# Autocatalytic Networks with Intermediates I:

## Irreversible Reactions

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**Abstract**

A class of autocatalytic reaction networks based on template dependent replication and specific catalysis is considered. Trimolecular "elementrary steps" of simple replicator dynamics are resolved into two consecutive irreversible reactions. The extreme cases, competition for common resources and hypercycle-like cooperative feedback, were analyzed in some detail. Although the dynamics of the extended networks resembles corresponding replicator dynamics in general, there are significant differences. Most notably, the interior fixed points in the cooperative model turned to be are asymptotically stable for an arbitrary number of species whereas simple replicator dynamics predict an asymptotically stable fixed for four species and less and a stable periodic orbit for all other cases.

## 1. Introduction

Spiegelman's pioneering studies [40] on replication of Q$\beta$ RNA and evolution *in vitro* initiated a great number of investigations dealing with the design of self-replicating chemical and biochemical systems. Non-natural molecules were synthesized that can act as templates and undergo self-replication in enzyme-free environments [15, 32, 34, 31, 46]. Catalytic activities of RNA include also limited capacities for ligation and replication [4, 5]. These results encouraged the suggestion that "early life" consisted of a world of molecular replicators, RNA molecules or simpler precursors. The existence of an *RNA world* thus is a promising hypothesis in this context [19]. Whether or not a scenario of competing molecular replicators has played an fundamental role in prebiotic chemistry, the behavior of collections of interacting replicator species is basic to any theory of molecular evolution.

In parallel to the advances in template chemistry a theory of molecular evolution based on chemical reaction kinetics and mathematics of dynamical systems has been developed by Eigen and Schuster [6, 9, 10, 11]. These studies focussed on a simplified kind of "over-all" kinetics of replication and ignored all finer stuctural and mechanistic details. Replicator dynamics is considered as mass action kinetics of sets of autocatalytic "chemical" reactions neglecting most or all reaction intermediates. In its most condensed form the kinetics of error-free replication of interacting molecular species is casted into the *autocatalytic reaction network*

$$(M) + I_k + I_l \longrightarrow 2I_k + I_l + (W) \qquad k,l = 1,\dots,n. \qquad (\mathcal{R})$$

where $I$ is the replicator and $(M)$ denotes the energy-rich building material for replicators, for example the four activated nucleotides in form of nucleoside triphosphates ATP, UTP, GTP, and CTP. $(W)$ accounts for the low-energy "waste" that accompanies the formation of replicators. Since $M$ is assumed to be buffered at constant concentration and $W$ does not show up in the kinetic differential equations for irreversible reactions, they are both put in parentheses. Often the model is extended by consideration of the uncatalyzed replication reaction, see e.g. [10, 42].

$$(M) + X_i \to 2X_i + (W) \tag{$\mathcal{R}'$}$$

The dynamical system that are most commonly associated with these two reaction schemes are a second order *replicator equation* of the form

$$\dot{x}_k = x_k \left( \sum_{j=1}^{n} b_{kj} x_j - \sum_{i,j} b_{ij} x_i x_j \right)$$

and a first order *replicator equation* of the form

$$\dot{x}_k = x_k \left( a_k - \sum_i a_i x_i \right)$$

for $(\mathcal{R})$ and $(\mathcal{R}')$, respectively. Originally developed as a model of prebiotic evolution, replicator equations have been encountered since then in many different fields [37]: populations genetics, mathematical ecology (where they occur disguised as Lotka-Volterra equations [24]), economics, or laser physics. The mathematical properties of replicator equations have been the subject of hundreds of research papers, see [29] and the references therein. One of the major advantages of simple replication kinetics consists in its straightforward extension to mutation that is understood as a parallel process to correct replication. Both first and second order replication with mutation have been studied extensively, see e.g. [6, 7, 8, 9] for the first order and [43, 44] for the second order case.

Straighforward extensions of the replicator model deal with two different issues:

(i) Second order replicator equations $(\mathcal{R})$ involve trimolecular encounters which are generally improbable according to collision theory. In order to avoid unlikely occurring events trimolecular encounters can be resolved in consecutive bimolecular encounters (for example see [13] and this contribution).

(ii) Polymerization kinetics involves a number of individual reaction steps that are repeated for every monomer to be incorporated into the growing polymer chain. Replication of templates of a thousand monomers consists of several thousand individual steps. From the point of view of reaction kinetics replication of polynucleotides is an overwhelmingly complicated process involving a large number of intermediates [3].

It is by no means self-evident that the global features of such a complicated reaction mechanism can indeed be captured by an over-all replicator dynamics that treats replication events quasi as elementary steps and encodes all structural and functional details into a small set of reaction rate constants. A variety of mechanisms based on more involved reaction schemes have been investigated. Many of them reproduce the qualitative behavior of pure replicator networks quite well (see, e.g., [13, 18]). A model involving replication and translation has be formulated and studied by computer simulation [11]. This system can be viewed, for example, as a singularly-perturbed replicator equation [20].

In this contribution we introduce and analyse a mechanism that resolves the trimolecular reaction of second order replicator equations ($\mathcal{R}$) into two consecutive bimolecular steps (and thus is an analogue of the previously reported extended hypercycle model [13]):

$$\begin{aligned} M + X_i &\xrightarrow{g_i} X_i + S_i \\ X_i + S_j &\xrightarrow{c_{ij}} 2X_i \end{aligned} \tag{$\mathcal{I}$}$$

This reaction scheme involves an intermediate product $S_i$ which, for example, can be interpreted as a specifically activated form of the substrate. According to mass action kinetics the relations $g_i > 0$ and $c_{ij} \geq 0$ are always fulfilled. In addition we shall include the first order (uncatalyzed) replication reaction:

$$M + X_i \xrightarrow{k_i} 2X_i \,. \tag{$\mathcal{I}'$}$$

The purpose of this contribution is neither to provide a detailed description of realistic replication kinetics in a contemporary organism nor to simulate real *in vitro* evolution experiments. We are interested here in the validity and the limits of simple replicator dynamics. To this end we consider here a model that is still much simpler than models of RNA replication kinetics devised by Biebricher and Eigen [2, 3], but which is sufficiently complicated to show a significant influence of the resolution of "over-all" kinetics into more detailed elementary steps resulting in deviations from the replicator scenario. On the other hand, our model is simple enough to allow for an (at least partial) analytical treatment.

The paper is organized as follows. In section 2 we outline the mathematical model and describe its limiting cases by means of singular perturbation theory. Sections 3 and 4 contain detailed descriptions of the competitive and the cooperative cases, respectively. In section 5 we discuss the relation of our system to other classes of autocatalytic networks. Mathematical details are compiled in two appendices: Appendix A compiles the proofs of the lemmas and theorems quoted in the main text. A brief discussion of the properties of the Jacobian matrix for our system is the topic of appendix B.

## 2. Model Equations

Assuming mass action kinetics it is straightforward to write the reaction mechanism $(\mathcal{I}, \mathcal{I}')$ in form of kinetic equations:

$$\begin{aligned} \dot{x}_i &= x_i \left( ak_i + \sum_{j=1}^{n} c_{ij} s_j - \Psi \right) \\ \dot{s}_i &= g_i a x_i - s_i \sum_{j=1}^{n} x_j c_{ij} - s_i \Psi \ . \end{aligned} \tag{1}$$

Explicit expressions for substrate concentration $a = [M]$ and dilution flux $\Psi$ specify the dynamical boundary conditions. In the case of *constant organization* (CO) we have $a \equiv 1$ (after a suitable transformation of the time axis) and $\sum_i (x_i + s_i) = 1$ with a suitable normalization of the concentrations. The total concentration $c_0$ is then contained as an implicit multiplicative factor in the second order rate constants $c_{ij}$. As a consequence we obtain

$$\Psi_{\mathrm{CO}} = a \sum_{j=1}^{n} (k_j + g_j) x_j = \sum_{j=1}^{n} \kappa_i x_i \overset{\mathrm{def}}{=\!=} \Phi \, . \tag{2}$$

Here we define: $\kappa_i \stackrel{\text{def}}{=} k_i + g_i$. Note that the form of the flux function $\Psi_{\text{CO}}$ is quite different from the quadratic form in the second order replicator equation. Since the overall concentration is held constant, the phase space is the unit simplex

$$\mathbf{S}_{2n} = \left\{ (x_1, \ldots, x_n, s_1, \ldots, s_n) \;\middle|\; x_i, s_i \geq 0 \wedge \sum (x_i + s_i) = 1 \right\}.$$

In the CSTR setting the concentration of the substrate varies and we have to take into account its influence explicitly. Then, $\Psi_{\text{CSTR}} = r$ is a constant flux rate, while the building material $a$ satisfies the differential equation:

$$\dot{a} = a_0 r - a \left( \sum_{j=1}^{n} \kappa_i x_i + r \right) . \tag{3}$$

For convenience we use the same notation for variables as in the constant organization setting since most of the results are very similar. As usual in the CSTR, the total concentration $c_0 = a + \sum_i (x_i + s_i)$ converges to $a_0$. Therefore all fixed points lie on the $2n+1$-dimensional simplex

$$\mathbf{S}_{2n+1}(a_0) = \left\{ (x_1, \ldots, x_n, s_1, \ldots, s_n, a) \;\middle|\; x_i,\; s_i,\; a \geq 0 \wedge a + \sum (x_i + s_i) = a_0 \right\}.$$

From equ.(1-3) we see that if the replicating species $X_i$ vanishes at a certain fixed point, then the corresponding intermediate $S_i$ must also vanish and vice versa. We can therefore characterize a fixed point $P_I$ by its *index set* $I$, i.e., by the set of the species with positive concentrations at the fixed point. The number of these species is denoted by $|I|$. It will be useful therefore the introduce the following definition:

> **Definition.** An index set $I$ is *admissible* if the corresponding fixed point $P_I$ exists in a non-empty range of total concentrations or flux rates in the CSTR setting, respectively.

The concentrations of the individual species are coupled only via $\Phi$ or $a$, respectively. Thus the computation of the equilibrium concentrations is the same for fixed points in the interior and on the boundary of the simplex because the boundary consists of subsimplices on which the dynamics is given by a lower dimensional analogue of equation (1). The stability of the fixed points, however, depends of course on all coordinates not only on those that belong to non-vanishing species. Let $(\bar{x}, \bar{s})$ or $(\bar{x}, \bar{s}, \bar{a})$ be a fixed point with admissible index set $I$. Then we can arrange the Jacobian matrix in the following form

$$\mathbf{J} = \begin{pmatrix} \mathbf{J}_1 & 0 & \dots & 0 & \\ 0 & \mathbf{J}_2 & & 0 & \\ \vdots & & \ddots & & \mathbf{0} \\ 0 & 0 & \dots & \mathbf{J}_{n-|I|} & \\ & & \mathbf{X} & & \mathbf{J}_I \end{pmatrix}$$

where $\mathbf{J}_i$ is $2 \times 2$ matrix belonging to a species $i \notin I$. The derivatives with respect to $a$ and derivatives of $\dot{a}$ form the last row and the last column, respectively, in the CSTR case. The blocks $\mathbf{J}_i$ are of the form

$$\mathbf{J}_i \stackrel{\text{def}}{=} \begin{pmatrix} \frac{\partial \dot{x}_i}{\partial x_i} & \frac{\partial \dot{s}_i}{\partial x_i} \\ \frac{\partial \dot{x}_i}{\partial s_i} & \frac{\partial \dot{s}_i}{\partial s_i} \end{pmatrix} = \begin{pmatrix} ak_i + (Cs)_i - \Psi & 0 \\ ag_i & -[(xC)_i + \Psi] \end{pmatrix}$$

in both the CSTR and the constant organization model. By $\mathbf{X}$ we denote a matrix of expressions that have no influence on the eigenvalues of the Jacobian. $\mathbf{J}_I$, finally, describes the linearized ODE on the subsimplex of the non-vanishing species.

The eigenvalues of the Jacobian matrix of (1,2) or (1,3) can therefore by subdivided into three classes:

(i) *Transversal* eigenvalues belong to the species that vanish on boundary points. These are the diagonal entries of the the $2 \times 2$ blocks $\mathbf{J}_i$ with $i \notin I$. One of them is always negative. The form of the other one is reminiscent of the transversal eigenvalues of the second order replicator equation [25]. The transversal eigenvalues describe the stability of a fixed point on the boundary against the invasion of an additional species.

(ii) The *external* eigenvalue $-\bar{\Phi}$ or $-r$, respectively corresponds to a left eigenvector with entries of unity for $i \in I$ and zero for $l \notin I$. It decribes the approach of the system to the simplex $\mathbf{S}_{2n+1}(a_0)$ in the CSTR. Under constant organization it reflects the normalization constraint and has no physical interpretation at all.

(iii) All other eigenvalues are called *internal*. They depend only on the non-vanishing species $j \in I$, that is on the block $\mathbf{J}_I$. In contrast to transversal and external eigenvalues it is not possible in general to obtain explicit expressions for the internal eigenvalues.

Not much can be said about the general model. A few partial results on low-dimensional equilibria can be found in [22]. Two opposite extreme cases, however, can be analysed with considerable detail:
The **competitive case**, in which each species replicates independent of all the other ones can be viewed as a generalization of the Schlögl model [35]. The interaction matrix $C$ has the entries $c_{ij} = f_i\delta_{ij}$, where $\delta_{ij}$ is Kronecker's symbol. The species interact only via substrate and flux, i.e., they compete for a common resource.
In the **cooperative case** specific interactions between different species are a prerequisite for replication. We consider here only the most prominent example: $X_i$ produces $S_i$, which in turn produces $X_{i+1}$ for $i = 1, \ldots, n-1$ and and $S_n$ produces $X_1$. This type of cyclic catalysis is known as the *hypercycle* [9, 10, 11]. The interaction matrix is of the form $c_{ij} = f_i\delta_{i-1,j}$ with the indices taken modulo $n$.

Before we return to the description of the two-step replication mechanism $(\mathcal{I}, \mathcal{I}')$ we consider a few limiting cases. A good introduction to singular perturbation theory is for instance [33]. We shall see that our model "reduces" to replicator equations in certain singular-perturbation limits. The results discussed in [16, 23, 30, 36] explain in what sense a singularly perturbed dynamical system of the form

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

can be derived from the limiting case $\epsilon \to 0$. Here $x \in X$ and $y \in Y$ are the slow and fast variables, respectively. $A \subseteq \mathbb{R}^p$ is the admissible set of parameters $q$ and $K \subset X \times Y$ is compact such that $\operatorname{int} K$ is simply connected. We will be interested only in the dynamics of (A) 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 stable on $X \times A$, i.e., there is a positive constant $\vartheta > 0$ such that real value of all eigenvalues of $J(x, q)$ is bounded above by $-\vartheta$ 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) $\psi$ satisfies $\lim_{\epsilon \to 0} \psi(x, q, \epsilon) = \varphi(x, q)$ and $\lim_{\epsilon \to 0} \dfrac{\partial \psi}{\partial x}(x, q, \epsilon) = \dfrac{\partial \varphi}{\partial x}(x, q)$ uniformly on $X \times A'$.

(iii) 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

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

The limit of the above differential equation for $\epsilon \to 0$ is known as the *degenerate system*

$$\dot{x} = F(x, q) \stackrel{\text{def}}{=\!=} f(x, \psi(x, q, 0), q, 0) . \tag{B}$$

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 (A) *reduces to* the degenerate problem (B) on the slow manifold for $\epsilon \to 0$. If (A) 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 (A) nearby, at least for sufficiently small $\epsilon$. In particular, $\hat{x}_\epsilon$ is asymptotically stable iff $\hat{x}_0$ is asymptotically stable [45].

(ii) If the degenerate system has a non-degenerate closed orbit $\hat{\pi}_0$ with primitive period $T_0$, then (A) contains a nearby non-degenerate closed orbit $\hat{\pi}_\epsilon$ with primitive period $T_\epsilon$ 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 (A) for sufficiently small $\epsilon > 0$ [36, Theorem 3.1'].

We return now to the two-step replication mechanism $(\mathcal{I}, \mathcal{I}')$.

**Theorem 1.** The dynamical system (1,3) in the CSTR setting reduces to the inhomogeneous replicator equation

$$\dot{y}_i = y_i \left[ k_i + \sum_j c_{ij} y_j - \sum_l y_l \left( k_l + \sum_j c_{lj} y_j \right) \right]$$

when the formation of the intermediates is fast, i.e., for $g_i \to \infty$.

Interestingly, the CSTR version of this model does not reduce to the analogous constant organization equation in the limit $r \to 0$. In stead we have

**Theorem 2.** The dynamical system (1,3) in the CSTR reduces in the limit of small flux rates, $r \to 0$, to the non-linear replicator equation

$$\dot{y}_i = y_i \left[ f_i(y) - \sum_j y_j f_j(y) \right] \tag{C}$$

with the response function

$$f_i(y) = k_i + \frac{\sum_j c_{ij} g_j y_j}{\sum_j c_{ij} y_j} \,. \tag{D}$$

Another interesting limit is obtained when the replication step is very fast, i.e., if $c_{ij} = d_{ij}/\epsilon$ and $\epsilon \to 0$. In the constant organization case this correspond to large total concentrations $c_0 \to \infty$. Interestingly, we obtain the same limit as above in this case:

**Theorem 3.** The dynamical system (1) in both the constant organization and the CSTR setting reduces to the nonlinear replicator equation (C) with response function (D) in the limit large rate constants $c_{ij}$.

The replicator equation (C,D) will be discussed elsewhere. We remark here only that for all $g_i = g$ we have a first order replicator equation with fitness values $k_i + g$.

# 3. Competition

Both in the CSTR and in the constant organization setting we can perform a fairly complete analysis of the fixed points. Since the criteria for the existence of fixed points are very similar for both boundary conditions we shall discuss them together. Except for section 3.3 we shall assume that all parameters $k_i$ are different. Since the diagonal form of the coupling matrix $C$ is not changed if we relabel the species, we may assume that that the constants $k_i$ form a decreasing sequence.

The differential equations describing the competitive model under constant organisation are:

$$\begin{aligned} \dot{x}_i &= x_i(k_i + f_i c_0 s_i - \Phi) \\ \dot{s}_i &= g_i x_i - s_i(f_i c_0 x_i + \Phi) \end{aligned} \tag{4}$$

For the CSTR model we obtain

$$\begin{aligned} \dot{x}_i &= x_i(k_i a + f_i s_i - r) \\ \dot{s}_i &= g_i a x_i - s_i(f_i x_i + r) \\ \dot{a} &= a_0 r - a(r + \sum_i (k_i + g_i) x_i) \end{aligned} \tag{5}$$

## 3.1. Existence of Equilibria

The equilibrium concentrations at the fixed point $P_I$ (denoted by bars) are

$$\bar{s}_i = \frac{\bar{\Phi} - k_i}{f_i c_0} \qquad \bar{x}_i = \frac{\bar{\Phi}(\bar{\Phi} - k_i)}{f_i c_0(\kappa_i - \bar{\Phi})} \tag{6}$$

for all $i \in I$ in the case of constant organization. For the CSTR we find the equilibrium concentrations

$$\bar{s}_i = \frac{r - k_i \bar{a}}{f_i}, \qquad \bar{x}_i = \frac{r(r - k_i \bar{a})}{f_i(\kappa_i \bar{a} - r)} \tag{7}$$

In addition there is the *trivial* fixed point at which all replicating species and intermediates vanish: $\bar{a} = a_0$. It corresponds to the index set $I = \emptyset$.

**Lemma 1.** A fixed point of type $P_I$ exists if and only if $k_i < \bar{\Phi} < \kappa_i$ or if $k_i < r/\bar{a} < \kappa_i$ for all $i \in I$, respectively.

**Proof.** Obvious. ∎

The extremal indices $m, \mathcal{M} \in I$ are defined by $\kappa_m = \min_{i\in I} \kappa_i$ and $k_{\mathcal{M}} = max_{i\in I} k_i$, respectively. For all admissible index sets $I \neq \emptyset$ we set $I' = I \setminus \{\mathcal{M}\}$.

**Lemma 2.** (i) If $I \neq \emptyset$ is admissible then $I'$ is also admissible.
(ii) $I \neq \emptyset$ is admissible if and only if $k_{\mathcal{M}} < \kappa_m$.
(iii) $\emptyset$ is admissible for the CSTR.

**Proof.** This is a by-product of the proofs of the following theorems. ∎

We shall use the following notation for bifurcation points. A *transcritical* bifurcation involving fixed points of types $P_I$ and $P_J$ will be denoted by $I \bullet J$. A *saddle node bifurcation* involving two fixed points of the same type will we indicated by $*I$, and Hopf bifurcations will be denoted by $I\circ$. The symbols are used as superscripts of the bifurcation parameter for the critical values.

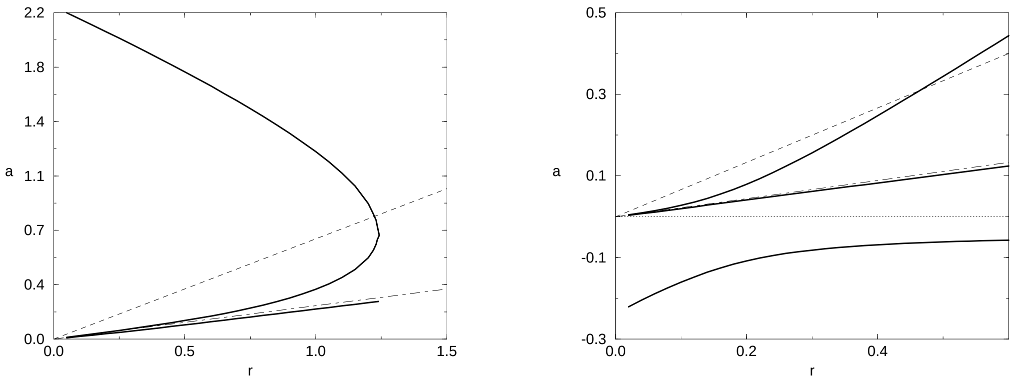
**Theorem 4.** Let $I$ be an admissible index for the competitive model under constant organization. Then the following assertions are true:
(i) If $|I| = 1$ then $P_I \in \mathbf{S}_n$ for all $c_0$.
(ii) If $|I| \geq 2$ then there is exactly one fixed point of type $P_I \in \mathbf{S}_n$ for sufficiently large values of $c_0$. At a certain total concentration $c_0^{I\bullet I'}$ a transcritical bifurcation with the fixed point of type $P_{I'}$ takes place. For $c_0 < c_0^{I\bullet I'}$ we have $P_I \notin \mathbf{S}_n$.

**Theorem 5.** Let $I$ be an admissible index for the competitive model in the CSTR. Then the following assertions are true:
(i) For sufficiently small flux rates $r$ there is exactly one fixed point of type $P_I$.
(ii) There exists a finite flux rate $r^{I\bullet I'} > 0$ at which a transcritical bifurcation occurs which involves a fixed point $P_I$ and a fixed point $P_{I'}$.
(iii) If $r > r^{I\bullet I'}$ one of the following three alternatives is true:
(a) There is no fixed point of type $P_I$ in the simplex.
(b) There are two fixed points of type $P_I$ with different concentrations $\bar{a}$ of the substrate (Figure 1a). In this case we observe a saddle node bifurcation

at a critical flux rate $r^{*\boldsymbol{I}} > r^{\boldsymbol{I}\bullet\boldsymbol{I}'}$.

(c) There is a single fixed point of type $P_{\boldsymbol{I}}$ in the simplex (Figure 1b). Furthermore we find case (a) for all $r > r^{*\boldsymbol{I}}$ and case (b) for all flux rates $r$ in the range $r^{*\boldsymbol{I}} > r > r^{\boldsymbol{I}\bullet\boldsymbol{I}'}$.

Two characteristic scenarios for two species and different choices of the rate constants are shown in Figure 1.




**a** **b**

**Figure 1:** Bifurcation patterns in the competitive case.
Stationary concentrations of the substrate $\bar{a}$ are shown as a function of the flow rate $r$ in the CSTR. The parameters are $n = 2$, $k_1 = 1.5$, $k_2 = 1$, $g_1 = 3$, $g_2 = 5$, $a_0 = 1$ for both cases and **a**) $f_1 = 7$, $f_2 = 2$; **b**) $f_1 = 0.8$, $f_2 = 0.3$. Physically acceptable solutions are confined to the region between the two dashed lines determined by equation (7).

### 3.2. Stability of Equilibria

Under constant organization the corresponding eigenvalues are $-\bar{\Phi}$ and $k_l - \bar{\Phi}$, respectively. In the CSTR we have the transversal eigenvalues $-r$ and $k_l\bar{a} - r$, respectively. We shall use the abbreviation $\boldsymbol{I}^l \stackrel{\text{def}}{=\!=} \boldsymbol{I} \cup \{l\}$. Three cases can be distinguished for the transversal eigenvalues:

(1) $\underline{k_l < k_{\mathcal{M}}}$. The eigenvalues are negative for all values of $c_0$ because $\bar{\Phi} > k_{\mathcal{M}}$ (or $r > k_{\mathcal{M}}\bar{a}$, respectively) the eigenvalue is always negative both in the CSTR and under constant organization

(2) $\underline{k_l > \kappa_m}$. There is one positive and one negative transversal eigenvalue for all total concentrations. (The fixed point $P^{I^l}$ does not exist, since $I^l$is not admissible) This is true for both the CSTR and constant organization.

(3) $\underline{k_{\mathcal{M}} < k_l < \kappa_m}$. Under constant organisation the behavior of the fixed points is fairly simple: There is a transcritical bifurcation with of $P_I$ with $P_{I^l}$ at $c_0^{I\bullet I^l} = \sum_{i\in I} \kappa_i(k_l - k_i)/f_i(\kappa_i - k_l)$. For total concentrations below this value, one of the transversal eigenvalues is positive and one negative. Above this value, both eigenvalues are negative.
The situation is much more involved in the case of the CSTR since there may be more than one fixed point with index set $I$. The behavior of the transversal eigenvalue can therefore be summarized as follows. For more details and proofs we refer to [22]. At $r^{I\bullet I^l}$ there is a transcritical bifurcation of $P_{I^l}$ with (one of the) fixed point(s) $P_I$. If $P_{I^l}$ passes through $P_I^{(1)}$, its transversal eigenvalue is positive for flux rates above $r^{I\bullet I^l}$. Since $\bar{a}^{(2)} > \bar{a}^{(1)}$, it is clear that the transversal eigenvalue is also positive for $P_I^{(2)}$. Reverting this argument we see that if $P_{I^l}$ passes through $P_I^{(2)}$, the transversal eigenvalue is negative for both fixed points $P_I$ at flux rates above $r^{I\bullet I^l}$, while it is positive for $P_I^{(2)}$ for lower flux rates.

Not much can be said about the internal eigevalues. As far as we could see, there is little difference in the behavior of the model between CSTR and constant organisation. Explicit expressions are available only for $|I| = 1$. Under constant organization there is one internal eigenvalue, which is negative. In the CSTR case we find two internal eigenvalues for $|I| = 1$ for each of the two fixed points of type $P_I$: for $P_I^{(1)}$ both are negative, for $P_I^{(2)}$ one is positive and one negative.

For the case of constant organization it can be shown that the determinant of the internal part of the Jacobian is negative for even $|I|$ and positive for odd $|I|$, see [22]. Consequently, there must be at least one positive internal eigenvalue for even $|I|$. Numerical studies for both boundary conditions indicate that there are always at least $|I| - 1$ positive internal eigenvalues, i.e., only fixed points with $|I| = 1$ can be stable.

For constant organization we have: A fixed point $P_{\{i\}}$ is stable if $\kappa_i > k_l$ for all $l$ and if $c_0 > c_0^{I \bullet I^j}$ for all $j$ with $k_j > k_i$. Numerical computations suggest that these are the only stable equilibria. The corresponding result for the CSTR is: A fixed point $P^{(1)}_{\{i\}}$ is stable if $k_l < \kappa_i$ for all $l$ and $r < r^{I \bullet I^j}$ for all $j$ with $k_j > k_i$. Numerical simulations again suggest that all other fixed points are unstable.

### 3.3. Special Case: The Symmetric Model

A more detailed analysis is possible in the special case of equal reaction constants for all species, i.e., if $k_i = k$, $g_i = g$, and $f_i = f$ for $i = 1, \ldots, n$. The symmetry in the rate constants induces symmetry in the equilibrium concentrations: $\bar{x}_i = \bar{x}$ and $\bar{s}_i = \bar{s}$ for all $i \in I$. Under these conditions a fairly complete stability analysis of the fixed points is possible. The properties of the Jacobian are discussed in appendix B.

Let us consider the constant organization model first. The differential equations simplify to

$$\begin{aligned} \dot{x}_i &= x_i(k + c_0 f s_i - \Phi) \\ \dot{s}_i &= g x_i - s_i(c_0 f x_i + \Phi) \end{aligned} \tag{8}$$

where $\kappa = k + g$ and the flux is given by $\Phi = \kappa \sum x_i$. The equilibrium concentrations at the fixed point $P_I$ are

$$\bar{x}_i = \frac{\bar{\Phi}(\bar{\Phi} - k)}{f c_0(\kappa - \bar{\Phi})}, \qquad \bar{s}_i = \frac{\bar{\Phi} - k}{c_0 f} \tag{9}$$

for all $i \in I$. Since $\kappa > k$, all nonempty index sets are admissible. Thus we have $2^n - 1$ fixed points. The flux can also be obtained explicitly for all fixed points:

$$\bar{\Phi} = \frac{\kappa(|I|k + c_0 f)}{|I|\kappa + c_0 f} \tag{10}$$

and we finally obtain the coordinates of the fixed points in terms of the kinetic constants only:

$$\bar{x}_i = \frac{1}{|I|} \cdot \frac{|I|k + c_0 f}{|I|\kappa + c_0 f}, \qquad \bar{s}_i = \frac{g}{|I|\kappa + c_0 f} \tag{11}$$

for all $i \in I$. Note that symmetry implies $x_i + s_i = 1/|I|$ for all $i \in I$. All fixed points exist for all values of $c_0$: in contrast to the general model, where only fixed points with $|I| = 1$ exist for all total concentrations, there are no transcritical bifurcations in the symmetric case.

The differential equations for the CSTR case simplify to

$$\begin{aligned} \dot{x}_i &= x_i(ka + fs_i - r) \\ \dot{s}_i &= gx_i a - s_i(fx_i + r) \\ \dot{a} &= a_0 r - a\left(r + \kappa \sum_i x_i\right) \end{aligned} \tag{12}$$

All possible index sets are admissible, i.e., there are $2^n$ admissible index sets. The equilibrium concentrations at a fixed point $P_I$ are

$$\bar{x} = \frac{r(r - k\bar{a})}{f(\kappa\bar{a} - r)}, \qquad \bar{s} = \frac{r - k\bar{a}}{f}. \tag{13}$$

The equilibrium concentration of the building material fulfills:

$$\bar{a}^2\kappa(f - |I|k) - \bar{a}(fa_0\kappa + fr - |I|\kappa r) + fa_0 r = 0. \tag{14}$$

Thus there is a transcritical bifurcation with the trivial fixed point at $r^{I\bullet\emptyset} \stackrel{\text{def}}{=\!=} ka_0$ for all index sets. We have to distinguish two cases: If $f > f^c = |I|k\kappa \,/\, g > |I|k$ then there is a saddle node bifurcation at

$$r^{*I} = \frac{a_0\kappa f}{(\sqrt{f - |I|k} + \sqrt{|I|g})^2}, \qquad a^{*I} = \frac{a_0 f}{f - |I|k + \sqrt{(f - |I|k)|I|g}}. \tag{15}$$

Otherwise there are no fixed points of type $P_I$ in the simplex for $r > r^{I\bullet\emptyset}$.

Exploiting the symmetry of the (internal part of the) Jacobian, we can calculate all internal eigenvalues, see appendix B. We obtain essentially the same result for both boundary conditions.

**Theorem 6.** All fixed points with $|I| = 1$ are stable and all remaining fixed points are unstable in the case of constant organisation. All fixed points with $|I| \geq 2$ are unstable in the CSTR case. A fixed point $P_I$ with $|I| = 1$ is stable if and only if it is either the only one of this type in the simplex or if has the lower substrate concentration in the case that there are two such fixed points.

The phase portrait of the symmetric case is shown in Figure 2. It is in complete agreement with the corresponding trajectories of the simple replicator system.

### 3.4. Summary

We find close similarities between the CSTR and the constant organization model. Appart from details we observe the same behavior when $c_0$ is increased or $r$ is decreased, respectively. This does not come as a surprise. For the replicator equation it was shown recently [21] that the CSTR can be viewed as a singularly perturbed constant organization model in the limit $r \to 0$. In this limit the full capacity of the CSTR is filled with polymeric materials, i.e., $c_0 = \sum_i (x_i + s_i)$ approaches $a_0$. We can therefore interpret $c_0$ and $1/r$ as conceptually the same bifurcation parameter.

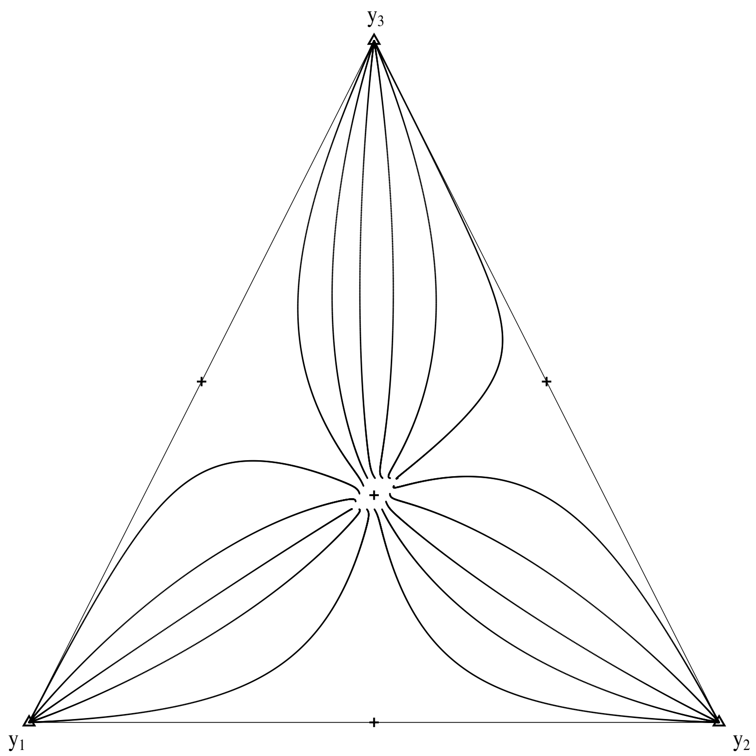



**Figure 2:** The competitive model with $n$=3 under constant organization. Constants for different species are chosen to be equal. Trajectories are shown for sums of concentrations: $y_i = x_i + s_i$. The parameters used are: $k = 0.1$, $c_0 = 3$, $f = 1.5$ and $g = 2$.

Secondly we find a cascade of transcritical bifurcations as $c_0$ or $1/r$ increases, in which fixed points with an increasing number of species are introduced into the physically meaningful part of the state space. This is due to the fact that $c_0$ or $r$ affect the relative importance of the first order and the second order reactions. For very small $c_0$ the first order term dominates which leads to the selection of a single species, i.e., there is a single stable fixed point. In the CSTR only the trivial fixed point is stable if $r$ becomes very large, of course.

For larger $c_0$ (or small $r$) the model behaves just like a replicator model: all 1-species equilibria are stable, all other fixed points are unstable. This matches exactly the phase portrait of the Schlögl model [35] in the replicator equation setting. We conclude hence, that the competitive model with intermediates in essence reproduces the behavior of the corresponding inhomogeneous replicator equation [42].

## 4. Cooperation

The differential equations for the cooperative model under constant organization are

$$\begin{aligned} \dot{x}_i &= x_i(k_i + f_{i-1}c_0 s_{i-1} - \Phi) \\ \dot{s}_i &= g_i x_i - s_i(f_i c_0 x_{i+1} + \Phi) \end{aligned} \tag{16}$$

with the flux term $\Phi = \sum_{j=1}^{n} \kappa_i x_i$. The total concentration $c_0$ will again be used as a bifurcation parameter in the constant organization case. The kinetic equations for the CSTR model read

$$\begin{aligned} \dot{x}_i &= x_i(k_i a + f_{i-1}s_{i-1} - r) \\ \dot{s}_i &= g_i x_i a - s_i(f_i x_{i+1} + r) \\ \dot{a} &= a_0 r - a(r + \sum_{j=1}^{n}(k_j + g_i)x_j) \end{aligned} \tag{17}$$

Unless stated otherwise, we assume that the constants $k_i$ are all different. Without loosing generality we can then label the species so that $k_1$ is the largest rate constant of a first order reaction.

Due to the form of the interaction between the reactants, there is a sharp contrast between the fixed point(s) in the interior and those on the boundary of the simplex in the mutualistic model. While in the former case we have a closed catalytic cycle, in the latter there are only catalytic chains. We can show that all fixed points on the boundary are unstable if there is an interior fixed point. If we omit the uncatalyzed formation ($k_i = 0$), there are no fixed points on the boundary of the simplex.

### 4.1. Boundary Equilibria

The non-empty admissible index sets are the same for constant organization and the CSTR. The set $\mathcal{N} = \{1, \ldots, n\}$ belongs to the interior rest point(s).

**Lemma 3.** Let $I \neq \emptyset$ be admissible. Then
(i) there are indices $j$ and $k$ such that $I = \{j, j+1, \ldots, k-1, k\}$, i.e., the species in a boundary fixed point form a *catalytic chain*.
(ii) $k_j = \max_{i \in I} k_i$.
(iii) The set $I' = I \setminus \{k\}$ is admissible.
(iv) If $k_1 > k_2 > \ldots > k_n$ then there are $n(n+1)/2$ admissible set. The is the largest possible number.
(v) If $k_1 > k_n > k_{n-1} > \ldots > k_2$ then there are only $2n-1$ admissible sets, which is the smallest possible number.

**Theorem 7.** Let $I$ be an admissible index set. Then there exist constants $c^{\boldsymbol{I \bullet I'}}$ and $r^{\boldsymbol{I \bullet I'}} < a_0 k_j$ for the constant organization case and the CSTR with $|I| > 1$, respectively such that:

(i) There is a unique fixed point of type $P_I$ in the physically meaningful part of the state space if $c_0 > c_0^{\boldsymbol{I \bullet I'}}$ or $r < r^{\boldsymbol{I \bullet I'}}$, respectively.
(ii) A transcritical bifurcation $I \bullet I'$ occurs at the critical value.
(iii) There is no fixed point of type $P_I$ in the simplex if $c_0 < c_0^{\boldsymbol{I \bullet I'}}$ or $r > r^{\boldsymbol{I \bullet I'}}$, respectively.

In addition we have the trivial fixed point $P_\emptyset$ at which only the substrate is present in the CSTR: $\bar{a} = a_0$. It is easy to check that it is stable if and only if $r > a_0 k_1$, i.e., if $r/a_0$ exceeds the largest of the kinetic constants $k_i$.

Let us now turn to the stability of the non-trivial boundary equilibria. In complete analogy to the discussion of the competitive model we distinguish external, transversal, and internal eigenvalues. No useful expressions were obtained for the internal eigenvalues except for equilibria with $|I| = 1$. Explicit expressions for the transversal eigenvalues are compiled in table 1. It will be convenient to use the notation $\hat{I} \stackrel{\text{def}}{=} I \cup \{k+1\}$, i.e., $\hat{I}' = I$.

**Table 1.** Transversal eigenvalues of boundary equilibria

| eigenvalues | | number | sign |
|---|---|---|---|
| constant organization | CSTR | | |
| $-k_j$ | $-r$ | $n - \|I\| - 1$ | $-$ |
| $-(k_j - k_s)$ | $-r(k_j - k_s)$ | $n - \|I\| - 1$ | $*$ |
| $-(k_j + c_0 f_{k+1}\bar{x}_k)$ | $-(r + f_{k+1}\bar{x}_k)$ | 1 | $-$ |
| $-(k_j - k_{k+1}) + c_0 f_k \bar{s}_k$ | $-(r - k_{k+1}\bar{a}) + f_k \bar{s}_k$ | 1 | † |

* For all $s \notin \hat{I}$. There is at least one $s$ such that $k_s > k_j$ unless $j = 1$, i.e., at least one of these eigenvalues is positive if $j \neq 1$.

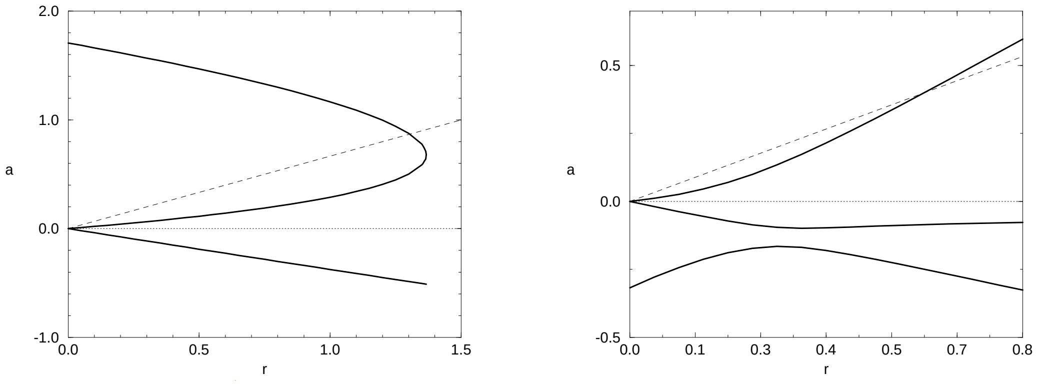
† Negative for small enough values of $c_0$ or large enough values of $r$, respectively, provided $k_j > k_{k+1}$, i.e., if $\hat{I}$ is admissible.

A boundary equilibrium is saturated [25, 29] if all transversal eigenvalues are non-positive. An immediate consequence of the expressions in table 1 is the following result:

**Lemma 4.** If $P_I$ is a saturated boundary equilibrium then $1 \in I$.
If $P_J$, $J \neq \mathcal{N}$ is contained in the physical state space then no fixed point $P_I$ with $I \subset J$ can be saturated. In the case of constant organization this is also true for $J = \mathcal{N}$.

In the constant organization model we have the following bifurcation pattern. For sufficiently small values of $c_0$ there are the $n$ boundary equilibria $P_{\{i\}}$ corresponding to isolated species. Of these $P_{\{1\}}$ is stable (and we suspect globally stable). As $c_0$ increases $P_{\{1,2\}}$ passes through $P_{\{1\}}$ in a transcritical bifurcation and becomes stable in an interval bounded below by $c_0^{\{1\}\bullet\{1,2\}}$. If $c_0$ increases further, however, there might be a Hopf bifurcation that makes $P_{\{1,2\}}$ unstable before the transcritical bifurcation with $P_{\{1,2,3\}}$. In fact, there is a cascade of bifurcations of the type $I \bullet \hat{I}$ as $c_0$ increases until, at sufficiently high values of $c_0$, there exists an interior equilibrium $P_{\mathcal{N}}$. At this point all boundary equilibria have become unstable. Analogous cascades of bifurcations may exists for the fixed points belonging to other admissible sets, say $\{2\} \bullet \{2,3\}$, etc. These families involve however only unstable equilibria.

We find almost the same behavior in the CSTR when $r$ is reduced. For sufficiently large flux $r$ the trivial fixed point is globally stable. If $r$ decreases below $r^{\emptyset \bullet \{1\}}$ then $P_{\{1\}}$ becomes stable, and we observe the same cascade of transcritical bifurctions as above when $r$ is decreased further. Only the final step can be more complicated: The interior fixed point either enters the simplex via the transcritical bifurcation $\mathcal{N} \bullet \mathcal{N}'$ (Figure 3b), or there is a saddle node bifurcation $\mathcal{N}*$ which gives birth to a pair of interior fixed points one of which leaves the simplex through $\mathcal{N} \bullet \mathcal{N}'$ at an even lower flux rate (Figure 3a).




**a** **b**

**Figure 3:** Bifurcation diagrams for the cooperative case.
Stationary concentrations of the substrate $\bar{a}$ are shown as a function of the flow rate $r$ in the CSTR. The parameters are $n = 2$, $k_1 = 1.5$, $k_2 = 1$, $g_1 = 3$, $g_2 = 5$, $a_0 = 1$ for both cases and **a**) $f_1 = 7$, $f_2 = 2$; **b**) $f_1 = 0.8$, $f_2 = 0.3$. Physically acceptable solutions are confined to the region between $a = 0$ and the dashed line.

### 4.2. Interior Equilibria

It is not possible to obtain complete analytical results on the stability of the interior equilibria. Their number and conditions for their existence, however, can be determined explicitly. For the constant organization model the situation is quite simple. We can rule out the occurrence of bifurcations that would change the number of rest points in the interior of the state space while bifurcations of the boundary can be treated explicitly.

**Theorem 8.** Let $P_{\mathcal{N}}$ be an interior equilibrium of the cooperative model under constant organization. Then its Jacobian is regular, i.e., all eigenvalues are non-zero.

**Theorem 9.** There is a critical value $c_0^{\mathcal{N}'\bullet\mathcal{N}} > 0$ such that there is no interior rest point for all $c_0 < c_0^{\mathcal{N}'\bullet\mathcal{N}} > 0$ and there is unique interior rest point for all $c_0 > c_0^{\mathcal{N}'\bullet\mathcal{N}} > 0$ in the cooperative model under constant organization.

The situation is more involved for the CSTR. We have

**Theorem 10.** There are at most two interior equilibria in the cooperative model for the CSTR. In more detail we have:

(i) For sufficiently small flux rates, there is exactly one interior fixed point. At $r = r^{\mathcal{N}\bullet\mathcal{N}'}$ there is a transcritical bifurcation of an interior fixed point with the unique fixed point $P_{\mathcal{N}'}$.

(ii) There are two ways in which this bifurcation can happen:

(a) The fixed point that lies inside the simplex may pass through $P_{\mathcal{N}'}$ and leaves the simplex. In this case there is no interior rest point for $r > r^{\mathcal{N}\bullet\mathcal{N}'}$.

(b) a second fixed point enters the simplex. In this case there is a saddle node bifurcation which annihilates the two interior equilibria at a flux rate $r^{*\mathcal{N}} > r^{\mathcal{N}\bullet\mathcal{N}'}$; there is no interior fixed for any $r > r^{*\mathcal{N}}$.

### 4.3. Special Case: The Symmetric Model

A fairly complete stability analysis can be performed if we set $k_i = k$, $g_i = g$, and $f_i = f$. We have

$$\begin{aligned} \dot{x}_i &= x_i(k + c_0\, f\, s_{i-1} - \Phi) \\ \dot{s}_i &= g x_i - s_i(c_0\, f\, x_{i+1} + \Phi) \end{aligned} \tag{18}$$

with $\Phi = \kappa \sum x_i$ in the case of constant organization and

$$\begin{aligned} \dot{x}_i &= x_i(ka + f s_{i-1} - r) \\ \dot{s}_i &= g x_i a - s_i(f x + r) \\ \dot{a} &= a_0 r - a(r + \kappa \sum_i x_i) \end{aligned} \tag{19}$$

for the CSTR. It is easy to characterize the admissible index sets.

**Lemma 5.**The set $\mathcal{N}$ is admissible. A nonempty set $I \neq \mathcal{N}$ is admissible if and only if it does not contain two indices $i$ and $j$ with $|i - j| = 1$ (where the indices are taken modulo $n$. In addition, the empty set is admissible in the CSTR setting.

**Lemma 6.** All boundary equilibria (except the trivial one) are unstable both under constant organization and for the CSTR.

The elementary hypercycle $\dot{x}_i = x_i(x_{i-1} - \Phi)$ has the same properties [38, 44].

**Theorem 11.** The symmetric cooperative model under constant organization has a unique interior equilibrium for all $c_0 > 0$. This fixed point is stable if $c_0$ is large enough.

(i) For $n = 2$ the interior equilibrium is always stable.

(ii) The interior fixed point is stable for both small and large value of $c_0$ for $n = 3$. If $g > 63.75k$ then there are two Hopf bifurcations with $0 < c_0^{\circ 1} < c_0^{\circ 2}$, and the interior rest point is unstable $c_0^{\circ 1} < c_0 < c_0^{\circ 2}$.

(iii) For $n = 4$ we have a single Hopfbifurcation at $c_0^{\circ} = 4(g - k)/f$ if $g > k$. In this case the equilibrium is unstable for $0 < c_0 < c_0^{\circ}$. If $g < k$ then the interior rest point is stable for all $c_0 > 0$.

(iv) For $n > 4$ there is a single Hopfbifurcation at $c_0^{\circ} > 0$. The interior equilibrium is unstable for $c_0 < c_0^{\circ}$ and stable for $c_0 > c_0^{\circ}$.

Again the situation is more involved for the CSTR:

**Lemma 7.** It $r < a_0 k$ there is a unique interior rest point. There is no interior rest point for $r > a_0 k$ if $f < f^c = nk\kappa/g$. If $f > f^c$ there are two interior rest points for

$$a_0 k < r < r^* = \frac{a_0 \kappa f}{(\sqrt{f - |I|k} + \sqrt{ng})^2}\,, \tag{20}$$

and there are no interior rest points for $r > r^*$.

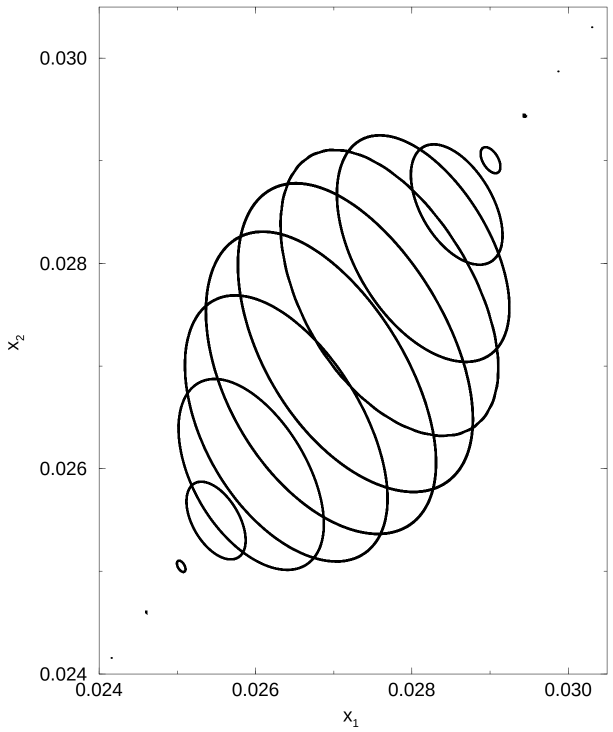



**Figure 4:** The cooperative model with $n$=3 under constant organization. The constants for different species are chosen to be equal: $k = 0.1$, $f = 1.5$, $g = 6.4$ and $c_0$ ranges from 0.80-1.08 in 0.02 steps from left to right.

Let us now turn to the stability of the interior equilibria.

**Theorem 12.** For the symmetric cooperative model in the CSTR setting the follwing is true:

(i) If there are two interior equilibria then at most one of them is stable.

(ii) For small enough flux rates there is a unique interior equilibrium which is asymptotically stable.

(iii) The trival fixed point is stable for all $r > a_0 k$.

(iv) If $n = 2$ then $P_{\mathcal{N}}^{(1)}$ is stable whenever there is an interior rest point; $P_{\mathcal{N}}^{(2)}$ is unstable whenever it exists.

(v) Suppose $f < f^c$, i.e., there is at most one interior rest point.
For $n = 3$ there are two Hopf bifurcation is $g/k$ is sufficiently large. The fixed point is stable for both small and large flux rates and unstable in between (Figure 4). If $g/k$ is small there is no Hopf bifurcation and the interior rest point is always stable.
For $n = 4$ there is a single Hopf bifurcation that leads from a stable fixed point to a saddle if $g > k$. Otherwise the fixed point is always stable.
For $n > 4$ there is always a Hopf bifurcation.

(vi) If $f > f^c$, i.e., if there can be two interior rest points, it depends on the value of $f$, at which of the two fixed points the Hopf bifurcation(s) take(s) place. Generally speaking, the Hopf bifurcations occur at $P_{\mathcal{N}}^{(1)}$ for small $f$ and at $P_{\mathcal{N}}^{(2)}$ for large $f$. In the latter case $P_{\mathcal{N}}^{(1)}$ is stable at all flux rates at which it exists.

### 4.4. Summary

As in the competitive model there is little difference in the qualitative behavior of CSTR and constant organization. A cascade of transcritical bifurcations introduces fixed points with an increasing number of species into the system as $c_0$ and $1/r$ increase. These are either stable or associated with stable limit cycles. This phenomenon has been observed is a variety of quite different dynamical systems that describe replication and selection: as the capacity $c_0$ of the environment increases the number of species that can be sustained increases as well, see e.g., [14, 17, 27, 28, 39].

The second order replicator equation corresponding to the limit of larger $c_0$ or small $r$, respectively, is the elementary hypercycle [12]. Our model exhibits a single, stable interior fixed point in this limit. The elementary hypercycle, on the other hand, shows stable limit cycles for $n > 4$ [26]. In our present model we find stable limit cycles also for $n = 3$ and $n = 4$.

## 5. Discussion

Most of the previous work on autocatalytic networks was based on the trimolecular "over-all" mechanism $M+I+C \to 2I+C$ for the replication of $I$ in the presence of a catalyst $C$. The corresponding dynamical systems, replicator equations, Lotka-Volterra equations, and to a lesser extent the equations for the reactions in the CSTR are well understood, see [29]. This family of dynamical systems is properly characterized as being *replicator-like*. The models are sufficiently simply to allow for a very detailed analysis with analytical methods. On the other hand, a single-step "over-all" replication kinetics is certainly a very restrictive assumption. It has been argued repeatedly that this is a good approximation but only a few papers tried to substantiate this claim, see e.g. [11, 13, 18, 21, 41].

The range of validity of replicator-like models determines whether these systems can provide a useful description of the dynamics of prebiotic evolution scenarios or contemporary populations. This calls for a novel type of perturbation theory that deals with qualitative modifications of the model rather than with mere changes of the reaction constants. As a first step we consider here the dynamics of a model in which the trimolecular replication step is resolved into two irreversible bimolecular steps: (i) the formation of an "activated" intermediate and (ii) the template directed conversion of this intermediate into a copy of the template.

The simple observation that the flux term $\Phi$ is a linear instead of a quadratic function indicates that this model is only a rather distant relative of the second order replicator equations. Nevertheless the model reduces to replicator equations in certain limits. Furthermore we observe a number of analogies to second order replicator equations in a very broad range of parameters: Both descriptions of autocatalytic networks exhibit very similar dynamics irrespective of whether the reactions are considered under constant organization or embedded in a CSTR. The reactor capacity $c_0$ (in the constant organization case) plays the role of the inverse flux rate $1/r$ (in the CSTR). Using $c_0$ or $1/r$, respectively, leads to very similar bifurcation diagrams. For small $c_0$ uncatalyzed replication dominates: we observe survival of the fittest, i.e., of the species with largest first order rate constant. For large $c_0$ the catalyzed reactions determine the behavior of the system. In the competitive case we observe selection of the most frequent species, quite as in Schlögl's classical model [35]. For the cyclic arrangement of catalytic coupling, corresponding to the hypercycle, we observe stable coexistence of all species. The details of the dynamics are different, however. While the elementary hypercycle always leads to stable limit cycles for more than 4 species, we find a single stable fixed point in certain parameter ranges of the two-step model.

We conclude hence, that resolving the replication step into a two-step mechanism does not lead to drastic changes. While details of the dynamics are different, the qualitative picture is still essentially the same as in the second order replicator equation. This paper is considered as a first step towards answering the question that motivated this work: What are the modifications to a reaction scheme that leave global dynamics intact — and which changes will lead to a dramatic alterations of the dynamical behavior? More variations of the replicator theme still need to be conceived and analyzed before a final answer can be given.

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## Appendix A: Proofs of Lemmas and Theorems.

Most of the proofs involve quite tedious manipulations of algebraic equations which have been performed using the symbolic mathematics packages `Mathematica` and `Reduce`. We present only outlines of some of the proofs and we frequently omit explicit expressions when they are too complicated to allow for a direct interpretation. A more complete presentation of this material can be found in the doctoral thesis [22].

**Proof of Theorem 1.** Let $y_i = \dfrac{g_i x_i}{\sum_j g_j x_j}$. Then $x_i = \dfrac{g_i^{-1} y_i}{\sum_j g_j^{-1} y_j}$ and $\sum_j y_j = 1$. A short calculation yields

$$\begin{aligned}
\dot{y}_i &= y_i \left\{ k_i + \sum_j c_{ij} s_j - \sum_l y_l \left( k_l + \sum_j c_{lj} s_j \right) \right\} \\
\dot{s}_i &= g_i x_i - s_i \sum_j (k_j + c_{ij} + g_j) x_j
\end{aligned}$$

Now we set $g_i = \gamma_i/\epsilon$. The second equation becomes

$$\epsilon \dot{s}_i = \frac{1}{\sum_l y_l/\gamma_l} \left\{ y_i - s_i - \epsilon \sum_j \frac{s_i}{\gamma_i}(k_j + c_{ij}) \right\} .$$

In the limes $\epsilon \to 0$ this reduces to $s_i = y_i$. In order to verify that this solution is stable we compute the Jacobian

$$\frac{\partial \dot{s}_i}{\partial s_j} = -\delta_{ij} \frac{1}{\epsilon \sum_j \gamma_j^{-1} y_j} \left( \epsilon \sum_j c_{ij} \gamma_j^{-1} y_j + 1 + \epsilon \sum_j k_j \gamma_j^{-1} y_j \right) \quad < 0 ,$$

which is stable for all $y$. Thus (1,3) is in fact a stable singular perturbation of the inhomogeneous replicator equation. ∎

**Proof of Theorem 2.** In order to verify that the reaction vessel is completely filled with replicating species and the intermediates we follow the discussion in [21]. We find that $a/r$ remains finite in the limit $r \to 0$.
Hence we can use the transformation $b = a/r$. Furthermore we set $u_i = s_i/r$ and introduce $\Phi = \sum_j (k_j + g_j) x_j$. This yields

$$\begin{aligned} \dot{x}_i &= x_i \left( k_i + \frac{1}{b} \sum_j c_{ij} u_j - 1 \right) \\ r\dot{u}_i &= g_i x_i - \frac{u_i}{b} \left( \sum_{j=1}^{n} c_{ij} x_j + r \right) , \\ r\dot{a} &= -\Phi + \frac{a_0}{b} - r \end{aligned}$$

In the limit $r \to 0$ we obtain the finite values

$$u_i = \frac{b g_i x_i a_0}{a_0 \sum_j c_{ij} x_j} .$$

and $b = a_0/\Phi$. This solution is stable since the Jacobian

$$\begin{aligned} \frac{\partial \dot{u}_i}{\partial u_j} &= -\frac{\delta_{ij}}{r} \left( \sum_j c_{ij} x_j + r \right) & \qquad \frac{\partial \dot{b}}{\partial u_j} = 0 \\ \frac{\partial \dot{u}_i}{\partial b} &= \frac{1}{b^2} \left( \sum_j c_{ij} x_j + r \right) & \qquad \frac{\partial \dot{b}}{\partial b} = -\frac{a_0}{b^2} \end{aligned}$$

has block-diagonal form and all eigenvalues are negative for all $x$. Thus the equation for $x$ becomes

$$\dot{x}_i = x_i \left( k_i + \frac{\sum_j c_{ij} g_j x_j}{\sum_l c_{il} x_l} - \frac{\Phi}{a_0} \right)$$

in the singular limit. Introducing the new variables $y_i = x_i / \sum_j x_j$ finally yields a non-linear replicator equation with response function $f_i(y)$. ∎

**Proof of Theorem 3.** The proof is the same for both the CSTR and the constant organization case. Set Let $c_{ij} = d_{ij}/\epsilon$ and $D_i = \sum_j d_{ij}$ and define $u_i = D_i s_i/\epsilon$. We obtain

$$\begin{aligned}
\dot{x}_i &= x_i \left( a k_i + \sum_j \frac{d_{ij} u_j}{D_j} - \Psi \right) \\
\epsilon \dot{u}_i &= D_i \left( g_i a x_i - \frac{\epsilon u_i}{D_i} \left( \sum_{j=1}^{n} \frac{d_{ij}}{\epsilon} x_j + \Psi \right) \right) \\
\dot{a} &= -a \sum_j (k_j + g_j) x_j + r(a_0 - a)
\end{aligned}$$

In the limit $\epsilon \to 0$ we find $\dfrac{u_i}{D_i} = \dfrac{g_i a x_i}{\sum_j d_{ij} x_j}$ because the Jacobian

$$\left. \frac{\partial \dot{u}_i}{\partial u_j} \right|_x = -\delta_{ij} u_i \left( \sum_j \frac{d_{ij}}{\epsilon} x_j + \Phi \right) < 0$$

of the fast variables is stable. Thus we obtain for both constant organization and the CSTR

$$\dot{x}_i = x_i \left( a \left( k_i + \frac{\sum_j g_j d_{ij} x_j}{\sum_l d_{il} x_l} \right) - \Psi \right)$$

For the CSTR we have in addition:

$$\dot{a} = -a \sum_j (k_j + g_j) x_j + r(a_0 - a)\,.$$

Introducing the rescaled variables by $y_i = x_i / \sum_j x_j$ we arrive at a nonlinear replicator equation with response function

$$k_i + \frac{\sum_j d_{ij} g_j y_j}{\sum_j d_{ij} y_j} = k_i + \frac{\sum_j c_{ij} g_j y_j}{\sum_j c_{ij} y_j} = f_i(y)$$

as in theorem 2. ∎

**Proof of Theorem 4.** The equilibrium flux $\bar{\Phi}$ in equ.(6) can be determined by the condition that the normalization condition $\sum_i (s_i + x_i) = 1$. With the definition

$$F(\Phi, c_0) \stackrel{\text{def}}{=} 1 - \frac{1}{c_0} \sum_{i \in I} \frac{\Phi - k_i}{f_i} \left(1 + \frac{\Phi}{\kappa_i - \Phi}\right)$$

an equilibrium is characterized by $F(\bar{\Phi}, c_0) = 0$. This alegbraic equation has order $s_I + 1$ in $\Phi$, where $s_I$ is the number of different values of $\kappa_i$, $i \in I$.
For index sets with $|I| = 1$, i.e. of the form $I = \{i\}$, we can solve directly for the coordinates of the fixed point:

$$\bar{x}_i = \frac{c_0 f_i + k_i}{c_0 f_i + \kappa_i}, \qquad \bar{s}_i = \frac{g_i}{c_0 f_i + \kappa_i}, \qquad \bar{\Phi} = \frac{\kappa_i (c_0 f_i + k_i)}{c_0 f_i + \kappa_i}.$$

In this case the fixed point lies in the simplex for all total concentrations.
At $\Phi = \kappa_i$, $F(c_0, \Phi)$ goes to infinity and changes sign; there is at least one solution between each pair of two adjacent lines $\Phi = \kappa_i$ and $\Phi = \kappa_j$. None of these $s_I - 1$ solutions lies in the simplex. Furthermore, there is one solution with a negative value of the equilibrium flux. This solution is unphysical as well. Consequently there is at most one solution in the simplex. We observe that $F(k_{\mathcal{M}}, c_0)$ is negative for

$$c_0 < c_0^{I \bullet I'} = \sum_{i \in I} \frac{\kappa_i (k_{\mathcal{M}} - k_i)}{f_i (\kappa_i - k_{\mathcal{M}})}$$

and positive otherwise. Furthermore, $F(\kappa_m - \epsilon, c_0) < 0$ for sufficiently small $\epsilon > 0$. It follows that there is one fixed point in the simplex for $c_0 > c_0^{I \bullet I'}$ and none for $c_0 < c_0^{I \bullet I'}$. The fixed point $P_I$ enters the simplex at $c_0^{I \bullet I'}$ via a transcritical bifurcation with $P_I'$. ∎

**Proof of Theorem 5.** The equilibrium concentration of the substrate is implicitly given by $F(\bar{a}(r), r) = 0$ with the function

$$F(a, r) \stackrel{\text{def}}{=} a_0 - a - \sum_{i \in I} \frac{r - k_i a}{f_i} \left(1 + \frac{r}{\kappa_i a - r}\right).$$

If there are $s_I$ different values of $\kappa$ in $I$, the equation is of order $s_I + 1$. We have not found an analytical solution for arbitrary $|I|$.

$F(a,r)$ approaches infinity and changes sign at each of the the lines $a = r/\kappa_i$, and there is at least one solution between each adjacent pair of such lines. These $s-1$ solutions cannot lie in the simplex. Thus there can be at most two solutions on the simplex. $F(a,r)$ is positive along the line $a = r/k_{\mathcal{M}}$, if

$$r < r^{I\bullet I'} = \frac{a_0 k_{\mathcal{M}}}{1+\Gamma_I} \qquad \text{with} \qquad \Gamma_I = \sum_{i\in I} \frac{\kappa_i(k_{\mathcal{M}} - k_i)}{f_i(\kappa_i - k_{\mathcal{M}})} > 0$$

Since $F(r,(r/\kappa_m)+\epsilon)$ is negative for sufficiently small $\epsilon > 0$, there is one solution if $r < r^{I\bullet I'}$, and two or none if $r > r^{I\bullet I'}$. At $r = r^{I\bullet I'}$ there is a transcritical bifurcation of $P_I$ with $P_{I'}$. For fixed points with $|I| = 1$, this means that $P_{\{i\}}$ passes through the trivial fixed point at $r^{\{i\}\bullet\emptyset} = a_0 k_i$.

There are two ways in which this bifurcation can happen: either the interior fixed point leaves the simplex or a second fixed point enters it. In the latter case the fixed point that enters the simplex in a transcritical bifurcation has the higher value of $\bar{a}$; we call it $P_I^{(2)}$. There is a saddle node bifurcation in which the fixed points $P_I^{(1)}$ and $P_I^{(2)}$ disappear at some flux rate $r^{I*} > r^{I\bullet I'}$, because neither of these fixed points can leave the simplex as we raise the flux rate and because we know that only the trivial fixed point exists at sufficiently high flux rates. ∎

**Proof of Theorem 6.** Let us first consider constant organization. The eigenvalues of the Jacobian can be computed explicitly by the method described in Appendix B. We find that there is one eigenvalue $-(|I|\kappa + c_0 f) < 0$ and $|I|-1$ pairs of eigenvalues of the form

$$\lambda = \frac{1}{2}\left(-c_0 f\bar{x} - \bar{\Phi} \pm \sqrt{(c_0 f\bar{x} + \bar{\Phi})^2 + 4fc_0\bar{x}(\kappa - \bar{\Phi})}\right)$$

It is not hard to check that each pair consists of a positive and a negative eigenvalue. Hence a fixed point with $|I|$ non-vanishing species has $|I|-1$ positive and $|I|$ negative eigenvalues negative internal eigenvalues as predicted by our conjecture for the general case. The transversal eigenvalues are $-\bar{\Phi}$ and $k - \bar{\Phi}$. They are all negative since $k < \bar{\Phi}$. It follows that all fixed points with $|I| = 1$ are stable and all remaining fixed points are unstable.

The eigenvalues of the Jacobian can be obtained for the CSTR case by the same method. There are $|I|-1$ pairs of internal eigenvalues of the form

$$\lambda = \frac{1}{2}\left(-f\bar{x} - r \pm \sqrt{(f\bar{x} + r)^2 + 4f\bar{x}(\kappa\bar{a} - r)}\right)$$

Half of these eigenvalues are positive, the other ones are negative. The explicit expressions for the remaining two internal eigenvalues are very complicated. They can be found in [22]. It is not hard to show, however, that for the fixed point with the lower equilibrium concentration of the substrate both are negative, while for the other fixed point (if it exists) one eigenvalue is positive and the other one is negative. ∎

**Proof of Lemma 3.** Suppose $I$ contains two distinct indices $j$ and $j'$ with the property that both $j-1$ and $j'-1$ are not contained in $I$. Then $\bar{s}_{j-1} = \bar{s}_{j'-1} = 0$ implies $\bar{x}_j(k_j - \Phi) = \bar{x}_{j'}(k_{j'} - \Phi) = 0$ contradicting the assumption that all parameters $k_i$ are different. Thus there is only a single index $j \in I$ such that $(j-1) \notin I$. Now we see that $\bar{\Phi} = k_j$ at the fixed point $P_I$, which in turn implies the equilibrium conditions $\bar{s}_i = r(k_j - k_{i+1})/(c_0 f_i)$ for all $i \in I \setminus \{k\}$ where $k$ is the unique index for which $(k+1) \notin I$. Hence $k_j > k_i$ for all $i \in I \setminus \{j\}$, i.e., item (ii) is true. This implies in turn that $1 \in I$ if and only if $j = 1$ and hence item (i) is true as well. The remaining assertions follow immediately. ∎

**Proof of Theorem 7.** The coordinates of the boundary equilibria can be computed explicity. Under constant organization we find:

$$
\begin{aligned}
\bar{s}_i &= \frac{k_j - k_{i+1}}{c_0 f_i} \qquad\qquad \text{if}\, i \in I \setminus \{k\} \\
\bar{s}_k &= \frac{g_k}{f_{k-1} \sum\limits_{i\in I} \kappa_i \mu_{k-1}^{(i,j)}} \left( 1 - \frac{1}{c_0} \sum_{i \in I} \kappa_i \sum_{l=i}^{k-1} \mu_l^{(i,j)} \right) \\
\bar{x}_i &= k_i \left( \frac{\bar{s}_k f_{k-1}}{g_k} \mu_{k-1}^{(i,j)} + \frac{1}{c_0} \sum_{m=i}^{k-1} \mu_m^{(i,j)} \right) \qquad \text{if} \quad i \in I \\
\mu_m^{(i,j)} &\stackrel{\text{def}}{=\!=} \frac{1}{f_m} \prod_{l=i}^{m} \frac{k_j - k_{l+1}}{g_l} \;\; > 0
\end{aligned}
$$

Lemma 3 implies that $\mu_m^{(i,j)} \geq 0$ for all $i, j$ and $\mu_m^{(i,j)} > 0$ if $i$ is not the smallest index in $I$. The fixed point lies on the simplex if

$$
c_0 > c_0^{I \bullet I'} \stackrel{\text{def}}{=\!=} \sum_{i=j}^{k} \kappa_i \sum_{l=i}^{k-1} \mu_l^{(i,j)} > 0\,.
$$

For the CSTR we find the equilibrium concentrations

$$\bar{s}_i = \frac{r(k_j - k_{i+1})}{f_i k_j} \qquad \text{for } i \in I \setminus \{k\}$$

$$\bar{s}_k = \frac{a_0 k_j - r\left(1 + \psi^{j,k} - K^{(i,j)} + k_j \sum\limits_{i=j}^{k-1} \sum\limits_{m=i}^{k-1} \mu_m^{(i,j)}\right)}{k_j\left(1 + \frac{k_j f_{k-1}}{g_k} \sum\limits_{i=j}^{k} \mu_{k-1}^{(i,j)}\right)}$$

$$\bar{x}_i = \bar{s}_k \frac{k_j f_{k-1}}{g_k} \mu_{k-1}^{(i,j)} + r \sum_{m=i}^{k-1} \mu_m^{(i,j)} \qquad \text{for } i \in I$$

with the abbreviations

$$\mu_m^{(i,j)} \stackrel{\text{def}}{=} \frac{1}{f_m} \prod_{l=i}^{m} \frac{k_j - k_{l+1}}{g_l}, \qquad \psi^{(j,k)} \stackrel{\text{def}}{=} \sum_{i=1}^{k-1} \frac{k_j}{f_i}, \qquad K^{(i,j)} \stackrel{\text{def}}{=} \sum_{i=1}^{k-1} \frac{k_{i+1}}{f_i}.$$

Thus there is only one fixed point $P_I$ for $I \neq \mathcal{N}$. It lies on the simplex iff

$$r < r^{(I \bullet I')} \stackrel{\text{def}}{=} \frac{a_0 k_j}{\left(1 + \psi^{(j,k)} - K^{(j,k)} + k_j \sum_{i=j}^{k-1} \sum_{m=1}^{k-1} \mu_m^{(i,j)}\right)}$$

because $\bar{s}_k$ (which is linear in $r$) becomes negative if this condition is violated. By construction we have $\psi^{j,k} \geq K^{(j,k)}$, hence the $r^{I \bullet I'} > 0$. The same argument implies that the denominator cannot be smaller that 1 and hence $a_0 k_j > r^{I \bullet I'}$. ∎

**Proof of Theorem 8.** In order to show that the Jacobian is regular we demonstrate explicitly that its rows are linearly independent, i.e., that there is no non-trivial solution of the system of linear equations

$$\sum_{i=1}^{n} \alpha_i \frac{\partial \dot{x}_l}{\partial x_i} + \sum_{i=1}^{n} \beta_i \frac{\partial \dot{x}_l}{\partial s_i} = 0$$

$$\sum_{i=1}^{n} \alpha_i \frac{\partial \dot{s}_l}{\partial x_i} + \sum_{i=1}^{n} \beta_i \frac{\partial \dot{s}_l}{\partial s_i} = 0$$

with variables $\alpha_i$ and $\beta_i$, $1 \leq i \leq n$. Substituting the Jacobian at the interior rest point yields

$$0 = \sum_{i=1}^{n} \alpha_i \kappa_i \bar{x}_l - \beta_l \bar{x}_l f_{l-1} c_0$$

$$0 = -\bar{s}_l \left(\sum_{i=1}^{n} \alpha_i \kappa_i\right) + \alpha_l g_l - \alpha_{l+1} \bar{s}_l f_l c_0 - \beta_l (f_l c_0 \bar{x}_{l+1} + \bar{\Phi}) = 0\,.$$

From first equation we obtain $\beta_l = \dfrac{1}{f_l c_0}\sum_{i=1}^{n} \alpha_i \kappa_i$. Substituting this into the second line yields

$$-\left(\sum_{i=1}^{n} \alpha_i \kappa_i\right)\left(\bar{s}_l + \bar{x}_{l+1} + \frac{\bar{\Phi}}{f_l c_0}\right) + \alpha_l g_l - \alpha_{l+1}\bar{s}_l f_l c_0 = 0\,.$$

Summing this equation over all $l$ and using the normalization $\sum(x_i + s_i) = 1$ yields after some further rearrangements

$$\sum_{i=1}^{n} \alpha_i \left(1 + \frac{\kappa_i}{c_0}\sum_{l=1}^{n}\frac{1}{f_l}\right) = 0\,.$$

Since the terms in brackets are all positive, it is clear that there must be at least one positive and one negative $\alpha$. If $\sum \alpha_i \kappa_i > 0$ and $\alpha_{l+1}$ is positive, we see from previous equation that $\alpha_l$ is positive as well. Applying this argument $n$ times, we see that all $\alpha_l > 0$ for $l$, which is a contradiction. If $\sum \alpha_i \kappa_i < 0$, assume that $\alpha_{l+1}$ is negative for some $l$. The same argument as above shows that $\alpha_i < 0$, i.e., $\sum_i \kappa_i \alpha_i = 0$. Now $\kappa_i > 0$ implies $\alpha_i = 0$ for all $i$. The explicit expressions for $\beta_i$ above prove that $\beta_i = 0$ as well. Thus the Jacobian has rank $2n$ and therefore it is regular. ∎

**Proof of Theorem 9.** The equilibrium concentrations at the interior fixed point can be expresses as

$$\bar{s}_i = \frac{\bar{\Phi} - k_{i+1}}{f_i c_0}, \qquad \bar{x}_i = \frac{\bar{\Phi}}{c_0\left(1 - \Gamma\phi_{1,n}\right)}\sum_{l=1}^{n}\gamma_{i,l}\phi_{i,l}$$

with the abbreviations

$$\gamma_{i,l} = \frac{1}{f_{i+l-1}}\prod_{m=0}^{l-1}\frac{1}{g_{i+m}}, \qquad \Gamma = \prod_{l=1}^{n}\frac{1}{g_l}, \qquad \phi_{i,l} = \prod_{m=1}^{l}(\bar{\Phi} - k_{i+m})\,.$$

If there is an interior equilibrium then is fulfils $\bar{\Phi} \geq k_1$, otherwise $\bar{s}_1$ would be negative. Substituting the above expressions into the normalization condition $\sum_i(\bar{x}_j + \bar{s}_j) = 1$ yields

$$\bar{\Phi}\left(\psi^{(1,n)} + \frac{\sum_{i=1}^{n}\sum_{l=1}^{n}\gamma_{i,l}\phi_{i,l}}{1 - \Gamma\phi_{1,n}}\right) + K^{(1,n)} - c_0 \;=\; 0$$

with $K^{(1,n)} = \sum_{l=1}^{n} \frac{k_{l+1}}{f_l}$ and $\psi^{(1,n)} = \sum_{l=1}^{n} \frac{1}{f_l}$. We know from the discussion in section 4.1 that the interior fixed point enters the simplex by means of a transcritical bifurcation with $P_{\mathcal{N}'}$. Hence we can compute the value of $\bar{\Phi}$ at the bifurcation by setting $\bar{s}_n = 0$, which implies $\bar{\Phi} = k_1$ and we can explicitly compute the critical value of $c_0$:

$$c_0^{\mathcal{N}'\bullet\mathcal{N}} = k_1 \left( \psi^{(1,n)} + \sum_{i=1}^{n-1} \sum_{l=i}^{n-1} \mu_l^{i,1} \right) + K^{(1,n)} > 0$$

Since this is the only solution, no other fixed point can enter the interior of the simplex. Moreover, we can verify by implicit differentiation of that $\partial\bar{\Phi}/\partial c_0$ is positive at $c_0 = c_0^{\mathcal{N}\bullet\mathcal{N}'}$ and hence $\bar{\Phi} > k_1$ if the total concentration is raised above the critical value. Thus there is no interior fixed point for $c_0 < c_0^{\mathcal{N}\bullet\mathcal{N}'}$ and exactly one for $c_0 > c_0^{\mathcal{N}\bullet\mathcal{N}'}$, since the regularity of the Jacobian, proved in the previous theorem, implies that the solution of the above system of equations is unique. ∎

**Proof of Theorem 10.** (i) The equilibrium concentrations at the interior fixed point are

$$\bar{x}_i = \frac{r}{\bar{a}^n - \Gamma\phi_{1,n}} \sum_{l=1}^{n} \gamma_{i,l} \bar{a}^{n-l} \phi_{i,l}\,, \qquad \bar{s}_i = \frac{r - k_{i+1}\bar{a}}{f_i}$$

with the abbreviations

$$\gamma_{i,l} = \frac{1}{f_{i+l-1}} \prod_{m=0}^{l-1} \frac{1}{g_{i+m}}, \qquad \Gamma = \prod_{m=1}^{n} \frac{1}{g_m}, \qquad \phi_{i,l} = \prod_{m=1}^{l} (r - k_{i+m}\bar{a})\,.$$

The equilibrium concentration of the substrate $\bar{a}$ is then implicitly determined by the equation

$$\mathcal{F}(a,r) \stackrel{\text{def}}{=} a - a_0 + \sum_{i=1}^{n} x_i + s_i = 0\,.$$

The function $\mathcal{F}$ has the explicit representation

$$\mathcal{F}(a,r) \stackrel{\text{def}}{=} a(1 - K^{(1,n)}) - a_0 + r\psi^{(1,n)} + \frac{r \sum_{i=1}^{n} \sum_{l=1}^{n} a^{n-l} \gamma_{i,l} \phi_{i,l}}{a^n - \Gamma\phi_{1,n}}$$

with the abbreviations $K^{(1,n)} = \sum_{i=1}^{n} \frac{k_{i+1}}{f_i}$ and $\psi^{(1,n)} = \sum_{i=1}^{n} \frac{1}{f_i}$. The equilibrium condition hence becomes $\mathcal{F}(\bar{a}(r), r) = 0$.

(ii) Consider the equation $a^n - \Gamma\phi_{1,n} = 0$. It has a unique solution $a_P(r)$ in the interval $[0, r/k_1]$, which is strictly increasing in $r$ and intersects the line $a = a_0$ at a finite value $\tilde{r}$. We define

$$\mathcal{S} = \left\{ (r,a) \,\middle|\, r > 0, \quad 0 < a < \min[a_0, r/k_1, a_P(r)] \right\}.$$

This set is obviously compact. The expression in item (i) imply that $(\bar{a}, r) \in \mathcal{S}$ for an interior equilibrium. Since $\partial^2\mathcal{F}/\partial a^2$ is positive on $\mathcal{S}$, there are at most two solutions of $\mathcal{F}(a,r) = 0$ on $\mathcal{S}$.

(iii) There is exactly one flux rate at which a solution of $\mathcal{F} = 0$ intersects the line $a = r/k_1$, namely

$$r^{\mathcal{N}\bullet\mathcal{N}'} = \frac{a_0 k_1}{1 - K^{(1,n)} + k_1\psi^{(1,n)} + k_1 \sum_{i=1}^{n-1} \sum_{l=i}^{n-1} \mu_l^{(i,1)}} > 0$$

The value of $\mathcal{F}$ is negative along the line $a = r/k_1$ for $r < r^{\mathcal{N}\bullet\mathcal{N}'}$. For sufficiently small $\epsilon > 0$ we observer $\mathcal{F}(a_P(r) + \epsilon, r) > 0$. Thus there is at least one solution of $\mathcal{F} = 0$ in $\mathcal{S}$ for small flux rates. Since the number of solutions must be odd but there cannot be more than two we know that there is indeed a unique solution. It is easy to check that the interior fixed point approaches $P_{\mathcal{N}'}$ at the critial flux rate $r^{\mathcal{N}\bullet\mathcal{N}'}$. Thus there is in fact a transcritical bifurcation.

(iv) In scenario (a) $\mathcal{F}$ is positive on the part of $\mathcal{S}$ to the right of the solution of $\mathcal{F} = 0$, since $\partial\mathcal{F}/\partial r > 0$ on $\mathcal{S}$ and hence $\mathcal{F}$ is monotonously increasing in $r$ on $\mathcal{S}$. Therefore, there is no interior fixed point for any flux rate greater than $r^{\mathcal{N}\bullet\mathcal{N}'}$.

(v) In scenario (b) there must be a saddle node bifurcation since $r^{\mathcal{N}\bullet\mathcal{N}'}$ is the only flux rate where a solution curve of $\mathcal{F} = 0$ can intersect the boundary of $\mathcal{S}$. From the monotonicity of $\mathcal{F}$ in $r$ we conclude that there is exactly one saddle node bifurcation. ∎

**Proof of Lemma 5.** Suppose there is a fixed point $P_I$ with $I \neq \mathcal{N}$. Then there is at least one index $j$ such that $(j-1) \notin I$ implying $\bar{\Phi} = k$. If $j+1 \in I$ then $k + c_0 f \bar{s}_j - \bar{\Phi} = 0$, i.e., $c_0 f \bar{s}_j = 0$ which contradicts $j \in I$. Repeating this argument shows that $i \in I$ implies $(i+1) \notin I$, and hence $i \in I$ implies also $(i-1) \notin I$. The same reasoning works for the CSTR model. ∎

**Proof of Lemma 6.** (i) Let us first consider constant organization. The equilibrium concentrations for fixed points on the boundary of the simplex are

$$\bar{x}_i = \frac{k}{|I|\kappa}\,, \qquad \bar{s}_i = \frac{g}{|I|\kappa}$$

for all $i \in I$. The Jacobian at fixed points on the boundary has $|I|$ eigenvalues $c_0 f \bar{s} > 0$ and hence they are all unstable.
(ii) The equilibrium concentrations of boundary fixed point $P_I$ in the CSTR model are

$$\bar{x} = \frac{a_0 k - r}{nk\kappa}\,, \qquad \bar{s} = \frac{g(a_0 k - r)}{n\kappa}\,, \qquad \bar{a} = \frac{r}{k}$$

for all $i \in I$. It is clear that these fixed points can exist only if $r < a_0 k$. The Jacobian has the $|I|$-fold transversal eigenvalue $f\bar{s} > 0$. The equilibrium $P_I$ is therefore unstable fixed points are unstable. ∎

**Proof of Theorem 11.** The coordinates of the interior fixed point are

$$\bar{x} = \frac{nk + c_0 f}{n(n\kappa + c_0 f)}\,, \qquad \bar{s} = \frac{g}{n\kappa + c_0 f}\,.$$

The eigenvalues of the Jacobian can be obtained using the method outlined in Appendix B. We find explicitly

$$\lambda_j^{+/-} = \frac{1}{2}\left(-u \pm \sqrt{u^2 - 4v + 4w(\cos\phi + \imath \sin\phi)}\right) \qquad \text{for} \quad 1 \le j \le n-1$$

where $\imath$ denotes the imaginary unit, $\phi = 2\pi j/n$ and

$$u = \frac{nk + c_0 f}{n} \qquad v = \frac{c_0^2 f^2 g(nk + c_0 f)}{n(n\kappa + c_0 f)^2} \qquad w = \frac{c_0 f g(nk + c_0 f)}{n(n\kappa + c_0 f)}\,.$$

In addition we have the external eigenvalue $-\bar{\Phi}$ and the eigenvalue $-(n\kappa + c_0 f) < 0$. The eigenvalues corresponding to $j = n/2$ (if $n$ is even) are real and negative. For $j \neq n/2$ the eigenvalues for $j$ and $n-j$ are complex conjugates. We are interested in their real parts only, hence we only need to consider $1 \le j < n/2$. The real parts of the eigenvalues with the minus sign before the square root ($\lambda_j^-$) is always negative. It is not hard to verify that $\lambda_1^+$ is has the largest real part of all the eigenvalues $\lambda_j^+$. Hence it determines the stability of the fixed point.

The eigenvalues $\lambda_j^+$ are all zero at $c_0 = 0$, hence we can determine their sign for small values of $c_0$ from the derivative

$$\left(\frac{\partial \mathrm{Re}\lambda_j^+}{\partial c_0}\right)_{c_0=0} = \frac{fg\cos\phi}{n\kappa}\,.$$

Thus $\mathrm{Re}\lambda_1^+$ is positive for $n > 4$ and negative for $n < 4$ for small $c_0$. For $n = 4$, examination of the second and third derivative show that the real part of $\lambda_1^+$ is positive at small total concentrations if $g > k$ and negative if $g < k$.
The real part of the eigenvalue changes sign if

$$c_0^2 f^2 (1-\cos\phi) + c_0 f n \left(k(1-2\cos\phi) - g(\sin^2\phi + \cos\phi)\right) \\ - n^2 k\kappa\cos\phi \;=\; 0\,.$$

For $n = 2$ there is no positive value of $c_0$ which satisfies the equation. The interior fixed point is therefore always stable.
For $n = 3$ there are either two or Hopf bifurcations or none. They take place at

$$c_0 = \frac{g - 8k \pm \sqrt{g^2 - 64gk + 16k^2}}{4f}$$

if the argument of the square root is positive, which requires that $g > 63.75k$. The fixed point is stable for small total concentrations, becomes unstable in the first Hopf bifurcation and stable again in the second.
For $n = 4$ the absolute coefficient vanishes, i.e., we encounter a Hopf bifurcation at

$$c_0^\circ = \frac{4(g-k)}{f}$$

if $g > k$. In this case the fixed point is a saddle below $c_0^\circ$ and a sink above this value. If $g < k$, the fixed point is stable at all values of $c_0$.
The quadratic coefficient of is always positive; the absolute coefficient is negative if $n > 4$. Therefore, if $n > 4$, there is exactly one positive value $c_0^\circ$ at which the real part of $\lambda_1^+$ vanishes; since the fixed point is unstable at small total concentrations, it becomes stable if $c_0$ exceeds this critical value. ∎

**Proof of Lemma 7.** The equilibrium concentrations at an interior equilibrium are

$$\bar{x}_i = \frac{r(r-k\bar{a})}{f(\bar{a}\kappa - r)} \qquad \bar{s}_i = \frac{r-k\bar{a}}{f}$$

where $\bar{a}$ is a solution of the equation

$$\bar{a}^2\kappa(nk-f)+\bar{a}[\kappa(fa_0-nr)+fr]-fa_0r=0\,.$$

Such a solution is physically meaningful if $a<a_0$ and $r/\kappa<\bar{a}<r/k$. The lemma follows easily from these conditions. ∎

**Proof of Theorem 12.** As for the constant organization case we can analyze the Jacobian matrix using the method described in appendix B. We find the external eigenvalue $-r$ and two eigenvalues which do not change sign with the flux rate. We do not give them here since their explicit expressions are very complicated. It can be shown, however, that one of them is always negative, while the other one is positive in one and negative in the other fixed point whenever there are two interior rest points $P_{\mathcal{N}}^{(1)}$ and $P_{\mathcal{N}}^{(2)}$.

The remaining eigenvalues are of the form

$$\lambda_j^{+/-}=\frac{1}{2}\left(-u\pm\sqrt{u^2-4v+w(\cos\phi+i\sin\phi)}\right)\qquad\text{for}\quad 1\le j\le n-1$$

with the abbreviations

$$u=f\bar{x}+r\,,\qquad v=f\bar{x}(r-k\bar{a})\,,\qquad w=fg\bar{x}\bar{a}$$

and $\phi=-2\pi j/n$. There can be Hopf bifurcations for all $\lambda_j^+$ with $j\neq n/2$, but since $\lambda_1^+$ has the greatest real part, only Hopf bifurcations at this eigenvalue change the stability of the fixed point.

For $n=3$, the real part of $\lambda_1^+$ changes sign at

$$r^\circ=\frac{a_0f}{14}\cdot\frac{2fg+20fk+33gk-48k^2\pm(2f-9k)\sqrt{g^2-64gk+k^2}}{2f^2+fg-8fk+6gk+6k^2}$$

There are either two Hopf bifurcations or none (the latter case occurs if $r^\circ$ is negative or complex).

For $n=4$ a Hopf bifurcation takes place if $g>k$. The critical value of the flux is

$$r^\circ=\frac{a_0f(g+k)}{2(f+4(g-k))}$$

The flux rate at which the real part of $\lambda_1^+$ changes sign can be determined for arbitrary $n$, but the general formulae are too complicated to be reproduced here.

It can be shown, however, that for $n \geq 5$ there is exactly one flux rate at which $\lambda_j^+$ changes is sign.

If $f > f^c$ there is another technical problem: Since the equation for the eigenvalues above has the same form for both interior fixed points it does not readily tell us at which one of them a Hopf bifurcation occurs. In order to decide this question we need to explicitly compute the equilibrium concentration of the substrate at the Hopf bifurcation.

At $r = 0$, $\bar{a} = 0$ and at $r = a_0 k$, $\bar{a} = a_0$, all eigenvalues $\lambda_j^+$ are zero. The sign of the eigenvalue near these critical flux rates can be determined from the sign of the derivative $\partial \mathrm{Re}(\lambda_j^+)/\partial r$. We find

$$\left( \frac{\partial \mathrm{Re}(\lambda_j^+)}{\partial r} \right)_{r=0,\bar{a}=0} = \frac{g}{\kappa}(\cos\phi - 1)\,.$$

This is negative for all $j$ and hence $\lambda_j^+$ is negative for sufficiently small flux rates. Near the transcritical bifurcation we find

$$\left( \frac{\partial \mathrm{Re}(\lambda_j^+)}{\partial r} \right)_{r=a_0 k,\bar{a}=a_0} = \frac{fg}{fg - nk\kappa} \cos\phi\,.$$

The denominator is positive if $f > f^c$, that is, if there are two interior rest points. In this case the sign of the real parts of the eigenvalues equals the sign of $\cos 2\pi j/n$ for flur rates $r$ that are not much larger than $a_0 k$. If $f < f^c$ the denominator is negative and the sign of the real part of the eigenvalue equals the sign of $\cos 2\pi j/n$ for flux rates not much smaller than $a_0 k$. ∎

## Appendix B: Eigenvalues of the Jacobian

In this section we briefly discuss the properties of the Jacobian matrix at an interior equilibrium for the symmetric models. Not much can be said about more general cases, unfortunately. The computations have been assisted by the symbolic mathematics packages `Reduce` and `Mathematica`. Since most of the explicit expressions are very complicated we present only a brief outline.

The Jacobian for the system under constant organization has the entries

$$\mathbf{U}_{ij} \stackrel{\text{def}}{=\!=} \frac{\partial \dot{x}_i}{\partial x_j}\,, \qquad \mathbf{V}_{ij} \stackrel{\text{def}}{=\!=} \frac{\partial \dot{x}_i}{\partial s_j}\,, \qquad \mathbf{W}_{ij} \stackrel{\text{def}}{=\!=} \frac{\partial \dot{s}_i}{\partial x_j}\,, \qquad \mathbf{X}_{ij} \stackrel{\text{def}}{=\!=} \frac{\partial \dot{s}_i}{\partial s_j}\,.$$

The matrices $\mathbf{U}$, $\mathbf{V}$, $\mathbf{W}$ and $\mathbf{X}$ have size $n \times n$. In the CSTR we have additional terms of the form

$$\vec{p}_i \stackrel{\text{def}}{=\!=} \frac{\partial \dot{x}_i}{\partial a}\,, \qquad \vec{q}_i \stackrel{\text{def}}{=\!=} \frac{\partial \dot{s}_i}{\partial a}\,, \qquad \vec{v}_i \stackrel{\text{def}}{=\!=} \frac{\partial \dot{a}}{\partial x_j}\,, \qquad \vec{w}_i \stackrel{\text{def}}{=\!=} \frac{\partial \dot{a}}{\partial s_j}\,, \qquad z \stackrel{\text{def}}{=\!=} \frac{\partial \dot{a}}{\partial a}\,.$$

The Jacobian can thus be represented in the form

$$\mathbf{J}_{c.o.} = \begin{pmatrix} \mathbf{U} & \mathbf{V} \\ \mathbf{W} & \mathbf{X} \end{pmatrix} \qquad \text{and} \qquad \mathbf{J}_{cstr} = \begin{pmatrix} \mathbf{U} & \mathbf{V} & \vec{p} \\ \mathbf{W} & \mathbf{X} & \vec{q} \\ \vec{v}^{+} & \vec{w}^{+} & z \end{pmatrix}\,,$$

respectively. The crucial observation is that the quadratic $n \times n$ blocks are *circulant* for the interior fixed point of both the symmetric cooperation and the symmetric comptetition model. The vectors $\vec{p}$, $\vec{q}$, $\vec{v}$ and $\vec{w}$ are multiples of the vector $\mathbf{1} = (1, \ldots, 1)$ in this case. Let $\mathbf{I}$ be the identity matrix and let $\mathbf{J}$ denote the matrix with all entries 1. The matrix $\mathbf{C}$ has the entries $\delta_{i,j+1}$ where the indices are taken modulo $n$. The zero-matrix is denoted by $\mathbf{O}$. Clearly, the matrices $\mathbf{I}$, $\mathbf{J}$, $\mathbf{O}$, $\mathbf{C}$ and its transpose $\mathbf{C}^{+}$ are circulant. With this notation we find explicitly:

*competitive model under constant organization*

$$\mathbf{J} = \begin{pmatrix} -\kappa\bar{x}\mathbf{J} & c_0 f \bar{x}\mathbf{I} \\ -\kappa\bar{s}\mathbf{J} + g(-\bar{s}c_0 f)\mathbf{I} & -(c_0 f\bar{x} + \bar{\Phi})\mathbf{I} \end{pmatrix}$$

*cooperative model under constant organization*

$$\mathbf{J} = \begin{pmatrix} -\kappa\bar{x}\mathbf{J} & -c_o f\mathbf{C} \\ -\kappa\bar{s}\mathbf{J} + g\mathbf{I} - c_0 f\bar{s}\mathbf{C}^{+} & -(c_0 f\bar{x} + \bar{\Phi})\mathbf{I} \end{pmatrix}$$

*competitive model in the CSTR*

$$\mathbf{J} = \begin{pmatrix} \mathbf{O} & f\bar{x}\mathbf{I} & k\bar{x}\mathbf{1} \\ (g\bar{a} - f\bar{s})\mathbf{I} & -(f\bar{x} + r)\mathbf{I} & g\bar{x}\mathbf{1} \\ -\kappa\bar{x}\mathbf{1}^{+} & \vec{0} & -(r + n\kappa\bar{x}) \end{pmatrix}$$

*cooperative model in the CSTR*

$$\mathbf{J} = \begin{pmatrix} \mathbf{O} & f\bar{x}\mathbf{C} & k\bar{x}\mathbf{1} \\ g\bar{a}\mathbf{I} + (k\bar{a} - r)\mathbf{C}^{+} & -(f\bar{x} + r)\mathbf{I} & g\bar{x}\mathbf{1} \\ -\kappa\bar{x}\mathbf{1}^{+} & \vec{0} & -r - n\kappa\bar{x}) \end{pmatrix}$$

The vectors

$$\vec{y}^{(j)} = (1, \zeta^{j}, \zeta^{2j}, \zeta^{3j}, \ldots, \zeta^{(n-1)j}) \qquad \text{with} \quad \zeta = \exp(2\pi\imath/n) \quad \text{and} \quad 0 \leq j < n$$

are eigenvectors of all circulant $n \times n$ matrices. They can be used to explicitly construct eigenvectors of the above Jacobian. In particular, the ansatz $\xi^{(j)} = (\vec{y}^{(j)}, \beta_j \vec{y}^{(j)})$ leads to a quadraric equation for the parameter $\beta_j$ in the constant organization case. In general we obtain two solutions for $\beta_j$ belonging to two different eigenvalues of $\mathbf{J}$. The details of this procedure for matrices consisting of $m \times m$ circulant blocks of size $n \times n$ has been described in detail in [20]. Explicit expressions for the eigenvalues are used in some of the proofs in appendix A.

The situation is similar for the CSTR case, where we have an additional row and column. An appropriate ansatz for the eigenvectors of $\mathbf{J}$ is $\xi^{(j)} = (\vec{y}^{(j)}, \beta_j \vec{y}^{(j)}, \omega_j)$. The procedure is simplified considerably by the observation that $\vec{y}^{(0)} = \mathbf{1}$ and that the vectors $\vec{y}^{(j)}$ are orthogonal. A short computation then shows that $\omega_j = 0$ for all $j \neq 0$. We therefore obtain a quadratic equation for $\beta_j$ which completely analogous to the constant organization case. For $j = 0$ we obtain a non-linear system of equations in the variables $\beta_0$ and $\omega_0$. Eliminating $\omega_0$ we obtain a cubic equation for $\beta_0$. One root is the external eigenvalue $-r$. The remaining quadratic equation can be solved explicitly. In general we obtain very complicated expressions, however, which we do not reproduce in this contribution. They can be found in the doctoral thesis [22].