INTRODUCTION

As more is understood about the biological importance of RNA, the ability to peer into this biomolecule’s dynamics on an all-atom level is of increasing interest. For example, it is known that RNA molecules (riboswitches) can detect the concentration of certain metabolites and, with recent force-field modifications, are able to properly sample RNA conformational distributions in agreement with experiment. This opens the door for the simulations we really want to perform; rather than simple assessment and validation of simulation results, we can use these powerful biomolecular simulation methods to provide significant insight into functional RNA structure and dynamics in riboswitches, ribozymes, interfering RNA, and protein–nucleic acid interactions.

METHODS & RESULTS

By using multi-dimensional replica exchange MD (M-REMD), we have shown that we can reproducibly and efficiently generate complete structure ensembles for a variety of RNA motifs. In previous simulations we found that a particular tetrannucleotide, rGCAC, sampled a wide range of conformations, though experimental nuclear magnetic resonance spectroscopy results indicated only two major structures were present [6,7]. Using Blue Waters, we have been able to diverge the limitation of sampling from the dynamics and structures described by the force fields, allowing a totally unbiased look at each force field’s description of both DNA and RNA [1–5].

WHY BLUE WATERS?

A key innovation enabling our work is the implementation of AMBER on NVIDIA GPUs. This results in the fastest molecular dynamics code available to date [10]. Improvements in the past year have included the ability to esparition the solute’s hydrogen masses, allowing us to double the simulation time step and achieve an almost instant two-fold increase in simulated time vs. real time [11]. Combined with the M-REMD framework, this very effectively reduced, by orders of magnitude, the real-world time needed to obtain the converged ensemble. With larger ensembles and combined ensembles enabled by the next generation of Track-1 systems, we will be able to move into the detailed investigation of more bio-relevant nucleic acid structures including riboswitches, ribozymes, and various protein–nucleic acid interactions with full reproducibility and convergence of the results.

PUBLICATIONS


Over the past 20-plus years, we have developed and used biomolecular simulation methods to provide insight into nucleic acid structure and dynamics. Along the way, we have faced significant challenges in the form of force-field and sampling limitations. With access to resources like Blue Waters, we have reached the tipping point where we can fully sample ensembles of small RNA molecules and DNA helices and, with recent force-field modifications, are able to properly sample RNA conformational distributions in agreement with experiment. This opens the door for the simulations we really want to perform; rather than simple assessment and validation of simulation results, we can use these powerful biomolecular simulation methods to provide significant insight into functional RNA structure and dynamics in riboswitches, ribozymes, interfering RNA, and protein–nucleic acid interactions.

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Executive Summary:

Convergence and reproducibility in simulations of nucleic acids

Over the past 20-plus years, we have developed and used biomolecular simulation methods to provide insight into nucleic acid structure and dynamics. Along the way, we have faced significant challenges in the form of force-field and sampling limitations. With access to resources like Blue Waters, we have reached the tipping point where we can fully sample ensembles of small RNA molecules and DNA helices and, with recent force-field modifications, are able to properly sample RNA conformational distributions in agreement with experiment. This opens the door for the simulations we really want to perform; rather than simple assessment and validation of simulation results, we can use these powerful biomolecular simulation methods to provide significant insight into functional RNA structure and dynamics in riboswitches, ribozymes, interfering RNA, and protein–nucleic acid interactions.

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