

Fragment-based modeling of protein-bound ssRNA

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Protein-RNA recognition supports many cellular functions, and abnormal protein-RNA interactions are crucial therapeutic targets in *e.g.* neurodegenerative diseases and RNA viruses infections. Moreover, synthetic RNA aptamers are used as protein modulators [ref in 1]. The rational conception of either aptamers or RNA-protein interaction inhibitors requires atomistic description of protein-RNA complexes. Yet their experimental resolution is arduous, and protein-RNA computational docking is hampered by the high flexibility of RNA single-stranded regions, which mostly provides recognition specificity. The lack of methodology for modeling ssRNA limits all protein-RNA docking methods [2].

We developed an original fragment-based approach, accurately predicting ssRNA-protein complexes structure from only protein structure and RNA sequence: We

- (i) cut the RNA sequence in overlapping trinucleotides, represented by sequence-specific conformer-ensembles in a fragment library built from known protein-RNA structures;
- (ii) dock each conformer-ensemble on the protein;
- (iii) select the spatially compatible poses;
- (iv) assemble them in a realistic conformation.

Moreover, we developed and validated an RNA-protein contacts predictor, based on statistical analysis of known complexes, which provides (optional) starting points for the fragments docking.

We applied them on ten complexes with various ssRNA sequences (6-11 nucleotides) and RNA-recognition domains. Without predicting specific contacts, we identify the RNA binding site more accurately than all existing methods [3]. Predicting 3-4 contacts, we model ssRNA within 1-2Å RMSD. Such crystallographic-like precision, never reached so far [1], reveals a methodological breakthrough in RNA-protein docking.

[1] Chauvot-de-Beauchene *et al* (2016) *NAR* 44(10):4565-4580

[2] Fulle, Gohlke (2010) *JMR* 23(2):220-231

[3] Chauvot-de-Beauchene *et al* (2016) *PloS.Comput.Biol.* 12(1):e1004697