

MD SIMULATION OF TATA-BOX DNA: PME CALCULATIONS AND THE EFFECT OF ELECTROSTATIC CUT-OFF

Jian Sun¹, Nina Pastor², Harel Weinstein¹

¹Dept. of Physiology and Biophysics, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, U.S.A. And ²Facultad de Ciencias, UAEM, Av. Universidad 1001, Col. Chamilpa, 62210 Cuernavaca, Morelos, México

INTRODUCTION

Molecular dynamics simulation of DNA systems depends on the force field and the manner in which the long-range electrostatic interactions are treated. Although the use of truncation usually leads to artificial ion accumulation at the cut-off distance[1], and an unstable trajectory of DNA during MD simulation with the AMBER force field[2], CHARMM does not show such severe drawback in such simulations. Pastor et al [3] showed that, in the study of a TATA-box system, CHARMM22 with cut-off gave comparable results to Amber4.1 with PME. The recent development in CHARMM27 force field has showed that the same sequence can adopt the A or B forms of DNA during simulation in different solution conditions, thus eliminating the force field dependence in simulation[4].

Here we compare Particle Mesh Ewald (PME) and cut-off in the simulation of a TATA-box system with CHARMM27. We consider their effect on the structural and dynamical properties of DNA, as well as their effect on the ion and solvent properties. We check for unstable trajectory, artifacts of cut-off, or any artificial over-stability from PME. We also test if this new version of the CHARMM force field yields the correct structural features of TATA-box through MD simulation, and compare it with the results from CHARMM22.

METHODS

Molecular system

We choose the same system as described by Pastor et al[3], and use the same initial coordinates. The system includes the *mp* TATA box dodecamer d-(CTATAAAAGGGC), 22 sodiums, and 3401 TIP3 waters, and is enclosed in a hexagonal prism with length 72Å and side 24Å.

Simulation protocol

Molecular dynamics simulations were run with CHARMM[5], using the CHARMM27 force field [4], Leap-frog integrator, periodic boundary conditions in the NVE ensemble. SHAKE was applied to all hydrogen-containing bonds. For PME, 10Å cutoff, sixth-order smoothing spline and kappa 0.35 were used. Periodic conditions were generated through the CRYSTAL module. For cut-off, 12Å cutoff value was used with shift and switch for electrostatic and VdW interaction, periodic boundary conditions were generated by IMAGE (CUT1 simulation) or CRYSTAL module (CUT2 simulation). The nonbond list was updated heuristically.

After initial minimization (1000 steps of SD, 4000 steps of ABNR) on the starting system, the system was heated up to 300K from 0K within 6ps with 2fs time step while keeping the DNA fixed. Then ions and water were equilibrated at 300K for 30ps. After that, the whole system was minimized (3000 steps of SD, 5000 steps of ABNR), then heated to 300K in 12ps with time step 0.15fs. For the PME simulation, equilibration lasted 90ps, for CUT1 simulation, 30ps, and for CUT2, 120ps. For production, PME was run for 1650ps, CUT1 for 1080ps, CUT2 for 1170ps, in which the last 1080ps were used for analysis. Structures were saved every 0.15ps.

Analysis on the data was done with Dials and Windows[6], and MMC[7].

RESULTS AND DISCUSSIONS

Overall DNA structure RMSD

Fig1 shows the RMSD of DNA heavy atoms to canonical A-DNA and B-DNA. It is clear that, all three trajectories of DNA are stable during the simulation, and remain close to B form DNA, rather than drifting to A DNA as in the simulation with CHARMM22[3]. The averaged RMS differences to A form DNA are 5.11±0.42Å (PME), 5.10±0.38Å (CUT1), and 4.65±0.40Å (CUT2). The averaged RMS differences from B form DNA are 2.33±0.42Å(PME), 2.37±0.28Å(CUT1), and 2.75±0.43Å(CUT2).

Based on these data during 1ns simulation, we did not find instability resulting from cut-off, nor lower flexibility from PME.

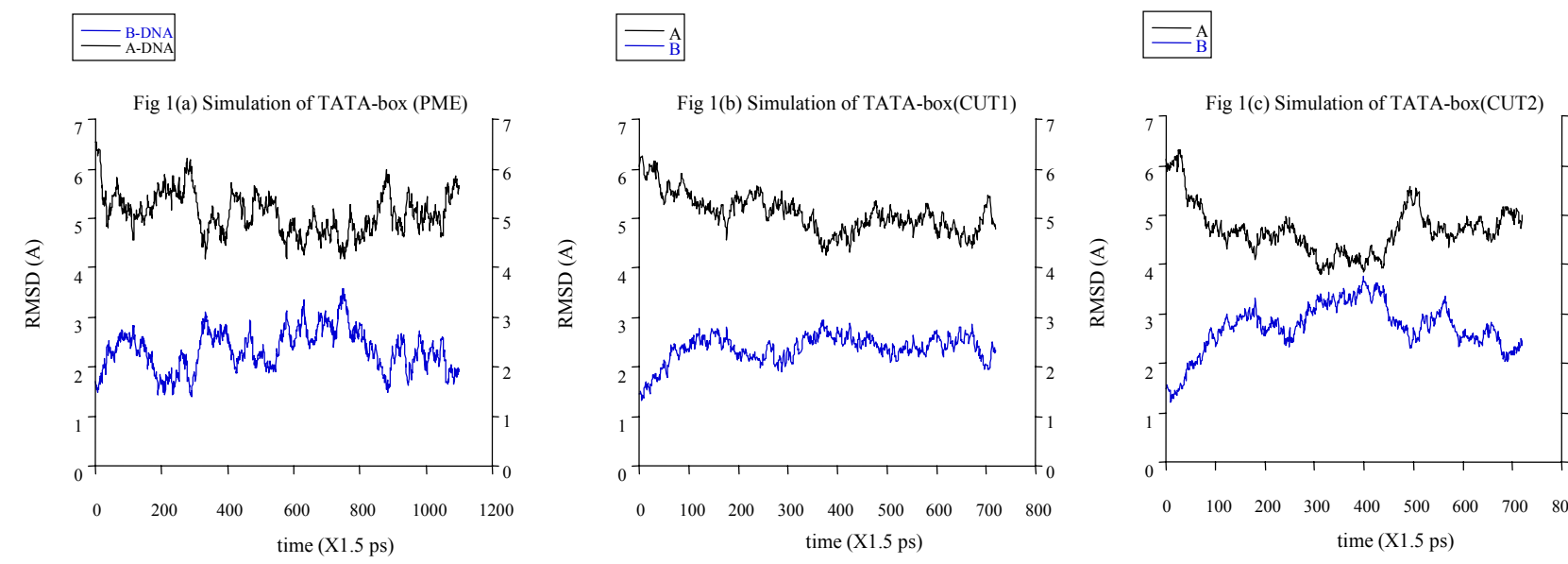


Fig1 shows the average structures from three simulations. The RMSD between PME and cut-off are 0.66Å(CUT1) and 0.93Å(CUT2), while RMSD between the two cut-off average structures is 1.04Å. The three average structures are very similar to each other. The average RMSD of the trajectory relative to their corresponding averaged structure are 1.20Å (PME), 1.06Å (CUT1), and 1.15Å (CUT2) respectively, the corresponding standard deviations are 0.24Å (PME), 0.16Å (CUT1) and 0.31Å (CUT2). Thus, the three trajectories with different methods show similar overall fluctuation around their averaged structures.

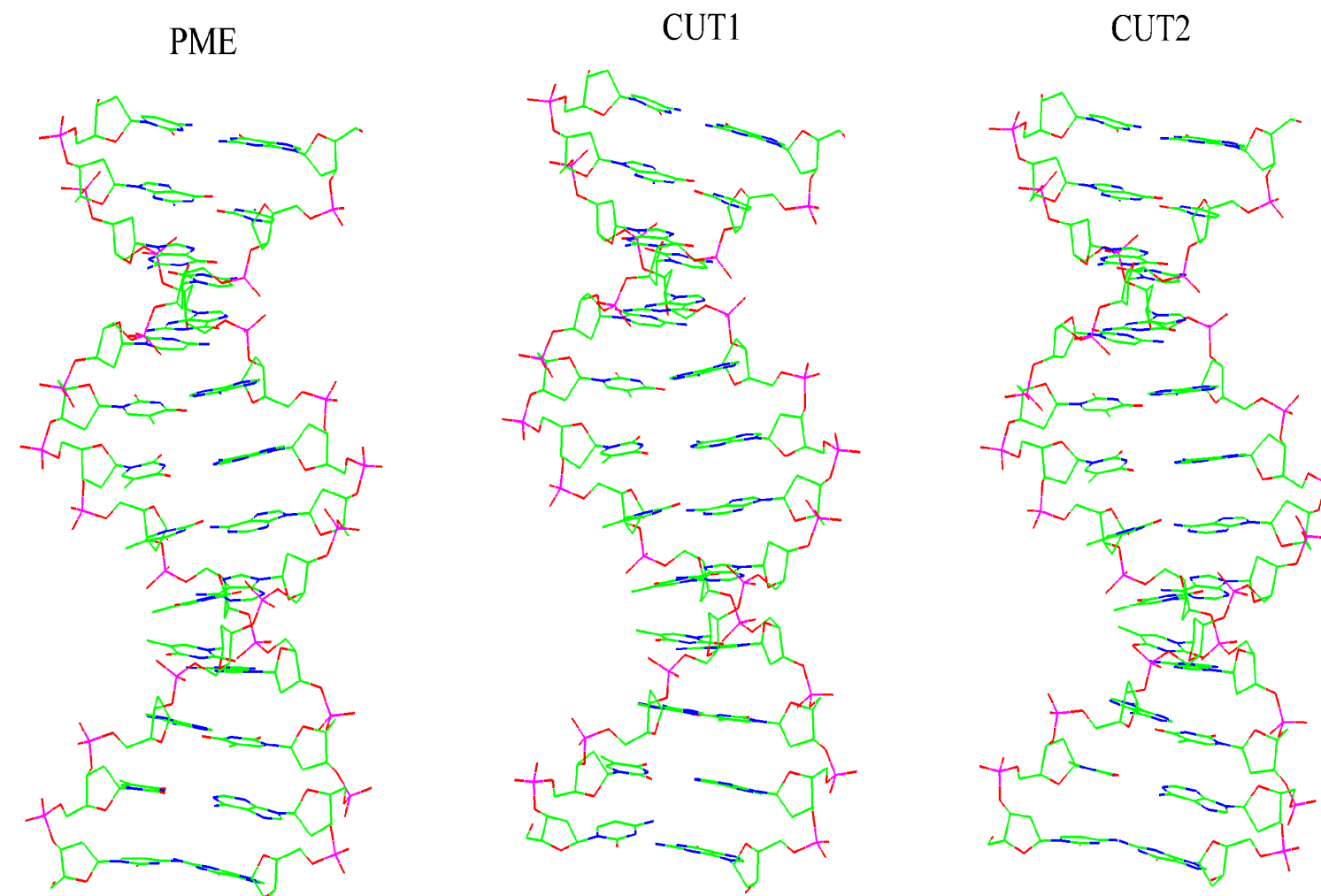


Fig 2 Average structures from the three trajectories

Backbone

The three trajectories give similar averaged backbone angles alpha, beta and gamma around 300, 170 and 50, with corresponding standard deviations around 15. Other backbone angles have larger fluctuations, correlating with the sampling of both A form and B form DNA. Delta, zeta, chi and pseudorotation angle distinguish A form and B form DNA. The averaged values of these angles are within the typical B form, while these angles also sample the range corresponding to A form DNA.

In addition to the comparable standard deviations, these three simulations all give large backbone dihedral angle fluctuations at base pair step T4-A5(T22-A23). In the study of the TATA-box, this feature of TA basepair step has been correlated with the recognition and binding of TBP [3].

This means that both PME and cutoff approaches can detect the intrinsic sequence-dependent flexibility in this new version of the CHARMM force field.

BI-BII transition

During the simulations, we observed BI to BII transitions in all three cases. The overall probability to sample BI and BII regions are around 95% and 5%, comparable to the simulation of EcoRI dodecamer[4]. Fig 3 shows the BI-BII transition at base T4, with PME showing more frequent transitions than cut-off.

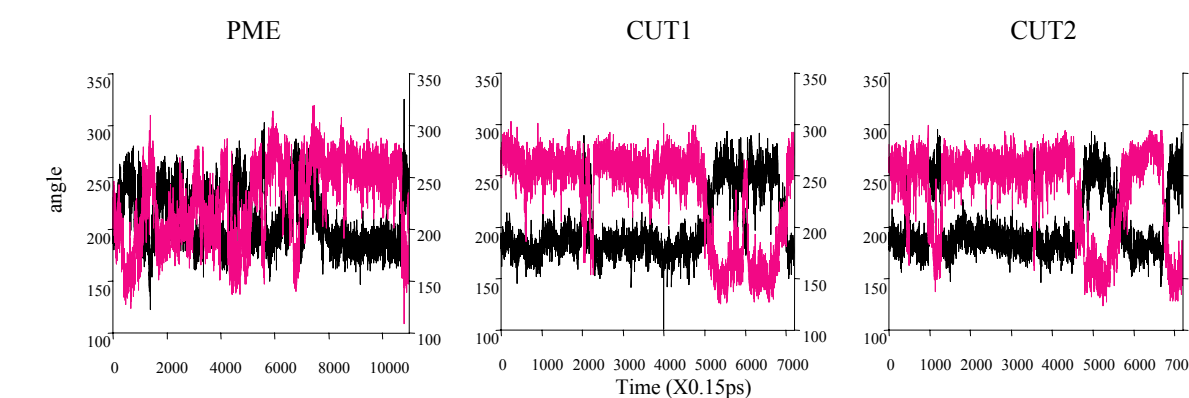


Fig 3 BI-BII transition at T4 base during simulations. Black line shows epsilon, red line shows zeta.

Base-pair step parameters

In spite of the structural difference between the trajectories in CHARMM22 and CHARMM27, our simulations in CHARMM27 consistently yield an unwinding at the A-T basepair step, and twist angles at A3-T4 step around 26. This is similar to the results from CHARMM22[3]. The high flexibility at T4-A5 step is reflected in its basepair step parameters. Thus, the structural and dynamic characteristics related to the specific DNA sequence are preserved in all the calculations.

Ions and solvent

Fig 4 and Fig 5 show the radial distribution of sodium around phosphorus, and the distribution of sodium to sodium. Overall these distribution profiles are similar, even though there are small fluctuations beyond 9Å in cutoff simulations. These small fluctuations are not sufficient to distort the whole distribution [1]. On the other hand, the local dynamic property of ions around DNA is different between PME and cutoff, as shown in Fig 6. The local mean squared displacement (MSD) of sodium within 6.5Å of DNA was calculated from the trajectories, and shown in Fig6. From the local MSD, the estimates for local diffusion constant are about 0.057Å²/ps(PME), 0.044Å²/ps(CUT1), and 0.040Å²/ps(CUT2).

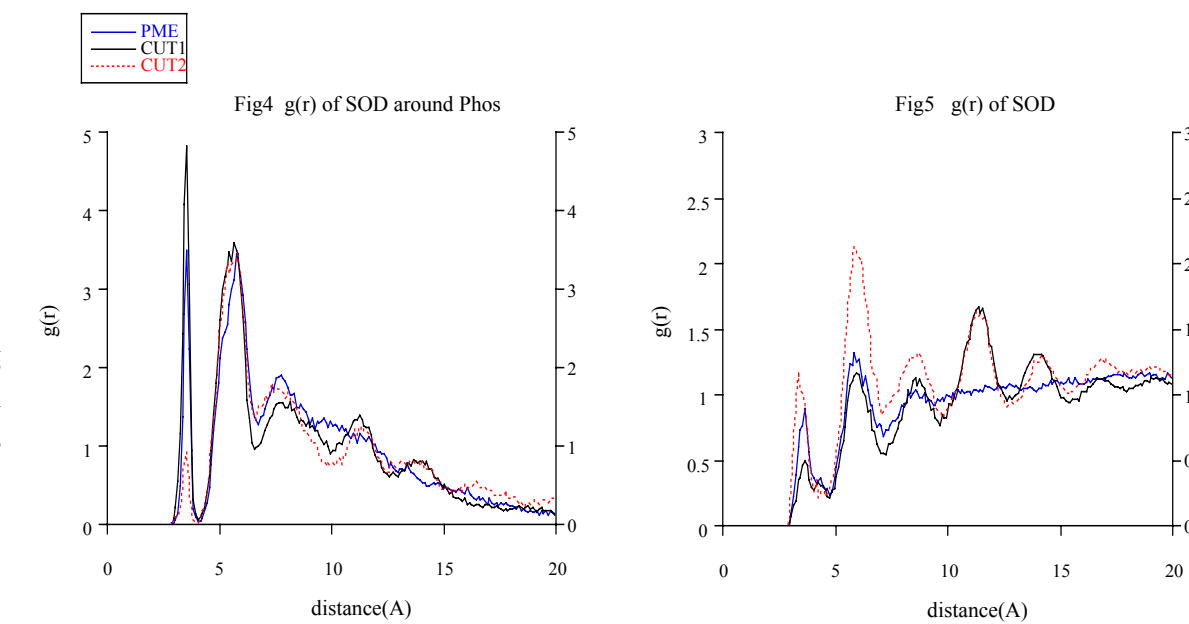


Fig7 shows the water radial distribution around DNA, comparable to the results in [3]. The three simulations give similar results, except that cut-off leads to some fluctuations beyond 9Å. The local water diffusion behavior is somewhat different between PME and cut-off, as found for sodium. Fig8 shows the local water mean squared displacement vs time. Here the local water is defined as within 6Å of DNA. As in the sodium diffusion, PME gives a higher local diffusion constant, while two cut-off simulations have the same MSD. The estimated local diffusion constant is 0.126Å²/ps (PME), 0.099Å²/ps (CUT1) and 0.098Å²/ps (CUT2).

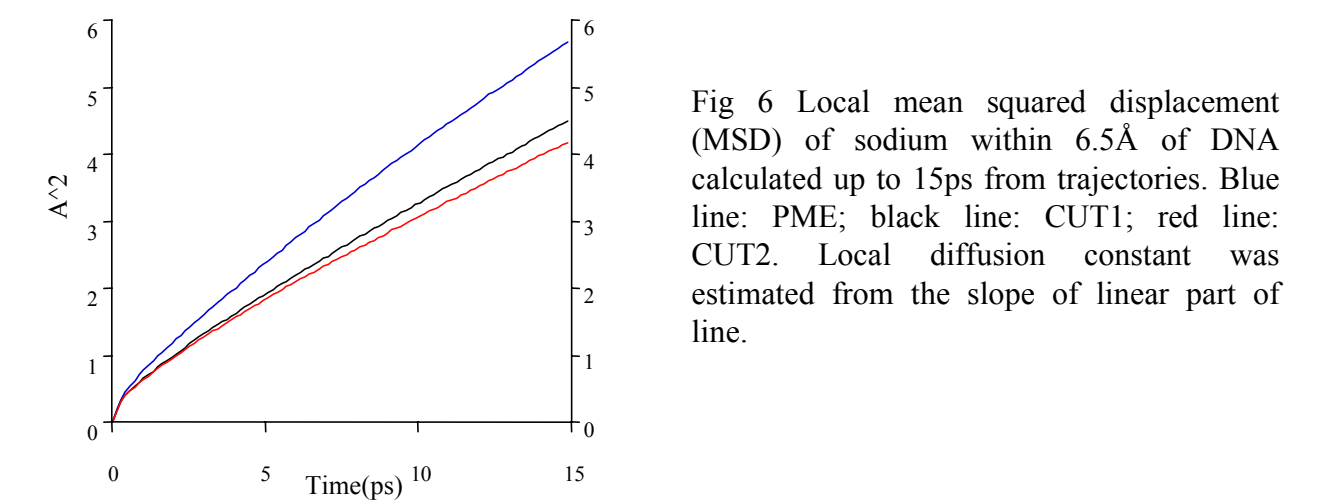
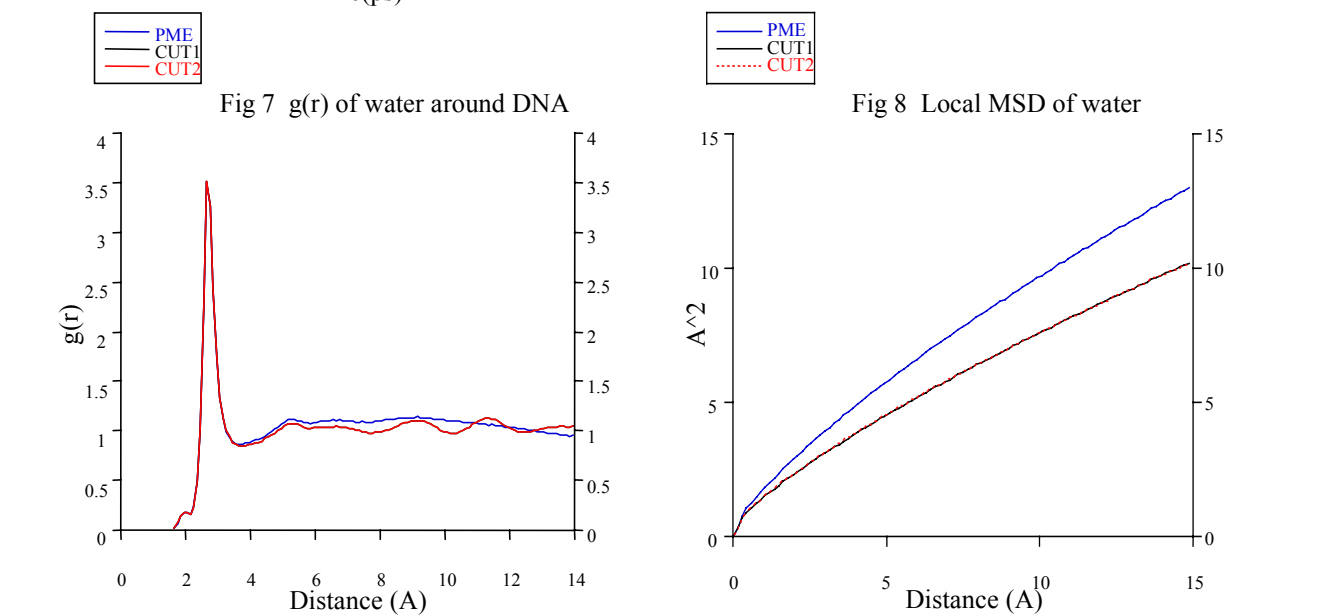


Fig 6 Local mean squared displacement (MSD) of sodium within 6.5Å of DNA calculated up to 15ps from trajectories. Blue line: PME; black line: CUT1; red line: CUT2. Local diffusion constant was estimated from the slope of linear part of line.



CONCLUSIONS

The new version of the CHARMM27 force field can produce a stable simulation of the TATA-box dodecamer. The trajectories are stable and close to canonical B form DNA during 1ns simulation. Comparison with the simulation on the same system with CHARMM22 has shown the improvement in ability to produce stable trajectory, while at the same time the sequence dependent features of DNA remains similar although the overall structure does not drift towards A-DNA.

Here we show that both PME and cut-off methods work well on the TATA-box with CHARMM27; they give similar results on the DNA structural and dynamical properties. PME and cut-off also give similar result of equilibrium properties of ion and water around DNA, but the dynamical properties, such as the local diffusion constant, are a little different between these two methods.

Regarding the stability of simulated trajectories, there is no difference between the PME and cut-off rmsd. This may reflect the specific feature of the CHARMM force field, as the use of AMBER force field has been reported to yield much differences [2].

REFERENCES:

- [1] Auffinger, P. and Beveridge, D.L.(1995) *J Am Chem Soc*, 117:1722.
- [2] Louise-May,S. et al. (1996) *Curr Opin Struct Bio*, 6:289.
- [3] Pastor, N. et al. (1997) *Biophys. J.* 73:640.
- [4] Mackerell, A.D. and Banavali, N.K. (2000) *J Comput Chem*, 21:105.
- [5] Brooks, B.R. et al(1983) *J Comput Chem*, 4:187.
- [6] Lavery, R.and Sklenar, H(1989) *J Biomol Struct Dyn*, 6:669
- [7] Mezei, M, MMC program(<http://fulcrum.physbio.mssm.edu/~Mezei/mmc>)