

Controlling segregation speed of entangled polymers by the shapes: A simple model for eukaryotic chromosome segregation

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We report molecular dynamics simulations of the segregation of two overlapping polymers motivated by chromosome segregation in biological cells. We investigate the relationship between polymer shapes and segregation dynamics and show that elongation and compaction make entangled polymers segregate rapidly. This result suggests that eukaryotic chromosomes take such a characteristic rod-shaped structure, which is induced by condensins, to achieve rapid segregation.

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I. INTRODUCTION

In eukaryotic cells, the extremely long genomic deoxyribonucleic acid (DNA) molecules that can be more than 1 m length in some species are stored in a spherical nucleus that is 10 μm in diameter. On entry into mitosis, the mass of chromatin distributed in the interphase nucleus is converted into a discrete set of chromosomes that have highly condensed rod-shaped structures. Two condensed sister chromosomes are juxtaposed with each other along their entire lengths (Fig. 1). This process is often referred to as mitotic chromosome condensation and avoids entanglements of different chromosomes and preserves their integrity.

The spatial organization of chromosomes in mitosis is a fundamental question of biology. Why do metaphase chromosomes in many species take on characteristic rod shapes instead of more simple spherical shapes?

Molecules responsible for chromosome condensation are condensin protein complexes [1]. Most eukaryotes possess two different condensin complexes, condensin I and II. In mitosis, both condensins are associated with chromosomes, are enriched on chromosome axes, and have distinct contributions to the chromosome construction. In Ref. [2], the authors showed that the relative amounts of condensin I and II determine the chromosome shapes. They showed that the rod diameter and the rod length of the condensed chromosomes can be varied by changing the relative ratio of condensin I and II, i.e., in a condensin II-rich environment, chromosomes take shorter and thicker shapes. In fact, condensin II is much less abundant in early embryonic extracts than in somatic cells [1], and metaphase chromosomes in early embryonic cells tend to be longer and thinner compared with those in somatic cells. During development, the chromosomes progressively decrease their lengths and increase their diameters [3–5]. In addition, another experiment [6] showed that knockout of a condensin I subunit results in the formation of short and thick chromosomes and that the chromosomes do not segregate and the cell division is arrested in metaphase for a long time. These facts imply that the time taken for segregation depends on the shapes of the chromosomes, and it is suggested that cells

regulate the length of the mitosis phase by changing relative amounts of condensin I and II.

The importance of chromosome shape in segregation dynamics can be addressed from the point of view of polymer physics. In Ref. [7], the authors investigated the relationship between cell shapes and chromosome segregation in bacteria. They showed that, by using coarse-grained molecular dynamics (MD) simulations, two entangled long chains in a rod-shaped confined box spontaneously segregate to maximize their chain entropy. However, as the box length becomes shorter in the longitudinal direction, the entropic force for the segregation decreases and, finally, the two entangled long chains cannot segregate in a box which is isotropic in size. In eukaryotic cells, the nucleus is spherical and two entangled long chains (chromosomes) are unable to segregate.

Eukaryotic chromosomes may use a segregation mechanism that differs from that of bacteria. Eukaryotic chromosomes take on condensed rod-shaped structures during segregation because of condensin functions, while bacterial chromosomes stay as simple long chains. Condensins make loop structures in chromosomes and increase the topological complexity. In general, increased topological complexity facilitates segregation of entangled polymers [8,9]. The condensins may facilitate chromosome segregation by introducing loop structures, which in turn induce rod-shaped compaction to drive eukaryotic chromosome segregation.

In this article, we investigate the relationship between polymer shapes and segregation dynamics by using coarse-grained MD simulations with the Langevin thermostat. We calculate the typical speed of segregation of variously shaped, initially entangled polymers and show that elongation and compaction make entangled polymers segregate rapidly. Using the calculation results, we describe the scaling of the segregation dynamics with polymer shape parameters and give simple explanations for them. In spite of the microscopic complexity induced by interactions between many particles and thermal randomness, the segregation dynamics of highly condensed polymers can be described by a few physical parameters that determine the polymer shapes. These capture the qualitative essence of polymer physics dynamics [10].

Based on these results we propose that eukaryotic chromosomes take on their characteristic rod-shaped structure, induced by condensins, to achieve rapid segregation.

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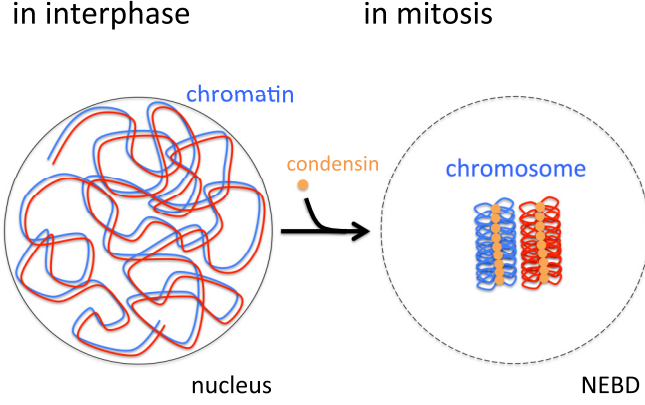


FIG. 1. Chromosome condensation in mitosis. The red and blue lines indicate two sister chromosomes. In mitosis, condensin-mediated chromosome condensation and nuclear envelope breakdown (NEBD) occur.

II. MODEL AND SIMULATION

A. Polymer model

In the MD simulations, we model the polymers using a bead-spring model. Each polymer consists of N beads with the diameter σ , which are connected linearly by springs to form a chain. There are additional attractive interactions between distant beads to introduce loop structures in the chain. Our model is described as three types of potential energies (Fig. 2),

$$U = U_{\text{excl}} + U_{\text{spr}} + U_{\text{strc}}, \quad (1)$$

where U_{excl} , U_{spr} , and U_{strc} represent the volume-exclusion among beads, spring interaction between neighboring beads

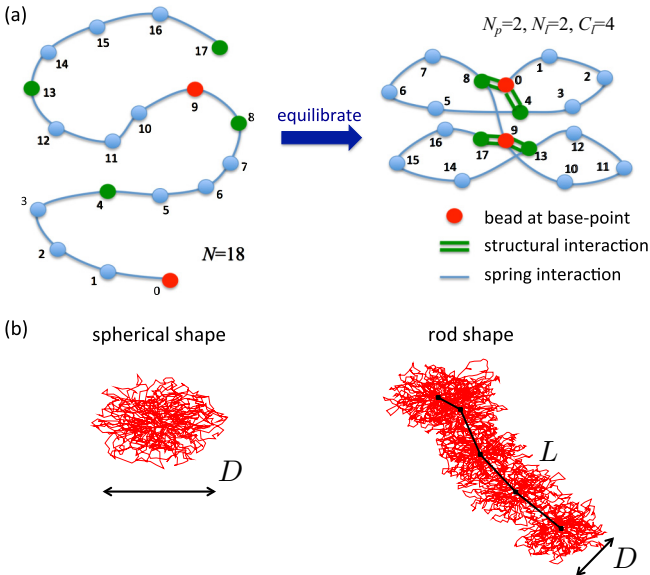


FIG. 2. (a) Simple illustration of the effects of the loop structural interactions. The interaction makes a long chain compact. (b) Examples of a spherical shape (left) and a rod shape polymer (right). The spherical and rod-shaped polymers have the structural parameters $(N_p, C_l, N_l) = (40, 21, 1)$ and $(40, 21, 4)$, respectively. Here only springs are illustrated and beads are ignored for visibility.

in the chain, and attractive interaction to form loop structures, respectively.

The volume-exclusion interaction U_{excl} is described by a Weeks-Chandler-Andersen (WCA) potential, which corresponds to the repulsive part of the Lennard-Jones potential:

$$U_{\text{excl}} = 4\epsilon_{\text{excl}} \sum_{j < i}^N \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 + \frac{1}{4} \right], \quad (2)$$

for $r_{ij} < \sqrt[6]{2}\sigma$ and 0 elsewhere. r_{ij} denotes the distance between centers of i th and j th beads. At $r_{ij} = \sigma$, the interaction energy is $\epsilon_{\text{excl}} = 1k_B T$, where k_B and T are the Boltzmann constant and the temperature, respectively. This models soft beads of diameter σ , whose centers cannot come much closer than σ to each other since the potential is quite steep. In the simulation, σ defines the basic length scale and ϵ_{excl} the energy scale. Our unit of mass is given by m , the mass of a bead. Having specified our basic units, the time unit is given by $\tau_{\text{excl}} = \sigma \sqrt{m/\epsilon_{\text{excl}}} = 1$. In the following, we will omit these units.

The spring interaction U_{spr} between neighboring beads in a chain is described by the harmonic potential:

$$U_{\text{spr}} = \epsilon_{\text{spr}} \sum_{i < N} \frac{1}{2} r_{i,i+1}^2, \quad (3)$$

where $r_{i,i+1}$ is the distance between the i th and $(i+1)$ -th bead centers and ϵ_{spr} is the spring coefficient and we chose $\epsilon_{\text{spr}} = 1k_B T$. The spring has no excluded volume (phantom spring). Thus, spring-spring and spring-bead can pass through each other, and hence two entangled chains can also pass through each other. In actual cells, topoisomerase II, the protein that cuts and reconnects DNA, enables DNA strands to pass through each other to avoid DNA entanglement [11]. This effect is incorporated in our model by the phantom spring. We chose a small-enough spring coefficient so the average distance between two neighboring beads becomes large and the passage between separate chains occurs frequently in simulations. We discuss the effects of this parameter on polymer segregation later.

The loop structural interaction U_{strc} introduces attractive forces among beads that are placed far apart along the chain. This gives loop structures and makes it compact. This interaction mimics the function of condensins on mitotic chromosomes in a biological context. We consider a long polymer chain with a total of N beads and make a compact structure as follows.

(1) We choose N_p beads at N/N_p intervals and call them the base-point beads (the red beads in Fig. 2).

(2) We choose N_l beads, which are arranged at every C_l bead between each consecutive base point and call them the attaching beads (the green beads in Fig. 2).

(3) The N_l attaching beads and the base-point beads attract each other.

Then we obtain a compact structure where N_p base points are arranged on an axis and each base point has N_l loops with the length C_l (Fig. 2). There are three structural parameters: N_p , the number of base-point beads; N_l , the number of loops gathered in each base point; and C_l , the number of beads in each loop (loop length). Total number of beads

$N = N_p N_l C_l + N_p$. Here, for simplicity, we consider that C_l (N_l) is the same in all the loops (bases). The loop structural interaction is described by the harmonic potential:

$$U_{\text{strc}} = \epsilon_{\text{strc}} \sum_{l=0}^{N_p-1} \sum_{m=1}^{N_l} \frac{1}{2} r_{L_p l, L_p l + C_l m}^2, \quad (4)$$

where $L_p = N_l C_l + 1$ and $r_{L_p l, L_p l + C_l m}$ is the distance between centers of the $(L_p l)$ -th and $(L_p l + C_l m)$ -th beads, and ϵ_{strc} is the interaction strength and we chose $\epsilon_{\text{strc}} = k_B T$. The $(L_p l)$ -th bead is the base point and the $(L_p l + C_l m)$ -th bead is the attaching bead to the base point.

We employ a velocity-Verlet MD integrator [12] with a fixed time step of 0.01; the system is kept at constant temperature by means of a Langevin thermostat with a fixed friction of $\gamma = m \tau_{\text{excl}}$, so $\tau^* = \tau_{\text{excl}} = 1$. Other parameters vary for the different simulation runs; see Table I.

B. Polymer shape and size

The geometric properties of polymers, such as shape and size, are usually characterized through the gyration tensor, G . The entries of this 3×3 coordinate matrix are given by

$$G_{ab} = \frac{1}{N} \sum_{i=1}^N (\vec{r}_{i,a} - \vec{r}_{\text{CM},a})(\vec{r}_{i,b} - \vec{r}_{\text{CM},b}), \quad (5)$$

where a and b run over the three Cartesian components and $\vec{r}_{\text{CM}} = \frac{1}{N} \sum_{i=1}^N \vec{r}_i$ is the spatial location of the polymer center of mass. The non-negative eigenvalues of G , ranked with decreasing magnitude, λ_1^2 , λ_2^2 , and λ_3^2 , correspond to the square length of the principal axes of the polymer gyration ellipsoid. Accordingly, their relative magnitude conveniently captures the overall spatial anisotropy of the polymers, while their sum yields the square radius of gyration R_g^2 and the product produces the square volume V^2 :

$$R_g^2 = \text{tr}(G) = \sum_{a=1}^3 \lambda_a^2, \quad V^2 = \det(G) = \prod_{a=1}^3 \lambda_a^2, \quad (6)$$

where tr and $\det$ are the trace and the determinant operators, respectively. To measure the typical size and anisotropy of the ensemble of the polymer, we compute the averages $\bar{\lambda}_a = \sqrt{\langle \lambda_a^2 \rangle}$, $\bar{R}_g = \sqrt{\langle R_g^2 \rangle}$, and $\bar{V} = \sqrt{\langle V^2 \rangle}$ where the brackets $\langle \dots \rangle$ denote averaging over a polymer of 50 independent equilibrium systems with the same condition.

These measurements are tuned by the structural parameters in the potential U_{strc} . In particular, the bead concentration $\bar{c} = N/\bar{V}$, the size and the aspect ratio $\bar{\alpha}$ of the polymer are determined by the structural parameters N_l , C_l , and N_p . The aspect ratio $\bar{\alpha}$ is given by $\bar{\alpha} = \bar{D}/\bar{L}$ with the diameter $\bar{D} = 2\bar{\lambda}_3$ and the length $\bar{L}$ along the rod, see Fig. 2(b). The length $\bar{L}$ is given by the sum of the pole-pole distance $\bar{L} = \langle \sum_{l=1}^{N_p-1} r_{L_p(l-1), L_p l} \rangle$. The aspect ratio is an indicator of the elongation of the polymer.

C. Two polymer segregation

In calculating the segregation dynamics, two fully entangled (overlapping) polymers with identical characteristics (N_l , C_l , N_p) are prepared as initial conditions. To create

TABLE I. The simulation parameters for the different runs. When the structural parameter $N_p = 1$ is fixed, the polymers take spherical shapes in all runs. The numbers in parentheses represent statistical errors of the last two or three digits.

N	C_l	R_g	t_i	t_s
421	21	7.093(59)	0.151(35)	0.392(59)
	14	6.544(35)	0.098(28)	0.243(31)
	10	5.941(28)	0.081(21)	0.150(24)
	7	5.448(61)	0.065(14)	0.095(21)
601	40	9.612(51)	0.294(85)	1.119(81)
	20	7.767(43)	0.233(31)	0.322(61)
	15	7.155(46)	0.189(27)	0.188(93)
	10	6.416(22)	0.122(32)	0.139(46)
	6	5.721(31)	0.085(16)	0.078(29)
841	60	10.97(86)	0.622(94)	1.664(95)
	42	10.20(54)	0.478(60)	1.083(73)
	28	9.390(69)	0.396(48)	0.717(81)
	21	8.391(52)	0.286(25)	0.412(68)
	14	7.592(38)	0.182(30)	0.276(39)
	12	7.275(23)	0.185(38)	0.181(28)
	7	6.404(13)	0.115(25)	0.101(23)
	7	6.404(13)	0.115(25)	0.101(23)
1261	84	14.82(45)	1.257(162)	3.516(137)
	70	13.80(61)	1.089(114)	2.617(83)
	60	13.20(69)	0.844(84)	2.094(90)
	42	11.68(42)	0.623(28)	1.122(75)
	30	10.44(36)	0.499(39)	0.636(69)
	21	9.314(41)	0.386(24)	0.362(54)
	18	8.767(38)	0.345(21)	0.259(63)
	14	8.281(21)	0.286(26)	0.209(41)
	7	7.028(38)	0.159(17)	0.102(27)
	7	7.028(38)	0.159(17)	0.102(27)
1681	84	15.64(97)	1.451(145)	3.024(115)
	70	14.64(63)	1.195(84)	2.382(87)
	60	13.95(56)	1.066(80)	1.898(78)
	42	12.39(30)	0.747(67)	0.957(85)
	30	10.99(28)	0.543(35)	0.562(73)
	21	9.898(21)	0.475(30)	0.315(60)
	14	8.830(16)	0.331(19)	0.193(55)
	7	7.533(24)	0.193(22)	0.105(21)
2101	70	15.79(71)	1.523(114)	2.496(92)
	60	14.82(50)	1.092(69)	1.890(84)
	50	13.90(66)	1.005(67)	1.554(87)
	42	13.10(53)	0.809(65)	0.925(40)
	30	11.46(46)	0.630(27)	0.479(36)
	21	10.40(33)	0.541(23)	0.313(49)
	14	9.271(49)	0.353(25)	0.242(35)
	7	7.531(36)	0.214(17)	0.126(29)
2521	70	16.66(57)	1.681(82)	2.558(81)
	60	15.24(63)	1.333(75)	1.856(72)
	42	13.10(56)	0.912(56)	0.919(50)
	30	12.18(43)	0.692(54)	0.509(48)
	21	10.91(34)	0.541(41)	0.354(37)
	14	9.646(65)	0.409(32)	0.210(32)
	7	8.309(46)	0.248(27)	0.120(36)
4201	42	14.22(74)	1.062(42)	0.905(45)
	21	12.15(67)	0.679(56)	0.365(42)
	14	10.66(41)	0.524(32)	0.209(34)
	10	9.787(26)	0.426(28)	0.159(37)
	7	9.035(13)	0.348(13)	0.140(20)

configurations of two overlapping polymers, the i th bead of one chain and the i th bead of the other chain are initially interconnected by weak harmonic bonds. This initialization is valid for our target biological system because two replicated sister chromosomes are bound to each other by cohesin protein complexes at mitotic onset [13]. We simulate the first several thousand steps with a softcore WCA potential to avoid a singularity of overlapping beads at initial random configurations, i.e., a WCA potential that has been modified such that the potential is linear for distances smaller than a radius r_{cap} and r_{cap} is reduced gradually to the plain WCA potential. After that, to equilibrate the system, we simulate for several million steps until the radius of gyration of the polymers converges to a value.

After the equilibration of the interconnected polymers, we remove the interconnecting bonds to obtain two separate chains that are entirely overlapping. We continue to simulate the system until the two chains have segregated and the chains do not overlap. This procedure is repeated independently, 50 times for various polymer shapes with different structural parameter sets.

For each of these data sets, we calculate the overlap fraction of the two chains as a function of time. The overlap fraction is defined as follows. The polymer region of a polymer chain is spanned by the series of spheres with the center $\vec{r}_l$ and the radius R_l given by

$$\vec{r}_l = \frac{1}{C_l} \sum_{i=C_l(l-1)+1}^{C_l} \vec{r}_i, \quad R_l = \max(|\vec{r}_i - \vec{r}_l|), \quad (7)$$

with the coordinate $\vec{r}_i$ of the i th bead in the l th loop constructed by the structural interaction. The overlap fraction O_v is defined by the bead number in the other polymer region per the total bead number. The average $\bar{O}_v = \langle O_v \rangle$ over the 50 runs is calculated every time step.

Figure 3 shows an example of time evolution of the overlap fraction $\bar{O}_v$, the distance $\Delta \vec{r}_{\text{CM}}$ of the center of masses between

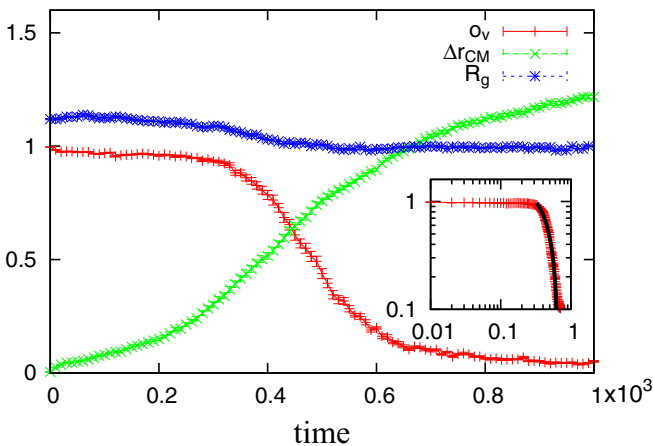


FIG. 3. MD time evolution of the overlap fraction $\bar{O}_v$, the distance of the center of masses Δr_{CM} between two polymers, and the radius of gyration, R_g , of one polymer. Δr_{CM} and R_g are both divided by the equilibrium mean value of R_g of one polymer. The small window shows the log-log plot of the overlap (+ symbol) and the fitting function (solid line). The polymers have the structural parameters $(N_l, C_l, N_p) = (40, 21, 1)$.

two polymers, and the radius of gyration $\bar{R}_g$ of one polymer during the segregation of two entangled polymers. During the process, $\bar{R}_g$ is almost constant (slightly decreases) because the structural interaction holds the polymer structures.

Calculation of $\bar{O}_v$ for many cases with various structural parameters shows that $\bar{O}_v$ decreases monotonically and almost linearly after the flat induction time as in Fig. 3. These results show that the segregation dynamics can be divided into three stages, i.e., the induction stage to initiate segregation dynamics, the segregation stage, and the diffusion stage after segregation. Here we define the induction time t_i when $\bar{O}_v$ is almost flat and the segregation time t_s when $\bar{O}_v$ decreases linearly. To extract these parameters, we fit $\bar{O}_v$ by a simple linear function, $\bar{O}_v = 1 - (t - t_i)/t_s$, in the linear decreasing region. Actually, we see that $\bar{O}_v$ can be fitted by the linear function in the region $0.2 < \bar{O}_v < 0.8$, where $\bar{O}_v$ linearly decreases for most cases.

III. RESULTS

A. Spherical shape polymers

First, we consider spherical shaped polymers for simplicity. This situation is realized by fixing the parameter $N_p = 1$ in the structural interaction where all of the attaching beads likely get together.

For the spherical shape polymer, the three eigenvalues $\bar{\lambda}_{1,2,3}$ of the gyration tensor take the same expectation values within the error and the radius of gyration $\bar{R}_g$ and the volume have relations $\bar{R}_g \approx \sqrt{3\bar{\lambda}_{1,2,3}}$, $\bar{V} \approx \bar{\lambda}_1 \bar{\lambda}_2 \bar{\lambda}_3 \propto \bar{R}_g^3$, respectively.

Figure 4(a) shows $\bar{R}_g$ as a function of C_l for several values of N . In the spherical case, $N_p = 1$ and only the N_l (or N) and C_l are variable among the structural parameters. The radius of gyration increases monotonically with C_l and N and is then roughly fitted by the following function assuming the scaling relationship:

$$\bar{R}_g \sim N^{\mu_g} C_l^{\nu_g} \quad (8)$$

and the scaling coefficients $\mu_g = 0.18 \pm 0.03$ and $\nu_g = 0.30 \pm 0.07$ are obtained by the least-squares method.

Figures 4(b) and 4(c) show the induction t_i and the segregation time t_s as a function of $\bar{R}_g$ for several values of N and C_l . All the data are taken from Table I.

Each set of data can be fitted by the function

$$t_\gamma(x) = (a_\gamma x_\gamma)^{b_\gamma}, \quad (9)$$

where $\gamma = i$ and $x_\gamma = \bar{R}_g$ in Fig. 4(b) and $\gamma = s$ and $x_\gamma = \bar{R}_g/\bar{c}$ in Fig. 4(c). The fitting parameters are, respectively,

$$a_i = 0.07247 \pm 0.0003, \quad b_i = 2.579 \pm 0.04, \quad (10)$$

$$a_s = 0.07399 \pm 0.0008, \quad b_s = 1.184 \pm 0.02. \quad (11)$$

The solid curves in Figs. 4(b) and 4(c) represent the fitting functions (9), respectively. These results show that both the induction t_i and the segregation t_s time can be approximately scaled by

$$t_i = (c_i \bar{R}_g)^3, \quad t_s = c_s \frac{\bar{R}_g}{\bar{c}}, \quad (12)$$

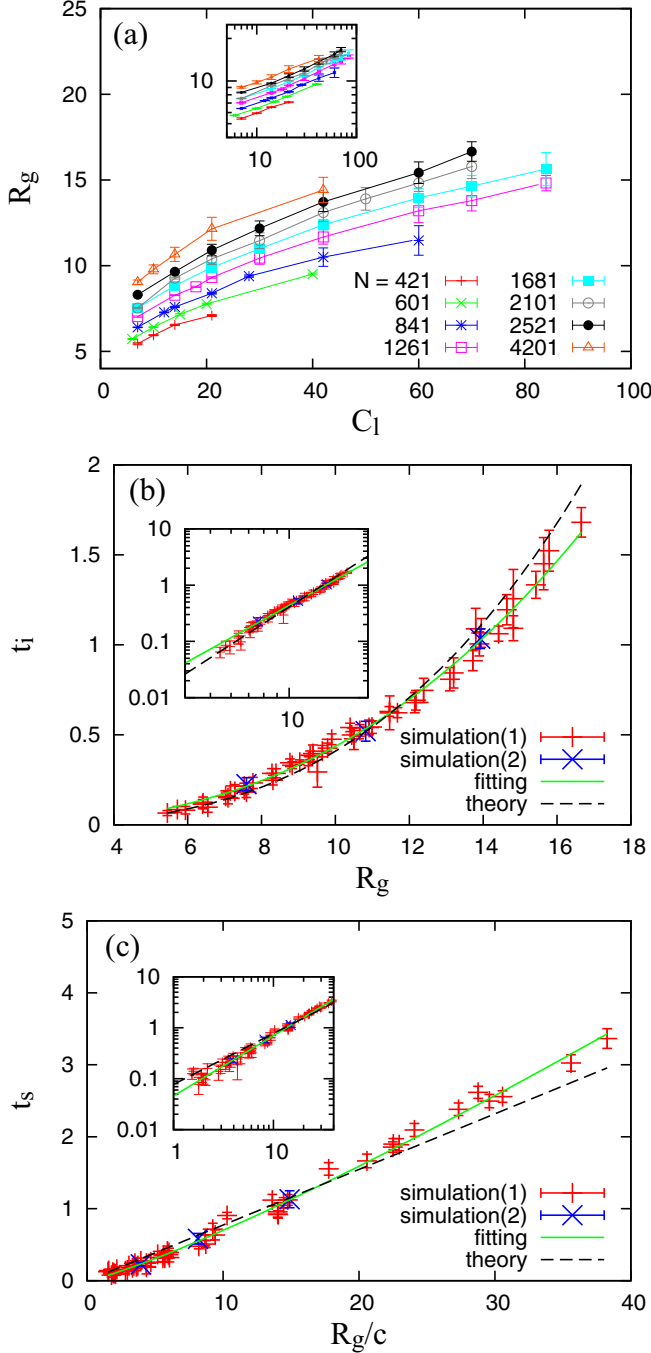


FIG. 4. (a) The radius of gyration R_g for several N in the spherical shape polymer. (b) The induction time t_i and (c) the segregation time t_s for several N in the spherical shape polymer. The small windows in each panels show the log-log plots.

where c_i and c_s are determined by fitting the data and $c_i = 0.0742 \pm 0.0004$ and $c_s = 0.0772 \pm 0.002$, respectively. The dashed curves in Figs. 4(b) and 4(c) represent the fitting functions of the theory (12), respectively.

The scaling laws (12) relate segregation dynamics to polymer shapes. The induction and the segregation time have different dependencies on the polymer shapes. The former depends on only the polymer size $\bar{R}_g$ (or $\bar{D}$) but not the concentration $\bar{c}$, while the latter depends on both the polymer

size and the concentration. This difference is reflected in differences in the dynamics.

The main driving force for the overlapping of two polymers is the volume exclusion between them. Because the volume-exclusion potential is an increasing function of the beads' concentration, the force is induced by the gradient of the concentration. For the initial induction time, the two polymers overlap entirely. In this case, the volume-exclusion interactions among beads are random and do not generate any directional repulsive forces between two polymers. Hence, the system initially shows purely diffusive behavior until a certain separation is reached. After the initial separation is realized, the segregation direction, which is the direction connecting the two centers of mass of the polymers, is determined and then the polymers segregate actively in the segregation time.

In the initial diffusion process, the induction time t_i is obtained by the time for the polymer to diffuse the ratio of the size $\bar{R}_g$ (or $\bar{D}$)

$$t_i \propto \bar{R}_g^2 / \bar{\mu} \propto \bar{D}^2 / \bar{\mu}, \quad \bar{\mu} \propto \bar{R}_g^{-1} \propto \bar{D}^{-1}, \quad (13)$$

where $\bar{\mu}$ is the mobility and it is proportional to the inverse diameter from Stokes' law in the continuum approximation. Therefore the induction time t_i is proportional to the volume $\bar{R}_g^3 \propto \bar{D}^3$.

For the segregation time, the two overlapping polymers spontaneously segregate from each other by the volume-exclusion interaction between the polymers. The repulsive interaction is induced by the gradient of the concentration c along the segregation direction as follows. In the mean-field approximation, the volume-exclusion potential U_{ex} is proportional to the concentration $\bar{c}$ and the overlapping bead number N_{ov} , i.e., $U_{ex} \propto \bar{c} N_{ov}$. N_{ov} is proportional to the overlapping length Δ_{ov} along the center-of-mass direction, $N_{ov} \propto \bar{c} \Delta_{ov}$, and then $U_{ex} \propto \bar{c}^2 \Delta_{ov}$. Each overlapping bead feels friction $\bar{\eta}_{ov}$ proportional the concentration $\bar{\eta}_{ov} \propto \bar{c}$. Combined with the volume exclusion and the friction, the decreasing speed of the overlapping region, i.e., the segregation speed is

$$\bar{v}_{ov} = - \left\langle \frac{1}{\eta_{ov}} \frac{\partial U_{ex}}{\partial \Delta_{ov}} \right\rangle \propto \bar{c}, \quad (14)$$

and then the segregation time is $t_s \propto \bar{R}_g / \bar{c} \propto \bar{D} / \bar{c}$.

For large $\bar{R}_g$ or small $\bar{c}$, the scaling laws (12) seem to deviate from the data. In the parameter regions, the loop length C_l is large and the bead concentration is small. Therefore the spatial fluctuation of the concentration is large and the mean-field approximation discussed above breaks down.

Here we discuss effects of the strength ϵ_{spr} of the spring interaction (3). Figures 4(b) and 4(c) show the ϵ_{spr} effects on the segregation times. In both figures, the plus and the cross symbols represent the MD simulation results with $\epsilon_{spr} = 1k_B T$ and $2k_B T$, respectively, when the other parameters are fixed to the same values. From these results, the relationship (12) is preserved unless the spring interaction is weak enough for the beads to pass through the springs easily. If the spring interaction becomes stronger, $\epsilon_{spr} > 3k_B T$, it is more difficult for the beads to pass through the springs and the segregation times become longer and deviate from the relationship (12).

TABLE II. The simulation parameters for the different runs for rod-shaped polymers. The numbers in parentheses represent statistical errors of the last two or three digits.

C_l	N_l	N_p	$\bar{D}$	$\bar{\alpha}$	t_i	t_s
21	20	1	8.191 (9)		0.151(35)	0.392(59)
		2	8.314(25)	1.815(14)	0.187(23)	0.417(26)
		3	8.427(19)	2.844(19)	0.206(34)	0.455(29)
		4	8.503(34)	3.755(29)	0.214(36)	0.492(39)
		5	8.791(71)	4.819(52)	0.217(33)	0.542(32)
		10	8.812(93)	9.631(134)	0.212(43)	0.579(34)
14	30	1	6.955 (7)		0.117(28)	0.213(54)
		2	7.064(15)	1.937(12)	0.126(23)	0.223(36)
		3	7.506(22)	2.812(22)	0.133(26)	0.272(45)
		4	7.767(31)	3.770(41)	0.143(28)	0.288(25)
		5	7.838(57)	5.035(72)	0.147(22)	0.293(53)
		10	8.142(91)	9.768(122)	0.152(35)	0.303(45)
21	40	1	9.491(12)		0.276(25)	0.412(68)
		2	9.668(17)	2.106(15)	0.286(28)	0.427(24)
		3	9.953(42)	3.133(19)	0.322(37)	0.441(29)
		4	10.03 (5)	4.266(39)	0.330(30)	0.466(45)
		5	10.11 (6)	5.463(56)	0.333(42)	0.488(66)
14	60	1	8.426 (6)		0.198(30)	0.226(39)
		2	8.498(14)	2.141(11)	0.207(34)	0.246(24)
		3	8.543(27)	3.286(17)	0.220(27)	0.259(26)
		4	8.766(48)	4.684(31)	0.224(39)	0.261(35)
		5	8.831(71)	5.265(67)	0.231(53)	0.265(67)

B. Rod-shaped polymers

Next, we consider rod-shaped polymers. This situation is realized by changing the parameter N_p from unity. Simulation parameters and results for the polymer shapes and dynamics are summarized in Table II. In Table II, the diameter $\bar{D}$ and the aspect ratio $\bar{\alpha}$ for the shapes, the induction t_i , and the segregation time t_s for the dynamics are presented.

For the polymer shapes, as N_p increases under fixed C_l and N_l , the diameters $\bar{D}$ of the polymer take almost the same values but slightly increase, while the aspect ratio $\bar{\alpha}$ increases proportionally. This situation corresponds to the case of polymer elongation under fixed $\bar{D}$ and the concentration $\bar{c} \approx N/(\bar{\alpha}\bar{D}^3)$. The induction t_i and the segregation time t_s slightly increase as N_p increases but seem not to depend on the aspect ratio $\bar{\alpha}$.

Figures 5(a) and 5(b) shows the induction t_i and the segregation time t_s as a function of $\bar{D}$ by varying the aspect ratio $\bar{\alpha}$ for several values of N and C_l ; all the data are taken from Table II. Here we multiply the horizontal axis by $\beta = \sqrt{3}/2$ in order to match the axis of the spherical cases, Figs. 4(b) and 4(c), where $\bar{R}_g = \beta\bar{D}$.

Each of the data sets can be fitted by a function,

$$t_\gamma(x) = (a_\gamma x_\gamma)^{b_\gamma}, \quad (15)$$

where $\gamma = i$ and $x_\gamma = \beta\bar{D}$ in Fig. 5(b) and $\gamma = s$ and $x_\gamma = \beta\bar{D}/\bar{c}$ in Fig. 5(c). The fitting parameters are, respectively,

$$\alpha_i = 0.07941 \pm 0.0015, \quad b_i = 3.001 \pm 0.11, \quad (16)$$

$$\alpha_s = 0.07377 \pm 0.0044, \quad b_s = 1.107 \pm 0.08. \quad (17)$$

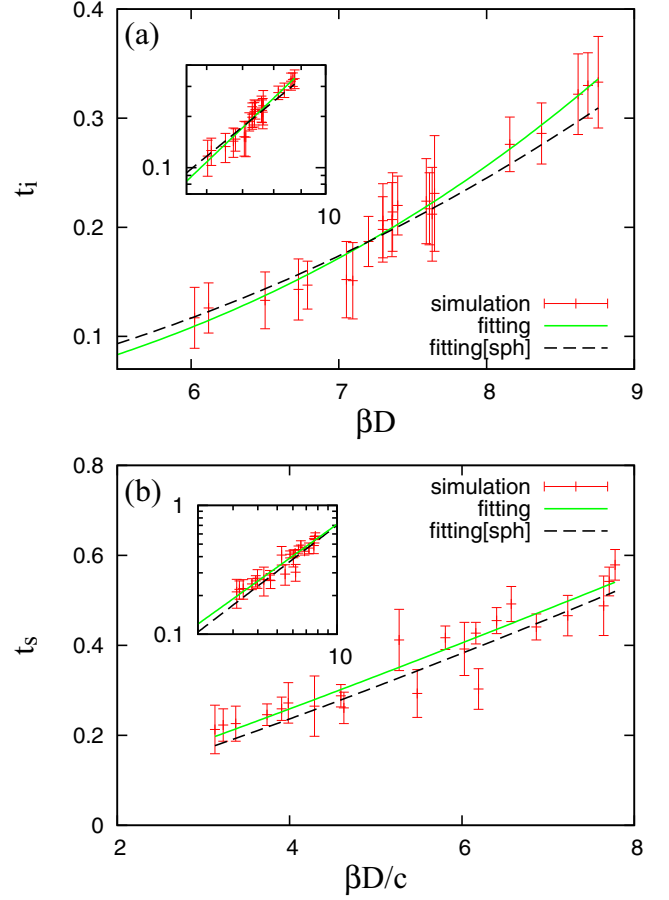


FIG. 5. (a) The induction time t_i and (b) the segregation time t_s for several N in the rod-shaped polymer. The horizontal axis is multiplied by $\beta = \sqrt{3}/2$ to match the axis of the spherical cases, Figs. 4(b) and 4(c), where $\bar{R}_g = \beta\bar{D}$.

The solid curves in Figs. 5(a) and 5(b) represent the respective fitting functions (15). The dashed curves are the same fitting functions as those of the spherical cases shown in Figs. 4(b) and 4(c). For the rod-shaped polymers, both t_i and t_s are almost on the same fitting curves as those for the spherical shape polymers as shown in Fig. 5, and then the segregation dynamics of the rod-shaped polymers can be described by the same scaling laws as those of the spherical-shaped polymers.

For the segregation dynamics, both the induction t_i and the segregation time t_s are not affected by increasing N_p under fixed C_l and N_l . These results mean that the segregation dynamics of two entangled polymers do not depend on the aspect ratio, i.e., the length, but depends on the diameter and the concentration. By combining this result and Eq. (9), we can get the following relationship between the polymer shapes and the segregation dynamics:

$$t_i \propto \bar{D}^3, \quad t_s \propto \bar{D}/\bar{c}. \quad (18)$$

This elongation insensitivity reflects the segregation dynamics as being substantially a one-dimensional phenomenon that occurs in the segregation direction.

TABLE III. The averaged DNA amount N_{Mb} and the chromosome diameter $\bar{D}$ and the length $\bar{L}$ of metaphase chromosomes for some species. Data are taken from Table 1 in Ref. [14]. N_{Mb} is the genome size divided by the chromosome number of each species. Human chromosome data are taken from the five largest chromosomes.

Species	N_{Mp} (Mbp)	$\bar{D}$ (μm)	$\bar{L}$ (μm)
<i>C. japonica</i>	125	0.5	1.7–3.3
Human	229	0.6	5.4–7.2
Barley	729	0.9	10–14
Pine	1917	1.0	14–21
<i>T. cristatus</i>	1958	1.1	11–36
<i>N. viridescens</i>	3382	1.0	10–20
<i>P. japonica</i>	7450	1.3	14–39

IV. DISCUSSION AND CONCLUSION

We have investigated the relationship between polymer shapes and segregation from entanglement by using MD simulation. We show that two entangled polymers at high concentration spontaneously segregate from each other and the segregation dynamics can be distinguished into three stages: the induction, the active segregation, and the diffusion stages. The induction and the segregation time relate to the shape of the polymer and both times depend only on the diameter and the concentration but not on the length due to the dimensionality. The induction time has particularly strong dependence on the diameter, $t_i \propto \bar{D}^3$.

In nature, the length of eukaryotic chromosomes is richly diverse. The chromosome dimensions of some species with a broad range of genome sizes are summarized in Table III [14]. The measurements shown in Table III include the small chromatids of *Chionographis japonica* to the very large chromatids of *Paris japonica*. In addition to the great variety in the DNA amount per chromosome, individual species have karyotypes with a great heterogeneity of chromosome sizes. In interspecies, the diameter differences may arise from differences in the relative amounts of condensins.

Table III shows that the metaphase chromosomes of many animal and plant species take elongated cylinder shapes. Furthermore, the diameters seem to be conserved for many species and karyotypes, while the DNA amount and the chromosome length have varieties. For humans, the largest chromosome, chromosome 1, has $N_{\text{Mb}} \approx 250$ Mb and $\bar{L} \approx 8 \mu\text{m}$, and the smallest chromosome, chromosome 22, has $N_{\text{Mb}} \approx 50$ Mb and $\bar{L} \approx 2 \mu\text{m}$. Despite the big difference in genomic and physical length, the two chromosomes have similar diameters $\bar{D} \approx 0.6 \mu\text{m}$. Cells appear to conserve chromosome width for some reason and/or advantage.

This conservation can be understood from the point of view of segregation time. The relationship (18) describes that the induction and the segregation time of two entangled polymers strongly depend on the diameter. If each chromosome has a different diameter, then in isotropic $\bar{D} \sim N^{1/3}$ each chromosome has a different segregation time $\sim \bar{D}^3 \sim N$, such as, for human, the largest chromosome has a 5-times-longer segregation time than the smallest one. In this case, it would be difficult for ordered cell division after chromosome segregation. Due to the necessity for orderly cell division, eukaryotic chromosomes may need to take shapes with such a conserved diameter.

The relationship (18) indicates that a more elongated compact polymer has a shorter segregation time. Actual eukaryotic chromosomes have limitations to their mobility because of the nuclear envelope and the other chromosomes. Due to this spatial limitation, chromosomes may not take longer shapes. It will be interesting to investigate these effects in future work.

The fact [3–5] that metaphase chromosomes in early embryonic cells tend to be longer and thinner compared with those in somatic cells (mentioned in the Introduction) may support our results. In the early embryo, the cell cycle is about 0.5 h, which is more rapid than the meiotic phase time of 1–2 h in somatic cells [15]. The metaphase chromosomes in the early embryo may take longer and thinner shapes in order to achieve a rapid cell cycle.

Our study contrasts with that of Ref. [7]; polymer shapes are constricted by internal forces, Eq. (4), in our study and are restricted by boundary conditions in Ref. [7]. This may correspond to the difference in polymer shaping strategies between eukaryotic and bacterial cells. Whether two entangled polymers spontaneously segregate depends on the boundary conditions in Ref. [7], whereas polymers shaped by internal force always segregate spontaneously in our study. This is because polymer constriction by internal force generates a repulsive force between two entangled polymers and the absence of boundary conditions allows polymers to diffuse away from each other. Based on our results, we speculate that in the evolution of eukaryotes, enlargement of the cell size provided space for chromosome segregation, and the introduction of constriction forces to accelerate segregation and to form rod-shaped chromosomes to control segregation speed.

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