
Rich Iovanisci
Ian Snyder
Nick Rego

National Institute of General Medical Sciences

NSF

Shameless Plugs

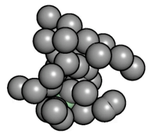


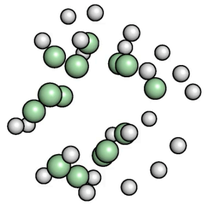
gnina

https://github.com/gnina

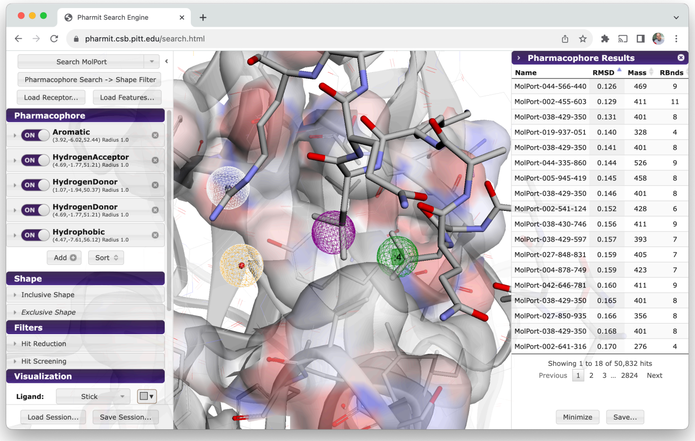
FlowMol3

https://github.com/Dunni3/FlowMol





Pharmit



https://pharmit.csb.pitt.edu



https://github.com/gnina/OMTRA

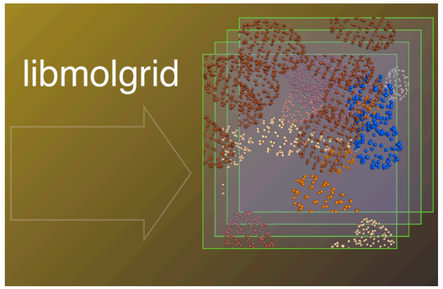
py3Dmol

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    p
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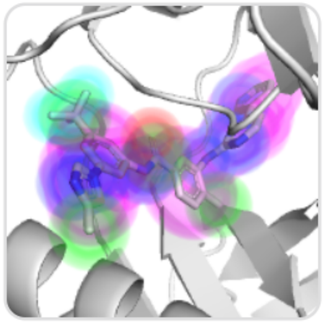


https://3dmol.org/



https://gina.github.io/libmolgrid/

Shameless Plugs

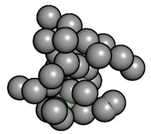


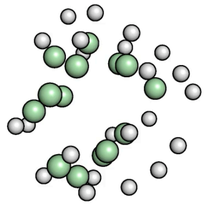
gnina

https://github.com/gnina

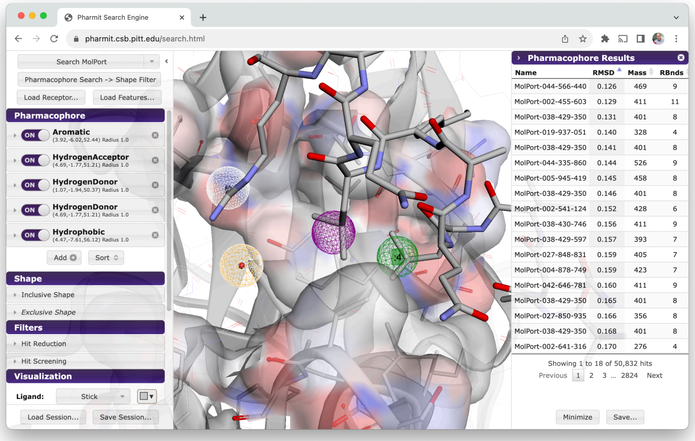
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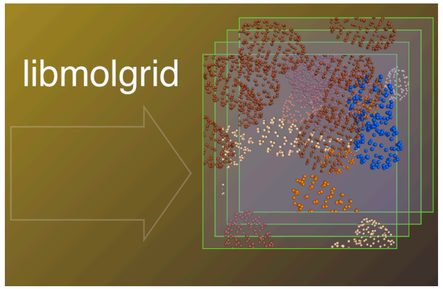
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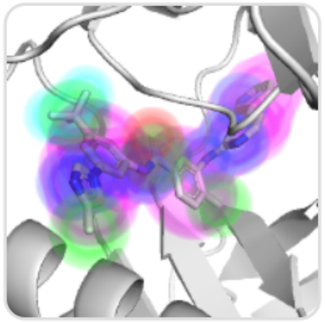


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Shameless Plugs



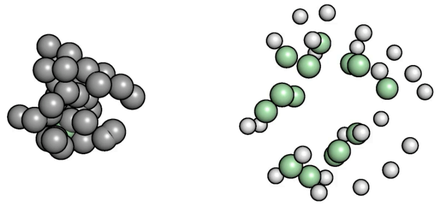
gnina

(NEE-na)

https://github.com/gnina

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py3Dmol

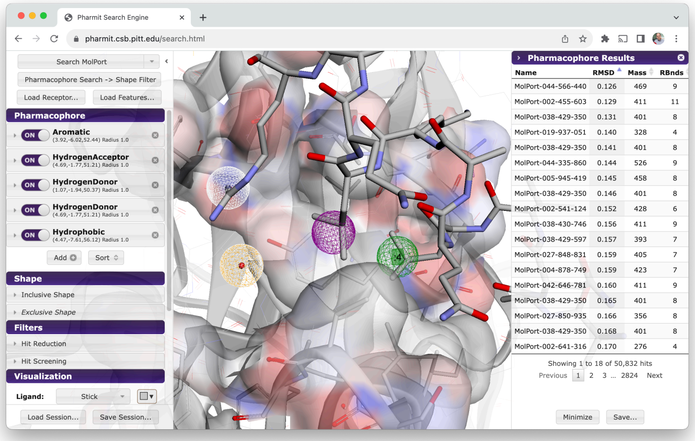
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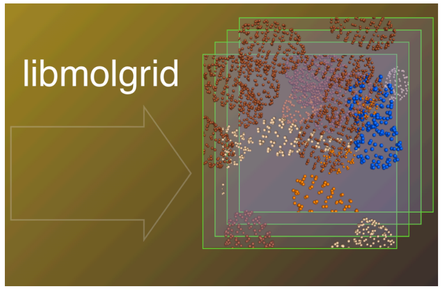
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