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Chromosome segregation in *Escherichia coli* division: A free energy-driven string model

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Abstract

Although the mechanisms of eukaryotic chromosome segregation and cell division have been elucidated to a certain extent, those for bacteria remain largely unknown. Here we present a computational string model for simulating the dynamics of *Escherichia coli* chromosome segregation. A novel thermal-average force field accounting for stretching, bending, volume exclusion, friction and random fluctuation is introduced. A Langevin equation is used to simulate the chromosome structural changes. The mechanism of chromosome segregation is thereby postulated as a result of free energy-driven structural optimization with replication introduced chromosomal mass increase. Predictions of the model agree well with observations of fluorescence labeled chromosome loci movement in living cells. The results demonstrate the possibility of a mechanism of chromosome segregation that does not involve cytoskeletal guidance or advanced apparatus in an *E. coli* cell. The model also shows that DNA condensation of locally compacted domains is a requirement for successful chromosome segregation. Simulations also imply that the shape-determining protein MreB may play a role in the segregation via modification of the membrane pressure.
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Keywords: Prokaryotic cell division; Chromosome segregation; DNA compaction; *Escherichia coli*; Self-organization

1. Introduction

Bacteria are simple organisms which maintain precise replication, segregation and division. Although much has been understood for eukaryotic cells, how replication, segregation and division are coordinated in prokaryotic cells remains elusive. In eukaryotic cells, chromosomes are wrapped into nucleosomes around highly positively charged histone proteins, further compacted by condensing and tied by cohesions. After replication, chromosomes are separated by a dedicated cytoskeletal apparatus (Kline-Smith and Walczak, 2004). Highly conserved, histones and cytoskeletal apparatus appeared later in evolution and are not present in bacteria. Instead, bacteria appear to deploy simpler mechanisms to orchestrate precise replication, segregation and division. For example, in *Escherichia coli*, placement of the division plane is determined in combination of the MinCDE and the nucleoid occlusion systems (Norris et al., 2004; Margolin, 2006). The MinCDE system coordinates an active oscillation of Min proteins that determines the location of *E. coli* division. Many mathematical models have been proposed to explain experimental observations (Howard et al., 2001; Meinhardt and de Boer, 2001; Kruse, 2002; Huang et al., 2003; Drew et al., 2005; Kerr et al., 2006; Pavin et al., 2006). To better understand the dynamics of chromosome replication, segregation and division, mathematical models and quantitative analysis of the mechanism is of help.

There are several hypotheses on how chromosomes segregate in bacteria. In 1963 Jacob et al. proposed a model in which bacterial chromosomes are attached to the membrane and they are separated as a result of the elongation of the membrane. As new membrane material is continuously inserted between the two attachments, the chromosomes are dragged apart (Jacob and Brenner, 1963; van Helvoort and Woldringh, 1994). Later findings on the speed of chromosome movement and cell elongation have shown that this model cannot fully explain experimental observations (Teleman et al., 1998; Daniel and Errington, 2003). In *Bacillus subtilis*, the average movement of chromosome is $0.17\,\mu m\,min^{-1}$, while the speed of cell elongation is $0.011–0.025\,\mu m\,min^{-1}$ (Webb et al., 1998). Chromosomes move much faster than the cell elongation rate. In 2001, Lemon and Grossman proposed an extrusion capture model. A stationary replisome stays at the middle of the cell and it constantly pulls

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the mother chromosome while pushes the new daughter chromosomes away from the center (Lemon and Grossman, 2001). However, in *Caulobacter crescentus*, the replisome was found to be moving during replication (Jensen et al., 2001). In 2002, Dworkin and Losick proposed that chromosomes are repelled by RNA polymerase extending between two duplicated replication origins (*ori*) (Dworkin and Losick, 2002). However, RNA polymerase is not stationary or partially immobilized but resides everywhere around the nucleoid (Lewis et al., 2000). Woldringh presented a coupled transcription–translation–insertion (transertion) model in which daughter chromosomes compete for membrane attachment space which leads to bidirectional segregation (Woldringh, 2002). However, the model requires daughter chromosomes tethered via a different set of proteins for different space (Rocha et al., 2003) and the mechanism is too complicated to be stable enough to achieve the rapid and precise separation of DNA segments (Ronen and Sigal, 2006).

Jun and Mulder presented an entropy-driven spontaneous segregation model and they applied the model to *E. coli* and *C. crescentus* (Jun and Mulder, 2006). They considered DNA to be polymer chains and used entropy maximization to guide each bead to less crowded positions. This model successfully describes the replication-segregation process of a cell cycle. However, they introduced an inner tube (a rod shaped envelope) to restrain the mother chromosome's movement and only allowed daughter chromosomes to occupy both the inner tube and outer tube space. When replication starts, daughter chromosomes occupy the empty space outside the inner tube and are pushed toward the poles. Since the mother and daughter chromosomes consist of the same DNA material, the spatial preference should be implied by the mathematical physico-chemical model, not imposed during simulations arbitrarily. Furthermore, whether such a differential space restriction for the mother and daughter chromosomes exists awaits additional experimental evidence.

In this study we present a free energy-driven string model that neither introduces differential spatial preference nor with advanced mitotic cytoskeletal guidance. Chromosomes are organized into a string of distinct topological domains (Staczek and Higgins, 1998; Postow et al., 2004) (Fig. 1). The migration of individual domains is predicted mathematically with our model and their locations can be compared to experimental observations of loci movement. Here we present the mathematical development of the proposed free energy-driven string model and simulation results.

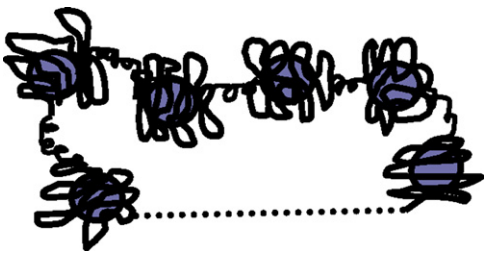

Fig. 1. Bacterial DNA organized into locally compacted–connected domains. A circular chromosome in *Escherichia coli* is thus represented as a string of interlinked domains.

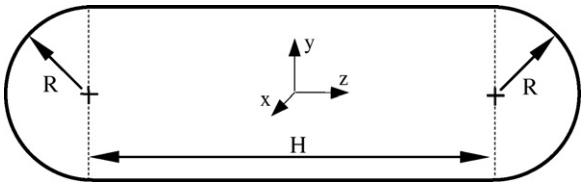

Fig. 2. The *E. coli* geometry is approximated by a cylinder of length H and two hemispheres of radius R at either end. The origin of the coordinate system (x, y, z) is placed at the center of the bacterium.

2. Methods

2.1. A free energy-driven string model

To analyze the dynamics of spatial organization of chromosomes during replication and segregation, we developed a computational model to simulate the dynamics of chromosome structures over the cell cycle. The dynamics is driven by gradients of the free energy. This theme has been used to develop theories of nanoparticles, viruses and macromolecules (Miao and Ortoleva, 2006a,b).

The *E. coli* geometry is approximated by a cylinder of length H and two hemispheres of radius R at either end (Fig. 2). Chromosome movement in *E. coli* is restricted in this boundary.

We construct the free energy of the chromosomal system as follows. Two neighboring domains are assigned a stretching energy

$$U_s(d) = k_s(d - d_0)^2 \quad \text{(stretching)}, \tag{1}$$

where k_s is the stretching rigidity, while d and d_0 are the actual/equilibrium distances of the two linked domains. The stretching force on domain i is computed via

$$\vec{F}_i^s = -2k_s[(d_{i-1} - d_0)\vec{u}_{i-1} - (d_i - d_0)\vec{u}_i] \quad \text{(stretching)}, \tag{2}$$

where d_i is the distance between domains i and $i+1$, and $\vec{u}_i$ is the unit vector pointing from i to $i+1$.

Each domain possesses a harmonic bending potential due to its interaction with left and right neighbors

$$U_b(\theta) = k_b(\theta - \theta_0)^2 \quad \text{(bending)}, \tag{3}$$

where k_b is the bending rigidity, while θ and θ_0 are the actual/equilibrium angles between two links. The corresponding bending force on domain i is given by

$$\vec{F}_i^b = -2k_b(\vec{A}_i - \vec{B}_i + \vec{B}_{i-1} - \vec{A}_{i+1}) \quad \text{(bending)} \tag{4}$$

with

$$\vec{A}_i = (\theta_i - \theta_0)\frac{\vec{u}_i + \vec{u}_{i-1}\cos\theta_i}{d_{i-1}\sin\theta_i},$$

$$\vec{B}_i = (\theta_i - \theta_0)\frac{\vec{u}_{i-1} + \vec{u}_i\cos\theta_i}{d_i\sin\theta_i}. \tag{5}$$

Since distances between domains are much larger than the van der Waals interaction range or the electrostatic Debye length of the intracellular medium, we approximate these interactions by a