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Structural Analysis and Identifiability of Biologically Motivated Complex System Models

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Abstract

This thesis is focused on structural analysis, identification and system theoretical realization theory of different dynamical system models. The main goals of this work are to establish novel approaches for identifiability analysis and provide methods for examining the relationship between dynamical model and network structure based representations of various system models with theoretical guarantees.

Structural identifiability, the property of unique parameterization, is examined for time delayed non-linear dynamical system models with the assumption that all the delays are constants. The time delays are treated as parameters of the model structure. The joint identifiability of ordinary system parameters and constant time delays is examined. A novel method for testing structural identifiability is proposed using the Volterra series representation of dynamical systems. The frequency domain representations of the Volterra series, i.e. the generalized frequency response functions, are used to derive sufficient conditions for identifiability in terms of linear algebraic equations. Unique solution of the resulting equations with respect to the parameters implies structural identifiability.

The class of discrete time linear dynamical systems is also studied. It is proved that the set of system (state transition) matrices associated to a Markov parameter (impulse response) sequence is convex, assuming all the other parameters are fixed. Making use of the convexity of the feasible set of system matrices and results from the theory of kinetic systems, algorithms for determining structurally different realizations of a given Markov parameter sequence are derived. Sparse and dense dynamically equivalent realizations are defined to the analogy of kinetic systems. Structural uniqueness of the dense realization is proved.

This thesis is also concerned with the formal model of discrete state Chemical Reaction Networks, which is known to be equivalent to mathematical models of theoretical computer science, such as Petri nets and Vector Addition Systems with States. In order to establish quantitative relationship between the network structure and dynamical behavior of reaction networks, the discrete state reachability problem is studied. An integer linear programming feasibility approach is employed. Novel upper bound on the maximal length of cycle-free state transition sequences is derived. Relaxed solutions are also obtained for the reachability problem. Finally, network structure and initial state dependent conditions are provided under which reachability problem is equivalent to the existence of a non-negative integer solution of the discrete state equation of the reaction network.

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Mathematical notations

In this section we summarize the notations extensively used throughout this thesis.

$\emptyset$	empty set
$\mathbb{R}$	the set of real numbers
$\mathbb{N}$	the set or natural numbers including 0
$\mathbb{Z}$	the set of integer numbers
$\mathbb{Z}_{\geq 0}$	the set of non-negative integer numbers
$\mathbb{T}^{n\times m}$	the set of $(n \times m)$-dimensional vectors over the set $\mathbb{T}$
$0^{n\times m}$	a zero matrix of dimension $n \times m$
$1^{n\times m}$	a matrix of dimension $n \times m$ for which all the entries are equal to 1
$\{0,1\}^{n\times m}$	the set of $(n \times m)$-dimensional binary vectors
$\{-1,0,1\}^{n\times m}$	the set of $(n \times m)$-dimensional vectors composed of the entries $-1, 0, 1$
$\ominus$	subtraction operator acting on a set and a matrix, $\mathcal{A} \ominus A$ is the set given by subtracting the matrix A from all the elements of $\mathcal{A}$
$[A]_{ij}$	the entry in the ith row of the jth column of matrix A
$[A]_{i,:}$	the ith row of the matrix A
$a \prec b$	for $a, b \in \mathbb{R}^n$, $a_i < b_i$ for $i = 1, \dots, n$
$a \preceq b$	for $a, b \in \mathbb{R}^n$, $a_i \leq b_i$ for $i = 1, \dots, n$

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List of abbreviations

GFRF	Generalized Frequency Response Function
SISO	Single Input Single Output
ARX	Autoregressive model with External Input
NARX	Non-linear ARX
DE	Difference Equation
DT-LDS	Discrete Time Linear Dynamical System
SVD	Singular Value Decomposition
ERA	Eigensystem Realization Algorithm
ERA/DC	ERA with Data Correlation
GRA	General Realization Algorithm
EEG	Electroencephalography
d-CRN	discrete state Chemical Reaction Network
LP	Linear Program
ILP	Integer Linear Program
VAS	Vector Addition System
VASS	VAS with States
EXSPACE	Exponential Space Complexity
NFAT	Nuclear Factors of Activated T-cells

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1 Introduction

It is known that several dynamical systems possess a graphical representation in which the nodes represent the individual components while edges correspond to the functional relations between components [1, 2, 3]. For example in a gene regulatory network individual genes can be written as nodes and edges represent functional connections between pairs of genes, such as activation, inhibition [4]. The dynamical model of a system may encode the network structure in terms of the parameters of the underlying differential or difference equation system. In the case of linear dynamical systems the state transition (system) matrix encodes the interaction pattern of state variables (individual components) by its non-zero off-diagonal entries [5]. In non-linear dynamical system models the differential equations may also convey information about the underlying network structure of the interacting components, e.g. in the class of kinetic systems it is proven that the model parameters and edges of the respective graph-based representation are quantitatively related to each other [6, 7]. In Figure 1.1 we illustrate that dynamical model and network-based representation can also be associated to the same biological process. Here it is also illustrated that the differential equation model can be used to derive the graphical representation of the same system.

This thesis is centered around structural analysis, realizability and identification of various system models. The main motivation of this work is to provide theoretically grounded computational methods for the analysis of biologically motivated system models, but the developed methods and algorithms can also be used for studying various systems of engineering and physical importance. We study the relationship between the network structure and dynamical behavior of different system models, such as discrete time linear dynamical systems and discrete state chemical reaction networks. We examine whether there exist structurally (topologically) different realizations of the same dynamical system. We wish to provide algorithms capable of determining structurally different realizations of a dynamical system model, assuming that the network-based representation is not unique. We also examine structural identifiability, a quantitative property ensuring parametric uniqueness, which is closely related to structural uniqueness of the underlying network representation. Structural identifiability can help us quantifying network structure related properties of dynamical system models as it is related to the parameterization of the dynamical system model. Since biologically motivated dynamical systems commonly involve time delayed terms, we consider structural identifiability of non-linear

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time delayed system with the assumption that time delays are constant parameters to be identified and we examine the joint identifiability of time delays and ordinary system parameters related to the underlying network structure.

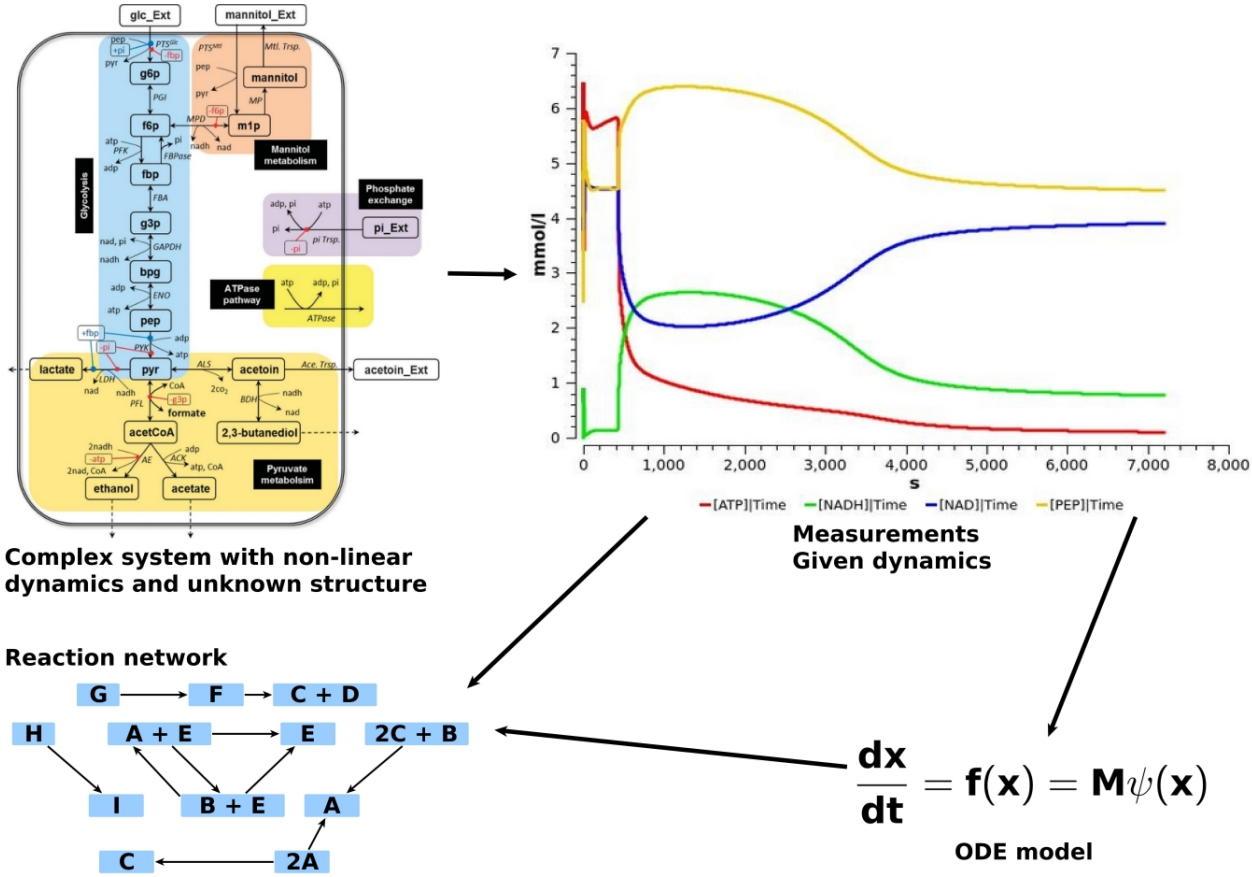

Figure 1.1: Illustration of different representations of a complex biological system. Based on the observed dynamical behavior of the underlying biological system one can (re)construct both a dynamical system model (ODE model) and a graphical representation (reaction network). It is also indicated by an arrow that the ODE model can be used to write out the graphical representation of the system.

Summary of contributions

Structural identifiability analysis of time delayed non-linear systems. In chapter 2 a novel method is proposed for structural identifiability analysis of non-linear time delayed systems. It is assumed that all the non-linearities are analytic functions and the time delays are constant. In the model structures time delays are treated as parameters and we consider the joint structural identifiability of the ordinary system parameters and the time delays. We employ the Volterra series representation of non-linear dynamical systems and make use of the frequency domain representations of the Volterra kernels, i.e. the Generalized Frequency Response Functions (GFRFs), in order to test parametric uniqueness. The advantage of representing non-linear systems with their GFRFs is that

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in the frequency domain representation the time delay parameters appear explicitly in the exponents of complex exponential functions from which they can be easily extracted. Since the GFRFs can be symmetrized to be unique, they provide us with an exhaustive summary of the underlying model structure. We use the GFRFs to derive equations for testing structural identifiability. Unique solution of the composed equations with respect to some parameters provides sufficient conditions for structural identifiability. Our method is illustrated on non-linear dynamical system models of different degrees of non-linearities and multiple time delayed terms. Since Volterra series representation can be applied for input-output models, it is also shown that after differential algebraic elimination of unobserved state variables the proposed method can be suitable for identifiability analysis of more general class of non-linear time delayed state space models.

Computational methods for finding structurally different realizations of discrete linear time invariant systems. In chapter 3 we investigate the realizability of discrete time linear dynamical systems (DT-LDSs) in fixed state space dimension. Assuming fixed sate space dimensionality (i.e. that all the feasible state space realizations are of the same dimension), one can associate a network structure to a DT-LDS of parametrization (A, B, C, D) so that state variables are represented by nodes and two nodes are connected by an edge if the respective off-diagonal value $[A]_{ji}$ is not equal to zero. Formally, the nodes associated to state variables x_i and x_j are connected by a directed edge from x_i to x_j iff $[A]_{ji} \neq 0$. In this graphical representation the edges are weighted by the respective values of A. This way the system matrix A of an DT-LDS encodes the underlying weighted interconnection pattern (structure) of the system. Then the existence of structurally different realizations of an DT-LDS implies that the same dynamical behavior can be obtained by different weighted network structures. Since the dynamical behavior of an DT-LDS is uniquely determined by its Markov parameter (i.e. impulse response) sequence, we examine whether there exist different $\theta = (A, B, C, D)$ state space realizations of a given Markov parameter sequence $\mathcal{Y}$ with fixed B, C and D state space realization matrices. Full observation is assumed in terms of the invertability of output mapping matrix C. We prove that the set of feasible state transition matrices associated to a Markov parameter sequence $\mathcal{Y}$ is convex, provided that the state space realization matrices B, C and D are known and fixed. Under the same conditions we also show that the set of feasible Metzler-type state transition matrices forms a convex subset. Regarding the set of Metzler-type state transition matrices we prove the existence of a structurally unique realization having maximal number of non-zero off-diagonal entries. Using an eigenvalue assignment procedure we propose linear programming based algorithms capable of computing different state space realizations. By using the convexity of the feasible set of Metzler-type state transition matrices and results from the theory of non-negative polynomial systems, we provide algorithms to determine struc-

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turally different realization. Computational examples are provided to illustrate structural non-uniqueness of network-based DT-LDSs.

Reachability analysis in discrete state reaction networks. In chapter 4 we consider the class of discrete state Chemical Reaction Networks (d-CRNs), a commonly used mathematical formulation for modeling the dynamical behavior of biologically motivated processes on discrete state space. D-CRNs can be used to model systems such as those arising in the fields of chemical reaction networks, epidemiology, population biology and systems biology. The model of d-CRNs is equivalent to Petri nets having many applications in theoretical computer science, e.g. modeling concurrent and distributed systems. Here we study the relation between network structure and dynamical behavior by making use of the concept of reachability: given a pair of initial and target states, is it possible to reach the target state from the initial one along the firings (occurences) of the reactions of the underlying d-CRN structure? In our study reachability problems of sub-and superconservative d-CRNs are considered, as conservation laws are commonly observed in biological systems. First an Integer Linear Programming (ILP) feasibility approach is employed for computationally solving the reachability problem. We provide novel bounds on the length of cycle-free state transition (reaction) sequences associated to a particular pair of initial and target states. It is known that a subconservative network has bounded reachable state space, while that of a superconservative one is unbounded. The reachability problem of superconservative reaction networks is traced back to the reachability of subconservative ones. This way it is proved that the reachability problem of superconservative d-CRNs can be reduced to an equivalent reachability problem in a bounded state space. Next we prove that the reachability problem of low-dimensional d-CRNs is equivalent to the existence of a non-negative integer solution of the respective d-CRN state equation characterizing the state evolution of the network. Then we consider d-CRNs of arbitrary high state space dimension so that the network structures are composed of reactions of at most one input and one output species beyond possible catalyzers. We give a proof that, assuming all the reactions are charged in the initial and target states, the reachability problems of sub-and superconservative reaction networks are equivalent to the existence of non-negative integer solution of the corresponding d-CRN state equations. Using the aforementioned results, the number of decision variables in the ILP feasibility formulation – and therefore the time complexity of the arising computational problems – can be significantly reduced. Then, by means of the Barvinok algorithm, the number of feasible trajectories satisfying a reachability relation can be counted in polynomial time in the number of species and in the distance of initial and target states, assuming fixed number of reactions in the system. Finally, we make use of the totally unimodular property of the stochoimetric matrix in the considered subclasses of d-CRNs. We prove that the reachability relation can be decided in polynomial time under the above conditions

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by linear program-based relaxation.

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2 Structural identifiability analysis of non-linear time-delayed systems

2.1 Mathematical notations

$M(.)$	notation of an analytical SISO input-output dynamical system
θ	parameters of a dynamical system $M(.)$
Θ	parameter space of a dynamical system $M(.)$
p	differential operator
$H_n(j\omega_1, \dots j\omega_n)$	n-th order Generalized Frequency Response Function (GFRF)
$H_n^{sym}(j\omega_1, \dots j\omega_n)$	n-th order symmetrized GFRF

Table 2.1: Notations specific to chapter 2.

2.2 Background

Several dynamical systems of physical, chemical and biological importance can be modeled by means of continuous differential equations [9, 52]. An important step in constructing precise mathematical models is estimating the model parameters [10, 11, 53, 54]. Accurate estimation of parameters is of paramount importance especially if the purpose is to make predictions based on the identified model. A related problem of parameter estimation is structural identifiability (also called prior, theoretical or qualitative identifiability): a set of parameters in a model structure is said to be structurally identifiable if the exact parameter values of the set can be uniquely determined in theory, assuming unlimited, noise-free observational data [55, 56, 57]. Structural identifiability is a quantitative property depending on the underlying model structure and initial conditions. It is independent of the quality and amount of available observation data. Examining structural identifiability of model structures is also important if the system parameters are endowed with physical significance.

Structural identifiability was introduced among the firsts by Bellman and Astrom in linear system theory [18]. They used the parameterized transfer function of the system as exhaustive summary in order to obtain necessary and sufficient conditions on structural identifiability. In the context of linear systems the similarity transformation approach is

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based on finding invertible transformations of the state space realization matrices [58]. Assuming joint observability and controllability, by Kalman's algebraic rank condition the similarity transformation approach provides necessary and sufficient conditions for structural identifiability. In the case of non-linear systems, deciding structural identifiability is computationally much more complicated. For uncontrolled autonomous systems the direct test approach provides a conceptually simple, but limited method by equating the system non-linearities of different parameterizations [59]. The similarity transformation based approach was extended to non-linear systems by means of the local state isomorphism theorem [60, 61]. For locally reduced systems (structural controllability and observability conditions have to be fulfilled), it seeks for state variable transformations and leads to solving a set of partial differential equations [62]. The Taylor series approach expands the model output in Taylor series around $t = 0$ [63]. The coefficients of the resulting power series are unique and provide an exhaustive summary for testing structural identifiability. Conceptually similar to the Taylor series based expansion, the generating series approach employs the Fliess series expansion of the observables [64]. The coefficients of the series, which are unique descriptors of the input-output behavior, are the Lie derivatives of the model output. Both Taylor series and generating series expansions provide sufficient conditions of structural identifiability, but the algebraic expressions obtained by the generating series approach are simpler [65, 66]. The differential algebra based approach reformulates the system equations so that the non-measured state variables are eliminated in order to obtain an equivalent set of differential algebraic equations containing only the model inputs, outputs and system parameters [17]. Elimination of unobserved variables can be performed by Ritt's pseudodivision algorithm [67]. The resulting set of equations is called the input-output map or characteristic set, which provides a Gröbner basis of the model equations [68]. Sufficient and necessary conditions on structural identifiability can be obtained by the characteristic set [17]. The implicit function theorem approach also eliminates the unobservable variables [69]. It determines a matrix composed of the derivatives of non-linearities with respect to the system parameters. Then structural identifiability testing translates to the non-singularity of the obtained matrix. Assuming constant input excitation, testing structural identifiability can be performed by means of the concept of non-linear observability [70, 71]. Viewing the constant parameters as state variables with zero dynamics, structural identifiability can be examined through the observability of the extended state vector involving the system parameters. Then identifiability can be examined through the rank of the extended non-linear observability matrix.

In practice several dynamical systems involve time delayed terms [72, 73, 74, 75, 76]. For example, metabolic regulatory networks may contain delayed signaling pathways, e.g. delayed feedback loops, which imply specific qualitative dynamical phenomena [77, 78, 79, 80]. Time delayed signals are also proven to be useful for controlling dynamics of

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biological networks [81]. Time delayed models are often employed to model the dynamical behavior of systems in population biology and epidemiology [72, 82]. Delayed terms are also used in models of chemical kinetics (e.g. if the dynamics is partially known or certain intermediates are omitted from the description for simplicity) [83, 84].

A related problem arising in modeling with time delayed differential equations is to examine the possibility of uniquely determining the constant delay parameters. Structural identifiability of time delayed systems – including the delays as parameters – has received less attention. Compared to ordinary system parameters, time delays appear implicitly in the inputs, outputs and internal state variables, which makes the respective identifiability problem more involved. Identifiability of delayed systems is typically analyzed in the context of dynamical systems of some specific structure. For linear time delayed systems sufficient condition on joint identifiability of ordinary parameters and delays can be obtained [86, 87]. Furthermore, it is shown that under sufficiently exciting input signal weak controllability provides sufficient and necessary condition for identifiability [88]. For linear retarded functional differential equations the unique identifiability of coefficients, delays and initial conditions were also examined, necessary and sufficient conditions for identifiability are available [85]. In case of non-linear systems, assuming constant integer time delays, identifiability was examined in [89], however, identifiability analysis was restricted to the ordinary parameters not including the delays. In [90] authors examined the class of non-linear systems with a single constant time delay and considered the identifiability problem of the delay parameter. It is shown that identifiability of the time delay parameter is a necessary condition of observability of state variables and identifiability of ordinary system parameters. The authors also showed that by state elimination, the resulting input-output relations can be used to decide identifiability of the delay parameter. Linear algebraic conditions are also obtained to eliminate explicit calculation of the input-output relations for testing identifiability. In [91] the case of delay identifiability in non-linear systems with unknown inputs was examined. The proposed approach is based on the deduction of an output-delay equation, which is proven to be related to identifiability. Assuming the existence of the output-delay equation, in the single delay case sufficient and necessary conditions were derived for delay identifiability. The results are shown to be necessary for the more general case of systems with multiple delays. For the class of kinetic systems (a subclass of non-negative polynomial systems) polynomial time algorithms were proposed for finding delayed system realizations with different parameterizations [J9]. This way an efficient computational method was obtained that can be employed to test (local) structural identifiability. However, the delays are assumed to be known, hence they cannot be involved in the identifiability analysis.

In this chapter a novel approach is proposed for testing structural identifiability of non-linear time delayed systems. It is assumed that in the model structure the non-linearities are analytic functions and the delays are constants. We consider the joint

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identifiability of the ordinary system parameters and the time delays. Making use of the Volterra series representation of non-linear systems, sufficient conditions are provided for structural identifiability. The generalized frequency response functions (GFRFs), i.e. the Fourier transforms of the Volterra kernel functions, are used to construct identifiability conditions. It is shown that structural identifiability of delayed systems can be traced back to the unique solution of a set of equations with respect to the ordinary system parameters and time delays.

2.3 Structural identifiability of time delayed systems

We consider a continuous SISO input-output dynamical system model

$$M(t, \theta, u, y, p) = 0, \tag{2.1}$$

where u and y are the input excitation and the respective output of the system. The signals u and y can involve arbitrary number of constant time delays, i.e.

$$\begin{aligned} u &= \Big\{u(t), u(t - T_1^u), \dots \ u(t - T_{k_u}^u)\Big\}, \\ y &= \Big\{y(t), y(t - T_1^y), \dots \ y(t - T_{k_y}^y)\Big\}, \end{aligned} \tag{2.2}$$

with k_u, k_y denoting the number of delayed components with respect to u and y, respectively. θ denotes the set of parameters, which includes the time delays

$$T_1^u, \dots T_{k_u}^u, T_1^y, \dots T_{k_y}^y \in \mathbb{R}_{\geq 0}.$$

θ is assumed to be independent of the initial conditions and the input signals. p denotes the differentiation operator. The system operator $M(.)$ is assumed to be analytic or it can be approximated with an arbitrary accuracy by polynomial systems. We note that the analytic assumption on $M(.)$ is not restrictive as it is satisfied by several important system classes, e.g. systems of polynomial non-linearities, which are widely used to model physical, chemical and biological systems. Throughout the chapter, we assume zero initial conditions for the system of in Eq. (2.1).

The input-output model structure defined by Eq. (2.1) may be obtained from non-linear state space models by differential algebraic elimination of unobserved state variables [17, 96].

Example 1. In order to illustrate the mapping $M(.)$ we use the following simple system model:

$$\dot{y}(t) = ay(t - T_1^y) + bu(t - T_1^u) + cy^3(t - T_2^y), \tag{2.3}$$

where $y^n(.)$ denotes the nth power of $y(.)$. The parameter vector is $\theta = \{a, b, c, T_1^u, T_1^y, T_2^y\}$,

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where $a,\ b$ and c are ordinary system parameters, while T_1^u , T_1^y and T_2^y are constant time delay parameters. In this particular case $M(.)$ takes the form

$$M(t,u,y,\theta,p) = \dot{y}(t) - ay(t-T_1^y) - bu(t-T_1^u) - cy^3(t-T_2^y). \tag{2.4}$$

Prior to any parameter estimation procedure performed on a model of E.q (2.1), it is useful to examine whether it is theoretically possible to uniquely determine the system parameters.

Definition 1. The model of Eq. (2.1) is said to be structurally globally identifiable (s.g.i.), if

$$y(t|\theta) = y(t|\hat{\theta}) \ \Rightarrow \ \theta = \hat{\theta} \tag{2.5}$$

for any admissible input and $t \geq 0$ and any measurable value of θ, where $y(t|\theta)$ denotes the output of the system Eq. (2.1) parameterized with θ.

If Eq. (2.5) is valid only in a bounded neighborhood $\mathcal{V}(\theta)$ of θ, then the system is said to be structurally locally identifiable (s.l.i.) around θ. If the system is not identifiable, it is called structurally unidentifiable (s.u.i.). If the identfiability definitions are restricted to a subset $\overline{\theta} \subset \theta$, then the respective parameters $\overline{\theta}$ are said to be s.g.i, s.l.i and s.u.i.

By involving the time delays in the parameter set θ, structural identifiability is considered jointly for the ordinary system parameters and the time delays.

Structural identifiability is a model property depending on the underlying model structure and initial conditions. It is independent of the amount and quality of data available about the system dynamics.

2.4 Input-output representation for identifiability analysis

2.4.1 Volterra series representation for non-linear input-output models

Here we provide the Volterra series representation for non-linear SISO system models. The equivalent frequency domain representation is also detailed which will be extensively used in the sequel for identifiability analysis.

The Volterra series representation of a dynamical system of the form of Eq. (2.1) can be written as [93]:

$$y(t) = y_0(t) + \sum_{i=1}^{\infty} y_i(t), \tag{2.6}$$

where $y_n(t)$ is the nth-order non-linearity, which is represented by a series of generalized

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convolutional integrals:

$$y_n(t) = \int_{-\infty}^{\infty} \dots \int_{-\infty}^{\infty} h_n(\tau_1, \dots \tau_n) \prod_{j=1}^{n} u(t - \tau_j) d\tau_j, \tag{2.7}$$

where $h_n(\tau_1, \dots \tau_n)$ is the nth-order Volterra kernel. $h_n(\tau_1, \dots \tau_n)$ is a so-called generalized impulse response function. Clearly, for a linear mapping $M(.)$, $h_1(\tau_1)$ is the impulse response function known from linear system theory [105]. Necessary and sufficient conditions for the existence of Volterra series representation of a non-linear dynamical system are derived in [94]. If all the non-linearities in Eq. (2.1) are analytic (e.g. polynomial systems) or can be approximated by polynomials with arbitrary precision, then the existence of input-output representation of the form Eq. (2.6) is guaranteed. Note that the introduction of time delays in the input and output does not affect the analytic property of the system model, hence Volterra series expansion is also available for time delayed systems [100].

The frequency domain description of non-linear systems through the Volterra series representation can be obtained by the multidimensional Fourier transformation of the Volterra kernels [95]:

$$H_n(j\omega_1, \dots j\omega_n) = \int_{-\infty}^{\infty} \dots \int_{-\infty}^{\infty} h_n(\tau_1, \dots \tau_n) e^{-j(\omega_1\tau_1 + \dots \omega_n\tau_n)} d\tau_1 \dots d\tau_n. \tag{2.8}$$

$H_n(j\omega_1, \dots j\omega_n)$ is called the n-order Generalized Frequency Response Function (GFRF) or simply the nth-order transfer function. Observe that for $n = 1$ $H_n(j\omega_1)$ is the known linear transfer function. Since $h_n(\tau_1, \dots \tau_n)$ and $H_n(j\omega_1, \dots j\omega_n)$ are related through the multi-variable Fourier transform, the n-order output can be expressed by the GFRFs:

$$y_n(t) = \frac{1}{(2\pi)^n} \int_{-\infty}^{\infty} \dots \int_{-\infty}^{\infty} H_n(j\omega_1, \dots j\omega_n) \prod_{k=1}^{n} U(j\omega_k) e^{j(\omega_1 + \dots + \omega_n)t} d\omega_k. \tag{2.9}$$

$h_n(.)$ and $H_n(.)$, $n \geq 1$ are independent of the input signal and they uniquely describe of the input-output behavior of underlying non-linear system [101, 102]. However, since the change of the order in the arguments $\tau_1, \dots \tau_n$ may result in different kernels without affecting the input-output behavior, $h_n(.)$ and $H_n(.)$ are not necessarily unique descriptors. Hence it is common to introduce the symmetrized GFRFs as follows:

$$H_n^{sym}(j\omega_1, \dots j\omega_n) = \frac{1}{n!} \sum_{\substack{all\ permutations \\ of \omega_1, \dots \omega_n}} H_n(j\omega_1, \dots j\omega_n). \tag{2.10}$$

The symmetric GFRFs are independent of the order of arguments and provide unique representation [100].

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2.4.2 Computation of the GFRFs

In this section computation of the GFRFs for SISO systems is reviewed using the harmonic probing method and the extraction operator [97, 98, 99]. Let us consider an arbitrary non-linear input-output dynamical system model

$$M(t, \theta, u, y, p) = 0, \tag{2.11}$$

for which a Volterra series representation of Eq (2.6) exists. Since the output of the system can be expressed by the GFRFs according to Eq. (2.9), Eq. (2.11) becomes

$$M(t, \theta, u, \mathcal{H}, p) = 0, \tag{2.12}$$

with $\mathcal{H} = \{H_n(j\omega_1, \ \dots j\omega_n)\}_{n\geq 1}$. Expressing $H_n(.)$ using Eq. (2.12) may lead to complicated integral equations, which make the problem computationally intractable. In order to remedy this problem, special input excitations can be employed. The harmonic probing technique applies a multi-tone input of R distinct frequency components:

$$u(t) = \sum_{i=1}^{R} e^{j\omega_i t}, \tag{2.13}$$

where $\omega_1, \dots \omega_R$ are arbitrarily chosen different frequencies. Then the respective Fourier transform $U(j\omega)$ is

$$U(j\omega) = \sum_{i=1}^{R} 2\pi\delta(j\omega - j\omega_r). \tag{2.14}$$

By applying the input Eq. (2.13) on the system Eq. (2.11), the output becomes

$$\begin{aligned} y(t) = \sum_{n=1}^{\infty} \sum_{r_1,\dots r_n=1}^{R} H_n(j\omega_{r_1}, \dots j\omega_{r_n}) e^{j(\omega_{r_1}+\dots+\omega_{r_n})t} = \\ \sum_{n=1}^{\infty} \sum_{\substack{[all\ combinations \\ of\ R\ frequencies \\ taken\ n\ at\ a\ time]}} \sum_{\substack{[all\ permutations \\ of\ \omega_{r_1},\dots\omega_{r_n}]}} H_n(j\omega_{r_1}, \dots j\omega_{r_n}) e^{j(\omega_{r_1}+\dots+\omega_{r_n})t} \end{aligned} \tag{2.15}$$

In order to determine $H_n(.)$, it is convenient to choose $n = R$ so that there is only one non-repetitive combination of frequencies $\{\omega_1, \dots \omega_R\}$. Then the nth-order output can be written as

$$y_n(t) = n! H_n^{sym}(j\omega_1, \dots j\omega_n) e^{j(\omega_1+\dots+\omega_n)t} + [terms\ of\ repetitive\ frequency\ components]. \tag{2.16}$$

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By substituting Eq. (2.13) and Eq. (2.15) into Eq. (2.11) one obtains

$$M(t, \theta, u(\Omega_R), \mathcal{H}) = 0, \tag{2.17}$$

where $u(\Omega_R)$ denotes the harmonic input of Eq. (2.13) and $\Omega_R = \{\omega_1, \dots \omega_R\}$ indicates the set of R distinct different frequency components. Since $M(t, \theta, u(\Omega_R), \mathcal{H})$ is a linear combination of distinct exponential basis functions, Eq. (2.17) is satisfied only with the trivial linear combination, i.e. all the coefficients of the exponential terms must be equal to zero. Then $H_n^{sym}(.)$ can be determined as the coefficient of the exponential term of the non-repetitive combination of the n distinct frequency components.

The harmonic probing technique is performed by means of the extraction operator $\varepsilon_n[.]$ [99].

Definition 2. The extraction operator $\varepsilon_n[f]$ on a differential algebraic expression f is defined by the following consecutive steps:

1. Substitute Eq. (2.13) and Eq. (2.15) (with $R = n$) to the given expression f.
2. Extract the coefficient of $e^{j(\omega_1 + \dots + \omega_n)t}$.

Clearly, the extraction operator $\varepsilon_n[.]$ returns the coefficient of the complex exponential basis function containing n distinct frequency components.

Making use of the extraction operator, the equation

$$\varepsilon_n[M(t, \theta, u, y, p)] = 0 \tag{2.18}$$

can be used to determine the nth-order GFRF $H_n(.)$.

We note that the discussed method is suitable for determining the GFRFs for non-linear time delayed system and recursive algorithms are also available for this purpose [100]. For a detailed explanatory computation of the GFRFs the Reader is refereed to [J1].

2.5 Testing structural identifiability with GFRFs

Making use of the generalized frequency response functions associated to a Volterra series representation, sufficient conditions for joint structural identifiability of ordinary system parameters and time delays can be derived in the form of algebraic equations. Compared to other series expansion based structural identifiability tests, the proposed method allows us for directly examining the identifiability of constant time delay parameters appearing in the model structure. This can be performed since the time delay parameters appear in the exponents of complex exponential functions in the GFRFs. From the exponents the delay parameters can be easily extracted.

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Assuming that the Volterra series representation exists for a dynamical system model $M(t, \theta, u, y, p) = 0$, the unique GFRFs provide us with an exhaustive summary:

$$s(\theta) = \left\{ H_k^{sym}(j\omega_1, \dots j\omega_k, \theta) \right\}_{k=1}^{\infty}, \tag{2.19}$$

where $H_k^{sym}(j\omega_1, \dots j\omega_k, \theta)$ denotes the parameterized GFRF of order k and θ stands for the set of parameters including time delays. Then testing structural identifiability translates to the following equations:

$$H_k^{sym}(j\omega_1, \dots j\omega_k, \theta) = H_k^{sym}(j\omega_1, \dots j\omega_k, \hat{\theta}), \quad \forall \omega_1, \dots \ \omega_k, \ k \geq 1. \tag{2.20}$$

Here $H_k^{sym}(.)$ is of the form of a fraction of complex exponential polynomials and we translate Eq. (2.20) to the equality of the nominator and denominator polynomials. Clearly, complex exponentials of different exponents are linearly independent of each other, which means that the existence of a particular exponent in one polynomial implies that an exponential function of the same exponent appears in the other polynomial [104]. Then the equality of exponential polynomials is equivalent to the equality of the respective coefficients. This way algebraic equations can be obtained for identifiability testing. Algebraic conditions on the time delay parameters are derived as the equality of the respective exponents.

Joint structural identifiability of ordinary parameters and time delays is equivalent to the unique solution of Eq. (2.20) with respect to θ. However, in general case $s(\theta)$ is composed of a countably infinite set of GFRFs, but in practice we are restricted to a finite set of $s(\theta)$. This way sufficient conditions for structural identifiability can be derived. Formally, if the relation

$$H_k^{sym}(j\omega_1, \dots j\omega_k, \theta) = H_k^{sym}(j\omega_1, \dots j\omega_k, \hat{\theta}), \ k \leq K \Longrightarrow \theta = \hat{\theta} \tag{2.21}$$

holds for some $K \in \mathbb{N}$, then the parameters θ are structurally globally identifiable. Clearly, if the above relation holds for a subset $\overline{\theta} \subset \theta$, the subset $\overline{\theta}$ is s.g.i.

Proposition 1. Let us consider a SISO dynamical system model $M(t, \theta, u, y, p)$. Assuming that $M(.)$ is an analytical function, sufficient condition of structural identifiability is obtained by the GFRFs as follows

$$H_k^{sym}(j\omega_1, \dots j\omega_k, \theta) = H_k^{sym}(j\omega_1, \dots j\omega_k, \hat{\theta}), \ k \leq K \Longrightarrow \theta = \hat{\theta} \tag{2.22}$$

for any $K \in \mathbb{N}$, $K > 0$.

Proof. Since $H_k^{sym}(j\omega_1, \dots j\omega_k, \theta)$ is unique for any $k \geq 0$, any feasible parametrization $\hat{\theta}$ satisfies

$$H_k^{sym}(j\omega_1, \dots j\omega_k, \theta) = H_k^{sym}(j\omega_1, \dots j\omega_k, \hat{\theta}), \ k \leq K \tag{2.23}$$

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for arbitrary $K \in \mathbb{N}$. The number of equations of the form Eq. (2.23) to be satisfied by a feasible parametrization $\hat{\theta}$ is infinitely countable, hence by a finite subset of K equations sufficient conditions can be obtained. □

Clearly, if Eq. (2.20) holds in a finite subset of the parameter space, then sufficient conditions for local structural identifiability are derived.

If the model structure under study is proven to be weakly non-linear (i.e. a finite number of non-zero GFRFs exist), then the proposed approach provides sufficient and necessary conditions for structural identifiability and structural non-identifiability of model parameters can also be determined.

We note that the proposed method can be viewed as an extension of the transfer function approach applied for identifiability analysis of linear time invariant systems [18]. If the system under study is linear, then the Volterra series expansion is composed of a single kernel function and the associated GFRF coincides with the frequency response function known form linear system theory. It is clear that constant time delay parameters appear explicitly in the exponents of the linear frequency response function. Since $s(\theta)$ involves only a one-dimensional function $H(j\omega)$, Eq. (2.20) reduces to a necessary and sufficient condition.

We also indicate the relation to the generating series approach. It is based on the Fliess functional series expansion of non-linear systems. In this case an exhaustive summary is obtained as the coefficients of Fliess series expansion, which are the Lie derivatives of the output signals. It can be shown that the Volterra series expansion is a reordering of the Fliess decomposition [92, 103].

2.6 Examples

In this section we provide examples for structural identifiability testing of time delayed non-linear model structures. First the GFRFs are determined using the harmonic probing technique along with the extraction operator. Then structural identifiability of parameters (including time delays) are assessed trough the equations Eq. (2.20).

Note that $H_k^{sym}(.)$ is a fraction of sums of complex exponential basis functions. We formulate structural identifiability of the system parameters as the equality of the coefficients of the complex exponential basis functions of the same exponents and identifiability of time delay parameters is algebraically expressed as the equality of the respective exponents.

1. *Duffing oscillator with time delay*

   As a biologically motivated dynamic input-output model we consider the Duffing oscillator, which is used for modeling EEG time series data [106]. The model is

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equipped with a time delayed term according to [100]. The differential equation model describing the delayed Duffing oscillator is as follows:

$$\ddot{y}(t) + k_1\dot{y}(t) + k_2\dot{y}(t-T) + c_1 y(t) + k_3 y^3(t) = bu(t), \tag{2.24}$$

where $T \in \mathbb{R}$ denotes a constant time-delay parameter. The parameter set of the above system is $\theta = \{k_1, k_2, k_3, b, c_1, T\}$.

In order to decide whether the parameters in θ are structurally identifiable, first the GFRFs are computed based on the harmonic probing technique. The GFRFs provide a set of algebraic equations in the system parameters so that the uniqueness of the solution is sufficient condition of structural identifiability.

The first GFRF $H_1^{sym}(j\omega)$ can be determined by applying the input signal

$$u(t) = e^{j\omega_1 t}. \tag{2.25}$$

Then the respective system output – according to Eq. (2.15) – becomes

$$y(t) = H_1(j\omega_1)e^{j\omega_1 t} \tag{2.26}$$

Applying the extraction operator $\varepsilon_1[.]$ on the system Eq. (2.25) involves substituting the input and the output into the system, and extracting the coefficient of $e^{j\omega_1}$. Then $H_1^{sym}(j\omega_1)$ can be obtained by solving the equation

$$\varepsilon_1[M(t, \theta, u, y, p)] = 0, \tag{2.27}$$

where

$$M(t, \theta, u, y, p) = \ddot{y}(t) + k_1\dot{y}(t) + k_2\dot{y}(t-T) + c_1 y(t) + k_3 y^3(t) - bu(t) \tag{2.28}$$

For the first order GFRF we obtain

$$H_1^{sym}(j\omega_1) = \frac{b}{(j\omega_1)^2 + k_1(j\omega_1) + k_2(j\omega_1)e^{-j\omega_1 T} + c_1} \tag{2.29}$$

The above solution of $H_1^{sym}(j\omega_1)$ provides the following equations for structural identifiability analysis:

$$\begin{gathered} b = \hat{b} \\ (j\omega_1)^2 + k_1(j\omega_1) + c_1 = (j\omega_1)^2 + \hat{k}_1(j\omega_1) + \hat{c}_1 \\ k_2(j\omega_1)e^{-j\omega_1 T} = \hat{k}_2(j\omega_1)e^{-j\omega_1 T} \end{gathered} \tag{2.30}$$

Clearly, b and c_1 are structurally globally identifiable. Depending on T two cases

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can be distinguished. If $T = 0$, then it follows that

$$k_1 + k_2 = \hat{k}_1 + \hat{k}_2, \tag{2.31}$$

i.e. k_1 and k_2 are not structurally identifiable. If $T \neq 0$, then k_1, k_2 and T are structurally globally identifiable. Note that the identifiability of k_3 cannot be analyzed via $H_1(j\omega_1)$, since it does not account for higher order non-linearities, but k_3 is the coefficient of a 3rd-order term in Eq. (2.25).

Since Eq. (2.25) has no 2nd-order non-linearities, $H_2^{sym}(j\omega_1, j\omega_2)$ is absent.

To determine $H_3^{sym}(j\omega_1, j\omega_2, j\omega_3)$, the input according to the harmonic probing technique is of the form

$$u(t) = e^{j\omega_1 t} + e^{j\omega_2 t} + e^{j\omega_3 t}. \tag{2.32}$$

Applying $u(t)$ along with the extraction operator $\varepsilon_3[.]$ on the system Eq. (2.25) results in the 3rd-order GFRF as follows:

$$H_3^{sym}(j\omega_1, j\omega_2, j\omega_3) = \frac{-k_3 H_1(j\omega_1)H_1(j\omega_2)H_1(j\omega_3)}{(j\omega_1 + j\omega_2 + j\omega_3)^2 + (k_1 + k_2 e^{(j\omega_1 + j\omega_2 + j\omega_3)T})(j\omega_1 + j\omega_2 + j\omega_3) + c_1}. \tag{2.33}$$

The above equation of $H_3^{sym}(.)$ implies

$$k_3 = \hat{k}_3, \tag{2.34}$$

from which it follows that k_3 is structurally globally identifiable and therefore the model is globally structurally identifiable with respect to the whole parameter vector θ if the delay is non-zero.

2. *Non-linear state space model with multiple time delays*

Let us consider the following non-linear delayed system model

$$\begin{aligned} \dot{x}_1(t) &= [\theta_1 x_2(t) + 1]u(t - \tau_1) - \theta_2 x_1(t), \\ \dot{x}_2(t) &= \theta_3 x_1(t), \\ y(t) &= \theta_4 x_2(t) + \theta_5 y(t - \tau_2), \end{aligned} \tag{2.35}$$

with θ_i, $i = 1, \ldots 4$ are ordinary parameters and τ_1, τ_2 are constant time delays. We wish to decide whether the system is structurally identifiable with respect to $\theta = \{\theta_1, \theta_2, \theta_3, \theta_4, \tau_1, \tau_2\}$.

Since Eq. (2.35) involves unobserved state variables, they must be eliminated in order to obtain an equivalent input-output relation containing the parameters θ.

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Such an input-output representation can be obtained by differential algebraic manipulations of the state space model.

We extended the equations with further derivatives

$$\begin{aligned}
\dot{x}_1(t) &= [\theta_1 x_2(t) + 1]u(t-\tau_1) - \theta_2 x_1(t), \\
\dot{x}_2(t) &= \theta_3 x_1(t), \\
y(t) &= \theta_4 x_2(t) + \theta_5 y(t-\tau_2) \\
\ddot{x}_1(t) &= \theta_1 \dot{x}_2 u(t-\tau_1) + \theta_1 x_2(t)\dot{u}(t-\tau_1) + \dot{u}(t-\tau_1) - \theta_2 \dot{x}_1(t) \\
\ddot{x}_2(t) &= \theta_3 \dot{x}_1(t) \\
\dot{y}(t) &= \theta_4 \dot{x}_2(t) + \theta_5 \dot{y}(t-\tau_2) \\
\ddot{y}(t) &= \theta_4 \ddot{x}_2(t) + \theta_5 \ddot{y}(t-\tau_2)
\end{aligned} \tag{2.36}$$

Then Eq. (2.36) involves 7 equations from which the state variables and their derivatives (6 unobserved variables) should be algebraically eliminated. In this example elimination was performed by Mathematica, the resulted input-output model associated to Eq. (2.35) is as follows:

$$\begin{aligned}
&-\theta_3\theta_4 u(t-\tau_1) + \theta_1\theta_3\theta_5 u(t-\tau_1)y(t-\tau_2) - \theta_2\theta_5\dot{y}(t-\tau_2) - \\
&\theta_5\ddot{y}(t-\tau_2) + \theta_2\dot{y}(t) + \ddot{y}(t) - \theta_1\theta_3 u(t-\tau_1)y(t) = 0
\end{aligned} \tag{2.37}$$

Now we can examine structural identifiability of θ based on the GFRFs associated to Eq. (2.37). First the harmonic probing method is employed to determine the first GFRFs.

For $H_1(j\omega_1)$ we have

$$H_1(j\omega_1) = \frac{\theta_3\theta_4 e^{-j\omega_1\tau_1}}{(j\omega_1)^2 + (j\omega_1)^2\theta_5 e^{-j\omega_1\tau_2} + \theta_2(j\omega_1) - \theta_2\theta_5(j\omega_1)e^{-j\omega_1\tau_2}} \tag{2.38}$$

From the nominator we obtain the following equation

$$\theta_3\theta_4 e^{-j\omega_1\tau_2} = \hat{\theta}_3\hat{\theta}_4 e^{-j\omega_1\hat{\tau}_2}. \tag{2.39}$$

Clearly, complex exponential basis functions are linearly independent, that is

$$\tau_1 = \hat{\tau}_1, \tag{2.40}$$

and τ_1 is structurally globally identifiable. Then it also holds that

$$\theta_3\theta_4 = \hat{\theta}_3\hat{\theta}_4, \tag{2.41}$$

from which the structural identifiability of θ_3 and θ_4 does not follow.

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From the denominator of $H_1(j\omega_1)$ we have

$$\begin{aligned}(j\omega_1)^2 + (j\omega_1)^2\theta_5 e^{-j\omega_1\tau_2} + \theta_2(j\omega_1) - \theta_2\theta_5(j\omega_1)e^{-j\omega_1\tau_2} = \\ (j\omega_1)^2 + (j\omega_1)^2\hat{\theta}_5 e^{-j\omega_1\hat{\tau}_2} + \hat{\theta}_2(j\omega_1) - \hat{\theta}_2\hat{\theta}_5(j\omega_1)e^{-j\omega_1\hat{\tau}_2}\end{aligned} \tag{2.42}$$

There are two different cases. If $\tau_2 = 0$, then the following equations hold for the ordinary parameters:

$$\begin{aligned}\theta_5 &= \hat{\theta}_5, \\ \theta_2 - \theta_2\theta_5 &= \hat{\theta}_2 - \hat{\theta}_2\hat{\theta}_5,\end{aligned} \tag{2.43}$$

from which we have that θ_5 is s.g.i. Regarding θ_5 there are two different cases. If $\theta_5 \neq 1$, then s.g.i of θ_2 is guaranteed, otherwise it is not necessarily s.g.i.

If $\tau_2 \neq 0$, then the linear independence of complex exponentials implies that $\tau_2 = \hat{\tau}_2$, i.e. τ_2 is s.g.i. and the following set of equations are arising:

$$\begin{aligned}(j\omega_1)^2 + \theta_2(j\omega_1) &= (j\omega_1)^2 + \hat{\theta}_2(j\omega_1), \\ (j\omega_1)^2\theta_5 - \theta_2\theta_5(j\omega_1) &= (j\omega_1)^2\hat{\theta}_5 - \hat{\theta}_2\hat{\theta}_5(j\omega_1),\end{aligned} \tag{2.44}$$

from which it can be seen that θ_2 and θ_5 are s.g.i.

In order to examine the identifiability of the remaining parameters let us consider the 2nd order GFRF:

$$H_2^{sym} = \frac{-\theta_1\theta_3\theta_5 H_1(j\omega_2)e^{-j\omega_1\tau_1} - \theta_1\theta_3\theta_5 H_1(j\omega_1)e^{-j\omega_2\tau_1} + \theta_1\theta_3 H_1(j\omega_2)e^{-j\omega_1\tau_1} + \theta_1\theta_3 H_1(j\omega_1)e^{-j\omega_2\tau_1}}{-\theta_2\theta_5 2!e^{-j(\omega_1+\omega_2)\tau_2}j(\omega_1+\omega_2) - \theta_5 2!e^{-j(\omega_1+\omega_2)\tau_2} + \theta_2 2!j(\omega_1+\omega_2) + 2![j(\omega_1+\omega_2)]^2} \tag{2.45}$$

Clearly, the structure of the denominator of $H_2(j\omega_1, j\omega_2)$ is equivalent to that of $H_1(j\omega)$, hence it does not provide us with further information on identifiability of parameters. The nominator gives rise to the following equations for identifiability testing:

$$-\theta_1\theta_3\theta_5 + \theta_1\theta_3 = -\hat{\theta}_1\hat{\theta}_3\hat{\theta}_5 + \hat{\theta}_1\hat{\theta}_3, \tag{2.46}$$

which cannot be used to prove identifiability of θ_1 and θ_3. Hence the 2nd-order GFRF does not provide further insight into parameter identifiability.

Finally, based on the 1st-and 2nd-order symmetrized GFRFs, using the proposed approach we obtained structural identifiability for a subset of parameters. We note that higher order GFRFs may provide further insight into the identifiability of system parameters.

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2.7 Summary

In this chapter a novel approach is introduced to examine joint structural identifiability of ordinary system parameters and constant time delays in non-linear dynamical system models. The systems under study are assumed to be of the form of input-output models in which all the non-linearities are analytic functions and the time delays are constants. From a practical point of view, the analytic assumption on the non-linearities is not restrictive, for example it involves the class of polynomial systems, which is widely used to model the dynamical behavior of complex physical, chemical and biological processes. We also note that there is no constraint on the number of different delay parameters.

We employed the Volterra series representation of non-linear dynamical systems. In order to test structural identifiability, the GFRFs, i.e. the Fourier transforms of the Volterra kernels were used. The GFRFs have the advantageous property of containing explicitly the time delay parameters of input and output signals. Since the symmetrized GFRFs are unique, they can be used to construct an exhaustive summary of the underlying dynamic input-output model structure. Based on the GFRFs, we derived equations of complex exponential polynomials which are suitable to examine parameter identifiability. Unique solution of the obtained equations with respect to some parameters implies parametric uniqueness, this way sufficient condition of structural identifiability of the respective parameters is guaranteed. Furteher property of the GFRF-based approach is that structural identifiability can be examined regardless of the input signals.

We illustrated the proposed method on time delayed non-linear system models. Among the provided examples we treated the case of non-linear state space models with unobserved state variables. Since the Volterra series modeling assumes input-output model structure, first we performed differential algebraic manipulations to eliminate unobserved variables. This way an equivalent input-output model structure can be obtained that contains all the parameters. In the provided example the resulting input-output representation was suitable to prove structural identifiability of a subset of the parameters by means of the proposed method.

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3 Computing different realizations of linear dynamical systems

3.1 Mathematical notations

Θ	parameters of a state space model, formally $\Theta = (A, B, C, D)$
A^d	notation of dense state transition matrix
A^s	notation of sparse state transition matrix
M	state feedback matrix, $M \in \mathbb{R}^{n \times n}$ where n is the dimension of the state vector

Table 3.1: Notations specific to chapter 3.

3.2 Background

Many problems in computer science and engineering involve sequences of real-valued multivariate observations. It is commonly assumed that observed quantities are correlated with some underlying latent (state) variables that are evolving over time. Assuming linear dependencies among the latent states and the observed variables leads us to linear dynamical systems. The application of linear systems is ubiquitous, ranging from dynamical systems modeling to time series analysis, including econometrics, meteorology, telecommunication, biomedical signal processing [8, 9].

The aim of system identification is to construct parametrized models of dynamical systems by observing their input-output trajectories [10, 11]. Estimating the parameters of linear dynamical systems is often solved by maximum likelihood method along with expectation maximization or numerical optimization [12, 13, 14, 15, 16]. Though the underlying mathematical representation of linear systems is simple, since the associated optimization problem to be solved is generally non-convex, estimating their parameters could be a computationally complicated task and efficient algorithms with theoretical guarantees are obtained only in restricted cases [15]. A related problem, structural identifiability examines the theoretical problem of whether it is possible to uniquely determine the model parameters, assuming perfect observational data [17, 18, 58]. It turns out that even in the case of linear dynamical systems, the underlying parameters may not be uniquely determined, i.e. different parametrizations of the same model structure may

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provide us with the same dynamical behavior. The structural identifiability of delayed non-linear input-output models is discussed in chapter 2.

Assuming linear dependence of the underlying state variables and outputs, the Markov parameters provide relationship between input-output data and state space realizations. Determining the Markov parameters of linear dynamical systems from input-output data is one of the fundamental problems of linear system identification. The difficulty with Markov parameter estimation from observations is that generally a large number of Markov parameters are required to precisely quantify the dynamical behavior, especially in the case of lightly damped systems. To remedy this problem the eigenvalue assignment procedure can be employed which reformulates the linear state equation in an equivalent closed-loop form [27, 28, 29]. If the closed-loop representation can be achieved by a stabilizing output feedback, then the number of distinct non-zero closed-loop Markov parameters is guaranteed to be finite and the respective input-output behavior of the system can be written in the form of a simple ARX model which can be easily identified. The system Markov parameters from that of the closed-loop system can be uniquely computed by means of an iterative procedure [27].

Once Markov parameters are obtained, one needs to recover the underlying state space model parameters of the observed system. Realization algorithms aims at determining the parameters of state space models from the identified Markov parameters. The first realization algorithm, known as the Ho-Kalman algorithm, computes the singular value decomposition (SVD) of the Hankel matrix. Using the SVD the observability and controlability matrices of the system can be determined [19, 20]. Then these can be used to compute state space matrices. Assuming that only a finite N_0 number of Markov parameters are given, the problem arising is called partial realization problem which can be solved by the Ho-Kalman algorithm: a minimal state space realization from the block Hankel matrix is constructed so that the first N_0 Markov parameters are equal to the prescribed ones [21]. The Eigensystem Realization Algorithm (ERA) extends the Ho-Kalman algorithm [22]. ERA constructs a minimal realization that mimics the output of the system when subjected to unit pulse input. In order to better handle noise and structural non-linearities an extension of ERA was also proposed which is called as ERA with data correlation (ERA/DC) [23]. General Realization Algorithm (GRA) extends the ERA by singular value decomposition of a weighted Hankel matrix which is constructued by explicitly using the input data. If the exciting signal is an impulse signals, GRA is reduced to ERA.

One can observe a growing interest in both quantitative and qualitative examination of the underlying interconnected structure of dynamical systems [33, 34, 35, 36, 37]. There is a growing importance of large scale distributed engineering systems, such as power grids, distributed computing networks and intelligent transportation networks that are composed of smaller functional subunits. The underlying interconnected structure

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of state variables attracted much attention in the context of physico-chemical systems such as chemically interacting species composing systems biological networks: gene regulatory networks, protein-protein interaction networks, metabolic networks and signal transduction pathways [39, 40]. Analyzing the locally connected structure of social networks could help us understand how viruses and information spread across the population [38, 45, 46, 47]. Subsystems, functional units are locally connected to each other according to some physical interaction topology encoded by their differential equation based description. The distributed, locally connected structure of dynamical systems poses important requirements towards efficient computational approaches, e.g. distributed controller synthesis methods over traditional centralized control algorithms [24, 25].

For kinetic systems – a class of non-negative polynomial systems having applications in modeling biochemical processes – it is known that a weighted directed graph structure can be associated. The graph contains information about the state variables and parameters of the system, this way encodes the functional interaction patterns of the components (state variables). It has been shown that in case of structural non-identifiability, different dynamically equivalent realizations may lead to structurally non-unique interaction patterns of the components [30, 31, J9], i.e. the same dynamical behavior is provided by different interaction topologies. The weighted directed graph topology is encoded in the form of a column conservation matrix, called Kirchhoff matrix, which takes part in formulation of the coefficient matrices of the associated polynomial differential equations. It has been shown that the feasible set of Kirchoff matrices associated to a particular kinetic system is convex. This result is extensively used to propose convex optimization based algorithms capable of determining structurally different realizations of kinetic systems so that they can also take into account convex parametric uncertainties and time delays [30, 31, J9].

In the context of linear dynamical systems the state transition matrix has the role of encoding the underlying interconnected topology of state variables. Structural non-identifiability of the entries in the state transition matrix may have important implication on the pattern of interaction topology of the variables: there may exist structurally different state transition matrices – i.e. different interconnected topologies of the state variables – providing the same Markov parameter sequence, i.e. input-output relation. Note that structural identifiability refers to the property of unique parameter identifiability of a system, while the structure of a state transition matrix means the non-zero patterns of the off-diagonal entries in the matrix.

In this chapter we investigate realizability and structural properties of discrete time linear (time invariant) dynamical systems (DT-LDS). We examine structural implications of non-unique realizability on the interaction pattern of the state variables as they are encoded in the state transition matrix. We examine the non-uniqueness of state transition matrix of DT-LDSs. Assuming fixed input matrix B and invertible observation matrix

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C we prove that the feasible set of system matrices formulate a convex set. We devote particular attention to DT-LDSs of state transition matrices that are constrained to be of Metzler property. This constraint involves important linear systems, e.g. multi-agent system models and social networks [26, 49, 50]. Using the eigenvalue assignment procedure we formulate a convex optimization based procedure that can be efficiently employed to find different realizations of DT-LDSs. Assuming the Metzler property and making use of the convexity of the feasible set of system matrices we provide algorithms capable of determining structurally different dynamically equivalent state space realizations.

3.3 Mathematical preliminaries and problem formulation

A discrete time linear dynamical system (DT-LDS) in state space representation is given by a tuple $\Theta = (A, B, C, D)$ and the associated system of difference equations (DEs) is as follows:

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k), \quad x(0) = x_0, \\ y(k) &= Cx(k) + Du(k), \end{aligned} \tag{3.1}$$

where $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{n\times n}$ and $D \in \mathbb{R}^{n\times m}$. $x(k) \in \mathbb{R}^n$ denotes the vector of state variables, $u(k) \in \mathbb{R}^m$ and $y(k) \in \mathbb{R}^n$ are the input and the associated output of the system.

Though the solution associated to a particular parametrization Θ and initial condition x_0 is unique, the parameters characterizing the underlying dynamics are not necessarily. There may exist distinct Θ, Θ' parametrizations of the same input-output behavior meaning that the system is not structurally identifiable. In order to make the chapter self-contained, here we define again structural identifiability in the context of DT-LDSs.

Definition 3. A system of the form of Eq. (3.1) is said to be structurally (globally) identifiable, if for any admissible input $u(k)$ and $k \geq 0$ we have that

$$y(k|\Theta_1) = y(k|\Theta_2) \;\Rightarrow\; \Theta_1 = \Theta_2,$$

where $y(k|\Theta)$ denotes the output of the system Eq. (3.1) parametrized by Θ.

If the condition of structural identifiability does not hold, the system is said to be structurally non-identifiable.

In case of structural non-identifiability, in order to quantitatively characterize the system, it is appealing to describe the feasible set of possible parameters. A quantitative characterization of the feasible set may help us finding realizations of favorable properties, such as sparsity.

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Definition 4. It is said that a tuple $\Theta' = (A', B', C', D')$ is a (dynamically equivalent) realization of a DT-LDS of the form Eq. (3.1) parametrized by Θ, if Θ' provides the same input-output behavior, i.e. $y(k|\Theta') = y(k|\Theta)$ for any admissible input signal $u(k)$, $k \geq 0$.

By recursively expanding Eq. (3.1) one can obtain the input-output equations – a common starting point of system identification – of the following form:

$$y(k) = CA^k x(0) + \sum_{i=0}^{k-1} Y_{k-i-1} u(i) + Du(k), \tag{3.2}$$

where the terms $Y_{k-i-1} = CA^{k-i-1}B$ and D are called the Markov parameters of the systems which are unique descriptors of the input-output behavior and are invariant to any invertible state transformations. Since Markov parameters are unique regarding the input-output behavior, we can formulate sufficient and necessary condition of dynamical equivalence with respect to the Markov parameters as follows: a tuple $\Theta' = (A', B', C', D')$ is a dynamically equivalent realization of $\mathcal{Y} = \{Y_k = CA^kB\}_{k\geq 0}$, if it satisfies $Y_k = C'A'^kB'$ for $k \geq 0$ and $D' = D$.

A related problem of structural non-identifiability of DT-LDSs is the existence of distinct, A, $A' \in \mathbb{R}^{n\times n}$ state transition matrices having different patterns in their non-zero entries, i.e. structurally different state transition matrices. Assuming that Eq. (3.1) describes the dynamical behavior of a network-based system, the state transition matrix A can be viewed as a weighted adjacency matrix characterizing the interactions – in terms of both the interaction pattern and the magnitudes – among the components, i.e. state variables [26]. Such a way structural non-uniqueness of a network topology can be recast as an identification problem, namely finding structurally different n-dimensional state space realizations.

In this work we concerned with the existence of different DT-LDS realizations and focus on the non-uniqueness and structure of the feasible state transition matrices.

Assumptions: throughout this chapter it is assumed that a DT-LDS is given by a state space realization $\Theta = (A, B, C, D)$ and the matrices B, C and D are fixed over all the dynamically equivalent realizations of interest. We set $C \in \mathbb{R}^{n\times n}$ to be invertible. Regarding the initial condition we assume $x(0) = 0^n$.

By fixing the matrices B, C and D we explicitly restrict our attention to dynamically equivalent realizations with different system matrices, but fixed input and output patterns. This is particularly important in the context of network-based dynamical systems where different state transition matrices incorporate distinct interaction patterns of the system components. We note that the invertibility of C covers the case of fully observable state variables.

Making use of the Markov parameter based description together with the above assumptions, the following constraint set can be employed in order to express dynamical

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equivalence of different realizations:

$$CA^kB = CA'^kB, \quad k \geq 0. \tag{3.3}$$

One difficulty with respect to the above constraint set is that generally we have a countably infinite set of Markov parameters $\mathcal{Y} = \{Y_k\}_{k\geq 0}$ implying infinitely many constraints of the from Eq. (3.3). On the other hand, the terms CA'^kB are non-linear and are not convex in the entries of A' – even for stable systems of nilpotent state transition matrices – which could easily make the identification problem computationally intractable.

In this chapter the identifiability of the above defined class of DT-LDSs is studied. Since the B and C state space realization matrices are fixed, structural identifiability is restricted to the state transition matrix A. We wish to quantitatively characterize the feasible set of state transition matrices in the studied class of DT-LDSs. We also address the problem of determining structurally different n-dimensional realizations of a DT-LDS given by a particular initial state space realization Θ.

3.4 Embedding eigenvalue assignment procedure

In this section a static full-output feedback based approach is used for stabilizing a DT-LDS and constructing a compressed set of closed-loop Markov parameters. The procedure detailed here is known as embedding eigenvalue procedure and applied in DT-LDS identification to recover the Markov parameters [27, 28].

Let us take a DT-LDS of Eq. (3.1). By taking an arbitrary $M \in \mathbb{R}^{n\times n}$ we can reformulate Eq. (3.1) as follows:

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) + My(k) - My(k) \\ y(k) &= Cx(k) + Du(k). \end{aligned} \tag{3.4}$$

Then for the state equation we have

$$x(k+1) = (A + MC)x(k) + (B + MD)u(k) - My(k). \tag{3.5}$$

Let us introduce the following matrices and new input variable

$$\overline{A} = A + MC, \tag{3.6}$$

$$\overline{B} = [B + MD, \ -M], \tag{3.7}$$

$$v(k) = [u(k) \ y(k)]^\top. \tag{3.8}$$

Then the state space model Eq. (3.1) can be reformulated in the following equivalent

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form:

$$\begin{aligned} x(k+1) &= \overline{A}x(k) + \overline{B}v(k) \\ y(k) &= Cx(k) + Du(k). \end{aligned} \tag{3.9}$$

Now by recursively expanding Eq. (3.9) the input-output behavior can be expressed as

$$y(k) = C\overline{A}^k x(0) + \sum_{i=0}^{k-1} C\overline{A}^{i-1}\overline{B}v(k-i) + Du(k). \tag{3.10}$$

If M can be chosen so that $\overline{A} = A + MC$ is a stability matrix, then for the Markov parameters asympthotically we have

$$\lim_{i\to\infty} C\overline{A}^i\overline{B} = 0 \tag{3.11}$$

In this case, Eq. (3.10) can be approximated as

$$y(k) \approx \sum_{i=0}^{p-1} C\overline{A}^{i-1}\overline{B}v(k-i) + Du(k) \tag{3.12}$$

for a suitably high $p \in \mathbb{N}$. In particular, if $A + MC$ is set to be nilpotent, then $(A + MC)^n = 0^{n\times n}$ holds. Note that such a stabilizing M matrix exists, if the system Eq. (3.1) is observable [27]. Such a way the countable set of Markov parameters $\mathcal{Y} = \{CB,\ CAB,\ CA^2B,\ \dots\}$ is compressed to a finite set

$$\overline{\mathcal{Y}} = \{C\overline{B},\ C\overline{AB},\ C\overline{A}^2\overline{B},\ \dots\ C\overline{A}^{n-1}\overline{B}\}. \tag{3.13}$$

For the compressed Markov parameters we introduce the notation $\overline{Y}_k = C\overline{A}^k\overline{B}$.

It can be shown that the system Markov parameters $\mathcal{Y}$ can be uniquely recovered from that of the closed-loop system $\overline{\mathcal{Y}}$ of Eq. (3.9) as follow: [27, 28]:

$$Y_k = \overline{Y}_k^{(1)} + \sum_{i=0}^{k-1} \overline{Y}_i^{(2)} Y_{k-i-1} + \overline{Y}_k^{(2)} D, \quad k \geq 1, \tag{3.14}$$

where

$$\overline{Y}_k = C\overline{A}^k\overline{B} = \begin{bmatrix} C(A+MC)^k(B+MD) & -C(A+MC)^kM \end{bmatrix} = \begin{bmatrix} \overline{Y}_k^{(1)} & \overline{Y}_k^{(2)} \end{bmatrix} \tag{3.15}$$

for $k \geq 1$.

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3.5 Representing different realizations using a compressed set of Markov parameters

In this section we show that dynamic equivalence of n-dimensional DT-LDS realizations can be traced back to a finite set of linear equations. We make use of the eigenvalue assignment procedure, such a way instead of a countably infinite set of Markov parameters $\mathcal{Y}$ one can consider a compressed set of n Markov parameters $\overline{\mathcal{Y}}$ of a (stabilized) closed-loop system. By an inductive proof a linear reformulation of the non-convex equations of Eq. (3.3) is provided. We also show the existence of a bijection between the original state space realizations and the closed-loop system realizations.

Making use of the embedding eigenvalue assignment procedure we can obtain a finite set of compressed system descriptors $\overline{\mathcal{Y}} = \{\overline{Y}_k\}_{k=0}^{n-1}$ which is unique with respect to the closed-loop system. Finding different realizations of $\overline{\mathcal{Y}}$ can be recast in the form of a finite set of non-linear equations:

$$C\overline{A'}^k\overline{B} = C\overline{A}^k\overline{B}, \quad k = 1, \ \dots n. \tag{3.16}$$

Note that the nilpotency of $\overline{A}$ implies that the nth equation is equivalent to $C\overline{A'}^n\overline{B} = 0^{n\times(n+m)}$, furthermore, the invertability of C means that $C\overline{A'}^k\overline{B} = 0^{n\times(n+m)}$ for $k \geq n$.

Eq. (3.16) together with $C\overline{A'}^n\overline{B} = 0^{n\times(n+m)}$ provide us with a finite set of constraints to be satisfied by all the dynamically equivalent realizations $(\overline{A'}, \overline{B}, C, D)$ of $\overline{\mathcal{Y}}$. However, Eq. (3.16) contains high non-linearities in $\overline{A'}$ which makes the identification problem non-convex and computationally intractable.

Proposition 2. Let us consider a DT-LDS of Markov sequence $\mathcal{Y}$ with a state space representation $\Theta = (A, B, C, D)$. Assume that $\exists C^{-1}$. Then we have that

$$CA^kB = CA'A^{k-1}B, \ k \geq 1 \tag{3.17}$$

holds for any feasible n-dimensional realization $\Theta' = (A', B, C, D)$ of $\mathcal{Y}$.

Proof. Let us assume that $\Theta' = (A', B, C, D)$ is a dynamically equivalent realization of $\mathcal{Y}$ we have that

$$CA^kB = CA'^kB, \ k \geq 0.$$

For $k = 1$

$$CAB = CA'B = CA'A^0B.$$

By induction assume that for some $k > 1$ the equation $CA^kB = CA'^kB$ holds. Then

$$CA^{k+1}B = CA'^{k+1}B = CA'A'^kB = CA'C^{-1}CA'^kB = CA'C^{-1}CA^kB = CA'A^kB.$$

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□

Making use of Proposition 2 the constraint set defined by Eq. (3.3) can be equivalently reformulated as $CA^kB = CA'A^{k-1}B$ for $k \geq 0$ which are linear in A'. Similarly one can formulate a finite set of linear constraints for the closed-loop system:

$$C\overline{A}^k\overline{B} = C\overline{A'A}^{k-1}\overline{B}, \quad k = 1, \ \dots \ n \tag{3.18}$$

By equipping Eq. (3.18) with a linear objective function $c : \mathbb{R}^{n\times n} \mapsto \mathbb{R}$, we result in a linear program of the decision variables A', e.g.:

$$\begin{cases} min_{\overline{A'}} \ c(\overline{A'}) \\ subject \ to \\ C\overline{A}^k\overline{B} = C\overline{A'A}^{k-1}\overline{B}, \ k = 1, \ \dots \ n \end{cases} \tag{3.19}$$

Such a way a computational model is provided to determining dynamically equivalent realizations $(\overline{A}, \overline{B}, C, D)$ of the closed-loop system $\overline{\mathcal{Y}} = \{C\overline{A}^k\overline{B}\}_{k=1}^n$. Furthermore, the feasible set of solutions of the linear program (3.19) provides all the dynamically equivalent realizations of $\overline{\mathcal{Y}}$. We note that in the optimization problem (3.19) the decision variables are the entries of the matrix A', i.e. the number of decision variables is n^2 where n is the dimension of the system.

Now it can be shown that the resulted closed-loop state transition matrix $\overline{A'}$ can be used to reconstruct an n-dimensional realization of the open loop system Eq. (3.1) described by the initial countable set of Markov parameters.

Proposition 3. Let us consider a closed-loop DT-LDS $\overline{\mathcal{Y}}$ with a state space representation $\overline{\Theta} = (\overline{A}, \overline{B}, C, D)$ so that $\overline{A}^n = 0^{n\times n}$, $\overline{A} = A + MC$ and $\overline{B} = [B + MD, -M]$ for some $A, M \in \mathbb{R}^{n\times n}$ and $B \in \mathbb{R}^n$. Assume that there exists $\overline{A'} \in \mathbb{R}^{n\times n}$, $\overline{A'} \neq \overline{A}$ so that

$$C\overline{A}^k\overline{B} = C\overline{A'}^k\overline{B}, \ k = 1, \dots n,$$

i.e. $\overline{\Theta'} = (\overline{A'}, \overline{B}, C, D)$ is a dynamically equivalent realization of $\overline{\mathcal{Y}}$. Then $\Theta' = (A', B, C, D)$ is a dynamically equivalent realization of $\mathcal{Y} = \{CA^kB\}_{k\geq 0}$, where $A' = \overline{A'} - MC$.

Proof. For the sake of convenience we introduce the following notations

$$\begin{aligned} &Y_k(A) = CA^kB, \quad \overline{Y}_k(A) = C\overline{A}^k\overline{B}, \\ &\overline{Y}_k^{(1)}(A) = C(A + MC)^k(B + MD), \quad \overline{Y}_k^{(2)}(A) = -C(A + MC)^kM \end{aligned}$$

to emphasize the dependence on a particular A. Eq. $C\overline{A}^k\overline{B} = C\overline{A'}^k\overline{B}$ implies that $\overline{Y}_k^{(1)}(A) = \overline{Y}_k^{(1)}(A')$ and $\overline{Y}_k^{(2)}(A) = \overline{Y}_k^{(2)}(A')$ hold for $k \geq 1$. Since $Y_0 = CB$ does not depend on the state transition matrix, applying recursively Eq. (3.14) for $k \geq 1$ we

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obtain that $Y_k(A) = Y_k(A'),\ k \geq 0$, i.e. $\Theta' = (A', B, C, D)$ is a dynamically equivalent realization of $\mathcal{Y}$. □

3.6 The geometrical structure of the set of feasible system matrices

In this section we consider the set of feasible n-dimensional system matrices. We prove that for fixed B, C and D parameters, the set of feasible system matrices with respect to any $\mathcal{Y}$ Markov sequence is convex. The set of feasible system matrices is denoted as follows:

$$\mathcal{A}(\mathcal{Y}, B, C, D) = \Big\{ A \;\Big|\; A \in \mathbb{R}^{n\times n},\ (A, B, C, D) \text{ is a realization of } \mathcal{Y} = \{Y_k\}_{k\geq 0} \Big\}. \quad (3.20)$$

Proposition 4. Let us consider a countable sequence of Markov parameters $\mathcal{Y}$ realizable by a state space realization (A, B, C, D) of order n and denote $\mathcal{A}(\mathcal{Y}, B, C, D)$ the set of feasible n-dimensional system matrices as it is defined by Eq. (3.20). Assume that C is invertible. Then $\mathcal{A}$ is convex.

Proof. Let us consider two matrices $A_1, A_2 \in \mathbb{R}^{n\times n}$ so that (A_1, B, C, D) and (A_2, B, C, D) are realizations of $\mathcal{Y}$. From Proposition 2 it follows that for any $a \in (0, 1)$

$$\begin{aligned} &CA^kB = aCA^kB + (1-a)CA^kB = \\ &aCA_1A^{k-1}B + (1-a)CA_2A^{k-1}B = C\Big(aA_1 + (1-a)A_2\Big)A^{k-1}B, \quad k \geq 1 \end{aligned} \quad (3.21)$$

In the sequel for the sake of convenience we use the notation $\hat{A} = aA_1 + (1-a)A_2$.

Now by induction we prove that $CA^kB = C\hat{A}^kB$ for $k \geq 1$.

For $l = 1$ we have

$$CAB = C\Big(aA_1 + (1-a)A_2\Big)B.$$

Using the inductive assumption $CA^lB = C\hat{A}^lB$ for general l we obtain that

$$\begin{aligned} &CA^{l+1}B = C\hat{A}A^lB = C\hat{A}C^{-1}CA^lB = \\ &C\hat{A}C^{-1}C\hat{A}^lB = C\hat{A}^{l+1}B \end{aligned}$$

We have that any convex combination $aA_1 + (1-a)A_2$ results in a feasible state space realization $(aA_1 + (1-a)A_2, B, C, D)$ of the Markov sequence $\mathcal{Y}$. □

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3.7 Characterizing structurally different system realizations

In this section we consider realizations of special structure in their state transition matrices. The off-diagonals are constrained to be non-negative. State transition matrices having non-negative off-diagonal entries are particularly important when the purpose is to model networks of interacting components: non-zero off-diagonal entries could represent the magnitude of interactions while negative diagonals may incorporate to information or mass leakage. Positive systems – in which all the entries of the state transition matrix are constrained to be non-negative – compose a widely-studied class of linear time invariant systems with the above structural properties [41]. Discrete time linear compartmental models – having many applications in modeling biological systems – also satisfy the above non-negativity condition [42, 43]. Social networks provide an important application field of modeling discrete time dynamical systems defined on networks [45, 46, 47, 48]. The DeGroot and Friedkin-Johnsen models are well-known discrete time linear models of opinion dynamics and information spreading in networks where the off-diagonal entries of state transition matrices are also constrained to be non-negative [49, 50].

Formally, for a Markov sequence $\mathcal{Y}$ we restrict our attention to realizations $\Theta = (A, B, C, D)$ so that A is Metzler, i.e. $[A]_{ij} \geq 0$ for $i \neq j$. Then the feasible set of state transition matrices can be defined as follows:

$$\mathcal{A}^p(\mathcal{Y}, B, C, D) = \left\{ A \;\middle|\; [A]_{ij} \geq 0 \text{ for } i, j = 1, \ \dots \ n, \ i \neq j, \ (A, B, C, D) \text{ is a realization of } \mathcal{Y} \right\}, \tag{3.22}$$

where the superscript p refers to the fact that we will be concerned with the positive off-diagonal entries. Note that the convexity of $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ is guaranteed as a corollary of Proposition 4 which can be seen as follows. For any $A_1, A_2 \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$, the convex combination $aA_1 + (1-a)A_2$ with $a \in (0, 1)$ is a feasible state transition matrix in $\mathcal{A}(\mathcal{Y}, B, C, D)$. Since a convex combination is a linear combination with non-negative coefficients, the sign of the off-diagonal entries remain non-negative, i.e. $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ is convex.

Now with respect to the set $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ we identify matrices having distinguished structural properties and show how they relate to all the other feasible state transition matrices.

In order to ease the discussion of structural properties state transition matrices, we introduce a simple graph-based description of DT-LDSs with state transition matrices of Metzler-type using the analogy of influence graphs in the literature of positive systems [41]. Considering a state transition matrix $A \in \mathbb{R}^{n \times n}$, the associated directed graph representation $G(A) = (E, V)$ is defined as follows. V, the set of nodes corresponds to the set of states of the associated DT-LDS. E, the set of edges represents the influences

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between state variables, i.e. $(i,j) \in E$ if and only if $[A]_{ij} > 0$. Such a way $G(A)$ provides a unique description of the structure of A.

In the sequel the term structure of a state transition matrix $A \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ refers to the structure (topology) of the associated directed graph representation $G(A)$ as it is defined above.

Definition 5. Let us consider a DT-LDS $\mathcal{Y}$ with fixed $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{n\times n}$ and $D \in \mathbb{R}^{n\times m}$. A matrix $A \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ is called dense (sparse) state transition matrix if it contains the maximal (minimal) number of non-zero off-diagonal entries. Then the associated realization $\Theta = (A, B, C, D)$ is said to be a dense (sparse) realization.

Definition 6. Let us consider a DT-LDS $\mathcal{Y}$ with fixed $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{n\times n}$ and $D \in \mathbb{R}^{n\times m}$. A state transition matrix $A \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ is said to have superstructure property, if its graph representation $G(A)$ contains the graph representations of all other feasible Metzler system matrices as subgraphs, formally $G(A') \subseteq G(A)\ \forall A' \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$.

It can be shown that a dense realization provides a superstructure with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$.

Proposition 5. Let us consider a DT-LDS of Markov parameters $\mathcal{Y}$ with fixed $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{n\times n}$ and $D \in \mathbb{R}^{n\times m}$ state space realization matrices. Any dense state transition matrix $A^d \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ is of superstructure property.

Proof. Assume that there exists a dense state transition matrix $A^d \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ so that A^d has no superstructure property. Then it follows that there exists a state transition matrix $A \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ for which there is an index-pair (i,j), $i \neq j$ so that $[A]_{ij} > 0$, but $[A^d]_{ij} = 0$. The convexity of $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ guarantees that for any $a \in (0,1)$ the resulted matrix $A' = aA + (1-a)A^d$ provides a dynamically equivalent realization with non-negative off-diagonal entries, i.e. $A' \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$. Such a way we obtained a state transition matrix A' having more non-zero off-diagonal entries, than A^d has, which is contradiction. □

Corollary 1. Let us consider a Markov sequence $\mathcal{Y}$. For any $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{n\times n}$ and $D \in \mathbb{R}^{n\times m}$, there exists a structurally unique state transition matrix A^d having maximal number of non-zero off-diagonal entries with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$.

3.8 Computational framework for finding structurally different realizations

In this section first we assume a state space realization $\Theta = (A, B, C, D)$ so that its respective Markov parameter sequence $\mathcal{Y}$ is of finite-length, i.e. $CA^kB = 0^{n\times m}$, $k \geq p$

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for some finite p. Examining the realizability of finite-length Markov sequences can be motivated by a partial realization problem or realizability analysis of stable and damping systems having only a finite number of non-zero Markov parameters [27, 44].

Algorithms for determining structurally different realizations of DT-LDS with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ are provided. Making use of the convexity of $\mathcal{A}^p(\mathcal{Y}, B, C, D)$, we adopt algorithms proposed for mass action law kinetic systems and show that structurally different realizations regarding the feasible set of Metzler system matrices $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ can be efficiently obtained [30]. We prove that a dense state transition matrix A^d in $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ can be computed in polynomial time using a convex optimization based procedure. Then it can be also shown that all the structurally different realizations of $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ can be determined by iteratively computing constrained dense realizations.

Finally we show that using the eigenvalue assignment procedure, the proposed algorithms can be extended to compute structurally different realizations of DT-LDSs of arbitrary Markov parameter sequences.

3.8.1 Algorithm for computing dense realization

Here we provide an algorithm capable of finding a dense realization with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ in polynomial time, given that $\mathcal{Y}$ is a finite sequence. The correctness of the algorithm follows from the convexity of $\mathcal{A}^p(\mathcal{Y}, B, C, D)$. First we define a subroutine denoted by **FindRealization** in order to determine feasible state transition matrices.

FindRealization:$\Big(\Theta = (A, B, C, D), L, H\Big)$: returns a tuple (A', P) so that $A' \in \mathbb{R}^{n\times n}$ is a feasible state transition matrix of Metzler-type, i.e. $A' \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$, and the objective function $\sum_{(i,j)\in H} [A']_{ij}$ is maximized by A', where H is a set of index pairs. L denotes a set of index pairs so that $[A']_{ij} = 0$, if $(i, j) \in L$. Formally, A' is obtained as the solution of the following linear program:

$$\begin{cases} max_{A'} \sum\limits_{(i,j)\in H} [A']_{ij} \\ subject\ to \\ CA^kB = CA'A^{k-1}B,\ k = 1,\ \dots\ p \\ [A']_{ij} = 0,\ (i, j) \in L \end{cases} \tag{3.23}$$

The optimization problem 3.23 is employed to find a dense dynamically equivalent realization. Algorithm **FindDenseRealization** 1 makes use of the convexity of the set of feasible state transition matrices. It computes a finite series of realizations by consecutively running **FindRealization** 3.23 with different constraints encoded by L. Note that L encodes the entries to be zero in the results returned by the optimization of **FindRealization**.

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Algorithm 1 FindDenseRealization
Input: $\Theta = (A, B, C, D), L$
Output: *Result*

$H \leftarrow \{1, \ldots, n^2 - n\}$
$P \leftarrow H$
$A^d \leftarrow \mathbf{0}^{n \times n}$
$loops \leftarrow 0$
while TRUE **do**
    $(A', P) \leftarrow$ FindRealization$(\Theta = (A, B, C, D), L, H)$
    if $P \neq \emptyset$ **then**
        BREAK
    end if
    $A^d \leftarrow A^d + A'$
    $H \leftarrow H \setminus P$
    $loops \leftarrow loops + 1$
end while
if $A_d \neq \mathbf{0}^{n \times n}$ **then**
    $A^d \leftarrow \frac{A^d}{loops}$
    return A^d //*Result* is a dense realization.
else
    return -1 //There is no feasible realization.
end if

Proposition 6. The state transition matrix A^d returned by algorithm **FindDenseRealization**$(\Theta = (A, B, C, D), L)$ provides a dynamically equivalent realization $\Theta' = (A', B, C, D)$ of the DT-LDS with Markov parameters $\mathcal{Y} = CA^kB$, $k = 1, \ldots p$. Furthermore, A^d is dense among all the state transition matrices in $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ satisfying the zero-constraints defined by L. A^d is computed in polynomial time.

3.8.2 Algorithm for computing all structurally different realizations

Here we describe an algorithm capable of determining all structurally different realizations of any DT-LDS $\Theta = (A, B, C, D)$ with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$, given that $\mathcal{Y} = \{CA^kB\}_{k=0}^p$ with $p > 0$ finite. Making use of Algorithm **FindDenseRealization** described in the previous section, the proposed computational method iteratively finds constrained dense realizations. Such a way all distinct structure can be obtained.

Assuming a fixed ordering of the state variables, we introduce the notation $\mathcal{R}$ to denote the set of binary sequences of length $(n \times n) - n$ encoding the structure of non-zero off-diagonal patterns of the system matrices. The i'th entry of $R \in \mathcal{R}$ is denoted by $R[i]$. An edge e is in the graph $G(A)$ iff there exists an index $i \in \Big\{1 \ \ldots \ |E(G(A))|\Big\}$ for which

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$e = e_i$ and $R[i] = 1$. We use z to denote the length of the sequence.

We introduce the array $Exist$ of $2^{|\mathcal{R}|}$ binary variables such that $Exist[R] = 1$ iff there exists a dynamically equivalent realization encoded by the sequence $R \in \mathcal{R}$.

A stack S is employed to temporarily store tuples of the form (R, k) with $R \in \mathcal{R}$ and $k \in \mathbb{N}$. The command 'push (R, k) into S' pushes the tuple (R, k) into S, while 'pop from S' returns the last tuple (R, k).

We say that the binary relation $=_k$ holds between the sequences $R, W \in \mathcal{R}$ ($R =_k W$) if for $i = 1 \ \ldots \ k$, $R[i] = W[i]$. The equivalence class of the relation $=_k$ for which R is a representative element is denoted by $C_k(R)$. Note that for an equivalence class more representative elements may exist.

The following subroutines are employed in the algorithm:

1. **FindDenseRealizationSequence**$(\Theta = (A, B, C, D), R, k, i)$: computes a dense state transition matrix A^d with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$, given a sequence $R \in \mathcal{R}$ and $k, i \in \mathbb{N}$. It returns a feasible state transition matrix $A \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ and the associated binary sequence $W \in \mathcal{R}$ so that $W =_k R$ and for every $W[j] = 0$ for $j = k + 1, \ \ldots \ i$. If such a reaction does not exist returns -1.

   Note that **FindDenseRealizationSequence** can be implemented by means of **FindDenseRealization**.

2. **FindNextOne**(R, k) returns the smallest index i for which $k < i$ and $R[i] = 1$. If $R[i] = 0$ for all $k < i$ then it returns $z+1$ where z denotes the length of the sequence encoding the graph structures.

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Algorithm 2 FindAllRealizations
Inputs: $\Theta = (A, B, C, D)$
Output: $Exist$

```
D ← FindDenseRealization(Θ = (A, B, C, D), ∅)
push (D, 0) into S
Exist[D] ← 1
while size(S) > 0 do
    (R, k) ← pop from S
    i ← FindNextOne((R, k))
    if i < z then
        push (R, i) into S
    end if
    while i < z do
        (A', W) ← FindDenseRealizationSequence(Θ = (A, B, C, D), R, k, i)
        if W < 0 then
            BREAK
        else
            i ← FindNextOne(W, i)
            Exist[W] ← 1
            if i < z then
                push (W, i) into S
            end if
        end if
    end while
end while
```

Proposition 7. Algorithm **FindAllRealizations**$(\Theta = (A, B, C, D))$ determines all structurally different dynamical equivalent state transition matrices of a DT-LDS given by $\Theta = (A, B, C, D)$ with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$, provided that $\mathcal{Y} = \{CA^kB\}_{k=0}^{p}$ for some finite $p > 0$.

3.8.3 Extension to arbitrary DT-LDS

This section extends the aforementioned results in order to find structurally different realizations of arbitrary DT-LDS. We consider a DT-LDS $\Theta = (A, B, C, D)$ so that there are no constraints on $\mathcal{Y} = \{CA^kB\}_{k\geq 0}$. The invertability of C implies that the pair (A, C) is observable, that is the eigenvalue assignment procedure can be employed. Then there exists $M \in \mathbb{R}^{n\times n}$ so that $\overline{A} = A + MC$ is nilpotent, i.e. $\overline{A}^n = 0$.

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Consider the linear program

$$\begin{cases} max_{\overline{A'}} \sum\limits_{(i,j)\in H} [\overline{A'}]_{ij} \\ subject\ to \\ C\overline{A}^k B = C\overline{A'A}^{k-1}B,\ k=1,\ \dots\ n \\ [\overline{A'}]_{ij} \geq [M]_{ij},\ i,j=1,\ \dots n,\ i \neq j \\ [\overline{A'}]_{ii} \leq [M]_{ii},\ i=1,\ \dots\ n \\ [\overline{A'}]_{ij} = 0,\ (i,j) \in L \end{cases} \tag{3.24}$$

Given a solution $\overline{A'}$ of the linear program Eq. (3.24), Proposition 3 guarantees that $A' = \overline{A'} - MC$ provides a dynamically equivalent realization of the system $\Theta = (A, B, C, D)$ and $A' \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$. Now we replace the linear program of Eq. (3.23) with Eq. (3.24) in **FindRealization** so that it returns (A', P) where $A' + MC = \overline{A'}$ is the solution of Eq. (3.24) and P is as it is defined above. Then we have that the resulted algorithms **FindDenseReal** and **FindAllRealizations** determine a set of matrices $\mathcal{A}$ for which $\mathcal{A} \ominus MC$ defines a set of structurally different realizations of $\Theta = (A, B, C, D)$. For each $\overline{A'} \in \mathcal{A}$, we have that $(A' - MC) \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$. This way structurally different realizations with Metzler-type state transition matrices of a DT-LDS – of arbitrary Markov sequence – can be computed.

3.9 Computational examples

In this section we provide examples to illustrate structural non-uniqueness of the non-zero off-diagonal patterns of state transition matrices associated to a Markov sequence $\mathcal{Y}$. By some simple linear dynamical system models we show that the set of feasible state transition matrices $\mathcal{A}(\mathcal{Y}, B, C, D)$ is not necessary unique and structurally different dynamically equivalent realizations can be computed. Throughout the section we restrict our attention to realizations with system matrices of Metzler-type.

In each example, first the system is stabilized by a full-state feedback M using the algorithm of [32] in order to obtain a closed-loop system of the form of Eq. (3.9) with a finite sequence of non-zero Markov parameters $\overline{\mathcal{Y}}$. In Example 3.9.1 Algorithm 1 and 2 are employed to determine all the structurally different realizations with respect to $\mathcal{A}^p(\overline{\mathcal{Y}}, \overline{B}, C, D)$. Then Proposition 3 guarantees that structurally different realizations of the open-loop system $\mathcal{Y}$ can be recovered by subtracting M from the closed-loop system matrices. Example 3.9.2 illustrate the structural non-uniqueness of a social network equipped with a linear dynamical behavior. Indirect sparsity and density constraints are employed in order to find different realizations.

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3.9.1 Example 1

Let us consider the following system

$$A = \begin{bmatrix} -2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & -2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & -2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{3.25}$$

$$B = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{3.26}$$

C is an $(n \times n)$-dimensional identity matrix and $D = 0^n$.

In order to employ the proposed method, first we need to determine a full-output feedback matrix $M \in \mathbb{R}^{11\times 11}$ so that the resulting matrix $(A + MC)$ is nilpotent. A full-output feedback M is obtained by the algorithm [32]. This way we obtain a system with finite sequence of non-zero Markov parameters $\overline{\mathcal{Y}}$. Then using Algorithm 2 we determined all the structurally different closed-loop system matrices in $\mathcal{A}^p(\overline{\mathcal{Y}}, \overline{B}, C, D)$. Finally, a set of structurally different state transition matrices with respect to $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ is computed by $\mathcal{A}^p(\overline{\mathcal{Y}}, \overline{B}, C, D) \ominus M$.

The dense dynamically equivalent realization returned by **FindDenseRealization** is depicted in Eq. (3.27).

Figure 3.1 depicts the number of structurally different realizations as the function of the number of non-zero off-diagonal entries in the state transition matrix. Table 3.2 provides a set of structurally different realizations in $\mathcal{A}^p(\overline{\mathcal{Y}}, \overline{B}, C, D)$ as they are determined in the above described way.

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$$A^d = \begin{bmatrix} -2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & -2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & -2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 100 & 100 & 100. & -100 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & -100 & 100 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 100 & -100 \end{bmatrix} \tag{3.27}$$

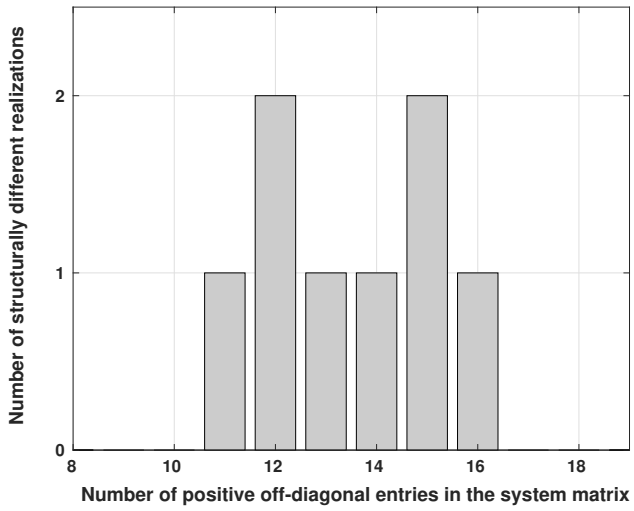

Figure 3.1: Structural non-uniqueness of feasible system matrices A associated to dynamically equivalent state space realizations.

3.9.2 Example 2

The Zachary karate club network is a widely studied social network representing the interactions of 34 members outside a Karate club [51]. Here we study the information flow across the network equipped with a particular weighted directed edge set as it is depicted in Figure 3.2. The weighted directed edges can be uniquely encoded in the form of an adjacency matrix $A \in \mathbb{R}^{34\times 34}$, assuming a fixed ordering of the nodes, i.e. state variables. For the entries of A see Appendix A. With the chosen edge directions we wish to simulate the information flow from the direction of the first node, i.e. x_1 (source) to the last nodes, x_{33} and x_{34} (sinks).

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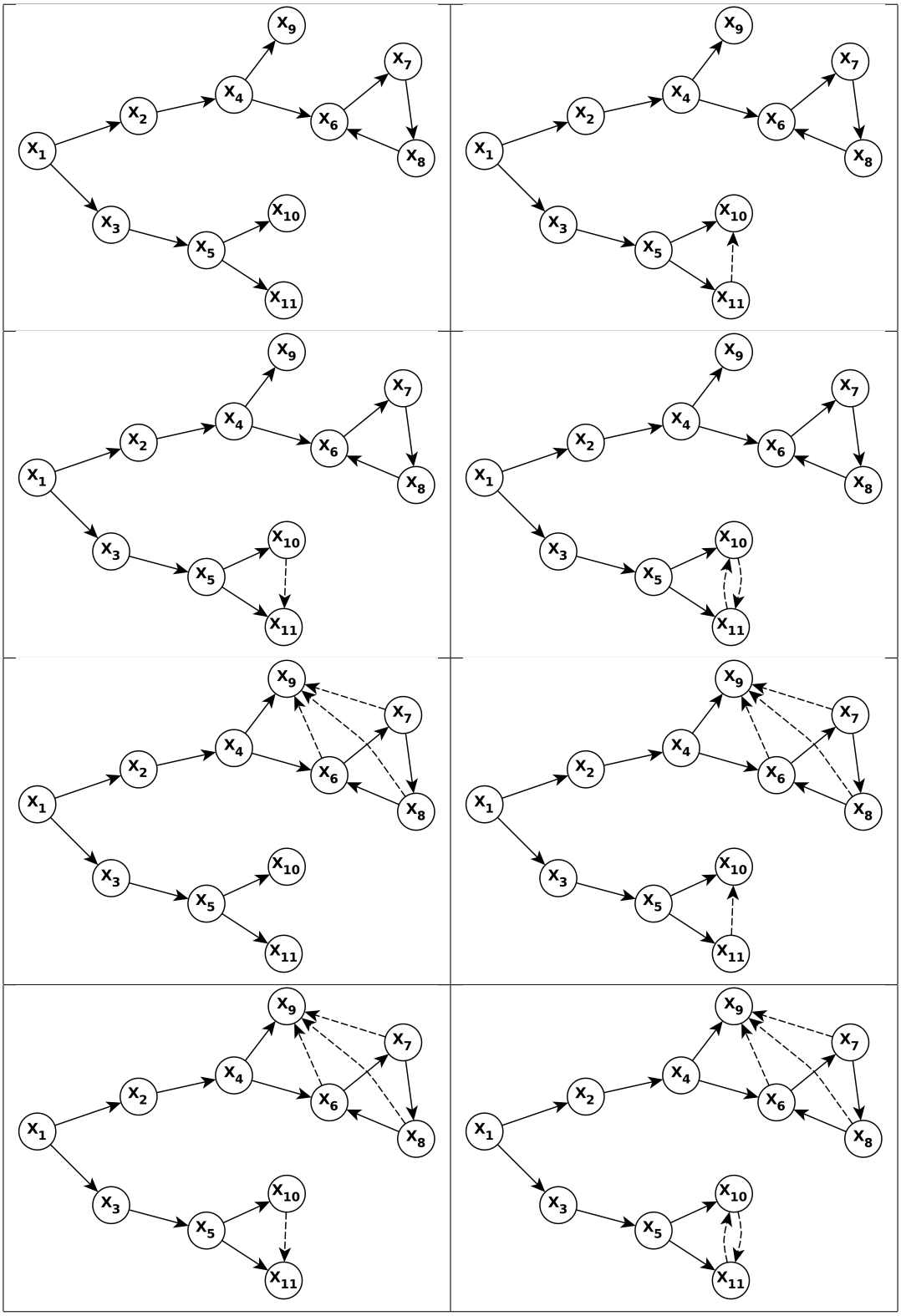

Table 3.2: Graph representations of all the structurally different state transition matrices computed by **FindAllRealizations**. Non-zero entries which are not contained in the initial realization are denoted by dashed lines.

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We make use of the adjacency matrix A of the network to define the dynamics of information flow over the nodes and formulate a simple DT-LDS of the from Eq. (3.1). The adjacency matrix A defines the state transition matrix, $[A]_{ij} > 0$ iff there is direct information flow from node j to node i. $B \in \mathbb{R}^{34}$ is set to be zero for all the entries except for the first one which is equal to 1, i.e. $[B]_1 = 1$ and $[B]_i = 0$ for $i = 2, \ \dots \ 34$. This way we can examine how an input signal $u(k) \in \mathbb{R}$, $k \geq 0$ – perturbing the state of the first node – propagates along all the other nodes. $C \in \mathbb{R}^{34\times 34}$ is the identity matrix, i.e. we assume that all the state variables are observable. $D = 0^{34}$. The state variable vector $x(t) \in \mathbb{R}^{34}$, $t \geq 0$ encodes the information content of the state variables. We assume that $x(0) = 0^{34}$.

Starting with the above defined state space model $\Theta = (A, B, C)$, first we performed the eigenvalue assignment procedure. A matrix $M \in \mathbb{R}^{34\times 34}$ is determined so that the resulting $\overline{A} = A + M$ be nilpotent. This way a stabilized closed-loop system $\overline{\Theta} = (\overline{A}, \overline{B}, C)$ – having at most 34 non-zero Markov parameters – is obtained, where $\overline{B} = [B, \ -M]$. In order to find a dynamically equivalent realization of the stabilized system $\overline{\Theta}$ with Metzler-type state transition matrix and sparsity constraint, we solved the following optimization procedure

$$\begin{cases} \max \sum\limits_{\substack{i,j=1 \\ i\neq j}}^{34} \left| [\overline{A'}]_{ij} \right| \\ \textit{subject to} \\ C\overline{A}^k B = C\overline{A'}\overline{A}^{k-1} B, \ k = 1, \ \dots \ 34 \\ [\overline{A'}]_{ij} \geq [M]_{ij}, \ i, j = 1, \ \dots 34, \ i \neq j \\ [\overline{A'}]_{ii} \leq [M]_{ii}, \ i = 1, \ \dots \ 34 \end{cases} \tag{3.28}$$

where the entries of $\overline{A'}$ correspond to the decision variables. Denoting the solution of (3.28) by $\overline{A^s}$, Proposition 3 guarantees that $\hat{A}^s = \overline{A^s} - M$ provides a dynamically equivalent realization of the initial system. The obtained realization $(\hat{A}^s, B, C)$ has 78 non-zero off-diagonal entries and its graph representation $G(\hat{A}^s)$ is isomorph to that of the initial state transition matrix $G(A)$. Next a dense realization $(\overline{A^d}, \overline{B}, C)$ is computed with respect to the closed-loop system $\overline{\Theta}$ using Algorithm 1. Proposition 3 guarantees that $\hat{A}^d = \overline{A^d} - M$ determines a dynamically equivalent realization with respect to the initial system Θ. We found that the obtained state transition matrix $\hat{A}^d$ contains 451 non-zero off-diagonal entries. The obtained matrices $\hat{A}^s$ and $\hat{A}^d$ are illustrated in Figure 3.3.

Since $[\overline{A^s}]_{ij} \geq [M]_{ij}$ and $[\overline{A^d}]_{ij} \geq [M]_{ij}$ hold for $i, j = 1, \ \dots \ 34$, $i \neq j$, the state transition matrices $\hat{A}^s$ and $\hat{A}^d$ are of Metzler-type. Furthermore, $[\overline{A^s}]_{ij} = [M]_{ij}$ and $[\overline{A^d}]_{ij} = [M]_{ij}$ for $i \neq j$ imply that $[\hat{A}^s]_{ij} = 0$ and $[\hat{A}^d]_{ij} = 0$, respectively, i.e. $G(\overline{A^s})$ and $G(\overline{A^d})$ are isomorph to $G(\hat{A}^s)$ and $G(\hat{A}^d)$, respectively. Such a way we can put indirectly sparsity and density constraints to state transition matrices of DT-LDS having arbitrary Markov parameters. However, it is important to note that the resulted state transition

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matrices $\hat{A}^s$ and $\hat{A}^d$ are not proved to be sparse and dense with respect to the initial system Θ, i.e. there may exist dynamically equivalent realizations having less or more non-zero off-diagonal entries, respectively.

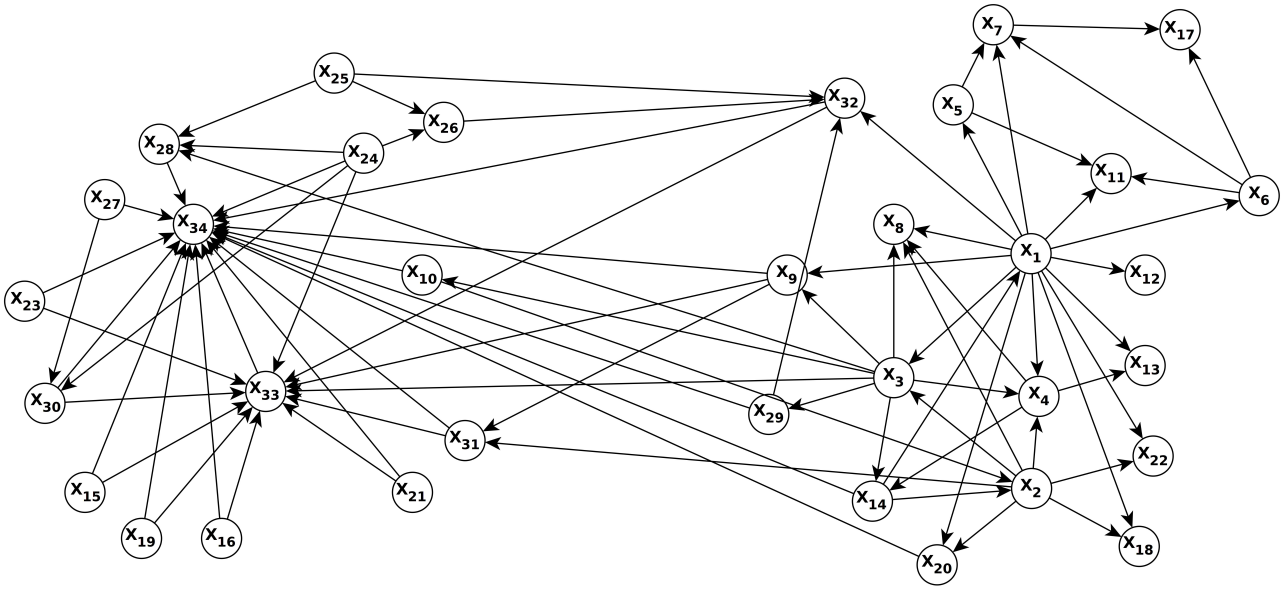

Figure 3.2: Illustration of Zachary's karate club network with a particular directed edge set.

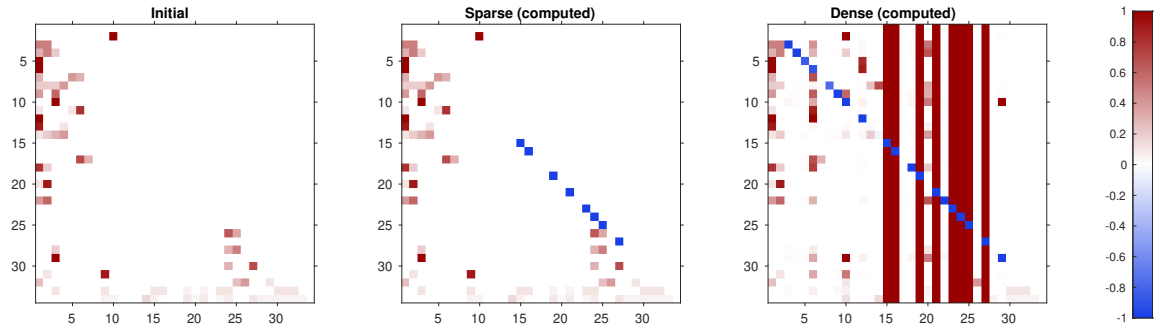

Figure 3.3: Graphical representation of state transition matrices associated to different realizations. **Initial:** the initial state transition matrix A. **Sparse (computed):** the state transition matrix $\hat{A}^s$ computed by posing l_1 sparsity constraints on the off-diagonal entries (i.e. decision variables). **Dense (computed)**: the state transition matrix $\hat{A}^d$ obtained by Algorithm 1. Note that the initial and sparse matrices are equivalent in terms of the pattern of their non-zero off-diagonal entries, i.e. $G(A)$ and $G(\hat{A}^s)$ are isomorphic graphs. We emphasize that sparsity, as a structural property, is understood with respect to the off-diagonal entries. The existence of structurally different state transition matrices implies that the same information propagation dynamics can emerge in structurally different networks.

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3.10 Summary

In this chapter we considered realizability of discrete time linear dynamical systems. Throughout the chapter we assumed that a DT-LDS is given by a Markov parameter sequence $\mathcal{Y}$ and that the state space realization matrices B, C and D are known and fixed. Under these assumptions the existence of different realizations of $\mathcal{Y}$ is equivalent to the existence of distinct state transition matrices of the same dimension that provides the same sequence $\mathcal{Y}$. Assuming that the state space realization matrix C is invertible, we quantitatively characterized the set of feasible state space realizations. It is proved that the set of state transition matrices $\mathcal{A}(\mathcal{Y}, B, C, D)$ associated to a Markov sequence $\mathcal{Y}$ is convex, given B, C and D matrices. Under the same conditions it is also shown that the subset of Metzler-type system matrices $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ is convex. Furthermore, we proved that there exists a structurally unique state transition matrix $A^d \in \mathcal{A}^p(\mathcal{Y}, B, C, D)$ of maximal number of off-diagonal entries whose respective graph representation $G(A^d)$ contains that of any other feasible state transition matrix in $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ as subgraph.

Making use of the eigenvalue assignment procedure, we reformulated dynamical equivalence of state space realizations in terms of a finite set of linear constraints in the entries of the state transition matrix. This way we proposed a convex optimization based algorithm that can be used to find different realizations of any Markov sequence. Since the existence of different system matrices implies structural non-identifiability of the underlying dynamical system, this way non-identifiability of DT-LDSs can be validated in fixed state space dimension in polynomial time. By making use of the convexity of $\mathcal{A}^p(\mathcal{Y}, B, C, D)$ and adopting results from the field of non-negative polynomial systems, we provided algorithms that can determine structurally different realizations of DT-LDSs with respect to Metzler-type state transition matrices. Representative examples are presented in order to illustrate that dynamically equivalent realizations of DT-LDSs are not necessary structurally unique, i.e. there may exist structurally different realizations of the same DT-LDS even in the case of fixed B, C and D state space realization matrices.

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4 Reachability analyis of discrete state Reaction Networks

4.1 Mathematical notations

σ_X	an ordered sequence of states
σ_r	an ordered sequence of reaction vectors
σ_S	an ordered sequence of species
σ_C	an ordered sequence of complexes
$\mathcal{Q}(\mathcal{O})$	the number of points with non-negative integer coordinates in a bounded set $\mathcal{O} \subset \mathbb{R}^n$

Table 4.1: Notations specific to chapter 4.

4.2 Background

Employing deterministic ordinary differential equation systems to characterize the dynamical behavior of complex networks of chemically interacting components (species) is a widely used approach in mathematical and computational systems biology [4, 107, 108]. Such a continuous state modeling approach assumes high molecular count of species and their homogeneous (well-mixed) distribution in the surrounding media [109]. However, in several (bio)chemically interesting systems – such as some enzymatic and genetic networks – the molecular count of different species are relatively low (e.g. < 100 molecules) [109, 110, 111] implying that the assumption of homogeneous species distribution does not hold [112, 113]. Hence it is necessary to introduce a discrete state model capable of keeping track the individual molecular counts in order to properly characterize the qualitative dynamical behavior of (bio)chemical networks of species with low number of molecules [116, 117]. There exist several mathematical models describing the state evolution of discrete state chemical reactions networks, such as Markov chain models [113, 117], stochastic Petri nets [118].

In the context of chemical reaction networks of several interacting components, in order to completely characterize the system it is needed to simultaneously study the dynamical behavior and the underlying network structure, as well. Moreover, it is also important to

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examine how the dynamical behavior and the network structure are related to each other, and how we can predict the dynamical behavior (e.g. in the form of possible state space trajectories) in aware of the underlying network structure. For continuous state reaction networks obeying the law of mass action it is recognized that the network structure (i.e. topology) is not necessarily unique, i.e. the same system of differential equations can be generated by different network topologies (different sets of interactions among the given species) [119, 120, 30, 31].

In the case of discrete state reaction networks the so-called reachability is a strictly related problem to the dynamical behavior, namely, is it possible to reach a prescribed target state from a given initial one through a finite sequence of transition (reactions)? It is known the reachability relation between any pair of non-negative initial and target states is determined by the network structure itself. Through the reachability analysis several problems of great importance can be analyzed, one of them having high interest is the existence of so-called extinction events: the existence of trajectories resulting in the irreversible extinction of some species from the system. It has been shown that under some conditions on the network structure a discrete state chemical reaction network exhibits an extinction event from any point of its state space [116, 121, 122]. The properties of recurrence (the ability of returning to any initial state) and irreducibility (the ability of reaching any state from any other one) are also examined in the context discrete state reaction networks [114, 115].

The mathematical model of discrete state chemical reaction networks is equivalent to an important model of theoretical computer science, namely the so-called vector addition systems with states (VASS) or equivalently Petri nets [127, 128]. Hence the discrete chemical reaction network reachability problem is equivalent to the extensively studied problem of vector addition system (VAS) reachability. The VAS reachability problem is known to be decidable [130, 131, 132, 133] and for the space complexity we have EXSPACE lower bound [134]. Unfortunately, contrary to the proven polynomial time complexity of reachability of rate independent continuous state chemical reaction networks [128], in the case of discrete state reaction networks it is not known whether there exists an algorithm of primitive-recursive time complexity deciding this problem [135].

The aim of this chapter is to study of the reachability problem of sub-and superconservative d-CRNs. We make use of the relation between the sub- and superconservative properties. An ILP feasibility approach is employed to computationally solve the reachability problem. We provide theoretical upper bounds on the maximal length of cycle-free state transition sequences associated to a pair of initial and target states. Our main contributions are summarized in Proposition 16 and Proposition 17, where necessary and sufficient conditions are given on the network structure and the initial- and target states under which the reachability relation is equivalent to the non-negative integer solution of the d-CRN state equation. These results in Corollary 3 and Corollary 4 are extended

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to a subclass of superconservative d-CRNs. Finally, in Proposition 18 we prove that – under the same consitions – the reachability relation can be decided in polynomial time by making use of the structural properties of the reaction networks.

4.3 Discrete state chemical reaction networks

A discrete state Chemical Reaction Network (d-CRN) with n species, m complexes and l reactions is a triple $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ so that:

$$\mathcal{S} = \{s_i \mid i = 1, \ldots, n\}$$
$$\mathcal{C} = \{y_j = \sum_{i=1}^{n} \alpha_{ji} s_i \mid s_i \in \mathcal{S},\ \alpha_{ji} \in \mathbb{Z}_{\geq 0},\ i = 1, \ldots, n,\ j = 1, \ldots, m\}$$
$$\mathcal{R} = \{r_v = y_{source(r_v)} \to y_{product(r_v)} \mid y_{source(r_v)}, y_{product(r_v)} \in \mathcal{C}, v = 1, \ldots, l\}$$

where s_i is the i'th species, y_j is the j'th complex and r_v is the v'th reaction of the network. Moreover, α_{ji} is the stoichiometric coefficient of the i'th species in the j'th complex. For a reaction $r_v = y_{source(r_v)} \to y_{product(r_v)}$ of $\mathcal{R}$, $y_{source(r_v)}$ and $y_{product(r_v)}$ are the source complex and the product complex, respectively.

For each complex $y_j \in \mathcal{C},\ j = 1, \ldots, m$, the stoichiometric coefficients of the species can be represented as a vector of the form:

$$\overline{y}_j = [\alpha_{j1}\ \alpha_{j2}\ \ldots\ \alpha_{jn}]^\top \tag{4.1}$$

For each $r \in \mathcal{R}$, a reaction vector $r_{ij} \in \mathbb{Z}^n$ can be associated to track the net molecular count changes of the species upon firing the reaction:

$$r_{ij} = \overline{y}_j - \overline{y}_i \tag{4.2}$$

so that y_j and y_i are the corresponding source and product complexes of r. In the sequel the notation r_i will be used for denoting both the i'th reaction of the d-CRN and the associated reaction vector, as well. We will also assume that for all the examined d-CRNs a fixed order of the reaction vectors is given, i.e. an order $r_1,\ r_2, \ldots, r_l$ is fixed and $l = |\mathcal{R}|$. We use the constraint that only a single reaction can occur at once.

A d-CRN can also be represented by a directed graph $G = G(V, E)$ such that the vertices and edges correspond to the complexes and the reactions, respectively, i.e.:

$$V = \mathcal{C} \tag{4.3}$$
$$E = \mathcal{R} \tag{4.4}$$

The direction of the edges are determined by the reactions of $\mathcal{R}$, so that if $y_i \to y_j \in \mathcal{R}$

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then there exists an edge $e \in E$ from the vertex representing y_i to the vertex of y_j. For each edge a weight corresponding to the reaction rate constant (also called intensity or propensity) corresponding to the respective reaction can also be associated.

Beyond the above representations it is also possible to describe a d-CRN in an algebraic way by means of its unique stoichiometric matrix.

Definition 7. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. The stoichiometric matrix $\Gamma \in \mathbb{Z}^{n \times l}$ of $\mathcal{N}$ is defined as

$$\Gamma = [r_1 \ \dots \ r_l] \tag{4.5}$$

Note that $[\Gamma]_{ij}$ encodes the net molecule count change on species s_i upon occuring rection r_j. Beside Γ we also define the following matrices:

$$\Gamma^+ = [\overline{y}^+_{r_1} \ \dots \ \overline{y}^+_{r_l}]^\top \tag{4.6}$$

$$\Gamma^- = [\overline{y}^-_{r_1} \ \dots \ \overline{y}^-_{r_l}]^\top \tag{4.7}$$

where $\overline{y}^+_{r_i}$ denotes the vector form of the product complex belonging to reaction r_i while $\overline{y}^-_{r_j}$ represents the vector of the source complex associated to reaction r_j. The relation among the above defined matrices is as follows:

$$\Gamma = \Gamma^+ - \Gamma^- \tag{4.8}$$

Example 2. Let us consider the d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ depicted in Figure 4.1. $\mathcal{N}$ characterizes a simple network of a bi-functional enzyme E having both phosphorylation and dephosphorylation activities on species I and I_p, respectively. This network is characterized by the following sets

$\mathcal{S} = \{I,\ I_p,\ E,\ EI,\ EI_p\}$
$\mathcal{C} = \{I + E,\ EI,\ I_p + E, EI_p\}$
$\mathcal{R} = \{E + I \to EI,\ IE \to E + I, EI \to I_p + E,\ E + I_p \to EI_p,\ EI_p \to E + I_p,\ EI_p \to E + I\}$

We fix the order of species and reactions as they are listed in the above sets.

The above model has no information on the probabilities of the reactions, but at any given time instant at most one reaction can occur.

The molecular count of each species of a d-CRN at any time $t \geq 0$ is given by its state vector $X(t) \in \mathbb{Z}^n_{\geq 0}$ and the time evolution of the system is characterized by the following discrete state equation:

$$X(t) = X(0) + \Gamma N(t) \tag{4.9}$$

where $X(0)$ is the state vector belonging to the initial time instant and

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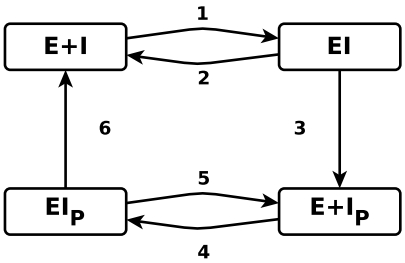

$$\Gamma = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ -1 & 1 & 1 & -1 & 1 & 1 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix}$$

Figure 4.1: A discrete state chemical reaction network. **Left:** reaction network structure as it is defined by Eq. (4.3) and Eq. (4.4). The nodes and directed edges represent the complexes and the reactions, respectively. The numbers on the edges denote a fixed ordering of the reactions. **Right:** the stoichiometric matrix associated to the system, i.e. $[\Gamma]_{ij}$ is the net change in the number of the i'th species upon occurring the j'th reaction.

$$N(t) = [N_1(t), N_2(t), \ \ldots \ N_l(t)]^\top \in \mathbb{Z}^l_{\geq 0} \tag{4.10}$$

such that $N_k(t) \in \mathbb{Z}_{\geq 0}$ stores the number of occurrences of the k'th reaction up to time t. We note that $N(t)$ is typically modeled as some point process [113, 117].

Since for our further analysis the time instants when the reactions have occurred are not of interest, but only the order of reactions, therefore we abandon the notation of time t in the formulas.

Definition 8. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. It is said that:

1. a species $s \in \mathcal{S}$ is a catalyzer of a reaction $r \in \mathcal{R}$ if it has the form of $r = s + s_1 \to s + s_2$ with $s_1, s_2 \in \mathcal{S}$,
2. a complex $y \in \mathcal{C}$ is charged at state $X \in \mathbb{Z}^n_{\geq 0}$ if $X \succeq y$,
3. a complex $y \in \mathcal{C}$ is called zero complex, if it does not involve any species, $y = \emptyset$,
4. a reaction $r \in \mathcal{R}$ is charged if its respective source complex is charged,
5. a state $X \in \mathbb{Z}^n_{\geq 0}$ reacts to a state $X' \in \mathbb{Z}^n_{\geq 0}$ (denoted by $X \to X'$) if there exists a reaction $r \in \mathcal{R}$ such that r is charged at state X and $X + r = X'$,
6. a reaction (vector) sequence σ_r is an ordered set of reaction vectors $\sigma_r = r_1 \ \ldots \ r_v$ where $r_i \in \mathcal{R}$, $i = 1, \ldots, v$,
7. a state transition sequence σ_X is an ordered set states $X_0, \ X_1, \ldots, X_p$ so that $X_1 \to X_2 \to \ldots \ \to X_{p-1} \to X_p$,
8. a state $X' \in \mathbb{Z}^n_{\geq 0}$ is reachable from a state $X \in \mathbb{Z}^n_{\geq 0}$ (denoted by $X \rightsquigarrow_{\mathcal{N}} X'$) if there exists a directed path in the state space so that $X = X_{\nu(1)} \to X_{\nu(2)} \to \ldots \to X_{\nu(v)} = X'$.

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9. A set of states $\mathcal{X} \subset \mathbb{Z}^n_{\geq 0}$ is said to be coverable from a state $X \in \mathbb{Z}^n_{\geq 0}$ if there exists a state $X^{'} \in \mathbb{Z}^n_{\geq 0}$ for which $X \rightsquigarrow_{\mathcal{N}} X^{'}$ and $X^{'} \succeq X^{''}$ for all $X^{''} \in \mathcal{X}$.

Considering a state transition sequence $\sigma_X = X_0\ X_1\ \ldots\ X_{p-1}\ X_p$, we call X_0 and X_p the initial and target states, respectively, while X_i for $i = 1, \ldots, p-1$ are called transition states of σ_X.

The condition that a reaction $r \in \mathcal{R}$ is charged at state $X \in \mathbb{Z}^n_{\geq 0}$ can be expressed by the inequality $X \succeq \overline{y}_r^-$. For a reaction sequence σ_r a state transition sequence $\sigma_X = X_0\ X_1 \ldots\ X_v$ can be uniquely associated so that

$$X_j = X_{j-1} + r_j, \quad j = 1, \ldots, h, \tag{4.11}$$

where the initial state X_0 is assumed to be given. A state transition sequence σ_X is said to be admissible if $X_i \succeq r_{i+1}$ for $X_i \in \sigma_X$, $i = 0, \ldots, v-1$, moreover, we say that a reaction sequence σ_r is admissible if the corresponding state transition sequence is admissible.

From the reachability of a state $X^{'} \in \mathbb{Z}^n_{\geq 0}$ from an initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$, it follows that the following equation has a non-negative integer solution $c \in \mathbb{Z}^l_{\geq 0}$:

$$X^{'} = X_0 + \Gamma c \tag{4.12}$$

where $[c]_i$ encodes the number of occurrences for reaction $r_i \in \mathcal{R}$ for $i = 1, \ldots, l$. However, it is important to note that from the existence of a non-negative integer solution c of Eq. (4.12), the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ does not necessary follow.

We note that c of Eq. (4.12) corresponds to $N(t)$ of Eq. (4.9). Since a solution $c \in \mathbb{Z}^l_{\geq 0}$ of Eq. (4.12) encodes the number of occurences for each reaction in a fixed order, the following equality is fulfilled:

$$\Gamma c = \sum_{i=1}^{h} r_i \tag{4.13}$$

where $h = \sum_{i=1}^{l} [c]_i$ and $r_i \in \mathcal{R}$ for $i = 1, \ldots, h$. When we want to emphasize that a reaction vector sequence is encoded by a particular $c \in \mathbb{Z}^l_{\geq 0}$ we will use the notation $\sigma_r^c = r_1, \ldots, r_h$ and the state transition sequence determined by σ_r^c will be denoted by σ_X^c.

Definition 9. Let us consider a d-CRN $\mathcal{N}$ with initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$. The reachable state space $Reach(\mathcal{N}, X_0)$ of $\mathcal{N}$ with initial state X_0 is the set of non-negative discrete states reachable from X_0:

$$Reach(\mathcal{N}, X_0) = \left\{ X \;\middle|\; X \in \mathbb{Z}^n_{\geq 0},\ X_0 \rightsquigarrow_{\mathcal{N}} X \right\} \tag{4.14}$$

In the sequel we will also use the following definitions in the analysis of d-CRNs:

Definition 10. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ where $\mathcal{R} = \{r_1,\ \ldots\ , r_l\}$. The

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stoichiometric subspace $\mathcal{X}_{\mathcal{R}}$ of $\mathcal{N}$ is the space spanned by the reaction vectors:

$$\mathcal{X}_{\mathcal{R}} = span(r_1, \ \dots \ , r_l). \tag{4.15}$$

We note that in the notation of the stoichiometric subspace the reaction set $\mathcal{R}$ appears in the subscripts as $\mathcal{X}_{\mathcal{R}}$ is completely defined by the set of reactions.

Definition 11. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ and a non-negative initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$. The non-negative stoichiometric compatibility class associated to X_0 is defined as:

$$\mathcal{X}_{X_0} = (X_0 + \mathcal{X}_{\mathcal{R}}) \cap \mathbb{R}^n_{\geq 0} \tag{4.16}$$

where $\mathcal{X}_{\mathcal{R}}$ is the stoichiometric subspace of $\mathcal{N}$.

Clearly, a reachable state space $Reach(\mathcal{N}, X_0)$ of a d-CRN $\mathcal{N}$ satisfies the following relation:

$$Reach(\mathcal{N}, X_0) \subseteq \mathcal{X}_{X_0} \cap \mathbb{Z}^n_{\geq 0}. \tag{4.17}$$

In the context of complexes and reactions the recurrency and transiency are also defined [121]:

Definition 12. 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 strongly recurrent from a state $X \in \mathbb{Z}^n_{\geq 0}$, if $X \rightsquigarrow_{\mathcal{N}} Y$ implies that there exists a state $Z \in \mathbb{Z}^n_{\geq 0}$ such that $Y \rightsquigarrow Z$ and y is charged at Z, otherwise y is called weakly transient from X.

2. A complex $y \in \mathcal{C}$ is called weakly recurrent from $X \in \mathbb{Z}^n_{\geq 0}$ if there exists a state $Y \in \mathbb{Z}^n_{\geq 0}$ such that $X \rightsquigarrow_{\mathcal{N}} Y$ and y is strongly recurrent from Y, otherwise y is strongly transient from X.

We also introduce the definition of extinction events, which are related to transiency and the reaction network structure [121].

Definition 13. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. It is said that $\mathcal{N}$ exhibits an extinction event on $\mathcal{C}' \subseteq \mathcal{C}$ from $X_0 \in \mathbb{Z}^m_{\geq 0}$, if every complex $y \in \mathcal{C}'$ is strongly transient from X_0.

4.4 Equivalent Model Formulations

In this section we briefly discuss some discrete state transition models which are equivalent to the class of discrete state reaction networks. The discussed models are commonly used in theoretical computer science to model systems of discrete state transitions, they are

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applied to model concurrent systems, communication protocols, asynchronous, distributed and parallel processes.

Definition 14. [143]
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, $P \cap T$,
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) $O : T \to P^{\infty}$.

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

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

P^{∞} denotes the multiset derived from P.

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. The input and output functions characterize the source and product complexes, respectively.

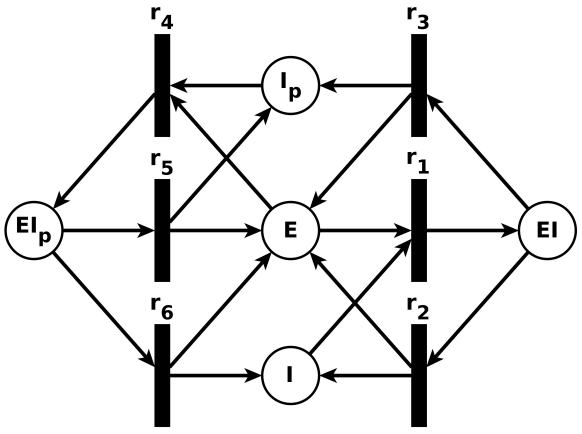

Figure 4.2: Equivalent Petri net representation of the d-CRN depicted in Figure 4.1. Species and reactions correspond to the places and transitions, respectively. The source and product complexes are characterized by the input and output functions.

Definition 15. [144]
A Vector Addition System with States (VASS) is a graph $G = (Q, \Delta)$ so that

1. Q is a non-empty finite set of control states,

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2. $\Delta \subseteq Q \times \mathbb{Z}^n \times Q$ is a finite set of transitions,

$Q \times \mathbb{N}^d$ is a set of configurations.

A run is a non-empty word $(q_0, m_0) \dots (q_k, m_k)$ of configurations such that $(q_{j-1}, m_j - m_{j-1}, q_j) \in \Delta$ for every $j = 1, \dots\ k$.

The existence of a run $(q_0, m_0) \dots (q_k, m_k)$ implies that q_k is reachable from q_0.

In a VASS the set of control states corresponds to the state space of the respective d-CRN model. The transitions characterize the state transitions in the state space of the reaction network. Note that a configuration (q, m) does not necessarily imply that the reaction corresponding to m is charged at q, hence additional constraints must be imposed on the VASS model to represent a semantically correct d-CRN model.

4.5 Integer Linear Programming

In this section some relevant concepts of mathematical programming are briefly reviewed that will be extensively employed later. An Integer Linear Programming (ILP) instance can be formulated as follows:

$$ILP \begin{cases} \min_x\{a^\top x\} \\ subject\ to \\ Ax \leq b \\ x \in \mathbb{Z}^n \end{cases} \tag{4.18}$$

where x is the n-dimensional vector of decision variables while $a \in \mathbb{Z}^n$, $A \in \mathbb{Z}^{m \times n}$ and $b \in \mathbb{Z}^m$ are fixed coefficients. Generally, the above ILP computational problem is known to be NP-hard that may highly confine our ability to efficiently solve problems of integers in high dimension.

However, if the value of the decision vector that minimizes (or maximizes) the prescribed objective function is not important for us, but only the existence of a $x \in \mathbb{Z}^n$ vector satisfying the set of specified constraints, then the problem is called ILP feasibility problem:

$$FP \begin{cases} P = \{x \mid Ax \leq b,\ A \in \mathbb{Z}^{m \times n},\ b \in \mathbb{Z}^m,\ x \in \mathbb{R}^n\} \\ P \cap \mathbb{Z}^n \stackrel{?}{=} \emptyset \end{cases} \tag{4.19}$$

An ILP feasibility problem – as a decision problem – addresses the question of whether the polytope P contains an integer lattice point, formally $P \cap \mathbb{Z}^n \stackrel{?}{=} \emptyset$. While a FP is also known to be NP-hard, it has well-decoupled time complexity with respect to the number of variables, the number of constraints and the maximum of the absolute values of the entries of A and b. Therefore, a feasibility problem of the form (4.19) – assuming fixed dimension n – can be decided in polynomial time in the number of constraints m

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and the maximum of the absolute values of the coefficients A and b by means of the Lenstra algorithm [136, 137]. Moreover, the number of integer lattice points in P can also be numerated in polynomial time in m and the maximum of the absolute value of the coefficients using Barvinok's integer lattice point counting algorithm [138, 139, 140, 141]. We note that for the Barvinok algorithm there exists an effective implementation called LattE [142].

The FP problem in Eq. (4.19) can be viewed as a potential relaxation approach to an NP-hard ILP in situations where only the knowledge of the existence of an integer solution is needed. By making use of specific structural properties in an ILP problem, additional relaxation can be obtained. Total unimodularity – as a property of the coefficient matrix A – provides relaxation for the respective NP-hard ILP problem. Let us introduce the definition of totally unimodular matrices [150]:

Definition 16. A matrix A is totally unimodular if each sub-determinant of A is 0, $+1$, or -1.

Note that in a totally unimodular matrix all the entries are 0 or ± 1.

If the coefficient matrix A in Eq. (4.18) is totally unimodular and b is an integer vector, then by relaxing the integer constraint on the decision variable vector x, the solution of the resulting linear program is proven to be optimal for the ILP [150, 151].

The following proposition provides condition on the coefficient matrix to be totally unimodular [150, 151]:

Proposition 8. A matrix A is totally unimodular, if there are no more than two non-zero entries in each column and the rows can be partitioned into two sets l_1 and l_2 so that:

1. if a column has two non-zero entries with the same sign, then they are in different partitions, l_1 and l_2;

2. if a column has two non-zero entries of different signs, then they are in the same partition, either l_1 or l_2.

4.6 Sub-and superconservative d-CRNs

We define conservativity and subconservativity in the same way as it was introduced e.g. in [109] and [121].

Definition 17. A d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ having stoichiometric matrix $\Gamma \in \mathbb{Z}^{n \times l}$ is called subconservative (superconservative) if there exists a strictly positive vector $z \in \mathbb{R}^n_{>0}$ for which $z^\top \Gamma \leq 0^{1 \times l}$ ($z^\top \Gamma \geq 0^{1 \times l}$) holds. The vector z is called a conservation vector.

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We note that the conservativity of d-CRNs is related to P-invariance (also called S-invariance) of Petri nets and this structural (network structure-related) property was previously examined in the context of the theory of reaction networks [121, 123, 115].

An important property related to subconservativity is the strong boundedness which is defined as follows.

Definition 18. A d-CRN $\mathcal{N}$ is said to be strongly bounded, if for any $X_0 \in \mathbb{Z}^n_{\geq 0}$ initial state, the reachable state space $Reach(\mathcal{N}, X_0)$ is bounded.

The subconservative property of the reaction network structure is a necessary and sufficient condition of strong boundedness [121, 129].

Proposition 9. [129] Let us consider a d-CRN $\mathcal{N}$. The following propositions are equivalent:

1. $\mathcal{N}$ is subconservative,
2. $\mathcal{N}$ is strongly bounded.

As a special case covered by the intersection of sub- and superconservativity, we can define the conservative property, as well.

Definition 19. Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with stoichiometric matrix $\Gamma \in \mathbb{Z}^{n \times l}$. The d-CRN $\mathcal{N}$ is said to be conservative if there exists a vector $z \in \mathbb{R}^n_{>0}$ satisfying the matrix equation $z^\top \Gamma = 0^{1 \times l}$.

We note that the above structural properties can be easily decided in polynomial time by means of an LP of the following form:

$$\begin{aligned} &\min_z \sum_{j=1}^{n} z_j \\ &\quad s.t. \\ &z^\top \Gamma \leq 0^{1 \times l} \ (or\ z^\top \Gamma \geq 0^{1 \times l}) \\ &z \succeq 0^n + \varepsilon^n,\ \varepsilon \succ 0^n \end{aligned}$$

The relationship between sub-and superconservativity can be expressed by the following proposition.

Proposition 10. A d-CRN $\mathcal{N}$ with stoichiometric matrix $\Gamma_{\mathcal{N}} \in \mathbb{Z}^{n \times l}$ is subconservative if and only if the d-CRN $\mathcal{N}'$ with stoichiometric matrix $\Gamma_{\mathcal{N}'} = -\Gamma_{\mathcal{N}}$ is superconservative.

Proof.

$$z^\top \Gamma \leq 0^{1 \times m} \quad \Longleftrightarrow \quad z^\top (-\Gamma) \geq 0^{1 \times l} \tag{4.20}$$

□

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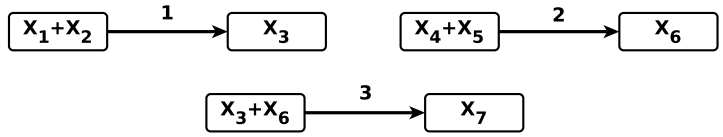
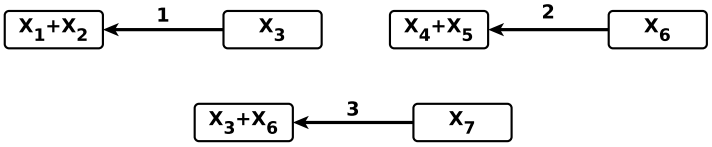
We note that $-\Gamma_{\mathcal{N}}$ means the change of the direction of each reaction in the d-CRN $\mathcal{N}$ of stoichiometric matrix $\Gamma_{\mathcal{N}}$.

Example 3. Figure 4.3 depicts two d-CRNs: a subconservative and a superconservative reaction network structure. Indeed, these networks are counterparts that can be easily transformed to each other by changing the sign of the entries in the stoichiometric matrices. Such a transformation results in the change of the direction of the edges in the reaction network.



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

(a)



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

(b)

Figure 4.3: A pair of sub- and superconservative reaction network structures denoted by $\mathcal{N}$ and $\mathcal{N}^{'}$, respectively. The ordering of the reactions are denoted by the numbers on the edges of the graphs. The two networks can be transformed to each other by changing the sign of the entries in their stoichiometric matrices. **a)** subconservative d-CRN. **b)** superconservative d-CRN.

From Proposition 10 it follows that instead of the reachability problem of a superconservative network structure one can consider an equivalent subconservative d-CRN reachability problem as it is discussed in Proposition 11.

Proposition 11. 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.

Proof.

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1. $X_0 \rightsquigarrow_{\mathcal{N}} X' \Rightarrow \exists c \in \mathbb{Z}^l_{\geq 0}$ *such that* $X_0 + \Gamma c = X'$ *which is equivalent to* $X' + (-\Gamma)c = X_0$.

   From $X_0 \rightsquigarrow_{\mathcal{N}} X'$ *it follows that the solution* $c \in \mathbb{Z}^l_{\geq 0}$ *can be decomposed to an admissible reaction vector sequence* $\sigma^c_r = r^c_1 \ \ldots r^c_h$, $h = \sum_{i=1}^{l} [c]_i$, *i.e. all the states of* σ^c_X *determined by* σ^c_r *are composed of non-negative entries. Then, by reversing* σ^c_X, *we obtain a non-negative state transition sequence* $\hat{\sigma}^c_X$ *from* X' *to* X_0 *which is uniquely determined by means of the reaction vector sequence* $\hat{\sigma}^c_r = -r^c_h \ \ldots \ -r^c_1$.

   It is also needed to show that $\hat{\sigma}^c_r$ *is an admissible reaction sequence. This can be done as follows: for each state* $X \in \sigma^c_X \setminus X_0$ *there exists a reaction* $r \in \sigma^c_r$ *so that upon firing* r *the resulted state is* X *from which it follows that* $X \succeq \overline{y}^+_r$, *moreover, considering the reversed reaction sequence* $\hat{\sigma}^c_r$, *the reaction vector to be occurred at state* X *is* $-r \in \hat{\sigma}^c_r$ *which is charged at* X *even if* $X \succeq \overline{y}^+_r$.

   Then the admissibility of $\hat{\sigma}^c_r$ follows.

2. The proof for the other direction $X' \rightsquigarrow_{\mathcal{N}'} X_0$ works analogously as above.

□

The importance of Proposition 11 is that the reachability problem of a superconservative d-CRN of unbounded reachable state space can be easily traced back to the reachability problem of a d-CRN of bounded reachable state space which can make the original decision problem computationally tractable.

4.7 Reachability analysis

In this section we consider the reachability problem arising in the context of d-CRNs. The classes of sub- and superconservative reaction networks are considered. First the exact problem statements are detailed. Next we reformulate the reachability problem in the form of integer linear feasibility problem. In order to tackle the obtained decision problem we derive upper bounds on the maximal number of reactions (state transitions) along the admissible reaction (state transition) sequences. In order to reduce the time complexity of the decision problem we determine subclasses of sub- and superconservative d-CRNs for which the reachability relation is equivalent to the existence of a non-negative integer solution of the d-CRN state equation. This way the number of decision variables in the integer feasibility problem can be significantly reduced.

4.7.1 Problem statement

We wish to solve the following decision problems of d-CRNs:

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1. Given a d-CRN $\mathcal{N}$, an initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$ and a target state $X^{'} \in \mathbb{Z}^n_{\geq 0}$. Does there exists a state transition sequence σ_X (or equivalently reaction sequence σ_r) so that $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ holds?

2. Given a d-CRN $\mathcal{N}$, an initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$ and a set of target states $\mathcal{X} \subset \mathbb{Z}^n_{\geq 0}$. Can we find a state $X' \in \mathbb{Z}^n_{\geq 0}$ for which $X_0 \rightsquigarrow X^{'}$ and $X^{'} \succeq T$ hold for all $T \in \mathcal{X}$?

It is important to emphasize that we consider sequences σ_X without cycles. Clearly, the existence of directed cycles in the reachability state space of a d-CRN does not affect any reachability relation.

The above decision problems are important in the analysis and synthesis of reaction networks. It could be crucial to examine the existence of some semantically meaningful states reachable from the initial state of a d-CRN. For example an undesired state may represent the agglomeration of toxic species and/or the fact that a reaction producing toxic species is able to fire (i.e. the respective source complex is charged). We also note the d-CRN reachability is equivalent to the gate-implementability problem in natural computing [149].

As the model of d-CRNs is equivalent to the model of Petri nets, the results detailed below can also be used to examine concurrent, asynchronous, distributed systems arising in the context of theoretical computer science, software engineering and telecommunications.

4.7.2 Constraint formulation

This section provides a simple reformulation of the d-CRN reachability and coverability problems in terms of integer feasibility problems.

Consider a d-CRN $\mathcal{N}$ of stoichiometric matrix $\Gamma_{\mathcal{N}}$. Let us denote the non-negative initial state by X_0. If a given state $X^{'} \in \mathbb{Z}^n_{\geq 0}$ is reachable from the initial state X_0 ($X_0 \rightsquigarrow_{\mathcal{N}} X'$), then there exists a – not necessarily unique – vector $c \in \mathbb{Z}^l_{\geq 0}$ satisfying the following Diophantine equation:

$$X_0 + \Gamma_{\mathcal{N}} c = X^{'}. \tag{4.21}$$

This can also be used to decide whether from the initial state we can reach a target state where a complex $y \in \mathcal{C}$ is charged:

$$X_0 + \Gamma_{\mathcal{N}} c \geq y. \tag{4.22}$$

If the state space of a d-CRN is bounded, the following inequality also holds:

$$X_0 + \Gamma_{\mathcal{N}} c \preceq X_{max}. \tag{4.23}$$

where $[X_{max}]_i \geq [X]_i$ for $i = 1, \ldots, n$ and $X \in Reach(\mathcal{N}, X_0)$.

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The inequalities described above do not guarantee that there exists a state transition sequence $X_0 = X_{\nu(1)} \to X_{\nu(2)} \to \ldots \to X_{\nu(l)} = X'$ encoded by c which is admissible: it is possible that there exists a state transition along the sequence of reactions where the source complex of the firing reaction is not charged at the actual state X_k, therefore, we have that for the succeeding state $[X_{k+1}]_i < 0$ for some $i = 1, \ldots, n$. To remedy this problem further constraints can be introduced.

First we introduce the notation of c_{max} to denote the upper bound of c (i.e. $c \prec c_{max}$). By summing up the entries of c_{max}, the overall number of reactions is given:

$$K = \sum_{i=1}^{l} [c_{max}]_i \tag{4.24}$$

While the entries of c_{max} correspond to the upper bounds of the maximal number of occurences of the reactions firing along a cycle-free state transition sequence σ_X from X_0 to X', K is equal to the associated upper bound for the number of reactions along a directed cycle-free path. Using the above notations we introduce the following decomposition:

$$c = \sum_{j=1}^{K} v_j \tag{4.25}$$

$$v_j \in \{0,1\}^l \qquad j = 1, \ldots, K \tag{4.26}$$

$$\sum_{i=1}^{l} [v_j]_i \leq 1 \qquad j = 1, \ldots, K \tag{4.27}$$

where the binary vector v_j, $j = 1, \ldots, K$ represents the reaction occurring in the network in the jth time step, and $[v_j]_i$ denotes the ith coordinate of v_j. Therefore, $[v_j]_i = 1$ encodes that the reaction r_i is firing at the jth time step. It can be seen from Eq. (4.25)-(4.27) that reactions of the forms $v_j = 0^l$ are technically allowed by the above decomposition. In order to apply the decomposition in practice, it is needed to determine an upper bound $c_{max} \in \mathbb{Z}^l$ for c such that $[c_{max}]_i < \infty$ for $i = 1, \ldots, l$. Based on the decomposition of Eq. (4.25), the kth state can be written as follows:

$$X_k = X_0 + \Gamma_{\mathcal{N}} \sum_{i=1}^{k} v_i \qquad k = 1, \ldots, K \tag{4.28}$$

In order to guarantee the semantic validity of the state transition sequence at X_k is that the source complex $y_{source(r_{k+1})}$ of the next reaction r_{k+1} – encoded by v_{k+1} – to be charged at X_k. This can be expressed by the following inequality:

$$X_0 + \Gamma_{\mathcal{N}} \sum_{i=0}^{k} v_i \geq \Gamma_{\mathcal{N}}^{-} v_{k+1} \qquad k = 0, \ldots, K-1 \tag{4.29}$$

where $v_0 = 0^l$ and $\Gamma_{\mathcal{N}}^{-}$ is defined by Eq. (4.7).

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The reachability and coverability problems of d-CRNs can be expressed by equations (4.21), (4.23)-(4.29) and equations (4.22)-(4.29), respectively. It can be seen that equations (4.21)-(4.29) contain linear equalities and inequalities with integer decision variables $v_j,\ j = 1, \ldots, K$. Hence, the computational problem of reachability and coverability can be written as integer programming (IP) feasibility problems.

4.7.3 Bounds for the length of reaction sequences

The maximal number of reactions is an important parameter affecting the time complexity of a reachability problem. Therefore, this subsection is devoted to deriving upper bounds for the length of reaction sequences in the particular cases subconservative and superconservative reaction network structures.

Subconservative case

In this section it is assumed that the examined d-CRN is subconservative and there exists at least one reaction producing at least one molecule of at least one species.

It is known that a (sub)conservative d-CRN has a finite state space [124, 129]. Based on the proof of finiteness of subconservative d-CRNs' state space, it is possible to compute an upper bound for the coordinates of the reachable states [124].

Lemma 1. Let us consider a subconservative d-CRN $\mathcal{N}$ with initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$ and conservation vector $z \in \mathbb{R}^n_{>0}$. Then for all $X' \in \mathit{Reach}(\mathcal{N}, X_0)$ states the following upper bound holds:

$$[X']_j \leq \frac{z^\top X_0}{\zeta} \qquad j = 1, \ldots, n \tag{4.30}$$

where $\zeta = \min\limits_{j \in \{1,\ldots,n\}} \{z_j\}$.

Proof. According to the subconservativity:

$$\exists z \in \mathbb{R}^n_{>0}: \quad z^\top \Gamma_{\mathcal{N}} \leq 0^{1\times m} \tag{4.31}$$

Let us take an arbitrary $X' \in \mathit{Reach}(\mathcal{N}, X_0)$. Since X' is reachable from X_0, there exists a non-negative finite linear combination of the reaction vectors $r_1,\ \ldots\ r_m$ for which:

$$X' = X_0 + a_1 r_1 + \ \ldots\ + a_m r_m \tag{4.32}$$

Let us take the following dot product:

$$z^\top (X' - X_0) = z^\top (a_1 r_1 + \ \ldots\ + a_m r_m) = \\ a_1 z^\top r_1 + \ \ldots\ + a_m z^\top r_m \leq 0$$

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Note that the dot product of the conservation vector z and an arbitrary reaction vector will be non-positive. From the above inequality:

$$z^\top X' \leq z^\top X_0 \quad \Longrightarrow \quad 0 \leq \sum_{i=1}^{n} z_j X_j' \leq z^\top X_0 = M \tag{4.33}$$

Let us define

$$\zeta = \min_{j \in \{1,\ \dots\ n\}} z_j > 0 \tag{4.34}$$

Then

$$0 \leq \zeta \sum_{i=1}^{n} X_i' \leq \sum_{i=1}^{n} z_i X_i' \leq z^\top X_0 = M \tag{4.35}$$

From the above inequality we can derive the following upper bound for X_j':

$$0 \leq X_j' \leq \frac{M}{\zeta} \tag{4.36}$$

□

The above bound can be tightened to an element-wise upper bound along each dimension [129]. For convenience, we give our own proof for this bound in the next proposition.

Proposition 12. Let us consider a subconservative d-CRN having initial state $X_0 \in \mathbb{Z}_{\geq 0}^n$ and conservation vector $z \in \mathbb{R}_{>0}^n$. Then for all $X' \in \mathit{Reach}(\mathcal{N}, X_0)$, the following element-wise upper bound holds:

$$[X']_j \leq \frac{z^\top X_0}{z_j} \qquad j \in \ \{1, \dots, n\} \tag{4.37}$$

Proof. (Indirect)
Let us assume that there exists a state X' which is reachable from X_0 and for some $j \in \ \{1\ \dots\ , n\}$:

$$[X']_j > \frac{z^\top X_0}{z_j} \tag{4.38}$$

Since X' is reachable from X_0 according to *Lemma* 1 we have that

$$\frac{z^\top X'}{\zeta} \leq \frac{z^\top X_0}{\zeta} \tag{4.39}$$

otherwise the maximal coordinate value of the states reachable from X' would be higher than $\frac{z^\top X_0}{\zeta}$, but this would also mean that the maximal coordinate value of the states reachable from X_0 is strictly higher than $\frac{z^\top X_0}{\zeta}$. From the above inequality and the indirect

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assumption we get:

$$z^\top X_0 \geq \sum_{i=1}^{n} z_i [X^{'}]_i = \sum_{\substack{i=1 \\ i \neq j}}^{n} z_i [X^{'}]_i + z_j [X^{'}]_j > \sum_{\substack{i=1 \\ i \neq j}}^{n} z_i [X^{'}]_i + z^\top X_0 \tag{4.40}$$

from which it follows that

$$\sum_{\substack{i=1 \\ i \neq j}}^{n} z_i [X^{'}]_i < 0 \tag{4.41}$$

Since $z_j > 0$ for all $j = 1, \ldots, n$, it follows that $[X^{'}]_j < 0$ for some j, which is a contradiction. Therefore, the bound of Eq. (4.37) holds.

□

In order to determine the above upper bound, one has to compute a conservation vector z. This can be done, e.g. by solving the following LP minimization:

$$\begin{aligned} &\min_z \sum_{j=1}^{n} z_j \\ &\quad s.t. \\ &z^\top \Gamma \leq 0^{1 \times m} \\ &z \succeq 0^m + \varepsilon^m, \ \varepsilon \succ 0^m \end{aligned}$$

Given the initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$, one can derive an n-dimensional hyperrectangle $\mathcal{H}_{X_0}$ containing all the states $X \in Reach(\mathcal{N}, X_0)$. One corner point of $\mathcal{H}_{X_0}$ is 0^n and the farthest point from 0^n is X_{max}, which is defined as

$$[X_{max}]_j = \frac{z^\top X_0}{z_j}, \qquad j = 1, \ldots, n. \tag{4.42}$$

By means of the non-negative integer points of $\mathcal{H}_{X_0}$, a conservative upper bound can be derived for the maximal length of admissible cycle-free reaction sequences from X_0 to $X^{'}$:

$$\sum_{i=1}^{l} [c_{max}]_i \leq \prod_{i=1}^{n} ([X_{max}]_i + 1) \tag{4.43}$$

The above inequality can be used to complete the feasibility problem of reachability and coverability defined by equations ((4.21), (4.23)-(4.29)) and equations ((4.22) - (4.29)).

It is possible to improve the upper bound given in Eq. (4.43) by making use of subconservative property of a d-CRN.

Proposition 13. Let us consider a subconservative d-CRN $\mathcal{N}$ with a conservation vector $z \in \mathbb{R}^n_{>0}$ and initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$. Introduce the notation $X_{max} \in \mathbb{Z}^n_{\geq 0}$ according to Eq. (4.42) for the vector containing the maximal coordinate values of the reachable states

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along each dimension. Then any state X' reachable from X_0 is an element of the simplex $\Sigma_{X_{max}}$ defined by X_{max}:

$$\Sigma_{X_{max}} = \left\{ x \in \mathbb{R}^n_{\geq 0} \middle| \sum_{i=1}^{n} \frac{x_i}{[X_{max}]_i} \leq 1 \right\} \tag{4.44}$$

Proof. Let us substitute X_0 into the equation of the above defined simplex (4.44)

$$\sum_{i=1}^{n} \frac{[X_0]_i}{[X_{max}]_i} = \sum_{i=1}^{n} \frac{[X_0]_i z_i}{z^\top X_0} = \frac{1}{z^\top X_0} \sum_{i=1}^{n} [X_0]_i z_i = 1 \tag{4.45}$$

Let us assume that there exists a state X' such that $X_0 \rightsquigarrow_{\mathcal{N}} X'$ and $\sum_{i=1}^{n} \frac{[X']_i}{[X_{max}]_i} > 1$ (i.e. X' is out of $\Sigma_{X_{max}}$ and reachable from X_0). Then the following holds:

$$\frac{z^\top X'}{z_i} \leq \frac{z^\top X_0}{z_i} \tag{4.46}$$

from which we get

$$\sum_{i=1}^{n} \frac{[X']_i}{[X_{max}]_i} \leq \sum_{i=1}^{n} \frac{[X_0]_i}{[X_{max}]_i} = 1 \tag{4.47}$$

This is a contradiction.

□

It can be seen that Eq. (4.44) explicitly contains the non-zero extreme points of the simplex as the entries of X_{max}. We note that $\Sigma_{X_{max}}$ can be equivalently defined using the initial state X_0 and the conservation vector z as

$$\Sigma_{X_{max}} = \left\{ x \in \mathbb{R}^n_{\geq 0} \;\middle|\; z^\top x \leq z^\top X_0 \right\}. \tag{4.48}$$

Making use of the subconservative property, instead of the hyperrectangle $\mathcal{H}_{X_0}$, $\Sigma_{X_{max}}$ can be used to construct an improved upper bound on the number of reactions along a cycle-free reaction sequence.

The number of non-negative integer points $\mathcal{Q}(\Sigma)$ of an n-dimensional simplex Σ defined by the points $[a_1\ 0\ \ldots\ 0]^\top$, $[0\ a_2\ \ldots\ 0]^\top$, $\ldots$, $[0\ 0\ \ldots\ a_n]^\top$, $[0\ 0\ \ldots\ 0]^\top$ can be bounded by the following expression [125]:

$$\mathcal{Q}(\Sigma) \leq \frac{1}{n!}(a_1(1+a)-1)(a_2(1+a)-1)\ \ldots\ (a_n(1+a)-1) \tag{4.49}$$

where $a = \frac{1}{a_1} + \frac{1}{a_2} + \ldots + \frac{1}{a_n}$, $a_i \geq 1$ $i = 1, \ldots, n$ and $n \geq 3$. Thus, if $n \geq 3$, the number of non-negative integer points in $\Sigma_{X_{max}}$ is bounded as follows:

$$\mathcal{Q}(\Sigma_{X_{max}}) \leq \frac{1}{n!} \prod_{i=1}^{n} \left[\frac{1}{z_i}(z^\top X_0 + \sum_{j=1}^{n} z_j) - 1 \right] \tag{4.50}$$

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Furthermore, if $z_i = z_j$ $i, j = 1, \ldots, n$, then Eq. (4.50) is simplified as follows:

$$\mathcal{Q}(\Sigma_{X_{max}}) \leq \frac{1}{n!}\Big(\frac{z^\top X_0 - \zeta}{\zeta} + n\Big)^n \tag{4.51}$$

Using the above inequalities, the new upper bound for the number of reactions along a directed cycle-free path is as follows:

$$\sum_{i=1}^{l} [c_{max}]_i \leq \mathcal{Q}(\Sigma_{X_{max}}) \tag{4.52}$$

Then the following extended result can be stated for the subconservative reachability problem.

Proposition 14. Let us consider a subconservative d-CRN $\mathcal{N}$ with conservation vector $z \in \mathbb{R}^m_{>0}$ and non-zero initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$. Let us define the maximal coordinate values along each dimension by the vector X_{max} according to (4.42). Consider an arbitrary non-negative state $X \in \Sigma_{X_{max}}$ and $X^* \notin \Sigma_{X_{max}}$. Then X^* is not reachable from X.

Proof. (Indirect)
Let us assume that there exists a state $X^* \in \mathbb{Z}^n_{\geq 0}$ such that $X^* \notin \Sigma_{X_{max}}$ and $X \rightsquigarrow X^*$ where $X \in \Sigma_{X_{max}}$. Then

$$\sum_{i=1}^{n} \frac{[X^*]_i}{[X_{max}]_i} = \sum_{i=1}^{n} \frac{[X^*]_i z_i}{z^\top X_0} > 1 \tag{4.53}$$

from which we get

$$z^\top X^* > z^\top X_0 \tag{4.54}$$

Since X^* is reachable from X: $\exists c \in \mathbb{Z}^l_{\geq 0}$ for which

$$X^* = X + \Gamma_{\mathcal{N}} c \tag{4.55}$$

Let us multiply both sides by $z^\top$:

$$z^\top (X^* - X) = z^\top \Gamma_{\mathcal{N}} c \tag{4.56}$$

Since $X \in \Sigma_{X_{max}}$, the inequality $z^\top X \leq z^\top X_0$ holds which implies that $z^\top (X^* - X) > 0$ while $z^\top \Gamma_{\mathcal{N}} c < 0$ which is a contradiction. □

Given the target state $X' \in \mathbb{Z}^n_{\geq 0}$ to be reached from a predefined non-zero initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$, consider the non-zero state $X'' = X' - v$ where all the entries of v are equal to 0 except for some $j = 1, \ldots, n$ for which $v_j = 1$. By means of X'' we define the following simplex:

$$\Sigma_{X''_{max}} = \left\{ x \in \mathbb{R}^n_{\geq 0} \mid \sum_{i=1}^{n} \frac{x_i}{[X''_{max}]_i} \leq 1 \right\} \tag{4.57}$$

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where $[X''_{max}]_i = \frac{z^\top X''}{z_i}$ for $i = 1, \ldots, n$. According to Proposition 14, all the reachable states are out of the simplex $\Sigma_{X''_{max}}$, thus one can reduce the bound of the maximal length along directed cycle-free paths from X_0 to X' by the number of non-zero integer points of $\Sigma_{X''_{max}}$:

$$\sum_{i=1}^{m} [c_{max}]_i \leq K^{sub} = \mathcal{Q}(\Sigma_{X_{max}}) - \mathcal{Q}(\Sigma_{X''_{max}}) \tag{4.58}$$

As a special case, let us consider a subconservative d-CRN for which $r_i \in \mathbb{Z}^m_{\leq 0}$ for all $i = 1, \ldots, l$. In this particular case the farthest point of the hyperrectangle $\mathcal{H}_{X_0}$ from 0^n is determined by X_0, i.e. $X_{max} = X_0$. Since there is no reaction producing new molecules, for all $X' \in \mathbb{Z}^n_{>0}$, $[X']_i > [X_0]_i$ for some $i = 1, \ldots, n$, X' is not reachable from X_0. Hence the maximal length of cycle-free reaction sequences can be bounded by the following term:

$$\sum_{i=1}^{l} [c_{max}]_i \leq \mathcal{Q}(\mathcal{H}_{X_0}) - \Big(\mathcal{Q}(\mathcal{H}_{X'}) - 1\Big) \tag{4.59}$$

Superconservative case

Making use of Proposition 11 the reachability problem of a superconservative d-CRN can be reformulated as the reachability problem of a subconservative reaction network. This way all the upper bounds obtained for reaction (state transition) sequences of subconservative reaction networks can be employed for the analysis of superconservative d-CRNs.

Conservative case

In this section we consider conservative reaction networks, i.e d-CRNs for which there exists a conservation vector $z \in \mathbb{R}^n_{>0}$ so that $z^\top \Gamma = 0$. Note that the conservativity of an n-dimensional d-CRN can be checked in polynomial time using the following LP formulation:

$$\begin{aligned} &\min_z \sum_{j=1}^{n} z_j \\ &\quad s.t. \\ &z^\top \Gamma = 0^{1\times l} \\ &z \succeq \varepsilon^l,\ \varepsilon \succ 0^l \end{aligned}$$

Due to the scalability of z, the choice of ε is arbitrary.

From the definition of conservativity it follows that $\mathcal{X}_{X_0}$ is a closed bounded hypersurface, hence it can be projected to a simplex of dimension $g = rank(\Gamma)$.

Let us consider the projection $\mathcal{P} : \mathbb{R}^n \to \mathbb{R}^g$ for which the transformation matrix is denoted by $T \in \mathbb{Z}^{n\times g}$. All the integer points of $\mathcal{X}_{X_0}$ – including all possible states reachable from X_0 (i.e. $\forall\ X \in Reach(\mathcal{N}, X_0)$) – will also be integer ones after applying

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the transformation, i.e.:

$$X \in \mathbb{Z}^n_{\geq 0} \; and \; X \in \mathcal{X}_{X_0} \Rightarrow \mathcal{P}(X) = TX \in \mathbb{Z}^g_{\geq 0}$$

Hence we can consider the integer point enumeration problem in the projected space, instead of that of $\mathcal{X}_{X_0}$. It is known that $\mathcal{P}(\mathcal{X}_{X_0})$ is an g-dimensional simplex of some points $[p_1\ 0\ \ldots\ 0]^\top$, $[0\ p_2\ \ldots\ 0]^\top$, $\ldots$, $[0\ 0\ \ldots\ p_g]^\top$, $[0\ 0\ \ldots\ 0]^\top$, where $p_1,\ p_2, \ldots, p_g \in \mathbb{R}_{\geq 0}$. In order to obtain upper bound for the integer points – by means of Eq. (4.49) – the exact values of $p_i,\ i = 1,\ 2,\ \ldots\ , g$ are needed, which can be easily bounded from above by X_{max}. This way an upper bound for the length of cycle-free reaction sequences for conservative d-CRNs can be provided as:

$$\sum_{i=1}^{m} [c_{max}]_i \leq K^{con} = \frac{1}{g!} \prod_{i=1}^{g} \left[\frac{1}{z_i} (z^\top X_0 + \sum_{j=1}^{g} z_j) - 1 \right] \tag{4.60}$$

4.7.4 Computational solution of the reachability problem

Using the upper bounds obtained in the previous sections for the maximal length of feasible cycle-free reaction sequences, in this section we formulate the reachability and coverability problems in the form of integer feasibility problems.

Consider a subconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. Let us denote the initial state of the system by $X_0 \in \mathbb{Z}^n_{\geq 0}$. We wish to decide the following problems:

(P_1) Let $X' \in \mathbb{Z}^n_{\geq 0}$ be an arbitrary target state. Is X' reachable from X_0?

(P_2) Let $y \in \mathcal{C}$ be an arbitrary complex. Is it possible to reach a state $X' \in \mathbb{Z}^n_{\geq 0}$ from X_0 so that y is charged at X'?

The above questions can be answered by the following IP feasibility problems:

(P_1)

$$\begin{cases} X_0 + \Gamma_{\mathcal{N}} c = X' \\ v_j \in \{0,1\}^l \qquad j = 1, \ldots, K \\ \sum_{i=1}^{l} [v_j]_i \leq 1 \qquad j = 1, \ldots, K \\ X_0 + \Gamma_{\mathcal{N}} \sum_{i=1}^{k} v_i \geq \Gamma^-_{\mathcal{N}} v_{k+1} \quad k = 1, \ldots, K-1 \\ \sum_{i=1}^{l} [v_j]_i \leq \sum_{i=1}^{l} [v_{j+1}]_i \quad j = 1, \ldots, K-1 \end{cases} \tag{4.61}$$

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(P_2)

$$\begin{cases} X_0 + \Gamma_{\mathcal{N}} c \geq y \\ v_j \in \{0,1\}^l \qquad j = 1, \ldots, K \\ \sum_{i=1}^{l} [v_j]_i \leq 1 \qquad j = 1, \ldots, K \\ X_0 + \Gamma_{\mathcal{N}} \sum_{i=1}^{k} v_i \geq \Gamma_{\mathcal{N}}^{-} v_{k+1} \quad k = 1, \ldots, K-1 \\ \sum_{i=1}^{l} [v_j]_i \leq \sum_{i=1}^{l} [v_{j+1}]_i \quad j = 1, \ldots, K-1 \end{cases} \tag{4.62}$$

where K is given by K^{sub} in (4.58) for subconservative and K^{con} in (4.60) for conservative d-CRNs. The lattice of feasible solutions in both cases is represented by the vectors v_j, $j = 1, \ldots, K$. The number of decision variables equals to $K \cdot l$. To check the feasibility of the above problems one has to find an integer lattice point in the feasibility regions defined by the inequalities and equalities.

It is important to note that, according to Eq. (4.58) and Eq. (4.60), K is not polynomial in n (the dimensionality of the d-CRN, i.e. $|S|$), but n is known to be constant for a given reaction network. Furthermore K can be greater than the minimally required number of steps for reaching a prescribed target state X', which may imply zero vectors v_j in the solution for some $j = 1, \ldots, K$. The position of zero vectors among the non-zero ones does not affect the solution but makes redundancy, hence the following ordering constraints are introduced to exclude additional feasible permutations of the same set of reactions:

$$\sum_{i=1}^{l} [v_j]_i \leq \sum_{i=1}^{l} [v_{j+1}]_i \quad j = 1, \ldots, K-1 \tag{4.63}$$

Once the feasibility problems (4.61) and (4.62) are equipped with the above inequality constraints each feasible solution represents a distinct reaction (state transition) sequences between the prescribed initial and target states. We note that the Barvinok's algorithm can be used to count all the distinct sequences. Furthermore, the feasibility problems can be easily extended with addition linear constraints on the decision variables to decide the feasibility in constrained convex sets.

The above feasibility problems can be easily equipped with linear objective functions to form integer programs. For example:

$$\min \left\{ \sum_{j=1}^{K} \sum_{i=1}^{l} [v_j]_i \right\} \tag{4.64}$$

can be used to find a path of minimal length.

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4.7.5 Examples

In this section we illustrate our methods on two examples. Beyond the IP feasibility approach, we equipped Eqs. (4.61) and Eqs. (4.62) with a linear objective function of the form $\sum_{j=1}^{m} c_j$. The resulting integer programs are capable of finding state transition sequences from the initial state X_0 to a prescribed target state X' (or a set of well-defined target states $\mathcal{X}'$). We also implemented the next reaction method [152] – as it was presented in [113] – to simulate the stochastic behavior of the studied d-CRNs. We note that theoretically it is also possible to count the number of feasible solutions using Barvinok's algorithm for which there exists computer implementation [142].

The algorithms were implemented in Python 2.7 and we employed Gurobi as mathematical optimization solver [153]. All the computations were performed on a Lenovo P51s workstation having two 2.70GHz i7-7500U CPUs and 32GB RAM (DDR4 2133 MHz).

Example 1: A conservative d-CRN with extinction event

Let us consider the d-CRN taken from [121]. The reaction network structure is depicted in Figure 4.4.

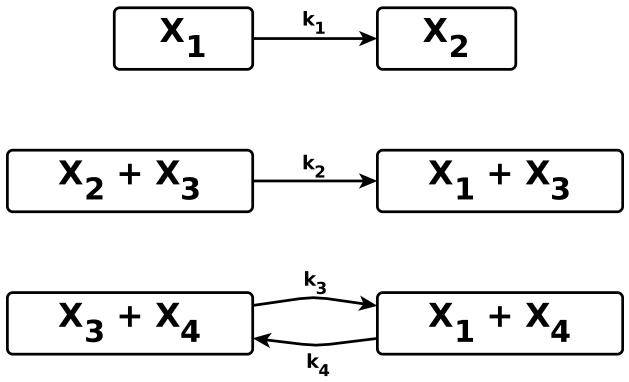

Figure 4.4: Reaction network structure of *Example 1*

The associated stoichiometric matrix is as follows

$$\Gamma = \begin{bmatrix} -1 & 1 & 1 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{4.65}$$

Based on the stoichiometric matrix Γ, it can be seen that the above d-CRN is conservative with a conservation vector $z = [1,\ 1,\ 1,\ 1]^\top$. Assuming deterministic mass action kinetics, one can describe this d-CRN with the following system of ordinary differential equations:

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$$\begin{aligned}
\frac{dx_1(t)}{dt} &= -k_1x_1(t) + k_2x_2(t)x_3(t) + k_3x_3(t)x_4(t) - k_4x_1(t)x_4(t)\\
\frac{dx_2(t)}{dt} &= k_1x_1(t) - k_2x_2(t)x_3(t)\\
\frac{dx_3(t)}{dt} &= -k_3x_3(t)x_4(t) + k_4x_1(t)x_4(t)\\
\frac{dx_4(t)}{dt} &= 0
\end{aligned} \tag{4.66}$$

where $x_i(t),\ i = 1,2,3,4$ denotes the concentration of the ith species at time t and $k_i,\ i = 1,2,3,4$ is the reaction rate constant associated to reaction r_i.

The time evolution of the molecular counts in the case of the respective stochastic d-CRN is given by the following state equations:

$$\begin{aligned}
X_1(t) &= X_1(0) - Y_1(k_1\int_0^t X_1(\tau)d\tau) + Y_2(k_2\int_0^t X_2(\tau)X_3(\tau)d\tau) - Y_3(k_3\int_0^t X_3(\tau)X_4(\tau)d\tau)\\
X_2(t) &= X_2(0) + Y_1(k_1\int_0^t X_1(\tau)d\tau) - Y_2(k_2\int_0^\tau X_2(\tau)X_3(\tau)d\tau)\\
X_3(t) &= X_3(0) - Y_3(k_3\int_0^t X_3(\tau)X_4(\tau)d\tau) + Y_4(k_4\int_0^t X_1(\tau)X_4(\tau)d\tau)\\
X_4(t) &= X_4(0)
\end{aligned} \tag{4.67}$$

where $X_i(t),\ i = 1,\dots,4$ denotes the molecular count for the ith species, and Y_j for $j = 1,\dots,4$ are independent unit-rate (unit-intensity) homogenous Poisson processes.

For a general initial state $X_0 = [K\ L\ M\ N]^\top \in \mathbb{Z}^4_{\geq 0}$, the target state $X' = [0\ (K + L + M)\ 0\ N]^\top$ is reachable which gives an extinction event, since X_2 depletes both X_1 and X_3 which are necessary for firing all of the reactions. In the sequel we justify this reachability argument by employing the proposed IP framework.

We consider this d-CRN with the following particular parametrization: $k_1 = 4.7$, $k_2 = 2.4$, $k_3 = 4.9$, $k_4 = 0.3$. The initial state is $X_0 = [X_1(0)\ X_2(0)\ X_3(0)\ X_4(0)]^\top = [15\ 10\ 20\ 20]^\top$. Assuming deterministic mass action kinetics, our parametrization from X_0 results in equilibrium with $x_1 \approx 12.27$, $x_2 \approx 31.98$, $x_3 \approx 0.75$ and $x_4 = 20$. Considering the discrete state system one can see that in the absence of X_1 and X_3 this d-CRN has no reaction which is able to fire. Employing the feasibility framework (4.61) one can check the reachability of such a target state, namely $X' = [0,\ 45,\ 0,\ 20]$. We solved the IP problem (4.61) equipped with the objective function $\sum_{j=1}^{l} c_j$. From the minimization we get that $c_{opt} = [35\ 0\ 20\ 0]^\top$, i.e. through the first and third reactions one can reach X' during 55 occurences of these reactions. The determined discrete state transition sequence of the shortest path is depicted in Figure 4.7.

After running the next reaction method several times from the prescribed initial state

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X_0, we obtained a representative sample path reaching the critical state $X^{'}$. This is shown in Figure 4.5. Note that the depicted state transition sequence is not the shortest path that we determined by the IP.

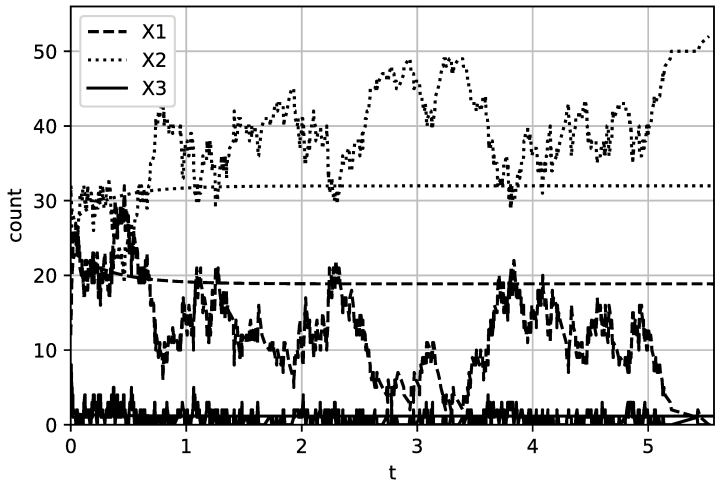

Figure 4.5: A sample trajectory of *Example 1* for which the finial state is equal to $X^{'} = [0,\ 45,\ 0,\ 20]^{\top}$. For each species the continuous deterministic trajectory (smooth curve) and the stochastic discrete state counterpart are depicted with the same line type. Note that the target state can also be reached by fewer occurences of the reactions.

The feasibility approach has the advantage that it can be easily generalized to check the reachability of a set of states having prescribed properties. It is known that considering deterministic mass action kinetics, the system reaches a positive equilibrium point, for which $x_2(t) \succ x_1(t)$. Modifying the framework (4.61) one can check the reachability of states significantly differing from the deterministic equilibrium point. Instead of $\Gamma c = X^{'} - X_0$ in (4.61), we employ the following inequalities for feasibility analysis:

$$\begin{aligned} [X_0 + \Gamma c]_1 &\geq X_2^{det} \\ [X_0 + \Gamma c]_2 &\leq X_1^{det} \\ [X_0 + \Gamma c]_3 &\leq X^{max} \end{aligned} \tag{4.68}$$

where $X_1^{det} = 20$, $X_2^{det} = 32$ are upper estimates for the deterministic case equilibrium values of x_1 and x_2, respectively, if the initial state is $X_0 = [13\ 32\ 8]^{\top}$. Based on the IP (4.61) equipped with the objective $\sum_{j=1}^{l} c_j$ to be minimized, we proved that there exists a reachable state for which the above conditions hold. The state transition sequence corresponding to the shortest path computed by *Algorithm 1* is depicted in Figure 4.7.

The existence of such a reachable state is also confirmed through simulation based on the next reaction method. A simulated sample path is depicted in Figure 4.6 and states of

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interest are denoted by an arrow: while the deterministic system approaches equilibrium, the stochastic counterpart satisfies the constraint set (4.68).

This example illustrates that by the proposed framework we can detect extinction events in the discrete model even if the continuous model exhibits steady state.

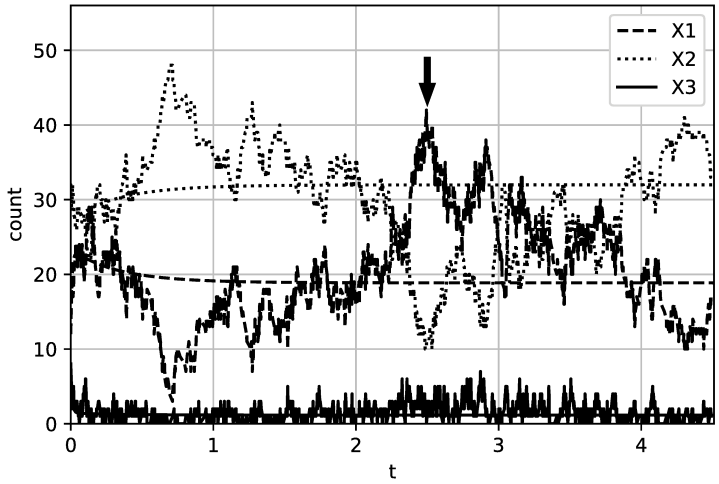

Figure 4.6: A sample trajectory of *Example 1* for which a subset of the states significantly differ from the equilibrium point of the deterministic mass action system. The arrow is pointing to the states where the conditions (4.68) hold, though the deterministic counterpart approaches positive equilibrium. The continuous deterministic (smooth) and the stochastic discrete state trajectories of the same species are depicted using the same line type.

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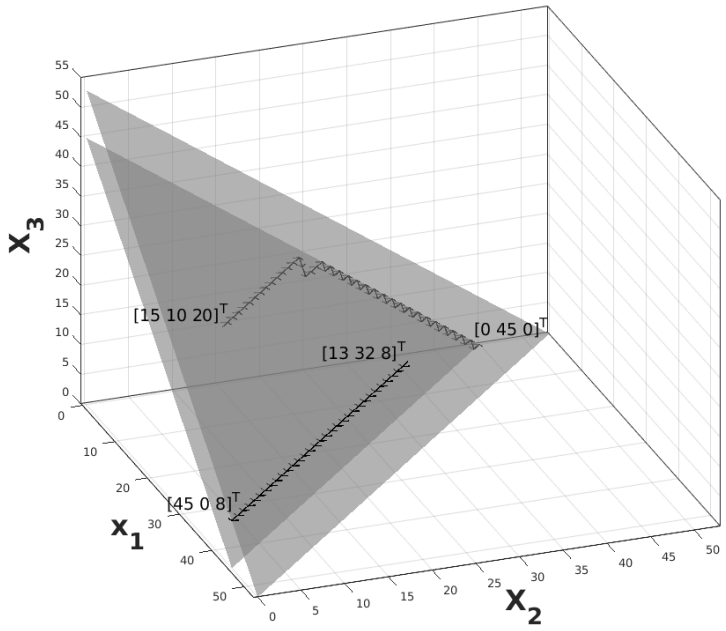

Figure 4.7: Minimal-length state transition sequences of *Example 1* proving the reachability cases $[13\ 32\ 8]^\top \rightsquigarrow [45\ 0\ 8]^\top$ and $[15\ 10\ 20]^\top \rightsquigarrow [0\ 45\ 20]^\top$, respectively. The conservativity surfaces (positive stoichiometric compatibility classes) associated to the initial states are denoted in gray color.

Example 2: A subconservative d-CRN

In the second example we consider a SIRS epidemiological model having three species and four reactions. The reaction network structure is depicted in Figure 4.8. The model describes the time evolution of the susceptible, infected and recovered species of a closed system. Susceptible species become infected with intensity proportional to β, while infected species get recovered with intensity proportional to γ. The death-rate of infected species is proportional to parameter μ. Recovered species get susceptible with intensity proportional to w.

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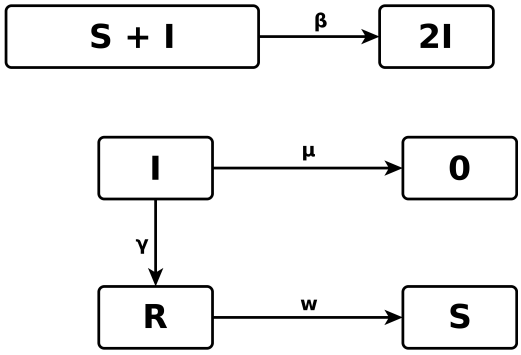

Figure 4.8: Reaction network structure of the epidemiological model in *Example 2*. Note that **0** denotes the zero-complex.

Assuming large population number, such a system can be characterized by the following deterministic differential equation system:

$$\begin{aligned}\frac{ds(t)}{dt} &= wr(t) - \beta s(t)i(t)\\ \frac{di(t)}{dt} &= \beta s(t)i(t) - \gamma i(t) - \mu i(t)\\ \frac{dr(t)}{dt} &= \gamma(t)i(t) - wr(t)\end{aligned} \tag{4.69}$$

where s, i, and r denote the continuous number of susceptible, infected, and recovered individuals, respectively.

For the case of small population numbers, we consider the following state equations:

$$\begin{aligned}S(t) &= S(0) + Y_1(w\int_0^t R(\tau)d\tau) - Y_2(\beta\int_0^t S(\tau)I(\tau)d\tau)\\ I(t) &= S(0) + Y_2(\beta\int_0^t S(\tau)I(\tau)d\tau) - Y_3(\gamma\int_0^t I(\tau)d\tau) - Y_4(\mu\int_0^t I(\tau)d\tau)\\ R(t) &= R(0) + Y_3(\gamma\int_0^t I(\tau)d\tau) - Y_1(w\int_0^t R(\tau)d\tau)\end{aligned} \tag{4.70}$$

where S, I, and R are the integer numbers of susceptible, infected, and recovered individuals, respectively. Moreover, Y_k for $k = 1, \ldots, 4$ are independent unit-rate Poisson processes.

The stoichiometric matrix associated to the system is the following:

$$\Gamma = \begin{bmatrix}-1 & 0 & 0 & 1\\ 1 & -1 & -1 & 0\\ 0 & 1 & 0 & -1\end{bmatrix} \tag{4.71}$$

Based on Γ it can be seen that the system is subconservative with a particular conservation vector $z = [1\ 1\ 1]^\top$.

In our simulation setting the parameters had the following values: $\beta = 0.18$, $\gamma = 0.9$,

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$\mu = 0.05$ and $w = 0.39$, respectively. Firstly, we consider the reachability of the target state $X^{'} = [0\ 52\ 0]^{\top}$ where all the individuals are infected. As initial states we choose $X_0^1 = [50\ 2\ 0]^{\top}$ and $X_0^2 = [10\ 26\ 10]^{\top}$.

Employing the IP (4.61) equipped with $\sum_{j=1}^{l} c_j$ we found that there exist paths from the above initial state to $X^{'}$. The determined shortest paths are depicted in Figure 4.9 with black color. Note that these are partially overlapping reaction sequences. The subconservativity surface which is the same for the two initial states is shown in gray. All the states reachable from X_0^1 and X_0^2 are located on the surface or below that.

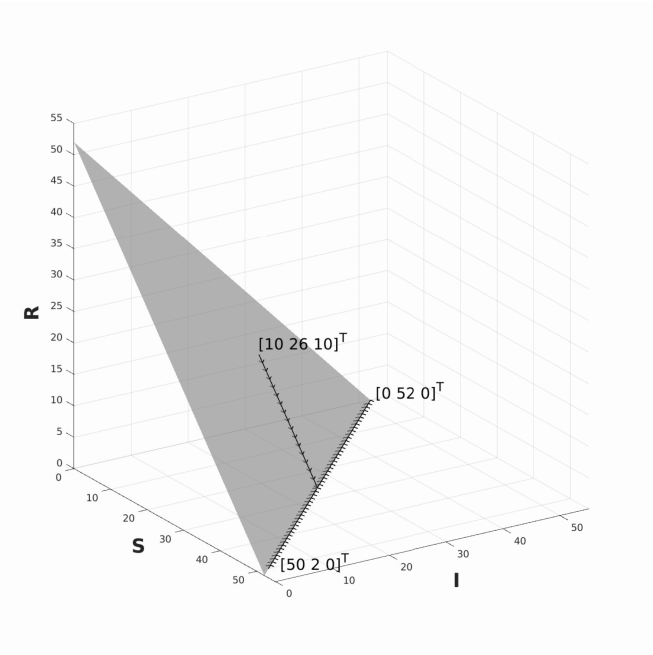

Figure 4.9: The bounded state space of *Example 2*. The conservativity hypersurface is denoted by gray color. Shortest state transition sequences starting from $[50\ 2\ 0]^{\top}$ and $[10\ 26\ 10]^{\top}$, respectively, and reaching $[0\ 52\ 0]^{\top}$ (where all the individuals are infected) are depicted in black color.

By means of the presented IP framework equipped with cost function $\sum_{i=1}^{m} c_i$ we determined a finite reaction sequence starting from $X_0 = [50\ 2\ 0]^{\top}$ for which the final infected count is equal to zero meaning the complete regression of the disease. This can be achieved by introducing the following linear equality constraint:

$$X^{'}(2) = 0 \tag{4.72}$$

Such a sample path simulated by the next reaction method is depicted in Figure 4.10 along the respective deterministic dynamical behavior. In Figure 4.11*a* one can see a shortest state transition sequence determined by the IP, while in Figure 4.11*b* the state transition sequence associated to the stochastic sample path in Figure 4.10 is shown.

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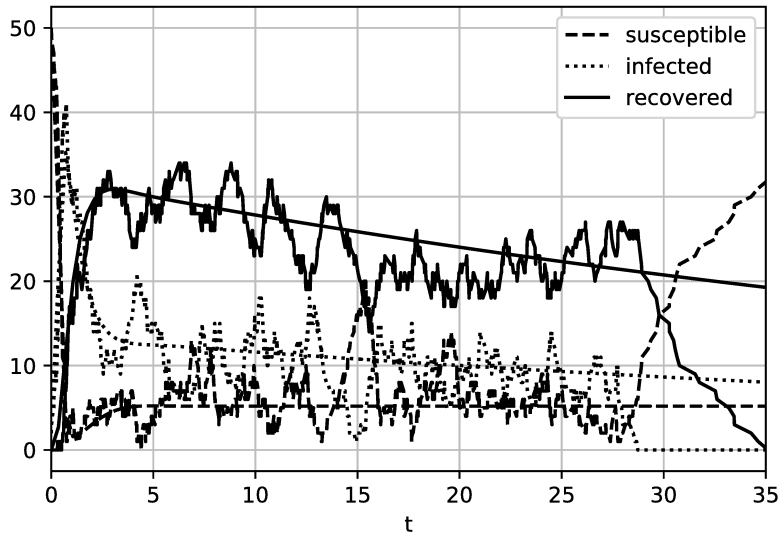

Figure 4.10: A sample path of *Example 2* for which the dynamical behavior significantly differs from that of the deterministic model. We use the same line type to denote the continuous deterministic (smooth) and the stochastic discrete state trajectories of the same species.

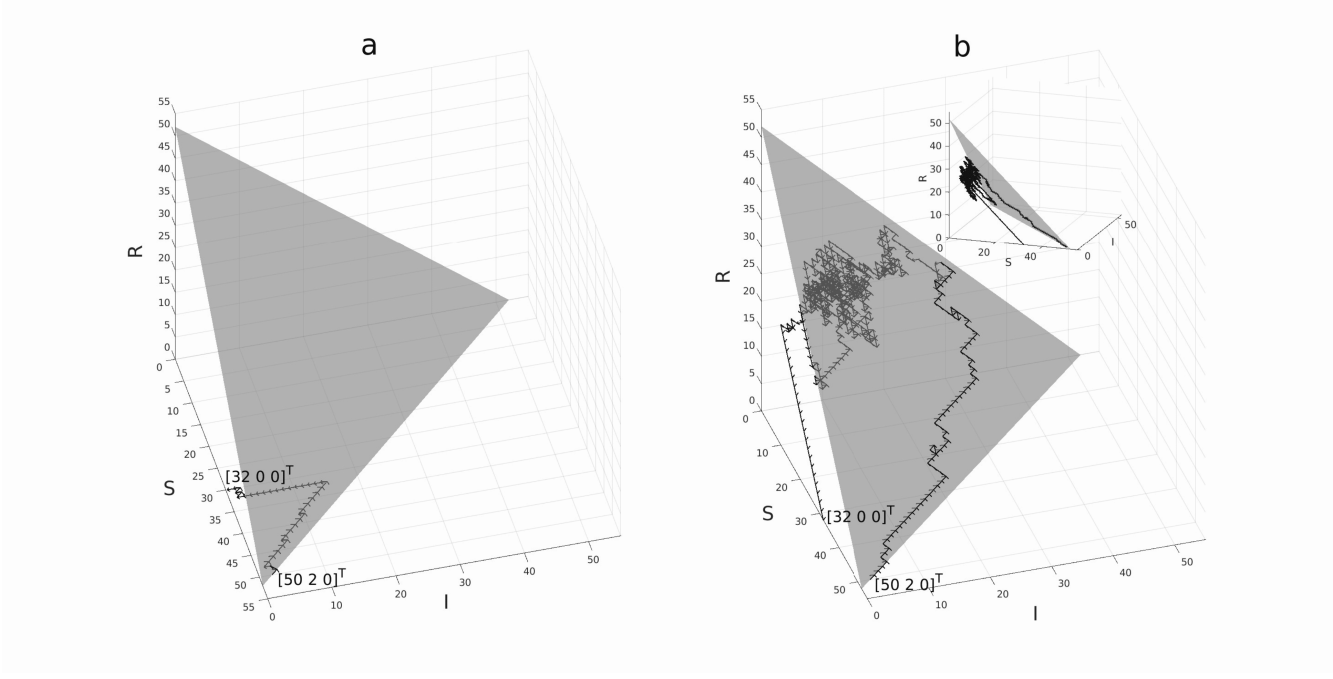

Figure 4.11: State transition sequences reaching the same target state $[32\ 0\ 0]^\top$ where the disease vanishes. The conservativity surface is denoted by gray color. **a)** the shortest path determined by IP, **b)** a path simulated by the next reaction method.

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4.7.6 Relaxed conditions for d-CRN reachability

This section provides conditions under which the d-CRN reachability problem is equivalent to the existence of a non-negative integer solution of the respective discrete state equation, formally we give condition for which:

$$X_0 + \Gamma c = X' \Leftrightarrow X_0 \rightsquigarrow X' \tag{4.73}$$

Low-dimensional case

In this section the case of low-dimensional ($rank(\Gamma) \leq 2$) sub-and superconservative d-CRNs are considered.

In order to discuss low-dimensional reachability problems we introduce a distinguished state $M = M(\Gamma^-)$ as follows:

$$[M(\Gamma^-)]_i = max\Big\{[\Gamma^-]_{ij} : j = 1, \ldots, l\Big\} \qquad i = 1, \ldots, n. \tag{4.74}$$

where Γ^- is defined by Eq. (4.7). Note that the set $\{X \mid X \in \mathbb{Z}^n_{\geq 0},\ X \succeq M\}$ contains all the states where each reaction is charged.

Proposition 15. Let us consider a subconservative d-CRN $\mathcal{N}$ with stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$. Assume that $rank(\Gamma) \leq 2$. We consider an initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$ and a target state $X^{'} \in \mathbb{Z}^n_{\geq 0}$ such that $X_0 \succeq M$ and $X^{'} \succeq M$ hold where $M = M(\Gamma^-)$ is defined by Eq. (4.74). Then the state $X^{'}$ is reachable from X_0 through a state transition sequence $\sigma_X = X_0 X_1 \ldots X^{'}$ for which $\forall X \in \sigma_X,\ X \succeq M$ if and only if the equation

$$\Gamma c = X^{'} - X_0 \tag{4.75}$$

has a non-negative integer solution c.

Proof.

1. If $X^{'}$ is reachable from X_0 through an admissible state transition sequence σ_X, then it follows that a solution $c \in \mathbb{Z}^l_{\geq 0}$ exists.

2. Assume that there exists $c \in \mathbb{Z}^n_{\geq 0}$ such that $X_0 + \Gamma c = X^{'}$ holds. Let us consider any reaction vector decomposition $\sigma_r = r_{\nu(1)} \ldots r_{\nu(h)}$ of c where $\sum_{j=1}^{h} r_{\nu(j)} = c$ and $\sum_{j=1}^{l} [c]_j = h$. We show that Algorithm 3 returns a permutation of σ_r so that for all the transition states X the inequality $X \succeq M$ holds.

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Algorithm 3

procedure REORDER(X_0 $[r_{\nu(1)}\ r_{\nu(2)} \dots r_{\nu(h)}]$, M)
  $X_{current} \leftarrow X_0$
  for $i = 1$ to h **do**
    if $X_{current} = X^{'}$ **then**
      return $[r_{\nu(1)}\ r_{\nu(2)}\ \dots\ r_{\nu(h)}]$
    end if
    if $[X_{current} + r_{\nu(i)}]_l < [M]_l$ **for some** $l = 1, \dots, n$ **then**
      Choose a transition vector $r_{\nu(j)}$, $i < j \leq h$ *so that* $X_{current} + r_{\nu(j)} \succeq M$
      $r^{'} \leftarrow r_{\nu(i)}$
      $r_{\nu(i)} \leftarrow r_{\nu(j)}$
      $r_{\nu(j)} \leftarrow r^{'}$
    end if
    $X_{current} \leftarrow X_{current} + r_{\nu(i)}$
  end for
  return $[r_{\nu(1)}\ r_{\nu(2)}\ \dots\ r_{\nu(h)}]$
end procedure

Let us assume that there exists a transition state $X_i, X_i \succeq M$ so that the forthcoming state X_{i+1} satisfies the inequality $[X_{i+1}]_d < [M]_d$ for some $d = 1, 2$. For the target state $X^{'}$ to be reached the inequality $X^{'} \succeq M$ holds, hence there exists a reaction increasing the state variable along the coordinate d. Let us assume that all the reactions increasing the state variable along X_i decrease the other coordinate $d^{'}$ so that the resulted forthcoming state X_{i+1} satisfies the inequality $[X_{i+1}]_{d'} < [M]_{d'}$. Then $X_i = M$ holds. Now there are two different cases:

(P_1) If $X^{'} = M$, then Algorithm 3 terminates, the correctness follows.

(P_2) If $X^{'} \neq M$, then the subconservativity of $\mathcal{N}$ implies that it is not possible to reach a state X, $X \succeq M$, $X \neq M$, i.e. $X^{'}$ is not reachable from X_i. This is contradiction, since arbitrary permutation of the initial ordering σ_r results in the same target state $X^{'}$, given the initial state X_0. Then the correctness of Algorithm 3 follows.

□

The above algorithm can be easily extended to the class of superconservative reaction networks.

Corollary 2. Let us consider a superconservative d-CRN $\mathcal{N}$ with stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^{-} \in 0, 1^{n \times l}$. Assume that $rank(\Gamma) \leq 2$ holds and consider an

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initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$ and a target state $X' \in \mathbb{Z}^n_{\geq 0}$ for which $X_0 \succeq M$ and $X' \succeq M$ hold where M is defined by Eq. (4.74). Then the state $X' \in \mathbb{Z}^n_{\geq 0}$ is reachable from X_0 if and only if the equation

$$\Gamma c = X' - X_0 \tag{4.76}$$

has a non-negative integer solution c.

Proof.
According to Proposition 11 we can consider a subconservative d-CRN $\mathcal{N}'$ of stoichiometric matrix $-\Gamma$ and take the reachability problem $X' \overset{?}{\rightsquigarrow}_{\mathcal{N}'} X_0$. Then Proposition 15 can be applied. □

Sub-and superconservative d-CRNs of arbitrary high state space dimension

In this section the reachability problem of arbitrary high-dimensional sub- and superconservative d-CRNs is considered. Firstly we examine network structures composed of reactions having at most one input and one output species. It is shown by an inductive proof that under some auxiliary condition, the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ is equivalent to the existence of a $c \in \mathbb{Z}^l_{\geq 0}$ solution of the d-CRN state equation $X_0 + \Gamma c = X'$. Then, according to the relation between sub-and superconservative reaction network structures, this result is generalized to a subclass of superconservative d-CRNs, as well. We also extend the results to d-CRNs containing second-order reactions by allowing catalyzer species.

Firstly we adopt the following necessary and sufficient condition of reachability from the theory of Petri nets (see Theorem 16, [143]) which will be extensively used in the sequel.

Lemma 2. Let us consider a d-CRN $\mathcal{N}$ with stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ such that for all $r \in \mathcal{R}$ reactions $\sum_{i=1}^n [\overline{y}^+]_i \leq 1$ and $\sum_{i=1}^n [\overline{y}^-]_i = 1$ holds. Assume that the reaction network of $\mathcal{N}$ does not contain directed cycle (i.e. $\mathcal{N}$ has an acyclic network structure). Consider two states $X_0, X' \in \mathbb{Z}^n_{\geq 0}$. Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ holds if and only if there exists $c \in \mathbb{Z}^l_{\geq 0}$ vector satisfying the state equation $X_0 + \Gamma c = X'$.

Now we can state the result on the reachability of subconservative d-CRNs composed of reaction having at most one input and one output species.

Proposition 16. Let us consider a subconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$ for which $\mathcal{C} = \mathcal{S} \cup \{0\}$. Assume that for all $r \in \mathcal{R}$ reactions $\sum_{i=1}^n [\overline{y}^+]_i \leq 1$ and $\sum_{i=1}^n [\overline{y}^-]_i = 1$ hold. Let us consider two states $X_0,\ X' \in \mathbb{Z}^n_{\geq 0}$ so that $X_0 \succeq M$ and $X' \succeq M$ hold where $M = M(\Gamma^-)$ is defined by Eq. (4.74). Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ holds if and only if there exists a vector $c \in \mathbb{Z}^l_{\geq 0}$ satisfying the state equation $X_0 + \Gamma c = X'$.

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Proof.

1. $X_0 \rightsquigarrow_{\mathcal{N}} X^{'} \quad \Longrightarrow \quad \exists c \in \mathbb{Z}^l_{\geq 0} : \; X_0 + \Gamma c = X^{'}$

   By the definition of reachability it is guaranteed that the state equation is satisfied with some $c \in \mathbb{Z}^l_{\geq 0}$.

2. $X_0 \rightsquigarrow_{\mathcal{N}} X^{'} \quad \Longleftarrow \quad \exists c \in \mathbb{Z}^l_{\geq 0} : \; X_0 + \Gamma c = X^{'}$

   For this side an inductive proof is employed.

   a) $k = 2$

   If a d-CRN is 2-dimensional, according to Proposition 15, the existence of a solution $c \in \mathbb{Z}^l_{\geq 0}$ of the state equation implies that the reachability relation holds.

   b) Inductive assumption

   For $k = n - 1$ we assume that the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ holds.

   c) $k = n$

   We have two different cases with respect to the existence of directed cycles.

   If the reaction network has no directed cycle, then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ is guaranteed by Lemma 2.

   Assume that the reaction network contains at least one directed cycle

$$\sigma_S = s_{\nu(1)} \dots s_{\nu(h)} \tag{4.77}$$

   where $h \leq n$, $s_{\nu(1)} = s_{\nu(h)}$ and $s_{\nu(i)} \neq s_{\nu(j)}$ for $i, j = 1, \dots, h$, $i \neq j$. Note again that $\mathcal{C} = \mathcal{S} \cup \{0\}$, hence σ_S can be considered as a directed cycle of complexes in the reaction network (i.e. $\sigma_S = \sigma_C = s_{\nu(1)} \dots s_{\nu(h)}$). Let us consider an arbitrary $r_{k_1 k_2} \in \mathcal{R}$ reaction defined between some $s_{k_1}, s_{k_2} \in \sigma_S$, i.e. $r_{k_1 k_2} = s_{k_1} \to s_{k_2}$.

   Now we construct a d-CRN $\mathcal{N}^{'} = (\mathcal{S}^{'}, \mathcal{C}^{'}, \mathcal{R}^{'})$ from the stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{(n-1)\times l}$ and $\Gamma^{-} \in \{0, 1\}^{(n-1)\times l}$ as follows:

$$[\Gamma^{'}]_{i,:} = \begin{cases} [\Gamma]_{i,:}, & i < k_{max}, \; i \neq k_{min}, \\ [\Gamma]_{k_{min},:} + [\Gamma]_{k_{max},:}, & i = k_{min}, \\ [\Gamma]_{i+1,:}, & k_{max} \leq i \leq n-1, \end{cases} \tag{4.78}$$

   and

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$$[\Gamma^{-'}]_{i,:} = \begin{cases} [\Gamma^{-}]_{i,:}, & i < k_{max},\ i \neq k_{min}, \\ [\Gamma^{-}]_{k_{min},:} + [\Gamma^{-}]_{k_{max},:}, & i = k_{min}, \\ [\Gamma^{-}]_{i+1,:}, & k_{max} \leq i \leq n-1. \end{cases} \tag{4.79}$$

where $k_{min} = min\{k_1, k_2\}$ and $k_{max} = max\{k_1, k_2\}$. This way we obtained a d-CRN $\mathcal{N}^{'}$ satisfying the assumptions of the proposition. Figure 4.12 gives an illustrative example of how $\mathcal{N}^{'}$ is constructed. Now we assign to each $r^{'} \in \mathcal{R}^{'}$ the ordered pair of source complex and product complex of $r \in \mathcal{R}$ from which it is obtained. In such a way every reaction of $\mathcal{N}^{'}$ is uniquely described by an ordered pair $(r^{'}, r) \in \mathcal{R}^{'} \times \mathcal{R}$. Then by the mapping $P((r^{'}, r)) = r$ one can uniquely determine the reaction $r \in \mathcal{R}$ from which $r^{'} \in \mathcal{R}^{'}$ is derived.

Let us construct the states $X_0^m \in \mathbb{Z}_{\geq 0}^{n-1}$ and $X^{m'} \in \mathbb{Z}_{\geq 0}^{n-1}$ as follow:

$$[X_0^m]_i = \begin{cases} [X_0]_i, & i < k_{max},\ i \neq k_{min}, \\ [X_0]_{k_{min}} + [X_0]_{k_{max}}, & i = k_{min}, \\ [X_0]_{i+1}, & k_{max} \leq i \leq n-1. \end{cases} \tag{4.80}$$

$$[X^{'m}]_i = \begin{cases} [X^{'}]_i, & i < k_{max},\ i \neq k_{min}, \\ [X^{'}]_{k_{min}} + [X^{'}]_{k_{max}}, & i = k_{min}, \\ [X^{'}]_{i+1}, & k_{max} \leq i \leq n-1. \end{cases} \tag{4.81}$$

Then we have that $X_0^m \succeq M(\Gamma^{-'})$ and $X^{'m} \succeq M(\Gamma^{-'})$, hence the $(n-1)$-dimensional d-CRN $\mathcal{N}^{'}$ with the initial and final states X_0^m and $X^{'m}$ satisfies the assumptions of the proposition. From $X_0 + \Gamma c = X^{'}$ we have that $X_0^m + \Gamma^{'} c = X^{'m}$ holds, hence, according to the $(n-1)$-dimensional inductive assumption, the reachability relation

$$X_0^m \rightsquigarrow_{\mathcal{N}'} X^{'m} \tag{4.82}$$

follows.

Let us consider an admissible reaction vector sequence $\sigma_r^{'}$ associated to the relation (4.82). Since for each $r^{'} \in \mathcal{R}^{'}$ we associated the reaction $r \in \mathcal{R}$ from which $r^{'}$ is obtained, making use of the mapping $P : \mathcal{R}^{'} \times \mathcal{R} \to \mathcal{R}$, we can consider the reaction vector sequence σ_r ($r \in \mathcal{R}\ \forall r \in \sigma_r$) uniquely determined by $\sigma_r^{'}$. We start from X_0 and modify the state variable $X \in \mathbb{Z}_{\geq 0}^n$ according the reaction vector sequence σ_r. We may get to two invalid cases:

(C_1) $[X]_{k_2} = 0$, but the source complex of the forthcoming reaction $r_{current} \in$

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σ_r is s_{k_2}. Then, according to the $(n-1)$-dimensional reachability, it is guaranteed that s_{k_1} is charged at the current state X. Let us insert $r_{k_1k_2}$ into σ_r before the current reaction $r_{current}$.

(C_2) $[X]_{k_1} = 0$, but the source complex of the forthcoming reaction $r_{current} \in \sigma_r$) is s_{k_1}. Then, according to the $(n-1)$-dimensional reachability, it is guaranteed that s_{k_2} is charged at the current state X. It is known that s_{k_1} can be reached from s_{k_2} along a reaction vector sequence σ_r^* in the reaction network of $\mathcal{N}$. Let us insert σ_r^* into σ_r before the current reaction $r_{current}$.

By modifying σ_r according to the above discussed cases (C_1) and (C_2), we obtain an admissible reaction vector sequence $\sigma_{r_{mod}}$ with respect to the reachability relation

$$X_0 \rightsquigarrow_{\mathcal{N}'} X^* \tag{4.83}$$

where $X^* \succeq 0^n$, $[X^*]_i = [X']_i$ for $i = 1, \dots n$, $i \neq k_1$ and $i \neq k_2$, moreover $[X^*]_{k_1} + [X^*]_{k_2} = X'$. According to the assumptions $\mathcal{N}$ contains directed paths both from s_{k_1} to s_{k_2} and from s_{k_2} to s_{k_1}, hence the reachability relation $X^* \rightsquigarrow_{\mathcal{N}} X'$ follows. Then, due to the transitivity of the relation $\rightsquigarrow_{\mathcal{N}}$, we have that $X_0 \rightsquigarrow_{\mathcal{N}} X'$ also holds.

□

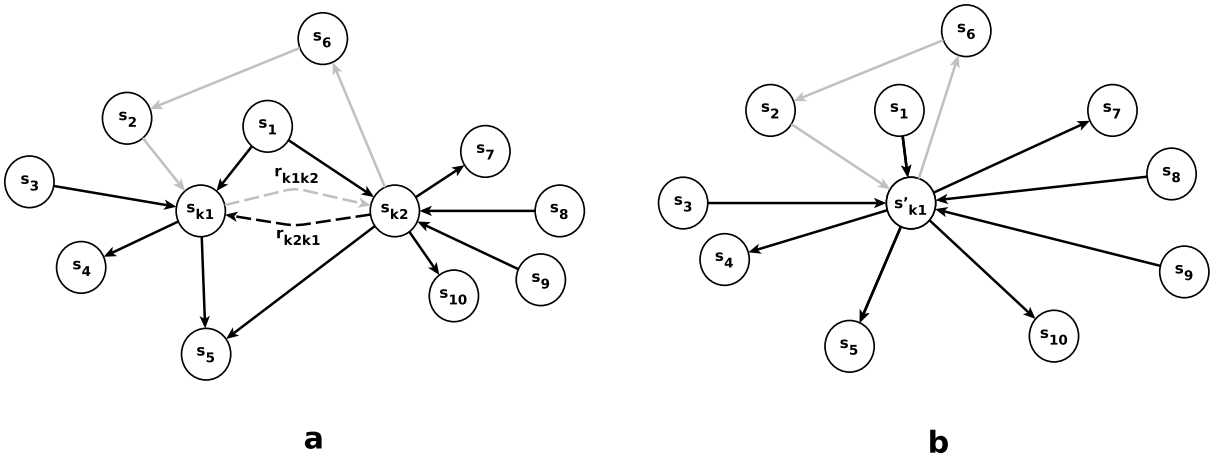

Figure 4.12: Graphical explanation how the reaction network structure of $\mathcal{N}'$ in the proof of Proposition 16 is constructed. **a)** Reaction network structure of an n-dimensional d-CRN $\mathcal{N}$. **b)** Reaction network structure of $\mathcal{N}'$ resulted in by merging the species s_{k_1} and s_{k_2} of $\mathcal{N}$ along their shared reaction $r_{k_1k_2}$ (and its reverse counterpart reaction $r_{k_2k_1}$). Note that by merging s_{k_1} and s_{k_2} we obtain a stoichiometric matrix Γ' having redundant reactions (e.g. (s_1, s_{k_1}), (s_1, s_{k_2}) result in (s_1, s'_{k_1}), (s_1, s'_{k_1})) and zero reaction vectors (i.e. self-loops on s'_{k_1}), but they are omitted in **b**. A dircted cycle onwhich the chosen reaction $r_{k_1k_2}$ lies is depicted in gray.

The above result can be extended to the case of superconservative d-CRNs.

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Corollary 3. Let us consider a superconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$ for which $\mathcal{C} = \mathcal{S}$. Assume that for all $r \in \mathcal{R}$ reactions $\sum_{i=1}^{n} [\overline{y}^+]_i = 1$ and $\sum_{i=1}^{n} [\overline{y}^-]_i \leq 1$ hold. Let us consider two states $X_0,\ X^{'} \in \mathbb{Z}^n_{\geq 0}$ so that $X_0 \succeq M$ and $X^{'} \succeq M$ hold where $M = M(\Gamma^-)$ is defined by Eq. (4.74). Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ holds if and only if there exists a vector $c \in \mathbb{Z}^l_{\geq 0}$ satisfying the state equation $X_0 + \Gamma c = X^{'}$.

Proof.
By changing the sign of the entries in the stoichiometric matrix Γ *we get a subconservative d-CRN* $\mathcal{N}^{'}$ *of stoichiometric matrix* $-\Gamma$. *Then we can consider the reachability problem* $X^{'} \overset{?}{\rightsquigarrow}_{\mathcal{N}'} X_0$. □

We can extend Proposition 16 by allowing the restricted application of catalyzer species as follows.

Proposition 17. Let us consider a subconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$. Assume that for each reaction r:

1. $r = s_1 \to s_2$ for some $s_1, s_2 \in \mathcal{S}$, $s_1 \neq s_2$, $s_1 \neq \mathbf{0}$, OR
2. $r = s + s_1 \to s + s_2$ where $s, s_1, s_2 \in \mathcal{S}$, $s \neq s_1 \neq s_2$, $s \neq \mathbf{0}$, $s_1 \neq \mathbf{0}$ and $\forall r^{'} \in \mathcal{R}$ $r^{'}$ does not consume s.

Let us consider two states $X_0, X^{'} \in \mathbb{Z}^n_{\geq 0}$ for which $X_0 \succeq M$ and $X^{'} \succeq M$ where $M = M(\Gamma^-)$ is defined by Eq. (4.74). Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ holds if and only if there exists a vector $c \in \mathbb{Z}^l_{\geq 0}$ satisfying the state equation $X_0 + \Gamma c = X^{'}$.

Proof.

1. $X_0 \rightsquigarrow_{\mathcal{N}} X^{'} \implies X_0 + \Gamma c = X^{'}$
   It follows from the definition of reachability.
2. $X_0 + \Gamma c = X^{'} \implies X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$
   Since in the initial state X_0 the number of each catalizer molecule is higher then or equal to 1 and there is no reaction in $\mathcal{N}$ consuming a catalyzer species, it follows that for each state reachable from X_0 the number of each catalyzer molecule is higher then or equal to 1. Let us remove all the catalyzer species of $\mathcal{N}$ from the reactions where they act as a catalyzer, i.e. for each $r \in \mathcal{R}$ of the form $r = s + s_1 \to s + s_2$ we erase the catalyzer s to obtain $r^{'} = s_1 \to s_2$. In such a way a d-CRN $\mathcal{N}^{'}$ is obtained so that for each $X \succeq M$, $X_0 \rightsquigarrow_{\mathcal{N}'} X$ iff $X_0 \rightsquigarrow_{\mathcal{N}} X$. $\mathcal{N}^{'}$ satisfies the conditions of Proposition 16, hence the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}'} X^{'}$ holds implying that $X_0 \rightsquigarrow_{\mathcal{N}} X^{'}$ also holds.

□

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According to the duality of the sub-and superconservaitvity properties we can extend Proposition 17 to the case of superconservative d-CRNs.

Corollary 4. Let us consider a superconservative d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of stoichiometric matrix $\Gamma \in \{-1, 0, 1\}^{n \times l}$ and $\Gamma^- \in \{0, 1\}^{n \times l}$. Assume that for each reaction r:

1. $r = s_1 \to s_2$ for some $s_1, s_2 \in \mathcal{S}$, $s_1 \neq s_2$, $s_2 \neq \mathbf{0}$, OR
2. $r = s + s_1 \to s + s_2$ where $s, s_1, s_2 \in \mathcal{S}$, $s \neq s_1 \neq s_2$, $s \neq \mathbf{0}$, $s_2 \neq \mathbf{0}$ and $\forall r' \in \mathcal{R}$ r' does not produce s.

Let us consider two states $X_0, X' \in \mathbb{Z}^n_{\geq 0}$ for which $X_0 \succeq M$ and $X' \succeq M$ where $M = M(\Gamma^-)$ is defined by Eq. (4.74). Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ holds if and only if there exists a vector $c \in \mathbb{Z}^l_{\geq 0}$ satisfying the state equation $X_0 + \Gamma c = X'$.

Proof. By changing the sign of the entries in the stoichiometric matrix Γ *we obtain a subconservative d-CRN* $\mathcal{N}'$ *of stoichiometric matrix* $-\Gamma$ *satisfying the conditions of Proposition 17. We can consider the reachability problem* $X' \overset{?}{\rightsquigarrow}_{\mathcal{N}'} X_0$.

□

By the above corollary, any reachability problem on a superconservative d-CRN satisfying the conditions of Corollary 4 can be easily traced back to that of a subconservative network, hence the problem is equivalent to finding a $c \in \mathbb{Z}^l_{\geq 0}$ solution for the respective d-CRN state equation.

The reaction network class covered by the above statements might be beneficial in modeling first and second order (bio)chemical reaction networks. For a representative example, see Example 4 below. We also note that any mass action type chemical reaction network can be dynamically described by an appropriately constructed reaction network containing at most second order reactions [146]. Moreover, the hypergraph representation of chemical reaction networks (see, e.g. [147]) is helpful for checking the conditions of Proposition 17.

Example 4. Nuclear factors of activated T-cells (NFAT) are proteins that can exist in highly phosphorylated states [148]. They act as transcription factors, i.e. they have regulatory role in transcription. NFAT1, which is a member of the NFAT familiy, has 13 residues that can be dephosphorylated upon stimulation. NFAT1 has two different states: active and inactive. The transition between active and inactive states of the protein is regulated by the level of phosphorylation such that the higher the level of phosphorylation is, the lower the rate of transition becomes from inactive state to the active one and vice versa. Phosphorylation and dephosphorylation are achieved by a kinease and calcineurin, respectively. In the mathematical model the activities of kinase and calcineurin are modeled as rate constants, hence the respective reactions can be considered as first-order ones. The protein might be located in the cytoplasm or the

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nucleus of the cell. Cytoplasmic active NFAT1 is imported to the nucleus, while inactive NFAT1 of the nucleus is exported back to the cytoplasm.

The reaction network structure is depicted in Figure 4.13. It is visible that each reaction is first order and there is no degradation and synthesis, hence the reaction network structure is conservative with a particular conservativity vector $z = 1^{56}$ and Proposition 16 can be applied.

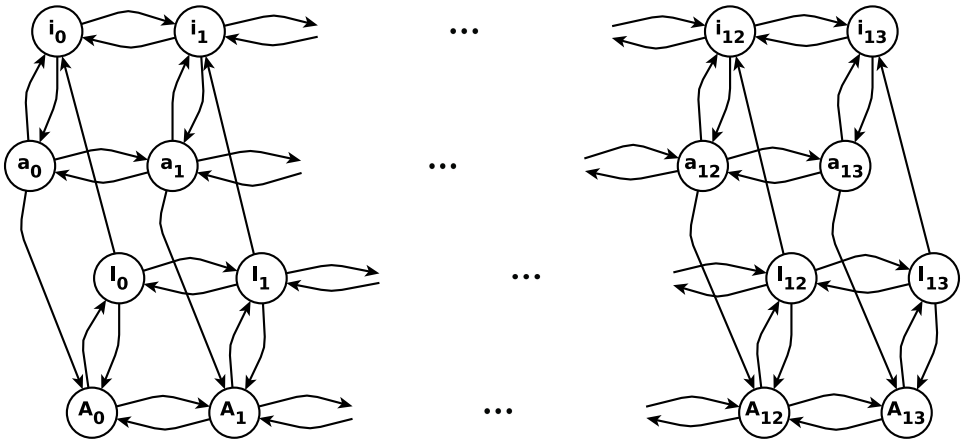

Figure 4.13: Conformational switch model of NFAT1 [148]. Lower case letters denote the protein located in the cytoplasm while upper case letters refer to the protein in the nucleus. a_j, A_j and i_j, I_j for $j = 0, \ldots 13$ denote the active and inactive proteins, respectively. Lower indices denote the number of phosphorylated residues.

We note that a reachability problem of the discussed reaction network class without additional constraints may be determined in polynomial time [145]. However, by using an ILP feasibility approach, the number of all distinct trajectories satisfying a prescribed reachability relation can be determined efficiently (see Remark 1), assuming the fixed number of reactions in the network. In addition, the ILP formulation can also be equipped with further linear constraints.

Remark 1. Let us consider a subconservative (superconservative) d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of n species, m complexes and l reactions. Assume that $\mathcal{N}$ satisfies the conditions of Proposition 17 (Corollary 4). Then for any $X_0, X' \in \mathbb{Z}^n_{\geq 0}$ initial and target states for which $X_0 \succeq M(\Gamma^-)$, $X' \succeq M(\Gamma^-)$ hold we have that the number of distinct trajectories σ_X satisfying the reachability relation $X_0 \overset{?}{\rightsquigarrow}_{\mathcal{N}} X'$ can be determined in polynomial time in the distance of X_0 and X', given the fixed number of reactions l in the d-CRN. The explanation of this is the following. According to Proposition 17 (Corollary 4) the reachability problem $X_0 \overset{?}{\rightsquigarrow}_{\mathcal{N}} X'$ is equivalent to the existence of a non-negative integer solution $c \in \mathbb{Z}^l_{\geq 0}$ of the state equation $X_0 + \Gamma c = X'$. In this way the reachability problem can be reformulated as an ILP feasibility problem in terms of c, and the Barvinok algorithm can be applied. Using the Barvinok algorithm in this particular case the following complexity bounds are obtained:

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1. exponential in the dimension of the decision variables, that is in the number of different reactions l,

2. polynomial in the number of constraints, that is in the number of species n,

3. polynomial in the maximum of the absolute values of the coefficients Γ, $X^{'} - X_0$.

The particular importance of Remark 1 is that the time complexity of the trajectory counting problem between a prescribed pair of states is polynomial in the number of constraints and in the distance of the initial and target states even in the case of superconservative d-CRNs for which the associated reachable state space can be unbounded for any X_0 initial state.

4.7.7 Computational example: a superconservative d-CRN of first order reactions

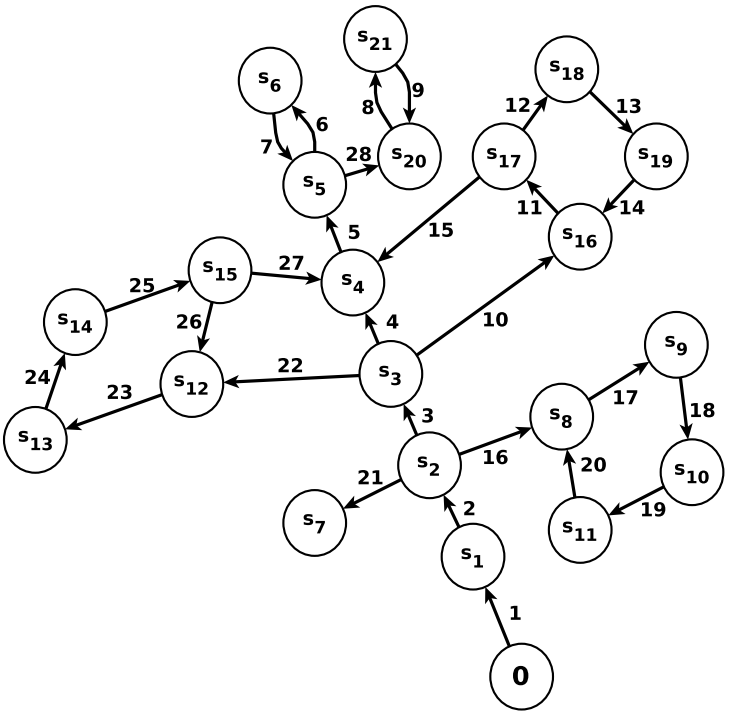

Figure 4.14: A superconservative d-CRN. **0** indicates the zero complex and the numbers denote the indices of the reactions onwhich they are located. Due to the superconservativity of the network structure the above d-CRN is unbounded for any initial state $X_0 \in \mathbb{Z}^n_{\geq 0}$.

Let us consider the d-CRN depicted in Figure 4.14. This system is superconservative with a particular conservation vector $z = 1^{21}$ implying the unboundedness of its reachable state space regardless of the initial state X_0. Making use of the above results, the reachability problem of $X_0 \overset{?}{\rightsquigarrow} X^{'}$ for any $X_0, X^{'} \in \mathbb{Z}^{21}_{\geq 0}$ can be reformulated as a subconservative d-CRN reachability problem for which the boundedness of the reachable state

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space – i.e. structural boundedness – is guaranteed and is equivalent to the existence of a non-negative integer solution of the respective subconservative d-CRN state equation.

As initial state we consider X_0 given by Eq. (4.85) that was randomly generated from $[10, 100]^{21}$. In order to find a target state $X^{'}$ satisfying the reachability relation $X_0 \rightsquigarrow X^{'}$ we randomly generated target states so that the number of each species was uniformly sampled from the interval $[40, 100]$. In the choice of the intervals from which we sample it was taken into consideration that the discrete state model of reaction networks are typically employed in the case of low molecular counts [109, 110]. In order to decide the reachability relation between a pair of particular states X_0 and $X^{'}$ we need to solve the following decision problem:

$$\begin{cases} \Gamma c = X^{'} - X_0 \\ c \in \mathbb{Z}^{28}_{\geq 0} \end{cases} \tag{4.84}$$

Clearly, Corollary 4 guarantees that $\Gamma c = X^{'} - X_0$ is satisfied with some $c \in \mathbb{Z}^{28}_{\geq 0}$ if and only if the reachability relation $X_0 \rightsquigarrow X^{'}$ holds. Let us consider the following initial and final states:

$$X_0 = [56\ 10\ 35\ 87\ 66\ 75\ 87\ 60\ 60\ 55\ 50\ 89\ 58\ 72\ 52\ 71\ 48\ 71\ 57\ 47\ 68]^{\top} \tag{4.85}$$

$$X' = [50\ 46\ 65\ 77\ 88\ 95\ 71\ 56\ 59\ 54\ 43\ 76\ 55\ 78\ 40\ 62\ 51\ 71\ 53\ 64\ 91]^{\top} \tag{4.86}$$

We found that for the target state $X^{'}$ given by Eq. (4.86) the reachability relation holds. To solve the decision problems of the form (4.84) the LattE [142] software was used.

Now, let us examine the reachability from X_0 to $X^{'}$ with additional constraints. One can observe that $X^{'}$ results in a significant increase of the number molecules in the species s_5, s_6, s_{20} and s_{21} and any tarjectory from X_0 to $X^{'}$ results in a net increase in the number of molecules. These together imply the flow of molecules from the zero complex (environment). The flow of molecules over the network from the zero complex to s_5, s_6, s_{20} and s_{21} can take place through different paths. We assume that the directed paths

$$\sigma_{S1} = s_3\ s_{12}\ s_{13}\ s_{14}\ s_{15}\ s_4, \tag{4.87}$$

$$\sigma_{S2} = s_3\ s_{16}\ s_{17}\ s_4 \tag{4.88}$$

are slow compared to the other ones, hence we wish to minimize the flow through them in order to lower their effect in c. This can be easily expressed by posing addition linear

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constraints on c as it is done in the decision problem (4.89).

$$\begin{cases} \Gamma c = X^{'} - X_0 \\ c \in \mathbb{Z}^{28}_{\geq 0} \\ [c]_{15} \leq 10 \\ [c]_{27} \leq 10 \end{cases} \tag{4.89}$$

We also determined a particular solution c by equipping (4.89) with the objective function $\sum_{i=1}^{28} [c]_i$ to be minimized:

$$c = [112\ 106\ 112\ 111\ 118\ 48\ 8\ 29\ 12\ 18\ 16\ 11\ 11\ 7\ 8\ 13\ 17\ 16\ 15\ 8\ 17\ 13\ 16\ 13\ 19\ 16\ 9\ 51]^{\top} \tag{4.90}$$

For implementation purposes we employed Python 2.7 programming language and the Gurobi mathematical optimization solver [153]. A Lenovo P51s workstation with two 2.70GHz i7-7500U CPUs and 32GB RAM (DDR4 2133 MHz) was used for all the computations.

4.7.8 Polynomial time reachability with theoretical guarantee

In this section we extend the d-CRN reachability results discussed in the previous sections [J7]. We provide a polynomial time relaxation of the following IP decision problem:

$$\begin{cases} \Gamma c = X^{'} - X_0 \\ c \in \mathbb{Z}^{l}_{\geq 0} \end{cases} \tag{4.91}$$

We prove that Eq. (4.91) can be relaxed to a linear program under the conditions of Proposition 16 and Corollary 3. The relaxed method has polynomial time complexity in the number of species (n). This way a computational method is provided for the d-CRN reachability problem with polynomial time complexity and theoretical guarantee [J7].

Proposition 18. 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, $X_0,\ X' \in \mathbb{Z}^{n}_{\geq 0}$ so that $X_0 \succeq M$, $X' \succeq M$ where $M = M(\Gamma^{-})$ is defined by Eq. (4.74). Then the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$ can be decided in polynomial time.

Proof. The conditions imply that the existence of a $c \in \mathbb{Z}^{l}_{\geq 0}$ for which $X_0 + \Gamma_{\mathcal{N}} c = X'$ holds is a sufficient and necessary condition of the reachability relation $X_0 \rightsquigarrow_{\mathcal{N}} X'$.

We make use of Proposition 8 to show that the stoichiometric matrix $\Gamma_{\mathcal{N}}$ is totally unimodular. The following propositions hold for $\Gamma_{\mathcal{N}}$:

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1. Every entry of $\Gamma_{\mathcal{N}}$ is 0, 1 or -1.
2. Every column of $\Gamma_{\mathcal{N}}$ contains at most 2 non-zero entries.
3. The rows of $\Gamma_{\mathcal{N}}$ can be partitioned into two disjoint subsets $\mathcal{S}_1$ and $\mathcal{S}_2$ so that:
   a) if two entries in a column of $\Gamma_{\mathcal{N}}$ have the same sign, then one is in $\mathcal{S}_1$ while the other one is in $\mathcal{S}_2$;
   b) if two entries in a column of $\Gamma_{\mathcal{N}}$ have the opposite sign, then they are in the same subset $\mathcal{S}_1$ or $\mathcal{S}_2$.

Clearly, each entry in $\Gamma_{\mathcal{N}}$ equals to $+1$, -1 or 0. Each reaction consumes at most one species and produces at most another one, that is each column of $\Gamma_{\mathcal{N}}$ has at most 2 non-zero entries. Multiple entries of the same sign in a column of $\Gamma_{\mathcal{N}}$ would imply that different species are consumed or produced by a reaction, but this is not possible in the considered class of reaction networks. Considering any column of $\Gamma_{\mathcal{N}}$, the (at most) two rows containing non-zero entries must be in the same set ($\mathcal{S}_1$ or $\mathcal{S}_2$). If the the reaction network graph is connected, then all the rows are put in the same set. Let us assume that the reaction network graph is not connected. In this case there exist 2 or more linkage classes in the reaction network graph. Note that the linkage classes are not necessarily strongly connected. The linkage classes cover disjoint sets of rows in $\Gamma_{\mathcal{N}}$ and for each linkage class we can choose arbitrarily, either $\mathcal{S}_1$ or $\mathcal{S}_2$, irrespective of the other linkage classes. Note that empty rows are not possible as we assume that isolated spacies are not allowed.

The above proof implies that $\Gamma_{\mathcal{N}}$ is guaranteed to be totally unimodular [151]. Clearly, for a totally unimodular matrix $\Gamma_{\mathcal{N}}$ the following LP provides an optimal integer solution:

$$\begin{cases} \min_c\{a^\top c\} \\ \text{subject to} \\ \Gamma_{\mathcal{N}} c = X' - X_0 \\ c \in \mathbb{R}^l_{\geq 0} \end{cases} \tag{4.92}$$

for any $a \in \mathbb{R}^l$.

□

The practical importance of Proposition 18 is that the reachability relation can be decided by a linear program, which has polynomial time complexity with respect to the state space dimensionality (n). The IP feasibility formulation employed the Lenstra and Barvonok algorithms and assumed fixed state space dimensionality to obtain polynomial time complexity in terms of the number of reactions and the maximum absolute value entry of the constraint matrices. However, the IP feasibility approach was exponential in the state space dimensionality (number of species).

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Proposition 18 provides theoretical guarantees that the feasibility of the relaxed LP implies reachability, while the infeasibility implies that the reachability relation does not hold.

We can naturally extend Proposition 17 and Corollary 4 by making use of the totally unimodular property of the stoichiometric matrix $\Gamma_{\mathcal{N}}$ similarly as we obtained Proposition 18. Finally, we note that by linear programming, the infeasibility can be decided with high accuracy. However, in the case of ILP problems, the infeasibility returned by a solver conveys lower accuracy.

Example 5. In this example an illustrative reaction network is provided from the literature of Chemical Reaction Networks [154]. Fig. 4.15 depicts a conservative reaction network structure $\mathcal{N}$ of 14 species (metabolites). The stoichiometric matrix associated to the system is given by Eq. (4.93). A suitable conservation vector for the d-CRN is given by $z = 1^n$: $z^\top \Gamma_{\mathcal{N}} = 0^{1\times l}$, $n = 14$, $l = 19$. Clearly, for any non-negative initial state, the reachable state space $Reach(\mathcal{N}, X_0)$ is an $(n-1)$-dimensional hyperplane.

$\mathcal{N}$ has a monomolecular reaction network structure with totally unimodular stoichiometric matrix. This implies that Proposition 18 can be applied. For any pair of state vectors $X_0,\ X' \in \mathbb{Z}^n_{\geq 0}$, $X_0,\ X' \succeq M(\Gamma^-_{\mathcal{N}})$, $M(\Gamma^-_{\mathcal{N}}) = 1^n$, the reachability relation $X_0 \rightsquigarrow X'$ can be validated in polynomial time by running a linear program of the form of Eq. (4.92) with some non-zero $a \in \mathbb{R}^l$.

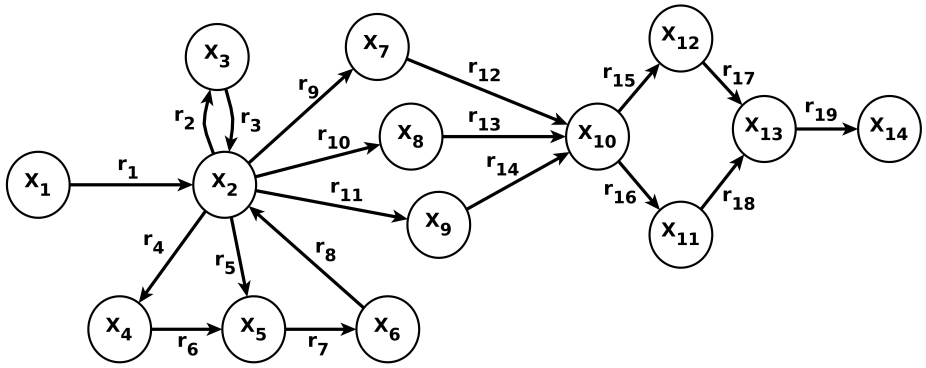

Figure 4.15: A conservative d-CRN $\mathcal{N}$ for which Proposition 18 holds. $\mathcal{N}$ is a monomolecular reaction network with totally unimodular stoichiometric matrix. This implies that the generally NP-hard problem of deciding the reachability relation can be relaxed to a linear program with guaranteed polynomial time complexity.

$$\Gamma_{\mathcal{N}} = \begin{bmatrix}
-1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & -1 & 1 & -1 & -1 & 0 & 0 & 1 & -1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & -1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & -1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix} \tag{4.93}$$

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Case	Continuous	Integer	Barvinok
A	0.1 [sec]	0.23 [sec]	>60 [min]
B	0.01 [sec]	0.01 [sec]	>60 [min]
C	<0.01 [sec]	<0.01 [sec]	>60 [min]

Table 4.2: Computational comparison of the different methods proposed for deciding the d-CRN reachability. **Continuous** represents the LP formulation given by Eq. (4.92). **Integer** denotes the integer program Eq. (4.91) equipped with a linear cost function of the form $\min_c\{a^\top c\},\ a = 1^{19}$. **Barvinok** stands for the implementation of the Barvinok's algorithm [142]. In Case **A**, $[X_0]_1 = 5$, $[X_1]_4 = 395$, otherwise $[X_0]_i = 200$, $[X_1]_i = 200$. In case **B**, $[X_0]_1 = 100$, $[X_1]_4 = 300$, otherwise $[X_0]_i = 200$, $[X_1]_i = 200$. Finally, in case **C**, $[X_0]_1 = 195$, $[X_1]_4 = 205$, otherwise $[X_0]_i = 200$, $[X_1]_i = 200$. In all the cases, the reachability relation holds. The table depicts the different methods with their respective running times.

Table 4.2 depicts the computational comparison of different algorithms proposed for deciding the d-CRN reachability. Eq. (4.91) and Eq. (4.92) were implemented in Python 3.7. using the Gurobi solver [153]. We used the LattE implementation of the Barvinok's algorithm. Note that Proposition 18 provides theoretical guarantee that the LP formulation of Eq. (4.92) has integer solution. Clearly, the feasibility of (4.91) and Eq. (4.92) implies the d-CRN reachability. In case **A**, the LP formulation can decide the reachability problem within half of the time of the IP solution. Note that the higher the Manhattan distance between the initial state X_0 and the target state X_1, the higher is the running time of the algorithms.

4.8 Summary

In this chapter the reachability problems of sub-and superconservative discrete state chemical reaction networks are considered. It is shown that the reachability problem of a superconservative reaction network of unbounded reachable state space can be transformed to that of a subconservative network for which the boundedness of the reachable state space is always guaranteed. We employed an ILP feasibility approach to computationally solve the reachability problem. Upper bound on the maximal length of cycle-free state transition (reaction) sequences are provided. Using an inductive proof we provided a set of necessary and sufficient conditions under which the equivalence between a d-CRN reachability problem and the existence of a non-negative integer solution of the corresponding state equations is guaranteed. In such a way the reachability problem can be traced back to an ILP feasibility (decision) problem for which the number of decision variables is significantly lower than that of employed in the literature. Moreover, the number of trajectories satisfying the reachability relation can also be enumerated efficiently, assuming a fixed reaction network structure. Finally, we proved that the reachability problem can be

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decided in polynomial time with theoretical guarantee in the studied d-CRN subclasses.

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5 Conclusion and Future Works

5.1 New scientific results

Thesis I. I proposed a novel method for testing structural identifiability in time delayed non-linear dynamical system models [J1].

I applied the Volterra series representation of single input single output non-linear dynamical systems with constant time delays to give sufficient conditions for the joint structural identifiability of system parameters and delays. Using the frequency domain representation of the Volterra kernels in the form of generalized frequency response functions (GFRFs), I showed that the unique solution of a set of appropriately constructed non-linear algebraic equations implies the joint structural identifiability of the delayed model.

Thesis II. I proved that the set of feasible state transition matrices of a discrete time linear dynamical systems (DT-LDS) is convex, assuming that the matrices B, C and D are fixed. Making use of the convexity of feasible system matrices I obtained convex optimization based algorithm for finding different dynamically equivalent n-order realizations with theoretical guarantee [J2].

I inductively proved that the set of feasible system (state transition) matrices of a DT-LDS is convex, assuming that the matrices B, C and D are fixed and C is invertible. I showed that the convexity of the set of system matrices can be used to determine different dynamically equivalent realizations of the system $\Theta = (A, B, C, D)$. I developed new algorithms from the theory of kinetic systems (mass action law reaction networks) to find structurally different realizations of a DT-LDS.

Thesis III. I developed a computational method for deciding reachability and coverability problems in discrete state chemical reaction networks with novel upper bound on the length of cycle-free state transition sequences [J3].

I employed an integer programming feasibility based computational approach for deciding the reachability problem of discrete state chemical reaction networks with novel upper bound on the number of decision variables. The method relies on the Lenstra algorithm capable of deciding integer programming feasibility problems in polynomial time, assuming fixed dimension in terms of the decision variables. I gave new upper bounds for

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the maximal length of cycle-free state transition sequences between any pair of initial and target states in subconservative reaction network structures. Considering subconservative reaction networks of state space dimension smaller than or equal to two, I proved that the reachability property is equivalent to the non-negative integer solution of the associated reaction network state equation.

Thesis IV. I gave network topology related conditions under which the d-CRN reachability relation for any pair of initial and target states is equivalent to the existence of a non-negative integer solution of the d-CRN state equation. This way an Integer Programming feasibility problem is obtained. I proved that under the same conditions, the resulting IP feasibility problem can be relaxed to a Linear Problem with guaranteed polynomial time complexity [J4, J7].

1. It is known that a subconservative network has bounded reachable state space, while that of a superconservative one is unbounded. I gave a proof that the reachability problem of superconservative reaction networks is equivalent to the reachability problem of subconservative reaction networks. The practical importance of the relation between the sub-and superconservative reachability is that the reachability problem of a superconservative system – with state space guaranteed to be unbounded – can be traced back to that of a subconservative network having bounded state space. In the classes of sub-and superconservative reaction networks I gave conditions for network structure under which the reachability property is equivalent to the existence of a non-negative integer solution of the associated state equation characterizing the time evolution of the chemical reaction networks. The equivalence, using the Lenstra algorithm, implies an integer programming based feasibility approach [J4].

2. I showed that the stoichiometric matrix – under the same conditions as IV/1 – is totally unimodular. It is known that an integer program with totally unimodular constraint matrix can be relaxed to a linear program. This way I obtained a linear program with guaranteed polynomial time complexity for the reachability problem [J7].

5.2 Application possibilities and future works

The main motivation behind the methods and computational procedures proposed in this thesis is to study the dynamical and structural properties in biologically motivated system models. An important aspect of this work is to quantitatively examine the relationship between dynamical (differential/difference equation-based) and structural (topological,

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graph-based) properties of system models. The main application can be to examine biological systems as they are commonly represented by both dynamical equations and network representations. The identifiability approach proposed in chapter 2 can be used as a prior step to any parameter estimation procedure performed on biological processes. The realizability results of chapter 3 are also related to structural identifiability. Clearly, the existence of structurally different dynamically equivalent realizations of a DT-LDS implies local structural unidentifiability. Furthermore, determining structurally different realizations can provide means for synthetic biology, it may possible to find the most suitable (biochemically feasible) network structure to implement a prescribed molecular functionality. The novel results obtained for d-CRNs can be used to computationally examine the properties of molecular circuits of low molecular multiplicity. Synthetic biology is also a possible application field as the gate-implementability problem is known to be equivalent to the d-CRN reachability problem [149]. Since the formal model of d-CRNs considered in this thesis is equivalent to Petri nets and VASS, the reachability results can also be applied to solve problems in theoretical computer science and related applications, such as verification of distributed, concurrent and parallel systems.

The following research directions are listed for future work:

1. Structural identifiability of delayed systems: we used the GFRFs to obtain sufficient conditions for joint structural identifiability analysis of ordinary model parameters and constant time delays. A possible extension is to examine whether there exists an upper bound (depending on the model structure) on the minimal number of distinct GFRFs to be computed for structural identifiability testing. Clearly, obtaining an upper bound with theoretical guarantees would imply necessary and sufficient condition of structural identifiability in non-linear time delayed systems. We also note that there exists a recursive formula for computing the GFRFs [99]. A recursive formula could provide means for examining the minimal number of GFRFs required for obtaining necessary and sufficient condition of structural identifiability.

2. Finding all structurally different realizations of DT-LDSs: extending the proposed computational methods to find all the structurally different realizations of DT-LDSs with theoretical guarantee. The embedding eigenvalue assignment procedure employed to reduce the number of non-zero Markov parameters is useful for determining structurally different realizations, but we have no theoretical guarantee that this way all the structurally different realizations can be computed. An interesting way for extending the proposed work is to examine whether it is possible to substitute the embedding eigenvalue assignment procedure with another method for which the obtained compressed set of Markov parameters is proven to be useful for finding all the structurally different realizations of the original DT-LDS.

3. Extension of the reachability results to more general classes of d-CRN structures:

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the network structure-related conditions for the equivalence of d-CRN reachability and the existence of a non-negative integer solution of the respective d-CRN state equation is restricted to certain sub-and superconservative network structure classes. An interesting way for further research is to examine whether it is possible to extend the above equivalence result to a wider class of d-CRN structures, e.g. by means of network structure transformations.

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Appendix A.

Non-zero entries in the initial adjacency matrix of the LDS depicted in 3.2.

$[A]_{2,10} = 1;$
$[A]_{3,1} = 0.5; [A]_{3,2} = 0.5;$
$[A]_{4,1} = 0.3; [A]_{4,2} = 0.5; [A]_{4,3} = 0.2;$
$[A]_{5,1} = 1;$
$[A]_{6,1} = 1;$
$[A]_{7,1} = 0.3; [A]_{7,5} = 0.4; [A]_{7,6} = 0.3;$
$[A]_{8,1} = 0.2; [A]_{8,2} = 0.2; [A]_{8,3} = 0.2; [A]_{8,4} = 0.4;$
$[A]_{9,1} = 0.4; [A]_{9,3} = 0.6;$
$[A]_{10,3} = 1.0;$
$[A]_{11,1} = 0.1; [A]_{11,5} = 0.1; [A]_{11,6} = 0.8;$
$[A]_{12,1} = 1.0;$
$[A]_{13,1} = 0.9; [A]_{13,4} = 0.1;$
$[A]_{14,1} = 0.1; [A]_{14,2} = 0.2; [A]_{14,3} = 0.3; [A]_{14,4} = 0.4;$
$[A]_{17,6} = 0.7; [A]_{17,7} = 0.3;$
$[A]_{18,1} = 0.8; [A]_{18,2} = 0.2;$
$[A]_{20,1} = 0.1; [A]_{20,2} = 0.9;$
$[A]_{22,1} = 0.4; [A]_{22,2} = 0.6;$
$[A]_{26,24} = 0.65; [A]_{26,25} = 0.35;$
$[A]_{28,3} = 0.2; [A]_{28,24} = 0.3; [A]_{28,25} = 0.5;$
$[A]_{29,3} = 1.0;$
$[A]_{30,24} = 0.3; [A]_{30,27} = 0.7;$
$[A]_{31,2} = 0.1; [A]_{31,9} = 0.9;$
$[A]_{32,1} = 0.25; [A]_{32,25} = 0.25; [A]_{32,26} = 0.4; [A]_{32,29} = 0.1;$
$[A]_{33,3} = 0.1; [A]_{33,9} = 0.1; [A]_{33,15} = 0.1; [A]_{33,16} = 0.1; [A]_{33,19} = 0.05; [A]_{33,21} = 0.05; [A]_{33,23} = 0.1;$
$[A]_{33,24} = 0.1; [A]_{33,30} = 0.1; [A]_{33,31} = 0.1; [A]_{33,32} = 0.1;$
$[A]_{34,9} = 0.05; [A]_{34,10} = 0.05; [A]_{34,14} = 0.15; [A]_{34,15} = 0.05; [A]_{34,16} = 0.01; [A]_{34,19} = 0.09; [A]_{34,20} = 0.02;$
$[A]_{34,21} = 0.08; [A]_{34,23} = 0.03; [A]_{34,24} = 0.07; [A]_{34,27} = 0.1; [A]_{34,28} = 0.05; [A]_{34,29} = 0.05; [A]_{34,30} = 0.05;$
$[A]_{34,31} = 0.05; [A]_{34,32} = 0.05; [A]_{34,33} = 0.05$