

## Gyration Radius and Energy Study at Different Temperatures for Acetylcholine Receptor Protein in Gas Phase by Monte Carlo, Molecular and Langevin Dynamics Simulations

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### ABSTRACT

The determination of gyration radius is a strong research for configuration of a Macromolecule. It also reflects molecular compactness shape. In this work, to characterize the behavior of the protein, we observe quantities such as the radius of gyration and the average energy. We studied the changes of these factors as a function of temperature for Acetylcholine receptor protein in gas phase with native structure,  $\alpha$ -helix and  $\beta$ -sheet conformation by Monte Carlo, Molecular and Langevin dynamics simulations. It was found when the temperature is increased the kinetic energy is increased too, and its diagram is linear. Monte Carlo simulation is a stochastic method and therefore, is the best method to evaluate gyration radius. Considering the gained values from Monte Carlo, Molecular and Langevin dynamics simulations for  $\alpha$ -helix conformation and little deviations from the experimental value, it can be understood that the second structure of this protein is the kind in which  $\alpha$ -helix is more. All the calculations were carried out using Hyperchem 8.0 program package. Gyration radius is calculated using VMD 1.8.6 Software.

**Keywords:** Protein folding; Monte Carlo simulation; Molecular dynamics simulation; Langevin dynamics simulation; Gyration radius.

### INTRODUCTION

The characterization of the protein folding process represents one of the major challenges in protein chemistry. Large theoretical and experimental research efforts have been devoted to this end [1-4]. Knowledge of the protein folding mechanism will result in a huge advance in general bioscience, especially in the fields of drug design and pharmaceutical chemistry. Prion disease and Alzheimer's disease, for example, have been found to be caused by miss-folding of proteins [5-6].

Two parameters are used to predict the dimensions of a macromolecule by statistical mechanics science: a) end- to- end distance b) gyration radius.

The radius of gyration is calculated using:

$$R_g = \sqrt{\frac{\sum_i^N m_i r_i^2}{\sum_i^N m_i}} \quad (1)$$

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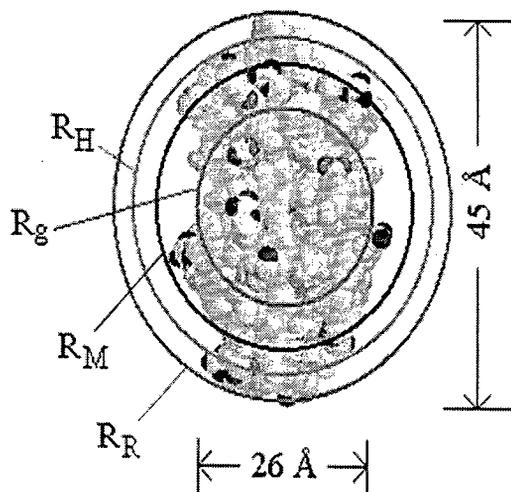


Fig.1. Comparison of gyration radius (Rg) to other radii for lysozyme.

Where  $m_i$  is the mass of the  $i^{th}$  atom in the particle and  $r_i$  is the distance from the center of mass to the  $i^{th}$  particle (Figure 1) [7-8].

This factor for each protein molecule is experimentally measurable by light-scattering and diffusion techniques. The gyration radius can experimentally be estimated by using the following relation for the small angles of  $\theta$ , in which  $\theta$  shows the angle of scattering:

$$\frac{1}{P(\theta)} = 1 + \frac{16\pi^2 R_g^2}{3\lambda^2} \sin^2 \frac{\theta}{2} \quad (2)$$

where

$$P(\theta) = \frac{\text{The intensity of the scattered radiation under the } \theta \text{ angle}}{\text{The intensity of the scattered radiation under the } \theta \rightarrow 0}$$

and  $\lambda$  is the wave length of the radiation [9]. Tyn and Gusek [10] proposed the following equation for proteins:

$$D = 5.78 \times 10^{-8} \left( \frac{T}{\eta \cdot R_g} \right) \quad (3)$$

where  $R_g$  is the radius of gyration of a protein in  $\text{\AA}$ , diffusion coefficient  $D$  is in  $\text{cm}^2 \cdot \text{sec}^{-1}$ , temperature  $T$  is in K and the solvent Viscosity  $\eta$  is in cp. By comparing the experimental amount with the calculated for a specific protein, a macromolecule shape can be known, to some extent. The gyration radius also reflects molecular compactness shape [11].

Computer simulation of the structure and dynamics of proteins and other biological macromolecules based on empirical potential energy functions [molecular mechanics (MM)] has become a widely used tool in the last two decades [12]. Molecular Mechanics uses an analytical, differentiable, and relatively simple potential energy function, for describing the interaction between a set of atoms specified by their Cartesian coordinates.

Molecular and langevin dynamics simulation [13-14], as well as Monte Carlo simulation [15-16], have been used to investigate protein folding pathways with some success. The Metropolis Monte Carlo was originally developed for calculating equilibrium properties of physical systems [17]. The dynamic interpretation of the MC algorithm for the protein folding process has been widely used in many studied [18-19]. The Metropolis algorithm performs a sample of the configuration space of a system starting from a random conformation and repeating a large number of steps. Each step consists of attempting a transition to a new conformation  $m$  choosing among a set of allowed moves, and accepting the attempt with probability  $\min [1, \exp(-u_{(m)} - u_{(n)})/kt]$  where  $u$  is the potential energy and  $T$  the absolute temperature in units of Boltzman's constant. This is equivalent to solve numerically the master equation:

$$\frac{dp_n(t)}{dt} = - \sum_{n \neq m} [P_n(t)w_{n \rightarrow m} - P_m(t)w_{m \rightarrow n}] \quad (4)$$

where  $P_n(t)$  is the probability of the system being in the conformation  $n$  at time  $t$ , and  $w_{n \rightarrow m}$  is the transition rates for  $n \rightarrow m$ . In equilibrium

$$\frac{dp_n(t)}{dt} = 0 \text{ and } P_n(t)w_{n \rightarrow m} = P_m(t)w_{m \rightarrow n}$$

Eq. (4) describes a tailor-made dynamics which, in principle, has nothing to do with the actual dynamics of a protein. The actual dynamics of the protein is described by langevin's equation [14]:

$$\frac{dp}{dt} = F - \frac{\gamma}{m} p + \eta \quad (5)$$

where  $p$  is the momentum of a given particle,  $F$  is the force acting on it,  $\gamma$  is the Friction

coefficient,  $m$  the mass and  $\eta$  a stochastic variable describing the interaction with the solvent, and  $D$  is the diffusion coefficient. Both Langevin's equation and the Metropolis algorithm are stochastic, containing some randomness [20].

Molecular dynamics simulation is one of the most promising approaches for solving the protein folding problem. In this method we observe the time behavior of atoms of the system. In MD simulation, new positions of atoms are calculated by numerical integration of Newton's equation of motion.

In the present work, to characterize the behavior of the protein, we observe quantities such as the radius of gyration and the average energy. These two quantities offer much insight into the general properties of the protein model [8].

## METHODS

For this study, a small designed protein (PDB cod; 1a11), consisting of only 25 amino acid (393 atoms) residues was selected (Figure 2). We open this file by using the VMD software [21], and determined torsion angles ( $\phi, \psi$ ) for every Amino acid by Ramachandran chart [22], and then designed this protein with these angles in Hyperchem 8.0 program package [23]. At first we optimized the designed protein by Monte Carlo simulation with Amber force field [24], at 300k, and after optimizing,  $R_g$  was determined by using VMD software at above-mentioned temperature. We did so in 310, 320, 330 to 400k. It's essential to say that, Hyperchem uses the Metropolis method. Kinetic, potential and total energy calculated by Monte Carlo simulation.

At next stage we optimized the designed protein by Molecular dynamics simulation with MM<sup>+</sup> force field [25], in 300k to 400k and determined Radius of gyration for that after optimizing. We did exactly the same work on Langevin dynamics simulation.



Fig.2. Crystal structure of Acetyl choline receptor from [www.pdb.org](http://www.pdb.org) with code number : 1A11

At first section, we designed the considered protein by using Ramachandran in Hyperchem. But at this part, we made protein from Amino Acids 1 to 25 respectively and selected  $\alpha$ -helix conformation for it. By Monte Carlo, Molecular and Langevin dynamics simulations we optimized in 300-400k, and calculated  $R_g$  in both of temperature after optimizing. We did exactly the same work on the  $\beta$ -sheet conformation.

## RESULTS AND DISCUSSION

All simulations were at different temperatures, the Run step and delta max For Monte Carlo simulation were 20000 and 0.001, respectively. The Run time and time step for Molecular dynamics simulation were 30 ps and  $10^{-3}$  ps, respectively. The time step and friction coefficient for Langevin simulation were  $10^{-3}$  ps and  $0.1 \text{ ps}^{-1}$ , respectively [26]. Monte Carlo simulations are commonly used to compute the average thermodynamic properties of a molecule or a system of molecules, and have been employed extensively in the study of the structure and equilibrium properties of molecules [17]. Monte Carlo simulations employ a statistical sampling technique to generate configurations, which represent a trajectory in phase space (discussed previously). Thus, unlike molecular dynamics or Langevin dynamics, which calculate ensemble averages by calculating averages over time, Monte Carlo calculations evaluate the averages of the ensemble directly by sampling configurations from the statistical ensemble. If the run takes enough time, Monte Carlo and molecular dynamics must give the same average results for the same system, such as rotational frequencies or transitional rates. On the other hand, Monte Carlo is generally better in sampling the allowed states of a system, and; thus, can often calculate the average properties more quickly and accurately. The total energy of the system, in these methods, are called Hamiltonian, which is the sum of kinetic and potential energy:

$$E_T = E_K + E_P \quad (6)$$

In table 1, the total energy, potential energy and kinetic energy are calculated by Monte Carlo, Molecular and langevin dynamics simulations.

The diagram of kinetic and potential energy has been drawn as a function of temperature for the native structure of the protein (Fig. 3,4). Kinetic energy increases as the temperature rises, and its diagram is linear in each three methods. The following relations can be gained by considering the regration calculations. Monte Carlo calculation will give:

$$E_k = 1.16T - 1.59 \times 10^4 \quad (7)$$

Correlation coefficient is one for it. From Molecular dynamics will have:

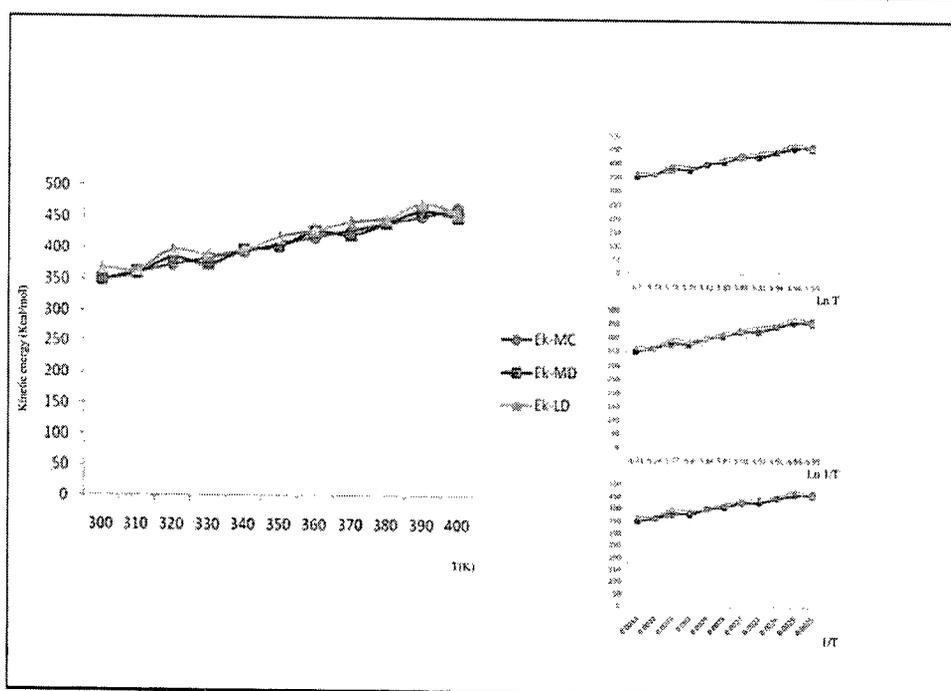
$$E_k = 1.11T + 19.78 \quad (8)$$

Correlation coefficient is 0.98 For it. From langevin dynamics will be obtained:

$$E_k = 1.1T + 34.01 \quad (9)$$

**Table1.** The Total energy, Potential and Kinetic energy (kcal/mol) calculated for Native structure by Monte carlo, Molecular and Langevin dynamics simulations

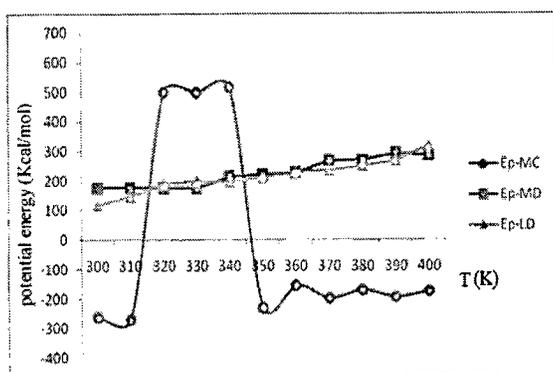
T	MC			MD			LD		
	Ek	Ep	Et	Ek	Ep	Et	Ek	Ep	Et
300	348.75	-260.14	88.60	349.80	175.44	525.23	368.50	117.52	486.02
310	360.38	-269.61	90.80	360.44	175.20	535.64	365.67	146.92	512.60
320	372.00	496.94	868.95	383.85	173.50	557.33	397.30	188.80	586.10
330	383.62	495.90	879.52	374.45	174.00	548.40	389.90	198.83	579.72
340	395.25	515.32	910.60	396.94	217.70	614.60	398.61	196.71	595.33
350	406.88	-230.80	176.11	404.08	219.05	623.12	419.01	210.40	629.50
360	418.50	-154.61	263.90	427.50	226.30	653.80	430.72	230.54	661.30
370	430.13	-198.28	231.84	422.68	267.35	690.02	444.22	235.30	679.50
380	441.75	-170.31	271.43	442.31	268.00	710.30	450.30	252.00	702.28
390	453.38	-194.01	259.40	461.47	291.25	752.72	475.00	268.22	743.20
400	465.00	-175.40	289.63	451.80	283.71	735.51	458.33	319.00	777.32



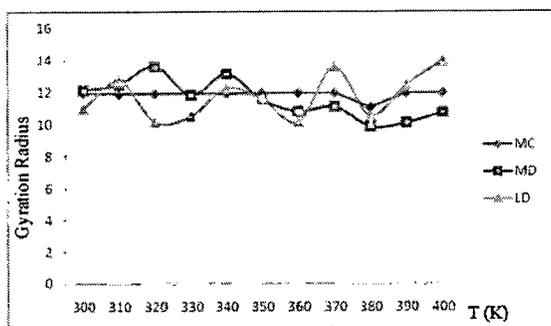
**Fig.3.** The kinetic energy (kcal/mol) calculated for Native structure by Monte carlo, Molecular and Langevin dynamics simulations as a function of temperature.

**Table 2.** The Radius of Gyration (Å) calculated for Native structure by Monte carlo, Molecular and Langevin dynamics simulations

T	MC	MD	LD
300	11.9695	12.1295	10.9903
310	11.9090	12.4787	12.7198
320	11.9318	13.6011	10.1516
330	11.9211	11.8045	10.5153
340	11.9293	13.1262	12.2353
350	11.9614	11.5427	11.5489
360	11.9638	10.7925	10.1598
370	11.9673	11.0996	13.5729
380	11.0720	9.8566	10.5571
390	11.9723	10.0855	12.4621
400	11.9740	10.7237	13.9504



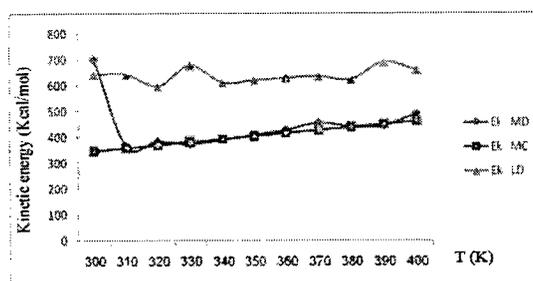
**Fig.4.** The Potential energy (kcal/mol) calculated for Native structure by Monte carlo, Molecular and Langevin dynamics simulations as a function of temperature.



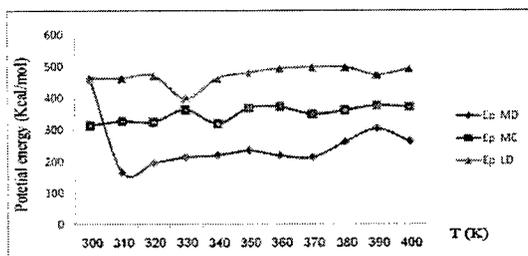
**Fig.5.** Gyration radius (Å) of Acetyl Choline receptor for Native structure as a function of temperature in gas phase.

For  $\alpha$  - helix conformation, Molecular dynamics shows some deviations for kinetic energy at less than 310k. both Monte Carlo and molecular dynamics make almost the same result at more than 310k (Fig. 6). The calculated potential energy by Monte Carlo, approaches langevin dynamics simulation at 340 k. Molecular dynamics simulation as well as kinetic energy shows some deviations for potential energy at less than 310 k and after that proceeds constantly (Fig. 7). Gyration radius diagram as a function of temperature for each three methods in figure 8 shows that Monte Carlo simulation is the best method to evaluate gyration radius as well. Experimentally gyration radius for the mentioned

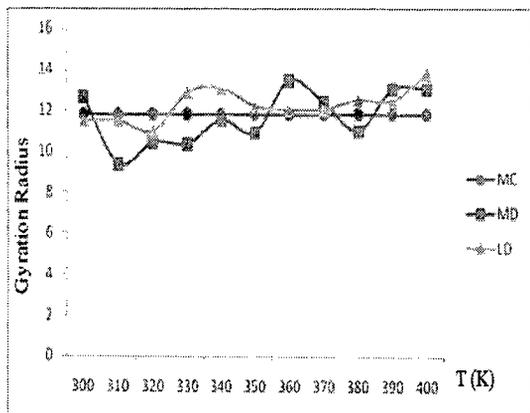
protein is 11.82 Å°. Considering the gained values from Monte Carlo, Molecular and langevin dynamics simulations calculations For  $\alpha$  - helix conformation and little deviations from the experimental values it can be understood that the second structure of this protein is the kind in which  $\alpha$  - helix is more.



**Fig.6.** The Kinetic energy (kcal/mol) calculated for  $\alpha$ -helix conformation by Monte carlo, Molecular and Langevin dynamics simulations as a function of temperature.



**Fig.7.** The Potential energy (kcal/mol) calculated for  $\alpha$  - helix conformation by Monte carlo, Molecular and Langevin dynamics simulations as a function of temperature.

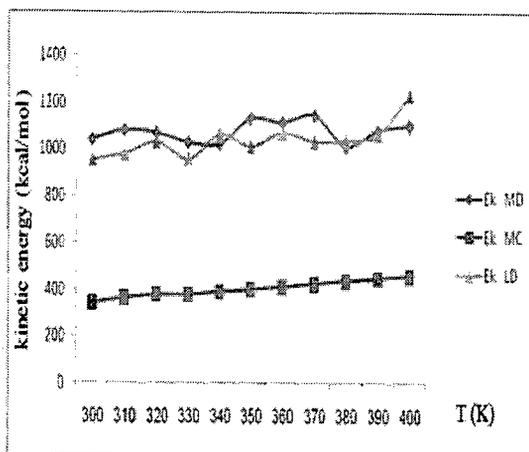


**Fig.8** . Gyration radius (Å) of Acetyl Choline receptor for  $\alpha$ -helix as a function of temperature in gas phase.

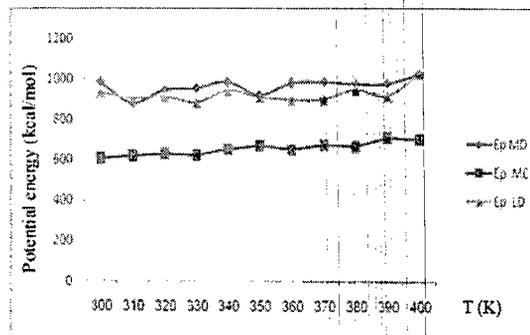
The kinetic and potential energy as a function of temperature for  $\beta$ -sheet conformation is linear in Monte Carlo simulation, while two other methods show some deviations when the temperature increased (Fig. 9,10). Linear relation of kinetic energy by the temperature in Monte Carlo simulation is the following equation:

$$E_k = 1.8T + 27.79 \quad (10)$$

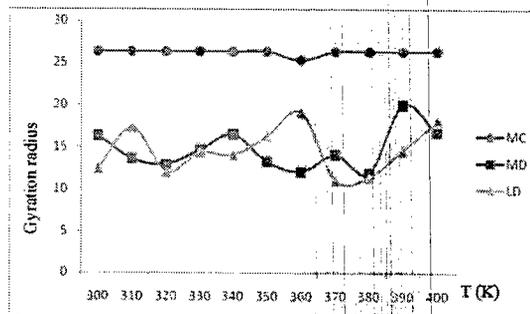
Correlation coefficient is 0.994. Considering the calculated gyration radius from three methods and almost the great difference from experimental gyration radius; we can conclude that the second structure of this protein isn't  $\beta$ -sheet (Fig. 11).



**Fig.9**. The Kinetic energy (kcal/mol) calculated for  $\beta$ -sheet conformation by Monte carlo, Molecular and Langevin dynamics simulation as a function of temperature.



**Fig.10**. The potential energy (kcal/mol) calculated for  $\beta$ -sheet conformation by Monte carlo, Molecular and Langevin dynamics simulation as a function of temperature.



**Fig.11**. Gyration radius (Å) of Acetyl Choline receptor for  $\beta$ -sheet as a function of temperature in gas phase.

## CONCLUSION

In the present article, using Monte Carlo, Molecular and Langevin dynamics simulations, in Hyperchem 8.0 package program, we present a detailed analysis of the average energy and gyration radius of Acetylcholine receptor protein at different temperatures.

1) In general, Langevin dynamics simulations are the same as molecular dynamics simulations. There are differences due to the presence of additional forces. Most of the earlier discussions on simulation parameters and strategies for Molecular dynamics had been applied to Langevin dynamics.

2) Our results show that when the temperature is increased, kinetic energy is enhanced.

3) Kinetic energy is a function of temperature, and its plot is linear.

4) We found that Monte Carlo simulation is the best method to evaluate gyration radius, because Monte Carlo is a stochastic method.

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