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► To cite this version:

Vijay Pande, Alexander Grosberg, Toyochi Tanaka. Phase diagram of imprinted copolymers. Journal de Physique II, 1994, 4 (10), pp.1771-1784. 10.1051/jp2:1994231 . jpa-00248077

HAL Id: jpa-00248077

<https://hal.science/jpa-00248077>

Submitted on 4 Feb 2008

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Classification

Physics Abstracts

61.40K — 87.15 — 36.20C — 82.35 — 64.60C

Phase diagram of imprinted copolymers

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(Received 10 April 1994, accepted 30 June 1994)

Abstract. — Recently, a model for the preparation of “protein-like” heteropolymers with a unique and stable ground state has been proposed and examined computationally. Formally, this model is similar to another recently proposed and computationally examined model of the evolutionary design of protein-like heteropolymers. Using mean field replica theory, we find, in addition to the freezing transition of random chains, a transition to the target “native” state. The stability of this state is shown to be greater than that of the ground state of random chains. The results derived here should at least qualitatively be applicable to known biopolymers, which are conjectured to be *in vivo* “designed” by evolution. Furthermore, we present a crude prescription for a laboratory procedure in which chains can be synthesized *in vitro*.

1. Introduction.

Due to its biological importance and physical complexity, the problem of the folding transition of copolymers has attracted considerable attention [1-3]. Biologically, proteins represent a sort of “designed” heteropolymer, in this case the result of evolution. It is also known that proteins have a unique structure. It is intriguing to consider that the existence of a *specific* (i.e. designed) unique ground state could be the result of evolution. This has been studied computationally, by a Monte Carlo procedure which swaps monomers via the Metropolis criterion such that the polymer energy is minimized [4].

A method to synthesize renaturable heteropolymers in a laboratory procedure has also been recently suggested. In this design procedure, monomers are equilibrated in space and then instantly polymerized. It has been shown computationally that the polymerization conformation will often be the ground state conformation, i.e. the polymerization conformation has been designed, or “imprinted” [5]. The significance of the imprinting of the polymerization conformation is that if monomers are equilibrated in the presence of a target molecule and then

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polymerized, the complementary site formed by equilibration of the monomers with the target molecule prior to polymerization would be preserved in the polymerization conformation. If this polymerization conformation is the ground state, then the sequence has been designed so that it folds to a conformation which has a site capable of recognizing the target molecule. Clearly, in spirit, these two design procedures are radically different. However, in the mean field approximation, both models are formally indistinguishable, as both choose sequences with a fixed monomer composition such that the energy of interaction is minimized [5].

In this paper, we employ the replica approach to describe the effect of design on the freezing transition previously predicted for random chains [2, 6]. The mean field replica approach is believed to be applicable to disordered polymers, as the polymer problem is similar to the *long range* SK spin-glass [7]. Indeed, due to polymer flexibility, all monomers can come in contact with each other in real space, and, therefore, interact with each other, no matter how far they are along the chain. In this sense, the heteropolymer is perhaps the best physical realization of the SK system, with a truly infinite radius of interaction [6].

The freezing transition in random copolymers is due to the competition between the entropic favorability of a large number of conformations and the energetic tendency toward one or a few conformations with distinctively low energies. Qualitatively, we expect that the design procedure should lead to sequences whose unique ground state conformation is the target conformation, as we have, in a sense, exerted a "field" which chooses an ensemble of sequences which have been optimized for the particular target conformation.

2. Formulation of the model.

Consider a heteropolymer chain with a frozen sequence of monomers s_I , where I is the number of monomer along the chain ($1 \leq I \leq N$) and s_I is the type of monomer in the given sequence. In the present model, we consider only two values for s , $s = \pm 1$, and have the interaction Hamiltonian of the form

$$\mathcal{H} = -\frac{1}{2}B \sum_{I,J}^N s_I s_J \delta(\mathbf{r}_I - \mathbf{r}_J) \quad (1)$$

where $\delta(\mathbf{r})$ is the Dirac delta function. As we wish to concentrate on heteropolymeric effects, we do not explicitly write, but implicitly assume, an overall attractive second virial coefficient as well as a repulsive third virial coefficient. Specifically, we assume that the complete Hamiltonian is given by the sum of heteropolymeric and homopolymeric terms:

$$\mathcal{H}' = -\frac{1}{2}B \sum_{I,J}^N s_I s_J \delta(\mathbf{r}_I - \mathbf{r}_J) + B_0\rho + C\rho^2 \quad (2)$$

where B_0 and C are the mean second and third virial coefficients. As we assume that $|B_0| \gg B$, we can optimize the free energy with respect to ρ independently of any heteropolymeric properties. Thus, these homopolymeric terms lead to a compact globular state with constant density $\rho = -B_0/2C$. Furthermore, B is due to heteropolymeric effects; it is the "preferential" energy: for two types of species labeled 1 and 2, the preferential energy is the energy difference $E_{12} - \frac{1}{2}(E_{11} + E_{22})$. The meaning and value of the preferential energy for any real system depends on the nature of the actual interactions involved (e.g. hydrogen bonding, hydrophobic forces, etc.). Essentially, some conformations with a given density (fixed due to the homopolymeric terms) might be more thermodynamically favorable than others, due to heteropolymeric effects. This will be the main subject of our analysis.

The partition function is expressed as

$$Z(\text{seq}) = \sum_{\text{conformations}} \exp \left[-\frac{1}{T} \mathcal{H}(\text{conf}, \text{seq}) \right] \quad (3)$$

Note that the Hamiltonian depends on both conformation and sequence. The standard way to approach the partition function of a system with frozen disorder is to employ, first, the principle of self-averaging of free energy and, second, the replica trick:

$$F(\text{seq}) \simeq F = \langle F(\text{seq}) \rangle_{\text{seq}} = -T \langle \ln Z(\text{seq}) \rangle_{\text{seq}} = -T \lim_{n \rightarrow 0} \frac{\langle Z^n(\text{seq}) \rangle_{\text{seq}} - 1}{n}, \quad (4)$$

where $\langle \dots \rangle_{\text{seq}}$ means average over the set of sequences.

In the works [2, 6], while averaging, the sequences were considered to be random. The main purpose of this work is to incorporate the fact that sequences are somehow selected. This means

$$\langle \dots \rangle_{\text{seq}} = \sum_{\text{seq}} P_{\text{seq}}, \quad (5)$$

where P_{seq} is the probability distribution for different sequences which appear in the process of design or synthesis of chains.

Both of the recently suggested models of sequence preparation [5, 4] (see above) employ in the selection process the same volume interactions with which the links of chains interact. In both cases, P_{seq} is governed by the Boltzmann factor related to the same Hamiltonian (1) taken for the “target” conformation \star . Since we are not interested in any particular \star conformation and, besides, this conformation seems to be out of control in any real (not computer) experiment, we average over the conformation \star :

$$P_{\text{seq}} = \frac{1}{z} \sum_{\star} \exp \left[-\frac{1}{T_p} \mathcal{H}(\star, \text{seq}) \right], \quad (6)$$

where T_p is “polymerization” temperature at which design procedure is performed and

$$z = \sum_{\text{seq}} \sum_{\star} \exp \left[-\frac{1}{T_p} \mathcal{H}(\star, \text{seq}) \right] \quad (7)$$

is the normalization constant. The probability P_{seq} includes all possible sequences, not only the ones with any given composition.

Collecting the above equations, we can write the n -replica partition function, up to the constant factors, as

$$\begin{aligned} \langle Z^n(\text{seq}) \rangle_{\text{seq}} &= \frac{1}{z} \sum_{\text{seq}} \sum_{\star} \exp \left[-\frac{1}{T_p} \mathcal{H}(\star, \text{seq}) \right] \left\{ \sum_{\text{conformations}} \exp \left[-\frac{1}{T} \mathcal{H}(\text{conf}, \text{seq}) \right] \right\}^n \\ &= \frac{1}{z} \sum_{\text{seq}} \sum_{C_0, C_1, \dots, C_n} \exp \left[-\frac{1}{T_p} \mathcal{H}(C_{\alpha=0}, \text{seq}) - \frac{1}{T} \sum_{\alpha=1}^n \mathcal{H}(C_{\alpha}, \text{seq}) \right], \end{aligned} \quad (8)$$

where $C_{\alpha} = C_0, C_1, \dots, C_n$ stand for conformations of replica number α , and index $\alpha = 0$ is attributed to the target conformation \star . As expected, we return to the usual case of completely random sequences at $T_p \rightarrow \infty$. The new physics which appears at finite T_p is the main subject of further analysis.

3. Replica theory analysis.

We write the n -replica partition function

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \frac{1}{z} \sum_{\text{seq}} \sum_{C_0, C_1, \dots, C_n} \exp \left\{ \sum_{\alpha=0}^n \frac{B}{2T_\alpha} \sum_{I,J=1}^N \int d\mathbf{R}_1 d\mathbf{R}_2 s_I \delta(\mathbf{r}_I^\alpha - \mathbf{R}_1) s_J \delta(\mathbf{r}_J^\alpha - \mathbf{R}_2) \delta(\mathbf{R}_1 - \mathbf{R}_2) \right\}, \quad (9)$$

where $T^\alpha = T_p$ for $\alpha = 0$ and $T^\alpha = T$ for $\alpha > 0$, and we perform Hubbard-Stratonovich transformation

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \frac{1}{z} \int \mathcal{D}\phi \sum_{C_0, C_1, \dots, C_n} \exp \left\{ -\frac{1}{2} \sum_{\alpha=0}^n \int d\mathbf{R}_1 d\mathbf{R}_2 \frac{T^\alpha}{B} \phi^\alpha(\mathbf{R}_1) \phi^\alpha(\mathbf{R}_2) \delta(\mathbf{R}_1 - \mathbf{R}_2) \right\} \\ \times \sum_{\text{seq}} \exp \left\{ \sum_{\alpha=0}^n \int d\mathbf{R} \sum_{I=1}^N \phi^\alpha(\mathbf{R}) s_I \delta(\mathbf{r}_I^\alpha - \mathbf{R}) \right\} \quad (10)$$

Here $\phi^\alpha(\mathbf{R})$ are the fields conjugated to the corresponding densities $\sum_{I=1}^N s_I \delta(\mathbf{r}_I^\alpha - \mathbf{R})$, $\int \mathcal{D}\phi$ means functional integration over all the fields $\{\phi^\alpha(\mathbf{R})\}$, and we have dropped all irrelevant multiplicative constants from the partition function. Note that the sum over sequences enters only in the last "source" term of (10). The summation over sequences can be easily performed to yield

$$\exp \{\text{source term}\} = \sum_{s_1, s_2, \dots, s_N = \pm 1} \prod_{I=1}^N \exp \left\{ s_I \sum_{\alpha=0}^n \int d\mathbf{R} \phi^\alpha(\mathbf{R}) \delta(\mathbf{r}_I^\alpha - \mathbf{R}) \right\} \\ = \prod_{I=1}^N \sum_{s = \pm 1} \exp \left\{ s_I \sum_{\alpha=0}^n \int d\mathbf{R} \phi^\alpha(\mathbf{R}) \delta(\mathbf{r}_I^\alpha - \mathbf{R}) \right\} \\ = \prod_{I=1}^N 2 \cosh \left\{ \sum_{\alpha=0}^n \int d\mathbf{R} \phi^\alpha(\mathbf{R}) \delta(\mathbf{r}_I^\alpha - \mathbf{R}) \right\} \quad (11)$$

We perform now the expansion over ϕ . It is the most important approximation of this work. The corresponding conditions of applicability will be given later. Keeping the terms up to $\mathcal{O}(\phi^2)$, we get the n -replica partition function in the form:

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \frac{1}{z} \sum_{C_0, C_1, \dots, C_n} \int \mathcal{D}\phi \exp [-\mathcal{E}\{Q_{\alpha\beta}\}], \quad (12)$$

where the effective energy of n -replica system is given by

$$\mathcal{E}\{Q_{\alpha\beta}\} = \frac{1}{2} \int d\mathbf{R}_1 d\mathbf{R}_2 \\ \times \left[\sum_{\alpha=0}^n \frac{T^\alpha}{B} \phi^\alpha(\mathbf{R}_1) \phi^\alpha(\mathbf{R}_2) \delta(\mathbf{R}_1 - \mathbf{R}_2) - \sum_{\alpha, \beta=0}^n \phi^\alpha(\mathbf{R}_1) \phi^\beta(\mathbf{R}_2) Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) \right], \quad (13)$$

and

$$Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) = \sum_{I=1}^N \delta(\mathbf{r}_I^\alpha - \mathbf{R}_1) \delta(\mathbf{r}_I^\beta - \mathbf{R}_2) \quad (14)$$

is the standard two replica overlap order parameter [6, 3]. Recall that the value of $Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2)$ has the very simple physical meaning: it is proportional to probability of finding simultaneously one monomer of the replica α at the point \mathbf{R}_1 and one monomer of the replica β at the point \mathbf{R}_2 . Also note that the normalization conditions

$$\int d\mathbf{R}_1 Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) = \rho_\beta(\mathbf{R}_2) \quad \text{and} \quad \int d\mathbf{R}_1 d\mathbf{R}_2 Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) = N \quad (15)$$

are obvious from the definition of $Q_{\alpha\beta}$, equation (14), where $\rho_\beta(\mathbf{R}_2)$ is the density. As we are concerned here with a large globule, density is assumed constant throughout the globule, such that

$$\rho_\beta(\mathbf{R}) = \rho \quad (\text{constant in space, same for all replicas}) ; \quad (16)$$

and therefore

$$Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) = Q_{\alpha\beta}(\mathbf{R}_1 - \mathbf{R}_2) . \quad (17)$$

We also mention that the diagonal element is given by

$$Q_{\alpha\alpha}(\mathbf{R}_1, \mathbf{R}_2) = \rho \delta(\mathbf{R}_1 - \mathbf{R}_2) . \quad (18)$$

We can therefore rewrite the effective n -replica energy in the form

$$\mathcal{E}\{Q_{\alpha\beta}\} = \frac{1}{2} \sum_{\alpha, \beta=0}^n \int d\mathbf{R}_1 d\mathbf{R}_2 \phi^\alpha(\mathbf{R}_1) \phi^\beta(\mathbf{R}_2) \left[\left(\frac{T^\alpha}{B} - \rho \right) \delta_{\alpha\beta} \delta(\mathbf{R}_1 - \mathbf{R}_2) - Q_{\alpha \neq \beta}(\mathbf{R}_1 - \mathbf{R}_2) \right] . \quad (19)$$

Now we pass from summation over conformations (microstates) to functional integration over $Q_{\alpha\beta}$ (macrostates). $Q_{\alpha\beta}$ is the only relevant order parameter. The corresponding entropy is given by [6]

$$e^{S\{Q_{\alpha\beta}\}} = \sum_{C_0, C_1, \dots, C_n} \delta \left(Q_{\alpha\beta}(\mathbf{R}_1, \mathbf{R}_2) - \sum_{I=1}^N \delta(\mathbf{r}_I^\alpha - \mathbf{R}_1) \delta(\mathbf{r}_I^\beta - \mathbf{R}_2) \right) , \quad (20)$$

and therefore

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \int \mathcal{D}Q \int \mathcal{D}\phi \exp \{ -\mathcal{F} + \mathcal{F}_0 \} ; \quad \mathcal{F} = \mathcal{E}\{Q_{\alpha\beta}\} - S\{Q_{\alpha\beta}\} ; \quad \mathcal{F}_0 = -\ln z . \quad (21)$$

The mean field evaluation of this partition function implies a saddle point approximation for the integral over Q (Eq. (21)). Normally, this means taking the maximal value of the integrand. It is commonly believed, however, that in order to find the correct analytic continuation in the $n \rightarrow 0$ limit, one has to take the *maximal* rather than the minimal value of the relevant free energy \mathcal{F} , because there are $n(n-1)/2$ off-diagonal elements in the $Q_{\alpha\beta}$ matrix, and therefore for the $0 < n < 1$ case, the integral over $Q_{\alpha\beta}$ represents summation over a *negative* number of variables. Following this principle, we write

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \int \mathcal{D}\phi \exp [-\text{Max}_{\{Q\}} \mathcal{F}\{Q\}] = \text{Min}_{\{Q\}} \int \mathcal{D}\phi \exp [-\mathcal{F}\{Q\}] , \quad (22)$$

i.e., we have to *maximize* the effective free energy functional (21).

4. Replica symmetry breaking.

We choose some standard function $\varphi(\mathbf{x})$, say Gaussian, with the normalization condition $\int d\mathbf{x} \varphi(\mathbf{x}) = 1$, and say that

$$Q_{\alpha\beta}(\mathbf{R}_1 - \mathbf{R}_2) = \frac{\rho}{(R_t^{\alpha\beta})^d} \varphi\left(\frac{\mathbf{R}_1 - \mathbf{R}_2}{R_t^{\alpha\beta}}\right), \quad (23)$$

where d is the dimensionality of space, $R_t^{\alpha\beta}$ can be interpreted as the diameter of the tube in which replicas α and β coincide, and the normalization condition defines the coefficient. We now repeat the arguments of [6]: as the entropy scales like $-(R_t^{\alpha\beta})^{-2}$ at $n < 1$, we get each $\alpha \neq \beta$ term of the free energy functional of the form

$$\mathcal{F}_{\alpha\beta} = -\frac{A_1}{(R_t^{\alpha\beta})^2} + \frac{A_2}{(R_t^{\alpha\beta})^d} \quad (24)$$

where A_1 and A_2 are positive numbers. For $d > 2$, which is the main concern of this work, we find two maxima, namely $R_t^{\alpha\beta} = \infty$ and $R_t^{\alpha\beta} = 0$ (in the later case, see the discussion in [6] concerning the short distance cut-off $R_t^{\alpha\beta} = v^{1/3}$, where v is the excluded volume). The first corresponds to two replicas, α and β which are independent and do not overlap at all ($Q_{\alpha\beta} = 0$), while the second corresponds to replicas which coincide at the microscopic level ($Q_{\alpha\beta} = \rho \delta(\mathbf{R}_1 - \mathbf{R}_2)$). Thus, from these scaling arguments in $R_t^{\alpha\beta}$, we conclude that $Q_{\alpha\beta}$ is of the form

$$Q_{\alpha\beta}(\mathbf{R}_1 - \mathbf{R}_2) = \rho q_{\alpha\beta} \delta(\mathbf{R}_1 - \mathbf{R}_2) \quad (\alpha \neq \beta), \quad (25)$$

where off-diagonal matrix elements of the new matrix $q_{\alpha\beta}$ are either 0 or 1. If we additionally define diagonal matrix elements $q_{\alpha\alpha}$ as

$$q_{\alpha\alpha} \equiv 1 - \frac{T^\alpha}{B\rho}, \quad (26)$$

we can write

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \frac{1}{z} \text{Min}_{\{q_{\alpha\beta}\}} e^{S\{q_{\alpha\beta}\}} \left\{ \int \mathcal{D}\phi \exp \left[\frac{1}{2} \sum_{\alpha, \beta=0}^n q_{\alpha\beta} \phi^\alpha \phi^\beta \right] \right\}^N, \quad (27)$$

where integration over \mathbf{R} disappears leaving the product of $N = \rho \int d\mathbf{R}$ integrals. Moreover, we can perform Gaussian integration over ϕ yielding ⁽¹⁾

⁽¹⁾ It is instructive to perform first the Gaussian functional integrals over ϕ^0 yielding

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \frac{1}{z} \text{Min}_{\{q_{\alpha\beta}\}} e^{S\{q_{\alpha\beta}\}} \left\{ \int \mathcal{D}\phi \exp \left[\frac{1}{2} \sum_{\alpha, \beta=1}^n \hat{q}_{\alpha\beta} \phi^\alpha \phi^\beta \right] \right\}^N, \quad (28)$$

where

$$\hat{q}_{\alpha\beta} = q_{\alpha\beta} + \frac{q_{\alpha 0} q_{0\beta}}{q_{00}} \quad (29)$$

In this form, we reduce the problem to a form similar to that of Sfatos *et al.* [2], with a new effective order parameter $\hat{q}_{\alpha\beta}$. This form explains that replica 0 plays the role of external field in replica space, adsorbing other replicas. In other words, two replicas $\alpha, \beta > 0$ attract each other directly, as in the random polymer, and, additionally, because both are attracted to target replica.

$$\langle Z^n(\text{seq}) \rangle_{\text{seq}} = \exp [-\text{Max}_{\{q_{\alpha\beta}\}} \mathcal{F}\{q_{\alpha\beta}\}] ; \mathcal{F}\{q_{\alpha\beta}\} = \frac{N}{2} \ln [\det (-q_{\alpha\beta})] - S\{q_{\alpha\beta}\} - \ln z . \quad (30)$$

where we have dropped all irrelevant additive constants.

To maximize the n -replica free energy over $q_{\alpha\beta}$ means in fact finding the optimal grouping of replicas. There is the following obvious transitivity rule: if, say, $R_t^{\alpha\beta} = 0$ and $R_t^{\beta\gamma} = 0$, meaning that conformations of replicas α , β and γ are all the same, then $R_t^{\alpha\gamma} = 0$ as well. In other words, if $q_{\alpha\beta} = 1$ and $q_{\beta\gamma} = 1$, then $q_{\alpha\gamma} = 1$ as well. Using matrix row and column operations, we can organize any such matrix into block diagonal form. This means gathering replicas that overlap in the groups and placing replicas of the same group into the same diagonal block in the matrix. One of the blocks is comprised of some $y + 1$ replicas which do overlap (i.e., practically coincide) with the "target" replica 0. Other $(n + 1) - (y + 1) = n - y$ replicas belong to n/x groups, some x replicas in each:

$$\begin{array}{c} \left. \begin{array}{c} y+1 \\ \left\{ \begin{array}{ccc|cc} 1 - \frac{T_p}{B\rho} & 1 & 1 & 0 & 0 \\ 1 & 1 - \frac{T}{B\rho} & 1 & 0 & 0 \\ 1 & 1 & 1 - \frac{T}{B\rho} & 0 & 0 \\ \hline 0 & 0 & 1 - \frac{T}{B\rho} & 1 & 0 \\ & & 1 & 1 - \frac{T}{B\rho} & 0 \\ & & & 1 - \frac{T}{B\rho} & 1 \\ & & & 1 & 1 - \frac{T}{B\rho} \end{array} \right\} \end{array} \right\} n+1 \\ \underbrace{\hspace{10em}}_x \end{array}$$

One can say that y replicas here are "adsorbed" on the target conformation, which plays the role of external field for n other replicas. A similar situation exists in neural networks [11], where the memorized image plays a similar role to the target conformation. On the other hand, the grouping of other replicas is due to spontaneous replica permutation symmetry breaking.

The determinant of the $q_{\alpha\beta}$ matrix can be directly calculated. First, since the matrix is block-diagonal, its determinant is the product of block determinants. Each $x \times x$ block has a $(x - 1)$ -fold degenerate eigenvalue $[\tilde{q} - q]$ and one distinct eigenvalue $[\tilde{q} - q + xq]$, where $\tilde{q} = 1 - T/B\rho$ and $q = 1$ are diagonal and off-diagonal matrix elements, respectively. As to the $(y + 1) \times (y + 1)$ block, it has one distinct diagonal element $q_{00} = 1 - T_p/B\rho = \tilde{q}_p$ and for this reason the eigenvalue $[\tilde{q} - q]$ is only (matrix size - 2) = $(y - 1)$ -fold degenerate, while the two others are $(1/2) \left[[\tilde{q} + \tilde{q}_p + q(y - 1)] \pm \sqrt{[\tilde{q} - \tilde{q}_p + q(y - 1)]^2 + 4yq^2} \right]$. Taking the product

of all eigenvalues throughout all blocks, and noting that $\det(-q_{\alpha\beta}) = (-1)^{n+1} \det(q_{\alpha\beta})$, we obtain

$$\ln[\det(-q_{\alpha\beta})] = \frac{n-y}{x} \ln\left[1 - \frac{B\rho}{T}x\right] + \ln\left[1 - \frac{B\rho}{T}\left(y + \frac{T}{T_p}\right)\right] + n \ln\left[\frac{T}{B\rho}\right] + \ln\left[\frac{T_p}{B\rho}\right], \quad (31)$$

To estimate the entropy $S\{q_{\alpha\beta}\}$ related to the grouping of replicas, we follow reference [2] to argue that due to the polymeric bonds connecting monomers along the chain, once one monomer is fixed in space, the next must be placed within a volume a^3 . Since replicas that belong in the same group coincide within a tube of radius $R_t \sim v^{1/3}$, there are a^3/v ways to place the next monomer and thus the entropy per monomer is $\ln(a^3/v)$. But since all replica conformations coincide within the group, we must restrict the position of the next monomer to a single place. Thus, the entropy loss for each group is $s(x-1)$, where $s = \ln(a^3/v)$ is related to the flexibility of the chain, and therefore

$$S = Ns \left[\frac{n-y}{x}(x-1) + y \right] \quad (32)$$

As to the last term in (30), $-\ln z$, it is formally related to the normalization condition for the probability P_{seq} , but physically it is the free energy of single replica 0 taken at the polymerization temperature T_p . It can be therefore easily found by taking $n = 0$, $y = 0$ in the preceding formulae:

$$-\ln z = N \cdot \ln \left[\frac{T_p}{B\rho} - 1 \right] \quad (33)$$

Collecting equations (30), (31), and (32), we obtain

$$\frac{1}{N}\mathcal{F} = \frac{n-y}{2x} \ln\left[1 - \frac{B\rho}{T}x\right] + \frac{1}{2} \ln\left[1 - \frac{B\rho/T}{1 - B\rho/T_p}y\right] + s \left[n - \frac{n-y}{x} \right] \quad (34)$$

where we have employed the fact that the last two terms in (31) cancel with normalization constants from Gaussian integration not explicitly written. We are left, therefore, only with maximization over x and y in the $n \rightarrow 0$ limit, yielding the opportunity to comment on the physics of the possible phases.

5. Phase diagram.

Let us discuss the possible values of x and y in the $n \rightarrow 0$ limit. For the replica system, when n is positive integer, we have $1 \leq x \leq n$ and $0 \leq y \leq n$. Clearly, $x = 1$ means there is no grouping, i.e. no replica symmetry breaking. On the other hand, $x = n$ means all the replicas belong to the same group, or replica symmetry is broken. When n becomes less than 1 and goes to 0, inequalities flip. Nevertheless, x must remain in between of n and 1, and approaching x to 1 means disappearance of replica permutation symmetry breaking. In other words, $x = 1$ corresponds to the freezing transition. This transition has been investigated in [2]. Maximizing

x in equation (34), we recover the result of [2] for random chains ⁽²⁾

$$2s = \ln \left[1 - \frac{B\rho}{T} x \right] + \frac{(B\rho/T)x}{1 - (B\rho/T)x} \quad (35)$$

The solution of this equation is of the form $x = T\xi(s)/B\rho$, where $\xi(s)$ is the function defined by the equation $2s = \ln(1 - \xi) + \xi/(1 - \xi)$. According to our discussion, this solution is valid when it gives $x \leq 1$, i.e. at $T \leq T_f$, where T_f is given by

$$T_f = \frac{B\rho}{\xi(s)} \quad \text{or} \quad 2s = \ln \left[1 - \frac{B\rho}{T_f} \right] + \frac{B\rho/T_f}{1 - B\rho/T_f} \quad (36)$$

T_f is the temperature of freezing transition for the chain with random sequence [2], and we can write

$$x = \begin{cases} T/T_f & \text{when } T \leq T_f \\ 1 & \text{otherwise} \end{cases} \quad (37)$$

We find that x_0 and T_f are independent of any design parameters such as y and T_p . This has a clear physical meaning: if one considers the chain prepared by our procedure in some particular conformation \star , then for almost all of the conformations except \star , this chain behaves as if it had a completely random sequence. This is why freezing into a random conformation is not at all affected by the procedure of sequence selection.

Consider now maximization with respect to y . The condition $0 \leq y \leq n$ is obvious for positive integer n : $y = 0$ means no replicas in the target group ⁽³⁾, while $y = n$ means all replicas are in the target conformation. When n becomes less than 1 and goes to 0, y remains in between 0 and n , which is also 0. Since y is always small, the second logarithmic term in (34) can be linearized to obtain

$$\frac{1}{N} \mathcal{F} = \frac{n}{2x} \left\{ \ln \left[1 - \frac{B\rho}{T} x \right] - 2s \right\} + sn - \frac{y}{2x} \left\{ \ln \left[1 - \frac{B\rho}{T} x \right] + \frac{(B\rho/T)x}{1 - (B\rho/T_p)x} - 2s \right\} \quad (38)$$

Thus, the effective free energy (38) is linear in y . The maximal value is therefore reached always at the boundary of the interval, i.e. either at $y = 0$ (no replicas in the target group) or at $y = n$ (all the replicas are in the target group). The corresponding phase transition occurs when the y dependence of the free energy flips sign, and the transition point T_p^{cr} can be easily found, since linear in y term of the free energy (38) vanishes at the transition point. We substitute s from the condition (36) and find

$$T_p^{\text{cr}} = \begin{cases} B\rho \left[1 - \frac{B\rho/T}{\ln \left[\frac{1 - B\rho/T_f}{1 - B\rho/T} \right] + \frac{B\rho/T_f}{1 - B\rho/T_f}} \right]^{-1} & \text{when } T > T_f \\ T_f & \text{otherwise.} \end{cases} \quad (39)$$

Clearly, this is a first order transition.

⁽²⁾In fact, this result corresponds exactly to the so-called Parisi *ansatz* [9] with one-step replica symmetry breaking. In our model, however, it can be obtained in a more sophisticated manner, without any *ansatz*. Indeed, we can easily consider the general case of some g groups of replicas, with different numbers x_i of replicas in each group. We have then $\sum_{i=1}^g \ln \left[1 - \frac{B\rho}{T} x_i \right]$ instead of $\frac{n-y}{x} \ln \left[1 - \frac{B\rho}{T} x \right]$ in the $\ln(\det(-q_{\alpha\beta}))$ term and $s \sum_{i=1}^g (x_i - 1)$ instead of $s \frac{n-y}{x} (x - 1)$ in the entropy term. Maximization with respect to x_i within the constraint $\sum_{i=1}^g x_i = n - y$ gives that all $x_i = x$ are the same, leaving us with the simplified version considered above.

⁽³⁾In thermodynamic limit, the probability to obtain given target conformation out of random choice is negligible.

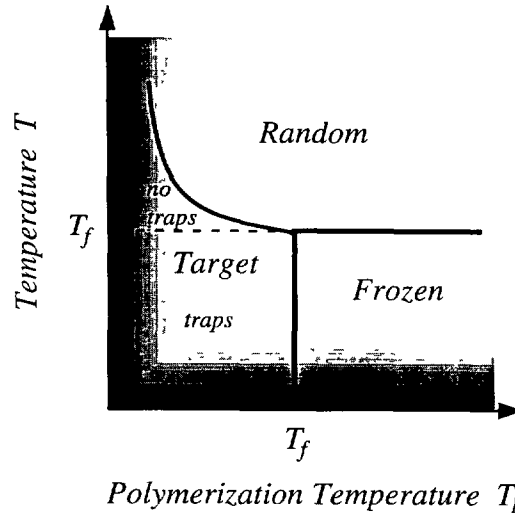


Fig. 1. — Phase diagram for designed copolymers. There are three phases: 1) *random globule*, in which a vast number of conformations (folds) are allowed for the chain in the equilibrium; 2) *frozen globule*, in which only a few conformations or even one conformation are allowed; 3) *target globule*, in which the designed conformation (*) is the only allowed one. Note that the target globule phase region of phase diagram can be divided in two parts: the target conformation is the most stable state in both, but a few of the other random conformations may be thermodynamically either metastable, thus serving as *traps* in kinetics, or unstable *without traps*. Lines at low T and T_p represent the areas of inapplicability of the theory.

Summarizing this discussion, we conclude that there are three different globular phases for heteropolymers prepared by our procedure: (i) *random globule*, essentially similar to homopolymeric one, where energetical preferences between monomers are not sufficient to stabilize any particular conformation, so that the thermodynamic equilibrium is realized as the mixture of astronomically large number of conformations; (ii) *frozen globule*, where each chain chooses some small number of the minimally frustrated [12] conformations, but the choice is essentially unpredictable and remains out of control; (iii) *target globule*, where chain chooses exactly the conformation prescribed in the preparation procedure. This is shown in phase diagram (Fig. 1).

Now we are prepared to finally perform the $n \rightarrow 0$ limit. Indeed, for both $y = 0$ and $y = n$ cases, the effective free energy (38) is linear in n . According to the original expression of the replica approach (4), the real free energy of the heteropolymer chain equals to

$$F = -T \lim_{n \rightarrow 0} \frac{\langle Z^n(\text{seq}) \rangle_{\text{seq}} - 1}{n} = -T \lim_{n \rightarrow 0} \frac{\exp(-\mathcal{F}) - 1}{n} \simeq \frac{T\mathcal{F}}{n} \quad (40)$$

From this, we write the free energies of all three globular phases: random ($x = 1; y = 0$), frozen ($x = T/T_f; y = 0$), and target ($x = T/T_f$ for $T < T_f$, $x = 1$ for $T \geq T_f$; $y = n$)

$$\frac{1}{N} F_{\text{random}} = T \ln \left[1 - \frac{T_f \xi(s)}{T} \right] \quad (41)$$

$$\frac{1}{N} F_{\text{frozen}} = T \ln [1 - \xi(s)] + \frac{T_f \xi(s)}{1 - \xi(s)} \left[\frac{T}{T_f} - 1 \right] \quad (42)$$

$$\frac{1}{N} F_{\text{target}} = T \ln [1 - \xi(s)] + \frac{T_f \xi(s)}{1 - \xi(s)} \left[\frac{T}{T_f} - \frac{1 - \xi(s)}{1 - \xi(s) T_f / T_p} \right] \quad (43)$$

Note that these are already *real* free energies, so that a lower free energy corresponds to a more stable phase, according to usual physical logic. By looking at the free energies above, one can easily reproduce phase diagram (Fig. 1): in each region of the diagram the corresponding free energy is minimal.

6. Discussion.

The free energies of both frozen and target phases do not depend on temperature in the low T limit:

$$\frac{1}{N}F_{\text{frozen}}(T \rightarrow 0) \equiv E_{\text{frozen}}^{\text{gnd}} = -\frac{\xi(s)T_f}{1 - \xi(s)} \quad (44)$$

$$\frac{1}{N}F_{\text{target}}(T \rightarrow 0) \equiv E_{\text{target}} = -\frac{\xi(s)T_f}{1 - \xi(s)T_f/T_p} \quad (45)$$

These limits are naturally interpreted as the energies of ground state conformations for a chain with random and selected sequence, respectively. The ground state energy for a random sequence is independent of T_p , while the energy of the target conformation increases with T_p . We see that the selection of sequences, or preparation of heteropolymers by our synthetic procedure, reduces the energy of the ground state. This implies a very peculiar character of the density of states of the selected chains (Fig. 2). Indeed, since the selected sequence looks random for all conformations except for the target one, its energy spectrum includes the target conformation as the ground state and the typical ground state of random chain as the first excited state.

As was recently understood [14], this kind of spectrum is very important from the point of view of the kinetic accessibility of the ground state. Of course, one cannot analyze kinetics purely by thermodynamic considerations. In general, self-organization of the correct globular structure includes coil-to-globule compaction and some search for the correct globular conformation. We are not in the position to estimate the time scales involved in those processes. However, we can qualitatively compare the kinetics if the target phase self-organization for the two cases $T < T_f$ and $T > T_f$.

Indeed, consider the target phase on the phase diagram and examine first the $T < T_f$ case. In this case, the frozen phase is, from a thermodynamic point of view, metastable. Even though it is less stable than the target state, metastability means that a macroscopic free energy barrier must be overcome to leave this state. It is, therefore, a very strong trap along the way of chain self-organization into the target conformation. We conclude, that at $T < T_f$, the target conformation may not be kinetically accessible, even though thermodynamically it is the most stable. On the other hand, at $T > T_f$, the randomly frozen conformation is not stable at all; thus, there are no effective long-living traps on the pathway of self-organization, and, therefore self-organization is expected to be considerably faster and more reliable.

We now analyze the conditions of applicability of our approach. In fact, besides the fact that we were doing mean field theory, there is only one delicate approximation which comes in equation (13), where we neglect higher order terms in the expansion over ϕ . It is easy to show, that all the subsequent terms in ϕ are positive (and therefore do not cause the divergence of the integrals over ϕ like Eq. (12)). In particular, the next term in ϕ looks like

$$\int d\mathbf{R}_1 d\mathbf{R}_2 d\mathbf{R}_3 d\mathbf{R}_4 \sum_{\alpha, \beta, \gamma, \delta=0}^n \phi^\alpha(\mathbf{R}_1) \phi^\beta(\mathbf{R}_2) \phi^\gamma(\mathbf{R}_3) \phi^\delta(\mathbf{R}_4) Q_{\alpha\beta\gamma\delta}(\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3, \mathbf{R}_4) . \quad (46)$$

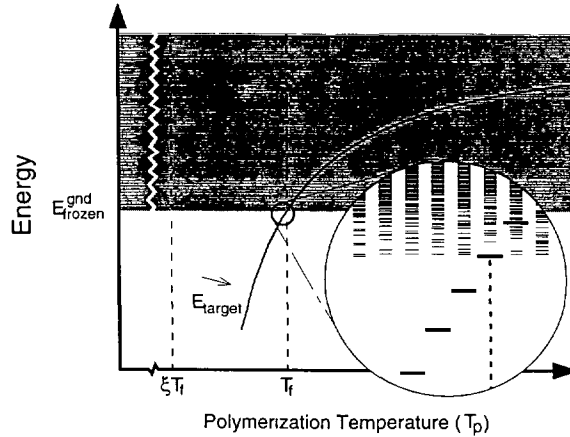


Fig. 2. — Sample energy spectra for sequences imprinted at different polymerization temperatures (T_p). The energy of the target conformation (E_{target}) vs. polymerization temperature (T_p) is plotted. As T_p is increased to T_f , E_{target} increases. In the region $T_p \approx T_f$ (magnified section), we see that E_{target} is equal to $E_{\text{random}}^{\text{nd}}$, the average ground state energy of a random chain. This is related to the phase transition between target and frozen phases (see phase diagram, Fig. 1). It is instructive to see a realistic representation of the very bottom part of the energy spectrum, as is shown here in the magnified section. As was shown in [13], conformations of low energy are absolutely different structurally, and therefore, different pairs of monomers are in contact and are contributing to the energy in those conformations. For this reason, the bottom part of the spectrum obeys the random energy model (REM) [8]. With the change of T_p , the energy of the target conformation changes in a regular fashion, as plotted. Other states represent different independent realizations of the REM system. Eight examples are shown in the inset. For $T_p > T_f$, the average energy for the target conformation state is larger than $E_{\text{random}}^{\text{nd}}$. Note that E_{target} is the average energy, and that for $T_p \gg T_f$, the probability distribution of the energy of the target conformation becomes (up to normalization) equal to the density of all other states.

This should be negligible compared to the $Q_{\alpha\beta}$ -term in equation (13) throughout the region of ϕ contributing to the integration over ϕ . In other words, if we treat equation (13) in terms of effective ϕ -dependent Landau free energy and write it schematically in the form $f = Q_2\phi^2 + Q_4\phi^4$, then the fourth power term should be negligible up to where quadratic term is of order one. From equation (27), it is clear that the quadratic term can be estimated as $N\lambda\phi^2$, where λ is the smallest, and therefore most dangerous, eigenvalue of the $-q_{\alpha\beta}$ matrix. On the other hand, the normalization condition for $Q_{\alpha\beta\gamma\delta}$ implies that $Q_4 \sim N$. Therefore, the condition of applicability is $N\lambda\phi_0^2 \gg N\phi_0^4$, where ϕ_0 is given by $N\lambda\phi_0^2 \sim 1$, yielding $\lambda \gg N^{-1/2}$. Note, that this has a clear physical meaning: λ goes to 0 means that the ϕ -dependent Landau free energy approaches a phase transition, which is known as microphase segregation [2]. Thus, our theory becomes inapplicable close to the microphase segregation regime. As to λ , we know all of the eigenvalues: they are $T/B\rho$, $T/B\rho - x$, and (at $y = 0$) $T_p/B\rho - 1$. From (36), we have $B\rho = T_f\xi(s)$; therefore, the condition of applicability of the approach can be written in the form

$$\frac{T}{T_f\xi(s)} - 1 \gg \frac{1}{\sqrt{N}} \quad \text{and} \quad \frac{T_p}{T_f\xi(s)} - 1 \gg \frac{1}{\sqrt{N}} \cdot \frac{T_p}{T_f} > \xi(s). \quad (47)$$

On the other hand, the mean-field approach for the globule is valid at $a^3/v \gg 1$, or $s \gg 1$. In

this case, $\xi(s) \simeq 1 - 1/2s$. If we define τ and τ_p according to $T = T_f(1 - \tau)$ and $T_p = T_f(1 - \tau_p)$, then the conditions of applicability (47) take the form

$$\tau \ll \frac{1}{2s} - \frac{1}{\sqrt{N}} \quad \text{and} \quad \tau_p \ll \frac{1}{2s} - \frac{1}{\sqrt{N}}. \quad (48)$$

Thus, our results are valid only in a rather narrow region below the phase transition. This is understandable physically: at low polymerization temperature phase segregation occurs in preparation system of two types of monomers, giving rise to very long homopolymeric parts of the prepared sequence. This of course prevents effective freezing of the chain to either random or target conformation. For this reason we expect, that not only our theory breaks closely below the freezing temperature, but also the very phenomenon of freezing and imprinting exists only in rather narrow region of parameters for the two-letter heteropolymer. To improve the situation, one has to pass to a richer set of monomer species, as it is indicated in computer simulations [5]. The corresponding analytic theory is therefore a challenging problem.

7. Conclusions.

In conclusion, we comment on the relevance of our results. First, in the mean field approximation, there is no difference between the sequence design model of biological evolution [4] and the imprinting model [5]. Thus, the above results should be valid for both. As for general heteropolymers, including proteins, we expect that the qualitative results found here should also be valid, as the physical origins of the transition to the target state is not deeply connected to the nature of the polymer investigated, but the existence of designed sequences.

From the experimental point of view, the imprinting model is a method to synthesize heteropolymers capable of renaturing to their polymerization conformation, and thus capable of recognizing some ligand molecule present prior to polymerization. In this theoretical work, we have indeed shown that this is possible. Moreover, based upon our results, we formulate the following crude prescription to the experimental realization of this theory. First, the polymerization temperature must be sufficiently low, or in other words, the set of monomers must be chosen such that the preferential energy (B) should be not less than the polymerization temperature. Furthermore, to provide fast reliable folding one has to choose the acting temperature in between the freezing and target phase transitions.

The existence of a simple procedure which is automatically, i.e. without the biochemical synthesis apparatus of the living cell, capable of producing fast and reliably folding polymer chains with specific active sites for molecular recognition may shed light also on a possible scheme for prebiotic evolution, since all of the elements in our polymerization procedure were most likely present in the "primordial soup" of early Earth.

After the completion of this work, we were informed of the work [15] discussing a similar subject. We are indebted to the authors for sending us the preprint of their work.

Acknowledgments.

We acknowledge helpful discussions with E. Shakhnovich and A. Gutin. The work was supported by NSF (DMR 90-22933) and NEDO of Japan. VSP acknowledges the support of an NSF Fellowship. AYG acknowledges the support of Kao Fellowship.

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