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Ultrametricity in the Externally-Induced Conformational Substates of Disordered Polymers

Ariel Fernández[1]

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We investigate the ergodicity breaking in phase space for biopolymers which fold under the influence of an external field. The polymers have random primary sequences and the interactions among monomeric units are of the volume-excluded type. The replica symmetry breaking is shown to have two distinct sources: the two-body interactions between disordered links and the interaction of the random self-avoiding coil with the localized attractive field.

1. INTRODUCTION

The theoretical models implemented so far to describe the glassy character of conformational substates (local equilibrium states) in proteins and other biopolymers are currently under intensive scrutiny (Bryngelson and Wolynes, 1987; Stein, 1985; Fernández, 1989). Such models are, on the whole, *heuristic* in nature: They are based on an observed analogy between certain disordered systems in condensed matter physics and the seemingly highly degenerate ground conformational state for some biopolymers. The two major lines of thought for conceptualizing the role of quenched disorder in folding emphasize two different sources of randomness: either the randomness is placed on the quenched two-body intrachain interactions with a rather arbitrarily assigned Gaussian probability distribution, or, more generally, it is placed on the disordered nature of the chain links, reflecting itself in random two-body interactions as well as in random interactions with external fields (Fernández, 1989). The essential feature is that both attempts try to account for the breaking of ergodicity in the globular state

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[1] Department of Biochemistry and Molecular Biology, School of Medicine, Miami, Florida 33101, Department of Chemistry, University of Miami, Coral Gables, Florida 33124.

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of the polymer by assigning a glassy character to the folded substates. There exists experimental evidence which substantiates this view: The glassy quality of conformational substates in proteins has been often invoked to account for the nonexponential kinetics in recombination experiments using myoglobin (Austin *et al.*, 1975). The existence of a whole set of scales of relaxation times has suggested a free energy landscape in configuration space which is reminiscent of the highly degenerated ground state of a spin glass. Mössbauer experiments (Keller and Debrunner, 1980) as well as X-ray diffraction data (Frauenfelder, 1989) seem to support this picture. Nevertheless, the actual topology of the set of substates about a given tertiary structure has not been convincingly investigated, nor has a hierarchical distribution in terms of clusters of substates been experimentally substantiated. Such results necessarily require an assessment of the structure of the order parameter, which, in our case of interest, is not a scalar, but a distribution $P(d)$ giving the probability that any two substates are at "distance" d from each other. In analogy with spin glasses, it is understood that $P(d)$ represents an average over the quenched disorder, that is, over the ensemble of primary sequences. The actual definition of d introduced in this work is naturally inspired by the notion of overlap $q(\mu, \mathscr{B})$ between two states μ and $\mathscr{B}$, familiar from spin glasses (Parisi, 1983; Mézard *et al.*, 1984). The degree of structure present in $P(d)$ reflects the replica symmetry breaking (RSB), a property with which disordered polymers with volume-excluded interactions are endowed (Fernández, 1989). Thus, the trivial case where, under the influence of an external attractive field, the random coil collapses into a unique folded state in a ferromagnet-like fashion, does not hold, since we shall demonstrate that $P(d)$ cannot be a simple delta distribution.

As we have mentioned, the RSB has been established for the case of disordered copolymers where the volume-excluded interactions are counteracted by an external attractive field inducing the coil-globule phase transition (Fernández, 1989). The derivation is rooted in the replica method to average over the quenched disorder, just like, in spin glasses, the replica method is used to average over macroscopic samples. In order to make the similarity with spin glasses more obvious, we need to introduce the random variable $s(t)$ (t being a continuous contour variable) representing the quenched disorder. Each particular realization of this variable is a primary sequence once t has been discretized ($t \to j$). Thus, if we allow for only two different kinds of monomers X and Y, then $s(t) = \pm\infty$, depending on whether the monomer at position t is X or Y. The reader should be aware that the source of disorder we are dealing with is different from that in previous approaches, where the sequence is fixed and the quenched interactions are random (Bryngelson and Wolnyes, 1987).

The replica method has been implemented in spin-glass theory to average observables over all realizations of the random pair interactions $\{J_{ij}\}$, where J_{ij} denotes the coupling between the spins σ_i and σ_j at positions i and j, respectively. Similarly, the average over realizations of $s = \{s_j\}$ should be performed for the polymer folding case to justify the assumption that the distribution of substates is hierarchical. In order to formulate our ansatz properly, we shall find it convenient to introduce a distance $d(\mu, \mathscr{B})$ between substates μ and $\mathscr{B}$ for a fixed realization of s in the following way:

$$d(\mu, \mathscr{B}) = (1/N^2 l^2) \sum_{i,j} [R_{ij}(\mu) - R_{ij}(\mathscr{B})]^2 \tag{1}$$

where l is the average length of a link and the $N \times N$ matrix of distances $R_{ij}(\mu)$ between link i and link j (N = number of links) defines the substate μ.

A synopsis of the discussion is given in Table I.

The key quantity in assessing the thermodynamics of a phase transition for our system of interest is $\langle \ln Z(s, N) \rangle$, where $\langle \cdot \rangle$ denotes the average over the ensemble of primary sequences and $Z(N) = Z(s, N)$ is the partition function for the chain. Notice that the partition function contains the disorder; thus, it is a largely fluctuating quantity which cannot be averaged over the ensemble of realizations of s. The relevant average has been evaluated making use of the replica method (Fernández, 1988, 1989). The results reveal that it is feasible to replace the $M \times M$ matrix $[Q(a, b)]$ for M replicas, introduced by Parisi (1983), by a function $Q(x)$, $x \in [0, 1]$, which holds in the limit $M \to 0$. The replica coupling matrix for the folding problem should be defined as follows (a, b denote replicas):

$$Q(a, b, R, R') = \int \overline{\delta(x_a(t) - R)\, \delta(x_b(t) - R')\, dt} \tag{2}$$

The paths $x_{a,b}(t)$ represent chain conformations and the bar on top of a quantity denotes a thermal or statistical average (over all substates). Higher-order correlators [$Q(a, b, c, R, R', R'')$, etc.] are defined analogously.

If the continuous representation $Q(x)$ exists and has a hierarchical structure in the limit $M \to 0$, then the RSB holds. Our task ahead can be

Table I. Formal Relationship between a Spin-Glass System and the Disordered Polymer System

Spin glass		Folded polymer
$\{J_{ij}\}$	Random variables	$\{s_j\}$
$\{\sigma_i(\mathscr{B})\}$	Degrees of freedom	$\{R_{ij}(\mathscr{B})\}$
$P(q)$	Order parameter	$P(d)$
$q(\alpha, \beta)$	Parameters defining topology of set of states	$d(\alpha, \beta)$

best described as proving that this hierarchical "ansatz" represents a sufficient but not necessary condition for the breaking of ergodicity, this last feature being a consequence of the RSB which results from the interaction between the random coil and the attractive external field.

2. THE COUPLING TO AN EXTERNAL FIELD AND THE RSB

The replica method has proven to be an adequate tool to investigate the effect of quenched disorder for the polymer folding problem (Bryngelson and Wolynes, 1987; Fernández, 1988, 1989; Obukhov, 1986). The primary manifestation of the randomness is the RSB: When the actual Hamiltonian of the system is replaced by a virtual one containing no disorder, identical replicas become coupled. Our main concern here is to examine the contribution to this coupling as a consequence of the presence of the external field which traps the random coil. As it turns out, this interaction determines the breaking of ergodicity in the globular state. Thus, we shall establish that *this property is not a peculiarity of a Gaussian distribution of quenched two-body interactions, but holds also in a realistic context where a random coil is trapped by an external field.*

The implementation of the replica method is rooted in a specific way of evaluating the thermodynamically meaningful average $\langle \ln Z(N)\rangle$. This is given by the *a priori* formal relation

$$\begin{aligned}\langle \ln Z(N)\rangle &= \lim_{M\to 0} (1/M)[\langle Z(N)^M\rangle - 1] \\ &= (\partial/\partial M)\langle Z(N)^M\rangle|_{M=0} \qquad (3)\end{aligned}$$

In order to endow this equation with physical meaning, we need an analytical continuation of $\langle Z(N)^M\rangle$ for M real and positive. Such an extension exists (Fernández, 1988, 1989) and, therefore, $Q(x)$ exists independently of the fact that it may or may not have a hierarchical structure. The average $\langle Z(N)^M\rangle$ can be expressed in terms of an effective Hamiltonian coupling replicas and containing no disorder, and the dispersion is determined by the nondiagonality of the effective Hamiltonian.

In order to obtain the contribution of disorder to the effective energy, we need to specify the field. The corresponding term in the actual Hamiltonian of the system is (Fernández, 1989)

$$H^F = \int_0^N [F_t(x(t))/T]\,dt = \text{attractive external field term} \qquad (4)$$

For mathematical simplicity, we shall assume that the field is a space-localized adsorption well (Fernández, 1988) given by

$$F_t(x(t))/T = -\ln[1 + T^{-1}(F_{\text{eff}} + \Lambda s(t))\delta(x(t))] \qquad (5)$$

The constants F_{eff} and Λ have the dimensions of temperature. The field must obviously be attractive in order to induce a phase transition. As the temperature is raised beyond a certain critical value, the well no longer holds the chain and a different correlation range regime, the random coil, emerges. *It is essential to notice that the disorder-dependent part of the field is the one responsible for the RSB, as reflected by the replica-coupling contribution $E_{eff}(r.c.)$ to the effective energy.* This contribution is given by

$$E_{\mathrm{eff}}(\mathrm{r.c.}) = \sum_{a \neq b} (\Lambda/2T)^2 \int Q(a, b, R, R')^2 \, dR \, dR' + \text{higher-order correlation terms} \tag{6}$$

The fact that we are neglecting certain terms merits an explanation. After some rather tedious algebra (Obukhov, 1986), we can see that the most important additional term in the rhs of (6) is given by

$$\text{third-order correlation term} = \sum_{a \neq b \neq c} (B\Lambda^2/2T^2) \int Q(a, b, c, R, R', R'')^2 \, dR \, dR' \, dR'' \tag{7}$$

where B is the standard variance of the link–link two-body interaction coupling variable. Thus, we see that the series in correlator order acts as a Landau expansion and therefore higher-order terms can be neglected in the vicinity of the transition.

3. CONCLUSION

The essential feature which emerges from our analysis is that the RSB arises as a consequence of the interaction of the disordered self-avoiding coil with the external field. The RSB means that the globularization is *nonergodic*: Each folded state is separated by high-energy barriers. In turn, a key *a priori* assumption on the structure of substates within each valley in the free energy profile allows us to derive the RSB property. In more formal terms, we can state that a hierarchical structure in $Q(x)$ leading to the ultrametricity of substates with respect to distance d is a *sufficient but not necessary* condition to yield the RSB in the polymer folding problem. However, the results presented suggest strongly that ultrametricity might be the only possible ansatz to compute averaged free energies by weighting conformational substates for each primary sequence. It might be possible to relax the condition on $Q(x)$, but the proof of this remains an open and challenging problem.

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