Dynamics of Protein–RNA Interfaces Using All-Atom Molecular Dynamics Simulations

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Facing the current challenges posed by human health diseases requires the understanding of cell machinery at a molecular level. The interplay between proteins and RNA is key for any physiological phenomenon, as well protein–RNA interactions[1]. For example, the formation of ribonucleoprotein particles (RNPs) including mRNAs is key for the post-transcriptional regulation of gene expression[2].As another example, many viruses manipulate the translation initiation complexes to ensure their replication, by recruiting the host ribosomes to translate their mRNA[3]. To understand these interactions, many experimental techniques have been developed, spanning a very wide range of spatial and temporal resolutions. In particular, the knowledge of tridimensional structures of protein–RNA complexes provides structural, mechanical, and dynamical pieces of information essential to understand their functions. However, obtaining high-resolution tridimensional structures through high-resolution techniques is still a challenging task as shown by the relatively small number of structures deposited in the Nucleic Acid Data Bank (NDB) [4]. The limited number of known complex structures is nevertheless constrained by the inherent flexibility of proteins and/or RNA and the size of the complexes. To overcome that, low resolution data have been used to model these structures. To get insights into the dynamics of protein–RNA complexes, we carried out all-atom molecular dynamics simulations in explicit solvent on nine different protein–RNA complexes with different functions and interface size by taking into account the bound and unbound forms. A detailed analysis was conducted on the RNA structure, including the change of ribose puckering upon binding for its potential interest to better understand biochemical reactivity data as SHAPE. Then, we focused on the characterization of the stability of their interfaces and interfacial water molecules. To determine the presence or the absence of interface substates, in each system, we analyzed in detail the time evolution of the contacts between interface residues and we performed a hierarchical clustering on our trajectories based on the interface residue–residue contacts. Moreover, we characterized the interactions at the interface and the interface geometries, as well as the evolution of the contacts between interface residues and water molecules and the pairs of residues involved in mediated interactions via water molecules. Finally, in the case of alternative interfaces obtained with our approach, we performed a dynamic network analysis to assess how the change of contacts at the interface could impact the communication in the complex and to gather novel biological insights.

Keywords: protein-RNA complexes; molecular dynamics simulations; interfaces; dynamics

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