On the Biological Advantage of Chirality

by

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Abstract

The presence of chirality in the main molecules of life may well be not just a structural artifact, but of pure biological advantage. The possibility of the existence of a phenomenon of a special mode of interaction, labeled as "chiral interaction" (CI), for which structural chirality is a necessary condition, is the main reason for such an advantage. In order to demonstrate such a possibility, macroscopic chiral devices are introduced and presented as analogies for such an interaction. For this purpose it is important to make a clear distinction between geometric and physical chiralities, where the latter are capable to perform chiral interactions with various media. Apart from chirality, a few other structural elements are required. In particular, the presence of an interface that separates between the chiral device and the

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medium with which it is interacting. The physical chirality is build into this very interface where chiral interaction is taking place. On a molecular level, soluble proteins in particular, the active medium is the presence of random ionic motion in the aqueous solvent. As a result of chiral interaction a certain perturbation, or current, is generated and flowing along the coils of α-helix structure in one preferred direction out of two possible ones. A model for such a chiral interaction is presented and a few significant consequences are pointed out. In particular, it is important to emphasize the time-irreversible feature of chiral interaction, which leads to its non-ergodic nature that is to be considered a necessary condition for evolutionary processes in biomolecules. As yet there exists no direct experimental evidence for the validity of chiral interaction on a molecular level, but there are quite a few indirect supporting evidences. In particular, there exists an experimental result by Careri et al. who found a clear linkage between the free protons motion in the hydration layer of proteins and their enzymatic activity. A few direct experiments for verifying the validity of chiral interaction on molecular level are proposed hereby for hydrophobic amino acids at the water-air interface, where chiral interaction may take place. Among these there is also a new approach of applying a SQUID to detect a weak magnetic field that is associated with the chiral interaction effect. If proven right, chiral interaction may open new approaches and possibilities for better understanding of the rather complex autocatalytic function of soluble proteins.
1. Introduction

The phenomenon of structural chirality has been recognized since the early 19th century when Arago [1] and Biot [2] demonstrated the effect of optical activity in quartz crystals. It was Louis Pasteur [3] who first observed chirality on a molecular level and he referred to this effect as dissymmetry. It was Kelvin [4] who first addressed this phenomenon as "chirality", since a chiral structure of an object does not necessarily imply a total lack of symmetry of such an object. According to Kelvin a given object or set is chiral if and only if it cannot be made to superimpose, or overlap, exactly its mirror image by any continuous transformation. (i.e. by any rotation and/or translation). The concept of chirality is of geometric nature in principle, but currently this very term is also being used in other domains such as high energy physics, which may cause semantic problems in its usage. In addition to this it is also important to address chirality within its own dimensionality. The space we live in is 3-dimensional (3d) so that chirality is usually regarded as a 3d property. In fact, such property exists also in 2-dimensional (2d) space, that is, within a plane. This can be demonstrated by two asymmetric triangles, one being the mirror image of another. Although these two triangles are geometrically identical, they cannot be made to superimpose one another by any rotation and/or translation within the plane they are contained in. In order to make them coincide with one another, it is necessary to take one of these triangles out of this plane, rotate it around in 3d space and then bring it back into the same plane. Then it becomes possible to make them overlap precisely with one another. Such a triangle is an example of 2d chiral figure...
or object. Any 2d chiral object is considered to be achiral in 3d space. As a matter of fact, such a consideration is not limited to 2d space. In principle, also a 3d chiral object "can be made" to coincide with its mirror image by "taking it out into a 4-dimensional (4d) space, rotating it around there and then bringing it back to 3d space". Such an operation is mathematically or imaginatively possible, but not practically. The reason for this is that our physical space is of 3-dimensions only.

In recent years there has been a considerable progress in the development and understanding of the mathematical aspects of chirality [5-6]. Among other things, there exist several attempts [7-9] of quantifying this very concept. These attempts are still having certain problems of uniqueness, so that a question such as: "What is the most chiral triangle?" obtains at least three different answers [10,11]. As a matter of fact, most approaches of treating chirality from mathematical aspects employ the geometric viewpoint of chirality, which hardly contains any physical meaning. In reality, the concept of chirality has a significant physical basis and this is meant to be one of the main features of the present article. For this reason it becomes necessary to distinguish between so-called geometric and physical chiralities [11,12]. Geometric chirality is referred to the shape of pure geometric bodies or sets, such as triangles or tetrahedrons or any arbitrary shapes in 2- or 3-dimensional spaces. Physical chirality is referred to the shape of any distribution in space of a physical property such as mass, charge, energy potential, or even quantum properties such as electronic wave-function distribution throughout a
molecule, or any other quantum mechanical property. If such a distribution does not contain any reflection symmetry plane, then, by analogy, it is to be referred to as a chiral physical distribution. There exist two major distinctions between physical and geometric objects. Geometric bodies are distributed homogeneously in space, whereas physical properties may be of varying densities, such as mass distribution, which is not necessarily homogeneous in space. This difference may well complicate the mathematical aspects of physical chiralities. A second distinction of major physical significance is the possibility of interaction that may exist between a distribution of physical property and some medium that happens to be present at the same vicinity. In the case of molecular structures it may be necessary to distinguish between various different physical distributions such as nuclear masses, (i.e. atomic locations within the molecule), or electronic distributions that are presented by the wave-function distributions. The possibility of a chiral distribution of a physical property is the origin of the biological advantage of chirality. In order to clarify this statement it may be helpful to look first at macroscopic objects where chirality plays a necessary and useful role in their function.

2. Macroscopic Chiral Devices

An intriguing question that is being repeated in many scientific publications concerns the ‘left’ (L) and ‘right’ (D) identity of chiral molecules, such as: "Why are amino-acids L and not D?". There exist several speculations that try to answer this interesting question. A more constructive question to be asked presently is: "why are the molecules of life chiral?", and this is
regardless of their being L or D. Is there any biological advantage in their chiral nature when compared to achiral molecules? And the answer given here to this question is: ”Yes”. The source of such an advantage comes from a specific type of interaction for which chirality is a necessary condition. Such an interaction is to be labeled as: ”chiral interaction” (CI) and it has already been treated in various publications [11,13-17].

Chiral interaction (CI) is not typical of molecular structure only, and there exist various macrodevices which function according to the same principle. The simplest and most spectacular one is the windmill. When wind blows at the rotors of a mill, it ‘knows’ immediately in which direction to rotate, clockwise or anti-clockwise. If the windmill, in particular its vanes, were symmetric, it would not be able to ‘make up its mind’ to select a definite rotational direction. The shape of vanes of a windmill, where contact is made with the wind, is designed to break the L-D symmetry, i.e., it is chiral. This structure is of useful dynamical advantage which enables the mill to transform energy from the wind to, say, a rotating millstone. Another simple mechanical device is a rotating water sprinkler, where the medium interacting with the sprinkler is the flow of water. The next example is somewhat more sophisticated because it depends on a different mode of chirality. This device is a variant of the Crookes’ radiometer (see figure 1). The active medium in this case is light radiation. The element of chirality here is in the difference of the colors of the rotating blades, being black and silver, respectively, and this is a special example of physical chirality. When light is shining on silver faces it is reflected away, whereas it is absorbed by the black ones.
Figure 1: A variant of Crookes’ radiometer offers an example of chiral interaction. The asymmetry in the optical absorption coefficient between the black and the silver vanes generates a temperature difference between these vanes when light is shining at the device. The air close to the black vanes expands as a result, which pushes the vane around the axis AB in the preferred direction of the black vane. The physical chirality is built into this device by the distribution of the black and silver colors, i.e. by the difference in the optical absorption coefficients in the vanes.
This causes the black faces to become warmer than the silver ones, which in turn expands the air in their close vicinity, so that the black wing is pushed backwards. The selection of the sense of rotation of this type of Crooke’s radiometer is made by the variance of the colors of the vanes, that is, by their respective optical absorption coefficient. The physical chirality in this device is presented by the distribution of the optical absorption coefficient, not by the shape of the vanes which is achiral.

All the examples presented here are of mechanical nature, i.e., the effect of chiral interaction (CI) results in a mechanical rotation in one preferred direction out of two possible ones around a given axis of the device. This is so because the source of the interaction, i.e. the medium, usually is external to the chiral device. In the case of an electric device which generates a static current flowing in one preferred direction out of two possible ones, the source of the interaction may be embedded within the device. This is the case, for instance, of an electric cell which consists of two different electrodes coming in contact with an electrolyte. It is obvious that in order to reverse the direction of the current it is necessary to interchange the two electrodes with one another, but this does not necessarily require any chiral operation. This is so because the source of the current flow is internal, so that the structure of the device can be completely symmetric, as is the case of a cylindric battery. In the case of an electric thermocouple, the operation can still be regarded as CI since the source of the interaction, i.e. the temperature difference, is external to the device.
Before proceeding to molecular systems, it becomes useful to summarize the main features of CI in macrodevices. In all these examples there exists a specific active medium with which each chiral device is interacting, and this happens always at an interface separating the device from the medium, where physical chirality is built into this interface. CI is a process by which energy is transferred from the medium to the chiral device, where one out of two possible modes of rotational motion is selected and generated. Such a feature of selectivity can be considered as a mode of organization. Two modes of different natures, namely, mechanical or electric motions, can be created within the device. The electric mode, i.e. the current, is of practically massless charge motion flowing along a conductor.

3. Chiral Interaction in Molecular Systems

3a. General Features and Physical Background.

The origin of CI in molecular systems is in the motion of free ions in aqueous solutions. This is to be considered as the necessary medium for CI, whereas the interacting ‘chiral device’, i.e. the chiral molecule, must include certain specific features which enable it to function as a ‘chiral device’. These conditions fit well soluble proteins that contain electric dipole moments that interact electrostatically with moving ions in the solvent. Owing to the large dielectric constant of water ($\epsilon = 81$), the range of CI is limited to approximately (10 – 20)Å. The permanent electric dipole moment [18] of the protein molecule consists of the amino ($\text{NH}^+$) and the carbonyl ($\text{CO}^-$) groups along the peptide bonding chains. This dipole moment is presented schematically by PN (see figure 2). Let us now examine the motion of a
Figure 2: The deflection of a positive ion $P_1$ from a linear track, presented by $P_1A$, into a curved track $P_1B$ due to an electric dipole moment PN. The curved motion of $P_1$ induces a non-zero time-averaged electric field $E_\parallel$ along PN. A negative ion (not shown here) is deflected in the opposite direction, but, being of opposite sign to $P_1$, it will induce $E_\parallel$ in the same direction of $P_1$. 
positive ion $P_1$ approaching PN. Let $E_\parallel(t)$ be the time dependent component of an electric field $\vec{E}$ induced by $P_1$ along PN. The time average of $E_\parallel(t)$ is given by:

$$E_\parallel = \frac{1}{T} \int_0^T E_\parallel(t) dt$$  \hspace{1cm} (1)

In the absence of any interaction $P_1$ moves along a straight line $P_1A$ so that for $T \to \infty$, we have $E_\parallel \to 0$. Since PN is in fact an electric dipole moment, the actual track of the ion $P_1$ is now presented by the orbit of $P_1B$ rather than $P_1A$. This is so because the ion is being deflected away from P and attracted by N. For this shape of an orbit, not being on a straight line, $E_\parallel \neq 0$ for $T \to \infty$, and it is pointing in the direction of $P$. Let us now look for the case of a negative moving ion, not shown in the figure. It is also deflected by the electric dipole but in the opposite direction in comparison to $P_1$. Being also of opposite charge, it will induce an electric field $E_\parallel$ in the same direction as the positive ion. In other words, $E_\parallel$ remains in the same direction for positive and negative ions alike. Another fact that is of significance is the independence of the motional direction of $P_1$. For instance, if $P_1$ moves backward on the same track in the opposite direction, it will still produce $E_\parallel$ in the same direction as before.

The electric field $E_\parallel$, caused by the deflection of random ionic motion in the solvent, due to the existence of a permanent dipole moment, becomes a source of repetitive perturbation of the molecular system. The system responds to such an external perturbation, according to the Le Chatelier law, in an attempt of maintaining an equilibrium state within the system,
i.e., it evokes an internal perturbation along closed loops of chemical bonds in an attempt to neutralize the external perturbation. Such an internal perturbation, or ‘current’, selects one out of two possible directions of motion as in the case in macrodevices, in particular, the electric cell. This effect is to be regarded as ‘Chiral Interaction’ (CI), on a molecular level scale [19]. Since the molecules involved in such an interaction, i.e. soluble proteins, are considerably heavier than the deflected ions in the solvent, any mechanical effects of CI can be neglected in comparison to its electric effect.

3b. The Necessity of an Interface

In the description of chiral macrodevices the necessary existence of an interface, where CI is taking place, has been emphasized. Surprisingly enough, such an interface becomes also necessary for molecular chiral systems. This is shown schematically in Figure 3. If moving ions approach a closed ring attached to an electric dipole PN, from all possible directions, the induced perturbation, i.e. CI, averages out to zero. This is so because $I_A$ cancels out $I_B$ on the average, so that the net induced perturbation becomes zero on the average. For this reason, in order to maintain a non-zero CI, it becomes necessary to limit the access of ions approaching the ring to about half of the space surrounding it, i.e., limit the access of $P_2$, in comparison to $P_1$. This can be accomplished by an interface (denoted by S), that prevents the access of free ions, i.e. $P_2$ from the space above $S$, so that CI can go on in one preferred direction, i.e. $I_A$, for an indefinite length of time.

In nature there exist several interfaces. Most obvious one is the solvent-air interface, which is macroscopic. At this interface there exists a strong
Figure 3: Schematic representation of why it is necessary to have an interface in order to maintain a non-zero chiral interaction. Let $P_1$ be a moving ion approaching an electric dipole moment PN fixed, for simplicity, on the diameter of a ring of closed chemical bonds. $P_1$ is deflected from its linear track according to its charge sign, and induces an electric field $E_A$ and a resultant chiral current $I_A$ in the ring. A similar ion $P_2$ approaches from above and induces $I_B$ in the opposite direction along the ring, so that on the average there exists no CI. In order to maintain a non-zero CI it is necessary to stop or limit the approach of ions from one of these two semicircles. This can be accomplished by a separating interface represented by S.
change, or gradient $\tilde{\nabla}c$, in the ionic strength $c$ of the solvent. This provides for a variation $|\tilde{\nabla} c \cdot d|$ in the ionic strength across a loop of chemical bonds such as $C_\alpha \cdot COO^- \cdot NH_3^+$, of a hydrophobic amino acid molecule \[13\] attached to the water surface, where $d \approx \text{few } \text{Å}$. The origin of the electric dipole moment along this loop is due to the existence of a zwitterion in amino acids in the presence of water. A sufficiently strong gradient in the ionic strength at the close vicinity of the water-air interface can maintain CI for molecules such as amino acids that are aligned normal to this interface. Another natural interface of molecular size exists at the surface of globular proteins. This interface intervenes between the solvent, where free ionic motion persists, and the the interior part of the molecule where no ionic motion exists. Owing to this interface, CI can occur for globular proteins in the bulk of the solvent. Somewhat surprising and encouraging is the observation that soluble proteins must become globular in order to function as enzymes \[20\]. This fact may indicate a possible linkage between CI and enzymatic activity of proteins, a possibility to be further discussed in what follows. Looking at the secondary $\alpha$-helix structure of proteins, each segment of such a loop, containing the NH$^+ \ldots$CO$^-$ bond, can be considered as a ‘chiral element’ with which free ions in the solvent are interacting (see figure 4). This mode of interaction, being CI on a molecular level, is schematically shown and described in figure 5.

3c. Formal Treatment of Chiral Interaction

Next, a formal treatment of the intrinsic molecular perturbation, or ‘chiral current’ $I_c$, is presented for a single chiral element.
This is carried out by applying the Langevin equation [13,21]:

\[
\frac{dI_c}{dt} = -\gamma I_c + F(t)
\] (2)

where \(\gamma = \tau_R^{-1}\) is the attenuation or dissipation constant of \(I_c\) and \(\tau_R\) is the relaxation time of the chiral perturbation or current \(I_c\). \(F(t)\) represents a series of stochastic events of random approaches of moving ions in the solvent to the chiral element presented in figure 4 or 5. \(F(t)\) is presented mathematically by:

\[
F(t) = \tau^{-1} \sum \alpha_i \delta(\theta - \theta_i) \exp[-\gamma(t - t_i)]
\] (3)

where \(\alpha_i\) is the i-th current, or perturbation increment occurring at time \(t_i\). \(\theta = t/\tau, \theta_i = t_i/\tau\) and \(\tau\) is the stochastic time constant, being the average time gap between two successive stochastic events of solvent ions approaching the chiral element. The solution of equation 2 yields:

\[
I_c = \sum \alpha_i \Theta(\theta - \theta_i) \exp[-\gamma(t - t_i)]
\] (4)

where \(\Theta(\chi)\) is a step-function. The time-average \(\langle I_c \rangle\) for long periods \(T_i \gg \tau\) and \((T_1 - T_2) \gg \tau\) is given by

\[
\langle I_c \rangle = \frac{1}{T_2 - T_1} \int_{T_1}^{T_2} I_c(t) dt
\] (5)

For a steady-state situation it is assumed that \(\langle dI_c/dt \rangle \approx 0\), so that [11,17]:

\[
\langle I_c \rangle = \frac{\alpha}{\gamma \tau} = \frac{\alpha \tau_R}{\tau}
\] (6)

where \(\alpha = \langle \alpha_i \rangle\) is the average chiral current perturbation generated per each stochastic event, and \(\alpha\) is proportional to the magnitude of the electric...
Figure 4: A segment of an α-helix structure which can be considered as a segment in a globular protein. The H-bond connecting two successive coils are presented by broken lines and they are all oriented in the same direction, i.e. from O(-) to N(+). The H-bonds together with the covalent bonds connecting N and O around the loop are considered as a 'chiral element'. (Original drawing by Irwin Geis).
Figure 5: A schematic representation of a chiral element in a globular protein. The electric dipole moment sticking into the solvent, that is, on the left hand side of the interface S, represents the H-bonds interconnecting the coils in the α-helix. The possible motion of ions (only positive ones are shown) in the solvent is shown, and so is the induced electric field $E$ that generates the chiral current $I$ in the chiral element. The interface $S$ represents the surface of the globular protein so that mobile ions exist only on the left side of $S$. 
dipole-moment in the peptide bond. $\tau$ is inversely proportional to $c$, which represents the ionic strength of the solvent, so that $\langle I_c \rangle$ is proportional to the product $\alpha \tau_R c$, that is: $\langle I_c \rangle \propto \alpha \tau_R c$. From equation 6 it can be deduced that if $\tau_R \ll \tau$ then $\langle I_c \rangle \to 0$. In other words, if the relaxation time $\tau_R$ of the chiral current perturbation is much shorter than the average stochastic time $\tau$, then CI vanishes. The physical meaning of this is that the ionic strength $c$ must be sufficiently large to maintain the chiral interaction CI.

3d. Estimates and Conclusions

In the absence of any experimental data concerning CI in molecular systems, it is still not easy to make reliable estimates for the size of the effect of CI. It is obvious that, owing to the large mass ratio of the protein relative to a moving ionic mass, only CI of the second kind can be invoked, i.e. of electronic or massless motion. The estimate of the energy involved in this process of CI is of the order of $(10^{-2} - 10^{-3})kT$ per stochastic event (17), which signifies it is a ‘subthermal effect’. The relatively small energy contents does not mean that such an effect can be ignored. On the contrary, the smallness of this effect, as well as the degree of its sophistication, may provide for information transfer throughout a complex molecule such as protein, and may be significant for its specific enzymatic function. This aspect will be further discussed in what follows. The necessary ingredients of CI on a molecular level may be now listed as:

1. The existence of a chiral element (or molecule) that includes an electric dipole moment as part of the chiral structure;
2. The presence of a polar solvent that is sufficiently rich in mobile ions;

3. The existence of closed loops of chemical bonds in the chiral element; and

4. The presence of an interface that separates between two media that differ largely in their respective ionic strength and/or in their ionic mobilities in the close vicinity of a chiral element.

It should be emphasized that CI in biomolecules is still a hypothesis awaiting for experimental verification. If confirmed, it may become of considerable significance as a mode of self-organization that is pertinent to the intrinsic control of enzymatic activity of proteins. It should also be stressed that all the ingredients required for CI occur in nature for globular proteins as well as for amino acids oriented at the water-air interface. It is also of interest to point out the relevance, or necessity, of the presence of nitrogen atoms in the structure of amino acids and proteins. The physical asymmetry between the amino NH$^+$ and the carbonyl CO$^-$ groups provides for the existence of an electric dipole moment which is a necessary condition for CI. Hydrocarbons alone, lacking the presence of N, cannot participate in the generation of CI. It is important to notice that physical effects of chirality have well been known for long [3], and they involve mainly optical phenomena, such as optical activity [22] and related effects. These effects are to be considered as ‘chiral scattering’ rather than ‘chiral interactions’ because they concern only the effect of chiral systems on electromagnetic radiation. In the case of CI, the main effect to be considered is the generation of an intrinsic perturbation
within the chiral system, which is ignored in the case of chiral scattering. In addition to this, CI is not limited to optical effects only, as is the case in the phenomena of chiral scattering. Needless to add that the distinction between chiral scattering and CI does not mean that there is no relation between these two concepts. The opposite is correct.

4. General Features and the Advantages of Chiral Interaction

4a Thermodynamic and Space-Time Symmetry Considerations

Thermodynamical aspects of CI have already been considered [11,16-17]. The basic effect of CI, where a molecule is being perturbed and thus is developing a persistent current in a single selected direction, is thermodynamically uncommon. Such a perturbation can be considered as an excited state of indefinitely long lifetime. This means that however small is the energy of such a perturbation, the system will never completely reach thermal equilibrium. That is, as long as the chiral system is surviving. Such a phenomenon has certain peculiar aspects and in order to better appreciate them let us now look back at the example of a windmill. While so doing, macroscopic effects such as friction and other energy dissipative effects are ignored. What we see now is a significant space-time symmetry feature of CI, being of time-irreversible nature, in contrast to many common mechanical examples. For instance, if flow of time is reversed, a satellite moving in space ‘will move’ on the same track in the opposite direction. This is so because of the nature of the forces acting on it in space. In the case of a windmill, or other chiral devices, if time is reversed the windmill ‘will not be able’ to move in the
opposite direction because of the shape of its rotors, which is still pushing it in the same direction. What does move backward is the mirror-image of the same windmill. Thus, in order to obtain a complete-reversal, it is also necessary ‘to reverse’ space. In the case of an electric cell, by reversing the flow of time the current ‘does flow’ in the opposite direction even though the electrochemical potential is still acting in the same direction, which contradicts the sense of the current motion. In order to reverse the flow of the current it is necessary to interchange the electrodes, i.e. to reverse also the sense of the electrochemical potential. To summarize on this symmetry consideration, CI is not a time-reversal process but rather of space-time invariance, and this is so because of the chiral nature of such an interaction. Let T represent a time-reversal operation and P is a space (or parity) reflection operation, then the main conclusion of this argument is that CI does not obey T-invariance but rather PT-invariance.

Moving back to CI on a molecular level, it can readily be deduced that such a symmetry consideration may have deep impact on the thermodynamical aspects of CI. In the absence of T-invariance on a molecular scale it means that CI does not obey the classical detailed balance principles [24]. Detailed balance implies that at equilibrium the number of occurrences of each chemical reaction in the forward direction is the same as that in the reverse direction. In other words, equilibrium does exist not only macroscopically but also for each individual microscopic reaction. A necessary condition for detailed balance is the conservation of time reversibility, which is not being obeyed by CI. Moreover, the persistence of CI in one selected
direction prevents the molecular system from reaching thermal equilibrium. This conclusion is related to the *ergodic assumption* introduced by Boltzmann over a century ago. According to this assumption, any property taken as an average over a large ensemble of particles within a closed box, being at thermal equilibrium with its environment, can also be obtained for a single particle under the same conditions, if averaged over a sufficiently long time. The behaviour of CI presents, therefore, a *non-ergodic* system. The origin for this is the generation of an intrinsic molecular perturbation that is moving in one selective direction out of two possible ones, as a result of a continuous interaction with random ionic motion in the solvent at the close vicinity of the molecule. Such a behaviour is uncommon for ordinary molecular systems and it is the consequence of several structural details listed above, in particular, its chiral structure as well as the presence of a microscopic interface.

**4b. Non-Ergodicity and Evolution**

The subject of thermal equilibrium and ergodicity may become of problematic nature dealing with systems that contain more sophisticated elements. As long as relatively simple objects, such as mass points, or plain molecules are concerned, the ergodic assumption seems to be fulfilled in general. The problem arises when less simple systems are involved, in particular, those which do not obey time reversal invariance. For example, suppose that an aqueous solution reaches thermal equilibrium and then a bacterium is thrown into it. A quasi-microscopic system, such as a living bacterium, is certainly not time-reversible in its function, and as long as it stays alive it also does not reach thermal equilibrium, i.e. it is a *non-ergodic* system.
A similar conclusion can be reached for any microscopic living system that happens to be immersed in a macroscopic surrounding being at thermal equilibrium. The question that can be asked now is: “what is the smallest system that can remain at a non-ergodic state within a macroscopic system being at thermal equilibrium”. Such a question cannot be readily answered. It seems reasonable to assume that any sufficiently complex microscopic system, or molecule, that can perform in a ‘machine-like’ mode of operation, being time-irreversible in nature, will remain non-ergodic under such a condition for as long time as it does not break down or decompose into simpler and smaller elements. Soluble proteins, as well as other sufficiently complex biomolecules, seem to comply with this requirement. It seems to be the case, and this is so to the best knowledge of the author, that only ‘machine-like’ biomolecules can be considered as microscopic non-ergodic systems. It may well be the case that also microelectronics systems may achieve such a state with further development. In view of this it becomes of much interest to point out that non-ergodicity may well be a phenomenon related to the microscopic level of function of life in nature.

Another question of much interest concerns the possible significance of non-ergodicity in nature. Microscopic systems or molecules that reach easily thermal equilibrium do not seem to be liable for any process of intrinsic organization. Another significant aspect of the function and operation of complex molecular systems has to do with its usefulness. Any time reversal activity can be regarded as completely ineffective from this viewpoint of usefulness. For this very reason the breaking of time-reversal invariance of
processes becomes necessary for a practical operation of any useful value. All machine operations are time-irreversible, and these include microscopic ‘machines’ as well, such as molecular proteins. Non-ergodicity becomes a feature closely related to time-irreversibility for sophisticated microscopic systems. Upon combining together these various features, it seems reasonable to deduce that the process of biomolecular evolution in nature is closely related to them. For this reason it becomes plausible to assume that non-ergodicity is to be regarded a necessary condition for molecular evolution [11]. The CI hypothesis has similar features to those described hereby, and it is based on well recognized structural details as well as on external source of random ionic motion, which provides for a physical well explicable model. For these reasons it is anticipated that CI may become of major value for better understanding of the function of operative biomolecules, soluble proteins in particular. This is so, provided that more experimental support is to be found for its viability.

4c. Order of Magnitude Estimate

Another aspect of CI perturbation concerns the size of its energy content, being of the order of \((10^{-1} - 10^{-2})kT\) per chiral element, which is rather small in comparison to thermal energy, being of the order of \(kT\). The significance of such subthermal perturbation is not relevant to the size of its energy content, but rather to its degree of ordering or sophistication. The energy content of a biomolecule is considerably larger, and this can serve as source of energy for its operational functions. The energy associated with CI can become operational upon ‘switching on’ and ‘switching off’ the active groups in the
molecule. In other words, CI may be relevant to the control mechanism of biomolecular function, rather than to its operational function, which requires much more energy. A similar comparison of amounts of energy can be made between a robot and a computer that controls its activity. The energy needed for control is considerably smaller than that required for the function of a robot, although its degree of sophistication is rather impressive. The relatively low energy content of CI has an additional advantage as well. Being of considerably lower energy than typical thermal energy of the order of $kT$, does help to increase its length of relaxation time $\tau_R$ which contributes to the persistence of CI. The reason for this effect is related to the presence of a large population of energy modes of similar energy levels, as is the case of thermal energy, which decreases their ‘life-times’ lengths, owing to the high liability of interactivity among such modes.

4d. Possible Magnetic Effect

This concerns the possibility of CI to induce magnetic fields along the axes of coils of the $\alpha$-helix segments of which the globular protein consists. The direction of this magnetic field follows the axis of each segment separately and its magnitude is crudely estimated to be of the order of 0.01T, or 100 gauss. It may well be too early to elaborate on the possible practical significance of such an intrinsic molecular magnetic field. However, it has already been emphasized by Steiner and Ulrich [24] that magnetic fields can have significant effects on the polarization of electronic and nuclear spins during chemical reactions, which may considerably affect chemical yields and
kinetics. It is important to emphasize that the size of magnetic fields, applied externally to chemical reactions, has negligible effect on these reactions. It is also important to point out that in contrast to regular chemical reactions, where an external magnetic field is applied in arbitrary direction with respect to any molecule participating in such a reaction, the intrinsic field induced by CI happens to be acting at the optimal location and direction where it is needed. This may well become a crucial feature of CI, which can efficiently contribute to the autocatalytic function of soluble proteins. Another interesting feature of such an intrinsic magnetic field induced by CI, is related to the description of ‘chiral favourable environment’ introduced by Barron [25], who proposes to apply a combination of electric and magnetic fields parallel to one another in order to generate an enantiomeric excess in a chiral synthesis performed in their close presence. Actually, such an intrinsic combination exists in the globular state of soluble proteins in the presence of CI. The electric field is generated by the electric dipole moment that exists along the peptide bond that comes into touch with the solvent surrounding the globular protein, whereas the magnetic field is induced in parallel to it by CI along the axes of the coils of the α-helix.

5. Experimental Verification and Support

5a. Background

The presence of CI perturbation along one selected direction may produce an additional effect. Although CI is largely still a hypothesis awaiting for an experimental verification, there exist several pieces of evidence supporting its validity. Let us first indicate that its very existence is based largely on general
physical principles which are hard to refute, as well as on general symmetry arguments. All macroscopic examples are based on such considerations. In addition, it is important to notice that CI is a special and uncommon molecular phenomenon, which requires a set of structural constraints for its possible validity, in analogy to macroscopic chiral devices. These include the presence of an electric dipole moment, as well as an interface separating between the active medium in the solvent and the inner part of the molecule. All these happen to exist for soluble proteins. Before looking at a possible and practical experiment, we note two specific difficulties that may affect the observation of CI. The first one concerns the size of the effect, which is quite small, and the second is the fact of its being an intrinsic molecular event, which limits its experimental accessibility. The second difficulty concerns proteins rather than amino acids, which are of more open structure. On the other hand, there are good reasons why it is desirable to observe CI. Such an effect can provide for a better understanding of the complex nature and operation of biomolecular function.

In the lack of any direct experimental evidence for the validity of CI it may be helpful to look for existing experimental results that may bear certain close relation to this phenomenon. For this very purpose an indirect experiment has been proposed [17], based on an assumption that CI is a necessary condition for enzymatic activity in soluble proteins. Such an assumption, reasonable as it may sound, presents a certain constraint that at best can provide for a strong positive experimental support of CI, rather than a direct verification of its validity. Such an experiment was actually performed
by Careri et al. [26,27]. This experiment concerns the effect of dehydration on the protonic motion throughout the hydration layers around soluble proteins. The amount of water surrounding each protein molecule is of crucial importance for free protonic motion around this molecule. This is associated with the so-called ‘percolation transition’ involving water clusters around the protein molecule. By dehydrating the water layers beyond the percolation transition, the protonic motion stops, and so does also, simultaneously, the enzymatic activity of the molecule. As soon as there exists enough water within the hydration layer surrounding the molecule, free protonic motion, or mobility, becomes possible and resumes again. This in turn causes also the onset of enzymatic activity in the protein molecule. Protonic motion is identical in fact, with free ionic mobility being a necessary condition for CI in soluble proteins. This fact links closely between chiral interaction and these experimental results. The close causal connection between protonic, or ionic, mobility and enzymatic activity in soluble proteins, fits precisely with the assumption of the existence of CI.

5b. Enantiomeric Excess Experiment

A direct experiment to observe CI has already been proposed [11,17,28]. In order to perform such an experiment, it is necessary to make use of some observable property that is generated by this effect. Such is the case with amino acid molecules attached to the water-air interface. For this purpose a racemic solution of a hydrophobic amino acid, such as tryptophan, may be employed, as is shown schematically in Figure 6. The side chain R attaches itself to the water surface, and CI occurs around the loop NH₃⁺.COO⁻.C,
which contains a zwitterion where an H-bond may exist between \( \text{NH}_3^+ \) and \( \text{COO}^- \). The ring of bonds may also contain a water molecule that relaxes the angular strain of the bonds [28]. CI becomes possible there, close to the water-air interface, owing to the gradient \( \nabla c \neq 0 \) of the ionic strength \( c \) across the ring of bonds at the water surface. CI induces there a magnetic dipole moment \( \vec{\mu} \), which has opposite components for the L and D enantiomers, respectively, with regard to the normal to the water surface. Next, an external magnetic field \( \vec{B} \) is applied normal to the water surface and this interacts with \( \vec{\mu} \) with energy \( E_\mu \):

\[
E_\mu = \pm \vec{\mu} \cdot \vec{B}.
\]

where the \( \pm \) signs depend on the L or D chirality respectively. This energy adds to the hydrophobic energy \( E_h \), i.e. \( E = E_h + E_\mu \) or:

\[
E = E_h \pm \vec{\mu} \cdot \vec{B},
\]

which results in an energy difference of \( 2E_\mu \) between the two enantiomers. This, in turn, creates a small population change \( \Delta n \) between the two enantiomers according to Boltzmann law:

\[
\Delta n = n_L - n_D
\]

which depends on the direction of \( \vec{B} \). In order to estimate the size of this effect, i.e. of \( \Delta n/n \), where \( n = n_L^0 = n_D^0 \) is the racemic population, it is necessary to estimate the magnetic dipole moment \( \mu \), and this is given [17] by: \( \mu \approx (10^{-1} - 10^{-2}) \mu_B \), where \( \mu_B \) is the Bohr magneton. Then

\[
\frac{\Delta n}{n} = \frac{2\mu B}{kT} \approx 10^{-3} \quad \text{(for } \mu \approx 10^{-1} \mu_B)\]

\[
(10)
\]
and $B$ is of the order of a few teslas.

The measurement itself can be performed by removing monolayers from the water surface [29] that contains the amino acid population and then by measuring their optical activity elsewhere, not in the presence of the magnetic field. Other advanced technologies may also be available for this purpose [30].

The physical reasoning behind this experiment resembles the reasoning leading to the natural selection of the L-anantiomer of amino acid in terrestrial biomolecular evolution. The mechanism may well be the same, but instead of an applied magnetic field there exists the vertical component of the terrestrial field. It is suggested that this process could have happened during the prebiotic era over a localized region of the earth, where the vertical component of the terrestrial magnetic field had a well defined component over a sufficiently time length, so that one enantiomer, presumably L, had a slight energy advantage over D. The difference in energy is rather small, being of the order of $(10^{-8} - 10^{-9})kT$. This energy estimate, although quite small, is still considerably larger, by some 7 or 8 orders of magnitude, than the weak nuclear current (WNC) interaction mechanism proposed by Kondepudi and Nelson [31] for the natural selection of the L-anantiomer. The present mechanism does not give an *a priori* advantage to either L or D enantiomer. This advantage is an accidental outcome of the direction of the normal magnetic field of earth that happened to exist at the specific region of the ocean where and when natural selection happened to occur. Recently, Barron [25] has proposed to apply a ‘chiral favorable environment’ of an electric and magnetic fields parallel to one another, which may prefer one enantiomeric chirality
over the other. In order to perform such an experiment, Barron proposes also to rotate charges mechanically, which would make it similar, though considerably more awkward, to the approach of CI.

5c. Detection of Associated Magnetic Effects

Apart from a possible enantiomeric excess effect, owing to an external magnetic field applied on a racemic solution, there exist also other magnetic effects of CI that can be detected experimentally. These have already been indicated above for the case of soluble globular proteins. Such a magnetic structure may be detected, perhaps, by polarized neutron scattering. Another quite fascinating possibility is related to the SQUID apparatus, an abbreviation of Superconducting Quantum Interference Device [32], which can detect extremely small magnetic fields with resolution of the order of one part in $10^{11}$ of the earth’s magnetic field, or of femtotesla ($10^{-15}$ tesla). This is so in addition to its possibility of detection very minute changes, or differences, in magnetic fields. For this purpose it is suitable to prepare monomeric solution of a single enantiomer, say L, of a hydrophobic amino acid in a sufficiently large concentration. Such a solution will create a magnetic monolayer at the water-air interface. This is due to the presence of a surface of magnetic moments induced by CI, all having parallel components in the same direction normal to the water-air interface. (See figure 6). Such a magnetic monolayer may generate a sufficiently strong magnetic field, normal to this surface, to be detectable by the SQUID. The size of the magnetic field produced by, say, $10^{12}$ molecules of amino acid per $1 \text{ cm}^2$ of this surface,
Figure 6: Two hydrophobic amino acid enantiomers L and D are shown. The side chain R penetrates the water-air interface LS. $\vec{B}$ is an external magnetic field applied normal to LS and interacts with the induced magnetic moments $\vec{\mu}$. Due to the opposite orientations of $\vec{\mu}$ with respect to $\vec{B}$ to L and D respectively, there exists a small energy difference of $2\vec{\mu}.\vec{B}$ between the two enantiomers, at the water-air surface LS.
is estimated to be of the order of $10^{-12}$ to $10^{-14}$ tesla at a distance of 1 mm above the surface. Such a magnetic field can, hopefully, be detected by a SQUID [32].

6. The Reality of Chiral Interaction

The main motivation of the present treatment of CI comes from fundamental questions such as: ”why are the molecules of life chiral?” or, more specifically, ”does chirality offer any biological advantage to biomolecules?”. CI may provide for a positive answer to such questions. For this very reason it has been helpful to inspect macroscopic chiral devices and draw conclusions for chiral molecules by pure analogy. Two modes of operation were found for CI, namely, massive rotational motion of the chiral device and a circular flow of massless perturbation, such as a current, throughout the device. Of these, only the massless mode of motion is found suitable for molecular CI. Moreover, given certain structural details, all happen to exist in soluble proteins, certain chiral molecules have the capability of interacting with randomly moving ions in a solvent. This interaction produces an intrinsic perturbation that moves in one preferred direction out of two possible ones. Such a capability does not exist for achiral molecules. This mode of perturbation within a chiral molecule gives rise to a certain degree of non-ergodicity, which may also be regarded as a certain amount of negative entropy. It is tempting to compare this to the somewhat naive conclusion of Shrodinger [33] in his book *What is Life?,* where he claims for such a phenomenon that: ‘it feeds on negative entropy’. In the present context CI enables proteins to reduce their
entropy, i.e. to avoid thermal equilibrium by a minute amount, which is to be regarded as a mode of ‘subthermal organization’. It is hereby conjectured [11,17] that such a phenomenon of non-ergodicity is to be considered as a necessary condition for evolutionary process in biomolecules. It is also important to observe that such features require CI to become a microscopically time-irreversible [34] phenomenon. In fact, if proteins are to be regarded as ‘biological machines’, there must exist an element of time irreversibility in their function.

These arguments are rather general and still somewhat speculative, since as yet CI has not been proven to be real on molecular level. Moreover, it may be quite plausible that such arguments are crucial to the function of proteins, though it is still not easy to describe exactly how. We still need a much better insight into their function. However, it is important to indicate that if CI is indeed of significance for protein function, then it can be useful to ascribe biological significance to various structural features of soluble proteins that otherwise would remain plain facts. Among these features the chirality of the protein molecule can be mentioned, in particular the charge distribution on the peptide H-bonds connecting the loops along the α-helix coils, which are of physical chiral nature. In addition, this also offers a certain meaning to the presence of nitrogen atoms in proteins and amino acid constitution, where the asymmetry between N and O atoms is responsible for the dipolar charge on the peptide H-bonds. By comparison, N atoms are totally absent in hydrocarbons. Also structurally meaningful is the existence of closed loops of chemical bonds in proteins, which provide for a means of delivering the
CI perturbation around the molecule. This holds for \( \beta \) sheets as well [19]. An additional meaningful fact is the parallelism, or consistency, of all dipolar moments along the \( \alpha \)-helix, which adds up to a total dipole moment in each separate segment of a globular protein along the narrow zone that happens to be in contact with the solvent. (see figure 4). All these structural details have already been considered in the assumptions leading to the proposal of CI, so that their biological significance is not surprising. More surprising is the fact that soluble proteins must become globular before they can function as enzymes. This fact has not been considered previously. It links up neatly with the necessity of an interface for the operation of CI. Another fact of biological importance is the presence of free mobile ions in a solvent, which leads to the preference of physiological, rather than pure or distilled water, as the solvent material. These mobile ions are necessary for generating CI in biomolecules. Most relevant and significant, so far, is the contribution made by the experiment [26,27] of Careri et al., which reveals the connection between protonic motion in the hydration layer of proteins and the onset of enzymatic activity. This experiment provides for an impressive support for the CI hypothesis.

Apart from these facts there exist two related points that are of biomolecular evolutionary significance. One of these has to do with the possibility that CI was playing an important role in the natural selection of the L-anantiomer of amino acids. The other is the evolutionary significance of the non-ergodic nature of CI. Although in nature there hardly exists any thermal equilibrium, it seems very likely that non-ergodic systems, such as proteins, become
much more susceptible to evolutionary processes in comparison to systems that readily reach thermal equilibrium. It is also interesting to indicate that any living system is non-ergodic as well.

Another aspect of CI concerns the amount of energy involved in such a process. This energy is rather small, subthermal in effect, which may evoke criticism as to its significance. Such criticism is rather common among scientists who attribute significance to energy according to its size. What is significant in complex systems such as proteins, may well be the quality, or the degree of sophistication of energy, rather than its size. For instance, information transferred by electromagnetic wave involves certain modulations of this wave and their respective energy is much less than the energy of the wave itself, though its content is of major importance and usefulness. Another example is the small amount of energy required to switch on and off a much larger source of energy. This is to be regarded as a mode of control energy which may be of main significance in CI. In the case of a robot controlled by a computer, we have a similar example. The quantity of energy required by a robot is considerably larger than that of the computer, but without this small quantity of energy, the robot cannot function coherently. Another, rather cruel example, concerns the size of energy change that occurs over the small interval during which a creature dies. This change in energy is very small, but its significance is enormous. This example may well indicate the significance of the content of such a small amount of energy. It is interesting, even fascinating, to point out that in the case of CI all this ordered energy comes from chaotic random motion of ions, and this
is mainly due to the chiral nature of CI. In addition to all these, it may be relevant to indicate that the density of energy states for subthermal energies in molecular systems is considerably smaller than that within the thermal range, which makes subthermal energies less convertible, or dissipative, than thermal modes of energy, and therefore functionally more efficient.

Another significant feature of CI is its time irreversibility. It is important to emphasize that any time-reversible operation is meaningless when regarded from aspects of usefulness. Any productive machine function becomes automatically time-irreversible if its operation is of any merit. For instance, even information transfer, which usually requires very little energy, is totally a time-irreversible process. The source of time reversibility in physics comes from the nature of the Newtonian mass point which is an ideally symmetric object. If instead of such a symmetric point mass, an elementary physical chiral object [11] is to be employed, then it becomes likely that instead of time-reversal invariance the rule of PT-invariance will dominate. This may well be the main source, or reason, for the biological advantage of chirality.

In conclusion, let it be reminded that in spite of strong but indirect support, such as that of the experiment of Careri et al. [26,27], the CI hypothesis is still in its infancy and requires much more insight, understanding and development, not to mention additional support from direct experiments as discussed here and elsewhere [11,17,28].
7. Conclusions

The phenomenon of chiral interaction has been described and treated in detail in this article. Various uncommon features of such an interaction are described and discussed. It is also claimed that chiral interaction may well be of significant biological advantage, and this is due to its possible linkage and relevance to enzymatic activity of soluble proteins. Another reason for such an advantage is that chiral interaction may be the source of non-ergodicity in biological molecules, which might be relevant to the process of biomolecular evolution in nature.

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