
Global Attractors of Reactantless and Inhibitorless Reaction Systems

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Summary. In this study, we explore the computational complexity of deciding the existence of fixed points and cycles that can be reached from any other states (also called *global attractors*) in the dynamics of inhibitorless and reactantless reaction systems. The same problems were proved to be **PSPACE**-complete in the case of unconstrained reaction systems. We show, in contrast, that in the considered resource-bounded classes deciding whether a global fixed point attractor exists can be done in polynomial time. Furthermore, we prove that only trivial cycles consisting of a single state can exist in the dynamics of inhibitorless systems, while in reactantless systems cycles of two states may occur, and it is **coNP**-hard to decide their existence.

1 Introduction

Introduced nearly two decades ago by Ehrenfeucht and Rozenberg [1], reaction systems are an abstract computational model inspired by the chemical reactions occurring in living cells. The notion at the heart of this model is that the biochemical processes within a cell can be simulated using a limited collection of entities that represent various substances, alongside a set of rules that mimic reactions. A reaction is characterized by its reactants, inhibitors, and products, and it occurs when the set of entities currently present in the cell (ie the system's state) includes all reactants and lacks any inhibitors, resulting in the reaction's products.

Whenever a set of reactions takes place in a certain state, the system's subsequent state is determined by the union of the products of all the occurred reactions. This process defines a dynamical system whose points are given by all the possible subsets of entities, ie all possible states of the reaction system. Determining the computational complexity of deciding on the occurrence of various behaviours of such dynamical systems has been the object of a great deal of research work [2, 3, 4, 5, 6, 7, 8].

Reaction systems operate on a qualitative basis, meaning that the presence of a reactant in a given state implies it is available in sufficient quantities for all reactions that require it, thus avoiding any conflicts over shared resources. Other

related models have been proposed in the literature that waive this assumption, see eg [9, 10, 11, 12, 13]. Nevertheless, the computational power of the simpler qualitative model has been demonstrated by several studies [14, 15, 16, 17, 18] showing that reaction systems can be effectively used to simulate various biological processes.

Although the conventional framework for reaction systems does not limit the number of reactants and inhibitors involved in each reaction, an alternative branch of research concentrates on systems with constrained resources. Ehrenfeucht et al. [19] first investigated how bounding the number of reactants and inhibitors in the reactions can affect the kinds of functions that a reaction system can define. Manzoni et al. [20] then classified resource-bounded systems in such a way that the reaction functions enjoy specific properties within each class: in particular, they identified the class of *inhibitorless* reaction systems, in which all reactions have an empty set of inhibitors; the class of *reactantless* systems in which the set of reactants is always empty; and the class of minimal-resources systems, later named *additive* [21], in which each reaction only uses one reactant and no inhibitors.

Dennunzio et al. [22] studied the complexity of reachability in several subclasses of inhibitorless and reactantless systems; Azimi et al. [23] studied how to list all steady states of a system whose reactions have a small quantity of both reactants and inhibitors; and Ascone et al. investigated the computational complexity of problems related to the existence of fixed points and attractors in reactantless and inhibitorless systems [24] and in additive systems [21].

Contributions.

In this paper, we study the computational complexity of deciding on the existence of fixed points and cycles that are also *global attractors* (ie they can be reached from every other state) in inhibitorless and reactantless reaction system. All these problems were shown to be **PSPACE**-complete in unconstrained reaction systems [25]: in contrast, we show that disabling either the set of reactants or the set of inhibitors reduces to polynomial the complexity of deciding whether a global fixed point attractor exists, as well as determining if a given state is a global attractor. Furthermore, we prove that only trivial cycles consisting of a single state can exist in the dynamics of inhibitorless systems, while in reactantless systems cycles of two states may occur, and it is **coNP**-hard to decide on their existence. Table 1 summarises our results.

2 Basics Notions

Given a finite set S of *entities*, a *reaction* a over S is a triple (R_a, I_a, P_a) of subsets of S ; we call R_a the set of *reactants*, I_a the set of *inhibitors*, and P_a the nonempty set of *products*. Note that, in this paper, the reactants and inhibitors of a reaction are allowed to be empty sets as in the original definition of reaction systems [1]. The set of all reactions over S is denoted by $\text{rac}(S)$. A *reaction system* (RS) $\mathcal{A} = (S, A)$

Problem	$\mathcal{RS}(\infty, \infty)$	$\mathcal{RS}(0, \infty)$	$\mathcal{RS}(\infty, 0)$
A given state is a global attractor	PSPACE-c [25]	P (Cor. 13)	P (Cor. 5)
\exists global fixed point attractor	PSPACE-c [25]	P (Cor. 14)	P (Cor. 6)
\exists global cycle attractor of length at least k	$k = 2$ PSPACE-c [25] $k > 2$ PSPACE-c [25]	coNP-hard (Thm. 18) $\#$ (Pro. 15)	$\#$ (Lemma 7) $\#$ (Lemma 7)

Table 1: Computational complexity of the problems studied in this work for different classes of reaction systems. $\mathcal{RS}(\infty, \infty)$, $\mathcal{RS}(0, \infty)$ and $\mathcal{RS}(\infty, 0)$ denote unconstrained, reactantless and inhibitorless reaction systems, respectively (see Def. 1). Light-blue cells contain the results proved in this paper.

where S consists of the finite set of entities S , called the *background set*, and a set $A \subseteq \text{rac}(S)$ of reactions over S .

We call any subset of S a *state* of the reaction system; a reaction a is *enabled* in a state T when $R_a \subseteq T$ and $I_a \cap T = \emptyset$, and the set of all the reactions from \mathcal{A} enabled in T is denoted by $\text{en}_{\mathcal{A}}(T)$. The *result function* $\text{res}_a : 2^S \rightarrow 2^S$ of a reaction a , where 2^S denotes the power set of S , is defined as

$$\text{res}_a(T) := \begin{cases} P_a & \text{if } a \text{ is enabled in } T \\ \emptyset & \text{otherwise.} \end{cases}$$

The definition of res_a naturally extends to sets of reactions: given any $T \subseteq S$ and $A \subseteq \text{rac}(S)$, we define $\text{res}_A(T) := \bigcup_{a \in A} \text{res}_a(T)$. Consistently, the result function res_A of the whole RS $\mathcal{A} = (S, A)$ is defined as equal to res_A , i.e., the result function of the whole set of reactions of the reaction system. In this way, any RS $\mathcal{A} = (S, A)$ induces a discrete dynamical system with state set 2^S and next state function res_A .

In this paper, we are interested in the dynamics of RS, i.e., the study of the successive states of the system under the action of the result function res_A starting from some initial set of entities. The *orbit* or *state sequence* of a given state T of a RS \mathcal{A} is defined as the sequence of states obtained by subsequent iterations of res_A starting from T , namely the sequence $(T, \text{res}_A(T), \text{res}_A^2(T), \dots)$. Note that since S is finite, for any state T the sequence $(\text{res}_A^n(T))_{n \in \mathbb{N}}$ is always ultimately periodic. In particular, the orbit of a state T is a *cycle* of length k if there exists $k \in \mathbb{N}$ such that $\text{res}_A^k(T) = T$, and $\text{res}_A^h(T) \neq T$ for every $h < k$. In the special case where $k = 1$, T is said to be a *fixed point*.

Any set of cycles forms an *invariant set* for \mathcal{A} , that is, a set of states $\mathcal{U} \subseteq 2^S$ such that $\bigcup_{U \in \mathcal{U}} \{\text{res}_A(U)\} = \mathcal{U}$. In particular, it is also true that any invariant set for \mathcal{A} is a set of cycles [25]. A *local attractor* for \mathcal{A} is an invariant set \mathcal{U} such that there exists an external state $T \notin \mathcal{U}$ such that $\text{res}_A(T) \in \mathcal{U}$. An invariant set \mathcal{U} is a *global attractor* if for all states $T \in 2^S$ there exists $k \in \mathbb{N}$ such that $\text{res}_A^k(T) \in \mathcal{U}$, i.e., \mathcal{U} is eventually reached from every possible state of \mathcal{A} . When a global attractor \mathcal{U} consists of only one state T , we say that T is a *global fixed-point attractor*. Similarly, \mathcal{U} is a *global cycle attractor* if all the states in \mathcal{U} belong to the same cycle.

We now recall the classification of reaction systems in terms of the number of resources employed per reaction [20].

Definition 1 ([20]). Let $i, r \in \mathbb{N}$. The class $\mathcal{RS}(r, i)$ consists of all RS having at most r reactants and i inhibitors for reaction. We also define the (partially) unbounded classes $\mathcal{RS}(\infty, i) = \bigcup_{r=0}^{\infty} \mathcal{RS}(r, i)$, $\mathcal{RS}(r, \infty) = \bigcup_{i=0}^{\infty} \mathcal{RS}(r, i)$, and $\mathcal{RS}(\infty, \infty) = \bigcup_{r=0}^{\infty} \bigcup_{i=0}^{\infty} \mathcal{RS}(r, i)$.

We will call $\mathcal{RS}(0, \infty)$ the class of *reactantless* systems, and $\mathcal{RS}(\infty, 0)$ the class of *inhibitorless* systems.

Note that the classification of Definition 1 does not consider the number of products as a parameter because RS can always be assumed to be in *singleton product normal form* [26]: any reaction $(R, I, \{p_1, \dots, p_m\})$ can be replaced by the set of reactions $(R, I, \{p_1\}), \dots, (R, I, \{p_m\})$ which produce the same result.

Five equivalence classes of RS implied by Definition 1 have a characterisation in terms of functions over the Boolean lattice 2^S [20], listed in Table 2. Recall that

Class of RS Subclass of $2^S \rightarrow 2^S$	
$\mathcal{RS}(\infty, \infty)$	all
$\mathcal{RS}(0, \infty)$	antitone
$\mathcal{RS}(\infty, 0)$	monotone
$\mathcal{RS}(1, 0)$	additive
$\mathcal{RS}(0, 0)$	constant

Table 2: Functions computed by several classes of RS.

a function $f : 2^S \rightarrow 2^S$ is *antitone* if $X \subseteq Y$ implies $f(X) \supseteq f(Y)$, *monotone* if $X \subseteq Y$ implies $f(X) \subseteq f(Y)$, *additive* (or an upper-semilattice endomorphism) if $f(X \cup Y) = f(X) \cup f(Y)$ for all $X, Y \in 2^S$. We say that the RS $\mathcal{A} = (S, A)$ computes the function $f : 2^S \rightarrow 2^S$ if $\text{res}_{\mathcal{A}} = f$.

3 Global Attractors of Inhibitorless RS

In this section, we study the complexity of deciding the existence of a global fixed-point attractor or a global cycle attractor in inhibitorless reaction systems.

3.1 Existence of a global fixed-point attractor

We begin with a simple observation which follows immediately from the definition of global fixed-point attractors.

Observation 2. A reaction system with a global fixed-point attractor cannot have any other fixed points or cycles.

In particular, Observation 2 implies that if a global fixed-point attractor exists, it is unique. Proposition 3 provides a characterization of global fixed-point attractors for monotone functions.

Proposition 3. *Let S be a finite set of n elements, $f : 2^S \rightarrow 2^S$ a monotone function and T a fixed point for f consisting of t elements. Then, T is a global fixed-point attractor for f if and only if $f^t(\emptyset) = T = f^{n-t}(S)$.*

Proof. \Rightarrow Consider the sequence $\emptyset \subsetneq f(\emptyset) \subsetneq \dots \subsetneq f^m(\emptyset) = f^{m+1}(\emptyset)$. If it was $f^m(\emptyset) \subsetneq T$, there would exist a fixed point different from T , therefore T would not be a global attractor by Observation 2. Thus it must be $f^m(\emptyset) = T$ and since $|T| = t$, because of the monotonicity of f , it must also be $m \leq t$, implying that $f^t(\emptyset) = T$. Consider now the sequence $S \supseteq f(S) \supseteq \dots \supseteq f^k(S) = f^{k+1}(S)$. If it was $f^k(S) \supseteq T$, then there would exist a fixed point different from T , therefore T would not be a global attractor. We obtain that $f^k(S) = T$; since $t = |T| = |f^k(S)| \leq n - k$ then by monotonicity it must be $k \leq n - t$, thus $f^{n-t}(S) = T$.

\Leftarrow We need to prove that $T = f^t(\emptyset) = f^{n-t}(S)$ is a global attractor. Consider any state $\emptyset \subsetneq T' \subsetneq S$: by monotonicity, it holds that $T = f^t(\emptyset) \subseteq f^t(T')$ and $f^{n-t}(T') \subseteq f^{n-t}(S) = T$. We divide two cases.

Case (i): $t \leq n - t$. Since $T \subseteq f^t(T')$, then it holds $f^{n-2t}(T) \subseteq f^{n-2t+t}(T') \Rightarrow T \subseteq f^{n-t}(T') \subseteq T$, and therefore T' reaches T in at most $n - t$ steps.

Case (ii): $t > n - t$. Since $T \supseteq f^{n-t}(T')$, then $f^{2t-n}(T) \supseteq f^{2t-n+n-t}(T') \Rightarrow T \supseteq f^t(T') \supseteq T$, therefore T' reaches T in at most t steps.

Proposition 3 thus immediately gives a criterion for deciding the existence of a global fixed-point attractor for monotone functions.

Corollary 4. *Given S a finite set of n elements, and $f : 2^S \rightarrow 2^S$ monotone, there exists a global fixed-point attractor if and only if $f^t(\emptyset) = f^{n-t}(S)$ for some $0 \leq t \leq n$.*

Proposition 3 and Corollary 4 can be directly applied to inhibitorless reaction systems, whose result functions are always monotone. We obtain the following results.

Corollary 5. *Given a RS $\mathcal{A} = (S, A) \in \mathcal{RS}(\infty, 0)$ and a state $T \subseteq S$, deciding if T is a global fixed-point attractor of \mathcal{A} is in \mathbf{P} .*

Proof. Since $\text{res}_{\mathcal{A}}$ is monotone [20], we can apply Proposition 3. Therefore, T is a global attractor for \mathcal{A} if and only if $\text{res}_{\mathcal{A}}^t(\emptyset) = T = \text{res}_{\mathcal{A}}^{n-t}(S)$ where t and n are the cardinalities of T and S , respectively. For any state $U \subseteq S$, $\text{res}_{\mathcal{A}}(U)$ can be computed in polynomial time: it suffices to check which reactions are enabled in U by intersecting their reactants and inhibitors with U , and then take the union of the products of the enabled functions. To decide if T is a global attractor we only need to evaluate $\text{res}_{\mathcal{A}}$ at most $|S|$ times, thus the problem is in \mathbf{P} .

Corollary 6. *Given a RS $\mathcal{A} = (S, A) \in \mathcal{RS}(\infty, 0)$ and a state $T \subseteq S$, deciding on the existence of a global fixed-point attractor for \mathcal{A} is in \mathbf{P} .*

Proof. Since $\text{res}_{\mathcal{A}}$ is monotone [20], we can apply Corollary 4. Therefore, there exists a global attractor for \mathcal{A} if and only if $\text{res}_{\mathcal{A}}^t(\emptyset) = \text{res}_{\mathcal{A}}^{n-t}(S)$ for some $0 \leq t \leq n$ where n is the cardinality of S . We conclude as in Corollary 5.

3.2 Existence of a global cycle attractor

We begin this section with a result that immediately follows from the Knaster-Tarki theorem [27] and excludes the existence of a global cycle attractor of length greater than one in the case of monotone functions. In particular, this implies that no global cycle attractor of length $k \geq 2$ can exist in the dynamics of inhibitorless reaction systems, as their result function is always monotone [20].

Lemma 7. *Let $f : 2^S \rightarrow 2^S$ be a monotone function. Then no global attractor k -cycle exists for any $k \geq 2$. Moreover, if \mathcal{U} is a global attractor invariant set, then at least one of the cycles in \mathcal{U} is a fixed point.*

Proof. By the Knaster-Tarki theorem, monotone functions always have a fixed point, therefore a global attractor k -cycle cannot exist for $k > 1$ by Observation 2. For the same reason, if \mathcal{U} is a global attractor invariant set, then at least one of the cycles in \mathcal{U} is a fixed point.

The rest of this section provides results on the existence of global attractors consisting of two fixed points for monotone functions (thus for inhibitorless reaction systems). These results will be useful in Section 4 to prove the complexity of deciding on the existence of global cycle attractors in *reactantless* systems. In Lemma 8, we prove that for any monotone function, a global attractor consisting of two fixed points must have a particular form.

Lemma 8. *Let $f : 2^S \rightarrow 2^S$ monotone and $\mathcal{U} = \{T_1, T_2\}$ a global attractor consisting of two fixed points, then $\mathcal{U} = \{f^n(\emptyset), f^m(S)\}$, with $n, m \geq 0$ such that $f^n(\emptyset) = f^{n+1}(\emptyset)$ and $f^m(S) = f^{m+1}(S)$.*

Proof. By monotonicity, $f^n(\emptyset) \subseteq T_i \subseteq f^m(S)$ for $i = 1, 2$. Suppose for a contradiction that the inclusions are both strict: then \mathcal{U} would not be a global attractor by Observation 2, a contradiction. We obtain the statement.

Lemma 8 implies that any global attractor consisting of two fixed points in a reaction system $\mathcal{A} \in \mathcal{RS}(\infty, 0)$ must be of the form $\{\text{res}_{\mathcal{A}}^n(\emptyset), \text{res}_{\mathcal{A}}^m(S)\}$. However, this characterization is not strong enough to give a polynomial time algorithm, and in Proposition 9 we prove that deciding if $\text{res}_{\mathcal{A}}^n(\emptyset)$ and $\text{res}_{\mathcal{A}}^m(S)$ are the only fixed points for \mathcal{A} is **coNP**-complete. The proof extends an idea from [24, Theorem 25].

Proposition 9. *Given $\mathcal{A} = (S, A) \in \mathcal{RS}(\infty, 0)$ such that \emptyset and S are fixed points, it is **coNP**-complete to decide if \emptyset and S are the only fixed points.*

Proof. The problem lies in **coNP** because there exists a simple non-deterministic algorithm which guesses a state T and then verifies in polynomial time that it is a fixed point different from \emptyset and S . To show **coNP**-completeness, we reduce

VALIDITY [28] to this problem. Given a Boolean formula $\varphi = \varphi_1 \vee \dots \vee \varphi_m$ in DNF over the variables $V = \{x_1, \dots, x_n\}$, let $\bar{V} := \{\bar{x}_j : x_j \in V\}$ and $\heartsuit_S := \{\heartsuit_i : 1 \leq i \leq n\}$. We define $\text{pos}(\varphi_r) \subseteq V$ the set of variables that occur non-negated in φ_r and $\overline{\text{neg}}(\varphi_r) \subseteq \bar{V}$ the set of variables that occur negated in φ_r . We then define a RS \mathcal{A} with background set $S := V \cup \bar{V} \cup \heartsuit_S \cup \{\diamond\}$ and reactions

$$(\overline{\text{neg}}(\varphi_j) \cup \text{pos}(\varphi_j) \cup \heartsuit_S, \emptyset, \{\diamond\}) \quad \text{for } 1 \leq j \leq m \quad (1)$$

$$(\{x_i\} \cup \heartsuit_S, \emptyset, \{\heartsuit_i, x_i\}) \quad \text{for } 1 \leq i \leq n \quad (2)$$

$$(\{\bar{x}_i\} \cup \heartsuit_S, \emptyset, \{\heartsuit_i, \bar{x}_i\}) \quad \text{for } 1 \leq i \leq n \quad (3)$$

$$(\{x_i, \bar{x}_i\} \cup \heartsuit_S, \emptyset, \{\diamond\}) \quad \text{for } 1 \leq i \leq n \quad (4)$$

$$(\{\diamond\} \cup \heartsuit_S, \emptyset, S). \quad (5)$$

Note that \emptyset and S are fixed points; furthermore, any $T \subseteq S$, it falls in one of the following cases:

- 1) $\heartsuit_S \not\subseteq T$. In this case, $\text{res}_{\mathcal{A}}(T) = \emptyset$, since no reaction is enabled;
- 2) $\diamond \in T$ and $\heartsuit_S \subseteq T$. In this case, reaction (5) is enabled and thus $\text{res}_{\mathcal{A}}(T) = S$;
- 3) T is of the form $Y \cup \heartsuit_S$, with $Y \subseteq V \cup \bar{V}$.

Thus \emptyset is reached from any state that does not fully contain \heartsuit_S , and S from any state containing both \heartsuit_S and \diamond . Let us now focus on the states falling in case (3). For any $Y \subseteq V \cup \bar{V}$, we define $\heartsuit_Y := \{\heartsuit_i : x_i \in Y \vee \bar{x}_i \in Y\} \subseteq \heartsuit_S$. The following subcases can happen:

- 3.1) $\exists i$ such that both $x_i, \bar{x}_i \in Y$. In this case, the i -th reaction of group (4) is enabled by $Y \cup \heartsuit_S$, thus $\diamond \in \text{res}_{\mathcal{A}}(Y \cup \heartsuit_S)$; if $\heartsuit_S \subseteq \text{res}_{\mathcal{A}}(Y \cup \heartsuit_S)$ or $\heartsuit_S \not\subseteq \text{res}_{\mathcal{A}}(Y \cup \heartsuit_S)$, then $\text{res}_{\mathcal{A}}(Y \cup \heartsuit_S)$ is either in case (1) or (2) above, implying that $\text{res}_{\mathcal{A}}^2(Y \cup \heartsuit_S) \in \{S, \emptyset\}$;
- 3.2) $\exists i$ such that both $x_i, \bar{x}_i \notin Y$. Then $\heartsuit_S \not\subseteq \text{res}_{\mathcal{A}}(Y \cup \heartsuit_S)$ since none of the i -th reactions in groups (2), (3) are enabled, therefore $\text{res}^2(Y \cup \heartsuit_S) = \emptyset$.
- 3.3) $x_i \in Y \Leftrightarrow \bar{x}_i \notin Y$ for every $1 \leq i \leq n$. In this case, $Y = X \cup \overline{V \setminus X}$ for some $X \subseteq V$, thus it encodes an assignment for φ where the variables in X are assigned true value and the variables in $V \setminus X$ are assigned value false. Note that being φ in DNF, it is satisfied if and only if at least one φ_i is satisfied; moreover, any clause φ_i , being a conjunction of variables, is satisfied if and only if all of its negated variables are assigned value false and all of its non-negated variables are assigned value true. Therefore, the assignment implied by $X \cup \overline{V \setminus X}$ satisfies φ if and only if $X \cup \overline{V \setminus X} \cup \heartsuit_S$ enables one of the reactions from the group (1). Hence, if $Y = X \cup \overline{V \setminus X}$ satisfies φ then $\diamond \in \text{res}(Y \cup \heartsuit_S)$, implying $\text{res}^2(Y \cup \heartsuit_S) = S$. If instead Y does not satisfy φ then $\text{res}(Y \cup \heartsuit_S) = Y \cup \heartsuit_S$ by reactions of groups (2) and (3).

We conclude that \mathcal{A} has no fixed points other than \emptyset and S if and only if all the assignments satisfy φ , ie φ is a tautology. Since the mapping $\varphi \mapsto \mathcal{A}$ is computable in polynomial time, the problem is **coNP**-hard.

Since a necessary condition for $\mathcal{U} = \{\emptyset, S\}$ to be a global attractor is that \emptyset and S are the only two fixed points, Proposition 9 has the following immediate corollary.

Corollary 10. *Given $\mathcal{A} = (S, A) \in \mathcal{RS}(\infty, 0)$ such that \emptyset and S are fixed points, it is **coNP**-hard to decide if $\mathcal{U} = \{\emptyset, S\}$ is a global attractor.*

4 Global Attractors of Reactantless RS

4.1 Existence of a global fixed-point attractor

We begin this section with a characterization of global fixed-point attractors when the function is antitone. Corollary 12, analogously to Corollary 4 for the monotone case, will then provide a criterion for deciding the existence of a global fixed-point attractor for antitone functions in polynomial time.

Proposition 11. *Let S be a finite set, $f : 2^S \rightarrow 2^S$ antitone and T a fixed point for f . Then, T is global fixed-point attractor for f if and only if T is a global fixed-point attractor for f^2 .*

Proof. \Rightarrow Since T is a fixed point for f , it is also a fixed point for f^2 . We need to prove that T is a global attractor for f^2 , but since for every state $T' \subseteq S$ there exists $t \in \mathbb{N}$ such that $f^t(T') = T$, then $(f^2)^t(T') = f^{2t}(T') = f^2(T) = T$.

\Leftarrow Consider T a global fixed-point attractor for f^2 . Then it must hold that $f(T) = T$, as otherwise, $f(T) \neq T$ would imply that $f^2(f(T)) = f(T)$ and thus $f(T)$ would be a fixed point for f^2 different from T , which is a contradiction by Observation 2. $f(T) = T$ implies that T is also a global fixed-point attractor for f , because for every $T' \subseteq S$, T' reaches T in t steps through f^2 , thus T' reaches T in $2t$ steps through f .

Corollary 12. *Given S a finite set and $f : 2^S \rightarrow 2^S$ antitone, a global fixed-point attractor for f exists if and only if there exists a global fixed-point attractor for f^2 .*

Proposition 11 and Corollary 12 can be straightforwardly applied to result functions of reactantless reaction systems, leading to the following two results.

Corollary 13. *Given a RS $\mathcal{A} = (S, A) \in \mathcal{RS}(0, \infty)$ and a state $T \subseteq S$, deciding if T is a global fixed-point attractor of \mathcal{A} is in **P**.*

Proof. Since $\text{res}_{\mathcal{A}}$ is antitone [20], Proposition 11 applies. Therefore, T is a global attractor for \mathcal{A} if and only if T is a global fixed-point attractor for $\text{res}_{\mathcal{A}}^2$. Since $\text{res}_{\mathcal{A}}^2$ is monotone, we can proceed as in the proof of Corollary 5, and decide whether T is a global attractor simply by evaluating $\text{res}_{\mathcal{A}}$ at most $2|S|$ times.

Corollary 14. *Given a RS $\mathcal{A} = (S, A) \in \mathcal{RS}(0, \infty)$ and a state $T \subseteq S$, deciding whether there exists a global fixed-point attractor of \mathcal{A} is in **P**.*

Proof. Since $\text{res}_{\mathcal{A}}$ is antitone [20], Corollary 12 applies, implying that there exists a global fixed-point attractor for $\text{res}_{\mathcal{A}}$ if and only if there exists a global fixed-point attractor for $\text{res}_{\mathcal{A}}^2$. We conclude as in Corollary 13.

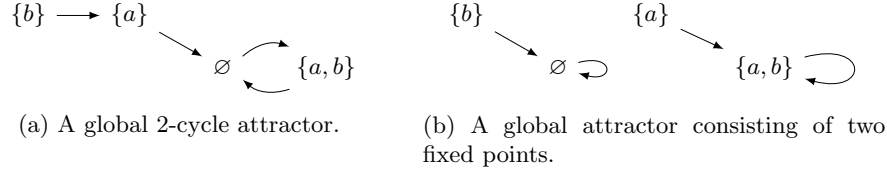


Fig. 1: Representation of the dynamics of Example 16.

4.2 Existence of a global cycle attractor

We begin this section by showing, in Proposition 15, that a global k -cycle attractor cannot exist for any antitone function for any $k > 2$: see also Example 16.

Proposition 15. *Let \mathcal{U} be a global cycle attractor for an antitone function $f : 2^S \rightarrow 2^S$, then there exists $T \subseteq S$ such that either $\mathcal{U} = \{T\}$ or $\mathcal{U} = \{T, f(T)\}$.*

Proof. Let $f^2(\mathcal{U}) := \{f^2(U) : U \in \mathcal{U}\}$; this is a global attractor invariant set for f^2 . Suppose \mathcal{U} is a $(2k+1)$ -cycle for some $k \geq 0$; then $f^2(\mathcal{U})$ is also a $(2k+1)$ -cycle. Since by Lemma 7 every global attractor invariant set for a monotone function must contain a fixed point, and since f being antitone implies f^2 being monotone, it must be $k = 0$ and thus $\mathcal{U} = f^2(\mathcal{U}) = \{T\}$ must be a global fixed-point attractor for f^2 . Suppose now \mathcal{U} is a $(2k)$ -cycle for some $k \geq 1$; then $f^2(\mathcal{U})$ consists two k -cycles. Since one of the two cycles must be a fixed point by Lemma 7, it must be $k = 1$ and thus $\mathcal{U} = \{T, f(T)\}$ for some $T \subseteq S$.

Example 16. Let $S = \{a, b\}$ and $f : 2^S \rightarrow 2^S$ given by:

$$f(\emptyset) = \{a, b\}; \quad f(\{a\}) = \emptyset; \quad f(\{b\}) = \{a\}; \quad f(\{a, b\}) = \emptyset.$$

f is clearly antitone and in the dynamics, we have a global 2-cycle attractor $\{\emptyset, S\}$: see Figure 1a. Consider now $f^2 : 2^S \rightarrow 2^S$, given by

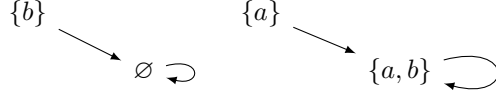
$$f^2(\emptyset) = \emptyset; \quad f^2(\{a\}) = \{a, b\}; \quad f^2(\{b\}) = \emptyset; \quad f^2(\{a, b\}) = \{a, b\}.$$

f^2 has a global attractor consisting of two fixed points, see Figure 1b. \lrcorner

From the proof of Proposition 15, we deduce that an antitone function $f : 2^S \rightarrow 2^S$ has a global 2-cycle attractor if and only if $f^2 : 2^S \rightarrow 2^S$ has a global attractor consisting of two fixed points.

The rest of this section is devoted to proving that deciding whether a reactantless RS has a 2-cycle global attractor reduces to the problem of Corollary 10 for inhibitorless systems, and it is, therefore, **coNP**-hard as well. We begin with an example that illustrates the workings of the reduction we will later provide in Theorem 18.

Example 17. Let $S = \{a, b\}$ and $\mathcal{A} = (S, A)$ an inhibitorless reaction system where $A = \{(\{a\}, \emptyset, \{a, b\})\}$. As already seen in Example 16, in the dynamics of \mathcal{A} there are two fixed points that form together a global attractor (same dynamics as Figure 1b):



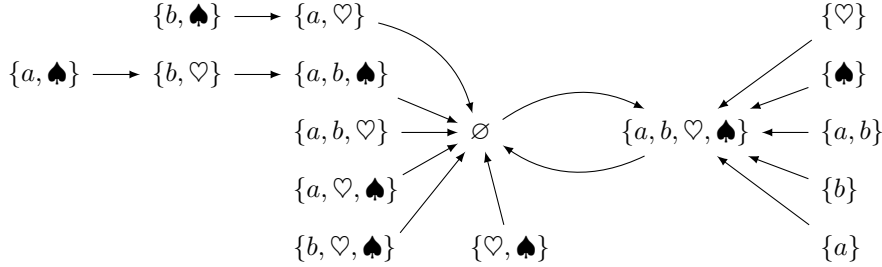
We want to construct a reactantless reaction system that can reproduce the dynamics of \mathcal{A} for states $\emptyset \subsetneq T \subsetneq S$ and transform the global attractor of \mathcal{A} , consisting of two fixed points, into a 2-cycle global attractor. We thus construct $\mathcal{B} = (S', B)$ where $S' = \{a, b, \heartsuit, \spadesuit\}$ and B is given by the following reactions:



It is straightforward to verify that $\text{res}_{\mathcal{B}}(\{b, \spadesuit\}) = \{a, \heartsuit\}$ and $\text{res}_{\mathcal{B}}(\{a, \spadesuit\}) = \{b, \heartsuit\}$, thus

$$\text{res}_{\mathcal{B}}^2(\{b, \spadesuit\}) = \emptyset \quad \text{and} \quad \text{res}_{\mathcal{B}}^2(\{a, \spadesuit\}) = \{a, b, \spadesuit\}.$$

Note that in the original inhibitorless RS \mathcal{A} we have $\text{res}_{\mathcal{A}}(\{b\}) = \emptyset$ and $\text{res}_{\mathcal{A}}(\{a\}) = \{a, b\}$, thus \mathcal{B} can reproduce the dynamics of \mathcal{A} in two steps starting from the states $\{a, \spadesuit\}$ and $\{b, \spadesuit\}$ and going through the states the states $\{a, \heartsuit\}$ and $\{b, \heartsuit\}$. The last three reactions of B ensure that there is a 2-cycle global attractor, as all the states except for $\{a, \spadesuit\}$, $\{b, \spadesuit\}$, and $\{b, \heartsuit\}$ reach the 2-cycle $\{\emptyset, S'\}$ in one step, which makes it a global 2-cycle attractor. The dynamics of \mathcal{B} is the following:



In Theorem 18, we extend and generalize the construction of Example 17 to any $\mathcal{A} \in \mathcal{RS}(\infty, 0)$ to reduce the problem of deciding whether $\mathcal{U} = \{\emptyset, S\}$ is a global attractor in inhibitorless reaction systems to the problem of deciding the existence of a global 2-cycle attractor in reactantless reaction systems.

Theorem 18. *Given $\mathcal{A} = (S, A) \in \mathcal{RS}(0, \infty)$, deciding if there exists a 2-cycle global attractor is **coNP**-hard.*

Proof. We reduce from the problem of deciding if $\mathcal{U} = \{\emptyset, S\}$ is a global attractor in inhibitorless reaction systems (see Corollary 10). More precisely, given $\mathcal{A} = (S, A) \in \mathcal{RS}(\infty, 0)$ such that \emptyset and S are fixed points, we want to construct in polynomial time a reaction system $\mathcal{B} \in \mathcal{RS}(0, \infty)$ such that $\{\emptyset, S\}$ is a global attractor for \mathcal{A} if and only if there exists a 2-cycle global attractor for \mathcal{B} . We construct a reactantless RS $\mathcal{B} := (S', B)$, with $S' := S \cup \{\heartsuit, \spadesuit\}$ and B is given by the following reactions:

$$(\emptyset, \{s, \heartsuit\}, \{s, \heartsuit\}) \quad \text{for } s \in S \quad (6)$$

$$(\emptyset, R_a \cup \{\spadesuit\}, P_a \cup \{\spadesuit\}) \quad \text{for } a = (R_a, \emptyset, P_a) \in A \quad (7)$$

$$(\emptyset, S \cup \{\heartsuit\}, S \cup \{\heartsuit, \spadesuit\}) \quad (8)$$

$$(\emptyset, S \cup \{\spadesuit\}, S \cup \{\heartsuit, \spadesuit\}) \quad (9)$$

$$(\emptyset, \{\heartsuit, \spadesuit\}, S \cup \{\heartsuit, \spadesuit\}). \quad (10)$$

Claim. All states of \mathcal{B} of the forms $\{\spadesuit\}, \{\heartsuit\}, S \cup \{\heartsuit\}, S \cup \{\spadesuit\}, T$, and $T \cup \{\heartsuit, \spadesuit\}$, for all $T \subseteq S$, reach $\{\emptyset, S'\}$ in one step. Furthermore, $\text{res}_{\mathcal{B}}(\emptyset) = S'$ and $\text{res}_{\mathcal{B}}(S') = \emptyset$.

Proof. We immediately note that for any $T \subseteq S$ we have $\text{res}_{\mathcal{B}}(T) = S \cup \{\heartsuit, \spadesuit\} = S'$ since reaction (10) is enabled, and $\text{res}_{\mathcal{B}}(T \cup \{\heartsuit, \spadesuit\}) = \emptyset$ since no reaction is enabled. By reactions (8) and (9), we also have $\text{res}_{\mathcal{B}}(\{\spadesuit\}) = \text{res}_{\mathcal{B}}(\{\heartsuit\}) = S \cup \{\heartsuit, \spadesuit\} = S'$. Furthermore, since $\text{res}_{\mathcal{A}}(\emptyset) = \emptyset$, then $R_a \neq \emptyset$ for each $a \in A$, thus $\text{res}_{\mathcal{B}}(S \cup \{\heartsuit\}) = \emptyset$ since no reaction is enabled, as well as $\text{res}_{\mathcal{B}}(S \cup \{\spadesuit\}) = \emptyset$. Finally, since all the reactions are enabled by \emptyset , and no reaction is enabled by $S' = S \cup \{\heartsuit, \spadesuit\}$, we have that $\text{res}_{\mathcal{B}}(\emptyset) = S'$ and $\text{res}_{\mathcal{B}}(S') = \emptyset$. See also Figure 2 for a visual representation of the dynamics.

Claim. The states $\{\spadesuit\}, \{\heartsuit\}, \{\heartsuit, \spadesuit\}, S, S \cup \{\heartsuit\}, T$, and $T \cup \{\heartsuit, \spadesuit\}$, for all $\emptyset \subsetneq T \subsetneq S$, cannot be reached from any states.

Proof. We can safely assume that in \mathcal{A} there are no reactions of the type $(R_a, \emptyset, \emptyset)$, because in any case, they do not affect the dynamic of \mathcal{A} . Therefore $\text{en}_{\mathcal{A}}(T) = \emptyset$ if and only if $\text{res}_{\mathcal{A}}(T) = \emptyset$. This implies that group (7) of the reactions of \mathcal{B} does not contain any reactions of the form $(\emptyset, R_a \cup \{\spadesuit\}, \{\spadesuit\})$, implying that the state $\{\spadesuit\}$ cannot be reached from any state. With a similar reasoning we deduce that the states $\{\heartsuit\}, \{\heartsuit, \spadesuit\}, S$, and T for all $\emptyset \subsetneq T \subsetneq S$ cannot be reached from any state as well.

Furthermore, none of the states of the form $T \cup \{\heartsuit, \spadesuit\}$ with $\emptyset \subsetneq T \subsetneq S$ can be reached from any state: indeed, suppose for a contradiction that $\text{res}_{\mathcal{B}}(T') = T \cup \{\heartsuit, \spadesuit\}$ for some $T' \subseteq S'$ and $\emptyset \subsetneq T \subsetneq S$. In order to obtain \heartsuit in the product, T' must enable some reactions from group (6); and to obtain \spadesuit , it must also enable reactions from group (7). This implies $\heartsuit, \spadesuit \notin T'$, thus $T' \subseteq S$ and thus, by Claim 18, $\text{res}_{\mathcal{B}}(T') = S \cup \{\heartsuit, \spadesuit\}$, which is a contradiction because by hypothesis $T \subsetneq S$. Finally, $S \cup \{\heartsuit\}$ cannot be reached from any state U because

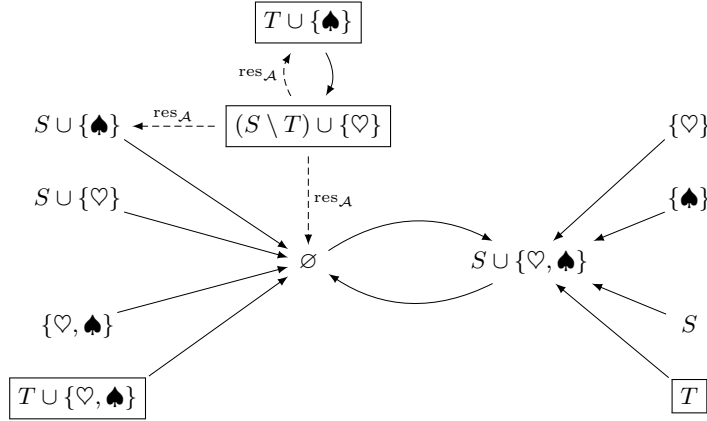


Fig. 2: Dynamics of the RS \mathcal{B} in the reduction of Theorem 18. The states T , $T \cup \{\heartsuit, \spadesuit\}$, $T \cup \{\spadesuit\}$ and $(S \setminus T) \cup \{\heartsuit\}$ are a synthetic representation of the $2^S - 2$ states (one for each $\emptyset \subsetneq T \subsetneq S$) of each type. The boxes around states $T \cup \{\spadesuit\}$ and $(S \setminus T) \cup \{\heartsuit\}$ hide the more refined dynamics for those states; dashed arcs represent the three existing possibilities for the dynamics of the states belonging to the boxes, as described after Claim 18.

this would require all and only the reactions from group (6) to be enabled in U , which can happen only if $U = \{\spadesuit\}$; but then reaction (8) is enabled as well, and indeed $\text{res}_{\mathcal{B}}(\{\spadesuit\}) = S'$ by Claim 18.

It remains to determine the dynamics for the states of the form $T \cup \{\spadesuit\}$ and $T \cup \{\heartsuit\}$ for some $\emptyset \subsetneq T \subsetneq S$. Because of the reactions from group (6), we obtain

$$\text{res}_{\mathcal{B}}(T \cup \{\spadesuit\}) = (S \setminus T) \cup \{\heartsuit\}; \quad (11)$$

and because of the reactions from group (7), in turn we have

$$\text{res}_{\mathcal{B}}((S \setminus T) \cup \{\heartsuit\}) = \begin{cases} \text{res}_{\mathcal{A}}(T) \cup \{\spadesuit\} & \text{if } \text{en}_{\mathcal{A}}(T) \neq \emptyset \\ \emptyset & \text{otherwise,} \end{cases} \quad (12)$$

since $(S \setminus T) \cup \{\heartsuit\}$ enables $(\emptyset, R_a \cup \{\spadesuit\}, P_a \cup \{\spadesuit\})$ if and only if $(S \setminus T) \cap R_a = \emptyset$, which is the case if and only if $R_a \subseteq T$ and thus T enables (R_a, \emptyset, P_a) in \mathcal{A} . As remarked in Claim 18, we have that $\text{res}_{\mathcal{A}}(T) = \emptyset$ if and only if $\text{en}_{\mathcal{A}}(T) = \emptyset$, which is true if and only if $\text{res}_{\mathcal{B}}((S \setminus T) \cup \{\heartsuit\}) = \emptyset$. We have obtained the following formula:

$$\text{res}_{\mathcal{B}}^2(T \cup \{\spadesuit\}) = \begin{cases} \text{res}_{\mathcal{A}}(T) \cup \{\spadesuit\} & \text{if } \text{en}_{\mathcal{A}}(T) \neq \emptyset \\ \emptyset & \text{otherwise.} \end{cases} \quad (13)$$

Therefore, iterating (13), if $\text{res}_A^i(T) \notin \{\emptyset, S\}$ for all $i = 1, \dots, k$, we obtain

$$\text{res}_B^{2k}(T \cup \{\spadesuit\}) = \text{res}_A^k(T) \cup \{\spadesuit\}. \quad (14)$$

Note that the states of the form $T \cup \{\heartsuit\}$ with $\emptyset \subsetneq T \subsetneq S$ coincide with the states of the form $(S \setminus T) \cup \{\heartsuit\}$; in particular, any such state $T \cup \{\heartsuit\}$ is reached from $(S \setminus T) \cup \{\spadesuit\}$ by Equation (11), and reaches either \emptyset or $\text{res}_A(S \setminus T) \cup \{\spadesuit\}$ according to Equation (12). In Figure 2, the states of the form $T \cup \{\heartsuit\}$ and $T \cup \{\spadesuit\}$ are compactly represented as boxed states, and their dynamics are not completely represented for the sake of readability.

We observe that the only candidate 2-cycle global attractor for \mathcal{B} is $\{\emptyset, S'\}$, as it is a 2-cycle by Claim 18 and it is the only candidate global attractor by Claim 18 and the discussion below its proof. The next claim gives us the thesis.

Claim. $\{\emptyset, S\}$ is a global attractor for \mathcal{A} if and only if $\{\emptyset, S'\}$ is a global attractor for \mathcal{B} .

Proof. \Rightarrow Let $\emptyset \subsetneq T \subsetneq S$: in this case, we already proved in Claim 18 that T and $T \cup \{\heartsuit, \spadesuit\}$ reach $\{\emptyset, S'\}$ in one step. By hypothesis, $\exists k \in \mathbb{N}$ such that $\text{res}_A^k(T) \in \{\emptyset, S\}$. Let k be the minimum number that satisfies this property, implying that $\text{res}_A^i(T) \notin \{\emptyset, S\}$ for $i = 1, \dots, k-1$. Thus we can apply Equation (14) and obtain

$$\text{res}_B^{2(k-1)}(T \cup \{\spadesuit\}) = \text{res}_A^{k-1}(T) \cup \{\spadesuit\}$$

Furthermore, applying Equation (11) to this result, we obtain

$$\text{res}_B^{2(k-1)+1}(T \cup \{\spadesuit\}) = \text{res}_B^{2k-1}(T \cup \{\spadesuit\}) = S \setminus \text{res}_A^{k-1}(T) \cup \{\heartsuit\}.$$

Since by hypothesis $\text{res}_A^k(T) \in \{\emptyset, S\}$, there are two cases: if $\text{res}_A^k(T) = S$, then $\text{res}_B^{2k}(T \cup \{\spadesuit\}) = S \cup \{\spadesuit\}$, implying that $\text{res}_B^{2k+1}(T \cup \{\spadesuit\}) = \emptyset$. Otherwise, $\text{res}_A^k(T) = \emptyset$, which happens if and only if $\text{en}_A(\text{res}_A^{k-1}(T)) = \emptyset$: in this case, $\text{res}_B^{2k}(T \cup \{\spadesuit\}) = \emptyset$ by Equation (13). In any case, $T \cup \{\spadesuit\}$ reaches $\{\emptyset, S'\}$ in at most $2k+1$ steps. For the state $T \cup \{\heartsuit\}$, we can reduce to the previous case using Equation (12). Together with Claim 18, we obtain that if $\{\emptyset, S\}$ is a global attractor for \mathcal{A} then $\{\emptyset, S'\}$ is a global attractor for \mathcal{B} .

\Leftarrow Let $\emptyset \subsetneq T \subsetneq S$: by hypothesis, there exists $k \in \mathbb{N}$ such that $\text{res}_B^k(T \cup \{\spadesuit\}) \in \{\emptyset, S'\}$. Let k be the minimum number that satisfies that property. We want to prove that T is always attracted by $\{S, \emptyset\}$. We define two cases, depending on whether k is even or odd.

- 1) $k = 2m$. We have $\text{res}_A^i(T) \notin \{\emptyset, S\}$ for all $i = 1, \dots, m-1$ as otherwise $k = 2m$ would not be the minimum. Thus we get $\text{res}_B^{2m-1}(T \cup \{\spadesuit\}) = (S \setminus \text{res}_A^{m-1}(T)) \cup \{\heartsuit\}$. Since $\emptyset \subsetneq \text{res}_A^{m-1}(T) \subsetneq S$, we have $\emptyset \subsetneq S \setminus \text{res}_A^{m-1}(T) \subsetneq S$, thus reaction (9) is not enabled by $(S \setminus \text{res}_A^{m-1}(T)) \cup \{\heartsuit\}$, implying in turn that $\heartsuit \notin \text{res}_B^{2m}(T \cup \{\spadesuit\})$, and thus $\text{res}_B^{2m}(T \cup \{\spadesuit\}) \neq S \cup \{\heartsuit, \spadesuit\}$. But since $\text{res}_B^{2m}(T) \in \{\emptyset, S'\}$ then $\text{res}_B^{2m}(T) = \emptyset$. Suppose

now for a contradiction that $\text{res}_{\mathcal{A}}^m(T) \neq \emptyset$: then it would also be $\text{res}_{\mathcal{B}}^{2m}(T \cup \{\spadesuit\}) = \text{res}_{\mathcal{B}}((S \setminus \text{res}_{\mathcal{A}}^{m-1}(T)) \cup \{\heartsuit\}) \neq \emptyset$, a contradiction. We deduce that $\text{res}_{\mathcal{A}}^m(T) = \emptyset$, thus T is attracted by $\{S, \emptyset\}$.

- 2) $k = 2m + 1$. Clearly, $\text{res}_{\mathcal{A}}^i(T) \notin \{\emptyset, S\}$ for $i = 1, \dots, m - 1$. Thus we have $\text{res}_{\mathcal{B}}^{2m-1}(T \cup \{\spadesuit\}) = (S \setminus \text{res}_{\mathcal{A}}^{m-1}(T)) \cup \{\heartsuit\}$. Since $\text{res}_{\mathcal{B}}^{2m}(T \cup \{\spadesuit\}) \neq \emptyset$ then $\text{res}_{\mathcal{A}}^m(T) \neq \emptyset$. Thus $\text{res}_{\mathcal{B}}^{2m}(T \cup \{\spadesuit\}) = \text{res}_{\mathcal{A}}^m(T) \cup \{\spadesuit\}$. Suppose for a contradiction that $\text{res}_{\mathcal{A}}^m(T) \subsetneq S$, then $\text{res}_{\mathcal{B}}^{2m+1}(T \cup \{\spadesuit\}) = S \setminus \text{res}_{\mathcal{A}}^m(T) \cup \{\heartsuit\} \notin \{\emptyset, S'\}$, a contradiction by the definition of k . We deduce that $\text{res}_{\mathcal{A}}^m(T) = S$, thus T is attracted by $\{S, \emptyset\}$.

Summing up, we proved that if $\{\emptyset, S'\}$ is a global attractor for \mathcal{B} then $\{\emptyset, S\}$ is a global attractor for \mathcal{A} .

Claim 18, together with Claim 18, directly implies that there exists 2-cycle global attractor for \mathcal{B} if and only if $\{\emptyset, S\}$ is a global attractor for \mathcal{A} . We also remark that the map $\mathcal{A} \mapsto \mathcal{B}$ can be constructed in polynomial time. By Corollary 10, deciding whether $\{\emptyset, S\}$ is a global attractor is **coNP**-hard, thus the thesis follows.

References

1. Ehrenfeucht, A., Rozenberg, G.: Basic notions of reaction systems. In: Developments in Language Theory, 8th International Conference (DLT). Volume 3340 of Lecture Notes in Computer Science., Springer (2004) 27–29
2. Formenti, E., Manzoni, L., Porreca, A.E.: On the complexity of occurrence and convergence problems in reaction systems. *Nat. Comput.* **14**(1) (2015) 185–191
3. Dennunzio, A., Formenti, E., Manzoni, L., Porreca, A.E.: Ancestors, descendants, and gardens of eden in reaction systems. *Theor. Comput. Sci.* **608** (2015) 16–26
4. Azimi, S., Gratie, C., Ivanov, S., Manzoni, L., Petre, I., Porreca, A.E.: Complexity of model checking for reaction systems. *Theor. Comput. Sci.* **623** (2016) 103–113
5. Barbuti, R., Gori, R., Levi, F., Milazzo, P.: Investigating dynamic causalities in reaction systems. *Theor. Comput. Sci.* **623** (2016) 114–145
6. Nobile, M.S., Porreca, A.E., Spolaor, S., Manzoni, L., Cazzaniga, P., Mauri, G., Besozzi, D.: Efficient simulation of reaction systems on graphics processing units. *Fundam. Informaticae* **154**(1-4) (2017) 307–321
7. Dennunzio, A., Formenti, E., Manzoni, L., Porreca, A.E.: Complexity of the dynamics of reaction systems. *Inf. Comput.* **267** (2019) 96–109
8. Barbuti, R., Bernasconi, A., Gori, R., Milazzo, P.: Characterization and computation of ancestors in reaction systems. *Soft Comput.* **25**(3) (2021) 1683–1698
9. Okubo, F., Kobayashi, S., Yokomori, T.: Reaction automata. *Theoretical Computer Science* **429** (2012) 247–257 Magic in Science.
10. Okubo, F., Yokomori, T. In: *The Computing Power of Determinism and Reversibility in Chemical Reaction Automata*. Springer International Publishing, Cham (2018) 279–298
11. Yokomori, T., Okubo, F.: Theory of reaction automata: a survey. *J. Membr. Comput.* **3**(1) (2021) 63–85
12. Okubo, F., Fujioka, K., Yokomori, T.: Chemical reaction regular grammars. *New Gener. Comput.* **40**(2) (2022) 659–680

13. Brodo, L., Bruni, R., Falaschi, M., Gori, R., Levi, F., Milazzo, P.: Quantitative extensions of reaction systems based on SOS semantics. *Neural Comput. Appl.* **35**(9) (2023) 6335–6359
14. Corolli, L., Maj, C., Marini, F., Besozzi, D., Mauri, G.: An excursion in reaction systems: From computer science to biology. *Theor. Comput. Sci.* **454** (2012) 95–108
15. Azimi, S., Iancu, B., Petre, I.: Reaction system models for the heat shock response. *Fundam. Informaticae* **131**(3-4) (2014) 299–312
16. Ivanov, S., Petre, I.: Controllability of reaction systems. *J. Membr. Comput.* **2**(4) (2020) 290–302
17. Barbuti, R., Bove, P., Gori, R., Gruska, D.P., Levi, F., Milazzo, P.: Encoding threshold boolean networks into reaction systems for the analysis of gene regulatory networks. *Fundam. Informaticae* **179**(2) (2021) 205–225
18. Barbuti, R., Gori, R., Milazzo, P.: Encoding boolean networks into reaction systems for investigating causal dependencies in gene regulation. *Theor. Comput. Sci.* **881** (2021) 3–24
19. Ehrenfeucht, A., Main, M.G., Rozenberg, G.: Functions defined by reaction systems. *Int. J. Found. Comput. Sci.* **22**(1) (2011) 167–178
20. Manzoni, L., Pocas, D., Porreca, A.E.: Simple reaction systems and their classification. *International Journal of Foundations of Computer Science* **25**(04) (2014) 441–457
21. Ascone, R., Bernardini, G., Manzoni, L.: Fixed points and attractors of additive reaction systems. *Natural Computing* (2024) 1–11
22. Dennyunzio, A., Formenti, E., Manzoni, L., Porreca, A.E.: Reachability in resource-bounded reaction systems. In: *Language and Automata Theory and Applications: 10th International Conference (LATA)*, Springer (2016) 592–602
23. Azimi, S.: Steady states of constrained reaction systems. *Theor. Comput. Sci.* **701** (2017) 20–26
24. Ascone, R., Bernardini, G., Manzoni, L.: Fixed points and attractors of reactantless and inhibitorless reaction systems. *Theoretical Computer Science* **984** (2024) 114322
25. Formenti, E., Manzoni, L., Porreca, A.E.: Cycles and global attractors of reaction systems. In: *Descriptive Complexity of Formal Systems: 16th International Workshop (DCFS)*, Springer (2014) 114–125
26. Brijder, R., Ehrenfeucht, A., Rozenberg, G.: Reaction systems with duration. *Computation, cooperation, and life* **6610** (2011) 191–202
27. Granas, A., Dugundji, J.: Elementary fixed point theorems. In: *Fixed Point Theory*. Springer New York, New York (2003) 9–84
28. Papadimitriou, C.: *Computational Complexity*. Theoretical computer science. Addison-Wesley (1994)