Assessment of Available AMBER Force Fields to Model DNA-Ligand Interactions

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Abstract: Deoxyribonucleic acid, commonly referred to as DNA, is a promising cellular target for anticancer agents. The interaction of drugs with nucleic acid is an essential feature of pharmacology. It has a pivotal role in understanding the mechanism of drug action and developing more efficient drugs with fewer side effects. Molecular Dynamics (MD) simulations are widely used to study the effects of ligand binding and stability with biomolecular systems. To obtain the best force field, we have assessed the performance of seven available versions of AMBER force fields available with the framework of GROMACS software suite. A minor groove binding ligand was put under 100ns MD simulation under all seven force fields. We performed a total of 700ns (0.7µs) of MD simulations for our assessment. The analysis of MD results revealed that among all the seven AMBER versions, AMBER99SB gives the best results, and the parameterization using AMBER94 was not proper. However, the DNA remains intact for all force fields for the whole duration of the simulation.

Keywords: deoxyribonucleic acid; docking; MD simulation; GROMACS; AMBER; force field.

1. Introduction

Deoxyribonucleic acid (DNA) is generally known to be a cellular target for several anticancer and antitumor drugs[1-10]. Studying the interactions between the drug and DNA has been of great interest. The information about the interactions between the drug and DNA facilitates the research community to make efficient drugs. Molecular docking predicts the best binding pose of the ligand concerning the target or the receptor[6,7,9,11-13]. The concept behind molecular docking is the calculation of the binding affinity of different poses of the ligand and then ranking the poses using the binding affinity. The best pose of the ligand corresponds to the pose with the least binding affinity. The best pose of the ligand is combined with the receptor structure to form a ligand-receptor complex. The complex's stability and time evolution are predicted using the Molecular dynamics (MD) simulation[9,12-14,15].

The MD simulation exhibits the potential functions in a differentiable function of individual atomic coordinates. Such kind of representation is known as the force field[16]. The first-order partial derivatives of the force field function with respect to the individual coordinates provide the forces on the atoms[16]. These forces are used further to obtain the time evolution of the system.

The force field represents the interaction potential of the molecular system. There are two types of interactions present in the molecular system, the first one is bonded, and the other
is non-bonded. Bonded interactions can be further divided into three types, stretching of bonds (1-2 interaction), bending of bond angle (1-3 interaction), and the last one is dihedral rotation (1-4 interaction). Similarly, there are two non-bonded interactions: Coulomb and Lennard-Jones (LJ)[17].

The stretching of bonds and the bending of bond angles are modeled in the form of Hook’s law. LJ interaction models the Diffusion attraction at long-range orders and Pauli exclusion repulsion at short-range orders[16]. The basic structure of a force field is as follows,

\[ E_{bonded} = \sum_{bonds} K_b (b - b_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} K_\chi [1 + \cos(n\chi - \sigma)] \]

And

\[ E_{nonbonded} = \sum_{nonbonded pairs} \left( \varepsilon_{ij} \left[ \left( \frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{min,ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}} \right) \]

The above equation contains parameters like equilibrium bond length \( b_0 \), rigidity towards the stretching of bonds \( K_b \), equilibrium bond angle \( \theta_0 \), etc. Different force fields incorporate different methods for the evaluation of these parameters. So, the results of MD simulations using different force fields varies significantly. Specific force fields have been reported to produce better results for specific molecular systems. The force field selection for a particular system depends upon the literature survey. So, we will test the versions of AMBER force fields pre-embedded in the GROMACS suite for the simulation.

GROMACS software will be utilized to perform the Molecular Dynamics (MD) simulations. The MD simulation of the complex will be done using the versions of AMBER force field pre-embedded in GROMACS software. The versions of AMBER force fields, pre-embedded in GROMACS are AMBER03[18], AMBER94[19], AMBER96[20], AMBER99[21], AMBER99SB[22], AMBER99SB-ILDN[23], and AMBERGS[24], and these will be termed as ff1, ff2, ff3, ff4, ff5, ff6, and ff7 respectively for further discussion in the paper. The results of the MD simulations will then be analyzed to conclude which force field is better for the simulation of the ligand-DNA complex.

2. Materials and Methods

2.1. System selection and preparation.

In the literatures (3,6-bis(4,5-dihydro-1H-imidazol-2-yl)-9H-carbazole) derivatives had been reported to be a groove binder[25]. Also, carbazole derivatives have been shown to have dynamical stability with DNA [25]. The ligand labeled as Lig1, a groove binder, has been screened from literature. The chemical structure of the ligand is shown in figure 1. The structure of target DNA sequence, B-DNA dodecamer D(CGCGTTAACGCG) (PDB ID-195D)[26] was downloaded from PDB[27]. Before starting the docking calculation, all the water molecules must be removed from the DNA sequence through UCSF Chimera[28].

![Figure 1. Structure of the Ligand Lig1.](https://biointerfaceresearch.com/)
2.2. **Molecular geometry optimization.**

Molecular geometry optimization is necessary before starting any computational calculation because it restricts the system in the state with minimum potential energy. The optimized structure has the least steric hindrances and the maximum possible bond lengths, angles, and dihedrals. Optimization allows the charges to get distributed evenly over the molecule[29].

In this study, the optimization was done using B3LYP functional of DFT at 6-31G level basis set in Gaussian 09 software [30]. The optimized structure of the ligand was used for molecular docking[31].

2.3. **Molecular docking calculation.**

In our study, we have used AutoDock4 software[32] to perform molecular docking. We have incorporated LGA (Lamarckian Genetic Algorithm) as a search algorithm. Before starting the docking calculations, AutoDock Tool (ADT) was used to add Gasteiger charges to the DNA-ligand complex. A grid box with different magnitudes of sides was prepared for each DNA-ligand complex, which surrounds the complex. 20 LGA run with a maximum cycle of 2500000 energy evaluations for the complex was performed. All the poses were ranked based on binding affinity; the lower the binding affinity, the better the rank. Among the different docked poses, the pose with rank 1, or in other words, with the least binding affinity, was extracted, and the complex so obtained was used for further study.

2.4. **Molecular dynamics simulation.**

Molecular dynamics simulation has been employed to investigate the dynamics of the molecular system over a specified time[17]. In the case of biomolecules, it is widely used to study protein folding, unfolding, drug-protein interaction, protein-protein interaction and to examine the complex's stability over a specified time[33-35]. MD simulation becomes more valuable for the cases where the experimental observations are challenging[16].

We have used GROMACS 5.1.1 software[36,37] to carry out the molecular dynamics simulation. The DNA-ligand complex obtained from molecular docking was selected for molecular dynamics simulation with a 100ns time scale using the seven versions of the AMBER force field. There are several pieces of literature comparing the force fields for nucleic acid[38-42]. Still, the AMBER force field, due to the presence of terminal nucleotide specific topologies, seems to be suitable for the nucleic acid simulations[41]. GROMACS has seven versions of AMBER force field already embedded in it, and topologies for the selected sequence of DNA were generated using these force fields separately. Topologies for the ligand were generated using the ANTECHAMBER module of the AMBER program through Python script "acppype.py"[43]. The next step was to solvate the complex. So, the complex was solvated in a box in conjunction with the TIP3P water model at 298K[44]. Then to neutralize the system, sodium ions were added to the box by randomly replacing the water molecules. Long-range interactions in periodic boundary conditions were handled using Particle Mesh Ewald (PME)[45]. Minimization of energy of the entire system was performed in 25000 steps implementing the steepest descent leap-frog integration method. Berendsen thermostat was used for nvt ensemble equilibration at a constant temperature of 300K for 50s [46]. After that, npt ensemble equilibration was done in 25000 steps using the steepest descent leap-frog
integration at a constant pressure of 1atm [46]. All the bonds with hydrogen atoms were constrained using the LINCS algorithm [47]. Xmgrace software was used for graph plotting [48].

3. Results and Discussion

3.1. Geometry optimization.

The ligand was optimized using B3LYP functional at 6-31G level to achieve the ligand structure with the lowest possible energy state and correspondingly maximum stability. The ligand structure after optimization is shown in Figure 2 below.

![Figure 1. Optimized Structure of the Ligand Lig1.](image)

3.2. Molecular docking.

The ligand was docked on the target DNA sequence to find the best-docked position. The docking result of the ligand with the selected DNA sequence is summarized in table 1. Figure 3 below shows the ligand's best-docked pose with the DNA sequence 195D (binding energy = -9.74 Kcal/mol) and their interactions. The figure indicates that the ligand binds itself in the minor groove of the DNA sequence. Table 1 below gives the details of the hydrogen bonds. Figure 4 and Figure 5 represent the hydrogen bond donor & acceptor region and the charge distribution about the binding site, respectively.

![Figure 3. (a) Docked Pose of the Ligand with 195D and (b) 2d representation of the interaction between them.](image)
Figure 4. (a) h-bond donor and acceptor site about the ligand (b) h-bond between ligand1 and DNA.

Figure 5. Charge distribution about the interaction site.

Table 1 Details of Hydrogen Bonds between DNA and Ligand.

| Sl. No. | Interacting Atoms     | Bond Length (Å) |
|---------|-----------------------|-----------------|
| 1.      | LIG1:H10 – DT6:O2     | 2.594087        |
| 2.      | LIG1:H10 – DA7:O4'    | 1.843068        |
| 3.      | DA20:C1' – LIG1:N1    | 3.705932        |
| 4.      | LIG1:C14 – DT18:O2    | 2.766987        |

3.3. Molecular dynamics simulation.

The results of the MD simulation were analyzed to examine the stability of the DNA-ligand complex. Various parameters like the radius of gyration, rmsd, rmsf, and hbond were analyzed. The graphs of these parameters using the mentioned seven force fields are compared.

3.3.1. Variation in Radius of Gyration.

The radius of gyration is a measure of the compactness of the structure and is given by the following equation

\[ R_g = \sqrt{\frac{\sum_i^N m_i r_i^2}{\sum_i^N m_i}} \]

here, \( m_i \) is the mass of the ith atom, \( r_i \) is the distance of the ith atom from the center of mass of the system[49]. The graphs of the radius of gyration are shown below in Figures 6 and 7. And the statistical values of the graphs are mentioned in table 2.
Figure 6. Comparison of Radius of gyration with simulation time for AMBER force fields.

Figure 7. Graphs of Radius of Gyration vs Simulation Time using AMBER force fields.
Table 2. Statistical values of the Graphs of Radius of Gyration.

| Force Field | Range        | Mean    | Standard Deviation |
|-------------|--------------|---------|--------------------|
| FF1         | 1.45594 - 2.40820 | 2.08783 | 0.1809400          |
| FF2         | 1.40796 - 1.89447 | 1.70169 | 0.1350980          |
| FF3         | 1.41531 - 2.39154 | 1.95687 | 0.1630220          |
| FF4         | 1.35889 - 3.89906 | 2.78326 | 0.4878010          |
| FF5         | 1.24221 - 1.74083 | 1.36525 | 0.0531752          |
| FF6         | 1.33761 - 2.35564 | 2.00462 | 0.1918220          |
| FF7         | 1.44100 - 2.59832 | 2.15995 | 0.1691940          |

It is clear from the table and the graph that the radius of gyration was the least for ff5. Hence, among all the seven force fields, ff5 restricts the DNA to be in the most compact form for the simulation time.

3.3.2. Root Mean Square Deviation (RMSD).

RMSD is a measure of the deviation of the molecular structure from its native or reference structure and is given by

\[ \sigma_{RMSD} = \sqrt{\frac{\sum_{i}^{N} m_i (r_i - r_{i, ref})^2}{\sum_{i}^{N} m_i}} \]

where \( m_i \) is the mass of the \( i \) th atom, \( r_i \) and \( r_{i, ref} \) are the position of \( i \)th atom at any instance and in the native or reference structure, respectively[50]. RMSD also serves to verify whether the system has achieved an equilibrium structure or not[49]. The graphs are shown in Figures 8 and 9.

Figure 8. Comparison of RMSD (complex with respect to complex) with simulation time.
It is evident from the graphs that all the DNA remains intact during the simulation time for all the force fields. But among them, ff5 shows the least variations in rmsd for the DNA-ligand complex and formed the most stable complex. The plateau region in the rmsd of DNA-Ligand for ff5 after 10ns, confirms the formation of equilibrated complex structure. The simulation using ff2 was not completed because of the improper parameterization.

3.3.3. Root Mean Square Fluctuation.

Root Mean Square Fluctuation (RMSF) measures the fluctuation of each subunit of a molecular system concerning the reference structure[51]. The jumps or peaks in the rmsf graph suggest the fluctuation of the set of atoms is greater than the fluctuation in other atoms of the molecule. In our case, the fluctuation of the ligand atoms was greater than the atoms corresponding to the DNA. The RMSF graph was plotted between the rmsf value and the atom number. The graphs of rmsf are shown in Figures 10 and 11, and the statistical values are given in table 3.

**Figure 9.** Graphs of RMSD using the mentioned Force Fields.

**Figure 10.** Variation of RMSF with simulation time.
Table 3 Statistical Values of the graphs of RMSF.

| Force Field | Range of RMSF | Mean   | Standard Deviation |
|-------------|---------------|--------|--------------------|
| FF1         | 0.1921-3.4384 | 0.830303 | 0.615188           |
| FF2         | 0.1080-1.5350 | 0.276464 | 0.281719           |
| FF3         | 0.2356-4.2439 | 0.783406 | 0.783653           |
| FF4         | 0.2134-4.7748 | 0.896153 | 0.897097           |
| FF5         | 0.0923-1.0225 | **0.216315** | **0.182600** |
| FF6         | 0.1849-3.9137 | 0.845027 | 0.695093           |
| FF7         | 0.2105-4.2037 | 0.863774 | 0.775285           |

It is evident from the graph that the fluctuation in the DNA atoms is significantly less than the fluctuations in the ligand atoms. The lower rmsf value indicates the stable structure, and hence comparatively, ff5 gives the best result among all other force fields.

3.3.4. Hydrogen bond.

The hydrogen bond is the key factor in the stability of the ligand-target structure. The greater the number of hydrogen bonds formed between the ligand and target structure, the more stable the complex is. The number of hydrogen bonds formed between the target and the ligand indicates bonding strength. The number of hydrogen bonds formed between the ligand and the DNA was plotted against the simulation time for the force fields, and these are given in Figures 12 and 13.
Figure 12. Variation of the number of hydrogen bonds with simulation time.

Figure 13. Graphs of the hydrogen bond between ligand and 195D.
4. Conclusions

It is clear from the above discussion that the force field selection for a system is not random. The force fields are system-specific, the selection should be based on the literature review and previous works. The computational studies on DNA using AMBER force fields have been reported to be in good agreement with the experimental results. But for the DNA-ligand complex, not all versions of the AMBER force field produce promising results.

Among all the seven versions of the AMBER force fields, pre-embedded in the GROMACS suite of programs, AMBER99SB performs better than the remaining force fields for the simulation of the DNA-ligand complex. And the parameterization of the DNA-ligand complex was not proper with AMBER94, which resulted in the non-completion of the simulation. The simulation using AMBER94 ended before completion.

The compactness of the DNA-ligand complex was examined by the radius of gyration; the lower the radius of gyration, the more compact is the structure. The rmsd and rmsf graphs reveal the stability of the complex. The lower the rmsd and rsmf, the more stable the structure is. Among all other versions of AMBER force fields, AMBER99SB produces the lowest values of the radius of gyration, rmsd, and rmsf; we can conclude that for our system selection, AMBER99SB is better among the tested force fields.

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Conflicts of Interest

The authors declare no conflict of interest.

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