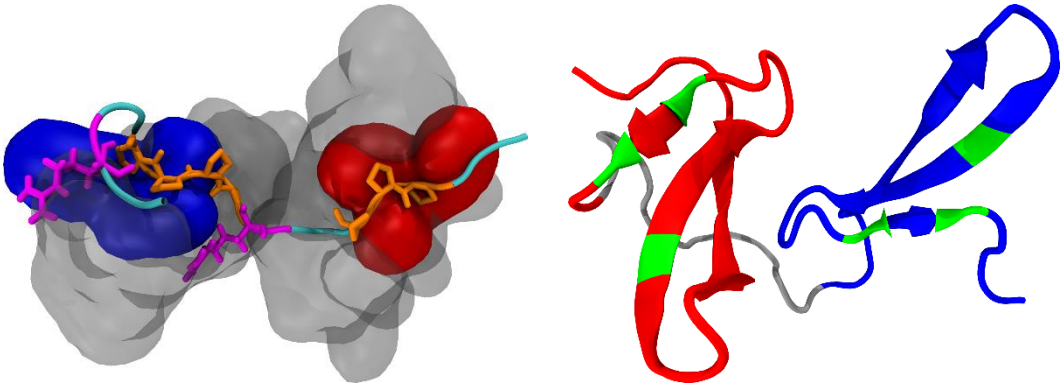
In search of binding competent structures of the tWW domain using classical molecular dynamics simulations

M. Wenz, S. Aleksić, B.G. Keller

Department of Biology, Chemistry and Pharmacy
Institute for Chemistry and Biochemistry,
Freie Universität Berlin,



WW domains, protein modules consisting of 35 to 40 amino acids, are known for mediating protein-protein interactions (PPIs) through recognition of proline-rich motifs (PRMs).[1-2] Their name is derived from two highly conserved tryptophanes (W) that have two tasks: first, stabilizing the main structure of the domain, a triple-stranded, antiparallel β −sheet, and second, forming the binding site together with serine (S) and tyrosine (Y).[3] WW domains can be found in many signalling and regulatory proteins such as the formin-binding protein 21 (FBP21).[4]

FBP21 contains two successive WW domains, forming the **tWW domain**. It is directly involved in the splicing process of the RNA as it can bind to the small nuclear ribonucleoprotein-associated protein SmB/B' that arises in four of the five major components of the spliceosome (small nuclear ribonucleoproteins).[5-6] This binding process can be traced back to the tWW domains of FBP21 recognizing a proline-rich sequence (PRS) that is formed by two PRMs of SmB/B'.[7-8]

In this work, the investigation of the apo-tWW domain with respect to the identification of possible, binding-competent structures is presented. Based on all-atom molecular dynamics simulations (MD simulations) and the density-based common-nearest neighbor algorithm [9-10], we show that it is possible to extract binding-promising metastable states out of the conformational ensemble of the tWW domain. Using the structure of a specific, literature-known PRS of SmB/B'[11], we performed docking experiments with HADDOCK protocol[12] for the most promising tWW structures. The docking results are in accordance to literature regarding the binding relevant residues.[6, 8] Ensuing MD simulations confirmed the stability of the obtained protein-protein complexes. Due to this, we can assume the tWW structures involved to be representative binding-competent structures. Running MD simulations of the protein-protein complexes, we also examined the influence of mutations within the PRS on the stability of the entire complex.

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