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Phase transitions in a "many-letter" random heteropolymer

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A "many-letter" sequence model of random heteropolymers is introduced and studied. We examine the case where there is a tendency for phase separation with respect to certain types of interactions as in the case of hydrophobic and hydrophyllic interactions in proteins. It is shown that a freezing transition to a state where a few conformations are thermodynamically dominant can prevent microphase separation even for flexible chains if enough letters are used in the sequence. The number of these letters is independent of the length of the chain. It is also found that a microphase separation with respect to a stronger type of interaction prevents microphase separation with respect to any other weaker type.

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I. INTRODUCTION

A protein in living cells has a unique three-dimensional conformation which is determined by the sequence of the amino acids from which it is formed [1]. Understanding the encoding of this information in the sequence and predicting the conformation of the protein based on this information is the most intriguing problem of molecular biology. Random heteropolymers have been studied extensively as models for proteins in order to understand which features of the protein behavior come from general properties of polymeric structure and heterogeneity and which ones are due to evolutionary selection [2].

The first approach to this problem introduced the *independent-interaction model* [3–6] in which the polymeric Hamiltonian contains a random quenched set of two-body interaction virial coefficients B_{ij} for monomers i, j which are in contact. The B_{ij} interactions were taken as independent random variables following a Gaussian distribution. This study showed that below a given temperature the system undergoes a phase transition to a glasslike phase, where only few low-energy conformations are thermodynamically dominant. In these low-energy states the conformation of the polymer is frozen to microscopic scale and therefore this phase is called *frozen phase.* It was shown that the conformations have no structural overlap with each other and consequently their energies are independent [4,7]. Therefore the system can be accurately described by the random-energy model (REM) of Derrida [8,9].

The heteropolymer problem, however, should be described by a random sequence, i.e., a set of random values $\{\sigma_i\}$ characteristic for each monomer. This model will be referred to as the *sequence model* [10–13]. In this model the interaction potentials B_{ij} are correlated. The sequence model seems to be more realistic for the description of a real heteropolymer which consists of a random sequence of monomers. In the case of a "two-letter" random copolymer, the sequence model is the only one that can be used to describe the problem. In this model the random values $\{\sigma_i\}$ take only the values ±1. In the two-letter model, when similar kinds of monomers attract each other and different ones repel each other, there is an energetic preference for microphase separation between monomers of different sign [11].

This model was recently solved [14] and the same features of the frozen phase were obtained. The sequence model gives additional information about microphase separation. It was shown in [14] that, for a stiff chain, microphase separation is not possible at all since the freezing transition temperature is high enough and the system undergoes a transition into the frozen phase, before microphase separation can be reached. Below this temperature the conformation does not change with temperature and therefore the system does not reach the phase separated state. If the chain is flexible enough, the freezing temperature T_c is suppressed below the microphase transition temperature T_a and freezing occurs at a lower temperature on a background of phase separation.

Proteins, however, are consisted of 20 amino acids, referred to as letters, and the possible number of different pairwise interactions is 210. For that reason it was originally argued that the independent-interaction model describes the protein problem sufficiently. However, the phase separation features revealed by the sequence model give a much richer phase diagram and it is interesting to retain them. The sequence Hamiltonian solved in [14] gives a clear picture for the two-letter problem, but flexibility plays a crucial role in the model and is difficult to be monitored or defined on a numerical lattice model [1,15–17], for example. If the flexibility is very large it can reduce the freezing temperature to such an extent that freezing may not be observed for kinetic reasons.

In the present work we study the many-letter sequence model, introduced by Garel and Orland [10], by assigning to each monomer i a set of p generalized charges $\{\sigma_i^\mu\}_{\mu=1}^{p}$ with every σ_i^μ taking values ±1 with equal probabilities. Then we have 2^p possible letters for each monomer. By increasing the number of letters we can increase the heterogeneity of the system and the freezing temperature. It can be seen immediately that this model has the certain advantage of introducing different types of interactions, the strength of which can be modified independently. It can therefore be used to reflect the fact that different features of amino acid interactions are not equally important. It has been suggested [18], for example, that hydrophobicity is the most important feature in proteins and hence proteins should be treated effectively as a two-letter polymer.

In what concerns the freezing transition we find that the number of charges necessary to lead to a freezing transition is of order unity and independent of the length of the chain. The possibility of phase separation of more than one charge is also examined and it is found that the separation transition of the strongest charge, i.e., with the strongest tendency for phase separation, which occurs first, prevents the phase separation with respect to any other weaker charge.

In Sec. II the many-letter model is introduced and a qualitative discussion of the order parameters related to freezing and microphase separation is given. In Sec. III the effect of heterogeneity on the microphase separation of one charge is discussed. In Sec. IV the effect of phase separation of charge on the phase separation of an other is described. In Sec. V a general discussion of the results is given including the effect of fluctuations to the microphase separation transition.

II. THE MODEL AND DEFINITION OF THE ORDER PARAMETERS

We consider a random heteropolymer where every monomer i in the quenched sequence has a set of p generalized charges $\{\sigma_i^\mu\}_{\mu=1}^p$ with each σ_i^μ taking values ±1 with equal probabilities. Therefore, we have 2^p possible letters for each monomer. The self-interactions between monomers is described by the Hamiltonian

$$\mathcal{H} = \sum_{i,j} B_{ij} U(\mathbf{r}_i - \mathbf{r}_j), \tag{2.1}$$

where the conformation is given in terms of the coordinates of its monomers $\{\mathbf{r}_i\}$ and $U(\mathbf{r}_i - \mathbf{r}_j)$ describes a short-range potential. The two-body interaction virial coefficient is given by

$$B_{ij} = \sum_{\mu=1}^{p} \chi_\mu \sigma_i^\mu \sigma_j^\mu, \tag{2.2}$$

where χ_μ is the Flory parameter for interactions between two charges of the same kind μ. In this problem we consider $\chi_\mu < 0$, so that positive charges of each kind will attract positive charges of the same kind and repel negative ones, etc.

We will also assume that there is an overall attraction constant in the two-body term, as well as a three-body repulsion. These two interactions have not been explicitly included in the Hamiltonian. The effect of these terms is to lead the polymer into a compact globular state with constant density [19]. In our study we keep only the terms related with heteropolymeric effects.

In this system, attraction between charges of each kind μ with the same sign generates an energetic preference for microphase separation. As has been discussed in previous studies [10,11], the order parameter which describes this phase separation is

$$m_\mu(\mathbf{R}) = \sum_i \sigma_i^\mu \delta(\mathbf{r}_i^\alpha - \mathbf{R}). \tag{2.3}$$

In a system with one charge, i.e., the usual two-letter copolymer, this energetic tendency for phase separation is influenced by quenched disorder in the polymeric sequence. From our study of the one-charge problem [14] we know that quenched disorder can influence the system in two ways.

(i) If the polymer chain is flexible it can undergo a microphase separation transition at some temperature T_a, described by a mean field theory for the order parameter defined in Eq. (2.3). At this stage, quenched disorder simply suppresses phase separation in large scales. At a lower temperature T_c, the system undergoes a phase transition into a phase where, due to frustration, only a few frozen conformations are thermodynamically important [7]. Below this temperature the free energy of the chain does not depend on temperature since the system has lost all its entropy.

(ii) If the polymer chain is stiff the transition into the frozen phase occurs at high enough temperature, so that microphase separation is not observed. Freezing prevents microphase separation only in stiff chains where it occurs at a temperature higher than the microphase separation transition temperature.

One simple way to approach the problem with many charges is to investigate the effect of the energetic preferences of additional charges on the microphase transition of one charge. For this purpose we can write the two-body term of Eq. (2.2) as

$$B_{ij} = \chi_1 \sigma_i^p \sigma_j^p + \chi_2 \sum_{\mu=1}^{p-1} \sigma_i^\mu \sigma_j^\mu, \tag{2.4}$$

where we assume that the tendency for phase separation of the designated pth charge is much stronger than of the other charges. For large values of p this model is equivalent to

$$B_{ij} = \chi_1 \sigma_i \sigma_j + \chi_2 B_{ij}^0, \tag{2.5}$$

where B_{ij}^0 takes independent random values following, for example, a Gaussian distribution [5]. In this case we have one charge plus noise. The sign of χ_2 is not important since the same approach developed in Sec. III can be modified for $\chi_2 > 0$. The effect of noise is described by an extra order parameter $Q_{\alpha\beta}$, which appears in the course of the replica calculation in Sec. III, defined as

$$Q_{\alpha\beta}(\mathbf{R}_1 - \mathbf{R}_2) = \sum_i \delta(\mathbf{r}_i^\alpha - \mathbf{R}_1)\delta(\mathbf{r}_i^\beta - \mathbf{R}_2). \tag{2.6}$$

From this definition we see that

$$\int d\mathbf{R}_1 Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) = \rho_\beta(\mathbf{R}_2). \tag{2.7}$$

Since we are considering the case of a collapsed chain of constant density throughout the globule, the density must be independent of position. Therefore, Eq. (2.7) implies that $Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) = Q_{\alpha\beta}(\mathbf{R}_1 - \mathbf{R}_2)$. This argument also applies to the case of an incompressible melt.

This order parameter shows the average structural overlap between two conformations and has been used to describe the transition into the frozen phase mentioned above [4,5]. For the heteropolymer models studied before it was found that the local minima of the potential surface of the system, usually called pure states, correspond to entirely different conformations. It was shown that

$$Q_{\alpha\beta} = \begin{cases} \rho\delta(\mathbf{R}_1 - \mathbf{R}_2) & \text{for } \alpha,\beta \text{ in the same state} \\ 0 & \text{for } \alpha,\beta \text{ in different states.} \end{cases} \tag{2.8}$$

In order to demonstrate how this order parameter describes the freezing transition it is useful to define [20,21] the probability $P(q)$ that any two conformations have an overlap q as

$$P(q) = \sum_{\alpha\beta} P_\alpha P_\beta \delta(Q_{\alpha\beta} - q), \tag{2.9}$$

where P_α, P_β are the Boltzmann factors for conformations α and β. At high temperatures, $P(q) = \delta(q)$ since all structurally different states are accessible through thermal fluctuations. As the temperature is lowered, low energy states become more important. Then, it was shown that the probability $P(q)$ changes into

$$P(q) = x_0\delta(q) + (1 - x_0)\delta(q - 1), \tag{2.10}$$

where the Boltzmann factors of the different states satisfy the relation

$$x_0 = 1 - \sum_\alpha P_\alpha^2. \tag{2.11}$$

The parameter x_0 is unity above the freezing transition temperature T_c and goes as $x_0 = T/T_c$ below T_c. Given the fact that $\sum_\alpha P_\alpha = 1$, it is seen that the smaller the temperature, i.e., the smaller the value of x_0, the fewer the thermodynamically dominant conformations. We see therefore how the Q order parameter monitors the freezing transition to a phase where the number of the thermodynamically dominant conformations are of order unity and their conformations are frozen to microscopic scale.

To return to the many-charge problem formulated according to Eq. (2.4), we will assume that the polymeric chain is flexible enough to allow microphase separation of the designated pth charge in the absence of other charges. We will calculate the effect of the extra charges on the microphase transition through their tendency to lead into freezing. This is described in Sec. III.

However, if the tendency of the additional charges to phase separation is comparable to that of the designated charge, we need to examine the effect of the microphase transition of one charge on the microphase transition of the other. This is described in Sec. IV.

The average over disorder is taken with the aid of the replica trick [22], which consists in taking the average of the logarithm of the partition function through the formula

$$\langle \ln Z \rangle_{\text{av}} = \lim_{n\to 0} \frac{\langle Z^n \rangle_{\text{av}} - 1}{n}. \tag{2.12}$$

The order parameter $Q_{\alpha\beta}$ appears formally as the overlap between conformations of different replicas. Due to the well known analogy of $P(q)$ introduced in Eq. (2.9) referring to replicas and pure states [23], this order parameter obtains the physical meaning explained above.

III. EFFECT OF NOISE CHARGES ON A STRONGLY SEPARATING CHARGE

In this section we will consider that a designated charge, such as hydrophobicity, has a much stronger tendency for phase separation than the other charges, as implied by Eq. (2.4). We will also consider a chain flexible enough to allow phase separation of the designated charge in the absence of other charges by suppressing the freezing temperature of the one-charge system at very low temperatures.

By applying the replica trick, we consider the average of the product of n identical copies of the partition function

$$\langle Z^n \rangle_{\text{av}} = \left\langle \int \mathcal{D}\mathbf{r}_i^\alpha g(\mathbf{r}_{i+1}^\alpha - \mathbf{r}_i^\alpha) \exp\left[\sum_\alpha \sum_{i,j} \left(b_1 \sigma_i^p \sigma_j^p + \sum_{\mu=1}^{p-1} b_2 \sigma_i^\mu \sigma_j^\mu \right) U(\mathbf{r}_i^\alpha - \mathbf{r}_j^\alpha) \right] \right\rangle_{\text{av}}, \tag{3.1}$$

where $g(\mathbf{r}_{i+1}^\alpha - \mathbf{r}_i^\alpha)$ is the Gaussian polymeric term [19], often called the elastic term given by

$$g(\mathbf{r}_{i+1}^\alpha - \mathbf{r}_i^\alpha) = \frac{1}{(2\pi a^2)^{3/2}} \exp\left[-\frac{(\mathbf{r}_{i+1}^\alpha - \mathbf{r}_i^\alpha)^2}{2a^2} \right], \tag{3.2}$$

and $b_1 = -\chi_1/T, b_2 = -\chi_2/T$, with $b_1 \gg b_2$.

The n-replica partition function can be rewritten as

$$\Big\langle\int \mathcal{D}\mathbf{r}_i^\alpha g(\mathbf{r}_{i+1}^\alpha-\mathbf{r}_i^\alpha)\int \mathcal{D}\Psi_\alpha^\mu(\mathbf{R})\exp\left[-\frac{1}{4b_1}\sum_\alpha\int d\mathbf{R}[\Psi_\alpha^p(\mathbf{R})]^2+\sum_\alpha\int d\mathbf{R}\Psi_\alpha^p(\mathbf{R})\sum_i\sigma_i^p\delta(\mathbf{r}_i^\alpha-\mathbf{R})\right]$$

$$\times\exp\left[-\frac{1}{4b_2}\sum_\alpha\sum_{\mu=1}^{p-1}\int d\mathbf{R}[\Psi_\alpha^\mu(\mathbf{R})]^2+\sum_\alpha\sum_{\mu=1}^{p-1}\int d\mathbf{R}\Psi_\alpha^\mu(\mathbf{R})\sum_i\sigma_i^\mu\delta(\mathbf{r}_i^\alpha-\mathbf{R})\right]\Big\rangle_{\mathrm{av}}, \quad (3.3)$$

by performing a Hubbard-Stratonovich transformation [24] with respect to the variable

$$\sum_i \sigma_i\delta(\mathbf{r}_i^\alpha-\mathbf{R}) \quad (3.4)$$

and also taking $U(\mathbf{r}_i^\alpha-\mathbf{r}_j^\alpha)$ as a δ function. The fields $\Psi_\alpha^\mu(\mathbf{R})$ have been introduced formally as integration variables.

We perform the disorder average separately for the designated-charge part and the noise-charge part. We call

$$I_1=\int \mathcal{D}m_\alpha^p(\mathbf{R})\exp\left\{-b_1\sum_\alpha\int d\mathbf{R}[m_\alpha^p(\mathbf{R})]^2+b_1\sum_\alpha\int d\mathbf{R}m_\alpha^p(\mathbf{R})\sum_i\sigma_i^p\delta(\mathbf{r}_i^\alpha-\mathbf{R})\right\}, \quad (3.5)$$

where we have rescaled the integration variable $m_\alpha=(1/2b)\Psi_\alpha$. By performing the disorder average and keeping only the Gaussian term, we get

$$\langle I_1\rangle_{\mathrm{av}}=\int \mathcal{D}m_\alpha^p(\mathbf{R})\exp\left\{-b_1[m_\alpha^p(\mathbf{R})]^2+b_1^2\sum_{\alpha,\beta}\int d\mathbf{R}_1d\mathbf{R}_2m_\alpha^p(\mathbf{R}_1)m_\alpha^p(\mathbf{R}_2)\sum_i\delta(\mathbf{r}_i^\alpha-\mathbf{R}_1)\delta(\mathbf{r}_i^\beta-\mathbf{R}_2)\right\}. \quad (3.6)$$

The noise charge part is similarly transformed into

$$\langle I_2\rangle_{\mathrm{av}}=\prod_{\mu=1}^{p-1}\int \mathcal{D}m_\alpha^\mu(\mathbf{R})\exp\left\{-b_2[m_\alpha^\mu(\mathbf{R})]^2+b_2^2\sum_{\alpha\beta}\int d\mathbf{R}_1d\mathbf{R}_2m_\alpha^\mu(\mathbf{R}_1)m_\alpha^\mu(\mathbf{R}_2)\sum_i\delta(\mathbf{r}_i^\alpha-\mathbf{R}_1)\delta(\mathbf{r}_i^\beta-\mathbf{R}_2)\right\}. \quad (3.7)$$

We recognize in this formula the order parameter $Q_{\alpha\beta}$ as defined in Eq. (2.6). By taking into account the translational invariance condition as explained in Eq. (2.7) we rewrite Eq. (3.7) as

$$\langle I_2\rangle_{\mathrm{av}}=\prod_{\mu=1}^{p-1}\int \mathcal{D}Q_{\alpha\beta}(\mathbf{k})\int \mathcal{D}m_\alpha^\mu(\mathbf{k})\exp\left[-\sum_{\alpha,\beta}\sum_{\mathbf{k}\neq0}[b_2\delta_{\alpha\beta}-b_2^2Q_{\alpha\beta}(\mathbf{k})]m_\alpha^\mu(\mathbf{k})m_\beta^\mu(-\mathbf{k})\right]$$
$$\times\delta\left(Q_{\alpha\beta}(\mathbf{k})-\sum_i e^{i\mathbf{k}(\mathbf{r}_i^\alpha-\mathbf{r}_i^\beta)}\right), \quad (3.8)$$

where $\mathbf{k}$ is the wave vector. We consider only nonzero wave vectors because in a system with equal probability for positive and negative signs of the same charge $m(\mathbf{k}=0)=0$.

Since there is, practically, no tendency for phase separation with respect to the $p-1$ weak charges, we can integrate out the $m_\alpha^\mu(\mathbf{k})$ variable, which is not a meaningful parameter for the system. After integration of $m_\alpha^\mu(\mathbf{k})$ and introducing the integral representation of the δ function we obtain

$$\langle I_2\rangle_{\mathrm{av}}=\int \mathcal{D}Q_{\alpha\beta}(\mathbf{k})\exp\left\{-(p-1)\sum_{\mathbf{k}\neq0}\ln[\det P_{\alpha\beta}(\mathbf{k})]\right\}$$
$$\times\int \mathcal{D}\vartheta_{\alpha\beta}(\mathbf{k})\exp\left\{-(p-1)b_2^2\sum_{\alpha,\beta}\sum_{\mathbf{k}\neq0}\left[\vartheta_{\alpha\beta}(\mathbf{k})Q_{\alpha\beta}(\mathbf{k})+\sum_i\vartheta_{\alpha\beta}(\mathbf{k})e^{i\mathbf{k}(\mathbf{r}_i^\alpha-\mathbf{r}_i^\beta)}\right]\right\}, \quad (3.9)$$

with the matrix elements given by $P_{\alpha\beta}(\mathbf{k})=b_2\delta_{\alpha\beta}-b_2^2Q_{\alpha\beta}(\mathbf{k})$.

We need to take the conformational (thermal) average. By combining the conformation dependent part of the results given in Eqs. (3.6) and (3.9), the conformational average resembles the partition function of a polymer in an external field [19]

$$Z_1=\int g(\mathbf{r}_{i+1}^\alpha-\mathbf{r}_i^\alpha)\exp\left[-(p-1)b_2^2\sum_{\alpha,\beta}\sum_i\vartheta_{\alpha\beta}(\mathbf{r}_i^\alpha-\mathbf{r}_i^\beta)+b_2^2\sum_{\alpha,\beta}\sum_i m_\alpha^p(\mathbf{r}_i^\alpha)m_\beta^p(\mathbf{r}_i^\beta)\right]. \quad (3.10)$$

This can be calculated by a high temperature expansion of the $[m^p]^2$ term [25], which is equivalent to a perturbation theory around a compact globule with ground state dominance, as has been shown before for the single charge problem [11]. We can now combine all this into one expression for the total nth power of the partition function

$$
\begin{aligned}
\langle Z^n\rangle_{\mathrm{av}} = \int & \mathcal{D}m^p_\alpha(\mathbf{k})\mathcal{D}Q_{\alpha\beta}(\mathbf{k})\mathcal{D}\vartheta_{\alpha\beta}(\mathbf{k}) \exp\left\{-(p-1)\sum_{\mathbf{k}\neq 0}\ln[\det P_{\alpha\beta}(\mathbf{k})] - b_1[m^p_\alpha(\mathbf{k})]^2\right\} \\
&\times \exp\left\{-(p-1)b_2^2\sum_{\alpha,\beta}\sum_{\mathbf{k}\neq 0}\left[\vartheta_{\alpha\beta}(\mathbf{k})Q_{\alpha\beta}(\mathbf{k}) + \ln Z_\vartheta\right]\right\} \\
&\times \exp\left\{b_1^2\sum_{\alpha\beta}\sum_{i}\sum_{\mathbf{k}_1,\mathbf{k}_2\neq 0} m^p_\alpha(\mathbf{k}_1)m^p_\beta(\mathbf{k}_2)\left\langle e^{i(\mathbf{k}_1\mathbf{r}_i^\alpha+\mathbf{k}_2\mathbf{r}_i^\beta)}\right\rangle_\vartheta\right. \\
&\left.+\frac{b_2^4}{2!}\sum_{\alpha,\ldots,\delta}\sum_{i,j}\sum_{\mathbf{k}_1,\ldots,\mathbf{k}_4\neq 0} m^p_\alpha(\mathbf{k}_1)m^p_\beta(\mathbf{k}_2)m^p_\gamma(\mathbf{k}_3)m^p_\delta(\mathbf{k}_4)\left\langle e^{i(\mathbf{k}_1\mathbf{r}_i^\alpha+\mathbf{k}_2\mathbf{r}_i^\beta+\mathbf{k}_3\mathbf{r}_j^\gamma+\mathbf{k}_4\mathbf{r}_j^\delta)}\right\rangle_\vartheta\right\}. \qquad (3.11)
\end{aligned}
$$

The average $\langle\,\rangle_\vartheta$ denotes the conformational average with respect to a Gaussian chain in external field ϑ and $-\ln Z_\vartheta$ the corresponding free energy. The value of the fields m, Q, ϑ, has to be determined by self-consistent equations. At this point we notice that if we consider the self-consistent equation $\partial f/\partial Q = 0$, the differentiation eliminates the m-dependent part. A solution can be obtained when the scale R_t of the ϑ field is equal to the scale of the Q field. Then the resulting equation is similar to the one of the random heteropolymer discussed previously in detail [14] and the arguments for the replica symmetry breaking pattern according to Eq. (2.8) hold true.

As a result there is no effect of the ϑ field above the freezing point. Then the expression in Eq. (3.11) is evaluated and we obtain the intensive free energy per replica

$$
\begin{aligned}
f/n = {} & (p-1)\frac{\ln(1-b_2x_0)}{x_0} - \frac{s}{x_0} \\
&+b_1\sum_{\mathbf{k}\neq 0}\left[c^2\mathbf{k}^2 - (b_1x_0 - 1)\right][m^p(\mathbf{k})]^2 \\
&+\frac{x_0^3b_1^4}{2}\sum_{\mathbf{k}_1,\mathbf{k}_2\neq 0}\frac{[m^p(\mathbf{k}_1)]^2[m^p(\mathbf{k}_2)]^2}{a^2(\mathbf{k}_1^2+\mathbf{k}_2^2)}. \qquad (3.12)
\end{aligned}
$$

The surface tension term $c^2\mathbf{k}^2$ has been eliminated by taking the potential as a precise δ function and is reintroduced here to prevent phase separation with large wave numbers. The parameter x_0 is the size of the Parisi diagonal block [26] and $s \sim \ln(v/a^3)$ is the flexibility parameter. The density of the incompressible system has been taken to be constant and equal to unity. From Eq. (3.12) we see immediately that phase separation is possible only when $b_1x_0 > 1$ and $b_2x_0 < 1$. Since the tendency of the pth charge to phase separate is much stronger than the tendency of the noise charges $b_1 > b_2$, the transition is possible. By performing the mean field with respect to m we find

$$
f/n \sim \frac{b_1(b_1x_0-1)^3a^2}{(b_1x_0)^3c^2} - \frac{s}{x_0} + (p-1)\frac{\ln(1-b_2x_0)}{x_0}. \qquad (3.13)
$$

Optimization with respect to x_0 gives

$$
3\frac{a^2}{c^2}\left(1-\frac{1}{b_1x_0}\right)^2 + s - \frac{(p-1)b_2x_0}{1-b_2x_0} - (p-1)\ln(1-b_2x_0) = 0. \qquad (3.14)
$$

First we observe that for $p = 1$ the freezing transition temperature at which $x_0 = 1$ is $T_c = |\chi_1|(1 - s^{1/2}c/a)$. as found in [14]. This indicates the possibility that at some finite flexibility T_c becomes zero. The many-charge model can change this behavior.

We consider the case of large flexibility s and also $b_1x_0 > 1$ and $b_2x_0 < 1$. In this case we can ignore the first term in Eq. (3.14) and expand the logarithm to lowest nonvanishing order for b_2x_0. For large values of p we can replace $p - 1$ by p to obtain

$$
b_2x_0 = (s/p)^{1/2}. \qquad (3.15)
$$

Since $b_2 = |\chi_2|/T$, then $x_0 = T/T_c$, where

$$
T_c = |\chi_2|(p/s)^{1/2}. \qquad (3.16)
$$

For any temperature above T_c the parameter x_0 is equal to unity. We see that the additional noise charges raise the freezing temperature by increasing the total heterogeneity of the system. This can be interpreted as a rescaling of the flexibility parameter. The increase of the freezing temperature is basically due to the existence of strong enough noise in the model described by Eq. (2.5). Then the freezing temperature can be raised above the microphase separation temperature T_a even for flexible chains. When $T_c > T_a$ the system freezes at a microscopic scale and does not depend on temperature. Therefore microphase separation is prevented.

We see that the noise charges have no effect on the microphase transition temperature or wavelength or amplitude. The absence of any effect of the noise on the phase separation, as long as $T_c < T_a$, is due to the mean field treatment of the freezing order parameter Q, according to which, above freezing, we set the field ϑ equal to zero. We performed another calculation where we treat the noise charges as perturbation. Even in this treatment we found that the noise has no effect on the $[m^p]^2$ term in free energy and therefore does not influence the transition

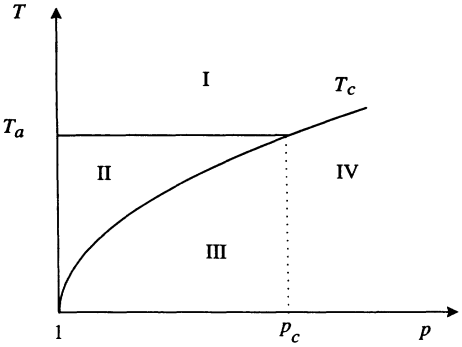

FIG. 1. Phase diagram of the many-charge model. It is assumed that for $p = 1$ the chain is very flexible to suppress the freezing temperature at $T = 0$. The freezing temperature T_c is plotted against the number of charges. The microphase transition temperature T_a is independent of the number of charges. Region I is the uniform homopolymeric globule without phase separation or definite conformation. In region II there is microphase separation without definite conformation. In region III there is microphase separation and definite conformation. In region IV there is definite conformation, but freezing to this conformation occurs above T_a and it prevents phase separation.

temperature within the mean field framework for m^p. By considering contributing diagrams in all orders we found that it does not affect the wavelength either, but it only alters the amplitude of the phase separation. This can be understood from the fact that the second-order term is a one-replica term and the relevant perturbation corrections are of the form $\langle \delta(\mathbf{r}_i - \mathbf{r}_j) \rangle$, which is an overall compression that has no effect since we are examining the incompressible globule or melt. On the basis of these results we can propose the phase diagram of Fig. 1 for the multiple charge heteropolymer Hamiltonian described by Eqs. (2.1) and (2.5).

We notice that our treatment of the many-charge problem in this section resembles formally, up to Eq. (3.11), the study of Amit *et al.* [27,28] of the effect of extensively many spin patterns on the retrieval ability of a neural network. It is important to distinguish the different physics of the two systems. In the neural network there is a glass phase only if the number of patterns scale as $p = \alpha N$, where α is a proportionality constant. In the polymer system, due to the three-dimensional space dependence of the order parameter, the additional space integration creates a volume factor and the noise term contributes to the free energy when the number of charges is of order unity. Therefore, in the polymer system the existence of additional charges of order unity can lead the system to a glasslike phase, which we call frozen phase, and prevent the system from "retrieving" microphase separation. Hence we arrive at the conclusion that additional charges increase the tendency of even flexible chains to undergo a freezing transition and the critical number of charges required to cause freezing is independent of the length of the chain.

IV. EFFECT OF THE PHASE SEPARATION OF ONE CHARGE ON THE PHASE SEPARATION OF ANOTHER

We will now consider very flexible chains for which, as shown in [14], phase separation occurs before freezing (this corresponds to the "MPS" domain of the phase diagram, Fig. 4 of [14]). In this regime there is no replica symmetry breaking and the relevant order parameter is the partial density m, while the two-replica order parameter Q is irrelevant.

We examine the case where the charges have comparable tendency for microphase separation. In that case we need to perform a mean field calculation for all microphase order parameters. We consider for simplicity two charges:

$$B_{ij} = \chi_1 \sigma_i^1 \sigma_j^1 + \chi_2 \sigma_i^2 \sigma_j^2. \tag{4.1}$$

Then the free energy of the system is given by

$$\begin{aligned} f = &\sum_{\mathbf{k}\neq 0} \Big[c^2\mathbf{k}^2 - (b_1 - 1/4)\Big] m_1^2(\mathbf{k}) \\ &+ \sum_{\mathbf{k}\neq 0} \Big[c^2\mathbf{k}^2 - (b_2 - 1/4)\Big] m_2^2(\mathbf{k}) \\ &+ \frac{1}{2} \sum_{\mathbf{k}_\alpha, \mathbf{k}_\beta \neq 0} (\mathbf{k}_\alpha^2 + \mathbf{k}_\beta^2)^{-1} \big[m_1^2(\mathbf{k}_\alpha) m_1^2(\mathbf{k}_\beta) \\ &+ m_2^2(\mathbf{k}_\alpha) m_2^2(\mathbf{k}_\beta) + 2 m_1^2(\mathbf{k}_\alpha) m_2^2(\mathbf{k}_\beta)\big]. \end{aligned} \tag{4.2}$$

One solution of this is $m_1(\mathbf{k}) = m_1 \Delta(\mathbf{k} - \mathbf{k}_1)$ and $m_2(\mathbf{k}) = m_2 \Delta(\mathbf{k} - \mathbf{k}_2)$, from which

$$\begin{aligned} f = &(c^2\mathbf{k}_1^2 - \tilde{b}_1) m_1^2 + (c^2\mathbf{k}_2^2 - \tilde{b}_2) m_2^2 \\ &+ \frac{1}{4} \left(\frac{m_1^4}{a^2\mathbf{k}_1^2} + \frac{m_2^4}{a^2\mathbf{k}_2^2} + \frac{m_1^2 m_2^2}{a^2(\mathbf{k}_1^2 + \mathbf{k}_2^2)} \right), \end{aligned} \tag{4.3}$$

where we have set $\tilde{b}_1 = b_1 - 1/4$ and $\tilde{b}_2 = b_2 - 1/4$. If the two charges have exactly the same tendency for phase separation $\tilde{b}_1 = \tilde{b}_2$, then we can replace $m_1^2 + m_2^2 = m^2$ and get the results of the single charge phase separation for the composite parameter m. In this case the existence of more than one charge only increases the degeneracy of this state.

More interesting appears the case where the two tendencies differ and the one phase transition precedes the other. Assume that $\tilde{b}_1 > \tilde{b}_2$, so that the phase separation of the charge "1" precedes at temperature T_1. At this point the equilibrium value for the second transition is $m_2 = 0$. Then the mean field values for $m_1, \mathbf{k}_1$ are found

$$\mathbf{k}_1^2 = \frac{\tilde{b}_1}{3c^2}, \quad m_1 = (2/3)\frac{\tilde{b}_1 a}{c} \tag{4.4}$$

and the transition is third order.

In the absence of the first phase separation a further decrease of temperature leads to a transition with respect to m_2 at temperature T_2. However, the existence of $m_1 \neq 0$ changes the picture dramatically. If we assume that the value of $m_1, \mathbf{k}_1$ is given by Eq. (4.4), substitution of this into Eq. (4.3) gives

$$\frac{f}{n}=\left(c^2\mathbf{k}_2^2+\frac{(4/3)\tilde{b}_1}{1+(3c^2/\tilde{b}_1)\mathbf{k}_2^2}-\tilde{b}_2\right)m_2^2+\frac{m_2^4}{4a^2\mathbf{k}_2^2}. \quad (4.5)$$

The minimum for the second-order term occurs for

$$\mathbf{k}_2^2=\frac{\tilde{b}_1}{3c^2} \quad (4.6)$$

and the second-order term coefficient becomes $\tilde{b}_1-\tilde{b}_2>0$, so the transition is impossible. This is due to this extra coupling term in Eq. (4.3), which is due to the polymeric effect and the quenched disorder in the sequence.

This result means that phase separation of a stronger charge prevents phase separation of weaker charges. This can be understood qualitatively by the fact that the wave number of the microphase separation is proportional to the strength of the charge, as can be seen from Eq. (4.4). The microphase separation of weaker charges occurs at lower temperature at smaller wave numbers, that is, at larger scales. In that case, the second phase separation would involve reorganization of the domains of the stronger charge and therefore loss of free energy.

V. DISCUSSION

In the present work we have solved the many-letter heteropolymer where different interaction types are allowed for every monomer. These interaction types are called charges. We consider the case of one charge having a strong tendency for phase separation, as, for example, in the case of hydrophobicity. The quenched disorder in the polymeric sequence introduces frustrations which can lead the system to a frozen state. However, in the absence of other charges it is known that flexibility can suppress the freezing temperature significantly. Introducing additional charges, which reflect other features of the monomers, we increase the heterogeneity of the system and therefore the frustrations and the tendency for freezing. It was shown here that the introduction of different charges in this model corresponds directly to the use of more letters of the protein alphabet and the use of these extra letters raises the freezing temperature by effectively rescaling the flexibility parameter.

Moreover, it was shown that the number of these letters is independent of the length of the polymer. This signifies that the number of letters that will lead to freezing in proteins is the same for proteins with 100 as well as for proteins with 500 amino acids. This result verifies the universality of the genetic code and is obtained by a model that considers only the heteropolymeric features of proteins without taking into account the evolutionary selection of sequences.

The discussion of microphase separation throughout this work and previously was based on a mean field theory for the order parameter $m(\mathbf{k})$. However, in an early study by Dobrynin and Erukhimovich [29] it was pointed out that, considering one-loop corrections due to fluctuations, the renormalized Green's function becomes of the form $G^{-1}(\mathbf{k})=(\mathbf{k}-\mathbf{k}_0)^2+r$ and resembles the Green's function of the Hamiltonian of the weak crystallization theory [30–32]. In his seminal work in weak crystallization theory [30] Brazovskii showed that in certain systems a continuous order transition of the type of the Landau Hamiltonian is impossible. Fluctuations stabilize the disordered phase and prevent the renormalized mass from becoming zero except for $T=0$. A phase transition, however, is possible because the ordered phase becomes first locally stable and eventually globally stable so that the phase transition is of first order. Brazovskii showed that this transition occurs at some large enough value of the renormalized mass coefficient r, so that the one-loop approximation is valid.

The Brazovskii theory, originally constructed to describe the nonuniform phase of the cholesteric liquid crystal [33,34], has very important implications on the theory of microphase separation of copolymers. In Leibler's mean field theory of periodic block copolymers [35] the Landau Hamiltonian has exactly the form considered by Brazovskii. This was pointed out by Fredrickson and Helfand [36], who calculated the changes in Leibler's phase diagram, by mapping Leibler's Hamiltonian onto Brazovskii's Hamiltonian. Later, Dobrynin and Erukhimovich [37] reproduced the results of Fredrickson and Helfand for the block copolymer introducing a variational method.

In the original study of the random copolymer in the context of fluctuational theory Dobrynin and Erukhimovich [29] speculated that the system belongs to the Brazovskii universality class and should undergo a first-order transition instead of the continuous third-order transition described by mean field. They did not, however, consider a detailed study of the system due to fluctuations. The same authors recently claimed [38] that application of their variational method to the random copolymer shows that this system does not undergo a phase transition at all and this result probably reflects also the behavior of the correlated random copolymer [25,39,40]. If this is correct and the ordered phase never becomes globally stable, as opposed to the mechanism of the Brazovskii theory, the one-loop approximation breaks down. This happens because one can reduce temperature further until, much before $T=0$, higher-loop corrections become more divergent than the one loop and a series of divergent diagrams with interchanging sign has to be summed. So it seems that absolute loss of stability of the disordered phase when $r\to 0$ is, in principle, possible. This case was mentioned by Brazovskii, but it was not studied. In any case, the results of a variational method for so delicate questions is not to be trusted and a direct calculation of the free energy of the ordered phase must be performed. This work is under current investigation.

It should be mentioned that if the transition occurs through the Brazovskii first-order mechanism all the results presented in Sec. IV are valid, although the study assumed a continuous transition, since in the first-order mechanism the mass coefficient of the bare Green's function has to become negative also. This was shown in Sec. IV to be impossible for the weak charge in the presence of phase separation for the strong charge. This effect can have interesting applications even for periodic sequences with two charges (four letters) or one periodic and one random charge. The charges can be chosen so that selection of the appropriate experimental conditions can activate or deactivate one charge or the other and lead to phase separation with respect to the scale of the one charge preventing the separation of the other and vice versa.

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