Revealing the Electrostatic Forces in Nucleic Acid Folding by SAXS

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In the last decade, it has become increasingly clear that RNA molecules - beyond their "traditional" roles as messengers between transcription and translation - carry out a range of biological functions in the cell, including the catalysis of chemical reactions and the regulation of gene expression, for example as riboswitches. In order to carry out these biological functions, RNA folds into specific three-dimensional structures. RNA folding, in turn, is highly dependent on the presence of cations that help to overcome the electrostatic repulsion of the highly negatively charged RNA sugar-phosphate backbone. While our understanding of RNA structure and folding is still limited compared to what is known about proteins, much progress has been made recently. SAXS has emerged as an important tool to study this RNA folding and its underlying forces.

To obtain a quantitative understanding of how counterions modulate the electrostatic repulsion in RNA folding, we developed a framework using a simple model system, a tethered duplex comprised of two DNA helices joined by flexible PEG linkers. Using a combination of Monte Carlo simulations and Poisson-Boltzmann (PB) theory, we obtained a comprehensive view of the predicted ensemble over a range of mono- and di-valent ionic conditions. We tested these computational results via SAXS. With monovalent cations, the experimental results are in quantitative agreement with the computational predictions. For divalent ions, in contrast, substantial systematic deviations suggest a role of ion-ion correlations. Thus, higher level computational approaches are needed to describe the fundamental electrostatic interaction energies between nucleic acids and their ion atmospheres.