The Discretizable Molecular Distance Geometry Problem

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Abstract

Given a weighted undirected graph G=(V,E,d), the Molecular Distance Geometry Problem (MDGP) is that of finding a function $x:G\to\mathbb{R}^3$, where ||x(u)-x(v)||=d(u,v) for each $\{u,v\}\in E$. We show that under a few assumptions usually satisfied in proteins, the MDGP can be formulated as a search in a discrete space. We call this MDGP subclass the Discretizable MDGP (DMDGP). We show that the DMDGP is **NP**-complete and we propose an algorithm, called Branch-and-Prune (BP), which solves the DMDGP exactly. The BP algorithm performs exceptionally well in terms of solution accuracy and can find all solutions to any DMDGP instance. We successfully test the BP algorithm on several randomly generated instances.

Keywords: Molecular Distance Geometry Problem, Branch-and-Prune Algorithm **AMS Classification**: 92E10, 90C26, 90C27, 65K05.

1 Introduction

It is well known that the role and function of a molecule is determined by both its chemical structure (the atoms that compose it and the way they bond) and its three-dimensional structure. Supposing the chemical structure is known, finding the conformation of the atoms in \mathbb{R}^3 is usually tackled by a mixture of chemical analysis and mathematical methods. Some insight as to the molecular spatial conformation can be gained by employing Nuclear Magnetic Resonance (NMR) techniques, which are able to give a measure of the distance between (but not of the positions of) pairs of atoms closer than around 5Å. The problem of finding the atomic positions given a subset of atomic distances can be formalized as follows.

MOLECULAR DISTANCE GEOMETRY PROBLEM (MDGP): given a weighted undirected graph G = (V, E, d), is there a function $x : G \to \mathbb{R}^3$ such that ||x(u) - x(v)|| = d(u, v) for each $\{u, v\} \in E$?

The atoms are represented by the set of vertices V, the atomic positions by x(v), for $v \in V$, and the inter-atomic distance between u and v is given by d(u, v), for $\{u, v\} \in E$. This problem has been shown to be **NP**-complete via a reduction from Subset-Sum [19], although the problem is solvable in linear

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time when all the inter-atomic distances are known [6]. The MDGP is usually formulated as a continuous nonconvex optimization problem:

$$\min_{x} g(x) = \sum_{\{u,v\} \in E} (||x(u) - x(v)||^2 - d(u,v)^2)^2.$$
 (1)

Obviously, x solves the problem if and only if q(x) = 0.

In practice the MDGP is usually solved via continuous optimization methods. In [8], the molecule is decomposed into clusters; each cluster's 3D structure is determined independently of the others, and then the clusters are recombined. In [13, 14], a Gaussian smoothing of (1) is derived in a closed analytical form depending on a smoothing parameter λ . The proposed algorithm is called Global Continuation Algorithm (GCA): the smoothed problem is locally solved for iteratively increasing values of λ (this brings the smoothed problem closer and closer to the original problem), each local solution process starting from the solution of the previous smoothing. In [1, 2], the MDGP is formulated as a D.C. (difference of convex functions) programming problems and solved using a variant of the D.C. Algorithm (DCA). In [10, 12], two different Variable Neighborhood Search-based algorithms are proposed. One of the most stringent limitations of all these algorithms is the solution accuracy. Because there exist many different spatial conformations having objective function values very near zero, it is important that the optimal solution should have an objective value as close to zero as possible. Continuous optimization methods, by the very limitations of floating point arithmetics, are not well suited to produce extremely accurate values. Two completely different approaches to solving the MDGP are given in [11] (based on quantum computation) and [21] (based on algebraic geometry).

A protein consists of a main backbone (a chain of atoms) and several "dangling" side chains. The NMR technique can of course be applied to proteins in particular, and indeed many of the algorithms to solve the general MDGP have been tested on proteins. However, proteins have a particular structure which makes it possible to formulate the MDGP applied to protein backbones as a discrete search problem: this has an enormous impact on the solution accuracy, as floating point arithmetics calculations are fewer than with continuous search methods. We formalize this by introducing the Discretizable Molecular Distance Geometry Problem (DMDGP), which consists of a certain subset of MDGP instances (to which most protein backbones belong) for which a discrete formulation can be supplied. The determination of the spatial position of the side chains is called the SIDE CHAIN PLACEMENT PROBLEM (SCPP), and its discrete version is known to be NP-complete [17, 18]. Although in this paper we only consider the determination of the protein backbone, it is clear that given a set of likely backbones, some of them can be discarded if the resulting SCPP instance turns out to be infeasible. In this sense, the DMDGP and the SCPP are largely complementary.

DISCRETIZABLE MOLECULAR DISTANCE GEOMETRY PROBLEM (DMDGP): given a weighted undirected graph G=(V,E,d) such that there exists an ordering $v_1,\ldots,v_n\in V$ satisfying the following requirements:

- 1. E contains all cliques on quadruplets of consecutive vertices: $\forall i \in \{4, ..., n\} \ \forall j, k \in \{i-3, ..., i\} \ (\{j, k\} \in E);$
- 2. the following strict triangular inequality holds: $d(v_{i-1}, v_{i+1}) < d(v_{i-1}, v_i) + d(v_i, v_{i+1})$, for i = 2, ..., n-1,

is there a function $x: G \to \mathbb{R}^3$ such that ||x(u) - x(v)|| = d(u, v) for each $\{u, v\} \in E$?

The distances $d(v_{i-1}, v_i)$ are called *bond lengths*, for i = 2, ..., n, and the angles $\theta_{i-2,i}$ between atoms v_{i-2}, v_{i-1}, v_i are called *bond angles*, for i = 3, ..., n (see Fig. 1). The ordering on V is called the *backbone ordering*. Furthermore, we partition E in two sets H and F such that $H = \{\{i, j\} \in E \mid |i - j| \le 4\}$ and $F = E \setminus H$.

In practice, Assumption 1 requires that the bond lengths and angles, as well as the distances between atoms separated by three consecutive bond lengths are known. The distances between atoms separated by two consecutive bond lengths may of course be trivially computed from the bond lengths and angles. Assumption 2 says that no bond angle may be a multiple of π . Assumption 1 is applicable to many proteins as NMR is able to compute distances of atoms which are close together, and groups of four consecutive atoms in the backbone ordering are usually closer than the threshold value of 5Å [4, 20]. Assumption 2 is also applicable to proteins as, to the best of our knowledge, no protein has bond angles of exactly π . In any case, the probability measure of a protein having a bond angle of exactly π is zero.

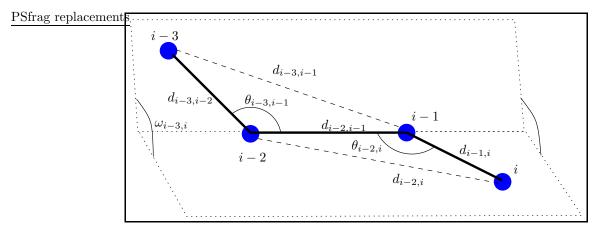


Figure 1: Definitions of bond lengths, bond angles and torsion angles.

We propose an algorithm based on the discrete formulation, called Branch-and-Prune (BP), to solve the DMDGP exactly. The BP algorithm is several orders of magnitude more accurate than other existing algorithms, and usually also much faster. Moreover, other algorithms targeting the MDGP address the question of experimental errors by introducing distance bounds. As it turns out, NMR not only produces systematic measurement errors (which may be dealt with by introducing distance bounds) but also, more importantly, a non-negligible quantity of completely wrong measures [3]. The BP algorithm is able to account for this type of error, and allows for a certain percentage of distances to be completely wrong.

In Section 2, we derive the discrete formulation of the DMDGP. In Section 3, we prove that the DMDGP is **NP**-complete. In Section 4, we discuss the BP algorithm to solve the DMDGP to optimality; Section 4.2 shows how the BP algorithm deals with the two main types of NMR error measurements. In Section 5, we show computational results on some randomly generated instances. Section 6 concludes the paper.

2 Discrete formulation of the MDGP

In what follows, we will restrict our attention to the DMDGP. Notationwise, we indicate $x(v_i)$ by x_i and $d(v_i, v_j)$ by $d_{i,j}$. For all $i \in V$, the neighbourhood $\delta(i)$ of i is the set $\{j \in V \mid \{j, i\} \in E\}$ of vertices adjacent to i. With respect to the order < on V given by the DMDGP definition, we let $\bar{\delta}(i) = \{j \in \delta(i) \mid j < i\}$ for all $i \in V$.

In order to describe a molecule with n atoms, in addition to the bond lengths $d_{i-1,i}$, for $i=2,\ldots,n$, and the bond angles $\theta_{i-2,i}$, for $i=3,\ldots,n$, we also have to consider the torsion angles $\omega_{i-3,i}$, for $i=4,\ldots,n$, which are the angles between the normals through the planes defined by the atoms i-3,i-2,i-1 and i-2,i-1,i (see Fig. 1). However, in most molecular conformation calculations, all the bond lengths and bond angles are assumed to be known a priori. Thus, the first three atoms of the molecule can be fixed and the fourth atom can be determined by the torsion angle $\omega_{1,4}$ (see Fig. 2). The fifth atom can be determined by the torsion angles $\omega_{1,4}$ and $\omega_{2,5}$, and so on.

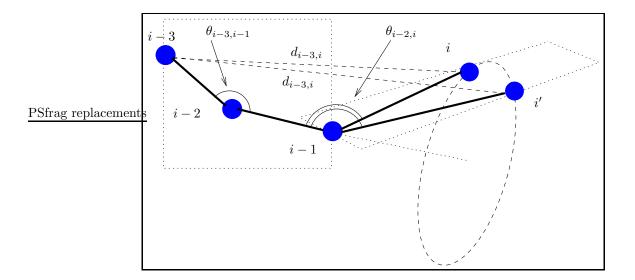


Figure 2: Discretization of the problem. The atom i can only be in the two shown positions (i and i') in order to be feasible with the distance $d_{i-3,i}$.

The geometrical intuition behind the discrete formulation is that the i-th atom lies on the intersection of three spheres centered at atoms i-3, i-2, i-1 and of radii $d_{i-3,i}, d_{i-2,i}, d_{i-1,i}$ respectively. By Assumption 2 and the fact that no two atoms can ever take the same position in space, the intersection of the three spheres defines at most two points (labeled i and i' in Fig. 2). This allows us to express the position of the i-th atom in terms of the preceding three, giving us 2^{n-3} possible molecules. Of course some of these will be infeasible with respect to the distances in F (i.e. distance between atoms which are further apart than 4 units in the backbone ordering), as well as with respect to other constraints (see Sec. 4).

It is known that [15], given all the bond lengths $d_{1,2}, \ldots, d_{n-1,n}$, bond angles $\theta_{13}, \ldots, \theta_{n-2,n}$, and torsion angles $\omega_{1,4}, \ldots, \omega_{n-3,n}$ of a molecule with n atoms, the Cartesian coordinates $(x_{i_1}, x_{i_2}, x_{i_3})$ for each atom i in the molecule can be obtained using the following formulae:

$$\begin{bmatrix} x_{i_1} \\ x_{i_2} \\ x_{i_3} \\ 1 \end{bmatrix} = B_1 B_2 \cdots B_i \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}, \ \forall i = 1, \dots, n,$$

where

$$B_{1} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \quad B_{2} = \begin{bmatrix} -1 & 0 & 0 & -d_{1,2} \\ 0 & 1 & 0 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix},$$

$$B_{3} = \begin{bmatrix} -\cos\theta_{1,3} & -\sin\theta_{1,3} & 0 & -d_{2,3}\cos\theta_{1,3} \\ \sin\theta_{1,3} & -\cos\theta_{1,3} & 0 & d_{2,3}\sin\theta_{1,3} \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix},$$

$$(2)$$

and

$$B_{i} = \begin{bmatrix} -\cos\theta_{i-2,i} & -\sin\theta_{i-2,i} & 0 & -d_{i-1,i}\cos\theta_{i-2,i} \\ \sin\theta_{i-2,i}\cos\omega_{i-3,i} & -\cos\theta_{i-2,i}\cos\omega_{i-3,i} & -\sin\omega_{i-3,i} & d_{i-1,i}\sin\theta_{i-2,i}\cos\omega_{i-3,i} \\ \sin\theta_{i-2,i}\sin\omega_{i-3,i} & -\cos\theta_{i-2,i}\sin\omega_{i-3,i} & \cos\omega_{i-3,i} & d_{i-1,i}\sin\theta_{i-2,i}\sin\omega_{i-3,i} \\ 0 & 0 & 0 & 1 \end{bmatrix}, \quad (3)$$

for i = 4, ..., n.

Since all the bond lengths and bond angles are assumed to be given in the instance, the Cartesian coordinates of all atoms of a molecule can be completely determined by using the values of $\cos \omega_{i-3,i}$ and $\sin \omega_{i-3,i}$, for i=4,...,n.

In order to state that the DMDGP can be formulated as a search in a discrete space, we need the following lemma.

2.1 Lemma

For instances of the DMDGP class, for all i = 4, ..., n, the value of $\cos \omega_{i-3,i}$ can be computed O(1).

Proof. This follows because for every four consecutive atoms $x_{i-3}, x_{i-2}, x_{i-1}, x_i$, the cosine of the torsion angle $\omega_{i-3,i}$, for i = 4, ..., n, is given by

$$\cos \omega_{i-3,i} = \frac{d_{i-3,i-2}^2 + d_{i-2,i}^2 - 2d_{i-3,i-2}d_{i-2,i}\cos\theta_{i-2,i}\cos\theta_{i-1,i+1} - d_{i-3,i}^2}{2d_{i-3,i-2}d_{i-2,i}\sin\theta_{i-2,i}\sin\theta_{i-1,i+1}},$$
(4)

which is just a rearrangement of the cosine law for torsion angles [16] (p. 278), and all the values in the expression (4) are given in the instance. We note in passing that in order for the above reasoning to hold, we obviously need the denominator of (4) to be nonzero. \Box

2.2 Theorem

Given a weighted undirected graph G = (V, E, d) associated to an instance of the DMDGP, the number of functions $x : G \to \mathbb{R}^3$ such that ||x(u) - x(v)|| = d(u, v) for each $\{u, v\} \in E$ is finite, up to orthogonality transformations.

Proof. The proof is by induction. For a molecule with 4 atoms, we can use the bond lengths $d_{1,2}, d_{2,3}$ and the bond angle $\theta_{1,3}$, in order to determine the matrices B_2 and B_3 , defined in (2), and obtain

$$x_{1} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix},$$

$$x_{2} = \begin{pmatrix} -d_{1,2} \\ 0 \\ 0 \end{pmatrix},$$

$$x_{3} = \begin{pmatrix} -d_{1,2} + d_{2,3}\cos\theta_{1,3} \\ d_{2,3}\sin\theta_{1,3} \\ 0 \end{pmatrix},$$

fixing the first three atoms of the molecule. Since we also know the distance $d_{1,4}$, by Lemma 2.1 we can obtain the value of $\cos \omega_{1,4}$. Thus, the sine of the torsion angle $\omega_{1,4}$ can have only two possible values: $\sin \omega_{1,4} = \pm \sqrt{1 - \cos^2 \omega_{1,4}}$. Consequently, by (3), we obtain only two possible positions x_4, x_4' for the fourth atom of the molecule, given by

$$x_4 = \begin{bmatrix} -d_{1,2} + d_{2,3}\cos\theta_{1,3} - d_{3,4}\cos\theta_{1,3}\cos\theta_{2,4} + d_{3,4}\sin\theta_{1,3}\sin\theta_{2,4}\cos\omega_{1,4} \\ d_{2,3}\sin\theta_{1,3} - d_{3,4}\sin\theta_{1,3}\cos\theta_{2,4} - d_{3,4}\cos\theta_{1,3}\sin\theta_{2,4}\cos\omega_{1,4} \\ d_{3,4}\sin\theta_{2,4}\left(\sqrt{1-\cos^2\omega_{1,4}}\right) \end{bmatrix},$$

$$x_4' = \begin{bmatrix} -d_{1,2} + d_{2,3}\cos\theta_{1,3} - d_{3,4}\cos\theta_{1,3}\cos\theta_{2,4} + d_{3,4}\sin\theta_{1,3}\sin\theta_{2,4}\cos\omega_{1,4} \\ d_{2,3}\sin\theta_{1,3} - d_{3,4}\sin\theta_{1,3}\cos\theta_{2,4} - d_{3,4}\cos\theta_{1,3}\sin\theta_{2,4}\cos\omega_{1,4} \\ d_{3,4}\sin\theta_{2,4}\left(-\sqrt{1-\cos^2\omega_{1,4}}\right) \end{bmatrix}.$$

Now suppose that for $i \ge 4$ atoms, we have a finite number of solutions to the DMDGP instance. Adding one more atom in the molecule and using Lemma 2.1 again, we can obtain the value of $\cos \omega_{i-2,i+1}$. From each solution of the molecule with i atoms, at most two new solutions can be obtained by using $\sin \omega_{i-2,i+1} = \pm \sqrt{1 - \cos^2 \omega_{i-2,i+1}}$ in matrix B_{i+1} , given in (3). This concludes the proof.

An immediate corollary is given below.

2.3 Corollary

For an instance of the DMDGP class with $n \ge 4$ atoms, there are at most 2^{n-3} possible solutions.

Note that each possible solution of the DMDGP is defined by a sequence of torsion angles $\omega_{1,4}, \ldots, \omega_{n-3,n}$. By using the matrices B_i (3), this sequence can be converted into another one of Cartesian coordinates $x = (x_1, \ldots, x_n) \in \mathbb{R}^{3n}$ and, using the objective function g defined in (1), a solution can be identified simply by testing if g(x) = 0.

2.1 Solution symmetry

In this section, we show that there is a solution symmetry around the plane defined by the first three atoms; more precisely, any solution on one side of this plane gives rise to a symmetrical solution on the other side. This allows us to reduce computational costs by half. First, we need two lemmata.

2.4 Lemma

Let the matrix Q_i be defined by

$$Q_i = B_4 \cdots B_i,$$

for i = 4, ..., n, where its elements are denoted by

$$Q_i = \left[egin{array}{cccc} q_{11}^i & q_{12}^i & q_{13}^i & q_{14}^i \ q_{21}^i & q_{22}^i & q_{23}^i & q_{24}^i \ q_{31}^i & q_{32}^i & q_{33}^i & q_{34}^i \ 0 & 0 & 0 & 1 \end{array}
ight].$$

If we invert the sign of $\sin \omega_{i-3,i}$ in all the matrices B_i (3), for i=4,...,n, and denote the new matrices obtained by B'_i , then the elements of the matrix Q'_i , defined by

$$Q'_i = B'_1 \cdots B'_i$$

is given by

$$Q_i' = \left[\begin{array}{cccc} q_{11}^i & q_{12}^i & -q_{13}^i & q_{14}^i \\ q_{21}^i & q_{22}^i & -q_{23}^i & q_{24}^i \\ -q_{31}^i & -q_{32}^i & q_{33}^i & -q_{34}^i \\ 0 & 0 & 0 & 1 \end{array} \right],$$

for i = 4, ..., n.

Proof. The proof is by induction. For n = 4, we obtain:

$$Q_4 = \begin{bmatrix} -\cos\theta_{2,4} & -\sin\theta_{2,4} & 0 & -d_{3,4}\cos\theta_{2,4} \\ \sin\theta_{2,4}\cos\omega_{1,4} & -\cos\theta_{2,4}\cos\omega_{1,4} & -\sin\omega_{1,4} & d_{3,4}\sin\theta_{2,4}\cos\omega_{1,4} \\ \sin\theta_{2,4}\sin\omega_{1,4} & -\cos\theta_{2,4}\sin\omega_{1,4} & \cos\omega_{1,4} & d_{3,4}\sin\theta_{2,4}\sin\omega_{1,4} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

and

$$Q_4' = \begin{bmatrix} -\cos\theta_{2,4} & -\sin\theta_{2,4} & 0 & -d_{3,4}\cos\theta_{2,4} \\ \sin\theta_{2,4}\cos\omega_{1,4} & -\cos\theta_{2,4}\cos\omega_{1,4} & -(-\sin\omega_{1,4}) & d_{3,4}\sin\theta_{2,4}\cos\omega_{1,4} \\ \sin\theta_{2,4} \left(-\sin\omega_{1,4} \right) & -\cos\theta_{2,4} \left(-\sin\omega_{1,4} \right) & \cos\omega_{1,4} & d_{3,4}\sin\theta_{2,4} \left(-\sin\omega_{1,4} \right) \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

Suppose now that the assertion is valid for n = i - 1. Rewritting Q_i , we get

$$Q_i = (B_4 \cdots B_{i-1})B_i$$
$$= Q_{i-1}B_i,$$

where the elements of Q_{i-1} are denoted by

$$Q_{i-1} = \begin{bmatrix} q_{11}^{i-1} & q_{12}^{i-1} & q_{13}^{i-1} & q_{14}^{i-1} \\ q_{21}^{i-1} & q_{22}^{i-1} & q_{23}^{i-1} & q_{24}^{i-1} \\ q_{31}^{i-1} & q_{32}^{i-1} & q_{33}^{i-1} & q_{34}^{i-1} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

and

$$B_i = \begin{bmatrix} -\cos\theta_{i-2,i} & -\sin\theta_{i-2,i} & 0 & -d_{i-1,i}\cos\theta_{i-2,i} \\ \sin\theta_{i-2,i}\cos\omega_{i-3,i} & -\cos\theta_{i-2,i}\cos\omega_{i-3,i} & -\sin\omega_{i-3,i} & d_{i-1,i}\sin\theta_{i-2,i}\cos\omega_{i-3,i} \\ \sin\theta_{i-2,i}\sin\omega_{i-3,i} & -\cos\theta_{i-2,i}\sin\omega_{i-3,i} & \cos\omega_{i-3,i} & d_{i-1,i}\sin\theta_{i-2,i}\sin\omega_{i-3,i} \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

Considering the product $Q_{i-1}B_i$, we obtain

$$Q_{i-1}B_i = \left[\begin{array}{cccc} V & X & Y & Z \\ 0 & 0 & 0 & 1 \end{array} \right],$$

where

$$V \ = \ \begin{bmatrix} q_{11}^{i-1}(-b) + q_{12}^{i-1}(cd) + q_{13}^{i-1}(ce) \\ q_{21}^{i-1}(-b) + q_{22}^{i-1}(cd) + q_{23}^{i-1}(ce) \\ q_{31}^{i-1}(-b) + q_{32}^{i-1}(cd) + q_{33}^{i-1}(ce) \end{bmatrix},$$

$$X \ = \ \begin{bmatrix} q_{11}^{i-1}(-c) + q_{12}^{i-1}(-bd) + q_{13}^{i-1}(-be) \\ q_{21}^{i-1}(-c) + q_{22}^{i-1}(-bd) + q_{23}^{i-1}(-be) \\ q_{31}^{i-1}(-c) + q_{32}^{i-1}(-bd) + q_{33}^{i-1}(-be) \end{bmatrix},$$

$$Y \ = \ \begin{bmatrix} q_{12}^{i-1}(-e) + q_{13}^{i-1}(d) \\ q_{22}^{i-1}(-e) + q_{23}^{i-1}(d) \\ q_{22}^{i-1}(-e) + q_{33}^{i-1}(d) \\ q_{33}^{i-1}(-c) + q_{33}^{i-1}(ac) + q_{13}^{i-1}(ace) + q_{14}^{i-1} \\ q_{21}^{i-1}(-ab) + q_{12}^{i-1}(acd) + q_{13}^{i-1}(ace) + q_{14}^{i-1} \\ q_{21}^{i-1}(-ab) + q_{32}^{i-1}(acd) + q_{33}^{i-1}(ace) + q_{34}^{i-1} \end{bmatrix},$$

and $a = d_{i-1,i}$, $b = \cos \theta_{i-2,i}$, $c = \sin \theta_{i-2,i}$, $d = \cos \omega_{i-3,i}$, and $e = \sin \omega_{i-3,i}$.

By induction hypothesis, we have

$$Q_{i-1}' = \left[\begin{array}{cccc} q_{11}^{i-1} & q_{12}^{i-1} & -q_{13}^{i-1} & q_{14}^{i-1} \\ q_{21}^{i-1} & q_{22}^{i-1} & -q_{23}^{i-1} & q_{24}^{i-1} \\ -q_{31}^{i-1} & -q_{32}^{i-1} & q_{33}^{i-1} & -q_{34}^{i-1} \\ 0 & 0 & 0 & 1 \end{array} \right].$$

Considering the product $Q'_{i-1}B'_i$, where

$$B_{i}' = \begin{bmatrix} -\cos\theta_{i-2,i} & -\sin\theta_{i-2,i} & 0 & -d_{i-1,i}\cos\theta_{i-2,i} \\ \sin\theta_{i-2,i}\cos\omega_{i-3,i} & -\cos\theta_{i-2,i}\cos\omega_{i-3,i} & -(-\sin\omega_{i-3,i}) & d_{i-1,i}\sin\theta_{i-2,i}\cos\omega_{i-3,i} \\ \sin\theta_{i-2,i}(-\sin\omega_{i-3,i}) & -\cos\theta_{i-2,i}(-\sin\omega_{i-3,i}) & \cos\omega_{i-3,i} & d_{i-1,i}\sin\theta_{i-2,i}(-\sin\omega_{i-3,i}) \\ 0 & 0 & 0 & 1 \end{bmatrix},$$

we obtain

$$Q_{i-1}'B_i' = \left[\begin{array}{cccc} V' & X' & Y' & Z' \\ 0 & 0 & 0 & 1 \end{array} \right],$$

where

$$\begin{array}{lll} V' & = & \left[\begin{array}{c} q_{11}^{i-1}(-b) + q_{12}^{i-1}(cd) - q_{13}^{i-1}(c(-e)) \\ q_{21}^{i-1}(-b) + q_{22}^{i-1}(cd) - q_{23}^{i-1}(c(-e)) \\ -q_{31}^{i-1}(-b) - q_{32}^{i-1}(cd) + q_{33}^{i-1}(c(-e)) \end{array} \right], \\ X' & = & \left[\begin{array}{c} q_{11}^{i-1}(-c) + q_{12}^{i-1}(-bd) - q_{13}^{i-1}(-b(-e)) \\ q_{21}^{i-1}(-c) + q_{22}^{i-1}(-bd) - q_{23}^{i-1}(-b(-e)) \\ -q_{31}^{i-1}(-c) - q_{32}^{i-1}(-bd) + q_{33}^{i-1}(-b(-e)) \end{array} \right], \\ Y' & = & \left[\begin{array}{c} q_{12}^{i-1}(e) - q_{13}^{i-1}(d) \\ q_{22}^{i-1}(e) - q_{23}^{i-1}(d) \\ -q_{32}^{i-1}(e) + q_{33}^{i-1}(d) \end{array} \right], \\ -q_{32}^{i-1}(e) + q_{33}^{i-1}(d) \\ -q_{32}^{i-1}(ac) + q_{12}^{i-1}(acd) - q_{13}^{i-1}(ac(-e)) + q_{14}^{i-1} \\ q_{21}^{i-1}(-ab) + q_{22}^{i-1}(acd) - q_{23}^{i-1}(ac(-e)) + q_{24}^{i-1} \\ -q_{31}^{i-1}(-ab) - q_{32}^{i-1}(acd) + q_{33}^{i-1}(ac(-e)) - q_{34}^{i-1} \end{array} \right]. \end{array}$$

Representing the matrix Q_i by

$$Q_i = Q_{i-1}B_i = \begin{bmatrix} q_{11}^i & q_{12}^i & q_{13}^i & q_{14}^i \\ q_{21}^i & q_{22}^i & q_{23}^i & q_{24}^i \\ q_{31}^i & q_{32}^i & q_{33}^i & q_{34}^i \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

and comparing the matrices $Q_{i-1}B_i$ and $Q'_{i-1}B'_i$ given above, we conclude that

$$Q_i' = Q_{i-1}'B_i' = \begin{bmatrix} q_{11}^i & q_{12}^i & -q_{13}^i & q_{14}^i \\ q_{21}^i & q_{22}^i & -q_{23}^i & q_{24}^i \\ -q_{31}^i & -q_{32}^i & q_{33}^i & -q_{34}^i \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

2.5 Lemma

Le $x_1, \ldots, x_n \in \mathbb{R}^3$ be the Cartesian coordinates associated to the torsion angles $\omega_{1,4}, \ldots, \omega_{n-3,n}$. If we invert the sign of $\sin \omega_{i-3,i}$ in all the matrices B_i (3), for $i=4,\ldots,n$, then the new Cartesian coordinates $x'_1,\ldots,x'_n \in \mathbb{R}^3$ is given by

$$\begin{bmatrix} x'_{i_1} \\ x'_{i_2} \\ x'_{i_3} \end{bmatrix} = \begin{bmatrix} x_{i_1} \\ x_{i_2} \\ -x_{i_3} \end{bmatrix},$$

for i = 1, ..., n.

Proof. For n = 1, 2, 3 the assertion is clearly true. By the lemma above, we have

$$\begin{bmatrix} x_{i_1} \\ x_{i_2} \\ x_{i_3} \\ 1 \end{bmatrix} = B_1 B_2 B_3 Q_i \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} = B_1 B_2 B_3 \begin{bmatrix} q_{14}^i \\ q_{24}^i \\ q_{34}^i \\ q_{34}^i \end{bmatrix}$$

and

$$\begin{bmatrix} x'_{i_1} \\ x'_{i_2} \\ x'_{i_3} \\ 1 \end{bmatrix} = B_1 B_2 B_3 Q'_i \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} = B_1 B_2 B_3 \begin{bmatrix} q^i_{14} \\ q^i_{24} \\ -q^i_{34} \\ 1 \end{bmatrix},$$

for i = 4, ..., n, and calculating the product $B_1B_2B_3$, we obtain

$$B_1 B_2 B_3 = \begin{bmatrix} \cos \theta_{1,3} & \sin \theta_{1,3} & 0 & -d_{1,2} + d_{2,3} \cos \theta_{1,3} \\ \sin \theta_{1,3} & -\cos \theta_{1,3} & 0 & d_{2,3} \sin \theta_{1,3} \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

Thus,

$$\begin{bmatrix} x_{i_1} \\ x_{i_2} \\ x_{i_3} \\ 1 \end{bmatrix} = B_1 B_2 B_3 \begin{bmatrix} q_{14}^i \\ q_{24}^i \\ q_{34}^i \\ 1 \end{bmatrix} = \begin{bmatrix} -d_{1,2} + q_{14}^i \cos \theta_{1,3} + q_{24}^i \sin \theta_{1,3} + d_{2,3} \cos \theta_{1,3} \\ q_{14}^i \sin \theta_{1,3} - q_{24}^i \cos \theta_{1,3} + d_{2,3} \sin \theta_{1,3} \\ -q_{34}^i \\ 1 \end{bmatrix}$$

and

$$\begin{bmatrix} x'_{i_1} \\ x'_{i_2} \\ x'_{i_3} \\ 1 \end{bmatrix} = B_1 B_2 B_3 \begin{bmatrix} q^i_{14} \\ q^i_{24} \\ -q^i_{34} \\ 1 \end{bmatrix} = \begin{bmatrix} -d_{1,2} + q^i_{14} \cos \theta_{1,3} + q^i_{24} \sin \theta_{1,3} + d_{2,3} \cos \theta_{1,3} \\ q^i_{14} \sin \theta_{1,3} - q^i_{24} \cos \theta_{1,3} + d_{2,3} \sin \theta_{1,3} \\ q^i_{34} \\ 1 \end{bmatrix},$$

for i = 4, ..., n. That is,

$$\begin{bmatrix} x'_{i_1} \\ x'_{i_2} \\ x'_{i_3} \end{bmatrix} = \begin{bmatrix} x_{i_1} \\ x_{i_2} \\ -x_{i_3} \end{bmatrix},$$

for i=1,...,n.

Finally, we can prove the following theorem.

2.6 Theorem

Consider a solution $x: G \to \mathbb{R}^3$ for the DMDGP, defined by the torsion angles $\omega_{1,4}, \ldots, \omega_{n-3,n}$. If we invert the sign of $\sin \omega_{i-3,i}$ in all the matrices B_i (3), for i=4,...,n, we obtain a new solution $x': G \to \mathbb{R}^3$ for the DMDGP.

Proof. Le $x_1, \ldots, x_n \in \mathbb{R}^3$ be the Cartesian coordinates associated to the torsion angles $\omega_{1,4}, \ldots, \omega_{n-3,n}$, $x'_1, \ldots, x'_n \in \mathbb{R}^3$ be the Cartesian coordinates of the new solution obtained by inverting the sign of $\sin \omega_{i-3,i}$ in all the matrices B_i , for $i=4,\ldots,n$, and $R:\mathbb{R}^3\to\mathbb{R}^3$ be the function defined by

$$R(x_{i_1}, x_{i_2}, x_{i_3}) = (x_{i_1}, x_{i_2}, -x_{i_3}).$$

Since R is a unitary operator,

$$||x_i - x_j|| = ||R(x_i) - R(x_j)|| \quad \forall (i, j) \in E,$$
(5)

where E is the set of pairs of atoms (i, j) whose Euclidean distances $d_{i,j}$ are known for the solution x. By the Lemma 2.4.,

$$||R(x_i) - R(x_j)|| = ||x_i' - x_j'|| \quad \forall (i, j) \in E.$$
(6)

Since x_1, \ldots, x_n is a solution for the DMDGP,

$$||x_i - x_j|| = d_{i,j} \quad \forall (i,j) \in E.$$

Thus, by (5) and (6), we get

$$||x_i' - x_j'|| = d_{i,j} \ \forall (i,j) \in E,$$

stating that x'_1, \ldots, x'_n is also a solution for the DMDGP.

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2.2Undiscretizable instances

As has been remarked, all DMDGP instances must obey a strict triangular inequality. When this does not hold, there may be bond angles with values $k\pi$ for $k \in \mathbb{Z}$. By (4), the torsion angle is undefined. Since the torsion angle is the angle between two normal vectors to given planes, it is undefined when at least one of the planes is undefined. This is indeed possible if the two vectors defining the plane are collinear. In other words, if a bond angle is a multiple of π , we have the situation depicted in Fig. 3, where $d_{i-3,i}$ is feasible for every position of atom i+3 on the circle shown in the drawing.

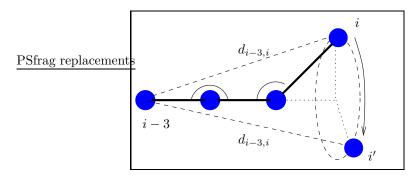


Figure 3: An instance which cannot be discretized. The i-th atom can be on any position on the circle shown without affecting the feasibility of the distance $d_{i-3,i}$.

Since the set $\{\pi\}$ has measure 0 in $[0,2\pi]$, the probability that any given protein gives rise to an undiscretizable instance is 0. To the best of our knowledge, no protein has bond angles of exactly π .

3 Complexity

In this section we show that the DMDGP is **NP**-complete by reducing it from the Subset-Sum problem.

Subset-Sum. Given integers a_1, \ldots, a_n , is there is a partition into two sets, encoded by $s \in \{-1, +1\}^n$, such that each subset has the same sum, i.e. $\sum_{i=1}^n s(i)a_i = 0$?

The MDGP is shown to be **NP**-complete in [19] (a helpful sketch of the proof is given in [13]) by reducing Subset-Sum to a 1-dimensional MDGP with distance constraints between successive atom (in an arbitrary atomic ordering) plus a single distance constraint between the first and last atom, forcing this distance to be zero. In the DMDGP however, we have additional distance constraints between any pairs of atoms 1, 2 or 3 indices apart in the atom sequence.

3.1 Theorem

The DMDGP is **NP**-complete.

Proof. We reduce from Subset-Sum. Given an instance a_1, \ldots, a_n of the latter, we define an instance of DMDGP on 3n + 1 points numbered 0 to 3n, with the following distance constraints:

$$d_{i,i+1} = a_{\lfloor i/3 \rfloor} \qquad \forall i \in \{1, ..., 3n-1\}$$

$$(7)$$

$$d_{i,i+1} = d_{\lfloor i/3 \rfloor} \qquad \forall i \in \{1, ..., 3n-1\}$$

$$d_{i,i+2} = \sqrt{d_{i,i+1}^2 + d_{i+1,i+2}^2} \qquad \forall i \in \{1, ..., 3n-2\}$$
(8)

$$d_{i,i+2} = \sqrt{d_{i,i+1}^2 + d_{i+1,i+2}^2} \qquad \forall i \in \{1, ..., 3n-2\}$$

$$d_{i,i+3} = \sqrt{d_{i,i+1}^2 + d_{i+1,i+2}^2 + d_{i+2,i+3}^2} \qquad \forall i \in \{1, ..., 3n-3\}$$

$$(9)$$

$$d_{0,3n} = 0 (10)$$

Now we claim that the Subset-Sum instance is has a solution iff the DMDGP instance has a solution.

For the easy direction, let $s \in \{-1, +1\}^n$ be a solution to the Subset-Sum-problem. We define the 3n+1 points as follows: $x_0 = (0,0,0)$ and for every $0 < i \le 3n$ with i = 3k+j we set $x_i = x_{i-1} + s_k a_k e_j$, where $e_0 = (1,0,0), e_1 = (0,1,0)$ and $e_2 = (0,0,1)$. By straightforward inspection this is a solution to the DMDGP instance.

For the other direction, let us assume that the DMDGP instance has a solution $x(v_1), \ldots, x(v_n)$. Without loss of generality we can assume that the $x(v_1) = (0,0,0)$, and that $x(v_2)$ lays on the x-axis. Now equation (8) implies that the bond angle between $x(v_1), x(v_2), x(v_3)$ is $\frac{\pi}{2}$. Again, without loss of generality assume that the second segment is parallel to the y-axis. By equation (9) there are only two possibilities for $x(v_4)$, and they force the third bond to be parallel to the z-axis. The same arguments apply to all other bonds, which shows that the bond β between v_{i-1} and v_i is parallel to the (i mod 3)-th axis (where x = 0, y = 1, z = 2). Now give the bond β an orientation from v_{i-1} to v_i (which can either be in the same or in the opposite direction of this axis). We define a sign vector $s \in \{-1, +1\}^{3n}$, which encodes these orientations. In this setting, point 3n + 1 has coordinates (x, y, z) defined by

$$x = \sum_{i \text{ mod } 3=0} s_i a_i$$
$$y = \sum_{i \text{ mod } 3=1} s_i a_i$$
$$z = \sum_{i \text{ mod } 3=2} s_i a_i$$

By equation (7) we actually have (x, y, z) = (0, 0, 0). Now let s^0, s^1, s^2 be three vectors from $\{-1, +1\}^n$, which are s restricted to indices $i \mod 3 = 0$, $i \mod 3 = 1$ or $i \mod 3 = 2$ respectively. Then any of those is a solution to the original Subset-Sum problem by the previous equations.

It is interesting to note that Assumption 1 is, in a certain sense, the tightest possible for the problem to be **NP**-complete. Assumption 1 states that each quadruplet of consecutive vertices in the defined order is a clique in the distance graph. Tightening the assumption further, we might ask whether the problem would still be **NP**-complete if each quintuplet of consecutive vertices were a clique. This, however, fails to be the case. A trilateration graph in \mathbb{R}^D is a graph with an order (v_1, \ldots, v_n) on the vertices such for all vertices v_i with i > D+1, $\{j, i\} \in E$ for all $j \in \{i-D-2, \ldots, i-1\}$ (i.e. each vertex is adjacent to the preceding D+1 vertices). In three-dimensional space, this implies having distances to at least 4 vertices earlier in the order, which means having a clique for each consecutive quintuplet. By [7] (Theorem 9), the MDGP problem associated to a trilateration graph can be solved in polynomial time.

4 Branch-and-Prune algorithm

In this section we present a Branch-and-Prune (BP) algorithm for the DMDGP. The approach mimicks the structure of the problem closely: at each step we can place the i-th atom in two possible positions x_i, x_i' . However, either or both of these positions may be infeasible with respect to a number of constraints. The search is branched on all atomic positions which are feasible with respect to all constraints; by contrast, if a position is not feasible the search scope is pruned. In this context we call the feasibility verifications pruning tests. The simplest (but very effective) type of these is the Direct Distance Feasibility (DDF) pruning tests: for all distance pairs $\{j,i\} \in F$ (with j < i-4, see Sec. 1, p. 2) we check that $(||x_j - x_i||^2 - d_{j,i}^2)^2 < \varepsilon$, where $\varepsilon > 0$ is a given tolerance. If the inequality does not hold, we prune the search node.

The BP algorithm is therefore an algorithmic framework whose definition is completed by expliciting the pruning tests. These can be of geometrical or of physical-chemical nature. These can be of geometrical or of physical-chemical nature. Apart from the DDF pruning tests, many other tests are possible; a few of them are discussed below. This algorithm, as described, will find all solutions to the problem. If we are interested in one solution only, we can stop the search as soon as we have placed the last atom in a feasible position.

4.1 Algorithmic Framework

Let T be a graph representation of the search tree. Initially, T is initialized to the search nodes $1 \to 2 \to 3 \to 4$ (no branching) since the first three atoms can be fixed to feasible positions x_1, x_2, x_3 and the fourth atom x_4 can be fixed to any of its two possible positions by Theorem 2.6. By the current rank of the search tree we mean the index of the atom being placed at the current node. At each search tree node of rank i we store:

- the position $x_i \in \mathbb{R}^3$ of the *i*-th atom;
- the cumulative product $Q_i = \prod_{j=1}^i B_j$ of the torsion matrices;
- a pointer to the parent node P(i);
- pointers to the subnodes L(i), R(i) (initialized to a dummy value PRUNED if infeasible).

Notice that the edge structure of the graph T is encoded in the operators P(), L(), R() defined at each node. The recursive procedure at rank i-1 is given in Algorithm 1. Let $y = (0,0,0,1)^{\top}$, $\varepsilon > 0$ a given tolerance and v a node with rank i-1 in the search tree T.

Algorithm 1 BP algorithm.

```
0: BranchAndPrune(T, v, i)
  if (i \le n-1) then
    Compute the possible placements for i-th atom:
    calculate the torsion matrices B_i, B'_i via Eq. (3);
    retrieve the cumulative torsion matrix Q_{i-1} from the parent node P(v);
    compute Q_i = Q_{i-1}B_i, Q'_i = Q_{i-1}B'_i and x_i, x'_i from Q_iy, Q'_iy;
    let \lambda = 1, \rho = 1;
    PRUNING TESTS:
    if (x_i \text{ is feasible}) then
       create a node z, store Q_i and x_i in z, let P(z) = v and L(v) = z;
       set T \leftarrow T \cup \{z\};
       BranchAndPrune(T, z, i + 1);
       set L(v) = PRUNED;
    end if
    if (x_i') is feasible) then
       create a node z', store Q_i and x_i in z', let P(z) = v and R(v) = z';
       set T \leftarrow T \cup \{z'\};
       BranchAndPrune(T, z', i + 1);
       set R(v) = PRUNED;
    end if
    Rank n reached, a solution was found:
    solution stored in parent nodes ranked n to 1, output by back-traversal;
  end if
```

4.2 Pruning tests and error tolerance

There are two types of experimental errors arising from NMR distance measurements: (i) systematic uncertainty on each measurement, and (ii) a certain percentage of completely wrong measurements [3]. Errors of the first type are usually dealt with by introducing distance bounds [14], which the BP algorithm can take into account without any problem. To the best of our knowledge, errors of the second type have only been tackled by the Error Correcting Code (ECC) proposed in [3]. Naturally, this ECC can (and should) be applied to the protein backbone distance matrix as a preprocessing step to running the BP algorithm. On top of this, however, many of the pruning tests are "natively" suited for attempting to correct this type of error probabilistically, if a measure of the infeasibility is provided by the test. We only show here how to adapt the DDF tests for the two types of NMR errors.

If we consider distance bounds like $d_{ji}^L \leq d_{ji} \leq d_{ji}^U$ for each $\{j,i\} \in F$ we simply have to modify the pruning tests as follows. Placing atom i at search node v, for $j \in \bar{\delta}(i) \cap F$,

- 1. for L(v): if $d_{ii}^L \leq ||x_j x_i|| \leq d_{ii}^U$ then x_i is feasible, else it must be pruned;
- 2. for R(v): if $d_{ji}^L \leq ||x_j x_i'|| \leq d_{ji}^U$ then x_i' is feasible, else it must be pruned.

As for the errors of the second type, let 100p (with $p \in [0,1]$) be the known average percentage of completely wrong measurements. We deal with these in a probabilistic way: suppose we are positioning the *i*-th atom in position x_i , w.l.o.g. at the left node L(v) (the reasoning for the right node is the same). A distance d_{ji} is infeasible for x_i if the corresponding Pruning test for L(v) fails. We prune L(v) from the search tree only if more than $p|\bar{\delta}(i) \cap F|$ distances are infeasible for L(v). The downside of this method is that it may introduce some false positives in the solution set.

4.3 Euclidean bounds pruning tests

These tests employ the fact that inter-atomic distances are assumed to be Euclidean. Much like the pruning of the search scope in point-to-point Dijkstra shortest-path searches on Euclidean graphs, we can prune away an atomic position i if it is too far with respect to the given distances. Consider atoms h, i, k with h < i < k such that $\{h, k\} \in E$ (so that d_{hk} is known). Assume that the BP has already placed atom h, and that we are now verifying feasibility for atom i. Let D(i, k) be an upper bound to the distance $||x_i - x_k||$ for all possible immersions $x : G \to \mathbb{R}^3$ which are feasible DMDGP solutions.

4.1 Lemma

If $D(i,k) < ||x_h - x_i|| - d_{hk}$ for all feasible $x : G \to \mathbb{R}^3$, then the BP search node for atomic position x_i can be pruned.

Proof. Suppose, to get a contradiction, that position x_i is feasible for the DMDGP instance being solved. By definition, $D(i,k) \ge ||x_i - x_k||$. Since distances are Euclidean, $||x_i - x_k|| \ge ||x_h - x_i|| - ||x_h - x_k||$. Hence $D(i,k) \ge ||x_h - x_i|| - d_{hk} > D(i,k)$, which is a contradiction.

By Prop. 4.1, every upper bound D(i,k) to the distance $||x_i - x_k||$ provides a valid pruning test. Furthermore, in all Euclidean graphs the Euclidean distance between two vertices is a lower bound to the cost of all paths joining the two vertices in the graph. We therefore let D(i,k) be the cost of the shortest path from i to k in G, which provides a valid pruning test.

4.4 Continuous optimization-based pruning tests

Global optimization techniques for the smooth nonconvex formulation (1) of the MDGP [8, 13, 14, 10, 12] can be employed to verify that the current backbone is feasible. As most of these techniques are usually computationally expensive, this type of pruning tests may only be performed once in a while. Although the GCA [13, 14] scores the best computation times, it usually provides solutions of rather low accuracy, so it may not be the best candidate.

4.5 Physical-chemical pruning tests

As mentioned in the introduction, a SCPP can be solved for every backbone in order to try to place the side-chain residues onto the backbone. If the SCPP is infeasible, this means that the backbone is also infeasible. Therefore, for every partial backbone we can try to solve the associated SCPP to attempt to prune some search branches. Since the SCPP is **NP**-complete (hence its solution may be computationally very expensive), this type of pruning tests should only be performed once in a while.

Other types of physical-chemical pruning tests can be devised on a per-molecule basis.

4.6 Detailed example

In this section we discuss the application of Algorithm 1 to a simple example (artificially generated as explained in [9], also see Section 5.3).

The instance in question (called lavor11_7), with all bond angles set to 1.91 radians, has 11 atoms:

```
\begin{array}{lcl} \delta(2) \cup F &=& \{9\}, d_2^F = (3.387634917) \\ \delta(3) \cup F &=& \{8,9,10\}, d_3^F = (3.96678038, 3.003368265, 3.796280236) \\ \delta(4) \cup F &=& \{8,9,10\}, d_4^F = (2.60830758, 2.102385055, 3.159309539) \\ \delta(5) \cup F &=& \{9,10\}, d_5^F = (2.689078459, 3.132251169) \\ \delta(6) \cup F &=& \{10\}, d_6^F = (3.557526815) \\ \delta(7) \cup F &=& \{11\}, d_7^F = (3.228657023). \end{array}
```

The distances in H are of course $\delta(i) \cup H = \{i+1, i+2, i+3\}$ for all $i \leq n-3$, $\delta(n-2) \cup H = \{n-1, n\}$, $\delta(n-1) \cup H = \{n\}$. The vector of the distances in H is:

```
\begin{array}{ll} d^{H} & = & (1.526, 2.491389536, 3.83929637, \\ & & 1.526, 2.491389536, 3.831422399, \\ & & 1.526, 2.491389536, 3.835602674, \\ & & 1.526, 2.491389535, 3.030585263, \\ & & 1.526, 2.491389534, 2.899348439, \\ & & 1.526, 2.491389536, 2.788611167, \\ & & 1.526, 2.491389536, 2.888815709, \\ & & 1.526, 2.491389537, \\ & & 1.526, 2.491389537, \\ & & 1.526). \end{array}
```

As can be seen from the BP tree given in Fig. 4 (this is actually the output of Algorithm 1 on the given instance), this instance has four solutions: the leaf nodes at rank 11 — the rank is given by the number of the leftmost node in each row. Notice that the earliest node when some pruning occurs is at rank 7, i.e. no pruning occurs before the placement of the 8-th atom. This happens because there are no distances

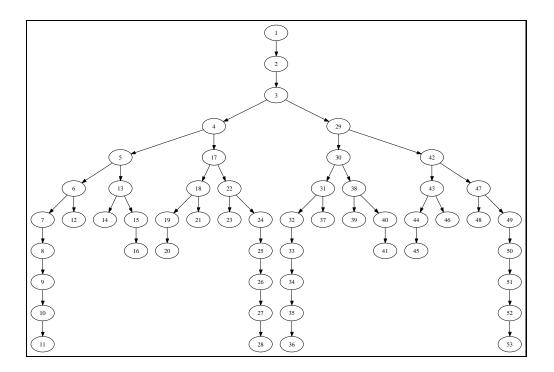


Figure 4: The BP tree of the instance of Section 4.6.

 $\{j,k\} \in F$ with k < 8, so each position for atoms with index i < 8 is feasible (by construction of x_i, x_i') with the distances in F. Again, there is pruning at ranks 8, 9, 10, i.e. during the placement of atoms 9, 10, 11, because there are distances $\{j,k\} \in F$ with k = 9, 10, 11. One of the solutions is shown in Fig. 5.

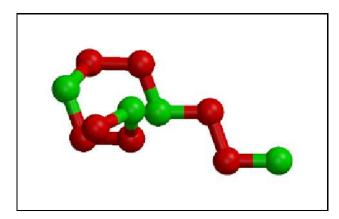


Figure 5: One of the possible solutions of the lavor11_7 instance.

5 Computational Results

In order to test the viability of the proposed method, we tested a class of randomly generated MDGP instances described in [9]. We present comparative results of BP (where only the DDF pruning tests have been implemented) and another existing MDGP software called dgsol implementing the GCA [14]. It turns out that BP is always superior to dgsol for solution accuracy, generally superior as regards speed,

and inferior as regards memory requirements. It is fair to remark here that the GCA is able to solve the MDGP, whereas BP is limited to solving the DMDGP only. In this sense the present comparison is not completely fair to GCA.

5.1 Software testbeds

The software code dgsol [14] (version 1.3) can be freely downloaded from

```
http://www.mcs.anl.gov/~more/dgsol/.
```

The algorithm implemented by the dgsol code is very different from ours. First, it targets a more general problem class: the Molecular Distance Geometry Problem with Distance Bounds. In this problem, lower and upper bounds to atomic distances are known, rather than the exact atomic distances. Since these are usually estimated through NMR techniques, it is realistic to assume that there is an experimental error in the measurements (our approach does not consider this issue yet). Secondly, dgsol needs to make no assumption whatsoever about the distances of triplets and quadruplets of consecutive atoms being known. Thirdly, dgsol is based on a continuous smoothing of the original problem to a form which has fewer local minima. An ordinary NLP optimization method is then applied to the modified problem, and the optimum is traced back to the original problem. This is a fully continuous optimization algorithm, whereas BP is a discrete method.

It turns out that the main advantages of BP over dgsol are:

- 1. tractability of larger instances;
- 2. higher solution accuracy;
- 3. BP can potentially find *all* feasible solutions, not just one.

By contrast, the main advantages of dgsol over BP are:

- 1. it targets a larger class of problems;
- 2. its running time seems to increase very slowly (and regularly) as a function of the number of atoms in the molecule, at least when the set of given distances is comparatively small;
- 3. the amount of memory needed to complete the search is negligible.

The BP algorithm behaves very unpredictably with respect to the amount of needed memory, sometimes requiring over 1GB RAM for relatively small molecules (40 atoms), sometimes solving 1000-atoms instances in a few seconds and very little memory.

5.2 Moré-Wu instances

The Moré-Wu instances are finite three-dimensional hypercubic lattices with s^3 atoms, as shown in Fig. 6. The bond lengths parallel to the coordinate axes are assumed to be 1. By providing the instances with the obvious atomic ordering (as shown in Fig. 6) and the bond angles, we can make them amenable to the application of our method. However, since many of the bond angles ϑ are equal to π (e.g. the angle between atom 1 and atom 3 in Fig. 6), these instances are undiscretizable (see Sect. 2.2). In particular we get $\sin \vartheta = 0$, so Eq. (4) ceases to hold.

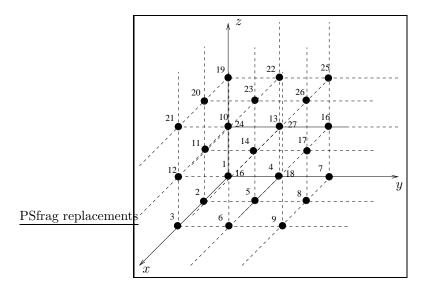


Figure 6: The s=3 Moré-Wu instance with 27 atoms.

In order to test these instances, we perturbed the lattice points $x_i = (x_{i1}, x_{i2}, x_{i3})$ in the following way:

$$\forall i \le s^3 \ (i \mod 3 = 0 \Rightarrow (x_{i3} \leftarrow x_{i3} + (-1)^i \eta)),$$
 (11)

where η was taken to be 0.25. This gave rise to instances which we call "modified Moré-Wu instances" (mmorewu-s, where s^3 is the number of atoms in the molecule). An example is shown in Fig. 7. It is worth mentioning that as the original Moré-Wu instances describe a molecular structure rarely, if ever, found in proteins, we feel our perturbation does not alter crucial molecular characteristics. We generated

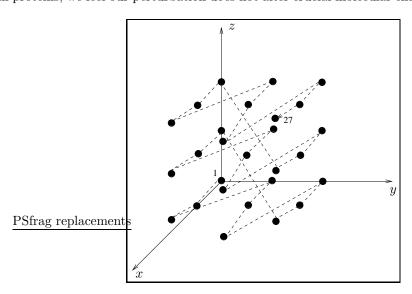


Figure 7: The modified Moré-Wu instance with 27 atoms. The dashed arrow indicates the atomic ordering.

all modified Moré-Wu instances from s=2 to s=6.

5.3 Lavor instances

These instances, described in [9], are based on the model proposed by [15], whereby a molecule is represented as a linear chain of atoms. Bond lengths and angles are kept fixed, and a set of likely torsion angles is generated randomly. Depending on the initial choice of bond lengths and angles, the Lavor instances give rather more realistic models of proteins than other randomly generated instances do (see for example the instances described in [14]). Fig. 5 gives an example of a Lavor instance. In the numerical tables, we labelled the Lavor instances by lavorn-m, where n is the number of atoms in the molecule and m is an instance ID (since there is a random element of choice in the generation of the Lavor instances, many different instances can be generated having the same atomic size).

We generated 10 different Lavor instances for each size n = 10, ..., 70 ("small set"), and 4 different Lavor instances for each size n in $\{100i | 1 \le i \le 10\}$ ("large set").

5.4 Hardware and memory considerations

All tests have been carried out on an Intel Pentium IV 2.66GHz with 1GB RAM, running Linux. The code implementing the BP algorithm has been compiled by the GNU C++ compiler v.3.2 with the -02 flag. As mentioned above, BP can be very memory-demanding. We deliberately took the choice of employing a low-end PC with just 1GB RAM to show just how powerful this technique can be even with modest hardware.

The BP algorithm is in general very fast, since all it does is testing feasibility with the known distances at each branched node. However, exploring the search space may require a lot of memory, especially if no pruning occurs early in the run. Consequently, when the physical RAM of the test machine is exhausted, and the operating system starts swapping to disk, the total CPU elapsed time size becomes unmanageable. Thus, it was decided to kill all jobs requiring more than 1 GB RAM. In particular, we solved almost all the Lavor instances in the "small set" and found one solution for each of the Lavor instances in the "large set".

5.5 Comparative results

The full results table for the complete test suite includes 655 instances and spans 14 pages: thus, only a sample will be presented in detail. The averages, however, are taken with respect to the whole suite. The ε parameter in the DDF pruning tests was set to 1×10^{-3} for all tests. Table 1 contains detailed results for the sample. The instances are described by their name, their atomic size n and the number of given distances |S|. Note that in order to use dgsol, the lower and upper bounds to these distances were set to $\pm 5 \times 10^{-4}$. Other than this, dgsol was used with all default parameter values. The results refer to three methods: dgsol, BP stopped after the first solution was found (BP-One), and BP run to completion (BP-All). For dgsol and BP-One, the user CPU time (in seconds) was reported, as well as the Largest Distance Error (LDE), defined as

LDE =
$$\frac{1}{|S|} \sum_{(i,j) \in S} \frac{|||x_i - x_j|| - d_{ij}|}{d_{ij}},$$

employed as a measure of solution accuracy (the lower, the better). For the (BP-All) method, we reported the user CPU time and the number of solutions found (#Sol). Missing values are due to excessive memory requirements (over 1GB RAM).

It is immediately noticeable that whereas dgsol always finds a solution, BP sometimes fails to find one within 1 GB RAM. It is instructive, however, to look at the solution accuracy (taken over the whole test suite): whereas dgsol ranges from 4.5×10^{-7} to 0.875 (excepting a couple of out-of-scale values clearly due to some numerical instability), BP scores a rather more impressive 4.74×10^{-11} to 5.62^{-6} .

Instance			dgsol		BP-One		BP-All	
Name	n	S	CPU	LDE	CPU	LDE	CPU	#Sol
mmorewu-2	8	28	0.02	2.63E + 5	0.00	4.37E-10	0.00	2
mmorewu-3	27	331	0.23	6.99	0.00	2.97E-09	0.00	2
mmorewu-4	64	1882	0.67	7.79E-6	0.00	5.56E-09	0.00	4
mmorewu-5	125	7105	2.94	3.54E-6	0.00	1.67E-08	0.01	4
mmorewu-6	216	21461	18.65	0.032	0.02	4.91E-08	0.03	4
lavor10_0	10	33	0.02	1.57E-5	0.00	5.36E-10	0.00	4
lavor15_0	15	57	0.10	4.04E-5	0.00	2.84E-09	0.00	16
lavor20_0	20	105	0.14	2.77E-5	0.00	6.13E-09	0.00	8
lavor25_0	25	131	0.84	1.18E-4	0.00	1.38E-09	0.00	8
lavor30_0	30	169	0.40	1.75E-5	0.00	1.23E-09	0.00	2
lavor35_0	35	171	0.81	9.33E-5	0.00	1.52E-09	0.00	64
lavor40_0	40	295	2.84	0.096	0.00	2.87E-09	0.00	2
lavor45_0	45	239	3.33	0.170	0.00	6.92E-09	0.00	2
lavor50_0	50	271	3.45	0.696	0.00	3.96E-08	0.46	4096
lavor55_0	55	551	5.80	0.257	0.00	2.66E-09	0.00	64
lavor60_0	60	377	5.15	0.049	0.00	3.51E-09	0.00	64
lavor65_0	65	267	2.61	0.065	0.00	7.76E-10	_	_
lavor70_0	70	431	8.73	0.107	0.02	1.64E-09	_	_
lavor100_2	100	605	6.95	0.167	2.26	4.01E-09	_	_
lavor200_2	200	1844	63.52	0.395	0.00	5.66E-08	_	_
lavor300_2	300	2505	100.99	0.261	0.03	1.56E-08	_	_
lavor400_2	400	2600	182.21	0.767	0.01	3.35E-09	_	_
lavor500_2	500	4577	329.29	0.830	0.27	4.69E-07	_	_
lavor600_2	600	5473	299.76	0.700	0.01	4.94E-08	_	_
lavor700_2	700	4188	281.34	0.569	0.16	1.83E-06	_	_
lavor800_2	800	6850	570.20	0.528	3.34	3.37E-06	_	_
lavor900_2	900	7965	550.26	0.549	3.08	5.62E-06	_	_
lavor1000_2	1000	8229	844.52	0.695	0.81	2.04E-06	_	_

Table 1: Computational results. Missing values are due to excessive memory requirements (> 1GB RAM).

On average, the solution accuracy obtained by dgsol is 9.55×10^{-2} whereas BP averages 4.56×10^{-8} . Furthermore, all the instances in the Lavor "large set" are solved by dgsol to a solution accuracy of order 10^{-1} : given that in BP pruning often occurs for feasibility differences of order 10^{-1} and even 10^{-2} , such a slack solution accuracy may mean that dgsol is not actually finding the correct solution.

Table 2 reports the averages of the same parameters as in Table 1 taken over 10 Lavor instances in a sample of the "small set" and over 4 Lavor instances in a sample of the "large set". It appears clear from these data that BP's strong points are indeed speed and accuracy. A graphical representation of the averages taken over the whole Lavor test set is shown in Fig. 8 (user CPU average taken to solve the instances in function of the molecular size by dgsol and BP-One) and Fig. 9 (average accuracy of the solution attained by dgsol and BP-One). Notice the huge y-axis scale difference in the two pairs of plots (around 300 times smaller in favour of BP for CPU and around 30000 times smaller in favour of BP for accuracy).

5.6 The number of solutions

It is remarkable that in Table 1 BP-All always finds a number of solutions which is a power of 2. Although we were not able to ascertain the exact reason why the Moré-Wu or Lavor instances had these properties,

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Instance	dgsol / avg.		BP-O	ne / avg.	BP-All / avg.		
n	CPU	\mathbf{LDE}	CPU	LDE	CPU	#Sol	
10	0.03	4.40E-01	0.00	1.19E-09	0.00	1.54E+01	
15	0.08	1.96E-02	0.00	1.23E-09	0.00	3.72E + 01	
20	0.23	3.20E-03	0.00	1.94E-09	0.00	6.90E+01	
25	0.56	1.58E-02	0.00	1.58E-09	0.02	1.14E+02	
30	0.65	1.03E-02	0.00	3.45E-09	0.01	2.65E+02	
35	1.10	5.43E-02	0.00	2.84E-09	0.10	3.35E+03	
40	1.41	2.61E-02	0.00	5.75E-09	0.02	8.48E + 02	
45	2.13	5.80E-02	0.00	6.25E-09	0.12	2.48E+03	
50	2.54	1.65E-01	0.00	6.62E-09	0.16	1.80E + 03	
55	4.10	7.29E-02	0.00	5.53E-09	0.03	4.28E+02	
60	4.47	1.59E-01	0.00	6.44E-09	0.04	3.49E+02	
65	4.64	1.16E-01	0.00	8.37E-09	1.21	3.80E + 03	
70	7.63	9.28E-02	0.01	1.07E-08	_	_	
100	10.57	3.53E-01	0.57	2.46E-09	_	_	
200	57.34	3.61E-01	0.02	2.00E-08	_	_	
300	109.91	4.03E-01	0.03	1.90E-08	_	_	
400	173.54	6.69E-01	0.10	1.05E-08	_	_	
500	273.66	6.19E-01	0.16	4.92E-07	_	_	
600	351.15	5.75E-01	0.01	5.47E-08	_	_	
700	365.37	7.03E-01	0.82	2.65E-06	_	_	
800	583.65	6.54E-01	2.72	1.90E-06	_	_	
900	714.39	6.88E-01	1.68	2.85E-06	_	_	
1000	787.30	6.88E-01	0.41	1.45E-06	_	_	

Table 2: Average statistics for Lavor instances (over 10 instances for the set of small instances and over 4 for the set of large instances).

we were able, through Theorem 3.1, to ascertain that this behaviour does not apply to all instances in the DMDGP.

5.1 Lemma

The instance $I = \{101, 102, 104, 108, 1001, 1002, 1004, 1008\}$ to the Subset-Sum problem has exactly 3 solutions.

Proof. We denote by S, \bar{S} the partition of I solving the Subset-Sum problem. Let 1008 be in S, then exactly one of $\{1001, 1002, 1004\}$ must also be in S, and the other two in \bar{S} This force set membership of 101, 102, 104, 108 in the following way: if 1000 + x is in S, then 100 + x is in \bar{S} and vice versa, for all $x \in \{1, 2, 4, 8\}$.

By the above Lemma and the proof of Theorem 3.1, there is a DMDGP instance with 2×27 solutions (the 2 factor is due to Theorem 2.6).

6 Final Remarks

In this paper we formally define an **NP**-complete subclass of the Molecular Distance Geometry Problem, related to proteins, for which a discrete formulation can be supplied. Instances of this class can be solved by employing a Branch-and-Prune algorithm which makes it possible to find very efficiently one or all the solutions to the problem instance. Furthermore, typical NMR measurement errors can be taken into

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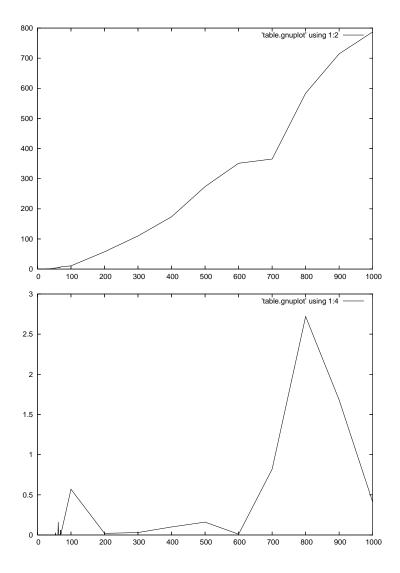


Figure 8: Average user CPU time (plotted against molecular size) taken by dgsol (top) and BP-One (bottom).

account by the algorithm. We illustrate the performance of our algorithm on a set of randomly generated instances.

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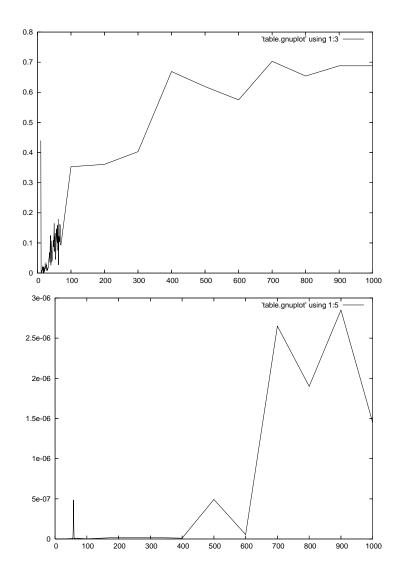


Figure 9: Average accuracy (plotted against molecular size) attained by dgsol (top) and BP-One (bottom).

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