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INTRODUCTION

Chromatin structure and dynamics are central to nearly every aspect of eukaryotic gene regulation. The spatial organization of the genome influences how genes are accessed, transcribed, and silenced, linking molecular interactions to cellular function and phenotype.

Over the past two decades, the field of chromatin biophysics has undergone a remarkable transformation. We have witnessed significant advances in experimental techniques, including high-resolution imaging, chromosome conformation capture, and single-molecule approaches, that have revealed striking features of higher-order chromatin organization and dynamics. In parallel, theoretical analyses and computational modeling have advanced rapidly, inspired and constrained by the increasingly rich experimental data. Together, these developments are reshaping our quantitative understanding of genome organization and the principles underlying chromatin function.

This special collection reflects that these methodologies are converging to produce quantitative, mechanistic insights into chromatin function. The collection highlights the synergy between experimental innovation and theoretical modeling that is redefining our understanding of genome organization across scales.

SUMMARY OF AREAS COVERED

The papers in this special issue span a wide range of scales, methodologies, and biological contexts. Together, they exemplify the creative integration of physical theory, simulation, and experiment in decoding chromatin organization.

Modeling nucleosome-level interactions and local structure

At the foundation of chromatin architecture lies the nucleosome, the fundamental repeating unit of eukaryotic chromosomes, formed by ~147 base pairs of DNA wrapped around a histone protein octamer. The arrangement and dynamics of nucleosomes along the genome, together with the interactions between neighboring particles, govern higher-order chromatin folding and accessibility.

Several contributions in this collection investigate how molecular features of nucleosomes give rise to higher-order chromatin organization. Nordenskiöld and colleagues incorporate explicit mobile ions to explore how electrostatic screening and cation concentration regulate fiber conformations and transitions between extended, flexible, and globular states.[1] Schlick and team extend this molecular perspective to epigenetic modifications, examining how histone methylation alters nucleosome flexibility and inter-nucleosome

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interactions, ultimately influencing chromatin fiber organization and gene regulation.[2] Olson and collaborators use complementary simulations of nucleosome-decorated DNA chains to reveal how the spatial arrangement of nucleosomes constrains DNA pathways and facilitates communication between distant protein-binding sites.[3]

Two additional studies focus on how molecular parameters controlling nucleosome interactions can themselves be modulated by the biochemical and ionic environment. Morozov and co-workers present a thermodynamic model that connects nucleosome-level interactions with chromatin fiber architecture, showing how partial DNA unwrapping ("breathing") and linker geometry give rise to distinct states of nucleosome density and explain genome-wide patterns of nucleosome positioning and occupancy.[4] In parallel, Szleifer and collaborators provide a theoretical analysis quantifying how the charge state of the nucleosome core particle varies with pH and divalent ion concentration, highlighting the roles of charge regulation, ion condensation, and histone side-chain chemistry in determining chromatin electrostatics.[5]

Together, these works provide a cohesive view of chromatin organization at the nucleosome scale, linking detailed molecular physics to the collective behavior of chromatin fibers and illuminating how electrostatics, sequence, and modification cooperate to shape genome accessibility.

Polymer models and mesoscale chromatin organization

While nucleosome-level studies reveal the molecular origins of chromatin flexibility and compaction, many structural features of genome organization emerge only at much larger length scales. Modeling these mesoscale structures at nucleosome resolution, while retaining key physicochemical interactions, remains computationally demanding. These challenges have motivated the development of polymer models that coarse-grain local molecular details while preserving the essential physical interactions needed to describe large-scale genome folding.

Beyond equilibrium interactions, several contributions in this collection focus on non-equilibrium processes that actively shape chromatin organization. Onuchic and colleagues present models inspired by energy landscape theory and the MiChroM framework, revealing how the competition between compartmentalization and motor-driven activity controls polymer compaction, territory formation, and inter-chromosome interactions.[6] Wolynes and co-workers develop related theoretical analyses that formalize how nonuniform distributions of active "swimming" motors, such as RNA polymerases and chromatin remodelers, can give rise to heterogeneous folding and chromatin compartmentalization.[7] Sasai and team extend whole-genome polymer simulations across multiple cell cycles, demonstrating how structural memory from mitosis guides chromosome positioning and the re-establishment of compartmentalization during interphase.[8] Finally, Mofrad and collaborators provide a comprehensive review that synthesizes the principal polymer frameworks, loop extrusion, strings-and-binders, and multi-loop subcompartment models and that outlines current challenges in connecting molecular mechanisms to genome-scale folding principles.[9]

Phase separation and chromatin dynamics

In addition to active processes, phase separation has emerged as another important physical principle for understanding the organization of chromatin and the formation of membraneless nuclear bodies. Many nuclear structures, including nucleoli, speckles, and transcriptional condensates, are now recognized as biomolecular condensates formed through liquid–liquid phase separation. Chromatin can both participate in the formation of these condensates and be reorganized by them, creating a dynamic, reciprocal coupling between chromatin state and nuclear environment. Chakraborty and colleagues examine condensates driven by electrostatic protein–RNA interactions, showing that RNA gradients at active promoters can direct condensate motion toward sites of transcription and modulate enhancer–promoter communication.[10]

Beyond its interactions with other nuclear condensates, chromatin itself can undergo phase separation. Guha uses coarse-grained simulations to reveal how multivalent DNA-bridging proteins can both compact and re-swell chromatin fibers depending on binder and monomer valency, identifying distinct physical mechanisms that control these transitions.[11] Dahirel and co-workers develop a minimal physical model coupling chromatin condensation with the phase behavior of the surrounding fluid, illustrating how liquid–liquid phase separation and the coil–globule transition can jointly regulate chromatin compaction and its response to changes in condensate protein concentration.[12] Finally, Vemparala and collaborators employ polymer-based models incorporating sequence-dependent protein binding and protein–protein interactions to demonstrate how the balance between biochemical specificity and multivalent attraction can promote or inhibit chromatin compartmentalization.[13]

Data-driven and integrative modeling

The increasing availability of high-resolution imaging, Hi-C, and single-cell sequencing data has ushered in a new era for chromatin biophysics, where experimental measurements and physical modeling are deeply intertwined. Several contributions in this collection exemplify how data-driven analyses and computational modeling can jointly reveal the physical principles underlying genome organization and function.

Gao and colleagues introduce the single-cell CTG (scCTG) algorithm, which combines convolution and diffusion processes to infer spatial distance matrices from single-cell Hi-C data, enabling accurate reconstruction of chromatin domains and compartmental boundaries.[14] Carlon and team analyze large-scale multiplexed fluorescence *in situ* hybridization (m-FISH) data from human and mouse cells, identifying two characteristic chromatin folding states that can be captured by heterogeneous random walk models.[15] Belan and collaborators develop a theoretical framework that models the joint statistics of contacts in single-cell Hi-C maps, linking polymer physics to single-cell conformational variability.[16] Extending these efforts to dynamic observations, Vasquez and co-workers apply topological data analysis (TDA) to live-cell single-particle tracking, demonstrating how loop-like features and complex spatial patterns

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in chromatin motion can be detected and quantified directly from experimental trajectories.[17]

Data-integrative modeling also offers a powerful approach to understanding how chromatin organization relates to cell state and disease. Wang and collaborators present a dynamic structural model of chromosomes in normal and lung cancer cells, showing that cancer-associated chromatin ensembles exhibit enhanced compartmentalization, greater configurational heterogeneity, and characteristic switching between active and inactive domains.[18] Sinha and colleagues connect genome topology to gene regulatory networks through a thermodynamic model of p53 signaling, demonstrating how long-range chromatin interactions can modulate network topology and cell-fate transitions across cancer cell lines.[19] Finally, Chiariello and co-workers employ polymer-physics-based modeling of SARS-CoV-2 infection, suggesting that viral infection can reprogram chromatin organization and thereby influence gene regulatory processes.[20]

CONCLUSIONS

The studies gathered in this special issue collectively underscore the vitality and interdisciplinarity of modern chromatin research. The integration of physics-based modeling, advanced computation, and cutting-edge experiments is transforming how we conceptualize genome organization and its functional consequences. As models grow in resolution and predictive power, they promise to bridge the gap between molecular interactions and cellular phenomena, ultimately illuminating how the physical principles of chromatin folding shape life's most fundamental processes.

We hope that this collection will inspire further cross-disciplinary collaborations between chemical physicists, biologists, and computational scientists and serve as a reference point for future explorations of chromatin structure and dynamics.

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AUTHOR DECLARATIONS

Author Contributions

Bin Zhang: Conceptualization (equal). **Tamar Schlick**: Conceptualization (equal).

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