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Utilizing Coarse-Grained Models in Simulations to Study Chromatin Organization

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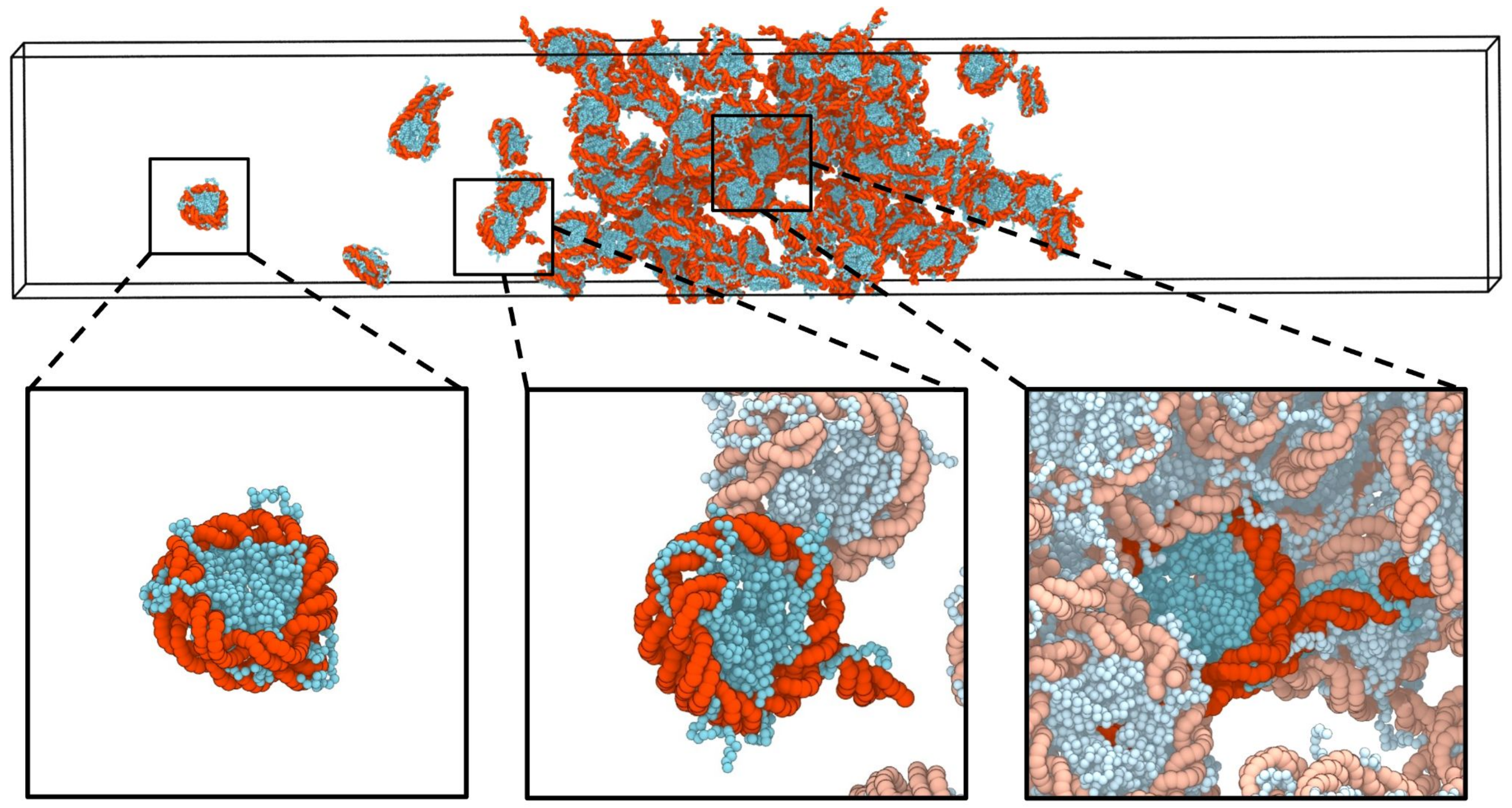
Introduction

Liquid-liquid phase separation (LLPS) in cells enables organization and compartmentalization of biomolecules into biomolecular condensates without the need for a membrane. Within the nucleus, LLPS of chromatin regulates the accessibility of DNA and therefore controls gene expression.

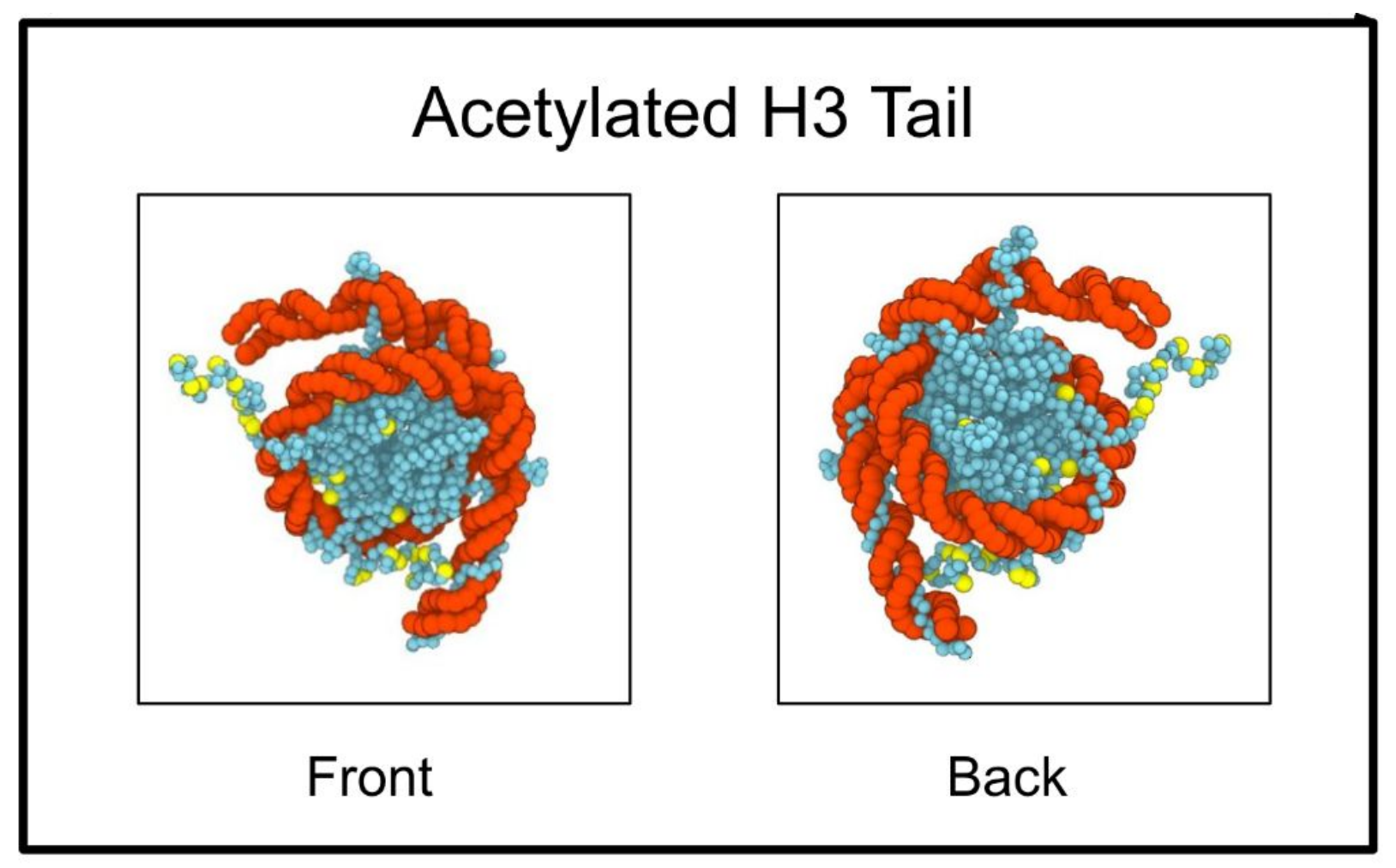
Our understanding of the LLPS process is limited: beyond experimental results that indicate when LLPS occurs, the critical motifs of biomolecules that initiate LLPS and how it is modulated by other biomolecules are unclear. If we know the underlying relationship between these motifs and LLPS, we can design controls for important cellular processes.

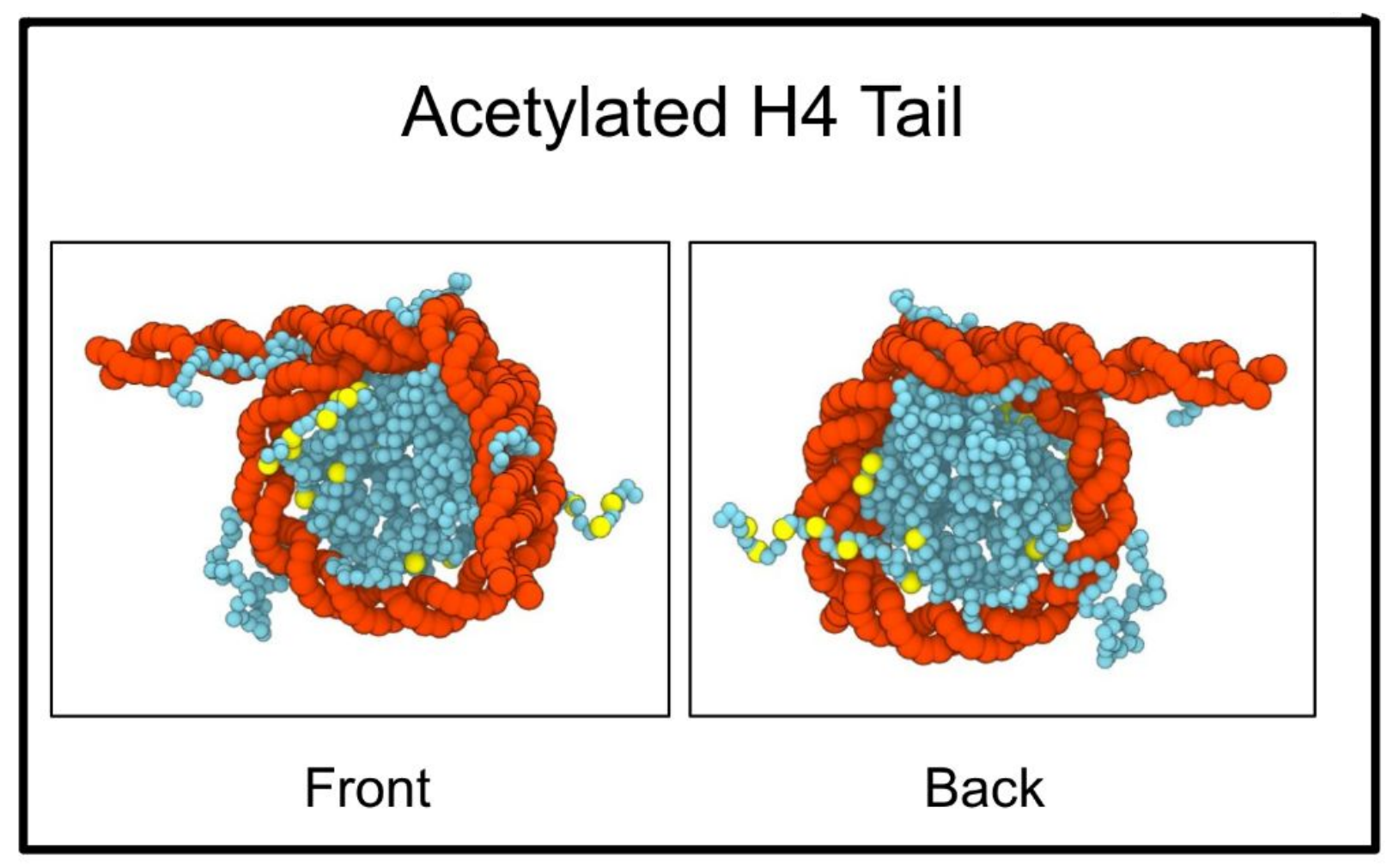
We utilized a coarse-grained model with residue resolution to simulate nucleosomes at different salt concentrations to explore the molecular mechanisms driving LLPS of chromatin. This model allows us to accurately and efficiently simulate chromatin interactions with sequence and epigenetic specificity.

Simulation

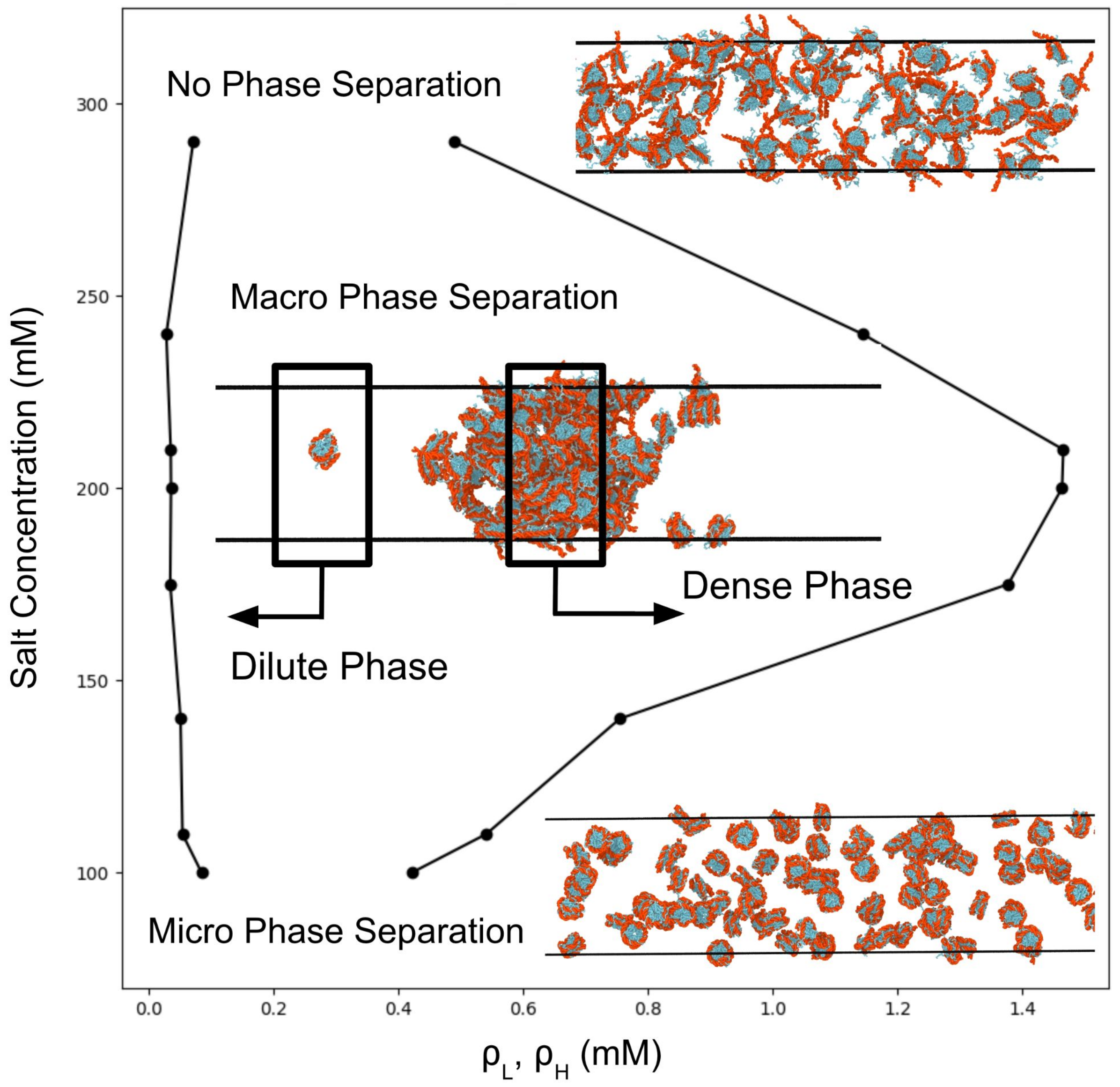


We utilized a residue-resolution coarse-grained chromatin model with implicit treatment of ions based on their concentrations. Specifically, the DNA was modeled with a coarse-grained Molecular Renormalization Group (MRG) model, and the proteins were modeled with a Maximum Optimized Force-Field (MOFF) model.



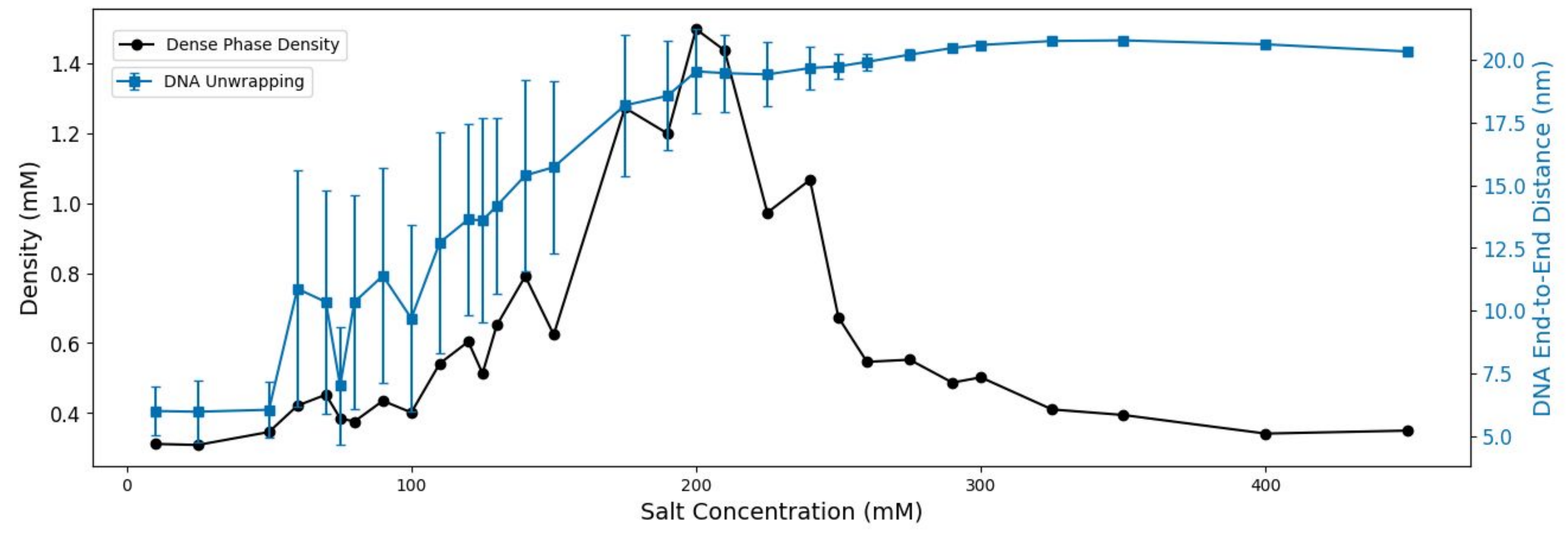


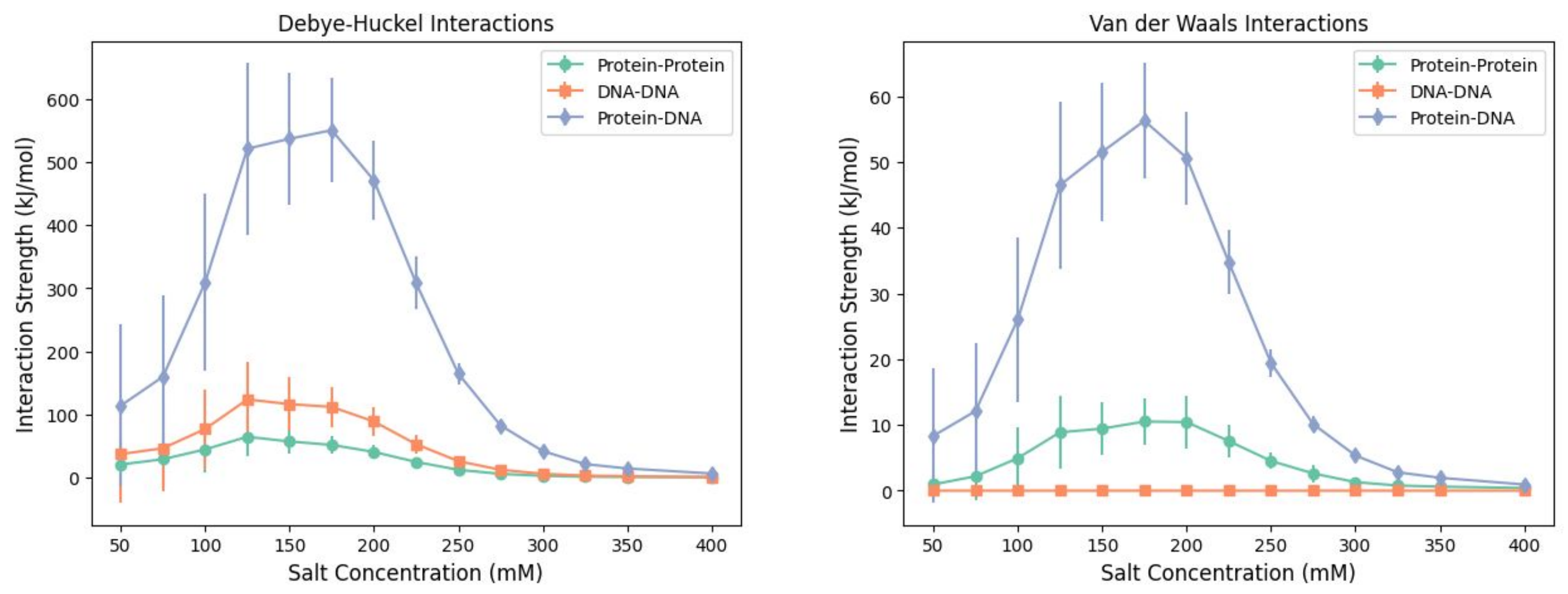
Non-monotonic Phase-separation of Nucleosomes



Phase diagram with representative condensate slab snapshots at low, physiological, and high salt concentrations.

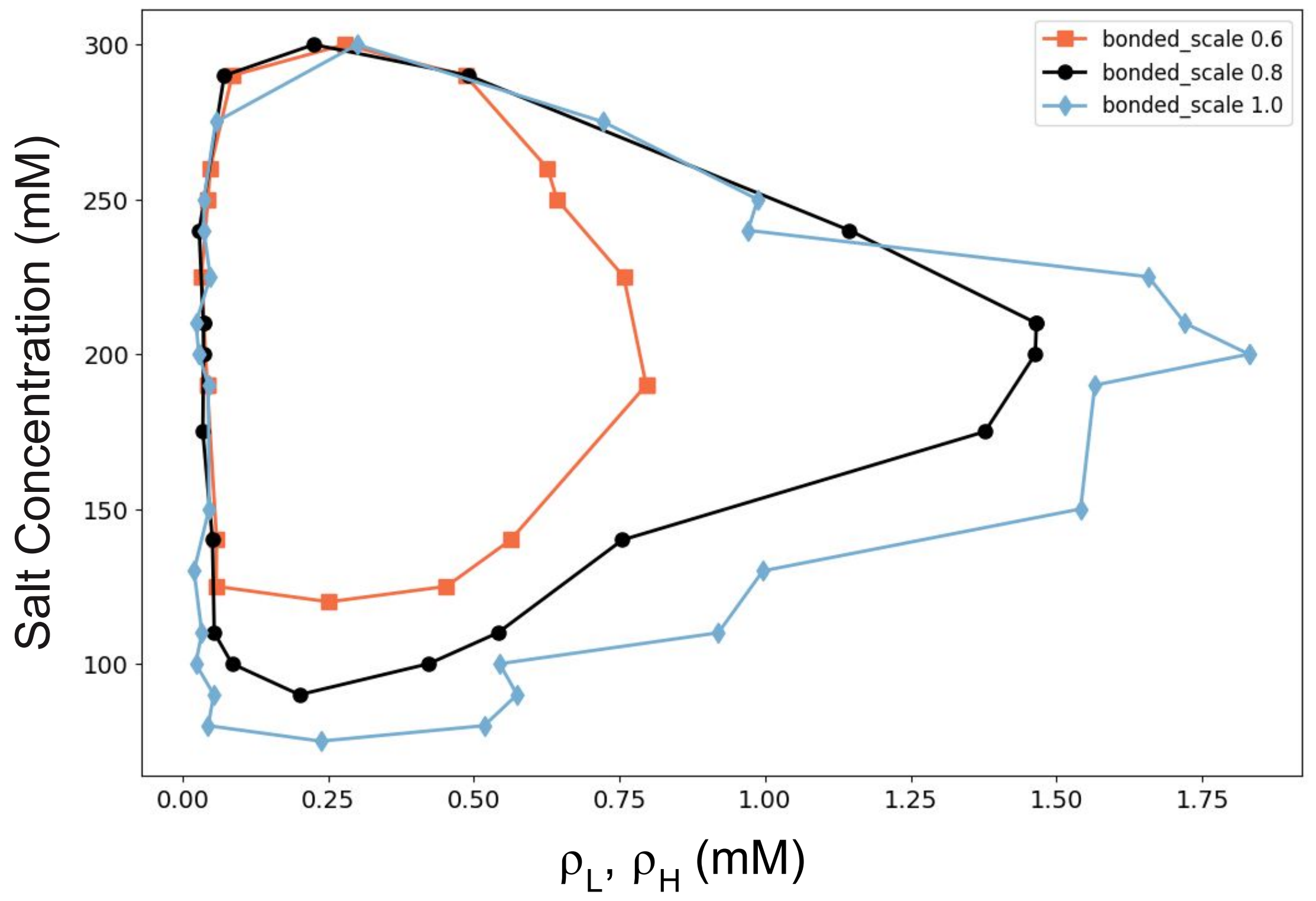
Local-Global Competitions of Electrostatic Interactions

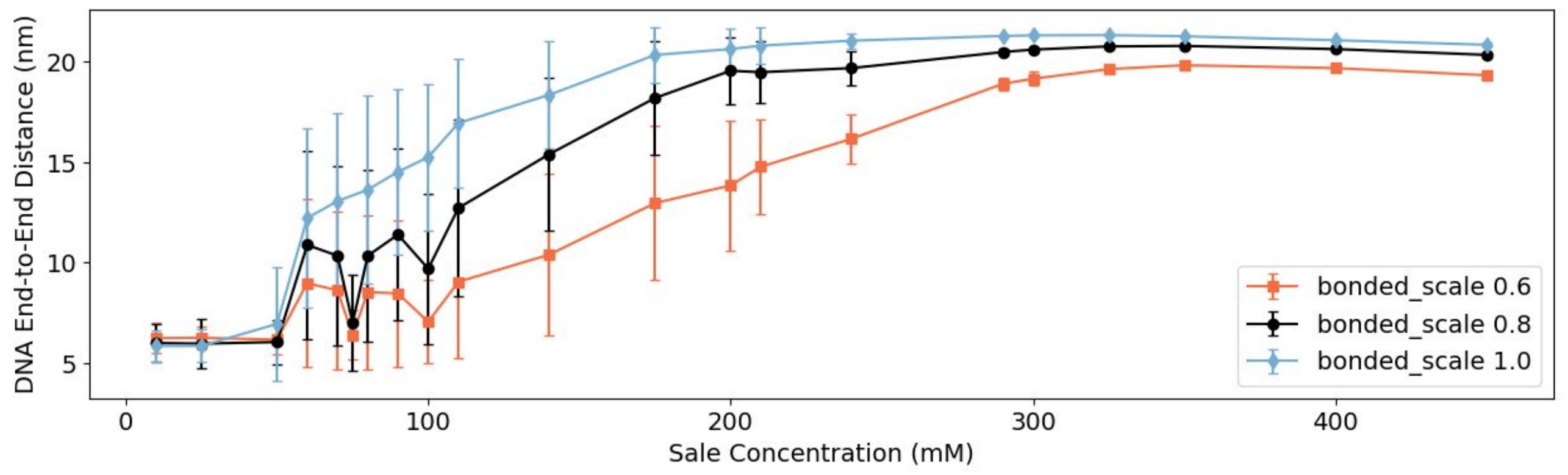




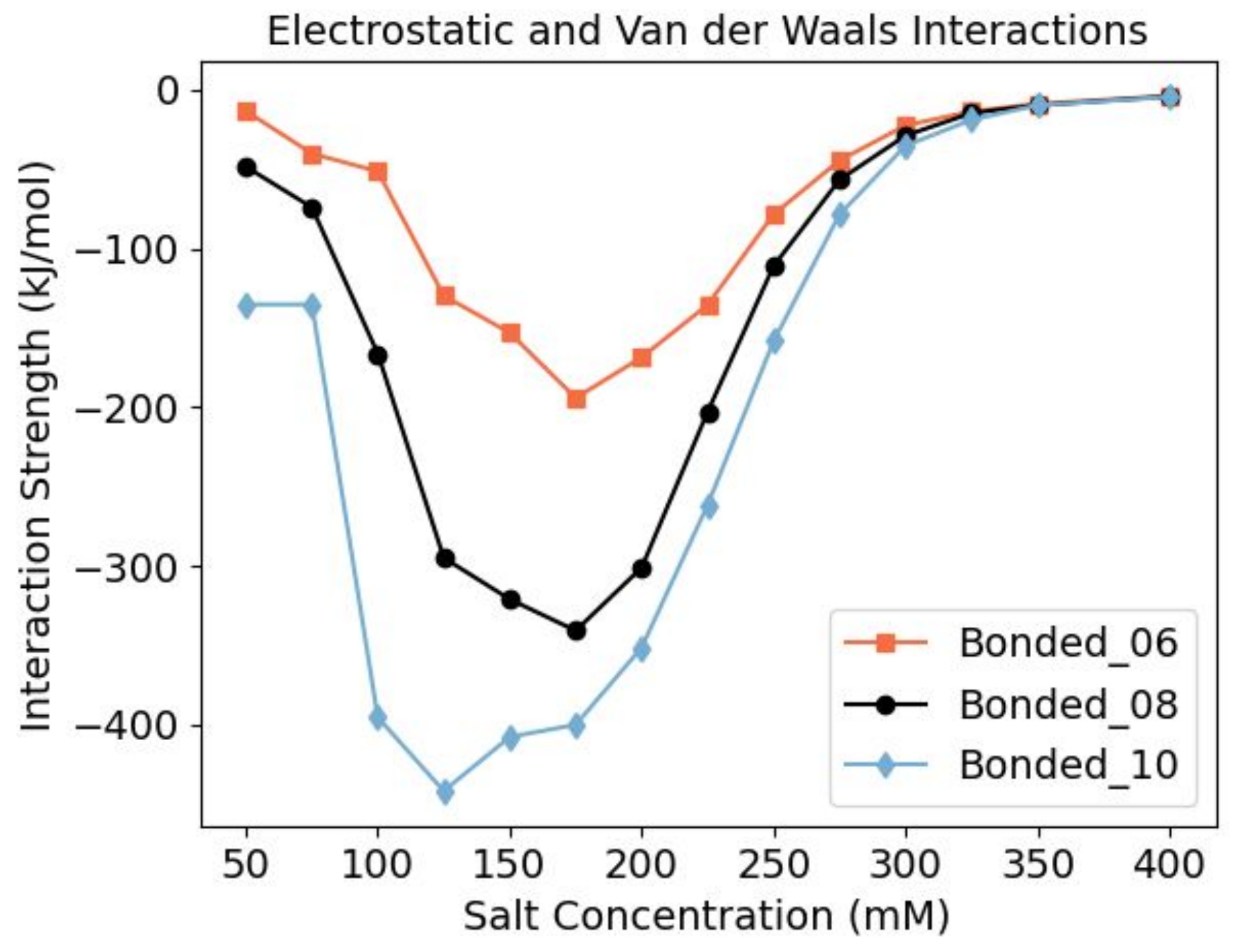
** This is the absolute value of all the interactions.

Effects of DNA Flexibility on Condensate Formation





The term “Bonded_Scale” refers to the strength of the bonds between neighboring DNA beads. If the the bonded_scale is weaker, then the DNA strands are more flexible.



Simulations of acetylated nucleosomes at physiological salt concentrations

We mimicked the effect of the post-translational modification (PTM) acetylation on histone tails by neutralizing the positive charges of the lysine residues to 0.