Local Dielectric Environment of B-DNA in Solution: Results from a 14 ns Molecular Dynamics Trajectory

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The dielectric behavior of solvent water around DNA is elicited in terms of Kirkwood−Grunwald theory from a 14 ns molecular dynamics trajectory of B-DNA developed in a medium of explicit waters and sodium counterions with particle mesh Ewald for long-range electrostatics. The computed dielectric profile near DNA increases rather rapidly with distance and displays bulk behavior beyond 5 Å. A proximity analysis of the dielectric function reveals that the relative permittivities in the first shell of DNA obey the following trend in the simulations: phosphate backbone > major groove > minor groove. Estimates of the local dielectric constants in the major groove are consistent with interpretations based on fluorescence measurements, indicating that MD models of solvent around DNA are providing a reasonably accurate account of the local solution environment of a complicated polyelectrolyte. The calculated dielectric profile is fit to a sigmoidal function, which can be used in estimating the strength of charge−charge interactions around DNA.

I. Introduction

Dielectric constant, ϵ, is a measure of the polarizability of a condensed phase system in the presence of an applied field. In an operational definition, ϵ is identified with the scaling parameter appearing in the denominator of Coulomb's law, determining the relative permittivity, the extent to which electrostatic interactions are scaled down relative to their vacuum value. In water, with $\epsilon = 78.3$ at room temperature, the effect on electrostatic interactions is profound. In the vicinity of a macromolecule in water, the local dielectric deviates from the bulk value as a consequence of the influences on solvent structure and motions. Thus theoretical descriptions of interactions with charged ligands will require a detailed knowledge of the local dielectric environment. This is especially important in polyelectrolyte nucleic acids, DNA and RNA, which exhibit a strong influence on as well as response to the local solvent environment. The local dielectric behavior of DNA assessed via fluorescence measurements on drug−DNA complexes[1] led to a relative permittivity close to 20 for the minor groove of DNA in the presence of the drug moiety, while the dielectric constant in the major groove was estimated[2] to be around 55. A theoretical account of this result based on a mixture model of water has been provided by Lamm and Pack[3] and follow results suggested by the finite difference Poisson−Boltzmann (FDPB) calculations which treat solvent as a dielectric continuum.

Recently, it has become feasible to perform large-scale molecular dynamics simulation on DNA surrounded by water and counterions,[4] and it is of considerable interest to investigate if the detailed description of molecular structure and motions of solvent water around DNA provides an accurate account of the dielectric behavior observed from fluorescence studies and described succesfully by ad hoc models with semiempirical parametrization. The surprisingly large difference in the local dielectric between the major and minor grooves is of particular significance in this system, since both grooves are binding sites for ligands, and a molecular level account of this phenomena serves as a critical test of the accuracy of MD models of DNA and its solution environment. In this article, the dielectric behavior of solvent water around a B-form DNA oligonucleotide is calculated based on an adaptation of Kirkwood dielectric theory[5] for pure solvents to solutions, from a 14 ns molecular dynamics trajectory of B-DNA developed in a medium of explicit TIP3P waters and Na^+ counterions with particle mesh Ewald for long-range electrostatics. The calculated dielectric behavior shows a sigmoidal behavior as predicted earlier by PB theory[3] and in this project is fit to a function as proposed by Hingerty et al.[6] and modified by others,[7−10] which can be used to estimate the strength of charge−charge interactions around DNA.

II. Background

A statistical mechanical treatment of the dielectric constant of a medium is provided by Kirkwood's theory,[5,11−13] wherein an ensemble average (or time average) of the vector sum of the dipole moments of the individual molecules in a spherical region is formed and related to the dielectric constant. Treating the static dielectric constant as the zero-frequency component of the power spectrum of the dipole−dipole correlation function offers another computational route based on simulations.

Theoretical determinations of the dielectric properties of explicit solvent MD on biomacromolecules have become feasible only recently with the advent of nanosecond-length trajectories.[14−21] The literature to date is summarized in Table 1. The results on proteins suggest that the interior has a low dielectric constant (<5), but the highly mobile charged side chains at the protein−solvent surface exhibit a larger dielectric constant (>15). Studies on DNA triple helices similarly point to a low dielectric sugar, base interior (<5) and a high dielectric phosphate backbone (∼30). The SPC/E solvent water around DNA is found to be considerably ordered and restricted

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TABLE 1: Some Theoretical Estimates of Dielectric Constants of Biomolecules

reference	method	system	magnitude	remarks
1. Nakamura[14]	normal mode	BPTI	1−20	
2. King[15]	Kirkwood	trypsin	10	
	simulation		3−20	
3. Simonson[16]	Kirkwood	decaalanine	3.3	
		cytochrome *c*	3.5	
4. Smith[17]	simulation	BPTI	36	2 without
		lysozyme	30	3 side chains
5. Simonson[18]	Kirkwood	ferr0- & ferricytochrome *c*	16−37	4.7 & 3.4 for the protein interior
6. Simonson[19]	Kirkwood	myoglobin	11−21	2−3 for the protein interior
		apomyoglobin		
7. Loffler[20]	simulation	HIV1−Zn finger	water: 47	
		peptide	peptide: 15	
8. Yang[21]	simulation	DNA triple helix	water: 41.3	
			bases: 3.4	
			sugars: 2.0	
			phosphates: 33.0	
9. Lamm[3]	Kirkwood	B-DNA (PB study with continuum solvent)	major grove ∼50	distance dependence is sigmoidal
			minor groove ∼30	

orientationally, with a calculated dielectric constant around 40 compared to its bulk value of 71. Quantitative agreement between the calculated dielectric constants and experiment has been reported for a drug−DNA complex with PB studies.[3] A previous computation of the electrostatic potentials around DNA based on FDPB methodology,[22] however, indicated that better agreement with experiment was obtained if the dielectric profile near DNA was treated as a step function at the solvent interface (i.e., ϵ_{int} from the interior of the macromolecule up to the surface and ϵ_{ext} beyond the surface) rather than as a smoothly varying distance-dependent function.

Experimental measurements of fluorescence on drug−DNA complexes, as mentioned earlier, led to a relative permittivity estimate close to 20 for the minor groove of DNA in the presence of the drug moiety,[1] while the dielectric constant in the major groove was estimated[2] to be around 55. This surprisingly large disparity between the grooves warrants a molecular level appreciation of the details of water organization around DNA, its corresponding sequence dependence, and its relation to local dielectric constants in the absence and presence of DNA-binding ligands. The goal of this study is to characterize the dielectric behavior of solvent around duplex DNA in the B-form, using a 14 ns MD trajectory developed with explicit TIP3P waters and counterions. The details of the MD simulation and citations to the relevant literature have been presented previously,[4] and we focus herein on the determination of the dielectric behavior around the DNA.

II. Theory, Methodology, and Calculations

The theory of dielectric constants is described at the textbook level by Edsall and Wyman[12] and in a key article by Haggis et al.[13] Lamm and Pack[3] present a succinct overview of the historical evolution of the methodology. The dielectric constant (relative permittivity), ϵ, is calculated as

$$\epsilon = (2\pi\rho g\mu^2/k_B T) + n^2 \quad (1)$$

$$g = 1 + \langle \sum_{j \in S} \cos\theta_{ij} \rangle_i \quad (2)$$

$S = (4/3)\pi R_c^3$; $n^2 = 1.7689$; $\mu = 2.337$ D (TIP3P water value); $T = 298$ K. In the above eq 1, ρ refers to the dipole density. ρ is computed as $\langle N/V \rangle$, where $V = (4/3)\pi R_c^3$ for a water molecule, R_c is the radius of the Kirkwood sphere centered on the reference water molecule, and N is the number of waters occurring in the given volume around the reference water molecule "*i*" in a particular configuration of the system. The fluctutations in the number of waters as occurring in the simulation are accounted for. For water molecules that are close to DNA, the accessible volume for other water dipoles is less than V due to the volume excluded by the solute. This excluded volume in our analysis is accounted for, and ρ is computed as $\langle N/V \rangle$; that is, the fluctuations in the number of waters as well as those in the volume are taken care of. The excluded volumes are calculated by a grid representation of the system. Since the box dimensions vary during a constant pressure simulation, the grid is reconstructed for each structure sampled. The quantity $\cos\theta_{ij}$ in eq 2 is computed as the scalar product of the unit vectors of water dipoles "*i*", the reference water molecule at the center of the sphere of radius R_c, and "*j*", a neighboring water molecule occurring in this sphere around "*i*". Each water molecule is assigned to a DNA atom on the basis of the shortest distance criterion and to a radial bin (r) depending upon its distance from that atom. The values of ρ and $\sum \cos\theta_{ij}$ are accumulated for each water molecule in each configuration, and averages are computed suitably.

To analyze the local dielectric behavior in different regions of DNA; the DNA solute atoms are divided as follows: phosphodiester backbone {O1P, 02P, H5′1, H5′2, H4′, H3′); major groove {H6, H5,H41, H42, H8, N7, O6, H71, H72, H73, O4, H61, H62}; and minor groove {O2, H21, H22, N3, H2}. Using the proximity criterion,[23,24] relative permittivities from waters assigned to each of the above categories of atoms are analyzed separately. Some 1000 structures from the final 10 ns block of the MD simulation were used for this study.

III. Results and Discussion

Results on the relative permittivities for a pure TIP3P water simulation are shown in Figure 1 and for the solution of the sodium salt of B-DNA in TIP3P water in Figure 2 as a function of distance from the solute. The plots have been smoothed with a cubic spline interpolation. For the pure solvent, each solvent is treated as a solute, and the average dielectric profile around each solvent molecule is shown in Figure 1. The overall dielectric profile around DNA (Figure 2) closely resembles a steep sigmoidal function which tapers off to bulk values beyond 5 Å (to be compared with Figure 1). Much of the variation in the dielectric behavior is seen only in the proximity of DNA, i.e. from 1.4 to 4 Å. Saturation effects, if any, do not survive beyond a couple of solvent layers. This appears to partially account for the success of two dielectric models (step function

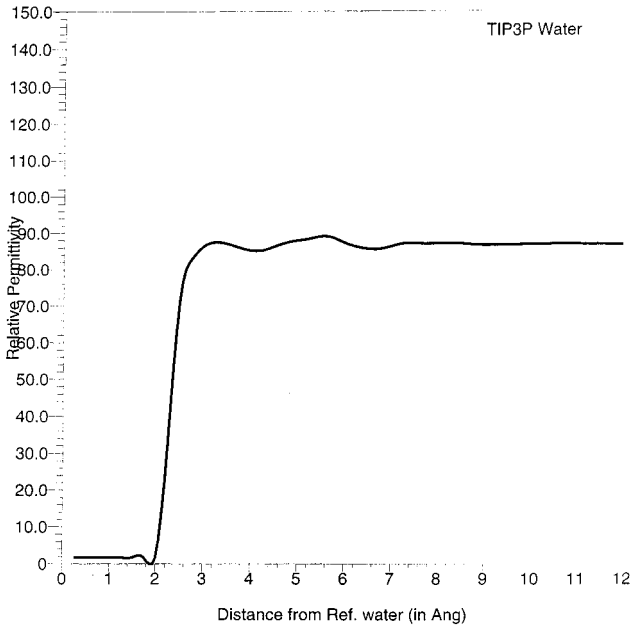

Figure 1. Calculated relative permittivities of TIP3P water shown as a function of distance from each water molecule.

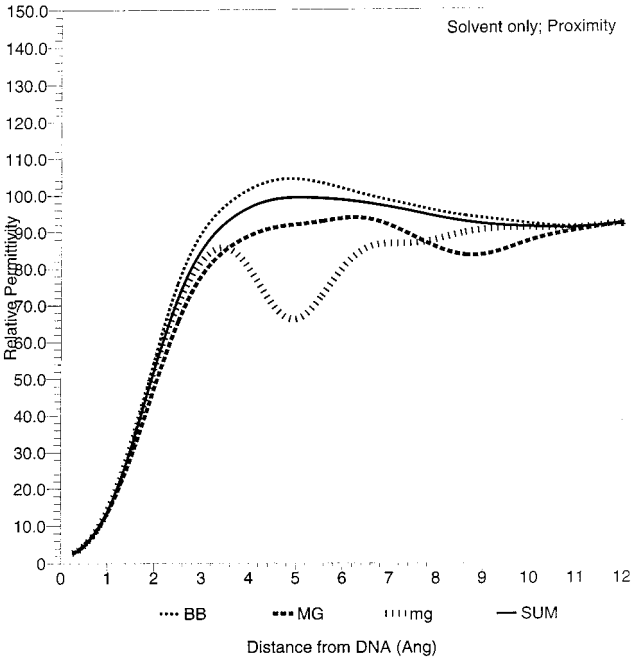

Figure 2. Calculated relative permittivities of solvent water around B-DNA shown as a function of distance from DNA. Only solvent contributions to the static permittivities are included. Proximity criterion is employed to assign reference waters to DNA atoms.

models) as integrated into the Poisson−Boltzmann methodology,[25] in their applications in particular, to estimations of thermodynamic properties. The limiting behavior in Figures 1 and 2, we believe, is within numerical uncertainities.

At a distance of 2.8 Å from the DNA (which corresponds to the maximum of the first peak in the DNA−water radial distribution function), the computed dielectric constants normalized to the bulk value of 80 are (backbone) BB (66) > sum (59) > (major groove) MG (53) ∼ (minor groove) mg (51). All these are consistently less than the bulk values. Whether this low dielectric implies a nonpolar environment or simply a reduced water activity or both needs careful analysis. A nonpolar environment results from a small value for the

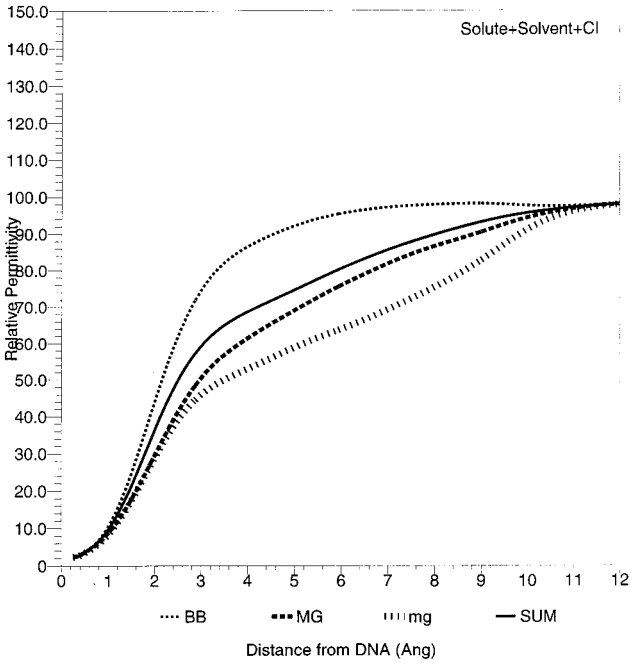

Figure 3. Calculated relative permittivities of solvent water around B-DNA shown as a function of distance from DNA. Solvent, DNA, and counterion contributions are included in the relative permittivity estimates.

magnitude of the dipole moment of the individual molecules. Water molecules have a larger dipole moment, but their orientations in the presence of a highly charged molecule (DNA) are such that the orientational correlations are reduced, leading to a lower polarizability. This may be identified as reduced water activity.

Another offshoot of the dielectric analysis is that the individual contributions from water molecules (vector sums of the dipole moments) to the dielectric constants particularly near phosphates assume both positive and negative values, the sum of which is quantified in Figure 2. Both dielectric saturation (decreased orientational mobility) and electrostriction (increased number density) are operational, with the latter dominating near the phosphates relative to the grooves.

The effect of the solute and counterion contribution on the solvent relative permittivity is also investigated via a multipole expansion of the charge distribution centered on the reference water; the dipole term of the solute is isolated and added to the vector sum of the solvent. Counterions in each structure sampled are treated as a part of the solute for this analysis. These results are shown in Figure 3. The general conclusion to emerge is that the dielectric values are slightly reduced because of the opposing moments (influence) of the solute and near by solvent molecules on any given reference water molecule. Once again relative ordering of the dielectric constants of solvent in different regions around DNA and the overall shape are retained. The above treatment, in fact, constitutes an extension of Kirkwood's theory to solutions. We noted post facto that this adaptation closely resembles the theory developed by Grunwald (eqs 13−16 of ref 26).

A model parameter of the dielectric calculations is the radius of the Kirkwood sphere. The dielectric constant 15 Å away from the DNA is calculated for different Kirkwood radii, and the results show only a weak dependence. Irrespective of the choice of the Kirkwood radius, the relative magnitudes and the overall shape of the dielectric function near DNA remain the same. The static dielectric constant is a low-frequency, low

wave vector property. This raises a question with regard to the validity of dielectric estimates from finite length simulations and from spheres of finite radii carved out in solvent. In practice however, the water structure converges on a much faster time scale than 14 ns and the dipole−dipole correlations become exceedingly small beyond three to four solvent layers when the molecular nature of the solvent is considered explicitly.

The dielectric behavior of the solvent within the vicinity of DNA as emerging from the simulations with explicit solvent (shown in Figure 3) is fitted to an empirical Hingerty−Lavery type sigmoidal dielectric function.[6−10]

$$\epsilon(r) = \epsilon - \left[\left(\frac{\epsilon - \epsilon_i}{2}\right)(\alpha^2 + 2\alpha + 2)e^{-\alpha}\right]$$

$\alpha = sr$; s = 1.2; $\epsilon = 80$; $\epsilon_i = 1.76$. We note that this function is strictly applicable to DNA−ligand interactions only if the ligand does not perturb the solvent structure and motions, which is an idealization.

The spatial inhomogeneities in the dielectric estimates are directly translatable to entropic considerations. Solvent in the major groove has a larger entropy than in the minor groove region. This in turn, together with the time-averaged interaction energies, establishes a connection between chemical potential and dielectric constants and hence activity coefficients and dielectric constants. This work is in progress.

IV. Conclusions

A dielectric analysis of the solvent around DNA based on molecular dynamics simulations of hitherto unprecedented length indicates that the average dielectric constant near DNA in water is almost half of the bulk value, but the dielectric profile rapidly approaches that of the bulk within 5 Å from the solute. The solvent water has a lower acitivity in the grooves than near the phosphates. The minor groove waters, presumably more ordered, exhibit a lower dielectric constant than waters in the major groove and in the vicinity of phosphates. The relative trends in the major groove and minor groove dielectric estimates are consistent with the existing experimental information from fluorescence measurements.

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