i.e., the DNAs diffuse faster in low ionic strength solutions. The decrease in the diffusion coefficients correlates with the decrease in the Debye length with increasing ionic strength. We therefore suggest that the diffusing unit in these measurements is the DNA molecule together with the surrounding Debye layer. The decrease in the Debye length with increasing ionic strength would increase the aspect ratio of the DNAs, increasing solvent friction and decreasing the diffusion coefficients.

1182-Pos Board B133

The Presence of Arginine Regulates the Selectivity and Binding Affinity of Lysine Receptors

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Post-translational modifications play an essential role in biological processes, such as gene expression and disease development. The methylation of lysine (Lys) on a histone protein, for example, can cause a gene to be repressed or activated. Dynamic combinatorial chemistry has been used to identify A_2N as a synthetic receptor for trimethyllysine (Kme_3). Recent studies have shown that A_2N binds to Kme_3 tighter than to non-methylated lysine (Kme_0). When a neighboring arginine (Arg) was mutated to glycine, the binding of A_2N to Kme_0 and Kme_3 weakened and A_2N became more selective for Kme_3. In sequences containing three Arg, A_2N proved to bind to Kme_0 and Kme_3 significantly tighter as compared to the previous sequences. However, in this case A_2N was considerably less selective for Kme_3. We hypothesized that the presence of Arg affects the binding affinity and selectivity of Lys and by shifting the position of Arg further from Lys the binding would greatly weaken. We noticed that when Arg was shifted further from Kme_0 and Kme_3 the binding of A_2N weakened, only partially in the tri-methylated state. As the distance between Arg and Lys increased A_2N became more selective for Kme_3. These findings suggest that Arg mediates the specificity of the binding affinity between Lys and A_2N independent of location within the sequence with an improved selectivity for Kme_3 as distance between Lys and Arg increased. The attraction between Arg and Lys will need to be further examined to understand the mechanism influencing the selectivity and binding properties of A_2N to Lys. Increasing awareness of this relationship may help to modify synthetic receptors and better understand post-translational modifications.

RNA Structure and Dynamics

1183-Pos Board B134

Force and Temperature Dependent Folding of a 2-Base-Pair RNA Kissing Complex

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The stability and function of proteins from thermophilic species can vary with temperature in a complex manner. However, in considering nucleic acids, ΔH is typically assumed to be constant when interpreting thermal melting results. Here we use temperature controlled optical tweezers or ''thermal tweezers'' to mechanically characterize the folding thermodynamics of a 2-base-pair kissing complex from the Moloney murine leukemia virus (MMLV) at temperatures ranging from 22°C to 42°C. At each temperature the folding free energy is directly determined from the reversible mechanical work to unfold the kissing complex. Surprisingly, the folding free energy of this basic RNA tertiary interaction depends non-linearly on temperature, indicating that ΔH changes with temperature. Based on mutational perturbation and molecular dynamics simulations, this non-linearity is attributed to the presence of a multi-step, temperature-sensitive, unfolding pathway. Specifically, at elevated temperatures, the unpaired flanking adenine bases in the hairpin loops are flipped out of their respective stacking positions, exposing the underlying kissing base pairs to water, thus reducing their stability. Our study suggests that at mesophilic temperatures, single-stranded residues can be thermally influenced, which may provide profound insights into temperature-dependent RNA folding and conformational dynamics.

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A Nucleobase-Centric Coarse-Grained Model for Structure Prediction of RNA Fragments

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The structural characterization of RNA usually poses additional challenges when compared to other biomolecular systems. For example, there is a relatively scarce amount of structural data available, which demands the development of three-dimensional structure prediction tools. In addition, full-resolution simulations can be a hard task not only because of the complexity of the interactions involved, but also due to the limitations of the current force fields. At this point, coarse-grained simulations are a good candidate to fill the gaps in this growing research field. The use of these techniques has rapidly increased in the past decades in the study of biological systems on which the experiments require an additional interpretation or where an atomistic computational approach results difficult or unfeasible. Nevertheless, the development of coarse-grained models involves the understanding of the main structural features of the original system, which can represent a challenge by itself.

In this work, we present a knowledge-base coarse-grained model for RNA structure prediction, representing each nucleotide by a single anisotropic particle. The mapping and the main interactions are designed to reproduce the geometrical distribution of the closest pairs of nucleotides, extracted from a set of ribosomal structures. The model is inspired in the ESCORE function [1], a knowledge-based scoring function that has been shown to perform better compared to fully atomistic techniques in identifying native-like structures from a set of decoys. Its minimalistic nature and successful application on a broad range of structures straightforwardly suggest a representation for a coarse-grained approach. We show the preliminary results of our simulations and discuss the role of pair interactions in the prediction of RNA structures.

[1] S. Bottaro, F. Di Palma and G. Bussi, ''The Role of Nucleobase Interactions in RNA Structure and Dynamics'', Nucleic Acids Res., accepted.

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Magnesium Dependence of the RNA Free Energy Landscape

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The RNA free energy landscape is highly sensitive to ionic concentrations, and especially to Mg^{2+}, as most RNA tertiary structure will not form in the absence of Mg^{2+}. At physiological concentrations, the energy landscape must be smooth and funneled to fold on biological time scales, but changes in ionic concentration may affect the relative stability of alternative states. We perturb a structure-based model, which captures the funneled nature of the energy landscape, to include electrostatic effects. Our model includes explicit Mg^{2+} and screening by implicit KCl. A dynamic model for the local competition between Manning condensed Mg^{2+} and KCl is introduced, which makes the model more broadly applicable and transferable than a previous static model. We use the excess Mg^{2+} ions associated with the RNA (Γ_{2+}) to test the model. Γ_{2+} is an ideal metric because it is closely related to the Mg^{2+}-RNA interaction free energy, and it is easily measurable in both experiment and simulation.

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An Additive Charmm Force Field for Modified Nucleic Acids

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Naturally modified nucleotides were found very common and play important roles in RNA involved biological process, especially the ribosomal tRNA decoding in peptide translation. To broaden the feasibility of molecular modeling on RNA system for CHARMM, an additive force field covering all naturally modified nucleotides has been determined. The force field includes the physiologically dominant states of each nucleotide and their possible tautomers as well. Additionally the backbone torsions of peptide nucleic acids (PNA) were updated in this force field too, to meet people's increasing interest in this artificial polymer.

The development of this force field adopted the same methodology of the precedent CHARMM force fields of nucleic acids, amino acids and drug-like compounds. The atomic charges were determined by solving the water-compound complexes, the internal geometries of bond and angle were determined by analyzing the molecular vibrational patterns and the potential energy scan were applied for flexible torsions.

A series thorough validation has been done. Molecular dynamic (MD) simulations in bulk phase were applied for mononucleosides, and some important modifications such as dihydrouridine and pseudourdine were further validated in oligonucleotides. The conformational effects of modified nucleic acids were also monitored in tRNA simulations. All conformations were sampled over 100 ns simulation period and compared with the corresponding NMR or crystal