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Allostery in Purine Nucleoside Phosphorylases Revealed by a Combination of Protein Crystallography and Molecular Dynamics Simulations

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PURPOSE OF THE ABSTRACT

Enzymes purine nucleoside phosphorylases (PNPs) [1] have been chosen as a model system for investigating allostery due to several compelling reasons. First, PNPs play a critical role in the purine salvage pathway by catalyzing the synthesis of purine nucleotides. This pathway is essential for maintaining cellular homeostasis and is conserved across various organisms. Second, PNPs exist in different oligomeric forms, such as homohexamers in bacteria and homotrimers in higher organisms, providing an opportunity to study the influence of the oligomeric state on allosteric behavior. Third, the structural and functional diversity observed in PNPs, coupled with the presence of allosteric binding sites, suggests the involvement of intricate communication networks within the protein. Investigating the allosteric mechanisms in PNPs can provide valuable insights into the general principles of allostery and aid in the design of novel strategies for modulating enzyme activity.

To fully comprehend the intricacies of allostery, which is fundamentally a dynamic phenomenon, it becomes imperative to move beyond the static structures obtained from X-ray crystallography and delve into the dynamic aspects using molecular dynamics simulations. Allosteric communication within proteins relies on non-covalent interactions between amino acids, and thus, unraveling the allosteric pathways necessitates an examination of the evolving interaction networks over time. Introducing time evolution through molecular simulations adds complexity that can only be managed by programmatic approaches capable of handling the vast quantities of data generated. In this context, machine learning methods emerged as invaluable tools, offering robust capabilities tailored specifically for processing and analyzing such voluminous datasets. By combining molecular dynamics simulations, programmatic data processing, and machine learning techniques, we started to uncover the intricate details of allosteric pathways in PNPs and gain deeper insights into the fundamental principles underlying protein function and regulation. This research is part of the ongoing project Allosteric communication pathways in oligomeric enzymes (ALOKOMP, https://alokomp.irb.hr/, financed by Croatian Science Foundation grant no. IP-2019-04-6764).

FIGURES

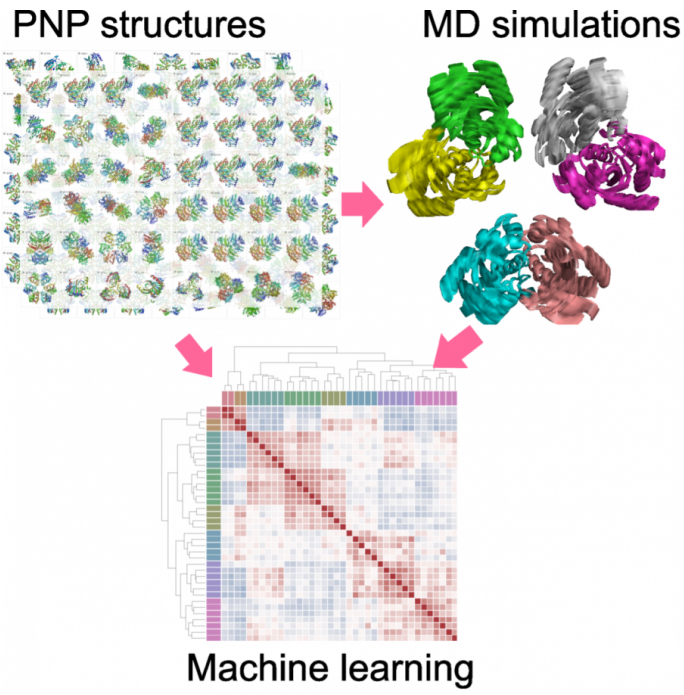

FIGURE 1

FIGURE 1

A scheme of the conducted research.

FIGURE 2

KEYWORDS

allostery | Purine Nucleoside Phosphorylases | protein crystallography | molecular dynamics simulations

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