

# A Methodology for Efficiently Sampling the Conformation Space of Molecular Structures

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Audrey Lee   Oliver Brock   Ileana Streinu\*

Bioinformatics Research Laboratory  
Department of Computer Science  
University of Massachusetts Amherst

\*Department of Computer Science  
Smith College  
Northampton, MA

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## Abstract

Motivated by recently developed computational techniques for studying protein flexibility, and their potential applications in docking, we propose an efficient method for sampling the conformational space of complex molecular structures. We focus on the *loop closure* problem, identified in the work of Thorpe and Lei [32] as a primary bottleneck in the fast simulation of molecular motions.

By modeling a molecular structure as a *branching robot*, we use an intuitive method in which the robot holds onto itself for maintaining loop constraints. New conformations are generated by applying random *external forces*, while *internal, attractive forces* pull the loops closed. Our implementation, tested on several model molecules with low number of degrees of freedom but many interconnected loops, gives promising results that show an almost four times speed-up on the benchmark cube-molecule of Thorpe and Lei.

## 1 Introduction

Macromolecules undergo conformational changes to perform their biological function. Experimental techniques, such as X-ray crystallography and NMR, are used to extract information on individual conformations or ensembles, but lack the capability of capturing the *entire* conformation space. In many biological processes, for example protein docking, a protein molecule transitions from one low-energy conformation to another in which it is able to bind the ligand. To determine the function of a macromolecule, it is therefore necessary to build a representation of feasible conformational changes.

Many biologically relevant macromolecules contain flexible rings. A valid conformation for such a molecule must satisfy the ring closure constraints [15] for every one of its loops. The set of all conformations that satisfy these constraints represents a vanishingly small portion of the overall conformation space. As a result, most conformations generated by the perturbation of a set of bond angles will violate the ring constraints. This makes the exploration of the valid conformation space for a molecule with flexible rings computationally very difficult.

Approaches to sample the conformation space of molecules with rings employ a two-step approach. Initially, a new configuration is obtained by rotating some of the bonds of the molecule. The resulting conformation violates the loop closure constraints. In a second step, these constraints are re-attained using iterative procedures.

We propose a new, faster method for sampling the entire conformation space of molecular structures containing loops. The key contribution of our papers consists of our approach of re-attaining loop closure constraints for a randomly perturbed conformation. This method is based on standard techniques from robotics. We model the molecule as a *branching robot* that holds onto itself to maintain loop constraints. New conformations can efficiently be generated by applying random *external forces*, while *internal, attractive forces* pull the loops closed.

Our work builds upon the general methodology of Thorpe and Lei [32], which is incorporated into the ROCK software system [22, 26]. They decompose a protein structure into regions with varying *degrees of flexibility*. Then they generate random motions of the atoms, while attempting to reinstate the constraints imposed by the bond lengths and angles of the structure. Substantial computational effort goes into satisfying the *loop closure* and *steric* constraints.

The proposed approach efficiently generates a representation of the valid conformation space of molecules with flexible rings. This valid conformation space is significantly smaller than the conformation space of all possible bond angles. Effectively, the proposed approaches exploits the kinematic constraints imposed by loops to determine a significantly reduced conformation space. Using this reduced space, it becomes computationally much more tractable to perform computations based on energetic considerations. In this paper, we focus on the computation of this smaller search space. Energetic considerations of search in this reduced space are not considered, but can be accomplished with a variety of methods found in the literature (see Section 2).

The loop closure problem is also relevant in other areas of molecular biology. In homology modeling, for example, the structure of a protein is predicted by assembling fragments from a number of homologs. The matching of the termini of these fragments can be viewed as an instance of the loop closure problem. Canutescu et al. [7], Lotan et al. [23] and Kolodny et al. [18] have successfully applied robotics techniques to this domain.

## 2 Related Work

Researchers have investigated a number of different approaches to sample the conformation space of molecules. Molecular dynamics [33] simulations numerically solve Newton’s equations of motion for a detailed model (such as an atomic model) of a molecule. This procedure generates a trajectory through the conformation space of the molecule. Since the trajectory is computed in a discretized fashion, we can say that this method samples the conformation space of the molecule. Molecular dynamics simulations require large amounts of computation. Consequently, they can only compute a small fraction of the total accessible conformation space of a large molecule in a reasonable amount of time.

In molecular structures, atoms do not move independently but instead are constrained by covalent bonds and other interactions with atoms in the molecule. To ensure that a molecular dynamics simulation does not violate these constraints, researchers have proposed a number of augmentations to the basic molecular dynamics algorithm. The Shake method [27] implements an iterative procedure to satisfy spatial constraints between atoms. The Rattle algorithm [2] extends Shake by also considering velocity constraints. Settle [25] further improves on Rattle by providing more efficient computations. These approaches consider the motion of every atom independently. Due to this independence, the motion of an atom will violate the constraints imposed by the molecular structure. The Shake, Rattle, and Settle methods employ an iterative approach to re-attain violated constraints. Because the various constraints are dependent, this is a computationally costly

procedure. In contrast, the approach proposed in this paper exploits techniques from robotics to maintain all but one constraint per loop during the motion. Consequently, only a single constraint has to be re-attained per loop, irrespective of the number of atoms present in that loop. This significantly reduces the computational cost compared to methods that move each atom of a molecule independently. The computational cost of the proposed algorithm depends on the number of loops per molecule, rather than the number of atoms, making it efficient even for very large molecules.

Monte Carlo simulations are a different method of sampling the conformation space of a molecule. They perform a random walk in conformation space, biased by the Metropolis criterion [24]. This random walk is not constrained by Newton’s law of motion, as it was the case in molecular dynamics simulations, and hence Monte Carlo simulations are computationally more efficient than molecular dynamics simulations. One of the drawbacks of Monte Carlo simulations is that they spend considerable computational resources exploring local minima. Researchers have devised a large number of extensions to the Monte Carlo algorithm to address this problem. These extensions include: the replica Monte Carlo method [30], the mutlicanonical ensemble method [3], entropic sampling [21], methods based on weighted histograms [19], parallel tempering [17], jump walking [14], multicanonical jump walking [34], smart walking [36], and local energy flattening [35]. These methods attempt to render the exploration of conformation space more efficient based on energetic considerations. However, in the context of molecules with flexible rings, the most severe constraints on configuration space are imposed by loop closure constraints and not by energetics. An energetically favorable conformation will generally have very few other favorable conformations in its neighborhood, since adjacent conformations may violate the loop closure constraints. Without an explicit treatment of loop closure constraints, these extensions to the Monte Carlo method are not well suited for molecules with flexible loops.

The proposed approach can be viewed as complementary to Monte Carlo simulations in the context of molecules with flexible loops. The method described in this paper determines the part of the conformation space of a molecule with loops that satisfies the loop closure constraints. This subset of the conformation space is computed without considering energetics. Monte Carlo simulations that are restricted to this valid subset of the overall conformation space can then be used to consider energetic considerations much more efficiently, as they will only sample conformations that satisfy loop closure constraints. Effectively, the method described in this paper exploits the kinematics constraints of molecules with loops to reduce the search space available to Monte Carlo simulations, thus significantly increasing their computational efficiency.

During a Monte Carlo simulation, the random change of a single bond angle may result in a large displacement of large portions of the molecule. This is not necessarily biologically plausible and therefore researchers have devised special Monte Carlo moves that only affect a local area of the molecule. A move consists of selecting a short linear segment of the molecule and changing its conformation without affecting other parts of the molecule. Note that the short linear segment can be viewed as a flexible loop. Methods to perform such local moves include random walks in a lattice [29], numerical approaches to determine valid conformations for the short linear segment [13], “wriggling” the chain and re-attaining constraints using linear algebra [6], and the local application of Shake [1]. All of these methods suffer from the same problems as Shake that were discussed above. Furthermore, they have only been applied to short segments, rather than loops of arbitrary length.

Another method of sampling the conformation space of molecules performs exhaustive search [4]. The search space for such an exhaustive search grows exponentially with the number of rotatable bonds. Consequently, these computations become intractable, even for relatively short molecules. Furthermore, this approach is not well suited for molecules with loops: depending on the discretization of the space, loop closure constraints cannot necessarily be satisfied by configurations chosen from a lattice in conformation space.

Thorpe and Lei [32] were the first to be explicitly concerned with molecules containing many interconnected, flexible loops. Given a conformation, Thorpe and Lei’s approach attempts to sample the space around it by randomly perturbing the angles at a chosen set of bonds. The difficulty of the loop closure problem lies in finding a solution to a complicated algebraic system of equations, accomplished by minimizing a fictitious *ring closure potential*. However, because the perturbed bond angles are often inter-dependent, a solution may not exist, resulting in a high rejection rate.

To the best of our knowledge, only one other approach has been proposed for generating molecular conformations, with loops taken under consideration. In the recent work of [10], the general technique for loop closure of [11], called *Random Loop Generator (RLG)*, is applied to proteins. RLG has been developed in robotics and follows from the work of LaValle et al. [20] and Han and Amato [16] in the domain of path planning. The algorithm of [20] breaks the loops, then uses iterative distance minimization to restore the loop constraints. Both [16] and [11] partition the loops into *active* and *passive* chains; forward kinematics is applied to the active chains, while inverse kinematics is applied to maintain the loop closure. More specifically, sampling is accomplished by selecting random values for the active chains, then finding values for the passive chains that close the loop; however, just as in the case of Thorpe and Lei’s approach, it is not always possible to find a valid configuration for the passive chains, resulting in a rejection.

### 3 Methodology

We describe now our method for efficiently sampling the conformation space of a molecular structure *when steric clashes are ignored*. Indeed, as we already pointed out, a *major* challenge in generating new conformations is loop closure.

#### 3.1 Initial framework

To begin with, we describe the framework used to model the molecular structure: a *branching robot*, whose key building block is a *simple robot arm*.

##### 3.1.1 Simple robot arm

The kinematics of robot arms is well-understood and covered in most graduate-level robotics texts, such as [12]. We present here a brief overview, adapted to our specific context.

**Frame assignment.** A *robot arm* is a single chain consisting of *joints* connected by *links*. It is important to note that the first and last elements of the chain are special; they actually are not considered joints and are called the *base* and *end effector*, respectively, of the robot arm. See Figure 1 for an example. We consider only *revolute* joints, i.e. joints that allow rotational motion about a fixed axis; we call  $\theta_i$  the variable representing this single degree of freedom. Joints are labeled  $1, \dots, n$ ; link  $i$  connects Joint  $i$  to Joint  $i + 1$ . In our model, revolute joints are associated with atoms and constant-length links with bonds.

We attach rigidly to each link a *coordinate frame*; although any frame may be chosen, there is a standard convention in robotics for frame assignment. Refer to Figure 1 for frame assignments on the example robot arm. We denote by Frame  $i$  the frame attached to link  $i$ ; by convention, its origin  $\mathbf{p}_i$  lies on Joint  $i$  and its  $\mathbf{z}_i$  aligns with Joint  $i$ ’s axis of rotation. The  $x$ -axis is on the common normal of  $\mathbf{z}_i$  and  $\mathbf{z}_{i+1}$ , and the  $y$ -axis is chosen to obey a right-hand coordinate system. A special *world frame*, denoted Frame 0, is chosen as the frame in which to express all others; for simplicity, its origin is chosen as the base’s position. Once frames have been chosen, a  $4 \times 4$  *homogeneous transformation matrix*  $T_i$  from the world frame to Frame  $i$  is determined.

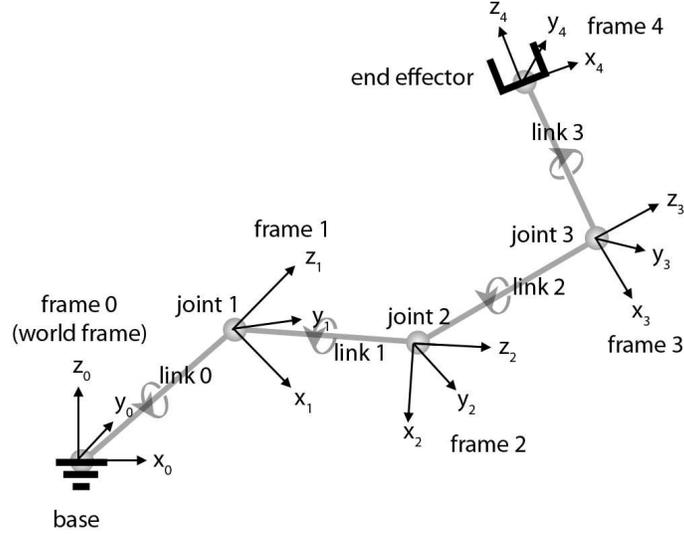


Figure 1: Example robot arm and attached frames.

**Force propagation.** The *Jacobian matrix*  $J$  relates the rate of change of the position and orientation of the end effector to those of the joints. We now show how to compute it. The  $6 \times n$  Jacobian consists of a column for each degree of freedom (or joint), with 3 rows corresponding to position and 3 rows corresponding to orientation, and is expressed as follows:

$$\begin{bmatrix} \mathbf{z}_1 \times \mathbf{p}_1 & \mathbf{z}_2 \times \mathbf{p}_2 & \cdots & \mathbf{z}_i \times \mathbf{p}_i & \cdots & \mathbf{z}_n \times \mathbf{p}_n \\ \mathbf{z}_1 & \mathbf{z}_2 & \cdots & \mathbf{z}_i & \cdots & \mathbf{z}_n \end{bmatrix}$$

For Joint  $i$ , we use the axis of rotation  $\mathbf{z}_i$  and origin  $\mathbf{p}_i$  of the frame attached to link  $i$ , found in the third and fourth columns of  $T_i$ , respectively.

The instantaneous effect of a force  $F$  (with 6 components, corresponding to position and orientation) at the end effector can now be expressed by the equation:

$$\tau = J^T F,$$

where  $\tau$  is an  $n$ -vector for the torques at each joint resulting from the force. We approximate the next configuration of the robot arm by updating each  $\theta_i$  to the value  $\theta_i + k\tau_i$ , where  $k$  is a constant that can be thought of as the time step; note that we consider all joints to have unit mass.

### 3.1.2 Branching robot

Molecular structures are often more complicated than a simple open chain. We introduce the concept of a *branching robot* to accommodate such structures. A branching robot is precisely its namesake: joints connected by links in a tree-like fashion. For such a robot, there is a special *base*, corresponding to the *root* of the tree. Every other joint is connected to the base by links along a single well-defined branch or path.

Branching robots [9] have the following theory established for force propagation. When a force is applied at a joint, we can consider the branch from the base to that joint to be a simple robot arm; the techniques from Section 3.1.1 are applied. If multiple forces are applied simultaneously, the resulting torques are additive and independent; thus, we simply accumulate the torques from each force before approximating the next configuration of the robot.

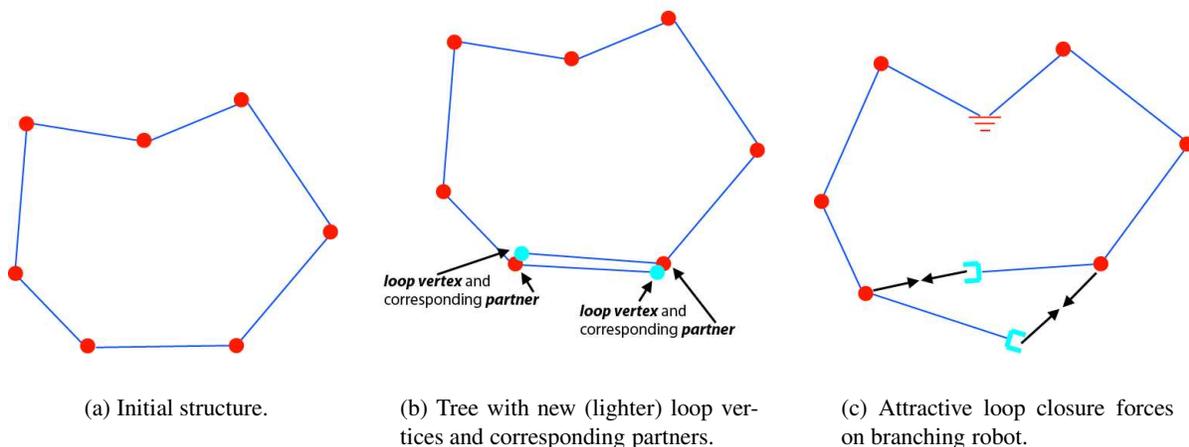


Figure 2: Initialization and loop closure on simple 2d example.

**Breaking loops.** Because our input structure is expected to have many interconnected loops, we initially break these constraints to associate a branching robot. We begin by viewing the structure as a simple graph on edges and vertices; a root and spanning tree are arbitrarily chosen for this graph (using a standard linear-time spanning tree algorithm, e.g. breadth-first-search), to allow the structure to be interpreted as a branching robot. Then we introduce several new vertices, to be used in the loop closure method, as follows. Consider the edges not included in the spanning tree; they correspond to loops that have been broken. For each such edge, we duplicate the endpoints; we call the duplicated endpoints the *loop vertices* and the corresponding originals their *partners*. See Figure 2 for a simple 2d example; Figure 3 contains a 3d example. Each duplicated endpoint is then attached to the opposite original loop endpoint, maintaining the tree constraint. This completes the construction of the branching robot.

### 3.2 Sampling the conformation space

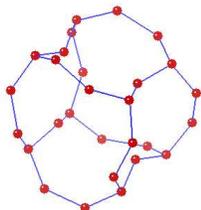
We now describe the sampling of the conformation space. While we experimented with a few other approaches, what we present here is the most effective and efficient. Generation of a new sample consists of two stages: the first stage breaks the loop constraints, while the second restores them.

#### 3.2.1 Stage 1: external force

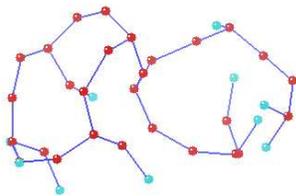
The first stage applies a random external force to the branching robot; the effect of such a force breaks the loop constraints. See Figure 3(b) for an example of the effect of such a force. Note that the lighter loop vertices are no longer aligned with their partners.

#### 3.2.2 Stage 2: internal, attractive forces

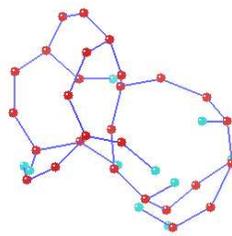
Once the loop constraints have been violated, we use internal, attractive forces to close the loops. Each loop vertex and partner that are not aligned result in an attractive force between them; see Figure 2(c) for a simple two-dimensional example illustrating this concept. We apply all such internal forces and iterate until the loop vertices and their partners align; note that we allow a small error tolerance. Because rotation about the loop edge is allowed, this satisfies the loop constraint. A more complex three-dimensional example of the loop closure approach is shown in Figure 3.



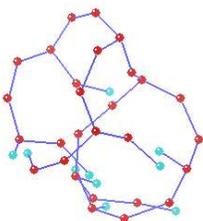
(a) Initial structure.



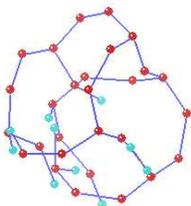
(b) A random external force breaks loop constraints; note tree structure with (lighter) loop vertices.



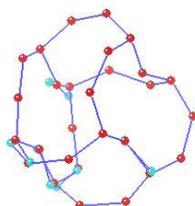
(c) Attractive, internal forces begin to close loops.



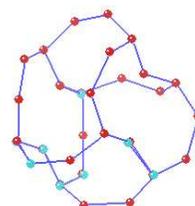
(d) Loop closure.



(e) Loop closure.



(f) Loop closure.



(g) Loops considered closed with a small error tolerance.

Figure 3: 3d example of loop closure approach.

## 4 Model Molecules and Results

To validate our method and compare timings, we present three model molecules. They correspond to subdivisions of the simplest platonic polyhedra: the tetrahedron, cube and octahedron. The *cube model molecule*  $C_8S_{20}H_8$  was designed in [32] to demonstrate the effectiveness of exploring conformation space of molecules with many interconnected rings. We use it to compare our method with [32]. We have designed several other models starting from pure mathematical principles: the reader is advised that we did not intend them to have any chemical meaning. They have exactly two degrees of freedom, to allow for the effective visualization of the conformation space sampling. The broken loops correspond to faces of the corresponding polyhedron and allow for a reliable mathematical accounting of the stated degrees of freedom. They permit an easy replication of our computational experiments, which suggest that the method scales well with the number of broken loops. The geometry for our models was found using the freely licensed ArgusLab software [31], which also attached atomic interpretations to the nodes and added the hydrogen atoms connected to the corner nodes of our polyhedra.

### 4.1 Cube model molecule

Figure 4 depicts an example conformation of the molecule. It consists of 8 carbon atoms (medium gray spheres) at the corners of a cube, with 8 hydrogen atoms (small white spheres) attached to each; 20 sulphur atoms (large gold spheres) make up the rest of the molecule. The distances between carbon and sulphur, sulphur and sulphur, and carbon and hydrogen atoms are  $1.805\text{\AA}$ ,  $2.019\text{\AA}$ , and  $1.120\text{\AA}$ , respectively. All bond angles about the carbon atoms are  $109.5^\circ$ ; sulphur bond angles are  $135^\circ$ . As stated in [32], the molecule has two degrees of freedom, which can be represented as torsional angles  $\theta_1$  and  $\theta_2$  in Figure 4.

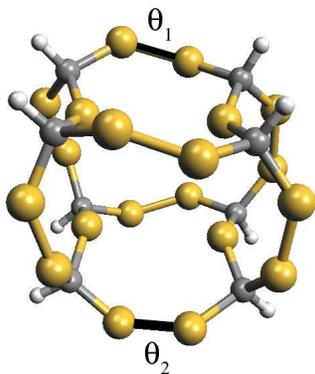


Figure 4: Model molecule  $C_8S_{20}H_8$ . There are 8 carbon atoms (medium gray spheres) with 8 hydrogen atoms (small white spheres) attached to each; 20 sulphur atoms (large gold spheres) make up the rest of the molecule. This molecule has two degrees of freedom, shown as torsional angles  $\theta_1$  and  $\theta_2$ .

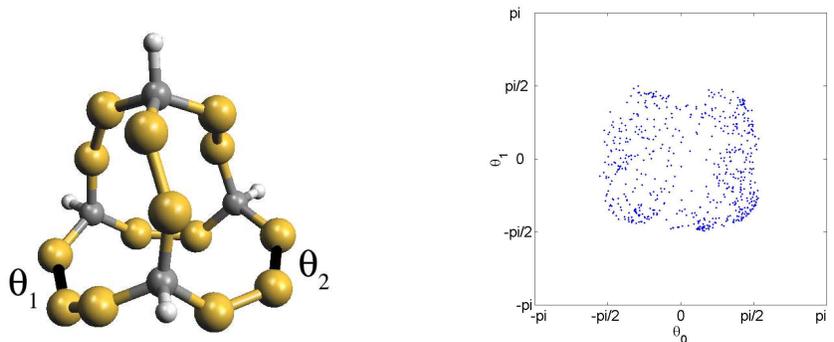
#### 4.1.1 Symmetries

The model molecule has two symmetries on  $\theta_1$  and  $\theta_2$ .

**Symmetry 1**  $(\theta_1, \theta_2) \rightarrow (\theta_2, \theta_1)$

**Symmetry 2**  $(\theta_1, \theta_2) \rightarrow (-\theta_1, -\theta_2)$

We make use of them in our sampling method, just like [32].



(a) Structure: there are 4 carbon atoms (medium gray spheres) with 4 hydrogen atoms (small white spheres) attached to each; 14 sulphur atoms (large gold spheres) make up the rest of the molecule. This molecule has two degrees of freedom, shown as torsional angles  $\theta_1$  and  $\theta_2$ .

(b) Sampled conformation space.

Figure 5: Tetrahedron model molecule and results.

## 4.2 Tetrahedron and octahedron model molecules

The *tetrahedron model molecule* (depicted in Figure 5(a)) has 4 carbon atoms (medium gray spheres) at the corners of a tetrahedron. Each carbon has a hydrogen atom (small white sphere) attached to it; 14 sulphur atoms (large gold spheres) lie along the edges of the tetrahedron. The *octahedron model molecule* is depicted in Figure 6(a). An octahedron is defined by the 6 carbon atoms (medium gray spheres) with 32 sulphur atoms (large gold spheres) on the edges. It is interesting to note that the sampling results for the tetrahedron molecule show that not all the values of the sampled degrees of freedom are present in the real conformations of the molecule.

## 4.3 Results

Our system was implemented in Java and run on a Intel Pentium M 1600 MHz processor. Figure 4.3 depicts several results on the cube molecule, showing that our approach quickly begins sampling the space (see Figure 7(a)); as more conformations are produced, the sampling becomes finer.

Note that the previously discussed symmetries on the cube model molecule were applied. An example generated conformation along with a zoom of the loop closures is shown in Figure 8.

Results for the tetrahedron and octahedron molecules are shown in Figures 5(b) and 6(b), respectively. Table 4.3 compares results on all three molecules.

## 5 Conclusions and Future Work

We have presented a new approach based on robotics methodology for effectively sampling the conformation space of molecular structures, particularly those with interconnected loops. By modeling a molecule as a branching robot, we apply external forces to generate new conformations, and use attractive, internal forces

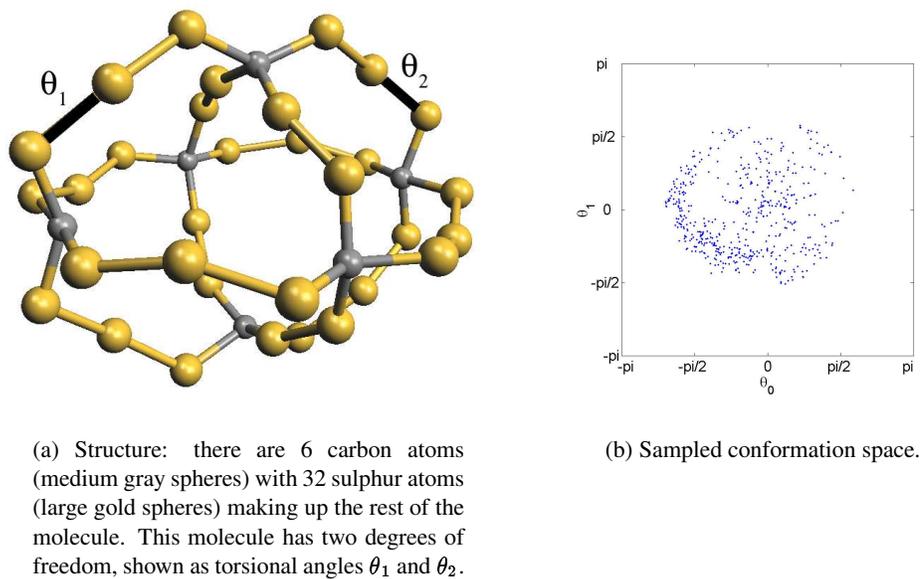
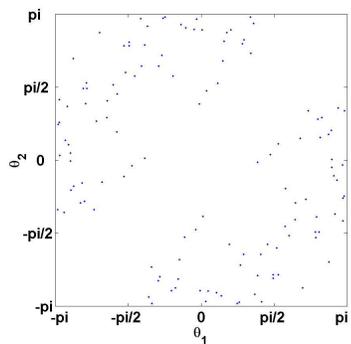


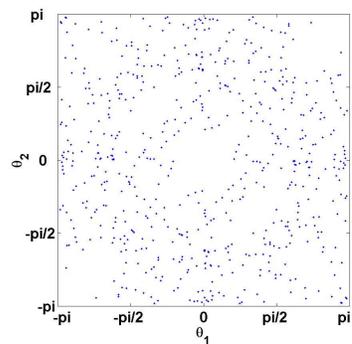
Figure 6: Octahedron model molecule and results.

	Number of atoms	Number of bonds	Number of "broken" loops	Time to generate 500 conformations
Tetrahedron	22	24	3	60 minutes
Cube	36	40	5	100 minutes
Octahedron	38	44	7	130 minutes

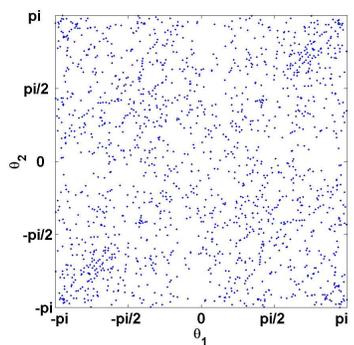
Table 1: Comparison of three model molecules.



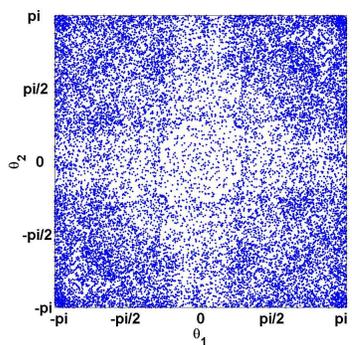
(a) 32 conformations in 6 minutes.



(b) 152 conformations in 22 minutes.



(c) 415 conformations in 73 minutes.



(d) 5,022 conformations in 13 hours, 27 minutes.

Figure 7: Sampled conformation space results; note that symmetries were applied to the generated conformations.

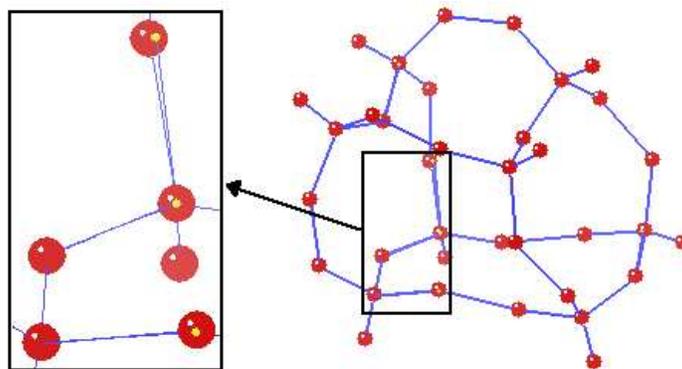


Figure 8: Generated conformation of model molecule. On the left is a zoom of several loop closures; the small vertices represent the loop vertices. Note the small amount of tolerated error.

to maintain loop closure constraints. While based on techniques from robotics, the background required in this field is minimal.

We are aware only of [32] and [10] as other algorithms for generating conformations of molecular structures with loop constraints taken under consideration. Both of them must deal with the problem that randomly perturbing portions of interconnected loops could result in an algebraic system with no solution; our approach is able to avoid the observed large rejection probability by using internal forces to pull loops closed.

The system, implemented in Java, was tested on several model molecules with many interconnected loops, but few degrees of freedom; even with no particular attention to code optimization, it performs almost four times as fast on the cube model molecule from [32]. Our results also show that the algorithm begins sampling the space very effectively within a short period of time (about 5 minutes), with the sampling becoming finer as more conformations are generated.

**Future directions.** While our results indicates significant speed-up in sampling conformational spaces, van der Waals overlap and energy calculations have not yet been considered in this paper. Their integration into our system, with a special attention paid to speed and accuracy and along with a systematic mathematical and bio-chemical validation, will be pursued next.

## Acknowledgements

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