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MODELING DNA IN AQUEOUS SOLUTIONS: Theoretical and Computer Simulation Studies on the Ion Atmosphere of DNA

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ABSTRACT

This article provides a review of current theoretical and computational studies of the ion atmosphere of DNA as related to issues of both structure and function. Manning's elementary yet elegant concept of ''counterion condensation'' is revisited and shown to be well supported by current state-of-the-art molecular simulations. Studies of the ion atmosphere problem based on continuum electrostatics, integral equation methods, Monte Carlo simulation, molecular dynamics, and Brownian dynamics are considered. Grand canonical Monte Carlo and non-linear Poisson Boltzmann studies have recently focussed on the determination and significance of the index of non-ideality in solution known as the ''preferential interaction coefficient,'' for which the relevant current literature is cited. The review concludes with a survey of applications to ligand binding problems involving drug-DNA and protein-DNA interactions.

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PERSPECTIVES AND OVERVIEW

A growing realization of the utility of computer simulation studies in developing an atomic view of biomolecular systems and advances made in the adaptation of numerical techniques to biomolecular problems have led to a surge in theoretical explorations of DNA structure and function in recent years. These theoretical efforts have sought to arrive at an accurate description of DNA in aqueous solutions, to present a molecular perspective on conformational transitions of DNA and sequence-specific structural modulations (fine structure) of DNA, and to understand the molecular basis of recognition in protein-DNA and drug-DNA systems. We present herein an overview of the recent theoretical and computational studies aimed at developing accurate theoretical models of DNA in aqueous solutions. We focus particularly on issues related to the structure and energetics of the counterion atmosphere of DNA. For a larger purview on the subject, see the more comprehensive and specialized reviews on condensation theory (77–79), ion atmosphere of DNA (2, 3, 113, 114), molecular electrostatic potentials (106, 107), electrostatic interactions in biomolecules (7, 30, 47, 52, 122, 123, 134), nucleic acid hydration (8, 9, 143), molecular mechanics and dynamics of DNA (14, 72, 111, 138, 141), free energy simulations on biomolecular systems (12, 68, 83), DNA supercoiling (99, 140), condensation of DNA by multivalent cations (18), and modeling DNA (15, 16, 53) and drug-DNA interactions (94).

Because the acidic phosphate groups are fully ionized, DNA at physiologic pH occurs as a polyanion (118). The presence of net equivalent number of counterions (e.g. Na^+, K^+, or Mg^{2+}) in the system ensures electroneutrality. The ions, being mobile, assume a statistical distribution around DNA, the microscopic details of which are not yet established fully. Additional ions from any added salt (e.g. NaCl, KCl, or $MgCl_2$), together with the original counterions and usually some organic ions, form the total ion atmosphere. Along with solvent water, this atmosphere constitutes the DNA environment in vitro. Both the base sequence and the aqueous ionic environment are expected to be major determinants of the structure and function of DNA.

COUNTERION CONDENSATION IN NUCLEIC ACID SYSTEMS

The counterion atmosphere of DNA neutralizes the charges of the anionic phosphates and imparts electrostatic stability to the system. DNA structure is sensitive to the composition and concentration of the ion atmosphere as well as to water activity. This sensitivity is most dramatically illustrated by the change in helix sense involved in the transition from right-handed B-DNA to left-handed Z-DNA at high salt in guanine-cytosine (GC)–rich sequences. The nature of the ion atmosphere of DNA has been the subject of considerable research attention, both experimental and theoretical, in recent years. Manning advanced an elementary theoretical model to account for the diverse macroscopic properties of DNA (78).

Manning's Theory

An important organizing principle in Manning's theory is the phenomenon of "counterion condensation" (CC) (77–79, 100): No matter how dilute the solution, a number of the counterions remain in close proximity to the DNA, thereby compensating a large percentage of the phosphate charges. These counterions, some fraction of the total, are said to be "condensed." The remaining counterions are considered to form a Debye-Huckel–type diffuse ionic cloud. Manning (78) analyzed the problem by a minimization of the phenomenologic free energy expression in the limit of infinite dilution and came to the vexingly simple conclusion that the percent condensation of monovalent mobile cations on B-form DNA was 76% and independent of salt concentration. (The net charge/phosphate in aqueous solutions of canonical B-DNA according to CC theory is -0.24 with sodium counterions and -0.12 with magnesium counterions.) The idea of CC follows simply from thermo-

dynamic arguments. Small ion pairing decreases with dilution because of the increased potential for a large entropy of mixing, which favors dissociation. For polyions like DNA, the superposition of the electrostatic potentials of the phosphate groups on any given mobile counterion makes enthalpic effects dominant in the equilibrium. Consequently, a significant fraction of counterions remain associated with the DNA. The fraction turns out to be essentially independent of the bulk salt concentration owing to the particular nature of enthalpy-entropy compensation in nucleic acid systems. Counterion condensation, therefore, is unique in polyelectrolytes compared with simple electrolyte systems.

The detailed structure (or lack of it) assumed by the counterions within the region of condensation is a point of interest. This feature is important in such diverse areas as the development of a molecular view of salt effects on protein-DNA and drug-DNA complexation and the selection of a suitable initial configuration for the treatment of counterions in molecular dynamics simulation studies on nucleic acids. Considerable ambiguity exists with regard to the underlying structural details of the ion atmosphere. Manning is careful to distinguish condensation (i.e. ions remaining associated with the DNA) from actual site binding. Nuclear magnetic resonance (NMR) experiments have been cited in support of Manning's (78) idea that "all small cations (condensed counterions) are in a state of complete hydration and free translational and rotational mobility," i.e. delocalized and rather loosely associated with DNA. The Manning radius (i.e. the radius of the coaxial cylinder around DNA that encloses 76% of net counterionic charge per phosphate) of the counterion condensate is typically approximately 7 Å beyond the surface of the DNA (and ~17 Å from the helix axis). Manning's theory has provided an account of diverse observed properties of DNA (e.g. colligative properties, transport properties, binding equilibria, melting temperatures, and intercalative binding of drugs to DNA) (40, 79), and the agreement between experiment and CC theory is considered good. Counterion condensation theory is phenomenologic in origin, and a rigorous structural interpretation/extension is beyond its scope. However, the basic concepts of CC in aqueous solutions of DNA have been strongly confirmed by computer simulation (59), as we discuss later. Figure 1 shows the counterion distribution around a DNA oligonucleotide calculated from a recent Monte Carlo computer simulation (59). The distinction between the condensed counterions and those beyond the CC region, some 10 Å from the DNA surface, is remarkably clear.

The CC theory was adapted recently to a more realistic representation of DNA as a three-dimensional discrete charge distribution (33). The results conformed to the inferences based on experiment and the simple

linear lattice model with a uniform dielectric constant (78), when dielectric saturation function was considered by means of a distance-dependent dielectric function for the interactions between phosphates on a double-helical array in a B-DNA geometry. The simpler the DNA model, the simpler the solvent description. Stated alternatively, a more realistic solute model necessitates a more complicated solvent description. Recent further extensions of Manning theory have been described in the area of structural and excluded volume effects (112a) and superhelical DNA (33a). Some new perspectives on the limitations of CC theory have been provided (102a, 108).

Related Experimental Studies

Results on counterions in nucleic acid systems from X-ray crystallographic studies are fragmentary (143). The NMR literature is extensive on cation resonance in DNA systems (17, 19, 36, 63, 97). Experiments involving ^{23}Na NMR indicate support in large measure to the condensation hypothesis (78), but the data have proved to be difficult to interpret unequivocally in terms of structure. Bleam et al (17) demonstrated a two-state approximation in which the observed invariance of the slope of the plot of NMR line widths as a function of salt concentration implies the constancy of the product of the extent of counterion association, and $(r_B - r_F)$ is the difference in relaxation rates of the bound and free sodium ions. Beyond this, there is some ambiguity in concluding that the two factors, r and $(r_B - r_F)$, are individually constant and in extracting a value for the condensed fraction. The NMR predictions of the condensed counterion fractions are in the range of 0.65 to 0.85 (17 and references therein) and, from a more recent study, approximately 0.53 (104). In both cases, however, a constancy of the condensed fraction is implied. Some uncertainty persists with regard to the character of the diffusional motion that dominates the relaxation mechanism and the extent of counterion association (25).

The DNA ion atmosphere has been the subject of numerous further experimental studies. The duplex rotation angle of DNA was found to vary systematically with cation type (97). An explanation for this finding might require some degree of site binding or at least local specificity. Multivalent cations seem to be more disposed to site binding than do monovalents (36). Recent ^{25}Mg, ^{43}Ca, and ^{59}Co NMR studies on the titration of NaDNA with multivalent cations point to the existence of multiple binding environments on B-DNA for the divalent cations (19, 145). DNA flexibility, torsional stiffness, and helical repeat were not influenced significantly by increases in the NaCl salt concentration (133). Light scattering experiments (60), however, showed a strong

ionic strength dependence of the persistence length, which is interpretable in terms of Manning's theory. Effects of Na^+ ions on the persistence length and excluded volume of T7 bacteriophage DNA were interpreted in terms of the CC theory (126). Counterion dependence on the dynamic behavior of water of hydration, studied by low frequency Raman and differential scanning calorimetry, was different for different counterions (K^+, Rb^+, Sr^{2+}, Ba^{2+}) (117, 136). Experimental studies of salt effects on helix-coil transitions (19, 145) in oligonucleotide systems indicate that the thermodynamic equivalent of approximately 0.08–0.13 Na^+ ions per phosphate are released on melting, which is consistent qualitatively with the CC theory predictions. The results also imply some sequence dependence in the condensed fraction. Small angle X-ray scattering measurements (23) of the monovalent (Tl^+) and divalent (Ba^{2+}) counterion distributions, that surround 500 Å long DNA fragments in aqueous solutions, appear to be in agreement with the Poisson-Boltzmann (PB) predictions. The agreement improved if the grooves of the double helix were assumed to accommodate 10% of the counterions.

POISSON-BOLTZMANN STUDIES

A well-known theoretical approach for determining the electrostatic potentials around macromolecules is based on solutions to the PB equation. The PB equation can be solved analytically for simple geometries, such as a line of charge and a uniformly charged cylinder at zero added salt in a dielectric continuum solvent characterized by a uniform dielectric constant. Numerical solutions can be sought in other cases. Solutions to the PB equation yield potentials from which other properties, such as electrostatic free energies and small ion (counter- and coion) concentrations, ensue.

Uniform Dielectric Models

The first studies of this genre were conducted on simplified models of DNA. (For earlier literature, see 2, 45, 54.) Zimm & LeBret (151) used the PB equation to show elegantly how a rodlike polyanion, like DNA, will condense counterions naturally on increasing dilution at a level intermediate between that of a charged sheet (100% condensation, the Gouy-Chapman double layer) and that of a charged sphere (~0%). Anderson & Record (2, 3) have investigated numerous aspects of the PB treatment of the ion atmosphere vis-a-vis thermodynamic measurements and NMR spectroscopy, with a focus on the salt dependence of the fraction of the condensed counterions. Limitations of the PB theory due to neglect of the finite size of the mobile ions and spatial correla-

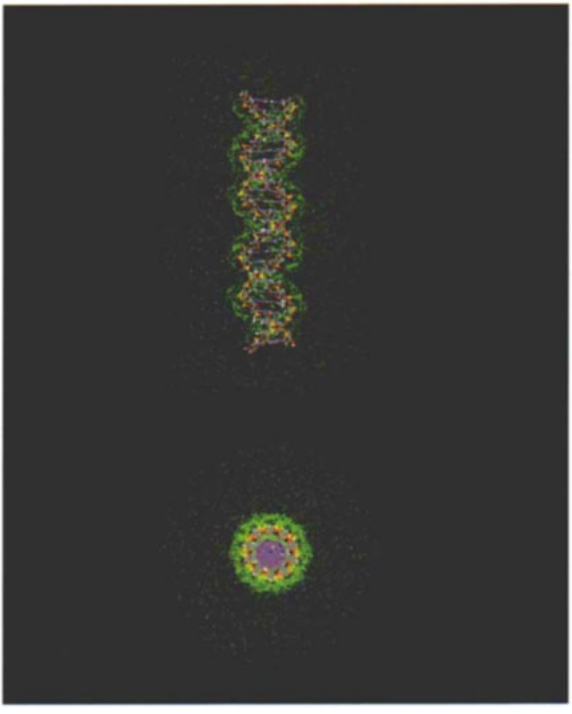

Figure 1 Counterion condensation of Na^+ cations on a DNA oliganucleotide. The calculated cation density is depicted by a superposition of 200 configurations from a 4 million step Monte Carlo Metropolis simulation on 22 mobile Na^+ ions around a fixed canonical B form of the DNA sequence. The effect of water is treated by means of a variable dielectric continuum (59). Graphic presentation prepared by M.A. Young.

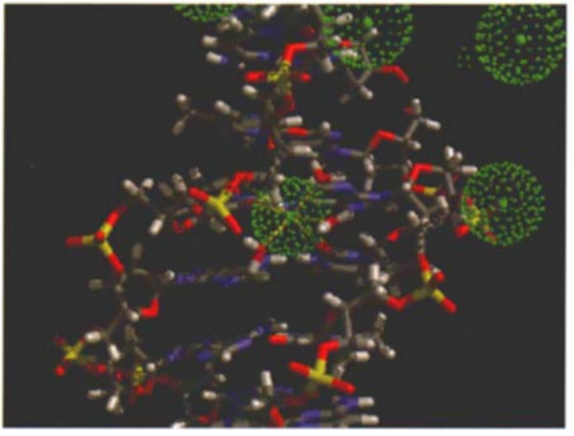

Figure 2 A snapshot from an MD simulation on the d(CGCGAATTCGCG) duplex, 4000 water molecules and 22 Na^+ counterions, depicting the intrusion of a mobile counterion into the minor groove spine of hydration (146a).

tions were characterized. In a recent analysis of the solutions of the cylindrical PB equation as applied to DNA in aqueous solutions, Rajasekaran & Jayaram (108) suggest the existence of certain spatial scales other than the "Manning radius," which are invariant to added salt. Lamm et al (71), on the basis of their PB and Monte Carlo calculations, advocate that the radius enclosing the region in which electrostatic potential is less than $-kT/e$, where e is the charge of an electron, offers a more suitable criterion than the Manning radius. A theory for the second virial coefficients of short DNA, in which interactions between charged cylinders of finite length were modeled, was developed with the use of the PB equation (128). Gueron & Demaret (44) arrived at an algebraic approximation for calculating the PB free energy of a composite cylinder and provided an explanation of the relative stabilities of the B and Z forms of DNA.

Theoretical studies of electrostatic interactions at finite salt concentrations have been extended to treat all-atom models of DNA. Klein & Pack (66) obtained electrostatic potentials from an iterative PB solution to a combination of Coulombic potentials from the fixed macromolecular charges and the distribution of mobile charges obtained from the Boltzmann equation. The results predicted significant concentration of mobile cations in the minor groove as well as along the sugar phosphate backbone, a consequence of the superposition of trans-groove anionic phosphate potentials. Hydrogen ion concentrations at the surface of the DNA, which might be of relevance to interaction of mutagenic epoxides, were estimated with the use of the PB approach (70). The pH was less by approximately 2–3 pH units compared with that of the bulk solvent. The above theoretical treatments assume that the dielectric constant ϵ is everywhere equal to 80, including inside the DNA.

Two-Dielectric Models

The potential influence of the dielectric boundary between the DNA (ϵ = 2–4?) and solvent at $\epsilon \cup 80$ was explored by several groups (58, 81, 135, 142). The Tanford-Kirkwood model was extended to arbitrary charge distributions with an overall cylindrical symmetry (54). This work suggested that a consideration of the details of the three-dimensional charge distribution, as opposed to a linear lattice description, was necessary to account for the stability of the B form of DNA relative to the Z form in aqueous solutions at low salt.

Troll et al (135) conducted a macroscopic simulation of duplex DNA represented by a clay model in an electrolyte tank. These authors found that interactions between charges on the same side of the DNA were enhanced as a consequence of a concentration of field lines by the low

dielectric DNA, thereby increasing both attractive phosphate–cation and repulsive phosphate–phosphate and cation-cation interactions. They also found that shielding was increased for charges on opposite sides of DNA by the presence of the low dielectric medium. Jayaram et al (58) incorporated dielectric boundary, solvent screening, and ionic strength into finite difference solutions to the PB equation (FDPB) for an all-atom model of DNA. In this study, the sequence dependence in electrostatic potentials appears as a natural consequence of the model with no extra assumptions. The distribution of the electrostatic potential in B-DNA shows an intrinsic dissymmetry (the minor groove of adenine-thymine (AT) sequences is more negative than the minor groove of GC sequences). Deepest potentials were located in the grooves rather than in the phosphate regions. The results are in general agreement with the pioneering work of Pullman and co-workers (106, 107) on the basis of quantum mechanical studies. The numerical results also support qualitatively the electrolyte tank observations on the angle dependence of the charge–charge interactions (135). Electrostatics appears to dominate the base pairing interactions (N Aneja, B Jayaram, and B Honig, unpublished data) but contributes negligibly to stacking interactions (37). The FDPB approach provides a conceptually simple and theoretically sound basis to investigate electrostatic interactions involving nucleic acids (biomolecules in general) under physiologic conditions (52). Pack et al (103) found that the presence of a dielectric boundary altered the electrostatic potentials significantly within the grooves of DNA, as in the FDPB studies cited above. These effects appear to be confined close to the surface. Application of the finite element technique to solve the nonlinear PB equation as applied to DNA was also reported (110).

Distance-Dependent Dielectric Models

Electric fields near an ion are on the order of 1 million volts/cm and are expected to be even larger for a polyanion such as DNA. Dielectric saturation thus assumes importance in studies on DNA. Hingerty et al (50) studied the role of dielectric inhomogeneity and the influence of dielectric saturation on oligonucleotide–small ion interactions by means of a distance-dependent dielectric screening function. This method was subsequently reparameterized and used in energy minimization studies on DNA by Lohman (75) and Ramstein & Lavery (109) with the JUMNA algorithm. Mazur & Jernigan (82) reviewed the applicability of distance-dependent dielectric functions. Their analysis indicated that the local helix geometry of the base pairs was affected strongly by the contributions of the electrostatic interactions to the stacking energy. A lower dielectric constant ($\epsilon = 10$) in the layer at

the first 1 Å from the surface resulted in a 70% increase in the calculated counterion density (103). Support for the inclusion of dielectric saturation in dealing with charge–charge interactions in DNA systems in the dielectric continuum solvent approach appears to be mounting. The results of Hecht et al (49), however, seem to imply that a distance-dependent dielectric function is not necessarily superior to the two-dielectric model for calculating electrostatic potentials around DNA in solution. Applications of the PB equation to cylindrical models of polyions and various other models of DNA continue to hold research attention (1, 29, 105, 125).

Numerical solution of the non-linear PB equation by finite difference methods for highly charged systems such as nucleic acids has been subject to convergence and stability problems, addressed heretofore by multigridding techniques (51b, 97a). A rapid new method for non-linear PB calculations, stable even for highly charged systems, has recently been developed based on the inexact Newton method (51a). The effect of ion size has been introduced into non-linear PB using self-consistent iteration schemes (103).

INTEGRAL EQUATION METHODS

The practice of deducing an effective two-body potential of mean force (pmf) and incorporating that in the Hamiltonian of a many-body system has a long history. Soumpasis (127) considered the phosphate backbone of DNA and the ion atmosphere as a fully dissociated 1:1 electrolyte of specified composition and thermodynamic state for the purpose of estimating the phosphate–phosphate pmf. The pmfs were calculated with the use of either the hyper-netted chain (HNC) formalism or the exponential mean spherical approximation (EXP-MSA), depending on the level of accuracy desired. This approach was shown to account quantitatively for the salt dependence of free energy differences between B and Z conformations of DNA from 0.1 to 4 M NaCl (62). The theory uses only one adjustable parameter, the distance of closest approach of an anion–cation pair (set equal to 4.9 Å for NaCl). The success of the theory is intriguingly remarkable considering that the derived pmfs between phosphate charges incorporate neither the effects caused by the presence of other atoms on DNA nor their connectivity along the backbone of DNA. The pmf approach was integrated subsequently into the AMBER molecular mechanics force field (41, 65), thereby replacing the electrostatic terms in it by the pmfs. This step enabled an investigation of the ionic distributions (64), as well as structural transitions of DNA in solution.

More recently, Hirata & Levy (51) discussed the application of a restricted interaction site model (RISM) theory developed for solvated polymers to a study of the salt effects on DNA conformation. Their studies predicted a transition from B to Z form at 3.6 M added salt in qualitative accord with experiments without any optimization of the model parameters involved. Their work further showed that the superposition approximation inherent in the pmf approach might be less severe than anticipated (in the B to Z transition) because of a cancellation of higher order correlations when the free energy difference between B and Z DNA was calculated (127).

Bacquet & Rossky (4) applied the HNC integral equation method to the system of DNA in aqueous 1:1 electrolyte solution. The HNC and CC approaches were in general qualitative accord but differed in quantitative predictions regarding the extent and concentration dependence of the CC approach. In a related study on ion distributions and competitive association in DNA/mixed salt solutions, composition near the polyion was more responsive to the changes in the bulk composition (5). The counterion size was of minor importance compared with its valence in determining the ionic distribution, except at immediate contact with the polyion. The calculated fluctuations in the electric field gradients experienced by the sodium nuclei correlated well with the observed NMR line widths.

The integral equation methods, accepting the approximations, are computationally more expedient than are molecular simulation methods for estimating free energies.

MOLECULAR SIMULATIONS

Canonical Ensemble Monte Carlo Studies

HYDRATION DNA presents a variable and sequence-dependent hydrogen bonding pattern in the major and minor grooves (119). Solvent water is expected to interact differently with the four bases—adenine, guanine, thymine, and cytosine—and show a differential, sequence-dependent, stabilization effect on the overall conformation. With the observation of the ''spine of hydration'' in the minor groove of B-DNA (31), the plausible role of solvent in deciding the fine structure of DNA, the implication of water-mediated hydrogen bonds in protein-DNA interactions (102), and their potential contribution to the thermodynamics of DNA-ligand binding (80, 117), there is a continued interest in the hydration of nucleic acids (8, 9, 143).

Early computer simulation studies on hydration used Monte Carlo (MC) methods and focused on nucleic acid constituents (13). MC studies were extended subsequently to hydration of oligonucleotides and in particular the Eco RI dodecamer of sequence d(CGCGAATTCGCG) (15). Subramanian et al (129) gave a theoretical account of the sequence-dependent hydration of the Eco RI dodecamer vis-a-vis X-ray and calorimetric studies. They noted that both AT and GC regions in the minor groove could support an extended network of water molecules owing to the geometric versatility of water–water hydrogen bonding. As anticipated, the penetration of water into the DNA was clearly greater for AT than for GC tracts. A recent analysis of the crystallographic data on the hydration of bases in oligonucleotide systems shows conformation-dependent differences in both geometry and extent of hydration (8, 9). (For a survey of the hydration of nucleic acid systems with a nearly complete citation to the literature, see 143.) MC simulations on water and counterions around DNA are sometimes performed as part of the equilibration procedure in molecular dynamics simulations of DNA in solution.

ION ATMOSPHERE MC or molecular dynamics (MD) calculations based on a fully explicit consideration of DNA, water, counterions, and added salt at a concentration of physiologic interest are a computationally expensive proposition, even for current day supercomputers. Studies aimed at pursuing the role of electrostatic interactions and the nature of the ion atmosphere of DNA on the basis of molecular simulation often take recourse to the primitive model. In all the simulation studies with the primitive model and variations thereof, ions are treated explicitly, and water is represented as a dielectric continuum. This is clearly a serious approximation, because the molecular nature of water as an associated liquid is neglected and its particular capacity for hydration, bonding, and solvation in different modes—hydrophilic, hydrophobic, and ionic—is denied. Also, there is no way to parametrize the heterogeneous qualities of the dielectric medium accurately from experimental data. Results of theoretical studies and simulations based on primitive models have to be interpreted in this context.

Extensive canonical MC studies on DNA counterion systems in the absence and presence of added salt have been reported by several groups. LeBret & Zimm (73) modeled DNA as a linear lattice of charges imbedded in an impenetrable cylinder and as a double helical array of charges, with mobile ions represented as hard spheres that interact with each other and with DNA via Coulombic potentials in a solvent treated as a uniform dielectric continuum. They found a striking accumulation

of counterions in a layer of concentration exceeding 1 M at the surface of the polyion in agreement with conclusions from previous PB studies and CC theory. Murthy et al (93) and Mills et al (86, 88) subsequently explored ion distributions in a solvent treated as a uniform dielectric continuum around a uniformly charged cylinder (and a lattice of discrete phosphates) that represented DNA. A comparison of their Monte Carlo results with those emerging from PB and HNC studies suggested that the PB approach underestimated counterion concentrations near DNA treated as a cylinder by approximately 12–18%. The empirical Manning radius decreased with increasing salt concentration in all these studies. Conrad et al (28) incorporated effects caused by dielectric discontinuity in their interaction potentials to evaluate small-ion DNA interactions. The modifications to Coulomb's law tended to drive the ions out of the grooves, especially the major groove. They ascribed this observation to repulsions between the ions, the low permittivity of the helix, and, partly, to the focusing of field lines of phosphates at the surface of the helix caused by dielectric discontinuity.

Jayaram et al (59) performed comparative simulations of the counterion distribution around DNA on the basis of a series of models for the aqueous dielectric medium that were likely to bracket the true physical nature of the system. The results showed that, in all cases of continuum solvent, counterion concentrations near DNA (i.e. ~10 Å from the helical axis) exceeded 1 M, even in the absence of excess salt. This finding was consistent with CC theory and previous MC and PB studies on DNA-counterion systems. An analysis of the simulation results based on different dielectric models indicated that the dielectric saturation model favored increased CC relative to the Coulombic model, with DNA–counterion interactions dominating the small ion repulsions. The dielectric saturation model produced an essentially salt-independent result for the fraction of condensed counterions over an added salt concentration range of 0 to 150 mM, which is consistent with inferences based on NMR and CC theory. The results with an energetic criterion, as opposed to a geometric radial criterion, for computing the condensed fraction of counterions around DNA were essentially similar to the above results with the dielectric saturation model (B Jayaram and DL Beveridge, unpublished data).

Gordon & Goldman (42) recently reported counterion and solvent distributions around a polyion, as seen in their MC calculations conducted with 15 counterions and explicit water. Interestingly, the uniformly charged cylindrical model led to a high degree of solvent polarization, which caused the counterions to avoid regions vicinal to the polyion. When a helical necklace of charges at the surface of a cylinder

was considered as a model for the polyion in conjunction with molecular solvent, the counterions formed a compact double layer near the surface. This formation resulted in an extensive screening of the polyionic charges, as found earlier in the numerous studies based on continuum solvent. Nishio (96) presented some exploratory MC simulations on the potentiometric behavior of aqueous salt-free solution of rodlike polyelectrolytes in a cylindrical cell system. A comparative study of the MC and mean field theory results on the titration behavior of linear polyelectrolytes was reported recently (116). Mills et al (89) reported MC calculations of ion distributions surrounding an oligonucleotide $d(ATATATATAT)_2$ in the B, A, and wrinkled D conformations. Significant counterion accumulation in the major groove of A-DNA and, to a lesser extent, of B-DNA was noticed. Results on D-DNA were similar to those for an impenetrable cylinder. Excluded volume effects therefore appeared to alter the ion distributions strongly, whereas the detailed charge distribution was affected minimally. Erie et al (32) extended MC methodology to generate a distribution of oligonucleotide conformations with feasible dinucleotide steps. Several loop conformations were compatible with the given experimental (spectroscopic and thermodynamic) data.

Grand Canonical Monte Carlo (GCMC) Studies

The (T,V, μ) ensemble simulations lead to direct calculation of the excess chemical potentials and excess free energies, which are not as easily accessible in the canonical Monte Carlo calculations. Almost all the GCMC studies to date on DNA use the primitive model to study the role of ion atmosphere on the bulk solution properties of DNA, and no hydration studies have been reported. Grand canonical Monte Carlo simulations with explicit solvent are slow to converge at particle densities of experimental interest. The GCMC simulations on the ion atmosphere have provided interesting information on non-idealities in aqueous solutions of DNA (55).

Vlachy & Haymet (139) used the GCMC method to obtain structural and thermodynamic data for model polyelectrolyte solutions. They treated the polyion as an impenetrable, rigid, infinitely long cylinder. The results were compared with PB and HNC integral equation studies with the use of the MSA. The authors concluded that the PB equation retained its semiquantitative utility even in the range of moderate to high (1 M) concentrations of added salt. Extensive GCMC studies on aqueous solutions of sodium salt of DNA in the presence of added simple salt were reported by Anderson, Record, and coworkers (3, 87, 98). The simulations were used to calculate mean ionic activity coefficients and "preferential interaction coefficients," [similar to the

Donnan salt exclusion factor (79) and the Donnan membrane equilibrium parameter (43)] for a cell model representation of NaDNA with added salt. The role of end effects on molecular and thermodynamic properties in oligoelectrolyte solutions was characterized via the GCMC method (98 and references therein). The results indicated that an oligoion that contained 48 or more phosphates behaved as a polyion. The thermodynamics of denaturation of oligonucleotides was also investigated. The GCMC studies of Anderson, Record, and coworkers on the preferential interaction coefficient, which they idenify as a thermodynamic measure of nonideality caused by small ion–polyion interactions, provided a considerably enhanced perspective on the problem (3, 97b). A recent detailed exposition of the theory has been provided (3a). Sharp (122a) has developed the relationship between preferential interaction coefficients and PB. Valleau (137) presented an extension of the GCMC method to a flexible polyelectrolyte immersed in primitive model aqueous electrolyte solutions.

Jayaram & Beveridge (55) recently reported GCMC simulation studies on aqueous solutions of sodium chloride and sodium salt of DNA in the presence of added salt. Results for the simple electrolyte indicated that a soft-sphere potential function for the ions in a solvent treated as a dielectric continuum, supplemented with a Gurney correction term for desolvation, described the behavior of activity coefficients as a function of concentration quite well, over a concentration range of 5 to 500 mM. The results on the NaDNA system in the presence of added simple electrolyte provided an account of the contravariant behavior of nonideality of mobile ions in polyelectrolyte vs simple electrolyte solutions. Excess chemical potentials calculated from these GCMC simulations suggested that the counterions interacted more strongly with DNA at low salt than at high salt (55). Nonideality of counter and coions in sodium salts of DNA in water in the presence of added sodium chloride salt, therefore, increases with dilution and decreases with added salt contrary to the behavior in simple electrolyte solutions.

Among the limitations of the canonical and GC Monte Carlo studies, as described above, are that the internal degrees of freedom of the solute (DNA) are frozen and that the solute does not respond to the fluctuating environment of the solvent and ion atmosphere. Zhurkin et al (149) presented a Monte Carlo study on the sequence-dependent bending of DNA by sampling the internal coordinates. Gabb et al (39) reported an internal coordinate furanose model on the basis of the pseudorotational variables, phase and amplitude, thus providing a method to deal with flexible rings in the context of Monte Carlo simulations. One further desirable, albeit difficult, course of research to follow would be to perform an internal coordinate Monte Carlo on DNA along-

side the counterion/solvent Monte Carlo. This study should enable probing the sequence-, solvent-, and ionic strength–dependent conformational flexibility of DNA. Of course, some methodologic improvements, particularly on the convergence and improving acceptance ratios, are desired to facilitate this line of research.

Theoretical studies of counterion atmosphere have recently been extended to branched nucleic acids (98b), conformational transitions and DNA triplexes (18a).

Molecular Dynamics Simulations

Currently, only a few molecular dynamics calculations on DNA systems that consider counterions and solvent water explicitly have been reported (14, 35, 111, 124, 131, 132). Considering, however, that the first molecular dynamics simulation on DNA was reported little more than 10 years ago (74), the popularity of this technique, with simpler models for solvent and small ions, is phenomenal. Most studies to date treat the effect of counterions implicitly, by reducing the charges on the phosphates from -1 to -0.25, -0.32, -0.34, -0.5 (14, 16, 95), i.e. fractional charge justified by CC theory, or even to zero (74)! This approach does make the DNA more stable electrostatically but obviously lacks the correct physics. Explicit inclusion of counterions has produced convergence problems in the simulations that currently are being investigated actively (111). The effect of the solvent and counterions has been incorporated implicitly via a distance-dependent dielectric function into numerous studies; the justification is in the quality of the results. Further, problems in analyzing molecular dynamics literature on DNA in aqueous solutions are twofold. No uniform method of analysis is adopted by different authors to facilitate a comparison among the different dynamic models. Root mean square deviations are too simplistic. Analysis based on Curves, Dials, and Windows (112) is helpful in providing a detailed characterization of the dynamic models of DNA. The other problem relates to comparison with experiment. We do not know yet what is absolutely correct regarding DNA structure in solution. Gross structural distortions, such as collapse of the groove structure and folding of the DNA, may be termed incorrect. Progress in the solution structure determinations via two-dimensional NMR, combined with the information collected from crystal structures, holds promise for a rigorous characterization of the different simulations on DNA, but the situation at present remains a complex one and nothing should be taken for granted. For an overview of all the molecular dynamics simulations of DNA published to date, see the reviews by Beveridge et al (14, 16, 111).

A general concern emerging from the molecular dynamics studies on DNA is that, in simulations with explicit ions and solvent molecules, the trajectories may be sensitive to the initial location of counterions. Overall, a better agreement with crystal structure has been obtained so far by starting with a scaled phosphate charge model. The truncation of potentials is also a particularly important issue in nucleic acid systems. A switching function is applied around the cutoff to feather the potentials smoothly off to zero, so that calculation of forces remains well conditioned. Truncation effects can be rather serious for a polyionic system such as DNA. In addition, if the range of the switching function is too narrow in potentials used for molecular dynamics on DNA, artifacts may be introduced as a consequence of charged groups that tend to cluster at the cutoff limit. This problem is remedied by extending the range of the switching function from 1 to 4 E, which frees the molecular dynamics from this artifact (14, 111). Cheatham et al (24) recently reported results from a nanosecond dynamics of DNA by using both the spherical cutoff and Ewald summation. These authors showed that more stable structures were observed by applying the Ewald summation. A proper protocol for the treatment of counterions and electrostatic interactions in the molecular dynamics simulations on DNA appears to be well within reach (85, 144, 147).

A sequence of ordered solvent peaks in the electron density map of the minor groove region of AT-rich tracts of the double helix is a characteristic of B-form DNA well established from crystallography (31). This feature, termed the ''spine of hydration,'' has been discussed as a central stabilizing feature of B-DNA, the structure of which is known to be sensitive to environmental effects. Lengthy molecular dynamics simulations on the DNA duplex of sequence d(CGCGAATTCGCG) have been carried out, including explicit consideration of 4000 water molecules and 22 Na^+ counterions (see Figure 2) and based on a new version of the AMBER force field (28a) with the particle mesh Ewald summation used in the treatment of long range interactions. The simulations were carried out for a heretofore unprecedented run length of 1.5 nanoseconds, and support a dynamical model of B-DNA closer to the B form that any previously reported (146b). Analysis of the dynamical structure of the solvent revealed that in over half of the trajectory, a Na^+ ion is found in the minor groove localized at the AT step. This position, the ''ApT pocket,'' was noted previously (72a) to be of uniquely low negative electrostatic potential relative to other positions of the groove, a result supported by the crystal structure of dApU (119a) and by calculations based on continuum electrostatics. The Na^+ ion in the ApT pocket interacts favorably with thymine O2

atom on opposite strands of the duplex, and is well articulated with the water molecules which constitute the remainder of the minor groove spine. This result indicates that counterions may intrude on the minor groove spine of hydration on B form DNA, and subsequently influence the environmental structure and thermodynamics in a sequence dependent manner. The observed narrowing of the minor groove in the AATT region of the d(CGCGAATTCGCG) structure may be due to direct binding effects and also to indirect modulation of the electrostatic repulsions that occur when a counterion resides in the minor groove ApT pocket.

Brownian Dynamics Simulations

Internal motions of DNA, as well as the distribution and dynamics of ions around DNA in the nanosecond regime and beyond, can be studied profitably with the use of Brownian dynamics simulations (84). Few such studies, however, have been reported. Barkley & Zimm (6) reported one of the earliest such calculations. They treated DNA as a semiflexible chain and developed a theoretical account of fluorescence depolarization. In an interesting extension of the Brownian dynamics formalism, which includes the accessible surface area, Kottalam & Case (69) computed Langevin modes of DNA hexamers. More recently, Briki et al (20) reported a Brownian dynamics simulation of a B-DNA $(dA)_5$ $(dT)_5$ oligomer. The lifetime of the base pair and the activation energy for the opening process were calculated to be 15 ms and 20 kcal/mol, respectively, which compared favorably with the corresponding experimental measurements obtained by hydrogen exchange studies.

Reddy et al (115) used stochastic dynamics simulations to probe counterion spin relaxation of the quadrupolar nuclei in the vicinity of DNA. The calculated relaxation behavior was in qualitative accord with experiments. Guldbrand et al (46) recently reported the distribution and dynamics of counterions around B-DNA, with a continuum solvent and an all-atom model of the solute via Brownian dynamics simulations. The continuum solvent model successfully reproduced the results of the fully explicit molecular dynamics simulations for the distribution of those counterions that maintained their hydration shells. The distributions of the counterions far away from the polyelectrolyte in their simulations agreed with the results of the PB approach. The Langevin equation has found applications in theoretical explanations of gel electrophoresis of DNA (76, 150) and in DNA supercoiling (26). Brownian dynamics simulations have been successfully extended to the study of concentrated DNA solutions (31a).

STUDIES ON PROTEIN-DNA AND DRUG-DNA SYSTEMS

The essential contributions to the free energy of association of a protein or a drug molecule with DNA come from (*a*) direct interactions between the protein or drug molecule and the DNA, both intra- and intermolecular; (*b*) release of some of the water molecules bound to both protein or drug and DNA; and (*c*) release of some of the counterions associated with DNA. The last contribution is known as the polyelectrolyte effect.

Polyelectrolyte Effects

Release of condensed counterions is considered to provide an entropic driving force for the DNA-ligand complex formation. Manning (78) and Record et al (113) developed a theoretical framework to understand the role of the ion atmosphere in DNA–ligand association and to quantify the contribution of electrostatic interactions to this process. A plot of log K_{obs} vs log [MX], where K_{obs} is the observed association constant for the DNA–ligand complex and [MX] is the salt concentration, gives a slope of $-Z$ (75). Here, Z is the thermodynamic equivalent of the number of counterions released during the DNA-ligand complex formation, and the phosphate charge is reduced by a value of 0.88, which is a sum of 0.76, to account for the condensed counterions, and 0.12, to approximate the screening effects caused by the remaining uncondensed Debye-Huckel–type diffuse ionic cloud in the system (118). The value of Z in such a log–log plot is interpreted commonly as indicating the number of ionic interactions in the complex. A small value for Z or a positive slope is taken to mean that the electrostatic contribution is not the driving force, whereas a large negative slope is taken to imply that it is the dominant mechanism. Theoretical methods based on molecular simulation can describe the complex in terms of intermolecular interactions and provide a basis for developing more detailed molecular models of the process together with estimates of the corresponding energetics.

The application of continuum electrostatics to the study of salt effects on the binding of minor groove antibiotics to DNA has been described by Honig and coworkers (91). A comparison of Poisson Boltzmann and limiting law counterion binding models provides evidence that the electrostatic free energy in PB contains a significant additional entropy contribution from water reorientation which contributes to the salt dependence of ligand binding (122b). The relationships between limiting law, PB and full MD simulation descriptions of these processes will be fully elaborated as supercomputer power makes molecular simulations on these problems tractable for a wide range of examples. A

recent review of the area of salt effects on nucleic acids is due to Sharp and Honig (123a).

Recent free energy simulations on the thermodynamics of λ repressor-operator association have shown that polyelectrolyte effects, in the region that favors protein-DNA association, are short ranged (57). The ion atmosphere contribution to the free energy of association is favorable and is at its maximum when the protein approaches the DNA from a distance of separation of approximately 7 Å, which is typically the radius of the counterion condensate around B-DNA. Displacement of the condensed counterions contributes favorably to the free energy of DNA–ligand complexation. The exact magnitude of this free energy is expected to depend on the nature of the ligand, as well as on the manner in which electrostatic interactions are treated and the direction of approach of the ligand toward the DNA.

The FDPB method was used to analyze salt effects on drug-DNA and protein-DNA complexation (90, 91, 148). Interestingly, the binding free energies turn out to be positive, whereas the slopes $(-Z)$ of log K_{calc} vs log (salt) plots are in good accord with experiment. A combined conformational search and PB study to flexible docking in the λ repressor-operator protein-DNA complex has been described (148). At this juncture, there is sufficient indication that theoretical calculations based on the FDPB methodology can account for ion atmosphere effects on protein-DNA and drug-DNA association quantitatively.

GCMC calculations have been reported on the salt dependence of oligocation binding incorporating structural detail of the DNA (98a).

In a recent study on the binding of the Tet repressor to nonspecific and specific DNA monitored by stopped flow techniques, Kleinschmidt et al (67) concluded that nonspecific binding was almost completely driven by the entropy change resulting from the release of three to four Na^+ ions from the double helix on protein binding. Formation of the specific complex was driven by a higher entropy term that resulted from the release of seven to eight Na^+ ions, along with a favorable free energy term that came from nonelectrostatic interactions attributable to specific contacts. Senear & Batey (121) reported a thorough experimental investigation of salt effects on the binding of λ cI repressor to the right operators (OR1, OR2 and OR3) and nonspecific DNA. The thermodynamic equivalent of the number of K^+ ions released varied as 5.9 ± 0.7 for OR1, 6.0 ± 0.6 for OR2, 3.8 ± 0.7 for OR3, and 4.8 ± 0.7 for nonspecific DNA. The observed differences suggested a role for ion binding in site specific recognition, which reflected different deformations of the repressor and/or different conformations of the DNA so that a different number of ions and, presumably, water molecules were removed from the interface on binding.

Other Related Studies

Few simulation studies have yet been conducted on protein-DNA and drug-DNA systems including explicit consideration of water molecules and small ions, largely because of heavy computational requirements. Molecular dynamics simulations with simpler treatment of solvent and counterions, however, have become an integral part of the X-ray and NMR structural refinement procedures for the protein-DNA and drug-DNA complexes (21). Orozco et al (101) analyzed the role of explicit solvent in modeling drug-DNA structures and advocated the use of a distance-dependent dielectric constant. Gago & Richards (40) performed free energy simulations on netropsin binding to poly[d(IC)] poly[d(IC)] and poly[d(GC)] poly[d(GC)] with a consideration of explicit water and counterions. The calculated free energy change ($\Delta\Delta G$) between the ATAT(ICIC) and GCGC sequences was 4.35 kcal/mol, in close correspondence with the experimental value of 4 kcal/mol. The width of the minor groove was proposed to be a determinant of specificity in these sytems. Results of free energy simulations on base specificity of daunomycin and acridine intercalation into DNA with the AMBER force field and implicit incorporation of water and solvated counterions showed qualitative agreement with experiment (27). Swaminathan et al (130) investigated the static and dynamic aspects of the intermolecular hydrogen-bonding network and the organization of water via molecular dynamics simulations on dCpG/proflavin complex. Cardozo & Hopfinger (22) used molecular dynamics simulations to investigate reaction pathways of the complex of dynemicin-A and DNA. A 100-ps molecular dynamics study of a triple helix explicit water and counterions showed that phosphate groups constitute primary centers of Na^+ attachment (92). Sekharudu et al (120) modeled a third poly(dT) strand Hoogsteen base-paired to the major groove of the poly-(dA) poly(dT) Watson-Crick (WC) base-paired duplex in the canonical B-DNA form and performed molecular dynamics simulations for a total period of 400 ps with explicit water and counterions. The geometry of the WC portion of the duplex turned out to be unique, differing from both the A and B forms of DNA. Jin et al (61) characterized the structural aspects of nucleic acid complexes with 2′,5″ and 3′,5″–phosphodiester linkages with the use of a combination of spectroscopic and calorimetric techniques and a computer-assisted search for macromolecular structures that exhibit features consistent with the experimental data. The latter were found to form either a duplex or triplex, depending on the sodium ion concentration, whereas the former formed either a triplex or no complex at all. Singh and coworkers (48) studied the dynamic properties of methyl phosphonate double-stranded DNA, a

potential therapeutic agent. Molecular dynamics simulations on DNA decamers with scaled phosphate charges and with disulfide crosslinks attached to exocyclic amines of the adenines in the central 5′-AT-3′ base pairs were performed (34), and the results compared with those of crystal and NMR studies. Brownian dynamics studies (56) that addressed some mechanistic issues of relevance to the kinetics of complexation suggested a nonspecific association of the protein to the DNA followed by a facilitated diffusion (in reduced dimensionality, such as sliding) to the target site, in conformity with the earlier interpretations of experiment by von Hippel and coworkers (146).

More experimental and theoretical studies are needed, and some are in progress in diverse laboratories, to develop a comprehensive view of the molecular aspects of protein-DNA and drug-DNA recognition, DNA fine structure, and the role of solvent and ion atmosphere around DNA.

CONCLUSION

DNA problems are unique in that the molecule per se and its surrounding water and counterions must be treated together as a molecular ecosystem in order to properly describe structure and function. This requires theoretical studies of either well crafted approximations such as continuum electrostatics or of exceedingly high dimensionality as in molecular simulation. Computational research currently has been concerned with the development and assessment of the protocols and force fields that underlie static and dynamic models of DNA in solution (14, 111). There is sufficient justified optimism that the theoretical studies summarized here would evolve very soon into predictive tools for investigations on sequence-dependent fine structure of DNA and protein-DNA recognition.

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