

# MOLECULAR DYNAMICS STUDY OF TIP3P, SPC/E AND TIP4P WATER MODELS AT ROOM TEMPERATURE

*A dissertation*

*Submitted for the partial fulfilment of the*

*Degree of*

**Master of Science in Chemistry**

*by*

**K Dayananda Sharma**

**Nivedita Rai**

**Pratik Biswal**

Under the Supervision of

**Dr. Madhurima Jana**



**DEPARTMENT OF CHEMISTRY  
NATIONAL INSTITUTE OF TECHNOLOGY, ROURKELA**

**May 2013**



**NATIONAL  
INSTITUTE OF  
TECHNOLOGY  
ROURKELA-769008  
INDIA**

**राष्ट्रीय  
प्रौद्योगिकी  
संस्थान,  
राउरकेला**

**DEPARTMENT OF CHEMISTRY**

---

### **CERTIFICATE**

This is to certify that the dissertation entitled, “ **Molecular Dynamics Study of TIP3P, SPC/E and TIP4P Water Models at Room Temperature** ” submitted by **Mr. K Dayananda Sharma, Ms. Nivedita Rai** and **Mr. Pratik Biswal** for the award of Master of Science in Chemistry during the period of August 2012- May 2013 in the Department of Chemistry, National Institute of Technology, Rourkela, is a record of authentic work carried out by them under my supervision. To the best of my knowledge, the matter embodied in this dissertation has not been previously submitted for any degree in this/any other Institute.

May 2013

Rourkela

Dr. Madhurima Jana

## ACKNOWLEDGEMENTS

We pay our cordial gratitude to our respected teacher and supervisor Dr. Madhurima Jana, Assistant Professor, Department of Chemistry, National Institute of Technology, Rourkela, whose splendid guidance and authentic supervision and co-operation enabled us to make out our research problem in the present form.

It is our great pleasure to pay our respect and love for Prof. B.G. Mishra, Head of the Chemistry Department, National Institute of Technology, Rourkela for providing us all the necessary facilities in making this research work a success.

We are also highly indebted to all the faculties of this department for their kind help and valuable suggestions. We would also like to appreciate Mr. Dayanidhi Mohata for his immense help and encouragement throughout our project work. We would also like to thank all of friends for making our stay in this institute a memorable experience.

Last but not the least, we thank our parents & GOD who has always been a source of our strength, inspiration and our achievements.

*K Dayananda Sharma*

*Nivedita Rai*

*Pratik Biswal*

## **ABSTRACT**

Molecular dynamics simulations of three water models, namely, TIP3P, SPC/E, and TIP4P which are commonly used in biomolecular simulations were carried out at room temperature. Multinano-second trajectories were generated to analyze the structural and dynamical properties of the three water models. It has found that depending on the water models the properties change significantly. The structural behavior of water was studied by calculating pair-correlation function between the oxygen atoms of water molecules. Interestingly, it has noticed that waters of TIP4P model are highly structured as compared to the other two models. Further translational motions of the water molecules were found to be highly restricted for the SPC/E model as compared to the other two models. The diffusion-coefficient of TIP3P water was found to be twice as compared to SPC/E water model. Our findings correlate well with the experimentally available data.

# **CONTENTS**

## **1. INTRODUCTION**

## **2. OBJECTIVES**

## **3. SIMULATION DETAILS**

## **4. RESULTS AND DISCUSSIONS**

4.1 Temperature, Edge length and Energy

4.2 Water Structure

4.3 Translational Motion

## **5. CONCLUSIONS**

## **6. REFERENCES**

## 1. INTRODUCTION

Water is the most abundant solvent in nature. It plays important role in several chemical and biological processes. Various physical properties of water such as density, dielectric constant, compressibility etc are well established. Beside this water have many unusual properties such as high dielectric constant, negative volume of melting, numerous crystalline polymorphs, anomalously high melting and high mobility transport for  $H^+$  and  $OH^-$  ions, boiling and critical temperatures for a low-molecular-weight substance etc. Such properties can be explained in the light of the formation of three dimensional water-water hydrogen bonding networks. Further, it has found that the structural and dynamical properties of biomolecules are highly dependent on the solvent like water surrounding them. These waters are popularly known as “biological water”<sup>1</sup>.

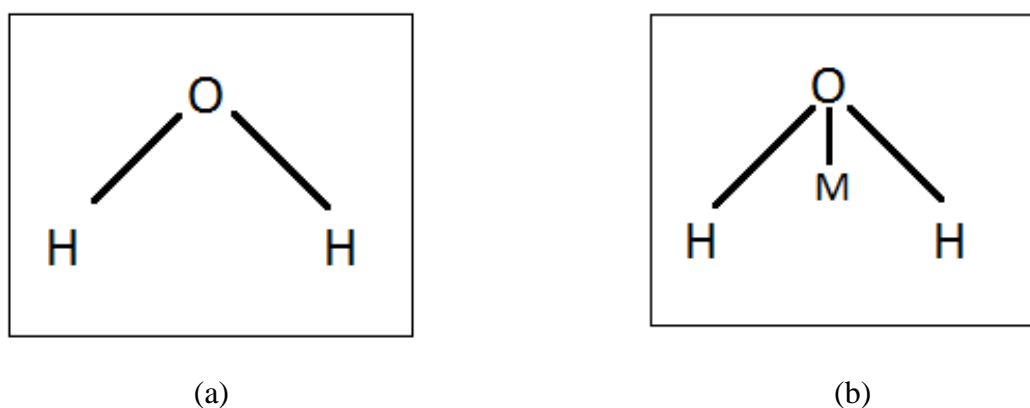
Although the macroscopic properties of liquid water have been studied extensively but the related microscopic properties are still unclear . In the last few decades a numerous experimental techniques such as microwave dielectric relaxation <sup>2</sup> , Raman spectroscopy <sup>3</sup> , light scattering spectroscopy <sup>4</sup> , nuclear magnetic resonance (NMR) <sup>5</sup> , small angle neutron scattering <sup>6</sup> etc. have been used to study the structural and dynamical properties of liquid water. A strong controversy on structure of liquid was raised by Wernet et al <sup>7</sup> when they used x-ray absorption (XAS) technique to study the structure of liquid water and suggested that majority of the liquid water experiences a distorted, asymmetric hydrogen (H) bonding environment. This result was in confliction with the well established fact that the waters are generally distributed by tetrahedral network of H bonds <sup>8 , 9</sup>. Soper <sup>10</sup> used empirical potential structure refinement (EPSR) technique and interpreted with existing neutron and x-ray diffraction data using an asymmetric water potential. The fitted data is in good agreement with the data obtained from x-ray and neutron diffraction in q space for all the models which has been tested <sup>11</sup>. Tokushima et al <sup>12</sup> used high resolution X-ray emission spectroscopy of liquid water and found that two distinct narrow lone-pair derived peaks, which were due to tetrahedral and strongly distorted hydrogen-bonded water respectively. The intermolecular partial pair correlation functions for liquid water have been studied by Neutron diffraction with isotopic substitution (NDIS) techniques <sup>13</sup>. Milles <sup>14</sup> used diaphragm-cell technique and Arata and co-workers <sup>15</sup> used NMR pulsed-gradient spin echo (PGSE) methods to study the self-diffusion co-efficient of pure bulk water at room

temperature. Recently, Wilke and co-workers<sup>16</sup> reported the microscopic structure of water at sub- and supercritical conditions by using X-ray Raman spectroscopy as well as ab initio molecular dynamics simulations, and density functional theory study. They showed that the distortions of hydrogen-bond network increase drastically when temperature and pressure of system increase to the supercritical regime. Recent development of spectroscopic techniques such as terahertz (THz) spectroscopy<sup>17</sup>, Raman echo<sup>18</sup>, and Optical Kerr effect spectroscopy<sup>19</sup> further provide valuable information of water dynamics in the time domain.

Besides various sophisticated experimental techniques several theoretical and simulation methods have been developed to describe the properties of liquid water. In this regards, it should be mentioned that computer simulation is a powerful tool to study the microscopic properties of chemical systems. From simulated trajectories one can measure several properties which can be directly compared with suitable experiments. Thus the method acts as a bridge between models and theoretical predictions as well as between models and experimental results. Researchers used these methods to provide a detail of microscopic properties of liquid water. These methods provide a detail of microscopic properties of liquid water. Over the last 30 years different potential models were used to reproduce the properties of water such as density, dielectric constant, diffusion coefficient, radial distribution functions, and many others, including their temperature or pressure dependency by using computer simulation techniques<sup>20-29</sup>. In these studies water monomer has been treated as rigid or as flexible, allowing all degrees of freedom for the OH bonds and HOH bond angle. Non-equilibrium classical molecular dynamic simulation is used by Ingrosso *et al*<sup>30</sup> for the theoretical study of the transfer of the water bend-to-liberation energy to liquid H<sub>2</sub>O. In a pioneer work Rahman and Stillinger<sup>31</sup> studied the molecular dynamics of liquid water and reported that the liquid water consists of large number of highly strained hydrogen network and the diffusion in the liquid is due to the cooperative interaction of the neighbouring molecules. Since the interaction potential models highly determine the results of computer simulations thus the properties of water depends upon the water model too. Therefore it will be interesting to compare the microscopic properties of liquid water depending upon the available potential models.

## 2. OBJECTIVES

Classical molecular dynamics simulation involves the integrations of equations of motions of many body systems of interacting particles. It can provide direct information on the structure and dynamics of molecules<sup>32, 33</sup>. In this thesis we have performed molecular dynamics simulation of different water models and compared their calculated bulk properties. In specific we looked into the structure and the self-diffusion of the waters and the results are once again compared with experimentally available data. In this study we have used three different water models namely, TIP3P<sup>20, 34</sup> (transferable intermolecular potential 3P), SPC/E<sup>35</sup> (extended simple point charge) and TIP4P<sup>36</sup>. The potential of these water models are composed of Lennard-Jones and Coulombic terms. Among the three models TIP3P and SPC/E have three site interactions whereas TIP4P has four sites of interactions. In Figure 1 we have presented a schematic diagram of the water models.



**FIGURE 1:** Schematic representation of (a) 3-sites and (b) 4-sites water models

In these models each atom is assigned a point charge and the oxygen atom gets Lennard Jones parameters. 3-sites water model is mostly used in simulation because of its simplicity and high computational efficiency. In 4-site water model negative charge is placed on a dummy atom (labelled as M in figure 1(b), along the bisector of HOH angle near oxygen atom.



### 3. SIMULATION DETAILS

Three separate simulations were carried out with TIP3P, SPC/E and TIP4P water models by using NAMD<sup>37</sup> code. In the rest of the thesis we will refer these simulations as S1, S2 and S3 respectively. The parameters of the three water models are given in Table 1.

**TABLE 1:** Parameters of TIP3P, SPC/E and TIP4P water models.

Parameters	TIP3P <sup>38</sup>	SPC/E <sup>39</sup>	TIP4P <sup>39</sup>
$\epsilon_{oo}$ (Kcal/m)	0.152	0.155	0.155
$\sigma_{oo}$ (Å <sup>0</sup> )	3.1506	3.1656	3.1540
rOH (Å <sup>0</sup> )	0.9572	1.000	0.9572
rOM (Å <sup>0</sup> )	-	-	0.15
HOH angle	104.52	109.47	104.52
$q_o$ (e)	-0.8340	-0.8472	-
$q_h$ (e)	0.417	0.4238	0.52
$q_m$ (e)	-	-	-1.04

The force field is the mathematical description of the potential which the atoms in the system experience. It consists of several terms and each of these describes either inter-molecular or intra-molecular interaction exhibited by the atoms in the system. A typical potential (V) can be given as,

$$\begin{aligned}
 V = & \sum_{(bonds)} K_b (b - b_0)^2 + \sum_{(angles)} K_\theta (\theta - \theta_0)^2 + \sum_{(dihedrals)} K_\phi [1 + \cos(n\phi - \delta)] + \\
 & \sum_{(improprs)} K_\omega (\omega - \omega_0)^2 + \sum_{(ureybradls)} K_u (u - u_0)^2 + \sum_{(non-bonded)} \epsilon \left[ \left( \frac{R_{\min ij}}{r_{ij}} \right)^{12} - \left( \frac{R_{\min ij}}{r_{ij}} \right)^6 \right] \\
 & + \frac{Q_i Q_j}{\Sigma r_{ij}}
 \end{aligned}$$

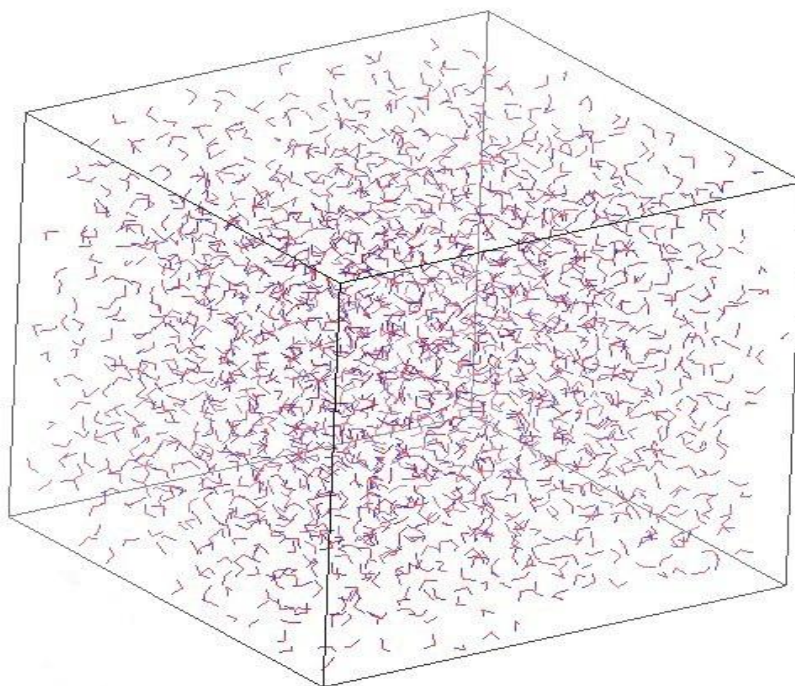
The first term in the above potential energy form accounts the stretching of bonds,  $k_b$  is bond force constant. The second term of the equation accounts for the bond angle,  $k_\theta$  is the angle force constant. The third term account for the dihedrals (torsion angle),  $k_\phi$  is the dihedral force constant,  $\eta$  is function multiplicity,  $\Phi$  is the dihedral angle and  $\delta$  is phase shift. The fourth term corresponds to the improvers (out of the plane bonding) where  $k_\omega$  is the force constant. The fifth term accounts for the angle bending of the 1,3 interaction. Sixth term accounts for the non-bonded interaction between the pair of atom. Parameters with zero subscript represent the corresponding equilibrium values. The initial configurations of water models were prepared from Packmol<sup>40</sup> code.

All the simulations were performed at 300K with periodic boundary conditions in a cubic box with side length 40.0 Å. Each box contained 2106 water molecules. The systems were first minimized using the conjugate gradient energy minimization method as implemented in the NAMD<sup>37</sup> code. Then gradually the temperature of each system was increased to the room temperature of 300 K within a short MD run. This was carried out at a constant pressure (P=1 atm) under the isothermal-isobaric ensemble (NPT) conditions. It was then followed by an NPT equilibration run at 300 K for 4.6 ns duration for each of the systems. The temperature and pressure of the systems was controlled by Langevin dynamics and Nose–Hoover Langevin piston methods<sup>41</sup>. The cell volumes were allowed to fluctuate isotropically during this period. At the end of these NPT runs, the volumes of the three systems attained steady values with cell edge lengths 39.68 , 39.48 and 39.65 Å for S1, S2 and S3 simulations. The dimensions of the simulation cells were then fixed and the conditions were changed to constant temperature (300 K) and volume (NVT ensemble). After 4.6 ns, a production run of 5.4 ns was carried out for each of the three systems. MD time step of 1 fs was employed for each of the simulations and the trajectories were stored every 500 fs for subsequent analysis.

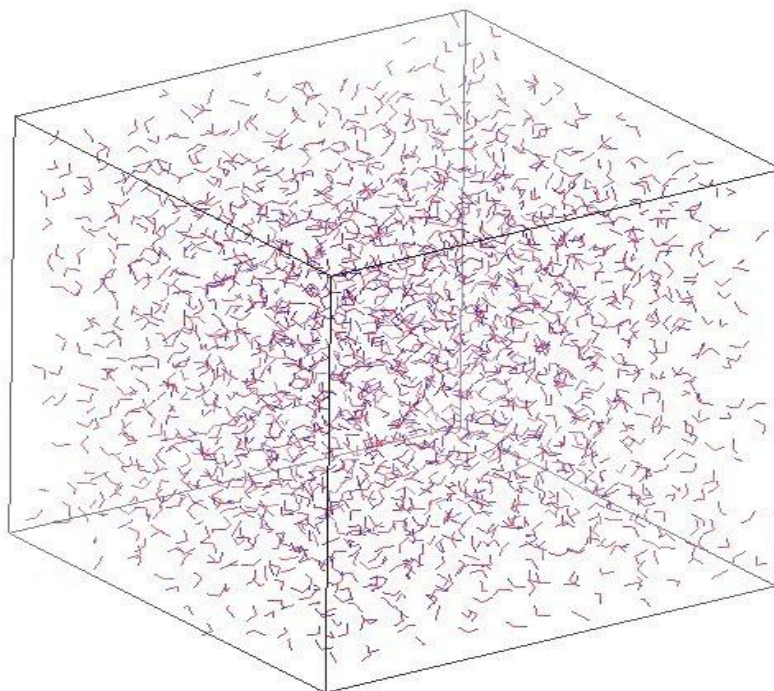
The minimum image convention<sup>32</sup> was employed to calculate the short range Lennard-Jones interactions using a spherical cut-off distance of 12 with a switch distance of 10 . The long-range electrostatic interactions were calculated by using the particle-mesh Ewald sum (PME) method<sup>42</sup>.

## 4. RESULTS AND DISCUSSIONS

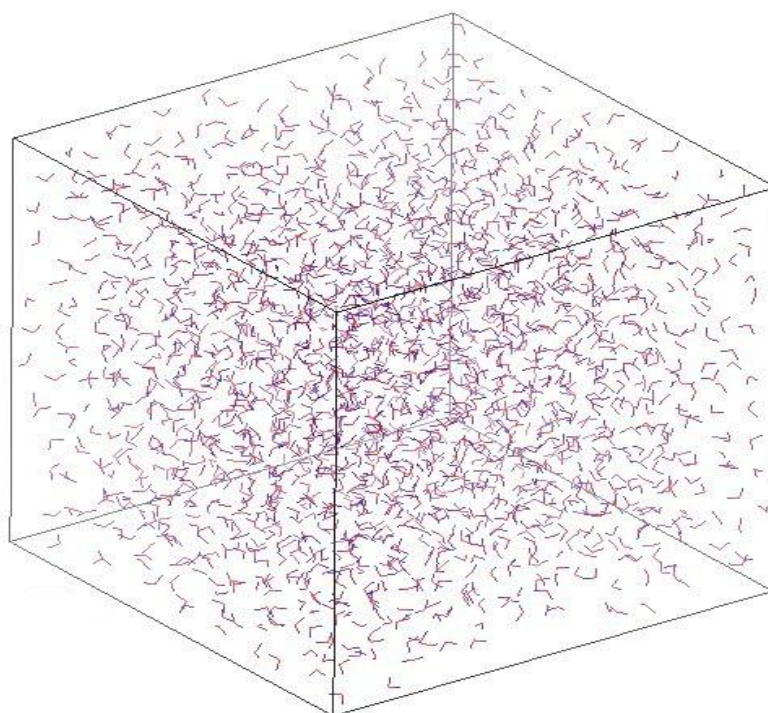
In Figure 2, 3 and 4 we have shown the snapshots of the simulated water box at different time steps as obtained from S1, S2 and S3 simulations. The initial boxes for the three systems are also displayed in the corresponding figures. In rest of the section we will discuss various microscopic properties of the waters as obtained from three different simulations.



(a)

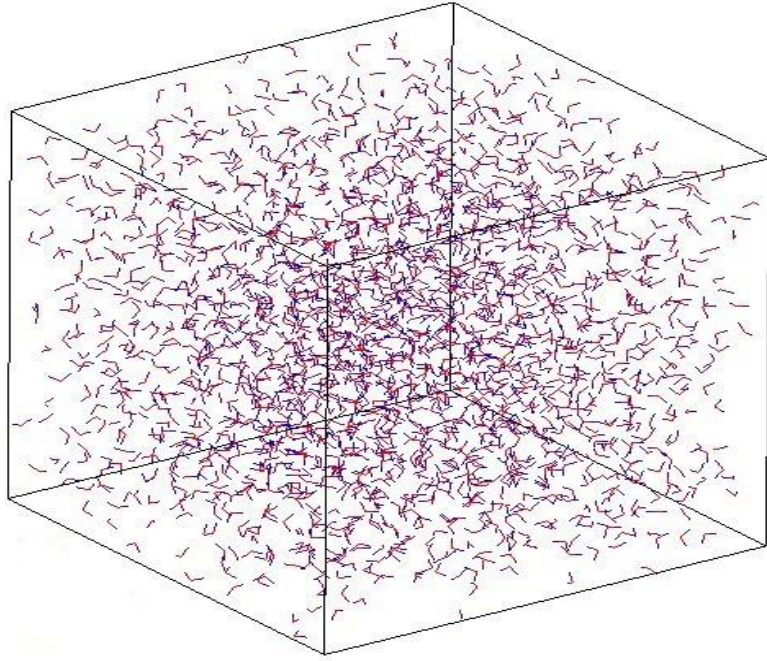


(b)

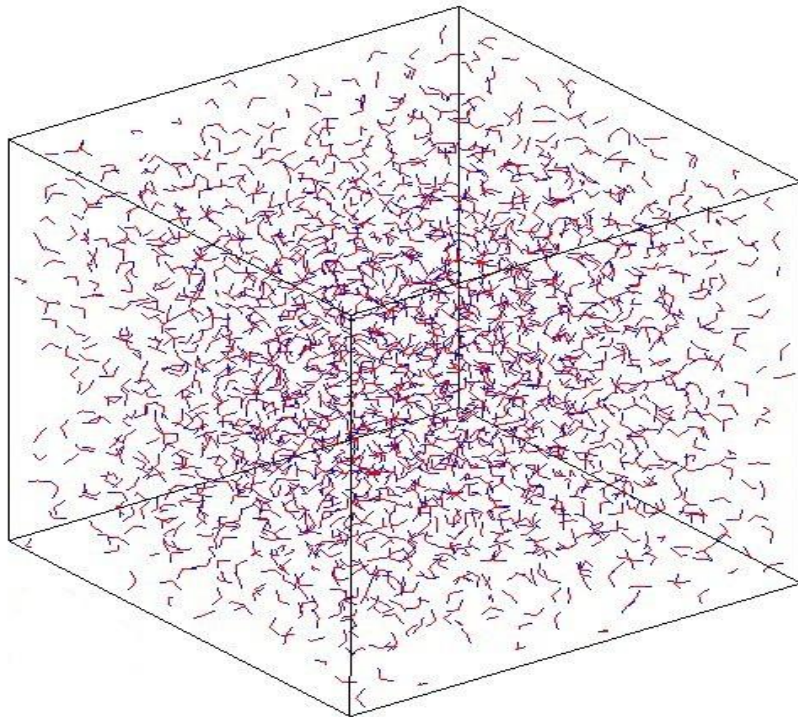


(c)

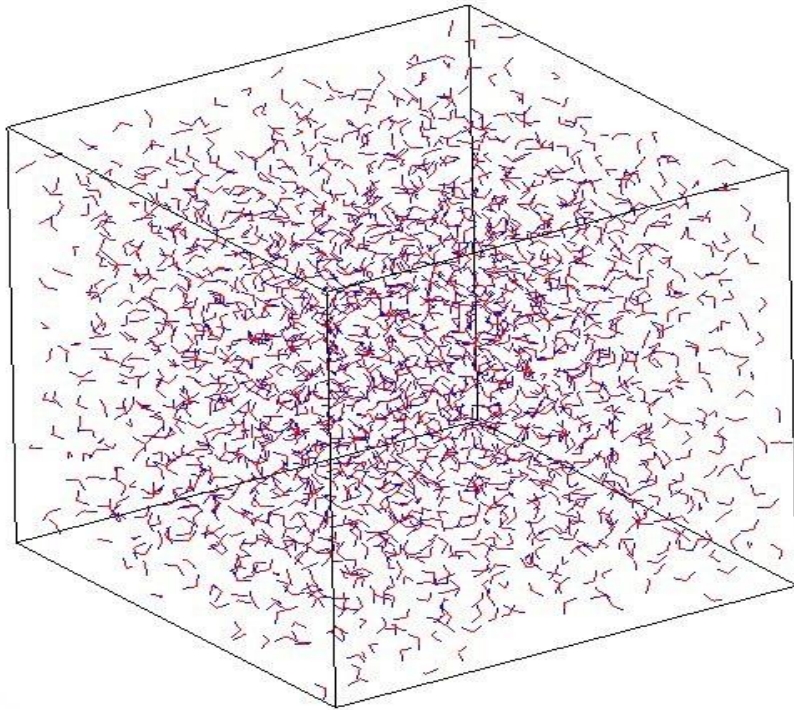
**FIGURE 2.** Snapshots of TIP3P water-box taken at different timesteps at (a)  $t=0$  (b)  $t=5$  and (c)  $t=10$  ns



(a)

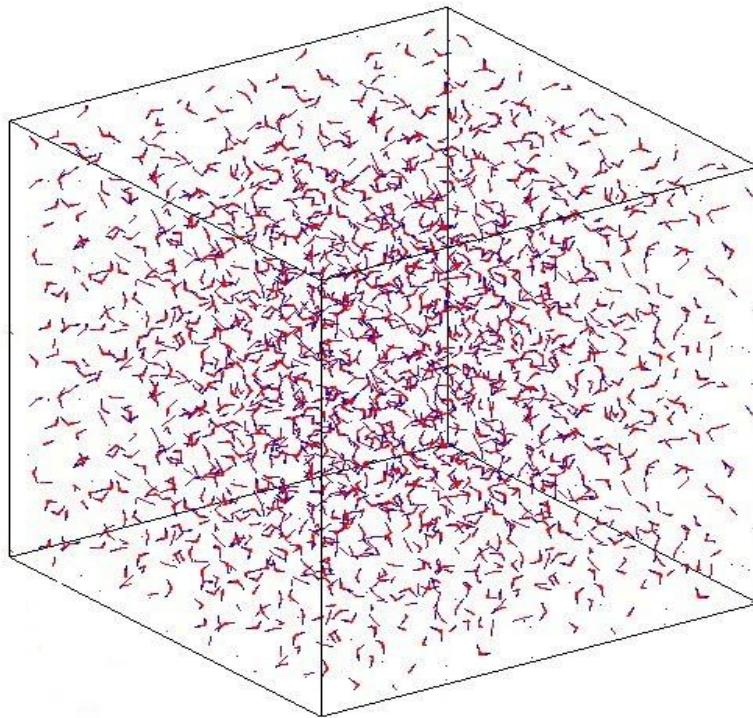


(b)

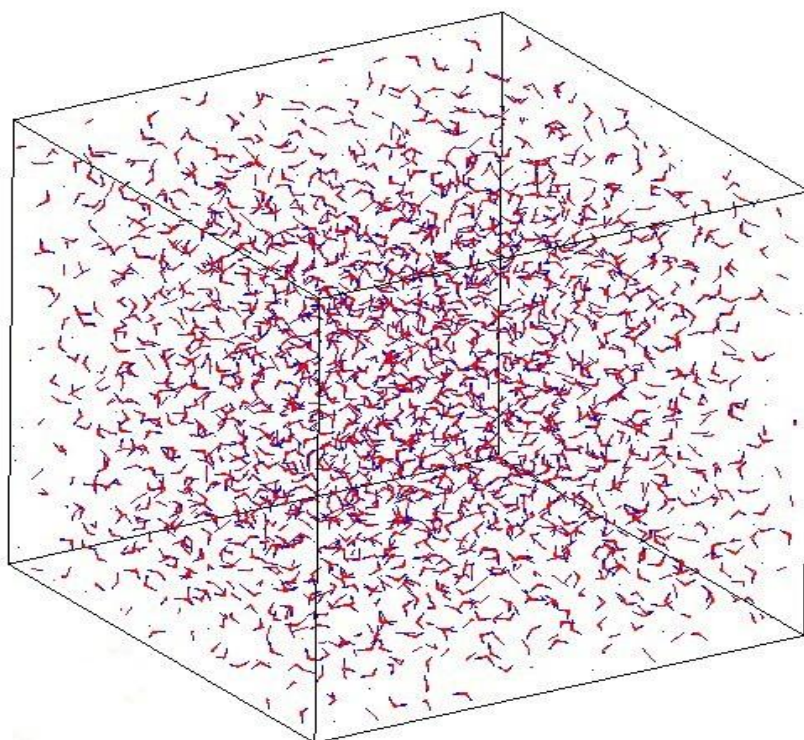


(c)

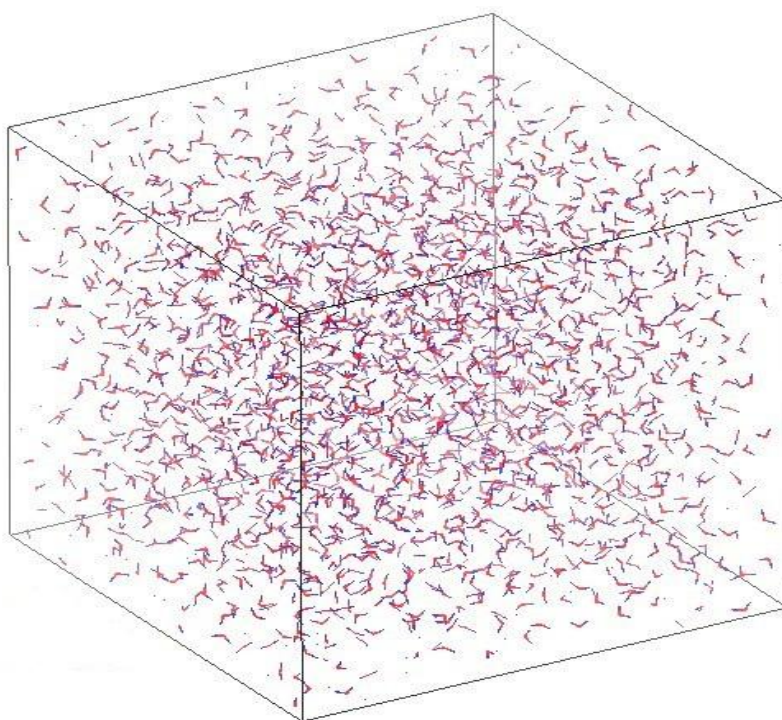
**FIGURE 3.** Snapshots of SPC/E water-box taken at different timesteps at (a)  $t=0$  (b)  $t=5$  and (c)  $t=10$  ns



(a)



(b)

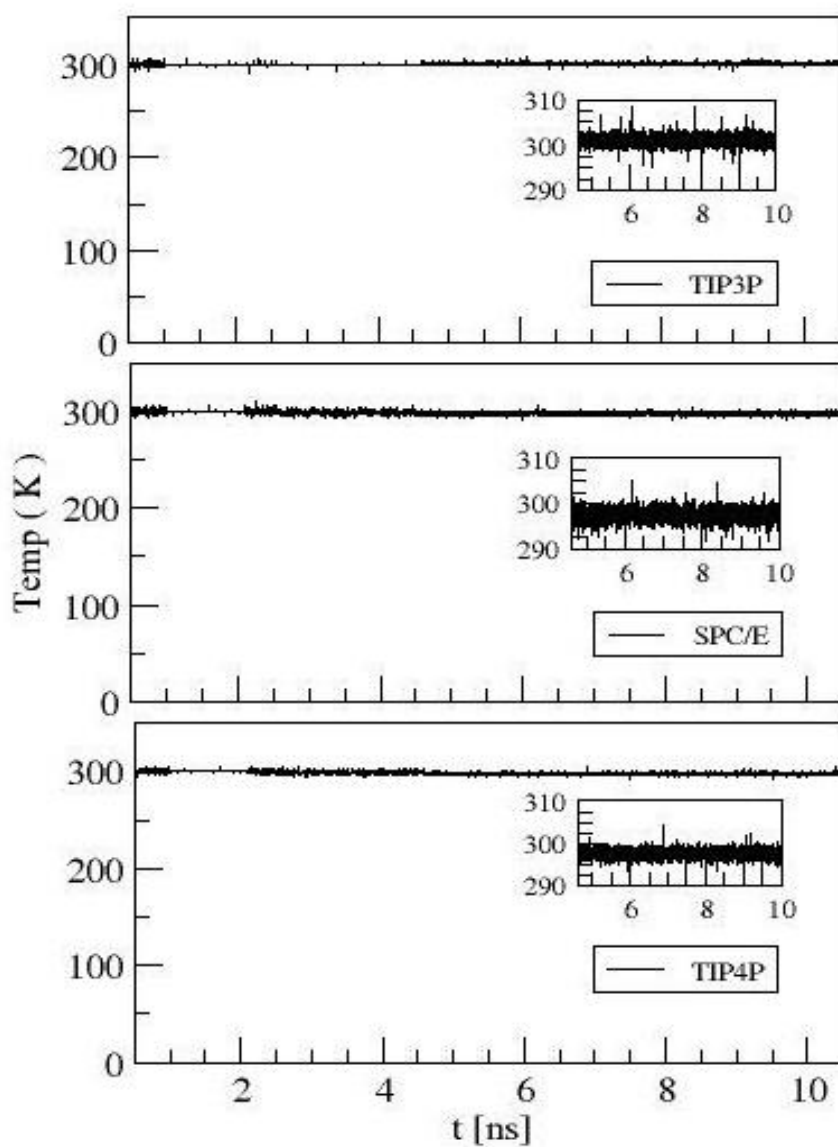


(c)

**FIGURE 4.** Snapshots of TIP4P water-box taken at different timesteps at (a)  $t=0$  (b)  $t=5$  and (c)  $t=10$  ns

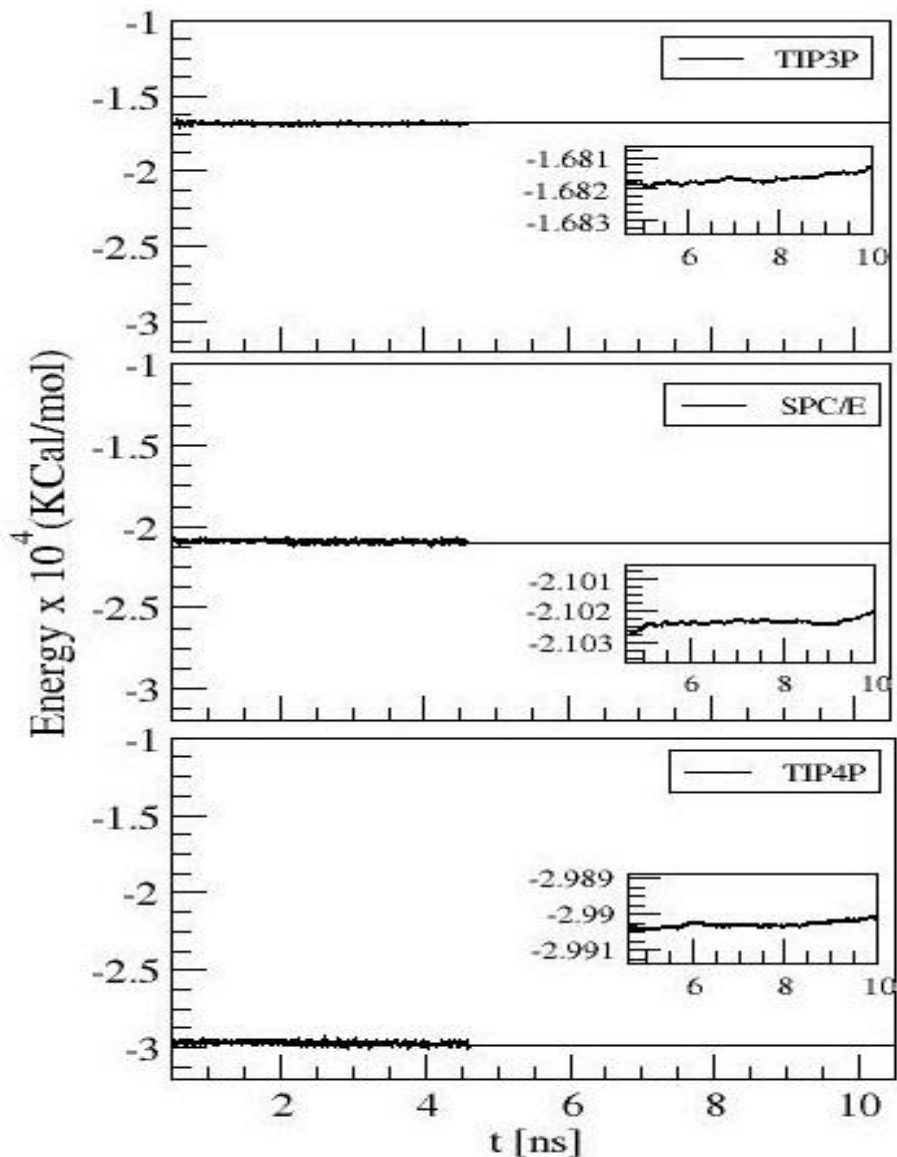
## 4.2. Temperature and Energy

The temperature and the energy of the S1, S2 and S3 simulations are shown in Figure 5 and 6 respectively.



**FIGURE 5.** Temperature plot of TIP3P, SPC/E and TIP4P water models as a function of time.



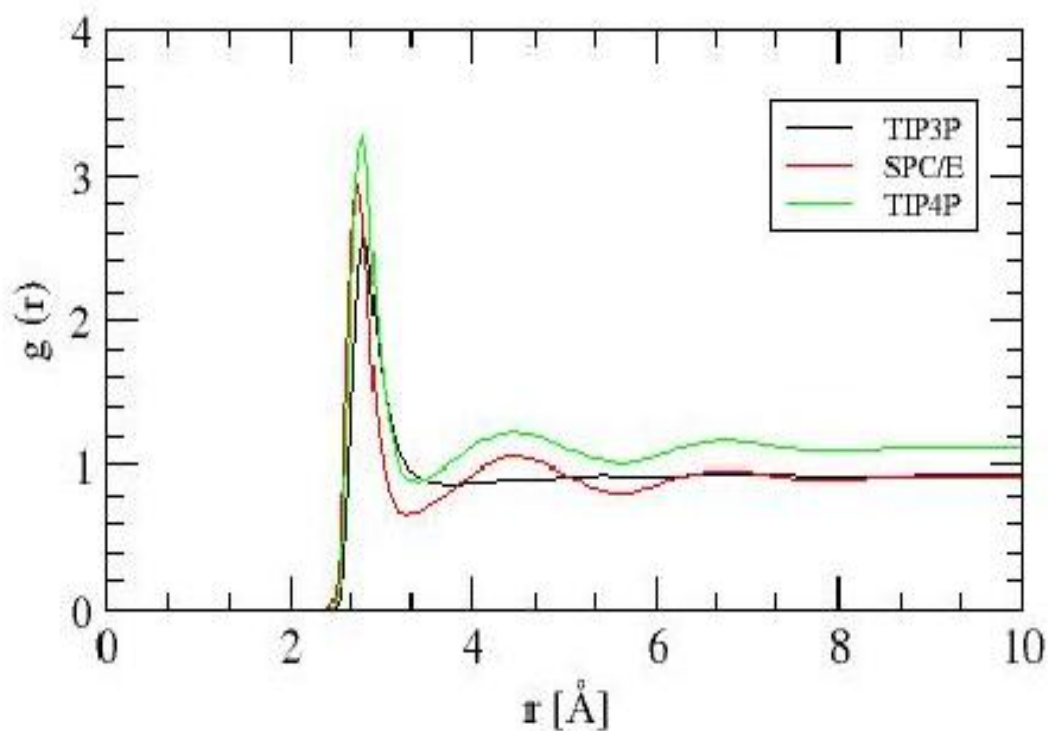


**FIGURE 6.** Total energy Plot of TIP3P , SPC/E and TIP4P water model as a function of time.

It is clear from the figures that during equilibration period there is fluctuations in temperature and energy values which is expected. Further it can be seen that during the production run the temperature of the three systems remain constant. The energy of the systems were also attains almost steady value. This indicates that the systems are well equilibrated.

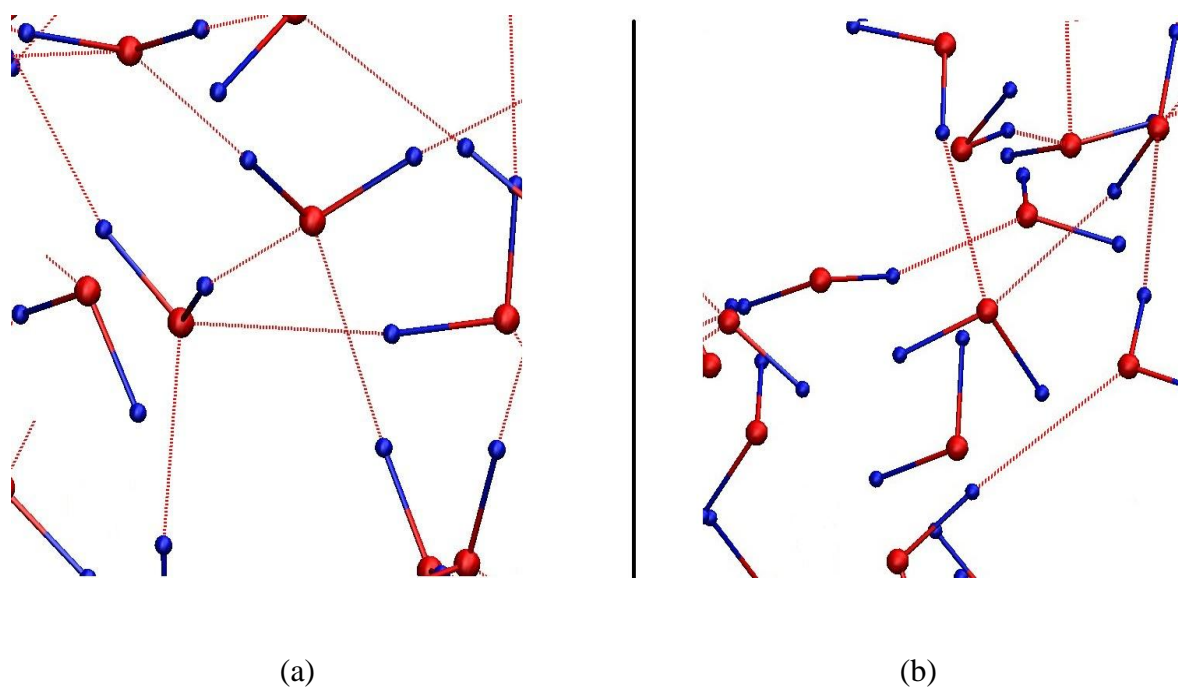
## 4.2 Water Structure

It is well known that the structure of liquid water can be studied by calculating pairwise correlation function, popularly known as radial distribution function,  $g(r)$ . X-ray<sup>43-46</sup> and neutron scattering<sup>47-50</sup> experiments provide direct information regarding the structure of water. Computer simulation plays an important role to characterize the structure of water and make a direct correlation with the experiments. In this work we have calculated  $g(r)$  between the oxygen atoms of the water molecules. The calculations were carried out for all the three water models, TIP3P, SPC/E and TIP4P and the results are compared with experimental data. The calculations were carried out by taking the average of all oxygen atoms of water molecules and the result is displayed in Figure 7.

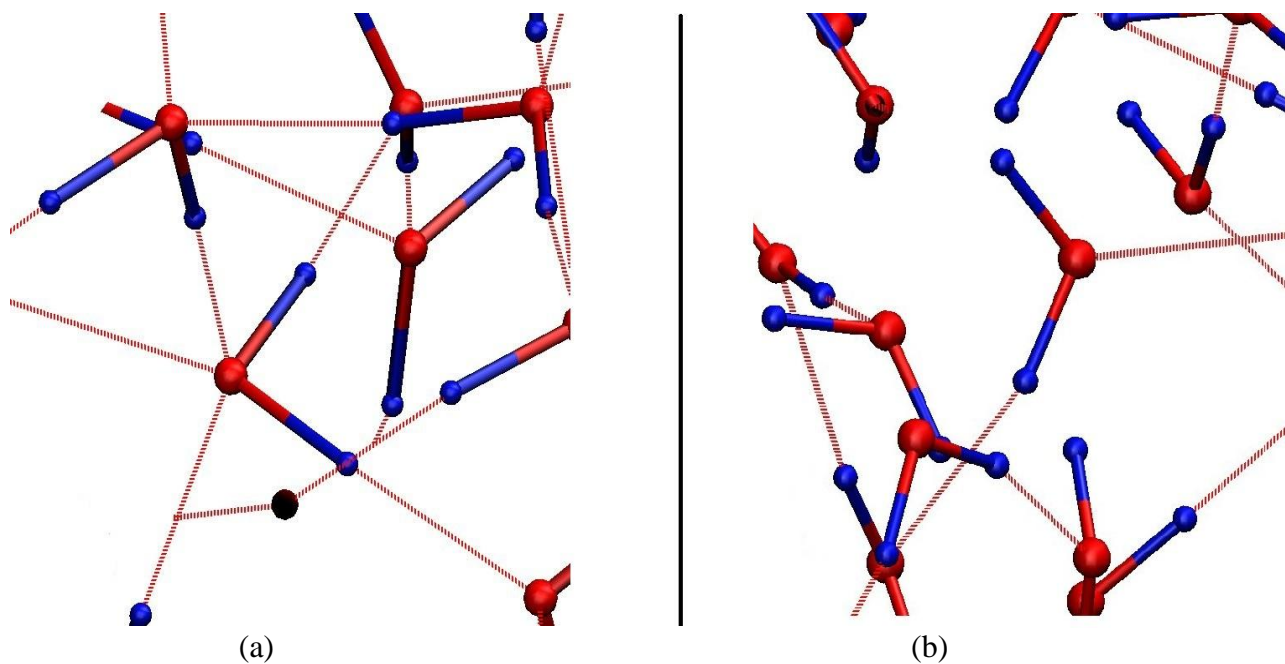


**FIGURE 7.** Pairwise correlation function,  $g(r)$ , of water molecules for the all three water models.

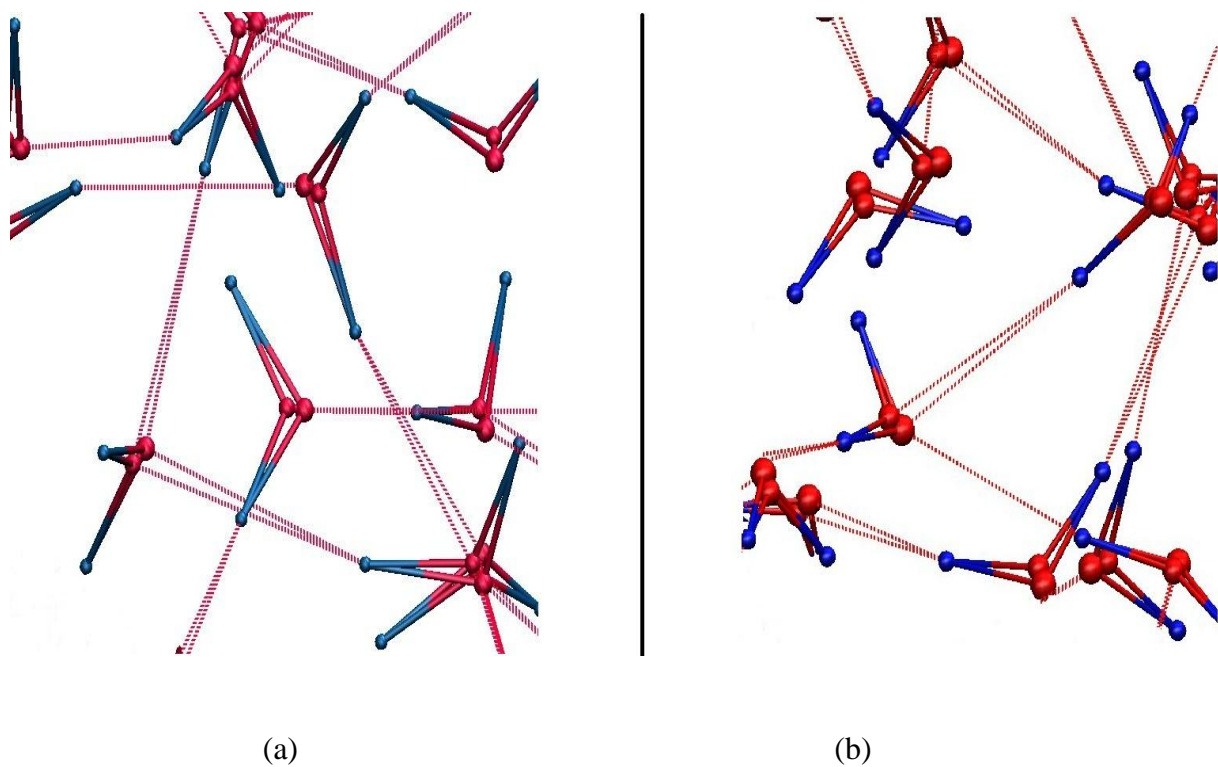
For all the three water models there is a distinct sharp first peak. The first peak for TIP3P, SPC/E and TIP4P appears at around 2.8 Å, 2.7 Å and 2.6 Å respectively. The first peak is followed by a second peak at around 4.6 Å for the TIP4P and SPC/E water models. Beyond that the structure of water almost disappears except for TIP4P model. Further among the three water models TIP4P water shows a high intense first peak which is followed by second and third peaks of low intensity, indicating highest structuring of TIP4P water model as compared to the other two models. The highest structuring of TIP4P model may be due to formation of large number of intermolecular hydrogen bonds than the other two models. However further studies are needed in its evidence.



**FIGURE 8.** Snapshots of intermolecular hydrogen bonding in TIP3P water model at (a)  $t = 0$  ns and (b)  $t = 10$  ns



**FIGURE 9.** Snapshots of intermolecular hydrogen bonding in SPC/E water model at (a)  $t = 0$  ns and (b)  $t = 10$  ns



**FIGURE 10.** Snapshots of intermolecular hydrogen bonding in TIP4P water model at (a)  $t = 0$  ns and (b)  $t = 10$  ns

In Figure 8 , 9 and 10 we have shown the snapshots of few representative hydrogen bonds that form among the water molecules. Further, we have compared the results obtained from our simulations with experimental data and it has found that the pair distribution function for SPC/E water correlates well with experimentally available data.<sup>52</sup>

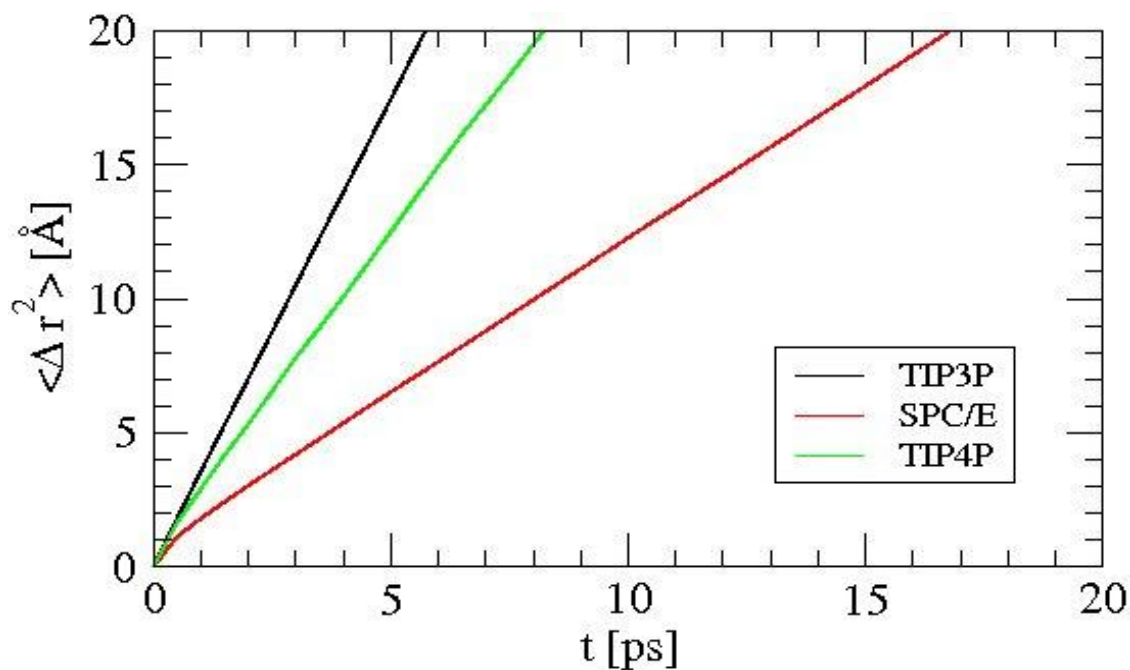
The differential water structure for the three models will affect the dynamics of water in differential manner. Therefore, it would be interesting to look into the dynamics of three different water models. In next sub-section we have studied the translational motions of the water molecules.

### 4.3 Translational Motion

The translational motion of water molecules were studied from the simulated trajectories by calculating the mean-square-displacements (MSD),  $\langle \Delta r^2 \rangle$  of water molecules. The MSD can be defined as,

$$\langle \Delta r^2 \rangle = \langle |r_i(t) - r_i(0)|^2 \rangle$$

where the  $r_i(t)$  and  $r_i(0)$  are the position vectors of the oxygen atom of the  $i$  th water molecule at time  $t$  and at  $t = 0$ , respectively.



**FIGURE 11:** Mean-square-displacement vs time plot for the water molecules of all three water models.

The averaging is carried out over all water molecules at different time origins. The calculations are carried out for the three models and the results are displayed Figure 11. It can be seen that the translational motion of water molecules are highly restricted for SPC/E and TIP4P water models as compared to the TIP3P model. This is particularly true for the SPC/E model. We have calculated the self-diffusion coefficient of the water molecules. It was estimated from the slope of the linear part of the figure 11. The values for the three models are shown in Table 2.

**TABLE 2.** Self-Diffusion co-efficient,  $D$  ( $10^{-9} \text{ m}^2 \text{ s}^{-1}$ ) values of TIP3P , SPC/E and TIP4P water models. The experimental  $D$  value for liquid water has also included in the table for comparison.

<b>Systems</b>	<b>Self diffusion co-efficients (D)</b>
TIP3P	5.8
SPC/E	2.8
TIP4P	3.8
Water (experiment) <sup>52,53</sup>	2.3

For comparison we have included the experimentally available self-diffusion coefficient value of water in Table 2. It has found that the diffusion co-efficient of TIP3P water is almost twice than that of SPC/E water which indicates TIP3P waters diffuse fast as compared to other two models. TIP4P waters show intermediate result. Further, we have compared the values with experimentally available data and found that among the three water models the self diffusion coefficient value for SPC/E waters correlate well with experimental value.

## 5. CONCLUSIONS

In this thesis we have shown the results obtained from the MD simulations of two 3-sites, TIP3P, and SPC/E and one 4-sites, TIP4P water models that are commonly used in biomolecular simulations. It has been seen that the energy of the three water models fluctuates significantly for the first 4.5 ns of the trajectories but after that they attained almost steady values. The temperature was maintained all over the simulations. These indicate that the trajectories were well equilibrated. In this study we have shown that depending upon the water models, the structure as well as dynamical properties of liquid water differ significantly. Our calculations showed that up to around 3.5 Å distance the water of all three models is highly structured. The high intense first peak followed by two low intense second and third peaks for TIP4P model confirms the highest water structure for this model as compared to TIP3P, and SPC/E. The translational motion of water molecules has been studied by calculating their mean-square-displacement. It has noticed that TIP3P water diffuses fast as compared to other two water models. The motion of SPC/E water is found to be highly restricted. Further, the experimental self-diffusion co-efficient value of liquid water correlates well with the value obtained from the linear fitting of MSD curves of the SPC/E water model as compared to the other two.

## REFERENCES

- (1) Kamat, V. P. *J. Phys. Chem. B* **2002**, *106*, 7729-7744.
- (2) Kaatze, U.; Uhlendorf, V. *Z. Phys. Chem. N. F.* **1981**, *126*, 151.
- (3) De Santis, A.; Sampoli, M.; Mazzacurati, V.; Ricci, M. A.; *Chem. Phys. Lett.* **1987**, *133*, 381.; De Santis, A.; Frattini, R.; Sampoli, M.; Mazzacurati, V.; Nardone, M.; Ricci, M. A.; Ruocco, G. *Mol. Phys.* **1987**, *61*, 1199.
- (4) Montrose, C. J.; Bucaro, J. A.; Marshall-Coakely, J.; Litowitz, T. A. *J. Chem. Phys.* **1974**, *60*, 5025.
- (5) Jonas, J.; DeFries, T.; Wilbur, D. J. *J. Chem. Physics.* **1981**, *65*, 581.
- (6) Soper, A. K.; Luzar, A.; *J. Phys. Chem.* **1996**, *100*, 1357.; *J. Chem. Phys.* **1992**, *97*, 1320.
- (7) Wernet, Ph.; Nordlund, D.; Bergmann, U.; Cavalleri, M.; Odelius, M.; Ogasawara, H.; Näslund, L.-Å.; Hirsch, T. K.; Ojamäe, L.; Glatzel, P.; Pettersson, L. G. M.; Nilsson, A. *Science.* **2004**, *304*, 995.
- (8) Guillot, B. J. *J. Mol. Liq.* **2002**, *101*, 219.
- (9) Stillinger, F. H. *Science.* **1980**, *209*, 451.
- (10) Soper, A. K. *Mol. Phys.* **2001**, *99*, 1503.; *Phys. Rev. B.* **2005**, *72*, 104204.
- (11) Soper, A. K. *J. Phys. Condens. Matter.* **2005**, *17*, S3273.
- (12) Tokushima, T.; Harada, Y.; Takahashi, O.; Senba, Y.; Ohashi, H.; Pettersson, L. G. M.; Shin, S. *Chemical Physics Letters.* **2008**, *460*, 387-400.
- (13) Postorino, P.; Tromp, R. H.; Ricci, M.-A.; Soper, A. K.; Neilson, G. W. *Nature* **1993**, *366*, 668. Soper, A. K.; Bruni, F.; Ricci, M. A. *J. Chem. Phys.* **1997**, *106*, 247.
- (14) Mills, R.; *J. Phys. Chem.* **1973**, *77*, 685.
- (15) Price, W. S.; Ide, H.; Arata, Y. *J. Phys. Chem. A.* **1999**, *103*, 448.



- (16) Christoph, J. S.; Sternemann, C.; Schmidt, C.; Lehtola, S.; Jahn, S.; Simonelli, L.; Huoturi, S.; Hakala, M.; Pylkanen, T.; Nyrow, A.; Mende, K.; Totan, M.; Hamaluinen, K.; Wilke, M. *proc. Natl. Acad. Sci. U.S.A.* **2013**, doi: 10.1073/pnas.1220301110.
- (17) Bertie, J. E.; Lan. *Z. Appl. Spectrosc.* **1996**, 50, 1047.
- (18) Berg, M.; Vanden Bout, D. A. *Acc. Chem. Res.* **1997**, 30, 65.
- (19) Palese, S.; Schilling, L.; Miller, R. J. D.; Staver, P. R.; Lotshaw, W. T. *J. Phys. Chem.* **1994**, 98, 6308.; Castner Jr, E. W.; Chang, Y. J.; Chu, Y. C.; Walrafen, G. E. *J. Chem. Phys.* **1995**, 103, 653.; Winkler, K.; Linder, J.; Bursing, H.; Vohringer, P. *J. Chem. Phys.* **2000**, 113, 4674.; Fecko, C. J.; Eaves, J. D.; Tokmakoff, A. *J. Chem. Phys.* **2002**, 117, 1139.
- (20) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, 79, 926.
- (21) Berweger, C. D.; van Gunsteren, W. F.; Müller-Plathe, F. *Chem. Phys. Lett.* **1995**, 232, 429.
- (22) Watanabe, K.; Klein, M. L. *Chem. Phys.* **1989**, 131, 157.
- (23) Jorgensen, W. L.; Jenson, C. *J. Comput. Chem.* **1998**, 19, 1179.
- (24) Dang, L. X. *J. Phys. Chem. B* **1998**, 102, 620.
- (25) Mahoney, M. W.; Jorgensen, W. L. *J. Chem. Phys.* **2001**, 114, 363.
- (26) Marti, J. *J. Chem. Phys.* **1999**, 110, 6876.
- (27) Asbury, J. B.; Steinel, T.; Stromberg, C.; Corcelli, S. A.; Lawrence, C. P.; Skinner, J. L.; Fayer, M. D. *J. Phys. Chem. A*.
- (28) Kuchitsu, K.; Morino, Y. *Bull. Chem. Soc. Jpn.* **1965**, 38, 814.
- (29) Neumann, M. *J. Chem. Phys.* **1985**, 82, 5663.
- (30) Ingrosso, F.; Rey, R.; Elsaesser, T.; Hynes, J.T. *J. Phys. Chem. A* **2009**, 113, 6657-6665.
- (31) Rahman, A.; Stillinger, H. F. *J. Chem. Phys.* **1971**, 7, 55.
- (32) Allen, M.P.; Tildesley, D.J. *Computer simulation of liquids*; Clarendon: Oxford, **1987**.
- (33) Frenkel, D.; Smit, B. *Understanding molecular simulations*. Oxford Press **2002**.
- (34) Neria, E.; Fischer, S.; Karplus, M. *J. Chem. Phys.* **1996**, 105, 1902.
- (35) Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, 91, 6269.
- (36) Jorgensen, W. L.; Madura, J. D. *Mol. Phys.* **1985**, 56, 1381.

- (37) Phillips, J. C.; Braun, R.; Wang, W.; Gumbart, J.; Tajkhorshid, E.; Villa, E.; Chipot, C.; Skeel, R. D.; Kale, L.; Schulten, K. *J. Comput. Chem.* **2005**, *26*, 1781 .
- (38) Neria, E.; Fischer, S.; Karplus, M. Simulation of activation free energies in molecular systems. *J. Chem. Phys.* **1996**, *105*, 1902.
- (39) Vega, C.; Abascal, J. L. F.; Conde, M. M.; Aragonés, J. L. **2009**, *141*, 251.
- (40) ) Martinez, L.; Andrade, R.; Birgin, E. G.; Martinez, J. M. *Journal of Computational Chemistry*. **2009**, *30*, 2157-2164.
- (41) Feller, S. E.; Zhang, Y.; Pastor, R. W.; Brooks, B. R. *J. Chem. Phys.* **1995**, *103*, 4613
- (42) Darden, T.; York, D.; Pedersen, L.; *J. Chem. Phys.* **1993**, *98*, 10089.
- (43) Karnicky, J. F.; Pings, C. J. *In Advances in Chemical Physics; Prigogine, I., Rice, S. A., Eds.; Wiley: New York, 1976; Vol. 34*
- (44) Hura, G.; Sorenson, J. M.; Glaeser, R. M.; Head-Gordon, T. *J. Chem. Phys.* **2000**, *113*, 9140-9148.
- (45) Morgan, J.; Warren, B. E. *J. Chem. Phys.* **1938**, *6*, 666.
- (46) Narten, A. H.; Levy, H. A. *In Water A Comprehensive Treatise; Franks, F., Ed.; Plenum Press: New York, 1972; Vol. 1*
- (47) Dore, J. C.; Sufi, M. A. M.; Bellissent-Funel, M. C. *Phys. Chem. Chem. Phys.* **2000**, *2*, 1599-1602.
- (48) Dore, J. C. *J. Mol. Struct.* **1991**, *250*, 193-211.
- (49) Postorino, P.; Ricci, M. A.; Soper, A. K. *J. Chem. Phys.* **1994**, *101*, 4123-4132.
- (50) Bellissentfunel, M. C.; Bosio, L. *J. Chem. Phys.* **1995**, *102*, 3727-3735.
- (51) Soper, A. K.; Phillips, M. G. *Chem. Phys.* **1986**, *107*, 47.
- (52) Mills, R. *J. Phys. Chem.* **1973**, *77*, 685.
- (53) Price, W. S.; Ide, H.; Arata, Y. *J. Phys. Chem. A*. **1999**, *103*, 448.
- .