Integrating NOE and RDC using semidefinite programming for protein structure determination

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Abstract

We revisit the established problem of protein structure determination from geometrical restraints from NMR, using convex optimization. It is well-known that the NP-hard distance geometry problem of determining atomic positions from pairwise distance restraints can be relaxed into a convex semidefinite program (SDP). However, in practice the distance restraints are imprecise, and sometimes sparse, for accurate structure determination. Residual dipolar coupling (RDC) measurements provide additional geometric information on the angles between atom-pair directions and axes of the principal-axis-frame. The optimization problem involving RDC is highly non-convex and requires a good initialization even within the simulated annealing framework. In this paper, we model the protein backbone as an articulated structure composed of rigid units. We estimate the rotation of each rigid unit using SDP relaxation that incorporates chirality constraints. The two SDP based methods we propose - RDC-SDP and RDC-NOE-SDP have polynomial time complexity in the number of amino-acids and run efficiently on a regular PC.

We further introduce a statistical tool, the Cramér-Rao bound (CRB) to provide an information theoretic bound on the highest resolution one can hope to achieve when determining protein structure from noisy measurements. Our simulation results show that when the RDC measurements are corrupted by Gaussian noise, for realistic noise magnitude our SDP algorithm attains the CRB. Through such comparison, the utility of CRB for benchmarking other procedures for structure determination in NMR is demonstrated.

Finally, we apply our proposed method in a divide-and-conquer fashion to determine the structure of ubiquitin from experimental distance restraints and RDC measurements obtained in two alignment media.

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1 Introduction

The problem of positioning a set of points from geometrical constraints between them arises naturally when calculating the protein structure from Nuclear Magnetic Resonance (NMR) spectroscopy data. The best established structural calculation methods are based on the through-space dipole interaction of the Nuclear Overhauser Effect (NOE) [33, 63]. The NOE gives rise to qualitative distance constraints of the following form

$$d_{nm}^{\text{lower}} \leq \| \mathbf{x}_n - \mathbf{x}_m \|_2 \leq d_{nm}^{\text{upper}}$$

(1)

where $\mathbf{x}_n, \mathbf{x}_m$ are the coordinate positions of atoms $n$ and $m$, and $d_{nm}^{\text{lower}}, d_{nm}^{\text{upper}}$ are lower and upper bounds, respectively, for the Euclidean distance between these atoms. Since the NOE interaction between a pair of atoms scales as $r^{-6}$, it is not possible to have constraints for pairs of atoms that are more than 6 Å apart are too small and imprecise for use. For large molecules, the extraction of NOE restraints through resonance assignment is difficult and often leads to missing, ambiguous, or incorrect NOE distance measurements. Hence the inverse problem of positioning from distance constraints alone, also known as the distance geometry problem, can be challenging and even ill-posed [64]. While multiple ingenious and interesting methods are used to address these issues [40, 47], it is still not easy to obtain a fully automated structural determination software based on NOE alone. As noted by [40], the process of filtering out the wrong NOE restraints may require manual intervention.

Residual dipolar coupling (RDC) measurements provide additional geometrical information involving pairs of atoms [55, 53]. RDC can be measured when the molecule ensemble in solution exhibits partial alignment with the magnetic field in an NMR experiment. The RDC measurements have relatively high precision due to the slower $1/r^3$ decay of interaction, and it provides alignment information involving pairs of atoms and the magnetic field. Under some technical assumptions, the RDC measurement $r_{nm}$ for atoms $n$ and $m$ is related to the positions of these atoms in the following way:

$$r_{nm} = \frac{(\mathbf{x}_n - \mathbf{x}_m)^T \mathbf{S} (\mathbf{x}_n - \mathbf{x}_m)}{d_{nm}^2},$$

(2)

where $d_{nm} = \| \mathbf{x}_n - \mathbf{x}_m \|_2$ is the distance between atoms $n$ and $m$, and $\mathbf{S}$ is a $3 \times 3$ symmetric matrix with vanishing trace. The matrix $\mathbf{S}$ is called the Saupe alignment tensor. Roughly speaking, the eigenvectors of the Saupe tensor encode how the molecule aligns with respect to the magnetic field. Performing NMR experiments at different alignment conditions may lead to different Saupe tensors, and consequently different RDC measurements. While in principle both the Saupe tensor and the molecular structure are unknown, in this paper we assume that $\mathbf{S}$ can be estimated a-priori [38, 67] and our goal is to determine the atom positions given $\mathbf{S}$. We primarily focus on protein backbone structure determination from RDC data. For detailed exposition of RDC and the Saupe tensor, we refer readers to the appendix and to [37, 7, 54].

The constraints we described so far are in terms of the Cartesian coordinates of the atoms. However, a protein can be viewed as an articulated structure which is composed of rigid planes and bodies that are chained together via hinges [26]. As we will see in later sections, the atom coordinates can therefore be expressed in terms of rotations.
associated with the rigid units. The determination of the rotations from RDC and NOE then provides the protein structure.

### 1.1 Existing Approaches

Most approaches to the structural determination problem apply a global optimization technique to obtain the global minima of a non-convex “energy” function. The energy function includes pseudo-potential terms that restrain the pairwise interatomic distances (NOE), dihedral angles \( J \)-coupling), packing (van der Waals interactions), and orientation with respect to a global magnetic field (RDC).

The mainstream approach to minimize the energy function is based on simulated annealing [31, 26, 15, 48]. In simulated annealing, the “tunneling” mechanism pushes the solution out of a local minimum with a certain probability and the procedure can be run for a long period of time in order to increase the chances of escaping local minima. In principle, this gives simulated annealing the versatility to deal with arbitrary non-convex energy functions, in particular, one can consider the following non-convex RDC potential term:

\[
\left( r_{nm} - \frac{(x_n - x_m)^T S (x_n - x_m)}{d_{nm}^2} \right)^2
\]

This RDC potential term yields, however, a rugged energy landscape with sharp local minima that hinders the success of finding the correct conformation in the absence of a good initial structure [14, 5]. For example, [41] reports that direct minimization of the RDC potential using simulated annealing can yield structures that are as much as 20 Å away from the correct structure. When using simulated annealing, a popular approach to protein structure determination from RDC is using the backbone constraints through molecular fragment replacement (MFR) [32]. MFR finds homologous short fragments of the protein in the Protein Data Bank with the aid of RDC and chemical shifts. The fragments are then merged together to form an initial structure that will be locally refined by simulated annealing. However, using existing structures as initialization leads to model bias. Moreover, there is still no guarantee that the initialization is good enough to avoid getting stuck at a local minima.

Besides stochastic optimization, a number of deterministic approaches based on branch and prune [65, 13] and dynamic programming [41] have been proposed more recently to find the globally optimal backbone structure. In particular, RDC-ANALYTIC [58, 59, 65] exploits that in the presence of two RDC measurements per amino-acid, the torsion angles that determine the orientation of an amino-acid have 16 possible value sets, and a solution tree with a total of \( 16^M \) possible structures can be built sequentially for a protein with \( M \) amino-acids. The main advantage of branch and prune type methods is their ability to deal with sparse RDC datasets when used with an efficient adjunct pruning device such as the Ramachandran plot [43] and NOE. It can also return multiple low-energy solutions when the protein has certain flexibility [56]. The dynamic programming approach [41] attempts to improve the robustness of the solution in tree searching based methods. However, as pointed out by the authors, it cannot readily incorporate additional information such as dihedral angles and distance restraints to improve the solution quality. Another approach with a similar flavor to the
tree-searching based methods, REDCRAFT [11], performs Monte-Carlo sampling of the torsion angles of a protein based on the Ramachandran distribution. RDC measurements are then used to select the possible torsion angles. In general, the methods based on building a conformation space and pruning the unwanted conformations can lead to slow running times. Both REDCRAFT and RDC-ANALYTIC need an hour or two to solve for the structure of typical size protein.

A separate line of research is based on convex relaxation, in which the minimization of the non-convex energy function is replaced by that of a convex surrogate function. When the global optimum of the convex surrogate problem coincides with the global optimum of the original non-convex problem, the solution can be efficiently recovered via convex optimization. For the distance geometry problem, semidefinite programming (SDP) relaxations [51, 6, 18] have been proposed. Under certain conditions on the distance measurements, it is shown that the solution to the NP-hard [46] distance geometry problem can be computed in polynomial time [51]. Since the introduction of the SDP relaxation, numerous efforts have been made for its computational speedup using additional relaxation [60], divide-and-conquer procedures [34, 17], and facial reduction [1]. While these methods are highly accurate in the presence of abundant distance restraints and do not suffer from local minima issues, their performance is unsatisfactory when lacking sufficient NOE measuremets (especially for large proteins due to spin diffusion [42]). In such cases, it is crucial to refine the solution obtained by SDP relaxation by minimizing the original non-convex energy using another method such as simulated annealing.

1.2 Scope of Approach

We limit our attention to the calculation of protein backbone structure, leveraging the RDC and NOE measurements for the backbone. Unlike previous convex relaxation approaches that focused solely on distance constraints, in this paper we propose an SDP relaxation for backbone structure determination that simultaneously incorporates both NOE and RDC measurements. An additional advantage of this combination method is that it can provide accurate solutions even when using RDC alone. We believe our proposed SDP algorithm provides a solution to the Open Problem posed in [20, Chapter 36]: “Use SDP and the concept of distance geometry with angle restraints to model RDC-based structure determination.”

Our algorithmic contribution is that we solve the non-convex structural calculation problem by relaxing the search space to a set of positive semidefinite matrices (PSD). Numerically, our proposed methods recover the optimal solution exactly when there is no noise in the RDC, and stably when noise is added to the RDC. In some sense, the structural calculation problem from RDC measurements of the form (2) can be regarded as the distance geometry problem in a metric space (corresponding to the Saupe tensor) different from the standard Euclidean space. Since the convex relaxations in [51, 6] proposed for the distance geometry problem only involve the Gram matrix (inner product matrix) [27] of the atom coordinates in the Euclidean space, these methods do not readily generalize to deal with RDC measurements that come from different inner product spaces. Such complication gives rise to the open problem in [20] and our idea is to use a convex relaxation that involves outer products of the atom coordinates to solve
the distance geometry problem in multiple inner product spaces. We further exploit the fact that a protein backbone is better viewed as multiple rigid units that are chained together, rather than just a loose set of points. The coordinates of the atoms can thus be determined by the rotations of these rigid units. Our convex-relaxed optimization problem explicitly solves for the rotations of individual units jointly instead of the atom coordinates. This has the advantage of lowering the number of variables and allowing facile incorporation of chirality constraints.

Unlike existing optimization approaches in torsion angle space [26] with RDC measurements alone, the cost and the constraints in our formulation are separable in the optimization variables (the rotations), i.e. each term in the cost and constraints only depends on a single rotation. This leads to an extremely efficient convex program- RDC-SDP with running time of about an order of magnitude faster than existing toolboxes that use RDC for de novo calculation of the protein backbone [11, 65]. This is rather remarkable as the computational problem of determining the orientations has its domain on the product manifold of special orthogonal matrices, with a search space that is non-convex and exponential in size. Fast and accurate determination of the initial structure could have potential applications in quick validation of backbone and NOE resonance assignment [25, 66] or refining Saupe tensor estimate through alternating minimization. To include both RDC and NOE restraints, we propose a different SDP - RDC-NOE-SDP, at the expense of increasing the running time. We also tested the algorithms in calculating the structure of ubiquitin fragments from experimental RDC and NOE data deposited in the Protein Data Bank (PDB). We successfully computed the backbone structure for short fragments of ubiquitin (each consisting of 12 amino acids on average) up to 0.6 Å resolution. To further assess the quality of our structural calculation procedure, we introduce a classical statistical tool, the Cramér-Rao lower bound, which provides the minimum possible variance of the estimated atomic coordinates for a given noise model on the RDC and NOE. While our method fails to achieve the CRB in the presence of only RDC measurements, it does attain the CRB when aided by NOE restraints.

It is in general difficult to determine the backbone structure of an entire protein at once using an RDC-based algorithm, since along the chain of rigid units there are typically some sites having only a few or no RDC being measured. Even with multiple RDCs in different orientating media, the potential for non-unique solutions remains [21]. Therefore we divide up the protein backbone and run RDC-SDP or RDC-NOE-SDP on each of the fragments. As a separate contribution, we propose an additional SDP that jointly solves for the relative translations of all fragments using inter-fragment NOE in order to form the global structure of the protein. In [65], a grid search is employed to find the translation that satisfies the NOE restraints between two fragments and the backbone is greedily and sequentially constructed based on the estimated pairwise translations. Our method, on the other hand, pieces all fragments at once rather than sequentially, and may therefore require fewer NOE measurements.

1.3 Broader Contexts beyond structural biology

In a broader context, our solution to the protein structuring problem presents a general strategy for determining the pose of an articulated structure, a common problem that
arises in robotics and computer vision [22, 3]. The way we model the articulated structure from rotation matrices results in a cost function and constraints that are separable in the rotations, which in turn facilitates subsequent optimization. We also strengthen the convex relaxation proposed in [4], which originally intends to minimize quadratic functions involving orthogonal matrices, in order to deal with special orthogonal transformations. This is particularly meaningful in practical applications as rigid units in an articulated structure do not usually undergo a reflection. As shown by our numerical experiments, the additional constraints specific to the special orthogonal group greatly enhance noise stability.

1.4 Organization

The rest of the paper is organized as follows. In Section 2, we formulate the problem of backbone structure determination from RDC and NOE as a problem of finding the pose of an articulated structure. In Section 3, we describe a semidefinite program (SDP) for solving optimization problems involving quadratic functions of rotation and we apply such SDP in Section 4 to determine the pose of an articulated structure. In Section 5, we propose an alternate SDP to find the relative translations between fragments, when estimating the full protein structure directly is not possible. In Section 6, we present the numerical results with synthetic data and also for experimental data of ubiquitin (PDB ID: 1D3Z [16]). In Section 9, we give a brief description of the RDC and we introduce the Cramér-Rao lower bound for the structure determination problem from RDC.

1.5 Notation

We use $I_d$ to denote the identity matrix of size $d \times d$. We frequently use block matrices built from smaller matrices. For a block matrix $A$, we use $A_{ij}$ to denote its $(i, j)$-th block, $A(p, q)$ to denote its $(p, q)$-th element, and $A_i$ to denote the $i$-th column of $A$. The size of the blocks will be made clear from the context. We use $A \succeq 0$ to denote that $A$ is positive semidefinite [10], that is, $u^T A u \geq 0$ for all $u$. We use $O(d)$ to denote the group of $d \times d$ orthogonal matrices. We use $|x|_2$ to denote the Euclidean norm of $x \in \mathbb{R}^n$ ($n$ should be clear from the context). We use vec$(A)$ to denote the vectorization of a matrix $A$, and mat$(a)$ to denote the inverse procedure. In this paper we only use the mat$(\cdot)$ operation to form a $3 \times 3$ matrix from a column vector in $\mathbb{R}^9$. We denote the trace of a square matrix $A$ by Tr$(A)$. The Kronecker product between matrices $A$ and $B$ is denoted by $A \otimes B$. The all-ones vector is denoted by 1 (the dimension should be obvious from the context). The $i$-th canonical basis vector is denoted as $e_i$.

2 Problem Formulation

2.1 Articulated structure and protein backbone

An articulated structure is a chain of rigid units where one unit is “chained” together with the next unit with non-overlapping joints (Figure 1a). When there is a joint between two consecutive units, the relative translation is fixed but not the relative rotation. If
there are two non-overlapping joints between two consecutive units, there is only one
undetermined degree of freedom corresponding to a rotation around the axis defined
by the two joints. This structure is also referred to as the body-hinge framework [62]
in rigidity theory. Let an articulated structure be composed of \( K \) points residing in \( M \)
rigid units. For such structure, we define a set of points \( \{ J_i \}_{i=1}^M \) as the joints between
the units where \( J_i \in \{ 1, \ldots, K \} \). The \( i \)-th unit is joined to the \( (i-1) \)-th unit at \( J_i \). Since
the coordinates in each unit are known a-priori up to a rigid transformation, we then use
\( x_k^{(i)} \) to denote the location of point \( k \) in the local coordinate system of the \( i \)-th rigid unit.
Notice that due to the rigid motion ambiguity, a Euclidean transform needs to be applied
to each of the local coordinates \( x_k^{(i)} \) for each \( i \) in order to form the global structure.

Let \( \zeta_k^{(i)} \) be the global coordinate of point \( k \) in the \( i \)-th unit. For an articulated
structure, it is possible to represent the global coordinates \( \zeta_k^{(i)} \) using the rotations
\( R_i, i = 1, \ldots, M \) associated with the \( M \) rigid units. For \( i = 1 \), we let
\[
\zeta_k^{(1)} = R_1 (x_k^{(1)} - x_{J_1}^{(1)}) + t
\] (4)
which amounts to orienting the first rigid unit with \( R_1 \) and adding a translation so that
\( \zeta_k^{(1)} \) are placed at \( t \in \mathbb{R}^3 \). The coordinates for the \( i = 2 \) rigid unit can be obtained as
\[
\zeta_k^{(2)} = R_2 (x_k^{(2)} - x_{J_2}^{(2)}) + \zeta_k^{(1)}
\] (5)
The above operations ensure that the \( i = 2 \) rigid unit is jointed to the \( i = 1 \) rigid unit
at joint \( J_2 \), since one can verify that \( \zeta_{J_2}^{(2)} = \zeta_{J_2}^{(1)} \). The same reasoning implies that in
general the recursive relationship
\[
\zeta_k^{(i)} = R_i (x_k^{(i)} - x_{J_i}^{(i)}) + \zeta_k^{(i-1)}
\] (6)
should hold. Applying induction to (6) results
\[
\zeta_k^{(i)} = R_i (x_k^{(i)} - x_{J_i}^{(i)}) + \sum_{s=1}^{i-1} R_s (x_{J_s}^{(s)} - x_{J_s}^{(s)}) + t.
\] (7)
The coordinate of each atom is thus expressed as a linear combination of the rotations
\( R_i \)'s and a global translation \( t \). As mentioned previously, when there are hinges in the
articulated structure the rotations have fewer degrees of freedom. To incorporate the
hinges, we define another set of joints \( \{ H_i \}_{i=1}^M \) where \( \{ H_i \}_{i=1}^M \cap \{ J_i \}_{i=1}^M = \emptyset \). Let \( \psi_{kl}^{(i)} \) be
the unit vector between the pair of points \( (k, l) \) in the frame of the \( i \)-th rigid unit. To
ensure two consecutive rigid bodies stay chained together by a hinge, \( R_i \)'s should satisfy
the hinge constraints
\[
R_i \psi_{Hi,l}^{(i)} = R_{i-1} \psi_{Hi,l}^{(i-1)}, \quad i = 2, \ldots, M.
\] (8)
Using the above framework, we can reduce the problem of finding atomic coordinates of a protein backbone into a problem of finding the special orthogonal transforms. This is because the protein backbone can be modeled as an articulated structure composed of peptide planes and CA-bodies. As depicted in Figure 1b, a peptide plane is a
2D rigid plane consisting atoms from two consecutive amino acids: CA, C, O from one amino acid and H, N, CA from the next amino acid. The CA-body is a 3D rigid body consisting of five atoms CA, N, C, HA and CB all coming from one amino acid. The bonds (N, CA), (C, CA) act like hinges between the rigid units.

Figure 1: Upper: Example of an articulated structure with joints with indices $J_i$’s (Red dots) and $H_i$’s. The hinges are represented by black bars in the figure. (Lower: Protein backbone consists of peptide planes and CA bodies. These rigid units are chained together at the bonds (N, CA) and (C, CA).
2.2 RDC data

In the setting of calculating protein structure, the RDC measurements described in Section (2) can be used to constrain the rotation for each rigid unit. Within each rigid unit, in principle all pairs of isotope-labeled atoms except those involving oxygen, O, can give rise to RDC, although in practice only a subset of these pairs have their RDC measured. Suppose \( N \) Saupe tensors for the protein in \( N \) different alignment media have been predetermined. In the \( j \)-th alignment media, the RDC measurements for the \( i \)-th rigid unit between the pair of atoms \((n,m)\), denoted \( r_{nm}^{(j)} \), can be modeled in the following way:

\[
r_{nm}^{(j)} = v_{nm}^{(i)} R_i^T S^{(j)} R_i v_{nm}^{(i)}, \quad (n,m) \in E_{RDC_i},
\]

\(i = 1, \ldots, M, \quad j = 1, \ldots, N.
\]

(9)

The set \( E_{RDC_i} \) is the set of edges that give rise to RDC in the \( i \)-th rigid unit, and \( S^{(j)} \) denotes the Saupe tensor in alignment media \( j \). The orientation of the peptide planes and CA-bodies can be obtained by solving equation (9) subject to the hinge constraint (8).

Due to experimental errors in measuring the RDC, (9) is only satisfied approximately, and orientations can be estimated by minimizing the following cost

\[
\sum_{i=1}^{M} \sum_{j=1}^{N} \sum_{(n,m) \in E_{RDC_i}} |v_{nm}^{(i)} R_i^T S^{(j)} R_i v_{nm}^{(i)} - r_{nm}^{(j)}|^p
\]

subject to (8). In the cost function (10) each bond is counted once, including bonds that lie in both the peptide plane and the CA-body (e.g., bond \((C-CA)\)). The choice of the parameter \( p \) depends on the specific noise model, and typical choices are \( p = 2 \) (least squares) and \( p = 1 \) (least unsquared deviations). We show in Section 9.3, the minimization of (10) with \( p = 2 \) corresponds to a maximum likelihood estimation when the noise on RDC is Gaussian. If robustness to outlier type noise is required, \( p = 1 \) can be used instead. The difficulty of minimizing target function (10) lies in the non-convex nature of both the cost and domain. Therefore, RDC measurements are typically used when refining an existing, high quality structure derived from solving the distance geometry problem from NOE or from homology modeling [14].

2.3 NOE data

We now rewrite the distance constraints in (1) in terms of the rotations. Instead of working with bounds on distances, we use bounds on squared distances, for reasons that will become apparent in Section 3. Assuming \( i > j \), from (7) we have

\[
\|\xi_m^{(i)} - \xi_n^{(j)}\|^2 = \|R_i(x_m^{(i)} - x_j^{(j)}) - R_j(x_n^{(j)} - x_j^{(j)})\| + \sum_{s=j+1}^{i-1} \|R_s(x_{s,j+1}^{(s)} - x_j^{(j)})\|^2.
\]

(11)

In this way, we write squared distances between two atoms, necessary for expressing NOE measurements, as quadratic functions of \( R_i \)'s. To satisfy the constraint (1), we can
minimize
\[ \max((d_{\text{low}}^2 - \| \xi_m^{(i)} - \xi_n^{(j)} \|^2_2)^p + \max(\| \xi_m^{(i)} - \xi_n^{(j)} \|^2_2 - (d_{\text{up}}^2)^2, 0) )^p \]  

where the choice of \( p \) again depends on the noise model. In practice, the NOE measurements for the backbone atoms are more reliable and can also be treated as relatively hard constraints.

3 Quadratic problem on \( \mathbb{O}(3) \) and \( \mathbb{SO}(3) \)

In this section, we introduce a novel convex relaxation to optimization problems of the form
\[ \min_{\mathbf{R}} f(\text{vec}(\mathbf{R})\text{vec}(\mathbf{R})^T) \quad \text{such that } \mathbf{R} \in \mathbb{SO}(3) \]  

where \( f \) is a convex function, upon which our method for estimating pose of an articulated structure relies. We note that a convex relaxation has been proposed previously in [4] to a close relative of problem (13), namely
\[ \min_{\mathbf{R}} f(\text{vec}(\mathbf{R})\text{vec}(\mathbf{R})^T) \quad \text{such that } \mathbf{R}^T \mathbf{R} = \mathbf{R} \mathbf{R}^T = \mathbf{I}_3, \]  

i.e. such that \( \mathbf{R} \) belongs to the orthogonal group. However, since we consider the group of \( \mathbb{SO}(3) \) instead of the orthogonal group we can further strengthen the relaxation in [4] by relating matrices in \( \mathbb{SO}(3) \) to their quaternion representation. Before proceeding we introduce some notations. The linear operator \( \mathcal{R} : \mathbb{R}^{9\times9} \rightarrow \mathbb{R}^{3\times3} \) is defined as
\[ \mathcal{R}(\mathbf{X})(i, j) = \text{Tr}(\mathbf{X}_{ij}) \]  

for any \( \mathbf{X} \in \mathbb{R}^{9\times9} \) where \( \mathbf{X}_{ij} \) denotes the \((i, j)\)-th \( 3 \times 3 \) block in \( \mathbf{X} \). The operator \( \mathcal{R} \) enables writing the product
\[ \mathbf{A}^T \mathbf{B} = \mathcal{R}(\text{vec}(\mathbf{A})\text{vec}(\mathbf{B})^T). \]  

for any two \( 3 \times 3 \) matrices \( \mathbf{A} \) and \( \mathbf{B} \). The linear operator \( \mathcal{L} : \mathbb{R}^{9\times9} \rightarrow \mathbb{R}^{3\times3} \) is defined as
\[ \mathcal{L}(\mathbf{X}) = \sum_{i=1}^{3} X_{ii}. \]  

Notice that for any \( 3 \times 3 \) matrices \( \mathbf{A}, \mathbf{B} \),
\[ \mathbf{A} \mathbf{B}^T = \mathcal{L}(\text{vec}(\mathbf{A})\text{vec}(\mathbf{B})^T). \]  

3.1 Convex relaxation: quadratic problem on \( \mathbb{O}(3) \)

We first discuss the instance of solving equation (14) where we only consider variables in the orthogonal group \( \mathbb{O}(3) \). In order to derive a relaxation of (14), we define a new variable
\[ \mathbf{Y} = \text{vec}(\mathbf{R})\text{vec}(\mathbf{R})^T \]  

\[ 10 \]
that consists of all degree 2 monomials of the elements of $\mathbf{R}$. To enforce orthogonality, we add the constraints

$$
\begin{align*}
I_3 &= \mathbf{R}\mathbf{R}^T = \mathcal{L}(\mathbf{vec}(\mathbf{R})\mathbf{vec}(\mathbf{R})^T) = \mathcal{L}(\mathbf{Y}), \\
I_3 &= \mathbf{R}^T\mathbf{R} = \mathcal{R}(\mathbf{vec}(\mathbf{R})\mathbf{vec}(\mathbf{R})^T) = \mathcal{R}(\mathbf{Y})
\end{align*}
$$

(20)

Although at this point the two constraints are redundant as $\mathbf{R}^T\mathbf{R} = I_3$ if and only if $\mathbf{R}\mathbf{R}^T = I_3$, its usefulness will be apparent when we apply convex relaxation. Using the newly defined variable $\mathbf{Y}$, we first consider rewriting the problem (14) as

$$
\begin{align*}
\min_{\mathbf{Y}, \mathbf{R}} & f(\mathbf{Y}) \\
\text{s.t.} & \mathcal{L}(\mathbf{Y}) = \mathcal{R}(\mathbf{Y}) = I_3, \\
& \mathbf{Y} = \mathbf{vec}(\mathbf{R})\mathbf{vec}(\mathbf{R})^T
\end{align*}
$$

(21)

The last constraint is equivalent to $\mathbf{Y} \succeq 0$ and rank($\mathbf{Y}$) = 1. We then drop the rank constraint on $\mathbf{Y}$ and obtain the following SDP relaxation

$$
\begin{align*}
\min_{\mathbf{Y}} & f(\mathbf{Y}) \\
\text{s.t.} & \mathcal{L}(\mathbf{Y}) = \mathcal{R}(\mathbf{Y}) = I_3, \\
& \mathbf{Y} \succeq 0
\end{align*}
$$

(22)

Semidefinite relaxation of this type was presented in [4]. It was further shown that for $f(\mathbf{Y}) = \text{Tr}(\mathbf{A}\otimes\mathbf{B}\mathbf{Y})$ where $\mathbf{A}, \mathbf{B}$ are general symmetric matrices, the non-convex problem in (21) can be solved exactly via this type of relaxation. Notice that if rank($\mathbf{Y}$) = 1 such that $\mathbf{Y} = \mathbf{vec}(\mathbf{R})\mathbf{vec}(\mathbf{R})^T$ for some $\mathbf{R} \in \mathbb{R}^{3 \times 3}$, the constraints $\mathcal{L}(\mathbf{Y}) = \mathcal{R}(\mathbf{Y}) = I_3$ are redundant. This is because $I_3 = \mathcal{L}(\mathbf{Y}) = \mathbf{R}\mathbf{R}^T$ implies $\mathbf{R}^T$ is the inverse of $\mathbf{R}$ leading to $\mathcal{R}(\mathbf{Y}) = \mathbf{R}^T\mathbf{R} = I_3$. This argument does not work if $\mathbf{Y} \neq \mathbf{vec}(\mathbf{R})\mathbf{vec}(\mathbf{R})^T$ for some $\mathbf{R} \in \mathbb{R}^{3 \times 3}$ hence $\mathcal{L}(\mathbf{Y}) \neq \mathbf{R}\mathbf{R}^T$ and $\mathcal{R}(\mathbf{Y}) \neq \mathbf{R}^T\mathbf{R}$. In fact for the following $\mathbf{Y}$ with rank($\mathbf{Y}$) = 3 where

$$
\mathbf{Y}_{ij} = \begin{bmatrix}
1 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}
$$

$i = 1, 2, 3$, and $\mathbf{Y}_{ij} = 0$ for $i \neq j$,

$\mathbf{Y} \succeq 0$ satisfies $\mathcal{L}(\mathbf{Y}) = I_3$ but $\mathcal{R}(\mathbf{Y}) \neq I_3$. Therefore after the rank relaxation both the constraints in (20) are needed and they are not redundant.

### 3.2 Convex relaxation: quadratic problem on $\mathbb{SO}(3)$

For physical problems, often we can further reduce the search space for $\mathbf{R}$ from $\mathbb{O}(3)$ to $\mathbb{SO}(3)$ due to chirality constraints. It would be beneficial if we can include the constraint $\det(\mathbf{R}) = 1$. We have seen that the orthogonality of $\mathbf{R}$ can be enforced through linear constraints in (22) due to the fact that any degree 2 polynomial in $\mathbf{R}$ can be expressed as a linear function of $\mathbf{Y} = \mathbf{vec}(\mathbf{R})\mathbf{vec}(\mathbf{R})^T$. However, the determinant constraint involves a degree 3 polynomial in the entries of $\mathbf{R}$ hence it cannot be expressed by the variables
in (22). We therefore enforce chirality constraints by relating the columns of \( \mathbf{R} \) through the cross products. Let

\[
\text{Cross}(\mathbf{A}) := \begin{bmatrix}
A(2,3) - A(3,2) \\
A(3,1) - A(1,3) \\
A(1,2) - A(2,1)
\end{bmatrix}
\] (23)

for any \( A \in \mathbb{R}^{3 \times 3} \). For two vectors \( \mathbf{v}_1, \mathbf{v}_2 \in \mathbb{R}^3 \), \( \text{Cross}(\mathbf{v}_1 \mathbf{v}_2^T) = \mathbf{v}_1 \times \mathbf{v}_2 \) where \( \mathbf{v}_1 \times \mathbf{v}_2 \) denotes the cross products between \( \mathbf{v}_1 \) and \( \mathbf{v}_2 \). For a rotation matrix \( \mathbf{R} \in \mathbb{SO}(3) \), the following constraints

\[
\begin{align*}
\mathbf{R}_1 &= \mathbf{R}_2 \times \mathbf{R}_3 = \text{Cross}(\mathbf{Y}_{23}), \\
\mathbf{R}_2 &= \mathbf{R}_3 \times \mathbf{R}_1 = \text{Cross}(\mathbf{Y}_{31}), \\
\mathbf{R}_3 &= \mathbf{R}_1 \times \mathbf{R}_2 = \text{Cross}(\mathbf{Y}_{12})
\end{align*}
\] (24)

specify the “handedness” of the coordinate frame established by \( \mathbf{R} = [\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3] \). Here \( \mathbf{Y} = \text{vec}(\mathbf{R}) \text{vec}(\mathbf{R})^T \) and \( \mathbf{Y}_{ij} \) is the \((i,j)\)-th \( 3 \times 3 \) block of \( \mathbf{Y} \). Let

\[
\mathcal{F}(\mathbf{Y}) := \begin{bmatrix}
\text{Cross}(\mathbf{Y}_{23}) & \text{Cross}(\mathbf{Y}_{31}) & \text{Cross}(\mathbf{Y}_{12})
\end{bmatrix},
\]

problem in (13) can be written equivalently as

\[
\begin{align*}
\min_{\mathbf{Y}, \mathbf{R}} f(\mathbf{Y}) \\
\text{s.t.} & \quad \mathcal{L}(\mathbf{Y}) = \mathcal{F}(\mathbf{Y}) = \mathbf{I}_3, \\
& \quad \mathbf{Y} = \text{vec}(\mathbf{R}) \text{vec}(\mathbf{R})^T, \\
& \quad \mathbf{R} = \mathcal{F}(\mathbf{Y})
\end{align*}
\] (25)

Since the constraint \( \mathbf{Y} = \text{vec}(\mathbf{R}) \text{vec}(\mathbf{R})^T \) is not convex, we replace it with \( \mathbf{Y} \succeq \text{vec}(\mathbf{R}) \text{vec}(\mathbf{R})^T \), which results in a convex relaxation for quadratic problems on \( \mathbb{SO}(3) \)

\[
\begin{align*}
\min_{\mathbf{Y}, \mathbf{R}} f(\mathbf{Y}) \\
\text{s.t.} & \quad \mathcal{L}(\mathbf{Y}) = \mathcal{F}(\mathbf{Y}) = \mathbf{I}_3, \\
& \quad \mathbf{Y} \succeq \text{vec}(\mathbf{R}) \text{vec}(\mathbf{R})^T, \\
& \quad \mathbf{R} = \mathcal{F}(\mathbf{Y})
\end{align*}
\] (26)

Interestingly in (26), the set of admissible \( \mathbf{R} \) is in the convex hull of the rotation matrices. This can be seen by relating the elements in \( \mathbb{SO}(3) \) to their unit quaternion representations, as shown in the appendix in Section 9.2.

We note that in [19], a similar convex relaxation using the cross products is proposed to optimize quadratic functions with their domain being the Stiefel functions.

\[
\{ \mathbf{Q} \in \mathbb{R}^{3 \times 2} \mid \mathbf{Q}^T \mathbf{Q} = \mathbf{I}_2 \}.
\] (27)

As in (21), such an optimization problem is convex in the PSD variable

\[
\mathbf{X} = \text{vec}(\mathbf{Q}) \text{vec}(\mathbf{Q})^T \succeq 0
\] (28)
if the rank-1 constraint on \( \mathbf{X} \) is to be dropped. The orthogonality of the columns of \( \mathbf{Q} \)
can be enforced through placing linear constraints on \( \mathbf{X} \), i.e.

\[
\text{Tr}(\mathbf{X}_{ij}) = \begin{cases} 
1 & \text{if } i = j \\
0 & \text{if } i \neq j 
\end{cases} \tag{29}
\]

where \( \mathbf{X}_{ij} \) denotes the \((i, j)\)-th \(3 \times 3\) block of \( \mathbf{X} \). In [19], an additional vector

\[
\mathbf{Q}_3 := \mathbf{Q}_1 \times \mathbf{Q}_2 = \text{Cross}(\mathbf{X}_{12}) \tag{30}
\]

is employed to further tighten this convex relaxation. Since the rows of the matrix \([\mathbf{Q}_1, \mathbf{Q}_2, \mathbf{Q}_3]\) are

\[
[\mathbf{Q}_1, \mathbf{Q}_2, \mathbf{Q}_3] [\mathbf{Q}_1, \mathbf{Q}_2, \mathbf{Q}_3]^T \preceq I_3, \tag{31}
\]

implying the following convex constraint

\[
\mathbf{X}_{11} + \mathbf{X}_{22} + \mathbf{Q}_3 \mathbf{Q}_3^T \preceq I_3. \tag{32}
\]

This mimics the first constraint in (20) when dealing with orthogonal matrices. However,
equality cannot be placed on equation (32) since this introduces non-convexity.

4 Convex relaxation for quadratic problem of articulated structures

In this section, we propose two convex relaxations for finding the pose of an articulated
structure. In this case, we need to solve for the rotation of each of the \(M\) rigid units
subject to the hinge constraints in (8). We first define variables

\[
\mathbf{R} = [\mathbf{R}_1, \ldots, \mathbf{R}_M] \in \mathbb{SO}(3)^M \tag{33}
\]

and

\[
\mathbf{Y} = \text{vec}(\mathbf{R})\text{vec}(\mathbf{R})^T. \tag{34}
\]

For convenience of indexing, in this section we view \( \mathbf{Y} \) as a \(M \times M\) block matrix where
\( \mathbf{Y}_{ij} = \text{vec}(\mathbf{R}_i)\text{vec}(\mathbf{R}_j)^T \). It is important to define such a matrix \( \mathbf{Y} \) since the measurements
involve quadratic functions of rotation matrices.

If the rigid units are not chained together, each \( \mathbf{R}_i \) can be solved for via the convex
relaxation proposed in (26). However, in an articulated structure the rigid units are not
independent of each other but related via (8)

\[
\mathbf{R}_i \mathbf{v}_{i\mathbf{H}_i}^{(i)} = \mathbf{R}_{i-1} \mathbf{v}_{i\mathbf{H}_i}^{(i-1)}, \quad i = 2, \ldots, M \tag{35}
\]

which are linear constraints between \( \mathbf{R}_i \) and \( \mathbf{R}_{i-1} \). Therefore all rotations have to be
optimized jointly. We now introduce a few redundant constraints. Equation (8) leads to
constraints on \( \mathbf{Y} \):

\[
\mathbf{v}_{j\mathbf{H}_i}^{(i-1)^T} \mathbf{R}_{i-1}^T \mathbf{e}_i \mathbf{R}_i \mathbf{v}_{j\mathbf{H}_i}^{(i-1)} = \mathbf{v}_{j\mathbf{H}_i}^{(i)^T} \mathbf{R}_i^T \mathbf{e}_i \mathbf{R}_i \mathbf{v}_{j\mathbf{H}_i}^{(i)} \quad \forall k, l = 1, 2, 3, \tag{36}
\]
where \( e_k \)'s are the canonical basis vectors in \( \mathbb{R}^3 \). Writing the constraints using \( Y \) we get

\[
\text{Tr}((v_{j,H_t}^{(i-1)} v_{j,H_t}^{(i-1)T} \otimes e_k e_k^T) Y_{(i-1)(i-1)}) = \text{Tr}((v_{j,H_t}^{(i)} v_{j,H_t}^{(i)T} \otimes e_k e_k^T) Y_{ii}). \quad (37)
\]

In the same spirit, another set of constraints

\[
v_{j,H_t}^{(i-1)} = R_{i-1} R_{i} v_{j,H_t}^{(i)} \quad (38)
\]

can be encoded as

\[
v_{j,H_t}^{(i-1)} = \mathcal{D}(Y_{(i-1)i}) v_{j,H_t}^{(i)} \quad (39)
\]

The redundant constraints (37) and (39) will no longer be redundant when \( Y = \text{vec}(R) \text{vec}(R)^T \) is relaxed to \( Y \succeq \text{vec}(R) \text{vec}(R)^T \).

Now, based on the convex relaxation (26) for the problem involving a single rotation, together with the hinge constraints equations (8), (37) and (39), we propose the following convex relaxation to solve for the rotations for an articulated structure:

\[
\begin{align*}
(P1) \quad \min_{Y,R} f(Y) \quad (40) \\
\text{s.t.} \quad & Y \succeq \text{vec}(R) \text{vec}(R)^T \quad (41) \\
& \mathcal{L}(Y_{ii}) = \mathcal{D}(Y_{ii}) = I_3, \ i \in [1, M] \quad (42) \\
& R_i = \mathcal{D}(Y_{ii}), \ i \in [1, M] \quad (43) \\
& R_{i-1} v_{j,H_t}^{(i-1)} = R_i v_{j,H_t}^{(i)}, \ i \in [2, M] \quad (44) \\
& R_{i-1} v_{j,H_t}^{(i-1)} = \mathcal{D}(Y_{(i-1)ii}) v_{j,H_t}^{(i)}, \ i \in [2, M] \quad (45) \\
& \text{Tr}((v_{j,H_t}^{(i-1)} v_{j,H_t}^{(i-1)T} \otimes e_k e_k^T) Y_{(i-1)(i-1)}) = \text{Tr}((v_{j,H_t}^{(i)} v_{j,H_t}^{(i)T} \otimes e_k e_k^T) Y_{ii}), \ k, l \in [1, 3], \ i \in [2, M] \quad (46)
\end{align*}
\]

Here \( f \) is a convex function determined by the measurements. As before, the relaxation is obtained by changing \( Y = \text{vec}(R) \text{vec}(R)^T \) to (41).

The SDP problem (P1) involves a PSD variable of size \((9M + 1) \times (9M + 1)\). In applications where the convex cost of (P1) can be decomposed as

\[
f(Y) = \sum_{i=1}^{M} f_i(Y_{ii}),
\]

i.e. each term in the cost involves a single rotation, the size of the variable used in (P1) can be further reduced. In this case, we propose the following size-reduced convex
All the constraints of (P2) are implied by the constraints in (P1) except (45). Notice that if the constraint (45) is not included in (P1), then (P2) and (P1) are in fact equivalent under the assumption that the cost function satisfies (47). From a solution $\mathbf{Y}^{\star}_{i}$ of (P2), a solution $\mathbf{Y}^{\star}$ in (P1) can be obtained by simply setting $\mathbf{Y}^{\star}_{ii} = \mathbf{Y}^{\star}_{i}$ and $\mathbf{Y}^{\star}_{ij} = 0$ for $i \neq j$, with the same $\mathbf{R}^{\star}_{i}$ from (P2).

We pause here for a remark about the convex relaxation in (P1). If the function $f$ only depends on $\mathbf{R}^{T}_{i}\mathbf{R}_{j}$ (which is the case when only NOE measurements are provided for protein structural determination), it suffices to use a classic SDP proposed for rotation synchronization problem involving a $3M \times 3M$ rank-3 Gram matrix [50, 17]

$$
\mathbf{G} := \begin{bmatrix}
\mathbf{R}_{1}^{T} \\
\vdots \\
\mathbf{R}_{M}^{T}
\end{bmatrix} \mathbf{R}_{1} \cdots \mathbf{R}_{M}.
$$

(54)

Define the $(i, j)$-th $3 \times 3$ block of $\mathbf{G}$ as $\mathbf{G}_{ij}$, we can minimize $f(\mathbf{G})$ ($f$ is convex) using the Max-Cut type SDP relaxation [23]

$$
\min_{\mathbf{G}} f(\mathbf{G}) \\
\text{s.t. } \mathbf{G} = \mathbf{I}_{3}, \\
\mathbf{G} \succeq 0, \\
\mathbf{v}_{ij}^{(i-1)} = \mathbf{G}_{ij} \mathbf{v}_{ij}^{(i-1)}, i \in [2, M], \\
\text{rank}(\mathbf{G}) = 3 \text{ (relaxed)}.
$$

(55)

In this context of $f$ arising solely from NOE restraints, this program can be used to solve the distance geometry problem. In this case, (P1) is an overly-relaxed convex relaxation as there are many more variables in (P1) compare to (55), with the same number of measurements. In the presence of both RDC and NOE constraints, (P1) is needed instead since the cost depends on individual columns of $\mathbf{R}_{i}$. We note that the problem (55) is embedded in (P1). More precisely, letting $\mathbf{G}_{ij} := \mathbf{R}(\mathbf{Y}_{ij})$, the constraints in (55) are implied by the constraints in (P1). While it is obvious to see this for the relaxation

(P2) $\min_{\mathbf{Y} \geq 0} \sum_{i=1}^{M} f(\mathbf{Y}^{(i)})$ (48)

s.t. $\mathbf{Y}^{(i)} \succeq \text{vec}(\mathbf{R}_{i})\text{vec}(\mathbf{R}_{i})^{T}$, $\mathbf{Z}(\mathbf{Y}^{(i)}) = \mathcal{R}(\mathbf{Y}^{(i)}) = \mathbf{I}_{3}$, $i \in [1, M]$, $\mathbf{R}_{i} = \mathcal{R}(\mathbf{Y}^{(i)})$, $i \in [1, M]$ (50)

$$
\mathbf{R}_{i-1} \mathbf{v}_{ij}^{(i-1)} = \mathbf{R}_{i} \mathbf{v}_{ij}^{(i)}, i \in [2, M],
$$

(51)

$$
\text{Tr}(\mathbf{v}_{jH}^{(i-1)} \mathbf{v}_{jH}^{(i-1)^{T}} \otimes \mathbf{e}_{i} \mathbf{e}_{j}^{T}) \mathcal{R}(\mathbf{Y}^{(i)})
$$

(52)

$$
= \text{Tr}(\mathbf{v}_{jH}^{(i)} \mathbf{v}_{jH}^{(i)^{T}} \otimes \mathbf{e}_{i} \mathbf{e}_{j}^{T}) \mathcal{R}(\mathbf{Y}^{(i)}),
$$

$k, l \in [1, 3]$, $i \in [2, M]$. (53)
linear constraints in (55), to see the PSD-ness of $G$, first let $R^*$ be the adjoint operator of $R$ defined through
\[
\text{Tr}(B^T R^*(A)) = \text{Tr}(A^T R^*(B))
\]
for any $A \in \mathbb{R}^{9 \times 9}$, $B \in \mathbb{R}^{3 \times 3}$. Then
\[
R^*(B) = B \otimes I_3.
\]
$G \succeq 0$ follows from the fact that for any $x \in \mathbb{R}^3$,
\[
x^T G x = \sum_{i=1}^{M} \sum_{j=1}^{M} \text{Tr}(x_i^T R(y_{ij}) x_j) = \sum_{i=1}^{M} \sum_{j=1}^{M} \text{Tr}(Y_{ij} R^*(x_i x_j^T)) = \text{Tr}(Y (xx^T \otimes I_3)) \geq 0 \quad (56)
\]
if $Y \succeq 0$.

### 4.1 RDC-NOE-SDP and RDC-SDP

When solving (P1) in the context of protein structural calculation from RDC and NOE, we name the proposed method *RDC-NOE-SDP*. The RDC cost (10) in terms of $Y$ is defined as
\[
f_{\text{RDC}}(Y) = \sum_{i=1}^{M} \sum_{j=1}^{N} \sum_{E_{\text{RDC}}} \text{Tr}((v_{nm}^{(i)} v_{nm}^{(j)} T \otimes S^{(i)}) Y_{ij}) - r^{(j)}_{nm} |^p. \quad (57)
\]
As for NOE, we simply note that the squared distances $\|\xi_{m}^{(i)} - \xi_{n}^{(i)}\|^2$ for $(m, n) \in E_{\text{NOE}}$ are quadratic in $R_i$’s (see Eq. (11)). Therefore the cost (12) can be written as
\[
f_{\text{NOE}}(Y) = \max((d_{mn}^{(i)})^2 - \text{Tr}(A_{mn} Y), 0)^p + \max(\text{Tr}(A_{mn} Y) - (d_{mn}^{(i)})^2, 0)^p \quad (58)
\]
using some coefficient matrices $A_{mn}$’s.

Given only RDC measurement, we can solve (P2) with the RDC cost target equation (10) to achieve a speed-up through reduction in variable size because the cost $f_{\text{RDC}}(Y)$ is of the form of equation (47). We call this method *RDC-SDP*.

### 4.2 Rounding: projection and manifold optimization

In this section, we detail a *rounding* scheme to extract rotations from the solutions of (P1) and (P2). We first examine the case of rounding from the solution of (P1). Denote the solution to (P1) as $Y^*, R^*$. When we apply the convex relaxation in (P1), it is
possible that $Y^* \neq \text{vec}(R^*)\text{vec}(R^*)^T$. To round, we first apply a rank 1 approximation to $Y^*$ via the eigen-decomposition

$$Y^* = \sum_{i} \lambda_i w_i w_i^T.$$  \hfill (59)

The rank-1 approximation to $Y^*$ is then $y^* y^*^T$, where

$$y^* = \sqrt{\lambda_1} w_1$$  \hfill (60)

and $\lambda_1$ and $w_1$ are the top eigenvalue and eigenvector of $Y^*$. We treat $y^*$ as a vector composed of $M$ blocks of $9 \times 1$ smaller vectors and use $y_i^*$ to denote the $i$-th block of $y^*$. To recover individual rotations, let

$$\hat{R}_i = \arg\min_{R \in O(3)} \|R - \text{mat}(y_i^*)\|_F^2$$  \hfill (61)

where $O(3)$ is the group of orthogonal $3 \times 3$ matrices. For any matrix $A$, its closest orthogonal matrix in Frobenius norm is given by $U V^T$ where the orthogonal matrices $U, V \in \mathbb{R}^{3 \times 3}$ are obtained from the singular value decomposition (SVD) $U \Sigma V^T$ of $A$. Notice that $y^*$ has a sign ambiguity and we choose the sign of $y^*$ such that $\det(\text{mat}(y_i^*)) > 0$ (and hence $\det(\hat{R}_i) > 0$) for the majority of $\det(\text{mat}(y_i^*))$'s. For those $\text{mat}(y_i^*)$ with negative determinants, we use

$$U \text{diag}([1, 1, -1]) V^T$$  \hfill (62)

as the projection of $\text{mat}(y_i^*)$ to the nearest special orthogonal matrix after SVD (also known as Kabsch algorithm [30]). When dealing with clean data, we expect $\det(\text{mat}(y_i^*)) > 0$ for all $i$ with the proper choice of the global sign. Even in the presence of noise, $\det(\text{mat}(y_i^*))$ is rather stable and we have not encountered a case where $\det(\text{mat}(y_i^*))$ turns out to be negative in our numerical simulation study.

A similar rounding procedure can be applied after using (P2). After obtaining the rank-1 approximation $y_i^* y_i^*^T$ to $Y^{(i)*}$, we find $\hat{R}_i$ from

$$\hat{R}_i = \arg\min_{R \in O(3)} \|R - \det(\text{mat}(y_i^*))\text{mat}(y_i^*)\|_F^2.$$  \hfill (63)

Notice that although it is possible to directly round $R_i^*$ obtained from (P1) and (P2), empirically we observe obtaining the rotations from $y_i^*$ is more robust to noise.

For the case when the solutions to (P1) and (P2) are not rank-1, the non-convex problem of finding the rotations of the rigid units is not solved exactly. After rounding there is no guarantee that $\hat{R}_i$ orient the rigid units optimally such that the costs (10) and (12) are minimized. In this case, since the pose recovery problem for an articulated structure is an optimization problem on the product of $SO(3)$ manifolds, we use the manifold optimization toolbox Manopt [9] to refine $\hat{R}_i$ further in order to obtain a solution with a lower cost. However, since ManOpt only handles unconstrained optimization problem on a Riemannian manifold, we have to use the penalty method to handle the hinge constraint (8) of the type $h(R) = 0$ by adding a penalty $(\mu/2)\|h(R)\|_2^2$ with increasing $\mu$. We note that without a good initialization, manifold optimization can easily get stuck in a local minima as it is essentially a gradient descent based approach that descends along the geodesics of a manifold.
4.3 Summary of the structural calculation algorithm

In this subsection we summarize the full procedures of RDC-NOE-SDP for structural calculation. The procedure of RDC-SDP follows similarly. We first solve the convex relaxed program (P1) to find the rotations that orient each rigid unit, under the hinge constraints that chain the rigid units together. Since the solution to (P1) does not necessarily yield transformations that satisfy the special orthogonality constraints, a rounding procedure detailed in Section 4.2 is employed to ensure special orthogonality. Using this approximate solution as a starting point, we further optimize the cost in (P1) locally using the ManOpt toolbox. The estimated rotations are then used to construct the backbone coordinates using the recursive relation introduced in (6), and we denote these coordinates as $\mathbf{\zeta}^{(i)}_k$.

**Algorithm 1 RDC-NOE-SDP**

**Require:**
- Local coordinates $x_k^{(i)}$, $k = 1, \ldots, K$, $i = 1, \ldots, M$, RDC and Saupe tensors in $N$ alignment media, and NOE measurements.

**Ensure:**
- Global coordinates $\mathbf{\zeta}_k^{(i)}$, $k = 1, \ldots, K$, $i = 1, \ldots, M$.

1: Find the solution $Y^*$ to problem (P1) with cost (57) and (58) using CVX.
2: Compute the top eigenvector $y^*$ of $Y^*$. Pick the sign of $y^*$ such that $\det(\text{mat}(y^*_i)) > 0$ for most $\text{mat}(y^*_i)$. Use Kabsch algorithm to project $\text{mat}(y^*_i)$ to $SO(3)$ if $\det(\text{mat}(y^*_i)) < 0$.
3: For $i \in [1,M]$, $\hat{R}_i = \arg\min_{R \in O(3)} \| R - \text{mat}(y^*_i) \|_F^2$. Refine $\hat{R}_i$, $i = 1, \ldots, M$ locally (e.g., using ManOpt).
4: $\mathbf{\zeta}_k^{(1)} = \hat{R}_1(x_k^{(1)} - x_J^{(1)})$, $\mathbf{\zeta}_k^{(i)} = \hat{R}_i(x_k^{(i)} - x_J^{(i)}) + \mathbf{\zeta}_k^{(i-1)}$ for $i \in [2,M]$.

5 Translation Estimation

In the presence of RDC measurements, the backbone conformation of the full protein can be determined from the calculated $R_i$’s, up to a global translation. However, it is usually the case that some of the amino-acid residues contain very few or no RDC’s being measured. While RDC-SDP will certainly fail in these situations, using RDC-NOE-SDP is also undesirable. As mentioned in Section 4, when the NOE set is the main constraint placed on the protein structure, it is unnecessary to use (P1) but instead, a smaller convex relaxation (55) can be used. The convex relaxation in (P1) is typically not tight if the geometric constraints mainly come from the NOE data. In this case we need to break up the protein and calculate the conformations for selected fragments of the protein backbone. Therefore it is necessary to figure out the relative translation between the fragments in order to combine the backbone segments coherently. In this section, we propose a semidefinite relaxation that jointly uses NOE restraints between all
fragments to piece them together. Let there be $F$ fragments. We denote the coordinate of the $k$-th atom in the $i$-th fragment as $z_k^{(i)}$. We note that in this section, the superscript "(i)" is no longer used as the index for rigid peptide plane or CA-body, but as the index of a fragment composed of multiple amino acid residues. The goal is to find $t_1, \ldots, t_F \in \mathbb{R}^3$ such that

$$\left( d_{kl}^{\text{low}} \right)^2 \leq \left\| z_k^{(i)} + t_i - (z_j^{(j)} + t_j) \right\|_2^2 \leq \left( d_{kl}^{\text{up}} \right)^2,$$

(64)

where $(k, l) \in E_{\text{NOE}}$. It should be understood that in this context, $E_{\text{NOE}}$ only contains the NOE distance restraints between the fragments. The squaring of the constraint is important to obtain a semidefinite relaxation to solve for the pairwise translations. Now let

$$T = \begin{bmatrix}
    t_1^T \\
    \vdots \\
    t_N^T \\
    t_1^T \\
    \vdots \\
    t_F^T
\end{bmatrix} \in \mathbb{R}^{(3+F) \times (3+F)}$$

(65)

where $T$ is rank 3 and positive semidefinite. Again, by writing (64) in terms of $T$ and by relaxing the rank 3 constraint for $T$ we can solve for the pairwise translations through the following semidefinite program

\begin{align*}
\text{(P3)} \quad & \min_{T \succeq 0, \epsilon_{kl}^{\text{up}}, \epsilon_{kl}^{\text{low}} \geq 0, (k,l) \in E_{\text{NOE}}} \epsilon_{kl}^{\text{up}} + \epsilon_{kl}^{\text{low}} - \gamma \text{Tr}(T) \\
\text{s.t.} \quad & 2(T(F + 1 : F + 3, i) - T(F + 1 : F + 3, j))^T (z_k^{(i)} - z_j^{(j)}) \\
& + T(i, i) + T(j, j) - 2T(i, j) + \left\| z_k^{(i)} - z_j^{(j)} \right\|_2^2 \\
& \leq \left( d_{kl}^{\text{up}} \right)^2 + \epsilon_{kl}^{\text{up}}, \quad (k, l) \in E_{\text{up}}, \\
& 2(T(F + 1 : F + 3, i) - T(F + 1 : F + 3, j))^T (z_k^{(i)} - z_j^{(j)}) \\
& T(i, i) + T(j, j) - 2T(i, j) + \left\| z_k^{(i)} - z_j^{(j)} \right\|_2^2 \\
& \geq \left( d_{kl}^{\text{low}} \right)^2 - \epsilon_{kl}^{\text{low}}, \quad (k, l) \in E_{\text{low}}, \\
& T(F + 1 : F + 3, F + 1 : F + 3) = I_3, \\
& T1 = 0.
\end{align*}

The last constraint is simply to remove the global translation ambiguity. Instead of using (64) as hard constraints to find pairwise translations that satisfy them, we penalize the violation of such bounds through the cost in (P3). This is necessary because errors in estimating individual fragment coordinates and also ambiguous NOE assignments may cause violations of (64). After obtaining the solution $T^\star$, we simply use $T^\star(F + 1 : F + 3, 1 : F)$ as the translations for the fragments. The extra maximum variance unfolding
type regularization − γ Tr(T) prevents the fragments from clustering too tightly by maximizing the spread of the translations [6].

We conclude this section with a toy example that demonstrates the superiority of joint translation estimation using SDP. For the convenience of illustration, we provide the example in 2D. In order to sequentially assemble the fragments from pairwise distances, it is necessary that there is a pair of fragments where there are at least two distance measurements between them. This is needed to fix the relative translation between the two fragments with two degrees of freedom. In the toy example in Figure 2, this necessary condition for greedy sequential methods is not satisfied, but even so with (P3) we are able to recover the correct positions of the fragments. This property of (P3) is quite important, since in practice there are typically only a few NOE restraints between secondary elements of the protein backbone (with the exception of β strands) [41].

Figure 2: Three fragments in 2D positioned by (P3) using the distance measurements (Blue dotted lines). While it is impossible to determine the translations sequentially with the distance measurement pattern shown here, with (P3) the three fragments can be assembled jointly.

6 Numerical experiments

6.1 Synthetic data

In this section, we present the results of numerical simulations with synthetic data for RDC-SDP and RDC-NOE-SDP. All numerical experiments are run on a Samsung NP940X3G laptop with a Intel(R) Core(TM) i5-4200 2.3GHz CPU and 4 GB of memory. We first describe the noise model in our simulations. Let \( \zeta = [\zeta_1, \ldots, \zeta_K] \in \mathbb{R}^{3 \times K} \) be the ground truth coordinates. We drop the superscript “(i)” when denoting the atom coordinate since the membership of an atom to a rigid unit is immaterial here. Now let \( E_{\text{RDC}} \) be the set of atom pairs with RDC measured, and assume that the RDC
measurements are generated through

\[
r_{nm}^{(j)} = v_{nm}^T S^{(j)} v_{nm} + \sigma \varepsilon_{nm}^{(j)},
\]

\((n, m) \in E_{RDC}, j = 1, 2,\) (66)

where the bond direction \(v_{nm}\) is related to the coordinates \(\zeta_n, \zeta_m\) through

\[
v_{nm} = \frac{\zeta_n - \zeta_m}{\|\zeta_n - \zeta_m\|_2}.
\]

(67)

We assume \(\varepsilon_{nm}^{(j)} \sim \mathcal{N}(0, 1)\) where \(\mathcal{N}(0, 1)\) is the standard normal distribution. While it is quite common for different types of atomic pairs with RDC measured at different levels of uncertainty, in this section we assume \(r_{nm}\)'s are all corrupted by i.i.d. Gaussian noise of same variance \(\sigma^2\) for the noise model introduced in (66).

In this simulation study, we use the \(\alpha\) helix of the protein ubiquitin (residue 24 - residue 33) to generate synthetic RDC data. The data file for the PDB entry 1D3Z contains RDC datasets measured in two alignment media. From the known PDB structure, we determine the two Saupe tensors \(S^{(1)}, S^{(2)}\) in these alignment media and use them for simulation purposes. We simulate synthetic RDC data using the noise model (66) where atom pair directions are obtained from the ground truth PDB model. For this simulation we use the pairs \{\((C, CA), (C, N), (N, H)\)\} from the peptide plane, and \{\((CA, HA), (CA, CB)\)\} from the CA-body to generate RDCs, as the RDCs associated with these pairs are commonly measured. In addition to RDC measurements, we also run the simulation with the aid of 16 NOE restraints on the backbone. The form of NOE restraints is in terms of upper and lower bounds. To measure the quality of a coordinate estimator \(\hat{\zeta}\), we use the Root-Mean-Square-Distance (RMSD)

\[
\text{RMSD} = \sqrt{\frac{\|\hat{\zeta} - \zeta\|^2}{K}}
\]

(68)

where \(\zeta\) is the starting PDB model. We evaluate the RMSD for the atoms CA, CB, C, N, H, O and HA in all amino acids.

We present the simulation results in Figure 3. We simulate RDC noise with \(\sigma \in [0, 5e^{-5}]\). Every data point is averaged over 30 noise realizations of RDC. We compare the scenarios of running (1) RDC-SDP without the chirality constraint (51), (2) RDC-SDP and (3) RDC-NOE-SDP with hard distance constraints provided by NOE, both with and without ManOpt refinement after the \(\mathcal{SO}(3)\) projection step. When there is no noise, for all scenarios RDC-SDP and RDC-NOE-SDP exactly recover the rotations. This is a property that simulated annealing based methods do not enjoy, as even without noise these methods can still suffer from local minima issue. The simulation also highlights the importance of the unit chirality constraint (51), as without such constraint RDC-SDP fails to attain 1 Å RMSD at high noise level. If the chirality constraint is included, we can achieve within 1 Å RMSD even without ManOpt refinement. As expected, the inclusion of NOE measurements in RDC-NOE-SDP can further reduce the RMSD. We also compare the results of various schemes both before and after ManOpt refinement, in order to show that local refinement has limited effect on the solution quality hence it
is crucial to have a high quality initialization. We further compare our results against the Cramér-Rao lower bound. The CRB provides an information-theoretic lower bound for the least possible variance that can be achieved by any coordinate estimator. The derivation of the CRB is given in Section 9.3. With RDC-SDP we are able to attain the CRB for moderate noise levels. In the case of RDC-NOE-SDP the CRB is attained at all noise levels. Here we remark that we slightly abused terminology by referring to the normalized RDC as RDC, where the un-normalized RDC is defined in (72). We emphasize that when $\sigma = 5e-5$, the magnitude of noise on the un-normalized RDC is rather large. For example, since the dipolar coupling constant for the N-H RDC is about $23 \text{ kHz}$, when $\sigma = 5e-5$ the actual noise is $1.15 \text{ Hz}$. This is larger than the typical experimental uncertainty of N-H RDC ($<0.5 \text{ Hz}$) [28].

We also provide a comparison of our methods with the molecular fragment replacement (MFR) method proposed in [5] using the full ubiquitin sequence with 76 amino acids and about 500 backbone atoms. We first give a brief introduction to the MFR method. MFR is an RDC-based method that determines the structure of a protein through finding homologous structures in the PDB for short fragments of the protein. For a short fragment, candidate structures from the PDB are used to construct the coordinates in (2). Then a least-squares procedure detailed in the appendix is used to obtain the Saupe tensor based on the experimentally measured RDC and the candidate structure. If a PDB candidate structure gives a low residual in the least-squares fitting, it will be deemed a structure similar to the protein fragment under inspection. Other experimental information such as chemical shifts can also be compared to the informa-
tion recorded in the database to find a similar structure. The homologous structures for short fragments of the protein are then merged and simulated annealing is applied to further refine the structure based on the RDC measurements. In this numerical study, we start simulated annealing with temperature of 600 K and cool down to 0 K in 30000 steps. For a fair comparison between MFR and our proposed methods, we do not use chemical shift information for the MFR procedure but only RDC and NOE. We again simulate RDC measurements from the noise model in (66) for the bonds \((C, CA)\), \((C, N)\), \((N, H)\), \((CA, HA)\), \((CA, CB)\), with noise levels \(\sigma = 2.5, 5e - 5\). We supplement the RDC with 187 experimentally reported backbone NOE's. For ubiquitin, the experimentally measured backbone NOE restraints have very few violations. The RMSD of five reconstructed ubiquitin fragments, each having 13 amino-acids on average, is reported in Table 1. Here we use the same fragments as in Section 6.2 where experimental data is used to reconstruct the ubiquitin structure. The choice of the fragments will be detailed in Section 6.2 and Table 2. The overall RMSD of the protein backbone is also reported after assembling the five fragments using (P3) in the last column of Table 1. It is shown that the total RMSD obtained from RDC-SDP and RDC-NOE-SDP is significantly lower than the RMSD from the MFR method. Since MFR relies heavily on initialization, when the noise is high, the identification of a wrong homologous structure can severely impact the solution quality of simulated annealing. It is expected that RDC-NOE-SDP outperforms RDC-SDP, at the expense of using more data, as in Figure 3. The total RMSD of the entire backbone is generally higher than the RMSD of the fragments, due to the imprecision of the NOE restraints and error accumulation when assembling the fragments. Here we remark that our simulation does not resemble the full capability of MFR, as we do not consider the use of chemical shift information at this point.

|         | 1     | 2     | 3     | 4     | 5     | Full backbone |
|---------|-------|-------|-------|-------|-------|---------------|
| \(\sigma = 2.5e-5\) |       |       |       |       |       |               |
| RDC-SDP | 0.27  | 0.49  | 0.71  | 0.19  | 0.47  | 1.75          |
| RDC-NOE-SDP | 0.27  | 0.32  | 0.10  | 0.11  | 0.53  | 1.35          |
| MFR     | 1.13  | 1.78  | 0.96  | 1.77  | 2.74  | 2.87          |
| \(\sigma = 5e-5\) |       |       |       |       |       |               |
| RDC-SDP | 0.67  | 0.59  | 1.07  | 0.86  | 2.34  | 2.34          |
| RDC-NOE-SDP | 0.40  | 0.48  | 0.27  | 0.57  | 0.84  | 1.72          |
| MFR     | 1.44  | 2.22  | 1.24  | 2.92  | 2.83  | 4.43          |

Table 1: RMSD (Å) of five ubiquitin fragments using RDC-SDP, RDC-NOE-SDP and MFR from simulated data with noise levels \(\sigma = 2.5e-5\) and \(5e-5\). The residue number in each fragment is reported in Table 2. The results are averaged over 10 noise realizations.

### 6.2 Experimental data

In this section, we present results on the analysis of experimental RDC data obtained in two alignment media for ubiquitin. We only consider the peptide planes and CA-bodies coming from the first 70 amino acids since the last 6 residues are highly flexible and do not contribute to rigid constraints. In real data there are on average 7 RDC measurements per amino acid in two different alignment media, arising from the bonds \((C, CA)\), \((C, N)\),
\((N, H), (CA, HA), (CA, CB)\). Unlike the simulated case, in experimental data there might be missing RDC measurements for some bonds. We again supplement the RDC with 187 experimentally reported backbone NOE’s. We use both RDC-SDP and RDC-NOE-SDP to solve the backbone structure of five ubiquitin fragments, each containing 12-13 residues on average. We split the fragments at amino-acid sites where there are too few or no RDC measurements. The results are summarized in Table 2. When using only RDC, it is more difficult to determine the backbone structure near the starting and end point of a fragment since RDC measurements are generally sparser in those regions. Therefore the fragments we used for RDC-SDP sometimes have smaller size than the fragments used for RDC-NOE-SDP which uses additional distance measurements. Typically, when using RDC-SDP, we can tell whether the rotation for a rigid unit is well-determined by simply examining how well \(\mathbf{Y}^{(i)}\) can be approximated by a rank 1 matrix. We can exclude those rigid units near the end of a fragment that give rise to high rank solutions when solving (P2). In terms of accuracy, due to the additional distance restraints, RDC-NOE-SDP outperforms RDC-SDP. The average RMSD of the fragments are 0.67 Å and 0.57 Å for RDC-SDP and RDC-NOE-SDP respectively when comparing with the X-ray structure 1UBQ [57]. To provide a different perspective, we also compare the results from our method with the high resolution NMR structure 1D3Z [16]. Since RDC-SDP only involves PSD variables of size \(9 \times 9\), whereas RDC-NOE-SDP involves variable of size \(9M \times 9M\), the running time of RDC-SDP is significantly lower than RDC-NOE-SDP. In particular, the running time for (P2) in RDC-SDP is never more than 2 seconds but the running time for (P1) in RDC-NOE-SDP can be as long as 5 minutes. When we combine the fragments using (P3), the conformation errors of the whole protein backbone obtained from fragments determined by RDC-SDP and RDC-NOE-SDP are 1.28 (1.25) Å and 1.07 (1.11) Å RMSD respectively when comparing to 1UBQ (1D3Z). In practice when calculating the protein backbone structure, we may want to use RDC-SDP instead of RDC-NOE-SDP to obtain an initial structure and add NOE measurements in the local refinement stage if running time is a concern. Figure 4 further compares the backbone traces obtained from our proposed methods and the X-ray structure. We also compare our results with MFR in Table 2. Comparing to RDC-SDP or RDC-NOE-SDP, structures calculated from MFR has a closer similarity to the X-ray structure 1UBQ, with average fragment RMSD and overall RMSD being 0.54 Å and 0.87 Å respectively. Since our proposed methods have not yet taken into accounts potential terms concerning radius of gyration, Van der Waals lower bound and infeasibility of the torsion angles, it is reasonable that the proposed methods still cannot compare with MFR.
| Residue No. | RDC-SDP | RDC-NOE-SDP | MFR |
|------------|---------|-------------|-----|
| 1-7        | 2-7     | 10-18       | 22-36| 39-53 | 54-70 |
| 10-18      | 10-18   | 22-36       | 37-53| 54-70 |
| 22-36      | 22-36   | 39-53       | 54-70|
| 39-53      | 39-53   | 54-70       |      |
| 54-70      | 54-70   |             |      |

| RMSD (Å)   | RDC-SDP | RDC-NOE-SDP | MFR |
|------------|---------|-------------|-----|
| 1UBQ       | 0.57    | 0.51        | 0.81|
|            | 0.70    | 0.78        |      |
| 1D3Z       | 0.56    | 0.48        | 0.78|
|            | 0.62    | 0.73        |      |

| Time (s)   | RDC-SDP | RDC-NOE-SDP | MFR |
|------------|---------|-------------|-----|
| 8 (0.5)    | 15 (6)  | 1560 (all 5 fragments) |
| 11 (0.5)   | 30 (17) |
| 63 (2)     | 231 (162) |
| 22 (1)     | 596 (450) |
| 23 (1.3)   | 312 (281) |

Table 2: Results of computing the structure of five ubiquitin fragments using RDC-SDP, RDC-NOE-SDP and MFR from experimental data. We compare with both the X-ray structure 1UBQ and the high resolution NMR structure 1D3Z. The time in brackets is the running time of the SDPs (P1) and (P2) used by RDC-NOE-SDP and RDC-SDP. The excess time is due to ManOpt refinement. For MFR we only report the total running time for calculating the entire backbone.

Figure 4: The trace of protein backbone drawn using N, CA and C. The black, blue and red curves come from the X-ray model 1UBQ, RDC-SDP solution and RDC-NOE-SDP respectively.
7 Conclusion

We present two novel convex relaxations RDC-SDP and RDC-NOE-SDP to calculate the protein backbone conformation from both RDC and NOE measurements. In simulations, our methods exactly recover the protein structure when there is no noise, whereas simulated annealing based methods can still suffer from local minima issue even when the data is clean. In the presence of noise, the error of our solution comes close to the CRB. We illustrate the robustness of our methods through comparing with the popular MFR homology modelling method in the high-noise regime in simulations. We further demonstrated the success of our methods by obtaining a backbone structure of 1 Å resolution for ubiquitin using real experimental data. Both proposed methods are fast in practice, in particular RDC-SDP can determine a protein fragment of typical size in just a few seconds. This is in sharp contrast to current methods such as MFR, RDC-Analytics and REDCRAFT that have running time ranging from tens of minutes to two hours. This property of our algorithm can be useful when iterating between estimating resonance or NOE assignments and structural calculation [25]. In a broader context, the proposed methods can also be applied to pose estimation problems for articulated structure in computer vision and robotics.

There are a few remaining issues we would like to address in future works. At this point, both RDC-SDP and RDC-NOE-SDP can only compute the structure of the protein backbone but not the protein side-chains. RDC measurements on side chains are complicated by the existence of rotamer states and only a few recent analyses are able to address this issue [35]. On the other hand, a major obstacle of obtaining complete NOE restraints for the protein side-chains is the ambiguity in NOE assignment, especially for larger systems. We hope to extend our proposed methods to help detecting the correct NOE assignments for the side-chains, through providing a high quality backbone conformation for assignment validations.

Currently, our method requires sufficient NOE restraints between the fragments when combining the fragments together using (P3). However, as noted in [65], there can be very few NOE restraints between the secondary structural elements. We observed such a situation when applying our algorithm to the protein DinI (PDB ID: 1GHH). While all the fragments in DinI can be determined by our proposed method to within 1 Å resolution, our method failed to assemble the fragments together due to the lack of inter-fragments NOE. We hope to solve this issue in the future by including database derived restraints. For example, torsion angle restraints can be derived from chemical shifts of backbone atoms using TALOS [49]. Furthermore, side-chain rotamer library [39] can be used to model protein side-chains, which can in turn provide additional NOE restraints arising from the side-chains.

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9 Appendix

9.1 The residual dipolar coupling and Saupe tensor

We give a brief introduction of RDC and the Saupe tensor and a detailed exposition can be found in [54] for example. Let $\mathbf{v}_{nm}$ be the unit vector denoting the direction of the bond between nuclei $n$ and $m$. Let $\mathbf{b}$ be the unit vector denoting the direction of the magnetic field. The RDC $D_{nm}$ due to the interaction between nuclei $n$ and $m$ is

$$ D_{nm} = D_{nm}^{\text{max}} \left\langle \frac{3(b^T \mathbf{v}_{nm})^2 - 1}{2} \right\rangle_{t,e}. $$

(69)

$D_{nm}^{\text{max}}$ is a constant depending on the gyromagnetic ratios $\gamma_n, \gamma_m$ of the two nuclei, the bond length $r_{nm}$, and the Planck’s constant $\hbar$ as

$$ D_{nm}^{\text{max}} = \frac{\gamma_n \gamma_m \hbar}{2\pi^2 r_{nm}^3}, $$

(70)

and $\langle \cdot \rangle_{t,e}$ denotes the ensemble and time averaging operator. As presented, RDC depends on the relative angle between the magnetic field and the bond. By extension of terminology, we refer to the normalized RDC

$$ r_{nm} = D_{nm}/D_{nm}^{\text{max}} $$

(71)

as simply the RDC.

It is conventional to interpret the RDC measurement in the molecular frame. More precisely, we treat the molecule as being static in some coordinate system, and the magnetic field direction being a time and sample varying vector. In this case the RDC becomes

$$ D_{nm} = D_{nm}^{\text{max}} \mathbf{v}_{nm}^T S \mathbf{v}_{nm}, $$

(72)

where the Saupe tensor $S$ is defined as

$$ S = \frac{1}{2} (3\mathbf{B} - \mathbf{I}_3), \quad \mathbf{B} = \left\langle \mathbf{b} \mathbf{b}^T \right\rangle_{t,e}. $$

(73)

We note that $S$ is symmetric and $\text{Tr}(S) = 0$. In order to use RDC for structural refinement of a protein, $S$ is usually first determined from a known structure (known $\mathbf{v}_{nm}$) that is similar to the protein.
We now detail a classical way of obtaining the Saupe tensor from a known template structure \[38\]. Using the fact that $SSS$ is symmetric and $\text{Tr}(SSS) = 0$, eq. (72) can be rewritten as

$$r_{nm} = (v_{nm2}^2 - v_{nm1}^2)S(2, 2) + (v_{nm3}^2 - v_{nm1}^2)S(3, 3) + 2v_{nm1} v_{nm2} S(1, 2) + 2v_{nm1} v_{nm3} S(1, 3) + 2v_{nm2} v_{nm3} S(2, 3)$$

(74)

where $v_{nmi}, i = x, y, z$ are the different components of $v_{nm}$ in the molecular frame. When there are $L$ RDC measurements, eq. (74) results in $L$ linear equations in five unknowns ($S(2, 2), S(3, 3), S(1, 2), S(1, 3) \text{ and } S(2, 3)$), that can be written in matrix form as

$$A s = r, s = \begin{bmatrix} S(2, 2) \\ S(3, 3) \\ S(1, 2) \\ S(1, 3) \\ S(2, 3) \end{bmatrix} \in \mathbb{R}^5, r = \begin{bmatrix} r_{n1m1} \\ \vdots \\ r_{nLmL} \end{bmatrix} \in \mathbb{R}^M$$

(75)

and $A \in \mathbb{R}^{L \times 5}$. An ordinary least squares procedure can be used to estimate $s$ if $A$ is full rank. This is also known as the SVD procedure in \[38\].

9.2 Unit quaternions and quadratic problem on $S\mathbb{O}(3)$

We first give a brief introduction to unit quaternions, where a detailed exposition can be found in many other sources (e.g. [2]). The group of unit quaternions consists of elements of the form

$$q = a + bi + cj + dk$$

(76)

which is a linear combination of the basis $1, i, j, k$ and

$$a^2 + b^2 + c^2 + d^2 = 1$$

(77)

The basis satisfies the multiplication rules

$$i^2 = j^2 = k^2 = ijk = -1$$

(78)

and these define the multiplication of any two quaternions. It is easy to see that the inverse $q^{-1}$ of a quaternion $q$ is

$$q^{-1} = a - bi - cj - dk$$

The group of unit quaternions can be used to represent a rotation in $S\mathbb{O}(3)$. If we parameterize the unit quaternion as $q = \cos(\theta/2) + \sin(\theta/2)(u_i l + u_j j + u_k k)$ it can be regarded as a rotation around the axis $[u_i, u_j, u_k]^T \in \mathbb{R}^3$ by angle $\theta$. More precisely, if we are to rotate any vector $v \in \mathbb{R}^3$ using a quaternion, we simply let

$$\bar{v} = v + v(1)l + v(2)j + v(3)k$$

28
and the rotation on $v$ is applied through

$$q^v q^{-1} = 0 + ai + bj + ck$$  \hfill (79)

The coefficients in front of $i, j, k$ give the rotated $v$ in $\mathbb{R}^3$. Notice that $q$ and $-q$ result in the same rotation on the vector $v$. From (79), a relation between rotation matrices in $SO(3)$ and unit quaternions can be obtained (also known as Euler-Rodrigues formula).

If we treat the unit quaternion $q$ as a vector in $\mathbb{R}^4$ such that $\|q\|_2 = 1$, the rotation matrix it represents is given by

$$\Phi(q) = \begin{bmatrix} 1 - 2q(3)^2 - 2q(4)^2 & 2(q(2)^2q(3) - q(4)q(1)) & 2(q(2)^2q(4) + q(3)q(1)) \\ 2(q(2)^2q(3) + q(4)q(1)) & 1 - 2q(2)^2 - 2q(3)^2 & 2(q(3)^2q(4) - q(2)q(1)) \\ 2(q(2)^2q(4) - q(3)q(1)) & 2(q(3)^2q(4) + q(2)q(1)) & 1 - 2q(1)^2 - 2q(2)^2 \end{bmatrix}. \hfill (80)$$

This map $\Phi$ is a surjective group homomorphism (epimorphism) from the group of unit quaternions to $SO(3)$. The kernel of this map is $\{[-1,0,0,0]^T, [1,0,0,0]^T \}$. This implies for a matrix $R \in SO(3)$, $R = \Phi(q) = \Phi(-q)$ for a quaternion $q$. Therefore the group of unit quaternions is known as the double cover of $SO(3)$, in other words,

$$\{ \{q, -q \} \mid q \in \mathbb{R}^4, \|q\|_2 = 1 \} \cong SO(3). \quad (81)$$

In light of this, if we construct the following set of rank-1 matrices

$\text{Quaternion}^2 := \{ Q \in \mathbb{R}^{4 \times 4} \mid Q = qq^T, \|q\|_2 = 1 \}$

and define a function $\Phi$ via $q$ as

$$\Phi(qq^T) := \Phi(q). \quad (83)$$

then the map

$$\Phi : \text{Quaternion}^2 \to SO(3) \quad (84)$$

is a bijection. It can be checked easily that the inverse map $\Phi^{-1}$ is

$$\Phi^{-1}(R) := \frac{1}{4} \begin{bmatrix} 1 + R(1,1) + R(2,2) + R(3,3) & R(3,2) - R(2,3) \\ R(3,2) - R(2,3) & 1 - R(2,2) - R(3,3) + R(1,1) \\ R(1,3) - R(3,1) & R(1,2) + R(2,1) \\ R(2,1) - R(1,2) & R(1,3) + R(3,1) \end{bmatrix} \hfill (85)$$

The bijection between Quaternion$^2$ and $SO(3)$ leads to the simple proposition.

**Proposition 1** $R \in SO(3)$ if and only if $\Phi^{-1}(R) \in \text{Quaternion}^2$.

Proposition 1 shows that we can use the constraint $\Phi^{-1}(R) \in \text{Quaternion}^2$ to enforce $R \in SO(3)$. Notice that

$$\Phi^{-1}(R) \in \text{Quaternion}^2 \quad (86)$$

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implies
\[ \Phi^{-1}(R) = qq^T \text{ for some } q \in \mathbb{R}^4, \|q\|_2 = 1 \] (87)

hence
\[ \Phi^{-1}(R)\Phi^{-1}(R) = \Phi^{-1}(R) \] (88)

This gives a linear constraint in \( Y \) and \( R \). Indeed, if
\[ \text{vec}(\Phi^{-1}(R)) := A \begin{bmatrix} \text{vec}(R) \\ 1 \end{bmatrix} \]

for some matrix \( A \in \mathbb{R}^{16 \times 10} \), then
\[
\Phi^{-1}(R)\Phi^{-1}(R) = \sum_{i=1}^{4} \left( A \begin{bmatrix} \text{vec}(R) \\ 1 \end{bmatrix} \right) \begin{bmatrix} \text{vec}(R)^T & 1 \end{bmatrix} A^T \\
= \Psi \left( \begin{bmatrix} Y & \text{vec}(R) \\ \text{vec}(R)^T & 1 \end{bmatrix} \right) \] (89)

where \( \Psi : \mathbb{R}^{4 \times 4} \to \mathbb{R}^{4 \times 4} \) is yet another linear operator. Specifically in (89), for a matrix \( X \in \mathbb{R}^{16 \times 16} \) we use \( X_{ii} \) to denote the \( i \)-th \( 4 \times 4 \) block on the diagonal. In this way, (88) can be written as
\[ \Phi^{-1}(R) \geq \Psi \left( \begin{bmatrix} Y & \text{vec}(R) \\ \text{vec}(R)^T & 1 \end{bmatrix} \right). \] (90)

It can be verified that any \( R \) that satisfies the last constraint in (26) also satisfies (90). This leads to the fact that \( R \) in (26) belongs to the convex hull of \( \mathbb{S}\mathbb{O}(3) \). To see this, notice that if \( Y \succeq \text{vec}(R)\text{vec}(R)^T \) then
\[
\begin{bmatrix} Y & \text{vec}(R) \\ \text{vec}(R)^T & 1 \end{bmatrix} \succeq 0, \] (91)

and so is
\[
A \begin{bmatrix} Y & \text{vec}(R) \\ \text{vec}(R)^T & 1 \end{bmatrix} A^T \] (92)

and its \( 4 \times 4 \) blocks along the diagonal. Therefore
\[ \Phi^{-1}(R) = \Psi \left( \begin{bmatrix} Y & \text{vec}(R) \\ \text{vec}(R)^T & 1 \end{bmatrix} \right) \succeq 0, \] (93)

in (26). We now state a theorem in [44, 45]:

**Theorem 1** [44, Proposition 1].
\[
\text{conv}(\mathbb{S}\mathbb{O}(3)) = \{ R \in \mathbb{R}^{3 \times 3} \mid \Phi^{-1}(R) \succeq 0 \}. \] (94)

Leveraging the theorem, we arrive at the conclusion that \( R \) in (26) is in the convex hull of \( \mathbb{S}\mathbb{O}(3) \).
9.3 Cramér-Rao lower bound

In this section, we introduce a classical tool from statistics, the Cramér-Rao bound (CRB) [12], to give perspective on the lowest possible error any unbiased estimator can achieve when estimating coordinates from noisy RDC measurements. We first describe the CRB for general point estimators. Let \( \theta \in \mathbb{R}^n \) be a multidimensional parameter which is to be estimated from measurements \( x \in \mathbb{R}^m \). Suppose \( x \) is generated from the distribution \( p(x|\theta) \). The Fisher information matrix is defined as the \( n \times n \) matrix

\[
I(\theta) = \mathbb{E}[\nabla_{\theta} \ln p(x|\theta)](\nabla_{\theta} \ln p(x|\theta))^T
\]

where expectation is taken with respect to the distribution \( p(x|\theta) \) and the gradient \( \nabla_{\theta} \) is taken with respect to \( \theta \). For any unbiased estimator \( \hat{\theta} \) of \( \theta \), that is \( \mathbb{E}(\hat{\theta}) = \theta \), the following relationship holds:

\[
\mathbb{E}[(\hat{\theta} - \theta)(\hat{\theta} - \theta)^T] \succeq I(\theta)^{-1}
\]

if \( I(\theta) \) is invertible. Therefore the total variance of the estimator \( \hat{\theta} \) is lower bounded by \( \text{Tr}(I(\theta)^{-1}) \). We also introduce the CRB in the case when \( \theta \) and \( \hat{\theta} \) are constrained to be in the set \( \{\theta | f(\theta) = 0\} \) where \( f: \mathbb{R}^n \rightarrow \mathbb{R}^k \) [52]. Let \( Df(\theta) \in \mathbb{R}^{k \times n} \) be the gradient matrix of \( f \) at \( \theta \) with full row rank, and \( Q \in \mathbb{R}^{n \times (n-k)} \) be a set of orthonormal vectors satisfying

\[
Df(\theta)Q = 0
\]

i.e. \( Q \) is an orthonormal basis of the null space of \( Df(\theta) \). In this case, for any unbiased estimator \( \hat{\theta} \) satisfying \( f(\hat{\theta}) = 0 \), the CRB is then

\[
\mathbb{E}[(\hat{\theta} - \theta)(\hat{\theta} - \theta)^T] \succeq QQ^T I(\theta)^{-1}Q^T
\]

if \( QQ^TI(\theta)Q \) is invertible.

We are now ready to investigate the CRB for estimating atomic positions from RDC data. Let \( \zeta = [\zeta_1, \ldots, \zeta_K] \in \mathbb{R}^{3 \times K} \) be the coordinates of the atoms we want to estimate. We aim to derive a lower bound for \( \mathbb{E}[\text{Tr}((\hat{\zeta} - \zeta)^T(\hat{\zeta} - \zeta))] \) for any unbiased estimator \( \hat{\zeta} \) of \( \zeta \). We assume that the RDC measurements are generated through the noise model in (66). We further assume that within each rigid unit, the distance between any pair of atoms is fixed. We therefore have a set of equality constraints

\[
d_{nm}^2 = \|\zeta_n - \zeta_m\|^2_2, \quad (n,m) \in E_{\text{fixed}}
\]

where \( E_{\text{fixed}} \) consists of all atom pairs within each and every rigid unit. Without loss of generality, we also consider the constraint

\[
\zeta 1 = 0
\]

which implies the points \( \zeta_1, \ldots, \zeta_K \) are centered at zero. This is due to the fact that

\[
\begin{align*}
\text{Tr}((\hat{\zeta} - \zeta)^T(\hat{\zeta} - \zeta)) &= \text{Tr}((\hat{\zeta} - \zeta - t1^T)^T(\hat{\zeta} - \zeta - t1^T)) \\
&= \text{Tr}((\hat{\zeta}_c - \zeta_c - t1^T)^T(\hat{\zeta}_c - \zeta_c - t1^T))
\end{align*}
\]
\[ \begin{align*}
&= \text{Tr}( (\hat{\xi}_c - \xi_c)^T (\hat{\xi}_c - \xi_c) ) + (1/K) \| t \|_2^2 \\
&= 2 \text{Tr}( (\xi_c - \hat{\xi}_c)^T ) \\
&\geq \text{Tr}( (\xi_c - \hat{\xi}_c)^T (\xi_c - \hat{\xi}_c) ) 
\end{align*} \] (101)

where \( \xi_c \) and \( \hat{\xi}_c \) denote the zero centered coordinates and coordinate estimators, and \( t \) is the relative translation between \( \xi \) and \( \hat{\xi} \). Eq. (101) implies that deriving a lower bound for \( \text{Tr}( (\hat{\xi}_c - \xi_c)^T (\hat{\xi}_c - \xi_c) ) \) is sufficient for obtaining a lower bound for \( \text{Tr}( (\xi - \hat{\xi})^T (\xi - \hat{\xi}) ) \). When there are atoms that are constrained to lie on the same plane, we need to add the constraint that any three vectors in the plane span a space with zero volume, i.e.

\[ \det((\xi_i - \xi_j; \xi_k - \xi_i; \xi_m - \xi_n)) = 0 \] (102)

for atoms \( i, j, k, l, m, n \) in the same plane.

To obtain the CRB for estimating \( \xi \) from RDC data generated through (66), we need to first derive an expression for the Fisher information matrix. From (66) and (67), the likelihood function for the coordinates is

\[ p\left( \{ r_{nm} \}_{(n,m) \in \text{RDC}} | \xi_1, \ldots, \xi_K \right) = \prod_{(n,m) \in \text{RDC}} \frac{1}{\sqrt{2\pi \sigma^2}} \exp \left( -\frac{(\xi_n - \xi_m)^T S^{(j)}(\xi_n - \xi_m) - r_{nm}^2}{2d_{nm}^2 \sigma^2} \right) \] (103)

and the log-likelihood is (up to an additive constant)

\[ l(\{ r_{nm} \}_{(n,m) \in \text{RDC}} | \xi_1, \ldots, \xi_K ) :\ln p(\{ r_{nm} \}_{(n,m) \in \text{RDC}} | \xi_1, \ldots, \xi_K ) \]

\[ = \sum_{(n,m) \in \text{RDC}} -\frac{(\xi_n - \xi_m)^T S^{(j)}(\xi_n - \xi_m) - r_{nm}^2}{2d_{nm}^2 \sigma^2} \]

\[ = -\sum_{(n,m) \in \text{RDC}} \frac{(\hat{e}_{nm}^{T} \xi^{T}) S^{(j)} \hat{e}_{nm} - r_{nm}^2 \sigma^2}{2d_{nm}^2 \sigma^2} \] (104)

where \( e_{nm} = e_n - e_m \). The derivative of \( l \) with respect to \( \text{vec}(\xi) \) is then

\[ \nabla_{\text{vec}(\xi)} l = -\sum_{(n,m) \in \text{RDC}} \frac{2(\hat{e}_{nm}^{T} \xi^{T}) S^{(j)} \hat{e}_{nm} - r_{nm}^2}{d_{nm}^2 \sigma^2} \]

\[ (\hat{e}_{nm}^{T} \otimes S^{(j)}) \text{vec}(\xi). \] (105)
It follows from the noise model \((66)\) and the independence of \(\varepsilon_{nm}'s\) that the Fisher information matrix

\[
I(\zeta) = \mathbb{E}\left((\nabla_{\text{vec}}(\zeta)) (\nabla_{\text{vec}}(\zeta))^T\right) = \sum_{(n,m) \in \mathcal{E}_{\text{RDC}}} \frac{4}{\sigma^2 d_{nm}^4} \left(\varepsilon_{nm}^T S^{(j)} \vec{(\varepsilon_{nm})} \vec{(\varepsilon_{nm})}^T \right)
\]

Having the Fisher information matrix, we now incorporate the constraints in (99) and (100) in order to obtain a bound as in (98). Stacking the equality constraints (99) into a \(|E_{\text{fixed}}| \times 1\) matrix, we get

\[
f(\text{vec}(\zeta)) := \left[\varepsilon_{nm}^T \zeta_{nm} - d_{nm}^2\right]_{(n,m) \in E_{\text{fixed}}} = 0
\]

The gradient matrix is thus

\[
Df(\text{vec}(\zeta)) = \text{vec}(\zeta)^T \left[\varepsilon_{nm} \varepsilon_{nm}^T \otimes I_3\right]_{(n,m) \in E_{\text{fixed}}}
\]

where \(Df(\text{vec}(\zeta)) \in \mathbb{R}^{|E_{\text{fixed}}| \times 3K}\). We note that \(Df(\text{vec}(\zeta))\) is known as the rigidity matrix [29], and the vectors in its null space indicate the direction of infinitesimal motion the atoms can take without violating (99). Even in the case when all pairwise distances between the atoms are known, there is still a 6-dimensional null space for \(Df(\text{vec}(\zeta))\), corresponding to an infinitesimal global rotation and translation to the coordinates \(\zeta\) that preserves all pairwise distances. We now augment \(f(\text{vec}(\zeta)) = 0\) with the centering constraint \(\zeta_1 = 0\), and this augments \(Df(\text{vec}(\zeta))\) with three rows \(1^T \otimes I_3\), i.e.

\[
Df(\text{vec}(\zeta)) = \left[\text{vec}(\zeta)^T \left[\varepsilon_{nm} \varepsilon_{nm}^T \otimes I_3\right]\right]_{(n,m) \in E_{\text{fixed}}} \quad 1^T \otimes I_3
\]

The inclusion of such centering constraint eliminates the three dimensional subspace in the kernel of the rigidity matrix that corresponds to the translational degree of freedom. Let \(Q\) be an orthonormal basis that spans the null space of \(Df(\text{vec}(\zeta))\). Together with (106) and (98) we obtain the desired CRB. We omit detailing the derivative for constraint (102) but simply note that the inclusion of such constraints eliminates the out of plane infinitesimal motion for atoms lying on rigid planar unit.

9.3.1 Inclusion of NOE constraints

We have so far neglected the use of NOE measurements when deriving the CRB. Unlike RDC, the NOE constraints remain more qualitative, with imprecise upper and lower bound [8] due to the \(r^{-6}\) scaling of the interaction. Therefore it is conventional to treat the backbone NOE as inequality constraints on distances. For an unbiased estimator \(\hat{\theta}\) of the parameter \(\theta\) where both \(\hat{\theta}\) and \(\theta\) lie in the set \(\{\theta\mid f(\theta) < 0\}\), it is shown in [24] that the CRB is the same as the unconstrained case (96), since roughly speaking the CRB only depends on the local curvature of the log-likelihood function around \(\theta\). Therefore if the original coordinates and the coordinate estimators strictly satisfy the distance constraints (1), then the CRB is the same as in the case with only RDC.
9.3.2 Infinitesimal rigidity and invertibility of the Fisher information matrix

In this subsection, we study the infinitesimal rigidity [36] of the protein structure given RDC and distance measurements and how it guarantees invertibility of the Fisher information matrix. Let a framework with coordinates \( \zeta \in \mathbb{R}^{3 \times K} \) be constrained by

\[
(\zeta_n - \zeta_m)^T (\zeta_n - \zeta_m) = d_{nm}^2, \quad (n, m) \in E_{\text{fixed}},
\]

and

\[
(\zeta_n - \zeta_m)^T \mathcal{S}^{(j)} (\zeta_n - \zeta_m) = r_{nm}^{(j)}, \quad j = 1, \ldots, N, (n, m) \in E_{\text{RDC}}.
\]

In order to derive a condition for infinitesimal rigidity, we first let \( \text{vec}(\zeta(s)) \) be a curve in dimension \( \mathbb{R}^{3K} \) parameterized by \( s \), where \( \zeta(0) \) satisfies (110) and (111). Taking derivative of the constraints in (110) and (111) with respect to \( s \) at \( s = 0 \), we have

\[
\begin{bmatrix}
    \text{vec}(\zeta(0))^T [e_{nm} e_{nm}^T I_3]_{(n,m) \in E_{\text{fixed}}} \\
    \text{vec}(\zeta(0))^T [e_{nm} e_{nm}^T \mathcal{S}^{(j)}]_{(n,m) \in E_{\text{RDC}}, j \in [1, N]}
\end{bmatrix} \frac{d}{ds} \text{vec}(\zeta(0)) = R(\zeta(0)) \frac{d}{ds} \text{vec}(\zeta(0)) = 0.
\]

The null space of the generalized rigidity matrix \( R(\zeta(0)) \) with dimension \( |E_{\text{fixed}}| + |E_{\text{RDC}}| \times 3K \) represents the direction of infinitesimal motion such that \( \zeta(s) \) satisfies the constraints (110), (111) for infinitesimally small \( s \). If \( R(\zeta(0)) \) only has a three dimensional nullspace, i.e. the global translations in \( x, y, z \)-directions, we say the framework \( \zeta(0) \) along with the constraints (110) and (111) is infinitesimally rigid.

Now we verify that the constrained Fisher information matrix is invertible if \( R(\zeta(0)) \) has a three dimensional null space corresponds to global translation of the points. Let \( Q \) again be the basis of the null space of \( Df(\text{vec}(\zeta)) \) defined in (109) such that \( Df(\text{vec}(\zeta))Q = 0 \). Let \( v \) satisfies

\[
Q^T I(\zeta)Qv = 0
\]

\( Q^T I(\zeta)Qv = 0 \) if and only if \( v \in \ker(Q) \) or \( Qv \in \ker(I) \). Since the columns of \( Q \) are linearly independent, \( Qv \neq 0 \) unless \( v = 0 \). This means \( Q^T I(\zeta)Qv = 0 \) if and only if \( v = 0 \) or \( Qv \in \ker(I) \cap \text{range}(Q) = \ker(I) \cap \text{range}(Q) = \ker(I) \cap \ker(Df(\text{vec}(\zeta))) \). Therefore if Therefore if

\[
\ker(I) \cap \ker(Df(\text{vec}(\zeta))) = 0,
\]

or in other words

\[
\text{span}(\text{range}(I) \cup Df(\text{vec}(\zeta))) = \mathbb{R}^{3K}
\]

then \( Q^T I(\zeta)Q \) is invertible. From the form of the (106), it is easy to show that the range condition (113) is satisfied if and only if the range of

\[
\begin{bmatrix}
    1^T \otimes I_3 \\
    \text{vec}(\zeta(0))^T [e_{nm} e_{nm}^T I_3]_{(n,m) \in E_{\text{fixed}}} \\
    \text{vec}(\zeta(0))^T [e_{nm} e_{nm}^T \mathcal{S}^{(j)}]_{(n,m) \in E_{\text{RDC}}, j \in [1, N]}
\end{bmatrix}
\]

is satisfied.

\[
1^T \otimes I_3 = R(\zeta(0)).
\]
is $\mathbb{R}^{3K}$. Then we arrive at the conclusion that if the framework $\zeta$ is infinitesimally rigid with the null space of $R(\zeta)$ being the global translations, the constrained Fisher information matrix defined as $Q^T I(\zeta) Q$ is invertible.

In [65], it is shown that if there exists RDC measurements for a bond in the peptide plane and a bond in the CA-body in a single alignment media, the solutions of the protein structure form a discrete set. Therefore under this condition, there is no infinitesimal motion other than global translation such that the protein framework satisfies the RDC and NOE constraints. We can thus compute the CRB safely under such condition.

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