Random walks in the space of conformations of toy proteins

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Monte Carlo dynamics of the lattice 48 monomers toy protein is interpreted as a random walk in an abstract (discrete) space of conformations. To test the geometry of this space, we examine the return probability \( P(T) \), which is the probability to find the polymer in the native state after \( T \) Monte Carlo steps, provided that it starts from the native state at the initial moment. Comparing computational data with the theoretical expressions for \( P(T) \) for random walks in a variety of different spaces, we show that conformational spaces of polymer loops may have non-trivial dimensions and exhibit negative curvature characteristic of Lobachevskii (hyperbolic) geometry.

Levinthal’s paradox [1] is universally considered to be the essence of the protein folding problem. In its most direct form, the paradox revolves around the exponentially large number of possible conformations being immeasurably larger than what a protein can conceivably test within the observable time scale. Levinthal’s paradox arises from thinking of protein folding as a search in a conformational space resembling a golf course with just one hole representing the native state. To resolve the problem, it has been conjectured in the literature [2–5] that volume interactions between monomers should provide an energetic bias towards the native state. However undoubtedly correct, this should not overshadow the necessity to understand the search in conformational space. Indeed, if we start from an open coil conformation, then volume interactions cannot provide any significant bias for a while, at least until after some minimal number of contacts has been formed. In macroscopic terms, this initial stage is an uphill climb over an entropic barrier. In microscopic terms, it is a random walk in conformation space. In order to initiate the energy-driven downhill slide towards the native state, or to enter the funnel-shaped area of the free energy landscape [6], a fluctuation has to provide a sufficient decrease in entropy, or, in other words, a random walk has to bring the system into the specific region in conformation space.

This way of thinking implies the following resolution of Levinthal’s paradox: there is no need for a random unbiased search to detect a single native state, it only needs to bring the system into some region, \( \omega \), in the conformation space. Physically, \( \omega \) corresponds to the transition (macro)state, most likely to a critical nucleus of some kind [7,8]. Therefore, the volume and shape of \( \omega \) in conformation space are dictated by both sequence specific energy factors and sequence independent properties of conformations. The system searches for this critical (macro)state \( \omega \) through a random walk in conformation space, largely unaffected by heteropolymeric interaction energies. Understanding this process is the problem of normal polymer dynamics [9] and in some cases it may be reduced to the kinetics of a homopolymer collapse [10]. Unfortunately, this problem is rather difficult and remains out of reach of current simulation techniques.

In order to pave the way to it, we will consider in this work another related problem of random walks in conformation space, namely that of fluctuations around the native state. This is itself a pressing issue in protein folding theory. Indeed, understanding these fluctuations is necessary in order to address the corrections to mean field theory which is formulated in terms of the Random Energy Model (see [1] and the review [12] with a multitude of references therein).

We will restrict ourselves with the standard lattice protein model of 48 monomers. In particular, we choose to work with the particular native state conformation addressed in [13]. In order to remain in the vicinity of

\[FIG. 1. \text{The } 48\text{-mer conformation. The dark contacts indicate critical folding nucleus for this particular conformation, according to the data of the work by Mirny et al \cite{14}. The loops considered in the present work are shown as thick lines.}\]
the native state, we can permanently fix the contacts which form the nucleus. The nucleus conformation, as conjectured in [13], is shown in Figure 1. Finding the nucleus even for one given native conformation is a difficult and unresolved problem in protein folding. Mirny et al. obtained the nucleus for the native state shown in Figure 1 by a procedure in which interactions between various monomer pairs were mutated. Those interactions which are necessary for a stable folded configuration were examined for a conserved set. The contacts belonging to the conserved set were inferred to be the nuclear contacts (see Figure 1). As a matter of fact, the procedure for determining the nucleus remains a subject of scrutiny and heated debate [14–23]. The various models of a single nucleus [7], of multiple nuclei [8], and of nucleation classes [23] are being debated but the choice among the different models is not the subject of this work. The nucleus from the work [13] which is being used in the present work has been chosen arbitrarily among a large number of possible conformations with nuclei surrounded by loops.

In order to address purely entropic factors, we shall examine folding of the polymer under no interactions (except for the constraints of polymer connectivity, excluded volume, and fixed contacts). The resulting structure is essentially that of many loops with fixed ends in the nucleus. For the discrete lattice model, we consider the conformational phase space as a graph in which the conformations are represented by nodes on the graph. If two conformations can be interconverted via a single Monte Carlo move (end flip, corner flip, or crankshaft), their corresponding nodes are connected by edges on the graph [34]. A Monte Carlo run is thus equivalent to a random walk on that graph. From that point of view, folding is equivalent to performing a random walk which returns to the origin. Thus, our plan is as follows: we will perform a long Monte Carlo run of the above described loop model, and we will record all the time moments (or Monte Carlo steps) of spontaneous folding, or random arrival to the origin, which is the native state. This will give us the return probability, \( P(T) \), as the function of Monte Carlo time, \( T \). In order to interpret these data, we will compare them with a summary of the known results for the expected behavior of \( P(T) \) in a variety of different spaces. Before proceeding with this plan, two short comments must be made: (a) We are referring to the return probability \( P(T) \), not the first return probability. In other words, the system said to return to the origin at time \( T \), no matter how many times it may have visited origin previously. (b) There is a potential source of terminological confusion due to the well known analogy between polymer conformations and trajectories of random walks. Indeed, the conformation shown in Figure 1 is often described in terms of some walker in 3D space. We would like to stress that we are speaking here about a completely different random walk. In our case, the walker is the entire protein chain, and the walk is being performed in the abstract space of conformations.

We are now ready to begin with a summary of the known results for the return probabilities in spaces of various geometries. We will consider only discrete spaces, assuming every elementary step of the random walk to be of unit length.

- For a random walk of \( T \) steps in an unbounded Euclidean space of dimension \( d \), the probability of return is
  \[
  P(T) = (2\pi T/d)^{-d/2} \sim T^{-d/2} .
  \]

A square (or cubic) lattice is in this sense the discrete counterpart of Euclidean space with \( d = 2 \) (or \( d = 3 \)).

- Equation (1) holds for a fractal space with non-integer \( d \), in this case \( d \) is the spectral dimension [15].

- It is important for us to consider a random walk in a bounded region, because the set of conformations is always finite for lattice models, and thus, the region of interest in the conformation space is also finite. For a random walk in a bounded "cavity" in Euclidean space, or on a bounded fractal,
  \[
  P(T) \approx \left\{ \begin{array}{ll}
  (2\pi T/d)^{-d/2} & \text{when } T < T^* \sim R^2 \\
  (\pi T/\lambda)^{-d/2} & \text{when } T > T^* \sim R^2
  \end{array} \right.
  \]

Here \( R \) is the "size" of the allowed conformation space (graph), \( M \) is the total number of allowed conformations (or graph nodes), \( z_0 \) and \( \bar{z} \) are the numbers of possible Monte Carlo moves (or incident graph edges), respectively, for the native state and averaged over all states. Equation (2) means that a random walk does not feel the bounds at "small" times until it arrives at the boundary. At later times, it covers all of the available region in a uniform manner, then the probability for visiting each point (conformation), \( \alpha \), is simply proportional to the number of ways, \( z_0 \), incident to that point. To better understand the meaning of \( R \), it is useful to define the "distance" \( R_{\alpha\beta} \) between two conformations, \( \alpha \) and \( \beta \), as the minimal number of elementary moves necessary to convert \( \alpha \) into \( \beta \). Then, according to graph theory, the diameter of the graph representing our conformation space should be defined as the maximum of \( R_{\alpha\beta} \) over all pairs of conformations. Our \( R \) is then typically on the order of one half of this diameter. Note that in the limit of very long loops, \( N \gg 1 \), we expect the space diameter and \( R \) to scale as \( R \sim N^{1/2} \).

- Equation (2) represents a particular example of switching, or crossing over, from one dimension to the other. In other words, the conformation space may appear to have one dimension close to the native state and another dimension far from the native state. In this sense, a bounded space has the dimension \( d \) at small scales and dimension 0 (like a point) at larger scales.

- For a random walk in a \( d \)-dimensional Lobachevskii space [16,17]
  \[
  P(T) \sim T^{-d/2} \exp(-T\lambda/2d) ,
  \]
  where \( \lambda \) is the Gaussian curvature (inverse squared curvature radius) of the space. This formula can be explained
in the following simple way. At the scale $T \ll 1/\lambda$, when typical distance from the origin remains smaller than the curvature radius, the space appears effectively flat and equation (3) reduces to (1). On the other hand, for very large $T$, $P(T)$ is dominated by the exponential term, which can be understood if one remembers that a Cayley tree graph is the discrete counterpart of Lobachevskii space. It is important to consider Lobachevskii geometry because, as we mentioned, the conformation space diameter scales as $N$ for very long loops in the $N \gg 1$ limit, while the number of conformations scales exponentially with $N$. This means that there is an exponential growth of the number of conformations as a function of the distance from any given conformation (e.g., native). Such an exponential growth is the signature of Cayley tree or Lobachevskii geometry [18].

- The analysis of loop conformations which arise from a fixed nucleus of contacts becomes more complicated if we have multiple loops. Still, if loops are independent of one another, then a simple estimate for the conformational space of all the loops combined can be obtained. Consider $k$ loops each having a fraction $f_i$ of the total number of movable monomers. When a monomer is chosen for a Monte Carlo move, the probability that it will be from loop $i$ is $f_i$. Assume that each loop lives in an unbounded Euclidean space so that the probability for loop $i$ to fold after $t_i$ Monte Carlo steps is $P(t_i) = t_i^{-d_i/2}$, neglecting constant factors. The probability for all loops to return after time $T$, $P(T)$, is thus

$$P(T) = \sum_{t_1, \ldots, t_k=0}^T \delta\left(T - \sum_i t_i\right) \prod_{i=1}^k f_i^{t_i} P_i(t_i) \frac{T!}{\prod t_i!}. \quad (4)$$

Using (i) Stirling’s approximation, (ii) $P_i(t) \sim t^{-d_i/2}$, and (iii) noticing that due to the combinatorial factor, the sum is dominated at large $T$ by the term in which $t_i = f_i T$, we obtain

$$P(T) \approx \frac{T!}{\prod t_i!} \prod_{i=1}^k f_i^{t_i} (f_i T)^{-d_i/2}$$

$$\sim T^{-d_{\text{eff}}/2}, \quad \text{where} \quad d_{\text{eff}} = \sum_{i=1}^k d_i. \quad (5)$$

For independent loops dimensions simply add to each other.

- In reality, different loops are not independent. To some extent they obstruct each other’s folding. In general, for obstructing loops, we expect

$$d_{\text{eff}} \leq \sum_{i=1}^k d_i. \quad (6)$$

With the summary of mathematical results for the return probability in different geometries, we can now proceed to the computer experiments [24] on the loops shown in Figure 3.

The return probability for loops 1, 2 and 3 is shown in Figure 2 as a function of return time. The log-log graphs indicate clearly the power law dependence characteristic of Euclidean geometry [10]. The dimensions in loop space for loops 1, 2, and 3, according to the Figure 2 are $d_1 = 1.74$, $d_2 = 0$, and $d_3 = 2.64$, respectively.

![Log-log plot of the return probability as a function of return time for loop 1, loop 2, and loop 3. The dimensions in conformation space for loops 1, 2, and 3 are $d_1 = 1.74$, $d_2 = 0$, and $d_3 = 2.64$. The lines shown have slopes of $-d_i/2$. Inset: Probability of return for loops 1&3, and for loops 2&3 combined. The corresponding dimensions are $d_{13} = 4.40 \approx d_1 + d_3$ and $d_{23} = 2.52 \approx d_2 + d_3$.](image)

To see why the dimension for loop 2 is 0, note that there are only two possible positions for loop 2. At any given time the probability for loop 2 to be in one position or the other is 1/2, which means that the probability of return must be $P(T) = 1/2$ or $\ln P(T) = -0.69$, consistent with the result shown in Figure 2. The leveling off expected according to equation (3) in a bounded space is also seen for loop 1. The saturation level (which corresponds to $1/P \approx \exp(3.3) \approx 27$) and saturation time ($T^* \approx 67$) are roughly consistent with both first and second line of the equation (4) given that the number of conformations for loop 1 is $M = 51$, and the number of allowed moves for the native state is $z_0 = 4$. Since loop 3 is much longer, it will undoubtedly exhibit leveling off, but at longer times, which we did not reach in our Monte Carlo experiment [23].

To see the effect of having multiple loops on the loop space dimension, we examine conformations in which both loops 1 and 3 are allowed to move and those in which loops 2 and 3 are allowed to move. The reason for this choice of loops is that loops 1 and 3 (and loops 2 and 3) are sufficiently far apart on the conformation that their interactions are negligible, consistent with our simple analytical estimate. The effective combined dimension for loops 1 and 3 is $d_{13} = 4.40 \approx d_1 + d_3$ and for loops 2 and 3 is $d_{23} = 2.52 \approx d_2 + d_3$ (see Figure 2) in agreement with the approximations given in Equation (5).

The conformational space becomes even more inter-
estimating with longer loops such as loop 4 (see Figure 3), which goes from monomer 20 to 33. As Figure 3 indicates, the behavior of \( P(T) \) for this loop is consistent with Lobachevskii geometry in which the return probability follows a power law at small return times but decays exponentially at sufficiently large return times (see equation (2)).

A least-squares fit of \( P(T) \) gives \( d = 1.5 \) and \( \lambda = 4.9 \times 10^{-8} \). Thus, at rather small scales the conformational space of the loop 4 is a usual fractal graph, while at larger scales it branches exponentially like a Cayley tree. Physical nature of branchings in the conformation space is very simple: when two different pieces of polymer are close together, each piece can move either on one or on the other side of the second piece, and to switch from one side to the other it has to go back, which is precisely the description of bifurcation point on the Cayley tree.

To conclude, simple Monte Carlo techniques are sufficient for obtaining dimensions of loops. In particular, we have shown that there exists a nontrivial geometry of the conformational space, with noninteger dimensions and with Lobachevskii type curvature. Returning to the introduction and the relation between Levinthal’s paradox and random walks in conformation space, one can ask: how long does it take for a random walk to bring the system into the critical region \( \omega \)? The most naive estimate of this time, \( t \), would be \( t \sim |\Omega|/|\omega| \), where \( \Omega \) is the entire conformation space, and \( |\omega| \) means the number of conformations in the domain. . . . This estimate is consistent with the original Levinthal formulation [1], except \( |\omega| = 1 \) there. However, we now know that such estimates are only valid in the long time limit of a walk in a bounded space (second line of equation (2)). Thus an understanding of random walks in conformational space is crucial to the understanding of protein folding.

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