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What docking studies tell us about the role of disordered protein fragments in macromolecular assembly

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Statement of the Problem: Many proteins present highly flexible or disordered fragments, either terminal tails or surface loops. Although they often form instable and transient interactions, these fragments play essential roles in regulating macromolecular association or controlling the architecture of supramolecular complexes. The role of their conformational variability in complex formation is poorly understood and requires the development of specific approaches.

Methodology & Theoretical Orientation: We have studied the effect of protein segment conformational variability in protein-protein complex formation as well as peptide docking using theoretical docking approaches. Notably, we have developed a flexible docking method that accounts for the presence of flexible loops, together with analysis protocols that capture the entropic effects associated to structural variability in flexible docking results.

Findings: Whether the flexible segment is a loop or a peptide, we have found that a given mode of association can be stabilized by different conformations of the segment. Alternatively, different loop conformations can stabilize different modes of protein-protein association.

Conclusion & Significance: Tolerance of a binding site to conformational variability, as observed in protein-peptide docking but also in the association of proteins with flexible loops or segments, can play a role in adding a conformational entropy component to the energy of association, thus favoring the initial binding of the flexible fragment to its binding site. For proteins that associate using different binding geometries, either with different partners or along a functional pathway, loop flexibility can also be used to regulate the choice of the binding geometry.

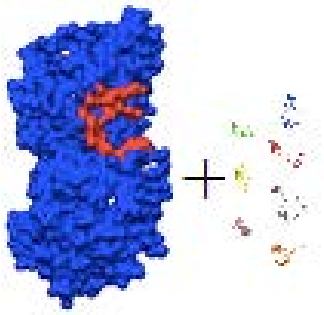

Figure1: *Mapping the interaction energy between the α, β tubulin dimer and the NFL-TBS.40-63 peptide from the docking simulations of seven different conformations of the peptide. The high affinity sites are shown in red, the low affinity sites are in blue. The affinity is defined as the energy-weighted probability of a tubulin surface atom to be involved in a docked interface.*

Biography

Chantal Prevost is a Researcher at the Theoretical Biochemistry Laboratory (LBT) of the French National Research Center (CNRS), in Paris. She has developed a large expertise in studying macromolecular self-assembly *in silico*, either by elaborating new algorithms for flexible proteins docking or by studying fundamental biological processes involving the transition between instable conformational substates. She presently applies this expertise to exploring the architecture or oligomeric assemblies as well as elucidating the mécanismes of homologués recombination, in collaboration with experimental partners.

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