SAXS data-driven modeling of RNA 3D structures

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The majority of known RNAs exert their cellular functions in complexes with other molecules (proteins and/or small molecules). Many RNAs are known to or have been predicted to interact with small molecule ligands, which emphasizes their importance as potential therapeutic targets. However, in order to discern the molecular functions of such interactions, it is important to understand the three-dimensional (3D) structure of the RNA molecules, in the presence and the absence of ligands. Due to the difficulties associated with the experimental determination of high-resolution RNA structures, experimental data-aided computational modeling has become an important approach in generating high-quality theoretical models[1]. The inherent flexibility of RNA molecules allows it to sample a large conformational space. This hints at the fact that its 3D structure is best represented by an ensemble of atomistic structures rather than a single structural model.

The small angle X-ray scattering technique describes the distribution of electron density in a molecule and hence can be used to interpret the low-resolution envelope of a biomolecule. My group has developed a computational workflow for SAXS data-driven modeling of RNA 3D structures and their ensembles. The workflow involves exploration of the conformational space with the SimRNA program (using a coarse-grained representation and a statistical potential to generate physically realistic structures)[2] to generate large sets of plausible conformations of the target RNA structure. The large sets of generated decoys are scored against experimental SAXS data using CRYSOL[3,4], followed by clustering, ensemble optimization[5,] and refinement with QRNAS. The structural ensemble collectively explains the scattering pattern of the RNA molecule. The workflow also allows the use of data from other sources, such as information about RNA secondary structure from computational predictions or experimental probing[6].

Our method is capable of modeling 3D structures of RNA molecules, as well as those of RNA-protein and RNA-ligand complexes. In case of complexes, this method in conjunction with experimental restraints from other techniques, also allows us to identify a predominant binding mode of the RNA and its partner. We have applied our methods to case studies involving RNA molecules and complexes of different size.

References

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