Autocatalytic Replication in a CSTR and Constant Organization

ROBERT HAPPEL[a], AND PETER F. STADLER[a,b,*]

[a]Theoretische Biochemie, Institut für Theoretische Chemie
Universität Wien, Vienna, Austria

[b]Santa Fe Institute, Santa Fe, NM

*Mailing Address:
Peter F Stadler, Inst. f. Theoretische Chemie, Univ. Wien
Währingerstr. 17, A-1090 Wien, Austria
Phone: [43] 1 40480 665   Fax: [43] 1 40480 660
E-Mail: studla@tbi.univie.ac.at

Abstract

The dynamics of a network of autocatalytically replicating species in a continuously stirred tank reactor can be described by a replicator equation in the limit of small flux rates.

Introduction. A number of different self-replicating chemical systems have been investigated experimentally since Spiegelman's [24, 36] serial transfer experiments with the *E.coli* phage Qβ. The hypothesis of an RNA world at the transition between prebiotic and biological evolution [17] is strongly supported by the discovery of catalytic activity of RNA for a broad variety of chemical reactions [4, 5, 8, 7, 6, 18, 38, 40] including a limited capacity for replication and self-replication [9, 10]. *Template chemistry* has emerged from the successful search for self-replicating molecular systems which are not based on the natural nucleic acids [28, 35, 15, 29, 39].

Networks of self-replicating molecules can be understood in terms of chemical kinetics [11, 12, 13, 14]. An autocatalytic reaction network consists of n species which act as templates and can act also a specific catalyst for the replication of a template. Building material (A) with low molecular weight is used for the production of the copy, and there might be low molecular weight waste (W). Hence we are dealing with a reaction network of the form

$$(A) + I_k \xrightarrow{I_1,\dots,I_n} 2I_k + (W)\,.$$

Its dynamics is described in by a system of coupled differential equations of the form

$$\dot{y}_k = f_k(y_1,\dots,y_n)\,y_k\,a - y_k R_k(t)$$

where y_k and a denote the concentrations of the selfreplicating species I_k and of the building material (A), respectively. The functions $f_k(y) \geq 0$ describes the catalytic activities of the different polymer species, and $R_k(t)$ is a removal term. The dynamics of the building material and the form of the removal terms are determined by the physical "boundary conditions" imposed on the reaction network.

Models. From the experimental point of view the most natural choice is the *continuously stirred tank reactor*, CSTR. It consists of a reaction vessel with constant volume V which is well stirred so that all concentrations are spatially homogeneous. An influx line introduces at a constant flux rate r which contains the the building material (A) at a constant concentration. The volume is kept constant by an outflux of the reaction mixture at the same flux rate r. The system of differential equations reads in this case

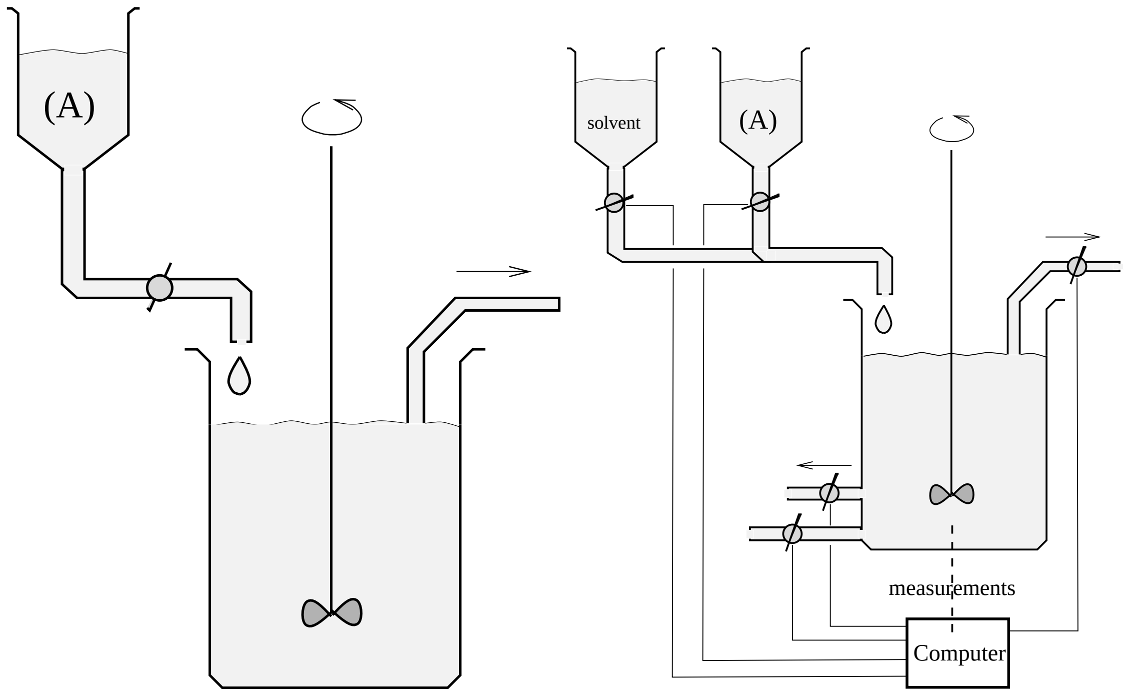
$$\begin{aligned} \dot{a} &= -a \sum_{j=1}^{n} y_j f_j(y) + r(a_0 - a) \\ \dot{y}_k &= y_k [a f_k(y) - r] \end{aligned} \tag{CSTR}$$

A simpler dynamical system can be obtained at the expense of a much more demanding experimental setting. The influx of the *evolution reactor* is regulated such that the concentration the building material (A) is constant in time, for instance by providing a large excess of (A) in the input flux. The outflux is regulated as well: two outflux channels, one for the reaction mixture and one equipped with a diaphragm that holds back all polymeric material are regulated such that both the volume of reaction mixture and the total concentration of the replicating species are kept constant. This setting has been termed *constant organization*. An approximate realization of an evolution reactor under constant organization is Husimi's *cellstat* [23]. The kinetic differential equations for this system read

$$\dot{y}_k = y_k a_0 f_k(y) - y_k \frac{a_0}{\sum_j y_j} \sum_{j=1}^{n} y_j f_j(y).$$

In this case it is convenient to introduce relative concentrations $x_k \overset{\text{def}}{=} y_k \Big/ \sum_{j=1}^{n} y_k$ and to rescale the units such that $a_0 = 1$. The differential equations above then simplify to

$$\dot{x}_k = x_k \left[f_k(x) - \sum_{j=1}^{n} x_j f_j(x) \right] \tag{R}$$



a) b)

Figure 1: CSTR and Evolution Reactor under Constant Organization.

a) The continuously stirred flow reactor (CSTR) is known also as "chemostat" in microbiology. The reaction is maintained by the continuous influx of a solution containing the materials which are necessary for replication. In the simplified model systems to discussed here, we assume only one energy rich compound (A). The evolutionary constraint is provided by the continuous outflux of solution from the reactor. Replicating molecules are injected into the reactor at $t = t_0$. Then, their concentrations may increase and eventually reach a stationary value, or they may be diluted out of the reactor depending on the input solution and the flow rate r which is commonly measured in terms of the reciprocal residence time of the solution in the tank reactor [26].

b) The evolution reactor is a more sophisticated version of a flow reactor. It consists of a reaction vessel which has walls which are impermeable to polymer material. Energy rich monomers are poured from the environment into the reactor. The degradation products are removed steadily. Material transport is adjusted in such a way that the concentrations of energy rich monomers are constant in the reactor. A dilution flux is installed in order to remove the excess of polymers produced by replication. Thus the sum of the polymer concentrations may be controlled by the dilution flux. Under "constant organization" it is adjusted such that the total polymer concentration is constant in time. This regulation requires internal control, which may be archived by analysis of the solution and data processing by a computer as indicated above.

This dynamical system has been termed *replicator equation* [32]. Originally developed as a model of prebiotic evolution replicator equations have been encountered since then in many different fields: populations genetics, mathematical ecology (where they occur disguised as Lotka-Volterra equations [21]), economics, or laser physics. Their properties have been the subject of hundreds of research papers by many research groups, see the book by Hofbauer and Sigmund [22] and the references therein. In this contribution we will be concerned with the relation between the dynamical systems (CSTR) and (R).

The limit of small flux rates r. In order to simplify the notation below we introduce the total concentration of the replicators $z = \sum_{j=1}^{n} y_j$ and the activity of the system $\Phi(y) = \sum_{j=1}^{n} y_j f_j(y)$. Throughout this contribution we will assume that the following to hypotheses hold:

(H1) there is a continuous function $h : \mathbb{R}_{0+} \to \mathbb{R}_{0+}$ such that $h(z) \leq f_j(y)$ on any compact subset of $\mathbb{R}^n_{+0}$ and $h(z) > 0$ for all $z > 0$.

(H2) the initial conditions fulfills $z(t = 0) > 0$.

Hypothesis (H1) means that we limit ourselves to the species that are capable of replication in the absence of all other replicators. The self-catalyzed selfreplication can, however, be much less effective then replication catalyzed by other polymers in the system. Hypothesis (H2) requires that some replicators are present in the initial condition.

It is well known that $a(t) + z(t)$ converges exponentially towards a_0 for $t \to \infty$ [33]. The following lemma shows that the for small enough flow rates r the CSTR will eventually be filled almost entirely by replicators (as opposed to being filled by unprocessed building material) provided (H1) and (H2) are true.

Lemma 1. *For any initial value problem* (CSTR) *fulfilling* (H1) *and* (H2) *there exist two constants* $m_1, m_2 > 0$ *independent of the initial condition and a constant* $r_0 = r_0(z(0)) > 0$ *such that for all* $r \leq r_0$ *there exists a finite time*

$T = T(r, a(0), y(0)) < \infty$ *with the property that the inequality* $m_1 r < a(t) < m_2 r$ *holds for all* $t \geq T$.

Proof. The first step is to show that there exists a constant $0 < \gamma < 1$, independent of r and the initial conditions such that $a(t) < \gamma a_0$. First we construct a differential equation for z:

$$\dot{z} = \sum_{j=1}^{n} \dot{y}_j = \Phi(y)a - rz \geq zh(z)a - rz\,.$$

Now suppose there is a $t^* > T$, which might depend on $r > r_0$, such that $a(t) > \gamma a_0$. Then

$$\dot{z}(t^*) \geq z(t^*)\underbrace{[\gamma a_0 h(z(t^*)) - r]}_{>0}$$

By continuity of h there is a continuous function $z_0(r) \geq 0$ such that $\gamma a_0 h(z) > 2r$ for all $z \geq z_0(r)$. Conversely, given $z(t^*)$, there exists a $r^* > 0$ such that the expression in the bracket is bounded from below by r^*. Then $z(t + t^*) \geq z(t^*)\exp(r^* t) \to \infty$, which contradicts the uniform upper bound $z(t) < 2a_0$, because of $z(t) + a(t) \to a_0$ for long times. Since γ is an arbitrary constant for which have only required $0 < \gamma < 1$ we have in particular $z(t) > a_0/2$ and $a(t) < a_0/2$ for all $t > T$.

The second step is to use the differential equation $\dot{a} = -a\Phi(y) + r(a_0 - a)$ for obtaining tighter bounds on $a(t)$. For large enough t one finds

$$\frac{1}{2}\min\frac{ra_0}{\Phi(y)+r} < a(t) < 2\max\frac{ra_0}{\Phi(y)+r}\,,$$

where the minimum and the maximum are taken over all $y(t)$ with $t > T$. The lower bound is easily obtained:

$$\frac{1}{2}\min\frac{ra_0}{\Phi(y)+r} > \frac{ra_0}{2}\cdot\frac{1}{\max\Phi(y)+r_0} > r\frac{a_0}{2}\cdot\frac{1}{2a_0M_1+r_0} \stackrel{\text{def}}{=} m_1 r\,,$$

where we have used that $\max\Phi(y) \leq \max z \cdot \max f_j(y)$ and M_1 is a uniform upper bound for $f_j(y)$ on the box $[0, 2a_0]^n$ which exists by the continuity assumptions of f_j. Analogously we observe that

$$\min\Phi(y) \geq \min z \cdot \min h(z) > \frac{a_0}{2}\min_{z>a_0/2}\Phi(z) = \frac{a_0}{2}\eta$$

where the constant $\eta \stackrel{\text{def}}{=} \min_{z>a_0/2} \Phi(z) > 0$ as an immediate consequence of (H1). Collecting the inequalities for the upper bound we find

$$a(t) < \frac{a_0 r}{(\eta/2) a_0} \stackrel{\text{def}}{=} m_2 r.$$

Observing that m_2 is independent of r completes the proof. ∎

Schuster and Sigmund [33] showed that the projections of the trajectories of (CSTR) to relatives concentrations x_k follow a replicator equation (R) provided all functions f_k, $1 \leq k \leq n$ are homogeneous of degree p. They were not concerned with the survival or extinction of the replicators. As a consequence of Lemma 1 we can resolve this problem.

Theorem 1. *Consider the system (CSTR) together with the hypotheses (H1) and (H2) and let f_k be a homogeneous function of degree p for $1 \leq k \leq n$. Then there is a constant $r_0 > 0$ such that for all $r \leq r_0$ we have $z(t) > a_0/2$ for large enough times t and the relative concentrations x_k are given by the solutions of the replicator equation (R) up to a finite change in velocity.*

Proof. It has been shown in [33] that the x_k fulfill the differential equation

$$\dot{x}_k = a x_k \left[f_k(y) - \sum_{j=1}^{n} x_j f_j(y) \right] = a(t) z(t)^p \cdot x_k \left[f_k(x) - \sum_{j=1}^{n} x_j f_j(x) \right]$$

Lemma 1 now implies that $a(t)z(t) > m_1 r (a_0/2)^p > 0$ for large enough times, and thus we can invoke a change in velocity in order to drop the time-dependent factor $a(t)z(t)$ without changing the phase portraits. ∎

Using $g \stackrel{\text{def}}{=} \ln(a/r)$ instead of a we can rewrite (CSTR) as

$$\begin{aligned} \dot{g} &= a_0 \exp(-g) - \Phi(y) - r \\ \dot{y}_k &= r y_k [f_k(y) \exp(g) - 1] \end{aligned} \qquad \text{(CSTR')}$$

Lemma 1 can be restated for this dynamical system in the following form:

Corollary 1. *Given $z_0 > 0$ there exists a constant $r_0 = r_0(z_0)$ such that the compact box $K \stackrel{\text{def}}{=} [\ln m_1, \ln m_2] \times [a_0/2, 2a_0]^n$ is strictly forward invariant under the flow of* (CSTR') *for all $r \leq r_0$, and K is reached in finite time from all initial condition fulfilling $z(0) \geq 0$.*

Lemma 2. *The phase portrait of* (CSTR') *and the phase portrait of the singular perturbation problem*

$$\begin{aligned} r\dot{g} &= \exp(-g)[a_0 \exp(-g) - \Phi(y) - r] \\ \dot{y}_k &= y_k[f_k(y) - \exp(-g)] \end{aligned} \tag{SPP}$$

are topologically equivalent on the compact box K provided $0 < r \leq r_0$.

Proof. The vector fields on the r.h.s of eqns. (CSTR') and (SP) differ by simply by the factor $r\exp(g)$. Lemma 1 implies immediately that $r\exp(-g) = a(t)$ is bounded away from 0 on the box K. Thus (SPP) is obtained from (CSTR') by a change in velocity. ∎

Singular Perturbation Theory. A good introduction to singular perturbation theory is for instance [27]. The following results [16, 20, 25, 31] explain in what sense a singularly perturbed dynamical system of the form

$$\begin{aligned} \dot{x} &= f(x, y, q, \epsilon) \\ \epsilon\dot{y} &= g(x, y, q, \epsilon) \end{aligned} \tag{$*$}$$

can be described by the limiting case $\epsilon \to 0$. Here $x \in X$ and $y \in Y$ are the slow and fast variables, respectively; $q \in A \subseteq \mathbb{R}^p$ is the admissible set of parameters, and $\epsilon \in [0, \epsilon_0] = I \subseteq R$. Furthermore let $K \subset X \times Y$ be compact such that int K is simply connected. We will be interested only in the dynamics of (*) in the compact set K. Suppose the vector field g has the following properties:

(i) There exists a unique smooth function $\varphi : X \times A \to Y$ which solves the algebraic equation $g(x, \varphi(x, q), q, 0) = 0$.

(ii) The Jacobian $J(x, q) = \dfrac{\partial g}{\partial y}(x, \varphi(x, q), q, 0)$ is uniformly hyperbolic on $X \times A$, i.e., there is a positive constant $\vartheta > 0$ such that absolute value of all eigenvalues of $J(x, q)$ is bounded below by ϑ for all $x \in X$ and all $q \in A$.

(iii) For fixed $q \in A$ we have $\{(x, \varphi(x,q)) | x \in X\} \cap K \neq \emptyset$.

Then there is an open sets $A' \subseteq A$, and an open interval $I' \in I$ such that for all $(q,\epsilon) \in A' \times I'$ there is a unique integral manifold $\mathcal{M}_{q,\epsilon} = \{y = \psi(x,q,\epsilon) | x \in X\}$ with the following properties:

(i) $\psi : X \times A' \times I' \mapsto Y$ is continuously differentiable.

(ii) ψ satisfies $\lim_{\epsilon \to 0} \psi(x,q,\epsilon) = \varphi(x,q)$ and $\lim_{\epsilon \to 0} \frac{\partial \psi}{\partial x}(x,q,\epsilon) = \frac{\partial \varphi}{\partial x}(x,q)$ uniformly on $X \times A'$:

If $J(x,q)$ is stable on $X \times A$ then the long-time behavior of a trajectory passing through a point x_0 in a suitably small neighborhood of the integral manifold $\mathcal{M}_{q,\epsilon}$ is determined by the dynamics on this manifold, that is, by the differential equation

$$\dot{x} = f(x, \psi(x,q,\epsilon), q, \epsilon)\,. \tag{**}$$

The limit of the above differential equation for $\epsilon \to 0$ is known as the *degenerate system* $\dot{x} = F(x,q) \stackrel{\text{def}}{=\!=} f(x, \psi(x,q,0), q, 0)$. If f is continuously differentiable with uniformly bounded derivatives on $X \times Y$, then there is a function $\theta_*(\epsilon)$ with $\theta_*(0) = 0$ such that $\sup\{\|\Delta(x,q,\epsilon)\|, \|\partial\Delta/\partial x\|\} < \theta_*(\epsilon)$. In other words the dynamics of trajectories near the integral manifold is described by the differential equation $\dot{x} = F(x,q) + \Delta(x,q,\epsilon)$ where $\Delta(x,q,\epsilon)$ is a regular perturbation of the degenerate system $\dot{x} = F(x,q)$. In such a case we say the singular perturbation problem (*) *reduces to* the degenerate problem (on the slow manifold) for $\epsilon \to 0$.

If (*) reduces to its degenerate system, then the following propositions are true:

(i) It the degenerate system has a hyperbolic equilibrium $\hat{x}_0$, then there is a hyperbolic equilibrium $\hat{x}_\epsilon$ of (*) nearby, at least for sufficiently small ϵ. In particular, $\hat{x}_\epsilon$ is asymptotically stable iff $\hat{x}_0$ is asymptotically stable [37].

(ii) If the degenerate system has a non-degenerate closed orbit $\hat{\pi}_0$ with primitive period T_0, then (*) contains a nearby non-degenerate closed orbit $\hat{\pi}_\epsilon$ with primitive period T_ϵ close to T_0 for small enough $\epsilon > 0$ [1]

(iii) The existence of a transversal homoclinic orbit in the degenerate system implies the existence of a nearby transversal homoclinic orbit in (*) for sufficiently small $\epsilon > 0$ [31, Thm. 3.1'].

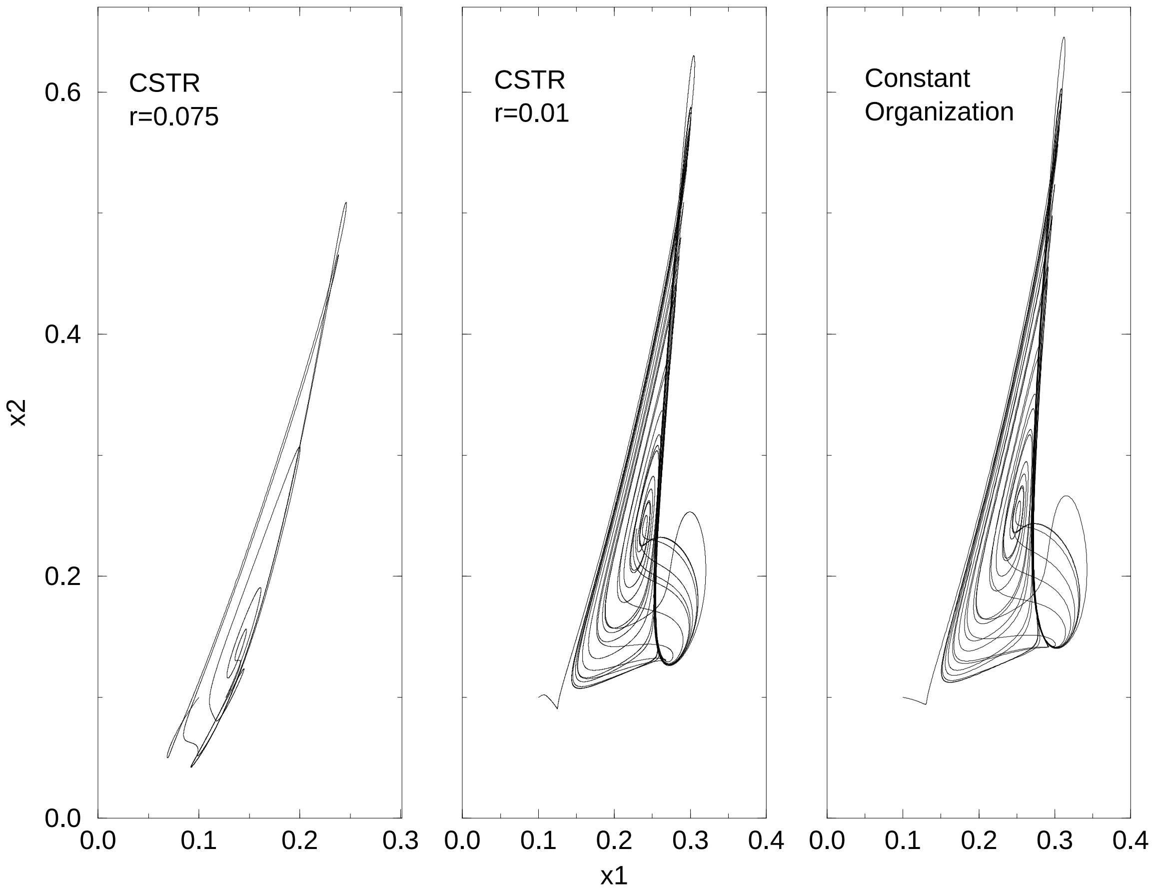


Figure 2: A numerical example of a chaotic attractor. For small r the dynamics of the CSTR and the corresponding replicator equation become virtually indistinguishable.
We consider four replicating species with interaction functions $f_k(y) = \alpha_k + \sum_j a_{kj} y_j$, where $\alpha_k = 0.1$ and

$$a_{ij} = \begin{pmatrix} 0 & 0.5 & -0.1 & 0.1 \\ 1.1 & 0 & -0.6 & -0.001 \\ -0.5 & 1 & 0 & 0.655 \\ 1.7 & -1 & -0.2 & 0 \end{pmatrix}.$$

A was chosen according to [2, 3, 30]. Initial conditions were $y_{1,2,3} = 0.1, y_4 = 0.7, a = 0.1$ and $a_0 = 1$. From left to the right the flow rate r was reduced ($r_1 = 0.075, r_2 = 0.01, r_3 = 0.0$) The right-hand figure represents constant organization.

Property (iii) also suggests that the existence of a strange attractor of the degenerate system implies the existence of chaotic orbits in the non-degenerate system

[19]. In special cases, for instance Silnikov's theorem [34] can be used to make this statement precise [31]. For a numerical example see figure 2.

The Main Result. Let us now return to the limit $r \to 0$ our singular perturbation version of the CSTR equation. The main result of this contribution is that (SPP) reduces to a replicator equation in the above sense.

Theorem 2. (CSTR) *reduces to* (R) *on* K *for small enough flow rates* r*.*

Proof. In our model the fast variable g is one-dimensional. Of course all our vector fields are smooth enough for the above arguments to be applicable to our models. For $r = 0$ the first equation reduces to $\Phi(\tilde{y}) = a_0 \exp(-\tilde{g})$, i.e., given y we obtain a unique solution for g on K. Its Jacobian at x is simply given by partial derivative

$$\frac{\partial \dot{g}}{\partial g} = \exp(-g)[a_0 \exp(-g) - \Phi(y) - r] - a_0 \exp(-2g) = -r\dot{g} - a_0 \exp(-2g)\,.$$

For sufficiently small r we have $|r\dot{g}| < a_0 \exp(-2g)$ on K and hence the solution for g is stable on K. Consequently (CSTR') reduces to (R) for small enough r. ∎

In particular there is a one-to-one correspondence of the fixed points of the replicator equation (R) and the equilibria of (SPP) for small non-zero flux rate r, *provided* the equilibria of the replicator equation are regular (i.e., if their Jacobian matrices are hyperbolic). Similarly, hyperbolic limit cycles carry over.

In general, if only the concentration of the low-molecular monomers is small enough then constant organization with its much less involved mathematics is sufficient to describe the dynamical behavior.

Acknowledgments. We thank Christian Forst for carefully reading this manuscript. Financial support by the Austrian *Fond zur Förderung der wissenschaftlichen Forschung* is gratefully acknowledged.

References

[1] D. Ansov. On limit cycles of systems of differential equations with a small parameter at the highest derivatives. *Mat. Sbornik*, 50:299–334, 1960.

[2] A. Arneodo, P. Coullet, J. Peyraud, and C. Tresser. Strange attractors in volterra equations for species competition. *J. math .Biol.*, 14:153–157, 1982.

[3] A. Arneodo, P. Coullet, and C. Tresser. Occurance of strange attractors in three- dimensional volterra equations. *Phys. Lett.*, 79A:259–263, 1980.

[4] D. P. Bartel and J. W. Szostak. Isolation of new ribozymes from a large pool of random sequences. *Science*, 261(5127):1411–1417, 1993.

[5] A. A. Beaudry and G. F. Joyce. Directed evolution of an RNA-enzyme. *Science*, 257:635–641, 1992.

[6] T. Cech. Conserved sequences and structures of group I introns: building an active site for RNA catalysis — a review. *Gene*, 73:259–271, 1988.

[7] T. Cech and B. Bass. *Ann. Rev. Biochem.*, 55:599–629, 1986.

[8] T. Cech, A. Zaug, and P. Krabowski. *Cell*, 27:487–496, 1981.

[9] J. Doudna, S. Couture, and J. Szostak. A multi-subunit ribozyme that is a catalyst of and and a template for complementary-strand RNA synthesis. *Science*, 251:1605–1608, 1991.

[10] J. Doudna, N. Usman, and J. Szostak. Ribozyme-catalyzed primer extension by trinucleotides: A model for the RNA-catalyzed replication of RNA. *Biochemistry*, 32:2111–2115, 1993.

[11] M. Eigen. Selforganization of matter and the evolution of macromolecules. *Naturwiss.*, 58:465–523, 1971.

[12] M. Eigen and P. Schuster. The hypercycle: A. emergence of the hypercycle. *Naturwiss.*, 64:541–565, 1977.

[13] M. Eigen and P. Schuster. The hypercycle: B. the abstract hypercycle. *Naturwiss.*, 65:7–41, 1978.

[14] M. Eigen and P. Schuster. The hypercycle: C. the realistic hypercycle. *Naturwiss.*, 65:341–369, 1978.

[15] M. Famulok, J. Nowick, and J. Rebek Jr. Self-Replicating Systems. *Act.Chim.Scand.*, 46(4):315–324, 1992.

[16] N. Fenichel. Geometric singular perturbation theory for ordinary differential equations. *J. Diff. Eqns.*, 31:53–98, 1978.

[17] R. Gesteland and J. Atkins, editors. *The RNA World.* Cold Spring Harbor Laboratory Press, Cold Spring Harbour, NY, USA, 1993.

[18] C. Guerrier-Takada and S. Altman. *Science*, 223:285–286, 1984.

[19] J. Guggenheimer and P. Holmes. *Nonlinear Oscillations, Dynamical Systems ond bifurkations of Vector Fields.* Springer, New York,Berlin,Tokyo, 1983.

[20] D. Henry. *Geometric Theory of semilinear parabolic equations*, volume 840 of *Lecture Notes in Mathematics.* Springer-Verlag, Berlin, 1978.

[21] J. Hofbauer. On the occurrence of limit cycles in Volterra-Lotka equations. *Nonlin. Anal.*, 5:1003–1007, 1981.

[22] J. Hofbauer and K. Sigmund. *Dynamical Systems and the Theory of Evolution.* Cambridge University Press, Cambridge U.K., 1988.

[23] Y. Husimi. Selection and evolution in cellstat. *Adv. Biophys.*, 25:1–43, 1989.

[24] D. Kacian, D. Mills, and S. Spiegelman. The mechanism of Qβ replication: sequence at the 5' terminus of a 6S template. *Biochim. Biophys. Acta*, 238:212–223, 1971.

[25] H. Knobloch and B. Aulbach. Singular perturbations and integral manifolds. *J.Math.Phys.Sci*, 18:415–424, 1984.

[26] M.Heinrichs and F. Schneider. Relaxation Kinetics of Steady States in the Continuous Flow Stirred Tank Reactor. Response to Small and Large Perturbations: Critcal Slowing Down. *J.Phys.Chem.*, 85:2112–2116, 1981.

[27] R. E. O'Malley, Jr. *Singular Perturbation Methods for Ordinary Differential Equations*. Springer-Verlag, New York, 1991.

[28] L. Orgel. Molecular Replication. *Nature*, 358:203–209, 1992.

[29] J. Rebek Jr. Synthetic Self-replicating Molecules. *Sci.Am.*, 271(1):48–57, 1994.

[30] W. Schnabl, P. F. Stadler, C. Forst, and P. Schuster. Full characterization of a strange attractor. *Physica D*, 48:65–90, 1991.

[31] K. R. Schneider. Singularly perturbed autonomous differential systems. In H. Bothe, W. Ebeling, A. Kurzhanski, and M. Peschel, editors, *Dynamical Systems and Environmental Models*. VEB-Verlag, Berlin, 1987.

[32] P. Schuster and K. Sigmund. Replicator dynamics. *J.Theor.Biol.*, 100:533–538, 1983.

[33] P. Schuster and K. Sigmund. Dynamics of evolutionary optimization. *Ber.Bunsen-Gesellsch.phys.Chem.*, 89:668–682, 1985.

[34] L. P. Silnikov. On a case of the existence of a countable set of periodic motions (Russian). *Dokl.Akad.Nauk SSSR*, 160:558–561, 1965.

[35] J. S.Novick, Q. Feng, and T. Tjivikua. Kinetic studies and modeling of a self-replicating system. *J. Am. Chem. Soc.*, 113(23):8831–8838, 1991.

[36] S. Spiegelman. An approach to the experimental analysis of precellular evolution. *Quaterly Review of Biophysics*, 4:213–251, 1971.

[37] A. Tichonov. Systems of differntial equations with a small parameter at the derivatives. *Mat. Sbornik*, 31:575–586, 1952.

[38] O. Uhlenbeck. A small catalytic oligonucleotide. *Nature*, 328:596–600, 1987.

[39] G. von Kiedrowski. Minimal replicator theory I: Parabolic versus exponential growth. In *Bioorganic Chemistry Frontiers, Volume 3*, pages 115–146, Berlin, Heidelberg, 1993. Springer-Verlag.

[40] F. H. Westheimer. Polyribonucleic acids as enzymes. *Nature*, 319:534, 1986.