The Discretizable Molecular Distance Geometry Problem

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Outline

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Introduction to the problem

- Let $X = \{x_1, x_2, \ldots, x_n\}$ be a set of points in a three-dimensional space
- Let us suppose that the coordinates of the points x_i are unknown
- Let us suppose that *some* of the distances d_{ij} between couples of points x_i and x_j are known
- Problem: can we find all the coordinates x_i from the known distances d_{ij} ??

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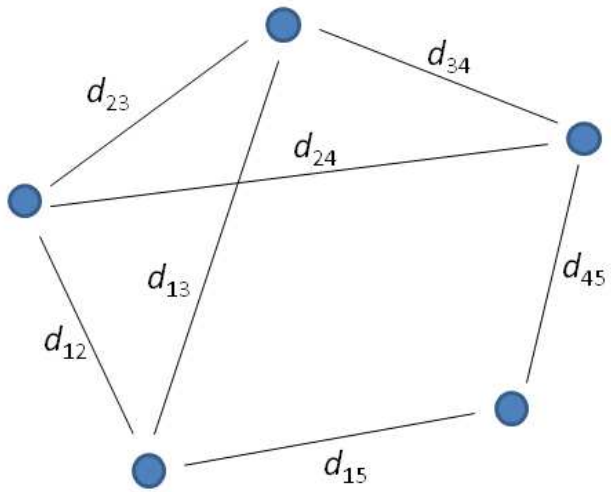
Introduction to the problem

$$\{d_{ij} : x_i, x_j \in X\} \supseteq D \longrightarrow X = \{x_1, x_2, \ldots, x_n\} \text{ ???}$$



If X is a molecular conformation, and each x_i represent an atom, this problem is known as

MOLECULAR DISTANCE GEOMETRY PROBLEM (MDGP)

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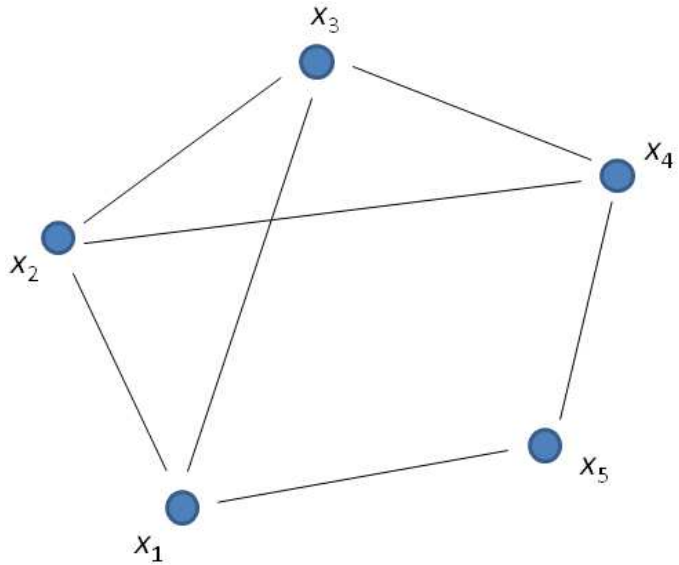

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MOLECULAR DISTANCE GEOMETRY PROBLEM (MDGP)

The MDGP

Formulation I

A molecular conformation is solution for the MDGP if and only if

$$||x_i - x_j|| = d(x_i, x_j).$$

This is a constraint satisfation problem

The MDGP

Formulation II

Let us define the function

$$g(X) = \sum_{\{i,j\}} (||x_i - x_j||^2 - d_{ij}^2)^2.$$

- A conformation X is solution for the MDGP if and only if $g(X) = 0$
- Solutions can be found by minimizing the function $g(X)$
- This is an unconstrained global optimization problem

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The MDGP

Formulation III

- Let $G = (V, E, d)$ be a weighted undirected graph, where
  - V is the set of indeces i of the atoms in X (the vertices of G);
  - E is the subset of couples of atoms whose distance is known (the edges of G);
  - d is the set of known distances (the weights of G).
- X is a solution for the MDGP if there is a function x such that
  - $X = \{x(v) : v \in V\}$, where $x : G \to \mathbb{R}^3$
  - $||x(u) - x(v)|| = d(u, v)$ for each $\{u, v\} \in E$

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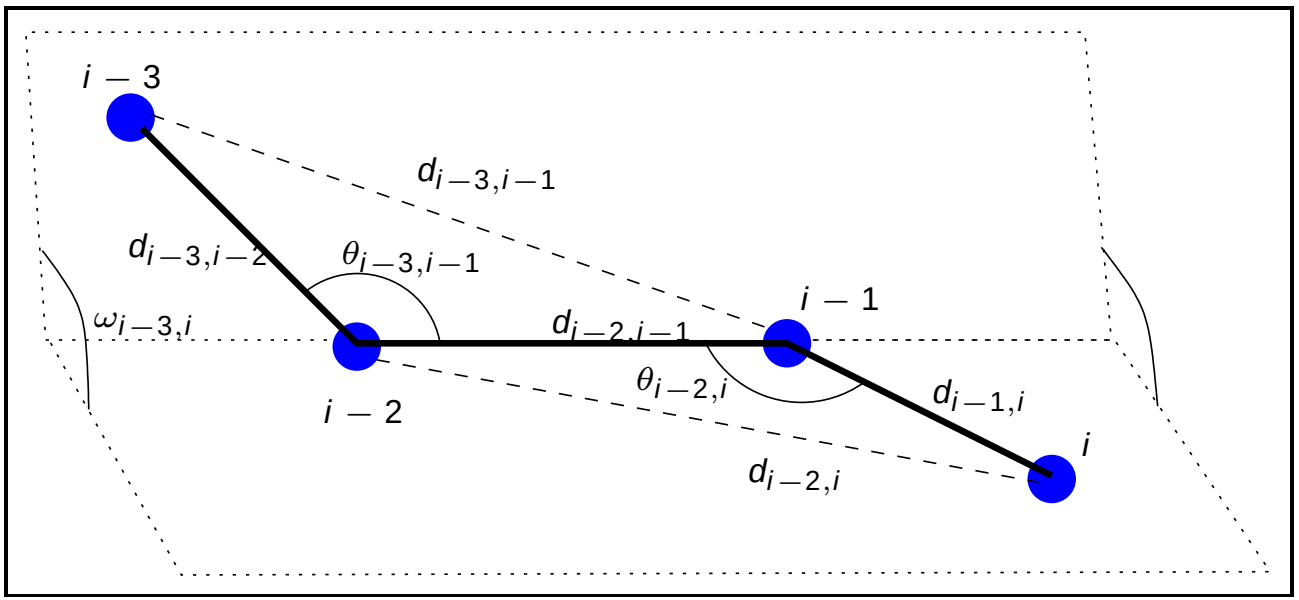
Outline

Our approach

Assumption I

E contains all cliques on quadruplets of consecutive vertices:

$$\forall i \in \{4, \ldots, n\} \; \forall j, k \in \{i-3, \ldots, i\} \quad \{j, k\} \in E$$

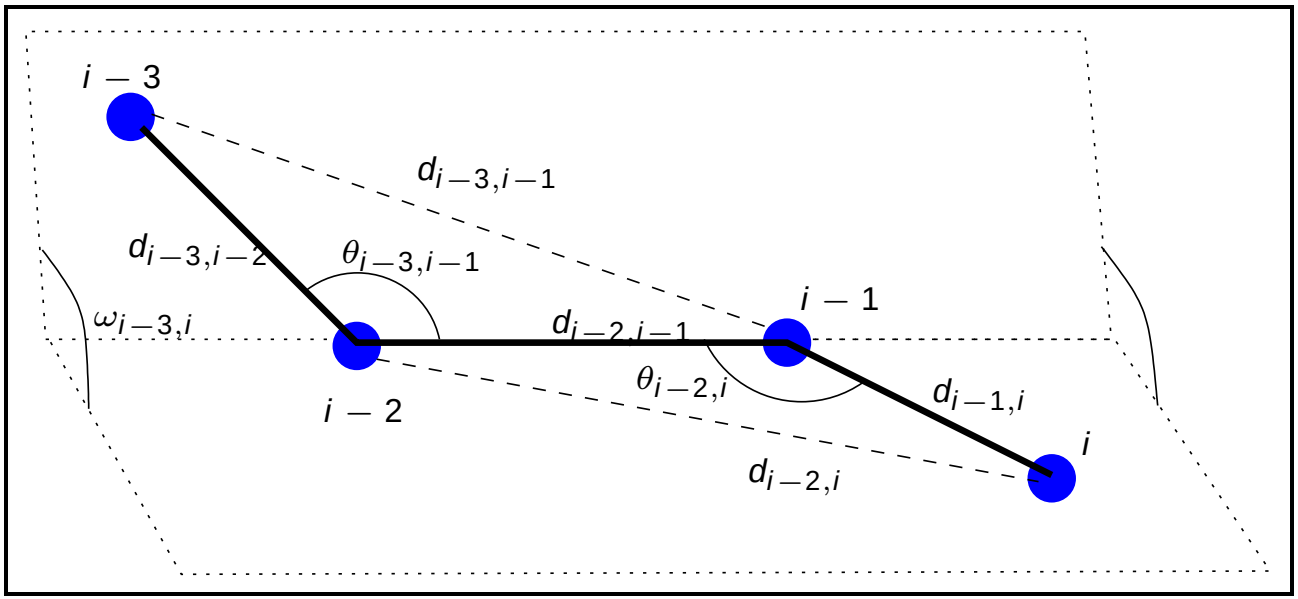


Our approach

Assumption II

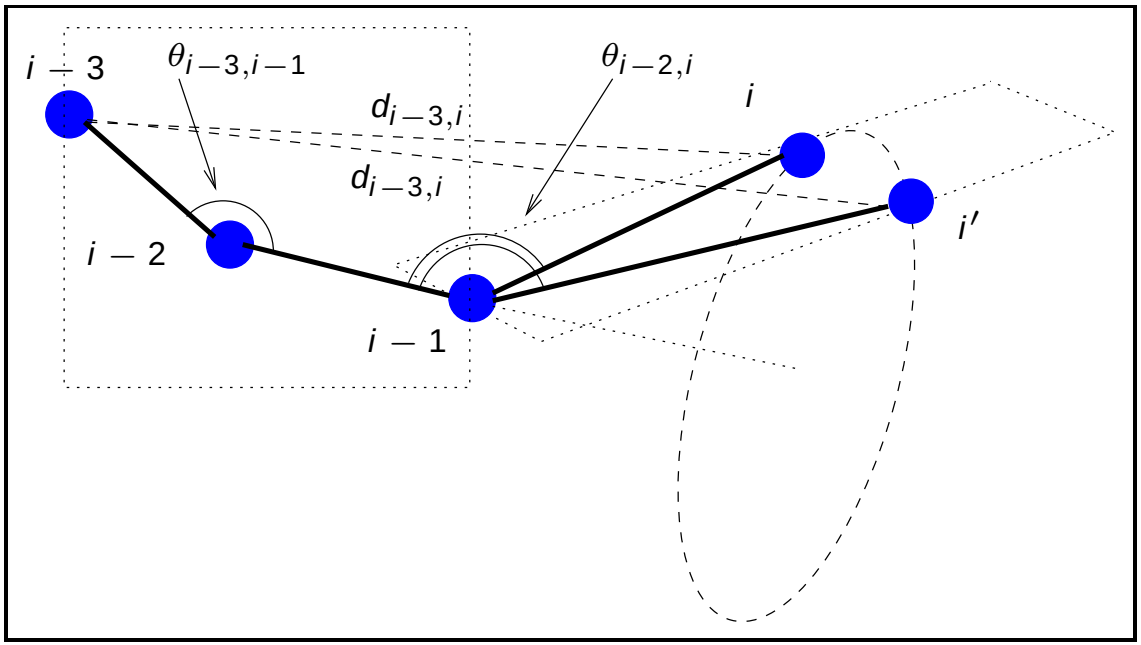
The following strict triangular inequality holds:

$$d_{i-1,i+1} < d_{i-1,i} + d_{i,i+1}, \quad i = 2, \ldots, n-1$$



The DMDGP

If Assumptions I and II hold, each atom can be placed in two possible positions only.



By exploiting the known distances and angles, the cosine of the torsion angle among 4 consecutive atoms can be computed.

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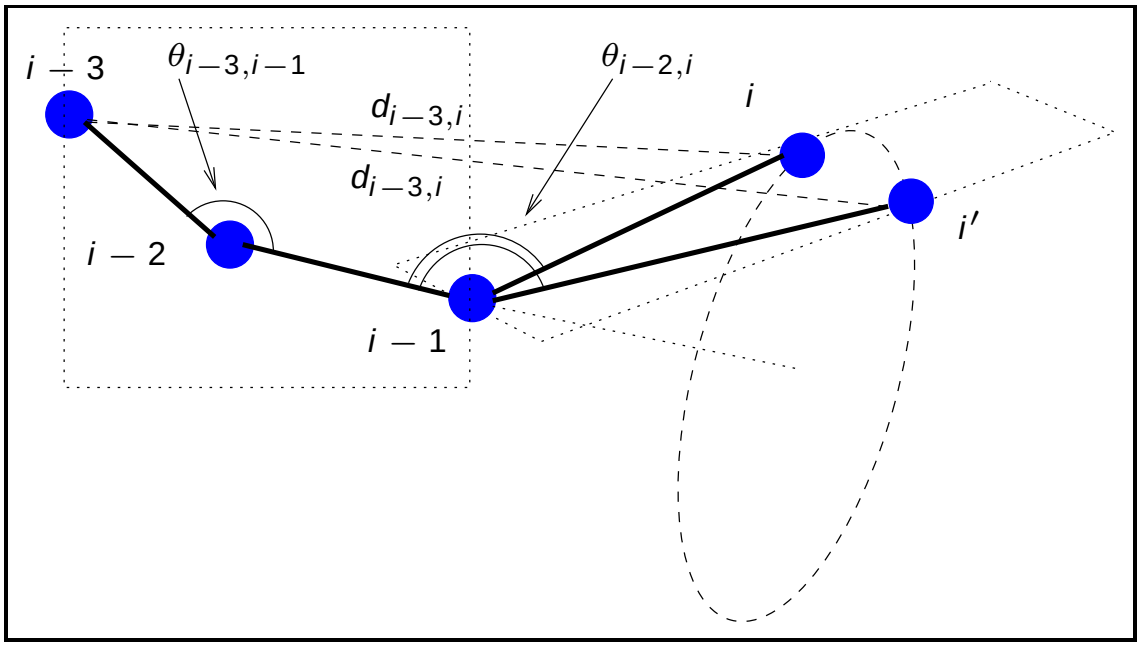

The cosine corresponds to two torsion angles ω, having opposite sign.

The DMDGP

We call Discretizable MDGP (DMDGP) the problem of finding a function

$$x : G \to \mathbb{R}^3$$

such that

$$||x(u) - x(v)|| = d(u,v) \quad \{u,v\} \in E$$

where $G = (V, E, d)$ is a weighted undirected graph and Assumptions I and II hold.

Symmetry

It is possible to prove that:

- If the DMDGP problem has a solution, then it has at least another symmetric solution
- Couples of solutions of the DMDGP are symmetric

Theorem

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

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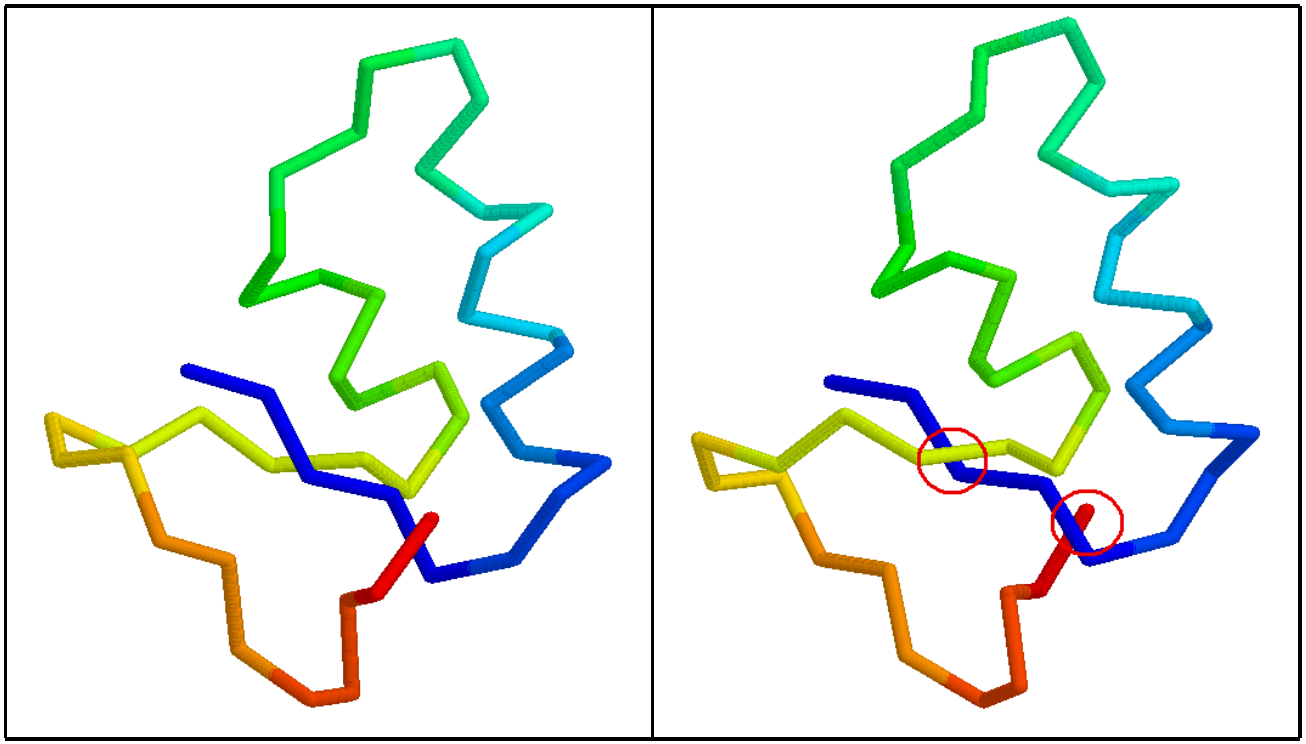

The two conformations look the same, but they are actually different!

Outline

Basic idea

- The BP algorithm mimicks the structure of the problem closely: we build a tree of possible choices for the atomic positions.
- At each step, the i-th atom can be placed in two possible positions x_i, x_i'
  - the two positions are both feasible: the search is branched;
  - only one position is feasible: the search procedees torwards one direction only;
  - both the positions are infeasible: the branch is pruned and the search is backtracked.
- How to check the feasibility of atomic positions? Using pruning tests.

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Two pruning tests

- Direct Distance Feasibility (DDF)
  - Known and obtained distances are compared and, if they differ, the new atom position is infeasible
    - $||x_j - x_i|| \neq d_{ij} \Longrightarrow j$ is infeasible
- Dijkstra Shortest-Paths (DSP)
  - If $D(i,k) < ||x_h - x_i|| - d_{hk}$ for all feasible $x : G \rightarrow \mathbb{R}^3$, then the BP search node for atomic position x_i can be pruned, where
    - $h < i < k$
    - $D(i,k)$ is the *shortest path* between i and k in the graph G;
    - $||x_h - x_i||$ is the computed distance between x_h and x_i;
    - d_{hk} is the known distance between x_h and x_k.
- DDF: simple and efficient;
- DSP: more complex and more efficient.

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A software procedure

A software procedure has been developed in C programming language.

Legend of the following Tables:

- *Name* - instance name;
- n - instance dimension;
- $|E|$ - number of known distances;
- *#Sol* - number of found solutions;
- *#DDF* - number of times DDF pruned atoms;
- *#DSP* - number of times DSP pruned atoms;
- *CPU* - CPU time;
- *LDE* - Largest Distance Error:

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

Experiments on artificial instances

Only one pruning test

Experiments have been carried out on a set of artificially generated instances [Lavor, 2006]. Only the pruning test DDF is used here.

Instance			*BP-One*			*BP-All*		
Name	*n*	$\|E\|$	*CPU*	*#DDF*	*LDE*	*CPU*	*#DDF*	*#Sol*
lavor10	10	24	0.00	0	1.63e-16	0.00	0	64
lavor15	15	70	0.00	7	1.08e-09	0.00	11	1
lavor20	20	103	0.00	9	1.28e-09	0.00	16	1
lavor25	25	106	0.00	10	1.62e-09	0.00	49	2
lavor30	30	219	0.00	15	3.86e-09	0.00	381	2
lavor35	35	166	0.00	13	1.22e-09	0.00	169	16
lavor40	40	306	0.00	16	5.61e-06	0.00	136	2
lavor45	45	351	0.00	30	4.79e-09	0.00	58	1
lavor50	50	203	0.00	49	6.50e-10	0.07	23364	512
lavor55	55	224	0.00	26	1.43e-09	3.45	1304580	262144
lavor60	60	227	0.00	17	2.05e-09	0.62	262428	8192
lavor65	65	455	0.00	1165	7.89e-09	0.02	5184	8
lavor70	70	331	0.00	25	1.23e-08	16.30	2798220	4194304

Note that the symmetric solutions that can be found by the Theorem on symmetry are not included.

Experiments on artificial instances

Two pruning tests

Both the pruning tests DDF and DSP are here used.

Instance			*BP-One*				*BP-All*			
Name	*n*	$\|E\|$	*CPU*	*#DDF*	*#DSP*	*LDE*	*CPU*	*#DDF*	*#DSP*	*#Sol*
lavor10	10	24	0.00	0	0	1.63e-16	0.00	0	0	64
lavor15	15	70	0.00	7	0	1.08e-09	0.00	11	0	1
lavor20	20	103	0.00	9	0	1.28e-09	0.00	16	0	1
lavor25	25	106	0.00	8	1	1.62e-09	0.00	24	5	2
lavor30	30	219	0.00	15	0	3.86e-09	0.00	277	10	2
lavor35	35	166	0.00	9	1	1.22e-09	0.00	145	8	16
lavor40	40	306	0.00	16	0	5.61e-06	0.00	64	4	2
lavor45	45	351	0.00	17	2	4.79e-09	0.00	39	3	1
lavor50	50	203	0.00	24	8	6.50e-10	0.05	5924	5648	512
lavor55	55	224	0.00	22	2	1.43e-09	7.02	1173508	65536	262144
lavor60	60	227	0.00	13	2	2.05e-09	1.22	221462	16387	8192
lavor65	65	455	0.00	720	115	7.89e-09	0.01	3200	528	8
lavor70	70	331	0.00	25	0	1.23e-08	38.50	2732664	32774	4194304

DDF+DSP are more efficient, because they prune atoms earlier on the search tree, but the computational time usually increases.

Comparisons to DGSOL

We compared the BP algorithm to DGSOL [Moré and Wu, 1999].

Instance			*DGSOL*	
Name	n	$\|E\|$	*CPU*	*LDE*
lavor10	10	24	0.03	3.01e+01
lavor15	15	70	0.05	0.00e+00
lavor20	20	103	0.08	0.00e+00
lavor25	25	106	0.24	2.62e-02
lavor30	30	219	1.02	4.43e-07
lavor35	35	166	1.38	1.00e-01
lavor40	40	306	0.57	1.94e-06
lavor45	45	351	1.33	9.47e-07
lavor50	50	203	1.55	7.43e-02
lavor55	55	224	2.06	2.31e-03
lavor60	60	227	0.41	1.50e+03
lavor65	65	455	2.94	1.27e-01
lavor70	70	331	5.10	9.60e-02

The computational time and quality of the solutions are not comparable with the ones of the BP algorithm.

Creating real instances

PDB file $\Longrightarrow$ MDGP instance

- the three-dimensional conformation of a protein molecule can be downloaded from the PDB
- all the distances between its atoms can be computed
- all the distances smaller than 6Å can be used for generating an instance for the MDGP
- this simulates data obtained from NMR experiments, which are able to detect only distances within such a range
- in these experiments, only the backbone atoms N, C_α and C are considered

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Experiments on real instances

Instance			*BP-One*		*BP-All*		*DGSOL*	
Name	*n*	$\|E\|$	*CPU*	*LDE*	*CPU*	*#Sol*	*CPU*	*LDE*
1aqr	120	929	0.00	1.86e-09	0.00	2	7.77	4.88e-01
2erl	120	1136	0.00	1.33e-14	0.00	1	9.38	2.92e-01
1crn	138	1250	0.00	2.24e-13	0.00	1	9.47	2.24e-01
1ahl	147	1205	0.00	1.50e-09	0.00	8	6.95	1.46e-01
1brz	159	1394	0.00	3.53e-13	0.00	2	11.39	4.66e-01
1hoe	222	1995	0.00	3.18e-13	0.00	1	16.83	2.06e-01
1lfb	232	2137	0.00	5.31e-14	0.00	1	38.94	2.88e-01
1pht	249	2283	0.00	2.73e-12	0.00	1	42.50	2.00e-01
1jk2	270	2574	0.00	2.09e-13	0.00	1	86.98	4.05e-01
1f39a	303	2660	0.00	2.68e-12	0.00	1	37.24	2.80e-01
1acz	324	3060	0.00	3.15e-12	0.02	4	35.97	3.97e-01
1poa	354	3193	0.00	1.36e-13	0.00	1	64.03	4.67e-01
1fs3	378	3443	0.00	8.08e-13	0.01	1	54.68	2.69e-01
1mbn	459	4599	0.00	1.36e-09	0.00	1	124.24	4.46e-01
1rgs	792	7626	0.00	4.22e-13	0.01	1	237.93	4.69e-01
1m40	1224	20382	0.02	1.00e-12	5.26	1	1142.49	4.89e-01
1bpm	1443	14292	0.02	2.85e-13	0.02	1	398.29	5.06e-01
1n4w	1610	16940	0.02	1.19e-12	0.02	1	994.51	5.26e-01
1mqq	2032	19564	0.02	4.90e-12	0.06	1	451.58	5.40e-01
1rwh	2265	21666	0.02	2.08e-13	0.06	1	934.29	5.38e-01
3b34	2790	29188	0.07	1.17e-11	0.07	1	940.95	6.47e-01
2e7z	2907	42098	0.08	4.26e-12	0.09	1	915.39	6.40e-01
1epw	3861	35028	0.16	3.19e-12	0.25	1	2037.86	4.92e-01

The instance 1aqr

The sequence of signs of the sine values in the 4 solutions of the instance 1aqr.

There are only 2 non-symmetric solutions.

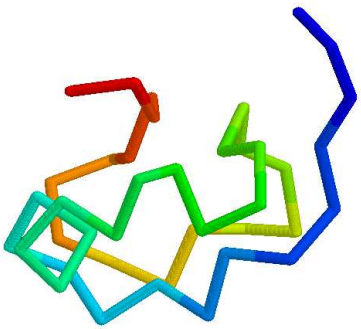
Their only difference stands in the 8^{th} torsion angle.

from atom 1 to atom 20																			
+	+	+	+	+	+	-	**+**	+	-	-	+	+	-	+	+	-	+	-	-
+	+	+	+	+	+	-	**-**	+	-	-	+	+	-	+	+	-	+	-	-
+	+	+	-	-	-	+	**+**	-	+	+	-	-	+	-	-	+	-	+	+
+	+	+	-	-	-	+	**-**	-	+	+	-	-	+	-	-	+	-	+	+
from atom 21 to atom 40																			
+	-	-	+	-	+	+	-	-	+	-	+	+	+	-	+	+	-	+	+
+	-	-	+	-	+	+	-	-	+	-	+	+	+	-	+	+	-	+	+
-	+	+	-	+	-	-	+	+	-	+	-	-	-	+	-	-	+	-	-
-	+	+	-	+	-	-	+	+	-	+	-	-	-	+	-	-	+	-	-
from atom 41 to atom 60																			
-	+	+	-	+	+	-	+	+	-	+	-	-	+	-	-	+	+	-	+
-	+	+	-	+	+	-	+	+	-	+	-	-	+	-	-	+	+	-	+
+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	-	+	-
+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	-	+	-

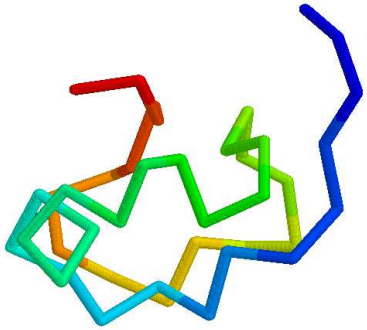
Only the first 60 backbone atoms are shown.

The instance 1aqr

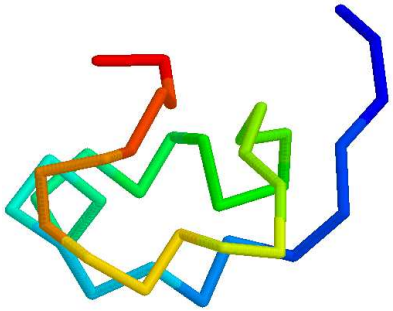
All the solutions of the instance 1aqr.



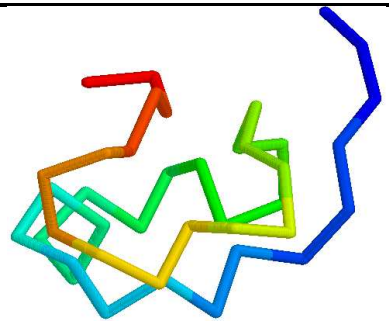
LDE = 7.42e-07, RMSD = 6.94e+00



LDE = 3.10e-13, RMSD = 6.94e+00



LDE = 3.10e-13, RMSD = **7.10e-08**



LDE = 7.42e-07, RMSD = 8.08e-04

Outline

An instance with 27 solutions

- You might have noted that the BP algorithm always found a power of 2 solutions for each considered instance.
- However, there are instances whose number of solutions is not a power of 2.
- For example, we have an instance with 27 solutions.
- Might the power of 2 rule hold only for protein conformations?

Outline

What if the accuracy lowers?

- Our final goal is to use data from NMR for generating protein conformations;
- data from the NMR are affected by experimental errors:
  - systematic uncertainty on each distance;
  - a certain percentage of completely wrong distances.
- the BP algorithm needs to be improved for managing experimental errors.

Summary

- We discussed the Discretizable Distance Geometry Problem
- We presented a Branch & Prune algorithm for DMDGP
- We showed that the Branch & Prune algorithm is able to solve instances of DMDGP related to protein conformations (artificially generated or real)
- We showed the effeciency and effectiveness of two possible pruning tests
- We showed the open problems on which we are still working

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