

Effects of Macromolecular Crowding on the Collapse of Biopolymers

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Experiments show that macromolecular crowding modestly reduces the size of intrinsically disordered proteins even at a volume fraction (ϕ) similar to that in the cytosol, whereas DNA undergoes a coil-to-globule transition at very small ϕ . We show using a combination of scaling arguments and simulations that the polymer size $\bar{R}_g(\phi)$ depends on $x = \bar{R}_g(0)/D$, where D is the ϕ -dependent distance between the crowders. If $x \lesssim \mathcal{O}(1)$, there is only a small decrease in $\bar{R}_g(\phi)$ as ϕ increases. When $x \gg \mathcal{O}(1)$, a cooperative coil-to-globule transition is induced. Our theory quantitatively explains a number of experiments.

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The importance of crowding in biology is gaining increasing appreciation because of the realization that cellular processes occur in a dense medium containing a polydisperse mixture of macromolecules. A number of studies have been performed to understand the role crowding particles play in inducing structural transitions in disordered chiral homopolymers [1,2], protein [3–5] and RNA folding [6–8], gene regulation through DNA looping [9], and genome compaction [10]. Some of the consequences of crowding can be qualitatively explained using the depletion interaction introduced by Asakura and Oosawa (AO) [11]. In the AO picture, the crowding particles, treated as hard objects, vacate the interstitial space in the interior of the macromolecule to maximize their entropy. As a result, an osmotic pressure due to crowders reduces the size of the macromolecule.

The predictions based on the AO theory rationalize the impact of crowding effects on synthetic and biological polymers qualitatively provided that only excluded volume interactions between the crowding particles and the macromolecules dominate. Even in this limit two questions of particular importance for experiments on biopolymers require scrutiny. (i) What is the extent of crowding-induced compaction in finite-sized polymer coils? These systems are minimal models for unfolded and intrinsically disordered proteins (IDPs), and in some limits (the random loop model) also provide a useful caricature of chromosome folding. (ii) For polymers with N monomers, what is the dependence of the average radius of gyration, $\bar{R}_g(\phi)$ [$\equiv \langle R_g^2(\phi) \rangle^{1/2}$], as a function of the volume fraction ϕ and the size of the crowders? It is important to answer these questions quantitatively to resolve the seemingly contradictory conclusions reached in recent experiments.

Here, we answer these questions using a combination of scaling arguments and computer simulations. The two length scales that determine the degree of polymer compaction in solution, with crowding particles interacting with each other and the polymer via hard repulsions, are $\bar{R}_g(0)$ (the size of the coil at $\phi = 0$), and the average distance, D , between the crowders. We propose a scaling relation to predict the dependence of $\bar{R}_g(\phi)$ on ϕ based on the expectation that when $D \lesssim \bar{R}_g(0)$, the osmotic pressure acting on the polymeric chain should reduce the polymer size. If correlations between the crowding particles are negligible, as explicitly shown here using simulations for ϕ as large as 0.4, the maximum ϕ in the cytosol, then a scaling ansatz would suggest $\bar{R}_g(\phi) = \bar{R}_g(0)f(x)$, where $f(x)$ is a function of the dimensionless variable $x = \bar{R}_g(0)/D$. For a given ϕ , $D \approx (4\pi/3)^{1/3}\sigma_c\phi^{-1/3}$, where σ_c is the radius of a spherical crowding particle and thus $x = (3/4\pi)^{1/3}\lambda\phi^{1/3}$, where $\lambda \equiv \bar{R}_g(0)/\sigma_c$. The form of $f(x)$ is difficult to calculate because of correlations in the fluidlike crowding particles [12]. Nevertheless, we anticipate distinct scenarios in two limits of x . (i) When $x \sim \mathcal{O}(1)$ [$D \sim \bar{R}_g(0)$], compaction of the coil should occur without altering the chain statistics, $\bar{R}_g(\phi) = l_\phi N^{3/5} \sim \bar{R}_g(0) = l_0 N^{3/5}$, where $l_0(l_\phi)$ are the Kuhn lengths in the absence (presence) of crowding particles; thus $f(x) \sim \mathcal{O}(1)$, implying that $\bar{R}_g(\phi)$ should depend weakly on ϕ . (ii) In contrast, when $x \gg \mathcal{O}(1)$ [$D \ll \bar{R}_g(0)$], we expect osmotic pressure to induce the collapse of the polymer coil to a globule so that $\bar{R}_g(\phi) \sim N^{1/3}$. These arguments suggest that the value of x controls the polymer size ($N \gg 1$) in a crowded environment where only the excluded volume interactions are relevant.

With the two scenarios, expressed in terms of $\bar{R}_g(0)$ and D as a guide, we performed Langevin simulations in explicitly modeled spherical crowding particles with varying sizes, σ_c , and for a range of ϕ . Despite considerable efforts to predict the effects of crowders on polymer size [13–17], it is difficult to accurately include the crucial effects of multiparticle correlations among crowding particles or a strong correlation of monomers in a polymer chain (stiff or flexible) using phenomenological analytic theories [12,18–20] or microscopic formalism [21]. To this end, we used a bead-spring model for the polymer and soft-sphere potentials to model interactions between the explicitly modeled crowder and the beads on the polymer [22]. Because of interactions among polymer segments and crowders, the effects of semiflexibility and the polyelectrolyte nature of the polymer are important on the local scale $\lesssim l_p$ (persistence length) [26]. However, in the length scale of our interest ($\gg l_p$), the self-avoiding bead-spring model suffices to capture the global characteristics of DNA. In this model, local interactions can be accommodated by a renormalization of the strength of the volume exclusion. Indeed, such models have been used to gain insights into chromosome folding [27]. Two variations of the random coils, one for IDPs and the other for DNA, are used to cover a range of x values.

When exploring compaction due to large crowders [$\lambda \sim \mathcal{O}(1)$], if $D \sim \bar{R}_g(0)$, there ought to be only a modest reduction in the polymer size because the statistics of the

polymer conformations [as assessed by the distribution of $R_g(\phi), P[R_g(\phi)]$] are essentially unchanged. The reduction in $\bar{R}_g(\phi)$ becomes greater with increasing λ [Fig. 1(a)]. However, the extent of compaction is only on the order of 5%–8% for $\lambda < 2.0$ [Fig. 1(a)]. At $\lambda = 3.8$, as ϕ increases from 0 to 0.4, $P[R_g(\phi)]$ clearly show a gradual shift towards smaller values of R_g [Fig. 1(b)]. The $R_g(\phi)$ distributions, plotted in terms of $t = R_g(\phi)/\bar{R}_g(\phi)$ for varying λ values, collapse onto a single universal curve [Fig. 1(c)], corresponding to that of a self-avoiding polymer [28,29]:

$$P(t) = \mathcal{N} e^{-(bt)^{-15/4} - (bt)^{5/2}}, \quad (1)$$

where b and \mathcal{N} are the parameters [22]. The radial distribution functions (RDFs) of crowders from the center of the polymer [30] [Fig. 1(d)] show that the crowders are depleted from the space occupied by the polymers. A snapshot of the simulation [Fig. 1(a), inset] shows that when $D \sim \bar{R}_g$, the polymer chain retains its shape, with only modest compaction in the space between the crowders.

We next examine the coil-globule transition due to small sized crowders ($\lambda \gg 1$). When the size of the crowders is decreased there is a dramatic effect on the polymer size if $\phi > \phi_c$, where ϕ_c is a critical volume fraction for the coil-globule transition. Figure 2(a) shows the $\bar{R}_g(\phi)$ of a self-avoiding walk (SAW) polymer with $N = 50$ for a minimal model of chromosome folding with crowders [10], which

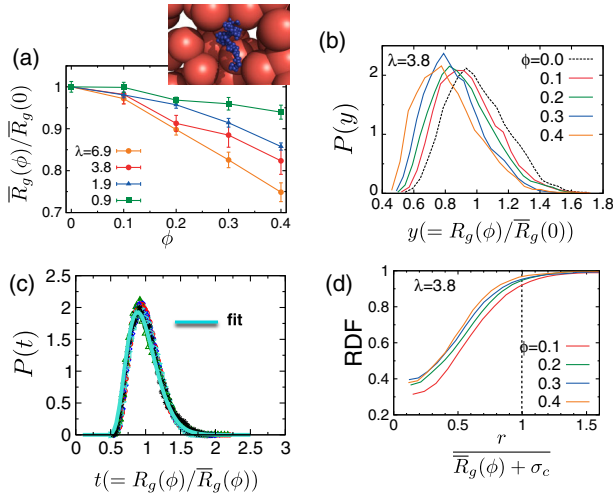


FIG. 1 (color online). Crowding effect on the conformation of a SAW chain ($N = 100$) for $\lambda \sim \mathcal{O}(1)$. (a) $\bar{R}_g(\phi)$ as a function of crowder volume fraction (ϕ). The λ values are shown in different colors. A snapshot of the SAW chain and the crowding particles on the top is for $\lambda = 1.9$ at $\phi = 0.3$. (b) Distribution of R_g , $P[R_g(\phi)]$ at $\lambda = 3.8$. (c) Collapse of $P[R_g(\phi)]$, with $\phi = 0.1-0.4$ and $\lambda = 0.9-6.9$, onto a universal curve [Eq. (1)], with $b = 1.120$ and $\mathcal{N} = 13.69$ obtained by rescaling $R_g(\phi)$ by $\bar{R}_g(\phi)$ justifies that the statistics of the polymer coil does not change. The corresponding result for the end-to-end distance is in [22]. (d) RDF of crowders from the center of the SAW chain at varying ϕ .

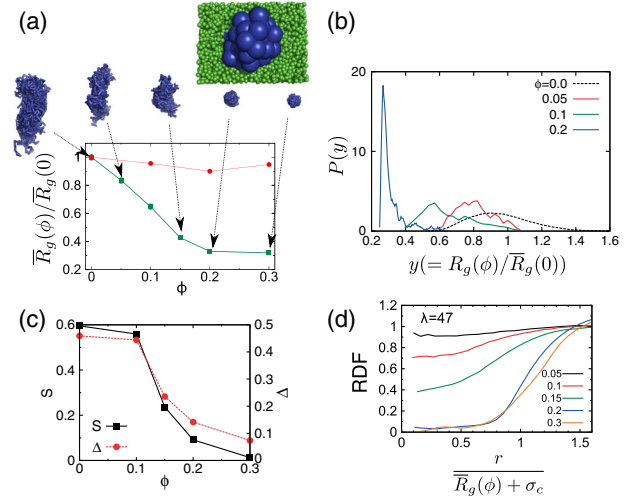


FIG. 2 (color online). Dramatic compaction of the SAW chain ($N = 50, \lambda = 47$). (a) $\bar{R}_g(\phi)/\bar{R}_g(0)$ of the SAW chain (the green square). The line with red circles is from Ref. [10], which simulated the effect of macromolecular crowding on the SAW polymer implicitly by using the effective depletion AO potential between two sites on a polymer. An ensemble of polymer conformations at each ϕ and a snapshot of the simulation at $\lambda = 47$ and $\phi = 0.2$ are shown at the top. (b) $P[R_g(\phi)]$ at $\lambda = 3.8$. (c) Shape parameter (S) and asphericity (Δ) of the SAW chain as a function of ϕ . (d) RDF of crowders from the center of the position in the SAW chain at varying ϕ .

gives $\lambda = 47$. When ϕ increases to 0.3, $\bar{R}_g(\phi)$ reduces by 70% from the original size $\bar{R}_g(0)$. The theoretical prediction, $\bar{R}_g(\phi)/\bar{R}_g(0) \approx (1 - c\lambda\phi)^{1/5}$ [31], where c is a constant, accounts for the simulation data in Fig. 2(a) for small $\phi \approx 0$. We note parenthetically that if the interaction between the beads were represented implicitly based on simulations of small N , as has been done previously [10], the dependence of $\bar{R}_g(\phi)$ on ϕ is qualitatively incorrect [the red circles in Fig. 2(a)].

The importance of the parameter λ as a key determinant of the coil size can also be appreciated by comparing the results in Figs. 1 and 2. In particular, $P(y)$ and the RDFs with $\lambda = 47$ (Fig. 2) differ qualitatively from those with $\lambda = 3.8$ (Fig. 1). For $\lambda = 47$, $P[R_g(\phi)/\bar{R}_g(0)]$, with $\phi = 0.2$, is peaked sharply at $R_g(\phi)/\bar{R}_g(0) \approx 0.25$ [Fig. 2(b)], whereas at lower ϕ the peak is at ≈ 1 , and the rather abrupt coil-globule transition is striking given the small size of the polymer. RDFs for $\lambda = 3.8$ [Fig. 1(d)] indicate that the crowders are essentially depleted from the region in which the polymer is localized, for all ϕ . In sharp contrast, for $\lambda = 47$ [Fig. 2(d)] at $\phi < 0.15$, there is a substantial probability that the crowders are in the vicinity of the polymer. Only after the coil-globule transition occurs at $\phi = \phi_c \approx 0.15$ – 0.2 , the crowders are fully excluded from the interior of the polymer $r \lesssim \bar{R}_g$, and, effectively, no crowder particle is present in the interior of the collapsed polymer at $\phi \geq 0.2$ [Fig. 2(d)].

To ascertain that the chain indeed forms a collapsed globule, we calculated the shape (S) and the asphericity (Δ) parameters [32,33]. Both quantities, which measure the anisotropy of an object, are identically zero for a perfect sphere. The ensembles of SAW configurations [Fig. 2(a)] change from a prolate at low ϕ [34,35] to a spherical shape as ϕ increases. The coil-globule transition, which has a tricritical character [31,36], is relatively sharp [Fig. 2(c)], mirroring the decrease in $\bar{R}_g(\phi)$ [Fig. 2(a)]. At $\phi = 0.3$, $S = 0.01$ and $\Delta = 0.07$ indicate that the polymer coil is collapsed to an almost perfect spherical globule.

We now turn to the critical ϕ for a coil-globule transition. The parameter x is a useful measure for assessing whether a polymer of a given length in the presence of crowders of a specific size would undergo a coil-globule transition. We estimate the critical ϕ (ϕ_c) of crowders for a given parameter λ by using $x_c = (3/4\pi)^{1/3} \lambda \phi_c^{1/3}$:

$$\phi_c = \left(\frac{4\pi}{3}\right) \left(\frac{x_c}{\lambda}\right)^3. \quad (2)$$

We estimate $x_c \approx 17$ because the polymer collapses at $\phi_c \approx 0.2$ for $\lambda = 47$. The specific value of x_c should, in principle, vary with N and the nature of interactions in the ternary system of the polymer, crowding particles, and solvent. Nevertheless, the estimated x_c is a guide to obtaining an approximate estimate of ϕ_c , and we show

below that it can be used to understand a number of experiments. Because of the restriction that $\phi_c < \phi_c^{\max} \approx 0.74$ (close packing) and the weak dependence of x on ϕ , it follows from Eq. (2) that as λ decreases, ϕ_c has to increase greatly in order for the crowding particles to induce coil-globule transition. Therefore, for a small λ , one can only expect a modest reduction in $\bar{R}_g(\phi)$ [Fig. 1(a)].

When applied to experiments, the combination of the scaling-type arguments and our simulation results offers a unifying framework for understanding experimental results on the effects of crowding on two entirely different classes of biopolymers. 1. DNA: Since the discovery by Lerman [37], it has been noted that addition of polyethylene glycol (PEG) to a coiled DNA induces cooperative coil-globule transition [16]. Because $N \gg 1$ for DNA, collapse transition is accompanied by a substantial volume change ($N^{3\nu} \rightarrow N^1$). For T4-DNA, whose contour length $L_c \approx 3.27 \times 10^5$ nm and $l_p \approx 50$ nm [16], $\bar{R}_g(0) \approx l_p(L_c/l_p)^{3/5} \approx 0.97 \times 10^5$ nm, and $\sigma_c \approx 0.195 \times P^{0.583}$ nm (with P being the polymerization index) for PEG [22], $\lambda \approx 4.97 \times 10^5 \times P^{-0.583}$, which leads to $\phi_c \ll 1$ for almost any P . Our theory shows that only a small amount of PEG is sufficient to induce the coil-globule transition of DNA of a genomic size, as has been established experimentally. 2. Intrinsically disordered proteins (IDPs): There has been considerable interest in the effects of crowding on IDPs, which have critical functional roles, especially in eukaryotes [38]. Based on recent single molecule [39] and small angle neutron scattering [40] experiments, it has been concluded that for certain IDPs, crowding induces a very small ($\sim 5\%$) reduction in size, whereas for others the effects are larger ($\sim 30\%$). These results—which apparently cannot be explained by scaled particle theory, which only accounts for excluded volume interactions—have led to *ad hoc* explanations that are difficult to rationalize [40]. Our theoretical results for neutral polymer coils nearly quantitatively account for the experimental findings for those IDPs with relatively small net charge per residue, for which the polymer model used here is most appropriate. A typical IDP with $N \approx 100$ has $\bar{R}_g(0) \approx 3$ nm from $\bar{R}_g(0) \approx 0.193 \times N^{0.598}$ [41]. For an IDP in the presence of PEG [39], we estimate $\lambda \approx 15.4 \times P^{-0.583}$; thus, $\phi_c \approx (4\pi/3) \times (x_c/15.4)^3 \times P^{1.75}$. If x_c is large, as is required for inducing globule formation, ϕ_c would be greater than ϕ_c^{\max} , even for small PEGs with $P = 1$. For PEG 6000 ($P \approx 136$) [39], $\lambda \approx 0.88$ and $\phi_c > \phi_c^{\max}$. Therefore, our first conclusion is that there ought to be no coil-globule transitions in IDPs in Ref. [39] using neutral crowders if one assumes the IDP as a self-avoiding polymer. This is in accord with experiments probing the crowding effects on five IDPs [39,40].

A more precise comparison with experiments can be made using our results for those IDPs with small net charge for which coil description is most appropriate. We

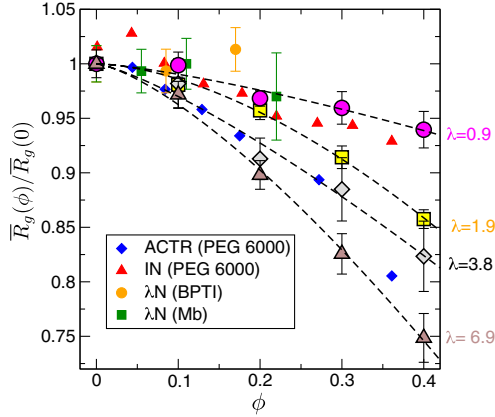


FIG. 3 (color online). Compaction of IDPs, ACTR, and IN in an increasing volume fraction of PEG 6000 [39], and λ N in BPTI or metmyoglobin (Mb) [40]. To compare experiments, we superimposed our simulation results with $N = 100$ and $\lambda = 0.9, 1.9, 3.8$. The compaction of IN, λ N (BPTI), and λ N (Mb) is described by $\lambda = 0.9$, and ACTR by $\lambda = 3.8$.

consider the activator for thyroid hormones and retinoid receptors activator (ACTR), and the N -terminal domain of the HIV-1 integrase (IN) with PEG as the crowding agent [39], and bacteriophage λ N with (nearly folded but likely hydrated) bovine pancreatic tyrosin inhibitor (BPTI) and equine metmyoglobin as crowding agents [40]. Figure 3 shows the $R_g(\phi)$ of the IDPs. The excellent agreement between theory and experiments with *no adjustable parameters* shows that λ controls the size. Thus, for these IDPs the present analysis, which relies on excluded volume as the dominant factor, suffices. Recently, other experimental studies have also noted that the size of unfolded proteins is insensitive to varying concentrations of crowders such as dextran, Ficoll, polyvinylpyrrolidone (PVP), bovine serum albumin (BSA), and lysozyme [40,42,43], leading the authors to suggest that attractive crowder-protein interactions, which compensate for the effects of excluded volume interactions, are at play. However, the λ calculated for the systems in these studies all lie in the range of $\lambda \approx \mathcal{O}(1)$, and hence $x \sim 1$, where the effect of neutral crowders on protein size is expected to be minimal. Thus, our theory of neutral crowders based on two competing length scales, $\bar{R}_g(0)$ and D , fully explains the minimal effect of macromolecular crowding on IDPs in Refs. [39,40] and proteins in Ref. [42].

We conclude with a few additional remarks. (i) It is tempting to use the depletion potential obtained for a small N as a potential of mean force (PMF) for simulating a polymer with large N . Kim *et al.* [10] obtained an effective ϕ -dependent PMF between two beads of a small polymer in a crowded environment and used the resulting PMF to simulate the crowding effect on the compaction of a long polymer. As shown in Fig. 2(a) (the red circles), they found

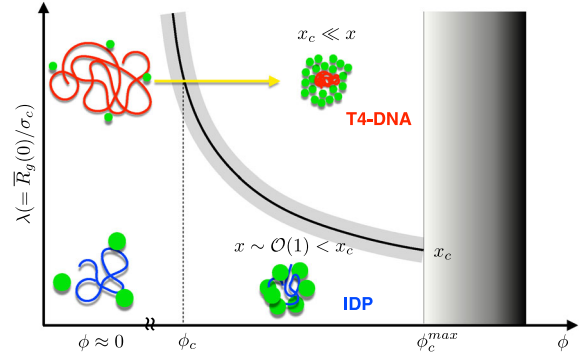


FIG. 4 (color online). Diagram of a polymer collapse which varies depending on the value of parameter x . For $x \sim \mathcal{O}(1) < x_c$, the size of the polymer decreases with an increasing ϕ while maintaining its coil statistics ($\bar{R}_g \sim N^{3/5}$). By contrast, for $x_c \ll x$, the polymer undergoes a coil-globule transition. ϕ_c greater than the volume fraction of close packing is not accessible ($\phi \gtrsim \phi_c^{\max}$). The difference between the crowding-induced dynamics in the two regimes of x is illustrated with IDP and T4-DNA.

a slight nonmonotonic turnover of $\bar{R}_g(\phi)$ at $\phi = 0.2$ and ascribed their finding to the ϕ -dependent repulsive barrier in the depletion potential. Their argument is that the energy cost to squeeze out the crowders from the space between the monomers increases with ϕ . Our study, which simulates the SAW polymer in *explicit* crowding particles with the identical parameters used in Ref. [10], shows a monotonic reduction of $\bar{R}_g(\phi)$ [the green squares, Fig. 2(a)]. Crowding effects on chain conformations for long polymers require that the crowders be explicitly treated at all scales. (ii) Based on the finding that the extent of the crowding-induced polymer compaction or collapse is determined by the parameter $x [= \bar{R}_g(0)/D]$, we propose a phase diagram (Fig. 4), which should serve as a useful guide in anticipating the results of crowding experiments on biopolymers. Our estimate of x explains that a small amount of PEG suffices to induce coil-globule transition in DNA, whereas an IDP whose size is $N \approx 100$ would not display collapse transition even at high ϕ . (iii) For IDPs with highly charged residues, the polymer model used here is inadequate because electrostatic interactions as well as potential correlations between charged residues are not taken into account. It is likely that if a minimal polymer model for such systems is constructed, which will naturally involve an additional length scale due to polyampholyte effects [44,45], then scaling theories along the lines used here will provide insights into the effect of crowding particles.

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