# ELEMENTARY STEP DYNAMICS OF CATALYTIC HYPERCYCLES 

M. EIGEN ${ }^{\text {a }}$, P. SCHUSTER ${ }^{\mathrm{b}}$ *, K. SIGMUND ${ }^{\mathrm{b}}$ and R. WOLFF ${ }^{\text {b }}$<br>${ }^{2}$ Max-Planck-Institut für Biophysikalische Chemie, Göttingen, F.R.G. and ${ }^{\mathrm{b}}$ Institute für Theoretische Chemie und Strahlenchemie und Mathematisches Institut der Universität Wien, Austria

(Received October 9th, 1979)
(Revision received February 12th, 1980)


#### Abstract

Two model systems for hypercyclic organisation constructed from a series of uni- and bimolecular reaction steps were studied under the condition of unlimited growth by means of qualitative analysis and numerical integration of the corresponding differential equations. It is shown that both models lead, within wide ranges of parameter and initial conditions, to the same characteristic dynamical behaviour as the elementary hypercycles and hypercycles with translation introduced in 1978 by Eigen and Schuster.


## 1. Introduction

Catalytic hypercycles were introduced some years ago (Eigen, 1971) as the simplest kinetic systems that guarantee coexistence, mutual stabilization and coherent growth of self-reproductive units. In absence of catalytic coupling terms these units would compete, and selection would lead to the dominance of a single one. The basic dynamical properties of hypercycles, the possibilites of their physical realization, and their role in prebiotic evolution have been discussed extensively (Eigen and Schuster, 1977, 1978 a,b). A rigorous mathematical study of the corresponding systems of differential equations was presented in another series of papers (Schuster et al., 1978, 1979 a,b; Hofbauer et al., 1979). Most of the analysis and numerical work done so far on this class of non-linear dynamical systems was based on a kind of "overall" reaction kinetics: intermediate complex formation was treated under the assumptions valid at the low concentration limit. In particular

[^0]the steady state approximation was applied to all concentrations except those of the (monomeric) subunits of complexes.

There are several questions aiming at more quantitative aspects which deserve special interest, viz.
(1) How far, if at all, are the dynamics of catalytic hypercycles affected when the steady state assumptions are dropped?
(2) Do the most important predictions, such as cooperativity of individual selfreproductive units or hyperbolic growth of the combined system of self-reproductive units (Eigen and Schuster, 1978a) apply to more complex mechanisms of reprodurtion as well?
(3) How wide is the range of concentrations within which more complex systems may be described accurately enough by simplified models?

Occasional doubts have been expressed whether systems described more explicitly at the molecular level could exhibit the characteristic properties found for catalytic hypercycles at all.

In order to answer these questions at least in part we present here some analytic and numerical results on two model systems which describe catalytic hypercycles at the level of consecutive "elementary steps". The


Fig. 1. A survey of the compounds present in solution according to model I
individual steps chosen are not elementary in the same sense as commonly used in the kinetics of small molecules, but they do represent chemical reactions which are exclusively first or second order with respect to the macromolecules involved. The two models refer to the simple or "elementary" catalytic hypercycle, (Eigen and Schuster, 1978a) involving a class of macromolecules only, and to the hypercycle with translation, which deals explicitly with both classes, polynucleotides and polypeptides.

## 2. The simple catalytic hypercycle (model I)

The macromolecules, all belonging to one class of self-reproductive units, are assumed to form two kinds of aggregates: binary and ternary complexes. The different compounds we expect to be present in solution are summarized in Fig. 1.

Reproduction occurs via a series of consecutive steps involving complex formation, polymerization and complex dissociation:

$$
\begin{array}{r}
I_{N}+I_{1} \stackrel{f_{1}}{\stackrel{f_{-1}}{\rightleftharpoons}} I_{N 1} \\
I_{N 1}+\sum_{\lambda} \nu_{\lambda}^{(1)} A_{\lambda} \stackrel{k_{1}}{\rightleftharpoons} I_{N 11} \\
I_{N 11} \stackrel{h_{-1}}{h_{h_{1}}} I_{N 1}+I_{1} \tag{1c}
\end{array}
$$

$$
I_{1}+I_{2} \underset{f_{-2}}{\stackrel{f_{2}}{\rightleftharpoons}} I_{12}
$$

$$
I_{N-1, N, N} \stackrel{h_{-N}}{h_{N}} I_{N-1, N}+I_{N} .
$$

(1c ${ }^{(\mathrm{N}-1)}$ )
The symbols $A_{\lambda}$ represent the energy-rich building blocks of the polymers. They are to be incorporated into the polymeric chains in reactions of the form of (1b). In case of polynucleotides the $A_{\lambda}$ 's would be the four nucleoside triphosphates (ATP, U(T)TP, GTP and CTP). $\nu_{\lambda}{ }^{(i)}$ is the stoichiometric coefficient of base " $\lambda$ " in the synthesis of the polymer $I_{i}$. Throughout this paper we shall assume the concentrations of all low molecular weight compounds to be buffered:

$$
\left[A_{\lambda}\right]=\left[A_{\lambda}\right]_{0}=\text { const. } ; \quad \lambda=1,2 \ldots .
$$

Hence, these concentrations may be incorporated into the rate constants $k_{i}$ and need not be considered explicitly. The $f_{i}$ and $h_{i}$ are the rate constants for the complex formation. For an experimental verification of this condition, see e.g. the recent article on evolution reactors by Küppers (1979). Only the concentrations of macromolecules and their complexes will then appear as explicit variables:

$$
\left[I_{i}\right]=x_{i}, \quad\left[I_{p i}\right]=y_{i}
$$

and
$\left[I_{p i i}\right]=z_{i} ;$

$$
i=1,2 \ldots N \text { and } p=i-1+N \delta_{i 1} \cdot *
$$

*By $\delta_{i j}$ we denote the Kronecker symbol: $\delta_{i j}=1$ if $i=j$ and $\delta_{i j}=0$ if $i \neq j$. Thus $p$ is the precursor of $i$ in a cyclic array: $N-1, N, 1,2, \ldots, N-1, N$, $1, \ldots$ etc.

For our model system I we thus obtain the following $3 N$ kinetic equations:

$$
\begin{align*}
\frac{d x_{i}}{d t}=\dot{x}_{i}= & f_{-i} y_{i}+f_{-j} y_{j}+h_{-i} z_{i}-f_{i} x_{p} x_{i} \\
& -f_{j} x_{i} x_{j}-h_{i} x_{i} y_{i}  \tag{2a}\\
\frac{d y_{i}}{d t}=\dot{y}_{i}= & f_{i} x_{p} x_{i}+h_{-i} z_{i}-f_{-i} y_{i} \\
& -h_{i} x_{i} y_{i}-k_{i} y_{i} \tag{2~b}
\end{align*}
$$

$\frac{d z_{i}}{d t}=\dot{z}_{i}=h_{i} x_{i} y_{i}+k_{i} y_{i}-h_{-i} z_{i}$

$$
i=1,2, \ldots, N ; j=i+1-N \delta_{i N}
$$

and

$$
p=i-1+N \delta_{i 1}
$$

The indices $i, j$ and $p$ are defined in such a way that they lead to cyclic coupling: $N \rightarrow 1 \rightarrow 2 \rightarrow \ldots \rightarrow N$.

In order to facilitate further dicussion we introduce total concentrations for each macromolecular species
$x_{i}^{0}=x_{i}+y_{i}+2 z_{i}+y_{j}+z_{j} ;$

$$
\begin{equation*}
j=i+1-N \delta_{i N} \tag{3}
\end{equation*}
$$

and their sum
$c=\sum_{i} x_{i}^{0}=\sum_{i}\left(x_{i}+2 y_{i}+3 z_{i}\right)$.

It is easy to verify that they fulfil the following differential equations
$\dot{x}_{i}^{0}=k_{i} y_{i}$
and

$$
\begin{equation*}
\dot{c}=\sum_{i} k_{i} y_{i} \tag{5b}
\end{equation*}
$$

$2 A$. The steady state assumption
We assume that the rate and equilibrium constants for complex formation
$F_{i}=\frac{f_{i}}{f_{-i}}=\frac{\bar{y}_{i}}{\bar{x}_{p} \bar{x}_{i}}$
$H_{i}=\frac{h_{i}}{h_{-i}}=\frac{\bar{z}_{i}}{\bar{x}_{i} \bar{y}_{i}}$
where the bars denote equilibrium concentrations, are such that the $x_{i}$ and $y_{i}$ remain essentially equilibrated, while the dissociation of the $z_{i}$ is fast enough that the polymerization reactions (1b) determine the growth rate of the $x_{i}$
$\dot{x}_{i}=k_{i} y_{i}=k_{i} F_{i} x_{p} x_{i}$.

Since the time derivative of $x_{i}^{0}$ is also $k_{i} y_{i}$ (eqn. 5), it also is given by
$\dot{x}_{i}^{0}=k_{i} F_{i} x_{p} x_{i}$.

We thus find that model system I leads under these assumptions to the differential equations of the "elementary hypercycle" (Eigen and Schuster, 1978a §VII,7,c). We shall return to the question of validity and usefulness of the steady state assumption in Section 2C.

2B. Model system I with two species $(N=2)$
The dynamical system with $N=2$ is worth looking at more closely since it is small enough to permit qualitative analysis. We have to distinguish two different physical situations, which, apart from some minor detail, lead to the same general results.

1. The polymers $I_{1}$ and $I_{2}$ form just one complex $I_{12}$. The complete reaction scheme,
slightly different from eqn. (1),

$$
\begin{array}{r}
I_{1}+I_{2} \stackrel{f_{a}}{f_{d}} I_{12} \\
I_{12}+\sum_{\lambda} \nu_{\lambda}^{(1)} A_{\lambda} \stackrel{k_{1}}{\rightleftharpoons} I_{211} \\
I_{211} \stackrel{h_{-1}}{h_{h_{1}}} I_{1}+I_{12} \\
I_{12}+\sum_{\lambda} \nu_{\lambda}^{(2)} A_{\lambda} \xrightarrow{k_{2}} I_{122} \\
I_{122} \\
\overbrace{h_{2}}^{h_{-2}} I_{2}+I_{12}
\end{array}
$$

thus requires five variables: $\left[I_{1}\right]=x_{1} ;\left[I_{2}\right]=$ $x_{2} ;\left[I_{12}\right]=y ;\left[I_{211}\right]=z_{1}$; and $\left[I_{122}\right]=z_{2}$, in order to make translation into a dynamical system possible. The differential equations are:
$\dot{x}_{1}=f_{d} y+h_{-1} z_{1}-f_{a} x_{1} x_{2}-h_{1} x_{1} y$
$\dot{x}_{2}=f_{d} y+h_{-2} z_{2}-f_{a} x_{1} x_{2}-h_{2} x_{2} y$
$\dot{y}=f_{a} x_{1} x_{2}+h_{-1} z_{1}+h_{-2} z_{2}-f_{d} y-\dot{k}_{1} y$

$$
-k_{2} y-h_{1} x_{1} y-h_{2} x_{2} y
$$

$\dot{z}_{1}=k_{1} y+h_{1} x_{1} y-h_{-1} z_{1}$
$\dot{z}_{2}=k_{2} y+h_{2} x_{2} y-h_{-2} z_{2}$.

The equilibrium constants $H_{1}$ and $H_{2}$ are identical with those given in eqn. (6) except that $\bar{y}_{i}$ has to be replaced by $\bar{y}$. The equilibrium constant for binary complex formation will be denoted by

$$
\begin{equation*}
F=\frac{f_{a}}{f_{d}}=\frac{\bar{y}}{\vec{x}_{1} \cdot \bar{x}_{2}} \tag{6a'}
\end{equation*}
$$

In order to facilitate qualitative analysis we assume some rate and equilibrium constants to be equal:
$h_{1}=h_{2}=h_{a}, h_{-1}=h_{-2}=h_{d}, k_{1}=k_{2}=k$
and consequently $H_{1}=H_{2}=H$.
These assumptions certainly are less serious than they appear at first glance. In the case of the elementary hypercycle, $\dot{x}_{i}=k_{i} x_{p} x_{i}$, $i=1, \ldots, N$ and $p=i-1+N \delta_{i 1}$, one can make a kind of barycentric transformation which leads to equal rate constants in the scaled concentration variables (Schuster et al., 1979b). Thus the dynamical systems with unequal and equal rate constants are topologically equivalent, the apparent difference between them is removable by a non-linear scaling of the coordinate axes representing the concentrations $x_{i}$.

We introduce new variables $x=x_{1}+x_{2}$, $z=z_{1}+z_{2}, \xi=x_{1}-x_{2}$ and $\zeta=z_{1}-z_{2}$ and obtain the following system of differential equations:
$\dot{x}=2 f_{d} y+h_{d} z-1 / 2 f_{a}\left(x^{2}-\xi^{2}\right)-h_{a} x y$
$\dot{y}=1 / 4 f_{a}\left(x^{2}-\xi^{2}\right)+h_{d} z-f_{d} y-h_{a} x y-2 k y$
$\dot{z}=2 k y+h_{a} x y-h_{d} z$
$\dot{\xi}=h_{d} \zeta-h_{a} y \xi$
$\dot{\zeta}=h_{a} y \xi-h_{d} \zeta$.
From these equations we can immediately derive differential equations for the sum, $c=x_{1}^{0}+x_{2}^{0}$ as in eqns. 3 and 4 , and the difference, $\Delta=x_{1}^{0}-x_{2}^{0}=\xi+\zeta$, in total concentrations:
$\dot{c}=\dot{x}_{1}^{0}+\dot{x}_{2}^{0}=2 k y$
(cf. eqn. 5b), and
$\dot{\Delta}=\dot{x}_{1}^{0}-\dot{x}_{2}^{0}=\dot{\xi}+\dot{\xi}=0$.

Equations (11) and (12) show that the sum of the total concentrations grows steadily, since $y \geqslant 0$ is trivially fulfilled, whereas the difference $\Delta$ remains constant. In relative concentrations, therefore $x_{1}^{0} / c$ and $x_{2}^{0} / c$ will gradually approach each other. We shall show in the following part that under realistic assumptions concerning the rate constants the total concentration $c$ will indeed grow to infinity* and hence $\lim _{t \rightarrow \infty}(\Delta / c)=0$ or $x_{1}^{0} \sim x_{2}^{0}$ after long enough time.

The forthcoming analysis will be based on the assumption that the variable $y$ is essentially constant. In this case we can separate the system of five differential equations into two dynamical systems which will be analysed one after the other. Although there may be conditions under which $y$ changes more slowly than $\xi$ and $\zeta$, this will not be true in general. As we shall see at the end of this analysis a time dependent function $y(t)$ will not change any of the conclusions as long as $y(t)>0$. Explicit consideration of "time dependent rate constants" nevertheless would complicate the analysis substantially.

By separating eqns. (10) we obtain:
(a) The two-dimensional system describing internal equilibration.
$\dot{\xi}=h_{d} \xi-h_{a} y \xi$
$\dot{\zeta}=h_{a} y \xi-h_{d} \zeta$.
Let us initially assume that $y$ is constant and set $h_{a} y=a$ and $h_{d}=d$. Now we subject this linear dynamical system to an orthogonal linear transformation which immediately reveals a linear dependence.
$\xi^{\prime}=\frac{1}{\left(a^{2}+d^{2}\right)^{1 / 2}}(d \xi+a \zeta)$
*By "growth to infinity" we shall always understand the behaviour of the mathematical model, which is not restricted to finite boundary conditions as is the physical system it describes.
and

$$
\begin{equation*}
\zeta^{\prime}=\frac{1}{\left(a^{2}+d^{2}\right)^{1 / 2}}(-a \xi+d \zeta) \tag{14}
\end{equation*}
$$

leading to
$\dot{\xi}^{\prime}=(d-a) \xi^{\prime}$
$\dot{\zeta}^{\prime}=-(a+d) \zeta^{\prime}$.
The system no longer depends on $\xi^{\prime}$ and solution curves are obtained by simple integration:
$\zeta^{\prime}(t)=\zeta_{0}^{\prime} \cdot \exp [-(a+d) t]$
and
$(a+d)\left(\xi^{\prime}-\xi_{0}^{\prime}\right)=(d-a)\left(\zeta_{0}^{\prime}-\zeta^{\prime}\right)$.
The latter relation, of course, is identical with the condition $\xi+\zeta=\xi_{0}+\zeta_{0}$. By $\xi_{0}, \zeta_{0}, \xi_{0}^{\prime}$ and $\zeta_{0}^{\prime}$ we denote the values of these variables at a certain time $t=t_{0}$ from which integration started.


Fig. 2. The vector field and the trajectories of the dynamical system described by eqns. (15); choice of constants: $a=h_{a} y=2, d=h_{d}=3$, unit: $\left[t^{-1}\right]$.

The trajectories of this dynamical system (15) simply follow straight lines in the $\xi^{\prime}$, $\zeta^{\prime}$-plane (Fig. 2). Each trajectory ends in some point lying on the $\xi^{\prime}$ axis $\left(\zeta^{\prime}=0\right)$. From eqns. (15) it follows immediately that each point on this line is a stable fixed point. Consequently, the system is indifferent to changes in $\xi^{\prime}$ and fluctuations may shift the system stochastically along the $\xi^{\prime}$ axis. In the growing system, however, fluctuations in population numbers or concentrations will be of less and less importance with increasing $c$ and after a long enough period $\xi$ and $\zeta$ will be negligibly small compared to $x$ and $z$ or $c$ and $z$, respectively.

Let us visualize now what is going to happen in case $y$ is not constant. In our system $y(t)$ in almost all cases will grow during the equilibration of the dynamical system (13). Then $\alpha(t)$ will increase and consequently the decay of $\zeta^{\prime}$ will accelerate according to eqn. (15b). Moreover, the "normal modes" $\xi^{\prime}$ and $\zeta^{\prime}$ are no longer constant. As seen from eqn. (14), they will change during the course of the reaction. Provided $y(t)>0$ the conclusions drawn above are still valid.
(b) The remaining three differential equations in $\mathrm{x}, \mathrm{y}$ and z . Returning to the remaining equations we recall that $\xi$ will be always smaller in absolute value than $x$ provided
$x_{2} \neq 0$ or $x_{1} \neq 0$, respectively. Moreover, there is no systematic growth of $\xi$ over many orders of magnitude, as there is for $x, y$ and $z$. It seems therefore to be well justified to neglect $\xi^{2}$ relative to $x^{2}$ in eqns. (10) or in other words to start the system with $\xi_{0}=0$ and $\zeta_{0}=0$. Now we make use of the initial assumption, $k$ being small enough to guarantee slow growth, and conclude that the system is always sufficiently close to the association equilibria. These are simply determined by the relations:
$\dot{z}=0=h_{a} \bar{x} \bar{y}-h_{d} \bar{z}$
or
$\frac{h_{a}}{h_{d}}=H=\frac{\bar{z}}{\bar{x} \bar{y}}$
$\dot{y}=0=1 / 4 f_{a} \bar{x}^{2}-f_{d} \bar{y}$
or
$\frac{f_{a}}{4 f_{d}}=F^{\prime}=\frac{\bar{y}}{\bar{x}^{2}}$.

These two equations are formally identical


Fig. 3. Distribution of monomers $(x)$, dimers ( $y$ ) and trimers ( $z$ ) according to an equilibrium as in eqn. (17) as a function of total concentration $c$; choice of constants: $F^{\prime}=1 / 2, H=2 / 3$, unit: $\left[c^{-1}\right]$.
with those of trimer formation:
$X+X \stackrel{F^{\prime}}{\rightleftharpoons} Y$
$Y+X \stackrel{H}{\rightleftharpoons} Z$
The equilibrium concentration of free monomer $\bar{x}$ then is obtained as a solution of the cubic equation:
$\bar{x}^{3}+\frac{2}{3 H} \bar{x}^{2}+\frac{1}{3 H F^{\prime}} \bar{x}-\frac{1}{3 H F^{\prime}} c=0$.

A characteristic distribution of monomers, dimers and trimers varying with increasing concentration $c$ is shown in Fig. 3.

From eqn. (18) we can easily determine the low and high concentration limits:
$c \rightarrow 0: \quad \bar{x} \sim c$
$c \rightarrow \infty: \quad \bar{x} \sim\left(\frac{c}{3 H F^{\prime}}\right)^{1 / 3}$.
Consequently, we shall observe the following asymptotic behaviour of growth rates:
$c \rightarrow 0: \quad \dot{c}=2 k \bar{y} \sim 2 k F^{\prime} c^{2}$
$c \rightarrow \infty: \quad \dot{c}=2 k \bar{y} \sim 2 k\left(\frac{F^{\prime}}{9 H^{2}}\right)^{1 / 3} c^{2 / 3}$.
Thus, at low enough concentration the system will start to grow hyperbolically according to the definition given previously (Eigen and Schuster, 1978a). After some transition period the growth rates will decrease with respect to the power of $c$ and finally go over into a kind of "subexponential" growth according to the asymptotic solution curve
$c(t)=\left(c_{0}^{1 / 3}+\gamma t\right)^{3}$
with

$$
\begin{equation*}
\gamma=2 / 3 k\left(\frac{F^{\prime}}{9 H^{2}}\right)^{1 / 3} \tag{20c}
\end{equation*}
$$

In an $\ln c, t$-plot eqn. (20c) will show up as a concave-downwards function in contrast to hyperbolic growth, which leads to concaveupwards solution curves.

It seems to be important to consider the kinetics of the reaction scheme (8) under partial release of the constraints imposed by eqn. (9). In particular, we generalize to different values for the rate constants of the two irreversible reaction steps: $k_{1} \neq k_{2}$. Accordingly, we find
$\dot{c}=\dot{x}_{1}^{0}+\dot{x}_{2}^{0}=\left(k_{1}+k_{2}\right) y$
and
$\dot{\Delta}=\dot{x}_{1}^{0}-\dot{x}_{2}^{0}=\left(k_{1}-k_{2}\right) y$
The difference in total concentrations, $\Delta$, thus is neither constant nor does it approach a constant value. Additionally, there is no easy way to find transformation to internal and external coordinates as it was in the case of equal rate constants (see eqns. 10). Nevertheless, we can analyse the asymptotic behaviour of the total concentrations:
$\frac{\dot{x}_{1}^{0}}{\dot{x}_{2}^{0}}=\frac{k_{1}}{k_{2}}$ and hence $\int d x_{1}^{0}=\frac{k_{1}}{k_{2}} \int d x_{2}^{0}$.

By integration along the trajectory we find
$x_{1}^{0}(t)-x_{1}^{0}(0)=\frac{k_{1}}{k_{2}}\left[x_{2}^{0}(t)-x_{2}^{0}(0)\right]$,
wherein the initial values of total concentrations are denoted by $x_{1}^{0}(0)$ and $x_{2}^{0}(0)$. In analogy to eqns. (19) and (20) $x_{1}^{0}(t)$ and $x_{2}^{0}(t)$ exhibit unlimited growth. Hence, their ratio approaches asymptotically the constant value
$\lim _{t \rightarrow \infty} \frac{x_{1}^{0}(t)}{x_{2}^{0}(t)}=\frac{k_{1}}{k_{2}}$.
2. The polymers $\mathrm{I}_{1}$ and $\mathrm{I}_{2}$ form two physically distinguishable complexes $\mathrm{I}_{12}$ and $\mathrm{I}_{21}$.

The complete reaction scheme in this case is identical with that given initially in eqn. (1) for $N=2$ and consequently the corresponding six differential equations follow from eqn. (2). As with the previous case we simplify the equations by the assumption of equal rate and equilibrium constants:
$f_{1}=f_{2}=f_{a}, \quad f_{-1}=f_{-2}=f_{d}, \quad h_{1}=h_{2}=h_{a}$,

$$
h_{-1}=h_{-2}=h_{d} \text { and } k_{1}=k_{2}=k
$$

and hence
$F_{1}=F_{2}=F \quad$ and $H_{1}=H_{2}=H$.
Again we introduce sum and difference variables $x=x_{1}+x_{2}, y=y_{1}+y_{2}, z=z_{1}+z_{2}$, $\xi=x_{1}-x_{2}, \eta=y_{1}-y_{2}$ and $\zeta=z_{1}-z_{2}$ to obtain the dynamical system:

$$
\begin{align*}
\dot{x}= & 2 f_{d} y+h_{d} z-f_{a}\left(x^{2}-\xi^{2}\right) \\
& -1 / 2 h_{a}(x y+\xi \eta) \tag{21a}
\end{align*}
$$

$\dot{y}=1 / 2 f_{a}\left(x^{2}-\xi^{2}\right)+h_{d} z-f_{d} y$

$$
\begin{equation*}
-1 / 2 h_{a}(x y+\xi \eta)-k y \tag{21b}
\end{equation*}
$$

$\dot{z}=k y+1 / 2 h_{a}(x y+\xi \eta)-h_{d} z$
$\dot{\xi}=h_{d} \zeta-1 / 2 h_{a}(x \eta+y \xi)$

As before we may study the sum and difference of the total concentrations, $c$ and $\Delta$, which are determined by the differential equations:
$\dot{c}=\dot{x}_{1}^{0}+\dot{x}_{2}^{0}=k y$
and
$\dot{\Delta}=\dot{x}_{1}^{0}-\dot{x}_{2}^{0}=\dot{\xi}+\dot{\xi}=k \eta$.

Again we notice that the system is steadily growing $(y>0)$. In contrast to the previous case, however, the difference in total concentrations is no longer constant and we have to do a more involved study in order to be able to decide whether the system is going to approach a state with controlled total concentrations, $x_{1}^{0} \sim x_{2}^{0}$, or not.

The system of six differential equations is separated in complete analogy to the preceding example: the variables $x$ and $y$ are assumed to be essentially constant. Now we may treat the dynamical systems in $\xi, \eta, \zeta$, and $x, y, z$ one after the other. Thus we obtain:
(a) The rapidly equilibrating threedimensional system
$\dot{\xi}=-a \xi-b \eta+c \zeta$
$\dot{\eta}=-a \xi-(b+d+k) \eta+c \zeta$
$\dot{\zeta}=a \xi+(b+k) \eta-c \xi$
where for convenience we have already set $1 / 2 h_{a} y=a, 1 / 2 h_{a} x=b, h_{d}=c, f_{d}=d$ and $k=k$. Now we subject the system to an orthogonal linear transformation, $\eta$ remaining unchanged,
$\xi^{\prime}=\frac{1}{\left(a^{2}+c^{2}\right)^{1 / 2}}(c \xi+a \zeta)$
and
$\zeta^{\prime}=\frac{1}{\left(a^{2}+c^{2}\right)^{1 / 2}}(-a \xi+c \zeta)$
and obtain

$$
\begin{align*}
& \dot{\xi}^{\prime}=\frac{a(b+k)-c b}{\left(a^{2}+c^{2}\right)^{1 / 2}} \eta+(c-a) \zeta^{\prime}  \tag{26a}\\
& \dot{\eta}=-(b+d+k) \eta+\left(a^{2}+c^{2}\right)^{1 / 2} \zeta^{\prime} \tag{26b}
\end{align*}
$$

$$
\begin{equation*}
\dot{\zeta}^{\prime}=\frac{a b+c(b+k)}{\left(a^{2}+c^{2}\right)^{1 / 2}} \eta-(a+c) \zeta^{\prime} \tag{26c}
\end{equation*}
$$

The dynamical system, as before, no longer depends on $\xi^{\prime}$ and hence we are dealing with a two-dimensional linear system which can be analysed by standard techniques. There is a strictly stable fixed point in the origin of the coordinate system, since both eigenvalues of the Jacobian matrix have negative real parts
$\lambda_{1,2}=-\frac{a+b+c+d+k}{2}$

$$
\begin{equation*}
x\left\{1 \pm\left(1-\frac{4(a d+a k+c d)}{(a+b+c+d+k)^{2}}\right)^{1 / 2}\right\} \tag{27}
\end{equation*}
$$

(The conditions $a>0, b>0, c>0, d>0$ and $k>0$ are trivially fulfilled) Moreover, it can be shown easily that both roots are real since*
$4(a d+a k+c d)<(a+b+c+d+k)^{2}$.
Thus both $\eta$ and $\xi^{\prime}$ will decrease exponentially and approach zero. During that period $\xi^{\prime}$ will


Fig. 4. Sketch of the vector field of the dynamical system described by eqns. (26); choice of constants: $a=1 / 2 h_{a} y=3, b=1 / 2 h_{a} x=2, c=h_{d}=4, d=f_{d}=$ $3, k=2$, unit: $\left[t^{-1}\right]$.
*Eliminate $b$ by setting $b=0$ and obtain a stronger inequality which trivially implies (28): $4(a d+a k+c d)<$ $(a+d+c+k)^{2}$. Now substract $4(a d+a k+c d+c k)$ from both sides of the equation. Thereby we find $-4 c k<(-a-d+c+k)^{2}$ q.e.d.
increase (eqn. 26a) and asymptotically reach a constant value. A sketch of the vector field in the $\eta, \zeta^{\prime}$ - plane for a typical example is shown in Fig. 4. Coming back to the initial question, we are now in a position to give a definite answer: Since $\lim _{t \rightarrow \infty} \eta=0$ and the decrease of $\eta$ follows an exponential function, the difference in total concentrations $\Delta$, which according to eqn. (23) is given by

$$
\Delta=\Delta_{0}+\int_{t_{0}}^{t} k \eta d \tau ; \quad \Delta_{0}=\Delta\left(t=t_{0}\right)
$$

will approach a constant value as in the previous example.

As in the previous example, time dependent values of the rate constants $a(t)$ and $b(t)$ will not alter the general conclusions as long as $a>0$ and $b>0$ are fulfilled. This will always be the case in growing systems where $a(t)$ and $b(t)$ are increasing.
(b) The remaining three differential equations in $\mathrm{x}, \mathrm{y}$ and z . We are now in the same position as before and can study the remaining three equations with the aid of analogous initial conditions $\xi(0)=\eta(0)=\zeta(0)=0$. Again we apply the equilibrium assumption to the simplified equations which are supposed to be a good approximation for the slowly growing system ( $k<h_{d}$ ) and find

$$
\begin{equation*}
\dot{z}=0=1 / 2 h_{a} \bar{x} \bar{y}-h_{d} \bar{z} \tag{29a}
\end{equation*}
$$

or
$\frac{h_{a}}{2 h_{d}}=H^{\prime \prime}=\frac{\bar{z}}{\bar{x} \bar{y}}$

$$
\begin{equation*}
\dot{y}=0=1 / 2 f_{a} \bar{x}^{2}-f_{d} \bar{y} \tag{29b}
\end{equation*}
$$

or
$\frac{f_{a}}{2 f_{d}}=F^{\prime \prime}=\frac{\bar{y}}{\bar{x}^{2}}$.

Apart from numerical factors the equations are identical with those of the previous example. Hence, we find again that the system fulfils relations analogous to trimerization equilibrium. All conclusions concerning the growth behaviour of the previous example remain valid.

The generalization to different values of the rate constants $k_{1}$ and $k_{2}$ is somewhat more involved than in the previous example. The ratio $x_{1}^{0} / x_{2}^{0}$, nevertheless, will approach again the constant value $k_{1} / k_{2}$ asymptotically.

The three major conclusions than can be derived from the analysis of these two cases are:
(1) The system described by model I will show unrestricted growth (until the resources are exhausted) for all its components, i.e. $\lim _{t \rightarrow \infty} c=\infty$ and hence $\lim _{t \rightarrow \infty} x=\infty, \lim _{t \rightarrow \infty} y=\infty$ and $\lim z=\infty$.
(2) As a consequence of (1) we find $\lim _{t \rightarrow \infty}(\Delta / c)=0$ and hence $x_{1}^{0} \sim x_{2}^{0}$ in the case of equal rate constants, $k_{1}=k_{2}=k$. For $k_{1} \neq k_{2}$ we obtain
$\lim _{t \rightarrow \infty} \frac{x_{1}^{0}}{x_{2}^{0}}=\frac{k_{1}}{k_{2}}$.

In both cases, the system controls the total concentrations of its components. This property which has been attributed to the elementary hypercycle as one of its most important features, is found again with the more complex dynamics of model I.
(3) Starting from low concentrations, the model system will pass through a period of hyperbolic growth (Eigen and Schuster, 1978a) and then after saturation follow a kind of parabolic function $c=(a+b t)^{n}$ with $n=3$.

Although the foregoing results were derived under the assumption of slow growth, the conclusions are also valid for systems growing at rates which are too fast to allow approximate equilibration, as we show by numerical examples presented in the next section. We
have not yet been able, however, to find a rigorous analytical proof for the expected behaviour of systems growing far from internal equilibration.

## 2C. Numerical integrations

In order to see whether the assumption made in the analysis presented in the last section is properly justified we decided to perform some numerical calculations. For that purpose we studied the dynamical system of eqns. (10) with different rate constants $k$. The solution curves of one typical example are shown in Fig. 5. Systems of higher dimension $(N>2)$, to which the analytical treatment is hardly transferable, seemed to be even more interesting. Therefore we performed additionally two individual integrations on


Fig. 5(a)


Fig. 5(b)


Fig. 5(c)

Fig. 5(d)
Fig. 5. Numerical integration of three differential equations according to eqns. ( $10 \mathrm{a}-\mathrm{c}$ ); choice of constants: $f_{a}=2, h_{a}=2 / 3, f_{d}=h_{d}=1, k=0.1$; initial concentrations: $x(0)=1 \cdot 10^{-3}, y(0)=z(0)=$ $1 \cdot 10^{-6}, \xi(0)=\xi(0)$. All values throughout this paper are given in arbitrary concentration [e] and time units [ $t$ ], e.g. the rate constants are either of dimension $\left[t^{-1}\right]$ or $\left[t^{-1} c^{-1}\right]$ depending on whether they refer to a unimolecular or bimolecular process. For practical purposes any concrete set of units may be inserted.

Fig. 6. Numerical integration of nine differential equations according to eqns. (2) with $N=3$; choice of constants: $f_{1}=1.0, f_{2}=1.1, f_{3}=0.9, f_{-1}=0.7$, $f_{-2}=0.6, f_{-3}=0.5 ; h_{1}=0.2, h_{2}=0.2, h_{3}=0.3$, $h_{-1}=0.4, h_{-2}=0.3, h_{-3}=0.2 ; k_{1}=2.0, k_{2}=2.5$, $k_{3}=3.0$; initial concentrations: $x_{1}(0)=x_{2}(0)=$ $x_{3}(0)=1 \cdot 10^{-3} ; y_{1}(0)=y_{2}(0)=y_{3}(0)=z_{1}(0)=$ $z_{2}(0)=z_{3}(0)=1 \cdot 10^{-6}$. Units: see caption to Fig. 5. The vertical broken line refers to the critical time of the "elementary" hypercycle (Eigen and Schuster, 1978b) calculated from eqn. (30) under the assumption of internal equilibration.





Fig. 7. Numerical integration of nine differential equations according to eqns. (2) with $N=3$. All rate constants were taken equal to 1 ; initial concentrations: $x_{1}(0)=1 \cdot 10^{-3}, x_{2}(0)=1.5 \cdot 10^{-3}, x_{3}(0)=$ $2 \cdot 10^{-3} ; y_{1}(0)=y_{2}(0)=y_{3}(0)=z_{1}(0)=z_{2}(0)=$ $z_{3}(0)=1 \cdot 10^{-6}$. Units: see caption to Fig. 5. Vertical broken line: see caption to Fig. 6.
the model system I with $N=3$ and one on the system with $N=5$. The solution curves are shown in Figs. 6-8.

First of all we easily recognize the hyper-


Fig. 8. Numerical integration of 15 differential equations according to eqns. (2) with $N=5$. All rate constants were taken equal to 1 ; initial concentrations: $x_{1}(0)=1.1 \cdot 10^{-3}, x_{2}(0)=1.2 \cdot 10^{-3}, x_{3}(0)=$ $1.3 \cdot 10^{-3}, x_{4}(0)=1.4 \cdot 10^{-3}, x_{5}(0)=1.5 \cdot 10^{-3}$, $y_{1}\left(0^{\circ}\right)=y_{2}(0)=\ldots=z_{5}(0)=1 \cdot 10^{-6}$. Units:see caption to Fig. 5. Vertical broken line: see caption to Fig. 6.

TABLE 1

Results of numerical integration for model system I (eqns. (10), initial conditions: $x(0)=1 \cdot 10^{-3}$, $y(0)=1 \cdot 10^{-6}, z(0)=1 \cdot 10^{-6} ; \xi(0)=\xi(0)=0 ;$ rate constants: $\left.f_{\alpha}=2, h_{\alpha}=\frac{2}{3}, f_{d}=h_{d}=1\right)$. The values are given in arbitrary concentration [c] and time units [ $t$ ] (see Fig. 5).

| $k$ | $\tau_{1} \cdot k \cdot 10^{-3 \mathrm{a}}$ | $\frac{y(\tau)}{x(\tau)^{2}} ; \tau=\frac{5 \cdot 10^{3 \mathrm{~b}}}{k}$ |
| :--- | :--- | :--- |
| $\lim k \rightarrow 0$ | $0.995^{\mathrm{c}}$ | 0.5 |
| 0.01 | 1.01 | 0.497 |
| 0.1 | 1.01 | 0.496 |
| 1 | 1.07 | 0.300 |
| 10 | 2.1 | 0.065 |
| 100 | 14.2 | 0.007 |

${ }^{\mathrm{a}} \tau_{1}$ is a measure for the critical time at which the "burst" in the $\ln c / t$ diagramm (Fig. 5) occurs. The concrete numerical value was taken at the point where $c=1$.
${ }^{\mathrm{b}}$ This ratio is taken as a measure for the distance the system is off equilibrium. In a fully equilibrated mixture we have $y / x^{2}=F^{\prime}$.
${ }^{\mathrm{c}}$ Calculated from eqn. (20a): $t_{\infty}^{e}=\left[c(0) \cdot 2 k F^{\prime}\right]^{-1}$.
bolic phase of growth in all the $\ln x, \ln x^{0}$ and $\ln c$ vs. $t$ plots: exponential functions would appear as straight lines, and hence concaveupward functions indicate growth which is faster than exponential and belongs, by definition (Eigen and Schuster, 1978a), to the hyperbolic range. Such curvature appears in the initial period of all plots shown in Figs. 5-8. After a rather sharp "burst" at some time ( $\tau_{1}$, see Fig. 5 and Table 1) the curves level off and approach a concave-downward, monotonously increasing function which is characteristic for "subexponential" growth.

The system with $N=2$ as described by eqns. (10) was studied under extensive variation of the rate constant $k$, which determines the rate of the irreversible reaction step (1b). Figure 5 shows the solution curves for one concrete example. In order to test the range of validity of the "close to equilibrium" assumption in slowly growing systems we compare the critical times, $t_{\infty}^{e}$, calculated
from the differential eqn. (20a)* and the instant of sudden growth, $\tau_{1}$, determined by numerical integration (Table 1). Deviations from "internal equilibrium" in the range of high concentrations can be estimated properly by a comparison of the asymptotic value of the ratio $y / x^{2}$ and the equilibrium constant $F^{\prime}$. Both measures provide essentially the same picture: the systems with $k=0.01$, 0.1 and 1.0 grow sufficiently close to "internal equilibrium". At larger values of $k$ the deviations become substantial ( $k=10$ and 100 in Table 1); the qualitative behaviour of the solution curves, however, remains the same.

Solution curves for the system with $N=3$ and $N=5$ were obtained by integration of eqns. (2) and are shown in Figs. 6-8. Although for technical reasons the integration could not be followed into the range of high concentrations as far as in the previous example it is quite evident that the curve for $\ln x_{1}$ levels off much more strongly than those for $\ln x_{1}^{0}$ or $\ln c$ (Fig. 6). This agrees well with the analytical results since $x_{1}$ is expected to grow asymptotically with $t$ whereas $x_{1}^{0}$ and $c$ should approach $(a+b t)^{3}$. In the intermediate range the variables $x_{i}$ may undergo a few oscillations; one is easily recognized in the plot of $\ln x_{1}$ in Fig. 6.

It is interesting to note that the same behaviour is observed in systems with a distribution of rate constants (Fig. 6) as in those where all constants have been put to equal values (Figs. 7 and 8). The ratios $k_{i} / f_{-i}$ and $k_{i} / h_{-i}$ used for the calculation shown in Fig. 6 lie between 3 and 15, while the two other cases were all equal to 1 . Nevertheless, the predictions of the last section are fulfilled although the system does not meet the conditions of slow growth at all. It seems that the general characteristics of growth will be observed over a wide range of conditions whether the system is close to internal equilibrium or not.

In a previous paper (Eigen and Schuster, 1978a) we derived a simple expression for the ${ }^{*} t_{\infty}^{e}$ is the time at which the instability $\lim _{t \rightarrow t_{\infty}^{+}} c=\infty$
occurs.
position of the instability occurring in elementary hypercycles under the assumption of internal equilibration:
$t_{\infty}^{e}=\bar{k}[c(0)]^{-1} ; \bar{k}=\left(\sum_{i=1}^{N} k_{i}^{-1}\right)^{-1}$.
This relation was found to predict approximate values for the critical times at which instabilities occur in different systems growing far from internal equilibrium. Due to systematic errors the predicted values were always somewhat too small by about $30 \%$. Interestingly enough eqn. (30) leads to useful predictions of the "burst" at the end of the hyperbolic range of growth in the systems studied here (see Figs. 6-8) provided the "steady state rate constants" as derived in eqn. (7), $k_{i}^{\prime}=k_{i} F_{i}$, are applied. Again the predictions yield somewhat too short initial periods, as they should from previous arguments. It is worth noticing that the predictions are substantially more accurate for the curves shown in Figs. 7 and 8 than in Fig. 6. Indeed those two systems should grow closer to internal equilibrium than the Fig. 6 case on the basis of the $k_{i} / f_{-1}$ and $k_{i} / h_{-1}$ values discussed above.

## 3. The hypercycle with translation (model II)

The second model system studied corresponds to the hypercycle with translation as introduced by Eigen and Schuster (1978a). It is much more complicated than the first model, because it deals explicitly with macromolecules of two classes:
(1) Self-reproductive units with properties similar to those of polynucleotides; and
(2) Catalytically active polymers which like polypeptides are obtained from molecules of the first class by a translation mechanism allowing for a unique assignment.

The polymers are assumed to form various types of binary and ternary complexes, as shown in Fig. 9. Polymer synthesis occurs via a series of consecutive steps involving complex


Fig. 9. A survey of the compounds present in solution according to model II.
formation, polymerization, translation and complex dissociation:

$$
\begin{gather*}
E_{N}+I_{1} \stackrel{h_{1}}{\underset{h_{-1}}{\rightleftharpoons}} E_{N} \cdot I_{1} \\
E_{N} \cdot I_{1}+\sum_{\lambda} v_{\lambda}^{(1)} A_{\lambda} \stackrel{g_{1}}{\rightleftharpoons} E_{N} \cdot 2 I_{1} \\
E_{N} \cdot 2 I_{1} \stackrel{l_{-1}}{\rightleftharpoons l_{1}} E_{N} \cdot I_{1}+I_{1} \\
I_{1}+\sum_{\mu} v_{\mu}^{(1)} B_{\mu} \xrightarrow{R_{1}} I_{1} \cdot E_{1} \\
I_{1} \cdot E_{1} \stackrel{f_{-1}}{f_{1}} I_{1}+E_{1} \\
E_{1}+I_{2} \xrightarrow[h_{-2}]{\stackrel{h_{2}}{\rightleftharpoons}} E_{1} \cdot I_{2} \\
\vdots \\
I_{N} \cdot E_{N} \frac{f_{-N}}{\rightleftharpoons} I_{N}+E_{N}
\end{gather*}
$$

As in the previous section the symbols $A_{\lambda}$ refer to the energy-rich building blocks for the synthesis of polynucleotide-like polymers (ATP, U(T)TP, GTP and CTP). By $B_{\mu}$ we denote suitably activated amino acids which are ready for polypeptide synthesis via translation of polynucleotides; in present-day cells they would be one of the aminoacyl-t-RNA's. The symbols $\nu_{\lambda}{ }^{(i)}$ and $\nu_{\mu}{ }^{(j)}$ denote the stoichiometric coefficients appearing in the equations for the synthesis of the polymers $I_{i}$ and $E_{j}$, respectively. Again we assume the low molecular weight materials to be buffered.
$\left[A_{\lambda}\right]=\left[A_{\lambda}\right]_{0}=$ const., $\quad \lambda=1,2 \ldots$
$\left[B_{\mu}\right]=\left[B_{\mu}\right]_{0}=$ const., $\quad \mu=1,2 \ldots$
and their concentrations thus will not appear explicitly in the differential equations.

Consequently the set of variables for the individual macromolecules and their complexes with which we have to deal is:

$$
\left[I_{i}\right]=x_{i}, \quad\left[E_{i}\right]=e_{i}, \quad\left[I_{i} \cdot E_{i}\right]=d_{i}
$$

$$
\left[E_{p}, I_{i}\right]=y_{i}
$$

and

$$
\left[E_{p} \circ 2 I_{i}\right]=z_{i} ; \quad i=1,2 \ldots \ldots N
$$

and

$$
p=i-1+N \delta_{i 1}
$$

Model system II is thus described by a system of 5 N differential equations:
$\dot{x}_{i}=f_{-i} d_{i}+h_{-i} y_{i}+l_{-i} z_{i}-k_{i} x_{i}-f_{i} x_{i} e_{i}$

$$
\begin{equation*}
-h_{i} x_{i} e_{p}-l_{i} x_{i} y_{i} \tag{32a}
\end{equation*}
$$

$\dot{e}_{i}=f_{-i} d_{i}+h_{-j} y_{j}-f_{i} x_{i} e_{i}-h_{j} x_{j} e_{i}$
$\dot{d}_{i}=k_{i} x_{i}+f_{i} x_{i} e_{i}-f_{-i} d_{i}$

$$
\begin{align*}
\dot{y}_{i}= & h_{i} x_{i} e_{p}+l_{-i} z_{i}-h_{-i} y_{i}-g_{i} y_{i} \\
& -l_{i} x_{i} y_{i}  \tag{32~d}\\
\dot{z}_{i}= & g_{i} y_{i}+l_{i} x_{i} y_{i}-l_{-i} z_{i} \\
i= & 1,2, \ldots, N ; j=i+1-N \delta_{i N} \tag{32e}
\end{align*}
$$

and

$$
p=i-1+N \delta_{i 1}
$$

As with model I the indices $i, j$ and $p$ are defined in such a way that they introduce cyclic coupling.

It is useful to define the total concentrations
$x_{i}^{0}=x_{i}+d_{i}+y_{i}+2 z_{i}$
for the self-reproductive units and
$e_{i}^{0}=e_{i}+d_{i}+y_{j}+z_{j} ; j=i+1-N \delta_{i N}$
for the catalytically active polymers. Additionally, we define total concentrations for whole classes of macromolecules, namely total polynucleotide and total polypeptide concentrations, through
$c_{N}=\sum_{i=1}^{N} x_{i}^{0} \quad$ and $\quad c_{P}=\sum_{i=1}^{N} e_{i}^{0}$.
The time derivatives of these quantities fulfil
$\dot{x}_{i}^{0}=g_{i} y_{i}$
$\dot{e}_{i}^{0}=k_{i} x_{i}$
and hence we have
$\dot{c}_{N}=\sum_{i=1}^{N} g_{i} y_{i}$
and
$\dot{c}_{P}=\sum_{i=1}^{N} k_{i} x_{i}$

## $3 A$. The steady state assumption

As with model system I we assume that polymer synthesis is a fairly slow process and that at low enough concentrations binary and tertiary complexes will be present only at small, stationary concentrations. By low enough we mean fulfilment of the inequality
$c_{N}, c_{P} \ll F_{i}^{-1}, H_{i}^{-1}, L_{i}^{-1} ; \quad i=1,2, \ldots, N$
where $F_{i}^{-1}, H_{i}^{-1}$ and $L_{i}^{-1}$ denote reciprocal equilibrium constants for complex formation:
$H_{i}=\frac{h_{i}}{h_{-i}}=\frac{\bar{y}_{i}}{\bar{e}_{p} \cdot \bar{x}_{i}}, \quad p=i-1+N \delta_{i 1}$
$F_{i}=\frac{f_{i}}{f_{-i}}=\frac{\bar{d}_{i}}{\bar{e}_{i} \cdot \bar{x}_{i}}$
$L_{i}=\frac{l_{i}}{l_{-i}}=\frac{\bar{z}_{i}}{\bar{x}_{i} \cdot \bar{y}_{i}}$
where the bars denote equilibrium concentrations.

We apply steady state assumptions to the concentrations of the complexes
$\dot{d}_{i}=0, \quad \dot{y}_{i}=0$
and
$\dot{z}_{i}=0, \quad i=1,2, \ldots, N$
and obtain $2 N$ differential equations for the remaining variables
$\dot{x}_{i}=g_{i} H_{i} e_{p} x_{i}, \quad p=i-1+N \delta_{i 1}$
and
$\dot{e}_{i}=k_{i} x_{i}$
We find that model system II approaches asymptotically the equations proposed pre-
viously for the low concentration limit of the hypercycle with translation (Eigen and Schuster, 1978a).

In contrast to model system $I$, the number of variables in model II cannot easily be reduced to two or three by well-justified physical arguments. Therefore we dispense with a discussion of various attempts to perform qualitative analysis and instead present three examples of numerical integration:

## 3B. Numerical integrations

Solutions for the 15 differential equations corresponding to eqns. (32) with $N=3$ were


obtained by numerical integration. In order to reduce the enormous variability introduced by the possibility of choosing 24 rate constants we set them all equal to 1 . This choice offers the advantage that all complexes are present at amounts comparable to the free polymer concentrations if these were set equal to 1 unit. All processes then occur at comparable rates and have an influence upon the solution vectors.

Three different initial conditions were studied:
(1) The initial polynucleotide concentrations are greater than the initial polypeptide concentrations, $c_{N}(0)>c_{P}(0)$, (Fig. 10);




Fig. 10. Numerical integration of 15 differential equations according to eqns. (32) with $N=3$. All rate constants were taken equal to 1 ; initial concentrations: $x_{1}(0)=0 \cdot 10, x_{2}(0)=0 \cdot 12, x_{3}(0)=0 \cdot 14 ; e_{1}(0)=9.0 \cdot 10^{-3}$, $e_{2}(0)=1.1 \cdot 10^{-3}, e_{3}(0)=1.3 \cdot 10^{-3}$. Units: see caption to Fig. 5.
(2) the initial polynucleotide and polypeptide concentrations are about equal, $c_{N}(0) \sim$ $c_{P}(0)$, (Fig. 11); and
(3) the initial polypeptide concentrations are greater than the initial polynucleotide concentrations, $c_{P}(0)>c_{N}(0)$, (Fig. 12). Within these limits the individual concentrations were assumed to differ somewhat.

All total concentrations $\left(x_{i}^{0}, e_{i}^{0}, c_{N}\right.$ and $c_{P}$ ) were found to grow monotonically and did not approach constant values within the time ranges of integration. This result is consistent with eqns. (35) and (36) (although it does not follow automatically from them since $x_{i}$ and $y_{i}$ might approach zero) and shows that the hypercycle with translation behaves very similarly to model I as far as the general growth property is concerned.

The long term behaviour does not depend markedly on initial concentrations, as we see from Figs. 10-11 and, even more clearly, from the numerical values shown in Table 2. Moreover, we recognize three other important facts:
(1) The polynucleotide concentrations ( $x_{i}$, $x_{i}^{0}$ and $c_{N}$ ) go through a period of hyperbolic growth, although this may be during a rela-
tively short time span only, as e.g. in Fig. 10. Comparing the solution curves for three different initial conditions (Fig. 10-12) we observe large differences with respect to this initial phase of growth.
(2) The polypeptide concentrations show a more complicated time development: drastic changes and oscillations in free concentrations, $e_{i}$, may occur for some choices of initial values. An example is the behaviour of $e_{1}$ in Fig. 12. At long times, however, the free protein concentrations approach a constant value lying close to $\lim _{t \rightarrow \infty} e_{i} \sim 3$ in all three examples studied.
(3) Internal equilibration between species ( $x_{1} \sim x_{2} \sim x_{3}, e_{1} \sim e_{2} \sim e_{3}$, etc.) is approached rapidly. The hypercycle with translation thus fulfils the requirement of controlling individual concentrations, as does the simpler model system I.

The problem of internal equilibration should be briefly looked at from another point of view. In a fully equilibrated system the ratios of concentrations in eqn. (37) are the equilibrium constants. Under non-equilibrium conditions they may be different. In Fig. 13 we show the time dependence of some of


Fig. 11. Numerical integration of 15 differential equations according to eqns. (32) with $N=3$. All rate constants were taken equal to 1 ; initial concentrations: $x_{1}(0)=1.0 \cdot 10^{-3}, x_{2}(0)=1.2 \cdot 10^{-3}, x_{3}(0)=1.4 \cdot 10^{-3} ; e_{1}(0)=$ $9.0 \cdot 10^{-3}, e_{2}(0)=1.1 \cdot 10^{-3}, e_{3}(0)=1.3 \cdot 10^{-3}$. Units: see caption to Fig. 5.


Fig. 12. Numerical integration of 15 differential equations according to eqns. (32) with $N=3$. All rate constants were taken equal to 1 ; initial concentrations: $x_{1}(0)=1.0 \cdot 10^{-3}, x_{2}(0)=1.2 \cdot 10^{-3}, x_{3}(0)=1.4 \cdot 10^{-3} ; e_{1}(0)=$ $0.90, e_{2}(0)=0.11, e_{3}(0)=0.13$. Units: see caption to Fig. 5.

## TABLE 2

Results of numerical integration for model system II after $t=900$ time units. The values are given in arbitrary concentration units [ $c$ ] (see Fig. 6).

|  | Initial conditions |  |  |
| :--- | :--- | :--- | :--- |
|  | $c_{N}(0)>c_{P}(0)$ <br> $($ see Fig. 10) | $c_{N}(0) \sim c_{P}(0)$ <br> $($ see Fig. 11) | $c_{N}(0)<c_{P}(0)$ <br> $($ see Fig. 12) |
|  | $2.10 \cdot 10^{2}$ | $1.76 \cdot 10^{2}$ | $1.95 \cdot 10^{2}$ |
| $x_{1}(900)$ | $2.09 \cdot 10^{2}$ | $1.76 \cdot 10^{2}$ | $2.03 \cdot 10^{2}$ |
| $x_{2}(900)$ | $2.09 \cdot 10^{2}$ | $1.76 \cdot 10^{2}$ | $2.03 \cdot 10^{2}$ |
| $x_{3}(900)$ | $1.77 \cdot 10^{5}$ | $1.25 \cdot 10^{5}$ | $1.59 \cdot 10^{5}$ |
| $x_{1}^{0}(900)$ | $1.77 \cdot 10^{5}$ | $1.25 \cdot 10^{5}$ | $1.60 \cdot 10^{5}$ |
| $x_{2}^{0}(900)$ | $1.76 \cdot 10^{5}$ | $1.25 \cdot 10^{5}$ | $1.67 \cdot 10^{5}$ |
| $x_{3}^{0}(900)$ | $5.30 \cdot 10^{5}$ | $3.76 \cdot 10^{5}$ | $4.86 \cdot 10^{5}$ |
| $c_{N}(900)$ | 3.00 | 2.99 | 2.86 |
| $e_{1}(900)$ | 2.98 | 2.99 | 3.12 |
| $e_{2}(900)$ | 2.99 | $6.31 \cdot 10^{4}$ | $8.02 \cdot 10^{4}$ |
| $e_{3}(900)$ | $8.88 \cdot 10^{4}$ | $6.30 \cdot 10^{4}$ | $8.38 \cdot 10^{4}$ |
| $e_{1}^{0}(900)$ | $8.87 \cdot 10^{4}$ | $6.31 \cdot 10^{4}$ | $8.03 \cdot 10^{4}$ |
| $e_{2}^{0}(900)$ | $8.89 \cdot 10^{4}$ | $1.89 \cdot 10^{5}$ | $2.44 \cdot 10^{5}$ |
| $e_{3}^{0}(900)$ | $2.66 \cdot 10^{5}$ |  |  |
| $c_{P}(900)$ |  |  |  |



Fig. 13. Plots of the functions $F_{1}^{\prime}(t)(-+-+-), H_{1}^{\prime}(t)(-\cdot-\cdot-)$ and $L_{1}^{\prime}(t)(-)$ which characterize the deviation of the system from internal equilibrium (eqns. (39)). The values are taken from the numerical integration described in Fig. 10. Units: $\left[c^{-1}\right],[t]$.
these ratios. At the end of the hyperbolic phase of growth the functions
$F_{i}^{\prime}(t)=\frac{d_{i}(t)}{e_{i}(t) x_{i}(t)}$
$H_{i}^{\prime}(t)=\frac{y_{i}(t)}{e_{p}(t) x_{i}(t)}$
and
$L_{i}^{\prime}(t)=\frac{z_{i}(t)}{x_{i}(t) y_{i}(t)}$
converge to values which are not far away from the equilibrium constants ( $F_{i}=H_{i}=$ $L_{i}=1$ ) although the choice of rate constants does not specifically favour internal equilibration. By numerical integration we found
$\lim _{t \rightarrow \infty} F_{i}^{\prime}(t) \sim 1.333, \quad \lim _{t \rightarrow \infty} H_{i}^{\prime}(t) \sim 0.667$, whereas $L_{i}^{\prime}(t)$ converges essentially to the value of the equilibrium constants.

## 4. Conclusion

Qualitative analysis and numerical integration of the differential equations describing two model systems which refine the elementary hypercycle and the hypercycle with translation to the level of physically plausible elementary steps between macromolecules showed that the two most important features of hypercyclic organization are retained despite the more refined mechanism:
(1) Starting from low initial concentrations both systems pass through a range of hyperbolic growth within which the individual concentrations increase by several orders of magnitude. Depending upon the choice of initial conditions this phase may be relatively short or long. After this initial period the growth rates are reduced and the system as a
whole grows further following a parabolic function of the type $c=(a+b t)^{n}(1<n<\infty)$. The change in growth behaviour is caused by a saturation phenomenon: prior to the transition most of the molecules are present as free molecules, whereas afterwards most are bound in complexes.
(2) Irrespective of the change in growth behaviour the relative amounts of all species integrated in the hypercycle are controlled. Thus, the species do not compete with one another. This kind of "equilibration" between species is observed in systems close to or far from thermodynamic equilibrium with respect to complex formation. The problem of internal "equilibration" during the various stages of growth is not yet fully understood. It deserves further interest and will be treated in a forthcoming study.

## Acknowledgement

One of the authors (P.S.) wants to express his gratitude to Professors J. Cizek and J. Paldus for their hospitality during his stay in Waterloo, Ontario. Generous supply of computer time by the "Interuniversitäres Rechenzentrum", Wien, is gratefully acknowledged. The authors are also indebted to Dr. Ruthild Winkler-Oswatitsch, Dr. Werner Jakubetz and Professor William Gardiner for helpful suggestions in preparing the manuscript.

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[^0]:    *Part of this work has been performed during a stay at the Dept. of Applied Mathematics, University of Waterloo, Ontario, Canada. The work in Wien was supported financially by the Austrian "Fonds zur Förderung der wissenschaftlichen Forschung" (Project No. 3502).

