Allostery is a fundamental property that allows the regulation of function and dynamic adaptability of enzymes and proteins. Gaining a detailed understanding of allostERIC mechanisms would provide more precise control of enzyme function and roadmaps for the expansion of drug discovery beyond the active site responsible for catalytic activity. Here, we combine molecular dynamics (MD) simulations, nuclear magnetic resonance (NMR), and correlation analysis of protein motions based on network theory methods (i.e., the studies of graphs as a representation of relations between discrete objects such as the amino acid residues in proteins) and elucidate the allostERIC mechanism of the enzyme imidazole glycerol phosphate synthase (IGPS) from the thermophile Thermotoga maritima. IGPS is a heterodimeric enzyme that catalyzes the hydrolysis of glutamine (Gln) (Fig. P1). IGPS is not present in mammals but is involved in essential biosynthetic pathways of microorganisms. In particular, many plant pathogens and, importantly, opportunistic human pathogens such as Cryptococcus, Candida, and Ajellomyces have an IGPS that is highly homologous to the T. maritima enzyme. The allostERIC IGPS complex is, thus, a potential target for antifungal, antibiotic, and herbicide development. We have elucidated the allostERIC pathway that correlates the IGPS effector and active sites. Such insight should provide useful information for the design of molecules that might hamper the activity of the sites. This study provides valuable insight to address these questions, we explore the effect of PRFAR on correlated motions of amino acid residues and use this information to evaluate how effector binding affects the protein network of the unbound (apo) enzyme. We find that PRFAR binding induces changes in fundamental interactions correlating the effector and active sites that are essential for the allostERIC mechanism. The resulting protein motions partially promote rotation of the conserved oxoanion strand, responsible for the inactive-to-active allostERIC transition (Fig. P1). The analysis thus shows evidence that PRFAR binding alters the community structure of interactions in the inactive IGPS, along with the collective pathways linking the effector and active sites. This study provides valuable insight.
into the mechanism of information transfer in this V-type allosteric enzyme.

The rearrangement of the communication pathways induced by PRFAR involves the flexible loop1 and the hydrophobic region ($fβ2$) near the allosteric site (Fig. P1); ionic interactions in the interdomain region next to loop1 (sideR), including residues in the $fa2$, $fa3$, and $ha1$ helices; as well as a hydrogen bond between the $Ω$ loop and the conserved 49-PGVG sequence (oxygen strand) adjacent to the glutaminase active site. The proposed allosteric mechanism is supported by the computational analysis of early protein dynamics in conjunction with NMR chemical shifts and relaxation dispersion experiments probing millisecond protein motions. Single amino acid residues, such as $fL50$, $fR59$, $fE91$, and $hP10$, play an important role in the allosteric mechanism and should be good candidates for unique mutagenesis studies. The combined approach we describe is an effective strategy for exploring the signaling pathways in any other allosteric systems.