Investigation of a Virtual Nested Two-dimensional Lattice Model for Representing the Diffusive Motion of a Transmembrane Protein in Cell Membrane

Atsushi OKUMOTO\textsuperscript{a}, Tomonari SUMI \textsuperscript{b}, Hideo SEKINO\textsuperscript{a,c}, Hitoshi GOTO \textsuperscript{a}\textsuperscript{*}

\textsuperscript{a}Department of Computer Science and Engineering, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi, 441-8580, Japan
\textsuperscript{b}Research Institute for Interdisciplinary Science, Okayama University, 3-1-1 Tsushima-Naka, Kita-ku, Okayama, 700-8530, Japan
\textsuperscript{c}Institute for Advanced Computational Science, Stony Brook University, Stony Brook, NY 11794, USA
\textsuperscript{*}e-mail: gotoh@tut.jp

(Received: December 5, 2016; Accepted for publication: January 10, 2017; Online publication: February 10, 2017)

As a refinement of the fluid mosaic model for explaining cell membrane functions, membrane-skeleton fence model and anchored membrane protein picket model have been proposed according to the tracing experiment of a single molecule in plasma membrane. In addition, the experimental observation that the diffusive motion of a transmembrane protein in plasma membrane leads to a normal diffusion through two-step relaxation has suggested that there are two types of nested compartments, large and small. In this paper, we propose a virtual nested two-dimensional lattice model that can express a nested compartment structure of plasma membrane using three parameters in order to represent such a single molecule diffusion movement. Using this 2D lattice model, various diffusive motion simulations of one particle random walks were performed and their trajectories were analyzed by Detrended fluctuation analysis. As a result, we have confirmed that both plasma membrane models, "fence" and "picket," can be represented by our virtual nested 2D lattice model.

Keywords: Transmembrane protein, Plasma membrane, Diffusion movement, Random walk, Detrended fluctuation analysis

1 Introduction

The fluid mosaic model [1] has played an important role in explaining the cell membrane function in elucidating the fundamental functions of cells such as intercellular signal transduction, ingestion of nutrients and excretion of metabolites. However, due to the proposal of lipid rafts [2], a more detailed cell membrane model is required to analyze the function of dynamic organization of proteins and lipids on cell membranes divided into small domains. As an example, Suzuki and co-workers observed the motion track of a single transmembrane protein molecule in the plasma membrane and have proposed the membrane-skeletal fence model and the anchored membrane protein picket model [3]. In the tracking experiment, it is further suggested that two large and small compartments may form a nested double compartment, because the motion trace has reached a normal diffusion through two-step relaxation. However, the existence of such a nested structure is not known. In this paper, we propose a virtual nested two-dimensional lattice model that can express a nested compartment structure of plasma membrane, and perform various diffusion motion simulations of one particle random walks using this lattice model to confirm whether two cell membrane models, "fence" and "picket," can be represented.

In the membrane-skeleton fence model, transmembrane
proteins move in a compartment surrounded by lattice-shaped skeletal fences of plasma membrane, and transit to the adjacent compartment through the gap between the membrane and the fence by thermal fluctuation. Then, it is thought that transmembrane proteins reach a free diffusion after such motions repeatedly occurs in adequate number of times. On the other hand, in the anchored membrane protein picket model, pickets exist as a part of the membrane skeletal fence where the transmembrane proteins anchored. When a transmembrane protein moving in plasma membrane is captured by the picket, the transition to the adjacent compartment is inhibited. Furthermore, since the surrounding area of the picket shows high viscous resistance due to lipid molecule aggregations, the diffusive motion of the transmembrane protein is considerably decreased. The tracking experiment showed that the diffusive motion of transmembrane proteins was shown as the mean-squared displacement divided by time (mSD/time) as a function of time (Figures 7 of reference 3) [3]. in this graph, it is thought that a free diffusing transmembrane protein in a compartment is subjected to an obstacle effect from "fence" or "picket" afterwards and diffuses again through the two-step relaxation.

In this work, to properly represent such observed features of the tracing experiment, we develop a two-dimensional lattice model shown in Figure 2. in this lattice model, it is possible to adjust a particle movement by using three parameters: the passage rate of the membrane skeletal fence \( d \), the capture rate of the picket to the membrane skeletal fence \( p \), and the escape rate \((1/v)\) based on the viscosity \( v \) in the surrounding area of "fence" and "picket." Here, we perform simulations of the diffusive motion of one particle random walk on this two-dimensional lattice model with an adequate set of three parameters and analyze the trajectories by using Detrended fluctuation analysis (DFA) to confirm that two cell membrane "fence" and "picket" models can be expressed.

2 Method

DFA is a method for analyzing the fractal properties inherent in data fluctuation, for example, characteristics of stochastic processes by removing the trend from time series signal data [4]. Algorithm of DFA is summarized as follows; For a given time series data \( B(i) \) \((i = 1,\ldots,N)\), the average \( B_{\text{avg}} \) is calculated by equation (1) and the cumulative summation of bounded deviations \( y(k) \) is by equation (2).

\[
B_{\text{avg}} = \frac{1}{N} \sum_{i=1}^{N} B(i)
\]

\[
y(k) = \sum_{i=1}^{k} (B(i) - B_{\text{avg}})
\]

Fluctuation \( F(n) \) employed in DFA method is defined by equation (3), where \( y_n(k) \) is a linear function value that is approximated by the least-squares method for each window size \( n \).

\[
F(n) = \left( \frac{1}{N} \sum_{k=1}^{N} [y(k) - y_n(k)]^2 \right)^{\frac{1}{2}}
\]

\[
F(n) \propto n^{-\alpha}
\]

When \( F(n) \) is proportional to a power of window size \( n \) as in equation (4), the scaling exponent \( \alpha \) is as Brownian (\( \approx 1.5 \)), \( 1/f \) (\( \approx 1 \)), and white noises (\( \approx 0.5 \)). In terms of a single particle motion in this study, Brownian noise shows a free diffusive motion with the higher diffusion coefficient, \( 1/f \) noise is a motion in which the coefficient decreases with fluctuating, and white noise corresponds to a kind of vibrational motion in which the coefficient rapidly drops.

Single particle diffusion simulations have been performed where one particle is located at the center of a two dimensional lattice shown in Figure 1 under the two-dimensional periodic boundary condition as a beginning state of random walk. Once the particle contacts a fence, the fence passing of the next step is decided by comparing a random number and \( d \) value. Skeletal fences of the 2D lattice are randomly replaced.
to pickets in frequency of \( p \) value. When the particle reaches the surrounding area of a picket, in the next step, it can escape from the trap area with probability of \( 1/v \) value. In general, the step size of random walk is always set to 1, but in this work, zero particle movement by step size 0 is allowed. The number of random walk steps is set to one million.

According to the tracking experiment [3], the MSD/Time in short time range is \( 39.8 \mu m^2/s \) and the small compartment size is \( 210 \) nm, therefore, \( D_0 \) (free diffusion coefficient) is \( 39.8/4 \mu m^2/s \). When the lattice length of the small compartment is set to 10, a unit distance and time for one step of random walk are corresponding to \( \Delta x = 210/10 = 21 \) nm and \( \Delta t = (\Delta x)^2(5D_0) = 8.86 \times 10^{-6} \) s, respectively.

The trajectory of one particle random walk corresponds to the movement of single transmembrane protein. An example of the arrangement of skeletal fences and picket is shown in Figure 1. If \( d = 1 \), the transmembrane protein will all pass through the skeletal fence and will be equal if there is no skeletal fence. If \( p = 0 \), there are no pickets. If \( v = 1 \), it indicates that movement due to viscosity is not restricted.

### 3 Results and Discussion

Figure 2a shows the result of DFA analysis of the trajectory for single particle simulations by varying \( d \) value with \( P = 0 \) and \( v = 1 \), that correspond to the "fence" model. As the \( d \) value decreases, a transient decrease of the \( \alpha \) value becomes larger and the minimum is shifted to the larger \( n \) value side simultaneously. At this time, it is considered that the particle has repeatedly tries to pass through the fence between 100–1000 steps.

Figure 2b shows the DFA result of changing \( p \) value with lower viscosity, corresponding to the "picket" model. As the \( p \) value is increased, a transient decrease of the \( \alpha \) value is temporarily observed, but it is understood that the particle is almost in a normal diffusion state. On the other hand, if the \( v \) value is high as shown in Figure 2c, a transient decrease of the \( \alpha \) value remarkably appears between 1000–10000 steps. This phenomenon, in which the diffusion motion of the particle decreases as the viscosity increases, corresponds to virtually expanding the compartment size in our model.

In this study, we have proposed a virtual nested two-dimensional lattice model using the three parameters and performed single particle random walk simulations on this lattice and their trajectory analyses using DFA. As a result, it has been confirmed that the membrane skeleton fence model and the anchored membrane protein picket model can be expressed by giving appropriate parameters. In order to reproduce the two-step relaxation observed in the tracking experiment [3], the best set of the three parameters is being optimized now. In parallel with this work, we are also studying various diffusion simulations by using discrete time master equation [5]. The details will be reported elsewhere.

### References