DNA and beyond : Structure, Dynamics and Interactions

Swiss Federal Institute of Technology

Lausanne 7th-9th April 2003

Organizers : Richard Lavery & John Maddocks

List of titles and abstracts

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Title :

Configurational Entropy Change In Protein-DNA Complexes: Estimates From Molecular Dynamics Trajectories

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Abstract :

The role of dynamic, flexible structures and the ensuing vibrational and configurational entropy effects in the thermodynamics of macromolecular association is an issue of significance that calls for attention as our knowledge of the structural properties and their thermodynamic effects buildup. In a recent observation, Jen-Jacobson and coworkers [Structure (2000), 8, 1015-1023] proposed a model for the thermodynamics of protein-DNA recognition that argues that structurally strained complexes such as the Catabolite Activator Protein (CAP) - DNA system are entropically driven while in contrast, unstrained complexes such as the λ cI repressor-operator system are enthalpically driven. The issue of motional properties in protein-DNA systems and their thermodynamic effects has been studied on the basis of stable molecular dynamics (MD) simulation trajectories of 4 ns or greater length for the λ cI repressor protein - OL1 operator complex and the CAP - DNA complexes and their component unbound forms. The covariances of positional fluctuations during the MD of these units are employed to extract an estimate of the configurational entropy change based on a quasi-harmonic approximation. The results support the proposed relation between the structural features of the complex in solution and the thermodynamic factors favoring complexation. The study also highlights the applicability and usefulness of such simulation based techniques for gaining insights into the dynamic structural properties of such large systems that are otherwise difficult to access.

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Title :

Comparison of Elastic Rod and All Atom Simulations of DNA Bending Dynamics

Thomas C. Bishop, Ricardo Cortez, Oleksander Zhmudsky
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Abstract :

The propagation of bend and shear waves through DNA is investigated using a geometrically exact nonlinear elastic rod model and all atom molecular dynamics simulations. The rod model allows for shear, extension/compression, bend and twist thus enabling us to study the dynamics of all types of elastic deformations. It is formulated using DNA helical parameters (roll,tilt,twist, shift,slide,rise) so that results can be readily compared to all atom simulations.

For the case of an intrinsically straight, untwisted rod, numeric and approximate analytic solutions demonstrate that the propagation of planar bend or shear disturbances of finite wavelength require bend, shear and extension/compression deformations. The wavelength of the extension/compression wave is half the wavelength the bend or shear wave.

For the case of an intrinsically straight, twisted rod planar bend-shear motion is investigated numerically and compared to a similar motion in an all atom simulation of 158 basepairs of DNA. The molecular dynamics simulations indicate that DNA supports the propagation of mechanical disturbances as predicted by elastic rod theory.

Prof. Thomas E. Cheatham

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Title :

Using computers to give insight into nucleic acid structure, dynamics and interactions: Can we accurately estimate free energies of drug binding?

Abstract :

Advances in the simulation methods and empirical force fields over the past decade have demonstrated a remarkable ability to reliably simulate the structure, dynamics and interactions in varied nucleic acid systems. This has ranged from simulations of standard nucleic acid duplexes showing proper response to changes in the environment to varied unusual DNA structures ranging from modified DNA and mismatches to triplexes and quadruplexes in a variety of research labs worldwide. In addition to reliable representation of DNA structure, significant efforts in simulation of RNA has demonstrated reliable representation of varied RNA structure including hypermodified tRNA molecules, hairpin loops, and even model codon-anticodon interactions. Despite the great successes, limitations in the force fields and effective sampling are still apparent. This becomes particularly noticable when investigating the effects of specific ion binding on structure and dynamics and also in estimating the free energy of drug interaction. The latter is particularly important to demonstrate that simulation can give useful insight into drug design. Building upon our recent work, in collaboration with the Sponer lab in the Academy of Sciences of the Czech Republic, investigating multiple binding modes of DAPI to DNA, we have expanded the series of drugs and sequences investigated to match those studied experimentally by the Wilson lab at Georgia State University. Preliminary results of these simulations will be presented, along with an overview of where we are in terms of reproducing DNA structure, dynamics and interactions.

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Title :

Modelling DNA at the base-pair level

Abstract :

We present a model to treat the elasticity of DNA at the base-pair level. We use a variant of the Gay-Berne potential to represent the stacking energy between neighboring base-pairs. The sugar-phosphate backbones are taken into account by semi-rigid harmonic springs with a non-zero spring length. The competition of these two interactions and the introduction of a simple geometrical constraint leads to a stacked right-handed B-DNA-like conformation. The mapping of the presented model to the Marko-Siggia and the Stack-of-Plates model enables us to optimize the free model parameters so as to reproduce the experimentally known observables such as persistence lengths, mean and mean squared base-pair step parameters. For the optimized model parameters we measured the critical force where the transition from B- to S-DNA occurs to be approximately $160\mbox{pN}$. We recover an overstretched S-DNA conformation with highly inclined bases that enables at least partially a stacking of successive base-pairs.

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Title :

Preliminary results on the molecular dynamics simulation of the B-DNA sequence AAAA(AC)4CCC. GGG(GT)4TTTT

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Abstract :

A 2.2 ns MD simulation of a 15 base pair DNA corresponding to the consensus sequence recognised by the protein MC1 was performed using AMBER 5 with parm98 and PME. DNA is fully hydrated and Na+ counterions are present. The initial structure is a canonical B-DNA. A preliminary analysis of the last 1.2 ns is presented. All the base pairs are strongly maintained at the exception of the first AT. The root mean square deviation from B-DNA is stabilised at 3 Å. Analysis with CURVES reveals that the pucker of all nucleotides remains near C2' endo. All the glycosidic angles and all the δ angles are also characteristic of a B conformation. A slight curvature of about 20° toward the large grove is observed. Both strands exhibit a regular alternation of large and small twists all along the sequence. On the first strand, residues A4, C8 and C12 adopt a B-II conformation while the others are in B-I. On the second strand only G3 is in B-II but ζ of residues T5, G6, G8, T9 and G10 exhibit transitions between gauche- and trans while their ε remain trans.

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Title :

Energetical and conformational aspect of base opening within the DNA double helix

Abstract :

Nucleic acids undergo a wide variety of thermally induced fluctuations which occur on timescales ranging from picoseconds to milliseconds and with spatial extents ranging from fractions of an angstrom to tens of angstroms. Amongst the larger deformations of the double helix, base pair disruption plays an important role in making reactive sites on the bases accessible for chemical attack. Since the bases are held within the double helix both by Watson-Crick hydrogen bonding and by base stacking, base opening involves higher activation energies than other helical deformations, typically of the order of 10-20 kcal mol-1, and consequently it occurs on longer timescales, of the order of tens of milliseconds.

We present here a study of the base pair opening pathway and the energetic details associated with the opening process for central A, T, G, C bases within a d(GAGAGAGAGAGAG)2 oligomer, using an explicit water and counter-ion environment and a biased sampling approach. Bending and other structural consequences of opening as well as changes in solvent distribution around the oligomer are analyzed and compared with experiment. To conclude, we discuss the sequence and structure effect comparing our precedent result with the simulations of a modified d(GAGAGAGAGAGAG)2 oligomer involving two GC®AT substitutions and resulting in a five base pair A-tract, d(GAGAGAAAAAGAG) and an A-RNA, using the original GA alternating sequence, r(GAGAGAGAGAGAG).

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Title :

Computer simulation of the forced unbinding of DNA by AFM - the role of entropy

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Title :

Analyzing the direct and indirect components of protein-DNA recognition

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Title :

Monte Carlo Analysis of Sequence-dependent DNA Structure in Supercoiled DNA: Making Contact with Elastic-rod Models

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Abstract :

We describe an enhanced Monte Carlo model of superhelical DNA molecules containing intrinsic bends or regions of altered flexibility that greatly extends our homogeneous, discrete wormlike-chain representation of supercoiled DNA described previously (Vologodskii et al. J. Mol. Biol. 227, 1224-1243 (1992)). Ensembles of superhelical conformations generated by Metropolis Monte Carlo sampling permit equilibrium statistical mechanical properties to be computed for molecules containing any arbitrary combination of intrinsic bends or other sequence-dependent features. The capability of modeling superhelical structures with arbitrary elastic minima enables rigorous connections to be established between the Monte Carlo simulations and elastic-rod models of sequence-dependent DNA structure. We investigated the effect of intrinsic-bend magnitude and phasing on the global conformation of superhelical plasmids and demonstrate that even modest local distortions of DNA structure arising from a sequence of closely-spaced, out-of-phase intrinsic bends can have global consequences in terms of overall superhelix conformation.

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Title :

Computational Studies of Base Flipping in DNA Alone and Bound to the Cytosine-5-methyltransferase from HhaI

Abstract :

Base flipping represents a simple, but biologically important conformational change in DNA. Flipping events are essential for a number of DNA repair and modification enzymes and have been implicated as initial steps in DNA opening associated with transcription and replication. Potential of mean (PMF) calculations were performed on the DNA dodecamer, GATAGCGCTATC, alone and in the presence of the cytosine-5-methyltransferase from HhaI (M.HhaI) to obtain free energy profiles that encompass flipping though both grooves and for the fully flipped states. Results, in good agreement with experimental data based on NMR imino proton exchange, show that base flipping is feasible through both the minor and major grooves in DNA alone. When bound to M.HhaI, flipping of the target C is facilitated by the enzyme through the major groove pathway. Atomic details from the PMF calculations suggest a mechanism for sequence dependent effects of base flipping in DNA and the mechanism by which M.HhaI facilitates base flipping.

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Title :

Elastic Rod and Elastic Bi-rod Models of DNA

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Title :

Improving Monte Carlo techniques for biomolecular simulations : successes and failures

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To be announced

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Title :

Can't Walk and Chew: A Non-stationary View of DNA Repair

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Abstract :

Structures of damaged DNA in complex with repair enzymes show that the proteins distort the DNA and induce a base flip into an extra helical conformation. These two structural elements control the efficiency of base excision repair through the dynamics of bending and flipping. A combination of experimental and theoretical approaches has been applied to investigate the effect of sequence on the efficiency of DNA repair by uracil DNA glycosylase (UDG). We show that local DNA structure and dynamics play a role in UDG efficiency. Specifically, sequences requiring less distortion energy are better UDG substrates. Fluorescence spectroscopy using the adenine analogue, 2-aminopurine, and molecular dynamics (MD) simulations suggest a sequence-dependent bending flexibility, which is supported by a full kinetic analysis of UDG activity. These results allow the formulation of a relationship between local DNA bending flexibility and UDG activity. MD simulations of DNA with G•U mismatches show sequence-dependent bending and opening properties. Analysis of the factors that contribute to the sequence-dependence shows that base stacking is the major discriminant for partial base opening. Based on the results of the simulations and experiments we present a dynamic model of specific recognition of DNA damage by repair enzymes.

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Title :

Thermal denaturation of an helicoidal DNA model

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Nikos Theodorakopoulos, Theoretical and Physical Chemistry Institute, Athens, Greece

Abstract :

We study the static and dynamical properties of DNA in the vicinity of its melting transition, i.e. the separation of the two strands upon heating. The investigation is based on a simple mechanical model which includes the helicoidal geometry of the molecule and allows an exact numerical evaluation of its thermodynamical properties. Dynamical simulations of long-enough molecular segments allow the study of the structure factors and of the properties of the denaturated regions. The nature of stacking interaction controls the melting transition in a crucial way. Although the theoretical analysis shows that the transition is second order, simulations of finite chains display most of the hallmarks of a first order transition. Moreover the double-helix geometry imposes topological constraints which may have important consequences on the denaturation.

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Title :

Monte Carlo simulations in a suitable collective variable space yield fast conformational equilibration of nucleic acid structures

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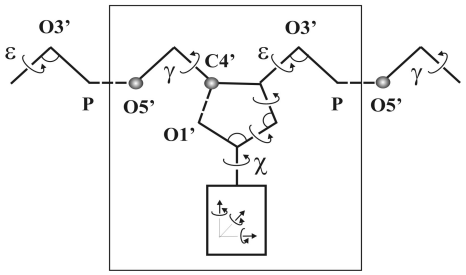
Abstract :

Recent developments of the Chain Breakage/Closure (CBC) algorithm have led to an efficient Monte Carlo (MC) technique for fast conformational equilibration of molecular rings and chains. By using the constant bond lengths approximation and solving the CBC problem in the bond/torsion angle space, collective variables have been defined that maintain structural moves entirely local and allow for large conformational changes in Monte Carlo (MC) simulations. It is essentially this choice of independent variables that enables conformational equilibration on an acceptable CPU time scale, which is considered to be a necessary condition for deriving meaningful structural data from the trajectories of molecular simulations. The currently implemented molecular model for nucleic acids is shown in the Figure. It includes 14 independent chain and ring variables per nucleotide: six rigid body variables of the base, four sugar ring variables, three torsion angles (χ, ε, γ), and the bond angle at O3'. The P-O5' and O1'-C4' bonds are chosen for CBC, where the positions of atoms O5' and C4', respectively, are determined by the closure equations. Associated Jacobians and a suitable probability model for the selection of one of the two closure solutions are included in the Metropolis acceptance criterion for MC moves.



Performance and results of this approach will be demonstrated by applications to several DNA decamers with palindromic sequences and to a ligand/DNA complex. The Amber94 force field has been used for energy calculations, and solvent electrostatic effects were taken into account by a continuum model of the aqueous solvent with explicit counter-ions for neutralizing the phosphate charges. Fast equilibration of counter-ions was found to be important for observing frequent conformational transitions in the DNA oligomers. Accumulated averages and fluctuations of structural parameters show the sequence effects emerging in the course of simulations. In the case of palindromic sequences, the degree of equilibration is indicated by the differences observed for equivalent base pair steps. The simulations of the example sequences show that such differences, compared with sequence-induced differences, are already very small after 10^6 MC cycles, which need less than one week CPU time on a currently available PC under Linux. This result was confirmed by some simulations started from distinctly different initial structures, where the final averaged structures with a RMSD in the order of 0.2Å are virtually the same. The averaged structures show the characteristics of B-form DNA with sequence-dependent helical step parameters that are mostly close to the averages calculated for the ten different dinucleotide steps from crystallographic data bases. The MC trajectory however comprises a broad spectrum of different conformations, where many of them are visited more than ten times. For example, the conformational ensemble of the $d(CG)_5$ dodecamer contains the full range from A-like structures (negative x-displacement, positive inclination, low twist) to D-like structures (positive x-displacement, negative inclination, high twist) and shows that averaged structures and parameter fluctuations do not fully describe the sequence-dependent dynamics of the system. A more detailed insight is obtained from occupancy distributions and correlation analysis of relevant conformational parameters, including sugar pucker parameters, the torsion angles χ, ε/ζ, and α/γ, and the helical parameters. It should be emphasized that the results, thanks to the almost full conformational equilibration, uniquely reflect the behavior of the molecular model under the force field used for energy calculations. Accordingly, the suggested MC simulation technique easily allows for exploring the effect of modified force fields and, in particular, of the approximations used for describing solute/solvent interactions on the results in comparison with available experimental data.

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Title :

Molecular dynamics simulation of unusual DNA and RNA forms. What can we learn by modern theory ?

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Abstract :

Selected results from our recent investigations of a wide range of nucleic acid molecules will be presented. Special attention will be given to highlight what new results and predictions can be obtained by MD simulations, in order to complement the experiments. I will show, for example, how non-Watson Crick segments of nucleic acid molecules as well as DNA-drug complexes can be stabilized by tightly bound water molecules with residency times of several ns and by monovalent cation binding sites with higher than 50% occupancy in the inner-shell binding mode. MD simulations represent an exceptionally exciting tool to characterize such interactions. I will also report several problems we have identified in our recent work and which highlight the limitations of contemporary all-atom molecular dynamics of DNA and RNA. Some of them look rather grim.

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Title :

Extracting Rigid Base-Pair Energy Parameters from Molecular Dynamics Simulations

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Title :

Free energy studies of base flipping in DNA

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Title :

Modeling the DNA conformational transformations on the mesoscopic scales

Abstract :

Basing on the four-mass model approach developed earlier for the description of the low-frequency vibrations of the double helix and due to the transition to the consideration of the joint motions of the structural elements along the conformational pathways the unifying model for the DNA conformational mobility study is constructed. The model describes the mobility of the DNA structure elements on the mesoscopic scales in the frame of the double-helical state (transitions of B-A type or close preopened states, heteronomic transformations).
For the possible trajectories of the DNA structure transformations the expression for the macromolecule free energy is obtained in the two-component form. One model component is the degree of freedom of the elastic rod and another component - the effective coordinate of the conformational transformation. In the model both components are interrelated, as it is characteristic for the soft macromolecule structure of the DNA. As shown the kinetic energy of the conformational transformation of the heterogeneous DNA may be put in the homogeneous form. At the same time the potential energy remains dependent on the nucleotide sequence and in the case of the description of the double helix preopening - on the nucleotide content also.
Two types of the conformational transformations are considered: the transition from the basic state to metastable and the transition between the equivalent states in the condition of the DNA bistasbility (for example, B-A equilibrium). For both types of structural transformations the possible static states of the macromolecule were determined. In the frame of the unifying model the forms of the static excitation were found for internal and external components. The comparison of these data with the experiment on intrinsic DNA deformability shows good qualitative agreement and demonstrates the effectiveness of the proposed approach. The correlation between the macromolecule deformation and the number of the intrinsic conformational excitations are shown.

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Title :

Nucleosome Positioning DNA Sequences

Abstract :

The sequence-dependent structure and mechanics of DNA strongly influences the relative affinity of nucleosomes for one DNA sequence versus another. In earlier work we selected, from a diverse chemically random pool, those DNA sequences having especially high affinity for histone octamer and a correspondingly great nucleosome positioning power. The selected sequences revealed equivalences between certain dinucleotide steps and anti-correlations of others that cannot be understood in terms of existing dinucleotide parameter sets. In recent work we established the rotational orientation of these various dinucleotide steps in the nucleosomal DNA, discovered and quantified plasticity in the allowed locations of these steps, and computed an alignment of the selected sequences.

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Title :

DNA-Cation Interactions

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Title :

Challenges Relating Nanosecond Dynamics to Experimental Biology

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Title :

Long-duration molecular dynamics studies of ion distributions around DNA