Algorithms for Alignment and Reconstruction

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Outline

• Alignment and Reconstruction used in molecular and cellular imaging
• Optimization problem
• Refinement algorithms
• Getting an initial guess
Goals:
- Visualize 3D cell structure (location of proteins and other organelles)
- Understand biological process at cellular level (e.g., cell division, endocytosis etc.)

Methodology:
- Illuminate cell specimen with soft X-ray
- Measure absorption contrast (Beer-Lambert law)
Single axis rotation tomography

Ideal image formation model

\[ b(x', y') = \int f(x', y', z') \, dz' \]

where \( y' = y \),

\[
\begin{pmatrix} x' \\ z' \end{pmatrix} = \begin{pmatrix} \cos \theta & \sin \theta \\ -\sin \theta & \cos \theta \end{pmatrix} \begin{pmatrix} x \\ z \end{pmatrix}
\]

Optimization problem

\[
\min_{f} \sum_{i=1}^{k} \| b - P(\theta)f \|^{2}
\]

180 or 360 degree full angular coverage at some angular increment
More realistic imaging condition in X-ray tomography

- Rotation axis tilted away from the y-axis
- Image drift due to stage vibration
A more realistic image formation model

\[
b(x', z') = \int f(x', y', z') dz', \text{ where}\\
\begin{pmatrix}
x' \\
y' \\
z'
\end{pmatrix} = R(\psi)R(\theta)R(\phi) \begin{pmatrix} x \\ y \\ z \end{pmatrix} + \begin{pmatrix} \Delta x \\ 0 \\ \Delta z \end{pmatrix}
\]

- Optimization problem

\[
\min_{f, \{\psi_i, \phi_i, \Delta x_i, \Delta z_i\}} \sum_{i=1}^{m} \|b_i - P(\psi_i, \phi_i, \Delta x_i, \Delta z_i)f\|^2
\]

Rotation around the rotation axis \( \theta_i \) is known
Challenge

- Nonlinear coupling between the orientation and 3D structure
- Large volume of data ($1024 \times 1024$ pixels per image), 180-360 images per reconstruction
- Noise contamination
Single-particle cryo-electron microscopy
Single Molecular Diffraction Imaging

Particle injection

X-ray beam

Diffraction pattern

| a slice of 3D Fourier transform |
Image Reconstruction Problem

- Nonlinear optimization to recover 3D scattering intensity $f$ from 2D diffraction patterns $b_i$:
  \[
  \min_{Q_i, f} \sum_{i=1}^{m} \| P f(Q_i r) - b_i \|^2
  \]
  - If projection directions (relative orientations of molecules) can be determined in advance, reconstructing $f$ becomes a linear least squares problem.

- Solve a 3D phase retrieval problem
  \[
  g(r) = \mathcal{F}^{-1}\{f e^{i\phi}\}\]
Current strategy (AREC3D)

- Initial alignment
  - Correct for rotation axis tild
  - Correct for drift
- Refinement (alternating direction)
  - Fix orientation parameters
    \[
    \min_f \sum_{i=1}^{m} \| P_i f - b_i \|^2
    \]
  - Fix 3D structure, optimize orientation parameters \( \psi_i, \theta_i, \phi_i, \Delta x_i, \Delta z_i \)
Initial alignment

- Correction for tilt angle

Apply $R(\alpha)$ to all images
Initial translational alignment

- Align two adjacent images by cross-correlation to correct for translation induced by vibration.
- Align the first image ($\theta = 0$) with its mirror image $\theta = \pi$ to correct for a global drift.

\[
x' = (x - x_0) \cos 0 + (y - y_0) \sin 0 + \Delta
\]
\[
x'' = (x - x_0) \cos \pi + (y - y_0) \sin \pi + \Delta
\]
\[
x - x'' = 2\Delta
\]
Refinement

\[ \min_f \sum_{i=1}^{k} \|b_i - P_if\|^2 \]

- Real space reconstruction by conjugate gradient

\[ \sum_{i=1}^{m} P_i^T P_if = \sum_{i=1}^{m} P_i^T b_i \]

- Main cost: projection \( P_if \) and back projection \( P_i^T b_i \) (interpolation, take advantage of the cylindrical geometry)

- Regularization by controlling iteration
Other reconstruction algorithms

- Fourier reconstruction
  - Need to perform large FFTs (pad with zeros to reduce interpolation artifacts)
  - Use non-uniform FFTs to interpolate from 2D projection grid to 3D volume grid
- Use sparse algorithm?
  - Number of unknowns: $nk^2$, e.g., $n = 1024, k = 500, nk^2 = 256M$
  - Number of data points: $180nk$ or $360nk$
- Weighted least squares (noise
Orientation optimization by projection matching

- $\theta_i$ is assumed to be accurate
- In-plane angular alignment by rotational cross-correlation to correct for $\psi_i$
- Translational cross-correlation to correct for shifts
- No correction for $\phi_i$
Examples
Convergence
Alignment and reconstruction solved as a maximum likelihood estimation problem

- Construct a (log) likelihood function
  \[ L(f; \{b_i\}) \]
- Maximize \( L(f; \{b_i\}) \)
- First order necessary condition
  \[ \sum_{k=1}^{n_f} P_k^T \left( \sum_{i=1}^{m} g_k^{(i)} \right) P_k^T f = \sum_{k=1}^{n_f} P_k^T \left( \sum_{i=1}^{m} g_k^{(i)} b_i \right) \]

Normalization factor

\( g_k^{(i)} \) is a probability with respect to \( k \), a function of \( f \)

- Fixed point iteration or quasi-Newton
The EM Algorithm for Maximum Likelihood Estimator

• Ideal likelihood function:
  \[ L(f \mid \{b_i\}) = \prod_{i=1}^{m} p(b_i \mid f, Q_i) \]

• But \( Q_i \) is unknown, so \( \{b_i\} \) is considered incomplete

• Maximize the expected likelihood by integrating out \( Q_i \)
  – Expectation: \( \bar{L}(f \mid b_i, \hat{f}) = \int_Q \prod_{i=1}^{m} p(b_i \mid Q, f) g(Q \mid b_i, \hat{f}) \)
  – Maximization: \( f = \arg\max_f \bar{L}(f \mid b_i, \hat{f}) \)
The Choice of the Likelihood Function

\[ \bar{L}(f | b_j, f^{(i)}) = \int p(b_j | Q, f)g(Q | b_j, f^{(i)})dQ \]

- The choice of \( p \)
  - Poisson: (Loh & Elser 2009)
  - Gaussian: (Doerschuk et al. 2000, Schere et al. 2006)

- The choice of \( g \) (use Bayes theorem)

\[ p(b_j | P_kf) = \frac{e^{-P_kf}(P_kf)^{b_j}}{b_j!} \]

\[ p(b_j | P_kf) = \frac{1}{\sqrt{2\pi}\sigma} \exp \left[ -\frac{\|P_kf - b_j\|^2}{2\sigma^2} \right] \]

\[ g(Q | b_j, f^{(i)}) = \frac{p(b_j | Q, f^{(i)})h(Q | f^{(i)})}{\int p(b_j | Q, f^{(i)})h(Q | f^{(i)})dQ} \]
Derivation for Gaussian Likelihood

- Expected log likelihood

\[
\bar{L}(f | \{b_i\}) = \sum_{k=1}^{n_r} \left[ \sum_{i=1}^{m} \log(p(b_i | Q_k, f)) \right] g(Q_k | b_i, \hat{f})
\]

- Bayes rule:

\[
g(Q | b_i, \hat{f}) = p(Q | b_i, \hat{f}) = \frac{p(b_i | Q, \hat{f})h(Q | \hat{f})}{\sum_{k=1}^{n_r} p(b_i | Q_k, \hat{f})h(Q_k | \hat{f})}
\]

- \( p(b | Q_k, f) = \exp\left[ -\frac{\| p_k f - b \|^2}{2\sigma^2} \right] \)

- Setting derivative to zero yields

\[
\sum_{k=1}^{n_r} p_k^T \left( \sum_{i=1}^{m} g_k^{(i)} \right) p_k^T f = \sum_{k=1}^{n_r} p_k^T \left( \sum_{i=1}^{m} g_k^{(i)} b_i \right)
\]
Derivation for Poisson Likelihood

• \( p(b_i | Q, f) = \prod_{j=1}^{n_{pix}} \left[ e^{-e_j^T P_{if} \frac{(e_j^T P_{if})^{\beta_{ji}}}{\beta_{ji}!}} \right] \)

• Setting the derivative of \( \bar{L}(f | \{b_i\}) \) to zero yields

\[
\sum_{k=1}^{n_r} \left[ \sum_{i=1}^{m} \left( P_k^T g_k^i e - P_k^T g_k^i \text{Diag}(P_k f)^{-1} b_i \right) \right] = 0
\]

• Define \( w_k \equiv P_k f \)

sufficient condition: \( w_k = \left( \sum_{i=1}^{m} g_k^{(i)} \right)^{-1} \sum_{i=1}^{m} g_k^{(i)} b_i \)

• Solve \( \min_f \sum_{k=1}^{n-r} \| P_k f - w_k \|^2 \)
Ab initio orientation determination

- The optimization problem solved by the refinement procedure is non-convex
- Need a good starting point to avoid local minimizer
  - Not a problem in soft Xray cell tomography
  - Experimental techniques in Cryo-EM
  - Methods based on common line
  - Methods based on manifold embedding
Common Curves and Lines

- Rotating the object is equivalent to rotating an Ewald sphere with respect to the origin.
- Two Ewald spheres intersect along a curve.
- When Ewald surface is flat, common curves reduce to common lines.
**Eigenvector Method**

- Identify common lines among pairwise images and the corresponding angles

![Diagram with angle symbols](image)

- Construct a matrix $S$ whose elements are

$$\cos \theta_{ij} \cos \theta_{ji}, \sin \theta_{ij} \sin \theta_{ji}, \cos \theta_{ij} \sin \theta_{ji}, \sin \theta_{ij} \sin \theta_{ji}$$

- Compute the largest 3 eigenvalues and the corresponding eigenvectors $\mathbf{x}$ of $S$

- Recover relative projection directions from $\mathbf{x}$
Common line identification

• Difficult to identify common lines by cross correlation when SNR is low

• Create image clusters with the same viewing direction (but different in-plane rotation)
  – Angular synchronization
  – Diffusion map
  – Vector diffusion map
Orientation determination via diffusion map

• Choose a distance threshold $t$
• Choose a diffusion rate $\epsilon$
• Construct

$$W_{ij} = \begin{cases} 
1 & \text{if } i = j \\
\exp\left(-\frac{\|x_i - x_j\|^2}{\epsilon}\right) & \text{if } \|x_i - x_j\| \leq t \\
0 & \text{otherwise}
\end{cases}$$

• Normalize
• Compute the 10 largest eigenpairs of the normalized adjacency matrix
• Construct rotation matrices from these eigenvectors by solving a nonlinear least squares
Conclusion

• Alignment and reconstruction problems arise from a number of molecular and cell imaging experiments
• Formulate as nonlinear optimization or statistical estimation
• Equivalence of projection matching and the EM algorithm
• Getting a good initial guess remains to be a challenging problem