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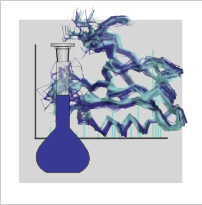

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Probing the Dynamic Nature of Protein Allostery *via* NMR

Henry Wetton, Olivia Gampp, and Roland Riek*

*Correspondence: Prof. R. Riek, E-mail: roland.riek@phys.chem.ethz.ch
Institute of Molecular Physical Science, Vladimir-Prelog-Weg 2, CH-8093 Zurich

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Since the cooperative interaction between haemoglobin and oxygen was first described over 60 years ago, protein allostery – two ligands binding to a protein at different sites influencing each other's binding affinities – has fascinated structural biologists due to its potential in understanding enzyme regulation, elucidating biological mechanisms, and developing new therapeutics.

Studies of allosteric systems began using only static X-ray crystal structures and have now progressed to simulated trajectories of atomic motion to provide insights into changes in structural dynamics. Thanks to developments in NMR methods, it is also possible to analyse protein motion directly using experimental data in the proteins' native environment.

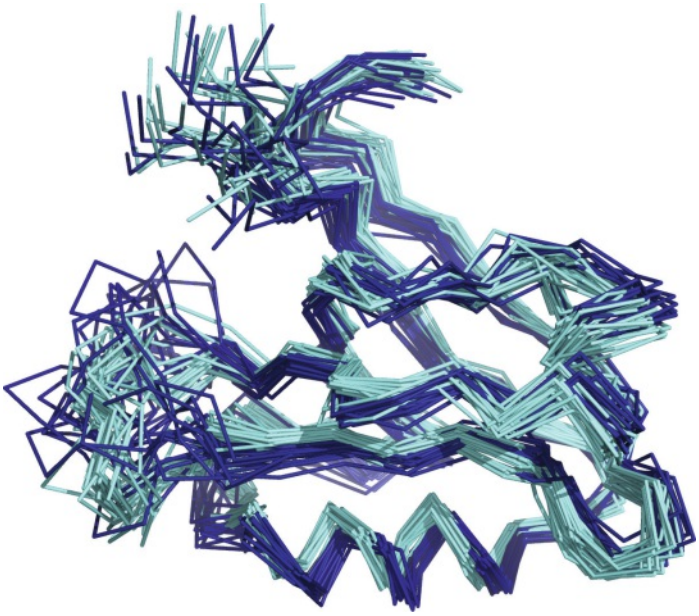

Fig. 1. Two-state structure of the PDZ2 domain of the protein human tyrosine phosphatase 1E, determined using eNOE NMR spectroscopy (PDB ID 7QCX). State A is shown in cyan and state B in blue. Each state is represented by 20 conformers, highlighting the quality of the data (root mean square deviation).

Many NMR techniques used for allostery studies are based on differences in spectra upon addition of a known allosteric ligand to a protein. Others use specific pulse programs to capture structural changes on a long timescale. Our eNOE (exact Nuclear Overhauser Effect) technique takes a different approach by building on the standard NOESY method of protein structure determination by NMR and significantly increasing the number and precision of distance restraints extracted from the primary data. This allows structure calculation of multiple states from a single set of measurements, thus enabling experimental investigation of allostery at an atomic level. For example, applying this method to the PDZ2 domain of human tyrosine phosphatase 1E in a recent study yielded detailed insights into its allosteric regulation mechanism upon binding of a peptide ligand.

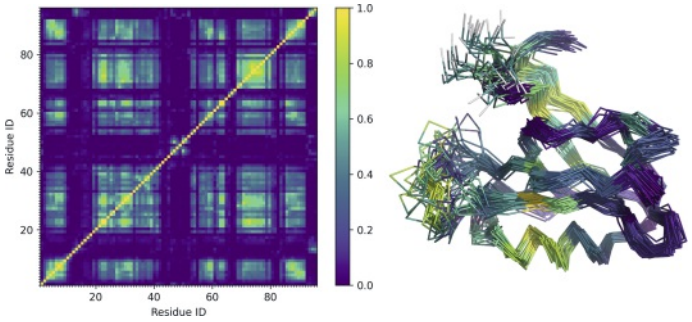

Fig. 2. **Left**: Inter-residue correlation values obtained from distance-based PDBCor analysis of multi-state PDZ2, representing the allosteric network. **Right**: Average correlation between each residue and its neighbours projected onto the 7QCX protein structure using the same colour scheme.

An additional challenge is the detection of correlated motion or allosteric networks given an ensemble of protein structures. Many approaches originate in the molecular dynamics field and require 3D superposition of each available structure prior to analysis. Our software package PDBCor provides an alternative approach to this problem by using information theory to identify correlation based purely on dihedral angles or intra-structural distances in a bundle of protein conformers.[1]

In conclusion, NMR spectroscopy is an ideal method for the experimental investigation of protein allostery at atomic resolution due to its dynamic nature and the development of specifically tailored methods.

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Reference

[1] O. Gampp, H. Kadavath, R. Riek, *Curr. Opin. Struct. Biol.* **2024**, *86*, 102792, https://doi.org/10.1016/j.sbi.2024.102792.

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Please contact: Dr. Veronika R. Meyer, Unterstrasse 58, CH-9000 St. Gallen
Tel.: +41 71 222 16 81, E-mail: analytical_highlights@chimia.ch