Spatiotemporal identification of binding sites with computer vision

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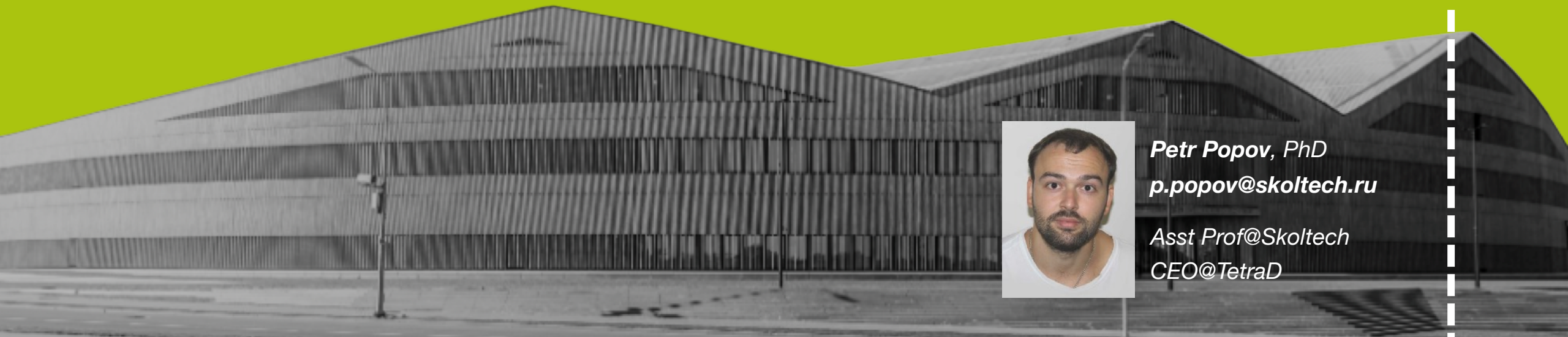

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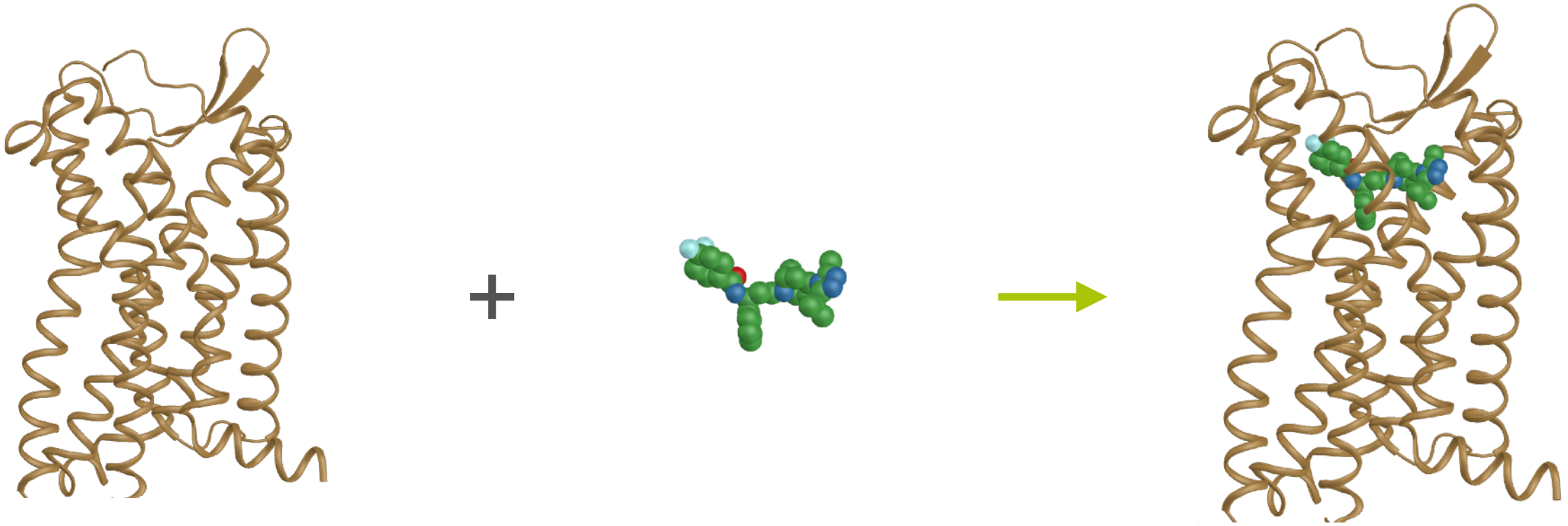
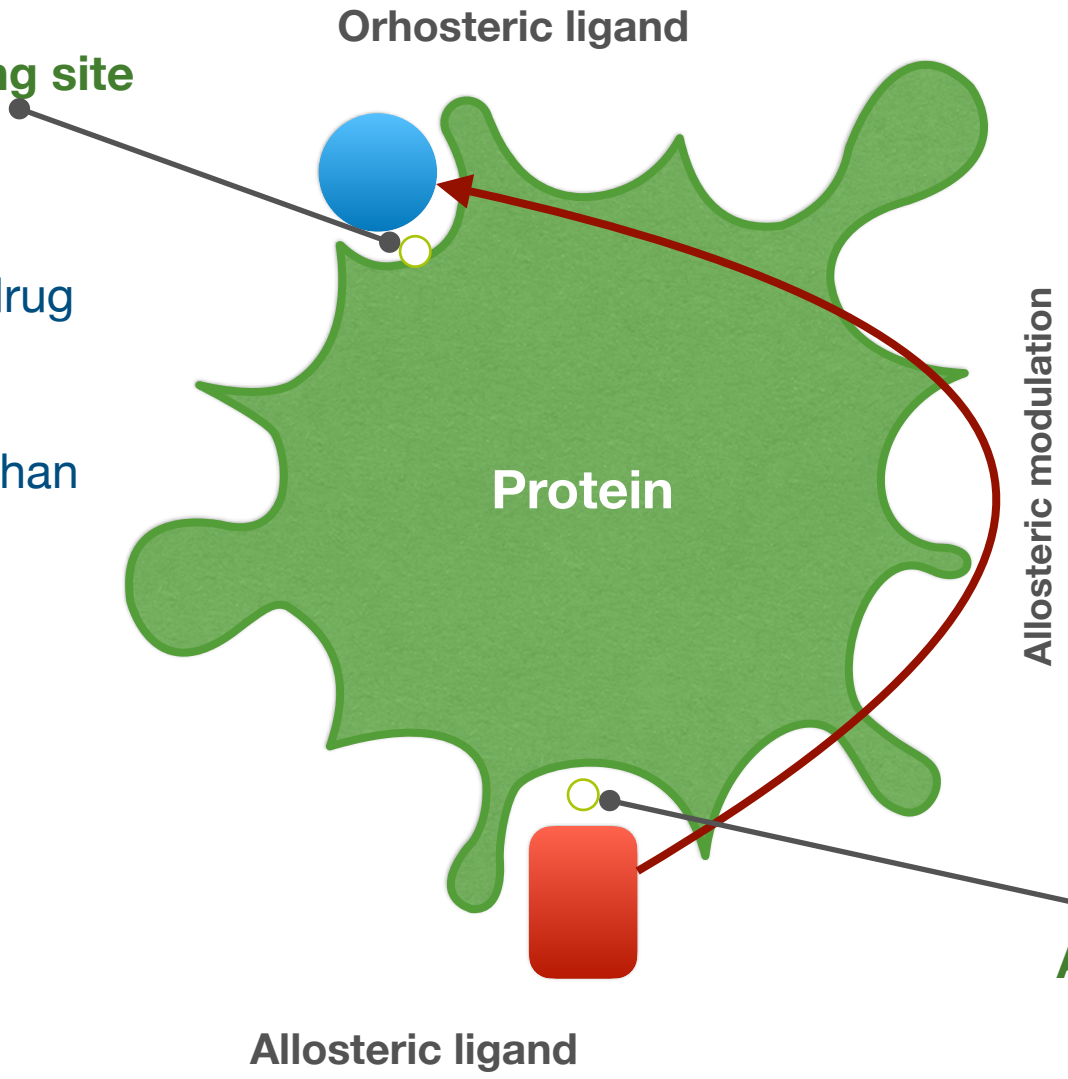
Binding sites



Target ligand Target-ligand complex

- Binding site is a spatial region, where a ligand (drug, endogenous molecule, …) binds to a target

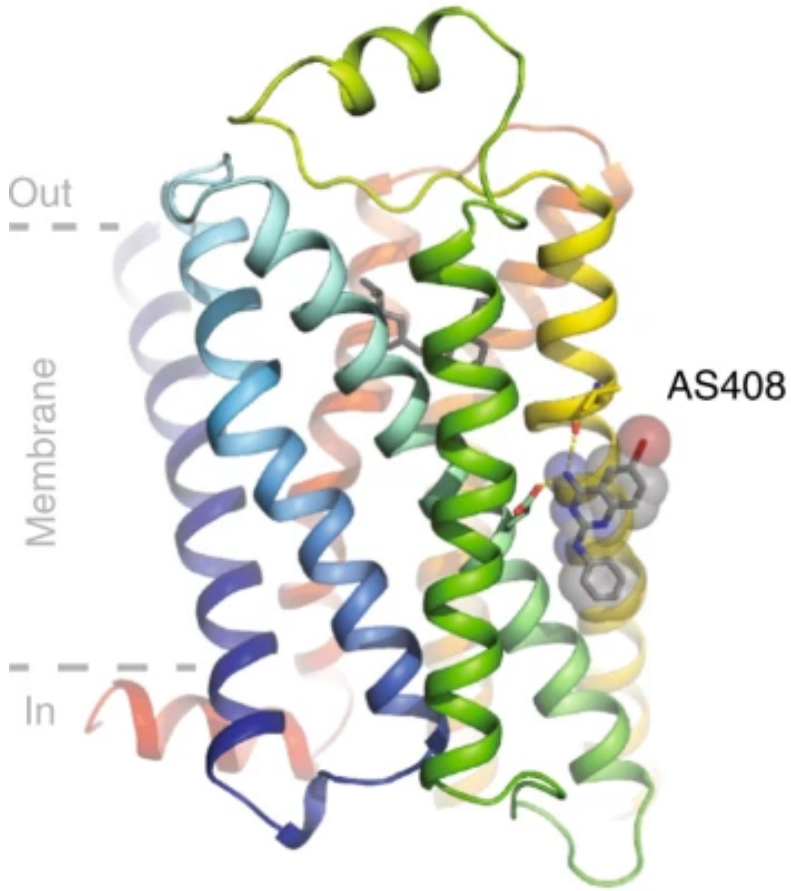
Binding sites in drug discovery



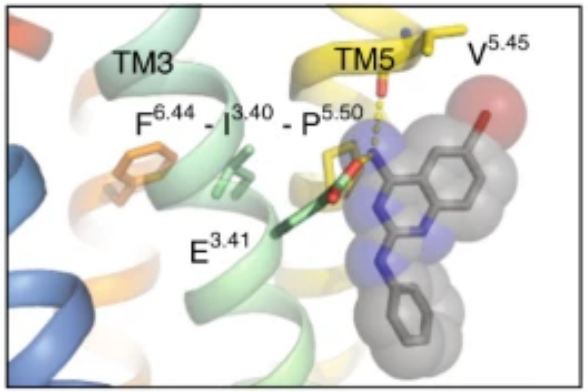
- Classical hot spot for drug discovery campaigns
- Unknown for some orphan proteins
- May carry missense mutations affecting therapeutic effect

- Can be used to design more selective, safer, more effective drugs
- Hot spot for Positive (PAMs) or Negative allosteric modulators (NAMs)

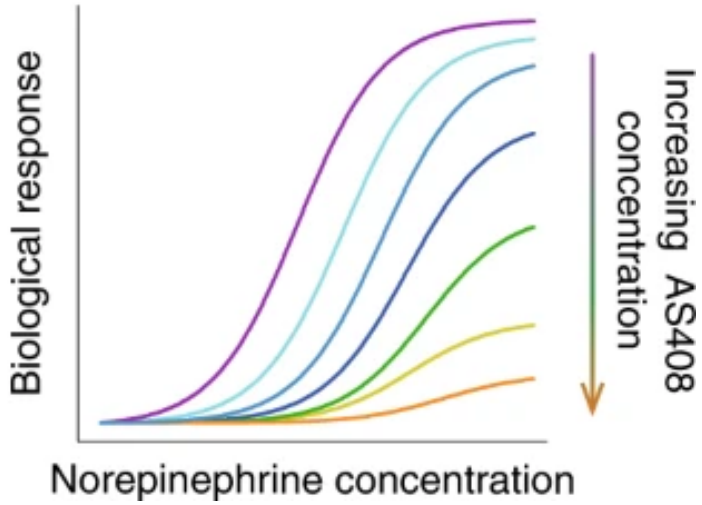
Human β_2AR in complex with negative allosteric modulator at membrane interface



Binding site of allosteric modulator

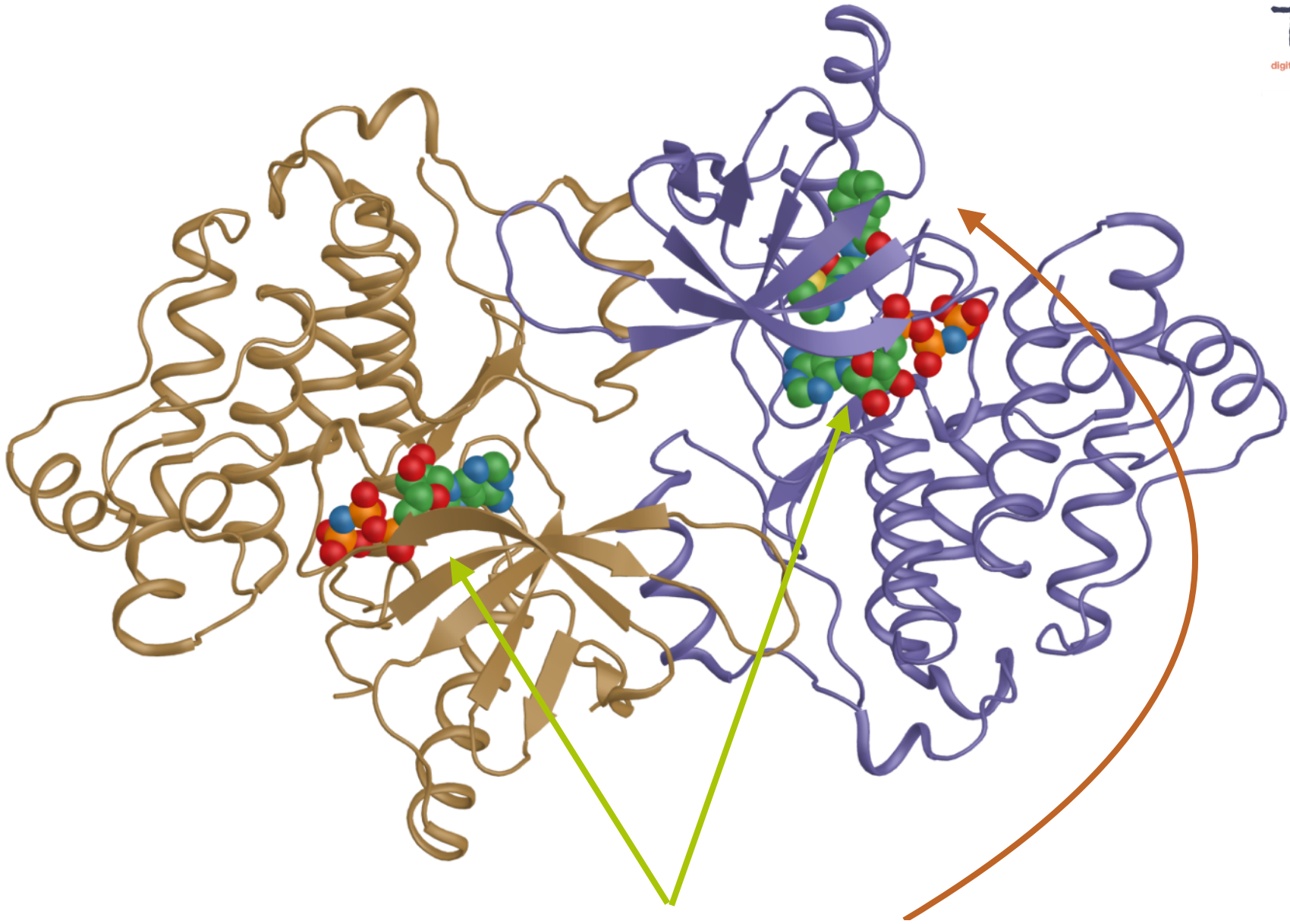


Modulated receptor activation



Allosteric binding site discovered in 2020 for β_2 adrenergic receptor - a pharmacological target with long history

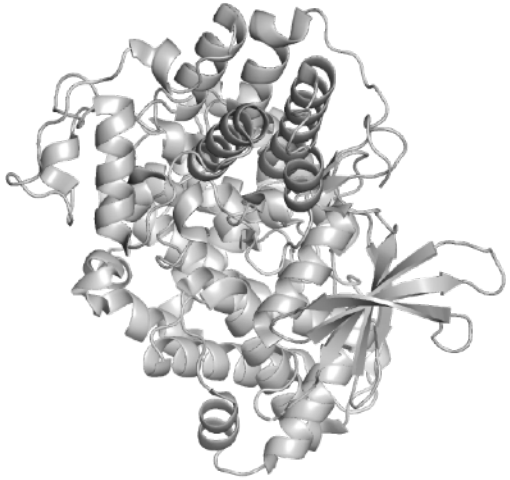
Liu, X., Kaindl, J., Korczynska, M. *et al.* An allosteric modulator binds to a conformational hub in the β2 adrenergic receptor. *Nat Chem Biol* **16,** 749–755 (2020).



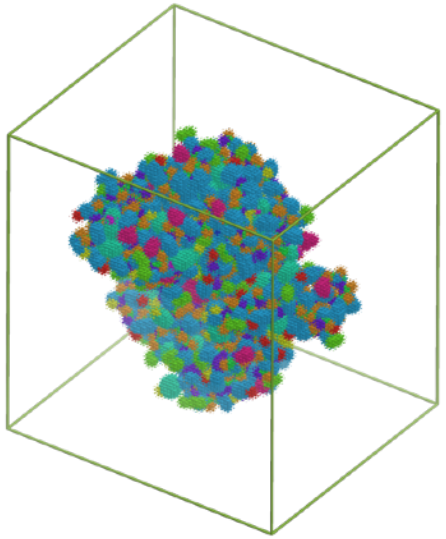
Assymetric 3D structure of EGFR with orthosteric and allosteric bioactive molecules

Jia, Yong, et al. "Overcoming EGFR (T790M) and EGFR (C797S) resistance with mutant-selective allosteric inhibitors." *Nature* (2016)

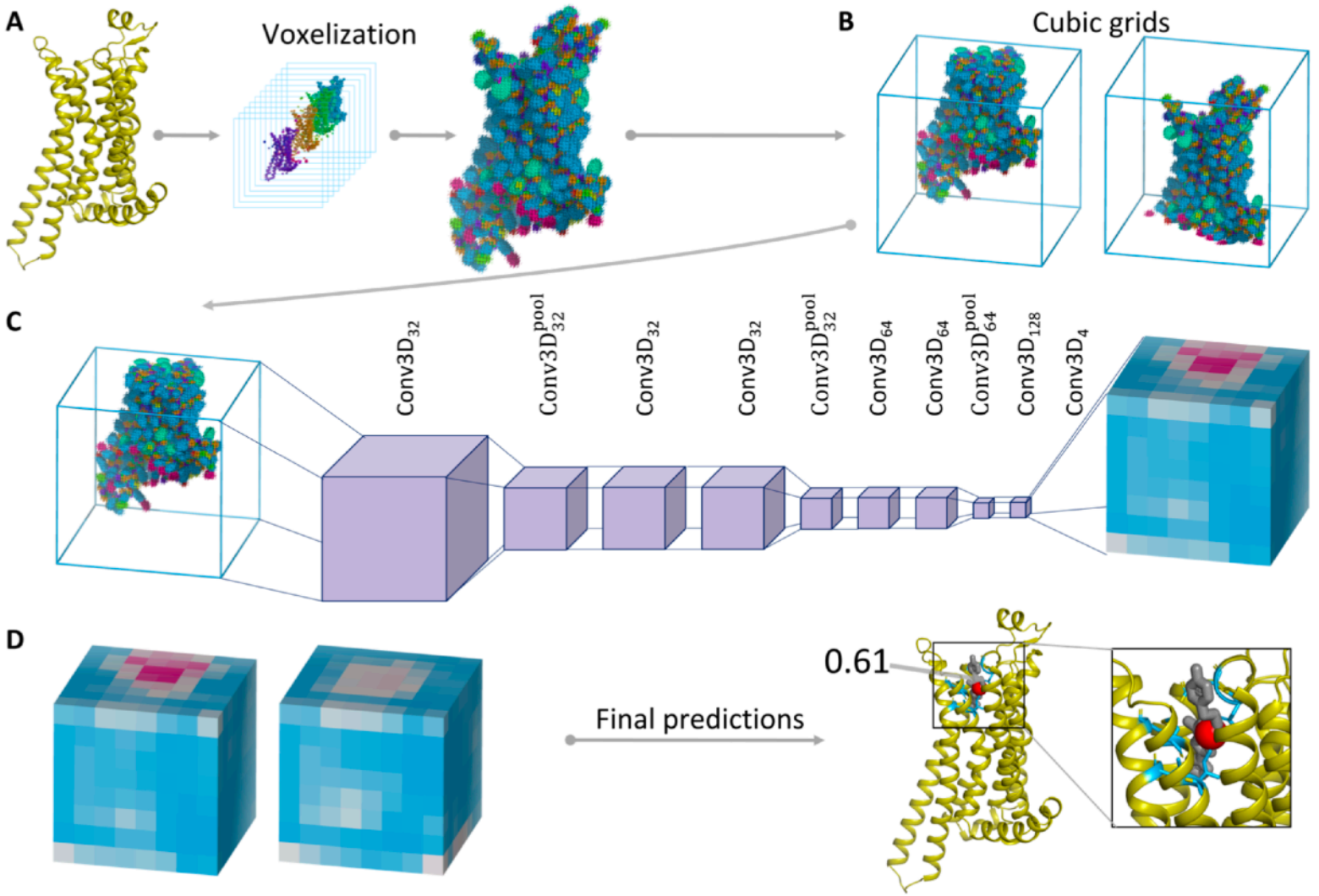
Data



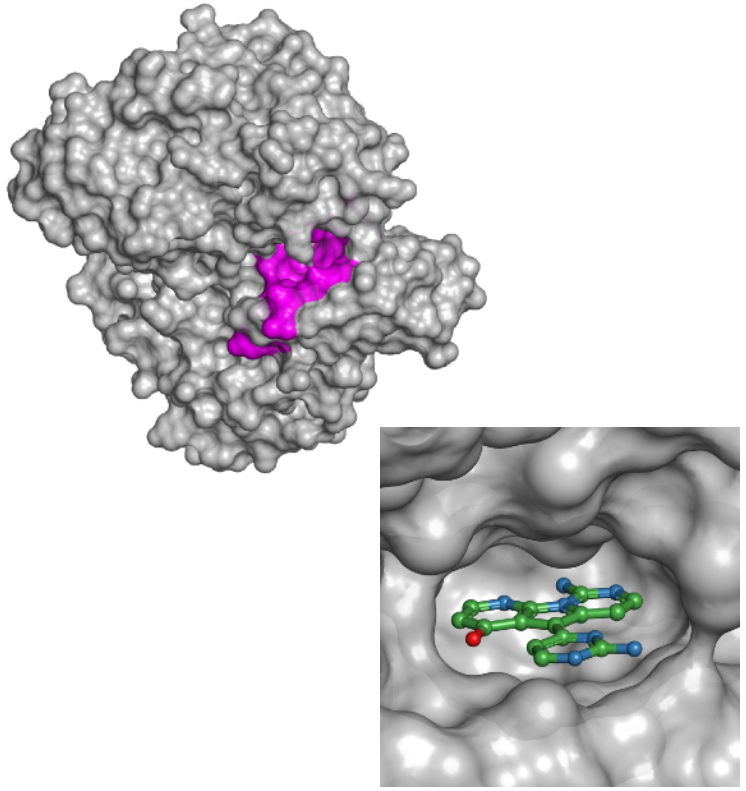
- Protein Data Bank : 3D structures containing protein and ligand
- Label binding and non-binding sites
- Conversion to 3D image



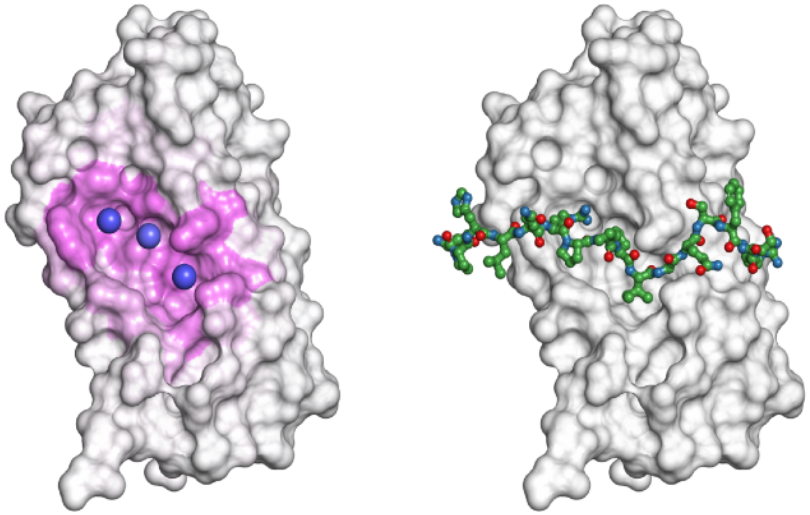
Convolutional Neural Network



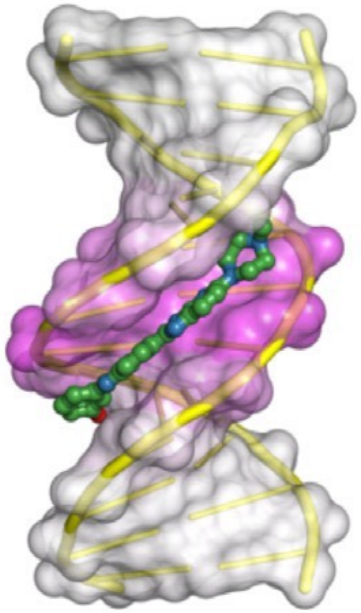
Different types of binding sites as different objects to detect



small molecule binding site



peptide binding site



small molecule binding site for nucleic acids

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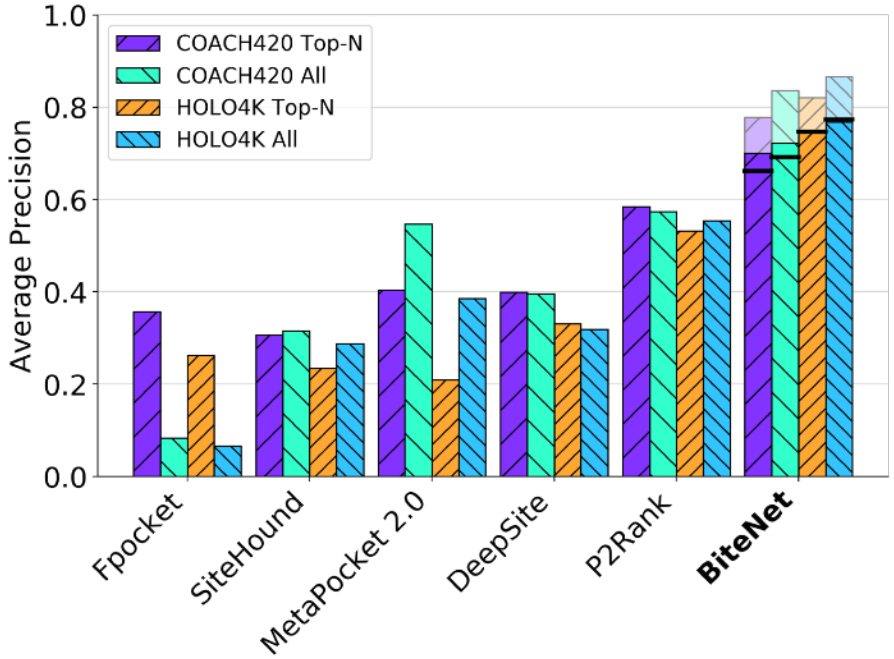
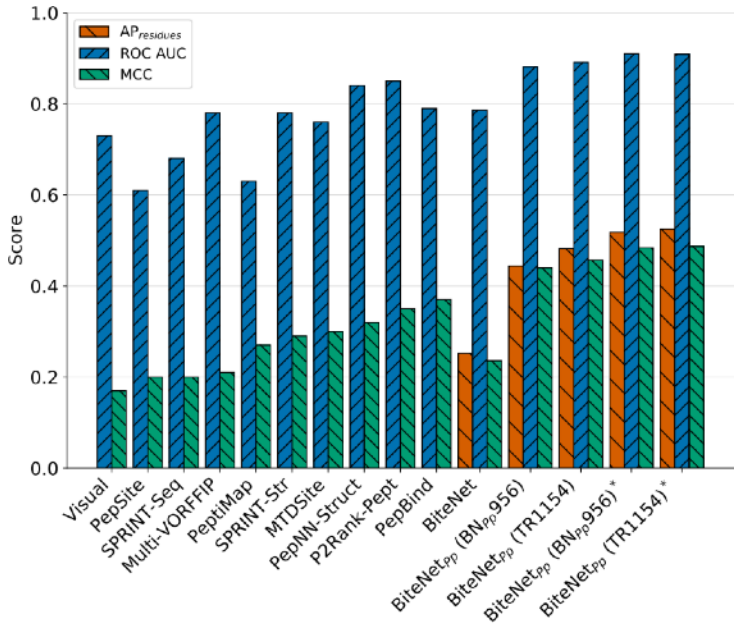
Benchmarks

Performance metric:
Average precision
(Area under precision-recall curve)

$$AP = \sum_n (R_n - R_{n+1}) P_n$$



Kozlovskii, I., & Popov, P. (2020). Spatiotemporal identification of druggable binding sites using deep learning. *Communications biology*, 3(1), 1-12.



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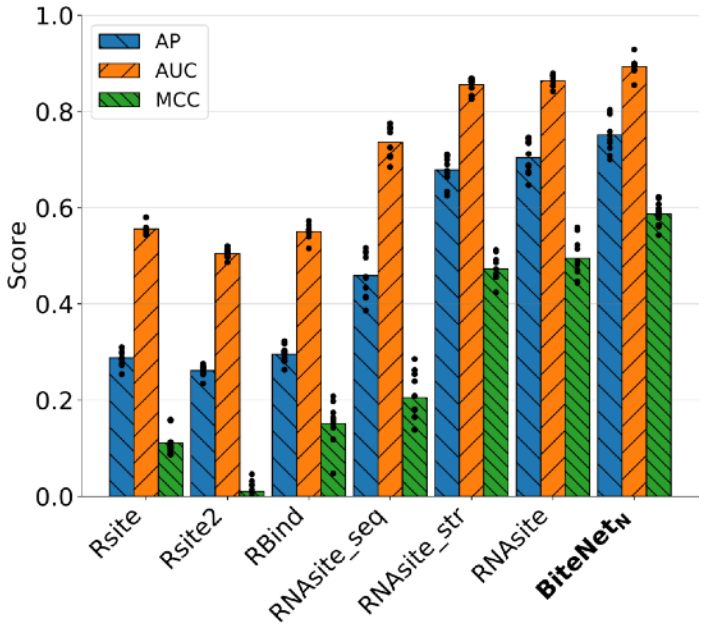

Kozlovskii, I., & Popov, P. (2021). Structure-based deep learning for binding site detection in nucleic acid macromolecules. *Nucleic Acid Research Genomics and Bioinformatics*

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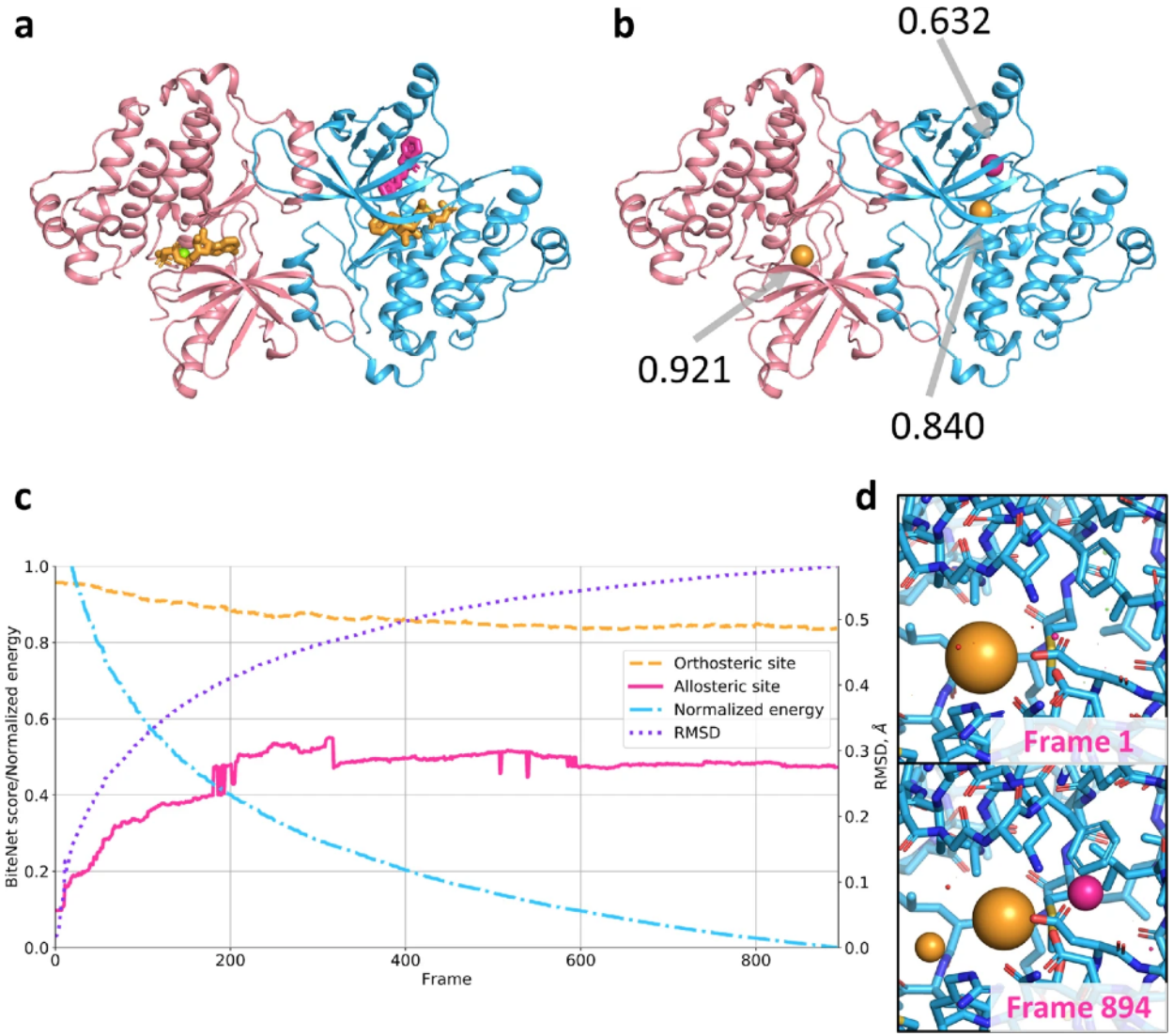
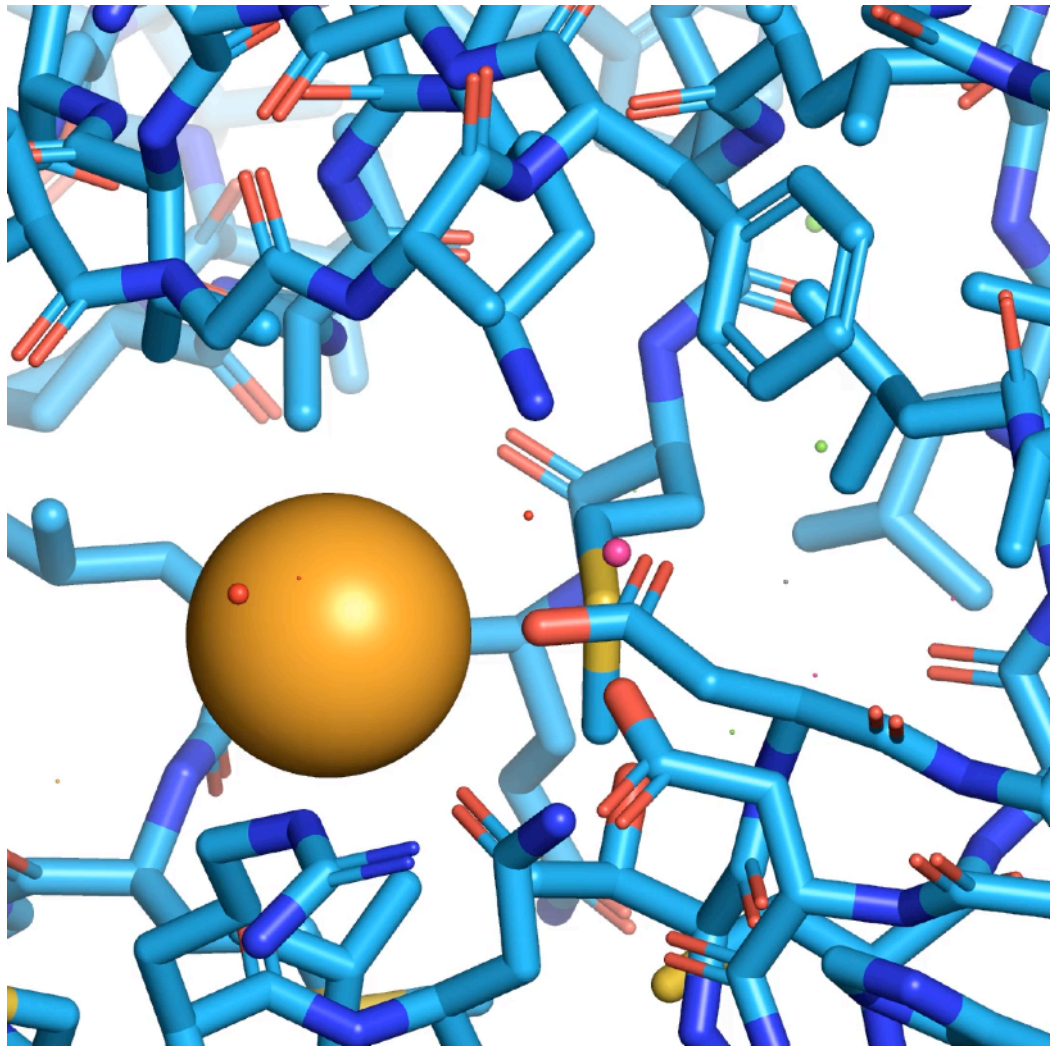
Spatiotemporal binding site detection





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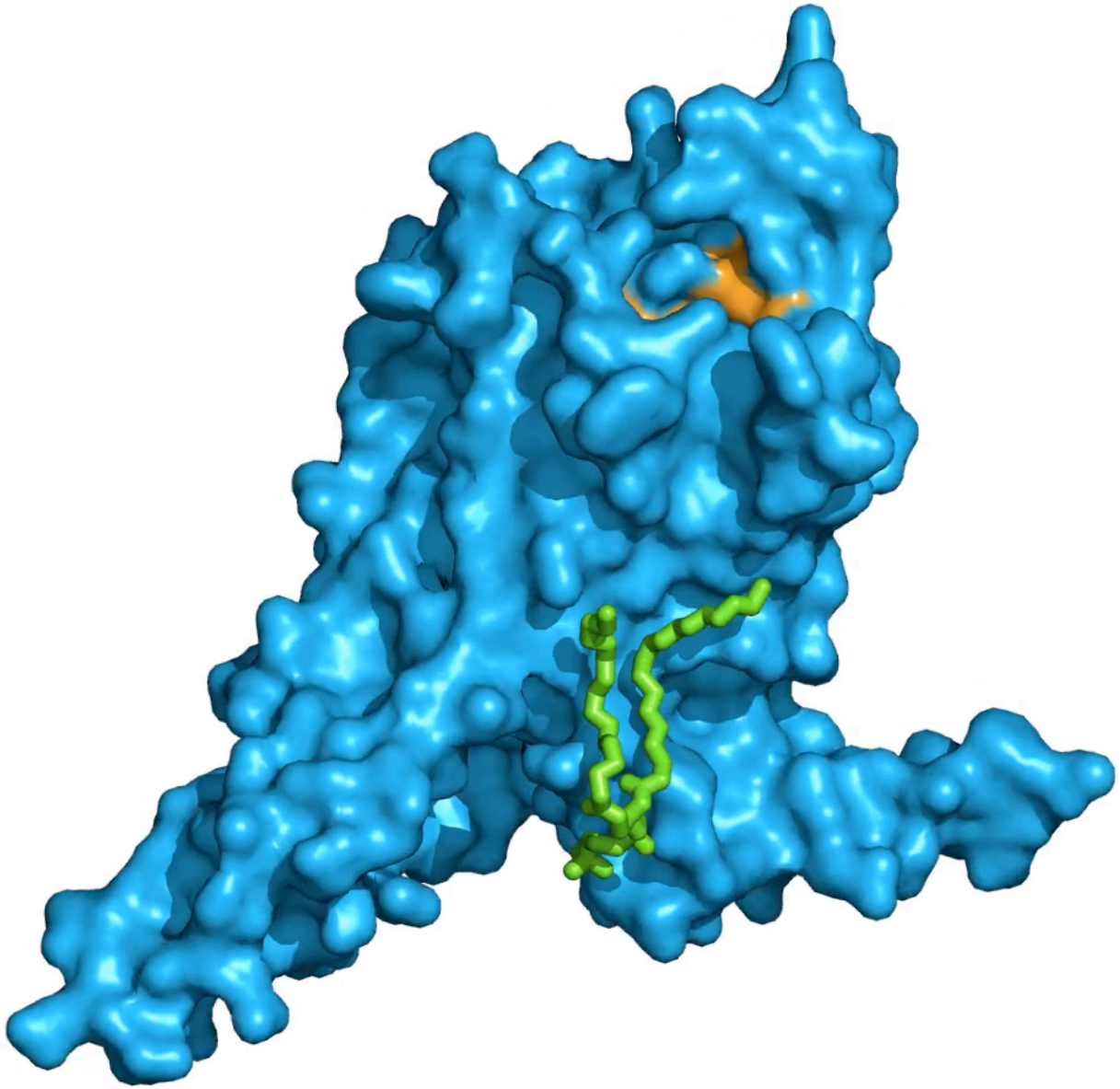

thx.

BiteNet web-server is available for academia
https://sites.skoltech.ru/imolecule/tools/bitenet/

Feel free to contact for collaboration

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