

# Molecular Dynamics Simulation of Protein Translocation across a Membrane

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## 1 Introduction

Biological membranes, their spontaneous formation or phase transitions and the molecular dynamics therein, have long been studied intensively. On the other hand, the structure and function of the membrane proteins are central problems in molecular biology and are attracting tremendous interest. However, the cooperative process of lipids and proteins occurring within the membrane is still very difficult to understand. Recent advances in computer technology have proved the molecular simulation approach to be very promising in various fields of research, and here we demonstrate a possible application of the simulation method to the molecular process of protein translocation across the membrane.

## 2 Model and Method

The lipids that constitute the cell membranes are amphiphilic molecules that have both the hydrophilic head groups and the hydrophobic tails. We here consider 305 amphiphilic molecules, each of which is composed of three hydrophilic atoms and seven hydrophobic atoms. The membrane protein is modeled as a sequential block copolymer made of 13 alternating hydrophilic and hydrophobic segments, each made of 15 atoms. In addition, we introduce 3675 water-like particles surrounding the membrane and the protein.

Molecular mechanisms of the spontaneous membrane formation and the translocation of the protein across the membrane are investigated by the molecular dynamics (MD) simulation method; we solve the Newton's equations of motions for several thousands of atoms and reproduce detailed microscopic molecular process that occurs within the membrane. One protein molecule and 305 lipid molecules in addition to 3675 water molecules are introduced into the MD cell with periodic boundary conditions, with system sizes of  $7.6 \times 7.6 \times 7.6 \text{ nm}^3$ . Values of the molecular parameters used are listed in Table 1.

Table 1: Molecular parameters used in the simulation.

Parameters	in absolute units	in reduced units
$l_0$	0.152 (nm)	0.4
$k_b$	$3.46 \times 10^7$ (J/mol/nm <sup>2</sup> )	10000
$\sigma_{\text{lipid}} = \sigma_{\text{protein}}$	0.38 (nm)	1.00
$\sigma_{\text{water}}$	0.33 (nm)	0.88
$\epsilon_{\text{lipid}} = \epsilon_{\text{protein}}$	500 (J/mol)	1.0
$\epsilon_{\text{water}}$	2000 (J/mol)	4.0
$m$	$14.0 \times 10^{-3}$ (kg/mol)	1.0

## 3 Results and Discussions

### 3.1 Spontaneous membrane formation and protein conformation in water

Molecular aggregation of lipids is a result of subtle balance of interactions among the head groups, the chain tails, and the water molecules. Depending on the relative density or the PH of the solvent, the

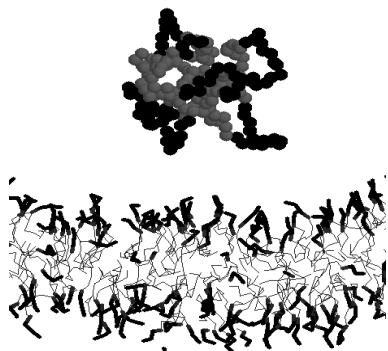


Figure 1: Bilayer and protein in water phase, where water molecules are omitted. Hydrophilic and hydrophobic atoms are depicted in black and gray, respectively.

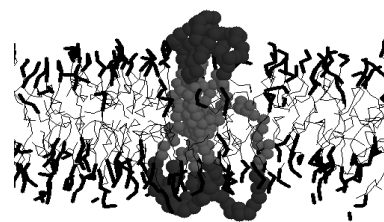


Figure 2: Molecular snapshot of the inserted protein, where water molecules are omitted. Hydrophilic and hydrophobic atoms are depicted in black and gray, respectively.

system forms micelle, vesicle, or membrane [3]. We first simulated the molecular process of spontaneous membrane formation from the complete random mixture of lipids and water. The snapshot of the bilayer given in Fig. 1 shows one obtained after 0.1 ns. Since the chain tails are highly flexible, the observed bilayer membrane has large internal disorder, which makes possible the quick response to external perturbations.

Before discussing protein insertion into the bilayer, we give a glimpse at the protein conformation in the water phase. Also shown in Fig. 1 is a typical equilibrium conformation of the model protein made of sequential hydrophilic and hydrophobic segments. Six hydrophilic arms are stretching into the water phase, while the hydrophobic segments tend to segregate and form a spherical core in the center. This characteristic initial conformation of the protein in water has profound significance in the insertion process when it comes close to touch the bilayer membrane.

### 3.2 Protein insertion into the membrane [1, 2]

When the protein molecule is set free to interact with the membrane, the extended arms of the protein start interacting with the hydrophilic head groups of the membrane lipids. The interaction gives strong perturbation to the membrane structure and results in a local opening (hole) of the membrane, the opening area of which has high affinity with the hydrophobic core of the protein. With the aid of amphiphilic lipid molecules, both the hydrophilic and the hydrophobic segments of the protein tend to form reverse and normal micelles, respectively, which helps rapid insertion of the protein. Through considerable reorganization of the lipids-protein complex, the protein molecule is found to complete the insertion into the membrane. Typical protein conformation obtained after 1.0 ns of simulation is given in Fig. 2.

## References

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