Chirality and Symmetry Measures: A Transdisciplinary Review

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Received: 20 April 2003 / Accepted: 3 July 2003 / Published: 3 July 2003

Abstract: Many quantitative measures of the degree of chirality or symmetry of a set have been proposed in the literature. The main approaches from various areas are reviewed: chemistry, physics, mathematics, computer sciences, biology, and psychophysics. Relations between chirality, symmetry, and other concepts such as similarity, disorder and entropy, are discussed.

Keywords: chirality; symmetry; measure; continuous; quantitative; chiral index; direct symmetry index; asymmetry coefficient; skewness; chirality functions; quasi-symmetry; fuzzy symmetry.

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1 Introduction

The symmetry concept is used in a large number of situations [1], but is usually viewed dichotomically: there **is** symmetry, or there **is not**. In euclidean space, geometric chirality is related to indirect symmetry, as stated by Lord Kelvin [2]: **"**I call any geometrical figure, or group of points, *chiral*, and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.**"**. Following this definition, a set **is** or **is not** chiral. The scope of this paper is to review the main approaches considering symmetry and chirality as quantitatively measurable parameters: i.e. a set is **more** or **less** symmetric, and is **more** or **less** chiral.

It is emphazised that symmetry and chirality have particular meanings in chemistry [3], and it is known that dynamic and stochastic aspects should be considered when chirality is related to an observable physical phenomenon, such as optical activity. Then, the contrast between the usual dichotomic aspect of chirality and the quantitative nature of the physical phenomenon has been noted [4]. Although most applications of quantitative chirality theories appear in chemistry and physics, this review deals only with their mathematical aspects. Thus, any further occurrence of the word "chirality" is to be taken in some geometric meaning, but not in any physical or chemical sense.

Provided that some points in euclidean space may have identical coordinates, weighted points may exist, and thus the masses can be considered as a part of any geometric model of symmetry or chirality. The strictly geometric situation, i.e. without any mass, can be viewed as a particular situation for which all points have equal masses. The chirality of a non-signed charge distribution can be handled with the same tools as for a mass distribution.

2 Chirality measures in chemistry and physics

2.1 From asymmetry products to chirality functions

The oldest definition of a continuous function of a set, which vanishes at achirality, seems to be the asymmetry product of Guye [5-8]. It was empirically correlated with the optical rotatory power, and goes back to 1890. The set is assumed to be a regular terahedron with a weighted ligand centered at each of its four vertices. The asymmetry product P_A is:

$$P_A = d_1 \cdot d_2 \cdot d_3 \cdot d_4 \cdot d_5 \cdot d_6 \tag{2.1.1}$$

where the six quantities d_i are the distances from the mass center to the six planes of symmetry of the regular terahedron. The masses of the ligands being m_1, m_2, m_3, m_4, the asymmetry product is shown to be proportional to the product P of the six differences of the masses:

$$P = (m_1 - m_2)(m_1 - m_3)(m_1 - m_4)(m_2 - m_3)(m_2 - m_4)(m_3 - m_4) \tag{2.1.2}$$

The asymmetry product is a pseudoscalar. Its absolute value is invariant under isometries, and its sign is changed upon inversion. Exchanging two ligands in equation (2.1.2) inverts the sign of the asymmetry product. A similar concept was also proposed in 1890 by Brown [9], where the mass could be replaced by a more general function of the ligand, this latter not being described. It was also intended for empirical correlations with the optical rotatory power. A formal analog of equation (2.1.2) was obtained in 1934 by Boys [10,11], as part of a theoretical calculation of the optical rotatory power, based upon a physical model.

Generalizations of the asymmetry product appeared during the end of the sixties [12-15], and were named "chirality functions" by Ruch and Schönhofer when they published the first general theory in 1970 [15]. Later, numerous papers related to chirality functions were published [16-41], dealing with the mathematical properties of chirality functions and their relations with group theory, and several controversies arose about these properties. A chirality function is specific to a class of molecular models, such as the tetrahedron class or the trigonal bipyramid class, but is not common to both classes. An example of a chirality function for the trigonal bipyramid class is [13]:

$$P = (\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1)(\lambda_4 - \lambda_5) \tag{2.1.3}$$

where the vertices of the base of the bipyramid are labelled 1, 2, 3, the two other vertices are labelled 4 and 5, and λ is some function of the ligand.

Thus the magnitude of the chirality function could be used as a quantitative measure of chirality, but only within a predefined class. Following this concept, the maximal chirality triangle in R^2 has been shown to be asymptotically linear [42]. The sign of the chirality function is also problematic, just as the homochirality concept. Quoting again Lord Kelvin [2]: **"**Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar or 'allochirally' similar (but heterochirally is better).**"**. However, it has been noted that there are classes for which homochirality is meaningless [14,43].

For example, consider the following chiral set of five indistinguishable points in R^3, which is related to the trigonal bipyramid class: $x_1 = (-1, 1/2, 1/2)$, $x_2 = (2, 0, 0)$, $x_3 = (0, 3, 0)$, $x_4 = (0, 0, 4)$, and $x_5 = (0, -5, -5)$. Now, setting $x'_1 = (1, 1/2, 1/2)$, we consider the following family of sets: $\{\alpha_1 \cdot x_1 + (1 - \alpha_1) \cdot x'_1, \alpha_2 \cdot x_2, x_3, x_4, x_5\}$, α_1 and α_2 being real numbers. Starting with $\alpha_1 = 1$ and $\alpha_2 = 1$, which is our original set, we consider continuously decreasing values of α_1 from 1 to 0, then continuously decreasing values of α_2 from 1 to -1. Obviously, every member encountered in the family is chiral, and the final set is the mirror image of the initial one through the yz plane. A continuous function of the coordinates, taking null values only for achiral figures, should therefore keep the same sign for these two mirror images. The conclusion is the same when the points are all distinct, i.e. when they have all different colors.

In fact, it has been shown that any d-dimensional set containing $n \geq d + 2$ point can be transformed continuously into its mirror image without passing through an achiral arrangement [44] (see also [45-48]). The existence of chemical compounds such that enantiomeric conformations are interconverted by rotameric changes without passing through geometric achirality was postulated by Mislow in 1954 [49], who gave as an example meso-4,4'-di(s-butyl)-2,6,2',6'-tetramethylbiphenyl. The synthesis of an analog was reported one year later [50].

It follows that empirical correlations between chirality functions and physical pseudoscalar properties should be handled with care. The existence of continuous pseudoscalar chirality functions having "chiral zeroes" has been postulated, but they are inadequate as chirality measures [51].

A pseudoscalar quantity, proposed in 1983 by Damhus and Schäffer [52], is not related to chirality functions theory, but has some similarities. A class of molecular models is defined, such that an ordered triplet of oriented segments is defined. The triple product is the pseudoscalar quantitative chirality measure.

2.2 Measures based on the Hausdorff distance

Quantitative chirality measures were reviewed in 1992, and classified into two categories [53]: the first kind of measure arises from a deviation of the chiral set from an idealized achiral reference, and the second kind from a similarity measure between the set and its mirror image, this measure being minimized for all rotations and translations. For these two situations, a similarity measure is needed. Rassat proposed in 1984 [54] to use the Hausdorff distance as a similarity measure, in order to define a left-right classification. Provided that a primary distance $d(x, y)$ between two elements x and y in a metric space is defined, the Hausdorff distance between two subsets X and Y of this metric space is:

$$H(X,Y) = Max\{Sup_{\{x\in X\}}(Inf_{\{y\in Y\}}d(x,y)), Sup_{\{y\in Y\}}(Inf_{\{x\in X\}}d(x,y))\} \quad (2.2.1)$$

The advantage of the Hausdorff distance in our context, comes from its applicability both to discrete sets of points and to homogeneous solids (domains of euclidean space). In 1992 Buda and Mislow [55] used the minimized Hausdorff distance between the mirror images, normalized to the diameter of the set (i.e. the upper bound of the distances between two points of the set). The computation of the minimized distance was performed with an iterative numerical procedure. This latter chirality measure has been used for empirical correlations [56], and a normalized minimized Hausdorff distance between enantiomorphic configurations of charges has been reported [57]. The concept introduced by Rassat was extended by Mezey [58] to molecular electron density clouds using fuzzy sets theory (see section 2.4).

2.3 Volume overlap-related measures

Gilat proposed in 1985 the following second kind of chirality measure [59], which takes values between 0 and 1:

$$\chi = (V(A \cup A') - V(A \cap A'))/V(A) \quad (2.3.1)$$

where A' is the mirror image of A, $V(A \cup A')$ is the volume of their union, $V(A \cap A')$ is the volume of their intersection, and V(A) is their common volume.

The d-dimensional volume of the symmetric difference has the mathematical properties of a distance, and was introduced by Dinghas [60]. It is also equal to the sum of the individual volumes, minus twice the volume of the intersection. Kitaigorodskii [61] proposed the usual 3D volume of the symmetric difference as a similarity criterion in the 3D space. The square root of the Dinghas distance is the L^2 distance Δ between the indicator functions 1_A and $1_{A'}$ of the domains:

$$\Delta^2(1_A, 1_{A'}) = \int (1_A(x) - 1_{A'}(x))^2 dx \qquad (2.3.2)$$

The d-dimensional integrals in (2.3.1) and (2.3.2) are of course minimized for all rotations and translations of either A or A'.

Gilat has proposed measures of chirality from formal analogs of (2.3.1) and (2.3.2) using masses, charges, inertias [59], and surfaces and wavefunctions [62]. It is known that the surface is not adequate to define a distance, because $A \subset B \Rightarrow S(A) \leq S(B)$ is an erroneous assumption, except for convex sets [63].

Conditions for an achiral intersection in (2.3.1) have been derived [64], and non-trivial upper bounds have been found for convex bodies [65]. Gilat noted that the volume-based chirality measures are unable to handle subdimensional objects, although Hausdorff distance chirality measures are difficult to compute for continuous sets [66].

In 1991 Buda and Mislow computed maximal chirality triangles using a criterion related to (2.3.1): see [67,68] and references cited in [67].

The L^2 scalar product $S(f_A, f_B)$ of two functions f_A and f_B, normalized to the product of their induced norms, is the formal analog $C(f_A, f_B)$ of the cosine of two vectors, and takes values between -1 and $+1$. The distance induced by the norm is $\Delta(f_A, f_B)$:

$$S(f_A, f_B) = \int f_A(x) \cdot f_B(x) dx \qquad (2.3.3)$$
$$C(f_A, f_B) = S(f_A, f_B)/(S(f_A, f_A) \cdot S(f_B, f_B))^{1/2} \qquad (2.3.4)$$
$$\Delta^2(f_A, f_B) = S(f_A, f_A) + S(f_B, f_B) - 2 \cdot S(f_A, f_B) \qquad (2.3.5)$$

Maximizing for rotations and translations of B, either $S(f_A, f_B)$ or $C(f_A, f_B)$, is equivalent to minimize $\Delta(f_A, f_B)$.

Provided that f is fixed, and assuming that A' is the mirror image of A, second kind of chirality measures based on $C(f_A, f_{A'})$ or on any normalized value of $S(f_A, f_{A'})$ or $\Delta(f_A, f_{A'})$ all induce the same chirality scale.

The chirality coefficients $1 - C(f_A, f_{A'})$ proposed in 1991 by Meyer and Richards [69] and in 1993 by Seri-Levy and Richards [70,71] are related to those of Gilat. The function f was either the electrostatic potential or the indicator function of the van der Waals volume. Both chirality coefficients were computed numerically.

Mezey proposed in 1997 a volume overlap-based chirality measure [72], which reduces in fact to that of Gilat. In 1999 Mezey et al. proposed to use the scalar product of electron densities as a chirality measure [73].

2.4 Quasi-symmetry and fuzzy sets

Maruani and Mezey proposed in 1987 to use fuzzy set theory to quantify quasi-symmetry via the "syntopy" concept [74-78], both for direct and indirect symmetry. In 1991 Mezey proposed to use resolution based similarity measures to define chirality measures [79]. This was done via approximation of a set by equally sized contiguous cells or cubes. The minimal number of cells to be removed or added to obtain an achiral structure or polycube, normalized to the initial number of cells, defines the two chirality measures [80]. Weinberg and Mislow updated the classification of chirality measures in 1995 [81]: first and second kinds of chirality measures (see section 2.2) were grouped in the class of "congruity measures", although the symmetry deficiency measures were in the class of "resolution measures". The fuzzy set approaches were considered to fall into either of the classes.

A family of second kind of chirality measures using a fuzzy Hausdorff-type distance was defined by Mezey [58]. It is based on density domains limited by a fixed value of the membership function. This membership function is a generalization of the indicator function, and is allowed to take any value between 0 and 1.

2.5 Asymmetry functions and dissymmetry functions

The second kind of chirality measures of a 3D set of weighted points (atoms), introduced by Kuzmin and Stelmakh in 1987 [82], were called either "asymmetry functions", or "dissymmetry functions", depending on the papers and their English translation from Russian.

The set is oriented in its principal axis of inertia, and the atoms are partitioned according to their type. The mirror image is generated via one of the following symmetry operations: S_1, S_2, S_4 and S_6. The reflections through each of the three principal planes are considered successively. For a given reflection, each of the n atoms of the set is associated with an atom of its mirror image of the same type. When several pairs are posible, they are selected according to the smallest length criterion. The sums of the lengths of the n pairs are DA_x, DA_y and DA_z for the reflection through the yz, zx, and xy plane, respectively. The degree of asymmetry associated with a given symmetry operation is DA^{S_k}, with $k = 1, 2, 4, 6$, and AF is the overall asymmetry function:

$$DA^{S_k} = (DA_x^{S_k} \cdot DA_y^{S_k} \cdot DA_z^{S_k})^{1/3} \qquad (2.5.1)$$
$$AF = (DA^{S_1} \cdot DA^{S_2} \cdot DA^{S_4} \cdot DA^{S_6})^{1/4} \qquad (2.5.2)$$

Kuzmin and Stelmakh proposed also to define the function AF from other parameters rather than from the masses, such that van der Waals volumes, refraction, or unit masses [83]. The atomic parameter may be weighted by its squared distance from the center, and AF may be normalized or not. Calculations have been performed and used for empirical correlations [83-85]. Taking in account all possible ways of proceeding with the four operations S_k along the three coordinate axis, led Kuzmin et al. to extend in 1992 the second member of equation (2.5.2) to a product of ten terms, such that the geometric average, now called DF, is an 1/10 power of this product of ten terms [86]. Calculations have been performed for empirical correlations [87,88], and stereochemical analysis [89]. Alikhanidi and Kuzmin introduced in 2000 some further refinements in the dissymetry function, including the consideration of $S_{k>6}$ and C_k symmetries [90].

2.6 Chirality measures from the folding/unfolding process

Hel-Or, Peleg and Zabrodsky proposed in 1988 a method based on the polar representation of a 2D arc of curve, for which the cumulated length associated with an increasing radius differs from the cumulated length associated with a decreasing one. Pixels were considered for practical calculations. The authors found that the method works only for some 2D figures [91]. Hel-Or, Peleg and Avnir applied a related method in 1990 to planar molecular models of alkanes [92]. Avnir and Meyer measured in 1991 the chirality of halogenated hydrocarbons, from the deviation between the center of an achiral reference conformer and the center of the chiral substituted compound [93].

CSM (Continuous Symmetry Measures) and CCM (Continuous Chirality Measures) were introduced in 1992 by Zabrodsky, Peleg and Avnir [94]. Many papers about these measures have been since published [95-137], most of them dealing with applications in chemistry or computer sciences. The measures are based on the folding/unfolding process [98,121], which defines an idealized reference figure. The CSM is associated with a given symmetry, and the CCM is associated either with a reflection or with an improper rotation axis.

The CCM associated with a reflection has been defined from the following steps [102]:

(a) The set is centered, and normalized to the squared highest distance from the mass center, or to the mean square [116].
(b) A reflection axis or plane passing through the origin is selected.
(c) Divide the points into pairs and single points. Two points associated in a pair should be of the same type (e.g. two hydrogens of a same methyl group).
(d) Perform the folding/unfolding process as follows. We consider two points p_1 and p_2 separated by the reflection axis or plane σ. The mid-point of p_1 and of the symmetric of p_2 through σ is $\hat{p}_1$ (folding step and averaging step). The symmetric of $\hat{p}_1$ through σ is $\hat{p}_2$ (unfolding step). When p_1 is a single point, a duplicate $p_2 = p_1$ is created, $\hat{p}_1 = p_1$ and $\hat{p}_2$ is the symmetric of p_2 through σ.
(e) Compute the sum S of the n squared distances $d^2(p_i, \hat{p}_i)$.
(f) Repeat steps (b), (c), (d), (e) to minimize S for all axis and divisions of the points.

$$CCM = \frac{100}{n} Min(S) \qquad (2.6.1)$$

The optimal division of the points is a combinatorial problem. When the points are the atoms at the vertices of a chemical graph, the combinatorial problem is related to the enumeration of graph isomorphisms of order 2 [102]. For a 2D set of points associated pairwise, the optimal axis is known analytically [102].

The CCM associated with an improper rotation of odd order has been defined as the CCM associated with a reflection, and the CCM associated with an improper rotation of even order k has been defined from the following steps [102]:

(a) The set of points is centered and normalized as previously.

(b) An improper rotation axis passing through the origin is selected.

(c) Divide the points into k-uplets of ordered points, pairs of points, and single points. Each pair of points is duplicated $k/2$ times, and each single point is duplicated k times. The total number of points p_i is n, and is now a multiple of k: $n = m \cdot k$. There are m tuples of points. The k points in a tuple are ordered and should be of the same type.

(d) Fold the tuples by applying the k improper rotations associated with the axis, to each of the k members of each tuple. Each of the m generated clusters of k points is averaged, and the m average points are unfolded into $m \cdot k$ points $\hat{p}_i$ by applying to them the reverse k improper rotations.

(e) Compute the sum S of the n squared distances $d^2(p_i, \hat{p}_i)$.

(f) Repeat steps (b), (c), (d), (e) to minimize S for all axis and divisions of the points.

The set of $n = m \cdot k$ points is an idealized symmetric reference, and the CCM is computed according to equation (2.6.1).

Alikhanidi and Kuzmin proposed in 1998 to modify the CSM and CCM by weighting the squared distances with various parameters, and to reduce the search of the optimal 3D axis to the principal axis [122]. In 1999 they modified the CCM again, and used the minimized sum of squared distances from the reflected image [123]. The associated optimal orientation was computed iteratively, using the four Euler quaternionic parameters. The chirality measure was named EDF (Enantiomeric Dissimilarity Factor) [124].

Still in 1999, Salomon and Avnir used the (4×4) matricial representation of the quaternions to compute analytically the optimal rotation associated with their own CCM [125].

2.7 Using distance functions

Murray-Rust, Bürgi and Dunitz considered in 1978 linear combinations of internal coordinates (angles and lengths) to evaluate deviations from symmetric configurations, such as the tetrahedron [139-141]. The tetrahedron is both symmetric and achiral, and measuring the deviation could be viewed as an attempt to quantify either direct or indirect symmetry. Following the idea of working in the conformational space, Auf der Heyde, Buda and Mislow computed in 1991 a maximal chirality triangle from the minimal distance to the closest achiral triangle [142].

Weinberg and Mislow [143] proposed in 1993 to use various distance functions to define both first and second kinds of chirality measures (i.e. the distance is computed either between the set and an achiral reference, or between the two mirror images). They considered the Hausdorff distance (equation (2.2.1)), and the p-euclidean distance D_p between two points x and y in R^d:

$$d_p(x,y) = (\sum_{i=1}^{i=d}(x_i - y_i)^p)^{1/p} \quad (2.7.1)$$
$$d_\infty(x,y) = Max_{\{i=1..d\}}|x_i - y_i| \quad (2.7.2)$$

The distance D_p was applied to triangles in R^2. Denoting by $d_p(A)$, $d_p(B)$, and $d_p(C)$, the distances from the vertices A, B, and C to the nearest neighboring vertices of the enantiomorph (or of an achiral reference), the associated chirality measure χ_p is:

$$D_p(d_p(A), d_p(B), d_p(C)) = (d_p^p(A) + d_p^p(B) + d_p^p(C))^{1/p} \quad (2.7.3)$$
$$\chi_p = Min\{D_p(d_p(A), d_p(B), d_p(C))\} \quad (2.7.4)$$

The authors found that the Hausdorff distance coincides with D_∞, and considered that the CCM [94] (see previous section) is a just a particular case of first kind of chirality measure for $p = 2$. They calculated various maximal chirality triangles.

Zimpel calculated also a maximal chirality triangle in 1993 [144], with the second kind of chirality measure related to equation (2.7.4) for $p = 2$, constraining the inertia of the triangle to unity.

2.8 *Miscellaneous methods, appearing from 1995 to 1997*

Osipov, Pickup and Dunmur used in 1995 a formal analog of the dipole-dipole interaction tensor to derive two chirality indices [145]. The elements of this chirality tensor are quadruple integrals of a function proportional to the product of the four densities associated with the interaction. The two indices are expressed from the elements of the chirality tensor. The authors found that the two indices vanish both for achiral objects and for some chiral objects having direct symmetry. They extended their 3D approach to 2D systems in 1998 [146].

Randic and Razinger used in 1996 a binary code to describe the molecular shape and the chirality of benzenoids [147]. The bits are set to 1 or 0, depending on the local orientation of the edges at the periphery of the set of fused hexagons. The chirality measure arises from the comparison of the cyclic binary code and its reversed copy.

Moreau defined in 1997 atomic chirality as the sum of atomic environment chiralities. Each of these latter is considered to be proportional to the product of the three principal coordinates of a specified atom [148]. The author found the measure defective for chiral structures having a direct rotation axis of order 3 and above.

Smirnov, Evtushenko and Lebedev pointed out in 1997 the relation between symmetry elements and principal axis and planes [149]. The authors classify chirality into three basic types and four mixed types, depending on how two semifigures lying on each side of a principal plane differ [150]. They defined both a first and second kind of chirality measure, this terminology being not in the sense of section 2.2. There are three pairs of neighboring semifigures, and there are three vectors measuring the deviation between the mean point of a semifigure and the mean point of its associated reflected neighbouring semifigure. The normalized determinant of the (3×3) matrix of these vectors is used as a first kind of chirality measure [151]. Considering the cosines of the deviations between principal directions of these semifigures, there are now three matrices of deviations, constituting a 3-order tensor. The achirality was related to the equality of one of the three matrix with the identity matrix [152]. The authors updated their theory in 1999, introducing four basic types of noncoincidences of semifigures [153].

Raji and Cossé-Barbi proposed in 1997 [154,155] to use a molecular similarity procedure which they published the same year [156], to quantify the similarity of enantiomers. This procedure looks for a motif common to two sets of 3D points, after projecting one of the sets on three orthogonal planes, and interpolating each of the three planar projections with cubic spline functions. For the xy and xz planes, the sum of the squared distances between the points of the other set and their projections on the splines is computed. The two sums of squares are added, the overall sum is minimized for 3D rotations and translations, and an optimal correspondence is deduced. The authors introduced user-defined constraints to search this optimal correspondence, and proposed to classify chirality scales according to the presence or absence of these constraints [157]. They published their similarity procedure again in 1999, pointing out the use of the RMS criterion for chirality measurement [158].

2.9 The RMS chiral index and its relation to probability theory

The RMS chiral index χ was defined in 1997 by Petitjean [159] for a d-dimensional set of n colored points, from the sum D^2 of the n squared distances between the points and their mirror image. The sum is minimized for all rotations R and translations t of the image, and for all permutations P authorized by the colors of the points. The minimized sum is normalized to the inertia T of the set:

$$\chi = d \cdot (Min_{\{P,R,t\}} D^2)/4T \tag{2.9.1}$$

When the points are the vertices of a graph, the authorized permutations arise from the graph automorphisms enumeration [160]. A set of colored points is just a colored graph without edges. The optimal translation is obtained by centering, and the optimal rotation is known analytically for $d = 2$ [159] and $d = 3$ [161]. A freeware is downloadable from the following web page:
http//petitjeanmichel.free.fr/itoweb.petitjean.freeware.html#QCM

The chiral index was extended to weighted sets in 2001 [162], and then to colored mixtures in 2002 [163]. The colored mixture model may be viewed from the replacement of the colored points by whole distributions. It handles discrete and continuous sets, finite or not, provided that the inertia is finite. A colored mixture X is a random variable taking values in the product space of R^d by the space of colors (assumed to be measurable), such that the distribution of X is a mixture of distributions, each of them being biunivocally associated with a color. The weights of the components of the mixture have the same meaning as those of an ordinary mixture of distributions. These colored components should not be confused with the d numerical coordinates: although d is finite, the number of colors in the mixing distribution may be infinite.

We denote by W a joint density of two colored mixtures X and Y, such that Y is distributed as a mirror image of X in the product space, and such that the marginals of X and Y in the space of colors are fully correlated. The general expression of the chiral index is expressed by the lower bound of an expectation:

$$\chi = d \cdot (Inf_{\{W,R,t\}} E[(X-Y)^t \cdot (X-Y)])/4T \tag{2.9.2}$$

Thus, formula (2.9.1) is just an instance of (2.9.2), and an authorized permutation P is n times the bistochastic matrix of a joint density W. The numerator of the expression of χ in (2.9.2) is the Wasserstein distance between X and Y, minimized for all rotations and translations of Y. The chiral index varies from 0 to 1. It is null if and only if X is achiral. The "only if" part of this latter property is induced by the proportionality of χ to the Wasserstein distance, which is a probability metric [164]. Some distributions or mixtures maximizing χ, are known [159,161,163].

In expression (2.9.2) the optimal translation is obtained at null expectation, and the optimal rotations for $d = 2$ and $d = 3$ are still known analytically, even when Y is not the mirror image of X. Moreover, the well-known least squares superposition method between two sets of n points, known either as the RMS superposition method or as the Procrustes algorithm, is shown to derive from this latter situation, and is thus extended to continuous and/or infinite sets [163].

For $d = 1$, equation (2.9.2) leads to express χ with the lower bound r_{min} of the correlation coefficient between the colored one-dimensional mixture X and a colored mixture having the same distribution:

$$\chi = \frac{1+r_{min}}{2} \tag{2.9.3}$$

The chiral index of an ordinary set of n observations ($d = 1$, no colors) is easily computable with a pocket calculator [159]: (a) sort the set with increasing values and then with decreasing values, (b) compute the correlation coefficients between the sorted sets, (c) add 1 and then divide by 2. Since there is no color, the correlation coefficient cannot be positive.

Let $x_{i:n}, i = 1, 2, ..., n$ be the observations sorted with increasing values, $\bar{x}$ being their mean, and σ_x being their standard deviation. The chiral index is an expression of the squared midranges or range lengths:

$$\chi = [\sum_{i=1}^{i=n} (\tfrac{x_{i:n}+x_{n+1-i:n}}{2})^2 - n \cdot \bar{x}^2]/(n\sigma_x^2) \tag{2.9.4}$$

$$\chi = 1 - [\sum_{i=1}^{i=n} (\tfrac{x_{i:n}-x_{n+1-i:n}}{2})^2]/(n\sigma_x^2) \tag{2.9.5}$$

As a consequence of the convergence theorem in [163], the chiral index of a sample of n observations of a random vector in R^d converges to the chiral index of its parent distribution.

Fowler noted in 1992 that there is a need to consider simultaneously the electron density and the atomic nuclei to evaluate chirality [165]. The colored mixture model is an answer to this problem, one component of the mixture being associated with the negative charge distribution, and the other being associated with the positive charge distribution. If needed, a third component could be associated with the mass distribution.

2.10 Recent works, appearing since 1998

Mezey noted in 1998 the need to consider infinite domains for electron densities [166], and proposed to use the Alexandrov one-point compactification of euclidean space E^n, mapping this latter onto the sphere S^n to which a supplementary point (the north pole) is added. The electron density is now a hypersurface in E^4. The first three dimensions correspond to the position, and the fourth corresponds to the density. Molecular isodensity contours of increasing size are considered. The associated sequence of graphs representing the neighborhood of density domains defines a rooted tree structure, which is stored as a sequence of integers: the semilattice tree code. The topological symmetry of the code is used to evaluate direct or indirect symmetry deficiency of the original object [166].

Grimme used in 1998 the expectation of the hermitian product of the wavefunction and its inverted image to measure the chirality [167]. The measure is a linear combination of the modules of the expectations of the hermitian products associated with individual orbitals, and is minimized for rotations and translations. This method is formally related to overlap methods (see section 2.3).

Ferrarini and Nordio defined in 1998 a second order helicity tensor q by integration over the molecular surface of a function of the normal to the surface [168]. The diagonal element q_{ii} is interpreted as the amount of surface rotation associated with translation along the direction of the i axis, and is the helicity along the i direction. Since there are three principal directions, this chirality measure is not a scalar quantity.

Le Guennec introduced in 1998 the concepts of absolute and relative chirality [169-172]. Using the polar representation of a function $\Phi(r,\theta)$ in the complex plane C^1, the absolute radial function is defined as $\Delta_n = \int_0^{2\pi} \Phi(r,\theta)\cdot e^{-in\theta}d\theta$, i being the complex root of unity, and n being related to a C_n symmetry. The path $\Delta_n(r)$ is called the absolute chiral loop. For a fixed value of n, the absolute achirality of Φ_n is related to the linear shape of the absolute chiral loop. The author defined a relative chirality concept [172] from the relative radial function $\Delta_{n,m}(\Phi_n^1, \Phi_m^2)$, and its associated relative chiral loop, which is related to the presence of a common indirect symmetry element between Φ_n^1 and Φ_m^2. Functions Φ in C^d are handled via projections on C^1. As stated by the author [169], this chirality concept should not be confused with the usual quantitative chirality concept.

Describing a density in 3D space with spherical coordinates, Harris, Kamien and Lubensky used in 1999 the tensor moments obtained by integration over the radial coordinate, and showed that an infinite number of pseudoscalar chiral parameters, computed from the moments, quantify chirality [173]. The authors found that, when a molecule with more than four atoms is inverted, continuous deformations exist such that these pseudoscalars do not vanish [173,174] (see also section 2.1).

In 2000 Benigni et al. submitted the (N, N) similarity matrix associated with a family of N molecules to principal component analysis, and looked for a principal axis discriminating the R and S populations [175]. The difference of the coordinates attached to this axis for the R and the S isomers is used as a chirality measure.

In 2001 Randic combined data from molecular graphs of benzenoids with data from their planar representation, to define a chirality measure [176] (see also the approach of Randic and Razinger in section 2.8), and extended it to 3D n-alkane rotamers.

Raos investigated in 2002 the degree of chirality of helical structures [177]. Using cylindrical coordinates, two chirality measures were proposed, one being related to overlap methods (section 2.3), the other being related to the approach of Harris et al. (see above, in this section).

Làszlo and Rassat proposed in 2002 [178] to use a distance function such as the Hausdorff distance (see section 2.2) to measure the chirality of fullerenes. Rassat, Làszlo and Fowler proposed in 2003 to use the mean square topological rotational strength to measure the chirality content of a polyhedral graph [179]. After diagonalization of a modified adjacency matrix such that the eigenvector system is a formal analog of the eigenvector system encountered in the Hückel theory, the chirality measure is defined through a physical interpretation of the meaning of these eigenvectors.

3 Measuring direct symmetry in chemistry and physics

There are two major differences between direct and indirect point group symmetries: (a) a set having no direct symmetry in a d-dimensional euclidean space is still not symmetric after immersion in a higher dimensional space, although a chiral set becomes flat, and thus achiral, when a dimension is added; (b) direct symmetry is based on the existence of a non degenerate rotation, and thus cannot appear in one-dimensional space.

Although many efforts were done to measure chirality, few direct symmetry measures have been proposed (see also in section 6 the discussion of the formal definition of direct symmetry measures).

Quasi-symmetry measures arising from fuzzy set theory, such as the syntopy introduced in 1987 by Maruani and Mezey, apply both to direct and indirect symmetry, and have been mentioned in section 2.4.

The CSM (Continuous Symmetry Measure) was introduced in 1992 by Zabrodsky, Peleg and Avnir [94], with the CCM (Continuous Chirality Measure). Both measures are based on the folding/unfolding process: see theory and references in section 2.6.

The direct symmetry index defined in 1999 by Petitjean [161], looks like the chiral index defined in section 2.9 (see equation 2.9.1). It is defined for a d-dimensional set of n colored points, from the sum of the n squared distances between the points and their rotated and translated copy. The sum is minimized for all rotations and translations, and for all permutations allowed by the colors of the points, the identity permutation being excluded. The direct symmetry index is the minimized sum, divided by twice the inertia of the set. As for the chiral index, when the points are the vertices of a graph, the allowed permutations arise from the graph automorphisms enumeration. When there are not at least two equivalent points, the direct symmetry index is undefined. Some minimal symmetry figures have been identified [161]. The freeware mentioned in section 2.9 computes simultaneously the chiral index and the direct symmetry index.

4 Symmetry measures in the mathematical literature

4.1 Measures restricted to convex sets

A very interesting review of symmetry measures of convex sets was presented by Grünbaum during a symposium of the AMS held in 1961, and published in 1963 [180]. The measures denote real non-negative functions defined for convex sets, with value 0 only for centrally symmetric sets. Clearly, these measures are related either to direct or indirect symmetry, depending on the parity of the dimension d of the space. For example, for $d = 2$, a center of symmetry is related to direct symmetry, but for $d = 1$ and $d = 3$, it is related to indirect symmetry. Grünbaum noted the difficulty of retrieving symmetry measures from the literature, because they are not always declared as being symmetry measures. The oldest reference cited was the work published in 1897 by Minkowski [181].

Some works about symmetry measures for convex sets appeared in the sixties [182-187]. The axial symmetry measures of ovals proposed by DeValcourt in 1966 and 1967 [185-187] and by Cieslak and Zajac in 1985-1986 [188] are chirality measures of convex sets. In 1994 and 1996, Margolin et al. and Tuzikov et al. used reflection symmetry measures for convex sets [189,190], mostly in a plane. Central symmetry measures of convex sets were again investigated in 1996 by Kaiser [191] and in 2000 by Groemer [192].

4.2 Measures arising from probability theory

4.2.1 Asymmetry and skewness: generalities

An asymmetry coefficient is expected to vanish for a symmetric distribution, this symmetry being an indirect symmetry when the distribution is one-dimensional. Asymmetry coefficients and skewness measures may be used to quantify the departure from symmetry. Another problem is to test, on the basis of a sample, the hypothesis H_0 that a parent distribution is symmetric, against the alternative that it is not symmetric. There are specialized versions of H_0 with various alternatives, depending on the knowledge of location parameters, and on which kind of symmetry is considered. A frequently encountered application is to test normality.

Some definitions of multivariate symmetry found in recent papers are given below. The reference may correspond to the first occurrence or not. Older definitions may be found in [193] for the univariate case, and in [194] for the bivariate case. X is a random vector in R^d, θ is a constant vector, H is a closed halfspace, and A is a full rank constant $d \times d$ matrix. The euclidean norm is denoted $\|\cdot\|$, and $\stackrel{d}{=}$ denotes an equality in distribution.

Symmetry definition	Ref.
$A\cdot(X-\theta)/\|A\cdot(X-\theta)\|$ uniformly distributed on the unit d-sphere and independant of $\|A\cdot(X-\theta)\|$ (Elliptical symmetry)	[195]
$A\cdot(X-\theta)/\|A\cdot(X-\theta)\|$ uniformly distributed on the unit d-sphere (Symmetry with elliptical direction)	[195]
$(X-\theta) \stackrel{d}{=} (\theta - X)$ (Reflection symmetry or central symmetry)	[195,196]
Equivalently: $u^t\cdot(X-\theta) \stackrel{d}{=} u^t\cdot(\theta-X)$, for each unit vector u in R^d	[196]
Equivalently: $Prob\{(X-\theta)\in H\} = Prob\{(X-\theta)\in -H\}$, for each H	[196]
$A\cdot(X-\theta)/\|A\cdot(X-\theta)\| \stackrel{d}{=} A\cdot(\theta-X)/\|A\cdot(X-\theta)\|$, or,	[195]
$(X-\theta)/\|(X-\theta)\| \stackrel{d}{=} (\theta-X)/\|(X-\theta)\|$ (Angular symmetry)	[196]
$Prob\{X\in H\} \geq 1/2$ for all H with θ on the boundary (Halfspace symmetry about θ)	[196]

Elliptical symmetry implies symmetry with elliptical direction. Central symmetry implies angular symmetry, and angular symmetry implies halfspace symmetry [196].

Any symmetry measure computable for a sample is potentially useful for testing H_0, provided that we have knowledge of the distribution of the measure under H_0, at least asymptotically. This knowledge often has more practical importance than other properties of the measure, such as being scale-free or not vanishing for non-symmetric distributions. This is why only some of the known symmetry measures have been used as statistics for testing. Conversely, some statistics are indeed useful for testing symmetry, but are not adequate quantitative measures of symmetry. Examples of these latter are found in rank tests of symmetry [197], and more generally in symmetry tests involving the signs of various functions of the observations rather than their values [194,195,198-208].

4.2.2 Skewness measures: the univariate case

The skewness, i.e. the centered third-order moment μ_3 normalized to the cube of the standard deviation σ, is well known as an asymmetry coefficient of a one-dimensional distribution [209]. The square of this quantity was introduced by Pearson in 1895 (see ref. [210], p. 351), together with some other measures of skewness based on the deviation ($mean - mode$) (see ref. [210], p. 370). The quantity $(mean - median)/\sigma$ has also been used as a skewness measure, and was shown by Hotelling and Solomons in 1932 to vary between -1 and +1 [211]. There are non-symmetric distributions for which these measures vanish. Nevertheless, they have been used for many years. Nichols and Gibbons computed in 1979 four measures of skewness, for several Gamma, Lognormal, and Weibull distributions [212]. These measures were $\gamma_3 = \mu_3/\sigma^3$, $(mean - mode)/\sigma$, $3(mean - median)/\sigma$, and $\gamma_3(\gamma_4 + 6)/2(5\gamma_4 - 6\gamma_3^2 + 6)$, where γ_4 is the centered fourth order moment normalized to σ^4.

David and Johnson used in 1954 a skewness measure attributed to Yule, going back to 1912 (see last reference cited in [213]). It is based on the upper and lower 75% quartiles, both centered to the median. Denoting these two centered quantities x_{um} and x_{lm} respectively, the measure is $(x_{um} + x_{lm})/(x_{um} - x_{lm})$ [213,214].

Hogg, Fisher and Randles proposed in 1975 [215], a family of statistics based upon averaged quantiles, such as: $(\bar{U}_{.05} - \bar{M}_{.5})/(\bar{M}_{.5} - \bar{L}_{.05})$, and $(\bar{U}_{.05} - \bar{L}_{.05})/(\bar{U}_{.5} - \bar{L}_{.5})$, where $\bar{U}_{.05}$, $\bar{M}_{.5}$ and $\bar{L}_{.05}$ are the averages of the largest 5%, the middle 50%, and the smallest 5% of the order statistics, respectively.

Let $X_{i:n}, i = 1, 2, ..., n$ be these order statistics. Finch proposed in 1977 to test symmetry with a family of statistics V, based on the right gaps $R_i = X_{n-k+i} - X_{n-k+i-1}$ and the left gaps $L_i = X_{k+2-i} - X_{k+1-i}$: $V = \sum_{i=1}^{i=k} w_i(R_i - L_i)/(R_i + L_i)$, where w_i are fixed weights [216] (see also Antille et al. 1982 [217]).

Smirnov introduced in 1947 the following symmetry criterion for a random variable X having a continuous distribution function F and a median μ: $[F(\mu + x) + F(\mu - x) - 1]$ is null for all x [218]. Setting $\bar{F}(\mu + x) = 1 - F(\mu - x)$, the distribution function $\bar{F}$ is that of the reflected random variable $\bar{X}$ around μ, provided that F is continuous. Thus the symmetry criterion is: $[F - \bar{F}]$ is null for all x. Note that the empirical distribution function $\bar{F}_n$ of a sample of n observations is not continuous. Thus, setting $\bar{F}_n(\mu + x) = 1 - F_n(\mu - x)$, $\bar{F}_n$ is not the distribution function associated with the reflected sample.

Assuming that F is continuous, Butler used in 1969 a statistic proportional to the quantity $S = Sup_{\{x \leq 0\}} |F_n(x) + F_n(-x) - 1|$, to test symmetry about zero [219]. This quantity S is the L^∞ norm of $[F_n - \bar{F}_n]$. Generalizations were proposed in 1972 by Orlov, who considered functionals of $[F_n - \bar{F}_n]$ [220].

Doksum introduced in 1975 [221] the empirical symmetry function $[x - \bar{F}_n^{-1}(F_n(x))]/2$ and some other functionals related to Smirnov's criterion. Other generalizations were proposed in 1977 by Doksum, Fenstad and Aaberge, who used a positive weight function $\Psi(F(x), \bar{F}(x))$ to normalize the difference $[F_n - \bar{F}_n]$ before computing statistics [222].

A Cramér-von Mises type symmetry test was proposed by Filippova in 1962, to test symmetry about zero from a sample of size n [223]. It was rediscovered in 1972 by Rothman and Woodroofe [224]. Assuming that the distribution function F is continuous, and setting $F_n^*(x) = (F_n(x^+) + F_n(x^-))/2$, the symmetry test statistic is: $n \cdot \int_{-\infty}^{+\infty} [F_n^*(x) + F_n^*(-x) - 1]^2 dF_n(x)$. This type of symmetry test has been investigated by several authors: see Orlov 1972 [220], Srinivasan and Godio 1974 [225], Hill and Rao 1977 [226], Koziol 1980 [227], Aki 1981 [228], and Boos 1982 [229]. The symmetry test of Aki considered general estimators of the location parameter μ, and Boos estimated this latter with the median of the n^2 mid-intervals $(X_i + X_j)/2$.

Locke and Spurrier introduced in 1976 a family of symmetry tests based on U-statistics [230]: $U_{pn} = [6/n(n-1)(n-2)] \sum_{i=1}^{i=n-2} \sum_{j=i+1}^{j=n-1} \sum_{k=j+1}^{k=n} \phi(X_{i:n}, X_{j:n}, X_{k:n})$, where $X_{i:n}$ are the order statistics, $\phi(X_{1:n}, X_{2:n}, X_{3:n}) = (X_{3:n} - X_{2:n})^p - (X_{2:n} - X_{1:n})^p$, and $p = 1$ or $p = 2$.

In 1977 [231] Feuerverger and Mureika noted that the characteristic function, $c(t) = [u(t) + i \cdot v(t)]$, is real if and only if the distribution function F is symmetric about the origin, and proposed the symmetry test statistic $\int_{-\infty}^{+\infty} [v_n(t)]^2 dG(t)$, where $c_n(t) = [u_n(t) + i \cdot v_n(t)]$ is the empirical characteristic function, and G is some given distribution function symmetric about the origin.

In 1987 Csörgö and Heathcotte [232] introduced the characteristic symmetry function $\theta(t) = t^{-1} arctan[v(t)/u(t)]$, which is constant when the random variable X is symmetrically distributed around θ. Under weak conditions on the moments $E(X) = \theta = lim_{t \to 0} \theta(t)$.

In 1986 Shorack and Wellner investigated the properties of the symmetry process $n^{1/2}|F_n - \bar{F}_n^-|$, where $\bar{F}_n^-$ is the distribution of the reflected sample [233], and MacGillivray presented a brief historical survey of univariate asymmetry measures. He noted that skewness was used either as an asymmetry measure, or as a tool to compare distributions [234]. The main measures are presented above.

Working with the random variable $2F(X)$ rather than with the random variable X leads to look for the symmetry of F around the constant 1, F being assumed to be continuous and strictly increasing. This approach was followed by Aki in 1987 [235] (see also Nabeya 1987 [236], Aki and Kashiwagi 1989 [237]). Given n independent and identically distributed random variables $F_1, ..., F_n$ taking values over $[0, 1]$, Aki considered a family of symmetry test statistics proportional to the norm of the function $v_n(t) = \sum_{i=1}^{i=n} [2 \cdot 1_{]-\infty, 1/2]}(F_i) - 1] \cdot 1_{[0,t]}(Z_i)$, with $Z_i = 2F_i$ when $F_i \leq 1/2$, and

$Z_i = 2(1 - F_i)$ when $F_i > 1/2$, and $1_{[,]}$ denotes the indicator function. The norm was either the L^∞ norm, or the L^1 or L^2 norm relative to the measure associated with the empirical distribution function of the Z_i [235-237].

Assuming an absolutely continuous distribution function F, Eubank, LaRiccia and Rosenstein tested in 1987 [238,239] the symmetry about zero with a sample, via estimation of the Fourier coefficients of the function $d(u) = f(H^{-1}(u))/h(H^{-1}(u))$, f being the density of F, and h being the density of H, with $H(x) = (F(x) + 1 - F(-x))/2$. The overall measure was: $\int_0^1 (d(u) - 1)^2 du$.

Providing that there is a density f, another family of symmetry criterions is obtained by derivation of $[F(\mu + x) + F(\mu - x) - 1]$ at x. This derivative is null for all x when the density f is symmetric about μ. Assuming that μ is known, Li and Morris introduced in 1991 the following asymmetry measure: $\eta = \int_{-\infty}^{+\infty} |f(\mu + x) - f(\mu - x)|dx$, such that the density has to be symmetric if η is null [240]. The authors found that this latter property was not achieved by other skewness measures.

Assuming an invertible distribution function F, Benjamini and Krieger analyzed in 1996 [241] the concept of skewness, by writing $F^{-1}(y)$ as the sum of three terms:
$F^{-1}(y) = F^{-1}(1/2) + SP(y) + SK(y)$.
$F^{-1}(1/2)$ is the median,
$SP(y) = (F^{-1}(y) - F^{-1}(1-p))/2$, is the spread function, and
$SK(y) = (F^{-1}(y) + F^{-1}(1-p) - 2F^{-1}(1/2))/2$, is the skewness function.

Then, $dH(y)$ being some signed measure on $y \in (0, 1)$ such that $\int_0^1 dH(y) = 0$, the proposed skewness measures were:
$S^*_H(F) = [\int_0^1 F^{-1}(y)dH(y)]/[\int_0^1 -F^{-1}(1-y)dH(y)]$, and:
$S_H(F) = [\int_{1/2}^1 SK(y)(dH(y) - dH(1-y))]/[\int_{1/2}^1 SP(y)(dH(y) + dH(1-y))]$,
this latter being obtained by considering the monotonic transformation $(x-1)/(x+1)$.

4.2.3 Skewness measures: the multivariate case

One of the earliest multivariate symmetry test family was presented by Lancaster in 1965 [242]. The tests were devoted to permutation symmetry, i.e. the d-variate distribution is unchanged upon any permutation of its d arguments. When $d = 2$, this is an indirect symmetry around the first bisector. The tests were based on the invariance upon the $d!$ permutations of the generalized correlation coefficients defined by the author [242].

A family of skewness measures of a multivariate sample was used in 1970 by Mardia, to test multivariate normality [243]. In the one-dimensional case, they reduce to the correlation between the sample mean and the sample variance, which is shown to be asymptotically proportional to the absolute value of the third order moment.

Malkovich and Afifi defined in 1973 the multivariate skewness of a random vector X, as: $Max_{\{C\}}[E\{(C^t \cdot X - C^t \cdot EX)^3\}]^2/[Var(C^t \cdot X)]^3$, where C is any non-null vector [244] (see also Baringhaus and Henze 1991 [245]). In the univariate case, this is the squared normalized centered third-order moment μ_3^2/σ^6.

Smith, in 1977 [246], defined a von Mises type bivariate circular symmetry test, using the expression of the distribution function $F(r,\theta)$ in polar coordinates. The marginals are $R(r)$ and $\Theta(\theta)$. The distribution is circularly symmetric if and only if R and Θ are independent and Θ is uniformly distributed on the circle. Considering a sample of size n, the test statistic was: $U_n = \int\limits_0^\infty \int\limits_0^{2\pi} (Z_n(r,\theta) - \bar{Z}_n(r))^2 dF_n(r,\theta)$, with $Z_n(r,\theta) = F_n(r,\theta) - R_n(r)\theta/2\pi$, and $\bar{Z}_n(r) = [\int\limits_0^{2\pi} Z_n(r,\theta)d\theta]/2\pi$.

Baringhaus modified and generalized in 1991 this test for spherical symmetry of multivariate distributions in R^d [247]. The bivariate symmetry test statistic is modified:

$T_n = (n/2\pi) \cdot \int\limits_0^\infty [\int\limits_0^{2\pi} (Z_n(r,\theta) - \bar{Z}_n(r))^2 d\theta] dR_n(r)$.

The expression of T_n is then rewritten:

$T_n = (1/n) \sum\limits_{i=1}^{i=n} \sum\limits_{j=1}^{j=n} h(X_i^t \cdot X_j \cdot \|X_i\|^{-1} \cdot \|X_j\|^{-1}) \cdot min\{1 - (\xi_{ni} - 1)/n, 1 - (\xi_{nj} - 1)/n\}$,

where ξ_{nk} is the rank of $\|X_k\|$ in the sample $\|X_1\|, ..., \|X_n\|$, and $h(t) = [1/12] - [arccos(t)/4\pi] + [(arccos(t))^2/8\pi^2]$. The generalization to multivariate spherical symmetry is made via expansion of $h(t)$ with Gegenbauer polynomials of order $d/2$.

Kariya and Eaton derived in 1977 [248] robust tests for spherical symmetry. When the distibution of X has spherical symmetry around the origin, the unit vector $X/\|X\|$ is uniformly distributed on the unit d-sphere. The tests are based on the invariance of the quadratic form $z^t \cdot V^{-1} \cdot z$, where z is any unit vector and V is the covariance matrix of X.

Isogai generalized in 1982 the skewness measure $(mean - mode)/\sigma$, with the following measure [249]: $S = (\mu - \theta) \cdot w^{-1}(V) \cdot (\mu - \theta)$, where μ is the mean, θ is the mode, and $w(V)$ an appropriate function of the covariance matrix V. It was used to test multivariate normality.

Oja gave in 1983 multivariate generalizations of the skewness, which, in the univariate case, are normalized functions of the deviation $(mean - median)$ [250].

The multivariate generalization of the skewness proposed in 1984 by Srivastava is the quadratic mean of the d quantities μ_3/σ^3, taken in the d principal axis of the distribution [251]. It was used to test multivariate normality.

Blough considered in 1989 [252] multivariate symmetry around one or several p-dimensional hyperplanes in R^d, $0 \leq p \leq (d-1)$. A unit vector u minimizing an univariate symmetry test such as that of Doksum et al. [222] (see section 4.2.2) is sought. If the test is passed, the projection pursuit method continues in the subspace orthogonal to u. The degree of symmetry of the distribution is the number of tests passed. When all the d tests are passed, the distribution is declared to be centrosymmetric.

As mentioned for the univariate case, the characteristic function $c(t) = [u(t)+i\cdot v(t)]$ is real when the centered random vector X is centrosymmetric around the origin. Thus, in 1992 [253] Ghosh and Ruymgaart extended the symmetry measure of Feuerverger and Mureika (see section 4.2.2) to the multivariate case. Heathcotte, Rachev and Cheng defined in 1995 [254] the characteristic symmetry function $\theta(t) = arctan[v(t)/u(t)]$, this latter differing from the characteristic symmetry function defined by Csörgö and Heathcotte (see section 4.2.2). The departure from linearity of the empirical characteristic symmetry function is used to test symmetry around a fixed or estimated constant.

Aki extended in 1993 [255] his univariate symmetry tests (see Aki 1987 and 1989 in section 4.2.2 [235-237]), working now on a d-dimensional hypercube rather than on $[0,1]$.

In 1993 Mori, Rohatgi and Székely used the vector $E(X^t \cdot V^{-1} \cdot X \cdot V^{-1/2} \cdot X)$ as a multivariate measure of the skewness of a centered random variable X having a non-singular covariance matrix V [256,257]. In the univariate case, this is the normalized centered third-order moment μ_3/σ^3.

Avérous and Meste used in 1997 median balls with center c and radius λ as multivariate generalizations of the interquantile intervals [258]. The center is defined as a function of λ, and generalizes the median when λ is null. The mapping $c(\lambda)$ defines a skewness function, and denoting by h a fixed unit vector, the scalar product $c^t \cdot h$ defines a function of skewness in the h direction. It generalizes the deviation between the median and the center of an interquantile. Integrating $c(\lambda)$ for some measure of λ (related or not to the original distribution) gives a vector measuring the skewness of the original distribution. Its scalar product with h quantifies the skewness. In the same paper, the authors proposed a similar approach, based on the difference between the weights of the two directed tails of the distribution in the h direction, centered on the generalized median.

Koltchinskii developed in 1997 [259,260] a measure of spherical symmetry of the distribution function F, based on the functional $Q(t) = \int_{R^d} [(t-x)/\|t-x\|]dF(x)$. The measure is: $\gamma(F) = Sup_{\{t\}}\|Q(t+Q^{-1}(0)) - \psi(\|t\|)\cdot(t/\|t\|)\|$, where, denoting by S^{d-1} the boundary of the unit d-sphere, $\psi(\lambda) = \int_{S^{d-1}} v^t \cdot Q(\lambda v + Q^{-1}(0)) \cdot dU(v)$, U being the uniform probability distribution on S^{d-1}. Q^{-1} is a multivariate quantile function. $\gamma(F)$ is null if and only if F is spherically symmetric [259], and $Q^{-1}(0)$ is the center of symmetry.

In 2000 Koltchinskii and Sakhanenko [261] defined ellipsoidal symmetry measures of the distribution P of a random vector X from spherical symmetry measures of $Y = V^{-1/2} \cdot (X - \mu)$, where μ is the expectation of X and V its covariance matrix. The expectation $E = \int_{R^d} f(V^{-1/2} \cdot (x - \mu))P(dx)$ is considered, f being an adequate bounded Borel function on R^d. When Y is spherically symmetric, denoting by U the uniform distribution on the boundary S^{d-1} of the unit d-sphere, and Π being the distribution of $\|Y\|$, the expectation $E_0 = \int_0^{+\infty} \int_{S^{d-1}} f(ru)U(du)\Pi(dr)$ is equal to E. The elliptical symmetry measure is $|E - E_0|$.

Székely and Mori used in 2001 an asymmetry measure of a random vector X, which vanishes if and only if X and $-X$ are identically distributed [262]. Y being a random vector independent and identically distributed to X, and $E\|X\|$ being the expectation of the euclidean norm of X, the measure is: $(E\|X + Y\| - E\|X - Y\|)/2E\|X\|$.

5 Contributions not arising from chemistry, physics, and mathematics

5.1 Symmetry measures in computer sciences

The CSM/CCM measures and the folding/unfolding process of Zabrodsky, Peleg and Avnir, which were presented is section 2.6, result from a collaboration between chemists and computer scientists. The references to applications in computer vision and pattern recognition have been given in section 2.6.

An indirect symmetry measure was used in 1989 by Marola [263] to detect a symmetry axis in a digitized 2D image from the intensity function w: assuming that there are pairs of points in symmetric positions with respect to a given axis, the measure is:

$\beta = \int\int w(x,y)w(\bar{x},\bar{y})dxdy / \int\int w^2(x,y)dxdy$,

where $(\bar{x},\bar{y})$ is the point paired to (x,y). The coefficient is maximized for a perfectly symmetric image. The intensity function is the formal analog of a density function.

In 1993 Masuda, Yamamoto and Yamada measured rotational symmetry of 2D images via the directional correlation concept [264], which is related to the L^2 distance between the gradient of the intensity function and the gradient of the rotated intensity function. Indirect symmetry is measured similarly, via the rotated and inverted intensity function.

Bonneh, Reisfeld and Yeshurun defined in 1994 [265] a concept of local symmetry associated with a point x of a 2D image. Assuming that there is a set $\Gamma(x)$ of couples of indices i, j such that $x = (x_i + x_j)/2$, the contribution C_{ij} of x_i and x_j to the symmetry associated with x is a function of ∇x_i and ∇x_j, where ∇x_k denotes the gradient of the intensity at $x_k, k = 1..n$. The symmetry associated with x is a weighted sum of the contributions C_{ij} over the set of couples of indices $\Gamma(x)$.

The symmetry measures for convex sets developed by Margolin et al. in 1994 [189], and Tuzikov et al. in 1996 [190] have been mentioned in section 4.1.

In 1995 Cham and Cipolla [266] defined the symmetricity concept to measure local skew symmetry in 2D images. The symmetricity is computed for paired contour points, and measured according to a Mahalanobis distance, i.e. the metric is defined by an inverted covariance matrix. An overall symmetry measure is obtained by averaging symmetricities, and computed for each member of a generated ranked list of hypotheses for the axis of symmetry. Starting with initial hypotheses for the symmetry axis, an iterative procedure looks for the optimal symmetry measure.

5.2 Symmetry measures in biology

Assuming that a biological 2D or 3D object has a bounded contour expressed in spherical coordinates, Köhler used in 1991 the Fourier coefficients of the radial form function R to quantify symmetry [267]. For example, for a 2D object, the radial function satisfies $R(\phi) = R(\phi \mp 2\pi/n)$ for an n-fold rotation point, and $R(\phi_s - \phi) = R(\phi_s + \phi)$ for a mirror line located at ϕ_s. The symmetry measure for a given symmetry G is the sum of the Fourier coefficients which do not vanish when G exists, divided by the sum of all Fourier coefficients.

In 1993 [268] Köhler proposed to quantify symmetry via the L^1 norm of the difference between R and its transform R' by G: $\int_0^{2\pi} |R'(\phi) - R(\phi)| d\phi$.

One year later [269] Köhler considered finite sets of n points, and quantified symmetry via the number n_c of points pertaining to the intersection domain of the set and its transformed image via G, provided that the contour of the set is defined. The symmetry measure was n_c/n. He proposed to quantify symmetry of 2D domains or figures, on the basis of the area of the intersection of the figure with its transformed images via G [269,270], the area being normalized to the area of the domain. This measure is related to overlap methods (see section 2.3).

In 1999 Köhler considered again finite sets of n points [271], and quantified symmetry via the sum of the distances between the points and their transformed image via G, minimized over the $n!$ possible correspondences.

Marzec analyzed in 1999 [272] the deviations of 3D morphological structures of viruses from reference platonic solids, using the coefficients of their Fourier transform.

5.3 Symmetry measures in psychophysics

Zusne used in 1971 [273] the third-order moment and the self-overlap area as symmetry criteria of 2D figures.

Yodogawa defined in 1982 [274] the symmetropy concept to evaluate the symmetry of a 2D pattern, the intensity function of the image being discretized in gray levels. The symmetropy is an entropy-like, four-component vector measure based on the parity of the coefficients of 2D discrete Walsh functions. A 2D discrete Walsh function takes only two values: -1 or $+1$, and operates on a matrix, similarly to a 2D Fourier transform.

6 Relations with other fields and discussion

There is a fundamental relation between chirality or symmetry measures, and similarity measures: many chirality measures are defined from the similarity between a set and its mirror image, and there are symmetry measures defined from the similarity between the set and its rotated and translated copies. There is a vast literature about similarity in chemistry (e.g., see [275,276]), and in mathematics, for which the underlying concept is "distance".

As an example, there are probability metrics [164], which may be used to define chirality measures of distributions. Probability metrics are themselves related to the Monge-Kantorovitch transportation problem [277]: quantifying the chirality of a distribution is related to the minimized cost of transportation of the distribution on its inverted image. The relation with optimal superposition problems appears: e.g. the previously mentioned RMS (root mean square) chiral index derived from the Wasserstein distance, is formally related to RMS superposition methods such as Procrustes algorithms [163], which are commonly encountered in chemistry and data analysis.

Defining a chirality measure from some normalized minimized distance between an object and its inverted image is easy in many situations. Note that the major defect of most chirality measures is that there are chiral objects having a null chirality measure, like achiral objects. The axiom that $d(X,Y)=0 \Rightarrow X=Y$, X and Y being two objects in the space metrized by d, is the key to avoid this defect. Defining direct symmetry measures is more difficult. Let us try to define them by a general procedure.

First step: we consider a set E of objects, provided that the equality between any two objects is rigorously defined. Note that the definition of "equality" may be simple or not, depending of what objects are considered: distributions, labelled graphs, lattices,...

Second step: we consider a set of operators $\{T\}$, and the product between two operators is defined, mapping $\{T\} \otimes \{T\}$ on $\{T\}$. The set $\{T\}$ has a group structure for this product, and the neutral element is I. The group operates on E, offering the associativity property: $T_1(T_2X) = (T_1T_2)X$, the neutral element I being such that $IX = X$. Note that this model is not adequate for indirect symmetry, since improper isometries have no group structure and no neutral element.

Definition: an object $X \in E$ is symmetric if and only if there exists $T \neq I$ such that $TX = X$. In other words, symmetry arises when an object is identical to one of its non-trivial transforms.

Some immediate properties follow. Denoting by T^{-1} the symmetric element of T, a symmetric object X is obviously such that $T^{-1}X = X$, and it is proved by recurrence that $T^nX = X$ for any signed integer n. When X is symmetric for both operators T_1 and T_2, then $T_1T_2X = T_2T_1X = X$, meaning that T_1 and T_2 operate commutatively on X.

Third step: the space E is metrized with a distance d. Thus, an object $X \in E$ is symmetric if and only if there exists $T \neq I$ such that $d(TX,X) = 0$.

Fourth step: consider the quantity $Inf_{\{T\neq I\}}d(TX,X)$, and normalize it, if possible. Intuitively, quasi-symmetry is related to a small distance between the object and one of its non-trivial transforms [278], the smallness being evaluated by the normalizing factor, such as an upper bound of the distance, if any. This fourth step fails when it happens that $Inf_{\{T\neq I\}}d(TX,X) = 0$ despite the fact there is no $T \neq I$ such that $d(TX,X) = 0$. This failure cannot occur when the set $\{T\}$ is of finite cardinality, but many direct symmetry models involve an infinite number of isometries.

A similar problem arises with skew indirect symmetry. An object having skew symmetry is the image of a symmetric object through a full rank linear transform A^{-1}. Consider an imperfectly skew symmetric object for which A is specified: its degree of symmetry could be defined as being that of its transformed image through A. Now, evaluating indirect skew symmetry without knowledge of A leads one to consider the lower bound of some chiral index, taken either over the set of all full rank transforms, or more specifically, over a subset of this latter such that there are at least two vectors of A allowed to have arbitrarily close directions. Since A may be arbitrarily close to some non-full rank transform, the lower bound of the chiral index is null, provided that this chiral index has the adequate continuity property (it is built to have it). It should be noted that considering a finite set of transforms avoids this problem, and that a skew symmetry index defined without considering any linear transform is just an ordinary symmetry index.

Other mathematical fields related to symmetry measures are group theory (see the chirality functions in section 2.1), fuzzy set theory (section 2.4), and information theory. Close relations betwen symmetry with information theory and entropy were outlined by Lin in 1996 [279] and 2001 [280], and some chirality measures derived from thermodynamical models are related to entropy (see Chauvin 1992 and 1996 [281,282]).

The relations between disorder and randomness can be clarified with quantitative symmetry arguments. For example, we consider a sequence of samples of increasing size n, from the uniform law over a segment. It is often intuitively assumed that the disorder increases with the size of the sample, because more random points there are, more disorder there is. On the other hand, the chiral index of the sample tends to the chiral index of the parent distribution (see section 2.9), i.e. it tends to zero, because the parent distribution is achiral. Thus the (indirect) symmetry increases with n. Disorder is assumed to decrease when symmetry increases: a contradiction. Our intuitive assumption is false, and the paradoxical conclusion from this example is: more random points there are, more symmetry there is, and less disorder there is.

Thanks to their many applications, chirality and symmetry measures are related to a number of scientific fields or physical phenomena, such as optical rotatory power, Jahn-Teller effect [283], kaon decays [284], etc. A summary of demonstrated applications was given by Avnir, Zabrodsky and Mezey in 1998 [285].

Many symmetry-related shape coefficients and sphericity coefficients have been ignored here, owing to their triviality. However, some important symmetry measures are missing, owing to the complexity of the underlying symmetry concepts. Among them are symmetry of lattices, or infinite distorted helices or, more generally, infinite mass media. Despite the usefulness of the related symmetry or chirality concepts, (e.g. see Sokolov 1985 [286]), elaborating a symmetry measure theory seems to be an open problem in these situations.

7 Conclusions

This review is not exhaustive, and probably many important works have not been cited. One of the reasons is that searching references in databases such as Chemical Abstracts, Zentralblatt MATH, or MathSciNet does not reveal all works about symmetry and chirality measures, because these latter are not declared as such in the title, in the summary or in the keyword list.

There is a diversity of methods, partly due to the diversity of potential or effective applications. In order to clarify the text, sophisticated methods have been roughly summarized, and the reader is invited to look at the original works.

As a final comment, it must be pointed out that some concepts appeared in the literature, were rediscovered independently by several authors, because they were working in quite different fields. Thus, it is hoped that this transdisciplinary review about symmetry and chirality measures will be useful to people who are concerned, or solely interested, by this fascinating research area.

Acknowledgments:

I am very grateful to Profs. David Avnir, Victor Kuzmin, Istvan Làszlo, Jean Maruani, Kurt Mislow and André Rassat for providing bibliographic references. I am also very grateful to Dr. Shu-Kun Lin for having encouraged me to write this review, and for a useful discussion about symmetry. I am indebted to Dr. Gyorgy Darvas, Prof. Joe Rosen, and Prof. Ehsan S. Soofi, for helpful comments on the manuscript. Many thanks to our documentalist, Mrs Danielle Samuel, for bibliographic assistance.

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