Journal of Mathematical Chemistry 17 (1995) 35–53

A unification of chirality measures

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Received 21 July 1994; revised 7 October 1994

A general classification of chirality measures is suggested, based on a new unifying scheme. Two classes of measures - congruity and resolution type - are defined and discussed. All chirality measures so far reported in the literature are found to belong to one of these two classes. At a higher level of unification, a more general construction is suggested that includes congruity and resolution measures as limiting cases. It is shown that congruity measures are nested in clusters of eight, generated by 2^3 combinations of their possible choice of a reference object (chiral vs. achiral), representation form (optimized vs. factorized) and type of chiral object under consideration (discrete vs. continuous). Each of the eight cases can have an infinite number of variations depending on the choice of averaging scheme. The problem of dimensionality is discussed for congruity measures and is shown to be unresolvable only for the case of chirality measures based on the discrete metric (e.g. overlap measures).

1. Introduction

Since Guye's pioneering work on chirality functions, more than a century ago [1], there has been a continuing interest in the development of methods for the quantification of chirality (for a recent review see [2]). This interest continues unabated (for example, see [3–10]).

An object X (no matter whether physical or geometrical) is chiral if and only if it is nonsuperposable upon its mirror image $\bar{X}$ ($X \neq \bar{X}$). *A chirality measure* χ that quantifies this property *can equal zero if and only if the object is achiral* [2]:

$$\chi(X) = 0 \quad \Leftrightarrow \quad X = \bar{X} . \tag{1}$$

It has been demonstrated [11] that *any two chiral objects in three- and higher-dimensional space can be chirally connected.* This has immediate implications for the choice of functions suitable for use as chirality measures: no sign-changing continuous functions, and, in particular, no continuous pseudoscalar functions, $\eta(\bar{X}) = -\eta(X)$, can be used as chirality measures in three- and higher-dimensions since *such functions necessarily have chiral zeroes* ($\eta(X) = 0$ *for* $X \neq \bar{X}$) and this violates conditions (1). Thus, only sign-preserving functions can be used as chirality measures, and therefore, without loss of generality, we can restrict ourselves exclusively to nonnegative functions:

$$\chi(X) \geqslant 0\,. \tag{2}$$

It has been recognized [2] that chirality measures can be subdivided into two types: those that gauge the extent to which a chiroid differs from an achiral reference object (*measures of the first kind*) and those that gauge the extent to which two enantiomorphs differ from one another (*measures of the second kind*). Subsequently it was demonstrated [6] that the Hausdorff chirality measure [12] and the "continuous symmetry measure" [4] represent special cases within the same class of functions defined within the framework of a unified approach. Still, a more general unification would be highly desirable as "the measure of chirality is already becoming diverse and uncorrelated owing to different and inconsistent approaches of quantifying chirality" [9]. In what follows we introduce such a scheme and demonstrate that all chirality measures suggested so far fit into that unified scheme.

It is shown in section 2 that almost all chirality measures fall into the same class, one in which the degree of chirality of a chiroid X is defined with reference to another, chiral or achiral object X_{ref}: the less these two objects match, the more chiral is X. We call these *congruity-based chirality measures* (*congruity measures* for short). There is, however, one approach [5] that does not fit into this picture and that opens up an entirely new dimension in discussions of chirality. In this approach, the degree of chirality is estimated by the lowest resolution sufficient to recognize that an object is chiral. Following Mezey [5], we call these *resolution-based chirality measures* (*resolution measures* for short) and discuss them in section 3. We conclude with section 4, which introduces a construction that unifies congruity and resolution measures.

An important problem is the extent to which chirality measures can be generalized, and, in particular, the extent to which they can be applied to *discrete vs. continuous* and to *sub- vs. equi-dimensional objects* [9]. We discuss this below and show that most chirality measures are universal enough to handle this problem, or at least can be easily upgraded to such a universal form.

2. Congruity measures

2.1. DEFINITIONS: DISTANCES AND MEASURES

The measures of this type, which seem to be the most popular ones due to their transparent and natural definition, gauge the chirality of a chiroid X by its degree of nonsuperposability with a given reference object X_{ref}. The latter can be either an appropriately selected achiral object X_o (measures of the first kind) or the enantiomorph $\bar{X}$ (measures of the second kind). The choice of $\bar{X}$ as X_{ref} seems to have certain advantages since this object is fully defined by reflection. In the case of an achiral reference object X_o, shape and size are not rigidly fixed, and need to be varied depending on the mutual orientation of X and X_o. This makes the problem more complex, especially in the case of continuous sets where the number of degrees of freedom determining the shape and size of X_o may be infinite.

In order to measure the degree of congruity of X and X_{ref}, a *discrimination function* $d(x, x')$ has to be chosen, which is defined on $X \otimes X_{ref}$ and which shows how far or how distinct are $x \in X$ and $x' \in X_{ref}$. This is usually a distance (in most cases Euclidean) between x and x' in the embedding space, but other functions can also be used, subject to restrictions discussed below. Obviously, this function depends parametrically on the mutual spatial arrangement of X and X_{ref}.

For a given mutual arrangement of X and X_{ref} determined by a set of orienting parameters $\mathbf{q}$ (which include translations and rotations of X and X_{ref}, as well as the shape and size of X_{ref} if it is achiral), the deviation of $x \in X$ from X_{ref} is described by a function $g(x; \mathbf{q})$ which is defined in terms of $d(x, x')$. Usually,

$$g(x, \mathbf{q}) = \inf_{x' \in X'} d(x, x') \quad \text{for given } \mathbf{q}\,, \tag{3}$$

although other expressions can be used as well, including various types of averaging.

Based on $g(x; \mathbf{q})$, we define the *G_p-distance between X and X_{ref}* as its power-p average

$$G_p(\mathbf{q}) = \left[\int_X g^p(x; \mathbf{q})\, dx\right]^{1/p} \tag{4}$$

or, more generally, as a weighted average

$$G_p(\mathbf{q}) = \left[\frac{\int_X g^p(x; \mathbf{q})\omega(x)\, dx}{\int_X \omega(x)\, dx}\right]^{1/p} \tag{5}$$

with a weight function $\omega(x)$.

The denominator of the right-hand part of eq. (5) is a measure of set X: volume or area, if $\omega(x) = 1$; mass, if $\omega(x)$ is density; number of electrons, if $\omega(x)$ is electron density; etc. The numerator is the norm $\|g(x; \mathbf{q})\|_p$ of function $g(x; \mathbf{q})$ in the L^p space of integrable functions [13]. Expressions (4)–(5) are quite general and include, as specific cases, regular average ($p = 1$), root-mean-square average ($p = 2$), and harmonic mean ($p = -1$). At $p \to \infty$ they turn into [13]

$$G_\infty(\mathbf{q}) = \sup_{x \in X} g(x; \mathbf{q})\,. \tag{6}$$

They are equally applicable to *both continuous and discrete* objects. For convenience, a discrete chiroid $Q = \{x_i | i \in I\}$ (with the index set I being a finite or infinite subset of integers) is considered to be embedded into a continuous set $X : Q \subset X$, and is described by a discrete weight function, $\omega(x)$, represented by a weighted sum

$$\omega(x) = \sum_{i \in I} w_i \delta(x - x_i) \tag{7}$$

of Dirac δ-functions with weighting factors w_i. Substituted in (5), function (7) turns integration into summation

$$G_p(\mathbf{q}) = \left[\sum_{i \in I} w_i g^p(x_i, \mathbf{q}) \Big/ \sum_{i \in I} w_i \right]^{1/p}$$

that for $w_i = 1$ reduces G_p to distance functions D_p

$$D_p = \left[\frac{1}{N} \sum_{i \in I} g^p(x_i, \mathbf{q}) \right]^{1/p}, \quad N = \text{card}\, I\,,$$

discussed earlier [6] in their application to chirality measures.

One more remark should be made regarding the integration domain in eqs. (4)–(5). Strictly speaking, the *G_p-distance* that characterizes the degree of nonsuperposability of a chiroid X and a reference object X_{ref} should reflect contributions from both X and X_{ref}. This can be attained by extending integration over the union $X \cup X_{ref}$. Function $g(x; \mathbf{q})$ (eq. (3)) has to be correspondingly modified to

$$g(x, \mathbf{q}) = \begin{cases} \inf\limits_{x' \in X_{ref}} d(x, x') & \text{for } x \in X\,, \\ \inf\limits_{x' \in X} d(x', x) & \text{for } x \in X_{ref}\,. \end{cases}$$

We are now in a position to define a *congruity measure* based on the G_p-distance between X and X_{ref}. Function $G_p(\mathbf{q})$ cannot be directly used as a chirality measure unless parameter $\mathbf{q}$ is properly selected. There are two ways to do this. The first is to optimize $G_p(\mathbf{q})$ with respect to $\mathbf{q}$, and to use $G_p(\mathbf{q})$ at optimum superimposition of X and X_{ref} as a chirality measure (eq. (8)):

$$\chi_c = \min_{\mathbf{q}} G_p(\mathbf{q})\,. \tag{8}$$

Another approach is to select a set $\{\mathbf{q}_s | s \in S\}$ of different mutual arrangements $\mathbf{q}_s$ of X and X_{ref} according to expected symmetry properties of X, and to define a chirality measure as a product of respective $G_p(\mathbf{q}_s)$'s for different $\mathbf{q}_s$'s (eq. (9)):

$$\chi_c = \prod_{s \in S} G_p(\mathbf{q}_s)\,. \tag{9}$$

The forms of chirality measures defined by eq. (8) and (9) can be called *optimized* and *factorized*, respectively. Optimized-form chirality measures have obvious advantages, as they are well-defined and independent of particular choices of parameters $\mathbf{q}$.

Definitions (8)–(9) impose a constraint on the choice of discrimination functions $d(x,x')$ and $g(x,\mathbf{q})$: they have to be nonnegative, since otherwise function $G(\mathbf{q})$, and, correspondingly, its global minimum (8) (if it exists) or product (9), can be negative, which contradicts condition (2) and hence condition (1).

2.2. DISCUSSION

2.2.1. Examples of congruity measures in the literature

Any given congruity measure is characterized by a particular choice of reference object X_{ref}, discrimination function $d(x,x')$, power p and weight function $\omega(x)$, and representation forms (8) or (9). This implies a virtually endless variety of measures belonging to this type. Table 1 lists congruity measures reported in the literature. It is interesting to note that for a particular choice of Euclidean metric $d(x,x')$, discrete weight function $\omega(x)$ (eq. (7)), and $p=2$, three of the four possible combinations of kinds and forms of measure have already been proposed by different authors [3,4,7] (entries 5–7 in table 1). Measures χ_v [14] and W [15] (entries 12 and 18) represent another example of a related pair of measures suggested by different authors.

Measures of the second kind prevail among those listed in table 1. Inspection of the table also shows that in most cases (entries 2–11) the Euclidean metric has been used as the discrimination function $d(x,x')$, mainly for discrete sets. The only example of a measure defined for both discrete and continuous cases is the Hausdorff measure $f(Q)$ [2] (entries 2–3), but there is no reason why most other measures cannot be modified to cover continuous sets as well, by a proper choice of a continuous weight function (*e.g.* $\omega(x)=1$) instead of the discrete function (7).

Symmetry coordinates. Chirality measure $\mathbf{d}$ [2] (entry 11 in table 1) represents a special case, considerably different from other entries in table 1. Its specific feature is that both chiroid X and an achiral reference object X_o are represented by their single points x_1 and x_o in the conformational space:

$$X=\{x_1\}\,,\quad X_o=\{x_o\}\,.$$

As a result, eqs. (3) and (5) represent trivial transformations and the G_p-distance in this case is merely a Euclidean distance $d(x_1,x_o)$ between x_1 and x_o in symmetry coordinates [16].

2.2.2. The problem of dimensionality

It has been noted [2,9] that *overlap measures* as defined in [14] cannot be applied to sub-dimensional objects. This problem of dimensionality is seen in [9] as "one of the main obstacles that stands in the way towards generalizing and unifying the measure of chirality", or, in other words, as a general limitation inherent to all chirality measures. The analysis of eqs. (3)–(5) shows, however, that this presents a problem only in the case of the discrete metric [17]

$$d(x,x')=\begin{cases}1 & \text{if } x\neq x',\\ 0 & \text{if } x=x'\end{cases} \tag{10}$$

Table 1
Congruity measures reported in the literature.

Entry	Measure [Ref] [a)]	Discrimination function $d(x, x')$	Weight function $\omega(x)$	Power p	Kind of measure (type of X_{ref})	Form of representation [b)]
1	Chirality polynomials, category a [19]	$\lambda_i - \lambda_k$	$\sum_i \delta(x - x_i)$	1	2	f
2	$f(Q)$, eq. (i) [2]	Euclidean metric	$\sum_i \delta(x - x_i)$	∞	2	o
3	$f(Q)$, eq. (h) [2]	Euclidean metric	1	∞	2	o
4	χ_p, eq. (4) [6]	Euclidean metric	$\sum_i \delta(x - x_i)$	1 to ∞	1 and 2	o
5	CMS [4]	Euclidean metric	$\sum_i \delta(x - x_i)$	2	1	o
6	[7]	Euclidean metric	$\sum_i \delta(x - x_i)$	2	2	o
7	DF^G [3]	Euclidean metric	$\sum_i \delta(x - x_i)$	2	2	f
8	DF^M [3]	Euclidean metric	$\sum_i m_i \delta(x - x_i)$	2	2	f
9	DF^V [3]	Euclidean metric	$\sum_i V_i \delta(x - x_i)$	2	2	f
10	DF^R [3]	Euclidean metric	$\sum_i R_i \delta(x - x_i)$	2	2	f
11	**d** [2]	Euclidean metric in symmetry coordinates	$\delta(x - x_1)$	–	1	o

12	χ_v, χ_s, eqs. (1)-(2) [14]	Discrete metric	1	1	2	o
13	χ_m, eq. (3) [14]	Discrete metric	Density $\rho(x)$	1	2	o
14	χ_m, eq. (4) [14]	$\lvert 1-\rho_o(x)/\rho(x)\rvert$	Density $\rho(x)$	1	2	o
15	χ_ψ, eq. (5) [14]	$\lvert 1-\lvert\psi_o\rvert^2/\lvert\psi\rvert^2\rvert$	Electron density $\lvert\psi\rvert^2$	1	2	o
16	χ_Ω, eq. (6) [14]	$\lvert 1-\lvert\psi_o^+\Omega\psi_o\rvert/\lvert\psi^+\Omega\psi\rvert\rvert$	$\lvert\psi^+\Omega\psi\rvert$	1	2	o
17	$1-R_{AB}$, eq. (1) [10]	$1-\frac{P_B}{P_A}\left(\frac{\int P_A^2\,dv}{\int P_B^2\,dv}\right)^{1/2}$	$\frac{P_A^2}{\int P_A^2\,dv}$	1	2	f[c]
18	W, eq. (2) [15]	Discrete metric	1	1	2	f[c]
19	Z, eq. (7) [15]	$\begin{cases} 1 & \text{if } x\in LGP \\ -1 & \text{if } x\in RGP \\ 0 & \text{otherwise} \end{cases}$	$\begin{cases} d(x,x_o) & \text{if } x\in LGP\cup RGP \\ 0 & \text{otherwise} \end{cases}$	1	1	f[c]
20	Z', eq. (8) [15]			1	1	f[c]
21	Z, eq. (5) [21]		$\begin{cases} d(x,x_o)\cdot\sin\alpha & \text{if } x\in LGP\cup RGP \\ 0 & \text{otherwise} \end{cases}$	1	1	f[c]

[a] Equations and notations are those used in the cited papers.
[b] Optimized (o) or factorized (f).
[c] Single term only.

that underlies the measure χ_v (entry 12 in table 1). Indeed, substituted in (3), function (10) leads to the step function

$$g(x) = \begin{cases} 1 & \text{if } x \notin X \cap X_{ref}, \\ 0 & \text{if } x \in X \cap X_{ref}. \end{cases} \tag{11}$$

Since in most cases the intersection $X \cap X_{ref}$ of sub-dimensional X and X_{ref} is a set of measure zero, function $G_p \equiv 1$ and thus fails to gauge different degrees of nonsuperposability of X and X_{ref}. For similar reasons, chirality measures based on the discrete metric (10) are inefficient as applied to discrete chiral sets. However, continuous metrics $d(x, x')$, *e.g.* Euclidean distance as in the case of the Hausdorff measure $f(Q)$ (entry 3 in table 1), produce continuous nonzero functions $g(x)$. Hence, these metrics lead to nontrivial integrals (4)–(5) and thus define reasonably sensitive chirality measures for sub-dimensional sets.

2.2.3. Chirality functions related to congruity measures

Chirality polynomials. Although chirality polynomials have been developed based on entirely different principles [18], they demonstrate a remarkable resemblance to some congruity measures.

Given a symmetric skeleton $Q = \{x_i | i \in I\}$ with a set of ligand parameters $\Lambda = \{\lambda_i | i \in I\}$ associated with its sites x_i, the discrimination function g for a measure of, say, the second kind can be defined as

$$g(x_i, \mathbf{q}) = |\lambda_i - \lambda_i'| \quad \text{if } x_i \in Q \text{ is superposed with } x_i' \in \overline{Q}.$$

Substitution in (5) with $\omega = \sum_i \delta(x - x_i)$ and $p = 1$ gives the G_p-function

$$G_1(\mathbf{q}_s) = \sum_{i \in I} |\lambda_i - \lambda_i'|,$$

which, substituted in (9), yields

$$\chi_c = \prod_{s \in S} \sum_{i \in I} |\lambda_i - \lambda_i'|. \tag{12}$$

For skeletons in category a [19] we can select superpositions of Q and $\overline{Q}$ in which only two reflection-related sites, i and $k = \sigma i$, have different ligand parameters. This reduces the sum in eq. (12) to a single term, $2 \cdot |\lambda_i - \lambda_k|$, and thus eq. (12) transforms into

$$\chi_c = c \cdot \prod_{i<k} |\lambda_i - \lambda_k| \quad (c = \text{const}, k = \sigma i), \tag{13}$$

which is exactly the absolute value of the corresponding chirality polynomial [18,19]

$$P = c \cdot \prod_{i<k} (\lambda_i - \lambda_k) \quad (c = \text{const}, k = \sigma i).$$

The situation is different for skeletons in category b [19]. Here the presence of the sum in eq. (12) is unavoidable. Still, the expressions for chirality measure (12) and the corresponding chirality polynomial are fairly close. Thus, for the square $\{1,2,3,4\}$ they are

$$\chi_c = |\lambda_1 - \lambda_3| \cdot |\lambda_2 - \lambda_4| \cdot (|\lambda_1 - \lambda_2| + |\lambda_3 - \lambda_4|) \cdot (|\lambda_1 - \lambda_4| + |\lambda_3 - \lambda_2|) \quad (14)$$

and

$$P = (\lambda_1 - \lambda_3) \cdot (\lambda_2 - \lambda_4) \cdot (\lambda_1 - \lambda_2 + \lambda_3 - \lambda_4) \,,$$

respectively. The extra parentheses in (14) are required to provide the symmetry of χ_c with respect to the permutation of indices. This is not needed in the case of P where the polynomial in the last parentheses already possesses the proper symmetry. The price is the existence of chiral zeroes for P, a problem that function χ_c is free of.

Rassat's function. Because Rassat's function δF [20] has chiral zeroes, it violates condition (1) and is therefore not, strictly speaking, a chirality measure [2,12]. In the context of the present paper it is worth mentioning, however, that this function is close to being a congruity measure because it is defined in terms of G_∞-distances with respect to two *fixed* chiral reference objects, X_{ref} and $\overline{X}_{ref}$:

$$\delta F = \min_{\mathbf{q}_1} G_\infty(X, X_{ref}; \mathbf{q}_1) - \min_{\mathbf{q}_2} G_\infty(X, \overline{X}_{ref}; \mathbf{q}_2) \,. \quad (15)$$

If $\overline{X}$ is chosen as a reference object

$$X_{ref} = \overline{X}$$

the second term in (15) vanishes and δF reduces to the Hausdorff measure $f(Q)$ [2].

Hel-Or's function. Chirality functions Z [15,21] (entries 19–21 in table 1) are formally constructed as congruity measures. However, because the respective discrimination function $d(x, x_o)$ can be negative (which, as discussed above, violates requirements (1)–(2)), functions Z do not qualify as chirality measures [2].

3. Resolutions measures

3.1. DEFINITIONS

Practically all chirality measures proposed so far belong to the class of congruity measures. There is, however, a single example, Mezey's measure [5], which does not fit into that scheme. It is based on an entirely different approach, one that does not require a comparison between a chiroid and a reference object. Instead, it focuses on the analysis of the properties of the system of sets covering the chiroid.

In this section we present a general scheme for the construction of chirality measures of this type. The examples chosen to illustrate this scheme are chiroids in 2D.

Given a chiroid X, we start with a proper choice of covering sets $u_k(r) \subset X$ [17]. These are selected to be all possible subsets of X of different sizes and locations in X, but all of the same shape (triangles, squares, disks, cubes, balls, etc.). Two examples of such sets are given in fig. 1. Parameter r, which determines the size of $u_k(r)$, is scaled so that $u_k(1)$ is the largest set of a given shape inscribable into X:

$$\max_{u_k(r) \subset X} r = 1 .$$

Index k characterizes a location of $u_k(r)$ in X. We use $K(r)$ to denote the set of all k's labeling sets $u_k(r)$ of a given size r. Because the system $U = \{u_k(r)|k \in K(r); r \in [0, 1]\}$ of sets $u_k(r)$ forms a covering of X, their union for all sizes and locations equals X:

$$\bigcup_r \bigcup_{k \in K(r)} u_k(r) = X . \tag{16}$$

Since set U includes all $u_k(r) \subset X$, we call it the *full inner covering* of X.

Some restrictions may be imposed on possible arrangements of $u_k(r)$ (cf. fig. 2), thus restricting U to its subsets

$$U_\tau = \{u_k(r)|k \in K_\tau(r) \subset K(r); r \in [0, 1]\} ; \quad \tau \in T .$$

Index set T is used to label those and only those U_τ which are coverings of X

$$\bigcup_r \bigcup_{k \in K_\tau(r)} u_k(r) = X . \tag{17}$$

Like (16), union (17) includes sets $u_k(r)$ of different sizes r, but the variety of locations k is now limited to a smaller subset $K_\tau(r) \subset K(r)$ due to the restrictions imposed.

Based on (17), chiroid X may be approximated at a limited resolution R. This *R-approximation* of X is defined as

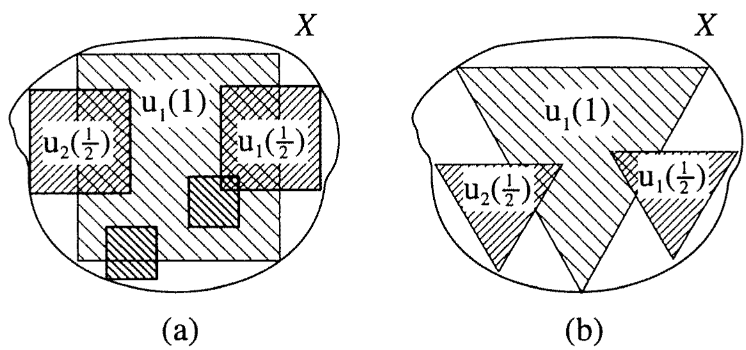

Fig. 1. Squares (a) and triangles (b) as covering elements $u_k(r)$ of chiroid X.

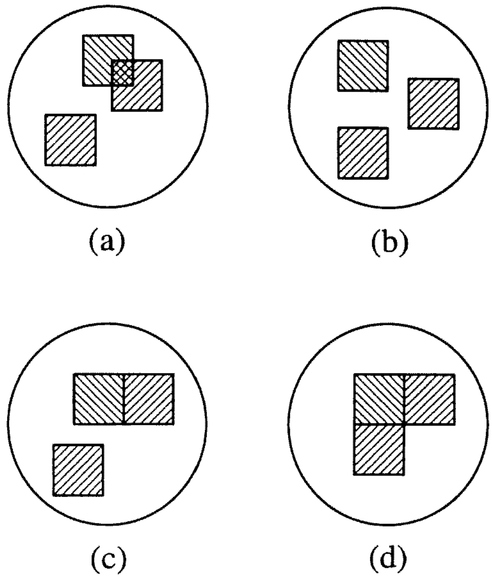

Fig. 2. Some arrangements of $u_k(r)$ (shaded squares): (a) no restrictions; (b) no overlap allowed: $\forall k, m \in K_\tau$, $u_k \cap u_m = \emptyset$; (c) no overlap of interiors allowed (no restrictions on boundaries): $\forall k$, $m \in K_\tau$, $\mathrm{int}(u_k) \cap \mathrm{int}(u_m) = \emptyset$; (d) no overlap of interiors allowed, and each square must share at least part of its boundary with another one: $\forall k, m \in K_\tau$, $\mathrm{int}(u_k) \cap \mathrm{int}(u_m) = \emptyset$, and $\forall k \in K_\tau$, $\exists m \in K_\tau$, $u_k \cap u_m \neq \emptyset$.

$$X_\tau(R) = \bigcup_{r \geqslant R} \bigcup_{k \in K_\tau(r)} u_k(r) . \tag{18}$$

It obviously follows from eqs. (17) and (18) that for any $\tau \in T$

$$X_\tau(0) = X .$$

One can call X *chiral at resolution* R if every $X_\tau(R); \tau \in T$ is chiral, and *achiral at resolution* R if *at least one* $X_\tau(R)$ is achiral.

If for every $R \neq 0$ all coverings U_τ for different $\tau \in T$ include the same number of sets $u_k(R)$ of size R, so that

$$n_\tau(R) = \mathrm{card}\ K_\tau(R) = \mathrm{const} = n(R) , \tag{19}$$

then $n(R)$ can be used as a measure of resolution R. This function increases as R decreases, which means that $n(R)$ can be inverted to give R as a function of n. One can call X *chiral at level* n if it is chiral at resolution $R = R(n)$.

If X is chiral at resolution R_1, this does not necessarily mean that it is also chiral at a higher resolution $R_2 < R_1$. We call X *apparently chiral* at resolution R_1 if there exists an $R_2 < R_1$ such that X is achiral at resolution R_2, and *genuinely chiral* at resolution R_1 if it is chiral at *any* resolution $R \leqslant R_1$.

A *resolution measure* χ_r is then defined as the upper bound of resolutions R at which X is genuinely chiral:

$$\chi_r = \sup\{R|\forall\tau : X_\tau(R) \textit{ is chiral}\}\,. \tag{20}$$

Under condition (19), χ_r can also be defined in terms of n.

Apparent chirality complicates the proper determination of chirality measure (20). This is, however, a property of a covering system rather than that of a covered set. We show in section 2.3 that for any chiroid X there exists at least one "good" covering system that does not produce apparent chirality. For such a system, X is achiral at any $R > \chi_r$ and chiral at any $R < \chi_r$.

3.2. MEZEY'S MEASURE: A DISCRETE RESOLUTION MEASURE

Mezey's measure [5] is a discrete-valued measure, which uses n rather than R to represent the level of resolution. The covering sets $u_k(r)$ are squares (or cubes, for 3D). Restrictions, similar to those of fig. 2(d), are imposed on their possible arrangements, so that unions at given sizes r_n form specific sets

$$A_n = \bigcup_{k\in K(r_n)} u_k(r_n)$$

called "internal filling animals" [5]. Due to restrictions imposed on the structure of "animals", apparent chirality is inherent to this approach [2,5].

3.3. A CONTINUOUS RESOLUTION MEASURE: A WAY TO AVOID APPARENT CHIRALITY

As mentioned above, if a covering system allows apparent chirality, the determination of a resolution measure χ_r becomes ambiguous. This problem can be easily avoided, however, if any restrictions on the arrangements of covering sets $u_k(r)$ are removed and the full covering system U is used to approximate X. R-approximations $X(R)$ are then defined in terms of its subsets as

$$X(R) = \bigcup_{r\geqslant R}\ \bigcup_{k\in K(r)} u_k(r)\,. \tag{21}$$

For a given R, $X(R)$ includes *all* $u_k(r) \subset X$ with $r \geqslant R$ as subsets.

If $X(R)$ is achiral, for *every* $u_k(r); r \geqslant R$ it includes both $u_k(r)$ and its mirror image $\sigma u_k(r)$. Since it includes *all* $u_k(r) \subset X$ of size $r \geqslant R$, every $u_k(r)$ in X has a symmetry-related set $\sigma u_k(r)$ if $r \geqslant R$. This means that for any $R_1 > R$ the union

$$X(R_1) = \bigcup_{r\geqslant R_1}\ \bigcup_{k\in K(r)} u_k(r)$$

of all $u_k(r); r \geqslant R_1$ is achiral. That is, apparent chirality is completely excluded because if $X(R)$ is achiral, then for any $R_1 > R$, $X(R_1) \subset X(R)$ is also achiral.

One can recognize a fuzzy-set structure [22] in the above construction if X is considered as a fuzzy set and $X(R)$ is its crisp subset of level R. Translation of the definition of the resolution measure into fuzzy-set language is straightforward: *given a fuzzy set X with a membership function $R(x)$; $x \in X$, its resolution chirality is the maximum level R_o below which all crisp subsets $X(R)$ of level R ($R < R_o$) are chiral.*

As seen from fig. 3, the fuzzy-set approach to resolution measures does not, in general, guarantee the absence of apparent chirality. There is, however, a simple geometrical model that induces a fuzzy-set structure on X and that is free of this problem.

Geometrical model. We define the *width of the set X at its point x* as the size R of the largest square (cube, ball, disk, etc.) $u_k(R) \subset X$ containing x. This width, interpreted as a membership function for x, defines a fuzzy-set structure on X. Its crisp subsets of level R, $X(R)$, include those and only those points x where X is wider than R. Since any point x of $X(R)$ belongs to a set $u_k(r)$, $r \geqslant R$, set $X(R)$ belongs to the union of sets $u_k(r)$, $r \geqslant R$. At the same time, since any point x of *any* set $u_k(r)$, $r \geqslant R$, belongs to $X(R)$, the union of sets $u_k(r)$, $r \geqslant R$, belongs to $X(R)$. This means that $X(R)$ can be represented as union (21), and hence that this geometrical model is equivalent to the one described at the beginning of the section. The model is therefore free of apparent chirality.

Figure 4 illustrates the model. Set X_1 is chiral, but at limited resolution $R > 1/2$ is perceived as an achiral object since its narrow parts, whose widths do not exceed $1/2$, cannot be "seen" at this resolution. At a higher resolution $1/2 > R > 1/4$, X_1 is already "seen" as a chiral object, though some of its thinner portion still remains

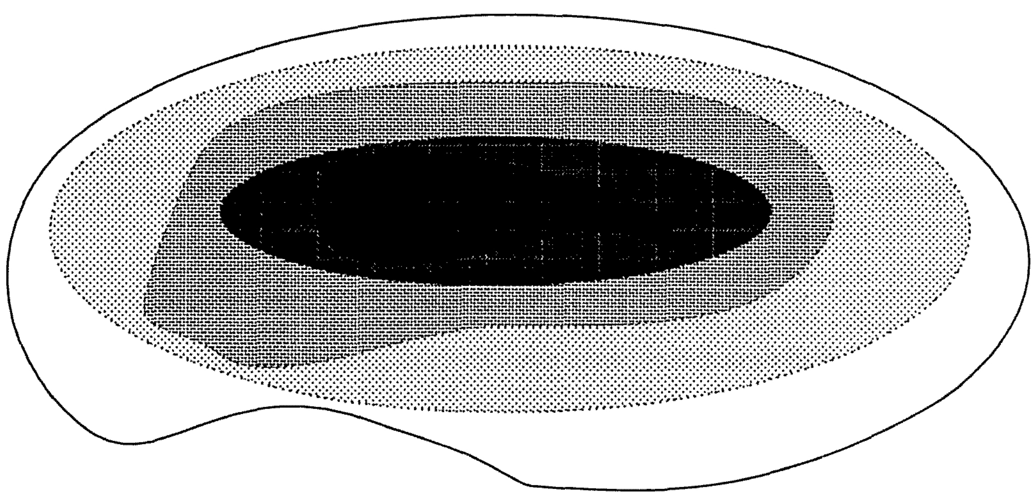

Fig. 3. Chiral fuzzy set X, and its crisp subsets of different levels R, $0 < R_1 < R_2 < R_3 < R_4 < R_5$: $X = X(0) \supset X(R_1) \supset X(R_2) \supset X(R_3) \supset X(R_4) \supset X(R_5)$. Higher levels of membership function are represented by darker shading. Subsets $X(R_1)$, $X(R_3)$, and $X(R_5)$ are achiral, whereas subsets $X(R_2)$ and $X(R_4)$ are chiral.

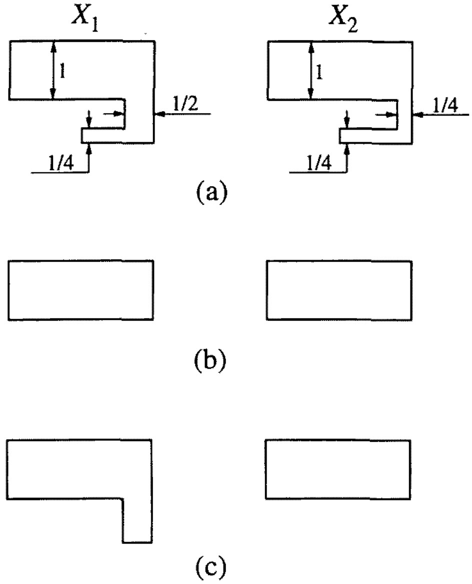

Fig. 4. (a) Sets X_1 and X_2. Perception of these sets at limited resolutions: (b) $R > 1/2$, (c) $1/2 > R > 1/4$.

"invisible". Chiral set X_2, though of a very similar shape, is narrower in some parts and "remains" achiral even at $1/2 > R > 1/4$. Accordingly, within the framework of the resolution-measure approach, X_2 should be considered less chiral than X_1.

3.4. RESOLUTION MEASURES FOR DISCRETE SETS: A CHEMICAL MODEL

Although the definition of resolution measure in terms of covering elements $u_k(r)$ is, strictly speaking, applicable only to continuous sets, the equivalent fuzzy-set definition can be extended to the case of discrete sets. An example of such a case is the chirality of $H(CH_2)_mC^*HD(CH_2)_mD$ [23]. This molecule can be represented by a discrete set X of atoms $x \neq C^*$. The fuzzy-set structure on X can be defined by the membership function

$$R(x) = \frac{1}{k},$$

where k is the number of bonds separating atoms x and C^*. All crisp subsets $X(R)$ of level $R \geqslant 1/m$ are achiral since they represent achiral fragments $C(CH_2)_{k-1}C^*HD(CH_2)_{k-1}C$. At $R < 1/m$ ($k = m + 1$), side chains $H(CH_2)_m$ and $(CH_2)_mD$ become different, and hence $X(R)$ becomes chiral. That is, the resolution measure for set X is

$$\chi_r = \frac{1}{m}.$$

Thus, the greater the value of m, the lower the degree of chirality of the molecule.

4. The $\chi(R)$ function of a fuzzy set: a conjunction of congruity and resolution measures

A general problem with all resolution measures is their insufficient sensitivity to the shape of a chiroid (cf. fig. 5). Such measures only reveal at what stage the "image" of an object becomes chiral, but do not address the question of *how* chiral it becomes. That is, these measures do not distinguish between any two objects, no matter how different they are in shape, if the "images" of these objects become chiral at the same resolution.

A simple but general solution of this problem can be achieved by extending the fuzzy set approach of the preceding section to include the congruity measures described in section 2. This can be done in the following way. Given an object X with a fuzzy set structure, we define its R-approximation $X(R)$ as the crisp subset of level R. A congruity measure $\chi(R)$ is then defined for each $X(R)$; this function $\chi(R)$ describes the degree of chirality of X at different resolutions R. Chiralities of two fuzzy sets can then be compared in terms of their $\chi(R)$ functions (cf. fig. 6). In this construction, congruity measure χ_c and resolution measure χ_r represent the limiting cases

$$\chi_c = \chi(R = 0)\,,$$

$$\chi_r = \min\{R|\chi(R) = 0\}\,,$$

and can be graphically represented as the points of intersection of the graph of $\chi(R)$ with the coordinate axes χ and R.

It is implied in the above construction that, although the perception of shape is limited at a given resolution R, the chirality $\chi(R)$ of the R-resolved image $X(R)$ of X can be detected with infinite accuracy. A more consistent approach, however, should also take into account inaccuracy in determining $\chi(R)$. Consider, for exam-

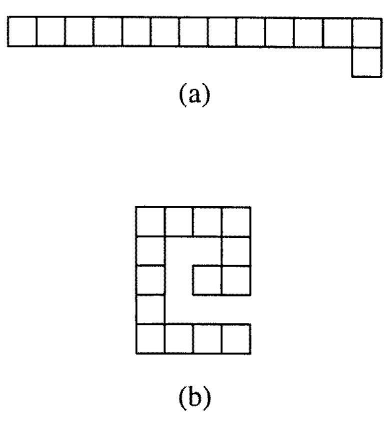

Fig. 5. Two chiroids of different shapes, but of the same resolution measure χ_r.

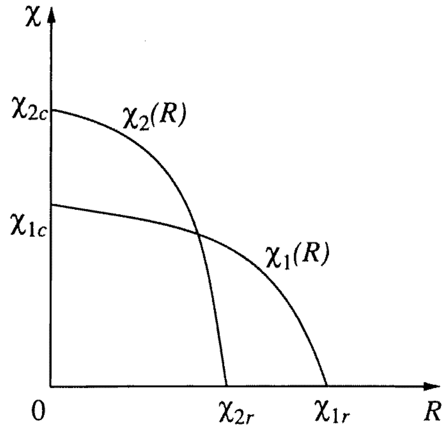

Fig. 6. Schematic representation of functions $\chi(R)$ for two chiroids, X_1 and X_2. χ_{1r} and χ_{2r}, their resolution measures, mark the resolutions R at which $X_i(R)$ become chiral. χ_{1c} and χ_{2c} are congruity measures of these chiroids, considered as crisp sets ($R = 0$). Graphs of $\chi_1(R)$ and $\chi_2(R)$ show that at low resolutions X_1 is more chiral than X_2, while at high resolutions the situation is reversed.

ple, a geometrical model of the type described in the preceding section. Chiroid X, as depicted in fig. 7, represents a square of unit size with a rectangle $1/2 \times 1/4$ attached to the upper part of its left side. At resolutions $R > 1/2$ it is perceived as a square, i.e. as an achiral object. Starting from $R = 1/2$, its rectangular part becomes "visible" as well. This means that at $R = 1/2$ we register *the change in the shape of* X. Do we detect any chirality at this moment? The answer depends on how we assess the chirality. If we follow the definition of chirality as nonsuperposa-

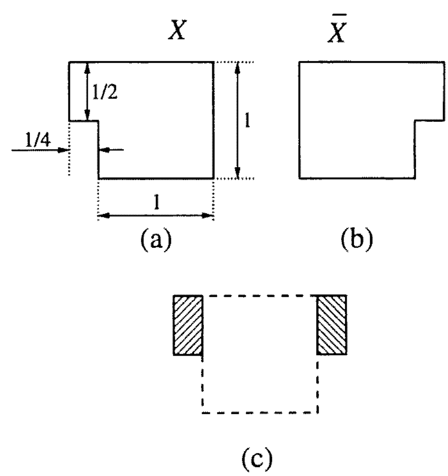

Fig. 7. Cryptochirality of a geometric set with a width-induced fuzzy structure (see text for details). (a) A chiroid X. (b) Its enantiomorph $\bar{X}$. (c) Superimposition of X and $\bar{X}$. The nonoverlapping parts are shaded.

bility of X with its mirror image $\bar{X}$, we have to overlap X with $\bar{X}$ and study nonoverlapping parts. In this case, the nonoverlapping parts are represented by two disjoint rectangles $1/2 \times 1/4$. Their width is $1/4$, and hence they are "invisible" at resolution $1/4 < R \leqslant 1/2$. This means that at this resolution X seems achiral, since no mismatch between X and $\bar{X}$ can be detected. In other words, even though we register the change in *shape* of X at $R = 1/2$, its *chirality* remains undetectable until $R \leqslant 1/4$. This is an example of *cryptochirality* [23], which is the appearance of a chiral object as seemingly achiral because its chirality is below the level of resolution (*operational null*). Another interpretation for function $\chi(R)$ is thus provided: given the operational null level $\chi_o(R)$, the intersection of this level with the graph of $\chi(R)$ determines the lowest resolution at which X is *detectably chiral*, and which therefore is an effective resolution measure χ_r, associated with a given operational null $\chi_o(R)$ (cf. fig. 8).

As was shown in sections 2 and 3, all chirality measures so far reported in the literature belong to one of two general classes, congruity or resolution measures. The concept of function $\chi(R)$ introduced in this section finalizes the unification scheme, since it includes congruity and resolution measures as limiting cases. Strictly speaking, $\chi(R)$ is not a chirality measure. This is a much richer construction since it maps the set of chiral objects into the set of functions rather than into the set of numbers, as chirality measures do. However, a number of different chirality measures can be generated based on function $\chi(R)$, of which probably the most interesting is the *integral chirality measure*

$$\chi_i = \int_0^1 \chi(R)\, dR\,. \tag{22}$$

This measure is a uniform average of $\chi(R)$ over the whole range [0, 1] of resolutions

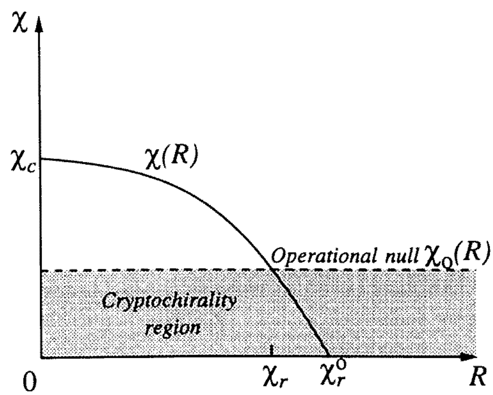

Fig. 8. Resolution measure at limited precision. The shaded area below the operational null level $\chi_o(R)$ represents the range of undetectable chirality χ (cryptochirality region). Only chirality above this level can be detected. As a result, an effective resolution measure χ_r associated with the given operational null $\chi_o(R)$ is shifted towards zero with respect to the resolution measure χ_r^o which corresponds to the limit of absolute accuracy ($\chi_o(R) = 0$).

R (cf. fig. 9(a)). If X is a crisp set, $\chi(R) = \chi_c$ for all R's (cf. fig. 9(b)). Substituted in (22), this yields

$$\chi_i = \chi_c \,.$$

If X is a fuzzy set and $\chi(R)$ is a simple "yes-no" (or "chiral-achiral") function, free of apparent chirality (cf. fig. 9(c)), then

$$\chi(R) = \begin{cases} 1 & \text{if } R < R_o \,, \\ 0 & \text{if } R > R_o \,. \end{cases} \tag{23}$$

Integration (22) gives

$$\chi_i = R_o = \chi_c \,.$$

Thus, χ_c and χ_r can be regarded as particular cases of measure χ_i.

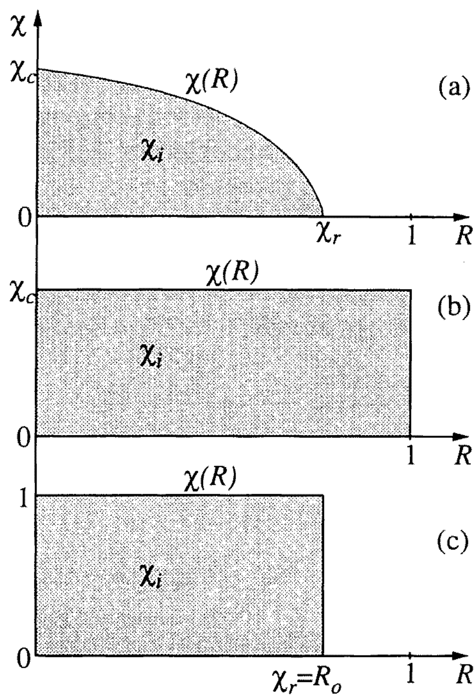

Fig. 9. Geometrical interpretation of the integral chirality measure χ_i as the area of a trapezoid bounded by the coordinate axes and the graph of function $\chi(R)$. (a) General case. (b) A crisp set: $\chi(R)$ is constant and equals χ_c, the congruity measure of the set. The area of the shaded region is the product of height χ_c and the unit base and thus equals χ_c. (c) A fuzzy set with "yes-no" function $\chi(R)$ (eq. (23)): at low resolutions $R > R_o$, $\chi(R) = 0$ (achiral); at high resolutions $R < R_o$, $\chi(R) = 1$ (chiral). The area of the shaded region is the product of the unit height and the base of length R_o, and thus equals R_o, which is, by definition (20), the resolution measure χ_r.

Acknowledgement

Support by the National Science Foundation is gratefully acknowledged.

References

[1] P.-A. Guye, C.R. Acad. Sci. (Paris) 110 (1890) 714.
See also: A. Crum Brown, Proc. Roy. Soc. Edin. 17 (1890) 181;
P.-A. Guye, C.R. Acad. Sci. (Paris) 116 (1893) 1378, 1451, 1454.
[2] A.B. Buda, T. Auf der Heyde and K. Mislow, Angew. Chem. Int. Ed. Engl. 31 (1992) 989.
[3] V.E. Kuz'min, I.B. Stel'makh, M.B. Bekker and D.V. Pozigun, J. Phys. Org. Chem. 5 (1992) 295.
[4] H. Zabrodsky, S. Peleg and D. Avnir, J. Am. Chem. Soc. 114 (1992) 7843.
[5] P.G. Mezey, J. Math. Chem. 11 (1992) 27, and references therein.
[6] N. Weinberg and K. Mislow, J. Math. Chem. 14 (1993) 427.
[7] Z. Zimpel, J. Math. Chem. 14 (1993) 451.
[8] T. Auf der Heyde, S. Afr. J. Chem. 46 (1993) 45.
[9] G. Gilat, J. Math. Chem. 15 (1994) 197.
[10] A. Seri-Levy and W.G. Richards, Tetrahedron: Asymmetry 4 (1993) 1917;
A. Seri-Levy, A. West and W.G. Richards, J. Med. Chem. 37 (1994) 1727.
[11] K. Mislow and P. Poggi-Corradini, J. Math. Chem. 13 (1993) 209.
[12] A.B. Buda and K. Mislow, J. Am. Chem. Soc. 114 (1992) 6006.
[13] F. Jones, *Lebesgue Integration in Euclidean Space* (Jones and Bartlett, Boston, 1993).
[14] G. Gilat, J. Phys. A: Math. Gen. 22 (1989) L545.
[15] Y. Hel-Or, S. Peleg and H. Zabrodsky, Proc. IEEE Comput. Vision Pattern Recognition (1988) 304.
[16] T.P.E. Auf der Heyde, A.B. Buda and K. Mislow, J. Math. Chem. 6 (1991) 255.
[17] C.G. Pitts, *Introduction to Metric Space* (Oliver & Boyd, Edinburgh, 1972).
[18] For a recent review, see: R.B. King, in: *New Developments in Molecular Similarity*, ed. P.G. Mezey (Kluwer Academic, Dordrecht, 1991) p. 131.
[19] E. Ruch, Angew. Chem. Int. Ed. Engl. 16 (1977) 65.
[20] A. Rassat, C.R. Acad. Sci. (Paris) 299 (1984) 53.
[21] Y. Hel-Or, S. Peleg and D. Avnir, Langmuir 6 (1990) 1691.
[22] A. Kaufmann, *Introduction to the Theory of Fuzzy Subsets* (Academic Press, NY, 1975);
G.J. Klir, T.A. Folger, *Fuzzy Sets, Uncertainty, and Information* (Prentice Hall, Englewood Cliffs, 1988).
[23] K. Mislow and P. Bickart, Isr. J. Chem. 15 (1976/77) 1.