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Developing an accurate force field for simulating modified RNA

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Motivation and Aim: Post-transcriptional modifications occur extensively in RNA and provide an additional layer of chemical coding that presumably alters the chemistry, structure and dynamics of the molecules. Molecular dynamics simulations offer a convenient tool to elucidate the mechanisms underlying the roles played by such modifications. However, since the reliability of the simulation results depend on the accuracy of the force field employed, we tested some of the available force field parameters for modified RNA residues for the AMBER molecular modeling suite of programs. The results from our work revealed that the available parameters from the AMBER distribution were inadequate in reproducing the experimentally observed conformational distributions [1].
Methods and Algorithms: We earlier adopted a procedure for reoptimizing the dihedral parameters of a few modified uridines using high-level ab initio calculations [2]. Subsequently, we have revised the method to incorporate the recalculation of partial charges and the reoptimization of selected dihedrals. The revised parameters are currently applicable to a much larger set of modified RNA residues.
Results: The reoptimized parameter set has been validated against experimentally observed conformational distributions for a considerable number of modified residues. We have also shown that for some of the modifications, like 2-thiolation of uridines and pseudouridylation, the modifications stabilize the RNA structure. A major role in such stabilization is played by the enhancement in stacking interaction.
Conclusion: The results obtained suggest that the combination of AMBER force field for RNA with our reoptimized set of dihedral parameters and the recalculated partial charges provide a better agreement with experimental data and as such should be more useful in producing a more accurate model of the structure and function of modified RNA.
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References

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