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University of Minnesota

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Chapter 6

Using Computer Simulations To Probe the Structure and Dynamics of Biopolymers

Ronald M. Levy, Fumio Hirata, Kwang Kim, and Peisen Zhang

Department of Chemistry, Rutgers University, New Brunswick, NJ 08903

The use of computer simulations to study internal motions and thermodynamic properties is receiving increased attention. One important use of the method is to provide a more fundamental understanding of the molecular information contained in various kinds of experiments on these complex systems. In the first part of this paper we review recent work in our laboratory concerned with the use of computer simulations for the interpretation of experimental probes of molecular structure and dynamics of proteins and nucleic acids. The interplay between computer simulations and three experimental techniques is emphasized: (1) nuclear magnetic resonance relaxation spectroscopy, (2) refinement of macromolecular x-ray structures, and (3) vibrational spectroscopy. The treatment of solvent effects in biopolymer simulations is a difficult problem. It is not possible to study systematically the effect of solvent conditions, e.g. added salt concentration, on biopolymer properties by means of simulations alone. In the last part of the paper we review a more analytical approach we have developed to study polyelectrolyte properties of solvated biopolymers. The results are compared with computer simulations.

The use of computer simulations to study the internal motions and thermodynamic properties of biological macromolecules is receiving increased attention as it becomes possible to simulate biologically important processes, e.g. the binding of a ligand to an enzyme. In the molecular dynamics computer simulation method, an empirical potential energy function is used to represent the energy of the system as a function of atomic coordinates, and the classical equations of motion for the macromolecule are solved on this potential surface. This approach has its roots in computational studies of the liquid state where molecular dynamics simulations have proven to be a very powerful tool for studying liquid properties. Many factors, however, distinguish molecular dynamics simulations of biopolymers (e.g. proteins and nucleic acids) from liquid state simulations so that it is difficult to use experience gained from molecular dynamics simulations of liquids to estimate the precision inherent in macromolecular simulations. While both liquid state and macromolecular simulations employ empirical po-
tential functions, the molecular mechanics potentials used to describe proteins and nucleic acids have far more adjustable parameters in the potential than is the case for liquids. Furthermore, for liquid simulations the basic system contains at least 100 identical molecules so that it is possible to take advantage of considerable statistical averaging in the calculation of quantities for comparison with experiment. For protein molecular dynamics simulations in contrast, the computational effort required to evaluate the large number of interatomic interactions within a single protein molecule limits the simulated system to one or at most a very small number of macromolecules. The highly anisotropic nature of the protein interior and intrinsic interest in extracting site-specific information further complicates the computational problem.

Additional features of macromolecular simulations that make them different from and more difficult than simulations of liquids and solids include the difficulty in obtaining exact results for comparison with trajectory averages, the slow convergence of the macromolecular simulations, the difficulty of incorporating the crystal or liquid environment in a realistic way, and the problem of treating quantum effects for large systems. A central feature of our research during the past few years has been the development of procedures for comparing the results of simulations with a wide variety of experiments. Such studies are necessary if the methodology is to be reliably used to study properties that are only indirectly accessible to experiment. Equally important, these studies lead to deeper insights into the relationship between experimental measurements and underlying molecular processes. In this paper we briefly review our past work concerning the use of molecular dynamics simulations to construct and interpret NMR relaxation and x-ray refinement models for macromolecules. We then discuss the development of new methods for simulating vibrational spectra using detailed molecular simulations. Methods we are working on to incorporate quantum effects in molecular simulations are also reviewed.

The treatment of solvent effects in biopolymer simulations is a difficult problem. While a few simulations have explicitly included the solvent surroundings\(^3\,\text{-}\,7\), most have been carried out in vacuo. With the increasing access to supercomputers it is becoming possible to include solvent explicitly in the simulation. It is still not possible to study systematically the effect of solvent conditions e.g., salt concentration, on biopolymer properties by means of brute force simulations because of the enormous amounts of computer time required. In this regard the development of more analytical methods for studying the interactions of biopolymers with the solvent surroundings not only makes it possible to study a range of environmental parameters not accessible to simulations but can provide limiting results useful for comparing with computer simulations and for focusing the computationally demanding simulations on the most interesting set of environmental variables. We have developed an approach suitable for treating the interactions of a polymeric solute molecule with the solvent surroundings, based on an integral equation method.\(^8\) The theory can be used to study polyelectrolyte properties in solution. In the final part of this paper we review the theory and the application to simple models in which atoms are arranged along a linear chain and on a helix. We use the new theory to consider the effect of added salt on the relative free energy stabilizing different forms of DNA.

**Nuclear Magnetic Resonance Relaxation**

Since NMR relaxation in proteins is determined by dynamics on the picosecond to nanosecond time scale, experimental NMR relaxation parameters can provide important information concerning picosecond motions. Time correlation func-
tions required for determining NMR parameters may be calculated directly from molecular dynamics trajectories. Protein trajectories have been used to study motional models used in the analysis of NMR T1, T2, and Nuclear Overhauser Enhancements and as an aid in the interpretation of experiments.\(^9\)–\(^{13}\) A direct comparison between the results of a 96 ps molecular dynamics simulation\(^9\) of pancreatic trypsin inhibitor (PTI) and an experimental \(^{13}\)C NMR relaxation study\(^9\) of this protein has been reported.\(^{11}\) This represented the first detailed comparison of the results of molecular dynamics simulations of a protein with experimental probes of motion on a similar time scale. Order parameters, which are measures of the extent of angular motion of the bonds were calculated from a 96-ps trajectory and compared with values extracted from the relaxation data. Although the relative flexibility of the residues studied was reasonably well described by the simulation, the theoretical order parameters were systematically larger than the experimental ones, indicating that there is less motional averaging in the 96 ps simulation than detected in experiment. It was suggested that this behavior occurred because the length of the trajectory was too short to statistically sample all accessible orientations. Recently, we have used a 300 ps molecular dynamics simulation of myoglobin to reexamine this question.\(^{16}\) For \(^{13}\)C NMR of protonated carbons with fixed bond lengths, the contribution of internal protein motions to NMR relaxation is determined by the angular correlation function, \(C(t)\):

\[
C(t) = \sum_{a=-2}^{+2} \langle Y_a^2 | \theta(t) \phi(t) \rangle \cdot \langle Y_a^2 | \theta(0) \phi(0) \rangle
\]  

\((II.1)\)

where \(Y_a^2\) are spherical harmonics and \((\theta, \phi)\) specifies the orientation of a \(^{13}\)C-H bond in a macromolecule fixed frame. Because of the restricted nature of the motion in the protein interior, the internal correlation function (Eq.II.1) usually does not decay to zero. Instead a plateau value is reached for which the internal correlation function is equal to the equilibrium orientation distribution obtained from the entire run:\(^9\)–\(^{11},17\)

\[
S^2 = \frac{4\pi}{5} \sum_a \langle Y_a^2(\Omega) \rangle^2
\]  

\((II.2)\)

The quantity \(S^2\) defined by Eq.II.2 is the order parameter describing the restricted motion of the \(^{13}\)C-H vector; for a rigid system \(S^2 = 1\), while for a completely flexible system \(S^2 = 0\).

To illustrate the convergence characteristics of NMR order parameters, in Fig. 1 selected order parameters for leucine residues calculated using the complete 300- ps myoglobin simulation are compared with the values calculated using the first 100- ps portion of the trajectory. The results shown in the figure are representative of the effects observed for all the residues studied. As expected order parameters for bond vectors \((C^\alpha - C^\beta)\) closer to the backbone are in general larger than those \((C^\gamma - C^{\delta 1})\) further out along the side chain. For the \((C^\alpha - C^\beta)\) bonds, the order parameters calculated from the different portions of the trajectory agree well; for the leucine methyl axis order parameters however, there are large discrepancies between the values calculated over the first 100- ps
Figure 1. (Top) Order parameters for each of the Leucine $C^\alpha-C^\beta$ bond vectors. ---, order parameters calculated using the 0–100 picosecond portion of the trajectory; ----, order parameters calculated using the entire 300 picosecond simulation. (Bottom) Same as top figure except that the calculations are for the leucine $C^\alpha-C^\alpha$ bond vectors. (Reproduced with permission from Ref. 16. Copyright 1985 Rockefeller University Press.)
of the trajectory as compared with the complete simulation. For fourteen of the eighteen leucines studied, the order parameters are smaller when the entire trajectory is used to evaluate the correlation functions as compared with the first 100-ps; for seven of the eighteen residues the order parameters decrease by more than 50% when the entire 300-ps distribution of bond vector orientations is used to evaluate the order parameters. It is clear from these results that the order parameter calculations have not converged for this 300-ps trajectory. The order parameter depends on the longtime behavior of the NMR correlation function which is determined by both the higher frequency local motions and more extensive conformational changes. We have examined the extent to which the decay of the NMR angular correlation function at short times varies for different portions of the simulation. We obtained results consistent with a model of protein motion in which groups of atoms (e.g. leucine side chains) oscillate about a mean conformation for tens of picoseconds and then move rapidly to a new conformation.\textsuperscript{16} The conformational change has a large effect on the order parameter. In addition, the effective potential in which the atoms move are somewhat different in the different conformations. From our study of NMR order parameters as well as atomic fluctuations in myoglobin a qualitative picture emerged which suggests that the longer time motions of proteins involves multiple minima. For myoglobin, temperature dependent kinetic experiments on oxygen re-binding\textsuperscript{18} and studies of x-ray temperature factors\textsuperscript{19} have provided experimental evidence for the existence of multiple conformational states of this protein. In the following section we review our use of computer simulations of biopolymers to analyze molecular information concerning macromolecular flexibility contained in crystallographic Debye-Waller temperature factors.

**Restrained X-Ray Refinement of Biopolymers**

Molecular dynamics simulations of proteins and nucleic acids provide a very powerful method for testing crystallographic refinement models. The simulations constitute the most detailed theoretical approach available for studying the internal motions of these macromolecules. From the time evolution of the atomic positions, time averaged X-ray intensities can be calculated and treated as data for crystallographic refinement. The final structure and temperature factors obtained from the refinement can then be compared with the "exact results" obtained directly from the trajectory. In this review, we discuss the results of an analysis\textsuperscript{20} of the temperature dependent molecular dynamics and X-ray refinement of a Z-DNA hexamer 5BrdC-dG-5BrdC-dG-5BrdC-dG for which the experimental X-ray data are available and whose crystal structure has been refined to high resolution.\textsuperscript{21} This hexamer crystallizes in the left-handed Z-conformation with the cytosine bases in the anti conformation and C(2')-endo sugar puckers, and the guanine bases in the syn orientation with C(3')-endo sugar puckers, except at the 3'-terminal guanine bases. The phosphodiester conformations are (gauche-plus, gauche-plus) at the CpG phosphates and (gauche-minus, trans) at the GpC phosphates. The refinement program used was NUCLSQ, which is the restrained least squares refinement program of Hendrickson and Konnert adapted to nucleic acids.\textsuperscript{21,22} The section is divided in two parts. First, the molecular dynamics calculations are described. The simulations were carried out at a series of temperatures between 100 K and 300 K. Second, the restrained refinements of the time averaged structure factors obtained from the molecular dynamics simulations at the various temperatures are discussed and the results compared with "exact" values calculated directly from the simulations and with experimental X-ray results. During the course of the work, it was found that low temperature molecular dynamics simulations
may be used advantageously in the refinement process against experimental data.²⁰

Methods for simulating restrained x-ray refinement data from molecular dynamics trajectories.

Molecular dynamics simulations were carried out on the 248 atom Z-DNA hexamer, using the AMBER nucleic acid force field with a distance dependent dielectric and excluding counterions.²⁵ Although the model treats electrostatic effects only in a qualitative way, recent molecular dynamics simulations for both peptides²⁴ and nucleic acids²⁵ have demonstrated that for localized conformations sampled during short molecular dynamics simulations, average properties are not very sensitive to the electrostatic model; it is the packing and hydrogen bonding terms which together with the vibrational potential (bond, bond angle and torsional stretching) which dominate the calculated equilibrium and dynamical properties. The crystal structure of the Z-DNA hexamer was first energy minimized with 200 conjugate gradient steps to relieve any initial strain in the structure before the molecular dynamics simulations were begun. The rms displacement between the crystal and energy minimized coordinates are less than 0.1 Å. Simulations were performed at a series of temperatures defined by the mean kinetic energy of the system between 100 K and 300 K. For each temperature, 10 trajectories, each 2 ps in length, were calculated by solving simultaneously the classical equations of motion for the atoms of the helix. The use of multiple short trajectories instead of a single long trajectory has been found to be a more efficient method for sampling conformations for macromolecular systems containing many harmonic degrees of freedom.²⁶

Crystallographic refinement is a procedure which iteratively improves the agreement between structure factors derived from X-ray intensities and those derived from a model structure. For macromolecular refinement, the limited diffraction data have to be complemented by additional information in order to improve the parameter-to-observation ratio. This additional information consists of restraints on bond lengths, bond angles, aromatic planes, chiralities, and temperature factors.

In the restrained refinement procedure a function of the form:

$$\Phi = \sum_Q W_Q ||F_o(Q)| - |F_c(Q)||^2 + \sum_i W_i \Delta_i^2$$  \hspace{1cm} (III.1)

is minimized. $W_Q$ is the weight assigned to the structure factors and it varies linearly with Q with coefficients adjusted so that low resolution structures are weighted more strongly than high resolution ones. $F_o$ (Q) and $F_c$ (Q) are respectively the observed and calculated structure factors. The second term in equation 1 contains the stereochemical restraint information, $\Delta$ is the deviation of a restrained parameter (bond lengths, bond angles, volumes, non bonded contacts, and temperature factors) from its ideal value and $W_i$ is the weight assigned to the restraint. The form of equation 1 is such that the weights $W_i$ correspond to the inverse of the variance $\Delta_i^2$ for each set of observations.

The structure factor $F(Q)$ in X-ray crystallography is the fourier transform of the electron density for the molecule:

$$F(Q) = \int d \rho(r) e^{iQ \cdot r}$$  \hspace{1cm} (III.2)
where $\rho(r)$ is the electron density at $r$. In a crystallography experiment the electron density varies with time due to thermal motion and the observed structure factor amplitude is the time average of equation III.2:

$$F_o(Q) = \langle F(Q) \rangle = \int dr \rho(r) e^{iQ\cdot r}$$  \hspace{1cm} (III.3)

In order to generate a set of calculated structure factors $F_c(Q)$ from a set of coordinates, it is necessary to introduce a model for the time variation of the electron density. The usual assumptions in macromolecular crystallography include harmonic isotropic motion of the atoms and in addition, the molecular scattering factor is expressed as a superposition of atomic scattering factors. With these assumptions the calculated structure factor (equation III.2) is given by:

$$F_c(Q) = \sum_{j=1}^{N} e^{i(Q\cdot r_j)} e^{iW_j(Q)} F_j(Q)$$  \hspace{1cm} (III.4)

where $F_j(Q)$ is the atomic scattering factor for atom $j$ and $r_j$ is the position of atom $j$ in the model structure. The thermal averaging of atomic motion is contained in the atomic Debye-Waller factor $\exp(\text{W}_j(Q))$. $W_j$ is given by:

$$W_j(Q) = -B_j |Q|^2$$

where $B_j$ is the atomic temperature factor. The mean square atomic fluctuation $\langle \Delta r_j^2 \rangle$ for atom $j$ is obtained from the refined temperature factors through the relation:

$$\langle \Delta r_j^2 \rangle = \frac{3}{8\pi^2} B_j$$  \hspace{1cm} (III.5)

There are therefore four adjustable parameters per atom in the refinement ($x_j$, $y_j$, $z_j$, $B_j$). In the computer experiments we have carried out to test the assumptions of the nucleic acid refinement model we have generated sets of "observed" structure factors $F_o(Q)$, from the Z-DNA molecular dynamics trajectories. The thermal averaging implicit in Equation III.3 is accomplished by averaging the atomic structure factors obtained from coordinate sets sampled along the molecular dynamics trajectories at each temperature:

$$F_o(Q) = \langle F(Q) \rangle = \frac{1}{M} \sum_{k=1}^{M} \sum_{j=1}^{N} F_j(Q) e^{iQ\cdot r_j^k}$$  \hspace{1cm} (III.6)

where $r_j^k$ is the position of the $j$th atom in the $k$th coordinate set along the trajectory and $M$ is the number of coordinate sets sampled. In the present study
structure factors corresponding to 3,195 reflections between 10Å and 1.7Å were calculated for each of 50 coordinate sets at each temperature. Only the 246 heavy atoms of the hexamer were included in the structure factor calculations; hydrogen atoms were not included in the refinement.

**Restrainted X-Ray Refinement of the Z-DNA Molecular Dynamics Trajectories.**

Refinement of molecular dynamics average structures against simulated X-ray diffraction intensities was carried out at four temperatures between 105 K and 300 K. The R factors, average temperature factors, rms deviations of the temperature factors and the number of "bad" distances obtained for the refinement of the molecular dynamics average structures against the simulated X-ray intensities at 105 K and 300 K are listed in Table I. At 105 K the initial R factor and number of bad distances before refinement are both very small (1.6% and 1 respectively) and are not changed significantly after refinement. At 300 K the initial R factor and number of bad distances are 22% and 50 respectively. With tight restraints on temperature factors the R factor decreased to 7% after three refinement cycles and the number of bad distances increased to 76. With no restraints on B the R factor decreased to 6.3% after three refinement cycles with 50 bad distances.

At the low temperature (105 K) the effect of refinement with strong temperature factor restraints is to increase the average temperature factor from 0.5Å² (exact result) to 0.7Å² and to decrease the variances in the temperature factors for the different classes of stereochemical constraints. With strong restraints on B, the refinement resulted in sharp differences between the cytosines and the guanines both for the sugars and bases which were not present in the temperature factors calculated directly from the 105 K trajectories. For example, the ratio of the temperature factors for guanine bases to cytosine bases which is 1.1 calculated directly from the molecular dynamics simulation, increases to 2.6 after refinement with strong B restraints. In contrast, when refinement is done without temperature factor restraints at 105 K the average temperature factors and the variances in the temperature factors are very close to the exact molecular dynamics values.

At 300 K the effect of the refinement both with and without strong restraints on temperature factors is to decrease the average thermal factor compared to the exact values. The temperature factor averaged over all atoms calculated directly from the room temperature trajectories is 5.9Å² and is reduced by 15% to 5.1Å² after refinement with strong B restraints. The average temperature factor (5.5 Å²) obtained from the 300 K refinement without temperature factor restraints is closer to the exact value. The error in the temperature factors introduced by the refinement at 300 K is largest for the atoms with the largest thermal fluctuations, the phosphates. This result is clearly demonstrated in Figure 2 which compares the phosphate temperature factors calculated directly from 300 K trajectories with the results of the two refinements, with and without temperature factor restraints. For example, the two atoms with the largest thermal fluctuations are the C5 and C11 phosphates. The exact B values for these atoms are 15.1Å² and 17.0Å², respectively; after the refinement without temperature factor restraints the B values are reduced to 10.8Å² and 10.9Å² and they are reduced even further to 8.8Å² and 8.3 Å² respectively after the refinement with temperature factor restraints. The errors introduced by the refinement are also apparent in the effect on the temperature factor variances. At room temperature the actual variances in temperature factors computed for each stereochemical class are considerably greater than 1Å² (they range from 2.4Å² for atoms connected by bonds not involving a phospho-
### Table I

Parameters for refinement of simulation X-ray intensities of Z-DNA hexamer. First line before starting refinement; second line after refinement with strong B restraints; third line after refinement without B restraints.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>165 K</th>
<th>300 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of bad distances(+)</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>R-factor</td>
<td>1.6</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Average temperature factor (Å²)</td>
<td>0.5</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>5.5</td>
</tr>
<tr>
<td>RMS of delta B’s (*)</td>
<td>0.3,0.3,0.4,0.3</td>
<td>2.4,3.5,8.2,5.6</td>
</tr>
<tr>
<td></td>
<td>.06,.08,.10,.13</td>
<td>.06,.07,.02,.06</td>
</tr>
<tr>
<td></td>
<td>0.3,0.3,0.3,0.3</td>
<td>3.0,3.5,3.8,4.1</td>
</tr>
</tbody>
</table>

(+) Distances which deviate from ideality by more than two standard deviations.

(*) The four values correspond to the difference in temperature factors for atoms connected by a bond length, for atoms connected by a bond angle, for P-O bond lengths, and for phosphate atoms connected by a bond angle or for atoms involved in hydrogen bonding.
Figure 2. Temperature dependence of mean square atomic fluctuations of the Z-DNA hexamer. (a) Mean square atomic fluctuations were calculated directly from the molecular dynamics trajectories. (b, c) Mean square atomic fluctuations were calculated using \((\Delta r)^2 = (3/8\pi^2)B\) with the Debye-Waller temperature factors \(B\) obtained from the X-ray refinement of the molecular dynamics trajectories with no restraints (b) and with tight restraints (c). Symbols: *, bases; —, sugars; x CpG, phosphates; Δ, GpC, phosphates. (Reproduced with permission from Ref. 20. Copyright 1986 Academic Press.)
rous to 8.2Å² for P and O atoms connected by a P-O bond). The refinement of the simulated X-ray intensities at 300 K with temperature factor restraints greatly reduces the variances in the B values for each of the stereochemical classes so that the final variances are all less than 1Å² (Table 1). These results are in accord with a recent analysis of the use of restraints in temperature factor refinements for proteins\(^2\)^\(^8\) for which it was shown that the weights used to restrain neighboring atom temperature factors are much more restrictive than the variation in neighboring temperature factor values obtained from protein molecular dynamics simulations. Restraints on the differences in temperature factors between bonded atom pairs have been shown to be uncorrelated with variances in the corresponding bond length distributions. From the present results concerning errors in predicted temperature factor restraints we conclude that the commonly used value of 1Å² or less between temperature factors on adjacent atoms is too restrictive.

Although, as discussed above there are quantitative errors in temperature factors introduced by the refinement procedure, the temperature dependence of the atomic mobilities as estimated by the refined temperature factors provides a reasonably accurate description of the true temperature dependence of the system. In fig. 2b and 2c the mean square atomic fluctuations extracted from the refinement simulations at each temperature and averaged by group are plotted as a function of temperature for comparison with the exact results shown in fig. 2a. As to the refinement without temperature factor restraints (fig. 2b), except for the phosphates at the highest temperature, the extent of anharmonicity (curvature) is in good agreement with the exact result despite the fact the refinement model assumes isotropic, harmonic motion. The ordering of the atomic fluctuations by groups (bases < deoxyriboses < CpG phosphates < GpC phosphates) at the two higher temperatures (275 K and 300 K) agrees with the exact results although the agreement is not as good at 165 K and 225 K even though the harmonic model would be expected to be more accurate at low temperature. It is clear from fig. 2c that when strong temperature factor restraints are introduced in the refinement, differences in the temperature dependence of the atomic fluctuations among the groups are suppressed, although the shapes of the curves agree qualitatively with the results calculated directly from the simulations (fig. 2a). The present results provide a theoretical foundation for the use of Debye-Waller factors obtained from refinements at several temperatures to extract information concerning the anharmonicity of the atomic displacements and underlying potential surface.\(^1\)\(^8\),\(^1\)\(^9\)

**Vibrational Spectroscopy**

Vibrational spectroscopy has played a very important role in the development of potential functions for molecular mechanics studies of proteins. Force constants which appear in the energy expressions are heavily parameterized from infrared and Raman studies of small model compounds. One approach to the interpretation of vibrational spectra for biopolymers has been a harmonic analysis whereby spectra are fit by geometry and/or force constant changes. There are a number of reasons for developing other approaches. The consistent force field (CFF) type potentials used in computer simulations are meant to model the motions of the atoms over a large range of conformations and, implicitly, temperatures, without reparameterization.\(^2\)\(^9\) It is also desirable to develop a formalism for interpreting vibrational spectra which takes into account the variation in the conformations of the chromophore and surroundings which occur due to thermal motions.

We have introduced a new method for calculating vibrational spectra from
classical molecular dynamics or Monte Carlo simulations.\textsuperscript{30} The method involves a quasiharmonic oscillator approximation in which a temperature dependent quadratic Hamiltonian is parameterized from the results of a simulation on the complete (anharmonic) potential. The parameterization is accomplished by fitting the first and second moments of the coordinate and momentum distributions obtained from a simulation on the exact surface to a harmonic model. The model provides a method for partially incorporating anharmonicity in the evaluation of spectroscopic and thermodynamic properties and estimating quantum corrections to the classical simulations.

As an illustration of the method, we recently reported the results of a vibrational analysis of a small molecule (butane) with six internal degrees of freedom using the quasiharmonic oscillator model.\textsuperscript{30} The empirical potential contained all the terms present in the potential for macromolecules, namely, bond stretching, bending, and torsional terms as well as nonbonded interactions. A novel aspect of the simulation procedure was the use of normal-mode eigenvectors as the independent coordinates for Monte Carlo sampling, which was demonstrated to substantially increase the convergence rate of the simulation. From a conventional normal mode analysis we extracted the frequencies of the model which ranged from 119 cm\textsuperscript{-1} for a pure torsional vibration to 1044 cm\textsuperscript{-1} for a mixed bond stretch-angle bend vibration. Classical simulations were performed on the complete surface at a series of temperatures between 5 K and 300 K. We demonstrated how anharmonic effects at higher temperatures can rotate the normal coordinates and shift the frequencies with respect to the harmonic values. For the lowest frequency mode (a torsion) increasing the temperature lowered the effective frequency and this was rationalized in terms of the shape of the quasiharmonic torsional potential. The quasiharmonic frequencies calculated from Monte Carlo trajectories on the anharmonic potential surface for trans and gauche butane are listed in Table 2. The effective frequency of the torsional mode is lowered by 25 cm\textsuperscript{-1} to 91 cm\textsuperscript{-1} at 300K. The anharmonicity of the exact potential results in the decreasing curvature of the quasiharmonic potential and the lowering of the effective torsional frequency with temperature. Fig. 3 shows a schematic illustration of the exact potential, the harmonic approximation, and quasiharmonic approximations at 100K and 300K for the torsional coordinate of trans butane.

The approach to the evaluation of vibrational spectra described above is based on classical simulations for which quantum corrections are possible. The incorporation of quantum effects directly in simulations of large molecular systems is one of the most challenging areas in theoretical chemistry today. The development of quantum simulation methods\textsuperscript{31} is particularly important in the area of molecular spectroscopy for which quantum effects can be important and where the goal is to use simulations to help understand the structural and dynamical origins of changes in spectral lineshapes with environmental variables such as the temperature. The direct evaluation of quantum time-correlation functions for anharmonic systems is extremely difficult. Our initial approach to the evaluation of finite temperature anharmonic effects on vibrational lineshapes is derived from the fact that the moments of the vibrational lineshape spectrum can be expressed as functions of expectation values of positional and momentum operators. These expectation values can be evaluated using extremely efficient quantum Monte-Carlo techniques. The main points are summarized below.

The starting point is the quantum partition function \( Z \) in the coordinate representation:

\[
Z = \int dx_1 \langle x_1 | e^{-\beta H} | x_1 \rangle \quad (IV.1)
\]
TABLE II
Quasi-Harmonic Frequencies\textsuperscript{a} Calculated from Monte Carlo Trajectories on the Exact Potential Surface for Trans and Gauche Butane

<table>
<thead>
<tr>
<th></th>
<th>trans</th>
<th></th>
<th></th>
<th>gauche</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>100 K</td>
<td>113 (5)</td>
<td>102 (17)</td>
<td>91 (25)</td>
<td>90 (33)</td>
<td></td>
</tr>
<tr>
<td>200 K</td>
<td>407</td>
<td>406</td>
<td>407</td>
<td>419</td>
<td></td>
</tr>
<tr>
<td>300 K</td>
<td>435</td>
<td>437</td>
<td>436</td>
<td>602</td>
<td></td>
</tr>
<tr>
<td>400 K</td>
<td>899</td>
<td>911</td>
<td>892</td>
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<td>1008</td>
<td>1014</td>
<td>1002</td>
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</tr>
<tr>
<td>1045</td>
<td>1055</td>
<td>1043</td>
<td>1034</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Frequency in cm\textsuperscript{-1}.

b. Monte Carlo trajectories constructed with Q\textsubscript{z} (mass-weighted Cartesian) as independent coordinates.

c. Numbers in parentheses indicate percent deviation from harmonic normal-mode eigenvalues; only deviations greater than 1% indicated.

Figure 3. Schematic illustration of the exact potential \( V^{\text{exact}} \), the harmonic approximation \( V^{H} \), and quasiharmonic approximations at 100K, \( V^{QH}\textsuperscript{100} \), and 300K, \( V^{QH}\textsuperscript{300} \) for the torsional coordinate Q of trans butane. The anharmonicity of the exact potential results in the decreasing curvature of the quasiharmonic potentials with increasing temperature. (Reproduced from Ref. 30. Copyright 1984 American Chemical Society.)
The $p$ point discretized path integral for $Z$ is obtained by inserting complete sets of states $p$ times:

\[
Z = \int dx_1 \cdots dx_p < x_1 | e^{-\beta H / P} | x_2 > < x_2 | e^{-\beta H / P} | x_3 > \cdots < x_p | e^{-\beta H / P} | x_1 >
\]

(IV.2)

It is not possible in general to evaluate the matrix elements in the path integral for arbitrary $H$. We define the exact Hamiltonian $H$ and a reference Hamiltonian $H_0$ by:

\[
H = \frac{p^2}{2m} + V
\]

(IV.2a)

\[
H_0 = \frac{p^2}{2m} + V_0
\]

(IV.2b)

where $V$ is the exact anharmonic potential and $V_0$ is a quadratic “reference” potential discussed below. Clearly:

\[
H = H_0 + (V - V_0) = H_0 + V'
\]

(IV.3)

We wish to separate the matrix elements involving $H$ in equation 10 into matrix elements of $H_0$ and $V$. For $p$ “large enough” we have:

\[
< x_i | e^{-\beta H_0 / P} | x_{i+1} > \approx e^{-\beta V'(x_i) / 2P} < x_i | e^{-\beta H_0 / P} | x_{i+1} > e^{-\beta V'(x_{i+1}) / 2P}
\]

(IV.4)

A lot has been accomplished in the separation, eq. IV.4 because for quadratic Hamiltonians the matrix elements can be evaluated analytically. As $P \to \infty$ eq. IV.4 becomes exact. In a $p$ point discretized path integral Monte Carlo simulation each quantal degree of freedom is simulated by $p$ “classical” degrees of freedom. If we wish to apply discretized path integral methods to simulate polyatomic systems, it is essential that eq. 6 hold for small values of $p$. The approximation of the path integral by $p$ discretized points for small $p$ depends on the construction of an appropriate reference Hamiltonian. Quadratic reference systems provide a promising avenue for study because the quantum density matrix elements have an analytical form. In a previous paper, we proposed the use of a temperature dependent harmonic (quasiharmonic) reference system for path integral Monte-Carlo simulations. We demonstrated that the use of this reference system resulted in a substantial computational advantage as compared to the use of the conventional free particle propagator. However, the use of a single fixed reference system over the entire range of the potential is clearly not optimal. We have recently developed a series of approximations to the propagator and diagonal density matrix which employ a different quadratic form (Variable Quadratic Reference System, VQRS) at each point on the potential. The VQRS Hamiltonian is given by:

\[
H_0(x_i, x_{i+1})(x) = \frac{p^2}{2m} + \omega(x_i, x_{i+1})(x - x_0)^2 + b
\]

(IV.5)
The notation is meant to suggest that the frequency is variable and depends on the propagator matrix elements. The following criteria have proved valuable in choosing the variable coefficients of eq. IV.5: (1) at low temperature, the VQRS reference should weight the region around the potential minimum most heavily, and (2) at high temperature, our approximation should approach the classical limit:

$$\lim_{\beta \to 0} G(x, x', \beta) = \exp \left[ \frac{(x - x')^2}{2\beta} + \frac{\beta}{2} (V(x) + V(x')) \right] \quad (IV.6)$$

For a potential with a single minimum, a straightforward interpolation scheme suggests itself. We choose $x_0$ to be the true minimum, $b$ to be $V(x_0)$. The frequency is determined by requiring that eq. IV.6 be satisfied. This condition is found to be:

$$\omega^2(x_i, x_{i+1}) = \frac{V(x_i) + V(x_{i+1})}{(x_i - x_0)^2 + (x_{i+1} - x_0)^2} \quad (IV.7)$$

For a potential with multiple minima, a simple generalization of the above is available; this will be discussed elsewhere.

We briefly review results we have obtained on model potentials with the VQRS reference system. The results obtained with the diagonal approximation to the propagator are superior to any previous such approximations that we are aware of. In table 3 classical and quantum results are presented for various moments of the quartic oscillator:

$$H = \frac{p^2}{2m} + ax^2 + bx^4 \quad (IV.8)$$

Results for a range of temperatures and anharmonicities are listed. The diagonal approximation to the propagator is very good. For example, at a reduced temperature corresponding to $\beta w = 10$ (i.e. a 2,000 cm$^{-1}$ vibration at room temperature) and anharmonicity $b = 0.05$, the classical second moment $<X^2>$ = 0.084 whereas the exact quantum result (calculated by basis set methods) is 0.445. Not surprisingly, quantum effects are very important at this reduced temperature. The $p=1$ quantum Monte-Carlo result for the second moment is within 10% of the exact value. This means that the computational effort required to calculate quantum expectation values for this model system is only slightly greater than that required to evaluate classical ensemble averages.

Given equilibrium quantum expectation values, we can calculate moments of the infra-red vibrational lineshape using a procedure originally outlined by Gordon. The infrared vibrational lineshape is given as the Fourier transform of the dipole moment correlation function:

$$I(w) = \frac{1}{2\pi} \int_{-\infty}^{\infty} <u(o)u(t)> e^{jwt} dt \quad (IV.9)$$
### TABLE IIIa Evaluation of $< X^2 >$

<table>
<thead>
<tr>
<th>Reference System</th>
<th>Exact Quantum Result</th>
<th>Quadrature Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta \hbar \omega = 10$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anharmonicity $b=0.05$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>basis set</td>
<td>0.445 (Classical = 0.094)</td>
<td>1 4 8</td>
</tr>
<tr>
<td>free particle</td>
<td>0.093 0.262 0.358</td>
<td></td>
</tr>
<tr>
<td>quasiharmonic</td>
<td>0.320 0.397 0.431</td>
<td></td>
</tr>
<tr>
<td>Variable harmonic</td>
<td>0.446</td>
<td></td>
</tr>
<tr>
<td>$\beta \hbar \omega = 2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anharmonicity $b=5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>basis set</td>
<td>0.161 (Classical - 0.093)</td>
<td>0.094 0.143 0.159</td>
</tr>
<tr>
<td>free particle</td>
<td>0.140 0.155 0.159</td>
<td></td>
</tr>
<tr>
<td>quasiharmonic</td>
<td>0.165</td>
<td></td>
</tr>
<tr>
<td>Variable harmonic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Evaluation of $< X^4 >$

<table>
<thead>
<tr>
<th>Reference System</th>
<th>Exact Quantum Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta \hbar \omega = 10$</td>
<td></td>
</tr>
<tr>
<td>Anharmonicity $b=5$</td>
<td></td>
</tr>
<tr>
<td>basis set</td>
<td>0.071</td>
</tr>
<tr>
<td>free particle</td>
<td>0.010 0.023 0.034</td>
</tr>
<tr>
<td>quasiharmonic</td>
<td>0.068</td>
</tr>
<tr>
<td>Variable harmonic</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE IIIb Evaluation of Higher Moments

<table>
<thead>
<tr>
<th>Property</th>
<th>Exact Quantum</th>
<th>Variable Quadratic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; X^8 &gt;$</td>
<td>1.45</td>
<td>1.15 $(p=1)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.52 $(p=2)$</td>
</tr>
<tr>
<td>$&lt; P^2 &gt;$</td>
<td>0.680</td>
<td>0.597 $(p=1)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.645 $(p=2)$</td>
</tr>
<tr>
<td>$&lt; P^2 X^2 &gt;$</td>
<td>-0.198</td>
<td>-0.175 $(p=1)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.192 $(p=2)$</td>
</tr>
</tbody>
</table>
By inverse Fourier transformation of eq. 1 and expansion of both sides in a Taylor series we obtain:

\[
\sum_{n=0}^{\infty} \frac{t^n}{n!} \frac{d^n}{dt^n} \left< u(0)u(t) \right|_{t=0} = \sum_{n=0}^{\infty} \frac{(it)^n}{n!} \int w^n I(w) dw \quad (IV.10)
\]

Equating coefficients of powers of \( t \):

\[
\frac{d^n}{dt^n} < u(0)u(t) >_{t=0} = (i)^n \int w^n I(w) dw \quad (IV.11)
\]

Thus the \( n \)th vibrational spectral moment is equal to an expectation correlation function, the \( n \)th derivative of the dipole moment autocorrelation function evaluated at \( t=0 \). By using the repeated application of the Heisenberg equation of motion:

\[
\frac{du}{dt} = i\hbar [H, u] \quad (IV.12)
\]

and substitution into equation IV.11, we can express the \( n \)th vibrational spectral moment as an expectation value of nested commutators of \( H \) with the dipole moment operator:

\[
\int w^n I(w) dw = \hbar^n < u(0) \cdot [H, [H, \ldots [H, u(0)]]] > \quad (IV.13)
\]

The expectation values on the right hand side of this equation depend only on the ensemble averages of position and momentum operators, which can be evaluated using the VQRS Monte-Carlo sampling scheme outlined above.

In table IV we present the first and second moments of the vibrational spectrum of the quartic oscillator calculated by the moments method. The quantum results were obtained from path integral Monte Carlo simulations using the variable quadratic reference. For comparison, the average frequency and linewidth obtained from classical Monte-Carlo evaluation of the moments is also listed. Spectral features for two values of the temperature (\( \beta \hbar \omega = 5 \) and 1.0) and two anharmonicities (\( b=0.05 \) and \( b=1.0 \)) are listed. As the anharmonicity or the temperature is increased the oscillator frequency and linewidth increase for both the classical and quantum simulations. The important point is that the classical spectrum is shifted less and broadened more as the temperature and anharmonicity increase. For example, choosing \( \beta \hbar \omega = 1 \) and \( b = 0.05 \) the classical spectrum is almost twice as broad as the quantum spectrum. The results presented in table IV demonstrate that for realistic values of the temperature and anharmonicity, quantum effects on the vibrational spectrum are important. However, the strong coupling of the lineshape broadening with the frequency shifting is a limitation of one dimensional models for which the only broadening mechanism is anharmonicity in the vibrational degree of
TABLE IV

Vibrational Spectrum of Quartic Oscillator by Moments Method

<table>
<thead>
<tr>
<th>Spectral Moment(^a)</th>
<th>Quantum</th>
<th>Classical</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ( \beta \hbar \omega = 5 )</td>
<td>(&lt; \omega &gt;)</td>
<td>1.12</td>
</tr>
<tr>
<td>( b = 0.05 )</td>
<td>(&lt; \omega^2 &gt;^{1/2})</td>
<td>0.03</td>
</tr>
<tr>
<td>B. ( \beta \hbar \omega = 5 )</td>
<td>(&lt; \omega &gt;)</td>
<td>1.96</td>
</tr>
<tr>
<td>( b = 1.0 )</td>
<td>(&lt; \omega^2 &gt;^{1/2})</td>
<td>0.3</td>
</tr>
<tr>
<td>C. ( \beta \hbar \omega = 1 )</td>
<td>(&lt; \omega &gt;)</td>
<td>1.19</td>
</tr>
<tr>
<td>( b = 0.05 )</td>
<td>(&lt; \omega^2 &gt;^{1/2})</td>
<td>0.12</td>
</tr>
</tbody>
</table>

\(^a\) \( \omega_o = 1, \ h = 1, \ m = 1 \)
freedom. Significant population of vibrationally excited states is required for thermal broadening. In contrast, it is the coupling of the vibrational degree of freedom to other modes, protein and or liquid which is of primary interest with respect to an understanding of the structural information content of chromophore lineshapes. The coupling of a chromophore vibration to a bath results in the time and spatial modulation of the energy spacing of the first few vibrationally excited states. This broadening mechanism can give rise to line broadening without significant frequency shifting. Path integral computer simulations of models for chromophoric molecules coupled anharmonically to additional solvent and biopolymer modes are presently underway.

We have described in this section methods for calculating vibrational lineshapes for anharmonic systems which incorporate quantum properties in a fundamental way. The methods have been demonstrated to be very powerful when applied to a variety of one dimensional problems. However, for one dimensional models alternative methods for calculating spectra are more direct. We are pursuing path integral approaches to the problem of calculating lineshapes because we believe the numerical methods can be generalized to polyatomic systems and that they will be much more stable and accurate than alternative approaches. One particularly attractive aspect of our approach is the ability to combine quantum and classical Monte-Carlo algorithms in a single simulation. For example the simulation of the vibrational spectrum of a chromophore with 10-20 degrees of freedom imbedded in a protein could be accomplished by combining quantum Monte-Carlo methods for the chromophore coordinates with classical Monte-Carlo trajectories for the protein atoms.

Modeling Solvation Effects on Biopolymers

A complete theoretical treatment of the structural, thermodynamic, and dynamical properties of biological macromolecules requires an analysis of solvation effects. Proteins and nucleic acids contain both polar and charged groups whose interactions are strongly influenced by solvent. To date, most simulations of biopolymers have not explicitly incorporated solvent. Instead, a primitive model is used in which a dielectric constant is employed to account for solvent screening implicitly. Various empirical forms have been suggested for the dielectric constant. It is very difficult to judge the accuracy of such ad hoc treatments of electrostatic interactions in biopolymers. While short time dynamical simulations of biopolymers starting from the x-ray structure reflect primarily packing effects, and thus are not very sensitive to solvent screening of long range interactions, accurate modeling of larger conformational changes will require a much more accurate treatment of solvent. Furthermore, to evaluate quantities such as the free energy of binding of ligands to proteins or electrolyte effects on nucleic acid conformation, brute force computer simulations are both very time consuming and subject to large sampling errors so that it is very difficult to obtain a complete set of results over a wide enough range of structural parameters. Alternative methods which can guide the development of appropriate computer simulations and provide limiting results for comparison with simulations are greatly needed. In this section we describe an approach we are pursuing in this area.

Considerable progress has been made in the last decade in the development of more analytical methods for studying the structural and thermodynamic properties of liquids. One particularly successful theoretical approach is based on an Ornstein-Zernike type integral equation for determining the solvent structure of polar liquids as well as the solvation of solutes. Although the theory provides a powerful tool for elucidating the structure of liquids in
which the component solute and solvent molecules are small, its application to biopolymers requires extension of the theory to a large number of interaction sites. This is in general a formidable task due to the size and complexity of the intramolecular correlation matrix which appears in the integral equation. One approach involves the application of a superposition approximation. Alternatively, we have formulated a new integral equation applicable to solvated biopolymers which possess periodicity (e.g. DNA). An outline of the theory, preliminary results, and comparison with computer simulations are presented below.

The general form of the (RISM) integral equation appropriate for treating solute-solvent interactions which has been derived in the literature is given by:

\[ \rho \rho = \omega \ast c \ast \omega + \omega \ast c \ast \rho \rho \]  

(V.1)

where \( \rho \) is the matrix of intermolecular pair correlation functions, \( c \) is the matrix of direct correlation functions, \( \rho \) is a diagonal matrix of site densities, and \( \omega \) is an intramolecular correlation function matrix. The solution of the RISM equations is obtained by supplementing them with a closure relation and then iterating. Because this set of coupled integral equations grows as the square of the number of sites on the solute molecule, its application has been limited to solutes containing no more than three or four atomic centers. However, when the solute molecule consists of a periodic array of atoms; for example the sites on a rod-like polyelectrolyte such as DNA, the size of the RISM matrix equations is reduced to those corresponding to a repeating unit of the polymer. We have carried out such a reduction and solved the RISM equations for several model systems of increasing complexity and we summarize results we have recently obtained for a linear chain of ions immersed in water and for helical charge distributions corresponding to B and Z DNA.

In the first example the model considered is a linear chain of positive ions solvated by water. The TIPS water model is employed for this study. The cations have unit charge, are placed along the z axis with a linear spacing of 2.07Å and have Lennard-Jones parameters \( \sigma = 1.897 \text{Å} \) and \( \epsilon = 1.116 \times 10^{-13} \). As an initial test of the polymer RISM theory, two sets of molecular dynamics simulations have also been carried out with parameters corresponding to this model. The results of simulations of a single ion in water and an ion-chain in water are compared with the polymer RISM results. The simulations of a single ion included 215 water molecules and one ion at the center of a cubic box with edge length 18.62Å. The linear chain simulation included 9 ions equally spaced (1= 2.07Å) along the z-axis. Ion-water site pair correlation functions were calculated from 10 ps. and 5 ps. trajectories for the single ion and the ion chain respectively.

The cation-oxygen correlation functions obtained from the molecular dynamics simulations are compared with the polymer RISM theory in fig. 4. In the results from the simulations two striking features are observed: a significant increase in the height of the first peak of the water distribution around the ion-chain as compared with the single ion, and the appearance of a well defined second peak in the distribution around the chain at about 3.73Å. The new RISM theory reproduces the first peak very well. This increase is not intuitively obvious, because the existence of neighboring chain ions reduces the number of solvent molecules in the first coordination shell due to volume exclusion. The appearance of a second peak corresponds to configurations in which a water molecule is bound by an adjacent ion along the chain. The polymer RISM result also produces a second peak close to the position found in the molecular dynamics simulations, although it is less well developed. A full analysis of the
Figure 4. The solute–oxygen distribution function for a linear chain of cations in water (1 g/cm³) at 298 K. (a) Single ion; (b) chain of ions. Circles: simulation; solid lines: polymer RISM. (Reproduced with permission from Ref. 8. Copyright 1987 North Holland Press.)
molecular dynamics simulation and comparison with the polymer RISM result will be presented elsewhere.42

One important area in which the polymer RISM theory will have applications is in the study of salt effects on DNA conformation. It is well known that the B to Z DNA transition is induced by high ionic strength. Qualitatively, this can be understood in terms of increased electrolyte shielding required to stabilize the higher negative (phosphate) charge density on the Z DNA helix. Using the polymer RISM theory we are in a position to evaluate how the solute-solvent free energy changes with helical parameters, as well as electrolyte valency and ionic strength. We note that alternative theories for treating this problem such as counter ion condensation43 or Poisson-Boltzmann44 drastically simplify the geometry of the phosphate charge configuration and do not appear to describe the electrostatics of the B to Z transition well.45 Alternatively, a study of ionic effects on DNA structural transitions based on an integral equation analysis of solvent screened phosphate interactions has appeared. While the phosphates were located correctly on the DNA helix in this study, the screened polion potential was derived from a superposition approximation which amounts to ignoring the effect of helix excluded volume and charge on the local solvent structure46. These drastic approximations are avoided in the polymer RISM theory.8,39

The solute solvent contribution to the free energy stabilizing the DNA polion can be calculated within the polymer RISM theory by a charging up process:47

$$\Delta F = 4\pi \rho \int_0^1 d\lambda \int r^2 dr u_{uv}(r) g_{uv}(r; \lambda)$$

(V.2)

where $g_{uv}$ is the polion (u) - electrolyte (v) radial distribution function $u_{uv}$ is the polion - electrolyte interaction potential (for which we have used a primitive model) and $\lambda$ is the charging parameter. That is, the polymer RISM equation is solved numerically for several intermediate values of the phosphate charge between zero and one and then equation V.2 is integrated numerically. The polymer RISM model predicts that the Z DNA geometry is differentially stabilized over B DNA as the salt (NaCl) concentration increases above 2.5M. This is the salt concentration range within which the B to Z conformational change is observed to occur.48 These preliminary results are very encouraging.

We have begun detailed Monte-Carlo simulations of the distribution of electrolyte around B and Z DNA forms for comparison with the polymer RISM model.

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REFERENCES


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