

Computing Hopf Bifurcations in Chemical Reaction Networks Using Reaction Coordinates

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Abstract. The analysis of dynamic of chemical reaction networks by computing Hopf bifurcation is a method to understand the qualitative behavior of the network due to its relation to the existence of oscillations. For low dimensional reaction systems without additional constraints Hopf bifurcation can be computed by reducing the question of its occurrence to quantifier elimination problems on real closed fields. However deciding its occurrence in high dimensional system has proven to be difficult in practice. In this paper we present a fully algorithmic technique to compute Hopf bifurcation fixed point for reaction systems with linear conservation laws using reaction coordinates instead of concentration coordinates, a technique that extends the range of networks, which can be analyzed in practice, considerably.

1 Introduction

In chemical and biochemical systems, reactions networks can be represented as a set of reactions. If it is assumed they follow mass action kinetics then the dynamics of these reactions can be represented by ordinary differential equations (ODE) for systems without additional constraints or algebraic differential equations (DAE) for systems with constraints. Particularly, in complex systems it is sometimes difficult to estimate the values of the parameters of these equations, hence the simulation studies involving the kinetics is a daunting task. Nevertheless, quite a few things about the dynamics can be concluded from the structure of the reaction network itself. In this context there has been a surge of algebraic methods, which are based on the structure of network and the associated Stoichiometry of the chemical species. These methods provide a way to understand the qualitative behaviour (e.g. steady states, stability, bifurcations, oscillations, etc) of the network. The analysis of chemical reaction networks by detecting of the Occurrence of Hopf bifurcation attracts especially more and more interests in chemical and biological field due to its linkage to the oscillatory behaviour. During the last decade many theoretical advances have been made for computing Hopf bifurcation in low dimensional systems [?]. However

the detection of Hopf bifurcation in high dimensional systems and in systems with constraints as the case in chemical and biochemical systems has proven to be difficult. A central method to overcome this difficulty is called stoichiometric network analysis (SNA). This method has been introduced by Clark in 1980 [] and based on the analysis of the system dynamic in the flux space instead in the concentration space and expand the steady states into a combination of subnetworks using convex geometry. For the steady state loci new coordinates that are called *reaction coordinates* can be introduced. These methods have been used in several “hand computations” in a semi-algorithmic way for parametric systems, the most elaborate being described in [1].

A fully algebraic method for the computation of Hopf bifurcation for systems with polynomial vector field has been introduced by El Kahoui and Weber [2] using the powerful technique of quantifier elimination on real closed fields [?]. This technique has already been applied to mass action kinetics of small dimension [3]. Although the method is complete in theory it fails for systems of higher dimensions in practice.

Our algorithmic method presented in this paper uses and combines the ideas of these methods and extends them to a new approach for computing Hopf bifurcation in complex systems using reaction coordinates also allowing systems with linear constraints.

2 Chemical Reaction Networks

2.1 Flux Cone and Reaction Coordinates

2.2 Constraints in Chemical Reaction Networks

some words on constraints in reaction systems

As the situation found in chemical reaction networks can easily be generalized, we will analyze the situation for the case of *pseudolinear ordinary differential equations*, which will contain all cases of constraints for chemical reaction systems discussed in this paper, as an instance.

3 Pseudolinear Ordinary Differential Equations

Definition 1. *We call an autonomous system of ordinary differential equations $\dot{\mathbf{x}} = \phi(\mathbf{x})$ for an unknown function $\mathbf{x} : \mathbb{R} \rightarrow \mathbb{R}^n$ pseudolinear, if its right hand side can be written in the form $\phi(\mathbf{x}) = N\psi(\mathbf{x})$ with a constant matrix $N \in \mathbb{R}^{n \times m}$ and some vector valued function $\psi : \mathbb{R}^n \rightarrow \mathbb{R}^m$.*

Obviously, any *polynomially* nonlinear system can be written in such a form, if we take for $\psi(\mathbf{x})$ the vector of all terms appearing on the right hand side of the system. As one can see from the following two lemmata, the pseudolinear structure is of interest only in the case that the matrix N does not possess full row rank and hence the range of N is not the full space \mathbb{R}^n . In the sequel, we will always assume that the function ψ satisfies $m \geq n$, as this is usually the case in applications like reaction kinetics.

Lemma 1. For a pseudolinear system $\dot{\mathbf{x}} = N\psi(\mathbf{x})$ any affine subspace of the form $\mathcal{A}_{\mathbf{y}} = \mathbf{y} + \text{im } N \subseteq \mathbb{R}^n$ for an arbitrary constant vector $\mathbf{y} \in \mathbb{R}^n$ defines an invariant manifold.

Proof. Obviously, we have $\dot{\mathbf{x}}(t) \in \text{im } N$ for all times t and $T_{\mathbf{x}}\mathcal{A}_{\mathbf{y}} = \text{im } N$ for all points $\mathbf{x} \in \mathcal{A}_{\mathbf{y}}$ by definition of an affine space. Thus, if $\mathbf{x}(0) \in \mathcal{A}_{\mathbf{y}}$, then the whole trajectory will stay in $\mathcal{A}_{\mathbf{y}}$. \square

Remark 1. For the application in reaction kinetics, the following minor strengthening of Lemma 1 is of interest. Assume that the function ψ satisfies additionally $\psi(\mathbf{x}) \in \mathbb{R}_{\geq 0}^m$ for all $\mathbf{x} \in \mathbb{R}_{\geq 0}^n$ which is for example trivially the case when each component of ψ is a polynomial with positive coefficients. If we solve our differential equation for non-negative initial data $\mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}_{\geq 0}^n$, then the solution always stays in the convex polyhedral cone $\mathbf{x}_0 + \{\sum_{i=1}^m \lambda_i \mathbf{n}_i \mid \forall i : \lambda_i \geq 0\}$ where the vectors \mathbf{n}_i are the columns of the matrix N . Indeed, in this case the tangent vector $\dot{\mathbf{x}}(t)$ along the trajectory is trivially always a non-negative linear combination of the columns of N .

Lemma 2. Let $\mathbf{v}^T \cdot \mathbf{x} = \text{Const}$ for some vector $\mathbf{v} \in \mathbb{R}^n$ be a linear conservation law of a pseudolinear system $\dot{\mathbf{x}} = N\psi(\mathbf{x})$ with a surjective ψ . Then $\mathbf{v} \in \ker N^T$. Conversely, any vector $\mathbf{v} \in \ker N^T$ induces a linear conservation law.

Proof. Let us first assume that $\mathbf{v} \in \ker N^T$. Then

$$\frac{d}{dt}(\mathbf{v}^T \cdot \mathbf{x}) = \mathbf{v}^T N\psi(\mathbf{x}) = (N^T \mathbf{v})^T \psi(\mathbf{x}) = 0.$$

If $\mathbf{v}^T \cdot \mathbf{x} = \text{Const}$ is a conservation law, then differentiation with respect to time yields $(N^T \mathbf{v})^T \psi(\mathbf{x}) = 0$. Since we assume that the function ψ is surjective, this implies that $N^T \mathbf{v} = 0$. \square

By a classical result in linear algebra (the four “fundamental spaces” of a matrix), we have the direct sum decomposition $\mathbb{R}^n = \text{im } N \oplus \ker N^T$ which is even an orthogonal decomposition with respect to the standard scalar product. Hence we may consider Lemma 1 as a corollary to Lemma 2, as the above described invariant manifolds are simply defined by all the linear conservation laws produced by Lemma 2.⁴

Remark 2. According to the paper by Gatermann and Huber, one speaks in chemistry of a conservation law only in the case that $v_i \geq 0$ for all components v_i of the vector \mathbf{v} . In mathematics, we are not aware of such a restriction and we cannot see any physical reason to impose it.

⁴ Note that the condition of surjectivity is always satisfied, if ψ consists of $m \geq n$ different monomials.

3.1 Reduction to Invariant Manifolds

If a dynamical system admits invariant manifolds, we may consider a system of lower dimension by reducing to such a manifold. However, in general it may not be possible to derive explicitly the reduced system. Nevertheless, for many purposes like stability or bifurcation analysis one can easily reduce to smaller matrices. The following result describes such a reduction process in the linear case. It represents an elementary exercise in basic linear algebra. In order to avoid the inversion of matrices, we consider here \mathbb{R}^n as a Euclidean space with respect to the standard scalar product.

Lemma 3. *Let A be the matrix of a linear mapping $\mathbb{R}^n \rightarrow \mathbb{R}^n$ for the standard basis and $\mathcal{U} \subseteq \mathbb{R}^n$ a k -dimensional A -invariant subspace. If the columns of the matrix $W \in \mathbb{R}^{n \times k}$ define an orthonormal basis of \mathcal{U} , then the restriction of the mapping to the subspace \mathcal{U} with respect to the basis defined by W is given by the matrix $W^T A W \in \mathbb{R}^{k \times k}$.*

Proof. Considered as a linear map $\mathbb{R}^k \rightarrow \mathcal{U} \subseteq \mathbb{R}^n$, the matrix W defines a parametrization of \mathcal{U} with inverse $W^T : \mathcal{U} \rightarrow \mathbb{R}^k$. Indeed, $W^T W = \mathbb{1}_k$, since the columns of W are orthonormal. If $\mathbf{v} \in \mathcal{U}$, then $\mathbf{v} = W\mathbf{w}$ for some vector $\mathbf{w} \in \mathbb{R}^k$ and thus $W^T \mathbf{v} = (W^T W)\mathbf{w} = \mathbf{w}$ implying that $(W W^T)\mathbf{v} = W\mathbf{w} = \mathbf{v}$, i. e. the matrix $W W^T \in \mathbb{R}^{n \times n}$ describes $\text{id}_{\mathcal{U}}$. By standard linear algebra, the matrix $W^T A W$ describes therefore the restriction of A to \mathcal{U} . \square

As a simple application, we note that in the case of a pseudolinear system $\dot{\mathbf{x}} = N\psi(\mathbf{x})$ the stability properties of an equilibrium \mathbf{x}_e of the pseudolinear system $\dot{\mathbf{x}} = N\psi(\mathbf{x})$ are determined by the eigenstructure of the reduced Jacobian

$$J = W^T N \text{Jac}(\psi(\mathbf{x}_e)) W \in \mathbb{R}^{k \times k}$$

where the columns of W form an orthonormal basis of $\text{im } N$. If parameters are present, then also for a bifurcation analysis the eigenstructure of this matrix and not of the full Jacobian (which is an n -dimensional matrix) are relevant.

3.2 Stability and Bifurcations for Semi-Explicit DAEs

The considerations indicated in the last section can be easily extended to more general situations, as they appear in the theory of DAEs. For simplicity (and as it suffices for our purposes), we assume that we are dealing with an autonomous system in the semi-explicit form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad 0 = \mathbf{g}(\mathbf{x}) \tag{1}$$

where $\mathbf{f} : \mathbb{R}^n \rightarrow \mathbb{R}^n$ and $\mathbf{g} : \mathbb{R}^n \rightarrow \mathbb{R}^{n-k}$. Furthermore, we assume that the above system of ordinary differential equations is involutive, i. e. that it contains already all its integrability conditions. This assumption is equivalent to the existence of a matrix valued function $M(\mathbf{x})$ such that

$$\text{Jac}(\mathbf{g}(\mathbf{x})) \cdot \mathbf{f}(\mathbf{x}) = M(\mathbf{x}) \cdot \mathbf{g}(\mathbf{x}). \tag{2}$$

Thus one may say that the components of \mathbf{g} are *weak* conservation laws, as their time derivatives vanish modulo the constraint equations $\mathbf{g}(\mathbf{x}) = 0$.

Let \mathbf{x}_e be an equilibrium of (1), i. e. we have $\mathbf{f}(\mathbf{x}_e) = 0$ and $\mathbf{g}(\mathbf{x}_e) = 0$. We introduce the real matrices

$$A = \text{Jac}(\mathbf{f}(\mathbf{x}_e)) \in \mathbb{R}^{n \times n}, \quad B = \text{Jac}(\mathbf{g}(\mathbf{x}_e)) \in \mathbb{R}^{(n-k) \times n}.$$

For simplicity, we assume in the sequel that the matrix B has full rank (or, in other words, that our algebraic constraints are independent) and thus that $\ker B$ is a k -dimensional subspace. The proof of the next result demonstrates clearly why the assumption that the system (1) is involutive is important, as the relation (2) is crucial for it.

Lemma 4. *The subspace $\ker B$ is A -invariant.*

Proof. Set $\bar{M} = M(\mathbf{x}_e)$. Differentiating (2) and evaluating the result at $\mathbf{x} = \mathbf{x}_e$ yields the relation $BA = \bar{M}B$. Hence, if $\mathbf{v} \in \ker B$, then also $A\mathbf{v} \in \ker B$ since $B(A\mathbf{v}) = \bar{M}(B\mathbf{v}) = 0$. \square

Remark 3. In the case that (1) is a linear system, i. e. by assuming that $\mathbf{x}_e = 0$ we may write $\mathbf{f}(\mathbf{x}) = A\mathbf{x}$ and $\mathbf{g}(\mathbf{x}) = B\mathbf{x}$, we can easily revert the argument in the proof of Lemma 4 and thus conclude that now (1) is involutive, if and only if $\ker B$ is A -invariant.

Proposition 1. *Let the columns of the matrix $W \in \mathbb{R}^{n \times k}$ define an orthonormal basis of $\ker B$. The linear stability of the equilibrium \mathbf{x}_e is then decided by the eigenstructure of the matrix $W^T A W$.*

Proof. Linearisation around the equilibrium \mathbf{x}_e yields the associated variational system $\dot{\mathbf{z}} = A\mathbf{z}$, $B\mathbf{z} = 0$. We complete W to an orthogonal matrix \widehat{W} by adding some further columns and perform the coordinate transformation $\mathbf{z} = \widehat{W}\mathbf{y}$. This yields the system $\dot{\mathbf{y}} = \widehat{W}^T A \widehat{W}\mathbf{y}$, $B\widehat{W}\mathbf{y} = 0$. Since by construction the columns of W span $\ker B$, the second equation implies that only the upper k components of \mathbf{y} may be different of zero. Furthermore, Lemma 4 implies that the matrix $\widehat{W}^T A \widehat{W}\mathbf{y}$ is in block triangular form with the left upper $k \times k$ block given by $W^T A W$. If we denote the upper part of \mathbf{y} by $\tilde{\mathbf{y}}$, we obtain thus the equivalent reduced system $\dot{\tilde{\mathbf{y}}} = W^T A W \tilde{\mathbf{y}}$ which implies our claim. \square

Remark 4. Let $\mathbf{v} \in \mathbb{R}^k$ be a (generalized) eigenvector of the reduced matrix $W^T A W$, i. e. we have $(W^T A W - \lambda \mathbb{1}_k)^\ell \mathbf{v} = 0$ for some $\ell > 0$ and $\lambda \in \mathbb{R}$. Since $W^T W = \mathbb{1}_k$ and $W W^T$ defines the identity map on $\ker B$ (see the proof of Lemma 3), we obtain $W^T (A - \lambda \mathbb{1}_n)^\ell W \mathbf{v} = 0$ implying that $W \mathbf{v} \in \mathbb{R}^n$ is a (generalized) eigenvector of A for the same eigenvalue λ , since the matrix W^T defines an injective map. Thus every eigenvalue of the reduced matrix $W^T A W$ is also an eigenvalue of A .

Remark 5. It is also not difficult to interpret the remaining (generalized) eigenvectors of A . By construction, they are transversal to the constraint manifold

defined by $\mathbf{g}(\mathbf{x}) = 0$ and they describe whether this manifold is attractive or repellent for the flow of the unconstrained system $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$. While this is for example of considerable importance for the numerical integration of (1), as it describes the drift off the constraint manifold due to rounding and discretization errors, it has no influence on the stability of the exact flow of (1).

The irrelevance of the remaining (generalized) eigenvectors of A becomes also apparent from the following argument. Recall that the differential part of (1) defines what is often called an *underlying differential equation* for the DAE, i. e. an unconstrained differential equation which possesses for initial data satisfying the constraints the same solution as the DAE. Consider now the modified system obtained by adding to the right hand side of the differential part an arbitrary linear combination of the algebraic part. It is easy to see that the arising DAE (which simply has a different underlying equation)

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}) + L(\mathbf{x})\mathbf{g}(\mathbf{x}), \quad 0 = \mathbf{g}(\mathbf{x}),$$

where $L(\mathbf{x})$ is a matrix valued function of appropriate dimensions, possesses exactly the same solutions as (1); in particular \mathbf{x}_e is still an equilibrium. If we proceed as above with the linear stability analysis of \mathbf{x}_e , the matrix B remains unchanged, whereas A is transformed into the modified matrix $\tilde{A} = A + \bar{L}B$ with $\bar{L} = L(\mathbf{x}_e)$. Obviously, $\ker B$ is also \tilde{A} -invariant and furthermore $W^T \tilde{A}W = W^T A W$, if the columns of W form a basis of $\ker B$ as in Proposition 1.

Thus all (generalized) eigenvectors lying in $\ker B$ are equal for A and \tilde{A} and thus the stability of \mathbf{x}_e is not affected by this transformation. However, the remaining (generalized) eigenvectors may change arbitrarily. One can for example show that by a suitable choice of the matrix L one may always achieve that the constraint manifold becomes attractive.

4 Algorithms for Computing Hopf Bifurcations in Chemical Reaction Networks Using Reaction Coordinates

In this section we present an algorithmic approach for computing the Hopf bifurcation in chemical systems. We consider here systems with at least three species (dimension ≥ 3) and with or without conservation laws. Two and various three dimensional systems can be analyzed in the concentration space without carrying out the coordinate transformation. The approach based mainly on three methods already presented in this paper: stoichiometric network analysis, method for reduction of manifold for systems with conservation laws and technique of quantifier elimination on real closed field. The following pseudo code (figure 1) and subsections outline the mainly steps of our algorithm:

4.1 Pre-processing: step 1

For starting the analysis of a chemical network we need two significant pieces of information to describe all reaction laws. The first information describes the occurrence of the species in each reaction. This can be presented by a stoichiometric

Input: a chemical reaction network \mathcal{N} with $\dim(\mathcal{N}) \geq 3$.

Output: statement about the existence of Hopf-bifurcation.

Begin

- 1: Generate the stoichiometric matrix \mathcal{S} and kinetic matrix \mathcal{K} from the reaction network.
- 2: Compute the minimal set \mathcal{E} of the vectors generating the flux cone.
- 3: **If** $size(\mathcal{E}) > 2$ compute all two faces and all three faces of the flux cone (subsystems).
Else consider the linear combination of the resulting vectors as the only subsystem.

For each subsystem \mathcal{N}_i **do**

- 4: Compute the transformed jacobian \mathcal{J}_i of \mathcal{N}_i using \mathcal{K} , \mathcal{S} and flux cone coordinates
- 5: **If** \mathcal{J}_i is singular compute the reduced manifold of \mathcal{J}_i calling the result also \mathcal{J}_i
- 6: Compute the characteristic polynomial of \mathcal{J}_i
- 7: Compute the Hurwitz determinant of \mathcal{J}_i
- 8: Compute the Hopf-existence condition for \mathcal{N}_i
- 9: Generate first-order existentially quantified formula \mathcal{F}_i using Hopf-existence condition, the constraints on concentrations and the constraints on the cone coordinates
- 10: Reduce and simplify the generated formulae

If exists a formula $\mathcal{F}_i = true$ **return** "There is Hopf bifurcation".

End

Fig. 1. Algorithms for Computing Hopf Bifurcations in Chemical Reaction Networks Using flux Coordinates

matrix \mathcal{S} , where the species build the rows and the reactions build the columns. Each entry of the matrix present the difference of the number of produced and consumed molecules of the corresponding specie in the corresponding reaction. The second information describes the velocities of the reactions. This can be presented by flux vector $v(x, k)$ or by kinetic matrix \mathcal{K} . The entries of this matrix present the information whether specie is a reactant (entry = stoichiometric coefficient of specie) and effects consequently the velocity of the reaction or not (entry = 0). To enable the computational analysis of a chemical Networks the reactions should be presented in a format that enables its accurate representation and allows the computational extraction of needed data. For our computations we use the XML based and in biological research widely used format SBML [?]. As Pre-processing step we parse the SBML file presenting the chemical network using Java library JSBML [?] to generate the stoichiometric matrix and kinetic matrix.

4.2 Geometrical Computations: step 2 and 3

To analyse a chemical system one is interested in the stationary reaction behaviour, which is observable in experiments, i.e one investigates the solution set of

$$\mathcal{S}.v(x, k) = 0. \quad (3)$$

The set of stationary solutions is usually considered in the concentration space \mathbb{R}_+^n , i.e in the variables x . Instead of the variables $x \in \mathbb{R}_+^n$ we will consider the variables z representing $v(x, k)$ which are called reaction coordinates or reaction rate coordinates and thus we consider the set of stationary solutions in the space of reaction rates \mathbb{R}_+^l . A first advantage ist that the Jacobian in the space of reaction rates is of the form [1, ?]:

$$Jac(x) = \widehat{Jac}(z).diag(1/x_1, \dots, 1/x_m). \quad (4)$$

As long as we split each reversible reaction into two irreversible reactions (forward and backward directions) the flux through this reactions must be greater or equal to zero, i.e

$$v(x, k) \geq 0 \quad (5)$$

The set of all possible stationary solutions over the network \mathcal{N} that fulfil the equation (3) and the constraint (5) defines the convex polyhedral cone *flux cone* [?, ?] and determine a minimal generating vectors \mathcal{E} called *extreme rays* or *extreme currents*. Each vector z can then as linear combination of the vector set \mathcal{E} with nonnegative coefficients. To compute the extreme currents we need to integrate that allows to deal with Polyhedral Computations. Thus we use *polymake* in the step 2 of our algorithm to compute the extreme currents \mathcal{E} for a generating stoichiometric matrix \mathcal{S} . *polymake* is an open source software tool written in Perl and C++ and designed for the algorithmic treatment of polytopes and polyhedra [?].

4.3 Transformation of Jacobian: step 4

4.4 Jacobian of Reduced Manifold : step 5

4.5 Generating Quantified Formula : step 6-9

4.6 Reducing Quantified Formula : step 10

5 Computation Examples

5.1

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This problem has already been investigated using its formulation in reaction coordinates in [3]. Using currently available quantifier elimination packages the problem could not be solved in its parametric form. Only when using the existential closure on the parameters it could be shown by successful quantifier eliminations performed in REDLOG that there exist positive parameters for which there exists a Hopf bifurcations fixed point in the positive orthant. When redoing the experiments we found that the situation described in [3] still applies.

5.2

Jacobian matrix is singular

hence in classical sense no Hopf bifurcations
but in reduced system following result

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