Predicting functional sites in disordered proteins – implications in disease

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Abstract. Proteins that exist without a stable, well-defined 3D structure in their isolated form (Intrinsically Disordered/Unstructured Proteins – IDPs/IUPs) are known to play crucial roles in biological systems. IDPs are often involved in molecular recognition processes via their disordered binding regions that can recognize partner molecules by undergoing a coupled folding and binding process. The unique thermodynamics properties of these interactions enable a very specific binding mode giving way to specific yet transient protein complexes. Apart from the structural approach of these interactions there exists an alternative model for the discussion of this binding mode, offered by the concept of linear motifs. This approach focuses on the sequence of the disordered proteins with a common ordered interaction partner. From the disordered sequences a short consensus sequence pattern (motif) is distilled, which are considered to mediate the interaction roughly independent from the rest of the protein.

Despite the several common examples, the full exploration of the complementary nature of the two description models is still lacking. In this talk we demonstrate a bioinformatics approach to predicting both disordered binding regions and linear motifs and the feasibility and biological relevance of their combination. The rationale behind the combined predictions are demonstrated not just on individual examples but at a systems level as well. These results show that these unified predictions not just offer a more efficient binding site prediction that can serve a wide range of practical implications, but can also shed light on the theoretical connection between the two co-existing interaction models. Furthermore, we also show that the functional protein regions thus identified can play a central role in tumorigenesis and a combined approach can highlight possible novel protein targets for treatment.

Keywords: disordered proteins; functional site prediction; linear motifs; disordered binding regions; ANCHOR; cancer