PROTEIN FOLDING AND SPIN GLASS

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Abstract

We explicitly show the connection between the protein folding problem and spin glass transition. This is then used to identify appropriate quantities that are required to describe the transition. A possible way of observing the spin glass transition is proposed.

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If a protein has to explore all the possible configurations to reach its biologically active form, then the time required would be \( \sim 10^{10} \) years compared to the real situation, which is of the order of few milliseconds to few seconds \([1]\). This is the Levinthal paradox, whose resolution seems to hinge on the similarities between this biologically important problem and the concept of a rugged free energy landscape of a spin glass in condensed matter physics \([2,3]\). Attempts have also been made to study the dynamics directly but so far these are necessarily restricted to small chains. Our purpose in this paper is to establish the connection with the spin glass quantitatively, and thereby identify the appropriate quantities that one should look at in experiments.

The first idea that there is a connection with spin glass came from the attempts to use a hierarchical tree structure of time scales \([4]\), and the random energy model \([5]\) to rationalize the observed dynamics of proteins \([6]\). The connection was made apparent by the seminal work of Garel and Orland \([7]\), and, independently, of Gutin and Shaknovich \([8]\). From these evolved the idea of statistical proteins. The key points in this approach are that proteins are not simple homopolymers and functionally similar proteins of different species need not have identical backbone structure. The variation in an ensemble of such similar proteins can be thought of as random (albeit correlated) sequence of monomers along the backbone. This randomness leads to random interactions among the monomers. Since the monomers do not change positions once fixed, one has to consider averaging of physical properties over the random realizations of monomer configurations (quenched averaging). There will be quantities whose average over the ensemble will be same as that of typical samples, while there will be ones for which this is not true. The former represent the class of quantities that are called "self-averaging". This class would represent the generic properties of the proteins while the second class of non-self-averaging quantities would be specific to samples (species). The second class is expected to play a significant role in mutants.

Granted the idea of statistical proteins, continuum path integral formulations were used in Ref \([7,8]\) to calculate physical properties by using the replica theory. In approximate calculations, similarities with the infinite state Potts glass were noted. In particular, Ref \([7]\) shows the importance of a finite bond length for a sensible theory. It was soon realized that the monomers in a real protein are not just distributed at random, but there is a correlation, at least to some extent, and the ensemble should be suitably restricted.

We take a model of finite bond lengths and exploit the correlation to choose a certain combination of variables as the independent random entities. Unlike the previous approaches, we use the bonds as the natural variables instead of the absolute coordinates of the monomers. We first establish that for correlated distribution of monomers, the problem can be mapped to a spin glass problem with long range interaction whose nature is determined by the correlation. We then identify the parameters that would describe the spin glass state of the protein, and this parameter is different from the measures of size of homopolymers. For the particular type of correlations considered, we obtain the exact scaling behaviour with the length. We then discuss how the parameter can be measured and the existence of a spin glass phase can be verified. The relevance to dynamics is also discussed.

Let us start with the Kuhn model for a polymer consisting of bonds of unit length freely joined at ends so that each can have complete free rotation without any hindrance \([9]\). See Fig 1. We consider the problem in \(d\) dimensions so that the orientation of each bond is given by a \(d\)-dimensional vector \(s_p\), with \(p\) going from 1 to \(N\), the total number of bonds. Since
the polymer configurations can be completely specified by the \( N \) direction vectors, we can as well consider the equivalent problem of \( d \) component spins arranged in one dimension, representing the one dimensionality of the chain. It is in this picture we formulate the problem.

Any two monomers \( p \) and \( q \) interact on contact with a coupling proportional to \( \epsilon_{pq} \), where \( \epsilon_{pq} \) is a quenched random variable. For a contact potential, this interaction is \( \epsilon_{pq} \delta(r_{pq}) \), where \( r_{pq} \) is the distance vector between monomers (sites) \( p \) and \( q \), where \( \delta(x) = 0 \) for \( x \neq 0 \) and \( = 1 \) for \( x = 0 \). In terms of the bond vectors, \( r_{pq} = \sum_{i=p}^{q-1} s_i \), the hamiltonian can be written as

\[
H = \sum_{p,q} \epsilon_{pq} \delta(\sum_p^{q-1} s_i/(q - p)).
\]  

This is the random version of the Domb-Joyce model for self avoiding walk, and a positive \( \epsilon_{pq} \) would represent a repulsive (self avoiding term) [10]. We replace this contact delta potential \( \delta(R) \) by a smoother potential \( 1 - R^2 \). Note that for the Kuhn model, \( 0 < |R| < 1 \), so that the replacement is equivalent to changing the discrete level 0 and 1 to a band between 0 and 1. This leads to much simplification afterwards. In a sense, two monomers interact with a truncated quadratic potential that can be repulsive or attractive. It is truncated just because the distance between the two cannot exceed a limit - a feature of the Kuhn model. The proposed Hamiltonian is therefore

\[
H = \sum_{ij} \frac{\epsilon_{ij}}{(j - i + 1)^2} \sum_{p,q \in [i,j]} s_p \cdot s_q,
\]  

ignoring a constant (disorder dependent) term that does not contribute to the thermodynamics. The Hamiltonian in this form involves two sums. Given a pair \( i < j \), that defines a cluster in the one dimensional chain, the inner sum involves a summation over all the pairs in the cluster. Let us rearrange the terms and do the outer sum first. For a pair \( p, q \), sum over all the clusters to which it belongs, to obtain terms of the type \( \sum_{i \leq p; j \geq q} \epsilon_{ij} (j - i + 1)^{-2} \). The correlation of the monomers along the backbone (i.e. of \( \epsilon_{pq} \)) is now invoked to write this sum over \( i \) and \( j \) terms of independent random elements. Specifically we choose,

\[
\sum_{m,n} \epsilon_{p-n,q+m} [(q - p) + (m - n)]^{-2} = \frac{J_{pq}}{(q - p)^\sigma},
\]  

with \( J_{pq} \) as the independent random variable and the exponent \( \sigma \) as a measure of the correlation. It is not necessarily true that all correlations can be expressed in terms of such a simple form, but this is the simplest situation. More complex situations can be handled by considering correlated, and, if necessary, inhomogeneously distributed, \( J_{pq} \). This does not invalidate the basic concepts introduced here. The ensemble we will be considering involves polymers that have a particular type of correlations, as given by the distribution of the couplings and the value of \( \sigma \).

The Hamiltonian now takes a form familiar in the spin glass context, namely

\[
H = \sum_{p,q} \frac{J_{pq}}{(q - p)^\sigma} s_p \cdot s_q,
\]  

\[3\]
where each $J_{pq}$ is an independent normal variable with a distribution $P(J_{pq}) = (2\pi J)^{-1/2} \exp(-J_{pq}^2 / 2J)$. This as a spin glass model is a generalization of the long range Ising model considered in Ref. [11] to vector spins [12].

A spin glass transition is described in the $h,T$ plane where $h$ is the magnetic field that orients the spins in a particular direction. The thermodynamic transition is heralded by a diverging spin glass susceptibility, $\chi_{SG}$, while the uniform, linear susceptibility, $\chi$, remains finite at the transition [13]. One sees a cusp in $\chi$ at $T_c$. In terms of the correlation functions, the two susceptibilities can be written as

$$\chi = N^{-1} \sum_{ij} \langle s_i \cdot s_j \rangle, \quad \text{and} \quad \chi_{SG} = N^{-1} \sum_{ij} (\langle s_i \cdot s_j \rangle)^2. \quad (5)$$

We shall restrict ourselves to the high temperature disordered phase, so that no special direction need be chosen. (In general, one should discuss the longitudinal and transverse correlations [12].) The important point to keep in mind is the extensivity of the two susceptibilities, i.e., the total susceptibilities (both linear and spin glass) are proportional to the number of spins, so that the densities defined above are independent of $N$. In addition to the divergence of $\chi_{SG} \sim |T - T_c|^{-\gamma}$, there is also a diverging correlation length $\xi \sim |T - T_c|^{-\nu}$ which describes the behavior of the correlation function $g_{ij} = \langle s_i \cdot s_j \rangle$. The decay of the correlation at $T_c$ is described by the exponent $\eta$, $g_{ij} \sim |j - i|^{-1+\eta}$. The response of the spin glass to an external field can be written as $m = \chi h + \chi_{nl} h^3$, where $m = N^{-1} \sum_i \langle s_i \rangle$ is the net magnetization in the field. For symmetric distributions, it is known that (a) the nonlinear susceptibility $\chi_{nl}$ is related to the spin glass susceptibility $\chi_{SG}$, a relation that is often used to infer $\chi_{SG}$ from experiments [14], and (b) only the diagonal correlations contribute to $\chi$.

We now translate these spin glass quantities to polymers. The spins in our problem correspond to the bonds of the polymer, so that the total magnetization $M = \sum_i s_i$ corresponds to the end-to-end distance of the polymer. This is the quantity of interest in pure problems [9]. Unless the polymer is in a stretched state, the configurational average of $M$ is expected to be zero, and the size $R$ of the polymer is given by the mean square end-to-end distance. The susceptibility is given by the variance of $M$, and so, with zero net magnetization, $\chi = \langle M^2 \rangle / N$. The linear susceptibility of the spin system is therefore related to the size of the polymer. Since, as a density, $\chi$ is independent of $N$, we find $R \sim N^{1/2}$, a result well-known from random walk. Remember that we are ignoring self avoidance - that’s why the random walk exponent. In the spin glass case, $\chi$ remains finite for all $T$, and, therefore, the size as measured by $R$ in our model will always be proportional to $N^{1/2}$, except that the temperature dependence in the strict thermodynamic limit will show a singularity. In contrast, close to the transition temperature $\chi_{SG}$ shows a different behavior. A finite size scaling analysis [12] gives, $\chi_{SG} \sim N^{\gamma/\nu}$, while away from $T_c$ it remains $O(1)$.

We, therefore, propose that for the folding problem the appropriate quantity to look at is

$$\Phi = \sum_{ij} \langle s_i \cdot s_j \rangle^2, \quad (6)$$

which goes like $\sim N^{1+\gamma/\nu}$ in the critical region, but like $N$ for $T >> T_c$. This is a different measure of size than conventionally used in pure problems. Its importance can be understood in terms of dynamics to be discussed below. It is possible to connect this $\Phi$ to the size of the polymer in the following way:
\[
\langle R^2 \rangle^2 \sim \sum \langle s_i \cdot s_j \rangle \langle s_p \cdot s_q \rangle,
\]
and if we assume the dominance of the diagonal terms then,
\[
\Phi \sim \langle R^2 \rangle^2.
\] (7)

This is a justifiable assumption, since we do not require any new exponent to describe the spin glass. Similar scaling is expected for the radius of gyration also. This gives an experimentally accessible quantity that can be probed in scattering experiments (see below).

Let us now go back to our Eq. 4. The spin glass problem can be studied in the replica framework following the method of Ref. [11]. Details are skipped. The relevant results we need here are the following: (1) There is a spin glass transition for \(1/2 \leq \sigma < 1\). (2) For \(\sigma < 2/3\), the behavior is meanfield like, and can as well be described by an infinitely weak infinite range model [12]. (3) Fluctuations play a major role for \(\sigma > 2/3\) and the one dimensional problem is expected to behave like a short ranged spin glass.

As already pointed out after Eq. 6, the behaviour we want to see comes from \(\gamma/\nu\) which, by a scaling relation, is equal to \(2 - \eta\) [13]. Our aim is therefore to calculate \(\eta\). Now, long range interactions do not require any renormalization [11]. As a result, the exponent \(\eta\) is known exactly to be \(\eta = 3 - 2\sigma\). Hence, the behavior of the fold parameter in the simple model is determined as

\[
\Phi \sim N^{2\sigma} \quad \text{for} \quad T \approx T_c
\]
\[
\sim N \quad \text{for} \quad T >> T_c,
\] (9)

for \(2/3 < \sigma < 1\). The restriction on \(\sigma\) is needed because finite size scaling is not valid for mean field theories [14]. In other words, for \(\sigma < 2/3\), no simple scaling form for \(\Phi\) is expected near the transition.

A direct way of measuring the fold parameter \(\Phi\) is to device an experiment that stretches the polymer. In the spin glass language, the external field tries to orient all the spins along its direction. This ordered state corresponds to a stretched rod-like configuration of the polymer. The analog of the magnetic field in spin glass is therefore a stretching force as can be obtained by pulling the polymer at two ends (say by putting tunable charges at the ends), or in extensional flows that lead to a coil-stretch transition. It is therefore suggested that to elucidate the spin glass type behavior, it is necessary to study the response of proteins in the glassy state to a (may be oscillatory) stretching force, and look for the nonlinear response.

Another way of measuring \(\Phi\) would be to look at the structure factor, especially in the leading correction (in momenta) to the small angle scattering. Let us for simplicity assume that optically the protein behaves as a homopolymer, i.e., in scattering, all the monomers behave identically, and the thermal averaging can be approximated by a gaussian average. The structure factor (see, e.g., Ref [9]) for a given realization of the polymer is then given by \(\exp(-k^2R_g^2)\) for a wavevector \(k\), where \(R_g^2 = N^{-2} \sum_{m>n} \langle (r_m - r_n)^2 \rangle\) is the square radius of gyration. A disorder averaged structure factor then gives \(R_g^2 \sim \chi\) as the leading term in small angle scattering (i.e., \(k \to 0\)). The next correction depends on \((R_g^2)^2\) which we argued to have the same scaling behavior as \(\Phi\).

So far we focussed on the equilibrium aspect of the problem. The important time dependent activities (i.e. biological functions) involve rearrangements (release of strains) through...
a sequence of functionally important motions (FIMs). FIMs are the movements of certain
segments of the molecules involving or surrounding the active site. In our bond picture, the
motion of a block from $i$ to $j$ can be executed by an interchange of the two spins $s_i$ and
$s_j$. For example, nearest neighbor $i,j$ interchange corresponds to the Verdier-Stockmeyer
type moves $[9]$ while the next nearest neighbor interchange corresponds to a crankshaft mo-
tion $[17]$. The FIMs can then be identified as two spin interchanges (blocks containing the
active site), and one needs to classify them according to time scales. The relevant quantity
to describe such motions in the native state is to look at the time correlation function

$$\Phi_1(\tau) = \lim_{N \to \infty} \langle \{s_i(t) \cdot s_j(t)\}\{s_i(t+\tau)s_j(t+\tau)\}\rangle,$$  \hspace{1cm} (10)

where the average is now a time average. For $\tau \to \infty$, $\Phi_1(\infty)$ is the counterpart of the
Edwards-Anderson order parameter $[13]$ for spin glasses. The fold parameter $\Phi$ comes from
Eq. 11 if the limits are taken in the reverse order, i.e., $\lim_{N \to \infty} \lim_{\tau \to \infty}$. It is known that
unlike $\Phi$, $\Phi_1(\infty)$, is not a self-averaging quantity.

The importance of self-averaging quantities in the protein context is that for such a
quantity any typical sample behaves like the average one. In contrast, large sample to
sample fluctuations are expected in non-self-averaging quantities. For biological activity,
mutants behave differently, mainly because FIMs get modified. It is, therefore, gratifying
to find that the measure $\Phi_1$ introduced above has the non-self-averaging property that can
distinguish a mutant or denatured protein from the native one.

In summary, we have shown (in the spirit of lattice gas models of liquid gas transition)
that for a correlated heteropolymer, the bonds variable are the suitable variables, and in
terms of these, the phase transition in the protein can be described by a one dimensional
vector spin glass model with long range interaction. We identified a fold parameter that
should be the measure for the folding problem. Its exact scaling behavior under certain
circumstances has also been determined. We find exactly that for certain types of correla-
tions, the geometric exponents are determined completely by $\sigma$ of Eq. 3. The correlations
along the backbone can also destroy the scaling property, if $\sigma$ is large enough. In other
words, unlike the uncorrelated cases of Refs $[7,8]$, our observations show that proteins need
not have a generic scaling behavior, and correlations do play a major role in it. We suggest
that elastic moduli in oscillatory stretching fields would help in the identification of the spin
glass type transition in proteins, if there is one at all. Moreover, the proteins are inevitably
of finite lengths, and therefore what one can observe is not a true transition but the finite
size scaling behavior of the spin glass transition. This in turn opens up the new possibility
of enriching our understanding of spin glasses via controlled experiments done on proteins
with easily accessible $T_c$. 

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[1] C. Levinthal, in Mossbauer spectroscopy in biological systems, P. DeBrunner et al (eds), U. Illinois Press (1969).
[2] H. S. Chan and K. A. Dill, Phys. Today, 24, Feb. 1993.
[3] J. D. Bryngelson, J. N. Onuchic, N. D. Socci and P. G. Wolynes, Proteins (in press), chem-ph/9411008, and references therein.
[4] H. Frauenfelder, in Structure and dynamics of nucleic acids, proteins, and membranes, Ed by E. Clementi and S. Chin (Plenum, 1986) and references therein.
[5] B. Derrida, Phys. Rev. B 24, 2613 (1981)
[6] J. D. Bryngelson and P. G. Wolynes, Proc Natl. Acad. Sci. USA, 84, 7524 (1987).
[7] T. Garel, and H. Orland, Euro Phys. Lett., 6, 307 (1988); ibid, 6, 597 (1988).
[8] E. Shakhnovich and A. M. Gutin, J. Phys. A: Math. Gen., 22, 1647 (1989).
[9] M. Doi and S. F. Edwards, The Theory of Polymer Dynamics, Oxford Science Publications, Clarendon Press, Oxford (1986).
[10] C. Domb and G. S. Joyce, J. Phys. C: Solid State Physics, 5, 956 (1972).
[11] G. P. Kotliar, P. W. Anderson, and D. L. Stein, Phys. Rev. B 27, 602 (1983).
[12] M. Gabay and G. Toulouse, Phys. Rev. Lett., 47, 201 (1981); D. M. Cragg, D. Sherrington, and M. Gabay, Phys. Rev. Lett., 49, 158 (1982).
[13] K. H. Fischer and J. A. Hertz, Spin Glasses, Cambridge univ. Press (1991).
[14] J. Chalupa, Solid State Comm., 24, 429 (1977); M. Suzuki, Prog. Theor. Phys., 58, 1151 (1977).
[15] See, e.g., M. N. Barber, in Phase transitions and Critical Phenomena Ed.s C. Domb and J. L. Lebowitz, (1983) Academic Press.
[16] E. Brezin, J. Phys. (Paris), 43, 15 (1982).
[17] H. S. Chan and K. A. Dill, J. Chem Phys., 99, 2116 (1993); ibid, 100, 9238 (1993).
FIG. 1. a) A segment of the Kuhn chain, and b) its one dimensional spin representation.