A distance geometry procedure using the Levenberg-Marquardt algorithm and with applications in biology ~~*but not only*~~

Antonio Mucherino

IRISA, University of Rennes 1

antonio.mucherino@irisa.fr

joint work with Douglas Gonçalves

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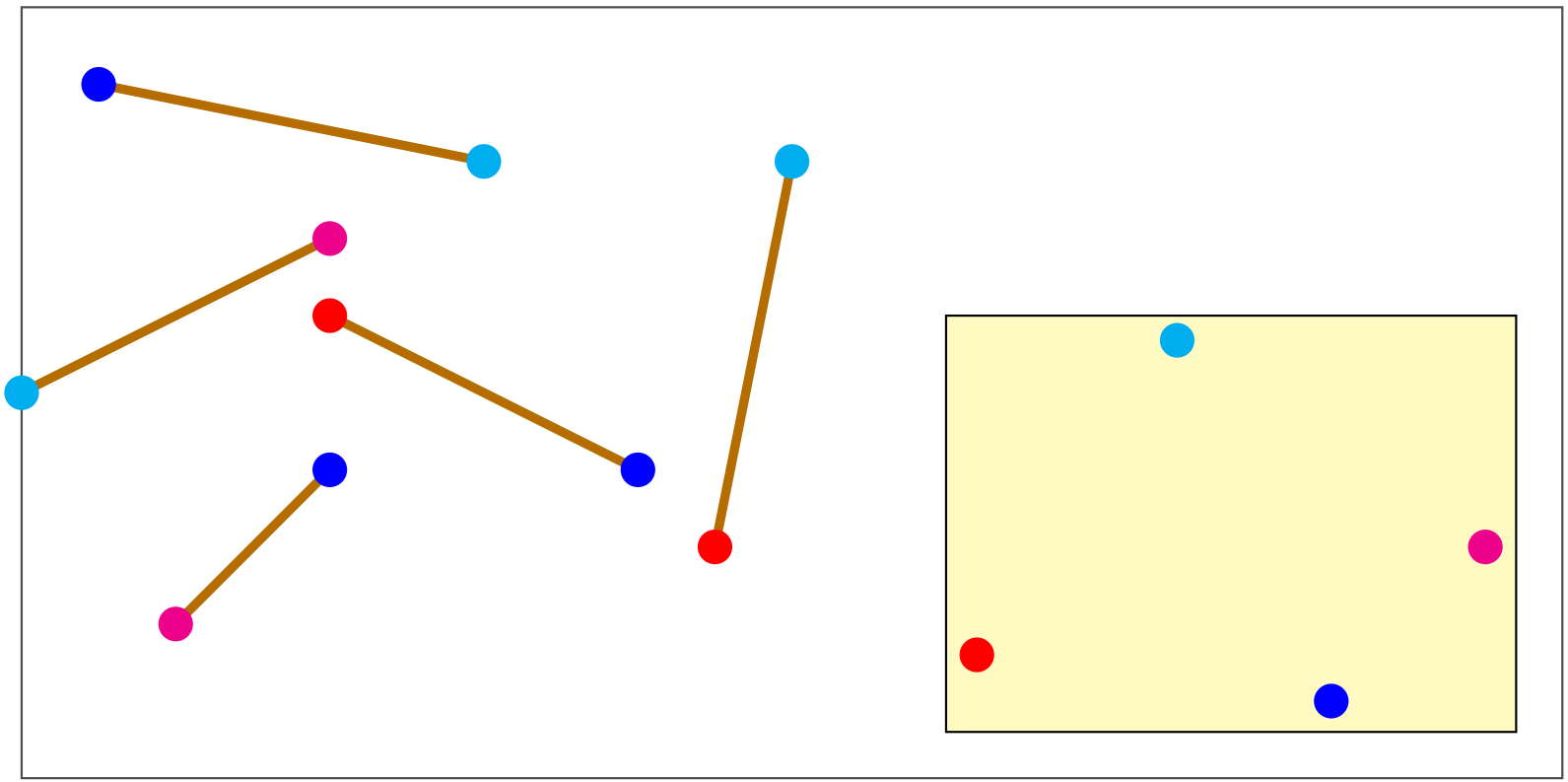
The Distance Geometry Problem

Can you see how the sticks (left side) are able to define the positions for the points (in the yellow box, right side) ?



The Distance Geometry Problem

Let $G = (V, E, d)$ be a simple weighted undirected graph:

- V represents a set of objects
- E indicates which distances are known
- d provides the "distance information"

Definition

The **DGP** in dimension K.
Determine whether there exists a realization

$$x : V \longrightarrow \mathbb{R}^K$$

of G in $\mathbb{R}^K$ such that, for all edges $\{u, v\} \in E$,

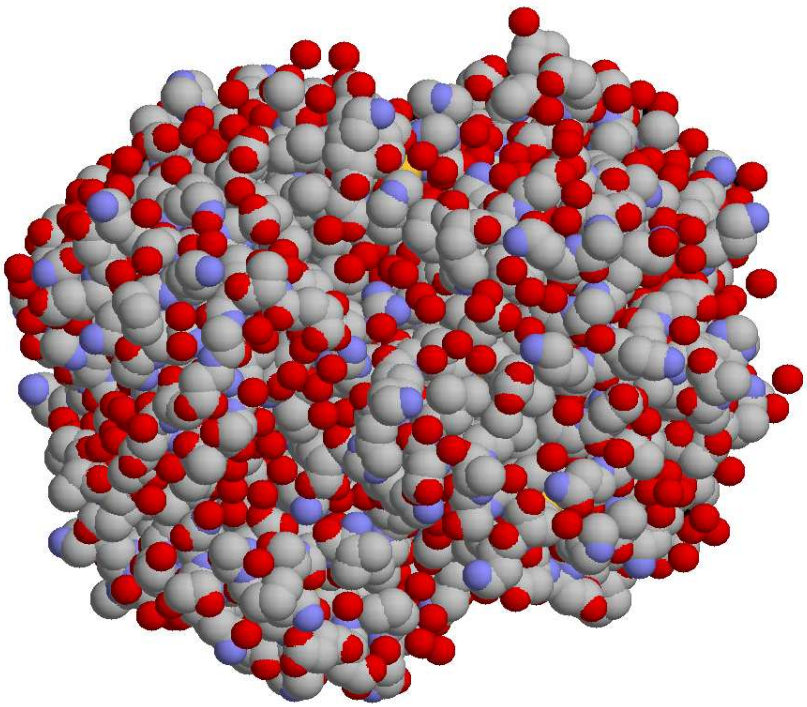
$$||x_u - x_v|| = d(u, v).$$

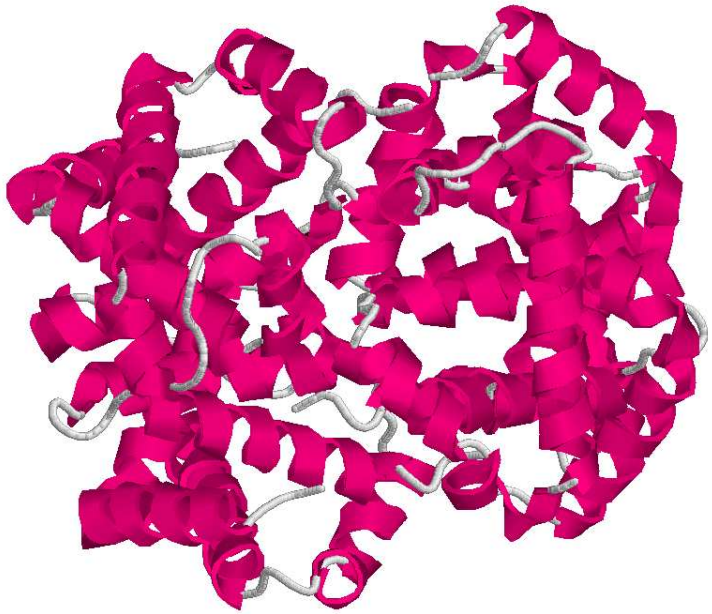
The **DGP** is NP-hard[1].

[1] J. Saxe, Embeddability of Weighted Graphs in k-Space is Strongly NP-hard, Proceedings of 17th Allerton Conference in Communications, Control and Computing, 480–489, 1979.

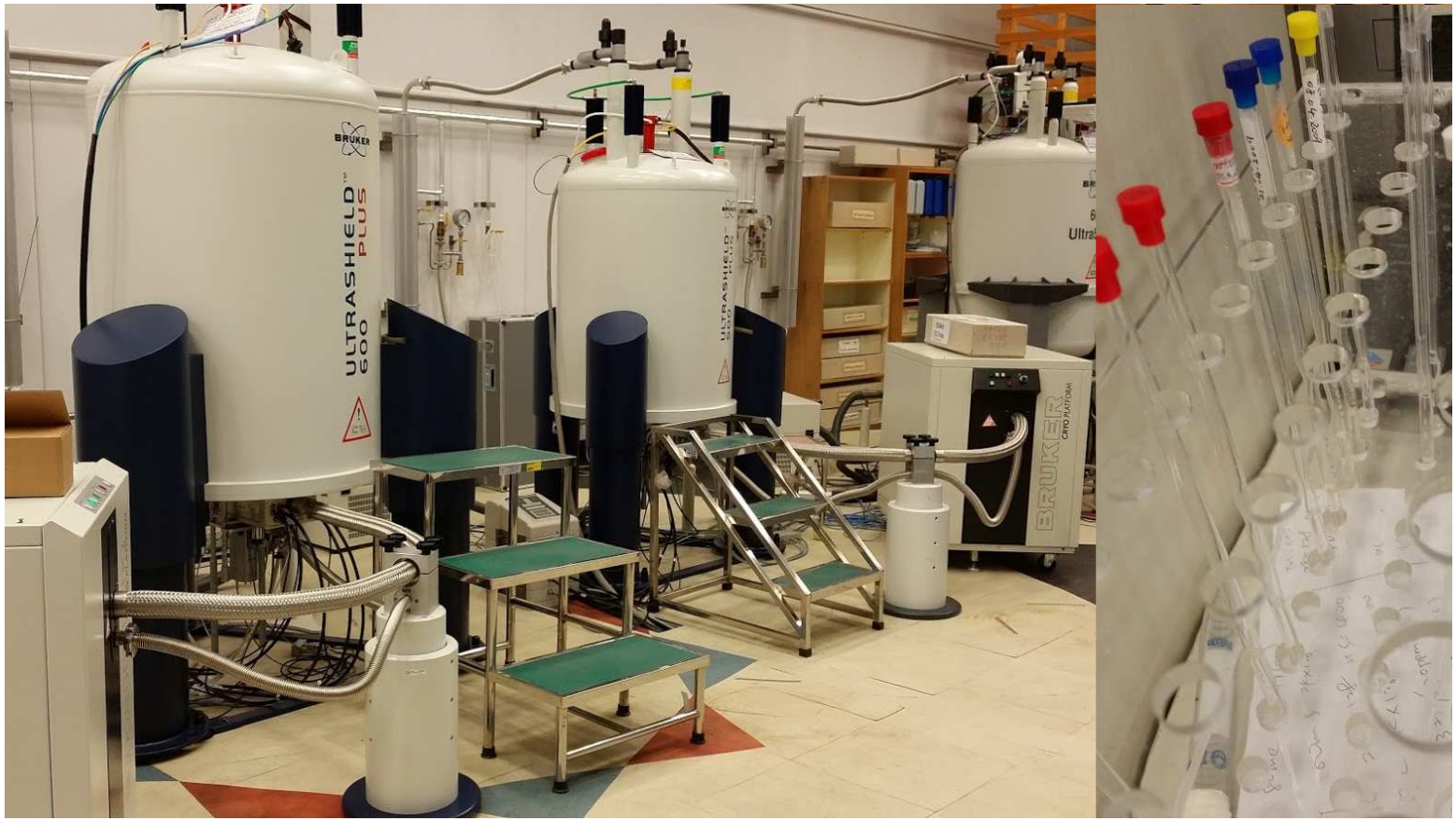
NMR protein structure determination

The hemoglobin:





NMR protein structure determination



Academia Sinica, Taiwan, June 2017.

DGP in structural biology

The DGP is generally reformulated as a *continuous global optimization* problem:

$$\min g(X), \quad \text{where } g(X) = \sum_{\{u,v\}} (||x_u - x_v||^2 - d(u,v)^2)^2$$

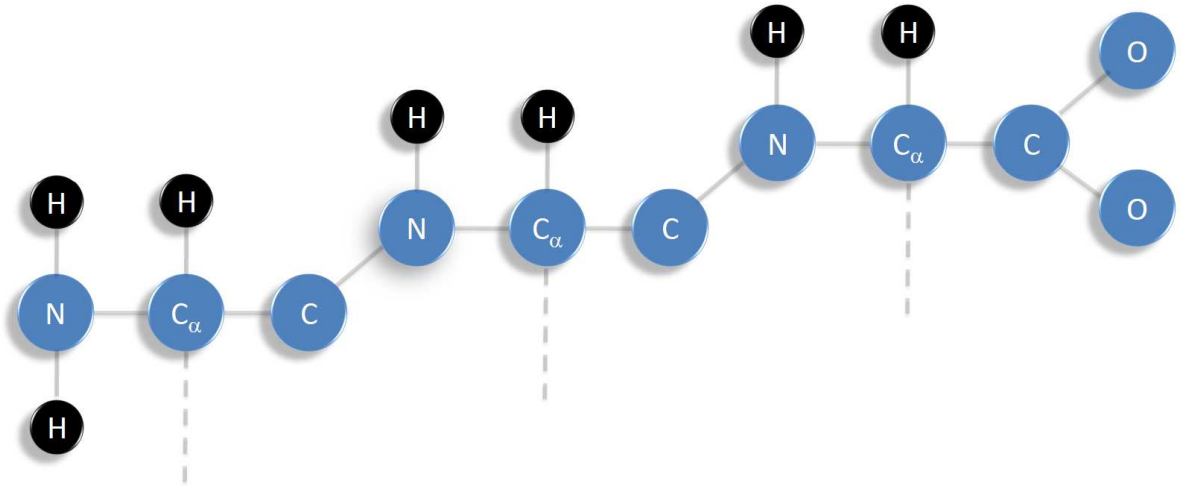
The majority of available NMR models of protein conformations were obtained by solving the corresponding DGP by the meta-heuristic Simulated Annealing (SA).

Some disadvantages:

- SA is not the best meta-heuristic search
- there are no guarantees to converge to the optimal solution(s)
- even with multi-start techniques, there is no hope to identify all optimal solutions

NMR protein structure determination

The chemical composition of a protein backbone:



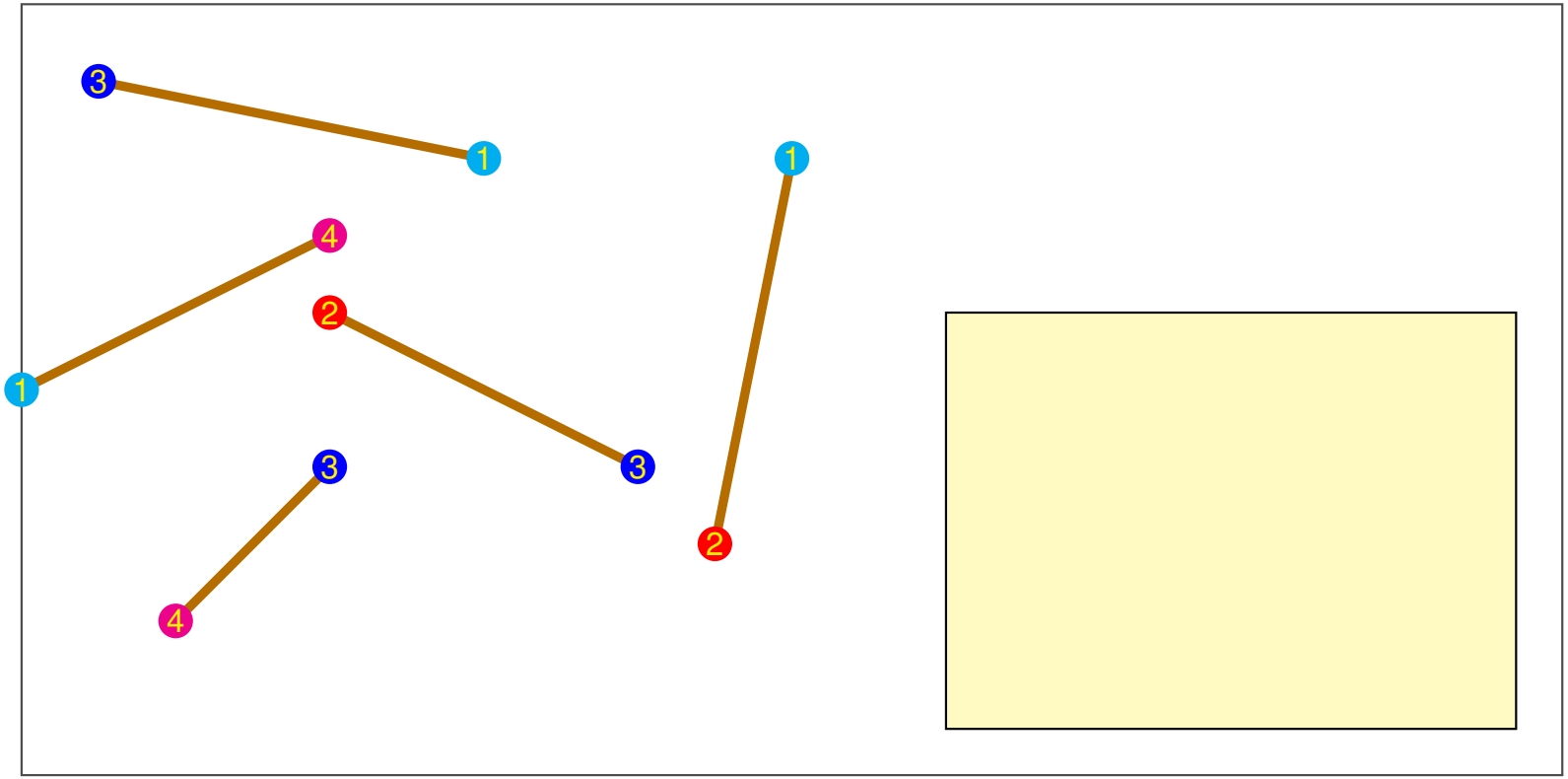
Exact distances can be derived from the chemical composition of the molecule

Interval distances are obtained through the NMR experiments:

- mostly distances between *hydrogens*
- *short* distances ($\leq$ 5Å)
- *large* range for intervals (about $2-3$Å $\Rightarrow$ uncertainty on the distance values)

Discretizable DGP

What about assigning a numerical label to every vertex, and to build up the solutions step by step?



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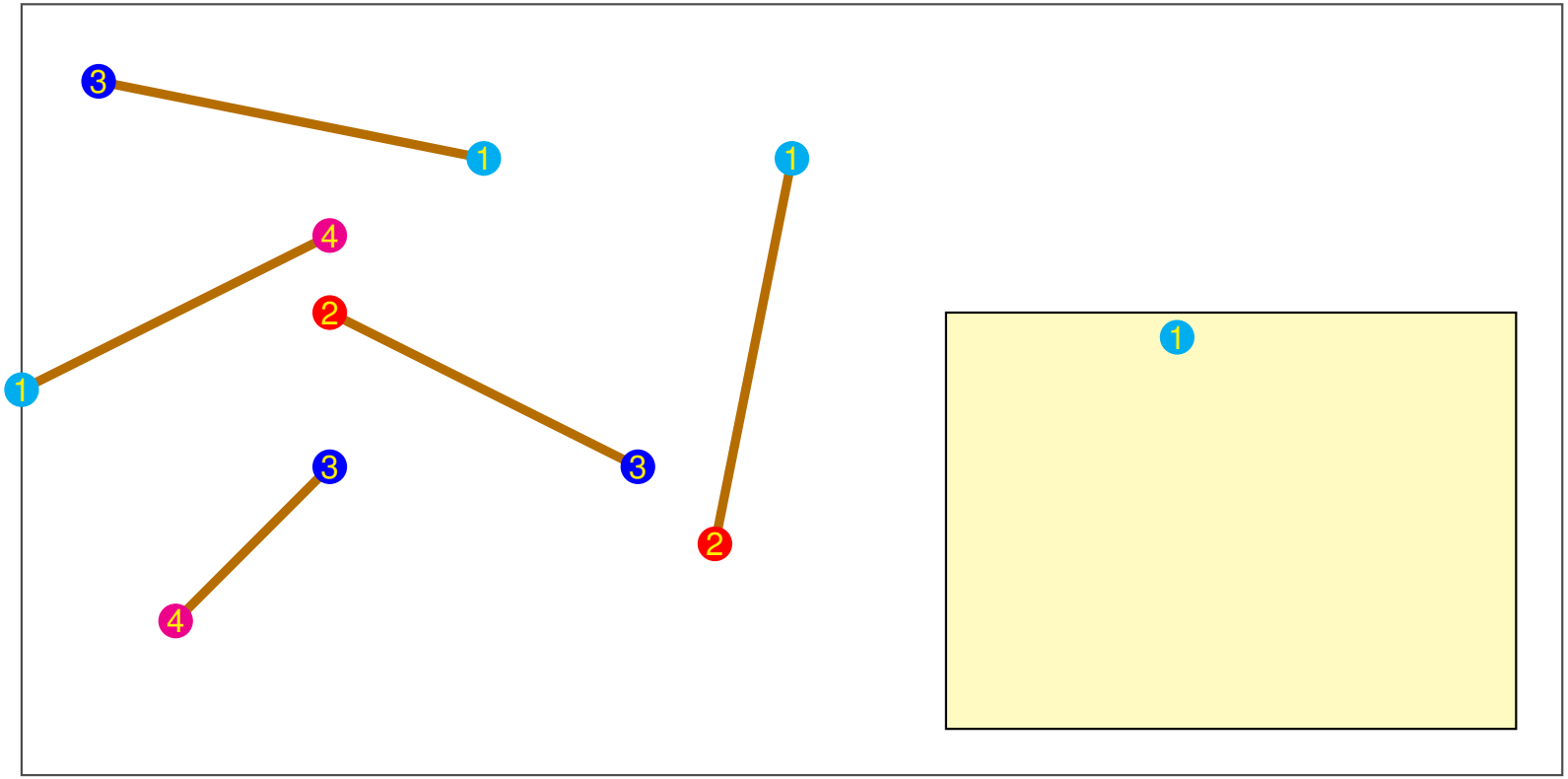

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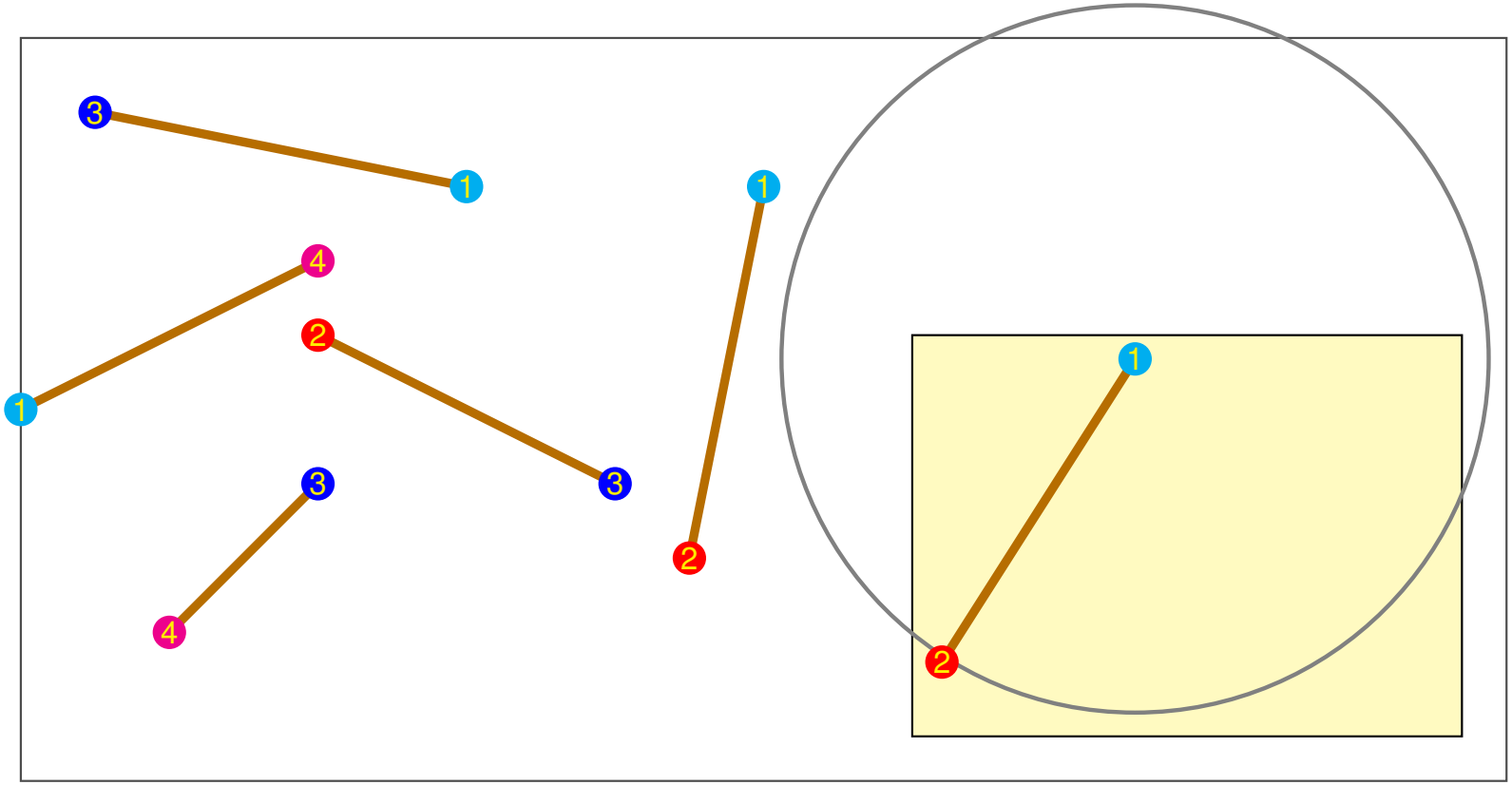

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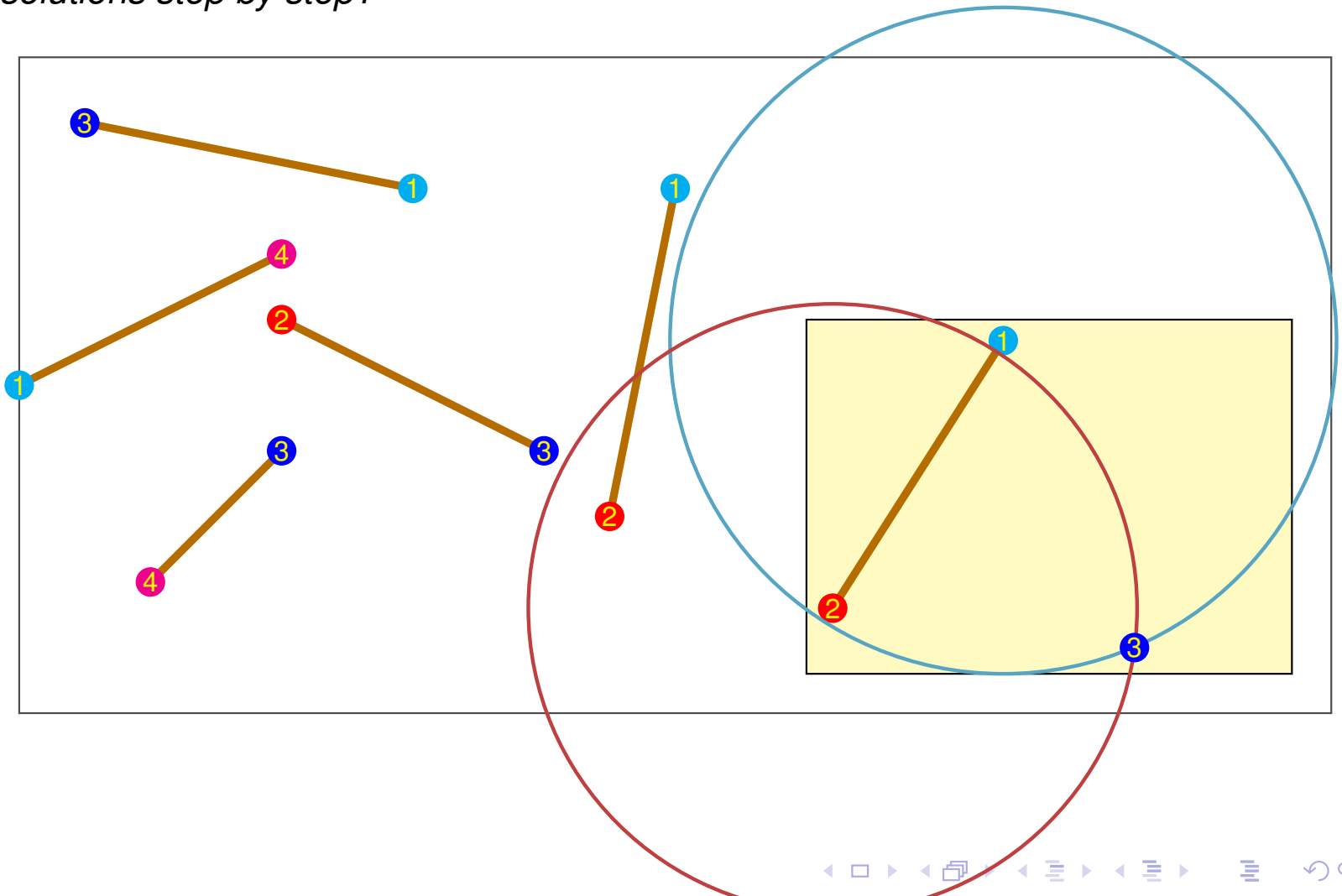

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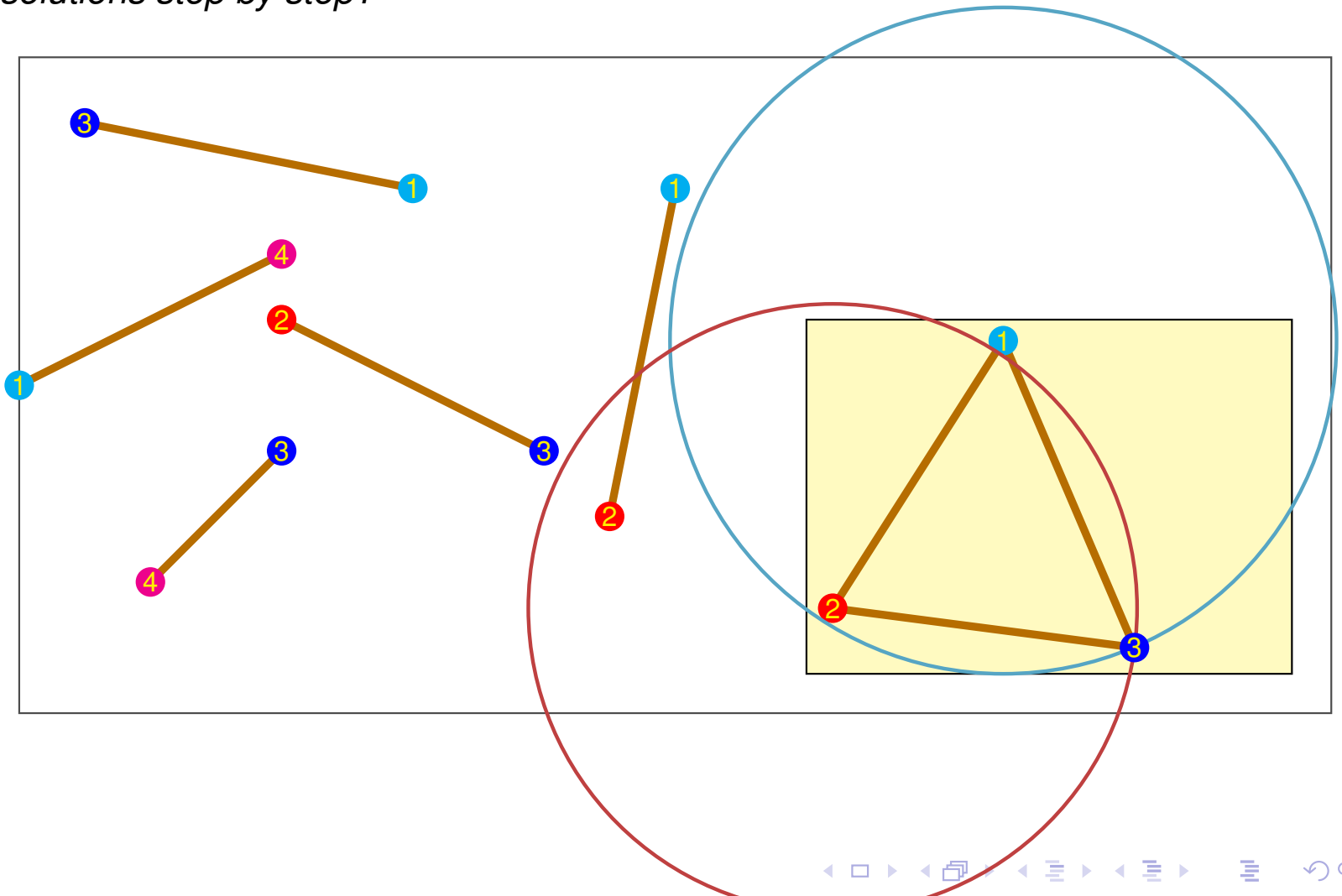

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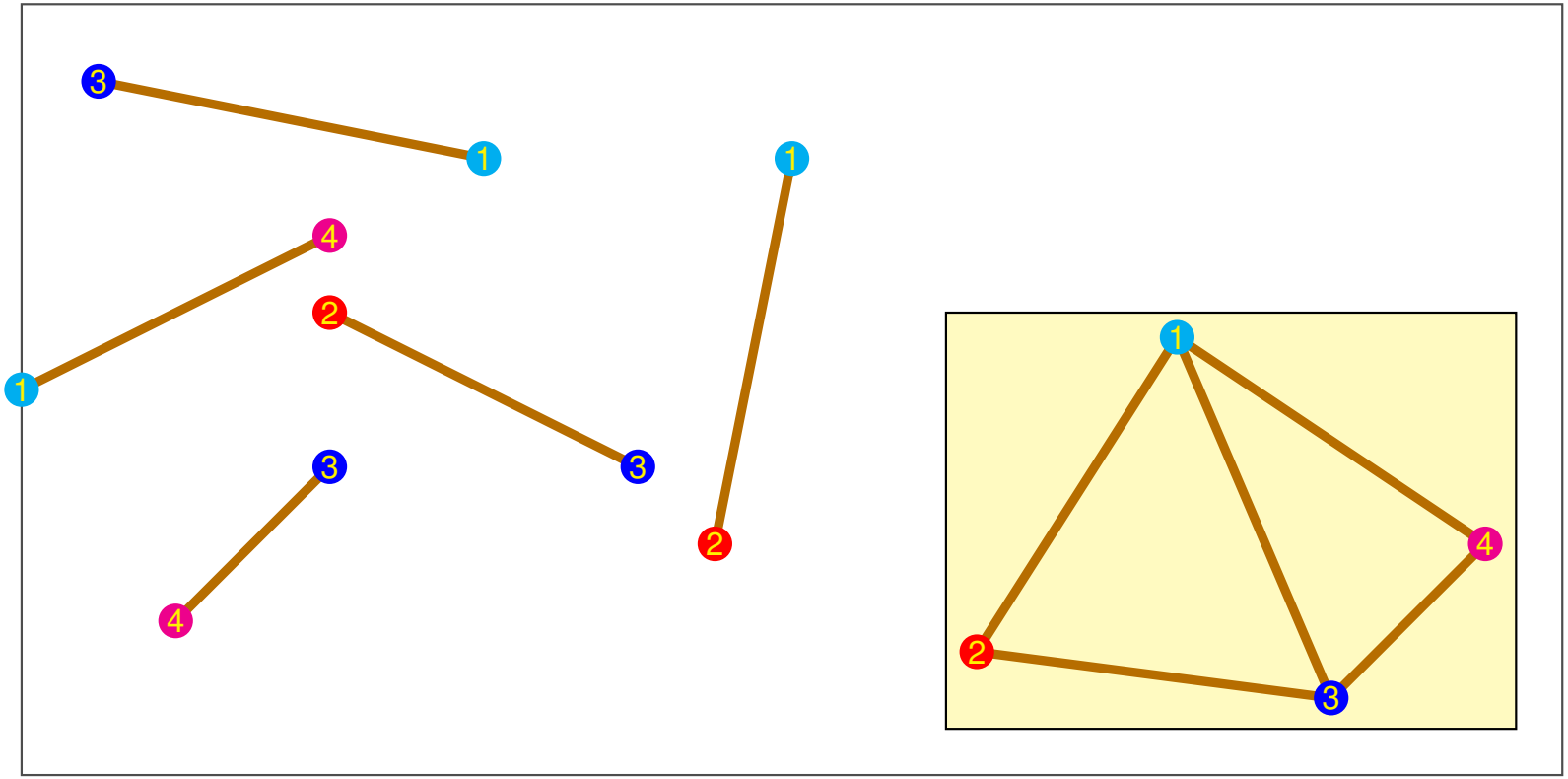


The intersection of two circles in 2D gives (in general) two points.

Discretizable DGP

Definition

Given a graph $G = (V, E, d)$, there must exist[2] a vertex order[3] on V such that

(A1) $G[\{1, 2, \ldots, K\}]$ is a clique;

(A2) $\forall v \in V : v > K, \quad \exists\, u_1, u_2, \ldots, u_K :$

$$\begin{cases} u_1 < v,\ u_2 < v,\ \ldots\ u_K < v, \\ \{\{u_1, v\}, \{u_2, v\}, \ldots, \{u_K, v\}\} \subset E, \\ \mathcal{V}(S[u_1, u_2, \ldots, u_K]) \neq 0, \end{cases}$$

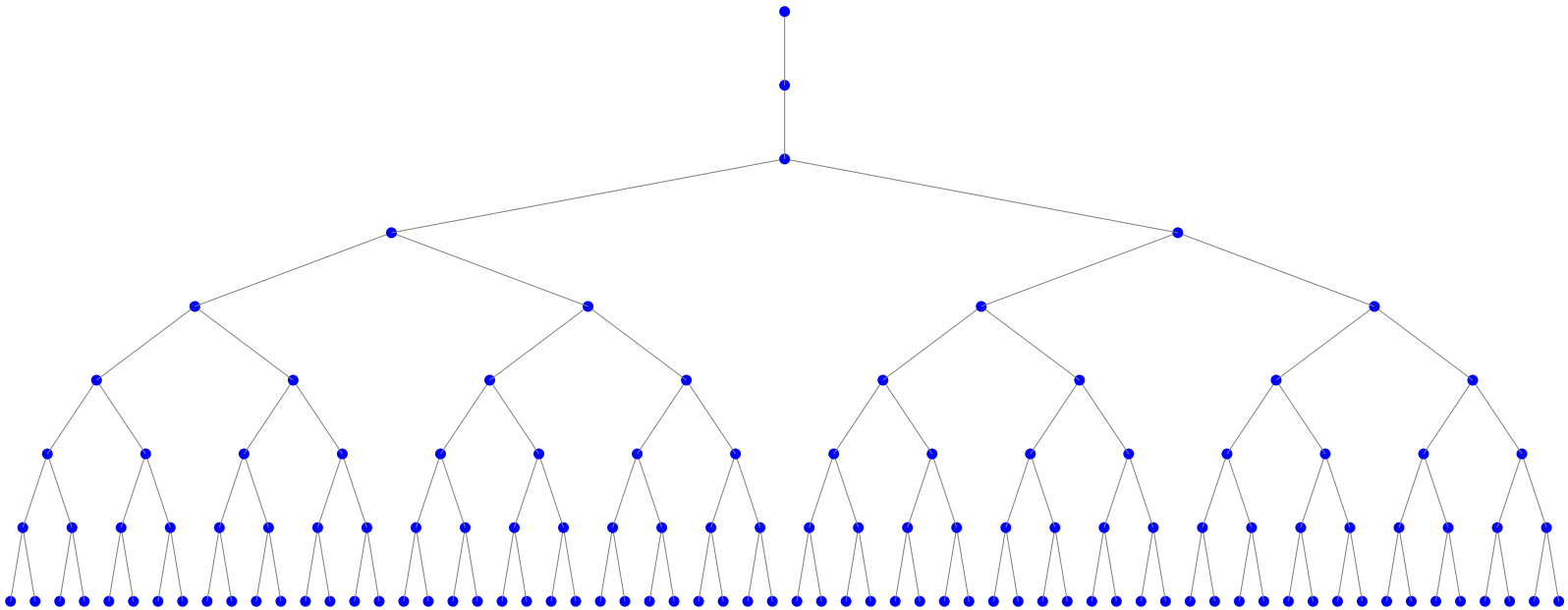
where $S[\ldots]$ is the simplex defined by u_1, u_2, $\ldots$, u_K, and $\mathcal{V}$ is the volume of its argument.

[2] L. Liberti, C. Lavor, N. Maculan, A. Mucherino, Euclidean Distance Geometry and Applications, SIAM Review **56**(1), 3–69, 2014.

[3] J. Omer, A. Mucherino, The Referenced Vertex Ordering Problem: Theory, Applications and Solution Methods, Open Journal of Mathematical Optimization **2**, article no. 6, 29 pages, 2021.

The Branch & Prune algorithm

The Branch & Prune (BP) algorithm[4] is based on the idea of branching over all possible positions for each vertex, and of pruning tree branches by exploiting distances not used in the discretization process (*pruning distances*).



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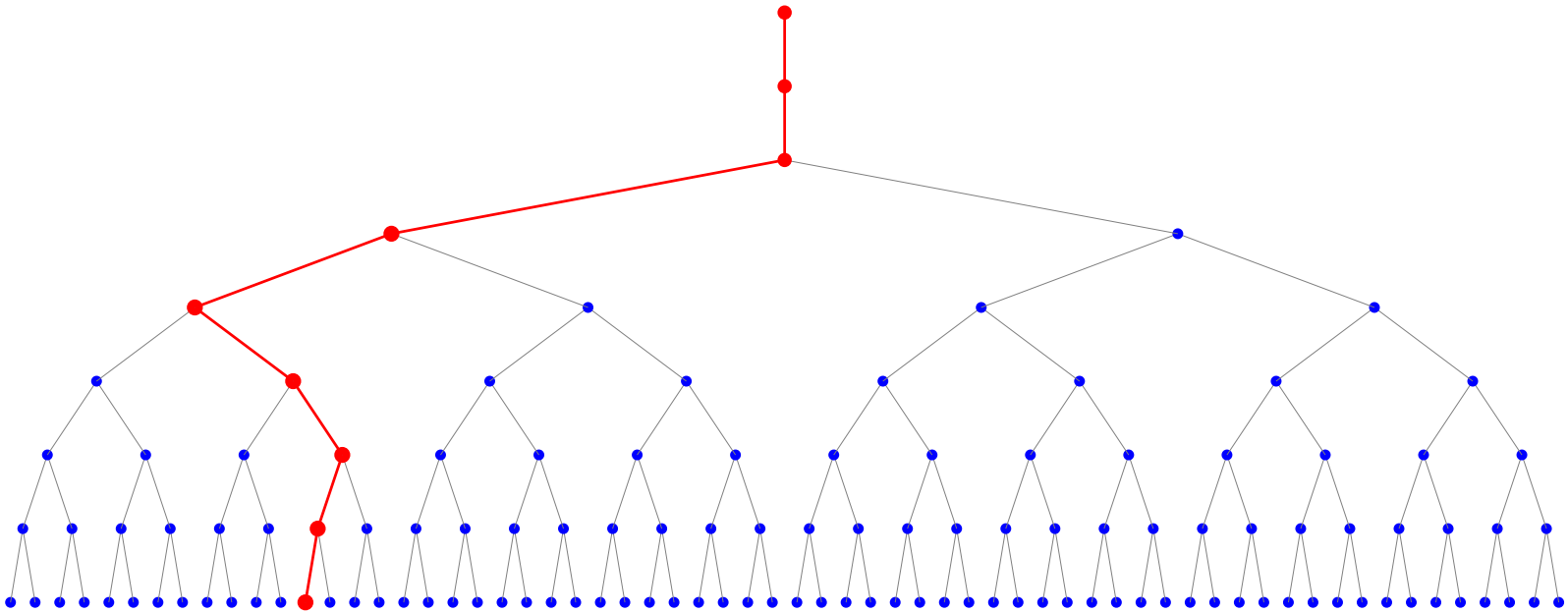

The DDGP is NP-hard $\Longrightarrow$ Exponential worst-case complexity!

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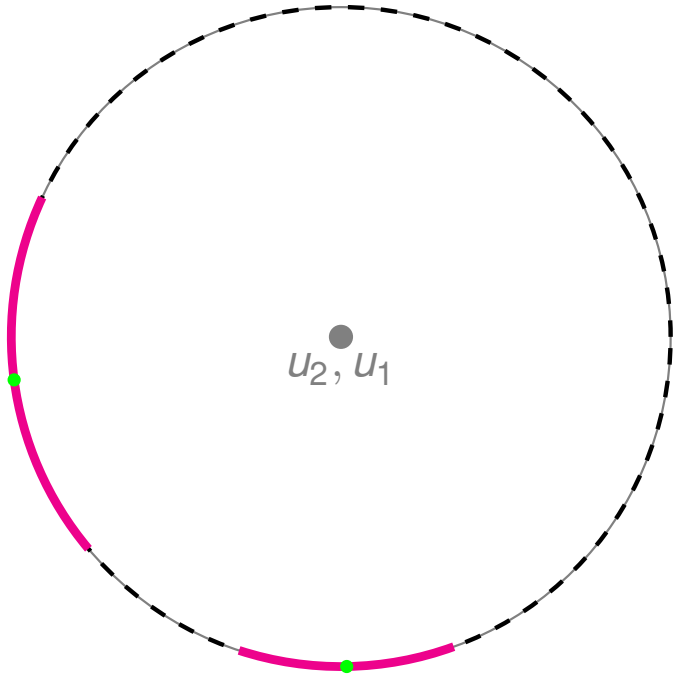
A coarse-grained representation

We consider a coarse-grained representation of the search domain.



In such a case, a pair (position,box) is associated to a new node of the tree.

The *position* in the *box* can subsequently be refined by *local optimization*.[5]

[5] A. Mucherino, J-H. Lin, D.S. Gonçalves, A Coarse-Grained Representation for Discretizable Distance Geometry with Interval Data, Lecture Notes in Computer Science **11465**, Lecture Notes in Bioinformatics series, I. Rojas et al (Eds.), Proceedings of the 7th International Work-Conference on Bioinformatics and Biomedical Engineering (IWBBIO19), Part I, Granada, Spain, 3–13, 2019.

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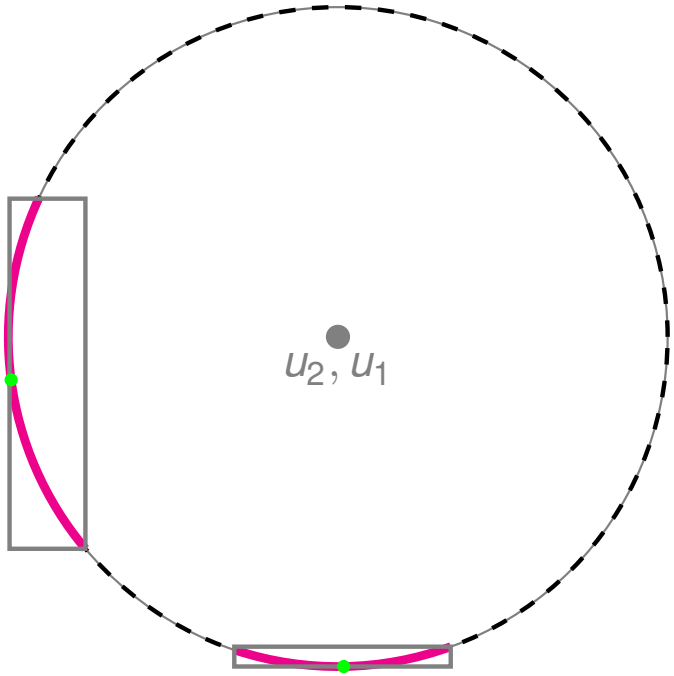

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Local refinement by local optimization

But how to perform the local optimization step?

- spectral projected gradient
- Gauss-Netwon second order method
- Levenberg-Marquardt method[6]

Preliminary experiments are showing that the use of local optimization is very effective in correcting the approximation errors that can propagate along the search domain.

[6] This paper!

Thanks!

antonio.mucherino@irisa.fr

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