Ring Polymers as a Model for Cellular Organization

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RING POLYMERS AS A MODEL FOR CELLULAR ORGANIZATION

by

Yu Zhu

A Thesis
Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Science

Major: Physics

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First of all, I would like to express my appreciation for my supervisor, Dr. Laradji, a responsible, respectable advisor, who has provided me with valuable guidance of my research in the past year. Without his enlightening instruction, patience, I could not make so much progress. He is not only my advisor but also my friend, who has influenced me from now to the future very deeply.

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ABSTRACT

A number of experimental studies have been reported on the spatial organization and collective motion of living cells during the past few decades. To explain the experimentally observed results, we propose a novel approach, in which the cells are modeled as semi-flexible ring polymers. We found that the basic physical properties of the polymer rings, such as average area per cell, elongation, and orientation highly depend on the areal polymer density. Investigations of systems composed of two types of ring polymers with different bending rigidities show that multi-component ring-polymer systems exhibit microphase separation. Simulations of the ring polymers on a unidirectional patterned substrate show that the polymers tend to orient along the direction of the substrate pattern. Simulations of the cells in the presence of non-equilibrium motile forces show that driven cell motility leads to aggregation of the cells with strong correlations in the velocity field.
Table of Contents

List of Figures ................................................................................................................... vii

1 INTRODUCTION ............................................................................................................. 1

2 LITERATURE REVIEW .................................................................................................... 5
  2.1 Cellular Potts Model .................................................................................................. 5
  2.2 Phase-Field Model .................................................................................................... 7
  2.3 Particle Models ......................................................................................................... 8

3. THEORETICAL MODEL AND COMPUTATIONAL METHODS .................................... 10
  3.1 Molecular Dynamics Method .................................................................................... 10
  3.2 Metropolis Monte Carlo Method .............................................................................. 11
  3.3 Canonical Ensemble .................................................................................................. 13
  3.4 Fluctuation-Dissipation Theorem ............................................................................ 14
  3.5 Interaction Potential Energies ................................................................................... 16
    3.5.1 Bonding potential energy .................................................................................. 16
    3.5.2 Bending potential energy .................................................................................. 17
    3.5.3 Repulsive potential energy ............................................................................... 18
    3.5.4 Cell-substrate interaction ................................................................................ 19
    3.5.5 Motile Forces .................................................................................................... 20
  3.6 Quantification Methods ............................................................................................. 21
    3.6.1 Shoelace formula .............................................................................................. 22
    3.6.2 Delaunay triangulation ..................................................................................... 22
    3.6.3 Moment of inertia ............................................................................................. 23
    3.6.4 Orientational order parameter ......................................................................... 25
  3.7 Integration Algorithm ................................................................................................. 26
    3.7.1 Velocity-Verlet integration algorithm ............................................................... 26
    3.7.2 Boxing Method .................................................................................................. 28
  3.8 Programming and Tools ............................................................................................ 28
  3.8 Model and Method Parameters .................................................................................. 32

4 RESULTS AND DISCUSSION ......................................................................................... 35
  4.1 Single Type Ring Polymer ....................................................................................... 35
  4.2 Two Type Ring Polymer with Different Rigidity ..................................................... 41
  4.3 Effect of Substrate Patterning .................................................................................. 45
### List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1. A configuration of different cells in a liquid state obtained from Monte Carlo simulation of the cellular Potts model. Different colors are used to distinguish between neighboring cells. Each cell is a domain of many lattice points with same value of σ.. This figure is adapted from ref. [20].</td>
<td>7</td>
</tr>
<tr>
<td>Figure 2. (A) A single cell described by a field, with a value of 1 indicating the bulk of the cell, and 0 indicating the outside environment of the cell. The cell boundary is defined by the gradient of the field. (B) shows cells boundaries of a system composed of many cells. From Ref. [17].</td>
<td>8</td>
</tr>
<tr>
<td>Figure 3. The collective motion of cells, each represented by a single rigid with an orientation field p.</td>
<td>9</td>
</tr>
<tr>
<td>Figure 4. (a) The relationship between angle θ, spring (ri − 1, ri), the triplet of particles(i − 1, i, i + 1). (b) the three potential energies are schematically presented by arrows with different colors. The bonding interaction (green arrows) is acts between connected particles. The bending energy (black arrows) is a function of the angle of the triplet (i − 1, i, i + 1), show in (a). The repulsive interaction (red arrows) is acts between any two non-directly connected particles when they are closer than some the cutoff distance req. It is important to emphasize that the repulsive interaction acts both within each cell as well as between different cells.</td>
<td>19</td>
</tr>
<tr>
<td>Figure 5. (a) The blue lines along the y-axis indicate the substrate’s pattern which tends to force the alignment of the walls of the red cells. (b) the influence of substrate track acts on cells will force the angle α between a bond and the substrate track to be close to 0.</td>
<td>20</td>
</tr>
<tr>
<td>Figure 6. (a) A snapshot of the cells at some given time. (b) The same cells (blue) shown with their centers of mass (red dots). (c) Delaunay triangulation (black) based on the cells’ centers of mass. Each cell is connected with its nearest neighbors only.</td>
<td>23</td>
</tr>
<tr>
<td>Figure 7. The shape of cells with their orientations determined by the eigenvector found from the eigenvalue problem, Eq. (3.43), with largest eigenvalue. Cells from left to right are with increasing lateral density of the cells in the system.</td>
<td>25</td>
</tr>
<tr>
<td>Figure 8. An of the angle between two nearest-neighbor cells defined as the angle between the eigenvectors (found from the moment of inertia eigenvalue problem, Eq. (3.41)) of the cells with largest eigenvalues.</td>
<td>25</td>
</tr>
</tbody>
</table>
Figure 9. The particles speed distribution for a system with (put all parameters), along with the theoretical Maxwell’s distribution. Note that the exact match between the simulation and the theory. ................................................................. 27

Figure 10. Workflow of the implementation of the periodic boundary conditions in two dimensions. ................................................................. 29

Figure 11. Workflow of the updates of the velocity, position and forces. ................................................................. 30

Figure 12. Workflow for generating the initial state of the system. ................................................................. 31

Figure 13 A cell boundary composed of N=40 particles connected by massless springs that are initially at rest. The angle between adjunct particles is $360^\circ \frac{N}{40} = 9^\circ$ and the initial length of the spring is $r_{eq}$. The initial radius of the cell is then $6.35 r_{eq}$. (b) An example of an initial configuration of a system composed of 484 cells distributed randomly in the system, without overlap. ................................................................. 33

Figure 14 Cells configurations (red) along with their orientation (black) for a system composed of a single type ring polymers at different densities. Other parameters here correspond to $k_{bond} = 100$, $k_{i} = 500$, and $k_{rep} = 25$. ................................................................. 37

Figure 15. (a) The average area of cells, calculated using Eq. (3.36), versus density (number of cells per unit of area) for the case of parameters in Table 1, at different values of the bending modulus. (b) Average moment of inertia, calculated using Eq. (3.43), used to characterize the elongation of the cells, versus density for different values of the bending modulus. (c) Average angle between neighboring ring polymers as the function of cells’ density at different values of the bending modulus. (d) Average number of rings with 6 neighbors, normalized by the total number of ring polymers versus density, for different values of the bending rigidity modulus. (e) Number of pairs of rings with an angle between 0 to 5 degrees versus density, for different values of the bending rigidity modulus. (f) The orientation order parameter, calculated using Eq. (3.44), versus cells’ number density. ................................................................. 38

Figure 16. This table presents the configuration for two different type of ring polymers at different densities. The red color stand for rigid ring polymer with $k_{high} = 400$, and the green color stand for soft ring polymer with $k_{low} = 20$. ................................................................. 42

Figure 17. Average area of stiff rings (black) corresponding to $k_{high} = 400$ and soft rings (red) corresponding to $k_{low} = 20$ as the function of density. (b) Polymers’ moment of inertia of two different type ring polymers as the function of density, respectively. (c) Average angle between neighboring rings (black), between neighboring stiff rings with $k_{high} = 400$ (red), between neighboring soft rings with $k_{low} = 20$ (blue), and between stiff and soft rings. (d) Number of ring polymer pairs versus density, for different angle
intervals ranging from 0 degree to 90 degrees. (e) Average number of rings with
different neighbors, labeled with the format: kbend_number of neighbors. .............. 44

Figure 18. The snapshot of orientation and configuration of single type ring polymer system with
external force constraint under different density, the alignment induced by the
simulation of track on substrate. ................................................................. 47

Figure 19. (a). Average area of ring polymers, versus density, of a system with an substrate force,
corresponding to (ksub=5). (b). Average moment of inertia of ring polymers, vs with
external force for different values of the bending rigidity. (c ) The average angle
between neighboring ring polymers with external force for different rigidity as the
function of density. (d) The number of hexagonal neighboring structure of ring polymer
with external force for different rigidity as function of density, a perfect smectic
structure presented when the density is 0.00868. (e) The order parameter of ring
polymers orientation with external force for different rigidity as the function of density
with (ksub=5). (f) The orientation order parameter of ring polymers with external force
for different strength of cell-substrate force as the function of density kbend=500). ... 49

Figure 20. This figure presents the velocity field (black) and configuration(red) of ring polymers
with motile force for different densities, a-d have same density at different time, where
the system formed small clusters and then combined to large one very fast. .............. 52

Figure 21. The results with the conditions (kbond = 100, kbend=500) (a) The average area of
ring polymers with motile force for different time steps τ and strength μ. (b) The
average area moment of inertia of ring polymers with motile force for different time
steps and strength. (c) The Average angle of neighboring ring polymers with motile
force for the feedback of different time steps and strength. (d) The average velocity
direction of ring polymers with motile force for the feedback of different time steps and
strength changes continuously as the function of time. (e) The orientational order
parameter of ring polymers with motile force for the feedback of different time steps
and strength. (f) The Velocity order parameter of ring polymers with motile force for
the feedback of different time steps and strength. ........................................... 54
1 INTRODUCTION

Active matter encompasses a wide range of fascinating macroscopic and microscopic systems in nature. Macroscopic active matter includes the ubiquitous flocks of birds and schools of fish. Much less visible active matter includes molecular motors, bacteria colonies and tissue. Most active matter systems are biological systems which are composed of a large number of active units or agents that consume energy from the environment and transfer it into mechanical work, thereby supporting the activity of each single unit. Many theoretical physics-based models and efficient computational tools, along with advanced microscopy tools, such as particle imaging velocimetry and traction microscopy have been developed during recent years. These developments have allowed for synergetic inter-disciplinary investigations of many microscopic active matter systems involving researchers from physics, biology and chemistry.

The understanding of the rich collective behavior of active matter has been driven by both basic science questions and a wide range of important applications pertinent to wound healing, cancer invasion and embryonic development. There already exist several theoretical models, which have been developed to understand the behavior of cell colonies and tissues. These models typically take into account the rate of activity, cells lateral density, cell-cell interaction, cell-substrate interaction, effect of external stimuli such as light, magnetic field, external flow, etc. These physical models include lattice models\cite{10,15,20}, particle models\cite{9,11,12} and phase field models\cite{8,13}. Different models vary widely in their degrees of complexity, and have advantages and limitations. Their suitability depends on the questions being addressed.
Lattice models are extensions of the well-studied Ising model[46], in which each cell is represented by a lattice point[10][15][20]. These models therefore integrate many cells internal degrees of freedom into few variables, thereby allowing them to be used for studying large scale collections of cells. Lattice models have widely been used to investigate the mechanisms of cell rearrangements with cell-cell or cell-substrates interactions. These models show the emergence of collective motility and transitions from static tissues to highly mobile cells, caused by cell-cell or cell-substrate interactions, motile force and adhesion [10] . Lattice models, are however not suitable for collective cell migration due to their difficulty in explicitly distinguishing between cell-cell and cell-substrate interactions, because of the calculation of interfacial tension highly depend on neighboring sites[12].

Particle models[21][22] are far more useful for studying collective migration of living cells and motility-induced phase separation. Particle models typically treat each cell as a single or two connected rigid beads, and therefore ignore many important cellular details. Particle models have been used to investigate effects such as the mechanisms of collective cell migration in epithelial tissues and steam cells and the mechanics of tissues[19][24].

Phase field models are based on the well-studied time-dependent Ginzburg-Landau theory[47], and are much more detailed than either lattice or particle models, and were introduced to investigate cell motility and cells collective behavior[17]. For example, the study by Löber et al. investigated the kinetics of inelastic collisions between cells, focusing in particular on the deformation of the cells resulting from their collision [13] . Phase field models, however, are very cumbersome involve a large range of parameters that cannot trivially be related to the system properties, and are more suitable to describe the kinetics of individual cells.
To address many of the above-mentioned shortcomings, we developed a relatively simple model that is suitable to investigate the collective behavior of cells, while accounting for some single cell properties. This model borrows from our extensive knowledge in polymer physics to treat cells as two-dimensional rings with various constraints. This model is then investigated numerically through molecular dynamics simulations to explore properties such as structure and orientation of the cells, and their positional and orientational correlations as a function of various constraints, including their areal density, rigidity, interaction with the substrate, and volume constraint.

A cellular colony in the present thesis is treated as a collection of semi-flexible ring polymers, with excluded volume, in a two-dimensional box with periodic boundary conditions. A bead-spring model with three-body interactions is used to describe the ring polymers. To account for the cells excluded volume, additional repulsive two-body interactions between any two non-connected beads are added to the model. Our investigation uses a molecular dynamics approach with a Langevin thermostat, in which the equations of motion, which are derived from the system’s Hamiltonian, are integrated out using the velocity-Verlet integration scheme. The model is first investigated at thermal equilibrium. To add more realistic features to the model, allowing it to be used as a cells’ model, constraints of the cell’s area, interaction with the substrate, and external driving forces are also added to the model.

We emphasize that the molecular dynamics code and all quantification codes are developed and written by the candidate. The quantification of the system is based on several calculated quantities, including the average number of nearest neighbor cells of each cell, determined from the Voronoi diagram of the system based on the cells’ centers of mass. We also used the moment of inertia tensors of the cells to determine their deformation, and in particular
their elongation. This is then used to determine the order parameter, as well as orientational correlations.

Our main results are summarized as follows: Both of the areal density and polymers bending rigidity contribute to the elongation of the cells and their organization at thermal equilibrium, to varying degrees. At low densities, the polymers morphology is isotropic, and are spatially distributed uniformly without short-range or long-range correlations. At intermediate densities, local spatial correlations between the polymers, with many having six nearest neighbors, are observed. Microphase separation was observed in binary systems composed of rigid and soft ring polymers. In addition, we found that anisotropically structured substrates are able to influence the alignment of the cells, leading to nematic or smectic phases depending on the cells areal density caused and strength of the substrate-cells interaction. Finally, the generalization of the model to account for external driving forces, show dynamically coordinated migration patterns of cells clusters formed at low cells areal densities.

A review of existing literature of previous theoretical and computational investigations of cells migration is found in Chapter 2. In Chapter 3, we present the model and numerical methods we used in this thesis. In Chapter 4, the results are presented and analyzed. Finally, a conclusion of this thesis and outlook toward future work is presented in Chapter 5. Note that throughout this thesis, a ring polymer is often loosely referred to as cell even at equilibrium conditions.
2 LITERATURE REVIEW

With a rising interest in a range of phenomenon in active matter and the development of various experimental tools used in biological laboratories, a lot of research has been devoted to the collective behavior of cells in tissues of eukaryotic cells and bacterial colonies[25][26][27]. For example, self-propelled rod-like bacteria are able to sense and navigate their environment in search of nutrients. This may be used to command their behavior, for example, through topological defects and patterned substrates, as shown recently by Peng et al.[14]. The collective migration of cells depend on many effects, such as motile force and usually involves inelastic collisions between neighboring cells[13]. The mechanics and dynamics of deformable cells and their motility were discussed in details by Löber[13]. The confinement, or areal density, of the cells also affects their spatial organization and collective dynamics [16]. In this chapter, we will review some theoretical models that have been used to investigate collective cell migration, the advantage of these models and their shortcomings. These models correspond to the lattice cellular Potts model[12], phase-field models[8][13], and particle models[9][11][12].

2.1 Cellular Potts Model

The cellular Potts (CP) model, introduced by Grander and Glazier [12], is a lattice model based on the Large q-State Potts model[28], previously used for many problems involving phase transitions and critical phenomena[20][10]. The Potts model was generalized to the biological field to learn the collective behavior and sorting of random mixtures of two different types of embryonic cells[12]. In the CP model, each lattice site $i = 1, ..., N$ is assigned a state variable $\sigma_i = 1, ..., m$ corresponding to one of the $m$ cells(with $m < N$). The state of each lattice is update numerically through the Metropolis Monte Carlo scheme at a sufficiently low effective temperature. The Hamiltonian of the CP model is given by the following equation[29]:

\[ H = -J \sum_{i,j} \mathbf{1}(\sigma_i \neq \sigma_j) \]
\[ \mathcal{H} = \sum_{\langle i,j \rangle} J(\sigma_i, \sigma_j) + \lambda \sum_{\sigma=1}^{m-1} (A_\sigma - A_0)^2 - P \sum_{\sigma=1}^{m-1} \vec{R}_\sigma \cdot \vec{p}_\sigma. \quad (2.1) \]

where the first term account for the interfacial tension between neighboring cells as well as between cells and the medium. The second term in Eq.(2.1) maintains the area of each cell around a preferred value \( A_0 (\lambda > 0) \). Third term in Eq.(2.1) is responsible for causing cell motility through a polar force \( \vec{p}_\sigma \) on cell \( \sigma \) with center of mass \( \vec{R}_\sigma \). The CP model is suitable for tissues or highly dense cultures of eukaryotic cells or bacteria. This model has then been widely used during the last few years for the modeling of two-dimensional cell migration while accounting for cell-cell and cell-substrate interactions as well as motility forces. The CP model is able to roughly describe the shape of cell and adhesion force between neighboring cells. A natural dissipative force of cell motions emerges comes from the Metropolis dynamics itself applied to system instead of a specific dissipative force. However, the model cannot distinguish between cell-cell friction and cell-substrate friction. For now, the CP model has successfully been used to learn the velocity correlations of cell migration [15], phase transition [20](Figure 1) between fluid and solid phase of the cell tissues[20], as well as tissue spreading[48]. Figure 1 shows cells in a liquid state from a Monte Carlo simulation of the cellular Potts Model to investigate the dynamical transition between a fluid-like and a solid-like phase in a confluent cell monolayer[20], where different cells were shown with different colors.
Figure 1. A configuration of different cells in a liquid state obtained from Monte Carlo simulation of the cellular Potts model. Different colors are used to distinguish between neighboring cells, Each cell is a domain of many lattice points with same value of $\sigma$. This figure is adapted from ref. [20].

2.2 Phase-Field Model

A phase field model for cell motility and cooperative behavior was developed by Fix[30] and Langer[31]. The model is a generalization of the Cahn-Hilliard free energy functional, commonly used to investigate the phase behavior of a wide variety of systems[32]. This approach is based on fields with two distinct values for the inner and outer environments of a cell, and gradual change between both values in the zone around the interface. This model was used to describe various cellular phenomena, such as rotation motion of pairs[18], tissue mechanics[33], cells inelastic collision[13], and extensile nematic behavior[8]. The cellular phase field model, the system is described by a constant (or slowly varying) field for the bulk of each cell, and the surrounding medium. The cells boundaries correspond to the high gradients in the field. The model is investigated by numerically integrating area-conserving Langevin equations, derived from the free-energy functional, combined with effective repulsive forces between cells to prevent their overlap and additional driving forces [17]. Figure 2(B) shows simulation results by Palmieri of the elastic mismatch between cells enhances motility, with Figure 2 (A) showing the field corresponding to a specific cell, in green.
Figure 2. (A) A single cell described by a filed, with a value of 1 indicating the bulk of the cell, and 0 indicating the outside environment of the cell. The cell boundary is defined by the gradient of the field. (B) shows cells boundaries of a system composed of many cells. From Ref. [17].

### 2.3 Particle Models

Matter is made up of many tiny particles, which implies that matter can be modeled as interacting particles with length scales depending on the question being asked. Particle models have thus also been used to investigate the behavior of cells. In this approach, each cell is treated as one or two circular beads [19] (e.g., see Figure 3). This approach therefore is not very detailed as far as the shape of the cells. However, this simplicity allows for using this model for systems composed of large number of cells. The two beads model of cells is able to account for shape anisotropy.
Figure 3. The collective motion of cells, each represented by a single rigid with an orientation field $\vec{\theta}$.

Particle-based cellular models account for self-propulsion forces, cell-cell interactions as well as cell-substrate interactions. Compared to the cellular Potts model and phase-field model, polarity interactions are much easier to include in particle models, and as a result, these models readily lead to cell-cell velocity alignment and flocking, despite the lack of, or reduced, details on cell shape in particle models.

In view of the three models which have been mentioned above, our attempt is to introduce a relatively simply model with the capability of accounting of both detailed shape of cells, interactions between cells, and motility forces while capable of studying systems composed of a large number of cells. This is achieved by borrowing ideas from polymer physics, and treating the boundary of a cell as a polymer ring. The shape of the cells is then controlled by the rigidity of the walls, the heterogeneity of the ring polymer, and the area constraint. Details of this model is presented in Chapter 3.
3. THEORETICAL MODEL AND COMPUTATIONAL METHODS

In the beginning sections of this chapter, we will present two well-established computational methods used to simulate both equilibrium and non-equilibrium systems, namely the molecular dynamics method and the Metropolis Monte Carlo method. The molecular dynamics method is the main method used in our simulation. However, in some cases, we also use a hybrid approach combining both the Metropolis Monte Carlo method with molecular dynamics, to bridle the shape of the cells. Later in this chapter, we will also briefly review some useful theoretical concepts that are important to the present thesis. These include the canonical ensemble, the fluctuation-dissipation theorem and the equipartition theorem. We will then proceed by presenting the generalized spring-bead model used to describe the cells. Next, we proceed by presenting the quantification methods such as the shoelace formula to quantify the enclosed area by each cell, the Voronoi diagram to determine cells nearest neighbors, the moment of inertia to extract the orientation of each cell, and the order parameter to quantify orientational (nematic) order in the system. Finally, we summarize this chapter with the program library and tools used during the whole study.

3.1 Molecular Dynamics Method

Molecular dynamics (MD) is a method introduced in the 1960s by Rahman[7] to numerically simulate the dynamics of classical many-body systems. Over the past decades, the MD approach has been extensively used to study the kinetic and thermodynamic properties of a wide range of systems of relevance to condensed matter physics, chemistry, engineering, biology and astronomy. The phase space trajectory of the configurations, of a system of interest, is obtained by integrating the equations of motion, for both coordinates and velocities, of the particles in the system.
The classical Hamiltonian of a system composed of \( N \) particles in a microstate \( \{ \mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N; \mathbf{p}_1, \mathbf{p}_2, ..., \mathbf{p}_N \} \), where \( \mathbf{r}_i \) and \( \mathbf{p}_i, i = 1, \ldots, N \), are the coordinate and the momentum of particle \( i \), and interacting via two-body, three-body as well as external forces, is given by,

\[
\mathcal{H} = E_k + E_p = \sum_{i=1}^{N} \frac{p_i^2}{2m_i} + \sum_{i>j=1}^{N} V_2(r_{ij}) + \sum_{i=1}^{N} \sum_{j\neq i, k \neq i}^{N} V_3(r_{ij}, r_{ik}) + \cdots + \sum_{i=1}^{N} V_{\text{ext}}(\mathbf{r}_i), \tag{3.1}
\]

where \( E_k \) is the net kinetic energy of the system and \( E_p \) is the net potential energy of the system. In Eq. (3.1), \( V_2(r_{ij}) \) is the two-body potential energy between particles \( i \) and \( j \), separated by a distance \( r_{ij} = |\mathbf{r}_i - \mathbf{r}_j| \). \( V_3(r_{ij}, r_{ik}) \) is the three-body potential energy and \( U_{\text{ext}}(\mathbf{r}_i) \) is the external potential energy. \( m_i \) is the mass of the \( i \)th particle. The position and momentum of each particle then must satisfy the following Hamilton’s equations

\[
\dot{r}_{i,\alpha} = \frac{\partial \mathcal{H}}{\partial p_{i,\alpha}} = \frac{p_{i,\alpha}}{m_i}, \tag{3.2}
\]

and

\[
\dot{p}_{i,\alpha} = \frac{\partial \mathcal{H}}{\partial r_{i,\alpha}} = f_{i,\alpha}, \tag{3.3}
\]

with \( \alpha = x, y \) or \( z \).

### 3.2 Metropolis Monte Carlo Method

The Monte Carlo method is a powerful and widely used method in many areas[35]. The method is based on the use of random numbers. A simple example where the Monte Carlo
method can be used is finding the area or volume contained inside a geometrical shape. The 
Metropolis Monte Carlo approach is a variant of the Monte Carlo approach that allows a system 
of many degrees of freedom to reach thermal equilibrium under specific thermodynamic 
constraints, and was introduced by Metropolis and Rosenbluth[34]. In the present study, this 
method is used to switch different types of particles. Recall that the probability that a system, at 
thermal equilibrium with a heat reservoir at temperature $T$, is at a specific positional microstate at 
time $t$, $R_t$, is 

$$W(R_t) = \frac{e^{-\frac{U(R_t)}{k_B T}}}{\int e^{-\frac{U(R')}{k_B T}} dR'}$$ 

(3.4)

where $k_B$ is Boltzmann’s constant and $U(R)$ is the energy of the microstate $R$. The Metropolis 
Monte Carlo approach allows for a diffusion in phase space through a Markov chain according to 
the following steps: 1) An attempted microstate $R'$ is generated from some distribution $g(R'|R_t)$. 
Though not necessary, to increase the acceptance rate, the deviation between $R'$ and $R_t$ is 
usually very small. 2) A ratio $\alpha = W(R')/W(R_t)$ is calculated. This will be used to decide 
whether the attempted configuration $R'$ is accepted or rejected. According to Eq. (3.4), the ratio 
is therefore $\alpha = \exp (-\Delta E/kT)$, where $\Delta E = U(R') - U(R_t)$ is the difference between the 
energies of the attempted and the current microstates. 3) If $\alpha \geq 1$, the attempted state $R'$ is then 
accepted as its probability is higher than or equal to that of $R_t$. However, if $0 \leq \alpha < 1$, a 
random number $u \in [0, 1)$, is generated from a uniform distribution. The attempted state is then 
accepted if $u \leq \alpha$, and the new microstate is set to $R_{t+1} = R'$. The attempted state is however 
rejected if $u > \alpha$, and $R_{t+1} = R_t$. 

12
3.3 Canonical Ensemble

The canonical ensemble is a statistical ensemble that describes the possible equilibrium states of a system of many degrees of freedom with a heat reservoir and the constraints of constant number of particles and temperature. This ensemble is often referred to as the NVT or NPT ensemble depending on whether the volume or pressure are constrained, respectively. The probability function used to describe this ensemble is written as:

\[ W(R, P) = \frac{1}{Z} e^{-\mathcal{H}(R, P) / k_B T} \]  

(3.5)

where \( R \) and \( P \) are the positional and momentum configurations of a specific microstate, and the normalization constant is the partition function. The statistical average of a physical quantity \( A \) and partition function are then given by

\[ \langle A \rangle = \frac{1}{Z} \int A(R, P) W(R, P) dRdP \]  

(3.6)

and

\[ Z = \int W(R, P) dRdP. \]  

(3.7)

In particular, the average of kinetic energy is given by

\[ \langle E_k \rangle = \left\{ \sum_{i=1}^{N} \frac{P_i^2}{2m_i} \right\} = \frac{G}{2} k_B \]  

(3.8)

where \( G \) is the total number of degrees of freedom of the system (2\( N \) for a system of \( N \) point particles), regardless of the interaction potential energy of system.
3.4 Fluctuation-Dissipation Theorem

The fluctuation-dissipation theorem[1] is an important theorem in statistical physics which states that a system, that is at thermal equilibrium with some heat reservoir, dissipates energy to the reservoir in the form of heat, while acquiring energy from the reservoir in the form of thermal fluctuations. In our simulations, the fluctuations-dissipation theorem is upheld by introducing two forces acting on each particle, corresponding to the random force, $F^R_i$, whose effect is to mediate the flow of random thermal energy excitations from the reservoir to the system, and the dissipative force, $F^D_i$, whose effect is to mediate the dissipation of heat from the system to the reservoir. To maintain thermal equilibrium, the amplitudes of the random and dissipative forces have to be related. Since the random force cannot lead to a drift in the motion of the system, it must satisfy

$$\langle F^R_i(t) \rangle = 0,$$  \hspace{1cm} (3.9)

and must be uncorrelated for any two different degrees of freedom and must be uncorrelated in time, i.e.,

$$\langle F^R_i(t) \cdot F^R_j(t') \rangle = 3\sigma^2 \delta_{ij} \delta(t - t').$$  \hspace{1cm} (3.10)

If a uniform distribution is used for the random force,

$$\rho(F^R_{i,\alpha}) = \begin{cases} c & \text{for } |F^R_{i,\alpha}| \leq a \\ 0 & \text{for } |F^R_{i,\alpha}| > a \end{cases}$$  \hspace{1cm} (3.11)

where $F^R_{i,\alpha}$ is the $\alpha$-th component of $F^R_i$. The normalization condition of the distribution $\rho$ leads to $c = 1/2a$. Eq. (3.11) implies that

$$\langle |F^R_{i,\alpha}(t)|^2 \rangle = \frac{\sigma^2 \delta_{ij}}{\Delta t},$$  \hspace{1cm} (3.12)
where we used a discrete approximation of the Dirac delta-function, i.e. \( \delta(0) \approx 1/\Delta t \). The calculation of \( \langle |r_{i,\alpha}(t)|^2 \rangle \) using the distribution in Eq (3.11) then leads to

\[
a = \sigma \sqrt{\frac{3}{\Delta t}}.
\]  

(3.13)

Therefore, each component of the random force at time \( t \) can be written as

\[
r_{i,\alpha}^R(t) = \sigma \sqrt{\frac{3}{\Delta t}} (2u - 1),
\]

(3.14)

where \( u \in [0,1) \) is a random number generated from a uniform distribution.

We use a dissipative force that is proportional to the velocity of the particle. The \( \alpha \)-th component of the dissipative force \( F_i^D \) is then given by

\[
F_{i,\alpha}^D(t) = -\Gamma v_{i,\alpha}(t).
\]

(3.15)

Since the fluctuation-dissipation theorem must be satisfied, the coefficients of the dissipative and random forces must be related through the equation

\[
\Gamma = \frac{\sigma^2}{2k_B T}
\]

(3.16)

3.4 Equipartition Theorem

Since the kinetic energy of each particle is quadratic in its velocity, the equipartition theorem leads to

\[
\langle \frac{1}{2} m v_i^2 \rangle = \frac{1}{2} k_B T
\]

(3.17)
The equipartition theorem was used to assign the initial velocities of all particles using the Maxwell’s speed distribution

\[ p(v) = \frac{m v}{kT} e^{-\frac{mv^2}{2kT}} \]  (3.18)

3.5 Interaction Potential Energies

The potential energy of our system has three contributions, corresponding to (1) a two-body bonding potential energy, necessary to maintain the connectivity between beads belonging to each ring polymer, (2) a three-body bending potential energy needed to provide a bending stiffness for each ring polymer, and (3) a two-body repulsive potential energy between any two non-bonded monomers, needed to maintain self-avoidance of each polymer and prevent overlap between the polymer rings. In the following three subsections, we will present each of these three potential energies in detail.

3.5.1 Bonding potential energy

In our model, each cell is represented by the projection of its boundary on the xy-plane. This projection is approximated by a two-dimensional ring polymer made-of point-particles (beads) that are bonded linearly, as shown schematically in Figure 4. A simple quadratic potential energy is used between monomers \(i\) and \(i+1\)

\[ U_{bond}(r_{i,i+1}) = \frac{k_{bond}}{2}(r_{i,i+1} - r_{eq})^2 \]  (3.19)

with \(i = 1, \ldots, N\), and the index \(N + 1 \equiv 1\). In Eq. (3.19), where \(r_{eq}\) is the preferred bond length, \(k_{bond} > 0\) is the spring constant of the bond and
From Eq. (3.20), the elastic force along the $\alpha$-th direction is then given by

$$F_{i,\alpha}^{\text{bond}} = - \frac{\partial U_{\text{bond}}(r_{i,i+1})}{\partial \alpha_i} = - \frac{k_{\text{bond}}(r_{i,i+1} - r_{eq})(\alpha_{i+1} - \alpha_i)}{r_{i,i+1}}$$

(3.21)

where $\alpha = x$ or $y$, and $F_{i+1,\alpha}^{\text{bond}} = -F_{i,\alpha}^{\text{bond}}$.

### 3.5.2 Bending potential energy

The bending potential energy in our model is considered as a three-body interaction given by

$$U_{\text{bend}}(\theta_i) = \frac{k_{i,\text{bend}}}{2} (\cos \theta_i - \cos \theta_{eq})^2,$$

(3.22)

where $k_{\text{bend}} > 0$ is the bending elasticity coefficient and is related to the bending modulus of the cell’s plasma membrane. $\theta_{eq}$ is a preferred angle, typically chosen as 180°, and $\theta_i$ is the angle of the triplet $(i - 1, i, i + 1)$ (Figure 4.a), defined by

$$\cos \theta_i = \frac{\hat{r}_{i-1,i} \cdot \hat{r}_{i,i+1}}{\hat{r}_{i-1,i} \cdot \hat{r}_{i,i+1}}.$$  

(3.23)

From Eq. (3.23), the $\alpha$-th component of the force resulting from the bending potential energy on particle $i$ is then given by,

$$F_{i,\alpha}^{\text{bend}} = - \frac{\partial}{\partial \alpha_i} U_{\text{bend}}(\theta_i)$$

$$= k_{i,\text{bend}} \left( \cos \theta_i - \cos \theta_{eq} \right)$$

$$\left\{ \frac{(\alpha_{i+1} + \alpha_{i-1} - 2\alpha_i)}{r_{i,i+1}r_{i-1,i}} + \left[ \frac{\alpha_i - \alpha_{i+1}}{r_{i,i+1}^3 r_{i-1,i}^3} + \frac{\alpha_i - \alpha_{i-1}}{r_{i,i+1}r_{i-1,i}^3} \right] \hat{r}_{i,i-1} \cdot \hat{r}_{i,i+1} \right\},$$

(3.24)

and the $\alpha$-th components of the bending forces on particle $i + 1$ and $i - 1$ are respectively given by
\[ F_{i+1,a}^{bend} = -\frac{\partial}{\partial \alpha_{i+1}} U_{bend}(\theta_i) = \]
\[ k_{i,bend} (\cos \theta_i - \cos \theta_{eq}) \left\{ \frac{(\alpha_{i+1} - \alpha_{i+2})}{\hat{r}_{i,i+1} \hat{r}_{i+1,i+2}} + \frac{(\alpha - \alpha_{i+1})}{\hat{r}_{i,i+1}^3 \hat{r}_{i+1,i+2}} \hat{r}_{i,i+1} \cdot \hat{r}_{i+1,i+2} \right\}, \quad (3.25) \]

and

\[ F_{i-1,a}^{bend} = -\frac{\partial}{\partial \alpha_i} U_{bend}(\theta_i) = \]
\[ k_{i,bend} \times (\cos \theta_i - \cos \theta_{eq}) \left\{ \frac{(\alpha_{i-1} - \alpha_{i-2})}{\hat{r}_{i-1,i-2}} + \frac{(\alpha_i - \alpha_{i-1})}{\hat{r}_{i-1,i-2}^3} \hat{r}_{i-1,i-2} \cdot \hat{r}_{i-1,i-2} \right\}. \quad (3.26) \]

### 3.5.3 Repulsive potential energy

The bending and bonding interactions act only within each ring polymer. As this model is being developed for living cells, two important aspects need to be accounted for. (1) The boundaries of each cell cannot self-cross and (2) cells cannot overlap which other. These two topological constraints are accounted for by the addition of a third repulsive interaction between any two non-bonded beads. To keep the model simple, we chose a quadratic repulsive potential energy,

\[ U^{rep}(r_{i,j}) = \begin{cases} \frac{k_{rep}}{2} \left( 1 - \frac{r_{i,j}}{r_{eq}} \right)^2 & \text{for } r_{i,j} < r_{eq}, \\ 0 & \text{for } r_{i,j} \geq r_{eq} \end{cases}, \quad (3.27) \]

where \( k_{rep} (> 0) \) is the strength of the repulsive force and \( r_{eq} \) is the cutoff of the interaction.

Therefore, the \( \alpha \)-th component of the repulsive force on the \( i^{th} \) particle is given by

\[ F_{i,\alpha}^{rep} = -\frac{\partial}{\partial \alpha_i} U^{rep}(r_{i,j}) = k_{rep} \left( 1 - \frac{r_{eq}}{r_{i,j}} \right) (\alpha_j - \alpha_i) \quad (3.28) \]
and the $\alpha$-th component of the repulsive forces on the $j^{th}$ particle is given by

$$F_{j,\alpha}^{rep} = -F_{i,\alpha}^{rep}. \quad (3.29)$$

Figure 4 (a) The relationship between angle $\theta_i$, spring $(r_i-1, r_i)$, particle $i$ and the triplet of particles $(i-1, i, i + 1)$. (b) The three potential energies are schematically presented by arrows with different colors. The bonding interaction (green arrows) is acts between connected particles. The bending energy (black arrows) is a function of the angle of the triplet $(i-1, i, i + 1)$, shown in (a). The repulsive interaction (red arrows) is acts between any two non-directly connected particles when they are closer than some the cutoff distance $r_{eq}$. It is important to emphasize that the repulsive interaction acts both within each cell as well as between different cells.

3.5.4 Cell-substrate interaction

In many cases, the substrate on which cells are cultured is heterogeneous. We have therefore also considered a case of an anisotropic substrate by adding a force that tends to align the cell walls with the patterned substrate. It has great potential to control the alignment and organization of cell by synthesizing patterned liquid crystal polymer network film experimentally. With the linear or circular patterns created by photopatterning technique, the cell’s alignment, migration and proliferation can be directed by the aligned polymer chains[45]. The particular model below corresponds to a substrate that is anisotropically patterned along the $y$-axis. The simplest potential energy that promotes the alignment of the ring polymers (cells) along the $y$-axis can be written as (see Figure 5)
\[ U_{\text{sub}}(\theta_i) = \frac{k_{\text{sub}}}{2}(\cos \theta_i - \cos \theta_{eq})^2 \] (3.30)

where \( k_{\text{sub}} > 0 \) is the strength of this interaction, \( \theta_i \) is the angle between the bond \( \vec{r}_{i,i+1} \) and the \( y \)-axis, and \( \theta_{eq} \) is some preferred angle, taken so far to be zero. Therefore, the \( x \)- and \( y \)-components of force due to the substrate acting on the \( i^{th} \) particle are given respectively by,

\[ F_{i,x}^{\text{sub}} = -\frac{\partial}{\partial x_i} U_{\text{sub}}(\theta_i) = k_{\text{sub}} \left( \frac{x_{i+1} - x_i}{r_{i,i+1}} - 1 \right) \left[ \frac{(x_{i+1} - x_i)^2}{r_{i,i+1}^3} - \frac{1}{r_{i,i+1}} \right] \] (3.31)

and

\[ F_{i,y}^{\text{sub}} = -\frac{\partial}{\partial y} U_{\text{sub}}(\theta_i) = k_{\text{sub}} \left( \frac{x_{i+1} - x_i}{r_{i,i+1}} - 1 \right) \left[ \frac{(x_{i+1} - x_i)(y_{i+1} - y_i)}{r_{i,i+1}^3} \right]. \] (3.32)

Figure 5. (a) The blue lines along the \( y \)-axis indicate the substrate’s pattern which tends to force the alignment of the walls of the red cells. (b) the influence of substrate track acts on cells will force the angle \( \alpha \) between a bond and the substrate track to be close to 0.

### 3.5.5 Motile Forces

There exist many models for motility forces[36][37][38], with the intendency of interaction between cells to align their polarities. The intendency induced by motility forces can
be came from migrate cells’ velocity, a hydrodynamic interactions between polar cells and substrate[39][40]; the elongated shape of cells, which mainly modified by cell-cell interactions[41][42]; or shear stress induced by inhomogeneous tissue flows, similar to molecules in liquid crystals[43][44]. Here we will use a model introduced earlier by Kabla[10], in which we assume that there exist a source of energy driving the motility of each cell along a direction determined by its polarity, $n_i(t)$, leading to a motile force,

$$ F_i(t) = \mu n_i(t). \quad (3.33) $$

The polarization $n_i(t)$, is a unit vector oriented along the mean velocity of the cell during the previous interval of time $\tau$

$$ \vec{n}_i(t) = \frac{\langle \vec{v}_i \rangle_{[t-\tau,t]} }{ \langle |\vec{v}_i| \rangle_{[t-\tau,t]} }, \quad (3.34) $$

Where

$$ \langle v_i \rangle_{[t-\tau,t]} = \frac{1}{\tau_M} \int_{t-\tau_M}^{t} v_i(t) dt. \quad (3.35) $$

The parameter $\tau$ is the evolution time scale of the cell’s polarity.

### 3.6 Quantification Methods

To investigate the collective behavior of the cells, as modeled by ring polymers, various tools were introduced to analyze the configurations obtained from the simulations. These tools include the determination of the area of each cell, anisotropy and orientation of each cell, number of nearest neighbors of each cell, and correlations between cells.
3.6.1 Shoelace formula

Thermal fluctuations, crowding, interactions between cells and substrate, and driving forces to lead to irregularities in the shape of the, including changes in the areas of each. Since our cells are polygons, we use the shoelace method to quantify the area of a cell composed of \( n \) monomers[5], i.e.,

\[
A = \frac{1}{2} \left| \sum_{i=1}^{n-1} x_i y_{i+1} + x_n y_1 - \sum_{i=1}^{n-1} x_{i+1} y_i - x_1 y_n \right|
\]

(3.36)

where \( A \) is the area of the irregular cell and \((x_i, y_i)\) are the cartesian coordinates of the \( i^{th} \) particle.

3.6.2 Delaunay triangulation

The Delaunay triangulation method is commonly used to find the nearest neighbors of a set of discrete points in space. The Delaunay triangulation is a graph of a subset of segments connecting points is such a way that the circumcircle of any triangle based on three segments is empty, i.e., does not contain any point [6]. The Delaunay diagram is used in this thesis to determine the list of nearest neighbors of each cell, based on their centers of mass. The numerical determination of the nearest neighbors is achieved here through the CGAL library [2]. An example of the Delaunay triangulation is shown in Figure 6.
3.6.3 Moment of Inertia

To quantify the elongation of cells’ shape (Figure 7), we borrow the idea of area of moment of inertia of each cell. The correlation of angle between neighboring cells (Figure 8) is also easy to investigate based on this quantification method. The moment of inertia is a tensor, with its elements, $I_{ij}$, defined for a set of $n$ point particles as,

$$I_{ij} = \sum_{k=1}^{n} m_k (r_k^2 \delta_{ij} - \alpha_{k,i} \alpha_{k,j}),$$

where, in two-dimensions, $i = 1$ or 2, $\alpha_{k,1} = x_k - x_{cm}$, $\alpha_{k,2} = y_k - y_{cm}$, $r_k^2 = \alpha_{k,1}^2 + \alpha_{k,2}^2$, and $\delta_{ij}$ is the usual Kronecker delta. The center of mass coordinates are $x_{cm} = (1/n) \sum_{k=1}^{n} x_k$ and $y_{cm} = (1/n) \sum_{k=1}^{n} y_k$. Therefore, for a cell composed of $n$ monomers, each of mass 1 unit, the elements of the moment of inertia are given by

$$I_{xx} = \sum_{k=1}^{n} (y_k - y_{cm})^2,$$
\[ I_{yy} = \sum_{k=1}^{n}(x_k - x_{cm})^2, \]  
(3.39)

and

\[ I_{xy} = I_{yx} = -\sum_{k=1}^{n}(x_k - x_{cm})(y_k - y_{cm}). \]  
(3.40)

The anisotropy of a cell is inferred from the analysis of the eigenvalue problem,

\[
\begin{bmatrix}
I_{xx} - \lambda & I_{xy} \\
I_{yx} & I_{yy} - \lambda
\end{bmatrix} \vec{v} = 0,
\]  
(3.41)

leading to two eigenvalues,

\[ \lambda_{\pm} = \frac{1}{2} \left[ (I_{xx} + I_{yy}) \pm \sqrt{4I_{xy}I_{yx} + (I_{xx} - I_{yy})^2} \right]. \]  
(3.42)

The degree of anisotropy of the cell is then defined by the ratio

\[ \alpha = \frac{\max(\lambda_{+}, \lambda_{-})}{\min(\lambda_{+}, \lambda_{-})}, \]  
(3.43)

and the orientation of the cell is defined by the direction of the eigenvector, \( \vec{v} \), corresponding to the largest eigenvalue. In Figure 7, a series of cells at different densities are shown along with their orientation determined by \( \vec{v} \) corresponding to largest eigenvalue.
Figure 7. The shape of cells with their orientations determined by the eigenvector found from the eigenvalue problem, Eq. (3.43), with largest eigenvalue. Cells from left to right are with increasing lateral density of the cells in the system.

Figure 8. An example of the angle between two nearest-neighbor cells defined as the angle between the eigenvectors (found from the moment of inertia eigenvalue problem, Eq. (3.41)) of the cells with largest eigenvalues.

3.6.4 Orientational order parameter

The spatial organization of elongated cells will be quantified through a quantity called orientational order parameter. This is defined as the average deviation of the orientational angles of the cells from the average orientation of all cells in the system:

\[ S = 2\langle \cos^2 \theta \rangle - 1 = \langle \cos(2\theta) \rangle, \]  

where \( \theta \) is the angle between the average direction of all cells in the system, and the direction of the eigenvector, with the largest eigenvalue of each cell. The bracket denotes an average over all
cells in a certain configuration. The ensemble average of the order parameter is obtained by further averaging over time.

The order parameter provides a convenient quantification of the cells’ alignment. $S = 1$ corresponds to a perfect alignment, i.e. all of cells along the average direction of the cells. This would correspond to a perfect nematic or smectic order. $0 < S < 1$ corresponds to partial alignment. Finally, $S = 0$ corresponds to configurations without long range orientational order.

### 3.7 Integration Algorithm

#### 3.7.1 Velocity-Verlet integration algorithm

There are many integration methods of the equations of motion in molecular dynamics[7]. These include the leap-frog integration method[48], the velocity-Verlet integration[4] and the Runge-Kutta integration method [3]. The difference between these methods lies in their accuracy, noting that a higher accuracy method requires a higher computational effort, and are therefore slower. For example, the Runge-Kutta method is accurate to fourth order with an error of $O(\Delta t^4)$, where $\Delta t$ is the integration time step. The Velocity-Verlet integration method is accurate to second order in $\Delta t$. In this thesis, we adopt the Velocity-Verlet approach due to its computational efficiency.

In this method, the position and velocity are given by the following equations:

$$\vec{r}_i(t + \Delta t) = \vec{r}_i(t) + \vec{v}_i(t)\Delta t + \frac{1}{2} \vec{a}_i(t)\Delta t^2, \quad (3.45)$$

and

$$\vec{v}_i(t + \Delta t) = \vec{v}_i(t) + \frac{\vec{a}_i(t) + \vec{a}_i(t + \Delta t)}{2} \Delta t, \quad (3.46)$$
where $\vec{r}_i(t)$, $\vec{v}_i(t)$ and $\vec{a}_i(t)$ are the position, velocity and acceleration of the $i^{th}$ particle, respectively, at time $t$ and $\Delta t$ is the time step. The timestep cannot be too large as this leads to numerical instabilities. In our simulations we used a maximum value of $\Delta t$ equal to 0.01. The distribution of velocity obtained from a typical simulations is compared with the theoretical Maxwell-Boltzmann velocity distribution describe by Eq. (3.18) is show in Figure 9. This figure demonstrates that the method allows the effective temperature of the system as well as velocity distribution to reach thermal equilibrium. Other properties of the system are monitored over time. The onset of thermal equilibrium is defined by the time at which all quantities become constant with fluctuations around some average values.

![Graph showing the comparison between simulation and theoretical Maxwell's distribution](image)

Figure 9. The particles speed distribution for a system with $(k_{bend} = 400, k_{bond} = 100)$, along with the theoretical Maxwell’s distribution. Note that the exact match between the simulation and the theory.
3.7.2 Boxing Method

To reduce the amount of computations associated with finding the list of particles that interact with each particle in order to calculate the two-body repulsive forces between them, the system is divided into a lattice of two-dimensional boxes with side $a \geq r_m$, where $r_m$ is the interaction cutoff.

3.8 Programing and Tools

In this section of this chapter, other details of the simulations, including the core workflow and few other tools used during this study are added. The simulation and quantification methods were all written by the candidate in C++. The standard library is the most important tool to store, update data and generate the random numbers. The API OpenMP (Open Multi-Processing) was used to realize the model of parallel calculation of forces between particles and updating their positions and velocities. The system was implemented with periodic boundary conditions to remove the effects of system boundaries, This is achieved by approximating an infinite system by using a small area. The workflow of this part is presented in Figure 10.
Figure 10. Workflow of the implementation of the periodic boundary conditions in two dimensions.

The workflow for updating the positions and velocities of the particles is presented in Figure 11.
Randomly generate the initial velocity \((v_x, v_y)\), the initial net force \((F_x, F_y)\), and the initial position \((x, y)\) at time \(t\)

Update the next velocity \((v'_x, v'_y)\) and next position \((x', y')\) at time \(t + \Delta t\), replace the current velocity and position with them

Calculate the net force \((F'_x, F'_y)\) for each particle based on current position \((x', y')\)

Update the next velocity \((v'_x, v'_y)\) based on \((F'_x, F'_y)\) at time \(t + \frac{1}{2}\Delta t\)

Recalculate the net force \((F'_x, F'_y)\) upon new velocity \((v'_x, v'_y)\) and replace current net force with it

Figure 11. Workflow of the updates of the velocity, position and forces.

The initial velocities and positions of the particles were generated randomly and are presented in Figure 12.
Generate a random coordinate \((X_c, Y_c)\) as the center of ring polymer, where the radius is \(R\)

Calculate the distance \(D\) between this polymer and all other presented ring polymer and boundary

If \(D > 2R\) and \(D > R\) for all cell-cell distance and cell-boundary distance respectively, accept this center coordinate, otherwise regenerate a new one.

Assign the coordinate for each particle base on the radius, center and number of particles

Assign the initial velocity for each particle based on equipartition theorem with random direction

Figure 12. Workflow for generating the initial state of the system.

All of the visualization video was made of VMD, ffmpeg and Video Mach, and graphs plotted by Xmgrace and Origin. Most of the simulations and quantification tools were run on the High Performance Computing cluster in the university of Memphis.
3.8 Model and Method Parameters

To simulate the model of single type ring polymer by using MD method, 19360 particles were selected to form 484 ring polymers, which means each of them made up of 40 particles connect with massless spring. We tried with Monte Carle method first, but each movement of particles are decided by the current positions of other neighboring particles which took too long time. To start with this generation, we set the area of system as $400 \times 400$, then fill it with uniform circular ring polymer with randomly. The initial radius of the ring polymer related to the number of particles and the length of spring, which means we can increase the area by increasing the number of particles in one cell. The density is defined as the ratio between the number of ring polymer and the area of system. It’s much more difficult to input new ring cells during the simulation mathematically than in the real experiment, the way we chosen to increase the density is by rescaling the whole system with a decimal. Although this method will cause some instabilities in some time, they will disappear with a few time steps.

The initial configuration of each cell in the present study is circular (see Figure 13. a). The centers of the initial cells are distributed randomly in the system, while avoiding overlap between the initial configurations. The initial distance between connected beads is equal to the equilibrium distance $r_{eq}$ in Eq. (3.19). An example of an initial configuration at an areal density 0.00302 is shown in Figure 13. b.
Figure 13 A cell boundary composed of N=40 particles connected by massless springs that are initially at rest. The angle between adjunct particles is \( \frac{360^\circ}{N} = 9^\circ \) and the initial length of the spring is \( r_{eq} \). The initial radius of the cell is then 6.35\( r_{eq} \). (b) An example of an initial configuration of a system composed of 484 cells distributed randomly in the system, without overlap.

In our scheme, all lengths are scaled by \( r_{eq} \), all energies are scaled by \( k_B T \), and all times are scaled by \( \tau = \sqrt{m_{eq}^2 / k_B T} \), where \( m \) is the mass of each bead. The parameters of the model used in this thesis are given in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/Definition</th>
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<tbody>
<tr>
<td>( k_{bond} )</td>
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</tr>
<tr>
<td>( k_{l,bend} )</td>
<td>20, 100, 200, 300, ...</td>
</tr>
<tr>
<td>( k_{rep} )</td>
<td>25</td>
</tr>
<tr>
<td>( \Gamma )</td>
<td>0.5</td>
</tr>
<tr>
<td>( L_o )</td>
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</tr>
<tr>
<td>( k_{mot} )</td>
<td>0.1, 0.5, 1</td>
</tr>
<tr>
<td>( N )</td>
<td>40</td>
</tr>
<tr>
<td>( N_c )</td>
<td>484</td>
</tr>
</tbody>
</table>

Table 1. Simulation parameters.
Table 1 (Continued)

<table>
<thead>
<tr>
<th>( \rho = \frac{N_c}{L^2} = 0.00302 \text{ to } 0.03071 \text{ in steps of } 0.0071 )</th>
<th>Areal number densities considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_{sub} = 0.1, 0.2, 0.3 \ldots 1, 2 \ldots 5 )</td>
<td>Coefficient of the substrate force ([k_B T])</td>
</tr>
<tr>
<td>( \Delta t = 0.01 )</td>
<td>Time step ([\tau])</td>
</tr>
<tr>
<td>( t_{max} = 500 \ 000 )</td>
<td>Total simulation time per system ([\tau])</td>
</tr>
</tbody>
</table>
4 RESULTS AND DISCUSSION

In this chapter, we would like to discuss the properties of single semi-flexible ring polymers as a function of density, as obtained from the simulations. After this, we will present the result of two different type of ring polymers with different bending rigidity coefficients. Lastly, we will present results based on simulations of the system with external forces corresponding to the force with the substrate and the motile forces introduced in Sections 3.5.4 and 3.5.5.

4.1 Single Type Ring Polymer

In this section, we present results of our simulations on systems composed of $N = 484$ polymers each composed of $N = 40$ monomers at different densities and for different values of the bending rigidity coefficient, $k_{bend}$. These simulations allow us to investigate the effects of both rigidity of the ring polymers as well as their areal density. Spatial configuration snapshots, at equilibrium, along with their corresponding cell orientation configurations, at different densities are shown for the case of $k_{bend} = 500$ in Figure 14. This figure shows that at low densities ($\rho = 0.00302$ and 0.00473), ring polymers are more-or-less circular in shape. This is due to the fact that at low densities the average size of each ring polymer is smaller than the average distance between nearest neighbor rings. We note that at these densities the polymers are very mobile. As the density is increased, close-packing emerges and is very clear at $\rho = 0.00569$. At this density, the cells are spatially organized into a quasi-two-dimensional triangular lattice, with clear short-range order. As the density is further increased to $\rho = 0.00703$, the distance between neighboring cells becomes shorter than the average diameter of each cells, leading to their squeezing and elongation. At this density, clear short-range correlations in the orientation field of the cells is clearly observed. The snapshots of the polymers’ orientations show that for densities
up to about 0.00569, the cells orientation lack both short-range and long-order. However, for densities higher than about 0.00703, clear short-range correlations in the polymers orientations are clearly noted, with this order becoming stronger with increasing density. However, we note that long-range nematic order is absent.
Figure 14 Cells configurations (red) along with their orientation (black) for a system composed of a single type ring polymers at different densities. Other parameters here correspond to $k_{bond} = 100$, $k_{i,bend} = 500$, and $k_{rep} = 25$. 

Density: 0.01632  

0.02013
Figure 15. (a) The average area of cells, calculated using Eq. (3.36), versus density (number of cells per unit of area) for the case of parameters in Table 1, at different values of the bending modulus. (b) Average moment of inertia, calculated using Eq. (3.43), used to characterize the elongation of the cells, versus density for different values of the bending modulus. (c) Average angle between neighboring ring polymers as the function of cells’ density at different values of the bending modulus. (d) Average number of rings with 6 neighbors, normalized by the total number of ring polymers versus density, for different values of the bending rigidity modulus. (e) Number of pairs of rings with an angle between 0 to 5 degrees versus density, for different
values of the bending rigidity modulus. (f) The orientation order parameter, calculated using Eq. (3.44), versus cells’ number density.

We now turn to the quantification of the spatial organization of the ring polymers in the system. Figure 15.(a) shows the average area of a single ring polymer as a function of density for different values of the polymers bending rigidity coefficient. This figure shows that the average area of a polymer decreases monotonically with increasing density, which is expected due to squeezing. The decrease in the average ring area is weakest up to about $\rho = 0.006$. This is in line with the fact that the density at which the polymers start to overlap is about 0.007 (see Figure 14.e). Figure 14 (b) shows the ratio between the highest and lowest eigenvalues of the inertia tensor, $\lambda_{\text{max}}/\lambda_{\text{min}}$. This figure shows that this ratio for $k_{\text{bend}} > 20$ is only slightly higher than 1 ($\lambda_{\text{max}}/\lambda_{\text{min}} = 1$ for a perfect circle) and almost constant for $\rho < 0.006$.

Again, this confirms that deviations from an almost circular shape of the ring polymers is the due to squeezing of the polymers prevented by their overlap at high densities. Figure 14 (b) also shows that the elongation of the polymers is more pronounced as $k_{\text{bend}}$ is decreased.

The confinement of the polymers as $\rho$ is increased beyond about 0.01 leads to a biconcave structure of the rings, which becomes more pronounced as $k_{\text{bend}}$ is increased (see Figure 14. h) for typical configurations of a single cell at $\rho = 0.0132$ for different values of $k_{\text{bend}}$. These configurations can be obtained from the minimization of the potential energy of a single polymer ring. Of course, for low values of $k_{\text{bend}}$, entropic effects are more important than for high values of $k_{\text{bend}}$. Hence, stronger deviation from the biconcave structure as $k_{\text{bend}}$ is decreased. The average angle between neighboring ring polymers, as defined in Figure 8, is shown in Figure 15.c as a function of density for different values of $k_{\text{bend}}$. At low densities, the ring polymer are randomly arranged, leading to the expected average angle equal to 45 degree,
As the density is increased, some locally alignment is induced due to the rings confinement resulting in their elongation. The decrease of the angle between the polymers is correlated with the elongation of the polymers, as shown by Figure 15.b.

The spatial organization of the ring polymers is also investigated in terms of the number of nearest neighbors. Figure 15.d shows the number of six nearest neighbors (which corresponds to a local hexagonal arrangement of the polymers) as a function of density for different values of $k_{bend}$. This figure shows that, independent of $k_{bend}$, the number of nearest neighbors is peaked at $\rho = 0.006$, which the average distance between cells is about the average diameter of a ring with circular geometry. This is consistent with the configurations shown in Figure 14. d. Figure 15.d also shows that the number of six nearest neighbors increases as $k_{bend}$ is increased. This is expected since a high bending rigidity favors circularly shaped rings. We also found that at this density, the kinetics of the polymers is very cooperative.

The distribution of the angle between nearest neighbor polymers is showed in Figure 14.e as a function of density for different values of $k_{bend}$. In this figure, we focus on the number of nearest neighbor pairs with an angle between 0 and 5 degree, as this indicate local nematic order between the polymers. Figure 14.f shows that for $k_{bend} < 200$, this number increases monotonically with the density. However, for higher $k_{bend}$, the number of nearest neighbor pairs with an angle between 0 and 5 degrees exhibits a local peak at a density about 0.01. This density is higher than that at which a hexagonal order is observed as discussed above. By inspecting the configurations shown in Figure 14 e-j, the local peak in Figure 14.e happens at a local density at which the polymers are elongated with straight sides. As the density is increased further, the polymers are more squeezed leading them to adopt a biconcave structure.
4.2 Two Type Ring Polymer with Different Rigidity

The goal of this part of the thesis is to investigate the effect of two types of ring polymers with same length but with different bending rigidities, and to detect whether this difference may lead to some segregation between the two types of ring polymers. Clusters of polymers, belonging to the same type, were determined by the construction of the Delaunay graphs mentioned in Section 3.6.2. Here, half of the polymers are rigid with high bending rigidity ($k_{bend} = k_{high}$), and the other half are soft polymers with a low bending rigidity ($k_{bend} = k_{low}$). In Figure 16, configuration snapshots of a system composed of 242 polymers with $k_{high} = 400$ and $k_{low} = 20$, are shown for different areal densities. One clear qualitative difference between the two types of polymers, is that the average area of the rigid cells is larger than that of the soft cells.
Figure 16. This table presents the configuration for two different type of ring polymers at different densities. The red color stand for rigid ring polymer with $k_{\text{high}} = 400$, and the green color stand for soft ring polymer with $k_{\text{low}} = 20$.

The average cell area versus density is shown in Figure 15.a. This figure quantitatively shows that the area per cell decreases with increasing the density, with that of the rigid polymers is higher than that of the soft polymers for any density. This implies that the net area of the system covered by the rigid polymers is higher than that covered by the soft polymers. This is expected since a larger bending rigidity prevents the rings from crumpling. The ratio $\lambda_{\text{max}} / \lambda_{\text{min}}$ (where $\lambda_{\text{max}}$ and $\lambda_{\text{min}}$ are the large and small eigenvalues of the moment of inertia tensor are shown in Figure 15b for both types of cells. This figure shows that $\lambda_{\text{max}} / \lambda_{\text{min}}$ is higher for soft cells than the rigid cells, and increases monotonically with the density. This is expected since the soft cells are more prone to deformation than the rigid cells. This figure also shows that the threshold density at which $\lambda_{\text{max}} / \lambda_{\text{min}}$ starts deviating from 1 is higher in systems composed of two cell types than in the case of one cell type (Figure 15.b). This is due to the fact that the presence of the soft cells in the mixture, which are more prone to deformation, allows the rigid cells to maintain there almost circular shape to larger values of density than the one-component case.

The dependence of the angle between nearest-neighbor cells on density in the two-component system, shown in Figure 15c, is similar to that in the one-component systems and
does not depend strongly on the type of pair, particularly for small densities. However, Figure 15c shows that for large densities, the average angle between nearest-neighbor rigid cells is smaller than that between nearest-neighbor soft cells. This indicates that the rigid cells, once deformed, tend to align parallel to each other more than soft cells. Figure 15.d further demonstrates that the count of pairs of neighboring cells with an angle smaller than 5 degrees is largest for all densities beyond about 0.007, again indicating that cells prefer a local nematic order. However, the configurations of Figure 16, clearly demonstrates that, as in the one-component case, long range nematic order does not occur. The number of cells with local hexagonal structure, i.e. with 6 nearest neighbors, is highest for both types of cells when the density is about 0.00569 for both rigid and soft rings.
Figure 17. Average area of stiff rings (black) corresponding to $k_{\text{high}} = 400$ and soft rings (red) corresponding to $k_{\text{low}} = 20$ as the function of density. (b) Polymers’ moment of inertia of two different type ring polymers as the function of density, respectively. (c) Average angle between neighboring rings (black), between neighboring stiff rings with $k_{\text{high}} = 400$ (red), between neighboring soft rings with $k_{\text{low}} = 20$ (blue), and between stiff and soft rings. (d) Number of ring polymer pairs versus density, for different angle intervals ranging from 0 degree to 90 degrees. (e) Average number of rings with different neighbors, labeled with the format: $k_{\text{bend}}$_number of neighbors.
4.3 Effect of Substrate Patterning

This section is focused on the effect of substrate pattern on the organization of the polymer rings. Here, we focus on a system composed of one type of cells and a substrate that is anisotropically patterned along the y-axis with a bias coefficient $k_{sub} = 5$ (see Section 3.5.4). Configuration snapshots at different values of the density are shown in table 1. In contrast to the configuration snapshot shown in Figure 14, it is easy to see that the patterned substrate leads to the alignment and elongation of the polymers along the substrate’s pattern, even at low densities. Clear nematic order is observed for $\rho < 0.007$, both translational orders also emerges, indicating smectic order for $\rho$ up to about 0.01. Note that at these densities, the edges of the ring polymers are straight. At higher densities, close packing leads the cells to adopt biconcave geometries, leading them to assemble into a zig-zag (herring-bone) structure, as clearly observed for $\rho$ larger than 0.01071. This zig-zag structure is due to a close-packing of the polymers in which the convex ends of a polymer are nested between the concave sides of two nearest neighbor polymers. One would expect that a structure where the polymers form long-range ordered layers at an angle from the y-axis to have a lower free energy than the herring-bone structure. The herring-bone structure, however, has a higher entropy than fully ordered structure without much increase in the internal energy. It is therefore possible that the large gain in entropy of the herring-bone structure promotes their thermodynamic stability at high densities.
Figure 18. The snapshot of orientation and configuration of single type ring polymer system with external force constraint under different density, the alignment induced by the simulation of track on substrate.

The average area of single cells, depicted in Figure 19.a, shows that the area decreases with increasing density or decreasing $k_{bend}$. This is similar to the case of a uniform substrate, discussed in Section 4.1. However, the area per cell is smaller for a patterned substrate than for a uniform substrate. This is again expected since the patterned substrate leads to elongation of the cells. The amplitude of elongation, defined by $\lambda_{max}/\lambda_{min}$ and, depicted in Figure 19.b also increases with increasing the cells areal density or decreasing $k_{bend}$. This is similar to the case of a uniform substrate. Here as well, we find that for a given $k_{bend}$ and density, $\lambda_{max}/\lambda_{min}$ is higher for a patterned substrate, in accord with Figure 19.a and the snapshots shown above.

Regardless of the areal density, the angle between the orientations of neighboring cells, shown in Figure 19.c, is much smaller than that for a uniform substrate (Figure 14.c). This
quantitatively demonstrates the nematic or smectic order induced by the patterned substrate. Interestingly, the angle between neighboring cells is minimized at intermediate densities, which correspond to ring polymers with smectic order. However, as the density is further increased, the angle between neighboring cells increases with density. This is the result of the cells adopting a biconcave shape which promotes the zig-zag arrangement shown for example by the configuration at density 0.01632 in Figure 18.

Figure 19.d, which depicts the number of nearest neighbors, shows that this is peaked at the density at which the polymers exhibit a smectic order. This implies, as corroborated by the configurations, that the cells in different lateral layers (along the x-axis) are staggered.

Finally, we also looked at the order parameter, as calculated using Eq. (3.44) and depicted in Figure 19.e, and found that it is much higher than that in the case of a uniform substrate (Figure 14.f). This further corroborates our conclusion that the substrate induces cells ordering. However, the order parameter also exhibits a peak at a density exactly matching that where the angle between neighboring cells is minimized (see Figure 19.c). The order parameter for different values of the strength of substrate-polymer interaction, $k_{sub}$, depicted in Figure 19.f, increases with increasing $k_{sub}$, which is expected since the patterning of the substrate promotes elongation of the cells.
Figure 19. (a). Average area of ring polymers, versus density, of a system with an substrate force, corresponding to ($k_{sub}=5$). (b). Average moment of inertia of ring polymers, vs with external force for different values of the bending rigidity. (c) The average angle between neighboring ring polymers with external force for different rigidity as the function of density. (d) The number of hexagonal neighboring structure of ring polymer with external force for different rigidity as function of density, a perfect smectic structure presented when the density is 0.00868. (e) The order parameter of ring polymers orientation with external force for different rigidity as the function of density with ($k_{sub}=5$). (f.) The orientation order parameter of ring polymers with external force for different strength of cell-substrate force as the function of density ($k_{bend}=500$).
4.4 Migration of Ring Polymers

The earlier parts of this thesis introduced a simple model of cells, in which each cell is presented by the projection of its cell membrane, and presented by a semi-flexible ring polymer. Repulsive interactions between monomers is added to prevent the polymers form overlap. Thus far, we investigated this model at thermal equilibrium focusing on the effects of areal density, bending rigidity of the cell membranes and on interactions between the cells and the substrate. However, cells are not equilibrium systems. They are highly dynamical and require continuous input of energy available in the immediate environment if each cell. To mimic non-equilibrium effects, we have therefore added motile forces which depend on the kinetic history of each, as described in Section 3.5.5. These motile force on cells are independent of the areal density of the cells and anisotropy of the cells.

Snapshot configurations for different densities at $k_{mot} = 1$ and bending rigidity $k_{bend} = 500$ are shown in Figure 20. This figure demonstrates that even at low areal densities, there is strong spatial organization of the cells, in complete contrast to the case of thermal equilibrium, as shown earlier in Section 4.1. In particular, Figure 20 shows that the additional motile force lead to local aggregation of the cells into large clusters (swarming) with strongly correlated motion. We tried this simulation with different time scales, $\tau$, and time strength, $\mu$, to see how do these two parameters affect the mechanism of migration, and found same qualitative results.
Figure 20. This figure presents the velocity field (black) and configuration (red) of ring polymers with motile force for different densities, a-d have same density at different time, where the system formed small clusters and then combined to large one very fast.

The expected results of average area per cell and the moment of inertia are similar to the cases discussed in Section 4.1 and presented in Figure 21.a and 21.b. The average angle of neighboring cells shown in Figure 21.c starts from 45 degrees at low densities, implying complete orientational disorder at low densities, and ends at around 30 degree at high densities.
The strength of the motile force affects the results mainly at low densities. High density results, however, are mostly independent from the strength of the motile force. As for the distribution of neighboring polymers and the hexagonal structures, they are extremely similar to the results we discussed in Section 4.1. Hence these results are not shown here.

We also calculated the usual order parameter, $S$, defined from the cell’s morphology, and an order parameter, $S_v$, using Eq. (3.4), but where the direction of the velocity field is used instead of the cells orientation defined from their shape anisotropy. Figure 21.e shows that the order parameter, $S$, is essentially zero and independent of the areal density, an indication that the shape of cell’s motility and aggregation does not induce long-range order. However, Figure 21.f shows that long-range correlations in the velocity field is induced by their motility, Figure 21.d shows that the average angle, as defined from the velocity field, of all polymers changes continuously with time, and is different from zero This again indicates the collective motion of the cells.

The average area and $\lambda_{\text{max}}/\lambda_{\text{min}}$ are similar to the equilibrium case discussed in Section 4.1 and presented in Figure 21.a and Figure 21.b. The average angle between nearest-neighbor cells shown in Figure 21.c starts from 45 degree which means totally disordered at low density and end at around 30 degree at high density. Therefore, the collective motion of the cells, due to the external forcing, does not affect much the local arrangement of the cells, and in particular, does not lead to further local ordering of the cells.

The order parameter of the cells’ velocity field and order parameter of the spatial orientation of the cell are totally uncorrelated, as shown by Figure 21 e and f.
Figure 21. The results with the conditions ($k_{\text{bond}} = 100, k_{\text{bend}} = 500$) (a) The average area of ring polymers with motile force for different time steps $\tau$ and strength $\mu$. (b) The average area moment of inertia of ring polymers with motile force for different time steps and strength. (c) The average angle of neighboring ring polymers with motile force for the feedback of different time steps and strength. (d) The average velocity direction of ring polymers with motile force for the feedback of different time steps and strength changes continuously as the function of time.
(e) The orientational order parameter of ring polymers with motile force for the feedback of different time steps and strength. (f) The Velocity order parameter of ring polymers with motile force for the feedback of different time steps and strength.
5 CONCLUSIONS AND OUTLOOK

In this study, the properties of ring polymers with different constraint conditions were investigated in detail through molecular dynamics simulations in two dimensions. The model is introduced such that it can be generalized to investigate the spatial organization and collective dynamics of living cells such as bacteria colonies. We summarize the main points of this thesis in the following:

1. This study begins with a single structure of N point particles connected by N harmonic springs and arranged into a topological ring in two dimensions. Molecular dynamics simulations of a system composed of many such polymers is then performed to investigate the equilibrium spatial organization of the polymers, under various constraints including density and bending rigidity of the polymers. Properties such as the polymers anisotropy and orientation, phase separation and migration are then extracted from the configurations time trajectories.

2. Cell-cell and cell-substate interaction while taking into account various constraints, including shape and area constraints are in fact much easier to implement in our model than in earlier more cumbersome models such as the phase field and particle models discussed in Chapter 2. Each ring polymer, in our model, not only has independent flexible properties, but also involved in the system with conditions that are separate and totally independent of each other.

3. The average area of each ring polymer and anisotropy of cells, extracted from the analysis of the two-dimensional moment of inertia tensor, is mainly affected by the density. The polymers bending rigidity has the effect that counters the decrease the area enclosed by each polymer. For all finite values of the bending rigidity, we found a small
range of areal densities, around 0.00569, at which hexagonal order is preferred. The density corresponds to that at which the radius of a single polymer at zero density is about the distance between neighboring polymers.

4. The substrate has a significant influence on the cell’s orientation at low density with the orientation order parameter around 0.97. The motile force works mostly affect the velocity through elastic collision, after a short time of random motion, all of cells move along one uniform direction.

This thesis represents a first attempt in using a simple model for cells organization and collective dynamics. There remain, of course, many interesting questions that have not been considered in this thesis. In the last few months’ work, we simply focussed on the properties as a function of density, but we also see the potential of this model in the field of active matter corresponding to the case many cells which consume energy from environment. These include bacteria colonies, embryo development, cancer metastasis or wound healing. In the future, my PI’s research group plans to integrate our model and experiment more closely so that they can support each other, and modify the model with more details to mitigate various current limitations. Furthermore, we also plan to modify interaction between cells to account for frictional forces, and cell-substrate interactions to investigate more interesting collective phenomena. In particular, we plan to investigate different substrate patterns and the effect that this has both on the cells organization at equilibrium and in the presence of non-equilibrium motile forces. The following is a list of few additional constraints we will incorporate in the model in the near future.
1. Firstly, we will constrain the area of each ring polymer, which will make the model more realistic. The details of cell’s shape can be also restricted by parameters of a preferred angle, length, and correlations between a cell velocity and its orientation.

2. Secondly, we will use cell models with intrinsic cell morphological polarity. This polarity can be coupled with the motile force, leading to correlations between the direction of the velocity field and polarity of the cells.
REFERENCES


