Multiscale genome organization symposium - annual biophysical society meeting 2023

Ehsan Akbari[1], Eui-Jin Park[2], Ajit K. Singh[3], Vinayak Vinayak[4], Ranya K. A. Virk[5], Jeff Wereszczynksi[6]*, Catherine A. Musselman[7]*

[1]Department of Physics, The Ohio State University, Columbus, OH 43210, USA
[2]Department of Biomedical Engineering, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919, Republic of Korea
[3]Department of Pharmacology, Larner College of Medicine, University of Vermont, Burlington, VT 05405, USA
[4]Department of Materials Science and Engineering, University of Pennsylvania, Philadelphia, PA 19104, USA
[5]Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA 94158, USA
[6]Departments of Physics and Biology, Illinois Institute of Technology, Chicago, Illinois, 60616, USA
[7]Department of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA
*Correspondence: catherine.musselman@cuanschutz.edu, jwereszc@iit.edu

We were thrilled to hold the Multiscale Genome Organization (MGO) subgroup symposium at the 2023 Biophysical Society (BPS) Annual Meeting in San Diego, California. MGO is a newly formed subgroup within the BPS umbrella which has grown significantly since our first symposium back in 2020, and the vision of Tamar Schlick and Tom Bishop has come a long way[1]. The mini-symposium continues to be a key event which brings together experimentalists, computationalists, and theoreticians, and provides a platform for the open exchange of thoughts and ideas across disciplines. While the main topic remains understanding genome organization at all relevant length- and time-scales, the varied structural and dynamical insights from different groups allows for a rich crosstalk from unique perspectives. Special emphasis is placed on having a balanced roster of invited speakers that prioritizes bringing together groups that tackle different aspects of the field. This strategy allows for vibrant discussions and the formation of new collaborations that all address the most pertinent and complex questions in the field.

The MGO symposium was held on February 18th with seven featured speakers from all over the globe. Drs. Bin Zhang and Alexey Onufriev chaired the session with Drs. Yamini Dalal and Anna Panchenko as the 2022 MGO co-chairs. The session and goals of the MGO subgroup were introduced by Dr. Panchenko, followed by talks from the invited speakers. The presentations showcased research at the forefront of the field and elicited high audience engagement. Here, we summarize the presentations of these invited speakers.

Job Dekker from University of Massachusetts Chan Medical School, Worcester, MA, USA presented recent work investigating the folding of chromosomes without knotting. In vertebrates, chromosomal folding also depends on DNA and chromosome topology in addition to compartmentalization and chromatin looping. Using multi-contact 3C experiments, Dr. Dekker

demonstrated that during interphase, chromosomal domains are not entangled; however, during metaphase, chromosomes become intra-chromosomally entangled and catenated[2]. Chromosome disentanglement during mitotic exit is a rapid process that mostly occurs during telophase. Topoisomerase II is required to convert catenated metaphase chromosomes into disentangled interphase chromosomes, a process that is also driven by decondensation of metaphase chromosomes. Finally, Dr. Dekker proposed a potential role for loop extrusion the decatenation and disentanglement process, as removal of cohesin reduced decatenation in a topoisomerase II-dependent manner.

Frank Alber from UCLA, Los Angeles, CA, USA, presented his multimodal data integration approach to characterize the structural variability of whole diploid genomes. Computational methodology from the Alber group is able to create a population of structures that reliably reproduce experimental data. The workflow is able to integrate sequencing-based (e.g., Hi-C, lamin B1 DamID) and microscopy-based (e.g., 3D HIPMap FISH) techniques, and is available through the Integrative Genome Modeling software package[3]. Applying this computational platform Dr. Alber has investigated how the nuclear microenvironment, composed of all structural features, influences genome function. For example, nuclear speckles were demonstrated to be associated with favorable transcriptional microenvironments. Additionally, cell-to-cell variability in the radial positioning of these speckles is correlated with functionality. Interestingly, different combinations of data types can result in the same population of structures, indicating that results discovered by this methodology do not depend on a particular combination of techniques.

Yaojun Zhang from Johns Hopkins University, Baltimore, MD, USA, described recent progress in understanding the impact of chromatin on dynamics of biomolecular condensate formation and size evolution[4]. Zhang lab research is mainly motivated by the role of densely packed chromatin on the slowed coarsening of optogenetically formed protein condensates in cell nuclei, as described by Zhang et al[4] and Lee et al[5]. Dr. Zhang implemented phase separation theory and coarse-grained molecular dynamic (MD) simulations to investigate the role of chromatin in regulating protein phase separation. She demonstrated that slowed condensate coarsening is due to a reduction in the rate of condensate merging and Ostwald ripening in the presence of chromatin cross-linking. She further showed that chromatin cross-linking can mechanically regulate the droplet number, size, and position in nuclei.

Igor Sharakhov from Virginia Tech, Blacksburg, VA, USA described the 3D genome architecture in human malaria vectors. The Sharakhov lab and his collaborators have determined that the 3D structure of chromatin observed in mosquitoes has several characteristics of chromatin organization that have been previously reported in *Drosophila*. The *Anopheles* mosquito reveals novel concepts of 3D genome organization, such as the existence of euchromatic and heterochromatic B-compartments in mosquitoes. Also, the anchors of the enormous chromatin loops in the *Anopheles* genome establish an evolutionarily conserved long-range interactions and are devoid of active genes. Aspects of the 3D genome architecture that are dynamic throughout mosquito development include the separation of active and inactive chromatin compartments, which is more apparent in adult mosquitoes than in embryos, and the Rabl-like chromosome configuration[6,7]. In the 3R arm of *Anopheles coluzzii*, there are long-range chromatin interactions that occur in specific stages and organs during mosquito development.

Ranya Virk from Northwestern University (Backman and Szleifer groups), Evanston, IL, USA, described how statistical chromatin packing can predict the phenotypic plasticity of cancer cells.

Using high-resolution Chromatin Scanning Transmission Electron Microscopy (ChromSTEM), her group discovered the existence of chromatin packing domains with similar statistical packing behavior[8,9]. These domains have highly heterogeneous structural properties, which are linked to transcriptional responsiveness using computational modeling. This model of transcription accounts for crowding-mediated effects, mainly due to chromatin density, the major nuclear crowder[10]. Integrating modeling with nanoimaging and sequencing experiments, Dr. Virk demonstrated that chromatin packing - which describes the statistical distribution of chromatin mass density - directly influences both transcriptional plasticity and survival probability of cancer cells in response to cytotoxic chemotherapy treatment.

Shasha Chong from Caltech, Pasadena, CA, USA, presented recent findings on the role of the low complexity domain (LCD) of oncogenic transcription factor (TF) EWS::FLI1, the primary driver of Ewing sarcoma, in transcriptional regulation [11]. Previous work [12] as shown that EWS::FLI1 undergoes multivalent LCD-LCD interactions at its endogenous target genes and such behavior play an essential role in the TF's transcriptional activation activity. The Chong group recently used quantitative single-cell and single-molecule imaging approaches to demonstrate how the transcriptional activation activity of EWS::FLI1 can be modulated by tuning the level and localization of its LCD-LCD interactions. They found that activation of endogenous genes by EWS::FLI1 requires narrow optimum of LCD-LCD interactions at the genes in Ewing sarcoma cells. Increasing LCD-LCD interactions toward phase separation represses transcription of these genes. Additionally, ectopically sequestering EWS::FLI1 into a phase-separating compartment, the nucleolus, represses EWS::FLI1-driven transcription and inhibits malignant transformation of Ewing sarcoma. Moreover, they showed that phase separation can change the diffusion dynamics of a TF and single-molecule diffusion measurement can be useful for diagnosing phase separation in living cells. These findings show how altering the balance of LCD-LCD interactions can influence transcriptional regulation and can help advance novel therapeutic strategies targeting pathological TFs.

Devarajan Thirumalai from University of Texas at Austin, Austin, TX, USA presented a newly developed computational framework that describes changes in chromosome structure driven by cohesion I and II motors during mitosis. This Active Generalized Rouse Model for Chromosomes (A-GRMC) model accurately predicted contact frequency, P(s), for mitotic chromosomes when condensin II was depleted. Moreover, by using the Hi-C-polymer-physics-structures (HIPPS) method, Dr. Thirumalai predicted the behavior of P(s) in the presence of both condensin I and II, as well as upon depletion of the two motors with high accuracy. Interestingly, the structures of the mitotic chromosome exhibited the random helix perversion (RHP) instead of the characteristics of periodic helix perversion (PHP)[13].

The wide range of topics covered through the presentations by our distinguished speakers testifies to the need of holding such symposiums, which are imperative in driving the community forward. The MGO subgroup is continuing a bimonthly webinar series organized by graduate student/postdoc officers. More information about the subgroup and webinars is posted at https://www.biophysics.org/subgroups/multiscale-genome-organization. In addition, MGO will host another symposium at the BPS Annual Meeting in Philadelphia in 2024. We hope you will join us!

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