IDPs are overrepresented in processes such as signalling and transcription, where proteins often interact with a range of partners. One much-studied key hub protein is the coactivator CBP/p300, whose folded KIX domain binds a number of different intrinsically disordered transcription factors at two separate sites on its surface. The interaction of KIX with several of its ligands has been well studied by equilibrium methods, and structural information is available for many of the complexes. By careful control and consideration of experimental conditions such as temperature and ionic strength we have been able to perform kinetic studies that reveal the mechanism of the association reaction of KIX with cMyb; the fastest protein-protein interaction yet reported. We further describe the mechanistic basis for the positive allostery between the two binding sites of KIX. Through comparative studies with several different binding partners we shed light on an important outstanding question in the IDP field: what is the advantage of disorder to a protein?

**Abstract**

IDPs are overrepresented in processes such as signalling and transcription, where proteins often interact with a range of partners. One much-studied key hub protein is the coactivator CBP/p300, whose folded KIX domain binds a number of different intrinsically disordered transcription factors at two separate sites on its surface. The interaction of KIX with several of its ligands has been well studied by equilibrium methods, and structural information is available for many of the complexes. By careful control and consideration of experimental conditions such as temperature and ionic strength we have been able to perform kinetic studies that reveal the mechanism of the association reaction of KIX with cMyb; the fastest protein-protein interaction yet reported. We further describe the mechanistic basis for the positive allostery between the two binding sites of KIX. Through comparative studies with several different binding partners we shed light on an important outstanding question in the IDP field: what is the advantage of disorder to a protein?

**References**

1. Ward et al., 'Prediction and Functional Analysis of Native Disorder in Proteins', 2004, JMB
2. Wright and Dyson, 'Linking Folding and Binding', 2009, Curr Opin Struct Biol
3. Tserkov et al., 'Molecular Recognition by the KIX domain and its Role in Gene Regulation', 2014, Nucl Ac Res
4. PDB codes 1SBQ, 1OD2, 2LUG, 2WOF, 2AZH, 2LXT
5. Somekeri et al., 'Spatial recognition of binding partners by the KIX domain', 2000, PNAS
7. Cooper and Dryden, 'Allosteric without Conformational Change – a Plausible Model', 1964, Eur Biophys J

**Figures**

- **Figure 1:** Mechanism of coupled folding and binding
- **Figure 2:** Mechanism of allostery
- **Figure 3:** Conformational Selection
- **Figure 4:** Mechanistic models