Applications of AI in drug design

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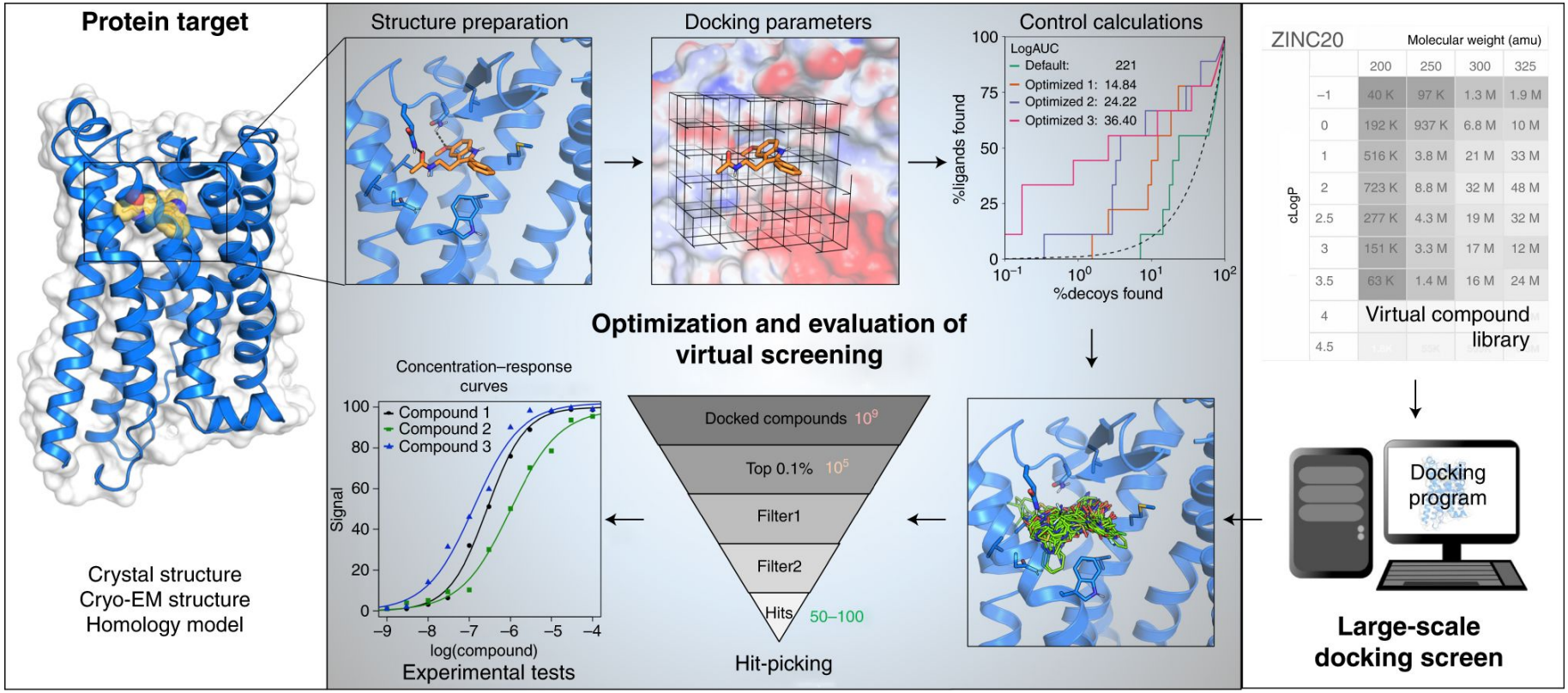
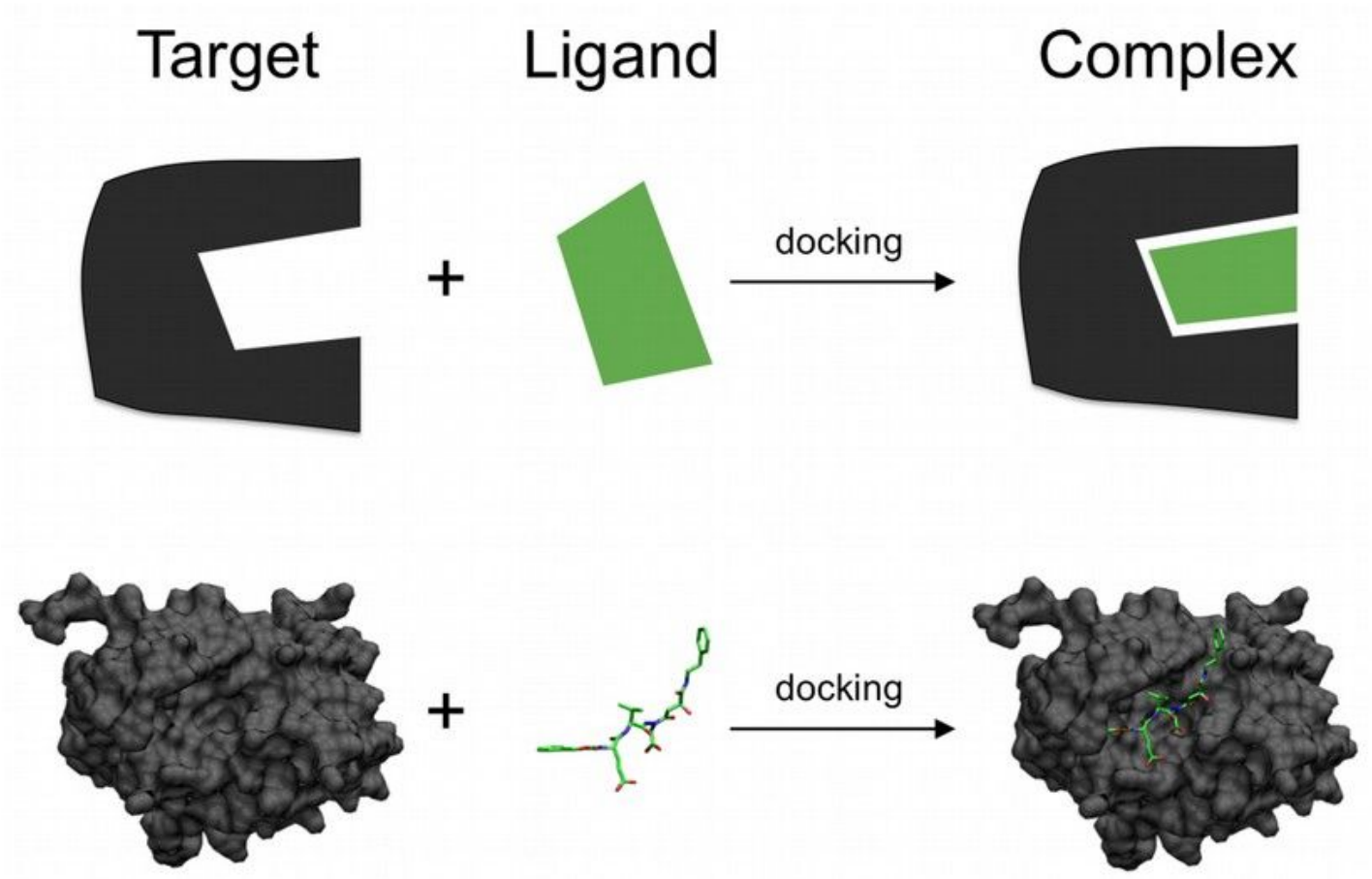
From desktop to experimental applications

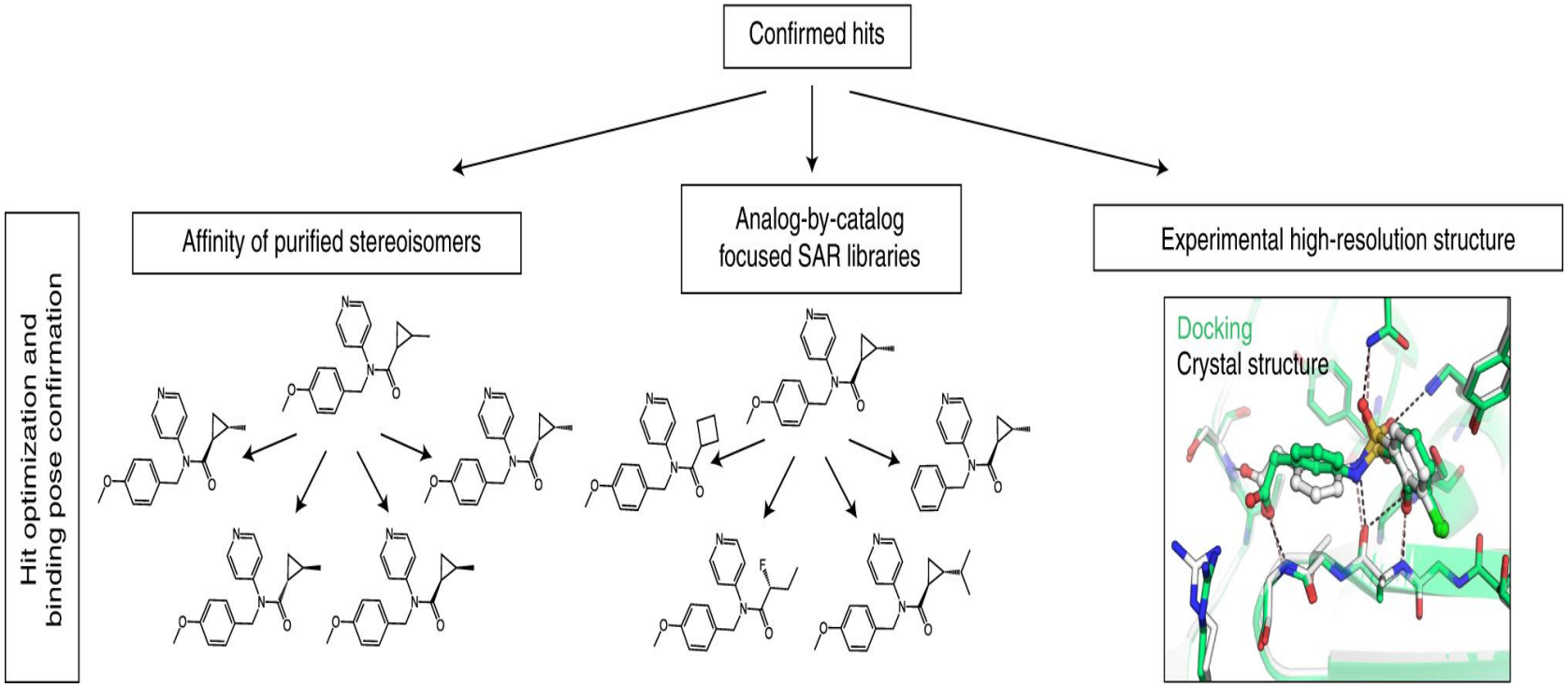


Bender, B. J.; Gahbauer, S. et al. A Practical Guide to Large-Scale Docking. Nat. Protoc. (2021)

Molecular docking: searching for small molecule design

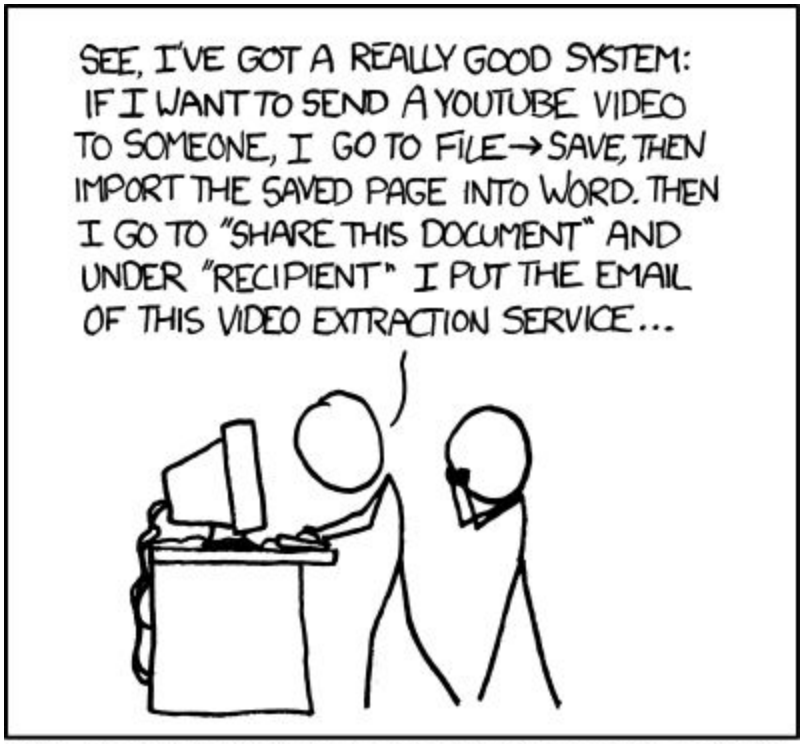


Drug design becomes an ennumerative problem based on increasing number of combinations

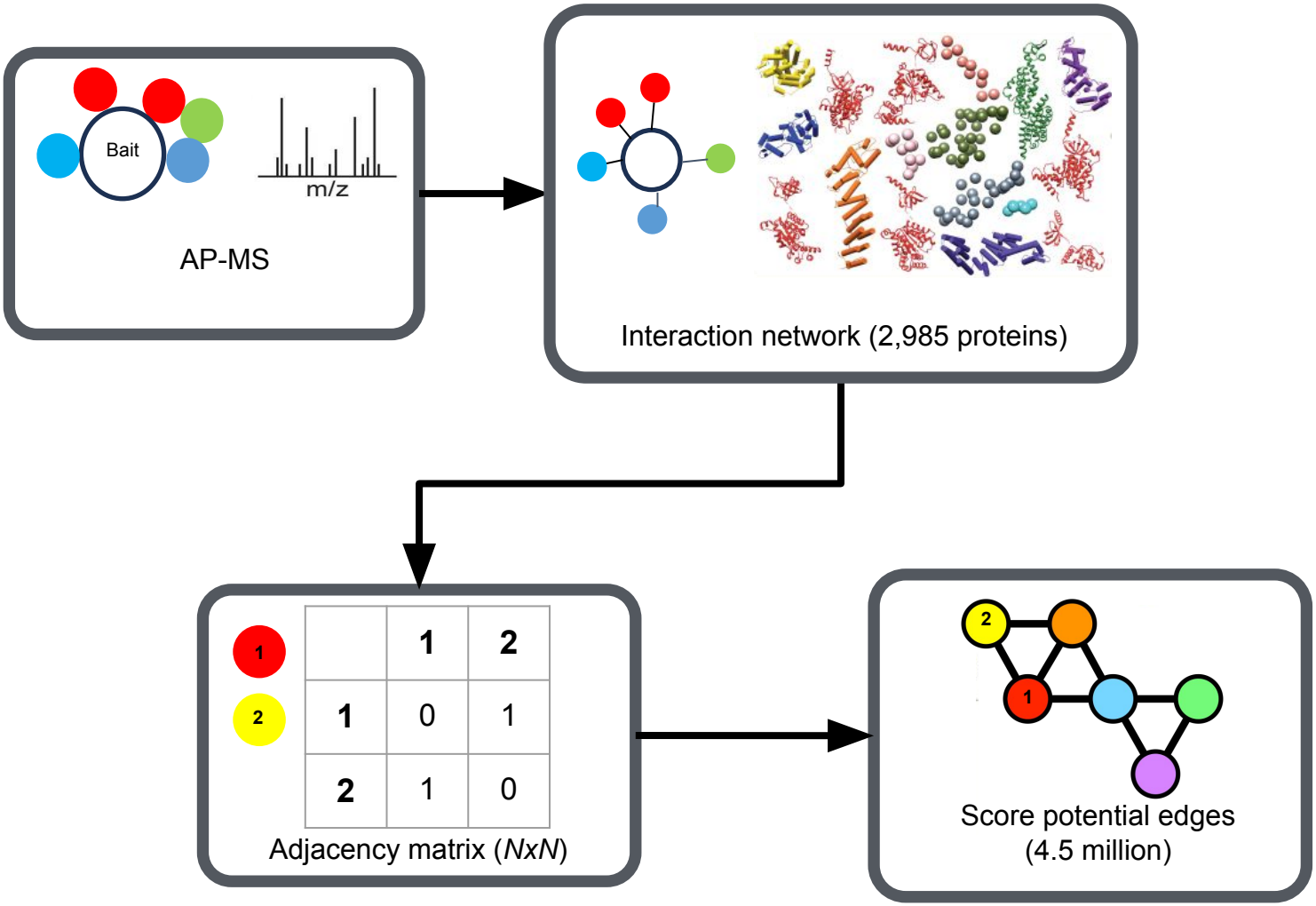


Hit Expansion

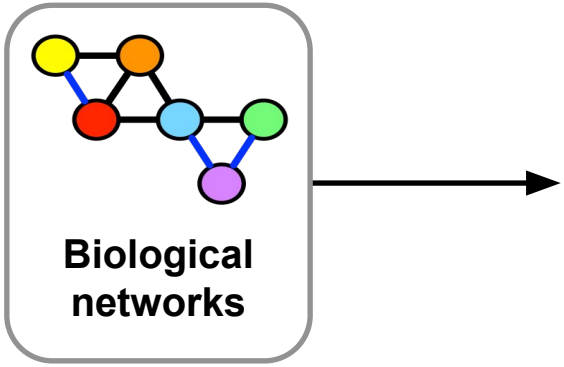
Does the solution fit the problem?

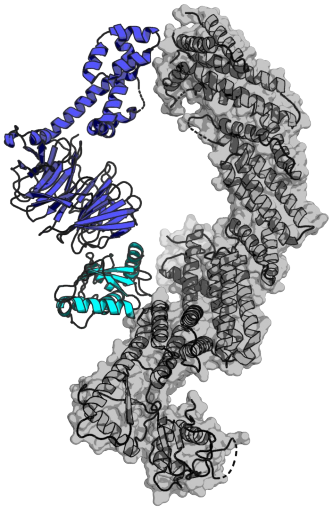


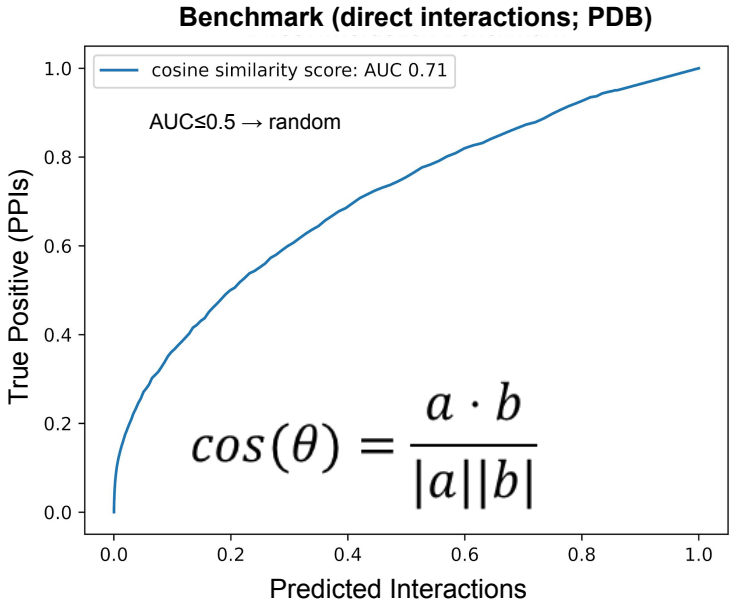
Machine learning: pattern searching and dimensional reduction of the data



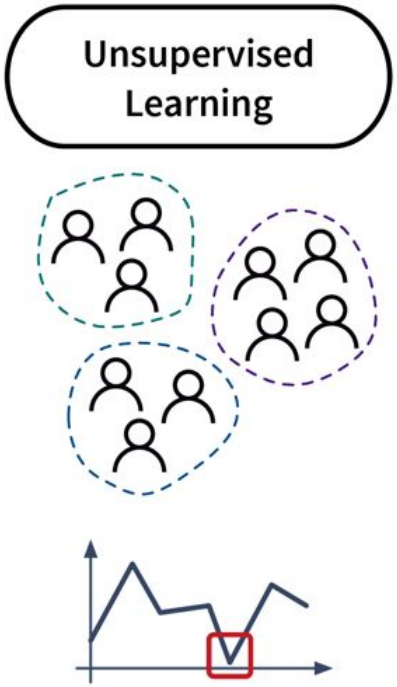
Machine learning: pattern searching and dimensional reduction of the data

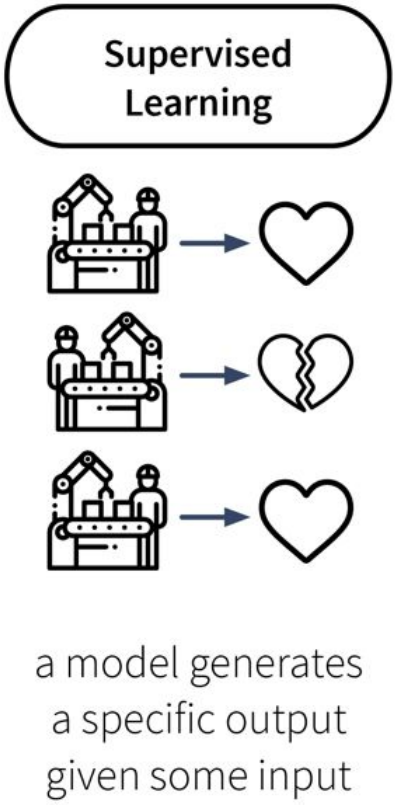


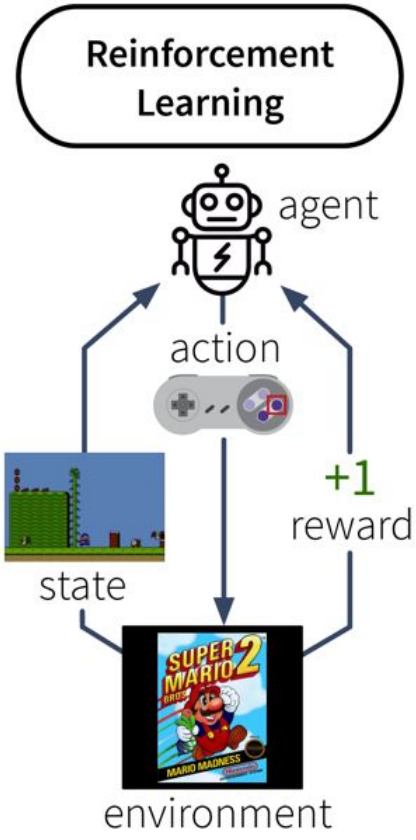




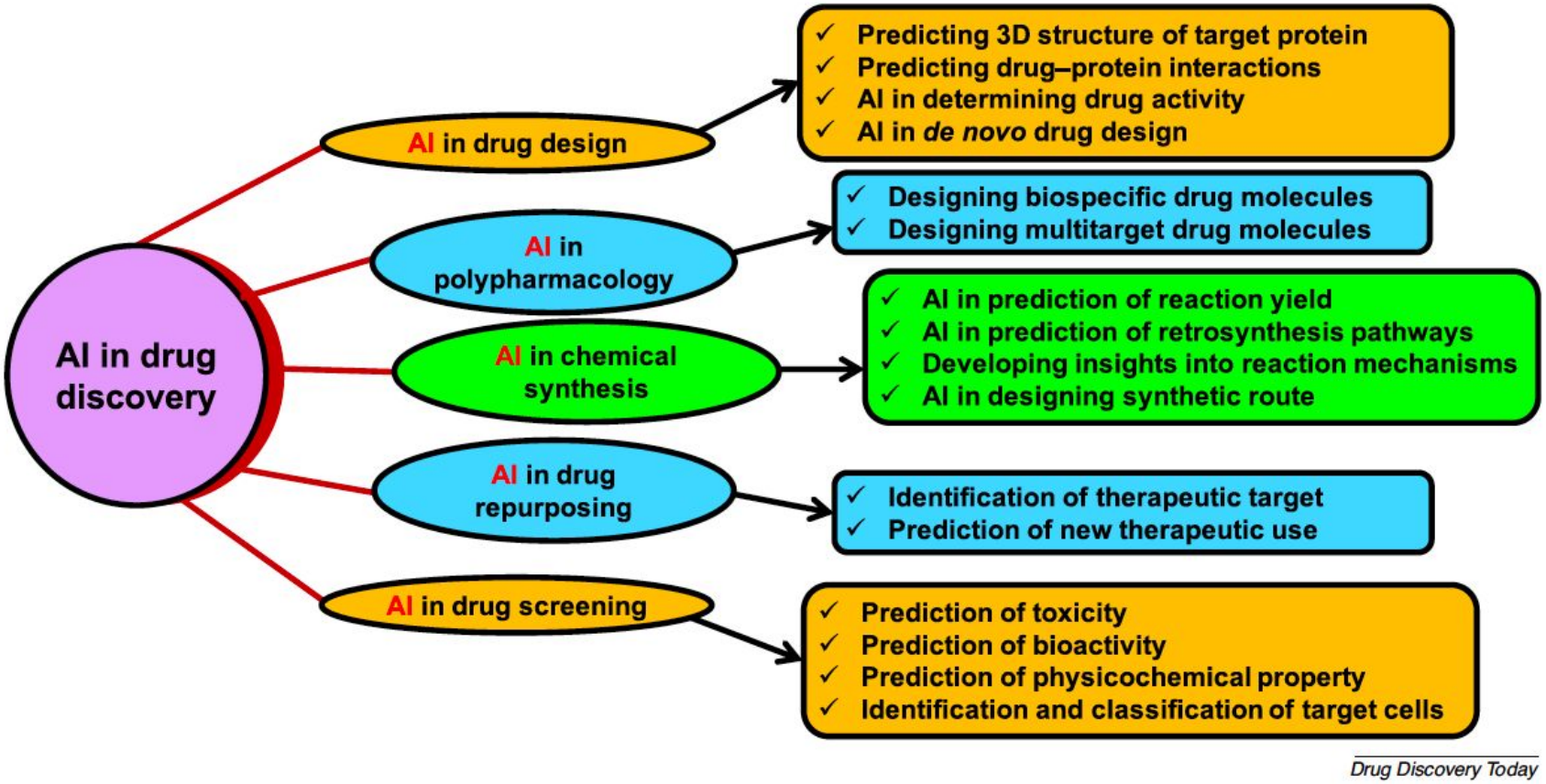
The triad of machine learning approaches



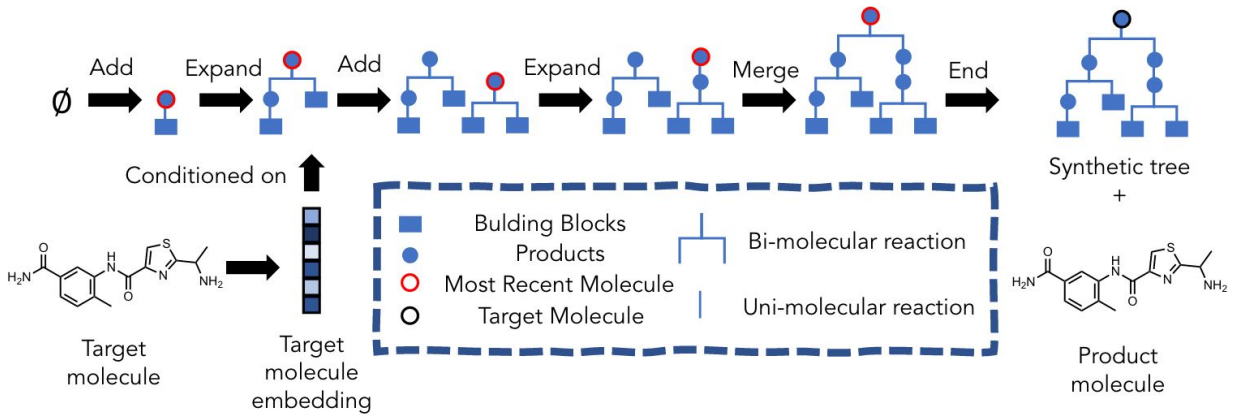


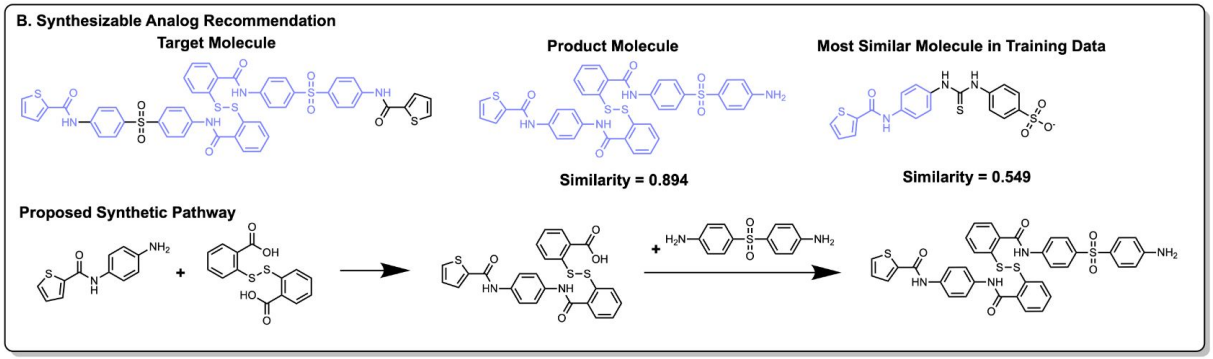


Drug design is a problem/environment largely denoted by a large amount of noise



De novo drug design by exploration of alternative synthetic pathways

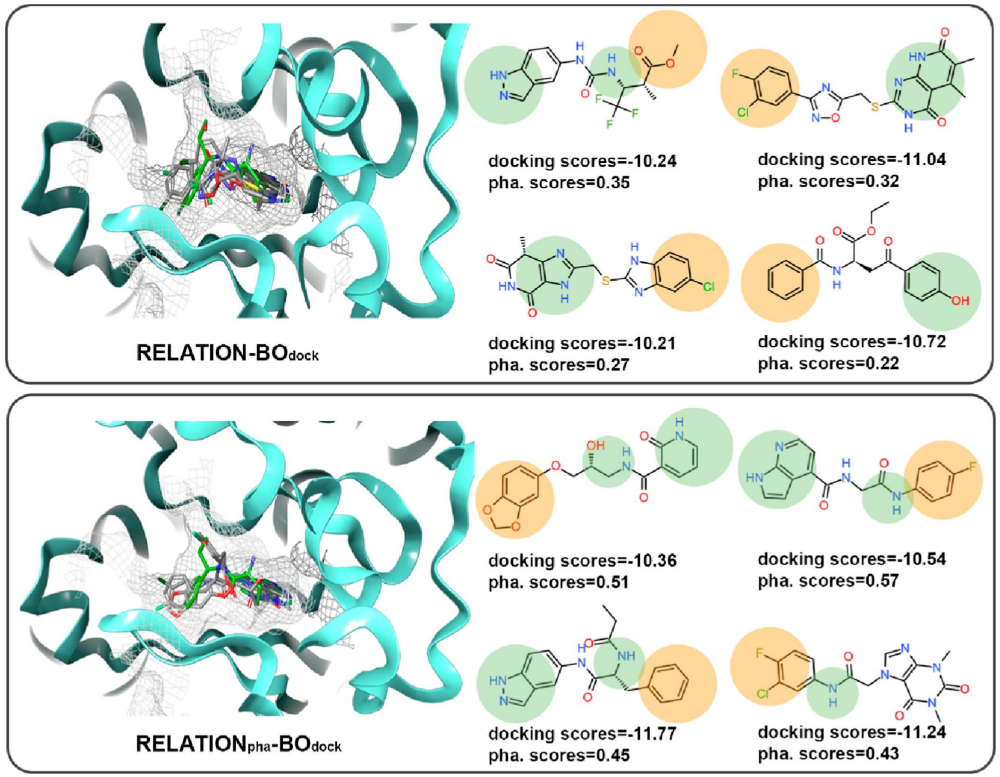




Gao, W.; Mercado, R.; Coley, C. W.. arXiv March 12, 2022.

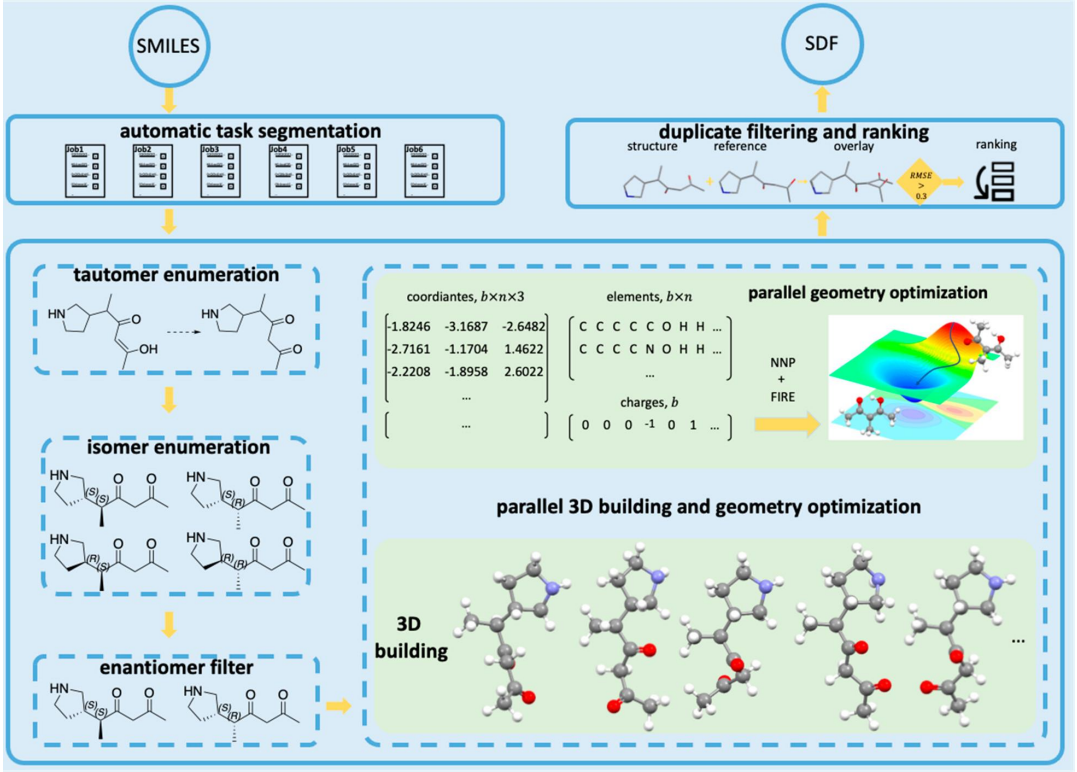
De novo drug design by exploration of alternative synthetic pathways

RELATION: A Deep Generative Model for Structure-Based De Novo Drug Design

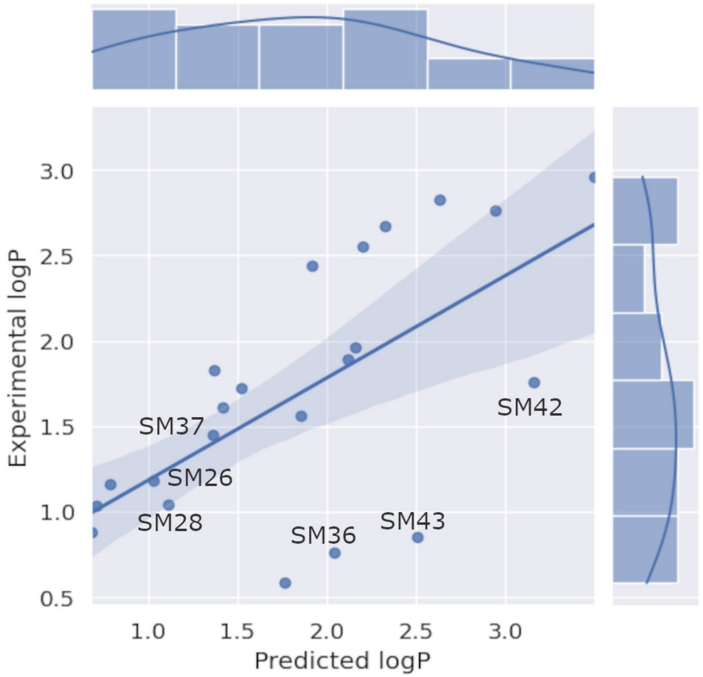


Wang, M. et al. *J. Med. Chem.* **2022**, *65* (13), 9478–9492.
https://github.com/micahwang/RELATION

3D conformer generation to assist in prediction of molecular properties



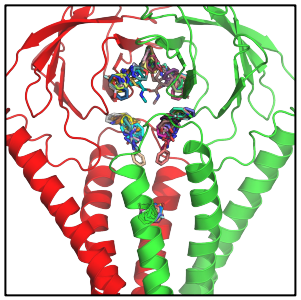
Auto3D: Automatic Generation of the Low-energy 3D Structures with ANI Neural Network Potentials



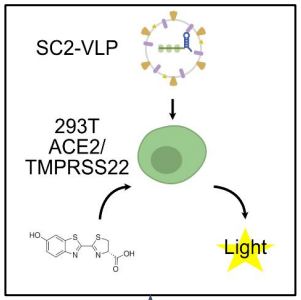
Liu, Z.; Zubatiuk, T.; Roitberg, A.; Isayev, O. *J. Chem. Inf. Model.* **2022**, *62* (22), 5373–5382.
https://github.com/isayevlab/Auto3D_pkg
Lenselink, Eelke B., and Pieter FW Stouten. *Journal of Computer-Aided Molecular Design* 35, no. 8 (2021): 901-909.

Case 1: Plurality of binding sites

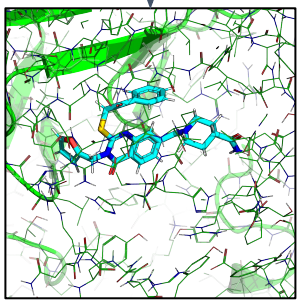
Identify ligand pocket



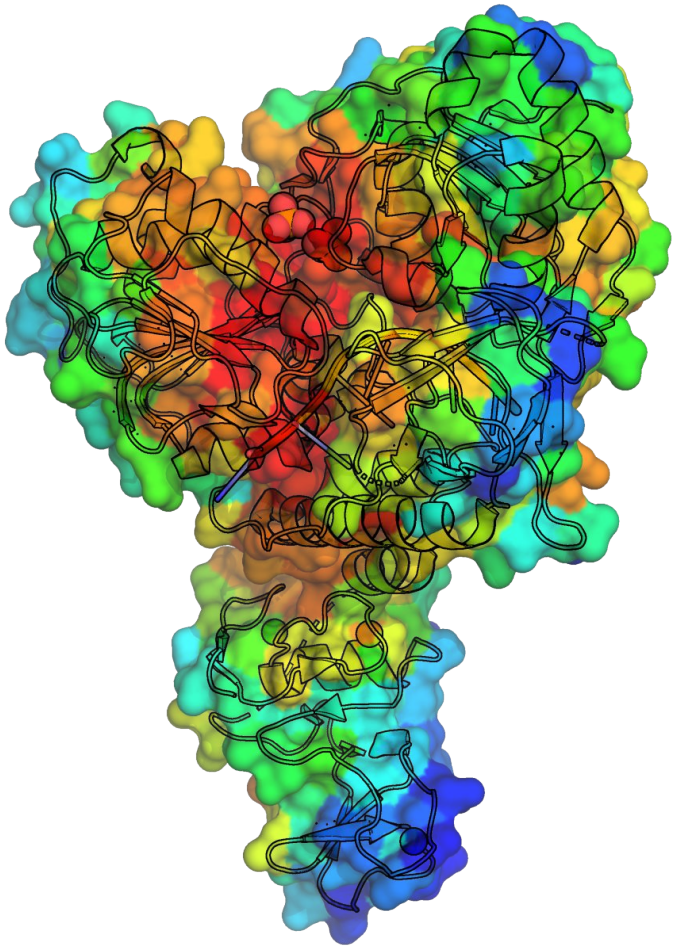
Verify activity with assays

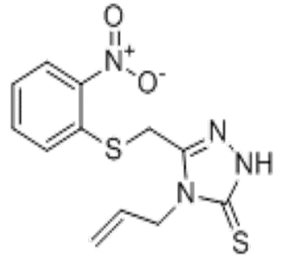


Optimize ligand design

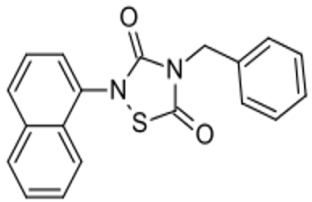


Multi-functionality of viral proteins ⇒multiple pockets





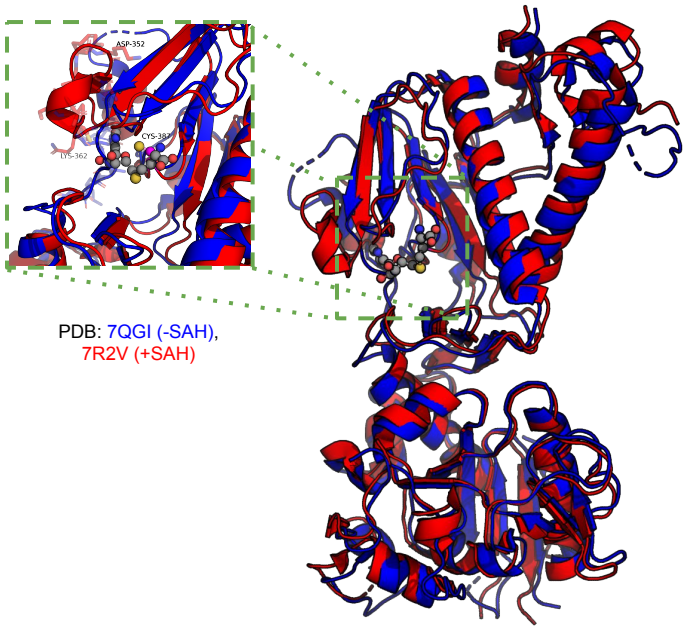
SSYA-10-001
IC50 = 0.6uM



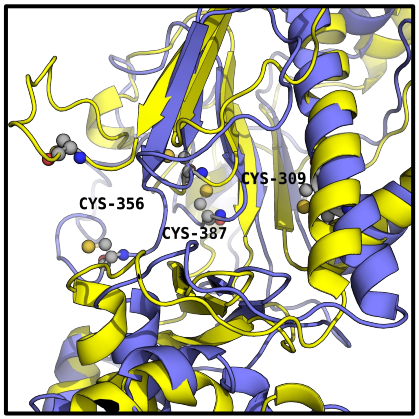
Tideglusib
IC50 = 25-50uM

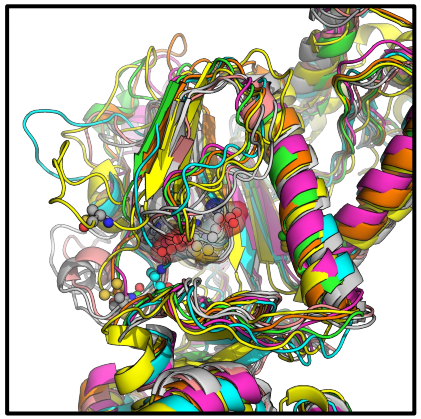
Case 2: Multi-state proteins increase search space for ligand discovery

Additional conformations in ligand pocket(s)

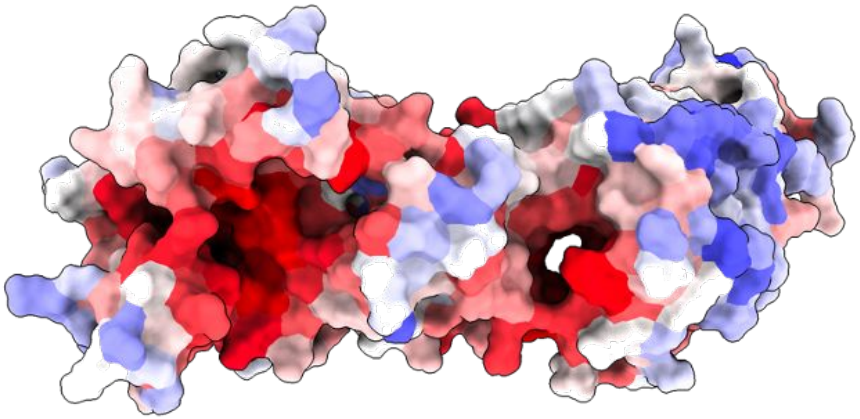


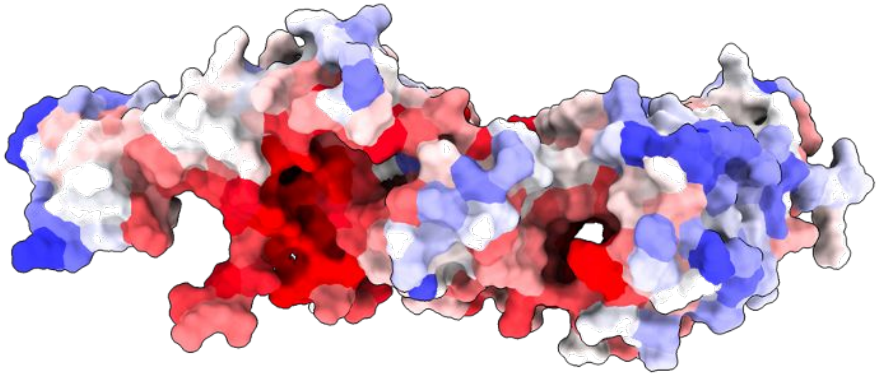
PDB: 7QGI (-SAH),
7R2V (+SAH)





Expanding range of potential ligand pockets





Surabhi Rathore; Fujimori; Vedadi, Shoichet Labs