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COMMENTARY

MGO on the go: Multiscale genome symposium - annual biophysical society meeting 2021

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At the virtual 2021 Biophysical Society (BPS) Annual meeting, we were happy to hold the first minisymposium of our newly formed subgroup, Multiscale Genome Organization (MGO). This idea for our subgroup emerged during the March/April 2019 BPS Thematic Meeting on chromatin multiscale modeling held at the picturesque Ecole des Physiques in the French Alps at Les Houches, France (Schlick 2020). Likely influenced by Mont Blanc in the background, inspiring us to be broad and ambitious, our dream — to bring together biologists, chemists, physicists, and mathematicians to discuss and launch collaborations and advance the field of chromatin structure, dynamics, function and applications through new conceptual approaches and perspectives — is now a reality. We are particularly excited about bringing together experimentalists and theoreticians/modelers and emphasizing the interplay between techniques and ideas concerning the complex multiscale features and properties of genomes, from bases to chromosomes. Such multiscale models and experimental strategies on many spatial and temporal scales are needed to address all components of the chromosome folding problem and the epigenomic regulation of gene expression.

Our minisymposium on February 22nd featured eight speakers spanning three continents and many time zones. Despite some technical glitches, we held great discussion and chats, clearly demonstrating how community members are eager to connect to one another despite the physical limitations of the pandemic. Below we briefly summarize aspects of the presentations.

Catherine Musselman from Colorado University, Anschutz, CO, USA, described recent work on probing histone tail conformations in different reporter systems captured by NMR and their relation to genome signalling. The specificity and selectivity of these interactions in reporter systems, including bromodomains (BD) for acetylation and methylation, in various contexts led her lab to suggest that selectivity is defined by the accessibility of the modified histone tails, direct recognition of the tails, and multivalent binding potential of each tail for different post-translational modifications (Morrison et al. 2018).

Garegin (Garyk) Papoian from University of Maryland, Baltimore, MD, USA, summarized what his group has contributed for over a decade on the energy landscapes, elasticity, and nucleosome structures from various modeling studies that combine concepts in mathematics, physics, biology and chemistry. These investigations provide mechanistic insights into chromatin compaction in the nucleus, acetylated nucleosome structures (where the group noted increased cohesive interactions in a cumulative manner, H4/K16 excepted), and structures and dynamics of modified nucleosomes (e.g., by linker histone or CENP-A, an H3 substitution) (Wu et al. 2021).

Lars Nordenskiöld from Nanyang Technical University, Singapore, presented the unusual properties of telomeric chromatin. Such systems are biologically and medically important because these segments protect DNA ends in chromosomes and are linked to cancer. Structurally they are largely uncharacterized. His group's work on telomeric chromatin by crystallography, NMR, SAXS, and Cryo-EM experiments reveals similar architecture in telomeric nucleosomes to the 145-bp canonical nucleosomes, with flexible TA and TT steps, enabling a well-defined DNA path. Nordenskiöld highlighted pronounced DNA deformations (in roll, slide, twist and shift), which are outliers from general DNA steps, as well as well-known acidic patch interactions.

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SAXS studies revealed a highly dynamic telomeric particle, with unwrapped DNA at the ends. Reconstituted telomeric chromatin fibers exhibit heterogeneity of nucleosome spacing and occupancy. Further, a telomeric tetranucleosome displayed a columnar structure with the dinucleosome unit showing strong stabilization by histone tails, which can help recruit chromatin modifying factors (Soman et al. 2020).

Helmut Schiessel, who just moved from Leiden University, Netherlands, to the Cluster for Excellence, TU, Dresden, Germany, described the sensitivity of nucleosome fluctuations to mechanical factors using coarse-grained nucleosome simulations by Monte Carlo. Graph machinery was used to describe these deformations. He showed that minima in the structures could be created anywhere in the genome using different signals (e.g., GC content) (Zuiddam and Schiessel 2019).

Hitoshi Kurumizaka from The University of Tokyo, Japan, described how GATA3, a model transcription factor, preferentially binds its target site. Specifically, GATA3's zinc fingers bind to solvent accessible target nucleosome sequences. The speaker further discussed structural insights from a Cryo-EM structure of human cGAS-bound nucleosome complex and differences between the human and mouse structures (Tanaka et al. 2020).

Yamini Dalal from National Cancer Institute, NIH, USA, described her group's AFM and fluorescence experiments probing a mechanical switch at a fragile site in the human genome centromere during mitosis. CENP-C propagates a mechanical signal from rigid to elastic nucleosomes, with functional consequences emerging from machine-learning analyses (Melters et al. 2019).

Michele Di Pierro from Northeastern University, USA, highlighted a machine-learning pipeline developed by his group that connects Hi-C maps to chromosomal structure. Using experimental chromosome frequency interactions from various cells and organisms, an energy landscape potential can be constructed that can be applied via molecular dynamics simulations to predict chromosome folding from an input of epigenetic information (Di Pierro et al. 2017).

Finally, **Andrzej Stasiak** from the University of Lausanne, Switzerland, presented topological analysis of oligopaint, high-resolution 3D chromosomal tracings. This method determines with 50-nm precision centroid positions of sequential 30-kb chromatin portions in Mb-long regions of interphase chromosomes in cultured human cells. All tracings which were topologically unaffected by intrinsic tracing errors turned out to be unknotted. This finding supports the notion that chromatin fibers in interphase chromosomes are essentially unknotted (Goundaroulis et al. 2020).

The mixture of theory, simulation, and experiments is clearly invaluable for deciphering the many levels of chromatin organization. The increased contribution of machine learning approaches can be anticipated in the future.

Our MGO subgroup launched a bimonthly zoom seminar series in April 2021, and other events will follow. We invite all interested biophysicists and other scientists interested in the fundamental structure of the genome to join the group and contribute. More information about the subgroup is posted at https://www.biophysics.org/subgroups/multiscale-genome-organization We welcome ideas for future events and collaborations.

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