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Computational characterization of protein allosteric pathways

The Science

A computational technique to identify key amino acids in the regulation of a bacterial enzyme essential for most microorganisms has been developed. The technique is based on the eigenvector centrality (EC) metric, which is also used by Google to rank webpage visits. Instead of web pages, we rank the importance of amino acid residues in the transmission of energy in the allosteric mechanism.

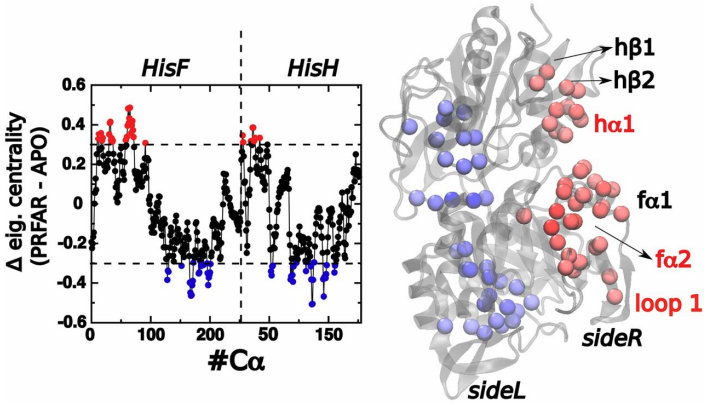

Illustration 2: *Centrality differences (PRFAR-bound – APO) for an exponential damping λ=5 Å as a function of the residue index (Left) and plotted on top of the protein representation (Right). Red and blue values are regions that, respectively, gain and lose centrality upon PRFAR binding. The domains with higher PRFAR-induced centrality increase are loop1 (HisF: 16–31), fα1 (HisF: 31–43), fα2 (HisF: 59–72), hβ1 (HisH: 1–5), hα1 (HisH: 12–25), and hβ2 (HisH: 30–35).*

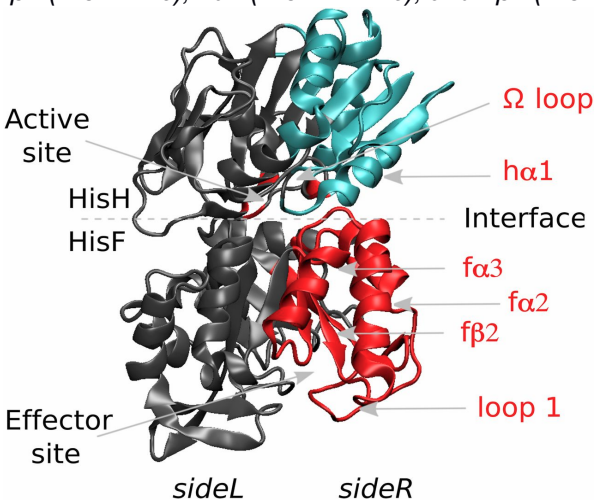

Illustration 1: *Molecular representation of IGPS. Red labels indicate secondary structure elements that are directly involved in the allosteric regulation. Communities h2 (cyan) and f3 (red) in the sideR of IGPS are also depicted.*

The Impact

Allosteric processes are ubiquitous in macromolecules and regulate biochemical information transfer between spatially distant sites. Despite decades of study, allosteric processes remain generally poorly understood at the molecular level. Here, we have introduced the eigenvector centrality measure of mutual information to disentangle the complex interplay of amino acid interactions giving rise to allosteric signaling. The analysis of eigenvector centrality is tested in imidazole glycerol phosphate synthase (IGPS), a prototypical V-type allosteric enzyme present in bacteria. The resulting insights allow us to pinpoint key amino acids in terms of their relevance in the allosteric process, suggesting protein-engineering strategies for control of enzymatic activity. This is hence an attractive target for antibiotic development.

Summary

The HisH part of the IGPS enzyme promotes the hydrolysis of glutamine (Gln) to produce ammonia, which diffuses to the HisF subunit and reacts with the effector (PRFAR) to form imidazole glycerol phosphate and AICAR. While Gln binding is unaffected by the presence of PRFAR, the hydrolysis of Gln is accelerated 5,000-fold upon PRFAR binding through a mechanism that, for many years, has remained elusive.

Proteins can be represented as networks where nodes correspond to amino acid residues. The strength of the edges correspond to the magnitude of a physical property. For a network of N nodes, we describe the corresponding graph by an $N \times N$ adjacency matrix A with elements $A_{ij} = r_{ij}\exp(-d_{ij}\lambda)$, where r_{ij} is the correlation coefficient between residues i and j, and d_{ij} the distance between them. λ is a damping factor that can be adjusted to filter out long distance correlations. One of the cornerstones of network analysis is the concept of centrality—that is, the relative importance of an individual member in a group. The EC values c_i are computed by diagonalizing A and keeping the eigenvector c corresponding to the maximum eigenvalue. The information encoded on the resulting eigenvector c reveals the importance of the nodes for the whole connectivity of the network. The nodes with the highest centralities will act as the principal "channels" for momentum transmission across the protein (see illustration 2). The eigenvalue ϵ, in turn, gives a measure of the overall network degree of connectivity.

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Publication

Eigenvector centrality for characterization of protein allosteric pathways; Christian F. A. Negre, Uriel N. Morzan, Heidi P. Hendrickson, Rhitankar Pal, George P. Lisi, J. Patrick Loria, Ivan Rivalta, Junming Ho, and Victor S. Batista; PNAS; December 10, 2018 https://doi.org/10.1073/pnas.1810452115

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