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On the Theory of the Condensed States of Heteropolymers

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The collapse (globulization) of an ideal heteropolymer chain under the action of an external attractive field is considered. The problem of the collapse of different types of primary structures, including mobile, periodic, large-block, and statistical structures, is formulated. It is shown that for a random heteropolymer, the mathematical image of the globular state is the chain-length independence of the probability distribution of a random thermal distribution function of the end monomer coordinates. The free energy per monomer of a chain in a globular state and local densities of monomers of all types are shown to be a self-averaging quantities. An exactly solvable model is proposed for a globule formed by a statistical heteropolymer chain. In this model, different types of monomers are attracted to different centers by linear elastic forces with identical elastic constants. The modulus of elasticity is obtained for a heteropolymer globule with respect to the attraction of different types of monomers in different directions. It is shown that this modulus is higher for a short-periodic polymer than for a statistical one.

KEY WORDS: Polymer collapse; heteropolymers; one-dimensional disordered systems.

INTRODUCTION

By heteropolymers we mean a molecular chain consisting of different types of links. The condensed globular states of such heteropolymers, like proteins and DNA, are of primary importance in biology. The discovery of the molten state of protein globules triggered the special interest in the physical theory of heteopolymer globules.$^{(5)}$

A systematic approach to the theory of homopolymer globules was first proposed by I. M. Lifshitz$^{(1)}$ and subsequently developed in a series of

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articles (see reviews in Refs. 2, 3). The predictions of the Lifshitz theory are in quantitative agreement with the available experimental results.[4]

The first step of the Lifshitz theory was the consideration of a homopolymer collapse without any volume interactions under the influence of an external attractive field. Hence, it is natural to use such a problem as the starting point for constructing the theory of heteropolymer globules.

A distinguishing feature of the heteropolymers is that different types of links are subjected to different fields $\varphi_\alpha(\mathbf{x})$, the index α running over the values corresponding to the types of links in the heteropolymer.

The problem of globulization of a heteropolymer in an external field is apparently independently interesting from a physical point of view due to the question concerning the adsorption of such macromolecules. The relative simplicity of this problem stems from fact that in the absence of volume interactions, a macromolecule remains one dimensional in a certain sense, and its wandering in spatially inhomogeneous fields is a Markov process.

2. GREEN'S FUNCTION AND THE PARTITION FUNCTION

It is convenient to write the Green's function, i.e., the partition function of a polymer with fixed ends, in the form

$$G\left(\begin{matrix}1\\ \mathbf{y}\end{matrix}\,\middle|\,\begin{matrix}N\\ \mathbf{x}\end{matrix}\right)=\int \delta(\mathbf{x}-\mathbf{x}_N)\prod_{t=2}^{N}\hat{Q}_{\alpha(t)\alpha(t-1)}\,\delta(\mathbf{y}-\mathbf{x}_1)\,d^3x_N\,d^3x_1 \tag{1}$$

Here, t is the number of the link in the chain, the function $\alpha(t)$ describes the primary structure, and the transfer operator has the form

$$\hat{Q}_{\alpha\alpha'}=\exp[-\varphi_\alpha(\mathbf{x})/T]\,\hat{g}_{\alpha\alpha'} \tag{2}$$

where the operator $\hat{g}_{\alpha\alpha'}$ characterizes the bond between the links α and α'; it can be assumed on the basis of the beads-on-a-string model[3] that this operator has a difference kernel $g_{\alpha\alpha'}(|\mathbf{x}-\mathbf{x}'|)$, for example, the Gaussian

$$g_{\alpha\alpha'}(\mathbf{x};\mathbf{x}')=\left(\frac{2\pi a_{\alpha\alpha'}^2}{3}\right)^{-3/2}\exp\left[-\frac{3(\mathbf{x}-\mathbf{x}')^2}{2a_{\alpha\alpha'}^2}\right] \tag{3}$$

$a_{\alpha\alpha'}$ being the length of the corresponding bond.

Since we are not interested in the translational entropy of the chain as a whole, we shall assume that the starting point of the chain is fixed at the origin ($\mathbf{y}=0$). Accordingly, we can use the simplified notation for the Green's function

$$G\left(\begin{matrix}1\\ 0\end{matrix}\,\middle|\,\begin{matrix}N\\ \mathbf{x}\end{matrix}\right)\equiv G_N(\mathbf{x}) \tag{4}$$

Obviously, the partition function Z_N of a chain is equal to

$$Z_N = \int G_N(\mathbf{x})\, d^3x \tag{5}$$

In this approach, the distribution function of the end of the chain plays the most significant role. This function can be written in the form

$$\psi_N(\mathbf{x}) = G_N(\mathbf{x})/Z_N \tag{6}$$

It is convenient to consider the Green's function as a vector in the corresponding functional space. It is important to note that all the components of this vector in the x representation are positive $[G_N(\mathbf{x}) > 0$ for all $\mathbf{x}(1))$. Z_N is the norm of the vector G_N. Correspondingly, the norm of the vector ψ_N is equal to unity $(\int \psi_N(\mathbf{x})\, d^3x = 1)$. On the basis of the geometric analogy, it can be stated that the quantities Z_N and ψ_N define the length and the direction, respectively, of the vector G_N.

From the definition (1) of the Green's function, the following recurrence relation is apparent:

$$G_{t+1}(\mathbf{x}) = \hat{Q}_{\alpha(t+1)\alpha(t)}\, G_t(\mathbf{x}) \tag{7}$$

or

$$[Z_{t+1}/Z_t]\, \psi_{t+1}(\mathbf{x}) = \hat{Q}_{\alpha(t+1)\alpha(t)}\, \psi_t(\mathbf{x}) \tag{8}$$

3. FORMULATION OF THE GLOBULIZATION PROBLEM FOR MAIN TYPES OF PRIMARY STRUCTURES

3.1. Homopolymer

Let us recall the main points of the Lifshitz theory for a homopolymer globule.(1) All operators $\hat{Q}$ are identical for a homopolymer, and the situation is determined by the form of the spectrum for the operator $\hat{Q}$. If the highest eigenvalue Λ of the operator $\hat{Q}$ is discrete and is separated from the next value by a gap, a repeated application $(t \to \infty)$ of the operator $\hat{Q}$ will make the vector G_t exponentially approach the direction of the highest eigenvector ψ of the operator $\hat{Q}(\hat{Q}\psi = \Lambda\psi)$ in accordance with (8), while the norm of the vector G will increase exponentially, i.e.,

$$\psi_N(\mathbf{x}) \cong \psi(\mathbf{x}), \qquad Z_N \cong \Lambda^N \qquad (N \to \infty) \tag{9}$$

According to the terminology used in Ref. 6, this situation is called the "ground-state dominance."

Stabilization of the distribution function for the terminal link is typical just of the globular state. Indeed, such a stabilization means that the characteristic volume of the chain localization is independent of N [since the function $\psi(\mathbf{x})$ belongs to the discrete spectrum, i.e., rapidly decreases with increasing $|\mathbf{x}|$), and is determined by the form of the potential well φ appearing in the expression (2).

On the other hand, if the operator $\hat{Q}$ has a continuous spectrum, the distribution function $\psi_N(\mathbf{x})$ for the chain end does not stabilize with increasing N and continues to spread indefinitely (the localization volume is of the order of $N^{3/2}$, i.e., tends to infinity as $N \to \infty$).

3.2. Mobile Primary Structure

The simplest case to be investigated is the one in which the affiliation of a link to a certain type (A or B) may change during the thermal motion either on account of the adsorption of small molecules from the solution$^{(7)}$ or due to the helix–coil transition (in the latter case, the secondary structure plays the role of mobile primary structure). Globulization of such a heteropolymer has been investigated in Ref. 8. In this case, the underlying idea is that the Green's function can be reduced to a "homopolymer" form, but the role of the operator $\hat{Q}$ here must be played by an appropriate matrix of the operators $\hat{Q}_{\alpha\alpha'}$.

3.3. Periodic Primary Structures

This case can be easily reduced to a homopolymer by considering a heteropolymer period as a link of an effective homopolymer.

3.4. Large-Block Primary Structures (= Block Copolymers)

If links of A and B type form long homogeneous series along a chain, and the operators $\hat{Q}_{AA}$ and $\hat{Q}_{BB}$ have discrete spectra, the function ψ_t is close to ψ_A or ψ_B for almost all values of t (i.e., close to the highest eigenfunctions of the operators $\hat{Q}_{AA}$ and $\hat{Q}_{BB}$, respectively). However, the norm of the vector G is multiplied by the cosine of the angle between the directions of ψ_A and ψ_B upon every transition from the block A to the block B and vice versa. Hence, the partition function is equal to

$$Z_N = [\Lambda_A^c \Lambda_B^{(1-c)}]^N \left[\frac{\int \psi_A(\mathbf{x})\, \psi_B(\mathbf{x})\, d^3x}{[\int \psi_A^2(\mathbf{x})\, d^3x \int \psi_B^2(\mathbf{x})\, d^3x]^{1/2}} \right]^{N_{AB}} \tag{10}$$

where c and $(1-c)$ are the fractions of links of A and B types, and N_{AB} is the number of boundaries between blocks A and B (N/N_{AB} is the average length of the block).

The meaning of this formula is quite simple. Basically, each homopolymer block is globulized (adsorbed) in its potential well, and the corresponding free energy per monomer is given by $f = [c \ln \Lambda_A + (1-c) \ln \Lambda_B] T$. However, the stretching of every segment of the chain connecting the neighboring A and B blocks between the wells φ_A and φ_B makes an additional contribution $\Delta f = -T \ln(\psi_A ; \psi_B)$. As expected, such a stretching is thermodynamically disadvantageous: $\Delta f > 0$, since the overlapping integral is less than unity.

3.5. Statistical Primary Structures

A special feature of statistical heteropolymers is that the number of different chains of length N increases exponentially with N and is equal to 2^N. Hence, any reasonable quantity of matter contains a negligibly small fraction of all possible macromolecules. Thus, the thermodynamic characteristics of a globule are, in principle, random quantities. Consequently, their statistical properties must be investigated. It should be emphasized that the quantities already averaged over ordinary thermal fluctuations are random due to a random choice of the primary structure realization. In other words, we must investigate the probabilistic statements that can be made about the spatial structure and thermodynamic functions of a globule on the basis of incomplete information on the primary structure of a chain.

For the sake of definiteness, we shall consider that the primary structure is the realization of the process of independent trials: the monomers A and B are assumed to occupy each position with probability c and $(1-c)$, respectively, regardless of the neighboors.

In the first place, it is necessary to consider the criterion for distinguishing between the coil and globular states for a statistical heteropolymer. According to the general definition given by Lifshitz,(1,2) a globule, unlike a coil, is a weakly fluctuating state of a macromolecule; the correlation length along the chain in a globular state must be small in comparison to the chain length.

In a homopolymer with a discrete spectrum of the operator $\hat{Q}$, this is ensured by an exponential stabilization of the distribution function ψ_t of the chain end. At a finite (i.e., small in comparison to $N \gg 1$) distance r, the chain terminal almost "forgets" the initial condition (concerning the fixing of the first link), and ψ_t becomes equal to ψ.

The stabilization of $\psi_t(\mathrm{x})$ in a heteropolymer is impossible, since different operators $\hat{Q}_{\alpha\alpha'}$ do not commute and have different complete systems of eigenfunctions. Hence, each application of the operator $\hat{Q}$ (7)

rotates the vector G_t at once through a finite angle. The quantity G_t is random, since it depends on the primary structure. However, the direction of the vector G_t in the globular state must depend not on the entire primary structure and, in particular, not on the length of the chain under consideration. The influence of the link $(t-\tau)$ on the distribution function $\psi_t(\mathbf{x})$ of the terminal link t in the globular state must decrease sharply with increasing τ. Roughly speaking, $\psi_t(\mathbf{x})$ is determined by the primary structure of the last segment of a chain of a certain finite length r. The number of different terminals of length r is equal to 2^r. Hence, the probability distribution of the quantity ψ_t for $t \gg r2^r$ must stabilize:

$$P_t\{\psi(\mathbf{x})\} \xrightarrow[t\to\infty]{} P\{\psi(\mathbf{x})\} \tag{11}$$

It should be recalled that the stabilization of the probability distribution of the phase variable is a common phenomenon in the theory of one-dimensional disordered systems (see, for example, Refs. 9 and 10). Such a stabilization in a polymer chain (11) is a distinguishing feature of the globular state. In the coil state, the functions $\psi_t(\mathbf{x})$ "spread" indefinitely with increasing t.

The functions $\psi_t(\mathbf{x})$ form a Markov chain, because operator $\hat{Q}_{\alpha(t)\alpha(t-1)}$ and the vector G_{t-1} in Eq. (7) are statistically independent. The transfer operator $\hat{K}$ of this chain ($\hat{K}P_t = P_{t+1}$) can be easily written formally. The operator $\hat{K}$ itself is not random, although it depends on the probability distribution of operators $\hat{Q}$, i.e., on the local statistical properties of the primary structure, i.e., on c. Apparently, the globularity condition (11) is satisfied if and only if the highest eigenvalue of the operator $\hat{K}$ is discrete. The limiting functional $P\{\psi\}$ is the highest eigenvector of the operator $\hat{K}$.

In accodance to (8), the free energy per monomer is equal to

$$f = -\frac{T}{N}\ln Z_N = -\frac{T}{N}\sum_{t=2}^{N}\ln\int \hat{Q}_{\alpha(t)\alpha(t-1)}\,\psi_{t-1}\,d^3x \tag{12}$$

In view of the boundedness of the correlation radius in a globule, the central limit theorem can be applied to the sum (12). Consequently, the globular free energy is a self-averaging quantity,(9) i.e., it has a normal distribution with a variance $\sim N^{-1/2} \ll 1$, and its mean value is equal to

$$\langle f\rangle = -T\left\langle \ln\int \hat{Q}\psi\, d^3x\right\rangle \tag{13}$$

It is easy to see that the density distributions of the monomers $n_\alpha(\mathbf{x})$ are self-averaging quantities also, and, respectively, mean values are equal to

$$\langle n_\alpha(\mathbf{x})\rangle = \exp[-\varphi_\alpha(\mathbf{x})/T](\langle \hat{g}\psi\rangle)^2 \tag{13a}$$

The averaging of the right-hand sides of (13) and (13a) is carried out by considering that (a) the operator $\hat{Q}$ and the function ψ are statistically independent; (b) the distribution of $\hat{Q}$ is determined by the value c; and (c) the distribution of ψ is the limiting functional $P\{\psi\}$ (11).

4. AN EXACTLY SOLVABLE MODEL OF A HETEROPOLYMER GLOBULE

It is desirable to consider a simple model in which the abstractions of the previous section could be defined more specifically by explicitly carrying out all calculations. As a matter of fact, the Green's function (1) for a chain with Gaussian bonds (3) can be easily calculated if all fields have a quadratic dependence on the coordinates[2]:

$$\varphi_\alpha(\mathbf{x}) = \tfrac{3}{2}k_\alpha(\mathbf{x}-\boldsymbol{\xi}_\alpha)^2 \tag{14}$$

For the sake of simplicity, we shall assume that all "centers of attraction" $\boldsymbol{\xi}_\alpha$ lie on the x axis, and that the lengths of all bonds a (3) are equal. Then evidently, the distribution function of the end of the t-link chain is given by

$$\psi_t(\mathbf{x}) = \text{const}\exp\left\{-\frac{3}{2}\frac{s_t^{\parallel}}{a^2}(x-\eta_t)^2 - \frac{3}{2}\frac{s_t^{\perp}}{a^2}(y^2+z^2)\right\} \tag{15}$$

The following recurrence relations for the parameters $s_t^{\parallel}$, $s_t^{\perp}$, and η_t can be easily derived with the help of (7):

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[2] The author is grateful to S. A. Molchanov for this comment.

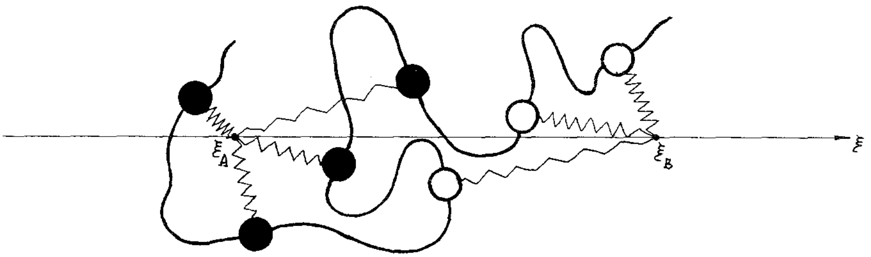

Fig. 1. Schematic picture of a heteropolymer globule. Black beads represent the A-type links, white stand for the B-type links. Due to the springs each α-type link has the potential energy $\varphi_\alpha = \frac{3}{2}k(x-\xi_\alpha)^2$.

$$s_{t+1}^{\|,\perp} = \frac{s_t^{\|,\perp}}{1 + s_t^{\|,\perp}} + \frac{a^2}{T} k_{\alpha(t+1)} \tag{16}$$

$$\eta_{t+1} = \frac{\eta_t \dfrac{s_t^{\|}}{1 + s_t^{\|}} + \xi_{\alpha(t+1)} k_{\alpha(t+1)} \dfrac{a^2}{T}}{\dfrac{s_t^{\|}}{1 + s_t^{\|}} + k_{\alpha(t+1)} \dfrac{a^2}{T}} \tag{17}$$

For any fixed primary structure $\alpha(t)$, all parameters of the function $\psi_t(\mathbf{x})$ can be calculated step by step.

Without loss of any qualitatively interesting features of the result, we shall assume for the sake of simplicity that all elastic constants k_α are identical. The opposite case, when $\xi_\alpha \equiv 0$ and k_α have different values, is considered in Ref. 11.

For the same values of k, the quantities $s_t^{\|}$ and $s_t^{\perp}$ meet at a stable fixed point as $t \to \infty$:

$$s_t^{\|} = s_t^{\perp} \cong s^* = \frac{ka^2}{2T} + \left\{ \frac{ka^2}{T} + \left(\frac{ka^2}{2T} \right)^2 \right\}^{1/2} \tag{18}$$

This simply means that a homopolymer in the parabolic field (14) is in the globular state, which is obvious from the physical point of view. By using (18), we can simplify relation (17) to the following form:

$$\eta_{t+1} = \eta_t \left(1 - \frac{ka^2}{Ts^*} \right) + \xi_{t+1} \frac{ka^2}{Ts^*} \tag{19}$$

Thus, the function $\psi_t(\mathbf{x})$ is determined by a single parameter η_t. Accordingly, it is sufficient to consider the probability distribution $P_t(\eta)$ instead of the functional $P_t\{\psi\}$. If $\mathscr{P}(\xi)$ is the probability distribution for ξ, we can easily find from (19) that

$$P_{t+1}(\eta) = \frac{Ts^*}{ka^2} \int \mathscr{P} \left(\eta \frac{Ts^*}{ka^2} - \eta' \left[\frac{Ts^*}{ka^2} - 1 \right] \right) P_t(\eta')\, d\eta' \equiv \hat{K} P_t \tag{20}$$

It is not difficult to verify that the operator $\hat{K}$ has a discrete spectrum, i.e., $P_t(\eta)$ tends to a stable fixed point as $t \to \infty$. Consequently, a random heteropolymer in the fields given by (14) is globulized.

The nature of the limiting distribution $P(\eta)$ can be easily determined for the case when a heteropolymer contains two types of links, i.e.,

$$\mathscr{P}(\xi) = c\delta(\xi - \xi_A) + (1 - c)\, \delta(\xi - \xi_B) \tag{21}$$

In this case, we can rewrite (20) in the following form:

$$P_{t+1}(\eta)=\left[1-\frac{ka^2}{Ts^*}\right]^{-1}\left\{cP_t\left(\frac{\eta-\xi_A\dfrac{ka^2}{Ts^*}}{1-\dfrac{ka^2}{Ts^*}}\right)\right.$$

$$\left.+(1-c)\,P_t\left(\frac{\eta-\xi_B\dfrac{ka^2}{Ts^*}}{1-\dfrac{ka^2}{Ts^*}}\right)\right\} \tag{22}$$

It can be verified that η lies in the interval $(\xi_A\,;\xi_B)$ for any primary structure, i.e., all $P_t(\eta)$ are concentrated over this interval. Using a graphic representation for relation (19) (Fig. 2) and starting with an arbitrary $P_0(\eta)$, say, with the uniform distribution in the interval $(\xi_A\,;\xi_B)$, we can see that each iteration (22) adds a system of intervals into the interval $(\xi_A\,;\xi_B)$, and within these additional intervals, the next and all subsequent distributions $P_t(\eta)$ vanish. The total length of all such intervals tends to $|\xi_A-\xi_B|$ as $t\to\infty$. Consequently, the limiting distribution $P(\eta)$ differs from zero only at points of a Kantor set with a measure equal to zero. In other words, $W(\eta)=\int_{-\infty}^{\eta}P(\eta')\,d\eta'$ is a Kantor function.$^{(12)}$ The physical meaning of such a singular result is quite simple: the set of possible primary structures is infinite but countable, and cannot densely cover a continuous interval. On the other hand, it can be easily seen that primary structure with only similar terminals contribute to any integral over a small segment on the η axis.

In order to avoid misunderstandings, it should be mentioned that the vanishing of $P(\eta)$ on a certain segment of the η axis rules out the impossibility of the center of $\psi(x)$ to belong to this segment. Naturally, the terminal monomer itself can lie at any point.

Let us now calculate the free energy of a heteropolymer globule. In this case, formula (13) assumes the form

$$\langle f\rangle=\frac{3T}{2}\ln(1+s^*)+\frac{3k}{2}\langle(\eta-\xi)^2\rangle \tag{23}$$

The statistical independence of η and ξ, as well as the distribution (21) for ξ, must be taken into account while averaging. In order to calculate $\langle\eta\rangle$, we must use the relation (22) and note that $\int\eta P_{t+1}(\eta)\,d\eta-\int\eta P_t(\eta)\,d\eta\to 0$ as $t\to\infty$. The value of $\langle\eta^2\rangle$ is obtained in a similar manner. As a result, we get

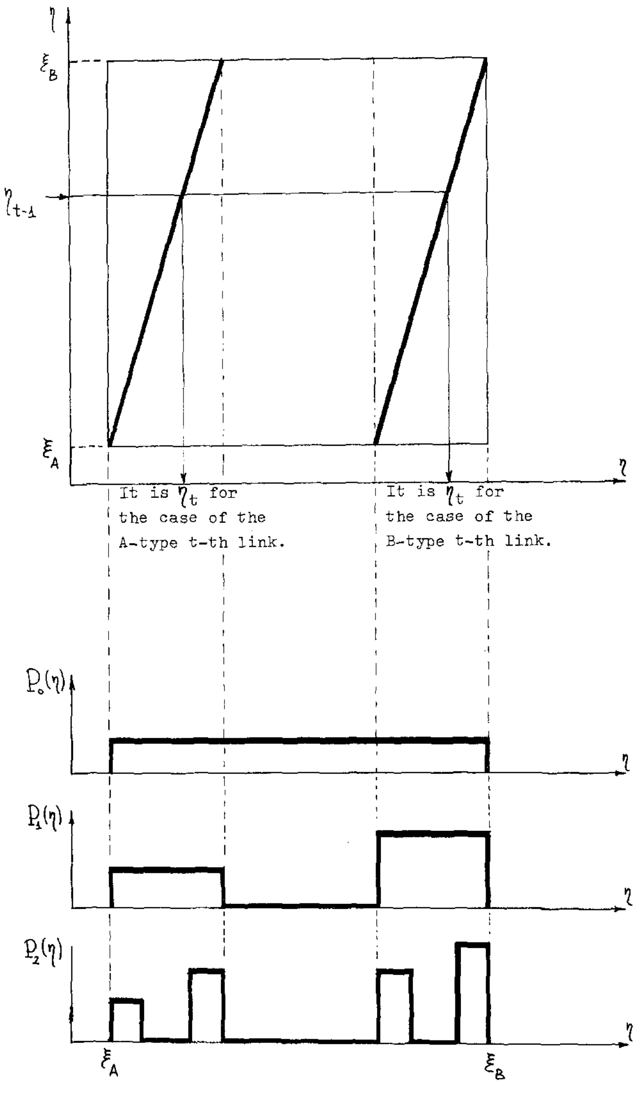

Fig. 2. An arbitrary (t-th) link undergoes a Brownian motion, η_t being its average coordinate. The value of η_t depends on the primary structure, i.e. on the type of links t, $t-1$, $t-2,\ldots$. This figure illustrates the graphic method of determination of η_t (if the value of η_{t-1} is given) for the cases of the A-type and B-type t-th link. The value $P(\eta)$ is proportional to the number of primary structures, for which the average coordinate of a terminal chain link is η. The graphic reccurence procedure of determination of $P(\eta)$ is also shown in the figure. It can be seen that at any η_0 the value of η_1 cannot appear in the middle part of the interval $(\xi_A\,;\,\xi_B)$; for η_2 we have 3 forbidden intervals etc. For η_∞ practically all the points are forbidden, the value of $P(\eta)$ is not equal to zero only in the points of the Kantor set.

the following expression for the free energy of a statistical heteropolymer [this calculation is possible due to the linearity of (19)]:

$$\langle f\rangle = \frac{3T}{2}\ln(1+s^*) + \frac{3k}{2+s^*}\,c(1-c)(\xi_A-\xi_B)^2 \tag{24}$$

The second term in this formula describes the entropic elasticity of a heteropolymer globule whose A links are attracted to the center ξ_A, and B links to the center ξ_B. The coefficient of $(\xi_A-\xi_B)^2$ can be interpreted as the corresponding elastic constant. It can be seen that the elasticity is maximum at $c=1/2$. Clearly, it is for $c=1/2$ that the number of unfavorable transitions from one well to another is maximum.

For the sake of comparison, let us consider the expression for the free energy of a globule formed by the periodic heteropolymer *...ABABAB...*:

$$f = \frac{3T}{2}\ln(1+s^*) + \frac{3}{2}k\frac{1+s^*}{(2+s^*)^2}(\xi_A-\xi_B)^2 \tag{25}$$

As expected, the elastic energy for a short-periodic heteropolymer is higher than for a random heteropolymer $[2(1+s^*)/(2+s^*)>1]$. Indeed, all bonds are stretched in a periodic polymer, while a fluctuational accumulations of similar links exists in a random polymer, and their bonds are not stretched [naturally, the elasticity (10) of a large-block polymer is much smaller, because $N_{AB} \ll N$].

It is also natural that the elastic constant vanishes for $ka^2 \ll T$ and increases with k. For $ka^2 \gg T$, when the monomers are in fact rigidly fixed to the appropriate centers, the elastic constant of a random globule is equal to $3c(1-c)/a^2$ per monomer. The corresponding value for a periodic globule is $3/2a^2$. These results are obvious, since $3/2a^2$ is the elastic constant for a single bond (3) and $2c(1-c)$ is the mean value of $(A\text{–}B)$ bonds concentration.

5. CONCLUDING REMARKS

The perturbation theory for the free energy of a globule has been constructed in Ref. 13 for the case when the fields φ_α (or the operators $\hat{Q}$) are similar. The self-consistent theory of a globule in the volume approximation has also been considered there. It was shown that in this approximation, a heteropolymer can be described as an effective homopolymer with mean virial coefficients. The consequences of this fact are analyzed in Ref. 14.

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