Anomalous Diffusion in Fractal Globules

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(Received 6 June 2014; revised manuscript received 22 November 2014; published 30 April 2015)

The fractal globule state is a popular model for describing chromatin packing in eukaryotic nuclei. Here we provide a scaling theory and dissipative particle dynamics computer simulation for the thermal motion of monomers in the fractal globule state. Simulations starting from different entanglement-free initial states show good convergence which provides evidence supporting the existence of a unique metastable fractal globule state. We show monomer motion in this state to be subdiffusive described by \( \langle X(t)^2 \rangle \sim t^{\alpha_F} \) with \( \alpha_F \) close to 0.4. This result is in good agreement with existing experimental data on the chromatin dynamics, which makes an additional argument in support of the fractal globule model of chromatin packing.

DOI: 10.1103/PhysRevLett.114.178102 PACS numbers: 87.15.H-, 05.40.Fb, 87.15.ap, 87.15.Vv

The question of how genetic material is packed inside a eukaryotic nucleus is one of the most challenging in contemporary molecular biology. This packing, apart from being very compact, has some striking biological properties including the existence of distinct chromosome territories, easy unentanglement of chromosomes and chromosome parts (needed in preparation to mitosis, and during transcription), and the ability of different parts of the genome to find each other in space strikingly fast in, e.g., so-called promoter-enhancer interactions. All these properties are very untypical for the compact states of generic synthetic polymers (known as the equilibrium globular state in classical polymer physics; see, e.g., [1,2]). Indeed, e.g., human chromatin fiber (that is to say, a composite polymer fiber consisting of dsDNA and associated histone proteins [3]) is so long that an equilibrium polymer globule made of it would be too entangled to perform any biological functions on any reasonable time scale [4].

The theories proposed to explain the chromatin packing tend to either be based on some ad hoc biological mechanism of stabilization [5–10] or argue that topological interactions prevent the chromatin chain from entangling itself on biological time scales [4,11–13]. The latter point of view relies on the analogy between the chromatin state and other topologically governed polymer states, such as fractal (crumpled) globules [11,14–16], and melts of non-concatenated polymer rings [17–21]. In recent years, the data obtained via novel experimental techniques to study genome structure, in particular FISH [22] and Hi-C [12,23,24] methods, seem to provide data supporting the topological fractal globule approach.

For the detailed overview of the state of the field we direct the reader to a recent review [25]; here we provide a brief summary of those presumed static properties of chromatin packing which we use in what follows. First, the fractal globule model assumes that chromatin fiber forms a compact fractal state with dimensionality 3; i.e., on all length scales the typical spatial distance \( R \) between monomers depends on genomic distance \( n \) between them as \( R \sim n^{1/d_f} = n^{1/3} \). Second, there are no entanglements in the fractal globule contrary to the equilibrium one. Because of that, parts of chromatin can easily fold out from the fractal globule conformation and form extended loops, and then retract back to refill into the dense state. Third, the fractal globule has a distinct territorial organization: parts of the genome close to each other along the chromosome are close to each other in space as well. These properties are dictated by the absence of knots on the chromatin chains and topological entanglements between them and are, therefore, shared between linear polymers in the unentangled state and non-concatenated unknotted rings; the difference is that while for rings the described fractal state is equilibrium, for linear chains it is but metastable, although it is supposed to be relatively long-lived. The question of how to prepare a fractal state with long-living stable properties is still a matter of debate, many different algorithms to prepare a fractal globule in computer simulations have been suggested [12,26–30], most of them appear to be evolving in time rather rapidly when the simulation starts. Here we use two different algorithms to prepare initial fractal states, then anneal them for some time before starting measurements. The observed convergence of the results obtained from two different initial states suggests that there indeed exists a unique metastable fractal globule state corresponding to a partial equilibrium of the polymer chain given the absence of topological entanglements.

Dynamics of a fractal globule state, which is a focus of this Letter, has been less studied so far. Clearly, self-diffusion in the fractal globule should be faster than in the equilibrium one due to the absence of entanglements [31]. Sometimes [26,32] the Rouse dynamics of the fractal state is assumed in order to estimate the relaxation times of the chain as a whole, while explicit measurements (e.g.,
computer simulations of nonconcatenated rings [33], experiments on the dynamics of unknotted ring bacterium genomes [34] and on the telomeres in the nuclei [35–37] suggest a slower than Rouse dynamics. Indeed, the discrepancy from Rouse theory is to be expected since it relies heavily on the absence of interactions between monomers that are not immediate neighbors along the chain [1], and cannot be directly applied to the fractal globule which is actually stabilized by this interaction. Recently, a theoretical approach to generalize the Rouse model to produce different scaling exponents was suggested [38], but without any discussion of what particular exponent one should choose in a physically relevant situation [39]. In what follows, we present a scaling theory and computer simulations of the self-diffusion in a fractal globule state resulting in a subdiffusive motion with an exponent similar to one observed experimentally in [34–37]).

We start with the Rouse model, which is the simplest model of the dynamics of an unentangled polymer. In the continuous limit the conformation of the Rouse chain \( X(s,t) \) (here \( X \) is the spatial coordinate, \( s \) is a coordinate along the chain, and \( t \) is time) satisfies the equation \([1,2]\)

\[
\frac{\partial X(s,t)}{\partial t} = \lambda \frac{\partial^2 X(s,t)}{\partial s^2} + \xi(s,t),
\]

where \( \lambda \) is some coefficient, \( \xi \) is the white thermal noise delta-correlated in space and time. This equation has a stationary solution, which is a Gaussian measure over all trajectories \( X(s,t) \). In what follows we restrict ourselves to discussing very long chains (or, equivalently, relatively short times), which makes the boundary conditions coupled to Eq. (1) irrelevant for internal monomers.

Equation (1) neglects any interactions between monomers not immediately adjacent along the chain, and, therefore, it cannot be directly applied to non-Gaussian equilibrium or metastable states of a polymer chain, which are stabilized by volume interactions. Many different generalizations of Eq. (1) are possible, e.g., by introducing fractional derivatives [38,43] or by introducing correlations into the noise term [44]. It is not clear which particular generalization is most valid microscopically for the fractal globule, so instead of modifying Eq. (1) we rely below on a more general scaling argument. Proceeding this way we lose the detailed information about the statistics of the monomer self-diffusion, but are able at least to recover the scaling exponent of the self-diffusion.

For the Rouse model the scaling argument goes as follows. Let \( x(s,t) \) be a stationary solution of Eq. (1). Then for any given time \( t \) and two positions along the chain \( s_1, s_2 \),

\[
\langle [x(s_1,t) - x(s_2,t)]^2 \rangle \sim |s_1 - s_2|^{\alpha_R},
\]

where triangular brackets correspond to averaging over stationary solutions of Eq. (1). Assume now that as time goes on the monomer displacement grows as

\[
\langle [x(s,t + \tau) - x(s,t)]^2 \rangle \sim (\tau)^\alpha,
\]

with some unknown \( \alpha \). Since the chain is connected and Eq. (2) holds at any given time, parts of the chain of length \( \delta s(\tau) = |s_1 - s_2| \sim (\tau)^{\alpha_R} \) are obliged to move collectively at a time scale \( \tau \). Moreover, if all monomers in this chain fragment experience independent random forces from the solvent, the collective effective diffusion constant of such a fragment is

\[
D(\delta s) \sim D_0/\delta s = D_0 \tau^{-\alpha},
\]

where \( D_0 \) is a microscopic diffusion constant [45]. Combining Eqs. (3) and (4) one recovers the well-known result

\[
\langle [x(s,t + \tau) - x(s,t)]^2 \rangle \sim (\tau)^\alpha \sim D(\delta s)\tau \sim \tau^{1-\alpha};
\]

\[
\alpha_R = 1/2,
\]

where we introduced notation \( \alpha_R \) for the scaling exponent of the Rouse model.

This scaling reasoning is much easier to generalize for the fractal globule case than Eq. (1) itself. Indeed, the principal change is the statistic of the state we consider (recall that we are only considering time scales much shorter than chain entanglement time, so we assume that the fractal globule state can be treated as stationary). This corresponds to replacing Eq. (2) with

\[
\langle [x(s_1,t) - x(s_2,t)]^2 \rangle \sim |s_1 - s_2|^{d_f/df};
\]

where \( d_f \) is a fractal dimensionality of the state under consideration, \( d_f = 3 \) for a fractal globule. The chain connectivity argument still holds, and the size of a collectively moving domain scales now as \( \delta s(\tau) \sim (\tau)^{d_f/2} \). If the random forces acting on monomers are still independent, the resulting scaling exponent of a fractal globule \( \alpha_f \) is

\[
\langle [x(s,t + \tau) - x(s,t)]^2 \rangle \sim (\tau)^\alpha \sim D_0 \frac{\delta s}{\delta s} \tau \sim \tau^{1-d_f/2};
\]

\[
\alpha_f = \frac{2}{2 + d_f} = 2/5.
\]
time and length scales the entanglements play a crucial role and the scaling theory [2] predicts $\alpha_{\text{ent}} = 1/4$.

To check the predictions of the scaling theory we held out extensive computer simulations using the dissipative particle dynamics (DPD) technique, which is known [64,65] to correctly reflect dynamics of dense polymer systems. The polymer model we use consists of renormalized monomers with the size of order of the chromatin persistence length, corresponding DPD time step is of order 1 nsec or more (see Ref. [47] for more details). Volume interactions between the monomers are chosen to guarantee the absence of chain self-intersections, the entanglement length is $N_e \approx 50 \pm 5$ monomer units [66]. The modeled chains have $N = 2^{18} = 262,144$ units confined in a cubic volume with periodic boundary conditions. In a chain that is long ($N/N_e \approx 5000$) the equilibration time by far exceeds the times accessible in computer simulation, so the choice of starting configurations plays a significant role. Here we provide a short outline of how we construct and prepare the initial states, addressing the reader to [47] for further details.

The first initial state we use is a randomized Moore curve similar to that described in Ref. [26], it has a very distinct domain structure with flat domain walls. The second initial state is generated by a mechanism which we call “conformation-dependent polymerization in poor solvent.” This algorithm, which, for the best of our knowledge, has never been suggested before, is constructing the chain conformation by consecutively adding monomer units in a way that they tend strongly to stick to the already existing part of the chain. In Ref. [47] we show that the resulting conformations show exactly the statistical characteristics expected from fractal globules, while a full account of this new algorithm will be given in Ref. [30]. In what follows, for brevity we call the globule prepared by the randomized Moore algorithm “Moore,” and one prepared by the conformation-dependent polymerization “random fractal.” As a control sample we use a standard equilibrium globule which we call “Gaussian.”

Prior to the diffusion measurements all three initial states are annealed for $t = 3.2 \times 10^7$ modeling steps. The statistical properties of the random fractal and Gaussian globule do not change visibly during the annealing time, while the Moore globule is evolving with domain walls roughening and its statistical characteristics (e.g., dependence of the spatial distance between monomers on the genomic distance $\langle R^2(n)\rangle$; see [47]) approaching those for the random fractal globule state.

Snapshots of conformations annealed from different initial states are shown in Fig. 1. In fractal states, contrary to the Gaussian one, fragments close along the chain tend to form domains of the same color. The states are further characterized in Fig. 2. The fractal globule curve appears very similar (but for the saturation at large $n$ due to the finite size effects) to the universal spatial size-length curve for unentangled rings discussed in Refs. [20,68]. $R^2(n)$ for the Moore state seems to approach the fractal globule curve with growing modeling time suggesting the existence of a unique metastable fractal globule state. Fractal globules prepared by two different techniques are significantly different at first, but converge with growing simulation time, making the results obtained after annealing insensitive to the details of the initial state.

Monomer spatial displacement was measured for $t = 6.5 \times 10^7$ DPD time steps after the annealing (corresponding to $\sim 0.1$ sec on the real time scale), with results shown in Fig. 3. Impressively, mean-square displacement for the
random fractal and Moore initial states is indistinguishable within the measurement error. As expected, it is slower than in the Gaussian state: the observed scaling exponent for Gaussian globule $\alpha_G$ is fairly close to $\alpha_{\text{ent}} = 1/4$ predicted by the reptation model, while for the fractal globule one gets $\alpha_F \approx 0.38$, which clearly is above $\alpha_{\text{ent}} = 1/4$ and below the Rouse exponent $\alpha_R = 1/2$, fairly close to our theoretical prediction $\alpha_F = 0.4 - 0.42$. Both our simulations and results known from the literature for computer simulation [33,69] and experiment [34–37] of similar unknotted polymer systems give scaling exponents similar but slightly below our theoretical estimate. We expect this discrepancy between theory and simulation to be due primarily to the fluctuation effects. We also examined the distributions of monomer displacements at various times for all three initial states [47]. For both fractal states the monomer displacement distributions stay Gaussian at all times despite the mean-square displacement growing subdiffusively, a behavior typical for fractional Brownian motion [43]. In turn, distribution of monomer displacements in the equilibrium globule shows visible deviations from the normal distribution.

FIG. 3 (color online). Average mean-square displacements of monomer units as a function of time. Globules starting from random fractal (red circles), Moore (blue triangles), and Gaussian (green squares) initial conformations. Note that the blue dots get almost completely covered by the red ones.

The ability of different parts of chromatin to find each other may be crucial for fast regulation of gene expression. As a by-product of our simulation we provide evidence that the long-living metastable fractal globule state is unique and has characteristics similar to the equilibrium state of nonconcatenated polymer rings.

The authors are grateful to V. Avetisov, A. Grosberg, M. Imakaev, S. N. Majumdar, R. Metzler, A. Mironov, S. Nechaev, E. Kepten, A. Semenov, K. Sneppen, and R. Voituriez for many illuminating discussions on the subject of this work. This work is partially supported by the IRSES project FP7-PEOPLE-2010-IRSES 269139 DCP-PhysBio, the RFBR Grant No. 14-03-00825, and the Skolkovo Institute of Science and technology via SkolTech/MSU Joint Laboratory Agreement 081-R.

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[1] P.-G. de Gennes, Scaling Concepts in Polymer Physics (Cornell University Press, New York, 1979).
[2] A. Yu. Grosberg and A. R. Khokhlov, Statistical Physics of Macromolecules (AIP Press, New York, 1994).
[3] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, Molecular Biology of the Cell, 5th ed. (Garland Science, New York, 2008).
[4] A. Rosa and R. Everaers, PLoS Comput. Biol. 4, e1000153 (2008).
[5] R. K. Sachs, G. van der Engh, B. Trask, H. Yokota, and J. E. Hearst, Proc. Natl. Acad. Sci. U.S.A. 92, 2710 (1995).
[6] C. Münkel and J. Langowski, Phys. Rev. E 57, 5888 (1998).
[7] J. Ostashevsky, Mol. Biol. Cell 9, 3031 (1998).
[8] J. Mateos-Langerak et al., Proc. Natl. Acad. Sci. U.S.A. 106, 3812 (2009).
[9] B. V. S. Iyer and G. Arya, Phys. Rev. E 86, 011911 (2012).
[10] M. Barbieri, M. Chotalia, J. Fraser, L.-M. Lavitas, J. Dostie, A. Pombo, and M. Nicodemi, Proc. Natl. Acad. Sci. U.S.A. 109, 16173 (2012).
[11] A. Y. Grosberg, Y. Rabin, S. Havlin, and A. Neer, Europhys. Lett. 23, 373 (1993).
[12] E. Lieberman-Aiden et al., Science 326, 289 (2009).
[13] L. A. Mirny, Chromosome research : an international Journal on the molecular, supramolecular and evolutionary aspects of chromosome biology 19, 37 (2011).
[14] A. Yu. Grosberg, S. K. Nechaev, and E. I. Shakhnovich, J. Phys. 49, 2095 (1988).
[15] S. K. Nechaev, A. Yu. Grosberg, and A. M. Vershik, J. Phys. A 29, 2411 (1996).
I. Bronstein, Y. Israel, E. Kepten, S. Mai, Y. Shav-Tal, E. J. D. Halverson, G. S. Grest, A. Y. Grosberg, and K. Kremer, Phys. Rev. E 85, 021806 (2012).

J. D. Halverson, G. S. Grest, A. Y. Grosberg, and K. Kremer, Phys. Rev. Lett. 108, 038301 (2012).

A. Yu. Grosberg, Soft Matter 10, 560 (2014).

Fluorescence in situ Hybridization (FISH): Protocols and Applications, edited by J. Bridger and E. Volpi (Humana Press Inc., Totowa, NJ, 2010), Vol. 659.

J. Dekker, K. Rippe, M. Dekker, and N. Kleckner, Science 295, 1306 (2002).

N. Naumova, M. Imakaev, G. Fudenberg, Y. Zhan, B. R. Lajoie, L. A. Mirny, and J. Dekker, Science 342, 948 (2013).

J. D. Halverson, J. Smrek, K. Kremer, and A. Yu. Grosberg, Rep. Prog. Phys. 77, 022601 (2014).

R. D. Schram, G. T. Barkema, and H. Schiessel, J. Chem. Phys. 138, 224901 (2013).

A. Rosa and R. Everaers, Phys. Rev. Lett. 112, 118302 (2014).

J. Smrek and A. Yu. Grosberg, Physica (Amsterdam) 392A, 6375 (2013).

A. Chertovich and P. Kos, J. Chem. Phys. 141, 134903 (2014).

L. Nazarov, M. Imakaev, S. Nechaev, and M. Tamm (to be published).

J. D. Halverson, W. B. Lee, G. S. Grest, A. Y. Grosberg, and K. Kremer, J. Chem. Phys. 134, 204905 (2011).

M. Imakaev and L. Mirny, Book of Abstracts of the Moscow Conference on Computational Molecular Biology, 141 (2011).

J. D. Halverson, W. B. Lee, G. S. Grest, A. Yu. Grosberg, and K. Kremer, J. Chem. Phys. 134, 204904 (2011).

A. Javer, Z. Long, E. Nugent, M. Grisi, K. Siritwatwetchakul, K. D. Dorfman, P. Cicuta, and M. Cosentino Lagomarsino, Nat. Commun. 4, 3003 (2013).

I. Bronstein, Y. Israel, E. Kepten, S. Mai, Y. Shav-Tal, E. Barkai, and Y. Garini, Phys. Rev. Lett. 103, 018102 (2009).

K. Burnecki, E. Kepten, J. Janczura, I. Bronstein, Y. Garini, and A. Weron, Biophys. J. 103, 1839 (2012).

E. Kepten, I. Bronstein, and Y. Garini, Phys. Rev. E 87, 052713 (2013).

A. Amitai and D. Holcman, Phys. Rev. E 88, 052604 (2013).

Note also papers [40,41] where different but related questions of the probe particle diffusion in a chromatin matrix is investigated. When this Letter was already submitted for publication we became aware of the paper [42] where fractal globule dynamics is addressed. The results of Ref. [42] are substantially different from ours (they predict a scaling exponent $\alpha_{F}\approx 0.26$), we believe that their result is due to a mistake in identifying all possible elementary movements of a chain.

C. C. Fritsch and J. Langowski, J. Chem. Phys. 133, 025101 (2010).

C. C. Fritsch and J. Langowski, Chromosome research : an international Journal on the molecular, supramolecular and evolutionary aspects of chromosome biology 19, 63 (2011).

J. Smrek and A. Yu. Grosberg, J. Phys. Condens. Matter 27, 064117 (2015).