

# Self-Avoiding Flexible Polymers under Spherical Confinement

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## ABSTRACT

We compute the free energy of confinement for a flexible self-avoiding polymer inside a spherical cavity. Accurate numerical results allow us to arbitrate between three competing scaling predictions. For moderate confinement, the free energy exhibits a power-law dependence on cavity size that is different from what is observed for planar and cylindrical confinement. At high monomer concentrations, crossover to a different scaling regime is observed, consistent with the screening of the excluded-volume interactions. We demonstrate how our findings lead to a revised prediction for the escape time of a polymer from a spherical confinement.

Confinement of a polymer reduces its number of accessible conformations drastically and thus results in an excess free energy. The precise behavior of this free energy has a relevance that extends well beyond the realm of fundamental polymer physics. It plays an important role in various biological problems, including the packaging of DNA inside virus capsids<sup>1–3</sup> and its subsequent injection into the host cell.<sup>4</sup> It also governs the translocation of polynucleotides<sup>5–7</sup> and has been suggested to affect the stability of folded proteins.<sup>8</sup> Furthermore, confinement of polymers is encountered in numerous applications, such as filtration, colloidal stabilization,<sup>9</sup> flow-injection problems,<sup>10</sup> and drug-delivery techniques.<sup>11</sup> The dependence of the excess free energy on the geometry, degree of confinement, and chain length determines the partitioning of polymer chains and the entropic force on the polymer. Although the corresponding scaling behavior is covered in standard texts,<sup>12,13</sup> there is an important lingering controversy, which we address in this Letter.

The calculation of the entropy loss due to the confinement of an ideal chain is indeed an old problem.<sup>14–16</sup> For a polymer confined between two parallel plates at separation  $R$ , the free energy,  $F$ , increases as

$$\beta\Delta F \sim \left(\frac{R_G}{R}\right)^2 \quad (1)$$

where  $R_G$  is the radius of gyration of the unperturbed chain and  $\beta = 1/(k_B T)$ , with  $k_B$  the Boltzmann constant and  $T$  the absolute temperature. This result can be obtained by means

of a “blob” description of the polymer<sup>16</sup> by assuming that  $\beta\Delta F$  scales linearly with the degree of polymerization,  $N$ , and depends only on the ratio  $R_G/R$ . Casassa<sup>14</sup> proved that (up to a prefactor) the *same* scaling relation holds for an ideal polymer forced inside an infinitely long capillary or a spherical cavity of radius  $R$ . For planar and cylindrical geometries, eq 1 can immediately be generalized to self-avoiding (nonideal) polymers<sup>16</sup>

$$\beta\Delta F \sim \left(\frac{R_G}{R}\right)^{1/\nu} \sim N\left(\frac{\sigma}{R}\right)^{1/\nu} \approx N\left(\frac{\sigma}{R}\right)^{1.70} \quad (2)$$

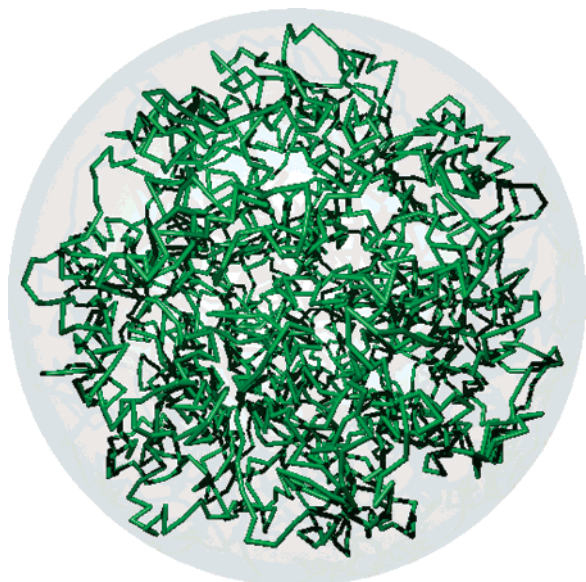
where  $\nu \approx 0.588$  is the Flory exponent<sup>17,18</sup> and  $\sigma$  denotes the monomer size. Experimentally, this prediction may be tested by the determination of equilibrium partitioning or possibly even via force measurements, but currently available verifications predominantly result from numerical simulations. Equation 2 indeed has been confirmed for chains confined within slits<sup>19,20</sup> and within tubes,<sup>21</sup> although an unexpectedly slow convergence toward the asymptotic behavior has been claimed.<sup>22</sup> However, it appears less widely appreciated that the applicability of eq 2 to *spherical* cavities (Figure 1) is controversial. Although some studies explicitly state<sup>23</sup> and employ<sup>24</sup> this relation for such a geometry, two alternative theories have been put forward.

First, self-consistent field theory (SCFT) predicts<sup>12,25</sup>

$$\beta\Delta F \sim N^2\left(\frac{\sigma}{2R}\right)^3 = N\phi \quad (3)$$

where  $\phi = N(\sigma/(2R))^3$  is the monomer volume fraction. This mean-field estimate is just the leading correction to the free energy of an ideal polymer due to excluded-volume interac-

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**Figure 1.** Snapshot of a polymer chain of  $N = 2048$  monomers confined within a spherical cavity at monomer concentration  $\phi \approx 0.03$ . For clarity, we depict the monomers smaller than their actual size.

tions.<sup>17</sup> Second, a blob scaling description has been proposed,<sup>12,26</sup> which explicitly recognizes that, unlike in a planar or cylindrical geometry, the monomer concentration in a spherical geometry increases upon confinement. As a result, the free energy is predicted to exhibit the same concentration dependence as in semidilute solutions<sup>27,28</sup>

$$\beta\Delta F \sim \left(\frac{R_G}{R}\right)^{3(3\nu-1)} \sim N\phi^{1/(3\nu-1)} \quad (4)$$

The differences between these predictions are by no means minor: Equation 4 predicts  $\Delta F \propto R^{-3.93}$ , compared to  $\Delta F \propto R^{-3}$  in eq 3 and  $\Delta F \propto R^{-1.70}$  in eq 2.

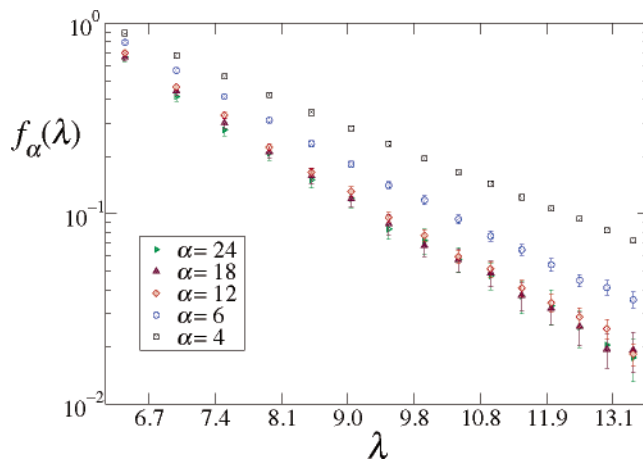
To the best of our knowledge, this discrepancy has not been addressed either by experiments or by computer simulations. It is the purpose of the present work to resolve the controversy by means of a systematic, accurate numerical study of the free-energy cost of confinement of nonideal, linear chains in a spherical geometry.

To be able to study long chains, we adopt a simple bead-spring model, in which the polymer is represented by a linear series of  $N$  spherical beads of diameter  $\sigma$  connected by bonds of maximal extension  $l_{\max} = 1.9\sigma$ . All monomers interact via a hard-core repulsion

$$u_m(r_{ij}) = \begin{cases} 0 & \text{if } r_{ij} > \sigma \\ \infty & \text{if } r_{ij} \leq \sigma \end{cases} \quad (5)$$

where  $r_{ij}$  is the pair separation. The nearest-neighbor bonds are described as

$$u_b(r_{i,i-1}) = \begin{cases} 0 & \text{if } r_{i,i-1} \leq l_{\max} \\ \infty & \text{if } r_{i,i-1} > l_{\max} \end{cases} \quad (6)$$



**Figure 2.** Force per monomer exerted by a polymer of length  $N = 256$  against the confining wall  $u_\alpha(\lambda)$  (eq 7) for different values of  $\alpha$ .

We explore the statistical properties of the model by means of Monte Carlo simulations involving local monomer moves. To demonstrate that this model reproduces the proper scaling dimensions, we compute the radius of gyration,  $R_G$ , for unconfined chains with  $32 \leq N \leq 1024$ . We find a power-law dependence  $R_G \propto N^{0.594 \pm 0.005}$ , in good agreement with the renormalization-group result.<sup>18</sup>

We encapsulate the chain in a spherical cavity mimicked by a confining potential centered around the origin

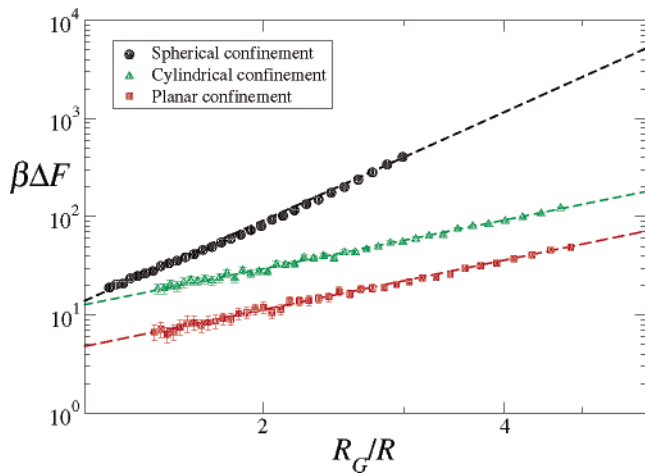
$$u_\alpha(\lambda) = k_B T \sum_{i=1}^N \frac{1}{(\lambda - r_i)^\alpha} \quad (\alpha > 0) \quad (7)$$

so that  $r_i$  is the distance of monomer  $i$  from the center of the sphere and  $\lambda$  represents the radius of the cavity (all distances are expressed in units of monomer diameter  $\sigma$ ). The free energy of confinement can now be computed via thermodynamic integration.<sup>29</sup> The free energy *difference* between two states identified by  $\lambda_1$  and  $\lambda_2$  is given by

$$\Delta F \equiv F(\lambda_2) - F(\lambda_1) = \int_{\lambda_1}^{\lambda_2} \left\langle \frac{\partial u_\alpha(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda \quad (8)$$

where  $\langle \dots \rangle_\lambda$  denotes the ensemble average in the presence of the potential  $u_\alpha(\lambda)$  at fixed sphere radius  $\lambda$ . Because  $\lambda_1 \gg R_G$  represents the limit of an unconfined chain,  $\Delta F(R)$  can be obtained by integrating over the range  $[\infty, R]$ . The normalized integrand,  $f_\alpha(\lambda) \equiv N^{-1} \langle \partial u_\alpha(\lambda) / \partial \lambda \rangle_\lambda$ , represents the force per monomer exerted by the polymer on the wall of the cavity. To ensure that our choice of  $\alpha$  in eq 7 does not affect the functional dependence of  $\Delta F$  on the size of the cavity, we measure  $f_\alpha(\lambda)$  as a function of  $\lambda$  for different values of  $\alpha$ . As shown in Figure 2, even for  $N = 256$ , the shortest chain length employed in this study,  $f_\alpha(\lambda)$  converges rapidly with increasing  $\alpha$  (i.e., when the confining potential becomes sufficiently steep). Thus, we adopt  $\alpha = 12$  for all further calculations.

Because the thermodynamic integration in eq 8 needs to be carried out numerically, we perform accurate simulations



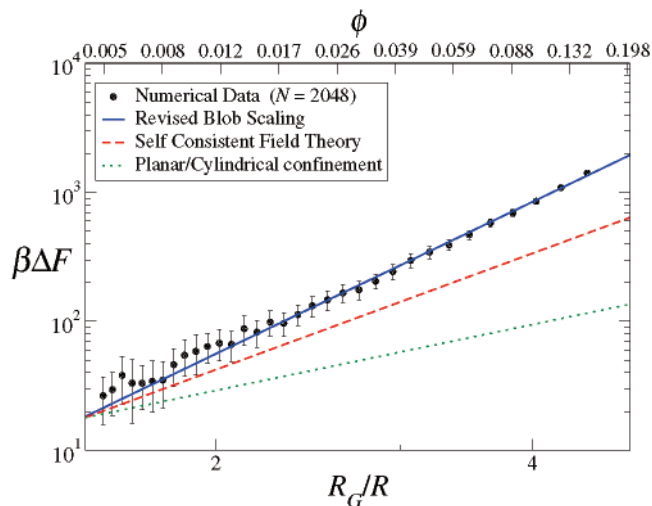
**Figure 3.** Free-energy cost of planar, cylindrical, and spherical confinement of a self-avoiding flexible polymer chain of  $N = 256$  monomers as a function of the compression parameter,  $R_G/R$ .

for a large number of sphere sizes with densely spaced values of  $\lambda$ . We fit the force per monomer,  $f(\lambda)$ , to a power law  $A/\lambda^x$  and integrate this expression to obtain  $\Delta F/N$ . Although the confining potential decays quite rapidly for  $\alpha = 12$ , it is important to take into account that the effective radius,  $R$ , is smaller than  $\lambda$ . Because a monomer has a potential energy  $k_B T$  at  $r = \lambda - 1$ , we define the radius,  $R$ , as  $(\lambda - 1) + 1/2$ , where the term  $1/2$  is added to account for the finite size of the monomers.

To check the validity of our approach, we also apply it to two cases that are known to be described by eq 2, namely, a polymer chain between two parallel plates and a chain confined within an infinitely long cylindrical shell. Figure 3 summarizes the findings for  $N = 256$  and permits two crucial observations.<sup>30</sup> First, it confirms that  $\Delta F$  exhibits the *same* power-law dependence  $R^{-\gamma}$  for planar and cylindrical confinement and shows that our approach yields a quite accurate estimate of this power law:  $(R_G/R)^{1.69 \pm 0.06}$  for parallel plates and  $(R_G/R)^{1.65 \pm 0.06}$  for a cylinder, both in good accordance with  $(R_G/R)^{1/\nu}$ . For both geometries, these results appear to be among the most accurate currently available and certainly in better agreement with the prediction than  $\gamma = 1.4 \pm 0.1$  ( $2.4 \pm 0.1$  for the force) observed for chain lengths as large as  $N = 8000$  in a simple cubic lattice model.<sup>22</sup> Second, spherical confinement clearly shows a *much stronger* increase of the free energy with decreasing  $R$ . To accurately determine the corresponding power law and to minimize possible artifacts due to the use of short chains, we present results for  $N = 2048$  in Figure 4. At small values of  $R_G/R$ , there are significant error bars. This is a physical effect: at weak confinement, the spherical cavity poses only a minor perturbation to the chain and thus there are considerable fluctuations. Nevertheless, we are able to follow the increase of the free energy over 2 orders of magnitude and observe a clear power-law dependence

$$\beta\Delta F \propto \left(\frac{R_G}{R}\right)^{3.8 \pm 0.1} \quad (9)$$

which is fully consistent with the prediction  $\gamma = 3/(3\nu - 1)$



**Figure 4.** Free energy of confinement for a self-avoiding flexible polymer ( $N = 2048$  monomers) in a spherical cavity of radius  $R$  as a function of the compression parameter,  $R_G/R$ . Along with the numerical data, three different scaling predictions are plotted as well.

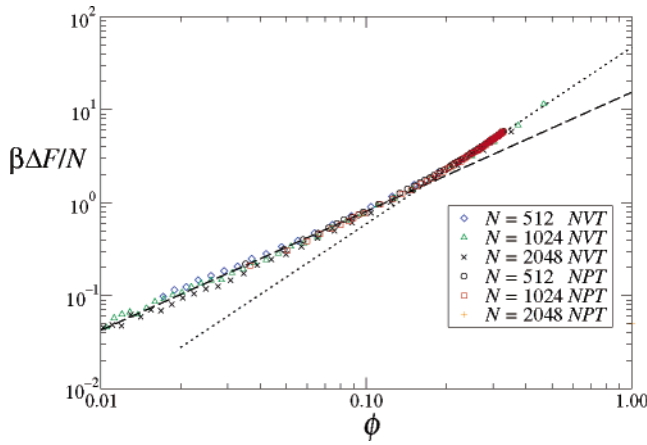
= 3.93 (eq 4). In fact, the agreement is even better if one realizes that the finite chains employed here have a slightly larger effective Flory exponent,  $\nu = 0.594$ , corresponding to  $\gamma = 3.84$ . Figure 4 also shows the alternative predictions, eq 2 ( $\gamma = 1.70$ ) and the SCFT result eq 3 ( $\gamma = 3$ ). Clearly, neither of these alternatives provides a valid description. This unambiguous confirmation of the revised blob scaling prediction (eq 4) is the central result of this Letter.

To ensure that no spurious nonuniversal effects are introduced by the monomer–wall interactions, we also employ a different method to obtain the free-energy density of confinement. We perform simulations in the conjugate ( $NPT$ ) ensemble,<sup>29</sup> in which a uniform external pressure,  $P$ , is imposed and the volume is allowed to fluctuate. The free energy difference is then recovered by determining the equation of state,  $P(\rho)$ , of the polymer and integrating it over the density  $\rho = 6/\pi \phi$

$$\frac{\Delta F}{N} = \int_0^\rho \frac{P(\rho')}{\rho'^2} d\rho' \quad (10)$$

In this ensemble, the spherical boundary is described as a hard wall, which eliminates any ambiguity in determining the effective volume of the cavity.

Figure 5 presents the free energy of confinement as a function of monomer volume fraction  $\phi$  for three different chain lengths ( $N = 512, 1024, 2048$ ), for the  $NPT$  as well as the  $NVT$  ensemble. It is rewarding that the results for both ensembles are in good agreement, ruling out ensemble-dependent artifacts. Furthermore, upon normalization per monomer, all curves collapse,<sup>31</sup> confirming the extensive character of the free energy at fixed  $\phi$ . For moderate values of  $\phi$ , all data coincide on a line with slope  $x = 1.28 \pm 0.06$ , in agreement with the prediction of eq 4,  $x = 1/(3\nu - 1) = 1.31$ , and in contrast with the linear concentration dependence predicted by SCFT (eq 3).



**Figure 5.** Concentration dependence of the free energy of confinement per monomer, obtained at constant volume (NVT) and constant pressure (NPT). The coinciding curves for different chain lengths confirm the extensive character of the free energy. For  $\phi < 0.15$ , the data exhibit a power-law behavior  $\Delta F \propto \phi^{1.28}$  (dashed line), in agreement with eq 4. The dotted line is a guide to the eye, indicating the systematic deviations at high concentrations (see the text).

It is of interest to also discuss the limitations of the scaling prediction. For concentrations exceeding approximately 0.2, the data cross over to a power-law behavior with an exponent  $x \approx 2$ . Although this crossover is consistent with the screening of the excluded-volume interactions in concentrated solutions (as discussed below), it is also important to emphasize the breakdown of the blob scaling description at sufficiently high concentrations. Indeed, we can estimate the number of monomers per blob,  $N_b$ , from scaling arguments.<sup>12,26</sup> The key ingredient is that the average monomer concentration,  $N_b/(2\xi)^3$ , within a blob of radius  $\xi$  must equal the global monomer concentration inside the cavity,  $\phi = N/(2R)^3$ , where we recall that all lengths are expressed in terms of the monomer diameter. For the self-avoiding polymers in our simulation,  $R_g = A_0 N^\nu$  with  $A_0 \approx 0.6$ , so that the blob radius can be estimated as  $\xi = A_0 N_b^\nu$ . Consequently, the typical number of monomers per blob reduces rapidly with increasing concentration,

$$N_b = (8A_0^3\phi)^{-1/(3\nu-1)} \quad (11)$$

For  $\phi = 0.1$  we find  $N_b \approx 10$ , but already for  $\phi = 0.25$ ,  $N_b$  is as small as three. These estimates indeed confirm that one cannot expect the scaling regime to hold above a threshold  $\tilde{\phi} \approx 0.15$ . Conversely, in the dilute regime we anticipate considerable finite-size effects because the total number of blobs becomes very small. For example, at  $\phi = 0.01$  there are approximately 200 monomers per blob so that even our longest chain (with  $N = 2048$ ) consists of only 10 blobs.

In experiments on the partitioning of poly(ethylene glycol) in protein nanopores<sup>32</sup> a strongly nonlinear chain-length dependence for the free energy was observed,  $\Delta F \propto N^{3.1 \pm 0.2}$  (indeed in disagreement with eq 2). Sakaue and Raphaël<sup>26</sup> argued that the chains are effectively confined in a spherical cavity, implying (from eq 4)  $\Delta F \sim N^{3\nu/(3\nu-1)} = N^{2.31}$ , and tentatively attributed the deviation to finite-size effects. We

observe that the deviation may also arise from comparatively high monomer concentrations within the pore. Indeed, for  $0.2 \leq \phi < 0.35$ ,  $\Delta F$  in our model is described by an effective power law  $\Delta F \sim N\phi^{1.97 \pm 0.07} \propto N^{2.97 \pm 0.07}$ , remarkably consistent with the experimental findings. Although the onset  $\tilde{\phi}$  of this regime is nonuniversal, the power law can be understood from the screening of the excluded-volume interactions in concentrated solution,<sup>16,27</sup> which reduces the effective Flory exponent to its Gaussian value. Thus, the exponent  $\nu$  in eq 4 must be set to  $1/2$ , yielding  $\Delta F \sim N\phi^2$ . The data in Figure 5 confirm this crossover from the semidilute to the concentrated regime.

One problem directly affected by our confirmation of eq 4 is the escape of a polymer from a spherical cavity. On the basis of classical nucleation theory and eq 2 it has been predicted<sup>24</sup> that, for a sufficiently strong entropic driving force, the average escape time scales as  $\tau \sim N(N/\phi)^{1/(3\nu)}$ . In light of our results, this prediction must be altered to

$$\tau \sim \frac{N}{\Delta\mu} = \frac{N}{\Delta F/N} \sim N\phi^{-1/(3\nu-1)} \quad (12)$$

where  $\Delta\mu$  is the chemical potential gradient per monomer. Thus, the escape time has a much stronger concentration dependence than predicted in ref 24 and at fixed concentration the escape time is *linearly* proportional to the length of the polymer rather than superlinearly. The chain-length dependence must be treated with some caution because it implies, for long chains, a translocation time that is smaller than the equilibration time. For translocation through a planar membrane, Kantor and Kardar<sup>33</sup> proposed the unimpeded motion of a polymer coil as a lower bound, yielding  $\tau \sim N^{1+\nu}/\Delta\mu$ . Applied to a spherical cavity, this implies that eq 12 is modified further as

$$\tau \sim \frac{N^{1+\nu}}{\Delta\mu} = \frac{N^{1+\nu}}{\Delta F/N} \sim N^{1+\nu}\phi^{-1/(3\nu-1)} \quad (13)$$

Coincidentally, for self-avoiding chains in three dimensions the power-law behavior,  $N^{1+\nu}$ , is numerically very close to the prediction<sup>24</sup>  $N^{1+1/3\nu}$ , but the physical origin of the exponent is very different. In addition, the corrected concentration dependence of eq 12 remains unaltered in eq 13.

In conclusion, we have demonstrated, for the first time, that the free energy of a flexible self-avoiding polymer confined to a spherical cavity exhibits a different dependence on pore size than the free energy of a polymer confined between parallel plates or within a cylindrical geometry. For moderate monomer concentrations, the free energy of confinement is in good agreement with the scaling law first introduced by Grosberg and Khokhlov,<sup>12</sup>  $\beta\Delta F \sim N\phi^{1/(3\nu-1)}$ . At strong confinement, excluded-volume interactions are screened and a crossover to a different scaling behavior is observed.

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- (30) The free energy depicted in the figures does *not* include energetic contributions resulting from the monomer-wall interactions (eq 7) and is thus of purely entropic origin.
- (31) The results for  $N = 256$  (not shown in this figure) exhibit minor deviations in the amplitude, owing to the short chain length.
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