Supplementary Information for

Autocorrelation analysis for cryo-EM with sparsity constraints: Improved sample complexity and projection-based algorithms

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Supplementary text
Legend for Movie S1
SI References

Other supplementary materials for this manuscript include the following:

Movie S1

Supporting Information Text

1. Proofs of auxiliary results for Theorems 1 and 2

A. Proof of Lemma 8. Note that S_{ij} is connected and compact, since $S_{ij} = \theta_{ij}(\mathrm{SO}(3))$ and $\mathrm{SO}(3)$ is compact and connected, while θ_{ij} is continuous. It also is semialgebraic, as $\mathrm{SO}(3)$ is a real algebraic variety and θ_{ij} is a polynomial map (see the Tarski-Seidenberg theorem (1)).

Define $T_{ij} \subseteq \mathbb{R}^2 \times \mathbb{R}^2$ as the set cut out by the three constraints in Eq. (14). Assume $((x_1, y_1), (x_2, y_2)) \in S_{ij}$. By definition of S_{ij}, there exist $R \in \mathrm{SO}(3)$ and $z_1, z_2 \in \mathbb{R}$ such that $R\mathbf{a}_i = (x_1, y_1, z_1)^\top$ and $R\mathbf{a}_j = (x_2, y_2, z_2)^\top$. Then

$$\|\mathbf{a}_i\|^2 - x_1^2 - y_1^2 = \|R\mathbf{a}_i\|^2 - x_1^2 - y_1^2 = z_1^2,$$

likewise $\|\mathbf{a}_j\|^2 - x_2^2 - y_2^2 = z_2^2$, and

$$\begin{aligned} (\langle \mathbf{a}_i, \mathbf{a}_j \rangle - x_1x_2 - y_1y_2)^2 &= (\langle R\mathbf{a}_i, R\mathbf{a}_j \rangle - x_1x_2 - y_1y_2)^2 \\ &= (z_1z_2)^2. \end{aligned}$$

Also, $x_1^2 + y_1^2 \leq \|R\mathbf{a}_i\|^2 = \|\mathbf{a}_i\|^2$, and similarly $x_2^2 + y_2^2 \leq \|\mathbf{a}_j^2\|^2$. These show that $((x_1, y_1), (x_2, y_2)) \in T_{ij}$, whence $S_{ij} \subseteq T_{ij}$.

For the converse, take $((x_1, y_1), (x_2, y_2)) \in T_{ij}$. Let

$$z_1 = \sqrt{\|\mathbf{a}_i\|^2 - x_1^2 - y_1^2} \quad \text{and} \quad z_2 = \varepsilon\sqrt{\|\mathbf{a}_j\|^2 - x_2^2 - y_2^2},$$

where $\varepsilon = \mathrm{sign}\left(\langle \mathbf{a}_i, \mathbf{a}_j \rangle - x_1x_2 - y_1y_2\right)$. Put $\mathbf{b}_i = (x_1, y_1, z_1)^\top$ and $\mathbf{b}_j = (x_2, y_2, z_2)^\top$ in $\mathbb{R}^3$. By the choice of z_1 and z_2,

$$\|\mathbf{b}_i\| = \|\mathbf{a}_i\| \quad \text{and} \quad \|\mathbf{b}_j\| = \|\mathbf{a}_j\|. \qquad [1]$$

Also, from the equality constraint in Eq. (14), it holds $z_1^2z_2^2 = (\langle \mathbf{a}_i, \mathbf{a}_j \rangle - x_1x_2 - y_1y_2)^2$. This with the choice of ε implies

$$\langle \mathbf{b}_i, \mathbf{b}_j \rangle = \langle \mathbf{a}_i, \mathbf{a}_j \rangle. \qquad [2]$$

From Eq. (1) and (2), there exists $R \in \mathrm{SO}(3)$ such $\mathbf{b}_i = R\mathbf{a}_i$ and $\mathbf{b}_j = R\mathbf{a}_j$. Hence $((x_1, y_1), (x_2, y_2)) \in S_{ij}$, whence $T_{ij} \subseteq S_{ij}$. We conclude $T_{ij} = S_{ij}$.

The dimension of S_{ij} as a semialgebraic set is the maximal dimension of a cell in any cylindrical algebraic decomposition of it (1, Cor. 2.8.9). This agrees with the maximal rank attained by the differential of θ_{ij}:

$$\dim(S_{ij}) = \max_R \mathrm{rank}(D\theta_{ij} : T_R(\mathrm{SO}(3)) \to T_{\theta_{ij}(R)}(\mathbb{R}^2 \times \mathbb{R}^2)),$$

where T denotes tangent space. We recall that the tangent space to rotation matrices is parameterized by skew-symmetric matrices. Specifically, $T_R(\mathrm{SO}(3)) = \{[s]_\times R : s \in \mathbb{R}^3\}$, where

$$[s]_\times := \begin{pmatrix} 0 & s_3 & -s_2 \\ -s_3 & 0 & s_1 \\ s_2 & -s_1 & 0 \end{pmatrix}.$$

Then, $D\theta_{ij}([s]_\times R) = (\pi[s]_\times R\mathbf{a}_i, \pi[s]_\times R\mathbf{a}_j) \in \mathbb{R}^2 \times \mathbb{R}^2 = T_{\theta_{ij}(R)}(\mathbb{R}^2 \times \mathbb{R}^2)$. Putting $(x_1, y_1, z_1)^\top := R\mathbf{a}_i$ and $(x_2, y_2, z_2)^\top := R\mathbf{a}_j$, we rewrite

$$D\theta_{ij}([s]_\times R) = W(R)s, \qquad \text{where } W(R) := \begin{pmatrix} 0 & -z_1 & y_1 \\ z_1 & 0 & -x_1 \\ 0 & -z_2 & y_2 \\ z_2 & 0 & -x_2 \end{pmatrix}.$$

Thus, $\dim(S_{ij}) = 3$, unless $W(R)$ is rank-deficient for all $R \in \mathrm{SO}(3)$. We claim it is rank-deficient for specific R if and only if (x_1, y_1, z_1) and (x_2, y_2, z_2) are linearly dependent or $z_1 = z_2 = 0$. This is proven using a computer algebra system, e.g. (2). Indeed, if I is ideal in the ring $\mathbb{Q}[x_1, y_1, z_1, x_2, y_2, z_2]$ generated by the 3×3 minors of $W(R)$, the claim follows from calculating the primary decomposition (3):

$$I = \langle z_1y_2 - y_1z_2, z_1x_2 - x_1z_2, y_1x_2 - x_1y_2 \rangle \cap \langle z_2^2, z_1z_2, z_1^2 \rangle.$$

Given the claim, $\mathrm{rank}(W(R)) < 3$ for all $R \in \mathrm{SO}(3)$ if and only if $\mathbf{a}_i$ and $\mathbf{a}_j$ are linearly dependent. In other words, S_{ij} has dimension 3 if and only if $\mathbf{a}_i$ and $\mathbf{a}_j$ are linearly independent. The proof of Lemma 8 is complete. □

B. Proof of Lemma 9. As mentioned in the main text, this is immediate from Definitions 6 and 7 and Eq. (10). □

C. Proof of Lemma 10. If X is a subset of a real Euclidean space $\mathbb{R}^k$, we write $\overline{X}$ for the Zariski closure in $\mathbb{R}^k$, and $\mathcal{I}(\overline{X})$ for the real radical ideal of $\overline{X}$.

First, note that $\overline{S_{ij}}$ is irreducible. This is because $S_{ij} = \theta_{ij}(\mathrm{SO}(3))$, θ_{ij} is polynomial and SO(3) is an irreducible algebraic variety. So, $\mathcal{I}(\overline{S_{ij}})$ is prime (1, Thm. 2.8.3(ii)). Also, $\overline{S_{ij}}$ has dimension 3 as an algebraic variety. This is by (1, Prop. 2.8.2), and Lemma 8 which states S_{ij} has dimension 3 as a semialgebraic set. So, $\mathcal{I}(\overline{S_{ij}})$ has height 1 (1, Def. 2.8.1). Here, every prime ideal with height 1 is principal, as $\mathbb{R}[x_1, y_1, x_2, y_2]$ is a unique factorization domain. It follows that

$$\mathcal{I}(\overline{S_{ij}}) = \langle f \rangle, \tag{3}$$

for some irreducible polynomial $f \in \mathbb{R}[x_1, y_1, x_2, y_2]$, where angle brackets indicate ideal generation.

By Lemma 8, we know $S_{ij} \subseteq \mathcal{Z}(q_{ij})$, where $\mathcal{Z}$ denotes the zero set in $\mathbb{R}^2 \times \mathbb{R}^2$. Taking closures, $\overline{S_{ij}} \subseteq \mathcal{Z}(q_{ij})$. Equivalently, $q_{ij} \in \mathcal{I}(\overline{S_{ij}})$. By Eq. (3), this means f evenly divides q_{ij}, say,

$$q_{ij} = fg, \tag{4}$$

for some $g \in \mathbb{R}[x_1, y_1, x_2, y_2]$. To conclude the proof, it suffices to prove that g is a nonzero scalar. Then $\langle q_{ij} \rangle = \langle f \rangle = \mathcal{I}(\overline{S_{ij}})$, and q_{ij} is irreducible because f is.

For a contradiction, assume that f has positive degree. Then, Eq. (4) implies

$$(q_{ij})_{\mathrm{top}} = f_{\mathrm{top}} g_{\mathrm{top}}, \tag{5}$$

where the subscript indicates the top total degree part of the polynomial. Here,

$$\begin{aligned} q_{ij} = & \left(\|\mathbf{a}_i\|^2 \|\mathbf{a}_j\|^2 - \langle \mathbf{a}_i, \mathbf{a}_j \rangle^2\right) - \|\mathbf{a}_j\|^2 x_1^2 - \|\mathbf{a}_j\|^2 y_1^2 - \|\mathbf{a}_i\|^2 x_2^2 - \|\mathbf{a}_i\|^2 y_2^2 \\ & + 2\langle \mathbf{a}_i, \mathbf{a}_j \rangle x_1 x_2 + 2\langle \mathbf{a}_i, \mathbf{a}_j \rangle y_1 y_2 + x_1^2 y_2^2 + y_1^2 x_2^2 - 2x_1 y_1 x_2 y_2. \end{aligned} \tag{6}$$

Thus,

$$(q_{ij})_{\mathrm{top}} = x_1^2 y_2^2 + y_1^2 x_2^2 - 2x_1 y_1 x_2 y_2 = (x_1 y_2 - y_1 x_2)^2.$$

From Eq. (5), the assumption that f has positive degree and unique factorization, we deduce that (possibly after multiplying by nonzero scalars)

$$f_{\mathrm{top}} = g_{\mathrm{top}} = x_1 y_2 - y_1 x_2.$$

Therefore,

$$\begin{aligned} f &= x_1 y_2 - x_2 y_1 + \alpha x_1 + \beta y_1 + \gamma x_2 + \delta y_2 + \varepsilon, \\ g &= x_1 y_2 - x_2 y_1 + \zeta x_1 + \eta y_1 + \theta x_2 + \iota y_2 + \kappa, \end{aligned} \tag{7}$$

for some $\alpha, \beta, \gamma, \delta, \varepsilon, \zeta, \eta, \theta, \iota, \kappa \in \mathbb{R}$. Now we insert Eq. (7) and Eq. (6) into Eq. (4). Equating the constants and the coefficients of $x_1^2, y_1^2, x_2^2, y_2^2$ gives

$$\begin{cases} \|\mathbf{a}_i\|^2 \|\mathbf{a}_j\|^2 - \langle \mathbf{a}_i, \mathbf{a}_j \rangle^2 = \varepsilon\kappa \\ -\|\mathbf{a}_j\|^2 = \alpha\zeta \\ -\|\mathbf{a}_j\|^2 = \beta\eta \\ -\|\mathbf{a}_i\|^2 = \gamma\theta \\ -\|\mathbf{a}_i\|^2 = \delta\iota. \end{cases} \tag{8}$$

All the left-hand sides in Eq. (8) are nonzero because $\mathbf{a}_i$ and $\mathbf{a}_j$ are linearly independent. Therefore, $\alpha, \ldots, \kappa$ are all nonzero. Next, we equate the coefficients of x_1, y_1, x_2, y_2 in Eq. (4). The result is that

$$\begin{pmatrix} \alpha & \zeta \\ \beta & \eta \\ \gamma & \theta \\ \delta & \iota \end{pmatrix} \begin{pmatrix} \kappa \\ \varepsilon \end{pmatrix} = 0,$$

whence the 4×2 matrix has rank 1. So all its 2×2 minors vanish, in particular

$$\alpha\eta - \beta\zeta = 0. \tag{9}$$

Finally, we equate the coefficients of $x_1 y_1$ in Eq. (4):

$$0 = \alpha\eta + \beta\zeta. \tag{10}$$

Eq. (9) and (10) imply

$$\alpha\eta = \beta\zeta = 0. \tag{11}$$

But this contradicts the earlier finding that $\alpha, \ldots, \kappa$ are all nonzero. So the assumption that f has positive degree is false, and f is a nonzero scalar. This proves Lemma 10. ☐

D. Proof of Corollary 11. By Lemma 9, the support of M_2 is $\cup_{i,j=1}^{p} S_{ij}$. This has Zariski closure $\cup_{i,j=1}^{p} \overline{S_{ij}}$. We claim its irredundant irreducible decomposition is

$$\{(\mathbf{x}_1, \mathbf{x}_2) : \mathbf{x}_1 = \mathbf{x}_2\} \ \cup \ \bigcup_{i \neq j} \overline{S_{ij}}. \qquad [12]$$

The claim follows from several facts. First, for all $i \neq j$, $\overline{S_{ij}}$ is irreducible. It has dimension 3 and defining equation q_{ij} (6), by **A1** and Lemma 10. When $i \neq j$, $i' \neq j'$ and $(i,j) \neq (i',j')$, then q_{ij} and $q_{i'j'}$ are not scalar multiples of each other by **A2** (cf. their coefficients on $x_1^2, x_2^2, x_1^2 y_1^2$). Hence $\overline{S_{ij}} \neq \overline{S_{i'j'}}$. Next, $\overline{S_{ii}} = \{(\mathbf{x}_1, \mathbf{x}_2) : \mathbf{x}_1 = \mathbf{x}_2\}$ (all i). Further, $\{(\mathbf{x}_1, \mathbf{x}_2) : \mathbf{x}_1 = \mathbf{x}_2\} \not\subseteq \overline{S_{ij}}$ (all $i \neq j$), because when we substitute $x_1 = x_2$ and $y_1 = y_2$ into Eq. (6) we get a nonzero result as the constant term does not vanish. All together, (12) is the claimed irredundant irreducible decomposition as wanted. □

E. Proof of Lemma 13. This follows from $\mathcal{I}(\overline{S_{ij}}) = \langle q_{ij} \rangle$ (Lemma 10), the expression (6) for q_{ij}, and the proof of (4, Thm. 3). □

F. Proof of Lemma 14. From Eq. (15), we have

$$M_2(S_{ij}) = \sum_{i',j'=1}^{p} w_{i'} w_{j'} \mu(\theta_{i'j'}^{-1}(S_{ij})).$$

Here $\mu(\theta_{ij}^{-1}(S_{ij})) = \mu(\mathrm{SO}(3)) = 1$ by definition of S_{ij}. On the other hand, for all $i', j' = 1, \ldots, p$ with $(i',j') \neq (i,j)$, $S_{ij} \cap S_{i'j'}$ is a semialgebraic set with positive codimension in $S_{i'j'}$ by the fact that (12) is an irredundant irreducible decomposition. Then $\theta_{i'j'}^{-1}(S_{ij}) = \theta_{i'j'}^{-1}(S_{ij} \cap S_{i'j'})$ is a semialgebraic set with positive codimension in SO(3). Since μ is absolutely continuous, it implies $\mu(\theta_{i'j'}^{-1}(S_{ij})) = 0$. Eq. (25) follows. □

2. Proof of Theorem 3

We show how to reduce the proof to an application of Theorem 1. We have

$$R \cdot \Phi(\mathbf{x}) = \sum_{i=1}^{p} w_i e^{-\frac{\|R\mathbf{x} - \mathbf{a}_i\|^2}{2\kappa^2}} = \sum_{i=1}^{p} w_i e^{-\frac{\|\mathbf{x} - R^T \mathbf{a}_i\|^2}{2\kappa^2}}. \qquad [13]$$

Writing $\mathbf{x} = (x, y, z)$ gives the following expression for the projection images

$$I_R(x,y) = \sum_{i=1}^{p} w_i e^{-\frac{\|(x,y) - \pi R^T \mathbf{a}_i\|^2}{2\kappa^2}} \int_{-\infty}^{\infty} e^{-\frac{(z - \pi_z R^T \mathbf{a}_i)}{2\kappa^2}} dz = \sum_{i=1}^{p} \sqrt{2\pi}\kappa w_i e^{-\frac{\|(x,y) - \pi R^T \mathbf{a}_i\|^2}{2\kappa^2}}, \qquad [14]$$

where $\pi_z(a_1, a_2, a_3) := a_3$ is the projection operator onto the last coordinate. The second moment M_2^G can then be written as

$$\begin{aligned} M_2^G((x_1,y_1),(x_2,y_2)) &= \sum_{i,j=1}^{p} 2\pi\kappa^2 w_i w_j \int_{\mathrm{SO}(3)} e^{-\frac{\|(x_1,y_1) - \pi R^T \mathbf{a}_i\|^2 + \|(x_2,y_2) - \pi R^T \mathbf{a}_j\|^2}{2\kappa^2}} d\mu(R) \\ &= \sum_{i,j=1}^{p} 2\pi\kappa^2 w_i w_j \int_{\mathrm{SO}(3)} e^{-\frac{\|(x_1,y_1) - \pi R \mathbf{a}_i\|^2 + \|(x_2,y_2) - \pi R \mathbf{a}_j\|^2}{2\kappa^2}} d\mu(R) = 2\pi\kappa^2 M_2 * (k \otimes k), \end{aligned} \qquad [15]$$

where the second equality used the fact that the Haar measure on SO(3) is invariant to transpositions (5, Theorem 4.36), and M_2 is the second moment in the model of Theorem 1. Since k has non-vanishing Fourier-transform, this equation can be deconvolved to obtain M_2. By Theorem 1, M_2 determines the weights and atomic positions $(w_i, \mathbf{a}_i)$ up to a joint rotation and reflection, which concludes the proof. □

3. Sample complexity: Proofs of Theorems 4 and Corollary 5

A. Proof of Theorem 4. The proof is divided into several steps.

Step 0: We state a general fact about real analytic functions that we will use: *Let $H(\mathbf{y}, \mathbf{z}) : \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}$ be real analytic jointly in $(\mathbf{y}, \mathbf{z})$. Let ν be a compactly supported and absolutely continuous measure on $\mathbb{R}^n$. Then $\int H(\mathbf{y}, \mathbf{z}) d\nu(\mathbf{z})$ is real-analytic in $\mathbf{y}$.* This can be justified by appropriately differentiating under the integral sign, see (6).

Step 1: We introduce notation.

First, define

$$X = (B(0,r) \times [w_-, w_+])^{\times p} \subseteq \mathbb{R}^{4p}, \qquad [16]$$

where $B(0,r)$ is the ℓ^2-ball of radius r in $\mathbb{R}^3$ centered at 0. X is the space of possible molecules.

Next, slightly modifying the notation in the main text, write

$$M_2^{[m]} : X \to \mathbb{R}^{2^m \times 2^m} \otimes \mathbb{R}^{2^m \times 2^m}$$

for the map associating a molecule to its pixelated second moment (Eq. (13)) when $2^m \times 2^m$ pixels are used. Explicitly,

$$M_2^{[m]}(\{(\mathbf{a}_i, w_i)\}) =$$
$$\left\{ \int_{j_4\tau}^{(j_4+1)\tau} \int_{j_3\tau}^{(j_3+1)\tau} \int_{j_2\tau}^{(j_2+1)\tau} \int_{j_1\tau}^{(j_1+1)\tau} \int_{\mathrm{SO}(3)} \sum_{i,j=1}^{p} w_i w_j \delta_{\pi R \mathbf{a}_i}(x_1, y_1) \delta_{\pi R \mathbf{a}_j}(x_2, y_2) * (k(x_1, y_1) k(x_2, y_2)) d\mu(R) dx_1 dy_1 dx_2 dy_2 \right\}$$

for $j_1, j_2, j_3, j_4 \in \{-2^{m-1}, \ldots, 2^{m-1} - 1\}$. Then, $M_2^{[m]}$ is a real analytic function by Step 0. Indeed, the Gaussian kernel $k(x, y)$ is real analytic, so the above integrand is real analytic in all variables. (Also, integration over SO(3) is replaced by integration against a compactly supported absolutely continuous measure on $\mathbb{R}^3$ if we parameterize SO(3) with Euler angles.)

Thirdly, we put

$$L^{[m]} : \mathbb{R}^{2^{m+1} \times 2^{m+1}} \otimes \mathbb{R}^{2^{m+1} \times 2^{m+1}} \to \mathbb{R}^{2^m \times 2^m} \otimes \mathbb{R}^{2^m \times 2^m}$$

for the obvious linear map which lowers the resolution of the second moment by a factor of two, i.e. $L^{[m]}(t) = s$ where

$$s_{j_1, j_2, j_3, j_4} = \sum_{\gamma_4 \in \{0,1\}} \sum_{\gamma_3 \in \{0,1\}} \sum_{\gamma_2 \in \{0,1\}} \sum_{\gamma_1 \in \{0,1\}} t_{2j_1 + \gamma_1, 2j_2 + \gamma_2, 2j_3 + \gamma_3, 2j_4 + \gamma_4}$$

for $j_1, j_2, j_3, j_4 \in \{-2^{m-1}, \ldots, 2^{m-1} - 1\}$. For all m, it holds

$$M_2^{[m]} = L^{[m]} \circ M_2^{[m+1]}. \qquad [17]$$

Step 2: We prove that a certain stabilization occurs as $m \to \infty$.

Consider $X^{\times 2} = (B(0, r) \times [w_-, w_+])^{\times p} \times (B(0, r) \times [w_-, w_+])^{\times p} \subseteq \mathbb{R}^{8p}$, where the variables on $\mathbb{R}^{8p}$ are $\{(\mathbf{a}_i, w_i)\}, \{(\mathbf{b}_i, v_i)\}$. Regard $X^{\times 2}$ as a semianalytic set (i.e., a subset of Euclidean space locally defined by real analytic equations and inequalities). Let $\mathcal{O}(X^{\times 2})$ denote the ring of real analytic functions on X. Then $\mathcal{O}(X^{\times 2})$ is a Noetherian ring, because X is compact (7, Théorème I, 9). (Note that $X^{\times 2}$ automatically satisfies the Stein hypothesis in *loc. cit.* since we are in the real case, see (8).).

We define

$$\mathcal{I}^{[m]} = \text{ ideal in } \mathcal{O}(X^{\times 2}) \text{ generated by the } 2^{4m} \text{ coordinate functions of } M_2^{[m]}(\{(\mathbf{a}_i, w_i)\}) - M_2^{[m]}(\{(\mathbf{b}_i, v_i)\}).$$

For all m, we have

$$\mathcal{I}^{[m+1]} \supseteq \mathcal{I}^{[m]}$$

by Eq. (17). From Noetherianity, there exists $m' = m'(p, r, w_+, w_-)$ such that

$$\mathcal{I}^{[m]} = \mathcal{I}^{[m']} \qquad \forall m \geq m'.$$

Thus the corresponding zero sets in $X^{\times 2}$ stabilize too:

$$\left\{ \big(\{(\mathbf{a}_i, w_i)\}, \{(\mathbf{b}_i, v_i)\} \big) : M_2^{[m]}(\{(\mathbf{a}_i, w_i)\}) = M_2^{[m]}(\{(\mathbf{b}_i, v_i)\}) \right\} \subseteq X^{\times 2} \text{ is constant in } m \text{ if } m \geq m'.$$

Equivalently, for all $\{(\mathbf{a}_i, w_i)\} \in X$ we have:

$$\text{the fiber } (M_2^{[m]})^{-1}\big(M_2^{[m]}(\{\mathbf{a}_i, w_i\})\big) \subseteq X \text{ is constant in } m \text{ if } m \geq m'. \qquad [18]$$

Step 3: We deduce an equality in which there is no pixelation.

Specifically, fix $\{(\mathbf{a}_i, w_i)\}, \{(\mathbf{b}_i, v_i)\} \in X$ such that $\{(\mathbf{a}_i, w_i)\}$ satisfies **A1-A2** in the main text and

$$M_2^{[m']}(\{(\mathbf{a}_i, w_i)\}) = M_2^{[m']}(\{(\mathbf{b}_i, v_i)\}) \qquad [19]$$

holds. We claim there is an equality between unpixelated (but still blurred) second moments:

$$M_2(\{(\mathbf{a}_i, w_i)\}) * (k \otimes k) = M_2(\{(\mathbf{b}_i, v_i)\}) * (k \otimes k). \qquad [20]$$

To see this, note by Step 0 that both sides of Eq. (20) are real-valued real analytic functions on $\mathbb{R}^2 \times \mathbb{R}^2$. From continuity, if they differ on $[-1, 1]^2$ there must exist a product of sufficiently small pixels where their integrals differ, i.e. $m \geq m'$ and $j_1, j_2, j_3, j_4 \in \{-2^{m-1}, \ldots, 2^{m-1} - 1\}$ such that

$$M_2^{[m]}(\{(\mathbf{a}_i, w_i)\})((j_1, j_2), (j_3, j_4)) \neq M_2^{[m]}(\{(\mathbf{b}_i, v_i)\})((j_1, j_2), (j_3, j_4)). \qquad [21]$$

However, Eq. (21) contradicts Eq. (19) and (18). Thus, Eq. (20) holds on $[-1, 1]^2 \times [-1, 1]^2$. By real analyticity, Eq. (20) then holds on all of $\mathbb{R}^2 \times \mathbb{R}^2$ as wanted.

Step 4: We undo the Gaussian blurring.

Continue with Eq. (20). Because $M_2(\cdot)$ is compactly supported, it identifies with a tempered distribution. The Fourier transform is thus applicable to Eq. (20). By the convolution theorem (9, Thm. 7.1.15), it gives

$$\widehat{M_2}(\{(\mathbf{a}_i, w_i)\})\, \widehat{k \otimes k} \;=\; \widehat{M_2}(\{(\mathbf{b}_i, v_i)\}\, \widehat{k \otimes k}. \qquad [22]$$

Note that the Paley-Wiener theorem (9, Thm. 7.1.14) implies $\widehat{M_2}(\cdot)$ is a function rather just a distribution (moreover it is extendable to an entire function). Also, $\widehat{k \otimes k}$ is a Gaussian function. Therefore, Eq. (22) can be regarded as an equality of functions rather than just distributions. Since $\widehat{k \otimes k} \neq 0$ everywhere, it implies

$$\widehat{M_2}(\{(\mathbf{a}_i, w_i)\}) \;=\; \widehat{M_2}(\{(\mathbf{b}_i, v_i)\}),$$

whence

$$M_2(\{(\mathbf{a}_i, w_i)\}) = M_2(\{(\mathbf{b}_i, v_i)\}), \qquad [23]$$

using the fact that the Fourier transform is an automorphism on tempered distributions.

Step 5: We use Theorem 2 to conclude.

The above steps have shown: there exists $m' = m'(p, r, w_+, w_-)$ such that if $m \geq m'$ then $\{(\mathbf{a}_i, w_i)\}, \{(\mathbf{b}_i, v_i)\} \in X$ and $M_2^{[m]}(\{(\mathbf{a}_i, w_i)\}) = M_2^{[m']}(\{(\mathbf{b}_i, v_i)\})$ imply $M_2(\{(\mathbf{a}_i, w_i)\}) = M_2(\{(\mathbf{b}_i, v_i)\})$. However by Theorem 2, $M_2(\{(\mathbf{a}_i, w_i)\}) = M_2(\{(\mathbf{b}_i, v_i)\})$ implies $\{(\mathbf{a}_i, w_i)\}$ and $\{(\mathbf{b}_i, v_i)\}$ are equal up to a rotation/reflection in $\mathbb{R}^3$, provided $\{(\mathbf{a}_i, w_i)\}$ satisfies **A1**-**A2**.

The proof of Theorem 4 is complete. □

B. Proof of Corollary 5. This now follows immediately from (10, Sec. 3) or (11, Sec. 2), because by Theorem 4 the second moment $M_2{}^{[m]}(\{(\mathbf{a}_i, w_i)\})$ uniquely determines the signal $\{(\mathbf{a}_i, w_i)\}$ up to the group action of $O(3)$, provided $\{(\mathbf{a}_i, w_i)\}$ satisfies the Zariski-open conditions **A1**-**A2**. □

4. Normalized Bessel functions and the Nyquist criterion

The spherical Bessel basis defined in the main text uses the normalized spherical Bessel functions $j_{\ell s}(k)$ defined by

$$j_{\ell s}(k) = \frac{1}{c\sqrt{\pi}|j_{\ell+1}(R_{\ell,s})|} j_\ell(R_{\ell,s}\frac{k}{c}), \qquad [24]$$

where j_ℓ is the ℓth spherical Bessel function of the first kind (12, Eq. 10.2.1), c the bandlimit of the projection images and $R_{\ell,s}$ the sth positive solution to $j_\ell = 0$. The Nyquist criterion determines the maximally allowable value of the truncation parameter S_ℓ by defining S_ℓ as the largest integer s satisfying,

$$R_{\ell,s+1} \leq 2\pi c R, \qquad [25]$$

assuming the projection images are supported on a disk of radius R (13). Our numerical experiments used $c = 0.5$ and a radius R of 32 voxels.

Movie S1. The movie shows a 3D view of the reconstructed molecule as a function of the iteration number.

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