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Mesoscale modeling techniques for studying the dynamics oscillation of min protein: a lattice Boltzmann method and pattern formation

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Abstract

We present an application of the Lattice Boltzmann Method (LBM) to study the dynamics of min proteins oscillations in *Escherichia coli.* The oscillations involve on MinC, MinD and MinE proteins, which are required for proper placement of the division septum in the middle of a bacterial cell. We specifically use the LBM to study the dynamic pole-to-pole oscillations of the min proteins in two dimensions. The LBM numerical results are in good agreement with previous findings and agree qualitatively well with experimental results. Our results indicate that the Min proteins pattern formation depends on the cell's shape. The results show that the oscillation pattern of Min proteins is the most consistent with the experimental results when the ratio of width and length of *Escherichia coli* cell are 1:2.

Keywords: Lattice Boltzmann method, Min protein oscillation, patternformation.

1. Introduction

Cell division is the process which the cell separates to two daughter cells after the DNA has been duplicated and distributed into two regions. For a successful cell division, the cell has to determine the optimal location of cell separation. In *E.coli* and other rod-shape bacteria, the two process are known to regulate the placement of the division site: nucleoid occlusion [1] and the oscillation of Min proteins [2]. The FtsZ ring [3] which is formed by the FtsZ proteins to localize the division site is prevented by nucleoid occlusion over nucleoid: nuclear region in prokaryotic cell. The Min proteins oscillation from pole to pole find the optimal division site [4-6]. The Min proteins system consists of three proteins: MinC, MinD and MinE. In our work, we focus only the Min proteins oscillation. Many scientist study the Min Protein oscillation by experiment or computational techniques. Since the computational techniques described Min Proteins oscillation in microscopic or macroscopic scale so we will propose the new technique: Lattice Boltzmann Method to study the Min proteins oscillation in mesoscopic scale. A number of mathematical modeling of Min protein oscillation have been proposed and studied. These models are based on the macroscopic nonlinear reaction-diffusion equations (RDE) and are solved using conventional finite different schemes. Howard *et al* [7] presented a reaction-diffusion model describing the diffusion of Min proteins along the bacterium and their transfer between the cytoplasmic membrane and cytoplasm. Then, the model of Meinhardt *et al* [8] showed that the pattern formation of Min system requires the interaction of self-enhancement and it long-ranging antagonistic and the dynamics of FtsZ proteins was also included in their model. After that Kruse [9] proposed the model which found the clustering of membrane-bound MinD in combination with attachment and detachment rate depends on the concentration of molecules present on the membrane. Ngamsaad *et al* [10] used the Lattice Boltzmann method (LBM) to study the dynamics of the oscillations of the Min proteins from pole to pole in one dimension. Huang *et al* [11] includes the realistic in vitro interactions of MinD and MinE based on 3 dimensional simulation. All of these model deal with macroscopic behavior by modelling the reaction-diffusion equations and do not provide microscopic details so we propose the Lattice Boltzmann technique to study Min proteins oscillation in *E. coli* based on Howard's model in mesocopic level .

2. Reaction-diffusion Equation model

We extend Extend the model of Howard *et al* from one-dimensional reaction-diffusion equation to two

dimensional. In dimensionless form, the dynamics are written as

$$\frac{\partial \rho_D}{\partial t} - D_D \nabla^2 \rho_D = R_D = -\frac{\sigma_1 \rho_D}{1+\sigma_1' \rho_e} + \sigma_2 \rho_e \rho_d \quad (1)$$

$$\frac{\partial \rho_d}{\partial t} - D_d \nabla^2 \rho_d = R_d = \frac{\sigma_1 \rho_D}{1+\sigma_1' \rho_e} - \sigma_2 \rho_e \rho_d \quad (2)$$

$$\frac{\partial \rho_E}{\partial t} - D_E \nabla^2 \rho_E = R_E = \frac{\sigma_4 \rho_e}{1+\sigma_4' \rho_D} - \sigma_3 \rho_D \rho_E \quad (3)$$

$$\frac{\partial \rho_e}{\partial t} - D_e \nabla^2 \rho_e = R_e = -\frac{\sigma_4 \rho_e}{1+\sigma_4' \rho_D} + \sigma_3 \rho_D \rho_E \quad (4)$$

Where ∇^2 is the Lapacian operator. Let $s = \{D, d, E, e\}$ which are represented the cytoplasmic MinD, the membrane bound MinD, the cytoplasmic MinE and the membrane bound MinE respectively. ρ_s is the mass density of particle of species s at time t and position (x, y). R_s is reaction term which depend on the density of the species (ρ_s) and on the density of the other species that react with species s. D_s is the diffusion coefficient. σ_1 describes the spontaneous association of MinD to the cytoplasmic membrane. σ_1' corresponds to membrane-bound MinE suppressing the recruitment of MinD from cytoplasm. σ_2 reflects the rate that MinE on the membrane drives the MinD on the membrane into cytoplasm. We let σ_3 be the rate that cytoplasmic MinD recruits cytoplasmic MinE to membrane while σ_4 describes the rate of dissociation of MinE from the membrane to the cytoplasm. Finally, σ_4' corresponds to the cytoplasmic MinD suppressing the release of the membrane-bound MinE.

3. Lattice Boltzmann Method

The dynamics determined by Equations (1)- (4) can be simulated by Lattice-Boltzmann method (LBM) in two dimensional. Let $f_\alpha^s(\vec{r},t)$ be the one particle distribution function of species s with velocity $\vec{c}_\alpha$ at some dimensionless time t and dimensionless space $\vec{r}.s = \{1,2,3,4\}$ represent the cytoplasmic MinD, membrane-bound MinD, cytoplasmic MinE and membrane-bound MinE respectively. The Lattice Boltzmann equation for $f_\alpha^s(\vec{r},t)$ can be written as

$$f_\alpha^s(\vec{r}+\Delta t \vec{c}_\alpha, t+\Delta t) = f_\alpha^s(\vec{r},t) + \Omega_\alpha^s(\vec{r},t) \quad (5)$$

where Ω_α^s is the collision operator for species S and depends on the distribution function f_α^s. The collision operator Ω_α^s can be separated into two parts [12]. The first term is elastic collision function, which is taken to be of Boltzmann Bhatnagher-Gross-Krook (BGK) approximation with a single relaxation time τ_s. The second term is reactive collision, i.e,

$$\Omega_\alpha^s(\vec{r},t) = -\frac{1}{\tau}(f_\alpha^s(\vec{r},t) - f_\alpha^{(eq,s)}(\vec{r},t)) + \phi_\alpha^s \quad (6)$$

where the $f_\alpha^{(eq,s)}$ is equilibrium distribution. Here we use the simple equilibrium distribution function corresponding to a system with zero mean flow as follow:

$$f_\alpha^{(eq,s)} = \omega_\alpha^s \rho_s \quad (7)$$

where ω_α^s is weight function which depends on the lattice symmetry [13]. We can write

$$\omega_\alpha = \begin{cases} 4/9 & \alpha=0 \\ 1/9 & \alpha=1,2,3,4 \\ 1/36 & \alpha=5,6,7,8 \end{cases} \quad (8)$$

The density of particle species s denote by ρ_s. For the reactive term ϕ_s, we use the simple isotropic form

$$\phi_s = \omega_\alpha^s R_s \quad (9)$$

The term R_s is non-linear reaction term and depends on the density of reacting species. By using the Chapmann-Enskog expansion, we get

$$\frac{\partial \rho_s}{\partial t} - \frac{1}{3}(\tau_s - \frac{1}{2})\nabla^2 \rho_s = R_s \quad (10)$$

We compare the Eq.(10) with the RDE equations therefore the relation between diffusion coefficient and relaxation time τ_s is

$$D_s = \frac{1}{3}(\tau_s - \frac{1}{2}) \quad (11)$$

The simulation process consists of two steps that are collision and streaming.

Collision step:

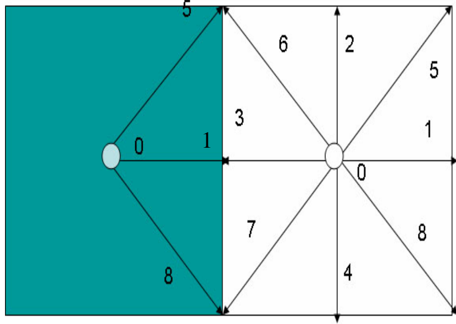
$$f_\alpha^{s,*}(\vec{r},t) = f_\alpha^s(\vec{r},t) - \frac{1}{\tau}(f_\alpha^s(\vec{r},t) - f_\alpha^{(eq,s)}(\vec{r},t)) + \omega_\alpha^s R_s$$

Streaming Step:

$$f_\alpha^s(\vec{r}+\vec{c}_\alpha, t) = f_\alpha^{s,*}(\vec{r},t)$$

Since the bounce-back boundary condition is suitable for high speed flow such as hydrodynamic system while the mirror-image boundary is good for low speed flow such as diffusion system. Therefore, we use the mirror-image boundary method for our simulation. The mirror-image boundary method suggested by Zhang *et al* [14]. For example shown in Figure1, the pro-collision and pre-streaming distribution function at the imaginary node I are

$$\begin{aligned} f_1(I,t) &= f_3(B,t) \\ f_5(I,t) &= f_6(B,t) \\ f_8(I,t) &= f_7(B,t) \end{aligned} \quad (12)$$



Imaginary node(I) Boundary node(B)

Figure 1. The mirror-image method

4.Numerical results and Discussion

We implemented the Lattice Boltzmann Method for RDE equations on PC using C programming. In the simulation, we use the same parameters given by Howard et al. We simulate the two-dimensional model. The parameters necessary for simulating this problem given by Howard are

$D_D = 0.28\mu m^2/s,\ D_E = 0.6\mu m^2/s,\ D_d = D_e = 0\mu m^2/s,\ \sigma_1 = 20s^{-1},$

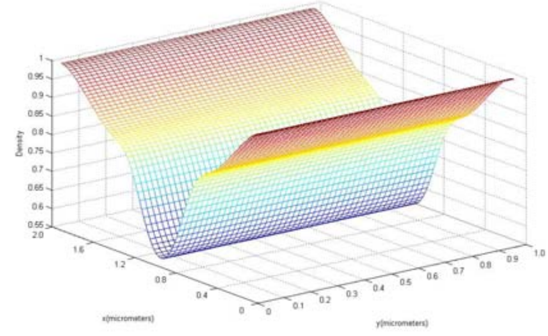
$\sigma_1' = 0.028\ \mu m, \sigma_1 = 0.0063\mu m/s,\ \sigma_2 = 0.04\mu m/s,\ \sigma_4 = 0.8s^{-1},\ \sigma_4' = 0.8\ \mu m$

But the LBM algorithm need every parameters to be dimensionless, we transform the original values of parameters by

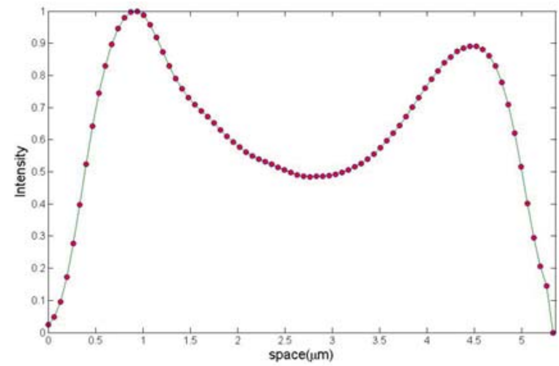
$n = \rho/\rho_0,\ \tilde{D}_D = D_D\delta t/\delta r^2,\ \tilde{D}_E = D_E\delta t/\delta r^2,\ \tilde{\sigma}_1 = \sigma_1\delta t$

$\tilde{\sigma}_1' = \sigma_1'\rho_0\ \ \tilde{\sigma}_2 = \sigma_2\rho_0\delta t \tilde{\sigma}_3 = \sigma_3\rho_0\delta t,\ \tilde{\sigma}_4 = \sigma_4\delta t,\ \tilde{\sigma}_4' = \sigma_4'\rho_0$

Where δt, δr and ρ_0, respectively, the time step, grid spacing and the unit of concentration, here we set $\rho_0 = 1/\mu m.$. The relaxation time τ_s is calculated by equation (11). The initial number of MinD and MinE is randomly initialized as 3000 for ρ_D, 170 for ρ_E and 0 for ρ_d and ρ_e Each simulation takes iterations until 10000 second of the time division of the bacterium. However, we wait some time for them to relax to the oscillation regime (about 500-1000 second). We therefore, throw away the transient and retain the data from that time step mark on. We allow the proteins diffuse in x- and y-axis and assume that the diffusion coefficients are isotropic. We can write the two-dimensional reaction-diffusion equations for the model of Howard et al., For the case of two-dimensional cell division, we used 50x100 grids to simulate the bacterium size 1x2 micron. The LMB scheme is D2Q9. We choose discrete space steps $\delta_x = \delta_y = 2 \text{ x } 10^{-2}\mu m$ and time step $\delta t = 4 \text{ x } 10^{-4}$ second. We set the unit for concentration $\rho_0 = 1/\mu m^2$, in this case.

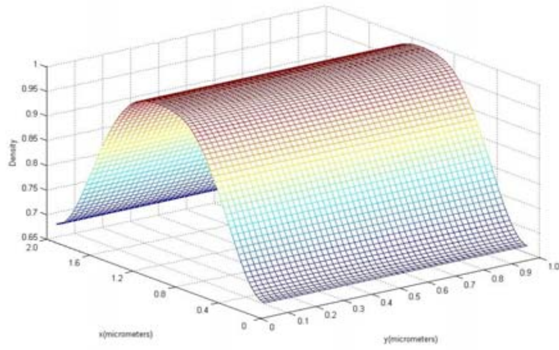


(a)

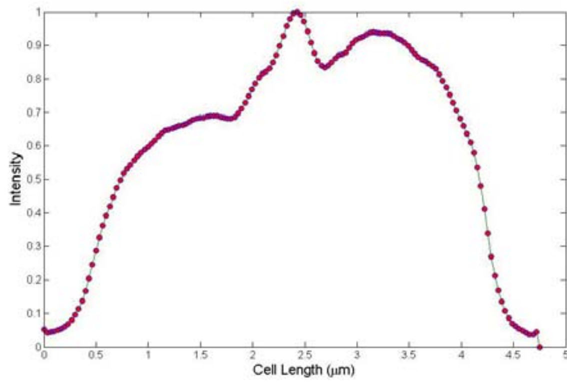


(b)

Figure2. The time average density (a) and the intensity of MinD along the *E. coli* cell.



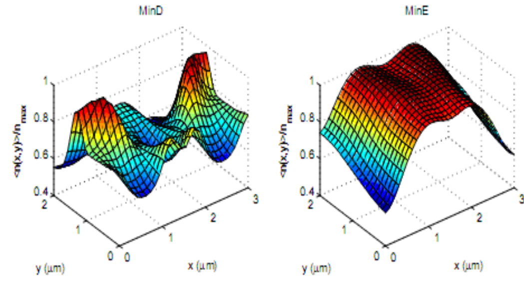
(a)



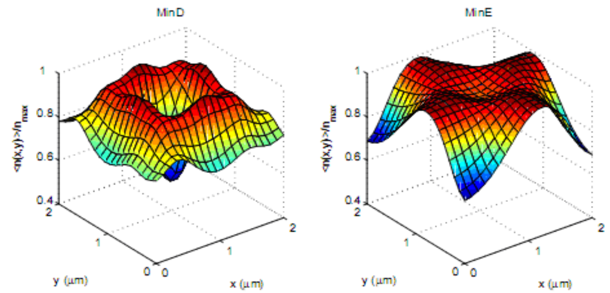
(b)

Figure3. The time average density (a) and the intensity of MinE along the *E. coli* cell.

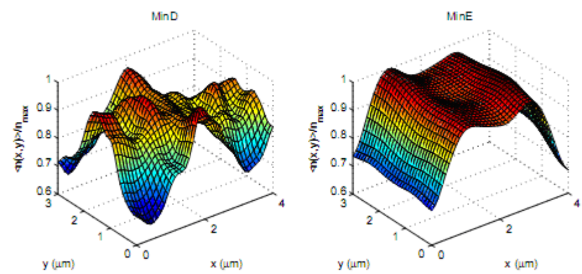
We consider two-dimensional system. We plot the time average of concentration of MinD and MinE in Figure(2a) and Figure(3a). The experimental intensity of two proteins are plotted in Fig (2b) and Fig(3b). The average concentration of MinD is minima at midcell site. It agrees with the experimental intensity. In the opposite situation, the average concentration of MinE is maxima at midcell site that also with experimental intensity.



(a)



(b)



(c)

Figure 8. The time average MinD (left) and MinE (right) densities $n(x,y)/n_{\max}$, relative to their respective time-average maxima, as a function of two-dimensional position $r=(x,y)$ along the bacterium. The bacterial shape is 2 x 3 μm (Fig a), 2 x 2 μm (Fig b) and 3x4 μm (Fig c).

We try to simulate the Mins proteins oscillation of several shape of bacterial as shown in Figure 8. According to computational effort, to use small number of grids, we choose discrete space steps $\delta_x = \delta_y = 1 \text{ x } 10^{-1} \mu m$ and time step $\delta t = 1 \text{ x } 10^{-2} s$. The results show that for the dimension $1 \text{ x } 2\ \mu m$ the oscillatory pattern is the most consistent with the experimental results. They also suggested that as the dimension approaches square the oscillatory pattern does no longer represent the cell division of the normal *E. coli.*

5. Conclustion

We have proposed LBM approach to investigate the dynamic pole-to-pole oscillations of Min proteins in two dimension used to determine the middle of bacterial cell division. We have developed a numerical scheme based on the LBM to simulate the RDE model. It is found that the agreement between the experimental and numerical results were found. Those are such as the intensity of MinD and MinE as observed in experiment. In addition, investigating the possible evolutionary connection between shape and cell division of *E. coli* was done. The LBM technique provides an alternative fast computational tool to study Min proteins oscillation and is useful scheme for simulating at the cellular level those biological system governed by the reaction-diffusion equations. In future work, we will apply the LBM to complicated reaction diffusion for Min proteins oscillation.

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7.References

1. Woldringh C.L, Mulder E, Huls P.G and Vischer N.,1991. Toporegulation of bacteria division according to the nucleiod occlusion model.Res.Microbiol. Vol.142, 309-320(1991).
2. De Boer P.A.J and Crossley R.E.,1989. A division inhibitor and a topological specificity factor coded for by the minicell locus determine proper placement of the division septum in E.coli. Cell ,Vol.56, pp 614-649.
3. Lutkenhaus J., 2002. Dynamics proteins in bacteria. Curr.Opin Microbiol ,Vol.5, pp548-552.
4. Bi E and Lutkenhaus J.,1993. Cell division inhibitors SulA and MinCD prevent formation of FtsZ ring. J.Bacteria, Vol.175, pp118-1125.
5. Hu Z, Mukherjee A and Lutkenhaus J.,1999. The MinC component of the division site selection system in E.coli interacts with FtsZ to prevent polymerization. Proc.Natl.Acad.Sci USA. Vol.96, pp14819-14824.
6. Raskin D.M and De Boer P.A.J,1999. Rapid pole-to-pole oscillation of a protein required for directing to the middle of *E.coli*, Proc. Natl. Acad. Sci, USA. Vol. 96,4971-4976.
7. Howard M, Rutenberg and De Vet S.,2001 Dynamic Compartmentalization of Bacteria: Accurate Division in E.coli. Physical Review Letters, Vol.87:27 , pp 278102.
8. Meinhardt H and De Boer P.A.J, Pattern formation in *Escheria coli*: A model for

   the pole-to-pole oscillations of Min proteins and the localization of the division site, Proc. Natl. Acad. Sci, USA, 98:25,14202-14207(2001).
9. Kruse K., 2002.A Dynamics Model for Determining the Middle of *E. coli*. Biophys. J, Vol. 82, pp 618-627.
10. Ngamsaad W, Triampo W, Kanthan P, Tang I.M.Nattavut N and Modchang C., 2005. A Lattice Boltzmann for modeling the dynamic pole-to-pole oscillation of Min proteins for determining the position of the midcell division plane. Journal of the Korean Physical Society, Vol. 46:4, pp 1025-1030.
11. Huang K.C, Meir Y and Wingreen N.S., 2003.Dynamic structures in *E.coli*: Spontaneous formation of MinE rings and MinD polar zones. Proc. Natl. Acad. Sci USA, Vol.100(22), pp 12724-12728.
12. Dawson S.P., Chen S. and Doolen G.D., 1993.Lattice Boltzmann computations for reaction-diffusion equations. J. Chem. Phys. Vol. 98, pp 1514-1523.
13. Blaak R and Sloot P.M.,2000. Lattice dependence of reaction-diffusion in lattice Boltzmann modeling. Comp. Phys. Comm.Vol. 129, pp 256-266.
14. Zhang X., Crawford J. W., Bengough A.G. and Young I. M., On boundary conditions in the lattice Boltzmann model for advection and anisotropic dispersion equation, Adv. Water Resour. 25, 601-609(2002).