

Crumpled globule formation during collapse of a long flexible and semiflexible polymer in poor solvent

A. Chertovich and P. Kos

Citation: *The Journal of Chemical Physics* **141**, 134903 (2014); doi: 10.1063/1.4896701

View online: <http://dx.doi.org/10.1063/1.4896701>

View Table of Contents: <http://scitation.aip.org/content/aip/journal/jcp/141/13?ver=pdfcov>

Published by the [AIP Publishing](#)

Articles you may be interested in

[Effect of hydrodynamic correlations on the dynamics of polymers in dilute solution](#)

J. Chem. Phys. **138**, 144902 (2013); 10.1063/1.4799877

[Effect of confinement on the collapsing mechanism of a flexible polymer chain](#)

J. Chem. Phys. **133**, 174904 (2010); 10.1063/1.3495479

[Cospectral polymers: Differentiation via semiflexibility](#)

J. Chem. Phys. **133**, 154905 (2010); 10.1063/1.3505147

[Simulating the collapse transition of a two-dimensional semiflexible lattice polymer](#)

J. Chem. Phys. **128**, 124905 (2008); 10.1063/1.2842064

[Interfacial properties of the mixture of flexible and semiflexible polymers](#)

AIP Conf. Proc. **574**, 252 (2001); 10.1063/1.1386847

PEROVSKITES

2014 Special Topics

2D MATERIALS

MESOPOROUS MATERIALS

BIOMATERIALS/
BIOELECTRONICS

METAL-ORGANIC
FRAMEWORK
MATERIALS

 **APL Materials**

Submit Today!

Crumpled globule formation during collapse of a long flexible and semiflexible polymer in poor solvent

A. Chertovich^{a)} and P. Kos^{b)}

Physics Department, Lomonosov Moscow State University, Moscow 119991, Russia

(Received 22 June 2014; accepted 17 September 2014; published online 2 October 2014)

By introducing explicit solvent particles and hydrodynamic interactions we demonstrate that crumpled globules are formed after the collapse of long polymer chains ($N = 10^4$) in a poor solvent. During the collapse crumples of all sizes form sequentially, but small crumples are not stable and convert to blobs with Gaussian statistics. The observed effective mean squared distance $R^2(n) \sim n^{0.38}$ at $n > N_e$ and contact probability index $p(n) \sim n^{-0.5}$ at $n \gg N_e$, which is not following either the model of a fractal globule, or the predictions for an equilibrium globule. Polymer chain stiffness pushes the system to form globular crystallite, and this freezes crumpled structure with $R^2(n) \sim n^{0.33}$ at $n > N_e$ as a stable state. We note that there is some similarity to crumple globule formation and crystallization of polymer melt. © 2014 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4896701>]

I. INTRODUCTION

In 1980s, the existence of chromosome territories was discovered and later confirmed by the development of the fluorescence *in situ* hybridization (FISH) technique.¹ Later in 1988, the first paper proposed crumpled globule structure and its connection to the organization of long biological molecules like DNA.² But in recent years this topic has become the subject of great interest because of the genome-wide chromosome conformation capture (Hi-C) method³ and consequent deeper understanding of chromatin organization inside the cell nuclei. In this paper, we will try to stay away from the biologists' results of nuclei organization and will not mimic the complexity of chromatin folding. Instead, we will focus on physics of long polymer chains, namely, their collapse to globule in a poor solvent. A polymer physicist's view of DNA conformation inside the living cell has stayed the same since the prediction of crumpled globule structure was done:^{4–6} double stranded DNA inside the cell nuclei is definitely not in the state of an equilibrium Gaussian globule conformation, which is random walk trajectory in confined geometry, but has to be in a crumpled or fractal globule state, which is more compact at small scale and knot-free.

While the general principles of long polymer chain “crumpling” are more-or-less understandable, there is still no clear observation of crumpled globule formation from single polymer chains in lab experiments or in computer simulations. The only result concerning the fractal globule formation obtained in computer simulations deals with Monte Carlo moves and artificial gravitation-like potential,⁵ excluding solvent particles and nature of segments pair interactions. Many other papers present simulations of polymer chains in more realistic conditions, several relevant examples are Refs. 7–10. In Ref. 11 and later in Ref. 12, the transition

from homopolymer coil with very short range interactions to crystal-like solid globule was studied, and some analogue of protein folding was discussed. But in all these cases sufficiently short chains were used and no clear crumpled structure or blobs hierarchy was presented. Moreover, in a recent paper by Schram *et al.*,¹³ the collapse of a homopolymer of $N = 4000$ was studied by Monte Carlo simulations and it was stated out that no fractal globule could be formed during the collapse. The conformation of the globule was very close to Gaussian statistics even immediately after the collapse. In addition, the stability of artificially constructed fractal globules was tested, and it was shown that fractal globules diffused very quickly into Gaussian-like globules. It was proposed that this is the feature of fast entanglement-free dynamics.

Several results from lab experiments, starting from Ref. 14 and later in Refs. 15 and 16, report the two-stage collapse of a synthetic single chain in a poor solvent. Unfortunately, the applied experimental technique of light scattering gives information only about objects size and density, which generally does not allow to describe chain conformations in details and to distinguish crumpled globule state. More probably the authors observed the merging of several initially formed pearls into a single globule rather than transformation of the globule after the united core was formed.

In addition to fully flexible chains, the so-called freely joined model, we study the collapse of long semiflexible chains by introducing the tangent hard spheres model. Beginning from the pioneer paper by Grosberg and Khokhlov,¹⁷ several researchers have addressed the question of coil-to-globule transition and globule structure formed by semiflexible polymer chains, see Refs. 10, 18, and 19 as recent examples of simulation. More details can be found in a recent review in Ref. 20 and the links therein. But most studies were focused on relatively short chains and authors inquired mainly in conformational changes like coil-to-torus transition, mimicking observation of torus and other non-trivial formations in a single strand DNA.²⁰ We

^{a)}chertov@polly.phys.msu.ru

^{b)}kos@physics.msu.ru

consider here the question of coil-to-globule transition of very long semiflexible chains with strong polymer-solvent interactions. Thus, the chain stiffness serves only as a small additional force, not changing the coil-to-globule transition by itself, but with the influence to the condensed globule's behavior.

In parallel to the coil-to-globule transition of single macromolecules, several theoretic and simulation papers address the properties of the so-called “melt of rings,” mimicking the organizational properties of chromatin matter.^{21,22} There is a significant increase in publications on that topic during this year.^{23–25} This is a well known model of polymer physics without topological limitations^{26,27} and the some physical behavior of such a system is naturally corresponds with experimental data from the research of chromatin structure.⁶

Nowadays, the so-called fractal globule model is the dominant model of the organization of chromatin in the nucleus of a human cell.³ Following Refs. 2 and 5 let us outline the most important properties of the fractal globule model. First of all, fractal globule is indeed a fractal with fractal dimensionality equal to 3. That is, on all length scales the typical spatial distance R between monomers is proportional to the distance along the chain n between them as $R \sim n^{1/3}$. Second, the probability p for two monomers within the distance n along the chain to be in spatial proximity of each other is in inverse proportion to n : $p \sim 1/n$.

In this case, we shall deliberately use the term *crumpled* and not *fractal* for our simulated globules, although we recognize that term “fractal globule” is more frequent in the recent literature. The reason is that the term “fractal” supposes a similarity of globule conformation on all length scales, and as mentioned above predicts the straightforward behavior of mean squared distance $R^2(n)$ and contact probability $p(n)$ at all n values. But our results do not support this picture and we only observe some features of crumpled conformation at large scales. Furthermore, the term “crumpled” looks more relevant from the historical point of view, since it was introduced in the pioneer paper by Grosberg *et al.*² In this work, we are going to show what globular structure can be formed during collapse of a long chain and what are the differences of our crumpled globules from model of the fractal globule.

While initial computer simulations test the formation of the crumpled globule by introducing the collapse into gravitational center,⁵ the later work in Ref. 13 does not predict the existence stable crumpled structure during the coil-to-globule transition with pair interactions and implicit solvent. We show that a crumpled globule exists only during the collapse of very long chains in a very poor solvent. In addition, we use the model with explicit solvent particles and correct hydrodynamic interactions (so-called DPD – Dissipative Particle Dynamics).²⁸ We believe that the usage of explicit solvent and hydrodynamic interactions is very important and a key to find crumpled globule after the collapse. Sommer *et al.* recently presented the results of the coil-to-globule transition with explicit solvent particles³¹ and have shown that only explicit solvent allows to simulate polymer behavior in a very poor solvent.

II. MODEL AND SIMULATION TECHNIQUE

DPD is a version of coarse-grained molecular dynamics adapted to polymers and mapped onto the classical lattice Flory-Huggins theory.^{32–35} Macromolecules represented in terms of the bead-and-spring model, with particles interacting by a conservative force (repulsion), a dissipative force (friction), and a random force (heat generator). The soft repulsive potential enhances the stability of the numerical scheme for integrating the equations of motion and makes it possible to increase a time step and thus allowing to work with large timescales when complex polymeric structures are studied. It was shown that such a model sufficiently describes the dynamics of polymer melts.^{29,30} Consider an ensemble of particles (beads) obeying Newton's equations of motion

$$\begin{aligned} \frac{dr_i}{dt} &= v_i; & m_i \frac{dv_i}{dt} &= f_i, \\ f_i &= \sum_{i \neq j} (F_{ij}^b + F_{ij}^c + F_{ij}^d + F_{ij}^r), \end{aligned} \quad (1)$$

where r_i , m_i , v_i are the coordinate, mass, and velocity of an i th bead, respectively, f_i is the force acting upon it. The summation is performed over all other beads within the cut-off radius r_c . We shall assume below that all quantities entering Eq. (1) are dimensionless and for simplicity set r_c and m_i for any i to unity. The first two terms in the sum are conservative forces.

F_{ij}^b is a spring force describing chain connectivity of beads

$$F_{ij}^b = -K(r_{ij} - r_0), \quad (2)$$

where K is a bond stiffness and r_0 is unperturbed bond length. If beads i and j are not connected, then $F_{ij}^b = 0$.

F_{ij}^c is a soft core repulsion between the i th and j th beads

$$F_{ij}^c = \begin{cases} a_{ij}(1 - r_{ij}), & r_{ij} \leq 1 \\ 0, & r_{ij} > 1 \end{cases}, \quad (3)$$

where a_{ij} is a maximum repulsion between beads i and j attained at $r_{ij} = 0$. Since F_{ij}^c is linear and has no singularity at small distances, a much larger time step than in the standard molecular dynamics can be used.

Other constituents of f_i are a random force F_{ij}^r and a dissipative force F_{ij}^d acting as a heat source and medium friction, respectively, they are taken as dictated by the Groot-Warren thermostat.³⁵ More detailed description of our simulation methodology can be found in Ref. 36.

It was shown that the DPD method is consistent with both the scaling theory of polymers (e.g., it gives correct relationships between the average radius of gyration of a coil and the number of units in the coil) and the Rouse dynamics.^{37,38}

The use of soft volume and bond potentials leads to the fact that the bonds within one chain are formally “phantom,” i.e., capable of intersecting in three dimensions. The phantom nature of chains does not affect the equilibrium properties (for example, the chain gyration radius or the phase behavior of the system); moreover, it greatly speeds up the equilibration of the system. However, if studying dynamic properties, such as the diffusion coefficient or features that require explicit consideration of the presence of entanglements between

chains it is necessary to introduce some additional forces that forbid the intersection of the bonds. These forces are usually quite cumbersome and considerably slow the computation. Nikunen *et al.*⁴⁰ described a method for turning chains nonphantom in DPD without introducing any additional conditions. Although the particles in DPD are formally point-like, they have an effective excluded volume radius r_{min} due to the presence of repulsive potential at any nonzero value of a_{ij} . Similarly, the existence of a bond potential causes the bond to have a maximum possible length l_{max} . The proposed methodology is based on geometrical considerations: the condition of self-avoiding chains is $\sqrt{2}r_{min} > l_{max}$. In our study, we set $a_{ii} = 150$, $r_0 = 0.5$, and $k = 150$. We checked the intersection of $\sqrt{2}r_{ij}$ and l_{bond} histograms, calculated over all monomer units at different regimes of collapse and found that our chain's segments never crossing each other.

In addition, we tested the case of stiff chain: $a_{ii} = 75$, $r_0 = 0$, and $k = 150$. The only difference appeared to be that the neighboring beads along the chain are located much closer to each other, and thus the additional repulsive interactions between i and $i \pm 1, 2, \dots$ units provide effective chain stiffness, with similarity to the so-called tangent hard spheres model.³⁹ In this case, the chain segments remain nonphantom, too. The resulting chain's persistent length was about 10 monomer units, which is shown in Figure 2(b) below. The other parameters are: DPD number density $\rho = 3$; noise parameter $\sigma = 3$; integration time step $\Delta t = 0.04$. The chain contour length is equal to approx. 6000 for the flexible chain and 3400 for semiflexible one (in DPD units).

In this study, we used rather long chains with $N = 10^4$ monomer units. To best of our knowledge, this is the longest single chain in solvent whose coil-to-globule transition was ever simulated in the literature. The initial conformation was a Gaussian coil, prepared by simple random walk in the simulation box. At starting time $t = 0$, the repulsion between polymer particle and solvent particle becomes $\Delta a = 30$ and the collapse begins. The corresponding Flory-Huggins parameter of polymer-solvent interaction could be calculated using

the common expression $\chi_{ij} = 0.306 * \Delta a_{ij}$ from the work in Ref. 35 and occurs to be $\chi_{PS} \approx 9$. It should be noted here, that we run simulations with smaller $N = 10^3$ and smaller $\Delta a = 10$ and 20, but no clear evidence of stable crumple globule was observed for these parameters. To run the simulations, we used a self-made domain-decomposition parallelized DPD code and performed simulations on the MSU supercomputer facilities.⁴¹ The simulation box was $48 \times 48 \times 48$ DPD units and the periodic boundary conditions were switched on. The maximum time we reached is 2×10^6 DPD steps, which is at least 100 times more than the coil-to-globule collapse time in our experiment.

To characterize the conformations during the collapse, we calculated squared spatial distance between two monomer units versus chemical distance along the chain $R^2(n)$ and contact probability of two monomer units to be at a contact in a space $p(n)$. The value $R^2(n)$ was calculated up to $n = N/2 = 5000$, and averaged by sliding window over all chain segments. In this paper, we present the plots obtained in one collapse run, but we ran a set of independent tests and in all runs the $R^2(n)$ and $p(n)$ curves looked very similar. We believe that such a long chain of $N = 10^4$ units allows us to have good self-averaging characteristics with respects of the properties which are calculated via sliding window approach.

III. RESULTS

Figure 1 shows the representative time set of chain conformations during the collapse from coil to globule. These are the real snapshots from our simulations, but time and space scale between different conformations are not fixed. Note that the semiflexible chain in the initial coil looks more "sparse" because of chain stiffness and there is clear formation of united crystallite in the final globular state. The transition to the globule state may be described through the well-known formation of connected pearls and its condensation into the united globule afterwards.^{10,42} Similar structures

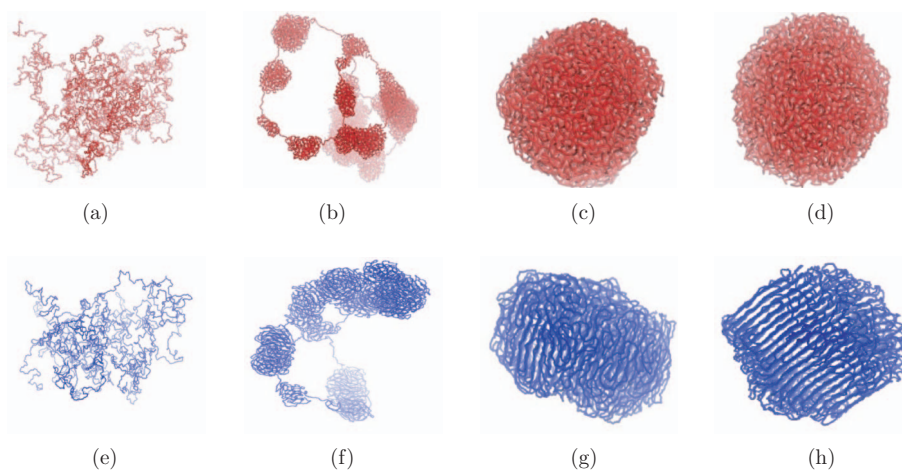


FIG. 1. Snapshot illustration of collapse scheme for flexible (Figures 1(a)–1(d)) and semiflexible (Figures 1(e)–1(h)) chains. $N = 10^4$, $\chi = 9$, overall simulation time (from first to last snapshot) is 2×10^6 DPD steps. (a) Random coil, $R \sim N^{1/2}$, (b) connected pearls, $R \sim N^{1/2}$, (c) crumpled globule, $R \sim N^{1/3}$, (d) equilibrium globule, $R \sim N^{1/3}$, (e) random coil, $R \sim N^{1/2}$, (f) connected pearls, $R \sim N^{1/2}$, (g) crumpled globule, $R \sim N^{1/3}$, (h) equilibrium globule, $R \sim N^{1/3}$.

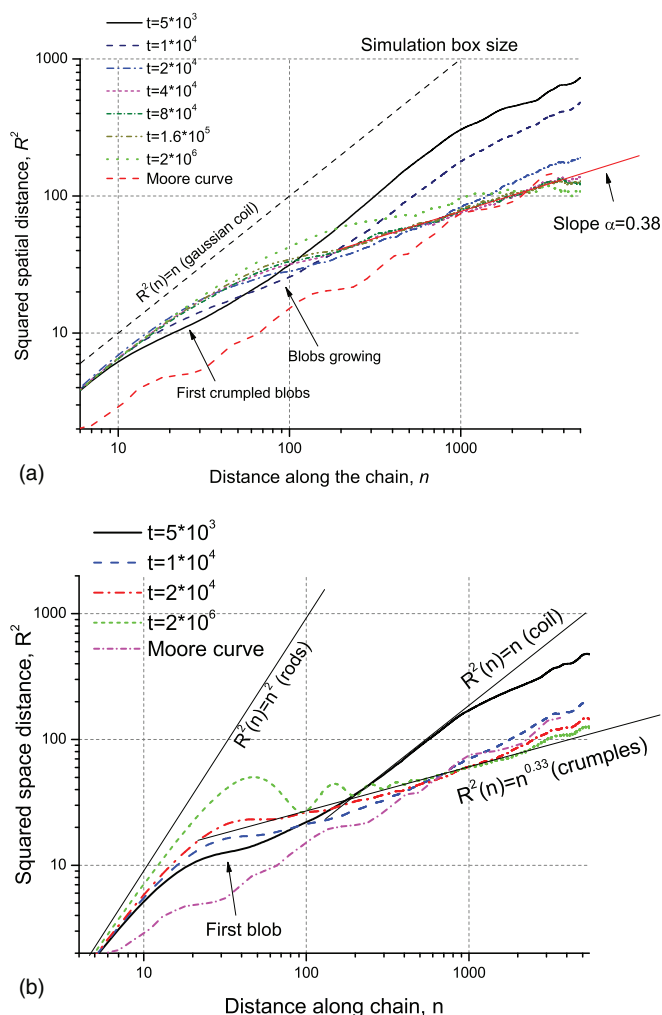


FIG. 2. Time set of mean squared distance versus distance along the chain for flexible (a) and semiflexible (b) chain. The lower curve goes the more compact conformation of the corresponding segment size has.

observed during the polyelectrolyte collapse, see Ref. 43 as an example of simulation study and the review in Ref. 44 for more information. The main difference is that our pearls are all different in size and are randomly arranged along a chain, while in the case of polyelectrolytes the pearls are roughly regular in size and space. Moreover, the pearls are not thermodynamically stable in our case, while there is more or less stable number of pearls in case of polyelectrolytes in a poor solvent.

The easiest way to distinguish a crumpled (or fractal) globule from an equilibrium globule is to observe the scaling of squared spatial distance versus chemical distance $R^2(n) \sim n^\alpha$: for a fractal globule $\alpha = 2/3$ and for a Gaussian globule $\alpha = 1$ at $n < N_e^{2/3}$ and $\alpha = \text{const}$ at $n > N_e^{2/3}$. Figure 2 presents a set of $R^2(n)$ curves at different times throughout the collapse. In addition, we add the so-called Moore curve to that plot, which is an example from a class of recursively defined Hilbert space-filling curves and appears to be the simplest realization of a fractal globule model having $\alpha = 2/3$. We constructed this curve in a similar way as it was done in Ref. 13. The physical meaning of this plot is very simple: the smaller

the spatial distance at particular range of n is, the more compact and crumpled conformation of the corresponding chain segment is.

There is first observation of crumpled blobs formation at times as short as $t = 5 \times 10^3$, with blob size of 20–40 monomer units. At this time moment chain segments longer than 50 monomer units do not feel the collapse yet, and overall chain conformation remains coil conformation with $R^2(n) \sim n$ at $n > 50$. Some deviation from this slope at $n > 1000$ is caused by finite simulation box. When we double the collapse time and examine $R^2(n)$ at $t = 1 \times 10^4$, we observe the growth of the size of crumpled blobs, up to 100 monomer units, while at larger scales the chain still preserves scaling similar to the Gaussian coil. It is noticeable that at this time initially formed small crumpled blobs of 20–40 monomer units start to relax into more Gaussian-like conformation. That is: $R^2(n < 50)$ at $t = 5 \times 10^3$ is always smaller than $R^2(n < 50)$ at $t = 1 \times 10^4$. Most probably there are two mechanisms behind this process: diffusional relaxation of the blob's crumpled conformation to the equilibrated Gaussian conformation and the increase of pearl volume. The increase of pearl size results in more friendly surrounding of a particular crumpled blob and enables it to spread into larger volume.

At larger times we observe increase of crumpled blobs size, crumpled structure gradually occupies the whole chain. At times $2 \times 10^4 < t < 1.6 \times 10^5$ there is clear evidence of compact crumpled structures at $n > 200$ units. It results in the effective slope $\alpha \approx 0.38$. At the same moment segments shorter than 50 units have Gaussian-like conformation with α close to 1.0. The value $n = 50$ corresponds well to entanglement length $N_e = 50 \pm 5$ which was measured independently for melt of Gaussian chains and our set of parameters. We used the methodology described in Ref. 45 to calculate N_e in a melt of chains with length $N = 300$. This N_e value corresponds to the so-called s-coil definition of N_e in the equilibrium melt. $R(n) \sim n$ at $n < 50$ indicates a fast relaxation of unentangled short segments till the moment they meet entanglements. Within the intermediate region $50 < n < 200$ there is some additional flat area, which could be attributed to the equilibration inside previously formed blobs and formation of a set of small Gaussian globules inside a large crumpled globule.

We believe that the main feature of our crumpled state is the Gaussian statistics at small scales. Thus, at larger scales the chain conformation looks even more compact than the fractal globule model: $R^2(n) \sim n^\alpha \sim n^{0.38}$ at $n > N_e$ has the slope much smaller than $\alpha \approx 0.66$ predicted by fractal globule model. We note here, that in fact there is no detailed experimental data on $R^2(n)$ behavior in the literature, available FISH experiments do not provide such information with necessary accuracy.⁴⁶ Thus, we believe that our crumpled globule is more relevant to the chromatin organization inside the cell nuclei than idealized fractal globule model.

During further increase of the simulation time we observe smooth transition to the Gaussian-like globule: longer and longer segments gradually transform to Gaussian conformations. Transformation from crumpled into Gaussian structure means segments expansion. This is expressed in the increase of their end-to-end distance and corresponding increase of

$R(n)$ function. The same behavior has been recently observed by Schram *et al.*¹³ when they studied relaxation of artificially constructed fractal globule by means of Monte Carlo simulation. Since chain crossing is not allowed in our model, the natural equilibration time of such a long chain is inaccessible long, longer than $N^3 = 10^{12}$ steps. Thus, there is no hope to reach this value and we claim that we can reach only preliminary “diffusion equilibration” of the globule, far away from real topology-equilibrated state with knots and slope $\alpha = 1.0$ up to $n = N^{2/3} \approx 460$ units.

In addition to fully flexible chain, we have studied semiflexible chain with the same polymer-solvent interactions and the same chain length. Figure 2(b) presents a set of $R^2(n)$ curves for several time moments during the collapse. At initial phase of the collapse one can see similarity to flexible chain behavior, with crumpled blobs formation and growing. The only difference is the slope for the short segments: $R^2(n) \sim n^2$ at $n < 10$. This is the effect of chain stiffness and such slope is natural for short rod-like segments. After the united globule is formed at time $t = 2 \times 10^4$ and the relaxation in condensed phase begins, chain stiffness starts to play the main role. Because of the chain stiffness segments are favorable to form liquid-crystal phase inside the dense globule. Thus, $R^2(n)$ curve finally shows nice oscillations with the period about 100 monomer units. This period corresponds well to the observed size of crystalline globule in Figure 1(h).

There is no relaxation of such crystalline globule to Gaussian-like conformations at larger timescales. The $R^2(n)$ scaling is close to $\alpha \approx 0.33$. This value is twice smaller than the value proposed for fractal globule model, and it is stable up to maximum available time $t = 2 \times 10^6$. Such crystalline globule cannot be called metastable crumpled globule, but it is stable single crystallite. Nevertheless, the nature of polymer chain crumples and the nature of crystallite folds are similar and the main feature of compactness of chain conformations at large scales remains valid. Several years ago Strobl⁴⁷ spec-

ulated that the growth of polymer crystallites included an intermediate metastable phase. According to his idea the crystalline nucleation phenomena and long-living structures in the melt affect a lot the crystallization process. Our study of semiflexible chains collapse partly supports this view, although we deal with single chain crystallization. The metastable crumpled globule state is the corresponding long-living structure in our interpretation. The crystallite structure during the crystallization of long polymer chains (in bulk or from solution) should exhibit some properties of crumpled conformations, similar to studied in this paper.

Finally, Figure 3(a) compares the contact probability $p(n)$ for flexible and semiflexible chains. $P(n)$ was calculated as normalized number of close contacts during relatively short time period after the collapse ($2 \times 10^4 < t < 1 \times 10^5$). Note that fluctuations are significant for probabilities $p < 10^{-3}$. This indicates that contact probability is not well self-averaged by single conformation, in contrast to mean squared distance $R^2(n)$. For flexible chain, one can see that there are two distinct asymptotes. At $n < 10$ contact probability scales as $n^{-3/2}$, which is similar to equilibrium globule properties and much lower than the fractal globule model prediction $p(n) \sim n^{-1}$. At $n > 1000$ there is power scaling with the slope close to -0.5 , which is much larger than the slope for the fractal globule model. There is a smooth crossover between these two regimes, and we believe that this transition is connected with the entanglement length N_e and transition from Gaussian blob at small scale ($n < N_e$) to crumpled blobs at large scale ($n > N_e$). Black solid line is for the eyes guide and displays the mentioned asymptotes. These asymptotes intersect in a very close vicinity of N_e . Schematic picture in Figure 3(b) gives the interpretation of our crumpled globule structure. At a large scale of the whole globule, the conformation is crumpled. At the intermediate scaling around N_e value, the conformation consists of many superimposed blobs. At small scales (smaller than N_e), these blobs have Gaussian conformations. We believe that such overlay of several soft and low-density

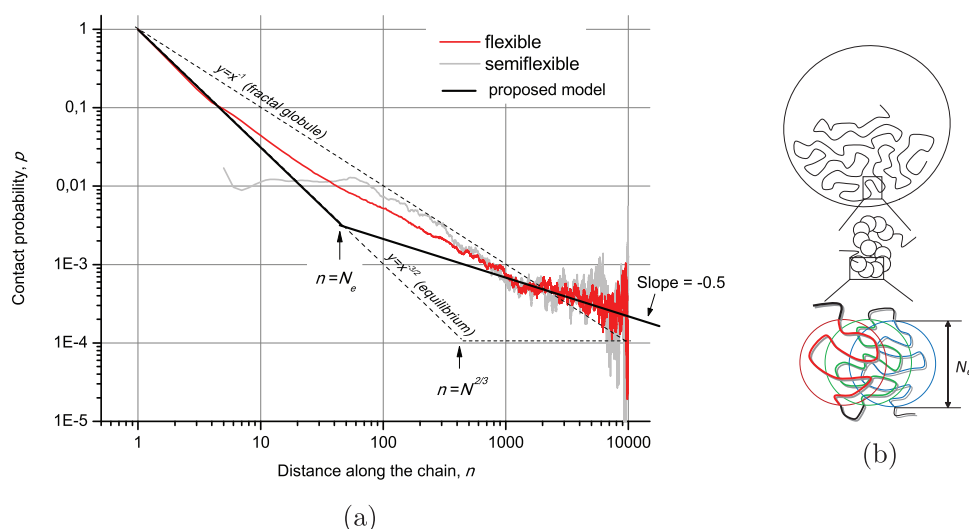


FIG. 3. Contact probability $p(n)$ for flexible and semiflexible chains (a). Dashed lines show the predictions for equilibrium and fractal globules, black solid line indicates proposed model behavior for crumpled globule. Schematic picture (b) displays the proposed hierarchy of blobs conformations and explains the increased contact probability of superimposed blobs.

blobs at intermediate scales gives the observed decrease of contact probability slope.

Recently, similar $p(n)$ behavior has been found in mitotic chromosomes.⁴⁸ Mitotic chromosomes are observed inside the cells which are prepared for division and whose chromatin is more compact in comparison with general metaphase state. The authors have proposed a special model of a compressed array by consecutive loops of phantom chain. Afterwards authors have fit the loop size to catch scaling law observed in experiments. Our results show that scaling -0.5 occurs automatically at large scales during simple collapse of a nonphantom chain in a poor solvent.

The contact probability for semiflexible chains differs dramatically from the case of flexible chain. In small n values, there is a plateau, indicating that there are rod-like conformations at $n < 100$. This is in a good agreement with periodicity observed in Figure 2(b) and gives us the crystallite size in monomer units. But later on we observe scaling which is very close to the fractal globule model, i.e., $p(n) \sim 1/n$. At very large n , there are strong fluctuations and actually no clear slope can be selected, but region $100 < n < 1000$ clearly demonstrates the fractal globule properties. We believe that the main reason of this is the following: crystallite folds are very dense and nonfluctuating objects, thus there is no overlapping or superimposing of the blobs in semiflexible chain.

IV. DISCUSSION AND CONCLUSIONS

We demonstrate here that metastable crumpled globules are indeed formed during the collapse of long polymer chains in a poor solvent. For this purpose, the solvent has to be sufficiently poor ($\chi_{PS} > 2$) and chain length has to be sufficiently long ($N \gg N_e$). Resulting crumpled globule is stable in relatively wide time interval and has significant differences from the model of fractal globule. The main difference is that short segments have Gaussian conformations, while at larger scale segments are crumpled, see Figure 3(b) as an illustration of the proposed crumpled globule structure. The physical explanation of such structure formation is that during the collapse crumpled blobs are formed at all length scales, but small blobs are very unstable and transform fast to Gaussian-like conformations. It happens with the segments with length up to $n \approx N_e$, where N_e value corresponds to entanglement length for a melt of Gaussian chains. Longer segments have relaxation restrictions caused by entanglements. This gives the effective mean squared distance $R^2(n) \sim n^{0.38}$ at $n > N_e$, for a given chain length of $N = 10^4$, which is much smaller than the $R^2(n) = n^{0.66}$ for the model of fractal globule.

In general, the $R(n)$ behavior is N -sensitive: it is governed by Gaussian statistics at $n < N_e$ and overall globule size $R \approx N^{1/3}$. This allows us to estimate the effective scaling $R^2(n) \sim n^\alpha$ of crumpled region as $\alpha = \frac{\lg N^{2/3} - \lg N_e}{\lg N - \lg N_e}$ at $n > N_e$, which gives $\alpha \approx 0.4$ in our case ($N = 10^4$ and $N_e = 50$). In the limit $N \rightarrow \infty$, this formula is consistent with fractal globule model and gives $R^2(n) \sim n^{2/3}$ at $n > N_e$. But let us consider more realistic values of DNA length in chromosome which is $\approx 10^8$ base pairs. In addition, we suppose that this DNA is

organized into chromatin filament with $\approx 10^2$ base pairs in a repeat unit.⁴⁹ Thus, the relevant chain length for DNA in a living cell is $N \approx 10^6$ in terms of our model. This gives $\alpha \approx 0.5$, which is already remarkably smaller than the fractal globule model value $\alpha = 0.66$.

Another interesting speculation can be done if we look accurately on Figure 3 at the region of $n > 1000$. We can see that the contact probability in that region is larger than that for the fractal globule model. This means that starting from the distance $n \approx 1000$ the i th and j th units have greater probability to meet each other in comparison with fractal globule model. The value $n = 1000$ monomer units in our model corresponds to $\approx 10^6$ in DNA base pairs, which correlates very well with the average distance of 1 Mbs = 10^6 base pairs between enhancer and promoter in the DNA.¹ Thus, the crumpled globule structure described in this paper probably is the natural way to increase the contact probability of enhancer and promoter and this is one of the ways to provide fast gene transcription in a living organism.

In case of some additional processes inside the globule, such as the liquid-crystallization process caused by chain stiffness, the crumpled structure at $n > N_e$ is stable and never transforms to Gaussian-like conformations. The contact probability for such crystalline globule $p(n) \sim 1/n$, which is well consistent with the fractal globule model. Mean squared distance scales as $R^2(n) \sim n^2$ at $n < N_e$ and $R^2(n) \sim n^{0.33}$ at $n > N_e$.

The globule size $R(N) \sim N^{1/3} \approx 21$ is considerably smaller than $N_e = 50$. Thus, the rod-like segments traverse the whole globule and we observe only single crystallite, rather than a set of several crystallites. Probably in larger system the crystallite size will be limited by N_e value, while the conformational movements at $n > N_e$ are kinetically suppressed by the entanglements. But the chain length should be at least 10 times larger to study this subject. We note here, that there is some analogy with single chain crumpling and polymer crystallization: both processes deal with formation of non-equilibrium, but kinetically stable states. Moreover, the crumpling itself is the formation of chain folds, which is in some sense the same as polymer crystallization.

ACKNOWLEDGMENTS

The authors are grateful to Alexey Gavrilov for providing the computational code and methodology help, Leonid Nazarov for calculations of Moore curve, MSU supercomputer center for processor time, Sergei Nechaev, Michael Tamm, and Viktor Ivanov for fruitful discussions during the paper preparation. This work is partially supported by the RFBR Grant No. 14-03-00825.

¹T. Cremer and C. Cremer, *Nat. Rev. Genet.* **2**, 292 (2001).

²A. Yu. Grosberg, S. K. Nechaev, and E. I. Shakhnovich, *J. Phys.* **49**, 2095 (1988).

³E. Lieberman-Aiden, N. L. van Berkum *et al.*, *Science* **326**, 289 (2009).

⁴A. Y. Grosberg, Y. Rabin, S. Havlin, and A. Neer, *Europhys. Lett.* **23**, 373 (1993).

⁵L. A. Mirny, *Chromosome Res.* **19**, 37 (2011).

⁶J. D. Halverson, J. Smrek, K. Kremer, and A. Y. Grosberg, *Rep. Prog. Phys.* **77**, 022601 (2014).

⁷G. E. Crooks, B. Ostrovsky, and Y. Bar-Yam, *Phys. Rev. E* **60**, 4559 (1999).

- ⁸A. N. Rissanou, S. H. Anastasiadis, and I. A. Bitsanis, *J. Polym. Sci. Part B: Polym. Phys.* **44**, 3651 (2006).
- ⁹J. Guo, H. Liang, and Z. G. Wnag, *J. Chem. Phys.* **134**, 244904 (2011).
- ¹⁰A. Lappala and E. M. Terentjev, *Macromolecules* **46**, 1239 (2013).
- ¹¹M. P. Taylor, W. Paul, and K. Binder, *Phys. Proc.* **4**, 151 (2010).
- ¹²S. Ruzicka, D. Quigley, and M. P. Allen, *Phys. Chem. Chem. Phys.* **14**, 6044 (2012).
- ¹³R. D. Schram, G. T. Barkema, and H. Schiessel, *J. Chem. Phys.* **138**, 224901 (2013).
- ¹⁴B. Chu, Q. Ying, and A. Yu. Grosberg, *Macromolecules* **28**, 180 (1995).
- ¹⁵J. Xu, Z. Y. Zhu, S. Z. Luo *et al.*, *Phys. Rev. Lett.* **96**, 027802 (2006).
- ¹⁶Y. Xiaodong, L. Yijie, S. Lei *et al.*, *Macromolecules* **40**, 4750 (2007).
- ¹⁷A. Yu. Grosberg and A. R. Khokhlov, *Adv. Polym. Sci.* **41**, 53 (1981).
- ¹⁸J. A. Martemyanova, M. R. Stukan, V. A. Ivanov *et al.*, *J. Chem. Phys.* **122**, 174907 (2005).
- ¹⁹B. Schnurr, F. Gittes, and F. C. MacKintosh, *Phys. Rev. E* **65**, 061904 (2002).
- ²⁰V. A. Ivanov, J. A. Martemyanova, A. S. Rodionova, and M. R. Stukan, *Polym. Sci. Ser. C*; **55**, 4 (2013).
- ²¹T. Sakaue, *Phys. Rev. Lett.* **106**, 167802 (2011).
- ²²J. D. Halverson, W. B. Lee, G. S. Grest *et al.*, *J. Chem. Phys.* **134**, 204904 (2011).
- ²³A. Yu. Grosberg, *Soft Matter* **10**, 560 (2014).
- ²⁴A. Rosa and R. Everaers, *Phys. Rev. Lett.* **112**, 118302 (2014).
- ²⁵M. Imakaev, K. Tchourine, S. Nechaev, and L. Mirny, e-print [arXiv:1404.0763](https://arxiv.org/abs/1404.0763).
- ²⁶M. E. Cates and J. M. Deutsch, *J. Phys.* **47**, 2121 (1986).
- ²⁷D. Gersappe and M. O. de la Cruz, *Phys. Rev. Lett.* **70**, 461 (1993).
- ²⁸M. V. Tamm, L. I. Nazarov, A. A. Gavrilov, and A. V. Chertovich, e-print [arXiv:1404.2558](https://arxiv.org/abs/1404.2558).
- ²⁹T. Soddemann, B. Dünweg, and K. Kremer, *Phys. Rev. E* **68**, 046702 (2003).
- ³⁰J. Farago, H. Meyer, and A. N. Semenov, *Phys. Rev. Lett.* **107**, 178301 (2011).
- ³¹C. Jentzsch, M. Werner, and J.-U. Sommer, *J. Chem. Phys.* **138**, 094902 (2013).
- ³²P. J. Hoogerbrugge and J. M. V. A. Koelman, *Europhys. Lett.* **19**, 155 (1992).
- ³³A. G. Schlijper, P. J. Hoogerbrugge, and C. W. Manke, *J. Rheol.* **39**, 567 (1995).
- ³⁴P. Espanol and P. B. Warren, *Europhys. Lett.* **30**, 191 (1995).
- ³⁵R. D. Groot and P. B. Warren, *J. Chem. Phys.* **107**, 4423 (1997).
- ³⁶A. A. Gavrilov, Ya. V. Kudryavtsev, and A. V. Chertovich, *J. Chem. Phys.* **139**, 224901 (2013).
- ³⁷N. A. Spenley, *Europhys. Lett.* **49**, 534 (2000).
- ³⁸F. Lahmar and B. Rousseau, *Polymer* **48**, 3584 (2007).
- ³⁹C. Vega, C. McBride, and L. G. MacDowell, *J. Chem. Phys.* **115**, 4203 (2001).
- ⁴⁰P. Nikunen, I. Vattulainen, and M. Karttunen, *Phys. Rev. E* **75**, 036713 (2007).
- ⁴¹Cluster “Lomonosov,” Intel Xeon X5570/X5670 processors and peak performance of 1.7 PFlops, MSU Supercomputer center, see <http://hpc.msu.ru/>.
- ⁴²C. F. Abrams, N. K. Lee, and S. P. Obukhov, *Europhys. Lett.* **59**, 391 (2002).
- ⁴³H. J. Limbach, C. Holm, and K. Kremer, *Europhys. Lett.* **60**, 566 (2002).
- ⁴⁴A. V. Dobrynin and M. Rubinstein, *Prog. Polym. Sci.* **30**, 1049 (2005).
- ⁴⁵A. Karatrantos, N. Clarke, R. J. Composto, and K. I. Winey, *Soft Matter* **9**, 3877 (2013).
- ⁴⁶M. Emanuel, N. H. Radja, A. Henriksson *et al.*, *Phys. Biol.* **6**, 025008 (2009).
- ⁴⁷G. Strobl, *Rev. Mod. Phys.* **81**, 1287 (2009).
- ⁴⁸N. Naumova, M. Imakaev, G. Fudenberg *et al.*, *Science* **342**, 948 (2013).
- ⁴⁹H. Wong, J.-M. Victor, and J. Mozziconacci, *PLoS ONE* **2**, e877 (2007).