MAS17-2017-000120

Abstract for an Invited Paper
for the MAS17 Meeting of
the American Physical Society

Progress and challenges in the atomistic simulation of nucleic acids

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Molecular dynamics (MD) simulation has become a powerful tool for characterizing at an atomic level of detail the conformational changes undergone by proteins. The application of such simulations to RNA structures, however, has proven more challenging, due in large part to the fact that the physical models ("force fields") available for MD simulations of RNA molecules are substantially less accurate in many respects than those currently available for proteins. Here, I will present a revision of a widely used RNA force field in which the parameters have been modified, based on quantum mechanical (QM) calculations and existing experimental information, to more accurately reflect the fundamental forces that stabilize RNA structures. We evaluated these revised parameters through long-timescale MD simulations of a set of RNA molecules that covers a wide range of structural complexity, including single-stranded RNAs, RNA duplexes, RNA hairpins, and riboswitches. The structural and thermodynamic properties measured in these simulations exhibited dramatically improved agreement with experimentally determined values. Based on the comparisons we performed, this new RNA force field appears to achieve a level of accuracy comparable to that of state-of-the-art protein force fields. Although it represents an improvement in various respects, the force field is still based on rather crude approximations of the physics, and outstanding issues will be discussed.