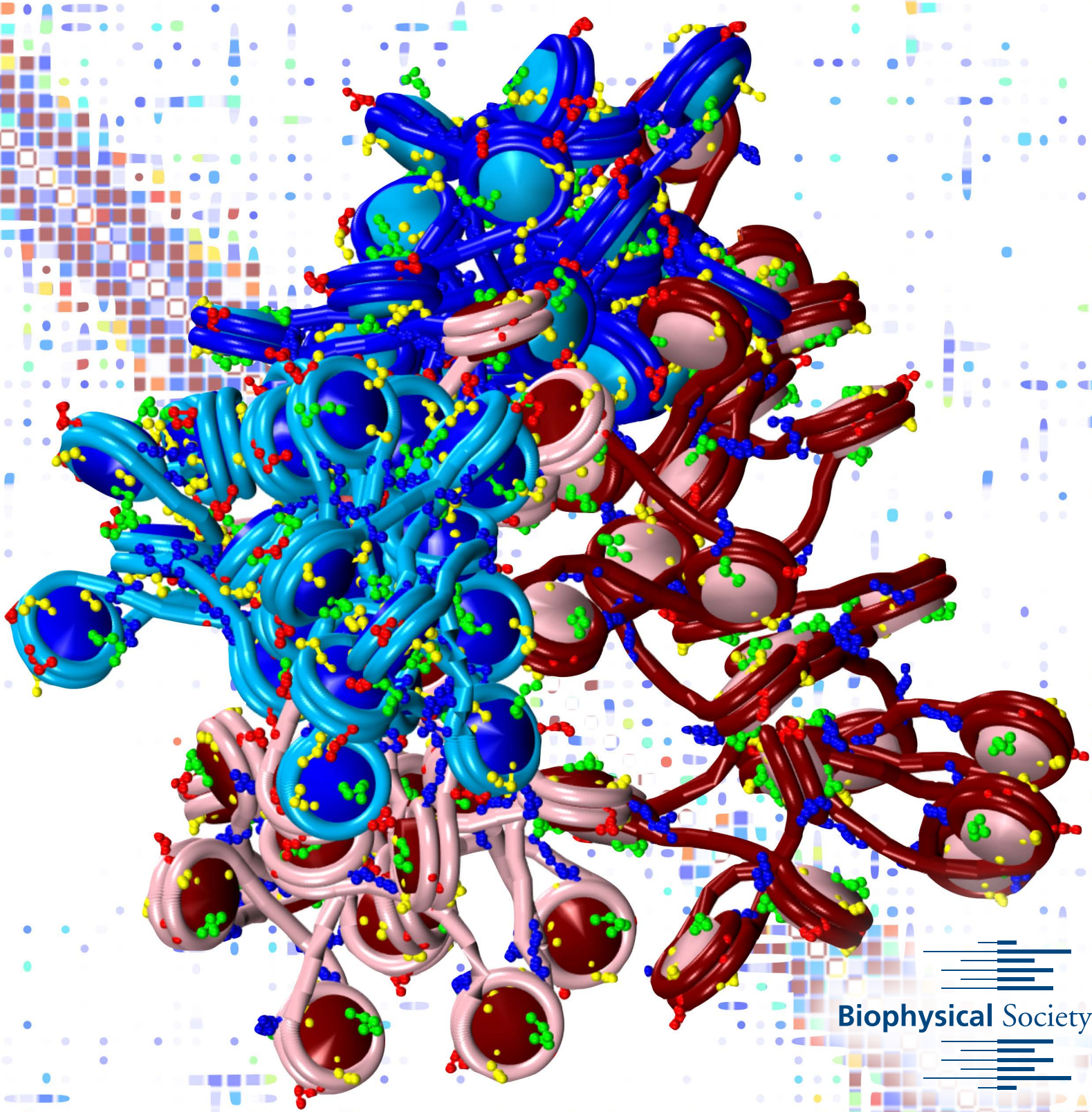
Multiscale Modeling of Chromatin: Bridging Experiment with Theory

Les Houches, France | March 31–April 5, 2019



Biophysical Society

Organizing Committee

Thomas Bishop, Louisiana Tech University, USA

Lars Nordenskiöld, Nanyang Technological University, Singapore

Tamar Schlick, New York University, USA

Andrzej Stasiak, University of Lausanne, Switzerland

March 2019

Dear Colleagues,

We would like to welcome you to the Biophysical Society Thematic Meeting, *Multiscale Modeling of Chromatin: Bridging Experiment with Theory* in Les Houches, France.

This meeting emphasizes the unique multiscale features and properties of chromatin, from DNA to nuclear organization and interactions, and encourages/enhances the development of multiscale models and experimental strategies needed to address all relevant components of the chromatin folding problem. Such multiscale approaches, combining experimental data and modeling/informatics, are necessary to extract and identify structure/function relationships on various scales, from individual base pairs to whole genomes, and to pursue important applications in epigenetics and medicine.

The meeting offers a full program with 36 lectures and 29 posters, bringing together around 70 scientists, students, and postdocs from different fields and countries. We hope that the meeting provides opportunities for attendees to share current scientific progress and foster future collaborations in the field of chromatin modeling and applications. Please use the networking times to explore the beautiful surroundings and talk with your colleagues informally. Suggestions for informal afternoon gatherings are most welcome!

Thank you for joining this meeting and we look forward to enjoying the science with all of you in Les Houches!

The Organizing Committee

Thomas Bishop, Louisiana Tech University, USA
Lars Nordenskiöld, Nanyang Technological University, Singapore
Tamar Schlick, New York University, USA
Andrzej Stasiak, University of Lausanne, Switzerland

Biophysical Society Code of Conduct Anti-Harassment Policy

Adopted by BPS Council November 2015

The Biophysical Society (BPS) is committed to providing an environment that encourages the free expression and exchange of scientific ideas. As a global, professional Society, the BPS is committed to the philosophy of equal opportunity and respectful treatment for all regardless of national or ethnic origin, religion or religious belief, gender, gender identity or expression, race, color, age, marital status, sexual orientation, disabilities, veteran status, or any other reason not related to scientific merit. All BPS meetings and BPS-sponsored activities promote a working environment that is free of inappropriate behavior and harassment by or toward all attendees of Society meetings and Society-sponsored activities, including scientists, students, guests, exhibitors, staff, vendors, and other suppliers.

This global policy applies to all locations and situations where BPS business is conducted and to all BPS-sponsored activities and events. This policy does not replace the specific staff policies for situations in which only staff are involved.

Reported or suspected occurrences of harassment will be promptly and thoroughly investigated. Following an investigation, BPS will immediately take any necessary and appropriate action. BPS will not permit or condone any acts of retaliation against anyone who files harassment complaints or cooperates in the investigation of same.

Definition of Harassment
The term "harassment" includes but is not limited to epithets, unwelcome slurs, jokes, or verbal, graphic or physical conduct relating to an individual's race, color, religious creed, sex, national origin, ancestry, citizenship status, age, gender or sexual orientation that denigrate or show hostility or aversion toward an individual or group.

Sexual harassment refers to unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature. Behavior and language that are welcome/ acceptable to one person may be unwelcome/offensive to another. Consequently, individuals must use discretion to ensure that their words and actions communicate respect for others. This is especially important for those in positions of authority since individuals with lower rank or status may be reluctant to express their objections or discomfort regarding unwelcome behavior. It does not refer to occasional compliments of a socially acceptable nature. It refers to behavior that is not welcome, is personally offensive, debilitates morale, and therefore, interferes with work effectiveness. The following are examples of behavior that, when unwelcome, may constitute sexual harassment: sexual flirtations, advances, or propositions; verbal comments or physical actions of a sexual nature; sexually degrading words used to describe an individual; a display of sexually suggestive objects or pictures; sexually explicit jokes; unnecessary touching.

Investigative Process
Anyone who feels harassed is encouraged to immediately inform the alleged harasser that the behavior is unwelcome. In many instances, the person is unaware that their conduct is offensive and when so advised can easily and willingly correct the conduct so that it does not reoccur. Anyone who feels harassed IS NOT required to address the person believed guilty of inappropriate treatment. If the informal discussion with the alleged harasser is unsuccessful in remedying the problem or if complainant does not feel comfortable with such an approach, he/she should contact BPS's Executive Director or the Society President, or any BPS Officer. All complaints will be promptly and thoroughly investigated.

All reports of harassment or sexual harassment will be treated seriously. However, absolute confidentiality cannot be promised nor can it be assured. BPS will conduct an investigation of any complaint of harassment or sexual harassment, which may require limited disclosure of pertinent information to certain parties, including the alleged harasser.
No retaliation will be taken against any employee, member, volunteer, exhibitor, or supplier because he or she reports a problem concerning possible acts of harassment. Employees, members, volunteers, exhibitors, or suppliers can raise concerns and make reports without fear of reprisal.

Investigative Procedure
Once a complaint of harassment or sexual harassment is received, BPS will begin a prompt and thorough investigation.

- An impartial investigative committee, consisting of the Past-President, current President, and President-Elect will be established.
- The committee will interview the complainant and review the written complaint. If no written complaint exists, one will be requested.
- The committee will speak to the alleged offender and present the complaint.
- The alleged offender will be given the opportunity to address the complaint, with sufficient time to respond to the evidence and bring his/her own evidence.
- If the facts are in dispute, the investigative team may need to interview anyone named as witnesses.
- The investigative committee may seek BPS Counsel's advice.
- Once the investigation is complete, the committee will report their findings and make recommendations to the Society Officers.

Disciplinary Actions
Individuals engaging in behavior prohibited by this policy as well as those making allegations of harassment in bad faith will be subject to disciplinary action. Such actions range from a verbal warning to ejection from the meeting or activity in question without refund of registration fees and the reporting of their behavior to their employer. Repeat offenders may be subject to further disciplinary action, such as being banned from participating in future Society meetings or Society-sponsored activities. In the event that the individual is dissatisfied with the results of the investigation, he or she may appeal to the President of the Society. Any questions regarding this policy should be directed to the BPS Executive Officer or other Society Officer.

BPS Management Responsibility
Every officer, director, supervisor, and manager is responsible for ensuring that BPS provides an environment free of harassment and inappropriate behavior and that complaints are handled promptly and effectively. The BPS Society Office and Officers must inform the Society membership and all vendors and suppliers about this policy, promptly investigate allegations of harassment, take appropriate disciplinary action, and take steps to assure retaliation is prohibited

Table of Contents

GENERAL INFORMATION

Registration Hours/Information Location and Hours

On Sunday, attendee will check-in after 15:00. The building entry codes were sent to you in the final logistic email. Upon arrival, attendees will find essential information in the hall of the Cecile Dewitt Building: the housing plan with list of participants, name of the accommodation building, bedroom number, and a map of the school. Name badges will be provided for each attendee. On Sunday, Monday, Tuesday, Wednesday, Thursday, and Friday registration/information will be located in the Cecile Dewitt Building. Hours are as follows:

Sunday, March 31	18:00 – 19:30
Monday, April 1 – Thursday, April 4	8:30 – 17:00
Friday, April 5	8:30 – 13:30

Instructions for Presentations

(1) Presentation Facilities:

A data projector will be available in Cecile Dewitt Building Lecture Room. Speakers are required to bring their own laptops and adaptors. It is recommended to have a backup of the presentation on a USB drive in case of any unforeseen circumstances. Speakers are advised to preview their final presentations before the start of each session.

(2) Poster Session:

1) All poster sessions will be held in the Cecile Dewitt Building of the École de physique des Houches.

2) A display board measuring 95 cm wide x 135 cm high (3.12 feet wide x 4.43 feet high) will be provided for each poster. Poster boards are numbered according to the same numbering scheme as listed in the e-book.

3) Posters should be set up in the morning of April 1and removed by noon April 5. All posters are available for viewing during all poster sessions; however, there will be formal poster presentations on Monday, Tuesday, Wednesday, and Thursday from 21:00-22:00.

4) During the assigned poster presentation sessions, presenters are requested to remain in front of their poster boards to meet with attendees.

5) All posters left uncollected at the end of the meeting will be disposed.

Meals and Coffee Breaks

There will be a 30 minute Welcome Reception on Monday Evening from 19:00 – 19:30. This reception will be held at the restaurant bar.

Breakfasts, Lunches, and Dinners (Monday, Tuesday, Wednesday and Thursday) will be served at the restaurant. On Sunday, only dinner will be provided and on Friday, breakfast and lunch will be

served. Box lunches will be available if you inform the restaurant one day prior. Meals will be served at the following time:

Breakfast	7:45 – 8:45
Lunch	12:30 – 13:30
Dinner	19:30 – 21:00

Coffee and tea will be provided at the restaurant bar after lunch and dinner. You can also purchase cold drinks from the bar by cash (Euros only). The bar will not accept credit card.

Coffee breaks will be held in the Cecile Dewitt Building.

Smoking

Please be advised that smoking is not permitted at the École de physique des Houches.

Name Badges

Name badges are required to enter all scientific sessions, poster sessions, and social functions. Please wear your badge throughout the conference.

Internet

Wifi will be provided at the venue. Attendees will receive account number and password onsite.

Contact

If you have any further requirements during the meeting, please contact the meeting staff at the registration desk from March 31-April 5 during registration hours.

In case of emergency, you may contact the following:

Daniel
Cell: (+33/0)6 789 852 40
Building : ALPENS 9

Ally Levine, BPS Staff
Email: alevine@biophysics.org

Multiscale Modeling of Chromatin: Bridging Experiment with Theory

Les Houches, France
March 31-April 5, 2019

PROGRAM

Sunday, March 31, 2019

18:00 – 19:30	**Registration/Information**	**Cecile Dewitt Building**
19:30 – 21:00	**Opening Dinner**	**Restaurant**

Monday, April 1, 2019

8:30 – 17:00	**Registration/Information**	**Cecile Dewitt Building**
8:45 – 9:00	Tamar Schlick, New York University, USA **Opening Remarks**	
Session I	Tamar Schlick, New York University, USA, Chair	
9:00 – 9:30	Mair Churchill, University of Colorado, Denver, USA ***Histone Trafficking During Chromatin Replication***	
9:30 – 10:00	Ivet Bahar, University of Pittsburgh, USA ***Chromatin Dynamics Studied by the Gaussian Network Model: Short- and Long-Range Couplings Between Gene Loci***	
10:00 – 10:30	Anna Panchenko, NCBI, NIH, USA ***Integrating in Silico and in Vitro Approaches to Characterize Nucleosome Structure and Dynamics with High Precision***	
10:30 – 11:00	**Coffee Break**	**Cecile Dewitt Building**
Session II	Helmut Schiessel, Leiden University, The Netherlands**,** Chair	
11:00 – 11:30	Garegin Papoian, University of Maryland, USA ***Structural Plasticity of Histone Oligomers and Their Interactions with Chaperones and Other Regulators***	
11:30 – 11:50	Alexey Onufriev, Virginia Tech, USA* ***DNA Accessibility Control in the Nucleosome: Insights from Physics***	
11:50 – 12:10	Jürgen Walther, IRB Barcelona, Spain* ***From DNA to Chromatin: Multiscale Models from Atomistic to KB Level***	
12:30 – 13:30	**Lunch Break**	**Restaurant**
13:30 – 17:00	**Networking**	
Session III	Lars Nordenskiöld, Nanyang Technological University, Singapore, Chair	
17:00 – 17:30	Helmut Schiessel, Leiden University, The Netherlands ***The Mechanical Genome***	

17:30 – 18:35	**Poster Pitches**	
19:00 – 19:30	**Welcome Reception**	**Restaurant**
19:30 – 21:00	**Dinner**	**Restaurant**
21:00 – 22:00	**Poster Session I**	**Cecile Dewitt Building**

Tuesday, April 2, 2019

8:30 – 17:00	**Registration/Information**	**Cecile Dewitt Building**
Session IV	Thomas Bishop, Louisiana Tech University, USA, Chair	
9:00 – 9:30	Mark Ellisman, University of California, San Diego, USA ***Imaging Local and Global Chromatin Structure as a 3D Continuum within the Nucleus: Progress and Future Strategies***	
9:30 – 10:00	Ariel Kaplan, Technion - Israel Institute of Technology, Israel ***Nucleosome Diffusion and Gene Expression Regulation: Insights from Single Molecule Studies***	
10:00 – 10:30	Thomas Bishop, Louisiana Tech University, USA ***Genome Dashboards: Framework and G-Dash Prototype***	
10:30 – 11:00	**Coffee Break**	**Cecile Dewitt Building**
Session V	Jie Yan, Mechanobiology Institute, National University of Singapore, Singapore, Chair	
11:00 – 11:20	Madhura De, Heidelberg University, Germany* ***Positioning the Linker Histone on a Chromatosome: What Role Does the DNA Play?***	
11:20 – 11:40	Anat Galis Vivante, Bar Ilan University, Israel* ***Chromatin Dynamics Governed by a Set of Nuclear Structural Proteins***	
11:40 – 12:00	Hugo van Ingen, Utrecht University, The Netherlands* ***Capturing Interactions to the Nucleosome Acidic Patch by Multi-Scale NMR***	
12:30 – 13:30	**Lunch Break**	**Restaurant**
13:30 – 17:45	**Networking**	
Session VI	Andrzej Stasiak, University of Lausanne, Switzerland, Chair	
17:45 – 18:05	Catherine Royer, Rensselaer Polytechnic Institute, USA* ***Superresolution Imaging of the Start Transcription Factors***	
18:05 – 19:05	**Poster Pitches**	
19:30 – 21:00	**Dinner**	**Restaurant**
21:00 – 22:00	**Poster Session II**	**Cecile Dewitt Building**

Wednesday, April 3, 2019

8:30 – 17:00	**Registration/Information**	**Cecile Dewitt Building**
Session VII	Garegin Papoian, University of Maryland, USA, Chair	
9:00 – 9:30	Hitoshi Kurumizaka, University of Tokyo, Japan ***Structural Studies of Chromatin: Toward Understanding the Regulation of Genomic DNA***	
9:30 – 10:00	Jie Yan, Mechanobiology Institute, National University of Singapore, Singapore ***Transfer-Matrix Calculation of the Effects of Physical Constraints Applied to DNA on DNA-Protein Interactions***	
10:00 – 10:30	Tamar Schlick, New York University, USA ***Folding Genes at Nucleosome Resolution***	
10:30 – 11:00	**Coffee Break**	**Cecile Dewitt Building**
Session VIII	Hitoshi Kurumizaka, University of Tokyo, Japan, Chair	
11:00 – 11:20	Pablo D. Dans Puiggròs, IRB Barcelona, Spain* ***Understanding Gene Regulation Through the 3d Structure of Chromatin and Chromosomes***	
11:20 – 11:40	Joshua Moller, University of Chicago, USA* ***Unveiling Chromatin Fiber Condensation Through Many-Body Nucleosome Interactions***	
11:40 – 12:00	Marina Katava, University of Texas at Austin, USA* ***On the Role of Chromatin Geometry in Epigenetic Domain Formation***	
12:30 – 13:30	**Lunch Break**	**Restaurant**
13:30 – 17:45	**Networking**	
Session IX	Mair Churchill, University of Colorado, Denver, USA, Chair	
17:45 – 18:15	Lars Nordenskiöld, Nanyang Technological University, Singapore ***Structure and Dynamics of the Telomeric Nucleosome and Chromatin***	
18:15 – 18:35	Quinn MacPherson, Stanford University, USA* ***Heterochromatin and the Nuclear Periphery: Specificity via Density***	
18:35 – 19:05	Toshio Tsukiyama, Fred Hutchinson Cancer Research Center, USA ***Mechanisms and Functions of Chromatin Condensation in Quiescent Yeast Cells***	
19:30 – 21:00	**Dinner**	**Restaurant**
21:00 – 22:00	**Poster Session III**	**Cecile Dewitt Building**

Thursday, April 4, 2019

8:30 – 17:00	**Registration/Information**	**Cecile Dewitt Building**

Session X	G.V. Shivashankar, Mechanobiology Institute, National University of Singapore, Singapore, Chair	
9:00 – 9:30	Amartya Sanyal, Nanyang Technological University, Singapore ***Connecting Genomic and Non-Genomic Mechanisms of Cancer Drug Resistance***	
9:30 – 10:00	Angelo Rosa, International School for Advanced Studies, Italy ***From Chromosome Territories to Ring Polymers: Physical Properties of Untangled Polymer Melts***	
10:00 – 10:30	Alexandra Zidovska, New York University, USA ***The "Self-Stirred" Genome: Bulk and Surface Dynamics of the Chromatin Globule***	
10:30 – 11:00	**Coffee Break**	**Cecile Dewitt Building**
Session XI	Erez Lieberman-Aiden, Baylor College of Medicine, USA, Chair	
11:00 – 11:20	Artemi Bendandi, University of Genoa, Italy* ***Mesoscale Bottom-Up Approach to the Study of Chromatin Topological Conformations: From the Nucleosome to 1Mbps***	
11:20 – 11:40	Soya Shinkai, RIKEN, Center for Biosystems Dynamics Research, Japan* ***Deciphering Hi-C Data into Polymer Dynamics***	
11:40 – 12:00	Michele Di Pierro, Rice University, USA* ***The Three-Dimensional Architecture of the Human Genome: It's Nuclear Physics!***	
12:30 – 13:30	**Lunch Break**	**Restaurant**
13:30 – 17:45	**Networking**	
Session XII	Amartya Sanyal, Nanyang Technological University, Singapore, Chair	
17:45 – 18:15	G.V. Shivashankar, Mechanobiology Institute, National University of Singapore, Singapore ***Mechanical Control of Chromosome Organization and Gene Expression***	
18:15 – 18:45	Erez Lieberman-Aiden, Baylor College of Medicine, USA ***A 3D Code in the Human Genome***	
18:45 – 19:05	Anne Shim, Northwestern University, USA* ***The Crowded Nanoenvironment Influences Gene Expression***	
19:30 – 21:00	**Dinner**	**Restaurant**
21:00 – 22:00	**Poster Session IV**	**Cecile Dewitt Building**

Friday, April 5, 2019

8:30 – 13:30	**Information**	**Cecile Dewitt Building**
Session XIII	John van Noort, Leiden University, The Netherlands, Chair	

9:00 – 9:30	Andrzej Stasiak, University of Lausanne, Switzerland ***TADs and chromatin supercoiling***	
9:30 – 10:00	Vlad Cojocaru, Max-Planck Institute for Molecular Biomedicine, Germany ***How Do DNA-Binding Proteins Interpret and Modify Nucleosome Dynamics?***	
10:00 – 10:30	**Coffee Break**	**Cecile Dewitt Building**
Session XIV	Alexandra Zidovska, New York University, USA, Chair	
10:30 – 11:00	John van Noort, Leiden University, The Netherlands ***Chromatin Higher Order Folding in Irregular Fibers: A Critical Role of Linker DNA***	
11:00 – 11:30	Wilma Olson, Rutgers University, USA ***Contributions of Nucleosome Architecture to Long-Range Communication on Chromatin***	
11:30 – 12:00	Thomas Bishop, Louisiana Tech University, USA **Closing Remarks and *Biophysical Journal* Poster Awards**	
12:30 – 13:30	**Lunch**	**Restaurant**

**Short talks selected from among submitted abstracts*

SPEAKER ABSTRACTS

HISTONE TRAFFICKING DURING CHROMATIN REPLICATION

Mair Churchill
University of Colorado, Denver, USA

No Abstract

CHROMATIN DYNAMICS STUDIED BY THE GAUSSIAN NETWORK MODEL: SHORT- AND LONG-RANGE COUPLINGS BETWEEN GENE LOCI

Ivet Bahar[1]; She Zhang[1];
[1]University of Pittsburgh, Computational and Systems Biology, Pittsburgh, Pennsylvania, United States

Understanding the three-dimensional (3D) architecture of chromatin and its relation to gene expression and regulation is fundamental to understanding how the genome functions. Advances in Hi-C technology now permit us to study 3D genome organization, but we still lack an understanding of the structural dynamics of chromosomes. The dynamic couplings between regions separated by large genomic distances (> 50 megabases) have yet to be characterized. We recently adapted a well-established protein-modeling framework, the Gaussian Network Model (GNM), to model chromatin dynamics using Hi-C data (1). We show that the GNM can identify spatial couplings at multiple scales: it can quantify the correlated fluctuations in the positions of gene loci, find large genomic compartments and smaller topologically-associating domains (TADs) that undergo en-bloc movements, and identify dynamically coupled distal regions along the chromosomes. We show that the predictions of the GNM correlate well with genome-wide experimental measurements. We use the GNM to identify novel cross-correlated distal domains (CCDDs) representing pairs of regions distinguished by their long-range dynamic coupling and show that CCDDs are associated with increased gene co-expression. We then analyze the GNM results obtained from the Hi-C maps of different cell types to show that while GNM mode shapes are mainly conserved, the contributions of individual modes to the overall dynamics of cell genome are cell-type specific. Combined with the previous findings on the association between chromosomal mobility and accessibility, computational results suggest that the spectrum of GNM modes in the low frequency regime are common modules of chromosomal dynamics shared by different cell types. How they are assembled may give rise to diverse gene expressions and finally lead to differentiated cellular phenotypes. Reference:

Sauerwald N, Zhang S, Kingsford C, Bahar I. (2017) Chromosomal dynamics predicted by an elastic network model explains genome-wide accessibility and long-range couplings *Nucleic Acids Res***45**:3663-3673

INTEGRATING *IN SILICO* AND *IN VITRO* APPROACHES TO CHARACTERIZE NUCLEOSOME STRUCTURE AND DYNAMICS WITH HIGH PRECISION

Anna Panchenko[1];
[1]National Institutes of Health, NCBI, Bethesda, Maryland, United States

At the heart of the interplay between protection and accessibility of the genetic material lies the nucleosome. Nucleosomes experience a broad repertoire of alterations that affect their structure, dynamics, and interactions with various chromatin binding partners. We use hydroxyl-radical footprinting, chemical crosslinking and molecular modeling to explore conformational polymorphism of nucleosomes both at local and global scales. Such an integrative approach enables insights into the functionally relevant motions in nucleosomes including coupling between conformations of histone tails and DNA geometry, the rearrangements in histone core and histone-DNA interactions, with important implications for binding of chromatin remodelers and nucleosome translocation. In addition, our methods allow to produce high resolution atomistic structural models of different variant nucleosomes refined by experimental data. Specific binding interfaces of variant nucleosomes have been identified that are composed of nuclesomal DNA and histone fold regions pointing to key molecular recognition features.

STRUCTURAL PLASTICITY OF HISTONE OLIGOMERS AND THEIR INTERACTIONS WITH CHAPERONES AND OTHER REGULATORS

Garegin A. Papoian[1];
[1]The University of Maryland, Chemistry and Biochemistry, IPST, College Park, Maryland, United States

To gain deeper insights into the nucleosomal particle, it is useful to deconstruct the histone octameric core into the constituent tetramer and two dimers. Towards achieving this goal, we used atomistic and coarse-grained simulations to investigate various histone oligomers, from dimers to the histone octamer in the nucleosome, and also subsequent complex formation with histone chaperones and other proteins regulating chromatin. We studied both canonical histones, as well as a centromeric histone H3 variant, CENP-A, finding that despite nearly identical structures, CENP-A nucleosomes are significantly more distortable and dynamic. We further traced this difference to the structural frustration or incompatibility between the preferred CENP-A/H4 tetramer structure and the corresponding octamer structure in the nucleosome. Furthermore, we found that various histone chaperones and binding partners, such as CENP-C, can rigidify the nucleosome in a switch-like fashion. In a separate line of work, we used coarse-grained simulations to study how the H1 linker histone interacts with nucleosomal DNA and other histones, regulating the distribution of nucleosomal conformations.

DNA ACCESSIBILITY CONTROL IN THE NUCLEOSOME: INSIGHTS FROM PHYSICS

Alexey V. Onufriev[1];
[1]Virginia Tech, Blacksburg, Virginia, United States

The nucleosome, a complex of 147 base-pairs of DNA with eight histone proteins, must protect its DNA, but, at the same time, allow on-demand access to it when needed by the cell. The exact mechanism of the control remain unclear.
We consider a series of physics-based models of the nucleosome, from the highly coarse-grained cylinders model, to fully atomistic, to multi-state atomistic.
One key conclusion is that at physiological conditions the nucleosome complex is close to the phase boundary separating it from the "unwrapped" states where the DNA is more accessible. A small drop in the positive charge (e.g. through acetylation of a lysine) of the globular histone core can significantly lower the DNA affinity to the core, and thus increase DNA accessibility. The findings suggest that charge-altering post-translational modifications in the histone core might be utilized by the cell to modulate accessibility to its DNA at the nucleosome level.
The multi-state atomistic model explores virtually all possible charge-altering post-translational modifications (PTMs) in the globular histone core. The model reveals a rich and nuanced picture: the effect of PTMs varies greatly depending on location, including counter-intuitive trends such as decrease of DNA accessibility for some lysine acetylations in the core. Most PTMs are non-cooperative, but there are exceptions, which is a consequence of the multiple states considered. A detailed connection to transcription regulation in-vivo is made.

FROM DNA TO CHROMATIN: MULTISCALE MODELS FROM ATOMISTIC TO KB LEVEL

Jürgen Walther[1]; Pablo Dans[1]; Modesto Orozco[1];
[1]IRB Barcelona, Barcelona, Barcelona, Spain

The three dimensional organization of chromatin inside the cell nucleus is expected to strongly depend on sequence specific properties of nucleosomal and linker DNA. However, recent experiments cannot capture yet the characteristics of chromatin arrangement on the resolution level of a single base-pair. To model the chromatin fiber with bp-level accuracy we developed a coarse-grained DNA model (MCDNA). MCDNA is available as a web tool (http://mmb.irbbarcelona.org/MCDNA/) for the three-dimensional simulation of free DNA and medium-sized chromatin fibers. The program implements a novel Monte Carlo algorithm based on a mesoscopic model, using a tetramer-dependent base-pair step model fitted to reproduce parmbsc1 atomistic molecular dynamics (MD) simulations. By projecting the Monte Carlo ensembles to the atomistics level the model accurately reproduces base-pair geometries, groove widths and backbone conformations compared to atomistic MD. The method provides ensembles of quality comparable to those obtained from atomistic MD, but at a tiny fraction of the computational cost, allowing to study systems much larger than those explored by atomistic MD. MCDNA is extended to a chromatin fiber model (Chromatin Dynamics). Chromatin Dynamics keeps the bp-step accuracy of MCDNA but is also able to simulate kb long fibers. Chromatin Dynamics is used for several applications, for example for modeling Micro-C/ high resolution Hi-C data, for visualizing oligo- and immuno-STORM microscopy images or for investigating the existence of an evolutionary-driven preferred chromatin fiber configuration.

THE MECHANICAL GENOME

Helmut Schiessel[1];
[1]Leiden University, Lorentz Institute, Leiden, Zuid-Holland, The Netherlands

This talk focuses on a second layer of information in DNA molecules, namely on sequence-dependent DNA mechanics that guides DNA packaging inside cells. We use a mutation Monte Carlo technique on a coarse-grained nucleosome model to calculate the sequence preferences of nucleosomes and to demonstrate the possibility of multiplexing mechanical and classical genetic information. This allows to guide on top of genes the packaging of DNA into nucleosomes with single base-pair precision. We demonstrate this explicitly for the genome of baker's yeast by mapping nucleosomal DNA sequences on weighted graphs. We then focus on transcription start sites of various organisms and find a simple general rule: on average, nucleosomes are intrinsically repelled from transcription start sites for unicellular life but the opposite holds true for multicellular life. We speculate about a possible biological reason behind this difference.

IMAGING LOCAL AND GLOBAL CHROMATIN STRUCTURE AS A 3D CONTINUUM WITHIN THE NUCLEUS: PROGRESS AND FUTURE STRATEGIES

Mark Ellisman[1]; Guillaume Castillon[1]; Thomas Deerinck[1]; Hiroyuki Hakozaki[1]; Mason Mackey[1]; Horng Ou[2]; Steven Peltier[1]; Sebastien Phan[1]; Ranjan Ramachandra[1]; Jan Soroczynski[2]; Jingwen Yin[2]; Clodagh O'Shea[2];
[1]University of California San Diego, Department of Neurosciences, National Center for Microscopy and Imaging Research (NCMIR), La Jolla, California, United States
[2]The Salk Institute , Biological Studies, La Jolla, California, United States

Recent 3D EM analyses have advanced knowledge of how local nucleosome organization and global 3D organization of DNA in the nucleus relates to the functional activity of our genome in different cell states. To provide insight and understanding on this front, we are actively developing new probes and methods for correlated, multimodal microscopy to enable the visualization of chromatin *in situ* across scales - from the global organization of chromatin polymers within megabase 3D domains to the level of individual nucleosomes. We have generated and the first 3D EM datasets and multiscale reference maps of chromatin ultrastructure in whole cell nuclei and made these data openly available. This work was enabled by our development of ChromEMT[1], which combines ChromEM with new advances in multi-tilt EM tomography (EMT)[2]. Progress on this ongoing project will be described with some emphasis given to future plans, focusing on new opportunities to further improve resolution, field-of-view, sample preservation and multimodal data integration. In particular, plans for the refinement and application of a new CryoChem technique[3], which allows for genetically labeled and cryofixed samples to be characterized with 3D CLEM, exploiting cryofixation for high quality ultrastructural preservation while retaining the use of diaminobenzidine labeling using genetic EM tags â€“ offering a roadmap to advance our EM (and cryoEM) imaging strategies into tissue. We also preview novel strategies for labeling specific genomic loci or intranuclear bodies that can be imaged with LM, mapped in 3D with x-ray microCT, and then localized and imaged at EM resolution with STEM tomography (and eventually cryo-STEM tomography).

NUCLEOSOME DIFFUSION AND GENE EXPRESSION REGULATION: INSIGHTS FROM SINGLE MOLECULE STUDIES

Ariel Kaplan[1];
[1]Technion - Israel Institute of Technology, Haifa, Israel

The structure of promoter chromatin determines the ability of transcription factors to bind the DNA and therefore has a profound effect on the expression levels of genes. Yet, the role of spontaneous nucleosome movements in this process is not fully understood. Here, we developed a single-molecule assay capable of simultaneously characterizing the bp-scale diffusion of a nucleosome on DNA, and the binding of a transcription factor (TF). Our results demonstrate that nucleosomes undergo confined diffusion, and that the incorporation of the histone variant H2A.Z serves to partially relieve this confinement, inducing a different type of nucleosome repositioning. The increase in diffusion leads to exposure of a TF's binding site and facilitates its association with the DNA, which in term biases the subsequent movement of the nucleosome. Our findings suggest the use of mobile nucleosomes as a novel and general transcriptional regulatory mechanism.

GENOME DASHBOARDS: FRAMEWORK AND G-DASH PROTOTYPE

Thomas C. Bishop[1]; Zilong Li[1]; Ran Sun[1];
[1]Louisiana Tech University, Ruston, Louisiana, United States

A dashboard is a console that displays data and provides controllers for navigating the physical world. A "genome dashboard" unifies sequence and spatial data, enabling genome pilots to navigate DNA, nucleosomes, chromatin and chromosome data or structures in real time. Here we present a framework for unifying studies of the 3D structure and dynamics of DNA with sequence based approaches. The framework is based on the idea that DNA is the common thread in all of genomics. As a 3D material the thread is a directed space curve that can be represented in an internal, material reference frame or in a Cartesian coordinate based laboratory reference frame. Mathematical expressions for converting between these representations are well defined and tools for computing these conversions are extremely fast. Masks are defined as external agents that alter the material properties, including conformation, of any segment of the DNA space curve. From this perspective genomics is the study of masked threads. We demonstrate the genome dashboard concept, using our prototype G-Dash to model chromatin. Inventories of nucleosome Masks can be manipulated in real time to generate atomic and coarse grained models from base pairs to entire chromosomes. The genome dashboard framework provides a basis for the data unification required to propose, test and validate structure-function relationships in genomics and to develop knowledge based potential functions for chromatin folding.

POSITIONING THE LINKER HISTONE ON A CHROMATOSOME: WHAT ROLE DOES THE DNA PLAY?

Madhura De[1]; Rebecca C Wade[2]; Katalin Tóth[1];
[1]German Cancer Research Center, Biophysics of Macromolecules, Heidelberg, Baden-Württemberg, Germany
[2]ZMBH, DKFZ-ZMBH Alliance and Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Heidelberg, Baden-Württemberg, Germany

The chromatosome comprises of the nucleosome with additional stretches of linker-DNA associated with the linker histone protein (LH). To study the effect of linker-DNA length and sequence on LH positioning, single-molecule FRET (sm-FRET) spectroscopy and sm-FRET with Alternating Laser Excitation (ALEX) on fluorescently labelled reconstituted chromatosomes were performed. sm-FRET measurements on chromatosomes labelled on the two linker-DNA arms confirmed that the LH (*Xenopus laevis* H1.0b) compacted the chromatosome at low salt. This observation was further supported by EMSA. At a given salt, the distance between the dyes placed on the DNA, 20bp away from the two entry/exit sites were found to be similar in both symmetric chromatosomes with equally long 40bp linker-DNAs, or asymmetric chromatosomes with one 40bp, and the other, 24bp linker-DNA. To study the sequence effects of linker-DNA, we used a symmetric 226bp Widom 601 DNA with 11bp GC-rich region on one entry/exit site, and 11bp AT-rich region on the other entry/exit site. Chromatosomes were reconstituted, having the acceptor dye on one or the other linker-DNA, and the LH labelled with the donor dye at either the C-terminal domain (CTD) or the globular domain (GD). The distances between the CTD or the GD and either linker-DNA arms were equal in unmodified, symmetric chromatosomes. However, for symmetric chromatosomes with 11bp AT-rich region, the LH position was found to be askew: the CTD was closer to the GC-rich linker-DNA and the GD was closer to the modified AT-rich arm. On swapping the GC and the AT-rich regions, keeping the rest of the DNA unchanged, the GD was again found to be closer to the AT-rich arm. This suggests that the LH positioning on a single chromatosome is variable, and is affected, among other factors, by DNA sequence. This DNA-directed LH positioning may have implications in higher-order structures.

CHROMATIN DYNAMICS GOVERNED BY A SET OF NUCLEAR STRUCTURAL PROTEINS

Anat Galis Vivante[1]; Irena Bronshtein[1]; Yuval Garini[1];
[1]Bar Ilan University, Physics Department & Nanotechnology Institute, Ramat Gan, Center, Israel

In eukaryotic cells, tens of thousands of genes are packed in the small volume of the nucleus. The genome itself is organized in chromosomes that occupy specific volumes referred to as chromosome territories. This organization is preserved throughout the cell cycle, even though there are no sub-compartments in the nucleus itself. The nuclear structure is strongly related to the dynamic properties. Hence, the dynamics of the nucleus content is fundamental for understanding its appropriate function. The organization and dynamics of chromatin are directly responsible for many functions including gene regulation, genome replication, and maintenance. In order to better understand the details of these mechanisms, we need to understand the role of specific proteins that take part in these processes. We use live imaging methods to characterize the dynamic properties of the chromatin and its organization in living cells. More specifically, we use single particle tracking of different genomic regions, and implement Continuous Photobleaching (CP) measurements which provide crucial information on the mobility and binding properties of the proteins. Through these methods, we studied lamin A, BAF, Emerin, lamin B, CTCF, and Cohesin and analyze their effect on chromatin dynamics. Finally, we suggest a model of chromatin organization and develop a new type of diagram for mapping and analyzing the regulating networks of chromatin organization.

CAPTURING INTERACTIONS TO THE NUCLEOSOME ACIDIC PATCH BY MULTI-SCALE NMR

Hugo van Ingen[1];
[1]Utrecht University, NMR Group, Utrecht, Utrecht, The Netherlands

Chromatin biology is driven by the specific interactions of wide range of protein factors with chromatin. The nucleosome forms the key docking platform for many of these proteins. Ultimately, an understanding of how such nucleosome-protein interaction occur in the native, cellular chromatin context is needed to fully appreciate the molecular basis of chromatin function. Motivated by its applicability across a wide range of sample phases, ranging from dilute solutions to cellular samples, our objective is to develop an NMR-based experimental, multi-scale approach to study nucleosome-protein interactions. Here, we present our recent results on three acidic patch binding proteins, each studied at a different level of complexity. For dilute solutions of mononucleosomes, solution NMR techniques are well suited to obtain atomic-resolution interaction data. Combining NMR, XL-MS and mutagenesis, we determined the structure of DNA repair factor and E3 ligase RNF168 bound to the nucleosome acidic patch. The structure highlights how the E3 directs the E2 enzyme towards to target lysine, thus explaining the ubiquitination specificity [1]. Second, we show that similar interaction data can be obtained in a dense phase formed by sedimented mononucleosomes, mimicking the crowded cellular environment. Here, we used state-of-the-art solid-state NMR to retrieve the binding site of the well-known LANA peptide on the nucleosome [2]. Finally, we discuss the prospects of in-cell NMR to study native chromatin interactions using chromatin factor HMGN2. Together, these results indicate that NMR may be appropriate source for multi-scale interaction data. [1] V. Horn et al. Structural basis of specific H2A K13/K15 ubiquitination by RNF168, revised version submitted. [2] S. Xiang, U.B. le Paige, et al (2018). Site-Specific Studies of Nucleosome Interactions by Solid-State NMR Spectroscopy. Angew. Chem. Int. Ed., vol. 57, p. 1-6

SUPERRESOLUTION IMAGING OF THE START TRANSCRIPTION FACTORS

Labe Black[1]; Sylvain Tollis[2]; Jean-Bernard Fiche[3]; Savanna B Dorsey[1]; Jing Cheng[2]; Marcelo Nollmann[3]; Mike Tyers[2]; **Catherine A Royer**[1];
[1]Rensselaer Polytechnic Institute, Biological Sciences, Albany, New York, United States
[2]Université de Montréal, Institute for Research in Immunology and Cancer, Montreal, Quebec, Canada
[3]CNRS, INSERM, Université de Montpellier, Centre de Biochimie Structurale, Montpellier, Hérault, France

An outstanding aspect of how the main G1/S transcription factors (TFs) in budding yeast, called SBF and MBF, function to regulate the commitment to division (Start) is the spatial organization of the ~200 G1/S promoters as cells progress through G1-phase. Here we have used super-resolution Photo-Activatable Localization Microscopy (PALM) to map the static and dynamic positions of mEos3.2 fusions of the G1/S TF components, Swi4, Mbp1 and Swi6, expressed from their natural loci in fixed and live G1-phase yeast cells. We found that 85% of each TF subunit is organized into a few nuclear clusters and that each cluster contains a cell-size independent number of TF copies (~8). The number of clusters increased during G1 phase from ~5 in small cells to ~30 in large cells, concordant with a size-dependent increase in TF copy number. This small maximum number of clusters compared to the ~200 target promoters implies close spatial proximity of several promoter sites within each cluster. Using live cell single particle tracking (spt)-PALM we observed slow and fast dynamic modes for each TF, which likely correspond to binding/dissociation from specific and non-specific DNA target sites, respectively, combined with diffusion on or off DNA. These results suggest that the promoters of the G1/S regulon are spatially organized into clusters that are titrated temporally in a hierarchical manner by increasing G1/S TF copy number as cells grow.

STRUCTURAL STUDIES OF CHROMATIN: TOWARD UNDERSTANDING THE REGULATION OF GENOMIC DNA

Hitoshi Kurumizaka[1];
[1]The University of Tokyo, Institute for Quantitative Biosciences, Tokyo, Tokyo, Japan

Objective: In eukaryotes, genomic DNA is highly compacted and accommodated in the nucleus. The genomic DNA associates with various nuclear proteins, forming a large complex called chromatin. Nucleosomes are the basic repeating units of the chromatin, which are connected by linker DNAs, and form a beads-on-a-strings appearance. In the nucleosome, two of each histone proteins, H2A, H2B, H3, and H4, form an octameric complex that left-handedly wraps about 150 base-pairs of DNA around its surface. The nucleosome formation renders the DNA inaccessible to DNA binding proteins that function in gene regulatory processes such as transcription. Therefore, DNA-binding proteins must overcome the nucleosomal barrier, when they express their functions within the chromatin. Increasing evidences suggest that versatility and dynamics of the nucleosome structure are pivotal to gene regulation, which promotes differentiation of cells in every developmental stage. However, the underlying mechanisms on how gene expression is regulated in the chromatin structure have remained elusive. Methods: We have established reconstitution systems for chromatin using purified histones. The X-ray crystallography and cryo-electron microscopy techniques are employed for structural analyses of reconstituted nucleosomes and chromatin. Results: We then studied the structural versatility of nucleosomes and chromatin, and analyzed various functional forms of chromatin. Conclusions: We solved various nucleosome and poly-nucleosome structures, and revealed how eukaryotic genes are activated or inactivated depending on the chromatin structure. These results suggest how chromatin structure and dynamics play important roles in the genomic DNA regulation.

TRANSFER-MATRIX CALCULATION OF THE EFFECTS OF PHYSICAL CONSTRAINTS APPLIED TO DNA ON DNA-PROTEIN INTERACTIONS

Jie Yan[1,2];
[1]National University of Singapore, Mechanobiology Institute, Singapore, South-West, Singapore
[2]National University of Singapore, Department of Physics, Singapore, South-West, Singapore

Organization of the chromosomal DNA and numerous biological processes taking place on chromosomes depends on the DNA interaction with a plethora of DNA-binding proteins. These interactions are subject to a variety of physical constraints, such as volume exclusion, finite binding size, force and torque, applied to the DNA. Recent development of single-molecule manipulation technologies has made it possible to quantify the interactions between DNA and proteins under these physical constraints, however, the exact effect of these constraints on the DNA-protein interactions is not completely understood. To fill this gap, we have developed a systematic theoretical framework based on the transfer-matrix calculation method that can be used to accurately describe the effects of these physical constraints on the behaviour of DNA-binding proteins. Potential applications of the developed theoretical approach are demonstrated by predicting how such constraints affect the DNA-binding properties of different types of architectural proteins, which have been found in living cells. Obtained results also provide important insights into potential physiological functions of physical constraints in the chromosomal DNA organization and transcription regulation by architectural proteins as well as into single-DNA manipulation studies of DNA-protein interactions.

FOLDING GENES AT NUCLEOSOME RESOLUTION

Tamar Schlick
New York University, USA

No Abstract

UNDERSTANDING GENE REGULATION THROUGH THE 3D STRUCTURE OF CHROMATIN AND CHROMOSOMES

Pablo D. Dans Puiggròs[1]; Marie Victoire Neguembor[2]; Diana Buitrago[1]; JürgenWalther[1]; Rafael Lema[1]; Pablo Romero[1]; Isabelle Brun-Heath[1]; Pia Cosma[2]; Modesto Orozco[1];
[1]Institute for Research in Biomedicine, Molecular Modelling and Bioinformatics Group, Barcelona, Barcelona, Spain
[2]Center for Genomic Regulation, Reprogramming and Regeneration, Barcelona, Barcelona, Spain

The linear sequence of DNA provided invaluable information about the nature of genes and regulatory elements and their distribution along chromosomes. However, to fully understand gene function and gene regulation we need to place the linear genome in the right context: the cell nucleus. Inside the nucleus, genes are organized forming complex three-dimensional structures that change over time. In this contribution, we study mechanisms that influence gene regulation, from local changes in nucleosome positioning to global three-dimensional rearrangements of chromatin under different stress conditions in *S. cerevisiae* (yeast), or subject to differentiation/reprogramming in human cells. We produced Hi-C data to obtain chromatin and chromosome contacts, along with Mnase-seq data to determine nucleosome positions, and RNA-seq for detecting changes in gene expression. These genome wide analyses were combined with optical microscopy and super resolution imaging allowing us to get the first super-resolution images of individual genes together with their regulatory regions. In addition, a strategy has been set up for the simultaneous visualization of genes and chromatin-associated proteins which localize protein binding in specific genes with nanometric precision. All these experimental techniques were integrated into two state-of-the-art coarse-grained models of chromatin to unravel the three-dimensional conformation and dynamics of genes and chromosomes in different conditions right into the nucleus.

UNVEILING CHROMATIN FIBER CONDENSATION THROUGH MANY-BODY NUCLEOSOME INTERACTIONS

Joshua Moller[1]; Joshua Lequieu[1]; Juan J de Pablo[1,2];
[1]University of Chicago, Institute for Molecular Engineering, Chicago, Illinois, United States
[2]Argonne National Laboratory, Lemont, Illinois, United States

The physics governing nucleosome interactions influence structural features of chromatin across a wide range of length-scales. Here, we assess the extent of these interactions through Brownian dynamics simulations using our recently-developed coarse-grained model of chromatin. This new model represents nucleosomes as rigid bodies to efficiently study the underlying nucleosome physics within the chromatin fiber. To this extent, simulations are used to interpret the hierarchy of interactions in chromatin fibers by quantifying the energetics of small-fibers, including di- and trinucleosomes, and isolating the factors that facilitate condensed configurations. Among these factors, we consider the influences of DNA sequence, nucleosome repeat length, and inclusion of the H1 linker histone. These small-fiber results are then used to assess the structure of larger chromatin fibers, revealing that the configurations of nucleosomes in larger fibers favor are influenced by those exhibited in the small-scale systems. We further demonstrate that correlations exist in the chromatin fiber beyond three body interactions. Lastly, we show that the linker histone significantly shifts the energetic minima of the smaller systems, which corresponds to similar configuration changes of larger chromatin fiber structure.

ON THE ROLE OF CHROMATIN GEOMETRY IN EPIGENETIC DOMAIN FORMATION

Marina Katava[1]; Guang Shi[1]; D. Thirumalai[1];
[1]University of Texas at Austin, Chemistry, Austin, Texas, United States

Establishment and inheritance of distinct genetic patterns that are not encoded in DNA sequence is strikingly obvious in multicellular organisms that maintain distinct cellular identities throughout cellular divisions. Proteins, identified as mediators in the establishment and maintenance of epigenetic domains, are homologous in eukaryotes, which indicates that a common principle underlies these processes. The role of chromatin polymer properties and three-dimensional genome organization and its consequences to the process of spreading is key to understanding the epigenome. For the purpose of studying epigenetic spreading, we develop a polymer-based model with histone modification recoloring implemented through the principles of stochastic kinetics. The model captures geometric considerations of the chromatin thread through the physical determinants of the polymer model, as well as the biochemical mechanism of spreading, implemented through distinct rules under which the reaction takes place. It requires a minimal number of parameters and exhibits epigenetic switching behavior over a narrow parameter range. We focus on inspecting whether the spreading process occurs linearly along the chromatin thread or through a three-dimensional spreading process. We show that polymer geometry can drive the formation of stable domains without the presence of barrier elements. Using *S. pombe* as an experimental model for comparison, we show that the three-dimensional spreading qualitatively reproduces fluorescent-signaled position-dependent spreading observed in experiments.

STRUCTURE AND DYNAMICS OF THE TELOMERIC NUCLEOSOME AND CHROMATIN

Lars Nordenskiöld
[1]Nanyang Technological University, School of Biological Sciences, Singapore, South-West, Singapore

Eukaryotic genomic DNA is condensed into chromatin: 146bp DNA wraps around the histone octamer (HO) comprising two copies each of the core histones H2A, H2B, H3 and H4 forming the nucleosome core particle (NCP). A string of nucleosomes folds into the so-called called "30nm" chromatin fibre, which compacts into metaphase chromosomes.

Human telomeres constitute the protective structure at the end of the chromosomes with repetitive TTAGGG sequences that are about 10kbp. Little is known about the consequences of this unique sequence for chromatin structural and dynamic properties. Although it is established that telomeric DNA is packaged in chromatin with an unusually short (157 bp) nucleosome repeat length (NRL) and can form nucleosomes and chromatin, almost nothing is known about the telomeric nucleosome core and telomeric chromatin structure at the detailed molecular level.

We have characterised the telomeric human HO 145 bp DNA NCP (Telo-NCP), using biophysical methods and determined its structure at 2.1 Å resolution with X-ray crystallography. Although the structure is largely similar to the well-known published atomic resolution NCP structures, several differences can be identified, e.g. DNA stretching on the Telo-NCP is different from that of the "601" (high-affinity nucleosome positioning sequence) and alpha satellite NCPs of the same length.

We have designed and prepared 20×157 bp telomeric DNA template repeats, reconstituted these with human HO and performed characterisation of the structural and dynamic properties of the telomeric chromatin fibres with EM, solid-state NMR and single molecule magnetic tweezer experiments. Telomeric chromatin fibres are considerably more homogeneous than corresponding 157 bp repeat fibres reconstituted from 601-DNA array templates. However, the structural and dynamic properties of individual telomeric arrays saturated with 20 nucleosomes, appear similar to equivalent 601 chromatin fibres under the influence of force in single molecule pulling experiment.

HETEROCHROMATIN AND THE NUCLEAR PERIPHERY: SPECIFICITY VIA DENSITY

Quinn J. MacPherson[1]; Bruno Beltran[4]; Andrew J Spakowitz[2,3];
[1]Stanford University, Physics, Stanford, California, United States
[2]Stanford University, Chemical Engineering, Stanford, California, United States
[3]Stanford University, Materials Science, Stanford, California, United States
[4]Stanford University , Biophysics, Stanford, California, United States

The spatial organization of chromatin in human cells is typified by a layer of transcriptionally repressed heterochromatin adjacent to the nuclear periphery. The factors that dictate the radial organization of chromatin are important for control of transcription, cellular function, and chromatin architecture. We demonstrate that epigenetically induced density variation between heterochromatin and euchromatin in conjunction with a non-specific chromatin-lamina interaction can explain the existence of peripheral heterochromatin.
We present a coarse-grained nucleosome polymer model of chromatin with beads corresponding to nucleosomes. The internucleosomal interaction depends on the measured epigenetic profile of the chromatin. Specifically, we model preferential binding of the HP1 protein to histones tails that are methylated at the ninth lysine (H3K9me3). Our bottom up approach uses experimentally measured energetics to keep the number of free parameters at a minimum. We implement internucleosomal interactions using an efficient particle-field Monte-Carlo algorithm that allows the simulation to be scaled up to chromosomal lengths. We find that the combined effect of the epigenetic state of many nucleosomes leads to a phase segregation between a chromatin-dense heterochromatic phase and a less dense euchromatic phase. The phase that each nucleosome is incorporated into is found to depend on the epigenetics many kilobase in either direction. Adding an interaction with the nuclear lamina which is equally attractive to heterochromatic and euchromatic nucleosomes results in the heterochromatin being specifically attracted to the nuclear periphery as a result of its higher density. We compare the resulting structures with microscopy, Hi-C, and Lamina Associated Domain data sets. Furthermore, we investigate the relevance of this density-based interaction on the positioning of chromosome territories.

MECHANISMS AND FUNCTIONS OF CHROMATIN CONDENSATION IN QUIESCENT YEAST CELLS

Sarah G Swygert[1]; Seungsoo Kim[2]; Xiaoying Wu[1]; Tianhong Fu[1]; Tsung-Han Hsieh[3]; Rando Oliver[3]; Jay Shendure[2]; Jeffrey McKnight[1]; **Toshio Tsukiyama**[1];
[1]Fred Hutchinson Cancer Research Center, Basic Sciences Division, Seattle, Washington, United States
[2]U Washington, Genome Sciences, Seattle, Washington, United States
[3]U Massachusetts Medical School, Biochemistry and Pharmacology, Worcester, Massachusetts, United States

Eukaryotic cells, from yeast to humans, spend most of their time in quiescence, a state in which cells exist for long periods of time without cycling until receiving external signals to resume division. We have been investigating molecular mechanisms underlying cell quiescence using *S. cerevisiae*as a model organism. One of the conserved hallmarks of quiescent cells is highly condensed chromatin. However, the molecular mechanisms and biological roles for chromatin condensation in quiescent cells remain unknown in any organism. To address this issue, we have performed Micro-C XL, a nucleosome resolution (200 bp) variant of Hi-C. This revealed that yeast cells have previously unidentified chromatin domains on the order of 10-60 kilobases across the genome. In quiescent cells, condensin binds at the borders of these chromatin domains and facilitates chromatin loop formation and interactions within the domains. Conditional depletion of condensin prevents chromatin condensation during quiescence entry and leads to widespread transcriptional de-repression. Finally, we confirmed that condensin-dependent chromatin compaction is conserved in quiescent human fibroblasts. Biological roles for condensin functions, molecular mechanisms of condensin targeting, and other aspects of chromatin condensation in quiescent cells will be discussed.

CONNECTING GENOMIC AND NON-GENOMIC MECHANISMS OF CANCER DRUG RESISTANCE

Amartya Sanyal[1];
[1]Nanyang Technological University, School of Biological Sciences, Singapore, South-West, Singapore

Drug resistance is a complex phenomenon adapted by cancer cells to evade chemotherapeutic drug challenge. It involves continuum of mechanisms including genetic aberrations, and alterations of gene expression and chromatin features. The non-coding regulatory regions of our genome are involved in adaptive response to environmental factors such as xenobiotic stress. These adaptations aid in the cellular state transition of cancer cell from sensitive to resistant phenotype over time. We have studied sensitive and drug-resistant lung cancer cells and unraveled interesting insights into the interrelationship of genetic and epigenetic mechanisms and chromatin topology. I will discuss our findings on chromatin-basis of alteration of gene-regulatory program during chemoresistance.

FROM CHROMOSOME TERRITORIES TO RING POLYMERS: PHYSICAL PROPERTIES OF UNTANGLED POLYMER MELTS

Angelo Rosa[1];
[1]Scuola Internazionale Superiore di Studi Avanzati (SISSA), Physics, Trieste, Trieste, Italy

In this talk, I will review my work on the physical modeling of eukaryotic chromosomes. In particular, I will present results of detailed molecular dynamics computer simulations of a minimalistic coarse-grained polymer model which is able to reproduce with great accuracy the large-scale features of chromosomes, like their confinement to specific regions of the nucleus (territories) and the formation of contacts. The talk will be concluded by a discussion focusing on the conceptual connection between nuclear chromosome organization and the physics of untangled ring polymers in concentrated solutions.

THE "SELF-STIRRED" GENOME: BULK AND SURFACE DYNAMICS OF THE CHROMATIN GLOBULE

Alexandra Zidovska[1];
[1]New York University, Center for Soft Matter Research, Department of Physics, New York, New York, United States

Chromatin structure and dynamics control all aspects of DNA biology yet are poorly understood. In interphase, time between two cell divisions, chromatin fills the cell nucleus in its minimally condensed polymeric state. Chromatin serves as substrate to a number of biological processes, e.g. gene expression and DNA replication, which require it to become locally restructured. These are energy-consuming processes giving rise to non-equilibrium dynamics. Chromatin dynamics has been traditionally studied by imaging of fluorescently labeled nuclear proteins and single DNA-sites, thus focusing only on a small number of tracer particles. Recently, we developed an approach, displacement correlation spectroscopy (DCS) based on time-resolved image correlation analysis, to map chromatin dynamics simultaneously across the whole nucleus in cultured human cells [1]. DCS revealed that chromatin movement was coherent across large regions (4â€“5Âµm) for several seconds. Regions of coherent motion extended beyond the boundaries of single-chromosome territories, suggesting elastic coupling of motion over length scales much larger than those of genes [1]. These large-scale, coupled motions were ATP-dependent and unidirectional for several seconds. Following these observations, we developed a hydrodynamic theory [2] and a microscopic model [3] of active chromatin dynamics. Here we investigate chromatin interactions with nuclear envelope and compare the surface dynamics of the chromatin globule with its bulk dynamics [4], which we also explore using naturally present cellular probes [5].[1] Zidovska A, Weitz DA, Mitchison TJ, *PNAS,* 110 (39), 15555-15560, 2013[2] Bruinsma R, Grosberg AY, Rabin Y, Zidovska A, *Biophys. J.,* 106 (9), 1871-1881, 2014[3] Saintillan D, Shelley MJ, Zidovska A, *PNAS*, 115 (45) 11442-11447, 2018[4] Chu F, Haley SC, Zidovska A, *PNAS,* 114 (39), 10338-10343, 2017 [5] Caragine CM, Haley SC, Zidovska A, *PRL,* 121, 148101, 2018

MESOSCALE BOTTOM-UP APPROACH TO THE STUDY OF CHROMATIN TOPOLOGICAL CONFORMATIONS: FROM THE NUCLEOSOME TO 1MBP

Artemi Bendandi[1,2]; Aymeric Le Gratiet[2]; Silvia Dante[2]; Walter Rocchia[3]; Alberto Diaspro[1,2];
[1]University of Genoa, Physics, Genoa, Genova, Italy
[2]IIT Genova, Nanoscopy & NIC@IIT, Genoa, Genova, Italy
[3]IIT Genova, CONCEPT Lab, Genoa, Genova, Italy

Understanding the mechanistic details underlying DNA compaction is key to the study of biological processes. While the first level of compaction, the nucleosome, has been studied in atomic resolution, the topology of the chromatin fibre remains debated. Therefore, there is a growing need for studies featuring a synergy between theoretical and experimental approaches, and the cross-validation of respective results. We propose a mesoscale bottom-up model: starting from the all-atom human nucleosome crystal structure, we move on to a coarse-grained approach where nucleosomes and linker DNA are each represented as three interacting centres. We parameterise our model with all-atom Molecular Dynamics (MD) and energetic estimates from the non-linear Poisson-Boltzmann equation. Starting from a map of nucleosome core particle (NCP) and linker DNA energy conformations varying relative position and orientation, we perform all-atom MD simulations on NCPs, linker DNA, and NCP with linker DNA. In our mesoscale force-field we consider three main kinds of interaction: mechanical, desolvation and electrostatic. This simplified model allows the study of larger conformations of the chromatin fibre, beyond the oligonucleosome level. We perform accompanying and complementary experiments, focusing on non-invasive methods that do not require aggressive sample preparation that could perturb the topology: Differential Scanning Calorimetry, Atomic Force Microscopy, Mueller Matrix Microscopy and, in future, Small Angle X-Ray Scattering. Our experiments will explore conformational states and changes depending on variations of parameters such as monovalent ion concentration, NCP number, and temperature. We validate intermediate results comparing them to existing oligonucleosome models in literature and to our own experiments, aimed at providing structural and thermodynamical information. Overall, we propose a cohesive mesoscale bottom-up model, combining simulations and experiments, thus testing different hypotheses in order to shed light on the determinants of chromatin conformation.

DECIPHERING HI-C DATA INTO POLYMER DYNAMICS

Soya Shinkai[1,2]; Masaki Nakagawa[2,3]; Takeshi Sugawara[2,4]; Yuichi Togashi[2,5]; Hiroshi Ochiai[5]; Ryuichiro Nakato[6]; Yuichi Taniguchi[7]; Shuichi Onami[1];
[1]RIKEN, Center for Biosystems Dynamics Research (BDR), Kobe, Hyogo, Japan
[2]Hiroshima University, Research Center for the Mathematics on Chromatin Live Dynamics (RcMcD), Higashi-Hiroshima, Hiroshima, Japan
[3]The University of Electro-Communications, Graduate School of Informatics and Engineering, Tokyo, Tokyo, Japan
[4]The University of Tokyo, Graduate School of Medicine and Faculty of Medicine, Tokyo, Tokyo, Japan
[5]Hiroshima University, Graduate School of Science, Higashi-Hiroshima, Hiroshima, Japan
[6]The University of Tokyo, Institute for Quantitative Biosciences (IQB), Tokyo, Tokyo, Japan
[7]RIKEN, Center for Biosystems Dynamics Research (BDR), Suita, Osaka, Japan

Genome-wide chromosome conformation capture methods have uncovered 3D genome organization in cell nuclei, and associated polymer modeling have revealed 3D genome structure. However, it is challenging to unravel 4D features from Hi-C data, as observed in live cell imaging experiments. We will show our recent progress on deciphering Hi-C data into polymer dynamics in terms of polymer physics. Firstly, we mathematically defined the contacts of Hi-C experiments. Next, we derived matrix transformations between the contact matrix and a polymer model. Based on the analytical matrix transformations, we developed an optimization algorithm for Hi-C data. Finally, here, we propose a 4D simulation method, PHi-C (Polymer dynamics deciphered from Hi-C data), that depicts dynamic organization of chromatin domains and provides physical insights into alterations in Hi-C patterns.

THE THREE-DIMENSIONAL ARCHITECTURE OF THE HUMAN GENOME: IT'S NUCLEAR PHYSICS!

Michele Di Pierro[1]; Ryan R Cheng[1]; Davit Potoyan[1]; Bin Zhang[1]; Erez Lieberman Aiden[1]; Peter G Wolynes[1]; Jose N Onuchic[1];
[1]Rice University, Center for Theoretical Biological Physics, Houston, Texas, United States

The human genome is composed of 46 DNA molecules - the chromosomes - with a combined length of about 2 meters. Chromosomes are organized in the cell nucleus in cell-specific conformations; this three-dimensional architecture is a key element of transcriptional regulation and its disruption often leads to disease. What is the physical mechanism leading to genome architecture? If the DNA contained in every human cell is identical, where is the information - the blueprint - of such architecture stored?
In a series of works[1, 2, 3], we were able to demonstrate that the architecture of interphase chromosomes is encoded in the one-dimensional sequence of epigenetic markings much as three-dimensional protein structures are determined by their one-dimensional sequence of amino acids. In contrast to the situation for proteins, however, the sequence code provided by the epigenetic marks decorating the chromatin fiber is not fixed but is dynamically rewritten during cell differentiation, modulating both the three-dimensional structure and gene expression in different cell types.
In vivo, segments of chromatin characterized by homogeneous epigenetic markings undergo a process similar to phase separation under the action of the proteome present in the nucleus. This process forms liquid droplets, which rearrange dynamically by splitting and fusing, thereby modulating DNA distal interactions and generating the genomic compartments characteristic of chromosomal architecture.
Our theory - together with our computational tools - allows predicting and studying the spatial conformation of genomes with unprecedented accuracy and specificity, thus opening the way to the study of the functional aspects of genome architecture.

1. Di Pierro, et al. "Transferable model for chromosome architecture." *PNAS* 113.43 (2016): 12168-12173.
2. Di Pierro, et al. "De novo prediction of human chromosome structures: Epigenetic marking patterns encode genome architecture." *PNAS* (2017): 201714980.
3. Di Pierro, et al. "Anomalous diffusion, spatial coherence, and viscoelasticity from the energy landscape of human chromosomes." *PNAS* 115.30 (2018): 7753-7758.

MECHANICAL CONTROL OF CHROMOSOME ORGANIZATION AND GENE EXPRESSION

G.V. Shivashankar[1];
[1]Mechanobiology Institute, National University of Singapore, Singapore, South-West, Singapore

Recent studies highlight the importance of 3D chromosome organization in regulating gene expression within living cells. However, cells are subjected to mechanical deformations within tissue microenvironment and it is unclear how such deformations affect chromosome organization, their intermingling and gene expression. To address this we use micro patterned substrates that allow quantitative methods to engineer mechanical deformations of cells. In this talk, I will show that the deformation of cells result in specific rearrangements in chromosome positions and nanoscale functional gene clustering correlating with their gene expression programs. Importantly, we show that the mechanical state of cells, and thus their chromosome organization and their intermingling, dictate micro-environmental control of gene expression programs. These results highlight an important layer of scale-dependent genome regulation resulting from the coupling between cell mechanics and 3D organization of chromosomes to maintain tissue homeostasis.

A 3D CODE IN THE HUMAN GENOME

Erez Lieberman-Aiden
Baylor College of Medicine, USA

No Abstract

THE CROWDED NANOENVIRONMENT INFLUENCES GENE EXPRESSION

Anne Shim[1]; Rikkert J Nap[1,3]; Luay Almassalha[1]; Hiroaki Matsuda[1]; Vadim Backman[1]; Igal Szleifer[1,2,3];
[1]Northwestern University, Biomedical Engineering, Evanston, Illinois, United States
[2]Northwestern University, Chemistry, Evanston, Illinois, United States
[3]Northwestern University, Chemistry of Life Processes Institute, Evanston, Illinois, United States

Gene expression is influenced, and perhaps regulated, by the chromatin nanoenvironment. Genes are highly crowded by biological macromolecules, including proteins and non-coding chromatin, which alter the kinetics and efficiency of transcriptional machinery at steady-state. However, owing to processes like chromatin translocation, protein diffusion, and DNA loop extrusion, macromolecular crowders are highly mobile, and the nucleus is almost certainly not at steady-state. Moreover, little is known about how crowding kinetics beyond steady-state integrate with gene expression. Therefore, we investigate, experimentally and computationally, how transcription kinetics are altered by the time-evolving, crowded chromatin nanoenvironment. We conducted a parametric study, whereby temporal changes in crowding density ("dynamic crowding") were nominated from experimental measurements and incorporated into a computational model of transcription. From experimental studies, ChromEMT quantified physiologically relevant crowding densities that exist *in vivo*, while Partial Wave Spectroscopic microscopy determined qualitative crowding movement within these densities. These measurements, together with steric and thermodynamic crowding effects determined from Brownian dynamics simulations of diffusion and Monte Carlo simulations of binding free energies, were integrated into a network model of transcription. We show that while transcription is governed by the local average crowding density as shown in previous studies, it also depends critically on the temporal properties of dynamic crowding. Furthermore, dynamic crowding regulates gene expression by influencing the rates of two different components of the transcription pathway-pre-mRNA processing and transcriptional protein search and binding kinetics-at different time points. Therefore, this work demonstrates that macromolecular crowding may play an even greater role in regulating transcription kinetics than previously understood, as it presents crowding kinetics within the bulk chromatin nanoenvironment as a novel regulatory framework for gene expression.

TADS AND CHROMATIN SUPERCOILING

Andrzej Stasiak
University of Lausanne, Switzerland

No Abstract

HOW DO DNA-BINDING PROTEINS INTERPRET AND MODIFY NUCLEOSOME DYNAMICS?

Vlad Cojocaru;
[1]The Hubrecht Institute for Developmental Biology and Stem Cell Research, In Silico Biolmolecular Structure and Dynamics Group, Utrecht, The Netherlands

I will present our recent efforts to explore how nucleosome dynamics modulate the binding of linker histones and transcription factors to nucleosomes. First, I will show how a combination of Brownian and molecular dynamics simulations revealed an ensemble of geometries for the complex between the nucleosome core particle and linker histones. Second, I will show our efforts towards revealing the structural basis for the binding of the pioneer transcription factor Oct4 to nucleosomes. Oct4 is a master regulator of stem cell pluripotency and is critical for cell fate transitions such as the induction of pluripotency in somatic cells.

*The research presented was performed in collaboration with Mehmet Öztürk, Rebecca Wade, Jan Huertas, Caitlin MacCarthy, and Hans R. Schöler

CHROMATIN HIGHER ORDER FOLDING IN IRREGULAR FIBERS: A CRITICAL ROLE OF LINKER DNA

John Van Noort[1];
[1]Leiden University, Institute of Physics, Leiden, Zuid-Holland, The Netherlands

Nucleosome-nucleosome stacking interactions drive nucleosomal arrays into dense fibers though resolving the structure and dynamics of these fibers remains challenging. The linker DNA that connects stacked nucleosome plays an important role in fiber folding due to its limited bending and twisting flexibility. Using single-molecule force spectroscopy, we recently measured the unfolding pathway of regular chromatin fibers with 1 bp increments in linker length and complemented these with rigid-bp Monte Carlo simulations. Both studies reveal a periodic variation of stacking energies. It appears that twist of the linker DNA is much more restrictive for nucleosome stacking than bend, yielding the most stable stacking interactions for linker lengths of multiples of 10 bps. In fibers with short linker DNA (20-30 bps) stacking is compromised, whereas longer linkers (45-55 bps) provide enough flexibility for optimal orientation of stacked nucleosomes. To get a better understanding of the folding of chromatin in vivo, we developed a protocol to pull down specific gene fragments from nuclear extracts, while keeping their native structure and composition intact. Subsequent force spectroscopy yields unfolding curves that allow for detailed comparison with regular reconstituted fibers. Unfolding native fibers of the 18S RNA gene featured larger compositional heterogeneity and signatures of tetrasomes next to full nucleosomes. Though we observed reduced unfolding forces, the native fibers showed similar stiffness and unfolding pathways. Our systematic single-molecule analysis of a large variety of chromatin compositions supports a general picture of nucleosomes stacking in 1- and 2-start topologies, whose stability is determined by the length of the linker DNA. These experimental results constrain the wide range of chromatin models and bring us closer to ab initio prediction of higher order chromatin folding.

CONTRIBUTIONS OF NUCLEOSOME ARCHITECTURE TO LONG-RANGE COMMUNICATION ON CHROMATIN

Wilma K. Olson[1];
[1]Rutgers, the State University of New Jersey, Chemistry and Chemical Biology, Piscataway, New Jersey, United States

Although many factors participate in transcription, understanding how DNA enhancers activate the production of RNA at distant promoter sites remains a mystery. New experimental studies of transcription on well-defined chromatin arrays by the Vasily Studitsky group in combination with base-pair level simulations of protein-decorated DNA from our laboratory are making it possible to dissect these mechanisms. The combination of computation with experiment suggests that internucleosomal interactions involving the histone tails are essential for highly efficient enhancer-promoter communication and that transient internucleosomal interactions mediate distant associations between enhancers and promoters on chromatin. Ensembles of modeled structures consistent with the observed transcript levels exhibit very different three-dimensional features upon repositioning or modification of the nucleosomes placed between the sites of regulatory protein binding. The positions/spacing of the nucleosomes, the mode of DNA entry/exit, the torsional stress imposed on DNA, and the selective removal of histone tails have critical effects on the spatial properties of the simulated oligonucleosome constructs. The â€˜localâ€™ structures and deformabilities of the nucleosomes in these model systems, in turn, influence the folding and interactions of longer stretches of chromatin. Reliable treatment of long-range interactions on long stretches of chromatin, however, requires knowledge of the configurational properties of numerous oligonucleosome arrays as well as improved understanding of the proteins that mediate these looped structures.

POSTER ABSTRACTS

MONDAY, APRIL 1
POSTER SESSION I
21:00 – 22:00
Cecile Dewitt Building

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Monday. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Armeev, Grigoriy	**1-POS**	**Board 1**
Fernandes, Vinicius	**5-POS**	**Board 5**
Huertas, Jan	**9-POS**	**Board 9**
Khamis, Hadeel	**13-POS**	**Board 13**
Lappala, Anna	**17-POS**	**Board 17**
Padinhateeri, Ranjith	**21-POS**	**Board 21**
Shi, Guang	**25-POS**	**Board 25**
Zülske, Tilo	**29-POS**	**Board 29**

Posters should be set up the morning of April 1 and removed by noon April 5.

1-POS Board 1

NUCLEOSOME MODELING AT ATOMISTIC DETAIL HELPS TO INTERPRET BIOPHYSICAL EXPERIMENTS

Grigoriy A Armeev[1]; Anna R Panchenko[2]; Alexey K Shaytan[1];
[1]Lomonosov Moscow State University, Faculty of Biology, Moscow, Moscow, Russian Federation
[2]National Institutes of Health, National Center for Biotechnology Information, Bethesda, Maryland, United States

Nucleosomes are the key structural elements of chromatin in all higher organisms. While X-ray crystallography studies of nucleosomes have consistently yielded similar atomistic structures, many biophysical and biochemical techniques suggest that nucleosomes and nucleosome complexes exhibit substantial conformational polymorphism, which is functionally important. Interpretation of such experimental data with sufficient details is often a tedious task. In this presentation we will show how atomistic modeling techniques, including MD simulations, may be exploited to interpret various experimental datasets.We performed full-atom molecular dynamics of nucleosomes and DNA fluorescent labels to sample the conformations used for single particle FörsterResonance Energy Transfer (spFRET) measurements. Such models allow us to correct for the structure of dyes and deduce the positions of labels' attachment points. We also implemented a set of methods for integrative modeling of nucleosome structures based on spFRET constraints. Using these approaches we have constructed (i) an atomistic model of histone chaperone FACT induced structural reorganization of nucleosomes and (ii) histone H1 induced conformational changes in the linker DNA region. Besides the distances, derived from spFRET, histone - DNA contacts are crucial for nucleosome formation and function. We used hydroxyl DNA footprinting data in conjunction with atomistic structures of nucleosomes enhanced by molecular dynamics simulations to develop a computational method for precise determination of DNA positioning in nucleosomes with single base pair resolution. This method is implemented in software package called HYDROID.This work was supported by Russian Science Foundation grant #18-74-10006 and by the Intramural research program of the national library of medicine, NIH.

5-POS Board 5

FAT NUCLEOSOME: ROLE OF LIPIDS ON CHROMATIN

Vinicius Fernandes[1,2]; Kaian Teles[1]; Camyla Ribeiro[1]; Werner Treptow[2]; Guilherme Santos[1];
[1]University of Brasilia, Laboratory of Molecular Pharmacology, Department of Pharmacy, BrasÃlia, Distrito Federal, Brazil
[2]University of Brasilia, Laboratory of Theoretical and Computational Biology, Department of Cell Biology, BrasÃlia, Distrito Federal, Brazil

Structural changes in chromatin regulate gene expression and define phenotypic outcomes. Most recently, the formation of condensed chromatin regions based on phase-separation in the cell, a basic physical mechanism, was proposed. Increased understanding of the mechanisms of interaction between chromatin and lipids suggest that small lipid molecules, such as cholesterol and short-chain fatty acids, can regulate important nuclear functions. New biophysical and computational data has suggested that cholesterol interacts with nucleosome through multiple binding sites and affects chromatin structure in vitro. Regardless of the mechanism of how lipids bind to chromatin, there is currently little awareness that lipids may be stored in chromatin and influence its state. Recently, we review the main impacts of lipids on the nuclear environment, emphasizing its role on chromatin architecture. We postulate that lipids that bind to nucleosomes and affect chromatin states are likely to be worth investigating as tools to modify disease phenotypes at a molecular level. Focusing on lipids that bind to nuclear receptors, clinically relevant transcription factors, we are exploring the interactions of the nucleosome with steroid hormones, bile acids and fatty acids. Preliminary computational studies, employing molecular docking and all-atom molecular dynamics simulations, suggest that other lipid chemotypes may also impact chromatin structure through binding to common cholesterol sites on the nucleosome. For better charectization of lipids influence on chromatin, we are now investigating the effects of these chemotypes on a chromatin coarsed-grained model with the SIRAH force field. Despite preliminary, these observations suggests that lipid-chemotypes, may bind at common sites on the nucleosome surface. Still consistent with that notion is the fascinating possibility that via non-specific low-affinity interactions, chromatin may work as a lipid depot for nuclear proteins.

9-POS Board 9

SIMULATING THE BINDING OF PIONEER TRANSCRIPTION FACTORS TO THE NUCLEOSOME

Jan Huertas[1]; Caitlin M MacCarthy[1]; Hans R Schöler; Vlad Cojocaru[2];
[1]Max Planck Institute for Molecular Biomedicine, Department of Cell and Developmental Biology , Munster, Nordrhein-Westfalen, Germany
[2]Hubrecht Institute, In Silico Biomolecular Structure and Dynamics, Utrecht, The Netherlands

Transcription factors are proteins that bind to DNA to regulate gene expression. In most cases, accessibility to DNA is a prerequisite for their function. However, in the nucleus the DNA is packed into chromatin, which is often inaccessible. The fundamental unit of chromatin is the nucleosome, in which 147 DNA basepairs are wrapped around a core of eight histone proteins. Interestingly, a series of transcription factors, known as pioneers, are able to bind to closed chromatin states, recognizing their binding sites even in the presence of nucleosomes. They can help open chromatin, increase DNA accessibility, and support binding of other transcription factors. For example, Oct4, a master regulator of stem cell pluripotency, is able to bind native nucleosomes in a sequence specific manner. To understand the nucleosome properties that are involved in the binding of Oct4, we performed all-atom simulations of three nucleosomes with different DNA sequences, in presence and absence of Oct4. By comparing three sequences with characteristic Oct4 binding profiles, we identified differences in dynamics and structural properties of the three nucleosomes, most of which are located in the regions known to be important for nucleosome unwrapping. We validated those findings by probing the stability of the nucleosomes in thermal unwrapping experiments. Moreover, we also characterized how the addition of Oct4 alters the dynamics of the nucleosomes, and which are the relevant nucleosome properties that explain the binding and behavior change. These findings help us understand the role of pioneer transcription factors in the binding ofclosed chromatin.

13-POS Board 13

SINGLE-MOLECULE DNA UNZIPPING REVEALS ASYMMETRIC MODULATION OF A TRANSCRIPTION FACTOR BY ITS BINDING SITE SEQUENCE AND CONTEXT

Hadeel Khamis[1]; Sergi Rudnizky[2]; Omri Malik[1,3]; Allison Squires [5]; Amit Meller[4]; Philippa Melamed[2]; Ariel Kaplan[1,2];
[1]Technion, Physics, Haifa, Haifa, Israel
[2]Technion, Biology, Haifa, Haifa, Israel
[3]Technion, Russell Berrie Nanotechnology Institute, Haifa, Haifa, Israel
[4]Technion, Faculty of Biomedical Engineering, Haifa, Haifa, Israel
[5]Boston University, Department of Biomedical Engineering, Boston, Massachusetts, United States

Most functional transcription factor (TF) binding sites deviate from their 'consensus' recognition motif, although their sites and flanking sequences are often conserved across species. Here, we used single-molecule DNA unzipping with optical tweezers to study how Egr-1, a TF harboring three zinc fingers (ZF1, ZF2 and ZF3), is modulated by the sequence and context of its functional sites in the *Lhb* gene promoter. We find that both the core 9 bp bound to Egr-1 in each of the sites, and the base pairs flanking them, modulate the affinity and structure of the protein-DNA complex. The effect of the flanking sequences is asymmetric, with a stronger effect for the sequence flanking ZF3. Characterization of the dissociation time of Egr-1 revealed that a local, mechanical perturbation of the interactions of ZF3 destabilizes the complex more effectively than a perturbation of the ZF1 interactions. Our results reveal a novel role for ZF3 in the interaction of Egr-1 with other proteins and the DNA, providing insight on the regulation of *Lhb* and other genes by Egr-1. Moreover, our findings reveal the potential of small changes in DNA sequence to alter transcriptional regulation, and may shed light on the organization of regulatory elements at promoters.

17-POS Board 17

MULTI-SCALE ANALYSIS OF CHROMOSOME STRUCTURE AND DYNAMICS: FROM 3D TO 4D

Anna Lappala[1]; Karissa Y Sanbonmatsu[1];
[1]Los Alamos National Laboratory, Theoretical Biology and Biophysics, Los Alamos, New Mexico, United States

We use fractal dimension analysis to study the morphology and the dynamics of chromatin folding. The fractal dimension provides a method for quantifying properties such as lacunarity (voids in a 3D structure) and asphericity, resulting in a unique measure of local connectivity and compaction morphology. The evolution of the fractal dimension as a function of compaction relates chromatin density and morphology to the process of folding. Using Molecular Dynamics simulations of coarse-grained polymers, we demonstrate a linear relation between the number of contacts (i.e., local density) z and packing fraction f, showing that a system becomes dynamically arrested, behaving like an amorphous solid (i.e. glass) at f~0.58. It has been demonstrated that similarly to glasses, density and local diffusivity in chromatin are non-uniform and dynamics heterogenous, with locally confined- and structurally open domains that are critical for its biological function. To demonstrate the connection between specific chromosome interactions and compaction, we compare the dynamics of chromatin with regular nucleosomes to macroH2A variants. We use experimental HiC maps to infer a 3D structure and calculate fractal dimensions for structures of increasing complexity from well-characterized nucleosome arrays to more complex 30-nm folds and even extend our approach to complete chromosomes. We analyze the evolution of fractal dimension over time, characterizing the dynamics of chromatin folding and distinguishing compact (inactive), extended (active) and intermediate (epigenetically poised) architectures.

21-POS Board 21

A THEORETICAL STUDY OF INHERITANCE OF NUCLEOSOME POSITIONING DURING DNA REPLICATION

Tripti Bameta[3]; Dibyendu Das[2]; **Ranjith Padinhateeri**[1];
[1]Indian Institute of Technology Bombay, Biosciences & Bioengineering, Mumbai, Maharashtra, India
[2]Indian Institute of Technology Bombay, Physics, Mumbai, Maharashtra, India
[3]UM-DAE Centre for Excellence in Basic Sciences, , Mumbai, Maharashtra, India

Nucleosome positioning is crucial for many cellular processes. How nucleosome positioning is inherited from mother chromatin to daughter is poorly understood. Accounting for experimentally known facts, we propose a model to study nucleosome reorganization during DNA replication. Our model has four kinetic events, namely, replication fork movement, nucleosome disassembly ahead of the fork, nucleosome deposition behind the fork and ATP-dependent repositioning of nucleosomes behind the fork. Simulating nucleosome re-organization during replication, we argue that short pausing of replication fork, associated with nucleosome disassembly, can be an event crucial for communicating nucleosome positioning from mother chromatin to daughter chromatin. Our simulations obtain de novo nucleosome assembly similar to what is observed in experiments and predict regions in parameter space where nucleosome positioning may be inherited during DNA replication.

25-POS Board 25

INTERPHASE HUMAN CHROMOSOME EXHIBITS OUT OF EQUILIBRIUM GLASSY DYNAMICS

Guang Shi[1]; Lei Liu[2]; Changbong Hyeon[2]; Devarajan Thirumalai[3];
[1]University of Maryland at College Park, Institute of Physical Science and Technology, College Park, Maryland, United States
[2] Korea Institute for Advanced Study, Seoul, Seoul, South Korea
[3]University of Texas at Austin, Chemistry Department, Austin, Texas, United States

Fingerprints of the three-dimensional organization of genomes have emerged using advances in Hi-C and imaging techniques. However, genome dynamics is poorly understood. Here, we create the chromosome copolymer model (CCM) by representing chromosomes as a copolymer with two epigenetic loci types corresponding to euchromatin and heterochromatin. Using novel clustering techniques, we establish quantitatively that the simulated contact maps and topologically associating domains (TADs) for chromosomes 5 and 10 and those inferred from Hi-C experiments are in good agreement. Chromatin exhibits glassy dynamics with coherent motion on micron scale. The broad distribution of the diffusion exponents of the individual loci, which quantitatively agrees with experiments, is suggestive of highly heterogeneous dynamics. This is reflected in the cell-to-cell variations in the contact maps. Chromosome organization is hierarchical, involving the formation of chromosome droplets (CDs) on genomic scale, coinciding with the TAD size, followed by coalescence of the CDs, reminiscent of Ostwald ripening.

29-POS Board 29

MODELLING SPATIAL STRUCTURE OF CHROMATIN BASED ON EXPERIMENTAL POSITIONS OF NUCLEOSOMES

Tilo Zülske[1] ; Michael Möhrl[1] ; Robert Schöpflin[1] ; Gero Wedemann[1] ;
[1]University of Applied Sciences Stralsund, Institute of Applied Computer Sciences, Stralsund, Mecklenburg-Vorpommern, Germany

In chromatin DNA is wrapped around histone proteins forming nucleosomes. The nucleosome chain folds into higher order structures as topological domains, chromosomes and the whole nucleus. Despite experimental advancements in electron microscopy, single molecule techniques and mapping of nucleosomes and their modifications, many fundamental features of chromatin remain undiscovered. Due to the poor experimental accessibility of chromatin, computer simulations are valuable tools for research. Computer simulation models of chromatin are usually coarse-grained models describing the main characteristics of the chromatin-fiber. While it is common practice in systems biology to make experimental data publicly available, simulation data of computer models is usually not published since no easy to use standard exchange format has been established. We analyzed the workflow from the experimental determination of the positions of the nucleosomes to the analysis of the output of the computer model describing this system. We defined standardized formats based on XML for artifacts generated by steps in this workflow. We found that XML is practical since it is possible to transform the XML-files applying XSLT into other formats for usage in other groups. We proved this workflow and the file formats with a complete example of computer simulation of chromatin domains based on experimentally determined nucleosome positions.

TUESDAY, APRIL 2
POSTER SESSION II
21:00 – 22:00
Cecile Dewitt Building

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Tuesday. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Beltran, Bruno	**2-POS**	**Board 2**
Gao, Yiqin	**6-POS**	**Board 6**
Ishibashi, Toyotaka	**10-POS**	**Board 10**
Kim, Chanwoo	**14-POS**	**Board 14**
Milstein, Joshua	**18-POS**	**Board 18**
Patluri, Govardhan Reddy	**22-POS**	**Board 22**
Sridhar, Akshay	**26-POS**	**Board 26**

Posters should be set up the morning of April 1 and removed by noon April 5.

2-POS Board 2

HETEROGENEITY IN NUCLEOSOME SPACING GOVERNS FUNCTIONAL CHROMATIN ORGANIZATION

Bruno G. Beltran[1]; Deepti Kannan[2]; Quinn MacPherson[3]; Andrew J Spakowitz[2,4,5];
[1]Stanford University, Biophysics Program, Stanford, California, United States
[2]Stanford University, Department of Physics, Stanford, California, United States
[3]Stanford University, Department of Applied Physics, Stanford, California, United States
[4]Stanford University, Department of Chemical Engineering, Stanford, California, United States
[5]Stanford University, Department of Materials Science and Engineering, Stanford, California, United States

In vivo, the myriad of proteins that bind DNA introduce heterogeneously-spaced kinks into an otherwise semiflexible DNA double helix. In particular, while the kinks induced by nucleosomes govern chromatin organization, no analytical model exists that accounts for these geometric effects. We present an exactly-soluble, analytical model for the effects of arbitrarily spaced, rigid kinks on the structure and dynamics of a semiflexible polymer, and use it to investigate the effects of nucleosome spacing on the chromatin fiber. For periodic kinks (i.e. constant linker lengths), we reproduce previous results on the sensitivity of the structure to the choice of linker length. However, we show that adding realistic heterogeneity in nucleosome spacing eliminates this sensitivity. Through simple, geometric arguments, we prove that our results are independent of the particular choice of linker length distribution. With as little as 1 bp of variability in the nucleosomes' positions, we observe the same universal behavior as when nucleosome positioning lacks any specificity. This universality allows us to make robust predictions about chromatin's structure that are independent of any particular model of nucleosome positioning. On time scales longer than nucleosome turnover, a single effective wormlike chain with a renormalized Kuhn length describes both the short and long scale behavior of our heterogenous chain exactly. On shorter time scales, when nucleosome positions are effectively fixed, modulating intervening nucleosomes can affect the rate of formation of kilobase-scale, functional chromatin loops by up to six orders of magnitude. This means that a cell can cause two distal loci to come into contact by locally altering the positions of intervening nucleosomes. Our model provides a simple framework for understanding the effects of nucleosome positioning on chromatin's structure and provides guidance for coarse-grained models of chromatin.

6-POS Board 6

THE PACKING OF MAMMALIAN CHROMOSOME: A PHASE TRANSITION PERSPECTIVE

Yiqin Gao[1];
[1]Peking University, College of Chemistry and Molecular Engineering, Beijing, Beijing, China

The chromatin structure plays important roles in gene regulation. Several models have been proposed about the relationship between epigenetics as well as transcription factors and chromatin structure. However, our understanding of chromatin structure formation in different cell types and how chromatin 3D structures including TAD and compartment are determined or affected by the most fundamental feature, DNA sequences, are far from clear. We identified two types of genomic domains (called forests and prairies) based on the uneven sequential distribution of CGIs and found them to be genetically, epigenetically, transcriptionally, and structurally distinct. The specific interactions of the two domain types relate to cell-type specific gene regulation and cell-identity establishment. Meanwhile, they continue to spatially segregate from each other in development, differentiation and senescence at multiple scales. Furthermore, spatial separation of the two domains prompts us to propose a phase separation mechanism for chromatin structure formation. This mechanism allows us to discuss in a unified framework the chromatin structure formation in various biological events, including development, differentiation and senescence. In this talk, we will also discuss possible biological consequences emerging naturally from domain segregation and the phase separation mechanism including the temperature dependence of chromatin structures, and speculated that the variation in sequential mosaicity between species may relate to their important biological differences.

10-POS Board 10

A NOVEL HISTONE H4 VARIANT REGULATES RIBOSOMAL DNA TRANSCRIPTION IN BREAST CANCER

Xulun Sun[1]; Mengping Long[1]; Dongbo Ding[1]; An Yanru [1]; Manjinder Cheema[2]; Christopher J Nelson[2]; Juan Ausio[2]; Yan Yan[1]; **Toyotaka Ishibashi**[1];
[1]Hong Kong University of Science and Technology, Division of Life Science, Hong Kong, , Hong Kong
[2]University of Victoria, Department of Biochemistry and Microbiology, Victoria, British Columbia, Canada

Histone variants, present in various cell types and tissues, are known to exhibit different functions. For example, histone H3.3 and H2A.Z are both involved in gene expression regulation, whereas H2A.X is a specific variant that responds to DNA double-strand breaks. In this study, we characterized H4G, a novel hominidae-specific histone H4 variant. H4G expression was found in a variety of cell lines and was particularly overexpressed in the tissues of breast cancer patients. H4G was found to localize primarily to the nucleoli of the cell nucleus. This localization was controlled by the interaction of the alpha helix 3 of the histone fold motif with the histone chaperone, nucleophosphomin 1. In addition, we found that H4G nucleolar localization increased rRNA levels, protein synthesis rates, cell cycle progression and cell growth rate. Furthermore, H4G-containing nucleosomes reconstituted *in vitro* indicated that H4G destabilizes the nucleosome, which may serve to alter nucleolar chromatin in a way that enhances rDNA transcription in breast cancer tissues.

14-POS Board 14

SEQUENCE-DEPENDENT CONFIGURATIONAL DYNAMICS OF BACTERIAL GENES

Chanwoo Kim[1]; Seungwon Lee[1]; Jejoong You[2]; Hajin Kim[1];
[1]Ulsan National Institute of Science and Technology, School of Life Sciences, Ulsan, Chungcheongnam-do, South Korea
[2]Institute of Basic Science, Center for Self-assembly and Complexity, Pohang, Gyeongsangbuk-do, South Korea

Recent studies on the fundamental physical properties of DNA suggest that local nucleotide sequence, chemical modifications, and sequence motifs critically influence the physical properties, thus possibly controlling the geometric configuration of the DNA and its temporal changes. Such control of DNA geometry and dynamics may relate to the mechanism of assembling and organizing long DNAs and chromatin in the cells. Here, we employ single molecule fluorescence resonance energy transfer (smFRET), transmission electron microscopy (TEM), confocal fluorescence microscopy, and molecular dynamics simulations to study the conformation and dynamics of *Escherchia coli* genes. We show that the compaction and looping properties of the DNA sharply depend on the sequence composition and the density of GATC motifs which significantly increase the local rigidity. Further increase of the DNA rigidity was observed when the GATC motif is methylated at the N6 position of the adenine (GmeATC). We find that the modulation of the compaction and looping properties relate to the phase separation behaviors of DNA. Our results propose that the sequence structure and chemical modifications controlling the phase separation of DNA might play a mechanistic role in large scale genome organization.

18-POS Board 18

GROWTH PHASE DEPENDENT CHROMOSOME CONDENSATION AND H-NS PROTEIN REDISTRIBUTION IN *E. COLI* UNDER OSMOTIC STRESS

Joshua Milstein[1]; Nafiseh Rafiei[2]; Martha Cordova[3]; William Navarre[3];
[1]University of Toronto, Department of Physics, Toronto, Ontario, Canada
[2]University of Toronto, IBBME, Toronto, Ontario, Canada
[3]University of Toronto, Department of Molecular Genetics, Toronto, Ontario, Canada

The heat-stable nucleoid-structuring (H-NS) protein is a global transcriptional regulator implicated in coordinating the expression of over 200 genes in *E. coli* bacteria. We have applied a combination of super-resolved microscopies to quantify the intracellular, spatial reorganization of H-NS in response to osmotic stress. We find that H-NS shows a growth phase dependent response to osmotic shock. In logarithmic phase, H-NS detaches from a tightly compacted bacterial chromosome and is excluded from the nucleoid volume. Such behaviour is completely absent in exponential phase but may be induced by exposing the culture to the DNA gyrase inhibitor coumermycin. This observation implies that the osmotic stress response in *E. coli* is coordinated in part by the level of supercoiling in the bacterial chromosome.

22-POS Board 22

MONONUCLEOSOME UNDER TENSION

Govardhan Reddy Patluri[1] ; Devarajan Thirumalai[2] ;
[1]Indian Institute of Science, , Bangalor, Karnataka, [2]India University of Texas at Austin, , Austin, Texas, United States

Nucleosome plays an important role in the intricate packing and arrangement of chromatin in the cell nucleus. The effect of external force on the DNA in a mononucleosome is studied using Brownian dynamics simulations and a coarse grained model of the nucleosome. The simulations in agreement with the experiments shows that DNA unravels from the histone protein core (HPC) in two major steps. The simulations show that in the first step, the outer turn of the DNA (1.6 turns to 1.0 turn of DNA) unravels from the HPC and is independent of the pulling direction indicating that the energy barrier in the transition is due to overcoming the DNA-Histone protein contacts. In the second step, which is the unfolding of the inner turn of the DNA (from 1.0 turn to less than 0.5 turns of DNA) from HPC depends on the strength of the interaction of the histone tails with the DNA and pulling direction indicating that kinetic barriers play a role in this transition. In the unfolding transition, the kinetic barriers arise due to the requirement of generating sufficient torque by the external force to rotate the HPC by 180o and the histone tails which interact with the DNA, prevents the HPC from rotating. The refolding of the DNA onto HPC in the second transition upon force quench occurs only when the principal moment of inertia of the HPC aligns along the pulling direction due to stochastic fluctuations, and the external force does not play any role in this alignment. This difference in the role played by the external force in the DNA folding and unfolding from the HPC can contribute to the hysteresis observed in the nucleosome force pulling experiments

26-POS Board 26

A METADYNAMICS APPROACH FOR THE MODELLING OF INTRINSICALLY DISORDERED CHROMATIN BINDING PROTEINS

Akshay Sridhar[1]; Rosana Collepardo-Guevara[1];
[1]University of Cambridge, Maxwell Centre, Cavendish Laboratory, Cambridge, Cambridgeshire, United Kingdom

DNA in-vivo is complexed with histone proteins to form chromatin - an array of nucleosomes separated by linker DNA. While enabling considerable condensation of DNA, chromatin also allows additional complexity above the genetic code as its structure is intimately linked to gene expression. A range of chromatin-binding proteins participate in the remodelling and maintenance of chromatin structure. However, the high-resolution modelling of these chromatin-binding proteins is often hindered by them being particularly enriched in Intrinsically Disordered Regions (IDR) - regions with structural diversity and high flexibility. Through two protein test cases - H1 and HP1, we demonstrate the applicability of Metadynamics simulations to improve sampling and thereby aid in discerning the structural mechanisms of functioning of such chromatin binding IDRs.
H1 Linker Histones (LH) are composed of a structured globular domain and unstructured terminal domains. However, structural studies of H1-nucleosome binding have been limited to the globular domain. Through a metadynamics setup that biases the IDP's secondary structure and its interactions with DNA, we demonstrate that the long unstructured C-terminal domain bridges DNA through flexible loops. Additionally, we show the shorter unstructured N-terminal domain to contribute to the differential binding of H1 subtypes through differences in their amphiphilic helical conformations.
Heterochromatin Protein 1 (HP1) binds to the H3 tails of nucleosomes and plays an important role in gene regulation and the formation of Heterochromatin. The protein consists of intrinsically disordered terminals together with a disordered central hinge region that bridges two structured domains. These disordered regions are hypothesised to enable the functioning of HP1 through a multitude of intra- and inter-molecular contacts. Using metadynamics simulations, we determine conformations of the unstructured N-terminal domain and the associated changes upon its Phosphorylation that enable HP1's binding to the nucleosomal H3 tails.

WEDNESDAY, APRIL 3
POSTER SESSION III
21:00 – 22:00
Cecile Dewitt Building

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Wednesday. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Bishop, Thomas	**3-POS**	**Board 3**
Heidarsson, Petur	**7-POS**	**Board 7**
Ishida, Hisashi	**11-POS**	**Board 11**
Kono, Hidetoshi	**15-POS**	**Board 15**
Minhas, Vishal	**19-POS**	**Board 19**
Perez-Rathke, Alan	**23-POS**	**Board 23**
Virk, Ranya	**27-POS**	**Board 27**

Posters should be set up the morning of April 1 and removed by noon April 5.

3-POS Board 3

GENOME DASHBOARDS: FRAMEWORK AND G-DASH PROTOTYPE

Thomas C. Bishop[1]; Zilong Li[1]; Ran Sun[1];
[1]Louisiana Tech University, Ruston, Louisiana, United States

A dashboard is a console that displays data and provides controllers for navigating the physical world. A "genome dashboard" unifies sequence and spatial data, enabling genome pilots to navigate DNA, nucleosomes, chromatin and chromosome data or structures in real time. Here we present a framework for unifying studies of the 3D structure and dynamics of DNA with sequence based approaches. The framework is based on the idea that DNA is the common thread in all of genomics. As a 3D material the thread is a directed space curve that can be represented in an internal, material reference frame or in a Cartesian coordinate based laboratory reference frame. Mathematical expressions for converting between these representations are well defined and tools for computing these conversions are extremely fast. Masks are defined as external agents that alter the material properties, including conformation, of any segment of the DNA space curve. From this perspective genomics is the study of masked threads. We demonstrate the genome dashboard concept, using our prototype G-Dash to model chromatin. Inventories of nucleosome Masks can be manipulated in real time to generate atomic and coarse grained models from base pairs to entire chromosomes. The genome dashboard framework provides a basis for the data unification required to propose, test and validate structure-function relationships in genomics and to develop knowledge based potential functions for chromatin folding.

7-POS Board 7

DISORDERED PROTEINS ENABLE HISTONE CHAPERONING ON THE NUCLEOSOME

Petur O. Heidarsson; Davide Mercadante[1]; Alessandro Borgia[1]; Madeleine Borgia[1]; Andrea Sottini[1]; Sinan Kilic[2]; Daniel Nettels[1]; Beat Fierz[2]; Robert Best[3]; Benjamin Schuler[1];
[1]University of Zurich, Biochemistry, Zurich, Zurich, Switzerland
[2]EPFL, , Lausanne, Genf, Switzerland
[3]National institutes of health, Laboratory of chemical physics, Bethesda, Maryland, United States

Chromatin-binding proteins are particularly enriched in disordered and positively charged regions which facilitate electrostatic interactions with their counterparts, the highly negatively charged nucleic acids. Remarkably, such electrostatically dominated interactions can be very strong even if no well-defined structure is formed upon binding. Although such polyelectrolyte interactions have long been known in the field of soft matter physics, their importance in biology has only recently started to be recognized. A particularly interesting case are the 'linker histones', which bind to nucleosomes and contribute to chromatin condensation largely through the action of their long disordered and positively charged C-terminal region. Here we show, using single-molecule fluorescence spectroscopy, that the presence of disorder can convey regulatory mechanisms that would be difficult to achieve in the classical lock-and-key framework of biomolecular binding. The highly unstructured negatively charged protein prothymosin alpha, a known histone chaperone, can extract the linker histone from the nucleosome by forming a transient ternary complex. By combining the experimental results with simulations, we establish a molecular model that implies how the disordered chaperone can invade the linker histone-nucleosome complex and drive dissociation through interactions between highly charged unstructured regions.

11-POS Board 11

FREE ENERGY PROFILES FOR UNWRAPPING THE OUTER SUPERHELICAL TURN OF NUCLEOSOMAL DNA UNDER TORSIONAL STRESS

Hisashi Ishida[1]; Hidetoshi Kono[1];
[1]National Institutes for Quantum and Radiological Science and Technology, Kizugawa, Kyoto, Japan

Torsional stress gives a significant impact on the structure and dynamics of chromatin. For example, the torsion stress generates supercoiling in chromatin, where negatively supercoiled domains form a decompacted large-scale chromatin structure and are highly transcribed. RNA polymerase imposes torsional stress on DNA in chromatin and unwraps the DNA from the nucleosome to access the genetic information encoded in the DNA. It has also been shown that mechanical torsional stress influences the nucleosome structure and stability. To understand how the torsional stress affects the nucleosome stability, we carried out all atomic molecular dynamics simulations to examine the unwraping of the outer superhelical turn of the nucleosomal DNA from the histone octamer under the torsional stress imposed on the edges of the DNA. First, using an adaptively biased potential method, a series of conformations of the unwrapping DNA from the histone core was generated without torsional stress. Second, the free energies required to unwrap the DNA under positive and negative torsional stresses were estimated using umbrella sampling simulations. It was found that the positive torsion facilitated the unwrapping of the overwound DNA, while the negative torsion facilitated the wrapping of the underwound DNA around the histone core. The difference in these free-energies was observed after the interaction between the DNA and H3 histone was disconnected. The conformational entropy of the unwrapped DNA increased under the negative stress, indicating that the underwound DNA becomes more flexible. The flexibility of the underwound DNA may facilitate the movement of the unwrapped DNA back to the histone core in the stable state. We concluded that the torsion stress has a significant impact on the free energy of the unwrapping DNA and its dynamics, which would contribute to the conformational change of chromatin.

15-POS Board 15

ENERGETICS OF UNWRAPPING AND UNSTACKING OF NUCLEOSOMES STUDIED BY ALL-ATOM MOLECULAR DYNAMICS SIMULATIONS

Hidetoshi Kono[1]; Shun Sakuraba[1]; Hisashi Ishida[1];
[1]National Institutes for Quantum and Radiological Science and Technology, Molecular Modeling and Simulation Group, Kizugawa, Kyoto, Japan

Nucleosomes create the diverse conformations of chromatin by the intra- and inter-nucleosome interactions. The key factors are the unwrapping of DNA and the unstacking of nucleosomes. We investigated the energetics using all-atom molecular dynamics simulations with an enhanced sampling method on a large scale.

As for the intra-nucleosomal interaction, free energy for unwrapping the outer superhelical turn of the nucleosomal DNA is about 11.5 kcal/mol, which agrees well with values obtained in single molecule experiments. At one end of the DNA, the first five bps unwrap, after which the next five bps unwrap at the same end with little increase in the free energy. The unwrapping then starts at the other end of the DNA, where 10 bps are unwrapped. At this point, further 15 bps unwrap at either end. The unwrapping of the outer superhelical turn is completed when the other end of the DNA unwraps. A detailed analysis of the free energy profile revealed a variety of conformational states, indicating there are many potential paths to outer superhelical turn unwrapping, but the dominant path is likely to be asymmetric.

As for the inter-nucleosomal interaction, the free energy profile for separating two nucleosomes revealed that the H4 histone tails diversify the orientation of the two nucleosomes. The force between the nucleosomes was attractive (about 15 pN per H4 tail), while the force between the nucleosomes was repulsive (about -5 pN) when the H4 tails were not involved in the interaction. The experimental data of the internucleosomal stretching would be the averaged value derived from many different conformations of the nucleosomes, where some nucleosomes have specific H4 tail bridge interactions and others have nonspecific interactions without the H4 tails being involved.

These results provide insight into the construction, disruption and repositioning of nucleosomes to understand chromatin dynamics.

19-POS Board 19

PERSISTENCE LENGTH OF DNA USING INVERSE MONTE CARLO: COMPARISON OF DIFFERENT FORCE FIELDS

Vishal Minhas[1]; Nikolay Korolev[1]; Lars Nordenskiold[1]; Alexander Lyubartsev[2];
[1]Nanyang Technological University , School of Biological Sciences, Singapore, North-West, Singapore
[2]Stockholm University, Department of Materials and Environmental Chemistry, Stockholm , Stockholms län, Sweden

A multiscale computational model is developed to understand the packing of DNA in a physiological ionic environment. We use bottom-up coarse-graining to bridge all-atom and meso-atom representations of all the principal chromatin components. To achieve this, 2 microsecond long all-atom MD simulations of underlying systems are performed, which are then bead-mapped to a coarse-grained representation and used for the calculation of the radial distribution functions (RDF), which are then used to derive the effective potentials using the Inverse Monte-Carlo method. Also, the RDFs obtained from the bead-mapped representation are then reproduced in the coarse-grained simulation using the effective potentials obtained to ensure structure properties of the system are conserved. Finally, to validate the model, coarse-grained MD simulations using the effective potentials are run to calculate the persistence length of DNA and a comparison with experiments is done. Two most popular nucleic acid force fields AMBER and CHARMM are compared on their prediction of persistence length of DNA using this model.

23-POS Board 23

MANY-BODY CHROMATIN INTERACTIONS IN SUPER-ENHANCER TADS

Alan Perez-Rathke[1]; Qiu Sun[2]; Valentina Boeva[3,4]; Jie Liang[1];
[1]University of Illinois at Chicago, Bioengineering, Chicago, Illinois, United States
[2]Shanghai Jiao Tong University, Biomedical Engineering, Shanghai, Shanghai, China
[3]Institut Curie, , Paris, Paris, France
[4]Institut Cochin, , Paris, Paris, France

Chromatin interactions are thought to be important for gene regulation via enhancer-promoter looping as well as for critical functions such as cellular specialization. There is now emerging evidence that many-body (>2) chromatin interactions may be an important feature of super-enhancer (SE) regions - for example, condensing the SE region into a cohesive transcriptional apparatus. Chromosome conformation capture techniques such as Hi-C have greatly contributed to our understanding of the chromatin folding landscape. However, Hi-C has limitations as it only captures pairwise chromatin interactions and the interaction frequencies mostly represent population averages. Therefore, it is generally not possible to directly infer the existence of significant many-body chromatin interactions. With the goal of solving these problems, we have developed a computational model which utilizes physical properties of chromatin folding (e.g. nuclear confinement and self-avoidance) as well the experimental Hi-C data to reconstruct the corresponding ensemble of 3-D polymers. We deeply sample from a Bayesian generative model to infer the existence of significant many-body chromatin interactions in topologically associating domains (TADs) bounding SE regions. Specifically, we investigate: i) the prevalence of significant many-body chromatin interactions beyond random polymer folding; ii) the extent of enrichment of many-body interactions in SE regions; iii) which epigenetic markers are predictive of many-body interactions. Our analysis is performed on GM12878 and K562 cell lines at 5 KB resolution. We compare our many-body predictions to split-pool recognition of interactions by tag extension (SPRITE) clusters in GM12878.

27-POS Board 27

CONSTRUCTING AN OPTIMAL CHROMATIN POLYMER MODEL FOR MACROGENOMIC ENGINEERING APPLICATIONS

Ranya Virk[1]; Kai Huang[1]; Igal Szleifer[1]; Vadim Backman[1];
[1]Northwestern University, Biomedical Engineering, Evanston, Illinois, United States

An emerging focus in cancer research is the effects of global chromatin organization on the regulation of transcriptional processes on a global scale. Using a combination of nanoimaging devices developed in Professor Backman's lab to measure chromatin organization, we have already determined that chromatin organization is more heterogeneous in malignant, chemoevasive cancer cells, which corresponds with an increase in transcriptional heterogeneity observed with single-cell RNA sequencing. We have also discovered adjuvant therapies, that reduce heterogeneity in chromatin organization and allow chemotherapies to be more efficacious by reducing transcriptional plasticity of cancer cells. However, we have not yet determined the principal biological, and physico-chemical interactions behind the control of chromatin organization. In order to understand the effect of altering the physico-chemical chromatin nanoenvironment on global chromatin organization we are developing a computational polymer model that realistically represents chromatin structure down to small ~nm length-scales. Potential polymer models include basic homopolymers under confinement such as the fractal globule and tension globule, models that represent biological mechanisms of chromatin organization such as block copolymers to represent A/B compartmentalization, Strings & Binders and loop extrusion to represent looping, and adding torsional stress to induce supercoiling, as well as the de novo self-returning random walk (SRRW) numerical model of chromatin recently developed in Professor Szleiferâ€™s lab. We compare experimentally observed biological properties of chromatin, general rules of polymer physics, and statistical properties of these different polymer models such as contact probability, mass scaling, and mass density distribution to determine which model or combination of models most accurately represents the chromatin polymer.

THURSDAY, APRIL 4
POSTER SESSION IV
21:00 – 22:00
Cecile Dewitt Building

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Thursday. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Bronshtein, Irena	**4-POS**	**Board 4**
Huang, Kai	**8-POS**	**Board 8**
Khalil, Ahmed	**12-POS**	**Board 12**
Kumar, Hemant	**16-POS**	**Board 16**
Nordenskiold, Lars	**20-POS**	**Board 20**
Rudnizky, Sergei	**24-POS**	**Board 24**
Wereszczynski, Jeff	**28-POS**	**Board 28**

Posters should be set up the morning of April 1 and removed by noon April 5.

4-POS Board 4

TRACKING OF GENOMIC SITES AT NANOSCALE LEADS TO THE UNDERSTANDING OF GENOME ORGANIZATION

Irena Bronshtein[1]; Yuval Garini[1];
[1]Bar Ilan University, Physics Department and Nanotechnology Institute, Ramat Gan, Center, Israel

The organization of the genome in the nucleus is believed to be crucial for cellular functions such as gene regulation and the maintenance of genome integrity along the cell cycle. We used live cell imaging to examine the organization of the genome in living cells. To characterise the dynamic properties of the chromatin, we analysed the diffusion of different genomic sites by measuring their trajectories through Single Particle Tracking (SPT) and thoroughly characterized their diffusion characteristics. Such experimental approach and data analysis enables the characterization of protein interactions with chromatin in live cells in an independent manner to biochemical essays. Chromatin diffusion in differentiated cells was found to be slow and anomalous; in vast contrast, absence of lamin A protein leads to a significant increase in genome mobility and the scanned nuclear volume, and induces a dramatic transition of genome dynamics from slow anomalous diffusion to fast and normal diffusion. Constrained chromatin mobility can have an important part in maintaining the chromosomal territories, which in turn prevents chromosomal entanglement and aberrations. Indeed, we found that lamin A depleted cells have a higher frequency of genomic aberrations compared to normal cells. We propose that chromatin acts like a scaffold folded into loops that are formed by dynamic lamin A crosslinking. This model naturally provides rigidity to the nucleus and explains the mechanism that maintains the chromosomal territories. Altogether, we demonstrate the importance of dynamic measurements in the nucleus for deciphering the mechanisms of genomic organization.

8-POS Board 8

INTERPHASE CHROMATIN AS A SELF-RETURNING RANDOM WALK

Kai Huang[1]; Igal Szleifer[1];
[1]Northwestern University, Biomedical Engineering, Evanston, Illinois, United States

We introduce a self-returning random walk to describe the structure of interphase chromatin. Based on a simple folding algorithm, our *de novo*model unifies the high contact frequency discovered by genomic techniques, and the high structural heterogeneity revealed by imaging techniques, which two chromatin properties we theoretically prove to be irreconcilable within a fractal polymer framework. Our model provides a holistic view of chromatin folding, in which the topologically associated domains are liquid-tree-like structures, linked and isolated by stretched out, transcriptionally active DNA to form a secondary structure of chromatin that further folds into a "3D forest" under confinement. The model pivots a wide array of experimental observations and suggests the existence of a universal chromatin folding principle. Based on a global folding parameter, the model reveals a unique structure-function relation of chromatin, which is abnormal from a polymer point of view but explains some experimental observations of how chromatin responses to stress.

12-POS Board 12

IDENTIFICATION AND INCORPORATION OF COPY NUMBER INFORMATION FOR CORRECTING HI-C DATA OF CANCER CELLS

Ahmed I.S. Khalil[1]; Anupam Chattopadhyay[1]; Amartya Sanyal[2];
[1]Nanyang Technological University, School of Computer Science and Engineering, Singapore, South-West, Singapore
[2]Nanyang Technological University, School of Biological Science, Singapore, South-West, Singapore

Hi-C and its variant techniques have been developed to capture the genome-wide chromatin interactions. Filtering and normalization of Hi-C data are essential for accurate modelling and interpretation of genome-wide contact map. Although several methods have been developed, they usually account for genome sequence biases and ignore the data-driven biases such as copy number variations (CNVs). Cancer genomes are plagued with widespread multi-level structural aberrations of chromosomes. These pose a challenge to accurately identify CNV profiles and their subsequent usage for better filtering and normalization of contact map.
Here, we propose a framework that utilize read depth (RD) of coverage from Hi-C or 3C-seq datasets to first identify their CNV profiles including both large-scale and focal events. Then, we integrate these CNV tracks with other systematic biases for correcting the interaction frequencies using Poisson regression model. We demonstrated that the RD signal, computed by combining valid read pairs with single-side mapped reads and read pairs mapped to same fragment, recapitulates the RD profile derived from input control of ChIP-seq data of same cell line. This allows identification of focal CNVs beside large-scale segmental alterations. Interestingly, we discovered that the chromatin contact frequencies of cancer cells are highly correlated with large-scale CNVs suggesting that ignoring these large segmental alterations may lead to biased interaction signal. We have applied this normalization technique on several Hi-C/3C-seq cancer datasets which effectively removes the data-driven biases.

16-POS Board 16

WHOLE GENOME ORGANIZATION AND CHROMATIN PLASTICITY USING DATA ANALYTICS INFORMED MD SIMULATIONS

Hemant Kumar[1]; Anastasiya Belyaeva[2]; G. V Shivashankar[3]; Caroline Uhler[2]; Vivek Shenoy[1];
[1]University of Pennsylvania, MSE, Philadelphia, Pennsylvania, United States
[2]Massachusetts Institute of Technology, Laboratory for Information and Decision Systems, Cambridge, Massachusetts, United States
[3]National University of Singapore, Mechanobiology Institute, Singapore, Central Singapore, Singapore

Recent advancements in the chromosome conformation capture techniques have revealed the crucial role played by the spatial organization of the genome in regulating transcriptional activities and cell fate. Using HiC data along with the 1D epigenome, we develop a modeling strategy that enables us to predict realistic ensembles of whole genome conformations consistent with contact maps observed in HiC experiments. Rigorous data analytics approach has been used to identify functional contacts from the sub-TAD contact frequencies measured in HiC, and experimentally-measured expression data for various regulatory markers have been used to arrive quantitative estimates of the functionality of different contact pairs. These quantitative estimates have been further used to optimize a polymer model which allows us to make structural predictions of all chromosomes simultaneously reproducing both intrachromosomal and interchromosomal contact maps observed in experiments. We further use this model to predict the chromatin configurations in various nuclear geometries which appear during different stages of cell migration and explore the impact of structural modifications of chromatin on the gene regulation. We demonstrate that chromatin configuration undergoes plastic deformations in response to nuclear geometry changes accompanied by modification of interchromosomal transcription hubs which potentially have important functional implications.

20-POS Board 20

A MULTISCALE ANALYSIS OF DNA PHASE SEPARATION: FROM ATOMISTIC TO MESOSCALE LEVEL

Lars Nordenskiöld[1], Vishal Minhas[1], Tiedong Sun[1,3], Alexander Mirzoev[1], Nikolay Korolev[1], Alexander P. Lyubartsev[2]

[1] School of Biological Sciences, Nanyang Technological University, Singapore 637551
[2] Department of Materials and Environmental Chemistry, Stockholm University, 10691 Stockholm, Sweden
[3]Present Address: Tiedong Sun, Department of Materials Science and Engineering, Institute of High Performance Computing, Agency for Science, Technology and Research (A*STAR), Singapore 138632

DNA condensation and phase separation is of utmost importance for DNA packing *in vivo* with important applications in medicine, biotechnology and polymer physics. The presence of hexagonally ordered DNA is observed in virus capsids, sperm heads and in dinoflagellates. Rigorous modelling of this process in all-atom MD simulations is presently difficult to achieve due to size and time scale limitations. We used a hierarchical approach for systematic multiscale coarse-grained (CG) simulations of DNA phase separation induced by the three-valent cobalt(III)-hexammine ($CoHex^{3+}$). Solvent-mediated effective potentials for a CG model of DNA were extracted from all-atom MD simulations. Simulations of several hundred 100-bp-long CG DNA oligonucleotides in the presence of explicit $CoHex^{3+}$ ions demonstrated aggregation to a bundled liquid crystalline-type ordered phase. Furthermore, adopting a second level "super coarse-grained" (SCG) DNA beads-on-a-string model, we show that this approach predicts the hexagonally ordered liquid crystalline phase of short DNA and toroid formation in hexagonal arrangement for kbp-size long DNA, giving mechanistic insight on the DNA condensation process. The mechanism of toroid formation is analysed in detail. The approach used here is based only on the underlying all-atom force field. In order to further advance our knowledge and pave the ground for detailed analysis of the compaction of DNA at mesoscale level in chromosomes, it is necessary to develop such chemically informed DNA models that do not rest on adjustable parameters. Such models should have the predictive power to be trusted in modelling biologically important phenomena at mesoscale level for experimentally unexplored scenarios. The present approach represents a first and successful step in this direction.

24-POS Board 24

THE BP-SCALE THERMAL DIFFUSION OF NUCLEOSOMES MODULATES BINDING OF TRANSCRIPTION FACTORS

Sergei Rudnizky[1]; Hadeel Khamis[2,3]; Omri Malik[2,3]; Philippa Melamed[1,3]; Ariel Kaplan[1,2,3];
[1]Technion - Israel Institute of Technology, Biology, Haifa, North, Israel
[2] Technion – Israel Institute of Technology, Physics, Haifa, North, Israel
[3] Technion – Israel Institute of Technology, Russell Berrie Nanotechnology Institute, Haifa, North, Israel

The structure of promoter chromatin determines the ability of transcription factors to bind the DNA and therefore has a profound effect on the expression levels of genes. Yet, the role of spontaneous nucleosome movements in this process is not fully understood. Here, we developed a single-molecule assay capable of simultaneously characterizing the bp-scale diffusion of a nucleosome on DNA, and the binding of a transcription factor (TF). Our results demonstrate that nucleosomes undergo confined diffusion, and that the incorporation of the histone variant H2A.Z serves to partially relieve this confinement, inducing a different type of nucleosome repositioning. The increase in diffusion leads to exposure of a TF's binding site and facilitates its association with the DNA, which in term biases the subsequent movement of the nucleosome. Our findings suggest the use of mobile nucleosomes as a novel and general transcriptional regulatory mechanism.

28-POS Board 28

DISCERNING THE EFFECTS OF LINKER HISTONES ON SINGLE AND POLY-NUCLEOSOMAL ARRAYS WITH ALL-ATOM SIMULATIONS

Jeff Wereszczynski[1];
[1]Illinois Institute of Technology, Physics & The Center for Molecular Study of Condensed Soft Matter, Chicago, Illinois, United States

Linker histones are essential epigenetic regulators which exert their influence by binding to and stabilizing the nucleosome core particle. Experiments have demonstrated that his can have dramatic effects on both the local and large-scale structures of chromatin fibers. Although they have been extensively studied, the principles underlying the molecular mechanisms of these proteins remain poorly understood. Here, I will discuss a series of all-atom molecular dynamics simulations aimed at discerning the effects of linker histone binding on both single nucleosomes and poly-nucleosomal arrays. Results of single nucleosome simulations show that on-dyad binding is energetically favored, whereas off-dyad binding is likely entropically favored irrespective of the linker histone isoform studied. Binding in each of these locations has distinct effects on the structure and dynamics of linker DNA. Simulations of octa-nucleosomal arrays show that these effects propagate into large scale changes in the structure and dynamics of chromatin. In these models of compact chromatin fibers, it is shown that H1 binding creates tighter and stiffer structures that better maintain tetra-nucleosomal repeats than similar systems that lack linker histones. Together, these results highlight the roles of linker histones in maintaining compact chromatin fibers and help reveal the physical processes underlying their mechanisms.