1 Symmetry/Pseudosymmetry: Chirality in Molecules, in Nature, and in the Cosmos

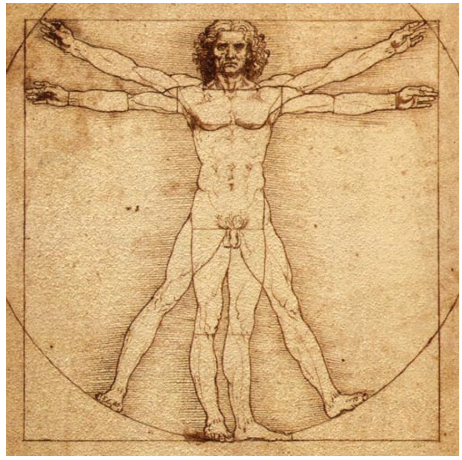
1.1 Introduction

Symmetry and emulation of symmetry (*pseudo*symmetry) play a major role in the world of esthetics and science. In our macro-surroundings, symmetry and *pseudo*symmetry are an ever-present source of "visual pleasure" whose origins may arise from our genes. At times, prior to the achievements of modern medical science, symmetrical appearance of a prospective mate may have symbolized physical well-being (health) – an essential attribute for both the child bearer/parent and the successful hunter/defender. Often, our perception of beauty and form is related to the observation of physical proportions whose ratio approximates the "golden ratio" ϕ (an irrational number $(1+\sqrt{5})/2$) where $\phi = 1.6180339887\ \ldots$ The golden ratio is derived from a Fibonacci sequence of numbers 0,1,1,2,3,5,8,13,21, … ,a,b whereby $\phi = b/a$.

Leonardo da Vinci's "Vitruvian Man" drawing (**1**) illustrates the beauty of *ideal human proportions* as described by Vitruvius, an architect in ancient Rome. The proportions of the circle's radius (centered at the navel) and the square's side (the human figure's height) are 1.659, which approximates the 1.618 value of the golden ratio. It is doubtful whether da Vinci and other great artists thought to themselves that they should paint figures and objects according to the dimensions specified by the golden ratio. Instead, they knew in their creative minds "what looks good" in their mind's eye in terms of proportions. They were probably gifted from birth (i.e., their genes) and did not have to learn about the importance of painting with the golden ratio as a novice students in art school.

Symmetry, Spectroscopy, and Crystallography: The Structural Nexus, First Edition. Robert Glaser.

Companion Website: www.wiley.com/go/Glaser/Symmetry



1

Prehistoric man's predilection to symmetry can be seen in anthropological findings of stone axe-heads. Increasingly symmetric stone axe-heads were unearthed at sites populated by progressively more developed societies. As the society of early prehistoric man matured, these finds seem to suggest that the hunter-gatherer crafted increasingly more functional hand tools that were also more visually pleasing [1]. David Avnir and coworkers have developed algorithms to measure distortion from an ideal symmetry and applied them to a morphological study of stone axe-heads unearthed at Pleistocene Age sites in the Jordan Valley. This enabled a quantitative correlation between increasing stone axe-head mirror *pseudo*symmetry and the decreasing age of the site. Illustrations **2–4** depict axe-heads dated 1.84 million years ago (the oldest site, (**2**)) 0.6(2)

2

3

4

million years ago (intermediate aged site, (**3**)), and 0.3(2) million years ago (the youngest site, (**4**)) [1].

The visual pleasure we receive from the "classic proportions" of the Municipal Arch (**5**, photo: Yael Glaser) in the Roman ruins of Glanum (Provence) is undoubtedly related to the golden ratio of its dimensions (8.8 m width and 5.5 m height). It is clear that its intimately related symmetry and esthetics were concepts well understood by talented architects in ancient times.

5

Our ancestors seem to have been greatly fascinated by objects of "*high symmetry*" (i.e., objects with more than one C_n rotation axis of order $n \geq 3$, where n denotes the number of times the rotation is performed on a subunit in order to return it to its original orientation). Gray illustration **6** illustrates a late Neolithic/Bronze Age (about 4500–5200 years ago) elaborately carved *regular tetrahedron* stone specimen with three of its knobs decorated with spirals or dots and rings. It was unearthed at Towie in Aberdeenshire, North-East Scotland. Simple carved regular tetrahedron (**7**) and octahedron (**8**) geometry objects were also unearthed in Aberdeenshire (*hedron* means "face" in Greek). The esthetically pleasing five convex regular polyhedra (tetrahedron, hexahedron, octahedron, dodecahedron, and icosahedron) were a source of learning, contemplation, and discussion for Plato and his students. In modern times, these geometrical structures were the impetus for creative organic syntheses of high-symmetry hydrocarbon molecules [2, 3].

6

7

8

1.2 Rudimentary Group Theory, Isometry, and Symmetry

Symmetry is based upon *mathematical transforms,* and to understand it, a short introduction to simple *Group Theory* will be presented. The *elements* (members) of a mathematical *set* all share some common trait. For example, the elements of a *symmetry set* are all the *symmetry operations* that can be performed for a particular object. This set may be acted upon by a *mathematical operation* (*multiplication* or *successive application*, that is, performing one operation followed by another). The combination of a set and an operation defines a *mathematical group.* The identity (E) element must be present in the set of every group. Multiplication of two elements always affords a third element that must also be an element of the set. For example, in the symmetry group C_2, the elements E and C_2 ($360°/2 = 180°$ rotation about an axis) are the symmetry operations of the set, and $C_2 \times C_2 = C_2^2 = E$. Every element has its own *inverse element* whereby multiplication of the element by its inverse affords identity. The inverse element must also be an element of the set. In the case of C_2, it is its own inverse. Symmetry groups that result in at least one point within the object remaining spatially invariant are called *point groups.* Mathematical group elements should not be confused with *symmetry elements.* Symmetry elements in an object are those single points, linear arrays of points (*axes*), or flat surfaces composed of points (*planes*) that remain *spatially invariant* after a symmetry operation is performed. Symmetry elements in an object (or between objects) are generated by calculating the array of midpoints between all pairs of symmetry-equivalent points.

Symmetry is a subset of *isometry* (*isos* in Greek means "equal," *metron* in Greek means "measure"), where the *distance matrix* between a set of points in one object is preserved when the operation generates a second object. Two objects are said to be *isometric* when their distance matrices are identical. The spatial orientation of two isometric objects may differ relative to external axes of reference. *Symmetry* should have actually been written as *sy**n**metry* (*syn* in Greek means "together"), but the letter "*n*" cannot precede the letter "*m*." Symmetry is an isometry in which full objects (or molecules), or subunits of an object, are exchanged while keeping their spatial orientations invariant. All symmetry operations are mathematical transforms performed using *symmetry operators*. These act upon a set of [*x*, *y*, *z*] coordinates of points defining an object to generate a new *exact copy* of the original object. One method (but not the only one) to make an exact copy is to generate the mirror image. When the mirror-image copied object or subunit is superimposable upon the original, then the object or subunit lacks the property called "*handedness.*" In other words, the object is *achiral*. When the mirror-image object is nonsuperimposable on the original, then it is *chiral* (from the Greek χειρ, pronounced "cheir", meaning "hand"). Objects that are chiral possess the property of (right- or left-) handedness or *chirality*.

Four of the eight known symmetry operations preserve an object's handedness. By this, we mean that after the operation is performed, a "right-handed" object/molecule remains "right," and a "left-handed" one remains "left," that is, they are *congruent*. These operations are denoted as being of the *First Kind*. Operations of the First Kind include *identity* (E), *rotation* around a "proper axis" (C_n, where "C" means *cyclic* and "n" is the *order* of the rotation operation, that is, the number of times the operation is performed on a subunit until it returns to its original orientation and position), *translation* (linear movement by a fixed distance), and n_m *screw-rotation* or *helical displacement* (combination of translation by m/n-th of the distance required for a full-turn of a helix plus rotation by $360/n$ degrees). Note: the m/n translation distance is the inverse of the descriptor's symbol n_m.

As noted earlier, when the mirror-image object or subunit is nonsuperimposable upon the original, then the object possesses the property of *chirality* or handedness. By this, we mean that the object's or subunit's "handedness" has been inverted by a symmetry operator, that is, a "right-handed" object/subunit becomes "left," and a "left-handed" one becomes "right."

The remaining four of the eight symmetry operations are those that invert the handedness of an object via symmetry transforms of the *Second Kind*. These are *reflection* (σ, where *sigma* comes from "Spiegel," which is German for "mirror"), *inversion* (i), *rotatory-reflection* (S_n, a combination of reflection and rotation by $360/n$ around an "improper axis"), and *glide-reflection* (g, a combination of reflection plus translation by one-half of the repeating distance in a linear periodic array of objects or molecules). Three of the eight known symmetry operations involve translation and, thus, can leave no point invariant in space. These are pure *translation, screw-rotation* (translation + rotation), and *glide-reflection* (translation + reflection). These three operations are found only in the 230 different *space groups* (groups of operations that describe the symmetry of a *periodic array* of objects or molecules). The remaining five (E, C_n, σ, i, and S_n) of the eight operations are found in both *point groups* and space groups.

There are 32 point groups and just five have sets containing only operations of the First Kind (those that preserve handedness). These five are known as *chiral point groups*: C_n (cyclic), D_n (dihedral), and the "high symmetry" T (tetrahedral, *tetra* in Greek means "four" and *hedron* in Greek means "face"), O (octahedral, *octa* in Greek means "eight"), and I (icosahedral, *icosa* in Greek means "twenty"). The other 27 point groups are *achiral* as their sets contain operations of both the First and Second Kinds.

In periodic ordered arrays of molecules (i.e., those within a crystal lattice), there is a sideways (or laterally or diagonally*) translational repeat unit* called a *unit cell* that builds the entire extended mosaic. Its volume is determined from the *cell parameters: a,b,c-axes lengths* (Å) and the *α,β,γ-angles* (°), where α is the angle between the *b,c*-axes, and so on. For ease of usage, crystallography uses *decimal fractions* of a unit cell axis length rather than Cartesian coordinates.

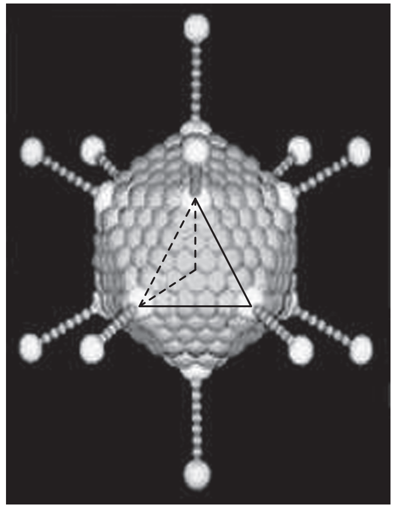
A *symmetry transform* is the mathematical basis for performing a symmetry operation. In this procedure, the set of $[x, y, z]$ coordinates defining all the atoms of a molecule or subunit is changed by a particular *symmetry operator* to generate the exact copy's new set of atoms. For example, the $[-y, x, z]$ symmetry operator engenders a C_4 rotational symmetry operation (C_n, where $n = 4$). When applied to the set of a molecule's *fractional* atomic coordinates, it produces a new same-handedness superimposable copy that has been rotated by $360°/n = 360°/4 = 90°$ about the Z-axis. The operator for a $+180°$ (*clockwise*) symmetry-equivalent position is $[-y, -x, z]$, and for a $+270°$ position, it is $[y, -x, z]$. What does this mean? It means that a $+90°$ *clockwise rotation* about the $+Z$-axis of an atom with coordinates $[x, y, z]$ will reposition that atom to $x_{\text{new}} = -y$, $y_{\text{new}} = x$, and $z_{\text{new}} = z$. For example, if $[x, y, z] = [0.0047(1), 0.2321(1), 0.0479(5)]$ for an initial atomic position, then a $+90°$ rotated atom will be at $[-0.2321(1),0.0047(1),0.0479(5)]$ based upon the $[-y, x, z]$ *symmetry operator.* The number in parenthesis is the *estimated standard deviation* (esd) of the *experimentally measured* position, that is, its *precision.* Note: the rotational *tropicity* (*tropos* means "directionality" in Greek) of all symmetry operations is *arbitrarily but consistently* chosen to be *always clockwise.* Why? Answer: by historical convention.

The symmetry operation for a $-90°$ rotation is C_4^3 (i.e., performing C_4 three times, i.e., $C_4 \times C_4 \times C_4 = C_4^3$). In a symmetry comparison, one compares only the *initial* and *final* objects. Thus, any intermediate steps leading up to C_4^3 (i.e., C_4 and $C_4 \times C_4 = C_4^2 = C_2$) are neglected. It is clear that the final position of the rotated atom is identical whether it was rotated either by $-90°$ or by $3 \times 90° = 270°$. An $[x, y, -z]$ symmetry operator acting upon all the original atoms of a molecule would afford a new exact copy that has been reflected through the *xy*-plane. Similarly, a $[-x, -y, -z]$ operator would produce a new exact copy that was *inverted* through the unit cell origin, while a $[-x, 1/2 + y, -z]$ operator would generate a new copy that has been 2_1 screw-rotated about the b-axis (combination of 180° rotation about the *b*-axis plus translation of 1/2 the unit cell repeating distance on that axis). The meaning of the 2_1 screw rotation operation will be explained later. The main purpose of this discourse is to emphasize that *genuine symmetry is a mathematical ideality.*

1.3
Asymmetric versus Chiral: The *I*-Symmetry of Viral Capsids

Asymmetry is a special case, since only objects exhibiting solely the *identity* operation are both *asymmetric* and *chiral*, that is, they have C_1 point group symmetry. Thus, while all asymmetric objects are chiral, certainly not all chiral objects are asymmetric. "Asymmetric" is definitely not a synonym for "chiral." The human adenovirus has an I-symmetry viral *capsid* (a protein shell without DNA or RNA; see **9** [4–6]. The cryo-electron microscopy and X-ray crystallography structure is presented in Protein Data Bank (PDB) entries 3IYN [7] and 1VSZ [8], respectively. I-symmetry is the highest chiral symmetry point group. The 120 I_h achiral group elements are: E, i, $6(C_5, C_5^2, C_5^3, C_5^4, S_{10}; S_{10}^3; S_{10}^7; S_{10}^9)$; $10(C_3, C_3^2, S_6; S_6^5)$ $15C_2$, and $15\sigma_h$, that is, $1 + 1 + (6 \times 8) + (10 \times 4) + 15 + 15 = 120$. The presence of only L-amino acids in the capsid removes the 60 group elements of the Second Kind, whereby the I-symmetry chiral group elements that remain are just E, $6(C_5, C_5^2, C_5^3, C_5^4)$; *10*$(C_3, C_3^2)$; $15C_2$, that is, $1 + (6 \times 4) + (10 \times 2) + 15 = 60$. The 60 C_n-rotation operations, where $n = 1, 2, 3,$ and 5, preserve the L-(*levo*)-handedness of all the capsid's amino acids.

The geometric considerations of the capsid's structure will be discussed next. The *asymmetric unit* of a unit cell is that minimal structural entity that will build the entire contents of the unit cell repeat unit using all of the symmetry operations of the point or space group (with the exception of translation for space groups). Molecules (or objects) that contain a symmetry element within themselves will have an asymmetric unit that is a fraction of the entity itself. The *Hexon* is the main structural protein of capsid **9**, and it is organized as a trimer. Four hexon trimer units reside within the capsid's *asymmetric unit* – a triangular shaped wedge extending from the interior center to the surface where it fills one-third of an equilateral triangular face (see dashed line triangular segment in **9**). Asymmetric units will be discussed in detail later on. Suffice it to say that the 12 hexons (3 hexons/*trimer* × 4 trimers/*asymmetric unit*) in this building-block unit will be duplicated by all the I-symmetry operations to generate the entire capsid. A threefold rotation axis through the face center copies the asymmetric unit's 12 hexon proteins 2 more times for a total of 36 hexon proteins/*face* (3 hexons/*trimer* × 4 trimers/*asymmetric unit* × 3 asymmetric units/*face*). Since there are 20 faces, this means a total of 720 hexon proteins reside within the capsid assembly. Obviously, this chiral supramolecular I-symmetry assembly, exhibiting 60 operations of the First Kind, can in no way be referred to as "asymmetric" [5].



9

Rod units (protein helical fibers with *knobs* at the very end) are located at each of the 20 locations of fivefold symmetry. The human adenovirus structure provides a useful example of how Nature sometimes modifies a symmetry motif in order to attain a particular functional advantage. Why do this? Symmetry causes structural constraints that sometimes need to be partially removed to facilitate a particular functional effect (in this case, it is a biological effect). For this *particular virus*, there is a *symmetry mismatch* between the capsid's fivefold axes of symmetry and the threefold symmetry within the knob domain. The reasons for this are yet to be discovered. Usually, the rods show fivefold symmetry.

Due to the mismatch, the adenovirus only shows *I-pseudo*symmetry both in the solid and solution states. The Flock House virus is an RNA virus isolated from insects and exhibits near-perfect *I*-symmetry. One wonders why Nature has chosen such high symmetry for many viral particles? One obvious reason is that icosahedral symmetry enables efficient packing of the viral constituents within the capsid. The genetic material (DNA or RNA), packed within, often also has *I*-symmetry geometry. However, perhaps the high symmetry of the capsid also imparts a statistical advantage so that its knobs can attain auspicious orientations required for effective binding to the cell surface no matter how it lands upon it.

David Goodsell [6] has discussed the function of the *adenovirus* in his Protein Database "Structure of the Month" webpage. The viral capsid's function is to locate a cell and deliver the viral genome inside. Most of the action occurs at the knobs located at each vertex. The purpose of the long knobs is to selectively bind to transmembrane receptors called *integrins* located on the cell's surface. Once the virus attacks this surface, it is drawn into *vesicles* (a small bubble within the cell's hydrophobic phospholipid bilayer membrane) by a process called *endocytosis*. Endocytosis is an energy-consuming process by which the cell *absorbs* molecules (i.e., large polar molecules) by engulfing them so that they can pass through the hydrophobic outer membrane. The next step involves breaking through the vesicle membrane and releasing the viral DNA into the cell. In the final stage, the *adenovirus* enters the cell's nucleus and builds thousands of replicas of new viruses. The ultimate result will cause the unfortunate recipient to suffer from respiratory illnesses, such as the common cold, conjunctivitis (eye infections), croup, bronchitis, and also pneumonia.

Note, for a lethal virus (e.g., ebola) to cause an epidemic, it has to kill the infected person slowly enough so that many people can come in contact with the dying victim (as with ebola). If the virus kills the sufferer too quickly, then a critical number of new victims will not arise to cause a chain reaction.

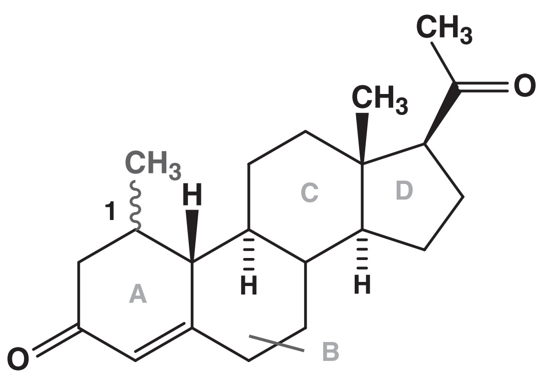
In the time of Louis Pasteur, rotationally symmetrical objects were called *dissymmetric*, while only achiral objects were referred to as symmetric. However, the prefix "*dis*" implies "a lack" of something, and thus, dissymmetric appears to be a synonym of asymmetric, which it is not. Since symmetry operations are both of the First and Second Kinds, there is no logical basis to restrict the general concept of "symmetry" to encompass only the second of the two types. On the other hand, the term chirality makes no distinction between asymmetric objects and those (like viral capsids) that exhibit high symmetry of the First Kind. Bottom line: all nonasymmetric objects are symmetrical by definition. Obviously, viral capsid **9** cannot be described as being *asymmetric.*

1.4 The Birth of Chirality as a Chemical Concept

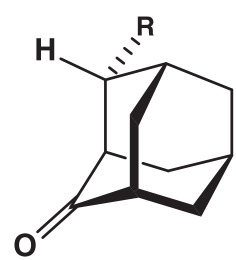
The use of the term "chirality" in a scientific sense owes its conception to Lord Kelvin (Sir William Thomson), who stated, in his lecture to the Oxford University Junior Scientific Club (1893), "I call any geometrical figure, or group of points, chiral, and say that it has chirality if its image in a plane, ideally realized, cannot be brought to coincide with itself." Its present use in a chemical context to mean the structural property giving rise to two nonsuperimposable mirror-image molecular structures, or right- and left-handedness, can be traced to one of the eminent scholars of stereochemistry, Kurt Mislow. For nonphysicists, such as the author, Mislow says that the phrase "ideally realized" refers to "geometrical chirality" coming from a "mathematical idealization" which is common in physics and science in general (K. Mislow, personal communication, January 13, 2014).

Kurt Mislow was the first to use the terms *chiral* and *chirality* in chemistry. To see how this came about, we should first set the stage and discuss some important aspects of stereochemistry in the 1950s. Carl Djerassi, Luis Miramontes, and George Rosenkranz were at the Mexico City laboratories of the Syntex Corporation and were performing research in the developing field of steroid chemistry. In 1951, they invented the first oral contraceptive drug, progestin norethindrone, which, unlike progesterone, remained effective when taken orally. The drug triggers a hormonal response that stops further egg production in the female body during the period of pregnancy. This discovery radically changed the manner in which men and women interact as they heed the call of primordial hormonal urges originally designed to ensure the continuation of our species. In 1978, at the Knesset (Parliament) in Jerusalem, Carl Djerassi was awarded the first Wolf Prize in Chemistry for his work in bioorganic chemistry and for the invention of the first oral contraceptive drug.

At the time of his work, a very useful empirical link was discovered between steroidal absolute configuration and the (+ or −) sign of the "Cotton Effect" (a *chiroptical* property based on ***O***ptical ***R***otatory ***D***ispersion (ORD) of *plane polarized light* in the $n \rightarrow \pi$ transition of steroidal saturated ketones). This was the empirically based *Octant Rule*. While the "rule" seemed to work nicely for steroidal ketones (**10**), later on, it was found that different (+ or −) signs of the Cotton Effect, versus those predicted by the Octant Rule, were experimentally observed for optically active, known absolute configuration 8-alkyladamantan-2-ones (**11**). Since this phenomenon was then dubbed the *Anti-Octant Rule*, it is logically apparent that, alas, *there is no rule.* The ORD chirotopical technique and octant rule will be discussed later when details of its related subtopics *circular birefringence* and *circular dichroism* are presented as a separate section.



10



11

The principal investigators of a project involving steroidal α,β-unsaturated ketones (**10**) and the sign of their Cotton Effects were a group of distinguished chemists Carl Djerassi, Kurt Mislow (a stereochemist), and Albert Moscowitz (a chemical physicist). In a letter to Djerassi dated 7 October 1961, Mislow was discussing the Cotton Effect's sign for 1-methyl epimers of 1-methyl-19-norprogesterones (see wavy gray line in **10**). Mislow wrote "In the α-isomer the 1-methyl group is *equatorial,* but in the β-isomer the 1-methyl is *axial,* and interaction with C_{11}-methylene forces A (the 1-methylcyclohex-4-ene-3-one ring, A) into a boat and changes the sense of chirality." The ketones in the letter, and other steroids, were then discussed at length in their paper where the following is written: " … Dreiding models point definitely to a given chirality … " [9] A copy of the original letter was published in an article on language and molecular chirality written by chemical historian Joseph Gal [10].

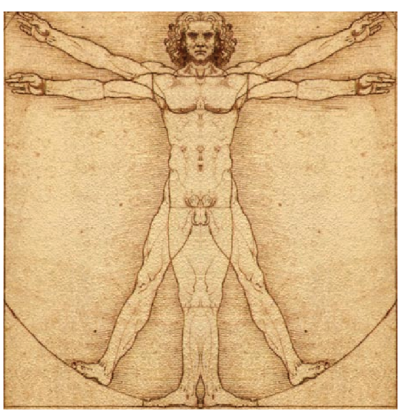
1.5 Apparent Symmetry (High-Fidelity *Pseudo*symmetry) and the Quantification of Distortion from the Ideal

It is common to use "symmetry" in a logically "*fuzzy*" manner, that is, a concept whose borders or limitations are not absolutely well defined, such as the usual about 95% probability of finding electron densities in atomic orbitals. The pleasurable symmetry that one observes in our macro-world obviously does not exist via mathematical transforms, and yet viewers often perceive nonmathematically symmetrical objects as being "symmetrical." This is the realm of *pseudo*symmetry. High-fidelity *pseudo*symmetry (rather than genuine symmetry) is the norm in our macro-world. Genuine symmetry in our world manifests itself as reflections in a plane mirror of high quality or in a pristine lake's windless surface (see **12**, photo courtesy of Shaul Barkai, Switzerland).

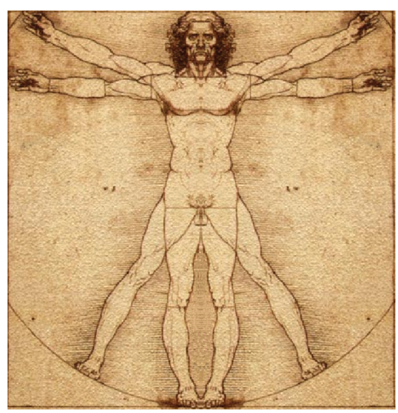
Aside from the aforementioned special cases of reflection symmetry, our senses do not, or cannot, note the small deviations from an ideal geometry when confronted with "almost symmetrical/nonmathematically symmetrical" objects. A second look at da Vinci's "Vitruvian Man" (**1**) shows that it does not have true mirror reflection symmetry. Illustration **13** shows a pseudo left-half (inverted right-hand) drawing next to a genuine right-half drawing, while **14** depicts a real left-half next to a pseudo right-half (inverted left-half) drawing. Since these differences between the right and left halves are clearly noticeable, one wonders if they were intentionally made by the artist for esthetic purposes.

Many objects "look symmetrical" since their *pseudo*symmetry *fidelities* are very high. At first glance, starfish **15** appears to have multiple symmetry elements (five-fold rotational symmetry and five mirror planes, each one passed through a leg), that is, C_{5v} point group symmetry. But, careful inspection of **16** and **17** shows that the left leg of starfish **15** is very slightly higher than its right leg. Note the very

12



13



14

small differences between **16** (inverted right next to a real right starfish) and **17** (genuine left next to inverted left) make **15**–**17** all appear to be *almost* identical.

15 **16** **17**

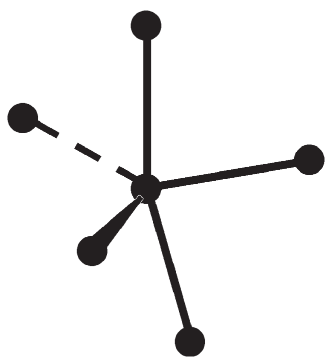
Our genes have programmed us to overlook minor distortions from ideal symmetry. Avnir and his students have provided us with very useful mathematical algorithms to quantify the *continuum of distortion from a genuine symmetry* element within an object [11]. Genuine symmetrical geometry is only the origin-point terminus of an ever-decreasing sliding scale of *pseudo*symmetrical fidelity, that is, the *less* an object is distorted from the ideal symmetry, the more it shows a *higher-fidelity pseudo*symmetry. Therefore, *pseudo*symmetry is a sliding-scale variable, while true symmetry is an ideal state (a mathematical singleton, a set with only one element). Molecules either possess a particular symmetry, described by mathematical transforms, or do not. On the other hand, what is undisputable is that objects or molecules can readily exhibit a "continuum of distortion" from a particular ideal geometry. In other words, they can appear to exhibit various degrees of being "almost symmetrical."

Avnir and his coworkers at the Hebrew University of Jerusalem have shown that distortions from ideal point group symmetry or from an ideal shape should be considered to be continuous properties. The Avnir algorithms are commonly referred to as "*Continuous Symmetry Measures*" (CSMs) [11–17]. The broad utility of the CSM tools has been extensively demonstrated for quantification of symmetry distortion within objects or molecules and has led to correlations of these values with a wide range of physiochemical phenomena [18–23]. *Continuous Chirality* [24] and *Continuous Shape Measures* (CShMs) have also been reported [25, 26]. The application of Symmetry Operation Measures to inorganic chemistry [27] and the use of CShM [28–31] measurements for analysis of complex polyhedral structures have also been reported by Alvarez and coworkers.

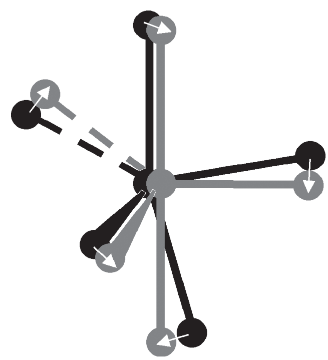
It is useful to take the time to understand (in a very simplified and general manner) some of the methodology of the important Avnir [18–23] symmetry distortion algorithms. The "S(X)" CSM numerical index calculated for an object or a molecule distorted from any *generic* ideal X-symmetry (**18**, where X is any point group) is a *normalized root-mean-square distance function* from the closest theoretical geometry object (**19**) that exhibits the ideal X-symmetry [11, 12, 14, 16]. The theoretical object is simply the *closest geometrical construct* exhibiting ideal point group X-symmetry that is calculated from the distorted input structure. Despite the fact that the construct was derived from a molecule's structure, its geometry is not real in terms of its *bonding parameters* (i.e., bond lengths, bond angles, and torsion angles).

For simplicity, the distance geometry algorithm is based on Eq. (1.1), where P_k = Cartesian coordinates of the actual shape (e.g., distorted trigonal bipyramid colored black in **18**); N_k = coordinates of the nearest ideal C_3-symmetry "geometrical construct" (colored gray in **19**); n = number of points (1 to n); and D = a normalization factor so that two objects differing solely in size will afford the same $S(C_3)$ value [11, 16].

$$S(C_3) = \frac{1}{nD^2}\sum_{k=1}^{n} |P_k - N_k|^2 \times 100 \tag{1.1}$$



18



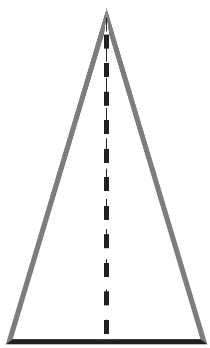
19

Any object with ideal generic X-symmetry will afford an S(X)-value equal to *integer number zero*, that is, it is a *special case* as it results from *symmetry constraints* upon the object's geometry. S(X)-values that are not integer zero are *general cases* (e.g., $S(X) = 0.0000001$ does NOT result from symmetry considerations). As the object is distorted more and more from $S(X) = 0$ *ideal* X-symmetry, the $S(X)$ value will increase. The $S(X)$ scale has been designed to range from 0 to 100, and users may refer to this scale as a continuous measure of the ability to perceive the existence of a particular generic *X-pseudo*symmetry element within an object. Ranges of $S(X)$-parameter numerical values have been interpreted in terms of either a *negligible loss, small loss, moderate loss,* or the *perceivable absence* of a generic symmetry element-X [11, 23]. Thus, one may paraphrase this interpretation by proposing a rule of thumb, which states that S-values of 0.01 or less indicate *negligible distortion* from an ideal symmetry (i.e., *high-fidelity pseudo*symmetry that is not perceivable by the naked eye) [11], whereas values up to 0.1 correspond to *small deviations* from the ideal, which may or may not be visibly perceivable (i.e., moderate-fidelity *pseudo*symmetry). Larger S-values up to 1.0 signify *structurally significant divergences* from the ideal (i.e., low-fidelity *pseudo*symmetry) [11, 23]. Values larger than 1.0 testify to important distortions that are large enough so that the absence of a particular *pseudo*symmetry element within an object is visually recognized. For example, an Avnir CSM quantification of mirror-plane distortion in the stone axe-heads (**2**–**4**) as a function of the archeological site's age was reported to be 1.84 $S(\sigma)$ for the *oldest* specimen (**2**), 0.77 $S(\sigma)$ for the *intermediate*-aged one (**3**), and 0.29 $S(\sigma)$ for the *youngest* axe-head (**4**) [1]. Inspection of axe-heads shows **4** to exhibit the highest fidelity mirror *pseudo*symmetry and the lowest $S(\sigma)$ value.

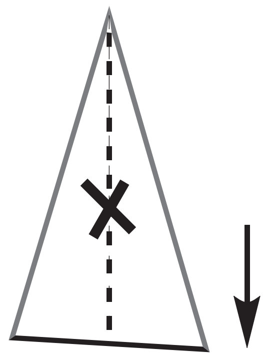
The closer the Avnir $S(X)$-value approaches integer zero (the object's distortion from an ideal generic symmetry), the harder it is for our eyes to differentiate between high-quality *pseudo*symmetric objects and those exhibiting genuine symmetry. In the world around us, it is only our knowledge that *perceived symmetry* is almost always nonmathematical that enables us to be cognizant that an object's shape or form is actually only a *high-quality emulation of symmetry* rather than being the real thing. When does our perception of *pseudo*symmetry end and our realization of *gross distortion* or a complete loss of *pseudo*symmetry begin? It is not simple, since the *pseudo*symmetry continuum's frontier with perceivable asymmetry is mathematically *fuzzy,* rather than being an easily recognized step-function.

Should experts in symmetry proclaim, to one and all, that only *pseudo*symmetry (and not mathematical symmetry) primarily exists in our macro-world? Definitely not! There is nothing wrong with using fuzziness in communication unless the distinction between *pseudo*symmetry and genuine symmetry is absolutely required to explain a particular phenomenon. Communication and language should be free and not hampered by awkward phraseology and unnecessary accuracy. As a corollary, does this mean that one should use the adjective "*pseudo*symmetrical" to describe objects in our world? Probably not a good idea, since many will not understand the term. There is nothing wrong in using the concept of symmetry in its *fuzzy* sense. However, as scientists studying molecular structure, we should be aware of the conceptual differences between *pseudo*symmetry and genuine symmetry.

The concept of chirality seems to be a continuum without an end, since the generation of *achiral* geometries is a very special case due to specific *symmetry constraints.* Avnir has elegantly shown that when one of the two reflection symmetry-related vertices of the isosceles triangle **20** (*isos* and *skelos*, respectively, mean "equal" and "leg" in Greek) is ever so slightly depressed, then the formerly achiral figure is transformed into scalene triangle **21** (a two-dimensional chiral object). It exhibits a "*small amount of chirality*" as the ideal σ-plane has ceased to exist. The amount of this chirality can increase as the vertex is moved further downward. It is thus clear that it is almost impossible to observe ideal achirality in our macro-world. The general case is that an object's geometry will have some finite degree of chirality. In other words, chirality is the "general rule" in our universe, while achirality is a "special case" since it requires structural and mathematical constraints.



20



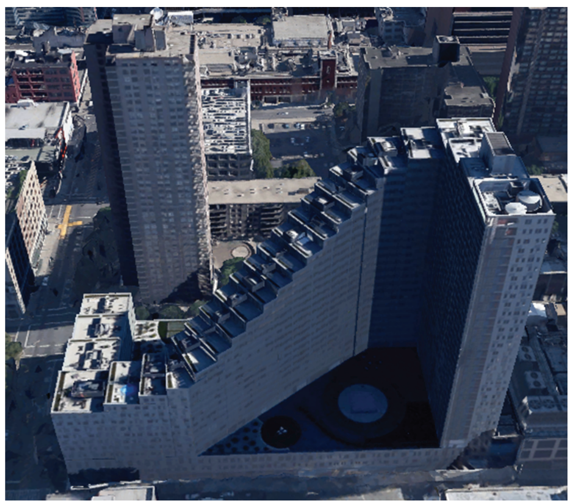
21

1.6
Chirality in Form and Architecture: Symmetry versus Broken Symmetry

Lest one thinks that esthetics in design, beauty of structure, and form are only expressed by dimensions of the golden ratio, Avnir and Huylebrouck have recently reported on the nexus between chirality and awe-inspiring cutting-edge architectural design [32]. To paraphrase the Nobel laureate Roald Hoffman (during a past visit to our university), he noted that breaking symmetry often imparts a warmer feeling of visual pleasure than that realized from "colder" symmetrical objects. While esthetic taste is certainly subjective, to the author (at least), broken symmetry can be as esthetically pleasing to the eye as genuine symmetry. The following two examples show different aspects of this subject. The first case deals with the graceful and prize-winning Mode Gakuen Spiral Towers building (**22**) in Nagoya, Japan (architects: Nikken Sekkei Ltd). Gakuen in Japanese means "academy." They were built to house three vocational schools: fashion, information technology, and medicine/welfare. The truncated gently spiraled edifice is composed of three unequal width, right-handed helical "tower" wings mutually connected to a common central core (i.e., similar to a spiraled triple helix). The tallest and widest wing gradually increases to a height of 36 stories, the "grooves" on either of its sides are equally larger than the third groove separating the two thinner wings. Photo **22** shows the widest helical tower facing the viewer and spiraling upward toward the right (the wider grooves are clearly seen on either side). The second highest helical tower is partially seen on the left-hand side, while the third and lowest helical tower is hidden.

The second example is Mercedes House (**23**) at 555 West 53rd street, Manhattan, New York. It is an apartment building built in the shape of an inclined letter “Z” gradually zigzagging upward from the 6th to the 32nd floor. It was ingeniously designed by Mexican architect Enrique Norten to provide the maximum number (60) of Hudson River view roof-top luxury apartments resulting from the 30 indentations of its gradually sloping roof. The building sits atop a large Mercedes-Benz dealership (hence the name) and is one of the latest structures built as part of urban renewal of the “Hell’s Kitchen” section of Manhattan.

22

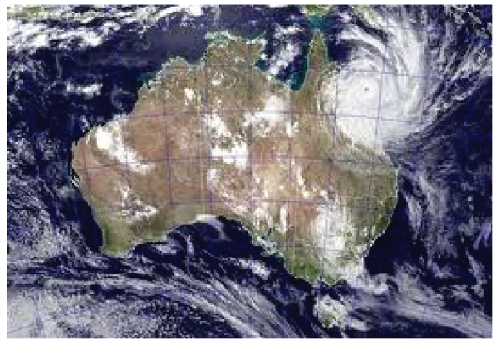


23

1.7 Chirality in Nature: Tropical Storms, Gastropods (Shells), and Fish

One observes numerous examples of chirality in our macro-world around us: arms and legs, flowers, right- or left-flounder flatfish, wind patterns in low-pressure regions, tornados, whirlpools, spiral sea shells, galaxies, and so on. For example, stationary orbit weather satellites view Northern hemisphere hurricanes as *anticlockwise* vortexes of clouds (see **24**, a hurricane off the Mexican Pacific coast), while Southern hemisphere cyclones/typhoons (**25**, a typhoon off the Queensland coast of Australia) are seen from space as a *clockwise* vortex of clouds. It should be noted that the terms *clockwise/anticlockwise* are relative to the orientation in which one views a *transparent* clock, that is, the tropical storms' *tropicity* (directionality) would be inverted when viewed from the ground to the sky.

24



25

The spiral sense of 90% of gastropods (shells, class: *Gastropoda*) show *dextral* (right-handed) coiling. It is very rare to walk along the seashore and find a left-handed specimen. However, there are large predatory sea snails called *Whelk*, which can be found not only in the common right-handed form, but also in the more unusual left-handed variety. The *Busycon carica* (**26**) species, representative of the overwhelming widespread *dextral* coiled sea shells, is found off North Atlantic coasts especially between New Jersey and Georgia. *Busycon contrarium* is a species found in the Gulf of Mexico with *sinistral* spirals (**27**: 20 cm length and 11 cm maximum width). It belongs to the *Busycon* genus within the *Buccinidae* family.

26

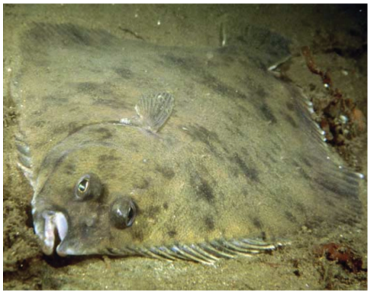
27

Amphidromus perversus butoti subspecies is an Indonesian air-breathing tree mollusk that exhibits either dextral or sinister coiling. These terrestrial gastropods (of 4–5 cm length and 2 cm maximum width) are *amphidromine* snails since both the dextral (**28**) and sinistral (**29**) forms can be found within the same population. This means that the *Amphidromus* genus is quite remarkable since a *single species* usually shows only one direction of coiling. For example, in the *Busycon* genus just discussed, the directionality of coiling is *species-specific.* Taking an overview of the situation, both the aforementioned examples of gastropods are quite remarkable since the vast majority of shells exhibit only dextral spiral sense.

28

29

Flatfish (e.g., flounder, skate) are another fascinating example of chirality in Nature. Flounder are *demersal* fish (bottom feeders) and are classified as *benthic* since they rest upon the sea floor. They belong to the *Pleuronectiformes* order in which one of the two eyes migrates to the other side of the fish so that it can then lie flat upon its side on the seabed. Right-eye flounders (**30**, e.g., the *Pleuronectidae* family) lie upon the sea floor on their *left sides.* Similarly, left-eye founders (**31**, e.g., the *Paralichthys lethostigma* species) rest upon the sea bottom on their *right sides.* Note: right- and left-eye descriptors are derived from the particular eye that has migrated to the other side (not the side of fish that faces upward). At birth, the tiny hatchlings appear achiral and swim upright like normal fish. But, after 6 months, one eye migrates to the other side of the fish (called *metamorphosis*), and the fish flips over on its side to lie in the sand of the seabed. A color change occurs as the stationary side darkens to blend in with the seafloor, while the other side remains white.



30

31

1.8
Extraterrestrial Macroscale Chirality: Spiral Galaxies, Martian Sand Devils, Jovian Great Red Spot, Neptune's Great Dark Spot, and Venusian South-Pole Cloud Vortex

In a similar manner to Terran (adjective of Latin name for "earth") tropical storms, the clockwise/anticlockwise tropicity of *spiral galaxies* is reversed when viewed from one side and then from the other. However, these spiral galaxies cannot be achiral, since the stars within do not symmetrically reside around the galactic mean plane. While not all galaxies are spiral, these galaxies are a common sight in the astronomer's telescope. Like the revolving cloud patterns of hurricanes and typhoons (photo **24**), the *tropicity* of a spiral galaxy will be reversed if viewers were able to observe it from the other side. NASA Photo **32** shows an edge-on view of galaxy NGC 5746 with a halo of hot blue gas around it. But can spiral galaxies, such as this, have a plane of reflection making them *achiral*? The answer is negative since the component stars are positioned about the equatorial belt according to gravitational forces and not by symmetry. Our telescopic images are simply not high enough in resolution to observe that the star distribution is actually asymmetric about the horizontal axis of rotation.

NASA photo **33** shows two colliding clockwise spiral galaxies NGC 5426 and NGC 5427 (collectively known as Arp 271). While they appear to be dangerously close to each other, the vastness of the galactic scale is such that researchers tell us that they will not collide. Instead, they will pass through each other, although it is expected that new stars will form out of the "bunching" of gas due to *gravitational tides.* Scientists predict that our own galaxy (the Milky Way – called the "Pharaoh's River" by the ancient Egyptians) will undergo a similar encounter with the neighboring Andromeda galaxy in a few billion years.

Counterclockwise columns of swirling Martian dust move across the surface in a similar manner as the same phenomenon on Earth and have been often photographed from rover exploration vehicles or by orbiting surveillance satellites. The Mars *Spirit Rover* photographed the anticlockwise dust devil in 2005

32

33

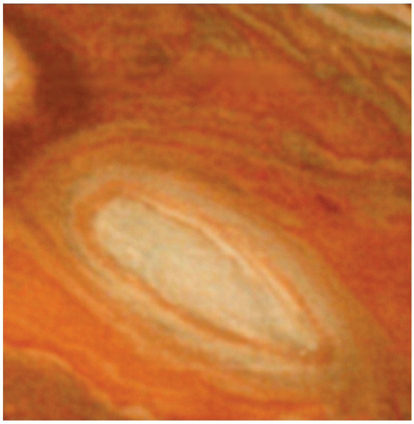
(**34**). On 14 March 2012, the NASA *Mars Reconnaissance Orbiter,* as part of a high-resolution imaging experiment, photographed an anticlockwise dust devil (**35**) as it flew over the Amazonis Planitia region of Northern Mars. This particular dust devil is quite large (30 m in diameter and 800 m in height).

34

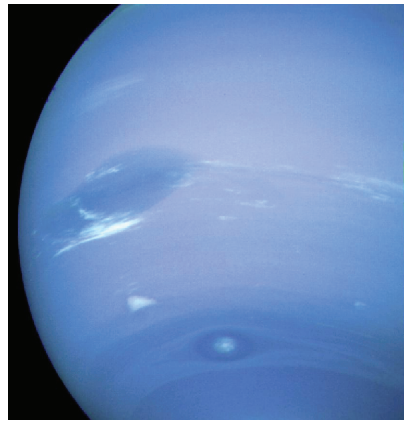
35

Another extraterrestrial analogue of tropical storms is the Jovian (adjective of the gas giant planet Jupiter named after the Roman god) anticlockwise "***G***reat ***R***ed ***S***pot", GRS, (**36**, NASA). Jupiter's GRS is the vortex of an atmospheric storm raging in the Jovian atmosphere of the South Equatorial Belt for at least 400 years (when early telescopes first observed it). Three Earths can fit into its diameter.

As opposed to the extremely long-lived Jovian GRS, the anticlockwise ***G***reat ***D***ark ***S***pots (GDS-89) in the Southern Hemisphere of Neptune are storms that form and dissipate once every few years or so. About half the time, Neptune has one of these spots. They are smaller than the GRS, since their volume is only about the same size as Earth. Its winds have been measured at about 2400 km h^{-1}

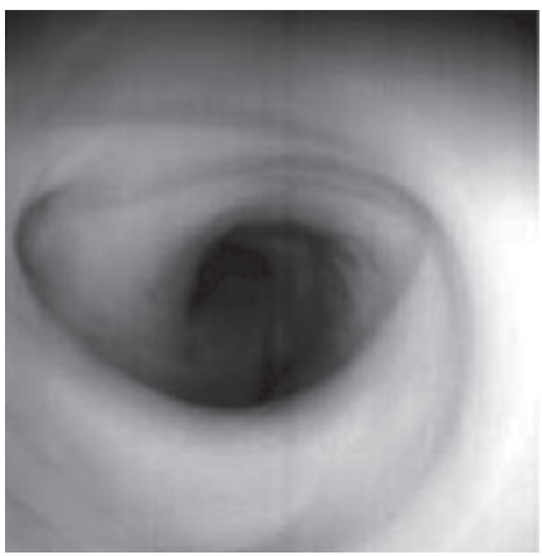


36



37

and are the fastest in the solar system. These dark spots have different shapes and are thought to be vortices in the methane clouds of Neptune (similar to the hole in the ozone layer of Earth). The *Voyager 2* spacecraft photographed the Southern Hemisphere GDS (with white cirrus-like clouds that change over a small period of time) and below it a smaller spot called "Scooter" with a bright center; see **37,** Jet Propulsion Laboratory, California Institute of Technology. Both spots rotate at different speeds.



38

The Venusian South Polar Giant Vortex (**38**) is another example of an anticlockwise cloud pattern. It was thermally imaged with infrared light by the Infrared Thermal Imaging Spectrometer of the European Space Agency's *Venus Express* spacecraft. The vortex is 65 km in height. Finally, while there is a 30 September 2013 report of a giant planet (1.5 times larger than Jupiter) outside our solar system (an *exoplanet*) called Kepler-7b, the image of its high clouds to the West and clear skies in the East unfortunately does not show chiral cloud patterns.

1.9 Analyses of Amino Acid Chirality in Extraterrestrial Samples with Gas–Liquid Chromatography Chiral Columns

In 1966, Emanuel Gil-Av and coworkers at the Weizmann Institute of Science reported the first instance of a reproducible α-amino acid enantiomer separation using gas–liquid chromatography with an optically active stationary phase [33]. The column used a dipeptidic phase *N*-TFA-L-valyl-L-valine cyclohexyl ester, but required that samples be derivatized to their *N*-TFA(trifluoroacetamido)-*O*-*tert*.-butyl esters prior to analysis. The drawback was that such esters of amino acids are not readily prepared. The dipeptidic column was later used in 1970 to analyze for α-amino acids in moon samples retrieved from the surface of the Sea of Tranquility by the crew members of Apollo 11 [34]. However, no measurable amounts of amino acids were found under conditions that would have detected less than 0.1 ppm of any amino acid. In 1971, Benjamin Feibush [35] reported a very highly efficient diamide phase, *N*-lauroyl-L-valine *tert*-butylamide, which could be used with more readily prepared *N*-TFA-α-amino acid methyl esters. However, the column suffered from relatively high column bleeding, which limited its working temperature to 130–140 °C [35]. This disadvantage was later overcome by the preparation of higher homologue chiral phases: *N*-docosanoyl-L-valine *tert*-butylamide and *N*-lauroyl-L-valine 2-methyl-2-heptadecylamide, which showed no loss of weight by thermogravimetric analysis (TGA) until 190° and 180°, respectively [36]. As this chapter was being written, an enantioselective column by Volker Schurig (a former postdoctoral research associate of Gil-Av) was onboard the ESA Rosetta mission spacecraft. The orbiter successfully landed the Philae rover on 12 November 2014 after an incredible 10 year 317 million mile journey to the 2.5 mile wide comet 67P/Churyumov–Gerasimenko. His chiral column has been selected for future space missions to Mars: Mars Science Laboratory (MSL) and ExoMars 2016.