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Competition and Cooperation in Catalytic Selfreplication

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Abstract. It is shown that in a flow reactor, hypercyclic coupling of self-reproducing macromolecular species leads to cooperation, i.e. none of the concentrations will vanish. On the other hand, autocatalytic selfreproducing macromolecules usually compete, and the number of surving species increases with the total concentration. Both results are proved under very general assumptions concerning the growth rates.

Key words: Catalytic selfreplication – Concentration simplex – Dynamical systems – Flow reactor – Hypercycle

1. Introduction

Considering chemical kinetics as a whole, autocatalysis plays rather the role of an interesting curiosity than that of a central issue. In biological systems, in contrary, selfreplication is an obligatory feature. Molecular biology reveals the details of multiplication on the molecular level. Although our present knowledge of these mechanisms is far from being complete we have learned a lot already from various in vitro experiments on viral and bacterial replication. One can study the replication of biological macromolecules in simple idealized model systems (see section 2) which are accessible to straightforward kinetic analysis. From the theorist's point of view it seems interesting now to learn more about the basic features of selfreplicating systems. Some studies performed along these lines were dealing with the role of error propagation in template induced replication (Eigen, 1971; Thompson and McBride, 1974; Jones et al., 1976; Eigen and Schuster, 1977).

Selfreplicating elements usually compete with each other. An important question, therefore, concerns the conditions and mechanisms which lead to cooperation or, in other words, force the system to avoid Darwinian selection of the "fittest" species (Eigen, 1971; Eigen and Schuster, 1978; Schuster et al., 1978, 1979 a and b; Hofbauer et al., 1979). For the sake of simplicity the autocatalysis of a

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hypercyclic mechanism was modeled by product terms of power two in the differential equations. It has been shown that these product terms result as asymptotic rate laws from more elaborate mechanisms under certain conditions, in particular sufficiently low concentrations (Eigen et al., 1980).

In this paper we make an attempt to generalize our previous proofs in order to become independent of a specific form of the rate equations.

In a somewhat similar spirit we generalize and globalize certain results by Epstein (1979a) concerning autocatalytic species in a flow reactor. This author investigated systems where the growth rates decrease monotonicly with concentration.

2. The Flow Reactor

The dynamics of polynucleotide replication, in general, is very complicated and difficult to analyze. Thus, we have to search for a model system which is accessible both to theoretical analysis and experimental verification. The primary goal of such a device is to be seen in the creation of a constant environment whose parameters may be easily controlled. At the same time the number of variables such as pressure, temperature and concentrations of supplementary material has to be

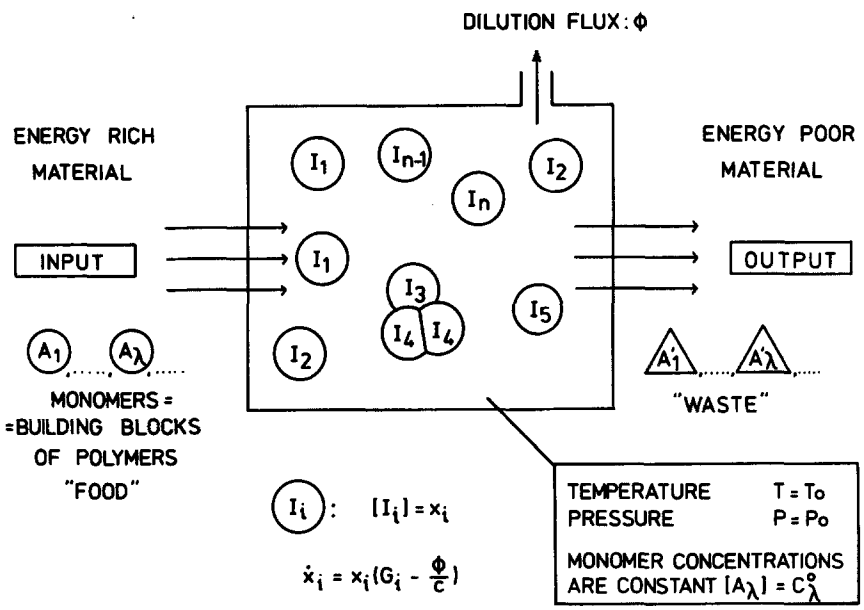


Fig. 1. The evolution reactor. This kind of flow reactor consists of a reaction vessel which allows for temperature and pressure control. Its walls are impermeable to the biological macromolecules, in particular to polynucleotides. Energy rich material ("food") is poured from the environment into the reactor. The degradation products ("waste") are removed steadily. Material transport is adjusted in such a way that food concentration is constant in the reactor. A dilution flux ϕ is installed in order to remove the excess of selfreplicative units produced by multiplication. The experimental verification of evolution reactors has been discussed extensively by Küppers (1979)

reduced to a minimum. The most simple and suitable system from the theorist's point of view is a kind of flow reactor shown in Fig. 1. The formal mathematics underlying chemical reactions in flow reactors has been derived by Feinberg and Horn (see e.g. Feinberg, 1977). As mentioned before we do not intend to discuss any particular mechanism for polynucleotide polymerization here, but attempt to generalize some common features of selfreplication. We shall simulate the whole replication process by an "over-all" single reaction step

$$I_i + \sum_{\lambda=1}^{m} \nu_{i\lambda} A_\lambda (+ I_j) \rightarrow 2I_i (+ I_j), \qquad i,j = 1,2,\ldots,n. \tag{2.1}$$

By I_i we denote an individual polynucleotide. A_λ are the activated building blocks, e.g. the nucleoside triphosphates ATP, UTP (TTP), GTP and CTP (ATP = adenosine 5′-triphosphate, UTP = uridine 5′-triphosphate, TTP = thymidine 5′-triphosphate, GTP = guanosine 5′-triphosphate, and CTP = cytidine 5′-triphosphate).

A first attempt to describe selfreplication under the conditions of a flow reactor has been made by Eigen (1971). It turned out to be useful to split the time dependence of the concentrations x_i into two contributions, a specific growth function and a global flux (Eigen and Schuster, 1978b). The differential equations then are of the following form:

$$\dot{x}_i = \Gamma_i - \frac{x_i}{c}\phi; \qquad i = 1,2,\ldots,n. \tag{2.2}$$

By Γ_i we denote the individual growth function for the polynucleotide I_i and ϕ is an adjustable global flux. We shall only consider the simplest case where $\phi = \sum_i \Gamma_i$. In this case we have

$$\sum_i \dot{x}_i = \sum_i \Gamma_i \left(1 - \frac{\sum_i x_i}{c}\right). \tag{2.3}$$

If $\sum_i \Gamma_i \geqslant 0$ then the total concentration $\sum_i x_i$ approaches the stationary value c. Thus, the orbits converge to the concentration simplex

$$S_n^c = \{(x_1,\ldots,x_n) \in R^n, x_i \geqslant 0, \sum x_i = c, i = 1,\ldots,n\}$$

which is invariant for (2.2). From now on we shall consider (2.2) restricted onto S_n^c and the stationary total concentration $\sum x_i = c$.

In the function Γ_i we subsume the mechanism of replication. Depending on the particular system to be considered these functions may vary from simple constants to highly complicated algebraic expressions involving all variables. A particular example which illustrates the meaning of this procedure is given below.

Let us assume a molecular mechanism as shown in Fig. 2. The formation of a binary complex precedes the replication of the molecule. Complex formation occurs reversibly whereas the synthetic reaction (2.4c) is an irreversible step. The variables, free concentrations of macromolecules and association complexes, are denoted by z_i and y_i respectively.[1] Then the total concentrations of macromolecules

[1] Indices are counted modulo n

COMPLEX FORMATION

$$I_{i-1} + I_i \xrightarrow{f_i} I_{i-1,i} \qquad (2\cdot4\,a)$$

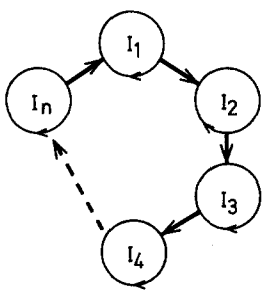
COMPLEX DISSOCIATION

$$I_{i-1,i} \xrightarrow{f_{-i}} I_{i-1} + I_i \qquad (2\cdot4\,b)$$

POLYMERIZATION

$$I_{i-1,i} + \sum_{\lambda} \nu_{i\lambda} A_\lambda \xrightarrow{k_i} I_{i-1,i} + I_i \qquad (2\cdot4\,c)$$

CYCLIC COUPLING



→ CATALYTIC ACTION VIA COMPLEX FORMATION

Fig. 2. An example for a mechanism of catalyzed selfreplication (see also Eigen et al., 1980). The index i is understood modulo n

are of the form

$$x_i = z_i + y_i + y_{i+1}. \qquad (2.5)$$

From equations (2.4a–c) we formulate the rate equations for unlimited growth ($\phi = 0$) according to mass action kinetics

$$\dot{z}_i = f_{-i}y_i + f_{-(i-1)}y_{i-1} + k_i y_i - f_i z_i z_{i-1} - f_{i+1} z_i z_{i+1} \qquad (2.6)$$

and

$$\dot{y}_i = f_i z_i z_{i-1} - f_{-i} y_i; \qquad i = 1, 2, \ldots, n. \qquad (2.7)$$

The time dependence of the total concentrations then has the simple form:

$$\dot{x}_i = \dot{z}_i + \dot{y}_i + \dot{y}_{i+1} = k_i y_i; \qquad i = 1, 2, \ldots, n. \qquad (2.8)$$

Now, we make two assumptions:

(a) Complex formation and dissociation described by (2.4a, b) are fast processes compared with polymerization (2.4c). Accordingly, reaction (2.4a, b) may be treated as a preequilibrium and hence

$$\frac{y_i}{z_i \cdot z_{i-1}} = K_i = \frac{f_i}{f_{-i}} \tag{2.9}$$

where K_i denotes the equilibrium constant.

(b) The concentrations are bounded, $\sum x_i = c < \infty$.

From equations (2.5) and (2.9) follows

$$x_i = z_i(1 + K_i z_{i-1} + K_{i+1} z_{i+1}). \tag{2.10}$$

These relations give z_i as implicit functions of the total concentrations $x_i, i = 1, 2, \ldots, n$. It is difficult to evaluate these functions explicitely. But we can make use of (2.8) and find

$$\begin{aligned} \dot{x}_i &= k_i K_i z_i z_{i-1} \\ &= x_i x_{i-1}\{k_i K_i (1 + K_i z_{i-1} + K_{i+1} z_{i+1})^{-1}(1 + K_{i-1} z_{i-2} + K_{i-1} z_i)^{-1}\} \\ &= x_i x_{i-1} F_i(x_1 \cdots x_n) = \Gamma_i. \end{aligned} \tag{2.11}$$

Again it is difficult to derive an explicit expression for F_i. We shall, however, prove our results on cooperativity in section 4 under the general assumptions that the functions F_i are continuous and bounded from below by positive constants a_i:

$$0 < a_i \leqslant F_i < \infty. \tag{2.12}$$

For the special mechanism used above as an example these inequalities hold because the total concentrations are bounded.

The experimental verification of selfreplicating systems dates back to the serial transfer experiments by Spiegelmann (1971). Polynucleotides, originally taken from $Q\beta$-bacteriophages, were allowed to multiply in solutions containing enzymes for replication and nucleoside triphosphates. Later experiments revealed a number of interesting molecular details of the replication process (Sumper and Luce, 1975; Küppers and Sumper, 1975; Küppers, 1979). By suitable technical devices the discrete step technique can be replaced by continuous reactions in a flow reactor. An example of replication studies with synthetic homopolynucleotides (poly(A) and poly(U) and RNA polymerase as catalyst) performed in a stirred flow reactor was recently reported by Schneider et al. (1979).

3. Competition of Selfreproducing Systems

Epstein (1979a) analyzes the fixed points of the equation

$$\dot{x}_i = x_i\left(\frac{1}{d_i + e_i x_i} - \frac{\phi}{c}\right); \qquad i = 1, \ldots, n \tag{3.1}$$

where $d_i \geqslant 0$ and $e_i > 0$ are constants. This equation models the competition – under the constraint of constant concentration – of macromolecules

whose self-reproduction is assisted by a specific enzyme in accordance with Michaelis-Menten kinetics.

First, we reproduce Epsteins results. Without restriction of generality one may assume

$$d_1 \leqslant d_2 \leqslant \cdots \leqslant d_n. \tag{3.2}$$

Defining

$$a_k = \sum_{j=1}^{k} \frac{d_k - d_j}{e_j}, \qquad k = 1, \ldots, n \tag{3.3}$$

it is easy to see that

$$0 = a_1 \leqslant a_2 \leqslant \cdots \leqslant a_n.$$

A fixed point exists in the interior of S_n^c iff $c > a_n$. In this case it is unique and stable. Its coordinates are

$$p_i = \left(\sum_{j=1}^{n} \frac{e_i}{e_j} \right)^{-1} \left(c + \sum_{j=1}^{n} \frac{d_j - d_i}{e_j} \right), \qquad i = 1, \ldots, n. \tag{3.4}$$

There are no stable fixed points on the boundary.

If $c \in (a_k, a_{k+1}]$ with $1 \leqslant k < n$, there exists a unique stable fixed point in S_n^c, given by

$$p_i = 0 \qquad \text{for} \qquad i > k$$

and

$$p_i = \left(\sum_{j=1}^{k} \frac{e_i}{e_j} \right)^{-1} \left(c + \sum_{j=1}^{k} \frac{d_j - d_i}{e_j} \right) \qquad \text{for} \qquad i = 1, \ldots, k. \tag{3.5}$$

This shows that as c grows, more and more species can coexist in a steady state.

Epstein (1979a) also shows that similar results are valid for the equation

$$\dot{x}_i = x_i \left(d_i - e_i x_i - \frac{\phi}{c} \right), \qquad i = 1, \ldots, n \tag{3.6}$$

which represents the competition of selfreproducing macromolecules. In this particular case it has been assumed that the macromolecules are degraded with a quadratic decay term.

In this section, we generalize Epsteins results by considering more general classes of growth terms, and globalize his theorems; the proofs are considerably shorter.

Thus we consider the equation

$$\dot{x}_i = x_i \left(G_i(x_i) - \frac{\phi}{c} \right), \qquad i = 1, \ldots, n \tag{3.7}$$

where the G_i are strictly decreasing functions from $\mathbb{R}^+$ into $\mathbb{R}$.

Theorem A. *For every $c > 0$, there exists a unique point $\mathbf{p} = (p_1, \ldots, p_n)$ in S_n^c which is the ω-limit of every orbit in the interior of S_n^c. If $\mathbf{p}$ lies in the interior of some face, then it is also the ω-limit of every orbit in the interior of this face. For sufficiently large c, $\mathbf{p}$ is in the interior of S_n^c.*

Proof. We assume without restricting generality that

$$G_1(0) \geqslant G_2(0) \geqslant \cdots \geqslant G_n(0) \geqslant 0 \tag{3.8}$$

where the last inequality follows from the fact that one can add a constant to all G_i's without changing the equation (3.7) on S_n^c.

Let us first show how to compute the coordinates p_i of the equilibrium $\mathbf{p}$. We shall show that to every $c > 0$ there exists a unique $K < G_1(0)$ and unique $p_1, \ldots, p_n$ with $\sum p_i = c$ such that

$$G_1(p_1) = \cdots = G_m(p_m) = K,$$

$$p_1 > 0, \ldots, p_m > 0,$$

and

$$p_{m+1} = \cdots = p_n = 0$$

where m is the largest integer j with $G_j(0) > K$.

Indeed, let G_i^{-1} be the inverse function of G_i defined on $(G_i(+\infty), G_i(0)]$. For $x \geqslant G_i(0)$ we set $G_i^{-1}(x) = 0$. The function

$$H = \sum_{i=1}^{n} G_i^{-1}$$

is defined on $(\max_{1 \leqslant i \leqslant n} G_i(+\infty), G_1(0)]$ and strictly decreases from $+\infty$ to 0. For any $c > 0$ there exists a unique $K < G_1(0)$ such that $H(K) = c$. Let

$$p_i = G_i^{-1}(K).$$

Obviously we have $\sum_{i=1}^{n} p_i = c$. If $G_i(0) \leqslant K$ then $p_i = 0$, if $G_i(0) > K$ then $G_i(p_i) = K$ and $p_i > 0$. Thus if $H(G_i(0)) < c$ then $p_1 > 0, \ldots, p_i > 0$. In particular, if all $G_i(0)$ are equal then for all $c > 0$, $\mathbf{p} = (p_1, \ldots, p_n)$ is in the interior of S_n^c. If the $G_i(0)$ are distinct, then with increasing c more and more p_i are strictly positive. Clearly $\mathbf{p}$ is a stationary point.

We next show that $\mathbf{p}$ is globally stable. Indeed, note first that the function

$$P = x_1^{p_1} x_2^{p_2} \cdots x_n^{p_n}$$

is strictly positive iff $x_i > 0$ for all i with $p_i > 0$, i.e. for all $i \leqslant m$. Also, its unique maximum on S_n^c is $\mathbf{p}$. This follows from

$$\frac{\partial P}{\partial x_i} = \frac{p_i}{x_i} P$$

and the constraint $\sum x_i = c$ which implies that at the maximum all $\partial P / \partial x_i$ have to be equal. We next show that

$$t \mapsto P(t) = x_1^{p_1}(t) \cdots x_n^{p_n}(t)$$

is a Lyapunov function. Indeed

$$\dot{P} = P \sum_{i=1}^{n} p_i \frac{\dot{x}_i}{x_i} = P \sum_{i=1}^{n} p_i \left(G_i(x_i) - \frac{\phi}{c} \right)$$

$$= P \left(\sum_{i=1}^{n} p_i G_i(x_i) - \frac{\phi}{c} \sum_{i=1}^{n} p_i \right)$$

$$= P \sum_{i=1}^{n} (p_i - x_i) G_i(x_i) \geqslant 0.$$

This last inequality follows from the fact that the strict monotonicity of the G_i's implies

$$\sum_{i=1}^{n} (p_i - x_i)(G_i(x_i) - G_i(p_i)) \geqslant 0$$

with equality only for $x_i = p_i$ and hence

$$\sum_{i=1}^{n} (p_i - x_i) G_i(x_i) \geqslant \sum_{i=1}^{n} (p_i - x_i) G_i(p_i)$$

$$= \sum_{i=1}^{n} p_i G_i(p_i) - \sum_{i=1}^{n} x_i G_i(p_i).$$

Now for $i \leqslant m$ we have $G_i(p_i) = K$ and $\sum_{i=1}^{m} p_i = \sum_{i=1}^{n} x_i = c$ and so the right-hand side is equal to

$$\sum_{i=1}^{n} x_i (K - G_i(p_i)) = \sum_{i=m+1}^{n} x_i (K - G_i(0)) \geqslant 0$$

since $K > G_i(0)$ if $i > m$.

Furthermore

$$\{\mathbf{x}\colon \dot{P}(\mathbf{x}) = 0\} = \{\mathbf{x}\colon P(\mathbf{x}) = 0 \text{ or } \mathbf{x} = \mathbf{p}\}$$

which is the union of those faces of S_n^c that are bounded away from $\mathbf{p}$ and $\bar{\mathbf{p}}$. From Lyapunov's theorem follows that all orbits in the interior of S_n^c and all faces touching $\mathbf{p}$ have $\mathbf{p}$ as ω-limit.

4. Cooperation in Generalized Hypercycles

We consider the equation

$$\dot{x}_i = x_i \left(x_{i-1} F_i(x_1, \ldots, x_n) - \frac{\phi}{c} \right); \qquad i = 1, \ldots, n \tag{4.1}$$

on the simplex S_n^c. We shall assume that the functions F_i are continuous on S_n^c and bounded away from 0. Thus there exists a constant $q > 0$ such that

$$F_i(x_1, \ldots, x_n) \geqslant q \tag{4.2}$$

for $i = 1, \ldots, n$ and all $\mathbf{x} = (x_1, \ldots, x_n) \in S_n^c$.

Examples of such functions are

$$F_i(\mathbf{x}) = k_i$$

(where the k_i are positive rate constants) and

$$F_i(\mathbf{x}) = \frac{k_i}{d_i x_i + e_i x_{i-1} + 1}$$

(where $k_i > 0, d_i \geqslant 0, e_i \geqslant 0$). The first case (the elementary hypercycle) has been discussed extensively in previous papers (Eigen and Schuster, 1978b; Schuster et al. 1978, 1979; Schuster and Sigmund, 1980b). In our main example, however, the functions F_i are described by (2.11), reflecting a chemically more realistic model of hypercyclic coupling.

Theorem B. *There exists a constant $\rho > 0$ such that if $x_i(0) > 0$ for $i = 1, \ldots, n$, then $x_i(t) > \rho$ for all t sufficiently large, $i = 1, \ldots, n$.*

Thus in our chemical model, if the initial concentrations are all strictly positive, then after some time all will be larger than ρ. None of the species, then, is threatened with extinction by a small perturbation. Similar results for special cases have been obtained in Schuster, Sigmund and Wolff (1979).

The proof begins with a series of definitions and lemmas.

Definition. Let F denote the set of fixed points of (4.1) on the boundary of S_n^c.

Lemma 1. $F = \{\mathbf{x} \in S_n^c \colon \phi(\mathbf{x}) = 0\} = \{\mathbf{x} = (x_1, \ldots, x_n) \in S_n^c \colon x_i x_{i-1} = 0 \text{ for all } i\}$.

Proof. (1) Suppose $\mathbf{x} \in F$. Since $\mathbf{x}$ is on the boundary of S_n^c, there exists a j with $x_j = 0$ but $x_{j+1} > 0$. Since $\mathbf{x}$ is a fixed point we have $\dot{x}_{j+1} = 0$. Hence $x_j F_{j+1}(\mathbf{x}) - \phi(\mathbf{x})/c = 0$ and so $\phi(\mathbf{x}) = 0$.

(2) Conversely, $\phi(\mathbf{x}) = 0$ implies $x_i x_{i-1} = 0$ and hence $\dot{x}_i = 0$ for all i.

Definition. Let $\mathbf{x} \in S_n^c$ and $T > 0$ be given and let U be an open subset of S_n^c. Let $\mathbf{x}(t)$ be the orbit of (4.1) with $\mathbf{x}(0) = \mathbf{x}$. The set

$$U_T = \{t \in [0, T] \colon \mathbf{x}(t) \in U\} \tag{4.3}$$

is a subset of $[0, T]$ open in the relative topology. We denote the Lebesgue measure on $[0, T]$ by m and set

$$p(\mathbf{x}, U, T) = \frac{1}{T} m(U_T). \tag{4.4}$$

$p(\mathbf{x}, U, T)$ is the fraction of time that the orbit of $\mathbf{x}$ spends in U, up to time T. Clearly $p(\mathbf{x}, U, T) \in [0, 1]$.

Definition. For any $r \in (0, 1)$, $\mathbf{x} \in S_n^c$ is called r-good for U if

$$p(\mathbf{x}, U, T) > r \text{ for some } T > 1. \tag{4.5}$$

(Instead of 1 we could use any other positive constant). If $\mathbf{x}$ is r-good for U, we may define

$$T_U^r(\mathbf{x}) = \inf\{T > 1 \colon p(\mathbf{x}, U, T) > r\}.$$

We denote by d the Euclidean metric on S_n^c.

Lemma 2. *The function T_U^r is upper semicontinuous, i.e. if it is defined for $\mathbf{x} \in S_n^c$, and if $\alpha > 0$ is arbitrary, there is a $\delta > 0$ such that $d(\mathbf{x}, \mathbf{y}) < \delta$ implies that T_U^r is defined at $\mathbf{y}$ and that $T_U^r(\mathbf{y}) < T_U^r(\mathbf{x}) + \alpha$.*

Proof. For any α, there exists a $T \in (1, T_U^r(\mathbf{x}) + \alpha)$ such that $p(\mathbf{x}, U, T) > r$, i.e. such that $m(U_T) > rT$. There exists a compact subset V_T of the set U_T such that $m(V_T) > rT$. Now choose $\varepsilon > 0$ such that the ε-neighborhood of the compact set $\{\mathbf{x}(t)\colon t \in V_T\}$ is contained in U. Since the solutions depend continuously on the initial conditions, there exists a $\delta > 0$ such that if $d(\mathbf{x}, \mathbf{y}) < \delta$ and if $\mathbf{y}(t)$ is the solution of (4.1) with $\mathbf{y}(0) = \mathbf{y}$, then $d(\mathbf{x}(t), \mathbf{y}(t)) < \varepsilon$ for all $t \in V_T$, and hence $p(\mathbf{y}, U, T) > r$. Thus $T_U^r(\mathbf{y})$ exists and is smaller than $T_U^r(\mathbf{x}) + \alpha$.

Lemma 3. *If U is an open neighborhood of F and $r \in (0,1)$, then every $\mathbf{x}$ in the boundary of S_n^c is r-good for U.*

Proof. Since U is a neighborhood of $\{\mathbf{x} \in S_n^c\colon \phi(\mathbf{x}) = 0\}$, there exists a $\delta > 0$ such that $\mathbf{z} \notin U$ implies $\phi(\mathbf{z}) > \delta c$. Let $\mathbf{x}$ be a given point on the boundary of S_n^c and $\mathbf{x}(t)$ the orbit with $\mathbf{x}(0) = \mathbf{x}$. We shall proceed indirectly and assume that $\mathbf{x}$ is not r-good for U. In particular, then, $\phi(\mathbf{x}(t))$ does not converge to 0, since otherwise $\mathbf{x}(t) \in U$ for all sufficiently large t.

The point $\mathbf{x}$ being on the boundary, there exist indices i such that $x_{i-1} = 0$ and $x_i > 0$. If for every such i we have $x_{i+1} = 0$, then by Lemma 1 $\mathbf{x} \in F \subset U$ and we are finished. Otherwise there exists a $k \geqslant 1$ such that

$$x_{i+1} > 0, \quad \ldots, \quad x_{i+k} > 0 \qquad \text{and} \qquad x_{i+k+1} = 0.$$

We shall show by induction that our assumption implies

$$x_i(t) \to 0, \quad x_{i+1}(t) \to 0, \quad \ldots, \quad x_{i+k-1}(t) \to 0 \qquad \text{for} \qquad t \to +\infty,$$

and hence $\phi(\mathbf{x}(t)) \to 0$, which is a contradiction.

(1) If $\phi(\mathbf{x}(t))$ does not converge to 0, there exists a sequence $t_1, t_2, \ldots \to +\infty$ and $\varepsilon > 0$ such that $\phi(\mathbf{x}(t_k)) > \varepsilon$, $k = 1, 2, \ldots$. Actually since $|\dot{x}_j| < M$ for some M and all j, the $x_j(t)$ and consequently also $\phi(\mathbf{x}(t))$ are uniformly continuous in t. Thus there exists a $\Delta > 0$ such that $\phi(\mathbf{x}(t)) > \varepsilon/2$ for all $t \in [t_k, t_k + \Delta]$. This and $x_{i-1} = 0$ implies

$$\frac{\dot{x}_i(t)}{x_i(t)} \leqslant -\frac{\varepsilon}{2c}$$

for all such t. Since moreover $\dot{x}_i(t) \leqslant 0$ for all t, we obtain $x_i(t) \to 0$.

(2) Suppose now $x_{i+s}(t) \to 0$, for some s with $0 \leqslant s < k - 1$. Choose $r_1 \in (r, 1)$ and ε such that

$$\varepsilon < \tfrac{1}{2}\delta(1 - r_1). \tag{4.6}$$

If t' is chosen large enough, our assumption implies

$$x_{i+s}(t) < \varepsilon \left(\max_{\mathbf{x} \in S_n^c} F_{i+s+1}(\mathbf{x}) \right)^{-1}$$

for all $t > t'$. Since $\mathbf{x}$ is not r-good, we have

$$m(U_T) \leqslant rT \tag{4.7}$$

for all $T \geqslant 1$. For T large enough, furthermore,

$$r\frac{T}{T-t'} < r_1 \tag{4.8}$$

and hence

$$\frac{m(\{t\in[t',T]\colon \mathbf{x}(t)\in U\})}{T-t'} \leqslant \frac{m(U_T)}{T-t'} \leqslant r_1. \tag{4.9}$$

For such T, then

$$m(\{t\in[t',T]\colon \phi(\mathbf{x}(t)) > \delta c\}) \geqslant (1-r_1)(T-t'). \tag{4.10}$$

Now

$$\frac{\dot{x}_{i+s+1}}{x_{i+s+1}} = x_{i+s}F_{i+s} - \frac{\phi}{c}.$$

Since $\phi \geqslant 0$, we have for any $t \geqslant t'$ that

$$\frac{\dot{x}_{i+s+1}(t)}{x_{i+s+1}(t)} \leqslant \varepsilon. \tag{4.11}$$

For those $t\in[t',T]$ with $\phi(\mathbf{x}(t)) > \delta c$, one has even

$$\frac{\dot{x}_{i+s+1}(t)}{x_{i+s+1}(t)} \leqslant \varepsilon - \delta. \tag{4.12}$$

By (4.10), (4.11) and (4.12), then,

$$\frac{\dot{x}_{i+s+1}(T)}{x_{i+s+1}(t')} \leqslant \exp\{[(1-r_1)(\varepsilon-\delta) + r_1\varepsilon](T-t')\} \leqslant \exp(-\varepsilon(T-t'))$$

the last inequality following from (4.6). Hence $x_{i+s+1}(T) \to 0$ for $T \to \infty$.

Let us consider the function $P(\mathbf{x}) = P(x_1, \ldots, x_n) = x_1 x_2 \cdots x_n$.

One has $P(\mathbf{x}) \geqslant 0$ for $\mathbf{x}\in S_n^c$, with equality if and only if $\mathbf{x}$ is on the boundary. On the compact set S_n^c, P attains its unique maximum at the point $(c/n, \ldots, c/n)$. For $p > 0$ we write

$$I(p) = \{\mathbf{x}\in S_n^c\colon 0 < P(\mathbf{x}) \leqslant p\}. \tag{4.13}$$

Lemma 4. *For every neighborhood U of F and any $r\in(0,1)$, there exists a $p > 0$ such that T_U^r is defined on*

$$\overline{I(p)} = \{\mathbf{x}\in S_n^c\colon 0 \leqslant P(\mathbf{x}) \leqslant p\}. \tag{4.14}$$

Proof. By Lemma 3, T_U^r is defined for every $\mathbf{x}$ in the boundary of S_n^c. By Lemma 2, T_U^r is defined on a neighborhood W of the boundary of S_n^c, and hence on $I(p)$ if p is chosen so small that $I(p) \subset W$.

Proof of the theorem. The function $t \mapsto P(\mathbf{x}(t))$ has as its time-derivative

$$\dot{P}(\mathbf{x}(t)) = P(\mathbf{x}(t))\left(s(\mathbf{x}(t)) - \frac{n}{c}\phi(\mathbf{x}(t))\right) \tag{4.15}$$

where

$$s(\mathbf{x}) = \sum_{i=1}^{n} x_{i-1} F_i(\mathbf{x}). \tag{4.16}$$

Since the F_i are bounded away from 0, and $\sum x_i = c$, there exists an $M > 0$ such that

$$s(\mathbf{x}) > M \qquad \text{for all} \qquad \mathbf{x} \in S_n^c. \tag{4.17}$$

Define

$$A = \left\{ \mathbf{x} \in S_n^c \colon s(\mathbf{x}) - \frac{n}{c}\phi(\mathbf{x}) > M \right\}. \tag{4.18}$$

It is easy to see that A is an open neighborhood of F. Define

$$m = \min_{\mathbf{x} \in S_n^c} \left(s(\mathbf{x}) - \frac{n}{c}\phi(\mathbf{x}) \right). \tag{4.19}$$

Note that m may be negative. Now choose $k \in (0, M)$ and then $r \in (0, 1)$ sufficiently large such that

$$Mr + m(1 - r) \geqslant k. \tag{4.20}$$

For these given A and r, choose p as in Lemma 4, so that T_A^r is defined on $\overline{I(p)}$. On this compact set there exists an upper bound $\bar{T}$ for the upper semicontinuous function T_A^r.

(A) We show that if $\mathbf{x}(0) \in I(p)$, then $\mathbf{x}(t) \notin I(p)$ for some $t > 0$.

Otherwise one would have $\mathbf{x}(t) \in I(p)$ for all $t \geqslant 0$. We shall show that this leads to a contradiction. Let $t_0 = 0$. By our assumption and Lemma 4, there exists a t_1, with $t_1 - t_0 \in (1, \bar{T})$, such that

$$p(\mathbf{x}(t_0), A, t_1 - t_0) > r. \tag{4.21}$$

Since we assume that $\mathbf{x}(t_1) \in I(p)$, there exists a t_2, with $t_2 - t_1 \in (1, \bar{T})$, such that $p(\mathbf{x}(t_1), A, t_2 - t_1) > r$. Proceeding inductively, we obtain a sequence $t_0, t_1, t_2, \ldots$ with $t_{i+1} - t_i \in (1, \bar{T})$ such that

$$p(\mathbf{x}(t_i), A, t_{i+1} - t_i) > r. \tag{4.22}$$

But this means that $\mathbf{x}(t)$, for $t \in [t_i, t_{i+1}]$, spends an amount of time larger than $r(t_{i+1} - t_i)$ in the set A, where, by (4.15) and (4.18),

$$\frac{\dot{P}}{P} \geqslant M. \tag{4.23}$$

For the remainder of the time, one has

$$\frac{\dot{P}}{P} \geqslant m. \tag{4.24}$$

Thus (4.23) and (4.24) imply

$$P(\mathbf{x}(t_{i+1})) \geqslant P(\mathbf{x}(t_i)) \exp\{[Mr + m(1 - r)](t_{i+1} - t_i)\} \tag{4.25}$$

and hence by (4.20)

$$P(\mathbf{x}(t_{i+1})) \geqslant P(\mathbf{x}(t_i)) \exp[k(t_{i+1} - t_i)] \geqslant P(\mathbf{x}(t_i))e^k \tag{4.26}$$

for $i = 0, 1, 2, \ldots$. This is a contradiction to the fact that P is bounded on S_n^c.

(B) We show next that there exists a $q \in (0, p)$ such that if $\mathbf{x}(0) \notin I(p)$, then $\mathbf{x}(t) \notin I(q)$ for all $t \geqslant 0$.

Note first that it is possible that $\mathbf{x}(t) \in I(p)$ for some $t > 0$. In this case, let

$$t_0' = \min\{t \geqslant 0, \mathbf{x}(t) \in I(p)\}. \tag{4.27}$$

Clearly $P(\mathbf{x}(t_0')) = p$. Now define

$$q = p \exp(-|m|\bar{T}(1 - r)). \tag{4.28}$$

Just as before, there exists a t_1' with $t_1' - t_0' \in (1, \bar{T})$ such that

$$p(\mathbf{x}(t_0'), A, t_1' - t_0') > r.$$

During the time-interval $[t_0', t_1']$, $\mathbf{x}(t)$ spends an amount of time less than $(1 - r)(t_1' - t_0') \leqslant (1 - r)\bar{T}$ outside of A, where

$$\frac{\dot{P}}{P} \geqslant m,$$

and the remainder of the time in A, where $\dot{P} \geqslant 0$. Hence for every $t \in [t_0', t_1']$ we have

$$P(\mathbf{x}(t)) \geqslant P(\mathbf{x}(t_0')) \exp[m(1 - r)(t_1' - t_0')] \geqslant p \exp[-|m|(1 - r)\bar{T}] = q.$$

Hence $\mathbf{x}(t)$ does not reach $I(q)$ for $0 \leqslant t \leqslant t_1'$. Furthermore, (4.26) (with t_1' and t_0' instead of t_{i+1} and t_i) shows that

$$P(\mathbf{x}(t_1')) \geqslant P(\mathbf{x}(t_0'))e^k > p$$

and hence $\mathbf{x}(t_1') \notin I(p)$, so that at time t_1' we are in the same situation as at time 0. Repeating this argument, we see that $\mathbf{x}(t)$ does not reach $I(q)$ in positive time.

Putting (A) and (B) together gives the desired result. If $\mathbf{x}(0)$ is not on the boundary of S_n^c, there exists a time $t' \geqslant 0$ such that $\mathbf{x}(t') \notin I(p)$. For all $t \geqslant t'$, $\mathbf{x}(t) \notin I(q)$.

Choosing $\rho < qc^{-n+1}$, we see that

$$x_i(t) > \rho \qquad \text{for all} \qquad t \geqslant t'.$$

5. Conclusion

As in the case of Epstein (1979b) we see that in our context one can also obtain precise mathematical results for chemical growth terms of a very general class. It was not necessary to attribute a concrete algebraic form to the kinetics. The properties are stable in the sense that perturbations of the functions within the given class do not lead to a change in behaviour. Another advantage of this procedure is that it is applicable to examples for which one does not know the precise form of the rate equations. This is the case not only in complex chemical systems but especially in biological applications. An important class of equations of the form (2.2) and (2.3) dealing with the concept of evolutionary stable strategies for animal behaviour (Maynard-Smith, 1974) can be found in Taylor and Jonker (1978), Hofbauer et al. (1979) and Zeeman (1979).

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