Geometric Buildup Methods for Protein Structure Determination

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June 12, 2012

Outline

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1. Problem Introduction

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2. Related Works

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3. Distributed Geometric Buildup Method

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3. Distributed Geometric Buildup Method
4. Two New Models

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2. Related Works
3. Distributed Geometric Buildup Method
4. Two New Models
5. Conclusions and Future work

Distance Geometry(DG) Problem

Find the coordinate vectors $x_1, x_2, \ldots, x_n$ that satisfy several given distances between them.

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  - distance bounds

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- applications:
  - graph realization
  - protein structure determination (3D)
  - sensor network localization (2D)
  - ...

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DG problem with full set of exact distances

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$$\begin{aligned} d_{i,j}^2 &= \|x_i - x_j\|^2 \\ &= \|x_i\|^2 - 2x_i^{\mathrm{T}} x_j + \|x_j\|^2 \\ &= d_{i,n}^2 - 2x_i^{\mathrm{T}} x_j + d_{j,n}^2 \qquad i,j = 1,2,\ldots,n-1 \end{aligned} \tag{1}$$

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- Define $X = (x_1, x_2, \ldots, x_n)^{\mathrm{T}}$ and
$D = \{(d_{i,n}^2 - d_{i,j}^2 + d_{j,n}^2)/2 : i,j = 1,2,\ldots,n-1\}$, (1) $\Rightarrow XX^{\mathrm{T}} = D$.

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- Let $D = U \Sigma U^{\mathrm{T}}$, and $V = U(:, 1:3), \Lambda = \Sigma(1:3, 1:3)$. Then $X = V \Lambda^{1/2}$ solves the problem. [Eckart and Young 1936]

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Zachary Voller, Zhijun Wu(2012), Distance Geometry Methods for Protein Structure Determination.

Determine one unknown atom

Given four determined atoms x_1, x_2, x_3 and x_4, which $x_i = (x_{i1}, x_{i2}, x_{i3})^{\mathrm{T}}$ are known, and four exact distances.

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- $d_{i,j}^2 = \|x_i\|^2 - 2x_i^{\mathrm{T}} x_j + \|x_j\|^2 \qquad i = 1, 2, 3, 4.$
- $\Rightarrow Ax_j = b$,

  where $A = 2 \begin{pmatrix} x_{11} - x_{21} & x_{12} - x_{22} & x_{13} - x_{23} \\ x_{21} - x_{31} & x_{22} - x_{32} & x_{23} - x_{33} \\ x_{31} - x_{41} & x_{32} - x_{42} & x_{33} - x_{43} \end{pmatrix}$

  and $b = \begin{pmatrix} (\|x_1\|^2 - \|x_2\|^2) - (d_{1,j}^2 - d_{2,j}^2) \\ (\|x_2\|^2 - \|x_3\|^2) - (d_{2,j}^2 - d_{3,j}^2) \\ (\|x_3\|^2 - \|x_4\|^2) - (d_{3,j}^2 - d_{4,j}^2) \end{pmatrix}.$

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- Inexact distances?

Linear and Nonlinear Least-squares Approximation

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  - $\min \|b - Ax_j\|$

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DG problem with inexact distances

Suppose l distances between the unknown atom to the determined atoms are known.

- linear least-squares
  - use only the l distances
  - $\min \|b - Ax_j\|$
- nonlinear least-squares
  - use all the distances among the $l+1$ atoms
  - solve a matrix decomposition problem
  - move the same points in two different reference system coincide

Atilla Sit, Zhijun Wu and Ya-xiang Yuan(2009), A geometric buildup algorithm for the solution of the distance geometry problem using least-squares approximation.

Laplacian Matrix

Given a graph (V, E), define its Laplacian matrix by L, whose entries $l_{i,j}$ are given by

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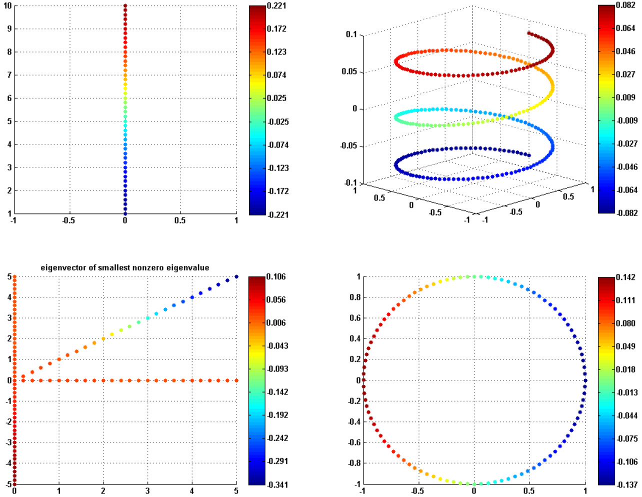
- $L = D - A$, where D is degree matrix, and A is its adjacency matrix.

- Properties:
  - L is always positive-semidefinite.
  - 0 is always its eigenvalue and its corresponding eigenvector is $(1, 1, \ldots, 1)^{\mathrm{T}}$.
  - The number of times 0 appears as an eigenvalue in the Laplacian is the number of connected components in the graph.

Eigenvector of smallest nonzero eigenvalue

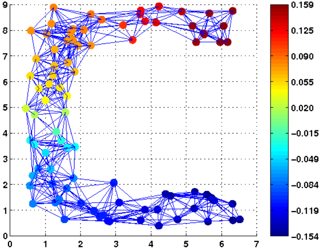


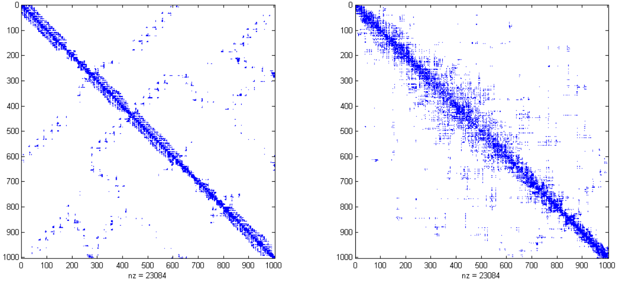
eigenvector of smallest nonzero eigenvalue

a Conjecture

Conjecture

Given a graph (V, E), its Laplacian matrix is defined as before, then the eigenvector of the smallest nonzero eigenvalue, which can be viewed as a function of the vertexes, monotonically decrease or increase along the main trend/direction of the graph.




0
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nz = 23084
0
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600
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Figure : 1AX8

Implement Details

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- computational order:

IAX8, 1003 atoms, cutoff=5Å, 2.3% exact		
order	RmsdErr	CPU time (s)
original	7.395926e+000	1.258295
greedy	9.281000e-005	2.346640
Laplacian	9.281000e-005	1.999627
random	7.372537e-007	4.980335
	1.726266e-007	2.946320
	3.858138e-003	2.988656
	2.437341e-008	3.517570
	1.223379e-005	4.757714
	1.169260e-003	5.339559
	1.399711e-006	2.478225
	1.771925e-005	4.957635
	9.559394e-009	2.750663
	8.637780e-007	5.196890

- computational order:

1MQQ, 5681 atoms, cutoff=6Å, 0.75%, exact		
order	RmsdErr	CPU time (s)
original	1.130061e+001	11.262673
greedy	4.310119e-003	53.904010
Laplacian	5.039401e-005	135.032459
random	5.315594e-003	23.218307
	1.612265e-002	67.657580
	2.928411e-004	142.834237
	2.262457e-007	29.632780
	3.823293e-006	70.646800
	3.165929e-003	140.470924
	8.535506e-001	254.812797
	6.665072e-005	214.758550
	4.334586e-001	141.894475
	2.888975e-001	23.932108

PDB ID	No.	greedy order				Laplacian order		
		RmsdErr	CPU time	NumDet		RmsdErr	CPU time	NumD
1PTQ	402	1.15e-012	1.22e+000	402		8.97e-013	4.98e-001	402
1HOE	558	1.50e-012	8.09e-001	558		1.08e-011	2.17e+000	558
1LFB	641	7.59e-010	9.10e-001	641		1.75e-010	1.51e+000	641
1PHT	811	1.61e-011	1.23e+000	811		1.67e-013	8.41e+001	4
1POA	914	6.17e-010	1.43e+000	914		3.31e-011	1.59e+000	914
1AX8	1003	1.24e-011	1.68e+000	1003		4.87e-007	3.62e+000	1003
1F39	1534	2.32e-006	3.86e+000	1534		4.03e-014	2.93e+002	1534
1RGS	461	2.61e-014	2.11e-001	4		3.33e-014	2.14e+000	4
1KDH	2846	7.15e-004	8.56e+000	2846		1.58e-001	5.17e+000	2846
1BPM	3671	4.45e-005	9.03e+000	3671		9.45e-013	9.92e+002	4
1RHJ	3740	3.47e-008	1.07e+001	3740		1.00e-006	1.19e+001	3740
1HQQ	3944	4.77e-006	1.22e+001	3944		2.76e+000	7.43e+000	3944
1TOA	4292	2.35e+001	2.79e+001	4292		1.09e-001	8.93e+000	4292
1MQQ	5681	4.31e-003	4.98e+001	5681		1.55e-002	5.48e+001	5681

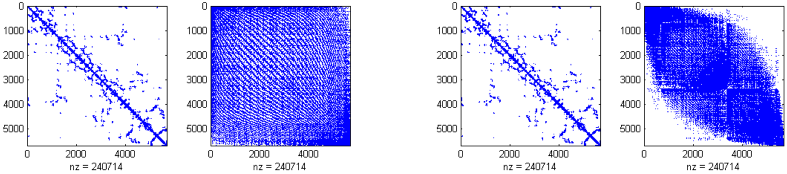

Figure : 1MQQ, greedy, theoretical VS. real order

Some other problems

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- not enough bases

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- bad condition number: say, cond$(A^{\mathrm{T}}A) > 10^6$

  $\Leftarrow$ bases almost in the same plane!

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- $\rightsquigarrow$ move to last

Motivation

1MQQ, 5681 atoms, cutoff=6Å, 0.75%, exact distances

Itr	RmsdErr	Itr	RmsdErr
300	1.020647e-012	3000	1.186818e-004
600	1.805403e-010	3300	3.477342e-004
900	2.059775e-007	3600	1.953754e-003
1200	6.691896e-007	3900	1.973875e-003
1500	3.358551e-006	4200	2.162615e-003
1800	4.677271e-006	4500	2.231129e-003
2100	7.869284e-006	4800	2.790680e-003
2400	2.062700e-005	5100	3.084867e-003
2700	6.988388e-005	5400	4.277911e-003

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- Error Accumulation!

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- Geometric Buildup at each patch
- Stitch together

How to divide

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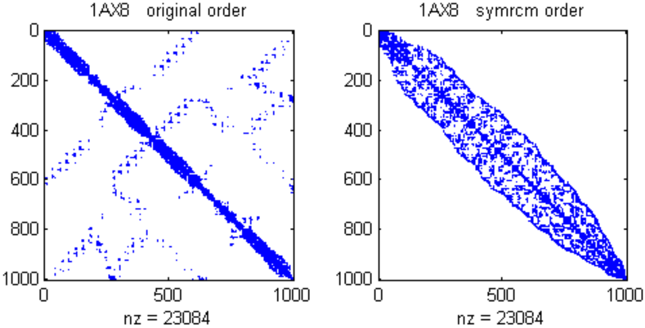
- symrcm: minimize the bandwidth

  Pratik Biswas, Kim-Chuan Toh and Yinyu Ye(2007), A Distributed SDP Approach for Large-scale Noisy Anchor-free Graph Realization with Application to Molecular Conformation.



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- R:

$$\begin{aligned} \min_{R} \quad & \|P - RQ\|_F^2 \\ \text{s.t.} \quad & R^{\mathrm{T}} R = I. \end{aligned} \tag{3}$$

Let $C = PQ^{\mathrm{T}}$, and $C = U\Sigma V^{\mathrm{T}}$, then $R = VU^{\mathrm{T}}$ solves (3). [Matrix Computation, Golub]

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- Remark: a fundamental problem in Machine Intelligence and Optical Science.

Numerical experiments

Distributed Buildup:

PDB ID	No. of atoms	RmsdErr	CPU time
1PTQ	402	1.781565e-012	0.912213
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1PHT	811	6.675090e-012	1.769367
1POA	914	6.173696e-010	1.563789
1AX8	1003	4.161234e-008	1.793236
1F39	1534	3.480137e-012	4.303442
1RGS	2015	1.804018e-009	4.713639
1KDH	2923	5.424939e+002	18.708290

A generalized DG problem

DG problem with distance bounds

Given the lower bounds $l_{i,j}$ and upper bounds $u_{i,j}$, the problem can be formulated as:

$$\begin{aligned}
\max_{x_i, r_i} \quad & \sum_{i=1}^{n} r_i \\
\text{s.t.} \quad & \|x_i - x_j\| + r_i + r_j \le u_{i,j} \\
& \|x_i - x_j\| - r_i - r_j \ge l_{i,j} \qquad \forall (i,j) \in S \\
& r_i \ge 0, \qquad i = 1, 2, \ldots, n.
\end{aligned}$$

Atilla Sit, Zhijun Wu(2011), Solving a Generalized Distances Geometry Problem for Protein Structure Determination.

Matrix Completion for DG

Matrix Completion for DG

- Given distance matrix D, we have

$$\begin{aligned} DD = D.^2 &= (d_{i,j}^2) \\ &= (\|x_i\|^2 - 2x_i^{\mathrm{T}}x_j + \|x_j\|^2) \\ &= E + E^{\mathrm{T}} - 2XX^{\mathrm{T}}. \end{aligned}$$

where E is a rank one matrix.

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- rank(DD)=5.
- FPCA, LMaFit

A new type of MC problem

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-

$$\begin{aligned}\min_{X,x_i} \quad & \|X - \sum_{i=1}^{r} x_i x_i^{\mathrm{T}}\|_F^2 \\ \text{s.t.} \quad & X_{i,j} = M_{i,j}, \quad \forall (i,j) \in S,\end{aligned}$$

A new type of MC problem

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  $$\text{s.t.} \quad X_{i,j} = M_{i,j}, \quad \forall (i,j) \in S,$$
- X is symmetric.

A new type of MC problem

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- X is symmetric.
- M has some special structure (not randomly sampled).

Conclusions and Future work

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  - propose a new model for DG
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  - finish some preliminary numerical experiments
- Future work:
  - theoretical analysis on eigenvector of Laplacian matrix
  - make clear the advantage and limitation of our distributed method
  - work on the new models

Thank you for your attention!