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Reduction of Chemical Reaction Networks with Approximate Conservation Laws*

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Abstract. Model reduction of fast-slow chemical reaction networks based on the quasi-steady state approximation fails when the fast subsystem has first integrals. We call these first integrals approximate conservation laws. In order to define fast subsystems and identify approximate conservation laws, we use ideas from tropical geometry. We prove that any approximate conservation law evolves more slowly than all the species involved in it and therefore represents a supplementary slow variable in an extended system. By elimination of some variables of the extended system, we obtain networks without approximate conservation laws, which can be reduced by standard singular perturbation methods. The field of applications of approximate conservation laws covers the quasi-equilibrium approximation, which is well known in biochemistry. We discuss reductions of slow-fast as well as multiple timescale systems. Networks with multiple timescales have hierarchical relaxation. At a given timescale, our multiple timescale reduction method defines three subsystems composed of (i) slaved fast variables satisfying algebraic equations, (ii) slow driving variables satisfying reduced ordinary differential equations, and (iii) quenched much slower variables that are constant. The algebraic equations satisfied by fast variables define chains of nested normally hyperbolic invariant manifolds. In such chains, faster manifolds are of higher dimension and contain the slower manifolds. Our reduction methods are introduced algorithmically for networks with monomial reaction rates and linear, monomial, or polynomial approximate conservation laws. We propose symbolic algorithms to reshape and rescale the networks such that geometric singular perturbation theory can be applied to them, test the applicability of the theory, and finally reduce the networks. As a proof of concept, we apply this method to a model of the TGF-beta signaling pathway.

Key words. model order reduction, chemical reaction networks, singular perturbations, multiple timescales, tropical geometry

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1. Introduction. The study of *chemical reaction networks* (CRNs) was motivated by important applications in physics and chemistry concerning models of nonequilibrium thermodynamics [47], catalytic reactions [59], combustion [51], etc. More recently, CRNs were used to model cell and tissue physiology [53] needed to advance the understanding of the fundamental mechanisms of living systems and how to fight disease.

Chemical reaction networks can be characterized by reaction *stoichiometry* and reaction rates [1]. Stoichiometry tells us how many molecules of each species are consumed and produced in a reaction. For instance, the reaction $A_1 + A_2 \to A_3$ consumes one molecule of each of A_1 and A_2 and produces one molecule of A_3. A useful construct is the stoichiometric matrix $\boldsymbol{S}$ in which each column represents the net numbers of molecules of each species produced by a particular reaction. A three-species CRN made up of the reactions $A_1 + A_2 \to A_3$ and $A_1 + A_1 \to A_1$ has the stoichiometric matrix

$$\boldsymbol{S} = \begin{pmatrix} -1 & -1 \\ -1 & 0 \\ 1 & 0 \end{pmatrix}.$$

With each reaction we also associate a positive function of species concentrations, called reaction rate, representing the number of occurrences of the reaction per unit time and volume. In this paper we assume that reaction rates are monomials. Therefore, the deterministic kinetics of CRNs is described by sets of polynomial ordinary differential equations (ODEs). For instance, if the reaction rates in the above example are $R_1 = k_1 x_1 x_2$ and $R_2 = k_2 x_1^2$, the CRN kinetics is described by $\dot{x}_1 = -k_1 x_1 x_2 - \frac{1}{2} k_2 x_1^2$, $\dot{x}_2 = -k_1 x_1 x_2$ and $\dot{x}_3 = k_1 x_1 x_2$.

Much effort has been dedicated to studying the behavior of *mass-action* networks [13]. In such networks, the probability that two species react is proportional to their abundance, and therefore the reaction rates are monomials in the concentrations of reactant species, with exponents equal to the number of molecules entering the reaction. The above example is of this type, but it will no longer be of this type if R_1 is changed to $k_1 x_1 x_2^2$, for instance. This constraint leads to algebraic properties exploited in *chemical reaction network theory* (CRNT), which has been initiated by Horn and Feinberg [13, 14]. In order to cover more general models, we do not impose the mass-action constraint on the reaction rates. Instead, to avoid the fact that some species become negative as a result of the CRN kinetics, we use the following weaker constraint: if a reaction consumes a species, then its rate is proportional to a strictly positive power of the concentration of this species. In spite of significant progress toward elucidating the properties of CRNs, important models are left aside because of their size and the complexity of their dynamics. For such examples, algorithmic model reduction, which transforms complex networks into simpler ones that can be more easily analyzed, becomes a necessity. A few attempts at developing model reduction algorithms used concepts of CRNT such as complex balance [16, 43], but they were limited to networks functioning at the steady state or based on ad hoc identification of the balanced complexes. Model reduction methods based on the theory of singular perturbations, employing concepts such as the intrinsic low dimensional manifold or quasi-steady state reduction, are often used in chemistry and systems biology [20, 52]. However, these methods lack general algorithms for finding appropriate small parameters and scalings, which are needed for the quasi-steady state reduction, and are limited to two timescales (slow-fast systems).

Recently, we proposed a symbolic method for algorithmic reduction of chemical reaction networks with multiple (more than two) timescales [26]. This method combines *tropical geometry* ideas for identifying the time and concentration scales [38, 45], dominance principles based on comparison of orders of magnitude [22, 23, 39] and singular perturbation results [7, 17] to justify the reduction. For a given timescale, the method defines three subsystems: a *slaved equilibrated* subsystem, a *driving evolving* subsystem, and a *quenched* subsystem. The variables of the slaved subsystem satisfy quasi-steady equations, defined as equilibria of the fast truncated ODEs in which all the remaining variables are considered fixed. The entire construction requires the hyperbolicity of the quasi-steady state, which is needed in the classical geometric singular perturbation theory of Fenichel [17]. Although general in its implementation, this reduction method fails in a number of cases. A major cause of failure is the degeneracy of the quasi-steady state when the fast dynamics has a continuous variety of steady states. Typically, this happens when the fast truncated ODEs have first integrals, i.e., quantities that are conserved on any trajectory, whose values depend on the initial conditions. The quasi-steady states are no longer hyperbolic, because the Jacobian matrix of the *fast* part of the dynamics is in this case singular. This type of singular perturbations, called *critical,* has been known since the work of Vasil'eva and Butuzov in the 1970s [55], but its origins can be traced back to the early theory of enzymatic reactions, as quasi-equilibrium is an instance of critical singular perturbations. Vasil'eva and Butuzov [55] propose asymptotic expansions of the solutions of singularly perturbed systems in the critical case based on their method of *boundary series,* which are two timescale expansions. Their method works in the case when the problem has rigorously two timescales but cannot be applied in the case when there are more than two timescales. We show in this paper that critical singular perturbations may have more timescales than are apparent after rescaling parameters and variables. We also provide algorithmic methods to compute these extra timescales that correspond to approximate conservation laws.

Exact conservation laws, i.e., first integrals of the full dynamics, were already used for model order reduction. If such quantities exist, the model can be reduced by eliminating a number of variables and equations equal to the number of independent conservation laws [28, 31]. In the present work, we introduce the *approximate conservation laws* that are quantities conserved by the fast dynamics. In models with multiple timescales, approximate conservation laws provide extra slow variables. Model reduction takes place by elimination of the fast variables. We thus provide algorithmic reduction methods covering the case of nonhyperbolic fast dynamics with conservation. Our algorithms are inspired from the well-known *quasi-equilibrium* approximation [23, 40]. Contrary to the quasi-equilibrium approximation that uses only linear approximate conservation laws, here we also exploit nonlinear conserved quantities. Similar ideas were developed in [2, 8] but without a full algorithmic solution. As in [26] we use tropical geometry to find appropriate time and concentration scales.

The topic of conservation laws is of broad interest, and its relation to symmetry was widely studied in classical and quantum mechanics (see Noether's theorems [35]). Closely related to this topic, referring to the broad range of phenomena in physics, from nuclear forces to gravitation, having *near symmetry,* Feynman concluded that "...God made the laws only nearly symmetrical so that we should not be jealous of His perfection" [18]. Approximate continuous symmetries (such as Lie–Bäcklund symmetries) were studied for differential equations with

and without a Lagrangian (see [3] and [25], respectively). Beyond their utility in the theory of regular and singular perturbations, exact and approximate symmetries can be used to gain insight into the dynamics of complex chemical reaction networks. Approximate conservation laws, valid for certain concentrations and not valid for other concentrations of biochemical species, imply that the same biochemical system can have multiple behaviors depending on internal or external stimuli. In biology, "imperfect" conservation allows living systems to be flexible, to evolve, and to adapt to changes in the environment. This also leads to multiple dynamical phenomena, such as slow metastable states, bifurcations in the fast dynamics of the system, and itineracy when the system switches from one metastable state to another [2, 22, 37].

The structure of this paper is as follows. Section 2 introduces the class of models we are dealing with. These are systems of ODEs whose right-hand sides are integer coefficient polynomials in species concentrations and reaction rate constants. Theorem 1 shows that these models are always endowed with a stoichiometric matrix. Section 3 introduces the concept of exact and approximate conservation laws, without methods for computing them. The methods for symbolic computation of exact and approximate conservation laws are presented in [9]. Section 4 introduces our reduction method based on tropically constrained formal scalings and approximate conservation laws. An important result here is that approximate conservation laws are always slower than all the species involved in their structure. This implies that they can be used as new, unconditionally slow variables, providing robust reductions. In section SM1 of the supplementary material, we illustrate the method via a case study from molecular biology of intracellular signal transduction.

2. Models.

In this paper we consider CRNs with n species $A_1, \dots, A_n$, whose concentrations $\boldsymbol{x} = (x_1, \dots, x_n)$ follow a system of ODEs of the form

$$\dot{x}_1 = f_1(\boldsymbol{k}, \boldsymbol{x}), \dots, \dot{x}_n = f_n(\boldsymbol{k}, \boldsymbol{x}), \tag{2.1}$$

where

$$f_i(\boldsymbol{k}, \boldsymbol{x}) = \sum_{j=1}^{r} S_{ij} k_j \boldsymbol{x}^{\boldsymbol{\alpha}_j} \in \mathbb{Z}[\boldsymbol{k}, \boldsymbol{x}] = \mathbb{Z}[k_1, \dots, k_r, x_1, \dots, x_n].$$

The monomials $\boldsymbol{x}^{\boldsymbol{\alpha}_j} = x_1^{\alpha_{j1}} \dots x_n^{\alpha_{jn}}$ appearing in the right-hand sides of (2.1) are defined by r multi-indices $\boldsymbol{\alpha}_j = (\alpha_{j1}, \dots, \alpha_{jn}) \in \mathbb{N}^n$, and for each monomial the variable k_j represents a rate constant. The variables $\boldsymbol{k} = (k_1, \dots, k_r)$ take values in $\mathbb{R}^r_{>0}$, and the integer coefficients S_{ij} form a matrix $\boldsymbol{S} = (S_{ij}) \in \mathbb{Z}^{n \times r}$, which is called the stoichiometric matrix. The concentration variables $\boldsymbol{x} = (x_1, \dots, x_n)$ take values in $\mathbb{R}^n_{>0}$. For reasons that will become clear in Remark 4.3 of section 4.2, we exclude zero concentrations. We denote the vector of right-hand sides of (2.1) by

$$\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}) = (f_1(\boldsymbol{k}, \boldsymbol{x}), f_2(\boldsymbol{k}, \boldsymbol{x}), \dots, f_n(\boldsymbol{k}, \boldsymbol{x}))^{\mathsf{T}}.$$

Mass action networks belong to this class of models. For a mass action reaction

$$\bar{\alpha}_{j1} A_1 + \dots + \bar{\alpha}_{jn} A_n \to \beta_{j1} A_1 + \dots + \beta_{jn} A_n$$

we have that $S_{ij} = \beta_{ji} - \bar{\alpha}_{ji}$ and that the reaction rate is $k_j \boldsymbol{x}^{\bar{\boldsymbol{\alpha}}_j}$; i.e., the stoichiometric coefficients $\bar{\boldsymbol{\alpha}}_j$ and the multi-indices $\boldsymbol{\alpha}_j$ coincide. But in general this must not be the case, meaning that the multi-indices $\boldsymbol{\alpha}_j$ and $\bar{\boldsymbol{\alpha}}_j$ in $S_{ij} = \beta_{ji} - \bar{\alpha}_{ji}$ and $k_j \boldsymbol{x}^{\boldsymbol{\alpha}_j}$ are not necessarily equal. In order to keep the positive orthant $\mathbb{R}^n_{>0}$ invariant, we consider that whenever a reaction consumes a species, its rate tends to zero when the concentration of this species approaches zero. This is equivalent to the next condition.

Condition 2.1. *$\alpha_{ji} > 0$ for all i, j such that $S_{ij} < 0$.*

Condition 2.1 is automatically satisfied by mass-action reactions but also covers the truncated ODE systems introduced in section 3.1 and used in section 4.

3. Approximate conservation laws.

3.1. A classical example and some definitions.

Example 3.1. Let us consider the irreversible Michaelis–Menten mechanism that is paradigmatic for enzymatic reactions. We choose rate constants corresponding to the so-called quasi-equilibrium studied by Michaelis and Menten. The reaction network for this model is

$$S + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3\delta} E + P,$$

where S is a substrate, E is an enzyme, ES is an enzyme-substrate complex, and k_1, k_2, k_3 are rate constants. Here $0 < \delta < 1$ is a small positive scaling parameter, indicating that the third rate constant is small.

According to mass-action kinetics, the concentrations $x_1 = [S]$, $x_2 = [ES]$, and $x_3 = [E]$ satisfy the system of ODEs

$$\begin{aligned} \dot{x_1} &= -k_1 x_1 x_3 + k_2 x_2, \\ \dot{x_2} &= k_1 x_1 x_3 - k_2 x_2 - \delta k_3 x_2, \\ \dot{x_3} &= -k_1 x_1 x_3 + k_2 x_2 + \delta k_3 x_2. \end{aligned} \tag{3.1}$$

We consider the truncated system of ODEs

$$\begin{aligned} \dot{x_1} &= -k_1 x_1 x_3 + k_2 x_2, \\ \dot{x_2} &= k_1 x_1 x_3 - k_2 x_2, \\ \dot{x_3} &= -k_1 x_1 x_3 + k_2 x_2, \end{aligned} \tag{3.2}$$

which is obtained by setting $\delta = 0$ in (3.1). The truncated system (3.2) describes the dynamics of the model on fast timescales of order $O(\delta^0)$.

The steady state of the fast dynamics is obtained by equating to zero the right-hand side of (3.2). The resulting condition is called *quasi-equilibrium (QE)* because it means that the complex formation rate $k_1 x_1 x_3$ is equal to the complex dissociation rate $k_2 x_2$. In other words, the reversible reaction

$$S + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES$$

functions at equilibrium. The QE condition is reached only at the end of the fast dynamics and is satisfied with a precision of order $O(\delta)$ during the slow dynamics [23]. Because of its approximate validity and purely kinetic origin, QE is different from the similar concept of detailed balance [6].

We introduce the linear combinations of variables $x_4 = x_1 + x_2$ and $x_5 = x_2 + x_3$ corresponding to the total substrate and total enzyme concentrations, respectively. Addition of the last two equations of (3.1) leads to $\dot{x}_5 = 0$, which means that for solutions of the full system, x_5 is constant for all times. We will call such a quantity an *exact conservation law.*

Addition of the first two and last two equations of (3.2) leads to $\dot{x}_4 = 0$ and $\dot{x}_5 = 0$. This means that x_4 is constant for solutions of the truncated dynamics, valid at short times $t = O(\delta^0)$, and is not constant at larger times $t = O(\delta^{-1})$. We call such a quantity an *approximate conservation law.* The quantity x_5 is both an exact and approximate conservation law.

More generally, let us consider the system (2.1). This model depends on the parameters $\boldsymbol{k} = (k_1, \ldots, k_r)$. After rescaling it by powers of a scaling parameter δ with $0 < \delta < 1$, it becomes (for details see section 4.1)

$$\begin{aligned} \dot{\bar{x}}_1 &= \delta^{b_1}(\bar{f}_1^{(1)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}) + \delta^{b'_1}\bar{f}_1^{(2)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}, \delta)) \\ &\vdots \\ \dot{\bar{x}}_n &= \delta^{b_n}(\bar{f}_n^{(1)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}) + \delta^{b'_n}\bar{f}_n^{(2)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}, \delta)), \end{aligned} \tag{3.3}$$

where $b'_i > 0$. The rescaled model (3.3) is rewritten in rescaled variables $\bar{\boldsymbol{x}} = (\bar{x}_1, \ldots, \bar{x}_n)$ and depends on the rescaled parameters $\bar{\boldsymbol{k}} = (\bar{k}_1, \ldots, \bar{k}_r)$.

The functions $\bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}, \delta)$ are infinitely differentiable, and their first derivatives in δ vanish at $\delta = 0$. We also have

$$f_i(\boldsymbol{k}, \boldsymbol{x}) = \delta^{b_i}(\bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}) + \delta^{b'_i}\bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}, \delta)).$$

For small δ and $b'_i > 0$ the terms in $\delta^{b'_i}\bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}}, \delta)$ are dominated by the terms in $\bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}})$. This justifies the introduction of the *truncated system* as the system of ODEs obtained by keeping only the lowest order dominant terms in (3.3), namely,

$$\dot{x}_1 = f_1^{(1)}(\boldsymbol{k}, \boldsymbol{x}), \ \ldots, \ \dot{x}_n = f_n^{(1)}(\boldsymbol{k}, \boldsymbol{x}), \tag{3.4}$$

where $f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = \delta^{b_i}\bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \bar{\boldsymbol{x}})$ for all $1 \le i \le n$.

Definition 3.2.

(a) *A function $\phi(\boldsymbol{x})$ is an* exact conservation law*, unconditionally on the parameters, if it is a first integral of the full system* (2.1)*, i.e., if*

$$\sum_{i=1}^{n} \frac{\partial \phi}{\partial x_i}(\boldsymbol{x}) f_i(\boldsymbol{k}, \boldsymbol{x}) = 0$$

for all $\boldsymbol{k} \in \mathbb{R}^r_{>0}$, $\boldsymbol{x} \in \mathbb{R}^n_{>0}$.

(b) *A function* $\phi(\boldsymbol{x})$ *is an* approximate conservation law*, unconditionally on the parameters, if it is a first integral of the truncated system* (3.4)*, i.e., if*

$$\sum_{i=1}^{n} \frac{\partial \phi}{\partial x_i}(\boldsymbol{x}) f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0$$

for all $\boldsymbol{k} \in \mathbb{R}^r_{>0}$, $\boldsymbol{x} \in \mathbb{R}^n_{>0}$.

(c) *An exact (approximate) conservation law of the form* $c_1 x_1 + \cdots + c_n x_n$ *with coefficients* $c_i \in \mathbb{R}$ *is called an* exact (approximate) linear conservation law*. If* $c_i \geq 0$ *for* $1 \leq i \leq n$*, the linear conservation law is called* semipositive*.*

(d) *An exact (approximate) conservation law of the form* $x_1^{m_1} \cdots x_n^{m_n}$ *with* $m_i \in \mathbb{Z}$ *is called an* exact (approximate) rational monomial conservation law*. If* $m_i \in \mathbb{Z}_+$ *for* $1 \leq i \leq n$*, the conservation law is called* monomial*. For simplicity, in this paper we will call both types* monomial*.*

(e) *An exact (approximate) conservation law of the form* $\sum_{i=1}^{s} a_i x_1^{m_{1i}} \cdots x_n^{m_{ni}}$ *with* $m_{ji} \in \mathbb{Z}_+$ *and* $a_i \in \mathbb{R}$ *is called an* exact (approximate) polynomial conservation law*.*

Remark 3.3. In the above definitions, $\phi(\boldsymbol{x})$ does not contain $\boldsymbol{k}$, and it exists for all admissible $\boldsymbol{k}$, which is a slight limitation. This condition facilitates the calculation of timescale orders needed for model reduction (see section 4.4). Of course, some conservation laws may depend on $\boldsymbol{k}$ and/or exist only for special values of $\boldsymbol{k}$, but finding them and their existence conditions is generally a much more difficult problem. Parametric conservation laws are considered in our parallel paper [9]. From now on, for the sake of simplicity and when it is clear from the context, we will refer to the categories in (a) and (b) of Definition 3.2 as conservation law and approximate conservation law, respectively. Let us note that an approximate conservation law can also be exact.

Some variables may not appear in a conservation law $\phi(\boldsymbol{x})$. This means that in the case of a linear conservation law some coefficients c_i may be zero, or in the case of a nonlinear conservation law some partial derivatives $\frac{\partial \phi}{\partial x_i}(\boldsymbol{x})$ may vanish. If r is the number of all nonzero quantities $\frac{\partial \phi}{\partial x_i}(\boldsymbol{x})$, then we say that the conservation law *depends on* r *variables.*

Definition 3.4. *An exact or approximate conservation law depending on* r *variables is called* simple *if it cannot be split into the sum or the product of two conservation laws such that at least one of them depends on a number* r' *of variables, with* $1 \leq r' < r$*.*

Definition 3.5. *For* $\boldsymbol{k} \in \mathbb{R}^r_{>0}$ *a steady state* $\boldsymbol{x}$ *is a positive solution of* $\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}) = 0$*, and we denote the* steady state variety *by* $\mathcal{S}_{\boldsymbol{k}}$*. A steady state* $\boldsymbol{x}$ *is* degenerate *or* nondegenerate *if the Jacobian* $D_{\boldsymbol{x}} \boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x})$ *is singular or regular, respectively.*

Degeneracy of steady states implies that $\mathcal{S}_{\boldsymbol{k}}$ is not discrete. Reciprocally, if the local dimension at a point $\boldsymbol{x}_0 \in \mathcal{S}_{\boldsymbol{k}}$ is strictly positive, then $\boldsymbol{x}_0$ is degenerate (Theorem 10 of [9]).

Definition 3.6. *A set*

$$\boldsymbol{\Phi}(\boldsymbol{x}) = (\phi_1(\boldsymbol{x}), \ldots, \phi_s(\boldsymbol{x}))^{\mathsf{T}}$$

of exact conservation laws is called complete *if the Jacobian matrix*

$$\boldsymbol{J}_{\boldsymbol{F},\boldsymbol{\Phi}}(\boldsymbol{k}, \boldsymbol{x}) = D_{\boldsymbol{x}}(\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}), \boldsymbol{\Phi}(\boldsymbol{x}))^{\mathsf{T}}$$

has rank n for any $\boldsymbol{k} \in \mathbb{R}^r_{>0}$, $\boldsymbol{x} \in \mathbb{R}^n_{>0}$ satisfying $\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}) = 0$. The set is called independent *if the Jacobian matrix of $\boldsymbol{\Phi}(\boldsymbol{x})^\mathsf{T}$ with respect to $\boldsymbol{x}$ has rank s for any $\boldsymbol{k} \in \mathbb{R}^r_{>0}$, $\boldsymbol{x} \in \mathbb{R}^n_{>0}$ such that $\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}) = 0$. In the case of a set $\boldsymbol{\Phi}(\boldsymbol{x})$ of approximate conservation laws, completeness is defined with $\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x})$ replaced by*

$$\boldsymbol{F}^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = \left(f_1^{(1)}(\boldsymbol{k}, \boldsymbol{x}), \ldots, f_n^{(1)}(\boldsymbol{k}, \boldsymbol{x})\right)^\mathsf{T}.$$

If a CRN has a complete set of conservation laws $\boldsymbol{\Phi}(\boldsymbol{x})$, then the set of positive solutions of $\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}) = 0$, $\boldsymbol{\Phi}(\boldsymbol{x}) = \boldsymbol{c}_0$ is finite (see Proposition 12 of [9]).

Remark 3.7. If the components of $\boldsymbol{\Phi}(\boldsymbol{x})$ are linear in $\boldsymbol{x}$ and come from a stoichiometric matrix, the set

$$\{\boldsymbol{\Phi}(\boldsymbol{x}) = \boldsymbol{c}_0\} \cap \mathbb{R}^n_{\geq 0}$$

is called a *stoichiometric compatibility class* or *reaction simplex* [14, 57]. Stoichiometric compatibility classes of systems with complete sets of linear conservation laws contain a finite number of steady states (see Proposition 12 of [9]). We note that some authors call completeness of linear conservation laws *nondegeneracy* [15].

Remark 3.8. Since our concern is the number of strictly positive solutions in $\boldsymbol{x}$ of the system $\boldsymbol{F}(\boldsymbol{k}, \boldsymbol{x}) = 0$, $\boldsymbol{\Phi}(\boldsymbol{x}) = \boldsymbol{c}_0$, in Definition 3.6 it would be more natural to consider the rank of $\boldsymbol{J}_{\boldsymbol{F},\boldsymbol{\Phi}}(\boldsymbol{k}, \boldsymbol{x})$ on $\mathcal{S}_{\boldsymbol{k}} \cap \{\boldsymbol{\Phi}(\boldsymbol{x}) = \boldsymbol{c}_0\} \cap \mathbb{R}^n_{>0}$. In fact, as this rank does not depend on $\boldsymbol{c}_0$, it is simpler and also equivalent to impose its value on $\mathcal{S}_{\boldsymbol{k}} \cap \mathbb{R}^n_{>0}$.

Remark 3.9. The independent linear conservation laws

$$\boldsymbol{\Phi}(\boldsymbol{x}) = (x_1 + x_2,\, x_2 + x_3)$$

of Example 3.1 are complete. More precisely, the Jacobian of $(\boldsymbol{F}(\boldsymbol{x}), \boldsymbol{\Phi}(\boldsymbol{x}))^\mathsf{T}$, where $\boldsymbol{F}(\boldsymbol{x})$ is the vector of right-hand sides of (3.2), has the 3×3 minor

$$M := \det(D_{\boldsymbol{x}}(-k_1 x_1 x_3 + k_2 x_2, \boldsymbol{\Phi}(\boldsymbol{x}))^\mathsf{T}) = -k_2 - k_1 x_1 - k_1 x_3.$$

This minor cannot be zero for positive $\boldsymbol{x}$, $\boldsymbol{k}$ on the steady state variety defined by the equation $-k_1 x_1 x_3 + k_2 x_2 = 0$, and therefore the rank of $\boldsymbol{J}_{\boldsymbol{F},\boldsymbol{\Phi}}(\boldsymbol{k}, \boldsymbol{x})$ is three.

Furthermore, all stoichiometric compatibility classes defined by $x_1 + x_2 = c_{01}$, $x_2 + x_3 = c_{02}$, $\boldsymbol{x} > 0$ contain a unique steady state

$$\begin{aligned} x_1 &= (k_1(c_{01} - c_{02}) - k_2 + \sqrt{\Delta})/(2k_1), \\ x_2 &= (k_1(c_{01} + c_{02}) + k_2 - \sqrt{\Delta})/(2k_1), \\ x_3 &= (k_1(c_{02} - c_{01}) - k_2 + \sqrt{\Delta})/(2k_1), \end{aligned}$$

where $\Delta = (c_{01} - c_{02})^2 k_1^2 + k_2^2 + 2k_1 k_2 (c_{01} + c_{02})$.

Remark 3.10. The following example shows that linear conservation laws are not always complete.

Example 3.11. One checks easily that the system

$$\dot{x}_1 = 1 - x_1 - x_2, \quad \dot{x}_2 = x_1 + x_2 - 1$$

has the linear conservation law $\Phi(\boldsymbol{x}) = (x_1 + x_2)$ and that the Jacobian of $(\boldsymbol{F}(\boldsymbol{x}), \boldsymbol{\Phi}(\boldsymbol{x}))^\mathsf{T}$ is constant and has rank 1. Trivially the Jacobian has everywhere rank 1, and so $\boldsymbol{\Phi}(\boldsymbol{x})$ is not complete. The explicit solutions of the ODE system are $x_1(t) = (1 - c_0)t + c_1$ and $x_2(t) = (c_0 - 1)t + c_0 - c_1$. One can easily show that all invariant curves are of the form $x_1 + x_2 = c_0$. We conclude that there are no further first integrals, and so the system has no complete set of conservation laws. We can also note that the intersection of the steady state variety $x_1 + x_2 = 1$ with a stoichiometric compatibility class $x_1 + x_2 = c_0$ is either empty or continuous.

Remark 3.12. The notions of completeness and independence in Definition 3.6 are effective and can be tested algorithmically using parametric rank computations (see Algorithms 3–5 in [9]).

4. Model reduction using approximate conservation laws.

4.1. Formal scaling procedure.

We consider CRN models described by a system of ODEs as in (2.1), where we assume that numerical values of the model parameters are given. We denote these parameters by $\boldsymbol{k}^*$.

For the scaling of the model parameters $\boldsymbol{k}^*$ we choose a new parameter $\epsilon_* \in]0,1[$ and rescale $\boldsymbol{k}^*$ by powers of ϵ_*, that is,

$$k_i^* = \bar{k}_i \epsilon_*^{e_i} \quad \text{for } 1 \le i \le r, \tag{4.1}$$

where the exponents e_i are in $\mathbb{Q}$. Furthermore, the prefactors $\bar{k}_i$ have order $O(\epsilon_*^0)$. More precisely, we have

$$(\epsilon_*)^\eta < \bar{k}_i \le (\epsilon_*)^{-\eta} \quad \text{for } 1 \le i \le r, \tag{4.2}$$

where η is a positive parameter smaller than one. A possible choice of the exponents is

$$e_i = \frac{\text{round}(g \log_{\epsilon_*}(k_i^*))}{g} \in \mathbb{Q}, \tag{4.3}$$

where g is a strictly positive integer controlling the precision of the rounding step, and *round* stands for round half down. This choice leads to prefactors $\bar{k}_i$ satisfying (4.2) with $\eta = 1/(2g)$.

We further rescale the variables $x_k = y_k \epsilon_*^{d_k}$, where $d_k \in \mathbb{Q}$, and transform (2.1) into the rescaled system

$$S_{\epsilon_*} \begin{cases} \dot{y}_1 &= \displaystyle\sum_{j=1}^{r} \epsilon_*^{\psi_{1j}} S_{1j} \bar{k}_j^* \boldsymbol{y}^{\alpha_j} \\ &\vdots \\ \dot{y}_n &= \displaystyle\sum_{j=1}^{r} \epsilon_*^{\psi_{nj}} S_{nj} \bar{k}_j^* \boldsymbol{y}^{\alpha_j}, \end{cases} \tag{4.4}$$

where $\psi_{i,j} = e_j + \langle \boldsymbol{d}, \alpha_j \rangle - d_i$ for $1 \le i \le n$ and $\boldsymbol{d} = (d_1, d_2, \ldots, d_n)$.

The parameter and concentration orders e_i and d_k should be understood as orders of magnitude. For instance, if $\epsilon^* = 10^{-1}$, a parameter or concentration of order $d = 2$ equals roughly 10^{-2}. Thus, small orders mean large parameters or concentration values.

At this stage, the variable rescaling is completely arbitrary, but in the next subsection the rescaling exponents d_k will satisfy important constraints.

From now on, we will transform the numerical parameters ϵ_*, $\boldsymbol{k}^*$ into variables ϵ, $\boldsymbol{k} = (k_1, \ldots, k_r)$ such that $k_i = \epsilon^{e_i}\bar{k}_i$ and consider the family of ODE systems indexed by ϵ,

$$S_\epsilon \begin{cases} \dot{y}_1 &= \displaystyle\sum_{j=1}^{r} \epsilon^{\psi_{1j}} S_{1j}\bar{k}_j \boldsymbol{y}^{\alpha_j} \\ &\vdots \\ \dot{y}_n &= \displaystyle\sum_{j=1}^{r} \epsilon^{\psi_{nj}} S_{nj}\bar{k}_j \boldsymbol{y}^{\alpha_j}. \end{cases} \tag{4.5}$$

Our initial model S_{ϵ_*} is a member of this family, obtained from (4.5) for $\epsilon = \epsilon_*$ and $\boldsymbol{k} = \boldsymbol{k}^*$. We are interested in characterizing the behavior of the solutions of this family of ODEs when $\epsilon \to 0$. This limit will correspond to a reduced model that is a good approximation to the initial model if ϵ^* is close to zero for $\boldsymbol{k} = \boldsymbol{k}^*$ and if several conditions ensuring the convergence of the solutions of S_ϵ are satisfied (see section 4.5). This remark suggests that ϵ^* should be chosen as small as possible, smaller than an upper bound depending on the convergence rate of the solutions of S_ϵ in the limit $\epsilon \to 0$. However, rounding effects in (4.3) imply that when ϵ^* is too small, the parameter orders e_i become zero for all $1 \le i \le r$. In practice, we need to differentiate parameters whose ratios are large (or small) enough, although it is generally difficult to establish what is the meaning of enough. However, this means that ϵ^* must be chosen larger than a lower bound depending on the common denominator d and on the minimum (or maximum) ratio of parameters that need to be consider as distinct.

In order to transform the exponents ψ_{ij} into positive integer orders and thus render the equations suitable for application of singular perturbation theory, we further perform the time scaling $\tau = \epsilon^\mu t$, where

$$\mu = \min\{\psi_{ij} \mid 1 \le i \le n,\, 1 \le j \le r,\, S_{ij} \ne 0\}$$

and separate lowest order terms in each equation. Letting

$$a_{ij} = \psi_{ij} - \mu \ge 0,\ \ a_i = \min\{a_{ij} \mid 1 \le j \le r,\, S_{ij} \ne 0\} \ge 0 \text{ and } a'_{ij} = a_{ij} - a_i > 0,$$

we obtain

$$y'_i = \epsilon^{a_i}\left(\sum_{a_{ij}=a_i} S_{ij}\bar{k}_j \boldsymbol{y}^{\alpha_j} + \sum_{a_{ij}\ne a_i} S_{ij}\bar{k}_j \epsilon^{a'_{ij}} \boldsymbol{y}^{\alpha_j}\right) \quad \text{for } 1 \le i \le n. \tag{4.6}$$

Defining $\delta = \epsilon^{1/o}$, where $o \in \mathbb{N}$ is the least common multiple of denominators of $a_{ij} \in \mathbb{Q}$, the equations in (4.6) become

$$y'_i = \delta^{b_i}(\bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{y}) + \delta^{b'_i}\bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{y}, \delta)), \tag{4.7}$$

where

$$\bar{f}_i^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{y}) = \sum_{a_{ij}=a_i} S_{ij}\bar{k}_j\boldsymbol{y}^{\alpha_j} \quad \text{and} \quad \bar{f}_i^{(2)}(\bar{\boldsymbol{k}},\boldsymbol{y},\delta) = \sum_{a_{ij}\neq a_i} S_{ij}\bar{k}_j\delta^{b'_{ij}}\boldsymbol{y}^{\alpha_j},$$

and all the powers of δ are positive integers as follows:

$$b_i = oa_i,\ b'_i = o\min\{a_{ij} \mid 1 \le j \le r,\, S_{ij} \neq 0,\, a_{ij} \neq a_i\} - b_i > 0,\ b'_{ij} = oa'_{ij} - b_i - b'_i > 0.$$

We call the system obtained by retaining only the minimal order dominant terms in (4.7) the *truncated system*

$$y'_i = \delta^{b_i}\bar{f}_i^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{y}) \quad \text{for } 1 \le i \le n. \tag{4.8}$$

Let us define the *truncated stoichiometric matrix* $\boldsymbol{S}^{(1)}$ as the matrix whose entries are

$$S_{ij}^{(1)} = \begin{cases} S_{ij} & \text{if } a_{ij} = a_i, \\ 0 & \text{if not.} \end{cases} \tag{4.9}$$

It then follows that

$$\bar{f}_i^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{y}) = \sum_{j=1}^{r} S_{ij}^{(1)}\bar{k}_j\boldsymbol{y}^{\alpha_j} \quad \text{for } 1 \le i \le n.$$

For several calculations it is convenient to return to the variables $\boldsymbol{x}$ and the time t. In the variables $x_i = y_i\delta^{od_i}$, the full system reads

$$\dot{x}_i = f_i^{(1)}(\boldsymbol{k},\boldsymbol{x}) + f_i^{(2)}(\boldsymbol{k},\boldsymbol{x}) \quad \text{for } 1 \le i \le n, \tag{4.10}$$

where

$$f_i^{(1)}(\boldsymbol{k},\boldsymbol{x}) = \delta^{od_i+b_i+o\mu}\bar{f}_i^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{y}) = \sum_{j=1}^{r} S_{ij}^{(1)}k_j\boldsymbol{x}^{\alpha_j}$$

and

$$f_i^{(2)}(\boldsymbol{k},\boldsymbol{x}) = \sum_{j=1}^{r} S_{ij}^{(2)}k_j\boldsymbol{x}^{\alpha_j}$$

with $S_{ij}^{(2)} = S_{ij} - S_{ij}^{(1)}$. In the same variables, the truncated system is

$$\dot{x}_i = f_i^{(1)}(\boldsymbol{k},\boldsymbol{x}) \quad \text{for } 1 \le i \le n. \tag{4.11}$$

Remark 4.1. It is useful to notice that $f_i^{(1)}$ and $\bar{f}_i^{(1)}$ are in fact identical as polynomials in $\mathbb{R}(\boldsymbol{k},\boldsymbol{x})$ for all $1 \le i \le n$.

Remark 4.2. The variables x_i (and y_i) change significantly on timescales given, in the same units as t, by the reciprocals of $\dot{x}_i/x_i = \dot{y}_i/y_i$. Because $\dot{x}_i/x_i$ scales with δ^{μ_i}, where $\mu_i = b_i + o\mu$, we call μ_i the timescale order of x_i, which is also the timescale of y_i. Changing

time units to the units of τ, $x_i'/x_i = y_i'/y_i = O(\delta^{b_i})$; in these units the timescales of the variables x_i and y_i have orders b_i.

By definition,

$$\min\{a_i \mid 1 \le i \le n\} = \min\{\psi_{ij} \mid 1 \le i \le n,\, 1 \le j \le r,\, S_{ij} \ne 0\} - \mu = 0,$$

and therefore $\min\{b_i \mid 1 \le i \le n\} = 0$, and up to a relabeling of the variables y_i one can assume that $b_1 = 0 \le b_2 \le \cdots \le b_n$. As the powers δ^{b_i} indicate the timescales of the variables y_i (in the same units as τ), the most rapid variable is y_1 and the slowest variable is y_n. Of course, several variables can have the same timescale order, i.e., the same value of b_i. Let us regroup the variables y_i into vectors $\boldsymbol{z}_k$. More precisely, $\boldsymbol{z}_k = (y_{i_k}, y_{i_k+1}, \ldots, y_{i_k+n_k-1})$ regroups all variables such that $b_{i_k} = b_{i_k+1} = \cdots = b_{i_k+n_k-1} = b_k$, where $n_1 + n_2 + \cdots + n_m = n$. We then obtain

$$\boldsymbol{z}_k' = \delta^{b_k}(\bar{\boldsymbol{f}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) + \delta^{b_k'}\bar{\boldsymbol{f}}_k^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{z}, \delta)), \tag{4.12}$$

where $b_1 = 0 < b_2 < \cdots < b_m$, $0 < b_k'$, $\bar{\boldsymbol{f}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) \in (\mathbb{Z}[\bar{\boldsymbol{k}}, \boldsymbol{z}])^{n_k}$, and $\bar{\boldsymbol{f}}_k^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{z}, \delta) \in (\mathbb{Z}[\bar{\boldsymbol{k}}, \boldsymbol{z}, \delta])^{n_k}$.

We regroup variables x_i into vectors $\boldsymbol{x}_k = (y_{i_k}\delta^{od_{i_k}}, y_{i_k+1}\delta^{od_{i_k+1}}, \ldots, y_{i_k+n_k-1}\delta^{od_{i_k+n_k-1}})$ for $1 \le k \le m$. Although the variables x_i in the same group $\boldsymbol{x}_k$ can have different orders, their timescales have the same order μ_k; the vector $\boldsymbol{x}_1$ contains the fastest variables, whereas $\boldsymbol{x}_m$ contains the slowest variables.

4.2. Tropical geometry constraints on the scaling.

4.2.1. General considerations. In the previous sections, the orders $\boldsymbol{d} = (d_1, \ldots, d_n)$ of the species concentrations are chosen arbitrarily. However, theories of singular perturbations and normally hyperbolic invariant manifolds imply that after a fast transient period, the dynamics of CRNs is confined to one low dimensional normally hyperbolic invariant manifold [17, 40], where it remains for a long period, after which it eventually switches to another invariant manifold. Normally hyperbolic invariant manifolds generalize the notion of hyperbolic fixed points [58]. Although normally hyperbolic manifolds can have both contracting and expanding directions, here we are only concerned with the fully attractive case. Invariant manifolds with expanding directions, such as saddle connections, are important for switching between attractive invariant manifolds, a phenomenon that will not be addressed in this paper.

Quasi-steady state (QSS) [4, 50, 51] and quasi-equilibrium (QE) [21] conditions provide lowest order approximations to these normally hyperbolic, attractive, invariant manifolds. Although a QSS manifold may lose normal hyperbolicity at singular points [11], the QSS approximation is valid in the stable region of this manifold. For CRNs with rational or polynomial rate functions, the QSS and QE conditions read as systems of polynomial equations, and the lowest order approximations of invariant manifolds are algebraic varieties [42].

Tropical geometry is the natural framework in which to study limits of algebraic varieties depending on one parameter. These limits are based on the Litvinov–Maslov dequantization of real numbers, leading to degeneration of complex algebraic varieties into tropical varieties [29, 56]. The name dequantization is inspired by the analogy with Schrödinger's dequantization in quantum mechanics where the small parameter is the Planck's constant h and the

limit $h \to 0$ allows one to obtain classical mechanics as a limit of quantum mechanics. By dequantization, multivariate polynomials become piecewise-linear functions (min-plus polynomials). Furthermore, null sets of multivariate polynomials become tropical hypersurfaces, defined as the set of points where the piecewise-linear functions are not smooth, i.e., where the minimum in the min-plus polynomials is obtained for at least two monomials.

4.2.2. Orders and valuations. In algebraic geometry, tropical hypersurfaces, prevarieties, and varieties establish a modern tool in the theory of Puiseux series [5]. Lowest orders in Puiseux series are called valuations [30].

In our problem, let us assume that the normally hyperbolic invariant manifold confining the reduced dynamics (defined by the QSS or QE conditions; see also section 4.5) can be approximate by the Puiseux series solutions $\boldsymbol{x}(\epsilon)$ of the system

$$f_1(\boldsymbol{x},\epsilon)=0,\ \ldots,\ f_m(\boldsymbol{x},\epsilon)=0, \tag{4.13}$$

where $f_i(\boldsymbol{x},\epsilon)=\sum_{i=1}^{n_i} M_{ij}(\boldsymbol{x},\epsilon)$ are polynomials and $M_{ij}(\boldsymbol{x},\epsilon)$ are monomials in $\boldsymbol{x}$ and ϵ.

Let us remark that a Puiseux series is a power series with rational exponents and with a minimum, eventually negative, exponent. By the multivariate version of the Newton–Puiseux theorem [5, 12, 30] the solutions of (4.13) read

$$x_i(\epsilon)=\sum_{k=k_{0i}}^{\infty} c_{ik}\epsilon^{k/n},$$

where $n>0$ and k_{0i} are integers, and $c_{ik_{0i}}\neq 0$. In general, $x_i(\epsilon)\in\mathbb{C}$, but here we are interested in real positive solutions, that is, when $x_i(\epsilon)\in\mathbb{R}_{>0}$.

The valuation of $x_i(\epsilon)$ is the smallest exponent of this Puiseux series, namely $V(x_i(\epsilon))=k_{0i}/n$. The valuation can also be defined as the limit

$$V(x_i(\epsilon))=\lim_{\epsilon\to 0}\log_\epsilon(x_i(\epsilon)). \tag{4.14}$$

Remark 4.3. Concentration valuations (4.14) and valuation based scalings can be defined only for strictly positive concentrations. This is why we assume that all the concentration variables are in $\mathbb{R}_{>0}$.

Valuations satisfy the tropical min-plus algebra as follows:

$$\begin{aligned} V(x_1(\epsilon)+x_2(\epsilon))&=\min\{V(x_1(\epsilon)),V(x_2(\epsilon))\},\\ V(x_1(\epsilon)x_2(\epsilon))&=V(x_1(\epsilon))+V(x_2(\epsilon)). \end{aligned} \tag{4.15}$$

According to rules (4.15) of the min-plus algebra, valuations of monomials are linear functions of valuations of parameters

$$V(k_j\boldsymbol{x}^{\boldsymbol{\alpha}_j})=e_j+\langle \boldsymbol{d},\boldsymbol{\alpha}_j\rangle,$$

and valuations of polynomials are min-plus polynomials, i.e., piecewise-linear functions

$$V\left(\sum_{j=1}^{r} S_{ij}k_j\boldsymbol{x}^{\boldsymbol{\alpha}_j}\right)=\min\{e_j+\langle \boldsymbol{d},\boldsymbol{\alpha}_j\rangle \mid 1\le j\le r,\ S_{ij}\neq 0\}.$$

Here we assume that elements of the stoichiometric matrix S_{ij} have order $O(\epsilon^0)$ and zero valuation.

In this paper, we will use valuations as a tool for computing orders of magnitude.

For instance, to each variable one can associate a characteristic time that is the reciprocal of $\frac{d\log(x_i)}{dt} = \frac{\dot{x}_i}{x_i}$. The valuation of $\frac{\dot{x}_i}{x_i}$, which we call timescale order, reads

$$
\begin{aligned}
V\left(\frac{\dot{x}_i}{x_i}\right) &= V(\dot{x}_i) - d_i = \min\{e_j + \langle \boldsymbol{d}, \boldsymbol{\alpha}_j \rangle \mid 1 \le j \le r,\, S_{ij} \neq 0\} - d_i \\
&= \min\{\psi_{ij} + \langle \boldsymbol{d}, \boldsymbol{\alpha}_j \rangle \mid 1 \le j \le r,\, S_{ij} \neq 0\},
\end{aligned} \tag{4.16}
$$

where ψ_{ij} is defined as in (4.4).

4.2.3. The tropical equilibration conditions. For Puiseux series solutions, the valuations represent the orders of magnitude introduced in subsection 4.1. In particular, $V(x_i) = d_i$.

By a theorem of Kapranov [30] the valuations are rational points on the tropical hypersurface, defined as the locus of points where the piecewise-linear tropical polynomials

$$V(f_i(\boldsymbol{x}, \epsilon)) = \min\{V(M_{ij}(\boldsymbol{x}, \epsilon)) \mid 1 \le j \le n_i\}$$

are nondifferentiable. In other words, the tropical hypersurface is the locus of points where the minimal valuation in $V(f_i(\boldsymbol{x}, \epsilon))$ is attained for at least two monomials.

In the case of Puiseux series of real positive solutions, which are of interest for our problem, in addition to the nonsmoothness we need also a sign condition. In this case, we obtain the following *tropical equilibration condition*: the minimal valuation is obtained for at least two monomials of opposite signs [32, 33, 40, 42, 44, 46].

Let us note that orders of magnitude satisfy the same properties as valuations. The smallest order monomials are also the largest in absolute value, and therefore the tropical equilibration condition means that each polynomial equation should contain at least two dominant terms of minimal order and opposite signs. These conditions were justified heuristically using the concept of compensation of dominant monomials [32, 33, 40, 42, 44, 46].

In systems with multiple timescales, slow dynamics occurs only when, for each dominant (i.e., much larger than the others) monomial on the right-hand side of (2.1), there is at least another monomial of the same order but with opposite sign.

In singular perturbation theory, only fast variables satisfy quasi-steady state or quasi-equilibrium equations that reduce the dimension of the dynamics. Slow variables need not satisfy such constraints. Therefore, only the fast variables and not necessarily the slow variables need to satisfy tropical equilibration conditions. This condition was called partial tropical equilibration in [10, 46].

Therefore, in order to obtain the constraints satisfied by the orders, we first partition the variables into the following two disjoint sets: fast equilibrated species variables with indices F, and slow nonequilibrated species variables with indices S, where $F \cup S = \{1, \ldots, n\}$ and $F \cap S = \emptyset$. This splitting is a priori arbitrary and changes from one partial equilibration solution to another.

To summarize, orders of variables have to satisfy several types of constraints as follows:

1. **Tropical equilibration of fast variables.** The equilibration condition follows from the properties (4.15) of valuations and reads as

$$\min\{\psi_{ij} \mid 1 \le j \le r,\, S_{ij} > 0\} = \min\{\psi_{ij} \mid 1 \le j \le r,\, S_{ij} < 0\} \tag{4.17}$$

for all $i \in F$.

2. **Tropical equilibration of exact conservation laws.** Let us assume that the reaction network has one or several conservations laws $\phi_i(\boldsymbol{x})$, where $1 \le i \le n_c$. These can be linear, monomial, or polynomial conservation laws

$$\phi_i(\boldsymbol{x}) = \sum_{j=1}^{r_c} z_{ij} \boldsymbol{x}^{\boldsymbol{\beta_j}}(\boldsymbol{x}),$$

where z_{ij} are integers, and $\boldsymbol{\beta_{ij}} \in \mathbb{N}^n$ are multi-indices. We consider the case where all z_{ij} are positive and have order $O(\epsilon^0)$.
Then the steady state variety must satisfy the polynomial equation $\phi_i(\boldsymbol{x}) = \bar{c}_i \epsilon^{f_i}$. Again, the Kapranov theorem adapted to real positive solutions leads to the condition

$$\min\{\langle \boldsymbol{d}, \boldsymbol{\beta_j} \rangle \mid 1 \le j \le r_c,\, Z_{ij} \ne 0\} = f_i \tag{4.18}$$

for all $1 \le i \le n_c$.

3. **Timescale conditions between fast and slow variables.** This condition simply means that the fastest slow variable is slower than any fast variable

$$\min\{\psi_{ij} \mid S_{ij} \ne 0,\, i \in S,\, 1 \le j \le r\} > \min\{\psi_{ij} \mid S_{ij} \ne 0,\, 1 \le j \le r\} \tag{4.19}$$

for all $i \in F$.

If $F = \{1, \ldots, n\}$, then all variables are equilibrated, and no timescale conditions are required. In this case, the set of constraints (4.17) and (4.18) defines *total tropical equilibration solutions*. If not all variables are fast, then the set of constraints (4.17), (4.18), and (4.19) defines *partial tropical equilibration solutions* (see [10]).

4.2.4. Importance of concentration valuations for the scaling. In many studies, scalings are applied only to parameters. This is because species concentrations are unknown and in this case it is handy to assume that all the chemical species are present in similar concentrations. However, this method has limited validity, as concentrations of different species can have different orders of magnitude.

To illustrate this common mistake, we consider the following example, adapted from [48].

Example 4.4. Let us consider the mass action CRN

$$\emptyset \xrightarrow{1} A_2 \xrightarrow{1/\epsilon} A_1 \xrightarrow{1} \emptyset, \quad A_2 + A_2 \xrightarrow{1/\epsilon} \emptyset.$$

The corresponding ODEs are

$$\dot{x}_1 = x_2/\epsilon - x_1, \quad \dot{x}_2 = -x_2/\epsilon - x_2^2/\epsilon + 1.$$

The model does not have exact conservation laws. By imposing total tropical equilibration conditions to the model, we get

$$d_2 - 1 = d_1, \quad \min\{d_2 - 1, 2d_2 - 1\} = 0.$$

These equations have the unique solution $d_1 = 0$, $d_2 = 1$, meaning that the valuations of x_1 and x_2 are different. The corresponding scaling is $x_1 = y_1$, $x_2 = y_2\epsilon$, and the rescaled ODEs read

$$\dot{y}_1 = y_2 - y_1, \quad \dot{y}_2 = \epsilon^{-1}(-y_2 - \epsilon y_2^2 + 1).$$

This scaling shows that y_1 and y_2 are slow and fast variables, respectively. The fast truncated system

$$\dot{y}_2 = \epsilon^{-1}(-y_2 + 1)$$

has a unique hyperbolic steady state $y_2 = 1$.

This model is not an example of approximate conservation, and standard singular perturbation theory techniques (quasi-steady state approximation) can be applied for its reduction.

Note that [48] used nonscaled concentrations for this example. By doing so, the truncated system is $\dot{x}_1 = x_2/\epsilon$, $\dot{x}_2 = -x_2/\epsilon - x_2^2/\epsilon$, where both variables x_1 and x_2 are fast. This scaling is different from ours. It leads to the nonlinear approximate conservation law $\phi(x_1, x_2) = x_1 + \log(1 + x_2)$ that was interpreted as a slow variable in [48]. This scaling, for which the two fast variables x_1, x_2 are not equilibrated, could describe the fast dynamics starting with initial concentrations $x_1(0)$, $x_2(0)$ of the same order, but it does not apply to later stages of the dynamics.

4.3. Reduction of the Michaelis–Menten model under quasi-equilibrium conditions. The Michaelis–Menten model has been used as a paradigmatic example because it allows one to introduce the main concepts of model reduction. Both QSS and QE reductions were discussed in [33, 42, 45] for a two variable Michaelis–Menten model obtained from the three variable one by exact reduction, using one exact linear conservation law. In this subsection we illustrate a slightly different approach that starts with the three variable model introduced in Example 3.1.

The scaling used to derive (3.1) is based on the total tropical equilibration solution $d_1 = d_2 = d_3 = 0$ and $\delta = \epsilon$. More general scalings, leading to equivalent results, can be found in [34]. According to this scaling, all three variables x_1, x_2, and x_3 have the same timescale. As already shown in section 3.1, the new variables $x_4 = x_1 + x_2$ and $x_5 = x_2 + x_3$ are conservation laws (approximate and exact, respectively).

We use the approximate and exact conservation laws to eliminate two out of the three variables x_1, x_2, x_3 and obtain

$$\begin{aligned} x_2 &= x_4 - x_1, \\ x_3 &= x_5 - x_4 + x_1. \end{aligned} \tag{4.20}$$

The remaining variables satisfy

$$\begin{aligned} \dot{x_1} &= -k_1 x_1 (x_5 - x_4 + x_1) + k_2 (x_4 - x_1), \\ \dot{x_4} &= -\delta k_3 (x_4 - x_1), \\ \dot{x_5} &= 0. \end{aligned} \tag{4.21}$$

System (4.21) shows that x_4 is a slow variable and x_5 is a conserved constant variable. The constant variable can be turned into a parameter $x_5 = k_4$, which leads to

$$\begin{aligned} \dot{x_1} &= -k_1 x_1 (k_4 - x_4 + x_1) + k_2 (x_4 - x_1), \\ \dot{x_4} &= \delta k_3 (x_4 - x_1). \end{aligned} \tag{4.22}$$

The system (4.22) is typically a slow-fast system with x_1 the fast and x_4 the slow variable [17, 54]. The fast dynamics is described by

$$\dot{x_1} = -k_1 x_1 (k_4 - x_4 + x_1) + k_2 (x_4 - x_1) \tag{4.23}$$

and has two hyperbolic steady states, where only one is positive and stable,[1] namely,

$$x_1^* = \frac{-(k_1(k_4 - x_4) + k_2) + \sqrt{(k_1(k_4 - x_4) + k_2)^2 + 4k_1 k_2 x_4}}{2k_1}. \tag{4.24}$$

It follows from singular perturbation theory [17, 24, 54] that the solutions of system (4.22) with appropriate initial conditions converge for $\delta \to 0$ to the solutions of the differential-algebraic system

$$\begin{aligned} 0 &= -k_1 x_1 (k_4 - x_4 + x_1) + k_2 (x_4 - x_1), \\ x_4' &= k_3 (x_4 - x_1), \end{aligned} \tag{4.25}$$

where the derivative of x_4 is with respect to the time $\tau = t\delta$.

Using the solution (4.24), the semi-explicit differential-algebraic system (4.25) can be transformed into the reduced ODE

$$x_4' = k_3 \left(x_4 - \frac{-(k_1(k_4 - x_4) + k_2) + \sqrt{(k_1(k_4 - x_4) + k_2)^2 + 4k_1 k_2 x_4}}{2k_1} \right). \tag{4.26}$$

Figure 1 illustrates the accuracy of this reduction.

4.4. Approximate conservation laws as slow variables. We have seen in the previous section that the approximate linear conservation laws of the Michaelis–Menten model are either exact conservation laws or slow variables. In this section we show that this property is true in general for any polynomial CRN model of type (2.1) and for all linear, monomial, or polynomial approximate conservation laws.

[1] All the eigenvalues of the Jacobian matrix computed in this state lie in the complex left half-plane.

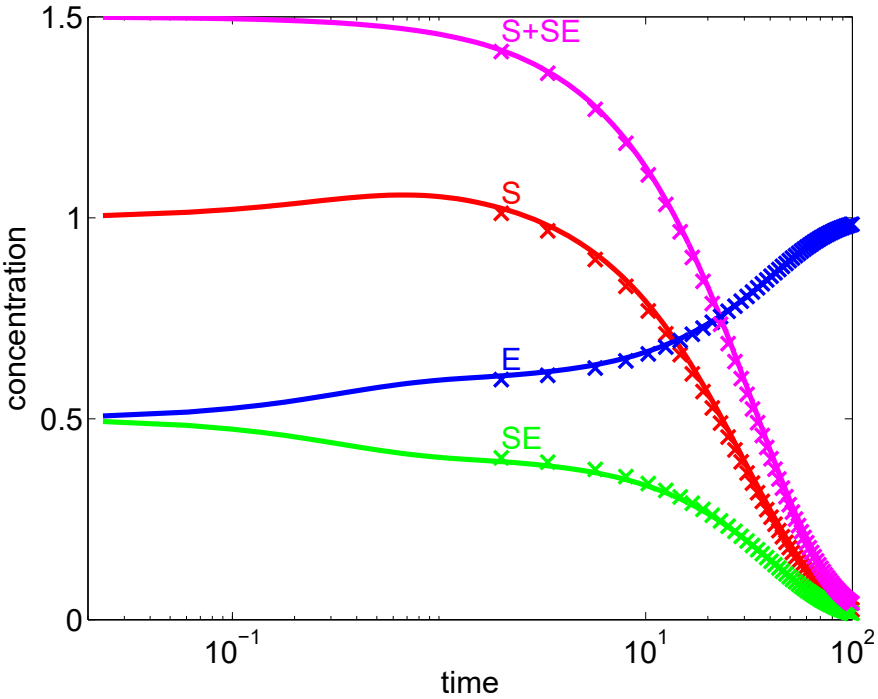


Figure 1. *Comparison of numerical solutions obtained with the full Michaelis–Menten (MM) model (solid lines) and with the reduced model (crosses). The variables S, E, and SE are fast and slaved (in the reduced model, their values are obtained as solutions of algebraic equations),and the approximate conservation law $S + SE$ is slow. The initial values are such that E and S have concentrations of the same order of magnitude; this is not compatible with the quasi-steady state (QSS) approximation* [45, 49] *of the MM mechanism but is compatible with the quasi-equilibrium (QE) approximation that has been used here. As discussed in* [33, 42, 45], *the QE and QSS approximations correspond to scalings obtained from different tropical equilibration solutions (the total equilibration for QE and a partial equilibration solution for QSS).*

4.4.1. Linear approximate conservation laws as slow variables. Linear approximate conservation laws correspond to "pools" of species that are conserved by fast cycling reactions. The exact and approximate linear conservation laws usually correspond to the total number of copies of a certain type of molecule in the pool. For instance, in Example 3.1, there is an exact and an approximate linear conservation law corresponding to the total numbers of enzyme and substrate molecules, respectively. The fast part of the dynamics ends with the equilibration of all species in the fast pool. This state is named quasi-equilibrium (QE) [23].

Let us consider an approximate linear conservation law

$$\phi(\boldsymbol{x}) = \sum_{i=1}^{n} c_i x_i, \quad \text{where } c_i \in \mathbb{N},$$

which is conserved by the truncated ODE system (4.11). Note that in the linear combination defining $\phi(\boldsymbol{x})$ we also admit that some of the coefficients c_i are zero. Let $I = \{i \mid c_i \neq 0\}$ denote the set of indices of species involved in the fast pool quantity. Furthermore, in most applications the c_i are small positive integers, and we will assume that $c_i = O(1)$. Using Definitions 3.2 and 3.4, we obtain the following result.

Theorem 4.5. *If $\phi(\boldsymbol{x})$ is a simple linear approximate conservation law, then the variable $q = \phi(\boldsymbol{x})$ is either constant or slower than all the variables $\{x_i \mid i \in I\}$ of the system (2.1). Furthermore, if the timescales of all x_i with $i \in I$ have the same order, then the concentrations of these variables have the same orders.*

Before we start with the proof of the theorem, we show the following lemma.

Lemma 4.6. *Let*

$$\phi(\boldsymbol{x}) = \sum_{i=1}^{n} c_i x_i$$

be a simple linear approximate conservation law, and let I be defined as above. Then all the polynomials $f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ in the truncated system (4.11) have the same order in δ, i.e., $od_i + b_i = od_{i'} + b_{i'}$ for all $i, i' \in I$. If furthermore, the timescales of the variables x_i have the same order in δ for all $i \in I$, i.e., $b_i = b_{i'}$ for all $i, i' \in I$, then the concentrations x_i also have the same order in δ, i.e., $d_i = d_{i'}$ for all $i, i' \in I$.

Proof of Lemma 4.6. In the variables $\boldsymbol{x}$ the truncated system reads (see (4.11))

$$\dot{x}_i = \delta^{od_i} \dot{y}_i = f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x}), \quad \text{where } f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = \delta^{od_i + b_i + o\mu} \bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{y}).$$

Since $\phi(\boldsymbol{x})$ is conserved by system (4.11), one has

$$\sum_{i=1}^{r} c_i f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0$$

for all $\boldsymbol{k}$, $\boldsymbol{x}$. This can only be satisfied if, for all $i \in I$, there is at least one $j \in I$ such that $f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ and $f_j^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ have a common monomial. Since q is simple, for all $i, j \in I$ with $i \neq j$, either $f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ and $f_j^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ share a monomial or there is a finite sequence $i = i_0, i_1, \ldots, i_k = j$ such that $f_{i_l}^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ and $f_{i_{l+1}}^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ share a monomial for $0 \leq l \leq k$. Since by the definition of the truncated system all the monomials in $f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ have the same order, it follows that all the polynomials $f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})$ for some $i \in I$ have the same order $\nu = od_i + b_i + o\mu$. The timescale order μ_i of x_i is the order of

$$\frac{\dot{x}_i}{x_i} = \frac{f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})}{x_i},$$

namely, $\mu_i = \nu - od_i = b_i + o\mu$. Thus, if all b_i are equal, then all d_i are equal for $i \in I$. ∎

Proof of Theorem 4.5. From the definition of q it follows that

$$\dot{q} = \sum_{i \in I} c_i \dot{x}_i.$$

Since q is conserved by the truncated system (4.11), we have that

$$\sum_{i=1}^{n} c_i \delta^{b_i + od_i + o\mu} \bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{y}) = 0 \tag{4.27}$$

for all $\bar{\boldsymbol{k}}$, $\boldsymbol{y}$, δ, and so

$$\dot{q} = \sum_{i=1}^{n} c_i \delta^{b_i + od_i + o\mu} \left(\bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{y}) + \delta^{b_i'} \bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{y}, \delta) \right) = \sum_{i=1}^{n} c_i \delta^{b_i + b_i' + od_i + o\mu} \bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{y}, \delta).$$

Thus $\dot{q} = 0$ if $f_i^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{y}, \delta)$ vanishes identically. In this case the approximate conservation law is also an exact one. If this is not the case, we can define μ_q as the order of the timescale of q, i.e., the order of $\frac{\dot{q}}{q}$. The order of q is $\min\{od_i \mid i \in I\}$, and so

$$\mu_q = \min\{b_i + b_i' + od_i + o\mu \mid i \in I\} - \min\{od_i \mid i \in I\}.$$

We prove now that q is slower than all x_i with $i \in I$; that is, we need to check that $b_i + o\mu < \mu_q$ for all $i \in I$. These conditions are equivalent to

$$b_i < \min\{b_j + b_j' + od_j \mid j \in I\} - \min\{od_j \mid j \in I\} \quad \text{for all } i \in I.$$

According to Lemma 4.6, $b_i = \nu - o\mu - od_i$ for all $i \in I$. Obviously, it is enough to prove that

$$\nu - o\mu - \min\{od_j \mid j \in I\} < \min\{b_j + b_j' + od_j \mid j \in I\} - \min\{od_j \mid j \in I\},$$

which leads us to the inequation $\nu - o\mu < \min\{b_j + b_j' + od_j \mid j \in I\}$. Since $\nu = b_j + od_j + o\mu$ and $b_j' > 0$ for all $j \in I$, all the above inequalities are satisfied.

The second part of the theorem follows from Lemma 4.6. ■

Theorem 4.5 suggests that there is a link between timescales and concentrations of species contributing to a linear approximate conservation law. This link can be made more precise by using the vectors $\boldsymbol{x}_k$ introduced in section 4.1, which group variables with the same timescale orders μ_k for $1 \le k \le m$. We have the following structure theorem for approximate linear conservation laws.

Theorem 4.7. *If $\phi(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_l)$ is a simple linear approximate conservation law depending on variables having timescale orders less than or equal to μ_l, then*

$$\phi(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_l) = \sum_{k=1}^{l} \delta^{d_q + \mu_l - \mu_k} \langle \boldsymbol{c}_k, \boldsymbol{z}_k \rangle, \tag{4.28}$$

where $\mu_1 < \mu_2 < \cdots < \mu_l$, $\boldsymbol{c}_k \in \mathbb{R}^{n_k}$, and d_q is the order of the variable $q = \phi(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_l)$. Thus,

$$\phi(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_l) = \phi^{(1)}(\boldsymbol{x}_l) + \phi^{(2)}(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_{l-1}),$$

where

$$\phi^{(1)}(\boldsymbol{x}_l) = \delta^{d_q} \langle \boldsymbol{c}_l, \boldsymbol{z}_l \rangle \quad \text{and} \quad \phi^{(2)}(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_{l-1}) = o(\delta^{d_q}).$$

$\phi^{(1)}(\boldsymbol{x}_l)$ contains the dominant lowest order terms of ϕ. In other words, variables of the same timescale orders contribute to terms of the same order in the conservation law; the dominant terms in the conservation law depend only on the slowest variables $\boldsymbol{x}_l$.

Proof. From (4.27) it follows that

$$\mu_i + od_i = \mu_l + d_q \tag{4.29}$$

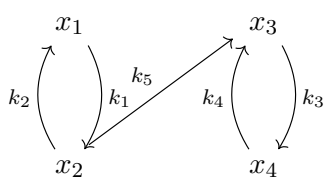
for all i with $c_i \neq 0$, where $d_q = \min\{od_i \mid c_i \neq 0\}$. From regrouping the coefficients c_i into vectors $\boldsymbol{c}_k$ corresponding to variables of the same timescales, we obtain

$$\phi = \sum_{k=1}^{l} \langle \boldsymbol{c}_k, \boldsymbol{x}_k \rangle = \sum_{k=1}^{l} \delta^{od_k} \langle \boldsymbol{c}_k, \boldsymbol{z}_k \rangle. \tag{4.30}$$

Finally, (4.28) follows from (4.30) and (4.29). ∎

Remark 4.8. A set of independent simple approximate conservation laws can be obtained from the truncated stoichiometric matrix $\boldsymbol{S}^{(1)}$ by using algorithms for the computation of a basis of simple vectors of the left kernel of a given integer coefficient matrix, i.e., vectors that cannot be decomposed as a sum of two nonzero kernel vectors having more zero elements [49].

Example 4.9. Consider the chemical reaction network



If the dynamics of this reaction network is of mass-action form, then it is given by the system of ODEs

$$\begin{aligned}
\dot{x}_1 &= k_2 x_2 - k_1 x_1,\\
\dot{x}_2 &= k_1 x_1 - (k_2 + k_5) x_2,\\
\dot{x}_3 &= k_5 x_2 + k_4 x_4 - k_3 x_3,\\
\dot{x}_4 &= k_3 x_3 - k_4 x_4.
\end{aligned}$$

Let us assume that the parameter orders are $e_1 = e_2 = e_3 = e_4 = 0$, $e_5 = 1$. Then the total tropical equilibrations are solutions of the system $d_1 = d_2$, $\min\{d_4, d_2 + 1\} = d_3$, $d_3 = d_4$, that is, $d_1 = d_2 \geq d_4 - 1$, $d_3 = d_4$. Assuming that the concentration orders are given by the total tropical equilibration solution $d_1 = d_2 = -1$ and $d_3 = d_4 = -2$, we obtain the rescaled system

$$\begin{aligned}
\dot{y}_1 &= \bar{k}_2 y_2 - \bar{k}_1 y_1,\\
\dot{y}_2 &= \bar{k}_1 y_1 - (\bar{k}_2 + \epsilon \bar{k}_5) y_2,\\
\dot{y}_3 &= \epsilon^2 \bar{k}_5 y_2 + \bar{k}_4 y_4 - \bar{k}_3 y_3,\\
\dot{y}_4 &= \bar{k}_3 y_3 - \bar{k}_4 y_4.
\end{aligned}$$

Since ϵ occurs only with integer powers, we have $\delta = \epsilon$. All species x_i for $1 \le i \le 4$ have the same timescale orders $\mu_i = 0$. The truncated system is

$$\begin{aligned}\dot{x}_1 &= k_2 x_2 - k_1 x_1,\\ \dot{x}_2 &= k_1 x_1 - k_2 x_2,\\ \dot{x}_3 &= k_4 x_4 - k_3 x_3,\\ \dot{x}_4 &= k_3 x_3 - k_4 x_4,\end{aligned}$$

and the truncated stoichiometric matrix reads

$$\boldsymbol{S}^{(1)} = \begin{pmatrix} -1 & 1 & 0 & 0\\ 1 & -1 & 0 & 0\\ 0 & 0 & -1 & 1\\ 0 & 0 & 1 & -1\end{pmatrix}.$$

The truncated system has two simple conservation laws $\phi_1(\boldsymbol{x}) = x_1 + x_2$ and $\phi_2(\boldsymbol{x}) = x_3 + x_4$. These correspond to the species pools $q_1 = x_1 + x_2$ and $q_2 = x_3 + x_4$ that have timescale orders $\mu_{q_1} = 1$ and $\mu_{q_2} = 2$, respectively. Thus, q_1 and q_2 are slower than the species x_i with $1 \le i \le 4$. Note that the species concentrations in these pools have equal orders $d_1 = d_2$ and $d_3 = d_4$, consistent with the fact that in simple pools, species with the same timescales have the same concentration orders (see Lemma 4.6). This CRN has also the exact conservation law $\phi_1(\boldsymbol{x}) + \phi_2(\boldsymbol{x})$, but this conservation law is not simple.

4.4.2. Monomial approximate conservation laws as slow variables. We consider now a monomial conservation law

$$\phi(\boldsymbol{x}) = \prod_{i=1}^{n} x_i^{m_i}$$

of the truncated system (4.11). As in section 3.1, we admit that some of the exponents m_i can be zero and define $I = \{i \mid 1 \le i \le n,\, m_i \ne 0\}$. This means that the variables x_i with $i \notin I$ do not appear in the conservation law.

Theorem 4.10. *If $\phi(\boldsymbol{x})$ is a simple monomial approximate conservation law, then the variable $q = \phi(\boldsymbol{x})$ is slower than all the variables $\{x_i \mid i \in I\}$ of system (2.1). Furthermore, all x_i with $i \in I$ have the same timescale orders.*

Proof. Let us note that

$$\dot{q} = q \sum_{i \in I} m_i \frac{\dot{x}_i}{x_i}.$$

Since $\phi(\boldsymbol{x})$ is conserved by the truncated system (4.11), we have that

$$\sum_{i \in I} \frac{m_i}{x_i} f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0 \tag{4.31}$$

for all $\boldsymbol{k}$, $\boldsymbol{x}$. As $\frac{f_i^{(1)}}{x_i}$ is a sum of rational monomials, (4.31) is only satisfied if for any $i \in I$ there is $j \in I$ such that $\frac{f_i^{(1)}}{x_i}$ and $\frac{f_j^{(1)}}{x_j}$ share a common monomial. Since $\phi(\boldsymbol{x})$ is simple, for all $i, j \in I$ either $\frac{f_i^{(1)}}{x_i}$ and $\frac{f_j^{(1)}}{x_j}$ share a common monomial or there is a sequence $i = i_0, i_1, \ldots, i_k = j$ such that $\frac{f_{i_l}^{(1)}}{x_{i_l}}$ and $\frac{f_{i_{l+1}}^{(1)}}{x_{i_{l+1}}}$ share a common monomial for $0 \le l \le k-1$. Hence, the orders of $\frac{f_i^{(1)}(\boldsymbol{k},\boldsymbol{x})}{x_i}$ are the same for all $i \in I$. As the timescale orders of x_i are the orders of $\frac{f_i^{(1)}(\boldsymbol{k},\boldsymbol{x})}{x_i}$, it follows that all x_i with $i \in I$ have the same timescale orders.

In order to compute the timescale of q we use

$$\frac{\dot{q}}{q} = \sum_{i \in I} m_i \frac{\dot{x}_i}{x_i} = \sum_{i \in I} m_i \delta^{b_i + o\mu} \frac{\bar{f}_i^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{y}) + \delta^{b_i'} \bar{f}_i^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{y}, \delta)}{y_i} = \sum_{i \in I} m_i \delta^{b_i + b_i' + o\mu} \frac{f_i^{(2)}(\bar{\boldsymbol{k}}, \boldsymbol{y}, \delta)}{y_i},$$

where the last equality follows from the fact that $\phi(\boldsymbol{x})$ is conserved by (4.11).

Let us denote by μ_q the order of the timescale of q, i.e., the order of $\frac{\dot{q}}{q}$. Assuming that all m_i are small integers of order $O(\delta^0)$, it follows that

$$\mu_q = \min\{b_i + b_i' + o\mu \mid i \in I\}.$$

To prove that q is slower than each of the variables $\{x_i \mid i \in I\}$, we need to show that for all $i \in I$ we have $\mu_i < \mu_q$. Thus we need to prove that $b_i < \min\{b_j + b_j' \mid j \in I\}$ for all $i \in I$. As for all $i, j \in I$ we have $b_i = b_j$ and $b_j' > 0$, it follows that $b_i = \min\{b_j \mid j \in I\} < \min\{b_j + b_j' \mid j \in I\}$ for all $i \in I$. ∎

Example 4.11. The model

$$\dot{x}_1 = x_1(x_2 - x_1) - \delta x_1, \quad \dot{x}_2 = x_2(x_1 - x_2)$$

is a mass-action network described by

$$A_1 + A_2 \xrightarrow{1} 2A_2, \quad A_1 + A_2 \xrightarrow{1} \emptyset, \quad A_2 + A_2 \xrightarrow{1} \emptyset, \quad A_1 \xrightarrow{\delta} \emptyset.$$

The truncated system

$$\dot{x}_1 = x_1(x_2 - x_1), \quad \dot{x}_2 = x_2(x_1 - x_2)$$

has a continuous steady state variety $x_1 = x_2$, on which its Jacobian is singular. This model has $\phi(x_1, x_2) = x_1 x_2$ as an approximate monomial simple conservation law. The intersection of the steady state variety with the set $\phi = c_0$ is the point $x_1 = x_2 = c_0/2$. The monomial conservation law is complete, since the 2×2 minor of the Jacobian

$$\det(D_{\boldsymbol{x}}(x_1(x_2 - x_1), x_1 x_2)^T) = -2x_1^2$$

does not vanish for $x_1 > 0$. Including $q = x_1 x_2$ among the variables leads to the ODE system

$$\dot{x}_1 = x_1(x_2 - x_1) - \delta x_1, \quad \dot{x}_2 = x_2(x_1 - x_2), \quad \dot{q} = -\delta q.$$

We note that in agreement with Theorem 4.10, x_1 and x_2 have the same timescale order, and that q is a slower variable.

4.4.3. Polynomial approximate conservation laws as slow variables. Let

$$\phi(\boldsymbol{x}) = \sum_{j=1}^{r} c_j \boldsymbol{x}^{\boldsymbol{m}_j}$$

be an approximate polynomial conservation law that is conserved by system (4.11), where $c_j \in \mathbb{R} \setminus \{0\}$ and $\boldsymbol{m}_j = (m_{1j}, \ldots, m_{nj}) \in \mathbb{N}^n$. Let $I = \{i \mid m_{ij} \neq 0 \text{ for some } j \text{ with } 1 \leq j \leq r\}$ so that $\phi(\boldsymbol{x})$ depends only on the variables x_i with $i \in I$.

Theorem 4.12. *If $\phi(\boldsymbol{x})$ is a simple polynomial approximate conservation law, then the variable $q = \phi(\boldsymbol{x})$ is slower than all variables x_i with $i \in I$ of system (2.1). Furthermore, if the timescales of the variables x_i have the same order in δ, i.e., $b_i = b_{i'}$ for all $i, i' \in I$, then the monomials in $\phi(\boldsymbol{x})$ have also the same order in δ, i.e., $\langle \boldsymbol{d}, \boldsymbol{m}_j \rangle = \langle \boldsymbol{d}, \boldsymbol{m}_{j'} \rangle$ for all $1 \leq j, j' \leq r$ such that $m_{i,j} \neq 0$ and $m_{i',j'} \neq 0$ for some $i, i' \in I$.*

Proof. We note that

$$\dot{q} = \sum_{j=1}^{r} c_j x^{\boldsymbol{m}_j} \left(\sum_{i=1}^{r} m_{ij} \frac{\dot{x}_i}{x_i} \right) = \sum_{i=1}^{n} \frac{\dot{x}_i}{x_i} \left(\sum_{m_{i,j} \neq 0} m_{ij} c_j \boldsymbol{x}^{\boldsymbol{m}_j} \right).$$

Let us define the sums of rational monomials

$$E_{i,j}(\boldsymbol{k}, \boldsymbol{x}) = \frac{f_i^{(1)}(\boldsymbol{k}, \boldsymbol{x})}{x_i} m_{ij} c_j \boldsymbol{x}^{\boldsymbol{m}_j}.$$

Then the expressions $E_{i,j}(\boldsymbol{k}, \boldsymbol{x})$ have the orders

$$b_i + o\mu + o\langle \boldsymbol{d}, \boldsymbol{m}_j \rangle.$$

As $\phi(\boldsymbol{x})$ is conserved by (4.11) it follows that

$$\sum_{1 \leq i \leq n,\, 1 \leq j \leq r,\, m_{i,j} \neq 0} E_{i,j}(\boldsymbol{k}, \boldsymbol{x}) = 0 \tag{4.32}$$

for all $\boldsymbol{k}$, $\boldsymbol{x}$. This is only possible if for any pair (i, j) with $m_{i,j} \neq 0$, there is a pair (i', j') with $m_{i',j'} \neq 0$ such that $E_{i,j}$ and $E_{i',j'}$ share a common monomial. Since $\phi(\boldsymbol{x})$ is simple, for all pairs (i, j) and (i', j') with $m_{i,j} \neq 0$ and $m_{i',j'} \neq 0$, either $E_{i,j}$ and $E_{i',j'}$ share a common monomial or there is a sequence of pairs

$$(i, j) = (i_0, j_0), (i_1, j_1), \ldots, (i_k, j_k) = (i', j')$$

such that E_{i_l, j_l} and $E_{i_{l+1}, j_{l+1}}$ share a common monomial for $0 \leq l \leq k-1$. Thus, the expressions $E_{i,j}$ have the same order for all pairs (i, j) with $m_{i,j} \neq 0$, i.e., we have that

$$b_i + o\mu + o\langle \boldsymbol{d}, \boldsymbol{m}_j \rangle = b_{i'} + o\mu + o\langle \boldsymbol{d}, \boldsymbol{m}_{j'} \rangle$$

for all pairs (i, j) and (i', j') with $m_{i,j} \neq 0$ and $m_{i',j'} \neq 0$. In particular, if all variables x_i have the same timescale order b_i for $i \in I$, it follows that the scalar products $\langle \boldsymbol{d}, \boldsymbol{m}_j \rangle$ are equal for all $1 \leq j < r$ with $m_{i,j} \neq 0$ for some $i \in I$. This proves the second part of the theorem.

As q is conserved by system (4.11), it follows that

$$\dot{q} = \sum_{i,j,m_{i,j}\neq 0} \delta^{b_i+b_i'+o\mu} \frac{\bar{f}_i^{(2)}(\bar{\boldsymbol{k}},\boldsymbol{y},\delta)}{y_i} m_{ij} c_j \delta^{o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle} \boldsymbol{y}^{\boldsymbol{m}_j}.$$

The timescale order of q is

$$\mu_q = \min\{b_i + b_i' + o\mu + o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle \mid m_{ij}\neq 0\} - \min\{o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle \mid 1\le j\le r\}.$$

Let $i\in I$ and j such that $m_{i,j}\neq 0$. Using

$$b_i + o\mu + o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle = \min\{b_i + o\mu + o < \boldsymbol{d},\boldsymbol{m}_j\rangle \mid m_{i,j}\neq 0\}$$

and $b_i' > 0$, we obtain

$$b_i + o\mu = \min\{b_i + o\mu + o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle \mid m_{i,j}\neq 0\} - o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle < \mu_q,$$

meaning that q is slower than all x_i with $i\in I$. ∎

As in the case of linear conservation laws, i.e., Theorem 4.7, we have a structure theorem for approximate polynomial conservation laws.

Theorem 4.13. *If $\phi(\boldsymbol{x}_1,\dots,\boldsymbol{x}_l)$ is a simple polynomial approximate conservation law depending on variables having timescale orders less than or equal to μ_l, then*

$$\phi(\boldsymbol{x}_1,\dots,\boldsymbol{x}_l) = \sum_{k=1}^{l} \delta^{d_q+\mu_l-\mu_k}\langle \boldsymbol{c}_k, \boldsymbol{\varphi}(\boldsymbol{z}_k)\rangle, \tag{4.33}$$

where $\mu_1<\mu_2<\cdots<\mu_l$, $\boldsymbol{c}_k\in\mathbb{R}^{n_k}$, $\boldsymbol{\varphi}(\boldsymbol{z}_k)\in\mathbb{R}^{n_k}[\boldsymbol{z}_k]$, and d_q is the order of the variable $q=\phi(\boldsymbol{x}_1,\dots,\boldsymbol{x}_l)$. Thus,

$$\phi(\boldsymbol{x}_1,\dots,\boldsymbol{x}_l) = \phi^{(1)}(\boldsymbol{x}_l) + \phi^{(2)}(\boldsymbol{x}_1,\dots,\boldsymbol{x}_{l-1}),$$

where

$$\phi^{(1)}(\boldsymbol{x}_l) = \delta^{d_q}\langle \boldsymbol{c}_l, \boldsymbol{\varphi}_l(\boldsymbol{z}_l)\rangle \quad \text{and} \quad \phi^{(2)}(\boldsymbol{x}_1,\dots,\boldsymbol{x}_{l-1}) = o(\delta^{d_q}).$$

$\phi^{(1)}(\boldsymbol{x}_l)$ contains the dominant lowest order terms of ϕ. In other words, variables of the same timescale orders contribute to monomials of the same order in the conservation law; the dominant monomials in the conservation law correspond to the slowest variables.

Proof. It follows from (4.32) that

$$\mu_i + o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle = \mu_l + d_q \tag{4.34}$$

for all pairs (i,j) with $c_j\neq 0$ and $m_{i,j}\neq 0$, where $d_q = \min\{o\langle \boldsymbol{d},\boldsymbol{m}_j\rangle \mid c_j\neq 0\}$. From (4.34) we obtain that the variables x_i, $x_{i'}$ appearing in the same monomial $c_j\boldsymbol{x}^{\boldsymbol{m}_j}$ of ϕ must have the same timescale orders, i.e., we have $\mu_i=\mu_{i'}$. By regrouping the coefficients c_i into vectors $\boldsymbol{c}_k$ corresponding to variables of the same timescales and using again (4.34), we obtain (4.33). ∎

4.5. The model reduction algorithms. To wrap up all the above developed concepts, we propose in this section several model reduction algorithms. These take into account approximate conservation laws and are applicable to CRN models with multiple timescales and polynomial rate functions. We consider the following two types of reductions:

(i) Reduction at the slowest timescale.

(ii) Nested reductions at intermediate timescales.

In type (i) all the variables except the slowest one are eliminated during the reduction procedure. The reduced model is an ODE for the slowest variable. The elimination of fast variables proceeds hierarchically, with the fastest variables being eliminated first.

In type (ii) all fast variables up to the $(l-1)$th fastest one satisfy polynomial quasi-steady state equations and can be eliminated. The remaining variables satisfy a reduced system of ODEs. The reduced dynamics takes place on the normally hyperbolic invariant manifold that is close to the critical manifold defined by the quasi-steady state equations. Changing l from $l=1$ to $l=m$, one obtains m nested attractive normally hyperbolic invariant manifolds, along which the reduced dynamics evolves at successively slower timescales. Of course (i) follows from (ii) with $l=m$.

For both types of reduction the elimination of the fast variables is possible only if the truncated system at the kth timescale (defined by the vector fields $\bar{\boldsymbol{f}}_1^{(1)},\dots,\bar{\boldsymbol{f}}_k^{(1)}$) has nondegenerate steady states (with $1\le k\le m$ in type (i) and $1\le k\le l$ in type (ii)). When there are approximate conservation laws which are conserved by the truncated system, the nondegeneracy condition is not fulfilled, and the standard reduction algorithm proposed in [26] does not apply. Our solution to this problem is to add approximate conservation laws to the set of variables, eliminate some of the fast variables, and obtain a modified system that has no approximate conservation laws and satisfies the hyperbolicity condition.

4.5.1. The slowest timescale reduction. As in [26] we introduce the small parameters $\delta_{l-1}=\delta^{b_l-b_{l-1}}$ for $2\le l\le m$ and the vector $\bar{\boldsymbol{\delta}}=(\delta_1,\dots,\delta_{m-1})$. Let us change the time variable to $\tau'=\tau\delta_1\delta_2\dots\delta_{m-1}$, the slowest timescale of the model. Then system (4.12) becomes

$$\begin{aligned}
\delta_1\delta_2\dots\delta_{m-1}\boldsymbol{z}_1' &= \bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z})+\bar{\boldsymbol{g}}_1(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})\\
&\vdots\\
\delta_{m-1}\boldsymbol{z}_{m-1}' &= \bar{\boldsymbol{f}}_{m-1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z})+\bar{\boldsymbol{g}}_{m-1}(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}}),\\
\boldsymbol{z}_m' &= \bar{\boldsymbol{f}}_m^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z})+\bar{\boldsymbol{g}}_m(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}}),
\end{aligned}\tag{4.35}$$

where $\bar{\boldsymbol{g}}_k(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})=\delta^{b_k'}\bar{\boldsymbol{f}}_k^{(2)}(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})$ satisfy $\bar{\boldsymbol{g}}_k(\bar{\boldsymbol{k}},\boldsymbol{z},0)=0$ for $1\le k\le m$. We assume that the functions $\bar{\boldsymbol{g}}_k$ are smooth in all their arguments. The smoothness in $\bar{\boldsymbol{\delta}}$ can be tested algorithmically with methods introduced in [26].

By setting $\bar{\boldsymbol{\delta}}=\boldsymbol{0}$ in system (4.35) we obtain the *slowest timescale reduced system*

$$\begin{aligned}
0 &= \bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z})\\
&\vdots\\
0 &= \bar{\boldsymbol{f}}_{m-1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}),\\
\boldsymbol{z}_m' &= \bar{\boldsymbol{f}}_m^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}).
\end{aligned}\tag{4.36}$$

For $\boldsymbol{k} \in \mathbb{R}^r_{>0}$ and $\boldsymbol{z}_m \in \mathbb{R}^{n_m}_{>0}$ a state $(\boldsymbol{z}_1, \ldots, \boldsymbol{z}_{m-1})$ satisfying the system of equations

$$\bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_{m-1}, \boldsymbol{z}_m) = 0, \ldots, \bar{\boldsymbol{f}}_{m-1}^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_{m-1}, \boldsymbol{z}_m) = 0 \tag{4.37}$$

is called a *quasi-steady state*. System (4.37) is called the *quasi-steady state condition*.

Assume that system (4.37) can be solved for $(\boldsymbol{z}_1, \ldots, \boldsymbol{z}_{m-1})$ in the following hierarchical way. First, there is a differentiable function $\tilde{\boldsymbol{f}}_1(\bar{\boldsymbol{k}}, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m)$ such that

$$\bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}}, \tilde{\boldsymbol{f}}_1(\bar{\boldsymbol{k}}, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m), \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m) = 0.$$

Next, consider that there is a differentiable function $\tilde{\boldsymbol{f}}_2(\bar{\boldsymbol{k}}, \boldsymbol{z}_3, \ldots, \boldsymbol{z}_m)$ such that

$$\bar{\boldsymbol{f}}_2^{(1)}(\bar{\boldsymbol{k}}, \tilde{\boldsymbol{f}}_1(\bar{\boldsymbol{k}}, \tilde{\boldsymbol{f}}_2(\bar{\boldsymbol{k}}, \boldsymbol{z}_3, \ldots, \boldsymbol{z}_m), \ldots, \boldsymbol{z}_m), \tilde{\boldsymbol{f}}_2(\bar{\boldsymbol{k}}, \boldsymbol{z}_3, \ldots, \boldsymbol{z}_m), \ldots, \boldsymbol{z}_m) = 0.$$

Assuming that the procedure can go on, consider finally that there is a function $\tilde{\boldsymbol{f}}_{m-1}(\bar{\boldsymbol{k}}, \boldsymbol{z}_m)$ such that

$$\bar{\boldsymbol{f}}_{m-1}^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_{m-1}, \boldsymbol{z}_m) = 0,$$

where $\boldsymbol{z}_1$, $\boldsymbol{z}_2$, …, $\boldsymbol{z}_{m-1}$ are recursively replaced by $\tilde{\boldsymbol{f}}_1(\bar{\boldsymbol{k}}, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m)$, $\tilde{\boldsymbol{f}}_2(\bar{\boldsymbol{k}}, \boldsymbol{z}_3, \ldots, \boldsymbol{z}_m)$, …, $\tilde{\boldsymbol{f}}_{m-1}(\bar{\boldsymbol{k}}, \boldsymbol{z}_m)$, respectively.

Consider the reduced system

$$\boldsymbol{z}'_m = \boldsymbol{f}^*_m(\bar{\boldsymbol{k}}, \boldsymbol{z}_m), \tag{4.38}$$

where $\boldsymbol{f}^*_m(\bar{\boldsymbol{k}}, \boldsymbol{z}_m)$ is obtained from $\bar{\boldsymbol{f}}_m^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_m)$ by substituting $\boldsymbol{z}_1$, $\boldsymbol{z}_2$, …, $\boldsymbol{z}_{m-1}$ as above.

Solutions of system (4.35) in the limit $\bar{\boldsymbol{\delta}} \to 0$ were studied by Tikhonov [54], Hoppensteadt [24], and O'Malley [36]. They showed that under appropriate conditions (roughly speaking, the nondegeneracy and hyperbolicity of the quasi-steady states $\boldsymbol{z}_{k-1} = \tilde{\boldsymbol{f}}_{k-1}(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m)$ for $2 \le k \le m$; see section 4.5.3), the solutions of the system (4.35) with initial conditions $\boldsymbol{z}_i(0) = g_i(\delta)$, where the $g_i(\delta)$ are differentiable functions, converge for $\bar{\boldsymbol{\delta}} \to 0$ to the solutions of the system (4.38) with initial conditions $\boldsymbol{z}_m(0) = g_m(0)$. By this reduction, called *quasi-steady state approximation*, all variables faster than the slowest one are eliminated, and the reduced model describes the dynamics at the slowest timescale. This type of reduction is the most popular one in applications, for instance, in physical chemistry (where it is known as the Semenov–Bodenstein quasi-steady state approximation [4, 51]) and in computational systems biology [40].

4.5.2. Nested intermediate timescale reductions. This type of reduction was proposed by Cardin and Teixeira [7] and algorithmically formalized by Kruff et al. in [26]. We call it nested, since the reduced dynamics at intermediate timescales is embedded in normally hyperbolic invariant manifolds that form a nested family (manifolds of slower variables are included in manifolds of faster variables). In [7] both manifolds were considered, the stable and the unstable. As in [26] we only consider here the stable case. The stable normally hyperbolic invariant manifolds attract and sequentially confine the dynamics of the system,

with rates from fastest to slowest, and are used to obtain reductions valid at intermediate timescales.

We provide here the formal description of the reduction at an intermediate timescale of order $\delta^{b_l} = \delta^{b_1}\delta_1\delta_2\ldots\delta_{l-1}$, where δ_l, $1 \le l \le m$, are defined as in the previous section.

Redefining the time into $\tau' = \tau\delta^{b_l}$, where $1 \le l \le m$, leads to the system

$$\begin{aligned}
\delta_1\delta_2\ldots\delta_{l-1}\boldsymbol{z}_1' &= (\bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_1(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}}))\\
&\vdots\\
\delta_{l-1}\boldsymbol{z}_{l-1}' &= (\bar{\boldsymbol{f}}_{l-1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_{l-1}(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})),\\
\boldsymbol{z}_l' &= (\bar{\boldsymbol{f}}_l^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_l(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})),\\
\boldsymbol{z}_{l+1}' &= \delta_l(\bar{\boldsymbol{f}}_{l+1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_{l+1}(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})),\\
&\vdots\\
\boldsymbol{z}_m' &= \delta_l\delta_{l+1}\ldots\delta_{m-1}(\bar{\boldsymbol{f}}_m^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_m(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})),
\end{aligned} \tag{4.39}$$

where $\bar{\boldsymbol{\delta}} = (\delta_1,\ldots,\delta_{m-1})$, and $\bar{\boldsymbol{g}}_k(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})$ is a smooth function with $\bar{\boldsymbol{g}}_k(\bar{\boldsymbol{k}},\boldsymbol{z},0) = 0$ for all $1 \le k \le m$. In what follows, we call the system

$$\begin{aligned}
0 &= \bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}),\\
&\vdots\\
0 &= \bar{\boldsymbol{f}}_{l-1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z})\\
\boldsymbol{z}_l' &= \bar{\boldsymbol{f}}_l^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}),\\
\boldsymbol{z}_{l+1}' &= \delta_l(\bar{\boldsymbol{f}}_{l+1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_{l+1}(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})),\\
&\vdots\\
\boldsymbol{z}_m' &= \delta_l\delta_{l+1}\ldots\delta_{m-1}(\bar{\boldsymbol{f}}_m^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) + \bar{\boldsymbol{g}}_m(\bar{\boldsymbol{k}},\boldsymbol{z},\bar{\boldsymbol{\delta}})),
\end{aligned} \tag{4.40}$$

where $\bar{\boldsymbol{\delta}} = (0,\ldots,0,\delta_l,\ldots,\delta_{m-1})$, which we obtained from (4.39) by setting δ_1, δ_2, $\ldots$, δ_{l-1} to zero, the reduced *system at the lth fastest time or slower*. In this case as well, the system of equations $\bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) = 0$, $\ldots$, $\bar{\boldsymbol{f}}_{l-1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}) = 0$ corresponds to the *quasi-steady state condition*. In [26] we have also defined the simpler reduced system obtained by setting δ_1, δ_2 $\ldots$, δ_{m-1} in (4.39) to zero, namely,

$$\begin{aligned}
0 &= \bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z})\\
&\vdots\\
0 &= \bar{\boldsymbol{f}}_{l-1}^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}),\\
\boldsymbol{z}_l' &= \bar{\boldsymbol{f}}_l^{(1)}(\bar{\boldsymbol{k}},\boldsymbol{z}),\\
\boldsymbol{z}_{l+1}' &= 0,\\
&\vdots\\
\boldsymbol{z}_m' &= 0.
\end{aligned} \tag{4.41}$$

This reduced model emphasizes three groups of variables: slaved variables $\boldsymbol{z}_1, \ldots, \boldsymbol{z}_{l-1}$, which are faster than δ^{b_l}; driving variables $\boldsymbol{z}_l$, which have timescale δ^{b_l}; and quenched variables $\boldsymbol{z}_{l+1}, \ldots, \boldsymbol{z}_m$, which are slower than δ^{b_l}. If regularity and hyperbolicity conditions are satisfied (see [7] and section 4.5.3), then the solutions of system (4.39) converge to the solutions of system (4.40) when $\epsilon_k \to 0$ for $1 \le k \le l-1$ (see the Corollary of Theorem A in [7]).

The limit $(\delta_l, \ldots, \delta_{m-1}) \to 0$ leading from system (4.40) to system (4.41) can be treated in the simpler framework of regular perturbations. Using the same regularity and hyperbolicity conditions, one can show that there is a time $T > 0$ such that the solutions of system (4.39) converge for $\bar{\boldsymbol{\delta}} \to 0$ uniformly on any close subinterval of $(0, T]$ to the solutions of system (4.41) (cf. Theorem 1 of [26]). This result implies that the reduction (4.41) is valid on a time interval $[t_1\delta^{-b_l}, t_2\delta^{-b_l}]$ with $[t_1, t_2] \subset (0, T]$. The reduction (4.40) has a broader validity, including times longer than δ^{-b_l}.

4.5.3. Hyperbolically attractive chains and quasi-steady state conditions. The two types of reductions presented in the previous section are based on hierarchical elimination of fast variables, previously discussed in [26]. We revisit here this construction, using the concept of the Schur complement.

Let us define

$$\boldsymbol{Z}_k = \begin{pmatrix} \boldsymbol{z}_1 \\ \vdots \\ \boldsymbol{z}_k \end{pmatrix} \quad \text{and} \quad \bar{\boldsymbol{F}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = \begin{pmatrix} \bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) \\ \vdots \\ \bar{\boldsymbol{f}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) \end{pmatrix}.$$

For any $1 \le k \le m$, the system of equations $\bar{\boldsymbol{F}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = 0$ defines the kth quasi-steady variety. The set of positive solutions $\boldsymbol{z}$ of $\bar{\boldsymbol{F}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = 0$ is denoted by $\mathcal{M}_k$ and represents the intersection of the kth quasi-steady state variety with the first orthant. For $1 \le l \le m$ we call the chain $\mathbb{R}^n_{>0} = \mathcal{M}_0 \supseteq \mathcal{M}_1 \supseteq \cdots \supseteq \mathcal{M}_l$ of nested quasi-steady state varieties lying in the first orthant an *l-chain*.

We solve the equations $\bar{\boldsymbol{F}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = 0$ by successive elimination of variables, starting with $\boldsymbol{z}_1$ and ending with $\boldsymbol{z}_k$. During the elimination process, intermediary functions $\boldsymbol{f}_k^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m)$, $\tilde{\boldsymbol{f}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m)$, and $\tilde{\boldsymbol{F}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m)$ are defined recursively. More precisely, let

$$\boldsymbol{f}_1^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_m) = \bar{\boldsymbol{f}}_1^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_m),$$

let $\boldsymbol{z}_1 = \tilde{\boldsymbol{f}}_1(\bar{\boldsymbol{k}}, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m)$ be the locally unique solution of $\boldsymbol{f}_1^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_m) = 0$, and set

$$\tilde{\boldsymbol{F}}_1(\bar{\boldsymbol{k}}, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m) = \tilde{\boldsymbol{f}}_1(\bar{\boldsymbol{k}}, \boldsymbol{z}_2, \ldots, \boldsymbol{z}_m).$$

Given this initial data, one then continues recursively for $2 \le k \le m-1$ in the following way: Define

$$\boldsymbol{f}_k^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m) = \bar{\boldsymbol{f}}_k^{(1)}(\bar{\boldsymbol{k}}, \tilde{\boldsymbol{F}}_{k-1}(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m), \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m), \tag{4.42}$$

determine the locally unique solution

$$\boldsymbol{z}_k = \tilde{\boldsymbol{f}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m) \tag{4.43}$$

of $\boldsymbol{f}_k^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m) = 0$, and then set

$$\tilde{\boldsymbol{F}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m) = \begin{pmatrix} \tilde{\boldsymbol{F}}_{k-1}(\bar{\boldsymbol{k}}, \tilde{\boldsymbol{f}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m), \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m) \\ \tilde{\boldsymbol{f}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m) \end{pmatrix}. \tag{4.44}$$

From the recursion, the following proposition follows immediately.

Proposition 4.14. *The vector* $\boldsymbol{z} = (\tilde{\boldsymbol{F}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m), \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m)$ *is a solution of* $\bar{\boldsymbol{F}}_k^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = 0$.

The existence of the implicit functions $\tilde{\boldsymbol{f}}_k$ and $\tilde{\boldsymbol{F}}_k$ needs the following nondegeneracy condition.

Condition 4.15. *The solution* $\boldsymbol{z}_k$ *of the equation* $\boldsymbol{f}_k^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \ldots, \boldsymbol{z}_m) = 0$ *is nondegenerate, i.e.,* $\det(D_{\boldsymbol{z}_k} \boldsymbol{f}_k^*) \neq 0$.

This condition can be written more conveniently.

Theorem 4.16. *For* $1 \leq k \leq l$, *the implicit functions* $\tilde{\boldsymbol{f}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m)$ *and* $\tilde{\boldsymbol{F}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m)$ *exist and are differentiable if and only if*

$$\det(D_{\boldsymbol{Z}_k} \bar{\boldsymbol{F}}_k^{(1)}) \neq 0 \text{ for all } \boldsymbol{z} \in \mathcal{M}_k. \tag{4.45}$$

In order to prove Theorem 4.16 we need the Schur complement, which occurs naturally during the Gaussian elimination of variables (see, for instance, [60]).

Definition 4.17. *Let* $M = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$ *be a block matrix with* A *invertible. The matrix* $M/A = D - CA^{-1}B$ *is called the Schur complement of the block* A *of* M.

The Schur complement can be obtained from the following successive computations:

- Solve $AX + BY = 0$ for X.
- Substitute X in $CX + DY$, which leads to $(M/A)Y$.

Moreover, the Schur complement has the following two simple properties [60]:

$$\det(M) = \det(M/A)\det(A) \qquad \text{(Schur formula)}, \tag{4.46}$$

$$\operatorname{rk}(M) = \operatorname{rk}(M/A) + \operatorname{rk}(A) \qquad \text{(Guttman rank additivity formula)}. \tag{4.47}$$

Returning to our problem, we prove now the following lemma.

Lemma 4.18. *The matrix* $D_{\boldsymbol{z}_{k+1}} \boldsymbol{f}_{k+1}^*$ *is a Schur complement. More precisely, we have*

$$D_{\boldsymbol{z}_{k+1}} \boldsymbol{f}_{k+1}^* = D_{\boldsymbol{Z}_{k+1}} \bar{\boldsymbol{F}}_{k+1}^{(1)} / D_{\boldsymbol{Z}_k} \bar{\boldsymbol{F}}_k^{(1)} \tag{4.48}$$

for all $1 \leq k \leq m-1$ *and* $\boldsymbol{z} \in \mathcal{M}_k$ *such that* $D_{\boldsymbol{Z}_k} \bar{\boldsymbol{F}}_k^{(1)}$ *is invertible.*

Proof. We differentiate (4.42) with respect to $\boldsymbol{z}_{k+1}$ and obtain

$$D_{\boldsymbol{z}_{k+1}} \boldsymbol{f}_{k+1}^* = (D_{\boldsymbol{Z}_k} \bar{\boldsymbol{f}}_{k+1}^{(1)}) D_{\boldsymbol{z}_{k+1}} \tilde{\boldsymbol{F}}_k + D_{\boldsymbol{z}_{k+1}} \bar{\boldsymbol{f}}_{k+1}^{(1)}.$$

From Proposition 4.14 we have that

$$\bar{\boldsymbol{F}}_k^{(1)}(\bar{\boldsymbol{k}}, \tilde{\boldsymbol{F}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m), \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m) = 0.$$

Differentiating the last equation with respect to $\boldsymbol{z}_{k+1}$, we obtain

$$(D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)})D_{\boldsymbol{z}_{k+1}}\tilde{\boldsymbol{F}}_k + D_{\boldsymbol{z}_{k+1}}\bar{\boldsymbol{F}}_k^{(1)} = 0$$

for $\boldsymbol{z} \in \mathcal{M}_k$. Finally, we get

$$D_{\boldsymbol{z}_{k+1}}\boldsymbol{f}_{k+1}^* = -(D_{\boldsymbol{Z}_k}\bar{\boldsymbol{f}}_{k+1}^{(1)})(D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)})^{-1}D_{\boldsymbol{z}_{k+1}}\bar{\boldsymbol{F}}_k^{(1)} + D_{\boldsymbol{z}_{k+1}}\bar{\boldsymbol{f}}_{k+1}^{(1)} = D_{\boldsymbol{Z}_{k+1}}\bar{\boldsymbol{F}}_{k+1}^{(1)}/D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)}. \quad \blacksquare$$

Now we can prove Theorem 4.16.

Proof of Theorem 4.16. Using Schur formula (4.46) and Lemma 4.18, we obtain that

$$\det(D_{\boldsymbol{z}_k}\boldsymbol{f}_k^*)\det(D_{\boldsymbol{Z}_{k-1}}\bar{\boldsymbol{F}}_{k-1}^{(1)}) = \det(D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)})$$

for $2 \le k \le l$ and that

$$\det(D_{\boldsymbol{z}_1}\boldsymbol{f}_1^*) = \det(D_{\boldsymbol{Z}_1}\bar{\boldsymbol{F}}_1^{(1)}).$$

This implies that $\det(D_{\boldsymbol{z}_k}\boldsymbol{f}_k^*) \neq 0$ for $1 \le k \le l$ is equivalent to $\det(D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)}) \neq 0$ for $1 \le k \le l$. $\blacksquare$

As discussed in [26] and [36], the validity of the quasi-steady state approximation depends also on the following hyperbolicity condition.

Condition 4.19 (hyperbolicity). *For all $1 \le k \le m$, the solution $\boldsymbol{z}_k = \tilde{\boldsymbol{f}}_k(\bar{\boldsymbol{k}}, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m)$ is a hyperbolically stable steady state of the ODE*

$$\boldsymbol{z}_k' = \boldsymbol{f}_k^*(\bar{\boldsymbol{k}}, \boldsymbol{z}_k, \boldsymbol{z}_{k+1}, \ldots, \boldsymbol{z}_m),$$

where $\boldsymbol{f}_k^*$ is defined as in subsection 4.5.3. Here, by hyperbolically stable we mean that all eigenvalues of the Jacobian matrix at the steady state have strictly negative real parts. The validity of the nested reduction at the lth fastest time or slower requires that Condition 4.19 is fulfilled for all $1 \le k \le l$.

As discussed in [26], an important concept for the geometric theory of singular perturbations is the hyperbolically attractive chain.

Definition 4.20. *An l-chain of nested quasi-steady state varieties $\mathcal{M}_0 \supseteq \mathcal{M}_1 \supseteq \cdots \supseteq \mathcal{M}_l$ is called a hyperbolically attractive l-chain if for all $1 \le k \le l$ all eigenvalues of $D_{\boldsymbol{z}_k}\boldsymbol{f}_k^*$ have strictly negative real parts for $\boldsymbol{z} \in \mathcal{M}_k$. In this case we write $\mathcal{M}_0 \rhd \mathcal{M}_1 \rhd \cdots \rhd \mathcal{M}_l$.*

Summarizing, the nested reduction (4.40) is valid up to the lth timescale if the l-chain $\mathcal{M}_0 \rhd \mathcal{M}_1 \rhd \cdots \rhd \mathcal{M}_l$ is hyperbolically attractive (see [7, 26]). The slowest timescale quasi-steady state reduction (4.38) is valid if the m-chain $\mathcal{M}_0 \rhd \mathcal{M}_1 \rhd \cdots \rhd \mathcal{M}_m$ is hyperbolically attractive.

From Lemma 4.18 we obtain the following proposition.

Proposition 4.21. *An l-chain is hyperbolically attractive if and only if $\det(D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)}) \neq 0$ for all $1 \le k \le l$, all eigenvalues of $D_{\boldsymbol{z}_1}\bar{\boldsymbol{f}}_1^{(1)}$ have negative real parts for all $\boldsymbol{z} \in \mathcal{M}_1$, and for all $2 \le k \le l$ all eigenvalues of $D_{\boldsymbol{Z}_k}\bar{\boldsymbol{F}}_k^{(1)}/D_{\boldsymbol{Z}_{k-1}}\bar{\boldsymbol{F}}_{k-1}^{(1)}$ have negative real parts for all $\boldsymbol{z} \in \mathcal{M}_{k-1}$.*

4.5.4. Approximate conservation laws and the quasi-equilibrium condition. Linear approximate conservation laws were already proposed as a tool for model reduction of CRNs when the so-called *quasi-equilibrium* (QE) condition [23, 40] is satisfied. At QE the direct and reverse rates of fast reversible reactions compensate each other, and the net rates of change of reactants and products are negligible. Products or reactants of fast reactions are fast species. However, although concentrations of fast species are equilibrated, these variables cannot be eliminated by using the quasi-steady state (QSS) equations. In the case of QE, linear combinations of concentrations of fast species are conserved by the fast dynamics and the QSS equations have degenerate solutions indexed by the values of the conserved quantities [23, 40].

In this paper we show that the degeneracy of solutions of QSS equations is valid more generally for any approximate conservation laws.

Let us denote by $\boldsymbol{x}_l$ and $\boldsymbol{X}_l = (\boldsymbol{x}_1, \ldots, \boldsymbol{x}_l)$ the set of variables of system (2.1) having timescale order μ_l and timescale orders smaller than or equal to μ_l, respectively. Furthermore, let $\boldsymbol{f}_l(\boldsymbol{k}, \boldsymbol{x})$, $\boldsymbol{f}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x})$,

$$\boldsymbol{F}_l(\boldsymbol{k}, \boldsymbol{x}) = \begin{pmatrix} \boldsymbol{f}_1(\boldsymbol{k}, \boldsymbol{x}) \\ \vdots \\ \boldsymbol{f}_l(\boldsymbol{k}, \boldsymbol{x}) \end{pmatrix} \quad \text{and} \quad \boldsymbol{F}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = \begin{pmatrix} \boldsymbol{f}_1^{(1)}(\boldsymbol{k}, \boldsymbol{x}) \\ \vdots \\ \boldsymbol{f}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x}) \end{pmatrix}$$

be the full and truncated vector fields whose flows have timescale order μ_l, and timescale orders smaller than or equal to μ_l, respectively. In other words, these vector fields are the unscaled versions of the vector fields $\bar{\boldsymbol{f}}_l(\bar{\boldsymbol{k}}, \boldsymbol{z})$, $\bar{\boldsymbol{f}}_l^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z})$, $\bar{\boldsymbol{F}}_l(\bar{\boldsymbol{k}}, \boldsymbol{z})$, and $\bar{\boldsymbol{F}}_l^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z})$ introduced in section 4.1.

Let $\phi_l(\boldsymbol{X}_l)$ be a linear, monomial, or polynomial approximate conservation law depending only on the variables $\boldsymbol{X}_l$ satisfying $D_{\boldsymbol{X}_l}\phi_l(\boldsymbol{X}_l)\boldsymbol{F}_l^{(1)} = 0$. This approximate conservation law can, eventually, also be exact, in which case it also satisfies $D_{\boldsymbol{X}_l}\phi_l(\boldsymbol{X}_l)\boldsymbol{F}_l = 0$. The existence of such an approximate conservation law implies the failure of condition (4.45) in Theorem 4.16 as in the following proposition.

Proposition 4.22. *Let us assume that there is an approximate conservation law $\phi_l(\boldsymbol{X}_l)$, where $1 \le l \le m$. Then $\det(D_{\boldsymbol{Z}_l}\bar{\boldsymbol{F}}_l^{(1)}) = 0$ if $\boldsymbol{z} \in \mathcal{M}_l$.*

Proof. The definition of approximate conservation laws yields

$$D_{\boldsymbol{X}_l}\phi_l(\boldsymbol{X}_l)\boldsymbol{F}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0. \tag{4.49}$$

Since, up to the change of variables $\bar{\boldsymbol{k}} \leftarrow \boldsymbol{k}$ and $\boldsymbol{z} \leftarrow \boldsymbol{x}$, the polynomials $\boldsymbol{F}_l^{(1)}$ and $\bar{\boldsymbol{F}}_l^{(1)}$ are identical, we find

$$D_{\boldsymbol{Z}_l}\phi_l(\boldsymbol{Z}_l)\bar{\boldsymbol{F}}_l^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = 0. \tag{4.50}$$

Differentiating (4.50) we obtain

$$\frac{d^2\phi_l}{d\boldsymbol{Z}_l{}^2}\bar{\boldsymbol{F}}_l^{(1)} + \frac{d\phi_l}{d\boldsymbol{Z}_l}\frac{d\bar{\boldsymbol{F}}_l^{(1)}}{d\boldsymbol{Z}_l} = 0,$$

where $\frac{d^2\phi_l}{d\boldsymbol{Z}_l{}^2}$ is the second derivative of ϕ_l with respect to $\boldsymbol{Z}_l$. If $\boldsymbol{z} \in \mathcal{M}_l$, then $\bar{\boldsymbol{F}}_l^{(1)}(\bar{\boldsymbol{k}}, \boldsymbol{z}) = 0$, and therefore

$$\frac{d\phi_l}{d\boldsymbol{Z}_l}\frac{d\bar{\boldsymbol{F}}_l^{(1)}}{d\boldsymbol{Z}_l} = 0.$$

Thus, the left kernel of the matrix $\frac{d\bar{\boldsymbol{F}}_l^{(1)}}{d\boldsymbol{Z}_l}$ contains the covector $\frac{d\phi_l}{d\boldsymbol{Z}_l} \neq 0$, and so $\det(D_{\boldsymbol{Z}_l}\bar{\boldsymbol{F}}_l^{(1)}) = 0$. ∎

In this case the quasi-steady state condition $\boldsymbol{F}_l^{(1)}(\boldsymbol{k}, \boldsymbol{X}_l, \boldsymbol{x}_{l+1}, \ldots, \boldsymbol{x}_m) = 0$ cannot be used to eliminate the fast variables $\boldsymbol{X}_l$. However, even in this case the CRN (2.1) can be transformed into an equivalent CRN that fulfills the nondegeneracy condition (4.45) for $1 \leq k \leq l$. The details of the transformation are presented below.

Let $\boldsymbol{\Phi}_l(\boldsymbol{X}_l) = (\phi_{1l}(\boldsymbol{X}_l), \ldots, \phi_{s_l l}(\boldsymbol{X}_l))^T$ be a set of s_l approximate conservation laws dependent on $\boldsymbol{X}_l$, and consider the equation

$$\boldsymbol{x}_l^c = \boldsymbol{\Phi}_l(\boldsymbol{X}_l). \tag{4.51}$$

Assuming that the conservation laws $\boldsymbol{\Phi}_l(\boldsymbol{X}_l)$ are independent as functions of $\boldsymbol{x}_l$, namely that

$$\mathrm{rk}(D_{\boldsymbol{x}_l}\boldsymbol{\Phi}_l(\boldsymbol{X}_l)) = s_l,$$

we have, up to a relabeling of the components of $\boldsymbol{X}_l$, the splitting $\boldsymbol{X}_l = (\boldsymbol{X}_{l-1}, \check{\boldsymbol{x}}_l, \hat{\boldsymbol{x}}_l)$, where $\boldsymbol{X}_{l-1} \in \mathbb{R}^{n_1+\cdots+n_{l-1}}$, $\check{\boldsymbol{x}}_l \in \mathbb{R}^{s_l}$, $\hat{\boldsymbol{x}}_l \in \mathbb{R}^{n_l - s_l}$, and $\det(D_{\check{\boldsymbol{x}}_l}\boldsymbol{\Phi}_l) \neq 0$. Hence, (4.51) defines the implicit function $\check{\boldsymbol{x}}_l = \boldsymbol{\Psi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c)$, which allows one to eliminate the variables $\check{\boldsymbol{x}}_l$.

The above splitting of $\boldsymbol{X}_l$ induces the splittings $\boldsymbol{F}_l = (\boldsymbol{F}_{l-1}, \check{\boldsymbol{f}}_l, \hat{\boldsymbol{f}}_l)$ and $\boldsymbol{F}_l^{(i)} = (\boldsymbol{F}_{l-1}^{(i)}, \check{\boldsymbol{f}}_l^{(i)}, \hat{\boldsymbol{f}}_l^{(i)})$ for $1 \leq i \leq 2$. Let us define the functions

$$\begin{aligned} &\boldsymbol{F}_k^{red}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m) \\ &\quad = \hat{\boldsymbol{F}}_k(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \boldsymbol{\Psi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c), \hat{\boldsymbol{x}}_l, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m), \end{aligned} \tag{4.52}$$

where $\hat{\boldsymbol{F}}_k = \boldsymbol{F}_k$ for $1 \leq k \leq l-1$, and $\hat{\boldsymbol{F}}_l = (\boldsymbol{F}_{l-1}, \hat{\boldsymbol{f}}_l)$. The transformed model obtained from the substitution $\check{\boldsymbol{x}}_l = \boldsymbol{\Psi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c)$ is

$$\dot{\hat{\boldsymbol{X}}}_l = \boldsymbol{F}_l^{red}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m), \tag{4.53}$$

$$\dot{\boldsymbol{x}}_l^c = ((D_{\boldsymbol{X}_l}\boldsymbol{\Phi}_l)\boldsymbol{F}_l^{(2)})(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \boldsymbol{\Psi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c), \hat{\boldsymbol{x}}_l, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m), \tag{4.54}$$

$$\dot{\boldsymbol{x}}_k = \boldsymbol{f}_k(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \boldsymbol{\Psi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c), \hat{\boldsymbol{x}}_l, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m),\ k \in \{l+1, \ldots, m\}. \tag{4.55}$$

We have seen in Theorems 4.7 and 4.13 that $\boldsymbol{\Phi}_l = \boldsymbol{\Phi}_l^{(1)}(\boldsymbol{x}_l) + o(\delta^{q_f})$, where $\boldsymbol{\Phi}_l^{(1)}(\boldsymbol{x}_l) = O(\delta^{q_f})$ is the lowest order (dominant) part of $\boldsymbol{\Phi}_l$. Furthermore, the dominant part $\boldsymbol{\Psi}_l^{(1)}$ of $\boldsymbol{\Psi}_l$ satisfies the equation

$$\boldsymbol{x}_l^c = \boldsymbol{\Phi}_l^{(1)}(\boldsymbol{\Psi}_l^{(1)}(\hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c), \hat{\boldsymbol{x}}_l). \tag{4.56}$$

Thus, the truncated versions of the functions $\boldsymbol{F}_k^{red}$ are

$$\begin{aligned}&\boldsymbol{F}_k^{red,1}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m)\\ &\quad = \hat{\boldsymbol{F}}_k^{(1)}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \boldsymbol{\Psi}_l^{(1)}(\hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c), \hat{\boldsymbol{x}}_l, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m),\end{aligned} \tag{4.57}$$

where $\hat{\boldsymbol{F}}_k^{(1)} = \boldsymbol{F}_k^{(1)}$ for $1 \le k \le l-1$, and $\hat{\boldsymbol{F}}_l^{(1)} = (\boldsymbol{F}_{l-1}^{(1)}, \hat{\boldsymbol{f}}_l)$.

We can now state the main result of this section. Let us assume that the following conditions are satisfied.

Condition 4.23.

1. *For any $\boldsymbol{k} \in \mathbb{R}_{>0}^r$ there exist $\boldsymbol{x} \in \mathbb{R}_{>0}^n$ such that $\boldsymbol{F}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0$. For all $\boldsymbol{x} \in \mathbb{R}_{>0}^n$ with $\boldsymbol{F}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0$, we have $\det(D_{\boldsymbol{X}_k} \boldsymbol{F}_k^{(1)}) \neq 0$ for all $1 \le k \le l-1$ and $\det(D_{\boldsymbol{X}_l} \boldsymbol{F}_l^{(1)}) = 0$.*
2. *There is a set of s_l simple approximate conservation laws*

$$\boldsymbol{\Phi}_l(\boldsymbol{X}_l) = (\phi_{1l}(\boldsymbol{X}_l), \ldots, \phi_{s_l l}(\boldsymbol{X}_l))^{\mathsf{T}}$$

depending only on $\boldsymbol{X}_l$ such that $(D_{\boldsymbol{X}_l} \boldsymbol{\Phi}_l) \boldsymbol{F}_l^{(1)} = 0$, where $0 < s_l \le n_l$. For all $\boldsymbol{k} \in \mathbb{R}_{>0}^r$ and $\boldsymbol{x} \in \mathbb{R}_{>0}^n$ such that $\boldsymbol{F}_l^{(1)}(\boldsymbol{k}, \boldsymbol{x}) = 0$ we have that

$$\operatorname{rk}\left(D_{\boldsymbol{X}_l} \begin{pmatrix} \boldsymbol{\Phi}_l^{(1)} \\ \hat{\boldsymbol{F}}_l^{(1)} \end{pmatrix} \right) = n_1 + \cdots + n_l. \tag{4.58}$$

3. *The conservation laws $\boldsymbol{\Phi}_l(\boldsymbol{X}_l)$ are independent as functions of $\boldsymbol{x}_l$, namely,*

$$\operatorname{rk}(D_{\boldsymbol{x}_l} \boldsymbol{\Phi}_l(\boldsymbol{X}_l)) = s_l. \tag{4.59}$$

Theorem 4.24. *If Condition 4.23 is fulfilled and*

$$\boldsymbol{F}_l^{red,1}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c, \boldsymbol{x}_{l+1}, \boldsymbol{x}_{l+2}, \ldots, \boldsymbol{x}_m) = 0,$$

then $\det(D_{\hat{\boldsymbol{X}}_k} \boldsymbol{F}_k^{(red,1)}) \neq 0$ for all $1 \le k \le l$, where $\hat{\boldsymbol{X}}_k = \boldsymbol{X}_k$ for $1 \le k \le l-1$ and $\hat{\boldsymbol{X}}_l = (\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l)$.

The proof of Theorem 4.24 uses the following lemma.

Lemma 4.25. *We have*

$$D_{\hat{\boldsymbol{X}}_l} \boldsymbol{F}_l^{red,1} = D_{\boldsymbol{X}_l} \begin{pmatrix} \boldsymbol{\Phi}_l^{(1)} \\ \hat{\boldsymbol{F}}_l^{(1)} \end{pmatrix} \Big/ D_{\check{\boldsymbol{x}}_l} \boldsymbol{\Phi}_l^{(1)}.$$

Proof. Differentiating (4.56) with respect to $\hat{\boldsymbol{X}}_l$ we obtain

$$D_{\hat{\boldsymbol{X}}_l} \boldsymbol{\Phi}_l^{(1)} + D_{\check{\boldsymbol{x}}_l} \boldsymbol{\Phi}_l^{(1)} D_{\hat{\boldsymbol{X}}_l} \boldsymbol{\Psi}_l^{(1)} = 0.$$

It follows from (4.57) that

$$D_{\hat{\boldsymbol{X}}_l} \boldsymbol{F}_l^{red,1} = D_{\hat{\boldsymbol{X}}_l} \hat{\boldsymbol{F}}_l^{(1)} + D_{\check{\boldsymbol{x}}_l} \hat{\boldsymbol{F}}_l^{(1)} D_{\hat{\boldsymbol{X}}_l} \boldsymbol{\Psi}_l^{(1)} = D_{\hat{\boldsymbol{X}}_l} \hat{\boldsymbol{F}}_l^{(1)} - D_{\check{\boldsymbol{x}}_l} \hat{\boldsymbol{F}}_l^{(1)} (D_{\check{\boldsymbol{x}}_l} \boldsymbol{\Phi}_l^{(1)})^{-1} D_{\hat{\boldsymbol{X}}_l} \boldsymbol{\Phi}_l^{(1)},$$

which completes the proof. ∎

Proof of Theorem 4.24. We prove that $D_{\hat{\boldsymbol{X}}_k}\boldsymbol{F}_k^{red,1}$ is invertible for all $1 \le k \le l$. Using the structure Theorems 4.7 and 4.13 we find that $D_{\boldsymbol{x}_l}\boldsymbol{\Phi}_l = D_{\boldsymbol{x}_l}\boldsymbol{\Phi}_l^{(1)}$. Thus, it follows from (4.59) that $\mathrm{rk}(D_{\boldsymbol{x}_l}\boldsymbol{\Phi}_l^{(1)}) = s_l$. Using (4.58), the Guttman rank additivity formula (4.47), and Lemma 4.25, we find that

$$\mathrm{rk}\left(D_{\hat{\boldsymbol{X}}_l}\boldsymbol{F}_l^{red,1}\right) = n_1 + n_2 + \cdots + n_l - s_l,$$

and so $D_{\hat{\boldsymbol{X}}_l}\hat{\boldsymbol{F}}_l^{red,1}$ is invertible. Since $\boldsymbol{\psi}_l^{(1)}$ does not depend on $\boldsymbol{X}_k$ for $1 \le k \le l-1$, it follows that $D_{\hat{\boldsymbol{X}}_k}\boldsymbol{F}_k^{red,1} = D_{\boldsymbol{X}_k}\boldsymbol{F}_k^{(1)}$. Since $D_{\boldsymbol{X}_k}\boldsymbol{F}_k^{(1)}$ is invertible, the same is true for $D_{\hat{\boldsymbol{X}}_k}\boldsymbol{F}_k^{red,1}$. ■

Remark 4.26. Because conservation laws are used to eliminate the variables $\check{\boldsymbol{x}}_l$, the rank conditions (4.58) and (4.59) are satisfied if

$$\det\left(D_{\boldsymbol{X}_l}\begin{pmatrix}\boldsymbol{\Phi}_l^{(1)}\\ \hat{\boldsymbol{F}}_l^{(1)}\end{pmatrix}\right) \neq 0$$

and $\det(D_{\check{\boldsymbol{x}}_l}\boldsymbol{\Phi}_l) \neq 0$, respectively.

Remark 4.27. Theorem 4.24 allows one to define l-chains in the case of a quasi-equilibrium. The set of positive solutions of the set of equations

$$\boldsymbol{F}_k^{red,1}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c, \boldsymbol{x}_{l+1}, \ldots, \boldsymbol{x}_m) = 0,$$

that is equivalent to

$$\hat{\boldsymbol{F}}_k^{(1)}(\boldsymbol{k}, \boldsymbol{X}_{l-1}, \boldsymbol{x}_l, \boldsymbol{x}_l^c, \boldsymbol{x}_{l+1}, \ldots, \boldsymbol{x}_m) = 0,\ \boldsymbol{\Phi}_l^{(1)}(\boldsymbol{x}_l) = \boldsymbol{x}_l^c,$$

is denoted $\mathcal{M}_k^{QE}$ and represents the kth *quasi-equilibrium variety* (intersected with the first orthant). These sets satisfy

$$\mathbb{R}_{>0}^n = \mathcal{M}_0^{QE} \supset \mathcal{M}_1^{QE} \supset \cdots \supset \mathcal{M}_l^{QE}.$$

The concept of hyperbolically attractive l-chains is applicable to quasi-equilibrium varieties as well.

By the results of section 4.4 the new variables $\boldsymbol{x}_l^c$ are slower than $\hat{\boldsymbol{X}}_l$, and by Theorem 4.24 the transformed model satisfies the nondegeneracy conditions $\det(D_{\hat{\boldsymbol{X}}_k}F_k^{(red,1)}) \neq 0$ up to order l. If the approximate conservation laws are also exact, the new variables $\boldsymbol{x}_l^c$ are constant and stand for new parameters. Then, the new equations (4.54) are not added to the transformed ones (4.53) and (4.55). In this case as well, the transformed model defined by (4.53) and (4.55) satisfies the nondegeneracy conditions up to order l.

4.5.5. Algorithmic solution for eliminating the approximate conservation laws. The previous section allows us to define an algorithm which transforms the CRN (2.1) into an equivalent one that does not have approximate conservation laws and that can be further reduced using the method introduced in [26]. During this transformation, some old variables are substituted by new ones, representing approximate conservation laws that are not exact. Also, each exact conservation law leads to the creation of a new parameter and to the elimination of one variable together with the corresponding ODE.

Algorithm 4.1 TransformCRNexplicit.

Input: A CRN given by a polynomial vector field $\boldsymbol{F}(\boldsymbol{k},\boldsymbol{x})$.
Output: A transformed CRN given by a modified polynomial vector field.

1: ScaleAndTruncate.
2: $l := 0$
3: **while** $l < m$ **do**
4: $\quad l := l + 1$
5: $\quad$ **while** $\det(D_{\boldsymbol{X}_l} F_l^{(1)}) \neq 0$ **do**
6: $\quad\quad l := l + 1$
7: $\quad$ **end while**
8: $\quad$ Find a complete set $\boldsymbol{\Phi}_l$ of independent conservation laws for $\boldsymbol{F}_l^{(1)}$ satisfying conditions (4.58) and (4.59).
9: $\quad$ Compute the solution $\check{\boldsymbol{x}}_l = \boldsymbol{\psi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c)$ of the equation $\boldsymbol{x}_l^c = \boldsymbol{\Phi}_l(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \check{\boldsymbol{x}}_l)$.
10: $\quad$ **for** $i := 1$ **to** s_l **do**
11: $\quad\quad$ **if** Φ_{il} is not exact **then**
12: $\quad\quad\quad$ Replace the ODE satisfied by $\check{x}_{il}$ with $\dot{x}_{il}^c = (D_{\boldsymbol{x}} \Phi_{il}) \boldsymbol{F}(\boldsymbol{k},\boldsymbol{x})$.
13: $\quad\quad$ **else**
14: $\quad\quad\quad$ Delete the ODE satisfied by $\check{x}_{il}$.
15: $\quad\quad\quad$ Define the new constant k_{il}^c and concatenate it with $\boldsymbol{k}$.
16: $\quad\quad\quad$ Substitute $x_{il}^c \leftarrow k_{il}^c$.
17: $\quad\quad$ **end if**
18: $\quad\quad$ Substitute $\check{x}_{il} \leftarrow \psi_{il}(\boldsymbol{X}_{l-1}, \hat{\boldsymbol{x}}_l, \boldsymbol{x}_l^c)$.
19: $\quad$ **end for**
20: $\quad$ ScaleAndTruncate.
21: **end while**

Algorithm 4.1 transforms the CRN into another CRN that satisfies the condition $\det(D_{\boldsymbol{X}_k} F_k) \neq 0$ for all $1 \leq k \leq l$ up to the lth timescale. It further iterates the procedure for increasing l and computes a rescaled and truncated version of the CRN at each step by using the algorithm ScaleAndTruncate introduced in [26].

If none of the approximate conservation laws used in the transformation is exact, then the resulting CRN has the same number of variables, ODEs, and parameters as the initial one. Any exact conservation law used in the transformation reduces the numbers of variables and ODEs by one and increases the number of parameters by one.

Because at each step l the total number of variables can only decrease, the total number of variables having timescales slower than $\boldsymbol{x}_l$ and remaining to be treated is strictly decreasing with l. Therefore, the algorithm terminates in a finite number of steps.

The applicability of Algorithm 4.1 is limited by the possibility of solving the equation $\boldsymbol{x}_l^c = \boldsymbol{\Phi}_l(\boldsymbol{X}_l)$ symbolically (elimination step 9 of the algorithm). This is always possible when all the approximate conservation laws $\boldsymbol{\Phi}_l$ are linear, but it may not be easy when the completeness condition (4.58) cannot be fulfilled without some polynomial conservation laws.

Algorithm 4.2 TransformCRNimplicit.

Input: A CRN given by a polynomial vector field $\boldsymbol{F}(\boldsymbol{k},\boldsymbol{x})$.
Output: A differential algebraic CRN given by a modified polynomial vector field and a set of algebraic constraints.

```
ScaleAndTruncate.
l := 0
while l < m do
  l := l + 1
  while det(D_{X_l} F_l^{(1)}) ≠ 0 do
    l := l + 1
  end while
  Find a complete set Φ_l of independent conservation laws for F_l^{(1)} satisfying
  conditions (4.58) and (4.59).
  for i := 1 to s_l do
    if φ_{il} is not exact then
      Replace the ODE satisfied by x̌_{il} with ẋ^c_{il} = D_x φ_{il} F(k, x).
      Add x^c_l = φ_{il}(x) to the set of algebraic constraints.
    else
      Delete the ODE satisfied by x̌_{il}
      Define new constants k^c_{il} and concatenate them to k.
      Add k^c_{il} = φ_{il}(x) to the set of algebraic constraints.
    end if
  end for
  ScaleAndTruncate.
end while
```

However, for most biochemical CRN models used in computational biology, this situation does not arise because linear conservation laws are enough to obtain completeness.

If one wants to avoid the elimination step (for instance, when there are polynomial conservation laws), there is another possible algorithmic solution whose output is a differential algebraic system. More precisely, at each step l one considers the truncated vector field $\boldsymbol{F}_l^{(1)}(\boldsymbol{k},\boldsymbol{x})$ and the conservation law $\boldsymbol{\Phi}_l(\boldsymbol{x})$. The former is used for the ODE part of the transformed model, and the latter defines the algebraic constraint (4.51). This choice is implemented in Algorithm 4.2. One should note that the symbolic reduction algorithms introduced in [26] also use an implicit formulation of the fast variables elimination that leads to differential algebraic reduced systems. Using Lemma 4.25 and Proposition 4.21, it follows that the hyperbolicity test justifying the reduction of the transformed model should be performed on the eigenvalues of the Schur complement

$$\left(D_{\boldsymbol{X}_l}\begin{pmatrix}\boldsymbol{\Phi}_l^{(1)}\\ \hat{\boldsymbol{F}}_l^{(1)}\end{pmatrix}\Big/ D_{\check{\boldsymbol{x}}_l}\boldsymbol{\Phi}_l^{(1)}\right)\Big/\left(D_{\boldsymbol{X}_{l-1}}\begin{pmatrix}\boldsymbol{\Phi}_{l-1}^{(1)}\\ \hat{\boldsymbol{F}}_{l-1}^{(1)}\end{pmatrix}\Big/ D_{\check{\boldsymbol{x}}_{l-1}}\boldsymbol{\Phi}_{l-1}^{(1)}\right).$$

5. Conclusions. In this paper we showed how to transform a system of polynomial ODEs with approximate conservation laws into an equivalent system without any approximate conservation laws. This allowed us to reduce the transformed system using a previously introduced method which uses geometric singular perturbation theory for multiple timescales [26].

The output of our reduction algorithm depends on the choice of a tropical equilibration solution. Changing this solution may lead to different timescale orderings of the variables, truncated systems, approximate conservation laws, and reduced models. However, continuous branches of tropical solutions lead to the same truncated systems, approximate conservation laws, and ordering of timescales. A branch of tropical equilibration solutions corresponds to a polyhedral domain in the space of logarithms of species concentrations [10]. Furthermore, the validity of a given reduction can be extended to neighborhoods of such polyhedra in logarithms of species concentrations. For these reasons, the reductions based on orders of magnitude comparison (including those discussed in this paper) are robust [22, 39, 40]. However, biochemical CRNs are often excitable, and their trajectories explore very large domains of species concentration space. In such cases, the CRN may change the branch of tropical solutions several times along the same trajectory. Thus, scalings, truncated systems, and even approximate conservation laws may change, and several different reductions must be used along the same trajectory [10, 41, 46]. The study of switching between different reduced models asks for different mathematical methods, such as *blow-ups* [27], and will be treated in future work.

In our method we consider that fast dynamics relaxes to a quasi-equilibrium or quasi-steady state. Approximate conservation laws can also be relevant in situations when fast dynamics is periodic. This situation, needing averaging techniques, has been discussed for perturbed Hamiltonian systems in [19]. The long-time behavior of such systems turns out to be universal and corresponds to slow random motion on the graph of connected components of the Hamiltonian level sets [19].

The general usefulness of reduced models follows from their reduced number of variables and parameters. A reduced model can be more easily simulated, analyzed, and learned from data. Beyond these benefits, the model reduction process unfolds useful information about the full model. First, it provides a classification of the parameters, according to their identifiability, that is very useful for machine learning applications [39, 40]. Parameters of the full model, not occurring in the reduced model, are *sloppy* in the sense of a lack of sensibility of model properties with respect to these parameters. Other parameters of the full model, occurring in the reduced model in a grouped manner, for instance as monomials, are not identifiable independently. The reduction process also outputs timescales of different variables. This is important for understanding the dynamics of the system and in certain cases can be used to gain biological understanding. In particular, slow variables are involved in memory mechanisms, important in learning processes, and are necessary for the maintenance of the biological identity, whereas fast variables are important in complex responses needed for adaptation to external changes.

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