How Does It Fold?
Searching for Folding Pathways using A Motion Planning Approach *

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Abstract

In this paper, we present a framework for studying folding problems from a motion planning perspective. The version of the motion planning problem we consider is that of determining a sequence of motions to transform an extended, or flat, configuration of a foldable object (the start) into a known folded configuration (the goal). Modeling foldable objects as tree-like multi-link objects allows us to apply recent techniques developed in the robotics motion planning community for articulated objects with many degrees of freedom (many links) to folding problems. An important feature of this approach is that it not only allows us to study foldability questions, such as, can one object be folded (or unfolded) into another object, but most importantly, provides us with another tool for investigating the dynamic folding process itself. For example, the folding sequences, or pathways, found might provide insight about how a protein folds in nature. Or, the inability to generate a folding sequence could offer insight regarding the foldability of a paper or box folding problem.

The framework proposed here has application to traditional motion planning areas such as automation, teaching through demonstration, and animation, and most interesting to us, presents a novel approach for studying folding pathways for proteins. We hope our approach, which constructs a folding sequence to the known native fold, will prove complementary to other methods and might offer additional insight into the larger question of protein structure prediction.

Indeed, our preliminary experimental results with traditional paper crafts (e.g., box folding) and a small peptide chain are quite encouraging.

Keywords: protein folding, folding pathways, motion planning, probabilistic roadmap methods.

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1 Introduction

Folding is a very common process in our lives, ranging from the macroscopic level – paper folding or gift wrapping – to the microscopic level – protein folding. In most instances, while one desires a particular final state to be reached (e.g., the package is wrapped, or the protein's structure is obtained), the knowledge of the dynamic folding process used to reach a particular state is of interest as well. For this reason, we believe motion planning has great potential to help us understand folding. In particular, while motion planning does have the ability to answer questions about the reachability of certain goal states from a given initial state, its primary objective is to in fact determine the motions required to reach the goal.

The problem of folding (and unfolding) is an interesting research topic and has been studied in several application domains. Lu and Akella [40] consider a carton folding problem and its applications in packaging and assembly. In computational geometry, there are various paper folding problems, such as, given gluing instructions for a polygon, construct the unique convex polyhedron to which it folds [42]. While in computational biology, one of the most important outstanding problems is protein folding, i.e., folding a one-dimensional amino acid chain into a three-dimensional protein structure.

There are large and ongoing research efforts whose goal is to determine the native folds of proteins (see, e.g., [38, 28]). In this paper, we assume we already know the native fold, and our focus is on the folding process, i.e., how the protein folds to that state from some initial state. Many researchers have remarked that knowledge of the folding pathways might provide insights into and a deeper understanding of the nature of protein folding [25, 44]. Although there have been some recent experimental advances [21], computational techniques for simulating this process are important because it is difficult to capture the folding process experimentally since protein folding happens so rapidly.

Motion planning, which has been well studied and applied in robotics, provides a natural approach to such problems. In particular, the version of the problem we consider is that of determining a sequence of motions to transform an extended, or flat, configuration of a foldable object (the start) into a known folded configuration (the goal).

Although our main interest lies in the intriguing protein folding process, our work, however, is motivated by and begins with our success with paper folding. While we recognize that protein folding is vastly more complicated than paper folding, we believe that our successes with paper folding provide some evidence of the feasibility and appropriateness of our motion planning approach for determining folding sequences. Thus, the paper describes some results related to paper folding, both to enable us to present the approach as a general framework for investigating folding problems, and to provide insight into the techniques we propose for incorporating the additional constraints presented by protein folding.

Our approach is based on the successful *probabilistic roadmap (*PRM*)* motion planning method [30]. We have selected the PRM paradigm due to its proven success in exploring high-dimensional configuration spaces (the configuration space, or C-space, of a movable object is the space consisting of all possible positions and orientations of the object). Briefly, PRMs work by randomly sampling points from C-space, and retaining those that satisfy certain feasibility requirements (e.g., they must correspond to collision-free configurations of the movable object). Then, these points are connected to form a graph, or roadmap, using some simple planning method to connect 'nearby' points. During query processing, paths connecting the start and goal configurations are extracted from the roadmap using standard graph search techniques. (See Figure 1.) A major strength of PRMs is that they are quite simple to apply, even for problems with high-dimensional configuration spaces, requiring only the ability to randomly generate points in C-space, and then test them for feasibility (the local connection can often be effected using multiple applications of the feasibility test).

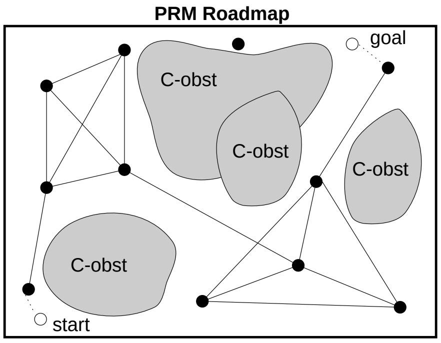


Figure 1: Querying a PRM roadmap (C-space).

To apply the PRM framework to studying folding processes, we must define the configuration spaces of the objects we are interested in folding. In particular, we model both the paper polygon and the amino acid sequence as multi-link tree-like articulated 'robots', where fold positions (polygon edges or atomic bonds) correspond to joints and areas that cannot fold (polygon faces or atoms) correspond to links. Using the same basic formulation for the various folding problems will enable us to utilize the same methodology to study them all. One complication we deal with in our models is that the kinematics of our tree-like structures are more complex and arbitrary than the serial linkages generally dealt with in the robotics literature (where one can often look-up or obtain nice closed-form solutions). To address this, we decouple the specification of the link's reference frame from its joint specifications, which results in a more general formulation that can be applied to arbitrary tree-like linkages. The protein folding problem has the additional complication in that the way in which the protein folds depends on factors other than the purely geometrical constraints which govern the polygonal problems. Nevertheless, we show that these additional factors can be dealt with in a reasonable fashion within the PRM framework.

Our preliminary experimental results with traditional paper crafts (e.g., box folding, see Figure 2) and a small 'protein' (actually a peptide chain) are quite promising.

Before describing our approach, we first review related work in computational geometry and computational biology.

1.1 Paper folding

Many problems related to the folding and unfolding of polyhedral objects have recently attracted the attention of the computational geometry, and to a lesser extent, the robotics communities (see, e.g., [9, 17, 18, 19, 40, 42]).

One class of problems concerns itself with the constructability of certain polygonal or polyhedral structures. Several interesting algorithmic questions relating to origami have attracted the attention of computational geometers, who have obtained some remarkable results (see, e.g., [7, 19, 31, 32, 34]). For example, [19] answers a long-standing open problem in origami design by showing that every polygon region (with holes) is the silhouette of some flat origami. They also show that every polyhedron can be 'wrapped' by folding a strip of paper around it, which addresses a question arising in three-dimensional origami, e.g., [3]. There are a number of other interesting questions related to three-dimensional polyhedral objects [42]. For instance, can every convex polytope's

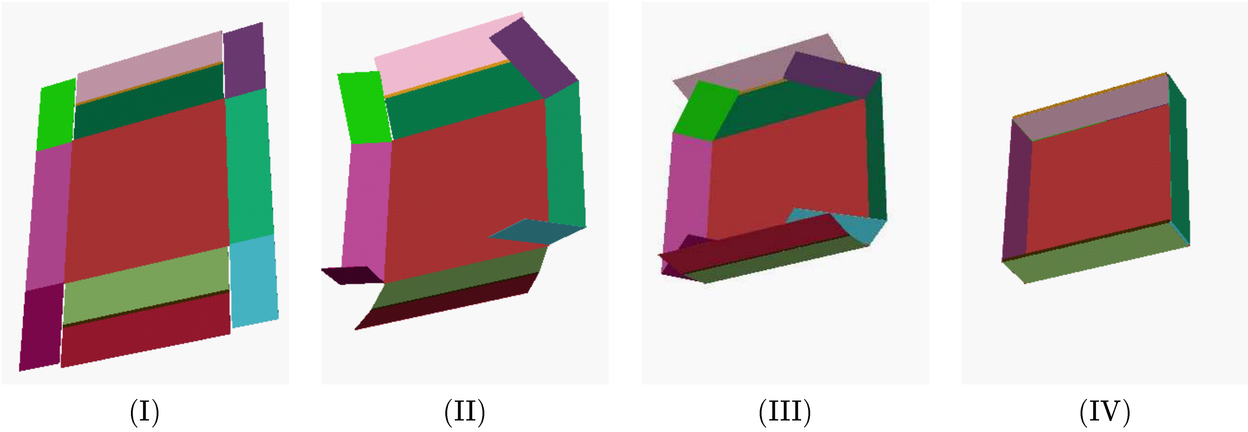


Figure 2: Snapshots of a carton folding path found by our planner.

surface be unfolded to a non-overlapping simple polygon by cutting along its edges [45]? This problem has application in manufacturing parts from sheet metal [23], where they are in fact more interested in the case of non-convex polyhedra, for which results are known for some particular classes of polyhedra [9]. The inverse problem of folding a polygon into a particular polyhedron has also been studied, and results have been obtained for some special cases (e.g., [41]).

Although the problems discussed above can be modeled as articulated objects, in most cases they cannot be modeled as trees. In particular, the incident faces surrounding a given face will form a cycle in the linkage structure. In terms of motion planning, these cycles, often called closed chains, impose additional constraints on the problem. In this paper we are interested in problems with tree-like linkage structures, i.e., objects whose linkage structures do not contain cycles. Although one might suspect this requirement significantly reduces the complexity, there are in fact some very difficult problems with this property. For example, it is still an open problem to determine whether a simple polygonal chain in the plane can be straightened in such a manner so that all intermediate configurations are simple (edges intersect only at vertices) [36]. However, it has recently been shown that not every tree-like linkage in the plane can be 'straightened' (called 'locking'), that is, there are some pairs of configurations of the linkage which cannot be connected if the links are not allowed to cross [8]. This result is relevant to the paper folding problems considered here. In three dimensions, it has recently been shown that there exist open (and closed) chains that can lock [8, 12], which is a relevant result for the protein folding problem. Finally, in dimensions higher than three, it has recently been established that neither open nor closed chains can lock [13].

The randomized motion planning approach we advocate here is somewhat different in nature to the previous approaches used to study these problems in the computational geometry community. In particular, as the methods we employ are not complete (i.e., they are not guaranteed to find a solution if one exists), they cannot be used to definitively answer a particular question. However, they can provide theorists with a valuable tool for understanding and isolating the difficulty (the 'bottleneck') of a particular folding problem, which might lead to important insights needed to obtain further theoretical results. As will be seen, we hold a similar philosophy regarding the possible benefits of our approach for approximating the protein folding process.

1.2 Protein folding and folding pathways

Proteins are the building materials for all life forms: they work as either structural elements or catalysts (enzymes) for synthesizing other proteins. A protein's function is solely determined by its

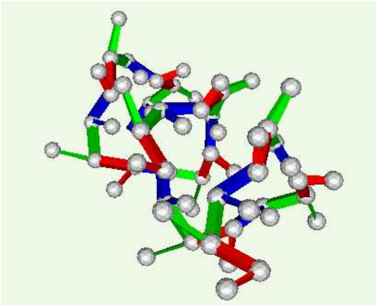


Figure 3: A protein.

three-dimensional structure, its tertiary structure. This three-dimensional conformation, in turn, is determined by the protein's amino acid sequence, the so-called primary structure of protein. The protein folding problem is to predict a protein's three-dimensional conformation based solely on its amino acid sequence. These spontaneous folding processes are critical in the functioning of all life forms, which makes understanding the mechanism of protein folding one of the most important problems in biology.

The fact that a protein's three-dimensional structure is determined by its amino acid sequence was first demonstrated in Anfinsen's pioneering work [6]. Since then, many different approaches have been attempted for predicting protein structure (see [47] for a review). A general, comprehensive answer is still unknown due to the intrinsic complexity of the problem.

In folding simulations, several computational approaches have been applied to this exponential-time problem, including energy minimization [39, 49], molecular dynamics simulation [37], Monte Carlo methods [14, 33], and genetic algorithms [11, 48]. Among these, molecular dynamics is most closely related to our approach. Much work had been carried out in this area [16, 20, 24, 37], which tries to simulate the true dynamics of the folding process using the classical Newton's equations of motion. The forces applied are usually approximations computed using the first derivative of an empirical potential function. The advantage of using molecular dynamics is that it helps us understand how proteins fold in nature. It also provides a way to study the underlying folding mechanism, to understand folding pathways, and can naturally provide intermediate folding states. However, the simulations required for this approach are computationally intensive and time-dependent. The simulation result also depends heavily on the start conformation and can easily result in local minima.

Despite the abundant work on predicting the native folds of various proteins and in the determination of folding pathways, most of the proposed techniques have tremendous computational requirements because they attempt to simulate complex kinetics and thermodynamics. In this paper, we present an alternative approach that finds approximations to the folding pathways while avoiding detailed simulations. Our motion planning approach is based on the successful *probabilistic roadmap* (PRM) method [30]. The PRM methodology has been used to study the related problem of ligand binding [29, 46], which is of interest in drug design. The results were quite promising. The advantages of the PRM approach are that it efficiently covers a large portion of the planning space, in this case, the conformation space, and that it also provides an effective way to incorporate and study various initial conformations. As explained below, these same strengths are applicable to the study of the more complex protein folding process as well.

2 Preliminaries: Models, C-Space, and Energy Calculations

As mentioned above, PRMs work by sampling points from the moving object's *configuration space*, and retaining those that satisfy certain *feasibility requirements* as roadmap nodes. Then, attempts are made to connect pairs of nearby nodes using (simple) *local planning* methods; successful connections will be saved as roadmap edges.

2.1 C-spaces of folding objects

Both the paper polygon and the amino acid sequence are modeled as multi-link tree-like articulated 'robots', where fold positions (polygon edges or atomic bonds) correspond to joints and areas that cannot fold (polygon faces or atoms) correspond to links. The fold positions of the paper polygon are modeled as revolute joints. For the amino acid sequence of the protein, we consider all atomic bond lengths and bonds angles to be constants, and consider only torsional angles, which we also model as revolute joints. Thus, in both cases, our models will consist of $n+1$ links and n revolute joints.

The joint angle of a revolute joint takes on values in $[0, 2\pi)$, with the angle 2π equated to 0, which is naturally associated with a unit circle in the plane, denoted by S^1. Assuming some position and orientation for one of the links (the base), the position of all the remaining links can be specified by the *joint angle* between each link and some adjacent link. Thus, since in the folding problems considered here we are not concerned with the absolute position and orientation of the object in the environment (i.e., we can use any nominal position for the base link), a *configuration* of a tree-like articulated object can be specified by a vector of n joint angles. That is, the configuration space of interest for our multi-link objects can be expressed as:

$$\mathcal{C} = \{q \mid q \in S^n\}. \tag{1}$$

Note that $\mathcal{C}$ simply denotes the set of all possible configurations, but says nothing about their feasibility. In our folding problems, we are not concerned with other obstacles in the environment. However, we do require that no collision exists among the links (this is usually called self-collision in the robotics literature). We denote by $\mathcal{C}_{free}$ the set of configurations $q \in \mathcal{C}$ which do not cause any self-collision among the links.

2.2 Kinematics of folding objects

To specify the connection between each pair of links, Denavit-Hartenberg (DH) notation is adopted [15]. The kinematics of each link (e.g., its position and orientation) can then be computed in a systematic way. In Craig [15], formulae are given for calculating the kinematics for serial linkages (such as most industry robots). However, these cannot be directly applied to our tree-like models since each link can have multiple forward links. The problem is that each link's body frame (local reference frame) is determined by the locations of its joints (one forward, one backward) and the system becomes overconstrained when more joints are present.

We solve this problem in the following way:

- For each link i, we set a body frame F_i, which is independent of any joint connections. Usually, we choose the center of mass as the origin of the body frame.
- For a joint that links body i and j, we use DH notation to define the transformation generated by this joint connection. To express this, we assign a 'DH-frame' to body i and to j, denoted

by DH_i and DH_j, respectively, and then use DH parameters to specify the connection between DH_i and DH_j. (In general, the DH-frames are different from the body frames.)

- To get the transformation from F_i to F_j, we first do the transformation from F_i to DH_i, then to DH_j, and finally to F_j.

The advantage of this approach is that a link's body frame and its joint specifications are decoupled, which makes the approach itself more general and applicable to any tree-like linked structure.

2.3 Potential energy computations

Finally, another complication is that the way in which the protein folds depends on factors other than the purely geometrical constraints (e.g., no self-collision) which govern the polygonal problems. In particular, there are constraints on the feasible configurations (often called *conformations*) that are related to the potential energy of the conformation. For example, during the node generation stage, we will reject all nodes whose potential energy is above some predetermined maximum value, $E_{\max}$. The potential energy of the conformations is also needed to simulate the protein folding process, to discover the folding pathways, and to determine if a path is energetically feasible or not.

In our potential energy calculations, we use the empirical potential when the molecule is considered to be in vacuum:

$$\begin{aligned} U_{tot} &= \sum_{bonds} \frac{1}{2} K_b (R - R_0)^2 + \\ &\sum_{angles} \frac{1}{2} K_a (\theta - \theta_0)^2 + \\ &\sum_{torsions} K_\phi [1 + cos(n\phi - \delta)] + \\ &\sum_{pairs} (A/r_{ij}^{12} - B/r_{ij}^{6}) + \\ &\sum_{electrostatic} \frac{k q_i q_j}{r_{ij}} \end{aligned}$$

The first two terms vanish since we have set the bond lengths and angles as constants. The electrostatic potential is considered only in terms of hydrogen bonds, which is represented in the special van der Waals's parameters between hydrogen atoms that are attached to peptide or amino nitrogen and oxygen atoms in a carbonyl or carboxyl group. The bond twisting constant K_ϕ is set as 2.0 KJouls/mol.

The van der Waals parameters, which are taken from [37], are listed in Table 1.

3 Motion Planning using Probabilistic Roadmap Methods

Given a description of the environment and a movable object (the 'robot'), the motion planning problem is to find a feasible (e.g., collision-free) path that takes the movable object from a given start to a given goal configuration. Automatic motion planning has applications in many areas such as robotics, virtual reality systems, and computer-aided design. Although many different motion planning methods have been proposed, most are not used in practice since they are computationally infeasible except for some restricted cases, e.g., when the movable object has very few degrees of freedom (dof) [35]. Indeed, there is strong evidence that any complete planner (one that

Van der Waals Parameters				
Bond Type	A	B	ε	r^0
H..H	290	1.07	0.0010	2.8525
O..O	145,834	328	0.18479	3.1005
N..N	3952850	2556	0.41315	3.8171
C..C	3075695	953	0.07382	4.3150
A..A	1200965	425	0.03763	4.2202
H..O	2913	241	5.0	1.7

Table 1: Van der Waals Parameters. -ε is the minimum potential energy at separaton r^0, which is the equilibrium radius. They are presented here for comparative purposes. The atom types are defined as follows: O is oxygen, N is nitrogen, H is hydrogen, C denotess extended carbon atoms, and A denotes carbon atoms in a carbonyl or carboxyl group. For the interactons of other atom pairs, we use the geometric means of the A and B values of the atoms involved, for example, $A_{O..N} = (A_{O..O} * A_{N..N})^{1/2}$[37].

is guaranteed to find a solution or determine that none exists) requires time exponential in the number of dof of the movable object [43]. For this reason, attention has focussed on randomized or probabilistic motion planning methods. In particular we note the *probabilistic roadmap methods*, or (PRMs), that have recently proven successful on many previously unsolved problems involving high-dimensional C-spaces (see, e.g., [2, 4, 10, 27, 30]).

As mentioned in Section 1, our approach to the folding problem is based on the PRM approach to motion planning [30]. We selected the PRM paradigm due to its proven success in exploring high-dimensional configuration spaces, which our folding problems have. Briefly, PRMs work by randomly sampling points from C-space, and retaining those that satisfy certain feasibility requirements (e.g., they must correspond to collision-free configurations of the movable object). Then, these points are connected to form a graph, or roadmap, using some simple planning method to connect 'nearby' points. During query processing, paths connecting the start and goal configurations are extracted from the roadmap using standard graph search techniques. (See Figure 1.)

A major strength of PRMs is that they are quite simple to apply, even for problems with high-dimensional configuration spaces, requiring only the ability to randomly generate points in C-space, and then test them for feasibility (the local connection can often be effected using multiple applications of the feasibility test).

The folding problems, especially protein folding, have a few notable differences from usual PRM applications. First, as our problems are not posed in an environment containing external obstacles, the only collision constraint we impose is that our configurations be self-collision free. Also, for the protein folding problem, our preference for low energy conformations leads to an additional constraint on the feasible conformations. Second, in PRM applications, it is usually considered sufficient to find *any* feasible path connecting the start and goal configurations. This is because the problems studied are so difficult that simply determining if a path exists is very challenging. For our folding problems, however, we are interested not only in whether there exists a path, but we are also interested in the *quality* of the path. For example, for the paper folding problems, one is interested in a path which makes a minimal number of folds, and for the protein folding we are interested in low energy paths.

The particular PRM used in this work is the obstacle-based PRM called OBPRM, [4, 5]. Briefly, in OBPRM, the roadmap nodes are generated on constraint surfaces (C-obstacles surfaces). Although there are no external obstacles present in our environments, OBPRM still proves effective for the folding problems since there still exist C-obstacles representing self-collision configurations.

3.1 Node generation

As described in Section 2.1, since all joints are revolute, a random configuration $q \in \mathcal{C}$ can be generated by assigning each joint angle a random value in its allowable range. Once all the joints angles are set, the object's three-dimensional structure is fully determined.

For the paper folding, the configuration of each link is then calculated and self-collision among the links is checked. The node is discarded if any collisions are found.

For the protein molecular model, after the joint angles are known, the coordinates of each atom in the system are calculated, and these are then used to determine the potential energy of the conformation, as defined in Section 2.3. The node is accepted and added to the roadmap based on its potential energy E with the following probability [46]:

$$P(E) = \begin{cases} 1 & \text{if } E < E_{\min} \\ \frac{E_{\max}-E}{E_{\max}-E_{\min}} & \text{if } E_{\min} \leq E \leq E_{\max} \\ 0 & \text{if } E > E_{\max} \end{cases}$$

This filtering helps us to generate more nodes in low energy regions, which is desirable since we are interested in finding the pathways that are most energetically favorable (low energy). If one thinks of the potential field in C-space as a high-dimensional terrain, a folding path is a path somehow snaking along the valleys. In our case, we chose $E_{\max} = 500$ KJouls/mol and $E_{\min} = 100$ KJouls/mol.

3.2 Constructing the roadmap

The second phase of the algorithm is roadmap connection. For each node, we first find its k nearest neighbors in the roadmap (using Euclidean distance in C-space), for some small constant k, and then try to connect it to them using some simple local planner. For both the paper folding and protein folding models, each connection attempt performs feasibility checks for N intermediate configurations between the two corresponding nodes as determined by the chosen local planner (the number of such configurations is, e.g., the resolution used for collision detection, which may be set by the user). If there are still multiple connected components in the roadmap after this stage (which is generally the case, and in fact is sometimes unavoidable, see, e.g., [8, 12]), other techniques will be applied to try to connect different connected components (see [4] for details).

When two nodes are connected, the corresponding edge is added to the roadmap. We associate a weight factor with each edge. For the paper folding, the weight factor is simply N, the number of intermediate configurations on the edge. For the protein folding, the weight is calculated in a different way. For two consecutive intermediate conformations i and $i+1$ on the edge, we first calculate their potential energies, i.e., E_i and E_{i+1}, and then the probability of moving from conformation i to $i+1$ is determined by:

$$P_i = \frac{1}{1+e^{\frac{E_{i+1}-E_i}{kT}}} = \frac{1}{1+e^{\frac{\Delta E}{kT}}},$$

and the total weight of the edge is [46]:

$$Weight = \sum_{i=0}^{N-1} -log(P_i),$$

Roadmap Construction Statistics (for successful folding)					
Model	**dof**	**Gen**	**Con**	**#CC**	**#Nodes**
Box	12(5)	38.7	201	1	1035
Periscope	11	13	177	1	883
Protein	20	8.58	53.8	1	47
		35.5	206	1	182
		116	733	1	624
		429	2770	1	2347

Table 2: Roadmap construction statistics for the Box, Periscope, and Protein models. The Box has 12 links, but its dof becomes 5 after symmetry is exploited. The label 'Gen' stands for node generation time and 'Con' for node connection time. #Nodes and #CC are the number of nodes and connected components, respectively, in the resulting roadmap. All times are shown in seconds.

By assigning the weights in this manner, we can find the shortest or most energetically feasible path when performing subsequent queries.

3.3 'Querying' the roadmap

The resulting roadmap can be used to find a feasible path between given start and goal configurations. This is done a bit differently than what is normally done at this stage. Usually, attempts are made to connect the start and the goal configurations to the same connected component of the roadmap. If this succeeds, a path is returned, otherwise failure is reported. In the process, the roadmap is kept intact.

For our folding problems, it is convenient to actually connect the start and the goal into the roadmap, just as was done for the other roadmap nodes in the connection phase. Dijkstra's algorithm is then used to find the smallest weight path between the start and goal configurations. If the path's weight is too large (as compared to some predetermined maximum), a failure is reported, otherwise the path is returned. The advantage of adding the start and the goal to the roadmap is two-fold. First, the roadmap is augmented after each query is performed (this has been noted as a possible optimization for regular PRM applications as well). Second, this facilitates our search for the lowest weight path.

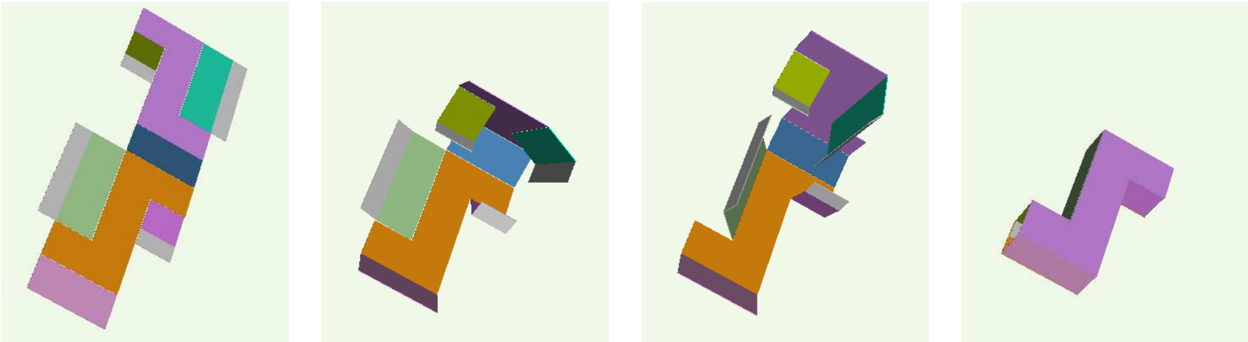
4 Results and Discussion

In this section we describe the use of the PRM motion planning approach to the study of three folding problems, two drawn from the realm of paper folding and one from protein folding.

4.1 Implementation details

The PRM code we used was OBPRM [4] (for the protein folding simulation, nodes were generated by standard PRM uniform sampling [30]), which required only minimal additions to support the decoupling of the reference frames of the links (body frames) from the joint specifications (DH parameters) as described in Section 2.2. We used the RAPID [22] package for three-dimensional collision detection.

The experiments were performed on an SGI Octane R10000 machine.



(I) (II) (III) (IV)

Figure 4: Snapshots of the folding of the periscope model.

4.2 Models studied

We study two paper folding models: a *box* and a *periscope*. The periscope has 11 degrees of freedom (11 joints) and the box has 12. However, for the box, the number of dof can be reduced to five using symmetry arguments. Both foldings require some intelligence: the flaps have to be folded in the proper order in order to reach the final folded state. Thus, these problems are not trivial, and in fact, correspond to what is known as the 'narrow passage' problem [26], which is thought to be the last major challenge for path planning of rigid bodies in static environments.

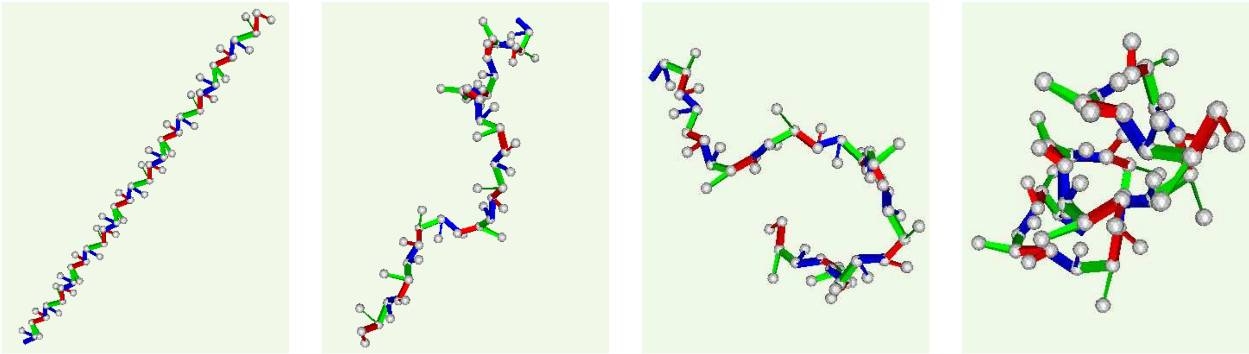
The 'protein' (a peptide chain) is a small amino acid chain that consists of ten Alanine amino acids, corresponding to 20 degrees of freedom. It folds from its extended (straight) conformation to a second structure known as an *alpha helix*, which is one of the common 'sub-structures' in proteins. The extended conformation's potential energy is around 85 KJouls/Mol and the right-helix has potential energy about 13 KJouls/Mol. These energies were calculated using the potential energy function. This model is from the IMB Jena Image Library of Biological Macromolecules [1].

4.3 Results

Table 2 shows some statistics regarding the roadmaps constructed for the three problems. As can be seen, in all cases the problems were 'solved' rather quickly with relatively small roadmaps.

The results for the paper folding examples are really quite remarkable. These problems are actually considered to be quite challenging motion planning problems. Nevertheless, we see that just a few minutes was needed to construct roadmaps containing solution paths. We believe our success with these problems can be attributed to the tendency of the OBPRM roadmaps to contain nodes near the constraint surfaces (i.e., near self-collision configurations) which include configurations necessary for successful paths. For example, configurations in which the flaps of the box fold over other flaps. In addition, it supports the modeling framework we adopted for tree-like linkages, which decouples the joint specifications from the body frames. Snapshots of the folding paths found are shown in Figures 2 and 4 for the box and the periscope, respectively.

The results for the protein folding example are also very interesting. We provided the goal conformation beforehand, and then searched in the roadmap for the minimum weight path connecting the extended aminio acid chain to the final three-dimensional structure, an alpha helix. By analyzing the paths found, we may be able to gain some insight into the natural folding process. Our work can potentially be extended to study the folding processes of larger and more complicated protein structures (provided their native folds are known), and we plan to do that soon. Snapshots



(I) (II) (III) (IV)

Figure 5: Snapshots of the protein folding.

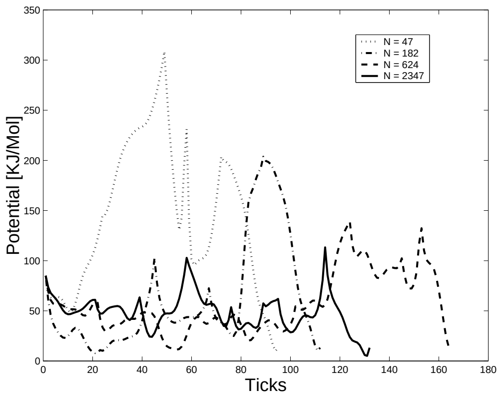


Figure 6: Potential along the folding path shown for each intermediate configuration on the path ('tick').

of a folding path found are shown in Figure 5.

In order to study the folding process, we analyzed the profile of the potential energies of the intermediate conformations on the folding path. This is shown in Figure 6 for roadmaps of four different sizes (with $47, 182, 624$ and 2347 nodes, respectively). It should be anticipated that as the number of roadmap nodes grows (the sampling is denser), the folding path should approach the 'ideal' path, i.e., the path with minimum folding difficulty, which is how proteins are thought to fold in nature. That is, when the number of nodes sampled is large enough, we will have a good approximation of the natural path. The results shown in Figure 6 and Figure 7 support this belief. They also give us an estimate of how many nodes should be sampled. Intuitively, this depends on the size of the structure studied. In particular, we see that as the number of nodes, N, is increased, the paths seem to improve in quality, and most notably have fewer and smaller peaks in their profiles.

Another interesting point is the similarity among the paths for all roadmap sizes. In particular, they all illustrate that there is a peak (or peaks) around the goal conformation. Such energy barriers around a folding state are crucial for a stable fold. One can see (Figure 6) that along the folding pathways, there are several other spots where the potential energies are as low. However, the depths of the potential wells around those conformations are not as deep (the profile is flatter), which makes those states less stable than the goal conformation. The similarity among these paths

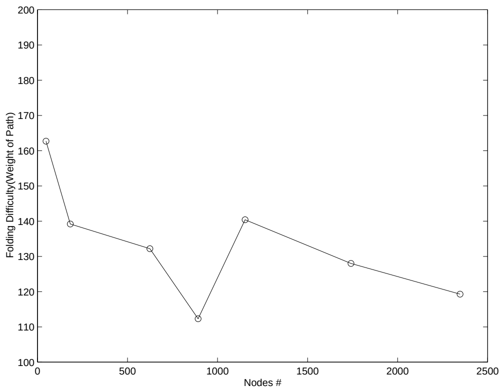


Figure 7: Folding Difficulty (weight of folding path) with respect to the number of nodes in the roadmap.

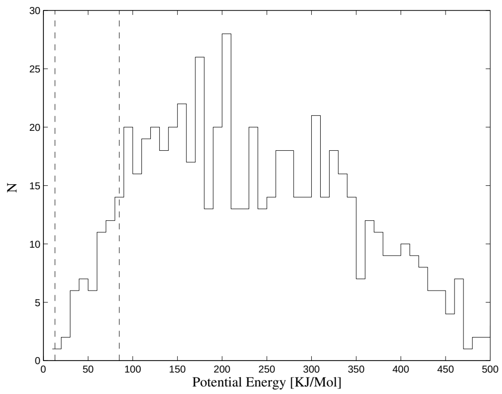


Figure 8: The distribution of the potential energies of the sampled nodes. The dashed lines denote the potential energies of the start and goal conformations, 85 KJ/mol and 13 KJ/mol, respectively. The total number of sampled nodes (conformation) is 624.

also implies that they may share some common conformations, or subpaths, and this knowledge could be used to bias our sampling around these regions, hopefully further improving the quality of the roadmaps. One may also notice from the potential profile that at some places along the path the potential energy is higher than that of the initial fold state. We believe this might be explained by the quantum tunneling effect which is very common at the microscopic level. It is for this reason that we purposely keep some nodes which have potential energies higher than the initial fold when we sample from the conformation space. In Figure 8, we plot the distribution of the potential energies of the nodes retained after sampling. The two dashed lines mark the potential energies of the start and the goal.

The folding difficulty of a path, which is proportional to the logarithm of the inverse of the probability, is shown in Figure 7. As anticipated from our discussion above, one can see that the folding difficulty initially decreases quite rapidly as more roadmap nodes are added, but begins to level off fairly quickly (ignoring what seem to be outliers).

5 Conclusion and Future Work

In this paper, we present a framework for studying folding problems from a motion planning perspective. Our approach, which is based on the PRM motion planning method, was seen to produce interesting results for representative problems in paper folding and protein folding. One of the most important benefits of this approach to folding problems is that it enables one to study the dynamic folding process itself. Unfortunately, it is difficult to appreciate this from the few path snapshots we are able to display in a paper. Nevertheless, we believe that this is a promising approach which deserves further investigation.

In current work, we are applying our method to more and larger, more complex, proteins.

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