MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **90** (2023) 471–494
ISSN: 0340–6253
doi: 10.46793/match.90-2.471I

Persistent Subspaces of Reaction-Based Dynamical Systems

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(Received January 4, 2023)

Abstract

Various types of dynamical systems, such as ordinary differential equations (ODEs) or partial differential equations (PDEs), are widely applied not only in chemistry but also in many scientific disciplines to model the dynamics arising from interactions described by reactions between molecules, individuals, or species. This study provides an overview of how Chemical Organization Theory (COT) can be used to analyze such systems by identifying all potentially persistent species solely from the underlying reaction network, without the need for simulations or even knowledge of reaction constants or kinetic laws. Two minimalist examples with only three resp. four species are used to introduce all fundamental definitions including a new, naturally arising concept of persistence, and to illustrate the fore-mentioned technique without mathematical details such as proofs. Thereby, COT is shown to provide measures to analyze,

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compare, and construct very complex systems on an abstract level and thus to complement other powerful techniques for the analysis of complex systems such as deficiency, RAF theory, elementary modes, graph theory, Lyapunov functions, and bifurcation theory.

1 Introduction

Reaction networks are used in various areas to describe the possible interactions of species [1–3]. As a result, reaction network analysis has expanded into a broad field that includes, among others, deficiency [4, 5], RAF theory [3], Chemical Organization Theory (COT) [6], subnetwork analysis [7], elementary modes [8], graph theory [9, 10] or Lyapunov functions [11] play an important role. The chemical organization theory (COT) was shown to play a meaningful role in the persistence of species in dynamical systems basing upon reactions in a sequence of three previous works [12–14]. The concept of the chemical organization was applied successfully in various constructive systems like chemical computing [15], social systems [16], virus dynamics [17–20] or checking systems biology models for inconsistencies [21] as well as in cell cycle control [22–24]. For the time being, the theory was completed in [14] and here it is presented in a brief and clear manner that omits mathematical details.

The stoichiometric matrix of a reaction network, together with reaction constants and a kinetic law, builds up the connection between the static reaction network and a dynamical system describing the dynamics of the species concentrations in time. When using continuous values for the concentrations, then the concentration of each species can be described by an ordinary differential equation (ODE). If a spatial dimension is incorporated then partial derivatives appear and the ODEs get partial differential equations (PDEs). Such a system of PDEs is called a reaction-diffusion system (RDS) if it includes diffusion terms. To conclude the list of continuous dynamical systems, patch-like systems are to be mentioned, that is, systems that are distributed to different patches with defined interconnections allowing for diffusion, convection, etc. This work focuses on RDS such that systems of ODEs and patch-like systems appear as special cases. It will become clear that the techniques can be easily transferred to other

types of systems as well such as discrete, stochastic systems as we have indicated in [25, 26].

Persistence is a topic concerning all types of dynamical systems. There are different types of persistence named with many different terms in various fields like ecology, chemistry, and biology. First, one has to distinguish between the different model types Including, discrete and continuous models, ODEs and PDEs-based models, deterministic or stochastic models, models having spatial properties or not, etc. As for the aforementioned types of models, for RDS there are different terms used with regard to persistence, such as permanence [27–30], coexistence [30, 31], extinction [31, 32], strong persistence [32], uniform persistence [31] etc. For an overview of these concepts, we refer the reader to [29, 32]. Concepts of persistence may vary with regard to whether a single species or a whole system of species is considered, whether a single solution or all possible solutions of a dynamical system are considered or with regard to the degree of persistence, such as, strong and weak persistence. In this work, a new concept of persistence is defined as capturing all possibly persistent subsets of species of a dynamical system with an underlying reaction network and relating them to each other. Thus, previous concepts are extended and refined and fixed-point analyses and bifurcation theory as techniques to analyze complex systems are complemented on a more abstract level. Figure 1 gives an overview of how this works and links different reaction network analyses and dynamical systems.

The paper is structured as follows: Firstly, we give some preliminaries on reaction networks and COT as well as the aforementioned different types of reaction-based dynamical systems. Furthermore, Theorem 1, the starting point of this work, is explained. The Preliminaries section is concluded by some remarks about persistence. In the Results, a new concept of persistence is introduced. Subsequently, distributed organizations (DOs) are defined as a generalization of organizations, which fits to the new concept of persistence, in that in connection with DOs the main result of this work, Theorem 2, holds. In the end, a conclusion and outlook on further research are given.

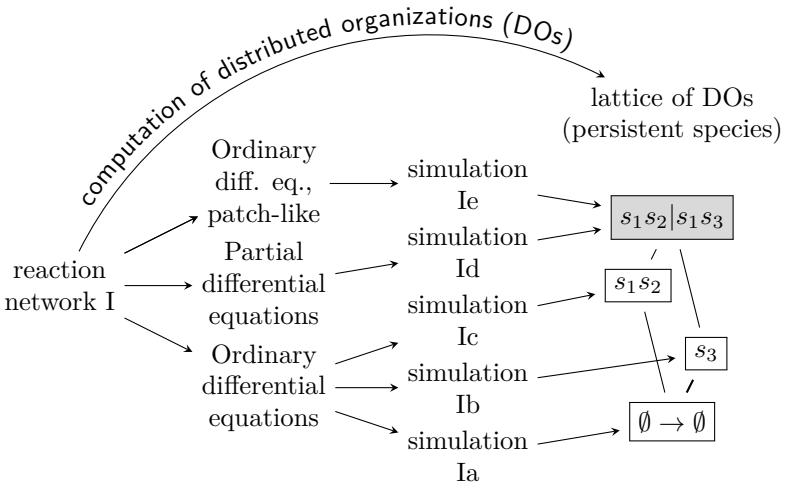


Figure 1. Overview of the topic of this paper illustrated for example reaction network 1 introduced in the Preliminaries. From left to right: From a reaction network, a dynamical system is constructed. Simulations (or solutions) of the dynamical system exhibit attractors with certain sets of persistent species in the long-run. The main result of this work (Theorem 2) states that these sets of persistent species are always so-called distributed organizations (DOs), which can be computed (without knowing the kinetics and reaction constants of the dynamical system) solely from the reaction network and form a lattice.

2 Preliminaries

2.1 Reaction networks

The example I is used to introduce the basic terms about reaction networks and Chemical Organization Theory (COT) It consists the set $\mathcal{S} = \{s_1, s_2, s_3\}$ of the following $n = 3$ species

$$s_1 = \text{substrate},$$
$$s_2 = \text{first competitor},$$
$$s_3 = \text{second competitor},$$

which interact according to the set $\mathcal{R} = \{r_1, \ldots, r_9\}$ of $m = 4$ reactions

$$\begin{aligned}
r_1 &: \; s_2 \xrightarrow{k_1} s_1 + s_2 && \text{production of substrate by } s_2,\\
r_2 &: \; 2s_1 + s_3 \xrightarrow{k_2} s_3 && \text{consumption of substrate by } s_3,\\
r_3 &: \; s_2 + s_3 \xrightarrow{k_3} \emptyset && \text{mutual destruction of competitiors,}\\
r_4 &: \; s_1 \xrightarrow{k_4} \emptyset && \text{outflow of substrate.}
\end{aligned} \tag{1}$$

Together, we call the set of species and the set of reactions a reaction network. The support $supp(r)$ of a reaction $r \in \mathcal{R}$ is the subset of species on the left-hand side of its reaction rule, for example, $supp(r_2) = \{s_1, s_3\}$. The products $prod(r)$ of a reaction r is the subset of species on the right-hand side of its reaction rule, for example, $prod(r_2) = \{s_3\}$. The stoichiometric matrix of the reaction network is

$$\mathbf{N} = \begin{pmatrix} 1 & -2 & 0 & -1 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & -1 & 0 \end{pmatrix} \in \mathbb{Z}^{3\times 4}, \tag{2}$$

which contains one column of integers for each reaction which describes the changes to the number of species caused by this reaction.

2.2 Organizations

An organization O is defined to be a subset of species with the following two properties:

1. O is closed, that is, no species can be produced by the reactions which can operate on O that are not already contained in O, or shortly, for every reaction $r \in \mathcal{R}$ holds:

$$supp(r) \subseteqq O \quad \Rightarrow \quad prod(r) \subseteqq O, \tag{3}$$

   and

2. O is self-maintaining, that is, there is an equilibrium such that every species that is reduced by a reaction is restored by another reaction,

or more precisely, there is a flux vector $\mathbf{v} \in \mathbb{R}^m_{\geq 0}$ for O with

$$Nv \geq 0 \tag{4}$$

and for all reactions $r \in \mathcal{R}$ holds

$$v_r > 0 \quad \Leftrightarrow \quad supp(r) \subseteqq O. \tag{5}$$

The set of organizations of a reaction network can be arranged in a so-called Hasse diagram of organizations. Thereby, each organization is represented by a node, which is positioned the higher in the diagram the more species it contains. Two organizations are linked with each other via a line if and only if one organization is a proper subset of the other. In Figure 2 the Hasse diagram of organizations of the Example I reaction network is shown.

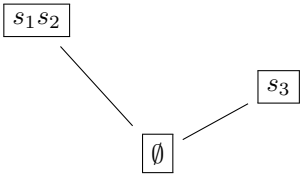


Figure 2. Hasse diagram of organizations of Example I. All organizations except for $\{s_1, s_2\}$ are non-reactive, that is, their fluxes indicating self-maintenance are all the null vector in $\mathbb{R}^4$. A flux vector v with $Nv \geq 0$ for $\{s_1, s_2\}$ is $(1, 0, 0, 1)^T$. Since s_2 and s_3 can not survive together there is no organization containing both of them.

2.3 Reaction-based dynamical systems

The theory presented in this work can be applied to various types of dynamical systems. Three of them are presented in what follows. The term "reaction-based dynamical system" means that the reactional part of each system can be written in the form $\dot{\mathbf{c}} = Nv(t) + \ldots$ with the species concentration vector $\mathbf{c}$, the stoichiometric matrix N, a flux vector $\mathbf{v}(t)$ and the dots representing optional terms for diffusion, for example. Each entry

$v_j(t) = v_j(c_1(t), \ldots, c_n(t)) \geq 0$ for $j \in \{1, \ldots, m\}$ of $\mathbf{v}(t)$ corresponds to exactly one reaction r_j such that $v_j(t) = 0$ if and only if $c_i(t) = 0$ for at least one species $s_i \in supp(r_j)$. This represents the logical fact, that a reaction can only be active and thus influence the concentrations of some species if and only if all the species of the reactions' support have strictly positive concentrations.

2.3.1 Ordinary differential equations (ODEs)

First, a system of ODEs based upon the reaction network of Example I is constructed. The species concentrations are considered to be time-dependent real-valued functions $c_i = c_i(t)$, $i = 1, 2, 3$, and their derivations $\dot{c}_i$ by time are defined by

$$\dot{\mathbf{c}} = N \cdot \mathbf{v}(\mathbf{c}) = N \cdot \mathbf{v}(\mathbf{c}(t)) = N \cdot \mathbf{v}(t) \tag{6}$$

with the flux vector function $\mathbf{v}(t)$ chosen according to mass-action kinetics, that is,

$$v(t) = (k_1 c_2(t), k_2 c_1^2(t) c_3(t), k_3 c_2(t) c_3(t), k_4 c_1(t))^T, \tag{7}$$

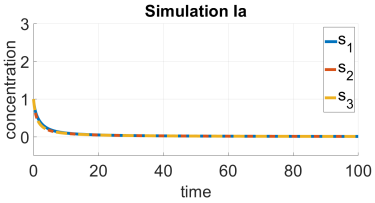
where k_1 to k_4 are strictly positive real numbers, the so-called reaction constants. Figure 3 shows the resulting system of ODEs together with the species concentration courses of the three simulations Ia, Ib and Ic exhibiting different fixed points in the long-run.

2.3.2 Partial differential equations (PDEs) and Reaction-diffusion systems (RDS)

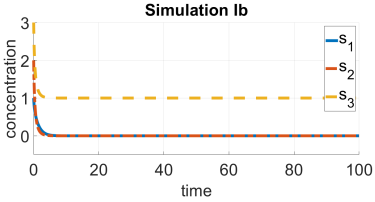
If a spatial variable $x \in \Omega$ from a domain Ω is added to the species concentrations $c_i(x, t)$, $i = 1, 2, 3$, then the derivation by time becomes a partial derivation and the differential equations turn to partial differential equations (PDEs). And if at least some of the differential equations contain a summand representing a diffusion term, that is, containing the second derivation by x, then the PDEs become a so-called RDS. Figure 4 shows PDEs based upon the reaction network of Example 1 plus the example

$$\begin{aligned}\dot{c_1} &= k_1 c_2(t) - k_2 c_1^2(t) c_3(t) - k_4 c_1(t)\\ \dot{c_2} &= -k_3 c_2(t) c_3(t)\\ \dot{c_3} &= -k_3 c_2(t) c_3(t)\end{aligned}$$

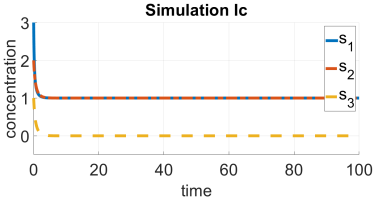
(a) ODEs based upon Example 1



(b) ICs: $c_1(0) = c_2(0) = c_3(0) = 1$.



(c) ICs: $c_1(0) = 1$, $c_2(0) = 2$, $c_3(0) = 3$.



(d) ICs: $c_1(0) = 3$, $c_2(0) = 2$, $c_3(0) = 1$.

Figure 3. (a) ODEs based upon the reaction network of Example 1 together with three example simulations performed with Matlab R2020a function "ode15s" (see subfigures (b), (c) and (d)) each with reaction constants $k_1 = \ldots k_4 = 1$ but with different initial conditions (ICs) and thus approaching different fixed points with different species persisting in the long-run.

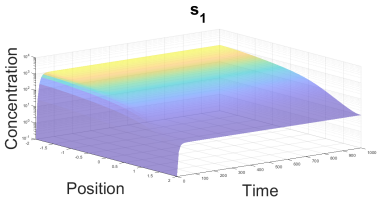
simulation Id for which only the species s_1 diffuses and boundary conditions are homogeneous Neumann.

2.3.3 A patch-like system

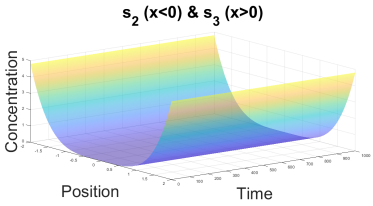
Now, a patch-like system is presented as the last type of dynamical system that bases upon a reaction network such as the one from Example 1. Let the patch-like system considered here consist of two patches: L (left) and R (right), so to speak a discrete, two-element domain $\Omega = \{L, R\}$. On each of the patches, one of two equally structured ODE systems describes the dynamics of the species concentrations and there is a coupling convection term for the species s_1 between the two patches, which is proportional to the difference between the concentrations of s_1 in patch L resp. patch R. Figure 5 contains the associated ODEs (with $c_{ij} = c_i(j,t)$ for $i = 1,2,3$ and $j = L, R$) as well as the results of the example simulation Ie, which is

$$\begin{aligned}\frac{\partial c_1}{\partial t} &= k_1 c_2 - k_2 c_1^2 c_3 \\ &\quad - k_4 c_1 + d_1 \frac{\partial^2 c_1}{\partial x^2} \\ \frac{\partial c_2}{\partial t} &= \frac{\partial c_3}{\partial t} = -k_3 c_2 c_3\end{aligned}$$

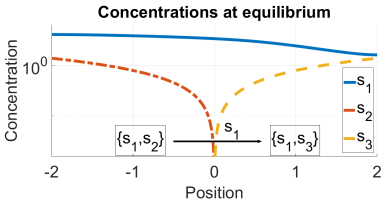
(a) PDEs based upon Example 1



(b) Concentration $c_1(x,t)$



(c) Concentrations $c_2(x,t)$ (for $x < 0$) and $c_3(x,t)$ (for $x \geq 0$))



(d) Concentrations at equilibrium state

Figure 4. (a) PDEs based upon the reaction network of Example 1 together with an example simulation (see subfigures (b), (c) and (d)) performed with Matlab R2020a function "pdepe" with reaction constants $k_1 = \ldots k_4 = 1$, homogeneous Neumann boundary conditions and only species s_1 diffusing. Whereas s_1 and s_2 exist in disjoint areas of the domain and remain constant over time s_1 is produced by s_1 via the reaction r_1 in the beginning and then diffuses to the right to settle the whole domain.

structurally very similar to the simulation Id.

2.4 Organizations and Fixed points of ODEs

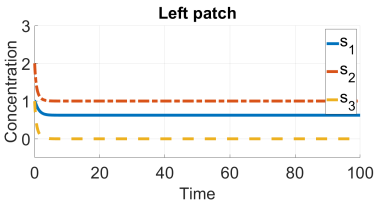
In [6], Theorem 1, a result about the relation of fixed points of ODE systems and organizations was proven.

$$\begin{aligned}\dot{c}_{1L} = \; & k_1 c_{1L} - k_2 c_{1L}^2 c_{3L} \\ & - k_4 c_{1L} - (c_{1L} - c_{1R}) \\ \dot{c}_{2L} = \; & - k_3 c_{2L} c_{3L} \\ \dot{c}_{3L} = \; & - k_3 c_{2L} c_{3L}\end{aligned}$$

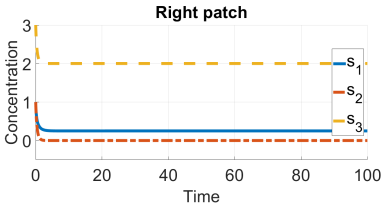
(a) ODEs for the left patch

$$\begin{aligned}\dot{c}_{1R} = \; & k_1 c_{2R} - k_2 c_{1R}^2 c_{3R} \\ & - k_4 c_{1R} + (c_{1L} - c_{1R}) \\ \dot{c}_{2R} = \; & - k_3 c_{2R} c_{3R} \\ \dot{c}_{3R} = \; & - k_3 c_{2R} c_{3R}\end{aligned}$$

(b) ODEs for the right patch



(c) ICs: $c_1(L,0) = c_3(L,0) = 1, c_2(L,0) = 2$



(d) ICs: $c_1(R,0) = c_2(R,0) = 1, c_3(R,0) = 3$

Figure 5. Patch-like system with two patches L and R each or which is ruled by ODEs based upon Example 1 and a convection term $(c_{1L} - c_{1R})$ of the species s_1 between the two patches. The example simulation Ie was performed with Matlab R2020a function "ode15s" with reaction constants $k_1 = \ldots k_4 = 1$. Similar to the RDS example simulation Id (see Figure 4), in the left patch, s_1 and s_2 persist whereas in the right patch, s_1 and s_3 persist.

Theorem 1 (The species present in a fixed point are an organization)**.** *Let* $\mathbf{c}^\star$ *be a fixed point of an ODE system of the form*

$$\dot{\mathbf{c}} = N\mathbf{v}(\mathbf{c}), \tag{8}$$

that is,

$$N\mathbf{v}(\mathbf{c}^\star) = N\mathbf{v}^\star = 0 \tag{9}$$

and N *be the stoichiometric matrix of a reaction network and* $\mathbf{v}(\mathbf{c})$ *is a non-negative flux-vector function, for which the entry* $v_j(\mathbf{c})$ *equals zero if and only if* $c_i = 0$ *for at least one species* $s_i \in supp(r_j)$*. Then, the set*

$$O^\star = \{s_i \in \mathcal{S} : c_i^\star > 0\} \tag{10}$$

is an organization.

Note, that to $\mathbf{c}^\star$ *belongs a flux vector* $\mathbf{v}^\star \in \mathcal{R}$ *with its strictly positive elements designating the active reactions of that fixed point. Roughly speaking, the set of species present in a fixed point is an organization.*

Table 1 illustrates Theorem 1 by relating the simulation examples Ia, Ib and Ic to the organizations corresponding to the fixed points approached. Nevertheless, the RDS simulation example Id has shown that Theorem 1

reaction network	**simulation**	**dynamical system type**	**approached organization**
example I	Ia	ODEs	$\emptyset$
	Ib	ODEs	$\{s_3\}$
	Ic	ODEs	$\{s_1 s_2\}$
	Id	PDEs (RDS)	no organization
	Ie	patch-like	no organization

Table 1. Overview of the simulation examples based upon the reaction network Example 1 and the organizations that are approached, if any. When comparing this table to Table 2 below it will become clear how the main result of this work (Theorem 2) generalizes Theorem 1.

does not necessarily hold for other types of dynamical systems since in the equilibrium point of simulation Id all species s_2, s_2 and s_3 are present but the set $\{s_1, s_2, s_3\}$ is not an organization of the underlying reaction network Example 1. The main topic of this work is a generalization of Theorem 1 to all types of reaction-based dynamical systems mentioned above. This includes understanding the persistence of species also in more complex types of long-term behavior such as periodicity, chaos, and heteroclinic orbits. This is the topic of the first subsection of the Results.

2.5 Persistence

One could say that a species persists if its concentration does not approach zero as time goes to infinity. But the fact, that there can be found many different definitions of persistence (or permanence) in literature (for example, in [29, 32]) indicates that the situation is more complex.

The example ODE simulations Ia to Ic from above all approach a static

equilibrium, that is, a fixed point $\mathbf{c}^\star$ with $\dot{\mathbf{c}}^\star = 0$. This represents the most simple type of dynamical behavior with regard to persistence because in this case a species s_i can be called persistent if and only if its concentration holds

$$c_i^\star = \lim_{t\to\infty} c_i(t) > 0. \tag{11}$$

For RDS (e.g., simulation Id) and patch-like systems (e.g., simulation Ie) a further integral about the domain Ω can be added as follows. For a RDS, a species s_i persists if and only if

$$\lim_{t\to\infty} \int_{x\in\Omega} c_i(x,t) > 0 \tag{12}$$

and for patch-like systems, a species s_i persists if and only if

$$\lim_{t\to\infty} \sum_{x\in\Omega} c_i(x,t) > 0. \tag{13}$$

Now, Example II is introduced together with an ODE system which illustrates that persistence gets more ambiguous if non-static behavior appears in the long-run of such systems. Example II is an extension of a three-species model presented in [30] which resembles, for example, the rock-scissors-paper game, the prisoner's dilemma with three participants or the coexistence of different strains of bacteria, such as E. coli, competing for nutrition, intoxicating, invading, and resisting one another. The species s_1, s_2 and s_3 interact symmetrically according to the following twelve reactions:

$$\begin{array}{lll}
r_1: s_1 \to 2s_1, & r_5: s_2 \to 2s_2, & r_9: s_3 \to 2s_3, \\
r_2: 2s_1 \to s_1, & r_6: 2s_2 \to s_2, & r_{10}: 2s_3 \to s_3, \\
r_3: s_1 + s_2 \to s_2, & r_7: s_2 + s_1 \to s_1, & r_{11}: s_3 + s_1 \to s_1, \\
r_4: s_1 + s_3 \to s_3, & r_8: s_2 + s_3 \to s_3, & r_{12}: s_3 + s_2 \to s_2.
\end{array} \tag{14}$$

Each species self-replicates (r_1, r_5, r_9), thus every subset of species is an

organization. Every species decays spontaneously (r_2, r_6, r_{10}) and each species can reduce any other (r_3, r_4, r_7, r_8, r_{11}, r_{12}). To construct Example II, a fourth species is added which is created by the previous three and decays spontaneously:

$$\begin{aligned} r_{13}: \; & s_1 + s_2 + s_3 \rightarrow s_1 + s_2 + s_3 + s_4, \\ r_{14}: \; & s_4 \rightarrow \emptyset. \end{aligned} \tag{15}$$

Figure 6 shows an ODE system basing upon the reaction network of Example II together with two simulations, IIa and IIb, which, in the long-run, exhibit a periodic orbit resp. a heteroclinic orbit.

The simulation example IIa (6b) shows non-static behavior, that is, the trajectory approaches an attractor for which the concentrations of all species are above a strictly positive threshold from a certain point in time on forever. For such attractors, which also can be chaotic, it is easy to decide which species persist, namely those, for which the concentration stays above a strictly positive threshold as time goes to infinity.

In simulation example IIb (6c) the trajectory approaches a so-called heteroclinic orbit, which contains different subsets of species alternating forever as time goes to infinity. Here it is more difficult to decide, which of these subsets is to be regarded as persistent and which is not. In literature, for example [32], the following definitions can be found:

1. A species s_i is strongly persistent if and only if

$$\liminf_{t\to\infty} \int_{x\in\Omega} c_i(x,t)\,dx > 0. \tag{16}$$

   This means that from some point in time on, the species concentration does not fall below a certain strictly positive threshold anymore.

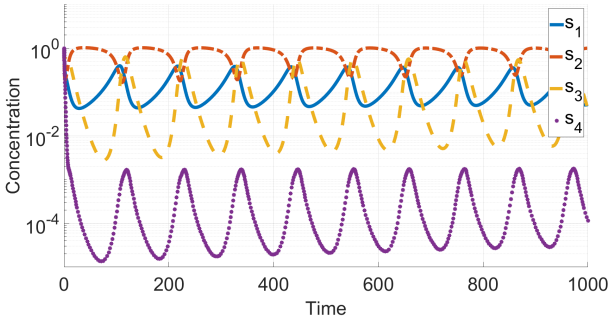
2. A species s_i is weakly persistent if and only if

$$\limsup_{t\to\infty} \int_{x\in\Omega} c_i(x,t)\,dx > 0, \tag{17}$$

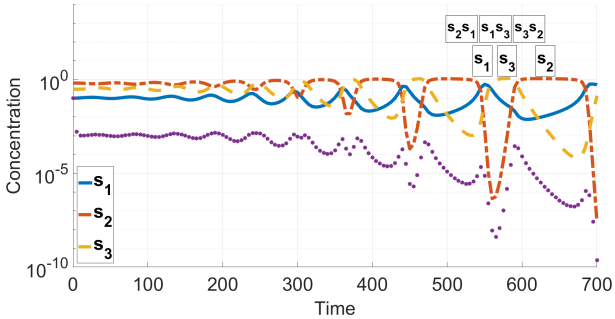
   which means that there is a strictly positive threshold for the concentration which is exceeded again and again until infinity.

$$\dot{c}_1 = 1.156c_1 - 2c_1^2 - c_1c_2 - c_1c_3,$$
$$\dot{c}_2 = 2c_2 - 1.75c_2^2 - (1 + 2.94)c_2c_1 - c_2c_3,$$
$$\dot{c}_3 = c_3 - 0.844c_3^2 - c_3c_1 - c_3c_2,$$
$$\dot{c}_4 = 0.05c_1c_2c_3 - 0.5c_4.$$

(a) ODEs basing upon reaction network Example II (14,15)



(b) Example simulation IIa with periodic orbit in the long-run



(c) Example simulation IIa with heteroclinic orbit in the long-run

Figure 6. (a) ODEs basing upon Example II (14,15). (b) Example simulation IIa with initial conditions $c_1(0) = c_2(0) = c_3(0) = c_4(0) = 1$ leading to a periodic orbit where all species $s_1, \ldots, s_4$ persist, that is, have concentrations above a strictly positive threshold as time goes to infinity. (c) Example simulation IIb with initial conditions $c_1(0) = 0.1$, $c_2(0) = 0.64$, $c_3(0) = 0.31$, $c_4(0) = 0.1$ leading, in the long-run, to a so-called heteroclinic orbit, that is a trajectory passing different subsets of species. Overall, the species s_1, s_2 and s_3 exhibit concentrations above a strictly positive threshold and concentrations approaching zero in periodic change as time goes towards infinity, such that they do not appear all together at the same time. Species s_4 does not persist as its concentration approaches zero.

Thus, if a species is strongly persistent, then it is also weakly persistent but the other direction does not hold. If the dynamical system does not have a spatial dimension then the integral over Ω is omitted, that is, $\int_{x\in\Omega} c_i(x,t)dx$ is replaced by $c_i(t)$.

For the example simulation IIb we find that all species are weakly persistent but none of them is strongly persistent. This statement does not capture the fact, that certain subsets of species persist but not all (for example, the subset $\{s_1, s_2, s_3\}$ does not persist). This is one of the problems that is solved by the new concept of persistence presented in the next subsection since it is based upon subsets of species instead of species.

3 Results

3.1 New concept of persistence

Before stating the new concept of persistence two other terms have to be introduced.

Definition 1. A monotonously increasing sequence $(t_j)_{j=1}^{\infty}$ of nonnegative real numbers tending towards infinity with

$$1 \leq t_{j+1} - t_j \leq Z,$$

$j \in \mathbb{N}$, for some $Z \in \mathbb{R}_+$ is called a *sequence of points in time.*

Definition 2 (Neighborhood of a subset of species in the space of concentrations)**.** Given a subset $S \subseteq \mathcal{S}$ of species and real numbers $\varepsilon, \delta > 0$, the set

$$S^{\varepsilon,\delta} \equiv \{c \in \mathbb{R}_+^n : \; c_s \begin{cases} > \varepsilon & \text{iff } s \in S \\ \leq \delta & \text{iff } s \notin S \end{cases}\} \subseteq \mathbb{R}_{\geq 0}^n \tag{18}$$

of concentration vectors is called the (ε, δ)-*neighborhood* of S.

The neighborhoods $S^{\epsilon,\delta}$ are illustrated in Figure 7.

Next, the new concept of persistence is defined.

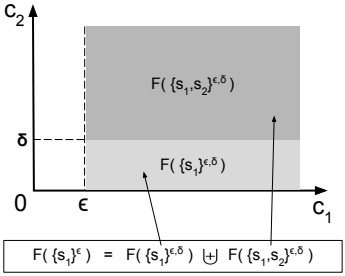


Figure 7. Illustration of Definition 2 for two species s_1 and s_2 (from [14]). The ε-environment of $\{s_1\}$, which is not explained in this work, is a disjoint union of the (ε, δ)-environments of $\{s_1\}$ and $\{s_1, s_2\}$.

Definition 3 (Persistent subsets of species and persistent species)**.** Given a bounded solution c of a reaction-based dynamical system (ODEs, PDEs or patch-like) with an underlying reaction network $(\mathcal{S}, \mathcal{R})$, a subset $S \subseteq \mathcal{S}$ of species is called *persistent* (with respect to c) if for all sequences $(t_j)_{j=1}^{\infty}$ of points in time there is an $\varepsilon > 0$ such that for all $\delta > 0$ the frequency of occurrence $F(S^{\varepsilon,\delta})$ of $S^{\varepsilon,\delta}$ with respect to c and $(t_j)_{j=1}^{\infty}$ is strictly positive, that is,

$$F(S^{\varepsilon,\delta}) = \limsup_{j\to\infty} \frac{1}{t_{j+1} - t_j} \int_{t_j}^{t_{j+1}} \int_{\{x\in\Omega:\ c(x,t)\in S^{\varepsilon,\delta}\}} dx\, dt > 0. \tag{19}$$

The set of persistent subsets of species is denoted $P(c)$, i.e.,

$$P(c) \equiv \{S \subseteq \mathcal{S} :\ S \text{ is persistent with respect to } c\}. \tag{20}$$

A single species $s \in \mathcal{S}$ is said to be persistent (with respect to c) if s is contained in at least one of the persistent subsets of species, i.e.,

$$s \in \cup\{S \subseteq \mathcal{S} :\ S \in P(c)\}. \tag{21}$$

A species $s \in \mathcal{S}$ is said to go extinct (with respect to c) if it is not persistent

with respect to c. The set of persistent species IS denoted $\Phi(c)$, i.e.,

$$\Phi(c) \equiv \{s \in \mathcal{S} : \ s \text{ is persistent with respect to } c\} = \cup\{S \subseteq \mathcal{S} : \ S \in P(c)\}. \tag{22}$$

Lemma 1 states that the new concept of persistence is a refinement of the strong and weak persistence of species defined above.

Lemma 1 (Relation between different definitions of persistence)**.** *Given a bounded solution c of a reaction-based dynamical system (ODEs, PDEs or patch-like) with an underlying reaction network $(\mathcal{S}, \mathcal{R})$ and an arbitrary species $s \in \mathcal{S}$, then the following two implications hold true:*

1. *If s is strongly persistent, then it is persistent.*
2. *If s is persistent, then it is weakly persistent.*

Thus, our new concept of persistence is a refinement of previous ones. The respective reverse implications are not true.

3.2 Distributed organizations (DOs)

Contrary to organizations, DOs might consist of more than one subset of species together fulfilling self-maintenance and each of which is closed.

Definition 4. Given a reaction network $(\mathcal{S}, \mathcal{R})$ with the stoichiometric matrix $N \in \mathbb{Z}^{3\times 4}$, a subset $D \subseteq \mathcal{S}$ is a DO if and only if there are k, $k \in \mathbb{N}$, different subsets $S_1, \ldots, S_k \subseteq D$ with

$$D = \cup_{i=1}^{k} S_i \tag{23}$$

such that

1. all S_i, $i = 1, \ldots, k$, are *closed*;
2. there is a vector $\hat{v} \in \mathbb{R}_+^m$, $\hat{v} \geq 0$, such that

$$N\hat{v} \geq 0; \tag{24}$$

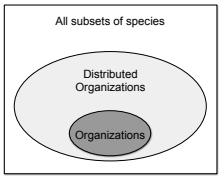


Figure 8. Illustration of the relation between organizations and distributed organizations [14]. Especially, there are DOs that are not organizations.

3. and there is a *feasible flux* $\hat{v}^i \in \mathbb{R}^m_+$, $\hat{v}^i \geq 0$, with respect to each subset S_i, $i = 1, \ldots, k$, with

$$\hat{v} = \sum_{i=1}^{k} \hat{v}^i. \tag{25}$$

Collectively, the second and third items of the list above are called the self-maintenance property of a DO. In the described setting, it is said that "*D is distributed to the* S_i" or "*the* S_i *are a distribution of D*". To list the elements of the subsets S_i, $i = 1, \ldots, k$, of species, a special notation is used, for example, if D is distributed to $S_1 = \{s_1, s_2\}$ and $S_2 = \{s_1, s_3\}$, one can write

$$D = S_1 \cup S_2 = \{s_1 s_2 | s_1 s_3\}. \tag{26}$$

Note that a species can be contained in several subsets S_i, $i = 1, \ldots, k$, of a DO, and also, a DO can be empty. The next lemma, which is proven in [14], elucidates the relation between organizations and DOs. The situation is illustrated in Figure 8.

Lemma 2 (Relation of organizations and DOs)**.**

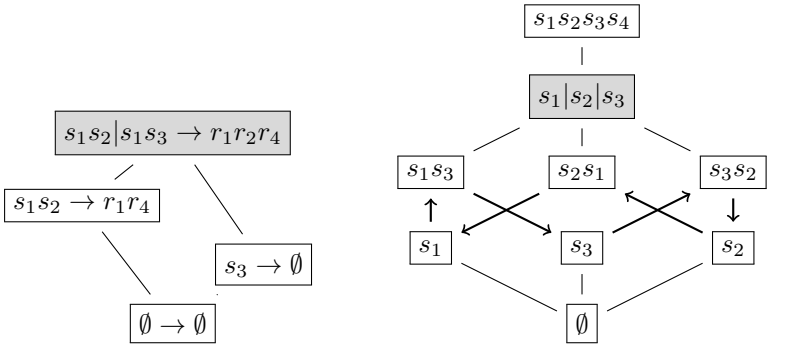
1. *Every organization of a reaction network* $(\mathcal{S}, \mathcal{R})$ *is a DO of that reaction network.*

2. *Every DO of a reaction network* $(\mathcal{S}, \mathcal{R})$ *that has a distribution to a single subset that is* $k = 1$ *in Definition 4 is an organization.*

3. *There exist reaction networks that exhibit DOs that are not organizations.*

4. *For a given reaction network, the set of DOs always forms a lattice (not only a Hasse diagram as it is the case for the set of organizations), that is, for any two DOs A and B there is a unique minimal DO ("infimum") that contains A and B and a unique maximal DO ("supremum") that is contained in A and in B (cf. Figure 9).*

As the gray boxes in 9 indicate, Example I and Example II both contain DOs that are not organizations. Note that the uniqueness of the minimal



(a) Lattice of DOs of Example 1. **(b)** Lattice of DOs of Example II (14,15)

Figure 9. Lattice of DOs of Example I and II. (a) Compared to the Hasse diagram of organizations (see Figure 2), the lattice is completed at the top by the DO containing all species. Besides the species, for each DO the set of reactions is inserted after a right arrow. The "behavior" of a DO is better described by its set of active reactions than by species that are possibly non-reactive. For the DO containing all species, the reaction r_3 is switched off by the distribution of its support to different compartments. This guarantees self-maintenance. (b) There is one DO which is not an organization (gray box) since if all species s_1, s_2 and s_3 were in the same compartment, s_4 would be produced and thus closedness would be violated. The arrows link those subsets of species that persist in simulation IIb in the order they appear in a periodic pattern in the long-run (cf. Figure 6c).

set which contains two given DOs A and B (stated in Lemma 2) allows for defining a generator operation for DOs. This in turn provides an instru-

ment to calculate all DOs of a reaction network. In the next subsection, the main result of this work is stated.

3.3 Main result about the relation of DOs and persistent species

Next, Theorem 2 is stated, which links DOs and persistence as defined in the previous subsections.

Theorem 2 (The set of persistent species is always a DO)**.** *Given a bounded solution c of a reaction-based dynamical system (ODEs, PDEs or patch-like), the set $\Phi(c)$ of persistent species (as defined in Definition 4) is a DO of the underlying reaction network $(\mathcal{S}, \mathcal{R})$.*

The proof of the self-maintenance of $\Phi(c)$ is based upon the construction of a flux vector

$$\hat{v} = \hat{v}(c, (t_l)_{l=1}^{\infty}) \equiv \lim_{j\to\infty} \frac{1}{t_{j+1} - t_j} \int_{t_j}^{t_{j+1}} \int_{x\in\Omega} v(c(x,t))\, dx\, dt \in \mathbb{R}_+^m \quad (27)$$

constructed from the solution c of the dynamical system. The structural similarity of this construction to the central equation 19 of persistence gives a clue as to why Theorem 2 holds. To exemplify 2, in Table 2, for all the simulation examples presented in this work the persistent subsets of species, that is, DOs are listed.

Thus, for a given reaction network, the lattice of DOs gives an overview of all subsets of species (and their inner structure) that have the potential to persist in the long-run of a solution/simulation of any dynamical system that is based upon that reaction network. Without knowing the kinetic laws or reaction constants applied this facilitates understanding such possibly huge systems for which the simulation effort might be enormous. In [17, 19] it was shown how this can be used to understand, compare, design and evaluate virus infection dynamics models. More general, many types of dynamics described by reaction rules can be analyzed this way, such as, for example, the photochemistries of the martian atmosphere on the dayside and on the nightside [33].

reaction network	simulation	dynamical system	attractor type	persistent DO
example I	Ia	ODEs	fixed point	$\emptyset$
	Ib	ODEs	fixed point	$\{s_3\}$
	Ic	ODEs	fixed point	$\{s_1 s_2\}$
	Id	PDEs (RDS)	fixed point	$\{s_1 s_2 \vert s_1 s_3\}$
	Ie	patch-like	fixed point	$\{s_1 s_2 \vert s_1 s_3\}$
example II	IIa	ODEs	periodic	$\{s_1 s_2 s_3 s_4\}$
	IIb	ODEs	heteroclinc	$\{s_2 s_1 \vert s_1 \vert s_1 s_3 \vert s_3 \vert s_3 s_2 \vert s_2\}$

Table 2. Overview of the example reaction networks presented in this work, the simulation examples built upon them, their types, the approached attractors, and the corresponding persistent subset of species, that is, DO. It is clear that the persistent subsets of all simulation examples are represented by a DO. Theorem 2, the main result of this work, states that this would be the case for all bounded solutions of dynamical systems fulfilling a certain continuity condition.

4 Conclusions

The aim of this work was to give an overview of how dynamical systems can be analyzed by using COT. Thereby, proofs and mathematical details were omitted, which can be found in [14]. It was shown that the lattice of DOs of a given reaction network contains all possibly persistent subsets of species of a dynamical system. This helps in understanding and evaluating the dynamics of such systems without simulating them and even without knowing details such as kinetic laws or reaction constants. This was shown, for example, in [17, 19], where the lattices of DOs were computed and compared for several virus infection dynamics models. This technique can be compared to fixed-point analyses of dynamical systems and to bifurcation theory in the sense that it provides a general overview of some aspects of a dynamical system, but COT works on a more abstract level and necessitates less information about the system. Unlike other reaction network analysis techniques, COT creates a connection to dynamical systems by providing information about them.

Currently, a publication of a tool to compute the DOs of a reaction network is in progress. The associated algorithm will also be published soon. There it will be shown that replacing DOs with their respective

active reactions leads to lattices (of reactions) again. This way, different behaviors (that is, different sets of active reactions) for one and the same DO can be described better.

We show that our technique can easily extend for example to different boundary conditions [18]. Future work will explore other systems in a similar way.

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