Proteinlike behavior of a spin system near the transition between ferromagnet and spin glass

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A simple spin system is studied as an analog for proteins. We investigate how the introduction of randomness and frustration into the system effects the designability and stability of ground state configurations. We observe that the spin system exhibits protein-like behavior in the vicinity of the transition between ferromagnet and spin glass. Our results illuminate some guiding principles in protein evolution.

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The folding of a protein into a specific three-dimensional (3D) biologically active structure is now often described by the funnel concept [1]. It is assumed that the energy landscape of a protein is rugged but with a sufficient overall slope towards the native structure [2]. Folding occurs by a multi-pathway kinetics and the particulars of the folding funnel determine the transitions between the different thermodynamic states [2,3]. While originally derived from studies of minimalistic protein models, evidence for the validity of the funnel concept was subsequently presented for real proteins [4].

A funnel-like energy landscape guarantees thermodynamic stability and kinetic accessibility for the biologically active structure of proteins. Both are necessary conditions for proteins to perform their biological functions. Hence, the funnel concept suggests that the optimal state of a protein is one of minimal frustration [5]. This is because a smoother energy landscape and a steeper slope leads to faster folding and greater stability. However, proteins are in general only marginally stable [3], and both stability and speed of folding can often be increased in protein engineering [4]. Hence, it appears that the sequence of amino acids in a protein is in general not optimized for smoothness of its energy landscape. The question arises then on why is this the case and why are proteins only marginally stable. Or what factors constraint the amount of frustration (and the ruggedness of the funnel landscape) in the evolution of proteins?

When studying the above questions one encounters the problem that the amount of frustration is difficult to control in protein models. For this reason, we propose to use the frustrated 3D-Ising model on a simple cubic lattice [8] with periodic boundary conditions as an analogy of proteins, and to study the above questions for this much simpler system in which the frustration can be easily measured. Unlike in earlier work [8,9] we interpolate continuously between the ferromagnet and the spin glass by varying the density of antiferromagnetic bonds. Our choice of the system is motivated by the observation that proteins are similar to spin glasses in that their
energy landscape is characterized by a huge number of local minima separated by high
energy barriers [11]. On the other hand, the global funnel-like topology of protein
energy landscapes, leading to an unique ground state, resembles more a ferromagnet.
Hence, it seems that proteins show behavior between that of a ferromagnet and a spin
glass. However, the limitations of the analogy between the frustrated Ising model
and proteins should be kept in mind. Spin systems do not fold, only the process
by which the system finds its ground state can be regarded as analogous to folding.
We can study only how for Ising models this process depends on the frustration and
under which conditions there are similarities to proteins.

Our model is described by the Hamiltonian

\[ H = - \sum_{<lm>}^{3N} J_{lm} \sigma_l \sigma_m \]  \hspace{1cm} (1)

where the sum goes over all 3N \((N\) the number of spins) pairs \(<lm>\) of nearest
neighbor spins \(\sigma_i = \pm 1\). A certain number \(M\) of randomly chosen bond variables,
\(J_{lm}\), are set to \(J_{lm} = -1\) while the remaining \(3N - M\) bonds are assigned the value
\(J_{lm} = 1\). The ratio \(R = M/3N\) is a measure for the randomness in our Ising system
and leads to the frustration in the systems which is as usual defined through

\[ F = \frac{1}{3N} \sum_{i} \delta(F_{\Box_i}, -1) \quad \text{with} \quad F_{\Box_i} = J_{12}J_{23}J_{34}J_{14} \]  \hspace{1cm} (2)

Here, \(J_{12},J_{23},J_{34},J_{14}\) are the four bond variables of the \(i\)-th elementary plaquette \(\Box_i\)
of the lattice, and the sum goes over all 3N elementary plaquettes.

Our simulations are done on a 4 x 4 x 4 lattice which is small enough that
simulated annealing will find the ground state. An even smaller lattice size may
have allowed exhaustive enumeration, but would have introduced severe finite size
effects. For a given value \(F\) of frustration, 2000 realizations of bond variables \(\{J_{lm}\}\)
are generated in random. For each realization, \(N_1\) simulated annealing runs are used
to search for the global minimum. In each run we cool down the system with step
size \(\Delta T = 0.1\) from temperature \(T=3\) to \(T=0.3\) performing 40 Monte Carlo sweeps
(one update for each spin) at each temperature. We define as ground state $C_g$ of one realization the configuration with the lowest energy $E_g$ obtained in the $N_1$ runs. To ensure reasonable statistics, we require that this energy is found in at least $N_2$ simulated annealing runs. The total number $N_1$ of runs is adjusted accordingly and the failure rate $N_F = (N_1 - N_2)/N_1$ defines an index for the difficulty to find the global minimum. In the next step, we check the $N_2$ ground state configurations for rotational and translational symmetries, and identify in this way the number $N_g$ of distinct ground state configurations found for the given realization. For small values of $R$ we set $N_2 = 10,000$. As the system approaches the spin glass, $N_g$ increases rapidly. Therefore, if $N_g > 1000$, we repeat the simulation with $N_2 = 100,000$ to obtain more accurate values for $N_g$.

By altering the frustration $F$ we can tune our system between a ferromagnet ($F = 0$) and a spin glass ($< F >_{av} = 0.5$) and investigate the relation between $F$ in the system and the occurrence of protein-like behavior. Since the native state of a protein is unique and commonly assumed to be its ground state, we define a realization $\{J_{lm}\}$ as protein-like if it has a single ground state. The number of protein-like realization $\{J_{lm}\}$ among 2000 realizations is denoted by $N_{SG}$. We display the frequency $f_{SG} = N_{SG}/2000$ of such realizations as a function of $F$ in Fig. 1 which shows that $f_{SG}$ decreases with growing $F$ and is almost constant for $F \geq 0.44$. The inset of Fig. 1 shows the same quantity as a function of $R$ and here flattening occurs for $R \geq 0.23$. Hence, the probability to find protein-like realizations decreases as a function of $F$ (or $R$). However, the total number of realizations is given by $N_{Realizations} = (3N)!/[3N(1 - R)! (3NR)!]$, i.e. grows much faster with increasing $R$. It follows that the total number of protein-like realizations which can be designed (a randomly chosen realization has vanishing small probability for a single ground state!) is also an increasing function of $F$ since the bond randomness $R$ and the average frustration over realizations $< F >_{av}$ are related through $< F(R) >_{av} = 4((1 - R)^3 R + (1 - R)R^3)$ \[8\].
We know that with growing $F$ the energy landscape becomes more and more rugged. The number of local minima separated by high energy barriers will grow, and the probability will increase that our simulated annealing runs get trapped in one of them and do not find the global minimum. This can be seen in Fig. 2 where we display the average failure rate $<N_F>$ as a function of $F$ for the case of all 2000 samples and for only these realizations with single ground state $N_g = 1$. In this plot we observe a steep increase of $<N_F>$ at $F_g = 0.44 \pm 0.02$ for the curve corresponding to the “all samples” case. Note that this value corresponds to $R_g = 0.23 \pm 0.02$ which is consistent with that for the transition between ferromagnetic and spin-glass order found in [12]. The transition between the ferromagnet and the spin glass can also be observed in the average number of ground states per realization $<N_g>$ as a function of $F$ which we display in the inset of Fig. 2. The location of the steep increase in this quantity, $F_g = 0.44 \pm 0.02$ (which corresponds to $R_g = 0.23 \pm 0.02$), is the same as for the failure rate and agrees with the point in [12].

The failure rate $N_F$ in Fig. 2 measures how often a simulation did not find the ground state and is therefore related to the “folding time”, i.e. the time which would be necessary to find the ground state in a simulation. The “folding time” itself is a measure for the kinetic accessibility of the ground states. For the frustrated Ising model we see from Fig. 2 that the failure rate (and consequently the “folding time”) is small for small $F$ and differs little from the time needed for the ferromagnet $F = 0$. This changes once we reach values of $F$ where the system behaves as a spin glass. At that point the failure rate and the “folding time” increases by orders of magnitude, and even for realizations $\{J_{lm}\}$ which have a single ground state, that state may no longer be kinetically accessible. Such a situation is not desirable for real proteins, which have only limited time to fold and therefore must have kinetically accessible native states. Hence, we can not assume that realizations $\{J_{lm}\}$ with $F \geq 0.44 \pm 0.02$ are protein-like even if they have a unique ground state. If the analogy between proteins and spin systems holds, then we can expect for proteins also an interplay
between the increasing entropy of sequences, which lead to an unique ground state structures, and the requirement that this state has to be kinetically accessible. On one hand the entropy of sequences increases with frustration while on the other hand the folding times become prohibitively large once the frustration exceeds a certain value. In the Ising model the transition to this spin glass behavior is pronounced and located at \( F_g = 0.44 \pm 0.02 \) \((R_g = 0.23 \pm 0.02)\). The above conjecture may explain why proteins are marginally stable: the entropy of marginally stable proteins is much higher than that of sequences optimized for thermodynamic stability and fast folding. However, a limiting minimal amount of thermodynamic stability is necessary to guarantee function of the protein.

The above conjecture implies that the “optimal” amount of frustration in proteins is where the system is “almost” at the point of becoming a spin glass. This is because in such a case the entropy of sequences which lead to a single and accessible ground state is maximal. However, a protein should also be stable in the sense that a mutation will not lead to an amino sequence with a different native structure or no unique ground state at all. Hence, such protein structures are preferred which can be realized by a maximal number of different amino acid sequences \([13]\). In the language of our spin system the above statement implies that these spin configurations are most protein-like which are single ground state for the largest number of realizations \(\{J_{lm}\}\). For this reason, we have further checked the \(N_{SG}\) protein-like ground state configurations on translational and rotational symmetries. This procedure leads to a much smaller number \(N_D\) of distinct single ground state configurations. \(N_D\) is displayed as a function of \(F\) in the inset of Fig. \(3\). \(N_D\) is an increasing function over the whole ferromagnetic range and more or less constant in the spin glass range. Hence, with increasing value of \(F\) not only the total number of protein-like realizations grows but also the variety of protein-like states.

From the inset of Fig. \(3\) we would expect that the situation in proteins would correspond to small values of frustration \(F\) in the Ising model where one single
ground state configuration dominates, which can be realized by many sets of bond variables \( \{ J_{lm} \} \). However, proteins have to change over the course of evolution. The requirement of evolutionary flexibility suggests that larger values of randomness and frustration should be preferred which increase the number of distinct ground state structures and enhance the chance that a mutation will lead from one structure to different one. Hence, we expect for proteins an interplay between the requirement that the native structure is stable under mutations, and the need for structural changes over the course of evolution.

In order to study this interplay we plot in Fig. 3 the ratio \( N_D / N_{SG} \). Note that this ratio corresponds to the inverse of the (averaged) “designability” and is a measure for the degeneracy of the various protein-like states (i.e. spin-configurations which are unique ground states for some realizations \( \{ J_{lm} \} \)) of our spin system. We see that this ratio has a step-like behavior at \( F_p = 0.41 \pm 0.02 \) (which corresponds to \( R_p = 0.17 \pm 0.02 \)). For smaller values of \( F \) the \( N_D \) types of ground state configurations are realized by many sets \( \{ J_{lm} \} \), while for larger values of \( F \) each spin configuration is realized by only one realization \( \{ J_{lm} \} \). Hence, we conclude that in our spin system the “optimal” frustration is at \( F_p \) where both a variety of different protein-like configurations can be realized, but at the same time these structures can be designed by more than one set of \( \{ J_{lm} \} \), and therefore are stable under mutations. Note that this point is close to, but smaller than, the glass transition point \( (F_g = 0.44 \pm 0.02) \). Our value of \( F_p \) also corresponds to the point where in Fig. 1 failure rate of realizations with single ground state diverges from the corresponding plot for all realizations: \( F = 0.41 \pm 0.03 \).

The above results suggest that in protein-like systems randomness and frustration is necessary to increase the designability of proteins. In our spin system, the absolute number of realizations with a single ground state will increase with frustration. On the other hand, once the frustration exceed a certain value, the system becomes a spin glass. The resulting rugged energy landscape implies now that the single
ground state, if existing, is no longer kinetically accessible. This would be biologically not desirable, and the frustration in proteins has to be below this critical value. In a similar fashion, the evolutionarily favorable increase in diversity of protein-like states with frustration is counteracted by the growing probability that a given configuration becomes unstable under mutations. If the frustration exceed a certain value, any mutation would lead to a different structure which is again biologically not desirable. We conjecture that proteins are not minimal frustrated but that in protein-like systems the competition between these factors leads to a maximal value of $F$ where the number of different kinetically accessible structures, which can be realized as single ground states by many sequences, is largest. For our spin system this point is $F_p = 0.41 \pm 0.02$ which is close to, but below the point $F_g = 0.44 \pm 0.02$ where the system starts to behave as a spin glass.

In order to demonstrate how the interplay of the above outlined factors may lead to an optimal value of $F$, we have made up the following game. Our starting point is the ferromagnet, i.e. $J_{lm} = 1$. The game consists of a series of Monte Carlo steps which simulate “evolution”. At each Monte Carlo step our system has two offspring before it dies. One of the offspring is a copy of the parent, the other carries a mutation. We simulate mutations by choosing at random one bond variable $J_{lm}$ and switching its sign. Only one of the offspring is allowed to survive, and the survival rate of the “mutant” is given by $P(F_N)/(P(F_N) + P(F_0))$. Here, $F_N$ and $F_0$ are the frustration of the “mutant” and the “unchanged system”, respectively, with $P(F) = f_{SG}(F)(1 - <N_F(F)>)(1 - N_D(F)/N_{SG}(F))$, where $f_{SG}(F)$, $<N_F(F)>$, and $N_D/N_{SG}$ are taken from our previous simulations and $<N_F(F)>$ corresponds to the curve $<N_F(F)>$ with $N_g = 1$ in Fig. 1. With these rules our system performs a random walk in $F$ shown in Fig. 4. The average value of $F$ throughout this random walk gives $F = 0.42 \pm 0.03$ which is consistent with $F_p = 0.41 \pm 0.02$ and supports our assumption that the evolution of protein-like systems leads to a optimal point of $F$ in the system.
In summary, we have studied the simple frustrated Ising model as an analog for proteins. Investigating this system as a function of frustration, we found that the spin system exhibits protein-like behavior at or slightly below the point at which a system changes from an ordered (ferromagnet) to a random system (spin glass). Whether this observation (which questions the common belief that proteins are minimal frustrated systems) holds for realistic protein models remains to be investigated. As a next step in this direction we have started simulations of a bond-diluted and site-diluted frustrated Ising model. In such a model, it may be possible to generate more realistic protein-like structures with backbone and side chains.

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FIGURES

FIG. 1. The frequency $f_{SG} = N_{SG}/N_T$ of realizations with single ground state as a function of $F$ and (inset) $R$.

FIG. 2. The average failure rate $< N_F >$ as a function of $F$. In the inset we display the average number $< N_g >$ of ground states as a function of $F$.

FIG. 3. The ratio $N_D/N_{SG}$ as a function of $F$. In the inset we show the number $N_D$ of truly different single ground state configurations, as a function of $F$.

FIG. 4. Time series of the bond randomness $F$ from a dynamic simulation described in the text.
Fig. 1 Lin, Hu, and Hansmann
Fig. 2 Lin, Hu, and Hansmann

\[ \langle N_F \rangle (\text{All}) \quad \langle N_F \rangle (N_g=1) \]
Fig. 3 Lin, Hu, and Hansmann
Fig. 4 Lin, Hu, and Hansmann