

Integrating Genomic Information with Molecular Simulation to Understand Protein Complex- and Active Conformation Formation in Two-Component Signal Transduction

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Protein function often requires a protein to form a complex or adopt multiple conformations during its functional cycle. Many of these states are transient or unstable and their full structural characterization remains a daunting experimental task. Here, we demonstrate a multi-disciplinary approach that can predict such structures for the common prokaryotic protein class of two-component signal transduction systems (TCS). TCS enable cells to sense and react to external stimuli. A membrane bound sensor histidine kinase (SK) detects an environmental stimulus and forms a complex with a transcription factor/response regulator (RR) transferring a phosphoryl group to mediate a cellular response. The complex is ruled by transient interactions. Despite decades of experimental studies, only few experimental structures are available: none of them trapped during autophosphorylation and only recently was a complex structure of a SK/RR pair structurally resolved [1]. Concurrently, we predicted this complex structure in high agreement (3.5 RMSD) with the experimental work by combining molecular dynamics and statistical genomic analysis [2,3]. Based on this theoretical work, it is now possible to also predict the structural changes occurring during autophosphorylation. Direct coupling analysis [3] identifies innerprotein pairings formed between the HisKa and ATP-binding domains which are not realized in the (inactive) crystal structure. This information can be used in molecular dynamics simulations to identify an active conformation adopted during autophosphorylation in agreement with biochemical mutagenesis data [4].

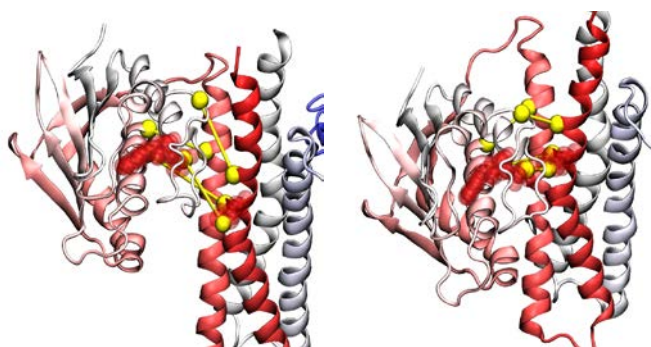


Figure 1: As part of its functional cycle histidine kinases autophosphorylate. A genomic analysis identifies inter-domain residue pairings (yellow) not realized in the crystal structure (left). This information is sufficient to predict the active conformation in Molecular Dynamics simulations. This active conformation is confirmed by mutagenetic experiments.

References

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- [3] Weigt M et al., *Identification of direct residue contacts in protein-protein interaction by message passing*, Proc Nat Acad Sci USA (2009) 106, 67-72
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