A Model for the Thermodynamics of Globular Proteins

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We review a statistical mechanics treatment of the stability of globular proteins based on a simple model Hamiltonian taking into account protein self interactions and protein-water interactions. The model contains both hot and cold folding transitions. In addition it predicts a critical point at a given temperature and chemical potential of the surrounding water. The universality class of this critical point is new.

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Biologically relevant proteins are macromolecules [1] whose structures are determined by the evolutionary process [2,3]. The folded conformation of globular proteins is a state of matter peculiar in more than one respect. The density is that of a condensed phase (solid or liquid), and the relative positions of the atoms are, on average, fixed. These are the characteristics of the solid state. However, solids are either crystalline or amorphous, and proteins are neither: the folded structure, while ordered in the sense that each molecule of a given species is folded in the same way, lacks the translational symmetry of a crystal. Unlike any other known solids, globular proteins are not really rigid, being able to perform large conformational motions while retaining locally the same folded structure. Finally, these are mesoscopic systems, consisting of a few thousand atoms.

Quantitatively, the peculiarities of this state of matter are perhaps best appreciated from thermodynamics. Delicate calorimetric measurements [4–6] on the folding transition of globular proteins reveals the following picture. The transition is first order, at least in the case of single domain proteins. The stability of the folded state, i.e., the difference in Gibbs potential \( \Delta G \) between the unfolded and the folded state is at most a fraction of \( kT_{room} \) per aminoacid. This is referred to as “cooperativity”. The Gibbs potential difference \( \Delta G \), as a function of temperature, is non monotonic: it has a maximum around room temperature (where \( \Delta G > 0 \) and consequently the folded state is stable), then crosses zero and becomes negative both for higher and lower temperatures. Correspondingly, the protein unfolds not only at high, but also at low temperatures. The melting transition under cooling is referred to as “cold unfolding” or “cold denaturation.” For temperatures around the cold unfolding transition and below, the enthalpy difference \( \Delta H \) between the unfolded and the folded state is negative; this means that cold unfolding proceeds with a release of heat (a negative latent heat), as is also observed experimentally; at the higher unfolding transition, on the contrary, \( \Delta H > 0 \) which corresponds to the usual situation of a positive latent heat. There are two peaks in the specific heat, corresponding to the two unfolding transitions, and a large gap \( \Delta C \) in the specific heat between the unfolded and the folded state. This gap is again peculiar to proteins: usually, for a melting transition \( \Delta C \) is small.

It is (however not universally) believed that from the microscopic point of view, the main driving force for folding is the hydrophobic effect; in the native state of globular proteins hydrophobic residues are generally found in the inside of the molecule, where they are shielded from the water, while hydrophobic residues are typically on the surface. Hydrogen bonds within the regular elements of secondary structure (\( \alpha \) helices and \( \beta \) sheets), while necessary for the stability of the native state, can hardly be thought of as providing the positive \( \Delta G \) of the folded structure, since the unfolded structure would form just as many hydrogen bonds with the water. When the protein unfolds, the hydrophobic residues of the interior are exposed; this accounts for most of the gap in the specific heat \( \Delta C \), according to the known effect that dissolving hydrophobic substances in water raises the heat capacity of the solution [7]. A recent discussion of hydrophobicity in protein folding may be found in Ref. [8].

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where we have introduced a scale parameter to the water and the interaction is zero. Returning to the new variables protein parametrized by $i$

the protein-water interactions. In order to model hydrophobicity, we assume the energy scale in the system — in particular $kT$ — which was introduced to describe the helix – coil transition. In this model, the relevant degrees of freedom (conformational angles) are modeled through binary variables. Each variable is either matching the ordered structure (helix), or in a “coiled” state. A related parametrization for the 3-d folding transition has been proposed by Zwanzig [14], describing it in terms of variables $\psi_i$, each of which is “true” (1) when there is local match with the correct ground state, or “false” (0) if there is no match. The term “local” is here defined through the parametrization index $i$. A zipper scenario that deals with the initial pathway of protein folding has been proposed by Dill et al. [15]. We can parametrize this model in the same way as done by Zwanzig by assigning the value one to each of the binary variables $\psi_i$ describing closed contacts in the zipper. Build into the model is that opening and closing of contacts occur in a particular order: They behave as the individual locks in a zipper. This ordering is characterized through imposing the constraints

$$\psi_i \geq \psi_{i+1} .$$

The variables $\psi_i$ alone cannot describe the degrees of freedom that become liberated when a portion of the zipper is open. The open part of the zipper may move freely ($\psi_i = 0$) whereas they cannot move in the part of the zipper where the contacts are closed ($\psi_i = 1$). In order to take into account this effect, we introduce a second, independent set of variables $\xi_i$. For simplicity, we also make these variables binary, taking the values 1 or -1. We are now in the position to propose a Hamiltonian for this zipper model,

$$H = -\sum_{i=1}^{N} \psi_i \xi_i ,$$

subjected to the constraints [1].

We note that for any finite value of $B$, parts of the protein may unfold inside the already folded region i.e. in the parts of the zipper where $\psi_i = 1$. In order to prevent this, we assume $B$ to be sufficiently large compared to any other energy scale in the system — in particular $kT$, where $T$ is the temperature — so that the $\xi_i$ variables never assume the value $-B$ as long as $\psi_i = 1$.

We will in the following use this Hamiltonian as a starting point for analyzing the hot and cold denaturation transitions of proteins when dissolved in water [10]. It is awkward to work with the Hamiltonian [2] directly because of the constraints [1]. We therefore make a transformation to a different set of variables where the constraints [1] are implicitly taken into account. We define a set of binary, unconstrained variables $\varphi_i$, by the following relation:

$$\psi_i = \varphi_1 \cdots \varphi_i .$$

In particular, $\psi_1 = \varphi_1$. In the limit when $B \rightarrow \infty$, the Hamiltonian [2] becomes

$$H = -\varphi_1 - \varphi_1 \varphi_2 - \varphi_1 \varphi_2 \varphi_3 - \cdots - \varphi_1 \varphi_2 \cdots \varphi_N ,$$

where there are no additional constraints [1]. The role of the variables $\xi_i$ — which is to provide entropy to the unfolded part ($\psi_i = 0$) of the zipper — is now played by the degeneracy introduced into the Hamiltonian in the following way: When a particular $\varphi_j = 0$, the Hamiltonian [2] will be degenerate with respect to the variables $\varphi_i$ where $i > j$.

The interactions between protein and water may be taken into account by adding to [2] a coupling parametrized through water variables $w_1, w_2, \ldots, w_N$ [10]. Returning for a moment to the original variables $\psi_i$, we propose an interaction $(1 - \psi_i \xi_i)w_i$. The rationale behind this form is that when a contact is open ($\psi_i = 0$), the part of the protein parametrized by $i$ is exposed to water and interact, while if the contact is closed ($\psi_i = 1$), there is no access to the water and the interaction is zero. Returning to the new variables $\varphi_i$, the resulting Hamiltonian is

$$H = -\mathcal{E}_0 (\varphi_1 + \varphi_1 \varphi_2 + \varphi_1 \varphi_2 \varphi_3 + \cdots + \varphi_1 \varphi_2 \cdots \varphi_N) + [(1 - \varphi_1)w_1 + (1 - \varphi_1 \varphi_2)w_2 + \ldots + (1 - \varphi_1 \varphi_2 \cdots \varphi_N)w_N] ,$$

where we have introduced a scale parameter $\mathcal{E}_0$ in order to vary the relative strength of the protein self interactions and the protein-water interactions. In order to model hydrophobicity, we assume the $w_i$ variables take values $\mathcal{E}_{\text{min}} + s\Delta$, $s = 0, 1, \ldots, g - 1$. Here, $\Delta$ is the spacing of the energy levels of the water-protein interactions. The equidistant
energy levels reflect the experimentally observed approximate constant heat capacity at intermediate temperatures, whereas the finite number of levels \( g \) takes into account that protein-water interactions vanish at high temperatures, in practice above 120 degree celsius.

The number of terms in the Hamiltonian \( \theta \). \( N \), is the number of contact in the zipper model. This number may be equal to the number of amino acids, but is a priori unknown. It is important to realize that if one parametrize the folding with fewer steps \( N \), each unit will be larger and energies and entropies appropriately increased (inversely proportional to \( N \)).

The calculation of the partition function is straightforward. We parametrize the states of the system by the number \( n \) of consecutive matches \( \varphi_1 = 1, \varphi_2 = 1, \ldots, \varphi_n = 1 \) and ending with \( \varphi_{n+1} = 0 \) and the values \( \{ s_{n+1}, \ldots, s_N \} \) where each \( s_i \in \{ 0, 1, 2, \ldots, g-1 \} \) for the \((N-n)\) \( \mu \) variables coupled to the unfolded portion of the protein. The energy of this state is

\[
\varepsilon(n, s_{n+1}, \ldots, s_N) = -n \varepsilon_0 + \sum_{i=n+1}^{N} (\varepsilon_{min} + \Delta \varepsilon s_i)
\]

where we have introduced the energy scale \( \varepsilon_0 \) for the protein variable in order to make the formulas dimensionally more transparent (up to now we used \( \varepsilon_0 = 1 \)). Denoting \( \beta = 1/T \) as the reciprocal temperature, the partition function is

\[
Z = \sum_{n=0}^{N-1} 2^{N-n-1} g^n \sum_{s_{n+1}=0}^{g-1} \cdots \sum_{s_{N}=0}^{g-1} \exp(-\beta \varepsilon(n, s_1, \ldots, s_N)) + g^N \exp(\beta \varepsilon_0 N)
\]

In the above equation the factor \( 2^{N-n-1} \) is the degeneracy of the unfolded protein degrees of freedom and the factor \( g^n \) is the degeneracy of water which is not exposed to the inside of the protein. Factorizing the sums over \( s_i \) into partition functions \( Z_w \)

\[
Z = \frac{1}{2} (2Z_w)^N \sum_{n=0}^{N-1} \left( \frac{g \exp(\beta \varepsilon_0)}{2Z_w} \right)^n + (g \exp(\beta \varepsilon_0))^N
\]

where the phase space for a water degree of freedom exposed to an unfolded protein degree of freedom is

\[
Z_w = \sum_{s=0}^{g-1} \exp(-\beta (\varepsilon_{min} + s \Delta \varepsilon)) = \frac{(\exp(-\beta \varepsilon_{min}) - \exp(-\beta \varepsilon_{max}))}{(1 - \exp(-\beta \Delta \varepsilon))}
\]

where \( \varepsilon_{max} = \varepsilon_{min} + g \Delta \varepsilon \). From Eq. 8 one sees directly that the state of the system is determined by the size of the quantity

\[
r = \frac{g \exp(\beta \varepsilon_0)}{2Z_w} = \exp(\beta f)
\]

If \( \Delta f > 0 \) then the system will be in the folded state because the sum in Eq. 8 is dominated by the last term, whereas for \( \Delta f < 0 \) the system will be unfolded.

The sum in Eq. 8 can be readily performed and the total partition function is

\[
Z = \frac{1}{2} (2Z_w)^N \frac{1 - (g \exp(\beta \varepsilon_0))/Z_w)^N}{1 - (g \exp(\beta \varepsilon_0))/Z_w} + (g \exp(\beta \varepsilon_0))^N
\]

The free energy is \( F = -T \ln(Z) \), the energy \( E = -d \ln(Z)/d \beta \) and the heat capacity \( C = dE/dT \). Because there is no pressure in the model, the energy \( E \) takes the place of the enthalpy \( H = E + pV \) and the free energy \( F = E - TS \) takes the place of the Gibbs potential \( G = H - TS \).

In Fig. 1 we show the heat capacity the three different choices of \( \varepsilon_{min} \), representing three different values of the chemical potential as we discuss later. The characteristic feature is that there are two peaks corresponding to warm and cold unfolding, and a gap \( \Delta C \) in the heat capacity between the unfolded and the folded form. At higher temperatures, i.e., \( T > g \Delta \varepsilon \), the gap goes to zero because the water becomes effectively degenerate again. In Fig. 2 we show the order parameter \( \langle n \rangle \) as function of temperature for three values of the chemical potential. The figure indeed confirms that the protein is folded between the two transitions.
We now calculate explicitly the difference in the thermodynamic functions between the unfolded and the folded state. We consider these quantities per degree of freedom. The thermodynamic functions associated to a folded (f) protein variable is the energy $e_f = -\mathcal{E}_0$, the entropy $s_f = \ln(g)$ and the free energy $f_f = -\mathcal{E}_0 - T \ln(g)$. The free energy associated to an unfolded (u) protein variable is given by the corresponding partition function of water multiplied by the degeneracy factor of an unfolded part of the protein: $f_u = -T \ln(Z_w 2)$. The difference in free energy between folded and unfolded state is accordingly

$$\Delta f = f_u - f_f = T \ln\left(\frac{g \exp(\beta \mathcal{E}_0)}{2 Z_w}\right)$$

which is the quantity we earlier identified as the one which decides whether the system cooperatively selects the folded or the unfolded state. To clarify the physical contents of this formula we rewrite it for small energy level spacings $\Delta E << T$:

$$\Delta f = \mathcal{E}_0 + \mathcal{E}_{\min} + T \ln\left(\frac{g \Delta E}{2 T}\right) - T \ln\left(1 - \exp(- (\mathcal{E}_{\max} - \mathcal{E}_{\min})/T)\right)$$

From this expression for the difference in free energy one easily obtains the corresponding differences in energy, entropy and specific heat. In particular, we obtain a gap in the specific heat between the folded and unfolded state of a protein (see Fig. 1).

To simplify the discussion let us consider the limit of large $\mathcal{E}_{\max}$ in (13). It is easily seen that $\Delta f$ has a maximum at the temperature $T_m \approx g \Delta E/2e$. The corresponding value of $\Delta f$ is $\Delta F(T_m) \approx (\mathcal{E}_{\min} + \mathcal{E}_0) + g \Delta E/2e$, so the condition for the existence of a region of stability of the ordered structure ($\Delta f > 0$) is:

$$\frac{g \Delta E}{2e} > -(\mathcal{E}_{\min} + \mathcal{E}_0).$$

This is of course always satisfied if $(\mathcal{E}_{\min} + \mathcal{E}_0) > 0$, however the more interesting situation is $(\mathcal{E}_{\min} + \mathcal{E}_0) < 0$, since then $\Delta F < 0$ at sufficiently low temperature, i.e. the phenomenon of cold unfolding appears. Under these conditions $\Delta E$ is also negative at sufficiently low temperature which means that we have a negative latent heat for cold unfolding.

Coming back to the partition function (11) and (12), we may write:

$$\mathcal{E} = -N \mathcal{E}_0 + (N - n)(\mathcal{E}_0 + \mathcal{E}_{\min}) + \sum_{i=n+1}^{N} \Delta \mathcal{E} s_i = -N \mathcal{E}_0 + \sum_{i=n+1}^{N} [\Delta \mathcal{E} s_i + \mathcal{E}_0 + \mathcal{E}_{\min}]$$

and

$$Z = e^{\beta N \mathcal{E}_0} \sum_{n=0}^{N-1} 2^{N-n-1} g^n \sum_{\{s_i\}} e^{-g \sum_{i=n+1}^{N} (\mathcal{E}_i - \mu)} + g^N \exp(\beta \mathcal{E}_0 N)$$

where we have set $\mathcal{E}_i = \Delta \mathcal{E} s_i$, $\mu = -(\mathcal{E}_0 + \mathcal{E}_{\min})$. From this expression for $Z$ we can identify $\mu$ with the chemical potential of the water, or, to be more precise, the difference in chemical potential of the water when it is in contact with the hydrophobic interior of the protein and when it is not. Therefore, $\mu > 0$ is the physically relevant situation. Experimentally, $\mu$ can be changed by adding denaturants, changing pH, etc., which indeed alters the stability of the ordered structure.

For an intermediate value of the chemical potential, $r$ — defined in Eq. (10) — just touches the line $r = 1$, that is $dr/dT = 0$ when $r = 1$, corresponding to a merging of two first order transitions. This defines a critical point. Around this point, $r$ varies quadratically in $T - T_c$ and linearly in $\mu - \mu_c$, as seen from expanding Eq. (11). In experiments of protein folding this point is accessible by changing the pH value of the solution. In fact, Privalov’s data on low pH values indeed indicate that such a critical point exists. The scaling properties around this point thus opens for a possibility to gain insight into the nature of the folding process, in particular whether the pathway scheme we suggest can be falsified.

In Fig. 2 we show heat capacity as a function of temperature for chemical potential at the critical value $\mu = \mu_c$. For the chosen values of $\mathcal{E}_0 = 1$ and level density $\Delta = 0.02$ and $g = 350$ the critical point is situated at $T_c = 1.33303 \ldots$, $\mu_c = 1.2833 \ldots$. That is, it is situated at a minimum of the heat capacity curve. This is at first sight surprising, usually heat capacity has a pronounced increase at the critical point. The minimum reflects a partial ordering, as envisioned in Fig. 3 where we show the degree of folding, counted by the average number of folded variables $\varphi_i = 1$,
are fulfilled [17]. However, the hyperscaling relation
\[ \mu_{\text{critical value}} = \text{value} \]
with \( \mu > \mu_c \) for different values of the size \( N \). For finite \( N \) we may express the singular part of the heat capacity in the form:
\[ C_{\text{sing}}(T) = C(T, \mu) - C(T, \mu_c) \]
where \( \mu \) is the critical point, reflecting that the system is on average half ordered at this point. Correspondingly the heat capacity dips to a value in between the value of an unfolded and a completely folded state.

To characterize the functional form of the dip in the heat capacity, we investigate analytically
\[ C_{\text{sing}}(T) = C(T, \mu) - C(T, \mu_c) \]
with \( \mu >> \mu_c \) for different values of the size \( N \). For finite \( N \) we may express the singular part of the heat capacity in the form:
\[ C_{\text{sing}} = |T_c - T|^{-\alpha} g \left( (T_c - T) N^{1/\nu} \right) \]  
(17)
where \( g(x) \to \text{const} \) when \( x \to \infty \) and \( g(x) \propto x^\alpha \) when \( x \to 0 \). We find analytically \( \alpha = \nu = 2 \) from differentiating the partition function \( \mathcal{G} \). Fig. 3 demonstrate this finite size scaling. Similarly we show in Fig. 4 the behavior of the order parameter \( \langle n \rangle \) as function of \( T - T_c \) and \( N \):
\[ \langle n \rangle = |T - T_c|^{\beta} f \left( (T - T_c) N^{1/\nu} \right) \]  
(18)
with \( f(x) \to \text{const} \) when \( x \to \infty \) and \( f(x) \propto x^{-\beta} \) when \( x \to 0 \). We find analytically \( \beta = 2 \), also found analytically. It may be surprising that \( \beta \) is negative, but this reflect in part the unusual use of an extensive (in \( N \)) order parameter, in part that for \( \mu = \mu_c \) then the order parameter only obtains a non-zero value at \( T = T_c \) when \( N \to \infty \).

Likewise, we find that the susceptibility \( \chi = d\langle n \rangle / d\mu \) scales as \( |T - T_c|^{-\gamma} \) where \( \gamma = 4 \) and that \( \langle n \rangle \propto (\mu - \mu_c)^{1/\delta} \) for \( \mu > \mu_c \) where \( \delta = -1 \). Thus the usual exponent relations, \( \alpha + 2\beta + \gamma = 2, \alpha + \beta(\delta + 1) = 2, \) and \( \gamma(\delta + 1) = (2-\alpha)(\delta - 1) \) are fulfilled [7]. However the hyperscaling relation \( \partial\nu = 2 - \alpha \), where \( \partial \) is the dimensionality of the system, is not fulfilled. However, this relation has no meaning, as there are no spatial degrees of freedom.

In terms of experiments on proteins, the relevant scaling behaviour is the how the degree of folding (order parameter) and the heat capacity behaves as function of temperature, when one changes chemical potential away from its critical value. The qualitative prediction is that the width of the singular part of the heat capacity has a minimum at the critical value \( \mu = \mu_c \). The broadening of the heat capacity is
\[ C_{\text{sing}}(T - T_c)^2 = h \left( \frac{T - T_c}{\Delta \mu^{1/2}} \right) \]  
(19)
for \( \mu > \mu_c \)
where \( h(x) \propto x^{-2} \) for \( x \to \infty \) and \( h(x) = \text{const} \) for \( x \to 0 \) and where \( \Delta \mu = \max(\mu - \mu_c, \Delta \mu_{\text{min}}) \) with \( \Delta \mu_{\text{min}} \propto 1/N \) takes into account the finite size sensitivity of the scaling. We show in Fig. 4 an example of such a data collapse. These predictions are experimentally accessible through the use of standard calorimetric techniques, where one should seek to obtain a data collapse above the critical point, i.e. the point of minimal width. The heat capacity below the critical \( \mu \) is complicated by the merging of two first order transitions. However, the distance between these moves away from each other in \( T \) as \( \Delta \mu^{1/2} \).

Likewise, we expect the degree of folding \( \langle n \rangle \) to show data collapse of the form
\[ \langle n \rangle (T - T_c)^2 \mu > \mu_c \]  
(20)
where \( k(x) \) behaves asymptotically as \( h \). We show this in Fig. 5. This quantity can be observed experimentally through fluorescence measurements.

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FIG. 1. Heat capacity, $C$, as a function of $T$ for three values of the chemical potential $\mu$. Here $g = 350$, $\Delta = 0.02$ and $N = 100$. The value $N = 100$ has been chosen as to be close to realistic values for this parameter.

FIG. 2. Degree of folding, $\langle n \rangle$, as a function of $T$ for three values of the chemical potential $\mu$. The parameters are chosen as in Fig. 1.

FIG. 3. Finite size scaling of the heat capacity for $\mu = \mu_c$, $g = 350$ and $\Delta = 0.02$. Here $\alpha = 2$ and $\nu = 2$.

FIG. 4. a) Finite size scaling of folding, $\langle n \rangle$ for $\mu = \mu_c$, $g = 350$ and $\Delta = 0.02$. Here $\beta = -2$.

FIG. 5. $C_{sing}(T - T_c)^2$ vs. $(T - T_c)/\Delta \mu^{1/2}$. We have chosen $N = 100$, $g = 350$ and $\Delta = 0.02$. Note the good quality of the data collapse in spite of smallness of the system.

FIG. 6. $\langle n \rangle(T - T_c)^2$ vs. $(T - T_c)/\Delta \mu^{1/2}$. We have chosen $N = 100$, $g = 350$ and $\Delta = 0.02$. Note the good quality of the data collapse in spite of smallness of the system.
Figure 1
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*A Model for the Thermodynamics of Globular Proteins*
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Figure 5

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Figure 6
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