CRITICAL EVALUATION OF MATHEMATICAL MODELS FOR THE AMPLIFICATION OF CHIRALITY

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ABSTRACT

The main types of models related to the origin of biological asymmetry are reviewed and new models are proposed. It is shown that in polymerization (in contrast to Yamagata's hypothesis) only a temporary amplification of asymmetry occurs. Models have been constructed in which always the same enantiomer survives, independently of any fluctuations or asymmetric initial conditions. Therefore, the question of the "by chance" or the causal origin of biological asymmetry remains still open, although with a slight preference for a causal origin.

1. ORIGIN OF CHIRALITY: CHANCE OR CAUSALITY ?

In the attempts to elucidate the origin of the asymmetry of biosphere two basic questions became obvious.

First, whether the present asymmetry is result of a historical accident, or is it due to some underlying physical asymmetry.

Second, at which stage of the chemical or biological evolution the (almost) perfect optical purity was attained.

A lot of experimental and theoretical work has been done (mainly in the last two decades) to answer these questions.

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It is commonly accepted that optically pure systems are more advantageous than mixed ones: all-L or all-D polymers are formed faster and are more stable than mixed polymers (1,2), the genetic code would have been more complicated if the handedness of the building blocks (e.g. amino acids) were also coded, etc. Thus it seems clear why the organisms became optically pure. The question is the choice between the two opposite chiralities.

Laboratory work has been devoted mostly to the search for possible asymmetric agents. Circularly polarized light (3-5) and weak interactions (6-8) are the most often assumed sources of external asymmetry, although a number of other sources are also suggested (9). Weak interaction is at present the only physical agent, for which an asymmetric effect is firmly established. Its contribution to the intra- and intermolecular interactions is, however, very small (Rein claimes that the intramolecular effect is not greater than 10^{-13} (10) or even 10^{-20} (11), therefore, the primary effect must be efficiently amplified in order to have any significant role in chemical evolution. Such amplification was looked for in synthesis or decomposition of molecules, in polymerization and crystallization, and even in oscillating reactions. Most of the experiments could not demonstrate any asymmetry in the products. (For a review of these experiments see e.g. (8, 12)).

The minuteness of the physical asymmetry led a number of researcher to the denial of its importance in the origin of the handedness of the biological materials. They assume that L-systems are quite as good as D-systems, and the preference for one particular handedness has been decided by mere historical chance. This chance might operate in several ways. Perhaps some step of the (prebiological or biological) evolution is very improbable, and therefore rare, event, which occurred only once on the Earth (13-16). This event may be the organization of the reproductive system, or the photosynthetic apparatus, or some other key step. It is also possible, that - perhaps following a partial territorial separation of the enantiomeric species - a single catastrophe destroyed the majority of one of the populations; the other therefore could easily overcome (15,24). A most intriguing possibility is the existence of systems with multiple steady states, only the highly asymmetric ones being

stable. Then an initial fluctuation is amplified until the favoured species becomes dominant (2, 16-24). It is claimed that in such multistable systems a slight asymmetry in the "fitnesses" of the two competing species only slightly modifies the basins (domains of attraction) of the stationary states, therefore a random fluctuation will outfit the small difference (24, 25).

In this contribution we review the main types of models related to the origin of biological asymmetry. A number of new models is also presented which show that this question cannot be decided on the basis of formal models. A real resolution of the dilemma requires a more precise reconstruction of the evolutionary timetable in order to see which models remain compatible with the actual events.

Single events are not taken into account in the models. Therefore we are confined to the physical asymmetry: does it have any possibility to grow up in spite of fluctuational or random disturbances ?

Not only models yielding a perfect optical purity will be considered but also those in which one species gains a relative predominance, as the optical purity might evolve in a long sequence of reactions each of them shifting somewhat the ratio of the enantiomers.

2. CLASSIFICATION OF THE MODELS

The models developed in the study of optical purity may be clssified according to several criteria. Some of these criteria will be listed in this paragraph.

2.1. Complexity of the reaction system.

The simplest models do not contain any reactions of higher order nor chains of reactions.

More complex are the models describing polymerization and/or crystallization, with long iterative sequence of reaction steps.

A qualitatively different level of complexity is reached in systems with autocatalytic steps of different order. Instead of an autocatalytic reaction selfinstructing cycles may be involved, where the

cycle as a whole is reproduced autocatalytically (26).

One aspect of the complexity of the system is the growth rate of the compounds of interest: it may be of linear, exponential, or hyperbolic type (the latter conrresponding to autocatalysis of second or higher degree) (27).

2.2. Interaction between the enantiomers

The enantiomeric objects may have no influence on each other at all, thus behaving as independent competitors (27). The simplest possible effect of one enantiomer on the other is through racemization or other parasitic reactions inducing the transformation of the enantiomers into each other. More pronounced interaction of the enantiomers may be through the constraints imposed on the whole system (27,28), or through direct collision (e.g. fight in the biological phase of evolution). This type of interactions is called heterochiral cooperative interaction by Morozov (25).

2.3. Constraints

In the majority of models the number of enantiomers is allowed to grow unlimited. Since in any real system there are limits for growth, different constraints are involved in the models. Eigen and Schuster (27) investigated the case of the constraint of constant overall organization (when the quantitiy of building blocks in the system remains constant), and briefly mentioned the constraint of constant fluxes. There may be, however, other realistic constraints too, e.g. the number of building blocks may be limited, and the system does not necessarily use all of them (28).

2.4. Ideality

In an ideal system the enantiomers are not directly transformed into each other (25,29). Therefore, the models that aim to describe chemical evolution are bound to be non-ideal as racemization should always be taken into account.

2.5. Underlying physical asymmetry

Some models try to explain the appearance of handedness regardless of any basic physical asymmetry. These models, with symmetric rate constants for both enantiomers, are called "free" by Morozov et al. (25).

They refer exclusively to the hypothesis of by chance origin. In the models including physical asymmetry, ("perturbed" models of Morozov), some rate constants are asymmetric. This type of models is appropriate for simultaneous study of the effect of both the physical asymmetry and the initial conditions or fluctuations.

2.6. Evolutionary timing

Logically several stages of evolution should be distinguished (26):

prebiotic "chemical" phase,
phase of selforganization to replicating "individuals"
evolution of individual species.

These phases are temporally not necessarily separated.

The optically pure state might in principle be selected at any of these stages. Therefore the models to be discussed refer also to different evolutionary environments. Spontaneous formation of different substances is mainly characteristic of the chemical phase. Autocatalytic growth may refer to all phases: chemical as well as purely biological. Polymerization is thought to bear significance in the first and especially in the second phase. Racemization refers only to the prebiological evolution, while sexual behaviour (30) clearly is related to the third phase.

In all of these phases there are models which account for the amplification of asymmetry. Therefore these models at the present are not suitable even for an approximate evolutionary timing.

3. MATHEMATICAL MODELS

In the following presentation we proceed from the simplest models to the more complicated ones. The advantages and limitations of the various models will be shown. (Our scope is limited to the discussion of the main types of the relevant models, not the enumeration of each of them.)

The enantiomers and their concentrations are denoted by the same symbol (L and D). Although the models may deal with chemical reactions or with changes of population sizes, we always refer to L and D as to concentrations.

In perturbation models some analogous rate constants are different for the L and the D species. This will be indicated by the subscripts L and D. The general convention is that if there is an asymmetry ε in the rate constants, then $k_L=k(1+\varepsilon)$ and $k_D=k(1-\varepsilon)$. (Usually $\varepsilon > 0$ is assumed.) The resulting asymmetry in concentrations is $\eta = \frac{L-D}{L+D}$.

3.1. Monomers

The simplest models treat the formation of the enantiomers in a single step, from a precursor present in great excess, and their destruction. The system of differential equations describing such a model is as follows:

$$\begin{aligned} \dot{L} &= v_L - k_D D - r(L-D) \\ \dot{D} &= v_D - k_D D + r(L-D) \end{aligned} \qquad (1)$$

The formation of complex molecules from the primordial athmosphere caused by radioactivity, lightning, ultraviolet light, etc. might show similar behaviour.

In these models (either with or without destruction, as well as implying racemization or not) asymmetry is never amplified (29). Even if starting with unequal initial concentrations the asymmetry tends to a limiting value which does not exceed the sum of the asymmetries of the rate constants, $|\varepsilon_v| + |\varepsilon_k|$.

For the case of β-particles Keszthelyi (31) proposed actual values of v and k (equal to 10^{10} s^{-1} and $5.10^{-19}s^{-1}$, resp.) Using ideal system (no racemization) he calculated the time necessary for the concentration difference to grow, starting from zero, above the level of statistical fluctuations. This time proved to be relativily short (around 10^4 years), even for small asymmetries in the rate constants. In the non-ideal system, however, racemization makes the process slowdown and the asymmetry can never exceed the statistical fluctuations, unless

$$\varepsilon_k > \frac{2r+k}{\sqrt{k(2v+2r+k)}} \qquad (2)$$

(for the case when only the decomposition is asymmetric (32)).

With Keszthelyi's data this means that for $\varepsilon_k < 5.10^{-15}$ the asymmetry will never exceed the noise. For larger ε's at any given racemization rate the concentration shift reaches m times the level of statistical fluctuations in T years if and only if $\varepsilon > Z_0$ (Z_0/m vs. r is shown in Fig. 1.)

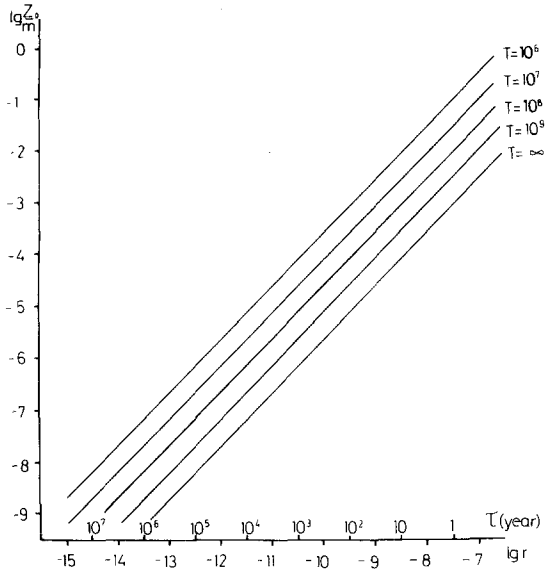

Figure 1. Dependence of the minimal required asymmetry in the decomposition rates on r, for several values of T.

At any rate, such systems may at the best preserve the physical asymmetry, but never amplify it.

3.2. Polymerization

Yamagata (33) was the first to point out that a significant amplification of asymmetry may, in principle at least, be attained through a very long sequence of consecutive reactions, each of them having a small preference toward one of the enantiomers. He claims that if in each step of the sequence $\rightarrow A \rightarrow B \rightarrow C \rightarrow D \rightarrow \ldots$

there is a relative difference ε in the rate constants of the L and D molecules, then the asymmetry of the nth product will be

$$\frac{(1+\varepsilon)^n - (1-\varepsilon)^n}{(1+\varepsilon)^n + (1-\varepsilon)^n} \qquad (3)$$

which (for small ε) may be in the order of $n\varepsilon$.

The most appealing possibility for such long reaction sequences is polymerization. Considering e.g. DNAs with $n \approx 10^6$, this indeed may give a remarkable amplification. (Another possibility is crystallization (34) with even greater number of steps, but its relation to biology is less obvious.)

To check Yamagata's hypothesis, we constructed a few simple models. One of them will be outlined here (a detailed description will be published elsewhere (35)).

Let us consider the synthesis of a linear polymer in the presence of a great excess of monomers. Suppose the formation of the dimers be characterized by rate constant k_0, whereas the rate constant of addition of each subsequent monomer to a chain be k, independently of the chain length. Then, denoting the concentration of the $n$mer through a_{n-1}, the system is described by the following set of differential equations:

$$\begin{aligned} \dot{a}_1 &= k_0 - k a_1 \\ \dot{a}_2 &= k a_1 - k a_2 \\ &\vdots \\ \dot{a}_n &= k a_{n-1} - k a_n \end{aligned} \qquad (4)$$

(constant concentration of the monomer is included in k and k_0).
Then starting from zero initial values, $a_n(0)=0$, the solution of equation (4) is the following:

$$a_n = \frac{k_0}{k} e^{-kt} \sum_{j=n}^{\infty} \frac{(kt)^j}{j!} \qquad (5)$$

It is easy to see, that a_n monotonically increases and tends to k_0/k.

Equation (4) may be put separately for the L and for the D molecules. If there is a relative difference ε both in k_0 and k, then the asymmetry in the nth product,

$$\frac{a_n^L - a_n^D}{a_n^L + a_n^D}$$, is a monotonic function of time.

At t=o it equals to the value given by Yamagata (see Equ. (3)), and monotonically decreases thereafter, approaching zero.

The time courses of the a_n's and their asymmetries are shown in Fig. 2., for ε=0.01 and several values of n.

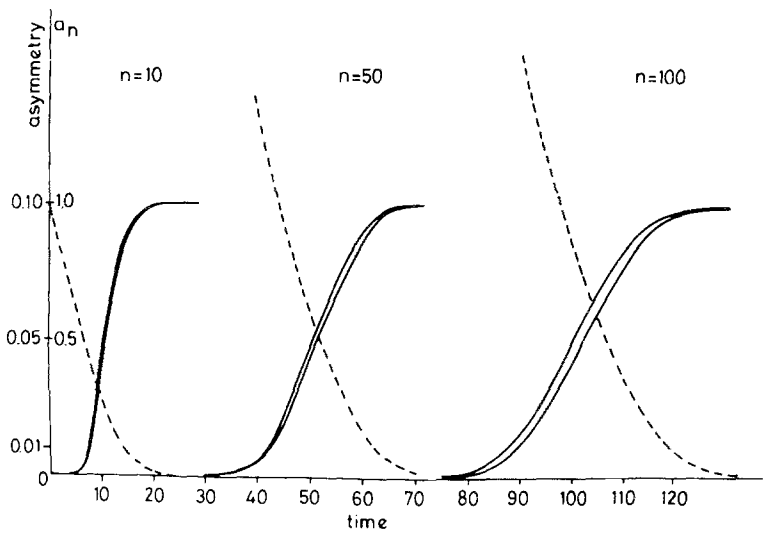

Figure 2. Time course of polymerization and the asymmetry of the nth products. (n=10, 50 and 100). k_0=k=1, ε=0.01.

It is apparent from Fig. 2. (and also from Equ. (5)) that the asymmetry in the k's causes a retardation of a^D relative to a^L, i.e. a^L_n at time t is the same as a^D_n at time

$$t \cdot \frac{1+\varepsilon}{1-\varepsilon}$$

Thus if $a^L(t)$ goes through a maximum (which is the case in some models), the asymmetry changes its sign in the vicinity of this maximum (and, generally, around each extremum) of the function.

Hence, it seems justified that asymmetry may indeed be amplified temporarily in reaction chains, but large amplification occurs only at the beginning of the process, when the quantity of products of interest is negligible. At the later, more consolidated phases of the reaction the amplification decreases, and even may change sign.

It is interesting to note, however, that one of the most convincing demonstrations of the effect of physical asymmetry is the series of crystallization experiments by Kovács (36), which would be most easily explained on the basis of Yamagata's hypothesis. Probably, the experiment does not allow to neglect the decrease of the concentration of the monomers, and, more generally, such a simplified treatment.

3.3. Autocatalysis, without heterochiral interaction

This type of models assumes the autocatalytic formation of the enantiomers from a symmetric precursor.

The simplest example is the so-called Jordan-Kuhn scheme (16):

$$\begin{aligned} \dot{L} &= k_L L - r(L-D) \\ \dot{D} &= k_D D + r(L-D) \end{aligned} \qquad (6)$$

In the ideal system (with r=0) both concentrations increase exponentially. If there is an asymmetry $\varepsilon>0$ in the rate constants, the asymmetry of the concentration will monotonically increase and tends asymptotically to unity. That is, in spite of the infinitely large pool of the handicapped enantiomer, its relative abundance tends to zero.

In a system involving also racemization, any initial asymmetry vanishes if $k_L=k_D$. If there is a difference, ε in the rate constants, the concentration asymmetry tends to

$$\eta = \frac{\varepsilon}{\frac{r}{k} + \sqrt{(\frac{r}{k})^2 + \varepsilon^2}} . \qquad (7)$$

This asymmetry may, with appropriate rate constants, significantly exceed the original asymmetry . (E.g. for $\varepsilon=10^{-13}$ and $r/k=10^{-6}$, η will be 5.10^{-8}.

If there is a second order autocatalytic reaction, the system of differential equations becomes (20, 25):

$$\begin{aligned} \dot{L} &= k_L L^2 \\ \dot{D} &= k_D D^2 \end{aligned} \qquad (8)$$

In this system both concentrations have singularities in finite time, i.e. the concentration reaches infinity at time $(k_L L_o)^{-1}$ and $(k_D D_o)^{-1}$, respectively. Thus, if, e.g., $k_L L_o > k_D D_o$ then as time approaches $(k_L L_o)^{-1}$, L becomes infinitely large whereas D remain finite, therefore the asymmetry tends to unity. If the rate constants are equal, only a difference in the initial concentrations may lead to a perfectly asymmetric final state, whereas in the case of perturbed systems, the effect of the difference in the rate constants may be balanced or even reversed by the difference in the initial values. This latter difference may result from fluctuations, or from some catastrophic event, etc.

As to the fluctuations, their standard deviation is usually assumed to be equal to the square root of the number of molecules (see e.g. Morozov (25) whose reasoning is used hereafter). Let the average number of L and D molecules be $\bar{N}_l = \bar{N}_D = N$. If the fluctuations in the initial state are distributed according to a certain function f(x) then the probability, that $k_L L_o < k_D D_o$, or, which is the same, that $k_L N_L < k_D N_D$, is equal to

$$\Pr\{\eta=+1\} = \int_{-\varepsilon\sqrt{N}}^{\infty} f(x)dx \qquad (9)$$

This is, at the same time, the probability of the final asymmetry being equal to +1. The complementary probability of a final state with asymmetry $\eta=-1$ will be

$$\int_{-\infty}^{-\varepsilon\sqrt{N}} f(x)dx \qquad (10)$$

The probability of $\eta=+1$ substantially exceeds 1/2 only if $\varepsilon\sqrt{N}$ is large enough. If, e.g., $f(x)$ is a Gaussian normal distribution, then the probability $\Pr\{\eta=+1\} = \mathrm{erf}(\varepsilon\sqrt{N})$ exceeds $1/2+\varepsilon$ only if $\varepsilon^2 > \frac{\ln N}{N}$, which at $\varepsilon=10^{-13}$ is fulfilled for $N > 10^{28}$ - quite a large number of molecules to start with. This means, that although the system always reaches a completely asymmetric state, the direction of asymmetry is not very much influenced by the asymmetry of the rate constants.

This model is instructive in that it clearly shows the drawbacks inherent in the models with unlimited growth. At some finite moment in time all the available resources are exhausted by the two enantiomers and we are left without any hint as to the subsequent evolution of the system which can no more obey the previously used equations.

3.4. Models with heterochiral interactions: The role of the initial concentrations

In these models there is direct interaction between the enantiomers. This interaction is mostly thought of in terms of mutual antagonism, leading to the elimination of both enantiomers from the system.

The investigation of these models started with the paper by Frank (17) describing what he called "specific mutual antagonism":

$$\begin{aligned} \dot{L} &= (k-k_2D)L \\ \dot{D} &= (k-k_2L)D \end{aligned} \qquad (11)$$

Although this model seems to be more adequate for the description of the co-evolution of two competing biological populations, it may also be interpreted as a chemical reaction system in which both enantiomers are autocatalytically synthesized from a constant precursor pool. In this system the symmetric stationary state $L=D=k/k_2$ is unstable . One of the forms grows exponentially. The asymmetry, obviously, tends to ±1. It depends solely on the initial conditions, which form dies out and which survives.

This model was thoroughly reinvestigated by Hochstim (24), and later by Morozov et al. (25). They have shown that even if there is a difference in the rates of synthesis, i.e. $k_L \neq k_D$, this asymmetry has practically no influence on the chances of the favoured enantiomer. If we were to start the system from the ideally racemic state, the more rapidly synthesized enantiomer would be the winner. If, however, one takes into account the fluctuations around the racemic state, the surviving species will be determined by the direction of the initial fluctuation alone.

This result is one of the main arguments against any role of the physical asymmetry in the origin of handedness.

If in the free system ($k_L=k_D=k$) racemization is also taken into account, i.e.

$$\begin{aligned} \dot{L} &= (k-k_2D)L-r(L-D) \\ \dot{D} &= (k-k_2L)D+r(L-D), \end{aligned} \qquad (12)$$

the behaviour of the system changes dramatically (29).

The qualitative phase portrait of the system for different racemization rates is shown in Fig. 3.

For large rates of racemization ($r > k/2$) the system tends to a symmetric stationary state $L=D=k/k_2$. For small racemization rates ($r < k/2$) one form grows infinitely, and the asymmetry tends to ±1, but the handicapped enantiomer does not disappear completely, rather it tends to a positive value r/k_2. In case of $r=k/2$ the asymmetry increases or decreases, depending on the initial concentrations, but it cannot reach the value of ±1.

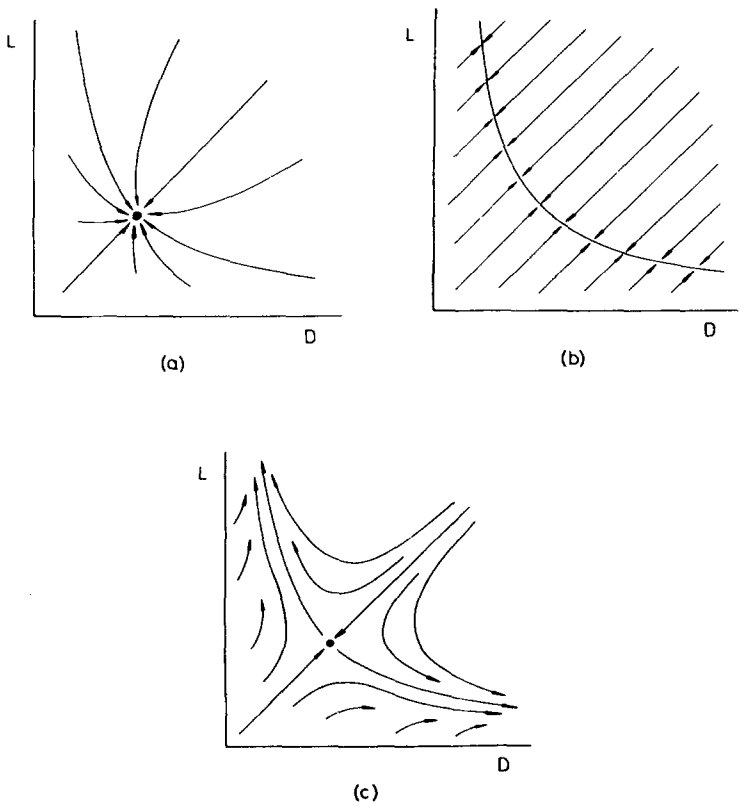

Fig. 3. Qualitative phase portrait of Frank's model of specific mutual antagonism with racemization.

a/ $r>k/2$, b/ $r = k/2$, c/ $r < k/2$

More sophisticated models of this kind with identical rate constants for the mirror image reactions were devised by Seelig and coworkers (21-24) and by Decker (18-20). Some of their works avoid the unpleasant aspects of the models of unlimited growth. For some values of the involved parameters they have two absolutely asymmetric stable stationary states, in which the concentration of one enantiomer is zero, while the other has a finite value. Such is e.g. the model of Decker (18). If, however, racemization is also taken into account, these stationary states - although remain asymmetric - cease to do absolutely so and both enantiomers have non-zero values (29).

3.5. Models with heterochiral interaction: The role of physical asymmetry

If in the model of specific mutual antagonism the enantiomers are formed with constant rates (instead of being produced autocatalytically), the following system of differential equations results:

$$\begin{aligned} \dot{L} &= k_L - k_2 LD \\ \dot{D} &= k_D - k_2 LD \end{aligned} \qquad (13)$$

If the rates of formation are equal, the system behaves exactly as shown on Fig. 3b. If, however, one of the enantiomers is formed more rapidly, the concentration of this enantiomer will grow above any limit, while the other vanishes. The phase portrait of the system for $k_L > k_D$ is shown in Fig. 4.

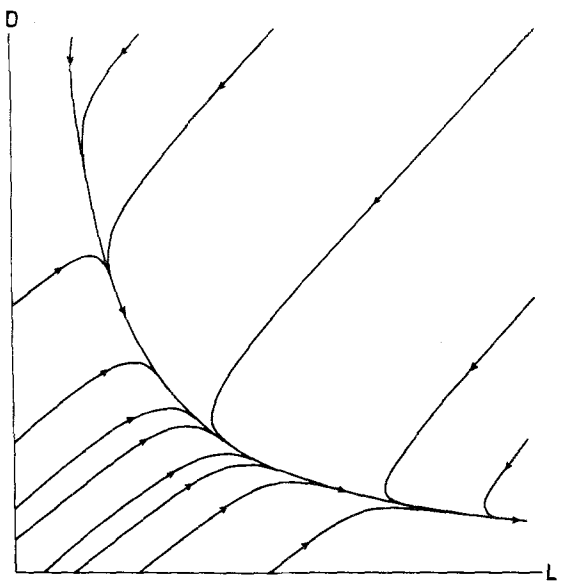

Fig. 4. Phase portrait of the model of specific mutual antagonism with spontaneous formation of the enantiomers.

In this system, however small the difference in the rates might be and however large excess of the competing enantiomer be present initially, always the molecule with the higher synthesis rate will survive, and the other dies out. It is an example of the extreme amplification of a physical asymmetry in spite of any fluctuations or other deviations from the symmetric starting conditions.

This model still contains the unattractive assumption of unlimited growth. This difficulty will be avoided in the following model.

Frank in the same paper which describes his widely cited model dealt with above, proposed also another model for "unspecific mutual antagonism" of the enantiomers. The enantiomers are formed autocatalytically from an apparently infinite precursor pool, and the collision between the asymmetric molecules - irrespective whether they are of the same or opposite chirality - leads to the elimination of the colliding molecules from the system. In the original model the rate constants of synthesis were taken equal, and the asymmetry did not change in time.

If, however, the rate constants are different, the model is described by the following equations:

$$\begin{aligned} \dot{L} &= k_L L - k_2(L+D)L \\ \dot{D} &= k_D D - k_2(L+D)D \end{aligned} \qquad (14)$$

The phase portrait of this system for $k_L > k_D$ is shown in Fig. 5.

Starting from any initial non-zero concentrations, the system always tends to the absolutely asymmetric state in which

$$L = \frac{k_L}{k_2} \quad \text{and} \quad D = 0.$$

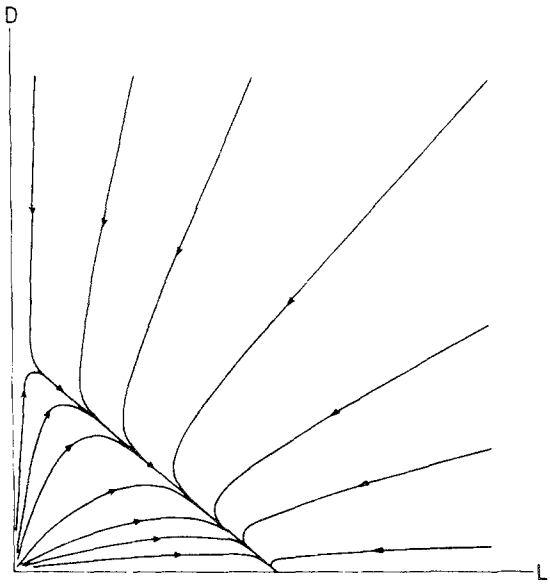

Figure 5. Phase portrait of the model of unspecific mutual antagonism

4. TYPES OF SELECTIVE BEHAVIOUR OF SEVERAL COMPETING SPECIES

The occurrence of optical purity may be sought of as a special case of selection between alternative features as well. Special because on the one hand there are only two alternatives, and on the other hand, there is no or only a very slight difference in the fitnesses of the two alternatives. Moreover, there exists racemization, i. e. spontaneous interconversion of the enantiomers (at least at the level of small molecules; in the case of macromolecules and selfreproducing systems such interconversion does not seem to take place).

Eigen (26,27) thoroughly investigated different types of selection between selfreplicating entities. It was shown that supposing unlimited growth an initial asymmetry will not be amplified in the case of linear growth, whereas it will tend to unity if autocatalytic processes are involved. However, in exponentially growing populations even the "defeated" species will have an infinitely great population size, while in hyperbolic growth (autocatalysis at least of

second order) one species grows infinitely while the other remains finite in number.

For the more realistic case of limited growth they studied mainly the case of the so called "constraint of constans organization". Under this constraint linearly growing populations coexist, while among several exponentially growing species the fittest wins. The outcome of he competition between hyperbolically growing populations will be again the survival of only one species, but it depends on the initial conditions which of them is preferred. The fitness here determines only the size of the basin (domain of attraction) of the different pure stationary states.

Although these models have been constructed for the second stage of evolution (selforganization to replicating "individuals"), they equally may be applied to the chemical evolution.

Only a few of the models aimed to study the optical asymmetry fits into this scheme of selection. Another constraints are to be taken into consideration, interaction of the enantiomers as well as racemization also should be included. The analysis of Eigen and Schuster, nevertheless, is very important for us, because it also leads to the conclusion: We have a great number of possible models for supporting any of the concurring hypotheses:

- that the two forms may coexist;
- that the form with any small "physical" advantage wins;
- that the winner is determined by chance.

5. CONCLUSIONS

The evaluation of different types of models describing the origin of asymmetry does not allow a choice in favour of either of the two concurring hypotheses. In some models an underlying physical asymmetry cannot overcome the statistical noise, unless this asymmetry is much higher than expected from theory, or the system starts from an unrealistic large population of molecules. In other models fluctuations and initial conditions do not play any role, and physical asymmetry alo alone govems the outcome of the process.

Nevertheless, one is tempted to ascribe greater importance to the physical asymmetry. It is conceivable

that during some periods of the evolutionary process there was a preference for "fluctuational amplification", while in other periods for "causal effects". According to the above considerations, however, the "causal periods" could produce asymmetry even by reversing the asymmetry reached by fluctuations, while in the "fluctuational periods" the level of asymmetry reached causally had to be further amplified.

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