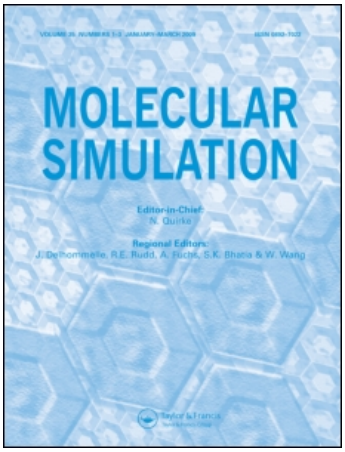

Molecular Simulation
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713644482

A Simple Solvation Model Along with A Multibody Dynamics Strategy (MBO(N)D) Produces Stable DNA Simulations that are Faster than Traditional Atomistic Methods

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To cite this Article Chin, Donovan N. , Sussman, Fredy , Chun, Hon M. , Czerminski, Ryszard , Schlick, Tamar and Mohan, V.(2000) 'A Simple Solvation Model Along with A Multibody Dynamics Strategy (MBO(N)D) Produces Stable DNA Simulations that are Faster than Traditional Atomistic Methods', Molecular Simulation, 24: 4, 449 — 463
To link to this Article: DOI: 10.1080/08927020008022387
URL: http://dx.doi.org/10.1080/08927020008022387

Molecular Simulation, 2000, Vol. 24, pp. 449–463
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A SIMPLE SOLVATION MODEL ALONG WITH A MULTIBODY DYNAMICS STRATEGY (MBO(N)D) PRODUCES STABLE DNA SIMULATIONS THAT ARE FASTER THAN TRADITIONAL ATOMISTIC METHODS

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(Received April 1999; accepted May 1999)

We are developing solvation strategies that complement the speed advantage of MBO(N)D (a multibody simulation approach developed by Moldyn) for simulating biomolecular systems. In this report we propose to approximate the effect of bulk waters on DNA by using only a thin layer of waters proximate to the surface of DNA (which we will call the 'thin shell approach' or TSA). We will show that the TSA combined with substructuring (the grouping of atoms into rigid or flexible bodies) of the Dickerson dodecamer produces good comparisons with standard atomistic methods (over a nanosecond trajectory) as judged by a variety of DNA specific geometric (*e.g.*, CURVES output) and dynamics (power spectra) properties. The MBO(N)D method, however, was faster than atomistic by a factor of six using the same solvation strategy and factor of 70 when compared to fully solvated atomistic system. The key to the speed of MBO(N)D is in its ability to use large time steps during dynamics. By keeping only a shell of molecules of water proximate to the dodecamer, we limit artifacts due to surface tension at the water-vacuum interface. These proximate waters are fairly immobile as compared to those in bulk and therefore do not severely limit the time step in the simulation. The strengths and limitations of this solvation approach, and future directions, will also be discussed.

Keywords: MBO(N)D; atomistic; solvation strategy; DNA; TSA

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INTRODUCTION

We have recently developed and tested a multi-body molecular dynamics protocol (called MBO(N)D, Chun *et al.*, submitted; Chin *et al.*, in the press), which allows for many fold speed-ups in molecular dynamics (MD) simulations by discarding high frequency motions that are unimportant for long-time scale properties. This method treats groups of atoms as rigid or flexible bodies. Flexible bodies are allowed to have small deformational motion by way of body based modes. Large motions between bodies are allowed by the multibody formulation. In addition to rigid and flexible bodies, individual atoms can be modeled as particles in the MBO(N)D methodology.

The main objective of this work is to develop a simple solvent model for MBO(N)D that is able to capture the main aspects of the solvated atomistic simulations, while providing a significant speed advantage. Given the importance of solvent effects on the structure, dynamics and function of biomolecules, it is necessary to develop a solvation method that can retain the speed-up advantage of the MBO(N)D simulations over atomistic MD. Our aim is to determine the effect of a thin shell of waters approach (TSA) on the dynamics and structure of a DNA molecule and to ascertain if the solvent effects observed in the molecular dynamics atomistic simulations can be reproduced by MBO(N)D based simulations.

Recent internal coordinate MD studies for the Dickerson dodecamer with waters located in the major and minor grooves (Mazur, 1998) demonstrated the utility of including a small number of waters in this kind of simulation. We have applied a similar approach to our MBO(N)D studies of the Dickerson dodecamer.

Our results indicate that the solvent effects of the TSA reproduce well a large number of DNA properties in the atomistic simulations with 5–6 fold increases in speed over comparable atomistic simulations. We have estimated that the increase in speed over a fully solvated DNA system is ~ 70, with the potential for even greater speed advantage (at least two orders of magnitude) if compared to systems with more waters that were used by us. This potential for speed up over traditional methodologies warrants more investigation into this simple but effective alternative solvation strategy.

METHODS AND SYSTEM

Molecular Dynamics Protocol

We performed MD simulations on the Dickerson dodecamer DNA (3bna.pdb) using the following two protocols:

1. **Atomistic simulations** All atoms are free to move (with SHAKE constrains applied to bonds with hydrogen atoms). These simulations were used as a reference for the multi-body dynamics.
2. **MBO(N)D simulations** Multi-Body Order(N) Dynamics is based on aggregating atoms of a macromolecule into groups of interacting flexible and rigid bodies. MBO(N)D allows for the unimportant high frequency modes of vibration to be excluded (Chun *et al.*, Chin *et al.*). MBO(N)D simulations mainly derive their speed from its ability to integrate equations of motion at longer time steps. All MBO(N)D protocols and simulation capabilities were accessed through InsightII.

MBO(N)D Substructuring

Most dodecamer nucleotides are divided into two rigid bodies (the phosphates and the bases), one partially flexible body (the sugar)–with flexibility modeled by the two normal modes with lowest frequency, and two atoms (the ester oxygens) (Fig. 2). The 3′-end sugars are held rigid because these groups have a much higher mobility than the other DNA sugars, possibly an artifact (due in part) to the low number of waters associated with the 3′-end of the DNA strands. Treating these sugars as rigid bodies allowed us to reach stable simulations with time-steps up to 8 fs.

Solvation Protocol

An 8 Å shell of waters was initially placed around each base of the dodecamer using the SOAK command that comes under the ASSEMBLY menu entry in InsightII. We then performed a short atomistic simulation to allow the water shell to addapt to the DNA structure. Molecules of water that were further away from the DNA that a certain cutoff distance were removed. Repeating this process for various cutoffs resulted in water shells containing 71, 178, and 295 water molecules. Finally the value of 295 waters was chosen from a limited study as the minimum number of waters needed to reproduce global properties from atomistic simulations (as we will show). The resulting molecular system can be seen in Figure 1.

Molecular Dynamics Regime

- All simulations were constant temperature runs (300 K) using Berendsen's thermal bath (Berendsen *et al.*, 1984) with 0.1 ps thermal bath coupling parameter
- Time step: atomistic simulations were performed with a 1 fs time step using SHAKE for bonds with hydrogen atoms, while MBO(N)D

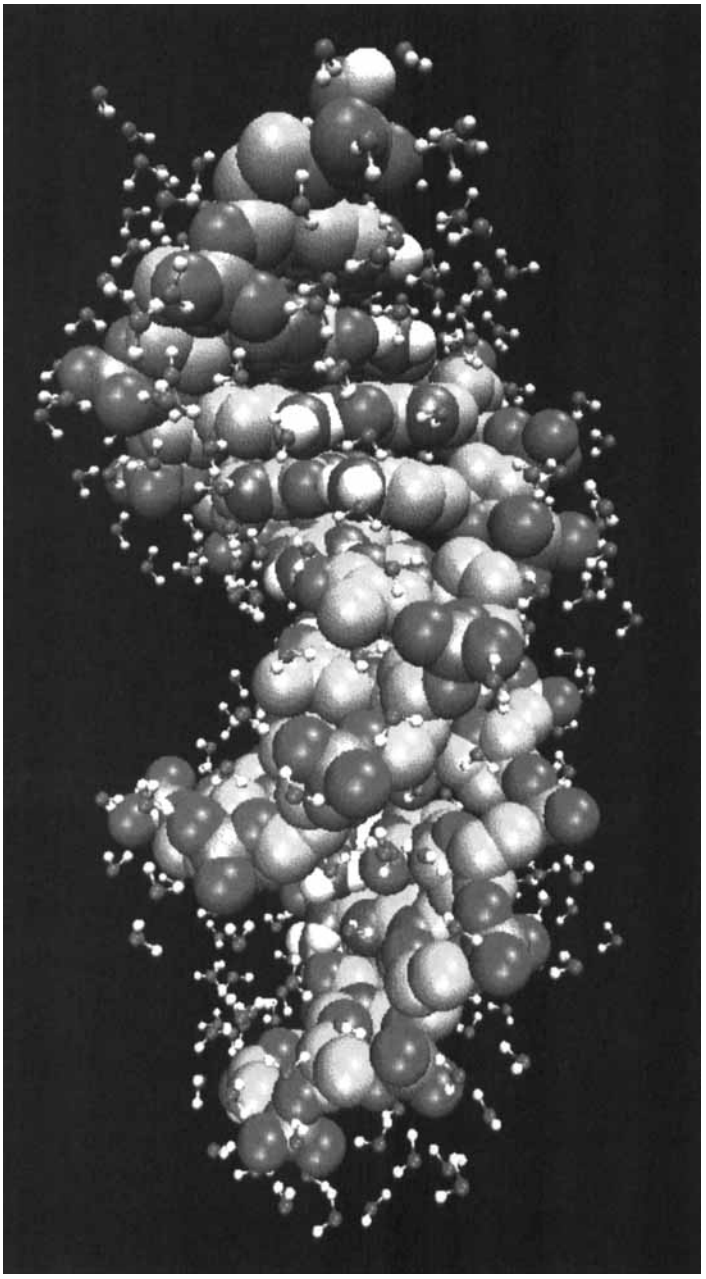


FIGURE 1 Dickerson Dodecamer $(CGCGAATTCGCG)_2$ surrounded by a 'thin shell' of 295 water molecules. The DNA is shown in a van der Waals representation, while the waters are shown as balls-and-sticks. (See Color Plate XXIV)

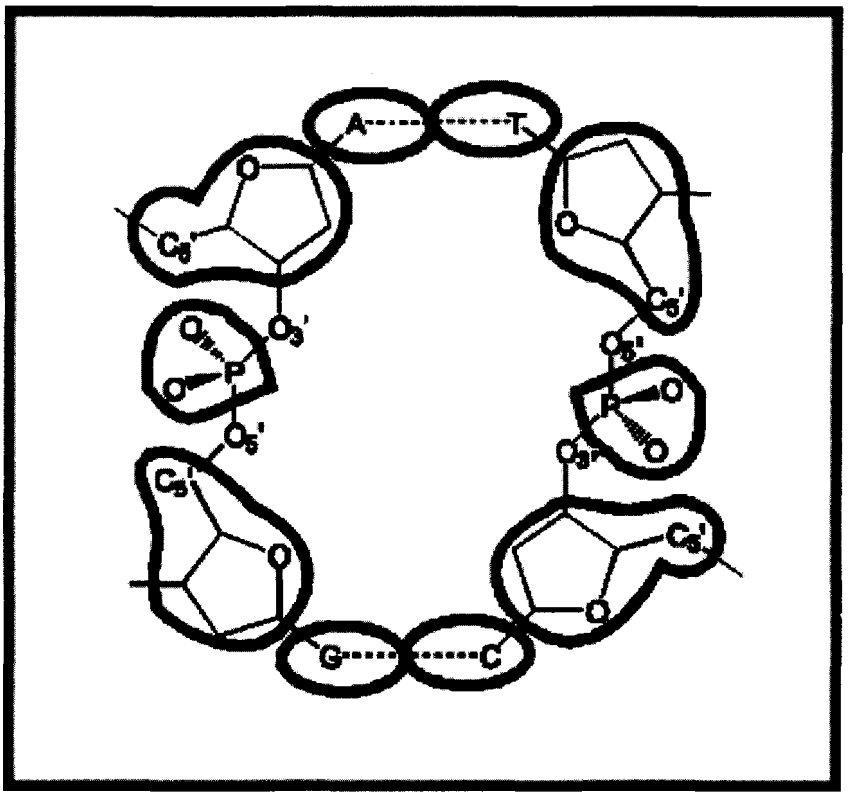


FIGURE 2 The substructuring used in the MBO(N)D simulations. Most DNA nucleotides are divided up into two rigid bodies (the bases and the phosphates), a partially flexible body (sugar) represented by the two lowest (in frequency) instantaneous modes, and two atoms (the ester oxygens). The 3′-end sugars of both DNA strands were held rigid.

simulations were performed using multiple time scales (MTS) methodology (Chun *et al.*) with a 6 fs base time step.

We found that the united-atom AMBER 3.0 force field was more successful in producing stable MBO(N)D simulations than all-atom force fields (CHARMM or AMBER). Although we have not determined the reason, it seems that MBO(N)D does not tolerate large time steps when the bodies contain much more atomistic elements of an all-atom force field than in united atoms force fields.

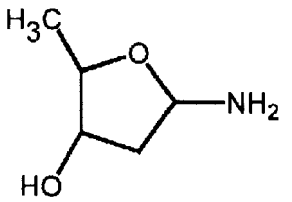
The MBO(N)D simulation we describe here will be referred to as (r5/2/6 fs) where r5 is the name of substructuring, 2 denotes the number of modes used for each flexible sugar body and 6 fs is the base time step.

Molecular System

Substructuring

RESULTS

In order to evaluate the effectiveness of modes in capturing puckering motion, we carried out the dynamic simulation for the model sugar system described below.



Modes Capture Sugar Puckering Well

We studied the simple sugar system (shown at the left) in order to determine the effectiveness of modes in capturing the important sugar puckering motions. The substructuring was five individual atoms (-NH2 and -OH groups) and one flexible body for the remaining atoms. The body was made flexible by including two modes with lowest frequencies calculated at the saddle point of the body between C2′-endo and C3′-endo conformers. The saddle point was found by using the TRAVEL module (Fisher and Karplus, 1992) in CHARMM (Brooks *et al.*, 1982).

- Modeling puckering of the sugar with the two lowest frequency modes allows for the C3′-endo to C2′-endo transitions.
- The power spectra of the pucker phase in the MBO(N)D simulation is dominated by the lowest frequency modes, as opposed to the atomistic simulation.

The TSA Approach Improves Stability Over Vacuum

- There is a clear solvent effect produced by the TSA approach as demonstrated by the root-mean-square deviation (RMSD) from the X-ray structure of the atomistic and MBO(N)D simulations with and without TSA. The atomistic vacuum run became unstable (Fig. 4, bottom)

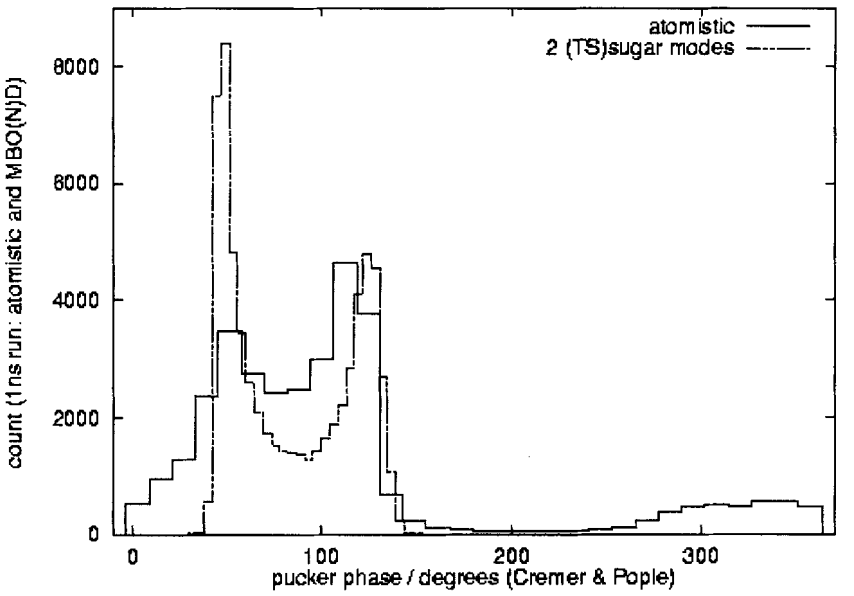


FIGURE 3a (top) Histogram of the pucker phase angle for the model sugar in atomistic representation and in two lowest frequencies modes representation. Modes have been calculated at transition state (TS) conformation.

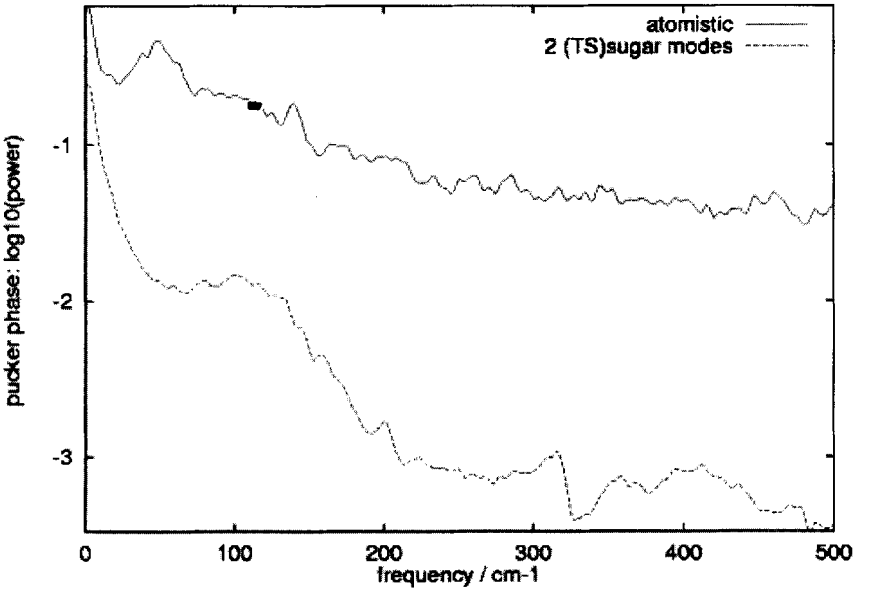


FIGURE 3b (bottom) Power spectra for the same property.

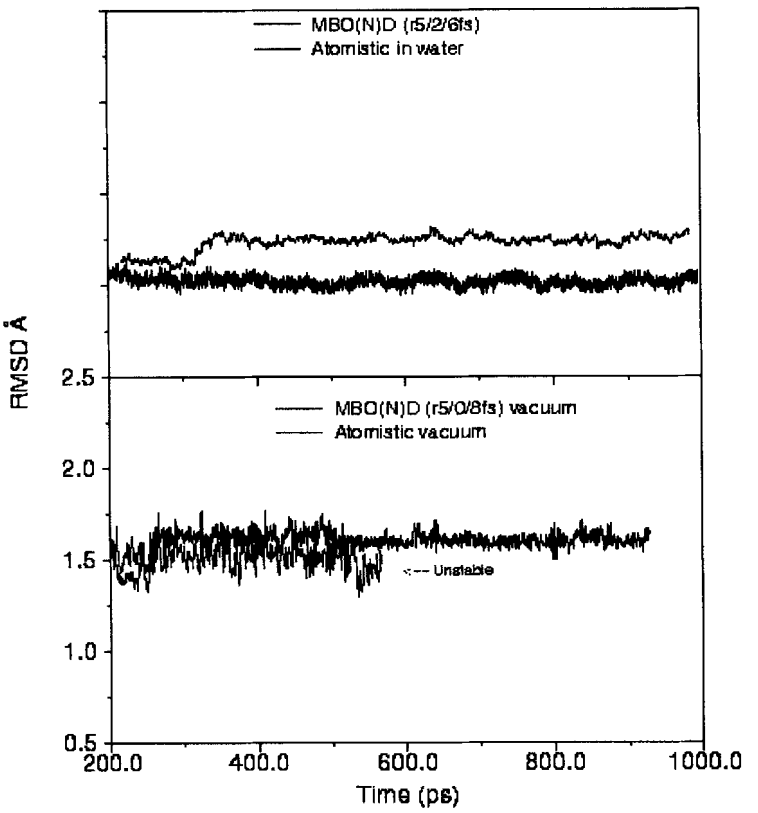


FIGURE 4 Time evolution of the RMSD from the X-ray structure for atomistic and MBO(N)D runs. The upper panel depicts the results from the TSA simulations, while the lower panel is for the RMSD results in vacuum. The MBO(N)D vacuum run (r5/0/8 fs) was performed with rigid sugars (the scale on the upper panel is the same as on the lower panel).

due to a failure of the MD integrator associated with a sudden change in the potential energy surface; whereas the TSA simulation were stable (Fig. 4, top).

- The TSA not only improves the stability of the simulation, but also keeps the structure of the DNA molecule closer to X-ray than the simulation in vacuum. The average RMSD's in vacuum are higher than those in water due either to the dampening effect of water on the DNA atom motions or to the stabilization effects of water on the conformations.

Atomistic Base-pair Properties

We determined various geometrical properties specific to DNA using analyses from CURVES and DIALS (Lavery and Sklenar, R. 1988). The

overall MBO(N)D results are quite similar to the atomistic ones. In general however, the interbase pair properties are reproduced better by MBO(N)D/TSA than for the intra base-pair properties.

DNA TORSION ANGLES AGREE BETWEEN MBO(N)D AND ATOMISTIC

Atomistic

- The behavior of the torsion angles is similar between the atomistic and the MBO(N)D simulations. For instance, 18 out of 22 delta angles – related to the pucker phase angles – are similar in both atomistic and MBO(N)D simulations.
- Due to the fact that the 3′-end sugars are held rigid, the values of the delta and phi angles for the G1 and G12 residues are constant.

MBO(N)D Simulation has the Same Dynamic Behavior as the Atomistic Simulations at Low Frequencies

- Reproducing the atomistic low frequency (long time scale) large scale dynamic behavior is the main goal of MBO(N)D. In order to determine how well this goal is accomplished we calculated the power spectrum for the time series of the DNA bending axis (the axis was computed with the CURVES code).
- Since the intensity of the power spectra is proportional to the RMS fluctuation, Figure 5 shows that the MBO(N)D simulation has a lower mobility at higher frequencies. In the MBO(N)D simulations, there is a tradeoff between accuracy and speed of the simulation. MBO(N)D is designed to capture the important global motion in the lower frequencies regime and to ignore the high frequency motions.
- The only significant difference is a slightly more structured (narrow) distribution for the Tau angle in the MBO(N)D simulations.
- Overall orientation of waters in both simulations is very similar indicating that the substructuring of the molecule in MBO(N)D does not dramatically affect the water distribution around DNA.

The Short Time Scale Diffusion of Waters is Similar Between MBO(N)D and Atomistic Simulations

The closeness of the curves indicates a very similar diffusion behavior for the atomistic and MBO(N)D simulations for the time range studied here.

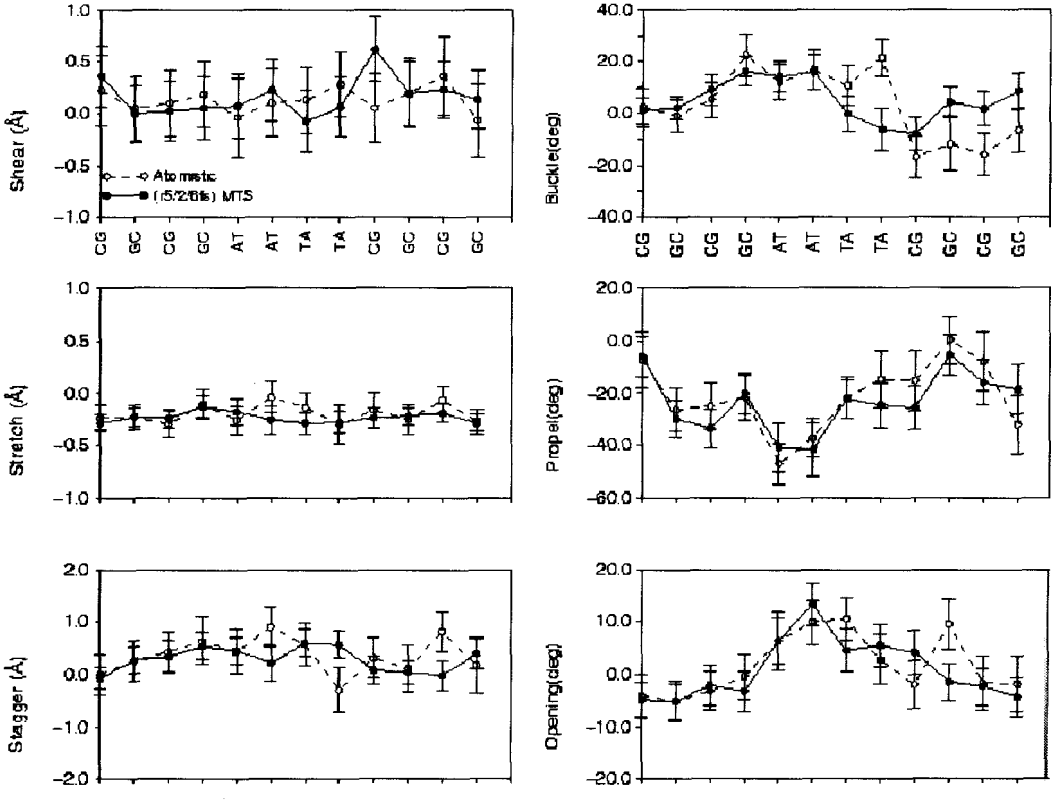


FIGURE 5 Values for the base-pair geometrical parameters for the solvated atomistic (open circles) and MBO(N)D dynamic simulations (filled circles) as obtained from the CURVES program. Each panel represents either a distance related base-pair property (Shear, Stretch, Stagger), or an angle related inter-base property (Buckle, Propeller and Opening).

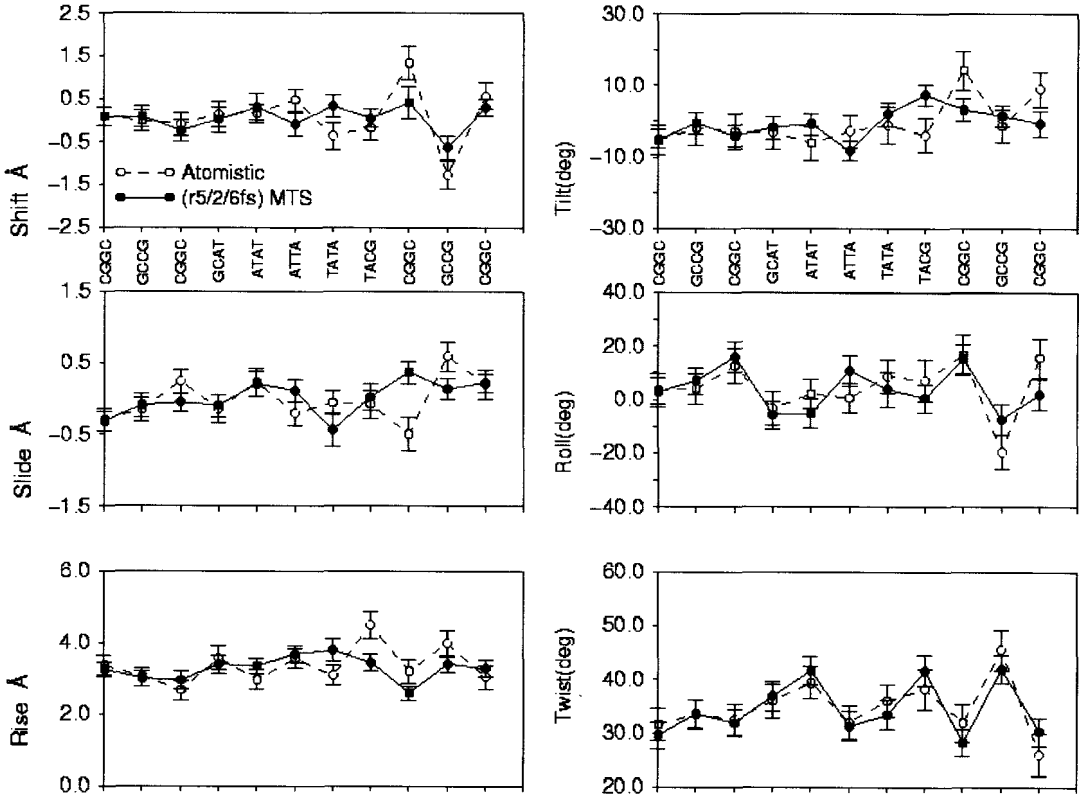


FIGURE 6 Values for the inter base-pair geometrical parameters for the solvated atomistic (open circles) and MBO(N)D (filled circles) dynamic simulations as obtained from the CURVES program. Each panel represents either a distance dependent property (shift, slide and rise) or an angle dependent property (twist, roll and tilt).

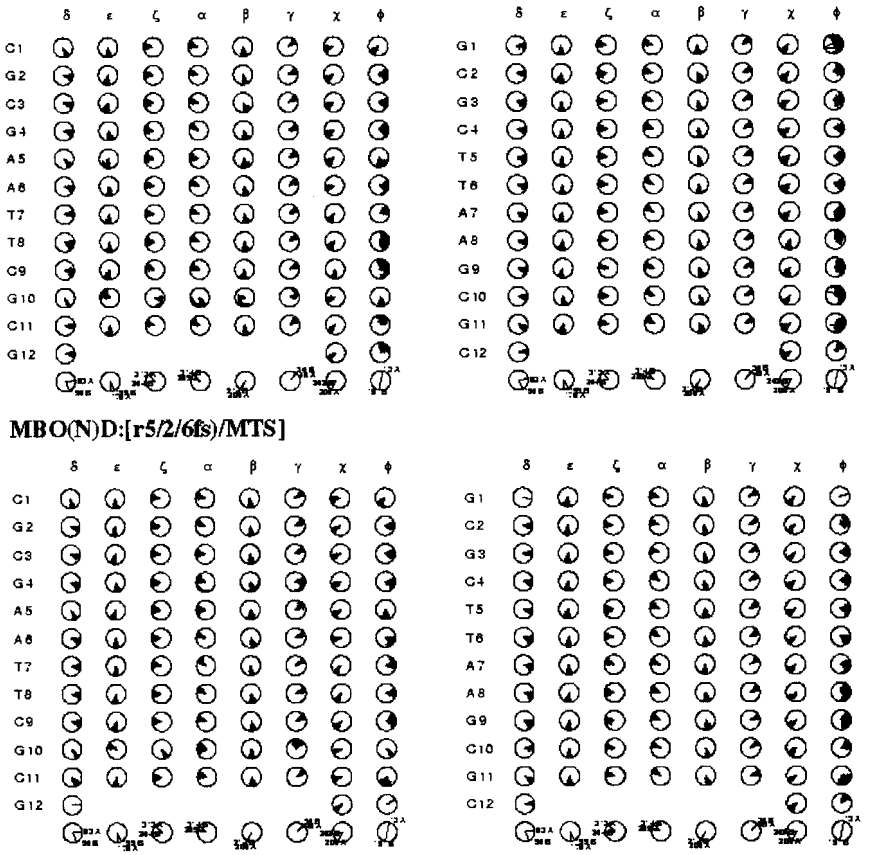


FIGURE 7 DIALS analyses of the DNA torsional angles for both strands of DNA (left column is for strand 1, right column is for strand 2). The upper two panels result from the atomistic simulations, while the two lower panels are the result of the MBO(N)D simulation. The bottom line on each of these panels corresponds to reference values for the canonical A and B forms of DNA.

CONCLUSIONS

We have shown that the structural and dynamical properties of the Dickerson dodecamer from MBO(N)D are similar to those from the atomistic simulations when TSA is used for solvation. The MBO(N)D/TSA protocol, however was faster than the Atomistic/TSA by a factor of six. Summary of our results follows:

- The deviation from X-ray structure is very similar for the MBO(N)D and atomistic simulations in solution. In both cases when simulations are

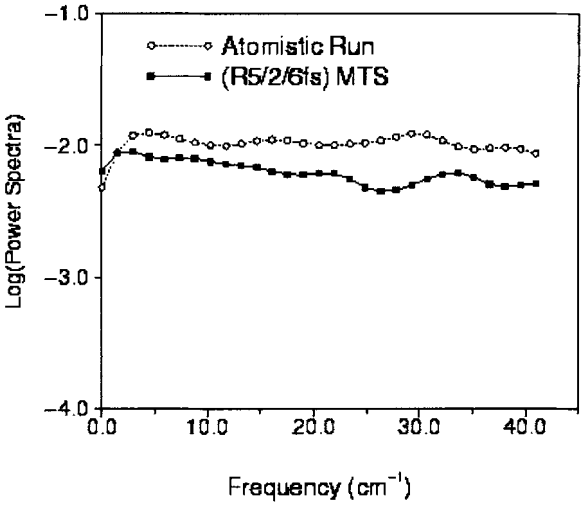


FIGURE 8 Power spectra for the bending of the dodecamer.

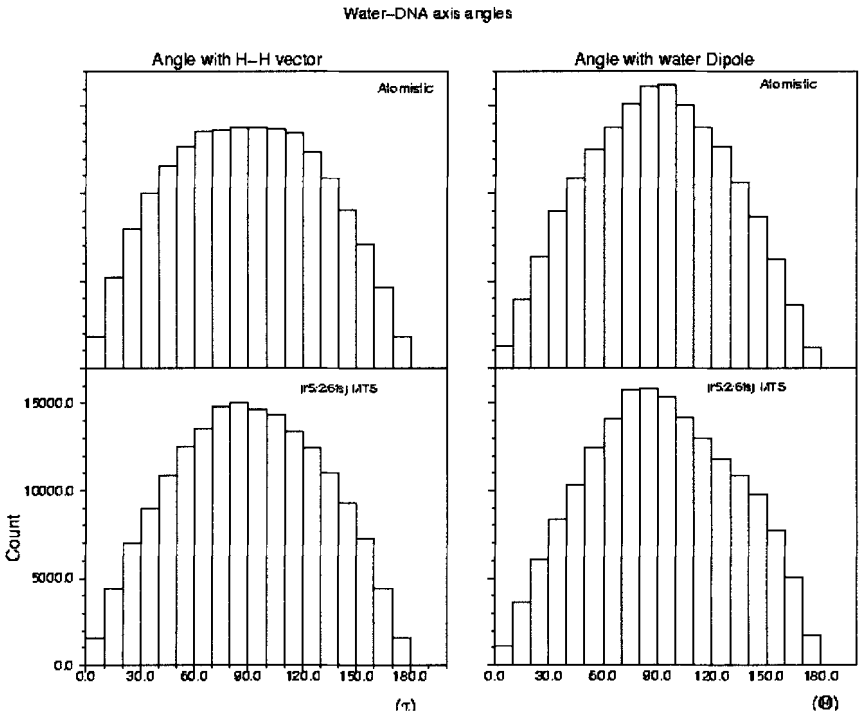


FIGURE 9 The left hand side panel shows the distribution of angles between the unit vector defined by the H-H atoms of every water molecule and the DNA axis unit vector. The right hand side panel depicts the distribution of angles between the unit vector of the water dipole and the DNA axis unit vector.

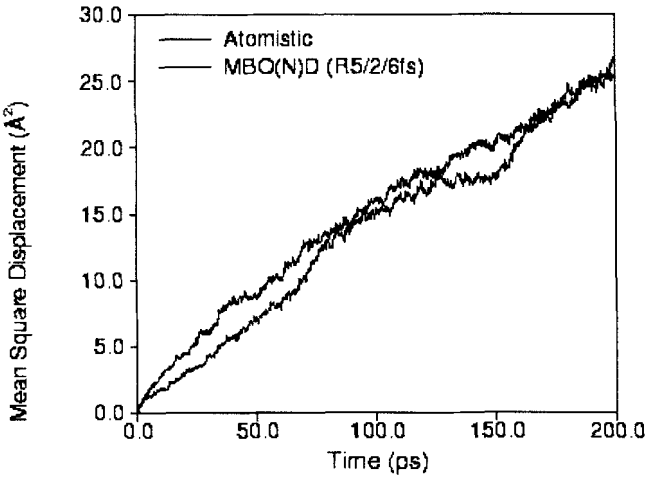


FIGURE 10 Mean-square-displacement for the waters from atomistic (upper curve) and MBO(N)D simulations.

performed with solvent, the DNA structure stays closer to the X-ray observed structure (RMSD < 1.25 Å) than the structure in vacuum simulations (RMSD < 1.5 Å). (Fig. 4).

- The structures provided by the MBO(N)D and atomistic simulations are very similar (see torsional angles (Fig. 7) and base-pair and inter-base pair parameters (Figs. 5 and 6).
- The power spectra of the DNA bending in the MBO(N)D simulation has the same dynamic behavior at low frequencies as the atomistic results (Fig. 8) (with smaller mobility in MBO(N)D simulations at higher frequencies – as expected).
- The waters around DNA behave very similarly in the MBO(N)D and atomistic simulations (Figs. 9 and 10)
- Two lowest frequency modes capture sugar puckering reasonably well (Figs. 3 and 7), since the two major sugar conformers are represented in the simulations.

Although the TSA strategy reproduces a large number of the characteristics of the atomistic simulations, it is probably not general enough for a broad range of applications. Research is needed to answer the following questions:

- Could water molecules fill exposed sites upon large conformational changes?

- What is the effect of the long range solvation electrostatics not included in the TSA approach?
- How well can TSA handle the presence of mobile counter ions?

The speed-up afforded by the MBO(N)D simulations over similar atomistic simulations can reach up to six fold using the TSA paradigm. We have determined that the speed-up over an atomistic fully solvated system with periodic boundary conditions can reach at least a factor of 70.

Acknowledgments

This poster was supported by grant number 2 R44 CA60211-02A1 from the National Cancer Institute. It contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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