Cryptic Pocket Detection Using Weighted Ensemble MD

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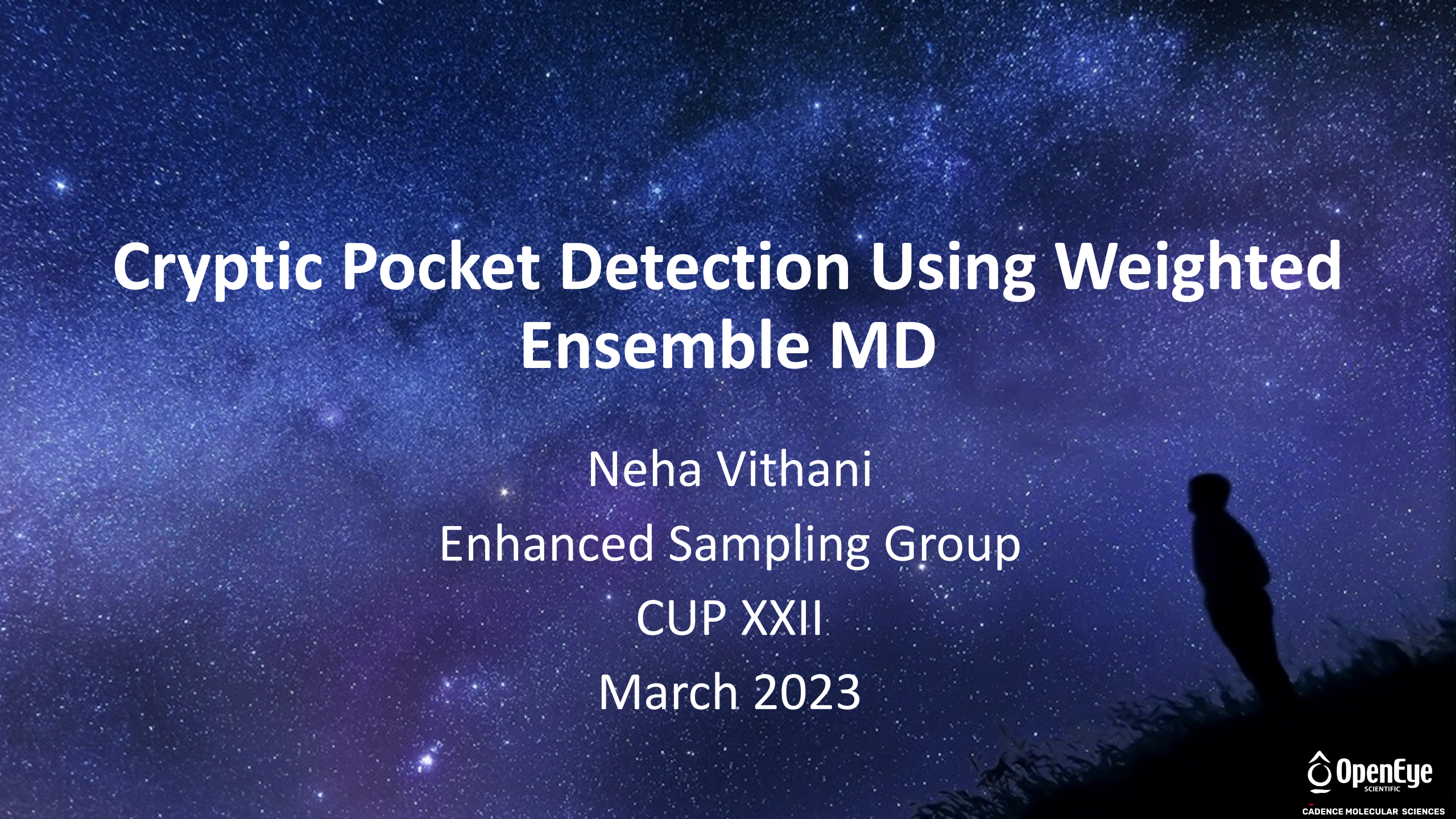
Enhanced Sampling Group

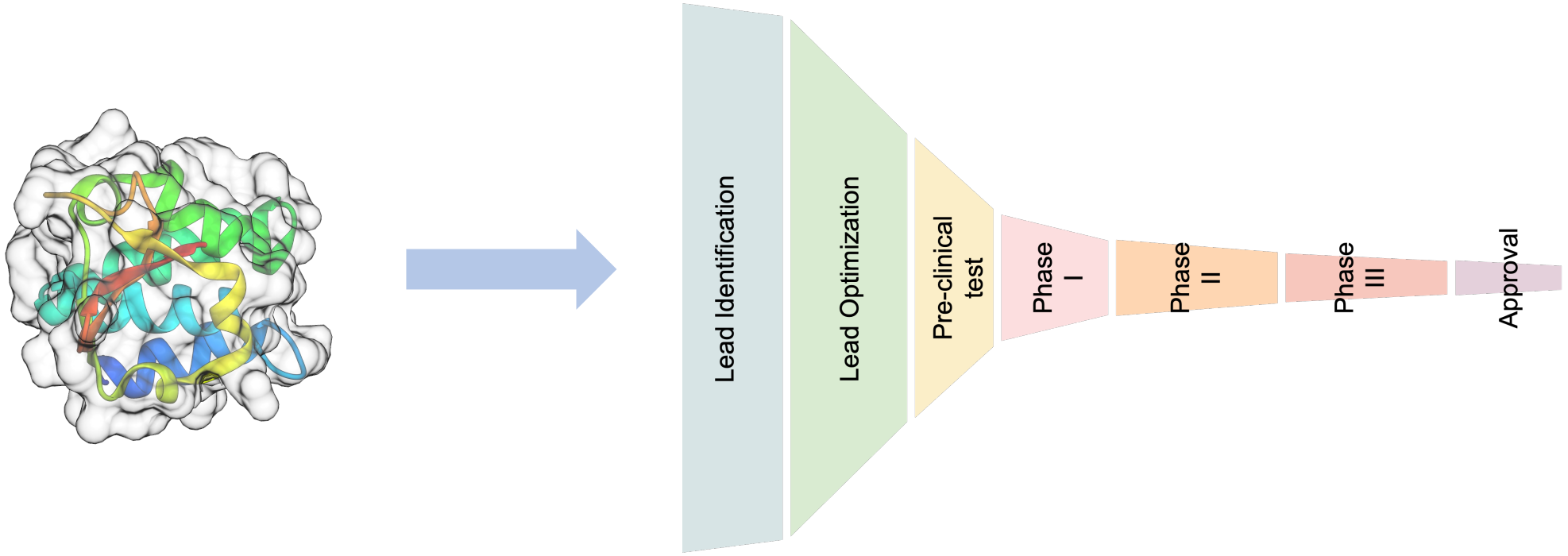
CUP XXII

March 2023

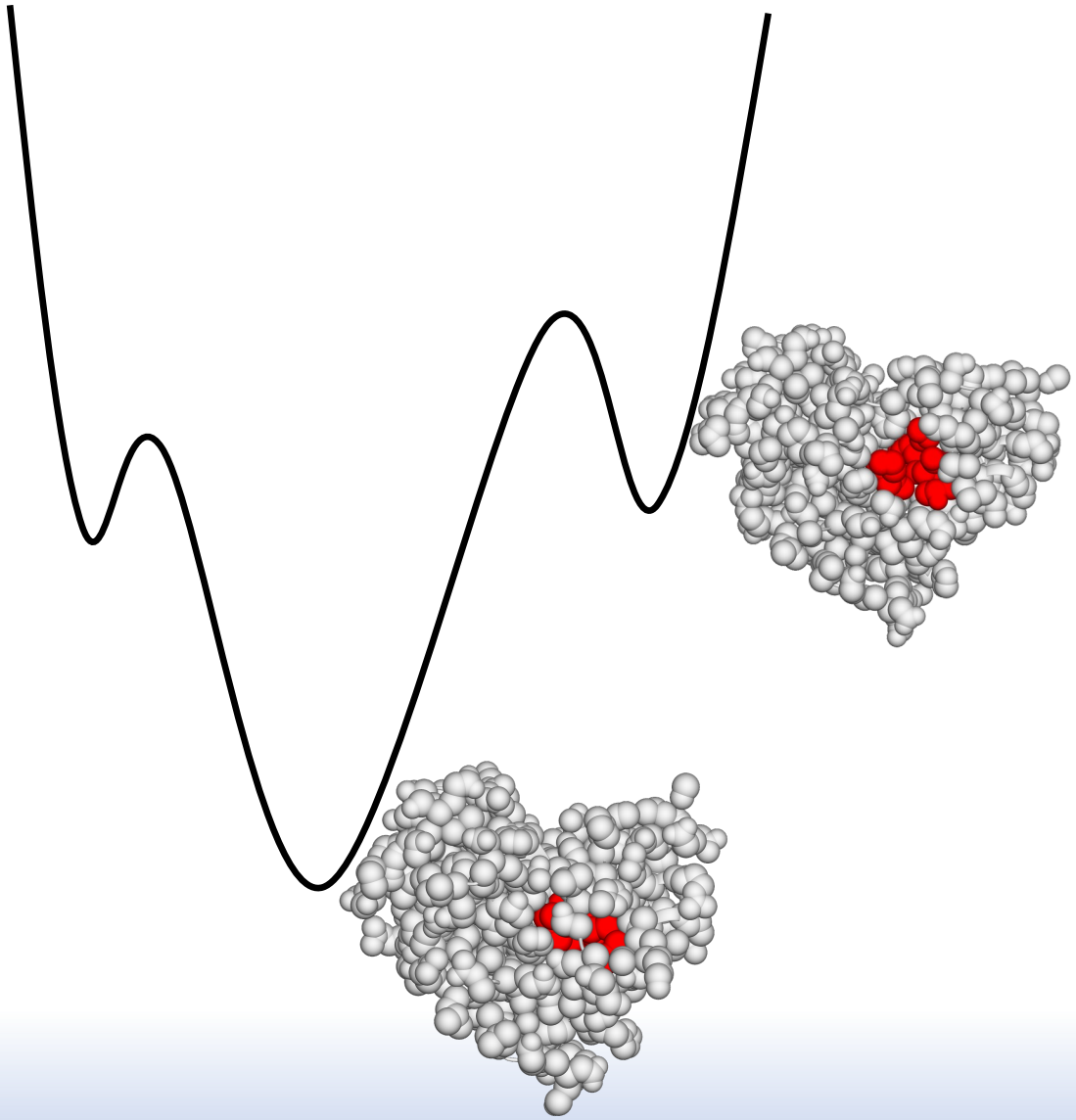


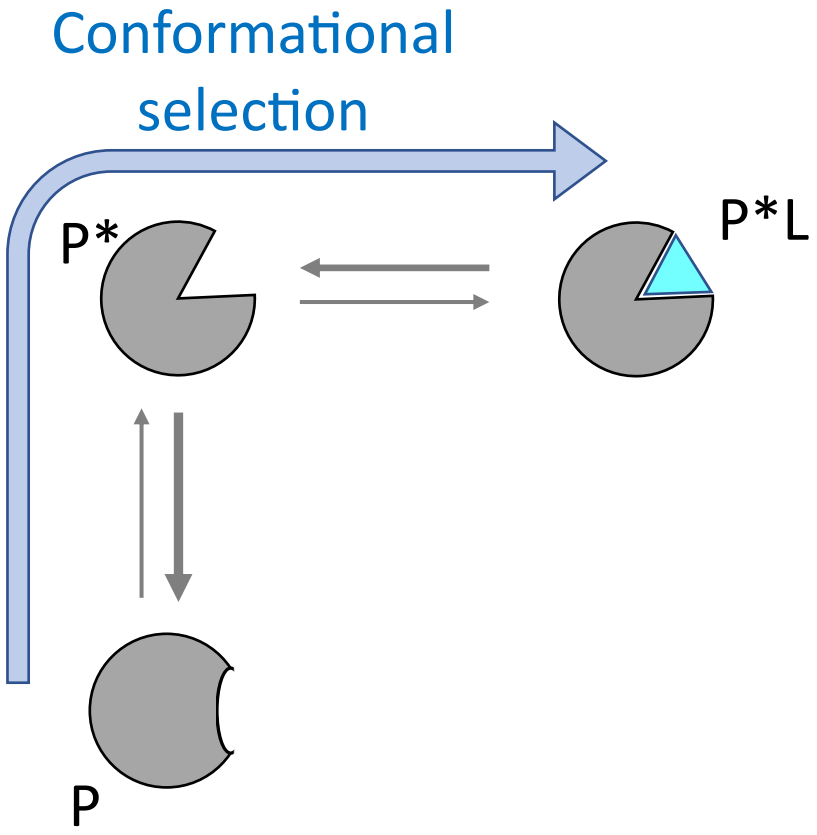
OpenEye SCIENTIFIC
CADENCE MOLECULAR SCIENCES

Is the target protein druggable?



What are cryptic pockets?





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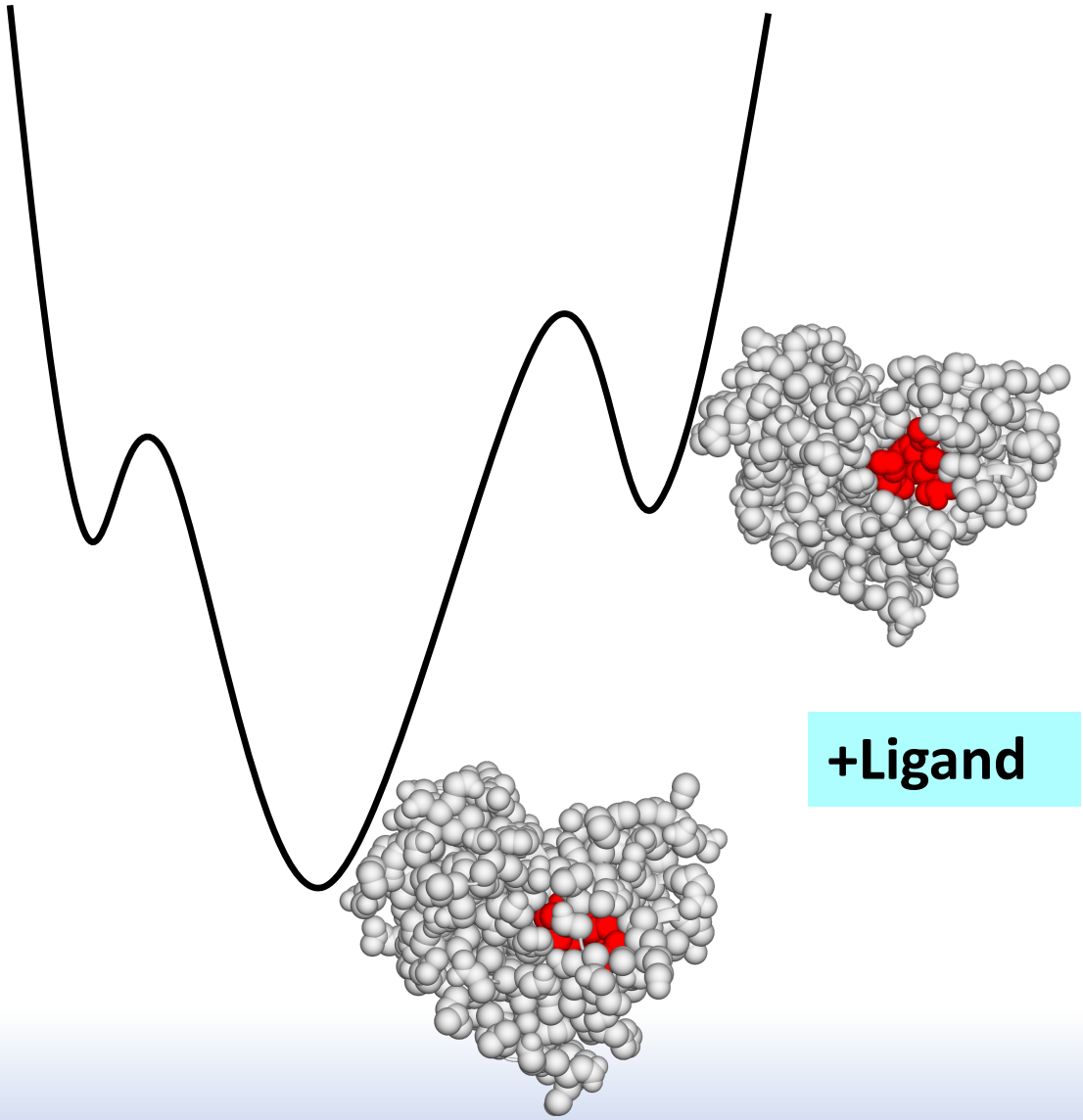
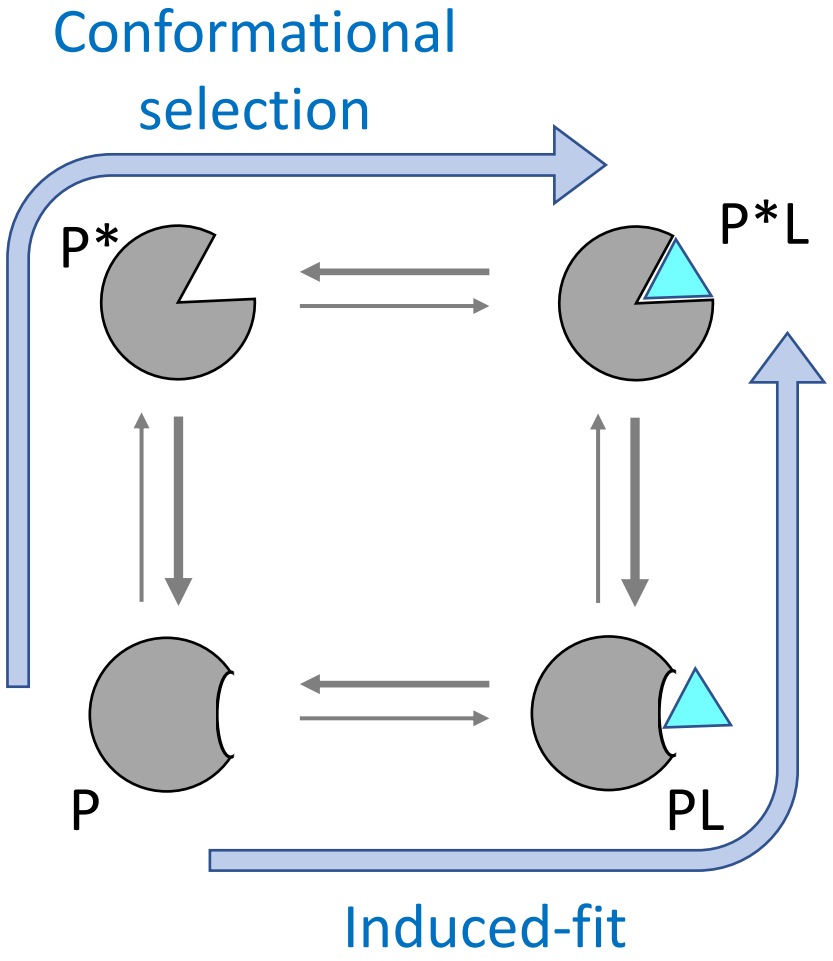
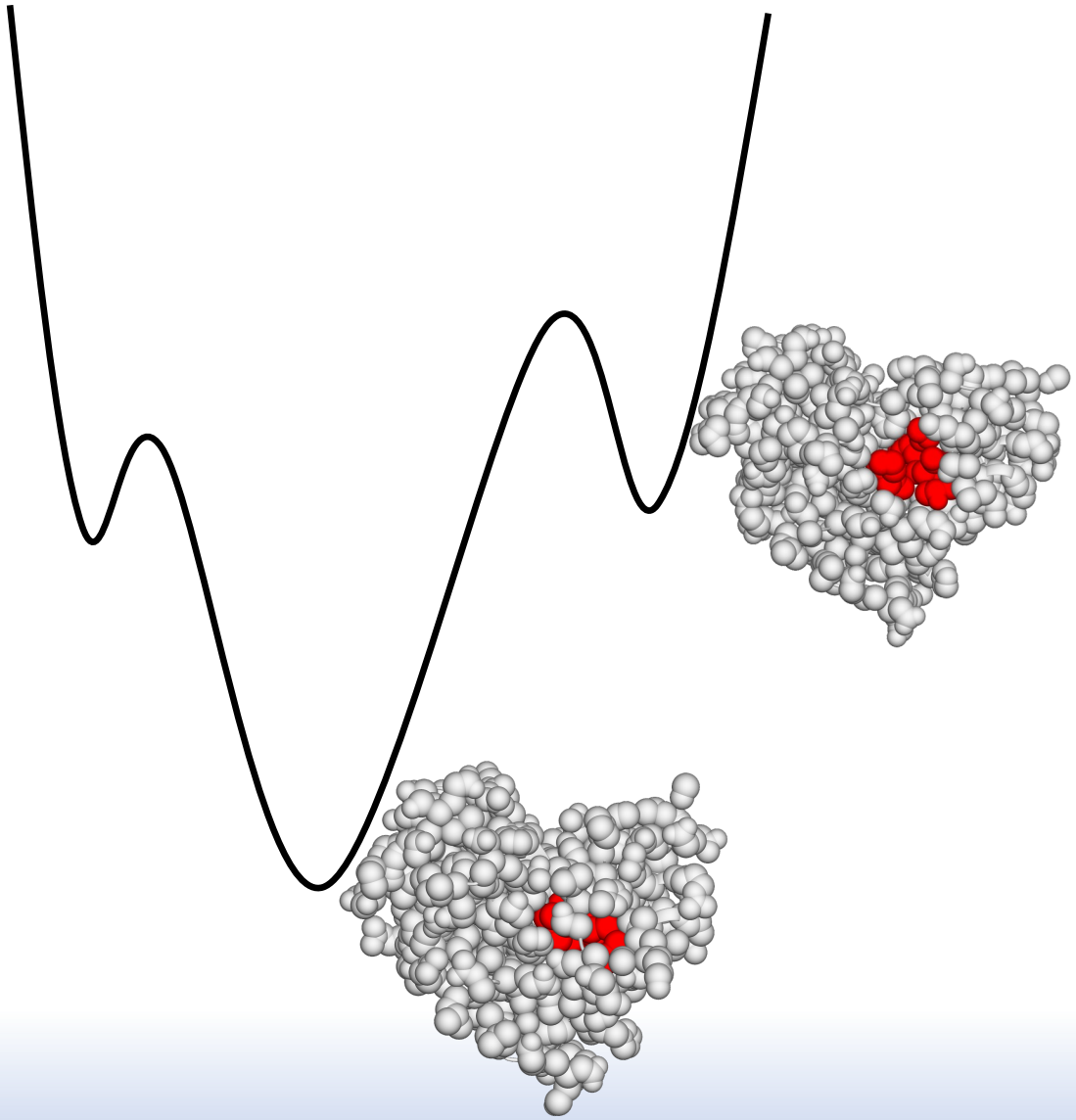
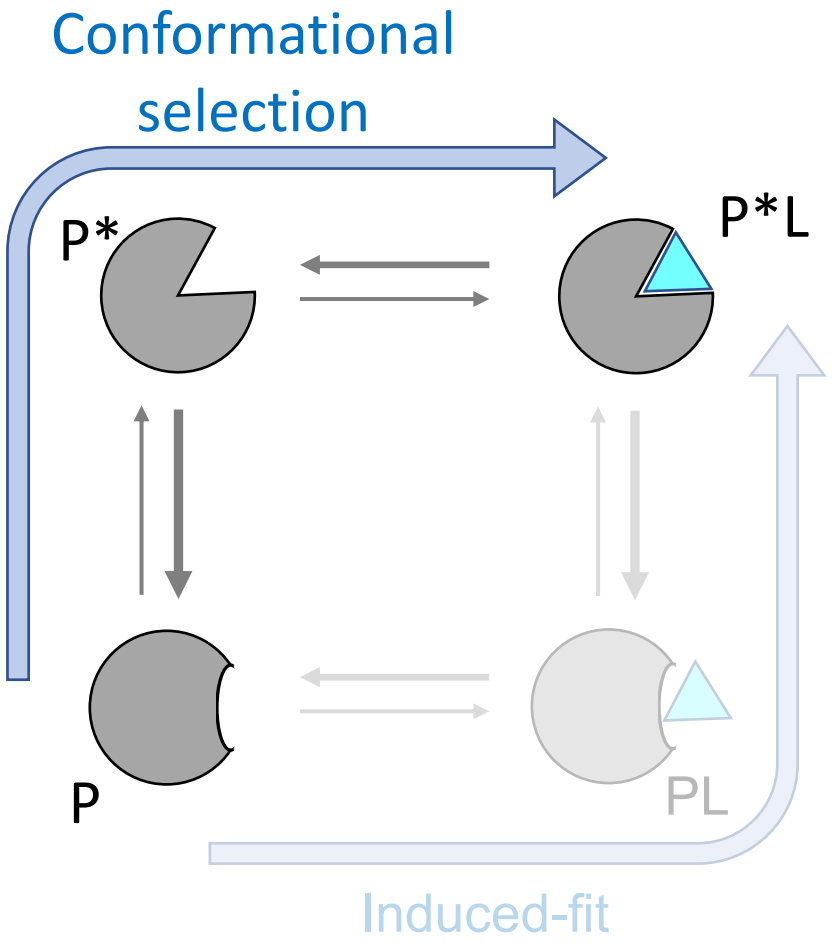


+Ligand



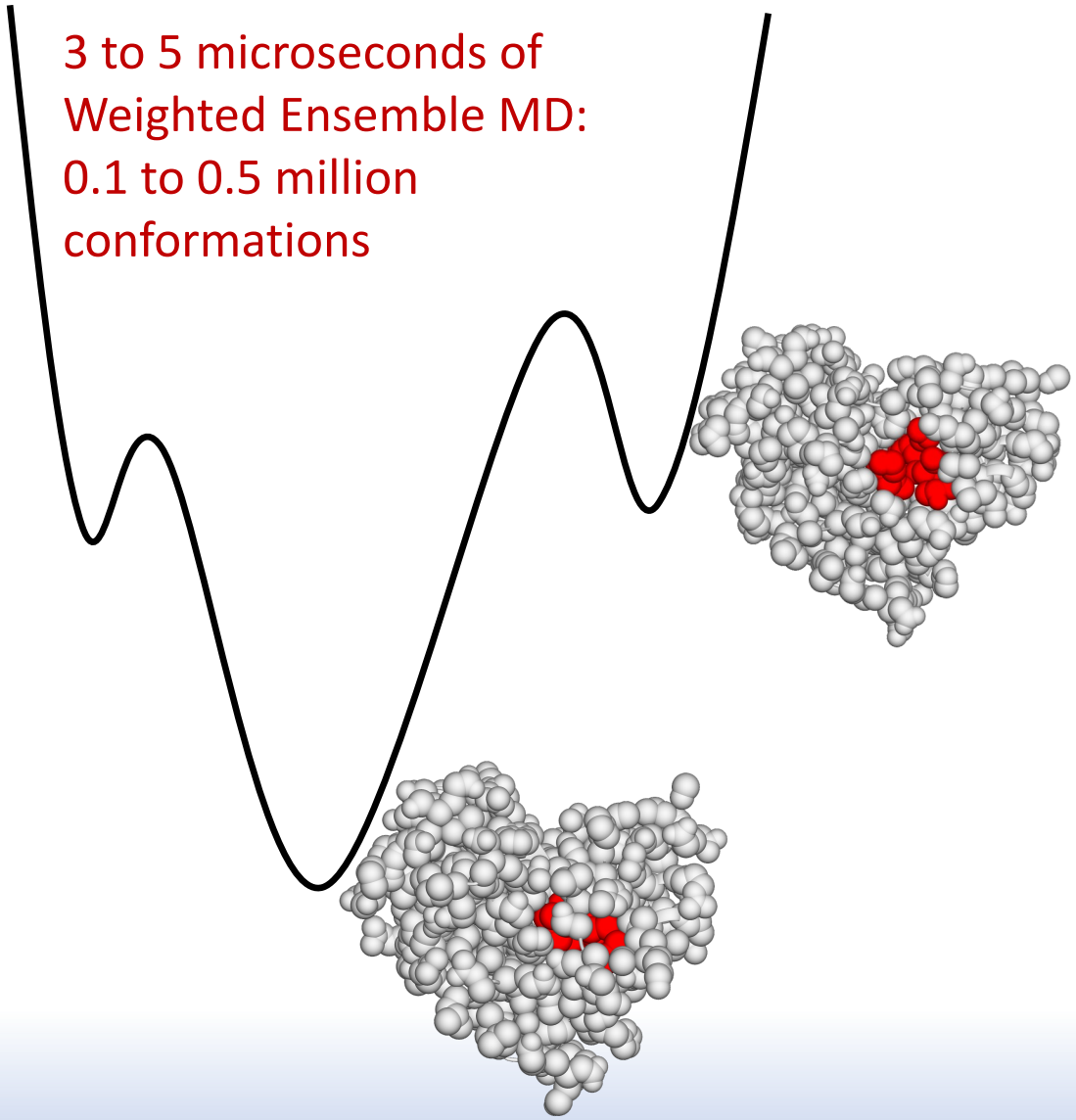
Finding cryptic pocket detection using weighted ensemble MD

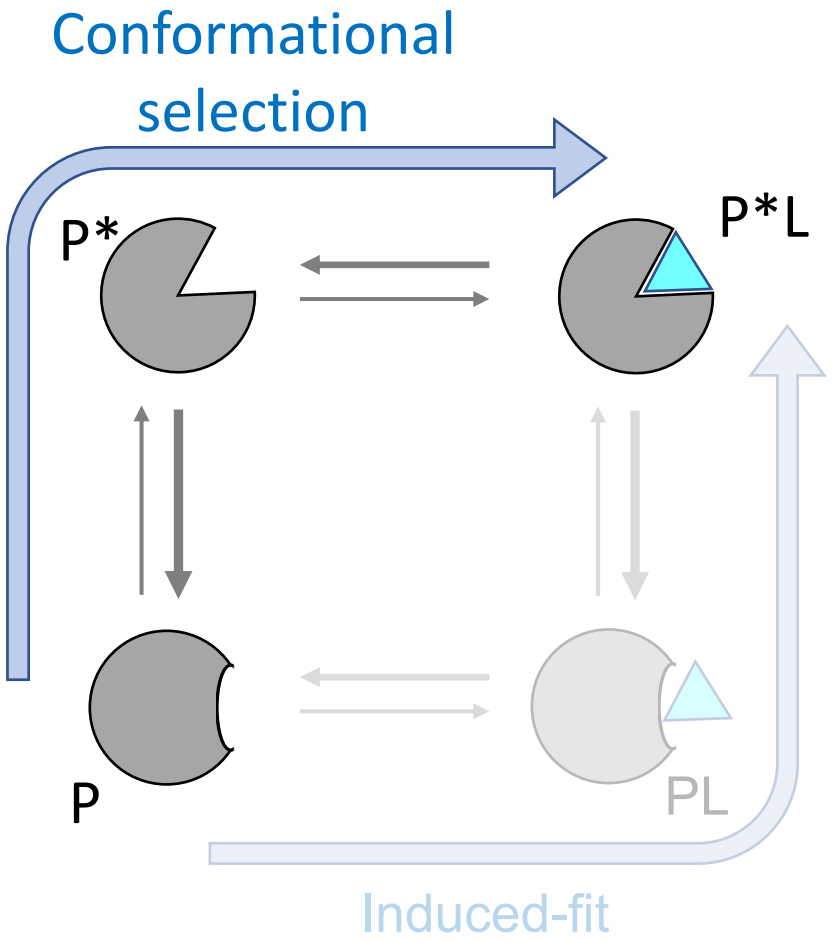




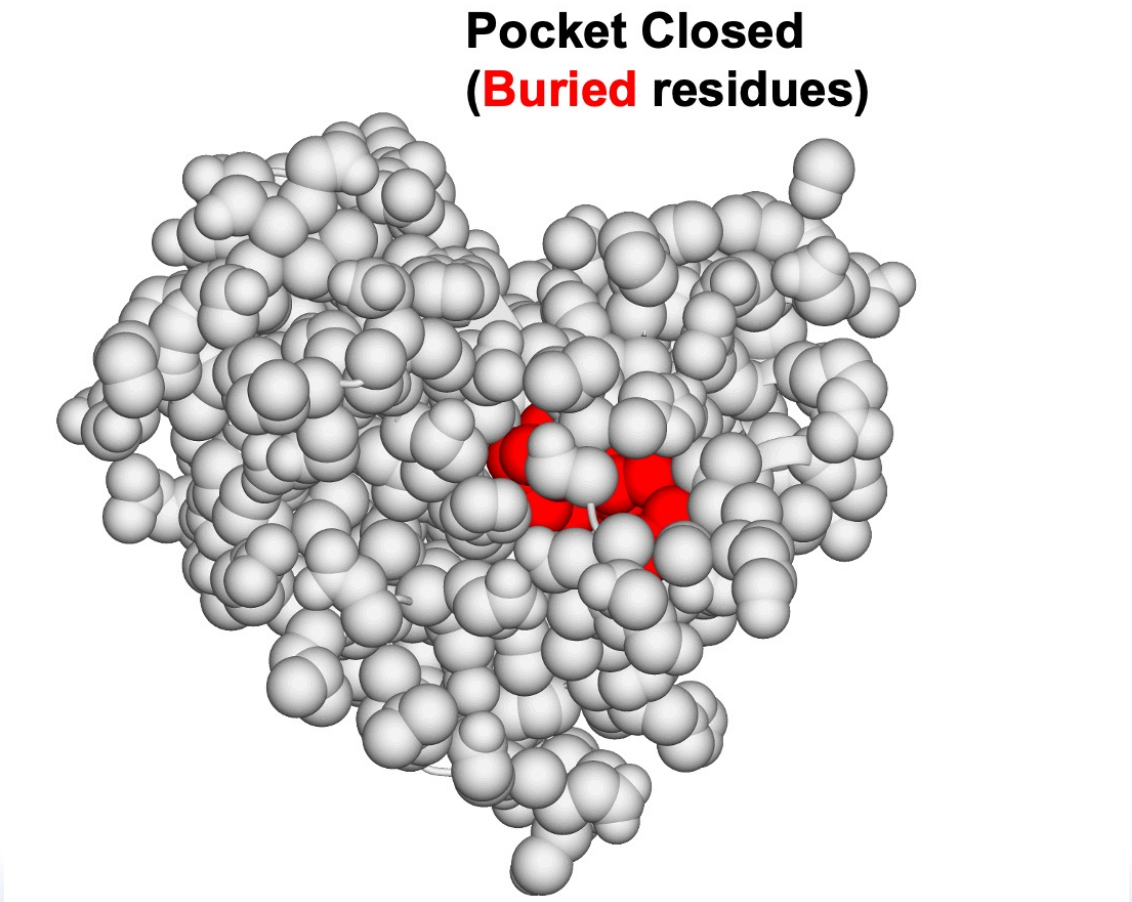
Finding cryptic pocket detection using weighted ensemble MD driven by normal mode analysis

3 to 5 microseconds of Weighted Ensemble MD: 0.1 to 0.5 million conformations



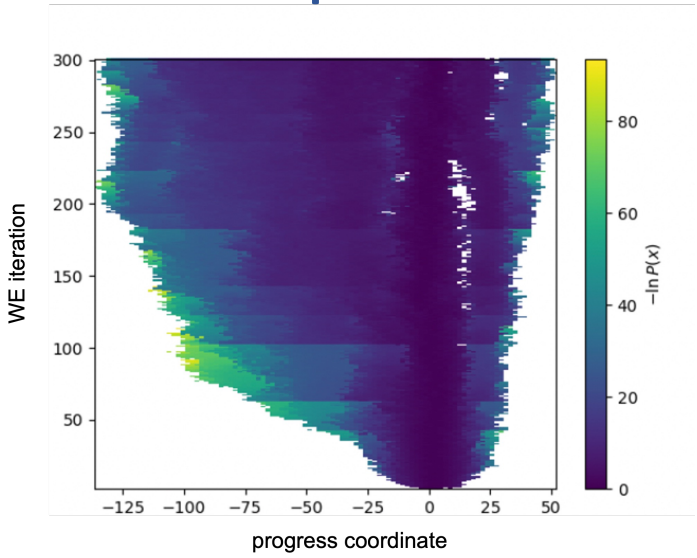


Exposon analysis: Identification of cooperative changes in residue solvent exposure



Porter et al, Biophys J (2019), 116:818

Characterization of WE MD conformations by similarity in per-residue solvent exposure



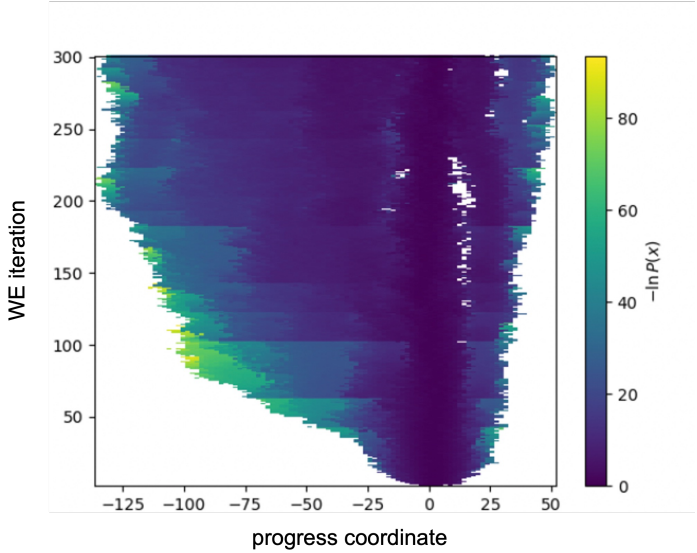
WE MD conformations

↓

Per-residue solvent accessible surface area

S_n: $[s_1, s_2, s_3, \ldots, s_r]$

Clustering WE MD data by similarity in per-residue solvent exposure

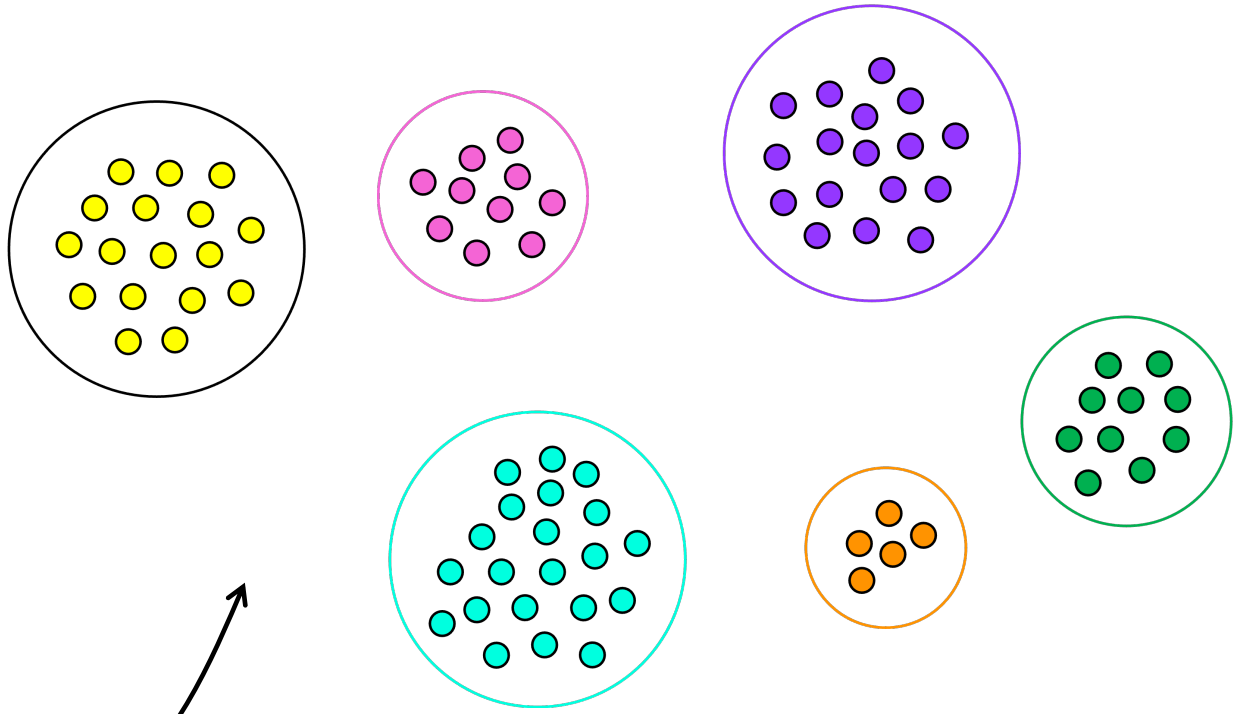


WE MD conformations

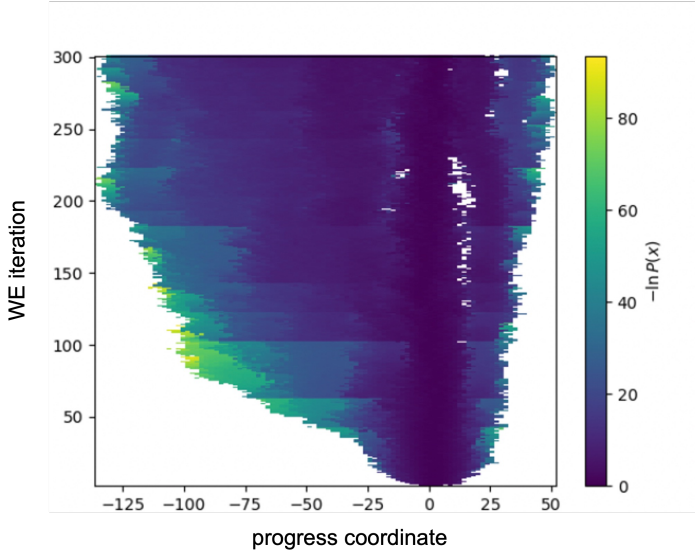
Per-residue solvent accessible surface area

S_n: $[s_1, s_2, s_3, \ldots, s_r]$

Clustering



Markov state model of protein dynamics



WE MD conformations

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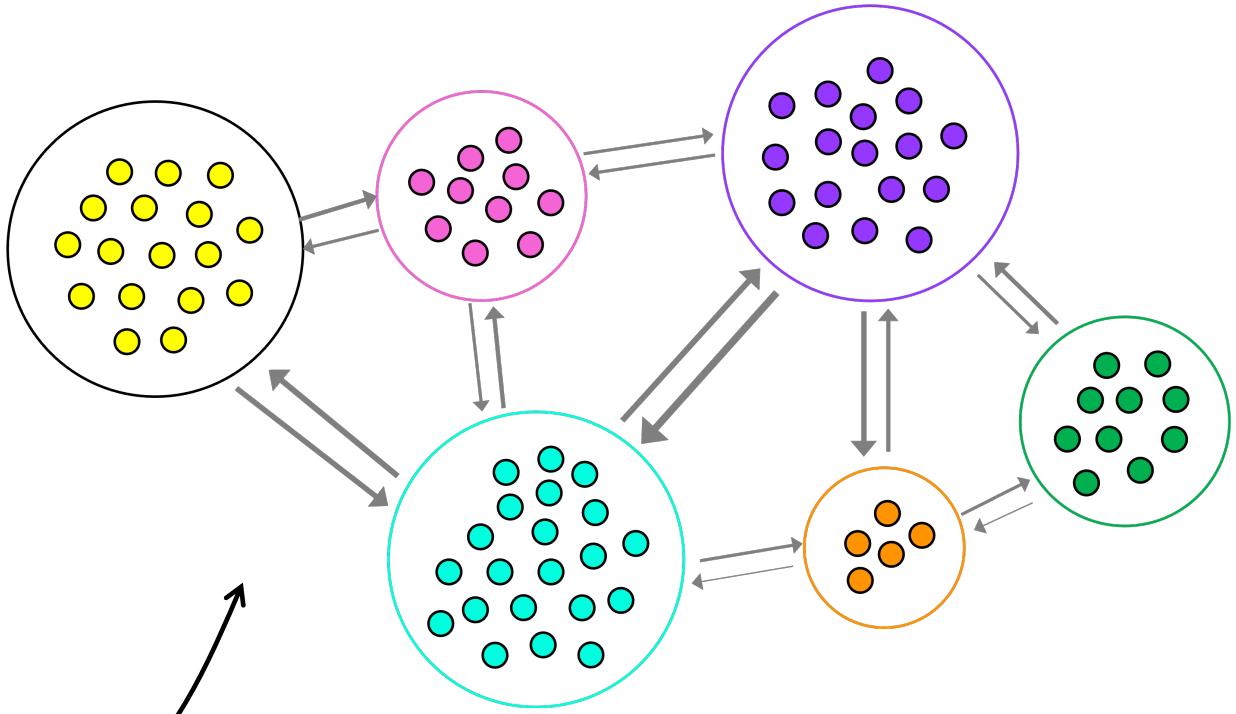


$\{P_1, P_2, P_3, \ldots, P_m\}$

Measurement of correlated changes in solvent exposure

Cluster center SASA feature vectors:

$$[s_1, s_2, s_3, \ldots, s_r]_1$$

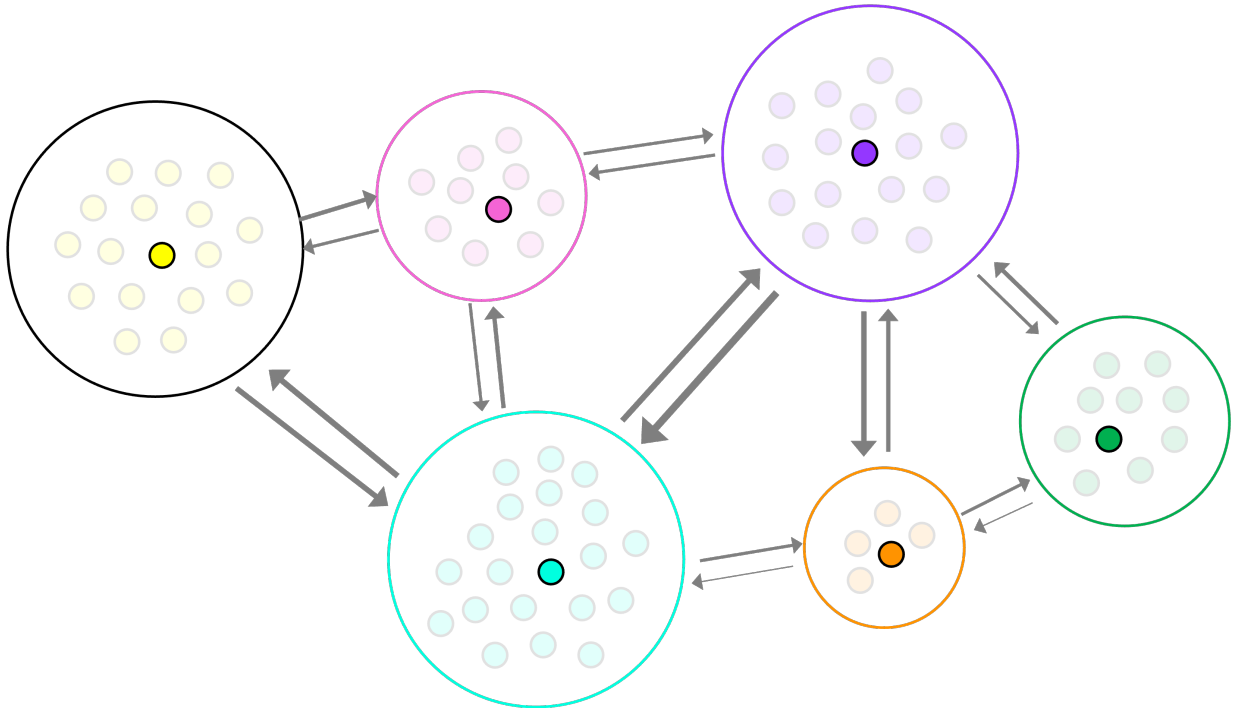
$$[s_1, s_2, s_3, \ldots, s_r]_2$$

$$[s_1, s_2, s_3, \ldots, s_r]_3$$

$$\vdots$$

$$[s_1, s_2, s_3, \ldots, s_r]_m$$

Equilibrium population: $\{P_1, P_2, P_3, \ldots, P_m\}$



Measurement of correlated changes in solvent exposure

$$I(X,Y) = \sum_{x \in X} \sum_{y \in Y} p(x,y)\, log\left(\frac{p(x,y)}{p(x)p(y)}\right)$$

$(X,Y):$ *A pair of residues*

$x:$ *solvent exposure state of residue X*

$y:$ *solvent exposure state of residue Y*

Measurement of correlated changes in solvent exposure

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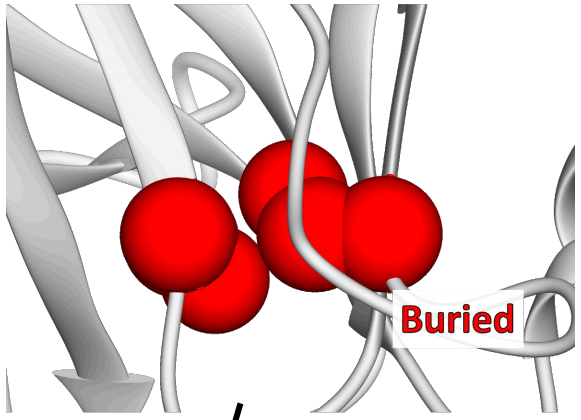

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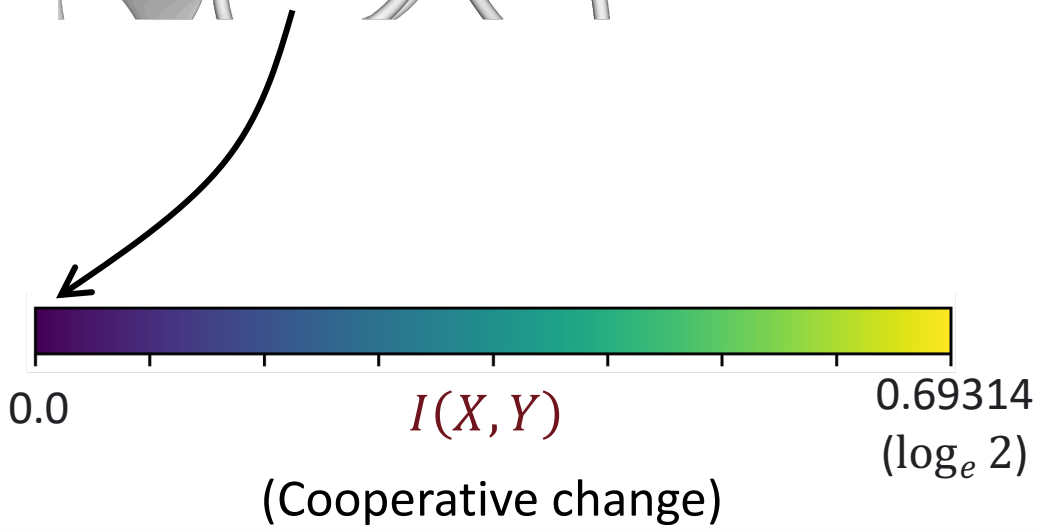

(Cooperative change)

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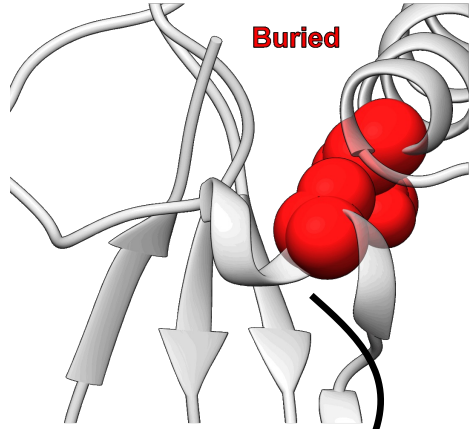

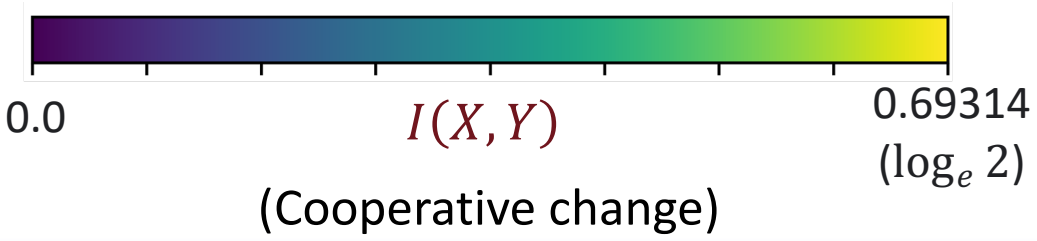

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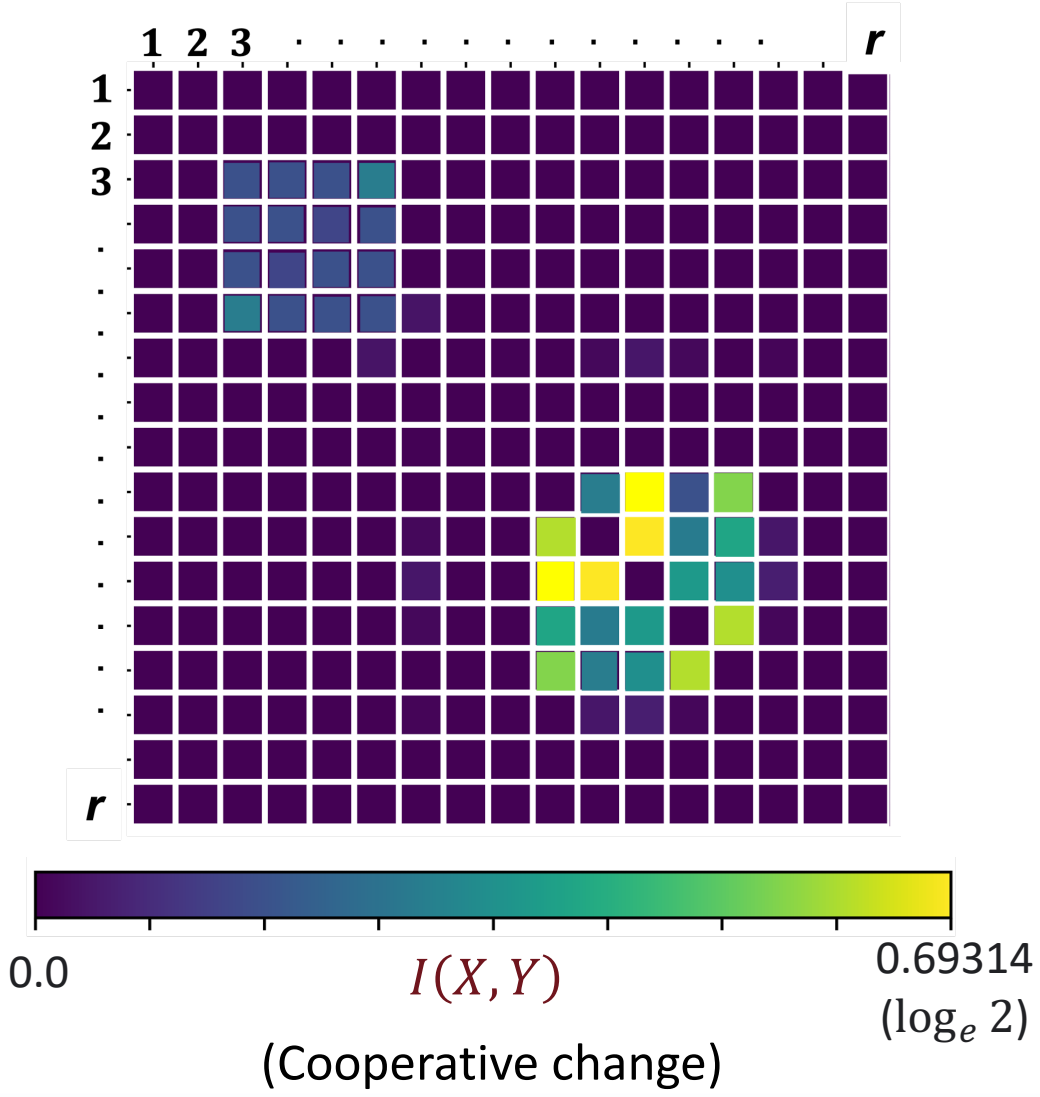
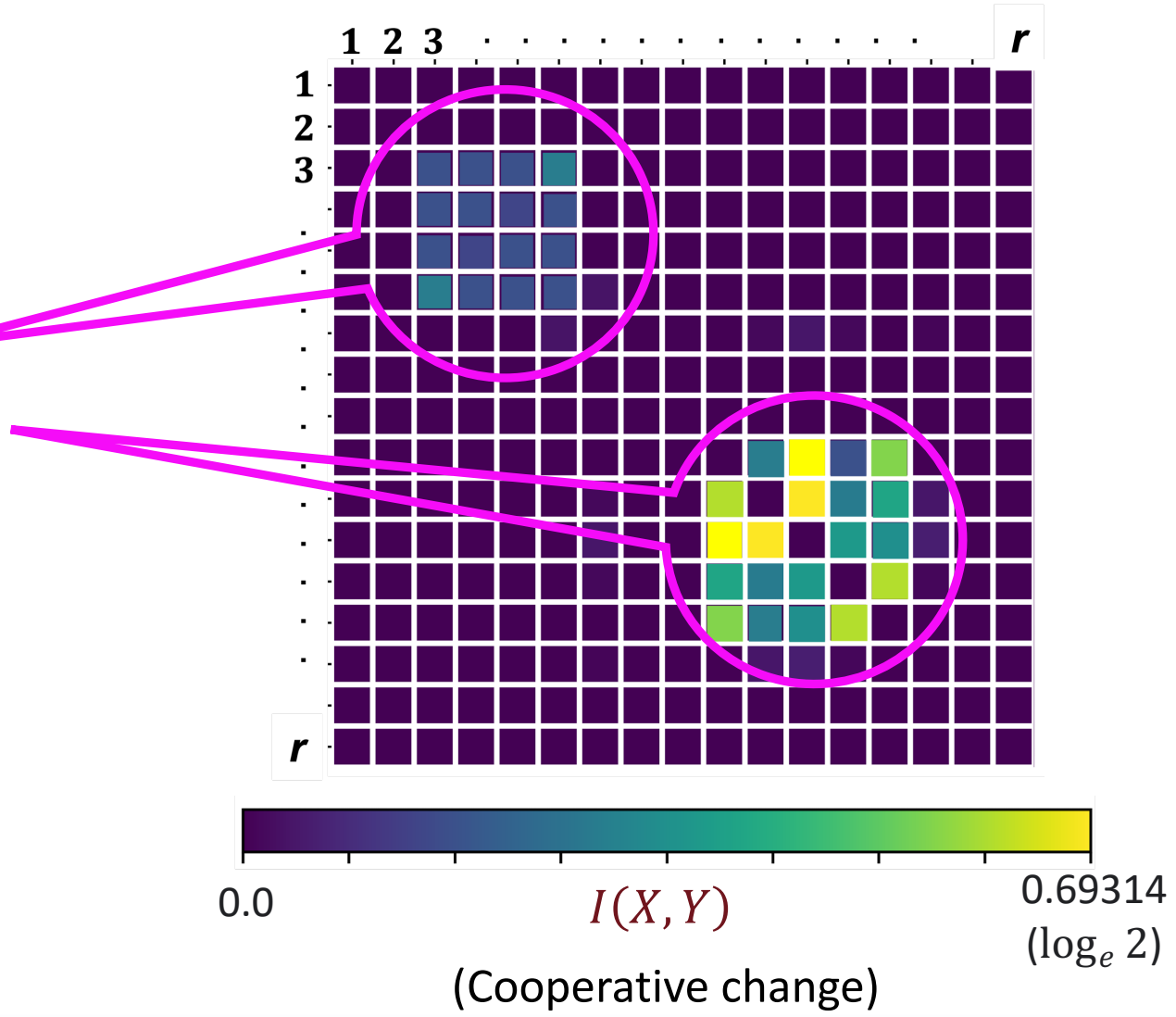


(Cooperative change)

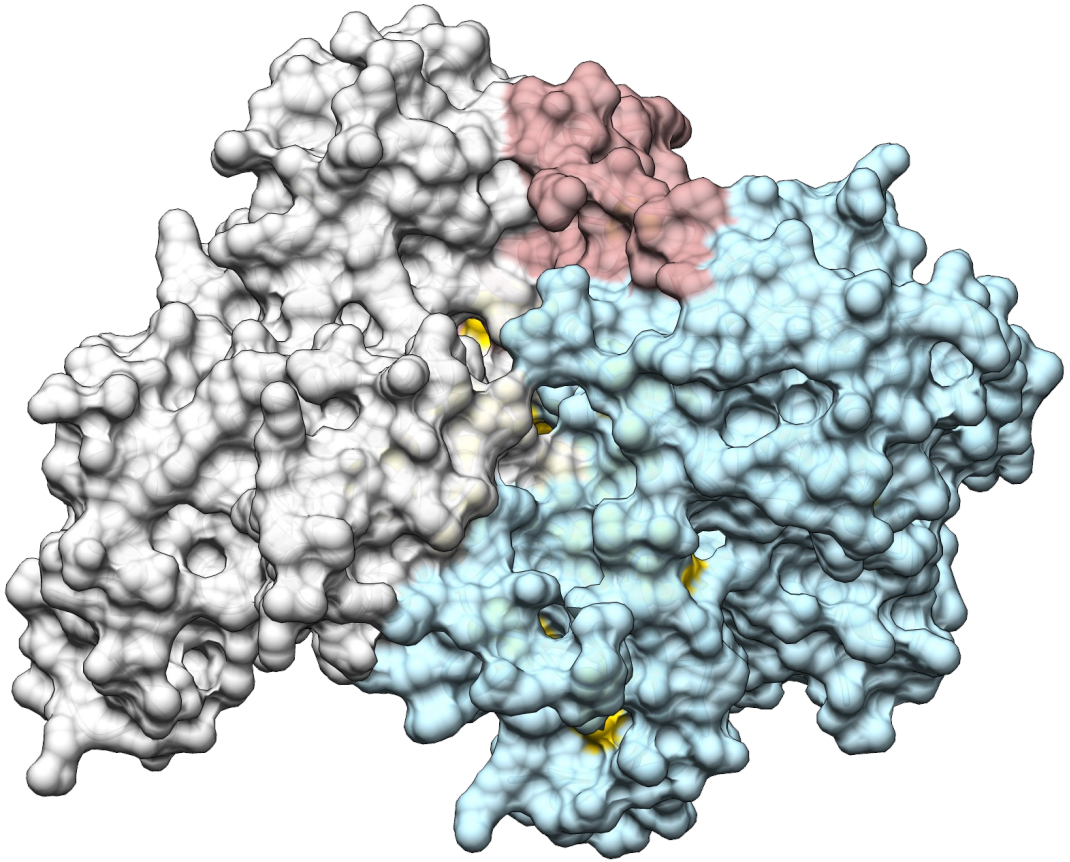
Measurement of correlated changes in solvent exposure

Exposon: A group of residues undergoing collective changes in solvent exposure




“OPEN SESAME!”

Does a pocket hide beneath the protein surface?



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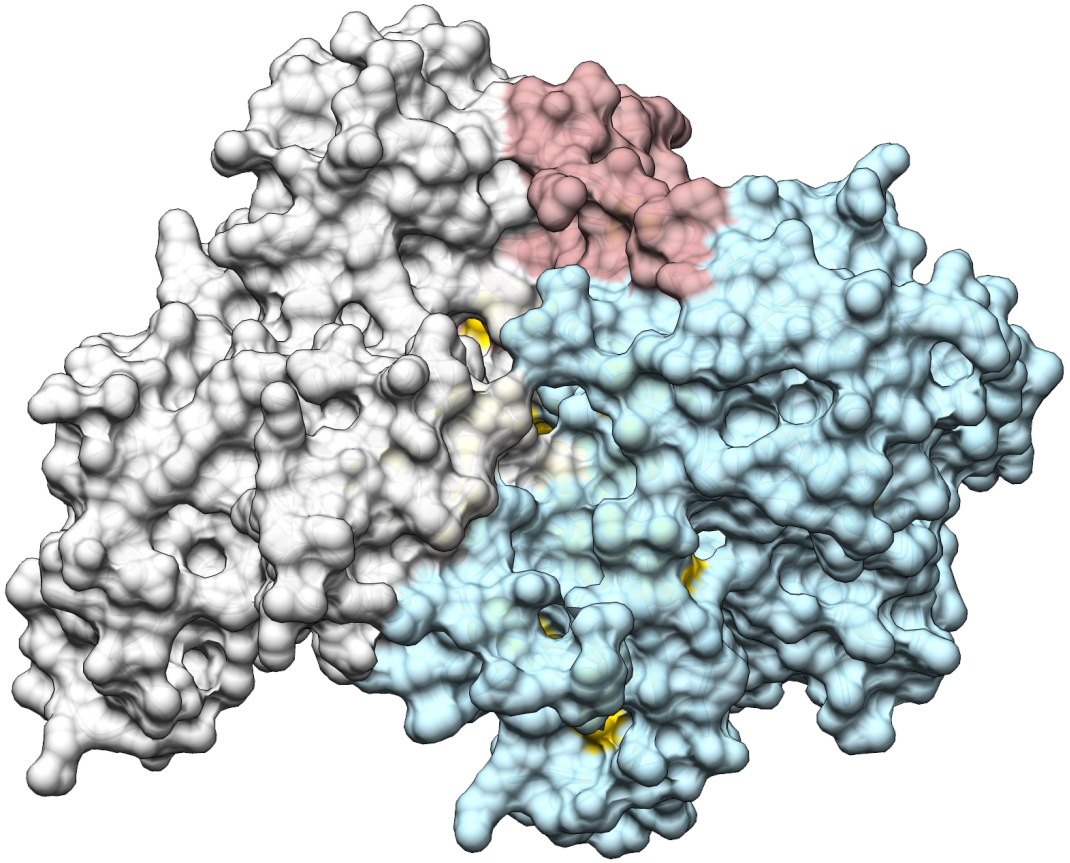
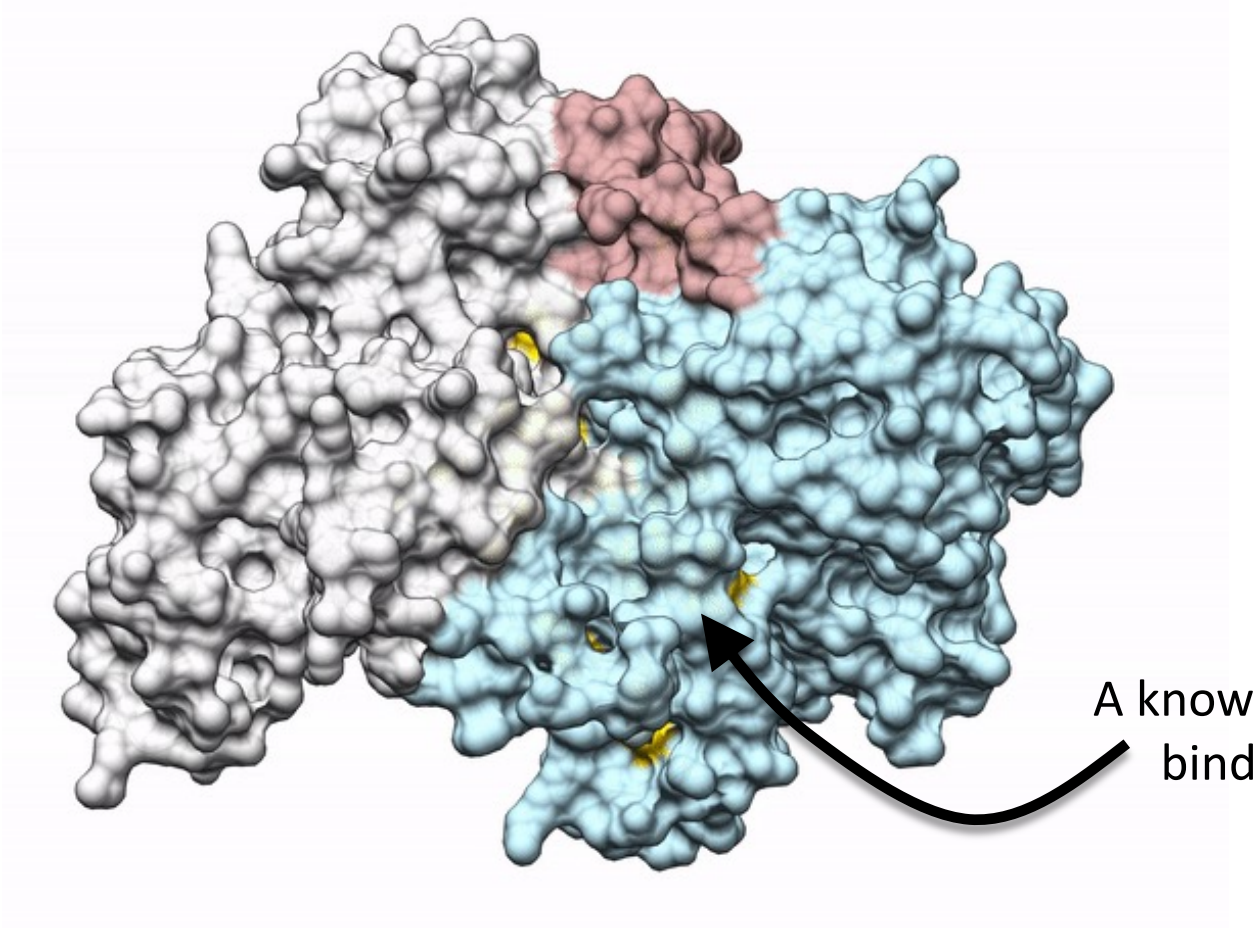


CDK activating kinase (CAK)
Popular cancer target – controls transcription initiation and participates in cell cycle

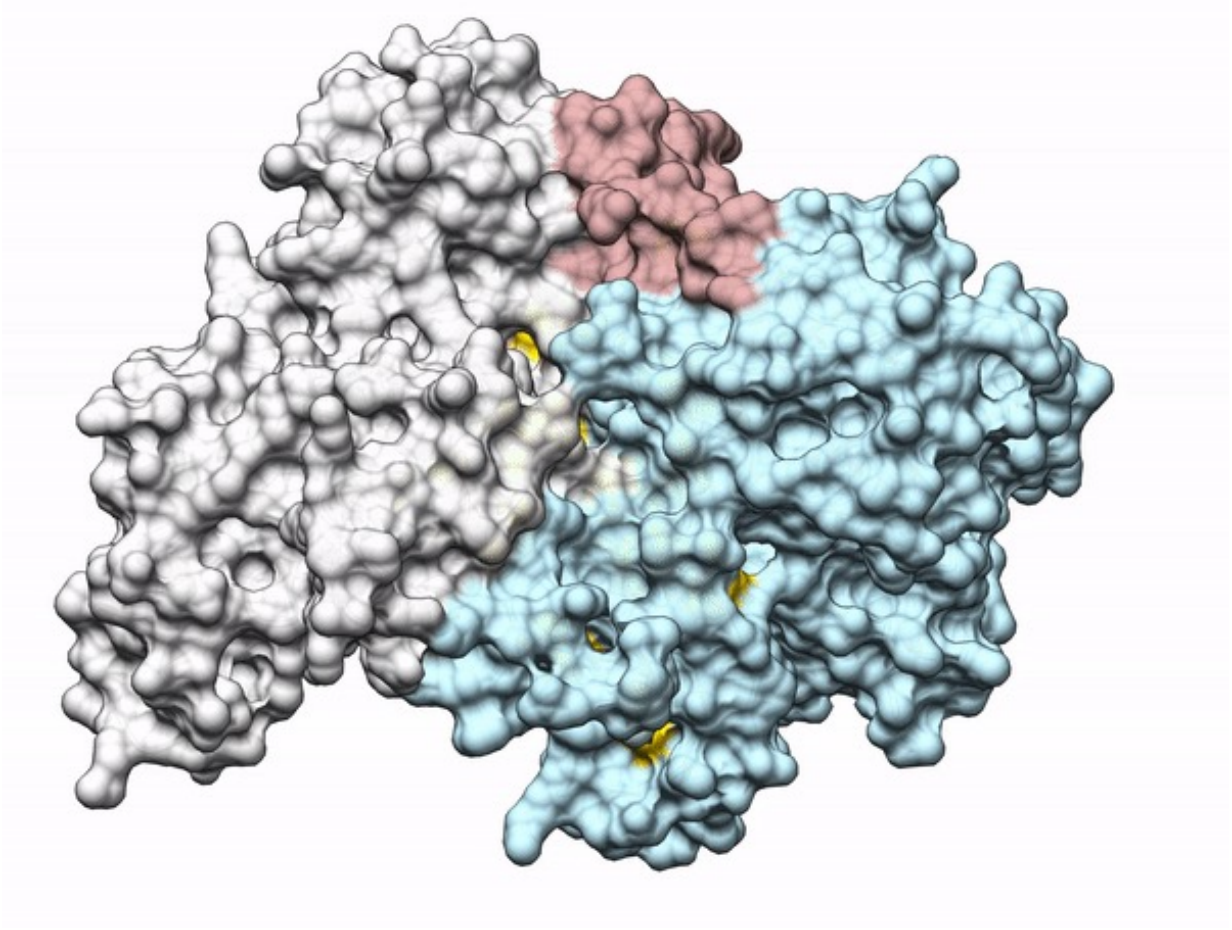
WE MD simulations of Apo CAK:
~8 microseconds

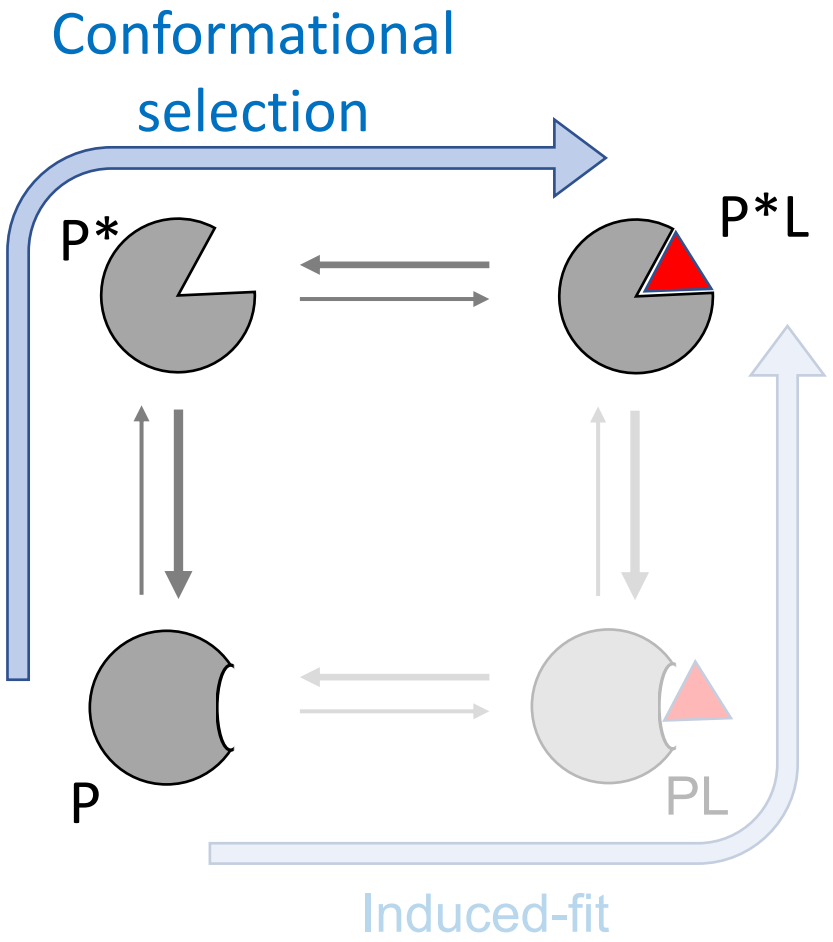
“EXPOSON ANALYSIS!”

Exposon analysis reveals a pocket in CAK



Finding cryptic pocket detection from molecular dynamics





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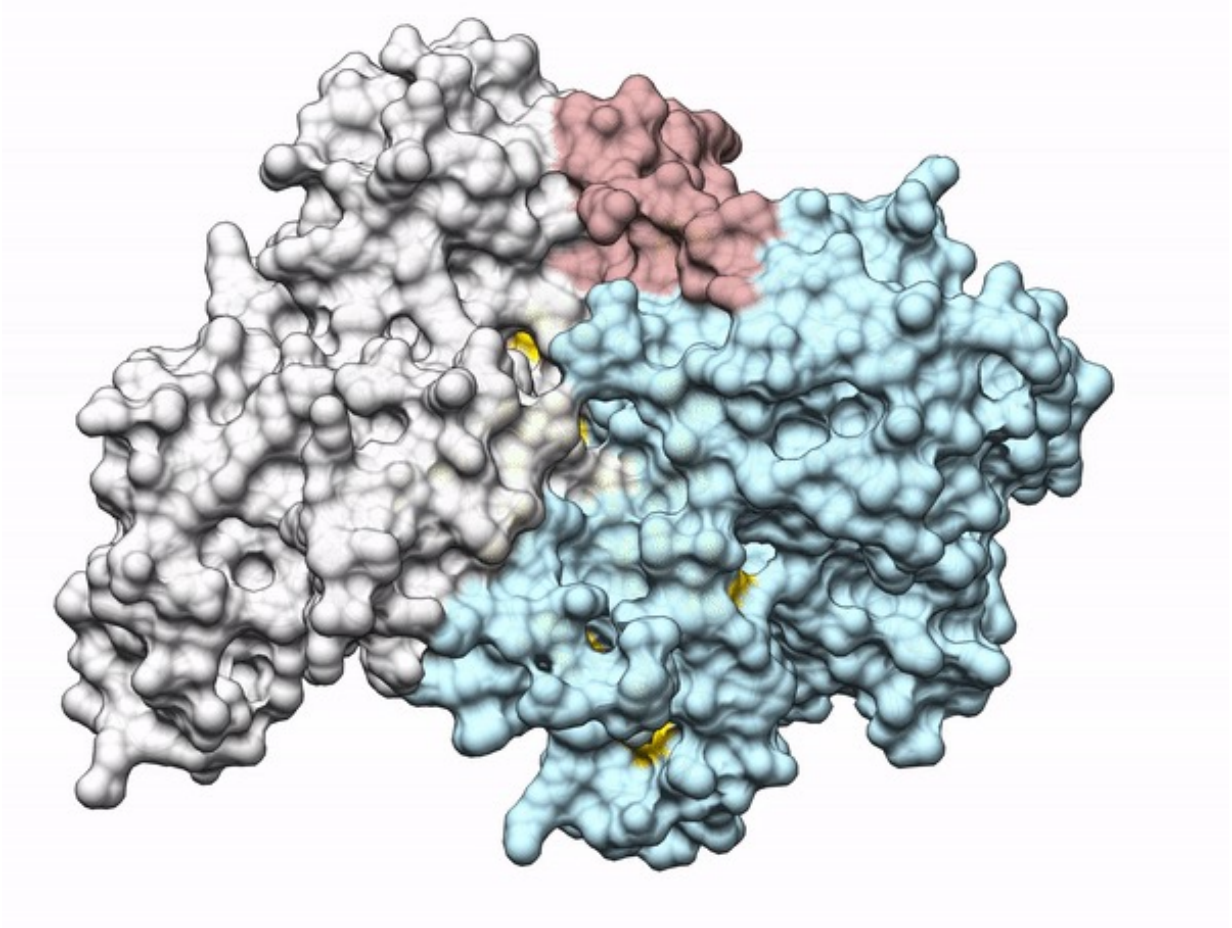
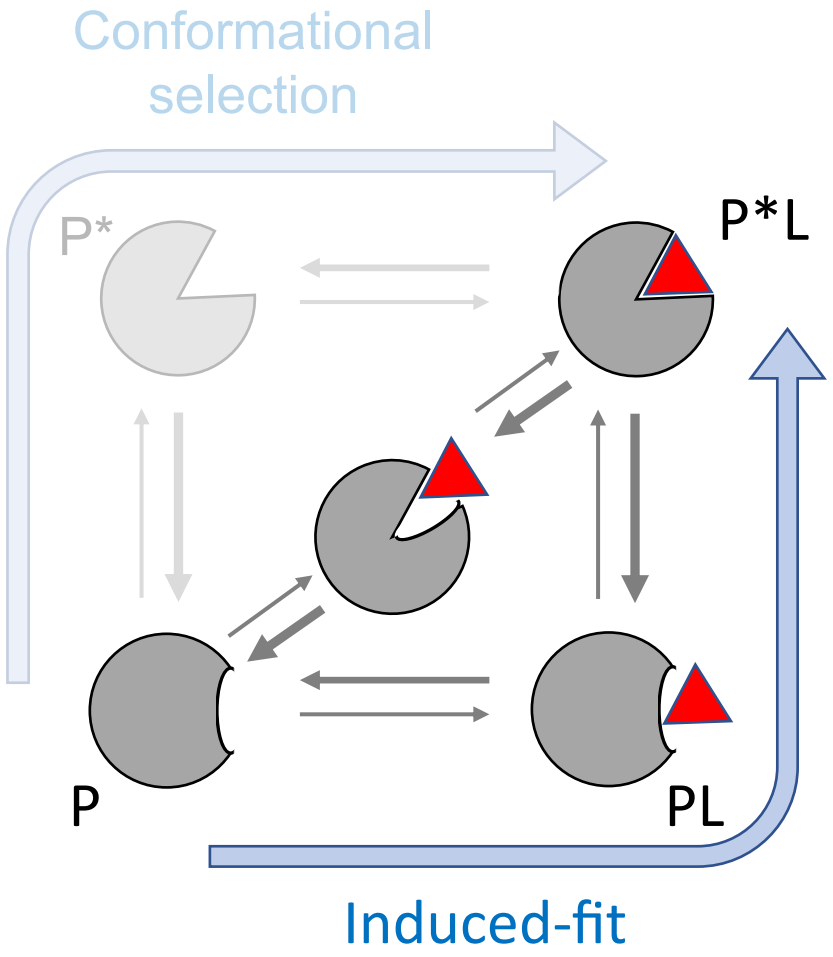
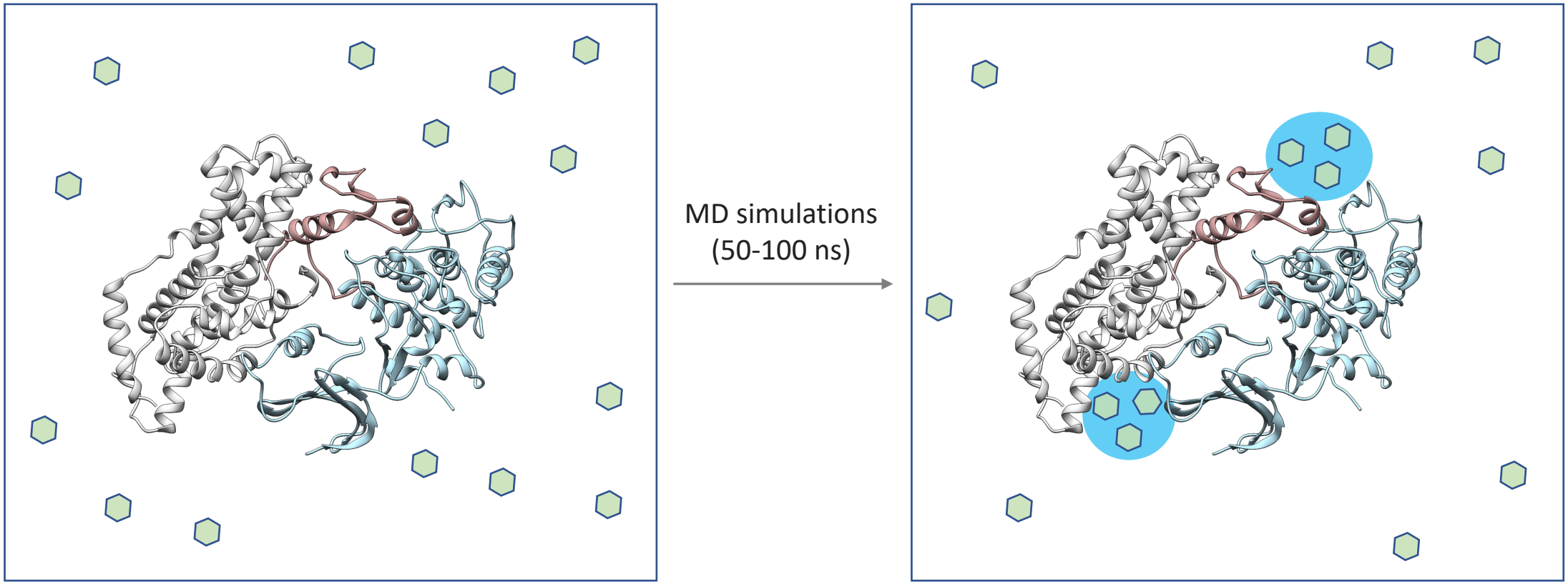




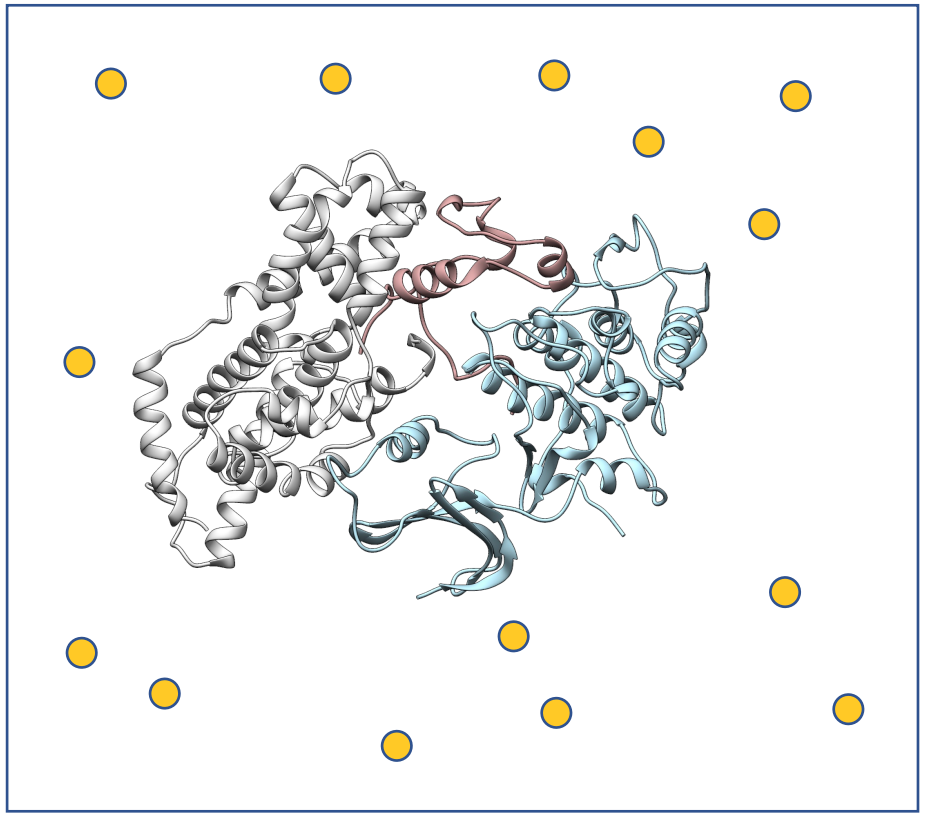
Cryptic pocket detection using mixed-solvent MD simulations

Detection of hydrophobic cavities using probe molecules (**benzene, phenol, isopropanol**)



Martinez-Rosell G et al, J. Chem. Inf. Model. 2020, 60, 2314
Kimura SR et al., J. Chem. Inf. Model. 2017, 57, 1388
Lexa, K. W.; Carlson, H. A. J. Am. Chem. Soc. 2011, 133, 200
Schmidt, D et al, J. Chem. Theory Comput. 2019, 15, 3331
Tan YS et al, J. Chem. Inf. Model. 2014, 54, 1821

Mixed-solvent MD using xenon as the probe (cosolvent)



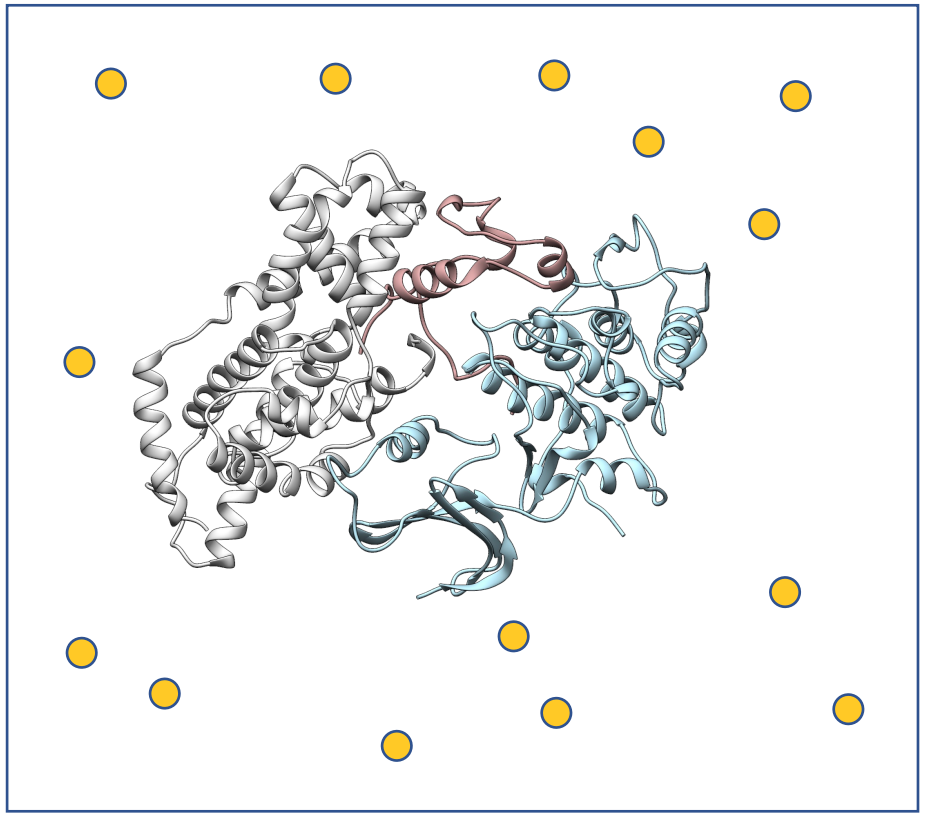
Xenon as a probe:

- Non-selective binding to hydrophobic sites[1]
- Fast diffusion[2]
- Xenon localization has been observed in pocket composed of hydrophobic and hydrophilic residues[1]

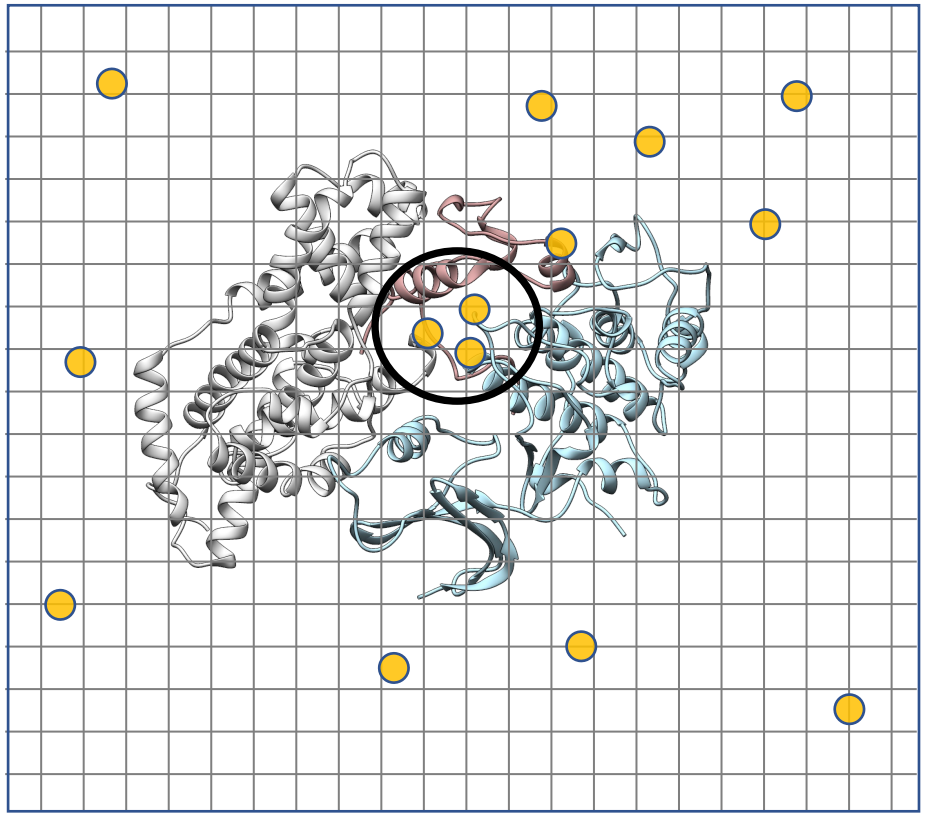
1. Schiltz M et al., Structure. 1995, 3, 309
2. Zhao Z et al., Biophys J. 2022 Dec 6;121(23):4635

Mixed-solvent WE MD simulations of CAK

150 mM Xenon + TIP3P water



Cosolvent binding free energy grid

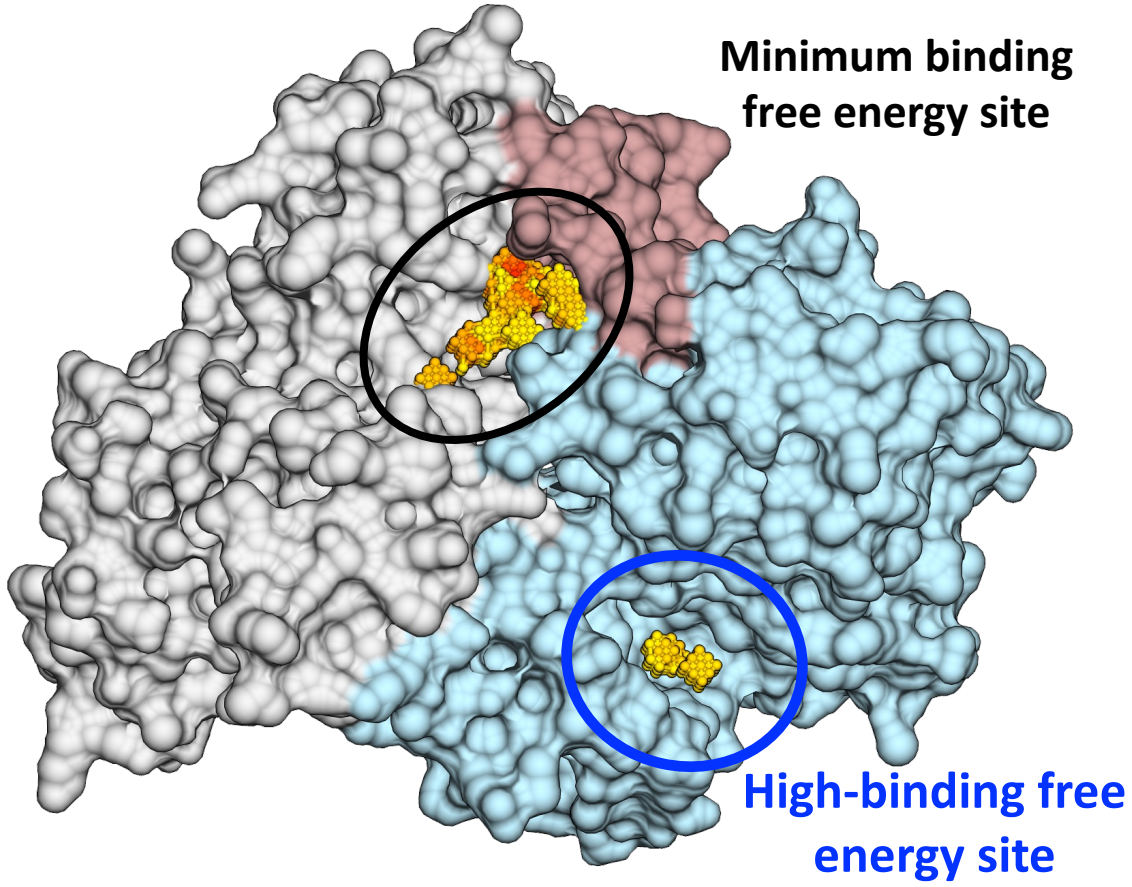


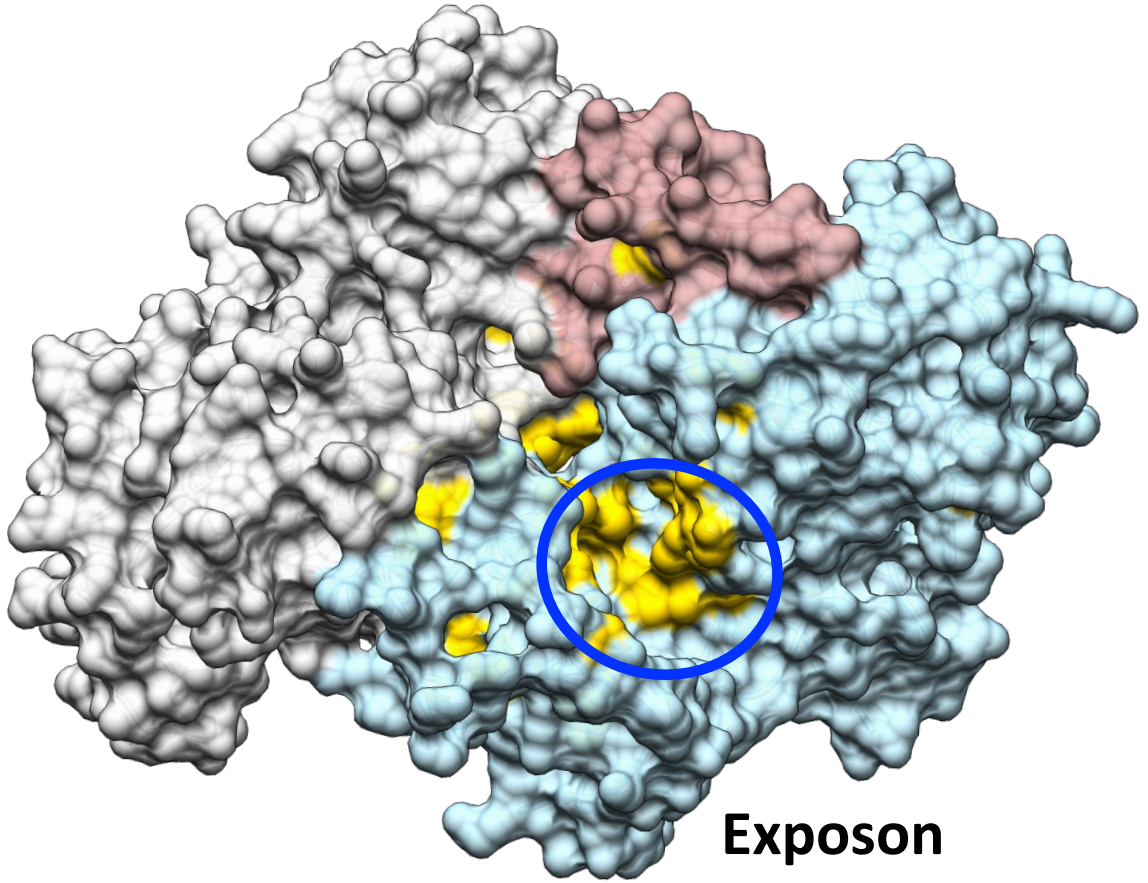
$$\Delta G_{binding} = -k_B T \ln \left[\frac{N_i}{N_0}\right]$$

N_i : Cosolvent occupancy in the grid cell
N_0 : Expected grid occupancy in the bulk solvent
k_B : Boltzmann constant (kcal.mol^{-1}.K^{-1})
T : Simulation temperature (K)

Martinez-Rosell G et al, J. Chem. Inf. Model. 2020, 60, 2314
Kimura SR et al., J. Chem. Inf. Model. 2017, 57, 1388

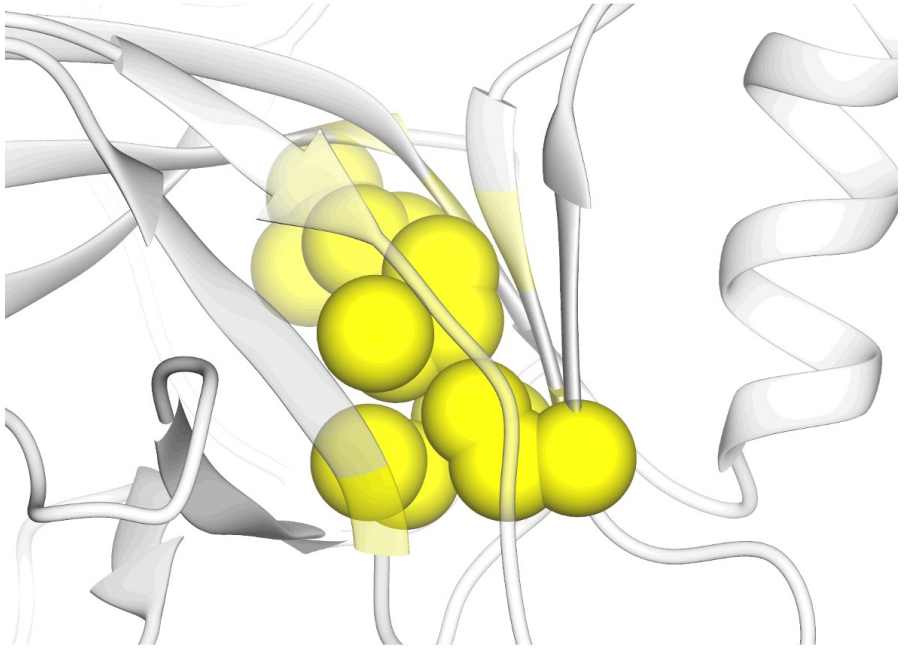
Xenon binding free energy grid reveals an additional pocket in CAK



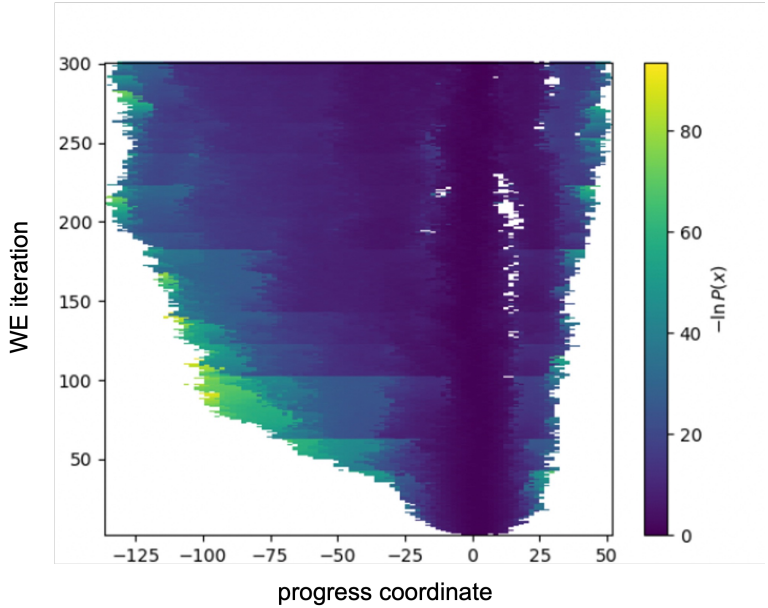


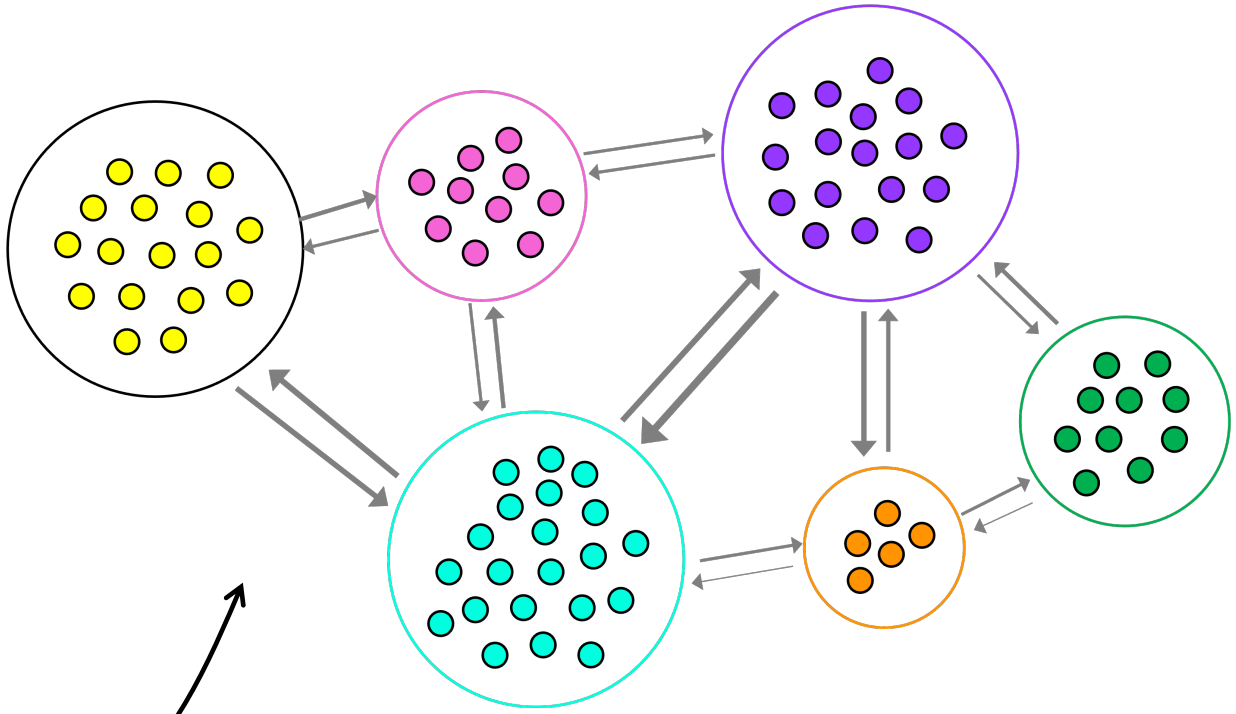
Using information theory to find cosolvent-binding sites

Detection of cryptic pockets as residues that show collective cosolvent-binding behavior



Markov state model of protein dynamics





Residue-cosolvent minimum distance

D_n: $[d_{11}, d_{12}, d_{13}, \ldots, d_{rx}]$

K-means clustering

$\{P_1, P_2, P_3, \ldots, P_m\}$

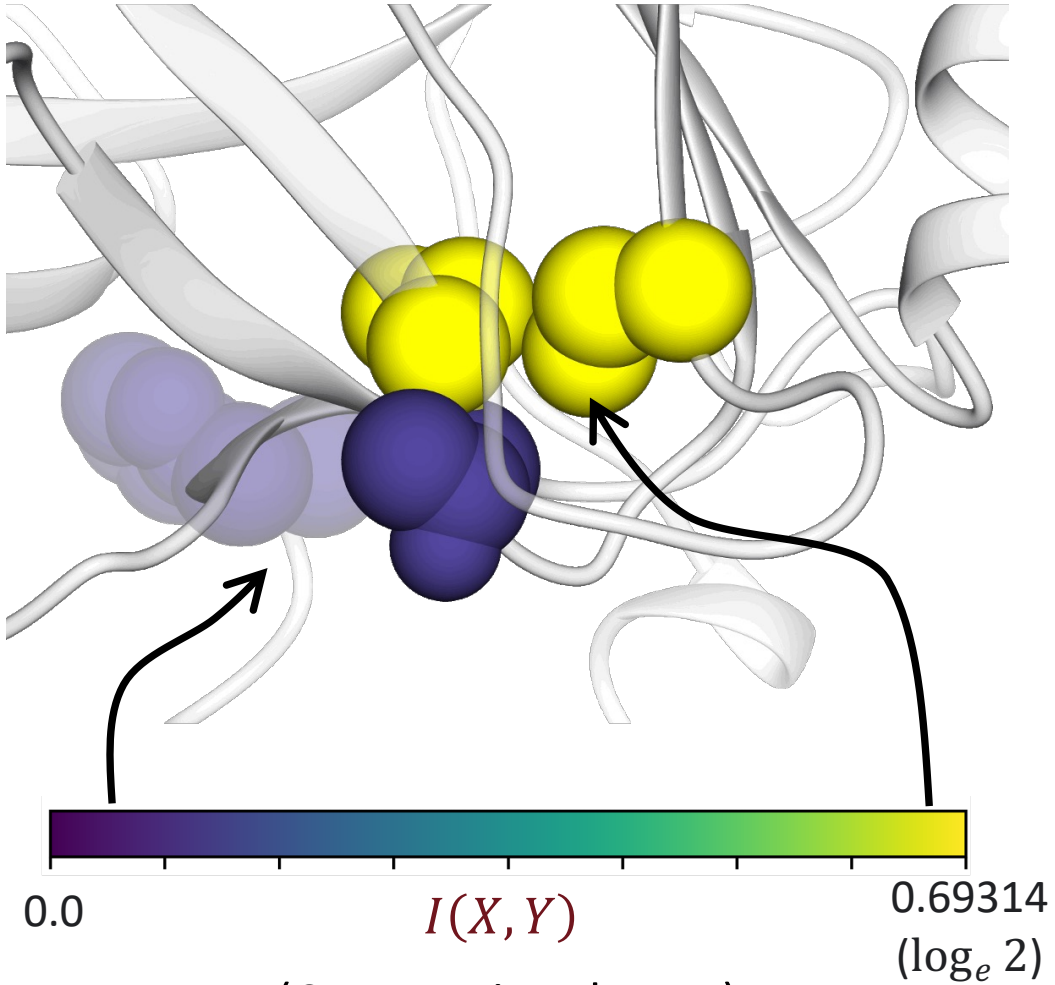
Measurement of correlated changes in cosolvent-binding

$$I(X,Y) = \sum_{x \in X} \sum_{y \in Y} p(x,y)\, log\left(\frac{p(x,y)}{p(x)p(y)}\right)$$

(X,Y) : *A pair of residues*

x : *xenon bound state of residue X*

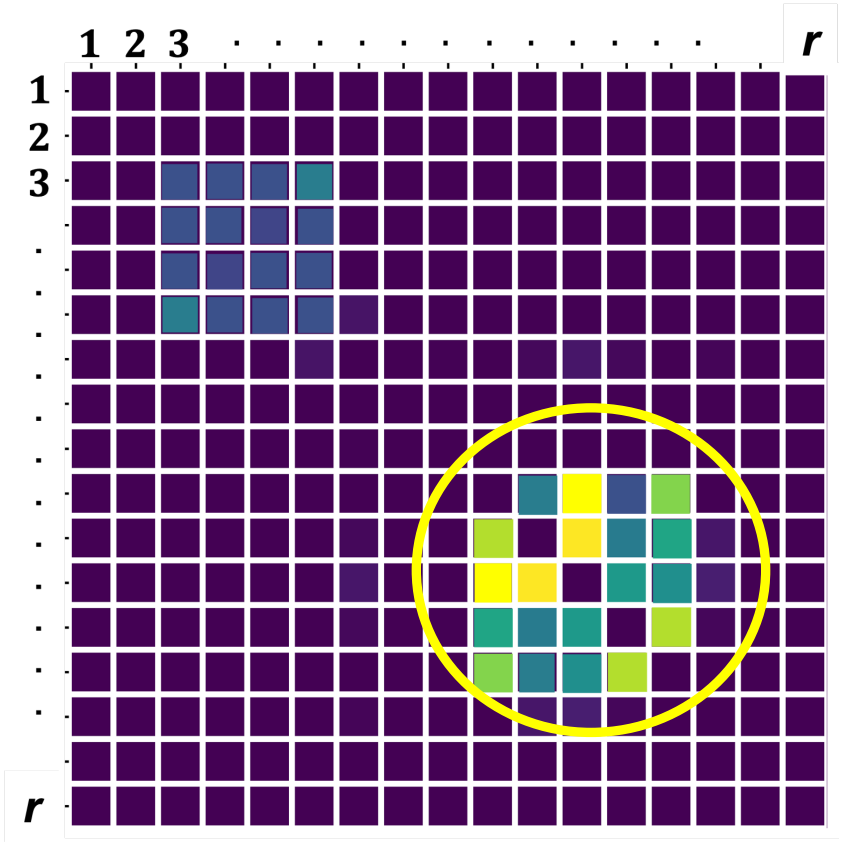
y : *xenon bound state of residue Y*

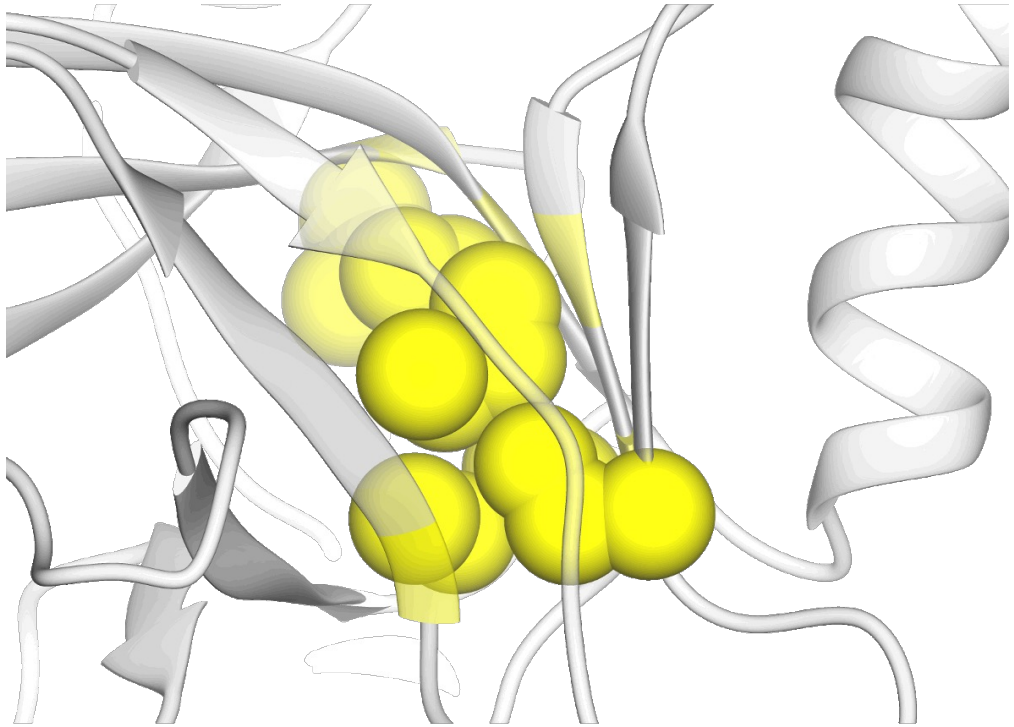


Xenon:

(Cooperative change)

Correlated changes in cosolvent-bound state of amino acids



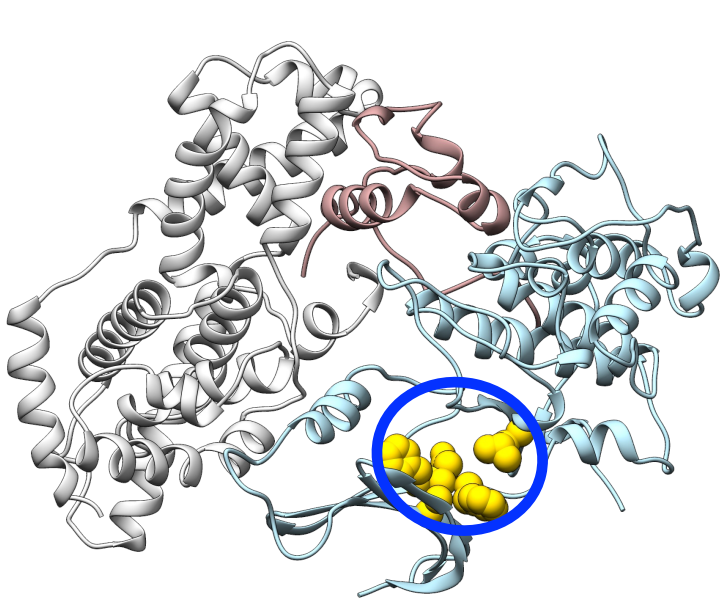


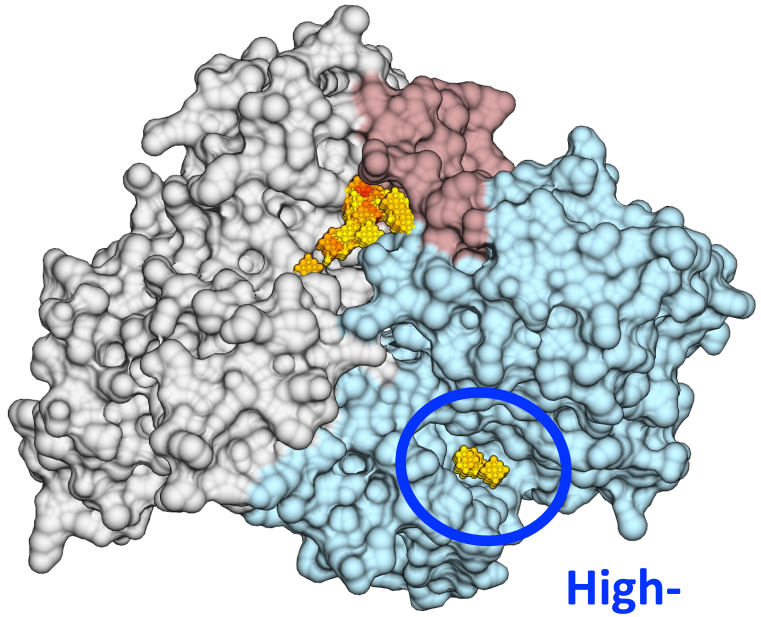
Xenon:

0.0 $I(X,Y)$ 0.69314 ($\log_e 2$)

(Cooperative change)

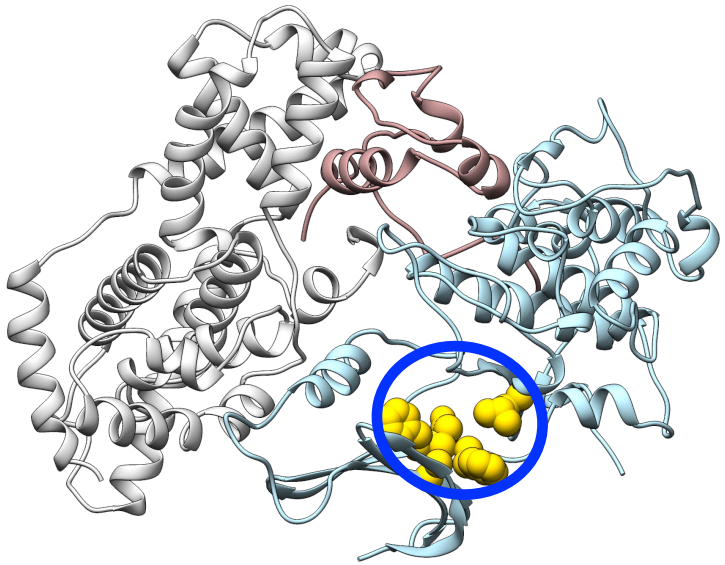
Cosolvent-binding site detection using mutual information



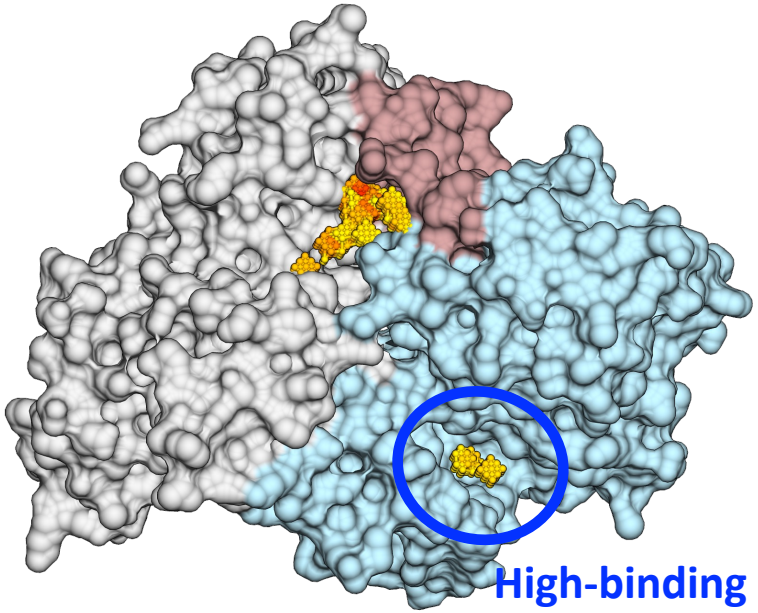


High-binding free energy site

Detection of a known inhibitor binding site using three independent methods



Cooperative xenon-binding behavior



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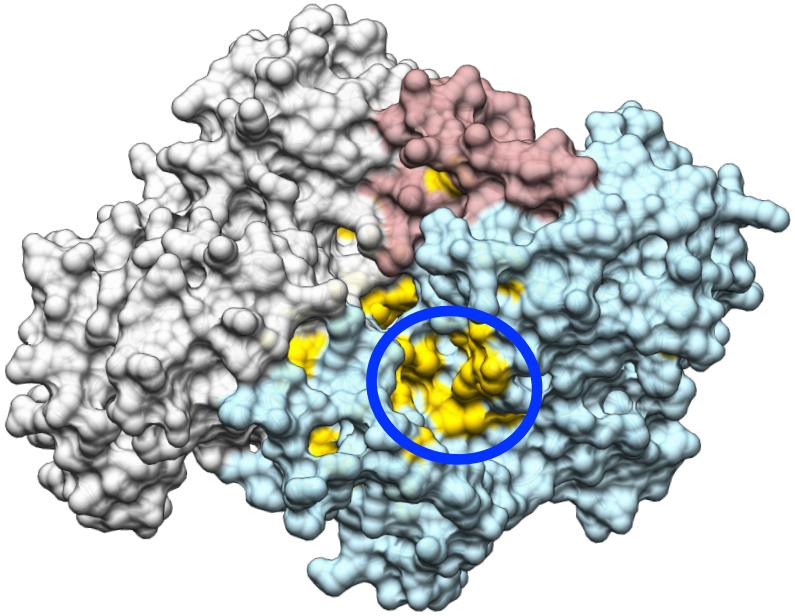
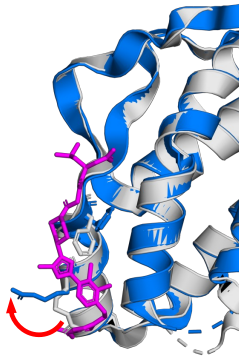


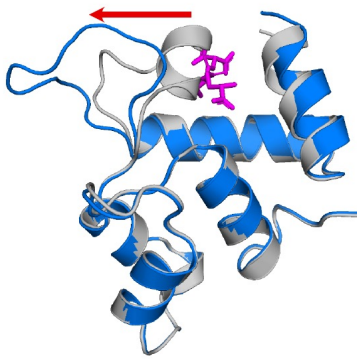
Exposon

(ICEC0942-binding site)

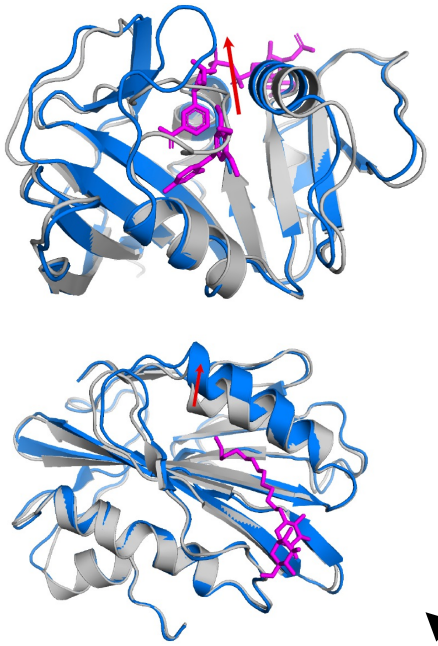
Motions associated with cryptic pocket opening



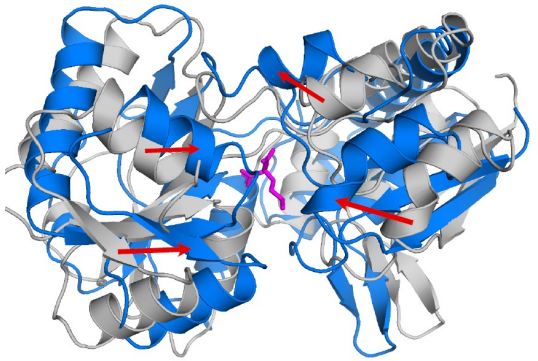
Side chain rotation



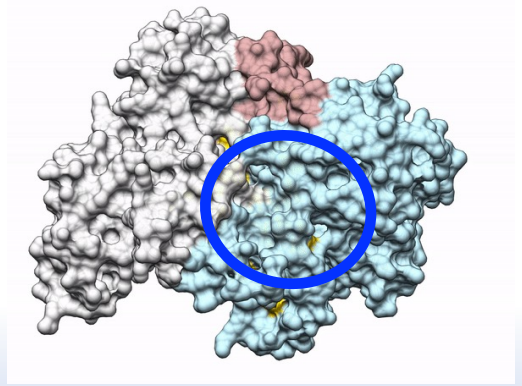
Secondary structure change



Loop/secondary structure motion



Inter-domain motion



Adapted from Meller A et al., Nat Commun. (2023), 14: 1177

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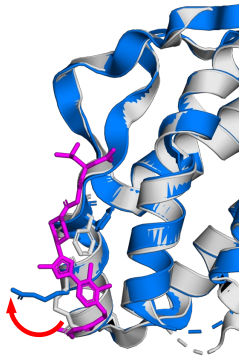
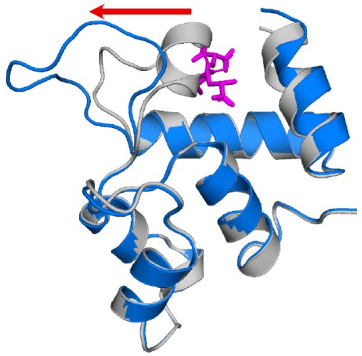
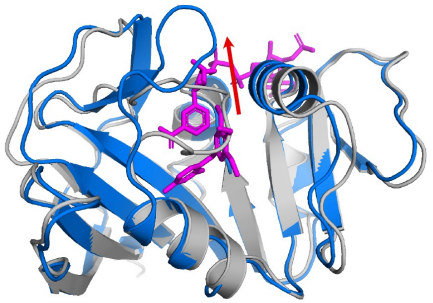
Motions associated with cryptic pocket opening

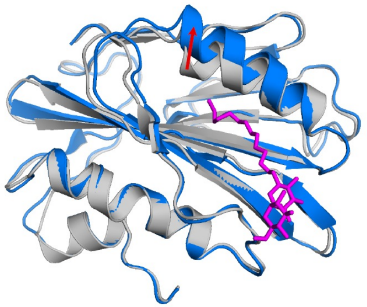


Side chain rotation

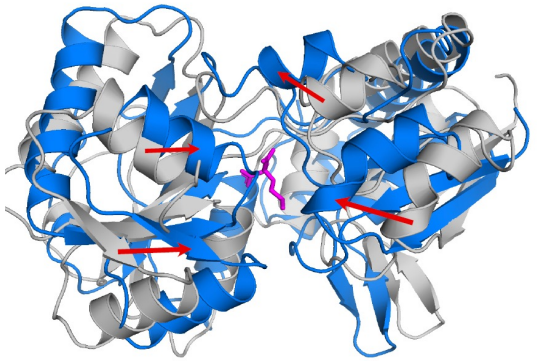


Secondary structure change



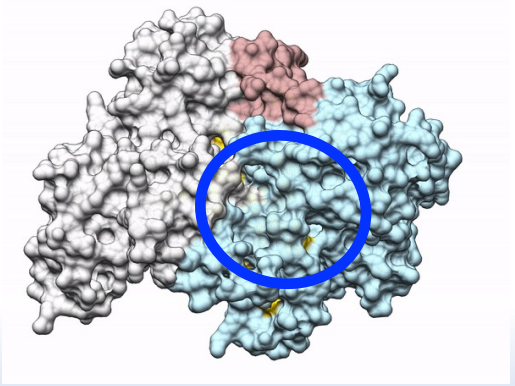


Loop/secondary structure motion



Inter-domain motion

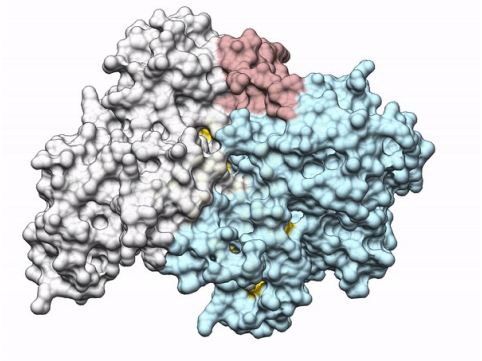
- **One more popular cancer target**
- **Confidential target in collaboration with Black Diamond Tx**



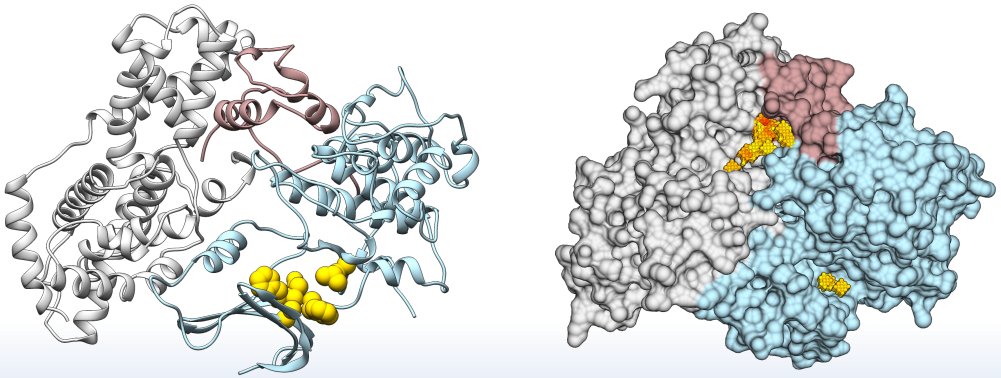
Adapted from Meller A et al., Nat Commun. (2023), 14: 1177

What can we achieve?

Detection of cryptic pockets that pre-exist in apo conformational ensemble



Detection of cryptic pockets that involve induced fit mechanism



"Nothing makes a man so adventurous as ~~an empty~~ a cryptic pocket." – Victor Hugo

Acknowledgements

OpenEye

Enhanced sampling Team
- David LeBard
- Jeff Thompson
- Junchao Xia
- Alex Demidov
- Lara Patel
- She Zhang

Steve Muchmore
Chris Neale
Geoff Skillman
Anthony Nicholls

Black Diamond Therapeutics

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Alex Balaeef (Currently @Launchpad Tx)
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Ahmet Mentes (Currently @ BMS)