
Understanding the interplay between RNA molecular flexibility, structure and chemical probing using all-atom molecular dynamics simulations

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Abstract

Ribonucleic acid (RNA) molecules are involved in most steps of the genetic expression including catalysis of central cellular functions. RNA function depends crucially on the specific tridimensional folding of the molecule which in turns depends on the sequence and on the way the bases pair through hydrogen bonds (secondary structure). Hence, determination of RNA tridimensional structures is fundamental for understanding their function. A common method to investigate RNA structures of large molecules is the use of chemical probes such as SHAPE (2'-hydroxyl acylation analyzed by primer extension) reagents, DMS (dimethyl sulfate) and CMCT (1-cyclohexyl- 3-(2-morpholinoethyl) carbodiimide metho-p-toluene sulfate), the reaction of which is dependent on the local structural properties of each nucleotide. In order to understand the interplay between local flexibility, sugar pucker, canonical pairing and chemical reactivity of the probes, we performed all-atom molecular dynamics simulations on a set of RNA molecules for which both tridimensional structure and chemical probing data are available and we analyzed the correlations between geometrical parameters and the chemical reactivity. Our study confirms that SHAPE reactivity is guided by the local flexibility of the different chemical moieties but suggests that a combination of multiple parameters is needed to better understand the implications of the reactivity at the molecular level. This is also the case for DMS and CMCT for which the reactivity appears to be more complex than commonly accepted.

Keywords: RNA, chemical probing, molecular modelling, flexibility

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