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Study of an error-prone hypercycle formed from two kinetically distinguishable species

M.A. Andrade, A.J. García-Tejedor and F. Montero

Departamento de Bioquímica y Biologia Molecular I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain

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Asymmetry within both the amplification factor values (A_k) and cross-catalytic hypercyclic constant (K_{jk}) and its influence on the stability of a two-membered error-prone hypercycle has been exhaustively studied from a deterministic point of view and the bifurcation diagram as a function of the quality factor (Q) has been obtained. In the more general case, several Q critical values appear, changing their relative position in the diagram depending on the A_k and K_{jk} values. The order of the Q critical values affects both the general properties of the system and the stability of the hypercyclic organization. The importance of this asymmetry in the selective and evolutionary properties of the hypercycle is also discussed.

1. Introduction

The hypercycle has been proposed as a singular event in the origin of life. Such an organization allows the information crisis originating from the increased complexity in quasispecies distribution to be overcome. It also has been proposed as a relevant model in order to explain the *once-for-all-time* decisions that took place in prebiotic evolution (for a review, see refs 1–3).

In the more general case two different hierarchical levels of organization coexist in a hypercycle. The first one involves non-catalyzed self-replication by means of the amplification factor of the species making up the hypercycle, and the other, the cross-catalyzed growth of each species as a consequence of the hypercyclic organization. The amplification factor of species k is termed A_k and the kinetic constant expressing the growth promotion of species j by the catalytic action of species k is denoted K_{kj}. The dynamics and properties of such an organization stem from the underlying existence of this two-level hierarchy: quasispecies competition at a lower level and hypercyclic cooperation at the higher one. Usually, the first one is not taken into account when hypercyclic properties are studied and attention is focused on the catalytic relationship. Non-equality in the catalytic properties of the different molecules that compose the hypercycle has been previously studied, and the way in which this non-equality can destroy this organisation has also been described. These studies have been performed mainly on catalytic hypercycles, i.e., those hypercycles where growth promotion takes place by means of proteins produced by translation of the hypercycle nucleic acids (for a detailed study, see ref. 2). Nevertheless, the plausibility of RNA sequences forming hypercyclic organization without any catalytic activity by proteins has been increased since the description of ribozymes (for a

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Correspondence address: F. Montero, Departamento de Bioquímica y Biologia Molecular I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain.

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review, see ref. 4. More recently, the RNA-catalyzed synthesis of complementary strand RNA has been pointed out [5] and the possibility of ribozyme self-replication also described [6]. Ribozyme can also display an RNA polymerase activity, carrying out the net elongation of an RNA primer [7]. Several authors have discussed the possible role of the enzymatic properties of ribonucleic acids in the earliest steps of prebiotic evolution [8,9].

Most of these models however, fail to take into account *error-prone* replication and the existence of an *error tail*. As pointed out by Schuster, [10], hypercycles do not generally sustain potentials, and this makes the solution of their kinetic equations difficult. Only in the case of free-mutation elementary hypercycles have the solutions of their kinetic equations been studied in depth [11].

Finally, the simultaneous influence of asymmetry at both of the above mentioned organization levels, quasispecies and hypercycle, has yet to be studied in detail. Amplification factor values must have had decisive importance in hypercycle nucleation, when the species then existing were a consequence of quasispecies selection and evolution. At the moment of nucleation these values may well have been larger than those of the catalytic constants K_{kj}.

We have previously studied from both a deterministic and a stochastic point of view a very simplified model of a two-membered error-prone hypercycle without translation machinery including these two levels of organization [12–15]. However, the model there considered was symmetric in amplification factor ($A_1 = A_2$) and catalytic constant ($K_{12} = K_{21}$) for the two species forming the hypercycle. In this paper we study a similar model, but including asymmetry at both organization levels. Asymmetry and error-prone self-replication have been simultaneously considered, and the influence of such an asymmetry on both the hypercycle stability and *error threshold* studied.

2. Generalization of the model

Fig. 1 shows a schematic representation of the model here developed. Error-prone replication of molecules I_1 and I_2 induces the appearance of an error tail (copies I_i). These molecules are assumed not to be hypercyclically coupled with copy I_1 or with copy I_2.

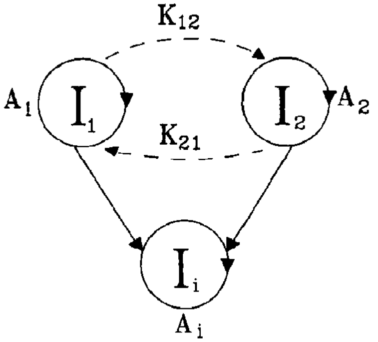

Fig. 1. Elementary hypercycle formed from two species: I_1 and I_2. Hypercyclic relationships and production of copies by replication of species I_1, I_2 and I_i are represented by dashed and solid lines, respectively.

In order to be able to carry out an analytical study of the system, the following assumptions had to be made:

(a) The amplification factor values of the error-tail species (A_i) have been assumed to be equal. The same holds for the degradation factor (D_i). As a consequence of this assumption, all mutants are lumped together into an error tail species, I_i. This simplification, usually named *single peak landscape*, has been routinely made by other authors, and each was extensively discussed by Eigen and McCaskill [16].

(b) Elements of the error tail (I_i) are produced by erroneous replication of either species I_1 or species I_2. They have no catalytic properties nor do they mutate back to the elements of the hypercycle (I_1 and I_2). The steps expressing the formation of copies I_1 and I_2 as a consequence of the error-prone self-replication of molecules *i* have been neglected, as is usual in these studies [17]. Moreover, Swetina and Schuster [18] and more recently Nowak et al. [19] have demonstrated using perturbation theory that for sufficiently long chain, the zeroth-order approximation, in which the above mentioned term is discarded, provides a proper fit for the system's evolution over time. The agreement between the zeroth-order and first-order approximations becomes better and better as the sequences lengthen.

(c) Mutations between the two species I_1 and I_2 are excluded. This is a reasonable assumption provided that the two catalytically active molecules (I_1 and I_2) have large Hamming distance and/or the number of digits in their chains is large enough to make the production of one of them by reverse mutation highly improbable.

(d) In contrast to the previously described model [12], $A_1 \neq A_2$ and $K_{12} \neq K_{21}$.

The following elementary steps can be set up:

$$I_1 \xrightarrow{A_1 Q} 2I_1 \tag{1a}$$

$$I_1 \xrightarrow{A_1(1-Q)} I_1 + I_i \tag{1b}$$

$$I_2 \xrightarrow{A_2 Q} 2I_2 \tag{1c}$$

$$I_2 \xrightarrow{A_2(1-Q)} I_2 + I_i \tag{1d}$$

$$I_i \xrightarrow{A_i} 2I_i \tag{1e}$$

$$I_1 + I_2 \xrightarrow{K_{21} Q} 2I_1 + I_2 \tag{1f}$$

$$I_1 + I_2 \xrightarrow{K_{21}(1-Q)} I_1 + I_2 + I_i \tag{1g}$$

$$I_1 + I_2 \xrightarrow{K_{12} Q} I_1 + 2I_2 \tag{1h}$$

$$I_1 + I_2 \xrightarrow{K_{12}(1-Q)} I_1 + I_2 + I_i \tag{1i}$$

$$I_1, I_2, I_i \xrightarrow{\phi_0} \tag{1j}$$

$$I_1, I_2, I_i \xrightarrow{D_1, D_2, D_i} \tag{1k}$$

ϕ_0 being the output flux parameter of information carrier molecules from the system.

From this kinetic scheme the following equations for the time evolution of the concentration of the different variables can be written:

$$\dot{X}_1 = A_1 Q X_1 + K_{21} Q X_1 X_2 - \phi_0 X_1 - D_1 X_1 \tag{2a}$$

$$\dot{X}_2 = A_2 Q X_2 + K_{12} Q X_1 X_2 - \phi_0 X_2 - D_2 X_2 \tag{2b}$$

$$\dot{X}_i = [1 - Q][A_1 X_1 + A_2 X_2 + (K_{12} + K_{21}) X_1 X_2] + A_i X_i - \phi_0 X_i - D_i X_i \tag{2c}$$

By applying the constant population (CP) constraint ($\Sigma_k X_k = N$, N being the total concentration of molecules) the following relationship among the variables is obtained:

$$X_i = N - X_1 - X_2 \tag{3a}$$

or

$$\dot{X}_1 + \dot{X}_2 + \dot{X}_i = 0 \tag{3b}$$

and thus the following expression for ϕ_0 can be derived from eq. 2:

$$\phi_0 = [1/N][A_1 X_1 + A_2 X_2 + A_i X_i + (K_{12} + K_{21}) X_1 X_2 - D_1 X_1 - D_2 X_2 - D_i X_i] \tag{4}$$

By substituting the values of X_i and ϕ_0 given by eqs 3a and 4, respectively, into eqs 2a and 2b, the system can be described by just two independent variables, X_1 and X_2. Assuming that D_1, D_2 and D_i are identical ($D_1 = D_2 = D_i = D$), the following kinetic equations are obtained:

$$\dot{X}_1 = A_1 Q X_1 + K_{21} Q X_1 X_2 - [X_1/N][A_1 X_1 + A_2 X_2 + A_i(N - X_1 - X_2) + (K_{12} + K_{21}) X_1 X_2] \tag{5a}$$

$$\dot{X}_2 = A_2 Q X_2 + K_{12} Q X_1 X_2 - [X_2/N] \times [A_1 X_1 + A_2 X_2 + A_i(N - X_1 - X_2) + (K_{12} + K_{21}) X_1 X_2] \tag{5b}$$

where the value of the parameter D does not affect the temporal evolution of the system.

3. Stationary states and linear stability analysis

By solving the system $\dot{X}_1 = \dot{X}_2 = 0$, the following stationary-state values, with at least one of the variables X_1^0 or X_2^0 equal to zero, can be obtained: (i)

$$X_1^0 + X_2^0 = 0 \tag{6a}$$

$$X_i^0 = N \tag{6b}$$

In this state only the error tail (molecules I_i) is selected, and its concentration is that of the total population, i.e., N. This implies that the system drifts randomly through sequence space, and thus that the information accumulated in the evolutionary process is being lost. This state is named the *random replication state*.

(*ii*)

$$X_1^0 = \frac{N(A_1Q - A_i)}{(A_1 - A_i)} \tag{6c}$$

$$X_2^0 = 0 \tag{6d}$$

$$X_i^0 = N - X_1^0 \tag{6e}$$

In this state both species I_1 and the error tail survive in a quasispecies distribution.

(*iii*)

$$X_1^0 = 0 \tag{6f}$$

$$X_2^0 = \frac{N(A_2Q - A_i)}{(A_2 - A_i)} \tag{6g}$$

$$X_i^0 = N - X_2^0 \tag{6h}$$

this solution being symmetric to solution *ii*.

If both X_1^0 and X_2^0 are non-zero, the following relationship between the variable values at the stationary state can be obtained from eqs 5a and 5b:

$$X_2^0 = \frac{K_{12}}{K_{21}} X_1^0 + \frac{A_2 - A_1}{K_{21}} \tag{7}$$

By substituting X_2^0 from eq. 7 into eq. 5a and setting it equal to zero, the following equation is obtained:

$$\begin{aligned}(X_1^0)^2\left[K_{12}K_{21} + K_{12}^2\right] \\ + X_1^0\left[K_{12}(2A_2 - A_1 - A_i)\right. \\ \left. + K_{21}(A_2 - A_i) - K_{12}K_{21}NQ\right] \\ + (A_2 - A_i)(A_2 - A_1) + K_{21}N(A_i - A_2Q) = 0\end{aligned} \tag{8}$$

This equation yields the values of two other stationary states (*iv* and *v*). Both of them imply the coexistence of species I_1 and I_2 and therefore the existence of the hypercyclic organization. If $K_{12} = K_{21}$ and $A_1 = A_2$, solutions *i*–*v* are identical to those previously described [12].

As can be seen in eq. 8, for a set of A_1, A_2, A_i, Q and N values, provided that $K_{12}N$ and $K_{21}N$ are maintained constant, the same values of X_1^0 and X_2^0 molar fractions (i.e., X_1^0/N and x_2^0/N) are obtained. This result is similar to that worked out from the simplified model described in ref. 12, where the normalized solutions were invariant with respect to the value of *KN*.

Linear stability analysis of eqs 5 when $K_{12} = K_{21}$ and $A_1 = A_2$ yields the Q-function bifurcation diagram shown in fig. 2. As can be seen in fig. 2, the stationary states that involve coexistence of both species I_1 and I_2 are in the $X_1 = X_2$ plane. This result is in agreement with the relationship

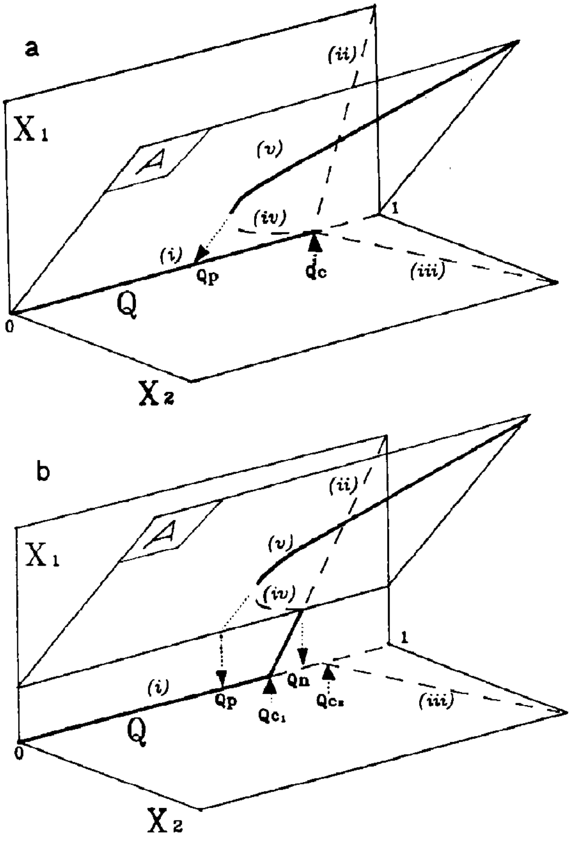

Fig. 2. Bifurcation diagram established as a Q function by linear stability analysis of eq. 5. The concentration value of both species I_1 and species I_2 at the steady states *i*–*v* are plotted. Stable and unstable solutions are represented by solid and dashed lines, respectively. Panels a and b show the symmetric ($K_{12} = K_{21}$; $A_1 = A_2$) and asymmetric ($K_{12} \neq K_{21}$; $A_1 \neq A_2$) cases, respectively. Parameter values: (a) $K_{12} = K_{21} = 0.20$, $A_1 = A_2 = 1$, $A_i = 0.8$ and $N = 100$; (b) $K_{12} = 0.05$, $K_{21} = 0.20$, $A_1 = 1.2$, $A_2 = 1$, $A_i = 0.8$ and $N = 100$. The arrows indicate the critical Q values at which bifurcation appears.

between X_1^0 and X_2^0 given in eq. 7. In fact, this equation is that of the plane containing both solutions *iv* and *v* in the bifurcation diagram. This plane is referred to as $\mathscr{A}$.

As can be observed in fig. 2, two Q critical values which are bifurcation points appear: Q_p and Q_c. Q_p is defined as the Q value beyond which solutions *iv* and *v* have real values. In other words, for $Q < Q_p$, *iv* and *v* values are complex.

The value of Q_p can be easily obtained from eq. 8. Q_p is the positive root of the following quadratic function:

$$\begin{aligned}
&Q_p^2\left[N^2K_{12}^2K_{21}^2\right]\\
&\quad+Q_p 2NK_{12}K_{21}\left[A_1K_{12}+A_2K_{21}\right.\\
&\quad\left.+A_i(K_{12}+K_{21})\right]+(A_1K_{12}+A_2K_{21})^2\\
&\quad+A_i^2(K_{12}+K_{21})^2-2A_i\left[A_1(K_{12}K_{21}+K_{12}^2)\right.\\
&\quad\left.+A_2(K_{12}K_{21}+K_{21}^2)\right]\\
&\quad-4NA_iK_{12}K_{21}(K_{12}+K_{21})=0 \qquad (9)
\end{aligned}$$

Q_c is another bifurcation point. It can be defined as the Q value beyond which the stationary states *ii* and *iii* appear, which implies the existence of quasispecies. The Q_c value can be obtained from either eq. 6c or 6g:

$$Q_c = A_i/A \qquad (10)$$

At Q_c the solution *iv* leaves the first octant of the cartesian coordinate system formed by X_1, X_2 and Q coordinates. Thus, the stationary-state value does not have any physical meaning beyond this Q value.

In previous papers [12,15], the projection of the plane $X_1 = X_2$ of this bifurcation diagram onto the plane (X_1, Q) or (X_2, Q) was shown, and the physical meaning of Q_p and Q_c was discussed. Concretely, Q_p was named there as Q_{hc}, because for Q values less than Q_p the hypercyclic organization is no longer localized and the information acumulated is lost due to an *error catastrophe*. In the more general case here considered there are situations in which $Q_{hc} \neq Q_p$, as is described below.

Fig. 2b shows the bifurcation diagram when $A_1 \neq A_2$ and $K_{12} \neq K_{21}$. The plane $\mathscr{A}$, containing the solutions *iv* and *v*, in the bifurcation diagram undergoes a rotation and a displacement with respect to the $X_1 = X_2$ plane as can be deduced from eq. 7. The rotation depends on the difference between the K_{12} and K_{21} values, and the displacement depends on the difference between the A_1 and A_2 values. Two different values of Q_c appear, Q_{c1} and Q_{c2}, which can be easily derived from eqs 6c and 6g, respectively:

$$\begin{aligned}
&Q_{c1} = A_i/A_1\\
&Q_{c2} = A_i/A_2 \qquad (11)
\end{aligned}$$

Beyond these Q values both stationary states *ii* and *iii* are positive. Furthermore, a new bifurcation point appears, named as Q_n. This is the Q value at which one of the real solutions *iv* or *v* changes sign (i.e., beyond this value the solutions have unlike signs). These solutions cut the $X_2 = 0$ plane at a Q value that can be obtained from both eqs 6c and 7:

$$Q_{n2} = \frac{A_1 - A_2}{A_1K_{12}N}(A_1 - A_i) + \frac{A_i}{A_1} \qquad (12a)$$

and cut the $X_1 = 0$ plane at a Q value that can be obtained from eqs 6g and 7:

$$Q_{n1} = \frac{A_2 - A_1}{A_2K_{21}N}(A_2 - A_i) + \frac{A_i}{A_2} \qquad (12b)$$

Consequently, $Q_n = \min\{Q_{n1}, Q_{n2}\}$. Thus, there are four different bifurcation Q values, namely Q_p, Q_{c1}, Q_{c2} and Q_n, as can be seen in the figure. The Q value beyond which the hypercycle ceases to exist, either because the values of states *iv* and *v* become complex or because state *v* leaves the first octant, will be now designated as Q_{hc}. This value will correspond to those of either Q_n or Q_p, depending on both the kinetic constant and amplification factor values.

4. Influence of the parameter values on the bifurcation diagram

To study the influence of the different parameter values (i.e., A_1, A_2, A_i, K_{12} and K_{21}) on the bifurcation diagram, the following change of variables is in order:

$$\alpha_1 = X_1/K_{21}$$
$$\alpha_2 = X_2/K_{12} \tag{14}$$

By substituting these values into eq. 7, the following equation for the plane containing stationary states *iv* and *v* in the cartesian coordinate system (α_1, α_2, Q) can be written:

$$\alpha_2 = \alpha_1 + \frac{A_2 - A_1}{K_{12}K_{21}} \tag{15}$$

Irrespective of the parameter values this plane always makes a dihedral angle of 45° with both planes (α_1, Q) and (α_2, Q), and intersects the α_2 axis at $(A_2 - A_1)/K_{12}K_{21}$. We will refer to this term as b:

$$b = \frac{A_2 - A_1}{K_{12}K_{21}} \tag{16}$$

Two different cases can be considered: $b = 0$, which implies that $A_1 = A_2$, and $b \neq 0$. We will study these two situations in the following sections.

4.1. *Influence of the parameter values on the bifurcation diagram as b = 0*

If $A_1 = A_2$ the plane represented by eq. 15 intersects the axis at the origin and $\alpha_1^0 = \alpha_2^0$ for stationary states *iv* and *v*. Thus, the K_{12} and K_{21} values affect the X_1 and X_2 values in this state as scaling factors. The bifurcation diagram so obtained will be like that shown in fig. 2a but with the X_1 and X_2 axes replaced by α_1 and α_2. The Q_{c1} value is identical to the Q_{c2} value, and $Q_{hc} = Q_p$. Additionally, $Q_n = Q_c$ and the Q axis is in the plane $\mathscr{A}$. The X_1 and X_2 values at these stationary states depend not only on the product $K_{12}K_{21}$ but also on the sum $K_{12} + K_{21}$ as can be seen from eq. 8. Thus, the values of these parameters affect the system not only as scaling factors, but also as modifiers of the bifurcation diagram.

Let us consider the following critical situations: when either the product $K_{12}K_{21}$ or the sum $K_{12} + K_{21}$ or one of the K_{kj} is declared constant.

4.1.1 *$K_{12}K_{21} = K$ (constant)*

In this case the situation $K_{12} = K_{21}$ implies a point of symmetry around which Q_p changes in a similar way as K_{12} increases and K_{21} decreases or vice versa. Thus, the Q_p value will become a maximum or minimum if $K_{12} = K_{21} = \sqrt{K}$. By substituting K_{21} for K/K_{12} in eq. 9 the following equality can be easily demonstrated:

$$\left[\frac{\mathrm{d}Q_p}{\mathrm{d}K_{12}}\right]_{K_{12}=\sqrt{K}} = 0 \tag{17}$$

Provided that

$$K \geqslant K_c = \frac{2A(A - A_i)}{NA_i} \tag{18}$$

it is possible to demonstrate that the second-order derivative with respect to K_{12} is positive when $K_{12} = K_{21} = \sqrt{K}$, thus the function at this K_{12} is a minimum. This K critical value (K_c) corresponds to the situation which *iv* and *v* change sign for $Q_c = Q_p$, and its value was derived in a previous paper [12]. In conclusion, in those cases where $K > K_c^2$, Q_p attains its minimum value at the symmetric point. The higher the value of one of the catalytic constants (the product $K_{12}K_{21}$ remaining constant), the higher is the value of Q_p. In addition, $Q_{hc} = Q_p$ for $K > K_c^2$. In the case $K < K_c^2$, Q_p attains its maximum value when $K_{12} = K_{21} = \sqrt{K}$, and in this situation $Q_{hc} = Q_c$ for the entire range of possible values of K_{12} and K_{21}. These aspects are shown in fig. 3a–c where the dependence of the Q_p, Q_c and α^p values (α^p being the α value at Q_p) on the K_{21} value is represented for $K > K_c^2$, $K = K_c^2$ and $K < K_c^2$, respectively.

The system tends to solution *ii* as $K_{12} \to 0$ and $K_{21} \to \infty$, and to solution *iii* in the opposite case, i.e., $K_{21} \to \infty$ and $K_{12} \to 0$. In both cases the Q_p value becomes identical to the Q_c value. As one of the quasispecies shows no catalytic properties at all, no hypercycle can exist. In fig. 4 bifurcation diagrams for several K_{12} values are shown, and in panel the above-mentioned limit case can be observed.

4.1.2. *$K_{12} + K_{21} = K$ (constant)*

In this case the point of symmetry will correspond to $K_{12} = K_{21} = K/2$. Following arguments

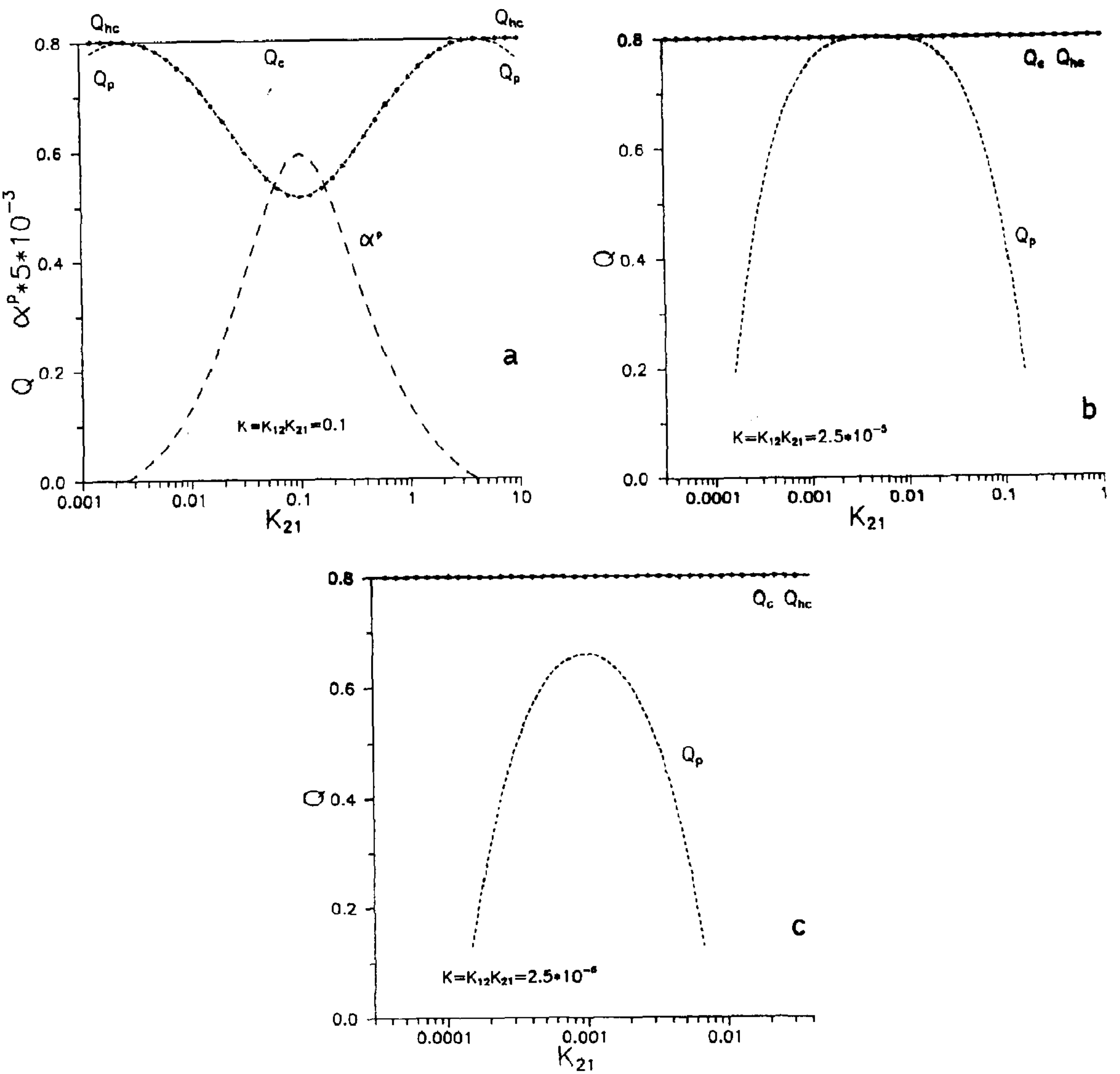

Fig. 3. Q_p(------) and Q_c (———) as a function of K_{21}, the product $K_{12}K_{21}$ being constant (K). Values of the parameters: $A_1 = A_2 = 1$, $A_i = 0.8$, $N = 100$ and (a) $K > K_c^2$ ($K = 0.1$); (b) $K = K_c^2$ ($K = 2.5\times10^{-5}$); and (c) $K < K_c^2$ ($K = 2.5\times10^{-6}$). The value of α_1^P is also represented (– – – – – –). In cases (b and c) α_1^P is negative in the overall range of K_{21} values. Q_{hc} has been drawn over (* * *).

similar to those in the previous case, it is possible to demonstrate that for $K_{12} = K_{21}$ the Q_p value is a minimum when $K > 2K_c$ and a maximum when $K < 2K_c$. In the extreme situation in which $K_{12} = 0$ and $K_{21} = K$ solution *ii* appears and the symmetrical one *iii* when $K_{21} = 0$ and $K_{12} = K$.

Fig. 5 shows the dependence of the Q_p, Q_c and α^P values on the K_{12} value for different K values.

4.1.3. K_{12} = constant; $0 < K_{21} < \infty$

A graph of Q_p, Q_c and α^P values vs the K_{21} value with K_{12} held constant is shown in fig. 6. Two different regions appear. Below a certain K_{21} critical value $[(K_{21})_c]$, α^P is negative. Thus, for K_{21} ranging from 0 to $(K_{21})_c$, $Q_{hc} = Q_c$. Beyond $(K_{21})_c$, as the K_{21} value increases, the Q_p value decreases. Q_p tends to a limit as $K_{21} \to \infty$. The value of this limit can be derived from eq. 9, and the following expression obtained:

$$\lim_{K_{21}\to\infty} Q_p = \frac{2\sqrt{A_i(A+NK_{12})}-(A+A_i)}{NK_{12}} \qquad (19)$$

4.2. Influence of the parameter values on the bifurcation diagram as $b \neq 0$

In this case plane $\mathscr{A}$, which contains solutions *iv* and *v*, makes a dihedral angle of 45° with both the (α_1,Q) and (α_2,Q) plane, but with a displacement from the Q axis determined by the values of parameters A_1 and A_2. This can be deduced from eq. 15. The general view of the bifurcation diagram will be similar to that shown in fig. 2b. Q_{c1} and Q_{c2} will have different values, because $A_1 \neq A_2$, and Q_n will coincide with neither of the two above-mentioned critical values of Q. Furthermore, depending on the values of the parameters A_1, A_2, K_{12} and K_{21}, the Q_{hc} value will become that of either Q_p or Q_n.

As can be seen, in fig. 2b several critical Q values appear (Q_p, Q_{c1}, Q_n and Q_{c2}) which are bifurcation points. As the parameter values are changed the relative positions of the critical values of Q also change, and different bifurcation di-

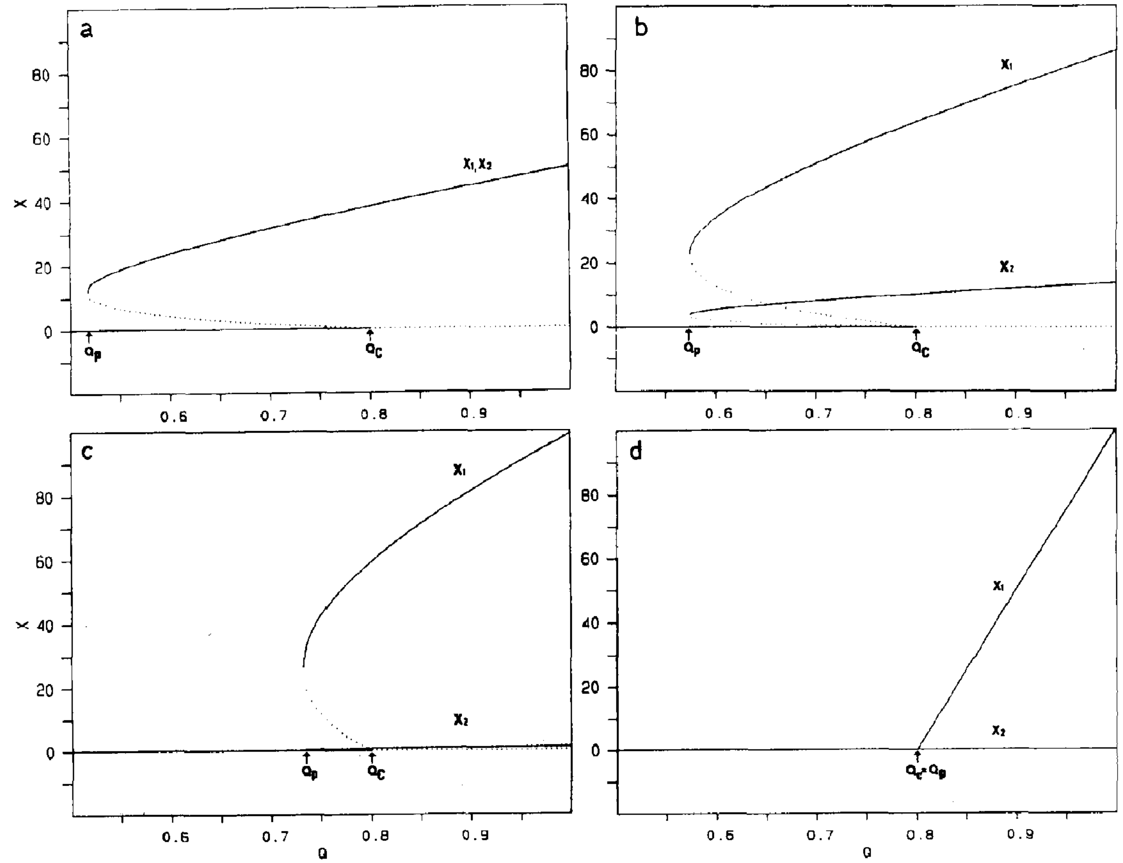

Fig. 4. Bifurcation diagram shown as a Q function when $K_{12}K_{21} = K$ (constant) for different values of K_{12}. The projections of the plane $\mathscr{A}$ onto both plane X_1Q and X_2Q are represented. Continuous and dashed lines represent stable and unstable steady states, respectively. Arrows indicate the Q critical values. Parameter values: $A_1 = A_2 = 1$, $A_i = 0.8$, $N = 100$, $K = 0.01$ and K_{12} equal to 0.1, 0.04, 0.01 and 0.0001 in cases (a–d), respectively.

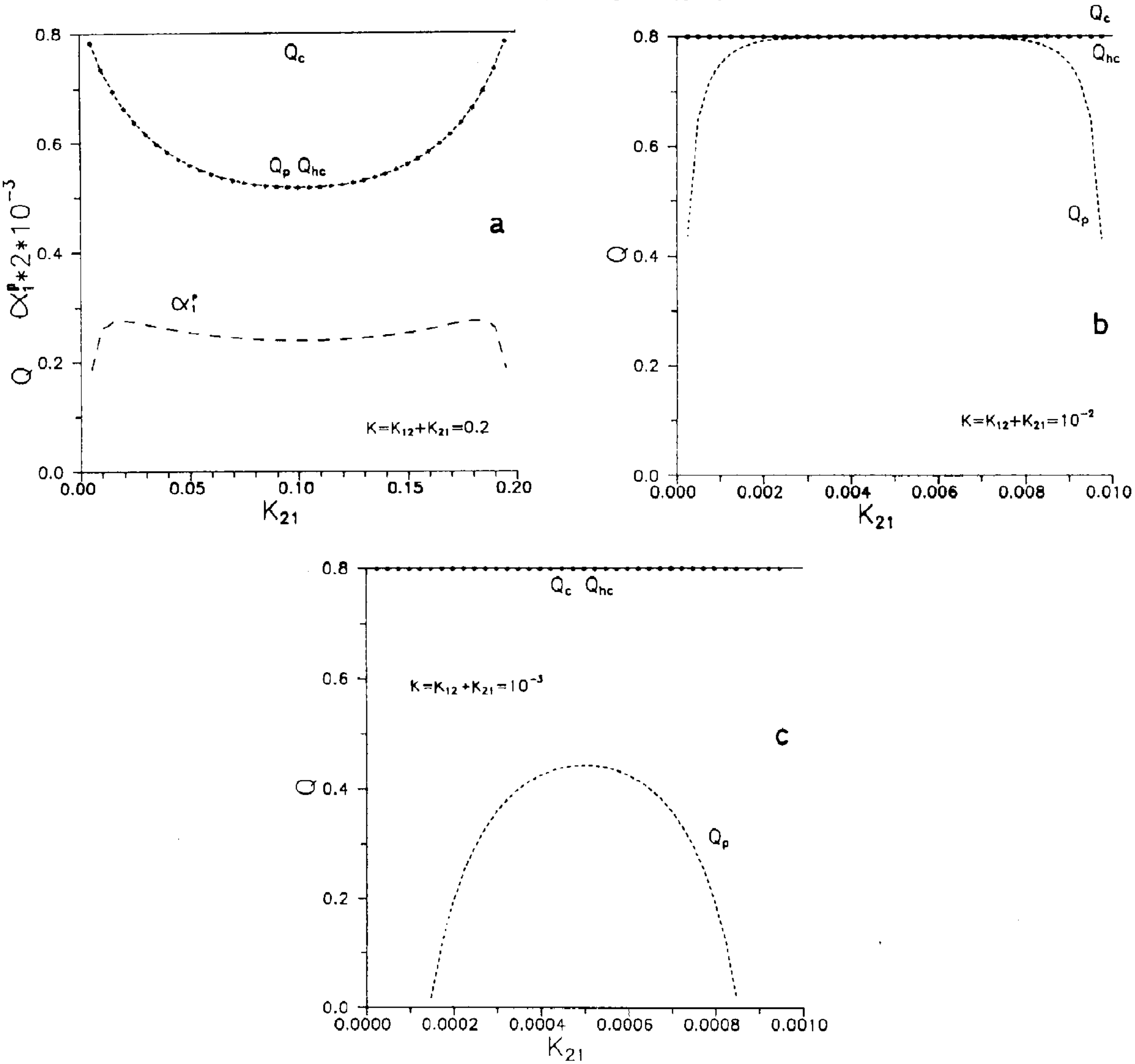

Fig. 5. Similar representation to those of fig. 3 for the case when the sum $K_{12} + K_{21}$ is maintained constant (K)-(a) $K > 2K_c$ $(K = 0.2)$; (b) $K = 2K_c$ $(K = 10^{-2})$ and (c) $K < 2K_c$ $(K = 10^{-3})$. The remaining parameter values are the same as those in fig. 3.

agrams and dynamic behavior are obtained from different sets of parameter values. The bifurcation diagrams can be classified in three main groups:

(1) Hysteretic behavior and *random replication* attractor. This situation appears when both α_1^p and α_2^p values are positive and the Q critical values obey the relationship $Q_p < \min\{Q_{c1}, Q_{c2}\} \leqslant Q_n$. Fig. 7a shows such a bifurcation diagram. As can be observed $Q_{hc} = Q_p$, i.e., the critical value of Q at which the stable hypercyclic organization (solution v) will arise, coincides with the Q_p value. For Q values ranging between Q_p and Q_n, bistability appears. The stationary state v is one of the attractors. However, another attractor can be either the random replication state $(Q_p < Q < \min\{Q_{c1}, Q_{c2}\})$ or one of the quasispecies $(\min\{Q_{c1}, Q_{c2}\} < Q < Q_n)$. When $Q > Q_n$ only one attractor appears: the stationary state v.

(2) Hysteretic behavior and quasispecies attractor.

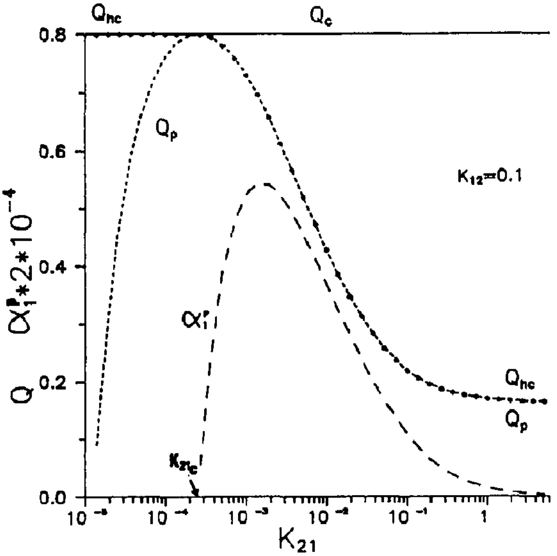

Fig. 6. Similar representation to those of fig. 3 for the case when $K_{12} = K$ (constant) and K_{21} ranging from 0 to ∞. The remaining parameter values are the same as those in fig. 3.

When both α_1^p and α_2^p values are positive and the order of the critical Q values is $\min\{Q_{c1}, Q_{c2}\} < Q_p < Q_n$, there are zones in the bifurcation diagram where the quasispecies appears as the only attractor. Fig. 7b shows such a bifurcation diagram. In these cases $Q_{hc} = Q_p$. As can be seen from this diagram, as Q decreases slightly below Q_{hc} an error catastrophe does not appear and the attractor is a quasispecies.

In both cases 1 and 2 hysteretic behavior can be deduced from the shape of their bifurcation diagrams.

(3) Elastic behavior and quasispecies attractor: α_1^p or $\alpha_2^p < 0$. In this case $Q_{hc} = Q_n$, as shown by fig. 7c and hysteretic behavior does not appear.

Eq. 15 shows that as the independent term b

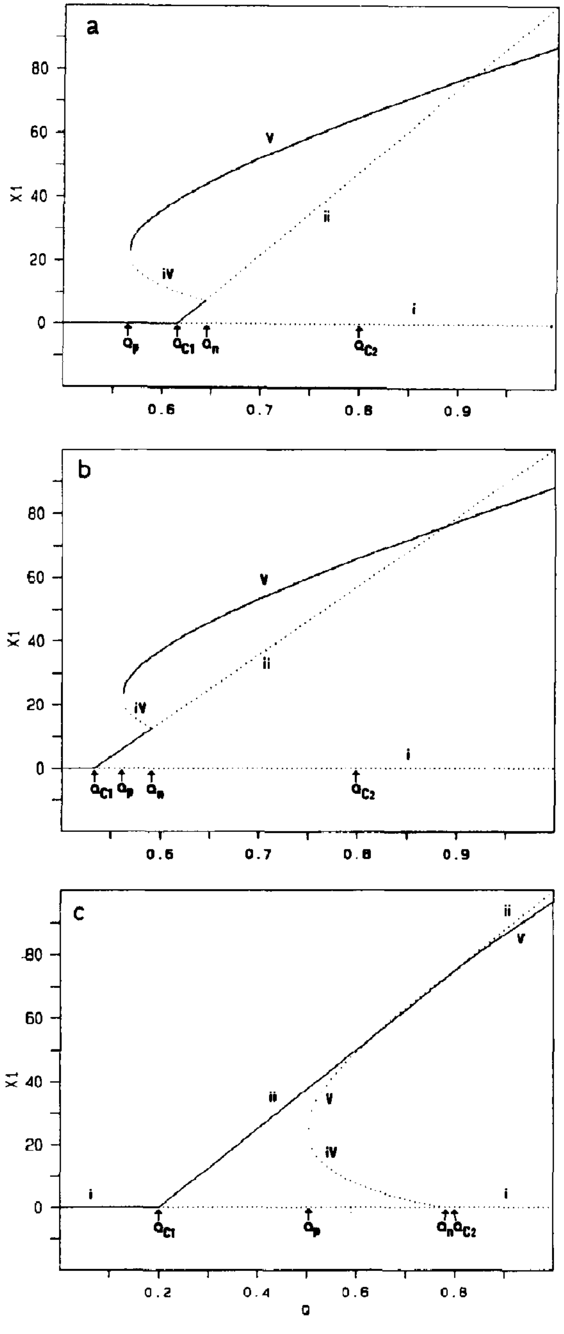

Fig. 7. Bifurcation diagrams shown as a Q function for the totally asymmetric case ($A_1 \neq A_2$ and $K_{12} \neq K_{21}$). Projection of plane $\mathscr{A}$ onto plane (Q, X_1) is shown. Also, the steady state *ii* lying in the plane (Q, X_1) and steady state *i* are plotted. Continuous and dashed lines represent stable and unstable steady states, respectively. Arrows indicate the Q critical values. Parameter values: $A_2 = 1$, $A_i = 0.8$, $K_{12} = 0.04$, $K_{21} = 0.25$, $N = 100$ and A_1 is equal to 1.3, 1.8 and 4.0 in cases (a–c), respectively.

remains constant, the plane $\mathcal{A}$, which contains the steady states which imply the coexistence of the two quasispecies (i.e., states *iv* and *v*), neither shifts nor rotates, although the different parameters expressed in that term do change their values. We have studied the behavior of the system for constant b much as in section 4.1. For all of the cases under consideration here, the values of the terms b, A_2 and A_i have been taken to be 100, 1 and 0.8, respectively. We will try to identify the different behaviors that appear as a consequence of the variation of K_{12} and K_{21} values.

4.2.1. $K_{12}K_{21} = K$ (constant)

Fig. 8a shows the Q_{c1}, Q_{c2}, Q_n and Q_p values for $K = 0.01$ as the K_{21} value changes. As can be

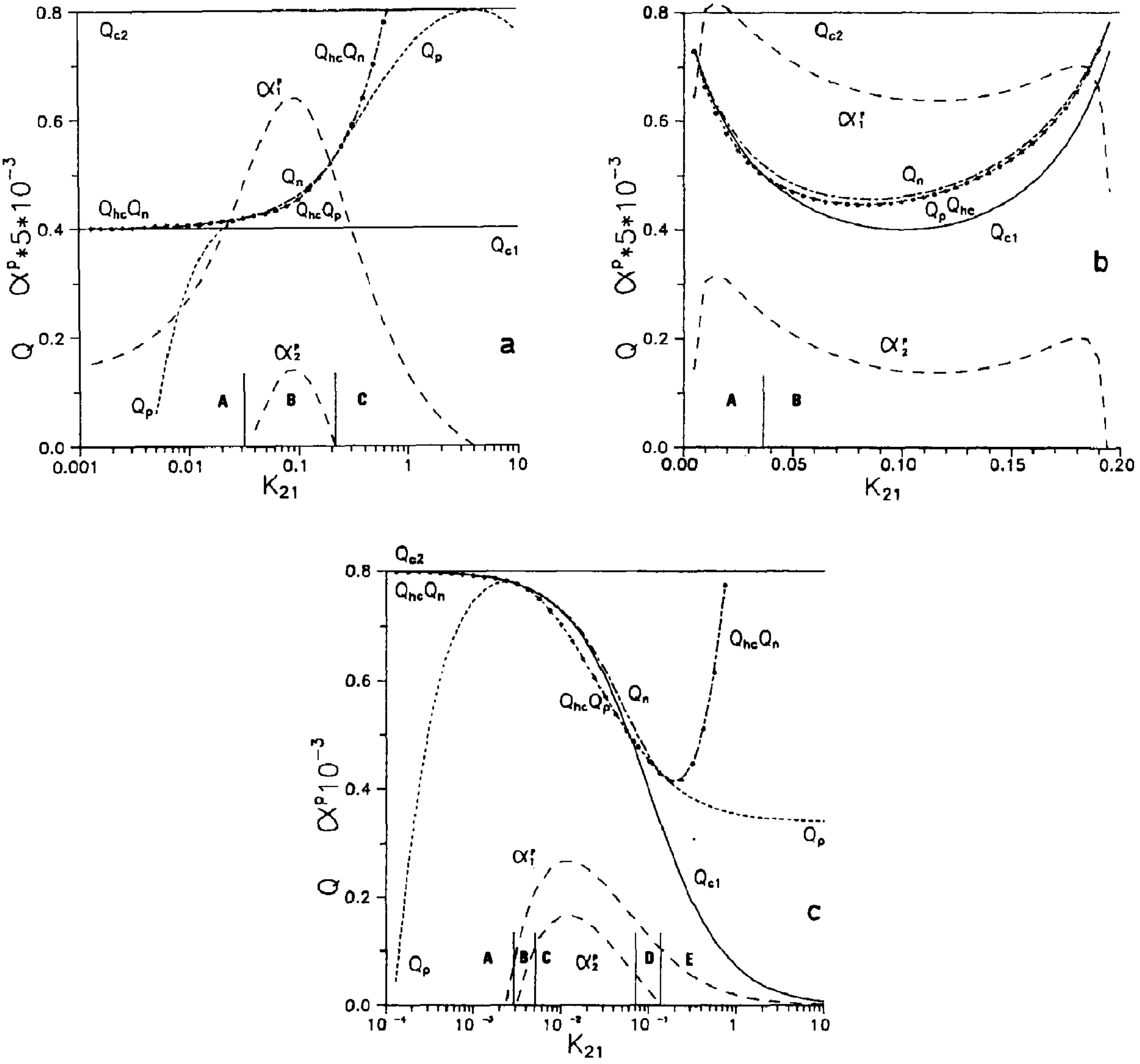

Fig. 8. Similar representation to those of fig. 3 for the totally asymmetric case ($A_1 \neq A_2$ and $K_{12} \neq K_{21}$). Q_n is also plotted (-····-). In all the cases $b=100$, $N=100$, $A_2=1$ and $A_i=0.8$. (a) $K_{12}K_{21}$ = constant ($K=0.01$) and $A_1=2$; (b) $K_{12}+K_{21}$ = constant ($K=0.2$); (c) K_{12} = constant ($K=0.1$).

seen in fig. 8, three different regions appear, labeled A–C. Obviously, at the point where the different lines represented in the figure intersect a change in the behavior of the system will occur.

In region A $\alpha_2^{\mathrm{p}} < 0$, so this region corresponds to case 3 mentioned above. Thus, $Q_{\mathrm{hc}} = Q_{\mathrm{n}}$, and hysteretic behavior does not appear.

Zone B corresponds to case 2; i.e., both α_1^{p} and α_2^{p} values are positive and $Q_{\mathrm{c1}} < Q_{\mathrm{p}} < Q_{\mathrm{n}} < Q_{\mathrm{c2}}$. $Q_{\mathrm{hc}} = Q_{\mathrm{p}}$ and hysteretic behavior may arise in this situation. For Q values ranging between Q_{c1} and Q_{p} the stable state corresponds to the stationary state $i(\alpha_1^0 \neq 0,\ \alpha_2^0 = 0)$, i.e., quasispecies I_1. Thus, the extinction of the hypercycle for these Q values implies not the error catastrophe, but the evolution of the system to a quasispecies distribution. Finally, zone C corresponds to state 3. Q_{hc} is again equal to Q_{n} and, in general, a phenomenology similar to those observed in zone A is obtained.

As clear from fig. 8, the symmetry of the system with respect to K_{12} and K_{21} observed when $A_1 = A_2$ (section 4.1 and fig. 3) has been lost. This can be attributed to unequal growth promotion values which are in turn due to unequal amplification factor values.

4.2.2. $K_{12} + K_{21}$ = constant (0.2)

In this case, as K_{12} or K_{21} are changed the A_1 value must change in order to maintain the b value constant. Fig. 8b shows the critical Q values as a function of the K_{21} values. In the figure, two main regions appear, labeled A and B. Here too, the symmetry of the system with respect to the K_{12} and K_{21} values is lost for much the same reason as in the previous case. In regions A and B the system displays behavior similar to that of the previously described states 1 and 2, respectively. Hysteretic behavior is obtained for a wide range of K_{21} values, though for Q values ranging between Q_{c1} and Q_{p} the system evolves either to the random replication attractor or to the quasispecies i, depending on the K_{21} values.

4.2.3. K_{12} = constant (0.1)

In this case both K_{21} and A_1 values have been changed in order to maintain b constant. Five different zones appear (A–E), as shown in fig. 8c. These zones correspond to states 3, 2, 1, 2 and 3, respectively, and exhibit the typical behavior of these states.

5. Discussion

A two-membered hypercycle formed by self-replicative error-prone species has been previously studied using both deterministic and stochastic techniques [12,14,15]. In that model two different but concurrent terms contribute to the growth of both species: the cross-catalytic activity term and the self-replication one.

Thus, the model assumed two hierarchical levels of organization corresponding to the quasispecies and hypercycle. However, the model was symmetric with respect to these two organization levels, i.e., $K_{12} = K_{21} = K$ and $A_1 = A_2 = A$. The bifurcation diagrams obtained from this model always displayed a range of Q values at which the hypercycle was stable. On the other hand, the stationary states that implied the existence of only one quasispecies were unstable, these steady states being saddle points. Furthermore, a region of bistability appeared, with one attractor corresponding to the hypercycle and the other to the random replication attractor. As was discussed there, the only effect of varying the K value was to shift the error threshold. A K critical value (K_{c}) existed below which the bistability zone disappeared, and the error threshold of the hypercycle coincided with those of the quasispecies. However, even for $K < K_{\mathrm{c}}$, the hypercycle was stable for Q values beyond the error threshold, while the quasispecies was not.

In this paper we have studied a model that is similar to that mentioned above, but in which asymmetry in both the catalytic constant ($K_{12} \neq K_{21}$) and amplification factor ($A_1 \neq A_2$) values has been included. Whereas the existence of non-catalyzed self-replication of molecules with asymmetric amplification factor values leads to competitive behavior among them, hypercyclic organization of species leads to their cooperative and non-competitive growth.

Perhaps a brief discussion of the two limiting cases would be in order: the pure hypercycle case,

$A_1 = A_2 = A_i = 0$, and the pure selection case, $K_12 = K_{21} = 0$. In the first one, there is no competition between the species I_1 and I_2 or between the error tail and the hypercycle. As can be easily seen from eq. 8, when $A_1 = A_2 = A_i = 0$ the value of one of the two coexistence-implying steady states is zero and unstable, and the other is positive and stable in the overall range of Q values, only vanishing at $Q = 0$. This implies that no kind of error threshold or bistability appears in the bifurcation diagram. Thus, bistability appears as a consequence of the terms expressing the uncatalyzed replication of the molecules. In the second case the system can be reduced to a quasispecies, and similar conclusions to those pointed out by Eigen and Schuster [1] can be deduced.

When asymmetry does not exist, as was studied in previous papers mentioned [12,14,15], the competitive properties have no effect on the overall properties of the system, because of the quality between the amplification factor values. However, as can be deduced from the present results, the existence of an asymmetry in the A values has consequences for the stability and concentration of the different steady states at certain Q values.

In section 4.1 we have exclusively studied the influence of the K values' asymmetry on the bifurcation diagram. The results thus obtained are similar to those previously described for the symmetric model: similar bifurcation points and overall behavior (region of bistability, hysteretic behavior, etc.). Two new facts did emerge:

(1) K_{12} and K_{21} have a scale factor effect on the steady-state concentration of both quasispecies. From a deterministic point of view this fact is irrelevant, because even with small concentrations of one of the species hypercyclic organization is ensured for certain Q values. However, from a stochastic point of view the internal fluctuations must be critical because they could lead to the disappearance of these species at lower concentration and thereby destroy the organization. This study must be carried out.

(2) As a consequence of the inequality $K_{12} \neq K_{21}$, there is a shift in the Q_p and Q_{hc} values. The more asymmetric the system, the higher the Q_{hc} value and error threshold.

Now, the higher the Q_{hc} value the lower the critical size of the molecules. So, asymmetry becomes disadvantageous for the accumulation of information. The disadvantage is not only with respect to the critical size of the molecules but also to the selective advantage of the system. It is not difficult to demonstrate that as the asymmetry of a hypercycle increases, the attraction basin of this hypercycle when competing with others decreases. The selective properties of a dynamic system are contained in the growth equations with no constraint, i.e., when $\phi_0 = 0$ in eq. 2. As is well known in the case of hypercycles, the integration of these equations yields a hyperbolic growth with an *explosion* of the population at a critical time, t_c [1]. The lower the t_c value, the larger is the attractor basin of that hypercycle when competing with others. If only the catalytic properties of the molecules are considered (setting the amplification values equal to zero), t_c can be evaluated as a function of the catalytic constants. When the system starts from initial conditions corresponding to those of an equillibrated hypercycle (where the ratios of concentrations of the different species composing the hypercycle are equal to those of the stationary state), t_c can be expressed as follows:

$$t_c = \frac{\Sigma_i \frac{1}{K_i}}{C_0} \tag{20}$$

C_0 being the initial concentration of the equilibrated hypercycle. In the present case (hypercycle formed by two quasispecies 1 and 2) we have:

$$t_c = \frac{\frac{1}{K_{12}} + \frac{1}{K_{21}}}{C_0} \tag{21}$$

If we assume either $K_{12}K_{21} = K$ (constant) or $K_{12} + K_{21} = K$ (constant) the existence of a minimum in the t_c value corresponding to $K_{12} = K_{21}$ can be demonstrated. In other words, the symmetrical situation corresponds to the minimum t_c value, i.e., the situation with a larger attractor basin. Fig. 9 shows the simplex of two hypercycles with equal value of $K_{12}K_{21} = K_{34}K_{43} = K$, symmetric (that formed by species I_1 and I_2)

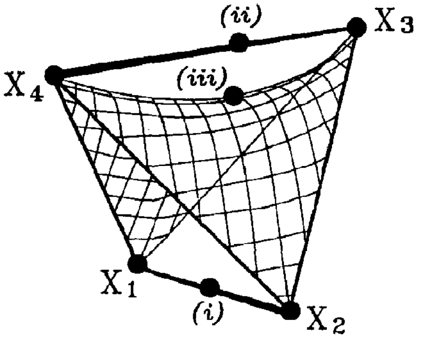

Fig. 9. Simplex of four free-error self-replicative species. Species I_1 and I_2 form a symmetrical hypercycle ($K_{12}=K_{21}$) and species I_3 and I_4 an asymmetrical one ($K_{34}\neq K_{43}$); but $K_{12}K_{21}=K_{34}K_{43}=K\approx 0.01$ ($K_{34}=0.05$ and $K_{43}=0.2$). (*i–iii*) are the steady states corresponding to the symmetrical hypercycle, the assymetrical one and the coexistence of both hypercycle, respectively. $A_1=A_2=A_3=A_4=1$; $N=100$.

and asymmetric (that formed by species I_3 and I_4), respectively. In this case an error-free self-replication ($Q=1$) has been considered. The separatrix surface, which contains an unstable saddle point-like stationary state implying the coexistence of both hypercycles, is also represented. As can be seen in the figure, the attraction basin of the symmetric hypercycle (1 and 2) is larger than that of the asymmetric one (3 and 4). More complex situations appear for $Q<1$.

The asymmetry in the amplification factor values has more significant consequences. For $A_1=A_2$ species 1 and 2 do not compete with each other, and any kind of hypercyclic organization arising will take hold. In the pure selection case, i.e., when $K_{12}=K_{21}=0$, the equality $A_1=A_2$ corresponds to the *selectivity neutral* case. From a deterministic point of view a degeneration in the value of the steady state appears, the final state of the system depending on the initial conditions. In this case a stochastic approach yields more accurate results.

Conversely, for $A_1\neq A_2$ the species will become competitive, and this competition in the hierarchical level of quasispecies can become preponderant over the cooperation that results as a consequence of the hypercyclic organization. This is seen in the bifurcation diagrams in fig. 7b and c, where at Q values ranging between Q_{c1} and Q_p in fig. 7b, and between Q_{c1} and Q_n in fig. 7c, the only stable stationary state corresponds to the quasispecies with higher amplification factor value. In these cases competition is more effective than cooperation. In the case $K_{12}=K_{21}$, a critical value of asymmetry $(A_1-A_2)_c$ can be easily evaluated as that value of (A_1-A_2) for which $Q_n=1$. Beyond this value of $(A_1-A_2)_c$ only the steady state corresponding to the quasispecies with larger A value will be stable for certain Q values, while that corresponding to the hypercycle will never be stable. An asymmetry in the A values implies a non-zero b parameter value in eq. 15. As the maximum value that any variable under the CP constraint can reach is N, this implies a restriction on the b values at which the hypercycle can exist. From eq. 7 the range of values at which the hypercycle exists can be derived:

$$-NK_{12}\leqslant A_1-A_2\leqslant NK_{21} \tag{22}$$

two critical A_1-A_2 values arising, ΔA_{c1} and ΔA_{c2}:

$$\Delta A_{c1}=NK_{21} \tag{23}$$

$$\Delta A_{c2}=-NK_{12} \tag{24}$$

From these equalities two main conclusions can be pointed out:

(1) The superiority of the competitive properties of the quasispecies with respect to the cooperative properties of the hypercycle does not depend on the absolute values of the amplification factor, but rather on the difference between them.

(2) The asymmetry of the K_{jk} values has a major effect on the way the hypercyclic organization can be destroyed as a result of competition between the quasispecies composing the hypercycle. If $K_{12}\gg K_{21}\approx 0$, a slight increase of the A_1 value over that of A_2 can destroy such organization. The converse is not true, i.e., the A_2 value can become much larger than the A_1 value without the hypercycle breaking up.

Could the hypercycle in some way benefit from asymmetry in the A values? The possibility of such a case occurring when $K_{12}<K_{21}$ and $A_2>A_1$ could be reasoned. This situation is represented in fig. 10. As a first approach, asymmetry in the K

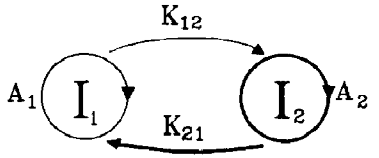

Fig. 10. Elementary hypercycle with $K_{21} > K_{12}$ and $A_2 > A_1$.

values will decrease the concentration of species 1, due to the above-mentioned scale factor. On the other hand, species 1 is more competitive than 2, and thus a greater concentration of species 1 will be obtained. However, asymmetry does not favor those species, as can be seen in fig. 8a. In fig. 8, $A_1 > A_2$ and the different Q critical values are plotted vs the K_{21} value, with $K_{12}K_{21} = K$(constant). As demonstrated in the figure, beyond the symmetric K_{21} value larger asymmetry in the K values implies larger Q_{hc} values. Undoubtedly, these properties must be important in the evolutionary and selective strategies of hypercycles, because as they became nucleated the molecules that compose them should have non-zero productivity values $(A_i - D_i)$, and thus the hypercyclic and quasispecies properties are superimposed.

Two main conclusions can be drawn from the present study:

(1) Regarding the self-replication level, a hypercycle formed by two quasispecies with a significant difference in their self-replicative terms (i.e., with asymmetric amplification factor values) will be displaced by a well-balanced hypercycle (i.e., those formed by two quasispecies with similar dynamics).

(2) Regarding the hypercycle dynamics itself, once such an organization is established only an increase in its symmetric cross-catalytic behavior will enhance its efficiency.

As has been established in the results shown herein the hypercycle can never benefit from selective advantages that imply an increase in the competition of the elements that compose it. Thus, the hypercycle will tend to maintain symmetry in the catalytic properties as well as in the non-catalyzed self-reproductive ones of the different species involved.

Acknowledgments

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