

**Polymer model with long-range interactions: Analysis and applications to the chromatin structure**

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Chromatin inside the cell nucleus consists of the DNA and its hierarchy of interacting molecules, which can be modeled as a complex polymer. To describe the chromatin dynamic, we develop and analyze here a polymer model that accounts for long-range interactions and not just those between the closest neighbors as in the Rouse polymer model. Our construction of the polymer model allows us to recover the local interaction between monomers from the anomalous diffusion exponent, which can be directly measured experimentally. We compute asymptotically for this polymer model the cross-correlation function for a given monomer and the mean time for a loop to be formed. Finally, we discuss some possible applications for interpretation of chromosome capture data.

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**I. INTRODUCTION**

Chromatin inside a cell nucleus consists of a DNA molecule and its hierarchy of interacting molecules. In spite of the recent progress in live cell microscopy, chromatin dynamics is still unclear. For example, a single locus on DNA bacteria or yeast chromosomes performs a motion that has been characterized as anomalous [1,2]. Anomalous diffusion is identified experimentally by calculating the mean square displacement (MSD) from a time lapse of the locus position. When the MSD grows as a power law in time such that  $\langle (R(t) - R(0))^2 \rangle \propto t^\alpha$ , with exponent  $\alpha \neq 1$ , the underlying stochastic motion differs from normal diffusion. For  $\alpha < 1$  the process is called subdiffusion. The origin of this behavior is not clear, although the motion of a tagged monomer which is part of a long Rouse polymer chain is anomalous and a direct computation (see Eq. 4.56 in [3]) shows that the exponent  $\alpha = 1/2$ . Other polymer models can exhibit different exponents. The Zimm model, for example, which takes into account hydrodynamical interaction, gives  $\alpha = 2/3$  [4], and for a polymer performing reptation  $\alpha = 1/4$  [5]. Interestingly, empirical data on a locus on the chromatin reveals an exponent  $\alpha = 0.33$  [6]. What are the properties of a polymer model that would give this exponent?

Our goal here is to construct a generic polymer model for which the anomalous exponent of a locus would be prescribed. Phenomenological models [1] based on the fractional Langevin equation lead to an MSD that exhibits a power law. The construction of the associated polymer model is based on modified Langevin equations convoluted by a kernel which decays algebraically. This kernel accounts for the motion of the loci in a viscoelastic fluid, which slows down the loci dynamics, resulting in a subdiffusion regime. However, the large variability of the anomalous exponent for the dynamics of a chromatin locus cannot be accounted for by the viscoelasticity alone. Subdiffusion with an exponent  $\alpha > 0.5$  can also appear in some polymer models [7], a case that is not considered here.

We develop here a general method to construct a polymer model with long-range interactions with a prescribed anomalous exponent. For a given measured anomalous exponent, we can reconstruct the local interaction rather than attributing the

anomalous behavior to the surrounding medium. Starting with the classical Rouse polymer model, we construct the long-range interaction in the Fourier space of the polymer. We then compute the cross-correlation function and obtain an explicit expression of the anomalous exponent as a function of the polymer properties. We derive a novel asymptotic expression for the mean first looping time for a polymer that has a given anomalous exponent. Finally, we discuss how such a long correlated polymer model can be used to analyze experimental data such as chromosome capture experimental data [8].

**II. POLYMER DYNAMICS****A. General properties of a Rouse chain**

A polymer is modeled as a collection of monomers positioned at  $\mathbf{R}_n$  ( $n = 1, 2, \dots, N$ ), moving under the influence of a random Brownian motion coupled to a force originating from the potential energy  $\phi(\mathbf{R}_1, \dots, \mathbf{R}_N)$ . In the Rouse model, only neighboring monomers interact via harmonic springs, ignoring both non-covalently bound interactions between monomers (such as hydrodynamics forces) and self-avoiding interactions.

The potential in the Rouse model [3] is given explicitly by

$$\phi(\mathbf{R}_1, \dots, \mathbf{R}_N)_{\text{Rouse}} = \frac{\kappa}{2} \sum_{n=1}^N (\mathbf{R}_n - \mathbf{R}_{n-1})^2, \quad (1)$$

where the spring constant  $\kappa = dk_B T / b^2$  is related to the standard deviation  $b$  of the distance between adjacent monomers [3], where  $k_B$  is the Boltzmann coefficient,  $T$  the temperature, and  $d$  the dimensionality. We work in units of  $k_B T$ ; thus  $\kappa = d/b^2$  and  $D = 1/\gamma$ , where  $\gamma$  is the friction coefficient. In the Smoluchowski limit of the Langevin equation [9], the dynamics of monomer  $\mathbf{R}_n$  in the potential  $\phi_{\text{Rouse}}$  is described by the stochastic equation

$$\frac{d\mathbf{R}_n}{dt} = -D\nabla_{\mathbf{R}_n}\phi_{\text{Rouse}} + \sqrt{2D}\frac{d\mathbf{w}_n}{dt}, \quad (2)$$

for  $n = 1, \dots, N$ , and each  $\mathbf{w}_n$  is an independent  $d$ -dimensional white Gaussian noise with mean 0 and variance 1.

Using the normal (Rouse) modes [3] allows diagonalization of the stochastic equations. Indeed the new coordinates are

$$\mathbf{u}_p = \sum_{n=1}^N \mathbf{R}_n \alpha_p^n, \quad (3)$$

where

$$\alpha_p^n = \begin{cases} \sqrt{\frac{1}{N}}, & p = 0; \\ \sqrt{\frac{2}{N}} \cos\left((n-1/2)\frac{p\pi}{N}\right) & \text{otherwise.} \end{cases} \quad (4)$$

In these new coordinates, called Rouse coordinates,  $\mathbf{u}_0$  represents the location of the center of mass and the potential  $\phi_{\text{Rouse}}$  defined in Eq. (1) reads

$$\phi(\mathbf{u}_1, \dots, \mathbf{u}_{N-1}) = \frac{1}{2} \sum_{p=1}^{N-1} \kappa_p \mathbf{u}_p^2, \quad (5)$$

where

$$\kappa_p = 4k \sin\left(\frac{p\pi}{2N}\right)^2. \quad (6)$$

The stochastic equations for the polymer, (2), are

$$\frac{d\mathbf{u}_p}{dt} = -D_p \kappa_p \mathbf{u}_p + \sqrt{2D_p} \frac{d\tilde{\mathbf{w}}_p}{dt}, \quad (7)$$

where  $D_p = D$  and  $p = 0, \dots, N-1$ .

Equations (7) are of the Ornstein-Uhlenbeck type and can thus be solved directly: the probability density functions of the variable  $\mathbf{u}_p$  are Gaussians with a time-dependent mean and a variance given by

$$\begin{aligned} \sigma_p^2(t) &= \frac{k_B T}{\kappa_p} (1 - e^{-2t/\tau_p}) \quad \text{for } p \geq 1, \\ \sigma_0^2(t) &= 2D_{\text{cm}} t. \end{aligned} \quad (8)$$

The equilibration (relaxation) times of the internal modes are

$$\tau_p = \frac{1}{D\kappa_p}, \quad (9)$$

while the diffusion constant is  $D_{\text{cm}} = D/N$ . There is a hierarchy of relaxation times: the shortest time scale is  $\tau_{N-1} \approx 1/(4D\kappa)$ , which is half of the time  $\tau_s = 1/(2D\kappa)$  during which a free monomer would diffuse a mean squared distance between the adjacent monomers ( $b^2 = 1/\kappa$ ). For the center of mass, the characteristic time is  $\tau_0 \equiv b^2 N/D_{\text{cm}} = N^2/(D\kappa)$  associated with diffusing over the size of the polymer. This time is of the same order as the longest internal relaxation time  $\tau_1$ . For long polymers  $\tau_0/\tau_1 \approx \pi^2$ .

By inverting Eq. (3), we obtain the position of a specific monomer:

$$\mathbf{R}_c = \sum_{p=0}^{N-1} \alpha_p^c \mathbf{u}_p. \quad (10)$$

Since each term in the above sum is (independently) Gaussian distributed, so is  $\mathbf{R}_c$ , and the variance is

$$\text{var}(\mathbf{R}_c) = d(\alpha_0^c)^2 \sigma_0^2(t) + d \sum_{p=1}^{N-1} (\alpha_p^c)^2 \sigma_p^2(t). \quad (11)$$

Utilizing Eq. (8), we distinguish three regimes:

(1) For short times,  $t \ll \tau_{N-1}$ , we can expand the exponential in Eq. (8) and obtain  $\sigma_p^2 \approx Dt$  independent of  $p$ . The sum in Eq. (11) then leads to  $\text{var}(\mathbf{R}_c) \approx 2dDt$ .

(2) For very long times,  $t \gg \tau_1$ , all the internal modes saturate to a variance that is independent of  $t$ . In this regime the additional time dependence comes from the first term in Eq. (11), corresponding to the slow diffusion of the center of mass.

(3) For intermediate times,  $\tau_{N-1} \ll t \ll \tau_1$ , the terms  $2t/\tau_p > 1$  contribute significantly to Eq. (11). Focusing on the corresponding modes, we see that

$$\text{var}(\mathbf{R}_c) \approx 2 \int_{p_{\min}}^{N-1} \frac{(\alpha_p^c)^2}{\kappa_p} dp, \quad (12)$$

where  $p_{\min}$  is such that  $\tau_{p_{\min}} = 2t$ . We see that  $\text{var}(\mathbf{R}_c) \sim t^{1/2}$ . We conclude that during this intermediate time interval, the dynamics is described as anomalous diffusion, due to the collective behavior of the modes. The size of this interval can be made arbitrarily large for  $N$  large.

## B. Dynamics of a monomer in an extended interacting Rouse chain ( $\beta$ model)

We propose in this section to derive a general polymer model based on Rouse such that the behavior of the cross-correlation function for intermediate times behave like  $t^\alpha$ , where the exponent  $\alpha$  is given and related to the intrinsic property of the polymer. We specifically consider the case of an anomalous exponent different from  $1/2$ . The main idea of the model is to extend the monomer interaction beyond the closest neighbors in the Rouse polymer.

We start with the classical Rouse model described in normal modes by Eq. (7). To define our new model, we modify in the Ornstein-Uhlenbeck equations

$$\frac{d\mathbf{u}_p}{dt} = -D_p \tilde{\kappa}_p \mathbf{u}_p + \sqrt{2D_p} \frac{d\tilde{\mathbf{w}}_p}{dt}, \quad (13)$$

the coefficients  $\tilde{\kappa}_p$ , and we now take

$$\tilde{\kappa}_p = 4k \sin^\beta\left(\frac{p\pi}{2N}\right), \quad (14)$$

with  $\beta > 1$ ,  $D_0 = D_{\text{cm}}$ , and  $D_p = D$  for  $p > 0$ . For  $\beta = 2$ , we recover the classical Rouse model. By using the reciprocal transformation of the one given by Eq. (3) between the original space and the Fourier space (the coefficients  $\alpha_p^n$  are unchanged), it is possible to write the novel stochastic equation for the polymer dynamics in real space. This procedure defines a unique potential, and as we see, it contains long-range interactions. At this stage, we have defined a polymer model in the Fourier space and we use the Rouse transformation to study its properties.

## C. Intermonomer interactions in the $\beta$ model

In the  $\beta$  model presented above, modifying the eigenvalues results in a long-range monomer-monomer interaction, leading to a potential different from the one of Eq. (1). Using the

inverse Fourier transform of the new diagonalized potential,

$$\tilde{\phi} = \frac{1}{2} \sum_p \tilde{\kappa}_p \mathbf{u}_p^2. \quad (15)$$

We obtain the structure of the novel potential. Indeed, using Rouse transformation in Eq. (4), we get

$$\begin{aligned} \tilde{\phi}(\mathbf{R}_1, \dots, \mathbf{R}_N) &= \frac{1}{2} \sum_p \tilde{\kappa}_p \left( \sum_{n=1}^N \mathbf{R}_n \alpha_p^n \right)^2 \\ &= \frac{1}{2} \sum_{l,m} \mathbf{R}_l \mathbf{R}_m \sum_p \tilde{\kappa}_p \alpha_p^l \alpha_p^m \\ &= \frac{1}{2} \sum_{l,m} \mathbf{R}_l \mathbf{R}_m A_{l,m}, \end{aligned} \quad (16)$$

where the coefficients are

$$\begin{aligned} A_{l,m} &= \sum_{p=1}^{N-1} \tilde{\kappa}_p \alpha_p^l \alpha_p^m \\ &= 4\kappa \frac{2}{N} \sum_{p=1}^{N-1} \sin^\beta \left( \frac{p\pi}{2N} \right) \cos \left( \left( l - \frac{1}{2} \right) \frac{p\pi}{N} \right) \\ &\quad \times \cos \left( \left( m - \frac{1}{2} \right) \frac{p\pi}{N} \right). \end{aligned} \quad (17)$$

For  $\beta \neq 2$ , all monomers are coupled and the strength of the interaction decays with the distance along the chain [Fig. 3(a)]. We compare the coefficient  $A_{50,m}$  as a function of  $m$  for a polymer of length  $N = 100$  [Fig. 1(b)] of the  $\beta$  model and the classical Rouse chain. Within the  $\beta$  model, all monomers are coupled and the strength of the interaction decays with the distance along the chain. We have summarized in Table I the  $A_{n,m}$  coefficients obtained for various values of  $\beta$ .

We now briefly mention that the  $\beta$  model can further be directly related to long-range interactions between the monomers as follows: For a quadratic potential where monomers interact by pairs, we use the following interaction

TABLE I. Values of the coefficients  $A_{l,m}$  (in units of  $\kappa$ ) for the middle monomer in a polymer chain of length  $N = 101$ , for different values of  $\beta$ .

$\beta$	$A_{51,51}$	$A_{51,50}$	$A_{51,49}$	$A_{51,48}$	$A_{51,40}$	$A_{51,30}$
2	2	-1	0	0	0	0
1.5	2.22	-0.95	-0.087	-0.029	$-1.07 \times 10^{-3}$	$-2.2 \times 10^{-3}$
1.2	2.40	-0.90	-0.14	-0.054	$-3.05 \times 10^{-3}$	$-7.9 \times 10^{-3}$
1	2.55	-0.85	-0.17	-0.073	$-5.48 \times 10^{-3}$	$-16.68 \times 10^{-3}$

energy:

$$\begin{aligned} \psi(\mathbf{R}_1, \dots, \mathbf{R}_N) &= \frac{1}{2} \sum_{ij; i>j} a_{i,j} (\mathbf{R}_i - \mathbf{R}_j)^2 \\ &= \sum_{i=1}^N \mathbf{R}_i^2 \sum_{j \neq i} \frac{a_{i,j}}{2} - \sum_{ij; i>j} a_{ij} \mathbf{R}_i \mathbf{R}_j. \end{aligned} \quad (18)$$

Thus the interaction coefficients  $a_{i,j}$  are related to that of the  $\beta$  polymer  $A_{l,m}$  [see Eq. (16)] by the following formula:

$$a_{l,m} = \begin{cases} \sum_{j \neq l} A_{jl}, & l = m; \\ -\frac{1}{2} A_{l,m} & \text{otherwise.} \end{cases} \quad (19)$$

In this way it is possible to reconstruct the amplitude of the interaction from the coefficient of the  $\beta$  model.

#### D. Time cross-correlation function of a single monomer position in the $\beta$ model

In this section, we compute the cross-correlation function of monomer  $\mathbf{R}_c$  using Eq. (10). Because the correlation function of each mode  $\mathbf{u}_p$  decays exponentially, (8), with a specific coefficient, we show here that the sum of exponentials can be approximated by a decaying power law. Using (15), for any time  $t_0$  and  $t$ , a direct computation from Eqs. (7) and (10),

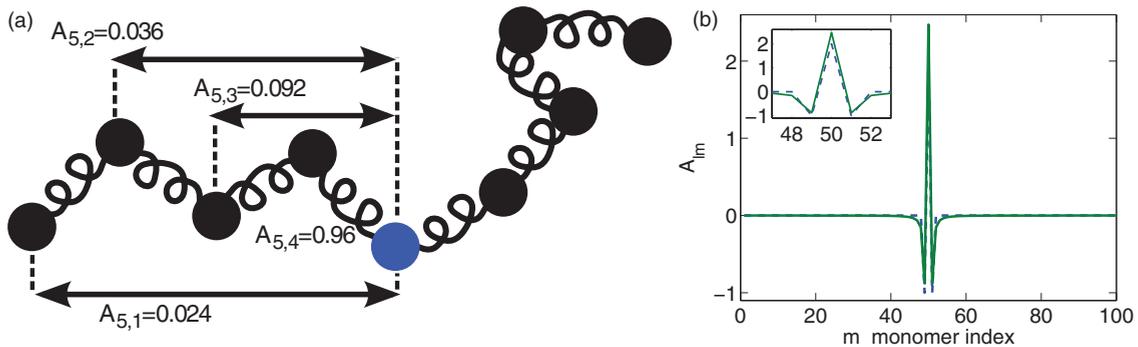


FIG. 1. (Color online) The  $\beta$  polymer. (a) Schematic of a  $\beta$  polymer, where all monomers are connected with a strength that decays with the distance along the chain. We show the interactions of the central monomer [lighter (blue) circle] with all other monomers in a chain of length  $N = 9$  for  $\beta = 1.5$ . Interaction units are  $\kappa = 3/b^2$ . (b) Monomer-monomer interactions in the modified Rouse polymer model ( $\beta$  model). The value of the coefficient  $A_{lm}$  (in units of  $\kappa$ ) represents the strength of the interaction between two monomers. The value of  $A_{lm}$  in the Rouse model ( $\beta = 2$ ), where the monomer  $l = 50$  is a part of a long polymer,  $N = 100$  [dashed (blue) line]. In this case only the nearest neighbors are coupled. Also shown are the coefficients  $A_{lm}$  for a polymer with  $\beta = 1.1$ , where the monomer  $l = 50$  is a part of a long polymer,  $N = 100$ . In this case all monomers interact with each other and the strength of the interaction decays with the distance along the chain.

and the correlation function of  $\mathbf{u}_p$ , which is  $\langle |\mathbf{u}_p(t_0 + t) - \mathbf{u}_p(t_0)|^2 \rangle = \frac{2}{\tilde{\kappa}_p} (1 - e^{-t/\tau_p})$ , we get

$$\begin{aligned} & \langle (\mathbf{R}_c(t_0 + t) - \mathbf{R}_c(t_0))^2 \rangle \\ &= \frac{d}{\kappa N} \sum_{p=1}^{N-1} \frac{\cos^2 \left( \frac{(2c-1)p\pi}{2N} \right)}{\sin^\beta \left( \frac{p\pi}{2N} \right)} (1 - e^{-t/\tau_p}) + 2dD_{\text{cm}}t, \quad (20) \end{aligned}$$

where  $\tau_p = 1/D\tilde{\kappa}_p$ . For large  $N$ , we use the Euler-Maclaurin formula to approximate the sum by an integral,

$$\begin{aligned} \sum_{p=1}^{N-1} f(p, N, \beta) &\approx \int_1^{N-1} f(p, N, \beta) dp \\ &+ \frac{f(1, N, \beta) + f(N-1, N, \beta)}{2} \\ &+ \frac{1}{12} (f'(N-1, N, \beta) - f'(1, N, \beta)), \quad (21) \end{aligned}$$

where

$$f(p, N, \beta) = \frac{\cos^2 \left( \frac{ap\pi}{2N} \right)}{\sin^\beta \left( \frac{p\pi}{2N} \right)} (1 - e^{-t/\tau_p}) \quad (22)$$

and  $a = 2c - 1$ . The detailed computations are given in the Appendix and we find that, for  $N \gg 1$ , the cross-correlation function behaves for intermediate times,  $\tau_{N-1} \leq t \leq \tau_1$ , as

$$\langle (\mathbf{R}_c(t_0 + t) - \mathbf{R}_c(t_0))^2 \rangle \propto t^{1-\frac{1}{\beta}}. \quad (23)$$

During that time regime, the center-of-mass diffusion is negligible. We plot in Fig. 2 the cross-correlation function of a monomer computed from Brownian simulations of a polymer of length  $N = 128$  and compare the cross-

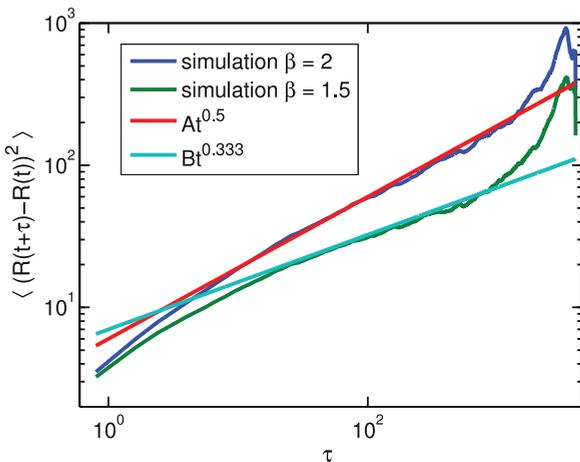


FIG. 2. (Color online) Cross-correlation of a specific monomer. Brownian simulations for a polymer of length  $N = 128$  for different values of  $\beta$ . The time cross-correlation function is calculated from the polymer trajectory. For  $\beta = 3/2$  (green line), the anomalous exponent  $\alpha = 0.33$  computed at intermediate times [Eq. (23)]. The trend line (cyan line) is also plotted. For  $\beta = 2$  (blue line), we obtain the Rouse model with anomalous exponent  $\alpha = 0.5$ . Also plotted is the trend (red) line according to Eq. (23).

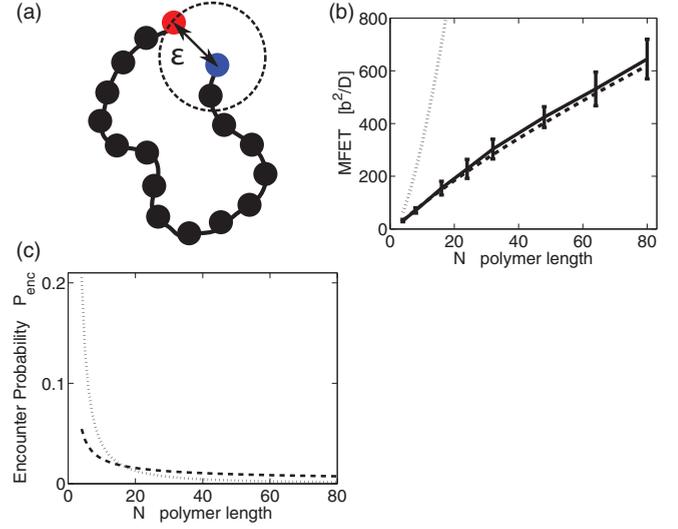


FIG. 3. (Color online) Monomer encounter in a  $\beta$  polymer. (a) Encounter between the two ends of a polymer at the activation radius  $\epsilon$ . (b) The MFET was found by Brownian simulation in a free domain for a  $\beta$  polymer with  $\beta = 1.5$  (solid line) for an activation radius  $\epsilon = 0.01b$ . Simulations are compared to the analytical formula, (39) (dashed line). Also shown is the MFET for the Rouse model (points) for which  $\beta = 2$ . (c) Normalized encounter probability for the polymer ends for a Rouse polymer for which  $\beta = 2$  (points) and a  $\beta$  polymer for which  $\beta = 1.5$  (dashed line).

correlation function for  $\beta = 3/2$  with that of the regular Rouse model ( $\beta = 2$ ).

### E. Mean first encounter time (MFET) between two monomers of a $\beta$ polymer

The MFET between two monomers is the mean time it takes for two monomers to reach a proximity of  $\epsilon$  to one another, at which they interact to create a chemical bond between them [Fig. 3(a)] [10–18]. This time is key in the regulation of many reactions in the cell. In [17], we have shown that the MFET is related to the inverse of the first eigenvalue of the associated Fokker Planck operator:

$$\langle \tau_\epsilon^\beta \rangle \approx \frac{1}{D\lambda_0^\epsilon}. \quad (24)$$

The eigenvalue  $\lambda_0^\epsilon$  can be calculated to the first order in  $\epsilon$  using the equation [17]

$$\lambda_0^\epsilon = \frac{4\pi\epsilon \int_{\text{C-P}} e^{-\phi(x)} dx_g}{|\tilde{\Omega}|} + O(\epsilon^2). \quad (25)$$

This is the ratio of the closed polymer (C-P) ensemble to the whole polymer configuration space. We now calculate integral (25). A direct computation using Gaussian integrals and the  $\beta$  potential, (15), gives

$$|\tilde{\Omega}| = \int e^{-\phi(x)} dV_x = (2\pi)^{(N-1)d/2} \left( \prod_{p=1}^{N-1} \tilde{\kappa}_p \right)^{-3/2}. \quad (26)$$

The integral in (25) involves the integration over the C-P ensemble

$$|S|_{\lambda_0^\epsilon} = |\tilde{\Omega}|^{-1} \int_{\text{C-P}} e^{-\tilde{\phi}(x)} d\mathbf{x}_g, \quad (27)$$

where  $d\mathbf{x}_g$  is the induced metric of the configuration space onto the set C-P. Direct integration of Eq. (27) gives [17]

$$\begin{aligned} |S|_{\lambda_0^\epsilon} &= |\tilde{\Omega}|^{-1} \left[ \frac{(2\pi)^{(N-2)} \sum_{p \text{ odd}} w_p^2}{\left( \sum_{p \text{ odd}} \frac{\omega_p^2}{\tilde{\kappa}_p} \right) \prod_p \tilde{\kappa}_p} \right]^{d/2} \\ &= |\tilde{\Omega}|^{-1} \left[ \frac{(2\pi)^{(N-2)} S_1(N)}{\frac{1}{4\kappa} S_2(N) \prod_p \tilde{\kappa}_p} \right]^{d/2}, \end{aligned} \quad (28)$$

where  $\omega_p = \cos(p\pi/2N)$  and the series

$$\begin{aligned} S_1(N) &= \sum_{i=0}^m \cos^2 \left( \frac{(2i+1)\pi}{2N} \right) = \frac{m+1}{2} + \frac{\sin \frac{(2m+2)\pi}{N}}{4 \sin \frac{\pi}{N}}, \\ m &= \begin{cases} \frac{N-2}{2}, & N \text{ even}, \\ \frac{N-3}{2}, & N \text{ odd}, \end{cases} \end{aligned} \quad (29)$$

and

$$S_2(N) = \sum_{p \text{ odd}} \frac{\cos^2 \left( \frac{p\pi}{2N} \right)}{\sin^\beta \left( \frac{p\pi}{2N} \right)}. \quad (30)$$

We approximate  $S_2(N)$  [Eq. (30)] by

$$\begin{aligned} S_2(N) &\approx \int_0^{\frac{N-1}{2}} g(q, N, \beta) dq + \frac{g\left(\frac{N-1}{2}, N, \beta\right) + g(0, N, \beta)}{2} \\ &\quad + \frac{1}{12} \left( g'\left(\frac{N-1}{2}, N, \beta\right) - g'(0, N, \beta) \right), \end{aligned} \quad (31)$$

where

$$g(p, N, \beta) = \frac{\cos^2 \left( \frac{(2p+1)\pi}{2N} \right)}{\sin^\beta \left( \frac{(2p+1)\pi}{2N} \right)}. \quad (32)$$

The integral was evaluated with Mathematica and we obtain

$$\begin{aligned} &\int_0^{(N-1)/2} g(s, N, \beta) ds \\ &= \frac{N}{3\pi} \cos \left( \frac{\pi}{2N} \right)^3 {}_2F_1 \left( \frac{3}{2}, \frac{1+\beta}{2}, \frac{5}{2}, \cos \left( \frac{\pi}{2N} \right)^2 \right), \end{aligned} \quad (33)$$

where  ${}_2F_1$  is the Gaussian hypergeometric function [19]. The terms

$$g(0, N, \beta) = \frac{\cos^2 \left( \frac{\pi}{2N} \right)}{\sin^\beta \left( \frac{\pi}{2N} \right)} \quad (34)$$

and

$$g'(0, N, \beta) = -\frac{\beta\pi \cos \left( \frac{\pi}{2N} \right)^3}{2N \sin \left( \frac{\pi}{2N} \right)^{1+\beta}} \quad (35)$$

in (31) are of order  $\mathcal{O}(N^\beta)$ . Thus, the series  $S_2(N)$  is approximated by

$$\begin{aligned} S_2(N) &\approx \frac{N}{3\pi} \cos \left( \frac{\pi}{2N} \right)^3 {}_2F_1 \left( \frac{3}{2}, \frac{1+\beta}{2}, \frac{5}{2}, \cos \left( \frac{\pi}{2N} \right)^2 \right) \\ &\quad + \frac{1}{2} \frac{\cos^2 \left( \frac{\pi}{2N} \right)}{\sin^\beta \left( \frac{\pi}{2N} \right)} + \frac{\pi}{24N} \frac{\beta \cos \left( \frac{\pi}{2N} \right)^3}{\sin \left( \frac{\pi}{2N} \right)^{1+\beta}}. \end{aligned} \quad (36)$$

Thus, substituting into (26), (28), (29), and (36) into Eq. (25), we get, for large  $N$ ,

$$\begin{aligned} \lambda_0^\epsilon &\approx 4\epsilon\kappa^{-3/2} \left[ \frac{2}{3} \cos \left( \frac{\pi}{2N} \right)^3 {}_2F_1 \left( \frac{3}{2}, \frac{1+\beta}{2}, \frac{5}{2}, \cos \left( \frac{\pi}{2N} \right)^2 \right) \right. \\ &\quad \left. + \frac{\pi \cos^2 \left( \frac{\pi}{2N} \right)}{N \sin^\beta \left( \frac{\pi}{2N} \right)} + \frac{\pi^2}{12N^2} \frac{\beta\pi \cos \left( \frac{\pi}{2N} \right)^3}{2 \sin \left( \frac{\pi}{2N} \right)^{1+\beta}} \right]^{-3/2}. \end{aligned} \quad (37)$$

For large  $N$

$$\begin{aligned} &{}_2F_1 \left( \frac{3}{2}, \frac{1+\beta}{2}, \frac{5}{2}, \cos \left( \frac{\pi}{2N} \right)^2 \right) \\ &= 3\pi^{3/2-\beta} 2^{-(1+\beta)} N^{\beta-1} + \mathcal{O}(1) + \mathcal{O}(N^{-2}), \end{aligned} \quad (38)$$

while the two other terms in the parentheses scale as  $N^{\beta-1}$ . Finally, the mean encounter time for the two end monomers is

$$\begin{aligned} \langle \tau_\epsilon^\beta \rangle &= \frac{1}{D\epsilon(2\kappa)^{3/2}} \\ &\quad \times \left[ \frac{2}{3} \cos \left( \frac{\pi}{2N} \right)^3 {}_2F_1 \left( \frac{3}{2}, \frac{1+\beta}{2}, \frac{5}{2}, \cos \left( \frac{\pi}{2N} \right)^2 \right) \right. \\ &\quad \left. + \frac{\pi \cos^2 \left( \frac{\pi}{2N} \right)}{N \sin^\beta \left( \frac{\pi}{2N} \right)} + \frac{\pi^2}{12N^2} \frac{\beta\pi \cos \left( \frac{\pi}{2N} \right)^3}{2 \sin \left( \frac{\pi}{2N} \right)^{1+\beta}} \right]^{3/2} + \mathcal{O}(1). \end{aligned} \quad (39)$$

The asymptotics for the MFET are quite different for the Rouse and the  $\beta$  polymer: For the Rouse polymer, the asymptotic scales with  $N^{3/2}$  [the  $\mathcal{O}(\epsilon)$  term], while for a  $\beta$  polymer, for  $N \gg 1$ , the MFET scales as  $N^{\frac{3}{2}(\beta-1)}$ . In Fig. 3(b) we compare a Brownian simulation for the MFET of a polymer with  $\beta = 1.5$  to the analytical formula, (39). We find that the first order in  $\epsilon$  is enough to capture the process for small  $\epsilon$ , over a large range of polymer lengths.

#### F. Application to chromosome capture experiments, discussion, and conclusion

We have presented here a method for construction of a polymer model with long-range interactions and for which the anomalous exponent is given. Interestingly, the analytical expression for the MFET leads to a novel scaling exponent [Eq. (39)] that depends on the anomalous exponent. We now discuss some applications of the  $\beta$  model to the chromatin structure in the cell nucleus.

Long-range interactions introduced by the  $\beta$  model can be generated by condensin proteins, part of the Structural Maintenance of Chromosomes (SMC) protein family [20]. Indeed, these proteins are capable of generating large hoops that tie together sites far apart along the chromosome. During mitosis, the concentration of the condensin increases, resulting in an

increased young modulus of the chromosome [21]. Another application of the  $\beta$  model is to reinterpret the interactions map of the human genome [22]. Indeed, chromosome capture data represent frequencies at which two sites encounter each other [8]. The encounter frequency has been fitted by the  $N^{-1}$  power law ( $N$  is the distance along the chain), which is not the one expected from the Rouse polymer model (where the scaling would be  $N^{-3/2}$ ). This result is attributed to the hypothetical fractal organization of the chromatin [23]. However, we present in Fig. 3(c) the graph for the encounter probability  $P_{\text{enc}}$  computed from relations (24) and (25) and the sums (29) and (30), which we normalized to

$$P_{\text{enc}}(N) = \frac{\langle \tau_\epsilon^\beta \rangle^{-1}(N)}{\sum_{N'=N_{\min}}^{N_{\max}} \langle \tau_\epsilon^\beta \rangle^{-1}(N')}, \quad (40)$$

where we choose  $N_{\min} = 4$  and  $N_{\max} = 80$ . Thus we propose a different interpretation for the decay of  $P_{\text{enc}}$ , which is neither  $N^{-3/2}$  nor  $N^{-1}$  but  $N^{-3/2(\beta-1)}$ , where  $\beta$  has to be identified by a fitting procedure that should be applied to experimental data [22]. We conclude that with the  $\beta$  model, it would be possible to link the empirical decay rate to the intrinsic properties of the chromatin, which is incorporated in the value of  $\beta$ .

Another example we discuss is the search for an homologous sequence in the nucleus as the template for repair [24] during homologous recombination in yeast. It is characterized by a higher anomalous exponent  $\alpha$ , close to 0.5 [25], while  $\alpha = 0.2$  for a locus dynamics in the absence of a break. We can now use these differences in  $\alpha$  to estimate the effects on the MFET. To perform these computations, we model the chromatin fiber as a chain composed of  $N$  monomers with a standard deviation of the bond length  $b = 30$  nm, representing a 30-nm fiber (we neglected the strand bending elasticity). Each monomer represents 3.2 kbps along the chromosome [26] and the diffusion coefficient of a monomer is  $D = 10 \times 10^3$  nm<sup>2</sup>/s [27]. Choosing an absorbing radius of  $\epsilon = 5$  nm and using formula (39), for a polymer of length  $N = 60$  (equivalent to 190 kbp) and  $\alpha = 0.2$  ( $\beta = 1.25$ ), we find that the MFET is 0.87 s for the two ends, while for  $\alpha = 0.5$  ( $\beta = 2$ ), it is 29.5 s. We conclude that modifying  $\beta$  from a normal nucleus to the homologous recombination situation is accompanied by drastic changes in the dynamics of encounters between sites. While the search is much faster compared to the resting situation, the looping time is drastically increased.

Finally, the  $\beta$  model can be used to interpret data obtained from single-particle trajectory experiments on a chromatin locus. The appropriate polymer model to explain the characteristics dynamics of such a locus is still under debate. Recently, it has been suggested [28] that yeast chromatin can be well approximated as a Rouse polymer because the anomalous exponent, computed from MSD averaging over a cell population, is approximately 0.5. However, in many cases and for different chromatin loci, lower anomalous exponents are measured [6,28]. In that context, the  $\beta$  model can account for the behavior of different loci. The heterogeneity of the anomalous exponent reveals that the chromatin can be remodeled constantly over a cell population or along the DNA strand.

## APPENDIX

In this Appendix, we compute the cross-correlation function of monomer  $\mathbf{R}_c$ ,

$$\begin{aligned} & \langle (\mathbf{R}_c(t_0 + t) - \mathbf{R}_c(t_0))^2 \rangle \\ &= \frac{d}{\kappa N} \sum_{p=1}^{N-1} \frac{\cos^2\left(\frac{(2c-1)p\pi}{2N}\right)}{\sin^\beta\left(\frac{p\pi}{2N}\right)} (1 - e^{-t/\tau_p}) + 2dD_{\text{cm}}t, \end{aligned} \quad (A1)$$

where  $\tau_p = 1/D\tilde{\kappa}_p$ . For large  $N$ , we use the Euler-Maclaurin formula, (21). The boundary terms for  $N \gg 1$  are approximated as

$$f(1, N, \beta) = \frac{\cos^2\left(\frac{a\pi}{2N}\right)}{\sin^\beta\left(\frac{\pi}{2N}\right)} (1 - e^{-t/\tau_1}) \approx \left(\frac{2N}{\pi}\right)^\beta (1 - e^{-t/\tau_1}) \quad (A2)$$

and

$$\begin{aligned} f(N-1, N, \beta) &= \frac{\cos^2\left(\frac{a\pi(N-1)}{2N}\right)}{\sin^\beta\left(\frac{(N-1)\pi}{2N}\right)} (1 - e^{-t/\tau_{N-1}}) \\ &\approx \frac{\cos^2\left(\frac{a\pi}{2}\right)}{\sin^\beta\left(\frac{\pi}{2}\right)} (1 - e^{-t/\tau_{N-1}}) = 0. \end{aligned} \quad (A3)$$

Using the derivative of  $f$ ,

$$\begin{aligned} \frac{\partial f}{\partial p}(p, N, \beta) &= \frac{2\beta D\kappa\pi t e^{-t/\tau_p}}{N} \cos^2\left(\frac{ap\pi}{2N}\right) \cot\left(\frac{p\pi}{2N}\right) \\ &\quad - \frac{a\pi(1 - e^{-t/\tau_p})}{2N} \sin\left(\frac{ap\pi}{N}\right) \sin^{-\beta}\left(\frac{p\pi}{2N}\right) \\ &\quad - \frac{\beta\pi(1 - e^{-t/\tau_p})}{2N} \cos\left(\frac{p\pi}{2N}\right) \cos^2\left(\frac{ap\pi}{2N}\right) \\ &\quad \times \sin^{-1-\beta}\left(\frac{p\pi}{2N}\right). \end{aligned} \quad (A4)$$

Then for large  $N$ ,

$$\begin{aligned} f'(1, N, \beta) &\approx 4\beta\kappa D t e^{-t/\tau_1} - \beta \left(\frac{2N}{\pi}\right)^\beta (1 - e^{-t/\tau_1}) \\ &\quad - 2a^2 \left(\frac{2N}{\pi}\right)^{\beta-2} (1 - e^{-t/\tau_1}), \end{aligned} \quad (A5)$$

and

$$f'(N-1, N, \beta) \approx -\frac{a\pi(1 - e^{-t/\tau_{N-1}})}{2N}. \quad (A6)$$

We now estimate the integral in Eq. (21),

$$I = \int_1^{N-1} f(p, N, \beta) dp = I_1 + I_2, \quad (A7)$$

where

$$\begin{aligned} I_1 &= - \int_1^{N-1} \frac{\cos^2\left(\frac{(2c-1)p\pi}{2N}\right)}{\sin^\beta\left(\frac{p\pi}{2N}\right)} e^{-t/\tau_p} dp \\ \text{and } I_2 &= \int_1^{N-1} \frac{\cos^2\left(\frac{(2c-1)p\pi}{2N}\right)}{\sin^\beta\left(\frac{p\pi}{2N}\right)} dp. \end{aligned} \quad (A8)$$

We begin with  $I_1$ . Using (9),

$$I_1 = - \int_1^{N-1} \frac{\cos^2\left(\frac{(c-1)p\pi}{N}\right)}{\sin^\beta\left(\frac{p\pi}{2N}\right)} \exp\left[-4\kappa D \sin^\beta\left(\frac{p\pi}{2N}\right)t\right] dp. \quad (\text{A9})$$

For large  $N$ , we can approximate the integral by

$$I_1 \approx - \left(\frac{2N}{\pi}\right)^\beta \int_1^{N-1} p^{-\beta} \exp\left[-4\kappa D \left(\frac{p\pi}{2N}\right)^\beta t\right] dp. \quad (\text{A10})$$

We perform a change of variables  $u = \frac{p^\beta t}{\tau_1}$  with  $\tau_1^{-1} = 4\kappa D \left(\frac{\pi}{2N}\right)^\beta$ :

$$I_1 = - \frac{1}{\beta} \left(\frac{2N}{\pi}\right)^\beta \left(\frac{t}{\tau_1}\right)^{1-\frac{1}{\beta}} \int_{\frac{t}{\tau_1}}^{(N-1)^\beta t/\tau_1} u^{\frac{1}{\beta}-1} e^{-u} du. \quad (\text{A11})$$

In the intermediate time where  $\tau_{N-1} \ll t \ll \tau_1 \approx N^\beta \tau_{N-1}$  (anomalous regime), we further approximate the integral as

$$\begin{aligned} I_1 &\approx - \frac{1}{\beta} \left(\frac{2N}{\pi}\right)^\beta \left(\frac{t}{\tau_1}\right)^{1-\frac{1}{\beta}} \int_0^\infty u^{\frac{1}{\beta}-1} e^{-u} du \\ &= - \frac{1}{\beta} \left(\frac{2N}{\pi}\right)^\beta \left(\frac{t}{\tau_1}\right)^{1-\frac{1}{\beta}} \Gamma\left(\frac{1}{\beta} - 1\right). \end{aligned} \quad (\text{A12})$$

The second integral is

$$\begin{aligned} I_2 &= \int_{p=1}^{N-1} \frac{\cos^2\left(\frac{(2c-1)p\pi}{2N}\right)}{\sin^\beta\left(\frac{p\pi}{2N}\right)} dp \\ &\approx \left(\frac{2N}{\pi}\right)^\beta \int_{p=1}^\infty p^{-\beta} dp = \frac{1}{(\beta-1)} \left(\frac{2N}{\pi}\right)^\beta. \end{aligned} \quad (\text{A13})$$

Finally, substituting Eqs. (A12) and (A13) into Eq. (A7), taking only terms of order  $\mathcal{O}(N^\beta)$  in Eqs. (A2) and (A5), and substituting all of them into Eq. (A7), we get

$$\begin{aligned} &\langle (\mathbf{R}_c(t_0 + t) - \mathbf{R}_c(t_0))^2 \rangle \\ &\approx \frac{d}{\kappa N (\beta - 1)} \left(\frac{2N}{\pi}\right)^\beta - \frac{d}{\kappa N \beta} \left(\frac{2N}{\pi}\right)^\beta \left(\frac{t}{\tau_1}\right)^{1-\frac{1}{\beta}} \Gamma\left(\frac{1}{\beta} - 1\right) + \frac{d}{\kappa N} \left(\frac{2N}{\pi}\right)^\beta \left(\frac{1}{2} + \frac{\beta}{12}\right) (1 - e^{-t/\tau_1}) + 2D_{\text{cm}}t \\ &= \frac{d}{\kappa N} \left(\frac{2N}{\pi}\right)^\beta \left[ \frac{1}{\beta - 1} + \left(\frac{1}{2} + \frac{\beta}{12}\right) (1 - e^{-t/\tau_1}) - \frac{\Gamma\left(\frac{1}{\beta} - 1\right)}{\beta} \left(\frac{t}{\tau_1}\right)^{1-\frac{1}{\beta}} \right] + \frac{2dDt}{N}. \end{aligned} \quad (\text{A14})$$

We conclude that for intermediate times ( $\tau_{N-1} \leq t \leq \tau_1$ ), the center-of-mass diffusion does not contribute to the process and thus the cross-correlation function scales with time as

$$\langle (\mathbf{R}_c(t_0 + t) - \mathbf{R}_c(t_0))^2 \rangle \propto t^{1-\frac{1}{\beta}}. \quad (\text{A15})$$

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