MS35 Artificial intelligence in photon and neutron crystallography, data mining, machine learning

MS35-05

Understanding Allostery in Purine Nucleoside Phosphorylases by Machine Learning and Molecular Dynamics Interaction Databases

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Abstract

Despite its fundamental importance, the mechanism of allostery is yet to be fully revealed in many proteins. One class of enzymes where allostery plays an intriguing role are Purine Nucleoside Phosphorylases (PNPs). These enzymes appear both in bacteria where they are homohexamers, and in higher organisms where they are present in homotrimeric form. They catalyse the synthesis of purine nucleotides in the purine salvage pathway and represent an ideal case for studying allostery. Although many 3D structures have been determined so far, understanding the mechanism by which monomeric subunits communicate in these enzymes has proven a daunting task by relying exclusively on structural data.

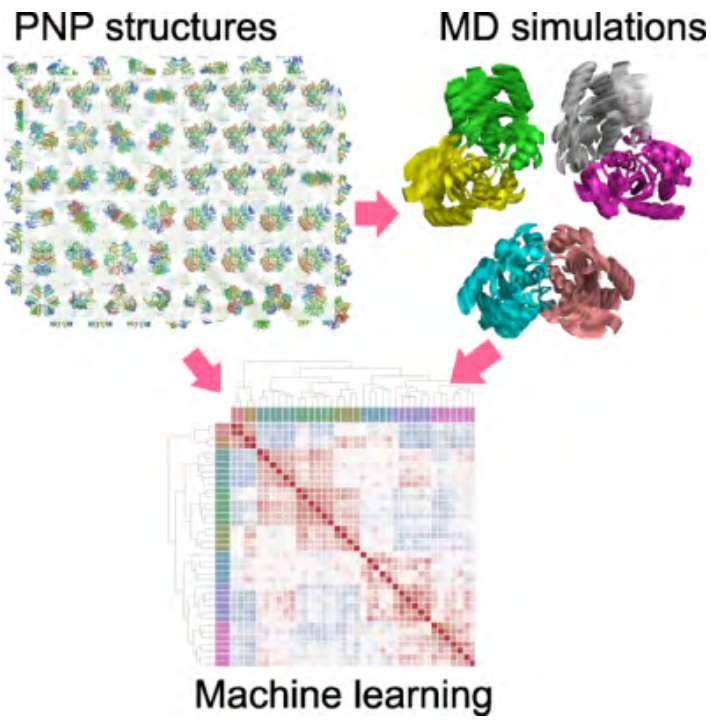
To understand allostery, which is in essence a dynamical phenomenon, it is necessary to employ not only static structures from X-ray crystallography, but also their dynamic counterparts from molecular dynamics simulations. If allosteric communication between amino acids is transmitted through non-covalent interactions, then the most natural way of tracing the allosteric pathways through protein is by following the time evolution of underlying interaction networks. Proteins can naturally be represented as networks, where nodes are amino acids and edges are various interactions between them, be it peptide bonds along the main chain, or various non-covalent interactions that may be present during time evolution.

However, tracing different communication pathways in static proteins structure provided by the X-ray experiments can be challenging. Adding a time evolution in form of molecular simulations on top of that multiplies the complexity of the problem many times, making it often unmanagable without using programmatic ways of processing the enormous amounts of data that are generated. To the rescue come powerful methods of machine learning that are specially adapted to process such quantities of data.

Helicobacter pylori represents a major global health threat. It is estimated that around 50% of the world population is infected with this bacterium. Because of the ever increasing number of antibiotic-resistant strains, there is a constant need for new drug targets of H. pylori. We have identified that PNP is a promissing drug target [1] against that pathogen. Specially designed molecular interaction databases have been applied in search for allosteric pathways in PNPs recently as part of the project Allosteric communication pathways in oligomeric enzymes (ALOKOMP, https://alokomp.irb.hr/). By enhancing the static information obtained from X-ray crystallography with dynamic time evolution obtained via molecular dynamics simulations and combining both in form of specially designed databases to which automated machine learning algorithms can be applied, it is hoped that elusive allosteric pathways can be identified in this class of enzymes.

References

[1] Marta Narczyk, Marta Ilona Wojtyś, Ivana Leščić Ašler, Biserka Žinić, Marija Luić, Elżbieta Katarzyna Jagusztyn-Krynicka, Zoran Štefanić & Agnieszka Bzowska (2022) Interactions of 2,6-substituted purines with purine nucleoside phosphorylase from Helicobacter pylori in solution and in the crystal, and the effects of these compounds on cell cultures of this bacterium, Journal of Enzyme Inhibition and Medicinal Chemistry, 37:1, 1083-1097, DOI: 10.1080/14756366.2022.2061965


PNP structures
MD simulations
Machine learning