The Abdus Salam
International Centre for Theoretical Physics

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smr2038

CONFERENCE:
From DNA-Inspired Physics to Physics-Inspired Biology
(1 - 5 June 2009)

(Miramare, Trieste, Italy)

(co-sponsored by: Wellcome Trust, London, U.K.)

ORGANIZERS:

A.A. KORNYSHEV	Imperial College London, UK
W.K. OLSON	Rutgers University, NJ, USA
V.A. PARSEGIAN	NIH, Bethesda, USA

LOCAL ORGANIZER:

R. GEBAUER	the Abdus Salam International Centre for Theoretical Physics, Trieste, Italy

BOOK OF ABSTRACTS

web-page: http://agenda.ictp.trieste.it/smr.php?2038

P R E F A C E

Modern theoretical physics methods have already penetrated into many areas of DNA research. The main goal of this conference is to highlight these achievements, and not only to expose them to colleagues - biophysicists, but also to inform a group of interested biologists about the findings obtained by physicists. On this two-way road the task is also to obtain an update from these biologists about the most challenging issues in their research disciplines.

The sessions are topically structured, each gathering presentations on -

DNA mechanics
DNA structure, interactions and aggregation
Recognition of homologous genes
Conformational dynamics, supercoiling and packing (including packing in virusus and in chromatin)
DNA-protein interaction and recognition
DNA in confinement (including pores and gene delivery vesicles)
Smart DNA based systems, including switches, nano-robots and liquid crystals

Invited shorter talks are in no way less important than the longer ones: they are intended to highlight hot, specific results. The compact poster fair will make it possible to devote maximal attention to the contributed results and to have intensive informal interactions with the presenters. This booklet contains the abstracts of both the oral and the poster presentations.

We acknowledge and give thanks to our co-sponsors Wellcome Trust for their kind contribution towards this event.

The Organizers wish you a most exciting and enjoyable conference.

Alexei A. Kornyshev
Wilma K. Olson
Adrian Parsegian
Ralf Gebauer
Doreen Sauleek

PROGRAMME

(as of 25 May 2009)

printed on:1st Jun 2009

The Abdus Salam
International Centre for Theoretical Physics

Conference: From DNA-Inspired Physics to Physics-Inspired Biology

Cosponsor(s): co-sponsored by: Wellcome Trust, London, U.K.
Organizer(s): Directors: A.A. Kornyshev, W.K. Olson, V.A. Parsegian. Local Organizer: R. Gebauer
Trieste - Italy, 01 - 05 June 2009

Venue: Leonardo da Vinci Building Main Lecture Hall

Programme

MONDAY, 1 JUNE 2009 (Room:Leonardo da Vinci Building Main Lecture Hall)

1 June 2009

08:30 - 09:30 --- REGISTRATION / ADMINISTRATIVE FORMALITIES ---
(Leonardo da Vinci Building - reception area)

09:30 - 10:50 **SESSION 1 - OPENING SESSION**
CHAIR: Alexei KORNYSHEV Greetings from ICTP

09:35 - 09:50 **Alexei KORNYSHEV** / *Imperial College London, U.K.*
Preamble: can one always judge the book by its cover?

09:50 - 10:20 **Arturo FALASCHI** / *SNS, Pisa & ICGE, Trieste, Italy*
From disciplinary borders to frontiers of science

10:20 - 10:50 **Lynn ZECHIEDRICH** / *Baylor College, Houston, U.S.A.*
The devil in the details: how DNA structure, sequence and counterions drive biology

10:50 - 11:20 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

11:20 - 12:50 **SESSION 2 - DNA MECHANICS**
CHAIR: Jorge LANGOWSKI

11:20 - 11:50 **Jim MAHER** / *Mayo Clinic College, Rochester, U.S.A.*
Approaches to understanding the origin and management of DNA stiffness

11:50 - 12:20 **Wilma OLSON** / *Rutgers University, U.S.A.*
DNA micromechanics and macromolecular organization

12:20 - 12:50 **Piotr MARSZALEK** / *Duke University, Durham, U.S.A.*
Nanomechanics of single and double stranded DNA

12:50 - 15:00 (Room: Leonardo da Vinci Building Cafeteria)
--- Lunch Break ---

15:00 - 16:00 **SESSION 3 - DNA MECHANICS**
CHAIR: Jorge LANGOWSKI

15:00 - 15:30 **John MADDOCKS** / *EPFL, Lausanne, Switzerland*
Multi-scale modelling of sequence-dependent DNA mechanics

15:30 - 16:00 **Evgueni STAROSTIN** / *University College London, U.K.*
Geometry and mechanics of condensed DNA: Toroids and beyond

16:00 - 16:30 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

16:30 - 18:15 **SESSION 4 - DNA STRUCTURE, INTERACTIONS AND AGGREGATION**
CHAIR: Adrian PARSEGIAN

16:30 - 17:00 **Sergey LEIKIN** / *NIH, Bethesda, U.S.A.*
Electrostatic interactions between DNA double helices

17:00 - 17:30 **Rudi PODGORNIK** / *University of Ljubljana, Slovenia*
Generalizations and ramifications induced by counterion structure in the strong and weak-coupling electrostatic interactions between macromolecules

17:30 - 18:00 **Brian TODD** / *Purdue University, West Lafayette, U.S.A.*
Counterion-mediated DNA-DNA interactions

18:00 - 18:15 **Aaron WYNVEEN** / *University of Duesseldorf, Germany*
Correlations and helical coherence in DNA structure: "straightening" the helix upon crystal packing

19:00 - 21:00 (Room: Leonardo da Vinci Building Terrace)
--- WELCOME RECEPTION ---

TUESDAY, 2 JUNE 2009 (Room:Leonardo da Vinci Building Main Lecture Hall) (**Republic's Day**)

2 June 2009

09:00 - 10:30 **SESSION 5 - DNA STRUCTURE, INTERACTIONS AND AGGREGATION**
CHAIR: Richard LAVERY

09:00 - 09:30 **Malek KHAN** / *Uppsala University, Sweden*
Simulations of DNA condensation

09:30 - 09:45 **Sergei GAVRYUSHOV** / *RAS, Engelhardt Institute of Molecular Biology, Moscow, Russia*
Mediating role of Alkaline earth metal ions in electrostatics of DNA: The long-range effects of solvent dielectric saturation

09:45 - 10:00 **Dominic LEE** / *Max-Planck-Institute for Complex Systems, Dresden, Germany*
How does helical structure influence correlation forces between DNA?

10:00 - 10:15 **Giovanni DIETLER** / *EPFL, Laussane, Switzerland*
DNA from the polymer physics point of view: Topology and dimensionality effects

10:15 - 10:30 **Ioulia ROUZINA** / *University of Minnesota, Minneapolis, U.S.A.*
Kinetics of force-induced DNA melting

10:30 - 11:00 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

11:00 - 12:45 **SESSION 6 - RECOGNITION OF HOMOLOGOUS GENES**
CHAIR: Jim MAHER

11:00 - 11:30 **Adi BARZEL** / *University of Tel Aviv, Israel*
How can two homologous needles find each other in the genomic haystack?

11:30 - 12:00 **Geoff BALDWIN** / *Imperial College London, U.K.*
Is recognition between homologous DNA double helices an intrinsic property of DNA?

12:00 - 12:30 **Mara PRENTISS** / *Harvard University, Cambridge, U.S.A.*
Single molecule studies of homolog pairing

12:30 - 12:45 **Alexei KORNYSHEV** / *Imperial College London, U.K.*
Homology recognition funnel

12:45 - 15:00 (Room: Leonardo da Vinci Building Cafeteria)
--- Lunch Break ---

15:00 - 18:30 **SESSION 7 - CONFORMATIONAL DYNAMICS, SUPERCOILING AND PACKING**
CHAIR: David BENSIMON

15:00 - 15:30 **Adam COHEN** / *Harvard University, Cambridge, U.S.A.*
Conformation and dynamics of single molecules of DNA in solution

15:30 - 16:00 **Aurelien CRUT** / *LASIM, Villeurbanne, France*
Dynamics of supercoiled DNA: some recent insights from single-molecule experiments

16:00 - 16:30 **Avinoam BEN-SHAUL** / *Hebrew University of Jerusalem, Israel*
Compactness and apparent circularization of ssRNA

16:30 - 17:00 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

17:00 - 17:30 **Laura FINZI** / *Emory University, Atlanta, U.S.A.*
DNA supercoiling and the lambda bacteriophage epigenetic switch

17:30 - 18:00 **Sarah HARRIS** / *University of Leeds, U.K.*
Computer simulations of DNA supercoiling at the atomic level

18:00 - 18:30 **Remus DAME** / *Leiden University, Leiden & VU, Amsterdam, The Netherlands*
Unravelling the organization of bacterial chromatin

WEDNESDAY, 3 JUNE 2009 (Room:Leonardo da Vinci Building Main Lecture Hall)

09:00 - 12:30 **SESSION 8 - CONFORMATIONAL DYNAMICS, SUPERCOILING AND PACKING**
CHAIR: Wilma OLSON

09:00 - 09:30 **Andrew TRAVERS** / *MRC-LMB, Cambridge, U.K.*
The organization and topology of chromatin

09:30 - 10:00 **Helmut SCHIESSEL** / *University of Leiden, The Netherlands*
Stacking plates and wedges: the physics of DNA compaction

10:00 - 10:30 **Jorg LANGOWSKI** / *GSRC, Heidelberg, Germany*
DNA and chromatin dynamics studied by single molecule methods and computer modelling

10:30 - 11:00 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

11:00 - 11:30 **David BENSIMON** / *ENS, Paris, France*
DNA, chromatin and remodeling factors

11:30 - 12:00 **James KADONAGA** / *UCSD, La Jolla, U.S.A.*
DNA and chromatin dynamics: Discovery of a novel ATP-dependent DNA rewinding motor

12:00 - 12:30 **Lars NORDENSKIOLD** / *Nanyang Technological University, Singapore*
Modelling chromatin with explicit ions: ion correlation effects and like charge attraction. Comparison with new experiments

12:30 - 12:45 **Maria BARBI** / *Universite Pierre et Marie Curie, Paris,France*
Modeling the hysteretic behavior of chromatin fibers under magnetic tweezers: why are nucleosomes left handed?

12:45 - 15:00 (Room: Leonardo da Vinci Building Cafeteria)
--- Lunch Break ---

15:00 - 16:30 **SESSION 9 - DNA COMPACTIZATION IN VIRUSES**
CHAIR: Helmut SCHIESSEL

15:00 - 15:30 **William GELBART** / *UCLA, Los Angeles, U.S.A.*
DNA ejection from bacterial and mammalian viruses

15:30 - 16:00 **Murugappan MUTHUKUMAR** / *University of Massachusetts, Amherst, U.S.A.*
Menagerie of viruses: diverse chemical sequences or simple electrostatics?

16:00 - 16:30 **Francoise LIVOLANT** / *CNRS, Orsay, France*
DNA structure and phase transitions in the bacteriophage capsid

16:30 - 17:00 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

17:00 - 18:00 **SESSION 10 - FEATURE PRESENTATION**
CHAIR: Helmut SCHIESSEL

17:00 - 17:30 **Rudolf ROEMER** / *University of Warwick, Coventry, U.K.*
Charge transport of cancer-related genes

17:30 - 19:30 (Room: Leonardo da Vinci Building, Lobby)
POSTER FAIR - Wellcome Trust Prizes for the best works of young participants
POSTER GALLERY (behind the Main Lecture Hall) refreshments available

THURSDAY, 4 JUNE 2009 (Room:Leonardo da Vinci Building Main Lecture Hall)

4 June 2009

09:00 - 13:00 **SESSION 11 - DNA-PROTEIN INTERACTION AND RECOGNITION**
CHAIR: Laura FINZI

09:00 - 09:30 **Loren WILLIAMS** / *Georgia Tech., Atlanta, U.S.A.*
Mechanisms of direct and indirect readout

09:30 - 10:00 **Gijs WUITE** / *VU, Amsterdam, The Netherlands*
A singular view of DNA transactions

10:00 - 10:30 **Ching-Hwa KIANG** / *Rice University, Houston, U.S.A.*
Single-molecule manipulation of DNA

10:30 - 11:00 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

11:00 - 11:30 **Richard LAVERY** / *BCP, Lyon, France*
DNA mechanics and protein-DNA recognition

11:30 - 12:00 **Anatoly KOLOMEISKY** / *Rice University, Houston, U.S.A.*
How proteins find their Targets on DNA

12:00 - 12:30 **Michael SCHURR** / *University of Washington, Seattle, U.S.A.*
Topoisomerase I equilibrates metastable secondary structure in relaxed supercoiled DNA's

12:30 - 12:45 **Yitzhak RABIN** / *Bar Ilan University, Ramat-Gan, Israel*
Binding of HU-proteins and DNA elasticity

12:45 - 13:00 **Luke CZAPLA** / *University of Uppsala, Sweden*
The effect of HU on DNA looping

13:00 - 14:30 (Room: Leonardo da Vinci Building Cafeteria)
--- Lunch Break ---

14:30 - 18:30 **Group and Project Meetings Networking**

18:30 - 22:30 --- CONFERENCE DINNER ---

FRIDAY, 5 JUNE 2009 (Room:Leonardo da Vinci Building Main Lecture Hall)

5 June 2009

09:00 - 12:00 **SESSION 12 - DNA IN CONFINEMENT**
CHAIR: Sergey LEIKIN

09:00 - 09:30 **Theo ODIJIK** / *TU Delft, The Netherlands*
Subtitles of nanoconfined DNA
(talk presented by Marc EMANUEL)

09:30 - 10:00 **Amit MELLER** / *Boston University, U.S.A.*
DNA capture in nanoscale pores - How does it happen?

10:00 - 10:30 **Serge LEMAY** / *TU Delft, The Netherlands*
Origin of the electrophoretic force on DNA in solid state nanopores

10:30 - 11:00 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

11:00 - 11:30 **Yan LEVIN** / *IF-UFRGS, Porto Alegre, Brazil*
Amphiphile-DNA complexes: adsorption, delivery and release

11:30 - 12:00 **Stephen GRILL** / *Max-Planck-Institute for Complex Systems, Dresden, Germany*
Backtracking by RNA polymerase: single molecule experiments vs theory

12:00 - 14:30 (Room: Leonardo da Vinci Building Cafeteria)
--- Lunch Break ---

14:30 - 16:00 **SESSION 13 - SMART DNA**
CHAIR: Rudi PODGORNIK

14:30 - 15:00 **Milan STOJANOVIC** / *Columbia University, New York, U.S.A.*
What is it like to be a molecular robot based on DNA?

15:00 - 15:30 **Andrew MOUNT** / *University of Edinburgh, U.K.*
Synthetic DNA Holliday junctions as controllable nanoswitch systems

15:30 - 16:00 **Mikhail OSIPOV** / *University of Stratchclyde, U.K.*
On the theory of cholesteric ordering in solutions of macromolecules

16:00 - 16:30 (Room: Leonardo da Vinci Building, Lobby)
--- Coffee Break ---

16:30 - 18:15 **SESSION 14 - PANEL-LED GENERAL DISCUSSION**
PANEL CHAIR: Adrian PARSEGIAN PANEL MEMBERS - T.B.C.

18:15 - 18:30 **CLOSING SESSION**

ABSTRACTS

OF

INVITED TALKS

(in order of presentation, as per programme updated 25 May 2009)

MONDAY, 1JUNE 2009

(updated as of 25 May 2009)

web-page: http://agenda.ictp.trieste.it/smr.php/2038

Arturo FALASCHI
(Scuola Normale Superiore, Pisa and International Centre for Genetic Engineering and Biotechnology, Trieste, Italy)

From disciplinary borders to frontiers of science

The triumphal march of molecular biology in the last decades has amply demonstrated that biology has to be considered a "hard" science, having shed the wrong image of a refined "stamp collecting" practice, still present among certified hard scientists in the first half of the previous century. For this remarkable success, the credit must be especially given to the marriage of biology with other scientific disciplines, starting with physics, a marriage impersonated by the very discoverers of the structure of DNA, the achievement that has opened the door to the tumultuous developments of the following decades. Many other examples could be given, but there is no doubt that biology today absolutely requires contamination with physics, chemistry, physical chemistry, mathematics, informatics, etc.. As examples of this requirement, we can consider the possibility of analysing single molecules in their *in vivo* context thanks to the progress of photonics, or in an *in vitro* one, through the use of optical or magnetic tweezers; the *a priori* prediction of protein structure and function, coupled to the refinements of the molecular dynamics approach; the challenge to informatics given by the exponentially growing wealth of genome sequences and the need to distil from them well-grounded concepts of genotype/phenotype relationships and on the process of biological evolution.

These requirements have brought the "Human Frontier Science Progress Organization", that in the last twenty years has promoted research and scientists at the frontier between the life sciences and other scientific disciplines, to launch a new scientific publication, the HFSP Journal, which aims precisely at transforming the borders between scientific disciplines into frontiers of scientific progress, striving to create what ha been defined in the past by P. Galison, "a new mode of producing scientific knowledge".

The hope of the HFSP Journal is also that of facing the novel challenges arising from the very success of molecular biology, namely the inundation of data, structures, "omics", that risks to create a blurred landscape where biology risks to return, through all these technical triumphs, back to stamp collecting. There is here a challenge to identify the possible emergence of novel, organising principles that might be at work at the mesoscopic scale, between the atoms and the visible world, that may offer a new interpretive landscape emerging from the collective phenomena. This search for emerging "new laws" is by definition an interdisciplinary exploration, for which the trained mind of physicists may offer the necessary insights.

In the last part of my intervention, I intend to give a brief report of the efforts of my research groups in the last decade to understand, exploiting also fluorescence transfer methodologies, the molecular and submolecular interactions underlying the process of regulation of human DNA replication.

THE DEVIL IN THE DETAILS: HOW DNA STRUCTURE, SEQUENCE, AND COUNTERIONS DRIVE BIOLOGY

Jonathan M. Fogg[1], Graham L. Randall[2], Daniel J. Catanese, Jr.[1], B. Montgomery Pettitt[2], and Lynn Zechiedrich[1,2]

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Most of what we know about the physical parameters of DNA derives from atomic structures and biophysical manipulations of DNA in its linear duplex form. This form of DNA is inert in cells and the measurements of bending rigidity, free energy, *etc.*, which are all derived from studies of the linear form *in silico* or in a test tube, are not applicable. Instead, DNA is maintained in a globally underwound conformation surrounded by counterions, proteins, and membranes. It is frequently separated into single strands. Thus, the linking number (*Lk*) of DNA is lower than that of linear DNA. ΔLk can be manifest as twist and writhe by the well-known equation $\Delta Lk = \Delta Tw + Wr$. Transiently, waves of extreme DNA underwinding and overwinding are generated during its replication, transcription, repair, and recombination. Depending upon the specific DNA metabolic event, these torsional stresses are either constrained, and therefore not allowed to writhe, or unconstrained, and writhed. Additionally, and importantly, DNA in cells contains no free ends. We have probed, using a combination of molecular dynamics simulations and biophysical characterizations, the effects of underwinding and overwinding DNA on its structure and how this structure influences counterions and protein recognition. We find dramatic sequence-dependent alterations in structure that alter the counterion distributions leading us to hypothesize the manifestation of these changes drives DNA replication, transcription, repair, and recombination. For an introduction to this topic, please see:

1. Fogg, J. M., Catanese, D. J., Jr., Randall, G. L., Swick, M. C., and Zechiedrich, L. (2009). Differences between positively and negatively supercoiled DNA that topoisomerases may distinguish. *Proc. Institute Math. App.* **150**, 73-123 in *Mathematics of DNA Structure, Function, and Interactions* (Benham, C.J., Harvey, S., Olson, W.K., De Witt L. Sumners, D.W.L., and Swigon, D., Eds.).
2. Liu, Z., Deibler, R. W., Chan, H. S., and Zechiedrich, L. (2009). The why and how of DNA unlinking. *Nucleic Acids Res.* **37**, 661-671.
3. Laboratory webpage: http://www.bcm.edu/labs/zechiedrich/

Approaches to understanding the origin and management of DNA stiffness

Jim Maher
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Duplex DNA, the genetic material in living cells, is an unusually inflexible biopolymer. The persistence length of duplex DNA corresponds to 150 base pairs under physiological conditions. Surprisingly, the physical origin of this DNA stiffness is unknown. In particular, the contribution of the high negative charge density of DNA to its stiffness remains both uncertain and controversial. The intrinsic inflexibility of DNA is managed in living cells by the formation of nucleoprotein complexes in which DNA is often dramatically bent, kinked and looped.

This presentation will review two related areas of interest to our laboratory. The first concerns approaches to measure or predict the effect of charge density on DNA stiffness. We ask to what extent DNA stiffness is due to DNA charge. The second concerns the mechanism of sequence-nonspecific proteins that stabilize highly-bent DNA structures, thereby reducing the apparent persistence length of DNA. Such proteins include the bacterial HU protein and eukaryotic HMGB proteins. We describe the results of ensemble and single-molecule experiments revealing the effect of HMGB proteins on apparent DNA stiffness. We then describe experiments in living *E. coli* bacterial cells emphasizing the importance of DNA flexibility enhancement by proteins to facilitate gene repression by DNA looping.

DNA micromechanics and macromolecular organization

Wilma K. Olson

Department of Chemistry & Chemical Biology, BioMaPS Institute for Quantitative Biology, Rutgers, the State University of New Jersey, 610 Taylor Road, Piscataway, NJ 08854, USA

Encoded in the strings of DNA bases that make up the genomes of living species are codes that regulate, control, and describe all sorts of biological processes. The underpinnings of these codes lie in the base sequence-dependent micromechanical properties of DNA, which determine the degree to which the long, threadlike molecule fluctuates and how it responds to the proteins that control its processing and govern its packaging. In order to understand the mechanisms by which DNA base sequence and tightly bound proteins control the biophysical properties of the long, threadlike molecule, we have developed a coarse-grained model, in which the DNA base pairs are treated as rigid bodies subject to realistic, knowledge-based energy constraints, and computational techniques to determine the minimum-energy configurations, intrinsic dynamics, and looping/cyclization propensities of these molecules. The presentation will highlight some of the unique, sequence-dependent spatial information that has been gleaned from analyses of the high-resolution structures of DNA and its complexes with other molecules and illustrate how this information can be used to gain new insights into sequence-dependent DNA polymeric behavior.

Nanomechanics of single and double stranded DNA

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We use atomic force spectroscopy to examine the fundamental mechanical properties of single and double stranded DNA and we also attempt to apply this methodology for developing nanoscale DNA diagnostics. While measuring the elasticity of synthetic single-stranded DNA homopoly-deoxynucletides, poly(dA) and poly(dT), we determined that as expected, poly(dT) exhibited the simple entropic elasticity behavior. However, poly(dA) unexpectedly displayed two overstretching transitions in the force-extension relationship. We suggest that these transitions, which occur at ~23 pN and ~113 pN directly captured the mechanical signature of base-stacking interactions among adenines in DNA, in the absence of base-pairing. Using a similar experimental approach we observed solvent driven structural transitions within polyadenylic acid, poly(A). Both AFM imaging and pulling measurements revealed complex strand arrangements within poly(A) induced by acidic pH conditions, with a clear fraction of double stranded molecules that increased as pH decreased. These molecules displayed the plateau transition forces similar to the BS transition previously observed for native double-stranded DNA (dsDNA). These results strongly suggests that in acidic pH conditions poly(A) can form duplexes that are mechanically stable. We hypothesize that under acidic conditions, similar structures may be formed by the cellular poly(A) tails on mRNA.

DNA mechanics critically affects the fundamental biological processes of transcription, replication, recombination and repair. We hypothesized that UV damage to DNA affects DNA mechanics and such alterations may have a detrimental effect on these fundamental DNA transactions. We used atomic force spectroscopy to investigate the effects of UV radiation on the mechanics of individual DNA duplexes. We find that the characteristic B-S plateau in the force spectrograms of irradiated DNA shortens in a UV dose dependent manner as compared to untreated DNA. The effect is stronger for homopolynucleotides such as polydA·polydT and polydG·polydC than for native DNA such as lambda-phage DNA. These mechanical effects likely represent the local unwinding of the double helix caused by a massive formation of pyrimidine dimers and (6-4) lesions. We propose that simple stretch-release measurements on individual DNA duplexes may have a diagnostic value.

Finally, we note that in atomic force spectroscopy, it is tacitly assumed that the pulling direction coincides with the end-to-end vector of the molecule fragment being stretched. By systematically varying the position of the attachment point on the substrate relative to the AFM tip, we investigated empirically and theoretically the effect of the pulling geometry on force-extension characteristics of double-stranded DNA. We found that increasing the pulling angle can significantly lower the force of the characteristic overstretching transition and increase the width of the plateau feature beyond the canonical 70%. We caution that these effects, when neglected, can adversely affect the interpretation of measured force-extension relationships of DNA and other molecules.

Multi-scale modelling of sequence-dependent DNA mechanics

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Abstract:

I will describe efficient numerical methods that allow looping probabilities of DNA to be estimated once a sequence-dependent coarse-grain energy is assumed. And I will describe estimates for such coarse grain energies arising from molecular dynamics simulations.

Geometry and mechanics of condensed DNA: Toroids and beyond

E.L. Starostin

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DNA, like other semiflexible polymer chains, is known to condense, under certain conditions, into compact structures. The shape of these structures results as a compromise between the costs of the elastic bending energy and the energy of the DNA-DNA and DNA-solution interactions. To achieve maximum density, DNA has to align itself to form a parallel hexagonal bundle which imposes constraints on the global geometry and topology of the condensate. A theoretical consideration of this perfect arrangement is given with particular attention to non-contractible shapes. An expression for the elastic energy of a perfectly packed bundle is derived. Ability of various conformations to minimise the total energy is summed up as a diagram of state for rod-like, toroidal and racquet conformations. A unified description is developed to describe the metamorphosis of toroidal globules into hollow biconcave and convex spheroids.

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Electrostatic interactions between DNA double helices

Generalizations and ramifications induced by the counterion structure in the strong and weak-coupling electrostatic interactions

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[5]*School of Physics, Institute for Research in Fundamental Sciences (IPM), P.O. Box 19395-5531, Tehran, Iran*
[6]*Materials Research Laboratory, University of California, Santa Barbara, CA 93106, USA*
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We present general arguments for the importance, or lack thereof, of the structure in the charge distribution of counterions for counterion-mediated interactions between bounding symmetrically charged surfaces. We show that on the mean field or weak coupling level, the charge quadrupole contributes the lowest order modification to the contact value theorem and thus to the intersurface electrostatic interactions. The image effects are non-existent on the mean-field level even with multipoles. On the strong coupling level the quadrupoles and higher order multipoles contribute additional terms to the interaction free energy only in the presence of dielectric inhomogeneities. Without them, the monopole is the only multipole that contributes to the strong coupling electrostatics. We explore the consequences of these statements in all their generality.

Counterion-mediated DNA-DNA interactions

Brian TODD, Donald C. Rau, V. Adrian Parsegian

The physical properties of DNA are strongly effected by small mobile counterions present in solution. In the most dramatic example, multivalent counterions (charge greater than +2) can precipitate DNA from dispersed solution to form a condensed phase. Microscopically, this indicates a shift from counterion-screened repulsive forces between DNA to counterion-induced attractions between DNA. These attractions appear to be outside the scope of traditional electrolyte theories and attempts to describe them go back over 30 years.

Using magnetic tweezers, we measured the strength of DNA-DNA interactions over a wide range of counterion conditions. We find that changes with counterion concentration can be explained using traditional electrolyte theories, provided that Bjerrum pairing at high concentration is accounted for. This explains the peculiar DNA condensation phase diagram, including the resolubilization seen at high counterion concentrations. Left unclear, however, is the physical mechanism for counterion-mediated attractions. By a combination of osmotic stress and magnetic tweezers measurements, we derive experimental constraints on the forces and discuss possible mechanisms for counterion-mediated attractions.

Correlations and helical coherence in DNA structure: "straightening" the helix upon crystal packing

Aaron Wynveen[1], Dominic J. Lee[2], Alexei A. Kornyshev[3], and Sergey Leikin[4]
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The twist, rise, and other parameters that define the arrangement of adjacent DNA base pairs depend on the identity of the constituent bases. This dependence may provide a structural fingerprint of the underlying DNA sequence, which could be important for DNA sequence recognition by proteins, packaging and maintenance of genetic material, and other interactions involving DNA. The conformation of a specific DNA sequence, however, may not be fully realized knowing average values of these parameters alone as variations exist in the stacking geometry of the same adjoining base pairs within different sequence contexts. Hence, we have investigated the problem of sequence-dependent DNA conformation through a statistical analysis of X-ray and NMR structures of DNA oligomers, determining how these parameters are correlated along a sequence. We define a corresponding helical coherence length, which is a cumulative parameter quantifying sequence-dependent deviations from the ideal double helix geometry. We find, e.g., that the solution structure of synthetic oligomers is characterized by a 100 - 200 Angstrom coherence length, which is similar to the 150 Angstrom coherence length of natural, salmon-sperm DNA. Packing of oligomers in crystals dramatically alters their helical coherence, however. Here, the coherence length increases to 800 - 1200 Angstroms, consistent with theoretical predictions of its role in interactions between DNA at close separations.

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Simulations of DNA condensation

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The effects of the presence of a mixture of counterions, with different valances, on DNA condensation are investigated with Monte Carlo simulations. It is well known that charged chains decrease in size forming condensed conformations when the strength of the electrostatic interactions is increased, e.g. by adding multivalent counterions.

For flexible charged polymers, this decrease in chain size is a smooth function of the amount of added salt. For DNA, a very stiff polyelectrolyte, the behaviour is qualitatively different. When a small amount of multivalent salt is added, stiff polyelectrolytes are only observed in elongated conformations, while for high amounts of salt only compact toroidal or rodlike structures are found. We have been able to show how, for intermediate amounts of multivalent salt, there is coexistence between the elongated and compact conformations. In this region a single chain is found in either of the two conformations, but does not show a gradual decrease in size as the flexible chain does. In terms of the free energy, the simulations show how a flexible chain always has one minima as a function of chain size, while the stiff chain has two for certain amounts of added multivalent salt.

MEDIATING ROLE OF ALKALINE EARTH METAL IONS IN ELECTROSTATICS OF DNA: THE LONG-RANGE EFFECTS OF SOLVENT DIELECTRIC SATURATION

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The epsilon-modified Poisson-Boltzmann (ε-MPB) equations [1,2] have been solved on a three-dimensional grid for an all-atom geometry model of B-DNA [1,3]. Results were obtained for the models of one and two DNAs in solutions of chlorides of alkali and alkaline earth metals and their mixtures. The ε-MPB approach is based on the primitive polarization model (PPM) of electrolyte [4] that is an implicit solvent model including finite sizes of hydrated ions and a dielectric approximation of the ion hydration shell. All PPM parameters approximating dielectric medium and hydration shells of ions were extracted from all-atom molecular dynamics simulations of ions in SPC/E water [2,4-6]. The study allows evaluations of the ion size, interionic correlation, and solvent dielectric saturation effects on the ion distributions around DNA and DNA-DNA interaction energies. It suggests that the dielectric saturation of the ion hydration shell drastically affects distributions of alkaline earth metal ions around DNA, resulting in high affinity of calcium or magnesium ions to the phosphate groups of DNA. As follows from the ε-MPB calculations, the dielectric saturation of the ion hydration shells leads to decrease of the mean permittivity around DNA, compensating the DNA-DNA attraction arising from interionic correlations. As a result, two DNA macromolecules in solution of $MgCl_2$ or $CaCl_2$ repel each other in accordance with experimental data. Calculations for B-DNA in a mixture of NaCl and $MgCl_2$ solutions suggest that adding a tiny fraction (1 mM) of Mg^{2+} drastically affects DNA-DNA interaction energies [1]. Even in this case the peculiar polarization properties of the cluster $[Mg(H_2O)_6]^{2+}$ lead to sharp condensation of Mg^{2+} onto phosphates of DNA and notably affect the mean force acting between two DNA macromolecules. Calculated ionic distributions around DNA and DNA-DNA interaction energies agree with previously published simulations and experimental data.

Acknowledgments

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How does helical structure effect correlation forces between DNA molecules?

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The Poisson-Boltzmann approximation of the electrostatic interaction between two macro-ions, immersed in salt solution, assumes that the interactions between ions are very weak. For helical molecules, by using such considerations, one may derive the Kornyshev-Leikin theory of interaction [1] to describe the long-range behaviour of the forces between them. However, there may be certain cases where Kornyshev-Leikin theory, on its own, may be insufficient in describing the interaction, especially at closer separations between macro-ions. For instance when the valance of salt ions and counter-ions are large, interactions between ions may give rise to short ranged correlation forces. These may be thought of as attractive forces due to fluctuations in the counter-ion and salt density, when correlations between ions are not too strong.

The shape of the mean counter-ion and salt density function about molecules could be very important. Helical structure in DNA may play an crucial role in the behaviour of such forces, as the positioning of phosphate charges indeed affect the structure of the mean distribution of counter-ions due charges. An important consequence is that DNA structure may, again, give rise to preferred orientations of molecules about their long axes: so called azimuthal correlations [2]. Indeed, in the limit of strong correlations this effect has been shown to be significant [3].

In this talk, I will show that for weak correlations one can derive expressions for correlation forces, which are in some ways analogous to those of the theory of [1]. However, because the density of small ions is important here, not the charge density, these forces could favour different azimuthal orientations between molecules than those forces originally considered in [1].

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Speaker: Giovanni Dietler, EPFL, Lausanne, Switzerland.
Titel : "DNA from the Polymer Physics Point of View: Topology and Dimensionality Effects"

Abstract:Single and double-stranded DNA molecules of different topologies (linear, circular and knotted) in 2 D and 3 D conformation were imaged using Atomic Force Microscopy (AFM). After tracing the trajectory of the molecules, it was possible to calculate different scale dependent statistical quantities like the radius of gyration, the end-to-end distance, the distribution of the end-to-end distance and the shape (asphericity). These quantities in turn permit to determine the critical exponents describing the divergence of the radius of gyration with the length of the DNA molecule and the distributions. It was possible to compare the experimental distributions for the above-mentioned quantities with the theoretical one. Additionally, because of the fact that DNA has a rather large persistence length (50 nm), theories for semi-flexible polymers could be tested. The above experiments were carried out with topologically constrained DNA molecules: namely linear, circular, and knotted DNA.

Kinetics of Force-Induced DNA Melting.

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The nature of the cooperative phase transition induced by force applied to the opposite ends of torsionally relaxed double stranded (ds) DNA at ~65 pN remains controversial. One model suggests that this is the transition from B-DNA to 1.7-fold longer double stranded S-DNA. The alternative picture argues that this is simply the DNA strand-separation, i.e. DNA force-induced melting (FIM). Historically, the major argument in favor of B-to-S transition was kinetic. Thus, the apparently pulling rate-independent force plateau was associated with the fast B-to-S transition, while the last ~10-20% of DNA elongation prior to strand separation happening at strongly rate-dependent forces far exceeding the equilibrium transition force were attributed to DNA melting from its S-state.

This work theoretically considers kinetics of the DNA FIM. We interpret the rate-dependent high forces of final DNA strand separation as DNA "ripping", in contrast to equilibrium DNA melting, that happens at pulling rates $< v^* \sim 1000$ nm/s. Such "ripping" happens when the terminal DNA base pair (bp) is forced to open with the rate higher then it's natural opening rate $k^* = v^*/\Delta x \sim 10^4$ s^{-1} (where $\Delta x \sim 0.2$ nm is the bp elongation upon melting). k^* is significantly smaller then the bp opening rate for the thermal melting transition $\sim 10^6$ s^{-1}. This happens, because, in contract to the temperature, that destabilizes duplex DNA by increasing bp opening rate, the force destabilizes duplex DNA by slowing its closing. Quantitative analysis of the pulling rate dependence of strand separation force yields the characteristic bp elongation associates with its opening, $x_{op} \sim 0.05$ nm « Δx. Thus, very high DNA strand separation forces at high pulling rates come from the poor ability of the force to facilitate bp opening beyond its natural rate k^*. In contrast to the equilibrium FIM of DNA, the non-equilibrium "ripping" is expected to be sensitive to the DNA strand attachment (i.e. 3'3' vs 5'5'), as indeed was observed in several recent experiments.

Furthermore, we predict that for the slow DNA pulling rates v « v^*, the majority of bp will open inside the ds DNA starting with long regions of relatively low stability. The melting force for such process is expected to be very weakly rate-dependent. Such inside DNA melting can happen despite of the free energy preference for melting from the ends, and due to the heterogeneity of the bp stability. The later is expected to make the end - melting of sufficiently long random heteropolymeric DNA at the equilibrium average melting force infinitely slow. We show, however, that this inside melting can dominate only in solutions of high ionic strength, when the mutual repulsion between the two melted strands within the bubbles is well screened. In lower salt, or at higher DNA puling rates approaching v^*, DNA melting is expected to switch to the free DNA ends or nicks, and to become more pulling rate dependent. Finally, once the pulling rate significantly exceeds the critical rate, i.e. for v » v^*, the transition force is expected to switch into the strongly rate-dependent "ripping" mode. This "ripping" mode for the transition midpoint force is similar to the "ripping" mode for the final strand separation, except that the later sets in at much lower pulling rates, since only a few helix/coli boundaries survive the end of strand separation transition.

How can two homologous needles find each other in the genomic haystack?

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Homologous recombination is a universal DNA repair mechanism that faithfully restores genomic integrity following DNA double strand breaks. Decades of research have unraveled many of the details concerning the transfer of information between two homologous sequences. By contrast, the processes by which the interacting molecules initially colocalize are largely unknown. Is homologous pairing the result of a damage-induced genome-wide homology search, or is it an enduring and general feature of the genomic architecture that facilitates homologous recombination whenever and wherever damage occurs? We will present recent studies shedding new light on the pattern of homologous pairing in different phyla using the yeast paradigm as a reference point. We will then discuss the implications reaching far beyond the range of DNA repair alone.

Is recognition between homologous DNA double helices an intrinsic property of DNA?

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Imperial College London

Organization, compaction and processing of genetic material involves direct interactions between DNA double helices at small distances. These interactions have many surprising features even in simple electrolytic solutions without proteins [Kornyshev & Leikin, Phys. Rev. Lett. **86**, 3666, 2001]. Invariably, they are assumed to be independent of the base pair sequence because the nucleotides are buried inside the double helix and shielded by the charged sugar-phosphate backbone. However, a recent theory challenged this concept, predicting that the sequence dependence of the backbone structure might affect the DNA-DNA interactions and even result in sequence homology recognition without unzipping of the double helix. To test this hypothesis, we imaged mixtures of fluorescently tagged DNAs with identical nucleotide composition and length, but different sequences. We report spontaneous segregation of these DNAs within liquid crystalline spherulites, revealing recognition between the double helices separated by more than a nanometre of water without any single-strand fragments.

DNA-DNA interactions and homology "recognition well"

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Mutual recognition of homologous sequences of DNA before strands exchange them is considered to be the most puzzling stage of homologous recombination[1]. In 2001, a mechanism was suggested for a double stranded DNA molecule to recognize from a distance its homologous match in electrolytic solution without unzipping.[2] Based on a theory of electrostatic interactions between helical molecules[3,4], the difference in the electrostatic interaction energy between homologous duplexes and that between nonhomologous duplexes, called the *recognition energy*, was calculated. First experiments that have verified the existence of the predicted phenomena were published in Ref.[5]

Here we report a theoretical investigation of the form of the potential well (the first account of which was recently reported in Ref. 6) which DNA molecules may feel sliding along each other. This well, the bottom of which is determined by the recognition energy, leads to trapping of the molecular tracks of the same homology in direct juxtaposition. A simple formula for the shape of the well was obtained. The well is quasi-exponential. Its half-width is determined by the *helical coherence length*, introduced first in the same 2001 paper, the value of which, as the latest study shows, is close to 10 nm[7].

In this talk various factors that may influence the shape of the well will be discussed together with several scenarios of possible single molecule experiments.

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Conformation and dynamics of single molecules of DNA in solution

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To study a single molecule in solution, one would like to hold the molecule still without perturbing its dynamics along internal degrees of freedom. We have addressed this challenge by building a machine we call an Anti-Brownian Electrokinetic trap (ABEL trap).[1, 2] The ABEL trap consists of a nanofluidic cell mounted in a fluorescence microscope. A real-time tracking system follows the Brownian motion of a single fluorescent molecule, and a feedback system generates a time-dependent electrokinetic drift that cancels this Brownian motion.

We used the ABEL trap to study the conformation and dynamics of single molecules of fluorescently labeled double stranded DNA. Shape fluctuations were observed with high speed fluorescence imaging, leading to an accumulation of nearly 60,000 images. These images were analyzed statistically to extract the density-density correlation functions of a single molecule.[3] Principal Components Analysis yields a set of conformational normal modes which are an efficient way to characterize the shape fluctuations of the molecule.[4] Many aspects of the data await theoretical explanation.

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Dynamics of supercoiled DNA: some recent insights from single-molecule experiments

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Abstract:

DNA supercoiling plays a crucial role in a number of essential cellular processes such as gene expression, DNA replication and recombination. To quantitatively understand how both physical processes (e.g. plectoneme diffusion) and biological processes (e.g. topoisomerase activity) contribute to supercoiling regulation, an accurate description of the dynamics of supercoiled DNA is required.

We have first studied the dynamics of single supercoiled DNA molecules in the absence of protein, using an apparatus that combines optical and magnetic tweezers to apply sudden changes in tension or torsion. Experimental results were accurately analyzed without having to include the rotational drag originating from supercoil removal, indicating fast internal dynamics of supercoiled DNA.

Recently, we have also studied the dynamics of enzyme-mediated DNA relaxation, by transposing previous experiments performed with topoisomerases to the case of DNA ligases. Indeed, these enzymes exhibit topoisomerase-like activity when provided an adequate cofactor. Interestingly, our experiments show that, contrary to topoisomerases, ligases do not significantly slow down DNA relaxation (no friction being experimentally observed), but occasionally dissociate from nicked DNA. They also yield a lower bound for DNA ligation rate.

Compactness and Apparent Circularization of ssRNA

A. Ben-Shaul*

Using the average maximum ladder distance $\langle MLD \rangle$ as a measure of the "compactness" of RNA secondary structure, we show that viral ssRNAs are consistently smaller than randomly permuted sequences of the same length and base composition. They are also smaller than natural, non-viral, ssRNAs, suggesting that viral RNAs are more compact owing to the evolutionary pressure to facilitate their packaging into small rigid protein capsids. We predict that the average $\langle MLD \rangle$s of large non-viral ssRNAs scale as $N^{0.70}$, where N is the number of nucleotides, and – by mapping the secondary structures onto linear polymer models – argue that their radii of gyration, R_g, vary as $\langle MLD \rangle^{0.50}$, and hence as $N^{0.35}$. We shall also discuss another – generic – property of linear ssRNA sequences, namely, the proximity of their 3' and 5' ends. We employ basic combinatorial and graph theory arguments to estimate the distance between the ends of linear sequences and argue that the secondary structures of linear and covalently-circularized RNAs are practically identical.

* Work in collaboration with A. Yoffe, P. Prinsen, A. Gopal, L. T. Fang, C. Knobler, and W. M. Gelbart

DNA supercoiling and the lambda bacteriophage epigenetic switch

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The effect of tension and supercoiling on CI-mediated loops that were shorter than wild type (393 bp vs. 2317 bp-long) was characterized using magnetic tweezers. The average lifetime of looped and unlooped conformations and ΔG of loop formation was measured. Loop probability was observed to decrease with tension, as expected, and increase with DNA negative supercoiling. Thus, DNA unwinding seemed to compensate for the adverse effect of tension. Furthermore, the writhe of this short CI-mediated loop was measured directly. Implications for molecular recognition and response to the energy state of the cell will be discussed.

Computer Simulations of DNA Supercoiling at the Atomic Level

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Co-authors: Jon Mitchell (Leeds); Charlie Laughton (Nottingham) and Tannie Liverpool (Bristol).

The discovery of the structure of duplex DNA revealed how cells store genetic information. However, we are far from understanding the more complex biological question of how this information is regulated and processed by the cell. DNA topology and supercoiling is known to affect DNA transcription and other DNA-associated processes. Changes in topology affect DNA conformation, and can thereby modify the interaction between regulatory DNA-binding proteins and their target sites. However, there is still little understanding of how cells use supercoiling to regulate gene expression at the molecular level. Genetic regulation involves many complex factors that are difficult to isolate *in vivo*, and it is difficult to obtain experimental information as to the supercoiling dependent structures of DNA and its complexes with other molecules.

Small DNA circles offer a controllable model system for the systematic exploration of the dependence of DNA structure on supercoiling. We use computational methods to explore the supercoiling-dependent conformation of small DNA circles, and how this is affected by supercoiling, salt concentration, DNA sequence and the size of the circles. The calculations use atomistic molecular dynamics simulation, and employ both implicit and explicit solvent models.

Unravelling the organization of bacterial chromatin

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The bacterial genome is folded and compacted into a body referred to as the nucleoid due to the activity of nucleoid-associated proteins (NAP's). As a consequence of their role in global genome organization these proteins also act as pleiotropic regulators of transcription. One of the key players in these processes is H-NS. This is an abundant, multimeric protein with a binding preference for A/T rich regions along the genome. Its binding to these regions is associated with transcriptional silencing and has been suggested to be a mechanism to specifically target and silence newly acquired foreign DNA and protect the host against its potentially harmful effects.

A lot of progress in the understanding of H-NS action has been booked in recent years. Our main aim has been to establish the structure, kinetics, mode of binding and the role of H-NS in global genome organization. To this purpose we used a combination of scanning force microscopy imaging, single-molecule micromanipulation and theoretical modeling of H-NS-DNA complexes. Initially, we demonstrated that H-NS organizes DNA by bridging two DNA duplexes and put forward evidence that this mode of binding is also key to the role of H-NS as repressor. In recent follow up studies, we showed that H-NS acts as a dimer, that H-NS dimers are stacked side-by-side between bridged duplexes and determined the dimensions of the dimer. Moreover, we determined the binding kinetics of *individual* H-NS dimers and the forces required to open up H-NS-bridged regions. Finally, combining the *in vitro* structural observations and *in vivo* ChIP-on-chip data for binding of H-NS along the genome, we can now explain the higher order organization of the genome in the long known topologically isolated domains.

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The organisation and topology of eukaryotic chromatin.

Micaela Caserta[1,2], Eleonora Agricola[1,2], Mark Churcher[3], Edwige Hiriart[3], Loredana Verdone[1], Ernesto Di Mauro[1,2] and Andrew Travers[3,4]

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In vivo nucleosomes often occupy well-defined preferred positions on genomic DNA. An important question is to what extent these preferred positions are directly encoded by the DNA sequence itself. We report the derivation from *in vivo* positions accurately mapped by partial micrococcal nuclease digestion in yeast a translational positioning signal that identifies the approximate midpoint of DNA bound by a histone octamer. Unlike previously described compilations of positioning sequences the midpoint is highly A/T rich (~73%) and, in particular, the dinucleotide TpA occurs preferentially at this and other outward-facing minor grooves. We conclude that in this set of sequences the sequence code for DNA bending and nucleosome positioning differs from the other described sets. The translational signature is primarily a property of nucleosomes adjacent to promoter sites but can be associated with several nucleosomes in an array. Since the signature occurs at a frequency greater than that of nucleosomes we infer that nucleosome positioning in yeast is neither completely statistical as previously proposed, but nor is it completely specified by the DNA sequence. We suggest that positioning of nucleosomes in an array *in vivo* requires an 'organiser' and that, at least in part, the translational signal associated with promoter nucleosomes contributes to the establishment of an array.

We also report a novel solution of the 'linking number paradox' and show that in principle the compaction of the chromatin fibre can be directly related to the extent of DNA wrapping around the histone octamer. The implications of this finding in relation to current studies will be discussed.

Stacking plates and wedges: the physics of DNA compaction

Helmut Schiessel

Instituut Lorentz, Leiden University, Netherlands

The DNA in eucaryotes is hierarchically folded with the help of proteins into a rather dense complex called chromatin. In my talk I will discuss two of the various levels of that genome compaction. (1) The well-known stacking of the basepairs forming the DNA "ladder" leads to the DNA double helix. I will outline how geometrical details on the basepair level can lead to exotic elastic properties of the helix, e.g. anisotropic bendability. This allows for a second code on top of the well-known genetic code, determining the positions of millions of protein cylinders around which the DNA is wrapped - leading to a string of so-called nucleosomes. (2) This structure folds into a 30nm thick chromatin fiber. I suggest that the geometry of these fibers can be predicted to be the result of the tight packing of the wedge-shaped nucleosomes -- invoking a principle similar to that of the basepair packing in the first part of the talk.

DNA and chromatin dynamics studied by single molecule methods and computer modeling

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The organization of the genome in the cell nucleus is fundamental for cellular function: transcription and its regulation, genome duplication, epigenetic effects and chromosome folding are all intricately connected to genome architecture. On the lowest level of genome organization, DNA folding is determined by its bending and twisting properties; superhelical DNA is a well-known model system to study these properties. Recent experiments by fluorescence correlation spectroscopy (Shusterman et al., (1008) Phys Rev Lett. **100**:098102) suggest that the internal dynamics of DNA strongly depend on its superhelical state. Using a Brownian Dynamics model of DNA, we have attempted to identify the basis for these observations by modeling the Brownian motion of a fluorophore attached to the DNA in the focus of a confocal setup. The results suggest that translational diffusion by itself cannot explain the dependence of the dynamics on supercoiling. Possible explanations such as rotational dynamics of the fluorophore or changes in DNA twisting dynamics will be discussed.
The next level of genome organization is the association of DNA with histones to form nucleosomes and the chromatin chain. I will present recent simulations of nucleosome internal dynamics using a new coarse-grained model that allows computing trajectories of the nucleosome over tens of microseconds. These simulations show histone-tail-dependent opening dynamics of the linker DNA arms. Further insight into nucleosome opening is obtained from Brownian dynamics simulations of force-induced DNA unrolling, which describe quantitatively the force-extension curves from single-molecule pulling experiments and can be used to estimate the binding energy of DNA to the histone core.

DNA, Chromatine and remodeling factors

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We have studied the elastic properties of DNA, chromatine and single nucleosomes. While we recover the reported behavior of chromatine under torsional and tensional stress we also show that single nucleosomes exhibit a more varied response under tension, presumably resulting from reversible DNA unwinding or nucleosome unraveling. We show that under tension DNA wound around single nucleosomes exhibit three distinct changes in extension of ~12nm, ~25nm and ~50nm, see Fig.1.

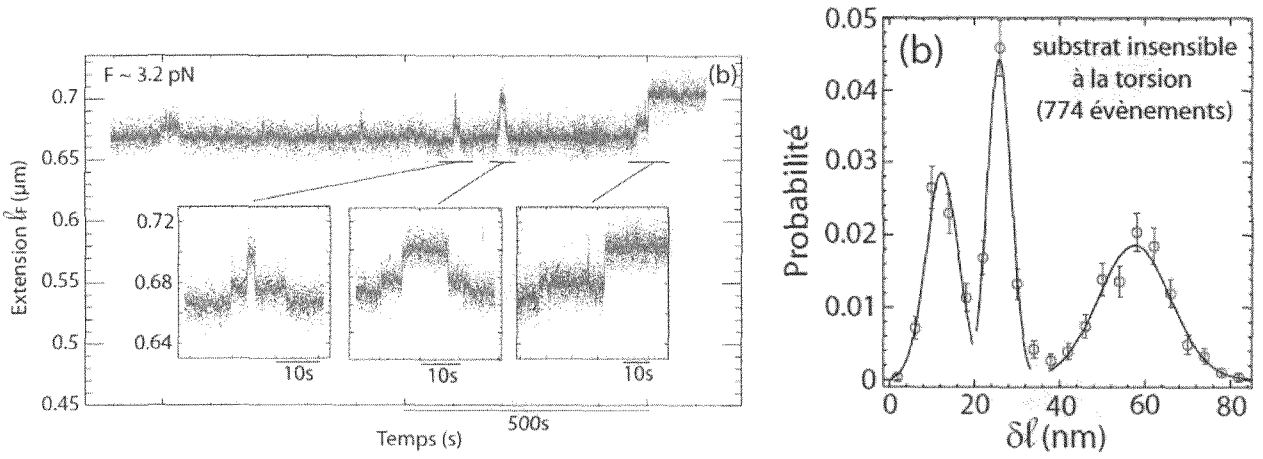

Fig.1 : *Typical extension signal of a single nucleosome under tension displaying discrete changes in extension and the histogram of these changes from many such events.*

We have also studied the response of bare DNA interacting with chromatine remodeling factors. We show that while RSC (a member of the SWI/SNF family) displays a ATP dependent chiral translocation activity on DNA, the yeast ISW1a (a member of the ISWI family) displays a ATP independent strong cooperative binding that is similar on (±)scDNA, see Fig.2.

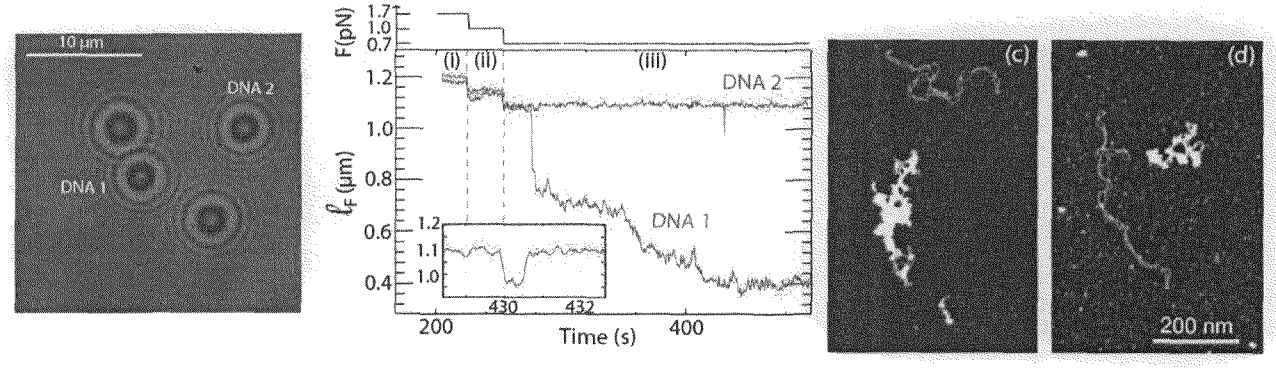

Fig.2 : *The very different behavior of the extension of two nearby stretched DNA molecules in the presence of ISW1a (no ATP). (c,d) The similar all or none binding of ISW1a on supercoiled DNA molecules observed with TEM.*

ABSTRACT

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DNA and Chromatin Dynamics: Discovery of a Novel ATP-dependent DNA Rewinding Motor

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The SNF2-like family of proteins comprises the ATPase subunits of all of the known chromatin remodeling factors as well as factors involved in transcription and DNA repair. We examined the function of human HARP, a distant member of the SNF2-like family. It was previously found that mutations in HARP are responsible for a rare disease termed Schimke immuno-osseous dysplasia (SIOD), but the molecular function of the protein was not known. We discovered that HARP possesses a new biochemical activity – it functions as an ATP-driven annealing/reverse helicase. Unlike a helicase that unwinds double-stranded DNA to yield single-stranded DNA bound by RPA (replication protein A, the major single-stranded DNA-binding protein in eukaryotes), HARP rewinds complementary, RPA-bound single-stranded DNA bubbles to give double-stranded DNA. Other related ATPases, including the DNA translocase Rad54, do not exhibit annealing/reverse helicase activity. Analysis of mutant HARP proteins suggested that SIOD is caused by a deficiency in annealing helicase activity. Moreover, the pleiotropy of HARP mutations is consistent with the function of HARP as an annealing helicase that acts throughout the genome to oppose the action of DNA-unwinding activities in the nucleus.

Modelling chromatin with explicit ions: ion correlation effects and like charge attraction. Comparison with new experiments.

Lars Nordenskiöld

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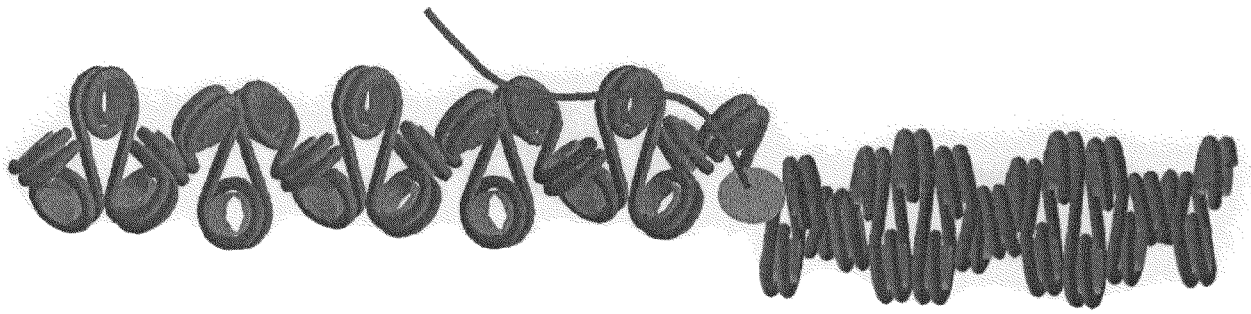
MD (Langevin) computer simulations in continuum description of coarse-grained chromatin and nucleosome core particle (NCP) models have been performed. The 12-mer chromatin array is described in a model with a central spherical particle with DNA in the form of connected charged beads wrapped around this central histone octamer. Protruding out from the core are 8 positively charged flexible "histone tails". Additional DNA beads modelling the linker DNA, connects such core particles to form an array. Explicit mobile counterions of charge and size mimicking Cl^-, K^+, Mg^{2+}, and $Co(NH_3)_6^{3+}$ are included to describe the effects of counterion valence and results are compared with calculations using salt represented by a DH screening potential. The latter description is found to be inadequate for multivalent ions. The simulation results with explicit ions agree with experimental trends (below) and are in accordance with polyelectrolyte theory and a mechanism of condensation due to salt screening, attractive ion-ion correlations and histone tail bridging.

Analytical ultracentrifugation, dynamic light scattering and precipitation assay measurements of cation induced compaction (folding) of recombinant 12-mer chromatin arrays are presented. Furthermore, counterion induced aggregation of such arrays as well as of recombinant 147 bp NCPs were investigated. Effects of the N-terminal tails have also been studied. The potency of inducing compaction or aggregation, in all three systems follow the order: spermine^{4+} > $Co(NH_3)_6^{3+}$ > spermidine^{3+} > $Mg^{2+} \approx Ca^{2+} > Na^+ \approx K^+$. This trend is the same as that observed for the condensation behaviour (compaction as well as aggregation) of DNA, which indicates similarity in the underlying electrostatic mechanism causing condensation in DNA and in chromatin.

Maria Barbi
(Laboratoire de Physique Théorique de la Matière Condensée, Paris, France)

Modeling the hysteretic behavior of chromatin fibers under magnetic tweezers: *why are nucleosomes left handed?*

Magnetic tweezers micromanipulations of chromatin fibers reveal unexpected mechanical properties of these assemblies. After having studied the highly resilient behavior of fibers at low number of turns **[1]**, we now address the question of modeling the hysteretic behavior observed at higher torsion, which involves dramatic structural changes of the nucleosomes. The experimental results are interpreted indeed by assuming that the nucleosomes undergo a chiral transition into a metastable right-handed structure called reversome **[2]**. A combined approach involving 3D modeling, geometrical analysis, mechanics, statistical physics and kinetic processes allows to reproduce the observed behavior and fit the experimental curves. Some possible *in vivo* implications of these results will be discussed.



[1] Structural reorganization of single chromatin fibers revealed by torsional nanomanipulation A. Bancaud, N. Conde e Silva, M. Barbi, G. Wagner, J-F. Allemand, J. Mozziconacci, C. Lavelle, V. Croquette, J-M. Victor, A. Prunell, J-L. Viovy *Nature Structural and Molecular Biology 13, 444-450, (2006)*

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DNA EJECTION FROM BACTERIAL AND MAMMALIAN VIRUSES

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ABSTRACT

In this talk I compare and contrast the nature of genome ejection in the cases of bacterial and mammalian DNA viruses, featuring several years of measurements on phage lambda and recent preliminary data on Herpes Simplex Virus. Both bulk solution and single-virus flow cell experiments are discussed.

Menagerie of Viruses: Diverse Chemical Sequences or Simple Electrostatics?

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The genome packing in hundreds of viruses is investigated by analyzing the chemical sequences of the genomes and the corresponding capsid proteins, in combination with experimental facts on the structures of the packaged genomes. A universal model, based simply on non-specific electrostatic interactions, is able to predict the essential aspects of genome packing in diversely different viruses, such as the genome size and its density distribution. Our result is in contrast to the long-held view that specific interactions between the sequenced amino acid residues and the nucleotides of the genome control the genome packing. Key issues related to the stability of assembled virus structures and the kinetics of their formation will be addressed theoretically.

DNA structure and phase transitions in the bacteriophage capsid

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Tailed bacteriophages are complex macromolecular machineries that deliver their genome into the host cytoplasm while their capsid and tail remain bound to the cell surface. Although several models have been proposed, DNA organization is still unknown in the phage head but dimensions of the capsids are adjusted to keep DNA at a concentration close to 500mg/ml independently of the species. DNA ejection from the capsid is triggered by specific interaction of a phage tail protein with a receptor inserted in the wall of the bacteria. DNA is injected into the cytoplasm through the tail. The bacterial receptor of the T5 bacteriophage has been isolated (1), allowing to reconstitute the ejection process *in vitro* (2) and to investigate the underlying mechanisms (3) that show differences compared to Lambda and SPP1 bacteriophages (4). The T5 genome is almost 40μm long (113.9kbp) and confined in a capsid 80nm in diameter.

Using cryoElectron microscopy (cryoEM), we follow the organization of DNA inside the capsid at different steps of the ejection process and correlate these observations with the lengths and concentrations of encapsidated DNA. The DNA chain occupies the total volume of the capsid and reorganizes under confinement. The structure turns from crystalline hexagonal to 2D hexagonal, cholesteric and isotropic, following the sequence reported for solutions of short DNA fragments (5).

The interactions between DNA strands can also be monitored and turned from repulsive to attractive by addition of multivalent cations that diffuse through the protein capsid. After partial ejection of DNA, each individual DNA chain (3000 to 55000bp *i.e.* 1.4-18μm long) is collapsed inside each capsid. The structure of toroidal DNA is analyzed. We show how the frustration arising between chirality and hexagonal packing combined with the strong curvature imposed by the small volume of the container impose phasing of the helices and variations the DNA helical pitch (6).

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Charge Transport of Cancer-Related Genes

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We report on theoretical studies [1] of point mutations effects on charge transfer properties in various DNA sequences related to genes from cancer databases, in particular the tumour-suppressor gene p53. On the basis of effective single-strand or double strand tight-binding models which simulate hole propagation along the DNA, we perform statistical analysis of charge transmission modulations associated with all possible point mutations. We find that in contrast to non-cancerous mutations, mutation hotspots tend to result in significantly weaker changes of transmission properties. This suggests that charge transport could play a significant role for DNA-repairing deficiency yielding carcinogenesis. The data for p53 is corroborated by another 34 cancer-related genes, including 20 of the most important tumour suppressors, with known genotype and phenotype analyzed. There are strikingly many properties of charge transport for these cancer-related genes which behave similar to the p53 gene. These new results strongly suggest that the aforementioned scenario of early pathogenesis related to charge transport can be applied to a wide range of disease-related genes.

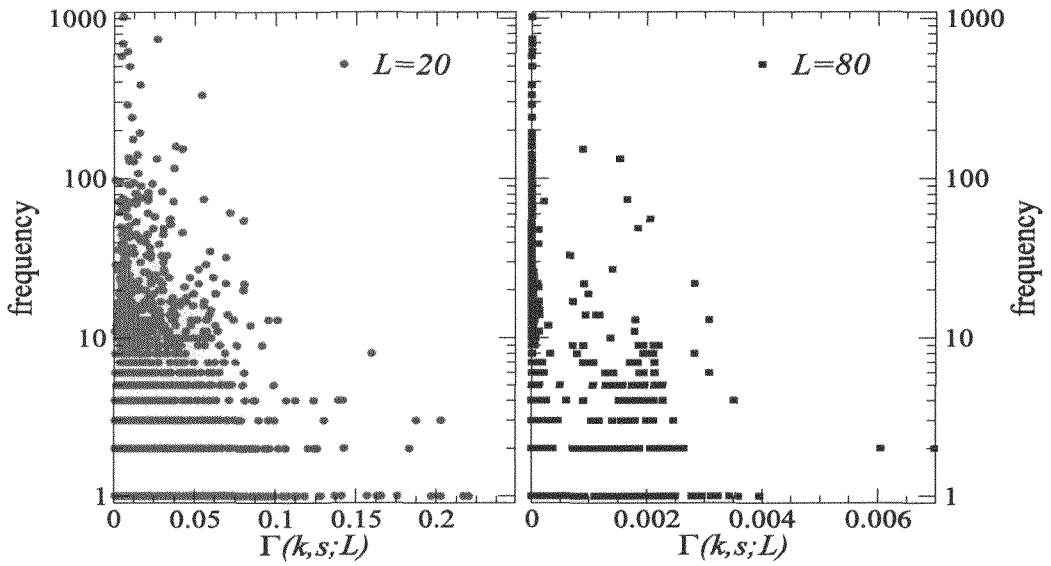

Figure 1 Scatter plots of the frequency of mutation versus the mean charge transport change for the p53 gene.

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THURSDAY, 4 JUNE 2009

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Mechanisms of Direct and Indirect Readout[≠]

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Based on high-resolution 3D structures, we are developing predictive models of direct and indirect readout of DNA sequence by proteins. *Indirect Readout; Reading DNA Sequence at a Distance.* The non-contacted bases in the centers DNA complexes of the 434 repressor, P22R and other HTH proteins are important determinants of affinity. These proteins can induce transitions from B-DNA to B'-DNA, which is characterized by a narrow minor groove and a zig-zag spine of hydration. The sequence is read by a sensing of the free energy of the transition from B- to B'-DNA, which depends on sequence. Thus, protein affinity is determined by known relationships between DNA sequence, conformation and hydration. *Direct Readout; Reading DNA Sequence by Direct Interactions.* DNA sequence can be read directly by shape complementarily. Therefore non-directional van der Waals interactions between protein and DNA confer sequence-specificity. For example a valine reside can occupy a cleft formed by four methyl groups on sequential base pairs of 5' TTAA 3'. The cleft is intrinsic to the DNA sequence and does not arise from protein-induced DNA conformational change. Hydrogen bonding can play a secondary role in specificity.

Gijs Wuite[1]

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A singular view of DNA transactions

The genetic information of an organism is encoded in the base pair sequence of its DNA. Many specialized proteins are involved in organizing, preserving and processing the vast amounts of information on the DNA. In order to do this swiftly and correctly these proteins have to move quickly and accurately along and/or around the DNA constantly rearranging it. In order to elucidate these kind of processes we perform single-molecule experiments on model systems such as restriction enzymes, DNA polymerases and repair proteins. The data we use to extract forces, energies and mechanochemistry driving these dynamic transactions. The results obtained from these model systems are then generalized and thought to be applicable to many DNA-protein interactions.

Single-Molecule Manipulation of DNA

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Abstract:

During DNA interactions, DNA is often stretched and stabilized by coupling with DNA binding proteins to serve as an intermediate state. The conformational and energetic changes of stretched DNA is of great interests because of their relevance in biological functions. Direct manipulation of DNA has yielded much of the information about the mechanical properties of DNA without the complication of interacting molecules. Stretching ssDNA has provided direct measurement of the base stacking mechanics and energetics. For example, polydA has been shown to have two transitions during overstretching. Using AFM, we have observed two pathways during the second transition. We have observed "hopping" between these two pathways during constant-force measurements. We have also observed an intermediate state during the double-stranded DNA overstretching transition. We will discuss the implications of such transition and its significance in biological functions.

DNA mechanics and protein-DNA recognition

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Molecular simulations make it possible to look at DNA structure and mechanics as a function of base sequence at both local and more global levels. Understanding this sequence-induced heterogeneity is a necessary step to understanding the indirect aspects of DNA recognition which play a major role in the formation of many protein-DNA complexes including multi-macromolecular assemblies such as the nucleosome. I will describe some recent work in this area based on large-scale molecular dynamics and molecular mechanics studies, notably involving our present interest in understanding how nucleosomes position themselves on genomic DNA.

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HOW PROTEINS FIND THEIR TARGETS ON DNA

Protein searching and recognizing the targets on DNA one of the most fundamental processes in biology, and it was the subject of many experimental and theoretical studies. It is often argued that some proteins are capable of finding their targets 10-100 times faster than predicted by the three-dimensional diffusion rate. Current views of this facilitated diffusion phenomena suggest that a combination of three-dimensional and one-dimensional searches could explain such behavior. However, recent single-molecule experiments showed that the diffusion constants of the protein motion along DNA are usually very small. We present a theoretical approach that describes some physical-chemical aspects of the target search on DNA. It is argued that correlations and non-specific interactions are critically important. Our analysis shows that the acceleration in the search time could be achieved at some intermediate strength of the protein-DNA binding energy and for intermediate concentrations of free protein molecules.

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Binding of HU proteins and DNA elasticity

We present a model of non-specific cooperative binding of proteins to DNA in which the binding of isolated proteins generates local bends but binding of proteins at neighboring sites on DNA straightens the polymer. We solve the statistical mechanical problem and calculate the effective persistence length, site occupancy and cooperativity. Cooperativity leads to non-monotonic variation of the persistence length with protein concentration, in qualitative agreement with recent single molecule experiments on HU-DNA complexes. Elastic effects on adsorption of proteins (a bent chain has a higher entropy!) lead to unusual shape of the binding isotherm.

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ABSTRACT:

The effect of HU on DNA looping

An overview of modeling non-specific and cooperative protein-DNA interactions within the theory of DNA elasticity is presented. Precise structural details of protein-DNA binding site geometries are obtained from high-resolution X-ray and NMR structures available in the Protein Databank (PDB) and incorporated into our models, in order to understand the effects of protein binding on DNA conformation. Monte Carlo simulation techniques that enable fast conformational searches within a precise statistical mechanical treatment are applied to ideal elastic DNA chains in the presence of non-specific binding of HU, an important architectural protein associated with bacterial chromosomes, at HU binding ratios approximating those in the cell.

Studies of DNA cyclization and DNA looping mediated by the lac repressor-operator assembly using these techniques are discussed in detail. The effect of multiple lac repressor tetramer conformations (e.g., open and closed states) and the binding of HU within the DNA loop is examined, in order to interpret experimental results for repression levels that are obtained in vivo and in complex multi-component solutions. Finally, the results of this theory will be interpreted in the context of common DNA structural motifs among architectural proteins and the experimental observations that similar proteins can substitute for HU in facilitating DNA cyclization and lac repressor-mediated DNA looping.

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DNA Capture in nanoscle pores - How does it happen?

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Abstract:

Nanopores are an emerging class of biosensors optimized for probing the structure of biopolymers at the single-molecule level. A unique, powerful feature of the nanopore method is its ability to linearly "slide and read" extremely long unlabeled biopolymers, particularly attractive for analyzing native (i.e., unamplified) DNA molecules. It is anticipated that nanopores will play a prominent role as the future-generation tool for DNA sequencing, where only a small number of genome copies will be required for complete genomic coverage, and where long read-lengths (>1 kbp) are crucial. While we as well as others has studied extensively the electrophoretic driven transport of DNA through nanopores, much less is known about its capture mechanism, which is pre-requisite for any nanopore analysis. Here I will report on new, and surprising results showing that the capture rate increases with DNA length for medium length biopolymers, but becomes length-independent for longer DNA. We introduce a simple non-equilibrium model (and numerical analyses) to explain these results, emphasizing the crucial role of electrostatics outside the pore. Moreover, we implement a simple way to manipulate the capture rate by introducing salt gradients across the pore, thus increasing the method's sensitivity by orders of magnitude, allowing us to detect unprecedentedly small DNA sample.

Origin of the electrophoretic force on DNA in solid-state nanopores

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Despite gel electrophoresis being one of the main workhorses of molecular biology, the physics of polyelectrolyte electrophoresis in a strongly confined environment remains poorly understood. Theory indicates that forces in electrophoresis result from interplay between ionic screening and hydrodynamics, but these ideas could so far be addressed only indirectly by experiments based on macroscopic porous gels. I will present a direct experimental based on measuring the electrophoretic force on a single DNA molecule threading through a solid-state nanopore as a function of pore size. The stall force gradually decreases on increasing the nanopore diameter from 6 to 90 nm, inconsistent with expectations from simple electrostatics and strikingly demonstrating the influence of the hydrodynamic environment. We model this process by applying the coupled Poisson–Boltzmann and Stokes equations in the nanopore geometry and find god agreement with the experimental results.

Amphiphile-DNA complexes: adsorption, delivery and release

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A theory is presented which quantitatively accounts for the cooperative adsorption of cationic surfactants to anionic polyelectrolyte [1,2]. For high salt concentrations, we find that the critical adsorption concentration (CAC) is a bilinear function of the polyion monomer and salt concentrations, with the coefficients dependent only on the type of surfactant used. Motivated by the theory, we have undertaken a study of the transfection of Vero cells by a a plasmid expressing the β-galactosidase enzyme [3]. The results obtained showed a low rate of transfection by linear DNA:liposome (Lipofectamine) complexes. To explore whether the structure of the complexes was interfering with the transfection, atomic force microscopy (AFM) was used. It has confirmed the difference between the linear and circular condensates: whereas the circular DNA:liposome complexes presented compact spherical or cylindrical structures of about 100-800 nm, the linear DNA showed pearl necklace-like structures, with pearls varying from 250 to 400 nm. On the basis of the theory a low concentrations of cationic amphiphile was then used to neutralize or reverse the DNA charge. Using this method, we were able to obtain the expression of the transgene without an associated toxicity observed with the linear DNA liposome delivery [3].

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Backtracking by RNA polymerase: single molecule experiments vs theory

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RNA polymerase II (RNAP II) is responsible for transcribing all mRNAs in eukaryotic cells in a highly regulated process that is conserved from yeast to human and that serves as a central control point for cellular function. We have investigated the transcription dynamics of single RNAP II molecules against force in a single-molecule dual-trap optical-tweezers assay. Remarkably, we found that the response of RNAP II to force is entirely determined by enzyme backtracking, a pause state that is involved in the proofreading of the RNA transcript. We found pause durations be broadly distributed and to follow a $t^{-3/2}$ power law, giving rise to both short and long-lived pauses. To understand the mechanism behind backtracking, we modeled backtracking as a force-biased random walk. Importantly, we found that this single mechanism naturally generates two populations of pauses that are distinct both in duration and trajectory: long-time pauses with the behavior expected for random-walk backtracks, and a new class of short-time backtracks with characteristics similar to those of the ubiquitous pause. We therefore suggest that pauses that have previously been suggested to stem from distinct mechanisms are to a significant extent simply due to backtracking. Finally, we studied the role of conformational characteristics of the RNA strand in the context of the early stages of transcription, during which the polymerase is prone to premature and irreversible stalling. Specically, we examined the hypothesis that the absence of long transcripts contributes to stalling in the vicinity of the promoter.

Taken together, we have shed light on the basic physical mechanisms that underly transcription by RNA polymerase II, using a combination of experimental and theoretical approaches.

"What is it like to be a molecular robot based on DNA?"

Milan Stojanovic (on behalf of the Center for Molecular Cybernetics)

One possible approach to defining molecular robotics is "we'll know it when we see it": it usually focuses on mimicking various macroscopic behaviors on molecular scale, often starting with walking. I will discuss an alternative approach to autonomous molecular robots pursued at our NSF Center for Molecular Cybernetics and inspired by Rodney Brooks Behavior-based Robotics. We start with sensor-actuator legs implementing local residency rules, and build higher level behaviors by adding connections between legs, and introducing various sensors. And, yes, our current design uses DNA.

Synthetic DNA Holliday junctions as controllable nanoswitch systems

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We have recently shown a class of DNA nanoswitches to be a highly novel detector, capable of specific nucleic acid recognition[1]. The detection principle (Figure 1) relies on monitoring the conformational transition, mediated by switching ions such as Mg^{2+}, between open and closed states of a Holliday Junction (HJ) formed from Watson-Crick base hybridization of probe and target strands.

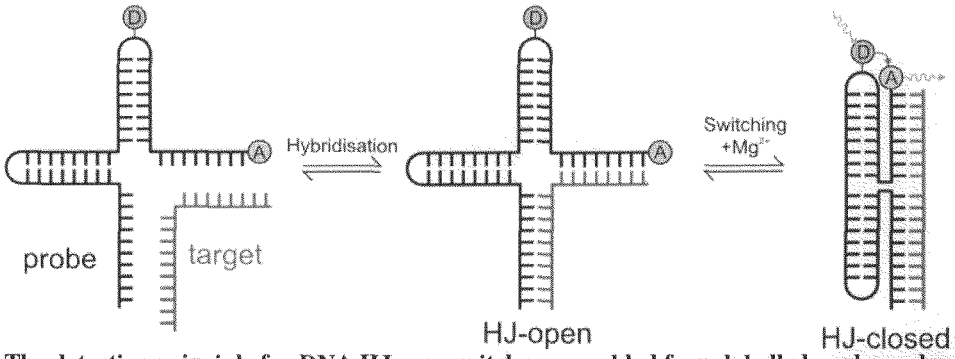

Figure 1 The detection principle for DNA HJ nanoswitches assembled from labelled probe and unlabelled target

Mutations in the unlabelled target located near the junction branch point influence the Fluorescence Resonance Energy Transfer (FRET) output of the dyes (D and A) in the labelled probe and thereby allow for spectroscopic resolution of single base target mismatches. Time-resolved donor fluorescence decays have been used to characterize these nanoswitch biosensors[2]. The fully matched target shows single peak distributions corresponding to the open and closed conformations, reflecting the binary nature of the nanoswitch. Single base target mutations lead to distinct bimodal distributions, in which both open and closed states are observed under ionic conditions where the perfectly matched junction is completely closed. This behaviour is consistent with mutation causing from modest (subtle structural perturbations) to marked (folding inhibition) effects. We have demonstrated the principle that selective probe target binding, combined with sequence-dependent conformational switching, affords molecular recognition precision beyond the limits imposed by the base-pairing energetics and avoids the need for target labelling. As such, these systems offer significant advantages over current biosensing technologies. The principle of electronic control of the molecular conformation of these synthetic HJs is also demonstrated, through the electrochemical generation and removal of switching ions. The methods developed here and the observations reported provide a basis for integrating electronic circuitry with these nanoscale biosensors. Such coupling is a necessary step towards the development of electronically-addressable biostructures.

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On the theory of cholesteric ordering in solutions of macromolecules.

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Main results of the general statistical theory of cholesteric ordering in solutions of rigid long macromolecules are presented including expressions for the helical pitch obtained in the second virial and mean-field approximations. Different kinds of chiral intermolecular interactions are discussed including steric and van der Waals interactions. It is shown that the temperature variation of the pitch in cholesteric solutions is mainly determined by the balance between steric and attraction interactions. It is discussed in detail how the theory enables one to explain experimentally observed helical sens ne inversions induced by the change of temperature , properties of the solvent of concentration. The role of biaxial ordering is also considered in detail. Finally we discuss the role of chiral electrostatic forces between DNA macromolecules which have been described recently by Kornyshev and Leikin, and consider how these novel chiral interaction potentials may be incorporated into the existing statistical theory of cholesteric ordering.

ABSTRACTS

OF

POSTERS

(in alphabetical order of author name as of 25 May 2009)

Non-specific DNA-protein interaction: Why proteins can diffuse along DNA

Vincent Dahirel (1) , Fabien Paillusson(2), Marie Jardat (1), Maria Barbi (2), Jean-Marc Victor (2)

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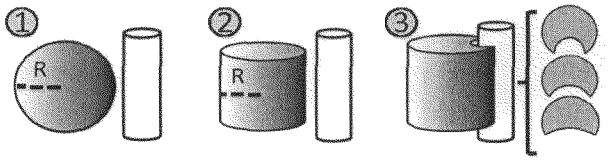
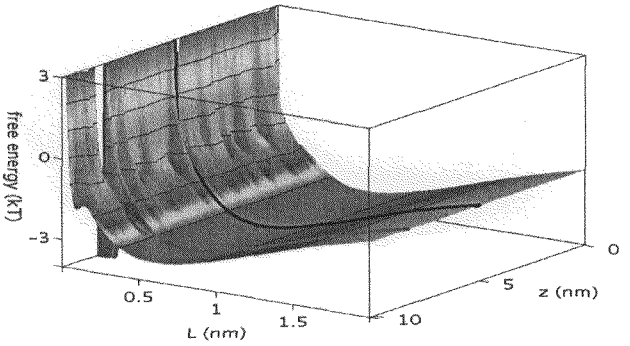
The structure of DNA binding proteins (DNA-BPs) enables a strong interaction with their specific target site on DNA through direct interactions with DNA base pairs. However, recent single molecule experiment reported that proteins can diffuse on DNA. Interactions between proteins and non-specific DNA should therefore play a crucial role during the target search. The question therefore arises of how these non-specific interactions optimize the search process, and how the protein structure comes into play.

Nucleotides being negatively charged, the positive surface of DNA-BPs is expected to collapse onto DNA. This is indeed what is observed by means of Monte Carlo simulations for an oversimplified model of the system where the DNA is represented by a cylinder and the protein by a sphere.

However, the most characteristic aspect of DNA-BPs is their shape complementarity with DNA [1]. We showed that, if the concave shape of DNA-BPs is taken into account, a counter-intuitive repulsion between the two oppositely charged macromolecules exists at a nanometer range, due to a local increase of the osmotic pressure exerted by the ions trapped at the interface [2]. For realistic protein charge densities, we find that the repulsion pushes the protein in a free energy minimum at a distance from DNA. Analytical calculations allowed us to better characterize this phenomenon [2,3]. As a consequence, a favorable path exists along which proteins can slide without interacting with the DNA bases. When a protein encounters its target, the osmotic barrier is completely counter-balanced by the local H-bond interaction, thus enabling the sequence recognition. This results unravel a subtle balance between long-range electrostatic attraction, short-range osmotic repulsion and short-range attraction, sensitive to the shape and charge of DNA-BPs, and to the salt conditions. Moreover, it provides a switching mechanism between a searching mode on non-specific sequences and a recognition mode at the sequence.

The implications of such a behavior on the protein 1D diffusion along DNA recently observed both *in vitro* and *in vivo* [4,5] will be the goal of future investigations.





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INTERACTION BETWEEN LIKE CHARGED MACROIONS MEDIATED BY NANOPARTICLES

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The interaction between equally charged surfaces, separated by a solution of multivalent nanoparticles was studied theoretically and experimentally. In our case the nanoparticles possess a spatially distributed electric charge. The mean field theory could not be used to describe highly charged systems [1,2]. More advanced methods have to be used in order to account for correlations. The system is theoretically described by using functional density theory and Monte-Carlo simulations [3,4,5]. Minimization of the total free energy is performed to obtain the equilibrium configuration of the system. . The solution of the variational problem shows that orientational ordering of nano-particles in the field of the system give rise to attractive interaction between equally charged surfaces [4,5]. Monte Carlo simulations confirm the theoretical predictions [3, 4]. Furthermore, we show that for sufficiently large dimensions (l) of nanoparticles and large charge densities the two equally charged surfaces an attractive force arises due to the spatially distributed charges within the nano-particles. Therefore the optimal distance D between the charged surfaces results from the bridging mechanism (D≈l). Recent measurements with multivalent rigid rod like ions confirm the theoretical predictions.

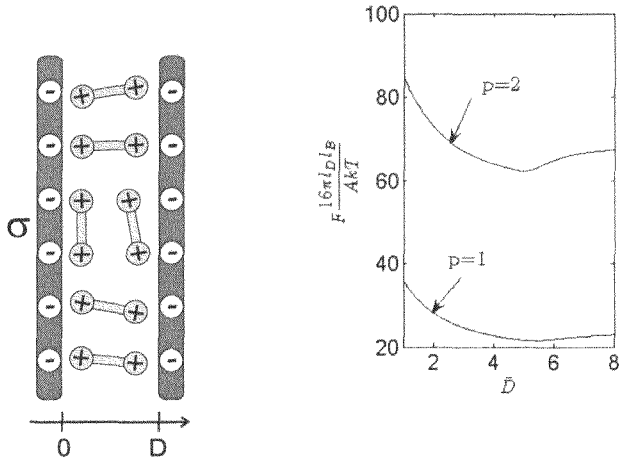

Fig. 1 Schematic presentation of the bridging mechanism and the scaled free energy as a function of the distance between the charged surfaces with the surface charge density parameter p [4]. The lengths are scaled by the Debye length [4].

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Statistical Mechanics of sub-graph identification problems

Serena Bradde

Abstract:

Network analysis, inference and optimization represent methodological challenges which play a central role in large scale data analysis. Their practical relevance arises from the huge quantity of empirical data that is being made available in many fields of science, biology and economics in first place.

In this talk we shall discuss some new statistical physics approaches to basic network optimization problems that come from sub-graph identification. Firstly we show how to approach the so called sub-graph isomorphism problem, one of the most fundamental NP-hard problems in graph theory. We display three applications: maximum clique identification, graph alignment and network motif counting. Secondly we discuss how to generalize the cavity method to deal with the problem of searching for sub-network which are subject to topological constraints. The specific case of bounded depth Steiner trees is discussed in some detail, together with a novel application to high dimensional data clustering.

STUDY OF INTERACTION BETWEEN DNA AND CHITOSAN DERIVATIVES.

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The interactions between chitosan and their derivatives containing phosphorylcholine (PC-CH) and poly(ethylene glycol) PEG-CH with calf thymus DNA (ct-DNA), were investigated using the ethidium bromide fluorescence assay, gel electrophoresis, dynamic light scattering and fluorescence microscopy. The size and colloidal stability of deacetylated chitosan (CH/DNA) and PC-CH/DNA and PEG/DNA complexes were strongly dependent upon PC and PEG contents, charge ratios and pH. The interaction strengths were evaluated from ethidium bromide fluorescence and, at N/P ratios higher than 5.0, no DNA release was observed in any synthesised PC-CH/DNA and PEG-CH/DNA polyplexes by gel electrophoresis. The PC-CH/DNA and PEG-CH/DNA polyplexes exhibited a higher resistance to aggregation compared to deacetylated chitosan (CH) at neutral pH. At low pH values highly charged chitosan and its their derivatives had strong binding affinity with DNA, whereas at higher pH values CH formed large aggregates and only PEG-CH and PC-CH derivatives were able to form small nanopartilces with hydrodynamic diameters varying from 200 to 300 nm. Nanoparticles synthesised at low ionic strength with PEG-CH (3-9 % of PEG 5kDa) and PC-CH(DS = 20 and 40%) remained stable at pH 7.4 after one day of preparation. Photomicrocopies of the rhodamine-labelled nanoparticles also confirmed that derivatives presented higher colloidal stability than those synthesised using deacetylated chitosan. Accordingly, due to their improved physicochemical properties these derivatives chitosans provide new perspectives for controlling polyplexes properties.

Degenerate polygonal tilings in simple animal tissues

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The salient feature of one-cell-thick epithelia is their en face view which reveals the polygonal cross-section of the close-packed prismatic cells. An outstanding challenge in developmental biology, the physical mechanisms that shape these tissues were hitherto explored using theories based on cell proliferation, which were either entirely topological or included certain morphogenetic forces. But mitosis itself may not be instrumental in molding the tissue. We show that the structure of simple epithelia can be explained by an equilibrium model where energy-degenerate polygons in an entropy-maximizing tiling are described by a single geometric parameter encoding their average aspect ratio. The three types of tilings found numerically disordered, hexatic, and hexagonal closely reproduce the patterns observed in Drosophila, Hydra, and Xenopus, and they generalize earlier theoretical results.

Single-base Mutation Detection of DNA using Bio-Chip

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Abstract

Advances in genomics and proteomics have provided us useful information about the origins of diseases. Genetic mutations are major cause for diseases like cancer. The detection of specific changes at genetic level can translate to early stage disease diagnostics improving treatments and survival rates. The current diagnostic tools for single base transition detection have certain limitations. Such limitations stem from many factors, like the need to alter the probe or target molecules, requirements of expensive optical imaging equipment necessitating certain level of expertise, or simple lack of sensitivity in measurements.

We are using nanotechnology and oligo-engineering for the detection of specific DNA sequences. Our approach uses free energy landscape associated with hairpin loop oligonucleotides towards electronics microarray probe design. Hairpin probes are immobilized on silicon chip surface between isolated nano-electrodes. Interactions of perfect-complementary target single-stranded DNA opens the hairpin probe. A reporter sequence carrying gold nanoparticles is then used to detect hairpin opening, with high selectivity. The reporter hybridizes with the stem region of opened hairpin and provides increased paths for charge conduction between nano-electrodes.

Such approach provides ultimate sensitivity of detecting single-base mismatch/mutation measured through electronics signatures of the hybridization. Direct current measurements across the nano-electrodes show three orders of increase in conductivity for as low as 2 femto-moles of complementary target molecules. The energy landscape of hairpin probe DNA is such that only perfectly complementary reporter sequence hybridizes to the stem thereby generating an electrical signal, and even a single base mismatch between reporter and probe results in no signal.

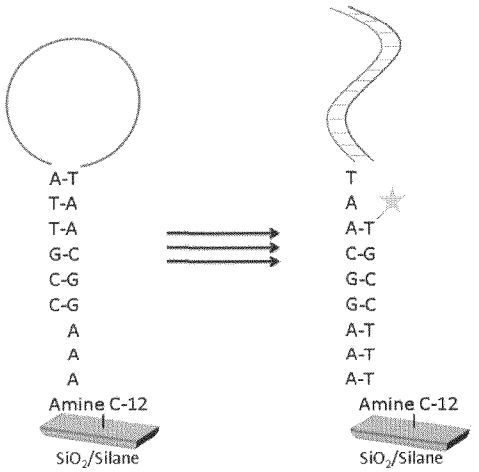

Figure depicting hairpin loop probe on chip surface that opens up when a perfect-complementary molecule interacts with it. A third sequence with nanoparticle acts to amplify the electrical signal.

Influence of immersion plating time on the surface morphology of Ni/Si nanocomposite system

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Abstract Metal nanocrystallite particles can producing obvious surface-enhanced Raman scattering (SERS) effect and great progress has been achieved in detecting low-concentration bio-molecules by SERS technique, therefore, study relevant to preparation proper nanostructed metal particles is a research hot point currently. In this paper, a composite thin film with regular pillar array structure was fabricated by deposition nickel on freshly prepared silicon nanoporous pillar array (Si-NPA) through immersion plating method, and influence of immersion plating time on the surface morphology of Ni/Si-NPA nanocomposite system were studied. Experimental results showed that the quantity and grain size of nickel increased along with time, at the same time, the pillar becoming thinner and thinner. The formation mechanism was analysed.

Key words: Surface enhanced Raman scattering (SERS), patterned silver structure, adenine, silicon nanoporous pillar array (Si-NPA)

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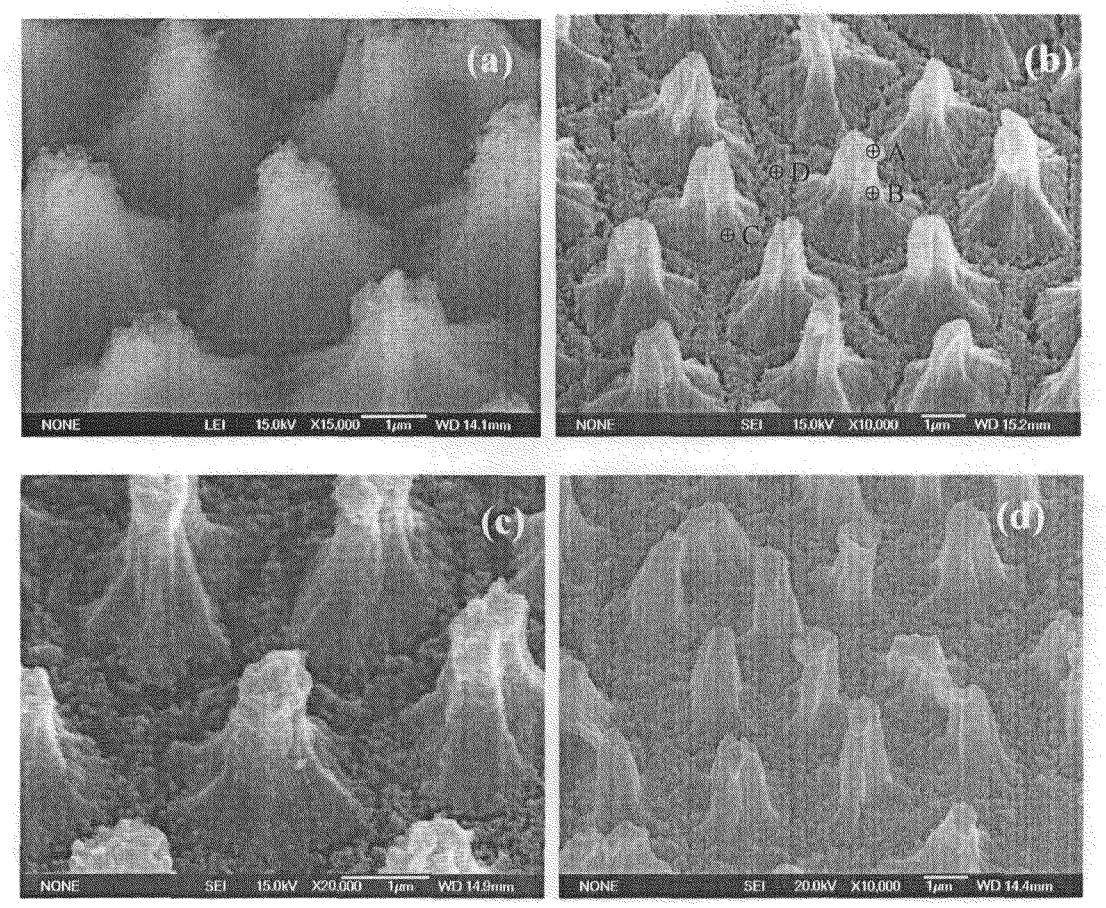

SEM images of Ni/Si-NPA synthesized for different immersion plating times: (a) 1 min, (b) 5 min, (c) 10 min, and (d) 30 min.

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Title:
Counterion-mediated Electrostatic Interaction between Helical Molecules

Abstract:
The appearance of DNA-DNA attractive force in the presence of multivalent ions cannot be described by standard mean-field approach. The attraction is a consequence of counterion correlations at small DNA-DNA distances. We present the model of two helical molecules, that can resemble two DNA or two DNA/CNT complexes. The electric charge of molecules is compensated by mobile counterions. We solve this problem by two limiting cases of analytical theory, namely weak coupling and strong coupling limit. In the weak coupling limit, which is Poisson-Boltzmann mean field approach and relevant for small valencies of counterions, DNA-DNA interactions are always repulsive. In the opposite case, the strong coupling limit, counterions of high valency are higly correlated and the approach is based on one-particle contributions to free energy. In this regime two equally charged molecules, DNA-DNA in this case, can also attract at certain distances.

Stretching single stranded DNA: What else?

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Abstract

Recently single molecule force spectroscopy provided many important information about elastic properties of single stranded DNA. However, theoretical efforts which followed these experiments could not provide satisfactory explanation of the outcome of these experiments. For example decrease in the extension with temperature at high force [1], multi step transition in force extension curve of poly(A) [2-3] etc. I am going to discuss few of these experiments and develop a simple lattice model, which describes some of the observed features [4-5]. We also propose an experimental setup [6] which will enable us to observe re-entrance a long standing issue related to force induced transitions.

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Polaron dynamics in the Peyrard-Bishop-Holstein model under dc fields

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The nucleotide sequence in synthetic poly(G)-poly(C) and poly(A)-poly(T) DNA molecules is periodic. Consequently they can be regarded as artificial crystals that can carry electric current when they are subjected to an external bias. Electrons in periodic potentials subjected to an applied electric field present dynamic localization and may undergo coherent oscillations[1,2]. Our aim here is to investigate whether the polaron performs sustainable BOs in biased DNA molecules, described by the Peyrard-Bishop-Holstein (PBH) model. This model has been previously introduced as an appropriate framework for the description of polaronic effects for charge migration in DNA[3-5].

We find that the polaron undergoes coherent oscillations when the electric field is applied along the stacking direction. The frequency of the oscillations is the same as in the rigid lattice (Bloch frequency), provided the carrier-lattice coupling is not large. Increasing the coupling the single peak of the Fourier spectrum splits into side-peaks around the Bloch frequency[6].

We also report on a more general description of polaron dynamics by introducing disorder in the well-established PBH model. We found the threshold value of the electric field to observe polaron motion when disorder is present. We also calculate the fluctuations of the electric current and find that they provide valuable information about the polaron dynamics[7].

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Zimm-Bragg model of DNA stretched against Multivalent Cation Induced Condensation

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Abstract

Motivated by measurements on double-stranded DNA, simultaneously condensed in the presence of multivalent cations and stretched by magnetic tweezers, we develop a qualitative Zimm-Bragg model for a quasi-first-order phase transition, using the degree of compaction as an order parameter.

The data provide estimates of effective persistence length and width of transition. In the thermodynamic limit of infinitely long chains, the width goes to zero as expected for a first-order transition. The heterogeneous and homogeneous chains are considered. The influence of sequence heterogeneity on the collapse transition in dsDNA is analyzed. The possible mechanism of dsDNA toroid growth limit is proposed.

Molecular Dynamics Simulations of Supercoiling in DNA Mini-circles

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[1]University of Leeds, [2]University of Nottingham and [3]University of Bristol.

DNA *in vivo* is predominantly in an under wound state (supercoiled) and thus under torsional stress. This can be relieved either by denaturation of the secondary structure or coiling of the tertiary structure (writhe). By studying DNA supercoiling in mini-circles with atomistic molecular dynamics we are able to investigate the interplay between these two forms of deformation. The introduction of writhe was dependent on circle size, sequence, salt concentration and the magnitude of winding. Denaturation occurred at a higher level in under wound, as opposed to over wound, circles and more commonly in A-T rich segments.

Measuring the Watson-Crick hydrogen-bond distances throughout the simulation allowed for denaturation to be closely monitored and quantified. Likewise, by first defining the helical axis, the writhe could be precisely measured. This was done by both sampling of the directional writhe from multiple angles and also by approximating the writhe integral as a summation. Currently we are running large (178 bp) implicitly and explicitly solvated simulations. With these, further thermodynamic analysis will be carried out. Additionally the experimentally proposed hypothesis that severe bending causes kinking while torsional stress results in the breaking of hydrogen bonds can be investigated.

How does polymerase kinetics depend on microchip PCR cycling?

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Abstract: DNA amplification is one of the unavoidable components of miniaturized devices that require on-chip DNA manipulation. With the development of bio-MEMS, DNA amplification has been achieved using polymerase chain reaction (PCR) in record time with highest specificity. Our group have developed a silicon-glass hybrid PCR device for 3 micro litres that is cycled through the temperature values using a novel non-contact induction heating system optimized for small volume. We achieved heating and cooling rates of 25 ^{0}C/s and 2.5 ^{0}C/s respectively with a stability of $\pm$ 0.1 ^{0}C. Unlike conventional real-time PCR instrument that measures single point fluorescence every cycle, we have developed home-built LED fluorescence set up to measure the intra-cycle fluorescence every 0.5s during PCR and estimate in-situ reaction kinetics. In microchip cycler with fast heating and cooling ramp rates, the rate-limiting step is the extension step in the protocol. Denaturation and annealing are known to happen instantaneously as soon as the correct temperature is reached, while extension of the template requires finite amount of time. Extension time depends on the polymerase, temperature, template size, reaction composition etc. Since some of these parameters are dynamic in nature, they vary with cycle numbers during a PCR that leads to variation of the extension stay time. We have measured how extension process depends on cycle numbers during Lambda DNA amplification using continuous fluorescence monitoring from microchip PCR. We are interested to know how the polymerase activity varies as a function of cycle numbers. These observations have led us to develop a smart PCR protocol where cycling parameters vary with cycle numbers. We will present few of the optimised kinetic parameters for on-chip amplification using real-time PCR data. We are interested in developing a model that will help us predicting polymerase efficiency from stay time to optimise reaction kinetics and total amplification time.

Polarization sensitive two-photon microscopy of DNA liquid crystalline phases

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DNA tightly packed in living cells as well as in concentrated solutions in vitro forms organized structures. These structures were explored by numerous techniques and recognized as lyotropic liquid crystalline phases (LLC) [1-2]. Self-organized LLC of DNA in aqueous solutions are a useful model for the studies of organization of DNA in physiological conditions.

This contribution reports on the investigation of the ordering of DNA by means of polarization-sensitive two-photon microscopy (TPM). Fluorescent dyes that binds to DNA can follow the organization of the strands . At first, LLC phases found in liquid crystalline cells as well as droplets were identified under polarized light microscope in DNA solutions doped with intercalator propidium iodide or groove binder Hoechst. Then, the samples were investigated by polarization sensitive TPM and the relative binding angles between the long axis of DNA helix and each of two dyes were determined. Analysis of the TPF signal in a function of polarization of the incident light provides the local orientation of molecules associated with DNA and thus the orientation of DNA chains in micrometric LLC domains [3-4]. The experimental results were compared to theoretical calculations based on the model developed in [5].

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"Solving Tangle Equations: An overview of the tangle model associated with site specific recombination and topoisomerase action"

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Abstract:

The tangle model was developed in the 1980's by DeWitt Sumners and Claus Ernst. The model uses the mathematics of tangles to model DNA-protein binding. An n-string tangle is a pair (B,t) where B is a 3-dimensional ball and t is a collection of n non-intersecting curves properly embedded in B. The protein is modeled as the 3-ball and the DNA strands bound by the protein as the non-intersecting curves. In the tangle model for protein action, one solves simultaneous equations for unknown tangles that are summands of observed knots/links. This poster will give an overview of the tangle model for site specific recombination and topoisomerase action including definitions and examples.

Single-stranded DNA adsorbed on graphite: Persistence length and scaling properties

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Laboratory of Physics of Living Matter, Ecole Polytechnique Fédérale de Lausanne (EPFL) CH-1015 Switzerland

Circular single-stranded DNA was adsorbed onto modified graphite substrates, and subsequently imaged by Atomic Force Microscopy. By analyzing the images we obtained information about the stiffness and the scaling properties, and we have compared our findings to the literature.
We quantified the stiffness using the persistence length as obtained from three quantities: 1) The exponential decay of the bond-correlation function for nearby segments, 2) the worm-like chain expression for the end-to-end distance, and 3) the distribution function of end-to-end distances (we use the expression from Ref. [1]). At a very low ionic strength of the solution, we found a value of the persistence length around 9 nm from the first two quantities, while the distribution function gave a slightly lower value. Increasing the salt concentration we found a clear decrease in the persistence length, to about 6 nm at 1 mM NaCl, and 4.5 nm at 10 mM NaCl. These values are comparable to the literature; see e.g. Ref. [2].
We have studied internal the end-to-end distance for large segment separations as well, and found a scaling behaviour consistent with a 2-dimensional self-avoiding random walk, i.e. a scaling exponent of 0.75. As we have shown previously [3], the internal end-to-end distance is a useful quantity for extracting the scaling behaviour of a circular molecule (for a sufficiently high total length-to-persistence length ratio). The 2-dimensional behaviour was further confirmed by studying the end-to-end distance distribution for large separations along the contour: This function is distinctively different from the one at short scales (where the persistence length enters as a parameter), and functions belonging to different values of the contour length should collapse onto a single graph provided the correct scaling exponent is used. Indeed, we observed a good data collapse using a value of 0.75 for the scaling exponent.

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Studies on Binding of Cationic Pheophorbide-a Derivative to Model Synthetic Polynucleotides

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Pheophorbide-a (Pheo) is an anionic porphyrin derivative. It is widely used as a photosensitizer in photodynamical therapy of tumors because of its high photosensitizing activity in vitro and in vivo [1, 2]. Modification of Pheo with the trimethylammonium group was carried out to obtain a cationic dye derivative (CatPheo) capable of polyanion binding. The interaction of CatPheo with double-stranded poly(A)·poly(U) and poly(G)·poly(C) as well as with four-stranded poly(G) homopolymer was investigated in buffered aqueous solutions (pH6.9) of low ionic strengths (2mM Na^+) by methods of absorption and polarized fluorescence spectroscopy in a wide range of molar phosphate-to-dye ratios, P/D. Determination of type of the complexes formed by CatPheo with the polynucleotides and definition of binding characteristics were carried out.

It was revealed two mechanisms of CatPheo binding to the polynucleotides: (i) chromophore intercalation between the nucleic bases; (ii) formation of the external complexes via electrostatic attraction of cationic dye to polynucleotide backbones. It was shown that (ii) type is predominant for double-stranded polynucleotides. However, in the case of four-stranded poly(G) containing systems it competes with the intercalation binding mechanism. Fluorescent technique was revealed to be efficient for recognition of the type of complex formed, because of CatPheo emission intensity increases upon its intercalation and quenches strongly upon the external stacking-association. It was established that for poly(G) at low P/D values ($P/D < 5$) the outside cooperative binding was predominated being accompanied with CatPheo associations due to chromophore stacking; while the P/D increase results in disintegration of these external complexes and prevalence of the intercalative binding mechanism. It was confirmed by rise in fluorescence polarization degree under P/D increase.

Simulation of the external binding to DNA on a system containing the single-stranded polyphosphate was carried out under the same conditions. It was established that at low P/D values CatPheo forms continuous stacking associates on the polyanionic matrix, and at large P/D it binds to polyphosphate in the dimer form. The increase in the solution ionic strength reduces the electrostatic binding efficiency due to CatPheo and Na^+ ions competition. However, even at the physiological ionic strength this interaction type gives essential contribution into the complex formation. The thermodynamic characteristics of external complex formation were estimated by Schwarz's method [3].

The improved photodynamical activity for CatPheo in comparison with that for Pheo is expected because of a good water solubility of CatPheo and the efficient dye binding with polyanionic biopolymers. Besides, the strong CatPheo binding with nucleic acids probably allows to use this porphyrin derivative in anticancer applications for targeting of G-quadruplexes of telomeric DNA.

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Force Induced DNA Melting

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Abstract

When pulled along the axis, double-strand DNA undergoes a large conformational change and elongates roughly twice its initial contour length at a pulling force about 70 pN. The transition to this highly overstretched form of DNA is very cooperative. Applying force perpendicular to the DNA axis (unzipping), double-strand DNA can also be separated into two single-stranded DNA which is a fundamental process in DNA replication. We study the DNA overstretching and unzipping transition using fully atomistic molecular dynamics (MD) simulations and argue that the conformational changes of double strand DNA associated with either of the above mentioned processes can be viewed as force induced DNA melting. As the force at one end of the DNA is increased the DNA start melting abruptly/smoothly after a critical force depending on the pulling direction. The critical force f_m, at which DNA melts completely decreases as the temperature of the system is increased. The melting force in case of unzipping is smaller compared to the melting force when the DNA is pulled along the helical axis. In the cases of melting through unzipping, the double-strand separation has jumps which correspond to the different energy minima arising due to different base pair sequence. The fraction of Watson-Crick base pair hydrogen bond breaking as a function of force does not show smooth and continuous behavior and consists of plateaus followed by sharp jumps.

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Title:

MODULATIONAL INSTABILITY AND EXACT SOLITON SOLUTIONS FOR A TWIST-OPENING MODEL OF DNA DYNAMICS

By

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Abstract:

We study the nonlinear dynamics of DNA which takes into account the twist-opening interactions due to the helicoidal molecular geometry. The small amplitude dynamics of the model is shown to be governed by a solution of a set of coupled discrete nonlinear Schrödinger equations. We analyze the modulational instability and solitary wave solution in the case. On the basis of this system, we present the condition for modulational instability occurrence and attention is paid to the impact of the backbone elastic constant K. It is shown that high values of K extend the instability region. Through the Jacobian elliptic function method, we derive a set of exact solutions of the twist-opening model of DNA. These solutions include Jacobian periodic solutions as well as kink and kink-bubble. *[Phys. Lett. A (2009) doi:10.1016/j.physleta.2009.04.052]*

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Predicting nucleosome positions on the DNA: combining intrinsic sequence preferences and remodeler activities

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Nucleosome positions on the DNA are determined by the intrinsic affinities to a given DNA sequence and by the ATP-dependent activity of nucleosome translocation complexes referred to as chromatin remodelers. Here, we report an approach to take into account both contributions. Two types of experiments have been considered: *in vitro* nucleosome reconstitution and *in vivo* genome-scale nucleosome mapping. In both cases, experimental nucleosome positions but not their relative occupancies are predetermined by the intrinsic sequence preferences. The algorithms of remodeler action were studied by iteratively redistributing the nucleosomes according to various remodeler activities, starting from their equilibrium positions until a new steady state was reached. Three main remodeler activities were identified: (i) the establishment of a regular spacing between nucleosomes in the vicinity of a strong positioning signal acting as a boundary, (ii) the enrichment/depletion of nucleosomes at pre-existing DNA sites through remodeler amplification of intrinsic nucleosome positioning signals, and (iii) the removal of nucleosomes from certain binding sites recognized by the remodeler. Using data from resting and activated human $CD4^+$ T-cells, it was found, that the redistribution of a nucleosome map to a new state is greatly facilitated if the remodeler complex translocates the nucleosome with a preferred directionality.

THE GENERALIZED MODEL OF POLYPEPTIDE CHAIN IN COMPETITIVE AND NON COMPETITIVE SOLVENT

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It is well known, that biopolymers functioning in water solution. Experimental investigations of biopolymers melting also performed in water and in other different solvents. Water can compete with repeated units for formation of hydrogen bonds, as well as interact with them in different conformational states.

The Generalized Model of Polypeptide Chain in competitive and non competitive solvent has been considered. The Hamiltonian of system includes basic GMPC term and terms which describe chain interaction with solvent competitive and non competitive means.

It has been shown, that simultaneous consideration of influence of competitive and non competitive solvents reduces to solving of basic model with independent redefining of temperature and entropic parameters. The qualitative different types of interactions have been considered. The Hamiltonian describes helix - coil transitions (melting), as well as coil-helix transitions (arrangement). As opposed to our previous results [1] the process of arrangement can progress also in case of dominance intramolecular interactions above the energy of intermolecular interaction. It has been shown, that in some conditions it can exist two temperature fields of helix state.

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Nucleosome structural variations characterized by single molecule FRET

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The nucleosome has a central role in the compaction of genomic DNA and the control of DNA accessibility for transcription and replication. We studied the effect of DNA sequence and selective histone acetylation on the structure, stability and disassembly of the mononucleosomes. Reversible disassembly was induced by increasing NaCl concentration. Quantitative single molecule FRET measurements between dyes attached to different parts of the DNA permitted us to detect the equilibrium between several subpopulations of reconstituted nucleosomes in solution. We obtained that the heterogeneity and stability of the samples are correlated with each other and influenced both by the DNA sequence and the histone acetylation. The path of the linker DNA is more sensitive to all studied effects than the DNA on the core. Intermediates of the disassembly pathway were identified and characterized.

Base pair opening and bubble transport in a DNA double helix induced by a protein molecule in a viscous medium

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Abstract

Protein-DNA interaction plays an important role in a large number of cellular processes and these processes are mediated or catalyzed by DNA-binding proteins and during this process most of the proteins are known to change the conformation of DNA when it binds to DNA. Therefore, we study the dynamics of a protein-DNA molecular system by treating DNA as a set of two coupled linear chains and protein in the form of a single linear chain sliding along the DNA at the physiological temperature in a viscous medium. The dynamics of the above molecular system in general is governed by a perturbed nonlinear Schrödinger equation. In the non-viscous limit, the equation reduces to the completely integrable nonlinear Schrödinger (NLS) equation which admits N-soliton solutions. The soliton excitations of the DNA bases make localized base pair opening and travel along the DNA chain in the form of a bubble. The perturbed NLS equation is solved using a perturbation theory by treating the viscous effect due to surrounding as a weak perturbation and the results show that the viscosity of the solvent in the surrounding damps out the amplitude of the soliton.

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Circular DNA in the melt, pressurized vesicles, lattice-animals: same family

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Polymer melts are an important subject of study in various fields and especially in biology where space constraints on DNA can be dramatic (cell nucleus, viral capsid). Linear polymers under these conditions are well understood and described by classical scaling concepts, whereas closed molecules, trough their topological constraint, represent a much more challenging problem. Only conjectures [1] have been made on this type of system, leaving number of questions open that have recently received new attention [2]. We focus here on the 2D case that allows for a statistical analysis at the single molecule level. Trough an AFM study of a 2D melt of circular DNA as well as trough Monte-Carlo simulations, we show that the behavior of these chains can simply be reduced to the one of molecules under pressure, generally called vesicles. This result is achieved trough the measurement of different statistical properties like the bond correlation function, the anisotropy or the asphericity. We explore two extreme cases. First molecules in the melt feel a negative pressure induced by the surrounding chains, and, as predicted [3], tend to collapse into lattice-animal conformations. Second, molecules whose interior area is "filled" with other ones feel a positive pressure, inflate, and behave like a more rigid polymer. In conclusion, we give here an experimental confirmation of the relations between circular polymer melts, vesicles under pressure, and the more general model of lattice-animal structure.

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Gene regulatory network model of Pancreatic Exocrine to â-cell Reprogramming

Joseph X. Zhou and Lutz Brusch

Abstract

The regulatory mechanisms underlying pancreatic exocrine to â -cell reprogramming are analyzed by means of gene regulatory network model in order to propose optimized reprogramming stimuli. Here we develop a mathematical model of coupled gene switches that reproduces experiment data on gene expression time courses and knock-out experiments. A novel gene switch mechanism is identified that alternates between bi-stable and tri-stable states. The model is then employed to quantitatively simulate a set of reprogramming strategies. Model results are compared to experiment data on reprogramming efficiencies which yields good agreement and allows for predictions of optimized strategies.

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