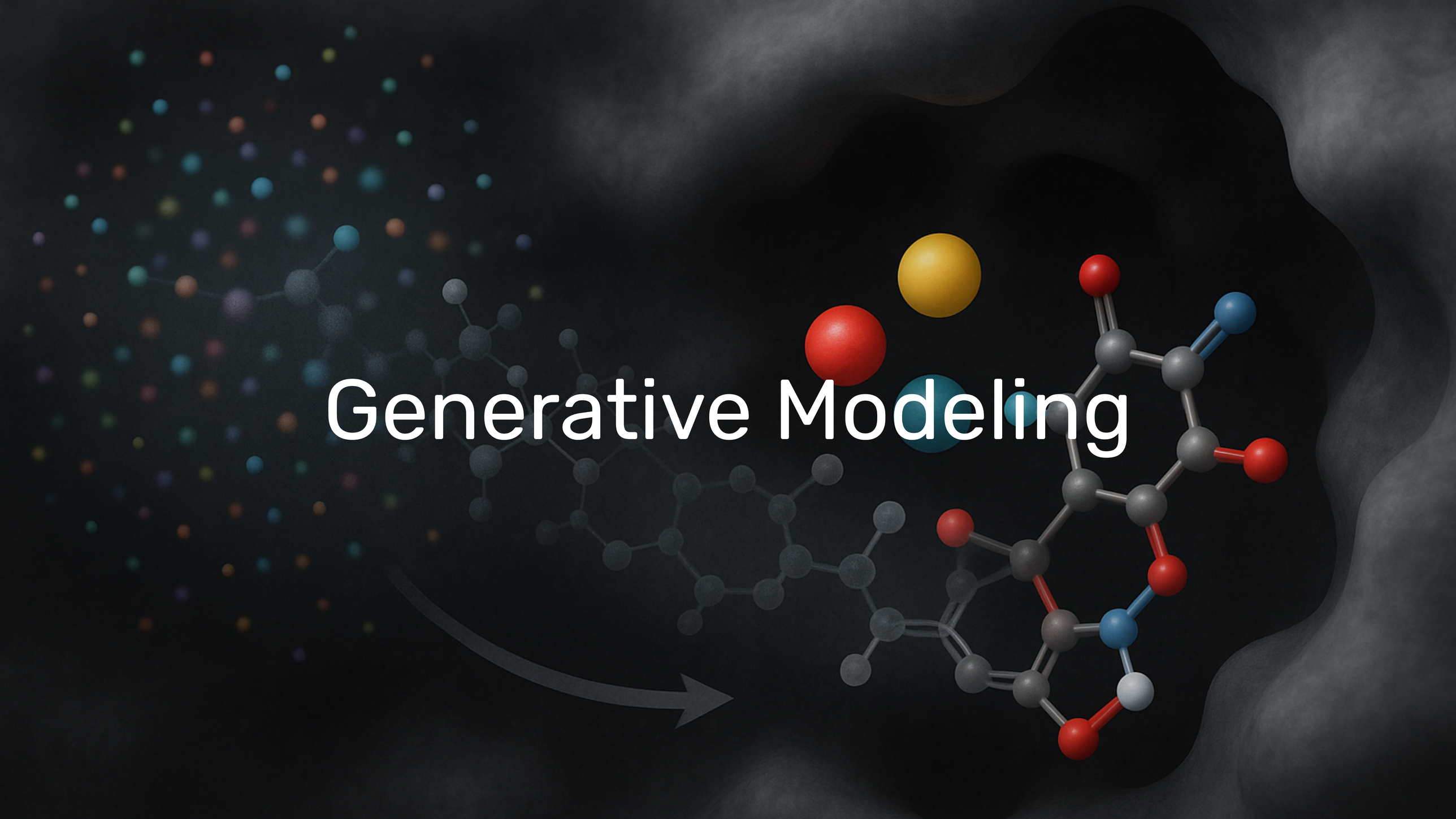
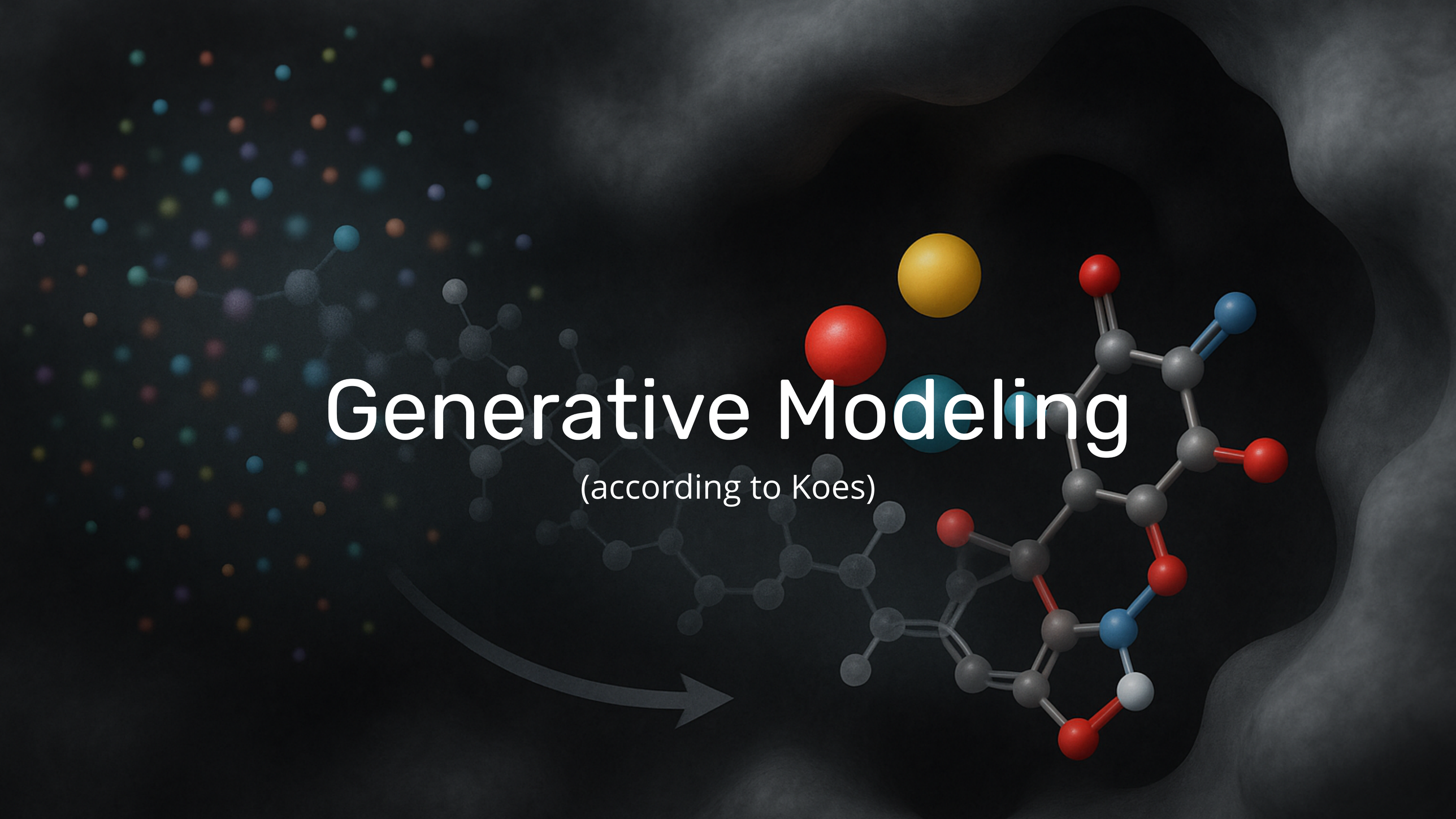
Generative Modeling

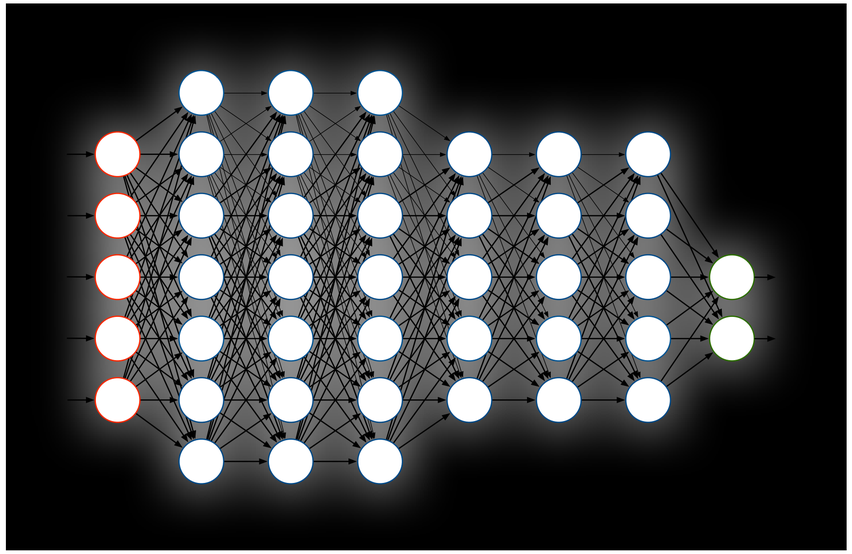


Generative Modeling

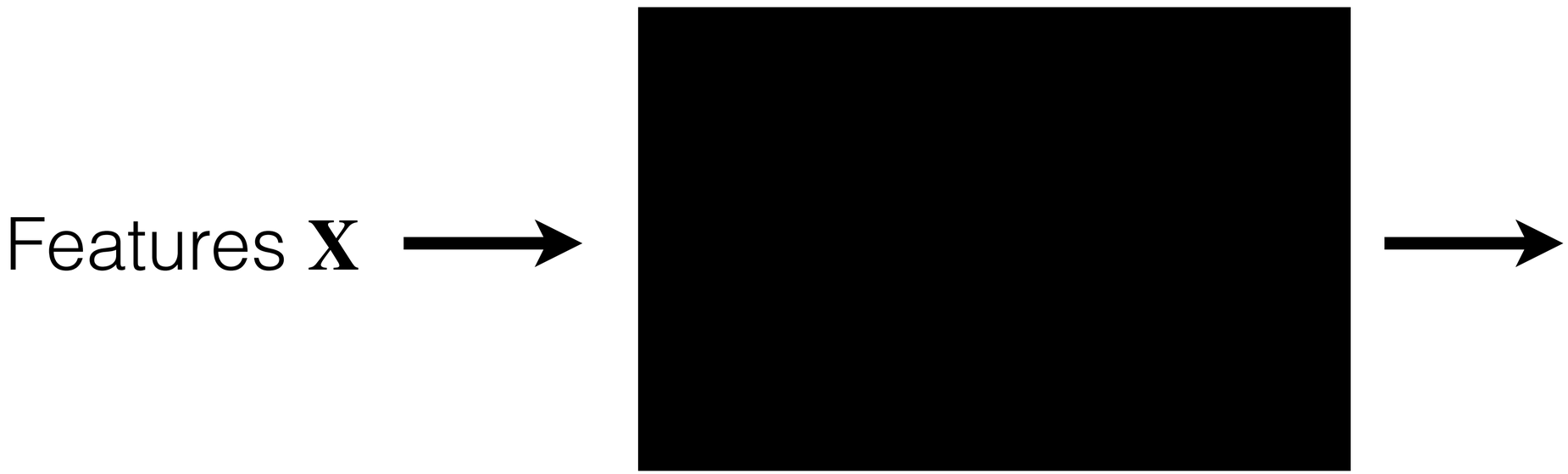
(according to Koes)



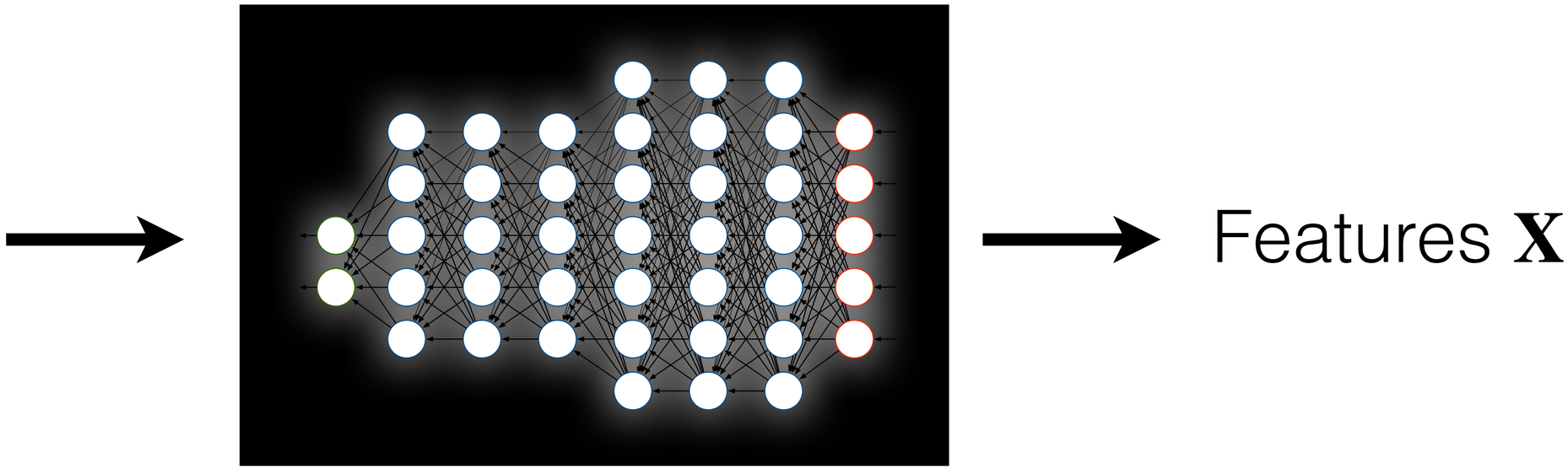
Discriminative Model

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

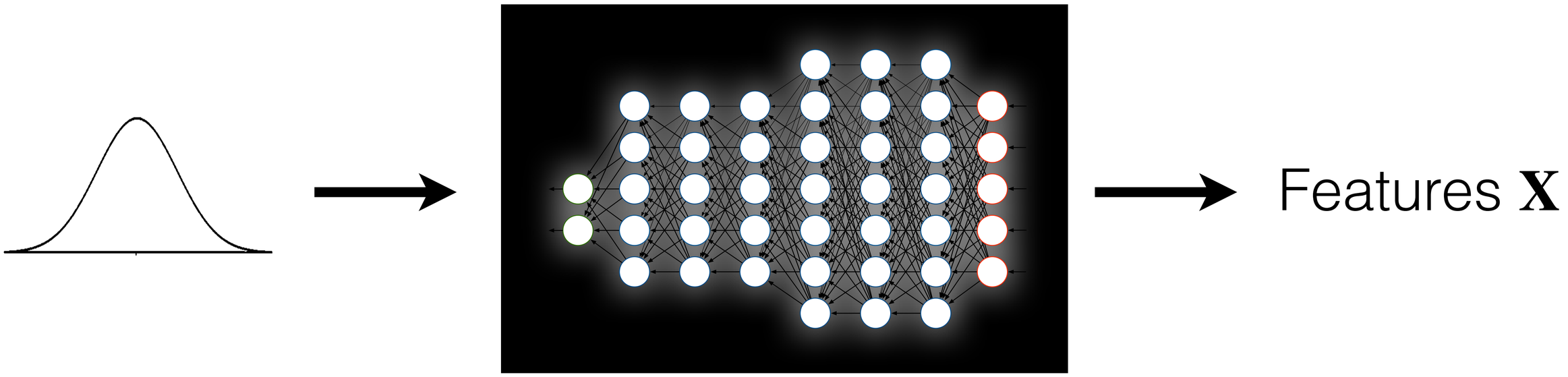
Generative Model



Generative Model



Generative Model



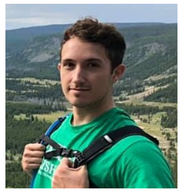
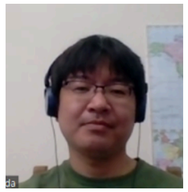
Learning a Continuous Representation of 3D Molecular Structures with Deep Generative Models

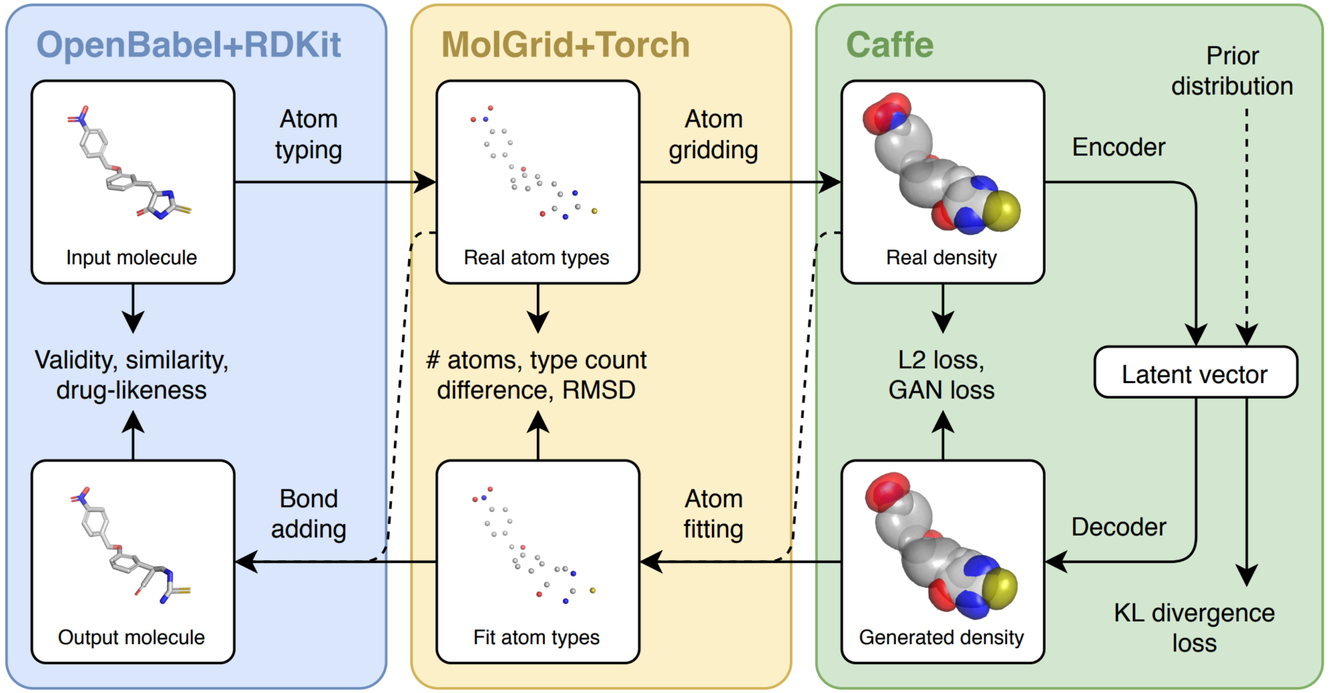
NeurIPS 2020 Workshop
Machine Learning for Structural Biology

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

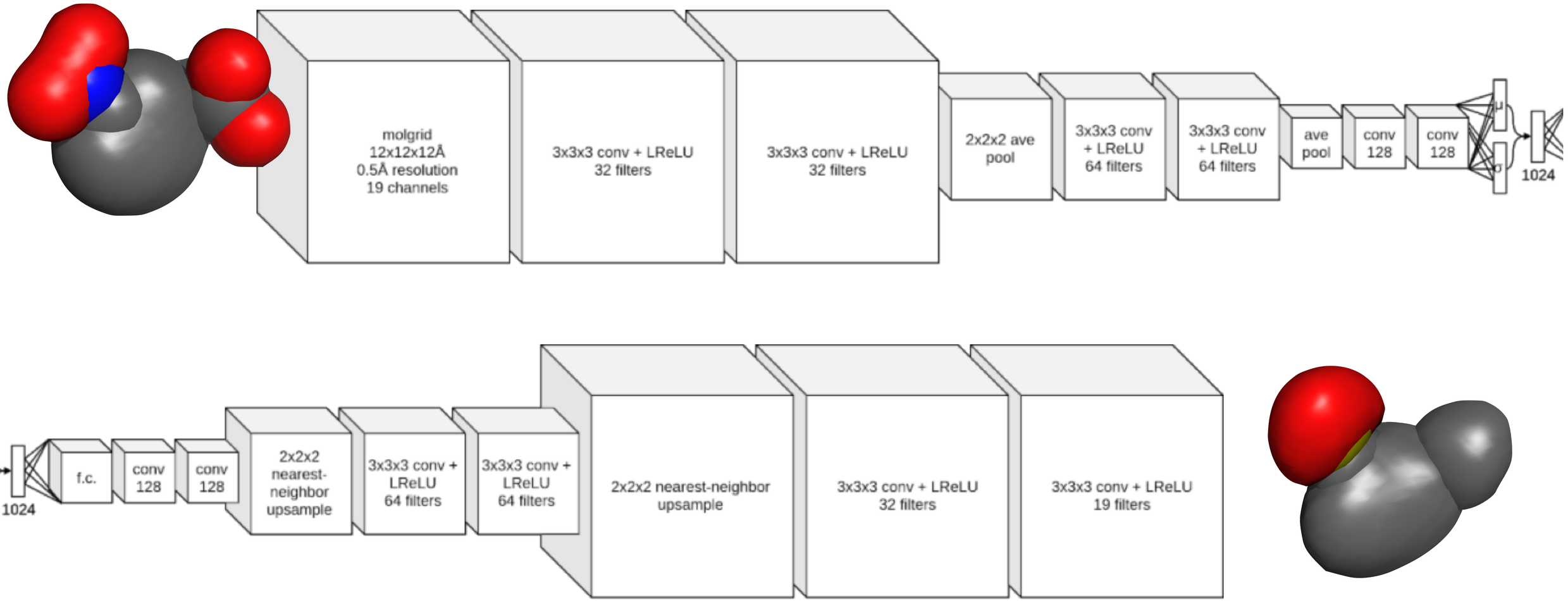
Tomohide Masuda*
Comp. & Systems Biology
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David Ryan Koes
Comp. & Systems Biology
University of Pittsburgh
Pittsburgh, PA 15213
dkoes@pitt.edu

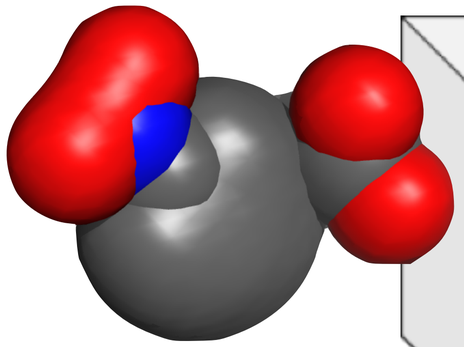


Model


molgrid
12x12x12Å
0.5Å resolution
19 channels
3x3x3 conv + LReLU
32 filters
3x3x3 conv + LReLU
32 filters
2x2x2 ave
pool
3x3x3 conv
+ LReLU
64 filters
3x3x3 conv
+ LReLU
64 filters
ave
pool
conv
128
conv
128
μ
σ
1024
1024
f.c.
conv
128
conv
128
2x2x2
nearest-
neighbor
upsample
3x3x3 conv +
LReLU
64 filters
3x3x3 conv +
LReLU
64 filters
2x2x2 nearest-neighbor
upsample
3x3x3 conv + LReLU
32 filters
3x3x3 conv + LReLU
19 filters

Model

Variational
Latent Space



molgrid
12x12x12Å
0.5Å resolution
19 channels

3x3x3 conv + LReLU
32 filters

3x3x3 conv + LReLU
32 filters

2x2x2 ave
pool

3x3x3 conv
+ LReLU
64 filters

3x3x3 conv
+ LReLU
64 filters

ave
pool

conv
128

conv
128

μ

σ

1024

1024

f.c.

conv
128

conv
128

2x2x2
nearest-
neighbor
upsample

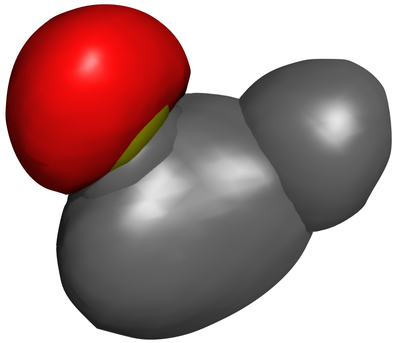
3x3x3 conv +
LReLU
64 filters

3x3x3 conv +
LReLU
64 filters

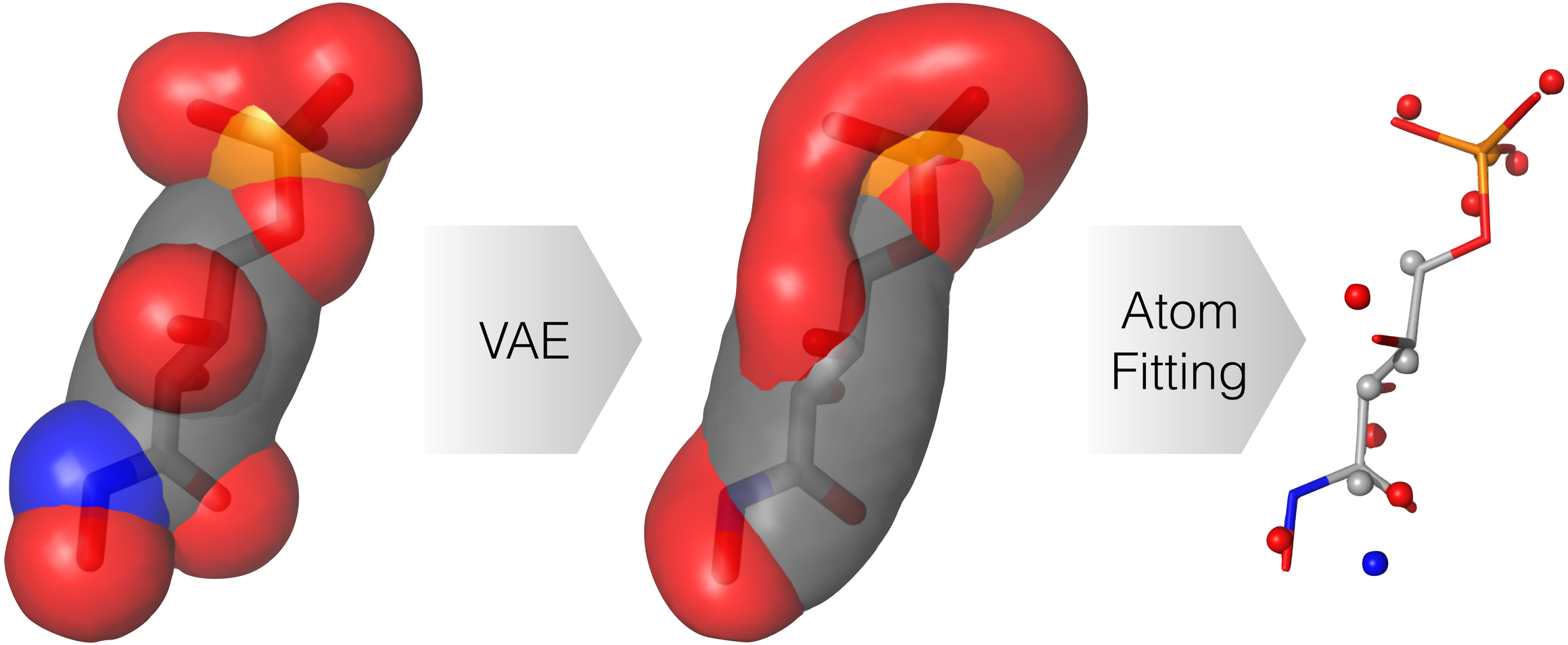
2x2x2 nearest-neighbor
upsample

3x3x3 conv + LReLU
32 filters

3x3x3 conv + LReLU
19 filters



Variational Autoencoding Examples



2BES

Different input molecules

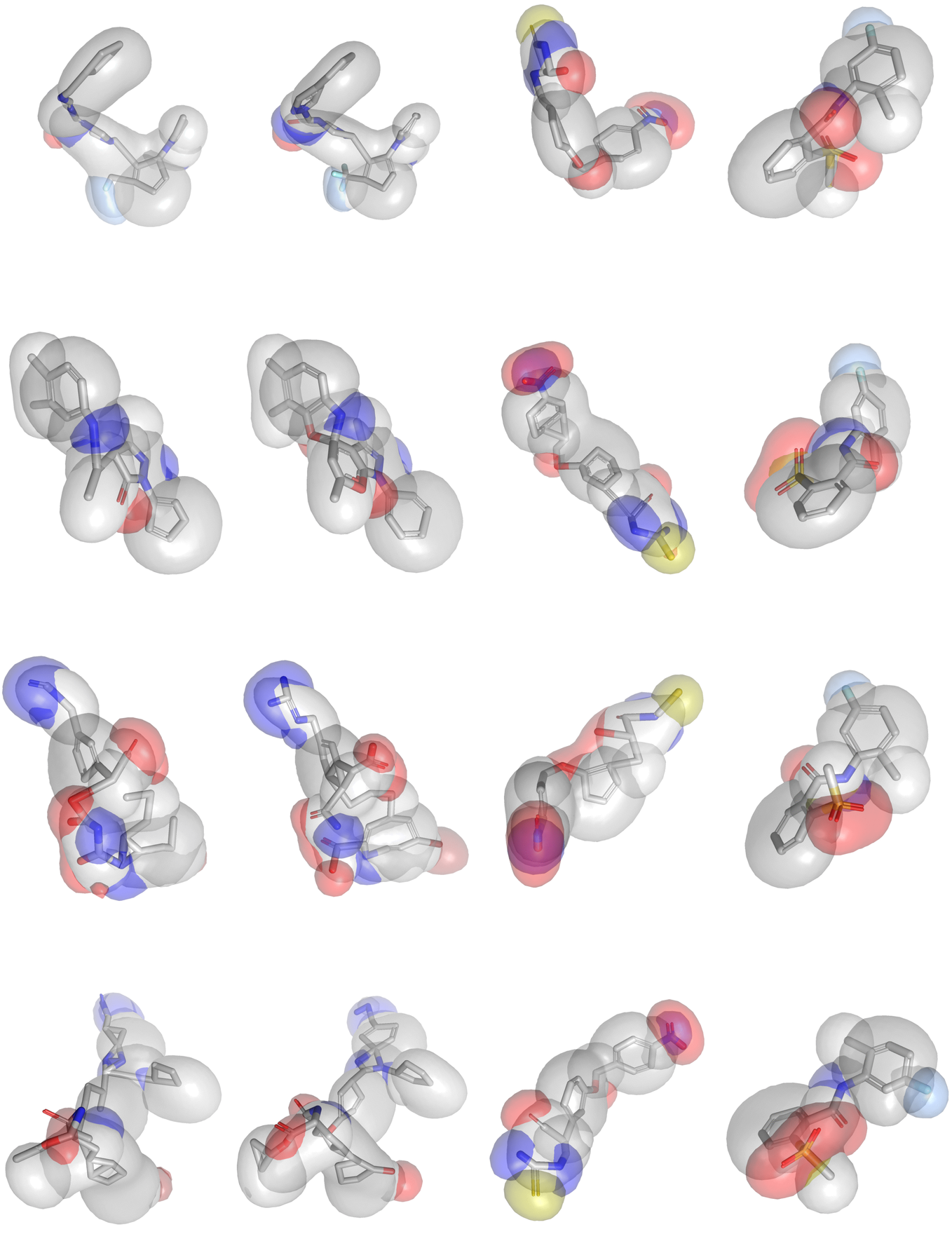
Same input molecules

VAE

AE

VAE

AE



University of Pittsburgh

Computational and Systems Biology

Different input molecules

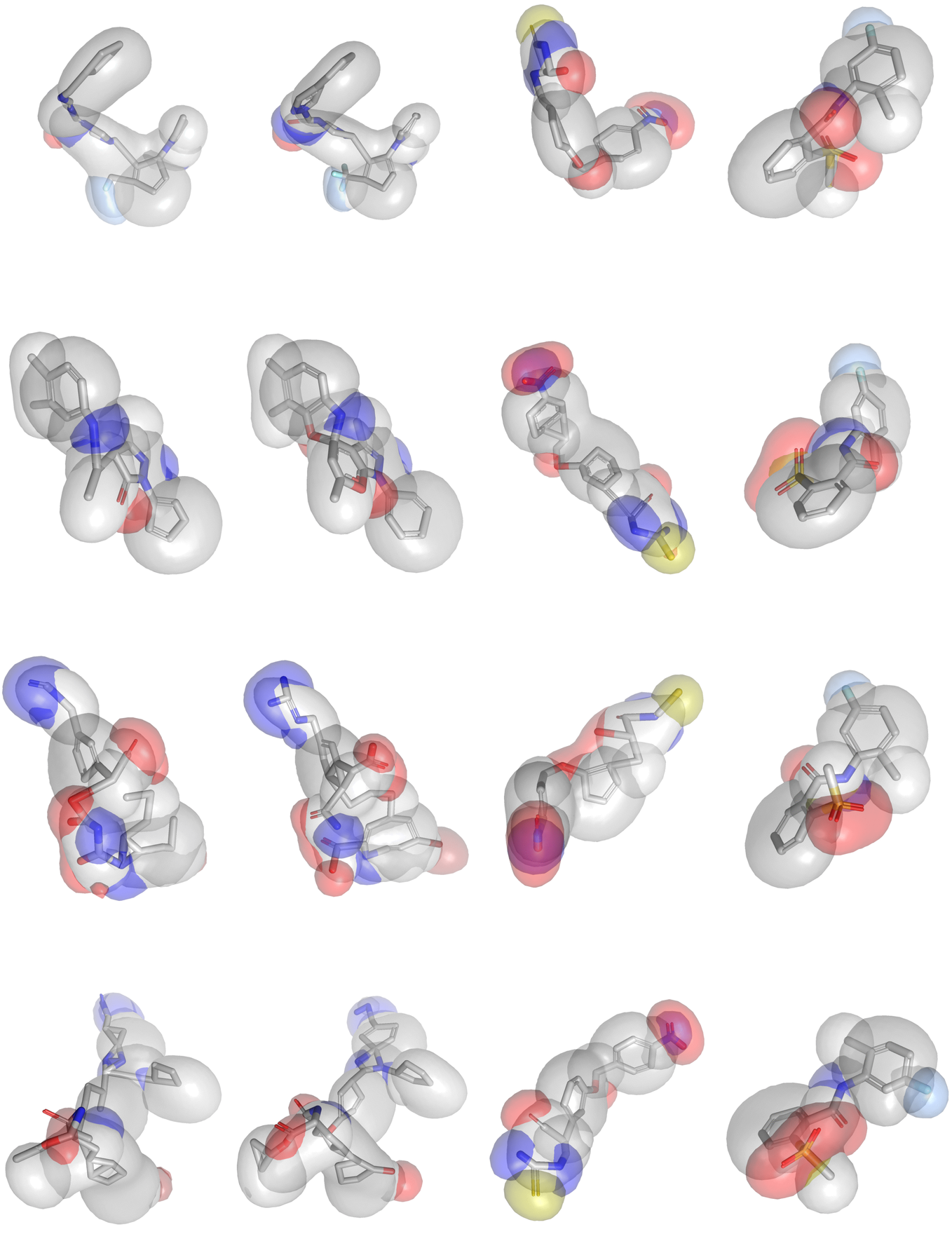
Same input molecules

VAE

AE

VAE

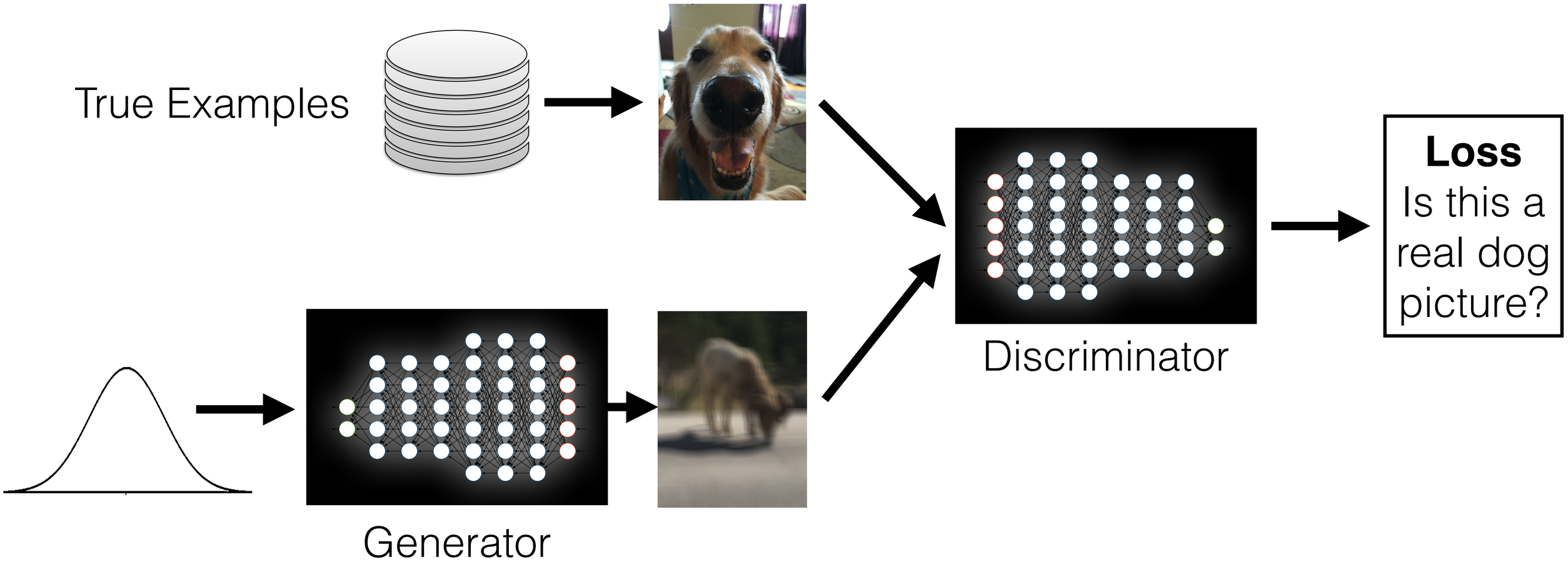
AE



University of Pittsburgh

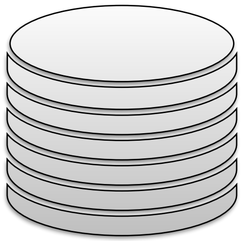
Computational and Systems Biology

Generative Adversarial Networks

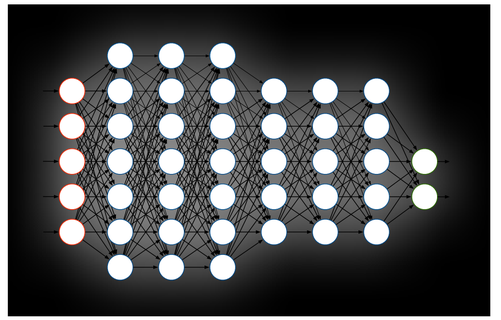


Generative Adversarial Networks

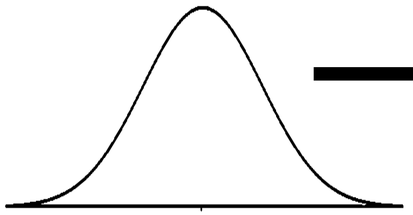
True Examples

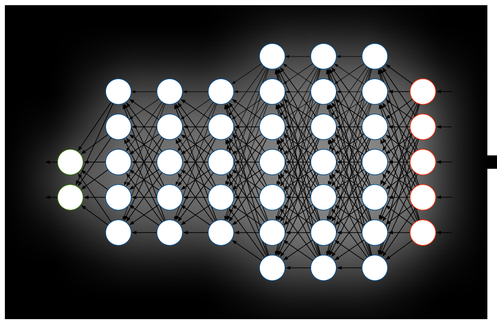






Loss
Is this a real dog picture?



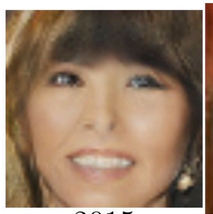


Generator

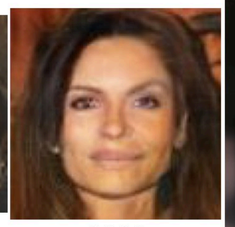




2014



2015



2016

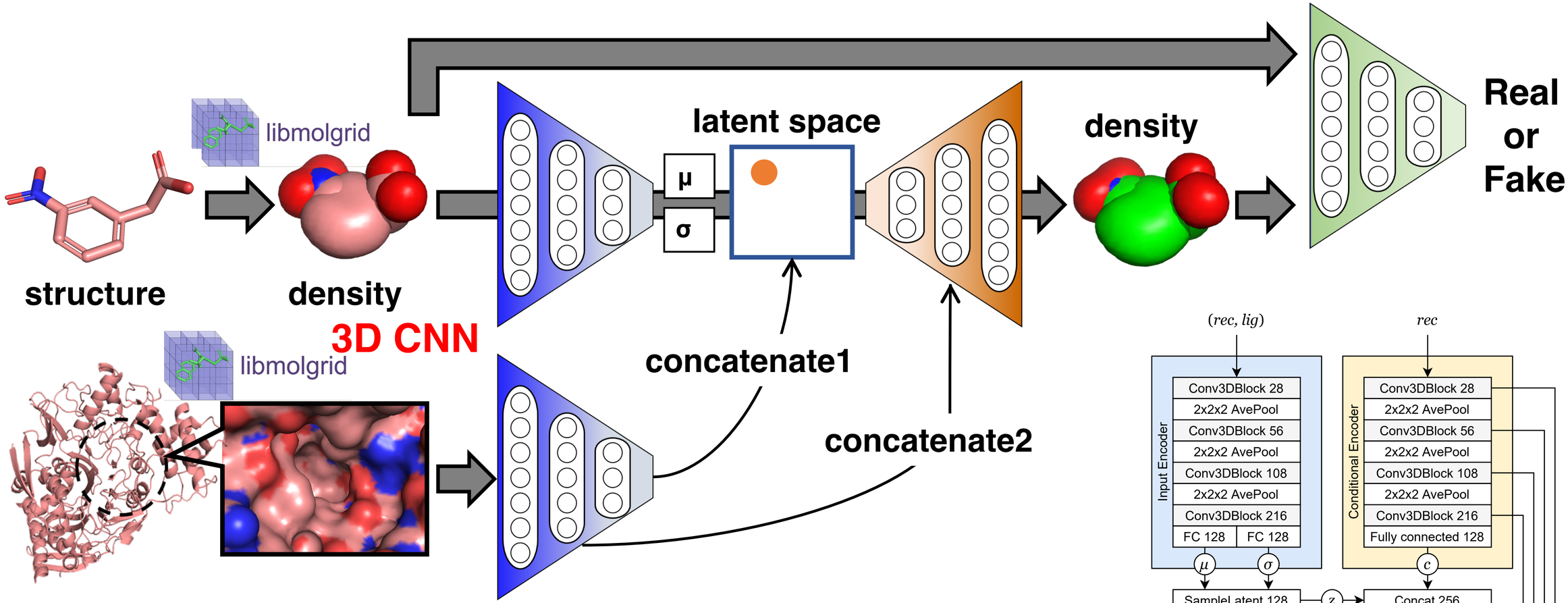


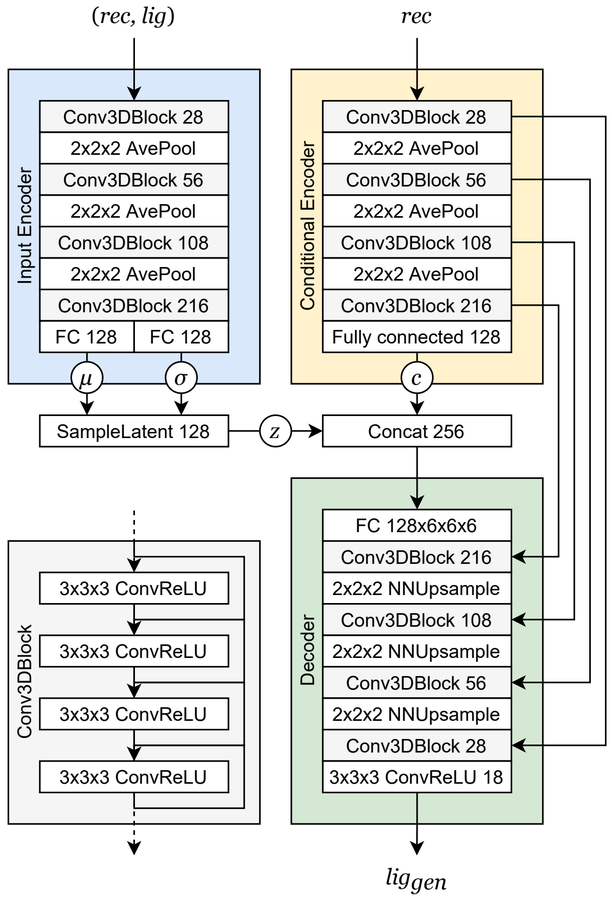
2017



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





Chemical Science

ROYAL SOCIETY OF CHEMISTRY

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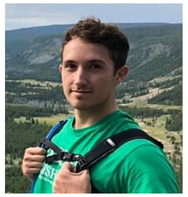
Check for updates

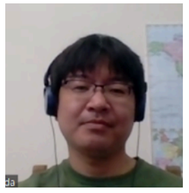
Cite this: *Chem. Sci.*, 2022, **13**, 2701

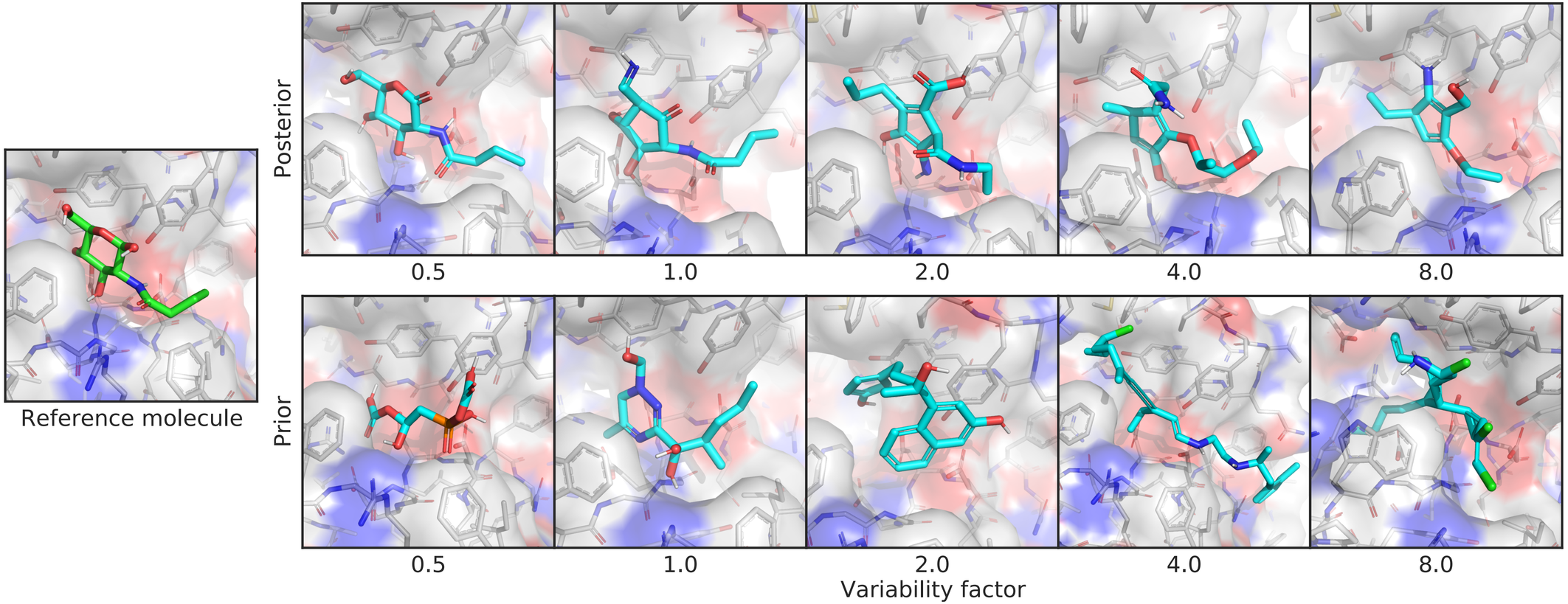
All publication charges for this article have been paid for by the Royal Society

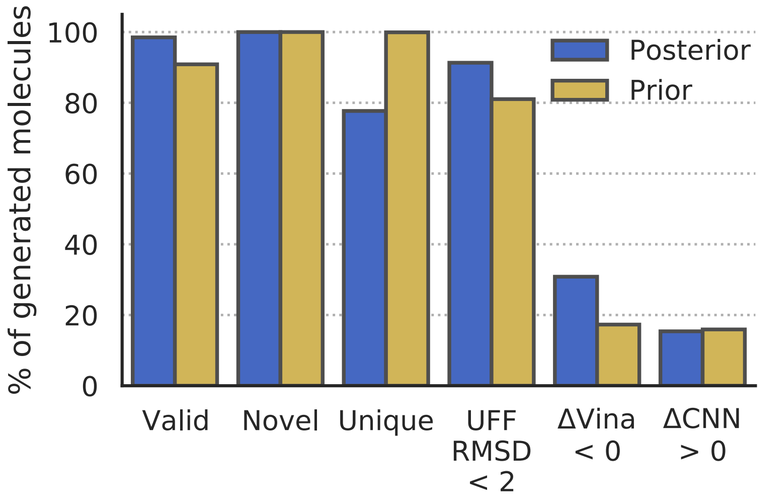
Generating 3D molecules conditional on receptor binding sites with deep generative models†

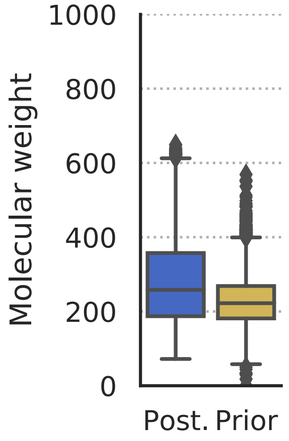
Matthew Ragoza, *[a] Tomohide Masuda[b] and David Ryan Koes[c]

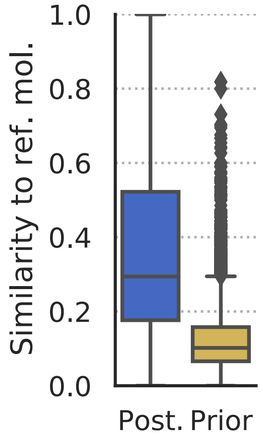


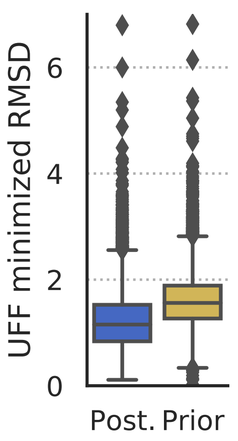


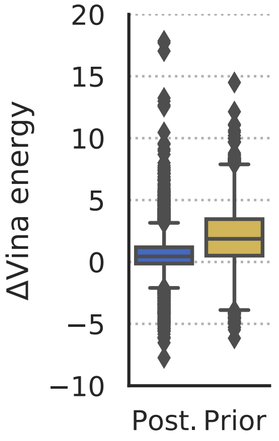

Reference molecule
Posterior
Prior
0.5
1.0
2.0
4.0
8.0
Variability factor

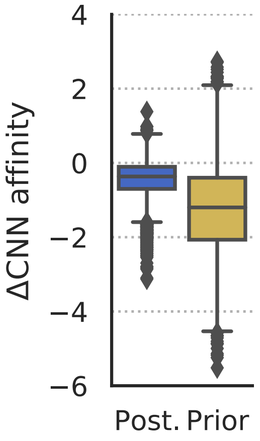

% of generated molecules
Posterior
Prior
Valid
Novel
Unique
UFF RMSD < 2
ΔVina < 0
ΔCNN > 0

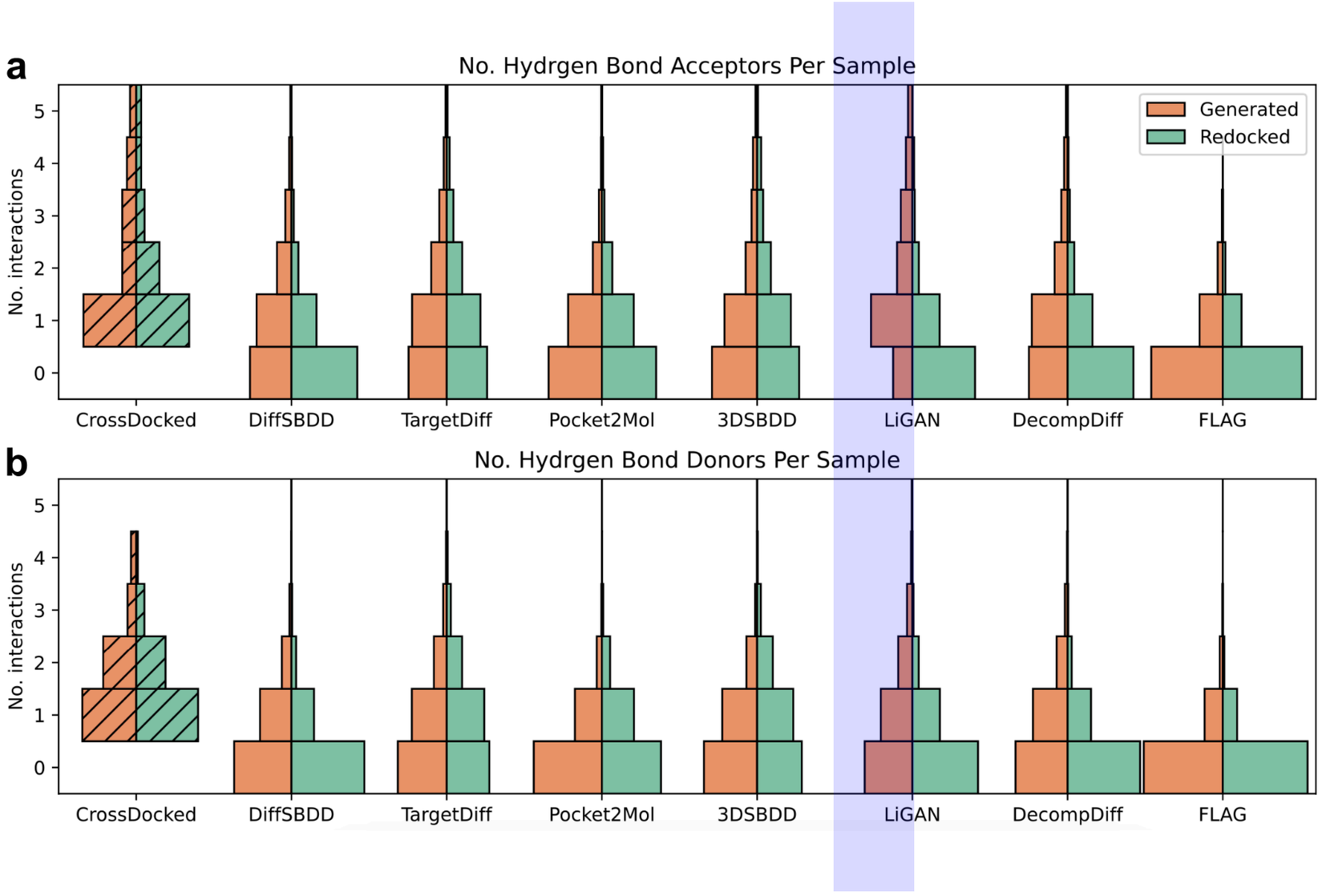

Molecular weight
Post. Prior


Similarity to ref. mol.
Post. Prior


UFF minimized RMSD
Post. Prior


ΔVina energy
Post. Prior


ΔCNN affinity
Post. Prior



PoseCheck: Generative Models for 3D Structure-based Drug Design Produce Unrealistic Poses

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cch57@cam.ac.uk

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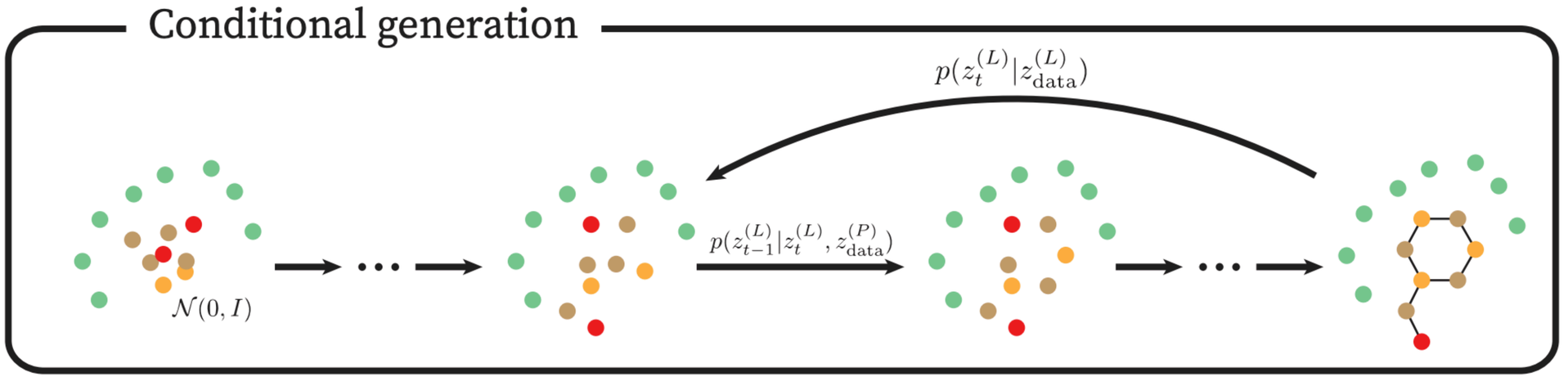
Chaitanya K. Joshi
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Diffusion Models



Structure-based Drug Design with Equivariant Diffusion Models

Arne Schneuing[1]*, Yuanqi Du[2]*, Charles Harris[3], Arian Jamasb[3], Ilia Igashov[1], Weitao Du[4], Tom Blundell[3], Pietro Lió[3], Carla Gomes[2], Max Welling[5], Michael Bronstein[6] & Bruno Correia[1]
[1]École Polytechnique Fédérale de Lausanne, [2]Cornell University, [3]University of Cambridge, [4]USTC, [5]Microsoft Research AI4Science, [6]University of Oxford

arXiv > q-bio > arXiv:2210.01776

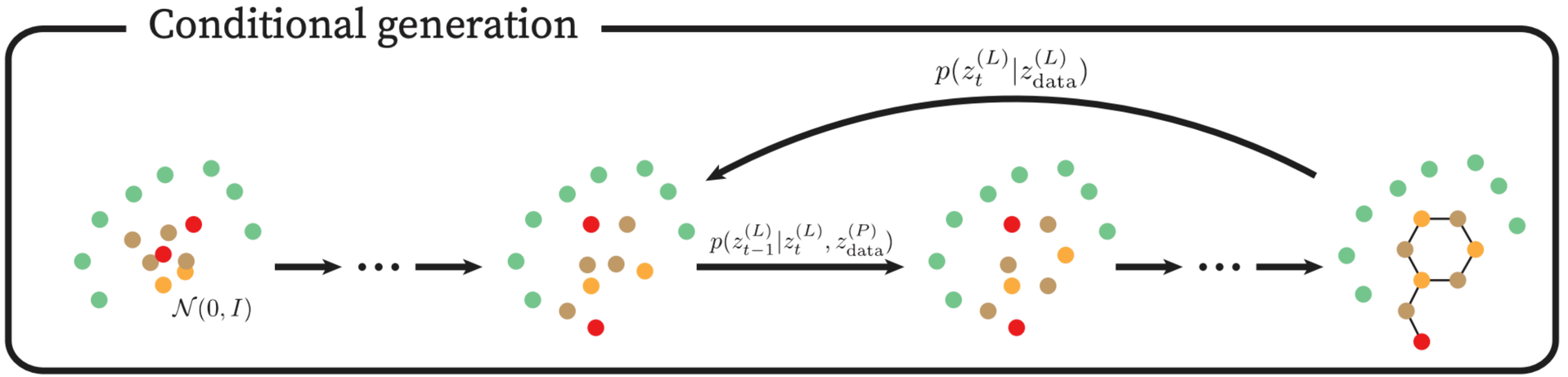
Quantitative Biology > Biomolecules

[Submitted on 4 Oct 2022 (v1), last revised 11 Feb 2023 (this version, v2)]

DiffDock: Diffusion Steps, Twists, and Turns for Molecular Docking

Gabriele Corso, Hannes Stärk, Bowen Jing, Regina Barzilay, Tommi Jaakkola

Diffusion Models



Structure-based Drug Design with Equivariant Diffusion Models

Arne Schneuing[1]*, Yuanqi Du[2]*, Charles Harris[3], Arian Jamasb[3], Ilia Igashov[1], Weitao Du[4], Tom Blundell[3], Pietro Lió[3], Carla Gomes[2], Max Welling[5], Michael Bronstein[6] & Bruno Correia[1]

[1]École Polytechnique Fédérale de Lausanne, [2]Cornell University, [3]University of Cambridge, [4]USTC, [5]Microsoft Research AI4Science, [6]University of Oxford

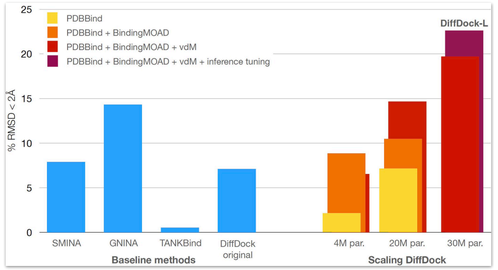
arXiv > q-bio > arXiv:2210.01776

Quantitative Biology > Biomolecules

[Submitted on 4 Oct 2022 (v1), last revised 11 Feb 2023 (this version, v2)]

DiffDock: Diffusion Steps, Twists, and Turns for Molecular Docking

Gabriele Corso, Hannes Stärk, Bowen Jing, Regina Barzilay, Tommi Jaakkola



Keypoint Conditioned Diffusion

Pocket Identification

↓

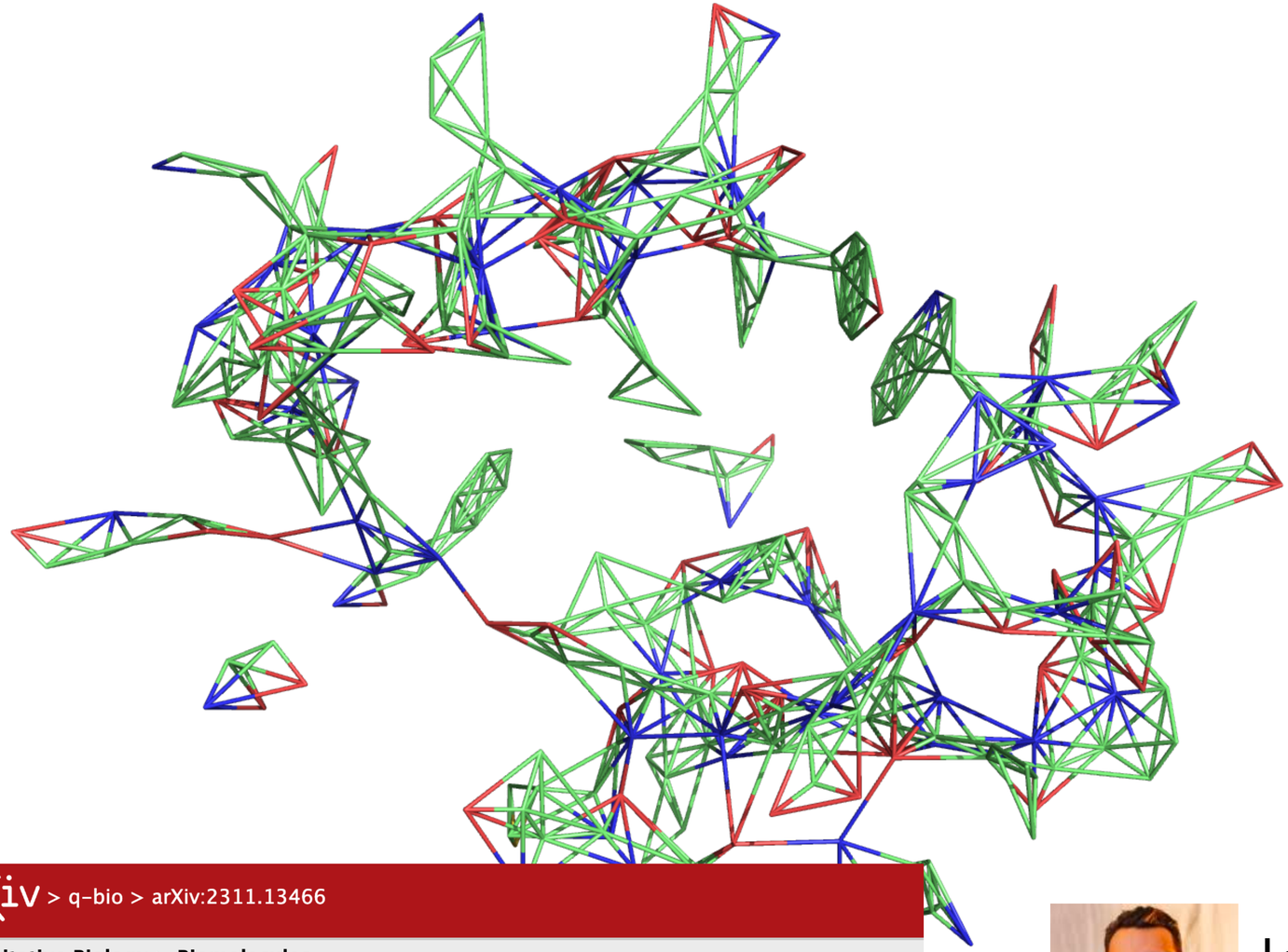
Atomic Message Passing

↓

Keypoint Generation

↓

Keypoint-Conditioned Diffusion



arXiv > q-bio > arXiv:2311.13466

Quantitative Biology > Biomolecules

[Submitted on 22 Nov 2023 (v1), last revised 8 May 2024 (this version, v2)]

Accelerating Inference in Molecular Diffusion Models with Latent Representations of Protein Structure

Ian Dunn, David Ryan Koes



Ian Dunn

Keypoint Conditioned Diffusion

Pocket Identification

↓

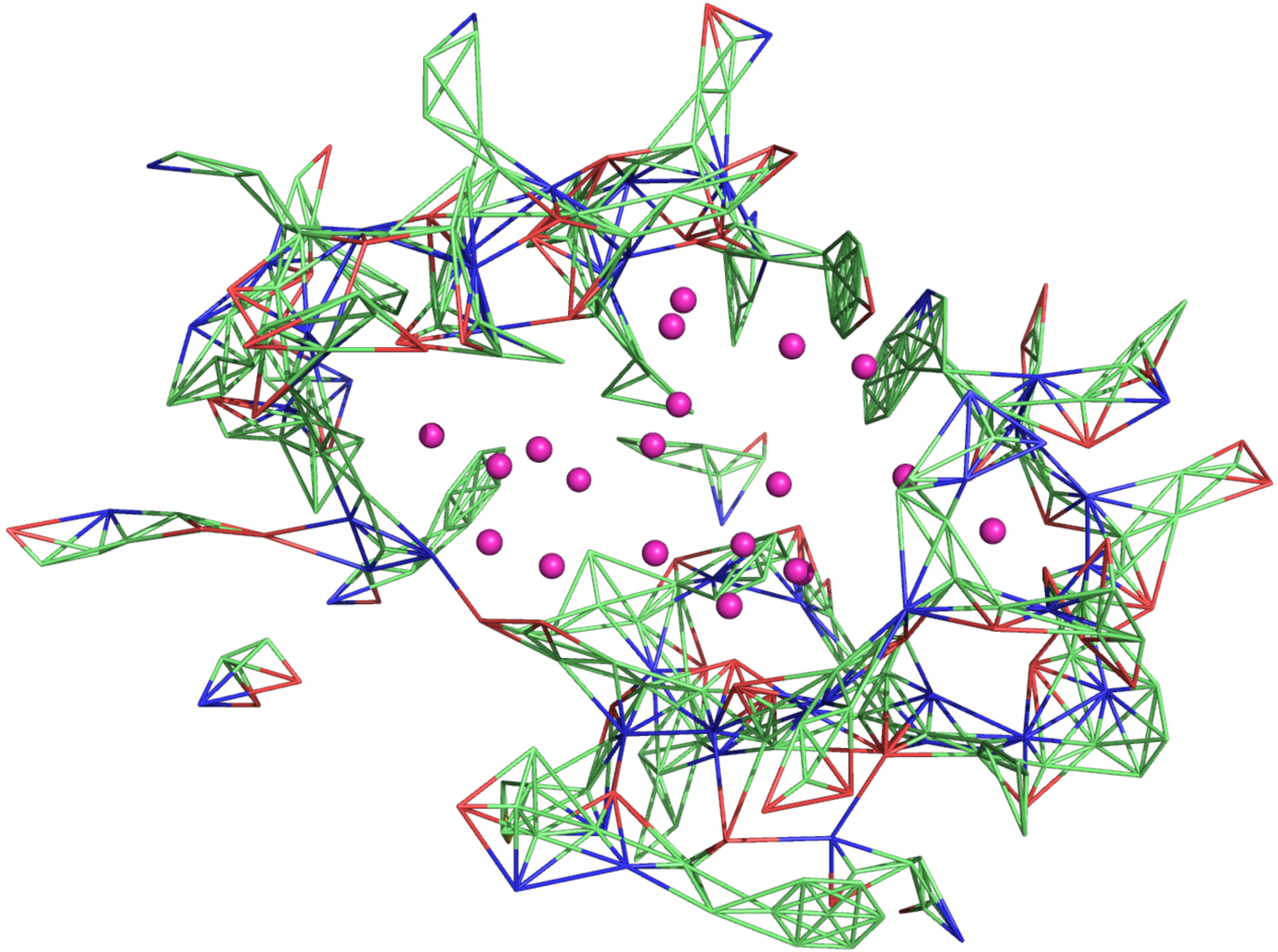
Atomic Message Passing

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Keypoint Generation

↓

Keypoint-Conditioned Diffusion



Keypoint Conditioned Diffusion

Pocket Identification

↓

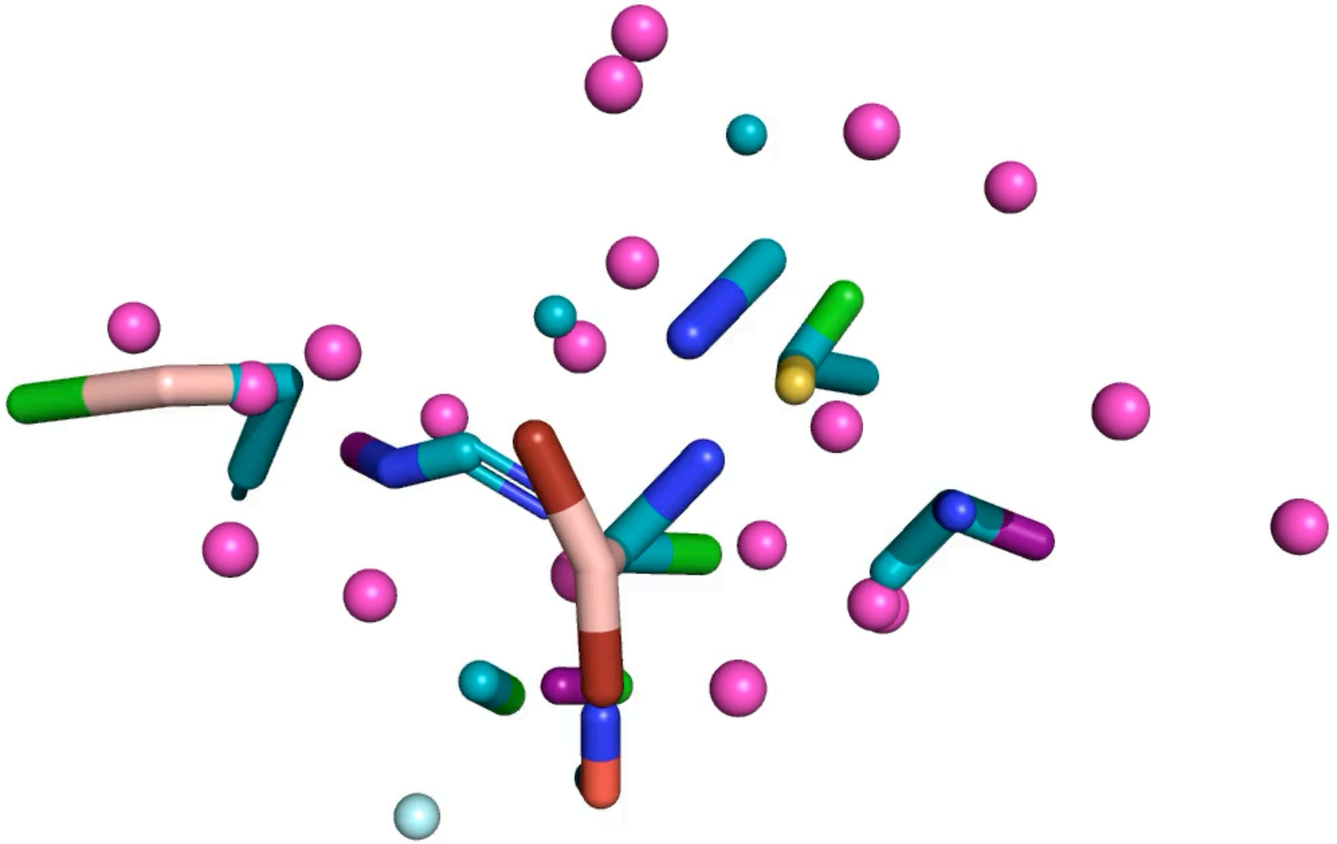
Atomic Message Passing

↓

Keypoint Generation

↓

Keypoint-Conditioned Diffusion



Keypoint Conditioned Diffusion

Pocket Identification

↓

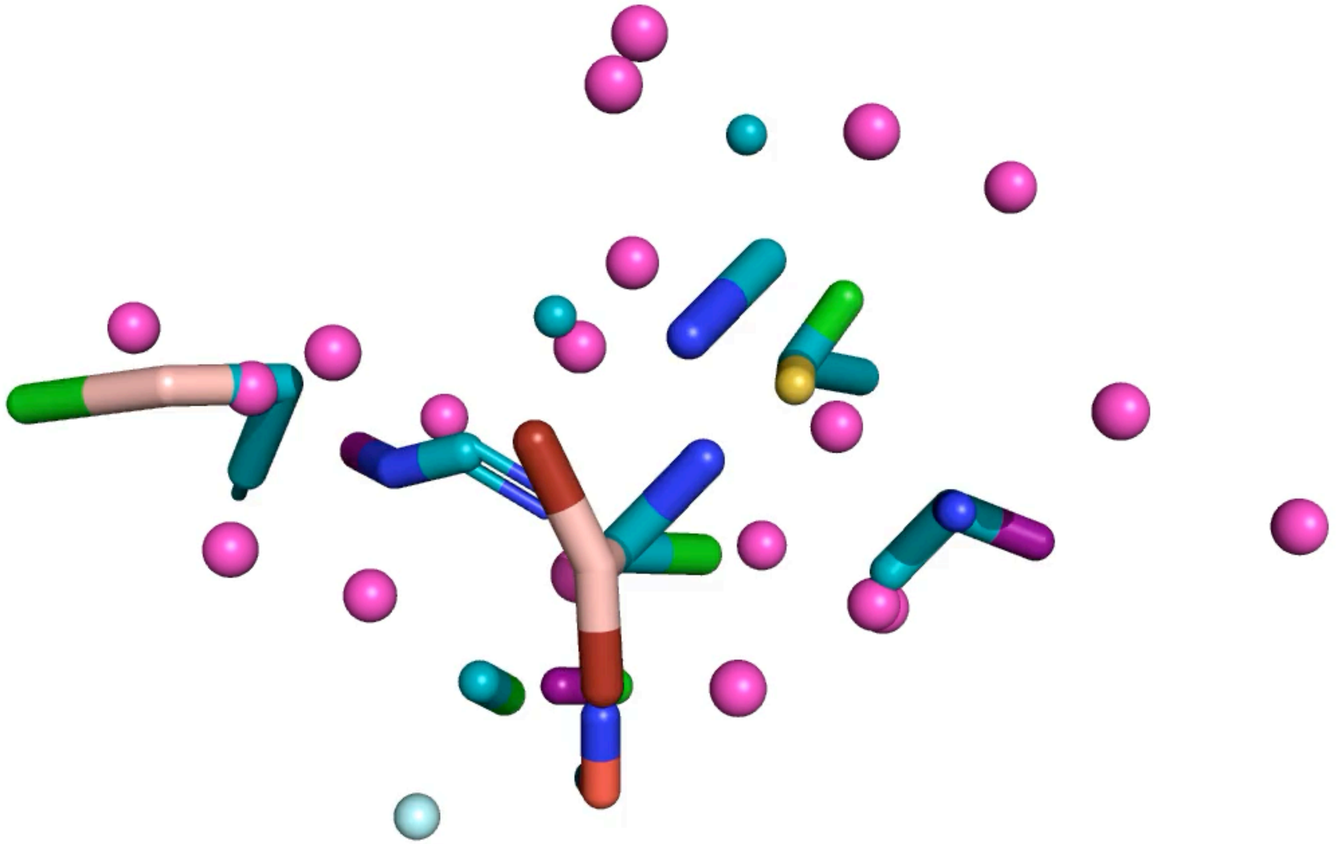
Atomic Message Passing

↓

Keypoint Generation

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Keypoint-Conditioned Diffusion



Keypoint Conditioned Diffusion

Pocket Identification

↓

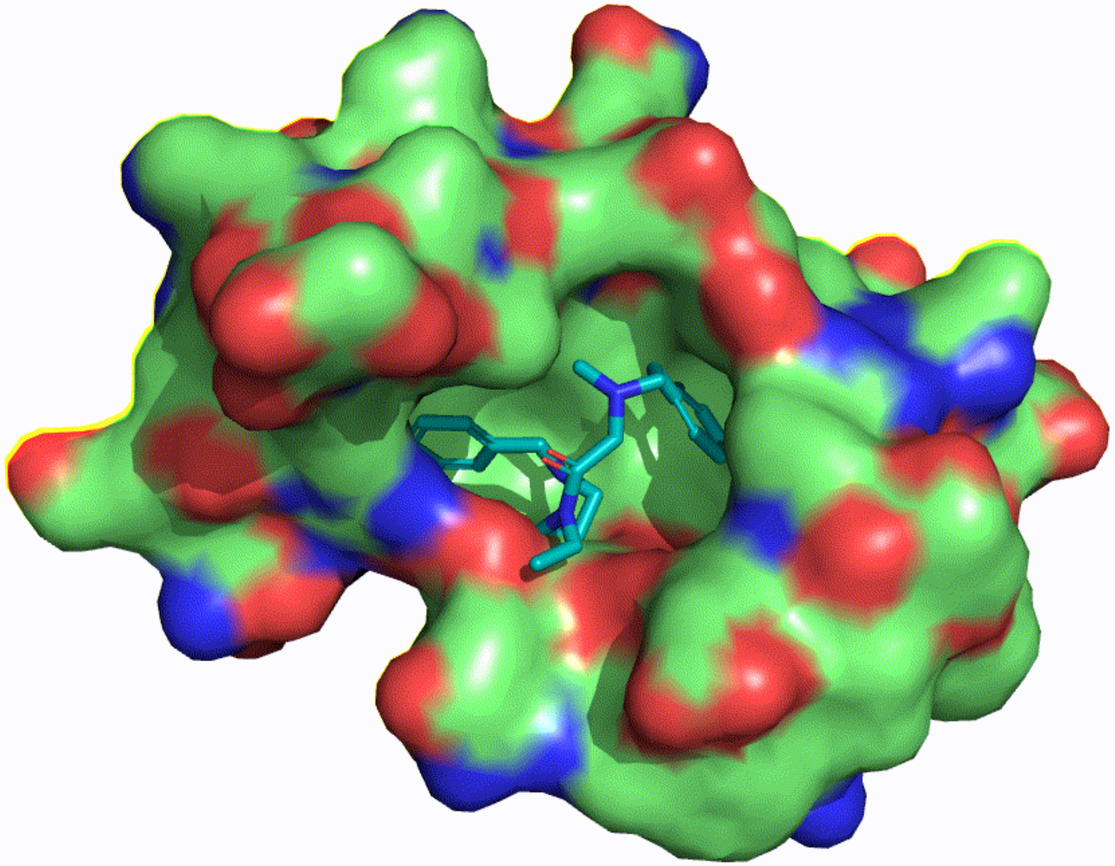
Atomic Message Passing

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Keypoint Generation

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Keypoint-Conditioned Diffusion



Keypoint Conditioned Diffusion

Pocket Identification

↓

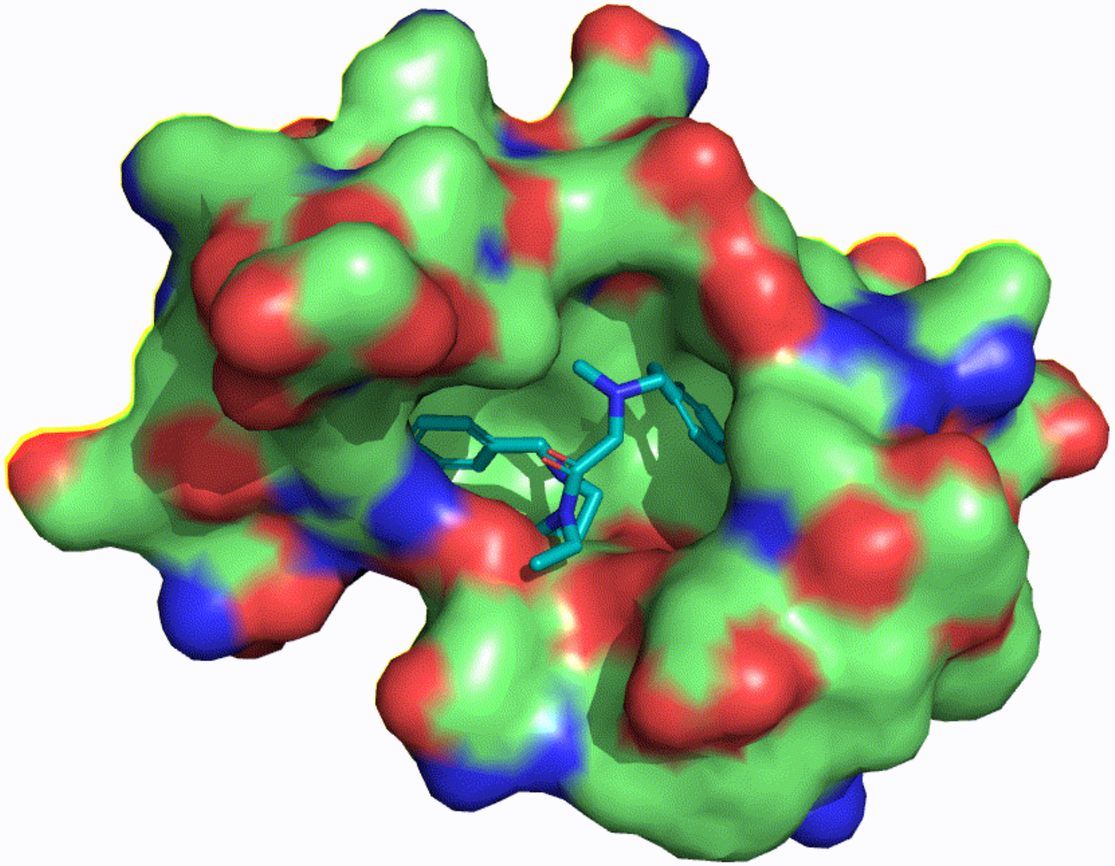
Atomic Message Passing

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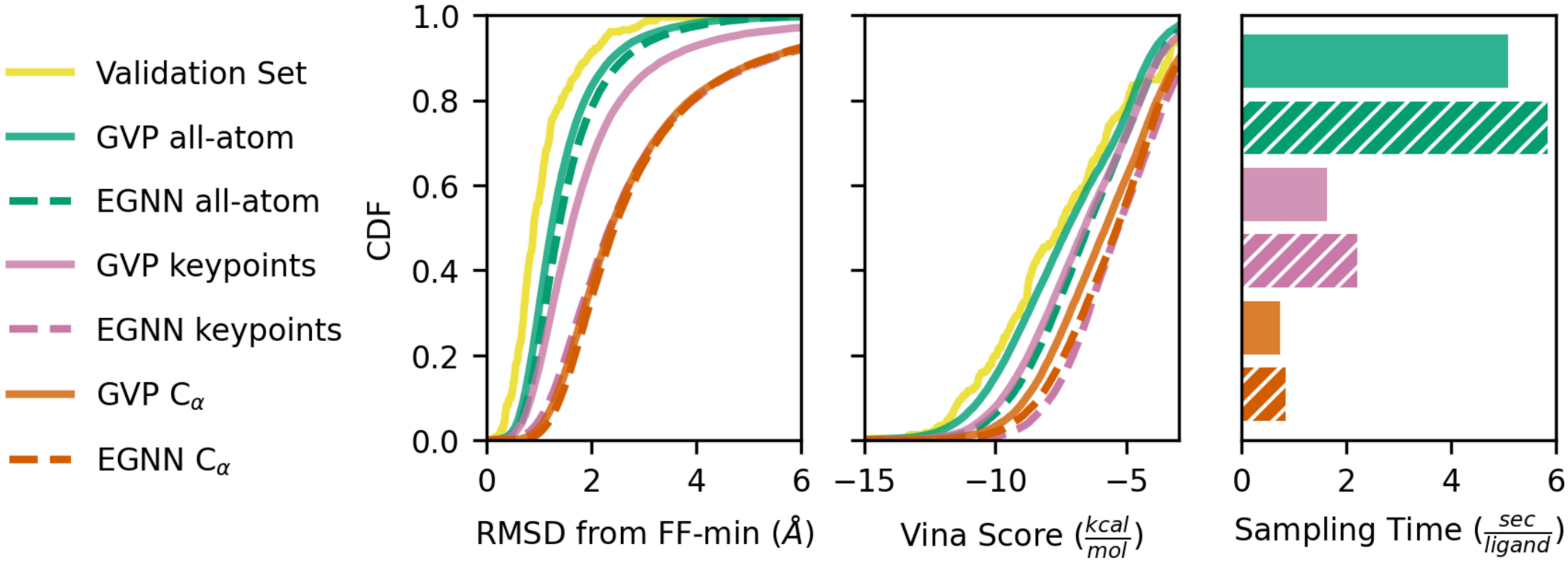
Keypoint Generation

↓

Keypoint-Conditioned Diffusion

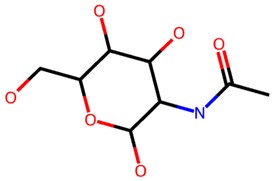


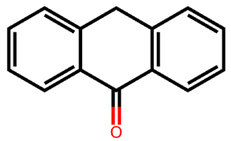
Keypoint Conditioned Diffusion

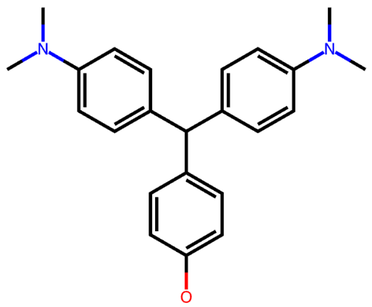


Generated molecules are not synthetically accessible or physically plausible

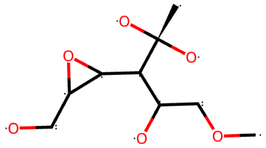
Reference Molecules

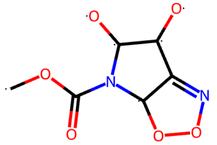


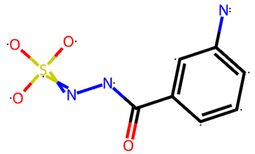


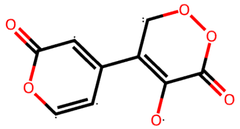


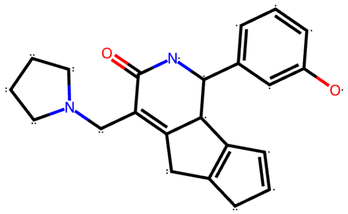
Generated Molecules

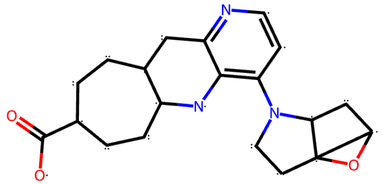






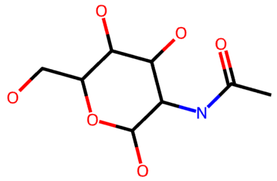


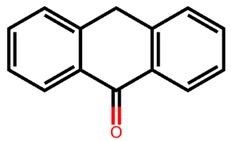


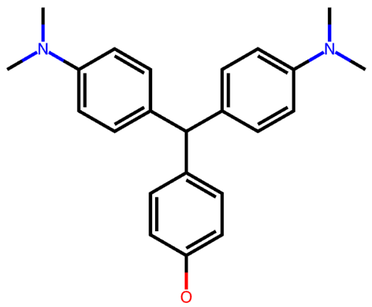


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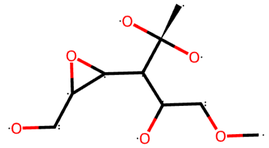
Reference Molecules

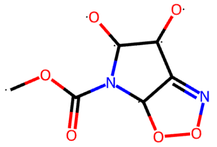




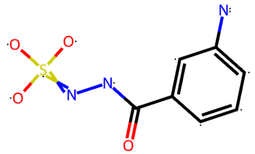


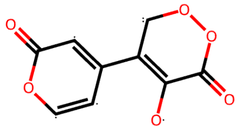
Generated Molecules

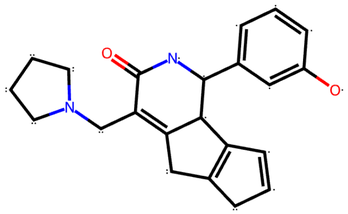


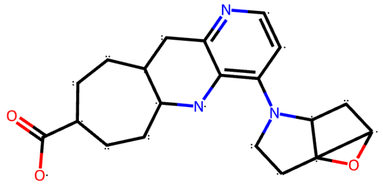


"epoxide, good luck with stability"



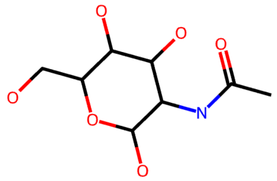


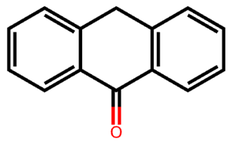


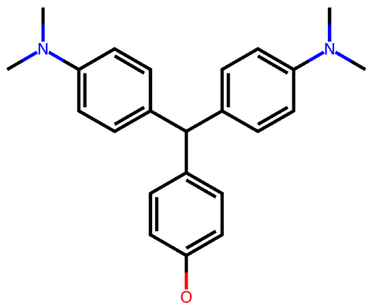


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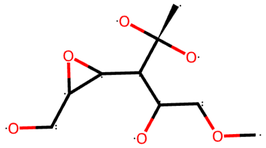
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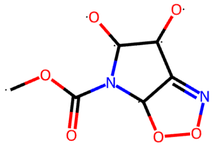




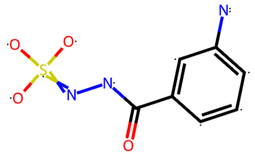


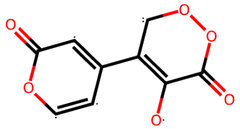
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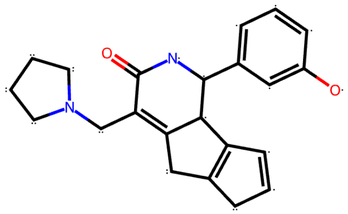


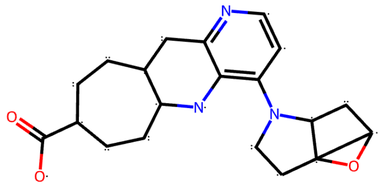


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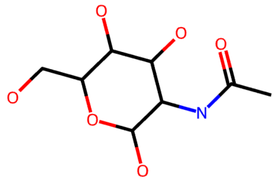


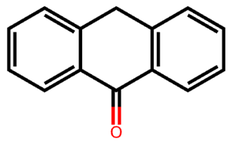


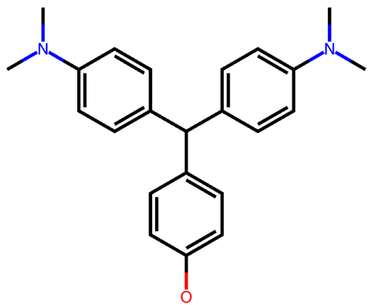
"certainly unstable"

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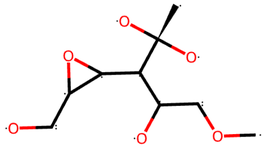
Reference Molecules

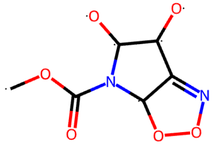




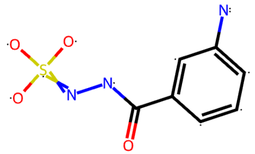


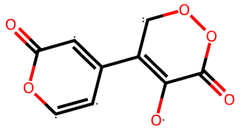
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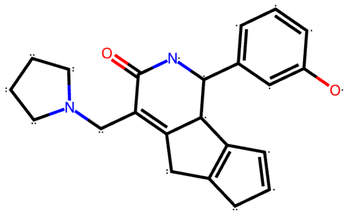


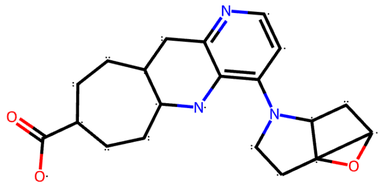
"epoxide, good luck with stability"





"no"

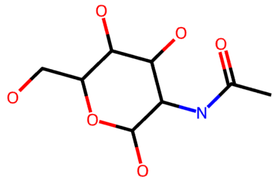


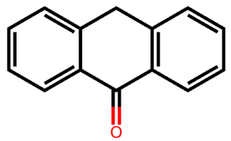


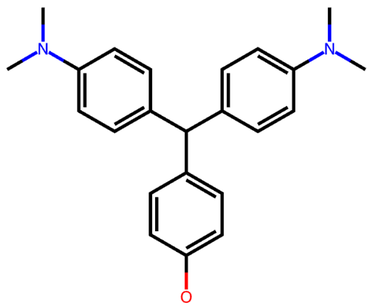
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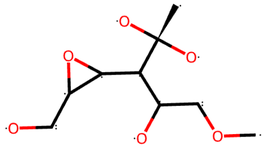
Reference Molecules



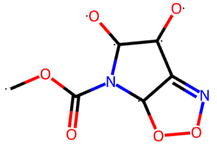




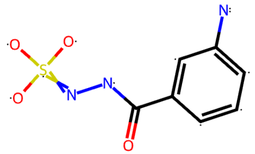
Generated Molecules



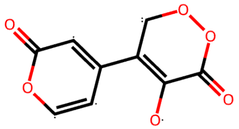
"epoxide, good luck with stability"

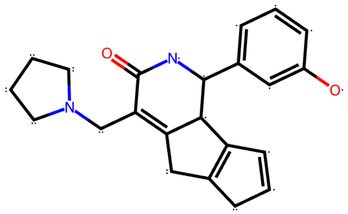


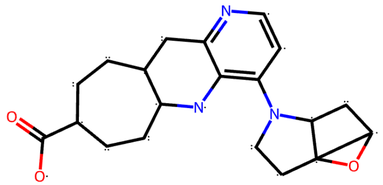
"f*** no"



"no"







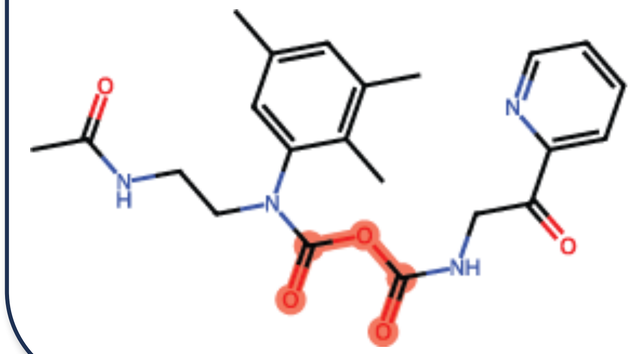
"certainly unstable"

Practical Measures of Molecule Quality

Existing literature primarily focuses on validity/valency; necessary but insufficient dimensions of molecule quality

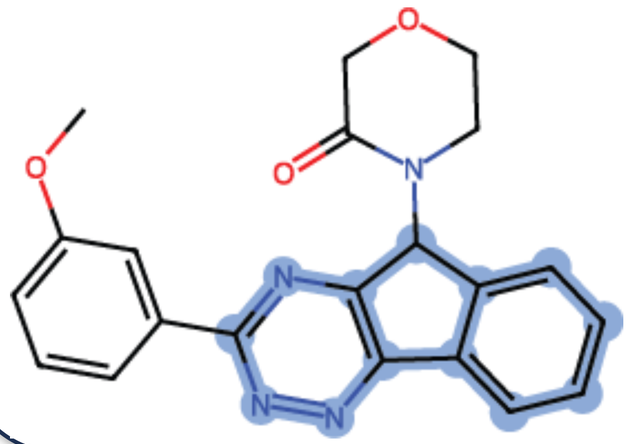
We propose to evaluate molecule quality at the level of **functional groups** and **ring systems**

Structural Alerts



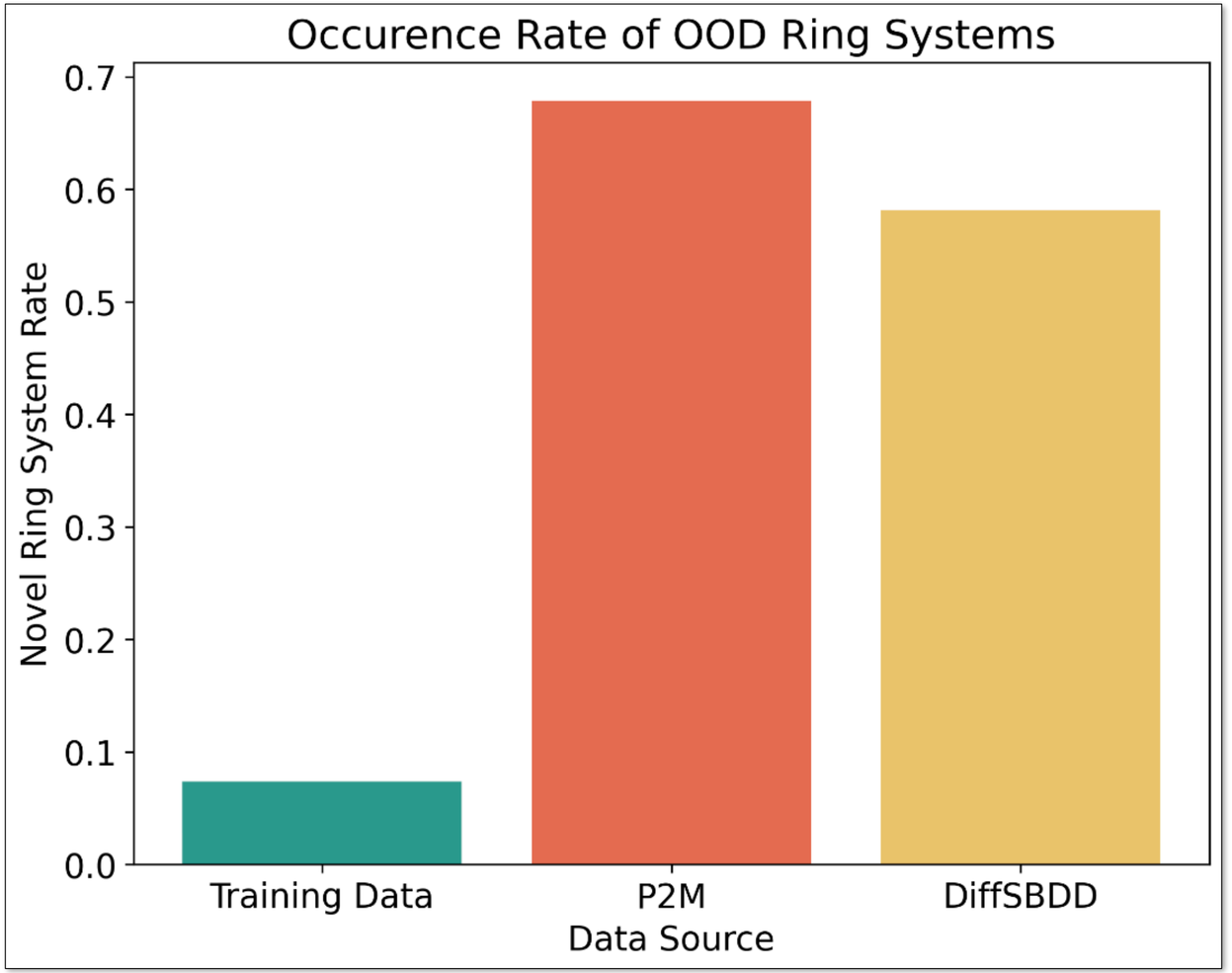
Functional groups typically used to filter libraries in virtual screening workflows

OOD Rings

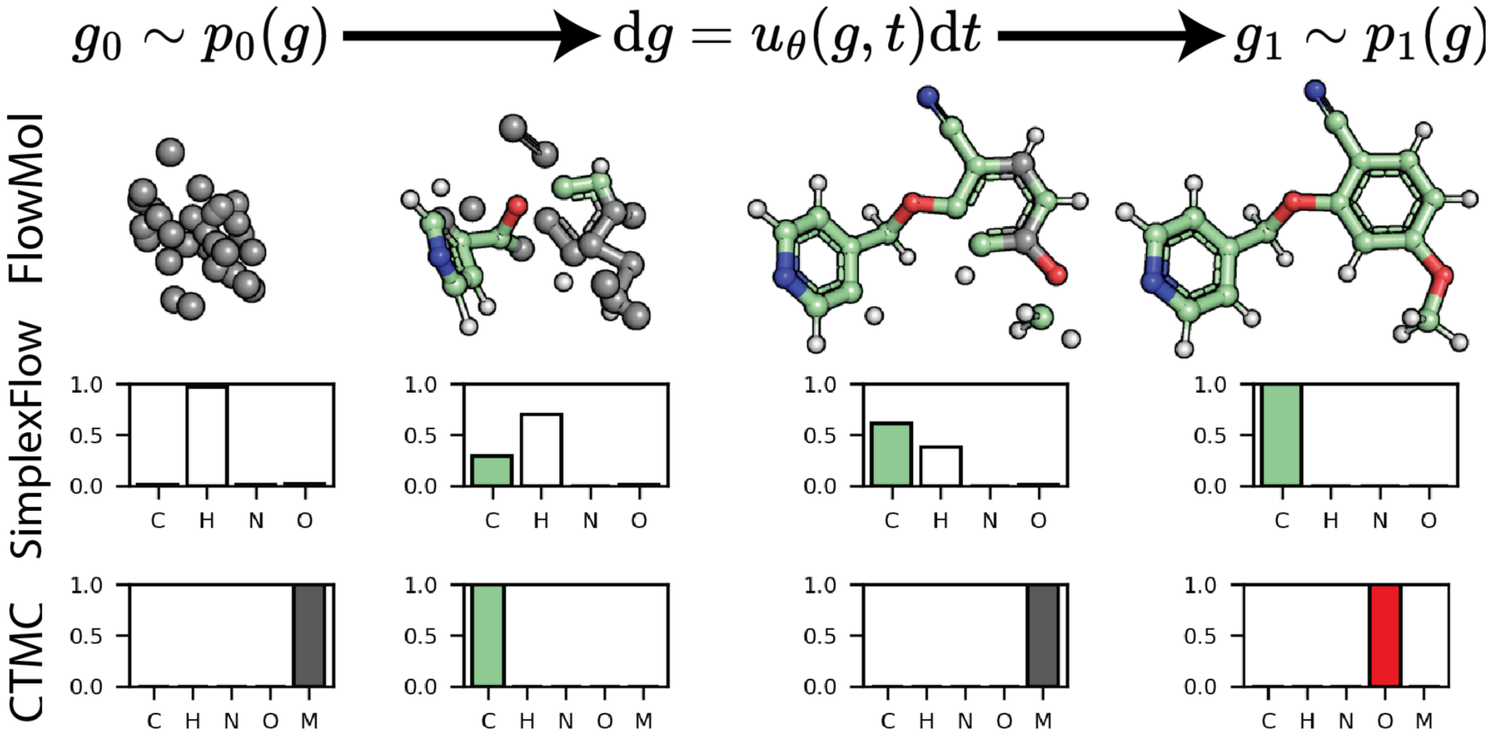


Ring systems that never appear in ChEMBL

Practical Measures of Molecule Quality



Unconditional Generation with FlowMol



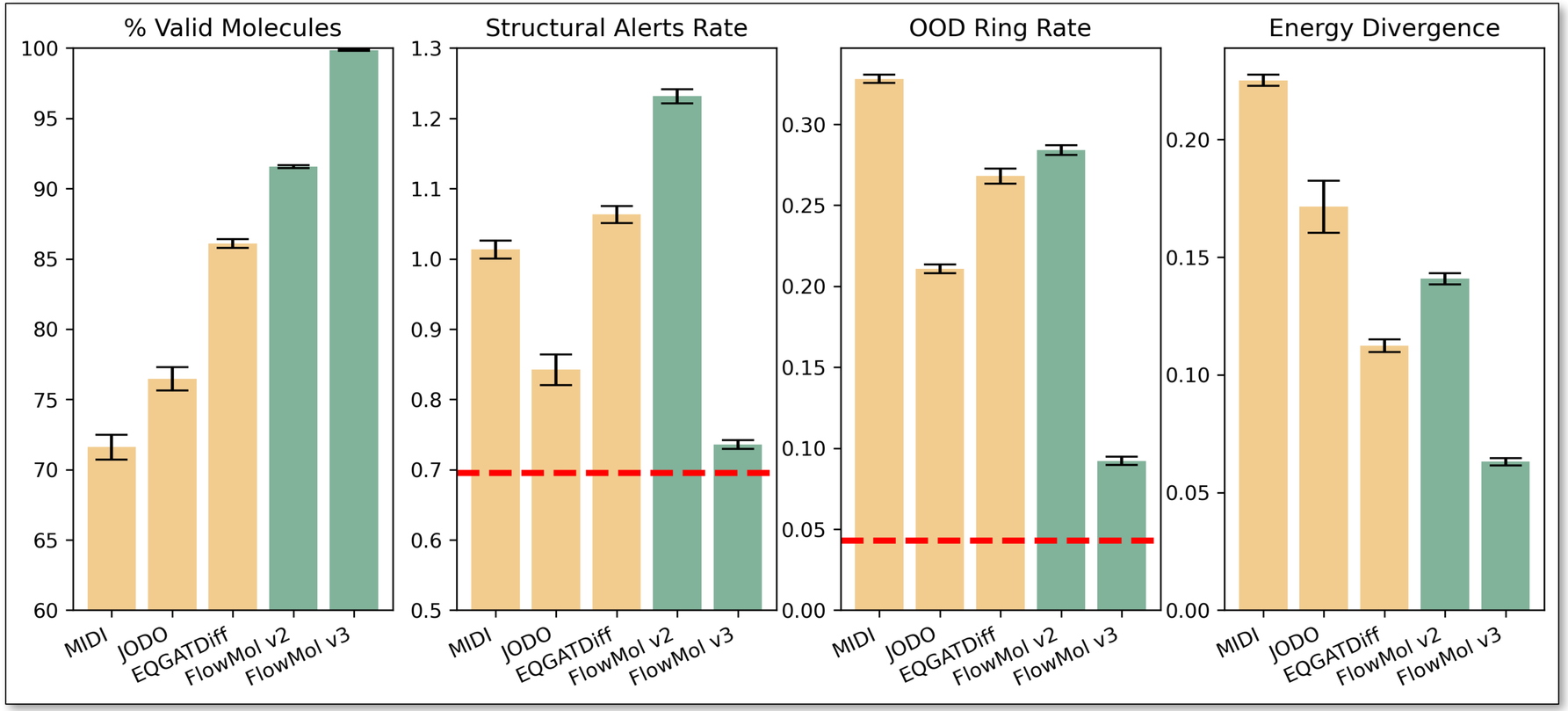
Exploring Discrete Flow Matching for 3D De Novo Molecule Generation

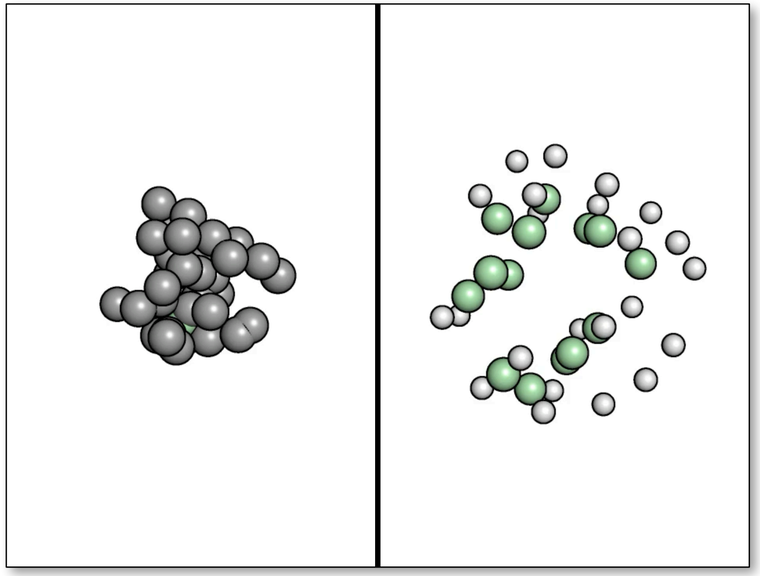


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FlowMol v3





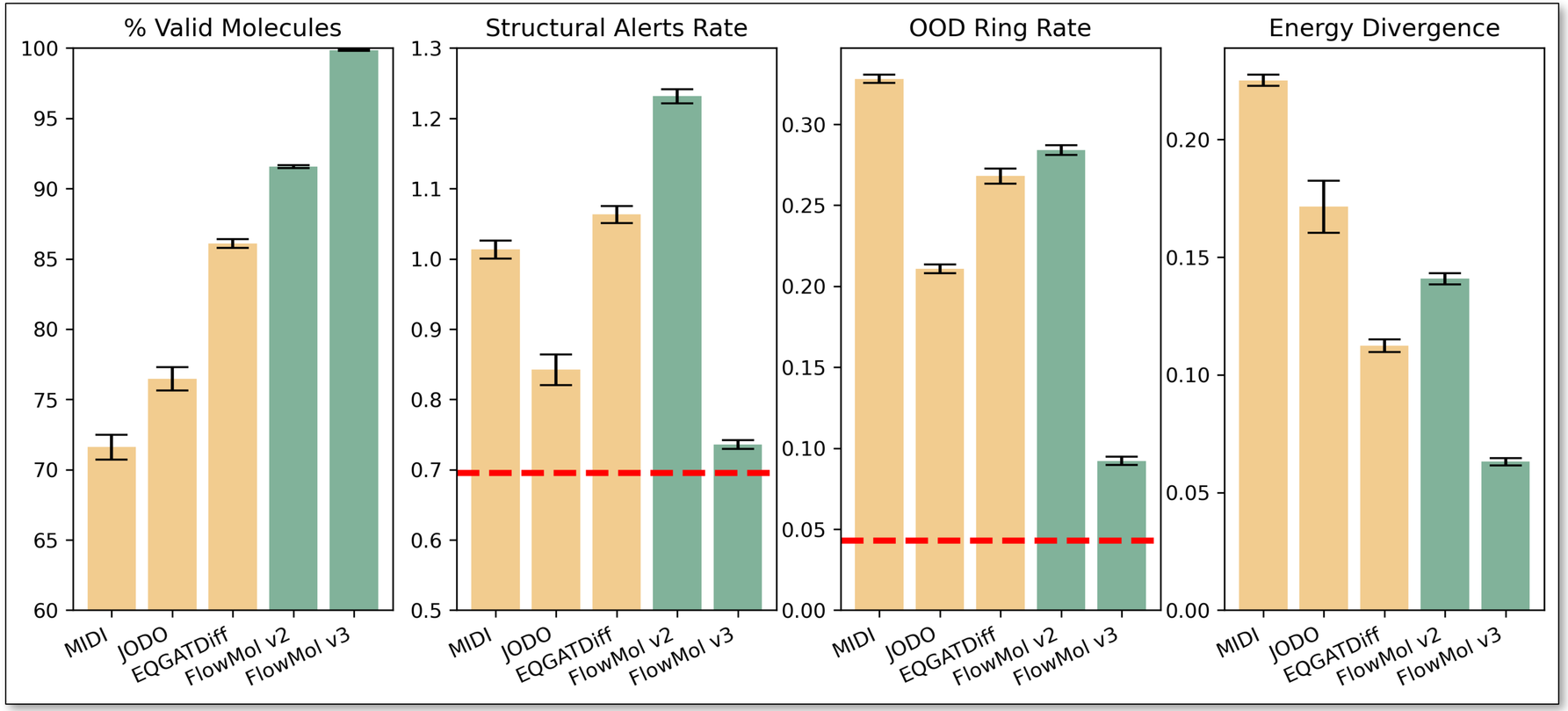
FlowMol Public

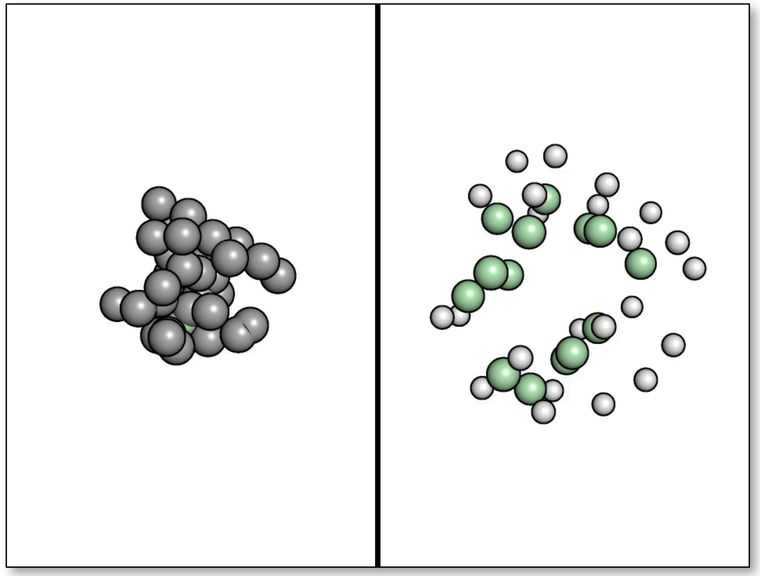
Mixed continous/categorical flow-matching model for de novo molecule generation.

Python ☆ 105 5

- State of the art validity
- Improves chemical plausibility and synthetic accessibility

FlowMol v3





FlowMol Public

Mixed continous/categorical flow-matching model for de novo molecule generation.

Python ☆ 105 5

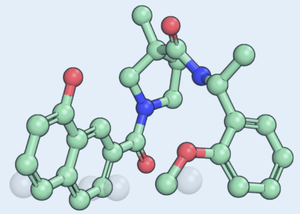
- State of the art validity
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OMTRA

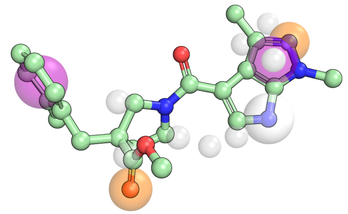
FlowMol3

De novo Generation

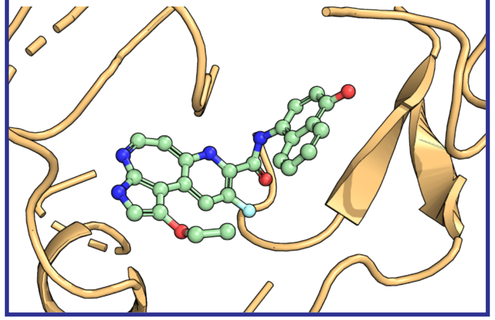
Unconditional



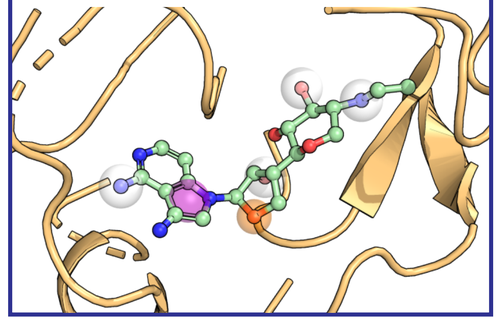
Pharmacophore Conditioned



Pocket Conditioned

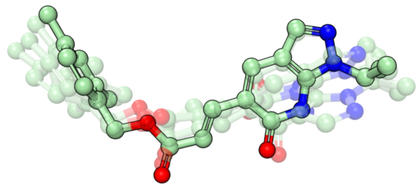


Pocket & Pharm. Conditioned

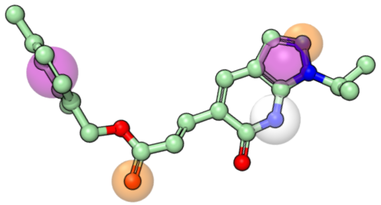


Conformer Generation

Unconditional

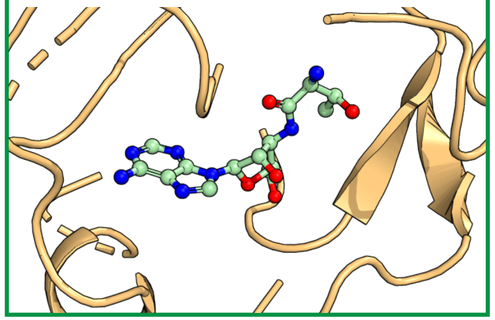


Pharmacophore Conditioned

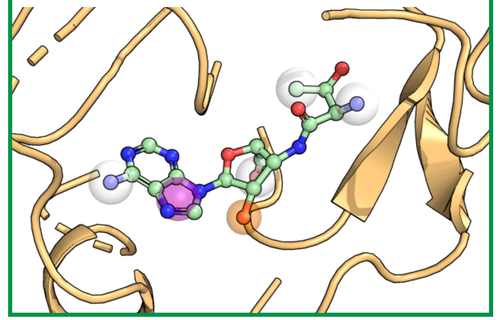


Docking

Pocket Conditioned



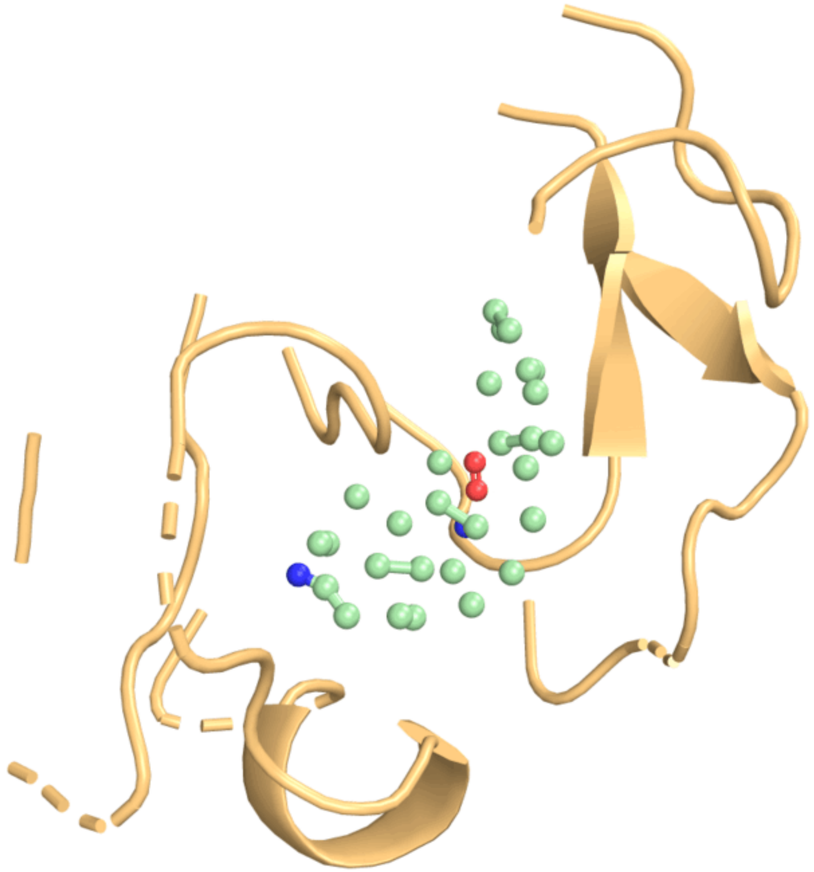
Pocket & Pharm. Conditioned



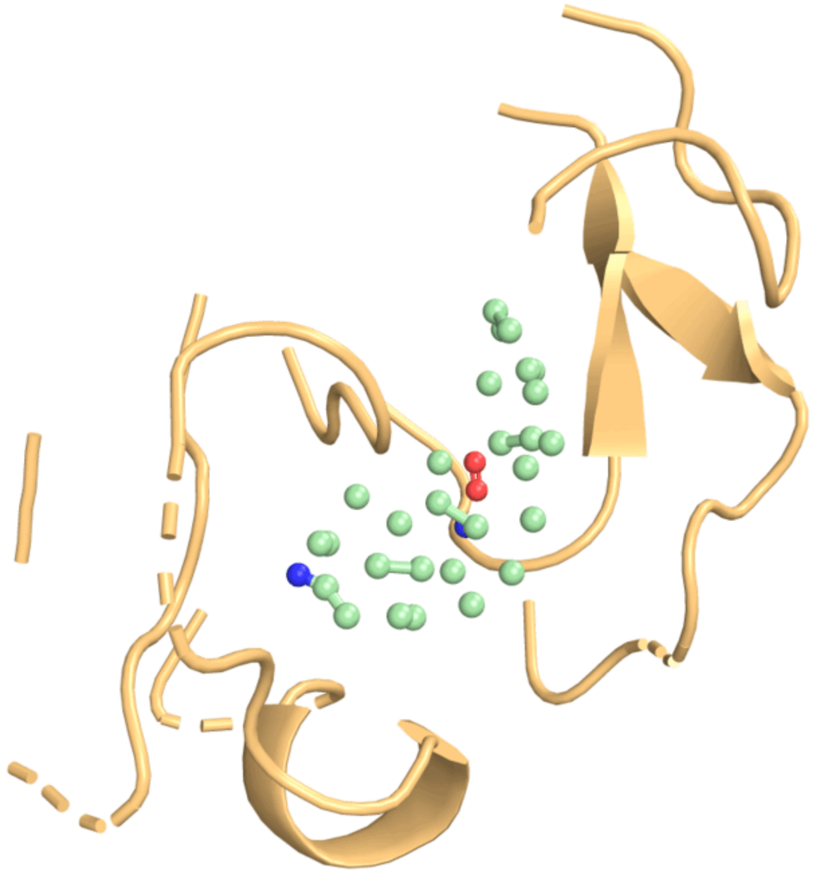
Ian Dunn Tyler Katz Liv Toft Riya Shah Juhi Gupta Ramith Hettiarachchi



OMTRA: De Novo Design

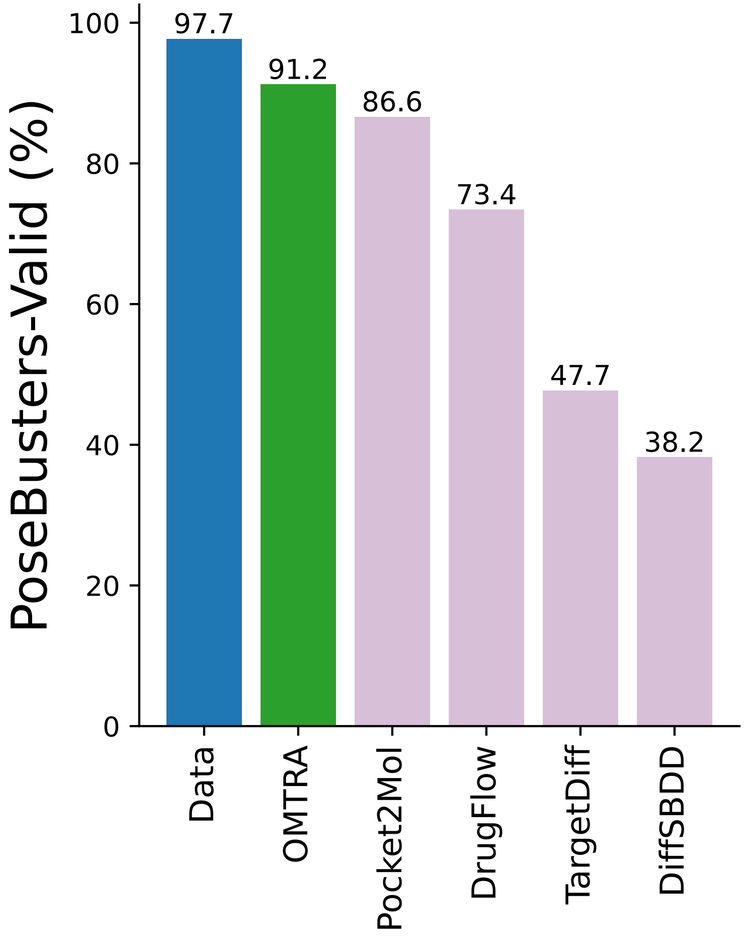


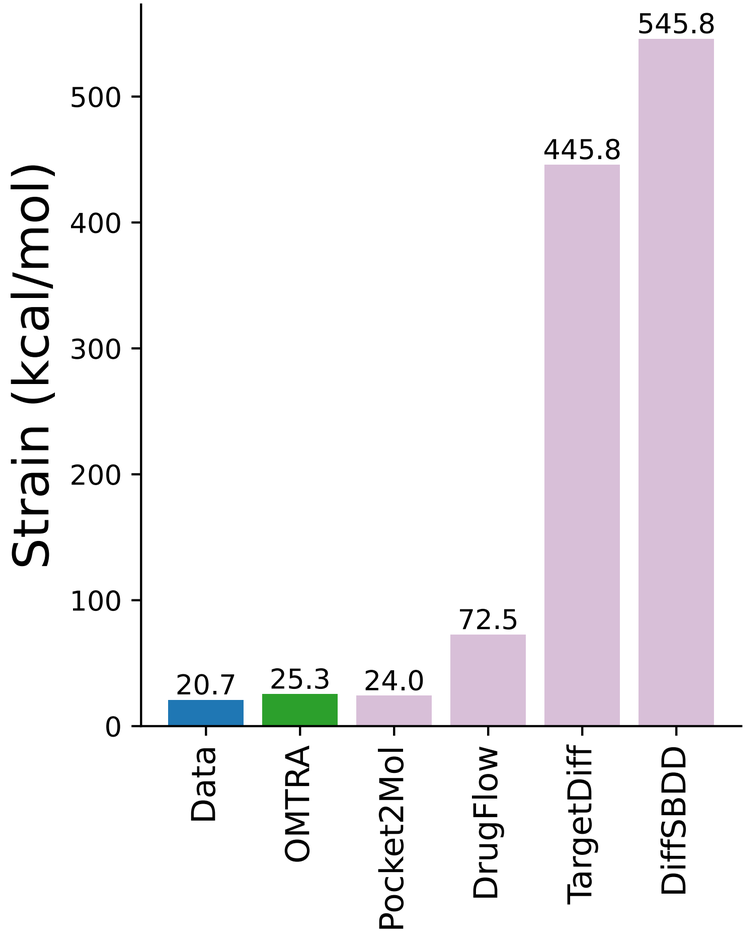
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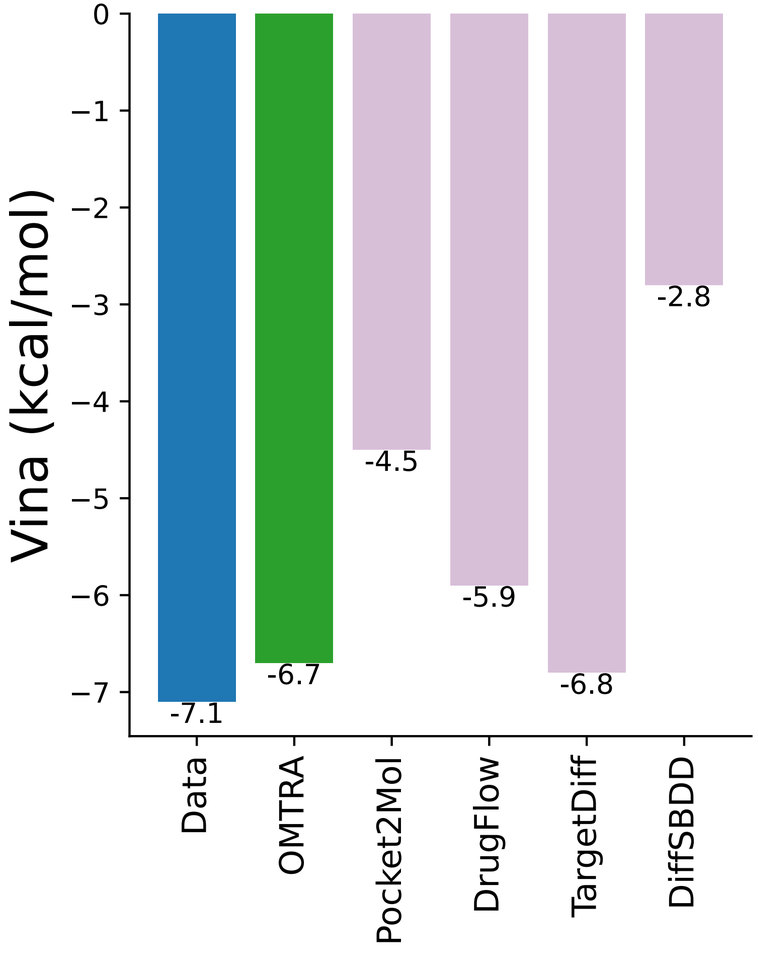


OMTRA: De Novo Design

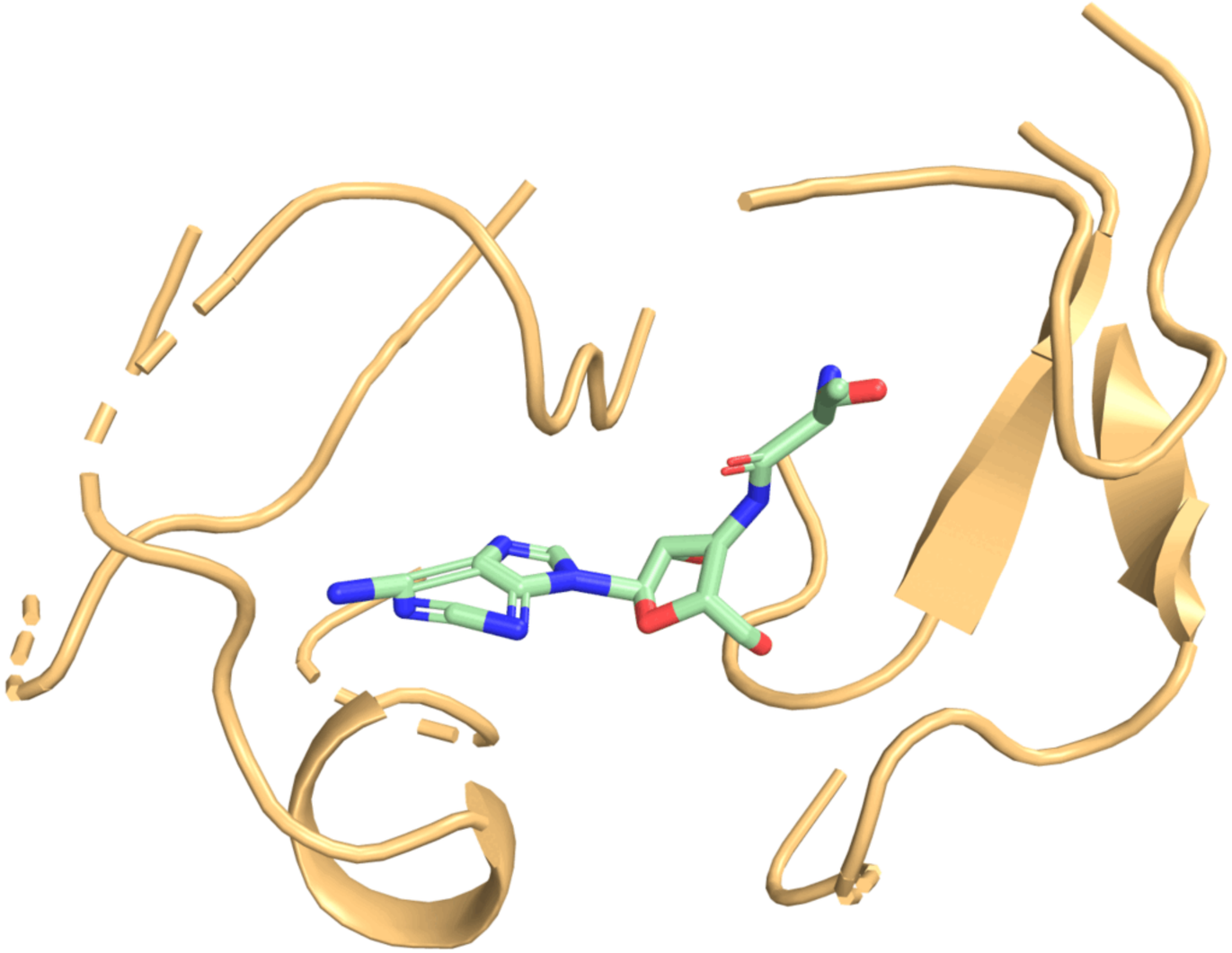
Evaluated on Luo et al CrossDocked test set.



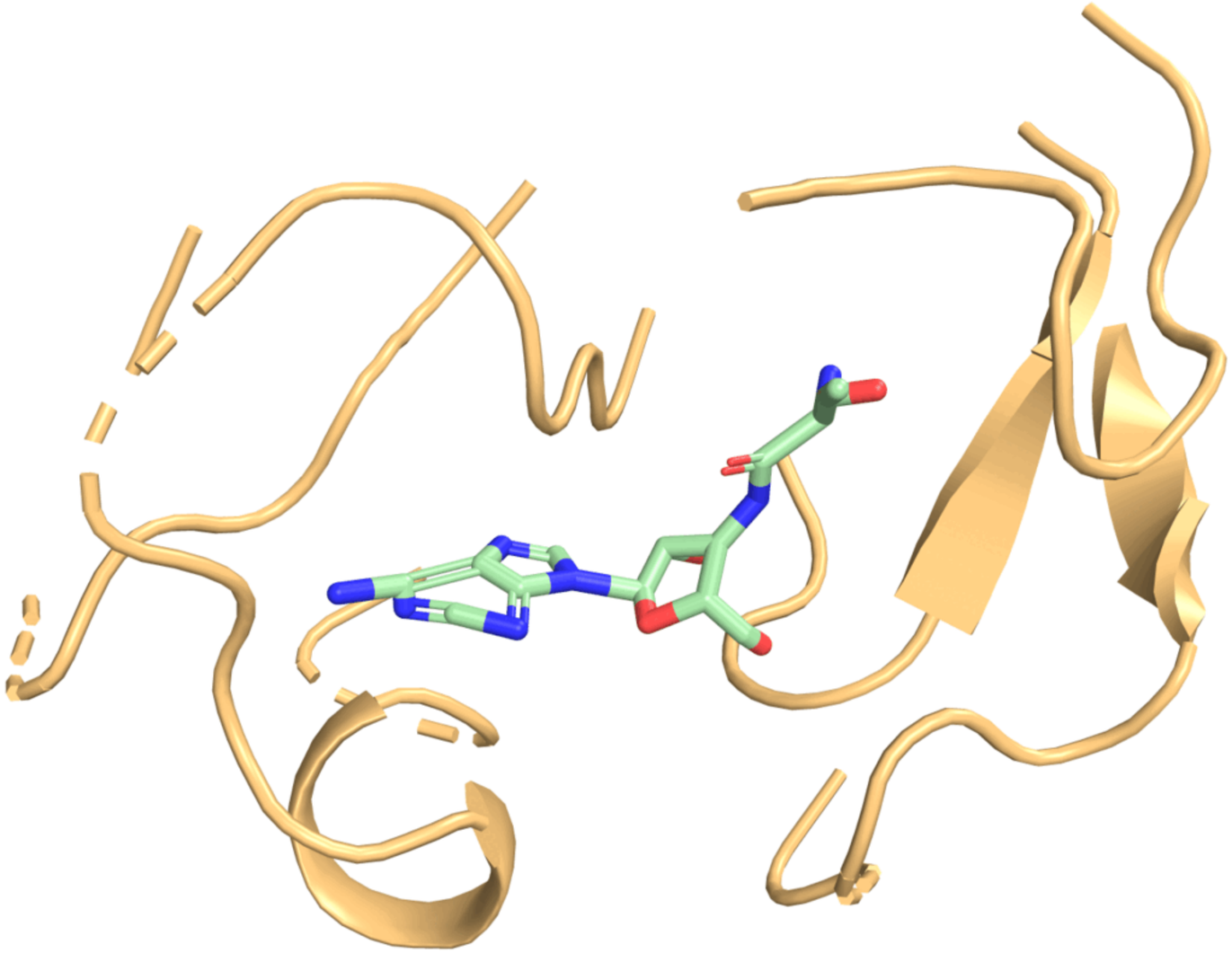




OMTRA: Docking

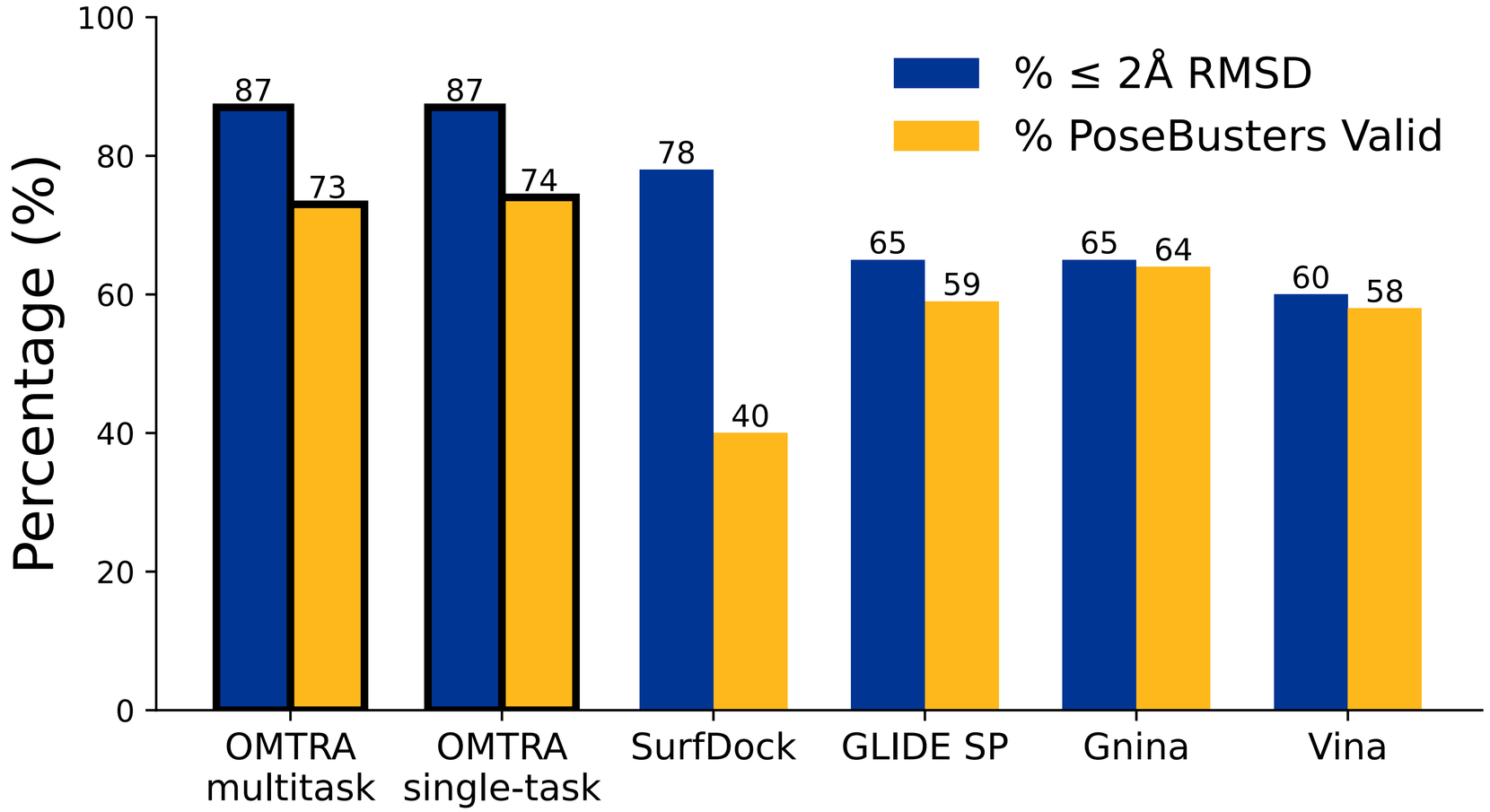


OMTRA: Docking



OMTRA: Docking

Evaluated on PoseBusters test set.

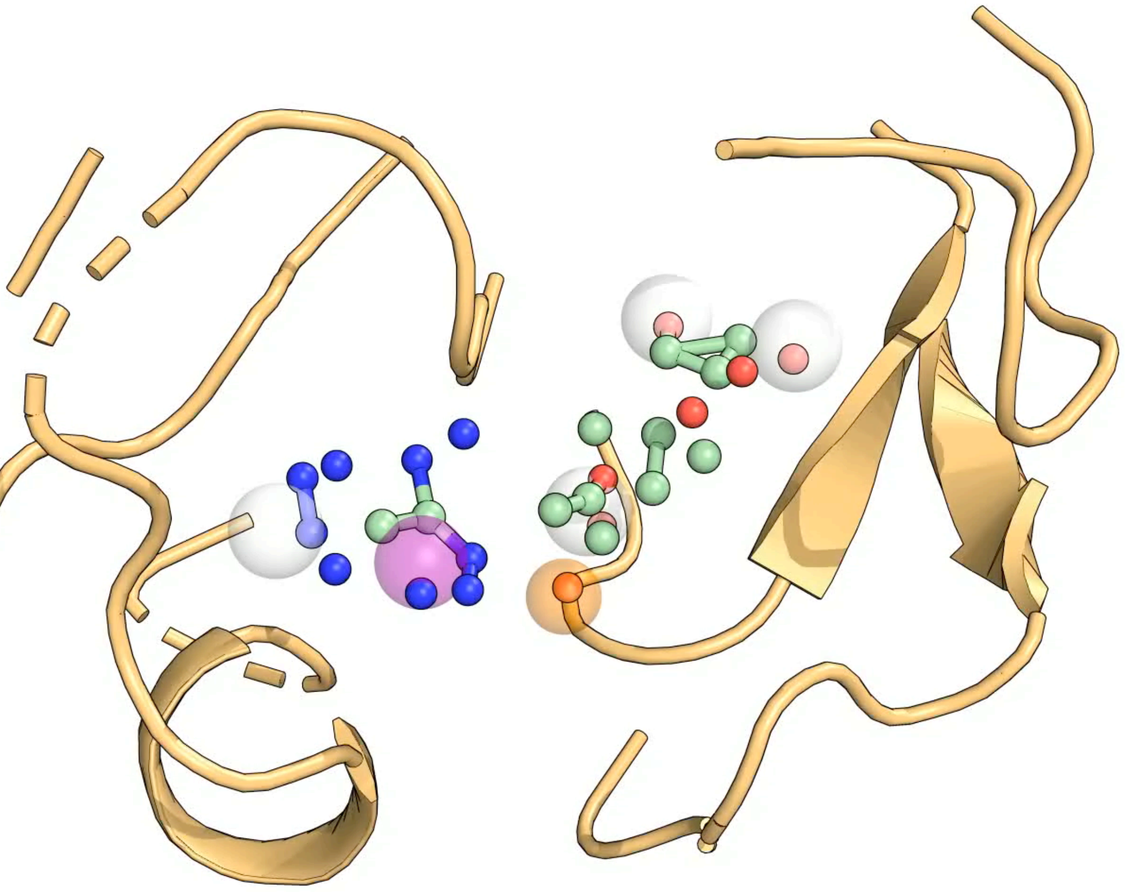


OMTRA: Transfer Learning?

Evaluated on PLINDER test set.

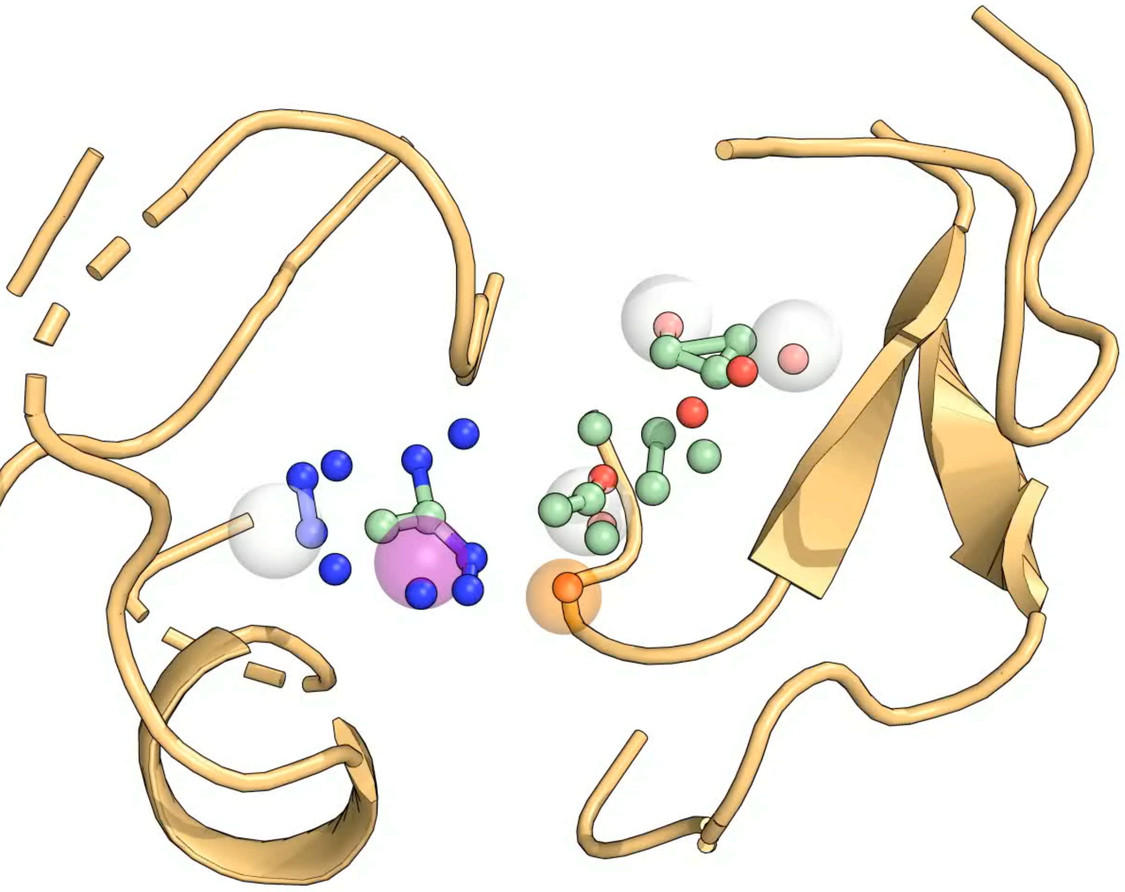
Multitask	Pretrained	*De Novo* Design			Docking	
		% Valid	%PB-Valid	strain	% $\leq$ 2Å	%PB-Valid
Data				94.0	39.2	
✗	✗	98.4	71.2	96.2	92.0	75.0
✗	✓	96.6	67.4	125.6	91.0	73.0
✓	✓	97.6	69.7	69.6	95.0	75.0

OMTRA: Pharmacophore Conditioning



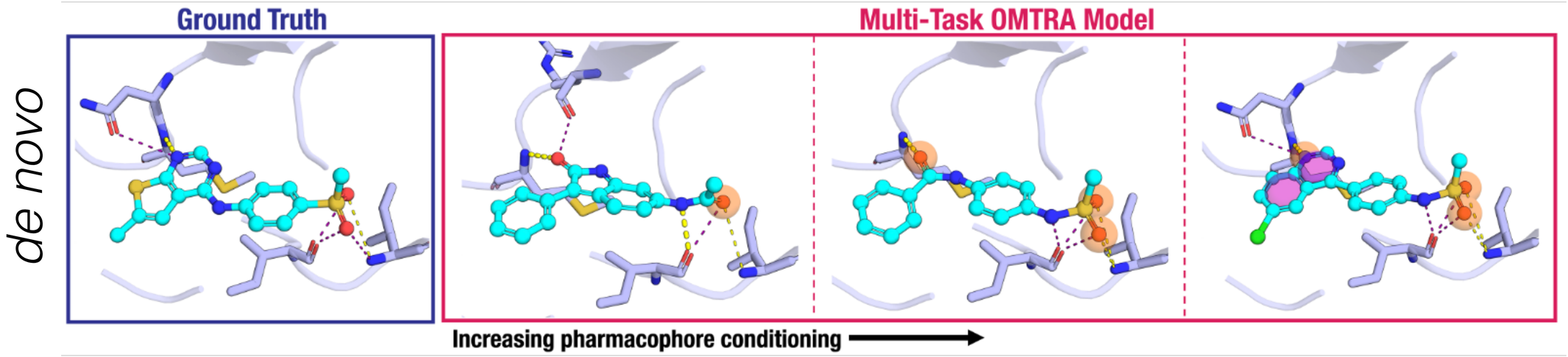
		Prot Conditioning	Prot + Pharm Conditioning
de novo design	%PB-Valid	67.5	66.2
	interaction recovery	51.0	67.4
	% Pharm Matches	-	96.9
docking	% RMSD $\leq$ 2Å	93.0	99.0
	%PB-Valid	73.0	81.0
	% Pharm Matches	-	99.5

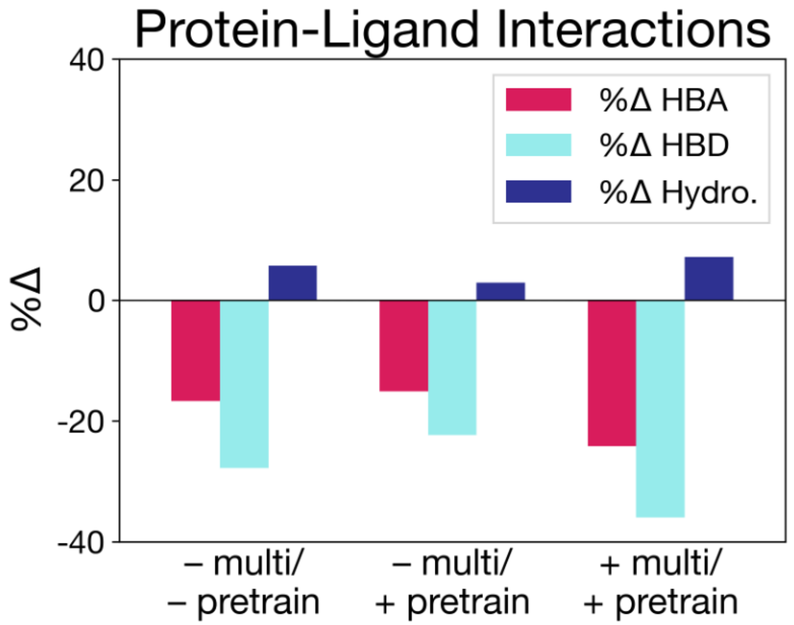
OMTRA: Pharmacophore Conditioning

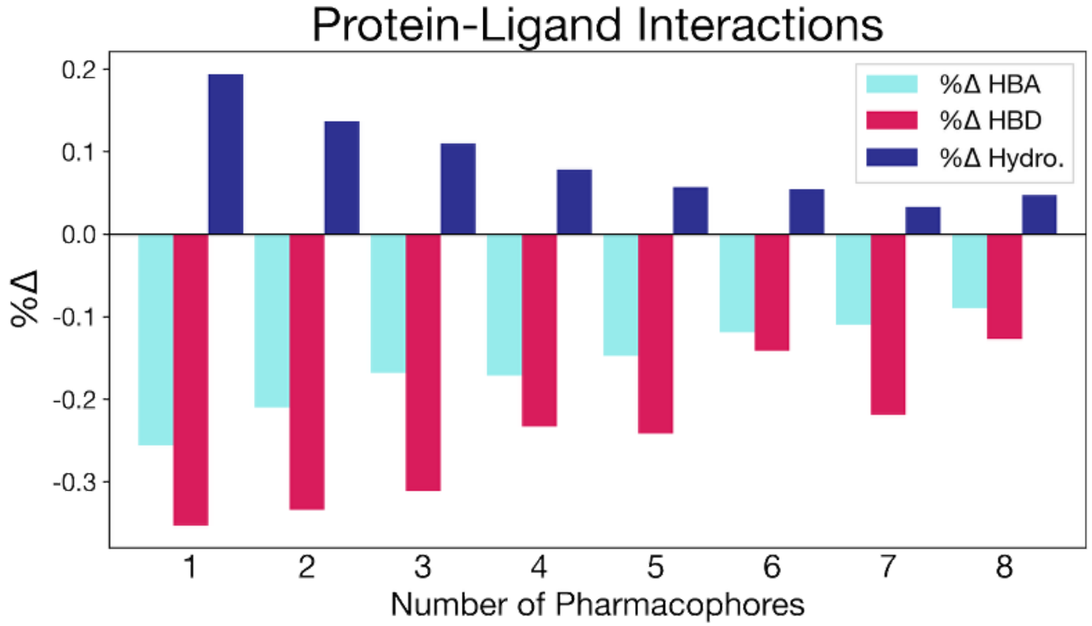


		Prot Conditioning	Prot + Pharm Conditioning
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OMTRA: Pharmacophore Conditioning

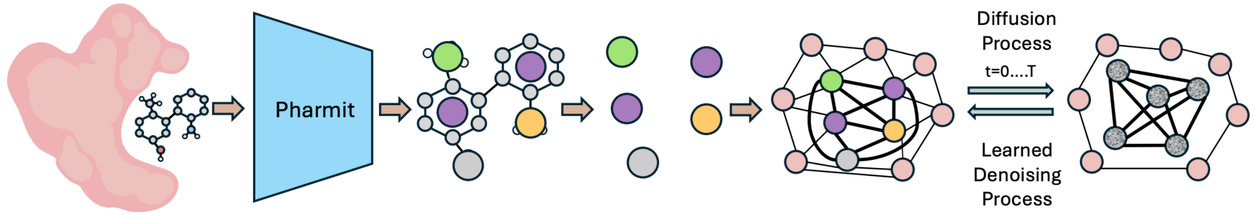


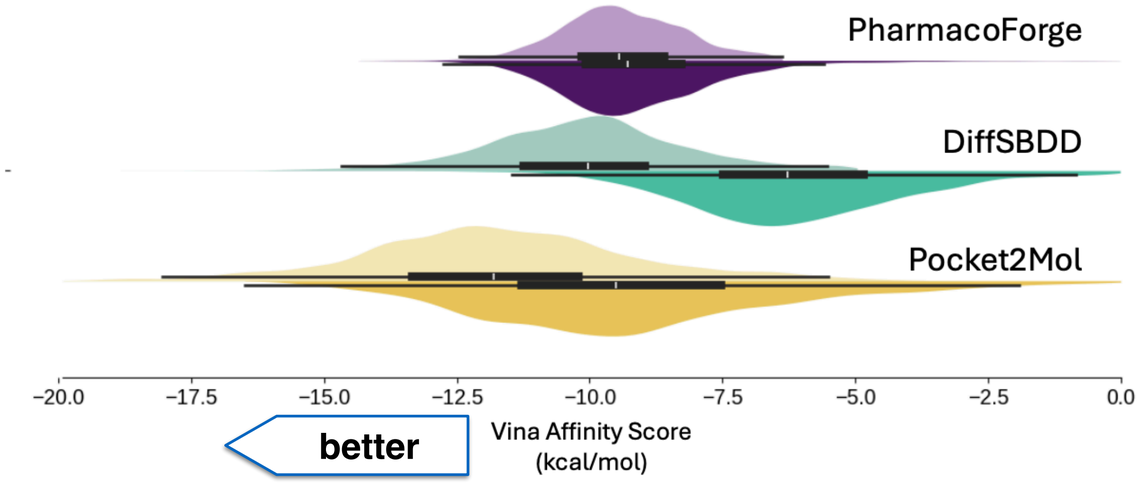




Generating *Descriptions* of Molecules

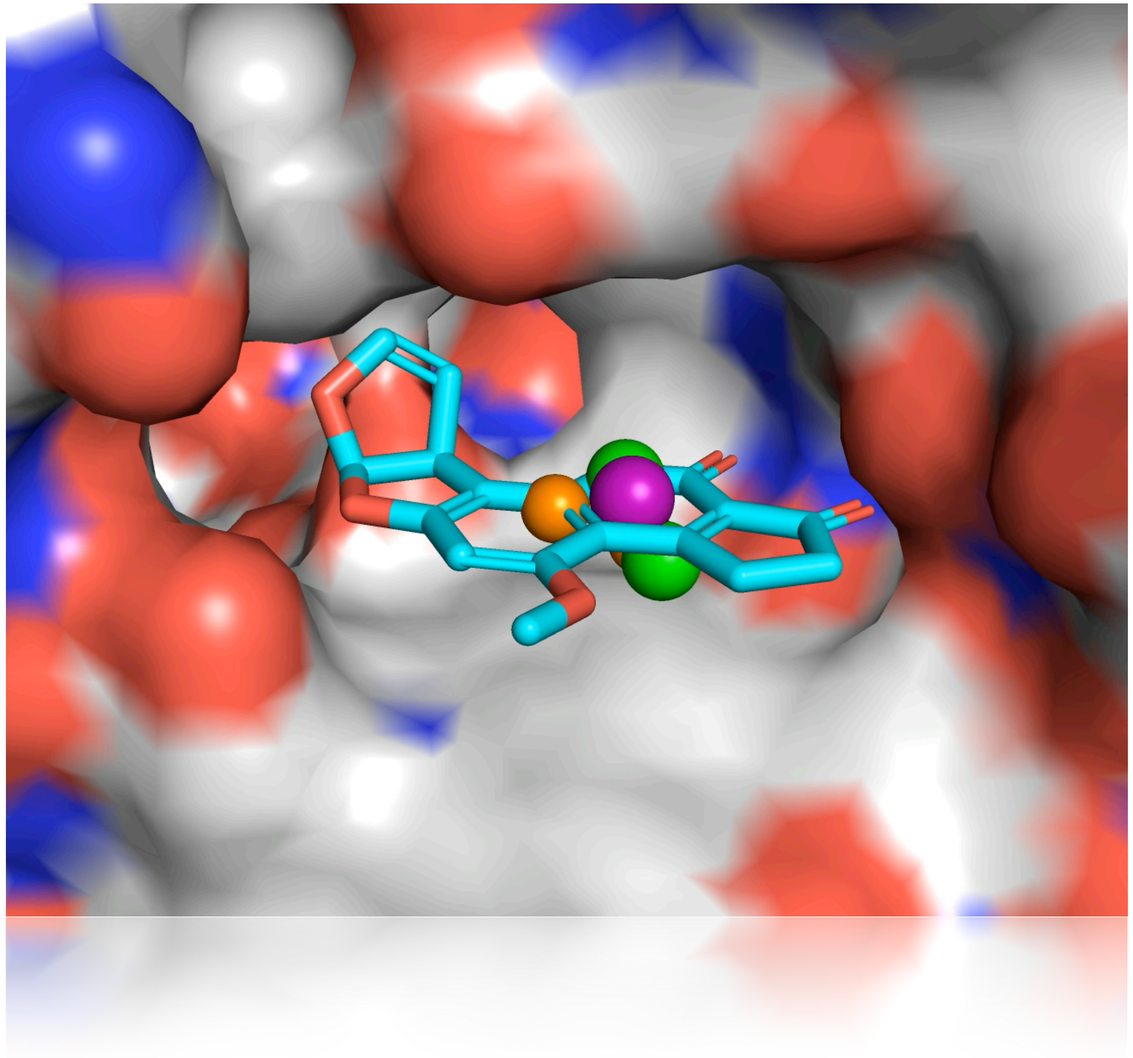
PharmacoForge









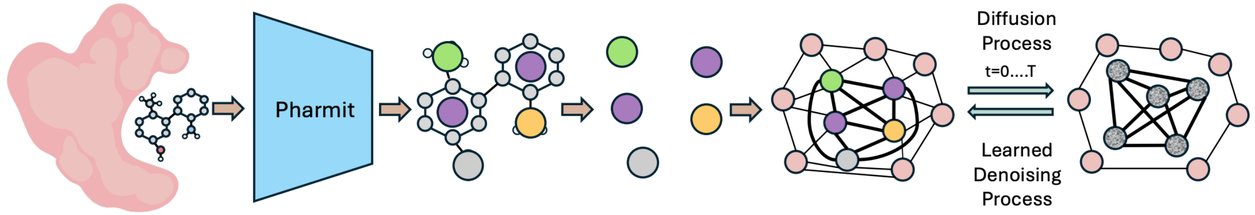



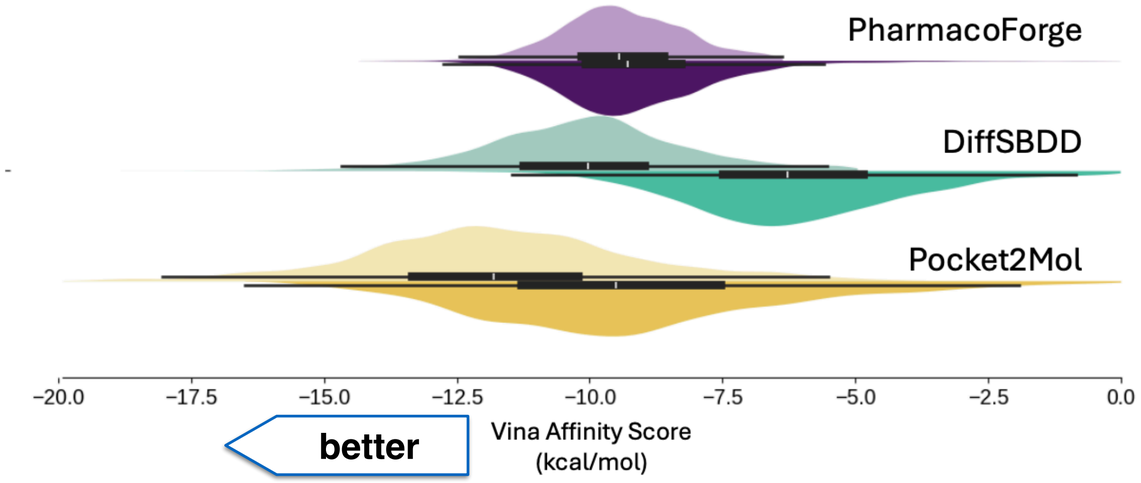
PharmacoForge: pharmacophore generation with diffusion models

Emma L. Flynn[1,2], Riya Shah [1], Ian Dunn [1,2], Rishal Aggarwal [1,2] and David Ryan Koes [1]*

frontiers | Frontiers in Bioinformatics

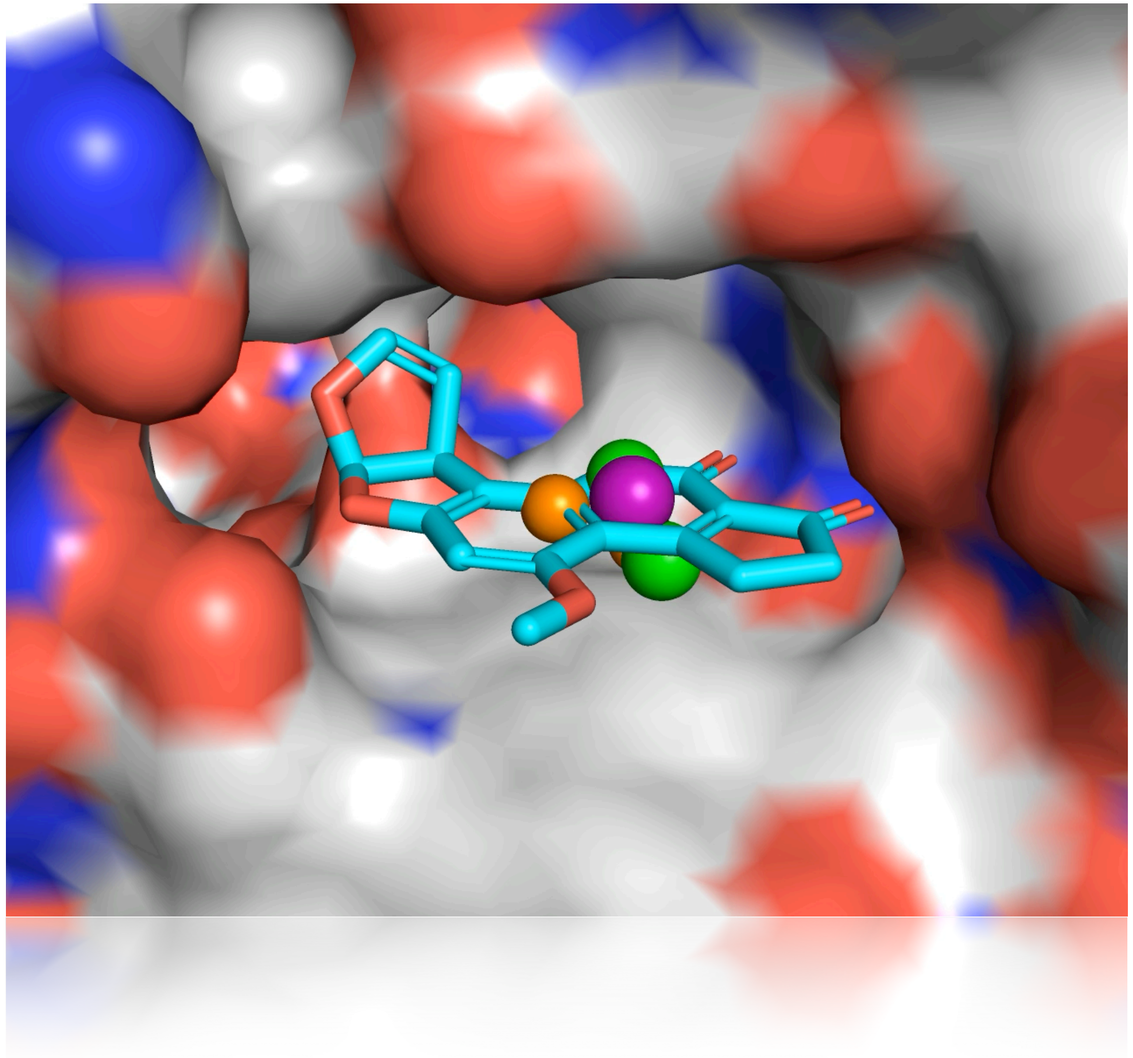
PharmacoForge









PharmacoForge: pharmacophore generation with diffusion models

Emma L. Flynn[1,2], Riya Shah [1], Ian Dunn [1,2], Rishal Aggarwal [1,2] and David Ryan Koes [1]*

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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/



