Intrinsically disordered proteins (IDPs) are attractive therapeutic targets as they are implicated in several classes of diseases such as cancers or neurodegenerative disorders. However because IDPs do not adopt a well-defined structure that could guide ligand discovery, few small molecule inhibitors of IDP function have been identified. An intriguing example is provided by a series of small molecules that inhibits the c-Myc/Max protein-protein interaction by binding to monomeric and disordered c-Myc, an IDP involved in several cancers.¹

To rationalize the mechanism of binding, structural ensembles for selected segments of the c-Myc bHLHzip domain that bind different small molecules were computed in the absence and presence of the ligands using classical force fields and the bias-exchange metadynamics simulation technique.² Accuracy of the computed ensembles was evaluated by comparison to predicted and measured observables (e.g. NMR chemical shifts). Comparison of the apo and holo equilibrium ensembles reveals that the ligands bind to multiple c-Myc conformations and inhibit c-Myc/Max formation through an extended conformational selection mechanism. These results suggest a computational strategy for the rational design of small molecule modulators of IDP function.