Stochastic modeling of the effect of an external electric field on the Min protein Dynamics in *E. coli*

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Abstract

Cell division in *Escherichia coli* and other rod-shaped bacteria depends on the precise placement of a division septum at the cell center. The MinCDE system consisting of three proteins: MinC, MinD, and MinE, controls accurate cell division at the center of the cell through pole-to-pole oscillation. With some simplifying assumptions and relying on our deterministic model, we present a one-dimensional stochastic model describing effects of an external electric field to the MinCDE system. Computer simulations were performed to investigate the response of the oscillatory dynamics to various strength of the electric field and the total number of Min proteins. Providing a strong enough electric field, it has been found, is capable of interfering with the MinCDE dynamics as a consequence of the possible change in the division process. Interestingly, it was found that the effects of an electric field do not depend on the total number of Min proteins. The noise involved has shifted the correct trend of Min proteins behavior. However, as a consequence of the robustness of the dynamics, the oscillatory pattern of the proteins still exists even though the number of Min proteins is relatively low. However, consideration of the correlations between the local and global minimum (maximum) of MinD (MinE) suggests that using high enough Min protein concentration would reduce the local minimum (maximum) effect, which is related to the probability of polar division in each single oscillator cycle.

Though the studied model is simple and neglects some complex mechanisms concerning protein oscillation in correlation with cell division, it is demonstrated to be good enough for positioning the dividing site. Therefore, with regards to this problem, more experimental and theoretical works are needed. Especially, more realistic model (of course more complicated model) development through deterministic and stochastic approaches is still very much in need. Lastly, it is to be mentioned that this study may be of significant importance in the development of new technological processes in the fields of agriculture, food and medicine.

1. Introduction

Cell division in *Escherichia coli* and other rod-shaped bacteria depends on the precise placement of a division septum at the cell center in order to ensure the equipartition of cytoplasmic components into the two daughter cells. It has been known that the dynamics of Min proteins, MinCDE, consisting of three proteins: MinC, MinD, and MinE, play a key role in determining the site of septal placement in *E. coli* (de Boer *et al*., 1989). Previous studies (Rothfield *et al*.,1999;Margolin,2001;Addinall *et al.*,2002) have shown that the earliest event in this process is the polymerization of the tubulin-like protein FtsZ at mid-cell into an annular structure called the Z-ring. In the absence of the Min system, Z-rings form at mid-cell as well as cell poles, resulting in the production of minicells (Akerlund et al.,1992). It has been shown that the three Min proteins must act in the certain way for cell dividing process to be achieved (de Boer et al.,1989).

MinC and MinD act in concert to form a nonspecific inhibitor of septation. MinC interacts with the division protein FtsZ to prevent formation of stable FtsZ ring marking the dividing site (Hu Z *et al*., 1999). In other words, MinC is an antagonist of FtsZ polymerization and a specific inhibitor of Z-ring formation (Hu *et al*.,1999; Hu and lutkanhaus,2000), while MinD plays a role is making MinC-mediated division inhibition sensitive to suppression by MinE (de Boer *et al*.,1992). Because MinC binds to MinD, the movement of MinC from pole to pole with relatively long polar dwell times and a short transit time blocks the formation of polar Z-rings but not medial rings (Meinhardt and de Boer, 2001; Margolin,2001). Therefore, the ATPase activity of MinD is presumed to provide the driving force for the pole-to-pole oscillation of the MinC division inhibitor.

The MinCD division inhibitor lacks site specificity, as evidenced by the observation that expression of MinC and MinD in the absence of MinE leads to a block in septation at all potential division sites, leading to formation of long nonseptate filaments. Filamentation is suppressed by MinE, which acts as a topological specificity factor to prevent the division inhibitor from acting at the midcell site while permitting it to block septation at polar division sites. Consistent with the ability of MinE to specifically counteract the division inhibitor at midcell, a MinE-green fluorescent protein (MinE-GFP) localizes to a ring-like structure at sites adjacent to the midcell, and this localization pattern requires the simultaneous expression of MinD (Raskin and de Boer, 1997). MinD is required to localize MinE at midcell (Raskin and de Boer,1997). It was shown in a related study that MinD localizes to the cell pole in a MinE-dependent fashion and undergoes a rapid oscillation from pole to pole (Raskin and de Boer 1999).

The necessity for quantitative modeling and simulations is especially compelling when the process of interest displays spatiotemporal pattern formation, such as the oscillations of the Min proteins. Several studies have been made with different reaction-diffusion models to explain these oscillations (Meinhardt and de Boer, 2001; Howard *et al*., 2001; Kruse, 2002; Howard and Rutenberg, 2003; Huang 2003, Modchang *et al*., 2005). It has also recently emerged that MinD forms helical filaments in living cells (Shih, 2003); recent mathematical models (Drew *et al.,* 2005; Meacci and Kruse, 2005; Pavin *et al*., 2005) have attempted to include this feature. The model by Drew et al. (Drew *et al*., 2005) includes polymer growth from nucleation sites at the ends of the cell. Both of these models use continuous partial differential equations. The model by Pavin *et al.* (Pavin *et al.*, 2005) differs in that it is a three-dimensional stochastic model, but it does not exhibit the observed large scale helical filaments. Incorporating stochastic feature introduced into Min modeling is nevertheless likely to be important for systems of this type (Howard and Rutenberg, 2003, Tostevin and Howard, 2006, Fange and Elf, 2006, Pavin *et al.*, 2006, Kerr *et al*., 2006).

Given the significance of the protein oscillation in correlation with the cell division, another interesting question may be asked: how the abnormal or unsuccessful cell division is affected by the abnormal protein oscillation? More specifically, under externally perturbation of stresses such as pH, heat, electric field, or magnetic field, how does each perturbation or combined perturbation affect protein oscillation in correlation with the cell division? Focusing on the effect of electric field is the central issue of this research work. Because the protein is typically charged, it thus could interact with the electric field (Simonson**,** 2003). For Min protein, MinCDE, they are membrane-bound and are diffusive in the cytoplasm and on the membrane. We believe that a high enough field could effect the dynamic movement of these proteins assuming that the cell survives. However, the motion mode and spatial distribution of these electric charged proteins may be greatly effected by this external electric field perturbation.

Motivated in part by this debate, in this study the effect of constant electric fields on MinCDE protein dynamics in *E. coli* has been examined. We present a simple one-dimensional stochastic model that may predict the experimental observations of the Min oscillations in the near future. The stochastic modeling approach is used in order to take into account the fluctuations or noises. With this approach, it will allow us to understand how the intrinsic chemical fluctuations in spatially extended systems can cause different properties than what would be described by a mean-field model or deterministic counterpart. The noise or fluctuation in non-homogeneous systems has, for instance, been shown to create new steady states (Togashi and Kaneko, 2004), drive spatial oscillations (Howard

and Rutenberg, 2003), cause spatial phase separation of a bistable system (Elf and Ehrenberg, 2004), or drive the irregular relocation dynamics of Soj protein in *Bacillus subtilis* (Doubrovinski and Howard, 2005). Random fluctuations in genetic networks are inevitable as chemical reactions are probabilistic and many genes, RNAs and proteins are present in low numbers per cell (Paulson , 2004).

In this paper, the relative concentrations of MinD and MinE are to be reported as functions of space and time. For each Min protein species considered, the characteristic model parameters, field strength J, and the number of Min proteins, are varied and comparatively interpreted. The highlighting aim of this study is to enhance the understanding of protein dynamic phenomena related to different intensity of electric treatments under various conditions. Here, we have tested the hypothesis that a direct current (dc) electric field may be one other extrinsic factor that can perturb cell division via protein oscillation. In addition, it has been reported that dc electric fields are able to induce directional responses such as cell migration (galvanotaxis/electrotaxis) and cell division in many cell types (Robinson, 1985; Song *et al*., 2002; Wang *et al.,* 2000; Zhao *et al*., 1999). We attempt to find out whether small dc physiological electric field can change the protein dynamic oscillation in *E. coli* cell division by using a computational stochastic modeling as a tool.

The discoveries and conclusions of this study may be of significant importance in the development of new technological processes in the fields of agriculture and food science, particularly fermenting process controls and eliminating the undesirable pathogenic microorganisms. Electric and electromagnetic treatments are among the many food preparation processes and /or conservation techniques used in recent years [Pathak *et al*., 2003, Espachs-Barroso *et al*., , 2003, Giner *et al*., 2003, Martin *et al*., 2003). The main objective of such treatments is to reduce or eliminate part of the often-undesirable microorganisms present.

Recently in cancer research, low-intensity, intermediate-frequency, alternating electric fields, delivered by means of insulated electrodes, have been found to have a profound inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines. These findings demonstrate the potential applicability of the described electric fields as a novel therapeutic modality for malignant tumors (Kirson *et al*., 2004, Hernandez-Bule *et al*., 2007, Janigro *et al*., 2006, Cucullo *et al*., 2005).

2. Model rationale of protein oscillatory perturbation under an external electric field

It has been known that studies of the response of living systems to uniform physical fields (i.e., electric, gravitational, and magnetic) are capable of yielding novel insight into a variety of biological processes(Denegre *et al*., 1998; Gerhart *et al*., 1989; Helmstetter, 1997.; Henderson *et al.*, 1998.; Valles, 2002; Yokota *et al*., 1992.; Zhao *et al.*, 1999). Particularly, the direct current electric fields are able to induce directional responses such as cell division in many cell types (Robinson, 1985; Song *et al*., 2002; Zhao *et al*., 1999). For example, Zhao *et al*. (1999) showed that the application of static electric fields to dividing human corneal epithelial cells causes the division planes to orient(Kirson *et* ., 2004).

Electrical phenomena govern many biological processes from molecular binding interactions to intercellular communication. Endogenous or exogenous perturbations of small extracellular electric fields have been observed to affect cellular processes, and several different mechanisms for these effects have been proposed (Weaver and Astumian, 1990). Diverse biological responses to electric fields continue to motivate experimental searches for mechanisms of electromagnetic interactions with cells. It has been shown that development (Jaffe, 1979), regeneration (Borgens *et al*., 1981.; Borgens *et al*., 1977; Jaffe and M-m., 1979.), and repair (Kenner *et al*., 1975.) are all effected by electric fields and that many other basic cellular functions including motility (Cooper and Keller, 1984.; Cooper and Schliwa, 1985.; Luther *et al.*, 1983) and receptor regulation (Young and M-m, 1983.) are modulated by applied external electric fields. In addition, cell membrane permeabilization and fusion are effected by applied fields (Knight and F, 1982. ; Tessie *et al*., 1982.; Zimmermann and Vienken.J, 1982.). Local perturbation of plasma membrane potentials provides a hypothetical mechanism of interaction of applied electric fields with cells. Electric fields of high strength applied as short time pulses (microsecond) to aqueous suspensions of living cells have remarkable effects on the cell membranes or even kill the organisms.

Electric fields can be applied to cell suspensions by the use of capacitor discharges as a part of a high voltage circuit (Hilsheger and Niemann, 1980; Sale and Hamilton, 1967). Some investigators have observed that sinusoidal electric fields alter fundamental cellular functions (Goodman et al., 1983); such studies have led to concern about potential biological hazards from exposure to environmental sinusoidal fields. Most of the proposed coupling mechanisms are the subject of substantial debate. The possibility of applying low-intensity electricity has been studied because of its

effects on viable microbial interactions (Bawcom *et al*., 1995; Rajnicek *et al*., 1994). In order to study the effects of a high-voltage electric current application (intensity > 25 kW cm $^{-1}$) on microorganisms, experiments were carried out on different yeasts and bacterial species (Palaniappan *et al.*, 1990). In other experiments, the same authors (Palaniappan *et al*., 1992) demonstrated that there was a notable reduction in the viability of bacterial cultures, indicating that this was due to chemical reactions induced by electric treatment. From the above mentioned reports, it can be seen that the behavior of a single cell or cell clusters in an external electric field may not be yet thoroughly understood. Moreover, to the best of our knowledge, no study has been performed to assess the effects of the electric field on the protein oscillatory dynamics of the cell, either theoretically or experimentally.

It is hypothesized that *E. coli*'s cell membrane may act as a "shield" or "absorber" to the cytoplasmic organelles including cytoplasmic and membrane bound Min proteins. It is possible that the field will eventually penetrate the membrane and interact with those interior components of the cell and consequently generate the electric force on charged objects including Min proteins. It is important to note that, if the field is too strong, the cell membrane may be damaged possibly resultint in cell death or abnormality (Bowcom, 1995; Zimmermann, 1974; Zimmermann, 1976; Zimmermann, 1982).

Another possibility is due to the generation of induced secondary field. High enough field strength could polarize or redistribute the somewhat mobile charges. With this induced polarization, it is possible to generate the secondary field inside the *E. coli* in the direction parallel but opposite to the direction of a primary applied field. This is based on the consideration that the cell membrane is a dielectric material as shown in **Figure 1**. It has been shown previously that these membrane dielectric properties are highly characteristic of, and rapidly affected by, alterations in physiological activities and induction of pathologic states in cells (Huang *et al*.,1992;Gascoyne *et al*., 1993; Gascoyne *et al*., 1994; Ginsa *et al*., 1991; Huang *et al*., 1996; Huang *et al*., 1999; Yang *et al*., 1999). Such differences can be not only used for cell characterization, but also exploited for selective cell manipulation, separation and sorting (Gascoyne., 1997; Pethig and Markx, 1997; Yang *et al.*, 1999; Yang *et al*., 2000). This situation is, in fact, very complicated and highly dependent on the electrolytic conditions. It is known that even in the absence of an external electric field, particles exposed to an ion cloud become charged. Ions will collide with the particle due to their thermal motions. As the particle becomes charged, it will repel ions of the same sign and leads to a nonhomogenous distribution of ions in its neighborhood. This phenomena can be viewed as nonlinear feedback. However, here our first step model will assume that this effect is somewhat negligible as far as the protein oscillatory behavior is concerned.

3. Possible experiments using fluorescent microscopy together with single particle tracking (SPT) technique

In the past decade, two important technological innovations have contributed to reshaping molecular biology research. The first was the development of fluorescent proteins that allow researchers to selectively label single proteins. The second is high-resolution fluorescence imaging that is made possible by the new generation of bright-field and confocal microscopes (Pierce *et al.*, 1997; Endow, 2001; Kain and Kitts, 1997). Because of new tools, biologists are able to study molecular dynamics within the living cell at sub-micron resolutions. They can record time-lapse series to study molecular transport or conformal changes within the cell. While these methods offer an enormous potential for increasing our understanding of biology, they also constitute a challenge for researchers in the field who have not yet devised efficient ways to exploit and quantitatively interpret this unprecedented flow of data. Currently, the large majority of data analysis and feature extraction is done manually, which is very time consuming, so that image processing technique have been developing to solve this problem.

Adopting the above mentioned techniques, a number of previous studies of Min protein oscillations focuses on the spatial-temporal pattern formation and the biochemical basis function (Rothfield *et al.*, 2005; Shih *et al*., 2002.). However, the experimental data of spatial-temporal pattern formation has been poorly interpreted for quantitative study. To cope with this drawback, here for the first time ever, we apply the Single Particle Tracking (SPT) technique (Saxton and Jacobson, 1997; Qian,1991) to explore the dynamics of GFP-MinD protein as the indicator of MinD dynamics. The analysis does not only concentrate on the ensemble positions of GFP:MinD, but also on the dynamics and localization via the ensemble positions. Data analysis is performed to provide the qualitative and quantitative interpretation is turn of the behavior of MinD oscillation. To the best of our knowledge, this SPT method has not yet been used for this specific protein problem. All previous quantitative results of the MinD dynamics were mostly obtained by either experimental approach via other techniques or modeling and simulations (Rothfield *et al*., 2005; Shih *et al*., 2002., Meinhardt and de Boer, 2001; Howard *et al*., 2001; Kruse, 2002; Howard and Rutenberg, 2003; Huang 2003).

Here we will briefly describe how one may use SPT technique to experimentally investigate the focused problem, namely the effect of an electric field on the Min protein oscillation. However, since works are still on going, we here present the framework for the case in the absence of the field.

Briefly, SPT technique is the method or an image processing technique used to follow the spot – like particle in the fluorescence image under the intensity of fluorescence signal. The data from SPT measurement generally yield a key characteristic of a cell membrane or membrane-bound proteins. It is not only a probe of membrane microstructure but it also has major influence upon reaction kinetics within the cell membrane. Therefore, the SPT technique has been used in a large field of biophysical research to measure the trajectory of individual proteins or lipids in the cell membrane, such as plasma and nuclear membrane (Saxton and Jacobson, 1997), nuclear trafficking of Viral Genes (Babcock *et al.*, 2004), chromosome dynamics (Sage *et al.*, 2005), and bacterial actins motion (Kim *et al.*, 2006). To demonstrate the idea of how one can perform the experiment to support our theoretical predictions (at least in principle), here the materials and experimental procedure are briefly described as follow.

In the experiment, *E. coli* RC1/pFX9 [Δ*min*/P_{lac}-*gfp::ΔminD ΔminE*] was used. For examination of MinD labeled with green fluorescent proteins (GFP), a starter of RC1/pFx9 cells were grown in the optimal condition media until the OD_{600nm} is approximately 0.4 (log phase). The centrifugation was performed to collect the cells. Finally, the sample will be treated with isopropyl-β-D-thiogalactopyranoside (IPTG) for protein induction, diluted with a media before use. In our experiment, the 5-7 μl of each *E. coli* sample was dropped in a glass slide coated with Poly-L-lysine then covered with a coverslip at room temperature before examination. After that fluorescence microscopy were used with an InVivo software to obtain fluorescence image sequence. In this process, a charge-coupled device (CCD) camera was attached to the video port of microscope to acquire images and movies. After the images are obtained, the SPT technique is used to follow the region of interest (ROI) which consists of the highest GFP:MinD concentration signal. The collected data in SPT measurement are supported by SpotTracker Java plugin of public domain ImageJ software. Typically, the acquired images are in the configuration of fluorescence signal that could have faded after about 4-5 minutes have passed and subsequently the final image sequence is noisy. Hence, to improve the quality of the acquired images, we used the software's function called Gaussian filter to reduce the noise. The improved images are further enhanced by using the rescaling option of SpotTracker plugin. Lastly, the tracking of ROI with SpotTracker plugin was performed to collect the positions at given times in text file (Sage *et al*., 2005). The positions of ensemble were then analyzed by MATLAB software. In this work, the focus is on the dynamics and localization patterns of MinD protein in quantitative manner. The summary of the procedure is shown in the **Figure 2**.

From the data without the field exposure, the ensemble GFP:MinD oscillations from pole to pole with the approximately 45 seconds of period was shown in **Fig.3(B)**, the 2D image sequence of pole-to-pole MinD oscillations at each successive time for the rescaled and enhanced signal is shown.

Each fluorescence image represents the ensemble of GFP:MinD signal locating at polar zones. The time(s) labeled on the left side of the column is the first time at which GFP:MinD assembles after switching to the new pole. The sequence of positions (x,y) at successive times can be used to determine the trajectory of GFP-MinD in x and y components as shown in **Figure 3 (C)** and (**D**), respectively.

To sum up, with the described technique the protein oscillatory dynamics can be studied. Though the case study of the protein oscillation under an electric field treatment has not been carried ort experimentally, with the modification and optimization, it is believed to be accomplished in the future. It is worth noting that things must be done with special care because of many possible problems including the noise, frame-shift, and optimal electric field strength. We believe that this particular research problem will open up very rich areas of future research and investigations in various aspects.

4. A Stochastic Model

Here, we present a simple one-dimensional stochastic model which predicts Min proteins oscillations in *E. coli*. Based on our deterministic model at the mean-field level (Modchang *et al.*, 2005.) , the dynamics of these Min proteins in the presence of an external field, are described by

$$\frac{\partial \rho_D}{\partial t} = D_D \frac{\partial^2 \rho_D}{\partial x^2} + J_D \frac{\partial \rho_D}{\partial x} - \frac{\sigma_1 \rho_D}{1+\sigma_1' \rho_e} + \sigma_2 \rho_e \rho_d \ , \tag{1}$$

$$\frac{\partial \rho_d}{\partial t} = D_d \frac{\partial^2 \rho_d}{\partial x^2} + J_d \frac{\partial \rho_d}{\partial x} + \frac{\sigma_1 \rho_D}{1+\sigma_1' \rho_e} - \sigma_2 \rho_e \rho_d \,, \tag{2}$$

$$\frac{\partial \rho_E}{\partial t} = D_E \frac{\partial^2 \rho_E}{\partial x^2} + J_E \frac{\partial \rho_E}{\partial x} - \sigma_3 \rho_D \rho_E + \frac{\sigma_4 \rho_e}{1+\sigma_4' \rho_D} \,, \tag{3}$$

and

$$\frac{\partial \rho_e}{\partial t} = D_e \frac{\partial^2 \rho_e}{\partial x^2} + J_e \frac{\partial \rho_e}{\partial x} + \sigma_3 \rho_D \rho_E - \frac{\sigma_4 \rho_e}{1+\sigma_4' \rho_D} \tag{4}$$

where ρ_D and ρ_E are the concentrations of the MinD and the MinE proteins in the cytoplasm, respectively, and ρ_d and ρ_e are the concentrations of the MinD and the MinE proteins on the cytoplasmic membrane, respectively. The first equation describes the time rate of change of the

concentration of MinD (ρ_D) in the cytoplasm. The second is for the change in the MinD concentration (ρ_d) on the cytoplasmic membrane. The third is for the change of the concentration of MinE (ρ_E) in the cytoplasm. The last one is for the change in the MinE concentration (ρ_e) on the cytoplasmic membrane. The constant σ_1 represents the spontaneous association of MinD to the membrane wall (Rowland *et al*., 2000), whereas the constant σ_2 describes ejection of MinD from the cell membrane by membrane-bound MinE. Similarly, the constant σ_4 represents the spontaneous membrane dissociation of MinE, whereas the constant σ_3 describes the recruitment of cytoplasmic MinE to the membrane by cytoplasmic MinD (Huang *et al.*, 1996). The constant σ_1' corresponds to the membrane-bound MinE suppression of the binding of MinD to the membrane, and σ_4' corresponds to the cytoplasmic MinD suppression of the release of the membrane-bound MinE. Since the experimental results given in the work of Raskin and de Boer (1999) show that the MinC dynamics simply follows that of the MinD protein, so, for the sake of simplicity, consideration of the MinC dynamics is omitted. In this model , we adopted the dynamic model of compartmentization in the bacterial cell division process proposed by Howard and Rutenberg (2003) (as schematically summarized in **Figure 4**) by adding an extra term that depends on the external electric field.

To investigate how the intrinsic chemical fluctuations in spatially extended systems can give rise to properties radically different from what would be described by a mean-field model in the Min systems, we modify our deterministic model to a discrete particle model, where the Min protein molecule is represented as a particle and may hop between lattices. The number of protein molecules at site k is n_i^k, with $i=\{D,d,E,e\}$ representing cytoplasmic MinD, membrane-bounded MinD, cytoplasmic MinE, and membrane- bounded MinE, respectively. Here, the dynamics of Min system is a reaction-diffusion system consisting of two processes. The first one is the diffusion process that describes diffusion of the Min proteins. At the molecular level the diffusion process often results in a net flow of chemical species from regions of higher concentration to regions of lower concentration. The second one is the reaction process that describes self-organization of biological systems.

For the diffusion process, in the absence of external electric field, at each time step Δt, these particles have an equal probability $D_i\Delta t/(\Delta x)^2$ to hop to one of its neighboring sites with lattice space Δx and time step Δt. When the external electric field is present, the probabilities for a particle to hop to the left neighboring site or to the right neighboring site are no longer equal, but, in this case, they become

$$P_L = \frac{D_i \Delta t}{(\Delta x)^2}\left(0.5 + \frac{J_i \Delta t}{2\Delta x}\right);\ P_R = \frac{D_i \Delta t}{(\Delta x)^2}\left(0.5 - \frac{J_i \Delta t}{2\Delta x}\right),$$

where P_L, and P_R are probabilities for a particle to hop to the left and right neighboring sites, respectively. J_i is an external field parameter. We assume that a chemical substance moving in the region of an external field will experience a force that is proportional to the external field parameter J_i. In general, $J_i = \mu_i E$, $i = \{D, d, E, e\}$, where E is the field strength and μ is the ionic mobility of the chemical substance, which is proportional to the diffusion coefficient and depends on the total amount of free charges in that substance.

For the reaction processes, at site k the following reactions may occur

		Probability:
$n_D^k \to n_D^k - 1,$	$n_d^k \to n_d^k + 1$	$P_{D\to d} = \sigma_1 \Delta t \Big/ \left(1 + \sigma_1' n_e^k\right),$
$n_D^k \to n_D^k + 1,$	$n_d^k \to n_d^k - 1$	$P_{d\to D} = \sigma_2 \Delta t\, n_e^k,$
$n_E^k \to n_E^k - 1,$	$n_e^k \to n_e^k + 1$	$P_{E\to e} = \sigma_3 \Delta t\, n_D^k,$
$n_E^k \to n_E^k + 1,$	$n_e^k \to n_e^k - 1$	$P_{e\to E} = \sigma_4 \Delta t \Big/ \left(1 + \sigma_4' n_D^k\right).$

The first (third) reaction indicates that each MinD (MinE) molecule at site k in the cytoplasm may bind to the cell membrane with equal probability $P_{D\to d}$ ($P_{E\to e}$) and the second (fourth) reaction indicates that each membrane-bound MinD (MinE) molecule at site k may be released to the cytoplasm with equal probability $P_{d\to D}$ ($P_{e\to E}$). These reactions are stochastic analogs of the reaction processes in our deterministic model (Modchang *et al*., 2005.). Since the protein synthesis can be blocked without affecting the protein oscillation (Raskin and de Boer, 1999), we do not include the protein synthesis or degradation in our model. We also assume that the total amount of MinD and MinE is conserved.

5. Simulations, conditions, and parameters

In our simulation, we use lattice spaces $\Delta x = 0.02\,\mu\text{m}$ and time steps $\Delta t = 2\times10^{-4}$ s. The length of the *E. coli* is taken to be $2\,\mu\text{m}$, there are 100 lattice sites covering the bacterium cell. We use $D_D = 0.28\,\mu\text{m}^2\text{s}^{-1}$, $D_d = 0.003\,\mu\text{m}^2\text{s}^{-1}$, $D_E = 0.6\,\mu\text{m}^2\text{s}^{-1}$, $D_e = 0.006\,\mu\text{m}^2\text{s}^{-1}$, $\sigma_1 = 20\ \text{s}^{-1}$ and $\sigma_4 = 0.8\ \text{s}^{-1}$ (Howard and Rutenberg, 2003; Howard *et al.*, 2001). To see how the effects of an external electric field on the oscillatory behaviors of Min proteins may change when the number of Min protein is changed, four representative parameter sets shown in Table 1 are used, where N is the total number of MinD which is equal to the total number of MinE. We use equal numbers of Min proteins because "wild type" oscillations are observed when both proteins are equally expressed on plasmids (Shih et al., 2002.).

To preserve the strength of the interaction between Min proteins when the total number of Min proteins is changed, the four parameters σ_1', σ_2, σ_3 and σ_4' are scaled as in Table 1. (Howard and Rutenberg, 2003).

Table 1. Scaled parameters used in the simulations

N	σ_1'	$\sigma_2(\text{s}^{-1})$	$\sigma_3(\text{s}^{-1})$	σ_4'
200	25.0	0.27	30.0	20.0
400	2.0	0.135	15.0	10.0
800	0.6	0.0675	7.5	5.0
1500	0.25	0.036	4.0	2.7

Since there are no experimental values of μ for either MinD and MinE, we assume that they have the same type of free charges and define a new parameter J such that

$$J_i = \mu_i E \equiv \frac{D_E J}{D_i},$$

where $i = \{D, d, E, e\}$. Initially, we assume that MinD and MinE are mainly at the opposite ends of the cell. The hard wall boundary conditions are imposed at both ends of the bacterium.

6. Results and discussions

Figure 5 shows space-time plots of the total $\left(n_D^k + n_d^k\right)$ MinD (above) and total $\left(n_E^k + n_e^k\right)$ MinE (below) concentration for $J = 0.0$ m/s to $J = 0.3$ m/s and (a) $N = 400$, (b) $N = 1500$. Clearly, in the absence of the field $J = 0.0$ m/s, the MinD and MinE are in good agreement with the experimental results. Namely, the MinE are more localized at midcell which then sweeps toward a cell pole, displacing the MinD to localize at the poles. Once the MinE cluster reaches the cell pole it disappears in the cytoplasm, only to reform at midcell where the process repeats, but in the other half of the cell. This process is repeated forever resulting in the Min proteins oscillations. When the external electric field is turned on $J \neq 0$, the oscillation patterns are no longer symmetric about the mid-cell. This is mainly because Min proteins themselves are charged macromolecules (MinD, molecular weight = 29,936.61D and charge: 4.5e; MinE, molecular weight = 10,416.08 D and charge: 0.5e. See www.eolproject.org:8080/). Hence, when protein molecules are in the electric field, they will be pushed in the direction of the fields (or opposite to the field direction, depending on its charges). In our simulation, we assume that MinD and MinE have the same type of charges which are consistent with the above data. As the external field parameter *J* increases from 0.0 m/s to 0.3 m/s, the period of the oscillation of both MinD and MinE increases from 100 s to 150 s. The periods measured from our systems are in good agreement with experiments, with periods from 30-120 s in the absence of the field. With respect to fluctuation driven instability, it is also found that in the case of a low N the stochastic fluctuated data could be very far off from the average behavior or those results obtained from the deterministic model. The noise involved has shifted the correct trend of Min proteins behavior. However, as a consequence of the robustness of the dynamics, the oscillatory pattern of the proteins still exists even though the number of min proteins is relatively low.

In **Figure 6**, the relative MinD and MinE concentrations as functions of *x* for *J* = 0.3 m/s with *N* = 400 and *N* = 1500 are shown. From their average lines, the minima of MinD and maxima of MinE are significantly shifted from the midcell ($x = 1$). It is also indicated by both **Figures 1 and 2** that, although both MinD and MinE are pushed in the same direction by the electric field, they tend to be more concentrated at the opposite ends when *J* is increased. A possible explanation is that this phenomenon arises because, in nature, MinD and MinE tend to repel each other, so that in the absence of an electric field, the location of the minimum of MinD is the location of the maximum of MinE. Moreover, although there is an electric force to push them in the same direction, this force cannot overcome the repelling forces between them. The fluctuations around the solid lines can be very large when *N* is small.

Figure 7 shows the relative concentration profiles of MinD (above) and MinE (below) as functions of position x along the bacterium length under the influence of an electric field with J = 0.3 m/s, at various total numbers of Min proteins. It indicateds that the position of the global minimum of MinD and a position of the global maximum of MinE do not change as the total number of Min proteins is changed. This implies that only J controls these global extremum positions. Moreover, the values of the global minimum relative concentrations of MinD protein appears to be lowered as N increases, while the global maximum of MinE protein concentration is higher. These demonstrate the significance of using fewer protein copies that could result in not only the degradation of the accuracy of the extremum, but also the central features. Of course the correlation between these minimum and maximum is constrained by the conservative law of the total number of the both Min protein copies, but fluctuation sets bounds on the concentration levels. These effects can also be discussed in the context of nucleoid occlusion (Yu, 1999) as follows. In the absence of the field, MinCDE system normally tends to prevent polar FtsZ rings, because the nucleoids will inhibit FtsZ rings elsewhere away from midcell. Considering the correlations between the local and global minimum (maximum) of MinD (MinE), it suggests that using high enough Min protein concentration would reduce the local minimum (maximum) effect, which is related to the probability of polar division in each single oscillator cycle. This leads us to believe that too low a concentration of Min proteins can result in an unacceptable probability of polar division. This may suggest that *E. coli* may be using the optimal number of Min proteins, trading off midpoint precision against the cost of protein synthesis [Howard 2003 PRL]. This activity of *E. coli* is believed to be even more subtle when the situation is more complicated including the presence of the electric field. .

Figure 8 shows relative concentrations of MinD (above) and MinE (below) as functions of position x along the bacterium length under the influence of an electric field for N = 1500. It is seen that, in the case of no external field (J = 0.0 m/s), the relative concentrations of MinD and MinE are symmetric about the midcell. MinD has a minimum at the midcell, whereas MinE has a maximum, which is in good agreement with that which was reported in a previous studies [Howard 2003]. When the external electric field is turned on, a shift in the minimum of MinD and maximum of MinE were once again observed to be J dependent. Both the positions of MinD concentration minimum and MinE concentration maximum are more pronouncedly shifted toward the left pole as J increases. It is noted that the minimum of MinD and the maximum of MinE are always shifted to the left pole. This difference arises because of the relative magnitudes of the forces acting on the two proteins. First of

all, there is an internal force between the MinD and the MinE proteins. This force causes MinE to repel MinD. In the absence of any other forces, this explains why the location of the maximum of MinE is the location of the minimum of MinD. When an external field is applied (as expressed by a non-zero value of *J*), then one must take into account the relative magnitudes of the two forces. These results are consistent, at least qualitatively, with those obtained with a deterministic partial differential model proposed by Modchang *et al.*(2005).

In **Figure 9** (a) and (b), we show the concentrations of the MinD and the MinE proteins at the left end grid and the right end grid versus time. In these figures, it is easy to see that when $J = 0.0$ m/s, the concentrations of MinD (or MinE) at the left end grid and the right end grid have the same patterns of oscillation with the same frequencies and amplitudes, but with a phase difference of 180º. When an external field is applied, the amplitudes of the oscillations at the two end grids are no longer equal. As *J* is increased, the amplitude of the oscillation at the left end grid of MinD is seen to decrease while those of the MinE increase.

6. Concluding remarks

We have used a stochastic model to study the effects of an external electric field and noise on the *E. coli* MinCDE system. Proper divisions of bacteria require accurate definition of the division site. This accurate identification of the division site is determined by the rapid pole-to-pole oscillations of MinCDE. The stochastic approach is motivated by previous studies of how the intrinsic chemical fluctuations in spatially extended systems can give rise to properties that are radically different from what would be described by a mean-field model. The model itself has been modified from that of Howard and Rutenberg (2003) together with that of Modchang *et al.*(2005).

We found that a strong enough external electric field can shift the MinD concentration minimum and MinE concentration maximum position from the mid-cell. Shifting from the mid-cell appears to depend on the strength of the electric field. We have also found evidence that the effects of an electric field may not depend on the total number of Min proteins in *E. coli.* The results from the use of this stochastic model are, at least qualitatively, consistent with that obtained by using our deterministic model (Modchang *et al*., 2005). With respect to the fluctuation driven instability, it was

also found that in the case of low N the stochastically fluctuated data could be very far off from the average behavior or those results from the use of a deterministic model. The noise involved has shifted the correct trend of Min proteins behavior. However, as a consequence of the robustness of the dynamics, the oscillatory pattern of the proteins still exists even though the number of Min proteins is relatively low. However, considering the correlations between the local and global minimum (maximum) of MinD (MinE), our result suggests that using high enough Min protein concentration would reduce the local minimum (maximum) effect, which is related to the probability of polar division in each single oscillator cycle. This leads us to believe that too low a concentration of Min proteins can result in an unacceptable probability of polar division.

Though the studied model is simple and neglects some complex mechanisms concerning protein oscillation in correlation with cell division, it was demonstrated to be good enough for positioning the dividing site. Therefore, with regards to this problem, more experimental and theoretical works are needed. More realistic model (which would of course be more complicated), either deterministic or stochastic, needs to be developed.

Lastly, it is to be mentioned that this study may be of significant importance in the development of new technological processes in the fields of agriculture, food and medicine. Moreover, with the correct link to other compartments like signal transduction or even at the level of system biology, we believe it will contribute greatly to the health and wellbeing of mankind of our communities.

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FIGURES

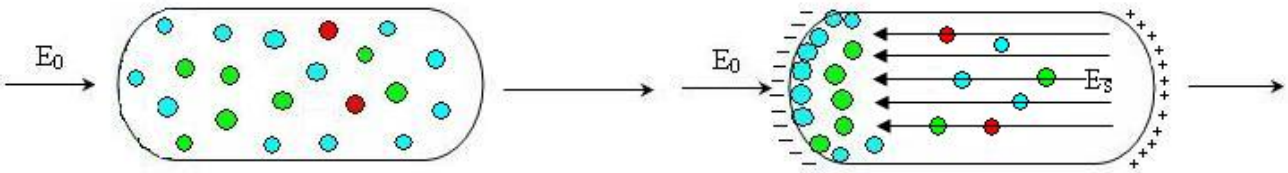

Figure 1. Dielectric like *E. coli* cell in a uniform field E_0, showing the polarization on the left and the polarization charge with its associated, opposing, electric field on the right.

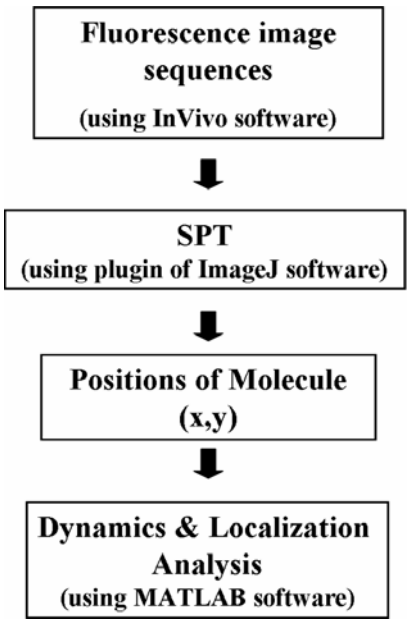

Figure 2: Fluorescence image analysis procedure.

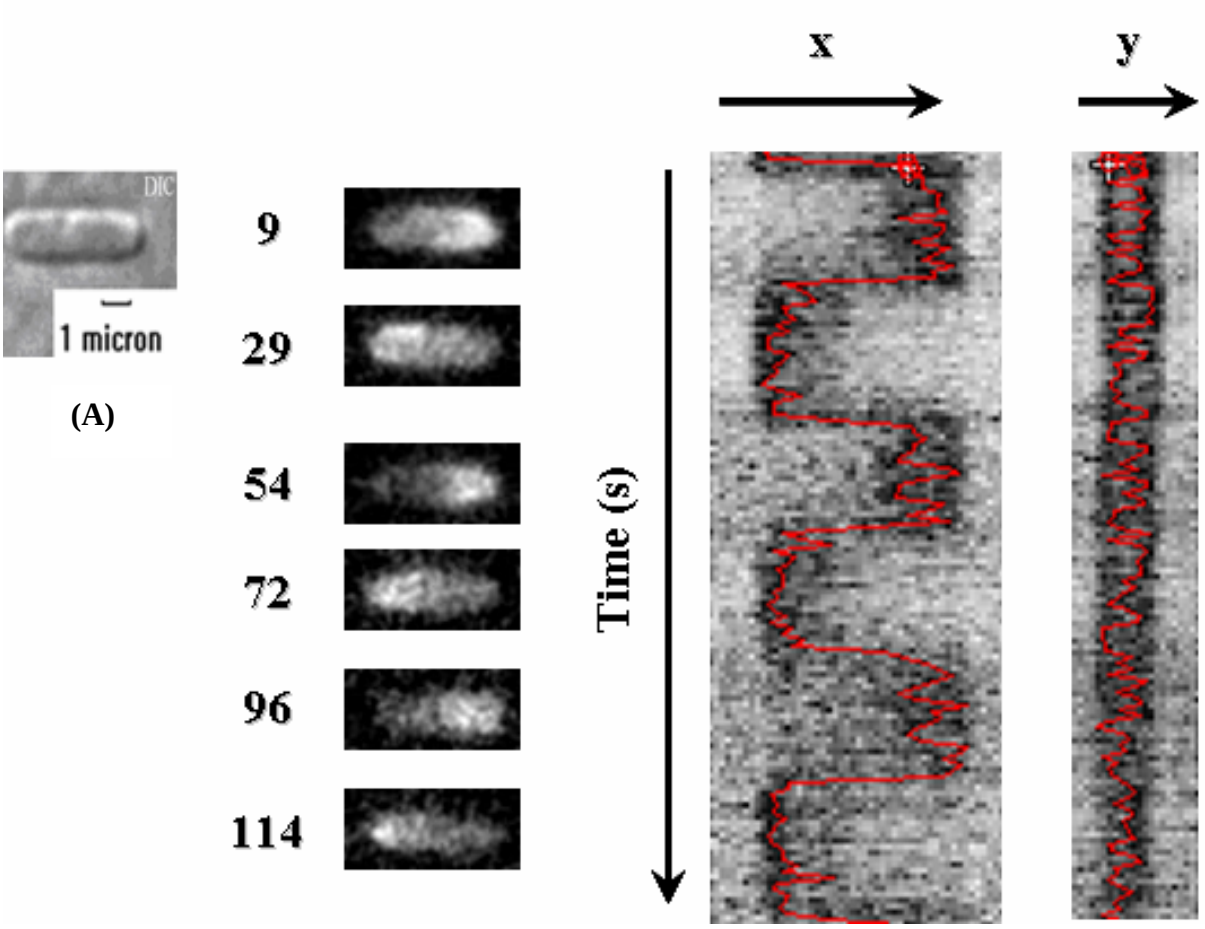

Fig.3: The GFP:MinD oscillations from pole to pole with the approximately 45 seconds of period. **(A)** The differential interference contrast (DIC) images showing cell length $\sim 4\ \mu m$. **(B)** The 2D image sequence of pole-to-pole MinD oscillations at each successive time. Each fluorescence image represents the ensemble of GFP:MinD signal locating at polar zones. The time(s) labeled on the left side of column is the first time of GFP:MinD assembles after switching to new pole. **(C)** The results of SPT show the GFP signal time evolution trajectory of MinD oscillations on the $x(t)$. The red line represents the ensemble of GFP:MinD trajectory. **(D)** Spot projection on $y(t)$ GFP signal time evolution trajectory of MinD oscillations.

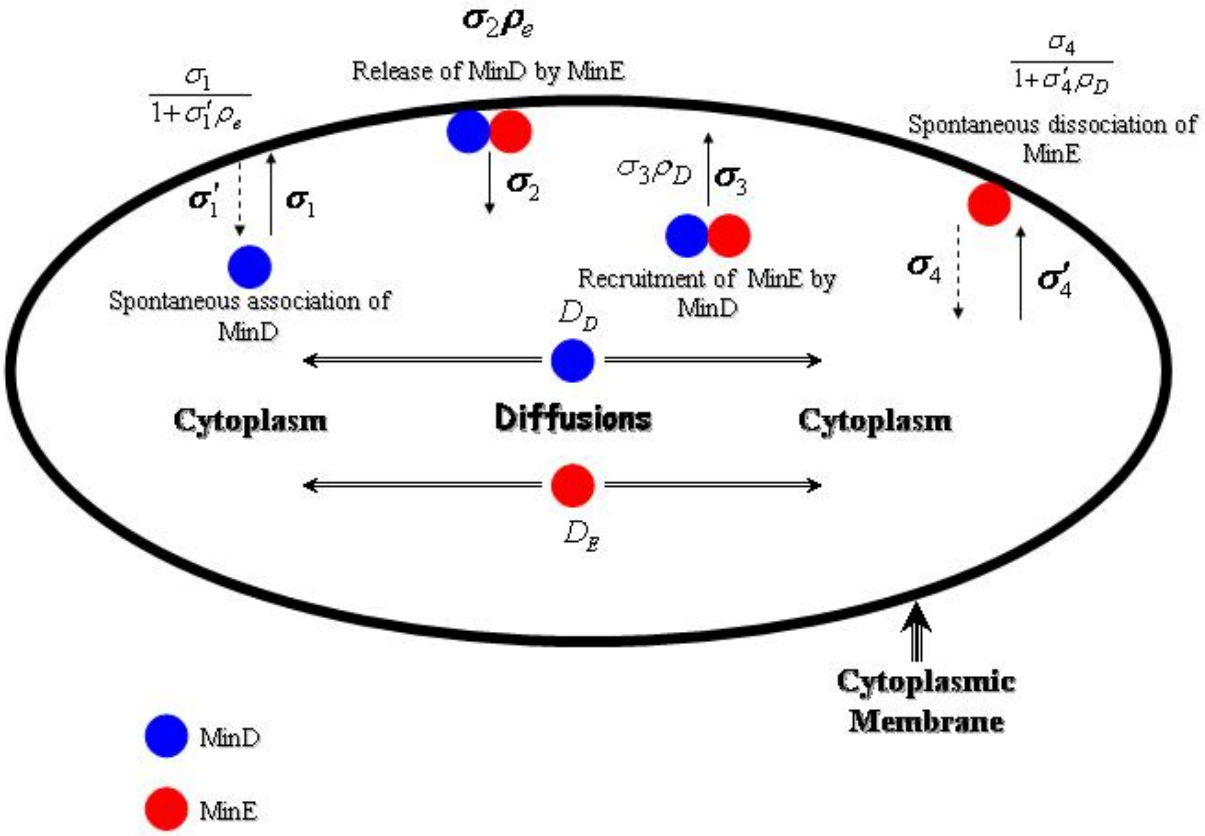

Figure 4. Schematic diagram of the MinCDE dynamics.

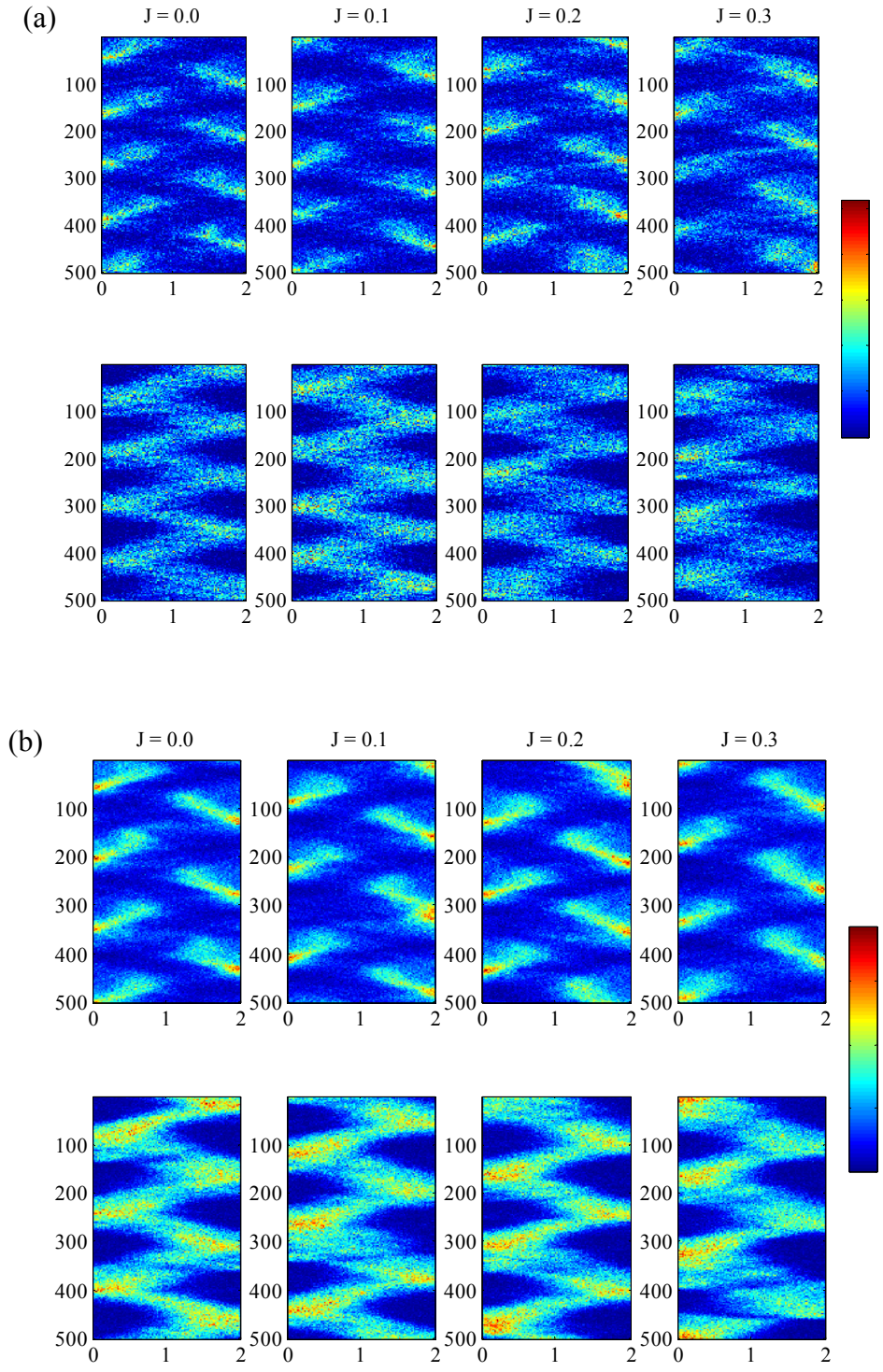

Figure 5. Space-time plots of the total $\left(n_D^k + n_d^k\right)$ MinD (above) and total $\left(n_E^k + n_e^k\right)$ MinE (below) concentrations for $J = 0.0$ m/s to $J = 0.3$ m/s where (a) $N = 400$ and (b) $N = 1500$. The color scale, running from blue to red, denotes an increase in the total numbers of Min proteins from the lowest to the highest. The vertical scale spans time for 500 s. The time increases from top to bottom. The horizontal scale spans the bacterial length $2\ \mu$m. Note the increase in the MinD concentration at the right pole and MinE concentration at the left pole.

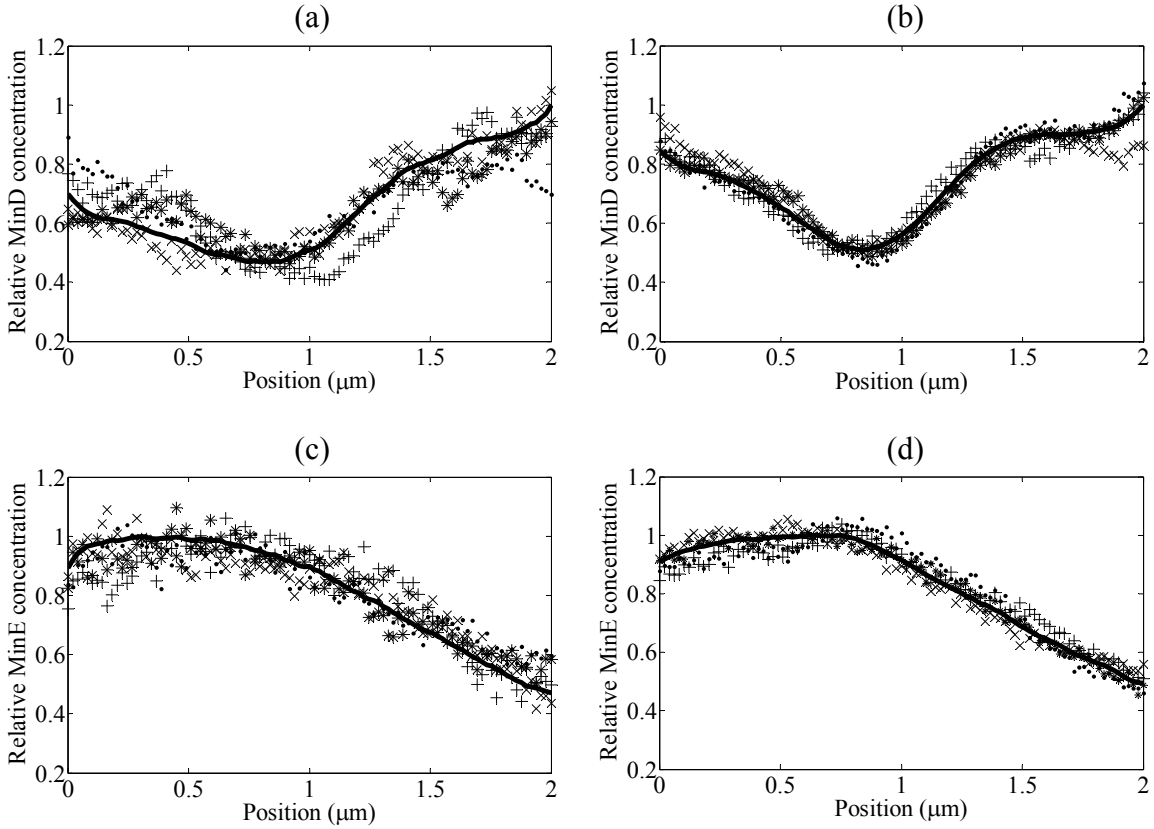

Figure 6. (a), (b) relative MinD concentrations and (c), (d) relative MinE concentrations as functions of x for $J = 0.3$ m/s. In (a), (c) $N = 400$ and (b), (d) $N = 1500$. Solid lines show averages over 15 successive cycles. Markers in the figures represent Min protein concentrations of four individual oscillation cycles.

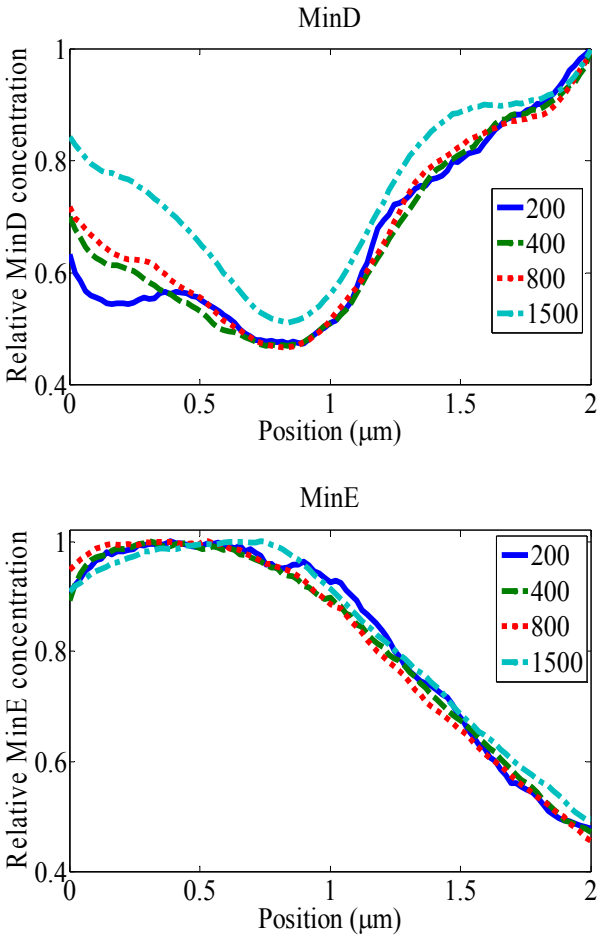

Figure 7. Relative concentrations of MinD (above) and MinE (below) as functions of position x along the bacterium length under the influence of an electric field with $J = 0.3$ m/s. The curves show that varying the total number of Min proteins does not change the MinD global minimum and MinE global maximum position.

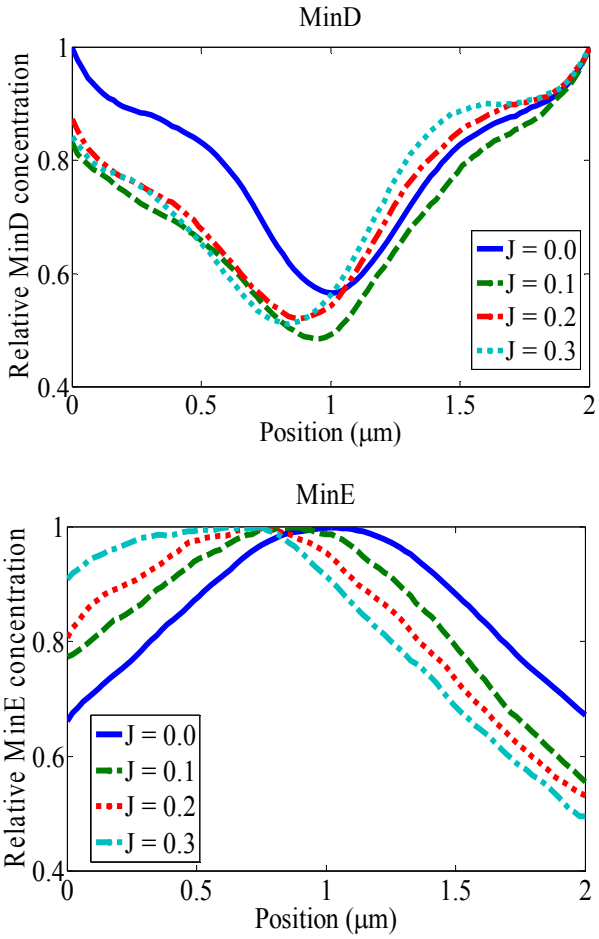

Figure 8. Relative concentrations of MinD (above) and MinE (below) as functions of position x along the bacterium length under the influence of an electric field for $N = 1500$. The curve shows a shift, which depends on the strength of the field, in the local minima of the MinD and the local maxima of the MinE from the mid-cell

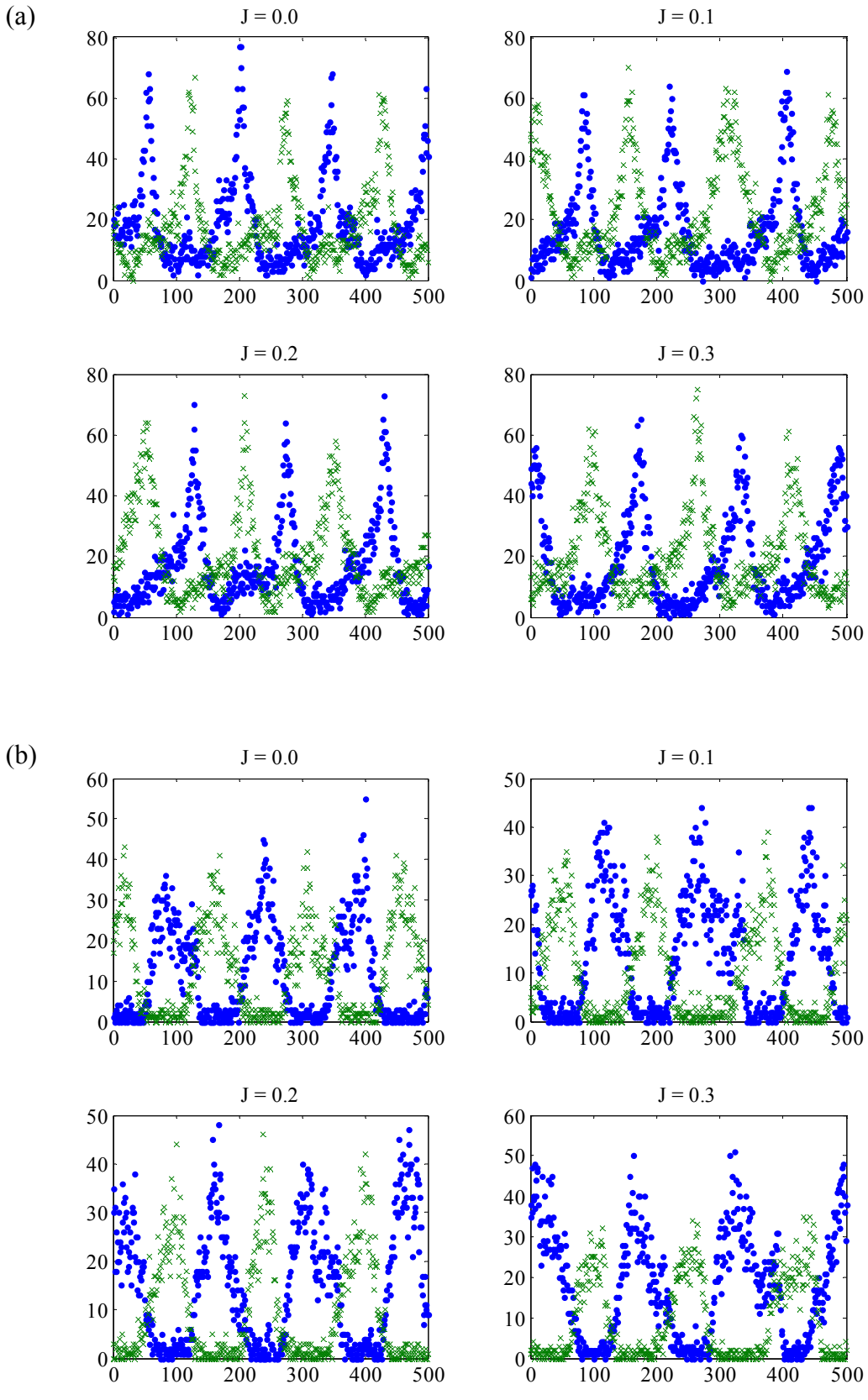

Figure. 9. Plots of the concentrations of Min proteins: (a) MinD and (b) MinE. The plots are focused at the left end grid (·), and the right end grid (x) as functions of time in seconds for $J = 0.0$ m/s to $J = 0.3$ m/s. The vertical scales denote numbers of protein copies in the system. The horizontal scale spans time for 500 s.