HANDEDNESS, ORIGIN OF LIFE AND EVOLUTION

Biological polymers have a preferred chirality and can replicate themselves. Physical arguments provide insight into which of these unique and apparently related properties evolved first, and by what mechanism.

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At first glance the nucleic acids and proteins that are the basis of life do not stand out in any way among all the possible polymeric structures. If we look at their functions, however, we find one unique feature of these biological polymers: self-replication, the distinctive property of living systems. What is self-replication, and how could this biologically primordial property have originated in an unorganized medium? The solution to the problem of life's origin lies in resolving the paradox of how polymers of rather common structure can exhibit such a distinctive function.

Let us examine this formidable problem from the viewpoint of physicists. By self-replication of polymers, we mean that there exists a process that leads to the formation of an exact copy of the initial polymeric structure. A profound physical problem lies hidden in this trivial assertion. Let an initial, "parental" structure consist of k types of monomers and have a length N. The number of possible kinds of various polymeric structures that can be assembled from such a "molecular construction set" is $p = k^N$. This number becomes catastrophically large when $N \gg 1$. For example, for proteins, which consist of 20 kinds of amino acids and are about 100 units long, $p = 20^{100}$. For DNA, the main carrier of hereditary information, $k = 4$ and $N = 10^6$, so that $p = 4^{10^6}$!

Thus, the problem of self-replication reduces to a "simple" physical problem: How can the one required kind of structure be generated out of the fantastically immense number of possible structures? According to statistics, the probability is proportional to k^{-N}, which is vanishingly small. Nevertheless, in biology, such processes are realized with a probability practically equal to 1. This higher probability results because biocatalysts, or enzymes, which play a major role in biochemical reactions, suppress the stochasticity inherent in "ordinary" chemical transformations and so ensure the uniqueness of biomolecular processes.

It turns out that biological macromolecules possess one specific property that physically distinguishes them from other polymeric structures. In the middle of last century Louis Pasteur discovered that mirror symmetry is broken in living things. Proteins (a category that includes enzymes) are constructed only from "left-handed" (denoted by L, for "levorotatory") amino acids, whereas nucleic acids (DNA and RNA) contain only "right-handed" (D, for "dextrorotatory") sugars. As one example, figure 1 depicts enantiomers of the amino acid alanine—that is, two isomers that are mirror images of each other. Polymeric structures containing either only L isomers or only D isomers are called homochiral.

The property of homochirality is just as remarkable as the existence of self-replicating systems: The probability of forming homochiral polymeric chains of length N is 2^{-N}, which becomes vanishingly small when $N \geqslant 100$. Surprisingly, most biologists have regarded homochirality as just one of numerous particular features of the amino acids and nucleotides that make up the biopolymers. For that reason the possible connection between homochirality and self-replication remained for a long time beyond the scope of scenarios for the origin of life.

There are two general classes of scenarios for the origin of life—"warm," or terrestrial,[1,2] and "cold," or extraterrestrial.[3–6] However, both of these scenarios are faced with the seemingly insoluble problems of explaining how the genetic code arose and how such crucial properties of living species as self-replication appeared.

In addition to the structural property of homochirality, the biological polymers possess a unique functional property that underlies self-replication, namely, specific activity. (Specific activity means a highly selective

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process by which enzymes favor one reaction over other possible ones. Enzymes with *stereo*specific activity favor reactions leading to molecules with particular spatial arrangements, such as chirality.) Is the existence of one of these properties a necessary precondition for the development of the other?

If the stereospecific, catalytic activity came before the homochirality, then evolution might have proceeded through the formation of heterochiral precursors of the biopolymers. If, on the contrary, homochirality appeared first, then how could homochiral polymeric structures have formed in the absence of stereospecific catalysts? If we can answer this question we will be on the way to constructing a scenario of prebiological evolution.

Homochirality and specific activity

Let us analyze how these two unique properties of biopolymers interact in the assembly of homochiral polymers having a length $N \gg 1$. Clearly, the sequence of L and D isomers in the polymeric chain depends on the ratio of concentrations of these enantiomers in the medium and on the mechanism of growth of the polymeric chain. We can account for the first of these factors by introducing the chiral polarization of the medium, $\eta = (x_L - x_D)/(x_L + x_D)$, where x_L and x_D are the concentrations of L and D isomers, respectively. But how can we account for the second factor, considering the great variety of possible mechanisms for chain growth? Specific features of the interactions of chiral molecules in the process of forming polymers can be compressed into a single characteristic: the stereoselectivity γ of the incorporation of the isomers into polymeric chains. The physical sense of γ is the "precision" with which each isomer is selected in the construction of a chain.

For example, in a biochemical process, the choice of which enantiomer is used in constructing a polymer is conditioned by enzymes, which behave as stereospecific catalysts. In abiogenic chain growth, that is, chain growth in the absence of enzymes, the selection is conditioned by the dependence of the interaction of chiral fragments on their isomeric form: The interaction of two fragments of L type or two fragments of D type may differ from the interaction of two enantiomers of different types. Therefore, the relative probability of adding this or that chiral fragment depends on the chirality of the isomer occupying the end position. In the general case, if the end segment of the chain is of the L type, then $\gamma = \omega_{LL} - \omega_{LD}$, where ω_{LL} and ω_{LD} are the relative probabilities of adding the L isomer or D isomer, respectively. If the end segment is of the D type, then $\gamma = \omega_{DD} - \omega_{DL}$. (From symmetry considerations, $\omega_{LL} = \omega_{DD}$ and $\omega_{LD} = \omega_{DL}$.)

The relative probability Ω of forming, for example, a homochiral polymer of the L type having a length N is

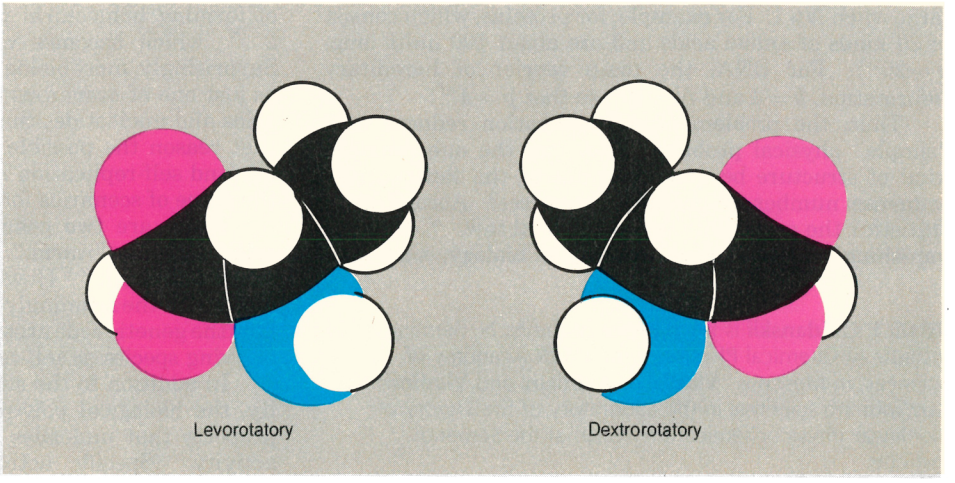
$$\Omega = (\omega \times \omega_{LL})^N = \exp\{N \times \ln(\omega \times \omega_{LL})\}$$

where $\omega = (1 + \eta)/2$ is the initial fraction of L isomers in the medium. Figure 2a shows schematically the formation of a homochiral polymer.

The value of Ω will not be exponentially small if

$$\frac{(1-\eta)(1-\gamma)}{2(1+\eta\gamma)} < N^{-1} \qquad (1)$$

This condition essentially means that to assemble a homochiral chain having a length $N \gg 1$ (at least after several trials), the mean number of errors in the course of assembly must not be much larger than 1. Figure 2b shows a graph in which the values of η and γ that satisfy this condition for $N \approx 100$ lie in the shaded area. One can see that the formation of homochiral polymers is an "all or nothing" situation: It requires either an essentially chirally pure medium and any stereoselectivity or an



Enantiomers of alanine. Enantiomers are molecules with identical compositions that are mirror images of one another. Alanine is an amino acid that, like all the amino acids in proteins (except glycine), exists in nature only in the form with a left-handed chirality (shown at the left). **Figure 1**

extremely high stereoselectivity and a medium with any chiral polarization.

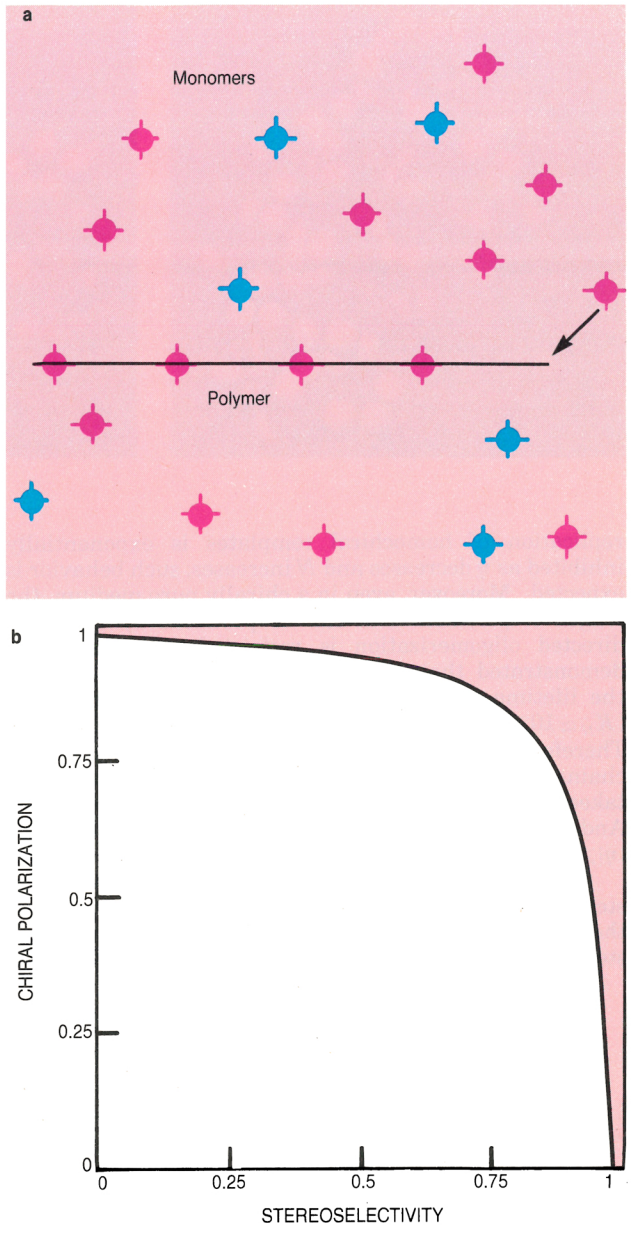
We have reached this conclusion by analysis from quite general and simple considerations, but the requirement for a chirally pure medium is already supported by experiment. Several years ago Leslie Orgel's group[7] investigated the oligomerization of nucleotides under abiogenic conditions, that is, in the absence of enzymes. (Oligomerization is the formation of a relatively short chain of monomers.) They placed chains of poly-D-cytosine, which acted as a homochiral template to direct the oligomerization, into solutions of compounds of guanosine, the nucleotide complementary to cytosine in a DNA double helix. In some cases the solution was chirally pure, containing only D-guanosine compounds, and in others, it was a so-called racemic (or "racemate") mixture—that is, it contained equal amounts of L and D isomers. They found that in the chirally pure solution, the nucleotides from the solution were assembled at the poly-D-cytosine template to form a homochiral oligomeric "complement" of poly-D-cytosine, poly-D-guanosine.

These poly-D-guanosine chains, in the presence of monomeric molecules of cytosine, can serve in turn as templates for further formation of poly-D-cytosine. The overall process is then similar to the self-replication of homochiral structures. Thomas Cech and Sidney Altman have independently demonstrated[8] that polynucleotide chains of RNA can have enzyme-like properties. The behavior of these "ribozymes" suggests the possibility of autocatalysis in systems such as the one in Orgel's experiment.

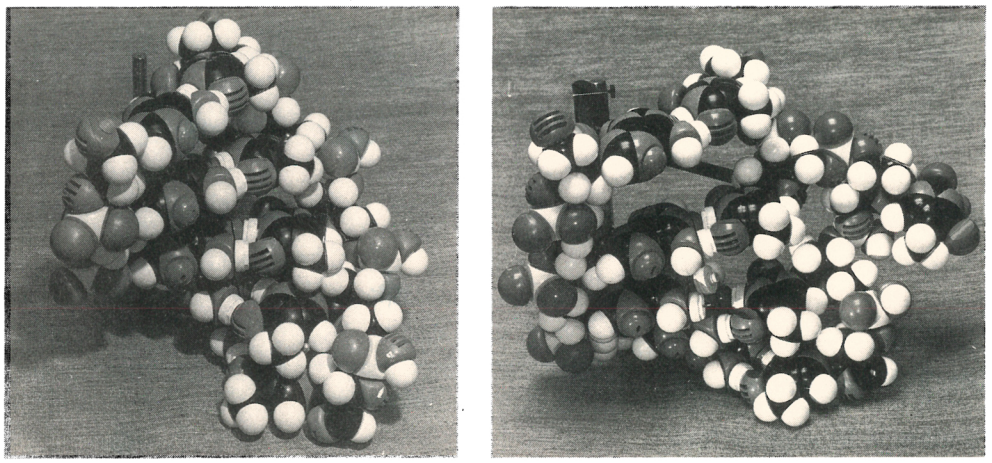
These experiments seem to demonstrate a natural and very elegant mechanism for the stereoselective polymeric takeover of the medium. (By "polymeric takeover," we mean the selective extraction of initial reactionable monomers from the system of reactants due to their transformation into polymeric products.) They also show the strong dependence of this mechanism on the chiral polarization of the medium: In the racemic solution the formation of poly-D-guanosine was nearly totally suppressed.

Based on the data from the experiments by Orgel and his collaborators, our group obtained quantitative estimates of the possible role of template-directed oligomerization in the polymeric takeover of a medium by homochiral structures.[9] We assumed that one started with a certain quantity of homochiral polymeric templates of length $N \gg 1$ in a medium with chiral polarization η. The growth of the number of homochiral polymers is then determined by the competition between two processes: the "replication" of homochiral templates, with the effective rate constant K_N^+, and their destruction (including the casual appearance of "chiral defects" in them), with the effective rate constant K_N^-. The takeover of the medium by homochiral polymeric structures of length N is possible only when $K_N^+ > K_N^-$. This requirement translates into conditions on the chiral polarization η of the medium and of the length N if we know the dependence of K_N^+ and K_N^- on these parameters.

From the experimental data on template-directed oligomerization of nucleotides we succeeded in "fishing out" the form of $K_N^+(\eta, N)$. It turns out that the



Assemblage of a homochiral polymer depends on both the chiral polarization η of the medium and the stereoselectivity γ. Stereoselectivity is the "precision" with which the reaction selects molecules of one specific spatial arrangement. **a:** A polymeric chain is formed from left-handed (red) monomers in a solution that contains right-handed (blue) monomers as well. **b:** A homochiral polymer can form only when the values of η and γ lie in the shaded region of the graph. Note that when the solution is racemic, the stereoselectivity must be nearly 1. **Figure 2**



Double-helix structure of DNA (left) is destroyed when a chiral defect is introduced (right), that is, when one nucleotide is replaced by a nucleotide of the wrong "handedness." Even a single defect introduces a strain large enough to break hydrogen bonds in neighboring, defect-free base pairs. The defect disturbs not only the structure of the DNA but also its ability to carry out functions with a specific activity. **Figure 3**

replication of homochiral templates is exponentially inhibited as η decreases and N increases; such behavior is expected. Moreover, even in a chirally pure medium, the length of polymers that can be produced by template-directed oligomerization is restricted. Our estimates demonstrated that even in the "limiting" case where the lifetime of polymers is equal to that of the Earth ($K_N^- \approx 10^{-17}$ sec^{-1}), N has a maximum value of about 300. Therefore, the characteristic length N of homochiral chains that can originate at the stage of polymeric takeover in a chirally pure medium is of the order 10^2. And polymers this long can form only in a medium with $|\eta| \geqslant 0.95$.

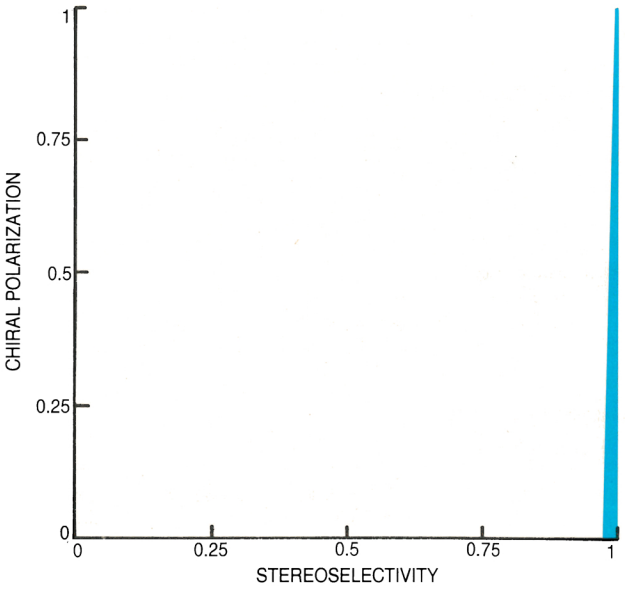
Using $|\eta| = 0.95$ in equation 1, we obtain $\gamma \approx 0.4$ as the stereoselectivity for template-directed oligomerization of the nucleotides. Thus, even in this case the value of stereoselectivity is still very far from the value (within 0.01 of 1.00) that is necessary for the replication of polymers with a length $N \approx 10^2$ in a racemic or weakly chirally polarized medium.

These estimates lend additional support to the important conclusions formulated above: If the mechanism for assembly of polymeric structures does not ensure a selection of enantiomers that is nearly perfectly precise, then homochiral polymers can originate only in a chirally pure medium. But if the mechanism does possess this extreme precision, then homochiral polymers can form in any chiral polarization and even in a racemic medium. This result, although almost obvious, may nevertheless provide a clue to the construction of a scenario of prebiological evolution. A very precise selection (γ within 0.01 of 1.00) is quite common in biosynthesis, but it is not inherent to ordinary chemical processes, where typically $\gamma \leqslant 10^{-1}$. Enzymatic transformations attain a

Physical advantage factors

	Meets symmetry requirements?	g^*
Local advantage factors		
Circularly polarized light	Yes	10^{-4}–10^{-2}
Static magnetic field (SMF)	No	
Static electric field (SEF)	No	
Gravitational field (GF)	No	
SMF + SEF	No	$\chi_i(EB)$
Rotation (Coriolis force) + GF	No	$\chi_l(\omega_v G) \simeq \chi_k(\Omega G)$
SMF + GF	No	$\chi_l(BG)$
Rotation + SMF + SEF	Yes	$\chi_m(\omega[EB]) < 10^{-4}$
Rotation + SMF + GF	Yes	$\chi_n(B[\omega G]) < 10^{-4}$
SMF + linearly polarized light	Yes	$\chi_p(Bk) < 10^{-4}$
Global advantage factors		
Weak neutral currents	Yes	$10^{-20}\,\chi_r Z^5 \dfrac{1}{k_B T} \simeq 10^{-17}$
Longitudinally polarized β particles	Yes	$\chi_q h_e \dfrac{\sigma^L - \sigma^D}{\sigma^L + \sigma^D} \simeq 10^{-9}$–$10^{-11}$

* Relative difference in rate constants for mirror-conjugated reactions. χ, factor determined by molecule structure; E, electric field; B, magnetic field; Z, atomic number; k_B, Boltzmann's constant; h_e, helicity of β particles $\langle sp \rangle$, where the operators s and p represent the spin and momentum of the particle; $\sigma^{L,D}$, cross sections for the interaction of polarized β particles with molecules.



Formation of a polymer with a regular alternation of L and D monomers requires a very low probability of chiral defects ω_{def}. The probability of selecting the right monomer for the end link of the chain is then $\gamma = 1 - 2\omega_{def}$. The shaded region shows the values of stereoselectivity γ and of chiral polarization η necessary for polymeric takeover of a medium through the assembly of a heterochiral chain. **Figure 4**

fantastic precision (with an error probability of approximately 10^{-8}).

Scenarios of prebiotic evolution

The problem of the origin of homochiral polymers is connected to that of the appearance of the stereospecific functions in two ways: Only homochiral structures appear to have these functions, and these functions are needed to form the homochiral polymers in a racemic environment. Two alternative scenarios for prebiotic evolution correspond to different choices of whether the structure or the function came first.

Scenario A: The polymeric takeover was preceded by strong mirror-symmetry breaking and the formation of a chirally pure medium—that is, a medium containing monomers of essentially only one enantiomer type. This medium afterwards became the stage for the formation of homochiral polymers and for the evolutionary changes toward the formation of structures possessing specific activity.

Scenario B: Initially the polymeric takeover proceeded in a racemic medium and led to the formation of heterochiral polymers. Then, in the course of the evolution of these polymers, there appeared heterochiral structures possessing specific (such as stereospecific) enzymatic activity. The evolution of the latter could have led (at least in principle) to the formation of enzymatically active homochiral polymeric structures and, based on these molecules, of systems capable of self-replication.

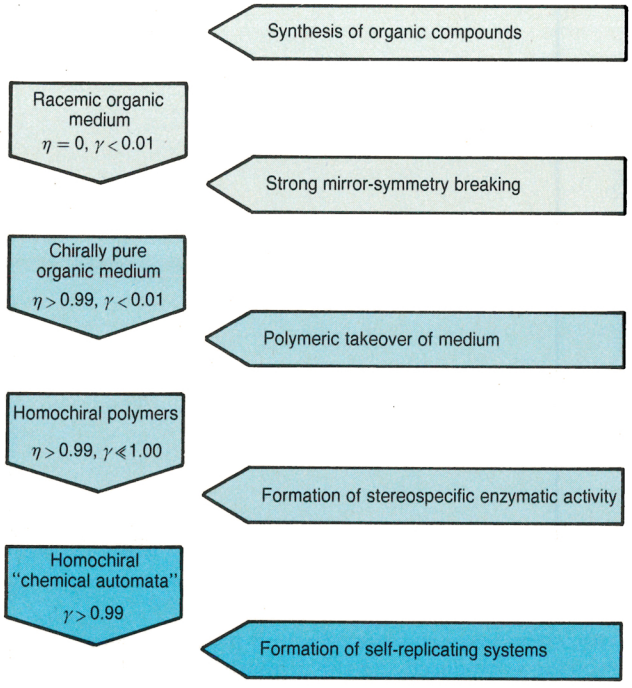
Thus, we must choose which came first: homochiral structures or stereospecific functions. This choice resembles the proverbial "chicken or egg" question. We can resolve this issue if we can demonstrate that homochirality is a necessary feature of stereospecifically active macromolecules.

Of course, a complete understanding of the self-organization of stereospecifically active structures is not yet in hand. Nevertheless it is already quite clear that the main specific feature of biological macromolecules is their complicated hierarchic structure, formed due to short- and long-range ordering of the spatial disposition of the units. This hierarchic structure of the biopolymeric chains makes it possible to organize the structural elements that are necessary for specific activity.

Is the presence of short- and long-range order preserved in heterochiral polymers? A number of studies[10,11] have shown that "chiral defects"—random disturbances of the homochirality of the primary structure—impede the formation of both the double helix in nucleic acids and α helixes and β sheets in proteins. In a chain with a random sequence of L and D isomers short-range ordering is hindered and the formation of rigid functional elements is prevented. Figure 3 illustrates the character of the double helix of DNA caused by a chiral defect.[10] The substitution of an enantiomer prevents the formation of hydrogen bonds between the bases at that position. Actually the strain brought about by even a single chiral defect is so strong that the hydrogen bonds between the neighboring, defect-free base pairs break as well. In this way even a single chiral defect destroys the secondary structure in a considerable part of the chain. Consequently, heterochiral polymers with a random sequence of enantiomers form "loose" structures and are not capable of carrying out functions with enzymatic activity.

However, in polymers where L and D isomers alternate in a regular fashion, generally speaking, the possibility of short- and long-range order is preserved.[12] Such polymers could have played an essential role in prebiological evolution only if they turned out to be capable of taking over the organic medium. However, for a heterochiral chain consisting of alternating L and D isomers, a chiral defect is a disturbance in the order of the isomers, and the stereoselectivity may be defined as the relative probability of the appearance of such a chiral defect. There is a finite probability of forming a heterochiral chain only if η and γ lie in an area represented by the narrow peak in figure 4. Thus, in the absence of a nearly perfect stereoselective mechanism for assembling the polymers, only chains with a random disposition of L and D isomers will form.

We conclude that heterochiral polymers cannot have any specific activity, either because of strong structural limitations (for a random disposition of L and D isomers in a chain) or because of a strong kinetic limitation (for a certain "unique" sequence of chiral fragments). Prebiological evolution can therefore be based only on scenario A. The main stages of prebiological evolution in this scenario are represented in figure 5. Two features there are fundamentally important: First, a strong mirror-symmetry breaking in the organic medium preceded the polymeric takeover and predetermined the formation of homochiral polymers. Second, the chiral purity of the medium had to be maintained not only at the stage of polymeric takeover but also subsequently, during the formation of structures and functions possessing the biochemical level of complexity. Only after the appearance of structures having specific (in particular, stereospecific) activity can



Prebiological evolution may have proceeded by five main stages, as shown. Each event listed on the right would have produced the result depicted on the left. **Figure 5**

the requirement of a chirally pure medium be dropped.

Strong mirror-symmetry breaking

Does a mechanism of strong mirror-symmetry breaking exist that meets these two requirements of prebiological evolution? For a long time chemists have held the firm conviction that any physicochemical transformations in chiral systems could lead only to a racemic mixture of enantiomers, because that is the mixture having maximal entropy. Consequently, even if the system initially contained an excess of one of the isomers, in the course of time it would come to a racemic state corresponding to thermodynamic equilibrium. The kinetics of racemizing processes is characterized by the relaxation time τ_r of the chiral polarization η of the system. The nature of these racemizing processes may be most diverse, and they proceed in any chiral system. They may be characterized by the so-called racemization factor.[13] As a measure of the racemization factor it is convenient to adopt a dimensionless quantity $K_R = \tau_0 \cdot \tau_r^{-1}$, where τ_0 is the characteristic time of chemical reactions in the system.

Sharing the chemists' belief in the universal tendency toward racemization, Pasteur was led to the hypothesis, still popular today, that the deracemization of the prebiotic "primordial soup" occurred through an external asymmetric agent of a physical or chemical nature: We call this an "advantage factor."[13] This idea seemed very attractive because it reduced the question of how homochirality arose to a search for an advantage factor that was capable of ensuring a large quantitative excess of one of the enantiomers over the other. The history of these searches is already more than 50 years old. One can find in the literature very diverse suggestions for advantage factors capable of breaking the mirror symmetry of the medium. The table on page 36 summarizes many of these, and groups them into two classes, local and global. Local advantage factors are those that might have existed in a particular region on the Earth's surface but varied from region to region, or that might have acted during a definite period of time. Global advantage factors are caused by the parity nonconservation in weak interactions. Many of the proposed local advantage factors fail to meet symmetry requirements[14] and in principle cannot lead to the mirror-symmetry breaking in chemical processes. (These advantage factors are indicated in the table.)

The action of both kinds of advantage factors leads to a difference in the rate constants k^L and k^D for mirror-conjugated reactions, and consequently the measure of an advantage factor may be defined as the relative difference

$$g = \left| \frac{k^L - k^D}{k^L + k^D} \right|$$

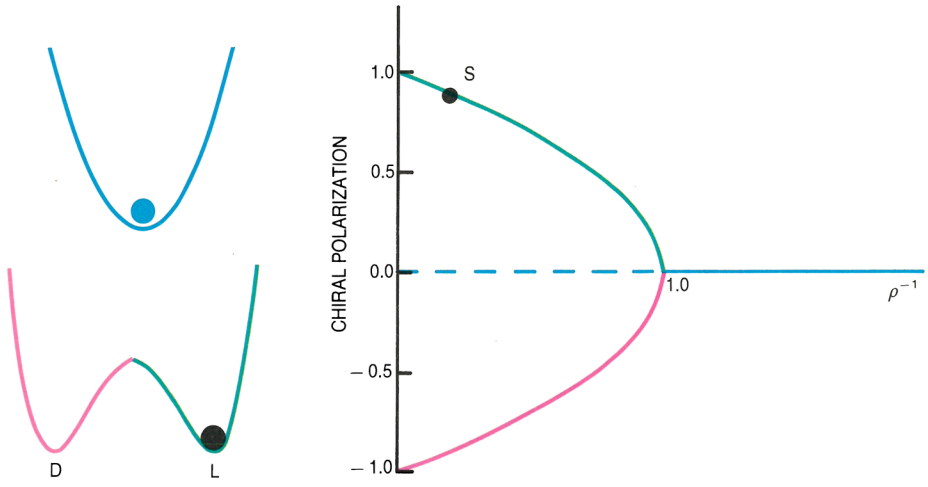
When an advantage factor acts in the racemizing processes, the chiral polarization of the system no longer tends to zero, but to a certain value that depends on the ratio between the advantage factor and the racemization factor. Strong mirror-symmetry breaking is possible only when $g/K_R \gg 1$. (In the case $g/K_R < 1$ the maximum chiral polarization the system can attain is of the order g/K_R.) This criterion is rather general in character,[15] embracing a broad class of racemizing processes with participation of the advantage factor.

The action of the advantage factor might, in principle, lead to an almost chirally pure state of the medium. But the strong mirror-symmetry breaking must maintain a chirally pure state of the medium not only in the course of the entire stage of polymeric takeover but also during the formation of the stereospecific function.

The racemizing processes do not meet this stringent requirement. Indeed, as homochiral polymers are formed, enantiomers of one type only (the type in excess) are predominantly selected from the monomeric medium. Therefore, if the action of the advantage factor tends to increase the chiral polarization of the system in one direction, the stereoselective polymeric takeover tends to increase it in the opposite direction. In this case the criterion for strong mirror-symmetry breaking takes the form

$$\frac{g - \tau_0 K\gamma}{K_R} \gg 1 \qquad (2)$$

where K is the reciprocal characteristic time of the polymer takeover process. The parameter $\tau_0 K\gamma$, competing with the advantage factor, may be termed stereoselective pressure.



Bifurcation diagram (right) shows that for values of the parameter ρ less than 1, the system S has only one stable state ($\eta = 0$). In that case the system is depicted by the black ball in the "potential" diagram at top left. For values of ρ greater than 1 the system has two stable states ($\eta > 0$ and $\eta < 0$), corresponding to chirally polarized solutions of D (red) or L (green) monomers. The system is shown in the L state at lower right. The stereoselectivity γ is assumed to be 0. **Figure 6**

Suppose now that under the action of a certain advantage factor the mirror symmetry of the medium proved to be strongly broken: $g/K_R \gg 1$. Moreover, let the condition of equation 2 be fulfilled in the course of polymeric takeover: The chiral polarization of the medium reaches the value $|\eta| \approx 0.99$, and abiogenic synthesis of homochiral polymers of length $N \approx 100$ ($\gamma \approx 10^{-2}$, $K \approx \tau_0^{-1}$) "entrains" monomers into the polymeric subsystem. At the following stage, in the formation of specific catalytic activity, γ inevitably tends to γ^*, with a value very close to 1, and K becomes greater than τ_0^{-1}; that is, the rate of chemical transformations is smaller than the rate of the polymeric takeover process. In this case, however, for any $g < 1$, condition 2 will be violated even before γ reaches the value γ^*; that is, the formation of specific activity will be blocked.

Thus processes in which symmetry breaking depends exclusively on the action of the advantage factor—no matter how strong—and occurs by gradual accumulation of asymmetry are not capable of strong deracemization of the organic medium in prebiological evolution. One needs a fundamentally different type of process that can effect a strong symmetry breaking without an advantage factor and can withstand the stereoselective pressure throughout the stages of polymeric takeover and formation of the specific activity. Processes of the "bifurcation" type, well known to physicists from the theory of equilibrium and nonequilibrium phase transitions, possess the required properties.

Deracemizing processes of this type are based on the cooperative (nonlinear) interactions of enantiomers and lead to self-organization of chirality in the system: Mirror-symmetry breaking occurs spontaneously as soon as critical conditions are reached. Those critical conditions depend in a complicated manner on all the parameters that characterize the physicochemical transformations of the enantiomers. This dependence is described by the so-called governing parameter of the system, and spontaneous deracemization takes place as soon as this parameter reaches its critical value, known as the bifurcation point. The first mathematical model of spontaneous mirror-symmetry breaking in biological evolution was proposed by F. Frank[15] in 1953. Later this approach was generalized and investigated in detail by Leonid Morozov.[16] (A broad class of kinetic diagrams and their corresponding dynamic equations are described, classified and analyzed in detail in reference 17.)

Bifurcation diagrams help illustrate the main features of spontaneous mirror-symmetry breaking and the role of stereoselective pressure. They demonstrate the dependence of the stationary values of a system's chiral polarization on its governing parameter. In the absence of any transformations advantageous for some of the enantiomers, the bifurcation diagram has the well-known form of a "fork" (see figure 6). The bifurcation equation corresponding to this diagram is

$$(1 - 1/\rho)\eta - \eta^3 = 0$$

where ρ is the governing parameter ($0 < \rho < \infty$). (Here and below we express this parameter in units of its critical value ρ_c.) At $\rho < 1$ only one stationary state, racemic, is stable in the system. When the critical value $\rho = 1$ is exceeded, this state loses stability and the system may pass over to one of the two chirally polarized states. Strong mirror-symmetry breaking is attained at $\rho \gg 1$.

Under stereoselective pressure the bifurcation equation has the structure

$$(1 - 1/\rho)\eta - \gamma(1 - \eta^2) - \eta^3 = 0$$

The bifurcation diagram corresponding to this case, with $\gamma = 0.1$, is sketched in figure 7. We are interested in knowing whether the system will remain in the neighborhood of the chirally pure state at the values $\rho = \rho^* \gg 1$ if γ tends to some value γ^* corresponding to stereospecific activity. An analysis shows that the growth of γ leads to a shift of the bifurcation point toward greater values of ρ, but it exerts no essential influence on the stability of the strongly polarized state. This state loses stability only when the bifurcation point reaches the value ρ^*, which happens at the same time that γ reaches the value γ^*. The physical meaning of this result is that the chirally pure state of the system loses stability just when the stereospecific precursors of biopolymers appear, that is, when the necessity for such a state of the medium disappears. From that moment on, the stereospecific activity behaves as a biological advantage factor, ensuring that the homochirality persists as the biochemical structures and functions evolve. Consequently, only the bifurcation-type processes meet the basic requirements of the scenario of prebiological evolution.

The problem of the sign of handedness

Is it by chance that the proteins and nucleic acids are made up of L amino acids and D sugars and not the opposite enantiomers?

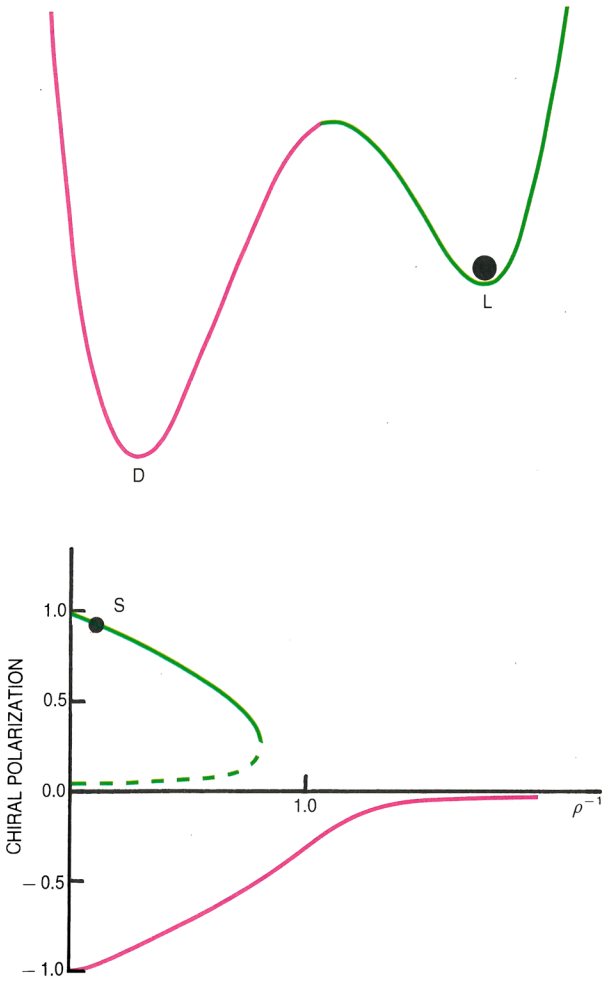
This question, which has a history nearly a century long, is not of fundamental importance to the origin of life because self-reproducing structures may with equal suc-

cess be realized based on either of the enantiomers, at least to the extent that the electromagnetic interactions underlying chemical reactions are mirror symmetrical. But after the discovery of parity nonconservation in the weak interactions of elementary particles it was natural to wonder whether the broken mirror symmetry of the microworld might have been translated to the macromolecular level. The mixing of a weak interaction with the electromagnetic one (due to weak neutral currents) does indeed provide a minor advantage precisely to the L isomers of amino acids and to the D isomers of sugars.[18] However, calculations show that the advantage factor brought about by parity nonconservation is extremely small ($g \leqslant 10^{-17}$; see the table on page 36).

Can such a small advantage factor predetermine the choice of the "sign" of the handedness at the stage of mirror-symmetry breaking? There seems to be no serious prohibition. Indeed, the advantage factor makes the chemical system asymmetric and singles out one of the stable states (branch L in the bifurcation diagram in figure 8). But natural fluctuations and inhomogeneity of regions in which deracemization occurs strongly compete with this advantage factor. As a result, the L state, though isolated "mathematically," can get no advantages physically. Furthermore, the question is not only about the choice of the sign of handedness, but also about the attainment of the state with strongly broken symmetry ($\rho \gg 1$).

Under what conditions could an advantage factor determine the sign of handedness? Let the system be far beyond the bifurcation point; that is, let $\rho \gg 1$. In this case, as analysis has shown,[19] the advantage factor dominates the fluctuation factor and determines the sign of handedness of the state with strongly broken symmetry only in systems with a number of chiral monomers much greater than g^{-2}. For weak neutral currents, this number is $N \gg 10^{34}$. But it is necessary to take into account the heterogeneity of such large systems: Investigation of spontaneous mirror-symmetry breaking in the case of spatial diffusion has shown that the advantage factor due to the weak neutral currents can determine the sign of the prebiosphere handedness only if the radius of curvature of the interface between areas with opposite handedness exceeds 10^{10} km, a distance much larger than the Earth's radius.[20]

Nevertheless, one more possibility remains. Note that the advantage factor deforms the bifurcation diagram very dramatically in the neighborhood of the critical point $\rho = 1$ (see the shaded region in figure 8). In this neighborhood the η values of two states of opposite handedness are separated by a distance of the order of $g^{1/3} \gg g$. Based on this fact Dilip Kondepudi and George Nelson[21] proposed the idea of the "anomalously strong" amplification of the advantage factor by "slow passing" of the bifurcation point. Frank Moss and Peter McClintock[22] have done a kind of computer simulation that supports the



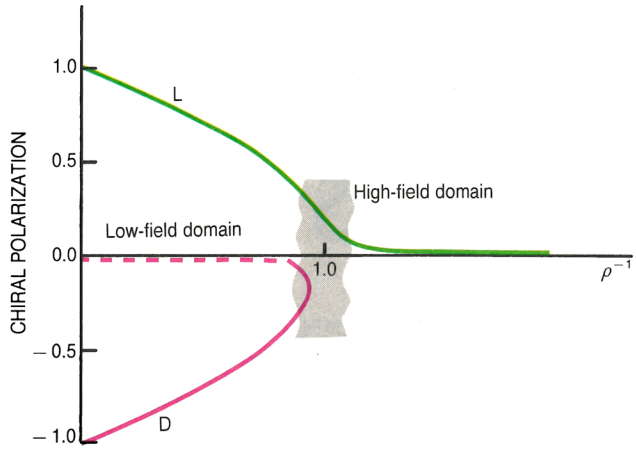
Stereoselective system has a bifurcation diagram (bottom) that gives different depths to the "potentials" (top) representing the two states D (red) and L (green). The system here is represented by point S on the left-hand branch. The stereoselectivity γ for the system shown is 0.1. Analysis shows that as the system becomes more stereoselective the bifurcation point shifts to the left, but that the chirally pure state S remains stable until the stereoselectivity reaches some critical value, beyond which it can maintain the chiral purity. **Figure 7**

predictions of Kondepudi and Nelson. Note, however, that this region is particularly vulnerable to fluctuations as fluctuations grow near the critical point. As a result, the system can end up on the other branch. Therefore, we feel that the requirements for "amplification" of the advantage factor in the vicinity of the critical point are contradictory: On the one hand, this region must be passed sufficiently slowly for the asymmetry to "accumulate." On the other hand, this region must be passed quickly enough to preclude the system from switching over into the opposite enantiomeric state.

The "slow passing" mechanism can work only within a very narrow vicinity of the bifurcation point.[23] This width, which is called the "high-field domain" in the study of phase transitions, has a characteristic scale $|1/\rho - 1| \approx g^{2/3}$ (approximately 10^{-12} for $g = 10^{-17}$) For the effective amplification of the extremely weak advantage factors the system must stay in this region for a very long time (approximately 10^5 years for $g \approx 10^{-17}$). However, at such a low rate of variation of the governing parameter, it would have taken so long to reach the values $\rho \gg 1$ that correspond to strong mirror-symmetry breaking that this mechanism could not have played any essential role in prebiological evolution.

The physical approach

The main objective of this brief survey was to demonstrate the fruitfulness of physical approaches to the problem of the origin of life. We tried to show that two properties of living systems that are unique from the standpoint of physics, namely, self-replication and homochirality, may serve as Ariadne's thread in the labyrinth of hypotheses concerning this problem. It is remarkable that the existence of only these two properties already predetermines the path of prebiological evolution. Life, based on self-replication of organic homochiral polymers, could have originated only if the prebiotic organic medium was capable of a bifurcation-type transition to the chirally pure state. We do not believe that making this conclusion requires us to locate any particular historical event, whether on Earth, on another planet, in dark interstellar clouds or somewhere else. Our considerations here certainly do not exhaust the problem of the origin of life. Nevertheless, they open up the curtain on one of its mysteries.



Narrow region around the bifurcation point (shaded) corresponds to what is called the "high-field domain" in phase transitions. Some have suggested that the precursors of modern biological polymers evolved slowly enough through this region that an advantage factor such as weak neutral currents could have determined the sign of the handedness. But it seems that the required time of passage would have been too long and that the fluctuations in this region could throw the system into the opposite handedness. **Figure 8**

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