Euclidean Distance Geometry

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[L., Lavor: *Introduction to Euclidean Distance Geometry*, in preparation]

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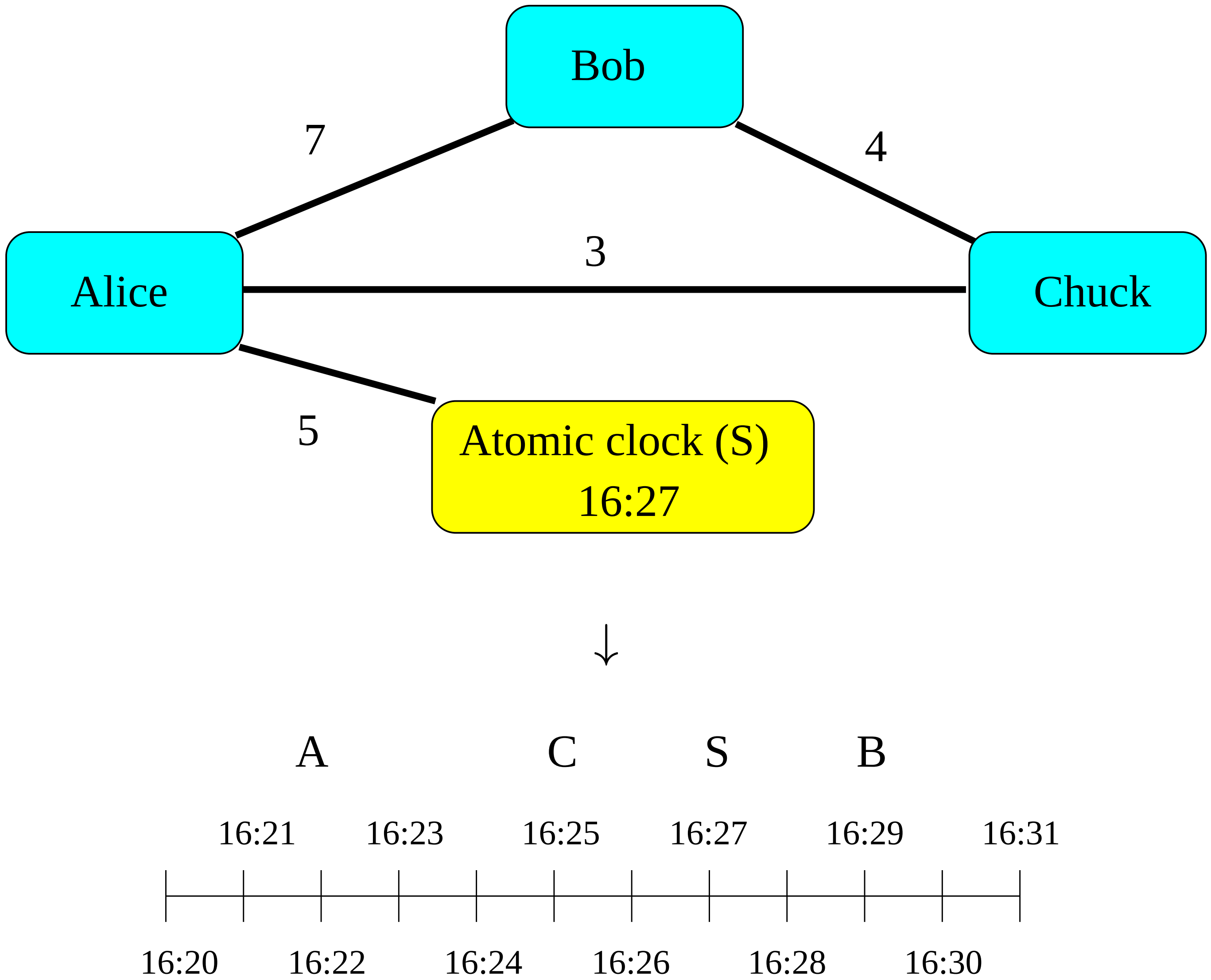
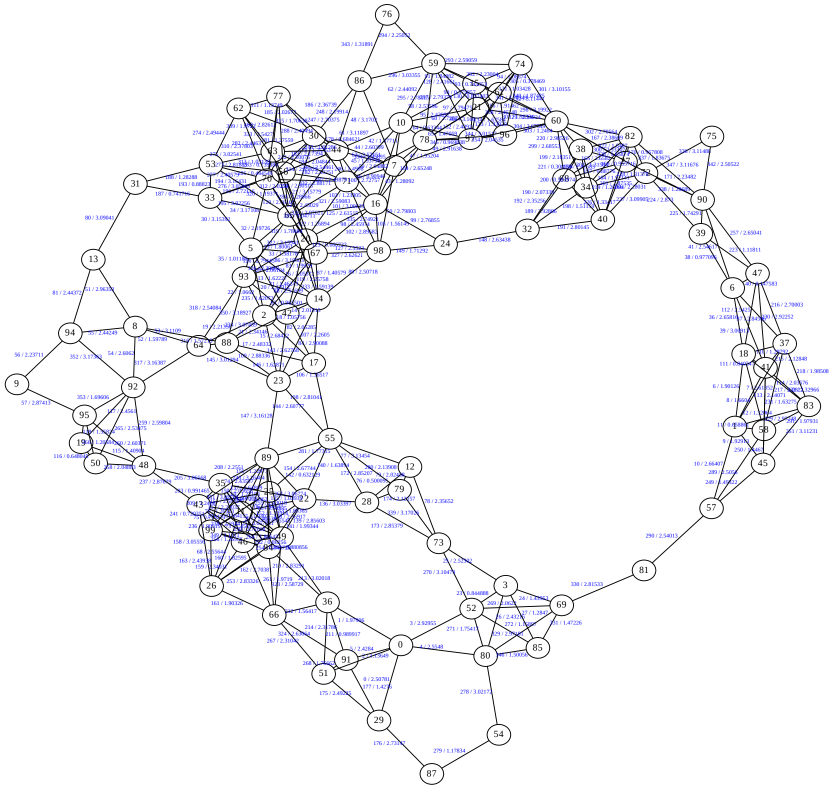
Clock Synchronization



[Singer, 2011]

Sensor network localization



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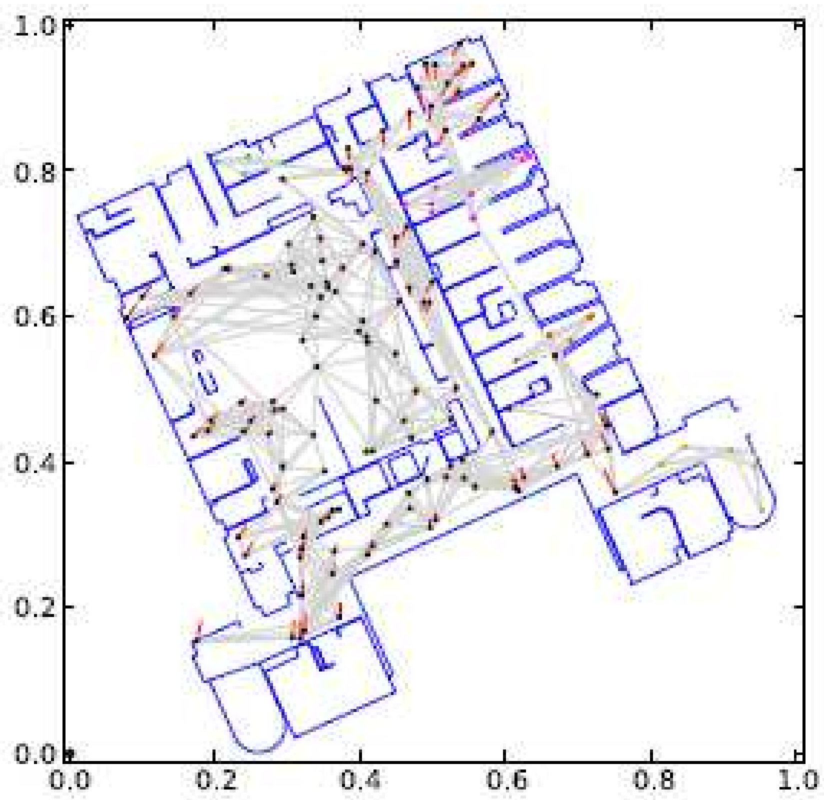
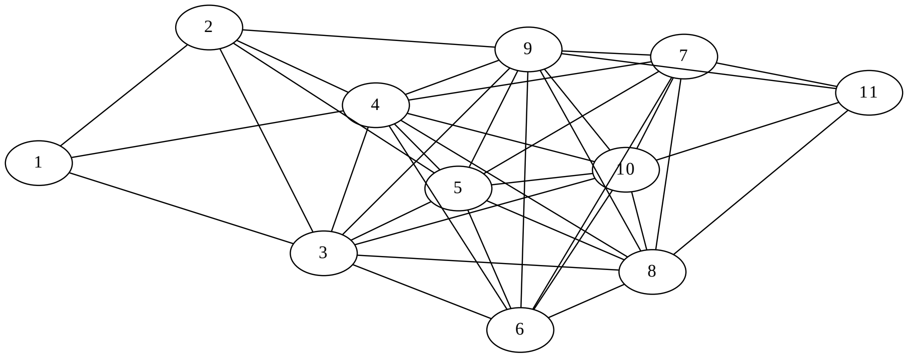
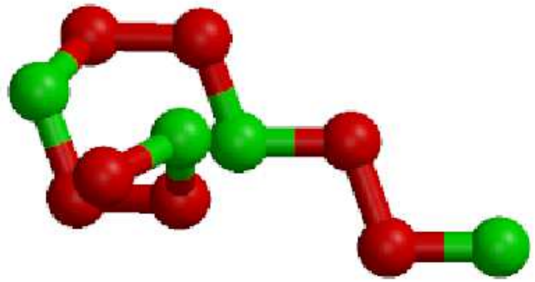


[Yemini, 1978]

Protein conformation from NMR data



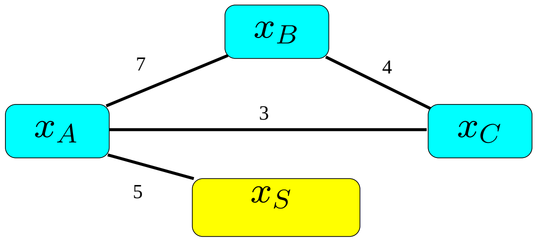
$\longrightarrow$

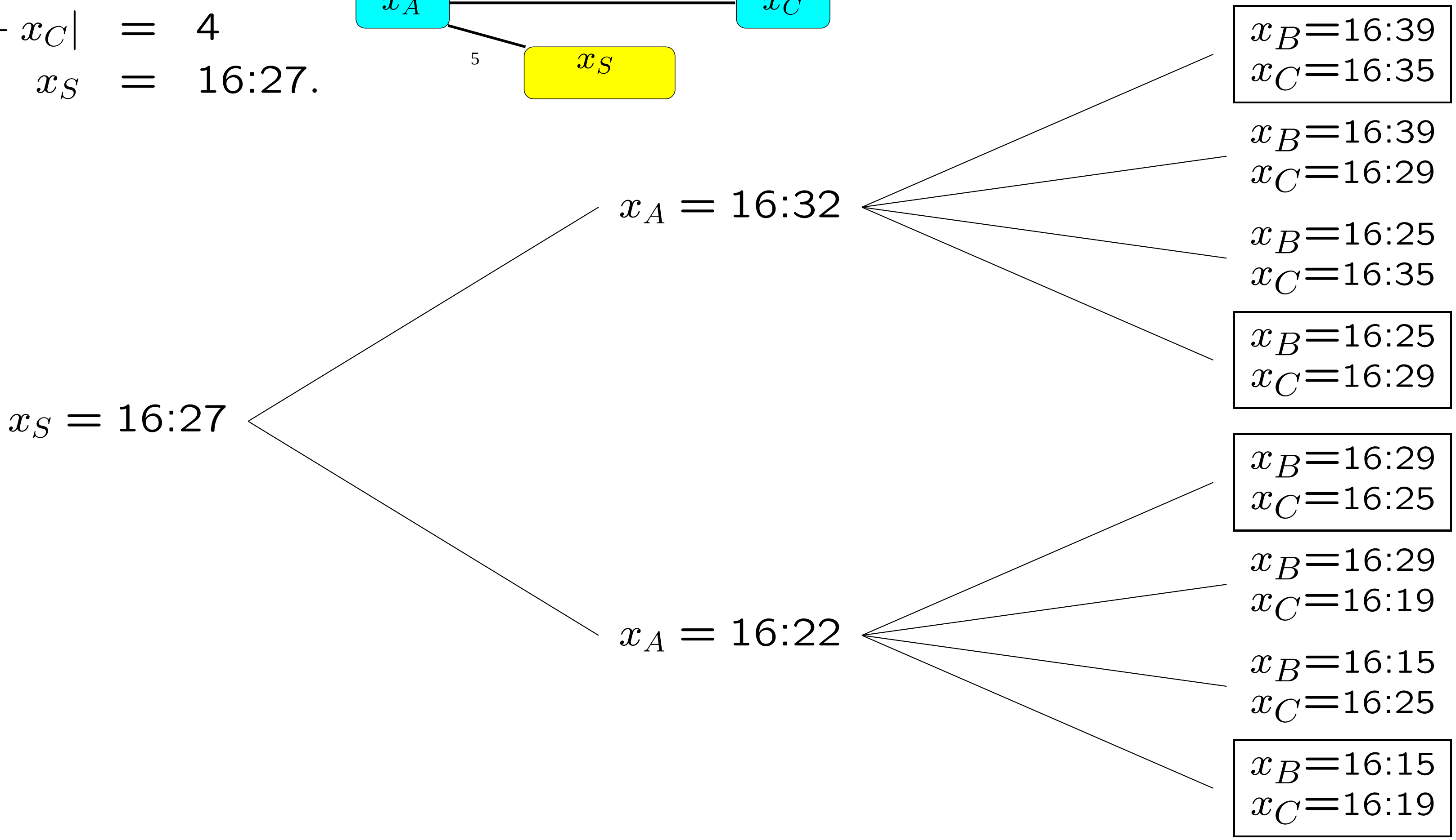


[Crippen & Havel 1988]

Clock synchronization: solutions

$$
\begin{aligned}
|x_A - x_B| &= 7 \\
|x_A - x_C| &= 3 \\
|x_A - x_S| &= 5 \\
|x_B - x_C| &= 4 \\
x_S &= 16{:}27.
\end{aligned}
$$





Distance Geometry Problem (DGP)

Given:

– a simple graph $G = (V, E)$

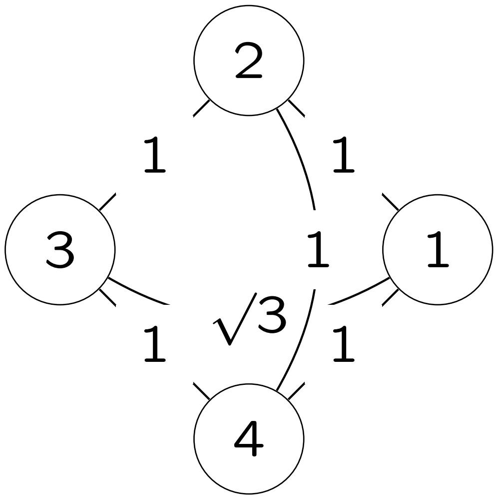
– an edge function $d : E \to \mathbb{R}_{\geq 0}$

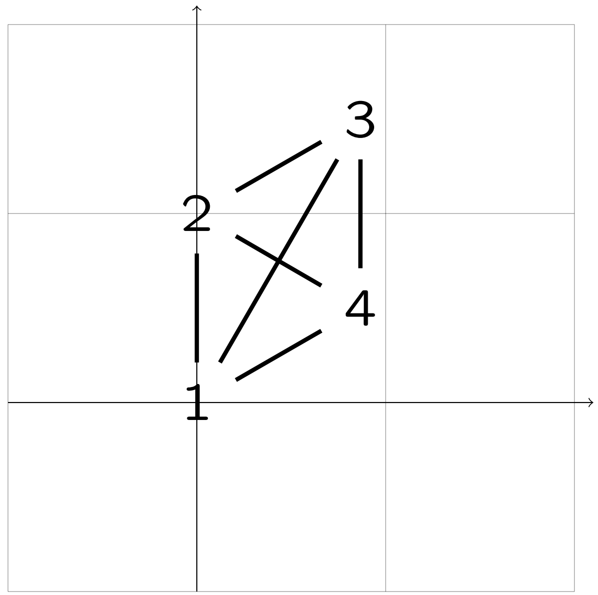
– an integer $K \in \mathbb{N}$

Determine whether ∃:

a *realization* $x : V \to \mathbb{R}^K$ s.t.

$\forall \{u, v\} \in E \quad \|x_u - x_v\|_2 = d_{uv}$





Let $n = |V|$

More applications

- Autonomous underwater vehicles [Bahr et al. 2009]

- Statics of rigid structures [Maxwell 1864]

- Matrix completion [Laurent 2009]

- Statistics [Boer 2013]

- Psychology [Kruskal 1964]

[Liberti et al., SIREV 2014]

Complexity primer

Definitions

- *Decision problem*: mathematical YES/NO-type question depending on a parameter vector π

- *Instance*: same as above with π replaced by given values v

- *Certificate*: proof that a given answer is true

- **P**: all decision problems solvable in at most $p(|\pi|)$ steps where p is a polynomial

- **NP**: all decision problems with $|\text{YES certificate}| \leq p(|\pi|)$ where p is a polynomial

Reductions

- P, Q: decision problems

- If $\exists$ algorithm A which:

  1. reformulates instances $\bar{P}$ of P into instances $\bar{Q}$ of Q
  2. has answer($\bar{P}$) = YES iff answer($A(\bar{P})$) = YES
  3. is polytime in the *instance size* $|\bar{P}|$

  then A is a *reduction* of P to Q

NP-hardness

- Q is **NP**-hard if every problem in **NP** reduces to Q

- Q is **NP**-complete if it is **NP**-hard and is in **NP**

Why does it work?

any P in **NP** $\xrightarrow{\text{polytime reduction}}$ Q: how hard?

- Suppose Q easier than P
- Solve P by reducing to Q in polytime and then solve Q
- Then P as easy as Q, against assumption
- $\Rightarrow$ Q at least as hard as P

So if Q is **NP**-hard it is as hard as any problem in **NP**

$\Rightarrow$ Q **is as hard as the hardest problem in NP**

NP-hardness proofs

Given a new problem Q, take any known **NP**-hard problem P and reduce it to Q

Why does it work?

P: **NP**-hard —polytime reduction→ Q: how hard?

- **As before**: Suppose . . . (etc.) $\Rightarrow$ Q at least as hard as P
- Since P is **NP**-hard, it is hardest in **NP**, and so is Q

$\Rightarrow$ Q is **NP**-hard

Complexity of the DGP

1. Applications
2. Definition
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4. **Complexity of the DGP**
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6. Mathematical optimization formulations
7. Realizing complete graphs
8. The Branch-and-Prune algorithm
9. Symmetry in the ^{K}DMDGP
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DGP $\in$ NP?

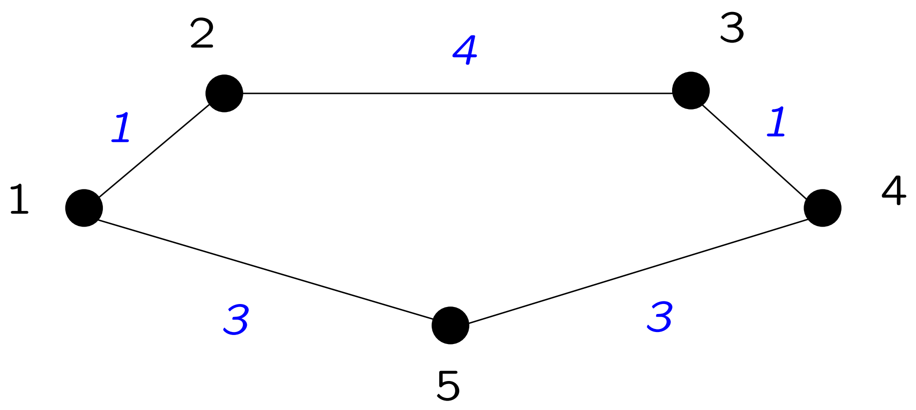
- **NP**: YES/NO problems with polytime-checkable proofs for YES
- DGP is a YES/NO problem
- $\text{DGP}_1 \in$ **NP**, since $d_{uv} = |x_u - x_v| \Rightarrow (d \in \mathbb{Q} \to x \in \mathbb{Q})$
- Solutions might involve irrational numbers when $K > 1$
- Some empirical evidence that DGP $\notin$ **NP** [Beeker et al. 2013]

The DGP is NP-hard

Partition

Given $a = (a_1, \ldots, a_n) \in \mathbb{N}^n$, $\exists\ I \subseteq \{1, \ldots, n\}$ s.t. $\sum\limits_{i \in I} a_i = \sum\limits_{i \notin I} a_i$?

- Reduce (**NP**-hard) Partition to DGP_1
- $a \longrightarrow$ cycle C with $V(C) = \{1, \ldots, n\}$, $E(C) = \{\{1, 2\}, \ldots, \{n, 1\}\}$
- For $i < n$ let $d_{i,i+1} = a_i$, and $d_{n,n+1} = d_{n1} = a_n$
- E.g. for $a = (1, 4, 1, 3, 3)$, get cycle graph:



[Saxe, 1979]

Partition is YES $\Rightarrow$ DGP$_1$ is YES

- **Given**: $I \subset \{1, \ldots, n\}$ s.t. $\sum\limits_{i \in I} a_i = \sum\limits_{i \notin I} a_i$

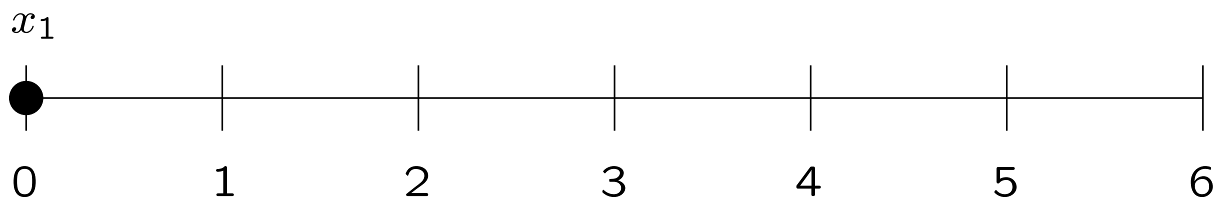
- **Construct**: realization x of C in $\mathbb{R}$

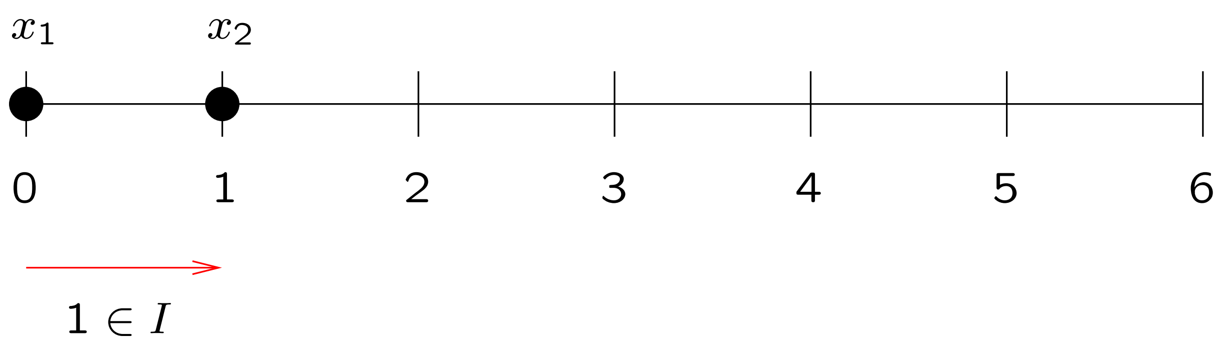
  1. $x_1 = 0$ `// start`

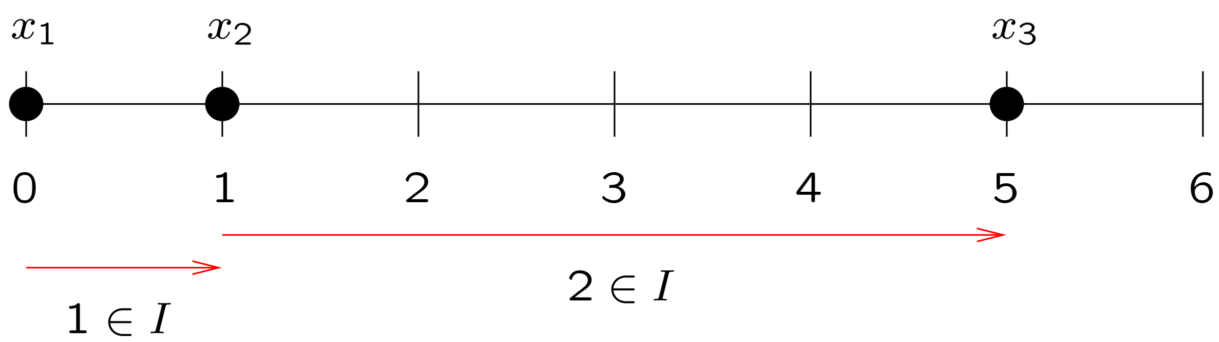
  2. **induction step**: suppose x_i known
     if $i \in I$
       let $x_{i+1} = x_i + d_{i,i+1}$ `// go right`
     else
       $x_{i+1} = x_i - d_{i,i+1}$ `// go left`

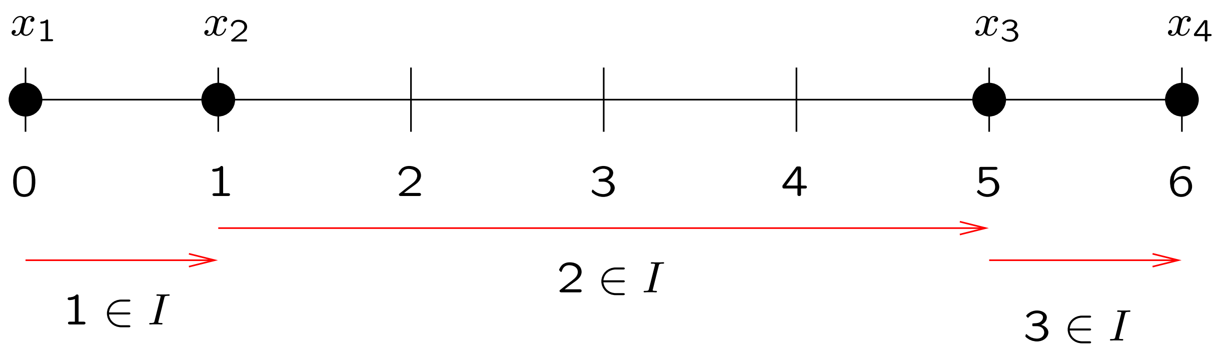
- **Correctness proof**: by the same induction
  but careful when $i = n$: have to show $x_{n+1} = x_1$

$I = \{1, 2, 3\}$

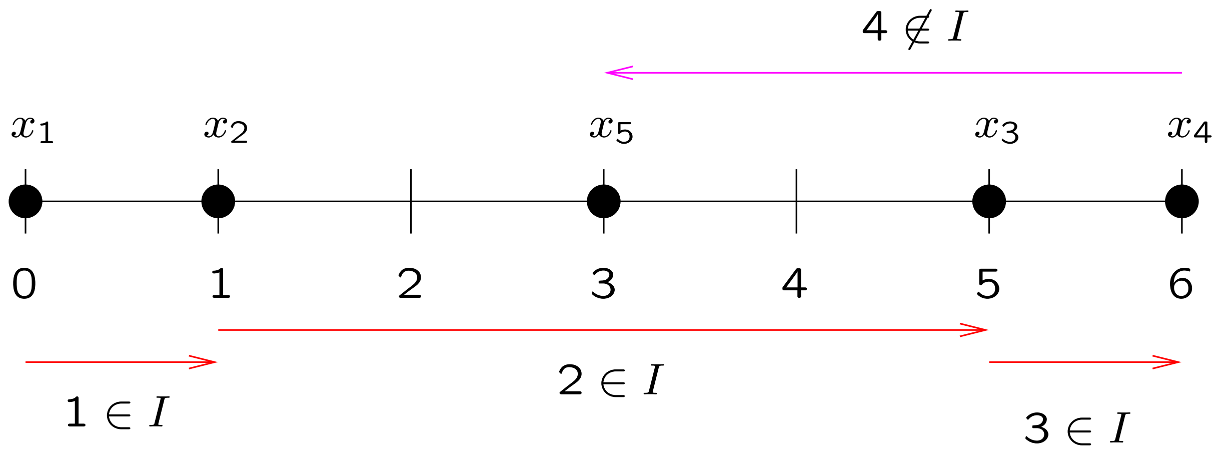



x_1
x_2
0
1
2
3
4
5
6
$1 \in I$

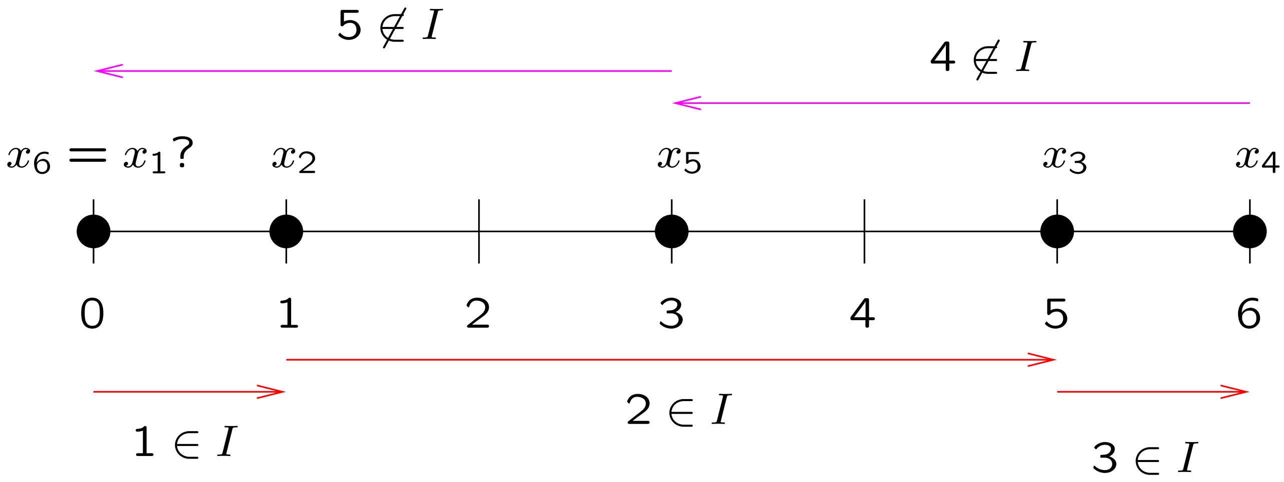

x_1
x_2
x_3
0
1
2
3
4
5
6
$1 \in I$
$2 \in I$



x_1
x_2
x_3
x_4
0
1
2
3
4
5
6
$1 \in I$
$2 \in I$
$3 \in I$



$4 \notin I$
x_1
x_2
x_5
x_3
x_4
0
1
2
3
4
5
6
$2 \in I$
$1 \in I$
$3 \in I$



$5 \notin I$
$4 \notin I$
$x_6 = x_1?$
x_2
x_5
x_3
x_4
0
1
2
3
4
5
6
$2 \in I$
$1 \in I$
$3 \in I$

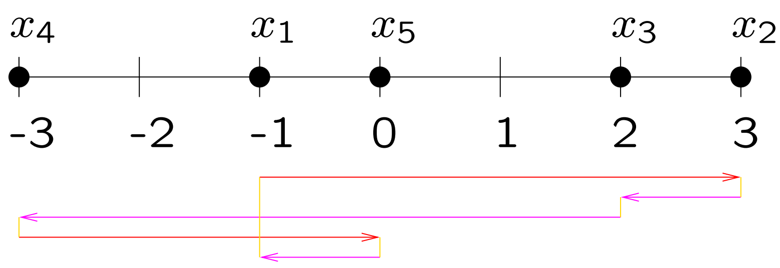
Partition is YES $\Rightarrow$ DGP$_1$ is YES

$$
\begin{aligned}
(1) = \sum_{i \in I} (x_{i+1} - x_i) &= \sum_{i \in I} d_{i,i+1} = \\
= \sum_{i \in I} a_i &= \sum_{i \notin I} a_i = \\
= \sum_{i \notin I} d_{i,i+1} &= \sum_{i \notin I} (x_i - x_{i+1}) = (2)
\end{aligned}
$$

$$
\begin{aligned}
(1) = (2) \Rightarrow \sum_{i \in I} (x_{i+1} - x_i) = \sum_{i \notin I} (x_i - x_{i+1}) \Rightarrow \sum_{i \leq n} (x_{i+1} - x_i) &= 0 \\
\Rightarrow (x_{n+1} - x_n) + (x_n - x_{n-1}) + \cdots + (x_3 - x_2) + (x_2 - x_1) &= 0 \\
\Rightarrow x_{n+1} &= x_1
\end{aligned}
$$

Partition is NO $\Rightarrow$ DGP$_1$ is NO

- By contradiction: suppose DGP$_1$ is YES, x realization of C
- $F = \{\{u,v\} \in E(C) \mid x_u \le x_v\}$, $E(C) \smallsetminus F = \{\{u,v\} \in E(C) \mid x_u > x_v\}$
- Trace $x_1, \ldots, x_n$: follow edges in F ($\rightarrow$) and in $E(C) \smallsetminus F$ ($\leftarrow$)



$$\sum_{\{u,v\}\in F} (x_v - x_u) = \sum_{\{u,v\}\notin F} (x_u - x_v)$$
$$\sum_{\{u,v\}\in F} |x_u - x_v| = \sum_{\{u,v\}\notin F} |x_u - x_v|$$
$$\sum_{\{u,v\}\in F} d_{uv} = \sum_{\{u,v\}\notin F} d_{uv}$$

- Let $J = \{i < n \mid \{i, i+1\} \in F\} \cup \{n \mid \{n, 1\} \in F\}$

$$\Rightarrow \quad \sum_{i\in J} a_i = \sum_{i\notin J} a_i$$

- So J solves Partition instance, contradiction
- $\Rightarrow$ DGP is **NP**-hard, DGP$_1$ is **NP**-complete

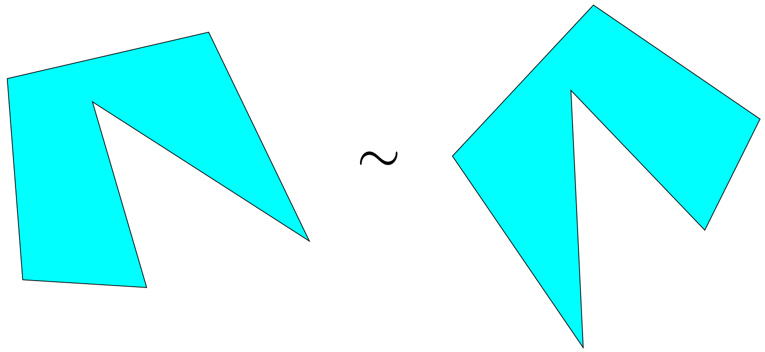
Number of solutions

With congruences

- (G, K): DGP instance
- $\tilde{X} \subseteq \mathbb{R}^{Kn}$: set of solutions
- *Congruence*: composition of translations, rotations, reflections
- $C =$ set of congruences in $\mathbb{R}^K$
- $x \sim y$ means $\exists \rho \in C\ (y = \rho x)$:
  distances in x are preserved in y through ρ
- $\Rightarrow$ if $|\tilde{X}| > 0$, $|\tilde{X}| = 2^{\aleph_0}$

Modulo congruences

- Congruence is an *equivalence relation* $\sim$ on $\tilde{X}$ (reflexive, symmetric, transitive)



- Partitions $\tilde{X}$ into *equivalence classes*

- $X = \tilde{X}/\sim$: sets of representatives of equivalence classes

- **Focus on $|X|$ rather than $|\tilde{X}|$**

Cardinality of X

- infeasible $\Leftrightarrow |X| = 0$
- rigid graph $\Leftrightarrow |X| < \aleph_0$
- globally rigid graph $\Leftrightarrow |X| = 1$
- flexible graph $\Leftrightarrow |X| = 2^{\aleph_0}$
- $|X| = \aleph_0$: impossible by Milnor's theorem

Milnor's theorem implies $|X| \neq \aleph_0$

- System S of polynomial equations of degree 2

$$\forall i \leq m \quad p_i(x_1, \ldots, x_{nK}) = 0$$

- Let X be the set of $x \in \mathbb{R}^{nK}$ satisfying S

- **Number of connected components of X is $O(3^{nK})$**
  [Milnor 1964]

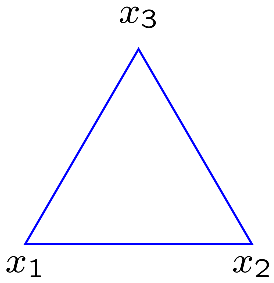
- If $|X|$ is countable then G cannot be flexible
  $\Rightarrow$ incongruent elements of X are separate connected components
  $\Rightarrow$ by Milnor's theorem, there's finitely many of them

Examples

$V^1 = \{1, 2, 3\}$

$E^1 = \{\{u, v\} \mid u < v\}$

$d^1 = 1$



ρ congruence in $\mathbb{R}^2$

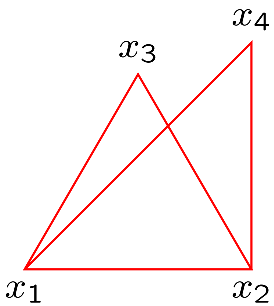
$\Rightarrow \rho x$ valid realization

$|X| = 1$

$V^2 = V^1 \cup \{4\}$

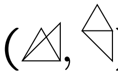
$E^2 = E^1 \cup \{\{1, 4\}, \{2, 4\}\}$

$d^2 = 1 \wedge d_{14} = \sqrt{2}$



ρ reflects x_4 wrt $\overline{x_1, x_2}$

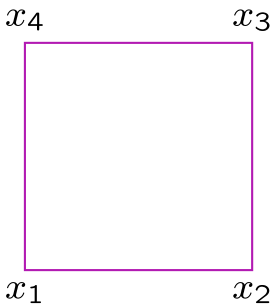
$\Rightarrow \rho x$ valid realization

$|X| = 2$ ()

$V^3 = V^2$

$E^3 = \{\{u, u+1\} | u \leq 3\} \cup \{1, 4\}$

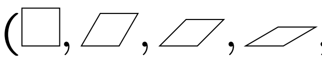
$d^1 = 1$



ρ rotates $\overline{x_2 x_3}$, $\overline{x_1 x_4}$ by θ

$\Rightarrow \rho x$ valid realization

$|X|$ is uncountable

(, ...)

Mathematical optimization formulations

System of quadratic constraints

$$\forall \{u,v\} \in E \qquad \|x_u - x_v\|^2 = d_{uv}^2$$

- Around 10 vertices
- Computationally useless

Quadratic objective

$$\min_{x \in \mathbb{R}^{nK}} \sum_{\{u,v\} \in E} (\|x_u - x_v\|^2 - d_{uv}^2)^2$$

- Globally optimal value **zero** iff x is a realization of G
- sBB: 10-100 vertices, exact solutions
- heuristics: 100-1000 vertices, poor quality

[Lavor et al., 2006]

Convexity and concavity

$$\begin{array}{rl} \max\limits_{x\in\mathbb{R}^{nK}} & \sum\limits_{\{u,v\}\in E} \|x_u - x_v\|^2 \\ \forall \{u,v\} \in E & \|x_u - x_v\|^2 \le d_{uv}^2 \end{array}$$

- Convex constraints, concave objective
- Computationally no better than “quadratic objective”

Pointwise reformulation

$$\begin{array}{rl} \max\limits_{x\in\mathbb{R}^{nK}} & \sum\limits_{\{u,v\}\in E, k\le K} \theta_{uvk}(x_{uk} - x_{vk}) \\ \forall \{u,v\} \in E & \|x_u - x_v\|^2 \le d_{uv}^2 \end{array}$$

- Convex subproblem in stochastic iterative heuristics
  "guess θ and solve"
- 100-1000 vertices, good quality

[L. IOS14/MAGO14(slides)]

SDP formulation

$$\min_{X \succeq 0} \sum_{\{u,v\} \in E} (X_{uu} + X_{vv} - 2X_{uv})$$

$$\forall \{u,v\} \in E \quad X_{uu} + X_{vv} - 2X_{uv} \geq d_{uv}^2$$

- Similar to those of Ye, Wolkowicz — works better for proteins
- 100 vertices, good quality

[D'Ambrosio et al., in progress]

Realizing complete graphs

1. Applications
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3. Complexity primer
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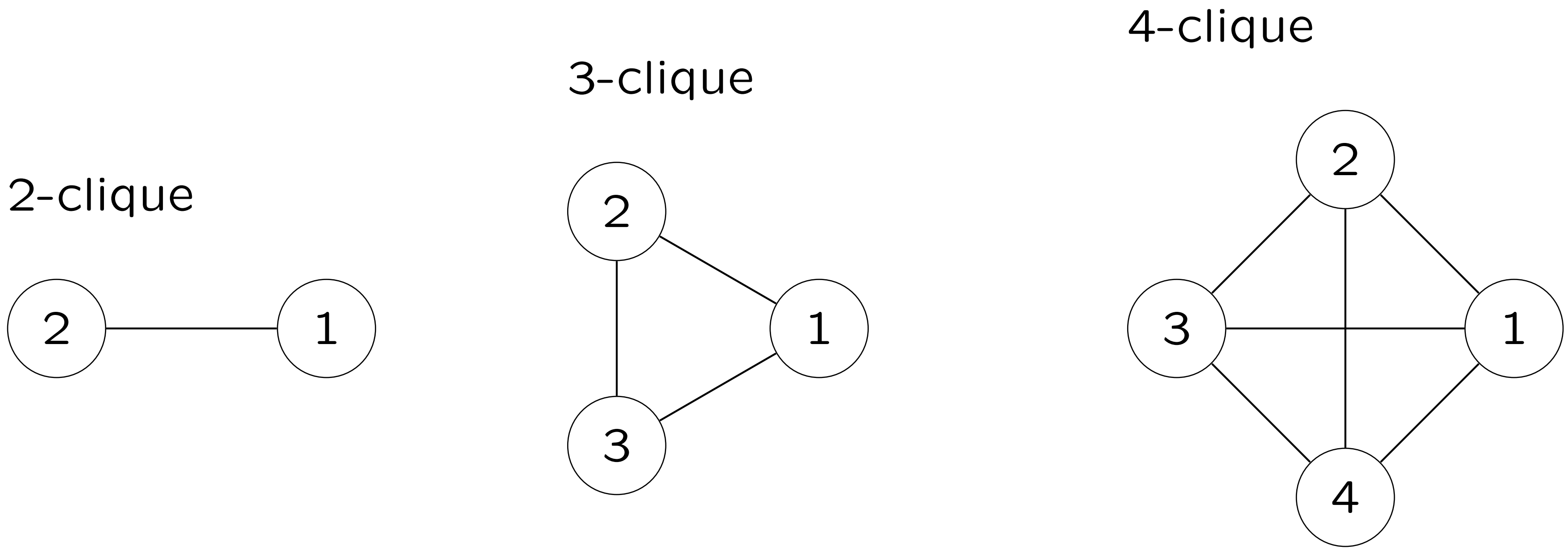
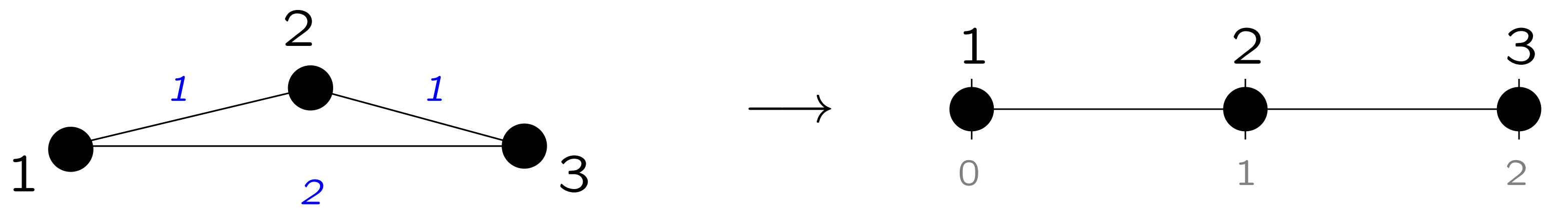
Cliques



$(K+1)$-clique $=$ K-clique $\oplus$ a vertex

Given a realization of the K-clique, find the position of the vertex

Triangulation



Example: realize triangle on a line

- From $\|x_3 - x_1\| = 2$ and $\|x_3 - x_2\| = 1$ get

$$
\begin{aligned}
x_3^2 - 2x_1x_3 + x_1^2 &= 4 \qquad (1)\\
x_3^2 - 2x_2x_3 + x_2^2 &= 1. \qquad (2)
\end{aligned}
$$

- (2) − (1) yields

$$
\begin{aligned}
2x_3(x_1 - x_2) &= x_1^2 - x_2^2 - 3\\
\Rightarrow \quad 2x_3 &= 4,
\end{aligned}
$$

- Hence $x_3 = 2$

Realizing a $(K+1)$-clique in $\mathbb{R}^{K-1}$

- Apply triangulation inductively on K
  assume $x_1, \ldots, x_K \in \mathbb{R}^{K-1}$ known, compute $y = x_{K+1}$

- K quadratic eqns ($\forall j \le K \ \|y - x_j\|^2 = d^2_{j,K+1}$) in $K-1$ vars

$$\left\{ \begin{array}{rcll} \|y\|^2 - 2x_1 \cdot y + \|x_1\|^2 & = & d^2_{1,K+1} & [1] \\ & \vdots & & \vdots \\ \|y\|^2 - 2x_K \cdot y + \|x_K\|^2 & = & d^2_{K,K+1} & [K] \end{array} \right.$$

- Form system $\forall j \le K-1$ ($[j] - [K]$)

$$\left\{ \begin{array}{rcll} 2(x_1 - x_K) \cdot y & = & \|x_1\|^2 - \|x_K\|^2 - d^2_{1,K+1} + d^2_{K,K+1} & [1] - [K] \\ & \vdots & & \vdots \\ 2(x_{K-1} - x_K) \cdot y & = & \|x_{K-1}\|^2 - \|x_K\|^2 - d^2_{K-1,K+1} + d^2_{K,K+1} & [K-1] - [K] \end{array} \right.$$

- This is a $(K-1) \times (K-1)$ linear system $Ay = b$

Solve to find y

[Dong, Wu 2002]

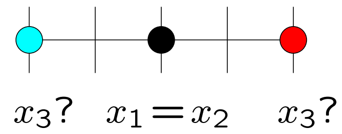
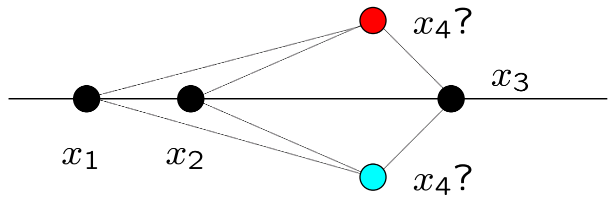
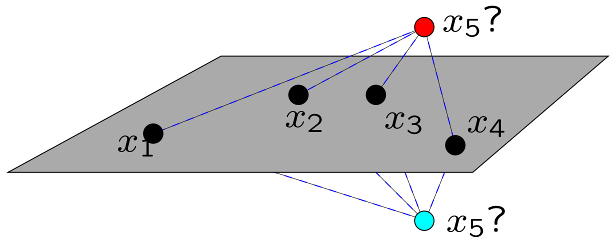
"Solve"?

1. What if A is singular?

2. Or: A nonsingular but instance is NO

Singularity: rk$A = K - 2$

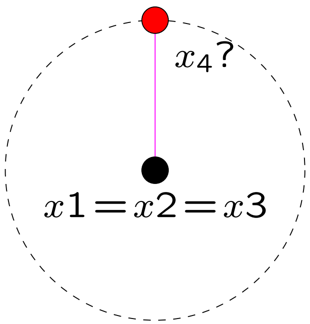
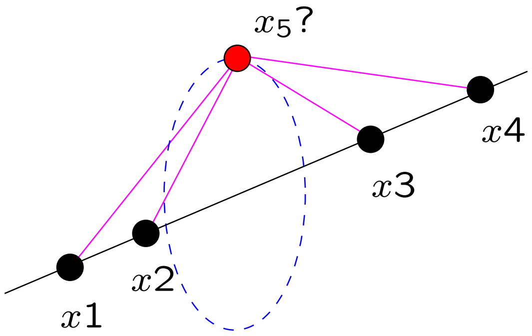
One row $x_j - x_K$ of A depends on the others

$K = 2$	triangle in $\mathbb{R}^1$	$x_1 - x_2 = 0$	
$K = 3$	4-clique in $\mathbb{R}^2$	x_1, x_2, x_3 on a line	
$K = 4$	5-clique in $\mathbb{R}^3$	$x_1, \ldots, x_4$ in a plane	

Trend continues: rk $A = K - 2 \Rightarrow |X| = 2$ (see later)

Singularity: rk$A = K - 3$

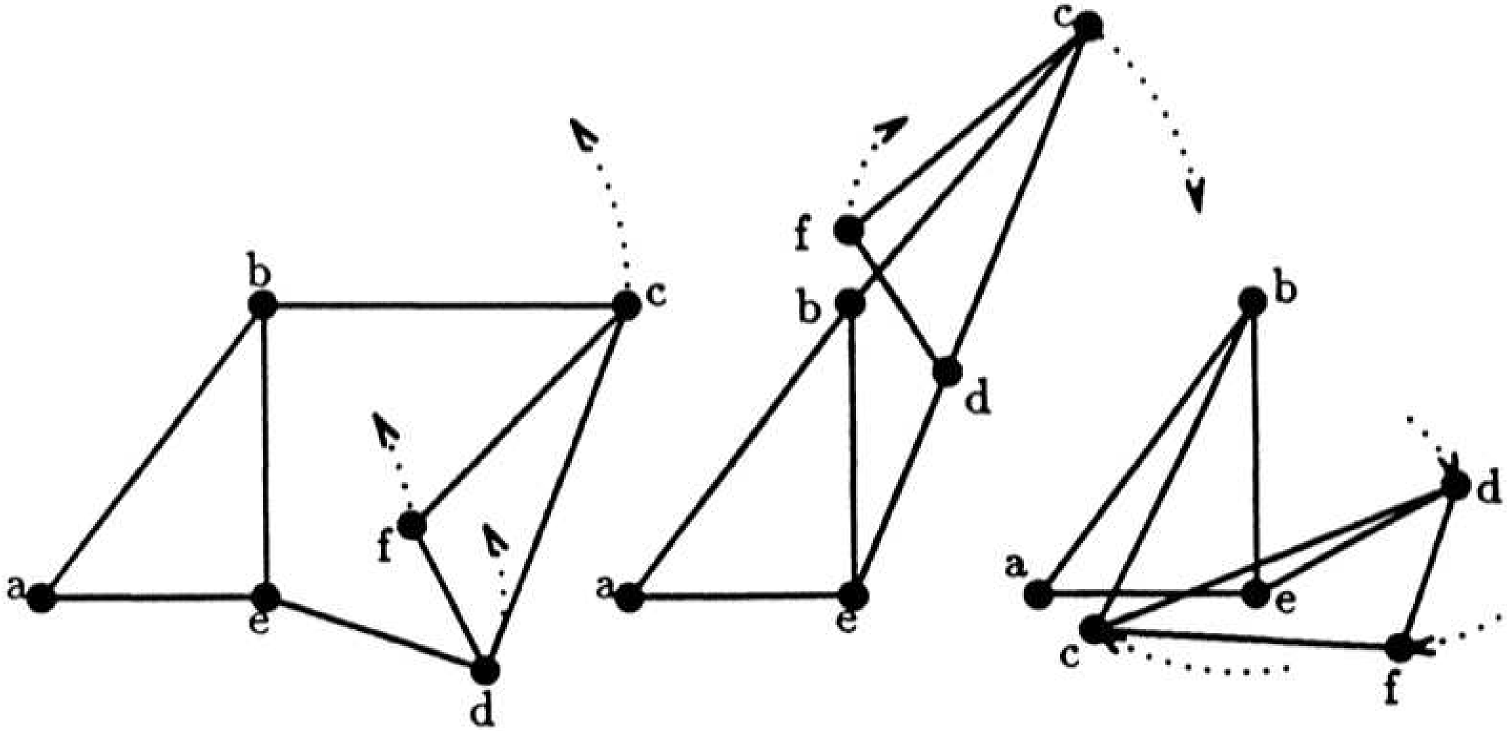
Two rows $x_j - x_k$ depend on the others

$K = 3$	4-clique in $\mathbb{R}^2$	$x_1 = x_2 = x_3$	
$K = 4$	5-clique in $\mathbb{R}^3$	$x_1, \ldots, x_4$ on a line	

Trend continues: [Hendrickson, 1992]

Thm. 5.8. *If a graph G is connected, flexible and has more than K vertices, X contains almost always a submanifold diffeomorphic to a circle*

Hendrickson's theorem also applies to non-cliques



Nonsingular matrix A with NO instance

- Infeasible quadratic system $\forall j \le K+1 \ \|x_j - x_K\|^2 = d_{jK}^2$
- Take differences, get nonsingular A and value for x_K
- ... but it's wrong!

Shit happens!

Every time you solve the linear system $Ay = b$
check feasibility with quadratic system

Algorithm for realizing complete graphs in $\mathbb{R}^K$

- Assume:

  (i) $G = (V, E)$ complete

  (ii) $|V| = n \geq K + 2$

  (iii) we know $x_1, \ldots, x_{K+1}$

- Increase K: we know how to realize x_{K+2} in $\mathbb{R}^K$

- Use this inductively for each $i \in \{K + 2, \ldots, n\}$

Algorithm for realizing complete graphs in $\mathbb{R}^K$

```
// realize next vertex iteratively
for i ∈ {K + 2, ..., n} do
    // use (K + 1) immediate adjacent predecessors to compute x_i
    if rkA = K then
        x_i = A^{-1} b // A, b defined as above
    else
        x_i = ∞ // A singular, mark ∞ and exit
        break
    end if
    // check that x_i is feasible w.r.t. other distances
    for {j ∈ N(i) | j < i} do
        if ||x_i − x_j|| ≠ d_ij then
            // if not, mark infeasible and exit loop *
            x_i = ∅
            break
        end if
    end for
    if x_i = ∅ then
        break
    end if
end for
return x
```

* the "ignore trouble" policy, a.k.a. "ignore probability zero events"

Complexity of Alg. 1

- Outer loop: $O(n)$
- Rank and inverse of A: $O(K^3)$
- Inner loop: $O(n)$
- Get $O(n^2 K^3)$
- But in most applications K is fixed
- **Get $O(n^2)$**

But how do we find the realization of the first $K+1$ vertices?

Realizing $(K + 1)$-cliques in $\mathbb{R}^K$

- Realizing $(K + 1)$-cliques in $\mathbb{R}^{K-1}$ yields "flat simplices" (e.g. triangles on lines)

- Use "natural" embedding dimension $\mathbb{R}^K$

- Same reasoning as above:
  get system $Ay = b$ where $y = x_{K+1}$ and $A_j = 2(x_j - x_K)$

- **But now A is $(K - 1) \times K$**

- *Same as previous case with A singular*

Almost square

How can you solve the following system $Ay = b$:

$$\begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1K} \\ \vdots & \vdots & \ddots & \vdots \\ a_{K-1,1} & a_{K-1,2} & \cdots & a_{K-1,K} \end{pmatrix} \begin{pmatrix} y_1 \\ \vdots \\ y_K \end{pmatrix} = \begin{pmatrix} b_1 \\ \vdots \\ b_{K-1} \end{pmatrix}$$

where A has one more column than rows and rank $K-1$?

Basics and nonbasics

- Since rk $A = K - 1$, $\exists$ $K - 1$ linearly independent columns
- $\mathcal{B}$: set of their indices
- $\mathcal{N}$: index of remaining column
- B: $(K-1) \times (K-1)$ square matrix of columns in $\mathcal{B}$
- $\Rightarrow$ B is nonsingular
- **Can partition columns as** $A = (B|N)$

  Column j corresponds to variable y_j
- Variables $y_{\mathcal{B}}$ are called *basic variables*
- Variable $y_{\mathcal{N}}$ is called *nonbasic variable*

The dictionary

$$\begin{aligned} (B|N)y &= b \\ \Rightarrow \qquad By_{\mathcal{B}} + Ny_{\mathcal{N}} &= b \\ \Rightarrow \qquad y_{\mathcal{B}} &= B^{-1}b - B^{-1}Ny_{\mathcal{N}} \end{aligned}$$

Basics expressed in function of nonbasic

One quadratic equation

- From value of $y_{\mathcal{N}}$, can use dictionary to get $y_{\mathcal{B}}$
- Use one quadratic equation

1. Pick any $h \in \{1,\ldots,K-1\}$, equation is $\|x_h - y\|_2^2 = d_{hK}^2$
2. $y = (y_{\mathcal{B}}|y_{\mathcal{N}})^\top$
3. Replace $y_{\mathcal{B}}$ with $B^{-1}b - B^{-1}Ny_{\mathcal{N}}$ in equation
4. Solve resulting quadratic equation in one variable $y_{\mathcal{N}}$
5. **Get 0,1 or 2 values for $y_{\mathcal{N}}$**
6. $\Rightarrow$ Get 0,1 or 2 positions for x_{K+1}

What if $B^{-1}N$ is zero?

- $y_\mathcal{B} = B^{-1}b - B^{-1}N y_\mathcal{N}$ reduces to $y_\mathcal{B} = B^{-1}b$

- Use one quadratic equation

  1. Pick any $h \in \{1, \ldots, K-1\}$, equation is $\|x_h - y\|_2^2 = d_{hK}^2$

  2. $y = (y_\mathcal{B} | y_\mathcal{N})^\top$

  3. Replace $y_\mathcal{B}$ with $B^{-1}b$ in equation

  4. Solve resulting quadratic equation in one variable $y_\mathcal{N}$

  5. **Get 0,1 or 2 values for $y_\mathcal{N}$**

  6. $\Rightarrow$ Get 0,1 or 2 positions for x_{K+1}

The difference

- $B^{-1}N \neq 0$: $y_{\mathcal{N}} \xrightarrow{\text{dictionary}} y_{\mathcal{B}}$

- Different values $y^+_{\mathcal{N}} \neq y^-_{\mathcal{N}} \longrightarrow y^+, y^-$ with different components

- $B^{-1}N = 0$: $y_{\mathcal{B}} \xrightarrow{\text{quadratic eqn.}} y_{\mathcal{N}}$

- Even if $y^+_{\mathcal{N}} \neq y^-_{\mathcal{N}}$, $K-1$ components of y^+, y^- are equal
  $\text{aff}(x_1, \ldots, x_{K-1}) = \{y \in \mathbb{R}^K \mid y_{\mathcal{N}} = 0\}$

The case of no solutions

- No realizations exist for this $(K+1)$-clique in $\mathbb{R}^K$

- **DGP instance is NO**

The case of one solution

- Assume for simplicity: $\mathcal{N} = K$, $h = 1$, $B^{-1}N \neq 0$
  Then $\|x_h - y\|^2 = d^2_{h,K+1}$ becomes:

$$
\begin{aligned}
\lambda y_K^2 - 2\mu y_K + \nu &= 0, \quad \text{where} \\
\lambda &= 1 + \sum_{\ell,j<K} \beta_{\ell j}^2 a_{jK}^2 \\
\mu &= x_{1K} + \sum_{\ell,j<K} \beta_{\ell j} a_{jK} (\beta_{\ell j} b_\ell - x_{1\ell}) \\
\nu &= \sum_{\ell,j<K} \beta_{\ell j} b_\ell (\beta_{\ell j} b_\ell - 2x_{1\ell}) + \|x_1\|^2 - d^2_{1,K+1}
\end{aligned}
$$

- (Exactly one solution for y_K) $\Leftrightarrow \mu^2 = \lambda\nu$, not a tautology

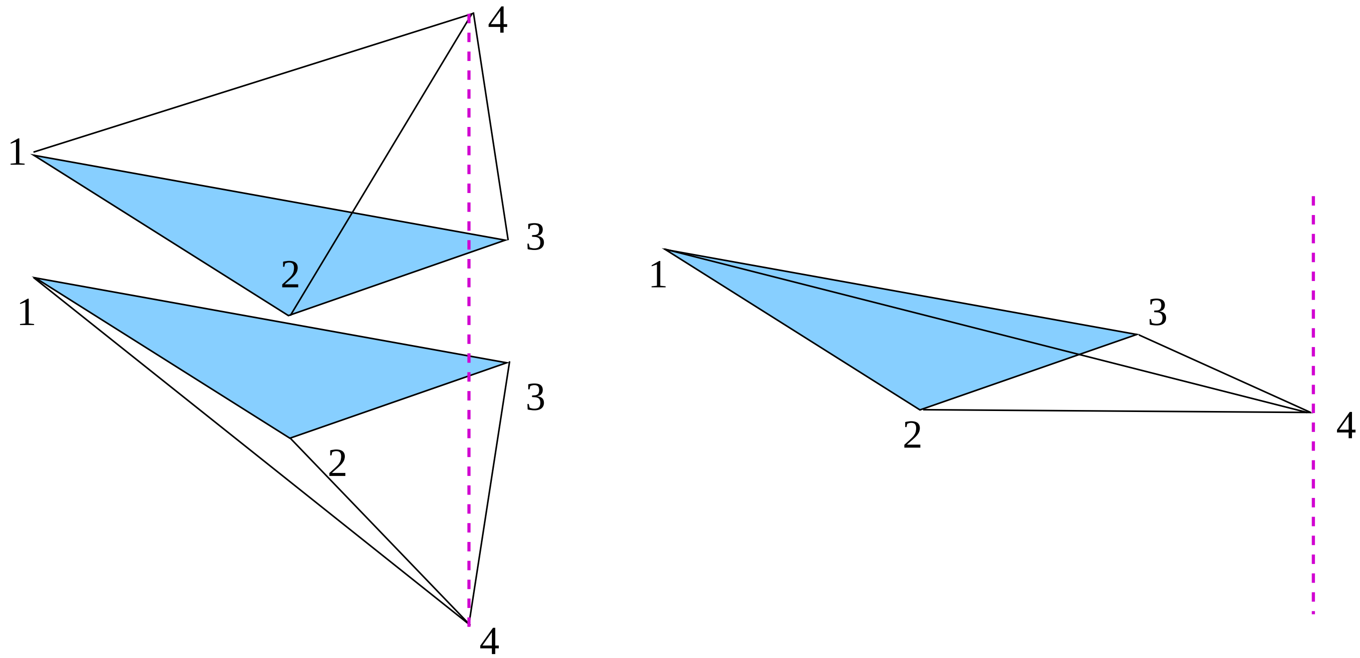
- The set of all $(K+1)$-clique DGP instances in $\mathbb{R}^K$ s.t. $\mu^2 = \lambda\nu$ has Lebesgue measure 0

- **Ignore them, they happen with probability* 0!**

* Assuming continuous distributions over the reals. For floating point number, who knows? . . .

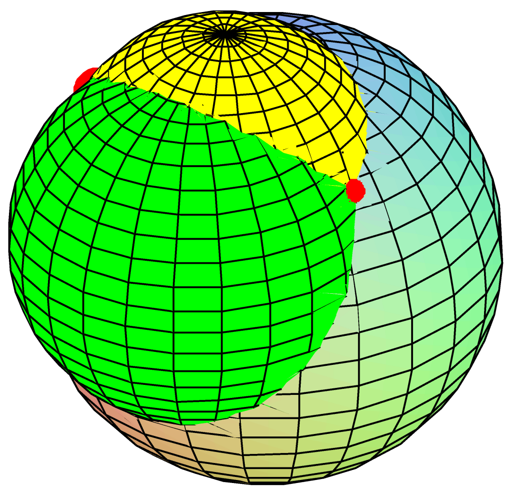
but we'll ignore these instances anyhow

Discriminant > 0, $= 0$



The case of two solutions

- K spheres $\mathbb{S}_1^{K-1}, \ldots, \mathbb{S}_K^{K-1}$ in $\mathbb{R}^K$
  centered at $x_1, \ldots, x_K$
  with radii $d_{1,K+1}, \ldots, d_{K,K+1}$
- x_{K+1} must be at the intersection of $\mathbb{S}_1^{K-1}, \ldots, \mathbb{S}_K^{K-1}$
- If $\bigcap_j \mathbb{S}_j^{K-1} \neq \varnothing$, then $|\bigcap_j \mathbb{S}_j^{K-1}| = 2$ in general



- *will not mention "probability 0" or "in general" anymore*

[Coope 2000]

Mirror images

- Let $x^{+} = \{x_1, \ldots, x_K, x^{+}_{K+1}\}$, $x^{-} = \{x_1, \ldots, x_K, x^{-}_{K+1}\}$
  assume $\dim \mathrm{aff}(x_1, \ldots, x_K) = K - 1$ (†)

- **Theorem**
  x^{+}, x^{-} are reflections w.r.t. hyperplane defined by $x_1, \ldots, x_K$

- *Proof*
  1. x^{+}, x^{-} congruent by construction
  2. $\forall i \leq K\ x_i \in x^{+} \cap x^{-} \to x^{+}, x^{-}$ not translations
  3. $|x^{+} \cap x^{-}| = K < |x^{+}| = |x^{-}| \to x^{+}, x^{-}$ not rotations by (†)
  4. $\Rightarrow$ must be reflections

Algorithm for realizing $(K+1)$-cliques in $\mathbb{R}^K$

// realize 1 at the origin

$x_1 = (0, \ldots, 0)$

// realize next vertex iteratively

for $\ell \in \{2, \ldots, K+1\}$ **do**

  // at most two positions in $\mathbb{R}^{\ell-1}$ for vertex ℓ

  $S = \bigcap_{i<\ell} \mathbb{S}_i^{\ell-2}$

  if $S = \varnothing$ **then**

    // warn: infeasible

    return $\emptyset$

  end if

  // arbitrarily choose one of the two points

  choose any $x_\ell \in S$

end for

// return feasible realization

return x

Complexity of Alg. 2

- Outer loop: $O(K)$
- Gaussian elimination on A: $O(K^3)$
- Some messing about to obtain x^+_{K+1}, x^-_{K+1}: $+O(K^2)$
- Get $O(K^4)$
- But in most applications K is fixed
- **Get** $O(1)$

Back to complete graphs

- Alg. 2: realize $1, \ldots, K+1$ in $\mathbb{R}^K$: $O(1)$
- Alg. 1: Realize $K+2, \ldots, n$: $O(n^2)$
- $\Rightarrow O(n^2)$
- **What about $|X|$?**
  - Alg. 1 is deterministic: one solution from $x_1, \ldots, x_{K+1}$
  - Alg. 2 is stochastic: pick one of two values K times

$$\Rightarrow |X| = 2^K$$

Let's look at sparser graphs

K-trilaterative graphs

- In Alg. 1 we only need each $v > K+1$ to have $K+1$ adjacent predecessors in order to find a unique solution for x_v
- Determination of x_v from $K{+}1$ adjacent predecessors: K-*trilateration*
- K-*trilaterative graph*:
  (i) has a vertex order ensuring this property
  (ii) the initial $K+1$ vertices induce a $(K+1)$-clique
  the order is called K-*trilateration order*
- Alg. 1 realizes all K-trilaterative graphs

The DGP restricted to K-trilaterative graphs in $\mathbb{R}^K$ is easy

[Eren et al. 2004]

The story so far

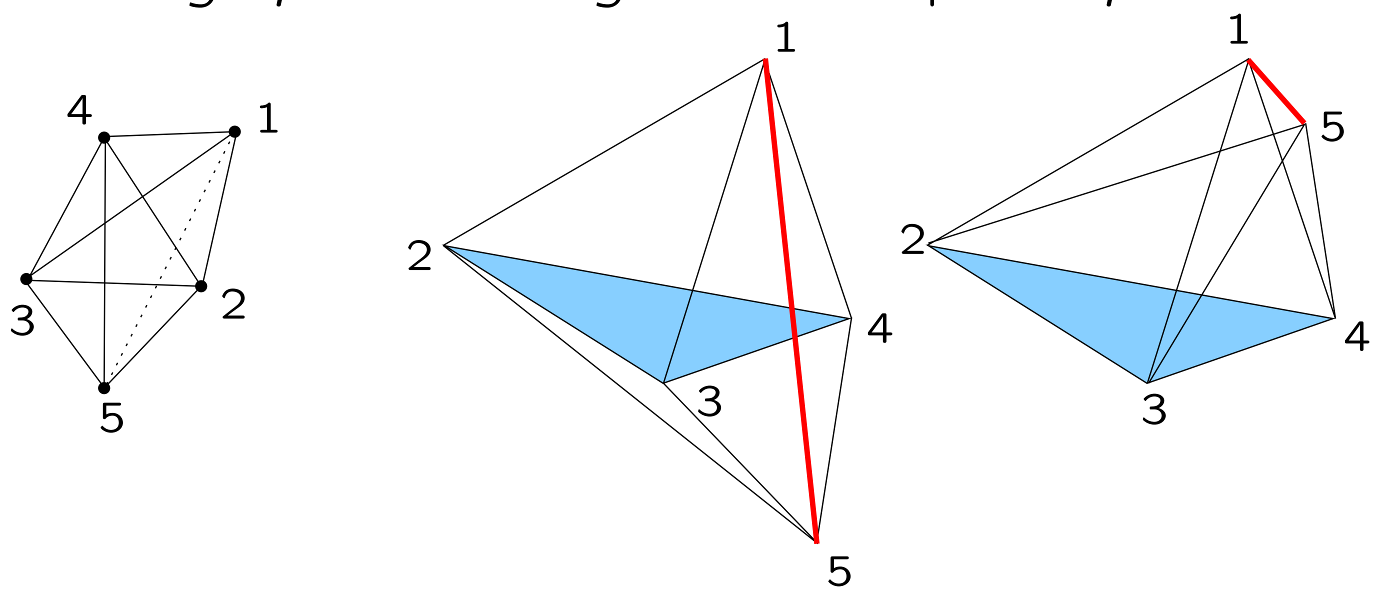
- Lots of nice applications
- DGP is **NP**-hard
- May have $0, 1$, finitely many or $2^{\aleph_0}$ solutions modulo congruences
- Continuous optimization techniques don't scale well
- Using $K + 1$ adjacent predecessors, realize K-trilaterative graphs in $\mathbb{R}^K$ in polytime
- **Do we** *need* $K + 1$ **adjacent predecessors, or can we do with less?**

The Branch-and-Prune algorithm

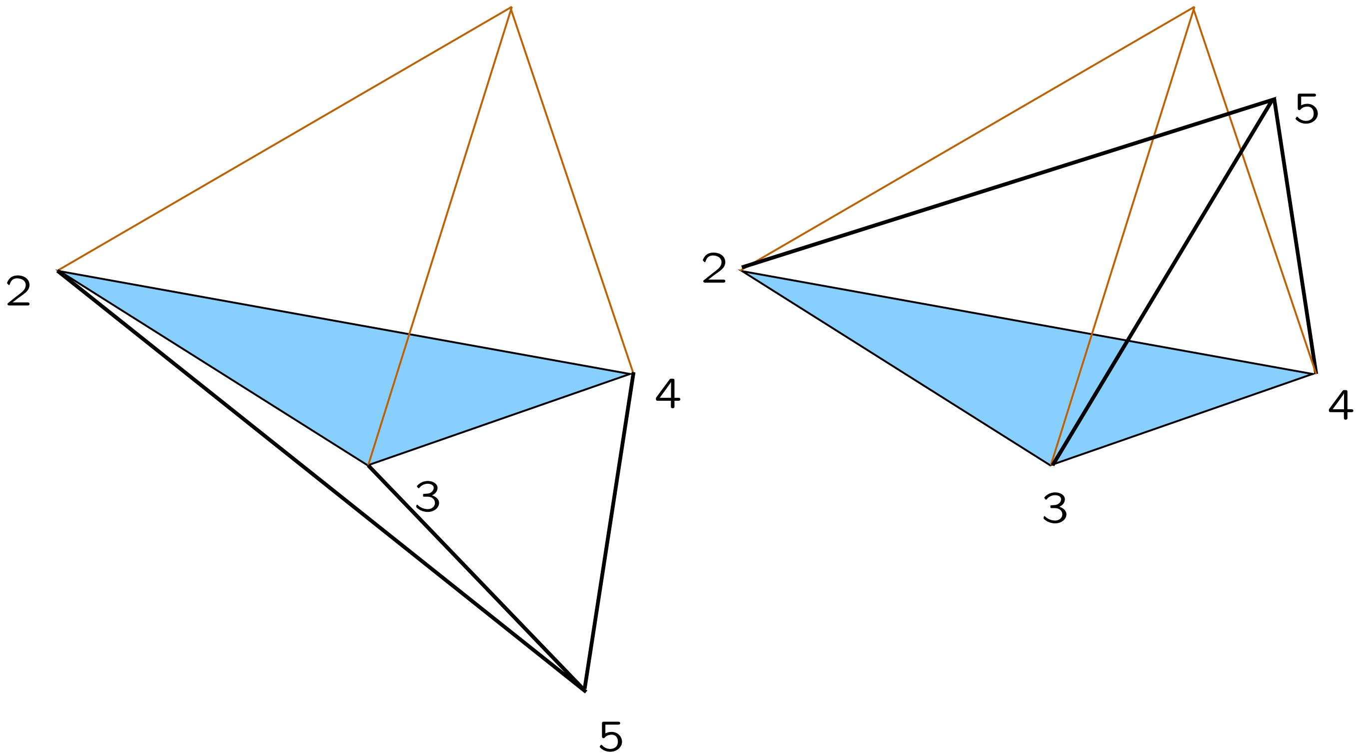
1. Applications
2. Definition
3. Complexity primer
4. Complexity of the DGP
5. Number of solutions
6. Mathematical optimization formulations
7. Realizing complete graphs
8. **The Branch-and-Prune algorithm**
9. Symmetry in the ^{K}DMDGP
10. Tractability of protein instances
11. Finding vertex orders
12. Approximate realizations

Fewer adjacent predecessors

- **Alg. 2 only needs K adjacent predecessor**
- Extend to n vertices: $(K-1)$-trilaterative graphs
- Can we realize $(K-1)$-trilaterative graphs in $\mathbb{R}^K$?
- *A small case: graph consisting of two $K+1$ cliques*



Take a closer look...



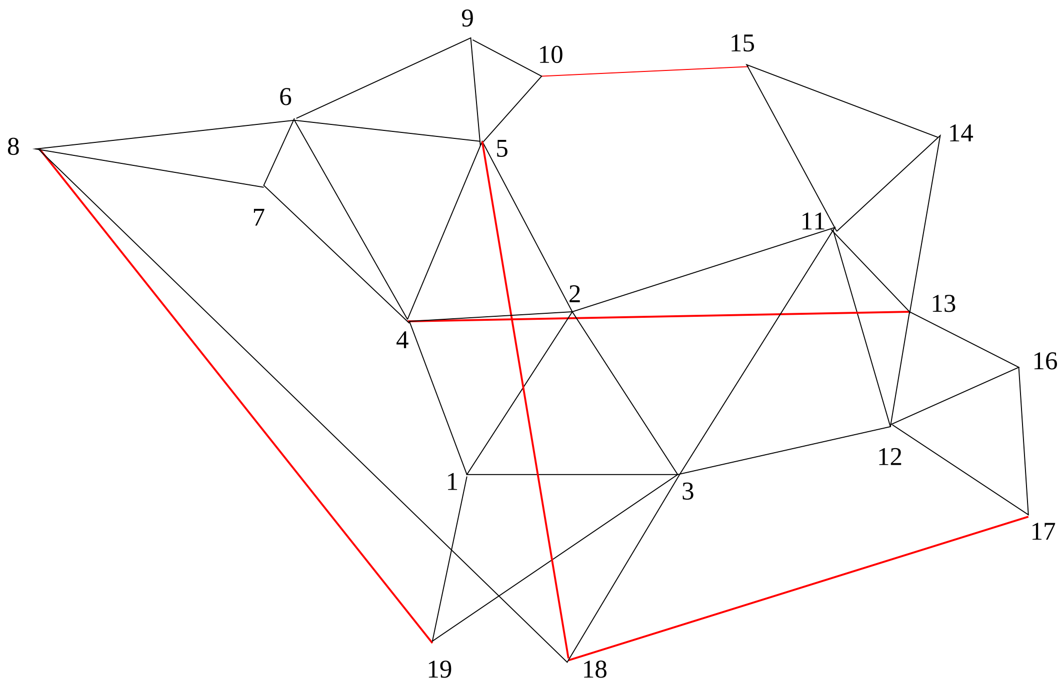
- Realization of a $K+1$ clique in $\mathbb{R}^K$ knowing $x_1, \ldots, x_K$
- **We know how to do that!**
- Consistent with 2 solutions for x_5, reflected across plane through x_2, x_3, x_4

Discretization and pruning edges

- $(K-1)$-*trilaterative graph* $G=(V,E)$:
  $\forall v > K\ \exists U_v \subset V\ (|U_v| = K\ \wedge\ \forall u \in U_v (u < v)\ \wedge\ \{u,v\} \in E)$

- **Discretization edges**:
  $$E_D = \underbrace{\{\{u,v\} \in E \mid u,v \le K\}}_{\text{initial clique}} \cup \underbrace{\{\{u,v\} \in E \mid v > K \wedge u \in U_v\}}_{\text{vertex order}}$$

- **Pruning edges** $E_P = E \smallsetminus E_D$

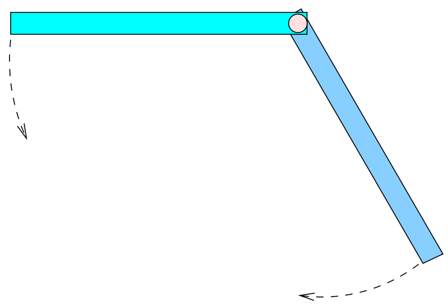


Role of discretization edges

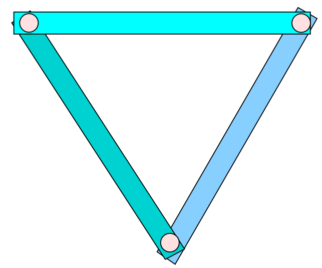
Missing discretization edge

$\Rightarrow$ non-rigid structure

$\Rightarrow X$ **uncountable**

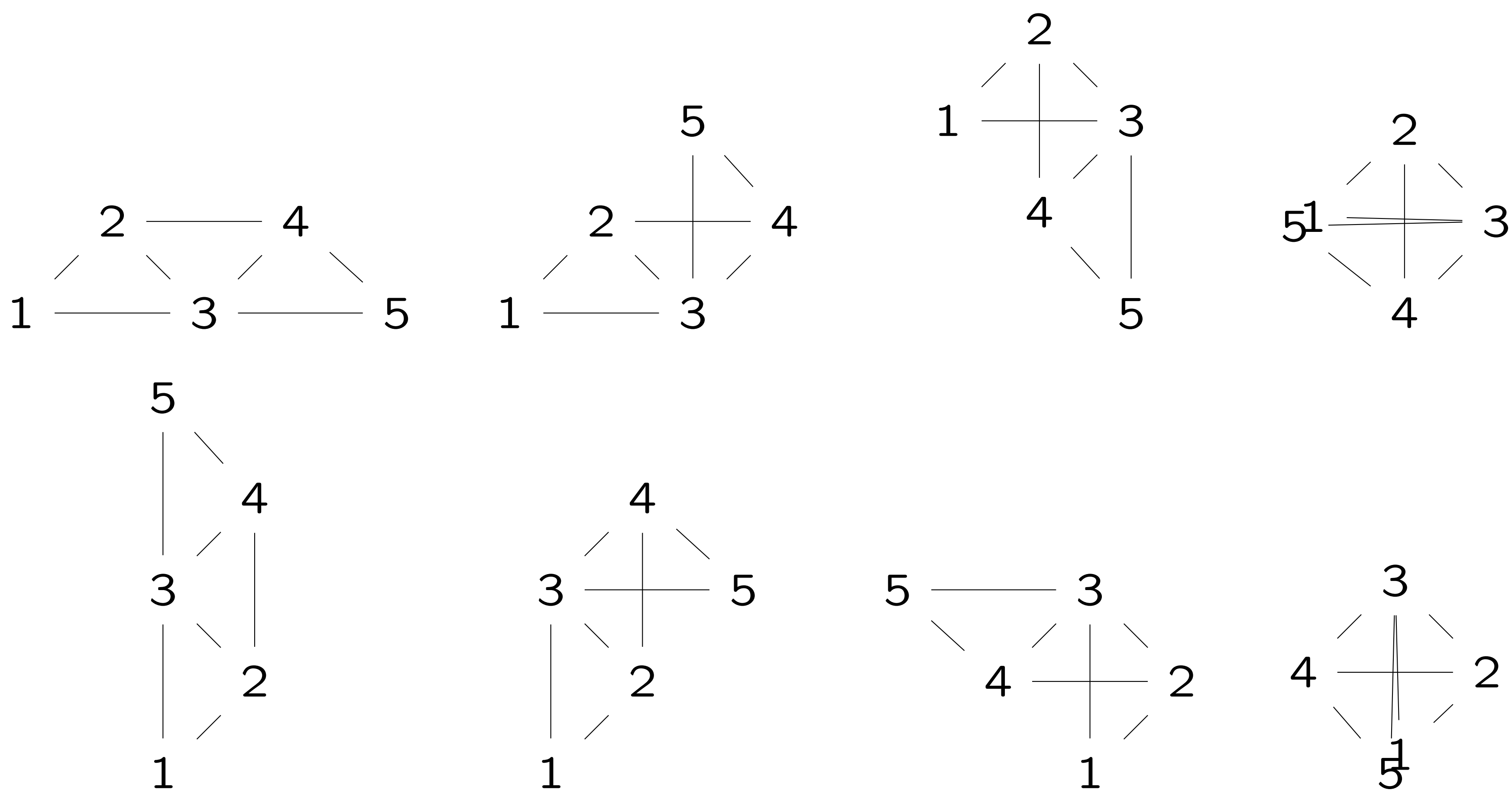


Else: X **finite**



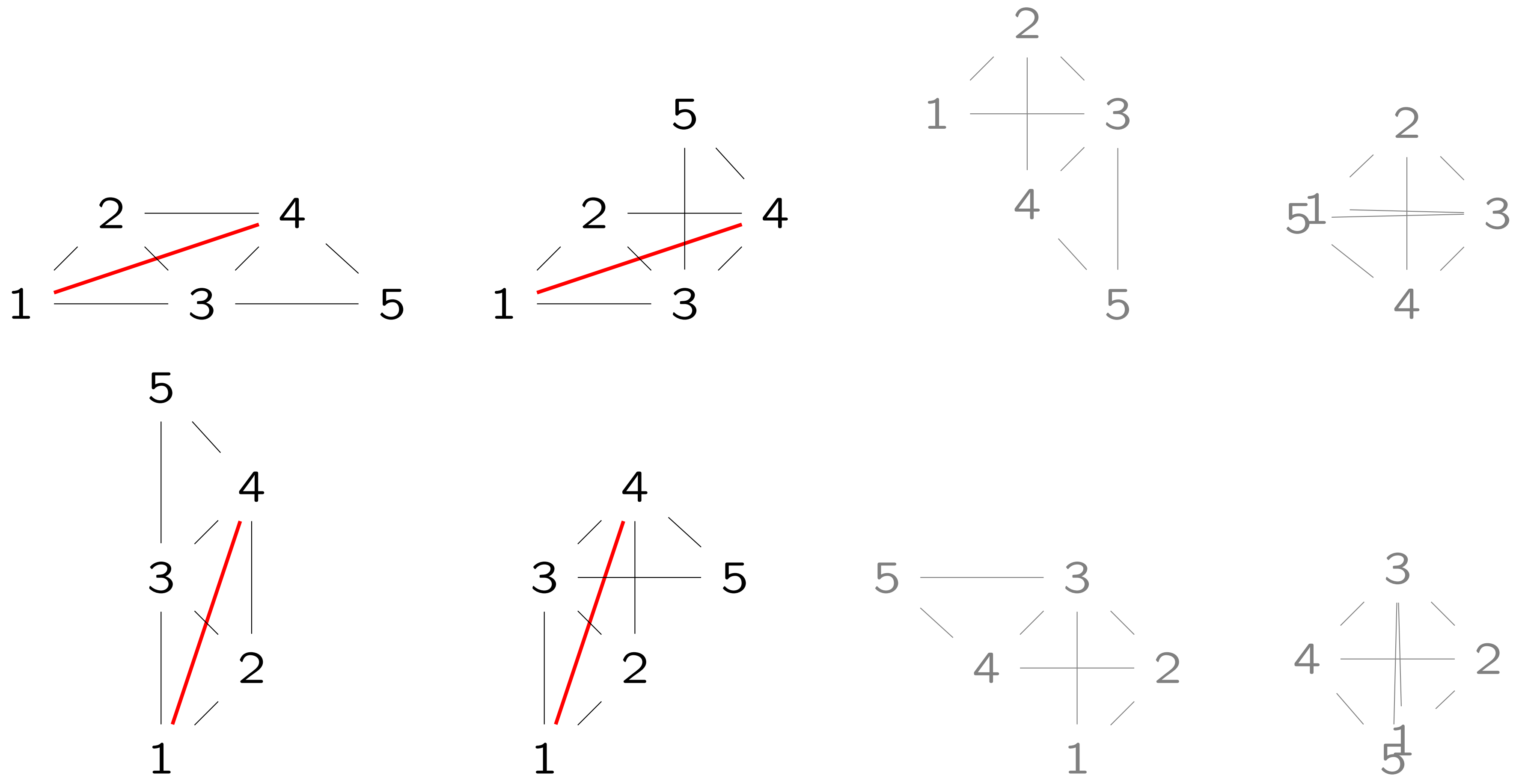
Role of pruning edges

No pruning edges: 8 incongruent realizations in $\mathbb{R}^2$



Role of pruning edges

Pruning edge $\{1, 4\}$: only 4 realizations remain valid



Motivation

Protein backbones

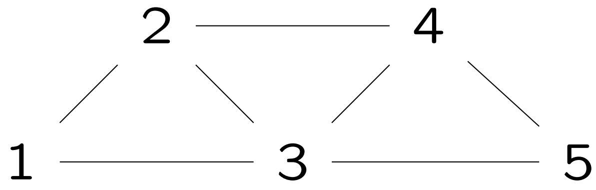
- Total order $<$ on V
- Covalent bond **distances**: $\{u-1, u\} \in E$
- Covalent bond **angles**: $\{u-2, u\} \in E$
- **NMR experiments**: $\{u-3, u\} \in E$
  (and other edges $\{u, v\}$ with $v - u > 3$)

Generalize "3" to K

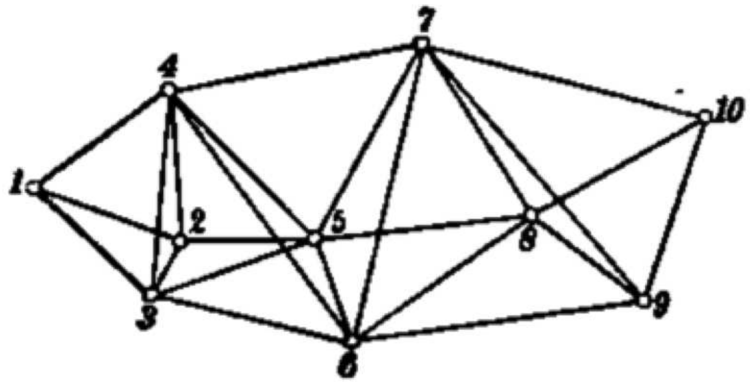
[Lavor et al., COAP 2012]

^{K}DMDGP graphs

$K = 2$



$K = 3$



Generalization of **protein backbone order**:

$v > K$ is adjacent to K **immediate predecessors** $v-1, \ldots, v-K$

^{K}DMDGP: Discretizable Molecular Distance Geometry Problem

The Branch-and-Prune (BP) algorithm

BP$(v,\ \bar{x},\ X)$:

1. Given $v > K$, realization $\bar{x} = (x_1, \ldots, x_{v-1})$
2. Compute $S = \bigcap_{u \in U_v} \mathbb{S}_u^{K-1}$
3. For each $x_v \in S$ s.t. $\forall \{u, v\} \in E_P \ (u < v \to \|x_u - x_v\| = d_{uv})$
   (a) let $x = (\bar{x}, x_v)$
   (b) if $v = n$ add x to X, else call **BP**$(v + 1,\ x,\ X)$

- Recursive: starts with **BP**$(K + 1,\ (x_1, \ldots, x_K),\ \varnothing)$
- **All realizations in X are incongruent***
- Can be easily modified to find only p solutions for given p
- Applies to all $(K - 1)$-trilaterative graphs in $\mathbb{R}^K$
- Specialize to ^{K}DMDGP graph by setting $U_v = \{v - 1, \ldots, v - K\}$

* with probability 1, and aside from *one* reflection at $v = K + 1$

[L. et al. ITOR 2008]

Complexity of BP

- Most operations are $O(K^h)$ for some fixed $h \Rightarrow O(1)$
- Distance check at Step 3: $O(n)$
- Recursion on at most 2 branches at each call: **binary tree**
- Only recurse when $v > K, v < n$: 2^{n-K} nodes
- **Overall** $O(n2^{n-K}) = O(2^n)$

Worst-case exponential behaviour

Hardness of ^{K}DMDGP

- The ^{K}DMDGP is **NP**-hard for each K
  - every DGP instance is also DMDGP if $K = 1$
  - reduction from Partition can be extended to any K
- $(K-1)$-trilateration graphs are **NP**-hard by inclusion
- **No polytime algorithm unless P=NP**

Trilaterative graphs in $\mathbb{R}^K$ *are complexitywise borderline at* K

Correctness

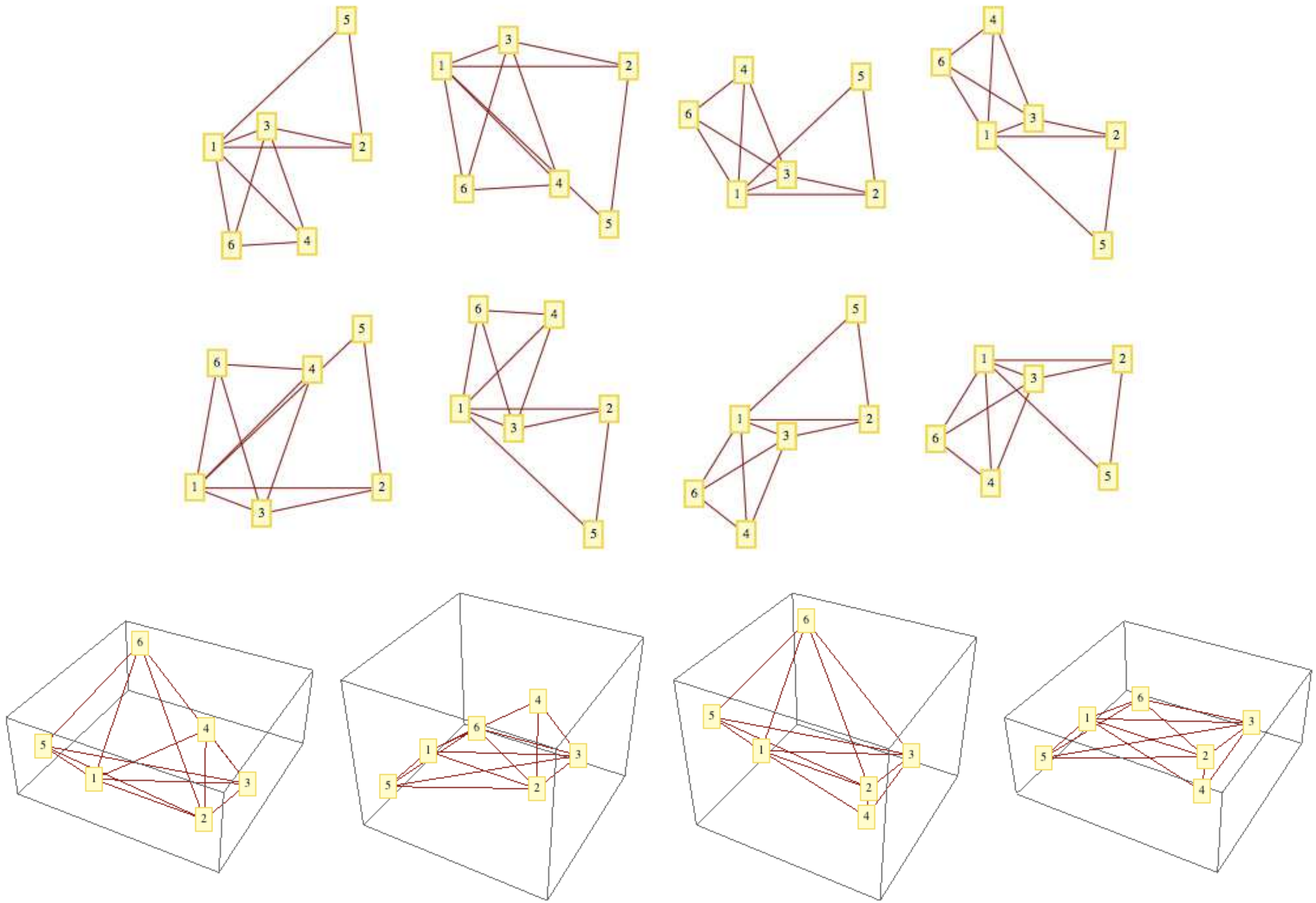
Thm.
When BP terminates, X contains every incongruent realization of G

Proof.

- Let $\bar{y}$ be any realization of G
- Since G has an initial K-clique, can rotate/translate/reflect $\bar{y}$ to $y[K] = x[K]$ for all $x \in X$
- BP exhaustively constructs every extension of $x[K]$ which is feasible with all distances, so $y \in X$

for a realization y, $y[h] = (y_1, \ldots, y_h)$ is the *initial segment* of y

Two examples



Empirical observations

- **Fast**: up to 10k vertices in a few seconds on 2010 hardware
- **Precise**: errors in range $O(10^{-9})$-$O(10^{-12})$
- Number of solutions always a power of 2:
  obvious if $E_P = \varnothing$, but otherwise mysterious
- **Linear-time behaviour on proteins**:
  this really shouldn't happen

Symmetry in the ^{K}DMDGP

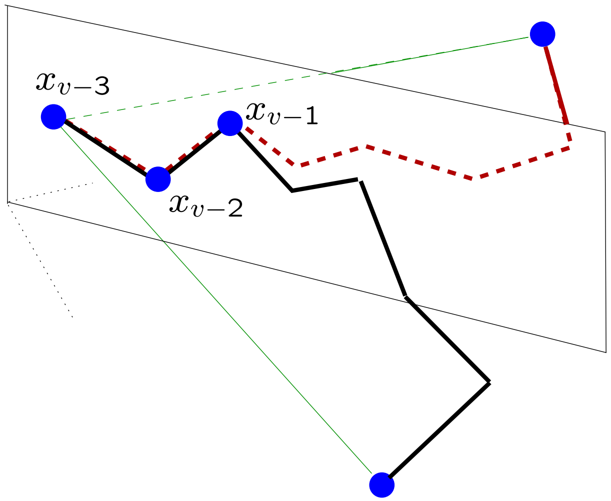
[L. et al. DAM 2014]

Partial reflections

- For each $v > K$, let

$$g_v(x) = (x_1, \ldots, x_{v-1}, R_x^v(x_v), \ldots, R_x^v(x_n))$$

be the *partial reflection* of x w.r.t. v



- Note: the g_v's are idempotent operators
- $G_D = (V, E_D)$: subgraph of G given by discretization edges
- $\forall v > K$ reflection R_x^v gives a binary choice in general*
- $X_D \subset \mathbb{R}^{nK}$ contains 2^{n-K} incongruent realizations of G_D

* subsequent results hold "with probability 1"

Discretization group

- $\mathscr{G}_D = \langle g_v \mid v > K \rangle$: the *discretization group* of G w.r.t. K
  subgroup of a Cartesian product of reflection groups

- An element $g \in \mathscr{G}_D$ has the form $\bigotimes_{v>K} g_v^{a_v}$, where $a_v \in \{0, 1\}$

- Action of $\mathscr{G}_D$ on X_D: $g(x) = \left(g_{K+1}^{a_{K+1}} \circ \cdots \circ g_n^{a_n}\right)(x)$

Commutativity of partial reflections

Lemma A $\mathscr{G}_D$ is Abelian

Proof Assume $K < u < v$. Then

$$\begin{aligned}
g_u g_v(x) &= g_u(x_1, \ldots, x_{v-1}, R^v_x(x_v), \ldots, R^v_x(x_n)) \\
&= (x_1 \ldots, x_{u-1}, R^u_{g_v(x)}(x_u), \ldots, R^u_{g_v(x)} R^v_x(x_v), \ldots, R^u_{g_v(x)} R^v_x(x_n)) \\
&= (x_1 \ldots, x_{u-1}, R^u_x(x_u), \ldots, R^v_{g_u(x)} R^u_x(x_v), \ldots, R^v_{g_u(x)} R^u_x(x_n)) \\
&= g_v(x_1, \ldots, x_{u-1}, R^u_x(x_u), \ldots, R^u_x(x_n)) \\
&= g_v g_u(x)
\end{aligned}$$

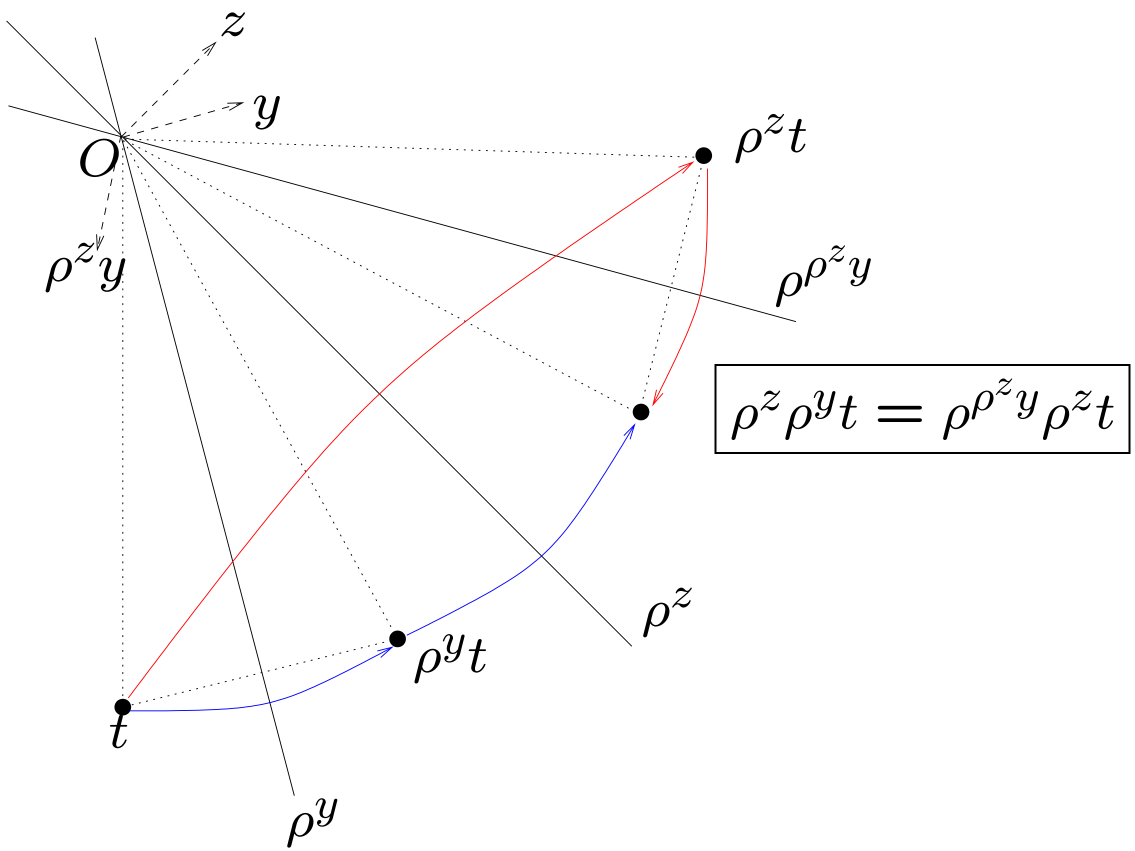
where equality of these terms holds by a Technical Lemma
(next slide)

[L. et al. 2013]

Commutativity of partial reflections

Technical Lemma

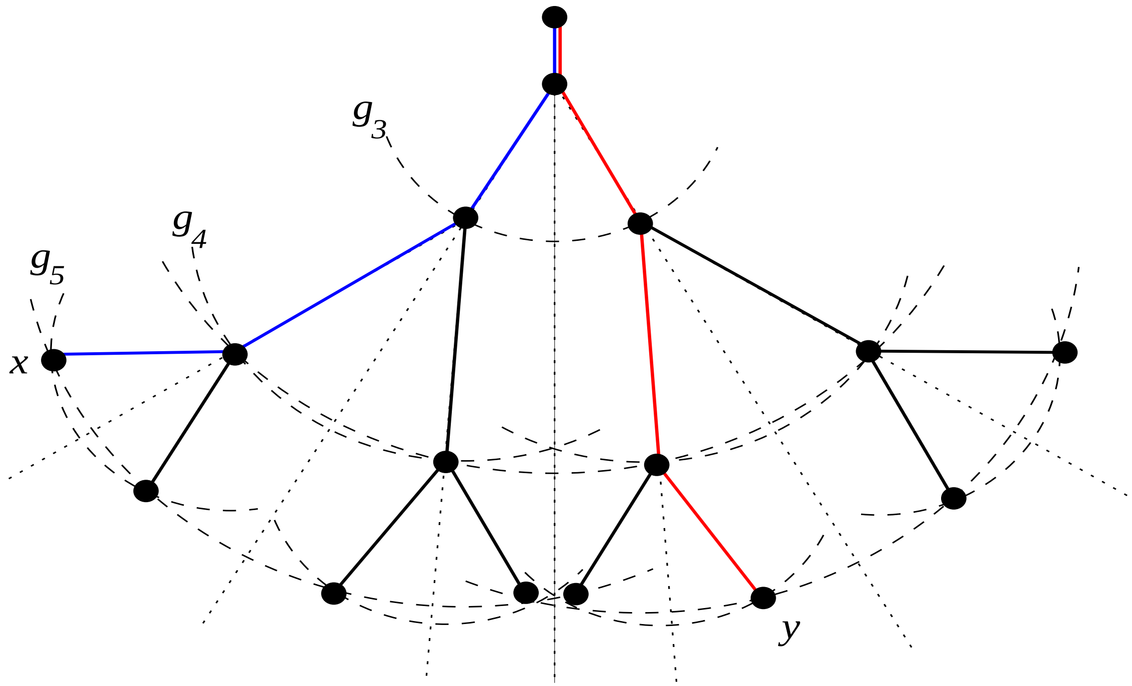
(Proof sketch for $K = 2$) Let $y \perp \mathrm{Aff}(x_{v-1}, \ldots, x_{v-K})$ and $\rho^y = R_x^v$



One realization generates all others

Lemma B The action of $\mathscr{G}_D$ on X_D is transitive

$K = 2$



$$\exists g \in \mathscr{G}_D \ (y = g(x))\text{: namely, } y = g_5(g_4(g_3(x)))$$

Proof By induction on v: assume result holds to $v-1$ with g', then either it holds for v and $g = g'$, else flip and let $g = g_v g'$

[L. et al. 2013]

Structure and invariance

- $\mathscr{G}_D$ is Abelian and generated by $n - K$ idempotent elements

$$\Rightarrow \mathscr{G}_D \cong C_2^{n-K}$$

- $\mathscr{G}_D \leq \mathrm{Aut}(X_D)$ by construction

Solution sets

- X: set of incongruent realizations of G

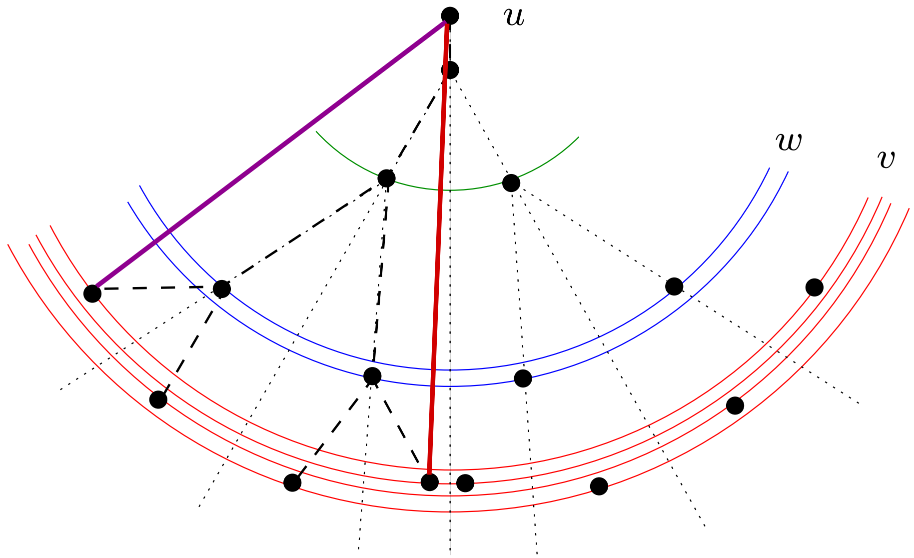
- G_D defined on same vertices but fewer edges
  $\Rightarrow$ fewer distance constraints on realizations
  $\Rightarrow$ more realizations

- All realizations of G are also realizations of G_D
  $\Rightarrow X \subseteq X_D$

Losing invariance on pruning edges

Lemma C Let $W^{uv} = \{u + K + 1, \ldots, v\}$ be the *range* of $\{u, v\}$
$\forall x \in X,\ u, w, v \in V\ (w \in W^{uv} \leftrightarrow \|x_u - x_v\| \neq \|g_w(x)_u - g_w(x)_v\|)$

Proof sketch for $K = 2$



Corollary If $\{u, v\} \in E_P$ and $w \in W^{uv}$, $g_w(x) \notin X$

[L. et al. 2013]

Pruning group

Define:

$$\begin{aligned} \Gamma &= \{g_w \in \mathscr{G}_D \mid w > K \wedge \forall \{u,v\} \in E_P \, (w \notin W^{uv})\} \\ \mathscr{G}_P &= \langle \Gamma \rangle \end{aligned}$$

Lemma D X is invariant w.r.t. $\mathscr{G}_P$

Proof

Follows by corollary, invariance of X_D w.r.t. $\mathscr{G}_D$ and $X \subseteq X_D$

Transitivity of the pruning group

Lemma E The action of $\mathscr{G}_P$ on X is transitive

- Given $x, y \in X$, aim to show $\exists g \in \mathscr{G}_P \; (y = g(x))$
- Lemma B $\Rightarrow \exists g \in \mathscr{G}_D$ with $y = g(x) \in X_D$
- Suppose $g \notin \mathscr{G}_P$ and aim for a contradiction
- $\Rightarrow \exists \{u, v\} \in E_P$ and $w \in W^{uv}$ s.t. g_w is a component of g
- Lemma C $\Rightarrow \|g_w(x)_u - g_w(x)_v\| \neq d_{uv}$
- If w is the only such vertex, $y = g(x) \neq x$ against hypothesis, done
- Suppose $\exists$ another $z \in W^{uv}$ s.t. g_z is a component of g
- Set of cases s.t. $\|x_u - x_v\| = \|g_z g_w(x)_u - g_z g_w(x)_v\|$ given $\|g_w(x)_u - g_w(x)_v\| \neq \|x_u - x_v\| \neq \|g_z(x)_u - g_z(x)_v\|$ has Lebesgue measure 0 in all DGP inputs
- By induction, holds for any number of components g_z of g with $z \in W^{uv}$
- $\Rightarrow y = g(x) \neq x$ against hypothesis, done

[L. et al. 2013]

The main result

Theorem $|X| = 2^{|\Gamma|}$

- Lemma A $\Rightarrow \mathscr{G}_D \cong C_2^{n-K} \Rightarrow |\mathscr{G}_D| = 2^{n-K}$
- $\mathscr{G}_P \leq \mathscr{G}_D \Rightarrow \boxed{\exists \ell \in \mathbb{N}\ (\mathscr{G}_P \cong C_2^{\ell})}$, with $\ell = |\Gamma|$
- Lemma E $\Rightarrow \forall x \in X\ \boxed{\mathscr{G}_P x = X}$
- Idempotency $\Rightarrow \forall g \in \mathscr{G}_P \quad g^{-1} = g$
  $\Rightarrow \forall g, h \in \mathscr{G}_P, x \in X\ (gx = hx \rightarrow h^{-1}gx = x \rightarrow hgx = x \rightarrow hg = I \rightarrow h = g^{-1} = g)$
  $\Rightarrow$ the mapping $\mathscr{G}_P x \rightarrow \mathscr{G}_P$ given by $gx \rightarrow g$ is injective
- $\forall g, h \in \mathscr{G}_P, x \in X\ (g \neq h \rightarrow gx \neq hx)$
  $\Rightarrow$ the mapping $gx \rightarrow g$ is surjective
- $\Rightarrow$ **the mapping $gx \rightarrow g$ is a bijection**
- $\Rightarrow |\mathscr{G}_P x| = |\mathscr{G}_P|$
- $\Rightarrow \forall x \in X \quad |X| = |\mathscr{G}_P x| = |\mathscr{G}_P| = 2^{|\Gamma|}$

[L. et al. 2013]

Symmetry-aware BP

- **Don't need to explore all branches of BP tree**
- Build Γ as a pre-processing step
- Run BP, terminating as soon as $|X| = 1$
- For each $g \in \mathscr{G}_P$, compute gx

[Mucherino et al. JBCB 2012]

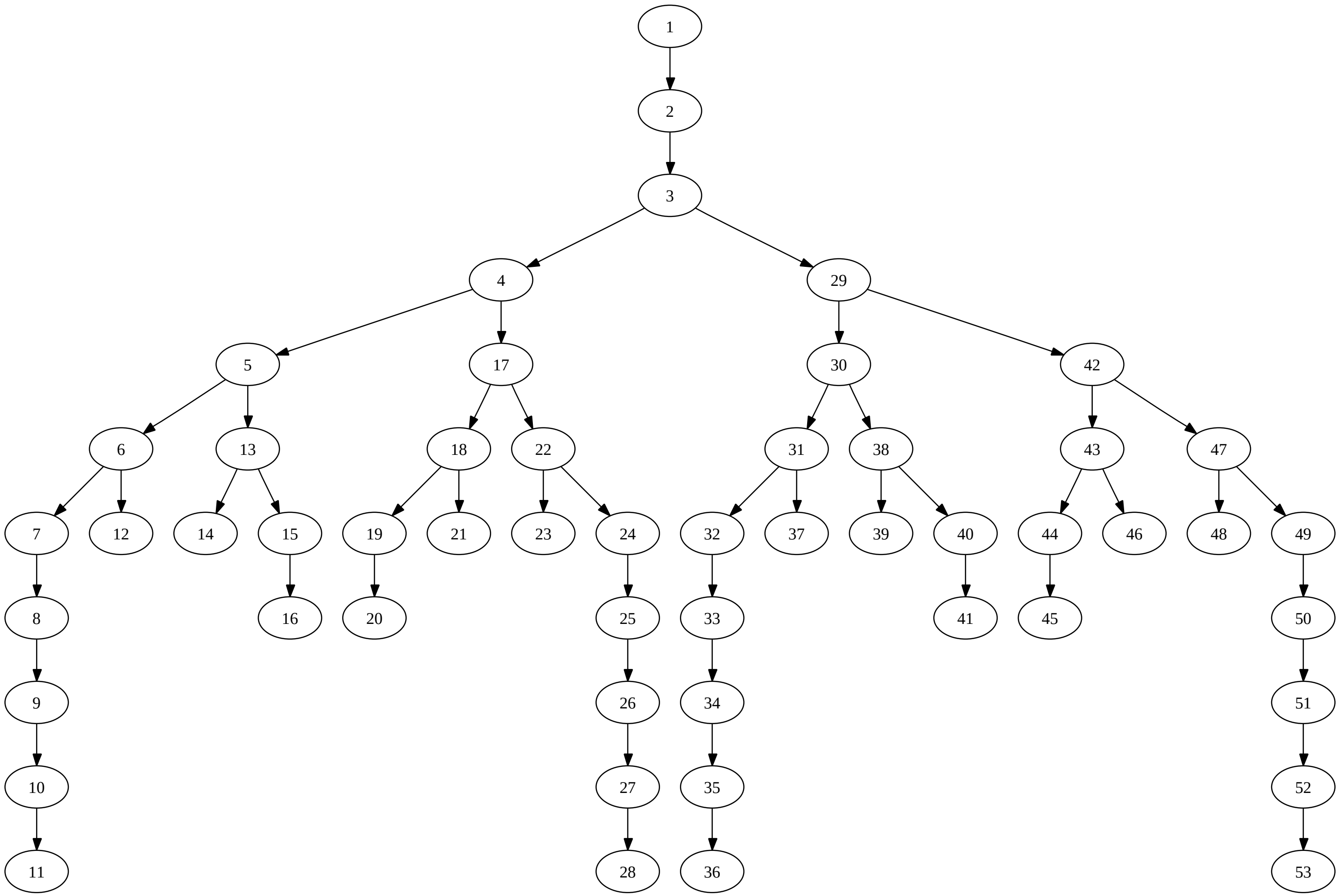
Complexity

- Computing Γ: $O(mn)$
  1. initialize indicator vector $\iota = (\iota_{K+1}, \ldots, \iota_n)$ for $g_v \in \Gamma$
  2. initialize $\iota = \mathbf{1}$
  3. for each $\{u, v\} \in E_P$ and $w \in W^{uv}$ let $\iota_w = 0$
- BP: $O(2^n)$
- Compute gx for each $g \in \mathscr{G}_P$: $O(2^{|\Gamma|})$
- **Overall: $O(2^n)$**
- **Gains depend on the instance**

Tractability of protein instances

[L. et al. 2013]

Let's handle the BP tree



Max depth: n, looks good! Aim to prove width is bounded

Number of solutions at each BP tree level

Depends on range of longer pruning edge incident to level v

$K+$	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
	2	4	8	16	32	64	128	256	512	no pruning edges
		2	4	8	16	32	64	128	256	
			2	4	8	16	32	64	128	
				2	4	8	16	32	64	
					2	4	8	16	32	
						2	4	8	16	
							2	4	8	
								2	4	
									2	pruning edges make graph K-trilaterative

Green path

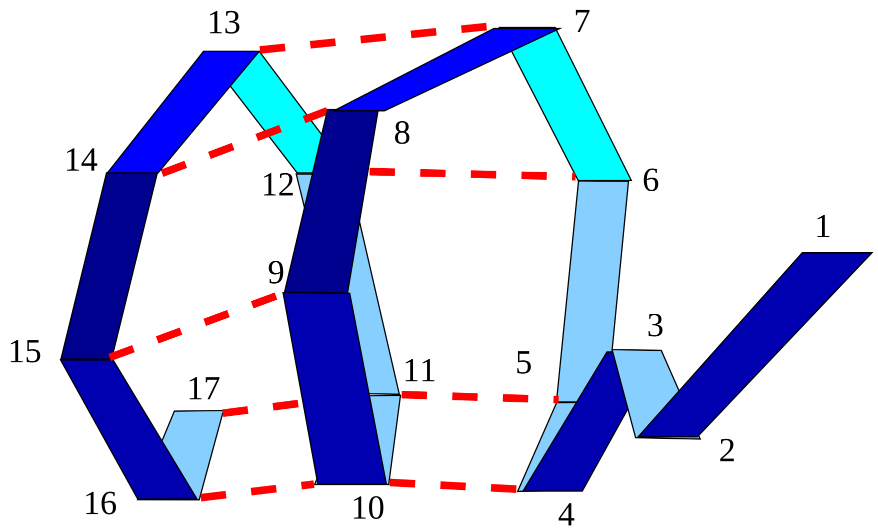
8 nodes at level $K+4$

$\{3, K+5\} \in E_P \Rightarrow g_{K+4}, g_{K+5} \not\in \Gamma$

$\Rightarrow$ no symmetry at levels $K+4$ and $K+5$

$\Rightarrow$ only 4 nodes at level $K+5$

Periodic pruning edges



4	5	6	7	8	9	10	11	12	...
2	4	8	16	32	64	128	256	512	
	2	4	8	16	32	64	128	256	
		2	4	8	16	32	64	128	
			2	4	8	16	32	64	
				2	4	8	16	32	
					2	4	8	16	
						2	4	8	
							2	4	
								2	

- 2^ℓ growth up to level ℓ, then constant: $O(2^\ell n)$ nodes in BP tree
- BP is **Fixed-Parameter Tractable** (FPT) in a bunch of cases
- For all tested protein backbones, $\ell \leq 5 \Rightarrow$ **BP linear on proteins!**

The story so far

- Nice applications, problem is hard, could have many solutions
- Continuous methods don't scale
- If *certain vertex orders* are present, use mixed-combinatorial methods
- Realize K-trilaterative in polytime but $(K-1)$-trilaterative are hard
- If adjacent predecessors are immediate, theory of symmetries
- Number of solutions is a power of two
- For proteins, BP is linear time
- **How do we find these vertex orders?**

Finding vertex orders

1. Applications
2. Definition
3. Complexity primer
4. Complexity of the DGP
5. Number of solutions
6. Mathematical optimization formulations
7. Realizing complete graphs
8. The Branch-and-Prune algorithm
9. Symmetry in the ^{K}DMDGP
10. Tractability of protein instances
11. **Finding vertex orders**
12. Approximate realizations

[Cassioli et al., DAM]

. . . wasn't the backbone providing them?

- NMR data not as clean as I pretended
- Have to mess around with side chains
- What about other applications, anyhow?

Methods for finding trilaterative orders automatically

Mostly bad news

- Finding K-trilaterative orders is **NP**-complete :-(
- **But also FPT :-)**
- Finding ^{K}DMDGP orders is **NP**-complete for all K :-(
- **It's also really hard in practice, and methods don't scale well**

Definitions

- Trilateration Ordering Problem (TOP)

  Given a connected graph $G = (V, E)$ and a positive integer K, does G have a K-trilateration order?

- Contiguous Trilateration Ordering Problem (CTOP)

  Given a connected graph $G = (V, E)$ and a positive integer K, does G have a $(K-1)$-trilateration order such that $U_v = \{v-1, \ldots, v-K\}$ for each $v > K$?

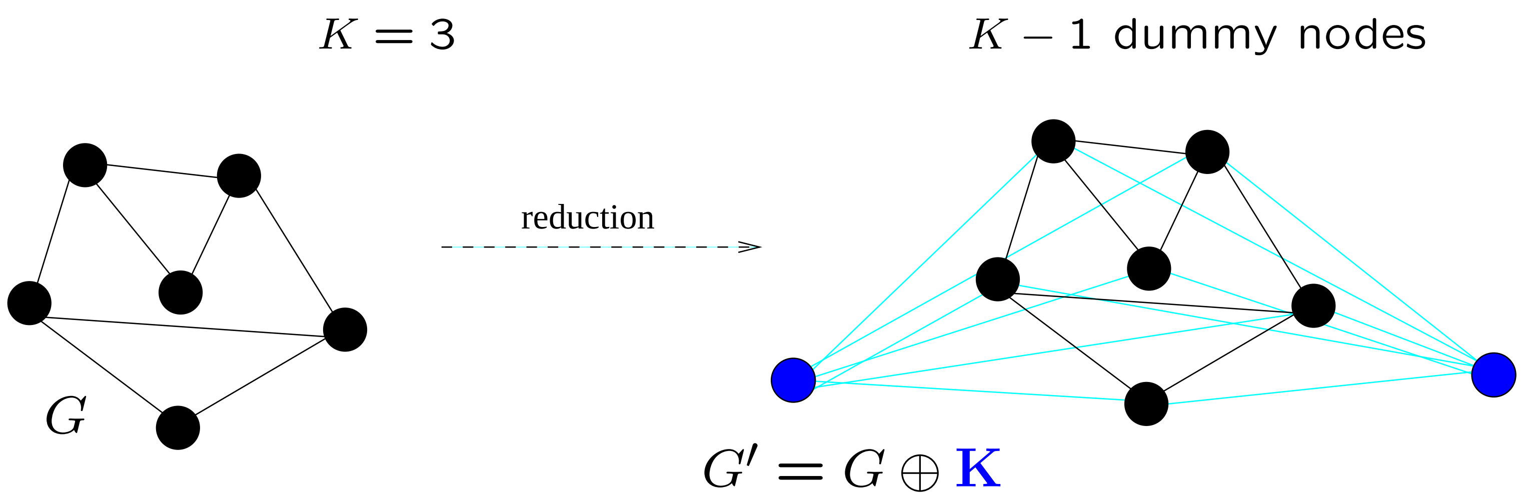
Both problems are in **NP**

Hardness of TOP

- Essentially due to finding the initial clique
  - brute force: test all $\binom{n}{K}$ subsets of V
  - $\binom{n}{K}$ is $O(n^K)$, polytime if K fixed
- Reduction from K-Clique problem:
  Given a graph, does it have a K-clique?

[Mucherino et al., OPTL 2012]

Reduction from K-Clique



- **If** K-Clique **instance is YES**
  - start with $\alpha =$ (initial clique of $G, \mathbf{K}$)
  - **induction**: if α_{v-1} defined, pick α_v at shortest path distance 1 from $\bigcup \alpha$
- **If** K-Clique **instance is NO**
  - **By contradiction**: suppose $\exists$ trilateration order α in G'
  - Initial clique $\alpha[K] = (\alpha_1, \ldots, \alpha_K)$ must have $K - 1$ vertices in G, 1 in $\mathbf{K}$
  - α_{K+1} must be in G, hence $\exists$ K-clique in G

[Cassioli et al., DAM]

Once the initial clique is known

Greedily grow a trilateration order α

- Initialize α with initial K-clique $\mathbf{K}$
- Let $W = V \smallsetminus \mathbf{K}$
- $\forall v > K \;\; a_v = |\text{vertices in } \mathbf{K} \text{ adjacent to } v|$
  // at termination, a_v will be the number of adjacent predecessors of v
- While $W \neq \varnothing$:
  1. choose $v \in W$ with largest a_v
  2. if $a_v < K$ instance is NO
  3. $\alpha \leftarrow (\alpha, v)$
  4. for all $u \in W$ adjacent to v, increase a_u
  5. $W \leftarrow W \smallsetminus \{v\}$
- Instance is YES

[Mucherino et al., OPTL 2012]

Greedy algorithm is correct

- **Assume TOP instance is YES, proceed by induction**
  - start: by maximality, $a_{K+1} > K$
  - assume α is a valid TOP up to $v - 1$, suppose $a_v < K$
  - but instance is YES so there is another $z \in W$ with $a_z \geq K$
  - contradicts maximality of a_v
- **Assume TOP instance is NO**
  - "YES" termination when $W = \varnothing$ contradicts the NO
  - hence it must terminate with $W \neq \varnothing$ and "NO" answer

Complexity

- Outer *while* loop: $O(n)$
- Choice of largest a_v: $O(n)$
- Inner loop on W: $O(n)$
- **Overall:** $O(n^2)$
- **If we add brute force initial clique:** $O(2^K n^2)$
- Polytime if K fixed, FPT otherwise

CTOP is hard

- Reduction from Hamiltonian Path (HP)

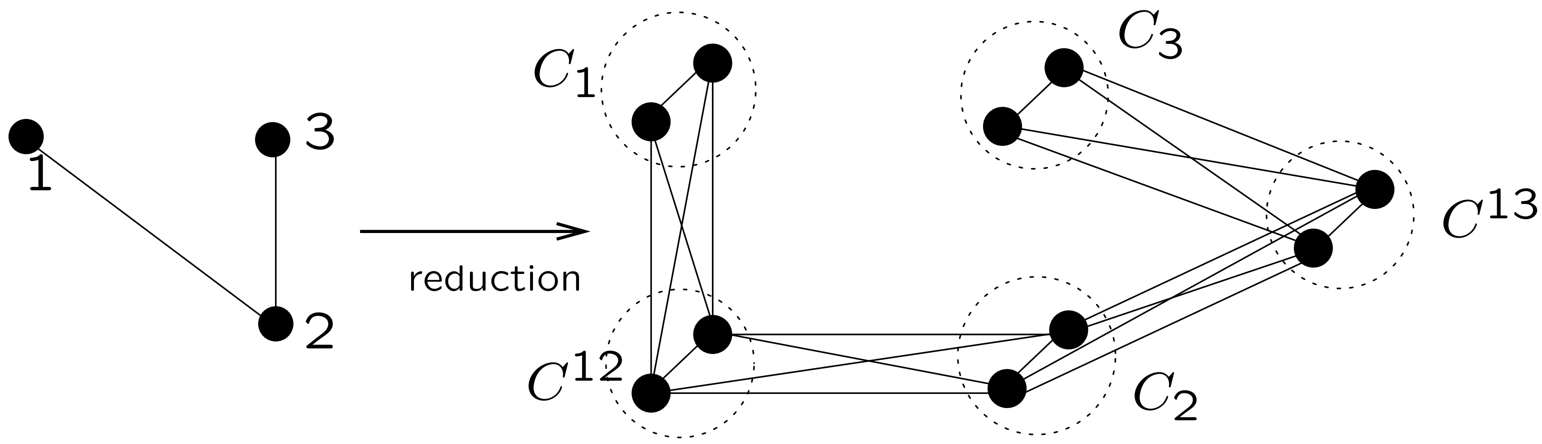
  Given a graph G, does it have a path passing through each vertex exactly once?

- α a H. path in $G \Rightarrow \forall v \neq 1, n$ α_v is adjacent to $\alpha_{v-1}, \alpha_{v+1}$
- Apart from initial 1-clique α_1
  every α_v is adjacent to its immediate predecessor
- $\Rightarrow$ α is a ^{K}DMDGP order in G with $K = 1$
- **HP is the same as CTOP with $K = 1$**
- $\Rightarrow$ **By inclusion, CTOP is NP-hard**

[Cassioli et al., DAM]

CTOP is hard for all K

- Reduction from HP



- Technical proof

[Cassioli et al., DAM]

How do we find ^{K}DMDGP orders?

Mathematical optimization & CPLEX

- $x_{vi} = 1$ iff vertex v has rank i in the order
- Each vertex has a unique order rank:

$$\forall v \in V \qquad \sum_{i \in \bar{n}} x_{vi} = 1;$$

- Each rank value is assigned a unique vertex:

$$\forall i \in \bar{n} \qquad \sum_{v \in V} x_{vi} = 1;$$

- There must be an initial K-clique:

$$\forall v \in V, i \in \{2, \ldots, K\} \qquad \sum_{u \in N(v)} \sum_{j < i} x_{uj} \geq (i-1) x_{vi};$$

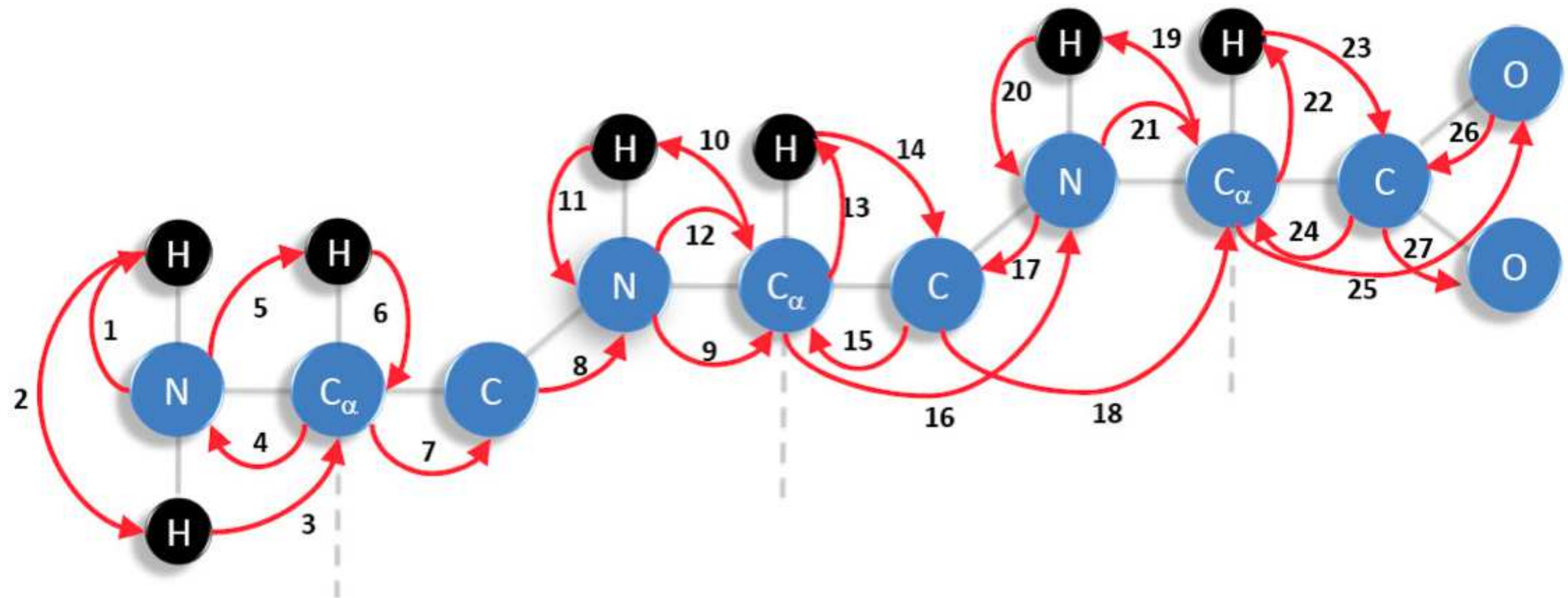
- Each vertex with rank $> K$ must have at least K contiguous adjacent predecessors

$$\forall v \in V, i > K \qquad \sum_{u \in N(v)} \sum_{i-K \leq j < i} x_{uj} \geq K x_{vi}.$$

- Do not expect too much; scales up to 100 vertices

How about those 10k-atom backbones?

We have Carlile for those

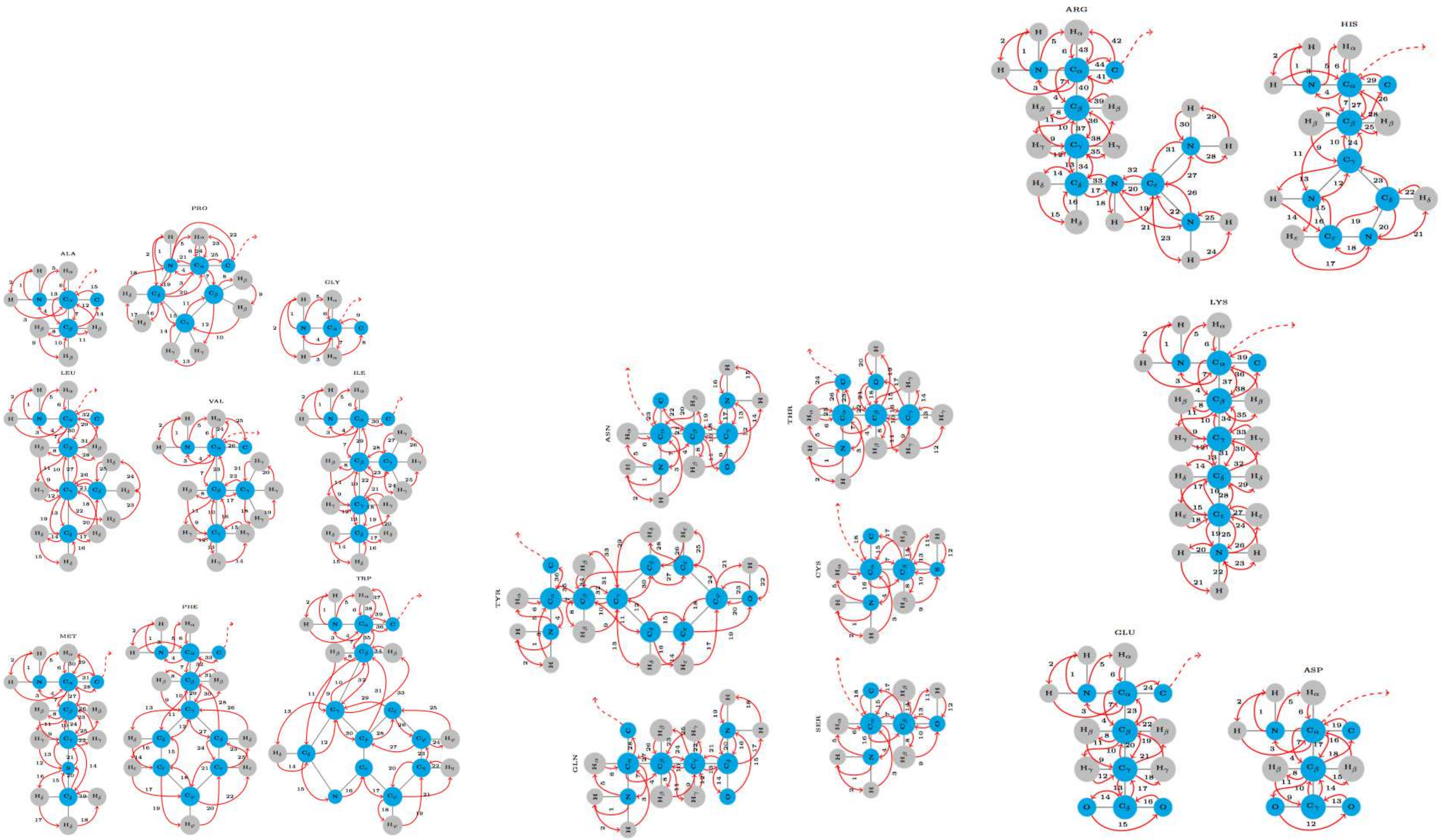


- Note the **repetitions** — they serve a purpose!
- Repetition orders are also hard to find for any K
- **. . . but Carlile knows how to handcraft them!**

[Lavor et al. JOGO 2013]

And what about the side-chains?

The Carlile+Antonio tool!



[Costa et al. JOGO, accepted]

Approximate realizations

Data errors

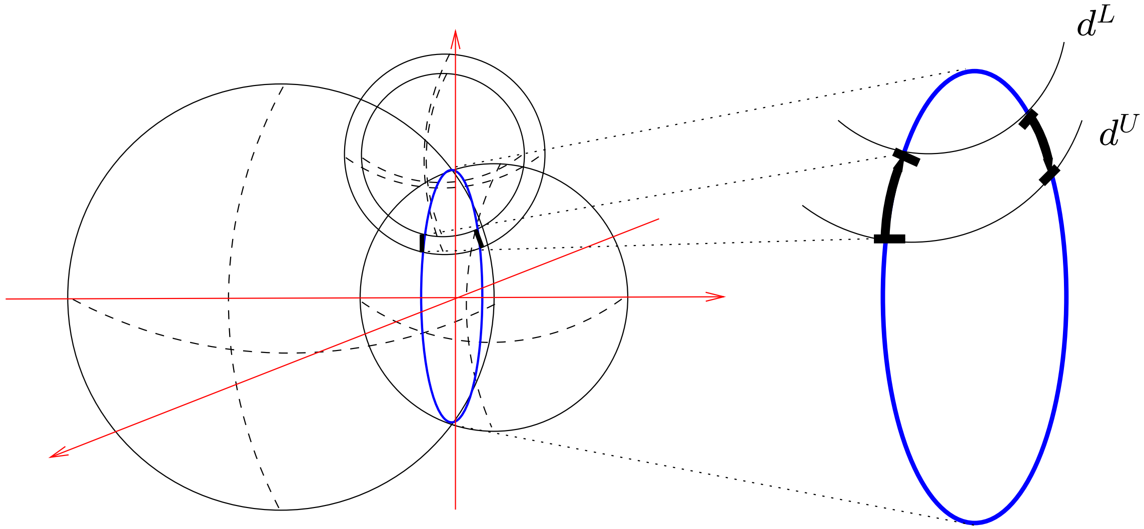
The "distance = real number" paradigm is a lie!

- Covalent bonds are fairly precise
- **NMR data is a mess** [Berger, J. ACM 1999]
  - experimental errors yield intervals $[d^L_{uv}, d^U_{uv}]$
  - NMR outputs frequencies of (atom type pair, distance value) weighted graph reconstruction yields systematic error
  - some atom type pairs yield more error ("only trust H—H")
- Properties of specific molecules give rise to other constraints
- **The protein graph may not be $(K-1)$-trilaterative based on the backbone**

The *Lavorder* comes to the rescue!

- **Carlile's handcrafted repetition orders properties**:
  - repetitions allow a "virtual backbone" of H atoms only
  - **discretization edges**: $\{v, v-i\}$ covalent bonds for $i \in \{1,2\}$, $\{v, v-3\}$ sometimes covalent sometimes from NMR
  - most NMR data restricted to pruning edges

- When $d_{v,v-3}$ is an interval: intersect two spheres with sph. shell

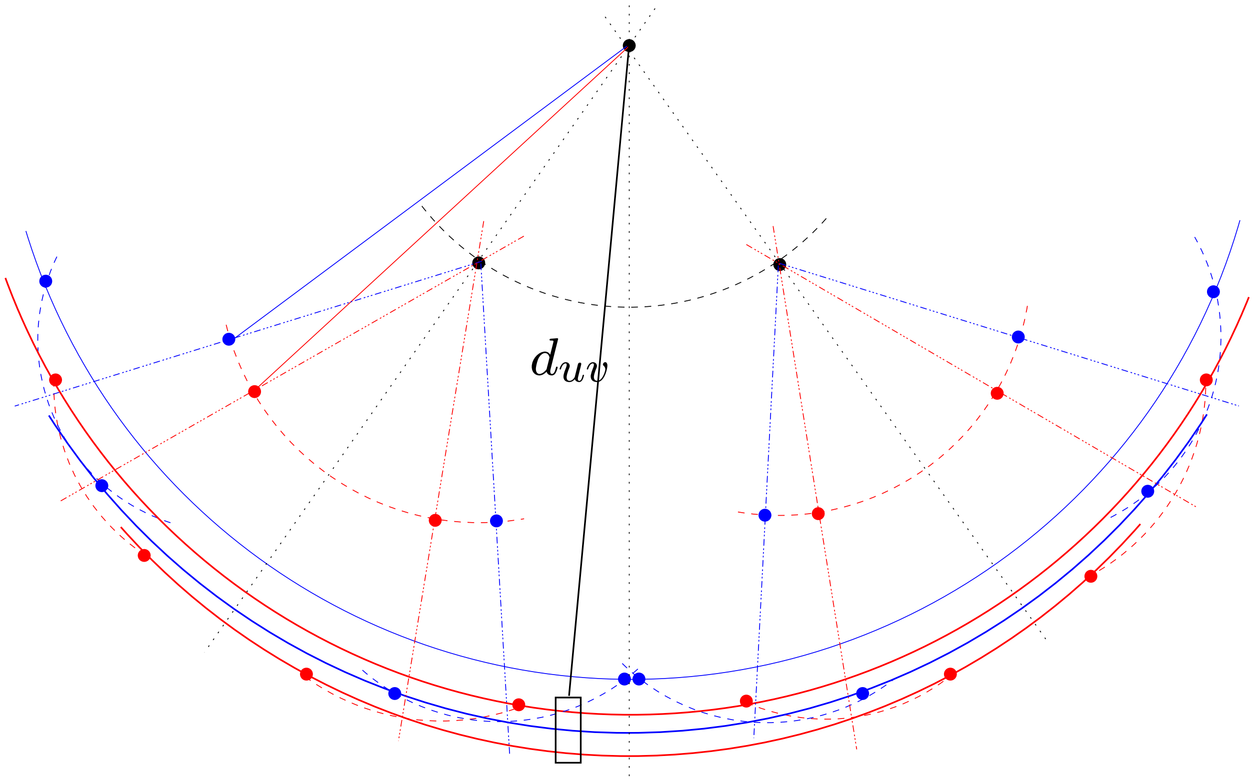


- Discretize circular segments and run BP with modified S

Algorithm no longer exhaustive

Die Symmetriktheoriedämmerung

- Intervals and discretization break the theory of symmetries

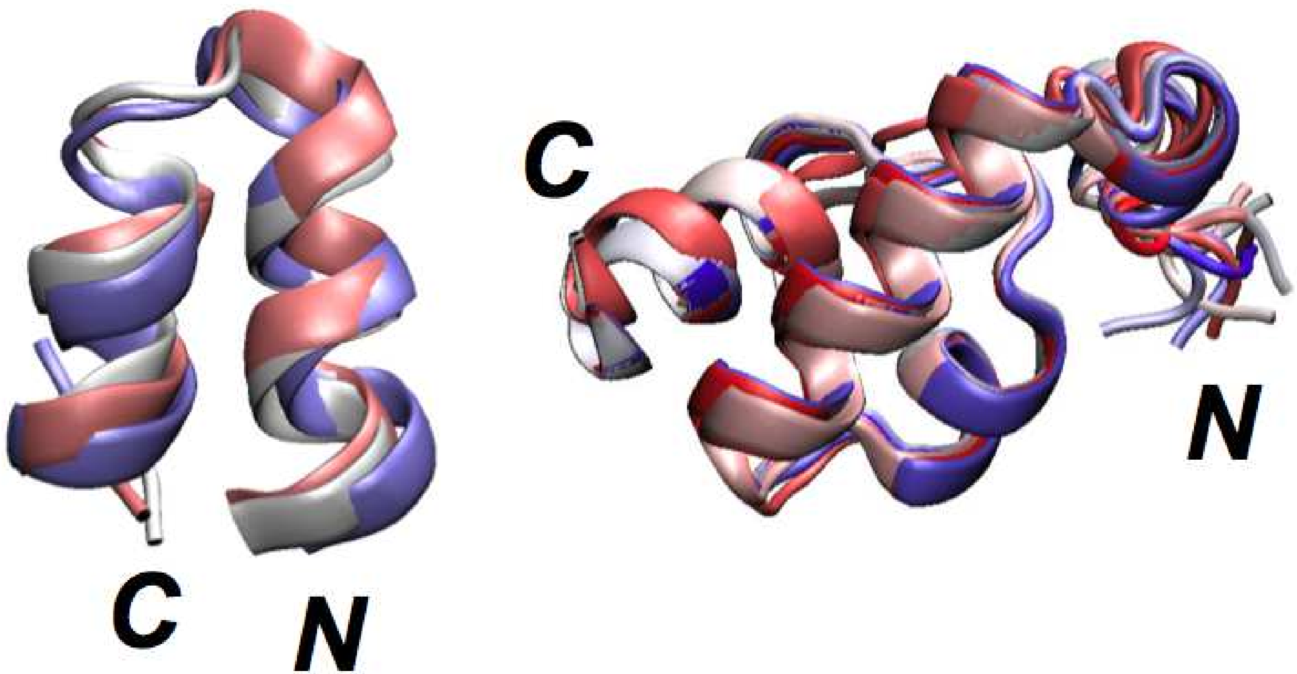


- Only some bounds for the number b of BP solutions:

$$\exists \ell, k \quad 2^{\ell} q^{k} \leq b \leq 2^{n-3} q^{M}$$

$q = |\text{discretization points}|$, $M = |\text{NMR discretization edges}|$

But at least it's producing results



Joint work with Institut Pasteur

[Cassioli et al., BMC Bioinf., submitted]

General approximate methods

- **All these methods are specialized to protein distance data from NMR**
- **What about general approximate methods?**
- Assume large-sized input data with errors
- No assumptions on graph structure

Ingredients

- PDM = Partial Distance Matrix (a representation of G)
- EDM = Euclidean Distance Matrix

1. **Complete** the given PDM d to a symmetric matrix D
2. **Find** a realization x (in some dimension $\bar{K}$)
   s.t. the EDM ($\|x_u - x_v\|$) is "close" to D
3. **Project** x from dimension $\bar{K}$ to dimension K,
   keeping pairwise distances approximately equal

Completing the distance matrix

- $\forall \{u, v\} \notin E$ let $D_{uv} =$ length of the shortest path $u \to v$
- Use Floyd-Warshall's algorithm $O(n^3)$

// $n \times n$ array D_{ij} to store distances
$D = 0$
for $\{i, j\} \in E$ **do**
    $D_{ij} = d_{ij}$
end for
for $k \in V$ **do**
    for $j \in V$ **do**
        for $i \in V$ **do**
            if $D_{ik} + D_{kj} < D_{ij}$ **then**
                // D_{ij} fails to satisfy triangle inequality, update
                $D_{ij} = D_{ik} + D_{kj}$
            end if
        end for
    end for
end for

Finding a realization

- Let's give ourselves many dimensions, say $\bar{K} = n$
- Attempt to find $x : V \to \mathbb{R}^n$ with $(\|x_u - x_v\|_2) \approx (D_{uv})$
- **If we had the *Gram matrix* B of x, then**:
  1. find eigen(value/vector) matrices Λ, Y of B
  2. since B is PSD, $\Lambda \geq 0 \Rightarrow \sqrt{\Lambda}$ exists
  3. $\Rightarrow B = Y \Lambda Y^\top = (Y\sqrt{\Lambda})(Y\sqrt{\Lambda})^\top$
  4. $x = Y\sqrt{\Lambda}$ is such that $xx^\top = B$
- **Can we compute B from D?**

Schoenberg's theorem

- **Standard method for computing B from D^2**
- Also known as classic MultiDimensional Scaling (MDS)
- Apply many algebraic manipulations to

$$d_{uv}^2 = \|x_u - x_v\|^2 = {x_u}^\top x_u + {x_v}^\top x_v - 2{x_u}^\top x_v$$

  where the centroid $\sum_{k \leq n} x_{uk} = 0$ for all $u \leq n$

- Get $B = -\frac{1}{2}(I_n - \frac{1}{n}\mathbf{1}_n)D^2(I_n - \frac{1}{n}\mathbf{1}_n)$, i.e.

$$x_u \cdot x_v = \frac{1}{2n} \sum_{k \leq n} (d_{uk}^2 + d_{kv}^2) - d_{uv}^2 - \frac{1}{2n^2} \sum_{\substack{h \leq n \\ k \leq n}} d_{hk}^2$$

- D "approximately" EDM $\Rightarrow$ B "approximately" Gram

[Schoenberg, Annals of Mathematics, 1935]

Project to $\mathbb{R}^K$ for a given K

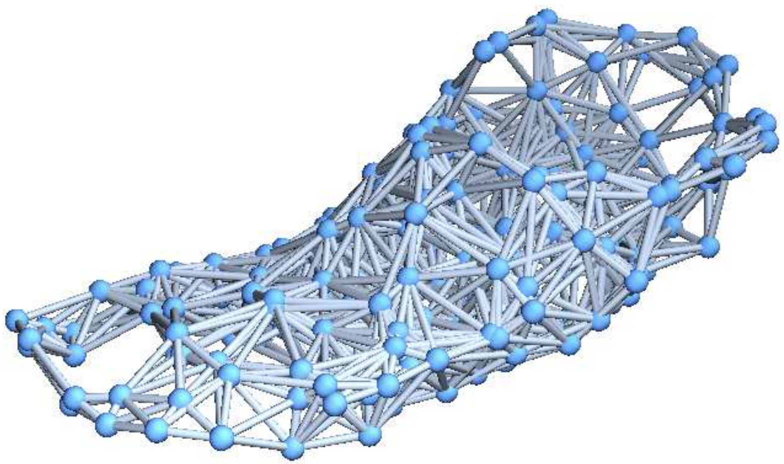
- Only use the K largest eigenvalues of Λ
- $Y[K] =$ K columns of Y corresp. to K largest eigenvalues
- $\Lambda[K] =$ K largest eigenvalues of Λ on diagonal
- $x = Y[K]\sqrt{\Lambda[K]}$ is a $K \times n$ matrix
- $Y[K]$ span the subspace where x "fills more space", i.e. neglecting other dimensions causes smaller errors w.r.t. the realization in $\mathbb{R}^n$

This method is called **Principal Component Analysis** (PCA)

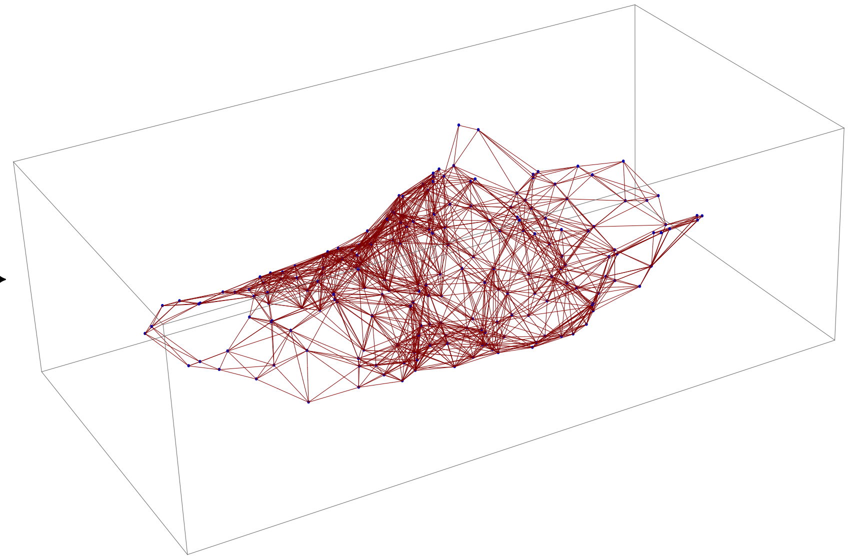
Isomap

Given K and PDM d:

1. $D = \texttt{FloydWarshall}(d)$
2. $B = \texttt{MDS}(D)$
3. $x = \texttt{PCA}(B, K)$



$\longrightarrow$



[Tenenbaum et al. Science 2000]

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THE END