THE DYNAMICS OF THE PARTITIONING OF THE BACTERIA: WITH AND WITHOUT AN EXTERNAL FIELD

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ABSTRACT

The cell division process is a crucial event of most living organisms. This process requires an accurate partitioning of the cell. For *Escherichia coli* and other rod-like bacteria, evidences have accumulated over the past few years which indicate that the separation into two daughter cells is achieved by forming a septum perpendicular to the parent cell's long axis. This determination of the midcell and the proper placement of the septum is essential and depends on the pole to pole oscillatory dynamics of the proteins MinC, MinD, and MinE (or MinCDE oscillation). This dynamics is considered as the key ingredient to predict and control an accurate cell division.

Exposure to a constant external field e.g., an electric field or magnetic field, could microscopically affect the MinCDE oscillation. Therefore, it might result in a macroscopic abnormality in the bacteria cell division. To gain insight into the effects of the external field phenomena , we have modeled the process using a set of deterministic reaction diffusion equations, which incorporate the influence of an external field, and *min* protein interactions as the source and sink terms in the pure diffusion model. Using a numerical method to solve the model and measure some relevant quantities such as the space-time concentrations of each protein species, we find some changes in the dynamics of the oscillations of the *min* proteins from pole to pole when compared to those without the external field. The findings suggest that a significant application of the field can interfere with the cytokinesis. To support our finding, we have tried to relate the results to some available experimental data and give some explanation or speculation.

KEY WORDS : EXTERNAL FIELDS / *ESCHERICHIA COLI* / BACTERIA
MIN PROTEINS / MINCDE OSCILLATION
REACTION DIFFUSION

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พลวัตของการแบ่งตัวของแบคทีเรีย ในกรณีมี และไม่มีสนามภายนอก (THE DYNAMICS OF THE PARTITIONING OF THE BACTERIA: WITH AND WITHOUT AN EXTERNAL FIELD)

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บทคัดย่อ

กระบวนการแบ่งเซลล์ เป็นเหตุการณ์ที่สำคัญอย่างยิ่งต่อการดำรงอยู่ของสิ่งมีชีวิต โดยกระบวนการดังกล่าวต้องการกระบวนการแบ่งตัวที่แม่นยำของเซลล์ สำหรับในกรณีของ *Escherichia coli* ตลอดจน แบคทีเรียที่มีรูปท่อนกลมยาวอื่นๆ มีหลักฐานที่ชัดเจนมากมายที่ บ่งชี้ว่า การแบ่งเซลล์จากหนึ่งเซลล์ ไปเป็น สองเซลล์นั้น จะบรรลุผลได้ก็ต่อเมื่อ มีการก่อผนังกั้นภายในเซลล์ต้นกำเนิด ซึ่งผนังดังกล่าวจะมีการก่อตัวตั้งฉากกับแกนตามแนวยาวของเซลล์ ด้วยเหตุนี้ การกำหนดตำแหน่งที่บริเวณกลางเซลล์ ตลอดจนความเหมาะสมของผนังกั้น จึงกลายมาเป็นปัจจัยที่มีความสำคัญต่อกระบวนการข้างต้น โดยที่ ปัจจัยดังกล่าวนี้ ขึ้นอยู่กับ พลวัตเชิงการสั่น ของโปรตีน MinC MinD และ MinE (หรือ การสั่นของ MinCDE) พลวัตนี้ได้ถูกพิจารณาว่า เป็น องค์ประกอบที่มีความสำคัญ ต่อการคาดการณ์ และ การควบคุม ความแม่นยำของการแบ่งเซลล์

สำหรับ การให้สนามภายนอก เช่น สนามไฟฟ้า หรือ สนามแม่เหล็ก กับแบคทีเรีย สนามเหล่านี้ สามารถมีผลต่อ โปรตีน MinCDE ซึ่งมีขนาดที่ถือว่าเล็กมาก ด้วยเหตุนี้ จึงส่งผลให้เกิดความผิดปกติของการแบ่งเซลล์ ของแบคทีเรีย ในระดับที่สามารถเห็นได้ นอกจากนี้ เพื่อความเข้าใจอย่างท่องแท้เกี่ยวกับผลของปรากฏการณ์ของสนามภายนอกดังที่ได้กล่าวมานี้ จึงได้นำเข้าสู่การสร้างแบบจำลองเพื่อ อธิบายปรากฏการณ์ดังกล่าว โดยการใช้เซตของสมการการกระจายตัวตามปฏิกิริยาเชิงกำหนด ซึ่งประกอบด้วย แบบจำลองของการกระจายตัว และ เทอมที่แสดงอันตรกิริยา ของโปรตีน *min* ในส่วนที่เป็นการเพิ่ม และ การลด จากสมการนี้ เราได้เพิ่มส่วนที่เป็นอิทธิพลของสนามภายนอกเข้าไป สำหรับแบบจำลองที่ได้มานี้ เราใช้วิธีการเชิงตัวเลข เพื่อแก้ปัญหา และวัดคุณสมบัติที่สำคัญ เช่น ความเข้มข้นเชิงปริภูมิและเวลา ของโปรตีนแต่ละชนิด ตลอดจนการหาการเปลี่ยนแปลงบางอย่างทางพลวัตการสันของโปรตีน *min* โดยที่ เราได้มีการเปรียบเทียบผลดังกล่าวกับกรณีที่ไม่มีสนามภายนอก ซึ่งแสดงเป็นนัยว่าสนามสามารถแทรกแซงการแบ่งไซโทพลาซึม อนึ่ง เพื่อที่จะสนับสนุนผลดังที่กล่าวมานี้เราจึงได้เชื่อโยงความสอดคล้องของผลที่ได้กับข้อมูลจากการทดลองที่มีอยู่ พร้อมการอธิบายที่เหมาะสม

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

In nature, the cell division process is a critical event in the life of every organism. Most bacteria divide symmetrically in a process that is subject to extensive regulation to ensure that both newly formed daughter cells contain a copy of the chromosome. Symmetric division seems very simple yet is poorly understood on a molecular level. For *Escherichia coli* (or *E. coli*) and other rod-like bacteria, evidences have accumulated over the past few years which indicate that the separation into two daughter cells is achieved by forming a septum perpendicular to the parent cell's long axis. To induce the separation, the FtsZ ring (Z ring), a tubulin-like GTPase is believed to initiate and guide the septa growth by a process called contraction [1]. The Z ring is usually positioned close to the center, but it can also form in the vicinity of the cell poles. Two processes are known to regulate the placement of the division site: nucleoid occlusion [2, 3, 4] and the action of the *min* proteins [5]. Both processes interferes with the formation of the Z ring that determines the division site. Nucleoid occlusion is based on cytological evidence that indicates that the Z ring assembles preferentially on those portions of the membrane that do not directly surround the dense nucleoid mass [6]. For *min* proteins, they control the division site via the pole-to-pole oscillatory mechanism.

1.2 System of MinCDE proteins

For *E. coli*, the gene products of the *minCDE* gene cluster are required for the normal division site selection process. In the absence of the *min* gene products, septation frequently occurs adjacent to a cell pole instead of at midcell, leading to formation of small spherical minicells that lack chromosomal DNA [10, 11, 12, 13]. It is experimentally

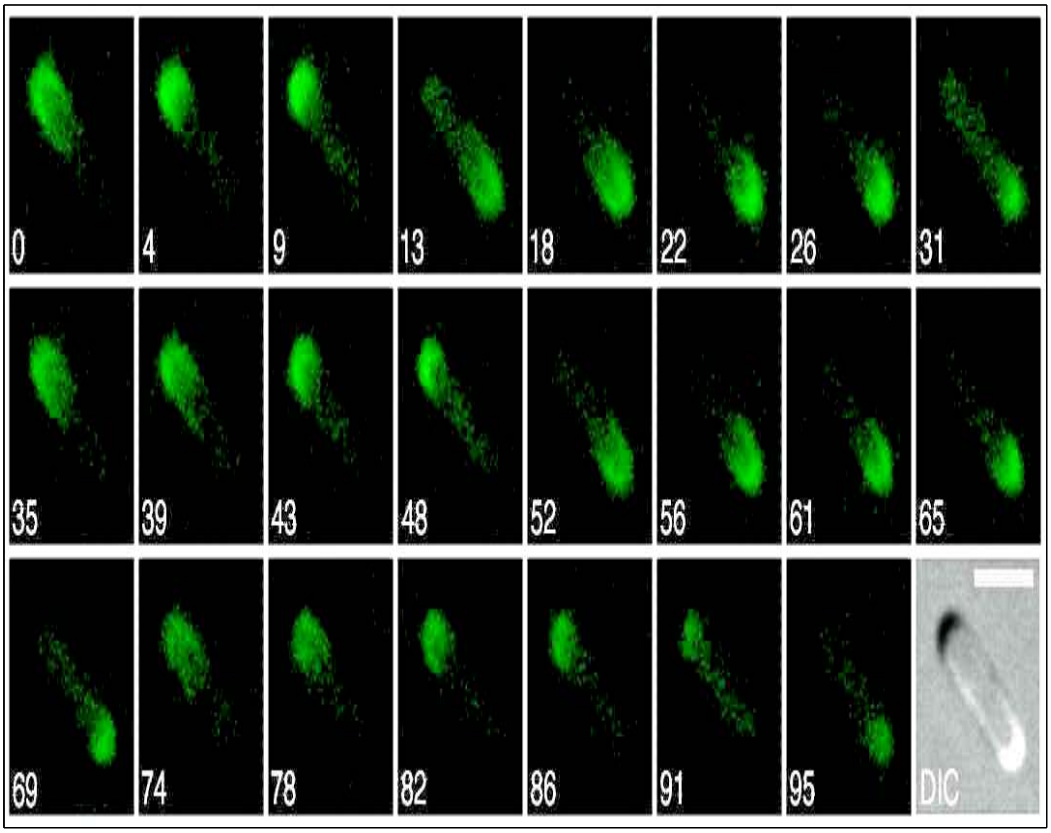

Figure 1.1: Time-lapse fluorescence micrographs showing the dynamic behavior of Gfp-MinC. MinC is a division inhibitor which associates, and co-oscillates, with MinD. Pole-to-pole oscillation of MinD, in turn, requires the activity of MinE. On time average, the center of the cell is exposed to the lowest level of division inhibitor. Times are indicated in seconds. The last panel shows the cell viewed with DIC (differential interference contrast) optics. The bar in this panel represents 2 μ m.
[7, 8]

fend that these Min proteins control the placement of the division site [5]. Experiments, involving the use of modified proteins show that the MinC is able to inhibit the formation of the FtsZ-ring [14]. MinD is an ATPase that is connected peripherally to the cytoplasmic membrane. It can bind to the MinC and activate the function of the MinC [15, 16]. Recent studies show that the MinD can also recruit the MinC to the membrane. This suggests that MinD stimulates the MinC by concentrating the MinC near to its presumed site of activation [17, 7]. MinE provides topological specificity to the division inhibitor [18]. Its expression results in a site-specific suppression of the MinC/MinD action so that the FtsZ assembly is allowed at the middle of the cell but is

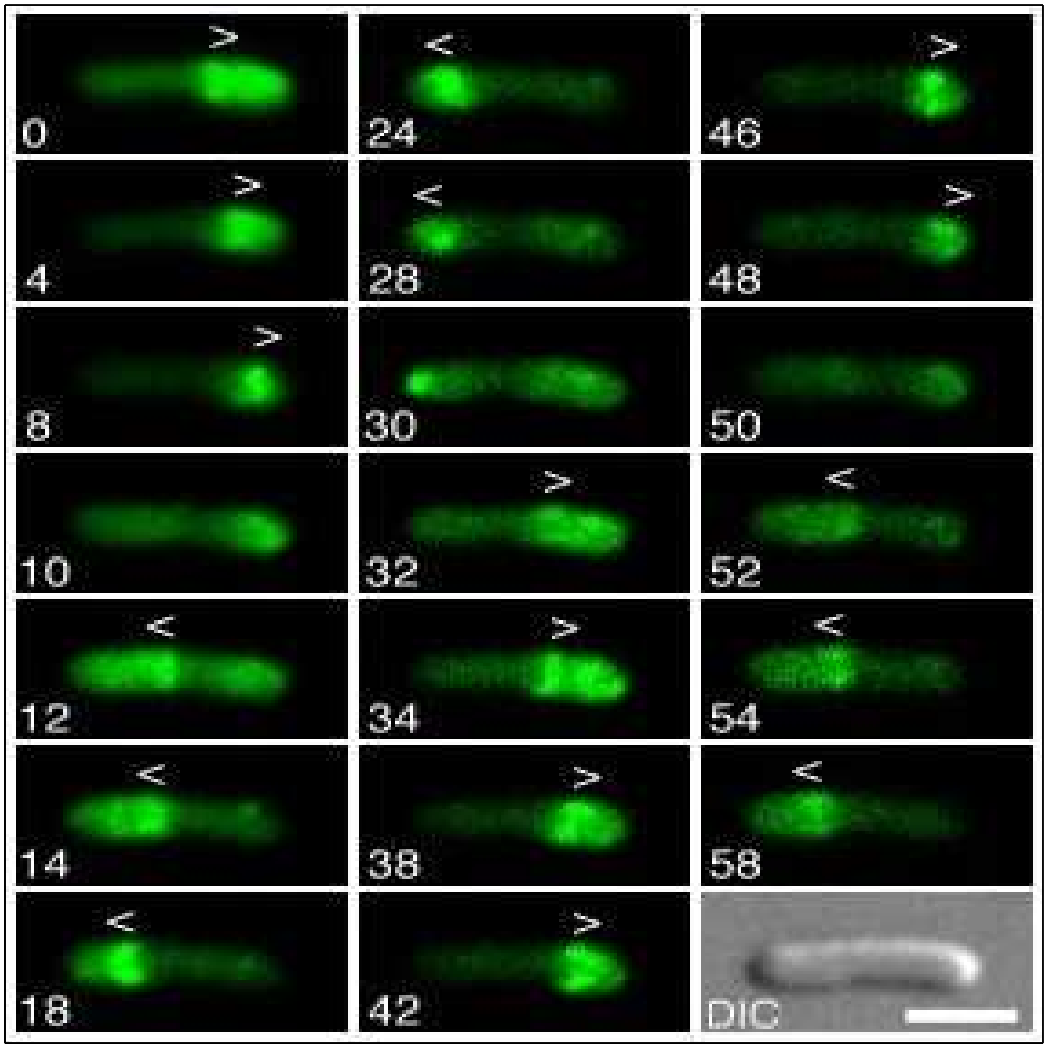

Figure 1.2: Time-lapse fluorescence micrographs showing the dynamic behavior of MinE-Gfp in normally dividing cells.Times are indicated in seconds. Note the accumulation of MinE-Gfp in the shape of a ring (the E-ring) as well as in an extra-annular peripheral pattern (PEA signal) which is present in between the ring and one of the cell poles. Note the net movement of a ring towards the pole with the PEA signal $(0-8s, 12-28s, 32-48s, 52-58s)$, the disappearance of a ring and PEA signal when the former approaches a cell pole $(8s, 28s, 48s)$, and the subsequent assembly of a new ring at/near midcell concomitant with the appearance of a new PEA signal in between the new ring and the pole previously devoid of signal $(12s, 32s, 52s)$. Arrowheads (or) indicate both the position of the ring as well as the direction of its movement.
[9]

blocked at the other sites [5]. In the absence of the MinE, the MinC/MinD is distributed homogeneously over the entire membrane. This results in a complete blockage of the Z-ring formation. The long filamentous cells, which are subsequently formed would not

be able to divide [17, 7, 8, 19]. Using fluorescent labeling technique(see Fig.(1.1)-(1.2)), the MinE is shown to attach to the cell wall only in the presence of the MinD [20, 17]. Because the MinD interacts with the MinC [16], it is likely that they oscillate together [17]. This would result in the concentration of the division inhibitor at the membrane on either cell end, alternating between being high or very low every other 20 s or so [17, 7]. The presence of the MinE is not only required for the MinC/MinD oscillation, it is also involved in setting the frequency of the oscillation cycle [8]. Several sets of evidence indicate that the MinE localization cycle is tightly coupled to the oscillation cycle of the MinD. Recent microscopy of the fluorescent labeled proteins involved in the regulation of the *E. coli* division have uncovered stable and coherent oscillations (both spatial and temporal) of these three proteins [9]. The proteins oscillate from one end to the other end of the bacterium, moving between the cytoplasmic membrane and cytoplasm. The detail mechanism by which these proteins determine the correct position of the division plane is currently unknown, but the observed pole-to-pole oscillations of the corresponding distribution are thought to be of functional importance.

1.3 The Effect of an External Field on Bacteria

The growth of the bacteria depends on culture conditions and environment (e.g., pH, light, and external field). One of interesting effects on the growth of the bacteria in subcellular process is due to an external field. In this thesis, we are concerned with the dynamics of Min protein molecules. The appropriate external fields for these situations can be the magnetic field and/or the electric field. Since, these field play an important role on the molecular scale or microscopic scale of molecules, atoms and ions. For the other field such as gravitational field, the field is far too weak at the molecular scale. Most of the experimental results concerning the effect of an external fields on bacteria are concerned with in the effect of magnetic fields(MF), which can affect various biological functions of living organisms, e.g., DNA synthesis and transcription [21], as well as ion transportation through cell membranes [22]. Almost all living organism experience

magnetic fields arising from one or other sources. The strength of the geomagnetic field on the surface of the earth is approximately 0.50-0.75 gauss ($1\ Tesla = 10^4\ gauss$). There have been several studies over the past decades on the effects of exposure to the magnetic field and several of them have produced conflicting results. Reportedly, the growth rate of the Burgundy wine yeast is seen to decrease when an extremely low magnetic flux density (MFD) of 4 gauss is applied [23]. However, the growth of *Trichomonas vaginalis* is accelerated when it is exposed to 460-1200 gauss [24]. The growth of *Bacillus subtilis* increases when exposed to 150 gauss and decreases when exposed to more than 300 gauss [25]. Similar results are reported for *Chlorella*, an exposure of less than 400 gauss increases the growth, while exposure to 580 gauss decreases the growth [26]. Most studies point to the magnetic field influencing the growth and survival of the living organisms differently at different MFD [27, 28, 29, 30, 31, 32, 33, 34]. Researchers have also studied the effects of the magnetic fields on the bacteria at the enzyme level [35] and at the genetic level [30].

CHAPTER 2

OBJECTIVES

This thesis focuses on the mechanism of cell division of bacteria specific for *Escherichia coli* under external fields such as electric field, and magnetic field. The main aims of this thesis are:

1. To understand the basis of cell division mediated by the Min protein oscillation.

2. To understand the effect of external field on the cell division.

3. To establish a line between the mathematical model to the real experimental data.

In order to study the dynamics and modeling of cell division described in chapter 3. This chapter will be cover the literature review of biological model and mathematical model. In addition, we will propose the model for explanation the the mechanism of cell division under external fields. In chapter 4, we shows the numerical results of the mathematical model in chapter 3, which covers the discussion. For the conclusion, we will shows in chapter 5. The knowledge of this study may be used to prevent for the risk from these microorganism.

CHAPTER 3

MATHEMATICAL MODEL OF MIN PROTEINS

In this chapter, we model the pole-to-pole protein oscillation by in corporation the same key relevant dynamics seen in the experimental data. The deterministic reaction diffusion partial differential equations are used. They are the coarse-grained equation at mean field level with throw any the fluctuation or the correlation between protein species. Two general models have been proposed for the MinCDE system.

In the first model, the MinCD division inhibitors can block division at all potential division sites in the cell and the MinE prevents this action at the midcell site [5]. This model is supported by the observation that MinCD can act as a global division inhibitor, leading to formation of non-septate filaments in the absence of MinE. When the MinE are localized at the midcell and suppresses the MinCD mediated division inhibition at the midcell site.

In the second model, the primary function of the Min system is to alter the conformation and/or positioning of chromosomal DNA. Loss of this activity leads indirectly to the polar septation events that lead to minicelling in the *min* mutants [2, 12]. This model is supported by the aberrant nucleoid distribution in the Min- cells and by the observation that perturbations of chromosome organization or replication pattern [36, 37, 38] can be associated with the production of small anucleate cells ranging down to the size of minicells [12].

3.1 Introduction

The dynamics for Min system can be modeled by a set of reaction-diffusion equations. These mathematical equations have often been used in biological system to model self-organization and pattern formation [39]. The reaction-diffusion models typically

have two components. The first is the reaction term in the biochemical reactions which produces transforms or removes chemical species from the system. The second component would be the diffusion process. At the molecular level, diffusion is due to the random motion of molecules in a medium. The random motion results in a net flow of molecules from the region of high concentration to the regions of lower concentration. This is a simple statistical effect, which does not depend on the detailed mechanism by which the molecules transit from one region to another.

These two processes have been proposed as being the mechanism for the Min protein motion. The model of Meinhardt *et al.* [40] shows the pattern formation of the Min system, which requires an interaction of a self-enhancing component and its long-ranging antagonist. They consider the dynamics of FtsZ proteins in their model. In the models of Howard *et al.* [41, 42], the reaction consists of an association and dissociation of the proteins on the membrane, and is clearly evident for the interaction of MinD and MinE. This model evince that MinE is recruited to the membrane by membrane-associated MinD. For the model of Kruse [43], the clustering of membrane-bound MinD in combination with attachment and detachment rates depends on the concentration of molecules presence on the membrane. All these models successfully generate oscillation patterns. Another model [44] includes the *in vitro* interactions of MinD and MinE takes into account the presence of the Min oscillations. In this thesis, we adopt the Howard *et al.* model as a first step model [41, 42], since it is a relatively simple one (Eq. (3.1)-(3.4)), which contains the essential positional information need describe the cell division of an *E. coli*.

3.2 Mathematical Model of Min proteins: Without external field

The dynamics of the Min proteins is described by a set of four non-linear coupled reaction-diffusion equations. In this thesis, we focus on the *E. coli* bacteria, which is a commonly studied rod shaped bacteria of approximately $2-6\mu m$ in length and around $1-1.5\mu m$ in diameter. *E. coli* divides approximately every hour via cytokinesis. In addition,

the study of the dynamics of the Min proteins started with a set of one dimensional deterministic coupled reaction-diffusion equations, which describe the dynamics of the interactions between the local concentration of the MinD and MinE proteins. These equations describe the time rates of change of the concentration due to the diffusion of the MinD and the MinE and to the transfer between the cell membrane and the cytoplasm. The dynamics of these Min proteins are described by:

$$\frac{\partial C_D}{\partial t} = D_D \frac{\partial^2 C_D}{\partial x^2} - \frac{\sigma_1 C_D}{1+\sigma_1' C_e} + \sigma_2 C_e C_d \tag{3.1}$$

$$\frac{\partial C_d}{\partial t} = D_d \frac{\partial^2 C_d}{\partial x^2} + \frac{\sigma_1 C_D}{1+\sigma_1' C_e} - \sigma_2 C_e C_d \tag{3.2}$$

$$\frac{\partial C_E}{\partial t} = D_E \frac{\partial^2 C_E}{\partial x^2} - \sigma_3 C_D C_E + \frac{\sigma_4 C_e}{1+\sigma_4' C_D} \tag{3.3}$$

$$\frac{\partial C_e}{\partial t} = D_e \frac{\partial^2 C_e}{\partial x^2} + \sigma_3 C_D C_E - \frac{\sigma_4 C_e}{1+\sigma_4' C_D} \tag{3.4}$$

where C_D are C_E the concentrations of protein MinD and MinE in the cytoplasm respectively. C_d, C_e are the concentrations of protein MinD and MinE on the cytoplasmic membrane. These parameters depend on the time t and the position x. These equations represent the time rate of change of the Min protein concentrations in cytoplasm and on cytoplasmic membrane. Since the experimental results given in [7], show that the MinC dynamics are similar to those of the MinD, we have not written out the equations for the MinC.

This model assume that the diffusion coefficients (D_D, D_d, D_E, D_e) are isotropic and independent of position x. If the Min proteins are immobilied on membrane ($D_d = 0, D_e = 0$), then the dynamics of Min proteins is shown schematically in Fig.(3.1). The constant σ_1 represents the association of MinD to the membrane wall [26]. σ_1' corresponds to the membrane-bound MinE suppressing the recruitment of MinD from the cytoplasm. σ_2 reflects the rate that the MinE on the membrane drives the MinD on the membrane into the cytoplasm. Based on the evidence of the cytoplasmic interaction between MinD and MinE [16], we let σ_3 be the rate that the cytoplasmic MinD recruits the cytoplasmic MinE to the membrane while σ_4 corresponds to the rate of dissociation

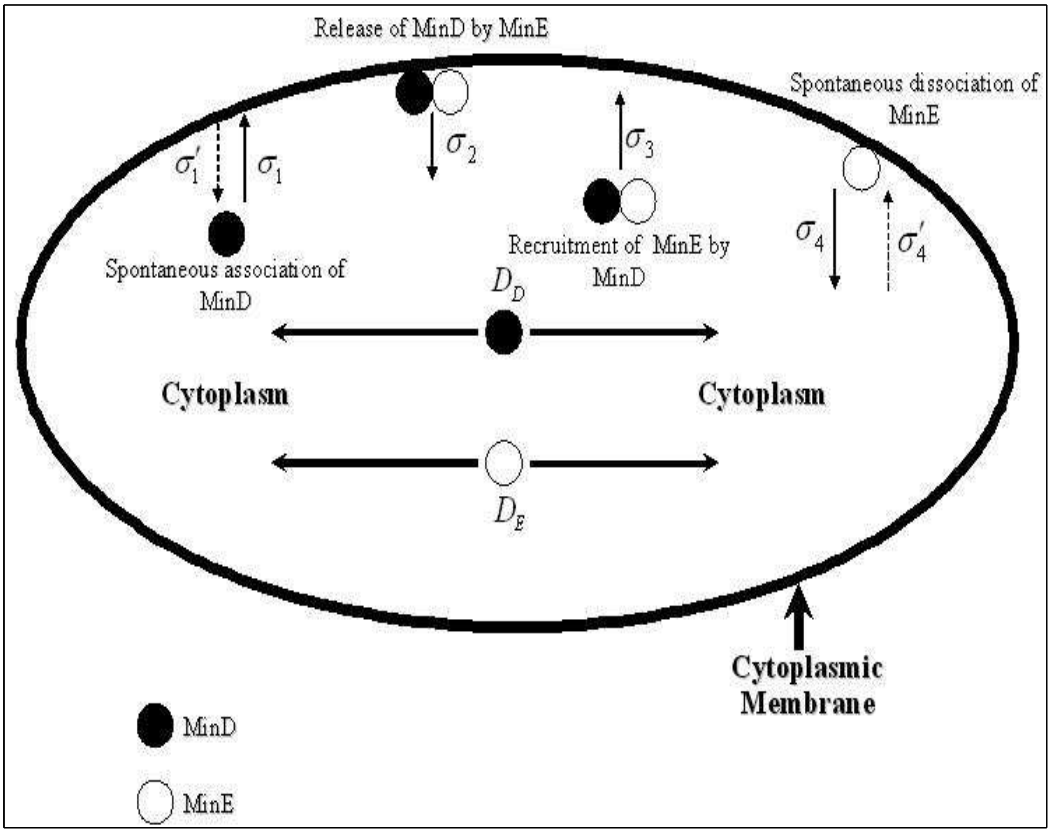

Figure 3.1: A schematic depiction of the dynamics of Min proteins transfer between cytoplasmic membrane and cytoplasm. For simplicity, only the top of bacterium are represented these dynamics. The black circle represent the MinD proteins and the circle represent the MinE proteins. The membane-bound in this situation do not diffuse. Then the diffusion of Min proteins occures inside the cytoplasm of bacterium.

of MinE from the membrane to the cytoplasm. Finally, σ_4' corresponds to the cytoplasmic MinD suppressing the release of the membrane-bound MinE. The definition of the reaction-diffusion equations are in Table(3.1).

3.3 Mathematical Model of Min proteins: With external field

In this section, we propose a mathematical model to investigate the influence of the external constant external field on the cytokinesis mediated by the Min protein pole-to-pole oscillation. This situation may change the Min protein oscillation mechanism for the bacteria cell division. We adopted the dynamic model of compartmentalization in the bacterial cell division process proposed by Howard *et al.* [41, 42] except that

Terms in Reaction Diffusion Model	**Meaning and Details**	**Biological Interpretation and Assumption**
$D_i \frac{\partial^2 C_i}{\partial x^2}$	Represent the random walk of the Min proteins in each species, where $i = \{D, d, E, e\}$. For the case of the Min proteins do not diffuses on membrane then D_d and D_e as zero.	The rate of protein diffusion in bacterial cytoplasm may constrain a variety of cellular functions and limit the rates of many biochemical reactions *in vivo*. Since the diffusion time is proportional to L^2 of cell.
$J_i \frac{\partial C_i}{\partial x}$	Represent the bias random walk for each species of Min protein. This term will be dominated system by increases the external field parameter"J_i", which carry the electrical charge of Min proteins.	Reflect the hypothesis for Min proteins under external field to change the concentration at each position in cell length with strength of field.
$\frac{\sigma_1 C_D}{1+\sigma_1' C_e}$	Association of cytoplasmic MinD with membrane is inhibited by MinE in membrane which takes care of singularity as MinE goes to zero.	MinE in membrane spatially blocks membrane for MinD similar to MinC blocking FtsZ association with membrane.
$\sigma_2 C_e C_d$	Dissociation of membrane MinD is stimulated by MinE in membrane, after MinD is ejected MinE stays in membrane.	Binding of MinE to MinD lowers affinity of MinD with membrane but membrane affinity of MinE remains unchanged.
$\sigma_3 C_D C_E$	Association of cytoplasmic MinE with membrane is stimulated by MinD in cytoplasm after delivery of MinE to the membrane; MinD drives back in the cytoplasm.	MinDE complex has high affinity to membrane since the diffusion of this complex doesn't appear in the model it should be very fast.
$\frac{\sigma_4 C_e}{1+\sigma_4' C_D}$	Dissociation of membrane MinE is inhibited by MinD in cytoplasm which takes care of singularity.	Cytoplasmic MinD blocks MinE on membrane go to cytoplasm. This situation relate to $\sigma_3 C_D C_E$ term.

Table 3.1: Term by term meaning of the reaction-diffusion equation model.

an external field is present. The dynamics at the mean-field level is described by a set of coarse-grained non-linear reaction-diffusion equations. We begin with the set of one dimensional deterministic coupled reaction-diffusion equations in Eq.(3.1) to Eq.(3.4). The equations describe the time rates of change of the densities due to the diffusion of the MinD and the MinE and to the mass transfer between the cell membrane and the cytoplasm. The dynamics of these Min proteins in the presence of an external field, are described by:

$$\frac{\partial C_D}{\partial t} = D_D \frac{\partial^2 C_D}{\partial x^2} + J_D \frac{\partial C_D}{\partial x} - \frac{\sigma_1 C_D}{1 + \sigma_1' C_e} + \sigma_2 C_e C_d \tag{3.5}$$

$$\frac{\partial C_d}{\partial t} = D_d \frac{\partial^2 C_d}{\partial x^2} + J_d \frac{\partial C_d}{\partial x} + \frac{\sigma_1 C_D}{1 + \sigma_1' C_e} - \sigma_2 C_e C_d \tag{3.6}$$

$$\frac{\partial C_E}{\partial t} = D_E \frac{\partial^2 C_E}{\partial x^2} + J_E \frac{\partial C_E}{\partial x} - \sigma_3 C_D C_E + \frac{\sigma_4 C_e}{1 + \sigma_4' C_D} \tag{3.7}$$

$$\frac{\partial C_e}{\partial t} = D_e \frac{\partial^2 C_e}{\partial x^2} + J_e \frac{\partial C_e}{\partial x} + \sigma_3 C_D C_E - \frac{\sigma_4 C_e}{1 + \sigma_4' C_D} \tag{3.8}$$

where J_D, J_d, J_E and J_e are the external field parameter of each species.

The addition features of our model are the second terms on the right hand side of the four equations. They represent the effect of the external field in the reaction-diffusion equation [45, 46] controlled by the external field parameter. These terms reflect the hypothesis that the external field can influence the change in the concentrations of Min proteins at each position in *E. coli* cell at any given time. If the field parameter is very large, the dynamics of Min system would then be totally controlled by the external field. In addition, these drift terms can be represent the bias random walk term, which will dominate the Min system when increased the strength of external fields. In the absence of the external field, the Min proteins will have the random walk behavior, which are represented in diffusion terms. In this thesis, the field parameters is an external field of constant strength. We assume that the Min protein molecules (or chemical substance) movement in the region of an external field will experience a force that is proportional to the external field parameter of each species. The normal form of the external field parameter is $J_i = \mu_i E$, where E is the field strength and μ_i is the ionic mobility. The

index i represent the species of Min protein molecules $\{i = D, d, E, d\}$. In addition, these parameters have the same value ($J_i = J$), sice we assume that the Min proteins have the charge and its dynamic do not depend on its structures. Under these assumption, the proteins have the same mobility.

In the present work, we assume that the Min proteins can bind/unbind from the membrane and that the protein does not degrad during the process. Experimental results indicate that the oscillatory protein dynamics is unaffected if the new protein synthesis is blocked [8]. The total amounts of each type of Min proteins are conserved. The zero flux boundary conditions are imposed. This boundary condition gives a closed system with reflecting or hard-wall boundary conditions. In addition, the resulting protein oscillations (in the case of non-external field) mark the midcell with a minimum of the time-averaged concentration of MinC/MinD and with a corresponding maximum of MinE.

CHAPTER 4

RESULTS AND DISCUSSION

In this chapter, we will present the numerical results with some discussion. We have used the explicit Euler method of integration [47] to solve the set of reaction-diffusion equations in one dimensional system. In our simulation system, we assume that there is homogeneity in all the spatial directions except for the x-direction. We consider the system of *E.coli* bacteria whose size is $2\mu m$ in length and $1\mu m$ in width. We assume that the total time needed in the simulation is approximately $10^4 s$ which is long enough for the Min system to regulate cell division throughout the division cycle of the cell. We discretized the space and time by taking the following increments to be $dx = 8 \times 10^{-3} \mu m$ and $dt = 1 \times 10^{-5} s$. The space covering the bacteria is divided into 250 grid points, while the time is divided into $10^9 s$ times steps (10^9 iterations). To reflect the fact that the Min proteins are uniformly distributed throughout the *E.coli* cell, we numerically impose the uniform random initial condition with the number of Min molecules in each cell being 3000 for the MinD population [15] and 170 for the MinE population [48]. Since we assume the boundary of the system to be the impermeable wall, we use the boundary condition of zero flux (or gradient of protein concentration is equal to zero) at both ends of the bacterium. Based on a linear stability analysis technique(see Appendix), the values of parameters are given in Table(4.1).

Qualitatively, to give a visual impression of the space-time evolution of the protein oscillation, we have ploted the the total MinD and MinE concentrations. Quantitatively, the following quantities have been measured after each time step unless otherwise state.

1. The time averages of the MinD and MinE concentrations both with and without the external field cases.

2. The cross-over times of the MinD and MinE as a function of different external field parameters.

3. Percentage of the shifting of the maximum of MinE and minimum of MinD.

4.1 Results of the case of the protein oscillation in the absence of an external field

In this section, we consider the dynamics of Min proteins in the absence of an external field based on Eq. (3.1)-(3.4). Here we set the diffusion on membrane be zero [41]. The numerical results are shown in Fig.(4.1)-(4.2).

Fig.(4.1) shows the space-time plots of the MinD and MinE concentrations for a cell of the length of $2\mu m$ at various time. The oscillation patterns of MinD and MinE are differences. We see that the concentrations of MinE at the midcell is more than that of the MinD. Most of the concentrations of MinD is concentrated at the two poles of an *E.coli* cell. This oscillation pattern is in good agreement with the experimental results [8, 17]. It reflects the fact that the MinE spontaneously forms a single band at midcell which then sweeps towards a cell pole, displacing the MinD, which then reforms at the opposite pole. Once the MinE band reaches the cell pole it disappears into the cytoplasm, only to reform at midcell where the process repeats, but in the other half of the cell. These patterns are stable over at least 10^9 iterations, which are appropriate for the Min system to regulate cell division throughout the division cycle of the cell. The periods measured from our numerics are around 128 s. Fig.(4.2), shows the time-averaged MinD and MinE concentrations as a function of position. For the plot of MinD, we see that the minimum concentration is at the midcell, which reflects the behavior of the removal of division inhibition at midcell (by MinE). For MinE, it peaks at midcell and becomes minimum at the cell poles. Both results clearly reflect the natural cell division of an *E.coli* which are in qualitative agreement with the experimental data [9, 10, 11, 12, 13].

Having reproduced the key features of the first step model proposed by Howard *et al.*, we now turn into the numerical results for the case of *E.coli* exposed to an external

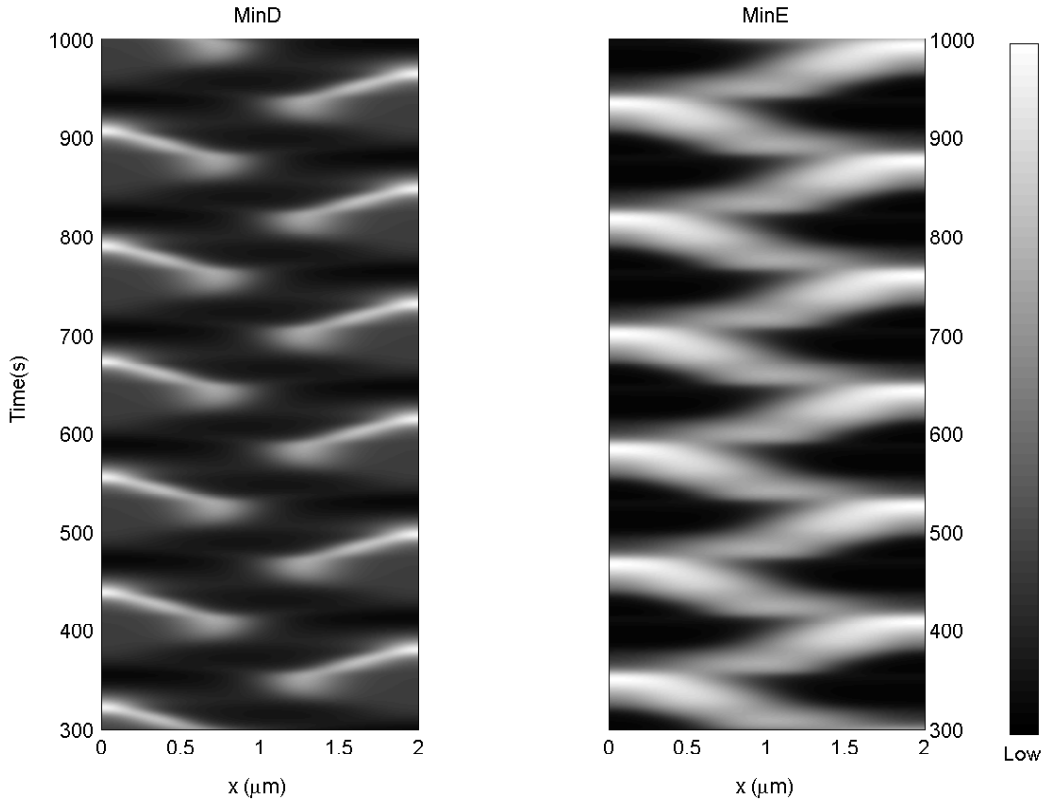

Figure 4.1: Space-time plots of the total MinD (left) and MinE (right) concentrations. This figure is the case of non-diffusion on membrane. The vertical scale spans a time passage of 300-1000 second. The horizontal scale spans the bacterial length ($2\mu m$).

field.

4.2 Results of the case of the protein oscillation in the presence of an external field

In this section, we consider the situation where an external field have the same influence throughout the cell including the cytoplasm and the cell membrane. We have numerically solved the one-dimensional coarse-grained equations (3.5)-(3.8) and the Min proteins have the same mobility. For the external field parameter$J$, we assume it to be a constant value ranging from $J = 0$ to $J = \pm 0.01$. Our focus in particular is centered on the oscillation patterns which occur for different values of the external field parameters. We have checked numerical solutions of the four reaction diffusion equations for

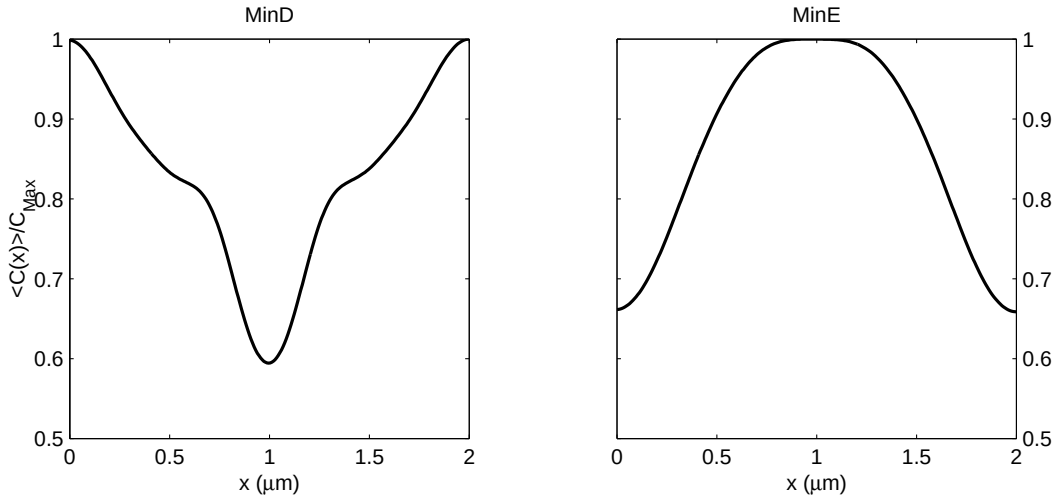

Figure 4.2: The time averages of the MinD (left) and MinE (right) concentrations $< C(x) > /C_{Max}$, relative to their respective time-averaged maxima, as a function of position x (in μm) along the bacterium axis. This figure is the case of non-diffusion on membrane.

the zero field ($J = 0$). They show that most of the proteins are concentrated at the membrane(see Appendix A). This means that the most of the Min proteins (MinD & MinE) is concentrated near the membrane. Then the distribution of the Min proteins in the cytoplasm will be a minimum. If the external field is applied to an *E.coli* cell, the Min proteins near the membrane will be influenced more than those in the cytoplasm. The total dynamics of the Min system is dominated by the dynamics of the Min proteins on or near the membrane.

For the situation of positive values of the external field parameter, the numerical results are seen in Fig.(4.3)-(4.8). In Fig.(4.3), we see the space-time plot of MinD and MinE concentrations for various values external field parameters(J) e.g., $J = 0.001$ to $J = 0.002$. These have the same features of oscillation patterns seen in the absence of an external field [41, 49]. However, as J increases the oscillation pattern shows a significant shifts in the concentrations of the Min proteins towards the left pole [50]. It is because

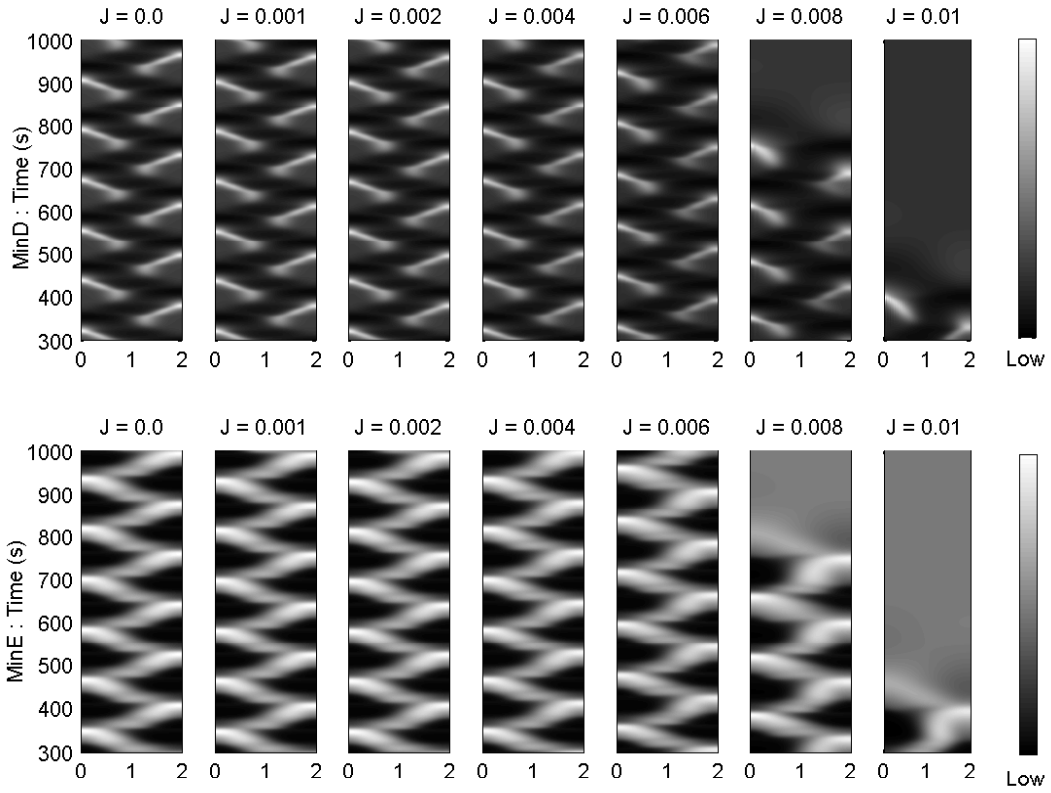

Figure 4.3: Space-time plots of the total MinD (above) and MinE (below) concentrations for various external field parameters of $J = 0$ to $J = 0.01$. The color scale (black to white) denotes an increase in the concentration from the lowest to the highest. The MinD depletion from midcell and the MinE enhancement at the midcell are immediately evident. The times increase from bottom to top and the oscillations in the pattern decrease when the external field parameter is increased. For the external field parameters $J = 0.008$ to $J = 0.01$ the oscillation dies out after a passage of time and the Min distribution becomes homogenous. The vertical scale spans a time passage of 1000 second. The horizontal scale spans the bacterial length($2\mu m$).

of the Min system for these field parameter values will be dominated by the diffusive behavior which does not changed the oscillation pattern. These patterns are similar to those for the normal case [41, 49] with $J = 0$.

For the case $J = 0.004$ to $J = 0.01$, the Min system is dominated by the drift due to the external field. In this case, the patterns of oscillation are dramatically changed from the normal harmonic oscillation pattern to the homogenous pattern of Min proteins marking the cross over time(t_c) for the harmonic phase to the homogenous phase. For

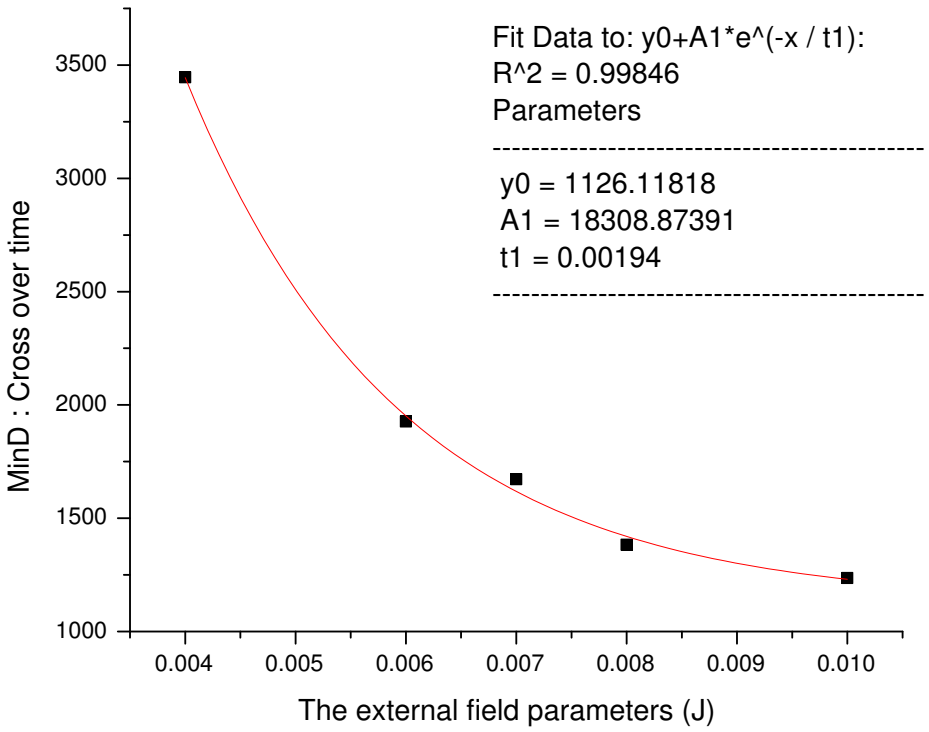

Figure 4.4: Plot of the cross over times for the MinD as a function of different external field parameter (J).

the other values of the field parameter J which are greater than 0.01, the oscillations die out or become homogeneous. The details of changing of harmonic phase is shown in Fig.(4.4)-(4.5). These figures reflect the transformation analysis of an oscillation phase to a homogenous phase marked by a cross over times. This cross over time is function of the field strength. We have determined that as the time passes the cross over time, the solutions corresponding to the homogeneous phase still exist. The homogenous phase does not exists for the case of zero external field. Fig.(4.4) and Fig.(4.5) are the data plot and associated curve fitting of the cross over times and the field strength. They can be fitted to an exponential decay function. This implies that as the field gets stronger, the faster the Min systems will enter the homogeneous phase. In Fig.(4.6), we show the time-averaged total concentration of MinD and MinE at different positions within the bacteria. For the case of the field parameter $J = 0$ to $J = 0.002$, the field term of this

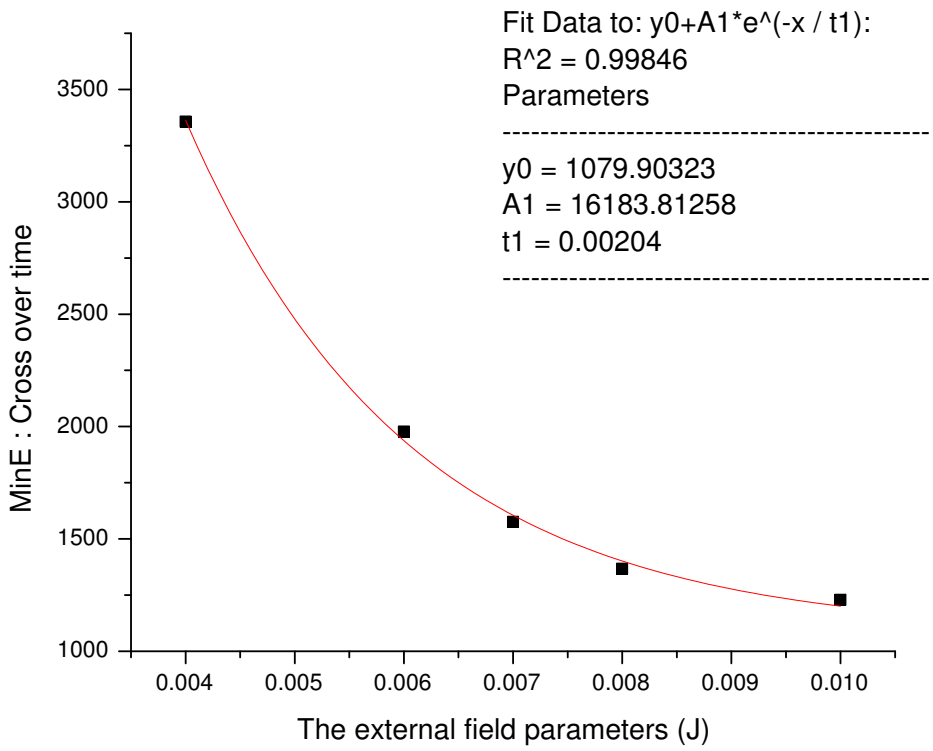

Figure 4.5: Plot of the cross over times for the MinE as a function of different external field parameter (J).

case has a small influence on the Min proteins, it does change the small concentration of these proteins at each position. This situation means that the bias random walk term(field) interferes with the random walk term(diffusion). We find that the minimum of the MinD concentration decreases. This reflects the fact that local concentration of MinD at midcell has to changed under the influence of external field or that the external field produce only very small changes in the concentrations of MinD. In addition, this situation reflects the effect of the field term of MinD drives the MinD assemble at the midcell. In nature, this phenomena can be observed by MinE proteins, which looks like a ring structure near the midcell that effectively positions the anti-MinCD activity to shield the midcell site from MinCD [20, 8]. Compared to the zero field case, again under the influence of the positive field the maximum of MinE is shifted from the midcell to

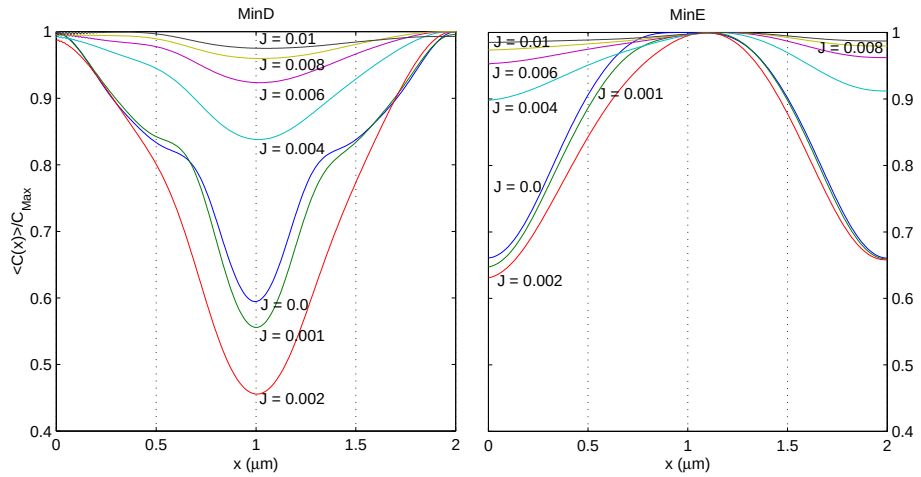

Figure 4.6: The time averages of the MinD (left) and MinE (right) concentrations $< C(x) > /C_{Max}$, relative to their respective time-averaged maxima, as a function of position x (in μm) along the bacterium axis under the influence of positive values of the static external field. Compared to the zero field case, the curves show a shift in the concentration of the MinD and MinE from the midcell depending on the strength of the field.

the right pole. It should be pointed out that the time-averaged behavior of MinE is more sensitive to the external field than that of MinD protein. This happens because the number of the MinE proteins is less than the MinD number.

For the values of the external field parameter between $J = 0.004$ and $J = 0.01$, the distributions of the MinD and MinE proteins depends on the strength of the external field. The time-averaged total concentration of this case are more than those for $J = 0$ to $J = 0.002$. When the field parameter J is more than 0.01, the oscillation pattern rarely occurs and the Min proteins distribution becomes homogenous along the cell length of the *E.coli* bacteria resulting in the pattern of time-average becoming a straight line. When the external field has a negative direction, the results are very similar to those of positive external field as expected. Now however, the curve for the time averages of the concentration of the Min proteins shifts from the midcell towards the left pole.

In Fig.(4.7) and Fig.(4.8), we have measured the percentages of the shifting of

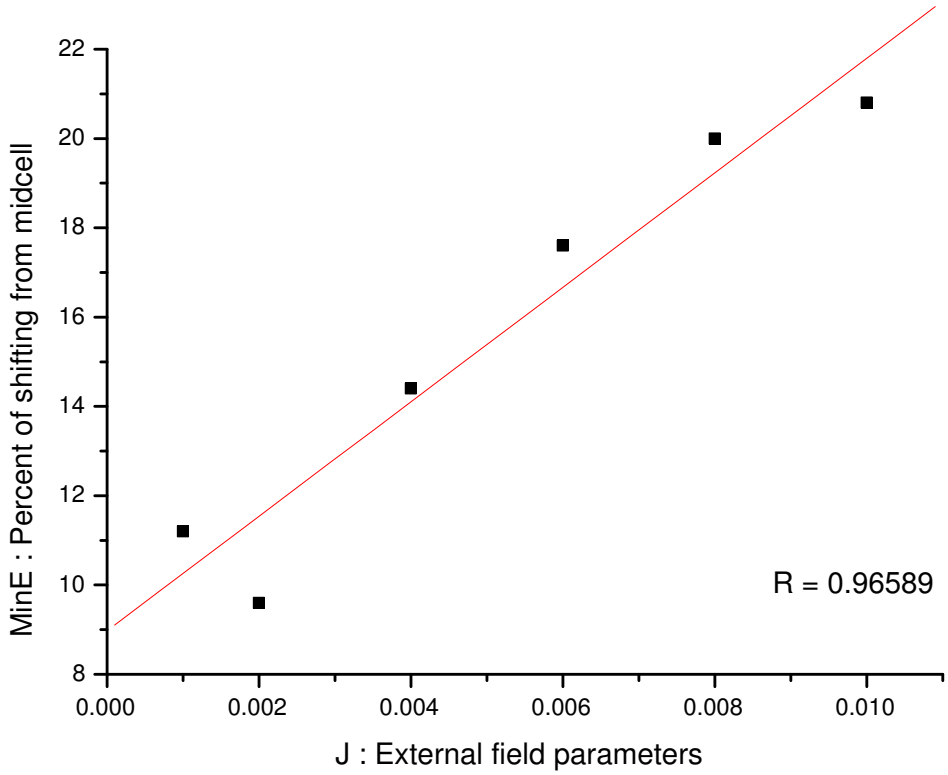

Figure 4.7: The shifting of the maximum of MinE protein (expressed as a percentage) from the midcell position for positive values of the external field parameters: $J = 0.001$, $J = 0.002$, $J = 0.004$, $J = 0.006$, $J = 0.009$ and $J = 0.01$. The R-value is 0.96589. The solid line is the best fit of the data to linear dependence of the shifting of the MinEconcentrations on the external field parameters.

Min proteins from midcell for $J = 0.001$ to $J = 0.01$. We have also carried out a least square fit of the data to $y = ax + b$. In Fig.(4.7), we see that the shifts of the MinE concentrations increase as the field parameter J increases [50]. The values of a and b in the linear dependence are $a = 1282.19$ and $b = 8.975$ with a $R = 0.96589$. The same fit is done for the MinD concentrations, they give $a = 499.72$, $b = -0.182$ with $R = 0.95549$ as shown in Fig.(4.8). It should be pointed out that the shift in the MinD concentration maximum from the midcell position is not very remarkable. The reason for this is that the number of MinD proteins in the system is relatively large and so are relatively less sensitive to the external field.

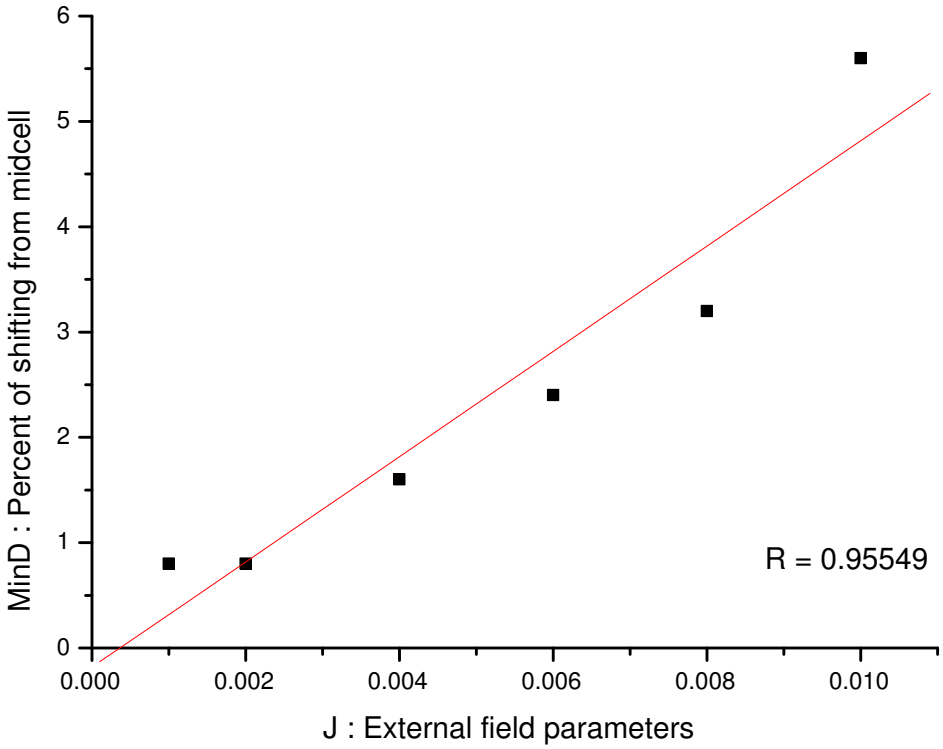

Figure 4.8: The shifting of the minimum of MinD protein from the midcell for positive values of the external field parameters: $J = 0.001$, $J = 0.002$, $J = 0.004$, $J = 0.006$, $J = 0.009$ and $J = 0.01$. The R-value is equal to 0.95549. The solid line shows the linear relation between the shifting (expressed as a percentage) of the MinD and the external field parameters.

We now make some connection between our numerical results and the laboratory results concerning the effects of the constant magnetic field on *E. coli*. As seen in our results, the identification of the midcell position become more and more inaccurate as the field strength is increased. These prediction corresponds to the experimental data show that the magnetic fields having the negative effect on the *E.coli* [32, 33, 34]. These results also show that the amount of *E.coli* decreases when exposed to strong magnetic fields and/or to longer exposure time. However, all experimental results can not clearly explained the mechanism in subcellular processes for the effect of magnetic field, which directly support our theory. Our numerical results show the time averages of MinD and

MinE (see Fig.(4.6)), which represent the positional information of cell division. The Minimum of MinD and the Maximum of MinE shift from the midcell with the strength of external fields, imply that the division site of *E.coli* cell have not been accurately selected at the midcell. In nature, if the division is not targeted accurately to midcell, then DNA will not be distributed evenly to both daughter cells, resulting in unviable anucleatet minicells. The results show the transformation of the oscillation phase to the homogenous phase, they may mirror that longer exposure time to magnetic field could cause the pole to pole oscillatory dynamics of Min proteins to be abnormal(see Fig.(4.3)). Other evidences that support this are the relation between the cross over times and the strength of external field(see Fig.(4.4)-(4.5)). It is an exponential decay function which reflects breakdown of the pole to pole oscillatory dynamics of Min proteins with respect to the strength of external fields.

Type of parameter	**Notation and Unit**	**Values**
Diffusion coefficient of cytoplasmic MinD	D_D $[\mu m^2 s^{-1}]$	0.28
Diffusion coefficient of MinD on membrane	D_d $[\mu m^2 s^{-1}]$	0.003
Diffusion coefficient of cytoplasmic MinE	D_E $[\mu m^2 s^{-1}]$	0.6
Diffusion coefficient of MinE on membrane	D_e $[\mu m^2 s^{-1}]$	0.006
The rate of association of MinD to the cytoplasmic membrane	σ_1 $[s^{-1}]$	20
The rate of membrane-bound MinE suppressing the recruitment of cytoplasmic MinD	σ_1' $[\mu m]$	0.028
The rate of dissociation of membrane-bound MinD	σ_2 $[\mu m s^{-1}]$	0.0063
The rate of association of MinE to the cytoplasmic membrane	σ_3 $[\mu m s^{-1}]$	0.04
The rate of dissociation of membrane-bound MinE	σ_4 $[s^{-1}]$	0.8
The rate of cytoplasmic MinD suppressing the release of membrane-bound MinE.	σ_4' $[\mu m]$	0.027

Table 4.1: The value of parameters

CHAPTER 5

SUMMARY AND CONCLUSION

The system of MinCDE proteins(*minC*, *minD* and *minE*) helps to accurately select the cell division sites in *E.coli* which normally divide by binary fission. The mechanism for the selection of the division plane significantly depends on the pole to pole oscillation (oscillating along the long axis) of these Min proteins. Even though, much work has been devoted to understanding this mechanisms, it still is not well understood and remains a challenging problem in the field of cell division biology. We have together two interesting problems together the Min protein oscillation and the effect of an external "electric" or "magnetic" field on the subcellular scale cytokinesis of *E.coli*. In fact, exposure to magnetic fields has becoming more important because of the more widespread use of the magnetic-based devices or instruments.

To see the influence of an external field to the *E.coli*, we have proposed a model to describe the dynamics of pole-to-pole oscillation model of MinCDE proteins under the external field using the system of reaction diffusion equations. From differential equations, we have applied the explicit Euler method of integration to numerically solve these equations. In addition, we have both qualitatively and quantitatively investigated the kinetic and collective behavior of MinD and MinE proteins driven by an external field to see weather and how this extended studies give any interesting and/or different results from our chosen base line model proposed by Howard *et al.* It was found that the changes in the oscillation patterns of Min proteins and the shifts in the minimum and maximum of MinD and MinE proteins respectively in an external field is larger for stronger field. In addition, the effect of the direction of the field was investigated by reversing the sign of the field and it was found that the direction of the field does not

change the conclusion of the observed effects. Other characteristic parameters such as oscillatory period of each protein are also measured. Some good agreement between the theoretical prediction and the experimental results have been found. Moreover, some interesting new finding compared to the earlier studied by Howard *et al.* have also been obtained. To support our finding, we have tried to relate the results with some available experimental data and give some explanation or speculation. Since we have not yet performed experiments(but work is in progress), then our results are not conclusive. Hence, we cannot present the precise rational to our findings or we have not yet been able to fully disentangle this theoretical findings

Finally, we conclude with some open questions and comments. While we have gained considerable insight into the theoretical finding from our model, it would be very interesting and possible to obtain experimental results on this problem. A much more detailed knowledge of the new discovery is needed. Work is in progress to improve our theories. By adding more cell division complexity, more interesting and realistic outcome may arise such as the effect of inhomogeneity, fluctuation on proteins, temperature etc. Especially, the fluctuations in this system should at lest affect the microscopic scale properties of the system. Also, it is that the competition between the diffusion and the bias terms may well be at its most subtle.

The influence of both static and dynamic external field on cell division is largely unexplored and requires and immense research effort with immense benefits that will be forthcoming in biological/medical applications related to human health and diseases.

APPENDIX A

LINEAR STABILITY ANALYSIS

The stability analysis is a tool for the analysis of mathematical model. This tool use to predict the qualitative behavior of the system, which reflected by the solution of the mathematical model. In this thesis, the mathematical model represented by the reaction diffusion equations. Consider the following two coupled differential equations:

$$\begin{aligned} \dot{u} &= f(u,v) \\ \dot{v} &= g(u,v) \end{aligned} \tag{A.1}$$

The nullclines are defined as:

$$\begin{aligned} \dot{u} = 0 &\rightarrow f(u_0, v_0) = 0 \\ \dot{v} = 0 &\rightarrow g(u_0, v_0) = 0 \end{aligned} \tag{A.2}$$

in order to solve Eq.(A.2) we linearize around the fixed point (u_0, v_0):

$$\begin{aligned} u' &\equiv u - u_0 \\ v' &\equiv v - v_0 \end{aligned} \tag{A.3}$$

If $f(u,v)$ and $g(u,v)$ are approximated by a first order Taylor expansion, Eq.(A.2) can be written as:

$$\begin{aligned} \dot{u} &\approx u' \left.\frac{\partial f}{\partial u}\right|_{(u_0,v_0)} + v' \left.\frac{\partial f}{\partial v}\right|_{(u_0,v_0)} \equiv au' + bv' \\ \dot{v} &\approx u' \left.\frac{\partial g}{\partial u}\right|_{(u_0,v_0)} + v' \left.\frac{\partial g}{\partial v}\right|_{(u_0,v_0)} \equiv cu' + dv' \end{aligned} \tag{A.4}$$

or in matrix notation:

$$\vec{\dot{X}} = A\vec{X} \tag{A.5}$$

where

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}, \ \vec{\dot{X}} = \begin{bmatrix} \dot{u} \\ \dot{v} \end{bmatrix} \ and \ \vec{X} = \begin{bmatrix} u' \\ v' \end{bmatrix}$$

The matrix A is characterized by its trace and the determinant:

$$\begin{aligned} \tau &= trace(A) = a + d \\ \Delta &= \det(A) = ad - bc \end{aligned} \tag{A.6}$$

Lets try to find a solution of the convenient form:

$$\vec{\dot{w}} = \lambda\vec{w} = A\vec{w} \tag{A.7}$$

This vector is called the eigenvector, λ is the corresponding eigenvalue. Eq.(A.7) can be solved by:

$$\det \begin{bmatrix} a-\lambda & b \\ c & d-\lambda \end{bmatrix} = 0 \tag{A.8}$$

This naturally develops into the quadratic equation:

$$\lambda^2 - (a+d)\lambda + (ad - bc) = 0 \tag{A.9}$$

leading to:

$$\begin{aligned} \lambda_1 &= \tfrac{\tau + \sqrt{\tau^2 - 4\Delta}}{2} \\ \lambda_2 &= \tfrac{\tau - \sqrt{\tau^2 - 4\Delta}}{2} \end{aligned} \tag{A.10}$$

or

$$\begin{aligned} \Delta &= \lambda_1\lambda_2 \\ \tau &= \lambda_1 + \lambda_2 \end{aligned} \tag{A.11}$$

For a stable fixed point both λ_1 and λ_2 should be negative. Therefore a stable fixed point is characterized by:

$$\begin{aligned} \Delta &> 0 \\ \tau &< 0 \end{aligned} \tag{A.12}$$

The above method show that the linear stability for the ordinary differential equation. However, this thesis focus on the reaction diffusion system, which represented by the partial differential equation. From Eq.(A.1), we add the diffusion terms:

$$\begin{aligned} \tfrac{\partial u}{\partial t} &= f(u,v) + D_u\nabla^2 u \\ \tfrac{\partial v}{\partial t} &= g(u,v) + D_v\nabla^2 v \end{aligned} \tag{A.13}$$

where D_u and D_v are the diffusion coefficients of species u and v, ∇^2 is the Laplacial, which represent the partial derivative with respect to space. From the fixed point (u_0, v_0) and Eq.(A.13), we can introduce variables describing the small perturbation of the state and then linearize the equations. However, the standard solution should be sought in the form of plane waves:

$$u', v' \sim e^{(\lambda t + ikr)} \tag{A.14}$$

where k's have dimension of inverse length and are known as wavenumbers. After substitution of these perturbation variables into the linearized system, we will get a new characteristic equation:

$$\begin{bmatrix} a - \lambda - k^2 D_u & b \\ c & d - \lambda - k^2 D_v \end{bmatrix} \tag{A.15}$$

The solution for the quadratic equation are:

$$\lambda(k^2) = \frac{-\tau_k \pm \sqrt{\tau_k^2 - 4\Delta_k}}{2} \tag{A.16}$$

where $\tau_k = k^2(D_u + D_v) + trace(A)$ and $\Delta_k = \det(A) + k^4 D_u D_v - k^2(aD_v + dD_u)$. We need to identify conditions under the real parts of $\lambda < 0$. If this condition is satisfied for all k, the stationary homogeneous state of the reaction diffusion equations is stable to all perturbations. Since $trace(A) < 0$, τ_k is always positive.

In addition, we can finding the conditions under the stationary state, which is not stable to spacial perturbations with $k \neq 0$. These conditions relate to the roots of the dispersion relation. We consider two roots of the dispersion relation $\lambda_k = \lambda(k^2)$. They are defined by:

$$\begin{aligned} \lambda_{k1} &= \frac{-\tau_k + \sqrt{\tau_k^2 - 4\Delta_k}}{2} \\ \lambda_{k2} &= \frac{-\tau_k - \sqrt{\tau_k^2 - 4\Delta_k}}{2} \end{aligned} \tag{A.17}$$

then

$$\begin{aligned} \tau_k &= -(\lambda_{k1} + \lambda_{k2}) \\ \Delta_k &= \lambda_{k1}\lambda_{k2} \end{aligned} \tag{A.18}$$

Since $trace(A) < 0$, B is positive for all k and the roots cannot be both positive. Therefore, the instability can be only achieved in case of different sings; $\lambda_{k1} > 0, \lambda_{k2} < 0$ or $\lambda_{k1} < 0, \lambda_{k2} > 0$. This can happen only if $C(k^2) < 0$. Consider again the expression for Δ_k for the condition $C(k^2) < 0$ the coefficient at k^2 must be positive:

$$aD_v + dD_u > 0 \tag{A.19}$$

This is a necessary but it is not a sufficient condition and we must request that the minimum of $C(k^2)$ is below zero.

$$\left[\frac{-(aD_v+dD_u)+i\sqrt{4D_uD_v\det(A)}}{2D_uD_v}\right]\left[\frac{-(aD_v+dD_u)-i\sqrt{4D_uD_v\det(A)}}{2D_uD_v}\right] > 0$$

and

$$\frac{(aD_v+dD_u)^2-4D_uD_v\det(A)}{4D_uD_v} > 0$$

then

$$\frac{(aD_v+dD_u)^2}{4D_uD_v} > \det(A) \tag{A.20}$$

Finally, we can assemble all the obtained throughout the analysis inequalities:

$$\begin{aligned} &trace(A) = a + d < 0 \\ &\det(A) = ad - bc > 0 \\ &aD_v + dD_u > 0 \\ &\frac{(aD_v+dD_u)^2}{4D_uD_v} > \det(A) \end{aligned} \tag{A.21}$$

Satisfaction of all four of them guarantees that the spatially homogeneous state corresponding to a stable state (u_0, v_0) becomes unstable to perturbations with wavenumbers k from a finite range:

$$k_1^2 < k^2 < k_2^2 \tag{A.22}$$

The boundary wavenumbers can be found as the roots of the equation:

$$k_{1,2}^2 = \frac{(aD_v+dD_u)\pm\sqrt{(aD_v+dD_u)^2-4D_uD_v\det(A)}}{2D_uD_v} \tag{A.23}$$

Now let us use the evaluate the stability of the Min system. We start with the four reaction diffusion equations Eq.(3.1-3.4), which diffuse on membrane of Min proteins as zero. We find the stability matrix by using those equations:

$$A = \begin{bmatrix} \frac{-\sigma_1}{1+\sigma_1' C_e} & \sigma_2 C_e & 0 & \frac{\sigma_1 C_D \sigma_1'}{(1+\sigma_1' C_e)^2} + \sigma_2 C_d \\ \frac{\sigma_1}{1+\sigma_1' C_e} & -\sigma_2 C_e & 0 & -\frac{\sigma_1 C_D \sigma_1'}{(1+\sigma_1' C_e)^2} - \sigma_2 C_d \\ -\frac{\sigma_4 C_e \sigma_4'}{(1+\sigma_4' C_D)^2} - \sigma_3 C_E & 0 & -\sigma_3 C_D & \frac{\sigma_4}{1+\sigma_4' C_D} \\ \frac{\sigma_4 C_e \sigma_4'}{(1+\sigma_4' C_D)^2} + \sigma_3 C_E & 0 & \sigma_3 C_D & -\frac{\sigma_4}{1+\sigma_4' C_D} \end{bmatrix} \tag{A.24}$$

This matrix comes from the derivative of Eq.(3.1-3.4) with respect to each species of Min protein concentrations. From this matrix, we can find the homogenous and steady state solutions of Min proteins, show in Fig.(A.1). We see that the cytoplasmic MinD is 116.873 μm^{-1}, cytoplasmic MinE is 3.36183 μm^{-1}, MinD on membrane is 1383.13μm^{-1} and MinE on membrane is 81.6382 μm^{-1}. The Min proteins on membrane have the large number when compare with the Min proteins in cytoplasm. It means that the dynamically assembles of Min proteins occurs near/on cytoplasmic membrane more than in cytoplasm. The next step, we will test stability of fluctuations around these homogenous solutions by using matrix A then:

$$\hat{A} = \begin{bmatrix} \frac{-\sigma_1}{1+\sigma_1' C_e} - D_D q^2 & \sigma_2 C_e & 0 & \frac{\sigma_1 C_D \sigma_1'}{(1+\sigma_1' C_e)^2} + \sigma_2 C_d \\ \frac{\sigma_1}{1+\sigma_1' C_e} & -\sigma_2 C_e & 0 & -\frac{\sigma_1 C_D \sigma_1'}{(1+\sigma_1' C_e)^2} - \sigma_2 C_d \\ -\frac{\sigma_4 C_e \sigma_4'}{(1+\sigma_4' C_D)^2} - \sigma_3 C_E & 0 & -\sigma_3 C_D - D_E q^2 & \frac{\sigma_4}{1+\sigma_4' C_D} \\ \frac{\sigma_4 C_e \sigma_4'}{(1+\sigma_4' C_D)^2} + \sigma_3 C_E & 0 & \sigma_3 C_D & -\frac{\sigma_4}{1+\sigma_4' C_D} \end{bmatrix} \tag{A.25}$$

where $-D_D q^2$ and $-D_E q^2$ are the adding terms, which come from the standard solution $C_n \sim e^{(\lambda t + iqx)}$ (where $n = \{D, d, E, e\}$, λ = wavelength and q = wavenumber). We will determine eigenvalues of stability matrix and find the real part of these eigenvalues, then we can plot the largest as a function of q, shown in Fig.(A.2).

From this figure, we can find the maximally linearly unstable oscillating mode by

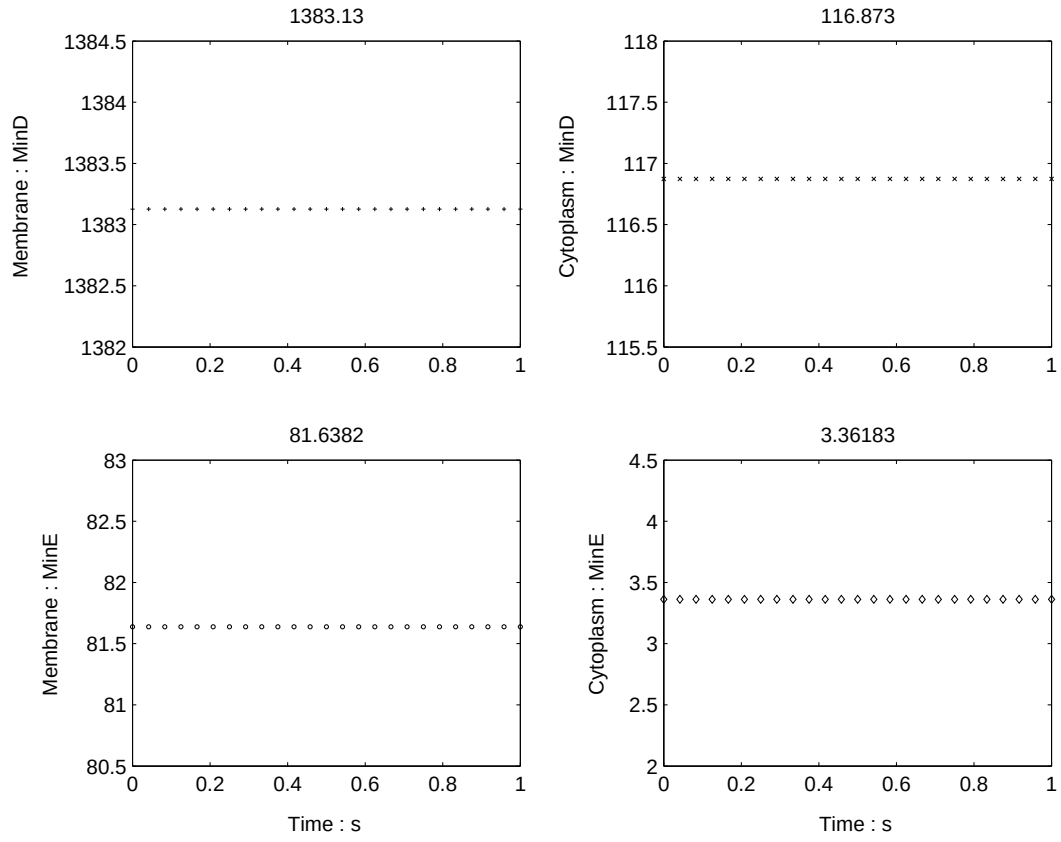

Figure A.1: The homogenous solutions of Min proteins in cytoplasm and on cytoplasmic membrane. The numbers on the top of each figures represent the concentrations of homogenous solutions. For the symbols, (+) represent the values of MinD on membrane, (x) represent the values of MinD in cytoplasm, (∘) represent the values of MinE on membrane and (♢) represent the values of MinE in cytoplasm.

using the q-wavenumber (which given the maximum of the real part of eigenvalue) and the formula $\lambda = 2\pi/q$. Then we will get $\lambda = 4.2\mu m$ where $q = 1.5\mu m^{-1}$. In addition, the instability behavior will induce the oscillation pattern, under the perturbation of fluctuations around the homogenous solutions. For the other case, we will consider the stability when the diffusion on membrane of Min proteins are not zero. From Eq (A.25),

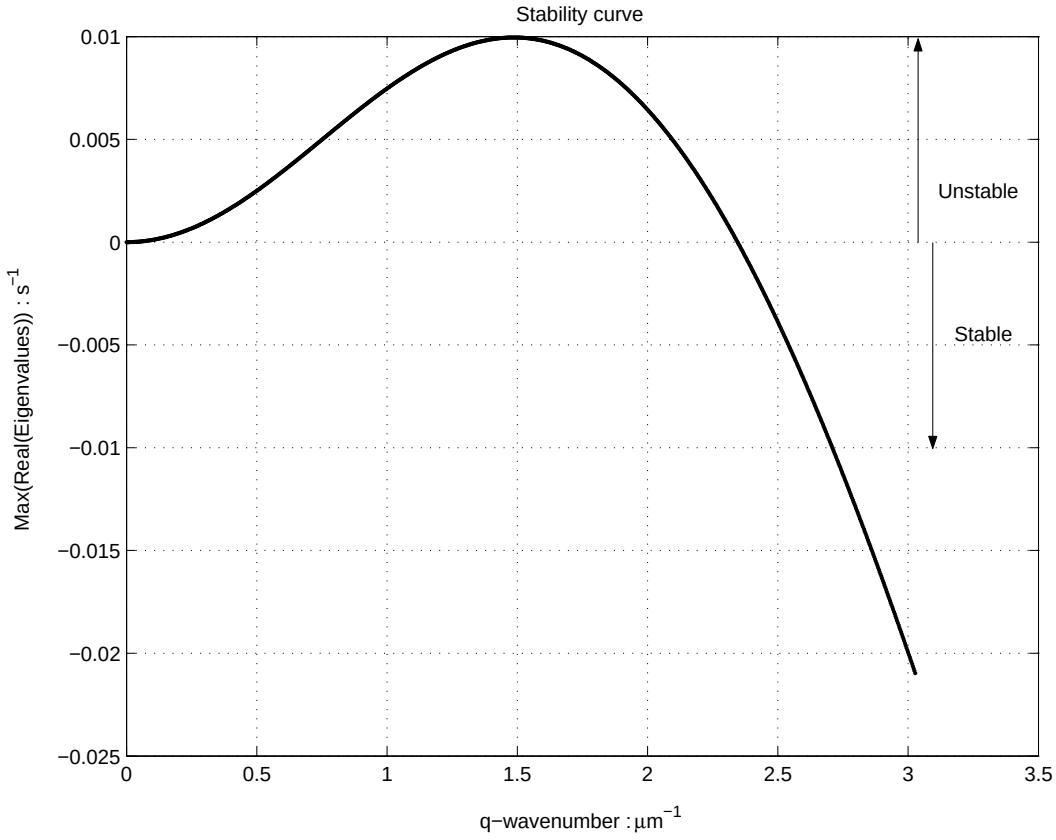

Figure A.2: The stability curve for diffusion on the cytoplasmic membrane of Min proteins as zero.

the matrix of testing stability of fluctuations around the homogenous solutions is:

$$\hat{A} = \begin{bmatrix} \frac{-\sigma_1}{1+\sigma_1' C_e} - D_D q^2 & \sigma_2 C_e & 0 & \frac{\sigma_1 C_D \sigma_1'}{(1+\sigma_1' C_e)^2} + \sigma_2 C_d \\ \frac{\sigma_1}{1+\sigma_1' C_e} & -\sigma_2 C_e - D_d q^2 & 0 & -\frac{\sigma_1 C_D \sigma_1'}{(1+\sigma_1' C_e)^2} - \sigma_2 C_d \\ -\frac{\sigma_4 C_e \sigma_4'}{(1+\sigma_4' C_D)^2} - \sigma_3 C_E & 0 & -\sigma_3 C_D - D_E q^2 & \frac{\sigma_4}{1+\sigma_4' C_D} \\ \frac{\sigma_4 C_e \sigma_4'}{(1+\sigma_4' C_D)^2} + \sigma_3 C_E & 0 & \sigma_3 C_D & -\frac{\sigma_4}{1+\sigma_4' C_D} - D_e q^2 \end{bmatrix} \quad \text{(A.26)}$$

where $D_d q^2$ and $D_e q^2$ are the new perturbations of fluctuations around the homogenous solutions, which means that the Min proteins diffuse near/on cytoplasmic membrane. From this matrix, we plot the stability curve, shown in Fig.(A.3). For the maximally linearly unstable oscillating mode in this case, we can find by using $q = 1.0\mu m^{-1}$, then $\lambda = 6.28\mu m$.

The interesting results of the stability analysis for the Min system can be sum-

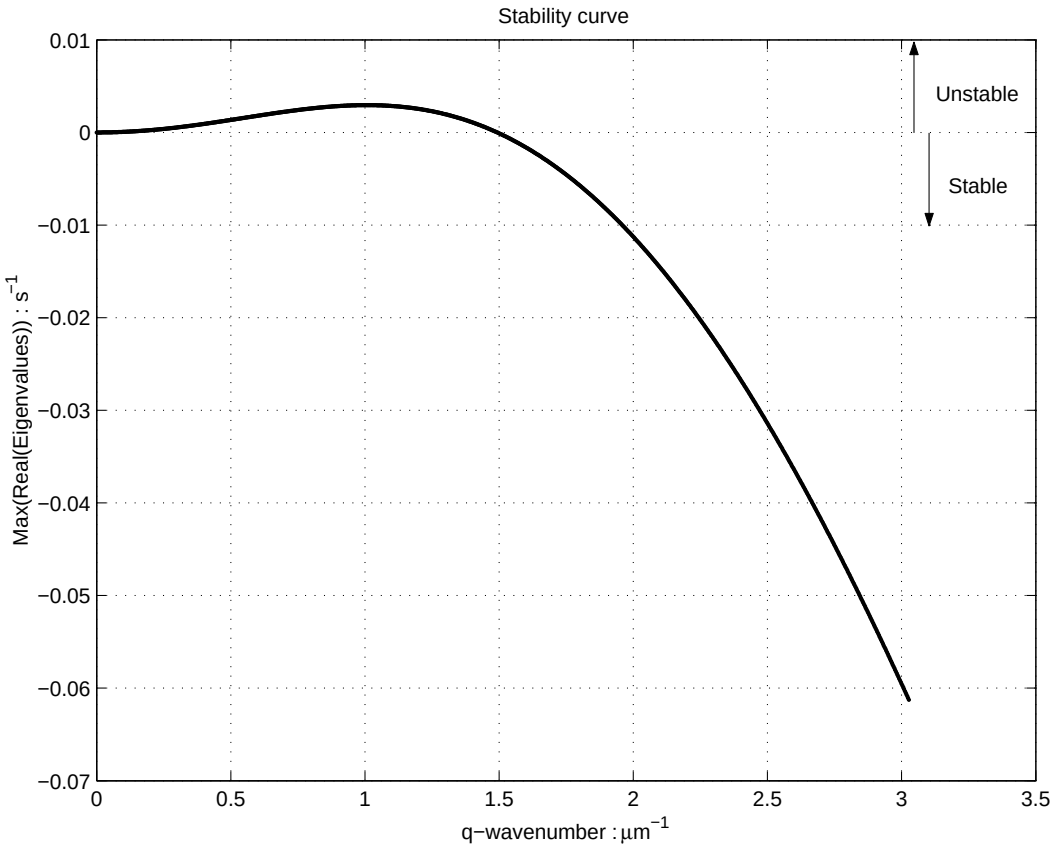

Figure A.3: The stability curve for diffusion on the cytoplasmic membrane of Min proteins as non-zero.

marized as follows:

1. The stability curves in both cases are different. This situation means that the stability of dynamics of Min system controlled by the diffusive behavior of the Min molecules.

2. The wavelength in both cases are differences, reflected by the values of wavenumber(q) at maximum positive eigenvalue. Then the oscillation behavior of Min proteins are different. For the case of non-diffusion on membrane, it formes oscillation pattern rapidity when compares with the case of diffusion on membrane, reflected from wavelength of the first case ($4.2\mu m$) less than the second case ($6.28\mu m$).

In fact, the physical origin of the instability lies in the disparity between the membrane and cytoplasmic diffusion rates, and also in the slower rate at which MinE disassociates from the membrane. This ensures that the MinE dynamics lags that of the

MinD, setting up the oscillating patterns.

APPENDIX B

PROGRAM

This is a program for finding the numerical results.

```
#include<stdio.h>
#include<math.h>
#define nx 250
#include<stdlib.h>
double ran();
 main()
 {     /*main*/
  FILE *inputdata,*checkdata,*outputdata,*diffsMinD,*diffsMind,
       *diffsMinE,*diffsMine,*TMinD,*TMinE;
  inputdata=fopen("inputdata.txt","r");
  outputdata=fopen("outputdata.txt","w+");
  diffsMinD=fopen("MinsD.txt","w+");
  diffsMind=fopen("sminsd.txt","w+");
  diffsMinE=fopen("MinsE.txt","w+");
  diffsMine=fopen("sminse.txt","w+");
  TMinD=fopen("TotalMinD.txt","w+");
  TMinE=fopen("TotalMinE.txt","w+");
  double D[251],newD[251];
  double d[251],newd[251];
  double E[251],newE[251];
  double e[251],newe[251];
```

```
checkdata=fopen("checkdata.txt","w+");
long int i,j,k,n;
long int save_step=90000;
double dx,dt,t,L,ntime,exf,z1,z2,z3,z4,zp1,zp4,re,ree,rd,rdd,rf,cd,ce;
double totalD,totalE,total1,total2,total3,total4;
total1=0.0;
total2=0.0;
total3=0.0;
total4=0.0;
totalD=0.0;
totalE=0.0;
fscanf(inputdata,"%lf",&z1); //20
fscanf(inputdata,"%lf",&zp1);//0.028
fscanf(inputdata,"%lf",&z2); //0.0063
fscanf(inputdata,"%lf",&z3); //0.04
fscanf(inputdata,"%lf",&z4); //0.8
fscanf(inputdata,"%lf",&zp4);//0.027
fscanf(inputdata,"%lf",&L);  //2.0
fscanf(inputdata,"%lf",&t);  //10000.0
fclose(inputdata);
dx=L/nx;    /* space unit is micrometre*/
dt=1.0E-5;
ntime=t/dt;
rd=0.28*dt/(dx*dx);
rdd=0.003*dt/(dx*dx);
re=0.6*dt/(dx*dx);
ree=0.006*dt/(dx*dx);
rf=dt/(2.0*dx);
```

```
  exf=0.0; // For change field parameters
  cd=0.003/0.28;// cb = control the external field for MinD on membrane
  ce=0.006/0.6;//  cd = control the external field for MinE on membrane
  printf("%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f\t%f \n",
          dx,dt,z1,z2,z3,z4,zp1,zp4,rd,rdd,re,ree,cd,ce,rf,exf,ntime);
  /*clear array*/
  i=0;
  for(i=0;i<=nx;i++)
    {     //1
     D[i]=0.0;
     d[i]=0.0;
     E[i]=0.0;
     e[i]=0.0;
     newD[i]=0.0;
     newd[i]=0.0;
     newE[i]=0.0;
     newe[i]=0.0;
    } //1
   /*initial condition*/
i=0;
   for(i=0;i<=nx;i++)
  {
          D[i]=((double)rand()/RAND_MAX)*3000.0;
          d[i]=((double)rand()/RAND_MAX)*0.0;
          E[i]=((double)rand()/RAND_MAX)*170.0;
          e[i]=((double)rand()/RAND_MAX)*0.0;
 }
                          /* Loop time */
```

```
n=0;
for(n=0;n<ntime;n++)
{                    /* Loop space */
     /* Zero calculation */
        newD[0]= (2.0*rd*D[1]) + ((1.0-(2.0*rd))*D[0])
           + (dt*((z2*e[0]*d[0])
           - (z1*D[0]/(1.0+(zp1*e[0])))));
        newE[0]= (2.0*re*E[1]) + ((1.0-(2.0*re))*E[0])
           + (dt*((z4*e[0]/(1.0+(zp4*D[0])))
           - (z3*D[0]*E[0])));
        newd[0]= (2.0*rdd*d[1]) + ((1.0-(2.0*rdd))*d[0])
           - (dt*((z2*e[0]*d[0])
           - (z1*D[0]/(1.0+(zp1*e[0])))));
        newe[0]= (2.0*ree*e[1]) + ((1.0-(2.0*ree))*e[0])
           - (dt*((z4*e[0]/(1.0+(zp4*D[0])))
           - (z3*D[0]*E[0])));
      /* 250 calculation */
    j=0;
    for(j=1;j<=nx-1;j++)
  { /* Central calculation */
  newD[j]= (rd*(D[j-1]+D[j+1])) + exf*rf*(D[j+1]-D[j-1])
      + ((1.0-(2.0*rd))*D[j])
      + (dt*((z2*e[j]*d[j])
      - (z1*D[j]/(1.0+(zp1*e[j])))));
  newE[j]= (re*(E[j-1]+E[j+1])) + exf*rf*(E[j+1]-E[j-1])
      + ((1.0-(2.0*re))*E[j])
      + (dt*((z4*e[j]/(1.0+(zp4*D[j])))
      - (z3*D[j]*E[j])));
```

```
          newd[j]= (rdd*(d[j-1]+d[j+1])) + cd*exf*rf*(d[j+1]-d[j-1])
              + ((1.0-(2.0*rdd))*d[j])
              - (dt*((z2*e[j]*d[j])
              - (z1*D[j]/(1.0+(zp1*e[j])))));
          newe[j]= (ree*(e[j-1]+e[j+1])) + ce*exf*rf*(e[j+1]-e[j-1])
              + ((1.0-(2.0*ree))*e[j])
              - (dt*((z4*e[j]/(1.0+(zp4*D[j])))
              - (z3*D[j]*E[j])));
          } /* end for central */
                newD[250]= (2.0*rd*D[249]) + ((1.0-(2.0*rd))*D[250])
                   + (dt*((z2*e[250]*d[250])
                   - (z1*D[250]/(1.0+(zp1*e[250])))));
                newE[250]= (2.0*re*E[249]) + ((1.0-(2.0*re))*E[250])
                   + (dt*((z4*e[250]/(1.0+(zp4*D[250])))
                   - (z3*D[250]*E[250])));
                newd[250]= (2.0*rdd*d[249]) + ((1.0-(2.0*rdd))*d[250])
                   - (dt*((z2*e[250]*d[250])
                   - (z1*D[250]/(1.0+(zp1*e[250])))));
                newe[250]= (2.0*ree*e[249]) + ((1.0-(2.0*ree))*e[250])
                   - (dt*((z4*e[250]/(1.0+(zp4*D[250])))
                   - (z3*D[250]*E[250])));
if( (n%save_step)==0 )
{
    for (i=1;i<nx+1;i++)
    {
    fprintf( diffsMinD, "%f\t", D[i]);
    fprintf( diffsMind, "%f\t", d[i]);
    fprintf( diffsMinE, "%f\t", E[i]);
```

```
    fprintf( diffsMine, "%f\t", e[i]);
    fprintf( TMinD, "%f\t", D[i]+d[i]);
    fprintf( TMinE, "%f\t", E[i]+e[i]);
    }
    fprintf( diffsMinD, "\n");
    fprintf( diffsMind, "\n");
    fprintf( diffsMinE, "\n");
    fprintf( diffsMine, "\n");
    fprintf( TMinD, "\n");
    fprintf( TMinE, "\n");
}
         /* update values*/
         k=0;
         for(k=0;k<=nx;k++)
            {
              D[k]=newD[k];
              d[k]=newd[k];
              E[k]=newE[k];
              e[k]=newe[k];
            }
            /*Boundary condition for Mind and Mine*/
            /*d[0]=d[2];
            e[0]=e[2];
            d[250]=d[248];
            e[250]=e[248];*/
        } /* end for "n" */
     i=0;
     for(i=0;i<=nx;i++)
```

```
       {
          totalD = D[i]+d[i];
          totalE = E[i]+e[i];
          fprintf(checkdata,"%f\t%f  \n",totalD,totalE);
          total1=total1+D[i];
          total2=total2+E[i];
          total3=total3+d[i];
          total4=total4+e[i];
       }
     fprintf(outputdata,"total= %f\t%f\t%f\t%f\n",total1,total2,total3,total4);
     fclose(checkdata);
     fclose(outputdata);
  fclose(diffsMinD);
  fclose(diffsMind);
  fclose(diffsMinE);
  fclose(diffsMine);
  fclose(TMinD);
  fclose(TMinE);
      return(0);
 }  /* end main */
```

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