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Polynomial Time Coverability Analysis in Discrete State Chemical Reaction Network Subclasses

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Abstract

In this paper the coverability problem of discrete state Chemical Reaction Networks (d-CRNs) is considered. We study certain sub-classes of d-CRN reaction network structures and prove that the coverability relation is implied by the reachability property in another reaction network class in which the reachability problem is proven to be decidable in polynomial time. We make use of the equivalent Petri net representation of d-CRNs and the concept of dual graph to obtain networks for which the reachability relation can be decided in polynomial time. Making use of the reachability relations of the dual graph, we provide theoretical guarantee for the coverability property in the initial network. This way sufficient condition is obtained for d-CRN coverability with polynomial time complexity. The studied sub-classes of d-CRNs include subconservative network structures, in addition, complexes composed of more than one species are allowed as well. The basic concepts and the new results are illustrated on several examples.

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1 Introduction

The formal models of Chemical Reaction Networks (CRNs) are commonly used to model the dynamical behavior and structural properties of a wide range of networked dynamical systems, such as biochemical reaction networks, gene-regulatory networks, protein-protein interaction networks, molecular signaling pathways, epidemiological systems and population dynamics [1, 5]. In case of high molecule counts and well-stirred (homogeneous) distribution of the interacting species, the dynamical behavior of CRNs are modeled by means of continuous state Ordinary Differential Equations (ODEs) [2–7]. In the case of various natural and synthetic systems of interacting species, however, the molecule counts of the interacting species are low (e.g. lower that few molecules per species), this way continuous state ODEs often cannot capture important features of the qualitative dynamical behavior of chemical reaction networks [8]. In the case of low molecular counts, discrete state models can be employed. There are multiple model classes used to describe discrete state chemical reaction networks, such as Petri nets, Markov chains [9–11, 34–36].

This paper is concerned with the structural properties of d-CRNs and their implication to the underlying qualitative dynamical behavior. We study the reachability and coverability problems of chemical reaction networks. Given a pair of non-negative initial and target states, if there exists a non-negative state space trajectory in the discrete state space of the d-CRN along which the target state can be reached from the initial state, then the target state is said to be reachable from the initial state. The reachability of d-CRNs is related by the structure (topology) of the reaction network, however it can have significant implication on the dynamical behavior. Specific subclasses of d-CRNs are proven to have bounded state space in terms of the reachable states, given a fixed initial state. The boundedness of the state space is proven to be determined by the complex composition and reaction network structure of the d-CRN and it is independent of the reaction rates of the dynamical equations. An extinction event is the irreversible extinction (zeroing) of some species in the state space of the d-CRN. It is proven that in specific d-CRN structure classes,

the existence of extinction events is determined by the d-CRN network topology [14, 15]. In addition to its implication to the dynamical behavior of d-CRNs, studying the reachability problem has syntehtic biology and network theory related motivation as well: the reachability problem of d-CRNs is equivalent to the gate-implementability problem of synthetic biochemical circuits [29].

The coverability problem gives a relaxation to the reachability problem. Given an initial state and a distinguished state, if there exists a target state that is reachable from the initial state so that the target state is element-wise greater than equal to the distinguished state, then the d-CRN from the initial state is said to be coverable with respect to the distinguished state. In particular, coverability is concerned with the feasibility of reaching a state in the state space of the d-CRN, where all the reactions can fire, provided an initial state. If there is no reachable state where a particular reaction can fire, then this reaction is called inactive reaction. Inactive reactions can have significant importance in biological systems [30]. In general case, the coverability problem is known to be of EXSPACE hard complexity, which impose a significant theoretical limitation on the efficient analysis d-CRNs [22, 23].

Generally, the reachability and coverability problems of d-CRNs can be formulated as an Integer Programming (IP) feasibility (decision) problem [26]. Compared to the case of continuous state CRNs, where the reachability problem can be decided in polynomial time, in the case of the d-CRN reacahbility it is an open problem wheteher there exists an algorithm with primitive recursive time complexity deciding the reachability problem [25]. In specific subclasses of sub and superconservative d-CRNs it is proved that the non-negative integer solution of the d-CRN state equation is equivalent to the reachability relation, this way the general d-CRN reachability problem can be relaxed in terms of the number of decision variables [26, 27, 27].

In this paper we aim at obtaining novel results on the coverability (decision) problem of d-CRNs in a well-defined class of reaction network structures. Leveraging on the existing results on relaxed time complexity reachability of sub-and superconservative d-CRN sub-classes, we derive

novel d-CRN structure (topology) classes for which coverability can be derived from the reachability relation in sub and superconservative d-CRN sub-classes where reachability is known to be decidable in polynomial time. Making use of the Petri net representation of d-CRNs, we compose the dual graph of the Petri net. Employing a constructive proof, it is shown that the coverability relation of the resulting d-CRN sub-class (obtained by taking the dual graph) is implied by the reachability in the initial d-CRN. This way sufficient condition is obtained for d-CRN coverability. The practical importance of the introduced coverability results is that the identified d-CRN structure sub-classes are not restricted to subconservative reaction network structures composed of single-species complexes.

2 Preliminaries

This chapter summarizes the main concepts and notations on equivalent formal models, discrete state Chemical Reaction Networks (d-CRNs) and Petri Nets. While the paper is focused on the d-CRN representation, we introduce the formal models of Petri Net as it is extensively used to facilitate the proof of the main results. As the main results rely on d-CRN reachability results, the relevant d-CRN reachability propositions of the literature are reviewed in this chapter.

2.1 Discrete state chemical reaction networks

Definition 1. A discrete state Chemical Reaction Network (d-CRN) with n species, m complexes and l reactions is defined by a tuple $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ for which

1. $\mathcal{S} = \Big\{ s_i \mid i = 1, \dots n \Big\}$,
2. $\mathcal{C} = \Big\{ y_j = \sum_{i=1}^{n} \alpha_{ji} s_i \mid s_i \in \mathcal{S},\ \alpha_{ji} \in \mathbb{Z}_{\geq 0},\ i = 1, \dots n,\ j = 1 \dots m \Big\}$,
3. $\mathcal{R} = \Big\{ r_k = y_{source(r_k)} \rightarrow y_{product(r_k)} \mid y_{source(r_k)},\ y_{product(r_k)} \in \mathcal{C},\ k = 1, \dots l \Big\}$,

where s_i is the ith species, y_j is the jth complex and r_k is the kth reaction of the d-CRN $\mathcal{N}$, given a fixed ordering of the entries in $\mathcal{S}$, $\mathcal{C}$ and $\mathcal{R}$. It is assumed that there is a fixed ordering for the species, complexes and reactions for all the d-CRNs discussed throughout the paper. $\alpha_{ji} \in \mathbb{Z}_{\geq 0}$ represents the stoichiometric coefficient of the ith species in the jth complex of $\mathcal{C}$. For any reaction $r \in \mathcal{R}$, we use the formal notation $r = y_{source(r)} \rightarrow y_{product(r)}$ where $y_{source(r)}$ and $y_{product(r)}$ denote the source complex and the product complex, respectively.

For $y_j \in \mathcal{C}$ $j = 1, \ \ldots \ m$, we define the following vector $\overline{y}_j$:

$$\overline{y}_j = [\alpha_{j1} \ \alpha_{j2} \ \ldots \ \alpha_{jn} \ ]^\top. \tag{1}$$

Then for each $r \in \mathcal{R}$, the reaction vector $r_{ij} \in \mathbb{Z}^n_{\geq 0}$ can be defined as follow:

$$r_{ij} = \overline{y}_j - \overline{y}_i, \tag{2}$$

where $y_i \in \mathcal{C}$ and $y_j \in \mathcal{C}$ are the vector representations of the source and product complexes of r in $\mathcal{N}$. In order to facilitate the formal discussion, in the sequel we employ the notation r_k to denote both the k'th reaction of $\mathcal{R}$ and its reaction vector representation as well.

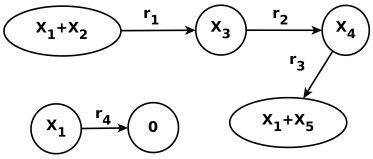
A d-CRN $\mathcal{N}$ can also be described by a directed graph $G_{\mathcal{N}} = G_{\mathcal{N}}(V, E)$, where the nodes represent the complexes and the directed edges denote the reactions so that edges point from the source complex to the product complex of the respective reaction. Formally, for a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$, the reaction graph is defined by $G_{\mathcal{N}} = G_{\mathcal{N}}(V, E)$, where $V = \mathcal{C}$ and $E = \mathcal{R}$ so that for each $r \in \mathcal{R}$, $r = y_i \rightarrow y_j$, there exists a unique edge $e \in E$ so that e points from the vertex corresponding to y_i to the vertex of y_j.

In the sequel, the terms structure and topology are used interchangeably to refer the reaction network graph $G_{\mathcal{N}}$ of a d-CRN $\mathcal{N}$.

In this paper it is assumed that there is no reaction $r \in \mathcal{R}$ for which $y = c \rightarrow c$ for some $c \in \mathcal{C}$. In addition, isolated complexes are not allowed, that is there is no complex $y \in \mathcal{C}$ for which there is no reaction $r \in \mathcal{R}$ with $y = source(r)$ or $y = target(r)$.

Example 1. Illustrative example of a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with $\mathcal{S} =$

$\{X_1, X_2, X_3, X_4, X_5, 0\}$, $\mathcal{C} = \{X_1 + X_2, X_3, X_4, X_1 + X_5, 0\}$. Note that **0** denotes the zero complex that is used to express a reaction in which a species is consumed (source complex), but there is no other species produced (target complex).



$$\Gamma_{\mathcal{N}} = \begin{bmatrix} -1 & 0 & 1 & -1 \\ -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}$$

Figure 1. Illustrative example. **Left:** d-CRN reaction graph $G_{\mathcal{N}} = G_{\mathcal{N}}(V, E)$ where the nodes and edges represent the complexes and reactions, respectively. The edges point from the source complex to the target complex of the respective reactions. **0** denotes the zero complex, that is the reaction $X_1 \to 0$ means that species X_1 is consumed in the reaction, but there is no other species produced. **Right:** stoichiometric matrix of $\mathcal{N}$. The columns of $\Gamma_{\mathcal{N}}$ are the reaction vectors of $\mathcal{N}$.

Definition 2. Let us consider a d-CRN $\mathcal{N}$ with reaction vectors $r_1, r_2, \ldots r_l$. The stoichiometric matrix $\Gamma_{\mathcal{N}} \in \mathbb{Z}^{n \times l}$ is defined as

$$\Gamma_{\mathcal{N}} = [r_1\ r_2\ \ldots\ r_l]. \tag{3}$$

$\Gamma^+_{\mathcal{N}}$ is defined as follows

$$\Gamma^+_{\mathcal{N}} = [\overline{y}^+_{r_1}\ \ldots\ \overline{y}^+_{r_l}], \tag{4}$$

where $\overline{y}^+_{r_k}$ for $k = 1, 2 \ldots\ l$ denotes the vector representation of the product complex of the reaction r_k, that is $[\overline{y}^+_{r_k}]_i$ encodes the stoichiometric coefficient of the i'th species for $i = 1, 2 \ldots\ n$.

$\Gamma^-_{\mathcal{N}}$ is defined as follow

$$\Gamma^-_{\mathcal{N}} = [\overline{y}^-_{r_1}\ \ldots\ \overline{y}^-_{r_l}], \tag{5}$$

where $\overline{y}^-_{r_k}$ denotes the vector representation of the source complex of r_k $k = 1, 2 \ldots\ l$.

For an arbitrary d-CRN $\mathcal{N}$ the following equality holds

$$\Gamma_{\mathcal{N}} = \Gamma^{+}_{\mathcal{N}} - \Gamma^{-}_{\mathcal{N}} \tag{6}$$

For a d-CRN $\mathcal{N}$, we can introduce the state vector $X \in \mathbb{Z}^{n}_{\geq 0}$ so that $[X]_i$ denotes the molecular count of the ith species in state X, that is

$$[X]_i : S_i \to \mathbb{Z}_{\geq o}, \text{ for } i = 1, \ \ldots \ n. \tag{7}$$

We note that the state vector $X \in \mathbb{Z}^{n}_{\geq 0}$ is unique, assuming a fixed ordering of the species in $\mathcal{S}$.

Next we introduce the state equation of d-CRNs.

Definition 3. Let us consider an integer state vector $X_0 \in \mathbb{Z}^{n}_{\geq 0}$, where $[X_0]_i$ encodes the molecule count of the i'th species in the initial state for $i = 1, \ 2 \ \ldots \ n$. The state transitions can be described by the d-CRN's discrete state equation

$$X' = X_0 + \Gamma_{\mathcal{N}} c \tag{8}$$

where $X' \in \mathbb{Z}^{n}_{\geq 0}$ is a state vector and $c \in \mathbb{Z}^{l}_{\geq 0}$ encodes the occurrences of the reactions along a state transition sequence from X_0 to X'. Clearly, $[c]_k$ encodes the number of times the k'th reaction occurred (fired) along a state transition sequence from X_0 to X'.

Definition 4. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$.

1. A complex $y \in \mathcal{C}$ is said to be charged at a state $X \in \mathbb{Z}^{n}_{\geq 0}$, if $X \succeq \overline{y}$, where $\overline{y}$ is the vector representation of y. A reaction $r \in \mathcal{R}$ is said to be charged at a state X if its source complex is charged.

2. A reaction vector sequence σ_r is an ordered set of reactions $\sigma_r = r_{\nu_{\mathcal{R}}(1)} \ \ldots \ r_{\nu_{\mathcal{R}}(v)}$ with $v \in \mathbb{Z}_{\geq 1}$ and $\nu_{\mathcal{R}}$ is an index function mapping the index $k \in \mathbb{N}$ to the index of the respective reaction, given a fixed ordering of the reactions in $\mathcal{R}$.

3. A state $X_1 \in \mathbb{Z}^{n}_{\geq 0}$ reacts to the state $X_2 \in \mathbb{Z}^{n}_{\geq 0}$, if there exists a reaction $r \in \mathcal{R}$ so that $X_1 + r = X_2$. The following notation is employed: $X_1 \to_{\mathcal{N}} X_2$.

4. A state (transition) sequence σ_X is an ordered sequence of states $\sigma_X = X_1 \dots X_v$ with $v \in \mathbb{Z}_{\geq 1}$ so that $X_i \to X_{i+1}$ for $i = 1, \dots v-1$.

5. A state X' is said to be reachable from a state X_0 ($X_0 \rightsquigarrow_{\mathcal{N}} X'$), if there exists a state transition sequence $\sigma_X = X_{\nu(1)} \dots X_{\nu(v)}$ so that $X_{\nu(1)} = X_0$, $X_{\nu(v)} = X'$ and for all $X \in \sigma_X$, $X \succeq 0^n$.

6. A state X' is said to be coverable from an initial state X_0, if there exists a state $\hat{X}$ so that $X_0 \rightsquigarrow_{\mathcal{N}} \hat{X}$ and $X' \succeq \hat{X}$.

7. A species $s \in \mathcal{S}$ is said to be a catalyzer with respect to a reaction $r \in \mathcal{R}$ if $r = s + s_1 \to s + s_2$ for some $s_1,\ s_2 \in \mathcal{S},\ s_1 \neq s_2$.

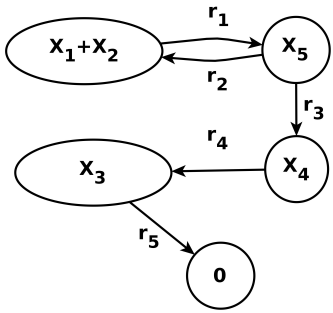
For a transition sequence $\sigma_X = X_0 \dots X_v$, X_0 is called the initial state, $X_v = X'$ is the target state and X_i for $i = 1, \dots v-1$ are called transition states. A state transition sequence σ_X is called admissible if $X \succeq 0^n$ for all $X \in \sigma_X$. Note that the definition of reachability is restricted to admissible state transition sequences.

For a d-CRN $\mathcal{N}$ with a pair of non-negative states $X_0, X' \in \mathbb{Z}^n_{\geq 0}$, the existence of a non-negative integer solution $c \in \mathbb{Z}^l_{\geq 0}$ of the state equation $X_0 + \Gamma_{\mathcal{N}} c = X'$ provides a necessary condition for the reachability relation of $X_0 \rightsquigarrow_{\mathcal{N}} X'$. Generally, the existence of a c non-negative integer solution of the state equation does not imply that the reachability relation holds. In this paper we make use of d-CRN reachability results obtained in sub and superconservative d-CRN reaction network structure (topology) subclasses where the reachability problem - as a decision problem - is proven to be equivalent to the existence of a non-negative integer solution of the d-CRN state equation [27, 28].

Now we introduce the definitions of sub and superconservativity.

Definition 5. A d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with stoichiometric matrix $\Gamma_{\mathcal{N}} \in \mathbb{Z}^{n \times l}$ is said to be subconservative (superconservative), if there exists a strictly positive vector $z \in \mathbb{R}^l_{>0}$ so that $z^\top \Gamma_{\mathcal{N}} \leq 0^{1 \times l}$ ($z^\top \Gamma_{\mathcal{N}} \geq 0^{1 \times l}$). Then the vector z is called conservation vector.

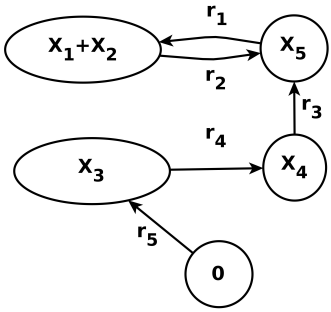
Example 2. Figure 2 depicts a subconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with $\mathcal{S} = \{X_1, X_2, X_3, X_4, X_5, 0\}$, $\mathcal{C} = \{X_1 + X_2, X_3, X_4, X_5, 0\}$. 0 denotes the zero complex.



$$\Gamma_{\mathcal{N}} = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 1 & -1 & 0 \\ 1 & -1 & -1 & 0 & 0 \end{bmatrix}$$

Figure 2. Illustrative example for a subconservative d-CRN. For any initial state X_0, all the states reachable from X_0 are bounded by an at most $(n-1)$-dimensional hyperplane.

Example 3. Figure 3 depicts a superconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with $\mathcal{S} = \{X_1, X_2, X_3, X_4, X_5, 0\}$, $\mathcal{C} = \{X_1 + X_2, X_3, X_4, X_5, 0\}$. A superconservative d-CRN can be obtained by reversing the direction of the edges of the reaction network graph of a subconservative d-CRN. Note that reversing the direction of the edges is equivalent to reversing the signs of the entries of $\Gamma_{\mathcal{N}}$.



$$\Gamma_{\mathcal{N}} = \begin{bmatrix} 1 & -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & -1 & 1 & 0 \\ -1 & 1 & 1 & 0 & 0 \end{bmatrix}$$

Figure 3. Illustrative example for a superconservative d-CRN. For any initial state X_0, all the states reachable from X_0 are lower-bounded by an at most $(n-1)$-dimensional hyperplane in the discrete state space $\mathcal{X}$ of $\mathcal{N}$.

Definition 6. A d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of stoichiometric matrix $\Gamma_{\mathcal{N}} \in \mathbb{Z}^{n \times l}$ is called conservative if there exists a vector $z \in \mathbb{R}^l_{>0}$ for which $z^\top \Gamma_{\mathcal{N}} = 0^{1 \times l}$ holds.

Sub-and superconservativity are topological (structural) properties of d-CRNs as they are determined by the reaction vectors composing the stoichiometric matrix. The conservative network structure (topology) subclass of d-CRNs gives a special case of sub-and superconservativity where all the reachable states are located on an at most $(n-1)$-dimensional hyperplane for any initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$.

2.2 Petri net representation for d-CRNs

In this section the Petri net description of d-CRNs is summarized based on [4,16]. Petri nets provide an equivalent discrete state model class to d-CRNs. They are commonly used in theoretical computer science to model systems of discrete state transitions, they are applied to model concurrent systems, communication protocols, asynchronous, distributed and parallel processes.

Definition 7. [16]

A Petri Net is a tuple $\mathcal{P} = (P, T, I, O)$, where

1. P is a finite set of places,
2. T is a finite set of transitions, $P \cap T = \emptyset$,
3. I is a finite set of input functions (preconditions) $I : T \to P^\infty$,
4. O is a finite set of output functions (consequences) $O : T \to P^\infty$.

where P^∞ denotes the multiset derived from P. $P \cap T = \emptyset$, $P \cup T \neq \emptyset$.

The graphical description of a Petri net is a biparite directed graph:

1. Vertices : $P \cup T$,
2. Edges : $I \cup O$.

The set of places of a Petri net corresponds to the set of species in the equivalent d-CRN model formulation. The transitions are the reactions while the input and output functions characterize the source and product complexes, respectively. We note that while the d-CRN reaction graph depicts the complexes as nodes, the equivalent Petri net representation

depicts the species and reactions as vertices so that source and product complexes are given by the input and output functions, $I()$ and $O()$, respectively.

The marking $M \in \mathbb{Z}^n_{\geq 0}$, $n = |P|$ of a Petri net is defined by the following equations:

$$[M]_i = p_i, \text{ for } i = 1, \ \ldots \ n \tag{9}$$

where p_i denotes the number of tokens (integer variables) at the i'th place of the Petri net $\mathcal{P}$. A fixed ordering of the places is assumed. This way M is equivalent to state vector of the equivalent d-CRN representation.

Definition 8. Let us consider a Petri net $\mathcal{P} = (P, T, I, O)$.

1. For any $t \in T$ the input and output places are defined as $I(t)$ and $O(t)$, respectively.
2. A transition $t \in T$ is said to be enabled if each input place of t has at least 1 token.
3. A firing of an enabled transition t removes 1 token from all the input places $I(t)$ and adds 1 token to each of the output places $O(t)$.

Note that we do not define weight function to the transitions of T, this way it is assumed that each $t \in T$ consumes 1 token from its respective input places and produces 1 token at its output places.

Example 4. Figure 4 depicts a d-CRN reaction graph of an enzymatic system where an enzyme E is responsible for the phosphorilation of the species I. The equivalent Petri net representation is depicted in the right. In the Petri net model the species and reactions are depicted as nodes, while the input and output functions, $I()$ and $O()$ determines the edges so that for each reaction, $I()$ defines the species composing the source complex, while $O()$ define the set of species providing the product complex.

Definition 9. Let us consider a Petri net $\mathcal{P} = (P, T, I, O)$. The dual graph of $\mathcal{P}$ is a Petri net $\overline{\mathcal{P}} = (\overline{P}, \overline{T}, \overline{I}, \overline{O})$ for which $\overline{P} = T$, $\overline{T} = P$, $\overline{I} = I^{-1}$ and $\overline{O} = O^{-1}$ where the inverse on I and O are meant element-wise.

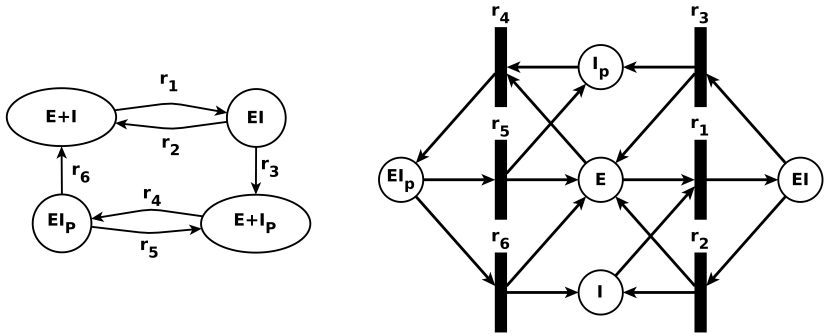


Figure 4. Left: d-CRN reaction graph of an biochemical system. **Right:** Equivalent Petri net representation of the d-CRN depicted in the left. Species and reactions correspond to the places and transitions, respectively. The source and product complexes are characterized by the input and output functions.

The interpretation of the dual graph is that the places are replaced with the transitions, the transitions are replaced with the places and the direction of the input and output functions are reversed.

Let us note that for any Petri net $\mathcal{P}$, the Petri net $\overline{P}$ obtained by constructing the dual graph of $\mathcal{P}$ is unique, that is there is a bijective mapping between $\mathcal{P}$ and $\overline{\mathcal{P}}$.

Example 5. Figure 5 depicts a Petri net $\mathcal{P} = (P, T, I, O)$ (left) and another Petri net $\mathcal{P}' = (P', T', I', O')$ (right) obtained by taking the dual graph of $\mathcal{P}$.

3 Overview of d-CRN reachability

In this section we recall the relevant known results on the decision problem of d-CRN reachability based on [26–28]. The reviewed reachability results are extensively used in the next chapter in the proof of the main result. We focus on specific sub-classes of subconservative reaction network structures.

From a computational point of view, the reachability of state X' from X_0 in the d-CRN state equation Eq. (8) can be traced back to the feasibil-

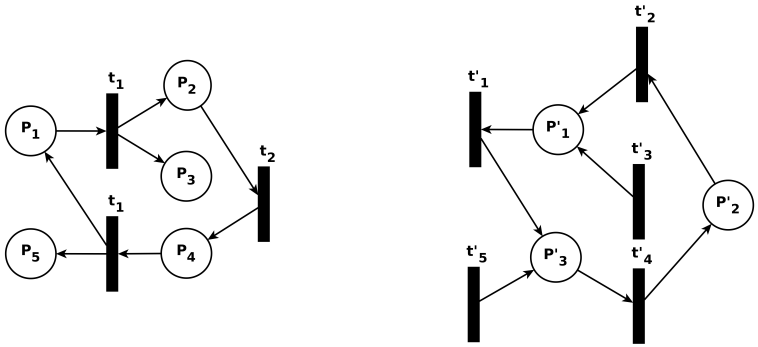


Figure 5. Illustrative example: a Petri net and its dual graph. Note that there is a bijective relationship between any Petri net and the Petri net obtained by taking its dual graph.

ity of an Integer Programming (IP) problem with c as the vector of decision variables. The existence of a non-negative c solution of the state equation is a necessary and sufficient condition of reachability [26, 27]. Moreover, it was also proven that the IP can be relaxed to a Linear Program (LP) by making use of the totally unimodular structure of the stoichiometric matrix in the studied d-CRN subclasses [28].

Let us introduce the following vector-valued function $M = M(\Gamma^-)$ [26, 27]:

$$[M(\Gamma^-)]_i = max\Big\{[\Gamma^-]_{ij} : \ j = 1, \dots \ l\Big\}, \qquad i = 1, \dots \ n. \tag{10}$$

Note that for any d-CRN $\mathcal{N}$ and state vector $X \in \mathbb{Z}^n_{\geq 0}$, $X \succeq M(\Gamma^-_{\mathcal{N}})$ implies that all the reactions (source complexes) of $\mathcal{N}$ are charged at X.

Proposition 1 provides us with conditions on the d-CRN network structure (topology) and the pair of initial and target states under which the existence of a non-negative integer solution c of the state equation is a sufficient and necessary condition of the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$.

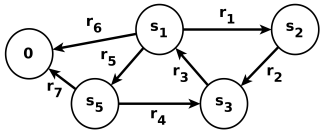
Proposition 1. *[27] Let us consider a subconservative or superconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$ and $\mathcal{C} = \mathcal{S} \cup \{\emptyset\}$. Let us assume that for each $r \in \mathcal{R}$, $\sum_{i=1}^n [\overline{y}^+]_i \leq 1$ and $\sum_{i=1}^n [\overline{y}^-]_i = 1$. Let us consider two arbitrary states, $X_0, \ X' \in \mathbb{Z}^n_{\geq 0}$ so that $X_0 \succeq M$, $X' \succeq M$ where $M = M(\Gamma^-)$ is defined*

by Eq. (10) *Then the reachability relation* $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *hold if and only if the there exists a vector* $c \in \mathbb{Z}^l_{\geq 0}$ *satisfying the dCRN state equation* $X_0 + \Gamma_{\mathcal{N}} c = X'$.

Proposition 1 results in the following IP decision problem [27]:

$$\begin{cases} \Gamma_{\mathcal{N}} c = X' - X_0 \\ c \in \mathbb{Z}^l_{\geq 0} \end{cases} \tag{11}$$

Example 6. Let us consider the reaction network in Fig. 6. Assuming that $X_0,\ X' \in \mathbb{Z}^n_{\geq 0}$, $X_0 \succeq M(\Gamma^-_{\mathcal{N}})$, $X' \succeq M(\Gamma^-_{\mathcal{N}})$, Proposition 1 guarantees that the reachability problem is equivalent to the existence of a non-negative integer solution c of the state equation $X_0 + \Gamma c = X'$.



$$\Gamma^-_{\mathcal{N}} = \begin{bmatrix} -1 & 0 & 0 & 0 & -1 & -1 & 0 \\ 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & -1 \end{bmatrix}$$

Figure 6. A subconservative d-CRN $\mathcal{N}$ for which the conditions of Proposition 1 hold.

In propositions 2 and 3 the reaction network structure classes covered in Proposition 1 are extended by allowing catalyzer species.

Proposition 2. *[27] Let us consider a subconservative d-CRN* $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ *with stoichiometric matrix* $\Gamma_{\mathcal{N}} \in \{-1, 0, 1\}^{n \times l}$ *and* $\Gamma^- \in \{0, 1\}^{n \times l}$. *Assume that for each* $r \in \mathcal{R}$*:*

1. $r = s_1 \to s_2$ *for* $s_1,\ s_2 \in \mathcal{S}$, $s_1 \neq s_2$, $s_1 \neq 0$, *or*
2. $r = s + s_1 \to s + s_2$ *for* $s,\ s_1,\ s_2 \in \mathcal{S}$, $s \neq s_1 \neq s_2$, $s \neq 0$, $s_1 \neq 0$ *and* s *is not consumed by any reaction* $r \in \mathcal{R}$.

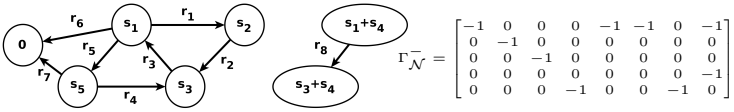
Let us consider a pair of states $X_0, X' \in \mathbb{Z}^n_{\geq 0}$ *so that* $X_0 \succeq M$ *and* $X' \succeq M$ *where* $M = M(\Gamma^-)$ *is defined by Eq.* (10). *The the relation* $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *holds if and only if there exists a non-negative integer solution* $c \in \mathbb{Z}^l_{\geq 0}$ *for which* $X_0 + \Gamma_{\mathcal{N}} c = X'$ *is satisfied.*

Proposition 3. *[27] Let us consider a superconservative d-CRN* $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ *with stoichiometric matrix* $\Gamma_{\mathcal{N}} \in \{-1, 0, 1\}^{n \times l}$ *and* $\Gamma^{-} \in \{0, 1\}^{n \times l}$. *Assume that for each* $r \in \mathcal{R}$:

1. $r = s_1 \to s_2$ *for* $s_1,\ s_2 \in \mathcal{S},\ s_1 \neq s_2,\ s_2 \neq 0$, *or*
2. $r = s + s_1 \to s + s_2$ *for* $s,\ s_1,\ s_2 \in \mathcal{S},\ s \neq s_1 \neq s_2,\ s \neq 0,\ s_2 \neq 0$ *and* s *is not consumed by any reaction* $r \in \mathcal{R}$.

Let us consider a pair of states $X_0, X' \in \mathbb{Z}^n_{\geq 0}$ *so that* $X_0 \succeq M$ *and* $X' \succeq M$ *where* $M = M(\Gamma^{-})$ *is defined by Eq.* (10). *The the relation* $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *holds if and only if there exists a non-negative integer solution* $c \in \mathbb{Z}^l_{\geq 0}$ *for which* $X_0 + \Gamma_{\mathcal{N}} c = X'$ *is satisfied.*

Example 7. Consider the reaction network in Fig. 7. It is visible that by reversing the edges of the reaction graph we obtain a superconservative reaction network structure that satisfies Proposition 2.



$$\Gamma^{-}_{\mathcal{N}} = \begin{bmatrix} -1 & 0 & 0 & 0 & -1 & -1 & 0 & -1 \\ 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -1 & 0 & 0 & -1 & 0 \end{bmatrix}$$

Figure 7. A subconservative d-CRN $\mathcal{N}$ for which the conditions of Proposition 2 hold.

In the next proposition the relationship between sub and superconservative reachability is given, assuming that a subconservative (superconservative) d-CRN is obtained by reversing the direction of the reactions of a superconservative (subconservative) d-CRN.

Proposition 4. *[27] Let us consider a subconservative d-CRN* $\mathcal{N}$ *characterized by the matrices* $\Gamma_{\mathcal{N}} = \Gamma$, $\Gamma^{+}_{\mathcal{N}} = \Gamma^{+}$ *and a superconservative d-CRN* $\mathcal{N}'$ *with matrices* $\Gamma_{\mathcal{N}'} = -\Gamma$, $\Gamma^{-}_{\mathcal{N}'} = \Gamma^{+}$. *Let us take an initial state* $X_0 \in \mathbb{Z}^n_{\geq 0}$ *and a target state* $X' \in \mathbb{Z}^n_{\geq 0}$. *Then the reachability* $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *holds if and only if* $X' \rightsquigarrow_{\mathcal{N}'} X_0$ *also holds.*

The next proposition gives polynomial time relaxation to the reachability problem by making use of the totally unimodular property of the

stoichiometric matrix in the considered sub-classes of sub-and superconservative d-CRN reaction networks.

Proposition 5. *[28] Let us consider a subconservative or superconservative d-CRN* $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ *with stoichiometric matrix* $\Gamma_{\mathcal{N}} \in \{-1, 0, 1\}^{n \times l}$ *and* $\Gamma_{\mathcal{N}}^{-} \in \{0, 1\}^{n \times l}$ *and* $\mathcal{C} = \mathcal{S} \cup \{\emptyset\}$. *Let us assume that for each* $r \in \mathcal{R}$, $\sum_{i=1}^{n} [\overline{y}^{+}]_i \leq 1$ *and* $\sum_{i=1}^{n} [\overline{y}^{-}]_i = 1$. *Let us consider two arbitrary states,* $X_0,\ X' \in \mathbb{Z}_{\geq 0}^{n}$ *so that* $X_0 \succeq M$, $X' \succeq M$ *where* $M = M(\Gamma^{-})$ *is defined by Eq.* (10). *Then the reachability relation* $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *can be decided in polynomial time.*

The practical importance of Proposition 5 is that the reachability relation can be decided in polynomial time by means of a Linear Program of the following form:

$$\begin{cases} \Gamma_{\mathcal{N}} c = X' - X_0 \\ c \in \mathbb{R}_{\geq 0}^{l} \end{cases} \tag{12}$$

Note that the infeasibility of the above formulated linear program implies that the reachability relation does not hold. In addition, it is important to note that proving the infeasibility of an LP is straightforward compared to an IP infeasibility with the same equations.

We can extend Proposition 2 and Proposition 3 by making use of the totally unimodular property of the stoichiometric matrix $\Gamma_{\mathcal{N}}$ in the same way as that of Proposition 5.

4 Main results

This section discusses the main coverability result of the paper given in Proposition 6. Using reachability results summarized in the previous section, we prove that the reachability relation implies the coverability for the d-CRN sub-classes obtained by taking the dual graph of the Petri net of the reaction network. It is also shown that the d-CRN reaction network subclasses covered by the new results include certain non-conservative reaction network structures which is a significant improvement.

Proposition 6. *Let us consider a subconservative d-CRN* $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ *with stoichiometric matrix* $\Gamma_{\mathcal{N}}$ *so that* $\mathcal{N}$ *satisfies the conditions of Proposition 1. Let us further assume that for each* $S \in \mathcal{S}$*, there exists a unique reaction* $r \in \mathcal{R}$ *so that* $S = source(r)$ *and there is no reaction* $r \in \mathcal{R}$ *for which* $source(r) = \emptyset$*. Let us consider two arbitrary states,* $X_0,\ X' \in \mathbb{Z}^n_{\geq 0}$ *so that* $X_0 \succeq M$*,* $X' \succeq M$ *where* $M = M(\Gamma^-_{\mathcal{N}})$ *is defined by Eq.* (10)*. Consider the d-CRN* $\overline{\mathcal{N}} = (\overline{\mathcal{S}}, \overline{\mathcal{C}}, \overline{\mathcal{R}})$ *obtained by taking the dual graph of the Petri net representation of* $\mathcal{N}$ *with the initial state* $\overline{X}_0 = X'$ *and target state* $\overline{X}' = X_0$*. Then the reachability relation* $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *of* $\mathcal{N}$ *implies that* $\overline{X}'$ *is coverable in* $\overline{\mathcal{N}}$*, provided the initial state* $\overline{X}_0$*.*

Proof. We prove that the coverability relation for $\overline{X}'$ in $\overline{\mathcal{N}}$ with initial state $\overline{X}_0$ is implied by the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ in $\mathcal{N}$ under the above conditions.

Let us assume that the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ holds with respect to the d-CRN $\mathcal{N}$. Then it follows that there exists an admissible state transition sequence σ_X so that

$$\sigma_X = X_0 X_1 \ \ldots \ X_{L-1} X_L \tag{13}$$

where $|\sigma_X| = L$.

Let us compose the d-CRN $\hat{\mathcal{N}} = (\hat{\mathcal{S}}, \hat{\mathcal{C}}, \hat{\mathcal{R}})$ where $\hat{\mathcal{S}} = \mathcal{S}$, $\hat{\mathcal{C}}$=$\mathcal{C}$ and $\hat{\mathcal{R}}$ is obtained from $\mathcal{R}$ by reversing the direction of the reactions. Then the following relation holds: $\Gamma_{\mathcal{N}} = -\Gamma_{\hat{\mathcal{N}}}$. Based on Proposition 4, the reachability relation of $X_0 \rightsquigarrow_{\mathcal{N}} X'$ implies that the following reachability relation holds:

$$\hat{X}_0 \rightsquigarrow_{\hat{\mathcal{N}}} \hat{X}', \tag{14}$$

where $\hat{X}_0 = X'$ and $\hat{X}' = X_0$. The reachability relation of Eq. (14) implies that there exists an admissible state transition sequence $\hat{\sigma}_X$ in $\hat{\mathcal{N}}$ so that

$$\hat{\sigma}_X = \hat{X}_0 \hat{X}_1 \ \ldots \ \hat{X}_{L-1} \hat{X}_L. \tag{15}$$

Then there exists a reaction vector sequence $\hat{\sigma}_r = \hat{r}_{\hat{\mu}(1)} \hat{r}_{\hat{\mu}(2)} \ \ldots \ \hat{r}_{\hat{\mu}(L)}$

so that $\hat{X}_{k-1} \rightarrow_{\hat{r}_{\hat{\mu}(k)}} \hat{X}_k$ for $1 \leq k \leq L$. Note that $\hat{\mu}()$ is an index function mapping the k'th entry of the reaction vector sequence $\hat{\sigma}_r$ to the $\hat{\mu}(k)$'th reaction of $\hat{\mathcal{N}}$, provided a fixed ordering of the reactions of $\hat{\mathcal{N}}$.

The state vector $\hat{X} \in \mathbb{Z}^n_{\geq 0}$ of $\hat{\mathcal{N}}$ can be expressed in the following way:

$$\hat{X} = \left[|\hat{S}_1| \ |\hat{S}_2| \ \ldots \ |\hat{S}_n| \right]^\top, \tag{16}$$

where $|\hat{S}_i|$ for $i = 1, \ \ldots \ n$ denotes the molecular count (number of tokens) of the i'th species $\hat{S}_i \in \hat{\mathcal{S}}$ in the state $\hat{X}$, provided a fixed ordering of the species in $\hat{\mathcal{S}}$.

Now we can compose the d-CRN $\overline{\mathcal{N}} = (\overline{\mathcal{S}}, \overline{\mathcal{C}}, \overline{\mathcal{R}})$ with stoichiometric matric $\overline{\Gamma}_{\overline{\mathcal{N}}}$ by means of the following bijective mappings:

$$f_{\hat{\mathcal{S}}} : \hat{\mathcal{S}} \rightarrow \overline{\mathcal{R}},$$
$$f_{\hat{\mathcal{R}}} : \hat{\mathcal{R}} \rightarrow \overline{\mathcal{S}}.$$

The tuple $(f_{\hat{\mathcal{S}}}, f_{\hat{\mathcal{R}}})$ provides a bijective map between the Petri net representations of the d-CRNs $\hat{\mathcal{N}}$ and $\overline{\mathcal{N}}$, respectively. In addition, it is easy to check that the Petri net representation of $\overline{\mathcal{N}}$ is the dual graph of the Petri net of $\mathcal{N}$.

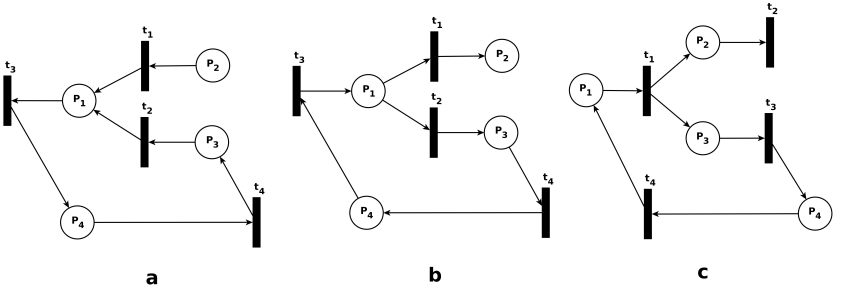


Figure 8. Illustration of the Petri nets composed as part of Proposition 6. **a:** the initial $\mathcal{N}$ d-CRN expressed in Petri net representation. **b:** the Petri net representation of $\hat{\mathcal{N}}$ obtained from $\mathcal{N}$ by reversing the direction of the reactions. **c:** the Petri net representation of d-CRN $\overline{\mathcal{N}}$ obtained from $\hat{\mathcal{N}}$ by replacing the species with transitions and transitions with species. The Petri net of $\overline{\mathcal{N}}$ is the dual graph of $\mathcal{N}$.

Making use of $(f_{\hat{\mathcal{S}}}, f_{\hat{\mathcal{R}}})$, the state vector $\hat{X}$ of $\hat{\mathcal{N}}$ translates to the following token vector of $\overline{\mathcal{N}}$:

$$\overline{t} = \Big[|\hat{S}_1| \ |\hat{S}_2| \ \ldots \ |\hat{S}_n| \Big]^{\top}. \tag{17}$$

The token vector $\overline{t}$ can be interpreted as follows: for each i, $1 \leq i \leq n$, $[\overline{t}]_i$ denotes the number of tokens at the i'th transition (reaction) of $\overline{\mathcal{R}}$. Eq. (17) implies that the molecular count (number of tokens) of i'th species in $\hat{X}$ of $\hat{\mathcal{N}}$ is equal to the number of tokens at the i'th transition of $\overline{\mathcal{N}}$ for $1 \leq l \leq n$. Note that the formal definition of d-CRNs and Petri nets do not allow us to define tokens (molecules) at the transitions (reactions), however, from graph-theoretical point of view, the bijective mapping $(f_{\hat{\mathcal{S}}}, f_{\hat{\mathcal{R}}})$ with a state vector (token configuration) $\hat{X}$ results in a Petri net where tokens are located at the nodes representing the transitions. This way $\overline{t}$ is interpreted as the token vector denoting the token count at the transitions of $\overline{\mathcal{N}}$.

The map $(f_{\hat{\mathcal{S}}}, f_{\hat{\mathcal{R}}})$ provides the following bijection between the state vectors of $\hat{\mathcal{N}}$ and token vectors of $\overline{\mathcal{N}}$:

$$f_{\hat{X}} : \hat{\mathcal{X}} \to \overline{\mathcal{T}}. \tag{18}$$

where $\overline{\mathcal{T}}$ denotes the subspace of token vectors in $\overline{\mathcal{N}}$.

By applying the bijective map $f_{\hat{X}}$ on the entries of the state transition sequence $\hat{\sigma}_X$ of $\hat{\mathcal{N}}$, we obtain the following token vector sequence of $\overline{\mathcal{N}}$:

$$\overline{\sigma}_t = \overline{t}_0 \overline{t}_1 \ \ldots \ \overline{t}_{L-1} \overline{t}_L. \tag{19}$$

Now we compose the state transition sequence $\overline{\sigma}_X = \overline{X}_0 \overline{X}_1 \ \ldots \ \overline{X}_{L-1} \ \overline{X}_L$ so that

$$\overline{X}_0 = \overline{t}_0, \tag{20}$$

$$\overline{X}_k = \overline{X}_{k-1} + \overline{r}_{\overline{\mu}(k)}, \text{ for } 1 \leq k \leq L, \ \overline{r}_{\overline{\mu}(k)} = f_{\hat{\mathcal{S}}}\Big(source(\hat{r}_{\hat{\mu}(k)}) \Big). \tag{21}$$

Eq. (20) is well-defined: for each $\hat{S} \in \hat{\mathcal{S}}$, $\overline{r} = f_{\hat{\mathcal{S}}}(\hat{S})$ is unique, and

there exists a unique source species $\overline{S} \in \overline{\mathcal{S}}$, $\overline{S} = source(\overline{r})$. That is, there is a unique relationship between the entries of $\hat{\mathcal{S}}$ and $\overline{\mathcal{S}}$. This way the dimension of the state space $\overline{\mathcal{X}}$ of $\overline{\mathcal{N}}$ is the same as that of $\hat{\mathcal{X}}$ for $\hat{\mathcal{N}}$.

Let us assume the ordering of the species in $\overline{\mathcal{S}}$ so that the index i of $\hat{S}_i = target(\hat{r}_{\hat{\mu}(k)})$ is the same as for $\overline{S}_i = target(\overline{r}_{\overline{\mu}(k)})$ with $\overline{S}_i = f_{\hat{\mathcal{R}}}(\hat{r}_{\hat{\mu}(k)})$. Note that we can take an arbitrary ordering of the species of $\overline{\mathcal{S}}$.

Note that the state $\overline{X}_k$ defined in Eq. (21) is unique for $k = 1 \ \ldots \ L$ since $source(\hat{r}) \in \hat{\mathcal{S}} \cup \emptyset$ is unique for all $\hat{r} \in \hat{\mathcal{R}}$ and $f_{\hat{\mathcal{S}}}$ is a bijective mapping.

We show that $\overline{X}_k \succeq \overline{t}_k$ for $0 \leq k \leq L$ by induction.

1. $k = 0$

   Making use of Eq. (20), the following relation holds:

   $\overline{X}_0 = \overline{t}_0 \ \Rightarrow \overline{X}_0 \succeq \hat{X}_0 = \overline{t}_0$

2. k (inductive assumption)

   $\overline{X}_k \succeq \hat{X}_k = \overline{t}_k$

3. $k + 1$

   Let us consider the reaction $\hat{r}_{\hat{\mu}(k+1)}$ driving the d-CRN $\hat{\mathcal{N}}$ to the state $\hat{X}_{k+1}$. Then we have a unique species $\overline{S}_m \in \overline{\mathcal{S}}$ for which

   $$\overline{S}_m = f_{\hat{\mathcal{S}}}(\hat{r}_{\hat{\mu}(k+1)}), \ 1 \leq m \leq n. \tag{22}$$

   Then Eq. (21) implies that $\overline{S}_m \in target(\overline{r}_{\overline{\mu}(k+1)})$. In addition, we have that $\overline{S}_p = source(\overline{r}_{\overline{\mu}(k+1)})$ for some $1 \leq p \leq n$, $p \neq m$. Since $\hat{S}_p \in \hat{\mathcal{S}}$ is charged at $\hat{X}_k$, it follows that $\overline{S}_p \in \overline{\mathcal{S}}$ is charged at $\overline{X}_k$, provided the inductive assumption for k. Then it follows that $[\overline{X}_{k+1}]_p \geq [\hat{X}_{k+1}]_p$. For m, we have that $[\overline{X}_k]_m \geq [\hat{X}_k]_m$ based on the inductive assumption, $\overline{S}_m \in target(\overline{r}_{\overline{\mu}(k+1)})$ and $\hat{S}_m = target(\hat{r}_{\hat{\mu}(k+1)})$ from which it follows that $[\overline{X}_{k+1}]_m \geq [\hat{X}_{k+1}]_m$. For all the other indices q, $1 \leq q \leq n$, $q \neq p$, $q \neq m$, the reactions $\overline{r}_{\overline{\mu}(k+1)} \in \overline{\mathcal{R}}$ and $\hat{r}_{\hat{\mu}(k+1)} \in \hat{\mathcal{R}}$ do not change the molecular count (number of tokens) at $\overline{S}_q \in \overline{\mathcal{S}}$ and $\hat{S}_q \in \hat{\mathcal{S}}$, that is $[\overline{X}_{k+1}]_q \geq [\hat{X}_{k+1}]_q$. Then it follows that $\overline{X}_{k+1} \succeq \hat{X}_{k+1}$.

It is shown that $\overline{X}_k \succeq \bar{t}_k$ for all k by induction. Then it follows that

$$\overline{X}_L \succeq \bar{t}_L = \hat{X}_L \tag{23}$$

Eq. (23) implies that $\mathcal{N}$ is coverable by $\bar{t}_L = \hat{X}_L$, given the initial state $\overline{X}_0$. ■

Remark 1. Proposition 6 is not restricted to d-CRNs composed of single-species complexes. The covered d-CRN structure class can include complexes containing more than one species in the product complex, which is an extension of the results obtained in [27, 28], where both the source and product complexes are assumed to be composed of at most one species. Note that there is no upper bound on the number of species in the product complexes, it can be any finite integer. Figure 9 depicts a Petri net representation of a CRN with 4 reactions (transitions), t_1, t_2, t_3 and t_4 with product complexes composed of more than 1 species.

We note that the d-CRN class covered by Proposition 6 is a sub-class of sub-conservative networks, but not conservative. For example r_6 (t_6) represents a reaction (transition) in which there is no product species generated, but there is a source species ingested, which implies sub-conservative reaction. In addition, the reaction networks of the dual graphs - for which the reachability relation is decidable in polynomial time - are conservative structures.

Proposition 6 can be extended by allowing catalyzer species.

Proposition 7. *Let us consider a subconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with stoichiometric matrix $\Gamma_{\mathcal{N}} \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$. Assume that for each $r \in \mathcal{R}$:*

1. *$r = s_1 \to s_2$ for $s_1,\ s_2 \in \mathcal{S}$, $s_1 \neq s_2$, or*
2. *$r = s + s_1 \to s + s_2$ for $s,\ s_1,\ s_2 \in \mathcal{S}$, $s \neq s_1 \neq s_2$, $s \neq 0$ and s is not consumed by any reaction $r \in \mathcal{R}$.*

Let us assume that for each $S \in \mathcal{S}$, there exists a unique reaction $r \in \mathcal{R}$ so that $s = source(r)$ and there is no reaction $r \in \mathcal{R}$ for which $source(r) = \emptyset$.

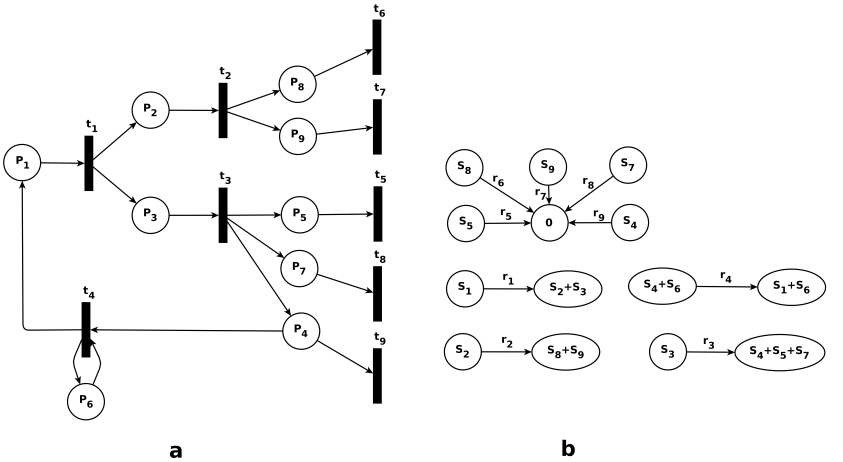


Figure 9. Representative example for Remark 1. **a:** Petri net representation. **b:** Equivalent reaction network representation. Note that Proposition 6 allows for reactions having more than 1 product species as it is depicted by reaction (transition) r_1 (t_1), r_2 (t_2), r_3 (t_3) and r_4 (t_4). In addition, there is no theoretical restriction on the number of species contained in a product complex, it can be any finite non-negative integer.

Consider a pair of states $X_0, X' \in \mathbb{Z}^n_{\geq 0}$ *so that* $X_0 \succeq M$ *and* $X' \succeq M$ *where* $M = M(\Gamma^-_{\mathcal{N}})$ *is defined by Eq.* (10). *Let us compose a d-CRN* $\overline{\mathcal{N}} = (\overline{\mathcal{S}}, \overline{\mathcal{C}}, \overline{\mathcal{R}})$ *obtained by taking the dual graph of the Petri net representation of* $\mathcal{N}$ *with the initial state* $\overline{X}_0 = X'$ *and target state* $\overline{X}' = X_0$.

Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *of* $\mathcal{N}$ *implies that the* $\overline{X}'$ *is coverable in* $\overline{\mathcal{N}}$, *provided the initial state* $\overline{X}_0$.

Example 8. Figure 10 provides an illustrative example for Proposition 6 and Proposition 7. By taking the dual graph of the Petri net depicted in Figure 10.a, we obtain a Petri net and equivalent d-CRN representation $\mathcal{N}$ satisfying the conditions in Proposition 6. Proposition 6 and Proposition 7 provide theoretical guarantee that the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ for $X_0 \succeq M$ and $X' \succeq M$, $M = M(\Gamma^-_{\mathcal{N}})$ in $\mathcal{N}$ implies a coverability relation of the d-CRN depicted in Figure 10.b, that is, X_0 is coverable, provided the initial state X' in $\overline{\mathcal{N}}$. The practical importance of the theoretical results of proposition 6 and Proposition 7 is that the coverability relation can be

decided in polynomial time in the case of d-CRNs containing complexes composed of multiple species.

Figure 11 depicts the Petri net and reaction network obtained by taking the dual graph of the Petri net of Figure 10. Note that the reaction network of Figure 11 satisfies the conditions of Proposition 2 and Proposition 5, this way the reachability $X_0 \rightsquigarrow X'$ of this d-CRN can be decided in polynomial time by a linear program of the form Eq. (12), assuming that $X_0 \succeq M,\ X' \succeq M$, where M is defined Eq. (10). Then Proposition 7 guarantees that the reachability $X_0 \rightsquigarrow X'$ with respect to the d-CRN depicted in Figure 11 implies the coverability of X_0 from initial state X' with respect to the d-CRN depicted in Figure 10.

Let us consider the following pair of states:

$$X_0 = [10\ 12\ 10\ 20\ 8]^\top,\ X' = [9\ 8\ 18\ 15\ 20]^\top, \tag{24}$$

where X_0 and X' denotes the initial state and target state, respectively. The linear program of Eq. (12) with X_0 and X' defined by Eq.(8) provides as integer solution with sub-second running time in Python 3.7. using the Gurobi solver [37]:

$$c = [5\ 4\ 0\ 0\ 3\ 0]^\top. \tag{25}$$

Proposition 5 implies that the reachability relation $X_0 \rightsquigarrow X'$ holds with respect to the d-CRN (and Petri net representation) depicted in Figure 11. Then Proposition 7 implies that the coverability of X_0 from initial state X' holds with respect to the d-CRN (and Petri net representation) depicted in Figure 10.

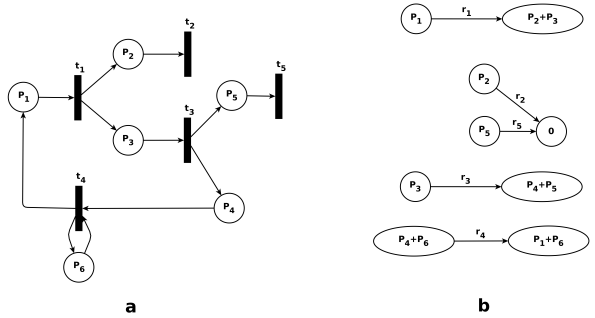


Figure 10. Illustrative example for Proposition 6 and Proposition 7. **a:** Petri net representation of a d-CRN $\mathcal{N}$. **b:** d-CRN reaction network representation. Note that Proposition 6 allows for reactions with product complex composed of more than 1 distinct species. Note that the operation of taking the dual graph of a Petri net is reflexive. Using the reflexivity together with Proposition 7, we can provide sufficient condition for d-CRN coverability by showing a reachability relation in the dual graph of the Petri net representation of $\mathcal{N}$.

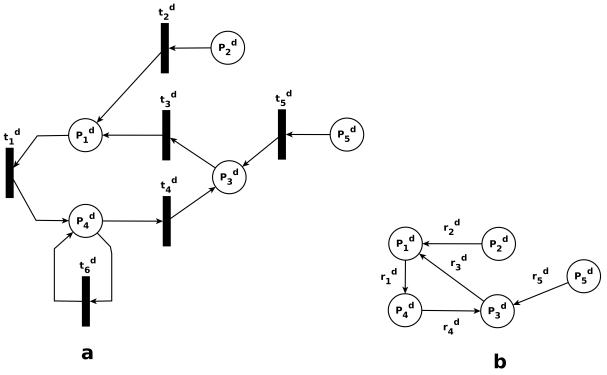


Figure 11. Dual graph (Petri net) and the equivalent d-CRN reaction graph representation of the subconservative d-CRN depicted in Figure 10. The dual graph of a Petri net is obtained by replacing places and transitions with transitions and places, respectively, then the direction of edges are reversed in the resulting graph. Algebraically a dual Petri net is obtained by taking the transpose of the stoichiometric matrix. The reachability relation $X_0 \rightsquigarrow X'$ with respect to this d-CRN translates to the coverability of state X_0 from initial state X' with respect to the d-CRN depicted in Figure 10.

5 Summary

In this paper the coverability problem of subconservative d-CRNs is studied. Leveraging on d-CRN reachability results in the case of restricted-structure subconservative reaction network sub-classes, it is proven that the coverability is implied by the reachability in well-defined sub-classes of reaction network structures. We define a sub-class of d-CRN reaction network structures obtained by taking the dual graph of the Petri net representation of the subconservative reaction network sub-classes assumed in [27, 28]. The coverability relation in the defined class is implied by the reachability problem of d-CRNs studied in [27, 28]. This way, instead of explicitly examining the coverability problem, an equivalent reachability problem can be considered which is known to be decidable in polynomial time and can be employed to prove coverability. The practical importance of the novel coverability result is that it is not restricted to subconservative reaction network structures containing single-species complexes.

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