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The dynamics of cholesterol molecules near the surface of protein farnesyltransferase - Computer simulation

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Abstract

We have made the molecular dynamics (MD) simulations for the cluster of cholesterols localized near the protein farnesyltransferase (1FT2) at the physiological temperature $T = 309.75$ K. We have observed that the cholesterol molecules form a lodgment on the surface of protein. Several physical characteristics of the deposited cholesterol cluster have been calculated among those: the mean square displacement, diffusion coefficient, linear and angular velocity autocorrelation function and their Fourier transforms.
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Keywords: Protein; Cholesterol; Cholesterol lodgment; Molecular dynamics; Computer simulation

1. Introduction

In last decade one observes an enormous activity in study of the macromolecular complexes of biological importance. Recently, the membrane localization and function of many cellular signal transduction molecules (complexes) is the subject of intensive investigation (Liu and Prestwich, 2004; Bokoch et al., 2004; Long et al., 2002). An example is protein farnesyltransferase (FTase) which catalyzes the addition of the 15-carbon farnesyl isoprenoid to the thiol of a cysteine residue that is the fourth amino acid from the C terminus of protein acceptors (Long et al., 2000). The detailed researches of the interactions of FTase with different intracellular and cellular membrane components are required. Experimental studies of such complicated systems still encounter difficulties. The computer simulations of these systems could be a valuable alternative method, although the signal transduction molecules contain several thousands of atoms and this leads to the elaborate preparation of data and the intensive, computer demanding calculations.

An important component of mammals cells is cholesterol. Cholesterol is present in higher concentrations in tissues which either produce more or have more densely packed membranes, for example, the liver, spinal cord and brain. Recent research shows that cholesterol has an important role for the brain synapses as well as in the immune system, including protecting against cancer (Bokoch et al., 2004; Long et al., 2000).

Here we study *via* MD method the system composed of protein farnesyltransferase dimer (1FT2), which appears in rattus norvegicus brain (Long et al., 1998), and cholesterol molecules. This paper presents the dynamical properties of cholesterol molecules located near the protein farnesyltransferase surface.

2. Simulation details

We simulated 1FT2 molecular complex plus twenty cholesterol molecules. We have used the standard Lennard–Jones (LJ) interaction potential $V(r_{ij})$ between the atoms (sites) of rigid-body cholesterol $C_{27}H_{45}OH$ and protein farnesyltransferase dimer (1FT2). Namely, $V(r_{ij}) = 4\varepsilon[(\sigma/r_{ij})^{12} - (\sigma/r_{ij})^{6}]$, where r_{ij} is the distance between the atoms ith and jth, ε the minimum of potential at a distance $2^{1/6}\sigma$, and k_B is the Boltzmann constant. The L–J potentials parameters ε and σ are given in Table 1 (Daura et al., 1998; la Cour Jansen, 2002; Kuznetsova and Kvamme, 2002). For a review on the phenomenological intermolecular potentials and the meaning of models parameters, see (Frenkel and Smith, 2002; Rapaport, 1995) and the references therein.

The 1FT2 macromolecular aggregate contains above 5×10^3 atoms. Its structure is given in (Long et al., 1998; see also Protein Data Bank).

The rigid-body cholesterol molecule (Fig. 1) includes lots of atomic sites, but in line with the common procedure for large

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Table 1
Lennard–Jones potential parameters

Atoms	ε/k_B (K)	σ (Å)	m ($\times 10^{-25}$ kg)
C	58.2	3.85	0.20
O	88.7	2.95	0.27
N	53.22	3.49	0.12
S	209.76	3.6	0.53
H	12.4	2.81	0.02
CH	43.30	3.8	0.22
CH_2	67.55	3.92	0.23
CH_3	101.04	3.88	0.25

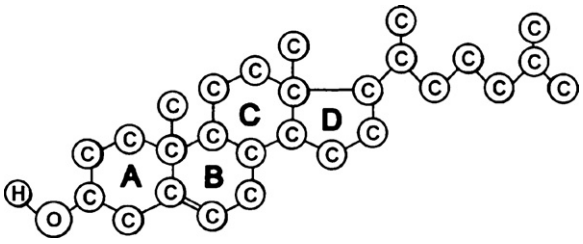

Fig. 1. The structure of the cholesterol molecule.

molecules (Frenkel and Smith, 2002; Rapaport, 1995) we treat CH, CH_2 and CH_3 atomic groups of cholesterol as a supersites (pseudoatoms). The L–J parameters for these groups are given in Table 1 (Daura et al., 1998; la Cour Jansen, 2002). Moreover, we have included the dipole moment of cholesterol (OH bonds) by putting the charge $-0.376e$ on oxygen and $0.376e$ on hydrogen atoms of OH bonds (Phelps and Dalby, 1966).

The L–J potentials parameters between unlike atoms and pseudoatoms were calculated by the Lorentz–Berthelot rules $\sigma_{A-B} = (\sigma_A + \sigma_B)/2$ and $\varepsilon_{A-B} = \sqrt{\varepsilon_A \varepsilon_B}$ (Allen and Tildesley, 1989), where A, B are C, O, N, S, H, CH, CH_2 and CH_3 atoms or pseudoatoms. The classical equations of motion were integrated up to 1 ns by predictor–corrector Adams–Moulton algorithm (Frenkel and Smith, 2002). The integration time step was 0.4 fs which ensured total energy conservation within 0.01%. The total simulation time was 10^3 ps (5×10^6 time steps). The initial distribution of molecules was generated by the Monte Carlo (MC) algorithm (Allen and Tildesley, 1989).

3. Results

We begin with the presentation of the snapshot of the instantaneous configuration of our system at the physiological temperature $T = 310$ K (Fig. 2). One can see that the cholesterols gather together near 1FT2 surface, forming the cholesterol rich domain (lodgment) on the protein farnesyl-transferase surface.

The calculated radial distribution function $g(r)$ (Allen and Tildesley, 1989) for the centre of mass of cholesterol is shown in Fig. 3. The first peak between 0.6 and 0.7 nm corresponds to the near cholesterol neighbours, the second group of three peaks between 1.3 and 1.8 nm is associated with the longer distance cholesterol neighbours (second shell). For the cholesterol intermolecular distance greater than 2 nm the value of $g(r)$ is very low and tends to the zero. This quantitatively

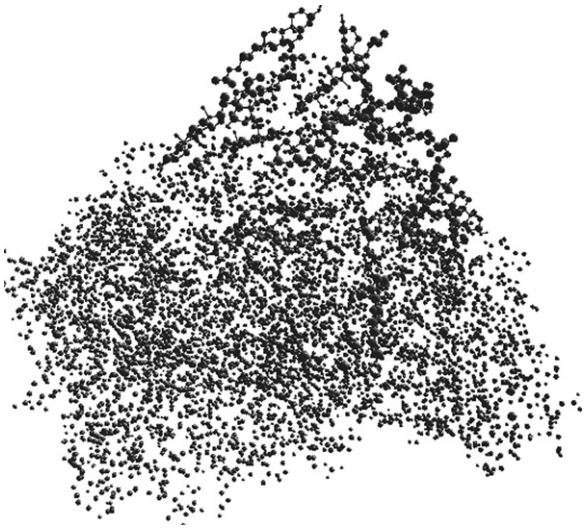

Fig. 2. An example of the instantaneous configuration of the protein farnesyl-transferase + $(C_{27}H_{45}OH)_{20}$ at $T = 310$ K.

proofs the appearance of cholesterol lodgment, observed in the snapshot.

The mean square displacement $\langle|\Delta\vec{r}(t)^2|\rangle$ of the centre of mass of cholesterol at $T = 310$ K, where $\langle|\Delta\vec{r}(t)|^2\rangle = \langle|\vec{r}(t) - \vec{r}(0)|^2\rangle$ and $\vec{r}$ is the position of centre of mass of a single molecule is shown in Fig. 4. The slope of $\langle|\Delta\vec{r}(t)^2|\rangle$ is connected with the translational diffusion coefficient *via* Einstein relation:

$$\langle|\Delta\vec{r}(t)^2|\rangle \approx 6Dt \tag{1}$$

The plot of $\langle|\Delta\vec{r}(t)^2|\rangle$ tells us that the cholesterol molecule in the domain located on the surface of 1FT2 shows up translational mobility, *i.e.* the cholesterol domain is not in a solid state phase. The slope of the linear part of mean square displacement of cholesterol equals 0.76×10^{-2} nm^2/ps. The value of diffusion coefficient, calculated from the linear part of $\langle|\Delta\vec{r}(t)^2|\rangle$ plot is $D = 1.26 \times 10^{-6}$ cm^2/s. To our knowledge, this is the first reported estimation of the diffusion coefficient of

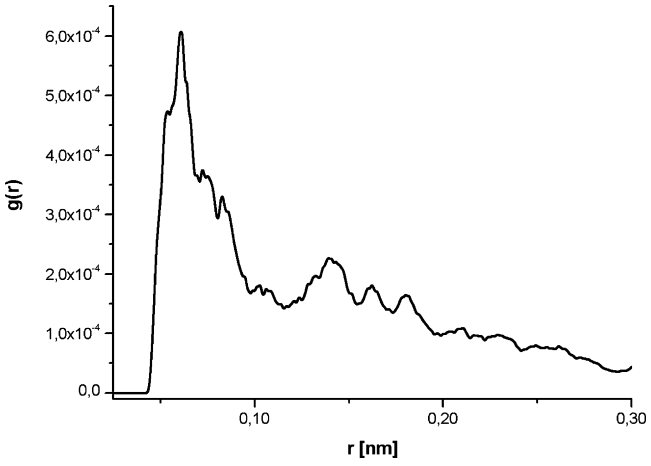

Fig. 3. The radial distribution function of the centre of mass of the cholesterol molecule in the cholesterol domain.

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