

## Investigation of Monte Carlo, Molecular Dynamic and Langevin dynamic simulation methods for Albumin- Methanol system and Albumin-Water system

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### ABSTRACT

Serum Albumin is the most abundant protein in blood plasma. Its two major roles are maintaining osmotic pressure and depositing and transporting compounds. In this paper, Albumin-methanol solution simulation is carried out by three techniques including Monte Carlo (MC), Molecular Dynamic (MD) and Langevin Dynamic (LD) simulations. By investigating energy changes by time and temperature (between 273 to 313K), it is found that MC method is not suitable for macromolecule simulations. Also by comparing optimized energy in Albumin-water system and Albumin-methanol system, it is distinguished that because of existing more hydrogen bondings Albumin-water system is more stable than Albumin-methanol.

**Keywords:** Albumin, Monte Carlo; Molecular dynamics; Langevin Dynamics; Simulation

### INTRODUCTION

Albumin is a globular protein which has the most amounts in human blood. It has a  $pH_I$  value about 4.8 and a molecular weight about  $65000 \text{ gmol}^{-1}$ . It is soluble in water and contains 584 amino acids in its two chains. Albumin has a half - life of about 20 days and is made only in alive systems. It coagulates when heated [1].

Albumin plays two important roles in body [2]: a) Transports some hormones and drugs. The most important compounds transported by Albumin are L-Tryptophan, Naproxen, Ibuprofen, Diazepam and fatty acids with medium chains [3, 4]. b) Regulates osmotic pressure in body.

There are several kinds of Albumin that the most important of them are Human Serum Albumin (HAS), Bovine Serum Albumin (BSA) and egg Albumin [5].

Sudlow has shown that Albumin has two active sites named Sudlow site I and II [6-10]. Sudlow site II is more important and it can bind to ligands tightly by hydrophobic interactions [8,9]. It can bind and transport some important drugs such as those given above.

Sudlow site I is less important than site II. It can transport drugs such as Warfarin, Salicylate and Sulphonamide. Its interactions are hydrophobic, too [11, 12].

Because of the importance of Albumin as a drug transporter, in this paper simulation of Albumin is carried out by three methods

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including Monte Carlo, Molecular Dynamics and Langevin Dynamics.

## MOLECULAR DYNAMIC SIMULATION

Solving time dependent equations of motion is the base of MD simulation. The accuracy of this simulation can be determined by potential energies between atoms which approximate interactions described by Hamiltonian operator in Schrodinger equation. These potentials are called forcefield. This simulation works in Cartesian coordinates. If there are some constraints in system between atom's coordinates, some degrees of freedom in system will be reduced. So in this condition Hamilton's equations of motion are used. Otherwise, Newton's equation of motion can be applied. At the first condition, some algorithms such as SHAKE [14] or LINCS [15] are used.

All of ensembles can be determined by three constants. In microcanonical ensembles  $N, V, E$  are constant. In canonical ensembles  $N, V, T$  are constant. In grandcanonical ensembles  $\mu, V, T$  are constant. In isothermal - isobaric ensembles  $N, P, T$  are constant and the last:  $\mu, P, T$  are constant.

Total energy in MD simulation that follows Newton's equation of motion is constant. So MD is performed in microcanonical ensembles. If we want to change the type of these ensembles, we have to change at least one of constants which describe these ensembles. For example we can put temperature constant and approach to Nose-Hoover scheme or thermostat [16]. Another way in MD in which  $T$  is constant named Berendsen thermostat [17]. Berendsen scheme is based on weak coupling which can be caused by a first order differential equation for  $T$  [18]. In Parrinello-Rahman pressure coupling, pressure and three vectors of periodic unit-cell can be constant in the same way of temperature [19].

If we combine Nose-Hoover thermostat with Parrinello-Rahman method, we can produce an isothermal-isobaric ensemble.

## THEORY

Monte Carlo (MC), Molecular Dynamics (MD) and Langevin Dynamics (LD) are three methods to simulate some molecules and macromolecules for understanding their structures and binding sites which can interact with other molecules [13].

## MONTE CARLO SIMULATION

If systems have difficult integrals to be solved and should produce some random number to generate uniform independent values statistically, it's better to use Monte Carlo simulation which can generate a canonical ensemble [20, 21]. Some important software libraries to produce random number are CERNLIB [22], CLHAP [23] and ROOT [24]. For selecting the best software, tests such as DIEHARD [25] or U01 [26] can be applied. Metropolis algorithm is used in MC more than other algorithms because of its simplicity [27]. The random displacement determines the accuracy of the algorithm. In small displacements, all moves can be accepted. But in large cases the range of acceptable moves is small. In MC calculation of energy is sufficient to simulate. But in MD the forces should be determined, too. This is one of the advantages of MC over MD. But MC method is useful for simulating small systems and for large systems using MD is better.

## LANGEVIN DYNAMIC SIMULATION

This method was developed by Sasaki and Sasai to determine molecular structure by minimizing a potential which is empirical multi-body.

LD produces canonical ensembles too. In this method we remove system's kinetic energy by adding a frictional force to the conservation force that is relative to velocity.

This method follows fluctuation-dissipation theorem. LD uses classical systems in which degrees of freedom are removed. This causes to exert conservative and frictional forces on all parts of system and we assume a random force to which all other forces are added [28].

## COMPUTATIONAL METHOD

In this work, Albumin's active sites are downloaded from RCSB PROTEIN DATA BANK. The PDB ID applied in this paper is 1GAB in which the structure of Albumin-binding domain is investigated by NMR techniques.

This PDB shows that active sites in chain A in Albumin consist of 53 residues (213-265) and its DSSP secondary structure is 73% helical (4 helices, 39 residues) and its chain type is polypeptide (L). Albumin's active sites sequences are as below:

THR ILE ASP GLN TRP LEU LEU LYS ASN ALA  
 LYS GLU ASP ALA ILE ALA GLU LEU LYS LYS  
 ALA GLY ILE THR SER ASP PHE TYR PHE ASN  
 ALA ILE ASN LYS ALA LYS THR VAL GLU GLU  
 VAL ASN ALA LEU LYS ASN GLU ILE LEU LYS  
 ALA HIS ALA

After finding this PDB, HyperChem 7 software is applied for investigation in methanol and water solutions of protein separately.

At first these active sites are put in methanol solution which has concentration about 6% (w-w). Then by using molecular mechanics level, opfs force field and Polak-Ribiere algorithm, the geometry of the system is optimized and for the optimized structure potential energy is evaluated by 3 techniques of simulation (MC, MD and LD) in different time steps and temperature range from 273K to 313K every 5 degrees. Then the potential energy versus temperature diagrams and potential energy

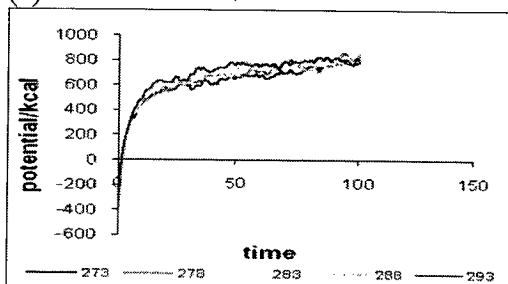
versus time step diagrams are described in different initial temperatures in these techniques.

Finally the energy of Albumin-water system has been optimized and compared by Albumin-methanol system. It is considerable that because of the large gradient in energy time steps are selected about 0.001 for methanol solution and about 0.0001 for water solution in MD and LD techniques.

## RESULTS AND DISCUSSIONS

The potential energy versus time step diagrams are shown in figures 1-3. Fig.1 displays results calculated by MC technique.

(a)



(b)

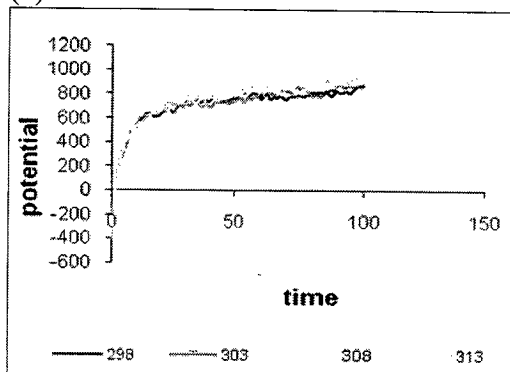


Fig.1. potential energy versus time step in MC simulation: a)273-293K b) 298-313K.

It can be seen the energy changes by time steps is not in a same way by increasing in initial temperature. It is understandable that there is a regular change in potential energy versus time step by increasing initial temperature in MD and LD simulation

techniques from Fig.2 and Fig.3 This difference is because of the techniques used in simulations. In macromolecules, MC simulation is not suitable for calculating energy and since Albumin is a macromolecule, so this irregular trend is obtained.

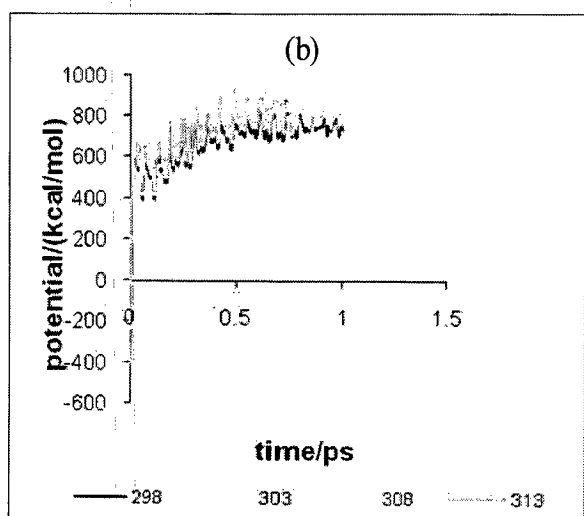
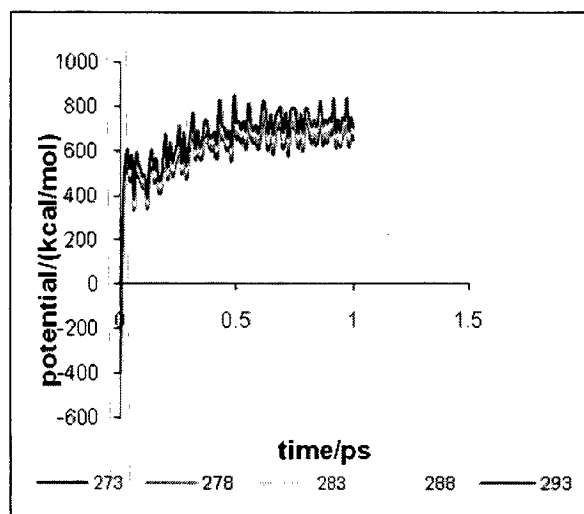


Fig.2. Potential energy versus time step in MD simulation: a)273-293K b)298-313K.

Also with analyzing Fig.4 and Fig. 5, it is obvious that potential energy changes with temperature inversely. By an increase in initial temperature, the potential energy increases too. But in every initial temperature, by decreasing temperature, the energy of system increases.

Because Albumin is a protein that is folded by hydrogen binds, so when temperature increases, it disturbs hydrogen bonds and so causes some instability in protein structure. So when temperature increases, the energy of system increases too and it shows instability of system in high temperature. Consider that these changes in LD and MD methods are in a same way. But in LD method, these changes are more regular.

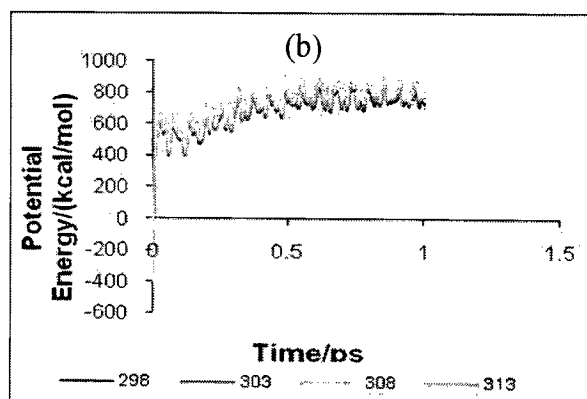
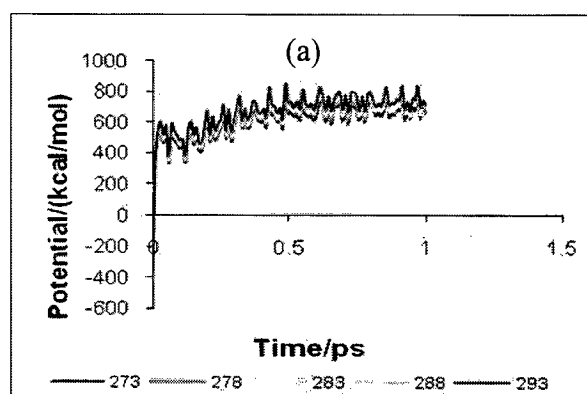


Fig .3. Potential energy versus time step in LD simulation. a) 273-293K b) 298-313K.

This research confirms that using MC method is not suitable for simulating macromolecules such as proteins and LD method is the best. Another result obtained in this work, is the optimized energy in Albumin - water system (-11413.1894 kcal/mol) is less than optimized energy in Albumin-methanol system (-399.918

kcal/mol). It can be related to more existence of hydrogen binding in water solution than methanol solution. These hydrogen bounds

cause the system more stable, so the energy decreases in compare with methanol solution.

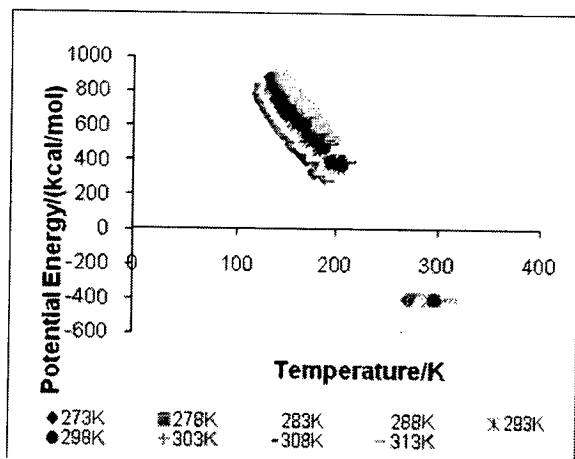


Fig.4. Potential energy versus temperature in MD .

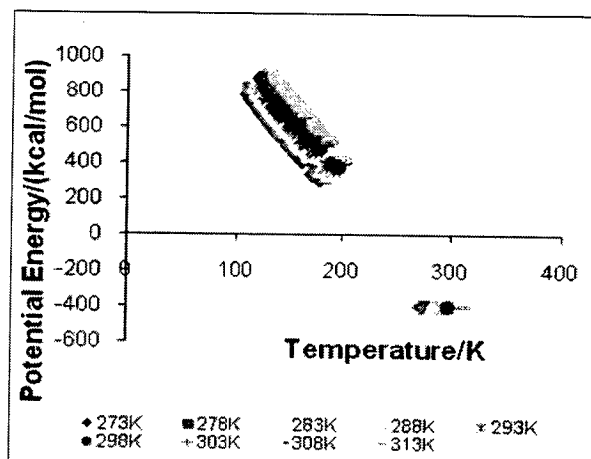


Fig.5. Potential energy versus temperature in LD Simulation .

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