Molecular Dynamics Simulations of a Single Stranded (ss) DNA

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ABSTRACT

The objective of this study was to develop an understanding of short-single stranded DNA (ssDNA) to aid the development of new DNA based biosensors. The various thermodynamic macroscopic observables (temperature and energy distributions) and Root Mean Square Deviation (RMSD) of nucleic acid backbone of 12 base-sequences of ssDNA of the P53 gene between 130 and 144 codon were studied using Molecular Dynamics (MD) Simulations. The AMBER program was utilized to prepare the ssDNA structure of the p53 sequence and MD simulations were carried out using NAMD program. In this study, we compared the outcome of the properties of ssDNA system by different ensembles. The microcanonical ensemble (NVE) and conical ensemble (NVT) and Isobaric–Isothermal (NPT) ensemble were employed to characterize the equilibrium behavior of ssDNA in aqueous solution.

Keywords: molecular dynamics, ssDNA, biosensor, RMSD

1 INTRODUCTION

In recent years the specific and selective hybridization of nucleic acids have been widely utilized for the development of novel nanostructures, including nanoelectronics, nanomechanics and biosensing devices [1-2]. The specific molecular recognition property and hybridization phenomenon of DNA significantly control the sensitivity and selectivity of DNA based biosensors [2,3]. The uniqueness of nucleic acid and the characteristic of biological recognition event proficiently modulate the function of a DNA biosensor [3,4]. DNA possesses a polyanionic backbone, composed of alternating sugar and phosphate groups, and has four different bases, namely, Adenine (A), Guanine (G), Cytosine (C) and Thymine (T) [3]. The specific molecular recognition property of DNA originates from the selective base pairing: A binds to T, and C binds to G [3,4]. Apart from this distinctly characteristic base-pairing property, the polyanionic backbone controls the physiochemical properties of DNA, such as, flexibility, electrostatic properties, and binding capacity to cationic nanoparticulates [5,6]**.** The DNA based biosensors fundamentally rely on the hybridization phenomenon, in which a single strand (ss) DNA selectively binds to its complementary strand under ambient conditions [2,7]. As a result of the exposed bases and lack of comparatively rigid double helix structure, ssDNA demonstrates considerable difference in electrostatic property and flexibility compared with double strand (ds) DNA [3,7]. Consequently, the single strand (ss) DNA plays a significant role in the hybridization process, as well as in the proper functioning of these nanostructure devices [2,3,7].

In view of the fact that the biosensing devices primarily use short DNA strands, this study focused on the 130-145 codon (15 codon) sequence of p53 gene, which is involved in tumor suppression [8], and any mutation in this codon sequence of p53 can cause cancer, in particular, lung cancer. The specific objective of this study was to theoretically understand the nature of short single strand of nucleic acids under various thermodynamic conditions. Accordingly, the description of the behavior of short-strands of the DNA system can be employed to improve the hybridization process, associated with the characteristic role of the biosensing devices. Molecular Dynamics (MD) Simulations of the ssDNA were performed for this theoretical investigation.

2 SIMULATION METHOD

MD simulations can delineate the atomistic details of the DNA system because molecular dynamics simulations compute atomic trajectories by solving equations of motion using empirical force fields that describe the actual atomic force in biomolecular systems [9]. The simulation was carried out by NAMD molecular dynamics program [10], which fundamentally uses the common potential energy function that considers various bonding and nonbonding energy contributions, including bond stretching, bending, and torsional bonded interactions [10]. The force field is the mathematical description of the potential which atoms in the system experience. In this study, AMBER force field was utilized, as it is widely applied to describe the nucleic acid system [11].

The long-range electrostatic interaction is a very important and challenging issue to obtain a valid result in a biomolecular simulation [10,12]. Since the Ewald method is very reliable for estimating electrostatic interactions in a

spatially limited system, the particle–mesh Ewald (PME) method has been adopted for a faster numerical computation of the electrostatic interaction in this study [10].

The simulation was carried out with the presence of explicit solvent molecules and Na+ counter ions. The periodic boundary condition was employed to perform the simulation**.** A TIP3P water model in a simulation box was used for solvating the DNA system [11]. The structural parameters and coordinates necessary for the ssDNA system were obtained by taking into consideration a helix from double stranded B-DNA constructed by the AMBER program with mentioned p53 sequence (130 -140 codon sequence) [11]. A single DNA strand containing 12 bases was prepared for this molecular dynamics study.

Energy minimization of the constructed ssDNA and equilibration of the system at particular thermodynamic conditions are the two initial important steps to accomplish accurate molecular dynamics [9,12]. The potential energy of the solvated ssDNA was minimized for 2000 steps to get the energy-minimized structure of ssDNA. The energy-minimization was done by the application of conjugate gradient method in the NAMD program [10]. Thereafter, the energy-minimized structure of the ssDNA was equilibrated maintaining proper thermodynamic conditions of the ensemble of interest. The equilibration was performed for Microcanonical (NVE), Canonical (NVT), and Isobaric-isothermal (NPT) ensembles. The temperature was maintained at 300 K for all ensembles. The pressure was maintained at 1 atm in the NPT ensemble. The consistency of temperature was maintained by performing Langevin Dynamics [9,10]. The constant pressure control was executed by the Langevin piston Nose-Hoover method, available in the NAMD program [10]. The VMD, molecular viewing program, was used to visualize the dynamics of the system [13]. The achievement of the dynamic equilibrium of the system was evaluated by how well energy, pressure, and temperature (thermodynamic properties of the system) were distributed in the system over a certain amount of time [9,12].

3 RESULTS AND DISCUSSIONS

Thermodynamic observables (pressure, temperature, and volume) play a conclusive role to set up the proper ensemble for the simulation study [10, 14]. The distribution of energy (kinetic and potential energy) exhibits the sign of the establishment of dynamic thermodynamic equilibrium. Since the force field in the MD simulations assumes that the bonded interactions (bonds, angles and dihedrals) portray the characteristics of harmonic oscillators [9,10], fluctuations in kinetic energy, and hence the temperature distribution can attribute to the equilibrium of the ssDNA system. The simulation was carried out in the microcanonical ensemble (constant N (number of atoms), V (volume), and E (energy)). The dynamics of system was observed for 100 ps after initial equilibration of 50 ps. The initial equilibration was performed at the constant temperature of 300 K.

The fluctuation in temperature during the dynamics study maintained the Gaussian distribution with a mean temperature of 303.99 K (Figure 1). The fluctuations in the temperature describe the effect of the finiteness of the system.

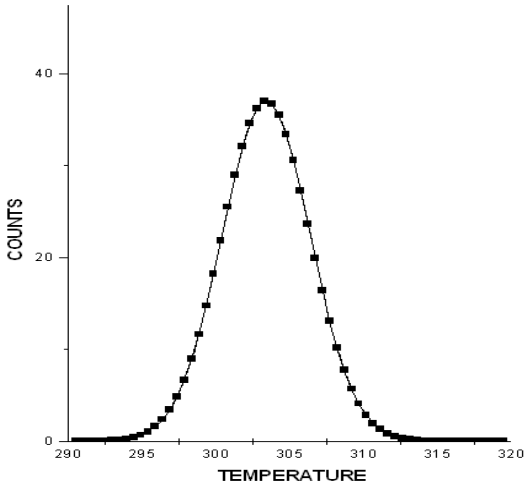

Figure 1: Temperature fluctuation observed in NVE ensemble

As the system leads to dynamic equilibrium, the total energy of the system approaches a constant value. The fluctuations in the total energy of the system depend on the number of atoms or particles present in the simulating systems. The average kinetic energy resulted in the temperature of the solvated ssDNA system.

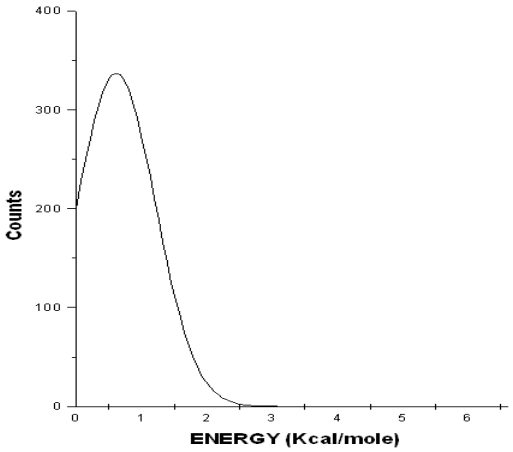

Figure 2: The distribution of kinetic energy of ssDNA system in NVT ensemble.

The distribution of the kinetic energy of the ssDNA system confirms the establishment of physiological temperature.

The kinetic energy distribution of solvated ssDNA system was computed by running the dynamics for 100 ps in the canonical (NVT) ensemble. The distribution of kinetic energy of the ssDNA system followed the Maxwell-Boltzmann distribution with the standard deviation of 0.602 Kcal/mole, which corresponded to a temperature of approximately 300 K (Figure 2). Thus, the desired equilibrium state was achieved by the proper sampling of the ssDNA configurations.

The Root Mean Square Deviation (RMSD) of the ssDNA backbone was computed for NVT and NPT ensembles (Figure 3 and 4). The RMSD provides the numerical measure of the difference between two structural states of the ssDNA [15,16]. The conformational stability of the ssDNA imparts a significant effect to designate the proper equilibrium state. The RMSD of the nucleic acid backbone illustrates the conformational state of the ssDNA with the progress of the dynamics [15,16]. As the RMSD of the nucleic acid strand changes over time, it provides the idea about the stability of the ssDNA at the particular state of equilibrium.

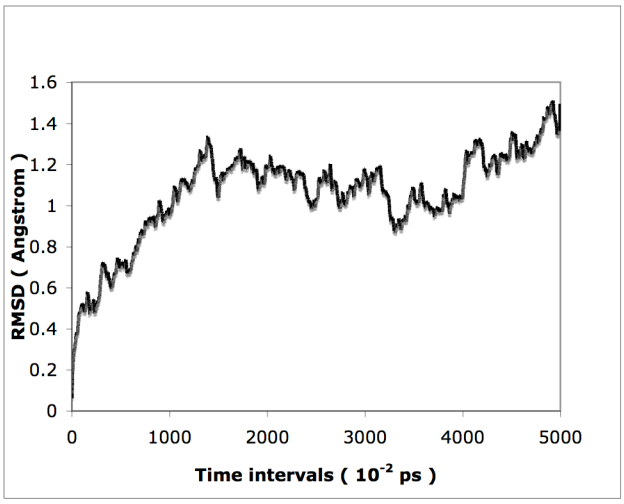

Figure 3: RMSD of ssDNA backbone in NVT ensemble

For the NVT ensemble study, at first, the ssDNA system was equilibrated for 50 ps at 300 K. The achievement of the dynamic equilibrium state was evaluated by examining the consistency in the total energy, temperature and volume. Thereafter, the dynamics of the system was studied for 50 ps. The RMSD of the nucleic acid backbone was calculated during this dynamics study to investigate the conformational change of the ssDNA from its apparent equilibrium structure. The RMSD of the ssDNA exhibited an approximately flattening curve (Figure 3) with the deviation of approximately 1.4 to 1.6 A^{o}. This result portrays a stable conformational state of the ssDNA under the prevailing thermodynamic conditions.

The RMSD of nucleic acid backbone was computed by a similar method for the NPT ensemble. The simulation was performed at 300 K temperature and 1 atm pressure. At first the ssDNA system was equilibrated for 50 ps followed by the dynamics study of 400 ps. The RMSD showed a change of approximately 3A^{o} with the progress of time (Figure 4) during the dynamics study. It indicated that the ssDNA had been undergoing the structural change from its previous conformation with time, in spite of the fact that the system maintained the consistency in the equilibrium thermodynamic conditions

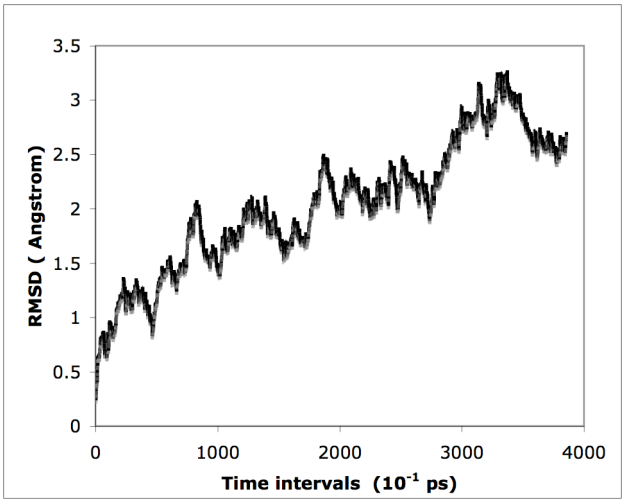

Figure 4: RMSD of ssDNA backbone in NPT ensemble.

As the NPT ensemble resembles a closer description of the biological conditions, this study provides an idea of the conformational flexibility of the ssDNA under the ambient conditions. The proper thermodynamic conditions and the suitable conformational states of the ssDNA regulate the rate of the hybridization process. The selectivity and specificity of the hybridization of nucleic acids depend significantly on the conformational stability and flexibility of the ssDNA. Our study indicated the effect of the thermodynamic conditions on the conformational state of the ssDNA, which could potentially modulate the qualitative features of the DNA based biosensing devices.

4 CONCLUSIONS

The conformational stability of the ssDNA depends on the thermodynamic conditions, and the flexibility of ssDNA undergoes alteration with the change in the thermodynamic parameters of the system.

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