Using Quaternions to Calculate RMSD

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Abstract: A widely used way to compare the structures of biomolecules or solid bodies is to translate and rotate one structure with respect to the other to minimize the root-mean-square deviation (RMSD). We present a simple derivation, based on quaternions, for the optimal solid body transformation (rotation-translation) that minimizes the RMSD between two sets of vectors. We prove that the quaternion method is equivalent to the well-known formula due to Kabsch. We analyze the various cases that may arise, and give a complete enumeration of the special cases in terms of the arrangement of the eigenvalues of a traceless, 4×4 symmetric matrix. A key result here is an expression for the gradient of the RMSD as a function of model parameters. This can be useful, for example, in finding the minimum energy path of a reaction using the elastic band methods or in optimizing model parameters to best fit a target structure.

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Introduction

We are interested in comparing the geometries of two solid objects. For example, often in computational biology there is a need to overlay the structure of one protein onto another in a way that minimizes the RMSD error. This is useful for comparing protein model structures to known database structures, or for assessing the geometric similarity of one protein with another, or comparing two conformations of the same protein. The first step in computing the RMSD error is to bring the two structures together as closely as possible, by rigid space motions (a proper rotation and translation). As is usual in such problems, we assume that there is already a proper assignment of the points on one object to the points on the other.

The mathematical statement of the problem is: "Given an ordered set of vectors $\mathbf{y}_k$ (target) and a second set $\mathbf{x}_k$ (model), $1 \leq k \leq N$, find an orthogonal transformation $\mathcal{U}$ and a translation $\mathbf{r}$ such that the residual E (weighted by w_k)

$$E := \frac{1}{N} \sum_{k=1}^{N} w_k |\mathcal{U}\mathbf{x}_k + \mathbf{r} - \mathbf{y}_k|^2 \qquad (1)$$

is minimized." The weight factor w_k allows us to emphasize various parts of the structure, such as the backbone of a polypeptide. Often, the weights will be equal to 1. Because the weights can be incorporated into $\mathbf{x}_k$ and $\mathbf{y}_k$, we omit w_k below.

The problem of optimal superposition has attracted the interest of a number of authors[1–10] (see also references in ref. 11). Among these, the solution by Kabsch[2] has been the most popular and widely used. The method produces the residual in terms of the singular value decomposition (SVD) of the 3×3 correlation matrix $\mathcal{R}$ [see eq. (5) below]. The method is applicable to vectors of arbitrary dimension, and it appears to have been first derived by Schönenman[1] in the context of Factor Analysis.

By making use of *quaternions* instead, a different formulation can be developed.[5,7] The quaternion corresponding to the optimal rotation is found as the leading eigenvector of a certain 4×4 matrix, $\mathcal{F}$ [see eq. (10) below], whose elements are formed from those of $\mathcal{R}$. Quaternion parametrization of rotations respects chirality and does not suffer from coordinate singularities such as those inherent in Euler angles.[11] In this note we establish the equivalence of the SVD and quaternion based results for the optimal rotation. We give a self-contained derivation of the best-fit RMSD, defined as $e := \sqrt{E_{\min}}$ in terms of quaternions. We show how one can use the formalism to arrive at both proper and

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improper rotations, and give a discussion of the issues related to degeneracy.

In Appendix B we provide a brief introduction to quaternions.

We then extend this formulation to show that the derivative of the RMSD e with respect to the model coordinates $\mathbf{x}_k$, $\partial e/\partial \mathbf{x}_k$, is simply the minimal residual. This quantity is useful for efficiently searching the parameter spaces to optimize objective functions that involve the best-fit RMSD.

For example, in the energy parameter optimization algorithm proposed by Rosen et al.,[12] the goal is to minimize the structural difference between the energy minimum and the target. In ref. 12, the RMSD based on a dihedral angle metric is used as a measure of structural deviation. Although the gradient of the dihedral RMSD is easy to compute, Cartesian RMSD gives a better measure of structural difference. The reason for this is that the dihedral RMSD does not capture the effect that perturbations of middle dihedral angles in a chain structure entail much larger structural changes than those of terminal angles. Our formula for $\partial e/\partial \mathbf{x}_k$ can be used to apply the method in ref. 12 to the problem in Cartesian measure.

Another example in which $\partial e/\partial \mathbf{x}_k$ is useful is in determining the minimum energy pathways of a reaction using the elastic band methods.[13,14] The elastic band methods employ a term involving the best-fit RMSD between neighboring states in a pathway, which contributes to producing an elastic chain of states between a reactant and a product. Reference 13 provides an argument based on symmetry, for the gradient of the RMSD, which has been implemented in the program CHARMM[15] in a form identical with ours. The gradient is used in this context to calculate elastic forces, and it is noted that in the (rare) occasion when the optimal rotation becomes degenerate, that is, when there are two different rotations producing similar fit between the structures, the degeneracy can result in arbitrary force fluctuations. To prevent that, an ad hoc continuation method is introduced[13] to switch from one branch to another when singular values cross. If one employs the quaternion approach, it is easily seen that at the degeneracy the quaternions of the two equivalent rotations are simply a basis of the invariant subspace corresponding to a degenerate eigenvalue. As such, any linear combination provides another quaternion (and, consequently, a rotation) that gives the same residual. In this way, the switching between branches may be accomplished accurately and efficiently.

The gradient of RMSD is also useful in studies involving biomolecular structures in reduced representations. Reduced protein folding models often capture essential features without invoking computationally expensive full atomic coordinates. Reduced models are also frequently used in protein structure prediction algorithms at earlier stages of prediction before final refinement with full atomic details. The computations can be sped up by reducing the number of degrees of freedom in the model by setting various quantities such as bond lengths and angles at canonical fixed values. Using the analytical expression for the gradient makes it possible to efficiently obtain the optimal reduced model structure, given a target structure.

The organization of the paper is as follows. The residual minimization is carried out in Section 2 where the quaternion-based derivation is contrasted to the SVD approach of Kabsch. The proof of the equivalence is provided in Section 3, where we also discuss issues related to chirality and degeneracy. A formula for the gradient of RMSD is derived in Section 4, and an example of using the gradient to find the best-fit reduced model to a target structure is presented. The procedure to compute RMSD and its gradient is summarized in Section 5. Finally, brief conclusions are given in Section 6. An overview of quaternions and their properties is presented in Appendix B. A FORTRAN 90 code used to generate the results in Section 4, with an implementation of RMSD and the RMSD gradient, is available at `http://dillgroup.ucsf.edu/rmsd/`.

The Optimal Rotation

We now find the optimal rigid body motion to minimize the residual E given by eq. (1),

$$E := \frac{1}{N}\sum_{k=1}^{N} |\mathcal{U}\mathbf{x}_k + \mathbf{r} - \mathbf{y}_k|^2. \tag{2}$$

Considering variations in $\mathbf{r}$ first, we find that for an extremum:

$$\sum_{k=1}^{N} (\mathcal{U}\mathbf{x}_k + \mathbf{r} - \mathbf{y}_k) = 0$$

so that

$$\mathbf{r} = \bar{\mathbf{y}} - \mathcal{U}\bar{\mathbf{x}} := \frac{1}{N}\sum_{k=1}^{N} \mathbf{y}_k - \mathcal{U}\,\frac{1}{N}\sum_{k=1}^{N} \mathbf{x}_k. \tag{3}$$

Shifting the two sets, $\{\mathbf{x}_k\}$ and $\{\mathbf{y}_k\}$, to their respective barycenters $\bar{\mathbf{x}}$ and $\bar{\mathbf{y}}$, we introduce:

$$\tilde{\mathbf{x}}_k := \mathbf{x}_k - \bar{\mathbf{x}},\ \tilde{\mathbf{y}}_k := \mathbf{y}_k - \bar{\mathbf{y}}.$$

Below we drop the tildes (i.e., we will assume that both sets have been shifted to bring their respective barycenters to the origin), and then the residual becomes:

$$E = \frac{1}{N}\sum_{k=1}^{N} |\mathbf{x}'_k - \mathbf{y}_k|^2 \tag{4}$$

where we set $\mathbf{x}' := \mathcal{U}\mathbf{x}$.

In the sequel we will make use of the $3 \times N$ matrices $\mathcal{X}$ and $\mathcal{Y}$ where the kth column of $\mathcal{X}$ is the vector $\mathbf{x}_k$, and similarly for $\mathcal{Y}$. Throughout we write a_{jk} for the jth component of the kth vector, $\mathbf{a}_k$.

Minimal Residual through SVD

A method proposed in 1976 by Kabsch[2] produces the residual in terms of the SVD of the correlation matrix, $\mathcal{R} = \mathcal{V}\Sigma\mathcal{W}^T$, where $\mathcal{V}$ and $\mathcal{W}$ are the matrices of left and right singular vectors,

respectively, and Σ is the positive semidefinite diagonal matrix of singular values[16] of the matrix

$$\mathcal{R} := \mathcal{X}\mathcal{Y}^T = \sum_{k=1}^{N} \mathbf{x}_k \mathbf{y}_k^T \rightarrow R_{ij} = \sum_{k=1}^{N} x_{ik} y_{jk},\ i, j = 1, 2, 3, \quad (5)$$

with x_{ik} denoting the ith component of $\mathbf{x}_k$, and likewise for y_{jk}.

The minimal residual is found as

$$E_{\min} = \frac{1}{N} \sum_{k=1}^{N} |\mathbf{x}_k|^2 + |\mathbf{y}_k|^2 - \frac{2}{N}(\sigma_1 + \sigma_2 + \chi\sigma_3)$$

where $\chi = sgn(\det \mathcal{R})$ and σ_i is the ith singular value of $\mathcal{R}$, with $\sigma_1 \geq \sigma_2 \geq \sigma_3 \geq 0$. The rotation matrix that brings the model to optimal superposition with the target is

$$\mathcal{U} = \mathcal{W} \begin{pmatrix} 1 & & \\ & 1 & \\ & & \chi \end{pmatrix} \mathcal{V}^T.$$

It is the rotation that aligns the right and left singular vectors of $\mathcal{R}$ when the determinant of $\mathcal{R}$ is positive, while it antialigns the third pair of singular vectors $\mathbf{w}_3$, $\mathbf{v}_3$, otherwise. Cases where an improper rotation, that is, a rotation combined with a reflection, is desired are also easily treated.

A simple derivation of the result, apparently first formulated by Schöneman[1] in Factor Analysis studies (see also the text by Horn and Johnson,[16] p. 431), is as follows:

$$NE = \sum_{k=1}^{N} |\mathbf{x}'_k - \mathbf{y}_k|^2 = Tr\{(\mathcal{X}' - \mathcal{Y})^T((\mathcal{X}' - \mathcal{Y})\} = Tr\mathcal{X}'^T\mathcal{X}'$$

$$+ Tr\mathcal{Y}^T\mathcal{Y} - 2Tr\mathcal{Y}^T\mathcal{X}' = \sum_{k=1}^{N} |\mathbf{x}_k|^2 + |\mathbf{y}_k|^2 - 2Tr\mathcal{Y}^T\mathcal{X}'$$

Using well-known properties of the trace:

$$Tr\mathcal{Y}^T\mathcal{X}' = Tr\mathcal{Y}^T\mathcal{U}\mathcal{X} = Tr\mathcal{X}\mathcal{Y}^T\mathcal{U} = Tr\mathcal{R}\mathcal{U}.$$

From the singular value decomposition of $\mathcal{R}$, we get:

$$Tr\mathcal{Y}^T\mathcal{X}' = Tr\mathcal{V}\Sigma\mathcal{W}^T\mathcal{U} = Tr\Sigma\mathcal{W}^T\mathcal{U}\mathcal{V} = \sum_{i=1}^{3} \sigma_i w_i^T \mathcal{U} v_i$$

$$= \sum_{i=1}^{3} \sigma_i T_{ii},$$

where we introduced the orthogonal matrix $\mathcal{T} = \mathcal{W}^T\mathcal{U}\mathcal{V}$. Because $|T_{ii}| \leq 1$, we see that

Table 1. The χ Factors for Extrema.

det $\mathcal{R}$	s	χ_1	χ_2	χ_3
+	1	1	1	1
+	2	1	−1	−1
+	3	−1	1	−1
+	4	−1	−1	1
−	1	1	1	−1
−	2	1	−1	1
−	3	−1	1	1
−	4	−1	−1	−1

$$Tr\mathcal{Y}^T\mathcal{X}' \leq \sum_{i=1}^{3} \sigma_i$$

The minimal residual is found when the above expression for the trace is maximized, that is, when the matrix $\mathcal{T}$ reduces to the identity, that is,

$$\mathcal{U} = \mathcal{W}\mathcal{V}^T.$$

However, this matrix represents an improper rotation if the singular vector matrices, $\mathcal{W}$ or $\mathcal{V}$, have opposite chirality, that is, if $\det \mathcal{R} < 0$. In that case, it can be easily shown, for example, by using Euler angles to express the rotation from $\mathcal{X}$ to $\mathcal{Y}$, that the best proper rotation gives $\mathcal{U}\mathbf{v}_i = \pm\mathbf{w}_i$ with the + sign for $i = 1, 2$ and − for $i = 3$, so that the rotation matrix is as given above. That is, the optimal alignment of $\mathcal{X}$ and $\mathcal{Y}$ by a proper rotation brings the sets of right and left singular vectors of $\mathcal{R}$ to coincidence if $\det \mathcal{R} > 0$ while it aligns the first two pairs of singular vectors and antialigns the third if $\det \mathcal{R} < 0$. In similar fashion, it can be shown that all the extrema of the residual are found as:

$$NE_s = \sum_{k=1}^{N} |\mathbf{x}_k|^2 + |\mathbf{y}_k|^2 - 2\sum_{i=1}^{3} \chi_{is}\sigma_i,\ s = 1, 2, 3, 4$$

with $\chi_{1s}\chi_{2s}\chi_{3s} = \text{sgn}\det \mathcal{R}$. The relationship between $s = 1, 2, 3, 4$ and the χ_{is}, $i = 1, 2, 3$ is defined in Table 1. The corresponding rotation operators are given by

$$\mathcal{U}_s = \mathcal{W} \begin{pmatrix} \chi_{1s} & & \\ & \chi_{2s} & \\ & & \chi_{3s} \end{pmatrix} \mathcal{V}^T.$$

Degeneracy is possible for the optimum rotation if $\det \mathcal{R} < 0$ and $\sigma_2 = \sigma_3$ because then $\mathcal{U}_1$ and $\mathcal{U}_2$ give the same minimal residual. In this case, it turns out that there is a 1-parameter family of rotations that also give the same minimal residual. In fact, in this case the singular vectors corresponding to the equal singular values form a subspace, any orthonormal basis of which would serve equally well to form the rotation matrix. The relationship among these is easier to uncover in terms of quaternions, as we shall see in the next subsection. In the negative correlation case, a

rotation–reflection will always give a better fit. Indeed, it is easy to see that the improper rotation $\mathcal{U}' = -\mathcal{U}_4$ will produce the least residual. We postpone discussion of higher degeneracy because this and related issues are easiest to classify when this method is contrasted to the quaternion method of the next subsection.

Minimal Residual through Quaternions

We now promote $\mathbf{x}_k$ and $\mathbf{y}_k$ to *pure quaternions* (see Appendix B), $x_k := (0, \mathbf{x}_k)$ with $x_k^c = -x_k$ and similarly for y_k. The rotation $\mathcal{U}(q)$ on $\mathbf{x}_k$ is then written as

$$(0, \mathcal{U}(q)\mathbf{x}_k) = qx_kq^c.$$

The residual is written, in terms of quaternions, as

$$E_q = \frac{1}{N}\sum_{k=1}^{N}(qx_kq^c - y_k)(qx_kq^c - y_k)^c. \tag{6}$$

Expanding and multiplying by N, eq. (6) becomes

$$NE_q = \sum_{k=1}^{N}((qx_kq^c)(qx_kq^c)^c + y_ky_k^c - (qx_kq^c)y_k^c - y_k(qx_kq^c)^c$$

$$= \sum_{k=1}^{N}(x_kx_k^c + y_ky_k^c + (qx_kq^c)y_k + y_k(qx_kq^c)), \tag{7}$$

where use has been made of the normalization $qq^c = 1$ and the property of pure quaternions $x^c = -x$. Because qx_kq^c and y_k are pure, and for a, b pure we have $ab + ba = 2(-\mathbf{a}\cdot\mathbf{b}, \mathbf{0}) = 2([ab]_0, \mathbf{0})$, the last two terms in eq. (7) can be combined as:

$$(qx_kq^c)y_k + y_k(qx_kq^c) = 2([y_k(qx_kq^c)]_0, \mathbf{0}),$$

that is, only the 0th component is nonzero. We write $y_k(qx_kq^c) = (y_kqx_k)q^c$ using the associativity of quaternions, and define $x_k := y_kqx_k$. The 4-vector form of z_k, $\mathcal{Z}_k$, can be written as $\mathcal{Z}_k = \mathcal{A}_L(y_k)\mathcal{A}_R(x_k)\mathcal{Q}$, where $\mathcal{A}_L(y_k)$ and $\mathcal{A}_R(x_k)$ are defined as in eq. (30). Putting these together,

$$-2\mathbf{y}_k^T\mathcal{U}(q)\mathbf{x}_k = 2[y_k(qx_kq^c)]_0 = 2[z_kq^c]_0 = 2(z_{k0}q_0 + \mathbf{z}_k\cdot\mathbf{q})$$
$$= 2\mathcal{Q}^T\mathcal{Z}_k = 2\mathcal{Q}^T\mathcal{A}_L(y_k)\mathcal{A}_R(x_k)\mathcal{Q}. \tag{8}$$

Collecting results, we find that the residual can be written as

$$NE_q = \sum_{k=1}^{N}(|\mathbf{x}_k|^2 + |\mathbf{y}_k|^2) - 2\mathcal{Q}^T\mathcal{F}\mathcal{Q}, \tag{9}$$

where

$$\mathcal{F} := -\sum_{k=1}^{N}\mathcal{A}_L(y_k)\mathcal{A}_R(x_k).$$

The explicit form of the matrix $\mathcal{F}$ in terms of the matrix elements of the correlation matrix $\mathcal{R}$ (5), is

$$\mathcal{F} = \begin{pmatrix} R_{11}+R_{22}+R_{33} & R_{23}-R_{32} & R_{31}-R_{13} & R_{12}-R_{21} \\ R_{23}-R_{32} & R_{11}-R_{22}-R_{33} & R_{12}+R_{21} & R_{13}+R_{31} \\ R_{31}-R_{13} & R_{12}+R_{21} & -R_{11}+R_{22}-R_{33} & R_{23}+R_{32} \\ R_{12}-R_{21} & R_{13}+R_{31} & R_{23}+R_{32} & -R_{11}-R_{22}+R_{33} \end{pmatrix}. \tag{10}$$

The problem has in this way been reduced to that of finding the extrema of a quadratic form $\mathcal{Q}^T\mathcal{F}\mathcal{Q}$ in the four variables q_i, $i = 0, 1, 2, 3$, subject to the constraint $\mathcal{Q}^T\mathcal{Q} = 1$. Note that here we are using the vector $\mathcal{Q}$, so that the squared norm q^cq is written equivalently as $\mathcal{Q}^T\mathcal{Q}$. $\mathcal{Q}^T\mathcal{F}\mathcal{Q}$ is the standard Rayleigh quotient for a symmetric matrix $\mathcal{F}$, and the maximum value achieved by $\mathcal{Q}^T\mathcal{F}\mathcal{Q}$ is equal to its largest eigenvalue. Thus, the desired minimization leads to the eigenproblem

$$\mathcal{F}\mathcal{Q} = \lambda\mathcal{Q}. \tag{11}$$

We see that the extremum λ is equal to one of the eigenvalues of a 4×4 symmetric, traceless matrix, and the corresponding eigenvector gives one of the candidate rotations that extremize the residual, as sought. We are thus led to the following expression for the best-fit RMSD e_q:

$$e_q = \sqrt{\min_{\|q\|=1} E_q} = \sqrt{\frac{\sum_{k=1}^{N}(|\mathbf{x}_k|^2 + |\mathbf{y}_k|^2) - 2\lambda_{\max}}{N}},$$

where $\lambda_{\max}$ is the maximum eigenvalue of $\mathcal{F}$. If a rotation reflection is allowed, then the minimal eigenvalue λ_4 must also be considered. If $-\lambda_4 > \lambda_1$, then the improper rotation $-\mathcal{U}(q_4)$ will give a better fit than the proper rotation $\mathcal{U}(q_1)$ [see Appendix B, eq. (33) for the construction of the rotation matrix $\mathcal{U}(q)$ from the quaternion q]. This is easily seen, because the matrix $\mathcal{F}$ is linear in both $\mathcal{X}$ and $\mathcal{Y}$; therefore, the substitution $\mathcal{X} \to -\mathcal{X}$ changes the sign of the eigenvalues. By examining the connection between the quaternion and SVD-based methods in the next section, we will see how these cases relate to the sign of the determinant of $\mathcal{R}$.

Chirality and the Relationship to Kabsch's Formula

A property, common to both the rotation matrix and quaternion formulations, is that their parameters (rotation matrix coefficients or quaternion components) appear quadratically in the expression for the residual, thus leading to linear eigenvalue problems. In this section we show that these two problems are equivalent and exploit the connection to give a complete classification of the various cases that may result in terms of the properties of the correlation matrix. Kabsch[2] finds the extremal of the residual to be equal to

$$E_{\min} = \frac{1}{2}\sum_{k=1}^{N}(|\mathbf{x}_k|^2 + |\mathbf{y}_k|^2) - \sum_{j=1}^{3}\sigma_j\sqrt{\mu_j},$$

where $\sigma_j = \pm 1$ with $\sigma_1\sigma_2\sigma_3 := \det \mathcal{R} = \pm 1$. Here the μ_j are the eigenvalues of the symmetric, positive definite matrix $\mathcal{R}\mathcal{R}^T$ where $\mathcal{R}$ is defined by eq. (5). The nine quantities appearing in matrix $\mathcal{R}$ enter both in

$$\mathcal{R}\mathcal{R}^T = \begin{pmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{pmatrix}\begin{pmatrix} R_{11} & R_{21} & R_{31} \\ R_{12} & R_{22} & R_{32} \\ R_{13} & R_{23} & R_{33} \end{pmatrix} \tag{12}$$

and in the traceless matrix $\mathcal{F}$(10). What is needed to show equivalence of the methods is that the set of eigenvalues of $\mathcal{F}$, λ_i with $i = 1, 2, 3, 4$, is the same as the set of values $\sum_{j=1}^{3}\sigma_j\sqrt{\mu_j}$. For this to happen, the characteristic polynomial of $\mathcal{R}\mathcal{R}^T$, $P_3(z) := \sum_0^3 b_j z^j$, must be the resolvent cubic of $P_4(\lambda) := \sum_0^4 a_j\lambda^j$, the characteristic polynomial of $\mathcal{F}$. It is well known that the quartic equation in canonical form

$$\lambda^4 + 6p\lambda^2 + 4q\lambda + r = 0 \tag{13}$$

has roots λ_i, $i = 1, 2, 3, 4$, that can be expressed as

$$\lambda_i = \sum_{k=1}^{3}\sigma_j\sqrt{z_k}$$

with $\sigma_j = 1$ and $\sigma_1\sigma_2\sigma_3 = \mathrm{sgn}(q)$, provided the z_k, $k = 1, 2, 3$ are the roots of the *resolvent* cubic

$$z^3 + 3pz^2 + \tfrac{1}{4}(9p^2 - r)z - \tfrac{1}{4}q^2 = 0. \tag{14}$$

The proof of this classical result can be found, for example, in Weisner,[17] (pp. 140–143). The characteristic polynomial of (10) clearly has the form (13) because the matrix $\mathcal{F}$ is traceless. With the coefficients p, q, r of the quartic (13) defined in terms of the entries of (10), it is a simple but tedious task, best carried out using a computer algebra system, to verify that the characteristic polynomial of (12) will then have the form of the resolvent cubic (14). The verification of this fact, as well as detailed forms of the coefficients of the two characteristic polynomials, computed with the computer algebra system *MAPLE* are given in Appendix C. As can be easily deduced

$$p := \frac{a_2}{6} = -\frac{1}{3}\|\mathcal{R}\|_F^2; \quad q := \frac{a_1}{4} = -2\det\mathcal{R}$$

$$b_2 = -\|\mathcal{R}\|_F^2; \quad b_0 = -(\det\mathcal{R})^2, \tag{15}$$

while the forms of $r := a_0$ and b_1 are quite complicated and will not be given here. $\|\mathcal{R}\|_F^2 = \Sigma_{ij}|R_{ij}|^2$ denotes the Frobenius norm.[16]

Given the form of the quartic, it is important to note that the only term that is sensitive to a sign inversion of all the coordinates (i.e., a point-reflection through the origin) is the linear coefficient. Because that term is equal to $-8\det\mathcal{R}$ we can relate the location of the eigenvalues of $\mathcal{F}$ to the type of best fit. Indeed, because the characteristic polynomial of $\mathcal{F}$, $P_4(\lambda) := \det(\mathcal{F} - \lambda\mathcal{I}) = \Pi_{i=1}^4(\lambda - \lambda_i)$ has the expansion:

$$\prod_{i=1}^{4}(\lambda - \lambda_i) = \lambda^4 - \left(\sum_{i=1}^{4}\lambda_i\right)\lambda^3 + \left(\sum_{i\neq j=1}^{4}\lambda_i\lambda_j\right)\lambda^2 - \left(\sum_{i\neq j\neq k=1}^{4}\lambda_i\lambda_j\lambda_k\right)\lambda + \prod_{i=1}^{4}\lambda_i$$

we have by comparing with eq. (13) and using eq. (15) that

$$-4q = 8\det\mathcal{R} = \lambda_1\lambda_2(\lambda_3 + \lambda_4) + \lambda_3\lambda_4(\lambda_1 + \lambda_2).$$

Because the matrix $\mathcal{F}$ is traceless so that the sum of the eigenvalues must vanish, that is, $\lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 = 0$, this can be written

$$8\det\mathcal{R} = (\lambda_1 + \lambda_2)(\lambda_3\lambda_4 - \lambda_1\lambda_2).$$

We can now relate the sign of $\det\mathcal{R}$ to the eigenvalues of $\mathcal{F}$. Throughout we assume $\lambda_1 \geq \lambda_2 \geq \lambda_3 \geq \lambda_4$. Then, $\lambda_1 > 0$ and $\lambda_4 < 0$ unless $\lambda_i = 0$, $i = 1, 2, 3, 4$. The following properties are easily deduced:

1. If $|\lambda_1| > |\lambda_4|$ then $\det\mathcal{R} > 0$ and we have the cases:
   (a) $\lambda_2, \lambda_3, \lambda_4 < 0$ while $\lambda_1 > 0$
   (b) $\lambda_4 \leq \lambda_3 < 0$ and $\lambda_1 \geq \lambda_2 > 0$. In this case $\lambda_1 = \alpha + \rho$, $\lambda_2 = \alpha - \rho$, while $\lambda_4 = -\alpha - r$, $\lambda_3 = -\alpha + r$, with $\alpha \geq \rho > r \geq 0$.
2. If $|\lambda_1| < |\lambda_4|$, then $\det\mathcal{R} < 0$, and we have the cases:
   (a) $\lambda_1, \lambda_2, \lambda_3 > 0$, while $\lambda_4 < 0$.
   (b) $\lambda_4 \leq \lambda_3 < 0$ and $\lambda_1 \geq \lambda_2 > 0$. In this case $\lambda_1 = \alpha + \rho$, $\lambda_2 = \alpha - \rho$, while $\lambda_4 = -\alpha - r$, $\lambda_3 = -\alpha + r$, with $\alpha \geq r > \rho \geq 0$.
3. If $|\lambda_1| = |\lambda_4|$, then also $|\lambda_2| = |\lambda_3|$, and $\det\mathcal{R} = 0$.

In case (1), the best fit possible is given by the proper rotation corresponding to q_1, the quaternion-eigenvector of the leading positive eigenvalue. In case (2), q_1 still gives the best fit by a proper rotation, but a reflection followed by a rotation by q_4 would give a better fit. In case (3), either a proper rotation by q_1 or a

reflection followed by a rotation by q_4 would produce equally good fits. The correlation determinant vanishes in this case. However, the point sets are not necessarily planar or mirror-symmetric, so that if a chiral inversion is undesirable, such as in the case of *L*-amino acid-based proteins, the chiral inversion associated with applying q_4 together with a reflection about the origin is not allowed and the proper rotation associated to q_1 is the only choice.

We examine now the various cases that arise when two eigenvalues of the matrix $\mathcal{F}$ become equal. The only case of possible interest in applications is when the degeneracy occurs in the leading eigenvalue, λ_1, and we limit our attention to it. Comparing the conditions in cases (1–3) we see that if the leading eigenvalue λ_1 is degenerate, that is, $\lambda_1 = \lambda_2$, then either $-\lambda_4 > \lambda_1$ and $\det \mathcal{R} < 0$ (case 2) or $-\lambda_4 = \lambda_1 = -\lambda_3 = \lambda_2$ and $\det \mathcal{R} = 0$ (case 3). In case (2a) it is also possible to have triple degeneracy, that is, $\lambda_1 = \lambda_2 = \lambda_3$. It is easy to translate these cases to the properties of the corresponding singular values. However, in the case of equal eigenvalues, the quaternion method has a slight advantage, as it gives an invariant subspace that is generated by any linear combination of q_1 and q_2 (and q_3, in case of a triple degeneracy). In the SVD-based method, the rotation matrices do not form a linear space and constructing a proper combination is not as readily accomplished.

Gradient of the RMSD and Application to an Optimization Problem

The gradient of the RMSD with respect to the model coordinates is required in several applications. For simplicity here we work with $E = e^2$. It is well known[13] that the gradient is equal to the residual vector in the form,

$$\nabla_{\mathbf{x}_k} E = \frac{2}{N}(\mathbf{x}_k - U^T \mathbf{y}_k). \tag{16}$$

We give here a simple derivation using the quaternion formalism, and present a calculation using the gradient to find the best-fit reduced model to a target structure.

We consider the case in which the model coordinates $\mathbf{x}_k$ are functions of a parameter set α. The parameter set α could be an energy parameter set that places $\mathbf{x}_k(\alpha)$ at the global energy minimum, or a set of geometrical variables that represents a reduced structure model. By the chain rule,

$$\frac{\partial E}{\partial \alpha_i} = \sum_{k=1}^{N} \sum_{l=1}^{3} \frac{\partial E}{\partial x_{lk}} \frac{\partial x_{lk}}{\partial \alpha_i},$$

where x_{lk} is the lth component of $\mathbf{x}_k$, and α_i is the ith component of α. The derivatives $\partial E/\partial \alpha_i$ provide the direction of steepest descent in the RMSD, which can be used in a search for the optimal parameter set α. For the first factor $\partial E/\partial x_{lk}$ we use the results derived in the previous section. Because

$$\frac{\partial E}{\partial x_{lk}} = \frac{2}{N}\left(x_{lk} - \frac{\partial \lambda_{\max}}{\partial x_{lk}}\right), \tag{17}$$

we need formulas for the quantities $\partial \lambda_{\max}/\partial x_{lk}$. From the general results in Appendix A,

$$V^T \frac{\partial \mathcal{F}}{\partial x_{lk}} V = \frac{\partial \Lambda}{\partial x_{lk}} + A\Lambda - \Lambda A,$$

where the eigenvalue matrix Λ, the eigenvector matrix V, and the generator matrix of rotation A are defined in Appendix A. Because the diagonal elements of $A\Lambda - \Lambda A$ vanish we have

$$\frac{\partial \lambda_{\max}}{\partial x_{lk}} = \mathcal{Q}^T \frac{\partial \mathcal{F}}{\partial x_{lk}} \mathcal{Q}, \tag{18}$$

where $\mathcal{Q} \equiv \mathcal{Q}_{\max}$ is the normalized eigenvector corresponding to the eigenvalue $\lambda_{\max}$. To show that this formula leads to eq. (16) we recall that $q^c y_k q = (0, \mathcal{U}^T(q)\mathbf{y}_k)$. Writing as above $q \equiv q_{\max}$ for the quaternion equivalent to the eigenvector $\mathcal{Q}_{\max}$, and fixing its value in dealing with the gradient operator as a matter of algebraic convenience we have, using eq. (8):

$$\begin{aligned}\nabla_{\mathbf{x}_k} \lambda_{\max} &= \mathcal{Q}^T \nabla_{\mathbf{x}_k} \mathcal{F} \mathcal{Q} = \nabla_{\mathbf{x}_k}(-\mathcal{Q}^T \mathcal{A}_L(y_k)\mathcal{A}_R(x_k)\mathcal{Q}) \\ &= \nabla_{\mathbf{x}_k}(\mathbf{y}_k^T \mathcal{U}(q)\mathbf{x}_k) = \nabla_{\mathbf{x}_k}(\mathbf{x}_k^T \mathcal{U}^T \mathbf{y}_k) = \mathcal{U}^T \mathbf{y}_k \end{aligned} \tag{19}$$

so that (17) is equivalent to (16).

Near a degeneracy in the leading eigenvalue (i.e., if $\lambda_1 \approx \lambda_2 > 0$), the one parameter family of rotations

$$\mathcal{U}(q(t)) := \mathcal{U}(\cos tq_1 + \sin tq_2), \quad 0 \le t < 2\pi$$

produces near minimal residual for all values of the parameter t. Of course, at the point of degeneracy, all such rotations produce equal, and minimal, residuals because $q(t)$ is also a unit eigenvector of eigenvalue $\lambda_{\max}$. In this case, the precise choice of optimal superposition needs to be kept in mind any additional requirements inherent in a given situation. For example, in the Nudged Elastic Band method[13] the above form could serve as an optimal switching function between branches near a degeneracy that would avoid large force fluctuations while remaining close to optimal superposition at all times.

We illustrate the use of the gradient of RMSD in an optimization problem. We consider a case in which a reduced protein model with only ϕ–ψ degrees of freedom is desired, and bond angles, bond lengths, and peptide torsion angles are fixed at canonical values. If the backbone atoms are reconstructed with the original ϕ–ψ angles, but together with the canonical bond angles and bond lengths, the structure deviates from the original structure significantly depending on the chain length, as shown in column "Initial RMSD" in Table 2. Top500 database of high resolution, nonredundant protein structures[18] are used as target structures for this calculation. The peptide torsion angles are fixed at 180°, and the bond lengths and angles are fixed at $\overline{NC_\alpha} = 1.45$ Å, $\overline{C_\alpha C} = 1.52$ Å, $\overline{CN} = 1.33$ Å, $\angle NC_\alpha C = 111.6°$, $\angle C_\alpha CN = 117.5°$, and $\angle CNC_\alpha = 120.0°$.

We optimized the ϕ–ψ angles to fit to the target structure at the canonical bond angles, bond lengths, and peptide torsion angles. The optimization successfully reproduces the original structure

Table 2. Statistics of the Optimization Results.

No. residues	No. proteins	Initial RMSD (Å)	Optimized RMSD (Å)
12–99	99	5.61	0.19
100–199	168	10.34	0.23
200–299	116	16.26	0.24
300–399	69	19.50	0.22
400–839	48	24.59	0.26

Initial RMSD and optimized RMSD are average RMS deviation of the reduced model structures from the crystal structures after reconstructing with the original and optimized ϕ–ψ, respectively.

with small RMSD, as shown in Table 2. The L-BFGS-B algorithm[19] is used for the minimization with a maximum gradient tolerance of 10^{-3}.

The Algorithm

The procedure of calculating the best-fit RMSD and the gradient of RMSD, given the two sets of vectors $\mathbf{x}_k$ and $\mathbf{y}_k$ and the weights w_k, is summarized below.

1. Multiply $\mathbf{x}_k$ and $\mathbf{y}_k$ by the weights w_k, and shift the coordinates to the barycenters, and call them $\tilde{\mathbf{x}}_k$ and $\tilde{\mathbf{y}}_k$.
2. Take the maximum eigenvalue $\lambda_{\max}$ and the corresponding eigenvector $\mathcal{Q}_{\max}$ of the 4×4 matrix $\mathcal{F}$ given by eq. (10) in terms of $\tilde{\mathbf{x}}_k$ and $\tilde{\mathbf{y}}_k$.
3. The best-fit RMSD is then given by

$$e = \sqrt{\frac{\sum_{k=1}^{N}(\tilde{\mathbf{x}}_k^2 + \tilde{\mathbf{y}}_k^2) - 2\lambda_{\max}}{N}},$$

   and the rotation matrix $\mathcal{U}(q_{\max})$ is obtained from the quaternion $q_{\max}$ using eq. (33).
4. The gradient of RMSD is

$$\nabla_{\mathbf{x}_k} e = \frac{1}{Ne}\,(\tilde{\mathbf{x}}_k - \mathcal{U}^T(q_{\max})\tilde{\mathbf{y}}_k).$$

Conclusion

We give a simple derivation of the optimal translation-rotation of one rigid body to minimize the Cartesian RMSD to another such body. We use quaternions. Our derivation of the RMSD is most similar to that of Kearsley,[7] and the results are equivalent. We also prove the equivalence of our quaternion-based formula to the widely used formula derived by Kabsch.[2] We exploit the connection between the two formulas to elucidate issues related to chirality and degeneracy. In addition, we derive the gradient of the RMSD with respect to model coordinates. Its simple quaternion-based form can be used to solve optimization problems that involve the RMSD in the objective function. Examples include optimizing energy parameters in models of protein folding and docking, using the elastic band methods to find reaction pathway, or finding optimal geometrical parameters in reduced dimensions.

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Appendix A: Perturbations of Symmetric Matrices

We review a simple calculation from matrix perturbation theory:[20]

Problem: Let $M(t)$ be a symmetric matrix, whose coefficients depend differentiably on the parameter t. Find expressions for the variation of its eigenvalues and eigenvectors with respect to t, that is, $(\lambda_t,\ \mathbf{v}_t)$.

Solution: We write

$$MV = V\Lambda,$$

where

$$\Lambda = \mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_N),$$

and we assume $\lambda_i \neq \lambda_j$ for $i \neq j$. The eigenvectors are orthonormal, $VV^T = I$. Because the columns of V form a complete, orthonormal set, we can write:

$$\frac{dV}{dt} = VA, \tag{20}$$

for some matrix A, that is, the $d\mathbf{v}_i/dt$ are written as linear combinations of the $\mathbf{v}_i$s. Because $V^TV = I$ we have

$$\frac{dV^T}{dt}\,V + V^T\frac{dV}{dt} = 0 \;\rightarrow\; A^T + A = 0,$$

so that the matrix A is skew, $A^T = -A$, which is to be expected because A is the generator of a rotation. Then, from $M = V\Lambda V^T$ we have

$$\frac{dM}{dt} = \frac{dV}{dt}\,\Lambda V^T + V\,\frac{d\Lambda}{dt}\,V^T + V\Lambda\,\frac{dV^T}{dt}$$

$$= V\left\{\frac{d\Lambda}{dt} + A\Lambda + \Lambda A^T\right\}V^T,$$

so that, finally:

$$V^T\frac{dM}{dt}\,V = \frac{d\Lambda}{dt} + A\Lambda - \Lambda A. \tag{21}$$

Appendix B: Quaternion Notation and Properties

We review basic properties of quaternions below. We follow the notes of Coutsias and Romero,[21] and refer the reader to these notes for more details. The book by Rappaport,[22] which discusses quaternions in the context of molecular dynamics, is also useful as an introduction. We define a quaternion q as a 4-vector $q = (q_0, q_1, q_2, q_3) \equiv (q_0, \mathbf{q})$, where $\mathbf{q} = (q_1, q_2, q_3)$, with the obvious addition law and the fundamental multiplication law given by

$$a = (a_0, \mathbf{a}), \quad b = (b_0, \mathbf{b}), \qquad a + b = (a_0 + b_0, \mathbf{a} + \mathbf{b}),$$
$$ab = (a_0 b_0 - \mathbf{a}\cdot\mathbf{b}, a_0\mathbf{b} + b_0\mathbf{a} + \mathbf{a}\times\mathbf{b}), \quad (22)$$

where the multiplication can be seen to be associative, $a(bc) = (ab)c$, but not commutative, $ab \neq ba$, in general. We also define the *conjugate* quaternion q^c, the squared norm of a quaternion $N(q)$, and the inverse quaternion q^{-1} by

$$q^c := (q_0, -\mathbf{q}), \quad (ab)^c = b^c a^c, \quad (23)$$

$$N(q) := q^c q = q q^c = q_0^2 + \mathbf{q}\cdot\mathbf{q}, \quad (24)$$

$$q^{-1} := \frac{q^c}{N(q)} = \frac{(q_0, -\mathbf{q})}{N(q)}. \quad (25)$$

An important class of quaternions is the *pure* quaternions, which have the form $q = (0, \mathbf{q})$. Pure quaternions can be considered as ordinary 3-vectors $\mathbf{q} = (q_1, q_2, q_3)$, which have been mapped to 4-vectors, $(0, \mathbf{q}) = (0, q_1, q_2, q_3)$. Note for pure quaternions a, b, eq. (22) and eq. (23) yield

$$a = (0, \mathbf{a}), \quad b = (0, \mathbf{b}), \qquad ab = (-\mathbf{a}\cdot\mathbf{b}, \mathbf{a}\times\mathbf{b}), \quad (26)$$

$$a^c = (0, -\mathbf{a}) = -a. \quad (27)$$

The quaternion product can be formulated as a matrix multiplication as follows:

$$pq =: \mathcal{A}_L(p)\mathcal{Q}, \quad p \text{ operates on } q \text{ from the left}, \quad (28)$$

$$qp =: \mathcal{A}_R(p)\mathcal{Q}, \quad p \text{ operates on } q \text{ from the right}, \quad (29)$$

where $\mathcal{A}_L(p)$ and $\mathcal{A}_R(p)$ are 4×4 matrices, and $\mathcal{Q} = (q_0, q_1, q_2, q_3)^T$ is the column 4-vector representation of quaternion q. By convention, the matrix multiplication form of the quaternion product (the right-hand side of the above) is defined to act from the left on a column 4-vector. For $p = (p_0, p_1, p_2, p_3)$ the matrices $\mathcal{A}_L(p)$ and $\mathcal{A}_R(p)$ are given by

$$\mathcal{A}_R(p) = \begin{pmatrix} p_0 & -p_1 & -p_2 & -p_3 \\ p_1 & p_0 & p_3 & -p_2 \\ p_2 & -p_3 & p_0 & p_1 \\ p_3 & p_2 & -p_1 & p_0 \end{pmatrix}, \quad \mathcal{A}_L(p) = \begin{pmatrix} p_0 & -p_1 & -p_2 & -p_3 \\ p_1 & p_0 & -p_3 & p_2 \\ p_2 & p_3 & p_0 & -p_1 \\ p_3 & -p_2 & p_1 & p_0 \end{pmatrix}. \quad (30)$$

Quaternions provide a natural coordinate system for $\mathcal{SO}(3)$, the group of proper rotations of 3-space. Thus, they can describe rotations without the singularities of, say, the Euler angles rotation matrices. For the 3-vector $\boldsymbol{r}'$ obtained by a rotation of the vector $\boldsymbol{r}$ via the orthogonal rotation matrix $\mathcal{U}$ we have

$$r' = (0, \mathbf{r}'), \quad r = (0, \mathbf{r}), \quad r' = qrq^c, \quad (31)$$

$$(0, \mathbf{r}') = (q_0, \mathbf{q})(0, \mathbf{r})(q_0, -\mathbf{q}) = (0, \mathcal{U}(q)\mathbf{r}). \quad (32)$$

Using the notation of eq. (30), we can express the rotation matrix as a product of two matrices, each depending linearly on a unit quaternion q ($qq^c = 1$):

$$\begin{pmatrix} 1 & \mathbf{0}^T \\ \mathbf{0} & \mathcal{U}(q) \end{pmatrix} = \mathcal{A}_L(q)\mathcal{A}_R(q^c).$$

The 3×3 rotation matrix $\mathcal{U}$ is given by

$$\mathcal{U}(q) = \begin{pmatrix} q_0^2 + q_1^2 - q_2^2 - q_3^2 & 2(q_1q_2 - q_0q_3) & 2(q_1q_3 + q_0q_2) \\ 2(q_1q_2 + q_0q_3) & q_0^2 - q_1^2 + q_2^2 - q_3^2 & 2(q_2q_3 - q_0q_1) \\ 2(q_1q_3 - q_0q_2) & 2(q_2q_3 + q_0q_1) & q_0^2 - q_1^2 - q_2^2 + q_3^2 \end{pmatrix}. \quad (33)$$

Because $\mathcal{U}$ is orthogonal we have $\mathcal{U}^{-1} = \mathcal{U}^T$. Note that by its construction, $\mathcal{U}(q)$ is a proper rotation whose angle θ and axis $\mathbf{c}$ are seen in the form of q:[21,22]

$$q = (q_0, \mathbf{q}) = (\cos(\theta/2), \sin(\theta/2)\mathbf{c}).$$

It is easy to see that $\{\theta, \mathbf{c}\}$ and $\{-\theta, -\mathbf{c}\}$ produce the same quaternion q and, hence, the same rotation. Also, q and $-q$ produce the same rotation, a fact easily deduced from the form of the rotation matrix $\mathcal{U}(q)$.

Appendix C: The Polynomial Coefficients

We give here the *MAPLE* script that was used for the verification of the two methods, as well as some of the polynomial coefficients;

the expressions for the other coefficients are lengthy and were omitted.

```
> with (LinearAlgebra):
> R:=Matrix([[R11,R12,R13], [R21,R22,R23],[R31,R32,R33]]):
> S3:=R.Transpose(R):
> P3 := CharacteristicPolynomial(S3,z):
> P33:=coeff(P3,z,3);
                                  P33:=1
> P32:=coeff(P3,z,2);
P32:= -R12^2 - R33^2 - R31^2 - R32^2 - R23^2 - R22^2 - R21^2 - R13^2 - R11^2
> P31:=coeff(P3,z,1):
> P30:=coeff(P3,z,0):
> S4:=Matrix([[R11+R22+R33, R23-R32,R31-R13,R12-R21],
> [R23-R32, R11-R22-R33,R12+R21,R13+R31],
> [R31-R13,R12+R21,-R11+R22-R33,R23+R32],
> [R12-R21,R13+R31,R23+R32,-R11-R22+R33]]):
> P4:=CharacteristicPolynomial(S4,y):
> P44:=coeff(P4,y,4);
                              P44:=1
> P43:=coeff(P4,y,3)/4;
                              P43:=0
> P42:=coeff(P4,y,2)/6;
P42:= -1/3 (R13^2 + R21^2 + R31^2 + R12^2 + R23^2 + R32^2 + R11^2 + R33^2 + R22^2)
> P41:=coeff(P4,y,1)/4;
P41:= 2 R11 (R23 R32 - R22 R33) - 2 R12 (R23 R31 - R21 R33) + 2 R13 (R22 R31 - R32 R21)
> P40:=coeff(P4,y,0):
> exp2:=P32-3*P42;
                              exp2=0
> exp1:=simplify(P31-(9*P42^-P40)/4);
                              exp1:=0
> exp0:=simplify(P30+P41^/4);
                              exp0:=0
```

We note that the last three lines of output provide the verification that the characteristic polynomial of $\mathcal{R}$ is indeed the resolvent cubic for the characteristic polynomial of $\mathcal{F}$, while the expression for $P41$ shows that $4q = -8 \det \mathcal{R}$.

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