ASSESSMENT OF MOLECULAR DYNAMICS FORCE FIELDS FOR DRUG-DNA INTERACTION

Summary of the Dissertation
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by

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Summary of the Dissertation

Titled

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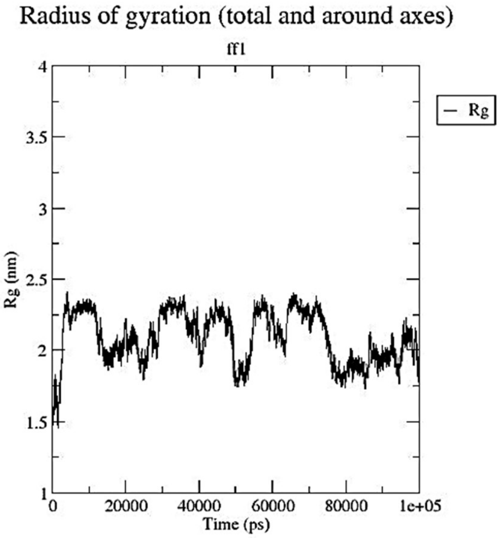
The work carried out in the present M.Phil. dissertation is divided into 4 chapters.

Chapter 1 contains the basic introduction of the DNA and the interactions of the drug with the DNA. In this chapter we have briefly discussed about the basic components of the DNA like, Phosphate, sugar, nitrogenous bases. We have also discussed the difference between the ribose and deoxyribose sugar. Difference between nucleotides and nucleosides is discussed in this chapter. The discussion about the interactions between the drug and the DNA is also discussed in this chapter. The three most general modes of binding of the drug with the DNA are Minor groove binding, Major groove binding and Intercalation and these modes are discussed herein.

Chapter 2 includes the discussion about some of the computational techniques used for the study of the drug-DNA interactions. These methods include Molecular Docking Simulation and Molecular Dynamics Simulation. Molecular Docking Simulation is used to predict the binding mode of the drug with the DNA whereas MD simulations are used to study the effects of the drug binding by predicting the dynamics of the drug-DNA complex. MD simulations uses force fields to generate the topologies of the molecular structure. This chapter presents the discussion on force fields and the methodology of performing the MD simulation.

Chapter 3 presents the introduction of the identified problem for this dissertation work. The lack of consensus about the selection of force field for the simulation of drug-DNA complex was the identified problem. This chapter includes the discussion about the methods used for the current work. The results of the molecular docking simulation and MD simulation are also discussed in this chapter. The results of the MD simulation are analysed based on the parameters like radius of gyration, root mean square deviation, root mean square fluctuation and the number of hydrogen bonds formed between the drug and the DNA.

The radius of gyration measures the compactness of the structure. The radius of gyration has been calculated for the drug-DNA complex. The radius of gyration has been plotted against the simulation time for seven versions of AMBER force fields available with GROMACS software. The seven versions of AMBER force fields are AMBER03, AMBER94, AMBER96, AMBER99, AMBER99SB, AMBER99SB-ILDN, and AMBERGS and will be termed as ff1,ff2, ff3,ff4, ff5, ff6, and ff7 respectively for further didcussion. The graphs of the radius of gyration is shown in the following figure 1.



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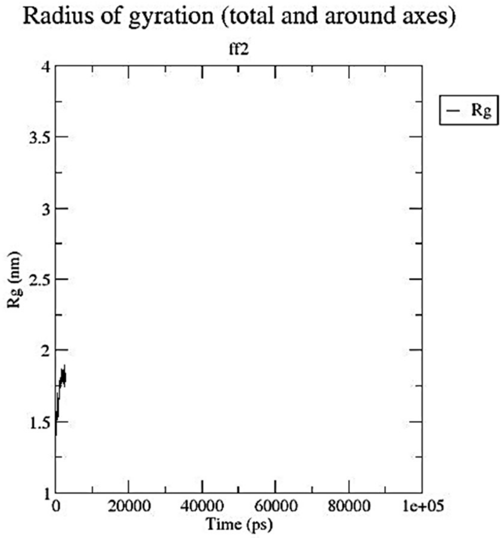

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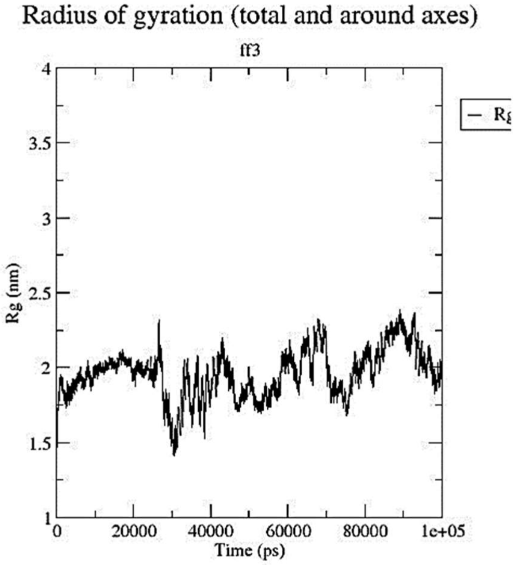

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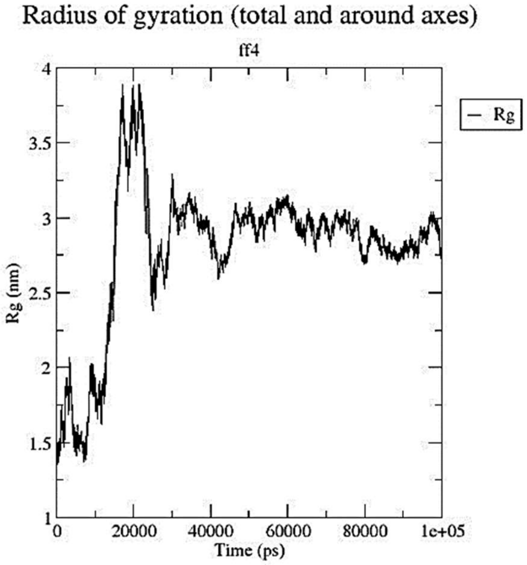

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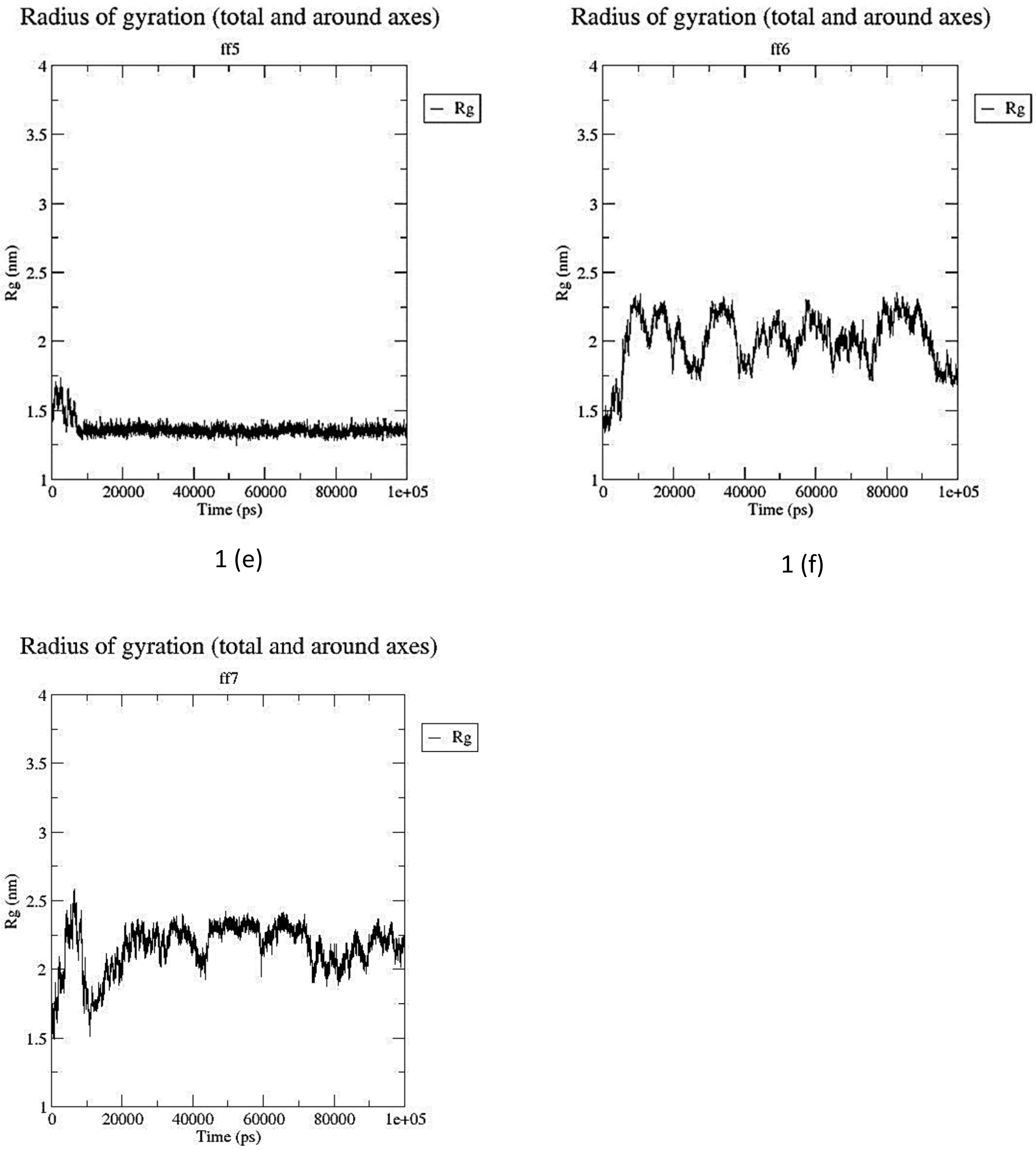


1 (e)

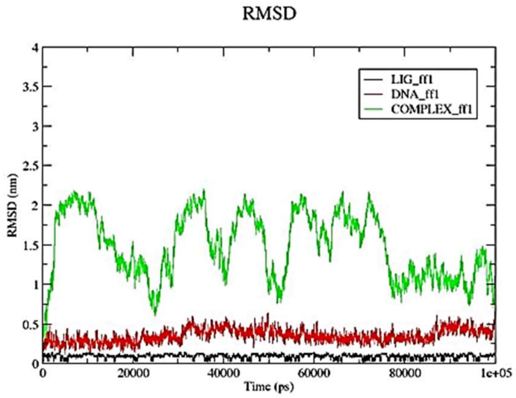
1 (f)

1 (g)

Figure 1 (a-g) Plot of Radius of Gyration vs simulation time

It has been observed from the graphs of radius of gyration that the force field ff5 which is AMBER99SB has predicted the most compact structure of the complex among all other versions. The plateau region of the plot for ff5 has also confirmed the formation of stable structure of the drug-DNA complex. The standard deviation of the value of radius of gyration for ff5 was lesser (~0.05nm) in comparison to that for other versions (0.13-0.48 nm).

The Root Mean Square Deviation (RMSD) indicates the fluctuations of the molecular structure from its native or reference structure. The RMSD has been plotted against the simulation time for the DNA atoms, drug (ligand) atoms, and for the drug-DNA complex for each of the seven force fields. The RMSD for the DNA atoms, drug atoms and drug-DNA complex has been shown by red, black and green, respectively in the following figure 2.



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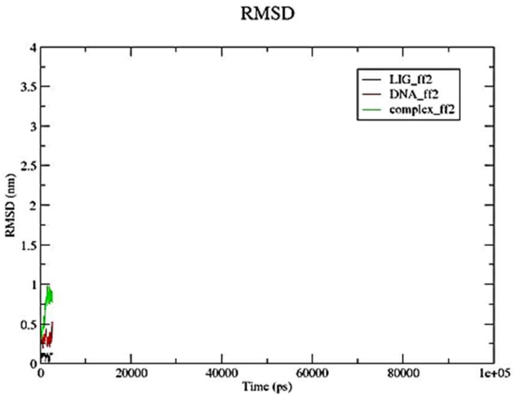

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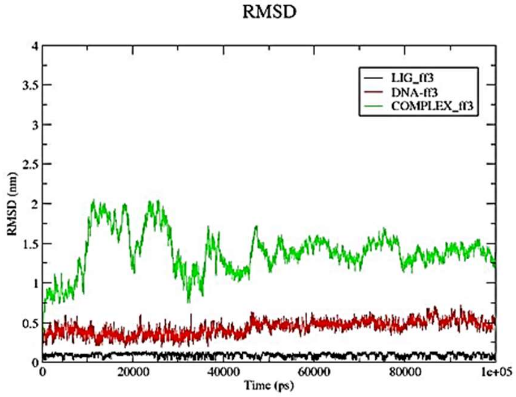

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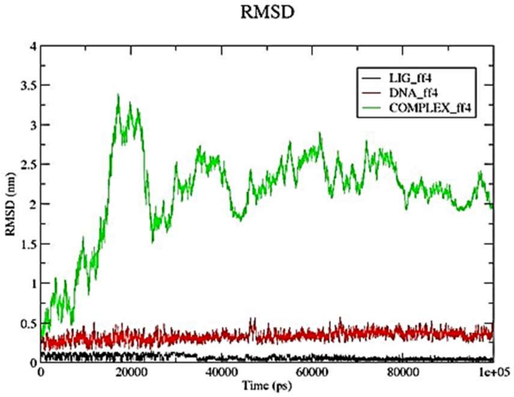

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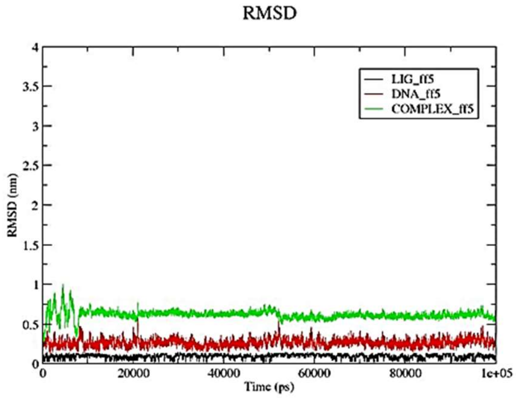

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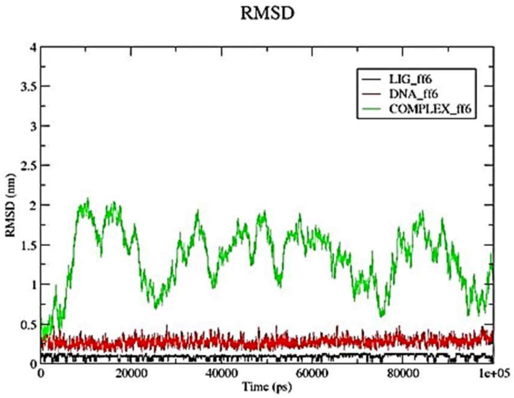

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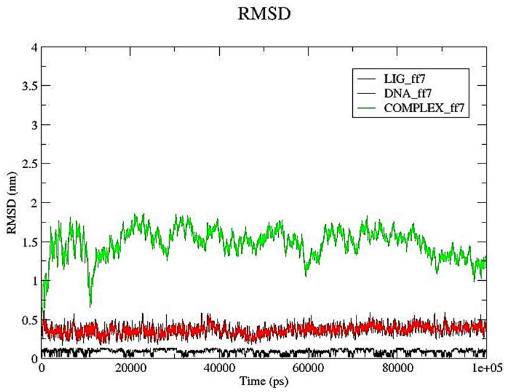
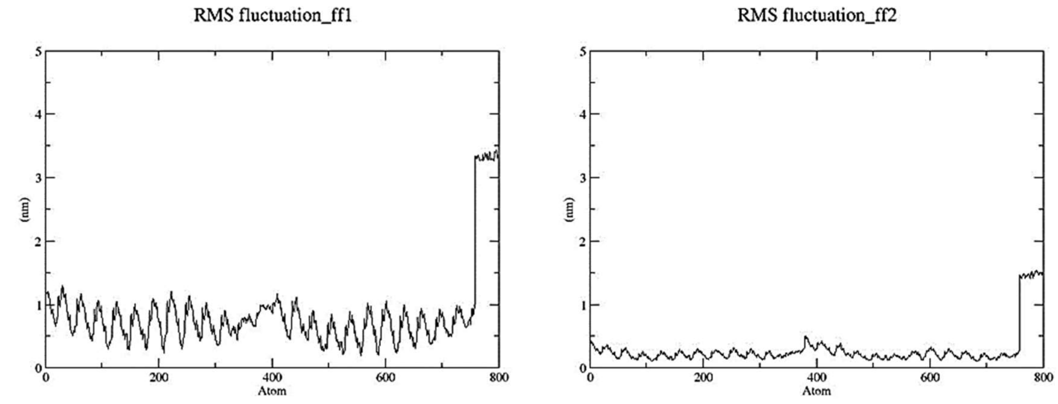


2 (g)

Figure 2 (a-g) RMSD vs Simulation time for each of the seven force fields

These plots indicate that the complex has not achieved the stability for throughout the simulation time for AMBER force fields except ff5 that is AMBER99SB. The stable structure has been achieved for the complex using AMBER99SB force field, which is clearly indicated by the plateau region of the plot.

The root mean square fluctuation (RMSF) measures the fluctuations of the subunits of the molecular structure. The RMSF has been plotted against the simulation time. The figure 3 represents the plot of the RMSF against simulation time.



3 (a)

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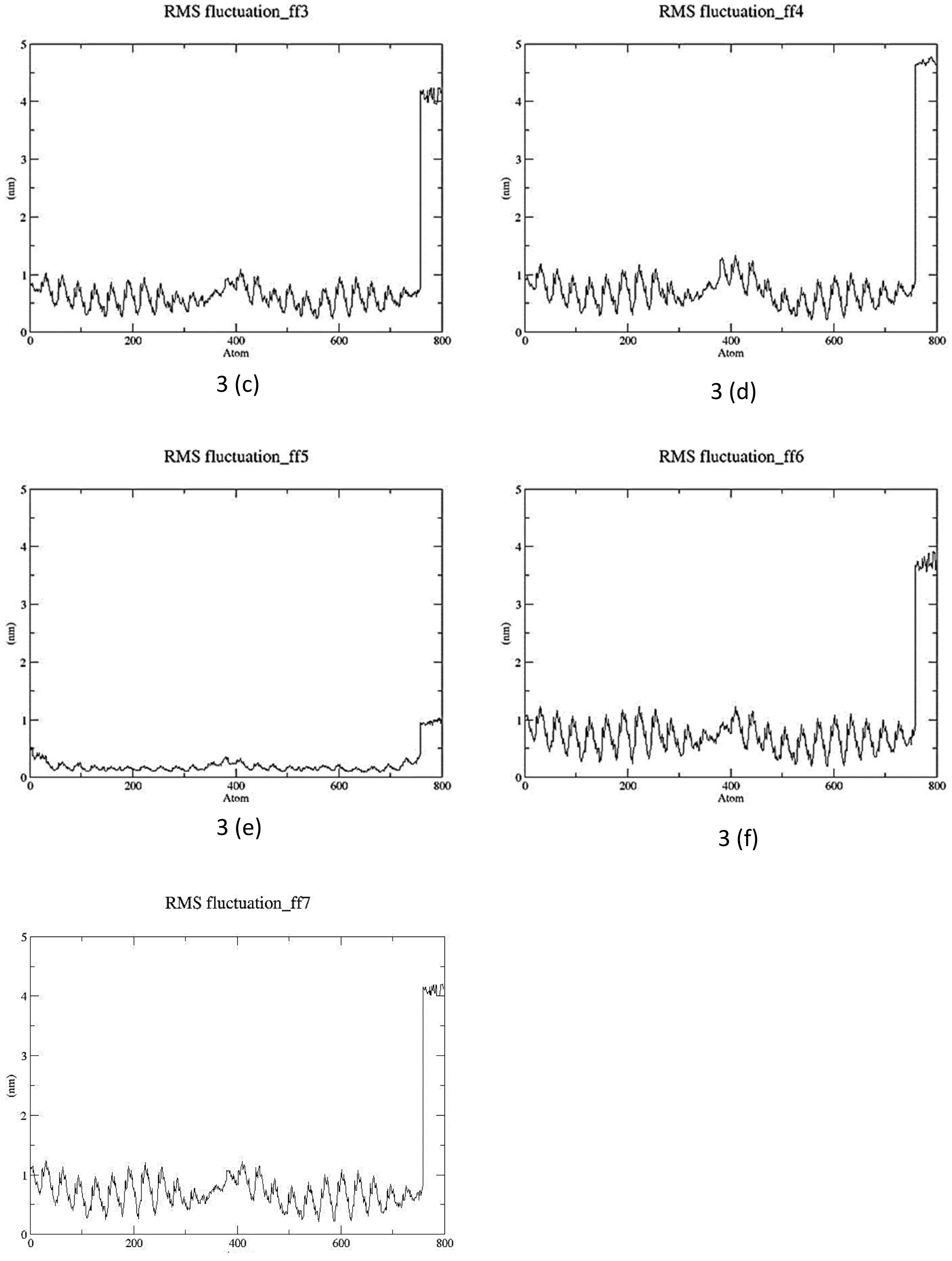

3 (c)

3 (d)

3 (e)

3 (f)

3 (g)

Figure 3 (a-g) The plots of RMSF vs Simulation Time

These plots represent that the fluctuations of the ligand atoms are greater than the fluctuations in the DNA atoms. Apart from that, ff5 that is AMBER99SB predicted the lowest overall fluctuations with mean ~0.22nm whereas other force fields predicted means that are in the range of 0.78 - 0.90nm except ff2 (AMBER94) which predicted mean about 0.28nm.

Chapter 4 gives the general conclusions drawn from the present dissertation and future research work that would be productive in the further understanding of performance of the force fields for the simulations of the drug-DNA complexes.

From the discussions on the parameters like radius of gyration, RMSD, and RMSF in chapter 3 of the dissertation, we came to the conclusion that the AMBER99SB force field performs better than other force fields available with the GROMACS software for the selected system (drug-DNA complex). This dissertation work also provides the methodology for the simulation of the molecular structures using GROMACS software. There is a wide scope of research related with this dissertation work. One can chose a different drug-DNA complex and compare the results on various parameters with the results obtained from this dissertation work to validate our findings. One can also assess the performance of other force fields available with several Molecular Dynamics Simulation softwares to identify the best force field for the simulation of drug-DNA complex.