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SELECTION AND SELF-ORGANIZATION OF SELF-REPRODUCING MACROMOLECULES UNDER THE CONSTRAINT OF CONSTANT FLUX

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We investigate the dynamic behavior of a set of self-reproducing macromolecules (e.g., polynucleotides) under conditions such that the fluxes of all monomer units into the system are kept constant. Such conditions might prevail in an evolution reactor or in certain naturally occurring situations. A general set of equations is developed to describe the behavior of both the macromolecule and the monomer concentrations. The question of how the rate of macromolecule synthesis varies with the monomer levels is discussed briefly. With the help of several physically reasonable approximations, we obtain an exact solution for a simplified constant flux system. Comparison with the corresponding system under the constraint of constant overall organization reveals important similarities, most notably in the existence and composition of quasispecies. Given the same set of physical and chemical parameters, a system subject to constant flux will always evolve toward selective equilibrium more slowly than under the constraint of constant organization.

1. Introduction

An understanding of the selective behavior of a set of self-replicating macromolecular species, such as RNA or DNA, in an environment which supplies resources in limited quantity is crucial to the study of the origin and evolution of life.

A set of equations suggested in an earlier paper [1] has given rise to a number of useful ideas about the selection and development of self-organization in such systems [2–5]. Relevant experimental work [6,7] has lent support to several of these notions, and offers promise of further testing of many of the hypotheses generated by the theory.

In specifying the manner in which the supply of resources (specifically, energy-rich monomers) for macromolecular synthesis is constrained, two natural choices present themselves [1]. The first, which in thermodynamic terms [8] corresponds to a condition of constant forces in the system, is the constraint of constant overall organization [CO] – i.e., the requirement that the fluxes of species in and out of the system be adjusted so that all monomer concentrations are buffered and so that the sum of the concentrations of macromolecules is also held fixed. The level of organization, i.e., the ratio of organized (polymerized) to unorganized (monomer) material is thus held constant. Such a constraint is very nearly maintained in the serial dilution experiments with Qβ-replicase first carried out by Speigelman [6].

The alternative selection constraint is that of constant fluxes [CF] of all monomeric species into the system. Experimentally, such a condition might be the natural one in an evolution reactor [9] in which monomers are fed into the system to polymerize in the presence of suitable enzymes.

The conditions under which evolution occurred in nature are, of course, far more complex than either of the above pure constraints. Nevertheless, elements of both should have come into play. Some monomer levels may well have been effectively buffered, either because the monomer was present in great excess, or because the other reactions which produced and consumed it were considerably faster than the incorporation of the monomer into the macromolecular species.

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Other monomers may have been produced at an essentially constant rate under the influence of a fixed (or effectively infinite) level of precursors and a constant (on the appropriate time scale) influx of solar energy. Knowing the results for both the CO and the CF constraint we may estimate more reliably the results for systems under natural conditions.

The selection equations under the CO constraint have been quite thoroughly investigated, with fruitful results. Exact solutions have been obtained for a variety of systems [1,2,4]. On the other hand, the CF constraint has been rather less closely studied. Some qualitative results as well as an exact, though not explicit solution for the case of two species have been given in an earlier paper [1]. Tyson [10] offers some enlightening insights into CF systems in the absence of mutation by examining the nature and stability of their steady states under a variety of conditions, including compartmentalization of the species.

Here we shall consider selection under constant fluxes more closely. We first formulate the equations quite generally. These equations turn out to be rather formidable mathematically, and, after a brief discussion, we suggest some reasonable simplifications which render the problem more tractable. We then obtain an exact solution of the modified problem and compare some of its features with those of the corresponding CO system.

2. General formulation

2.1. The equations

Our system will consist of k macromolecular species X_i, $i = 1, 2 \ldots k$ of concentration x_i which are formed from l monomolecular precursors M_q, $q = 1, 2, \ldots l$ having the concentrations m_q. For example, if the macromolecules are polynucleotides, the monomers M_q are the four nucleosidetriphosphates ATP, UTP, GTP and CTP. Let the number of units of M_q in species X_i be n_{qi}. Generalizing somewhat the CF equations of ref. [1], we may write

$$\dot{x}_i = (A_i Q_i F_{ii}(m) - D_i' - \phi_{0i})x_i + \sum_{j \neq i} w_{ij} F_{ij}(m) x_j , \qquad i = 1, 2, \ldots k , \tag{1}$$

where A_i is a phenomenological rate factor which may in general depend upon the x_j (but not on the m_q); for the present we shall assume all the A_i to be constant. Q_i is a copying quality factor, D_i' is the unimolecular rate constant for the decomposition of species X_i, ϕ_{0i} determines the flux of macromolecules out of the system, and w_{ij} is the rate constant for production of X_i by incorrect copying (mutation) of species X_j. The $F_{ij}(m)$ contain the dependence on monomer concentration of the rates of making species X_i on an X_j template. They will be discussed in more detail below.

We simplify the notation of eq. (1) somewhat by collecting all the production terms in a single matrix B defined by

$$B_{ij} = A_i Q_i \delta_{ij} + w_{ij}(1 - \delta_{ij}) , \tag{2}$$

δ_{ij} being the Kronecker symbol (i.e. $\delta_{ij} = 1$ for $i = j$ and $\delta_{ij} = 0$ for $i \neq j$).

The loss terms may also be grouped in a matrix D:

$$D_{ij} = (D_i' + \phi_{0i})\delta_{ij} . \tag{3}$$

Defining another matrix $\beta(m)$, the elements of which depend upon the monomer concentrations, we may write eq. (1) in matrix notation as

$$\dot{x} = (\beta(m) - D)x , \tag{4}$$

where

$$\beta_{ij}(m) = B_{ij} F_{ij}(m) . \tag{5}$$

The rate equations for the monomer concentrations are given by

$$\dot{m}_q = \Phi_q - \sum_{i,j} n_{qi} B_{ij} F_{ij}(m) x_j , \tag{6}$$

where Φ_q represents the (constant) flux of monomers M_q into the system. We assume that essentially all monomers are consumed by incorporation into macromolecules so that the flux of unincorporated monomers out of the system is negligible. Collecting the Φ_q in a vector $\boldsymbol{\Phi}$ and the n_{qi} in a matrix N, we may write eq. (6) as

$$\dot{m} = \boldsymbol{\Phi} - N\beta(m)x . \tag{7}$$

2.2. Steady states

The steady states of the system are obtained by

setting the right hand sides of eqs. (4) and (7) equal to zero. From eq. (7) we obtain

$$x^{ss} = \beta(m^{ss})^{-1} N^{-1} \Phi, \tag{8}$$

where the superscript ss denotes steady state. To obtain the steady state monomer concentrations m^{ss}, we use eq. (8) in eq. (4) and have after some manipulation

$$(D^{-1}N^{-1} - \beta^{-1}(m^{ss})N^{-1})\Phi = 0 . \tag{9}$$

Given the dependence of the rate terms $F_{ij}(m)$ on the monomer concentrations, eq. (9) constitutes a set of equations which may be solved to yield the steady state monomer levels which in turn provide the macromolecular concentrations x^{ss} via eq. (8). The nature of the $F_{ij}(m)$ is discussed below. Qualitatively, the solutions to eqs. (8) and (9) will be such that, at equilibrium, species X_i is favored whose composition n_{qi} most closely reflects the mix of incoming monomers Φ weighted by the rates of incorporation of the various monomers. The mechanism for bringing about this situation will be reflected in an increased rate of mutation toward species rich in the monomers which are fed in and incorporated fastest. That is, the *net* mutation rate $w_{ij}F_{ij}(m)$ terms are largest for species i containing large amounts of the abundant and/or rapidly incorporated monomers M_q. In effect, having the "right" composition under given flux conditions constitutes a selective advantage.

2.3. Dependence on monomer concentrations

Since little concrete experimental evidence exists for the dependence of the F_{ij} on the monomer levels, it seems unwise at this point to enter into a detailed study of eqs. (8) and (9). We should like, however, to point out some features of these terms which should hold rather generally. For template-directed, enzyme-assisted synthesis it seems likely that the rate-determining step in macromolecule formation will be chain elongation rather than nucleation or chain termination. We might expect the rate of successive elongation steps to be nearly independent of the detailed composition of the already formed chain and to depend primarily on the identity of the new monomer to be added. This dependence might be linear or of the Michaelis-Menten type. This line of reasoning suggests that the rate of formation of X_i should depend mainly upon its composition and much less strongly on the template X_j. Thus, roughly speaking, the terms $F_{ij}(m)$ should be independent of X_j

$$F_{ij}(m) = f_i(m) . \tag{10}$$

More specifically, let τ_i be the mean time required to form a macromolecule X_i. The above considerations suggest that

$$\tau_i \approx \sum_q n_{qi} t_q , \tag{11}$$

where t_q is the mean time required to add one unit of M_q to the growing chain. Note that with more detailed information about the composition of X_i (i.e., distribution of pairs of monomers), eq. (11) could be modified to take account of the dependence of elongation times on the identity of the last unit of the chain as well as the incoming unit. If the rate of elongation is linear in the monomer concentration, we have

$$t_q \approx 1/k_q m_q , \tag{12}$$

where k_q is the rate constant for adding an M_q unit to the chain. Corresponding expressions may easily be written for other elongation rate laws.

Inserting eq. (12) into eq. (11) we have

$$f_i(m) \approx \tau_i^{-1} \approx \left(\sum_q \frac{n_{qi}}{k_q m_q} \right)^{-1}$$

$$= \prod_q k_q m_q \Big/ \sum_q \left(n_{qi} \prod_{p \neq q} k_p m_p \right) , \tag{13}$$

Thus f_i is essentially a weighted harmonic mean of the products of monomer concentration and elongation rate, with the weighting factors being given by the macromolecule composition. Closer inspection of eq. (13) shows that, as expected, f_i will be largest for shorter macromolecules ($\Sigma_q n_{qi}$ small) and, for any fixed length of macromolecules, for those which have n_{qi} large when $k_q m_q$ is large.

3. A simplified system of equations

Even for the relatively simple form of the $F_{ij}(m)$ given by eqs. (10) and (13), solution of the general eqs. (4) and (6) constitutes an exceedingly difficult path toward elucidating the dynamic behavior of CF systems. Since we are primarily interested in qualitative insights, we offer in this section a few physically reason-

able simplifications which then allow for an exact solution of the resulting equations.

In most situations, the outward flux of polymer X_i will be proportional to its concentration, i.e., all the ϕ_{0i} in eq. (1) will be equal

$$\phi_{0i} = \phi_0 , \qquad i = 1, 2, \ldots k . \tag{14}$$

If, in addition, the decomposition rates D_i' do not differ greatly from one another and/or are considerably smaller than the flux rate ϕ_0

$$D_i' \ll \phi_0 , \tag{15}$$

we have, to a good approximation

$$D_{ii} = D_i' + \phi_0 = D , \qquad i = 1, 2, \ldots, n , \tag{16}$$

i.e., the matrix D of eq. (4) is a constant D times the identity matrix.

In a given experiment, all the species X_i are likely to be related to one another by mutation (as we approach equilibrium this statement becomes rigorously true), and most likely by modifications of no more than a small fraction of the total number of monomer units. Thus the percentage compositions of the X_i should not differ from one another by a great deal. In such a situation it is not unreasonable to approximate all of the terms $F_{ij}(m)$ by a single average term $F(m)$

$$F_{ij}(m) \approx F(m) , \qquad i, j = 1, 2, \ldots, k .$$

We further simplify the system by replacing the vector of monomer concentrations m by a single scalar variable m with scalar flux Φ, and the compositions n_{qi} by a single quantity n.

Eqs. (1) and (6) now become

$$\dot{x}_i = F(m) \sum_j B_{ij} x_j - D x_i , \qquad i = 1, 2, \ldots, k , \tag{17}$$

and

$$\dot{m} = \Phi - nF(m) \sum_{i,j} B_{ij} x_j , \tag{18}$$

with B_{ij} defined by eq. (2).

Conservation requires [1] that the factors A_i, Q_i and w_{ij} be related in such a way that

$$\sum_{ij} B_{ij} x_j = \sum_j A_j x_j , \tag{19}$$

so

$$\dot{m} = \phi - nF(m) \sum A_j x_j . \tag{20}$$

Eqs. (17) and (18) or (20) are the equations which, with one further restriction, we propose to solve for the species concentrations $x_i(t)$.

4. Solution of the equations

4.1. Quasi-species and trajectories

Let us write eq. (17) in matrix form as

$$\dot{\boldsymbol{x}} = F(m)\,\mathsf{B}\boldsymbol{x} - D\boldsymbol{x} , \tag{21}$$

and define a vector $\boldsymbol{y}$ by

$$\boldsymbol{x} = \boldsymbol{y}\, \mathrm{e}^{-Dt} . \tag{22}$$

Substituting eq. (22) in eq. (21), we obtain

$$\dot{\boldsymbol{y}} = F(m)\,\mathsf{B}\boldsymbol{y} . \tag{23}$$

Now, consider the matrix U which consists of the eigenvectors of B with associated matrix of eigenvalues λ, i.e.,

$$\mathsf{U}^{-1}\mathsf{B}\,\mathsf{U} = \lambda , \tag{24}$$

where

$$\lambda_{ij} = \lambda_i \delta_{ij} . \tag{25}$$

In scalar notation, for each i we have

$$\sum_j B_{ij} U_{jk} = \lambda_k U_{ik} . \tag{26}$$

Define another vector $\boldsymbol{z}$ by

$$\boldsymbol{y} = \mathsf{U}\boldsymbol{z} . \tag{27}$$

The variables $z_i \mathrm{e}^{-Dt}$, which are simply linear combinations of the x_i's, constitute our quasi-species. Substituting eq. (27) in eq. (23), multiplying by U^{-1} and using eq. (24), we can transform eq. (23) into

$$\dot{\boldsymbol{z}} = F(m)\lambda\boldsymbol{z} , \tag{28}$$

or

$$\dot{z}_i = F(m)\lambda_i z_i , \qquad i = 1, 2, \ldots k . \tag{29}$$

Since m is still a function of t, we cannot solve eqs. (29) without concomitantly obtaining a solution to eq. (20) written in terms of the z_i. We can, however,

generate the trajectories of the system in any $z_i - z_j$ plane. To do so, we simply divide eq. (29) by the corresponding equation for z_j. We have

$$\dot{z}_i/\dot{z}_j = \mathrm{d}z_i/\mathrm{d}z_j = \lambda_i z_i/\lambda_j z_j \,. \tag{30}$$

Eq. (30) is easily solved to yield

$$z_j/z_j(0) = (z_i/z_i(0))^{\lambda_j/\lambda_i} \,. \tag{31}$$

From eq. (31), given the initial conditions $z(0)$ (or equivalently $x(0)$) and the value of any one of the z_i at time t, we can immediately generate all the other $z_j(t)$. Eq. (18) can be transformed in terms of the z_j to

$$\dot{m} = \phi - nF(m) \sum_{ij} \lambda_j U_{ij} z_j \, \mathrm{e}^{-Dt} \,. \tag{32}$$

Using eq. (31), all z_j for $j \neq i$ may be eliminated from eq. (32) leaving a single first order equation in m and z_i, which, coupled with eq. (29) for z_i affords a system which is easily solved numerically for any given function $F(m)$. For an analytical solution, we require one further restriction.

4.2. The quasi-stationary case

We may expect that the unreacted monomer concentrations in the system will adjust themselves to the incoming flux rather more quickly than the distribution of information carriers will evolve to its final state. It thus seems to be a reasonable approximation [1] to assume that

$$\dot{m} \approx 0 \,. \tag{33}$$

If eq. (33) holds, then the total concentration of macromolecules

$$c = \sum_i x_i \,, \tag{34}$$

rapidly approaches its stationary value

$$\bar{c} = \Phi/nD \,, \tag{35}$$

for which the rate of introduction of the monomers required to make a polymer, Φ/n, just equals the rate D at which polymers leave the system. Addition of the k eqs. (17) and introduction of the condition (33) together with the definitions (34) and (35) leads to the following equation for c:

$$\dot{c}(t) = \Phi/n - Dc(t) \,, \tag{36}$$

which has the solution

$$c(t) = \bar{c} + (c(0) - \bar{c})\, \mathrm{e}^{-Dt} \,. \tag{37}$$

Let us now focus on a single quasi-species, say z_b, the one for which λ_b is largest. Using eq. (29) we may write

$$F(m) = \dot{z}_b/\lambda_b z_b \,, \tag{38}$$

and eq. (31) permits us to express all the z_j in eq. (32) in terms of z_b and the initial conditions. Making these substitutions, we obtain from eq. (32)

$$\dot{m} = \Phi - n \sum_{i,k} U_{ik} \frac{\lambda_k}{\lambda_b} \frac{z_k(0)}{(z_b(0))^{\lambda_k/\lambda_b}} \times (z_b)^{\lambda_k/\lambda_b - 1} \dot{z}_b \, \mathrm{e}^{-Dt} \,. \tag{39}$$

If we now invoke quasi-stationarity, eq. (33), we have an equation which may be integrated exactly to yield (after some rearrangement)

$$\frac{\Phi}{nD}(\mathrm{e}^{Dt} - 1) = \sum_{i,k} U_{ik} z_k(0) [(z_b/z_b(0))^{\lambda_k/\lambda_b} - 1] \,. \tag{40}$$

Noting that by virtue of eqs. (22), (27) and (34), we must have

$$\sum_{i,k} U_{ik} z_k(0) = \sum_i y_i(0) = \sum_i x_i(0) = c(0) \,, \tag{41}$$

we may rewrite eq. (40), using eq. (35), as

$$\sum_{i,k} U_{ik} z_k(0) (z_b(t)/z_b(0))^{\lambda_k/\lambda_b} = \bar{c}\, \mathrm{e}^{Dt} + (c(0) - \bar{c}) \,. \tag{42}$$

Eq. (42) constitutes a complete time dependent solution for $z_b(t)$. The other $z_j(t)$ may then be obtained via eq. (31).

4.3. Asymptotic behavior

From eq. (42) we see that as $t \to \infty$ the left hand side of eq. (42) must vary as e^{Dt}. Since we have chosen quasi species b so that $\lambda_k < \lambda_b$ if $k \neq b$, it is clear that at very long times eq. (31) requires that

$$z_b(t) \sim \mathrm{e}^{Dt} \,, \tag{43a}$$

$$z_j(t) \sim \exp(\lambda_j Dt/\lambda_b) \,. \tag{43b}$$

Thus the ratio

$$z_j(t)/z_b(t) \sim \exp[(\lambda_j/\lambda_b - 1)Dt] \to 0 \qquad \text{if } j \neq b \,, \tag{44}$$

as $t \to \infty$. That is, as in the CO case, only a single quasi species can survive in the long time limit. The ultimate population of any species X_i is thus given by

$$x_i(t) \to \sum_k U_{ik} z_k \, e^{-Dt} \to U_{ib} z_b(t) e^{-Dt} . \tag{45}$$

Since eqs. (42) and (44) imply that

$$z_b(t) \to \bar{c} \, e^{Dt} \Big/ \sum_j U_{jb} , \tag{46}$$

we have

$$x_i(t)/\bar{c} \to U_{ib} \Big/ \sum_j U_{jb} . \tag{47}$$

Thus, in the end, the relative concentration of species X_i is simply its relative contribution to the dominant quasispecies b. The same result is obtained from a steady state analysis; the only stable steady state of the system is found to correspond to eq. (47).

As long as the w_{ij} are small relative to the $A_i Q_i$, the perturbation expressions [1,2] are valid

$$\lambda_i \approx A_i Q_i + \sum_{j \neq i} \frac{w_{ij} w_{ji}}{A_i Q_i - A_j Q_j} , \tag{48}$$

$$U_{ij} \approx \delta_{ij} + w_{ij}/(A_j Q_j - A_i Q_i) . \tag{49}$$

Eq. (48) together with eq. (47) for the asymptotic behavior supports the earlier interpretation [1] of $W_i^F = A_i Q_i / D_i - 1$ as the selective value.

We should note that the fact that all the w_{ij} are non-negative insures that the components U_{ib} of the eigenvector corresponding to the dominant quasispecies are also non-negative [11], so our asymptotic solutions are physically meaningful. The eigenvectors corresponding to quasispecies with lower values of λ_i are not necessarily (and in fact, rarely, if ever – never if w_{ij} is symmetric) – composed only of non-negative elements.

5. A numerical example – constant flux versus constant organization

We consider here a numerical example in order to compare the relative rates of approach to equilibrium for the CF and CO constraints. We assume quasi-stationarity, and choose the following parameters:

$$k = 2, \quad D = 1, \quad \Phi = c(0) = \bar{c} = 10, \tag{50a}$$

$$A_1 = 5, \quad A_2 = 2, \quad Q_1 = Q_2 = 0.99,$$
$$w_{12} = 0.02, \quad w_{21} = 0.05, \quad F(m) = 1. \tag{50b}$$

The eigenvalues and eigenvectors of the matrix B (eqs. (2) and (24)) are then

$$\lambda = \begin{pmatrix} 4.95034 \\ 1.97966 \end{pmatrix}, \quad U = \begin{pmatrix} 0.983444 & -0.006734 \\ 0.016556 & 1.006739 \end{pmatrix}, \tag{51}$$

where we have normalized U so that

$$\sum_j U_{ji} = 1 , \qquad i = 1, 2 . \tag{52}$$

Note that $c(0)$ has been chosen so that the total concentration of macromolecules will stay fixed (eq. (37)) in order to facilitate comparison with the CO case. Thus

$$x_1(t) + x_2(t) = z_1(t) + z_2(t) = \bar{c} = 10 . \tag{53}$$

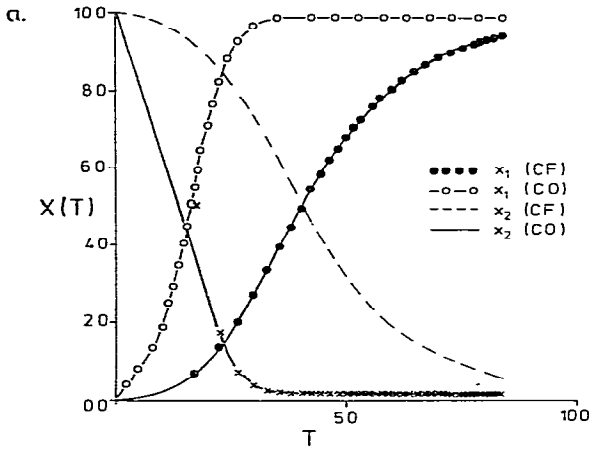
With the parameters chosen, eq. (53) holds, of course, for the CO case as well. The exact solutions under the constraint of constant organization are given by Jones et al. [2], and we note only that the eigenvectors U for the quasispecies are identical in the two cases, while the CO eigenvalues are

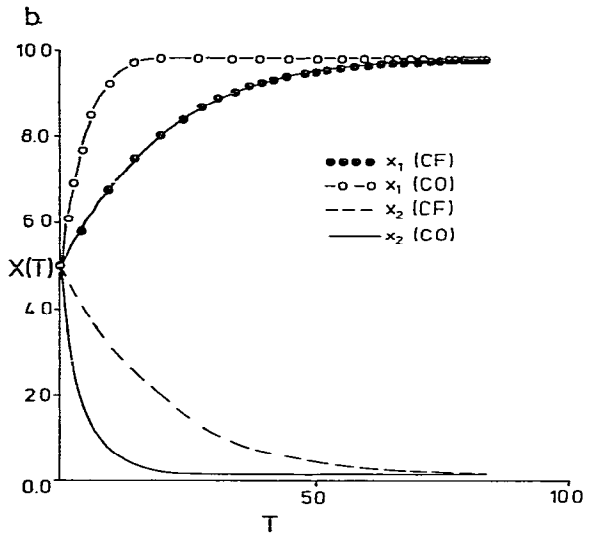
$$\mu = \begin{pmatrix} 3.950337 \\ 0.979663 \end{pmatrix} . \tag{54}$$

Note that the ratio of the eigenvalues is considerably larger in the CO case. This is a general feature which results from the fact that the selective value under constant organization depends on the difference between $A_i Q_i$ and D_i rather than upon their quotient as in the CF case. The equilibrium values of x_1 and x_2 are the same for the CF and CO cases, as they must be if the quasispecies are the same.

In fig. 1 we compare the rates of approach to equilibrium for the CF and CO constraints starting from several different initial conditions. If we had chosen the initial CF concentrations so that $x_1(0) + x_2(0) \neq \bar{c}$, the system would have taken even longer to reach equilibrium, since the total concentration would also have had to adjust itself. Nevertheless, in all cases, the CO system approaches its final state significantly more rapidly than the CF system. We may view this result in several ways:

a) Mathematically, the fact that $\mu_1/\mu_2 > \lambda_1/\lambda_2$





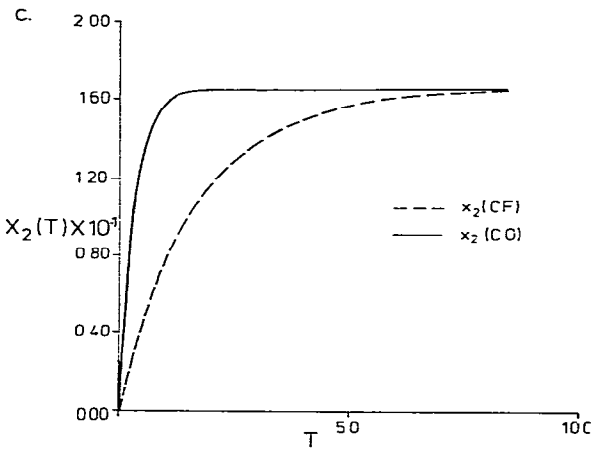


Fig. 1. Approach of a 2-species system to selective equilibrium. Parameters given by eq. (50) for both the CO and CF cases a) $x_1(0) = 0, x_2(0) = 10$. b) $x_1(0) = 5, x_2(0) = 5$. c) $x_1(0) = 10, x_2(0) = 0$. Equilibrium values $x_1(\infty) = U_{11} = 9.83444, x_2(\infty) = U_{12} = 0.16556$. In case c) only $x_2(t)$ is shown.

makes selection sharper in the CO case.

b) In both cases $\Sigma_i x_i$ is constant. The CF system has additional constraints, so it has less freedom to relax toward the final state.

c) The number of information carriers is fixed in both cases, but the CO system has an unlimited supply of starting material with which to seek its "optimum" state, while the CF supply is received at a constant rate Φ.

Thus we expect CO systems to be able to adapt more rapidly to changes in the environment. However, note that the final state reached by the system is the same in either case.

6. Discussion and conclusions

After presenting the selection equations under the constraint of constant flux, we have been able to obtain an exact solution within a set of physically reasonable approximations. This solution has revealed an important similarity, the usefulness of the quasispecies concept, between the CO and the CF cases, as well as the fact that CO systems are quicker to attain their selective ends.

The restriction to a single effective monomer concentration might be relaxed if a numerical solution were deemed sufficient. For nucleic acids with only

four different monomer types, numerical integration would be feasible given a relatively small number of competing macromolecules. We have only treated the case of linear autocatalytic replication, i.e., when all the A_i are independent of the x_j. If mutations are neglected, the problem is still soluble by the trajectory method if A_i is taken proportional to x_i to any power. Nothing unexpected results from assuming A_i proportional to x_i, at least in the absence of mutation. When mutations are present along with non-linear autocatalysis, the quasi-species transformation no longer succeeds in separating the variables.

It would be interesting to study both the evolution of CF systems and the form of the terms $F_{ij}(m)$ discussed in sect. 2.3. This latter objective might be achieved by using radioactively labeled monomers in a reactor containing a probe surrounded by a membrane permeable to monomers but not to polymers. Monitoring the monomer concentrations as well as the more easily detected rates of incorporation into macromolecules under different constant input fluxes should yield the dependence of macromolecule formation on the monomer concentrations.

Finally, we point out that the CF and CO cases constitute in a sense the two extreme cases of resource constraints. The fact that they result in such similar dynamics suggests that we may with some confidence apply the insights gained in studying such model systems to the consideration of selection and evolution under natural conditions where the constraints are considerably less well defined.

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