Thermodynamics of RNA Adsorption on Cationic Lipid Bilayers

Borna Fardsadegh and Harish Vashisth*

Department of Chemical Engineering and Bioengineering, University of New Hampshire, Durham, NH 03824

Email: Borna.fardsadegh@unh.edu (presenter), *harish.vashisth@unh.edu

Abstract

In this work, we employed all-atom molecular dynamics (MD) and non-equilibrium steered molecular dynamics (SMD) simulations to quantify the thermodynamics of RNA adsorption onto bn lipid membrane. Our chain-level analysis demonstrated that all RNA sequences spontaneously adsorb to the membrane interface, driven predominantly by electrostatic. To rigorously define the binding free energy, we performed 15 independent constant-velocity pulling simulations per system and reconstructed the Potential of Mean Force (PMF) profiles using Jarzynski's equality. The resulting free energy landscapes reveal deep minima ranging from -3.1 to -6.1 kcal/mol located within the lipid headgroup region, confirming that adsorption is thermodynamically favorable and significantly exceeds thermal fluctuations.

Aims

- ***Quantify Chain-Level Drivers**:* Determine the relative contributions of electrostatic and van der Waals forces in the adsorption of RNA chains to membranes.
- ***Characterize Structural Dynamics:*** Evaluate the conformational stability and compactness of adsorbed RNA strands ranging from short oligomers to longer mRNA fragments.
- ***Assess Membrane Integrity:*** Investigate the potential for RNA-induced lipid clustering or phase separation using Voronoi analysis.

Computational methods

Simulation/Visualization software: NAMD and VMD

SMD Force Calculation: The instantaneous force exerted by the harmonic spring on the RNA center of mass along the reaction coordinate (z) at time t′.

$$\mathrm{F}(t') = -k\left(z(t') - (z_0 + vt')\right)$$

Non-Equilibrium Work (W): The accumulated work performed on the system during the pulling process, calculated by integrating the force over the displacement.

$$\mathrm{W}_{0\to t} = -kv\int_0^t \left(z(t') - (z_0 + vt')\right)dt'$$

Potential of Mean Force (PMF): The equilibrium free energy profile (ΔG) recovered from the exponential average of non-equilibrium work values across 15 independent trajectories usin

$$\Delta G = -\beta^{-1}\ln\langle e^{-\beta W}\rangle$$

Acknowledgements:

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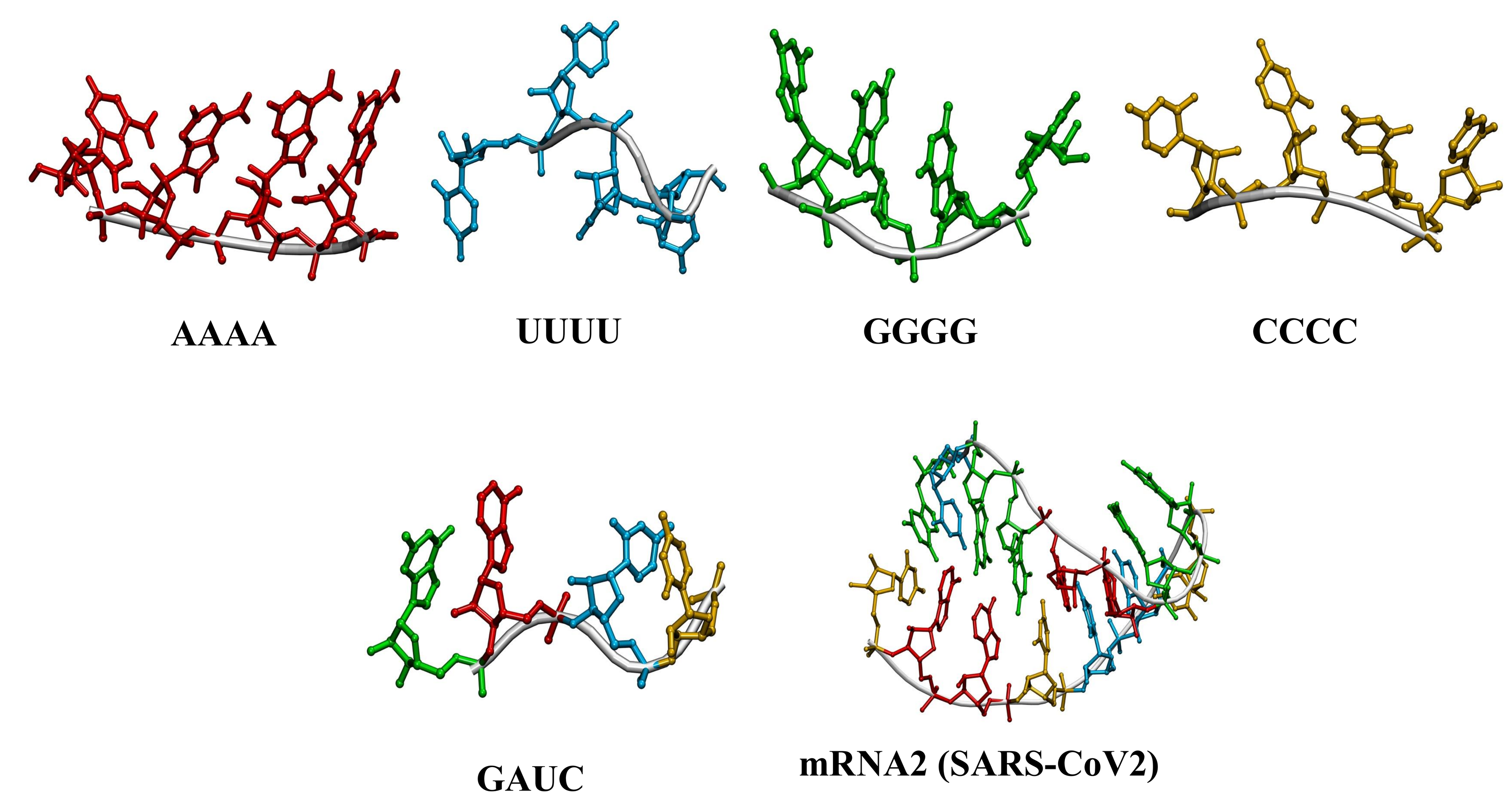
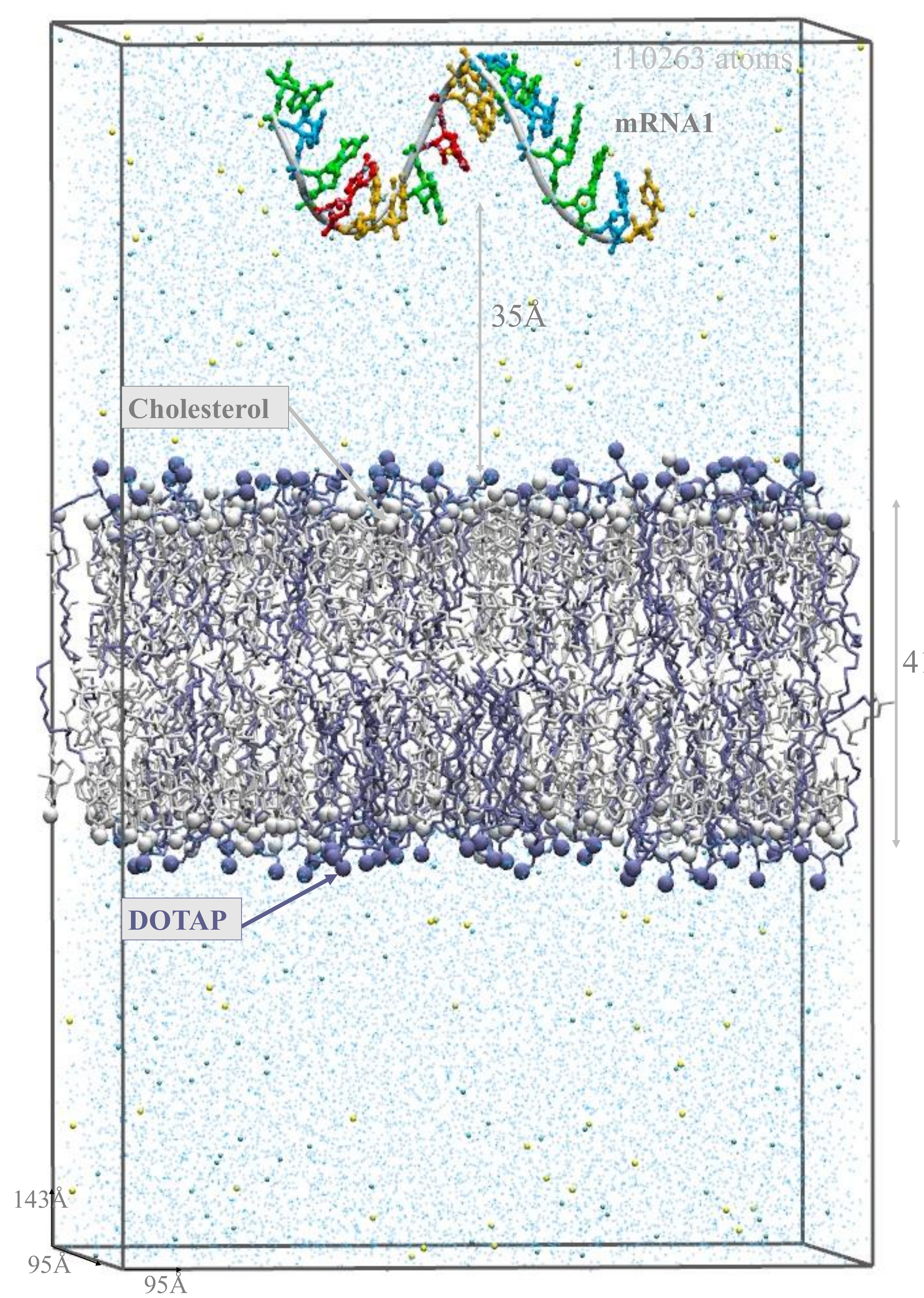
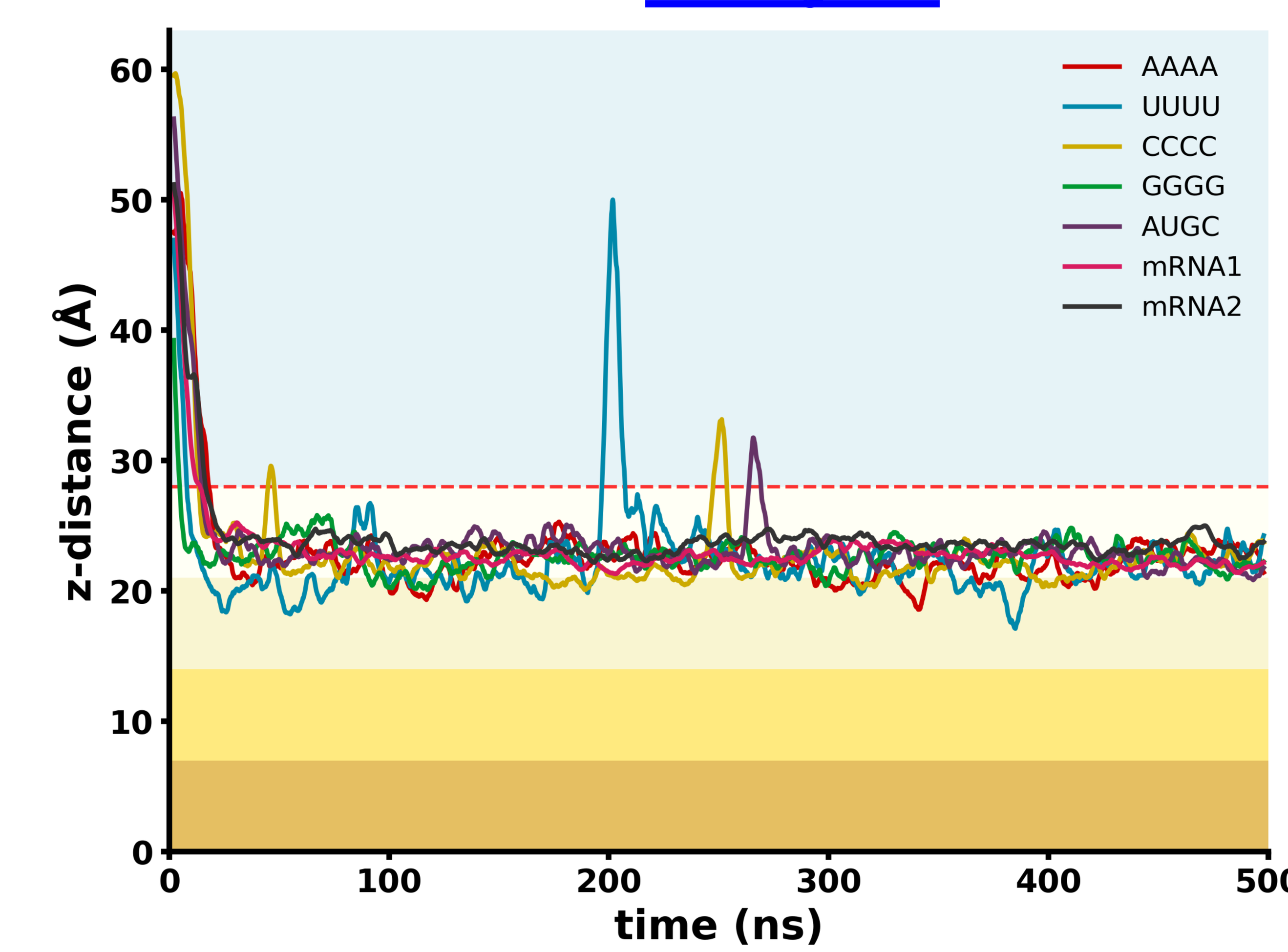
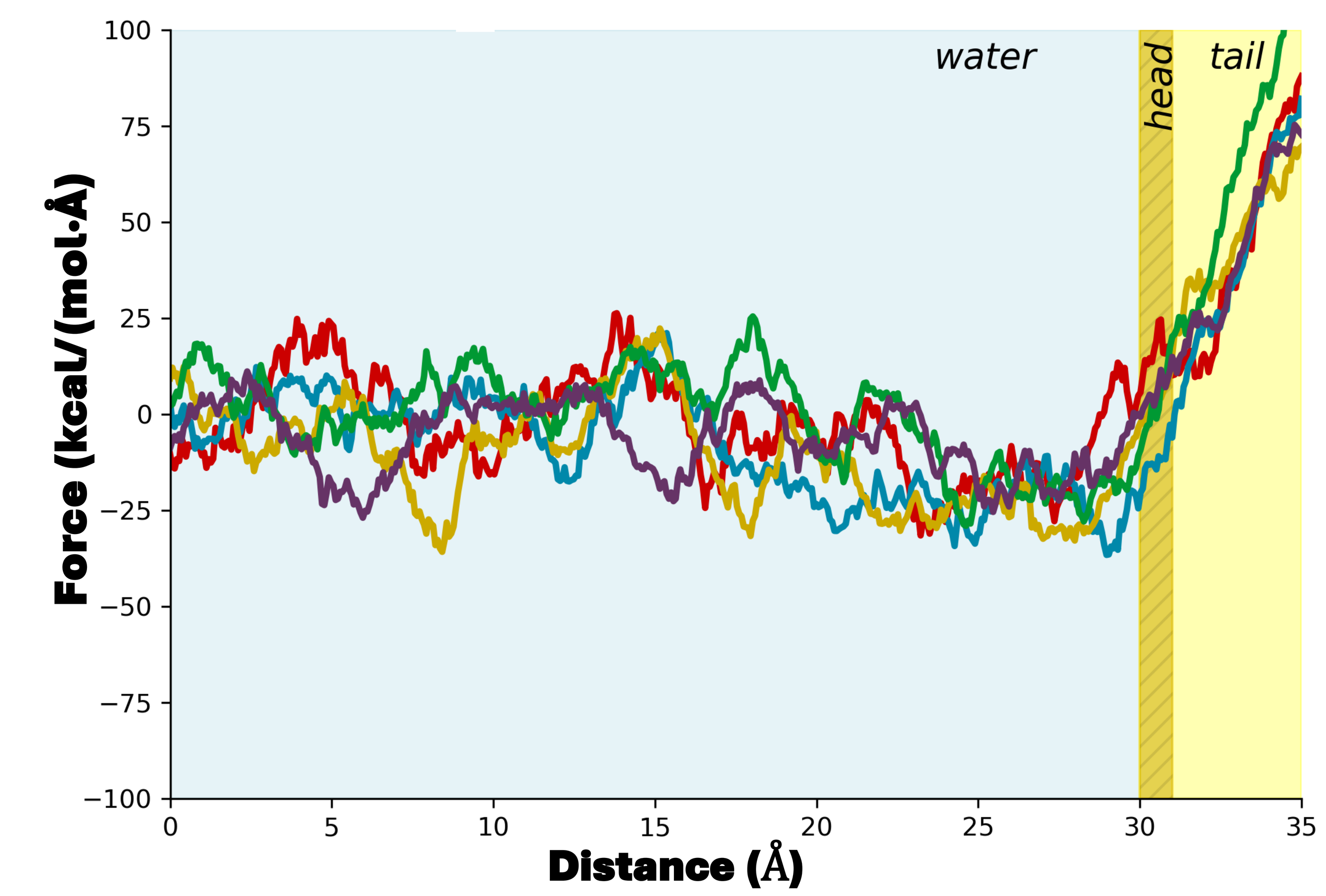
Simulation systems

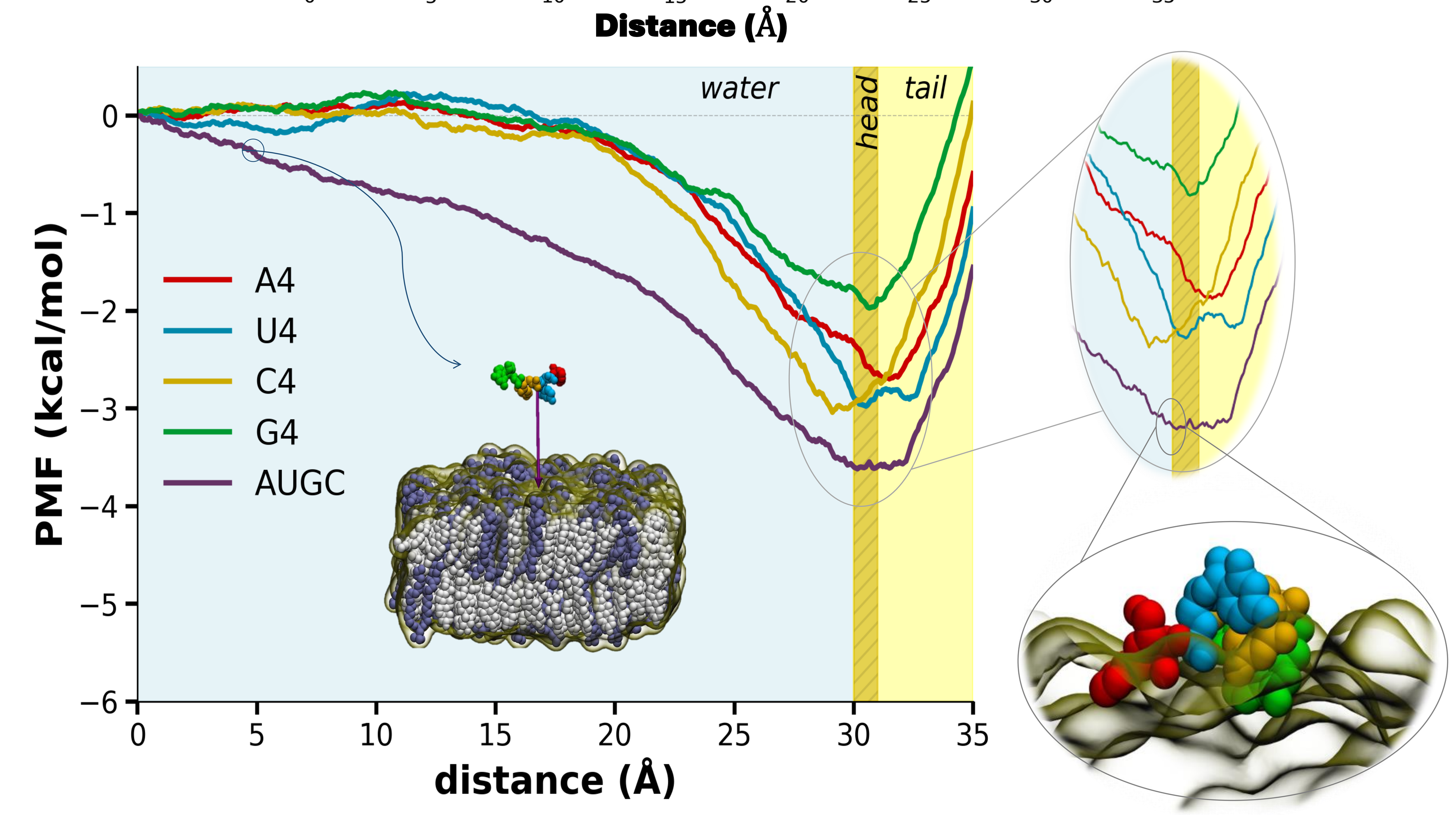




Analysis







Summary

- PMF profiles confirm that RNA adsorption is thermodynamically favorable.
- Adsorption is overwhelmingly driven by electrostatic interactions.
- A mechanistic distinction was identified where Guanine (G4) exhibits the strongest binding affinity, whereas Uracil (U4) achieves the deepest membrane penetration.
- Membrane analysis confirms that RNA binding does not induce lipid phase separation.