Finally, the analysis of chirality content of spiral DLAs given by Katzenelson et al.[1] appears to be purely two-dimensional. Ignoring the local arrangements of their constituent atoms, these systems are of course achiral in three dimensions. Care needs to be taken in extrapolating any associated physical properties to three dimensions because the physics of chirality in two dimensions is very different from that in three.[10] For example, chiral molecules on an isotropic surface can show new chiroptical phenomena such as huge circular intensity differences in second harmonic scattering, which are generated by pure electric dipole processes.[11]

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Reply to "On the Definition of Chirality"

Further Comments on the Chirality of Large Random Objects

David Avnir,* Omer Katzenelson and Hagit Zabrodsky Hel-Or

Prof. Barron has illuminated the question of the chirality of large random objects[1] from an additional point of view, and has added valuable comments to the discussion.[2] The main issue raised is that of geometric versus physical definitions of chirality. It is an important question, which was also addressed recently by Gilat.[3] It is our opinion that these two points of view are correlated and complementary. Thus, we have shown that the *geometric* measure of the degree of centrosymmetricity correlates smoothly with the hyperpolarizability of distorted benzene,[4] that continuous symmetry analysis nicely predicts the melting point of small clusters,[5] that the inhibition efficiency of a series of chiral acetylcholineesterase inhibitors depends linearly on the geometric degree of chirality of these inhibitors,[6] and more. Lord Kelvin has taken in his definition of chirality[7] the strict view of a geometer and not that of a physicist (and here we differ with Barron[2]), and rightly so: symmetry and chirality are strict geometric traits; their physical manifestation is an intimately linked, but totally different story, which may vary wildly with the physical property in question. Optical rotation, mentioned by Professor Barron, is actually a well-known example for this: it can be zero for chiral objects and therefore fails, in principle, to serve as a universal chirality measure. Lord Kelvin's geometric definition is simple in the positive sense and robust: the criterion of nonsuperimposability is general and a sufficient condition for chirality.

It was unnecessary for Barron to "defend" Lord Kelvin (although later on he criticizes Kelvin's definition, see below), because our starting point follows in Kelvin's footsteps with purely geometrical arguments. Our main contribution, as we see it, is to analyze how purely geometric arguments stand vis-à-vis realistic complex structures and the mechanisms of their formation. In fact, our work in reference [1] is a step towards a physical picture of chirality without leaving the safe grounds of geometry. In particular, the issues we emphasized, which have led to the extended treatment of the concept of chirality, are the following:

1. A (large) random object is always chiral even if it had no chiral bias in its construction. However, it is impossible to obtain its enantiomer by repetition of the construction process: the probability of hitting on the exact enantiomer is negligible. The only way to obtain the exact enantiomer is to resort to an alternative *nonrandom*, and therefore artificial construction of a mirror-image object, according to exact guide-lines provided by the original object. In chemistry we have been trained to treat chirality automatically as a structural property which is manifested by a pair of enantiomers. The extension to the always-chiral large random objects, which we call *incidentally chiral objects*,[1] is not trivial. Kelvin's exact superimposability criterion is applicable here as well because it is indifferent to the history of construction; however, its execution is imposable, or at most, artificial. Our link to physical situations is then straightforward: in supramolecular chemistry, randomness leads to chirality, but the enantiomer can never form by the same process (c.f., Ruch's potato[8] and Mislow's analysis of large collections[9]).

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2. Large random objects may be chiral not only because of their randomness, but also because their construction process is chirally biased to a certain degree. These objects, which we termed *inherently chiral*,[1] pose additional constraints on the physical interpretation of exact superimposability: First, one has to establish criteria for the distinction between incidental and inherent chirality. In chirality-related studies, the former may be "unimportant" background noise for the latter. The transition between the two is gray, and obviously depends on the sensitivity of analysis. Second, inherently chiral objects do allow the formation of "left–right" enantiomers by repetition of the same construction process (operated once in the chirally biased way and then by the reversed chiral route), yet the element of randomness blurs the exact superimposability criterion. One must therefore relax the exactness restriction in order to be able to treat these *natural enantiomers* as a chiral counterparts for all experimental and practical applications. As in the case of the incidentally chiral objects, here too, an exact natural enantiomer is never attainable by repetition of the construction process, and one is bound to resort to an artificial, block-by-block mirror-copying procedure in order to achieve it. Therefore, the main issue in the translation of Kelvin's definition to realistic laboratory practice is, again, its indifference to the question of how the exact enantiomer is formed, if at all.

This situation is true not only for the aggregates we analyzed in reference [1], but for any supramolecular structure: for instance, practically all mineral crystals found in their natural environment are incidentally chiral, with no hope of finding an exact enantiomeric pair. This hopeless situation exists even for inherently chiral crystals like quartz and tartrate; in principle, Pasteur never did see a pair of enantiomers of ammonium sodium tartrate![6]

3. The third issue is another important structural property to which Kelvin's definition did not refer, and which is cardinal to its physical implementation, especially in large objects: the dependence of structural properties on the resolution of observation, especially in objects of irregular shape.[10] Let us turn to the chiral DLAs (diffusion-limited aggregate) we analyzed in reference [1] and suppose that we wish to evaluate their chirality, as is often done, with a probe molecule. A very small probe molecule will have "no idea" that it is in a chiral environment; a very large probe will be too coarse to "feel" it as well; but there is a range of probe sizes that will "report" on chirality. Yet another manifestation of the resolution dependence of chirality in such cases is even simpler: defocus the DLA picture, and you may notice that the *degree* of chirality changes.

4. Indeed, the very concept of measuring symmetry in general[11] and chirality in particular,[3,12–14] on a continuous scale, is essential for the analysis of the transition from incidental to inherent chirality, and for the evaluation of resolution effects.[1] The detachment from the "either chiral or not" in Kelvin's definition, that is, the legitimization of mirrors that are not perfect, is the last but not the least important element of our extended treatment.

Let us now go back and see how our extended treatment of the concept of chirality refers to these issues by underlining five key words:

> *Chirality is the inability to coincide a structure with a statistical realization of its mirror image. The probe-dependent amount of this inability is the chirality content of the structure.*

"Statistical" refers to the situation where, although one can analyze the chirality of a single large random object, better insight into the physics and chemistry of such objects may be gained by looking at large enough populations. This may be needed, for instance, in cases where it is not clear if the chirality is incidental or inherent. "Realization" refers to the practical condition that one would prefer to obtain a counter-enantiomer by repetition of the construction process, and not by an artificial copying procedure. "Probe-dependent" refers to the situation where the amount of chirality is sensitive to the resolution of observation and to the physical characteristics of the probe. "Amount" and "content" refer to our general theme in recent years, that symmetry (achirality, in this case) is a measurable structural property.[15] In particular one should note that reference to these aspects of chirality does not contradict Kelvin's definition, but provides an extended interpretation of it; Kelvin's definition is retrieved by omitting the underlined words.

For the sake of completeness, we conclude by referring briefly to some additional specific points made by Barron:

- The main point of Barron is that "provided parity is conserved... the enantiomers have exactly the same energy". This, of course, is always true, but *not* the issue here. *Natural* enantiomers (i.e., enantiomers that are not identical to the mirror images of each other, but differ in details) do not have identical physical properties. Different structures may coincidentally lead to exactly identical physical traits, but the natural expectation is for some similarity, not identity. "In the language of ... physics, they are degenerate" – no, they are not; one has to convert to the analysis of the *degree of degeneracy*, dictated by the degree to which a given number of homochiral objects are *isochiral* (isochirality is the property of having the same amount of chirality).
- Optical rotation: Likewise, DLA's which are either homochiral or natural enantiomers, all constructed by the same process, will *not* have the same (or opposite) optical rotations; they may have, but only by coincidence.
- Quasi-enantiomers, statistical enantiomers: These very propositions of Barron seem to reveal that he too actually holds a view that DLAs and other random objects require an adaptation of the classical view of chirality.
- Statistical uncertainty: This applies to both enantiomers (and not as stated by Barron).
- We agree that in principle our approach is applicable to uncertainties in small molecules as well, and that in this case the effects we discuss are negligibly small. That is exactly why we stated that the perfection in Kelvin's definition is a special case of the more general definition.
- On the physical insignificance of geometric measures: As commented above, the complete detachment of physics from geometry, as suggested by Barron, narrows our ability to analyze correctly natural phenomena: the link between (geometric) structure and (physical, chemical) activity is a corner stone in chemistry, and claims to the contrary may lead us astray. Geometry is of course one of several parameters that dictate molecular performance, but to state that the purely

geometrical measures discussed "appear to have no significance at the small chiral molecule level" grossly contradicts observations, a few of which were cited above.

On the quantum-mechanical picture of averaging chirality by oscillations between enantiomers: Luckily, enzymes hold a different view (in most cases) and recognize chiral molecules; chromatographic materials recognize chirality; chiral reagents are capable of inducing chirality in substrates, and so on. It is this classical geometric chirality, which is of daily relevance in chemistry, biochemistry, and materials science, and which is the focus of our studies. Kelvin provided no indication in his definition that he means otherwise.

On the static picture of chirality: Throughout Barron's comment, there seems to be a contradiction between an (unnecessary, as explained above) effort to defend Kelvin's definition and Barron's deep disagreement with Kelvin's purely geometric picture. On this specific point, Barron criticizes both Kelvin and us for treating chirality as a static property. Regarding Kelvin's treatment, Barron is right; Kelvin does not mention dynamics. In our case, Barron is incorrect. Our papers on continuous symmetry and continuous chirality are full of dynamic examples: what we actually do is track symmetry and chirality changes with time. We indeed have not yet treated temporal chirality and symmetry, but this is in the pipeline. (Furthermore, one of us proposed, with his collaborators, to use rotation in a viscous medium as a measure of chirality.[16])

The two-dimensionality of the analysis: Barron's evaluation that the model DLAs we used "appear to be purely two dimensional" is clearly stated in our paper, and has apparently escaped his attention. Also stated in our paper is that *all* of the conceptual analyses we made are applicable to the same problem in any dimension; none of our arguments is dimension dependent. Obviously, a 2D chiral object is achiral in 3D, and some physical properties are affected by reducing the dimensionality (see our own experimental work on this effect in ref. [17]), but we could have written the whole paper on 3D DLAs and little would have been changed. We refer Barron to the many 3D examples we analyzed in our above-cited papers.

In conclusion, we thank again Prof. Barron for his illuminating comments, and for the opportunity to provide some necessary clarifications and further discussion points of this most fascinating topic.

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