Accelerating cryptic pocket discovery with deep learning

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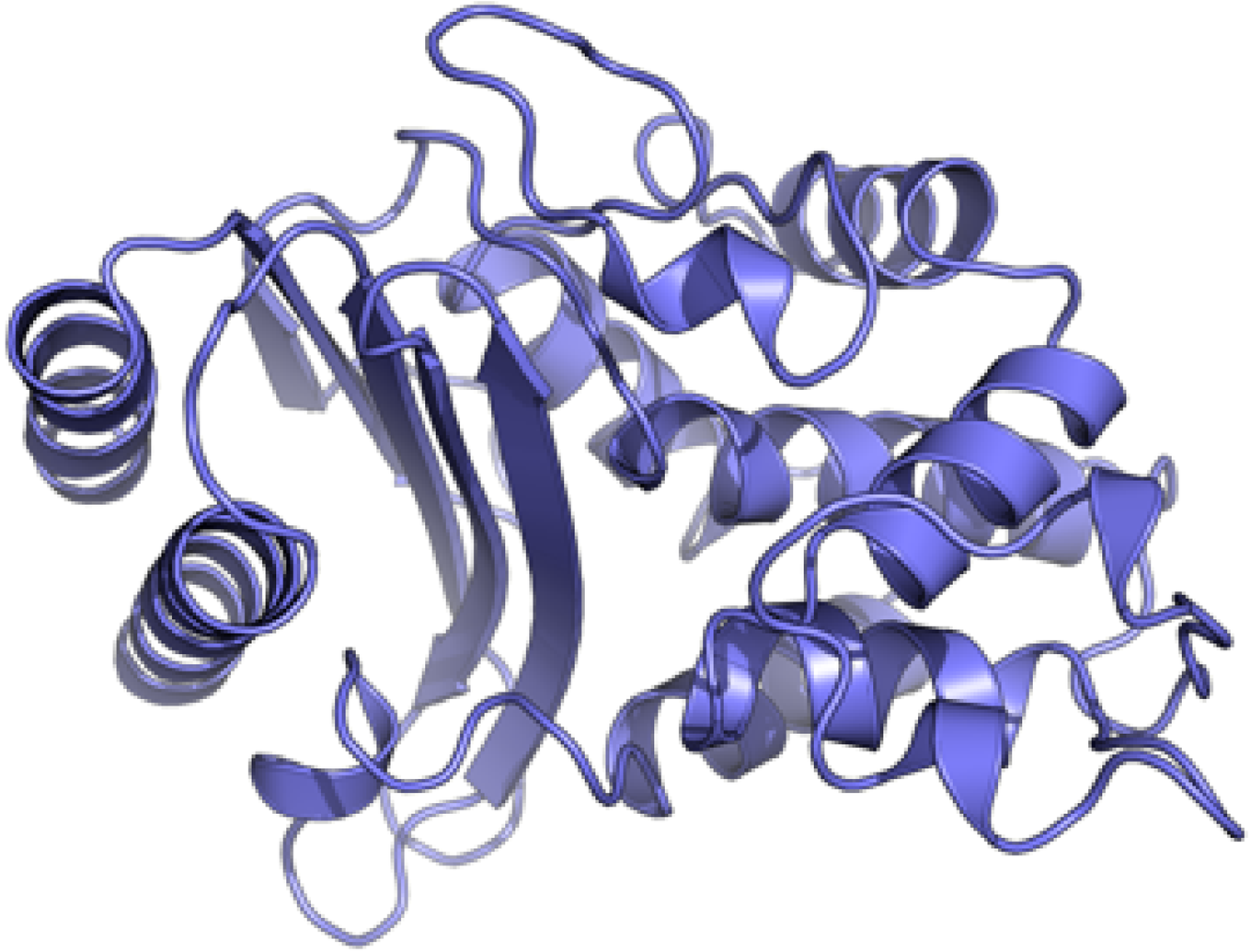
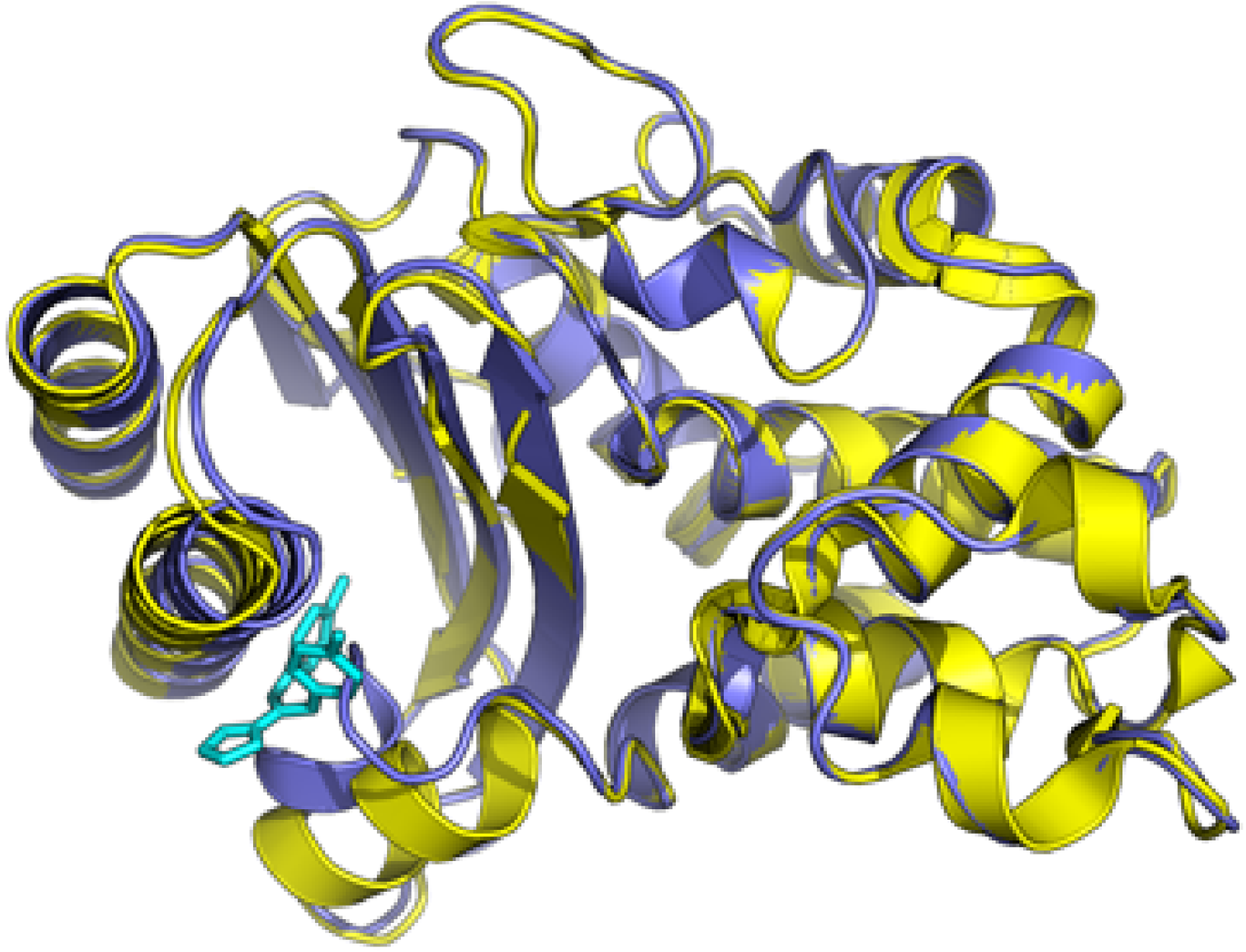
Disclaimer: Co-founder of Decrypt Bio

Structural snapshots are just the tip of the iceberg

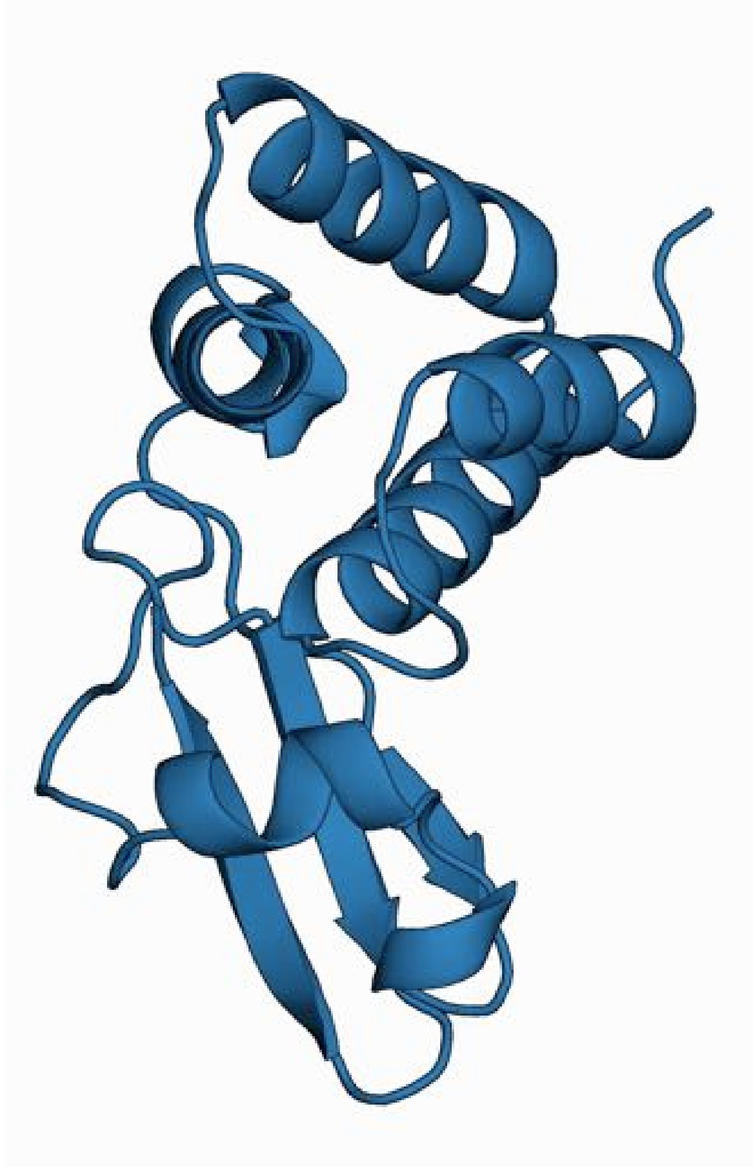


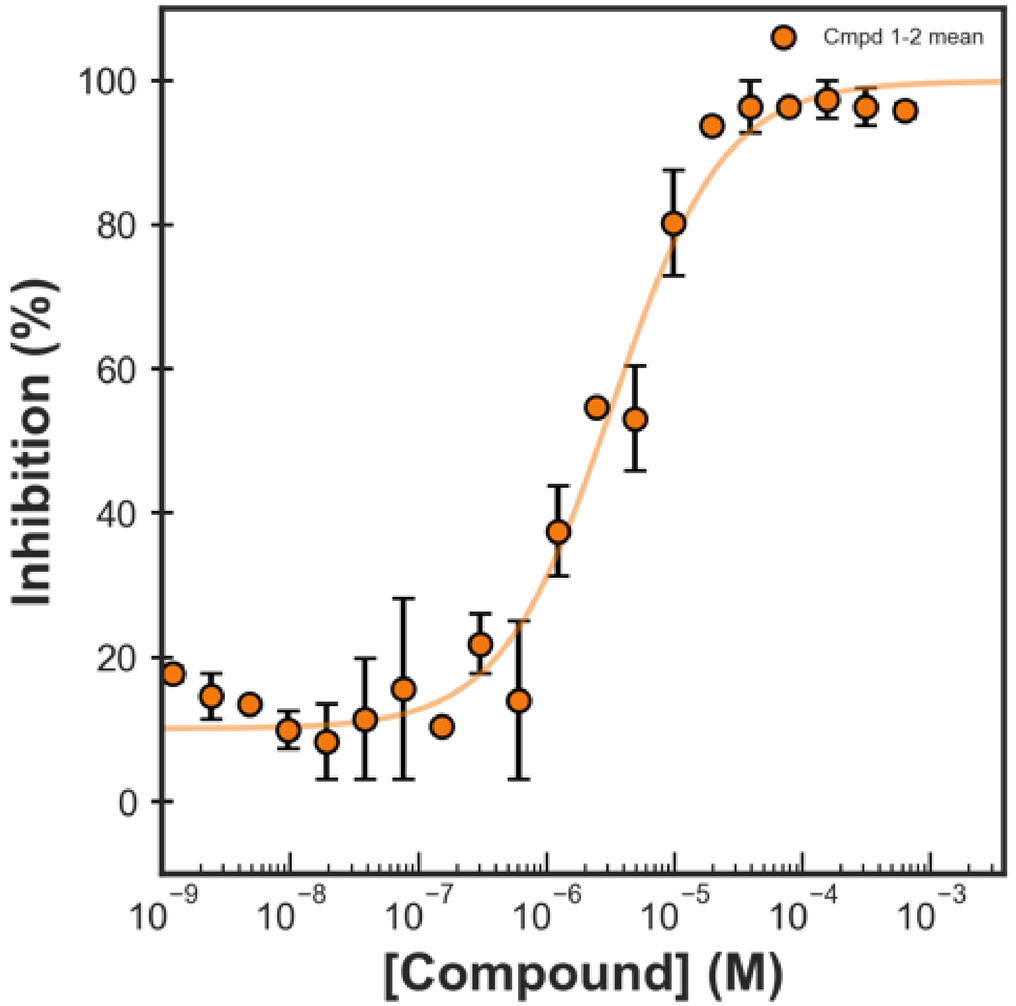
Cryptic pockets present new opportunities



Horn and Shoichet. *JMB* 2004.

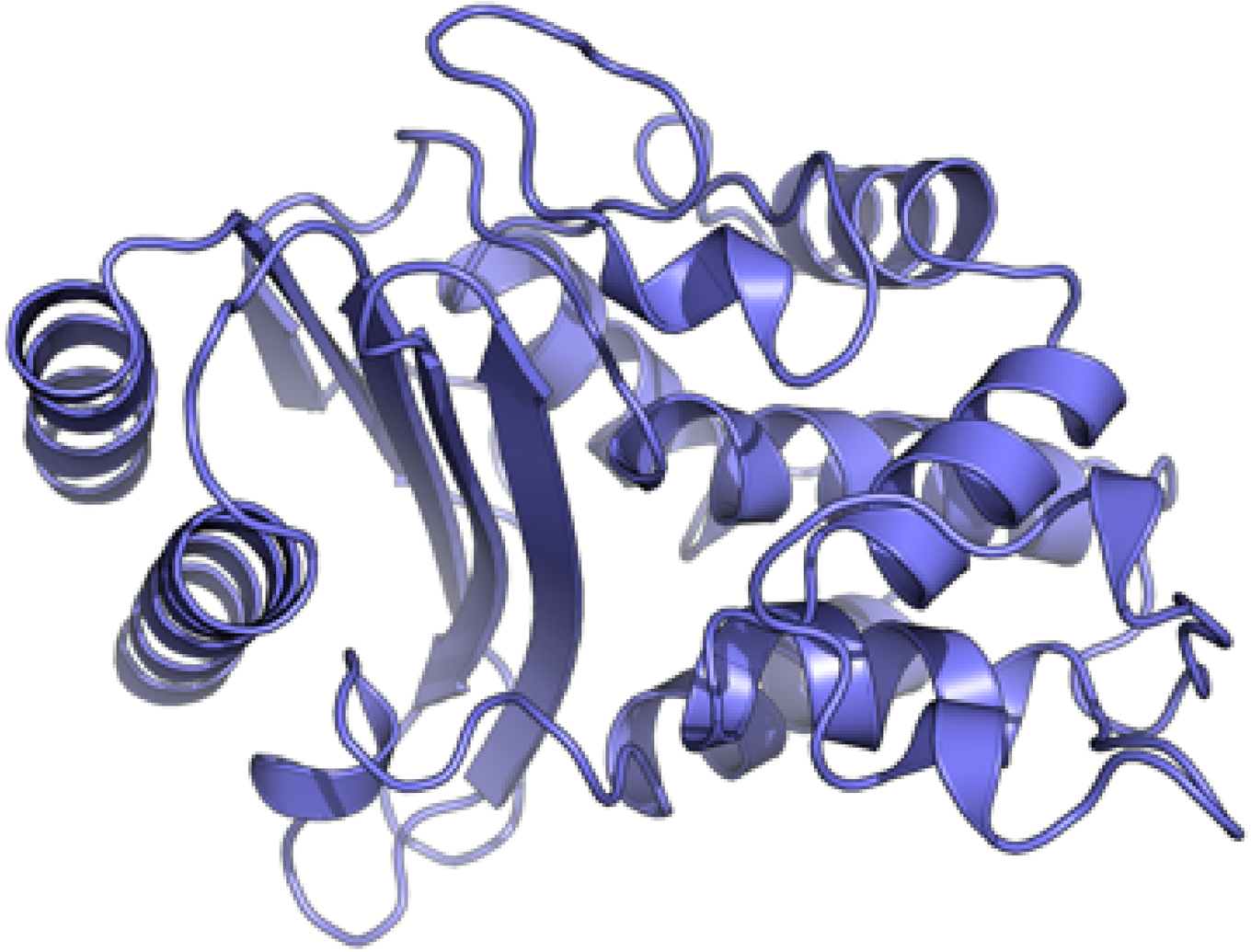
We're getting good at finding cryptic pockets with simulations





Cruz *et al. Nature Communications* 2022.

But where should we look for cryptic pockets?

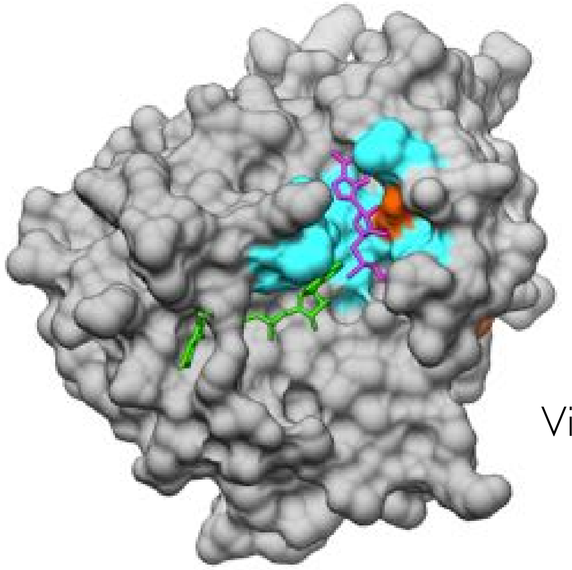


What data do we have to work with?

PDB ~200K structures

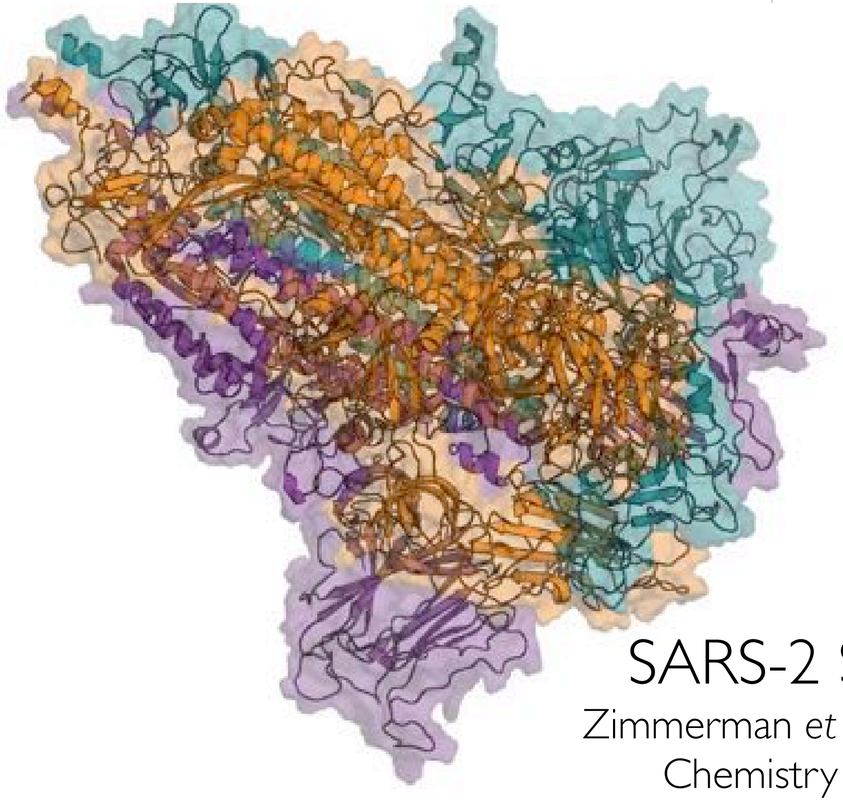
Only ~100 cryptic pockets

A second of simulation is a lot of data



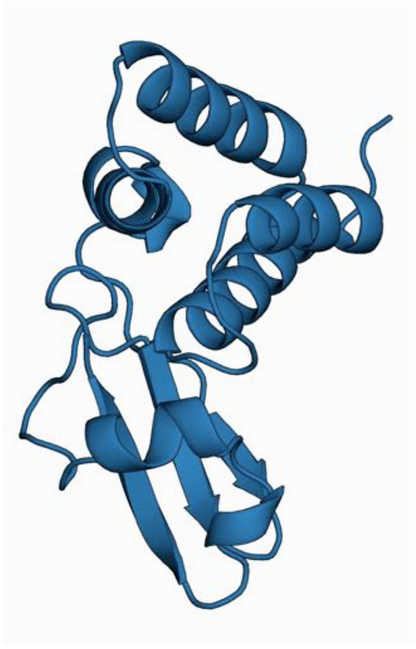
SARS-2 Nsp16

Vithani *et al. Biopsy's J 2021.*



SARS-2 Spike

Zimmerman *et al.* Nature Chemistry 2021



Ebola VP35

Cruz *et al.* Nature Communications 2022

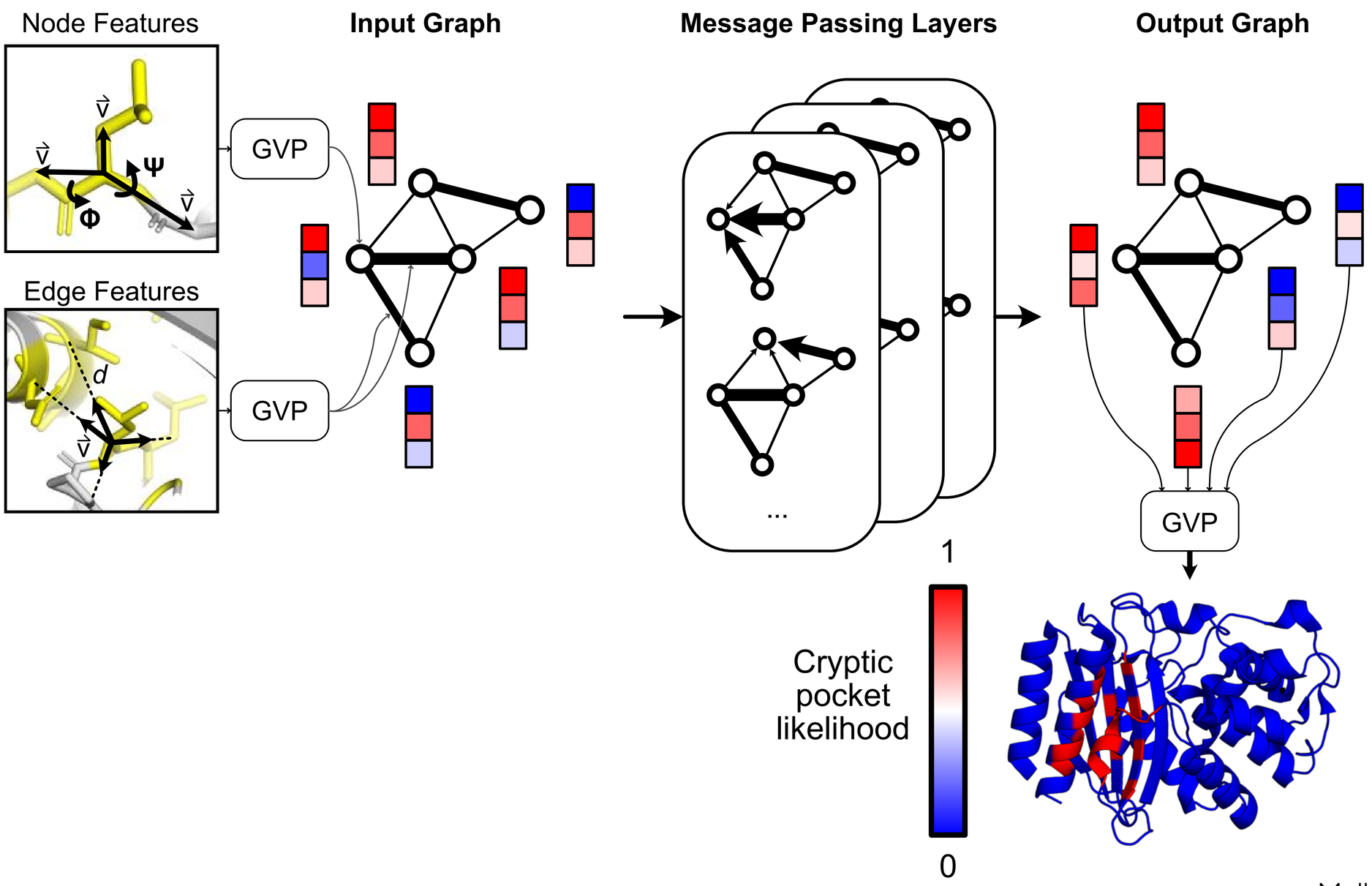
ApoE

Stuchell-Brereton *et al.* PNAS 2022

PocketMiner

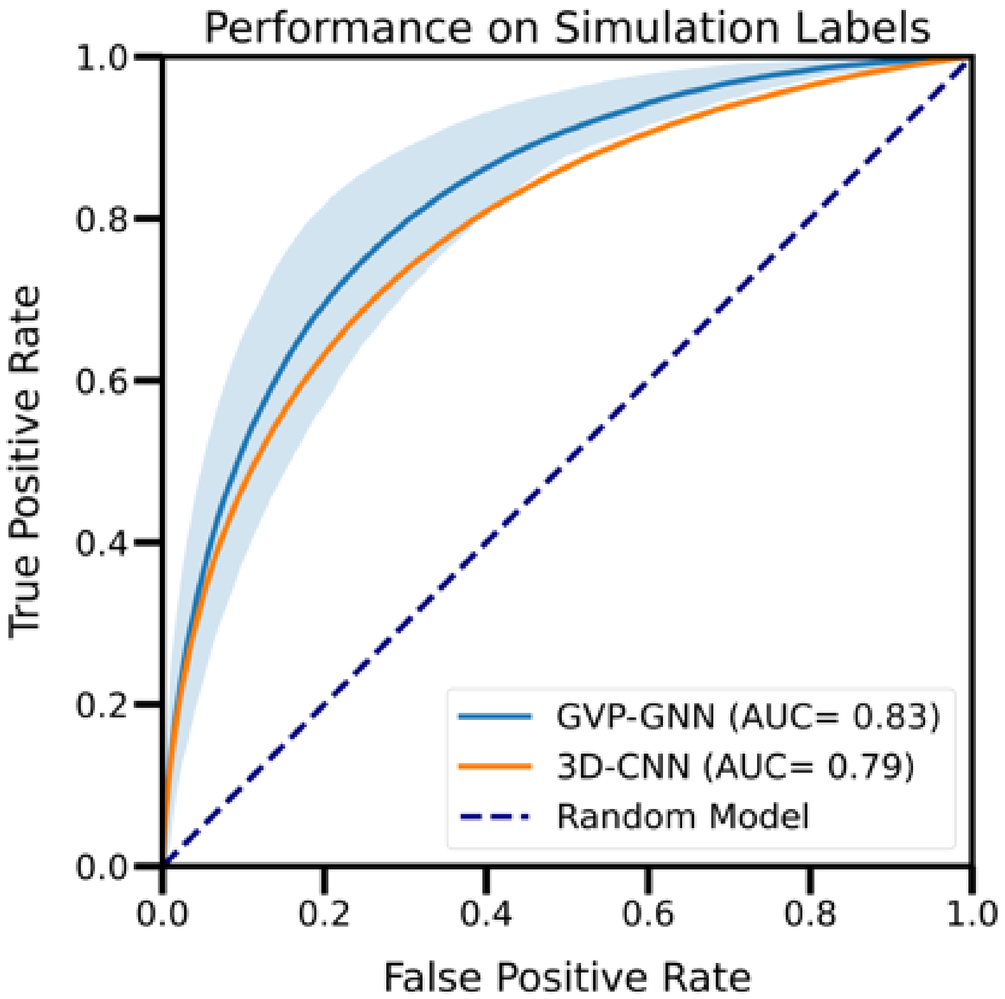
Cruz *et al. Nature Communications* 2022.

PocketMiner algorithm



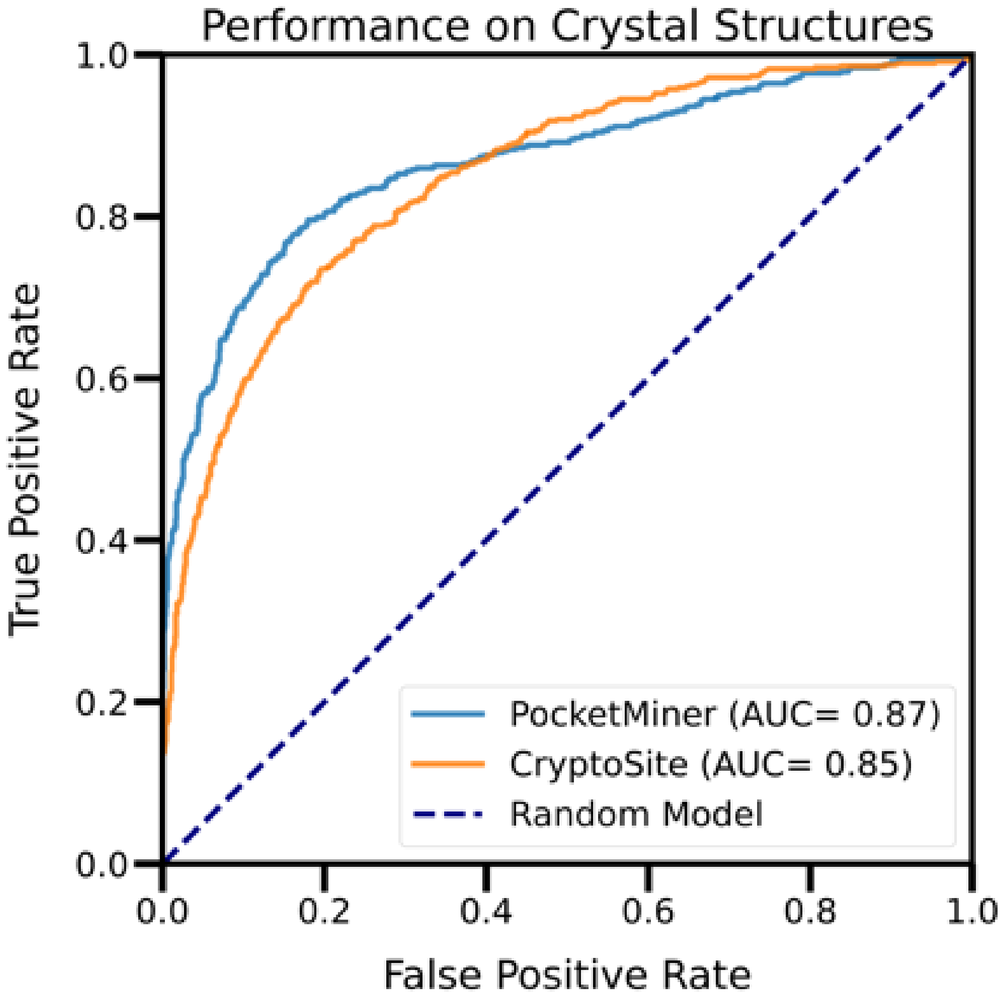
Meller *et al. bioRxiv* 2022.

PocketMiner performs well on simulation data



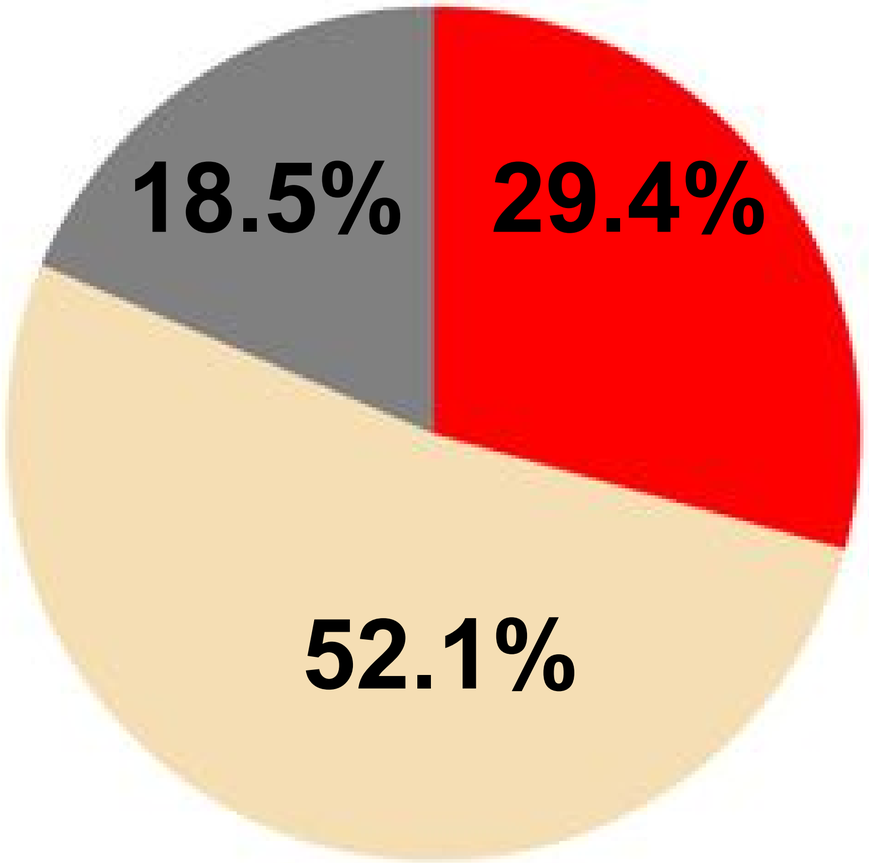
Meller *et al. bioRxiv* 2022.

PocketMiner performs well on crystal structures



Meller *et al. bioRxiv* 2022.

Cryptic pockets dramatically expand the potentially draggable proteome



Cryptic pocket
N=3172 (29.4%)

No pocket
N=2001 (18.5%)

Ground state pocket
N=5633 (52.1%)

Meller *et al. bioRxiv* 2022.

PocketMiner is predictive of simulations

Kinase PIM 2
(crystal structure)

Orthosteric ligand

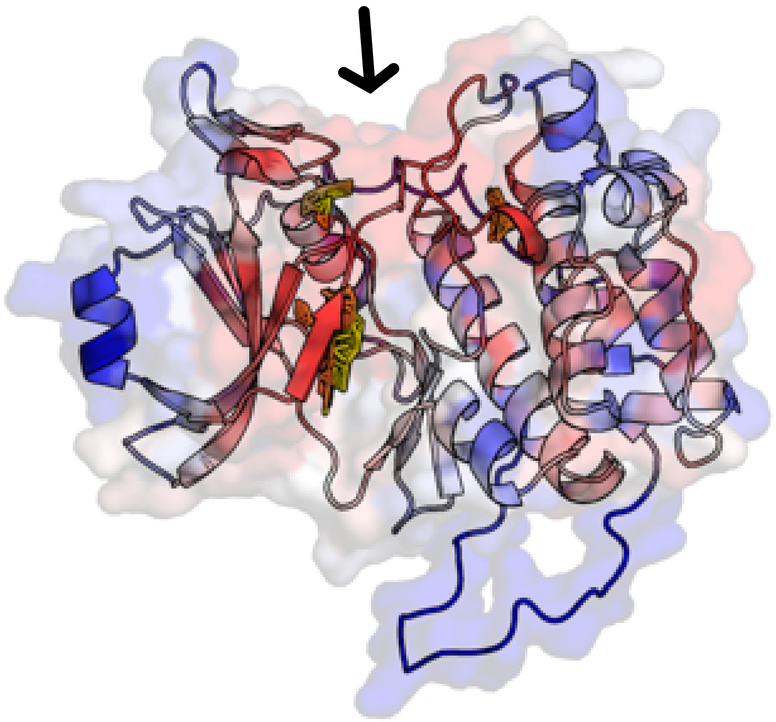
Meller *et al. bioRxiv* 2022.

PocketMiner is predictive of simulations

Kinase PIM 2
(crystal structure)

Orthosteric ligand

Predicted cryptic pocket



Meller *et al. bioRxiv* 2022.

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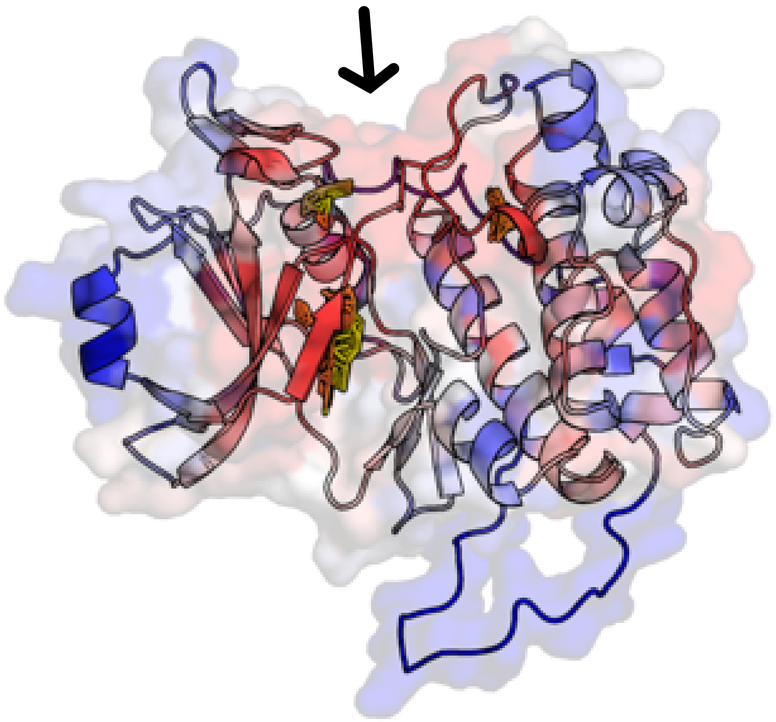
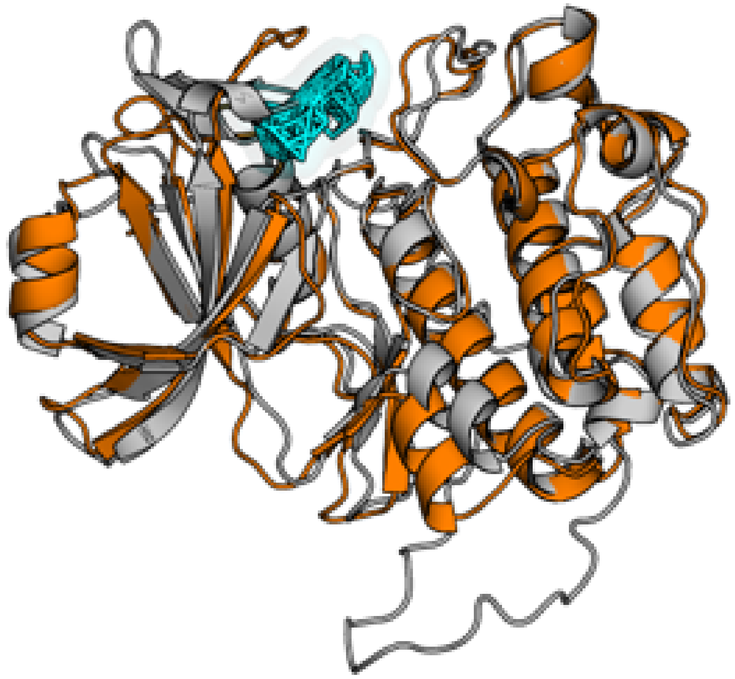


0 — 1

Cryptic pocket likelihood

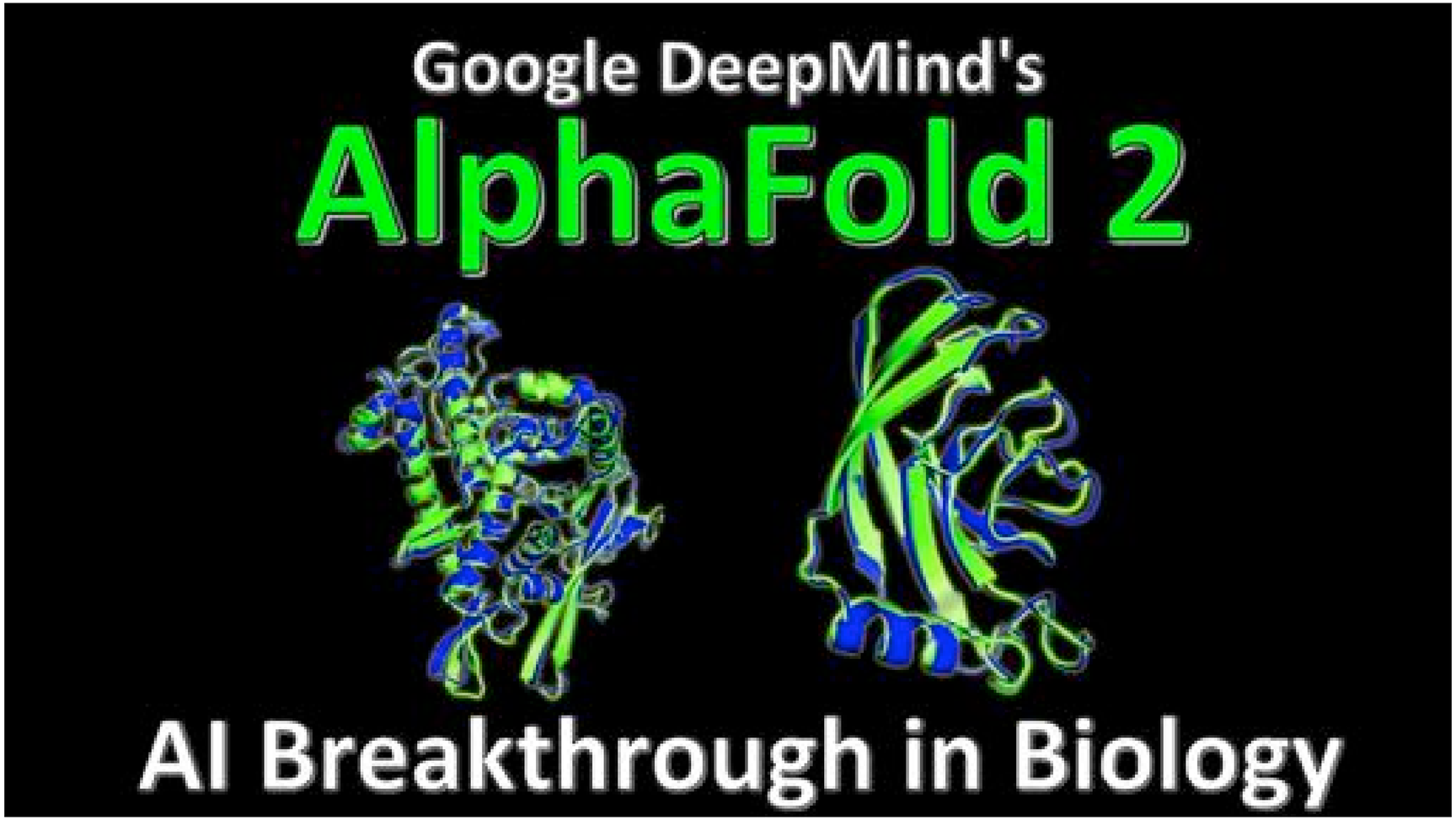
Pocket



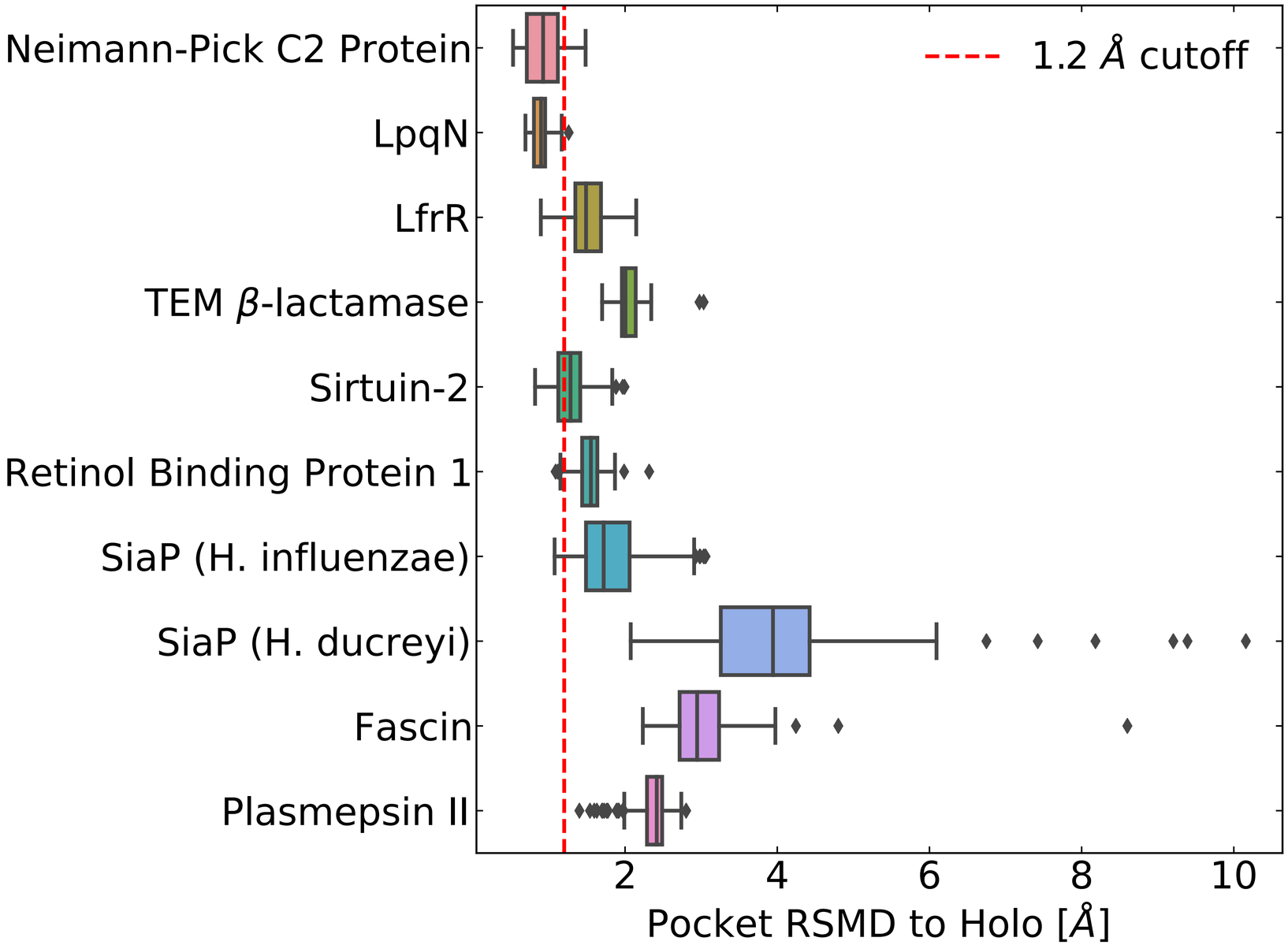
Simulated structure
Apo/template structure

Meller *et al. bioRxiv* 2022.

Can AlphaFold do it again?



AlphaFold sometimes helps

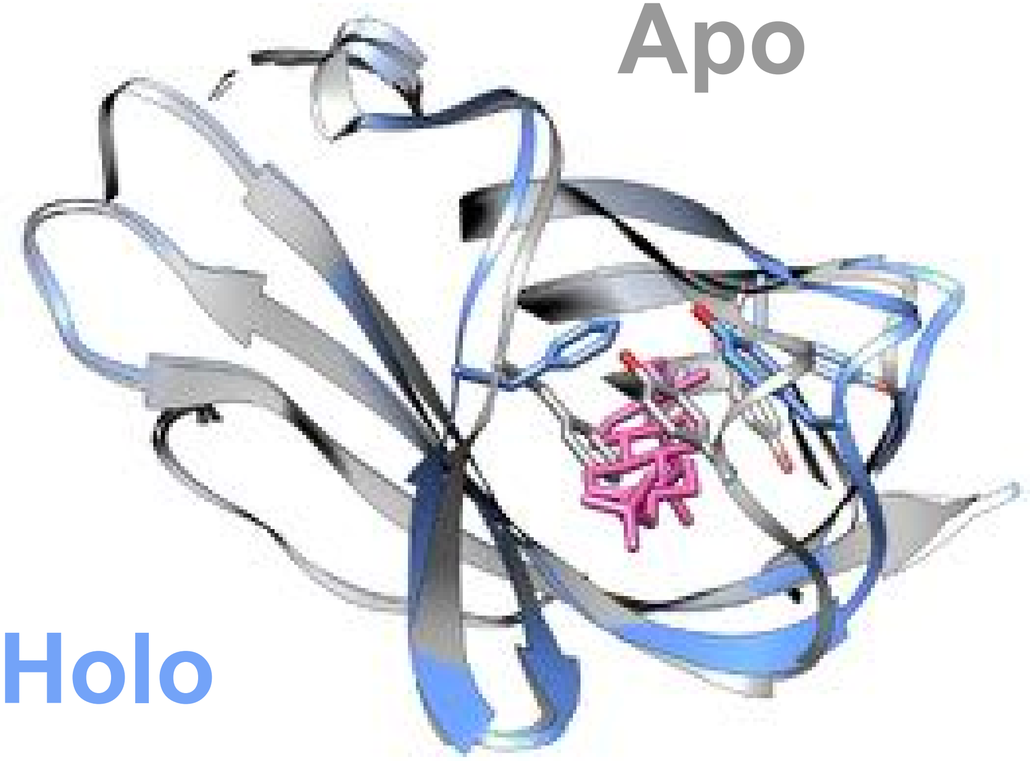


2nd Meller *et al. bioRxiv* 2022.

Example of a success

NPC2

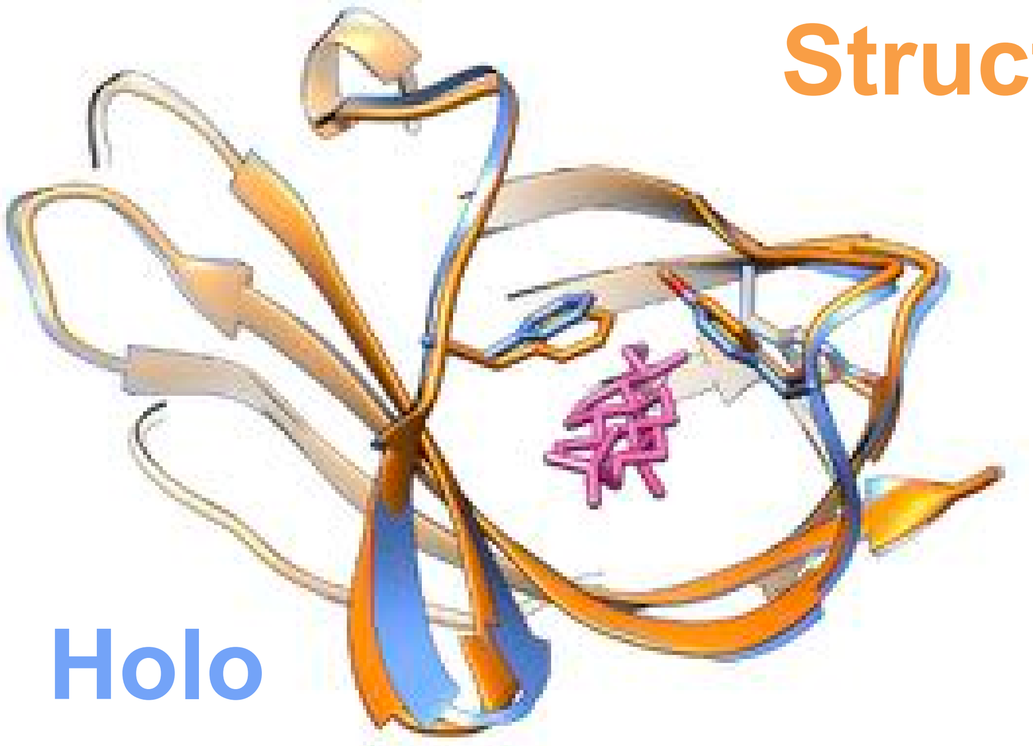
Apo



Holo

⇌

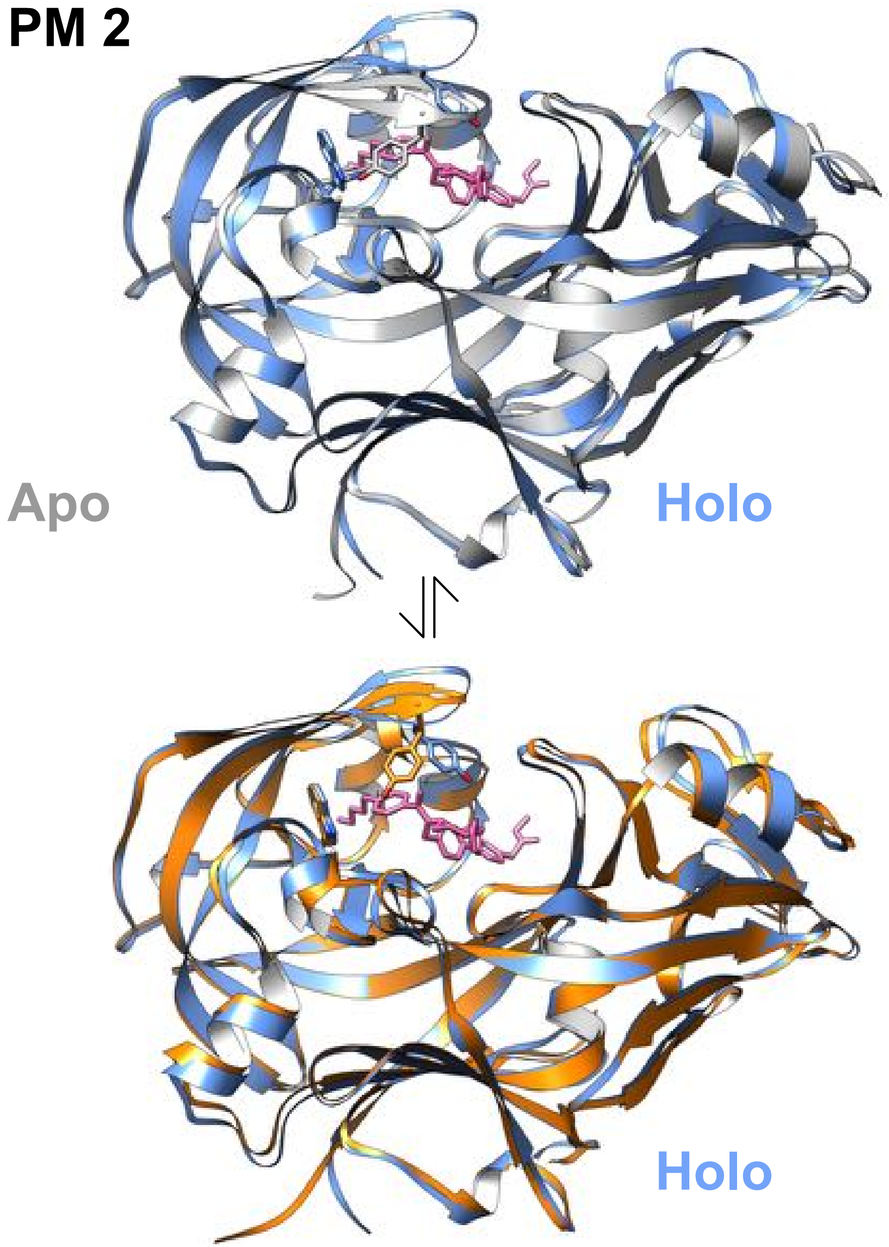
AF Structure

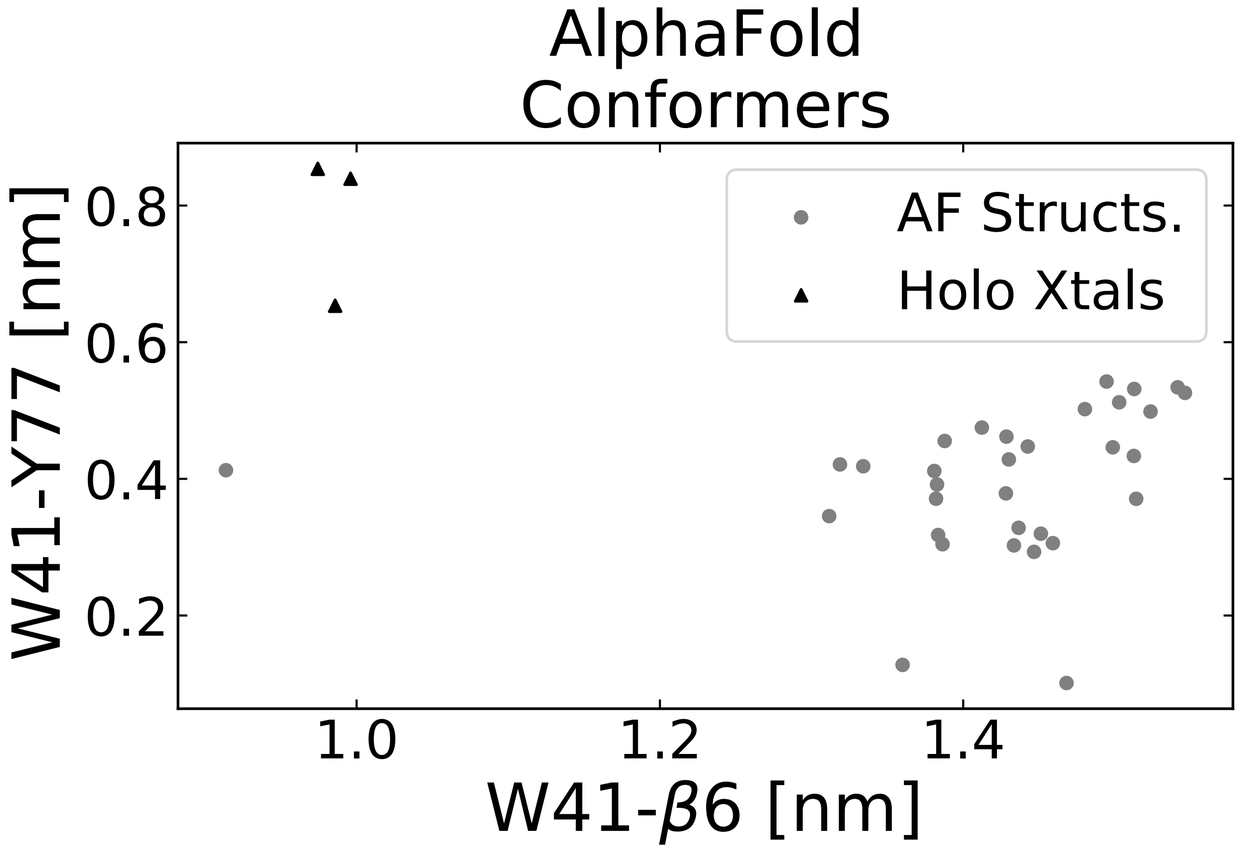


Holo

2nd Meller *et al. bioRxiv* 2022.

Example of a partial success





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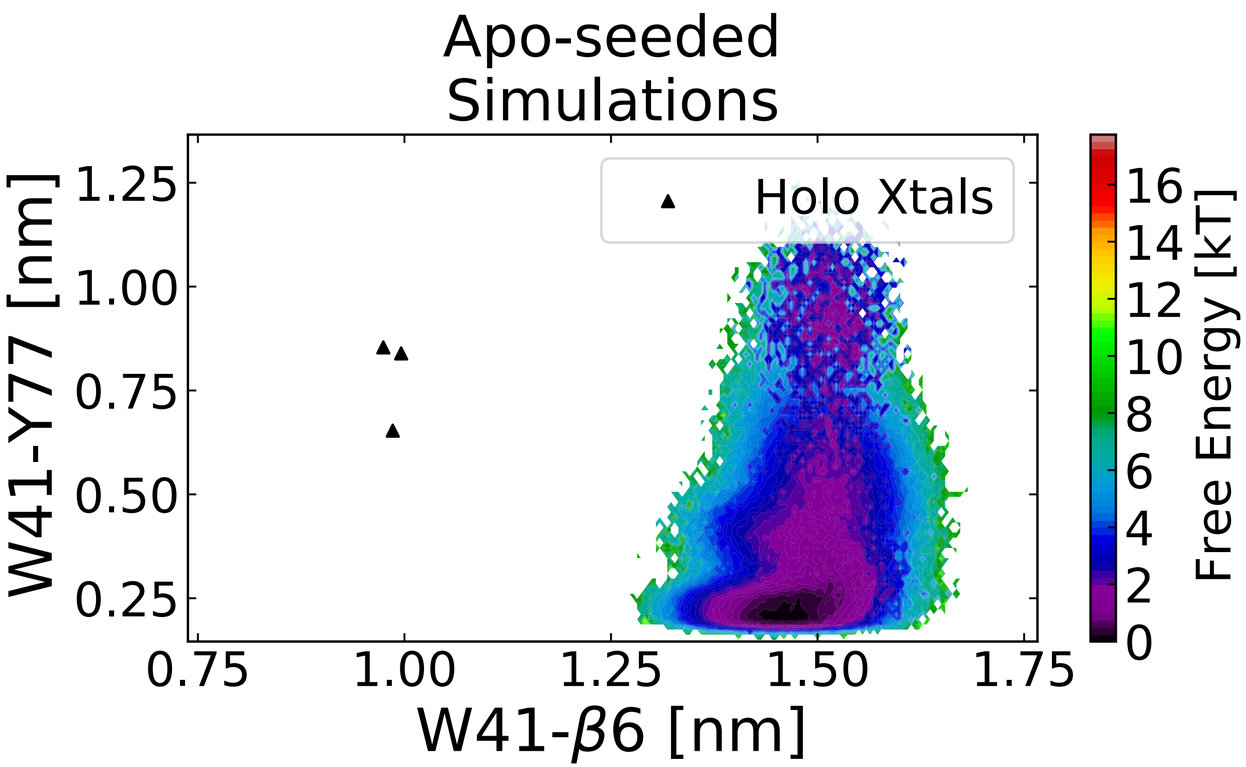
AlphaFold still helps jumpstart MD



2nd Meller *et al. bioRxiv* 2022.

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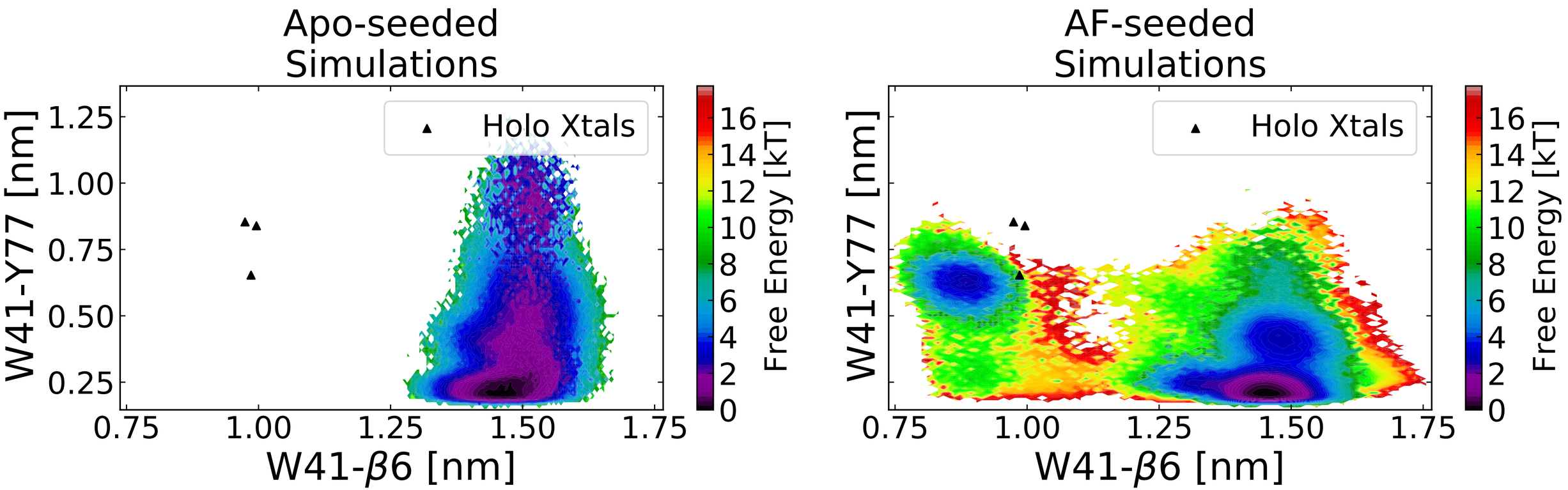
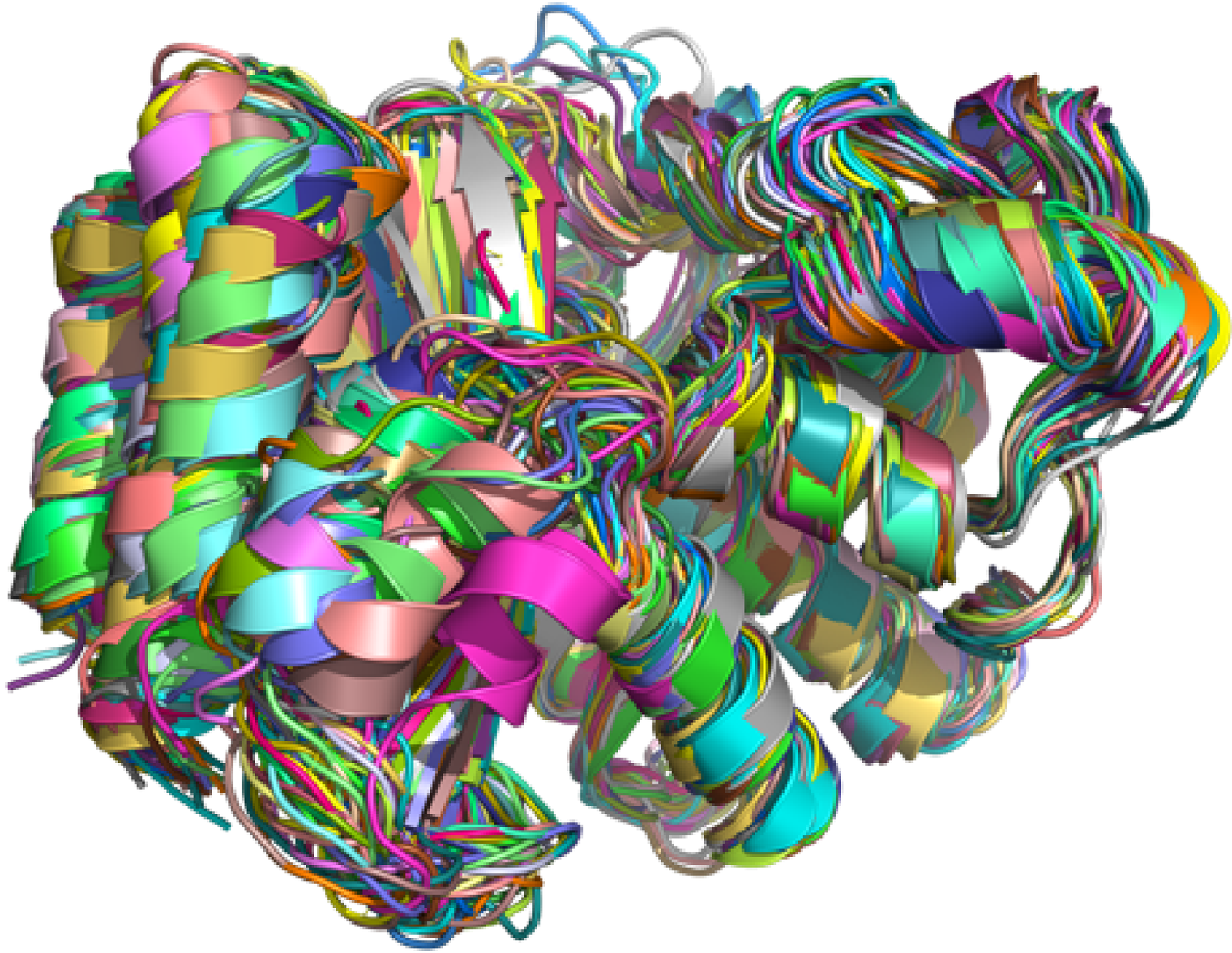
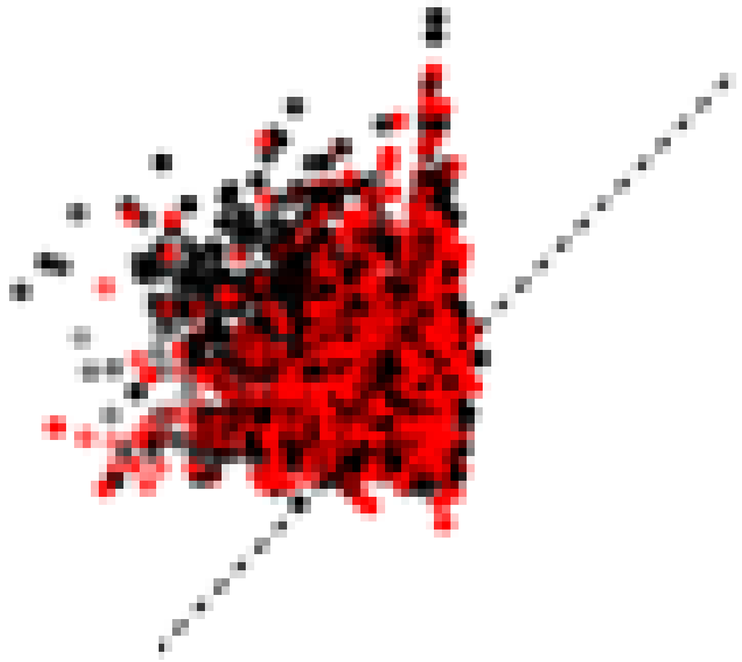


2nd Meller *et al. bioRxiv* 2022.

How do we find the key degrees of freedom when we don't know the answer?



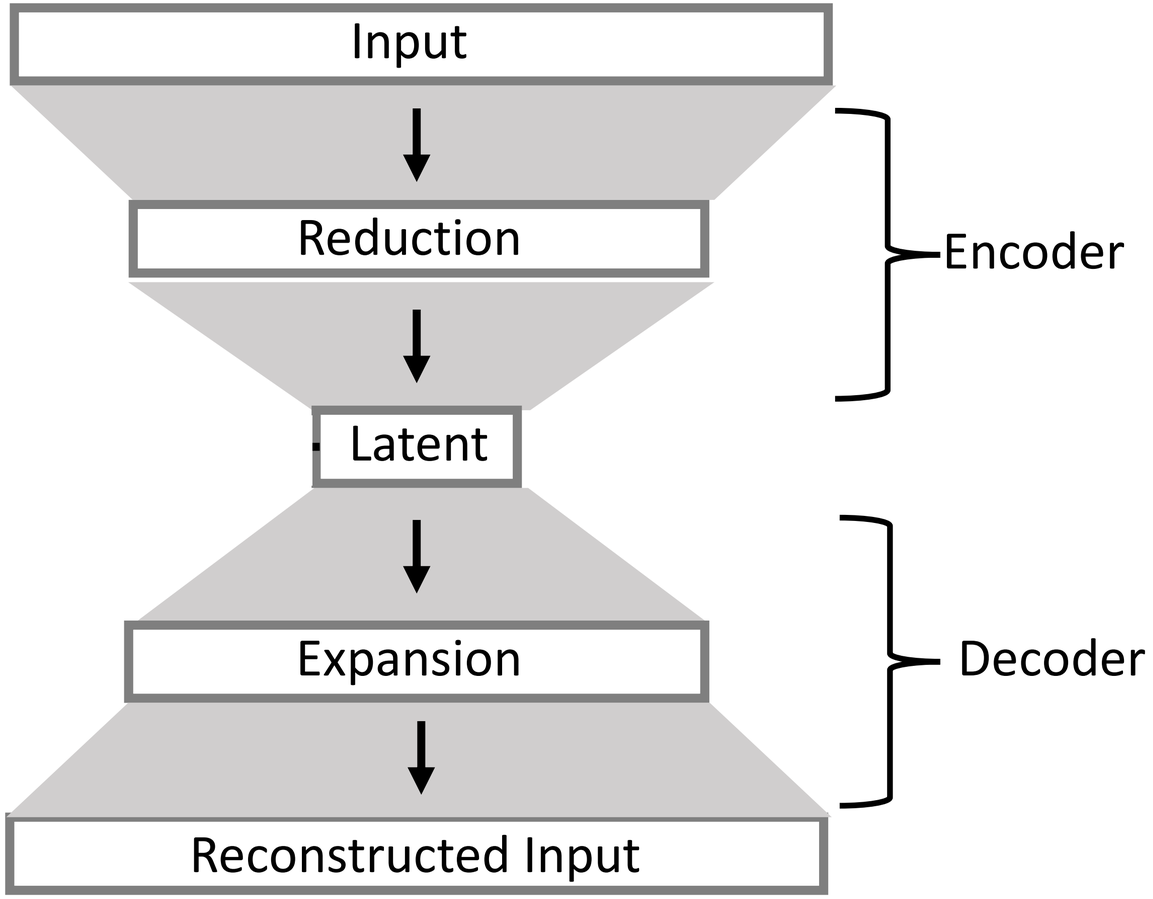
Making comparisons is hard given the assumptions made by existing methods



Variant 1
Variant 2
Decision boundary

Ward *et al. Nature Communications 2021.*

DiffNets automate the discovery of biochemically-relevant traits



Ward *et al. Nature Communications 2021.*

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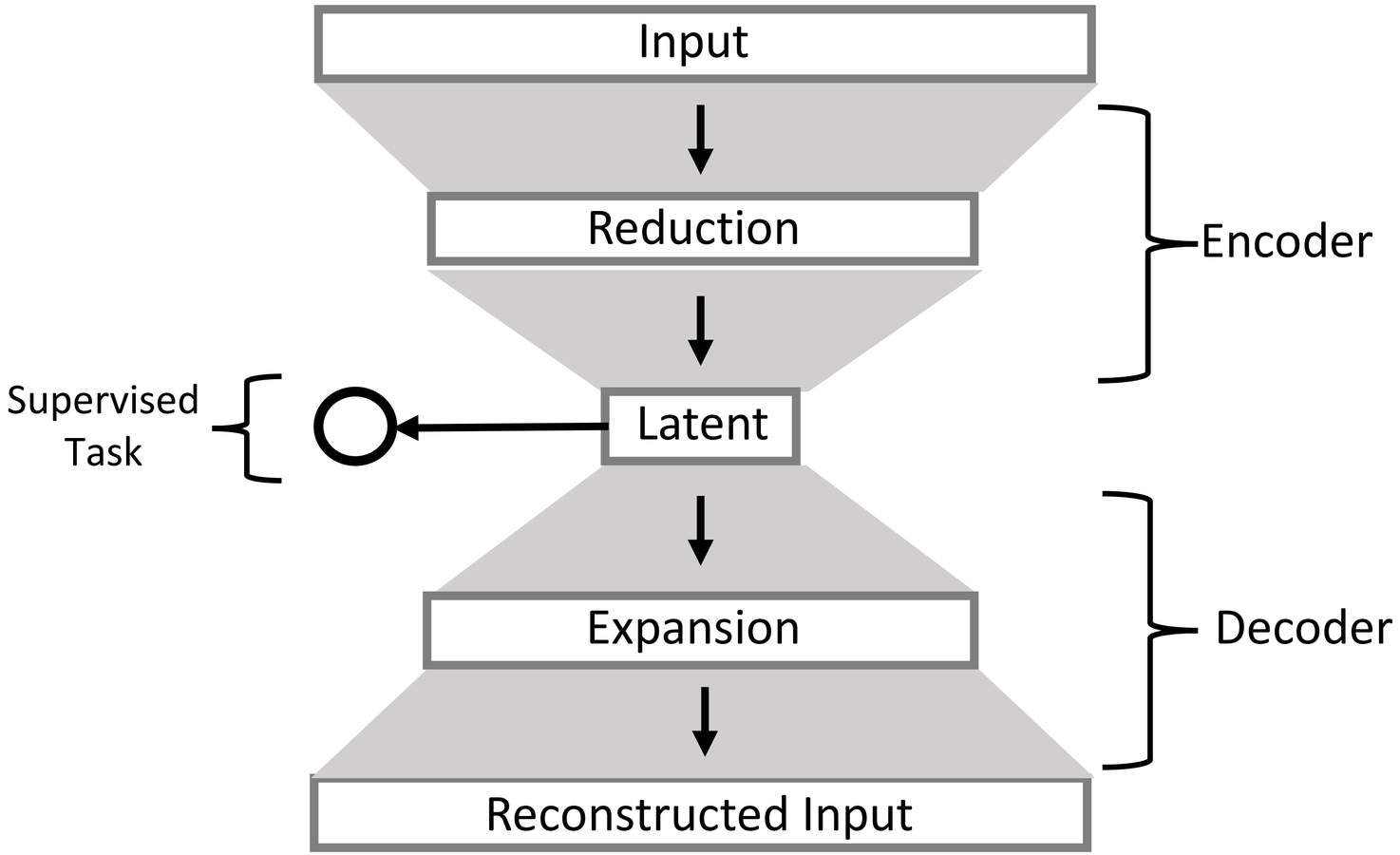
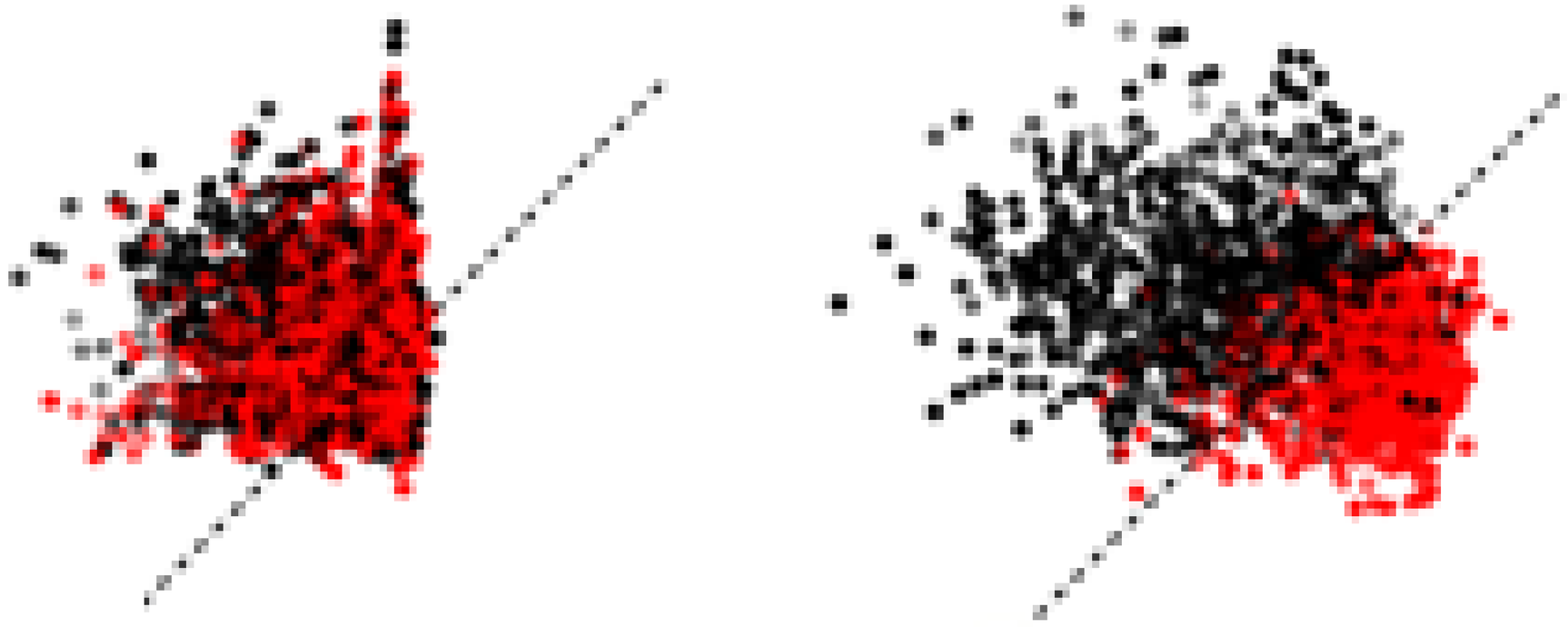


Ward *et al. Nature Communications 2021.*

DiffNets finds subtle structural differences that explain biochemical variation



Variant 1

Variant 2

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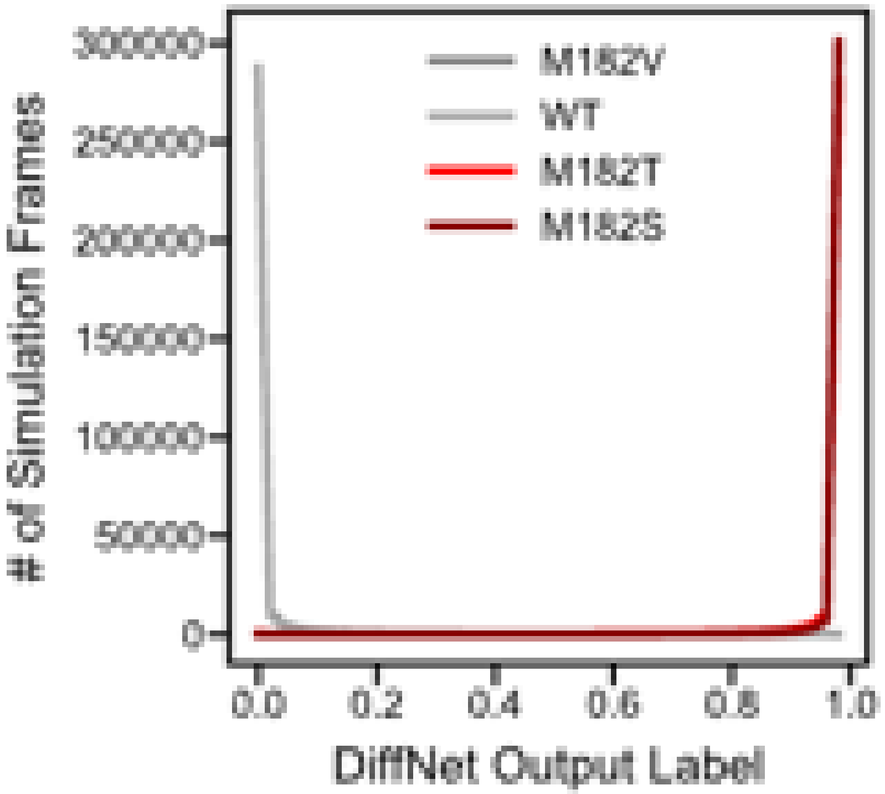
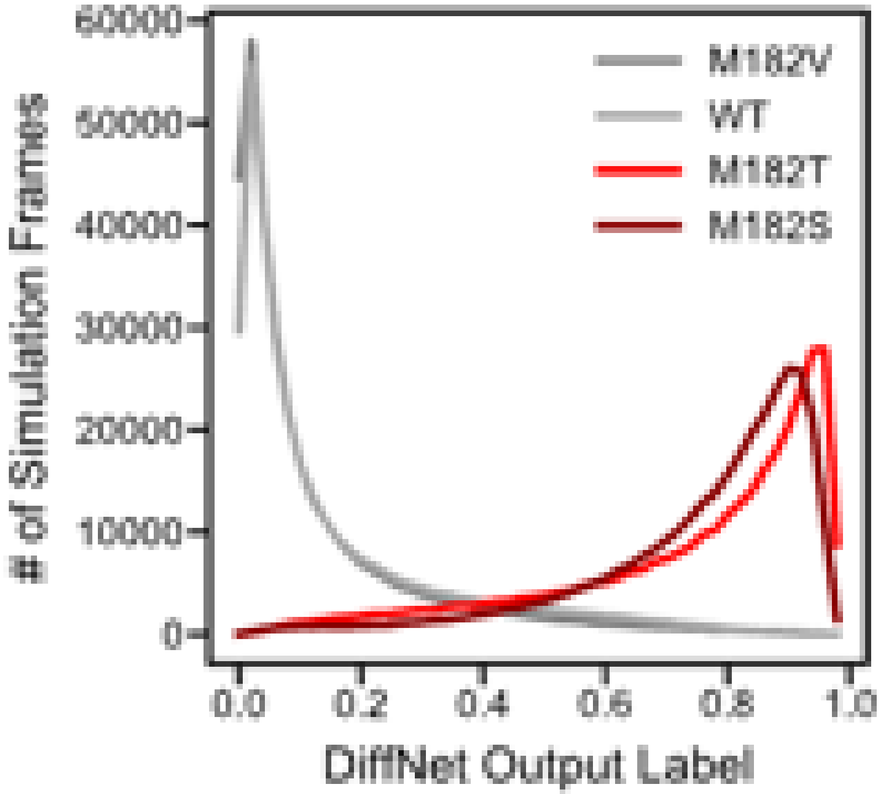
Ward *et al. Nature Communications 2021.*

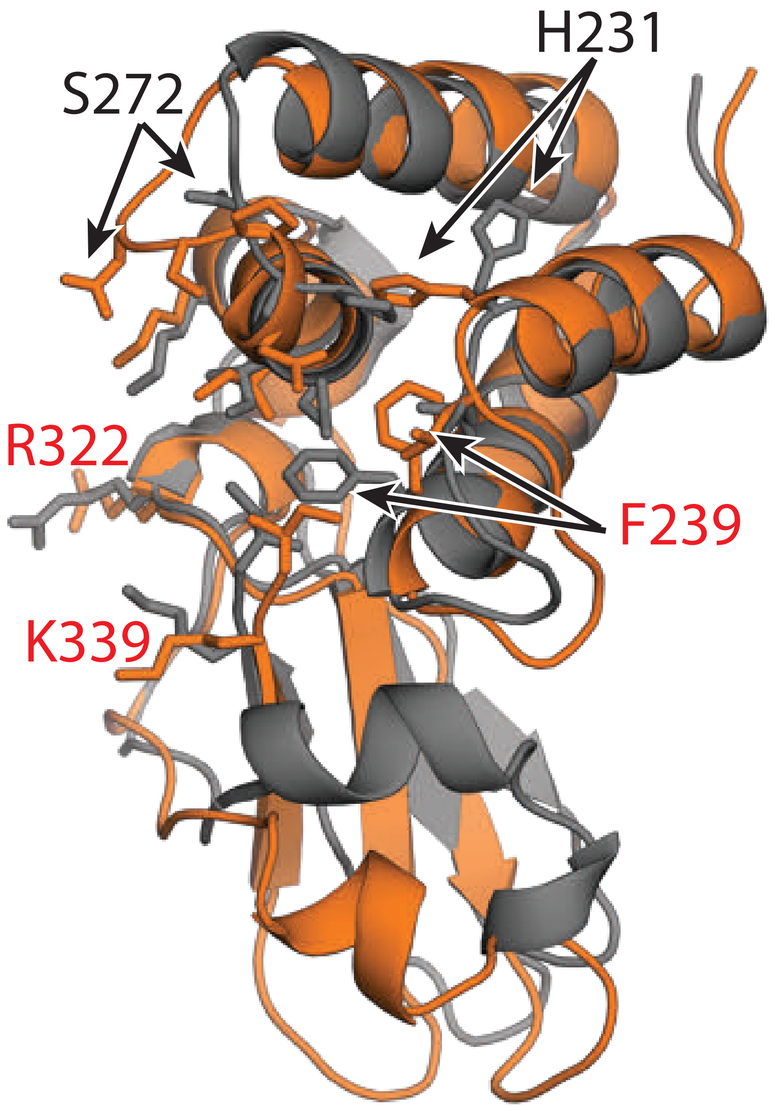
Relaxation of the labels

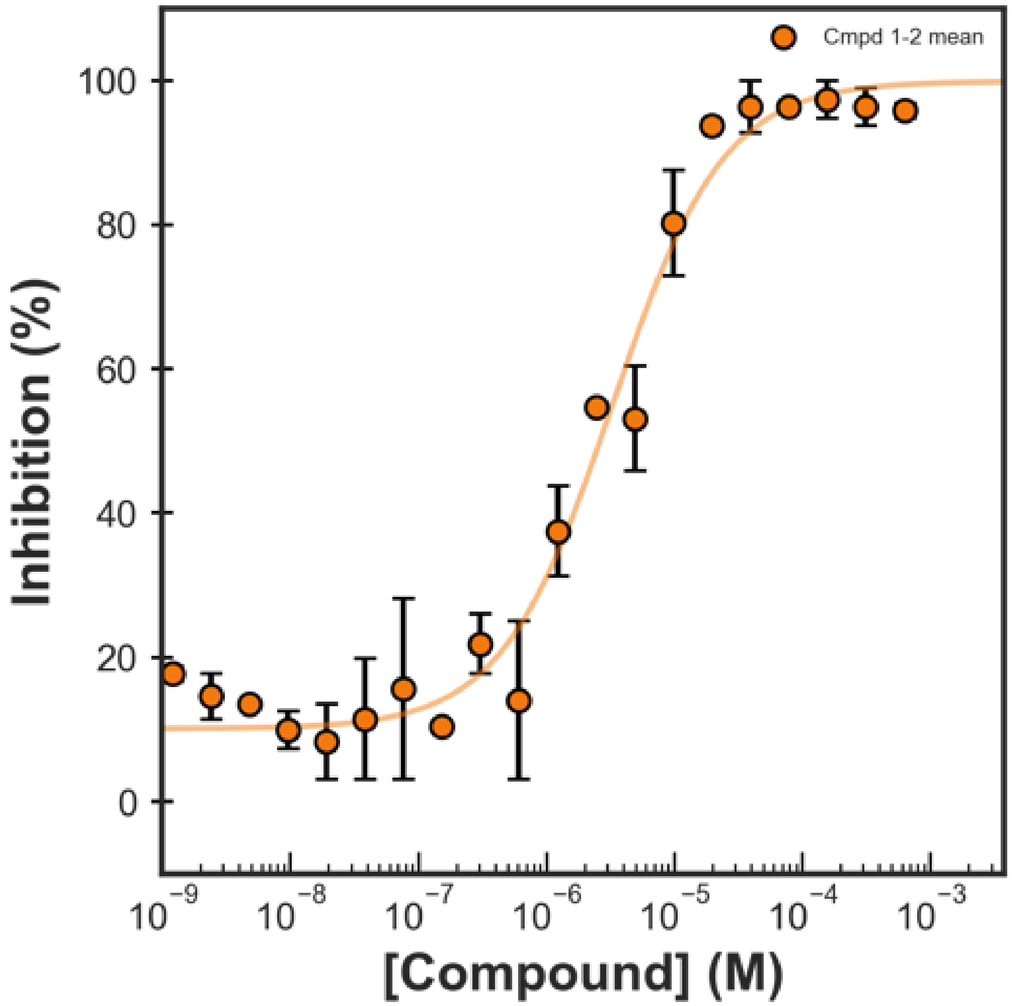




Ward *et al. Nature Communications 2021.*

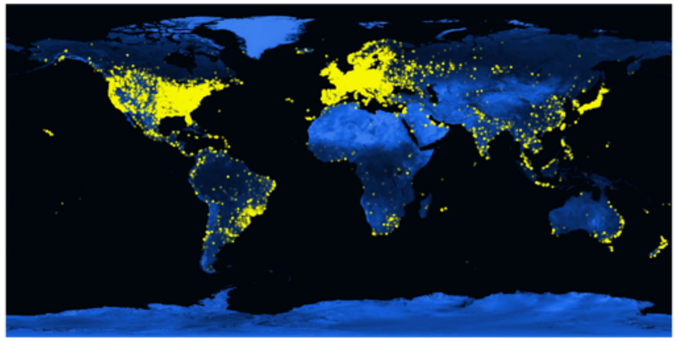
VP35's cryptic pocket is coupled to the blunt end-binding interface





Cruz *et al. Nature Communications* 2022.

Thanks!



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