Kinematics Meets Crystallography: The Concept of a Motion Space[1]

Gregory S. Chirikjian
Robot and Protein Kinematics Laboratory,
Department of Mechanical Engineering,
Johns Hopkins University,
Baltimore, MD 21218
e-mail: gregc@jhu.edu

In this paper, it is shown how rigid-body kinematics can be used to assist in determining the atomic structure of proteins and nucleic acids when using x-ray crystallography, which is a powerful method for structure determination. The importance of determining molecular structures for understanding biological processes and for the design of new drugs is well known. Phasing is a necessary step in determining the three-dimensional structure of molecules from x-ray diffraction patterns. A computational approach called molecular replacement (MR) is a well-established method for phasing of x-ray diffraction patterns for crystals composed of biological macromolecules. In MR, a search is performed over positions and orientations of a known biomolecular structure within a model of the crystallographic asymmetric unit, or, equivalently, multiple symmetry-related molecules in the crystallographic unit cell. Unlike the discrete space groups known to crystallographers and the continuous rigid-body motions known to kinematicians, the set of motions over which MR searches are performed does not form a group. Rather, it is a coset space of the group of continuous rigid-body motions, SE(3), with respect to the crystallographic space group of the crystal, which is a discrete subgroup of SE(3). Properties of these "motion spaces" (which are compact manifolds) are investigated here. [DOI: 10.1115/1.4028922]

Introduction

Theoretical kinematics is concerned with all aspects of rigid-body motions, as applied to the design of mechanisms and robots, as well as in the description and analysis of motion more generally [1–3]. The group of rigid-body motions (or "special Euclidean group") in n-dimensional Euclidean space is a Lie group denoted as SE(n) [4–7]. Many works in theoretical kinematics have been concerned with parameterizing this Lie group, defining metrics on it, and generating trajectories in it that have desirable properties [8,9]. Another field of study, crystallography, also studies rigid-body motions. However, in this field the motions of interest are those that describe the discrete symmetries of a crystal lattice [10–12]. At the beginning of the 20th century (almost in parallel with Ball's development of screw theory [13]), all possible lattices and their symmetries were characterized independently in Refs. [14–16] as summarized in Ref. [17]. The result of those studies concluded that that there are 230 distinct classes of crystallographic space groups. Of these, the vast majority have mirror reflections or glide planes, and only 65 are chiral (i.e., are "special" in the sense that they preserve handedness). The chiral space groups are particularly important in macromolecular crystallography, which has been responsible for determining the shape of 80% of the approximately 100,000 protein structures deposited in the protein data bank (PDB) [18].

Interestingly, the overlap between kinematics and crystallography over the past 100 years has been minimal despite the fact that the chiral crystallographic space groups are discrete subgroups of SE(3). The purpose of this paper is to examine hitherto unrecognized relationships between these fields. In particular, it is shown that if $G = \mathrm{SE}(3)$ and Γ is a crystallographic subgroup of G, then the coset space $\Gamma\backslash G$ is a compact manifold that describes the configuration space of all non-redundant poses of a protein in a crystal. This is the 6D search space of interest in the field of MR [19,20].

This paper is organized as follows. First, a review of concepts from theoretical kinematics and crystallography is presented. Then the concept is illustrated in the 2D case in a concrete way. This is followed by discussion of the MR problem and the role of motion spaces in this problem. And finally, the intricacies of the 3D problem are explored.

The Mathematics of Continuous and Discrete Rigid-Body Motions

Let Γ denote the discrete group of (chiral/proper) symmetries of a macromolecular crystal[2]. Γ, though discrete, has an infinite number of elements, and forms a subgroup of the group of rigid-body motions, $G = \mathrm{SE}(n)$. The latter consists of all rotation–translation pairs $g = (R, \mathbf{t})$ where R is an $n \times n$ rotation matrix, the set of which forms the special orthogonal group SO(n), and $\mathbf{t} \in \mathbb{R}^n$ is a translation vector. The group operation for this group (which is inherited by the subgroup Γ) is defined by

$$g_1 \circ g_2 = (R_1, \mathbf{t}_1) \circ (R_2, \mathbf{t}_2) = (R_1 R_2, R_1 \mathbf{t}_2 + \mathbf{t}_1)$$

It is possible to define $(n+1) \times (n+1)$ homogeneous transformation matrices of the form

$$H(g) = \begin{pmatrix} R & \mathbf{t} \\ \mathbf{0}^{\mathrm{T}} & 1 \end{pmatrix} \tag{1}$$

where $\mathbf{0}^{\mathrm{T}}$ is a row vector consisting of n zeros. Then the group law can be viewed as the matrix multiplication

$$H(g_1) H(g_2) = H(g_1 \circ g_2) \tag{2}$$

---

[1] This paper was originally presented at the ASME 2014 International Design Engineering Technical Conferences as Paper No. DETC2014-34243.

Contributed by the Design Engineering Division of ASME for publication in the Journal of Computing and Information Science in Engineering. Manuscript received August 23, 2014; final manuscript received August 28, 2014; published online February 2, 2015. Editor: Bahram Ravani.

[2] In reality such crystals exist only in three-dimensional Euclidean space, but for the purpose of generality in this introduction, the dimension n will be allowed to be general, with realistic examples having $n = 2$ or 3.

From this, it is easy to calculate that for any $g \in G, g^{-1} \circ g = g \circ g^{-1} = e$ and $g \circ e = e \circ g = g$, where

$$g^{-1} = (R^{\mathrm{T}}, -R^{\mathrm{T}}\mathbf{t}) \quad \text{and} \quad e = (\mathbb{I}_n, \mathbf{0})$$

Here, $\mathbb{I}_n$ is the $n \times n$ identity matrix, and e denotes the group identity element.

The distinction between the matrix representation of the group G in (1) versus G itself is often blurred so that G can either be thought of pairs $g = (R, \mathbf{t})$ together with an operator $\circ$, or as $H(g)$ with operation of matrix multiplication. The group law for SE(n) given above is that of a semidirect product, so that

$$\mathrm{SE}(n) = (\mathbb{R}^n, +) \rtimes \mathrm{SO}(n) \tag{3}$$

This means that every element of SE(n) can be decomposed into the product of a pure translation followed by a pure rotation as

$$g = \mathrm{trans}(\mathbf{t}) \circ \mathrm{rot}(R) = (\mathbb{I}_n, \mathbf{t}) \circ (R, \mathbf{0})$$

The above discussion holds in any dimension, n. The case $n = 3$ is of particular interest, and specialized notation can be established. For example, let

$$\Omega = \begin{pmatrix} 0 & -\omega_3 & \omega_2 \\ \omega_3 & 0 & -\omega_1 \\ -\omega_2 & \omega_1 & 0 \end{pmatrix}$$

and let $\omega = [\omega_1, \omega_2, \omega_3]^{\mathrm{T}}$. Then for any vector $\mathbf{x} \in \mathbb{R}^3$, $\Omega\mathbf{x} = \omega \times \mathbf{x}$, the cross product of ω and $\mathbf{x}$. Using the notation $\theta = ||\omega||$ and $\omega = \theta\mathbf{n}$, and $\Omega = \theta N$, it can be shown that every element of SO(3) can be expressed as the matrix exponential

$$e^{\theta N} = \mathbb{I}_3 + \sin\theta N + (1 - \cos\theta) N^2$$

This is equivalent to Rodrigues' rotation formula. A similar (though somewhat more complicated formula) holds for the matrix exponential for the group of rigid-body motions

$$g = \exp\begin{pmatrix} \theta N & \mathbf{b} \\ \mathbf{0}^{\mathrm{T}} & 0 \end{pmatrix} = \begin{pmatrix} e^{\theta N} & J(\theta, \mathbf{n})\mathbf{b} \\ \mathbf{0}^{\mathrm{T}} & 1 \end{pmatrix}$$

where the matrix function $J(\theta, \mathbf{n})$ is known in the kinematics literature. (See, for example, Refs. [21] and [22].)

In the special case when $\mathbf{b}$ points in the direction $\mathbf{n}$, the matrix exponential reduces to

$$\mathrm{screw}(\mathbf{n}, \theta, h) = \begin{pmatrix} e^{\theta N} & h\mathbf{n} \\ \mathbf{0}^{\mathrm{T}} & 1 \end{pmatrix}$$

This is a screw displacement in continuous space with pitch h, with screw axis intersecting the origin. The direction of the screw displacement is changed by conjugation by pure rotations as

$$(R, \mathbf{0}) \circ \mathrm{screw}(\mathbf{n}, \theta, h) \circ (R^T, \mathbf{0}) = \mathrm{screw}(R\mathbf{n}, \theta, h)$$

The axis of the screw displacement also can be translated by conjugating by a translation rather than a rotation.

Though continuous screw motions (both infinitesimal and finite) are known to kinematicians, discrete screw motions are important in crystallography. In the case when $\theta = 2\pi/\eta$ and $h = p/\eta$, where p and η are positive integers and $p \in \{1, 2, \ldots, \eta\}$, $\mathrm{screw}(\mathbf{n}, 2\pi/\eta, p/\eta)$ becomes a screw axis of type η_{p}, where

$$[\mathrm{screw}(\mathbf{n}, 2\pi/\eta, p/\eta)]^\eta = (\mathbb{I}, p\mathbf{n})$$

If we conjugate by translations before raising to the power, the result is the same because

$$\begin{aligned} &[(\mathbb{I}, \mathbf{t}) \circ \mathrm{screw}(\mathbf{n}, 2\pi/\eta, p/\eta) \circ (\mathbb{I}, -\mathbf{t})]^\eta \\ &\quad = (\mathbb{I}, \mathbf{t}) \circ (\mathbb{I}, p\mathbf{n}) \circ (\mathbb{I}, -\mathbf{t}) = (\mathbb{I}, p\mathbf{n}) \end{aligned}$$

For screw displacements that move three-dimensional crystal lattices back into themselves, the only allowable values for η are 2,3,4,6. And of particular interest are screws of the form 2_1 since they are so common in crystals of biological macromolecules.

Actions, Subgroups, and Coset Spaces. The group $G = \mathrm{SE}(n)$ acts on the set $X = \mathbb{R}^n$ as

$$g \cdot \mathbf{x} = R\mathbf{x} + \mathbf{t} \tag{4}$$

for all position vectors $\mathbf{x} \in X$. Any such position can be expressed as $\mathbf{x} = \sum_{i=1}^{n} x_i \mathbf{e}_i$ where $\{\mathbf{e}_i\}$ is the natural basis for $\mathbb{R}^n$ consisting of orthogonal unit vectors. Alternatively, in crystallographic applications it can be more convenient to write $\mathbf{x} = \sum_{i=1}^{n} x_i' \mathbf{a}_i$ where $\{\mathbf{a}_i\}$ are the directions from one lattice point to the corresponding one in an adjacent primitive unit cell. Sweeping through values $0 \leq x_i' \leq 1$ defines the primitive crystallographic unit cell. On the other hand, $\mathbf{x}$ denotes any of a continuum of positions, the set of all discrete translations of the form $\mathbf{t}_{\mathbf{m}} = \sum_{i=1}^{n} m_i \mathbf{a}_i$ for all $\mathbf{m} \in \mathbb{Z}^n$ forms the Bravais lattice, $\mathbb{L}$, and for any two fixed $\mathbf{m}, \mathbf{m}' \in \mathbb{Z}^n$, $\mathbf{t}_{\mathbf{m}} + \mathbf{t}_{\mathbf{m}'} = \mathbf{t}_{\mathbf{m}+\mathbf{m}'}$ is also in the lattice. The lattice together with addition is the group of primitive lattice translations, $T = (\mathbb{L}, +) \cong (\mathbb{Z}^n, +)$, which is infinite but discrete. In the discussion that follows, P will denote the proper point group consisting of rotations of the lattice $\mathbb{L}$, and Γ will denote the whole group of chiral crystallographic symmetry operations. The space group of a Bravais lattice is a semidirect product and can be thought of as a discrete version of SE(n). However, a crystal consists of both a Bravais lattice and a motif repeated inside of the unit cells. This changes the symmetry, by possibly removing some rotational symmetry operations and possibly introducing some discrete screw displacements.

$G = \mathrm{SE}(n)$ is a Lie group consisting of a continuum of elements. Two Lie subgroups of G are

$$\mathcal{T} = \{(\mathbb{I}, \mathbf{t}) | \mathbf{t} \in X\}, \quad \mathcal{R} = \{(R, \mathbf{0}) | R \in \mathrm{SO}(n)\} \tag{5}$$

These are the continuous groups of pure translations and pure rotations. The group of pure translations is isomorphic with $\mathbb{R}^n$ with the operation of addition, i.e., $\mathcal{T} \cong (\mathbb{R}^n, +)$, and the group of pure rotations is isomorphic with SO(n), i.e., $\mathcal{R} \cong \mathrm{SO}(n)$, where the operation for SO(n) is matrix multiplication. These subgroups are special because any element $g \in G$ can be written as a product of pure translations and rotations as $g = (\mathbb{I}, \mathbf{t}) \circ (R, \mathbf{0})$. In addition $\mathcal{T}$ is a normal subgroup of G, meaning that for all $h \in G$ and $t \in \mathcal{T}$, $h \circ t \circ h^{-1} \in \mathcal{T}$. This condition is written as $h\mathcal{T}h^{-1} \subseteq \mathcal{T}$, and in fact it can be shown that $h\mathcal{T}h^{-1} = \mathcal{T}$.

More generally, given any proper subgroup H contained in G (which is denoted as $H < G$), including (but not limited to) $\mathcal{T}, \mathcal{R}$, Γ, and T, left and right cosets are defined, respectively, as

$$gH = \{g \circ h | h \in H\}, \quad Hg = \{h \circ g | h \in H\}$$

It is well known that a group is divided into disjoint left (or right) cosets, and that only for a normal subgroup, N, it is the case that $gN = Ng$ for all $g \in G$. More generally, the left and right coset (or quotient) spaces that contain all left or right cosets are denoted, respectively, as G/H and $H \backslash G$. Normal subgroups are special because $G/N = N \backslash G$ and a natural group operation can be defined so that G/N is also a group.

Structure of Chiral Space Groups. We now briefly review the mathematical structure of crystallographic space groups. Recall that altogether there are 230 types of crystallographic groups in total in the three-dimensional case, 65 of which are proper/chiral. When referring to "space groups" one is really referring to "equivalence classes of space groups" in the sense that if Γ is a space group then when $\alpha\Gamma\alpha^{-1} = \{\alpha \circ \gamma \circ \alpha^{-1} | \gamma \in \Gamma\}$ is also a space group for some fixed affine transformation α, then Γ and $\alpha\Gamma\alpha^{-1}$ are considered to be equivalent. Here, α is a special affine transformation (i.e., $\alpha = (A, \mathbf{a})$ with $\det A > 0$) that converts one space group to another in the same class, and in general this imposes severe restrictions on the allowable α. The enumeration of equivalence classes of space groups is discrete, but since the affine group is continuous, an uncountably infinite number of equivalent space groups can be generated. In the planar case there are 17 types of wallpaper groups, five of which are chiral $(p_1, p_2, p_3, p_4, p_6)$. Space groups can be divided into two broad classes: the symmorphic groups, which can be written as a semidirect product of the translation and rotation subgroups, and the nonsymmorphic groups, which cannot. (Though all crystallographic groups have a subgroup of primitive translations which is the same as that for the Bravais lattice, the symmorphic nature of the Bravais-lattice-space-groups is not inherited by the majority of the crystallographic space groups.) In the planar case, all chiral wallpaper groups are symmorphic. In the three-dimensional case there are 73 symmorphic and 157 nonsymmorphic space groups. Of the 65 chiral space groups, 24 are symmorphic and 41 are nonsymmorphic. The most commonly adopted space group for crystals of biological macromolecules is called $P2_12_12_1$ and is group number 19 of the 230 as listed in the international tables of crystallography and the Bilbao server[3]. This is a nonsymmorphic symmetry group.

In both the symmorphic and nonsymmorphic cases it is possible to write

$$\Gamma = \bigcup_{i=1}^{|\mathbb{F}|} T(R_i, \mathbf{v}_{R_i}) = \bigcup_{i=1}^{|\mathbb{F}|} (R_i, \mathbf{v}_{R_i})T \tag{6}$$

where $\mathbb{F} = T\backslash\Gamma$ is the "factor group" and $g_i = (R_i, \mathbf{v}_{R_i})$ is an element of the set of symmetry operators for the crystal with minimal translation part. T is the translation group for the lattice $\mathbb{L}$ (which is common to each Bravais space group and the crystallographic groups that result from filling the primitive Bravais unit cells with crystal motifs). For symmorphic crystals, it is always possible to take $\mathbf{v}_{R_i} = \mathbf{0}$ for all i in which case these symmetry operations is a group, whereas at least some $\mathbf{v}_{R_i} \neq \mathbf{0}$ in the nonsymmorphic case, and the resulting set of coset representatives (symmetry operators) does not form a group. When these are not zero, $(R_i, \mathbf{v}_{R_i})$ describes a screw transformation.

In analogy with the way that a group is divided into coset spaces, a space, X, on which a group, G, acts is also divided into orbits. For example, $\mathcal{R}$ acting on X divides it into spheres. The set of all of these orbits is denoted as $G\backslash X$. Some books denote this as X/G, but to be consistent with the definition of action in Eq. (4), in which g acts on the left of $\mathbf{x}$, it makes more sense to write $G\backslash X$ in analogy with the way that $H\backslash G$ preserves the order of $h \circ g$ in the definition of $Hg \in H\backslash G$.

An immediate crystallographic consequence of these definitions is that if Γ is the full chiral symmetry group of a crystal, $\Gamma\backslash X$ can be identified with the asymmetric unit. And if $T < \Gamma$ is the largest discrete translation group of the crystal (and so $T < \mathcal{T}$ also), then $T\backslash X$ can be identified with the primitive unit cell, and so too can $T\backslash\mathcal{T}$. Since T is a normal subgroup of $\mathcal{T}$, the unit cell is actually endowed with a group structure, namely, periodic addition. For this reason, a unit cell in n-dimensional space is equivalent to an n-dimensional torus, $T\backslash\mathcal{T} \cong \mathbb{T}^n$. This fact is implicitly and extensively used in crystallography to expand the density in a unit cell in terms of Fourier series. Furthermore, the translational motion of the contents of a unit cell is easy to handle within the framework of classical mathematics. However, if one wishes to focus attention in MR searches on the asymmetric unit $\Gamma\backslash X$, which is smaller than $T\backslash X$, and therefore advantageous from the perspective of the number of grid points required to describe it, then there is no associated group operation. Furthermore, even in the case when the whole unit cell is considered, though periodic translations are handled in an effortless way within the context of classical Fourier analysis, rotations of the rigid contents within a unit cell of a crystal are somewhat problematic within the classical framework, which provides the motivation for the current work.

Demonstration Why $\Gamma\backslash G$ is a Manifold With a Planar Example

As a concrete way to visualize these complex spatial phenomena, consider a simple planar example. In the plane, elements of $G = \mathrm{SE}(2)$ are parameterized as

$$H(g(x, y, \theta)) = \begin{pmatrix} \cos\theta & -\sin\theta & x \\ \sin\theta & \cos\theta & y \\ 0 & 0 & 1 \end{pmatrix}$$

The simplest planar space group is $p1$ which is just the lattice translation group

$$p1 = \{g(z_1, z_2, 0) | z_1, z_2 \in \mathbb{Z}\}$$

A fundamental domain $F_{\mathrm{p1}\backslash\mathrm{SE}(2)}$ corresponding to $\mathrm{p1}\backslash\mathrm{SE}(2)$ is

$$F_{\mathrm{p1}\backslash\mathrm{SE}(2)} = \{(x, y, \theta) \in [0,1) \times [0,1) \times [0, 2\pi)\}$$

This is an exact statement, but sometimes it is more convenient to examine the interior and closures of this set, which have purely open or purely closed boundaries rather than having both kinds

$$F^{\circ}_{\mathrm{p1}\backslash\mathrm{SE}(2)} \subset F_{\mathrm{p1}\backslash\mathrm{SE}(2)} \subset \overline{F_{\mathrm{p1}\backslash\mathrm{SE}(2)}}$$

The opposing faces of $\overline{F_{\mathrm{p1}\backslash\mathrm{SE}(2)}}$ can be identified with each other in the usual way, indicating that $\mathrm{p1}\backslash\mathrm{SE}(2)$ is simply a three-torus, $\mathbb{T}^3$. A way to verify this is to define

$$\begin{aligned} y_1 &= \cos(2\pi x) \\ y_2 &= \sin(2\pi x) \\ y_3 &= \cos(2\pi y) \\ y_4 &= \sin(2\pi y) \\ y_5 &= \cos\theta \\ y_6 &= \sin\theta \end{aligned}$$

This embeds the coset-space manifold $\mathrm{p1}\backslash\mathrm{SE}(2) \cong \mathbb{T}^3$ in $\mathbb{R}^6$. If the above equations are written together as

$$\mathbf{y} = \mathbf{y}(g(x, y, \theta))$$

then applying an arbitrary $\gamma \in p1$, it is easy to see that

$$\mathbf{y}(\gamma \circ g(x, y, \theta)) = \mathbf{y}(g(x, y, \theta)) \tag{7}$$

This invariance of the embedding under the action of $p1$ indicates that it does indeed correspond to the coset space $\mathrm{p1}\backslash\mathrm{SE}(2)$.

Another of the planar crystallographic groups is $\Gamma = p4$ consists of a lattice translations by one unit in the x or y direction and rotations at multiples of $\pi/2$. That is,

---

[3] http://www.cryst.ehu.es/

$$\Gamma = \{g(z_1, z_2, k\pi/2) | z_1,\ z_2 \in \mathbb{Z},\ k \in \{0,1,2,3\}\}$$

is the group of translations and rotations of a square lattice.

The set $\Gamma\backslash G$ again can be visualized as a "fundamental domain" $F_{\Gamma\backslash G} \subset G$ in which a single point in G from each coset is recorded. For the case at hand, we can take the closure of the fundamental domain as

$$\overline{F_{\mathrm{p4}\backslash\mathrm{SE}(2)}} \cong \{(x,y,\theta) \in [0,1] \times [0,1] \times [0,\pi/2]\} \tag{8}$$

and the coset space itself, $\mathrm{p}_4\backslash\mathrm{SE}(2)$ is this fundamental domain with opposing faces appropriately glued. However, unlike the case of $p1$ where the opposing faces are glued in the obvious way, this time the gluing is more complicated. When done properly, this produces a three-manifold with the property that when Γ acts on the left, it leaves all points fixed, and similarly when G acts on the right.

The reason why $\cong$ is used in the above expression rather than $=$ is that there are many equivalent (but different) ways to define fundamental domains. For example, it is also possible to say

$$\overline{F_{\mathrm{p4}\backslash\mathrm{SE}(2)}} \cong \{(x,y,\theta) \in [0,1/2] \times [0,1/2] \times [0,2\pi]\} \tag{9}$$

In both cases, left action by p4 on these closures of fundamental domains will "tile" SE(2) "with a little grout left over" corresponding to overlapping sets of measure zero where faces meet. In short, all that is meant by $S_1 \cong S_2$ is that

$$\bigcup_{\gamma\in\Gamma} \gamma \cdot S_1 = \bigcup_{\gamma\in\Gamma} \gamma \cdot S_2 = G$$

and

$$\mathrm{Vol}((\gamma \cdot S_i) \cap (\gamma' \cdot S_i)) = 0$$

for all $\gamma, \gamma' \in \Gamma$ and $i = 1,\ 2$. It is not a statement of topological equivalence or isomorphism as groups (in fact, the objects of study here are not groups, since Γ is not a normal subgroup of G).

The fundamental domain itself is a tricky thing to define because it is a half-open half-closed object. But its closure, as defined above, is easy to define, as is its interior $F^{\circ}_{\mathrm{p4}\backslash\mathrm{SE}(2)}$ (which is defined in the same way as the closure, but with open intervals (0, 1) and $(0, \pi/2)$). The true fundamental domain is related to these as

$$F^{\circ}_{\mathrm{p4}\backslash\mathrm{SE}(2)} \subset F_{\mathrm{p4}\backslash\mathrm{SE}(2)} \subset \overline{F_{\mathrm{p4}\backslash\mathrm{SE}(2)}}$$

and all three differ by only sets of measure zero (i.e., points on the bounding faces).

In the case of planar motion spaces, the result after gluing faces of the fundamental domains is generally more complicated than a three-torus. For example, starting with (8) or (9) and identifying g and $\gamma \circ g$, the faces of $\overline{F_{\mathrm{p4}\backslash\mathrm{SE}(2)}}$ must be twisted before they are glued together. Examining the action of p4 on SE(2), the following things can happen:

$$\begin{aligned}
(x,y,\theta) &\to (x + z_1, y + z_2, \theta), \\
(x,y,\theta) &\to (-y + z_1, x + z_2, \theta + \pi/2), \\
(x,y,\theta) &\to (-x + z_1, -y + z_2, \theta + \pi), \\
(x,y,\theta) &\to (y + z_1, -x + z_2, \theta + 3\pi/2)
\end{aligned}$$

(The first of the above is the p1 action, which will be present in all planar space groups.) A three-dimensional manifold can be embedded or immersed in six-dimensional space in a way that is invariant under such transformations. First to kill the effects of integer translations, as in the torus case trigonometric functions with 2π periodicity are used, and other functions that are invariant under rotations by increments of $\pi/2$ are used. For example,

$$\begin{aligned}
y_1 &= \cos(2\pi x) + \cos(2\pi y) \\
y_2 &= \cos(2\pi x) \cdot \cos(2\pi y) \\
y_3 &= (\cos(2\pi x) + \cos(2\pi y)) \sin 4\theta \\
y_4 &= (\cos(2\pi x) + \cos(2\pi y)) \cos 4\theta \\
y_5 &= \cos 4\theta \\
y_6 &= \sin 4\theta
\end{aligned}$$

has the desired invariance property (7) for the case when $\gamma \in p4$. From this expression, the correspondence with the fundamental domain (8) is clear since the factor of 4 expands the range $\theta \in [0, \pi/2]$ to $[0, 2\pi]$. But this is not unique. After all, it is a 3D surface in a 6D space. As an analogy, the circle can be embedded or immersed in 3D Euclidean space in an infinite number of ways. For example, the circle can be embedded in different ways by having a plane slice a sphere from different angles, or it can be embedded as a knot, or it can be immersed as a figure-eight pattern.

Another choice that uses the full range of θ and only half of the range of both x and y is

$$\begin{aligned}
y_1 &= \cos(4\pi x) + \cos(4\pi y) \\
y_2 &= \cos(4\pi x) \cdot \cos(4\pi y) \\
y_3 &= \sin^2(2\pi x) + \sin^2(2\pi y) \\
y_4 &= \sin^2(2\pi x) \cdot \sin^2(2\pi y) \\
y_5 &= \sin(4\pi x) \cos\theta + \sin(4\pi y) \sin\theta \\
y_6 &= \sin(4\pi y) \cos\theta - \sin(4\pi x) \sin\theta
\end{aligned}$$

and this corresponds to the fundamental domain (9) since if x and y each span half the range then $x + y$ will span the full range $[0, 1]$, and here there is no factor of 4 where θ appears.

Another option is also possible in which half (rather than one quarter) of the translational range is used and half (rather than one quarter or the full $[0, 2\pi]$) of the orientational range is used.

$$\begin{aligned}
y_1 &= \cos(2\pi(x+y)) + \cos(2\pi(x-y)) \\
y_2 &= \cos(2\pi(x+y)) \cdot \cos(2\pi(x-y)) \\
y_3 &= \sin(2\pi x) \cdot \sin(2\pi y) \cdot \sin(2\theta) \\
y_4 &= \sin(2\pi x) \cdot \sin(2\pi y) \cdot \cos(2\theta) \\
y_5 &= \sin^2(2\pi x) \cos^2\theta + \sin^2(2\pi y) \sin^2\theta \\
y_6 &= \sin^2(2\pi x) \sin^2\theta + \sin^2(2\pi y) \cos^2\theta
\end{aligned}$$

A Mathematical Formulation of Molecular Replacement

This section addresses why coset-space manifolds of the form $\Gamma\backslash G$ are important for biomolecular crystallography in the case of $G = \mathrm{SE}(3)$ and Γ being one of the 65 chiral space groups. The simplest of these space groups is called $P1$ (capital P rather than lower case p). It is the group of discrete translations of a lattice. This can be thought of as the set of homogeneous transformations of the form $P1 \doteq \{\mathrm{trans}([z_1, z_2, z_3]^{\mathrm{T}}) | z_i \in \mathbb{Z}\}$. As in the planar case, every space group contains this group of lattice translations as a normal subgroup. This condition is written as $T \lhd \Gamma$. The space group Γ itself will generally contain these translations, pure discrete rotations, and discrete screw displacements.

Suppose that the macromolecular structure of interest has an electron density $\rho(\mathbf{x})$. That is, there exists a function $\rho : X \to \mathbb{R}$. This function may be constructed by adding densities of individual domains within the structure.

This means that the total electron density of the nonsolvent part of the crystal will be

$$\rho_{\Gamma\backslash X}(\mathbf{x}) \doteq \sum_{\gamma\in\Gamma} \rho(\gamma^{-1} \cdot \mathbf{x})$$

The symmetry group, Γ, and number of copies of the molecule in a given unit cell can both be estimated directly from the experimental data. The inverse of γ is applied under the function to move $\rho(\mathbf{x})$ by γ in analogy with the way a function on the real line, $f(x)$, is translated one unit in the positive direction along the x axis by evaluating $f(x-1)$. Note that such a function $\rho_{\Gamma\backslash X}(\mathbf{x})$ is "Γ-periodic" in the sense that for any $\gamma_0 \in \Gamma$,

$$\rho_{\Gamma\backslash X}(\gamma_0^{-1}\cdot\mathbf{x}) = \rho_{\Gamma\backslash X}(\mathbf{x}) \tag{10}$$

Now suppose that before constructing symmetry-related copies of the density $\rho(\mathbf{x})$, we first move it by an arbitrary $g \in G$. The result will be $\rho(\mathbf{x};g) \doteq \rho(g^{-1}\cdot\mathbf{x}) = \rho(g^{-1}\cdot\mathbf{x};e)$. It is easy to see that

$$\rho_{\Gamma\backslash X}(\mathbf{x};g) \doteq \sum_{\gamma\in\Gamma}\rho(\gamma^{-1}\cdot\mathbf{x};g) = \sum_{\gamma\in\Gamma}\rho((\gamma\circ g)^{-1}\cdot\mathbf{x})$$

In an x-ray diffraction experiment for a single-domain protein, $\rho(\mathbf{x})$ is not obtained directly. Rather, the magnitude of the classical Fourier transform of $\rho_{\Gamma\backslash X}(\mathbf{x};g)$ is obtained. In general, if $\{\mathbf{a}_i | i=1,\ldots,n\}$ are the vectors describing lattice directions, so that each element of the group T consists of translations of the form $\mathbf{t}(k_1,k_2,\ldots,k_n) = \sum_{j=1}^{n} k_j\mathbf{a}_j \in T$, then the classical Fourier series coefficients for $\rho_{\Gamma\backslash X}(\mathbf{x};g)$ (which for each fixed $g\in G$ is a function on $T\backslash\mathcal{T}$) is denoted as $\hat{\rho}_{\Gamma\backslash X}(\mathbf{k};g)$. There is duality between the Fourier expansions for T and $T\backslash\mathcal{T}$, and likewise $\hat{U}\cong\mathbb{Z}^n$ is the unitary dual of U.

Now, the g in each of these expressions can be taken to be in G, but this is wasteful because G extends to infinity, and the same result appears whether g or $\gamma\circ g$ is used for any $\gamma\in\Gamma$. Therefore, the rigid-body motions of interest are those that can be taken one from each coset $\Gamma g \in \Gamma\backslash G$. If all such representatives of cosets $\Gamma g\in\Gamma\backslash G$ are collected, the result will be the fundamental region $F_{\Gamma\backslash G}\subset G$. A goal of MR is then to find $g\in F_{\Gamma\backslash G}$ such that $|\hat{\rho}_{\Gamma\backslash X}(\mathbf{k};g)|$ best matches with the diffraction pattern, $\hat{P}(\mathbf{k})$. In other words, a fundamental goal of MR is to minimize a cost function of the form

$$C(g) = \sum_{\mathbf{k}\in\hat{U}} d\left(\left|\hat{\rho}_{\Gamma\backslash X}(\mathbf{k};g)\right|, \hat{P}(\mathbf{k})\right) \tag{11}$$

where $d(\cdot,\cdot)$ is some measure of distance, discrepancy, or distortion between densities or intensities. No matter what the choice of $d(\cdot,\cdot)$, the cost functions $C(g)$ in Eq. (11) inherit the symmetry of $\rho_{\Gamma\backslash X}(\mathbf{x})$ in Eq. (10) in the sense that

$$C(g) = C(\gamma\circ g)\ \forall\ \gamma\in\Gamma \tag{12}$$

This makes $C(g)$ a function on $\Gamma\backslash G$ (or, equivalently, on $F_{\Gamma\backslash G}$), in analogy with the way that a periodic function on the real line can be viewed as a function on the circle.

Finding maximal values of $C(g)$ is essentially what MR is about. With this, diffraction patterns can be phased, and the inverse Fourier transform can be used to recover the electron density of the macromolecule of interest. Phasing is a necessary step in determining their three-dimensional structure. The importance of these structures in understanding biological processes and in designing new drugs is well known [23].

Details Regarding the Structure of Chiral Space Groups in Three-Dimensional Space

Every Bravais lattice has a space group that can be written as the semidirect product of the lattice translation group, T, and a point group of a Bravais lattice, P. That is, $\Gamma_{\mathrm{L}} = T\rtimes P$. Moreover, every chiral crystallographic space group, Γ, has the group of lattice translations as a subgroup, $T\le\Gamma$ such that $T\backslash\Gamma = \mathbb{F}$ is isomorphic to a point group formed by stripping away the translational parts of any screw transformations in $\mathbb{F}$ and keeping only the pure rotations that remain from these and from any pure rotations in $\mathbb{F}$.

Three-dimensional space groups are divided into two categories [10–12,24]. The first, called symmorphic (or simple), are semidirect products of a group of discrete lattice translations and discrete lattice rotations. These can be thought of as discrete analogs of SE(3) which is a semidirect product of continuous translations and rotations. The second category of space groups is called nonsymmorphic, and surprisingly, they cannot be written simply as a semidirect product of pure lattice rotations and pure lattice translations. That is, they always contain residual lattice screw motions. The easiest nonsymmorphic space group is $P2_1$. It is generated by concatenating the following transformations: $(x_1,x_2,x_3)\to(x_1+z_1,x_2+z_2,x_3+z_3)$ (the lattice translations where $z_i\in\mathbb{Z}$, as with any space group) and $(x_1,x_2,x_3)\to(-x_1,-x_2,x_3+1/2)$. That is all! The second transformation is a 2_1 screw displacement along the x_3 direction. Squaring it results in a lattice translation by one unit in that direction. The group generated by all such translations and screw displacements cannot be written as a semidirect product of lattice rotations and lattice translations, since the translation by 1/2 is not a lattice translation and cannot be decoupled from the rotation by π that is part of the screw motion. Examples of more complicated space groups are given in the Appendix.

Let Γ_{s} and Γ_{ns}, respectively, denote symmorphic and nonsymmorphic chiral crystallographic space groups. Then $\Gamma_{\mathrm{s}} = T\rtimes P_{\mathrm{s}}$ and it is possible to select elements of Γ_{s} to form a fundamental domain with a finite number of elements, $F_{\mathrm{T}\backslash\Gamma_{\mathrm{s}}}\cong\mathbb{F}_{\mathrm{s}}$, where

$$F_{\mathrm{T}\backslash\Gamma_{\mathrm{s}}} = \{\mathbf{0}\}\rtimes P_{\mathrm{s}} \tag{13}$$

Moreover,

$$F_{\mathrm{T}\backslash\Gamma_{\mathrm{s}}} < \Gamma_{\mathrm{s}} \tag{14}$$

Note here the equality (as groups) and inequality (denoting a subgroup–group relationship) rather than the weaker statements that would be implied if these were, respectively, congruence, and set inclusion signs. In the nonsymmorphic case it is still possible to write

$$F_{\mathrm{T}\backslash\Gamma_{\mathrm{ns}}}\cong\mathbb{F}_{\mathrm{ns}} = T\backslash\Gamma_{\mathrm{ns}}\cong P_{\mathrm{ns}}\le P \tag{15}$$

and $F_{\mathrm{T}\backslash\Gamma_{\mathrm{ns}}}\subseteq\Gamma_{\mathrm{ns}}$, but it is no longer possible to write Eq. (13) and in general it is not the case that $F_{\mathrm{T}\backslash\Gamma_{\mathrm{ns}}}\subseteq\Gamma_{\mathrm{L}}$ or $\{\mathbf{0}\}\rtimes P_{\mathrm{ns}}\le\Gamma_{\mathrm{ns}}$ or statements that would follow from them analogous to Eq. (14).

The fact that $\mathbb{F}$ (which can be either P_{s} or $\mathbb{F}_{\mathrm{ns}}$) is a group follows from the fact that T is not only a subgroup but also normal in all cases. This means that $T\backslash\Gamma = \Gamma/T = \mathbb{F}$ is a group in its own right.

Let $X=\mathbb{R}^n$ and $G=\mathrm{SE}(n)$. The structure of space groups is important in the context of characterizing allowable motions within asymmetric units because the space $\Gamma\backslash G$ can be decomposed in different ways. For example, it is always possible to write

$$F_{\Gamma\backslash G}\cong\left(F_{\Gamma\backslash X}\right)\times\mathrm{SO}(3)$$

In other words, the fundamental region of the quasi-group can be taken as the product of translations within the asymmetric unit and the whole of the rotation group. Moreover, if Γ is symmorphic it is possible to write

$$F_{\Gamma_{\mathrm{s}}\backslash\mathrm{G}} = \left(F_{\mathrm{T}\backslash\mathrm{X}}\right)\times\left(F_{\mathrm{P_s}\backslash\mathrm{SO(3)}}\right) \tag{16}$$

This is convenient because when the fundamental region for T\X is taken to be the Wigner–Seitz cell, which has the point symmetry group $\mathrm{P_s}$, then the fundamental region for $\Gamma_s \backslash \mathrm{G}$ is invariant under conjugation with respect to elements of $\mathrm{P_s}$.

In the nonsymmorphic case, it can also be that the Wigner–Seitz unit cell has some rotational symmetries (corresponding to the subset of symmetry operations with $\mathbf{v}_{\mathrm{R}_i} = \mathbf{0}$). If there exists a nonempty subset of these operators that is closed under multiplication, then the resulting point group formed by these elements, P_{u}, will be a subgroup of $\mathbb{F}_{\mathrm{ns}}$.[4] Moreover, $T \rtimes P_{\mathrm{u}}$ will be a symmorphic subgroup of the nonsymmorphic group Γ_{ns} and P_{u} will be a subgroup of the point group P of the Wigner–-Seitz unit cell corresponding to $T \backslash X$. This means that

$$F_{(\mathrm{T} \rtimes \mathrm{P_u}) \backslash \mathrm{X}} \cong F_{\mathrm{P_u} \backslash (\mathrm{T} \backslash \mathrm{X})}$$

The reason why this is relevant to the main topic of the paper is that since most macromolecular crystals are nonsymmorphic, it cannot be assumed that (16) holds, and we seek alternative admissible ways to decompose $\Gamma \backslash G$. In prior work, sampling schemes for these spaces have been investigated [25,26,27–29].

In all cases

$$\mathrm{Vol}(T \backslash X) = |\mathbb{F}| \cdot \mathrm{Vol}(\Gamma \backslash X)$$

Therefore,

$$\mathrm{Vol}(T \backslash X) = |P_{\mathrm{u}}| \cdot \mathrm{Vol}((T \rtimes P_{\mathrm{u}}) \backslash X)$$

and

$$\mathrm{Vol}(T \backslash X) = |\mathbb{F}_{\mathrm{ns}}| \cdot \mathrm{Vol}(\Gamma_{\mathrm{ns}} \backslash X)$$

Equating these two expressions gives

$$\mathrm{Vol}((T \rtimes P_{\mathrm{u}}) \backslash X) = \frac{|\mathbb{F}_{\mathrm{ns}}|}{|P_{\mathrm{u}}|} \cdot \mathrm{Vol}(\Gamma_{\mathrm{ns}} \backslash X) \tag{17}$$

If $|\mathbb{F}_{\mathrm{ns}}| = |P_{\mathrm{u}}| + |S|$ (where $|S|$ is the number of screw symmetry operations) and since $P_{\mathrm{u}} < \mathbb{F}_{\mathrm{ns}}$, then from Lagrange's theorem $|P_{\mathrm{u}}| \backslash |\mathbb{F}_{\mathrm{ns}}| = |P_{\mathrm{u}} \backslash \mathbb{F}_{\mathrm{ns}}|$ must be a positive integer. Furthermore, $|P_{\mathrm{u}}| \backslash |\mathbb{F}_{\mathrm{ns}}| = 1 + |P_{\mathrm{u}}| \backslash |S|$, and so $|P_{\mathrm{u}}| \backslash |S|$ must be a nonnegative integer. And so the number of screw transformations in the set of coset representatives of $\mathbb{F}_{\mathrm{ns}} = T \backslash \Gamma_{\mathrm{ns}}$ must be an integer multiple of the number of coset representatives that are rotational transformations.

Conclusions

In search algorithms that seek to place rigid models of molecules in a lattice under symmetry constraints, the subset of rigid-body motions that is relevant is the fundamental domain $F_{\Gamma \backslash G} \subset G$ corresponding to an appropriately chosen set of representatives from each right coset in the space $\Gamma \backslash G$, where $G = \mathrm{SE}(3)$ and Γ is a crystallographic subgroup of G, which in general can consist of lattice translations, discrete rotations, and discrete screw transformations. The compact space $F_{\Gamma \backslash G}$ is not a group, and is referred to here as a motion space. Characterizing the size and shape of this space requires a combination of tools both from kinematics and from crystallography, as explained here and in a recent paper.

Acknowledgment

This work was supported by NSF Grant RI-Medium: IIS-1162095 and NIH Grant RO1 GM113240. The author would like to thank Dr. Sajdeh Sajjadi for useful discussions.

Nomenclature

$\mathbb{F}$ = the factor group $\Gamma/T = T \backslash \Gamma$
$F_{\Gamma \backslash G}$ = the fundamental domain in G corresponding to $\Gamma \backslash G$
G = shorthand for SE(3), a six-dimensional Lie group
$\mathbb{L}$ = a lattice in Euclidean space
$\mathbb{R}^n$ = n-dimensional Euclidean space
SE(n) = the special Euclidean group of n-dimensional space
T = the discrete group of translational symmetries of a lattice
$\mathbb{T}^n$ = the n-dimensional torus
X = shorthand for $\mathbb{R}^n$ (parameterized in Cartesian coordinates $\{x_i\}$)
$\mathbb{Z}$ = the integers
Γ = a chiral crystallographic space group

Appendix: Coset Representative for $T \backslash \Gamma$ for the Most Common Macromolecular Space Groups

The most commonly encountered space groups, Γ, in the PDB are listed below together with coset representatives of $P_1 \backslash \Gamma$ computed from the Bilbao crystallographic server [30]. The coset reps, γ, are listed as $\gamma \cdot \mathbf{x}$ where $\mathbf{x} = [x, y, z]^{\mathrm{T}}$ is an arbitrary position in the asymmetric unit. This is done instead of using the 4×4 matrix $H(g)$ to save space. A few of the most common space groups (defined by their action on arbitrary $\mathbf{x} = (x, y, z)^{\mathrm{T}} \in \mathbb{R}^3$ are listed below

(case 1) $P_{2_1 2_1 2_1}$: (x,y,z); $(-x+1/2, -y, z+1/2)$; $(-x, y+1/2, -z+1/2)$; $(x+1/2, -y+1/2, -z)$;
(case 2) P_{2_1}: (x,y,z); $(-x, y+1/2, -z)$;
(case 3) C_2: (x,y,z); $(-x,y,-z)$; $(x+1/2, y+1/2, z)$; $(-x+1/2, y+1/2, -z)$;
(case 4) $P_{2_1 2_1 2}$: (x,y,z); $(-x,-y,z)$; $(-x+1/2, y+1/2, -\mathrm{z})$; $(x+1/2, -y+1/2, -z)$;
(case 5) C_{222_1}: (x,y,z); $(-x,-y,z+1/2)$; $(-x,y,-z+1/2)$; $(x,-y,-z)$; $(x+1/2, y+1/2, z)$;
$(-x+1/2, -y+1/2, z+1/2)$; $(-x+1/2, y+1/2, -z+1/2)$; $(x+1/2, -y+1/2, -z)$;
(case 6) $P_{4_3 2_1 2}$: (x,y,z); $(-x,-y,z+1/2)$; $(-y+1/2, x+1/2, z+3/4)$; $(y+1/2, -x+1/2, z+1/4)$; $(-x+1/2, y+1/2, -z+3/4)$; $(x+1/2, -y+1/2, -z+1/4)$; $(y,x,-z)$; $(-y,-x,-z+1/2)$; The value of $|P_{\mathrm{u}}| \backslash |S|$ in these six cases are, respectively, 3, 1,1, 1, 3, and 3.

References

[1] Bottema, O., and Roth, B., 1990, *Theoretical Kinematics*, Dover, Mineola, NY.
[2] Angeles, J., 1988, *Rational Kinematics*, Springer-Verlag, New York.
[3] McCarthy, J. M., 1990, *Introduction to Theoretical Kinematics*, MIT Press, Boston, MA.
[4] Park, F. C., 1991, "The Optimal Kinematic Design of Mechanisms," Ph.D. thesis, Division of Engineering and Applied Sciences, Harvard University, Cambridge, MA.
[5] Murray, R. M., Li, Z., and Sastry, S. S., 1994, *A Mathematical Introduction to Robotic Manipulation*, CRC, Boca Raton, FL.
[6] Selig, J. M., 1996, *Geometrical Methods in Robotics*, Springer, New York.
[7] Karger, A., and Novák, J., 1985, *Space Kinematics and Lie Groups*, Gordon and Breach, New York.
[8] Park, F. C., and Ravani, B., 1995, "Bézier Curves on Riemannian Manifolds and Lie Groups With Kinematics Applications," ASME J. Mech. Des., **117**(1), pp. 36–40.
[9] Kazerounian, K., and Rastegar, J., 1992, "Object Norms: A Class of Coordinate and Metric Independent Norms for Displacement," *Flexible Mechanisms, Dynamics, and Analysis*, ASME, Vol. 47, pp. 271–275.
[10] Bradley, C., and Cracknell, A., 1972/2010, *The Mathematical Theory of Symmetry in Solids*, Oxford University, Oxford, UK.
[11] Burns, G., and Glazer, A. M., 1990, *Space Groups for Solid State Scientists*, 2nd ed., Academic, Boston, MA.
[12] Janssen, T., 1973, *Crystallographic Groups*, North Holland/Elsevier, New York.
[13] Ball, R. S., 1900, *A Treatise on the Theory of Screws*, Cambridge University Press, Cambridge, UK.
[14] Schoenflies, A., 1891, *Theory of Crystal Structure*, Teubner, Leipzig, Germany.

---

[4] In the symmorphic case $P_{\mathrm{u}} = \mathbb{F}_{\mathrm{ns}} = P_{\mathrm{ns}}$.

[15] Fedorov, E. S., 1971, *Symmetry of Crystals*, American Crystallographic Association, Paper Number 7, (English translation of 1885 book in Russian).

[16] Barlow, W., 1894, "Über die Geometrischen Eigenschaften homogener starrer Strukturen und ihre Anwendung auf Krystalle," Z. Krystallogr. Mineral., **23**, p. 1-63.

[17] Hilton, H., 1963, *Mathematical Crystallography and the Theory of Groups of Movements*, Dover, Mineola, NY.

[18] H. M. Berman, T. Battistuz, T. N. Bhat, W. F. Bluhm, P. E. Bourne, K. Burkhardt, Z. Feng, G. L. Gilliland, L. Iype, S. Jain, P. Fagan, J. Marvin, D. Padilla, V. Ravichandran, B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook, and C. Zardecki, 2002, "The Protein Data Bank," Acta Crystallogr., Sect. D: Biol. Crystallogr., **58**(6), pp. 899–907.

[19] Rossmann, M. G., and Blow, D. M., 1962, "The Detection of Sub-Units Within the Crystallographic Asymmetric Unit," Acta Crystallogr., **15**(1), pp. 24–31.

[20] Rossmann, M. G., 2001, "Molecular Replacement - Historical Background," Acta Crystallogr., Sect. D: Biol. Crystallogr., **57**(10), pp. 1360–1366.

[21] Chirikjian, G. S., and Kyatkin, A. B., 2001, *Engineering Applications of Noncommutative Harmonic Analysis*, CRC Press, Boca Raton, FL.

[22] Chirikjian, G. S., 2009/2012, *Stochastic Models, Information Theory, and Lie Groups: Volumes I + II*, Birkhäuser, Boston, MA.

[23] Rupp, B., 2010, *Biomolecular Crystallography: Principles, Practice, and Application to Structural Biology*, Garland Science, Taylor and Francis Group, New York.

[24] Senechal, M., 1980, "A Simple Characterization of the Subgroups of Space Groups," Acta Crystallogr., Sect. A: Found. Crystallogr., **36**(6), pp. 845–850.

[25] Chirikjian, G. S., 2011, "Mathematical Aspects of Molecular Replacement: I. Algebraic Properties of Motion Spaces," Acta. Crystallogr., Sect. A: Found. Crystallogr., **67**(5), pp. 435–446.

[26] Chirikjian, G. S., and Yan, Y., 2012, "Mathematical Aspects of Molecular Replacement: II. Geometry of Motion Spaces," Acta. Crystallogr., Sect. A: Found. Crystallogr., **68**(2), pp. 208–221.

[27] Yan, Y., and Chirikjian, G. S., 2011, "Molecular Replacement for Multi-Domain Structures Using Packing Models," ASME Paper No. DETC2011-48583.

[28] Yan, Y., and Chirikjian, G. S., 2012, "Almost-Uniform Sampling of Rotations for Conformational Searches in Robotics and Structural Biology," ICRA 2012, Minneapolis, MN, May 14–18, pp. 4254–4259.

[29] Yan, Y., and Chirikjian, G. S., 2013, "Voronoi Cells in Lie Groups and Coset Decompositions: Implications for Optimization, Integration, and Fourier Analysis," 52nd IEEE Conference on Decision and Control, Firenze, Italy, Dec. 10–13.

[30] Aroyo, M., Perez-Mato, J. M., Capillas, C., Kroumova, E., Ivantchev, S., Madariaga, G., Kirov, A., and Wondratschek, H., 2006, "Bilbao Crystallographic Server: I. Databases and Crystallographic Computing Programs," Zeitschrift für Kristallographie, **221**(1), pp. 15–27.