

Statistical Physics in Modeling Chromosome Movements During Nuclear Oscillation of Fission Yeast



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I would like to dedicate this thesis to my loving parents ...

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other university. This dissertation is my own work and contains nothing which is the outcome of work done in collaboration with others, except as specified in the text and Acknowledgements. This dissertation contains fewer than 65,000 words including appendices, bibliography, footnotes, tables and equations and has fewer than 150 figures.

Wenwen Huang
February 2017

Acknowledgements

And I would like to acknowledge ...

Abstract

This is where you write your abstract ...

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Chapter 1

Introduction

Many biological processes can be transferred to well-studied models in statistical physics. Examples are ranging from the random walk model of mRNA during the transcription [6–8] to the evolution of ecological systems [9–12]. Analysis of these extracted models could help us to get useful insights into the corresponding biological problems. In this thesis, we are interested in modeling a molecular level biological problem, i.e. the motion of chromosomes in fission yeast during meiotic cell division [13, 5, 14].

Interestingly, during Prophase I of meiotic fission yeast, the nucleus containing three pairs of chromosomes move from one pole of the rod-like cell to the other, forming an oscillation behavior last for about two hours. The period of the oscillation is about 10 minutes. Cells are divided into two after the oscillation is done [15–17].

We are going to model this oscillation processes quantitatively with the chromosomes represented by polymer models [18, 19]. The results we obtained from the modeling are used to explain relevant biological functionalities like chromosome alignment and gene recombinations [20].

In this chapter, we will introduce the biological backgrounds and some previous related studies about modeling chromosomes with polymers. We will propose our research goals and give an overview of the thesis in the last section.

1.1 Nuclear oscillation in fission yeast

In this section, we will introduce the biological basis of nuclear oscillation in fission yeast. We will firstly introduce our model organism, fission yeast. And then we show some basis of meiosis cell division. Next, we go into the nuclear structure of fission yeast and the movements of chromosomes, specifically during meiosis. The biological processes like

chromosome alignment and recombination are discussed. In the last subsection, we discuss some understandings for the biological role of the nuclear oscillation.

1.1.1 Fission yeast

Fission yeast, also named *Schizosaccharomyces pombe*, is a model organism that widely used in the study of molecular and cell biology. It is a unicellular eukaryote and has a rod-like shape. Typical size of fission yeast is 3-4 micrometres in diameter and 7-14 micrometres in length [21, 22]. See in Fig. 1.1 for a illustration of fission yeast.

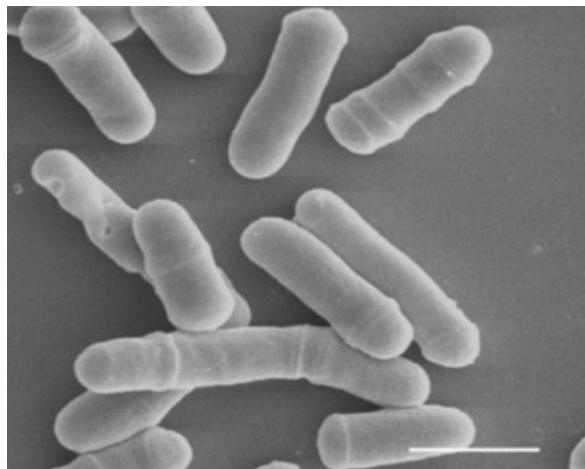


Fig. 1.1 Microscopic view of a fission yeast culture. The scalar bar indicates $10 \mu\text{m}$. Image reprinted from [1] with permission.

Fission Yeast is widely used in traditional brewing and baking. It was first discovered in 1893 in the sediment of millet beer [22, 23]. As a single-celled fungus, fission yeast has a simple genome with three different chromosomes. The genome of fission yeast is fully sequenced and the three chromosomes contain about 14Mb of DNA [24]. It has a rapid growth rate and easily manipulated to make mutants, which make it a perfect modeling organism for genetic studies. The growth of the fission yeast is simply by the elongation at the ends. After mitosis, division occurs by the formation a cell plate that cleaves the cell at its midpoint [21].

Fission yeast is normally a haploid cell. However, when put under stressful conditions, such as nitrogen deficiency, two cells will conjugate to form a diploid and then form four spores via meiosis [25]. This is easy to observe experimentally and this stage is exactly when the interesting nuclear oscillation happens [13]. In the next subsection, we will explain the basis of the meiosis in fission yeast.

1.1.2 Basis of meiosis

Meiosis is a kind of cell division that reduces the number of chromosomes in the parent cell by half and produces four genetically distinct gamete cells. This process occurs in all the sexually reproducing organisms, including human [26].

Meiosis begins with a parent cell with two copies of each chromosome, and is followed by two rounds of cell divisions which produce four potential daughter cells, each has half number of chromosomes as their parent cell. The two rounds of cell division are called *Meiosis I* and *Meiosis II*, respectively. It is during Meiosis I that the pair of chromosomes, one from the father and the other from the mother, separates into two offspring cells. Meiosis II is very similar to the mitosis where two sister chromatins separate [26, 27]. See an overview of meiosis in Fig. 1.2.

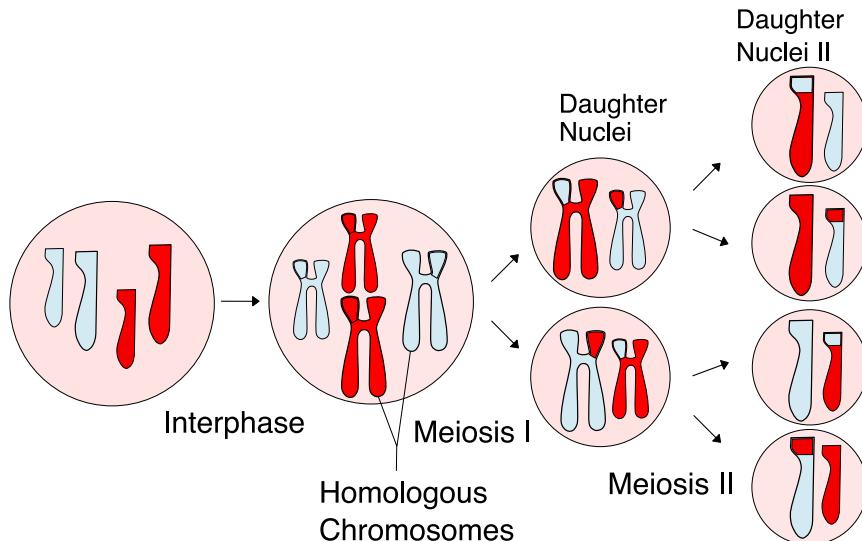


Fig. 1.2 Overview of meiosis and an illustration of recombination between homologous chromosomes resulting in four unique daughter cells. Image reprinted from [] with permission.

As in mitosis, each round of cell division can be divided in prophase, metaphase, anaphase, and telophase. We will elaborate Meiosis I in details, especially the Prophase I when the nuclear oscillation happens.

- *Prophase I*: prophase I is an important stage that many processes happened. Two of the examples are bouquet formation [28] and homologous recombination [29, 17], both occurring in generic organisms. In the early state of Prophase, chromosomes are reorganized spatially, usually, the telomeres are clustered and attached to a small region of the nuclear membrane, forming a bouquet structure. This is called bouquet formation or telomere clustering in biology [13, 28, 30], see in Fig 1.3 for an example in fission yeast. In the process of recombination, the homologous chromosomes, which are paternal and maternal

pairs, align and exchange some parts of their DNA and usually results in the chromosomal crossover. Homologous recombination is critical for pairing and accurate segregation of the chromosomes in the later stage of Meiosis I. More interestingly, this stage is exact the period when the nuclear oscillation happens in fission yeast [31, 32]. We will devote this part to next subsection.

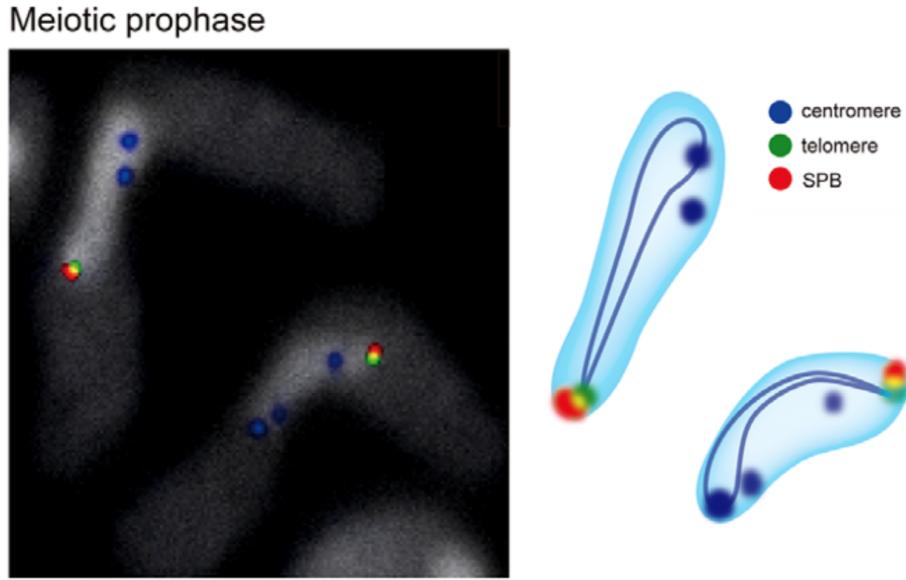


Fig. 1.3 The meiotic prophase I of fission yeast. Telomeres are clustered to form a bouquet structure. Image modified and reprinted from [2].

- *Metaphase I*: in this stage, homologous pairs move together along the middle plate, the microtubules from centrosomes attach to their respective chromosomes, the paired homologous chromosomes align along an equatorial plane that bisects the spindle. However, in Fission Yeast, the centromere is replaced by a functional equivalent organelle called spindle pole body (SPB) [26].
- *Anaphase I*: in this stage, the microtubules shorten, pulling homologous chromosomes to opposite poles. Notice here, chromosomes still consist of a pair of sister chromatids. The cell body elongates, preparing for cell division [26].
- *Telophase I*: in the last stage of Meiosis I, chromosomes arrive at the poles. The microtubules network of spindle disappears. New nuclear membrane appears. The two daughter cells now only have half the number of chromosomes [26].

After Meiosis I, Meiosis II occurs without DNA replication in between. The process is similar to Meiosis I except the sister chromatids segregate instead of homologous chromosomes [26]. Four unique daughter cells are formed after the completion of Meiosis. The homologous recombination process takes an important role for this uniqueness.

1.1.3 Nuclear oscillation

As mentioned in the previous subsection, nuclear oscillation happens during prophase I of meiosis in fission yeast, and so as the important processes of chromosomes homologous alignment and recombination [31]. Because the impressive shape of nucleus during this stage, nuclear oscillation also often mentioned as *horse-tail* movements in biology[33, 32, 29], see in Fig. 1.4 for a time-lapse illustration. We believe the chromosome movements play an important role in this process and decide to model it quantitatively. In this subsection, we are going to elaborate the details of nuclear oscillation. We will answer the questions like what is the internal structure of nucleus during oscillation, what is the driven force of the oscillation, how long the oscillation lasts and what is the time period of the oscillation, etc.

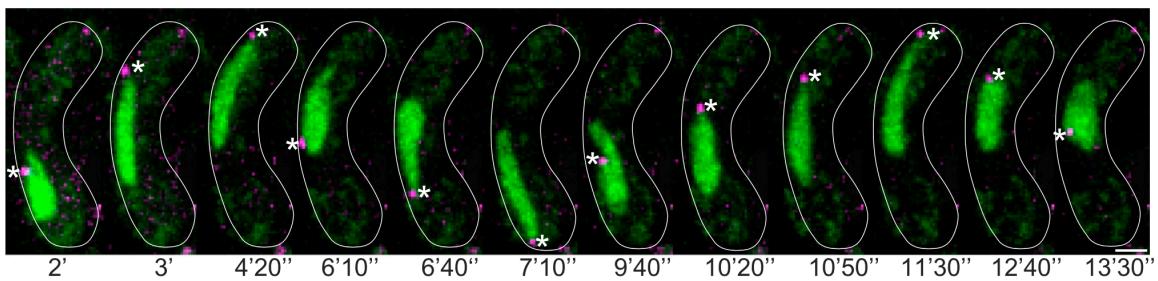


Fig. 1.4 Time-lapse experiments of nuclear oscillation in fission yeast, DNA marker in green (Rec8-GFP) and SPB marker in magenta (Sid4-mCherry) also indicated by asterisk. Reprinted from [3] with permission.

The looping structure of chromosomes

Before the nuclear oscillation, chromosomes are reorganized and the bouquet formation happens. In fission yeast, the SPB is anchored in the nuclear envelope, telomeres of chromosomes are clustered to the SPB region of the inner nuclear membrane. The chromosomes are condensed to be the rod-like chain. Notice that there are still two sister chromatins contained in one chromosome. With all the telomeres bond to the SPB, chromosomes form the looping structure, as we can see in Fig. 1.3.

Redistribution of dynein motors drives the nuclear oscillation

While the inner side of SPB bonds the chromosome telomeres, the outer side is attached to the microtubules in the cytoplasm. During the oscillation, dynein motors are the energy supplier. Interestingly, as one motor is not enough for the oscillation, the collective behavior of motors is observed to drive the nucleus motion. The spatial distribution of motor molecular

varies during the oscillation. Motors accumulates in the side of fission yeast that the nucleus moves toward to. It is found that the pulling force is the main contribution that drives the oscillation [5].

Related biological parameters of nuclear oscillation

To study the dynamics during oscillation, several parameters are estimated experimentally and input into our model later. These parameters are summarized in table 1.1.

Table 1.1 Parameters of fission yeast during meiosis

Parameter	Value
Typical size of nucleus	$3\mu\text{m}$
Chromosome number	Three pairs
Compaction ratio of chromatin	10^2bp/nm
Kuhn length of chromatin	$100 \sim 300\text{nm}$
Duration of nuclear oscillation	2 hours
Period of nuclear oscillation	10 min
Moving speed of nucleus	$2.5\mu\text{m/min}$
Viscosity of nucleoplasm	$1000 \times \mu_{\text{water}}$

1.1.4 The role of nuclear oscillation

Although we can clearly observe the nuclear oscillation in fission yeast, the biological role of it is not thoroughly understood. One intuitive hypothesize is that the movement facilitates the paring of homologous [16]. However, Koszul et al. proposed that the chromosome movement might play other roles than paring, such as resolve homologous entanglements or non-homologous connections [33]. Also, Mariola et al. stated a dual role for the nuclear oscillation, promoting initial paring and restricting the time of chromosome associations to ensure proper segregation [3].

We believe nuclear oscillation plays an important role for the chromosome alignment. However, it is hard to image the exact mechanism of the alignment without going deeper of the process. That is why we propose a quantitative model in this thesis and study the statistical and dynamical details of the model, trying to understand to the machinery of paring quantitatively.

1.2 Chromosomes modeled as the polymer

To quantitatively describe the chromosome, it is natural to model it as a polymer. In fact, there are already a lot of excellent examples in this direction [34–37]. However, depending on the situations under considering, different polymer models may applied.

In physics, a polymer model is usually described by beads connected by massless springs or rods. The interactions, usually characterized as different types of potentials, specify the setting of the model [19]. As we want to model the chromosome during nuclear oscillation in fission yeast, there are two major factors we need to take into account besides some other minor details. First, the topology of the chromosome is a ring structure as shown in Fig 1.3. Second, all chromosomes are bound to the SPB and pulled by an external force. According to these biological factors and the experimental measurements like Fig. 1.3, we propose a pulled polymer loop model for the chromosomes in this specific situation. See in Fig. 1.5 for a sketch of our model. We will leave the discussion of the model details in afterward chapters.

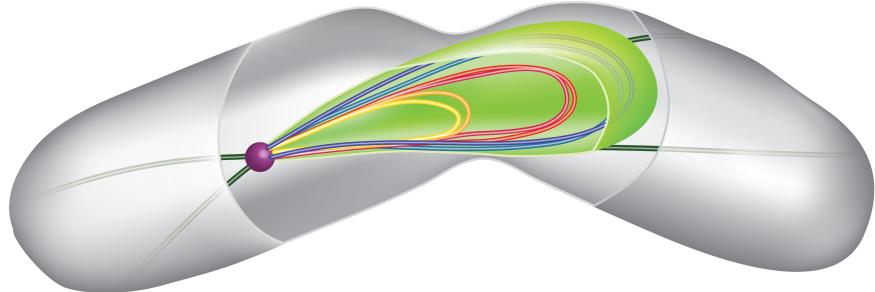


Fig. 1.5 The sketch of our pulled polymer loops model for chromosomes in meiotic fission yeast. Three pairs of chromosomes with all ends bound to SPB (shown in magenta) in the nucleus are indicated by different colors. The SPB is pulled by multiple dynein motors (not shown) walking along microtubules (dark green). The SPB is anchored to the nuclear envelope (light green) and entrains the whole nucleus.

To the best of our knowledge, there are not many works which are discussing on not only the polymer loops but also the polymer is pulled by an external force. In the following subsections, we will introduce two related aspects of previous works, i.e. works about the polymer loops and works related to pulled polymer.

1.2.1 The ring polymer model

Polymers forming a ring structure are ubiquitous in chemistry and biology [36, 38]. The study of ring polymer can go back to the years when polymer physics was built up [39, 40].

Kramers developed an equilibrium theory that possesses branch points and rings of the dilute polymer solution in 1946 [39]. Zimm calculated the statistics of mean square radii of molecules containing branches and rings in 1949 [40]. However, comparing to the simplest polymer chain model, research focus on polymer ring are far less than the former. We will review here some interesting and most related ones. Of course, it is not possible to exhaust all related works here, we pay our attention particularly to those that are related to the chromosome modeling.

Since Kramers and Zimm, there are a number of works trying to study the static and dynamical properties of the ring polymer from the theoretical point of view. In 1965, Casassa derived some statistical properties of flexible ring polymers, including mean square radius, the second Virial coefficient and angular distribution of scattering [41]. 1980, Burchard and Schmidt calculated the static and dynamical structure factors of flexible ring polymers [42]. Baumgärtner considered the self-avoiding effect of ring polymers in 1984 and found the asymptotic scaling exponents are the same as linear polymers [43]. In 1986, Cates et al. studied the nor-concatenated ring polymer melt and found the size of polymer R scales with the polymerization index N as $R \sim N^{2/5}$ and the diffusion constant D scales as $D \sim N^{-2}$ [44]. In 1994, Obukhov et al. considered the dynamics of a ring polymer in a gel and obtained the diffusion coefficient scales with the molecular weight as $D \sim M^{-2}$ and the longest relaxation time T scales as $T \sim M^{5/2}$ [45]. Carl investigated the configurational and rheological properties of multiple-twisted ring polymers using a long cyclic finitely extensible bead-spring model in 1995 [46]. He also presented a study on bead-spring chains in steady flows, various properties such like the power spectrum, the autocorrelation functions of configurational quantities were discussed in 1996 [47]. In 2001, Panyukov and Rabin studied the effects of thermal fluctuations on elastic rings. Analytical expressions are derived for some static and dynamical quantities [48]. Mukherji et al. studied a polymer ring or chain diffused around attractive surfaces. They found the diffusion constant scales as $D \sim N^{-3/2}$ linear chain and solid strong adsorbed surfaces, and $D \sim N^{-1}$ for ring polymer and soft surfaces in 2008 [49]. Sakaue proposed a simple mean-field theory for the structure of ring polymer melts which takes into account the many-body effects [50, 51]. In 2012, Kim et al. presented a self-consistent field theory formalism of topologically unconstrained ring polymers [52]. In 2013, Reigh performed lattice Monte-Carlo simulations to investigate the dependence of ring polymer conformation to the concentration, where the scaling of gyration radius with the concentration $R_g \sim \phi^{-0.59}$ was found [53]. In 2014, Lang et al. studied the tumbling dynamics of semiflexible ring polymers as a model of the cytoskeletal filament in a shear flow. They found the tumbling frequency scales f_c scales with the Weissenberg number as $f_c \sim Wi^{3/4}$ rather than the prediction of classical theory that $f_c \sim Wi^{2/3}$ [54].

Ring polymer with high concentration, like polymer melts, are often used in modeling interphase chromosomes. Interestingly, it is found that during interphase, the spatial organization for the multiple chromosomes in the nucleus is not homogeneous and well mixed. Instead, each chromosome forms its own “territories” [36]. Many interesting works can be found respecting to this problem. For example, in 2008, Rosa and Everaers used the simulation results of polymers to explain the existence and stability of territories of interphase chromosomes in genetic eukaryotes [55]. Because usually, the computation power required to simulate the whole genome is huge, they also developed an efficient multiscale numerical approach to study the conformational statistics of ring polymers melts in [56]. Dorier employed a very simple non-permeable freely jointed polymer model and recovered the chromosomal territories in a crowded nuclei [57]. This part of work is well reviewed in [36], the interested reader can refer to the references therein.

On the other hand, it is also possible that ring polymer structures are formed temporarily in chromosomes. This could be caused by the DNA replication process or binding proteins connecting two loci of chromosomes. Many great works were done also in this direction. In 1995, Sachs use a looping random walk model to study to the interphase chromosomes, fluorescence labeled data is compared to the theoretical prediction [58]. Marko considered a model of two polymer rings tethered one another and its application to chromosome segregation in 2009 [59]. The looping probabilities of interphase chromosomes were also discussed in [60]. In 2011, Zhang et al. modeled the meiotic chromosomes as a polymer that could form internal loops by binding proteins. They found the loops play an important role in the mechanical properties of the polymer [61]. Wong set up a polymer model and use it to predict the whole nuclear architecture of fission yeast [62]. Dekker and Giorgetti employed the computational polymer model to explain the 3C/HiC data [63, 64]. In 2014, Youngren employed ring polymer model to study the duplication and segregation of *E. coli* chromosomes [65]. These are just a few examples, more can be found if one is interested.

The confinement such as the nuclear membrane or cell shape could also take an important role in chromosome dynamics. One of the examples of this kind of work is Fritsche’s work in 2011, they studied the influence of confinement geometry to the spatial organization of semiflexible ring polymers [66]. The studies of the polymers (including chains and rings) under confinements were reviewed by Ha el al. in [67].

There are also a lot of great experimental work related to ring polymers. In 1992, Tead et al. employed polystyrene molecules to perform experiments and compared the diffusion of linear and ring polymers [68]. Kapnistos et al. found the stress relaxation of entangled ring polymer was power-law rather than exponential in [69]. Structure and dynamics of polymer rings by neutron scattering were studied by Brás et al. in 2011. Witz et al. employed the

atomic force microscopy to studied 2D circular DNA in [70, 71]. Gooßen et al. studied dynamics of polymer rings using neutron spin echo spectroscopy which space-time evolution of segmental motion could be observed [72, 73].

Due to its importance, the study of ring polymers is much intensive and causes much more attention nowadays. Besides what we have mentioned above, the shape of ring polymers is studied in [74–77]. Also, there are a series of works considering the ring polymer with entanglements and topological knots [78–86]. We are only able to list a few of those great works. Interested readers can refer to the references therein.

1.2.2 Pulled polymer model

As we mentioned above, in order to model the nuclear oscillation of fission yeast, we have to consider the pulling dynamics. If we transfer the coordinate and sit on the pulled monomer, a pulled polymer is also equivalent to a pinned polymer in an external flow or force field. In this section, we would like to review some previous works in this direction. Most of them are about pulled polymer chain. Whatsoever, we think it is still helpful to know what have been done about pulled polymers or tethered polymer in an external field.

A polymer chain with one end free and the other end pulled by an external force was first discussed by de Gennes [87, 18]. After that, another important progress was made by Pincus, he developed what is now called Pincus theory [88, 89], which consider the pulled polymer as a sequence of independent “blobs”. Brochard-Wyart further developed the “trumpet” and the “stem-flower” pictures of pulled polymer chain [90, 91, 4, 92]. When the pulling force is not too strong, the polymer presents as a series of independent blobs with increasing size, i.e. the portion of polymer near to the free end fluctuates more. As the pulling force increased to a strong regime, the polymer portion near to fixed end is totally stretched, forming a “stem-flower” like picture, see in Fig. 1.6. Using fluorescence microscope and optical tweezers, Perkins et al. performed the pulling experiments on single DNA molecule and found the results consistent with the Brochard-Wyart’s theory [93, 94]. They also measured the relaxation time of this pulled polymer and obtained the scaling $\tau \sim L^{1.66}$ [95]. Wirtz also confirmed the theory by measuring transport properties of a single DNA molecule in [96].

Rezehak et al. considered pinned polymer in a uniform flow with hydrodynamic interaction and proposed a so-called f-shell blob model [97]. Larson et al. performed Brownian Dynamics simulation for a DNA in an external flow field [98]. In 2000, Doyle measured the cyclic and stretching dynamics of a tethered DNA molecule in the shear flow [99, 100]. Sebastian studied the dynamics of pulling a polymer out of a potential well [101]. Cui performed the stretching and releasing experiment by pulling a single chicken erythrocyte

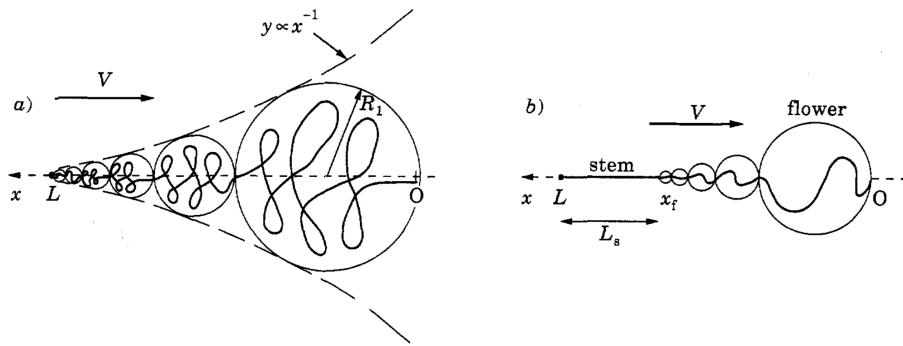


Fig. 1.6 Illustration of “stem-flower” picture for pulled polymer chain. (a) Trumpet picture at moderate pulling force; (b) Stem-flower picture at strong pulling force. Image reprinted from [4].

chromatin fiber with the optical tweezers [102]. Rzehak discussed the conformation fluctuation and relaxation of a tethered polymer in uniform flow [103]. In 2007, Mohan et al. employed Rouse theory to study the unraveling dynamics of tethered semiflexible polymer in uniform solvent flow [104]. Sing et al. studied flexible and semiflexible tethered polymers in the limit of high shear flows and consequently near-full extension of the chains in [105]. Sakaue et al. studied the conformation and dynamics of a single flexible polymer chain that is pulled by a constant force applied at its one end, finite extensibility, the excluded volume, and the hydrodynamic interactions are discussed [106]. Varghese et al. investigated the force fluctuations in stretching a tethered polymer [107]. In 2013, Dai and Doyle found in [108] that the scenario of a pulled polymer is very similar to a polymer confined in a cylinder with proper radius.

To the best of our knowledge, the discussion of pulled ring polymer is missing except our own work [20]. So we reviewed here the works about ring polymer on one side and the works of pulled polymer on the other side. Of course, the details are not shown here, interested readers can go into the references.

1.3 Outline

With the introduction of the biological problem and the background of polymer modeling in previous two sections, we are ready to go into the details of our study. There are several specific models and techniques used in this thesis, such as the ASEP model. In order not to break the logic of the thesis, we will leave the brief background introduction of those right before the using. In this section, we will propose our research goals for this thesis and give an overview for the organisation of the thesis.

1.3.1 Research goals

The research goals of this thesis is listed as following:

- Propose a polymer model to describe the chromosomes in fission yeast during nuclear oscillation. This is actually already mentioned in the previous section, i.e. the pulled polymer loop model. However, the details of the model will be discussed in the following chapters.
- Develop the quantitative theory for our pulled looping polymer model. As far as we know, there is no previous work on this issue. On the other hand, it is shown by the experimental facts that this model is the best one for our problem.
- Perform realistic numerical simulations of the nuclear oscillation of fission yeast using the polymer model. The theory is always simplified and has a lot of assumptions in order to analytically tractable. It is necessary to do a realistic simulation that can verify our theory on one hand, and comparable to the experimental data on the other hand.
- Using the physical insights to understand to biological processes such as chromosome alignment. Understand the biology is our ultimate goal. The chromosome movements during cell division are so important that many diseases are related to that, such as Down syndrome [109]. Our understanding from physical layer helps to fight with these diseases.

In one sentence, we want to quantitatively model the chromosome dynamics during the nuclear oscillation and use it to understand the biology.

1.3.2 Overview of the thesis

Add afterward.

Chapter 2

Model and Simulation Methods

To model the chromosome movements during nuclear oscillation in fission yeast, let us start from a single chromosome modeled by a single polymer loop. In this chapter, we will introduce the details of the polymer model for the chromosomes and the simulation methods that resolving the dynamics and statistics of the polymer.

2.1 Pulled polymer loop model

As mentioned in the previous chapter, there are three pairs of chromosomes in fission yeast. During nuclear oscillation, these three pairs of chromosomes bound to one point, i.e. the Spindle Pole Body (SPB). Now let us start with the simplest case and neglect the interactions between chromosomes, think about a single chromosome. It is a polymer with the ring structure, and an external force is exerted on the SPB. We have two choices to model this chromosome, i.e. the bead-rod model or the bead-spring model. We will use both models in this thesis but more discussions are focused on the bead-rod. Both models have their own benefits and shortcomings. Computationally, it is easier to manipulate the bead-spring model than the bead-rod. However, the bead-rod has the intrinsic property of finite extensible without resorting to some complex nonlinear spring potentials. This benefit we think is important because the chromosomes are highly condensed and are definitely finite extensible. In fact, we will show that the finite extensibility takes an important role for the polymer dynamics, see in the later chapters. And the simplicity of bead-rod model offers us the possibility to find analytical solutions.

In this section, we will introduce both the bead-rod and bead-spring model for modeling the chromosomes. However, before that, let us first do a coordinate transformation that makes our analysis much easier.

2.1.1 Coordinate transformation

Let us consider a single chromosome pulled at the SPB. The pulling force drives the chromosome moves with a velocity \mathbf{v} . In our model, the SPB is modeled as one monomer in the polymer loop. Other monomers representing the chromosome move together with the SPB because of the bonds. This scenario of pulled polymer loop is shown in Fig. 2.1 (a).

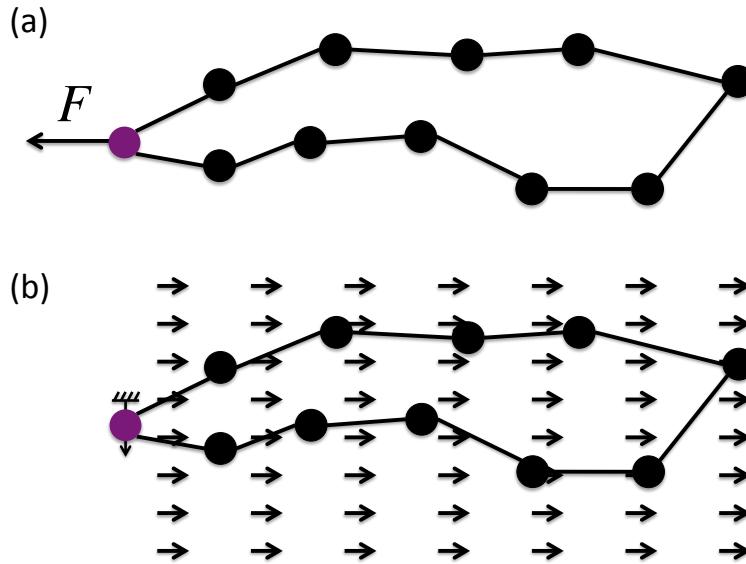


Fig. 2.1 Illustration of coordinate transformation. (a) a pulled polymer loop before transformation; (b) pinned polymer loop in an external field after transformation.

Now let us imagine we are sitting on the SPB. Then effectively, the SPB is pinned, and the polymer loop is immersed in a flow with velocity $-\mathbf{v}$, see in Fig. 2.1 (b). Let us assume the Stoke's law is valid and according to that, there is a force $\mathbf{F}^e = -\xi \mathbf{v}$ exerting on every bead. ξ is the friction coefficient for the bead in the solution.

In conclusion, the pulled polymer loop model is equivalent to the pinned polymer loop in an external force field. In our analysis, we will use the pinned polymer loop picture, because it is more easily to deal with both numerically and analytically. In the simulation, an extreme large pulling force is required if we use the first picture. The unusual force can easily become the bottleneck for the choosing of the integration time step. In theory, the force field picture offers a very clean energy landscape. Thus the pinned picture is preferred in our study.

2.1.2 Bead-rod model

Now let us come to a concrete polymer model for modeling the chromosomes, i.e. the bead-rod model. For this model, the beads representing chromosome segments are connected by the massless rigid rod. For simplicity, we assume the length of every rod is identical, denote by a . The rigidity of the rod means the distance between two neighboring beads is fixed.

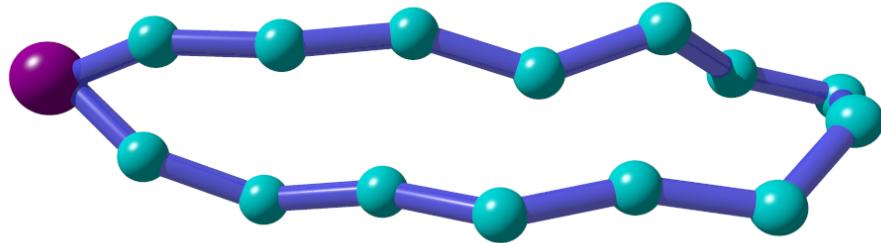


Fig. 2.2 Sketch of the bead-rod loop model. The magenta bead represents the SPB and other cyan beads represent the chromosome segments.

The dynamics of the polymer is specified by the motion of the beads. We shall first give out the dynamical equation and then explain how does it come from. Let us say the contour length of the polymer loop is L , i.e. there are L beads (including the SPB) and L rods in the polymer. Denote the beads by the index $i = 0, 1, 2, \dots, L-1, L$. Notice that the periodic index is used due to the looping structure, i.e. for any indexing quantities $x_0 = x_L$. Then the dynamical equation of i^{th} bead can be written as

$$\xi \frac{d\mathbf{r}_i}{dt} = \mathbf{F}_i^u + \mathbf{F}_i^c + \mathbf{F}_i^{pseudo} + \mathbf{F}_i^e + \mathbf{F}_i^b \quad (2.1)$$

where ξ is the friction coefficient of the bead in the solution, \mathbf{F}_i^u is the interaction force specified by some kind of potentials, \mathbf{F}_i^c is the constraint force that keeps the rod length fixed, \mathbf{F}_i^e is the external force and \mathbf{F}_i^b is the Brownian force caused by thermal fluctuations. And what is left in the right hand of Eq. (2.1) is \mathbf{F}_i^{pseudo} , which is a special type of force introduced in the bead-rod model in order to get the correct statistics. We will discuss more about it later.

Now let us come back to explain how does Eq. (2.1) come from. Firstly, notice that \mathbf{F}_i^b in the equation is a stochastic variable, so Eq. (2.1) is actually a stochastic differential equation. Secondly, the left-hand side of Eq. (2.1) is actually rearranged from the friction force of the bead in the solution $-\xi \mathbf{v}_i$. And we have assumed the solution is homogeneous so that the friction coefficient is independent of the space and time. Third, the inertial of the bead

is neglected due to millions of collisions per second from the water molecules. In another word, Eq. (2.1) essentially can be written as $\mathbf{F}_i^{total} = \mathbf{0}$. This is simply the Newton's law with inertial neglected. This kind of dynamics is commonly used in polymer physics and called Brownian Dynamics [110, 111].

Let us now discuss each term of the right-hand side of Eq. (2.1) one by one.

- Brownian force \mathbf{F}_i^b

The Brownian force can be caused by the enormous instantaneous collisions of the solvent molecules or by other sort of interactions between chromosomes and proteins in the nucleus. The level of fluctuation can be characterized by an effective temperature T . Mathematically, the Brownian force is described by a Gaussian process with the zero mean in space and time and the non-zero second moment, which can be written as:

$$\langle \mathbf{F}_i^b \rangle = \mathbf{0}, \quad (2.2a)$$

$$\langle \mathbf{F}_i^b(t) \mathbf{F}_j^b(t') \rangle = 2k_B T \xi \delta_{ij} \delta(t - t'), \quad (2.2b)$$

here, ξ is the friction coefficient. k_B is the Boltzmann constant. δ_{ij} is the Kronecker delta means there is no correlation for the Brownian force exerting on different beads. The second δ is the Dirac delta function.

- External force \mathbf{F}_i^e

The external force in our pinned polymer loop model is simply the equivalent flow field after coordinate transformation. So we have $\mathbf{F}_i^e = \xi \mathbf{v}_{SPB}$. In general, $\mathbf{v}_{SPB} = \mathbf{v}_{SPB}(t)$ is a function of time. However, when we consider the simplest case that the chromosome is pulled to move steadily in one direction, \mathbf{v}_{SPB} is a constant.

- Constraint force \mathbf{F}_i^c

The constraint force is the tension force on the rod to keep the length fixed. So the direction of the force is along the rod orientation. The rigid rod constraint can be written as

$$|\mathbf{r}_i - \mathbf{r}_{i-1}| - a = 0, \quad (2.3)$$

and $\mathbf{r}_0 = \mathbf{r}_L$ for the periodic indexing. The constraint force is an implicit force that depends on the other force exerting on the beads. We will discuss how to calculate this force in next section.

- *Pseudo* force \mathbf{F}_i^{pseudo}

The *Pseudo* force is a special virtual force that added in order to obtain the statistics we want. If we neglect the bending energy, excluded volume effect and other complex interactions in the model, we are essentially talking about the simplest freely joint polymer

model. For such a simple model, we expect the random walk statistics, i.e. the orientation of two consecutive rods is independent. So the distribution of the included angle of two rods should be uniform. However, we cannot obtain this statistics as we want without the *pseudo* force.

Let us take a simple example, the distribution of included angle of a trimer in 3D. Denote the angle as θ . The 3D spherical uniform distribution can be written as

$$p(\theta) = \text{const.} \sin \theta. \quad (2.4)$$

On the other hand, the distribution of rigid bead-rod trimer without *pseudo* force can be derived using the generalized coordinate

$$p(\theta) = \text{const.} (1 - \frac{1}{4} \cos^2 \theta)^{1/2} \sin \theta. \quad (2.5)$$

So they are not the same as we see here. The reason for this discrepancy is the rigidity of constraints reduce the phase space of the trimer from 6 dimensional gully to 4 dimension manifold. The simple Brownian force ensures the probability is uniform among the manifold but not θ .

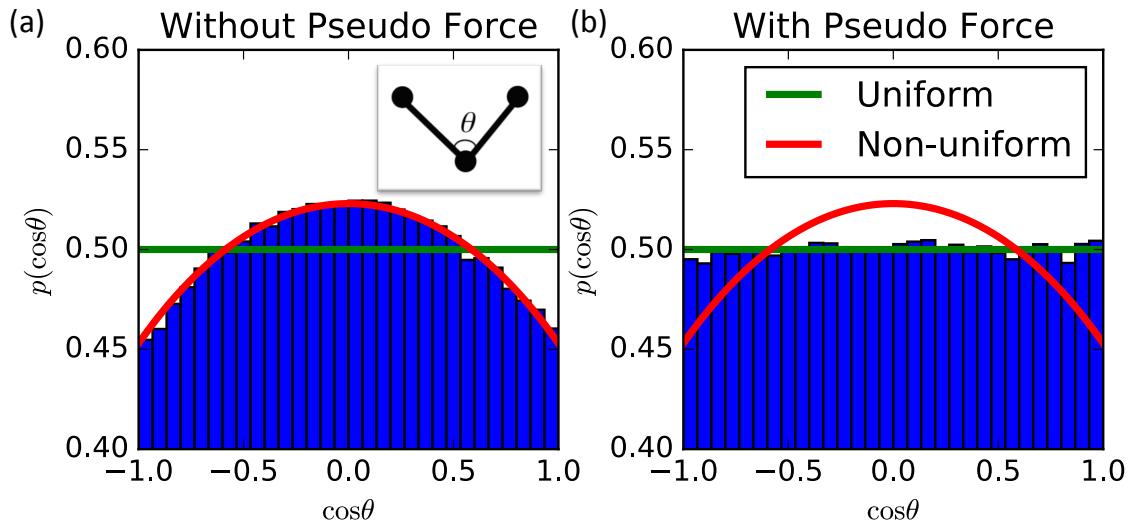


Fig. 2.3 The distribution of included angle of a bead-rod trimer. (a) without *pseudo* force; (b) with *pseudo* force. The blue bins are from Brownian Dynamics simulation results. Inset of (a) is a sketch for the trimer.

To solve the problem and obtain the statistics we want, Fixman introduced an effective *pseudo* potential depends on the polymer configuration [112], and hence we have a *pseudo*

force in Eq. (2.1). The explicit form of the *pseudo* force can be written as

$$\mathbf{F}_i^{pseudo} = -\frac{\partial U_{met}}{\partial \mathbf{r}_i}, \quad (2.6a)$$

$$U_{met} = \frac{1}{2} k_B T \ln(\det \mathbf{G}), \quad (2.6b)$$

where \mathbf{G} is the metric matrix of the bead-rod system [113]. We will show the details for the calculation of *pseudo* force in next section.

- Other potential forces \mathbf{F}_i^u

Other potential forces count the forces derived from bending energy, excluded volume effect, hydrodynamical interaction and other interaction potentials. The general form of this force can be written as

$$\mathbf{F}_i^u = -\sum_U \frac{\partial U}{\partial \mathbf{r}_i}, \quad (2.7)$$

here U can be different potentials. For instance, the bending potential can be calculated as

$$U_{bend} = -\frac{\kappa}{a} \sum_{i=1}^L \mathbf{u}_i \cdot \mathbf{u}_{i-1} \quad (2.8)$$

where $\mathbf{u}_i = (\mathbf{r}_i - \mathbf{r}_{i-1})/a$ is the unit vector of rod orientation, κ is the bending stiffness and a is the rod length.

For excluded volume effect, we usually model this interactive as pure repulsive Lennard-Jones potential

$$U_{LJ} = \begin{cases} 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right], & \text{if } r \leq r_c; \\ 0, & \text{if } r > r_c; \end{cases} \quad (2.9)$$

where r is the distance between two beads and $r_c = 2^{1/6}\sigma$, ϵ and σ are two parameters.

One can add more interaction potentials into the model. However, adding more potentials could easily lead to a complex model with many parameters. For the sake of simplicity, we will actually ignore these forces in most of our analysis. See in our later chapters.

2.1.3 Bead-spring model

Bead-spring model is another commonly used polymer model. There are several reasons that we use the bead-spring model complementary with the bead-rod model. First, the bead-spring model can work as a benchmark model of the bead-rod model. Unlike the bead-rod model, a *pseudo* force have to be added to obtain the correct random walk statistics, the model of beads connected by Hookean springs is intrinsically a system satisfied the random walk statistics.

Second, the role of finite extensibility can be understood by comparing the bead-rod and bead-spring model. Third, the computation power needed for the bead-spring model is much less than the bead-rod because we avoid calculating the *pseudo* force and implicit constraint force. Let us now look at the details of our bead-spring model.

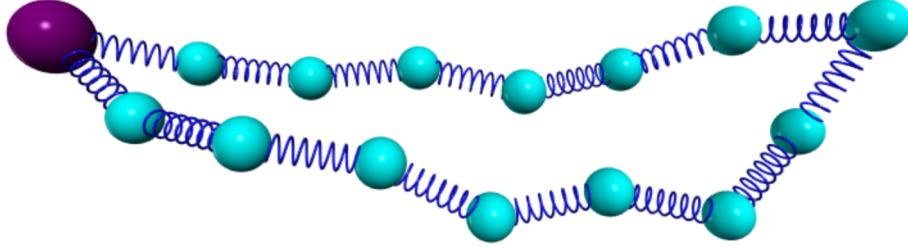


Fig. 2.4 Sketch of the bead-spring loop model. The magenta bead represents the SPB and other cyan beads represent the chromosome segments.

To model the chromosome in fission yeast during nuclear oscillation, we also need a looping structure like the bead-rod model above. The first bead represents the SPB, shown in Fig. 2.4. The dynamical equation is similar to the bead-rod model, can be written as following

$$\xi \frac{d\mathbf{r}_i}{dt} = \mathbf{F}_i^u + \mathbf{F}_i^{spring} + \mathbf{F}_i^e + \mathbf{F}_i^b. \quad (2.10)$$

The notations here are the same as the bead-rod model. In addition, the Brownian force, external force and the potential force are the same as in the bead-rod model. What is different is that the *pseudo* force is not needed and the constraint force is replaced by the spring force \mathbf{F}_i^{spring} . Notice that for a bead in the loop, there are two springs connecting to it. Thus

$$\mathbf{F}_i^{spring} = F_{i+1}^s(Q_{i+1})\mathbf{u}_{i+1} - F_i^s(Q_i)\mathbf{u}_i, \quad (2.11)$$

here, $F_i^s(Q_i)$ is the tension of the i^{th} spring and Q_i is the length of the spring. \mathbf{u}_i is the unit vector for the orientation of the i^{th} spring.

There are different types of springs one can use for the model. Here, we will introduce two most commonly used ones and both are used somewhere in the later chapters.

- Hookean spring

Hookean spring is a linear spring, where the tension of spring depends linearly on the length.

$$F^{Hookean} = H(Q - Q_0), \quad (2.12)$$

where H is the Hookean spring constant and Q_0 is the natural length of the spring. In practical Q_0 is set to a , which equals to the length of the bead-rod model. However, sometimes the zero length springs are used. We will point out when needed.

- Finite Extensible Nonlinear Elastic (FENE) spring

FENE spring is another commonly used spring. The force law of the spring is

$$F^{FENE} = \frac{HQ}{1 - (Q/R_0)^2}, \quad (2.13)$$

here R_0 is the maximal length of the spring. As we can see in Eq. (2.13), $F^{FENE} \rightarrow \infty$ when $Q \rightarrow R_0$.

In this section, we specify the dynamics and interaction details of our model for the meiotic chromosomes. The governing equations for the monomers are given. However, we have not talked about the special bead representing the SPB. We will discuss how to pin the SPB in next section.

2.2 Brownian Dynamics simulation method

After introducing the model, in this section, we will illustrate how to simulate the model numerically. Since we plan to do most of the theoretical analysis in the later chapters where the simulation results are used for the benchmark, it is convenient that we show the methods of simulation before that.

Brownian Dynamics (BD) simulation is a kind of Molecule Dynamics (MD) simulation technique. The governing equation of each monomer or particle is integrated to get the trajectories. And physical quantities are measured by ensemble average over trajectories of thousands of monomers. In our situation, the governing equations are Eq. (2.1) or Eq. (2.10). Our interested quantities are something like the average space distance between two beads, the typical size of the polymer and the characteristic time scale of the system dynamics. These are all tractable by BD simulations.

In the following subsections, we will introduce the algorithms used to do the bead-rod and bead-spring simulation separately. The simulation code is implemented in C++2011. Most the simulation are computed in our clusters with X86 architecture.

2.2.1 BD simulation of the bead-rod model

Essentially, the goal of the simulation is to solve the first order ordinary stochastic differential equation Eq. (2.1) numerically. However, the simple integration algorithm such as the Euler

algorithm would not work here. This is because of the implicit constraint force \mathbf{F}_i^c . Here we employ the predictor-corrector algorithm introduced by Liu [114].

To simplify the illustration of the algorithm, we will ignore all complex potential forces and the external force in Eq. (2.1), i.e. $\mathbf{F}_i^u = \mathbf{F}_i^e = \mathbf{0}$. It is easy to add them back after knowing the algorithm. The dynamical equation after simplification looks

$$\frac{d\mathbf{r}_i}{dt} = \frac{1}{\xi} \left(\mathbf{F}_i^c + \mathbf{F}_i^{pseudo} + \mathbf{F}_i^b \right). \quad (2.14)$$

The predictor-corrector algorithm is a two-step algorithm and can be divided into the prediction step and correction step. Let us discuss in details.

Prediction step

In the prediction step, the estimation of next time step bead position is evaluated without considering the constraints

$$\mathbf{r}_i^*(t + \Delta t) = \mathbf{r}_i(t) + \frac{1}{\xi} (\mathbf{F}_i^{pseudo} + \mathbf{F}_i^b) \Delta t. \quad (2.15)$$

In order to do the calculation, we need to evaluate the Brownian force and the *pseudo* force first. Here we will show how to do that one by one.

- Evaluation of the Brownian force \mathbf{F}_i^b

The Brownian force is mathematically generated by a Wiener process. Numerically, it is evaluated by a Gaussian distributed *pseudo* random number generated by the computer. Eq. (2.15) can be written more practically as

$$\begin{aligned} \mathbf{r}_i^*(t + \Delta t) &= \mathbf{r}_i(t) + \frac{1}{\xi} \mathbf{F}_i^{pseudo} \Delta t + \sqrt{\frac{2k_B T}{\xi}} d\mathbf{W}_i \\ &= \mathbf{r}_i(t) + \frac{1}{\xi} \mathbf{F}_i^{pseudo} \Delta t + \sqrt{\frac{2k_B T}{\xi} \Delta t} \mathbf{N}_i(0, 1), \end{aligned} \quad (2.16)$$

where $d\mathbf{W}_i$ is a Wiener process and $\mathbf{N}_i(0, 1)$ is a multi-dimensional Gaussian random number of mean 0 and variance 1.

- Evaluation of the *pseudo* force \mathbf{F}_i^{pseudo}

The expression for *pseudo* force is listed as Eq. (2.6). However, the evaluation is not easy and also expensive. To do that, let us first discuss the metric tensor \mathbf{G} .

$$G_{\alpha\beta} = \sum_i \frac{\partial g^\alpha}{\partial \mathbf{r}_i} \cdot \frac{\partial g^\beta}{\partial \mathbf{r}_i}, \quad (2.17)$$

where g^α is the rigid constraint that

$$g^\alpha(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_L) = 0. \quad (2.18)$$

In the case of a bead-rod loop, Eq. (2.3) is the constraint. And the $L \times L$ metric tensor looks like

$$\mathbf{G} = \begin{bmatrix} d_1 & c_1 & 0 & \cdots & c_L \\ c_1 & d_2 & c_2 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & c_{L-2} & d_{L-1} & c_{L-1} \\ c_L & \cdots & 0 & c_{L-1} & d_L \end{bmatrix}, \quad (2.19)$$

where diagonal elements $d_i = 2$, and the off-diagonal elements

$$c_i = -\mathbf{u}_i \cdot \mathbf{u}_{i-1} \quad (2.20)$$

Again here, the periodic index is applied, i.e. $\mathbf{u}_0 = \mathbf{u}_L$. Now, the *pseudo* force can be calculated as

$$\begin{aligned} \mathbf{F}_i^{pseudo} &= -\frac{1}{2}k_B T \frac{\partial \ln(\det \mathbf{G})}{\partial \mathbf{r}_i} \\ &= -\frac{1}{2}k_B T \sum_{\alpha,\beta} \frac{1}{\det \mathbf{G}} \frac{\partial \det \mathbf{G}}{\partial G_{\alpha\beta}} \frac{\partial G_{\alpha\beta}}{\partial \mathbf{r}_i} \\ &= -\frac{1}{2}k_B T \sum_{\alpha,\beta} G_{\beta\alpha}^{-1} \frac{\partial G_{\alpha\beta}}{\partial \mathbf{r}_i}. \end{aligned} \quad (2.21)$$

In order to calculate the *pseudo* force, we need to inverse the matrix \mathbf{G} . This operation is very expensive. Fortunately, the symmetric shape of \mathbf{G} in Eq. (2.19) makes it possible to find an efficient algorithm to do the computation. We employ the algorithm developed by Pasquali and Morse in [113]. They developed this algorithm for BD simulation of a bead-rod chain. We modified it and successfully applied it to our bead-rod ring model. See Appendix X for details.

Now the prediction of next time step bead position can be calculated straight forward using Eq. (2.16). The evaluation of other types of forces is quite simple if needed. And we are ready to discuss the correction step.

Correction step

The correction step utilizes the result of the prediction, and correct it with the constraint force to obtain the real next time step bead position.

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i^*(t + \Delta t) + \frac{1}{\xi} \mathbf{F}_i^c \Delta t. \quad (2.22)$$

And we known that the rigid rod constraints must be satisfied after the correction. Substitute Eq. (2.22) into Eq. (2.3) and also notice that

$$\mathbf{F}_i^c = \lambda_{i+1} \mathbf{u}_{i+1} - \lambda_i \mathbf{u}_i \quad (2.23)$$

where λ_i is the magnitude of tension on the i^{th} rod. Thus we obtain

$$\begin{aligned} & 2\Delta t \mathbf{b}_i \cdot (\lambda_{i-1} \mathbf{u}_{i-1} - 2\lambda_i \mathbf{u}_i + \lambda_{i+1} \mathbf{u}_{i+1}) \\ &= \xi (a^2 - \mathbf{b}_i \cdot \mathbf{b}_i) - \frac{(\Delta t)^2}{\xi} (\lambda_{i-1} \mathbf{u}_{i-1} - 2\lambda_i \mathbf{u}_i + \lambda_{i+1} \mathbf{u}_{i+1})^2. \end{aligned} \quad (2.24)$$

And $\mathbf{b}_i = \mathbf{r}_i^*(t + \Delta t) - \mathbf{r}_{i-1}^*(t + \Delta t)$. This is a set of nonlinear algebra equations. The second term at the right hand side is the nonlinear term. We can see from here, the nonlinear term is small when the time step Δt is small enough. Numerically, it is suitable to use the iteration methods such like the Picard's method to solve this set of equations. High order methods like the Newton's method are also applicable but require the calculation of Jacobian matrix every time step. In practical, a small time step is necessary for the convergence of root searching. We use a time step between $10^{-5} - 10^{-3}$ depends on different situations.

Once we solve the tension λ_i , plug in to Eq. (2.23) and then Eq. (2.22), the next time step bead position can be calculated straight forward.

Finally, We want to discuss a little bit about how to pin the first bead of the bead-rod model. One has several possible ways to do this. The first one is to use a very stiff zero-length spring attached it to the first bead and certain point. This method is very easy to implement. However, the use of the pinning spring will introduce a high-frequency factor into the polymer dynamics. This is not good when we analysis of the polymer dynamics. And the spring length is not perfectly zero when the polymer is subjected to a strong force field. So we use another method, i.e. pin the first bead use the zero-length rigid rods. In fact, we will need

three this kind of “ghost” rods in 3D, the orientation of the rods along three axes respectively. This method requires solving the additional constraint forces. And the calculation is more or less the same as we stated here. With this method, the bead can be pinned perfectly and no disturbing factor will be introduced.

2.2.2 BD simulation of the bead-spring model

The BD simulation of the bead-spring model is much simpler than the bead-rod model. There is neither implicit force nor complex forces need to evaluate during every time step. Of course, one can also use an implicit algorithm which allowed the using of a larger time step. However, we will simply use the explicit algorithms since they work pretty well.

We will introduce here two simple algorithms to simulate the bead-spring ring polymer, i.e. the Euler method and the stochastic Runge-Kutta method.

Euler method

Euler method, also called Euler-Maruyama method, is a 1/2 order integration scheme. In principle, the convergence is only guaranteed when $\Delta t \rightarrow 0$. However, it is still widely used because of its simplicity, especially when the variation of the drift and diffusive term in the stochastic differential equation is not too large. The beads connected by Hookean spring is a good example fits this method.

Using this method, the next time step bead position in our simple example can be calculated as

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \frac{1}{\xi} \mathbf{F}_i^{det} \Delta t + \sqrt{\frac{2k_B T}{\xi} \Delta t} \mathbf{N}_i(0, 1), \quad (2.25)$$

where $\mathbf{F}_i^{det} = \mathbf{F}_i^u + \mathbf{F}_i^{spring} + \mathbf{F}_i^e$ is the total deterministic force. Also notice that, the \mathbf{F}_i^{spring} is evaluated by Eq. (2.11) and the spring force law Eq. (2.12) or Eq. (2.13).

Stochastic Runge-Kutta method

Stochastic Runge-Kutta method is a higher order integration scheme than the Euler method. It was proposed by Honeycutt in [115]. In this method, the next time step bead position can be calculated as

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \frac{1}{\xi} (\mathbf{F}_i^{det} + \tilde{\mathbf{F}}_i^{det}) \frac{\Delta t}{2} + \sqrt{\frac{2k_B T}{\xi} \Delta t} \mathbf{N}_i(0, 1), \quad (2.26)$$

where \mathbf{F}_i^{det} and $\tilde{\mathbf{F}}_i^{det}$ are the total deterministic force evaluated using different bead position.

$$\begin{aligned}\mathbf{F}_i^{det} &= \mathbf{F}_i^{det}(\mathbf{r}_0(t), \mathbf{r}_1(t), \dots, \mathbf{r}_{L-1}(t)), \\ \tilde{\mathbf{F}}_i^{det} &= \tilde{\mathbf{F}}_i^{det}(\mathbf{r}_0^*, \mathbf{r}_1^*, \dots, \mathbf{r}_{L-1}^*),\end{aligned}\quad (2.27)$$

and \mathbf{r}_i^* is the mid-step bead position

$$\mathbf{r}_i^* = \mathbf{r}_i(t) + \frac{1}{\xi} \mathbf{F}_i^{det} \Delta t + \sqrt{\frac{2k_B T}{\xi} \Delta t} \mathbf{N}_i(0, 1). \quad (2.28)$$

Last but not least, in the simulations, the dynamical equation is nondimensionalized by rescaling the variable in the following way:

$$\mathbf{r}' \rightarrow \mathbf{r}/a; t' \rightarrow t/(\xi a^2/k_B T); \mathbf{F}' \rightarrow \mathbf{F}/(k_B T/a). \quad (2.29)$$

After the rescaling, the length unit is set to the size of the rod. The rescaling is helpful to avoid doing calculations with very small or big numbers, which might introduce larger numerical errors.

2.3 Monte-Carlo simulation of the bead-rod model

In the previous section, we present the BD simulation technique of the bead-rod and bead-spring polymer loop. As we can see there, the algorithm used to simulate the bead-rod model is actually quite complex and also time-consuming. Sometimes we do not need to do that if we only want to sample the equilibrium properties of the bead-rod system. In this section, we will introduce a Monte-Carlo algorithm that is much faster and efficient to obtain the equilibrium statistics of the bead-rod loop model.

Monte-Carlo technique has been used to simulate the polymer system for a long time [116]. However, there are some special factors one needs to take into account for our pinned polymer loop model. Basically, one has to preserve the loop structure and keep the rod length fixed when trying to do a Monte-Carlo flip. According to this, we propose the following main steps of our Monte-Carlo algorithm.

- Step I: prepare an initial configuration and compute the energy of this configuration. The way of calculating system energy depends on the setting of the model, whether the excluded volume effect or other interactions are taken into account or not. For example, the

energy of a pinned bead-rod loop in a constant external force field can be written as

$$E = U - \sum_{i=1}^L \mathbf{F}^e \cdot \mathbf{r}_i \quad (2.30)$$

where U is other kind of interaction energy. In the simplest case, we will assume U is independent of the configurations. To compare with the later evaluation, we denote the energy calculated here E_{old} .

- Step II: randomly choice two beads in the polymer loop, use the connecting line between the two beads as a rotation axis.

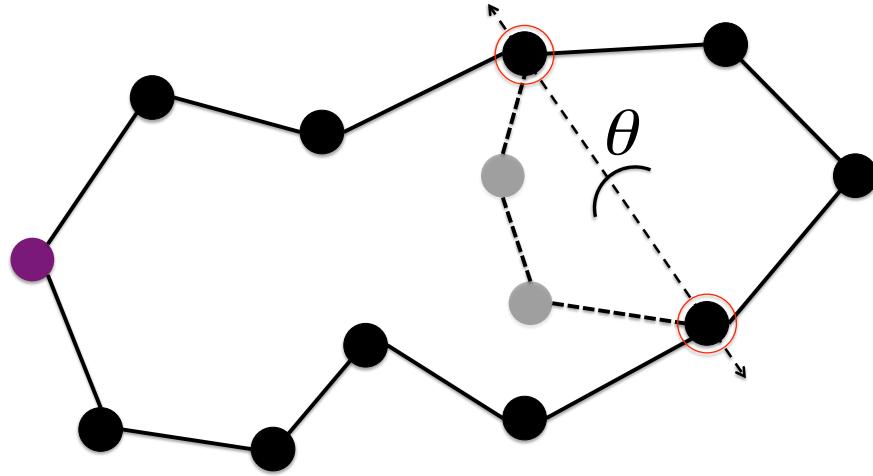


Fig. 2.5 Illustration of the Monte-Carlo configuration flip.

- Step III: choose the unpinned side of the polymer, and rotate this part of the polymer by a random angle $\theta \in [-\phi, \phi]$. ϕ is a parameter between $[0, \pi]$ and can be tuned to improve the efficiency of the algorithm. See in Fig. 2.5. If the pinned bead is selected, then randomly choose a side of the polymer to do the rotation.
- Step IV: calculated the energy of the configuration after rotation in the same way of E_{old} . Let us denote the new energy as E_{new} .
- Step V: the new configuration is accepted with probability

$$p = \min \left\{ 1, \exp \left(-\frac{\Delta E}{k_B T} \right) \right\}, \quad (2.31)$$

where $\Delta E = E_{new} - E_{old}$. If not accepted, then the polymer returns to the old configuration, and try again with new random number. An efficient sampling algorithm can be tuned by parameter ϕ so that the accept probability is around 0.5.

- Step VI: go back to step I and loop again and again to get enough independent samples. Physical quantities such like the statistical distance between two beads can be calculated by averaging over these samples.

The Monte-Carlo method introduced in this section is efficient and fast, we will use it to calculate most of the equilibrium quantities in next chapter. On the other hand, the Monte-Carlo results also work as a benchmark of the BD simulation and vice-versa.

2.4 Summary

In this chapter, we elaborated the details of our pulled polymer model for the chromosomes in meiotic fission yeast. We have shown that the pulled polymer loop is equivalent to the pinned polymer loop in external force field after a coordinate transform. The concrete bead-rod and bead-spring polymer loop models are discussed. And the BD simulation technique is discussed in details. A Monte-Carlo algorithm is introduced to calculate the equilibrium statistics of the bead-rod system and overcomes the disadvantages of heavy computation for the BD simulation.

The content of this chapter will be very useful in our later chapters. And we try to keep it concise, many related interesting models or methods are not mentioned here. Only those that will use in this thesis are discussed. Interested readers can refer to the cited references.

In next chapter, we will start to discuss the theory of equilibrium statistics of our polymer model and use the theory to explain the chromosome alignment in fission yeast.

Chapter 3

Equilibrium Statistics Applied to Chromosome Alignment

In previous chapter, we introduced the details of our polymer loop model for chromosomes and the simulation techniques. In this chapter, we will investigate the equilibrium statistics of the model and use the results to understand the chromosome alignment in fission yeast.

In order to tract the model analytically, we will neglect the complex interactions such as bending energy, excluded volume effect and hydrodynamical perturbations. In another word, our model is the simplest freely-jointed polymer loop model. The transferred coordinate is utilized so that the first bead representing SPB is pinned. And an external force field will be applied. The impact of those complex interactions will be studied numerically in the chapter 5.

We will start by introducing the setting of the model in the first section. The equilibrium statistics of 1D and 3D are discussed separately in section two and three. In the last two section, we will go back to the circumstance of fission yeast and discuss about some applications.

3.1 Pinned polymer loop in a constant force field

As we know, the nuclear oscillation in fission yeast is an oscillating dynamics. So in principle, the system is out of equilibrium by definition. However, notice that the time period of the nuclear oscillation is about 10 mins. The oscillation can be divided into two parts. The chromosomes move towards to the opposite direction in each part. If the relaxation time of the system is much less than half of the oscillation period, then it is proper to think the system as a equilibrium system. Actually, we will show in next chapter that this is indeed

true. The relaxation time of the chromosome system is calculated. It turns out the relaxation time scale is ~ 10 s. So the equilibrium assumption is justified.

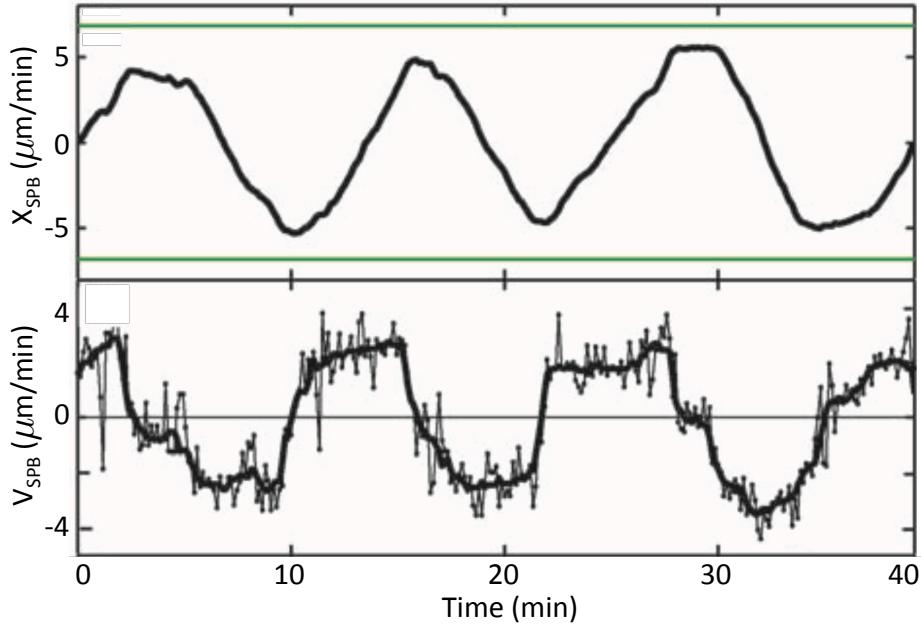


Fig. 3.1 Experimental trajectory and velocity of the SPB measured by fluorescence microscopy. The upper panel shows the trajectory of the SPB along the cell main axis. Green line is the boundary of the cell. The lower panel shows the corresponding velocity of the SPB. Image reprinted and modified from [5].

On the other hand, experimental evidence shows that the velocity of the SPB is almost constant when moving towards one direction. See in Fig. 3.1. So the corresponding setting of our model is pinned polymer loops in an constant external force field $\mathbf{F} = \xi v_{SPB}$. It is interesting to know what is the equilibrium statistics of this setting from theoretical point of view. In this chapter, we will use the bead-rod model to study this problem.

Let us first clarify some notations here. There are L beads (including the SPB) in the loop and the SPB is denoted by \mathbf{r}_0 or \mathbf{r}_L in periodic indexing. Without loss of generality, we assume it is pinned to the origin point, i.e. $\mathbf{r}_0 = \mathbf{r}_L = 0$. The length of each rod is a . And the constant external force field denotes by \mathbf{F} is in the z direction. The potential energy of the pinned polymer loop can be written as:

$$E = E_0 - a \sum_{i=1}^L \mathbf{F} \cdot \mathbf{r}_i \quad (3.1)$$

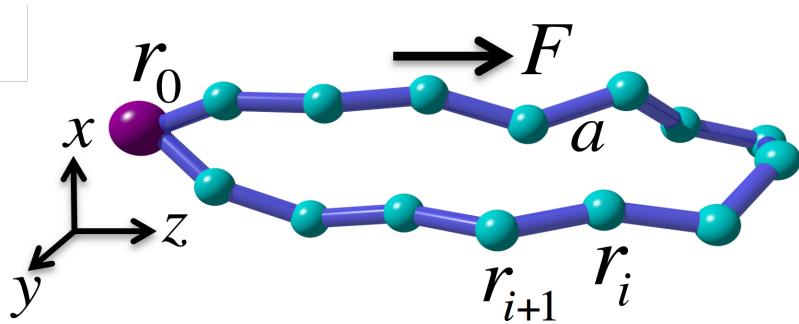


Fig. 3.2 Sketch for the pinned bead-rod loop and notations.

where E_0 is assumed to be a constant that denotes configuration independent energy. It is not important for the study of equilibrium statistics, we keep it here just for completeness. The orientation of the j^{th} rod is denoted by $\mathbf{u}_j = (\mathbf{r}_j - \mathbf{r}_{j-1})/a$. So the i^{th} bead position can be written as:

$$\mathbf{r}_i = a \sum_{j=1}^i \mathbf{u}_j. \quad (3.2)$$

Plug it into Eq. (3.1), we arrive at

$$E = E_0 - a \sum_{i=1}^L \sum_{j=1}^i \mathbf{F} \cdot \mathbf{u}_j. \quad (3.3)$$

Notice that the looping condition indicates

$$\sum_{j=1}^L \mathbf{u}_j = 0. \quad (3.4)$$

In the following two sections, we will solve the equilibrium statistics in 1D first and extend the theory to 3D.

3.2 Pinned Polymer Loop in 1D

As the same strategy to study many problems in physics, let us start to solve the equilibrium statistics from the simplest 1D case. The one dimensional polymer is possible because we neglect the exclusion volume effect so that the beads and rods are free to overlap. It is a simple idealized model. We will show in the following that an elegant mapping for the one dimensional pinned polymer loop to a famous classical physical model can be found.

3.2.1 Mapping to particles on 1D lattice

The pinned polymer in 1D is very simple. The configuration of the polymer can be specified by the orientation of the rods. In 1D, there are only two possible orientations for all rods, i.e. along the axis or against the axis.

Let us denote the j^{th} rod orientation by $u_j \in \{-1, +1\}$, where $u_j = +1$ means the rod orientates along the axis and $u_j = -1$ means the rod orientates against the axis. Again the i^{th} bead position in 1D is $z_i = a \sum_{j=1}^i u_j$. Now let us introduce a shifted and rescaled variable

$$n_j = (u_j + 1)/2. \quad (3.5)$$

We can easily find that $n_j \in \{0, 1\}$. The configuration of the 1D polymer can be denoted by $\{n_1, n_2, \dots, n_L\}$. Since n_j is a binary variable, we can interpret $n_j = 1$ as a lattice site occupied by a particle, and $n_j = 0$ as an empty lattice site. In this way, we find a one-to-one mapping from the configuration of polymers to particles on lattice sites. See in Fig. 3.3. The number of rods equals to the number of lattice sites. Without loss of generality, we have shown in the figure the right-orientated rod corresponds to an occupied site, and the left-orientated rod corresponds to an empty site.

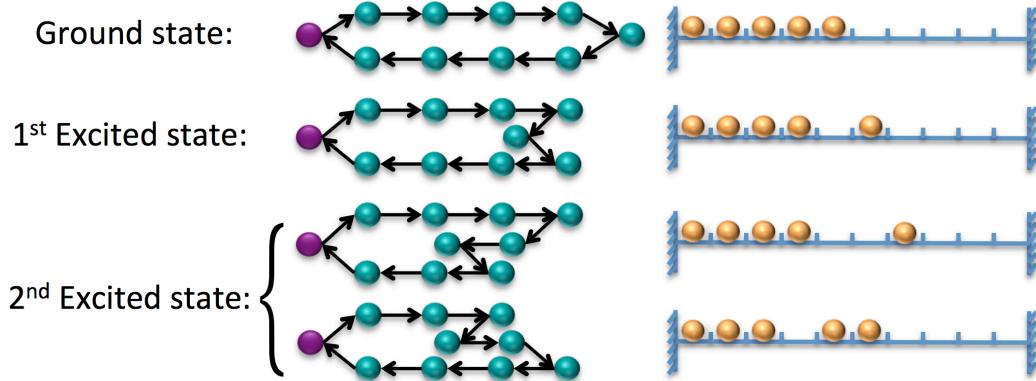


Fig. 3.3 Illustration for the mapping from 1D pinned polymer loop to Fermionic particles on 1D lattice sites.

Here are some remarks for the mapping:

- The mapped particles are exclusive to each other. It is not possible for one lattice site to be occupied by more than one particles. In another word, these particles are Fermions. This is because the system is a two state system, there is no correspondent polymer state for a site occupied by more than one particle.
- According to the looping condition Eq. (3.4), the total number of rods pointing to the right must be exact $L/2$. Correspondingly, the total number of particles also must be exact

$L/2$, i.e.

$$\sum_{j=1}^L n_j = \frac{L}{2}. \quad (3.6)$$

Furthermore, the number of particles must be conserved during the change of configurations.

- The dynamics of 1D polymer can be mapped to the particle hopping process on the 1D lattice. This part will be discussed in next chapter.
- The mapping is essentially from a two state system to a two state system. One can also interpret the two state as spin up and spin down or any other two state systems. We use the particle-lattice interpretation because it is familiar and intuitive to most people.

Now let discuss the energy of the system. Rewrite Eq. (3.3) in 1D we get

$$E = E_0 - Fa \sum_{i=1}^L \sum_{j=1}^i u_j. \quad (3.7)$$

Exchange the summation order in Eq. (3.7) and utilizing the loop condition $\sum_{j=1}^L u_j = 0$ we obtain

$$E = E_0 + Fa \sum_{j=1}^L j u_j. \quad (3.8)$$

Let us look at the energy from the particle-lattice picture. Substitute Eq. (3.5) into Eq. (3.8), we arrive at

$$E = \tilde{E}_0 + \Delta E \sum_{j=1}^L j n_j \quad (3.9)$$

where $\Delta E = 2Fa$ and $\tilde{E}_0 = E_0 - L(L+1)\Delta E/4$ is the unimportant energy offset. Let us ignore the offset in our discussion. Eq. (3.9) can be reinterpret as the summation energy of L lattice sites. When $n_j = 1$ (occupied site), we gain a energy of $j\Delta E$ and zero otherwise. One can clearly see that Eq. (3.9) is the energy of a system of $L/2$ fermions distributed over L equidistant energy levels $\Delta E, 2\Delta E, \dots, L\Delta E$. The lowest energy (ground state) corresponds to the configuration that the left half of lattice sites are fully filled by particles. And the corresponding polymer picture is the fulled stretched configuration. The correspondence of the 1st and the 2nd excited states also can be imagined, which is shown in Fig. 3.3.

The mapping from the polymer to the particle-lattice picture is very useful for searching the solution of equilibrium statistics. In the following subsections, we will solve the 1D statistics using two different methods. The first one based on the grand canonical ensemble is an approximate solution with a simpler formulism, while the second one is the exact solution based on the canonical ensemble but a more complex formulism. We will calculate the mean

position of beads and their variance. Because these are what we interested, the biological interactions can only happen when two segments are closer enough.

3.2.2 The grand canonical ensemble solution

We have mentioned in the previous subsection that the particle number is conserved to $L/2$ in the mapped particle-lattice picture. So in principle, the system is a canonical ensemble system. However, let us first release this constraint by allowing the particles exchange with the reservoir at both sides of the lattice. Thus the grand canonical ensemble can be applied. After that, we can reimpose the constraint using the Brownian bridge technique. We can obtain very accurate mean bead position and its variance use this method. Given that the formulation of this method is simple, we are quite satisfied with the results. Let us now illustrate the method in details.

The Fermi-Dirac statistics

As we have mentioned above, the particles on the lattice are Fermions. One wonderful thing of the grand canonical ensemble is the particles can be assumed to be mutually independent. So that we can directly use the famous *Fermi-Dirac* distribution. That is to say the probability of a lattice site is occupied can be written as

$$\mathbb{P}\{n_j = 1\} = \frac{1}{1 + \exp\left[\frac{\Delta E(j-\mu)}{k_B T}\right]}, \quad (3.10)$$

where μ is the chemical potential $\mu = (L+1)/2$ obtained from the requirement that on average there are $L/2$ particles in the system. And accordingly, the probability that a lattice site is empty writes

$$\mathbb{P}\{n_j = 0\} = 1 - \mathbb{P}\{n_j = 1\}. \quad (3.11)$$

Let us define a dimensionless quantity which we call it *dimensionless temperature*:

$$\tilde{T} = \frac{k_B T}{\Delta E} = \frac{k_B T}{2Fa} \quad (3.12)$$

Now we can see in Fig. 3.4 for an illustration of the *Fermi-Dirac* distribution of different \tilde{T} . When \tilde{T} is small, namely the external force is large, the distribution shows a strong bias. The left half sites are more likely to be occupied and the right half sites are more likely to be empty. In the polymer picture, this means the orientation of the first half rods is biased in the direction of force, whereas the second half of rods are more probable to point against the

force field. Physically, it is easy to understand because the pinned polymer in strong force field is almost stretched.

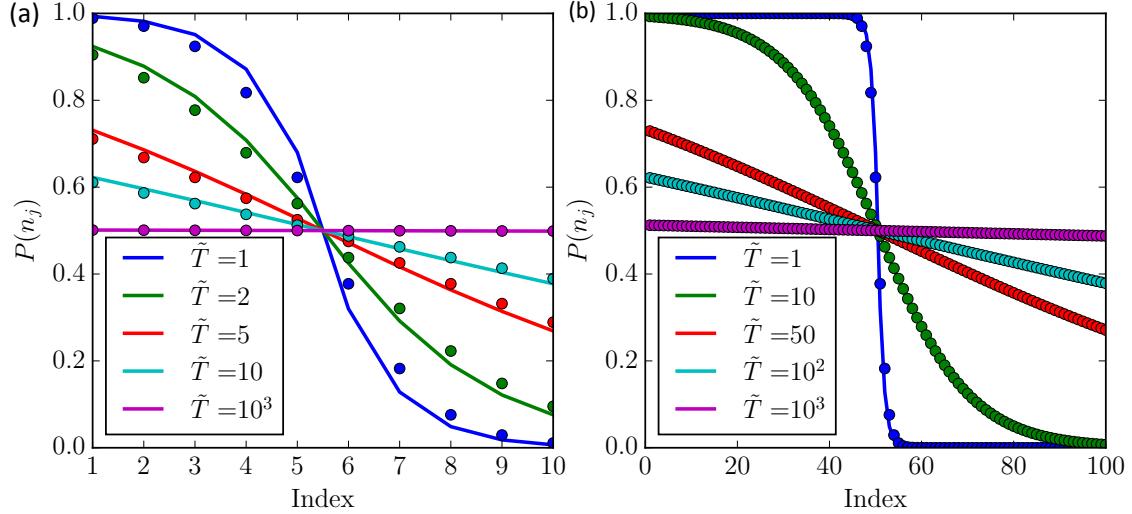


Fig. 3.4 Fermi-Dirac distribution compared with the exact solution from the number partition theory. Solid lines are the exact solution while the dots are Fermi-Dirac approximations. Different dimensionless temperature is indicated by different colors as shown in the legend. (a) $L = 10$, (b) $L = 100$.

With Eq. (3.10), the mean and variance of random variable n_j can be calculated straightforwardly:

$$\langle n_j \rangle = \mathbb{P}\{n_j = 1\}, \quad (3.13a)$$

$$\text{var}[n_j] = \mathbb{P}\{n_j = 1\} \cdot \mathbb{P}\{n_j = 0\} - \langle n_j \rangle^2. \quad (3.13b)$$

On the other hand, from Eq. (3.2) and Eq. (3.5) we can calculate the position of bead as

$$z_i = a \left(2 \sum_{j=1}^i n_j - i \right). \quad (3.14)$$

If we assume n_1, n_2, \dots, n_L are all mutually independent, then the mean and variance of bead position can simply calculated as

$$\langle z_j \rangle = a \left(2 \sum_{j=1}^i \langle n_j \rangle - i \right), \quad (3.15a)$$

$$\text{var}[z_j] = 4a^2 \sum_{j=1}^i \text{var}[n_j] \quad (3.15b)$$

The results of the above equations can be compared to the Monte-Carlo simulation (see Appendix B for details). We found that the formula for mean bead position works perfect. However, the formula for variance does not work so good. Notice that Eq. (3.15b) is monotonically increasing with the index i . We can take the simple symmetric argument that $\text{var}[z_i] = \text{var}[z_{L-i}]$. The result after that still can not match with the simulations. See in Fig. 3.5.

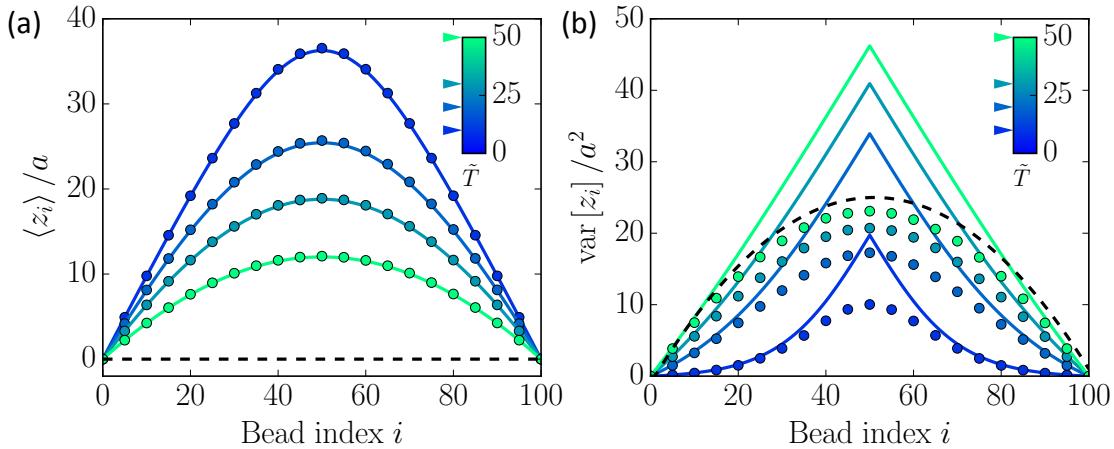


Fig. 3.5 Mean and variance of the 1D pinned polymer bead positions. MC simulation results (dots) are compared with theoretical results (solid lines) Eq. 3.15. The length of the polymer loop $L = 10$. The black dash line indicates the case $\tilde{T} \rightarrow \infty$, i.e. no external force field.

The reason for this mismatch is simple, the particles are not exactly independent and the loop condition is only fulfilled on average by choosing the chemical potential $\mu = (L + 1)/2$ in Eq. (3.10). In the following part, we will show how to solve this problem use the Brownian bridge technique.

The Brownian bridge condition

Let us consider the polymer loop as a random walk that returns to the origin point after L steps. This sort of random walk process is called the Brownian bridge [117, 118]. So each rod represents a random walk step. The segment connecting the k^{th} and the l^{th} bead corresponds to the propagator $\rho(z_l = z | z_k = 0)$. According to the Lindeberg-Feller central limit theorem [117], this propagator is Gaussian with the mean and variance equal to the sum of the mean and variance of all individual steps from k to l .

As we said above, the grand canonical ensemble only ensures the loop condition on average. To solve the problem, we now impose the Brownian bridge condition so that every single trajectory fulfills the loop condition. The Brownian bridge can be formulated as

following:

$$\rho^L(z_i = z) = \frac{\rho(z_i = z | z_0 = 0) \rho(z_{L-i} = z | z_L = 0)}{\rho(z_L = 0 | z_0 = 0)}, \quad (3.16)$$

where $\rho(z_i = z)$ is the probability density function of finding the i^{th} bead at position z , $\rho(z_k = z | z_j = 0)$ are the propagators. Eq. (2.2) means that the probability density equals two pieces of random walk trajectory of length i and $L - i$ meet at position z on the condition that they are belong to the same loop.

Notice that the propagators are Gaussian with the variance added up by the variance of individual steps, i.e Eq. (3.15b). So that $\rho^L(z_i = z)$ is also Gaussian. Its variance is given by

$$\text{var}[z_i] = 4a^2 \frac{\sum_{j=0}^i \text{var}[n_j] \sum_{j=L-i}^L \text{var}[n_j]}{\sum_{j=0}^L \text{var}[n_j]}. \quad (3.17)$$

Plug in Eq. (3.13b) and Eq. (3.15b) we can obtain the variance of bead position in the loop. For $\tilde{T} \gg 1$, we can obtain the close form expressions for mean and variance of bead position by converting the summation to integral

$$\langle z_i \rangle = 2a\tilde{T} \ln \left[\frac{1 + \exp\left(\frac{L}{2\tilde{T}}\right)}{\exp\left(\frac{i}{2\tilde{T}}\right) + \exp\left(\frac{L-i}{2\tilde{T}}\right)} \right] \quad (3.18a)$$

$$\text{var}[z_i] = 2a^2\tilde{T} \frac{\sinh\left(\frac{L-i}{2\tilde{T}}\right) \sinh\left(\frac{i}{2\tilde{T}}\right)}{\sinh\left(\frac{L}{2\tilde{T}}\right) \cosh^2\left(\frac{L-2i}{4\tilde{T}}\right)} \quad (3.18b)$$

We can see from the above formulas that the $z_i - z_{L-i}$ symmetry is satisfied. And a strong external force field leads to a stretched configuration and a small fluctuation of bead position. This result is compared with the Monte-Carlo simulations, see in Fig. 3.6.

In this subsection, we solved the mean and variance of bead position for 1D pinned polymer loop in an external force field. The strategy is using the *Fermi-Dirac* statistics and re-enforce the loop condition by the Brownian bridge technique. Excellent results verified by the Monte-Carlo simulation are obtained. However, we have to say, this is just an approximate method. In the next subsection, we will use the canonical ensemble to obtain the exact solution.

3.2.3 Canonical ensemble solution

In the particle-lattice picture, the system is actually a canonical ensemble system because of the conservation of particle number. In this section, we will calculate the exact partition

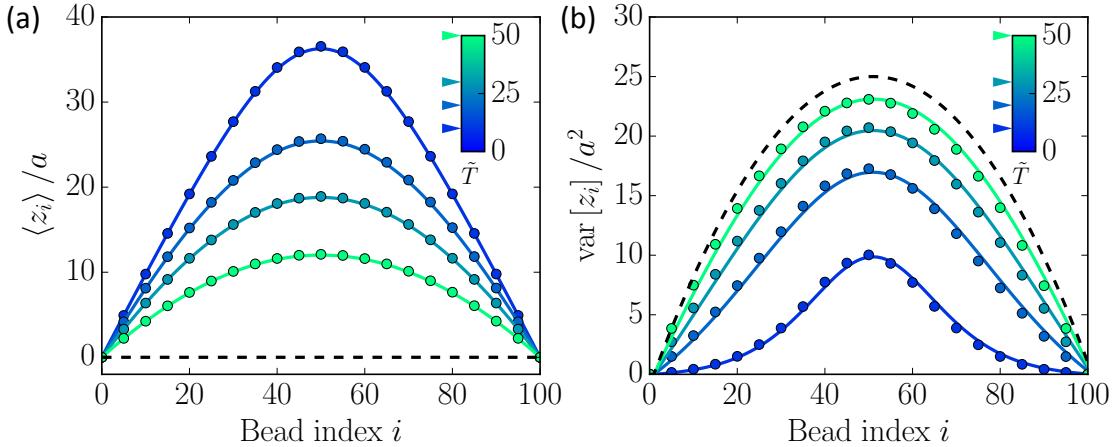


Fig. 3.6 Mean and variance of the 1D pinned polymer bead positions. MC simulation results (dots) are compared with theoretical results (solid lines) Eq. 3.18. The length of the polymer loop $L = 10$. The black dash line indicates the case $\tilde{T} \rightarrow \infty$, i.e. no external force field.

function using this ensemble. More interestingly, we will show the calculation can be recoded to a number partition problem. Exact results are obtained and compared with the results from the approximate approach above.

The number partition theory

Before the calculation of exact partition function, let us discuss an interesting number partition problem that share a lot of similarities with the former.

Consider a non-negative integer number K , which can be expressed into the summation of N non-negative integers:

$$K = \sum_{j=1}^N k_j \quad (3.19)$$

However, there is a constraint on the summation components $0 \leq k_1 \leq k_2 \cdots \leq k_N \leq M$. This kind of problem can be best visualized by what called Young diagram [119], shown in Fig. 3.7. In the Young diagram, each row represents a integer number. The number of blue boxes means the value of the j^{th} integer. Starting from the bottom, because of the constraint, the diagram is non-decreasing.

The question is, given a certain integer K , how many different ways are there to partition it into N non-decreasing pieces $\{k_1, k_2, \dots, k_N\}$. For the simple cases, one can tell the answer immediately. For examples, in the first two examples of Fig. 3.7, we illustrate that there are only one way to partition integer 0 or 1 into 4 non-decreasing integers. However, this question in the general case is not intuitive. Fortunately, this problem is well studied by

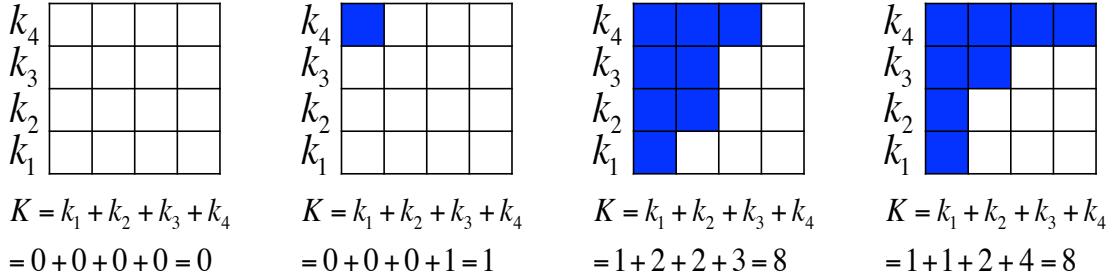


Fig. 3.7 Some examples of the Young diagram.

mathematicians. Let $g(M, N; K)$ denote the number of partitions of K with at most N parts, each of size at most M . Equivalently, these are the partitions whose Young diagram fits inside an $N \times M$ rectangle. Then we have the following generating function:

$$\Phi(q) := \sum_{K=0}^{MN} g(M, N; K) q^K = \binom{M+N}{N}_q \quad (3.20)$$

where q is an auxiliary number, and the notation at the right hand side of Eq. (3.20) is called q binomial coefficient or Gaussian binomial coefficient. It is defined as

$$\binom{L}{N}_q := \frac{[L]_q!}{[L-N]_q! [N]_q!}, \quad (3.21)$$

and $[N]_q := 1 + q + q^2 + \dots + q^{N-1}$ is called a q number [119].

Exact partition function

Now, let us start to calculate the partition function of our pinned polymer in the particle-lattice picture. The partition function of a canonical ensemble system with discrete energy can be written as:

$$\mathcal{Z}(T) = \sum_E g(E) \exp\left(-\frac{E}{k_B T}\right), \quad (3.22)$$

where $g(E)$ is the degeneracy of the microscopic states which have the same energy E . Once $g(E)$ is known, the partition function can be calculated straightforwardly.

Let us take a look at the energy of the system, i.e. Eq. (3.9). It is represented in the way of rod orientation u_j or occupation variable n_j . Here, we are going to use another way to represent the energy. In the particle-lattice picture, the system consists $N := L/2$ particles.

So the energy can be rewritten as:

$$E = \tilde{E}_0 + \sum_{j=1}^N E_j, \quad (3.23)$$

where E_j is the energy of the j^{th} particle in the external force field. Again, \tilde{E}_0 is an unimportant constant energy offset. Denote the position of the j^{th} particle as x_j , which is an integer $x_j \in [1, L]$. Then we can write $E_j = x_j \Delta E$. Also notice that, because of the exclusive condition, the sample space of the particle system is constrained in $\Omega = \{\mathbf{x} | 1 \leq x_1 < x_2 < \dots < x_N \leq L\}$.

Let us do a shift for the particle position by defining

$$k_j := x_j - j. \quad (3.24)$$

Notice now the constraint on x_j is transferred to $0 \leq k_1 \leq k_2 \dots \leq k_N \leq N$. And the energy of the system can be rewritten as:

$$E = \hat{E}_0 + \Delta E \sum_{j=1}^N k_j = \hat{E}_0 + K \Delta E, \quad (3.25)$$

Again \hat{E}_0 here is an unimportant constant energy offset, $\hat{E}_0 = \tilde{E}_0 + N(N+1)/2$. It is not difficult to find the range of the energy is $\hat{E}_0, \hat{E}_0 + \Delta E, \dots, \hat{E}_0 + N^2 \Delta E$.

Now we are closer to the number partition problem. Notice that $K = \sum_{j=1}^N k_j$ and we have the same type of constraint as in the number partition problem. In addition, because the mapping from integer K to energy E is one-to-one. So the degeneracy function $g(E)$ is exactly the number of ways to partition the integer K . Furthermore, let us denote $q := \exp(-\Delta E/k_B T)$. Then we have

$$\begin{aligned} \mathcal{Z}(T) &= \sum_E g(E) \exp\left(-\frac{E}{k_B T}\right) \\ &= \exp\left(-\frac{\hat{E}_0}{k_B T}\right) \sum_{K=0}^{N \times N} g(N, N; K) q^K \\ &= \exp\left(-\frac{\hat{E}_0}{k_B T}\right) \binom{L}{N}_q. \end{aligned} \quad (3.26)$$

With the exact partition function Eq. (3.26), the equilibrium distribution can be calculated straightforwardly:

$$P^e = \frac{1}{\mathcal{Z}(T)} \exp\left(-\frac{E}{k_B T}\right) = \frac{q^K}{\binom{L}{N}_q}. \quad (3.27)$$

We can see here the offset energy is not in the distribution function. That is why we always say it is not important. In principle, Eq. (3.27) is not an exact relation. It might still have a constant pre-factor which can be fixed by the normalization condition $\sum_{K=0}^{N^2} P^e = 1$. However, the constant is not important for our discussions, so we will just keep it in the form of Eq. (3.27).

With Eq. (3.26) and Eq. (3.27), in principle, one can calculate whatever equilibrium quantities. Here, we will calculate the probability distribution of rod orientation in order to compare with our previous approach based on grand canonical ensemble.

Exact probability distribution of the rod orientation

The probability distribution of rod orientation is equivalent to the probability distribution of the lattice site occupation. Previously, we have employed the *Fermi-Dirac* distribution. In this subsection, we will calculate the exact distribution of $\mathbb{P}\{n_j = 1\}$ to show how accurate the *Fermi-Dirac* distribution is.

In order to do that, let us first rewrite the equilibrium distribution Eq. (3.27) in the coordinate of particle position:

$$P^e(x_1, x_2, \dots, x_N) = q^{-\frac{N(N+1)}{2}} \binom{L}{N}_q^{-1} \prod_{i=1}^N q^{x_i}. \quad (3.28)$$

Now let us denote $P_i(x)$ the probability that the i^{th} particle is at position x . Then $P_i(x)$ can be calculated as

$$\begin{aligned} P_i(x) &= \sum_{1 \leq x_1 < \dots < x_{i-1} \leq x-1} P^e(x_1, x_2, \dots, x_N) \\ &\times \sum_{x < x_{i+1} < \dots < x_N \leq L} P^e(x_1, x_2, \dots, x_N) \\ &= q^{(N+1-i)(x-i)} \binom{x-1}{i-1}_q \binom{L-x}{N-i}_q \Bigg/ \binom{L}{N}_q. \end{aligned} \quad (3.29)$$

Finally, the probability that the j^{th} sites is occupied can be calculated as

$$\mathbb{P}\{n_j = 1\} = \sum_{i=1}^N P_i(x=j) \quad (3.30)$$

Eq. (3.30) simply means the probability of one site is occupied is the sum of the probability that it is occupied by any particles. Plug in Eq. (3.29), one can obtain the exact occupation probability distribution. This is compared with the *Fermi-Dirac* distribution in Fig. 3.4. As we can see in the figure, the discrepancy is quite small. It is only noticeable for a small lattice size at very strong external force field, see in Fig. 3.4 (a). So the Fermi-Dirac distribution is actually a very accurate approximation.

In this section, we solve the equilibrium statistics of the pinned polymer loop model in 1D. Utilizing the mapping from the polymer to a particle-lattice system, we solve the statistics by two different approaches. The first one employs the famous *Fermi-Dirac* distribution and the Brownian bridge technique. However, it is an approximate method. The second method based canonical ensemble and number partition theory is an exact solution. The exact results are compared with the first methods as well as the Monte-Carlo simulations. Our theory matches very well to the simulation results. In next section, we will extend our theory to the 3D system.

3.3 Equilibrium statistics in 3D

In 3D, the equilibrium statistics of the pinned polymer loop model can still be calculated using the similar stately. The orientation of rods have two more degree of freedom in 3D. As shown in section 3.1, the external force is assume in the z direction. Let us use the spherical coordinates to describe the polymer system. Denote θ_j the angle between the j^{th} rod and the z -axis, and ϕ_j the rotational angle along z -axis. Then the three dimensional loop condition can be written as

$$\sum_{j=1}^L \cos \theta_j = 0. \quad (3.31)$$

Using the above condition, the energy of the 3D polymer Eq. (3.3) can be rewritten as

$$E = E_0 + Fa \sum_{j=1}^L j \cos \theta_j. \quad (3.32)$$

In the following subsections, we will first derive the partition function, and then calculate the mean and variance of the three dimensional beads position.

3.3.1 Partition function

To calculate the equilibrium statistics of 3D bead-rod system, we will use the approach of grand canonical ensemble combined with the Brownian bridge condition. The grand canonical ensemble partition function can be written as:

$$\mathcal{Z} = \prod_{j=1}^L \mathcal{Z}_j = \prod_{j=1}^L \int_0^{2\pi} d\phi \int_0^\pi \exp\left(-\frac{(j-\mu) \cos \theta \Delta E}{k_B T}\right). \quad (3.33)$$

Here, $\mu = (L+1)/2$ is the chemical potential the same as in 1D. However, $\Delta E = Fa$ is different from the 1D case. Again, let us define the *dimensionless temperature*:

$$\tilde{T} = \frac{k_B T}{\Delta E} = \frac{k_B T}{Fa}. \quad (3.34)$$

There is a factor of two compare to the dimensionless temperature in 1D.

The integration can be calculated in Eq. (3.33), which turns out

$$\mathcal{Z}_j = \frac{\tilde{T} \sinh \frac{j-\mu}{\tilde{T}}}{j-\mu}. \quad (3.35)$$

So the mean and variance of the j^{th} rod orientation $u_{j,z} = \cos \theta_j$ can be calculated as

$$\begin{aligned} \langle \cos \theta_j \rangle &= \tilde{T} \partial_\mu \ln \mathcal{Z}_j = \coth \frac{\mu-j}{\tilde{T}} - \frac{\tilde{T}}{\mu-j}, \\ \text{var} [\cos \theta_j] &= \tilde{T}^2 \partial_\mu^2 \ln \mathcal{Z}_j = \frac{\tilde{T}^2}{(j-\mu)^2} - \operatorname{csch}^2 \frac{j-\mu}{\tilde{T}}. \end{aligned} \quad (3.36)$$

Notice that, for symmetry reasons, the average projection for x and y directions are zero: $\langle u_{j,x} \rangle = \langle u_{j,y} \rangle = 0$. The second moment of these component can be calculated as

$$\langle u_{j,x}^2 \rangle = \langle u_{j,y}^2 \rangle = (1 - \langle \cos^2 \theta_j \rangle)/2 \quad (3.37)$$

The above equations give the statistical properties of individual rod orientation. In next subsection, we will use the Brownian bridge technique to calculate the mean and variance of beads position.

3.3.2 Mean and variance of the bead position

In the case of 3D pinned polymer, according to Lindeberg-Feller central limit theorem [117, 118], the corresponding random walk is a multi-variate Gaussian process. It can be

factorized into the product of three Gaussian processes, each corresponding to a coordinate axis. Let us first discuss it in the z direction, i.e. the direction along the force field. The propagator in the z direction $\rho(z_k = z|z_0 = 0)$ is Gaussian with the following mean and variance:

$$\begin{aligned}\langle z_k \rangle &= a \sum_{j=1}^k \langle \cos \theta_j \rangle, \\ \sigma_{0 \rightarrow k, z}^2 &= a^2 \sum_{j=1}^k \text{var} [\cos \theta_j].\end{aligned}\quad (3.38)$$

Finally, by imposing the Brownian bridge condition, the variance of bead position can be written as

$$\text{var}[z_k] = a^2 \frac{\sum_{j=0}^k \text{var} [\cos \theta_j] \sum_{j=L-k}^L \text{var} [\cos \theta_j]}{\sum_{j=0}^L \text{var} [\cos \theta_j]}. \quad (3.39)$$

The analytical results above are compared with the 3D Monte-Carlo simulations (see section 2.3). We can see in Fig. 3.8 that again an excellent agreement is observed.

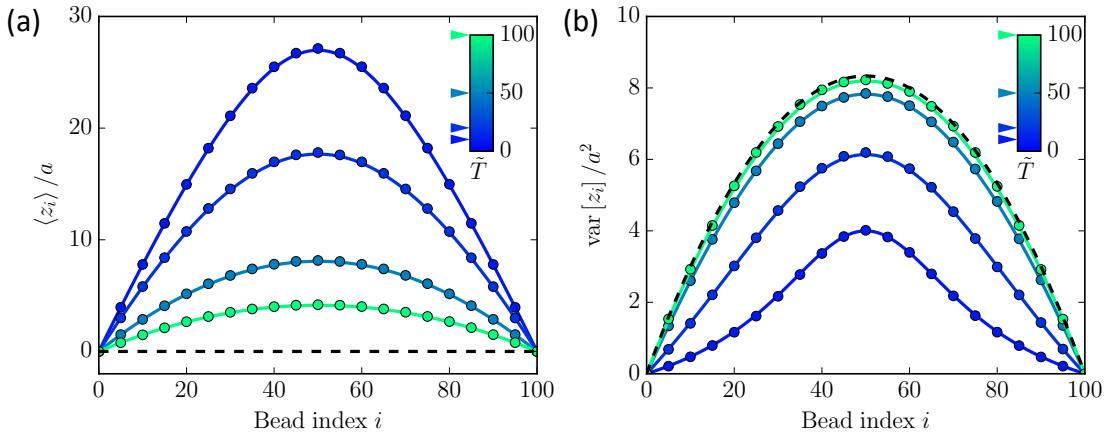


Fig. 3.8 Mean and variance of the bead position in the direction along the force field. Solid lines are theory and dots are Monte-Carlo simulation results. The black dash line indicates the case $\tilde{T} \rightarrow \infty$, i.e. no external force field.

Now let us discuss the directions perpendicular to the force direction. By symmetric reasons, we can immediately conclude that the statistics in x and y directions are identical. In addition, the mean position in both direction should be vanished because there is no bias. We can write as

$$\langle x_k \rangle = \langle y_k \rangle = 0. \quad (3.40)$$

On the other hand, using Eq. (3.37), the variance of x and y components of the j^{th} rod orientation can be written as

$$\text{var}[u_{j,x}] = \text{var}[u_{j,y}] = \langle u_{j,x}^2 \rangle - \langle u_{j,x} \rangle^2 = (1 - \langle \cos^2 \theta_j \rangle)/2 \quad (3.41)$$

Again, impose the Brownian bridge condition similar to Eq. (3.39), the variance of x and y components of the bead position can be obtained. Notice the variance in x and y directions are different from the variance in z direction. This is shown in Fig 3.9 together with the benchmark of our theory and the Monte-Carlo simulations.

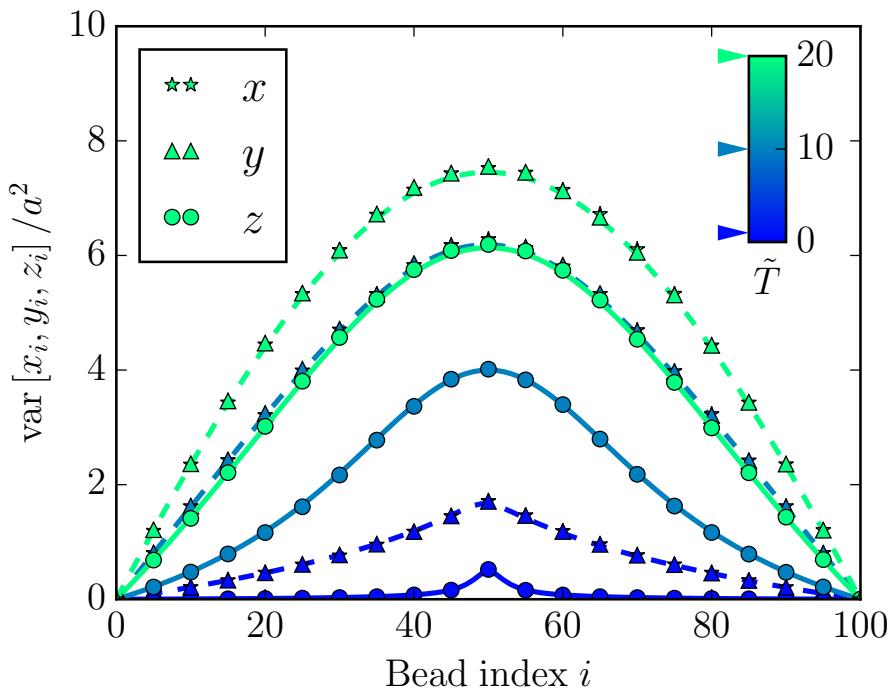


Fig. 3.9 Comparison of fluctuations in x , y and z directions. Symbols denote the Monte-Carlo simulations. Circles show the fluctuations along the z axis, whereas stars and triangles along x and y axis respectively. Colors correspond to different dimensionless temperatures. Solid and dashed lines are theoretical predictions for fluctuations along and orthogonal to the force field, respectively.

In this section, we discussed the three dimensional pinned polymer loop model and its equilibrium statistics. The mean and variance of each bead position are calculated using the grand canonical ensemble combined with Brownian bridge technique. After so many discussions about the model for chromosomes, in next section, we will come back to the biological problem. Using the insight from model analysis, we will discuss the paring problem of homologous.

3.4 Modeling the chromosome alignment

In fission yeast, the chromosomes are appearing in pairs during nuclear oscillation, which means there are two mechanically identical chromosomes. In total, there are three chromosome pairs in fission yeast. In this section, we will use the theory from the pinned polymer loop model to discuss the chromosome alignment problem in fission yeast. We will first discuss about the chromosome paring and alignment, and then fit our model to the biology.

3.4.1 Chromosome paring and alignment

In the prophase I of fission yeast, the dramatic chromosome movements are observed before the pair of chromosomes separate into two daughter cells. However, before the separation, the pair of chromosomes are supposed to align together in space. This process is called chromosome paring, which is the necessary condition for the correct segregation later.

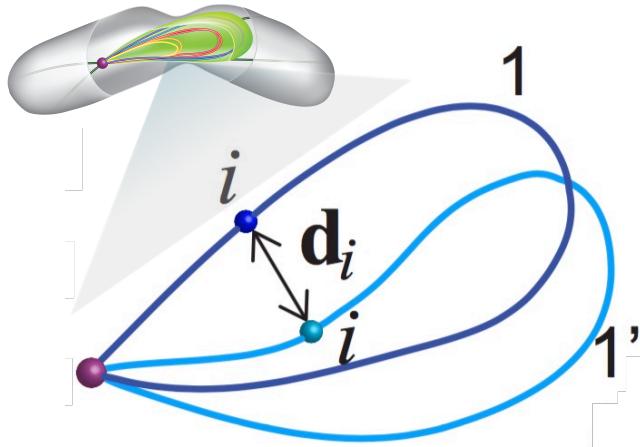


Fig. 3.10 A Pair of homologous chromosomes bound to the SPB. The distance of a pair of loci is illustrated as \mathbf{d}_i .

In the mean time of chromosome pairing, the nucleus of fission yeast is oscillating. As we discussed in Chapter 2, the oscillation can be divided into two pieces of steady motion, which can be further transferred to the scenario of pinned polymer loop in an external force field. One can intuitively imagine that the chromosomes will be more stretched when subjecting to an stronger external force field. So the statistical distance between two corresponding loci will be shorten. Biologically, if the statistical distance is smaller than 400nm, then it is said been paired. It is interesting to ask how does the pulling facilitate the paring of homologous.

We will calculate the statistical distance of \mathbf{d}_i (show in Fig. 3.10) for different external force field.

3.4.2 Theory fits to the biology

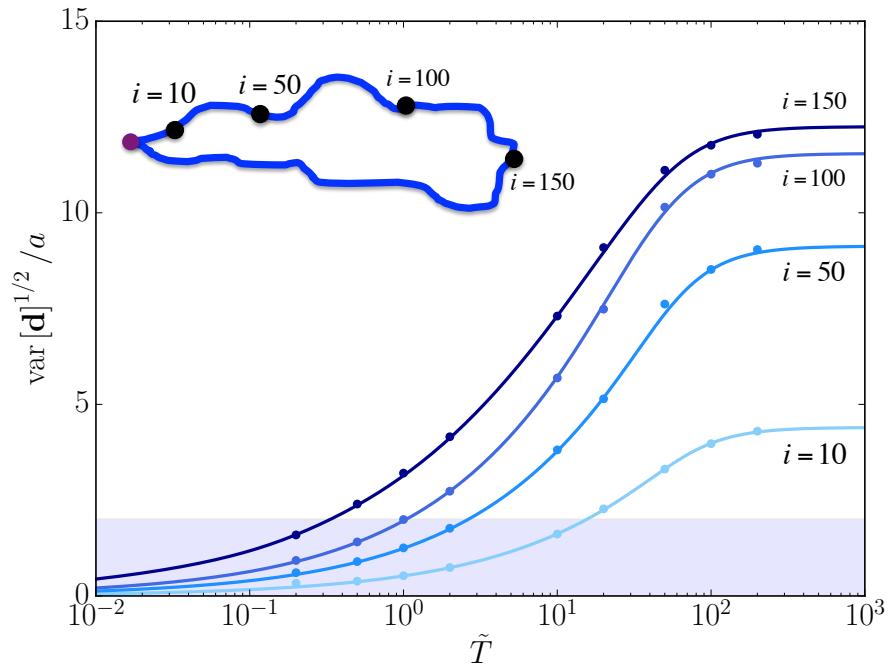


Fig. 3.11 paring

3.5 Two intersecting Loops

3.6 Summary

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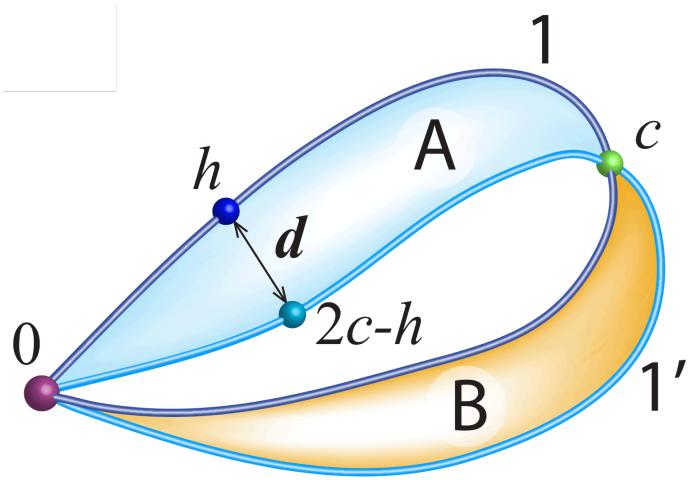


Fig. 3.12 centromere

Chapter 4

Dynamical Properties

4.1 Rouse Theory of the Pinned Bead-spring Loop

4.1.1 The Normal Modes

4.1.2 Relaxation Time

4.2 1D Pinned Bead-rod Loop Maps to ASEP

4.3 The Bethe-ansatz Solution of ASEP

4.3.1 Solution of Single Particle

4.3.2 Solution of Two Particles

4.3.3 Solution of General N particles

4.3.4 Relaxation Time

4.4 Relaxation Time of 3D Pinned Bead-rod Loop

4.5 The Single-file Diffusion

4.6 Summary

Chapter 5

Characterize the Nuclear Oscillation

5.1 Oscillation of the Pinned Polymer Loop

5.1.1 The Rouse Theory

5.1.2 Simulation Results

5.2 Characterize the Shape of Chromosomes

5.2.1 The Gyration Tensor

5.2.2 Asphericity and the Nature of Asphericity

5.3 Extract Shape Information From Experimental Data

5.3.1 Shape from Experimental Data

5.3.2 Compare to Theory and Simulation Results

5.4 Summary

Chapter 6

Conclusions and Outlook

6.1 Conclusions

6.2 Outlook

Appendix A

**An efficient algorithm to compute *pseudo*
force of bead-rod loop**

Appendix B

Monte-Carlo simulation of 1D particle-lattice model

Appendix C

The Bethe-ansatz Solution of Periodic ASEP

Appendix D

The Toeplitz Matrix

The Toeplitz M

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