Investigation of diffusion process inside the cell using Monte Carlo Cell (MCell)

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Abstract. Understanding a structure, function and molecular mechanisms of a cell are not easy. Even though, it is difficult, but it still has a solution to be investigated. The aim of this study is to investigate the compartment model as a structure of a cell and diffusion process inside a cell and nucleus by using Monte Carlo simulation. MCell was used to analyze the compartment model for mechanisms inside a cell and nucleus. Compartment model consist two icosphere with different size, with cell diameter for 0.8 μm and nucleus diameter varies for about 0.4, 0.5, and 0.6 μm, respectively. Another parameter was their width and a model of receptor on the surface of the nucleus. During investigation, an amount of receptor was 120, 150, and 180 grid element. The model was collected and separated. The diffusion process flew from cell to the nucleus and returned to the cell with 2000 molecules on surface. MCell successfully simulated compartment model for a cell and the nucleus. Diffusion process depended on the diameter of the nucleus. The greater the nucleus, more effective the speed of diffusion process would be because the concentration inside the cell was increase and concentration in the nucleus was decrease.

1. Introduction

Cells are the basic unit of life. Understanding structural, functional and molecular mechanisms in a cell [1, 2] is not easy. One of the solutions is by modeling it using a Monte Carlo method to investigate the diffusion processes inside the cell. Several well-identification processes are involved in cell mechanisms such as a molecule diffusion process from cell to the nucleus and vice versa. This process is influenced by diffusion rate, comparison of molecule concentration and amount in a cell and nucleus, and kinds of receptor. The molecule concentration depends on the molecule amount in the cell and nucleus, the comparisons of cell and nucleus dimension or both.

Previous computational studies in biology systems with simulation model of Monte Carlo Cell has shown an effect such as ligand kinetics, density receptor and dimension synapse [3, 4], and urinary system with compartment model [5].

Shape of an icosphere was used as a model of a cell and nucleus compartments in which the icosphere nucleus was inside of the icosphere cell. Simulations were carried out using a variety of nucleus dimension, a number of receptors, and a receptor model. A Variety of parameter and the dimension of compartment gave much information about mechanisms diffusion in a cell, but this model didn't really

represent a cell and nucleus in shape. This study is addressed to investigate the compartment model as the structure of a cell and the diffusion process as molecule mechanisms inside a cell and nucleus using Monte Carlo Simulation Cell (MCell).

2. Methods

Blender 2.69 was used to create and visualize the picture and movie for the compartments and added with CellBlender and Monte Carlo Cell (MCell). The simulation was carried out using MCell 3.1 [3, 6] (www.mcell.org) running on a Lenovo ThinkPad 2.2 GHz Intel Core i7 (Ubuntu 14.10).

The Cell in figure 1a represents a model target to create simulations.Fig 1a shows a fluorescent mouse cell that wasvisible under the microscope from Nagai-Group, Osaka University. Model illustrated in Fig 1b shows a result of a model for cell and nucleus. The cell has 0.8 μm diameter and the nucleus has varies diameter each of them were 0.4, 0.5 and 0.6 μm, respectively. Molecules with green color were molecules inside a cell; it called molecules A. Molecules A will be transferred to the nucleus using the diffusion process. Molecules with red color were a non-diffusing receptor on the top of a nucleus. Non-diffusing receptors at a density have two variation models that was collected and separated. Figure 1c shows a model that collected non-diffusion receptor and figure 1d shows a model that separate. The model has variable number of element grid, which represents the wide of area receptor such as120, 150, and 180, respectively.

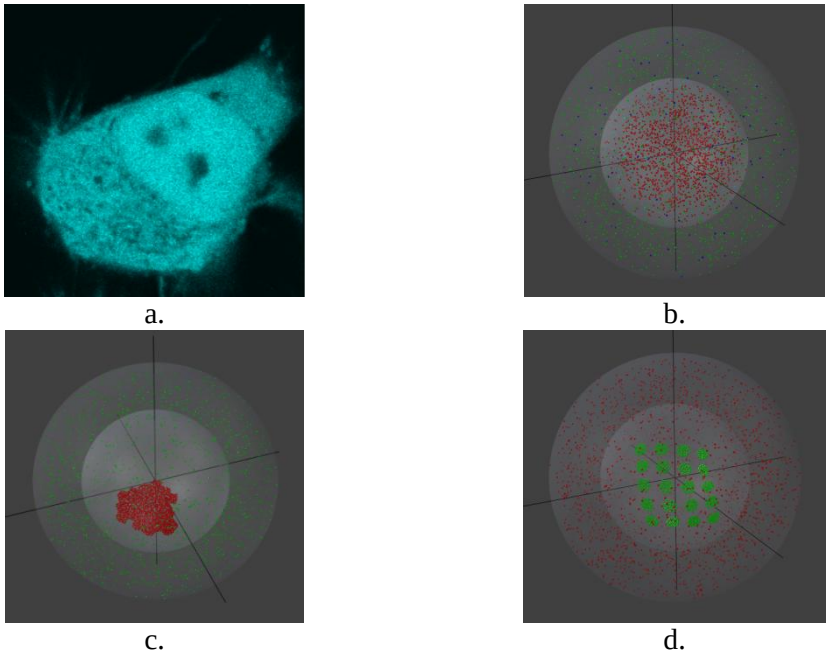

Figure 1. (a) Mouse cell visible under microscope fluorescent from Nagai-Group with permission, (b) Diffusion simulation at 0.01 s, (c) Model of collected non-diffusion receptor at 0.00 s (red), (d) Model of separate non-diffusion receptor at 0.00 s (green)

This study used two steps diffusion to describe the diffusion process in cell and nucleus. The first step from the cell happened as follow: molecules A diffused to the nucleus with reaction to molecules non-diffused t1 on the top of a nucleus with forward rate 2×10^{7} $M^{-1}.s^{-1}$ and the result of diffusion process was molecules B in the nucleus. The second step molecules B diffused back to the cell with forward rate 1×10^{7} $M^{-1}.s^{-1}$. And the reactions of diffusion process were formulated as below.

$$A'+t1' \xrightarrow{fwd1} B, +t' \xrightarrow{fwd2} C'+t1'$$

Simulations were carried out using a set of standard parameter values (table 1). Subsequently, it varied the parameters individually to test, the effect of the parameter on diffusion and a time step of 10 μs was used for simulation with standard parameters.

Table 1. Standard values of the parameters used in the simulations

Parameter	Standard Value
Diffusion constant molecules A, B, C (vol)	$1x10^{-6}$ cm^2s^{-1}
Diffusion constant of surface (Surf)	$1x10^{-8}$ cm^2s^{-1}
Forward rate 1 (Fr1)	$2x10^{7}$ cm^2s^{-1}
Forward rate 2 (Fr2)	$1x10^{7}$ cm^2s^{-1}
Number of molecules	2000
Wide of area non-diffusing (receptor)	120, 150, 180 e.g[a]

[a] e.g = element grid

3. Results and discussion

In this study, figure 2a shows the results of a diffusion process that occurs from the cell to the nucleus, then return to the cell again. Molecules that were diffused from the cell into the nucleus called molecule A marked with black which molecules A declined quickly until all molecules A diffused to the nucleus during 0.287s. The red color indicated that molecule B where the molecules presented in the nucleus as a result of diffusion process rose suddenly until its peak at t = 0.04s with 542 number of molecules. Finally, molecule B transferred to cell through diffusion mechanism and called molecules C with a blue line.

In the figure 2b shows half-saturation of molecules A with varying diameter of the nucleus occurs at $t_{0.5}$ = 0.015s, 0.031s and 0.051s that happened for nucleus diameter 0.6 μm, 0.5 μm, and 0.4 μm, respectively. The result shows bigger nucleus diameter influenced to the increasing molecule concentration in a cell because the volume of cell declined in molecules constant number. This condition caused the concentration difference between the cells and changed the nucleus in which the concentration inside a cell increased and inside the nucleus decreased, so the diffusion rate increased. The phenomenon shows the congruence between simulation resulting with a theory in which the diameter of 0.6 μm nucleus had a shorter of diffusion for about 0.015s followed by 0.5 μm and 0.4 μm during 0.031s and 0.051s, respectively. Duration of half-saturation had affected the number of molecules surviving in the nucleus in which the shortest duration 0.6 μm had 906 molecule number and then for 0.5 μm and 0.4 μm had 542 and 288, respectively as shows in figure 2c.

Receptors are gates that connect between the cell and the nucleus. In this investigation, a number of receptors had three wide varieties such as120, 150 and 180 element grids and two model receptors: converged receptor and separate receptor. Figure 2e shows a result of simulation wide varieties in which the receptor with the greater number of element grids had faster diffusion process. Figure 2f shows the receptor model converged and separated, in which the model of receptor which had large number of receptors did not have much effect on the speed of diffusion even though it had a different model, but the small number of receptors, converged model faster than the separated ones.

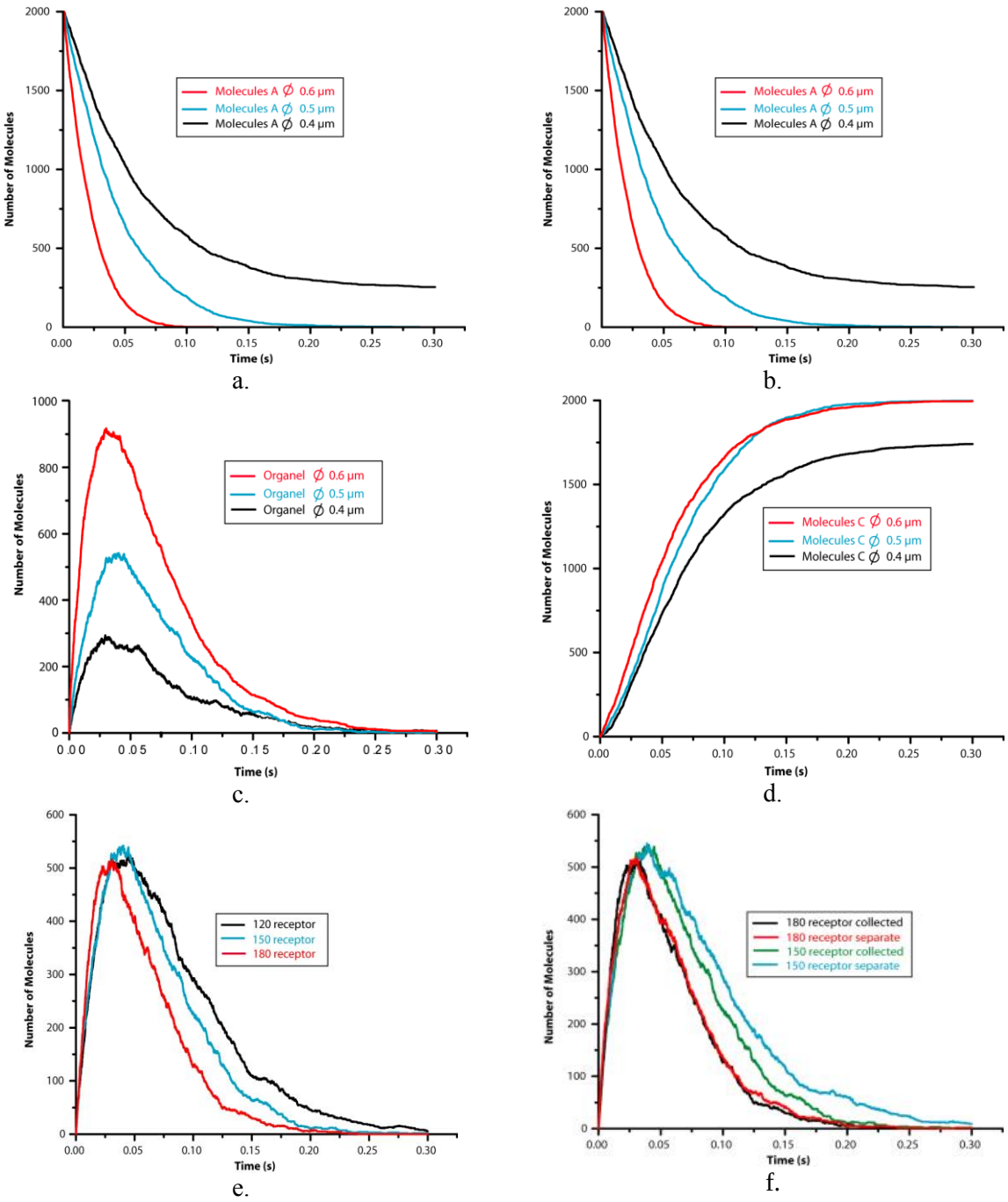

Figure 2. Results of simulation a. diffusion molecules A, B, C with diameter nucleus 0.5 µm, b, c, d diffusion molecules A, B and C with variety diameter nucleus, respectively, e. diffusion molecules B with variety number of receptor (non-diffusion), f. diffusion molecules B with variety model receptor (collected and separate).

4. Conclusions

MCell successfully simulated compartment model for a cell and nucleus. Diffusion process depends on a diameter of the nucleus. The greater the nucleus then the more effective the nucleus will be to speed the diffusion because the concentration inside cell increase and concentration inside the nucleus

decreases. The other result, the greater the amount of receptor shows the increasing of the diffusion process and it makes the model collected faster than separated.

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Acknowledgements

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Corrigendum: Investigation of Diffusion Process in Cell use Monte Carlo Cell (MCell)

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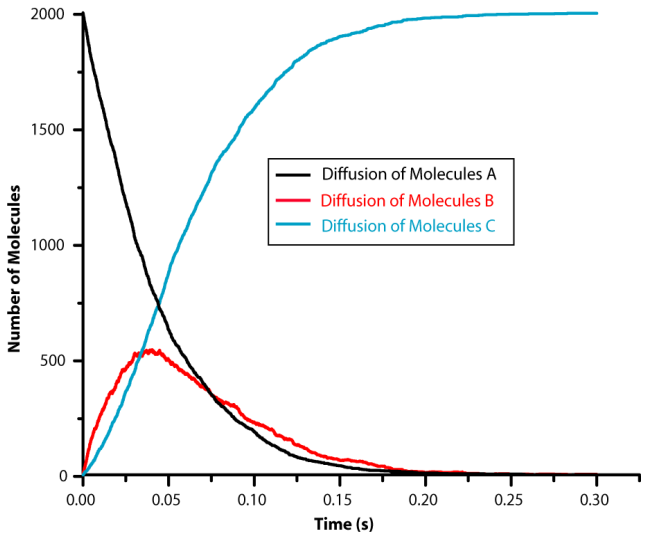
Figure 2a. Should be replaced by:



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