Paper Report — Unit Quaternion Description of Spatial Rotations in 3D cryoEM

Group Meeting

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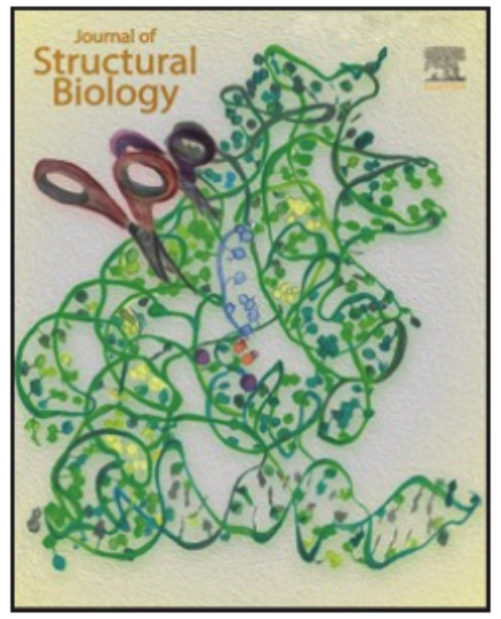

Review

Unit quaternion description of spatial rotations in 3D electron cryo-microscopy

Check for updates

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Outline

- Background of the Quaternion and Unit Quaternion
- Distance and Geodesic between Rotations by Unit Quaternion in cryoEM
- Uniform and Quasi-Uniform Sampling in SO(3)
- Statistics of Rotations in cryoEM

Description of Spatial Rotations

- To describe spatial rotations, three approaches widely used:
  - Rotation matrix
  - Euler angles
  - Unit quaternion

Rotation Matrix

- Most basic method
- Directly used to rotate a 3D vector/ object

- Required 9 parameters with non-linear constraints in a 3x3 matrix
  ➟ hard to estimate and optimize

Euler Angles

- Using three angle values to represent sequential rotations around three elemental axes

- Non-uniformity of rotation description
- Gimbal lock problem (in definition of intrinsic rotations)
- Multiple definitions and axis conventions

Unit Quaternion

- Used to perform basic rotations
- Generate uniform or quasi-uniform sampling in rotation space
- Cooperate with model building

Background of the Quaternion and Unit Quaternion

- $\vec{\mathbf{v}}$: The 3D vector
- $\hat{\mathbf{v}}$: The unit vector
- $\mathbf{q}$: The quaternion in vector form a 4D vector
- R : The spatial rotation operator
- $\mathbb{R}^3$: The 3D space
- S^2 : All unit 3D vectors form a 2D surface of a unit sphere in 3D space
- $\mathbb{R}^4$: The 4D space
- S^3 : All unit 4D vectors form a 3D hypersurface of the unit sphere in 4D space
- $SO(3)$: The set containing all 3D spatial rotations

Definition of the Quaternion

- A quaternion is an extension of a complex number.
- A quaternion $\mathbf{q}$ is defined as a hypercomplex number composed of **a real part** and **three imaginary parts**:

$$\mathbf{q} = q_0 + q_1\mathbf{i} + q_2\mathbf{j} + q_3\mathbf{k} = \begin{pmatrix} q_0 \\ q_1 \\ q_2 \\ q_3 \end{pmatrix} = \begin{pmatrix} q_0 \\ \vec{\mathbf{n}}_{\mathbf{q}} \end{pmatrix}, \quad \text{where } \{\mathbf{i}, \mathbf{j}, \mathbf{k}\} \text{ are three imaginary units,} \quad \vec{\mathbf{n}}_{\mathbf{q}} = \begin{pmatrix} q_1 \\ q_2 \\ q_3 \end{pmatrix}$$

- The conjugate of a quaternion:

$$\mathbf{q}^* = q_0 - q_1\mathbf{i} - q_2\mathbf{j} - q_3\mathbf{k} = \begin{pmatrix} q_0 \\ -q_1 \\ -q_2 \\ -q_3 \end{pmatrix} = \begin{pmatrix} q_0 \\ -\vec{\mathbf{n}}_{\mathbf{q}} \end{pmatrix}$$

- The norm of a quaternion $\mathbf{q}$ is defined by:

$$|\mathbf{q}| := \sqrt{\mathbf{q} \cdot \mathbf{q}^*} = \sqrt{q_0^2 + q_1^2 + q_2^2 + q_3^2} = \sqrt{q_0^2 + \vec{\mathbf{n}}_{\mathbf{q}} \cdot \vec{\mathbf{n}}_{\mathbf{q}}}$$

- The multiplication of two quaternions ($\otimes$: the quaternion product):
  - $1 \otimes 1 = 1$
  - $1 \otimes \mathbf{i} = \mathbf{i} \otimes 1 = \mathbf{i}$
  - $1 \otimes \mathbf{j} = \mathbf{j} \otimes 1 = \mathbf{j}$
  - $1 \otimes \mathbf{k} = \mathbf{k} \otimes 1 = \mathbf{k}$
  - $\mathbf{i}^2 = \mathbf{j}^2 = \mathbf{k}^2 = -1$
  - $\mathbf{i} \otimes \mathbf{j} = \mathbf{k}$, $\mathbf{j} \otimes \mathbf{k} = \mathbf{i}$, $\mathbf{k} \otimes \mathbf{i} = \mathbf{j}$
  - $\mathbf{j} \otimes \mathbf{i} = -\mathbf{k}$, $\mathbf{k} \otimes \mathbf{j} = -\mathbf{i}$, $\mathbf{i} \otimes \mathbf{k} = -\mathbf{j}$

$\times$	1	i	j	k
1	1	i	j	k
i	i	-1	k	$-j$
j	j	$-k$	-1	i
k	k	j	$-i$	-1

From https://zh.wikipedia.org/wiki/四元數

- The result of quaternion multiplication can also be written in vector form as:

$$\mathbf{q} \otimes \mathbf{q}' = \begin{pmatrix} q_0 \\ q_1 \\ q_2 \\ q_3 \end{pmatrix} \otimes \begin{pmatrix} q_0' \\ q_1' \\ q_2' \\ q_3' \end{pmatrix} = \begin{pmatrix} q_0q_0' - q_1q_1' - q_2q_2' - q_3q_3' \\ q_0q_1' + q_1q_0' + q_2q_3' - q_3q_2' \\ q_0q_2' - q_1q_3' + q_2q_0' + q_3q_1' \\ q_0q_3' + q_1q_2' - q_2q_1' + q_3q_0' \end{pmatrix} = \begin{pmatrix} q_0 \\ \vec{\mathbf{n}}_{\mathbf{q}} \end{pmatrix} \otimes \begin{pmatrix} q_0' \\ \vec{\mathbf{n}}_{\mathbf{q}'} \end{pmatrix} = \begin{pmatrix} q_0q_0' - \vec{\mathbf{n}}_{\mathbf{q}} \cdot \vec{\mathbf{n}}_{\mathbf{q}'} \\ q_0\vec{\mathbf{n}}_{\mathbf{q}'} + q_0'\vec{\mathbf{n}}_{\mathbf{q}} + \vec{\mathbf{n}}_{\mathbf{q}} \times \vec{\mathbf{n}}_{\mathbf{q}'} \end{pmatrix}$$

Complex form **Vector form**

- The complex form and vector form of quaternion multiplication are equivalent.

Basic Quaternion Algebra Property

- The properties of quaternions are similar to complex numbers, except that the multiplication of quaternions is **not commutative**: $\mathbf{q}_1 \otimes \mathbf{q}_2 \neq \mathbf{q}_2 \otimes \mathbf{q}_1$.
- The conjugation, norm, and multiplication of quaternions satisfies the following properties:
  - $(\mathbf{q}^*)^* = \mathbf{q}$
  - $(\mathbf{q}_1 \otimes \mathbf{q}_2)^* = \mathbf{q}_2^* \otimes \mathbf{q}_1^*$
  - $|\mathbf{q}| = |\mathbf{q}^*|$
  - $|\mathbf{q}_1 \otimes \mathbf{q}_2| = |\mathbf{q}_1| \cdot |\mathbf{q}_2|$
  - Multiplication is associative: $(\mathbf{q}_1 \otimes \mathbf{q}_2) \otimes \mathbf{q}_3 = \mathbf{q}_1 \otimes (\mathbf{q}_2 \otimes \mathbf{q}_3)$
  - 1 is the multiplicative identity: $1 \otimes \mathbf{q} = \mathbf{q} \otimes 1 = \mathbf{q}$

Unit Quaternion Description of 3D Spatial Rotation

- If norm equals to 1 : $|\mathbf{q}| = 1$ —> Unit quaternion
- A unit quaternion can be used to perform 3D rotation.
- The rotation of a 3D vector $\overrightarrow{\mathbf{v}}$ to another vector $\overrightarrow{\mathbf{v}}'$ is performed using a 3×3 orthogonal matrix $\mathbf{M}$ with a determinant of 1:

$$\overrightarrow{\mathbf{v}}' = \mathbf{M}\overrightarrow{\mathbf{v}}$$

- This operation can also be achieved by performing unit quaternion multiplication:

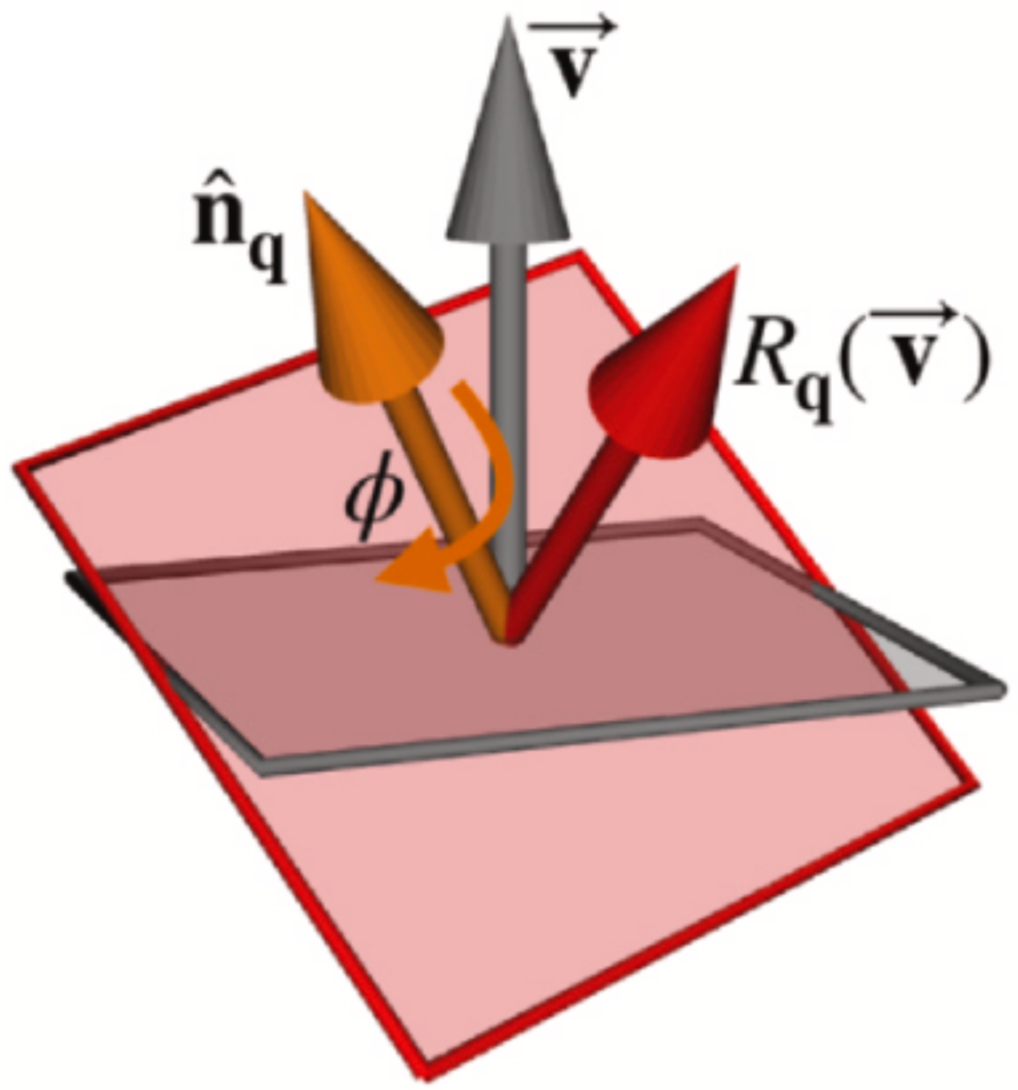
$$\mathbf{v}' = \begin{pmatrix} 0 \\ \overrightarrow{\mathbf{v}}' \end{pmatrix} = \mathbf{q} \otimes \begin{pmatrix} 0 \\ \overrightarrow{\mathbf{v}} \end{pmatrix} \otimes \mathbf{q}^* \equiv R_{\mathbf{q}}(\overrightarrow{\mathbf{v}})$$

- Because a pair of unit quaternion is involved in the multiplication, $\mathbf{q}$ and $-\mathbf{q}$ will yield same rotations: $R_{\mathbf{q}} = R_{-\mathbf{q}}$

Unit Quaternion Description of 3D Spatial Rotation

- A unit quaternion $\mathbf{q}$ can be written in the form:

$$\mathbf{q} = \begin{pmatrix} \cos\frac{\phi}{2} \\ \hat{\mathbf{n}}_{\mathbf{q}} \sin\frac{\phi}{2} \end{pmatrix}$$ —> a rotation about the axis $\hat{\mathbf{n}}_{\mathbf{q}}$ by the angle ϕ.



From this paper

- For sequential rotation, e.g. $R_{\mathbf{q}_1}$ followed by $R_{\mathbf{q}_2}$, is equivalent to $R_{\mathbf{q}_2 \otimes \mathbf{q}_1}$:

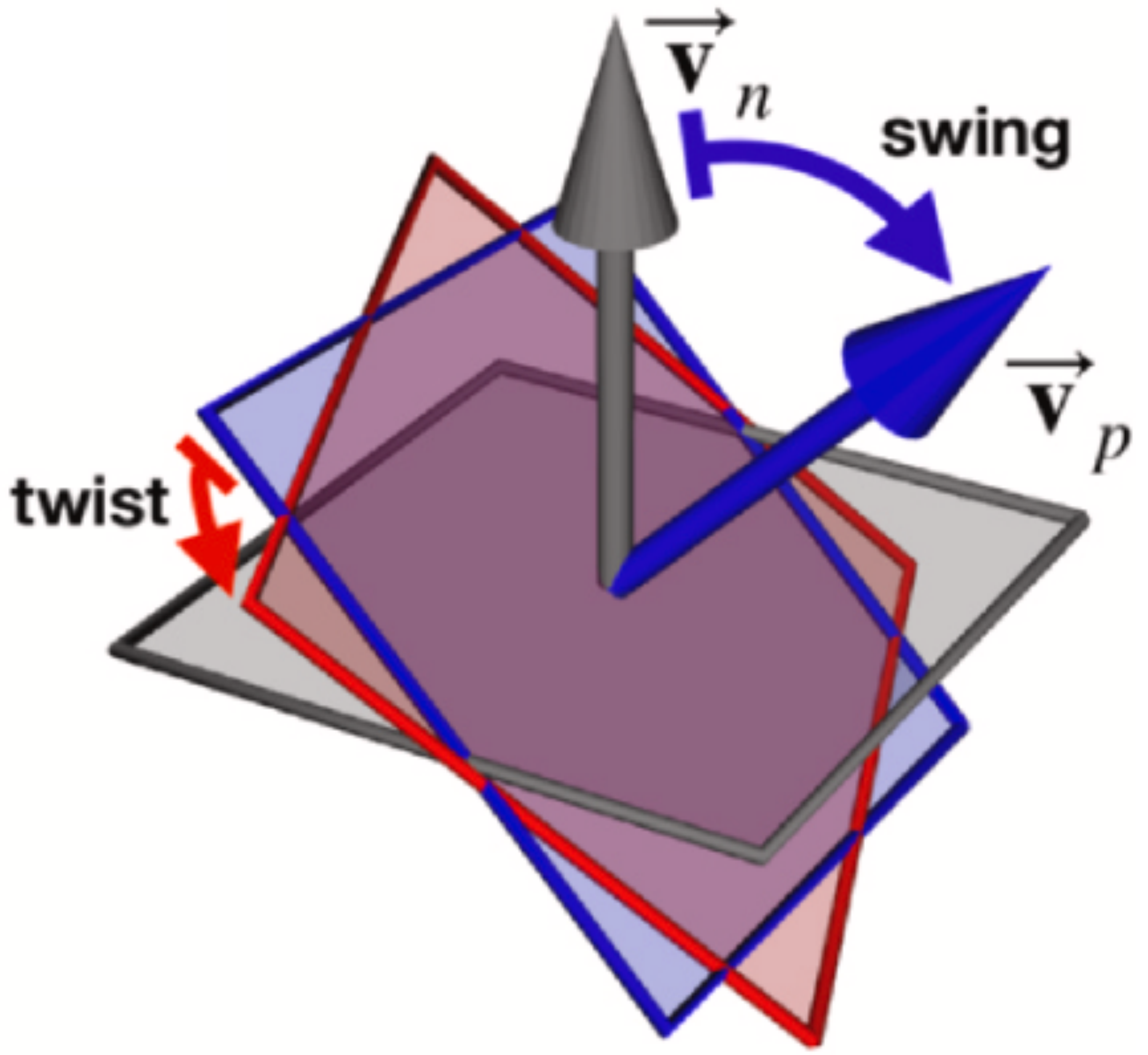
$$R_{\mathbf{q}_2}(R_{\mathbf{q}_1}(\vec{\mathbf{v}})) = \mathbf{q}_2 \otimes \left(\mathbf{q}_1 \otimes \begin{pmatrix} 0 \\ \vec{\mathbf{v}} \end{pmatrix} \otimes \mathbf{q}_1^* \right) \otimes \mathbf{q}_2^* = (\mathbf{q}_2 \otimes \mathbf{q}_1) \otimes \begin{pmatrix} 0 \\ \vec{\mathbf{v}} \end{pmatrix} \otimes (\mathbf{q}_2 \otimes \mathbf{q}_1)^* = R_{\mathbf{q}_2 \otimes \mathbf{q}_1}(\vec{\mathbf{v}})$$

- The dot and cross products of vectors are preserved under spatial rotations.
- The conversions between three rotation descriptions (rotation matrix, Euler angles, unit quaternion) are well-established.

Swing-Twist Decomposition

- Using a directional vector to represent the orientation of a 3D object, the 3D rotation of this object can be decomposed into the product of two rotations:
  - **Swing**: change the directional vector to another direction.
  - **Twist**: twist about the directional vector.

  ➟ Useful for rotation analysis and the application of constraints to rotations.



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- Consider a 2D experimental image in single particle cryoEM that is rotated using unit quaternion $\mathbf{q}$ to match the projection of a 3D object.
- Assume the experimental image initially lies in the XY-plane with norm vector $\vec{\mathbf{v}}_n = (0,\ 0,\ 1)^T$, the rotation can be perform in two steps:

- The image is rotated so that its norm vector $\vec{\mathbf{v}}_n$ is changed to be along the projection direction $\vec{\mathbf{v}}_p$.

$$\begin{pmatrix} 0 \\ \vec{\mathbf{v}}_p \end{pmatrix} = \mathbf{q} \otimes \begin{pmatrix} 0 \\ \vec{\mathbf{v}}_n \end{pmatrix} \otimes \mathbf{q}^*$$

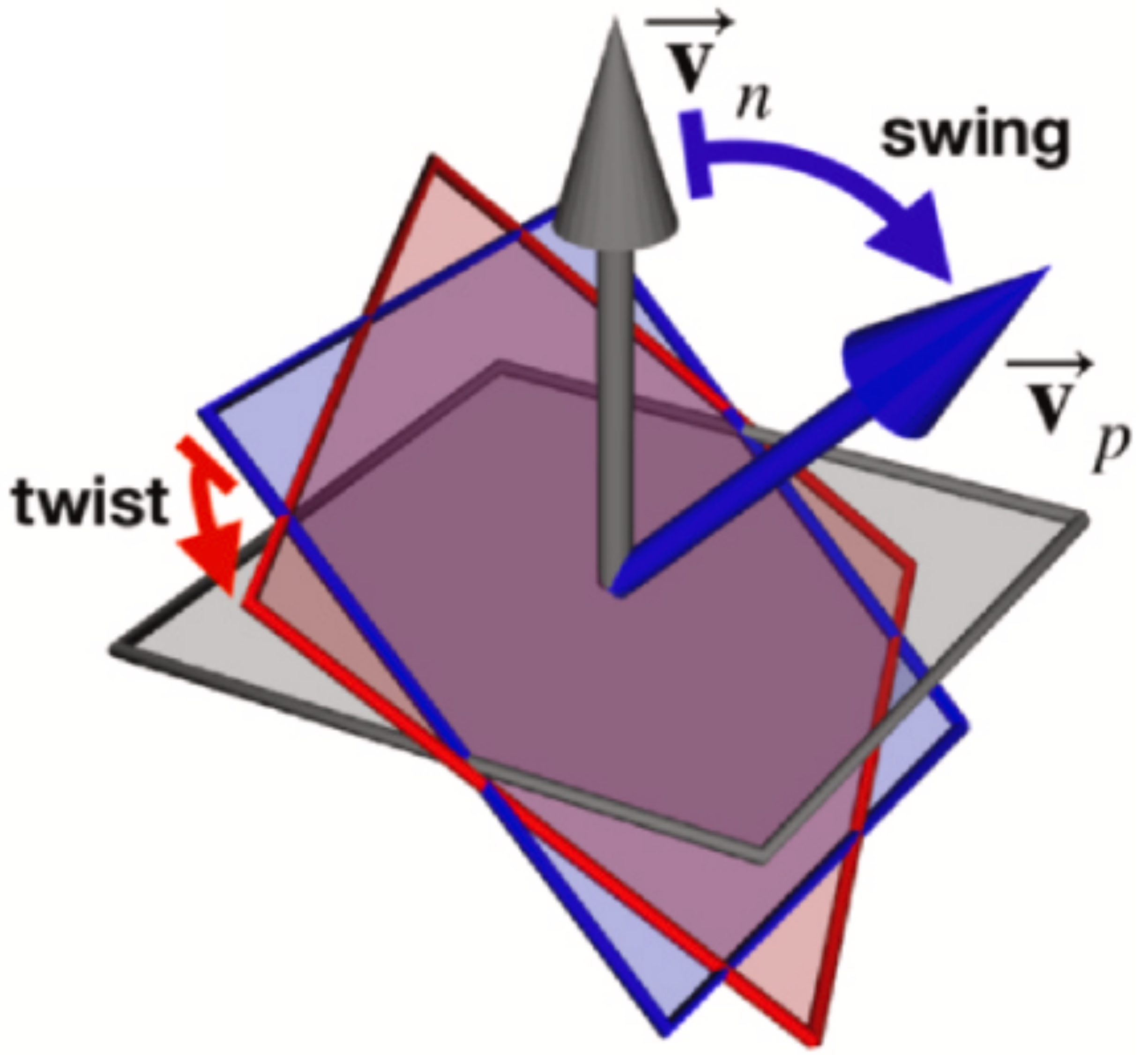
- The swing rotating $\vec{\mathbf{v}}_n$ to $\vec{\mathbf{v}}_p$ can be obtained by a rotation about the axis $\hat{\mathbf{v}}_r$ for the angle ψ_s :

$$\hat{\mathbf{v}}_r = \frac{\vec{\mathbf{v}}_n \times \vec{\mathbf{v}}_p}{|\vec{\mathbf{v}}_n||\vec{\mathbf{v}}_p|} \quad , \quad \boxed{\psi_s = \cos^{-1} \frac{\vec{\mathbf{v}}_n \cdot \vec{\mathbf{v}}_p}{|\vec{\mathbf{v}}_n||\vec{\mathbf{v}}_p|}}$$

Swing angle

- The swing quaternion is:

$$\boxed{\mathbf{q}_s = \begin{pmatrix} \cos \frac{\psi_s}{2} \\ \hat{\mathbf{v}}_r \sin \frac{\psi_s}{2} \end{pmatrix}}$$



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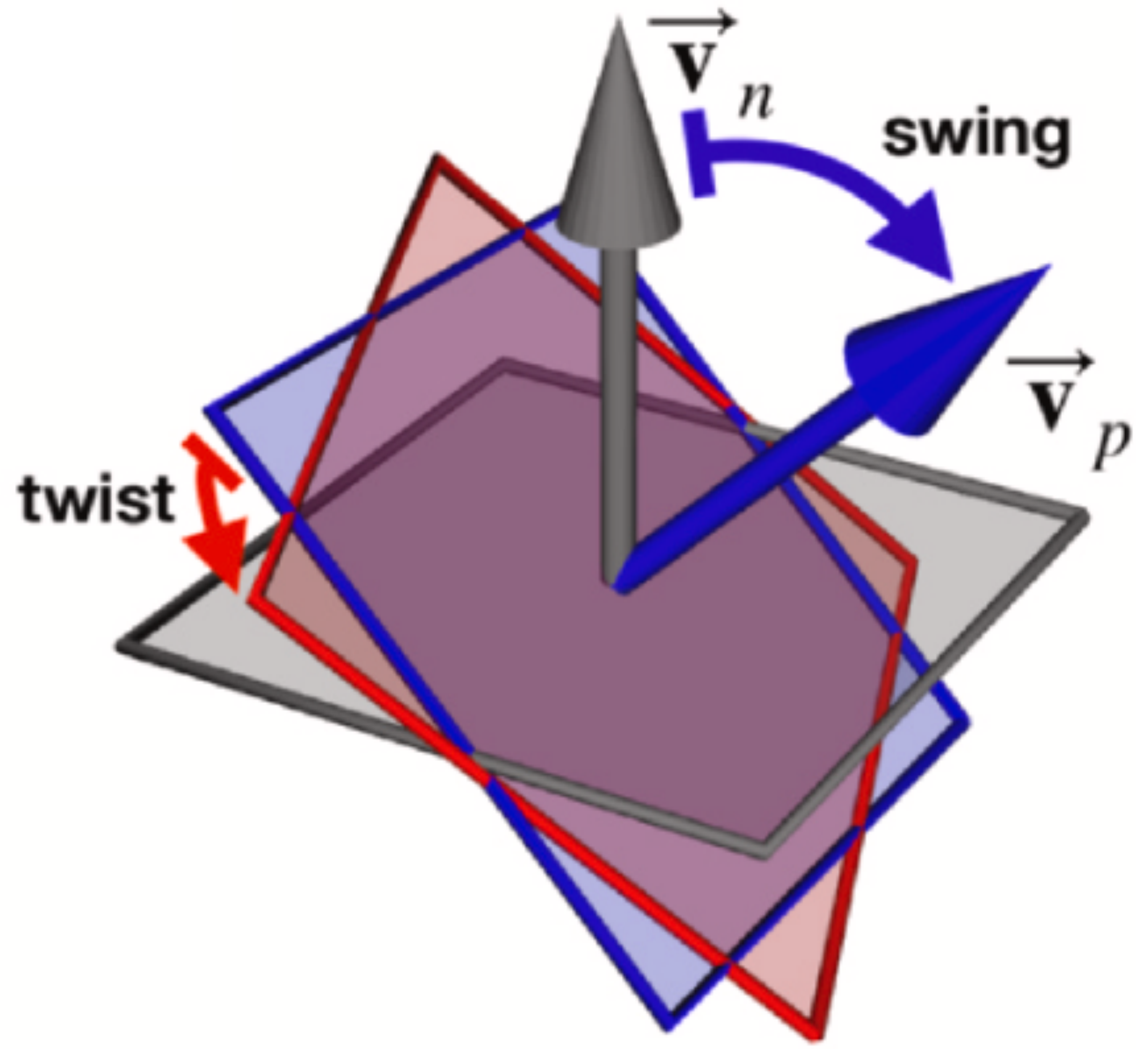
Swing-Twist Decomposition — Twist

- The image is in-plane rotated about its norm vector $\vec{\mathbf{v}}_p$ for angle ψ_t to match the projection of the object.
- The twist quaternion is:

$$\mathbf{q}_t = \begin{pmatrix} \cos\frac{\psi_t}{2} \\ \vec{\mathbf{v}}_p \sin\frac{\psi_t}{2} \end{pmatrix}$$

- From the definition of swing-twist decomposition: $\mathbf{q} = \mathbf{q}_t \otimes \mathbf{q}_s$ **Swing-before-twist form**
  - The twist quaternion can be calculated: $\mathbf{q}_t = \mathbf{q} \otimes \mathbf{q}_s^*$.
  - The twist angle ψ_t can be calculated.



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Distance and Geodesic between Rotations

- In cryoEM, it is important to examine the differences between rotation parameters. But there are no quantitative measure for such differences in cryoEM.

- This paper used the concept of distance between two rotations based on the unit quaternion system as a quantitative measure.

- The definition of the **distance** and corresponding **geodesic** based on the unit quaternion has shown its advantages as a general mathematical tool for angular analysis and rotational operations.

Distance between Rotation

- The angle between two 3D unit vectors $\vec{\mathbf{v}}_1$ and $\vec{\mathbf{v}}_2$ can be defined using the distance between them:

$$d_{S^2}(\vec{\mathbf{v}}_1, \vec{\mathbf{v}}_2) := \cos^{-1}(\vec{\mathbf{v}}_1 \cdot \vec{\mathbf{v}}_2)$$, ranges $[0, \pi]$

- Using the angle value as the distance is straightforward for orientation analysis, but the unit quaternion presents a rotation alternate to a 3D vector ➟ distance between two rotations is not explicit.

- There are several definitions of the distance between rotations in $SO(3)$, the definition of distance between two rotations in $SO(3)$, $R_{\mathbf{q}_1}$ and $R_{\mathbf{q}_2}$, in this paper is:

$$d_{SO(3)}(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}) := \max_{\vec{\mathbf{v}} \in S^2} d_{S^2}\left(R_{\mathbf{q}_1}(\vec{\mathbf{v}}), R_{\mathbf{q}_2}(\vec{\mathbf{v}})\right)$$

➟ the maximum distance between two 3D vectors, $R_{\mathbf{q}_1}$ and $R_{\mathbf{q}_2}$

- The distance can be calculated as:

$$d_{SO(3)}(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}) = 2\cos^{-1}(|\mathbf{q}_1 \cdot \mathbf{q}_2|) = 2\cos^{-1}\left(1 - \frac{|\mathbf{q}_1 \cdot \mathbf{q}_2|^2}{2}\right)$$

Distance between Rotation

- From the definition of the distance, $\cos^{-1}(|\mathbf{q}_1 \cdot \mathbf{q}_2|)$ is the shortest arc between $\mathbf{q}_1$ and $\mathbf{q}_2$ on the surface of sphere S^3.
- The absolute value in the calculation of $|\mathbf{q}_1 \cdot \mathbf{q}_2|$ indicates that $\mathbf{q}$ and $-\mathbf{q}$ represent the same rotation and will yield the same distance.
- The distance provides an estimate of the possible maximal changes of projection directions from different rotations by:

$$d_{SO(3)}\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}\right) \geq d_{S^2}\left(\overrightarrow{\mathbf{v}}_{p_{\mathbf{q}_1}}, \overrightarrow{\mathbf{v}}_{p_{\mathbf{q}_2}}\right)$$

➟ $\overrightarrow{\mathbf{v}}_{p_{\mathbf{q}_1}}$ and $\overrightarrow{\mathbf{v}}_{p_{\mathbf{q}_2}}$ are the projection directions from rotations $R_{\mathbf{q}_1}$ and $R_{\mathbf{q}_2}$, respectively.

- Measuring the distance of rotations between different rounds yields direct information on the convergence of 3D alignment.

Geodesic between Rotations

- In geometry, the geodesic is a curve or line indicating the **shortest path** between two points on a surface.
- Introduce the geodesic between two rotations, $R_{\mathbf{q}_1}$ and $R_{\mathbf{q}_2}$, can be used for the interpolation between two rotations.
- The geodesic between $R_{\mathbf{q}_1}$ and $R_{\mathbf{q}_2}$ can be described by:

$$f_l\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}, t\right), \text{ with the affine parameter } t \in [0,\ 1].$$

- The value of $f_l\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}, t\right)$ is also a unit quaternion representing the rotation ➟ this function describes the relation distance from $R_{\mathbf{q}_1}$:

$$t = \frac{d_{SO(3)}\left(R_{\mathbf{q}_1}, f_l\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}, t\right)\right)}{d_{SO(3)}\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}\right)} \Rightarrow \begin{array}{l} f_l\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2},\ 0\right) = \mathbf{q}_1 \\ f_l\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2},\ 1\right) = \mathbf{q}_2 \end{array}$$

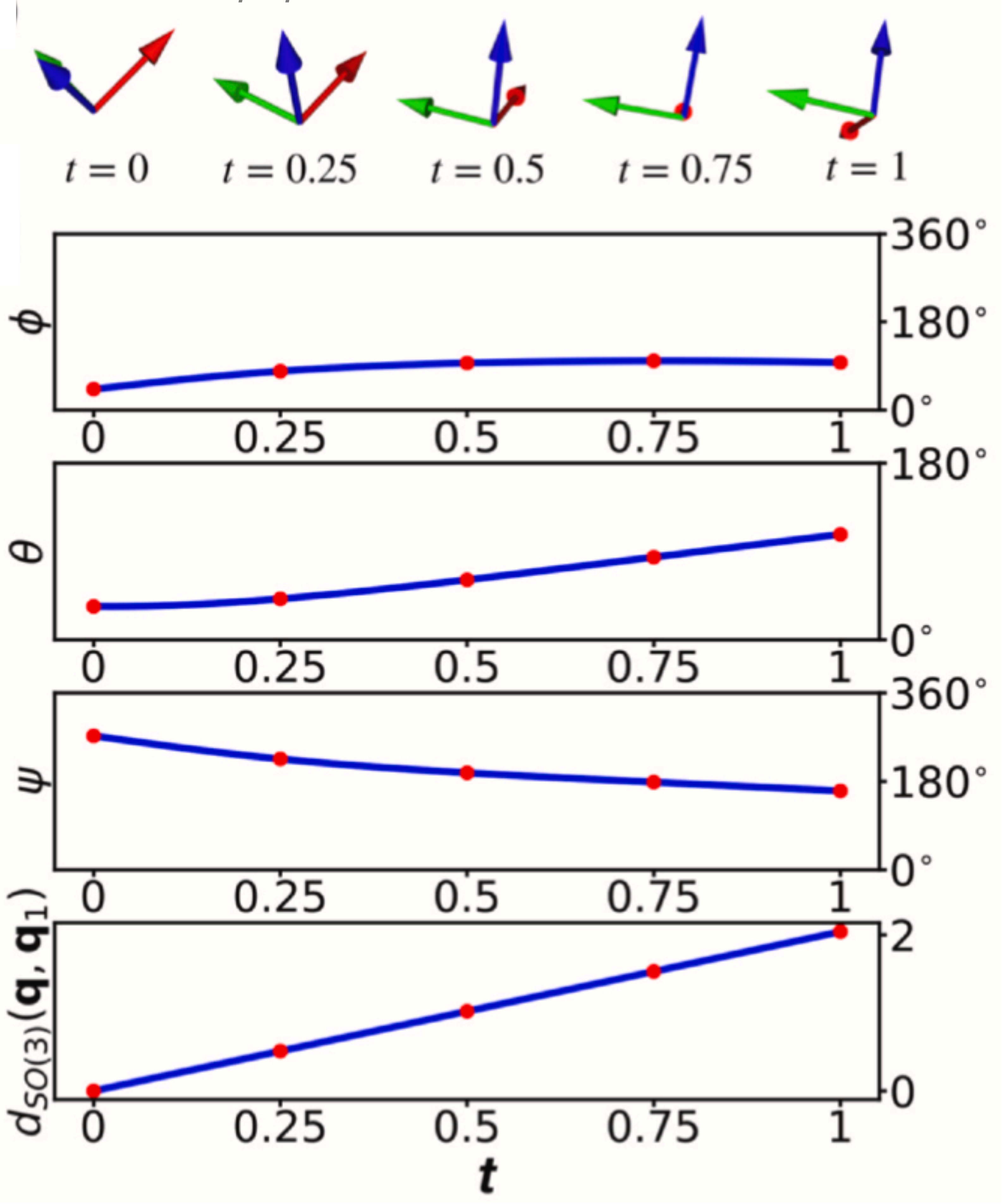
Geodesic between Rotations

- From the geometry of the geodesic, the analytical formula of the geodesic function can be derived as:

$$f_l\left(R_{\mathbf{q}_1}, R_{\mathbf{q}_2}, t\right) = \begin{cases} \frac{1}{\sin\phi}\left[\sin\left(\phi(1-t)\right)\mathbf{q}_1 + \sin\left(\phi t\right)\mathbf{q}_2\right] & \text{, if } \mathbf{q}_1 \cdot \mathbf{q}_2 \geq 0 \\ \frac{1}{\sin(\pi-\phi)}\left[\sin\left((\pi-\phi)(1-t)\right)\mathbf{q}_1 + \sin\left((\pi-\phi)t\right)\mathbf{q}_2\right] & \text{, if } \mathbf{q}_1 \cdot \mathbf{q}_2 < 0 \end{cases}$$

- The formula can be used to calculate interpolations between two rotations.
- The linear interpolation of Euler angles does not yield “linear” changes in the rotations.
- It is significantly difficult to define a geodesic in the Euler angle system.

From this paper



affine parameter

Uniform and Quasi-Uniform Sampling in SO(3)

- Uniform and quasi-uniform sampling in entire rotational space is frequently used in cryoEM alignment to search for the global optimal solutions of molecular orientations.

- The methods used in uniform and quasi-uniform sampling are in two categories:
  - Sampling points are drawn independently from a uniform distribution.
  - Based on a quasi-regular grid generated in the rotational space, sampling is performed by sampling at grid points, where the sampling point are not independent.

Sampling with Uniform Distribution

- Two methods have been predominantly used:
  - **Method 1**: By drawing three random numbers s, θ_1 and θ_2 , the uniformly unit quaternions $\mathbf{q}$ in S^3 can be performed.

$$\begin{matrix} s \sim U[0,\, 1] \\ \theta_1 \sim U[0,\, 2\pi] \\ \theta_2 \sim U[0,\, 2\pi] \end{matrix} \Rightarrow \mathbf{q} = \begin{pmatrix} \sqrt{s}\cos\theta_2 \\ \sqrt{1-s}\sin\theta_1 \\ \sqrt{1-s}\cos\theta_1 \\ \sqrt{s}\sin\theta_2 \end{pmatrix} \sim U_{S^3}$$

  - **Method 2**: Uses a 4D Gaussian distribution $N_4(\mathbf{0},\, \mathbf{I})$ with a mean of zero and covariance matrix of a 4×4 identity matrix $\mathbf{I}$ to sample a series of 4D vectors $\mathbf{v}$. By normalizing these vectors to have norm 1, the uniformly unit quaternions $\mathbf{q}$ in S^3 can be performed.

$$\mathbf{v} \sim N_4(\mathbf{0},\, \mathbf{I}) \Rightarrow \mathbf{q} = \frac{\mathbf{v}}{|\mathbf{v}|} \sim U_{S^3}$$

In both methods, the corresponding rotation $R_{\mathbf{q}}$ follows a uniform distribution in $SO(3)$.

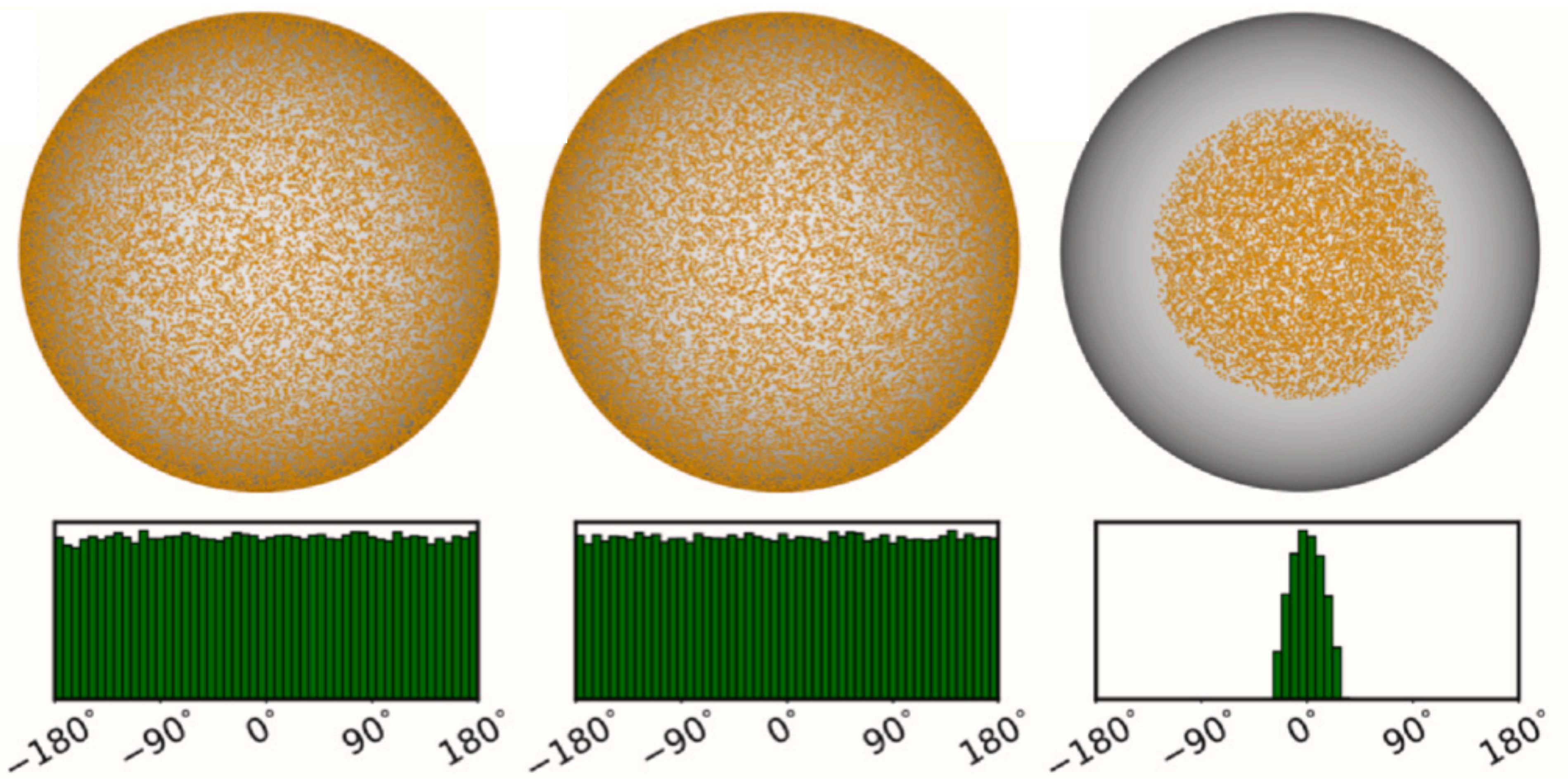
Test of Sampling with Uniform Distribution

- It's also possible to apply further selection from uniformly distributed rotations to obtain rotations in a restricted angle range $[-\phi_0, \phi_0]$.

$$\mathbf{q} = \begin{pmatrix} \cos\frac{\phi}{2} \\ \hat{\mathbf{n}}_{\mathbf{q}} \sin\frac{\phi}{2} \end{pmatrix}, \text{ with } \left|\cos\frac{\phi}{2}\right| \geq \cos\frac{\phi_0}{2}$$

  - Selecting unit quaternions in projection directions follow uniform distributions in given angle range about the projection axis.
  - In-plane rotational angles concentrate around 0°.

From this paper



Method 1

Method 2

Method 1 + with restricted angle of 60°

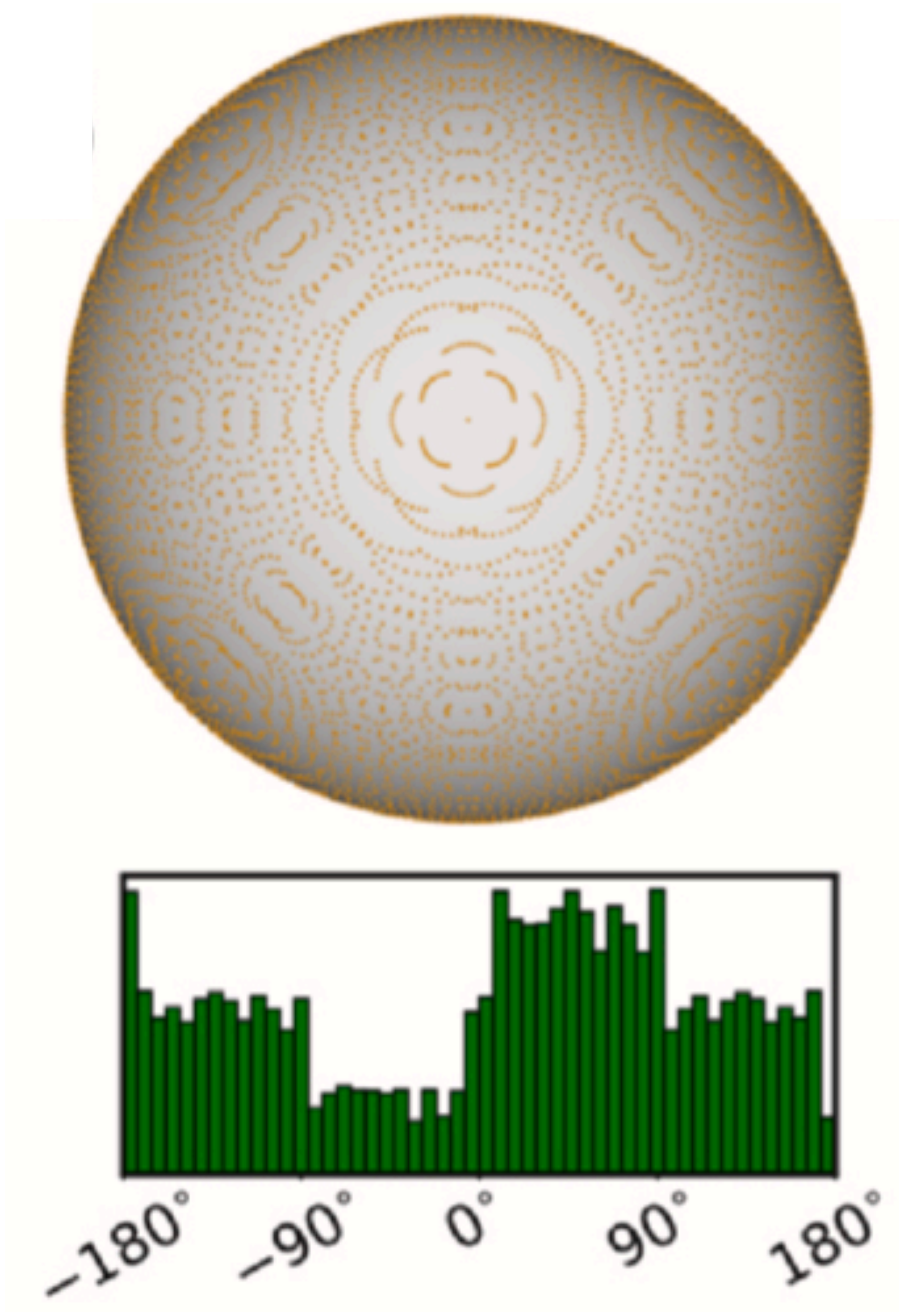
Sampling by Quasi-Regular Grid

- Two methods were used:

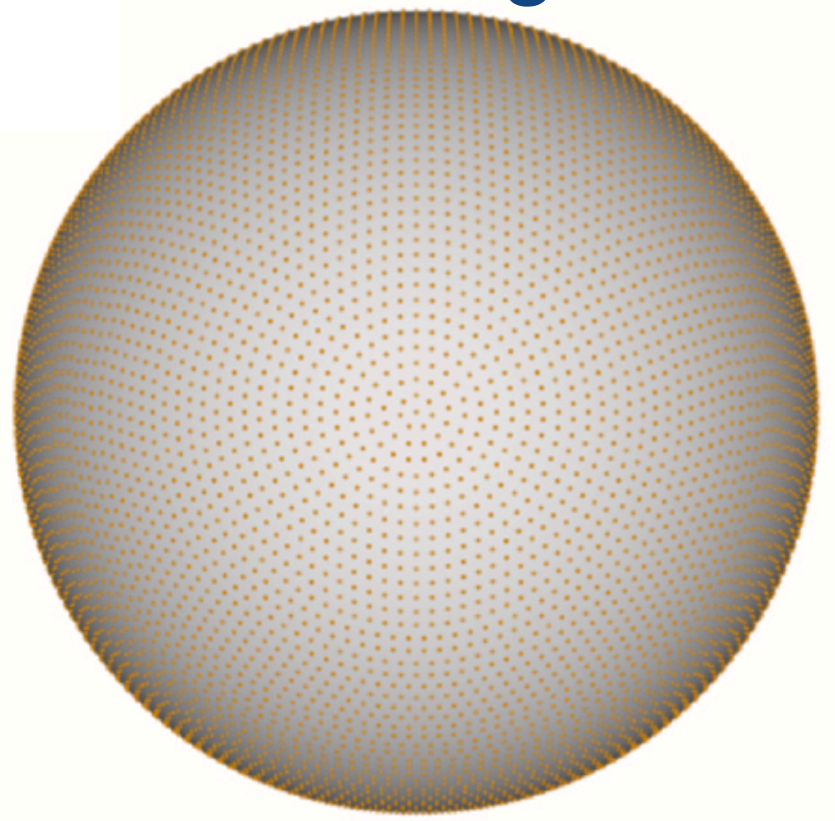
*K. M. Gorski et al., The Astrophysical Journal, 2005 ApJ **622** 759.*

  - **Method 1**: Base on 4D platonic solid. Apexes of a 4D platonic solid form a quasi-regular grid on S^3 are used to generate sampling grid.
  - **Method 2**: Use Euler angles to represent rotations (widely adopted in several cryoEM software). Involve three steps:
    - ➡ Quasi-regular grid is generated on S^2, presenting the space of projection directions, by either **scaled Euler angle method** or **HEALPix method**.
    - ➡ Sampling with equal spacing on a unit circle and representing the space of in-plane rotations is performed.
    - ➡ Cartesian products between projection samplings and in-plane rotation samplings are calculated to obtain a set of quasi-regular grid sampling on $SO(3)$.

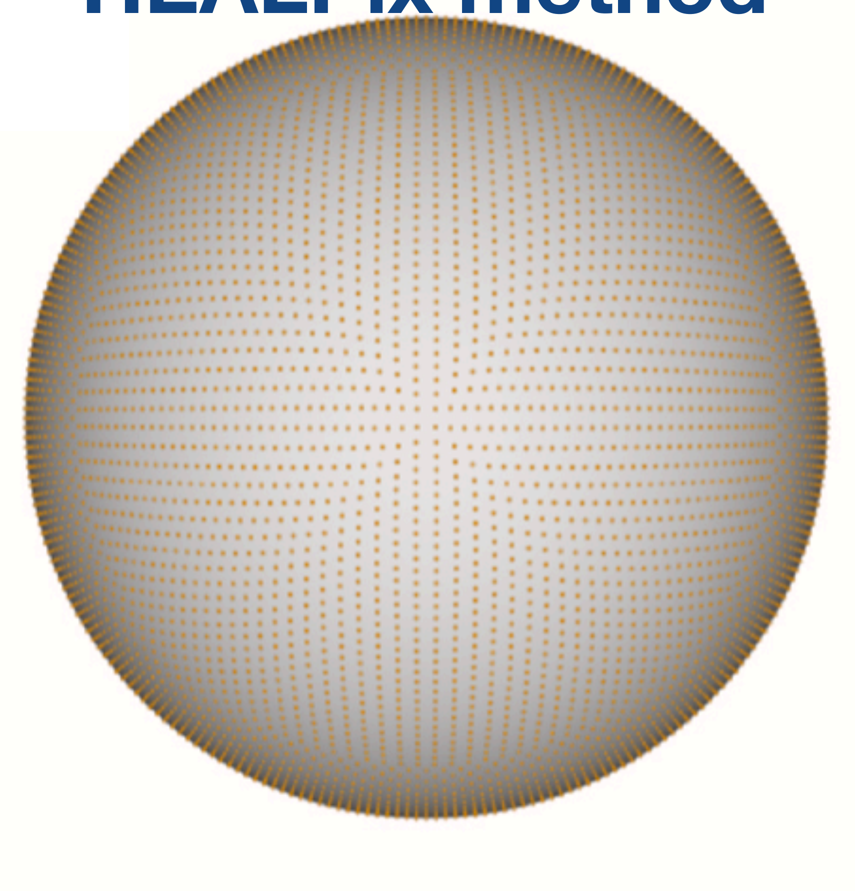
From this paper



Scaled Euler angle method



HEALPix method



In comparison, the unit quaternion based methods shows significant advantages in generating uniform samplings ➡ computationally simple + sampling points are independent of each other.

Statistics of Rotations in CryoEM

- Sampling and randomization in the rotational space is crucial for 3D reconstruction to prevent the so-called **local optimization problem**.

- Two types of requests for random sampling:
  - Generate samples in rotational space with a specific statistical distribution.
  - Estimate the statistical properties for a series of given rotation parameters. (Directional statistics)

- Statistical methods based on the unit quaternion is introduced in the following:
  - Calculate the average of rotations.
  - Angular Central Gaussian (ACG) Distribution.
  - Customized application of ACG distribution.

Average Rotations

- The geometric mean is defined as the average of a given set of rotations $\{R_{\mathbf{q}_i}\}_{1 \le i \le N}$ with corresponding weights $\{w_i\}_{1 \le i \le N}$ for each rotation:

$$arg \min_{R_{\mathbf{q}} \in SO(3)} \sum_{i=1}^{N} w_i d^2_{SO(3)}(R_{\mathbf{q}}, R_{\mathbf{q}_i})$$

- The geometric mean can be approximated by the projection arithmetic mean.
- A solution based on unit quaternion known as **the normalized principal eigenvector of the matrix**:

$$\mathbf{T} = \sum_{i=1}^{N} w_i \mathbf{q}_i \mathbf{q}_i^T$$

- Eigenvalues and eigenvectors can be determined using linear algebra techniques. Since only the principal eigenvector is required, use an iterative formula to approximate the principal eigenvector:

$$\bar{\mathbf{q}} \leftarrow \frac{\mathbf{T}\bar{\mathbf{q}}}{|\mathbf{T}\bar{\mathbf{q}}|}$$

Statistics Obtained Using ACG Distribution

- In local search of cryoEM 3D alignment:
  - Expect to perform intensive searches around a given rotation (orientation) with high probability.
  - If the distance from the given rotation increases, the probability of determining the accurate solution is decreased.
  - Sampling with a Gaussian distribution is used.

- The rotational space is not a linear space ➟ Gaussian distribution with a requirement of linear space.
- The ACG distribution provides a solution in rotational space with features similar to that of a Gaussian distribution.
- The ACG distribution is a useful tool in rota- tional space to generate or analyze samples with a maximal central distribution.

Definition of ACG Distribution

Tyler, David E., 1987. Biometrika 74 (3), 579–589.

- Similar to the uniform distribution, the generation and normalization of 4D vectors $\mathbf{v}$ from Gaussian distribution $N_4(\mathbf{0},\ \mathbf{A})$ with zero mean and covariance matrix $\mathbf{A}$ leads to unit quaternions $\mathbf{q}$, follows the ACG distribution:

$$\mathbf{x} \sim N_4(\mathbf{0},\ \mathbf{A}) \Rightarrow \boxed{\mathbf{q} = \frac{\mathbf{v}}{|\mathbf{v}|} \sim ACG(\mathbf{A})}$$

- The probability density function of the ACG distribution is:

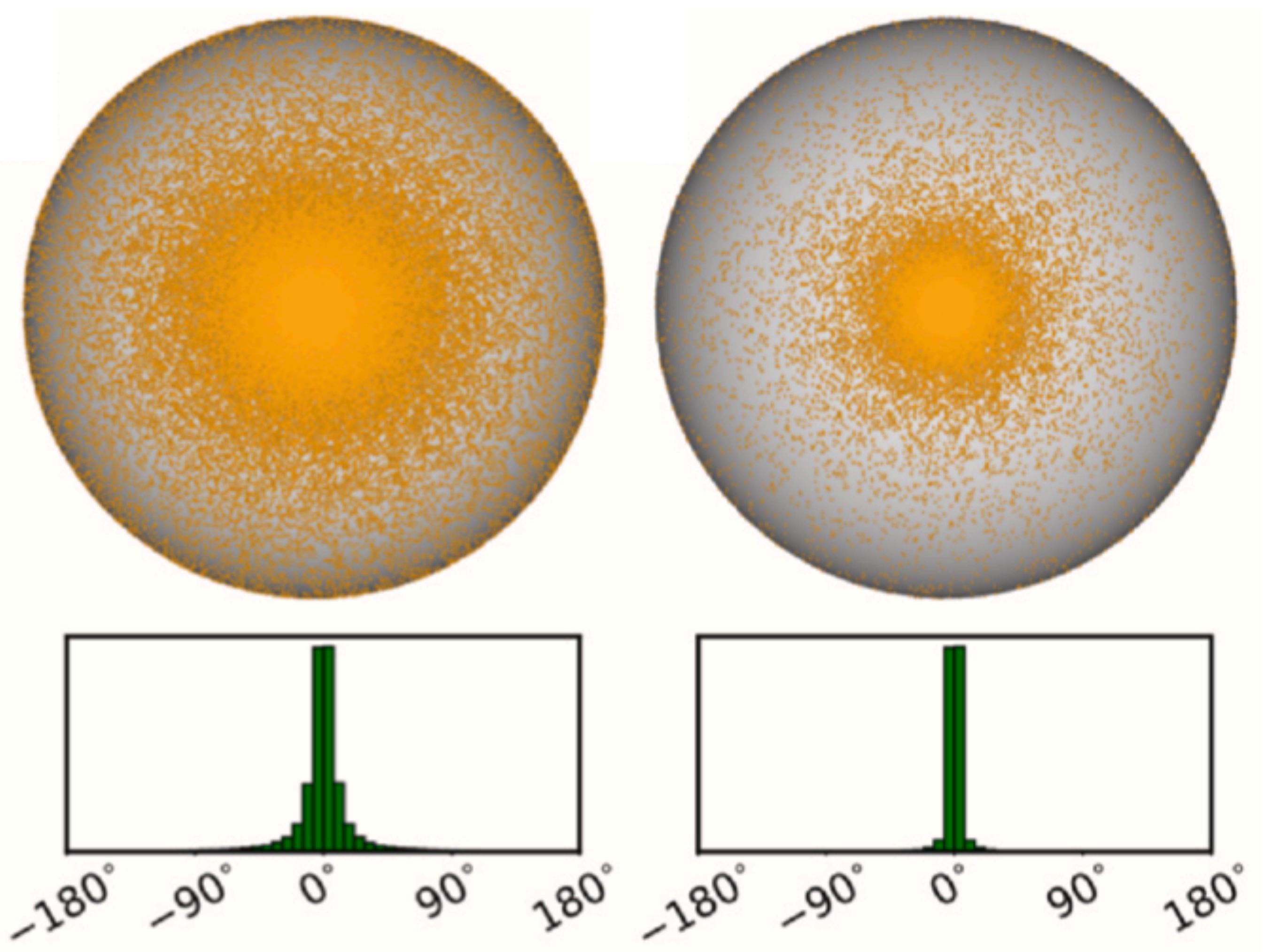
$$\boxed{p(\mathbf{q};\mathbf{A}) = |\mathbf{A}|^{-\frac{1}{2}}(\mathbf{q}^T\mathbf{A}^{-1}\mathbf{q})^{-2}}$$

  - Reach maximum if $\mathbf{q}$ equals the principal eigenvector of the covariance matrix $\mathbf{A}$.

- An iterative formula is usually used to approximate $\mathbf{A}$:

$$\boxed{\mathbf{A}^{(k+1)} = 4\left\{\sum_{i=1}^{N}\frac{1}{\mathbf{q}_i^T\mathbf{A}^{(k)^{-1}}\mathbf{q}_i}\right\}^{-1}\left\{\sum_{i=1}^{N}\frac{\mathbf{q}_i\mathbf{q}_i^T}{\mathbf{q}_i^T\mathbf{A}^{(k)^{-1}}\mathbf{q}_i}\right\}}$$

From this paper



$\mathbf{A} = \mathrm{diag}(20^2,\ 1,\ 1,\ 1)$ $\quad$ $\mathbf{A} = \mathrm{diag}(100^2,\ 1,\ 1,\ 1)$

Local Perturbation and Confidence Area

- Use a special form of covariance matrix to generate a set of rotations $\{R_{\mathbf{q}_i}\}_{1\le i\le N}$ that can be conveniently correlated with the angular accuracy of local search in cryoEM.
- A special covariance matrix is selected with $k > 1$:

$$\mathbf{A} = \begin{pmatrix} k^2 & & & \\ & 1 & & \\ & & 1 & \\ & & & 1 \end{pmatrix}$$

- The principal eigenvector of $\mathbf{A}$ is along $\mathbf{q_e} = (1, 0, 0, 0)^T$, $R_{\mathbf{q_e}}$ is a still rotate (no rotation).
- For the local search in cryoEM 3D alignment, the range of perturbations is directly correlated to the angular accuracy of orientation search.
- The probability density of the resulting unit vector $\vec{\mathbf{v}}$ from rotating an arbitrary unit vector $\vec{\mathbf{v}}_0$ by $\mathbf{q} \sim ACG(\mathbf{A})$:

$$p\left(\vec{\mathbf{v}}; \vec{\mathbf{v}}_{\mathbf{0}}, A\right) = \frac{1}{2\sqrt{2}k} \frac{\left(\frac{1}{k^2} - 1\right)z + \left(\frac{1}{k^2} + 3\right)}{\left[\left(\frac{1}{k^2} - 1\right)z + \left(\frac{1}{k^2} + 1\right)\right]^{\frac{3}{2}}}$$

, where $z = \vec{\mathbf{v}} \cdot \vec{\mathbf{v}}_0 \in [-1, 1]$

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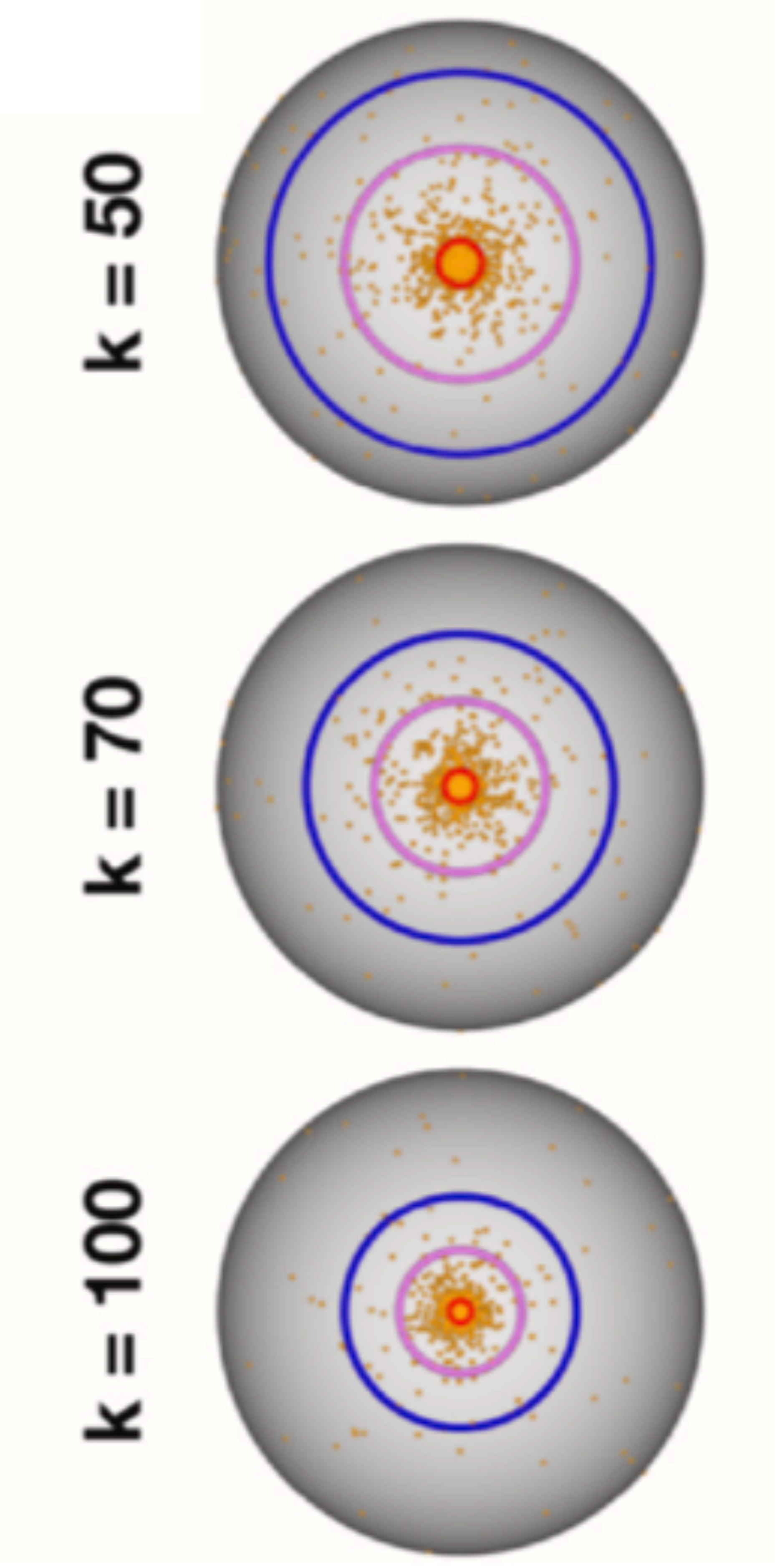


Local Perturbation and Confidence Area

- Introduce the concept of confidence area $[z_0, 1]$ under a confidence level a that satisfies:

$$\int_{\{\vec{\mathbf{v}} \mid \vec{\mathbf{v}}\cdot\vec{\mathbf{v}}_0 \in [\mathbf{z_0},\ \mathbf{1}]\}} p\left(\vec{\mathbf{v}}; \vec{\mathbf{v}}_{\mathbf{0}}, \mathbf{A}\right) \mathrm{d}\vec{\mathbf{v}} = a$$

- The confidence level can be considered as **the percentage of samples fallen in a range with angle distance up to $\cos^{-1}(z_0)$**

➡ Define $\epsilon = \cos^{-1}(z_0)$ as the angular precision of rotation sampling under a given confidence level a.

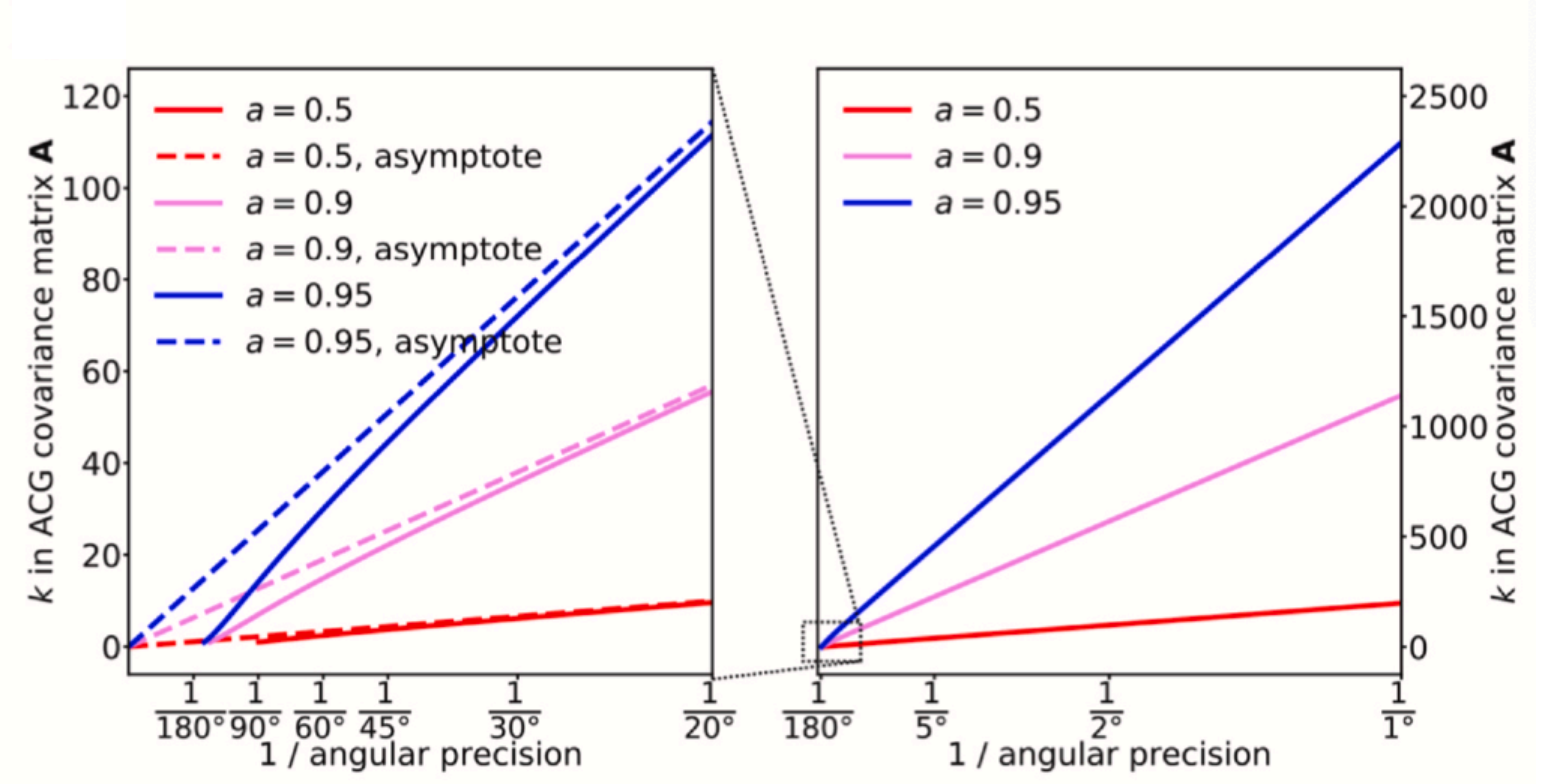
$$z_0 = \frac{(z_0')^2 - \left(\frac{1}{k^2}+1\right)}{\frac{1}{k^2}-1}, \quad z_0' = \frac{a' + \sqrt{(a')^2+8}}{2}, \quad a' = \frac{\sqrt{2}(1-k^2)(1-a)}{k}$$

➡ calculate z_0 with given k and a.

- An approximation formula to calculate angular precision ϵ from k and a:

$$\frac{1}{\epsilon} = \frac{1-a}{2\sqrt{2a-a^2}}k$$

➡ the asymptote of $\frac{1}{\epsilon}$ if $k \to \infty$.



Summary

- Unit quaternion systems have been shown as convenient and mathematically rigorous tools to manage and analyze the orientations of molecules or their projections.
- A disadvantage of the unit quaternion is its not intuitive compared to the Euler angles in representing the in-plane rotation and 3D orientation change ➟ addressed by the swing-twist decomposition.
- The rotation operations represented by unit quaternions are correlated with the 4D vector in the S^3 sphere in 4D space ➟ the properties of rotation can be directly derived/converted to the analysis of the 4D unit vectors.
- With distance and geodesic being well defined, statistics tools are established for 3D cryoEM image processing:
  - The definition of distance enables direct comparison of rotations, useful in the diagnosis of orientation stability of particles in 3D alignment.
  - The definition of geodesic enables interpolation and analysis for continuous changes of rotations that can be used in the analysis of flexible samples.
- Uniform and ACG distribution were developed from the 4D Gaussian distribution of 4D vectors ➟ powerful tools of sampling/inference of global/local optimization of molecule orientations.

Back Up

Converting Euler Angles to Unit Quaternion

- The rotation by Euler angles ϕ, θ, and ψ in ZYZ convention presented by corresponding unit quaternion is:

$$\mathbf{q}_{\phi\theta\psi} = \mathbf{q}_{\psi} \otimes \mathbf{q}_{\theta} \otimes \mathbf{q}_{\phi} \quad ; \quad \mathbf{q}_{\phi} = \begin{pmatrix} \cos\frac{\phi}{2} \\ 0 \\ 0 \\ \sin\frac{\phi}{2} \end{pmatrix} , \quad \mathbf{q}_{\theta} = \begin{pmatrix} \cos\frac{\theta}{2} \\ 0 \\ \sin\frac{\theta}{2} \\ 0 \end{pmatrix} , \quad \mathbf{q}_{\psi} = \begin{pmatrix} \cos\frac{\psi}{2} \\ 0 \\ 0 \\ \sin\frac{\psi}{2} \end{pmatrix}$$

Proof of Well-definiteness of Distance between Two Rotations

- 1. Symmetry property
- 2. Positive definiteness property
- 3. Triangle inequality property

Inference based on ACG Distribution

- An iterative method to determine the maximum-likelihood approximation of k from $\{\bar{\mathbf{q}}^{-1} \otimes \mathbf{q}_i\}_{1 \le i \le N}$:

$$k^2 = \frac{4}{N} \sum_{i=1}^{N} \frac{q_{0i}^2}{k^{-2} q_{0i}^2 + \vec{\mathbf{n}}_{\mathbf{q}_i} \cdot \vec{\mathbf{n}}_{\mathbf{q}_i}}, \quad \text{where } \begin{pmatrix} q_{0i} \\ \vec{\mathbf{n}}_{\mathbf{q}_i} \end{pmatrix} = \bar{\mathbf{q}}^{-1} \otimes \mathbf{q}_i$$

- A method to estimate the angular precision of the parameter search from a series of samples generated by the particle-filter algorithm in THUNDER.
- Performed the ab initio 3D reconstruction of a dataset of the proteasome (EMPIAR-10025) using 112,412 particles.

From this paper