Polymers with Internal Length and Displacement Constraints: Bounds and Exact Expressions for Free Energies

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ABSTRACT: Internal distance constraints in polymers often have a characteristic offset distance between the constrained monomers. This paper introduces a new kind of such constraint, the displacement constraint, which has particularly simple properties. The displacement constraint has both a characteristic offset distance and a characteristic offset direction. A simple, exact expression for the free energy of an ideal polymer with displacement constraints is derived. This expression is used to obtain bounds on the free energy of an ideal polymer with the more usual length constraints, which have a characteristic offset length but no characteristic direction. The form of these results suggest that the offset length can make an important contribution to the free energy if the offset distance is not negligible in comparison to the chemical distance between constrained monomers.

1. Introduction

Constraints are important in many chemical and biophysical applications of polymer theory. In this paper we study an especially common kind of constraint, an internal distance constraint in a single polymer chain. For example, this kind of constraint occurs in the determination of protein structure using NMR-derived distance constraints,[1,2] loops in chromosome structure,[3] and disulfide bonds between nonsequential monomers in proteins.[4,5]

Constraints induce qualitative changes in properties of random walks and complicate the mathematical analysis necessary to analyze physically significant properties.[6−9] Therefore, it makes sense to study simple models of constrained polymers to gain a basic understanding of their properties before considering more complex applications.

A common simple model of polymer configurations is the ideal chain model, based on the Gaussian random walk.[10−13] There are at least two motivations for the many applications of the ideal chain model in polymer physics. The first is that the ideal chain model for polymer configurations in dilute solution is suggested by the central limit theorem, and the second is that elementary properties of this model are relatively simple to calculate.

A standard technique for imposing constraints on random walk models is by means of δ functions. We refer to constraints imposed in this way as hard constraints.[14−17] δ functions have also been used in models of a single polymer chain with internal distance constraints.[18,19] However, hard constraints have severe limitations. For example, in polymer models with discrete monomers, there is an infinite free energy barrier between an unconstrained ideal polymer and an ideal polymer with hard internal constraints, so comparisons of the free energies of constrained and unconstrained polymers are meaningless with hard constraints. (However, this difficulty with hard constraints may not arise for models in which the polymer is represented as a continuous curve[12]).

A different approach to problems with constraints is to allow the distance between two monomers participating in a constraint to fluctuate about an average distance of zero. This approach crudely approximates the effects of thermal fluctuations. A convenient representation of this type of constraint is in terms of a Gaussian distribution of distances, where the Gaussian has a standard deviation σ. A hard constraint corresponds to the limit $\sigma \to 0$. We refer to the case of σ bounded away from 0 as a soft constraint. We shall discuss only Gaussian constraints here and presume that other approximations to the δ function do not change the conclusions in any significant way. This paper analyzes the effects of several Gaussian soft constraints on the free energy and entropy of an ideal polymer chain. Other properties of such constraints were recently discussed by Bryngelson and Thirumalai[20] and by Solf and Vilgis.[21]

In these two analyses the mean offset distance for a constraint was assumed equal to zero. However, in some applications it is more appropriate to allow the average distance in a constraint to differ from zero. For example, disulfide bonds in proteins and the distance constraints from NMR measurements have offset lengths not necessarily equal to zero.[1,2,4,5] A nonzero offset length can change the physics of the system; for example, if the offset distance is large enough, we would expect an elastic contribution to the free energy because the offset stretches the polymer chain.

This paper introduces and analyzes a new kind of Gaussian soft constraint with an offset, the displacement constraint. In a displacement constraint the mean offset of a constraint is equal to a vector, $\mathbf{a}$. Since a displacement constraint is characterized by an offset vector, $\mathbf{a}$, it has a mean offset length *and* a mean offset direction. A similar type of constraint will be termed a length constraint. A length constraint has only a mean offset length, a, but no offset direction. Length constraints occur more commonly in practice, but their properties are more difficult to analyze.

Free energy and entropy are useful quantities for the analysis of polymer systems. Returning to the examples above, knowing the entropy loss caused by a set of constraints can provide a direct and objective measure of the precision of a set of distance constraints derived from NMR measurements; the free energy for the formation of a set of disulfide bonds in a protein is needed to achieve a quantitative understanding of

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protein folding, and for comparing experiments where the disulfide bonds are intact with those where these bonds have been broken. Here we shall derive an exact free energy expression for an ideal polymer with a set of displacement constraints. The entropy can be computed trivially from this expression. This free energy expression has a "constraint" term which is independent of the offsets and an explicit "elastic" term due to the offsets. We shall also establish bounds on the free energy of ideal polymers with length constraints. The expressions for the exact free energy of displacement constraints and for the bounds for the free energy of length constraints simplify in an important special case and these expressions suggest a general criterion for situations where the offset length has no significant effect on the free energy of the constrained polymer.

2. Representations of Displacement and Length Constraints by Harmonic Terms

We distinguish between three kinds of internal constraints on an ideal polymer: distance constraints, length constraints, and displacement constraints. Any of these three kinds of constraints can be hard or soft. We shall analyze an ideal Gaussian chain consisting of N monomers with the root mean squared bond length between adjacent monomers equal to b. The parameter b may be thought of as the Kuhn length. We denote the position of monomer j by $\mathbf{R}_j$. The location of the monomers in an unconstrained Gaussian chain are described by a Gaussian joint probability density. This Gaussian chain can also be described in terms of the partition function of a harmonic chain of N particles at absolute temperature T, by using the potential energy function

$$E_{\mathrm{b}} = \frac{3k_{\mathrm{B}}T}{2b^2}\sum_{j=1}^{N\text{-}1}(\mathbf{R}_{j+1} - \mathbf{R}_j)^2 \qquad (1)$$

where k_{B} represents the Boltzmann constant. Henceforth, we shall measure all distances in terms of the mean bond length b, which is equivalent to using the dimensionless position variables $\mathbf{r}_j = (1/b)\mathbf{R}_j$. Thus, in the expressions that we use and derive in the remainder of this paper, distances are effectively measured in terms of the Kuhn length.

In ref 20 the system of M soft distance constraints was modeled in terms of a second harmonic term, E_{c}:

$$E_{\mathrm{c}} = \frac{3k_{\mathrm{B}}T}{2\gamma^2}\sum_{k=1}^{M}(\mathbf{r}_{k(2)} - \mathbf{r}_{k(1)})^2 \qquad (2)$$

where $\gamma = \sigma/b$ and σ is the standard deviation of the soft Gaussian constraint. The subscript $k = 1, ..., M$ indexes the constraints and $k(1)$ and $k(2)$ represent the monomer indices ($j = 1, ..., N - 1$) of the two monomers constrained by constraint k. This representation of soft constraints in terms of harmonic energies can be extended to length constraints and displacement constraints.

In the case of distance constraints the constraint energy (eq 2) is minimized when the position of two constrained monomers $k(1)$ and $k(2)$ coincide. In a length constraint, the constraint energy is minimized when the distance between the two constrained monomers equals a nonzero characteristic distance, a_k. We shall call a_k the kth offset distance. In terms of harmonic energies, this situation corresponds to a constraint energy term of the form

$$E_{\mathrm{l}} = \frac{3k_{\mathrm{B}}T}{2\gamma^2}\sum_{k=1}^{M}(|\mathbf{r}_{k(2)} - \mathbf{r}_{k(1)}| - a_k)^2 \qquad (3)$$

where a_k is the offset distance between constrained monomers $k(1)$ and $k(2)$.

A displacement constraint is characterized by an characteristic vector that specifies the average position of monomer $k(2)$ with respect to monomer $k(1)$. We call this characteristic vector the offset vector, $\mathbf{a}_k$. A system of soft displacement constraints is modeled by the constraint energy term

$$E_{\mathrm{d}} = \frac{3k_{\mathrm{B}}T}{2\gamma^2}\sum_{k=1}^{M}(\mathbf{r}_{k(2)} - \mathbf{r}_{k(1)} - \mathbf{a}_k)^2 \qquad (4)$$

where $\mathbf{a}_k$ is the offset vector separating constrained monomers $k(1)$ and $k(2)$.

3. Free Energy with Displacement Constraints

The total energy of a polymer with soft displacement constraints is $E = E_{\mathrm{b}} + E_{\mathrm{d}}$, and the equivalent joint probability density for the position vectors can be written as $p(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N) = (1/Z)\exp[-U(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N)]$ in which $U = E/(k_{\mathrm{B}}T)$ is a dimensionless energy and Z is the partition function. This terminology allows us to define a free energy for the system by $F = -k_{\mathrm{B}}T \log Z$. Henceforth we shall use statistical mechanical terminology rather than talking about the joint probability density. For displacement constraints the free energy can be evaluated exactly and can be decomposed into the sum of a constraint term and an elastic term.

3.1 Exact Free Energy. In the Gaussian model, the partition function, Z, is expressed in terms of the $N - 1$ difference variables $\Delta\mathbf{r}_j = \mathbf{r}_{j+1} - \mathbf{r}_j$ as

$$Z = \int ... \int \exp\left[-\frac{3}{2}\sum_{j=1}^{N\text{-}1}(\Delta\mathbf{r}_j)^2 - \frac{3}{2\gamma^2}\sum_{k=1}^{M}\Big(\sum_{l=k(1)}^{k(2)\text{-}1}\Delta\mathbf{r}_l - \mathbf{a}_k\Big)^2\right]\prod_{j=1}^{N\text{-}1} d^3\Delta\mathbf{r}_j \qquad (5)$$

This partition function is the appropriate one for comparing the free energy of the constrained chain with that of the unconstrained chain, as shown in the appendix. Equation 5 for the partition function does not contain the temperature, T. Therefore, the free energy is entirely entropic, so the partition function merely counts the number of allowed configurations. The partition function is temperature independent because we made the effective spring constants proportional to absolute temperature in eqs 1–4 for the energy terms. This temperature dependence of the spring constants cancels the $1/T$ in the Boltzmann factor and leads to temperature independent average bond and constraint lengths. Therefore, the partition function is a purely geometric quantity.

The partition function in eq 5 can be evaluated exactly by using standard Gaussian integral formulae.[12,22] Straightforward application of these formulae to eq 5 yields an expression that contains an $(N - 1) \times (N - 1)$ matrix.[19,20] For typical applications $N - 1 > M$, so we use an identity to transform (5) into another Gaussian integral that naturally reduces to an equivalent expression that contains a (smaller and hence more convenient) $M \times M$ matrix. Specifically, we use the identity

$$\exp\left(-\frac{\mathbf{x}_k{}^2}{2\lambda}\right) = \left(\frac{\lambda}{2\pi}\right)^{3/2} \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} \exp\left(-\frac{\lambda}{2}\mathbf{y}_k{}^2 - i\mathbf{x}_k\cdot\mathbf{y}_k\right) d^3\mathbf{y}_k \quad (6)$$

for each of the M constraints by setting $\lambda = \gamma^2/3$ and $\mathbf{x}_k = (\sum_{k(1)}^{k(2)-1} \Delta\mathbf{r}_l) - \mathbf{a}_k$. Integrating over $\{\Delta\mathbf{r}_j\}$ yields a Gaussian integral over $\{\mathbf{y}_k\}$. Applying the standard formulae to this Gaussian integral yields an expression that contains an $M \times M$ matrix which summarizes the set of constraints. We call this matrix $\mathbf{B}$ and express it as

$$\mathbf{B} = \mathbf{I} + \gamma^{-2}\mathbf{V} \quad (7)$$

where $\mathbf{I}$ is the $M \times M$ identity matrix and $\mathbf{V}$ contains information related to the constraints. To express the matrix $\mathbf{V}$, we introduce the $M \times (N - 1)$ indicator matrix $\mathbf{S}$ having the elements

$$(\mathbf{S})_{kj} = \begin{cases} 1 & \text{if } k(1) \le j \le k(2) - 1 \\ 0 & \text{otherwise} \end{cases} \quad (8)$$

In terms of this indicator matrix, the $M \times M$ matrix $\mathbf{V}$ can be written as $\mathbf{V} = \mathbf{S}^{\mathrm{T}}\mathbf{S}$, where the superscript T denotes matrix transpose. Since $\mathbf{V}$ is positive semidefinite,[23] $\mathbf{B}$ is positive definite and therefore nonsingular. An identical matrix appears in the work of Bryngelson and Thirumalai.[20]

The exact free energy of an ideal polymer with displacement constraints is

$$F = F_0 + \frac{3k_{\mathrm{B}}T}{2}\log(\det\mathbf{B}) + \frac{3k_{\mathrm{B}}T}{2\gamma^2}\sum_{k=1}^{M}\sum_{l=1}^{M}(\mathbf{B}^{-1})_{kl}\mathbf{a}_k\cdot\mathbf{a}_l \quad (9)$$

where $F_0 = -[3(N - 1)k_{\mathrm{B}}T/2]\log(2\pi/3)$ is the free energy of the unconstrained polymer and $(\mathbf{B}^{-1})_{kl}$ denotes the kl element of $\mathbf{B}^{-1}$. As mentioned, the free energy is entirely entropic, and therefore has the form $F = -TS$. It would contain an additional energetic term if the energies defined in Section 2 were not proportional to the temperature.

3.2. Constraint and Elastic Contributions to the Free Energy. The constraints cause a free energy change $\Delta F = F - F_0$. In the case of displacement constraints, F is given exactly by eq 9. This free energy change can also be interpreted as an entropy change, $\Delta S = -\Delta F/T$, as noted earlier. The change in free energy can be decomposed into the sum of two contributions, a constraint term and an elastic term.

The change in free energy caused by constraints with no offsets, *i.e.*, $\mathbf{a}_1 = \mathbf{a}_2 = ... = \mathbf{a}_{\mathrm{M}} = 0$, is

$$\Delta F_{\mathrm{c}} = \frac{3k_{\mathrm{B}}T}{2}\log(\det\mathbf{B}) \quad (10)$$

which depends only on the positions of the constraints in the polymer sequence.[20] We call this term the constraint free energy.

For displacement constraints a second term appears which accounts for the effect of the nonzero offset vectors, $\{\mathbf{a}_{\mathrm{k}}\}$. This new term will be called the elastic free energy, ΔF_{e}. If we write

$$\Delta F = \Delta F_{\mathrm{c}} + \Delta F_{\mathrm{e}} \quad (11)$$

then ΔF_{e} is found to be

$$\Delta F_{\mathrm{e}} = \frac{3k_{\mathrm{B}}T}{2\gamma^2}\sum_{k=1}^{M}\sum_{l=1}^{M}(\mathbf{B}^{-1})_{kl}\mathbf{a}_k\cdot\mathbf{a}_l \quad (12)$$

which, not unnaturally, is quadratic in the offsets.

We call ΔF_{e} the elastic free energy because it can be interpreted as a sum of terms of the form $\kappa_k|\mathbf{z}_k|^2$, where the $\mathbf{z}_k$ are normal coordinates defined by the positive–definite, Hermitian matrix $\mathbf{B}^{-1}$ and the κ_k are strictly positive elastic constants.

4. Bounds on the Free Energy of an Ideal Polymer with Length Constraints

Unfortunately, the methods we used for displacement constraints cannot be used to evaluate the free energy for a polymer with length constraints. These methods require the energy to be quadratic in the components of the $\mathbf{r}_j$ and $\mathbf{a}_k$ vectors. The presence of absolute values in the expression for the energy of a system of length constraints (see eq 3) means that this energy cannot be expressed as a quadratic function of the vector components. However, our results for displacement constraints *can* be used to obtain bounds on the free energy of an ideal polymer with length constraints.

These free energy bounds are obtained by considering, for each length constraint, the set of offset vectors with magnitude equal to the offset length of that constraint. More concretely, consider an ideal polymer with a fixed set of length constraints between the M pairs of monomers $\{k(1),k(2)\}$ with corresponding offset lengths $\{a_k\}$ and denote the free energy of this length constraint system by $F_{\mathrm{l}}(\{a_k\})$. Next, for each offset length, a_k, construct a set of offset vectors $\{\mathbf{a}_k\}$ with the property that $|\mathbf{a}_k| = a_k$. Consider an ideal polymer with a fixed set of displacement constraints between the *same* M pairs of monomers $\{k(1),k(2)\}$ considered previously, with the set of offset vectors $\{\mathbf{a}_k\}$, and denote the free energy of this displacement constraint system by $F_l(\{a_k\})$. The free energy bounds come from the inequality $F_{\mathrm{d}}(\{\mathbf{a}_k\}) \ge F_{\mathrm{l}}(\{a_k\})$, which is true for any valid set of offset vectors $\{\mathbf{a}_k\}$. This free energy inequality is proven by showing that, for any valid set of $\{\mathbf{a}_k\}$, the energy of a system of displacements constraints, $E_{\mathrm{d}}(\{\mathbf{a}_k\})$, given by eq (4) and the energies of a corresponding system of length constraints, $E_{\mathrm{l}}(\{a_k\})$, given by eq (3), obey the inequality $E_{\mathrm{d}}(\{\mathbf{a}_k\}) \ge E_{\mathrm{l}}(\{a_k\})$, which follows directly from the vector inequality $|\mathbf{r}||\mathbf{a}| \ge \mathbf{r}\cdot\mathbf{a}$. The free energy inequality means that $F_{\mathrm{d}}(\{\mathbf{a}_k\})$ is an upper bound on $F_{\mathrm{l}}(\{a_k\})$ for all directions of the $\{\mathbf{a}_k\}$ vectors.

A particularly simple bound on $F_{\mathrm{l}}(\{a_k\})$ results from averaging $F(\{\mathbf{a}_k\})$ over all possible directions of the displacement vectors $\{\mathbf{a}_k\}$. We call this bound the quenched free energy, $F_{\mathrm{q}}(\{a_k\})$, in analogy to the terminology used in the statistical mechanics of disordered systems, because the offset directions are fixed (quenched) before the thermal averages are taken. The simple expression for the quenched free energy results from averaging eq 9 for the free energy of an ideal polymer with fixed displacement constraints over all the directions of the $\{\mathbf{a}_k\}$ and using $\overline{\mathbf{a}_i\cdot\mathbf{a}_j} = a_i{}^2\delta_{i,j}$ to obtain

$$F_{\mathrm{q}}(\{a_k\}) = F_0 + \frac{3k_{\mathrm{B}}T}{2}\log(\det\mathbf{B}) + \frac{3k_{\mathrm{B}}T}{2\gamma^2}\sum_{k=1}^{M}(\mathbf{B}^{-1})_{kk}a_k{}^2 \quad (13)$$

5. Disjoint Constraints and the Relative Magnitude of the Elastic Term

Some special cases of constraints give rise to simple results which provide insight into the properties of general constrained polymer systems. One such set of cases are systems of disjoint constraints. We call a *pair* of constraints k and l disjoint (or nonoverlapping) if $V_{kl} = 0$. (Disjoint constraints are called "unrelated" constraints in ref 24.) We call a *system* of constraints disjoint if all pairs are disjoint, *i.e.*, $V_{kl} = 0$ for all $k \neq l$. Systems of disjoint constraints have particularly simple additive forms for their free energies which suggests a rough criterion for neglecting the elastic term.

If a polymer has only one displacement constraint, for example, constraining monomers j and k ($>j$), then the decrease in entropy depends only on the amplitude $a(=|\mathbf{a}|)$ and not on any directional information

$$\Delta F = \frac{3k_{\rm B}T}{2}\log\left(1+\frac{L}{\gamma^2}\right) + \frac{3k_{\rm B}Ta^2}{2(\gamma^2+L)} \tag{14}$$

where $L = k - j$ is the chemical distance between the constrained monomers, in units of Kuhn length. Equation 14 indicates the physically reasonable result that the free energy change is less sensitive to the offset length a as the chemical distance between the two constrained monomers increases.

More generally, the free energy takes a simple, additive form, which is a generalization of (14) for arbitrary M, whenever the constraints are disjoint. For systems of disjoint constraints the **B** matrix is diagonal. In consequence, the free energy change can be written in additive form as

$$\Delta F = \frac{3k_{\rm B}T}{2}\sum_{k=1}^{M}\log\left(1+\frac{L_k}{\gamma^2}\right) + \frac{3k_{\rm B}T}{2}\sum_{k=1}^{M}\frac{|\mathbf{a}_k|^2}{\gamma^2+L_k} \tag{15}$$

where $L_k = |k(2) - k(1)|$. Once again ΔF depends on only the length of the displacement vectors and not on their direction. Since ΔF is independent of the directions of the displacement constraints (for disjoint constraints), all of the bounds on the free energy for length constraints that are based on the inequality $F_{\rm d}(\{\mathbf{a}_k\}) \geq F_{\rm l}(\{a_k\})$ are equal, so all of these bounds must equal the quenched free energy bound,

$$F_{\rm q}(\{a_k\}) = F_0 + \frac{3k_{\rm B}T}{2}\sum_{k=1}^{M}\log\left(1+\frac{L_k}{\gamma^2}\right) + \frac{3k_{\rm B}T}{2}\sum_{k=1}^{M}\frac{a_k^{\,2}}{\gamma^2+L_k} \tag{16}$$

The form of eqs 15 and 16 suggests a general criterion for safely ignoring the free energy of elastic term relative to that of the constraint term. This criterion may be useful for length constraints where the evaluating the elastic free energy is nontrivial. Notice that the elastic terms in the exact free energy in eq 15 and the free energy bound in eq 16 scale as $\sim a_k/(L_k + \gamma^2)$. Thus, on the assumption of reasonably tight constraints, as defined by $\gamma^2 \ll L_k$, the constraint will term dominate the elastic term when $\log(L_k/\gamma^2) \gg a_k/L_k$ for each of the constraints.

When the constraints overlap, the expressions for the free energy change for displacement constraints become considerably more complicated. For example, when $M = 2$ the expression for the free energy reduces to

$$\Delta F = \frac{3k_{\rm B}T}{2}\log\left[\left(1+\frac{L_1}{\gamma^2}\right)\left(1+\frac{L_2}{\gamma^2}\right) - \frac{V_{12}^{\,2}}{\gamma^4}\right] + \frac{3k_{\rm B}T}{2}\,\frac{(\gamma^2+L_2)|\mathbf{a}_1|^2 + (\gamma^2+L_1)|\mathbf{a}_2|^2 - 2V_{12}(\mathbf{a}_1\cdot\mathbf{a}_2)}{(\gamma^2+L_1)(\gamma^2+L_2) - V_{12}^{\,2}} \tag{17}$$

However, even for this more complex situation the general pattern of the relative size of the elastic and constraint free energies noted above still holds. Instead of considering a specific constraints, let L represent the scale of the chemical distance between two constrained monomers and let a represent the general length scale of an offset. For a typical set of constraints, one has $V_{kl} \sim L$. Using the same reasoning as above for this less precise description of the constraint system yields, as a very rough criterion for the neglect of the elastic term, the inequality $\log(L/\gamma^2) \gg a/L$.

6. Discussion

We have defined a new kind of internal distance constraint, the displacement constraint. This constraint has especially simple mathematical properties which allow a simple derivation of exact expressions for the free energy (9) for a single ideal chain with these constraints. The exact free energy can be divided into a pure constraint term, which depends only on the positions of the constrained monomers in the polymer sequence, and an elastic term, which depends on the offset vectors. Thus, the addition of a displacement length does indeed change the free energy of a constrained polymer; it adds an elastic term to the free energy. We have also derived upper bounds on the free energy of an ideal polymer chain with the more physical length constraints. We argued that the form of our exact results and our bounds suggest that the elastic free energy is negligible compared with the constraint free energy when the chemical distance between the constrained pairs of monomers is much larger than the offset length. In other situations the elastic free energy may be important.

Several open problems clearly remain to be explored. First, the analysis of the effect of length constraints should be pursued further than it is here. Second, the effects of chain stiffness should be included in order to make application to practical problems more reliable and transparent. Finally, the most difficult, the effects of excluded volume should be investigated.[25−27] Excluded volume effects are likely to be important in internally constrained polymer chains because a sufficient number of constraints will cause chain collapse,[20] and excluded volume effects may profoundly change the properties of this collapse. Furthermore, the offsets tend to expand the chain, so there will be an interesting tradeoff between the elastic entropy, which decreases the entropy of the polymer as the offset lengths get bigger, and the excluded volume, the (entropy reducing) effects of which decrease as the chain expands.

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7. Appendix: δ Function Constraints, Prefactors, and the Partition Function

In calculating the partition function for the constrained polymer, one is tempted to write the partition function as an average over Gaussian distributions that represent the constraints, yielding the partition function $Z' = (3/2\pi\gamma^2)^{3M/2}Z$. Here Z is the partition function in eq 5, from which most of the results in the body of this paper are derived. A seeming advantage of using Z' for the partition function is that the thermodynamic functions are well-defined and finite for the limit $\gamma \rightarrow 0$, which corresponds to hard constraints. Using the procedure developed in the body of this paper, we find the free energy corresponding to this partition function to be

$$F' = F_0 + \frac{3k_BT}{2}\log\left[\left(\frac{2\pi}{3}\right)^M \det \mathbf{C}\right] + \frac{3k_BT}{2}\sum_{k=1}^{M}\sum_{l=1}^{M}(\mathbf{C}^{-1})_{kl}\mathbf{a}_k\cdot\mathbf{a}_l \quad (18)$$

where, in the notation of the body of this paper, $\mathbf{C} = \gamma^2\mathbf{I} + \mathbf{V}$. Note that $\mathbf{C}$ is well-defined for $\gamma = 0$, so the free energy F' is finite for the case of hard constraints whenever $\mathbf{V}$ is nonsingular. The free energy expression (9) in the body of the paper approaches infinity as γ goes to 0. Which partition function and free energy correctly describe the constrained polymer?

To answer this question, first let Z_0 represent the partition function of the unconstrained chain and let $Z(\gamma)$ represent the partition function of the constrained chain considered as a function of γ. In the limit of $\gamma \rightarrow \infty$, the effects of the constraints vanish because in this limit the harmonic constraining forces go to zero. Thus, a partition function that produces correct comparisons with the properties of the unconstrained chain should obey the consistency condition $\zeta_\infty = \lim_{\gamma\rightarrow\infty}(Z(\gamma)/Z_0) = 1$. The partition function Z' has $\zeta_\infty = (3/2\pi\gamma^2)^{3M/2}$, in violation of the consistency condition. Therefore, Z' is unsuitable for calculating thermodynamic quantities that are to be compared with those of the unconstrained chain. On the other hand, the partition function used in the body of the paper has $\zeta_\infty = 1$ and is therefore the appropriate partition function for our purposes.

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