Conservation Laws in Biochemical Reaction Networks

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Abstract

We study the existence of linear and non-linear conservation laws in biochemical reaction networks with mass-action kinetics. It is straightforward to identify the linear conservation laws as they are related to the left null-space of the stoichiometry matrix. The non-linear conservation laws are much more difficult to study and so far have rarely been considered in the context of mass-action reaction networks. Our aim is to give structural conditions – that is, parameter independent conditions, on a reaction network to guarantee the existence of non-linear conservation laws of some type. We do so by means of Darboux theory of integrability. We show that $F(x) = x_i$ is a Darboux polynomial if and only if the reaction network fulfil a certain structural condition. Furthermore, this allows us to conclude that a specific type of a non-linear first integral (similar to that of the Lotka-Volterra system) only exists if the reaction network fulfils the same structural condition. The existence of such a first integral generally implies that the system is persistent and has stable steady states. We illustrate our results by examples.

Keywords: Darboux polynomial; dynamical system; mass-action; non-linear conservation law; persistence; Lotka-Volterra

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1. Introduction

Typical models of biochemical reaction networks are systems of polynomial ordinary differential equations (ODEs). Generally, these ODE systems are difficult to solve and analyse, and little can be said about their solutions, exactly or qualitatively, except in special cases [8, 24]. However, in many applications it is important to know whether the solutions oscillate, are attracted towards steady states, or are persistent.

To study the dynamics, a potentially promising strategy would be to look for *first integrals* (i.e. conservation laws). First integrals are quantities depending on the variables of the system, that are conserved over time. Typically, differential systems (equivalently vector fields) do not admit first integrals, however, when they do, and can be found, the benefit can be significant [24, 15, 3]. In connection with reaction networks, first integrals have been used to demonstrate oscillatory behaviour [24], chaos [23] and Turing instability [22] in particular examples.

The ODE system of a reaction network is composed of two parts: a stoichiometric (structural) representation of the reactions and a specification of the rates by which the reactions occur. Only the second part is parameter dependent. Our aim is twofold. First of all, we are interested in finding sufficient and/or necessary structural conditions – that is, conditions that are independent of the parameters – for the existence of non-linear first integrals. Secondly, for a given reaction network, we ask, what can we learn about the qualitative behaviour of the solutions from the existence of non-linear first integrals? We make use of Darboux theory of integrability [4, 5], which is a powerful tool in determining the non-linear first integrals [18, 16].

In relation to the first aim, we show that $F(x) = x_i$ is a Darboux polynomial (see Definition 11) if and only if the reaction network fulfils a certain structural condition on the form of the reactions. This in turn allows us to conclude that a particular type of non-linear first integral only exists for a class of reaction networks defined by the structural condition. This class contains a standard reaction network-representation of the Lotka-Volterra model. We find this re-

sult appealing because the condition is easy to check, simply by looking at the reactions. However, the condition is only necessary and not sufficient for the existence of a first integral of the desired form. We show this by example and demonstrate the first integral might not exist at all, or might exist for some or all parameter values. For the second aim, we show that the existence of a first integral of the desired form for a conservative system implies that it is persistent and has a unique non-attracting, but stable, steady state in each stoichiometric compatibility class (these classes are determined by linear first integrals).

The use of linear first integrals in reaction network theory is common. With some exceptions the non-linear first integrals have rarely been considered [1, 17, 20]. Quadratic first integrals have been characterised in [20]. Ideally, one would in general like to give conditions for the existence of first integrals of certain forms, irrespectively of the reaction rate constants. Our results might be seen as a first step in this direction. Also our results are in this sense analogous to other results in reaction network theory, for example, the deficiency zero and one theorems that give structural conditions for the existence of steady states [8], and the persistence criteria given in [2].

It is generally difficult to establish the existence or non-existence of Darboux first integrals. This typically depends on the reaction rate constants in intricate ways [12, 13, 17, 11]. We hope that this paper would inspire further work to characterise the existence and form of non-linear first integrals for reaction networks. As our results show, non-linear first integrals might be useful to study qualitative aspects of the dynamics.

2. Reaction networks with mass-action kinetics

Here we define a reaction network and show how to construct a system of polynomial ODEs describing the evolution of the species concentrations.

2.1. Reaction networks

Denote by $\mathbb{N}$ the set of non-negative integers, and by $\mathbb{R}_{>0}$ the set of positive (non-negative) real numbers. For $x = (x_1, \ldots, x_n) \in \mathbb{R}_{>0}^n$ and $\alpha =$

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$(\alpha_1, \ldots, \alpha_n) \in \mathbb{R}^n$, we let $x^\alpha = \prod_{i=1}^n x_i^{\alpha_i}$. If $\alpha_i > 0$ for all $i = 1, \ldots, n$, we allow $x \in \mathbb{R}^n_{\geq 0}$. In the following, Ω denote an open set of $\mathbb{R}^n$.

Definition 1 (Network). A *network* is a triplet $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ such that:

(a) $\mathcal{S} = \{A_1, \ldots, A_n\}$ has n elements, called species.

(b) $\mathcal{C}$ has p elements, called complexes, being a linear combination of species,
$y = \alpha_1 A_1 + \ldots + \alpha_n A_n \in \mathcal{C}$, with $\alpha_i \in \mathbb{N}$, $i = 1, \ldots, n$.

(c) $\mathcal{R}$ has m elements, called reactions, and each reaction $r \in \mathcal{R}$ is an ordered pair of distinct complexes, written $y \to y'$, and therefore $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$.

In the following we assume that the sets $\mathcal{S}, \mathcal{C}$, and $\mathcal{R}$ are ordered. It is common to assume that $\mathcal{C}$ only contains complexes which are part of reactions, and $\mathcal{S}$ only contains species which are part of complexes. In that case, $\mathcal{S}$ and $\mathcal{C}$ are determined by $\mathcal{R}$.

Example 1 (Volpert's network [24]). Consider the following reaction network

$$A_1 + A_2 \longrightarrow 2A_2, \qquad A_2 + A_3 \longrightarrow 2A_3, \qquad A_3 + A_1 \longrightarrow 2A_1 \qquad (1)$$
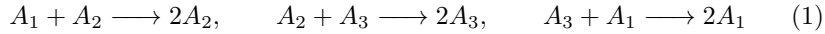
There are six complexes, $\mathcal{C} = \{A_1 + A_2, 2A_2, A_2 + A_3, 2A_3, A_3 + A_1, 2A_1\}$ and three species, $\mathcal{S} = \{A_1, A_2, A_3\}$.

A reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ has a natural representation in terms of a (directed) graph, as in Example 1, where the vertices are the complexes and the (directed) edges between vertices are the reactions. The connected components of the undirected graph are called *linkage classes* and the strongly connected components of the directed graph are called *terminal linkage classes*. In Example 1 there are three linkage classes (e.g., $A_1 + A_2 \to 2A_2$) and three terminal linkage classes (e.g., $2A_2$).

2.2. Stoichiometric subspace and compatibility class

Consider a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. Identify each species A_i with the i-th unit vector in $\mathbb{N}^n$, that is, the vector with one in the i-th entry and zero

elsewhere. Thus, a complex $y = \alpha_1 A_1 + \ldots + \alpha_n A_n$ is identified with the element $(\alpha_1, \ldots, \alpha_n)$ of $\mathbb{R}^n$.

For the j-th reaction $y_j \rightarrow y'_j$, we let $\gamma_j = y'_j - y_j \in \mathbb{R}^m$ be the net production of species in the reaction. The vector γ_j is referred to as the j-th reaction vector.

Definition 2 (Stoichiometry matrix)**.** The *stoichiometry matrix* Γ is define as the $n \times m$ matrix whose columns are the reaction vectors, that is, $\Gamma = (\gamma_1, \ \gamma_2, \ldots, \gamma_m)$.

Definition 3 (Stoichiometric subspace)**.** The *stoichiometric subspace* is the vector subspace $S \subseteq \mathbb{R}^n$ defined as $S = \mathrm{span}\{\gamma_1, \ldots, \gamma_m\}$.

Definition 4 (Stoichiometric compatibility class)**.** The *stoichiometric compatibility classes* are the affine vector subspaces in $\mathbb{R}^n$ defined by $(x + S) \cap \mathbb{R}^n_{\geq 0}$, where $x \in \mathbb{R}^n_{\geq 0}$.

2.3. Reaction networks with mass-action kinetics

Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. Denote by x_i the *concentration* of the species A_i and the vector of species concentrations by $x(t) = (x_1(t), \ldots, x_n(t))$. Before we show how to describe the time evolution of the vector of concentrations, we need some preliminary definitions and notation.

A *rate function* for a reaction $y_j \rightarrow y'_j$, $j = 1, \ldots, m$, is a function $v_j(x)$: $\mathbb{R}^n_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$ that describes the instantaneous change in the species composition $x = (x_1, \ldots, x_n)$ due to this reaction.

A *kinetics* $\mathcal{V}$ is an assignment to each reaction $y_j \rightarrow y'_j$, $j = 1, \ldots, m$, of a rate function $v_j(x)$: $\mathbb{R}^n_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$. We can think of $\mathcal{V}$ as a set of rate functions indexed by the elements of the reaction set, that is $\mathcal{V} = \{v_j(x)\colon j = 1, \ldots, m\}$. Let $v(x) = (v_1(x), \ldots, v_m(x))$.

Definition 5 (ODE system of a reaction network)**.** Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. The evolution of the concentrations $x(t) = (x_1(t), \ldots, x_n(t))$ under the kinetics $\mathcal{V}$ is given by the ODE system

$$\frac{dx}{dt} = \sum_{j=1}^{m} v_j(x)\gamma_j = \Gamma v(x), \quad \text{and} \quad x(0) = x_0 \in \mathbb{R}^n_{\geq 0}, \tag{2}$$

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where $v(x) = (v_1(x), \ldots, v_m(x))$ is the vector of the rate functions.

It follows from (2) that the evolution of the species concentrations is confined to the stoichiometric subspace

$$x(t) \in (x_0 + S) \cap \mathbb{R}^n_{\geq 0}, \quad \text{where} \quad x(0) = x_0.$$

Non-negativity of the solutions follows from the assumption that the rate functions are non-negative, in particular at the boundary of $\mathbb{R}^n_{\geq 0}$ [21].

We are particularly interested in mass-action kinetics.

Definition 6 (Mass-action kinetics). A kinetics is called *mass-action* if the rate functions take the form

$$v_{\kappa,j}(x) = k_j \prod_{i=1}^{n} x_i^{\alpha_{ji}} = k_j x^{y_j}, \tag{3}$$

where $y_j = (\alpha_{j1}, \ldots, \alpha_{jn})$, and $k_j > 0$ is a positive *reaction rate constant*. We denote the vector of reaction rate constants by $\kappa = (k_1, \ldots, k_m)$.

Example 2 (Volpert's network, part 2). Consider the reaction network given in (1) with the mass-action kinetics. The corresponding system of ODEs is given by

$$\frac{dx}{dt} = \Gamma v_\kappa(x) = \begin{pmatrix} k_3 x_1 x_3 - k_1 x_1 x_2 \\ k_1 x_1 x_2 - k_2 x_2 x_3 \\ k_2 x_2 x_3 - k_3 x_1 x_3 \end{pmatrix} \tag{4}$$

where

$$\Gamma = \begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix}, \quad \text{and} \quad v_\kappa(x) = \begin{pmatrix} k_1 x_1 x_2 \\ k_2 x_2 x_3 \\ k_3 x_1 x_3 \end{pmatrix}.$$

2.4. Linear conservation laws

Proposition 7. *Let (2) be an ODE system for a reaction network. For any row vector $\omega = (\omega_1 \ \omega_2 \ \ldots \ \omega_m)$ such that $\omega \, \Gamma = 0$, the quantity*

$$H = \sum_{j=1}^{m} \omega_j x_j$$

is a linear conservation law. Moreover, there are at least $s = n - \mathrm{rank}(\Gamma)$ independent linear conservation laws.
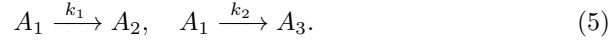
Proof. We have

$$\frac{dH}{dt} = \omega \frac{dx}{dt} = \omega \, \Gamma v(x) = 0.$$

The left kernel of Γ has dimension s, hence there must be at least s independent linear conservation laws. □

Remark 8. A linear conservation law is a linear first integral, see Definition 10 below.

Consider the reaction network

$$A_1 \xrightarrow{k_1} A_2, \quad A_1 \xrightarrow{k_2} A_3. \tag{5}$$

In this case, $s = 1$ as $H_1 = x_1 + x_2 + x_3$ is a conserved quantity corresponding to the vector $\omega^1 = (1, 1, 1)$. It is easy to see that $H_2 = k_2 x_2 - k_1 x_3$ is another linear conservation law for all $\kappa = (k_1, k_2) \in \mathbb{R}^2_{>0}$, although $\omega^2 = (0, k_2, -k_1)$ is not in the kernel of Γ. The two vectors ω^1 and ω^2 are linearly independent for all reaction rate constants.

Proposition 9 ([10])**.** *Let $S_\kappa = \mathrm{span}(\Gamma v_\kappa(\mathbb{R}^n_{\geq 0})) \subseteq S$ for a reaction network with mass-action kinetics, as in (3). If the number of linkage classes equals the number of terminal linkage classes, then $S_\kappa = S$ and the number of linear conservation laws is $s = n - \mathrm{rank}(\Gamma)$.*

In (5), there is one linkage class but two terminal linkage classes (A_1, and A_2), hence the proposition does not apply. As a second example, consider the

reaction network

$$A_1 \xrightarrow{k_1} 2A_1, \quad A_1 \xrightarrow{k_2} 0. \tag{6}$$
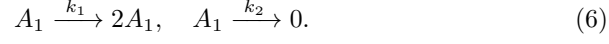
The function $H = x_1$ is a linear conservation law if $k_1 = k_2$, but $\omega = (1)$ is not in the left kernel of Γ, that is, ω is not of the form in Proposition 7. Indeed $s = 0$. If $k_1 \neq k_2$ then there are no linear conservation laws. Indeed, $S_{(k,k)} = \mathbb{R}$, while $S_{(k_1,k_2)} = \{0\}$ for $k_1 \neq k_2$.

Example 2 (see also Example 1) has three linkage classes and three terminal linkage classes, and hence there is only $s = 1$ conservation law for all κ, namely $H = x_1 + x_2 + x_3$.

3. Non-linear conservation laws via Darboux theory

The theory developed by Darboux [4, 5] is one of the most useful tools for identifying the first integrals of polynomial differential equations. Here our aim is to review the main elements of the Darboux method and subsequently show how it can be applied to search for nontrivial (non-linear) conservation laws of the reaction networks with mass-action kinetics.

We start by considering an n-dimensional polynomial differential system

$$\frac{dx_1}{dt} = P_1(x), \ldots, \frac{dx_n}{dt} = P_n(x), \tag{7}$$

where $x = (x_1, \ldots, x_n) \in \mathbb{R}^n$ and $P_i(x) \in \mathbb{R}[x]$ are polynomials in x. Whenever convenient we omit the argument x in $P_i = P_i(x)$ and other functions of x.

For any system of differential equations (7) we define a *derivation* by

$$\mathcal{D} := P_1 \frac{\partial}{\partial x_1} + \ldots + P_n \frac{\partial}{\partial x_n}. \tag{8}$$

Let

$$\mathcal{D}(H) := P_1 \frac{\partial H}{\partial x_1} + \cdots + P_n \frac{\partial H}{\partial x_n}$$

be the derivation evaluated at a $\mathcal{C}^1$-function $H \colon \Omega \to \mathbb{R}$. In the examples, Ω can be taken to be $\mathbb{R}^n_{>0}$.

The degree of the system (7), or of the derivation (8), is defined as

$$d = \max\{\deg(P_1), \dots, \deg(P_n)\},$$

where $\deg(P)$ denotes the total degree of a polynomial P.

Definition 10 (First integral). We say that a $\mathcal{C}^1$-function $H \colon \Omega \to \mathbb{R}$, where $\Omega \subset \mathbb{R}^n$ is a *first integral* of system (7), or of the derivation $\mathcal{D}$, if $\mathcal{D}(H) = 0$, and H is not locally constant on any positive Lebesgue measure subset of Ω.

Definition 11 (Darboux polynomial). A *Darboux polynomial* of the system (7) is a polynomial $F \in \mathbb{C}[x]$, such that

$$\mathcal{D}(F) := P_1 \frac{\partial F}{\partial x_1} + \cdots + P_n \frac{\partial F}{\partial x_n} = KF \tag{9}$$

for some cofactor $K \in \mathbb{C}[x]$.

Remark 12. A polynomial first integral is also a Darboux polynomial with cofactor $K = 0$. If the degree of the derivation (8) is d, then the degree of any cofactor in (9) is bounded by $d - 1$.

Definition 13 (Exponential factor). An *exponential factor* of the system (7) is a function $E = \exp(G/F)$, with $F, G \in \mathbb{C}[x]$, such that

$$\mathcal{D}(E) := P_1 \frac{\partial E}{\partial x_1} + \cdots + P_n \frac{\partial E}{\partial x_n} = LE,$$

for some cofactor $L \in \mathbb{C}[x]$, where the degree of L is lower than the degree of $\mathcal{D}$.

Remark 14. Notice that the polynomial F in the expression of $E = \exp(G/F)$ is a Darboux polynomial. Moreover it can be easily deduced that $\mathcal{D}(G) = K_F G + LF$, where K_F is the cofactor of F.

The Darboux theory of integrability relates the number of Darboux polynomials and exponential factors with the existence of a Darboux first integral. A *Darboux function* is a product of complex powers of Darboux polynomials and

exponential factors. Note that a *rational function* (a ratio of two polynomials) is a special case of a Darboux function. A *Darboux first integral* is a Darboux function that is a first integral according to Definition 10.

Theorem 15. *Assume that a derivation $\mathcal{D}$ of degree d admits r Darboux polynomials F_i, $i = 1, \ldots, r$, and s exponential factors E_j, $j = 1, \ldots, s$. Let $N = \binom{n+d-1}{n}$. Then the following statements hold.*

(a) *If $r + s \geq N + 1$, then the derivation $\mathcal{D}$ admits a Darboux first integral.*

(b) *If $r + s \geq N + n$, then the derivation $\mathcal{D}$ admits a rational fist integral.*

Theorem 15(a) is due to Darboux [5, 4], whereas Theorem 15(b) is attributed to Jouanolou [14]. Theorem 15 casts the burden of finding first integrals into finding Darboux polynomials.

As an illustration of the bound in Theorem 15(a) consider the case $n = 2$, that is, a system in two variables. As noted earlier, for Darboux polynomials F_i with cofactors K_i and exponential factors E_j with cofactors L_j, we have

$$\max\{\deg K_1, \ldots, \deg K_r, \deg L_1, \ldots, \deg L_s\} \leq d - 1.$$

Since the number of linearly independent polynomials in two variables of degree at most $d-1$ is $\binom{d+1}{2}$, there must be a linear combination of cofactors summing to zero, whenever $r + s$ is strictly bigger than $\binom{d+1}{2}$. Hence Theorem 15 applies.

Theorem 16. *Assume the derivation $\mathcal{D}$ admits r Darboux polynomials F_i with respective cofactors K_i, $i = 1, \ldots, r$, and s exponential factors E_j with respective cofactors L_j, $j = 1, \ldots, s$. If there exist $\lambda_1, \ldots, \lambda_r, \mu_1, \ldots, \mu_s$ in $\mathbb{C}$, such that*

$$\sum_{i=1}^{r} \lambda_i K_i + \sum_{j=1}^{s} \mu_j L_j = 0, \tag{10}$$

then the Darboux function

$$\Phi(x) = F_1^{\lambda_1} \cdots F_r^{\lambda_r} E_1^{\mu_1} \cdots E_s^{\mu_s}$$

is a first integral of (7), provided Φ is not locally constant on any positive Lebesgue measure subset of its domain of definition.

Proof. We first note that if $\Phi(x)$ is a first integral, then the composition $F(\Phi(x))$ is another first integral, where F is any $\mathcal{C}^1$-function. Now we prove that $\log \Phi$ is a first integral. We have

$$
\begin{aligned}
\mathcal{D}(\log \Phi) &= \sum_{i=1}^{r} \lambda_i \mathcal{D}(\log F_i) + \sum_{j=1}^{s} \mu_j \mathcal{D}(\log E_j) \\
&= \sum_{i=1}^{r} \lambda_i \frac{\mathcal{D}(F_i)}{F_i} + \sum_{j=1}^{s} \mu_j \frac{\mathcal{D}(E_j)}{E_j} = \sum_{i=1}^{r} \lambda_i K_i + \sum_{j=1}^{s} \mu_j L_j.
\end{aligned}
$$

The theorem follows from (10). $\qquad\square$

4. A particular class of reaction networks

We start by making a connection between the existence of certain Darboux polynomials and the structural form of a class of reaction networks. This form is shared by many reaction networks, in particular the standard representation of the Lotka-Volterra system.

Proposition 17. *Consider an n-dimensional polynomial differential system (7) with mass-action kinetics. Then for $1 \le i \le n$ the following three statements are equivalent:*

(i) *The function $F = x_i$ is a Darboux polynomial with cofactor $K \in \mathbb{C}[x]$.*

(ii) *$P_i = K x_i$ with $K \in \mathbb{C}[x]$.*

(iii) *If $\alpha'_{ji} > 0$, then $\alpha_{ji} > 0$ for all $j = 1, \dots, m$.*

Proof. The equivalence between (i) and (ii) follows from the definition of a Darboux polynomial.

Assume (iii). Consequently x_i is a factor of $(\alpha'_{ji} - \alpha_{ji})x^{y_j}$, if the term is not zero. If $\alpha'_{ji} = 0$ and $\alpha_{ji} > 0$, then x_i is also a factor of $(\alpha'_{ji} - \alpha_{ji})x^{y_j} = -\alpha_{ji}x^{y_j}$ by definition of mass-action kinetics. Hence $P_i = \sum_{j=1}^{m}(\alpha'_{ji} - \alpha_{ji})x^{y_j}$ factorises

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as $P_i = Kx_i$ for some polynomial $K \in \mathbb{C}[x]$. If P_i is zero, then $K = 0$ and (ii) is proved.

For the reverse statement, assume (ii), that is, $P_i = Kx_i$ (which might be zero), for some $K \in \mathbb{C}[x]$, and $\alpha'_{ji} > 0$ for some $j = 1, \ldots, m$. We need to show that $\alpha_{ji} > 0$. Assume the opposite that $\alpha_{ji} = 0$. Then $\alpha'_{ji}k_j x^{y_j}$ is a term in P_i, not involving x_i, by definition of mass-action kinetics. Hence it must cancel with terms from other reactions with the same monomial x^{y_j}, that is, $0 = \sum_{\{j': y_{j'} = y_j\}}(\alpha'_{j'i} - \alpha_{j'i})k_{j'}x^{y_j}$. Since x_i is not a factor of x^{y_j}, we have $\alpha_{j'i} = 0$, and hence $0 = \sum_{\{j': y_{j'} = y_j\}}\alpha'_{j'i}k_{j'}x^{y_j} \geq \alpha'_{ji}k_j x^{y_j}$, implying $\alpha'_{ji} = 0$, and we have reached a contradiction. $\qquad\square$

Condition (iii) is independent of the parameters of the reaction network, and hence it is fulfilled for all κ or for none at all. Thus, we have given a structural characterisation of networks with Darboux polynomials $F = x_i$ for all i.

System (6) fulfills all three statements of Proposition 17 with $K = k_1 - k_2$. Also system (5) fulfills all three statements of Proposition 17 for $i = 1$, that is, $F = x_1$ is a Darboux polynomial.

Example 3 (Volpert's network, part 3)**.** Consider Volpert's reaction network in Example 1 and 2 with mass-action kinetics. According to Theorem 15 we need to find

$$\binom{3 + 2 - 1}{3} + 1 = 5$$

Darboux polynomials to guarantee the existence of a conservation law. However, fewer might suffice if some linear combination of cofactors equals zero, see Theorem 15. Using (1) and (4), it follows from Proposition 17, that the system admits the Darboux polynomials $F_i(x) = x_i$ for $i = 1, 2, 3$ with cofactors

$$K_1 = k_3x_3 - k_1x_2, \quad K_2 = k_1x_1 - k_2x_3, \quad K_3 = k_2x_2 - k_3x_1.$$

Now we aim to check if the above cofactors are linearly dependent. Since $k_2K_1 + k_3K_2 + k_1K_3 = 0$, this is so, and the network admits, according to Theorem 15,

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the Darboux first integral

$$H_1 = x_1^{k_2} x_2^{k_3} x_3^{k_1},$$

for any values of the reaction rate constants $k_1, k_2, k_3 > 0$. In addition, according to Proposition 7 and 9, there is one independent linear conservation law $H_0 = x_1 + x_2 + x_3$.

Theorem 18. *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network with mass-action kinetics and reaction rate constants κ and let $I \subseteq \{1, \ldots, n\}$. If*

(i) $H = \prod_{i \in I} x_i^{\lambda_i} e^{\delta_i x_i}, \quad \lambda_i, \delta_i \in \mathbb{R}, \ \lambda_i \neq 0, \ i \in I,$

is a first integral of the reaction network, then

(ii) *if $\alpha'_{ji} > 0$ then $\alpha_{ji} > 0$ for all $j = 1, \ldots, m$ and $i \in I$.*

Proof. If (i) is fulfilled, then x_i is a Darboux polynomial of P_i [6]. Then (ii) follows from Proposition 17. $\qquad\square$

The proof shows that under the assumptions of the theorem, there is a linear combination of cofactors for the Darboux polynomials $F_i = x_i$ and the exponential factors $G_i = e^{\delta_i x_i}$, yielding the first integral H. The reverse statement is not true in general: system (6) fulfills condition (ii) in Theorem 18, but cannot have a conservation law of the form (i) as it is one-dimensional (unless $k_1 = k_2$, in which case $x(t) = x(0)$ for all $t > 0$).

Example 4 (Lotka-Volterra network)**.** Consider the following version of the Lotka-Volterra system in $\mathbb{R}^2_{\geq 0}$,

$$A_1 \xrightarrow{k_1} 2A_1, \quad A_1 + A_2 \xrightarrow{k_2} 2A_2, \quad A_2 \xrightarrow{k_3} 0$$
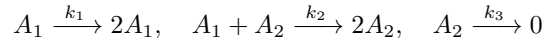
(prey reproduce, predators eat prey and reproduce, predators die). Proposition 17(iii) is fulfilled, hence $F_1 = x_1$ and $F_2 = x_2$ are Darboux polynomials. The corresponding cofactors are
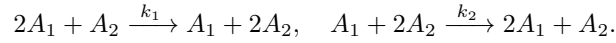
$$K_1 = k_1 - k_2 x_2, \quad K_2 = k_2 x_1 - k_3.$$

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In addition, $E = \exp(x_1 + x_2)$ is an exponential factor with cofactor $L = k_1 x_1 - k_3 x_2$. Note that $k_2 L + k_3 K_1 + k_1 K_2 = 0$, hence

$$H = x_1^{k_3} x_2^{k_1} e^{k_2(x_1 + x_2)}, \quad (x_1, x_2) \in \mathbb{R}_{>0}^2$$

is a first integral of the reaction network, which is well known [24].

Example 5 (Reversible network). Consider the following reaction network with mass-action kinetics

$$2A_1 + A_2 \xrightarrow{k_1} A_1 + 2A_2, \quad A_1 + 2A_2 \xrightarrow{k_2} 2A_1 + A_2.$$

The reaction network is said to be reversible because the second reaction is the first reversed. Proposition 17(iii) is fulfilled, and $F_1 = x_1$ and $F_2 = x_2$ are Darboux polynomials with cofactors

$$K_1 = k_1 x_2^2 - k_2 x_1 x_2, \quad K_2 = -k_1 x_1 x_2 + k_2 x_1^2,$$

but they are not linearly dependent and there is no first integral as in Theorem 18. In fact, since $H = x_1 + x_2$ is a linear conservation law, we might reduce the system to a one dimensional ODE, which cannot have a law of the form as in Theorem 18 (unless trajectories are constant).

It follows from the so-called deficiency zero theorem that the network in Example 5 has precisely one steady state in each stoichiometric compatibility class (given by $H = x_1 + x_2$) and that this steady state is asymptotically stable. It also follows that there cannot be periodic orbits [8], which is also consequence of the fact that the system essentially is one dimensional.

5. First integrals and dynamics

In this section, we show by examples how to apply the Darboux method to determine non-linear conservation laws of mass-action reaction networks. Additionally, we demonstrate how first integrals might be used to study dynamical

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properties of the system. For that purpose we use different generalisations of Volpert's reaction network (Example 1) that fall into the class of reaction networks characterised in Proposition 17.

We start with a definition of persistence and a lemma.

Definition 19 (Persistance). An ODE system for a reaction network is said to be *persistent* if any trajectory starting from a positive initial point is bounded away from the boundary of $\mathbb{R}^n_{\geq 0}$, that is,

$$0 < \liminf_{t \to \infty} x_i(t) \quad \text{for} \quad i = 1, \ldots, n.$$

Lemma 20. *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network with mass-action kinetics and reaction rate constants κ. Assume the system admits the following first integrals*

$$H_0 = \prod_{i=1}^{n} x_i^{\lambda_i} e^{\delta_i x_i}, \qquad H_k = \sum_{i \in I_k} \omega_i x_i, \quad k = 1, \ldots, r,$$

where $r \in \mathbb{N}$, $\omega_i, \lambda_i > 0$ are positive constants, $\delta_i \in \mathbb{C}$, $\cup_{k=1}^r I_k = \{1, \ldots, n\}$, $I_k \cap I_{k'} = \emptyset$ for $k \neq k'$, and there are no other linearly independent linear first integrals. Then the system is persistent.

In addition, if $\delta_i = 0$ for all i, then there exists at least one stable positive steady state $x^* = (x_1^*, \ldots, x_n^*)$ in each stoichiometric compatibility class (determined by H_k, $k = 1, \ldots, r$), given by

$$x_i^* = \frac{\lambda_i H_k}{\omega_i \sum_{j \in I_k} \lambda_j}, \quad i \in I_k, \quad k = 1, \ldots, r.$$

No trajectories apart from the constant trajectory $x(t) = x^*$, $t \geq 0$, are attracted towards x^*, that is, there exists $\epsilon > 0$, depending on the initial condition $x(0)$, such that $|x(t) - x^*| > \epsilon$ for all $t \geq 0$.

Proof. By assumption $H_k \geq 0$ for all $k = 1, \ldots, r$. It follows that each concentration x_i, $i \in I_k$, is bounded by $0 \leq x_i \leq M := \max\{M_k \mid k = 1, \ldots, r\}$, where $M_k = H_k / \min\{\omega_i \mid i \in I_k\}$, and from H_0 that x_i cannot get arbitrary close to zero as this would imply that at least one other concentration, say x_j, would

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become arbitrarily large, contradicting that $x_j \leq M$ for all j. Hence the system is persistent.

Choose an element $i_k \in I_k$ for each k and define $J_k = I_r \setminus \{i_k\}$. By inserting $\omega_{i_k} x_{i_k} = H_k - \sum_{i \in J_k} \omega_i x_i$ into H_0 with $\delta_i = 0$ we obtain

$$
\begin{aligned}
H_0 \prod_{i=1}^{n} \omega_i^{\lambda_i} = \prod_{i=1}^{n} (\omega_i x_i)^{\lambda_i} &= \prod_{k=1}^{r} \prod_{i \in I_k} (\omega_i x_i)^{\lambda_i} \\
&= \prod_{k=1}^{r} \left[\left(H_k - \sum_{i \in J_k} \omega_i x_i \right)^{\lambda_{i_k}} \prod_{i \in J_k} (\omega x_i)^{\lambda_i} \right],
\end{aligned}
\tag{11}
$$

which attains its global maximum at $x^* = (x_1^*, \ldots, x_n^*)$, where

$$
x_i^* = \frac{\lambda_i H_k}{\omega_i \sum_{j \in I_k} \lambda_j}, \quad i \in I_k, \quad k = 1, \ldots, r.
$$

Any trajectory starting out at x^* must remain there, hence x^* is a positive steady state in the given stoichiometric class. Since H_0 is continuous as a function of x, it follows that any trajectory that starts close to x^* remains close to x^* for all $t > 0$. Hence the steady state x^* is stable.
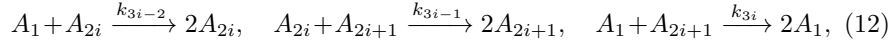
For the last part, consider the right hand side of (11) as a continuous function of $(x_i)_{i \in J}$, $J = \cup_{k=1}^{r} J_k$ (with fixed values of $H_1, \ldots, H_k$). Assume some trajectory $x(t)$ converges towards x^* as $t \to \infty$. Hence by continuity, $H_0(x(t)) \to H_0(x^*)$ as $t \to \infty$. Since H_0 is constant along trajectories, it follows that $H_0(x(t)) \neq H_0(x^*)$, unless $x(t) = x^*$. $\qquad\square$

Remark 21. In [2] (see also [19]), a structural condition for persistence is introduced. A siphon $\Sigma \subseteq \mathcal{S}$ is a subset of the species set with the property that if $A_i \in \Sigma$ and $\alpha'_{ij} > 0$ for some reaction R_j, then there is a species $A_k \in \Sigma$ such that $\alpha_{kj} > 0$ for the same reaction. If all siphons of the network contain the species of a linear first integral, then the network is persistent. If a network fulfills the structural condition given in Theorem 18, then it does not satisfy this condition. Any species A_i for which $\alpha'_{ij} > 0$ constitutes a siphon, but $\Sigma = \{A_i\}$ will only contain the support of a linear first integral if the concentration x_i of

A_i is constant through time.

5.1. Generalized Volpert network, example A

Consider the following chemical reaction network

$$A_1+A_{2i} \xrightarrow{k_{3i-2}} 2A_{2i}, \quad A_{2i}+A_{2i+1} \xrightarrow{k_{3i-1}} 2A_{2i+1}, \quad A_1+A_{2i+1} \xrightarrow{k_{3i}} 2A_1, \quad (12)$$

where $i = 1,\ldots,\ell$. This is a generalization of the system in Example 1 for which $\ell = 1$. This general system has $n = 2\ell + 1$ species $\mathcal{S} = \{A_1,\ldots,A_{2\ell+1}\}$, and $p = 5\ell + 1$ complexes, $\mathcal{C} = \{A_1 + A_2,\ldots,A_1 + A_{2\ell+1}, A_2 + A_3,\ldots,A_{2\ell} + A_{2\ell+1}, 2A_1,\ldots,2A_{2\ell+1}\}$. There are $m = 3\ell$ reactions.

Proposition 22. *For any values of the reaction rate constants $k_1,\ldots,k_{3\ell} > 0$ the polynomial differential system corresponding to the reaction network in (12) admits the following two first integrals of Darboux type*

$$H_0 = x_1 \prod_{i=1}^{\ell} x_{2i}^{k_{3i}/k_{3i-1}} \prod_{i=1}^{\ell} x_{2i+1}^{k_{3i-2}/k_{3i-1}}, \qquad H_1 = \sum_{i=1}^{2\ell+1} x_i,$$

the latter being the only linear first integral of the system. The first integral is the only possible first integral of the form $H_0 = \prod_{i=1}^{n} x_i^{\lambda_i}$.

Proof. The differential equations associated with (12) are given by

$$\frac{dx_1}{dt} = x_1 \sum_{i=1}^{\ell} \left(-k_{3i-2}x_{2i} + k_{3i}x_{2i+1} \right),$$
$$\frac{dx_{2i}}{dt} = x_{2i}\left(k_{3i-2}x_1 - k_{3i-1}x_{2i+1} \right),$$
$$\frac{dx_{2i+1}}{dt} = x_{2i+1}\left(k_{3i-1}x_{2i} - k_{3i}x_1 \right),$$

for $i = 1,\ldots,\ell$. In total we have $2\ell+1$ equations and 3ℓ reaction rate constants. Since there are $2\ell + 1$ linkage classes, $2\ell + 1$ terminal linkage classes, and $s = n - \mathrm{rank}(\Gamma) = 1$, then H_0 is the only linear conservation law according to Proposition 9, for all values of the reaction rate constants.

It follows from Proposition 17 that the system admits at least $2\ell+1$ Darboux polynomials, namely $F_i = x_i$, where $i = 1, \ldots, 2\ell + 1$, with the following $2\ell + 1$ cofactors

$$K_1 = \sum_{i=1}^{\ell} -k_{3i-2}x_{2i} + k_{3i}x_{2i+1}, \quad K_{2i} = k_{3i-2}x_1 - k_{3i-1}x_{2i+1}, \quad K_{2i+1} = k_{3i-1}x_{2i} - k_{3i}x_1.$$

In order to find a Darboux first integral one needs to find $\lambda_1, \ldots, \lambda_{2\ell+1}$ such that

$$0 = \lambda_1 K_1 + \ldots + \lambda_{2\ell+1} K_{2\ell+1}$$
$$= x_1 \sum_{i=1}^{\ell}(\lambda_{2i}k_{3i-2} - \lambda_{2i+1}k_{3i}) + \sum_{i=1}^{\ell}(\lambda_{2i+1}k_{3i-1} - \lambda_1 k_{3i-2})x_{2i} + \sum_{i=1}^{\ell}(\lambda_1 k_{3i} - \lambda_{2i}k_{3i-1})x_{2i+1}.$$

This expression is zero only if each coefficient of x_i is zero. It follows that any solution is proportional to

$$\lambda_1 = 1, \qquad \lambda_{2i} = \frac{k_{3i}}{k_{3i-1}}, \qquad \lambda_{2i+1} = \frac{k_{3i-2}}{k_{3i-1}}.$$

Hence, according to Theorem 16, $H_1 = \prod_{i=1}^{n} x_i^{\lambda_i}$ is a Darboux first integral.

Oppositely, if $H_0 = \prod_{i=1}^{n} x_i^{\lambda_i}$ is a first integral for some $\lambda_i \in \mathbb{C}$, then so is $\log(H_0)$. It follows that $\mathcal{D}(H_0)$ is a linear combination of the cofactors K_i, hence λ_i must take the form stated above. $\square$

The assumption of Lemma 20 is fulfilled for the reaction network above; hence the conclusions apply. In particular the system is persistent. Volpert [24] showed that for $\ell = 1$ ($n = 3$) any trajectory starting in a positive initial point is periodic.

5.2. Generalized Volpert network, example B

Consider the following chemical reaction network

$$A_i + A_{i+1} \xrightarrow{k_i} 2A_{i+1}, \quad A_n + A_1 \xrightarrow{k_n} 2A_1, \tag{13}$$

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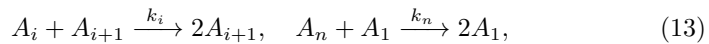
where $i = 1, \ldots, n$. This is a generalization of the system in Example 1, for which $n = 3$. The general system has n species, and $p = 2n$ complexes, $\mathcal{C} = \{A_1 + A_2, \ldots, A_{n-1} + A_n, A_n + A_1, , 2A_1, \ldots, 2A_n\}$. There are $m = n$ reactions.

Proposition 23. *For any values of the reaction rate constants κ, the polynomial differential system corresponding to the network* (13) *admits only one linear conservation law, namely*

$$H_1 = \sum_{i=1}^{n} x_i.$$

Moreover, if $n \geq 3$ is odd, then for any values of the reaction rate constants κ, there is an additional non-linear conservation law

$$H_{0,\text{odd}} = \prod_{i=1}^{n} x_i^{\prod_{j=1}^{(n-1)/2} k_{[(2j+i) \bmod n]+1}}.$$

If $n \geq 4$ is even and the following constraint on the rate constants is fulfilled,

$$1 = \frac{k_n k_{n-2} \ldots k_2}{k_{n-1} k_{n-3} \ldots k_1}, \tag{14}$$

then there are two non-linear conservation laws of the form $H_{0,\text{even}} = \prod_{i=1}^{n} x_i^{\lambda_i}$ with

$$\lambda_1 = 1, \quad \lambda_{2i+1} = \frac{k_{2i-1} \ldots k_1}{k_{2i} \ldots k_2}, \quad \lambda_{2i} = 0, \tag{15}$$

and

$$\lambda_2 = 1, \quad \lambda_{2i+2} = \frac{k_{2i} \ldots k_2}{k_{2i+1} \ldots k_3}, \quad \lambda_{2i-1} = 0, \tag{16}$$

for $i = 1, \ldots, \frac{n}{2}$.

For general $n \geq 3$, any first integral of the form $H_0 = \prod_{i=1}^{n} x_i^{\lambda_i}$ is a product $H_0 = (H_{0,\text{even}}^1)^\gamma H_{0,\text{even}}^2$, where $\gamma \in \mathbb{C}$, $H_{0,\text{even}}^1$ has λ_i chosen as in (15), *and $H_{0,\text{even}}^2$ has λ_i chosen as in* (16).

Proof. The polynomial differential system associated to the network (13) is

$$\frac{dx_1}{dt} = x_1\big(k_n x_n - k_1 x_2\big)$$

$$\frac{dx_i}{dt} = x_i\big(k_{i-1} x_{i-1} - k_i x_{i+1}\big)$$

$$\frac{dx_n}{dt} = x_n\big(k_{n-1} x_{n-1} - k_n x_1\big),$$

for $i = 2, \ldots, n - 1$. It is straightforward to check that H_1 is a conservation law. Since there are n linkage classes, n terminal linkage classes, and $s = n - \mathrm{rank}(\Gamma) = 1$, then H_1 is the only linear conservation law according to Proposition 9, for all values of the reaction rate constants. According to Proposition 17, the system admits the Darboux polynomials $F_i = x_i$, $i = 1, \ldots, n$, with cofactors given by

$$K_1 = k_n x_n - k_1 x_2, \quad K_i = k_{i-1} x_{i-1} - k_i x_{i+1}, \quad K_n = k_{n-1} x_{n-1} - k_n x_1,$$

$i = 2, \ldots, n - 1$. In order to find a Darboux first integral one needs to find $\lambda_1, \ldots, \lambda_n$ such that

$$0 = \lambda_1 K_1 + \ldots + \lambda_n K_n \tag{17}$$

$$= (\lambda_2 k_1 - \lambda_n k_n)x_1 + \sum_{i=2}^{n-1}(\lambda_{i+1} k_i - \lambda_{i-1} k_{i-1})x_i + (\lambda_1 k_n - \lambda_{n-1} k_{n-1})x_n.$$

This expression is zero only if each coefficient of x_i is zero. If $n \geq 3$ is odd, then (17) is fulfilled by choosing

$$\lambda_1 = \prod_{j=1}^{(n-1)/2} k_{2j}, \qquad \lambda_i = \prod_{j=1}^{(n-1)/2} k_{[(2j+i)\,\mathrm{mod}\,n]+1},$$

for $i = 2, \ldots, n$.

If $n \geq 4$ is even, then the equations $\lambda_{i+1} k_i - \lambda_{i-1} k_{i-1} = 0$ in (17) lead

recursively to the equations

$$\lambda_{2i+1} = \frac{k_{2i-1}}{k_{2i}}\lambda_{2i-1} = \ldots = \frac{k_{2i-1}\ldots k_1}{k_{2i}\ldots k_2}\lambda_1, \tag{18}$$

and similarly for λ_{2i}. By choosing $\lambda_1 = 1$ and $\lambda_2 = 0$ gives (15), and by choosing $\lambda_1 = 0$ and $\lambda_2 = 1$ gives (16). for $\lambda_{2i-1}, \lambda_{2i}$ in terms of λ_1, λ_2, respectively. The equation $\lambda_1 k_n - \lambda_{n-1} k_{n-1} = 0$ gives, using (18),

$$\lambda_{n-1} = \frac{k_n}{k_{n-1}}\lambda_1 = \frac{k_{n-3}\ldots k_1}{k_{n-2}\ldots k_2}\lambda_1,$$

which implies the constraint (14), if $\lambda_1 \neq 0$. Similarly, the equation $\lambda_2 k_1 - \lambda_n k_n = 0$ also implies the constraint (14), if $\lambda_2 \neq 0$.

Oppositely, if $H_0 = \prod_{i=1}^{n} x_i^{\lambda_i}$ is a first integral for some $\lambda_i \in \mathbb{C}$, then so is $\log(H_0)$. It follows that $\mathcal{D}(H_0)$ is a linear combination of the cofactors K_i, hence λ_i must take the form stated above. $\qquad\square$

Lemma 20 is applicable for n odd. In order to apply Lemma 20 for n even, we need to choose two first integrals for which different λ_i's are zero and combine them into one first integral. Hence, the assumption of Lemma 20 is fulfilled and therefore also the conclusions hold.

Acknowledgements

References

[1] Aybar, I.K., Aybar, O.O., Fercec, B., Romanovski, V.G., Samal, S.S., Weber, A., 2015. Investigation of invariants of a chemical reaction system

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with algorithms of computer algebra. MATCH Commun. Math. Comput. Chem., 74:465–480.

[2] Angeli, D., De Leenheer, P., Sontag, E.D., 2007. A petri net approach to the study of persistence in chemical reaction networks. Math. Biosci., 210(2):598–618.

[3] Arnold, V.I., 2012. Geometrical methods in the theory of ordinary differential equations, volume 250. Springer Science & Business Media.

[4] Darboux, G., 1878. De lemploi des solutions particulières algébriques dans lintégration des systèmes déquations différentielles algébriques. CR Math. Acad. Sci. Paris, 86:1012–1014.

[5] Darboux, G., 1878. Mémoire sur les équations différentielles algébriques du premier ordre et du premier degré. Bulletin des Sciences Mathématiques et Astronomiques, 2(1):151–200.

[6] Dumortier, F., Llibre, J., Artés, J.A., 2006. Qualitative theory of planar differential systems, Springer-Verlag, Berlin.

[7] Edelstein, B.B., 1970. A biochemical model with multiple steady states and hysteresis. J. Theor. Biol., 29:57–62.

[8] Feinberg, M., 1987. Chemical reaction network structure and the stability of complex isothermal reactors I. The deficiency zero and deficiency one theorems. Chem. Eng. Science, 42(10):2229–2268.

[9] Feinberg, M., 1995. Multiple steady states for chemical reaction networks of deficiency one. Arch. Rational Mech. Anal., 132:371–406.

[10] Feinberg, M., Horn, F.J.M., 1977. Chemical mechanism structure and the coincidence of the stoichiometric and kinetic subspaces. Arch. Rational Mech. Anal., 66(1):83–97.

[11] Ferragut, A., Mahdi, A., Valls, C., Wiuf, C., 2016. On the Darboux integrability of a the Edelstein system in $\mathbb{R}^3$. Submitted.

[12] Ferragut, A., Valls, C., 2016. On the Darboux integrability of a cubic CRN model in $\mathbb{R}^5$. Chaos, Solitons and Fractals 82:131–138, 2016.

[13] Ferragut, A., Valls, C., 2015. On the complete integrability of the Raychaudhuri differential system in $\mathbb{R}^4$ and of a CRNT model in $\mathbb{R}^5$. Preprint.

[14] Jouanolou, J.P., 1979. Equations de Pfaff algébriques. Springer.

[15] Li, G., Rabitz, H., Tóth, J., 1994. A general analysis of exact nonlinear lumping in chemical kinetics. Chem. Eng. Sci., 49(3):343–361.

[16] Llibre, J., Mahdi, A., Valls, C., 2013. Darboux integrability of the Lü system. J. Geom. Phys., 63:118–128.

[17] Llibre, J., Valls, C., 2012. Liouvillian and analytic first integrals for the Brusselator system. J. Nonlin. Math. Phys., 19(02).

[18] Mahdi, A., Valls, C., 2011. Integrability of the Nosé–Hoover equation. J. Geom. Phys., 61(8):1348–1352.

[19] Marcondes de Freitas, M., Feliu, E., Wiuf, C., 2016. Intermediates, catalysts, persistence, and boundary steady states. J. Math. Biol., to appear.

[20] Nagy, I., Tóth, J., 2014. Quadratic first integrals of kinetic differential equations. J. Math. Chem., 52(1):93–114.

[21] Smirnov, G., 2002. Introduction to the theory of differential inclusions, volume 41 of 'Graduate Studies in Mathematics'. American Mathematical Society, Providence.

[22] Szili, L., Tóth, J., 1993. Necessary condition of the turing instability. Phys. Rev. E, 48(1):183–186.

[23] Tóth, J., Hárs, V., 1986. Orthogonal transforms of the lorenz- and rö"ssler-equations. Physica, 19D:135–144.

[24] Volpert, A.I., 1972. Differential equations on graphs. Mathematics of the USSR-Sbornik, 17(4):571.