Temperature Dependancy of Transport Property of Dimer in Sickle and Normal Hemoglobin Protein (Three Day National Workshop, PANE-2026) Organised By Bodoland University Assam, India



Presented By

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Outlines

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Introduction

• It is basically common among people whose ancestors originate from former and current malaria zones of the world; for example Africa, Asia, the Middle and Far East, Mediterranean islands, and South America (Carter & Mendis, 2002; Weatherall, 2008).



Figure: a) RBC with normal and sickle shape and b) Impact of sickle cell dieasease (Retrieved from Google, 22th sept. 2022)

• The mutation in hemoglobin occurs due to the change of neucleotide adenine (A) to neucleotide thymine (T), which forms abnormal beta globin generating deformed sickle cell (Platt et al., 2000), i.e. an amino acid, called glutamic acid, is mutated into another amino acid, valine

• This mutated hemoglobin causes red blood cells to become rigid and sticky like sickle cell.

Introduction

• Due to variations in the medium densities, particles begin to diffuse and continue to do so in all directions until equilibrium is reached.
• Diffusion, an important transport property, is the phenomenon in which mass is transferred as a result of random molecular motion(Jin & Chen, 2000).
• Molecular dynamics (MD) simulations(Virk et al., 2015) have been performed to study the diffusion phenomenon of amino acids in water.
• These studies were mainly concerned about the effect of concentration, polarity, and temperature on the diffusion of Hb(Koirala et al., 2020).

Introduction

• In normal hemoglobin dimer there is glutamic acid wherease in sickle emoglobin there is valine in 6th residue

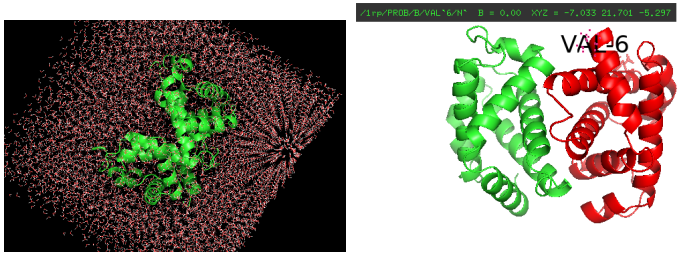
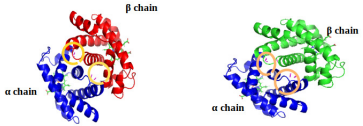


Figure: a) The normal hemoglobin structure b) The sickle hemoglobin structure

Introduction

• Binding free energy for these systems of sickle and normal hemoglobin was estimated as (5.97 $\pm$ 0.27) kcal/mol and (6.64 $\pm$ 0.27) kcal/mol respectively (Powrel et al., 2023).
• The difference of binding free energy, calculated by utilizing the umbrella sampling technique, is found to be (0.67$\pm$0.06) kcal/mol.



(a) (b)

Figure: Binding site in (a) sickle HbS dimer and (b) normal hemoglobin dimer

• Figure (a) illustrates how the mutant beta chain in the sickle hemoglobin dimer connects with the alpha chain by just three polar bonds(Powrel et al., 2025), whereas Figure (b) illustrates how the beta chain and alpha chain are bound by seven polar bonds in normal Hb.

Methodology

Molecular Dynamics study by NAno scale Molecular Dynamica(NAMD) and GROMACS

- PDB are taken from RCSB.org (Research Collaboratory for Structural Bioinformatics)
- Systems are design by using CHHARMM GUI
- Visualisation by VMD
- Computer simullation by NAMD and GROMACS
- Result analysis by NAMD and GROMACS
- Xmgrace

Methodology

• The system containing three HbS and xxxx water molecules in a cubic box with a dimension of yyy nm was subjected to molecular dynamics simulations at five distinct temperatures: 300 K, 305 K, 310 K, 315 K, and 320 K.
• The simulations were conducted using the Optimized Potentials for Liquid Simulations-All Atom (OPLS-AA) force field parameters and the Extended Simple Point Charge (SPC/E) water model.
• The parameters for the SPC/E26 water model are contained in the file spce.itp that is intrinsic to GROMACS 5.1.1.27, whereas all of the bonded and non-bonded interaction parameters are automatically assigned in the OPLS-AA force field.
• Furthermore, depending on the group of attachment, the same atom can have many partial charges.
• The partial charge that exists in atoms and molecules is what causes the Coulomb interaction. Similarly, Van der Waal's interactions occur following induced bipolar interactions.

Methodology

• The sixth slope of the graph applied during the mean square displacement compared to time evaluates the value of the self-diffusion coefficient.
• Also, the binary or mutual diffusion coefficient in binary mixture of two constituents X and Y can be calculated using Darkenâs phenomenological relation (Darken, 1948).
• According to the relation, if D_X and D_Y are self diffusion coefficients of two individual constituents X and Y with mole fraction N_X and N_Y respectively, the binary diffusion coefficient D_XY of the system is: $D_{XY} = N_Y D_X + N_X D_Y$
• Diffusion is a transport phenomenon. Out of many other factors, temperature is a factor upon which diffusion depends.
• Density of system decreases with increase in temperature and hence the region for random walk of diffusing particles becomes more.
• As a result, particle velocity increases with increase in temperature and hence rate of transfer of particle i.e. diffusion coefficient increases (Thapa & Adhikari, 2013).

Results and Discussion:

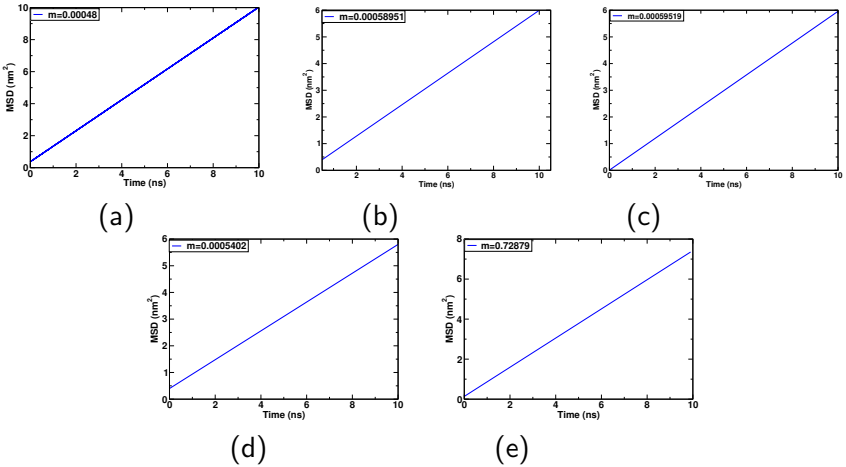


Figure MSD graph of sickle hemoglobin at (a) 306 K, (b) 308 K (c) 310 K, (d) 312 K and (e) 313 K.

Results and Discussion:

Table: MSD of sickle hemoglobin at temperatures of 306 K, 308 K, 310 K and 312 K and 313 K

For	Slope		Diffn (10^{-10} m ^{2} s $^{-1}$)	
Temp.(K)	Sickle Hb	Water	Sickle Hb	Water
306	0.000568	0.031081	0.0000946	0.005180
308	0.000572	0.03219	0.0000953	0.005365
310	0.000605	0.033022	0.0001008	0.0055037
312	0.000680	0.033957	0.0001133	0.0056595
313	0.00040205	0.033981	0.000067	0.0056635

Results and Discussion:

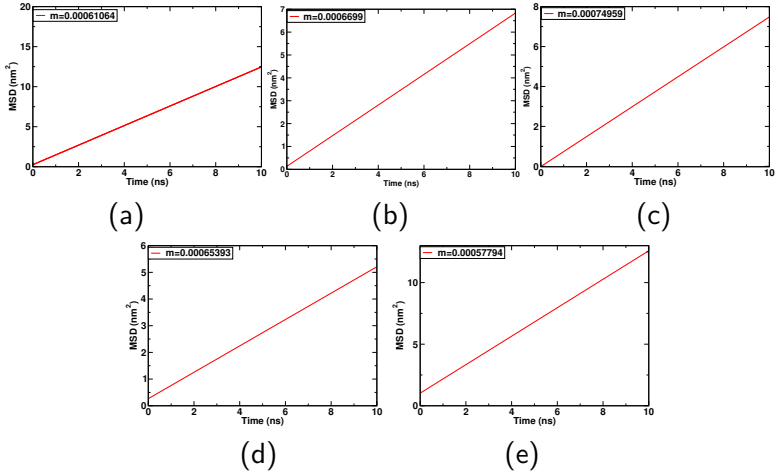


Figure: MSD graph of normal hemoglobin at (a) 306k (b) 308 K (c) 310 K, (d) 312 K and (e) 313 K

Results and Discussion:

Table: 1. slope of MSD graph of normal hemoglobin at temperature of 306 K, 308 K, 310 K, 312 K and 313 K.

For	Slope		Diffussion ($\times 10^{-10}$ m^2 s^{-1})	
Temp.(K)	Normal Hb	Water	Normal Hb	Water
306	0.00061064	0.031081	0.0001017	0.005180
308	0.00067	0.03219	0.000112	0.005365
310	0.00075	0.03301	0.000125	0.005502
312	0.00065393	0.033957	0.000109	0.0056595
313	0.0001742	0.033981	0.000029	0.0056635

Results and Discussion:

Table: 2. Temperature dependancy of diffussion Coefficient of TIP3P water, sickle and normal hemoglobin Protein

Tempr. (K)	Diffusion coefficients (DPBC) (10^{-10} m^2 s^{-1})							
	D_{self} of HbS		D_{self} of HbA		D_{self} of Water		Binary Diff.(D_B)	
	Th.	Ex.	Th.	Ex.	Th.	Ex	HbS	HbA
06	0.0000946		0.0001017		0.005180			
308	0.0000953		0.000112		0.005365			
310	0.0001008		0.000125	*	**	24	0.000633	0.000844
312	0.0001133		0.000109		0.0056595			
313	0.0000670		0.000029		0.0056635			

*Experimental value is 0.7×10^{-10} m^2 s^{-1}

**:(s) $0.0055037/(n)0.005502$.

Results and Discussion:

- The diffusion of sickle and normal hemoglobin in *TIP3P* water varies with temperature. The results are tabulated in Table 2
- It is seen that the variation of diffusion coefficient occurs with the variation in temperature (Table 2).
- The experimentally determined diffusion coefficient of blood at 310 K is 7 $\times 10^{-11}$ $m^2 s^{-1}$.
- It is observed that as the temperature of both proteins increased from 306 K to 310 K, their diffusion rates also increased. However, above body temperature of 310 K the diffusion rate does not change smoothly due to the high temperature noises in the systems (Table 2)).
- The Table 2 demonstrates that the simulated values of the self-diffusion coefficients are in agreement with those of experimental values within the minimum percentage error.

Conclusions

• Moleculardynamics simulations were employed to investigate the temperature dependent transport properties of sickle hemoglobin (HbS) and normal hemoglobin(HbA) dimers in aqueous solution.
• The study revealed that the self diffussion coefficients of both hemoglobin varients and water generally increase with temperature upto physiological condition, indicating enhance molecular mobility.
• Normal hemoglobin exhibited slightly higher diffussion coefficients than sickle hemoglobin, reflecting differences in their structural interaction.
•The simulated diffussion values showed good agreement with available experimental data.
• These findings demonstrate the usefulness of molecular dynamics methods for understanding transport behavior and temperature effects in biologically important protein system.

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Thank You