DISTANCE GEOMETRY ALGORITHMS

INTRODUCTION (1)

- Distance Geometry Problems:
  - There are various problems that come under this heading.
  - In general, we are given a set of distances between atoms and we are required to compute the coordinates of all atoms.
  - Computed coordinates are typically with respect to a frame of reference that has its origin at some pre-specified atom.
- Notation:
  - The coordinates of the atoms are $\left\{x^{(i)} \middle| i = 1, 2, \ldots, n\right\}$.
    - So, we are dealing with a molecule that has n atoms.
    - We want to calculate these $x^{(i)}$, when given all or some subset of:
  - $d_{i,j} = \left\| x^{(i)} - x^{(j)} \right\| \quad 1 \le i, j \le n.$

INTRODUCTION (2)

- Variants of the problem differ with respect to:
  - Number of distances given:
    - The full set of "n choose 2" distances makes the problem fairly easy to solve.
    - In most practical applications we are only given a $O(n)$ sparse set of distances.
  - Accuracy of distances given:
    - Distances may be considered as exact, or
    - The problem may specify upper and lower bounds on distances.
    - Distance may be given as probability distributions.

INTRODUCTION (3)

- So, there are four types of problems:

P1: A complete set of exact distances

P2: A complete set of approximate distances

P3: A sparse set of exact distances

P4: A sparse set of approximate distances.

MOTIVATION (1)

- NMR
  - While most of the protein structures in the PDB have been computed using X-ray analysis, about 15% have been determined by NMR (Nuclear Magnetic Resonance).
  - Advantages:
    - Unlike X-ray analysis, NMR does not require crystals – the proteins may be in solution.
    - Consequently, we can have more confidence that their conformations are close to that present in the cytosolic environment.

MOTIVATION (2)

- NMR
  - Disadvantages:
    - NMR experiments only report distances between atoms.
      - The atoms must be close to one another (typically within 5 Å of each other).
        - This means the number of distances is much less than n choose 2.
      - These distances have some experimental error.
        - This means we have reduced accuracy.
    - NMR can only be used for shorter proteins.
      - "Short proteins" means less than a few hundred amino acids.

NOTATION

- Recall, we work in a 3D Euclidean vector space:
  - The coordinates of the atoms are $\left\{ x^{(i)} \,|\, i = 1, 2, \ldots, n \right\}$.
    - So, we are dealing with a molecule that has n atoms.
    - We want to calculate these $x^{(i)}$, when given all or some subset of the inter-atomic distances:

$$d_{i,j} = \left\| x^{(i)} - x^{(j)} \right\| \quad 1 \le i, j \le n.$$

  - An n by n matrix X is used to store the $x^{(i)}$ vectors in a column by column fashion.
    - The n by n symmetric matrix D holds the **squares of distances**:

$$\{D\}_{ij} = d_{ij}^2.$$

The Gram matrix G is defined by: $\{G\}_{ij} = x^{(i)\mathrm{T}} x^{(j)}$.

We use $\hat{d}_{ij}$ to represent an approximation of the distance d_{ij} and we set

$$\left\{\hat{D}\right\}_{ij} = \hat{d}_{ij}^2.$$

A USEFUL IDENTITY (1)

- Given all the d_{ij}^2 values, we can compute a Gram matrix using the "double centering formula":

$$\frac{1}{2}\left[\frac{1}{n}\left(\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2 \right) - d_{ij}^2 - \frac{1}{n^2} \sum_{\alpha=1}^{n} \sum_{\beta=1}^{n} d_{\alpha\beta}^2 \right] = x^{(i)\mathrm{T}} x^{(j)} = G_{ij}.$$

  - Note: For consistency and clarity we will always use i and j to index a matrix entry while α and β are used for summation indices.

A USEFUL IDENTITY (2)

- Proving the Double Centering Formula:
  - Start with: $d_{ij}^2 = \left\| x^{(i)} - x^{(j)} \right\|^2$

$$= \left(x^{(i)} - x^{(j)} \right)^{\mathrm{T}} \left(x^{(i)} - x^{(j)} \right)$$

$$= x^{(i)\mathrm{T}} x^{(i)} - 2 x^{(i)\mathrm{T}} x^{(j)} + x^{(j)\mathrm{T}} x^{(j)}.$$

  - We will further assume that the $x^{(i)}$ vectors have their centroid at the origin. This means:

$$\sum_{\alpha=1}^{n} x^{(\alpha)} = 0.$$

    - Note:

$$x^{(j)\mathrm{T}} \sum_{\alpha=1}^{n} x^{(\alpha)} = 0 \Rightarrow \sum_{\alpha=1}^{n} x^{(j)\mathrm{T}} x^{(\alpha)} = 0 \Rightarrow \sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(j)} = 0.$$

A USEFUL IDENTITY (3)

- Proving the Double Centering Formula:
  - Since $d_{ij}^2 = x^{(i)\mathrm{T}} x^{(i)} - 2 x^{(i)\mathrm{T}} x^{(j)} + x^{(j)\mathrm{T}} x^{(j)}$ we get:

$$\sum_{\alpha=1}^{n} d_{\alpha j}^2 = \sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(\alpha)} - 2 \sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(j)} + \sum_{\alpha=1}^{n} x^{(j)\mathrm{T}} x^{(j)} = \sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(\alpha)} + n x^{(j)\mathrm{T}} x^{(j)}.$$

=0 independent of α

  - Similarly: $\sum_{\beta=1}^{n} d_{i\beta}^2 = \sum_{\beta=1}^{n} x^{(\beta)\mathrm{T}} x^{(\beta)} + n x^{(i)\mathrm{T}} x^{(i)}.$
  - Combining: $\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2 = 2 \sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(\alpha)} + n x^{(i)\mathrm{T}} x^{(i)} + n x^{(j)\mathrm{T}} x^{(j)}.$

A USEFUL IDENTITY (4)

- Take the last line of the previous slide and multiply through by n:

$$n\left(\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2\right) = 2n\sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(\alpha)} + n^2\left(x^{(i)\mathrm{T}} x^{(i)} + x^{(j)\mathrm{T}} x^{(j)}\right).$$

  - Also, from last slide: $\sum_{\beta=1}^{n} d_{i\beta}^2 = \sum_{\beta=1}^{n} x^{(\beta)\mathrm{T}} x^{(\beta)} + n x^{(i)\mathrm{T}} x^{(i)}.$
  - So: $\sum_{\alpha=1}^{n}\sum_{\beta=1}^{n} d_{\alpha\beta}^2 = \sum_{\alpha=1}^{n}\sum_{\beta=1}^{n} x^{(\beta)\mathrm{T}} x^{(\beta)} + n\sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(\alpha)} = 2n\sum_{\alpha=1}^{n} x^{(\alpha)\mathrm{T}} x^{(\alpha)}.$
  - Subtract this from the first equation: (Recognizing same sums!)

$$n\left(\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2\right) - \sum_{\alpha=1}^{n}\sum_{\beta=1}^{n} d_{\alpha\beta}^2 = n^2\left(x^{(i)\mathrm{T}} x^{(i)} + x^{(j)\mathrm{T}} x^{(j)}\right).$$

A USEFUL IDENTITY (5)

- Take the last line of the previous slide and divide through by n^2:

$$\frac{1}{n}\left(\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2\right) - \frac{1}{n^2}\sum_{\alpha=1}^{n}\sum_{\beta=1}^{n} d_{\alpha\beta}^2 = x^{(i)\mathrm{T}} x^{(i)} + x^{(j)\mathrm{T}} x^{(j)}.$$

  - This allows us to eliminate $x^{(i)\mathrm{T}} x^{(i)} + x^{(j)\mathrm{T}} x^{(j)}$ from our very first equation: $d_{ij}^2 = x^{(i)\mathrm{T}} x^{(i)} - 2x^{(i)\mathrm{T}} x^{(j)} + x^{(j)\mathrm{T}} x^{(j)}$ which can be rewritten as:

$$x^{(i)\mathrm{T}} x^{(j)} = \frac{1}{2}\left(x^{(i)\mathrm{T}} x^{(i)} + x^{(j)\mathrm{T}} x^{(j)} - d_{ij}^2\right)$$

  to give:

$$x^{(i)\mathrm{T}} x^{(j)} = \frac{1}{2}\left[\frac{1}{n}\left(\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2\right) - d_{ij}^2 - \frac{1}{n^2}\sum_{\alpha=1}^{n}\sum_{\beta=1}^{n} d_{\alpha\beta}^2\right]$$

A USEFUL IDENTITY (6)

- Another expression for the "double centering formula":

$$\frac{1}{2}\left[\frac{1}{n}\left(\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2\right) - d_{ij}^2 - \frac{1}{n^2}\sum_{\alpha=1}^{n}\sum_{\beta=1}^{n} d_{\alpha\beta}^2\right] = x^{(i)\mathrm{T}} x^{(j)} = G_{ij}.$$

It can be rewritten as: $G = -\frac{1}{2} H^{\mathrm{T}} D H$

where: $H = I - \frac{1}{n}\bar{1}\bar{1}^T$

and $\bar{1}$ is an n-dimensional vector with each component equal to 1.

A USEFUL IDENTITY (7)

- Showing that: $G = -\frac{1}{2} H^{\mathrm{T}} D H$
  - Note:

$$-H^{\mathrm{T}} D H = \left(\frac{1}{n}\bar{1}\bar{1}^T - I\right)^{\mathrm{T}} D\left(I - \frac{1}{n}\bar{1}\bar{1}^T\right) = \frac{1}{n}\left(\bar{1}\bar{1}^T D + D\bar{1}\bar{1}^T\right) - D - \frac{1}{n^2}\bar{1}\bar{1}^T D\bar{1}\bar{1}^T.$$

Also, $D\bar{1}$ is an n by 1 column vector with i^{th} entry $\sum_{\beta=1}^{n} d_{i\beta}^2$.

so, $D\bar{1}\bar{1}^{\mathrm{T}}$ is an n by n matrix with $D\bar{1}$ as each column.

Similarly, $\bar{1}^T D$ is a 1 by n row vector with j^{th} entry $\sum_{\alpha=1}^{n} d_{\alpha j}^2$

and $\bar{1}\bar{1}^T D$ is an n by n matrix with $\bar{1}^T D$ as each row.

A USEFUL IDENTITY (8)

- Showing that: $G = -\frac{1}{2} H^{\mathrm{T}} D H$ (continued)
  - The observations on the previous slide explain the two sums: $\sum_{\alpha=1}^{n} d_{\alpha j}^2 + \sum_{\beta=1}^{n} d_{i\beta}^2.$
  - Note also that: $\bar{1}^T D \bar{1} = \sum_{\alpha=1}^{n} \sum_{\beta=1}^{n} d_{\alpha\beta}^2.$

    This is a scalar, so

    $$\bar{1}\bar{1}^T D \bar{1}\bar{1}^T = \left(\sum_{\alpha=1}^{n} \sum_{\beta=1}^{n} d_{\alpha\beta}^2 \right) \bar{1}\bar{1}^T$$

    which is an n by n matrix with each entry equal to the double sum. This explains the double sum term in the double centering formula.

P1: DERIVING COORDINATES GIVEN G (1)

- The double centering formula allows us to calculate G when given all the squares of the inter-atomic distances (set up in D).
  - Then using G, we need an algorithm to calculate X, the matrix with $x^{(i)}$ stored in column i.
  - Before going on, note that D contains $O(n^2)$ entries but our solution X contains only $3n$ values for a 3D space.
    - This means that the entries in D are **not arbitrary**; they must be **consistent** with n atoms in a 3D space.
    - The next theorem gives us the necessary constraints.

P1: DERIVING COORDINATES GIVEN G (2)

- Theorem:
  - Given matrix D, there exists a set of points $\left\{ x^{(i)} \mid i = 1, 2, \ldots, n \right\}$ in $\mathbb{R}^k$ such that $d_{i,j} = \left\| x^{(i)} - x^{(j)} \right\| \quad 1 \le i, j \le n$ if and only if G is positive semidefinite with rank at most k. In this case $G = X^{\mathrm{T}} X$.
    - The theorem essentially says that an X solution **always exists** for any symmetric D matrix, but if the rank of G is more than 3, we cannot expect the $x^{(i)}$ coordinates to be in a 3D space!
      - This has serious implications for noisy distance data.

P1: DERIVING COORDINATES GIVEN G (3)

- To calculate X we start with the spectral decomposition of G:

$$G = \sum_{m=1}^{n} \lambda_m u^{(m)} u^{(m)T} \quad \Rightarrow \quad G_{ij} = \sum_{m=1}^{n} \lambda_m u_i^{(m)} u_j^{(m)}.$$

  - We eventually want the $k = 3$ case but for now it is more informative to consider any fixed integer $k \in \{1, 2, \ldots, n\}$.

P1: DERIVING COORDINATES GIVEN G (4)

- We form the k by n matrix $Y(k)$ defined as:

$$Y(k) = \sqrt{\Lambda(k)}\left[U(k)\right]^{\mathrm{T}} \quad \Rightarrow \quad i^{\text{th}} \text{ column of } Y(k) \text{ is:}$$

$$\left[y(k)\right]^{(i)} = \left[\sqrt{\lambda_1}u_i^{(1)}, \sqrt{\lambda_2}u_i^{(2)}, \cdots, \sqrt{\lambda_k}u_i^{(k)}\right]^{\mathrm{T}}$$

where $\sqrt{\Lambda(k)}$ is the k by k matrix $diag\left(\sqrt{\lambda_1}, \sqrt{\lambda_2}, \cdots, \sqrt{\lambda_k}\right)$ and $U(k)$ is the n by k matrix with column i equal to eigenvector $u^{(i)}$.

P1: DERIVING COORDINATES GIVEN G (3)

- Then it can be shown that:

$$\left[y(k)\right]^{(i)\mathrm{T}}\left[y(k)\right]^{(j)} = \sum_{m=1}^{k} \lambda_m u_i^{(m)} u_j^{(m)} \quad \Rightarrow$$

$$G_{ij} - \left[y(k)\right]^{(i)T}\left[y(k)\right]^{(j)} = \sum_{m=k+1}^{n} \lambda_m u_i^{(m)} u_j^{(m)}.$$

- If the given inter-atomic distances are all exact and consistent with a set of n atoms in a 3D Euclidean space then the rank of the Gram matrix will be 3 and all eigenvalues beyond λ_3 will be zero.
- In this case, the last sum is zero.
- Consequently, we can take X to be the 3 by n matrix $Y(3)$ and this becomes our solution for problem P1.

P2: DERIVING COORDS GIVEN NOISY G (1)

- When given a complete set of distances that have been subjected to a *small* amount of noise, we follow the strategy used by Trosset (1998), which reformulates the problem as follows:

$$\text{minimize } \left\| C - \hat{G} \right\|_F^2 \quad \text{subject to } C \in S_n^+(k)$$

where $\hat{G} = -\frac{1}{2} H^{\mathrm{T}} \hat{D} H$ and

$S_n^+(k)$ is the set of non-negative n by n semidefinite matrices of rank k.

P2: DERIVING COORDS GIVEN NOISY G (2)

- They solve the minimization problem by using the following theorem:

Let $\hat{\lambda}_1 \geq \hat{\lambda}_2 \geq \ldots \geq \hat{\lambda}_n$ denote the eigenvalues of $\hat{G}$ with spectral decomposition $\hat{G} = \hat{U} \hat{\Lambda} \hat{U}^{\mathrm{T}}$ where

$$\hat{\Lambda} = diag\left(\hat{\lambda}_1, \hat{\lambda}_2, \ldots, \hat{\lambda}_n\right).$$

Define:

$\tilde{\lambda}_i = \max\left\{0, \hat{\lambda}_i\right\}$ for $i = 1,2,\ldots, k$ and

$\tilde{\lambda}_i = 0$ for $i = k+1,,\ldots, n$.

Let $\tilde{\Lambda} = diag\left(\tilde{\lambda}_1, \tilde{\lambda}_2, \ldots, \tilde{\lambda}_n\right)$.

Then $C^* = \hat{U} \tilde{\Lambda} \hat{U}^{\mathrm{T}}$ is a global minimiser (and we can use the strategy for P1 with C^* replacing G).

SPARSE DISTANCES

- Suppose we have a subset of the inter-atomic distances.
  - For example, NMR gives us all inter-atomic distances characterized as being less than 5 Å.
  - It can be shown that the problem is NP-hard.
  - However, there are heuristics that may be used to get approximate solutions.
  - Various approaches exist.
    - We cover one such strategy called "Geometric Buildup" originally presented in:

Dong, Q. & Wu, Z., "A linear-time algorithm for solving the molecular distance geometry problem with exact inter-atomic distances", Journal of Global Optimization, 2002, 22:365-375.

GEOMETRIC BUILDUP

- Suppose we are given a subset of inter-atomic distances.
- Recall that we designated this as Problem P3.
  - In geometric buildup we let R represent the set of atoms with known coordinates.
  - That is, R is the "determined" set.
  - Initially, R is empty and the algorithm works by steadily bringing new atoms into R until the coordinates of all the atoms are determined.

P3: SPARSE BUT EXACT DISTANCES (1)

- For problem P3 we are given exact distances but only for atoms that are closer than some upper threshold.
- Geometric Buildup (Wu et al. 2003, 2007, 2008)
  - Find four atoms, not in the same plane, such that ***all*** inter-atomic distances are known.
  - Using the P1 strategy described earlier, derive the coordinates of all four atoms (so R starts with 4 atoms).
  - While there are atoms with undetermined positions repeat:
    - Find an atom with undetermined position but with known distances to four other non-coplanar atoms whose positions are known.
    - Determine the position of the undetermined atom using a triangulation strategy.

P3: SPARSE BUT EXACT DISTANCES (2)

- Triangulation:
  - Let $x^{(k_i)}\ i=1,2,3,4$ represent the coordinates of four non-coplanar atoms (in R) with known positions and let $x^{(j)}$ be the undetermined coordinates of a nearby atom (not in R) such that all distances between this atom and the four are known. Then:

$$\left\|x^{(k_i)}\right\|^2 - 2x^{(k_i)\mathrm{T}}x^{(j)} + \left\|x^{(j)}\right\|^2 = d^2_{k_i,j} \quad i=1,2,3,4$$

  - For each i = 1,2,3 we subtract equation i from equation i+1:

$$\left\|x^{(k_{i+1})}\right\|^2 - 2x^{(k_{i+1})\mathrm{T}}x^{(j)} + \left\|x^{(j)}\right\|^2 = d^2_{k_{i+1},j}$$

$$\left\|x^{(k_i)}\right\|^2 - 2x^{(k_i)\mathrm{T}}x^{(j)} + \left\|x^{(j)}\right\|^2 = d^2_{k_i,j}$$

$$\left\|x^{(k_{i+1})}\right\|^2 - \left\|x^{(k_i)}\right\|^2 - 2\left(x^{(k_{i+1})} - x^{(k_i)}\right)^{\mathrm{T}} x^{(j)} = d^2_{k_{i+1},j} - d^2_{k_i,j}$$

$i=1,2,3.$

P3: SPARSE BUT EXACT DISTANCES (3)

- Rearranging terms:

$$\left(x^{(k_{i+1})} - x^{(k_i)}\right)^{\mathrm{T}} x^{(j)} = \frac{1}{2}\left(\left\|x^{(k_{i+1})}\right\|^2 - \left\|x^{(k_i)}\right\|^2 - d^2_{k_{i+1},j} + d^2_{k_i,j}\right) \quad i = 1,2,3.$$

- Set these three equations in matrix form:

$$Bx^{(j)} = c$$

where:

$$B = \begin{bmatrix} \left(x^{(k_2)} - x^{(k_1)}\right)^{\mathrm{T}} \\ \left(x^{(k_3)} - x^{(k_2)}\right)^{\mathrm{T}} \\ \left(x^{(k_4)} - x^{(k_3)}\right)^{\mathrm{T}} \end{bmatrix} \qquad c = \frac{1}{2}\begin{bmatrix} \left\|x^{(k_2)}\right\|^2 - \left\|x^{(k_1)}\right\|^2 - d^2_{k_2,j} + d^2_{k_1,j} \\ \left\|x^{(k_3)}\right\|^2 - \left\|x^{(k_2)}\right\|^2 - d^2_{k_3,j} + d^2_{k_2,j} \\ \left\|x^{(k_4)}\right\|^2 - \left\|x^{(k_3)}\right\|^2 - d^2_{k_4,j} + d^2_{k_3,j} \end{bmatrix}$$

P3: SPARSE BUT EXACT DISTANCES (4)

- Geometric buildup continued:

We now have the linear system: $Bx^{(j)} = c.$

Since the $x^{(k_i)}$ $i = 1,2,3,4$ are not coplanar, B is invertible and we can solve for $x^{(j)}$ using:

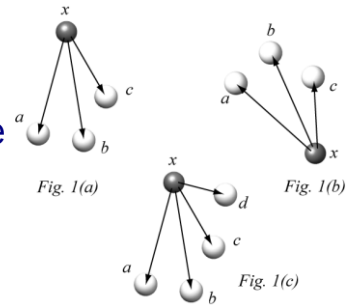
$$x^{(j)} = B^{-1}c.$$

Then move $x^{(j)}$ into R.

Repeat the last steps (following the determination of the first four atoms) **until all atoms are in R.**

P3: SPARSE BUT EXACT DISTANCES (5)

- Triangulation issues:
  - If only three atoms with known positions were used then the position of the undetermined atom would be ambiguous (Fig. 1(a) or Fig. 1(b)?)
  - So, we need four atoms but they cannot be coplanar.
  - Even if they are "almost coplanar" we have a problem. An ill-conditioned system is very susceptible to noise.



P3: SPARSE BUT EXACT DISTANCES (6)

- According to the authors:
  - "The advantage of using the geometric building algorithm is that it not only is more efficient than the SVD method, but also requires a smaller set of distances and is easier to extend to problems with sparse sets of distances."
- There is no discussion about numerical stability.
  - Issues to be considered:
    - Consider the first four atoms: They could be at the beginning of a chain or somewhere near the center of a hydrophobic core. Does it matter?
    - Intuitively, it would seem that small errors in the inter-atomic distances for the initial atoms of R could propagate throughout the entire solution. Do these small errors magnify as the algorithm progresses?

P4: SPARSE AND NOISY DISTANCES

- Recall Problem P4: we are given approximate distances for atoms that are closer than some upper threshold.
  - As long as the distances are positive there is always a solution, but it may reside in a space with dimension higher than 3.
  - If the given distances are true 3D distances with a small amount of error then the first three eigenvalues will be quite different from 0 and the fourth and later eigenvalues will be quite close to 0.
  - Simply ignoring these values (in effect, projecting from a high dimension space down to 3D) can produce an approximate solution typically characterized as "crowded" since contributions to a distance are being ignored.

P4: MDS & OVERLAPPING CLIQUES (1)

- We now describe a strategy for handling the P4 problem (sparse and noisy distances).
- Clique formation:
  - Start by grouping neighbouring atoms to form "cliques":
    - All inter-atomic distances are known for the atoms in a clique.
    - Recall that we are given all inter-atomic distances less that some threshold (say, τ Angstroms).
    - Each clique will surround a particular atom called the clique center.

P4: MDS & OVERLAPPING CLIQUES (2)

- A clique formation heuristic
- Suppose atom A is to be a “clique center”.
  - Place all atoms that are within $\tau / 2$ Angstroms of *A* into an initially empty clique set.
  - Collect all the atoms that are within τ Angstroms but beyond $\tau / 2$ Angstroms from atom *A*, and sort them in ascending order with respect to their distance from *A*.
  - Go through the sorted list formed in the previous step and add an atom to the clique set if the input data includes all inter-atomic distances between that atom and every current member of the clique set .

P4: MDS & OVERLAPPING CLIQUES (3)

- Choosing clique centers
- Clique centers are chosen so that the clique has biological relevance. Each amino acid provides centers for two cliques:
  - A clique centered on the alpha carbon atom:
    - Since the clique center is also a chiral center, we can be sure that the computed coordinates have the appropriate chirality.
  - A clique centered on the carbonyl oxygen atom.
    - This clique overlaps the alpha carbon clique and also includes the hydrogen bonds responsible for helix and strand formation.

P4: MDS & OVERLAPPING CLIQUES (4)

- Calculating atomic positions
- For each clique there is a full set of distance values and so we can use the P2 algorithm discussed earlier.
  - Sometimes called an MDS (Multidimensional Scaling) strategy.
- The coordinates of all atoms in a clique will be relative to a frame of reference that is only suitable for that clique.
  - We need to modify coordinates so that all atoms are in the same frame of reference.

P4: MDS & OVERLAPPING CLIQUES (5)

- Combining cliques
- When cliques overlap, with at least 4 atoms in their intersection, we may combine them:
  - This involves a translate and rotate of the second atom set so that both sets have the frame of reference used by the first atom set.
  - The atoms in the intersection will define the appropriate translate and rotate operations.
  - The intersection atoms cannot be coplanar.

P4: MDS & OVERLAPPING CLIQUES (6)

- Combining cliques (continued)
- Recall that we are using $C^* = \hat{U}\tilde{\Lambda}\hat{U}^{\mathrm{T}}$ where $\tilde{\Lambda} = diag\left(\tilde{\lambda}_1, \tilde{\lambda}_2, \tilde{\lambda}_3, 0, \ldots, 0\right)$ and $\tilde{\lambda}_i = \max\left\{0, \hat{\lambda}_i\right\}\ \ i = 1, 2, 3.$
  - Noise in the given distance data will increase the magnitude of $\hat{\lambda}_4$ and thus compromise the ability of C^* to yield the "true" 3D coordinates.
  - Consequently, the positions of atoms in the intersection of two cliques will not be precise.

P4: MDS & OVERLAPPING CLIQUES (7)

- Combining cliques (continued)
  - Repeating: Because of noise in the distance data, the computed positions of atoms in the intersection of two cliques are not exact:
    - The translate and rotate operations when doing clique combining can still proceed because the super-positioning of atoms in the intersection is done in the least squares sense.
    - However, it is still necessary to determine the final positions of atoms in the intersection.

P4: MDS & OVERLAPPING CLIQUES (8)

- Modifying distance estimates:
- **Before** getting both cliques into the same frame of reference we can try to reduce distance errors by averaging:
  - We can recalculate the squares of distances by using the C^* matrix:

$$\left(d^*_{i,j}\right)^2 = C^*_{i,i} - 2C^*_{i,j} + C^*_{j,j}.$$

P4: MDS & OVERLAPPING CLIQUES (9)

- Modifying distance estimates (continued):
- For any pair of atoms (indexed by i, j) within the intersection, each clique will have a different value of $\left(d^*_{i,j}\right)^2$.
  - We can try to reduce distance errors by computing an average and then replacing all such distances with the average distance.
  - After this is done, coordinates are computed and one clique can be brought into the frame of reference of the other clique.