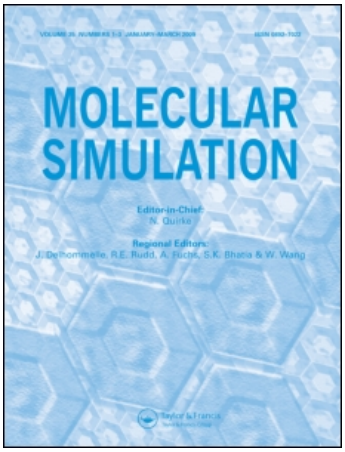

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Effect of frictional force on urea and thiourea during an intramembrane transport: an explicit solvent Langevin dynamics simulation method

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Effect of frictional force on urea and thiourea during an intramembrane transport: an explicit solvent Langevin dynamics simulation method

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An explicit solvent Langevin dynamics (LD) simulation method is employed to investigate the effect of frictional force on the solute–solvent interactions in urea and thiourea, which are subjected to varied degree of frictional forces akin to diffusional transport across the membrane system. Utilizing the frictional force concept in LD method, the effect of increasing frictional coefficient is studied on the microscopic properties such as single-point energy and N—C—N bond angle of urea and thiourea in aqueous solutions. The present work follows a self-conscious approach by explicitly including the solvent molecules in the LD simulations. The results are further compared with the standard Langevin approach without explicitly specifying solvent molecules. An analysis of the results reveals that the two cases differ strongly in the intermediate (Brownian) regime of frictional coefficient.

Keywords: Molecular simulation; Frictional force; Langevin dynamics; Nonlinear simulation; Explicit solvent

1. Introduction

For all solution-phase systems, interactions between molecules determine both the microscopic and bulk properties, which are essentially true for different transport phenomena across a membrane system. An analysis of the effect of frictional coefficient on solute–solvent interactions is quite important to study the solute–polymer interactions that can have a direct effect on intramembrane transport properties [1–4]. Since these interactions are extremely complex, a detail understanding of them is an exceedingly tough task, especially when the persistence time for such interactions is only a few picoseconds ($1\,\text{ps} = 10^{-12}\,\text{s}$). Here, the motion of molecules is subjected to random collisions and varied frictional forces that can be studied using different simulation techniques [5–7]. In this paper, we present a study of microscopic properties at atomistic level, namely, single-point energy and N—C—N bond angle, of urea and thiourea molecules subjected to varying frictional forces, the strength of which is comparable to that a molecule may experience during diffusional transport in a membrane like environment. Although, solvent may have only a little effect on the bond angle or bond lengths of the solute molecule, however, accurate modeling of solvent is crucial for understanding molecular dynamics (MD) of the solute molecule in a membrane like environment [8]. For solvation modeling, various sophisticated computer simulation techniques are now available both with explicit solvent methods [9] as well as implicit solvent methods (based on continuum solvation models) [10]. The explicit solvent methods, with an explicit molecular representation of the solvent, provide an atomistic level resolution. MD simulation [11–14], an explicit solvent method, has been extensively employed and proven quite successful for investigating various phenomenon such as urea-denaturation mechanism [15,16], modeling and simulation of relaxation processes [17], solvation effects across Nafion membranes [18–20], hydrophobic interactions [21], conformational equilibrium [22], salt effects on molecular interactions [23] and catalyzed decomposition of urea [24], etc. The dynamics of biological membranes has also been investigated in detail by MD method [25]. However,

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explicit solvent methods become computationally unmanageable for large systems and therefore, are quite expensive. Alternative to explicit solvent methods are continuum solvation models based on Langevin dynamics (LD) [26,27]. LD simulates the motion of molecules subjected to random collisions and frictional forces, and is used to model solvated systems without explicitly including solvent molecules. In general, in a practical standard LD simulation, the mean structural effects of solvent on solute molecules are considered via the frictional and random forces on the solute molecules and the effective forces between them, hence managing the computational resources well within the limit. Moreover, the advanced continuum solvation models like generalized Born/surface area or models based on Poisson–Boltzmann theory, can precisely predict free energy of solvation as can be predicted with explicit solvent methods.

However, the routine simulation of molecules in membrane like environment requires inclusion of potential arising from viscosity, dielectric shielding, and hydrogen-bond acceptor/donor aspects of the surroundings of solute molecule. In addition, the membrane–solvent interface poses several problems. Although, various implicit (continuum) solvent models for molecular simulation may represent the effect of explicit solvent, yet, no continuum solvent model can completely account for the dynamic as well as structural effect of explicit inclusion of solvent [28]. Therefore, in order to account for it, in the present work we had followed a self-conscious approach by including the solvent (water) molecules explicitly during a LD simulation of urea and thiourea molecules. This ensures that structural and dynamical effects of solvent in a membrane like environment are expressed unambiguously in the solute–solvent interactions at atomistic level. These computations are further compared with the standard LD simulations, which included the frictional forces but explicitly exclude the solvent molecules.

This paper is organized as follows: The present method is briefly described in Section 2, while the details of the present model and simulation performed are given in Section 3 and 4, respectively. The results are discussed in Section 5 and finally, Section 6 makes a few concluding remarks.

2. The method

A typical MD simulation [4,5] establishes the prospect positions and velocities of atoms, based on their recent positions and velocities. In the present work, we are concerned in the microscopic properties, at atomistic level, of a molecule that is interacting with solvent molecules in a membrane like environment. However, the addition of many solvent molecules will make a MD simulation much slower. A faster solution is to simulate the motion of the molecule of interest using LD method which imitates the effect of molecular collisions and the resulting energy (or enthalpy) change that occur in real solvents, without explicitly including solvent molecules. This is accomplished by adding a random force (to model the effect of collisions) and a frictional force (to model dissipative losses such as frictional drag across the membrane) to each atom at each time step. Precisely, this is articulated by the Langevin equation of motion:

$$a_i = \frac{F_i}{m_i} - \gamma_i v_i + \frac{R_i}{m_i}, \tag{1}$$

where a_i is the acceleration of each atom (of mass m_i) with corresponding force F_i on each atom. γ is the frictional coefficient of the solvent, in units of ps^{-1} and R_i is the random force on the solute atoms by the solvent. The frictional coefficient (γ) is related to the diffusion constant D of the solvent at a temperature T, by Einstein's relation:

$$\gamma = k_B T / mD. \tag{2}$$

The change in velocities, v_i, is equal to the integral of acceleration over time, and the change in the position, r_i, is equal to the integral of velocity over time. Using this, kinetic energy of the system can be calculated in terms of the velocities of the atoms, and potential energy in terms of momentum of atoms (p_i). The total energy (or enthalpy) of the system is then given as the sum of the kinetic (KE) and potential (PE) energies:

$$H(r_i, p_i) = \mathrm{KE} + \mathrm{PE}. \tag{3}$$

From this, other properties of interest are then easily followed.

Next, in order to mimic diffusional transport across an intramembrane system, we had followed an unusual self-conscious approach in LD method. Since during an intramembrane transport, solvent molecules are higher in concentration, which exerts an additional frictional drag on the solute molecules during their passage across the membrane, affecting the passive diffusion and other relevant transport properties. In the present method, we introduce this decisive frictional drag (during an intramembrane transport) on the solute molecules. In the present LD method, in contrast to the traditional LD method, simulations are performed on solute molecule surrounded by explicit solvent molecules. The total system is finally investigated by varying frictional coefficient (γ) for the two LD systems. The description of present model and the details of simulation are further presented in the following sections.

3. Description of the model

For the simulation reported in the present work, no explicit membrane model system is employed. In a standard LD simulation, collision and frictional forces are mainly introduced to mimic collision of solute molecules

with its environment (solvent) that are not included explicitly. However, in comparison to an explicit membrane–solvent model, the inclusion of explicit solvent molecules surrounding the solute atoms in the proposed Langevin simulation cell (alongwith varying frictional coefficient) significantly mimics certain aspects of intramembrane transport properties, particularly diffusional transport, in a more realistic fashion. Although, this may seems to be a crude representation of solute–solvent interactions, particularly when the frictional term in LD takes care of solute–solvent interactions both short range as well as long-range interactions in an aggregate manner. Nevertheless, the present model offers certain distinct aspects of stochastic dynamics of solute during intramembrane transport, which cannot be modeled through the traditional LD simulation. Moreover, hydration of solute molecule, whereby solvent (water) sticks to diffusing particle making it larger, slows down diffusional transport. Even though, increasing the frictional coefficient and inclusion of appropriate force-field parameters can take care of the hydration, but would be lacking in molecular details of solute–solvent interactions both in structure and dynamics. Further, the inclusion of solvent molecules surroundings the solute atoms creates an additional potential (in terms of random force) around solute atoms, which mimics the surrounding environment during intramembrane transport. Therefore, in the present model, the solvent molecules in an immediate surroundings of solute atoms, is presented explicitly during a Langevin simulation which otherwise models the solvent as featureless, dielectric material even in an immediate surroundings of solute. However, the frictional term remains the same for all the atoms in the simulation cell. But, in the present work, we are not interested in effects of degree of hydration or in the successive layers of the solvent as in case of distant-dependent dielectric models. Our main focus is purely on the study of structural and dynamic effects of solvated environment in terms of atomic level properties such as single-point energy and bond angle of diffusing solute molecule. The dynamic effect of solvent is considered via performing simulation with increasing frictional coefficient (γ). To further specify it, the results were compared in three distinct regimes of frictional coefficient, namely, lower regime ($\gamma < 10^{-5}\,\mathrm{ps}^{-1}$), intermediate (Brownian) regime ($10^{-5} \leq \gamma \leq 10^{5}\,\mathrm{ps}^{-1}$) and upper regime ($\gamma > 10^{5}\,\mathrm{ps}^{-1}$) as discussed in results and discussion section.

4. The details of simulation

Computationally, an isolated gas phase molecule is simplest to study. However, much of the chemistry takes place in the liquid or solid state. To treat such strong phases, one must simulate continuous, constant density, macroscopic conditions for such systems. The standard approach is to invoke periodic boundary conditions. This simulates a large system (an order of Avogadro's number) as a continuous replication in all directions of a small box. In this methodology, only the molecules in the single small box are simulated and the other boxes are just copies of the single box. The solvent water molecules come from a pre-equilibrated box of water. The solute is properly immersed and aligned in the box and then water molecules closer than some prescribed distance are omitted. In the present work, we have used HyperChem™ (HyperChem(TM) Professional 7.52(Eval.), Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, USA) to simulate our system under study. The details are described as follows:

First, the molecules under investigations, urea or thiourea, are refined for their molecular structure using molecular mechanics (MM^{+}) geometry optimization with a gradient appropriate for room temperature simulation. It should be pointed here that although the optimization using MM methods are not accurate as compared to quantum mechanical optimization procedures, however, since we have performed further simulations using MM, therefore, while making comparison with solvated and isolated systems, it would ensure and will be more appropriate to consider the full process under similar conditions (i.e. starting from the initial structure obtained under similar conditions). Further, the minimized molecule is solvated with water molecules with periodic box conditions such as to contain 48 water molecules. However, before the solvation, the solute is oriented according to its inertial axes such that the box size needed to accommodate it is minimized (minimizing the number of water molecules). Then, the molecules under study was solvated with 48 water molecules which comes from a previously equilibrated box of 216 water molecules using Monte-Carlo simulation performed with TIP3P potential. The value of dielectric constant was set to 1.0 for TIP3P water molecules in a periodic box. This is necessary because parameterization of TIP3P molecules using a distance-dependent dielectric constant or a value other than 1.0 yields deviant results.

The solvated system is then simulated by LD, following the present self-conscious approach, for different frictional coefficients ranging from $5.0 \times 10^{-6}\,\mathrm{ps}^{-1}$ to $10^{6}\,\mathrm{ps}^{-1}$ with simulation temperature set to 300 K. It should be noted that the initial solvated system remains the same for each simulation; only the frictional coefficient is being varied. These are further compared with LD simulations without explicitly including the solvent molecules. When frictional coefficient is set to zero, LD simulation is equivalent to MD simulation. The snapshots of a sequence of configurations at successive time points are taken to analyze the time evolution of dynamics. These dynamics can be used to obtain macroscopic information by sampling a microscopic simulation over a long period of time. The different energetic properties such as single-point energy and geometric quantities like N—C—N angle are analyzed as the frictional coefficient is varied, which is further

compared with properties of isolated molecules. The results are discussed in the next section.

5. Results and discussion

The present results for single-point energies (in kcal mol^{-1}) as a function of increasing frictional coefficient γ (in ps^{-1}), are depicted in figure 1(a) for urea molecule, and in figure 1(b) for thiourea molecule. The figure 1 also compares the results from present LD simulation method (explicitly including solvent molecules) with that from standard LD method (without explicitly including solvent molecules). Similarly, the results for N—C—N bond angles (in degrees) at different frictional coefficient γ (in ps^{-1}), are represented in figure 2(a) for urea molecule and figure 2(b) for thiourea molecule. For analysis of these results for the two simulation methods, let us consider three different regimes for the strength of frictional coefficient: low friction regime (or energy diffusion regime) ($\gamma < 10^{-5}$ ps^{-1}), intermediate (Brownian) regime ($10^{-5} \leq \gamma \leq 10^{5}$ ps^{-1}) and upper regime ($\gamma > 10^{5}$ ps^{-1}).

In the two limiting regimes, lower and upper regimes, of frictional coefficient, computed values of single-point energies for the two methods are very much similar. However, in the intermediate regime, the two methods differ considerably. For example, at $\gamma = 8.0 \times 10^{-2}$, the single-point energy differs by ~27% for urea and, ~57% for thiourea molecule, while N—C—N bond angle differs by ~3% for urea and ~5% for thiourea molecule. Such wide variation, however, is not limited to the single-point energy only, but can also be seen for the N—C—N bond angle. For example, at $\gamma = 2.0 \times 10^{-2}$, N—C—N bond angle differs by ~6% for urea and ~9% for thiourea molecule while comparing two simulation methods. Similar trends are quite evident at other values of frictional coefficient in the intermediate regime ($10^{-5} \leq \gamma \leq 10^{5}$ ps^{-1}). This regime of frictional coefficients lies around $\gamma = 1.0$, which corresponds to mD $\approx k_B$T (equation (2)). From figures 1 and 2, it is relatively clear that as γ increases, particularly in the intermediate regime, significant fluctuations occurs in the behaviour of calculated single-point energy and N—C—N bond angle using present LD method. The standard LD approach, however, shows much lesser fluctuations in these properties as γ is varied. In the limiting regimes when $\gamma \rightarrow 0$ or $\gamma \rightarrow \infty$, present LD approach (with explicit solvent molecules) and the standard LD approach (without explicitly including solvent molecules) gives similar results. These can be explained as follows:

As $\gamma \rightarrow 0$, solute moves with constant velocity, and in the upper regime, when $\gamma \rightarrow \infty$ (high friction regime),

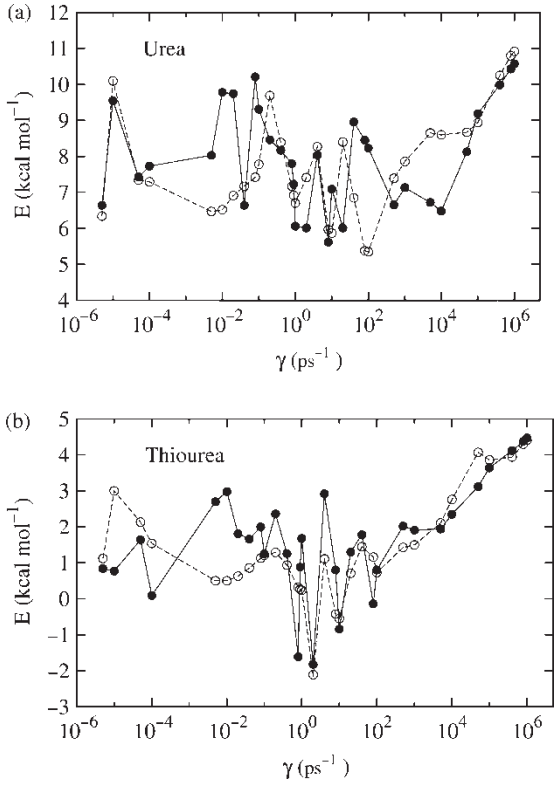

Figure 1. Single-point energy E (in kcal mol^{-1}), of urea (a) and thiourea (b), after solvation, as a function of frictional coefficient γ (in ps^{-1}), using present LD method explicitly including solvent molecules (filled circles) and without including solvent molecules (open circles).

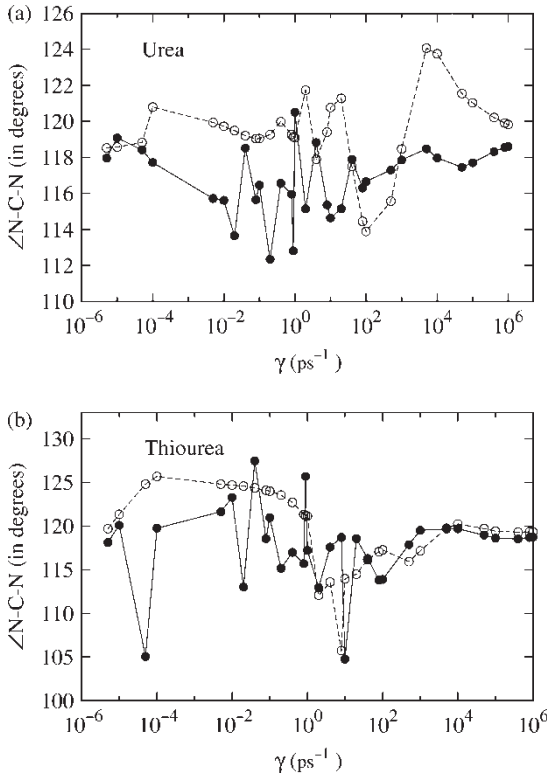

Figure 2. N—C—N bond angle of urea (a) and thiourea (b), after solvation, of urea (a) and thiourea (b), after solvation, as a function of frictional coefficient γ (in ps^{-1}), using present LD method explicitly including solvent molecules (filled circles) and without including solvent molecules (open circles).

particle motion is purely diffusive. However, in the intermediate regime, as γ increases, the Brownian dynamics is considerably enhanced owing to presence of explicit solvent molecules. These resulting fluctuations can contribute an appreciable affect on the diffusion rate. In the lower regime of frictional coefficient, diffusion rate is limited by energy exchange with the environment and vanishes at $\gamma = 0$, since particle cannot gain energy to overcome the barrier. As frictional coefficient become finite (in the intermediate regime), solute can exchange energy with its environment, leading to interactions with surrounding solvent molecules. The presence of additional solvent molecules induces a realistic stochastic force on the diffusing solute particle, which may not be modeled in the standard LD approach in addition to already included random forces that accounts for fluctuation-dissipation. This is clearly depicted in the nonlinear behaviour observed for single-point energy and bond angle, though it is generally presumed that solvent has no effect on these properties of solute molecules. However, the present results show that this may well prove to be an important contributing factor for the microscopic properties of solute–solvent interactions during a diffusional transport. The present approach is, therefore, likely to be more appropriate in the Brownian regime. However, the accuracy and a quantitative comparison with the experimental results are difficult to ascertain under the present LD approach. Nevertheless, these features, discernible from the standard LD approach, are inherent in the macroscopic properties such as viscosity, which are related to the frictional coefficient (through Stokes–Einstein equation and its variants). These nonlinear features can be arrived by following the phenomenological approach [1]. The detail investigation of such nonlinear problems would be focus of our future study.

6. Conclusion

In conclusion, our basic objective of this study was to show that LD simulations performed with explicitly including solvent molecules might deliver significantly different results from that obtained from the traditional LD approach, in particular for the microscopic properties such as single-point energy and bond angle of solute molecule, when subjected to varying frictional forces of intermediate degree akin to diffusional transport across the membranes. In the present LD approach (which included explicit solvent molecules), simulation results for urea and thourea molecules show a nonlinear behaviour in their microscopic properties, namely, single-point energy and N—C—N bond angle, particularly in the intermediate range of frictional coefficient. This was mainly attributed to the stochastic dynamics induced by presence of additional solvent molecules. And, such stochastic forces (accounting for structural and dynamical effects at atomistic level) may not be fully modeled in the standard LD method, which eventually affects the macroscopic properties like flux, viscosity and other thermodynamics properties of the system. However, computation for the results in quantitative agreement with experimental results, for such macroscopic properties of system under study, is a quite challenging and extremely difficult task, especially in non-equilibrium thermodynamics. Nevertheless, the present results may provide an appropriate guidance towards this.

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