East European Journal of Physics. 3. 466-470 (2023)
DOI:10.26565/2312-4334-2023-3-52 ISSN 2312-4334

EXPLORING THE IMPACT OF LIPID DOMAIN SIZE ON THE LIFETIME: A DISSIPATIVE PARTICLE DYNAMICS STUDY[†]

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Received June 19, 2023; revised July 3, 2023; accepted July 4, 2023

In this research, we have used the dissipative particle dynamics (DPD), a mesoscopic simulation technique, in order to investigate the dynamics of lipid domains in near critical temperature. Our specific focus has been on exploring the influence of lipid domain size on its lifetime, which mimics the behavior of lipid rafts within cellular membranes. The lipid membranes used in this study were composed of saturated and unsaturated lipids, which have been immersed in water. Through the simulation of these membranes close to their critical temperature, we have successfully generated fluctuating domains that mimic the lipid rafts observed in cellular systems. We have proposed a method to obtain the lifetime of the fluctuating domains by analyzing the sizes of the lipid domains at specific intervals of time. Our investigations have revealed a linear correlation between the initial size of the lipid domain and its lifetime. Our research finding give an insight into the underlying mechanisms that govern lipid rafts and their vital role in various cellular processes.
Keywords: *Lipid bilayer; Dissipative particle dynamics; Domain fluctuation lifetime*
PACS number: 87.16.dt, 87.16.dj

INTRODUCTION

There is a small component (10-200 nm) known as lipid rafts that float on the surface of lipid membranes [1-3]. Lipid rafts primarily consist of saturated lipids and cholesterol, which results in a higher density compared to their surroundings. Certain proteins, such as GPI-anchor proteins, can attach to lipid rafts and carry out their functions [4]. It is believed that lipid rafts serve as platforms for specific biological activities within the cell membrane, such as signal transduction [5]. Very recently lipid rafts were thought to involve in COVID 19 entry [6] and cancer cell [7].

To study lipid rafts, researchers often employ giant unilamellar vesicles (GUVs) instead of real cell membranes due to their simplicity in lipid composition [8]. Lipid domains in GUVs are larger compared to lipid rafts in real cell membranes, making them detectable using standard optical instruments. In 2008, experiments on giant plasma membrane vesicles extracted from real cell membranes suggested that lipid domains that mimic the behavior of lipid rafts can be found by tuning the vesicles to their critical temperature [9]. For signal transduction to occur, a raft should persist for minutes [10].

Lipids with a structure consisting of both saturated and unsaturated lipids are referred to as hybrid lipids [11]. Hybrid lipids tend to accumulate at the boundary between saturated and unsaturated lipids in order to reduce line tension [12]. Interestingly, hybrid lipids have been proposed to prolong the lifetime of lipid rafts. In 2013, a theoretical work by Palmieri and Safran demonstrated that the inclusion of hybrid lipids can increase the domain lifetime by three orders of magnitude compared to cases without hybrid lipids [13]. Subsequent computational studies using dissipative particle dynamics (DPD) simulations for the similar system can be found in Ref. [14].

However, it is necessary to explore the lifetime of lipid domains at different sizes, as lipid rafts in real cell membranes exhibit varying sizes [22]. It is possible that the lifetime of large lipid rafts may be sufficient for cellular processes. Currently, computer simulations on lipid bilayers have been employed to obtain data that is challenging to acquire experimentally. Mesoscopic simulation methods, such as dissipative particle dynamics (DPD), have been widely used to simulate lipid membrane systems [12, 14-17]. DPD is preferred in lipid membrane simulations due to its reduced computational resource requirements and time compared to classical molecular dynamics (MD) methods. Moreover, DPD is more suitable for studying the physical properties of lipid membranes. In this study, we aim to investigate the effect of lipid domain size on the duration of lifetime using dissipative particle dynamics. Additionally, we propose a method to measure the lifetime by examining lipid domain sizes.

MODEL AND SIMULATION

The lipid bilayer is constructed by arranging two layers of lipid molecules. Each lipid molecule consists of a head group with two DPD particles and tails with three DPD particles each. There are two types of lipids, namely lipid A and lipid B, which have the same structure but exhibit unfavorable repulsion in their tail groups, as indicated by the interaction parameter provided below. Three water molecules are represented by a single DPD particle. In our computational experiment, the bilayer is positioned at the center of the simulation box, which has dimensions of $(60\times60\times40)r^3$, as shown in Figure 1. The areas above and below the bilayer are filled with DPD water particles. Each DPD particle experiences three forces: a conservative force $\vec{F}_{ij}^{C}=a_{v_i\mu_j}\omega(r_{ij})\hat{r}_{ij}$, a dissipative force $\vec{F}_{ij}^{D}=\gamma_{ij}\omega^2(r_{ij})(\hat{r}_{ij}\cdot v_{ij})\hat{r}_{ij}$, and a random force

[†] ***Cite as:*** K. Sornbundit, East Eur. J. Phys. 3, 466 (2023), https://doi.org/10.26565/2312-4334-2023-3-52

$\vec{F}_{ij}^{R}=\frac{\sigma_{ij}}{(\delta t)^{1/2}}\omega(r_{ij})\theta_{ij}\hat{r}_{ij}$. The notion in the force equations are explained as follows: $\vec{r}_{ij}=\vec{r}_j-\vec{r}_i$, $\hat{r}_{ij}=\vec{r}_{ij}/|\vec{r}_{ij}|$,$\vec{v}_{ij}=\vec{v}_j-\vec{v}_i$ and δt represents the computational steps, and the coefficients of the dissipative and random forces are related by $\gamma_{ij}=\sigma_{ij}/k_BT$ [18] where T is temperature, k_B is the Boltzmann constant, type of particle $i(j)$ are denoted by $\nu_i\left(\mu_j\right)$. The symmetric random variable θ_{ij} obeys $\langle\theta_{ij}(t)\rangle=0$, and $\langle\theta_{ij}(t)\theta_{kl}(t')\rangle=(\delta_{ik}\delta_{jl}+\delta_{il}\delta_{jk})\delta(t-t')$, where $i\neq j$ and $k\neq l$. The weight function in $\omega(r)$ is given by $\omega(r)=1-r/r_c$ for $r\leq r_c$ and is zero elsewhere. The length scale of the system is r_c. The equations of motions for DPD particle i are given by $\frac{d\vec{r}_i(t)}{dt}=\vec{v}_i(t)$ and $\frac{d\vec{v}_i(t)}{dt}=\frac{1}{m}\sum_j\left(\vec{F}_{ij}^{C}+\vec{F}_{ij}^{D}+\vec{F}_{ij}^{R}+\vec{F}_{ij}^{S}\right)$. The mass of every bead is assumed to be equal $m_i=m$. The interaction strength $a_{\nu_i\mu_j}$ in $\vec{F}_{ij}^{C}$ are given by the following table

Table 1. the interaction strength in the ε/r_c unit

h_A	h_B	t_A	t_B	w	
25	25	200	200	25	h_A
25	25	200	200	25	h_B
200	200	25	X	200	t_A
200	200	X	25	200	t_B
25	25	200	200	25	w

Where ε is the energy scale, $h_A(h_B)$ represents head group of saturated lipids (unsaturated lipid), $t_A(t_B)$ represents the tail group of saturated lipids (unsaturated lipid) and w represent a group of water. The notion X is 100(26) for two(one) phase regime.

For the lipid molecules, consecutive particles are subjected to a harmonic force described by the following equation $\vec{F}_{i,i+1}^{s}=-C(1-r_{i,i+1}/b)\hat{r}_{i,i+1}$, where $C=100\varepsilon$ is the positive constant and $b=0.45r_c$ is the desired bond length.

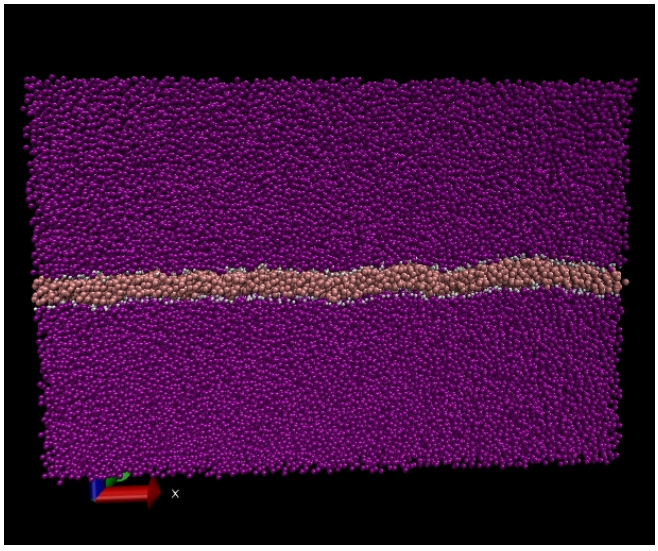

Figure. 1 Lipid bilayer position in the simulation box. White particles represent the lipid head group, and pink particles represent the lipid tail group. Purple particles denote water

Simulations were conducted at $k_BT=\varepsilon$ with the fluid density $\rho=3.0r_c^{-3}$. The amplitude of the noise is $\sigma_{ij}=\sigma=(\varepsilon m/r_c^2)^{1/4}$. The velocity-Verlet algorithm [19, 20] was used to integrate the equation of motion. The time unit used all simulations are denoted by $\delta t=0.05\tau$, where the time scale $\tau=(mr_c^2/\varepsilon)^{1/2}$.

To conduct the simulation, we initially create a bilayer consisting of a single type of lipid. The system is allowed to evolve for 1000 steps. Subsequently, two opposing circular domains, one on each layer, with a specific diameter are generated, and the systems are allowed to equilibrate for 5000 steps. It is important to note that the circular shape of the domains is maintained due to the unfavorable interaction between the two lipid types, resulting in the lowest free energy state for the system.

Next, the domains are allowed to decay by adjusting the interaction parameter between unlike tails from 100 to 26, which is slightly larger than the interaction parameter between tails of the same type. This adjustment promotes a mixing situation between the two types of lipids, as referenced in [14]. In order to determine the lifetime of the domains, the size of the domains (D) is calculated every 100-time steps using the relation $D=\pi/k^*$, where k^* represents the dominant wave vector [21]. The methodology for domain size calculation is explained in Ref. [12].

The lifetime of a domain is defined as the time at which the domain size is half of its initial value. Since the shape of the domain becomes irregular after decay, we use the term “domain size” instead of “domain diameter”. The lifetime is calculated using the equation

$$\text{Life time}=\frac{(D(0)+\bar{D})}{2},$$

Where $D(0)$ represents the size at the beginning of the decay process, $\bar{D}$ denotes the averaged size calculated from the equilibrium region (the region where the size reaches saturation).

It should be noted that the chosen definition for calculating the lifetime of fluctuating domains does not have a universally accepted consensus. However, we have adopted this definition because a domain at half its initial size should not be functioning properly. Please note that the lifetime calculation method described here differs from the one presented in Ref. [14], which is suitable for much smaller domain fluctuations.

RESULTS AND DISCUSSION

The results are presented and discussed in this section. Figure 2 reveals a snapshot of the upper domain with an initial diameter (D) of 8 r_c at various time points since the decay process began. In this figure, time $t = 0\ \delta t$ corresponds to a simulation time of $t = 6 \times 10^3\ \delta t$, as we are solely considering the decay process. It is customary to designate this time as $t = 0\ \delta t$. Initially, the domain exhibits a circular shape, as shown in Fig. 2a. Subsequently, the domain starts to decay, and Fig. 2f represents the snapshot at which the size of the domain is half of its initial value, which we define as the lifetime. It is evident that the domain fractures into smaller domains. At $t = 1 \times 10^4\ \delta t$, the domain is completely decomposed into numerous small domains. By $t = 3 \times 10^4\ \delta t$, these small domains disperse further from each other, indicating a mixing scenario.

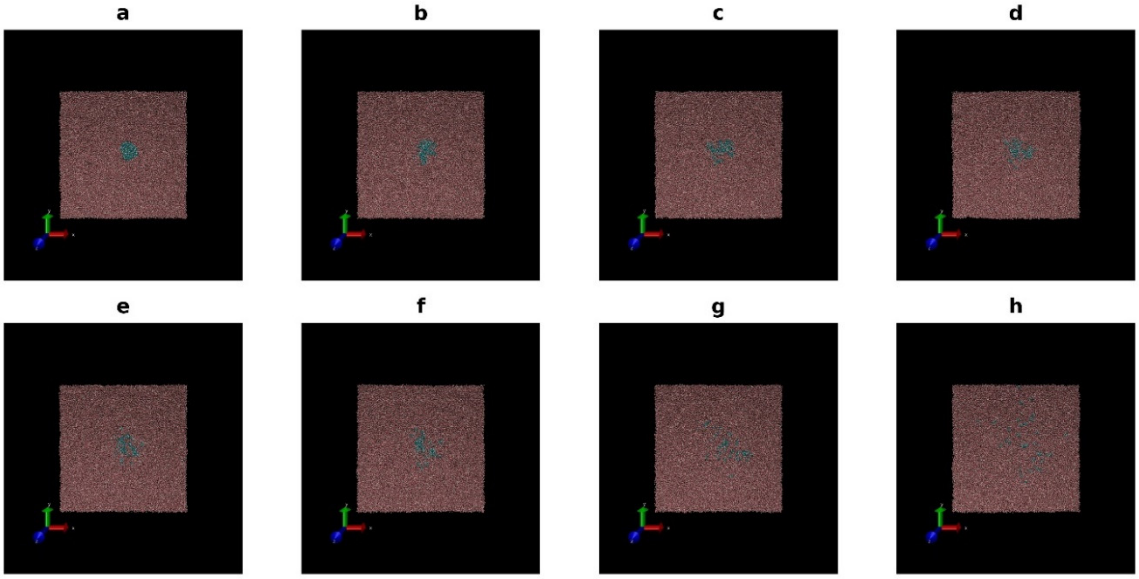

Figure 2. Snapshot (a-h) representing the upper layer of lipid bilayer at t=0, 1×10^3, 2×10^3, 3×10^3, 4×10^3, 4.7×10^3, 1×10^4, 3×10^4 δt, respectively

Figure 3 illustrates the average domain size over time for initial diameters ranging from D = 3.0 to 8.0 r_c. It is noticeable that the domains decay rapidly from the beginning. When the system reaches a mixing state, the domain size stabilizes around 4 r_c.

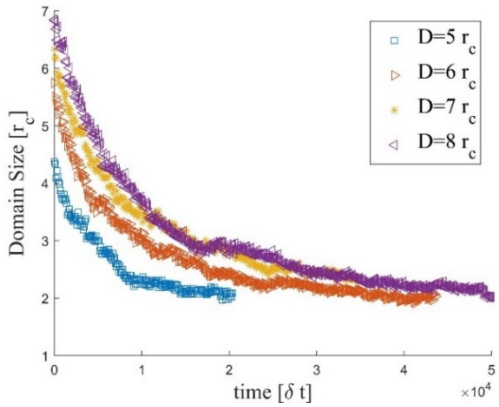

Figure 3. Characteristic domain sizes versus time for domains of initial diameter D = 3.0 to 8.0 r_c

As depicted in Fig. 3, larger domains require more time to reach saturation. Hence, it is worthwhile to investigate the relationship between the initial domain size and the lifetime. Fig. 4 demonstrates a linear relationship between the initial domain size and lifetime. Consequently, cell membrane's activities that take a certain amount of time may occur on large domains.

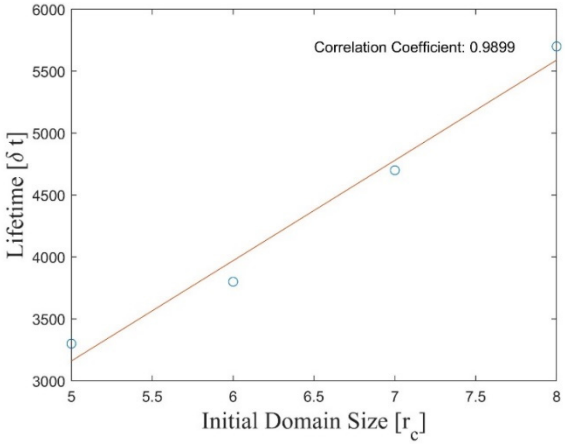

Figure 4. The linear relationship between initial domain sizes and their lifetime

CONCLUSION

This study has revealed that the initial size of a domain plays a crucial role in its lifetime. Larger domains exhibit a longer lifetime compared to smaller domains. Furthermore, a linear relationship between the initial domain size and its lifetime has been established. These findings contribute to our understanding of domain dynamics and have implications for cell membrane activities on large domains.

Acknowledgement

I would like to express my sincere gratitude to the Ratchaburi Learning Park, King Mongkut's University of Technology Thonburi (Ratchaburi), for providing me with the opportunity to conduct this research.

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ВИВЧЕННЯ ВПЛИВУ РОЗМІРУ ЛІПІДНОГО ДОМЕНУ НА ТРИВАЛІСТЬ ЙОГО ЖИТТЯ: ДОСЛІДЖЕННЯ ДИНАМІКИ ДИСИПАТИВНОЇ ЧАСТИНКИ

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У цьому дослідженні використана дисипативна динаміка частинок (DPD), мезоскопічна техніка моделювання, для дослідження динаміки ліпідних доменів при температурі, близькій до критичної. Наша спеціальна увага була зосереджена на дослідженні впливу розміру ліпідного домену на його тривалість життя, що імітує поведінку ліпідних плотів у клітинних мембранах. Ліпідні мембрани, використані в цьому дослідженні, складалися з насичених і ненасичених ліпідів, які були занурені у воду. Завдяки моделюванню цих мембран, близьких до їх критичної температури, ми успішно створили флуктуаційні домени, які імітують ліпідні плоти, що спостерігаються в клітинних системах. Ми запропонували метод визначення тривалості життя флуктуючих доменів шляхом аналізу розмірів ліпідних доменів через певні проміжки часу. Дослідження виявили лінійну кореляцію між початковим розміром ліпідного домену та часом його життя. Результати дослідження дають зрозуміти основні механізми, які керують ліпідними плотами, і їх життєво важливу роль у різних клітинних процесах.

Ключові слова: *ліпідний бішар; дисипативна динаміка частинок; час життя домену флуктуації*