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Title : Accessing RNA Conformational Ensembles through Kino-Geometric Sampling

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RNA molecules often exhibit significant conformational flexibility, especially when they interact with ligands, proteins or nucleic acid partners to form assemblies. Efficiently probing large conformational changes can have important applications to structure determination of these assemblies or in silico docking algorithms to better understand their interactions and cellular function [1-4]. While some progress has been made for proteins [5], efficient algorithms and tools to explore conformational space of nucleic acids remain underdeveloped.

We have extended the robotics-inspired, Jacobian-based conformational sampling algorithm KGS [6] to RNAs. KGSrna interprets an RNA molecule as a kinematic linkage, with groups of atoms as links and rotatable dihedral angles as joints. In this representation hydrogen bonds define a large number of interdependent kinematic cycles, requiring dihedral angles to be perturbed in a coordinated fashion to maintain the hydrogen bonding network. In doing so, the method naturally accesses the preferential modes of deformation of a biomolecule allowing for rapid, diffusive sampling of the folded state. Preliminary tests on RNA molecules in ‘bound’ and ‘unbound’ conformations demonstrate that the conformational ensembles generated by KGSrna include both of these states. Thus, by sampling large conformational changes KGSrna can enhance the performance of in silico docking experiments.

1. Perez-Cano, L., B. Jimenez-Garcia, and J. Fernandez-Recio, A protein-RNA docking benchmark (II): extended set from experimental and homology modeling data. Proteins, 2012. 80(7): p. 1872-82.
2. Barik, A., et al., A protein-RNA docking benchmark (I): nonredundant cases. Proteins, 2012. 80(7): p. 1866-71.
3. van Dijk, M. and A.M. Bonvin, Pushing the limits of what is achievable in protein-DNA docking: benchmarking HADDOCK's performance. Nucleic Acids Res, 2010. 38(17): p. 5634-47.
4. van Dijk, M. and A.M. Bonvin, A protein-DNA docking benchmark. Nucleic Acids Res, 2008. 36(14): p. e88.
5. DiMaio, F., et al., Improved molecular replacement by density- and energy-guided protein structure optimization. Nature, 2011. 473(7348): p. 540-3.
6. Yao, P., Zhang, L., & Latombe, J.-C. (2012). Sampling-based exploration of folded state of a protein under kinematic and geometric constraints. Proteins, 2012. 80: p. 25-43.

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