Editors' Suggestion

Fractal Folding and Medium Viscoelasticity Contribute Jointly to Chromosome Dynamics

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Chromosomes are key players of cell physiology, their dynamics provides valuable information about its physical organization. In both prokaryotes and eukaryotes, the short-time motion of chromosomal loci has been described with a Rouse model in a simple or viscoelastic medium. However, little emphasis has been put on the influence of the folded organization of chromosomes on the local dynamics. Clearly, stress propagation, and thus dynamics, must be affected by such organization, but a theory allowing us to extract such information from data, e.g., on two-point correlations, is lacking. Here, we describe a theoretical framework able to answer this general polymer dynamics question. We provide a scaling analysis of the stress-propagation time between two loci at a given arclength distance along the chromosomal coordinate. The results suggest a precise way to assess folding information from the dynamical coupling of chromosome segments. Additionally, we realize this framework in a specific model of a polymer whose long-range interactions are designed to make it fold in a fractal way and immersed in a medium characterized by subdiffusive fractional Langevin motion with a tunable scaling exponent. This allows us to derive explicit analytical expressions for the correlation functions.

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The dynamic reorganization of chromosomal DNA plays a fundamental role in key biological processes at the cellular level, such as transcription, replication, segregation, and recombination [1,2]. Measurements of dynamic fluctuations of chromosomes provide important evidence on the physical nature of the intracellular crowded medium comprising genome and surrounding medium (bacterial cytoplasm or eukaryotic nucleoplasm) [3–7]. Specifically, relevant information comes from tracking chromosomal loci [3,8–13]. One can try to rationalize the observed subdiffusion of tagged loci as a relaxation of Rouse modes [14,15], i.e., fluctuations of a Gaussian chain (see, e.g., Refs. [9,16].) However, the scaling exponents for monomer subdiffusion found experimentally in different species and conditions vary and typically differ from the value of 0.5 expected in a simple Rouse model.

In turn, the medium surrounding the chromosome is reported to be "viscoelastic"; i.e., tracer particles put into it show subdiffusive ergodic motion, with an anticorrelation dip in the velocity-velocity correlation function [9,17]. The physical explanation of such behavior is unclear but it might be, e.g., a consequence of crowding. The dynamics of a chromosome in such a medium has been described [17,18] by coupling the Rouse model with monomer-media interactions described by a fractional Langevin equation. This approach reproduces the data on single loci subdiffusion [17], and appears to be a natural starting point for developing predictions on the effects of stress propagation on the dynamics of multiple loci. Specifically, this approach is consistent with the available experimental evidence on subdiffusion of cytoplasmic particles [9,10], telomere motion in human cells [19], and provides an explanation for the dynamics of chromosome segregation in *E. coli* [20]. Moreover, this model leads to specific predictions for two-point time-dependent correlation functions between different loci on a same chromosome [17] separated by arclength distance s. The main feature of these correlation functions is that as the lag time increases, the dynamics of loci pairs changes from being uncorrelated to effectively behaving as a single object. This transition defines a characteristic time scale for the stress propagation between loci through the polymer backbone, allowing us to extract additional information from two-loci measurements as compared to the single-locus ones.

However, this scenario assumes an oversimplified picture of the folded state of the chromosome, which influences stress propagation. Indeed, chromosome packing typically does not follow the Rouse prediction for the static exponent [21–23] and, therefore (see, e.g., Refs. [2,24]), it is incompatible with the Rouse dynamics. While the existing

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theoretical framework [17,18] assumes that the ratio of the subdiffusive exponent of a particle in the embedding medium and a monomer unit of a polymer is 2, the available data for subdiffusive exponents of chromosomal loci and cytoplasmic or nucleoplasmic particles deviate sensibly from this ratio for *E. coli* [9,12,17], budding yeast [25,26], and mammalian cells [11]. This indicates that (i) a more flexible background where the ratio between these two exponents may be different from 2 is needed, and (ii) direct measurement of stress propagation along the chain may give more detailed information than a simple estimate of subdiffusive exponents. Several recent studies started to analyze the real-time dynamics of two fluorescently labeled loci simultaneously [27–29], but such measurements lack a theoretical basis to link the observed dynamics to their physical origins.

Chromosome packing has been described in some cases by a fractal-globule model [30–34] with fractal dimension $d = 3$ (to compare with $d = 2$ for a Rouse chain). Generally, it is possible that due to the presence of a hierarchy of loops caused by bridging and/or loop-extruding protein complexes a chromosome may effectively behave, in a certain range of scales, like a fractal with some intermediate dimension d. If it is the case, this would affect both its local dynamics and the propagation of stresses. Figure 1 illustrates how the stress propagating through the embedding medium is felt by distant regions along the DNA chain in a fashion that it is dependent on the dimension of the folded state.

In this Letter, we define a general scaling framework, taking into account both viscoelastic medium generating subdiffusion and arbitrary dimension d of a folded structure of a chromosome (we work under the simplifying assumption that the folded state is self-similar and, thus, d is fixed). We study the relative impact of these two ingredients on the stress-propagation time between loci pairs at given arclength distance. Additionally, based on a

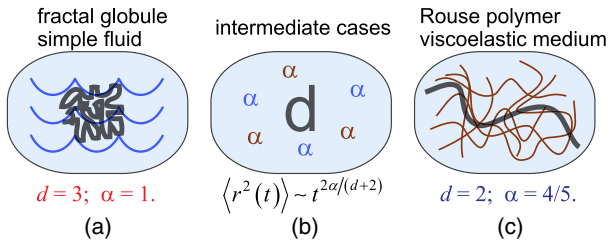

FIG. 1. Illustration of the problem. Three panels represent different scenarios for a polymer whose folded configuration has a generic fractal dimension d, immersed in a viscoelastic medium characterized by a subdiffusive exponent α. (b) The general case studied in this work. (a) Limiting case of a space-filling fractal ($d = 3$) in a simple Newtonian fluid. (c) Limiting case of an ideal polymer in a viscoelastic medium. Scaling analysis predicts a subdiffusive exponent $2\alpha/(d+2)$ for the segment mean-square displacement $r^2(t)$ in the Rouse regime. Hence, the limiting cases of parameter values illustrated by the left and right panel cannot be distinguished by tracking single segments.

mathematical model for the Gaussian self-similar polymer states [35], we derive analytically the two-loci correlation functions depending on the properties of both the medium and the packing. This calculation confirms our scaling argument and yields precise analytical estimates for the asymptotic behavior of the correlation functions. The results show how combining single-loci and two-loci tracking experiments might disentangle the contributions of medium viscoelasticity from the effects of the folded geometry of a chromosome.

Scaling considerations for the joint effects of fractal packing and viscoelasticity of the medium.—Consider a polymer chain whose configuration is described by a function $R_n(t)$, where $n \in \{0, 1, \ldots, N-1\}$ is the discrete coordinate along the chain, and assume that the steady state chain conformation is fractal, i.e.,

$$R_{nm}^2 \equiv \langle (R_n(t) - R_m(t))^2 \rangle = A s^{2/d}, \tag{1}$$

where $s \equiv |n - m|$ is the arclength distance between the loci, and d is the fractal dimension of packing (for long chains, and far from the chain ends, the prefactor A in Eq. (1) becomes m, n independent). The long-time limit of the Rouse model corresponds to ideal polymer chains with $d = 2$, while the compact fractal globule has $d = 3$. For complex bacterial and eukaryotic chromosomes, the contributions of (i) incomplete relaxation to equilibrium [36], (ii) partial collapse [32,37], (iii) looped structures due to bridging proteins and active enzymes [1,21–23,38], and (iv) branched supercoiled structure due to plectonemes [39] may result in a fractal-like organization (in a range of length scales) with d between 2 and 3. Movement of a single locus on a chain can be characterized by the mean-square displacement

$$r^2(t) \equiv \langle (R_n(t + t_0) - R_n(t_0))^2 \rangle_{t_0} \sim t^{2/z}, \tag{2}$$

where z is the dynamic exponent and the averaging is over both initial conditions and t_0. The standard line of argument [24] is to derive the connection between z and fractal dimension d for a fractal object in a simple fluid by assuming that at lag-time t, due to stress propagation, a region of spatial size $x(t) \sim t^{1/z}$ behaves as a single monomer. In the "free-draining" limit (negligible hydrodynamic interactions), the diffusion constant of this coherent region needs to depend on the number of monomers involved as $D_{\text{eff}} \sim n[x(t)]^{-1} \sim x^{-d}$. Therefore, the mean-square diplacement of the region is $D_{\text{eff}} t \sim t^{1-d/z}$, leading to $2/z = 1 - d/z$, i.e., $z = 2 + d$, the well-known result going back to de Gennes [40].

This generalized Rouse approach relies on the assumption that chromosome chain dynamics is not restrained by topological entanglements, it is not clear if it is the case in chromosomes [36,41]. A proper description of the entanglement-dominated regime needs a generalization of the reptation model [15] for polymer melts;

theories for such a reptationlike dynamics in fractal globules and ring melts have been suggested recently in Refs. [42,43].

Consider now a polymer whose monomers are embedded in a viscoelastic medium (cytoplasm or nucleoplasm), characterized by a scaling exponent $\alpha \leq 1$, so that an isolated tracer particle moves subdiffusively with mean-square displacement $r_0^2(t) \sim t^{\alpha}$. The simplest assumption might be that the effects of polymer configuration and embedding medium on the monomer mean-square displacement are factorized, i.e., $r^2(t) \sim t^{2\alpha/(2+d)}$. Consider then the movement of two monomers separated by arclength distance s. At small times their displacements are essentially independent, but starting from a typical time which we denote $t^*(s)$ they become strongly coupled. This $t^*(s)$ gives an estimate of the time required for the stress to propagate between the two monomers. It can be estimated as a time at which each monomer diffuses a distance comparable to the spatial distance between the two: $(t^*)^{\alpha/(2+d)} \sim s^{1/d}$. Hence,

$$t^* \sim s^{(2+d)/(\alpha d)}. \tag{3}$$

The time scale $t^*(s)$ is expected to be measurable from two-point correlation functions (see Fig. 2).

The assumption that the effects of medium and polymer folding can be factorized is, so far, arbitrary. The following scaling argument proves it should indeed be the case. The monomer displacement and the monomer-to-monomer distance are expected to be scale invariant until the displacement becomes of order of the spatial size of the chain. Therefore, the one-locus mean-square displacement $r^2(t)$ and the two-point correlation function, defined as

$$G(s,t) \equiv \langle [R_n(t+t_0) - R_m(t+t_0)][R_n(t_0) - R_m(t_0)] \rangle_{t_0}, \tag{4}$$

are expected to obey the standard scaling forms

$$r^2(t) = Bt^{2/z}, \qquad G(s,t) = As^{2/d}\mathcal{G}(ts^{-b}), \tag{5}$$

for the time lags $t \lesssim N^{z/d}$. These conditions imply a scaling relation between z, d, and b. Indeed, scaling hypothesis means that there exist some a such that all dimensionless quantities are invariant under the simultaneous transformation $s \to \gamma s$, $t \to \gamma^a s$. For the combination $G(s,t)/r^2(t)$ this invariance implies $2a/z - 2/d = a - b = 0$, leading to $z = bd$.

Hence, there is a single independent scaling exponent, which we can determine by a more rigorous version of the above argument [24]. Assume one can describe the viscoelasticity of the medium by the fractional Langevin equation [17,18], so that monomers obey the equation

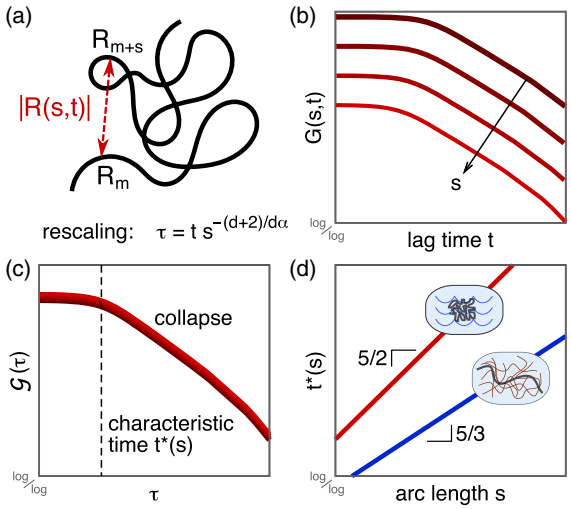

FIG. 2. Scaling predictions for monomer-monomer correlations. (a) Our calculations quantify stress propagation by the fluctuations of the physical distance between monomers at arclength distance s. (b) Sketch of the decay (in log-log scale) of the correlation function $G(s,t) = \langle [R_n(t) - R_m(t)][R_n(0) - R_m(0)] \rangle$, for different values of s. (c) Scaling analysis predicts the collapse of $G(s,t)$ on the master curve $\mathcal{G}$ upon rescaling of time by a characteristic scale $t^*(s) \sim s^{(2+d)/(\alpha d)}$. For each value of s, t^* corresponds to a fixed value of τ in this plot. (d) The characteristic time t^* is a power law in s (sketched here in log-log scale), which distinguishes the two limiting-case scenarios illustrated in Fig. 1.

$$\xi_\alpha \int_0^t dt' K_\alpha(t-t') \frac{dR_i(t')}{dt'} = F_i(t) + F_i^{\text{polym}}(t), \tag{6}$$

where ξ_α is a generalized friction constant, F_i is a random thermal force acting on the ith monomer, F_i^{polym} is a force acting on the ith monomer from the other monomers of the surrounding chain, and the memory kernel K_α is

$$K_\alpha(t) = \frac{(2-\alpha)(1-\alpha)}{t^\alpha}, \tag{7}$$

[it reduces asymptotically to the standard Brownian kernel $K_\alpha(t) \to \delta(t)$ as $\alpha \to 1$]. The fluctuation-dissipation theorem implies that thermal noise $F_i(t)$ in the right-hand side of Eq. (6) satisfies $\langle F_i(t) F_i(t') \rangle = 6k_B T \xi_\alpha K_\alpha(|t-t'|) = C_\alpha(t-t')$.

The additional ingredient that allows us, similarly to the free-draining assumption in the Rouse model, to calculate ζ and b is the assumption that thermal forces acting on different monomers are uncorrelated, $\langle F_i(t) F_j(t') \rangle = \delta_{i,j} C_\alpha(t-t')$. As a result, the effective diffusion constant for a collective motion of a group of monomers is inversely proportional to the number of monomers in the group. Indeed, the center of mass of a subchain of n monomers $R_{\text{c.m.}}(t) = n^{-1} \sum_{i=1}^{n} R_i(t)$ obeys the fractional Langevin

equation (6), where random force $F_{\mathrm{c.m.}}(t) = n^{-1}\sum_{i=1}^{n} F_i(t)$ has an amplitude $\sqrt{n}$ times smaller than the force acting on a single monomer, $\langle F_{\mathrm{c.m.}}(t)F_{\mathrm{c.m.}}(t')\rangle = n^{-1}C_\alpha(t-t')$. Therefore, at short times, when displacement of the subchain does not exceed its spatial extension and, therefore, random force dominates over the deterministic one, $F_{\mathrm{c.m.}}^{\mathrm{polym}}$, the center of mass of the subchain undergoes subdiffusion with the effective diffusion constant $D_\alpha^{\mathrm{eff}} = D_\alpha/n$. In turn, the number of monomers moving collectively by time t can be estimated as $n \sim [r(t)]^d \sim t^{d/z}$. Therefore,

$$r^2(t) \sim t^{2/z} \sim D_\alpha^{\mathrm{eff}} t^\alpha \sim (D_\alpha t^{-d/z}) t^\alpha, \tag{8}$$

thus yielding

$$z = \frac{2+d}{\alpha}; \qquad b = \frac{2+d}{\alpha d}, \tag{9}$$

which is a direct generalization of Ref. [17] for the case of a fractally packed polymer and of Ref. [24] for a viscoelastic embedding medium.

Analytical estimates of the correlation function for the beta model in a viscoelastic medium.—To provide a specific setting for these general scaling arguments, consider an analytical model for a Gaussian self-similar polymer in a viscoelastic medium, based on the "beta model" of Ref. [35]. This model is defined referring to the behavior of the Rouse modes $u_p(t)$, $p = 0 \ldots N-1$:

$$u_p(t) = \sqrt{\frac{1+\delta_{0,p}}{N}} \sum_{n=0}^{N-1} R_n(t) \cos\frac{p\pi(n-1/2)}{N}. \tag{10}$$

In the conventional Rouse model these modes satisfy a set of independent Ornstein-Uhlenbeck equations,

$$\frac{du_p}{dt} = -t_p^{-1}u_p + f_p; \qquad t_p = t_{\min}\sin^{-2}\left(\frac{\pi}{2}\frac{p}{N}\right), \tag{11}$$

where $t_{\min} = \xi a^2/12k_BT$ is the typical time needed for a monomer to diffuse by a distance equal to its own size a.

The beta model is defined formally by replacing the second power of the sine in Eq. (11) with an arbitrary power β [35]. In terms of the continuous Rouse equation [15,44] this corresponds to replacing the second derivative over the arclength coordinate by a fractional derivative of order β (see Ref. [45]). Introducing a viscoelastic medium in this model corresponds to replacing the time derivative of order one in Eq. (11) with a fractional derivative as prescribed by Eq. (6). As a result, the Rouse modes now satisfy

$$\int_0^t dt' K_\alpha(t-t')\frac{du_p(t')}{dt} = -\tilde{t}_p^{-\alpha}u_p(t) + f_p(t), \tag{12}$$

where the memory kernel $K_\alpha(t)$ is defined by Eq. (7) and

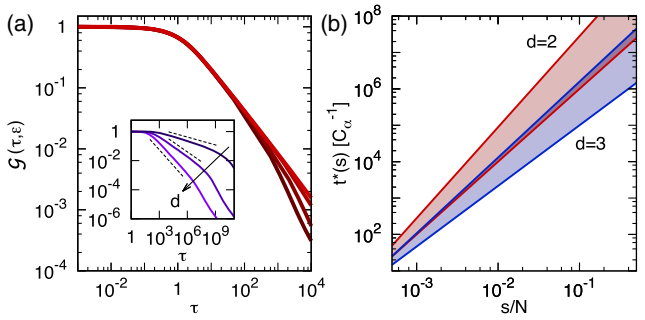

FIG. 3. Analytical predictions from the beta model in a viscoelastic medium correspond to the scaling expectations. (a) Collapse of the two-point correlation function $\mathcal{G}(\tau,\epsilon)$, given by Eq. (17) as a function of τ. The red curves refer to $d = 3$, $\alpha = 0.9$ and different values of s. Inset: change of slope of the master curve $\mathcal{G}$ with varying values of the polymer fractal dimension d ($d = 4/3, 2, 3$, increasing in the direction of the arrow) at fixed $\alpha = 0.9$. The dashed lines are the predictions of Eq. (20). (b) Scaling of $t^*(s)$ (plotted in units of C_α^{-1}) for $d = 2$ (red) and $d = 3$ (blue). The shaded areas of the two colors correspond to the empirically relevant interval, $0.8 < \alpha < 1$.

$$\tilde{t}_p = \tilde{t}_{\min}\sin^{-\beta/\alpha}\frac{p\pi}{2N}, \tag{13}$$

with $\tilde{t}_{\min}$ having the meaning of a microscopical time needed for a monomer to diffuse by its own size in the viscoelastic medium,

$$\tilde{t}_{\min} = \left(\frac{\xi_\alpha a^2}{12k_BT}\right)^{1/\alpha}, \tag{14}$$

and random force correlation function is

$$\langle f_p(t)f_{p'}(t')\rangle = 6k_BT\xi_\alpha^{-1}K_\alpha(t-t')\delta_{p,p'}. \tag{15}$$

The connection between Eq. (12) and the scaling considerations above comes from the fact that regardless of the value of the viscoelastic exponent α, the beta model converges at long times to a fractal equilibrium state with fractal dimension $d = 2/(\beta-1)$. Additionally, single-monomer displacement scales as

$$r^2(t) \sim t^{\alpha(\beta-1)/\beta}, \qquad \text{i.e., } z = \frac{2\beta}{\alpha(\beta-1)} = \frac{2+d}{\alpha}, \tag{16}$$

confirming Eq. (9).

Finally, and most importantly, the solution of Eq. (12) allows us to compute directly the asymptotics of the scaling function $\mathcal{G}(\tau)$ defined in Eq. (5) for $N \to \infty$. Additionally, this calculation can be carried out accounting for finite-chain-size corrections to the long-chain limit. Indeed (see Ref. [45]), a more general scaling function $\mathcal{G}(\tau,\epsilon)$, where $\epsilon = s/N \ll 1$, can be estimated as

$$\mathcal{G}(\tau,\epsilon)\sim\sum_{k=1}^{\infty}(-1)^{k+1}\frac{\pi^{2k}}{(2k)!}\int_{\epsilon}^{1}x^{2k-\beta}E_{\alpha}(-\tau^{\alpha}x^{\beta})dx, \quad (17)$$

where $\tau=[\Gamma(3-\alpha)]^{-1/\alpha}(t/\tilde{t}_{\min})s^{-\beta/\alpha}$ and $E_{\alpha}(x)$ is the Mittag-Leffler function,

$$E_{\alpha}(x)=\sum_{j=0}^{\infty}\frac{x^{j}}{\Gamma(1+\alpha j)}, \quad (18)$$

which reduces to a simple exponential for $\alpha=1$. Importantly, Eq. (17) goes beyond the approximation of Eq. (5), as it allows for a small but finite ϵ, while the scaling theory describes only the case of $\epsilon=0$. Integrals in Eq. (17) can be expressed in terms of the 2,2-order Wright function whose asymptotics are known [53]; this allows us to distinguish the following three regimes (see Ref. [45] for technical details):

In the short-time limit $\tau\ll 1$ one gets

$$\mathcal{G}(\tau,\epsilon)\sim 1-A\exp(-\tau^{\alpha}). \quad (19)$$

At intermediate times, $\epsilon^{-\beta/\alpha}\gg\tau\gg 1$, i.e., at times much smaller than relaxation time of the whole chain, the scaling function is ϵ independent. In this case, the correlations decay as a power law

$$\mathcal{G}(\tau,\epsilon)\sim\tau^{\alpha(1-3\beta^{-1})}\quad \text{for } 3/2\le\beta<3. \quad (20)$$

These two ϵ-independent regimes, visible in Fig. 3, are in full agreement with the scaling theory. Indeed, Eqs. (19), (20) are of the type prescribed by Eqs. (5) and (9), and the crossover at $\tau=t^{*}s^{-\beta/\alpha}\approx 1$ leads to the estimate $t^{*}\sim s^{\beta/\alpha}=s^{(d+2)/d\alpha}$ coinciding with Eq. (3).

Finally, for small but finite ϵ a third regime arises for $\tau\gg\epsilon^{-\beta/\alpha}$. It corresponds to the relaxation of the whole chain, and is akin to the behavior of single particle correlation functions in simple (for $\alpha=1$) and viscoelastic (for $\alpha<1$) medium:

$$\begin{aligned}&\mathcal{G}(\tau,\epsilon)\sim\epsilon^{1-2\beta}\tau^{-1}\exp(-\tau\epsilon^{\beta})\quad \text{for } \alpha=1,\\ &\mathcal{G}(\tau,\epsilon)\sim\epsilon^{1-2\beta}\tau^{-\alpha}\quad \text{for } \alpha<1.\end{aligned} \quad (21)$$

In conclusion, a combination of the beta model with the approach of Refs. [17,18] gives a framework for the dynamical description of both eukaryote chromatin and bacterial chromosomes [7,41,54,55], and can be generalized to the case of nonequilibrium fluctuations [56].

The suggested scenario of stress propagation generalizes the recent results [17]. We predict that joint measurement of two functions $r^{2}(t)$ and $G(s,t)$ allows us to disentangle the effects of chain organization and embedding medium. Two independent measurements of the exponents z (from single-locus MSD) and b (from two-loci correlations) allow us to reconstruct d and α:

$$d=\frac{z}{b};\qquad \alpha=\frac{2b+z}{bz}. \quad (22)$$

Importantly, one can infer α directly from the polymer dynamics, without reliance on external probe particles. Assuming average folding dimension $d\approx 2.5$ and typical viscoelastic parameter $\alpha\approx 0.78$ for bacterial cytoplasm [57], (22) gives $b\approx 2.3$ for the relaxation exponent and $2/z\approx 0.35$ for MSD of a single locus, which is in agreement with experimental observations [9]. Hopefully, direct experimental measurements of two-loci autocorrelation functions will provide a deeper insight into the mechanisms of stress propagation in chromosomes.

Our model assumes that the fractal dimension of the polymer chain d and the dynamic exponent of the medium α are constants, which, generally speaking, is not the case. Parts of chromosomes in different epigenetic states might fold and move differently, and both d and α should vary with the cell cycle. Additionally, our results are obtained under the "free-draining" assumption that the reaction of the viscoelastic medium is local in space and hydrodynamic interactions are screened. Possibly, hydrodynamic interactions play a role at some length scales, a topic of further investigation both experimentally and theoretically.

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[1] J. Dekker and L. Mirny, Cell **164**, 1110 (2016).
[2] V. Benza, B. Bassetti, K. Dorfman, V. Scolari, K. Bromek, P. Cicuta, and M. Cosentino Lagomarsino, Rep. Prog. Phys. **75**, 076602 (2012).
[3] I. Bronshtein, I. Kanter, E. Kepten, M. Lindner, S. Berezin, Y. Shav-Tal, and Y. Garini, Nucleus **7**, 27 (2016).
[4] G. Tiana, A. Amitai, T. Pollex, T. Piolot, D. Holcman, E. Heard, and L. Giorgetti, Biophys. J. **110**, 1234 (2016).
[5] A. Amitai, M. Toulouze, K. Dubrana, and D. Holcman, PLoS Comput. Biol. **11**, e1004433 (2015).
[6] M. Cosentino Lagomarsino, O. Espéli, and I. Junier, FEBS Lett. **589**, 2996 (2015).
[7] N. Kleckner, J. K. Fisher, M. Stouf, M. A. White, D. Bates, and G. Witz, Curr. Opin. Microbiol. **22**, 127 (2014).
[8] V. Levi, Q. Ruan, M. Plutz, A. S. Belmont, and E. Gratton, Biophys. J. **89**, 4275 (2005).

[9] S. C. Weber, A. J. Spakowitz, and J. A. Theriot, Phys. Rev. Lett. **104**, 238102 (2010).
[10] S. C. Weber, A. J. Spakowitz, and J. A. Theriot, Proc. Natl. Acad. Sci. U.S.A. **109**, 7338 (2012).
[11] I. Bronstein, Y. Israel, E. Kepten, S. Mai, Y. Shav-Tal, E. Barkai, and Y. Garini, Phys. Rev. Lett. **103**, 018102 (2009).
[12] A. Javer, Z. Long, E. Nugent, M. Grisi, K. Siriwatwetchakul, K. D. Dorfman, P. Cicuta, and M. Cosentino Lagomarsino, Nat. Commun. **4**, 3003 (2013).
[13] A. Javer, N. J. Kuwada, Z. Long, V. G. Benza, K. D. Dorfman, P. A. Wiggins, P. Cicuta, and M. C. Lagomarsino, Nat. Commun. **5**, 3854 (2014).
[14] P. E. Rouse, J. Chem. Phys. **21**, 1272 (1953).
[15] M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics* (Oxford University Press, New York, 1986).
[16] E. Kepten, I. Bronshtein, and Y. Garini, Phys. Rev. E **83**, 041919 (2011).
[17] T. J. Lampo, A. S. Kennard, and A. J. Spakowitz, Biophys. J. **110**, 338 (2016).
[18] S. C. Weber, J. A. Theriot, and A. J. Spakowitz, Phys. Rev. E **82**, 011913 (2010).
[19] K. Burnecki, E. Kepten, J. Janczura, I. Bronshtein, Y. Garini, and A. Weron, Biophys. J. **103**, 1839 (2012).
[20] T. J. Lampo, N. J. Kuwada, P. A. Wiggins, and A. J. Spakowitz, Biophys. J. **108**, 146 (2015).
[21] M. V. Imakaev, G. Fudenberg, and L. A. Mirny, FEBS Lett. **589**, 3031 (2015).
[22] A. Hofmann and D. W. Heermann, FEBS Lett. **589**, 2958 (2015).
[23] M. Nicodemi and A. Pombo, Curr. Opin. Cell Biol. **28**, 90 (2014).
[24] M. V. Tamm, L. I. Nazarov, A. A. Gavrilov, and A. V. Chertovich, Phys. Rev. Lett. **114**, 178102 (2015).
[25] R. Wang, J. Mozziconacci, A. Bancaud, and O. Gadal, Curr. Opin. Cell Biol. **34**, 54 (2015).
[26] H. Hajjoul, J. Mathon, H. Ranchon, I. Goiffon, J. Mozziconacci, B. Albert, P. Carrivain, J.-M. Victor, O. Gadal, K. Bystricky *et al.*, Genome Res. **23**, 1829 (2013).
[27] J. S. Lucas, Y. Zhang, O. K. Dudko, and C. Murre, Cell **158**, 339 (2014).
[28] M. P. Backlund, R. Joyner, K. Weis, and W. E. Moerner, Mol. Biol. Cell **25**, 3619 (2014).
[29] B. Petrova, S. Dehler, T. Kruitwagen, J. K. Heriche, K. Miura, and C. H. Haering, Mol. Cell. Biol. **33**, 984 (2013).
[30] A. Y. Grosberg, S. K. Nechaev, and E. I. Shakhnovich, J. Phys. USSR **49**, 2095 (1988).
[31] A. Grosberg, Y. Rabin, S. Havlin, and A. Neer, Europhys. Lett. **23**, 373 (1993).
[32] E. Lieberman-Aiden, N. L. van Berkum, L. Williams, M. Imakaev, T. Ragoczy, A. Telling, I. Amit, B. R. Lajoie, P. J. Sabo, M. O. Dorschner *et al.*, Science **326**, 289 (2009).
[33] L. A. Mirny, Chrom. Res. **19**, 37 (2011).
[34] J. D. Halverson, J. Smrek, K. Kremer, and A. Y. Grosberg, Rep. Prog. Phys. **77**, 022601 (2014).
[35] A. Amitai and D. Holcman, Phys. Rev. E **88**, 052604 (2013).
[36] A. Rosa and R. Everaers, PLoS Comput. Biol. **4**, e1000153 (2008).
[37] T. Odijk, Biophys. Chem. **73**, 23 (1998).
[38] V. F. Scolari and M. Cosentino Lagomarsino, Soft Matter **11**, 1677 (2015).
[39] F. Benedetti, J. Dorier, Y. Burnier, and A. Stasiak, Nucleic Acids Res. **42**, 2848 (2014).
[40] P. G. de Gennes, Macromolecules **9**, 587 (1976).
[41] R. Bruinsma, A. Y. Grosberg, Y. Rabin, and A. Zidovska, Biophys. J. **106**, 1871 (2014).
[42] J. Smrek and A. Y. Grosberg, J. Phys. Condens. Matter **27**, 064117 (2015).
[43] T. Ge and S. Panyukov, and M. Rubinstein, Macromolecules **49**, 708 (2016).
[44] A. Grosberg and A. Khokhlov, *Statistical Physics of Macromolecules* (AIP Press, Woodbury, NY, 1994).
[45] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.120.088101 for the details of the calculations concerning the beta model, which includes Refs. [46–52].
[46] M. Rubinstein and R. Colby, *Polymer Physics* (Oxford University Press, Oxford, UK, 2003).
[47] I. Bahar, A. R. Atilgan, and B. Erman, Folding Des. **2**, 173 (1997).
[48] T. Haliloglu, I. Bahar, and B. Erman, Phys. Rev. Lett. **79**, 3090 (1997).
[49] R. D. Groot and P. B. Warren, J. Chem. Phys. **107**, 4423 (1997).
[50] R. Metzler and J. Klafter, Phys. Rep. **339**, 1 (2000).
[51] S. G. Samko, A. A. Kilbas, and O. I. Marichev, *Functional Integrals and Derivatives: Theory and Applications* (Gordon and Breach, Yverdon, 1993).
[52] W. Deng and E. Barkai, Phys. Rev. E **79**, 011112 (2009).
[53] R. B. Paris, Eur. J. Pure Appl. Math. **3**, 1006 (2010).
[54] A. Zidovska, D. A. Weitz, and T. J. Mitchison, Proc. Natl. Acad. Sci. U.S.A. **110**, 15555 (2013).
[55] T. Pederson, M. C. King, and J. F. Marko, Mol. Biol. Cell **26**, 3915 (2015).
[56] H. Vandebroek and C. Vanderzande, Phys. Rev. E **92**, 060601 (2015).
[57] I. Golding and E. C. Cox, Phys. Rev. Lett. **96**, 098102 (2006).