Exploring the energy landscape of model proteins: a metric criterion for the determination of dynamical connectivity

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A method to reconstruct the energy landscape of small peptides is presented with reference to a 2d off-lattice model. The starting point is a statistical analysis of the configurational distances between generic minima and directly connected pairs (DCP). As the mutual distance of DCP is typically much smaller than that of generic pairs, a metric criterion can be established to identify the great majority of DCP. Advantages and limits of this approach are thoroughly analyzed for three different heteropolymeric chains. A funnel-like structure of the energy landscape is found in all of the three cases, but the escape rates clearly reveal that the native configuration is more easily accessible (and is significantly more stable) for the sequence that is expected to behave as a real protein.

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I. INTRODUCTION

Several states of matter are characterized by a rich energy landscape (EL), which, in turn, hints at peculiar structural and dynamical features. Supercold liquids, glasses, atomic clusters and biomolecules are typical examples of systems whose complex thermodynamic behavior can be traced back to the intricate topological properties of the EL. The pioneering work by Stillinger and Weber on “inherent” structures of liquids revealed the importance of investigating the stationary points of the EL for characterizing their dynamical and thermodynamic properties. Similar approaches have been proposed and successfully applied to the identification of the structural-arrest temperature in glasses and supercooled liquids.

More recently, this kind of analysis has been extended to the study of protein models. They suggest that also the folding process of a protein towards its native configuration (NC) depends on the structure of its EL. This has been found to possess a funnel-like shape: the NC is located inside the so-called native valley (NV) at the bottom of the funnel.

Below the folding temperature, the evolution from a coil state to the NC is determined by the propensity of the protein to enter the relatively small fraction of states composing the NV without having to visit the entire phase-space. In a statistical sense, the folding process can be viewed as a weighted sampling mechanism which favours specific intermediate configurations. They correspond to assembling the building blocks which eventually constitute the NC. Well above the folding temperature, no marked difference exists among the various states and the protein spends most of the time jumping between different random coil configurations.

In the absence of external forces, only thermal fluctuations can drive the protein dynamics through different regions of the EL. In particular, below the folding temperature, the protein is expected to evolve mainly inside the NV. Nonetheless, large deviations from the NC cannot be avoided, but they are both rare and very short lived. This scenario was confirmed by simulations performed in a 2d off-lattice model. A more detailed analysis of the model revealed that the protein dynamics can viewed as a sequence of jumps between pairs of minima separated by one saddle, that we call directly connected pairs (DCP). Each jump is a thermally activated process: the protein performs random oscillations in the basin of a local minimum until a sufficiently large thermal fluctuation allows it to overtake the energy barrier separating the minimum from a neighbouring one. In a high-dimensional space, the transition rate can be computed as the product of the Arrhenius factor times an entropic weight which depends on the DCP and on the saddle curvatures (see Section IV). In other words, the relevant information about the protein dynamics can be obtained from the knowledge of the DCP and of the corresponding saddles. However, the reconstruction of the EL is a very difficult task to be accomplished in practice. Indeed, the identification of DCP by a systematic exploration of the entire set of the N identified minima requires to exploring $N^2$ pairs, which is already on the order of $10^9$ for the partial database generated (see the Appendix for a description of the algorithm) in the relatively small polypeptidic chains investigated in this paper (see section III). It is therefore, crucial to develop effective strategies for identifying DCP within the set of all, a priori possible, candidates. This is the main issue addressed in this paper.

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It is reasonable to conjecture that the distance separating DCP is typically smaller than that between generic pairs of minima. It is therefore tempting to restrict the analysis to those pairs whose mutual distance is smaller than some prescribed threshold. However, whether this approach effectively works may depend on several factors one of which is the adopted definition of distance. For this reason, in section [11] we introduce and compare different conformational distances. It turns out that the bond–angle distance, defined by the absolute–value norm of a few˚

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III. ANALYSIS OF THE ENERGY LANDSCAPE

As pointed out in the introduction, the main problem for reconstructing the EL amounts to finding DCP and the corresponding saddles of the potential energy \( V = V_1 + V_2 + V_3 \) (see Eq. 2). An exhaustive search of DCP among all pairs of minima rapidly becomes unfeasible with increasing the chain length \( L \), due to the exponential increase of the number of minima with \( L \) itself. Since the total number of DCP is a rather small fraction of all possible pairs (see, e.g., the Table in the Appendix), it would be very helpful finding an effective criterion to restrict the search of potentially directly connected minima. A priori, the distance seems to be the right indicator to discriminate between connected and not-contiguous pairs of minima. In this section we investigate several definitions of distance with the goal of identifying the most appropriate one to identify DCP.

As a first candidate, we introduce the generalized angular distance \( \delta^\theta(C_1, C_2) \) between configurations \( C_1 \) and \( C_2 \),

\[
\delta^\theta(C_1, C_2) = \left( \frac{1}{L - 2} \sum_{i=2}^{L-1} |\theta(i; C_1) - \theta(i; C_2)|^q \right)^{1/q},
\]

where \( \theta(i, C) \) is the \( i \)-th bond angle of the configuration \( C \). Notice that this angular distance is much sensitive to local fluctuations along the chain. A generalized distance which depends more on the global than on the local structure of a configurations is

\[
\delta^\varphi(C_1, C_2) = \left( \frac{2}{L(L - 1)} \sum_{i>j+1} |r(i, j; C_1) - r(i, j; C_2)|^q \right)^{1/q},
\]

where \( r(i, j; C) \) is the intra– bead distance between ith and jth monomer of the configuration \( C \). This distance is related to the \( \gamma \)-indicator, previously employed in the analysis of the folding dynamics in on– and off–lattice models of heteropolymers in 2d and 3d. For \( q = 1, 2 \), and \( +\infty \), both definitions of generalized distances reduce to the standard absolute–value, Euclidean and maximum norms, respectively. Such distances have been computed for all the pairs of minima in the databases of the sequences S0, S1 and S2. The algorithm used to generate the databases is described in the Appendix. We want to point out that any numerical procedure, including ours, cannot guarantee the identification of all minima and saddles in the EL. Nonetheless, we have independently verified that the algorithm allows obtaining at least a very accurate description of the native valley.

Then, we have computed the probability densities of the generalized distances between generic \( P(\delta) \) and directly connected \( P_c(\delta) \) pairs of minima. In all cases, \( P \) has a bell shape with a maximum close to 1, while \( P_c \) is sharply peaked at much smaller values (see, e.g., Fig. 4) where \( P(\delta_{\theta}^{(1)}) \) and \( P_c(\delta_{\theta}^{(1)}) \) are plotted for the sequences S0, S1 and S2). This confirms the naive idea that DCP are typically much closer than randomly chosen pairs of minima.

![Graphs of angular distances](image)

FIG. 1: Probability density of angular distances \( \delta_{\theta}^{(1)} \) for all the pairs of minima, \( P_\delta \) (dashed line), and for DCP, \( P_c \) (solid line), for the sequences S0 (a) and S1 (b) and S2 (c).

A qualitatively similar difference between \( P \) and \( P_c \) is observed also for different choices of \( q \) as well as for the global distance \( \delta^{(0)} \). In order to identify the most appropriate value of \( q \), it is convenient to introduce the integrated fraction \( R(\delta) \) of pairs of minima whose distance is smaller than \( \delta \)

\[
R(\delta) = \int_{0}^{\delta} P(x)dx
\]
and, equivalently,
\[
R_c(\delta) = \int_0^\delta P_c(x)dx, \tag{6}
\]
relative to DCP. Upon considering \(\delta\) as a dummy variable, it is possible to plot \(R_c\) versus \(R\). A fast convergence of \(R_c\) to 1 means that almost all DCP can be already identified by limiting the search to relatively close pairs of minima. The data plotted in Fig. 2a for \(S_1\) and \(q = 1\) indeed reveal such a fast growth of \(R_c\), that almost 90% of the DCP can be obtained by investigating only 1% of all pairs both by considering the angular \(\delta_\theta^{(a)}\) and the global \(\delta_c^{(g)}\) distance. The curves in Fig. 2b show that significantly worse performances are obtained when the maximum norm \((q = \infty)\) is used to classify the pairs of minima. In order to clarify the role of the parameter \(q\), in Figs. 3, 4, we have plotted \(R_c\) versus \(R\) for different values of this parameter. There we see that, upon decreasing \(q\) from \(\infty\) down to 1, \(R_c\) exhibits an increasingly fast saturation, while the opposite is observed when \(q\) is further decreased below 1. The bad performance observed at high \(q\)-values has a quite intuitive explanation: in that limit, the norm reduces to the maximum norm and the slow growth of \(R_c\) tells us that distances between DCP are not uniformly small along all directions: DCP may significantly differ along specific directions in spite of being “on the average” much closer than generic pairs of minima. The relatively bad performance observed for \(q \rightarrow 0\) has a complementary explanation. In that limit, the average distance is strongly biased by small differences \(\delta\theta\) or \(\delta r\), whose occasional occurrence may induce to classify as “close”, configurations that are significantly different instead. In all configurations we have investigated, it turns out that \(q \approx 1\) is the best compromise between the above two effects. Having established that \(q = 1\) is the best choice, from now on, we limit ourselves to considering that value and drop the superscript (1) in the definition of the distance.

In practice, since it is eventually necessary to identify a threshold distance \(\delta_\theta^\ast\), it is convenient to look also at the dependence of \(R_c\) on \(\delta_\theta\) and to introduce
\[
\rho(\delta_\theta) = \frac{R_c(\delta_\theta)}{R(\delta_\theta)}.
\]

From Fig. 3 we see that \(\delta_\theta^\ast = 0.5\) is a good choice, since \(\rho(0.5) \sim O(10^{-2})\), while \(R_c(0.5) \sim 99\%\). Even reducing the threshold value to \(\delta_\theta^\ast = 0.2\) a large fraction of DCP are still recovered \((R_c(0.2) \sim 90\%)\).

These results indicate that if one restricts the search of DCP to the set of minima whose distance is smaller than a prescribed threshold \(\delta_\theta^\ast\), one can reduce significantly the most time-consuming part of the systematic search algorithm, which amounts to testing whether a generic pair of minima is separated by a single saddle.

The drawback is that for any choice of \(\delta_\theta^\ast\), those DCP whose mutual distance is anomalously large are going to be missed. In the next Section we analyse the EL with the main goal of concluding whether such a component is of some relevance in the overall reconstruction of the EL.
FIG. 4: Integrated probability density $R_c$ versus $R_a$ for the angular distance for various norms for the sequences S1 (a) and S2 (b). The notations are the same as in Fig. 3.

IV. A CLOSER INSPECTION OF THE ENERGY LANDSCAPE

A faithful reconstruction of the EL requires a sufficiently large database of stationary points, i.e. minima and saddles. The procedure described in the Appendix is quite reliable in this respect, but it is also computationally very time-consuming as already stated. In the previous section we have seen that a large fraction of DCP can be obtained by adopting a suitable metric criterion. However, it is not a priori clear whether the long-distance tail of $P_c$ is qualitatively irrelevant too.

In order to shed some light on this question we have divided the minima into “shells”: the $n$–th shell is defined as the collection of all minima which are separated from the NC by at least $n$ saddles. The identification of the minima belonging to each shell can be achieved recursively:

- the 0-th shell coincides with NC;
- a minimum $C_1$, directly connected to a minimum $C_2$ of the $i$–th shell, is identified as part of the $i+1$-st shell if $C_2$ does not belong to a shell of order $j \leq i$.

In Fig. 5 we report the average value $\delta_\theta$ of the distance between DCP belonging to consecutive shells for all of the three sequences. This figure indicates that the inter-minimum distance grows in the vicinity of the NC. The average distance $\langle \delta_\theta \rangle$ between DCP lying inside the same shell exhibits the same behaviour. Finally, this rarefied density of minima in the vicinity of the NC is confirmed also by plotting the mutual distance versus the actual distance from the NC. In this case, in order to smoothen the wild pair-to-pair fluctuations, a coarse-graining has been performed by averaging over bins of width 0.01 along the $\delta_\theta$ axis (see Fig. 7).

Altogether, the significative increase of the average distance close to the NV indicates that some of the DCP that are missed by the metric criterion discussed in previous section lie in the most relevant region for the characterization of the folding/unfolding processes. However, considering the limited number of minima in the NV, such a difficulty can be easily overcome by complementing the overall application of the metric criterion with an extensive comparison of such minima with all configura-
tions in the database: the additional cost in terms of the computing time is indeed a minor one.

The increased distance between neighbouring minima hints at possibly deeper valleys and is, in turn, suggestive of the presence of a funnel in the EL, a structure that is typically expected to appear in true proteins. However, we find this scenario in all of the three sequences analyzed in this paper, including the homopolymer S0 which cannot be certainly considered a reasonable model for a protein. In order to further clarify this point, we have computed the escape rates from the single valleys. Given any two directly connected minima \( C_1 \) and \( C_2 \) characterized by the potential energies \( V_1 \) and \( V_2 \) \((V_1 \leq V_2)\), the escape rate from the minimum \( C = \{C_1, C_2\} \) through the saddle \( C_s \) (with potential energy \( V_s \)) is given by

\[
\Gamma_C = \frac{\omega_||}{\pi \gamma} \frac{\prod_{i=1}^{L'} \omega_C^{(i)}}{\prod_{i=1}^{L'-1} \omega_{-1}^{(i)}} \exp \left\{ -\frac{W_C}{k_B T} \right\} .
\] (7)

This formula, proposed by Langer [15], is obtained by considering the harmonic approximation of the potential in the vicinity of \( C_1, C_2, \) and \( C_s \). The \( \omega_C^{(i)} \)'s are the \( L' = 2L - 3 \) non zero frequencies of the minimum \( C \) \((\omega_C^{(i)} = \sqrt{-\Lambda_C^{(i)}} \), where \( \Lambda_C^{(i)} \) is the \( i \)-th negative eigenvalue of the Hessian of the potential energy \( V \)). Analogously, \( \omega_s^{(i)} \)'s are the \( L' - 1 \) non zero frequencies of the saddle (those corresponding to the stable directions), while \( \omega_|| \) is associated with the only expanding direction. Finally, \( \gamma \) is the dissipation rate [14], while the Arrhenius exponential factor depends on the height of the barrier, \( W_C = V_s - V_{1,2} \), normalized to the reduced temperature \( K_BT \), \( K_B \) being the Boltzmann constant.

The above expression has been shown to reproduce reasonably well the numerically obtained escape rates for heteropolymers in 2d at moderate temperatures for \( T < \approx T_\theta [10] \). Accordingly, in that regime, both the folding and the unfolding dynamics towards and from the NC are driven by thermal activation processes, which determine the transitions between DCP. Small \( \Gamma \)-values suggest that the heteropolymer may be trapped into some local valley of the EL, far from the NC. Eq. (7) shows explicitly that in high-dimensional spaces, the escape rate does not simply depend on the energy barriers but also on entropic factors, which depend on geometrical features of basins of attractions of the stationary configurations in the EL.

In Fig. 8 we have plotted the rates \( \Gamma_C \) as a function of \( \delta_\theta \) for the three sequences at \( T = T_f \) and \( \gamma = 1 \) (since past simulations indicate that the effective value of \( \gamma \) is the same at least in the whole NV, there is no need to know it when a comparative analysis is being carried out). There we notice a striking difference between S0 and S1 at large distances: actually the escape rates of S0 are two orders of magnitude smaller than those of S1. Moreover, \( \Gamma_{C_2} \sim O(1) \) almost in the whole range of distances \( \delta_\theta \) for S1, indicating that no trapping is expected in the shallower minima, while it exhibits an almost exponential decrease for S0. An intermediate situation is observed for S2 at large distances. As a result, we see that a true funnel-like structure is markedly present only in the EL of the sequence S1, that was indeed already identified as a good folder by looking at different indicators [6, 13].

V. CONCLUSIONS AND PERSPECTIVES

In this paper we have analyzed the structure of the energy landscape (EL) of a 2d off-lattice model of a polypeptidic chain and found that the relative closeness between neighbouring minima can be exploited to implement an effective algorithm to identify directly connected minima. In order to put the analysis on firm quantitative grounds, we have tested several definitions of distance between configurations, finding that the best performances are obtained for the angular distance \( \delta^{(1)}_\theta \) (see Eq. (6)). In fact, the \( \delta^{(1)}_\theta \) distances corresponding to DCP are more sharply concentrated at small values than for all other definitions of distances. In particular, we have found that restricting the systematic search to all pairs
of minima whose distance is smaller than $\delta_\theta^{(1)*} = 0.5$, one can recover almost 99% of all DCP. The drawback of this approach is that a tiny fraction of DCP is unavoidably missed, but the consequences are not a priori clear. Since our analysis of the native valley has shown that minima are more rarefied in the vicinity of the native configuration (see Fig. 7), we conclude that it is wise to complement the above metric criterion with an extensive search limited to the minima of the native valley. It is now important to verify to what extent such a scenario extends to more realistic 3D systems, where the implementation of effective algorithms to reconstruct the EL is even more crucial than in 2D. Furthermore, important hints about the true relevance of missing links in a connectivity graph will come after imposing a dynamics on the graph itself by adding the activation rates $\Gamma$ relative to the transitions between directly connected minima. By comparing the resulting evolution with that of the original system one can in particular determine the minimal fraction of DCP that is necessary to identify for a meaningful reconstruction of the folding process.

Finally, in order to test how the observed rarefied density of minima in the vicinity of the NC is connected to the presence of a true funnel-like structure, we have computed the activation rate $\Gamma$ inside the NV. It turns out that moving away from the NC, while in the homopolymer $\Gamma$ decreases very rapidly, it stays almost constant in the sequence S1, previously identified as a good folder by other means. This is a clear indication that the homopolymer can be trapped in several minima far from the minimal energy state, while an accessible native valley does exist for S1.

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**Appendix**

The database containing the minima of a model sequence can be used to determine the first-order saddles directly connecting neighboring minima. The method we propose to accomplish this goal is based on two different algorithms to solve the following two problems:

- Given two minima $C_1$ and $C_2$ and two configurations $P_1$ and $P_2$ belonging to their basins of attraction, one wants to determine two configurations $Q_1$ and $Q_2$ on the segment $P_1P_2$ arbitrarily close to the ridge dividing the two basins and lying on its opposite sides;
- given $Q_1$ and $Q_2$, as defined above, one wants to apply an iterative procedure, leading the two points to converge on the saddle.

The procedure is here described in more details:

1. given $Q_1 = P_1$ and $Q_2 = P_2$, an intermediate configuration $C$ is defined, by setting its bond angles equal to the average of the corresponding angles of $Q_1$ and $Q_2$;
2. a steepest descent procedure is applied to $C$ until a minimum $C_m$ is reached;
above

It amounts to performing a high-temperature (typically applying the algorithm to an initial database of min-

the EL relevant for protein dynamics.

suitable for a complete exploration of all the features of

proposed can then be viewed as an “all purpose” method

finally refined by means of a standard Newton’s method.

laxed according to a steepest descent dynamics and fi-

point a series of configurations, which are afterwards re-

space. The resulting trajectory is then sampled to pin-

pected to visit a large portion of the accessible phase

5. when, during the steepest descent, the gradient of

4. we let \( Q_1 \) and \( Q_2 \) evolve in time according to a

steepest descent relaxation until \( d_E(Q_1(t), Q_2(t)) \)

becomes larger than \( \delta \) and go back to (1), identifying

\( P_1 \) with \( Q_1(t) \) and \( P_2 \) with \( Q_2(t) \);

5. when, during the steepest descent, the gradient of

the potential both in \( Q_1 \) and \( Q_2 \) becomes smaller

than another given threshold, we assume \( Q_1 \) and

\( Q_2 \) to be close enough to a first order saddle and

refine the configuration by means of a Newton’s method.

This procedure was used for identifying a small database

of 50-100 collapsed states for each of the three sequences
described in section II.

All possible pairs in these initial minima databases

were then searched for DCP by means of our saddle-

finding algorithm. The new minima found during each

run of the algorithm on all possible pairs were stored in

the database to be investigated in successive runs. Ac-

ually the number of pairs of minima grows much faster

than the number of pairs investigated, thus making im-

possible a complete analysis. The number of minima and

saddles that were identified after three runs is reported

in Table II.

In order to perform a complete search of all DCP at

least in a restricted set of minima, we have selected all

configurations of energy lower than \( V_f = V_0 + LT_f \).

In this restricted database all pairs of minima characterized

by an angular distance smaller than 0.5 where investi-

gated. The total number of saddles found by this proce-

dure is reported in Table II.

| TABLE I: Number of minima in the whole database and in the first and second shell. Number of investigated pairs and number of DCP found. Data have been reported for all the three examined sequences. |
|-----------------|-----------------|-----------------|
|                 | S0              | S1              | S2              |
| Total number of minima | 2.3 x 10^5     | 7.2 x 10^4     | 6.4 x 10^4     |
| Number of minima in the 1st shell | 64              | 50              | 49              |
| Number of minima in the 2nd shell | 1,181           | 465             | 348             |
| Number of minima below \( T_f \) | 66,470          | 5,883           | 8,670           |
| Number of investigated pairs | 9.1 x 10^6     | 0.94 x 10^6    | 1.3 x 10^6     |
| Number of connected pairs | 84,990          | 10,470          | 14,356          |

[1] D.J. Wales, Energy Landscapes, Cambridge University Press, Cambridge, 2003.
[2] F.H. Stillinger and T.A. Weber, Science 225 (1984) 983.
[3] S. Sastry, P.G. Debenedetti, and F.H. Stillinger, Nature 393 (1998) 554.
[4] L. Angelani, R. Di Leonardo, G. Ruocco, A. Scala, and F. Sciortino, Phys. Rev. Lett. 85 (2000) 5356.
[5] S.V. Krivov and M. Karplus, J. Chem. Phys 117 (2002) 10894.
[6] D.A. Evans and D.J. Wales, J. Chem. Phys 118 (2003) 3891.
[7] A. Baumketner, J.-E. Shea, and Y. Hiwatari, Phys. Rev. E 67 (2003) 011912.
[8] P.E. Leopold, M. Montal, and J.N. Onuchic, Proc. Natl. Acad. Sci. USA 89 (1992) 8721.
[9] A. Torcini, R. Livi, and A. Politi, J. Biol. Phys. 27 (2001) 181.
[10] L. Bongini, R. Livi, A. Politi, and A. Torcini, Phys. Rev. E 68 (2003) 061111.
[11] F.H. Stillinger, T.H. Gordon, and C.L. Hirshfeld, Phys. Rev. E 48 (1993) 1469.
[12] E. Marinari, and G. Parisi, Europhys. Lett. 19 (1992) 451.
[13] A. Irbäck and F. Potthast, J. Chem. Phys. 103 (1995)
10298.

[14] A. Irbäck, C. Peterson, and F. Potthast, *Phys. Rev. E* **55** (1997) 860.

[15] P.G. De Gennes, *Scaling Concepts in Polymer Physics* Cornell University Press, 1979, New York.

[16] T. Veitshans, D. Klimov, and D. Thirumalai, *Folding & Design* **2** (1997) 1.

[17] J.S. Langer, *Ann. Phys.* **54** (1969) 258

[18] P. Hänggi, P. Talkner, and M. Borkovec, *Rev. Mod. Phys.* **62** (1990) 251.

[19] This is a free parameter, which has to be fixed according to some physical criterion.