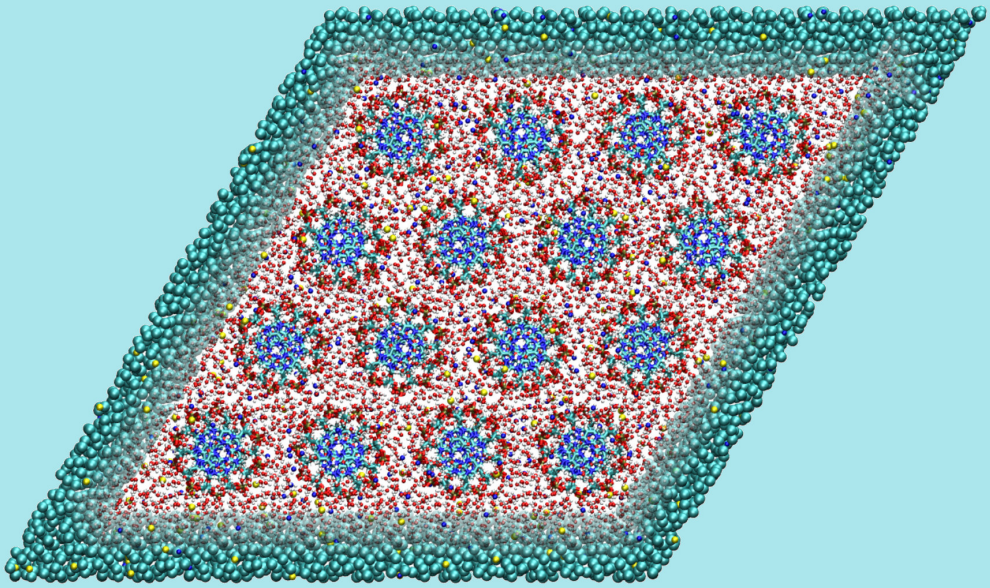
CECAM and IUPAP workshop on

High density DNA arrays: models, theories and multiscale simulations



Book of abstracts

Ljubljana, Slovenia

July 24 2019 – July 26 2019

CECAM and IUPAP workshop on

High density DNA arrays: Models, theories and multiscale simulations

Book of abstracts

National Institute of Chemistry, Ljubljana, Slovenia

July 24 2019 – July 26 2019

Workshop
High density DNA arrays: Models, theories and multiscale simulations

Organized by
Theory Department, National Institute of Chemistry

Editors
Matej Praprotnik, Miha Ravnik, Primož Ziherl, and Rudolf Podgornik

Technical editors
Matej Praprotnik and Jurij Sablić

Issued by
National Institute of Chemistry

Printed by
Infokart d.o.o., Ljubljana

Place and year of publication
Ljubljana, 2019

Circulation
55 issues

Complimentary publication

CIP - Kataložni zapis o publikaciji
Narodna in univerzitetna knjižnica, Ljubljana

577.21(082)

CECAM and IUPAP Workshop on High Density DNA Arrays: Models, Theories and Multiscale Simulations (2019 ; Ljubljana)

Book of abstracts / CECAM and IUPAP Workshop on High Density DNA Arrays: Models, Theories and Multiscale Simulations, Ljubljana, Slovenia, July 24 2019 - July 26 2019 ; [organized by Theory Department, National Institute of Chemistry ; editors Matej Praprotnik ... et al.]. - Ljubljana : National Institute of Chemistry, 2019

ISBN 978-961-6104-45-6
1. Praprotnik, Matej, 1974-
COBISS.SI-ID 300897536

Contents

General Information

Organizing Committee

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Primož Ziherl, Faculty of Mathematics and Physics, University of Ljubljana, and Jožef Stefan Institute, Ljubljana, Slovenia
Rudolf Podgornik, University of Chinese Academy of Sciences, Beijing, China

Venue

National Institute of Chemistry

address: Hajdrihova 19, Ljubljana, Slovenia

web page: **https://www.ki.si**

Accommodation

Hotel Mrak

address: Rimska cesta 4, Ljubljana, Slovenia

phone: +386 1 421 96 50

web page: **https://hotelmrak.si**

How to get from Ljubljana Airport to the accommodation?

There are several options how to get from the airport to the accommodation:

- the accommodation offers the transfer from the airport to the hotel. The price is around 38 EUR for one way transfer and around 60 EUR for return transfer. The transfer must be booked

in advance by contacting the hotel directly.

- transfer by Taxi Association Ljubljana

  phone: +386 1 234 90 00, +386 31 234 000

  web page: **http://en.taxi-ljubljana.si/**

  The transfer costs approximately 35-38 EUR (one way) depending on the traffic. In order to avoid waiting for the taxi at the airport, it is advisable to book it in advance and the taxi driver will wait for the costumer at the airport at the arranged hour.

- transfer by one of the taxis, parked in front of the airport, is the most expensive way of transfer. The price ranges between 40 and 60 EUR (one way).

- transfer by GoOpti shuttle. The transfer must be booked in advance on the web page: **https://www.goopti.com/en/**. They can take the costumer from the airport directly to the accommodation. The costumer might have to wait up to 30 minutes at the airport for the transfer to arrive. The company sends all the details by e-mail and SMS a day before the arranged transfer. The transfer costs approximately 10-15 EUR (one way).

- transfer by Nomago shuttle. This transfer costs approximately 10-15 EUR (one way). The ticket can be purchased directly from the driver, but it is advisable to book the ticket in advance on the web page: **https://shuttle.nomago.si/en/book-ticket**. The timetable of the departures from the airport can be found at: **https://www.fraport-slovenija.si/pripone/2491/Vozni red LJU APT novo.pdf**. However, this transfer takes the costumer from the airport to the main bus station in Ljubljana, which is 1.5 km away from the accommodation.

How to get from the accommodation to the venue?

The accommodation is located 1 km, i.e. approximately a 12 minute walk, from the venue. The map is attached below.

Cafes and Restaurants

There are several restaurants in the vicinity of the venue:

- Restaurant Mirje (address: Tržaska 5 – approx. 8 minutes from the venue)
- Gostilnica in pivnica Vič (address: Trg mladinskih delovnih brigad 8 – approx. 10 minutes from the venue)
- Trnovski zvon (address: Eipprova 17 – approx. 11 minutes from the venue)

and there are many more in the city center. As far as cafes are concerned, the following ones are located near the venue:

- Bar Kolezija (in front of the venue)
- Langus kavarna (address: Langusova ulica 4 – approx. 5 minutes from the venue)
- Corner pub (address: Tržaška cesta 19 – approx. 5 minutes from the venue)
- Čin Čin (address: Tržaška cesta 2 – approx. 9 minutes from the venue)

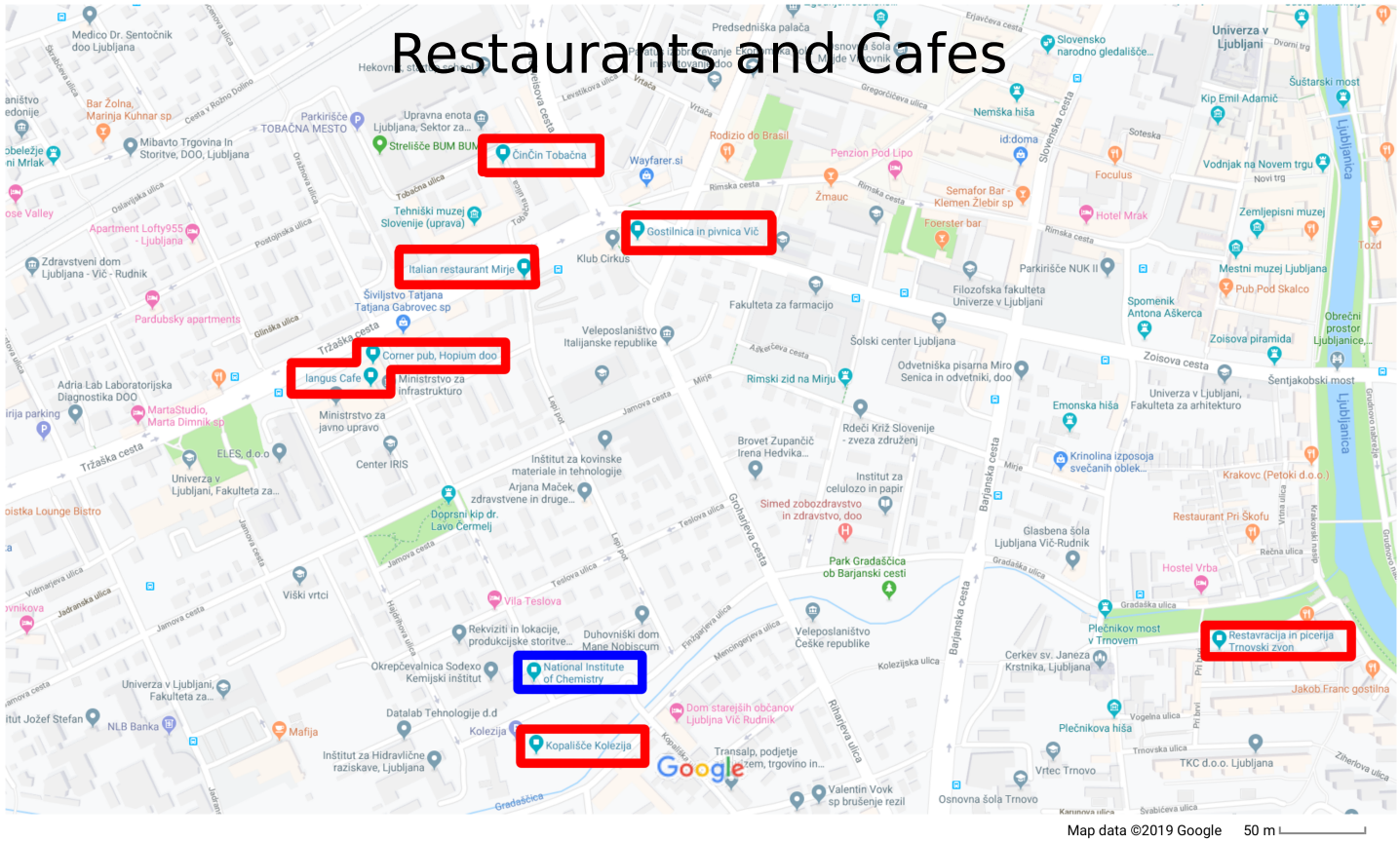
The mentioned restaurants and cafes are circled in red on the map below. The venue is circled in blue.

The workshop dinner

The workshop dinner will take place on Thursday, July 25, at the restaurant Kobjeglava, which is located in a village in the Karst region. The bus transfer from the venue to the restaurant will be organized. More information about the restaurant is available at:
https://q-komel.com/en.

Accommodation - Venue
Hotel Mrak
National Institute of Chemistry
Google
Tripsty
Barjanska cesta
Murnikova ulica
Grobeljeva cesta
Tržaška cesta
Aškerčeva cesta
Zoisova cesta
Gradaška ulica
Eipprova ulica
Langusova ulica
Jamova cesta
Bičevje
Lepi pot
Mirje
Rimska cesta
Oražnova ulica

Restaurants and Cafes



Description

Densely packed DNA arrays exhibit hexagonal and orthorhombic local packings, as well as a weakly first order transition between them, as affected also by the length of the DNA strands or fragments. While we have some underanding of the interactions between DNA molecules in aqueous ionic solutions, the structural details of its ordered phases and the mechanism governing the respective phase transitions between them remain less well understood.

Since at high DNA densities, i.e., small interaxial spacings, one can neglect neither the atomic details of the interacting macromolecular surfaces nor the atomic details of the intervening ionic solution, the atomistic resolution is a sine qua non to properly describe and analyze the interactions between DNA molecules. In fact, in order to properly understand the details of the observed osmotic equation of state, one needs to implement multiple levels organization, spanning the range from the molecular order of DNA itself, the possible ordering of counterions, and then all the way to the induced molecular ordering of the aqueous solvent and then mesosopic level, all coupled together by electrostatic, steric, thermal and direct hydrogen-bonding interactions. Multiscale approaches coupling atomistic, mesoscopic, and macroscopic levels of detail therefore appear as singularly suited to connect the microscopic details of this system with its macroscopic thermodynamic behavior.

With the proposed workshop, we wish to address the simulation approaches to the dense DNA arrays with different local packing symmetries, the solvent structural order, and counterion types. The aim of the meeting is to discuss numerical and theoretical methods and models at different length scales applicable to such systems to analyze the osmotic equation of state, to identify the most important contributions to the DNA-DNA interactions at high DNA densities, to determine possible liquid crystalline ordering profiles and explore means for

controlling the DNA packing and ordering. In an unrestrained atmosphere of an interdisciplinary workshop including physicists, chemists, and biologists these goals may be reached to mutual benefit of the participants as well as indirectly of the scientific community.

Overall, there is a growing need for a clear jump forward by the community in the methodology and approaches capable of addressing dense DNA arrays, and we are convinced that the proposed CECAM workshop could be notable contribution in this direction, opening a focused but broadly relevant forum for novel discussions and advances in these issues.

The objective of the workshop is to address the following main open issues:

- multiscale methods coupling different models at various length scales
- performing open grand-canonical molecular simulations that exchange energy, momentum, and matter with the external environment
- determination of phase transitions between DNA subphases beyond invoking the general Lindemann criterion, using enhanced sampling techniques
- determination of DNA to surface interactions (surface anchoring) in view of orientational and positional order of DNA
- identification of material regimes and system parameters for use of dense DNA materials as advanced macroscopic materials, such as in bio-photonics

Having IUPAP Conference Endorsement, this CECAM workshop is a satellite meeting of the **Joint 12$^{\text{th}}$ EBSA 10$^{\text{th}}$ ICBP-IUPAP Biophysics Congress, Madrid, Spain**. We therefore subscribe to the **statement on free circulation of scientists** in addition to CECAM's own policies.

Schedule

Day 1 – Wednesday – July 24

8:00-8:45	*Registration*
8:45-9:00	*Opening*
9:00-9:45	**Aleksei Aksimentiev** (invited lecture) *Modeling high density DNA arrays: Mission accomplished!*
9:45-10:30	**Jonathan Doye** (invited lecture) *Lyotropic cholesteric phases of DNA and its assemblies*
10:30-11:00	*Coffee break*
11:00-11:45	**Christoph Cremer** (invited lecture) *Super resolution microscopy of DNA packaging in mammalian cell nuclei*
11:45-12:30	**Jurij Sablić** (invited lecture) *Open boundary molecular dynamics of star-polymer melt and DNA in salt solution*
12:30-14:00	*Lunch*
14:00-14:45	**Alexander Lyubartsev** (invited lecture) *Multiscale simulations of DNA aggregation by multivalent ions*
14:45-15:30	**Nikolay Korolev** *Analysis structures and forces defining chromatin condensation*
15:30-16:00	*Coffee break*
16:00-16:45	*Round table*
16:45-17:30	**Amélie Leforestier** (invited lecture) *Nucleosome conformational variability in interphase nuclei and in solution explored by cryo-electron microscopy and tomography of vitreous sections*

17:30-18:15 **Bart Bruininks**
Genetic outbreak from the endosome:
A molecular perspective on gene therapy

18:15-18:45 **Salvatore Assenza**
Multiscale simulations of double-stranded DNA
with sequence-dependent mechanical
and conformational properties

Day 2 – Thursday – July 25

9:00-9:45 **Kurt Kremer** (invited lecture)
Polymer globules in bulk and in confinement

9:45-10:30 **Achille Giacometti** (invited lecture)
Toward controlled self-assembly of peptides

10:30-11:00 *Coffee break*

11:00-11:45 **Tommaso Bellini** (invited lecture)
DNA without DNA:
Watson-Crick selectivity controls the self-assembly
of mononucleotides

11:45-12:30 **Jure Dobnikar** (invited lecture)
Spontaneous domain formation in spherically-confined
elastic filaments

12:30-14:00 *Lunch*

14:00-14:45 *Round table*

14:45-15:30 **Christian Holm** (invited lecture)
How to model DNA translocation through nanopores –
A multiscale simulational exploration

15:30-16:15 **Cristian Micheletti** (invited lecture)
Effect of knots during viral DNA packaging and ejection

16:15-16:30 *Coffee break*

16:30-17:15 **Daniel Svenšek** (invited lecture)
Density-nematic coupling in isotropic linear polymers:
acoustic and osmotic birefringence

17:15- *Dinner (Kobjeglava, Štanjel by bus)*

Day 3 – Friday – July 26

9:00-9:45 **Alexei Kornyshev** (invited lecture)
Homology recognition without proteins
[DNA sequence-structure relationship, helical coherence, and a universal homology recognition mechanism - theory vs experiments]

9:45-10:30 **Angelo Rosa** (invited lecture)
From chromosome territories to ring polymers: Physical properties of untangled polymer melts

10:30-11:00 *Coffee break*

11:00-11:45 **Irena Drevenšek Olenik** (invited lecture)
"Genetics" in two dimensions: DNA base pairing in thin surface films

11:45-12:30 **Franci Merzel** (invited lecture)
Atomistic MD simulations as a tool to elucidate mechanical properties of DNA/RNA systems

12:30-14:00 *Lunch*

14:00-14:45 *Round table*

14:45-15:30 **Nataša Adžić** (invited lecture)
DNA-based dendrimers: From a single molecule to the dense solution description

15:30-16:15 **Clemens Jochum** (invited lecture)
Free energy landscapes for dendrimer-like DNAs via neural networks

16:15-16:30 *Coffee break*

16:30-17:00 **Stanard Mebwe Pachong**
Dynamics and organization of cyclic polymers melt in a confinement

17:00-17:30 **Matej Kanduč**
Aqueous nanoclusters govern ion partitioning in dense thermoresponsive polymer membranes

17:30-18:00 *Open discussion and Conclusion*

Abstracts – invited lectures

Modeling high density DNA arrays: Mission accomplished!

Aleksei Aksimentiev
University of Illinois at Urbana-Champaign, Urbana, IL, USA

Only ten years ago, fully atomistic simulations of dense DNA arrays presented formidable challenges. The simulations were computationally expensive because of their relatively large size, the molecular force fields had several critical artifacts and the nanoseconds simulation timescale raised legitimate questions about the conformational sampling. In this talk, I will summarize recent advances made by our group to overcome these problems. Starting with a brief description of our improved parameterization of the molecular force fields, I will review our recent discovery of effective interactions between double-stranded DNA governed by their methylation patterns. I will then describe our efforts to develop accurate multi-resolution models of dense DNA systems and show how such models can be used to simulate self-assembled DNA nanostructures and viral genome packaging.

Lyotropic cholesteric phases of DNA and its assemblies

Jonathan Doye
University of Oxford, United Kingdom

Although it is unsurprising that rod-like chiral mesogens form chiral liquid-crystalline phases, accounting even for the handedness of experimental cholesteric phases in terms of the microscopic structure of the mesogenic particles has generally proved elusive. So far, the most useful approach is a geometric argument dating back to Straley that weakly-twisted (thread angle > 45 degrees) screw-like objects will have a cholesteric handedness opposite to that of the handedness of the mesogens (and vice versa for strongly-twisted mesogens), as this allows a better close-packing of the threads. The results from theory and simulations of rigid objects seem to confirm this basic picture, albeit with some system-specific variation in the exact crossover thread angle. However, cholesterics phases formed from DNA duplexes and DNA origamis illustrate the difficulty when trying to apply this argument to experimental systems. For example, the DNA double helix is right-handed with a thread angle of ~ 30 degrees, but solutions of persistence length DNA exhibit a left-handed cholesteric phase. Somewhat similarly, long six helix-bundle DNA origamis that are weakly-twisted show a tendency for cholesteric phases that are of the same handedness as the internal twist. Thus, both seem to show opposite behaviour to the Straley argument. We attempt to resolve these questions by applying a classical density functional theory that can account for the fluctuations of stiff (but not rigid) mesogens together with a description of the structure, mechanics and intermolecular interactions provided by the oxDNA coarse-grained DNA model. For both systems, when the objects are assumed to be rigid the predictions are in line with Straley's argument, but opposite to that of experiment. For the duplexes, although we weren't able to progress further, both because we weren't able to converge the calculations with respect to the thermal fluctuations and because persistence duplexes aren't sufficiently stiff to consistently apply the theory, the necessity of accounting for flexibility is clear. However, for the much stiffer DNA origamis, our results agree well with experiment when flexibility is included. The effects of the chiral shape fluctuations of the origamis dominate over their intrinsic twist, with these fluctuations having a net helical character of opposite handedness to their intrinsic twist, as this helps to reduce the internal stress that is responsible for the twist.

Super resolution microscopy of DNA packaging in mammalian cell nuclei

Christoph Cremer[1,2,3]

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[2]Institute for Pharmacy and Molecular Biotechnology (IPMB), University Heidelberg & Kirchhoff-Institute for Physics (KIP), D-69120 Heidelberg (Germany)
[3]Max-Planck Institute for Chemistry, D-55128 Mainz (Germany)
e-mail: c.cremer@imb-mainz.de, cremer@kip.uni-heidelberg.de, www.optics.imb-mainz.de

The advent of super-resolution light microscopy (SRM) methods [1,2] has made it possible to quantitatively investigate the spatial consequences of models of nuclear genome organization [3] on the nanoscale. Here we report on SRM results obtained by Single Molecule Localization Microscopy (SMLM) and Structured Illumination (SI) approaches. Using such techniques, the spatial distribution of chromatin in the nucleus and the compaction of individual chromatin domains was measured. The DNA compaction of specifically labelled nuclear gene domains was determined by SI, yielding estimates up to 200 Mbp/µm^3. The overall DNA distribution across entire nuclei was quantitatively determined by SMLM at the nanoscale, applying both photoswitching and spatial switching of standard DNA dyes [4,5]; recently, it became possible to determine in an individual nuclear optical section up to ca. 4 million individual DNA bound single fluorophore molecule positions (ca. 1 position/nucleosome), with a density up to 70,000 individual molecule positions/µm^2. The smallest intranuclear single molecule distance measured was ca. 10 nm; positional differences of 3 nm were still discernible. Nuclear intensity profile analysis of the intranuclear DNA distributions indicated sharp transitions between high density domains and low density compartments, with differences up to almost two orders of magnitude, while compacted domains had a minimum size down to ca. 30-50 nm diameter. In contrast to these results, conventional resolution imaging of the same nuclear sites indicated only small differences in the compaction of different regions, combined with very smooth density transitions across the nucleus. Such quantitative nanoscale data may contribute to improved numerical simulations of the consequences of DNA compaction in the transcriptional control in mammalian cell nuclei.

[1] C. Cremer, B.R. Masters (2013) Resolution enhancement techniques in microscopy. Eur. Phys. J. H **38**: 281-34.

[2] C. Cremer, A. Szczurek, F. Schock, A. Gourram, U. Birk (2017) Super-resolution microscopy approaches to nuclear nanostructure imaging. Methods **123**: 11-32.

[3] T.Cremer et al. (2015) The 4D nucleome: Evidence for a dynamic nuclear landscape based on

coaligned active and inactive nuclear compartments. FEBS Letters **589**: 2931-2943.

[4] I.Kirmes et al. (2015) A transient ischemic environment induces reversible compaction of chromatin. Genome Biology **16**:246.

[5] A.Szczurek et al. (2017) Imaging chromatin nanostructure with binding-activated localisation microscopy based on DNA structure fluctuations. Nucleic Acids Research. doi: 10.109 3/nar/gkw1301.

Open boundary molecular dynamics of star-polymer melt and DNA in salt solution

Jurij Sablić
Laboratory for Molecular Modeling, Theory Department, National Institute of Chemistry, SI-1001 Ljubljana, Slovenia

We present Open Boundary Molecular Dynamics (OBMD) simulation of melts of star polymers and of a DNA molecule immersed in salt solution. OBMD allows for MD simulations of open systems [1]. Systems can thus exchange the matter with the surroundings and the method also enables the imposition of the external boundary condition onto the simulated system. First, we use the OBMD to simulate a star-polymer melt in equilibrium and under shear flow [2,3]. All simulations are carried out under constant normal load, which is, together with shear flow, introduced into the system via the external boundary condition. We observe that in equilibrium the melt behaves in accordance with the grand-canonical predictions. Interestingly, out of equilibrium the melt experiences the decrease of density with the increase of the strength of shear flow, which leads to redistribution of pressure, when compared to the closed MD set-up. Apart from that, we also observe that the rheological properties of open and closed melt differ. Second, we use a slightly modified OBMD method to study the properties of a DNA molecule in a salt solution [4]. The concentration of the electrolyte in the solvent plays an important role in such systems and may affect the properties of the DNA molecule. Due to the computational limitations, the MD simulations of the solvation of macromolecules are usually performed at higher concentrations than the physiological one. To overcome this difficulty, the explicit water molecules and salt ions surround the DNA only in its close vicinity. Farther away the salt ions are still de facto present in simulation, while water is present implicitly, i.e. described as a continuous dielectric medium. This implicit region can thus be extended significantly, without the increase of the computational costs. The system also exchanges water molecules with the surroundings, which makes the simulation open for water, while the number of salt ions remains constant during the course of simulation. We use the described setup to carry out the simulation of a DNA molecule in aqueous sodium chloride solution at the physiological (0.15 M) and higher (1 M) concentration. We observe that some properties, such as root mean-square displacement and root mean-square fluctuations of the DNA's backbone heavy atoms with respect to the crystal structure, are not affected by the difference in concentration. On the contrary, some properties, such as the charge compensation around the DNA, differ substantially for both cases. OBMD can thus be used to simulate biologically

relevant macromolecules at physiological concentrations of the electrolyte.

[1] R. Delgado-Buscalioni, J. Sablić, and M. Praprotnik, Eur. Phys. J. Special Topics **224**, 2331 (2015).

[2] J. Sablić, M. Praprotnik, and R. Delgado-Buscalioni, Soft Matter **12**, 2416 (2016).

[3] J. Sablić, R. Delgado-Buscalioni, and M. Praprotnik, Soft Matter **13**, 6988 (2017).

[4] J. Zavadlav, J. Sablić, R. Podgornik, and M. Praprotnik, Biophys. J. **114**, 2352 (2018).

Multiscale simulations of DNA aggregation by multivalent ions

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

[1]Department of Materials and Environmental Chemistry, Stockholm University, Stockholm, Sweden

[2]School of Biological Sciences, Nanyang Technological University, Singapore

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 not feasible to achieve due to size and time scale limitations. Here a hierarchical approach for systematic multiscale coarse-grained (CG) is used to simulate DNA phase separation induced by the three-valent cobalt(III)-hexammine ($CoHex^{3+}$). First we parameterized atomistic force field for $CoHex^{3+}$ on the basis of ab-initio simulations data. Using these parameters, we have run atomistic simulations of four 40 bp fragments of DNA in presence of $CoHex^{3+}$ ions and extracted solvent-mediated effective potentials for a CG model of DNA using the Inverse Monte Carlo approach. This approach provides maintaining of the structural properties (radial distribution functions and distributions of intramolecular degrees of freedom) in the CG model compared to the reference (atomistic) model. Simulations of several hundred 100-bp-long CG DNA oligonucleotides in the presence of explicit $CoHex^{3+}$ ions demonstrated aggregation to a liquid crystalline hexagonally ordered phase. These simulations were used as a basis for further coarse-graining resulting in a super-coarse-grained DNA model with implicit solvent and ions. This model allowed us to run simulations of an 10.2-kbp-long DNA, which showed phase separation to either a toroid or a fibre with distinct hexagonal DNA packing in agreement with electron microscopy observations. The mechanism of toroid formation is analysed in detail. The approach used here is based only on the underlying all-atom force field and uses no adjustable parameters and may be generalized to model DNA assembling in chromatin in principle up to chromosome size.

Nucleosome conformational variability in interphase nuclei and in solution explored by cryo-electron microscopy and tomography of vitreous sections

Mikhail Eltsov[1⋆], Diana Grew[1], Françoise Livolant[2], Amélie Leforestier[2]

[1]Buchmann Institute for Molecular Life Sciences, Goethe University, 60438 Frankfurt am Main, Germany

[2]Laboratoire de Physique des Solides, UMR 8502 CNRS, Université Paris-Sud, Université Paris-Saclay, 91405 Orsay Cedex, France

⋆Present address: Abteilung Biophysik, GSI Helmholtzzentrum für Schwerionenforschung GmbH, Planckstraße 1, 64291 Darmstadt, Germany

In most eukaryotic cells, DNA is packed into the chromatin "bead on string" filament. Its basic unit, the nucleosome, is formed by 145-147 bp DNA wrapped into 1.65 turn of a left-handed superhelix around a histone octamer (two copies of H2A, H2B, H3 and H4). Atomic resolution structures of the particle have been obtained from X-ray crystallography or, more recently, from cryo-electron microscopy of identical, symmetric and highly stable engineered particles, which has led, together with a highly conserved structure, to a canonical and static view of the particle. However nucleosomes are now being recognised as pleiomorphic and dynamical entities. They are neither chemically nor structurally homogeneous. Histone variants, post-translational modifications and DNA sequence variability result in structural and dynamical diversity that are documented *in vitro* and *in silico*, but unknown in the cellular context.

Using cryo-electron microscopy and tomography of vitreous sections we investigate the structure and local organisation of nucleosomes in situ, within interphase nuclei of different cell types (human cell lines, *Drosophila* embryo). We visualise individual nucleosomes at a level of detail that allows us to analyse the conformation of the DNA wrapped at their surface. We show that nucleosome conformation is variable and more open than in canonical structures, with an increase of the distance between DNA gyres. These observations are compatible with a "gaping" conformation, proposed to result from fibre compaction by theoretical approaches and detected experimentally *in vitro*, in dilute solutions.

To decipher the mechanisms at work in this conformational variability, we analyse isolated native nucleosomes solubilised at physiologically relevant concentrations (25-50 %) in various ionic environments. We evidence a salt-dependant behaviour, with high salt conformations resembling the canonical crystallographic nucleosome, and low salt ones, more open, being closer to the nucleosome conformation *in situ*. This highlights the role of ionic effects, already known to play a central role at many levels of chromatin

organization (from histone tails that condense or extend, inter-particle interactions, order-disorder transitions and folding of the filament, to phase separation between chromatin compartments or coil-globule transitions of chromosome domains): at the nucleosome level, DNA gyres open or close.

This opens a route to access chromatin structure *in situ* at the nucleosome level. Nucleosomes are known to play a fundamental role not only in genome packaging but also in the regulation of chromatin functions: transcription, replication and repair. Further particle characterisation and cartography are now needed to understanding the relationship between the nucleosome conformational variability and chromatin functional states.

Polymer globules in bulk and in confinement

Stanard Mbebwe Pachong[1], Jan Smrek[2], Kurt Kremer[1]
[1]Max Planck Institute for Polymer Research, Mainz, Germany
[2]University of Vienna, Vienna, Austria

We study static and dynamic properties of ring polymers and globular open chains in bulk and subject to confinement. In bulk systems with up to $N = 1600$ monomers, corresponding to roughly 58 entanglement lengths in a standard polymer melt are investigated. In confinement systems of 46 polymers are considered. Next to equilibrium properties we especially focus on quasi active polymers. Activity is modeled through different bead mobility. Different bead mobility of only a part of the chains leads to symmetry breaking in the dynamics and as a result polymers assume new metastable conformations. Similarities as well as differences to characteristic density maps in cell nuclei are discussed as well.

J. Halverson, J. Smrek, K. Kremer, A. Yu Grosberg, Rep. Prog. Phys. **77**, 022601 (2014)

J. Smrek, K. Kremer, PRL **118**, 098002 (2017)

J. Smrek, K. Kremer, A. Rosa, ACS Macro Lett. **8**, 155 (2019)

Toward controlled self-assembly of peptides

Achille Giacometti
University of Venice, Italy

We discuss the relation between the emergence of new phases with broken symmetry within the framework of simple models of biopolymers. We start with a classic model for a chain molecule of spherical beads tethered together, with the steric constraint that non-consecutive beads cannot overlap, and with a pairwise attractive square well potential accounting for the hydrophobic effect and promoting compaction. We then discuss the consequences of the successive breaking of spurious symmetries. First, we allow the partial interpenetration of consecutive beads. In addition to the standard high temperature coil phase and the low temperature collapsed phase, this results in a new class of marginally compact ground states comprising conformations reminiscent of α-helices and β-sheets, the building blocks of the native states of globular proteins. We then discuss the effect of a further symmetry breaking of the cylindrical symmetry on attaching a side-sphere to the backbone beads along the negative normal of the chain, to mimic the presence of side chains in real proteins. This leads to the emergence of a novel phase within the previously obtained marginally compact phase, with the appearance of more complex secondary structure assemblies. The potential importance of this new phase in the de novo design of self-assembled peptides is highlighted.

DNA without DNA: Watson-Crick selectivity controls the self-assembly of mononucleotides

Tommaso Fraccia[1], Marco Todisco[1], Giuliano Zanchetta[1], Greg Smith[2], Noel Clark[2], Tommaso Bellini[1]

[1]Dept. of Medical Biotechnology, Università di Milano, Italy
[2]Dept. of Physics, University Colorado Boulder, USA

The transfer and memory of genetic information relies on Watson-Crick selective base pairing of DNA and RNA chains, universally considered a defining characteristic of these polymers. We found that the self-assembly of mononucleotides triphosphates (NTP) into columnar chromonic liquid crystal (LC) phases retains the same selectivity: among all solutions of adenosine, cytosine, guanine and thymine NTPs and their mixtures, liquid crystal ordering is found only in the A-T and C-G combinations. X-ray diffraction demonstrates that these phases are formed by columnar stacks of paired bases, a geometry that closely resembles the famed double helical structure. In stoichiometrically unbalanced mixtures, the system phase separates, expelling unpaired bases from the LC matrix, thus providing a molecular selection mechanics [1].

In parallel, we have found that LC ordering of DNA and RNA oligomers has a significant effect on the chemical binding of their terminals: the ligation rates are boosted, and the resulting elongated chains are linear, while the formation of circular chains is dominant in isotropic media [2,3].

The combination of these results suggests that NTP could spontaneously polymerize when prompted by their LC ordering. If this were true, DNA and RNA would emerge as a bona fide "self-synthesizing material", i.e. a system that catalyzes the formation of molecules that stabilize their own structure [4]. We are currently testing this notion.

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Spontaneous domain formation in spherically-confined elastic filaments

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Although the free energy of a genome packing into a virus is dominated by DNA-DNA interactions, ordering of the DNA inside the capsid is elasticity-driven, suggesting general solutions with DNA organized into spool-like domains. Using analytical calculations and replica exchange molecular dynamics simulations of a long elastic filament confined in a spherical container, we show that the ground state is not a single inverted spool as assumed hitherto, but an ordering mosaic of multiple homogeneously-ordered domains. At low densities, we observe concentric spools, while at higher densities, other morphologies come into play, such as twisted tori and "Hopf links". We discuss our results in the context of metallic wires, viral DNA, and flexible polymers.

How to model DNA translocation through nanopores – A multiscale simulational exploration

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In this talk I will describe our efforts to understand the current modulations that a double-stranded DNA will produce when it translocates in an electrolyte bath of varying concentration through a nanopore device via an externally applied electric field.

The complete understanding of this electrokinetic process is important to develop novel DNA sequencing tools, or to use the nanopore as a sensor device for various macromolecular analytes. There are by now already commercial applications of such nanosequencers available.

Understanding can be gained on various length scales, and to this end we will start with atomistic simulations of dsDNA in explicit water. The comparison with experimental results helped us in constructing an accurate electrokinetic coarse-grained model for dsDNA. Going to even larger length scales requires the usage of continuum theories which can help us to understand the electrokinetic transport of charged macromolecules through millimetre long glas nanocapillaries.

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Effect of knots during viral DNA packaging and ejection

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DNA of even small viruses, such as the P4 bacteriophage, is inevitably knotted due to its high packing density inside the viral capsid [1-2]. It has long been recognised that the type and abundance of such knots are reflective of how the DNA is arranged inside the capsid, though obtaining a quantitative agreement of the knot spectrum from models with that of experiment has proved challenging. In addition, how exactly the knotting of DNA inside viral capsids could still allow for the ejection of the genome through the narrow tail has long been an open problem. I will discuss how coarse-grained models with increasing level of structural detail can shed light on both aspects [3-5].

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Density-nematic coupling in isotropic linear polymers: acoustic and osmotic birefringence

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Linear polymers and other connected "line liquids" exhibit a geometrical coupling between density and equilibrium nematic order on the macroscopic level that gives rise to a Meyer-de Gennes vectorial conservation law [1-4] for polar orientational order, or its amended version for apolar nematic order when described as "recovered" polar order [5]. They generally exhibit fluctuations of orientational order, starting with its lowest moment, the polar order, which in the isotropic phase is geometrically decoupled from density. As a contrast, quadrupolar (nematic) orientational fluctuations are inherently coupled to density fluctuations already in the isotropic system and not subject to the existence of an orientational phase transition. To capture this, it takes the tensorial description of the nematic order, leading to a geometrical coupling between density and orientational order in the form of a tensorial conservation law [6,7]. This coupling implies that a spatial variation of density or a local concentration gradient will induce nematic order and thereby an acoustic or osmotic optical birefringence even in an otherwise isotropic polymer melt/solution [7]. The theoretical conceptions are validated by performing detailed Monte Carlo simulations of isotropic melts of "soft" worm-like chains with variable length and flexibility, and comparing the numerically determined orientation correlation functions with predictions of the macroscopic theory [7]. This also exposits a means of determining the macroscopic parameters by microscopic simulations to yield realistic continuum models of specific polymeric materials.

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Homology recognition without proteins [DNA sequence-structure relationship, helical coherence, and a universal homology recognition mechanism-theory vs experiments]

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Recognition of homologous genes prior genetic recombination is one of the remaining mysteries of molecular biology [1,2,3]. This talk will overview the principles of earlier suggested "universal" (sequence-nonspecific) snapshot gene-gene homology recognition mechanism, based on commensurability-incommensurability of sequence related helical charge motifs on the interacting DNA [4,5,6,7,8,9,10,11] and the key experimental evidences of protein-free DNA-DNA recognition at the molecular level [12,13,14,15,16].

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From chromosome territories to ring polymers: Physical properties of untangled polymer melts

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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.

"Genetics" in two dimensions: DNA base pairing in thin surface films

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Due to their specific binding and molecular recognition properties, building blocks of DNA are very interesting as components for constructing single- and multi-layer supramolecular surface architectures. Such architectures can be formed from lipophilic nucleoside derivatives by the use of the Langmuir-Blodgett (LB) technique. Our recent studies of self-assembly of different nucleoside derivatives in Langmuir films at the air-water interface reveal that guanosine derivatives exhibit very distinctive behaviour from analogous derivatives containing other nucleobases (Fig. 1) [1]. They also demonstrate that the number of lipophilic chains attached to the sugar hydroxyl groups affects the assembly much stronger than the length of these chains [2,3]. Besides this, important factors for surface self-assembly are the type and concentration of ions present in the water subphase [4]. All the above mentioned features provide effective methods for tuning intermolecular organization of DNA nucleosides in thin film configurations.

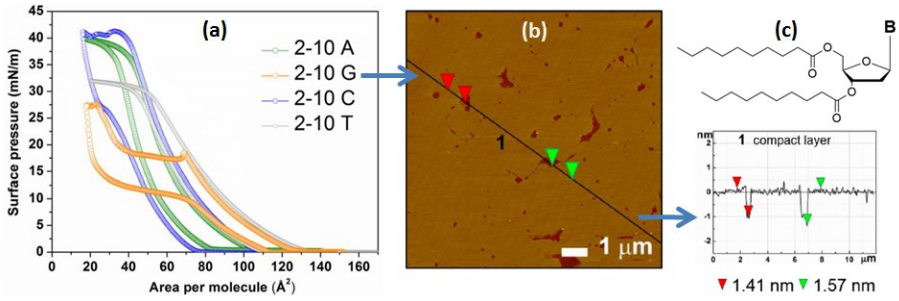

Figure 1: (a) Surface pressure versus molecular area isotherms of different nucleoside derivatives with two hydrocarbon tails. (b) AFM image of the LB film of guanosine derivative deposited onto mica surface. (c) Molecular structure of derivatives with two hydrocarbon tails (B denotes nucleobase: A, G, C or T).

We also investigated mixed Langmuir films composed of nucleosides of different nucleobases to elucidate base pairing "rules" in such films. Due to

steric restrictions for nucleobase orientation imposed by the air-water interface, those rules can be quite different from the highly selective C-G and A-T base pairing known in 3D systems. The observations suggest that in 2D layers the selectivity (recognition)between "complemetary bases" is less profound [5]. To resolve in-situ the formation and possible breakage of hydrogen bonds in such films, we developed an optical detection method based on azofunctionalised guanosine derivatives in which the trans-cis isomerisation and the cis-trans back-isomerisation can be induced by irradiation with UV and blue light, respectively (Fig. 2). The typical time for the spontaneous trans-cis back-isomerization (at room temperature) of the investigated derivatives is around 12 hours, which provides sufficient time for experiments with irradiation taking place either prior to deposition of the material on water surface or during any phase of the compression/expansion cycle. The isomerization causes changes in the surface pressure of the film, which were analysed within the theoretical model based on the 2D Van der Waals equation of state. For mixed films of guanosine and cytidine derivatives, the analysis revealed a significant modification of the strength of intermolecular interaction caused by the optical irradiation, while no such modifications were identified in mixed films involving other nucleobases. The difference is attributed to light-induced breaking of the hydrogen bonding that is established only between the G-C base pairs. Our results demonstrate that photosensitive nucleoside derivatives can be used as an efficient probe of base-pairing in Langmuir monolayers [6].

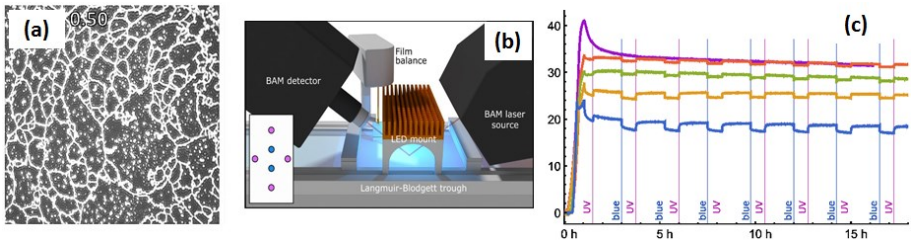

Figure 2: (a) BAM image of surface structure of a mixed film from Azo-G and C derivatives at the air-water interface. (b) Schematic drawing of experimental setup for optical irradiation of the film. (c) Photo-induced modifications of surface pressure observed in films with different proportions of photo-sensitive guanosine derivatives.

Acknowledgments

We acknowledge the financial support of Slovenian Research Agency (ARRS) in the framework of research program P1-0192 and research project J7-9399. We thank also the University of Bologna (RFO) for financial support.

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Atomistic MD simulations as a tool to elucidate mechanical properties of DNA/RNA systems

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Using atomistic simulations together with experimental techniques like neutron scattering and electron microscopy is of great importance in molecular biophysics because such an approach provides a complementary information about structural and dynamical details of biological systems. Several examples of application of classical force-field MD simulations to the interpretation of experimental data are examined and the resulting ideas on the general characteristics of bio-molecular motions discussed in terms of their functional implications.

As an example we demonstrate the DNA neutron scattering experimental data is interpreted with the aid of MD simulations and large scale, all-atom, phonon calculations opening a view into the stiffness of DNA and its structural integrity on different length scales. Another example referring to the electron microscopy data reveal the role of the single stranded RNA for helical architecture of Potato Virus Y (PVY).

DNA-based dendrimers: From a single molecule to the dense solution description

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We present a joint theoretical-experimental study of a novel class of macromolecules, the so-called DNA-based dendrimers. They have recently been synthesized from the enzymatic ligation of Y-shaped DNA unit, a three-armed structure consisting of double-stranded DNA (ds-DNA), formed via hybridization of three single-stranded DNA chains (ss-DNA), each of which has partially complementary sequences to the other two [1]. In order to describe such dendrimers of various generations we have employed two independent models: a bead-spring model and the oxDNA model. In the bead-spring model, base-pairs of a single DL-DNA molecule are modeled by charged monomers, whose interactions are chosen to mimic the equilibrium properties of DNA correctly. On the other hand, the oxDNA model allows us to take a closer look into the DNA structure, treating DNA as a string of rigid nucleotides which interact through potentials that depend on the position and orientation of the nucleotides. We have performed Molecular Dynamics Simulations and we have also employed dynamic/static light scattering in order to determine equillibrium properties and conformational characteristics of all-DNA dendrimers as well as the behavior of their solutions. We have investigated their behavior in ionic solution, paying particular attention on their salt-responsiveness. Our computational and experimental results reveal that the DL-DNA are rigid objects with low internal monomer concentration, regular voids in their interior, with high persentage of absorbed counterions, and that show high resistance to stimuli-responsiveness [2]. These properties shape the behaviour of their solutions. Namely, both experimental as well as computational results show anomalous structure factor of dense DL-DNA solutions, as it had been predicted theoreticaly in Ref [3]. In this way we have found the object which was a missing puzzle in understanding the full phase diagram of star polymer solutions.

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Free energy landscapes for dendrimer-like DNAs via neural networks

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We consider dendrimer-like DNAs (DL-DNAs, as thoroughly discussed in the contribution by Natasa Adžić) [1] which we model within a monomeric bead-spring model: the DNA base-pairs are modeled by charged monomers and their interactions are chosen to mimic the equilibrium properties of DNA correctly [2].

The huge number of internal degrees of freedom of this model drastically limits its use in simulations of concentrated solutions: even with the use of optimized code packages (such as GROMACS, ESPResSo MD, LAMMPS or oxDNA) simulations of ensembles of typically 50 (or at most 100 DL-DNAs) are within reach.

This limitation calls for suitable strategies to cope with this problem: one standard route is the use of effective potentials obtained by suitably integrating over the degrees of freedom of the monomeric entities. Here we represent such effective potentials with artificial neural networks,relying on their capacity to accurately reproduce complex high-dimensional functions. Once properly trained with reference data calculated via the monomeric model, neural networks provide access to effective potential energies and analytically derived forces, which can then be used in molecular dynamics simulations. The latter ones can be performed for our system at a fraction of computational costs as compared to the simulations of the monomeric model. In this contribution we report about first results of these investigations. Recently, Luo and his co-workers at Cornell University synthesized dendrimer-like DNA (DL-DNA) via enzymatic ligation of Y-shaped DNA building blocks.

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Abstracts – contributed lectures

Analysis structures and forces defining chromatin condensation

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In living cells, the natural polyelectrolyte, DNA, is densely packed into chromatin, a linear array of DNA-histone complexes, nucleosomes. Using experimental and computer modelling approaches we study formation, folding and aggregation of the nucleosomes and nucleosome arrays formed either by DNA with high positioning histone specificity ("601" Widom DNA) or by repetitive human telomeric sequences, $(TTAGGG)_n$, which has one of the lowest known affinities for the histone octamer. Both sorts of DNA form nucleosome core particles (NCPs) and nucleosome arrays. The structure, stability, folding, self-association and other biophysical properties of nucleosome arrays with the 601 or the telomeric DNAs were studied by single molecule magnetic tweezers, and other techniques.

Higher order (beyond nucleosome) chromatin compaction is driven by the energetically favourable interaction between NCPs. Close NCP-NCP contact, stacking, is a primary structural element of condensed chromatin. We study molecular structure of stacked NCPs as well as the nature and scale of the forces involved in its formation. A set of parameters (NCP-NCP distance, shift, rise, tilt, and others) is proposed that allows numerical description of the mutual positions of the NCPs in condensed chromatin. Geometry of the NCP-NCP contacts in the published crystal and cryoEM structures were analysed and statistics of the parameters defining the stacking was determined. In addition, coarse grained (CG) molecular dynamics simulations modelling NCP condensation were carried out. The CG modelling takes into account details of the nucleosome structure and adequately describes the long range electrostatic forces as well as excluded volume effects acting in chromatin. CG simulations showed good agreement with experimental data and reveal the importance of the H2A and H4 tail bridging and screening as well as tail-tail correlations in stabilization of the NCP stacking.

Genetic outbreak from the endosome: A molecular perspective on gene therapy

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The use of non-viral vectors for in vivo gene therapy could drastically increase safety, whilst reducing the cost of preparing the vectors. However, the transfection rates of non-viral vectors are low compared to their viral counterpart. A promising approach to non-viral vectors makes use of DNA/cationic liposome complexes (lipoplexes) to deliver the genetic material. For such lipoplexes it is of utmost importance to escape the endosome before the genetic material gets degraded in the lysosome. The molecular details on how genetic material escapes the lipoplex and endosome are poorly resolved. Here we use coarse-grained molecular dynamics simulations to show the molecular mechanism underlying efficient gene transfer from lipoplexes. Our computational fusion experiments of lipoplexes with endosomal membrane models show that there are two distinct modes of transfection: parallel and perpendicular. In the parallel fusion pathway, DNA aligns with the membrane surface, showing very quick release of genetic material shortly after the initial fusion pore is formed. In the perpendicular pathway, DNA instead aligns with the membrane normal. This pathway also leads to transfection, but release is slower. We further show that the composition and size of the lipoplex, as well as the lipid composition of the endosomal membrane, have a significant impact on fusion efficiency. Our results provide a key understanding to the molecular mechanism of lipoplex mediated gene transfection, and contribute to a more rational design of these type of transfection vectors.

Multiscale simulations of double-stranded DNA with sequence-dependent mechanical and conformational properties

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We will discuss past and current work in our group focused on the dependence of mechanical and conformational properties of double-stranded DNA (dsDNA) on its sequence. This includes results from all-atom simulations, where stretching and torsional moduli were estimated together with their coupling. From a conformational perspective, we will discuss our recent findings from systematic all-atom simulations with different sequences, which unveiled the mechanisms underlying stretching of dsDNA and enabled a direct mapping between the local curvature of the helical axis, as quantified by the crookedness, and the corresponding elastic constant. Finally, preliminary results on a coarse grained approach based on these simulations will be presented, which may potentially enable the simulation of large dsDNA molecules with a detailed account of local mechanical and conformational properties.

Dynamics and organization of cyclic polymers melt in a confinement

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Chromosomes' large scale organization is a beautiful interplay between Physics and Biology. The field of epigenetics shows that the gene expression can be altered without changing the underlying DNA sequence [1]. This has given rise to independent lines of investigations and new models. Starting here with a fairly simple model to mimic the nucleus of the eukaryotic cell, we use temperature as a parameter to repress/enhance genes activity. We show that the idea of active segregation is consistent with the real cell nucleus [2]. The dynamics and the size analysis indicate that the chain swells when a part of it is activated. This eventually leads to a slower diffusion of the chain compared to its counterpart chain with all genes repressed. The structural organization of the chains within the confined sphere reveals a fairly good organization of chains maintained for long time intervals between the configurations as predicted by Fluorescent spectroscopy experiment performed on chromosomes during interphase [3].

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Aqueous nanoclusters govern ion partitioning in dense thermoresponsive polymer membranes

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The uptake and sorption of charged molecules by responsive polymer membranes and hydrogels in aqueous solution is of key importance for the development of soft functional materials, e.g., for biomedical applications. Here we investigate the partitioning of simple monoatomic and molecular ions within a dense, electroneutral PNIPAM membrane using explicit water molecular dynamics simulations. Inside the rather hydrophobic environment we find that water distributes very heterogeneously in a percolating network of polydisperse water nanoclusters. The average cluster size determines the mean electrostatic self-energy of the simple ions, which preferably locate deep inside the high-dielectric clusters; we therefore find substantially larger partition ratios, $K \simeq 0.1$ than expected from a simple Born picture using a uniform dielectric constant. In spite of their irregularities of shapes and sizes we observe that the water clusters possess a universal negative electrostatic potential with respect to their surrounding, as is known for aqueous liquid-vapor interfaces. This potential, which we find concealed in cases of symmetric monoatomic salts, can dramatically impact the transfer free energies of larger charged molecules because of their weak hydration and increased affinity to interfaces. As a consequence, and in stark contrast to the simple ions, the molecular ions can have a partition ratio much larger than unity, typically $K > 10$ (depending on the cation type). These results also suggest that ionizing a molecule can even enhance the partitioning in a collapsed, rather hydrophobic gel, which strongly challenges the traditional simplistic reasoning.


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