Disguised Toric Dynamical Systems

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SISSA Junior Math Days 2022

December 6, 2022

SISSA

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[1]Disguised toric dynamical systems. J. Pure Appl. Algebra 226 (2022), no. 8, Paper No. 107035, 24 pp.

Motivation

Nonlinear dynamical systems: infectious diseases, dynamics of concentrations in biochemical reaction networks, dynamics of populations for species.

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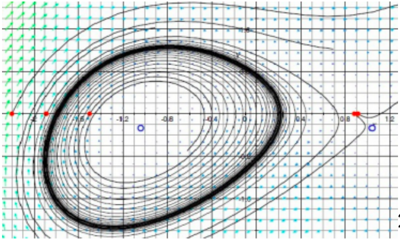
Second part of Hilbert 16th problem

Motivation - Hilbert 16th Problem II

What can we say about the number and location of Poincaré limit cycles of a planar polynomial vector field of degree n?


[2]

$$\frac{dx}{dt} = P(x,y), \ \frac{dy}{dt} = Q(x,y),$$

where $P, Q : \mathbb{R}^2 \to \mathbb{R}$, polynomials of degree n.

[2] "Limit Cycles, Abelian Integral and Hilbert's Sixteenth Problem", Marco Uribe, Hossein Movasati, https://impa.br/wp-content/uploads/2017/08/31CBM_06.pdf

Hilbert 16th Problem II

- Finiteness - proven.

Hilbert 16th Problem II

- Finiteness - proven.

- Many open questions (even in the quadratic case). E.g., is it true that the number of limit cycles is bounded by a constant depending only on n?

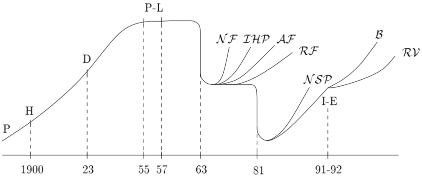
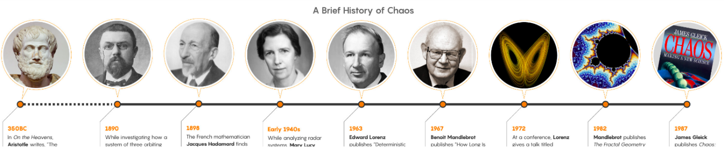


FIGURE 1. Summary of the history of Hilbert's 16th problem. Roman letters stand for names, calligraphic ones for new developments. P—Poincaré; H—Hilbert, D—Dulac, P-L—Petrovskii-Landis, E—Ecalle, I—Ilyashenko; $\mathcal{NF}$—normal forms, $\mathcal{AF}$—analytic foliations, $\mathcal{IHP}$—infinitesimal Hilbert 16th problem, $\mathcal{NSP}$—nonlinear Stokes phenomena, $\mathcal{RF}$—resurgent functions, $\mathcal{B}$—bifurcations, $\mathcal{RV}$—restricted versions of the Hilbert 16th problem.

History of Hilbert 16th problem (Ilyashenko, 2002)

Dynamical properties of nonlinear systems

Possible behaviours of the systems: uniqueness and stability of the steady state, bistability, oscillation or even *chaos*[3] - the butterfly effect of the Lorenz systems.



[3] www.quantamagazine.org/hidden-heroines-of-chaos-ellen-fetter-and-margaret-hamilton-20190520/

Toric dynamical systems

- remarkably stable;
- also called complex balanced / vertex balanced dynamical systems Yu and Craciun, 2018;
- family of polynomial dynamical systems inspired by **reaction networks**, under the assumption of mass-action kinetics;
- introduced by Horn and Jackson in 1972;

Toric dynamical systems

Dynamical aspects

- known to be locally stable;
- exceptionally strong dynamical properties;
- conjectured: this equilibrium is **globally** asymptotically stable.

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Algebraic aspects

- steady state set is a toric variety;
- monomial parametrization;
- tools from real algebraic geometry, computational algebraic geometry, commutative algebra.

Existence of toric dynamical systems

Good news:

- Under some algebraic conditions on the parameters, the system is toric.
- Set of parameters that satisfies the conditions is called the *toric locus*; it is a toric variety (Craciun et al., 2009).

Existence of toric dynamical systems

Good news:

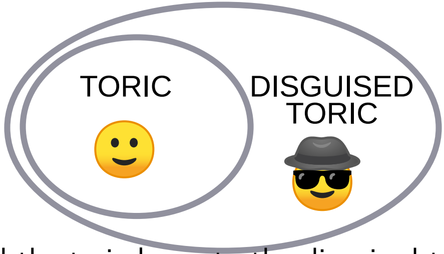
- Under some algebraic conditions on the parameters, the system is toric.
- Set of parameters that satisfies the conditions is called the *toric locus*; it is a toric variety (Craciun et al., 2009).

Bad news:

- The toric locus is usually a set of Lebesgue measure zero in the space of parameters.

Main results - I, [Moncusí, Craciun, and Sorea, 2022]

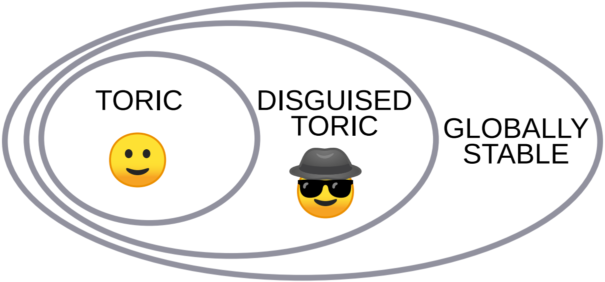
The nice properties of toric dynamical systems are true for a larger class: **disguised toric dynamical systems!**



- we extend the toric locus to the disguised toric locus with positive Lebesgue measure;
- we leverage dynamically equivalent systems (Craciun, Jin, and Yu, 2020);
- an algorithm to detect the disguised toric locus.

Main results - II, [Moncusí, Craciun, and Sorea, 2022]

∃ globally stable systems that are not disguised toric?



Overview

Background: Reaction Networks
Toric dynamical systems
–> dynamics and algebra
–> toric locus and deficiency

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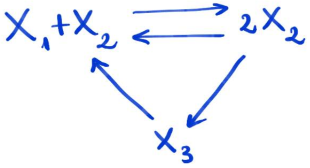
Main contribution: Disguised toric dynamical systems
–> larger disguised toric locus
–> leverage dynamical equivalence
–> disguised toric vs globally stable
–> algorithm

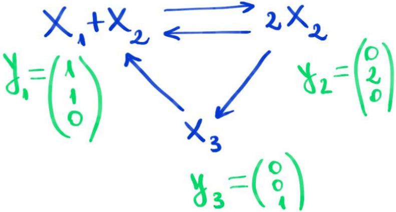
Reaction Networks

Chemical complexes: formal linear combinations of species.



4 reactions (edges);
3 species (X_1, X_2, X_3);
3 complexes (vertices: $X_1 + X_2, 2X_2, X_3$).

Euclidean Embedded Graphs (E-graphs)



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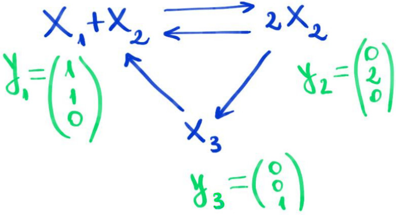
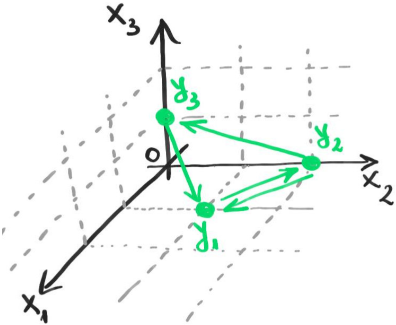
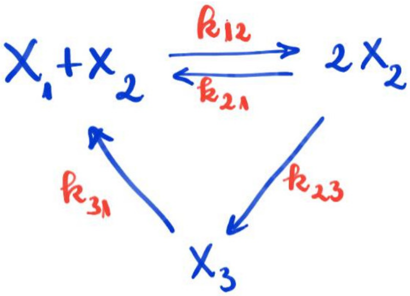




Mass-action kinetics and polynomial ODEs on $\mathbb{R}^n_{>0}$



$$\frac{\mathrm{d}}{\mathrm{d}\,t}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = k_{12}x_1x_2\begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix} + k_{21}x_2^2\begin{pmatrix} 1 \\ -1 \\ 0 \end{pmatrix} + k_{23}x_2^2\begin{pmatrix} 0 \\ -2 \\ 1 \end{pmatrix} + k_{31}x_3\begin{pmatrix} 1 \\ 1 \\ -1 \end{pmatrix}.$$

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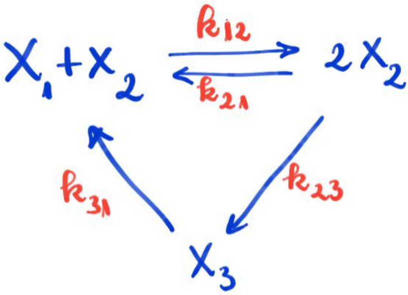

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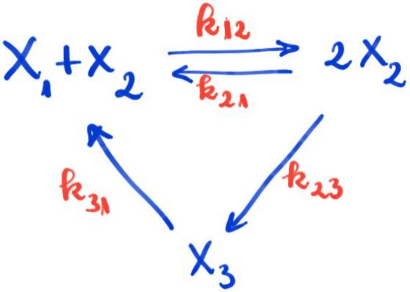
Definition

The dynamical system generated by G and $\mathrm{k} \in \mathbb{R}^E_{>0}$ *is the following:*

$$\frac{d\,\mathrm{x}}{d\,t} = F_{G,\mathrm{k}}(\mathrm{x}), \ \textit{where } F_{G,\mathrm{k}}(\mathrm{x}) := \sum_{\mathrm{y}\to\mathrm{y}'\in E} k_{\mathrm{y}\to\mathrm{y}'}\mathrm{x}^{\mathrm{y}}(\mathrm{y}'-\mathrm{y}) \tag{1}$$

Vertex balanced steady states

A steady state $\hat{x} = (\hat{x}_1, \hat{x}_2, \hat{x}_3) \in \mathbb{R}^3_{>0}$ is **vertex-balanced** if, for every vertex v, the flux into v is equal to the flux out of v.



$$\begin{aligned} k_{21}\hat{x}_2^2 + k_{31}\hat{x}_3 &= k_{12}\hat{x}_1\hat{x}_2 \\ k_{21}\hat{x}_2^2 + k_{23}\hat{x}_2^2 &= k_{12}\hat{x}_1\hat{x}_2 \\ k_{23}\hat{x}_2^2 &= k_{31}\hat{x}_3. \end{aligned}$$

Similar to Kirchhoff's Junction Rule.

Toric locus

Polynomial equations with coefficients in $\mathbb{R}_{>0}$.

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Toric locus: set of $k_{ij} > 0$ s.t. there exists a VB solution $\hat{x}$.

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- real quantifier elimination,
- elimination ideals...

Vertex balanced/Toric dynamical systems

Theorem (Horn and Jackson, 1972)

If a mass-action system has a VB steady state x^*, *then:*

- *all positive steady states are VB, and there is exactly one steady state up to conservation laws;*
- $\exists$ *a strictly convex Lyapunov function of this system, with global minimum at* $x = x^*$.
- *every positive steady state is locally asymptotically stable (up to conservation laws).*

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Conjecture (Horn and Jackson, 1972)

Vertex balanced equilibria are globally asymptotically stable.

Toric dynamical systems (dynamics)

Global attractor conjecture (Horn 1974): toric dynamical systems are globally stable within each positive stoichiometric compatibility class, that is, they have a globally attracting point (up to conservation laws).

[4] Gheorghe Craciun. *Toric Differential Inclusions and a Proof of the Global Attractor Conjecture*. url: https://arxiv.org/abs/1501.02860

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- proven under mild hypotheses;
- a recently proposed proof in all generality by Craciun (2015) [4].

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Toric dynamical systems (algebraic)

Theorem (Gatermann, 2001)

The steady state set of a toric dynamical system is a toric variety.

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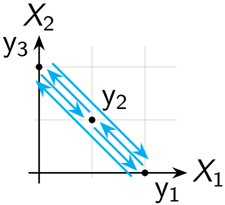
Theorem (Craciun, Dickenstein, Shiu, Sturmfels, 2009)

The moduli space associated to any toric dynamical system is a toric variety (after a change of coordinates).



$$(k_{21}k_{31}+k_{32}k_{21}+k_{23}k_{31})(k_{13}k_{23}+k_{21}k_{13}+k_{12}k_{23})-(k_{12}k_{32}+k_{13}k_{32}+k_{31}k_{12})^2=0.$$

Toric locus - Example

New coordinates, given by the Matrix-Tree Theorem:
$K_1 := k_{21}k_{31} + k_{32}k_{21} + k_{23}k_{31}$;
$K_2 := k_{12}k_{32} + k_{13}k_{32} + k_{31}k_{12}$;
$K_3 := k_{13}k_{23} + k_{21}k_{13} + k_{12}k_{23}$.
In the new coordinates, the toric locus: $K_1K_3 - K_2^2 = 0$.

$$(k_{21}k_{31}+k_{32}k_{21}+k_{23}k_{31})(k_{13}k_{23}+k_{21}k_{13}+k_{12}k_{23})-(k_{12}k_{32}+k_{13}k_{32}+k_{31}k_{12})^2 = 0.$$

For most networks, the set in parameter space that gives rise to toric systems (i.e., the **toric locus**) has *Lebesgue measure zero*.

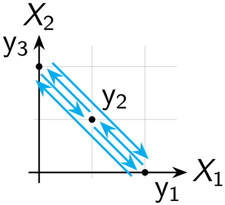
Deficiency of a Reaction Network

Definition

Let us consider a Euclidean embedded graph G. Denote by s the dimension of the stoichiometric subspace $\mathcal{S}$, by l the number of connected components of G, and by m the number of vertices of G. The deficiency of G is

$$\delta := m - s - l. \tag{2}$$

For example, the complete digraph with three nodes, $\delta = 1$:



Toric locus

Theorem (Craciun, Dickenstein, Shiu, Sturmfels, 2009)

The codimension of the toric locus in the k-space equals the deficiency.

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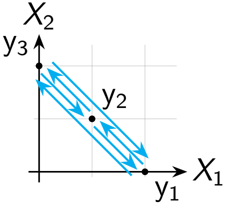

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Disguised toric dynamical system

Definition 1 (Craciun, Jin, and Yu, 2020)

Two reaction networks (G, k) and (G', k') are **dynamically equivalent** if they generate the same ODE

$$\sum_{\mathrm{y}\to\mathrm{y}'\in E_G} k_{\mathrm{y}\to\mathrm{y}'}\mathrm{x}^{\mathrm{y}}(\mathrm{y}'-\mathrm{y}) = \sum_{\mathrm{y}\to\mathrm{y}'\in E_{G'}} k'_{\mathrm{y}\to\mathrm{y}'}\mathrm{x}^{\mathrm{y}}(\mathrm{y}'-\mathrm{y}).$$

Definition 2 (Brustenga, Craciun, S., 2022)

A particular dynamical system

$$\frac{\mathrm{d}\,\mathrm{x}}{\mathrm{d}\,t} = f(\mathrm{x})$$

has a realization using an E-graph $G = (V, E)$ if there exists $\mathrm{k} \in \mathbb{R}^{E}_{>0}$ with

$$F_{G,\mathrm{k}}(\mathrm{x}) = f(\mathrm{x}) \text{ for all } \mathrm{x} \in \mathbb{R}^{n}_{\geq 0}.$$

Definition 3 (Brustenga, Craciun, S., 2022)

Given a dynamical system

$$\frac{\mathrm{d}\,\mathrm{x}}{\mathrm{d}\,t} = f(\mathrm{x}) \text{ on } \mathrm{x} \in \mathbb{R}^n_{\geq 0}, \tag{3}$$

we say that it is a *disguised toric dynamical system* if there exist an E-graph $G = (V, E)$ and $\mathrm{k} \in \mathbb{R}^E_{>0}$ such that

$$f(\mathrm{x}) = F_{G,\mathrm{k}}(\mathrm{x}) \text{ for all } \mathrm{x} \in \mathbb{R}^n_{\geq 0}$$

and the couple (G, k) satisfies the complex balanced condition. When (3) is a disguised toric dynamical system, we also say that it *has a complex balanced realization using the graph G*.

$$K(G) := \{\mathrm{k} \in \mathbb{R}^E_{>0} \mid \text{ the system generated by } (G, \mathrm{k}) \text{ is toric}\},$$

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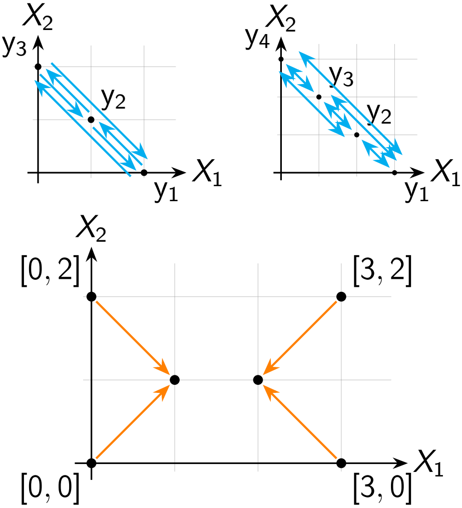
$$\hat{K}(G) := \{\mathrm{k} \in \mathbb{R}^{E}_{>0} \mid \text{ the system generated by } (G, \mathrm{k}) \text{ is disguised toric}\}.$$

Disguised Toric Dynamical Systems



Triangle on a line

The 3 nodes on a line graph is a disguised toric dynamical system.

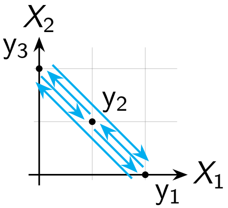


Figure: Triangle on a line G.

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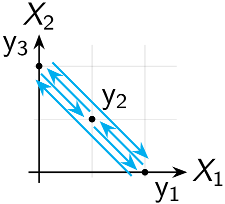


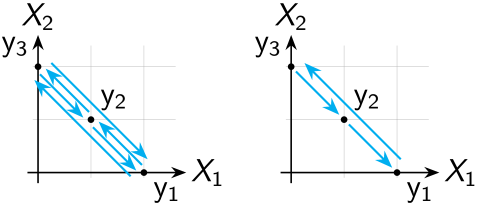
Figure: Triangle on a line G.

Deficiency $\delta = 1$, so the toric locus is a codimension one variety.

Theorem 4 (Brustenga, Craciun, S., 2022)

The disguised toric locus of the complete graph on three nodes is the whole space of rate constants.

Sketch of the proof of Theorem 4 - Step 1



- reduce the E-graph G to have only one reaction per source;

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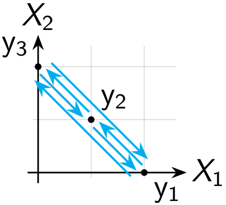

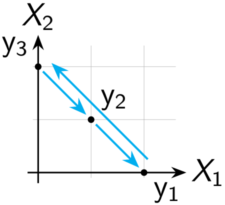

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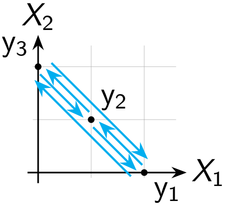

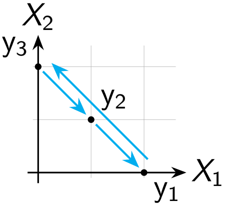

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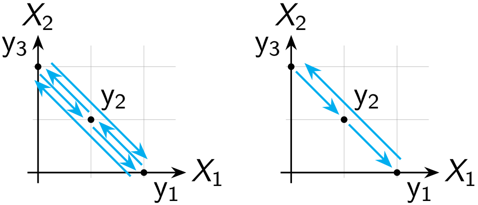

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- realize the system generated by (G, k) by a cycle directed graph G^* over $\mathrm{y}_1, \mathrm{y}_2, \mathrm{y}_3$;

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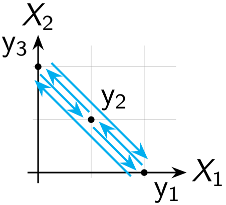

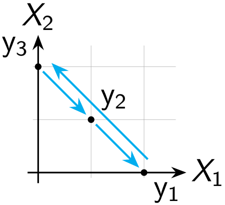

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  $\mathbf{u}_i := \sum_{\mathbf{y}_i \to \mathbf{y}_j \in E} k_{ij}(\mathrm{y}_j - \mathrm{y}_i)$;

  $\mathbf{u_1} = k_\mathbf{1}^* \begin{pmatrix} -2 \\ 2 \end{pmatrix}$; $\mathbf{u_3} = k_\mathbf{3}^* \begin{pmatrix} 1 \\ -1 \end{pmatrix}$; $\mathbf{u_2} = k_\mathbf{2}^* \begin{pmatrix} 1 \\ -1 \end{pmatrix}$.
- realize the system generated by (G, k) by a cycle directed graph G^* over $\mathrm{y}_1, \mathrm{y}_2, \mathrm{y}_3$;
- by construction, the dynamical systems generated by G, k and by G^*, $\mathrm{k}^* = (k_1^*, k_2^*, k_3^*) \in \mathbb{R}_{>0}^{E^*}$ are equal;

Sketch of the proof of Theorem 4 - Step 2

Goal: prove that the disguised toric locus $\hat{K}(G^*)$ is $\mathbb{R}^3_{>0}$.

- we realize the system generated by G^*, k^* using the graph G;
- fix k^* and consider the E-graph $\hat{G} = G$ and the rate constants $\hat{\mathrm{k}}$ given by $(a, b, c > 0)$

$$\hat{k}_{32} := \frac{1}{1+a} k_3^* \qquad \hat{k}_{21} := k_2^* + b \qquad \hat{k}_{12} := 2\frac{c}{1+c} k_1^*$$
$$\hat{k}_{31} := \frac{a}{2(1+a)} k_3^* \qquad \hat{k}_{23} := b \qquad \hat{k}_{13} := \frac{1}{1+c} k_1^* \tag{4}$$

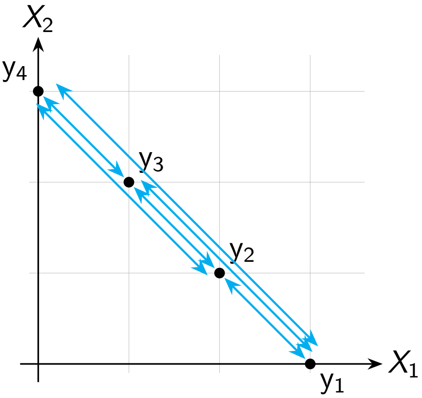
- $$K(\hat{G}) = \{(\hat{k}_{21}\hat{k}_{31} + \hat{k}_{32}\hat{k}_{21} + \hat{k}_{23}\hat{k}_{31})(\hat{k}_{13}\hat{k}_{23} + \hat{k}_{21}\hat{k}_{13} + \hat{k}_{12}\hat{k}_{23}) - (\hat{k}_{12}\hat{k}_{32} + \hat{k}_{13}\hat{k}_{32} + \hat{k}_{31}\hat{k}_{12})^2 = 0\}.$$

- $$\varphi(a,b,c) := \left(\frac{k_3^*(b+k_2^*)}{a+1} + \frac{(ak_3^*)(b+k_2^*)}{2(a+1)} + \frac{b(ak_3^*)}{2(a+1)}\right)\left(\frac{k_1^*(b+k_2^*)}{c+1} + \frac{bk_1^*}{c+1} + \frac{b(2ck_1^*)}{c+1}\right) - \\ - \left(\frac{k_1^* k_3^*}{(a+1)(c+1)} + \frac{k_3^*(2ck_1^*)}{(a+1)(c+1)} + \frac{(ak_3^*)(2ck_1^*)}{(2(a+1))(c+1)}\right)^2. \tag{5}$$

- there exists $a_0, b_0, c_0 > 0$ such that $\varphi(a_0, b_0, c_0) = 0$ (intermediate value theorem).

Quadrilateral on a line

Consider the complete directed graph G on four nodes:



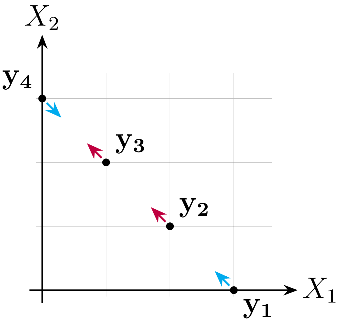
$$\frac{d}{dt}\begin{pmatrix}x_1\\x_2\end{pmatrix} = \mathbf{u}_1 x_1^3 + \mathbf{u}_2 x_1^2 x_2 + \mathbf{u}_3 x_1 x_2^2 + \mathbf{u}_4 x_2^3 =$$

$$= (k_{12} + 2k_{13} + 3k_{14})\begin{pmatrix}-1\\1\end{pmatrix} x_1^3 +$$

$$+ (k_{21} - k_{23} - 2k_{24})\begin{pmatrix}1\\-1\end{pmatrix} x_1^2 x_2 +$$

$$+ (2k_{31} + k_{32} - k_{34})\begin{pmatrix}1\\-1\end{pmatrix} x_1 x_2^2 +$$

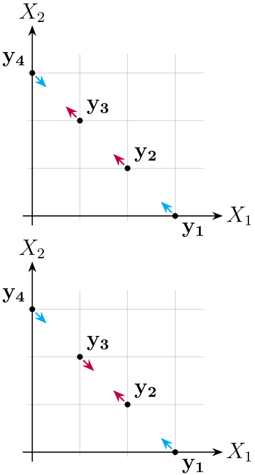
$$+ (3k_{41} + k_{43} + 2k_{42})\begin{pmatrix}1\\-1\end{pmatrix} x_2^3.$$



$$k_1^* := k_{12} + 2k_{13} + 3k_{14};$$
$$k_4^* := 3k_{41} + 2k_{42} + k_{43}.$$

$$k_2^* := \begin{cases} k_{21} - k_{23} - 2k_{24} & \text{if } k_{21} - k_{23} - 2k_{24} > 0 \\ -k_{21} + k_{23} + 2k_{24} & \text{otherwise} \end{cases}$$

$$k_3^* := \begin{cases} 2k_{31} + k_{32} - k_{34} & \text{if } 2k_{31} + k_{32} - k_{34} > 0 \\ -2k_{31} - k_{32} + k_{34} & \text{otherwise.} \end{cases}$$

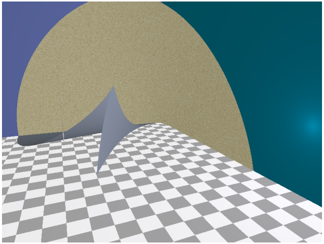


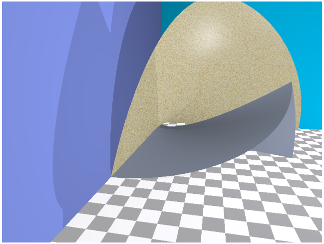
X_2
$\mathbf{y_4}$
$\mathbf{y_3}$
$\mathbf{y_2}$
$\mathbf{y_1}$
X_1

Theorem 5 (Brustenga, Craciun, S., 2022)

The complete digraph on four nodes is disguised toric if and only if

1. k *belongs to a single-sign-change chamber or*
2. k *belongs to the 4th chamber and* $k_3^* k_2^* \leq k_4^* k_1^*$.





Sketch of the proof of Theorem 5 (2)

Fix k in $\mathcal{C}_4$.
The system generated by G, k is equal to the system generated by G^* (with one reaction per source) and k*.
Consider $\hat{G}$ obtained by the detail-balance completion which contains the same source vertices as the E-graph G^*.

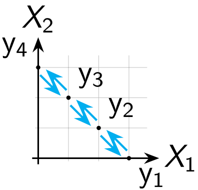


Figure: Detailed balanced extension of $\mathcal{C}_4$.

Consider the rate constants $\hat{\mathrm{k}}$ given by

$$\hat{k}_{12} := k_1^* \qquad \hat{k}_{23} := a \qquad \hat{k}_{43} := k_4^*$$
$$\hat{k}_{21} := k_2^* + a \qquad \hat{k}_{32} := b \qquad \hat{k}_{34} := k_3^* + b$$

where $a, b > 0$.

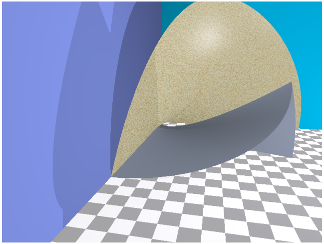
1. show that for every k^* satisfying $k_3^* k_2^* \leq k_4^* k_1^*$, there exist $a, b > 0$ for which the couple $(\hat{G}, \hat{\mathrm{k}})$ satisfies the detailed balance condition (and then also the complex balanced condition).
2. show that if the system generated by G^*, k^* is disguised toric, then the condition $k_3^* k_2^* \leq k_4^* k_1^*$ is necessarily satisfied.

Globally stable but not disguised toric

Proposition (Brustenga, Craciun, S., 2022)

The dynamical system in the fourth chamber is globally stable iff

$$(k_3^* k_2^*)^2 - 4k_4^*(k_2^*)^3 - 4(k_3^*)^3 k_1^* - 27(k_4^* k_1^*)^2 + 18k_4^* k_3^* k_1^* k_2^* < 0. \quad (6)$$



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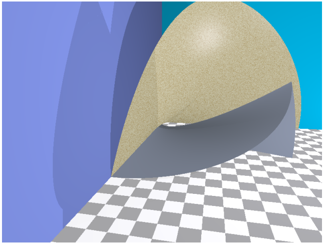
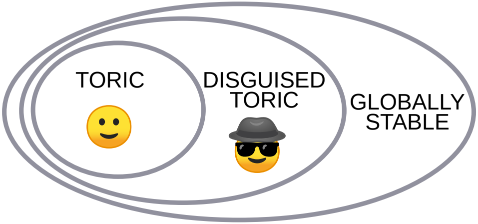




Single-sign-change chambers

Theorem 6 (Brustenga, Craciun, S., 2020)

Consider the "N-gon on a line" network given by $G = (V, E)$. Given $\mathrm{k} \in \mathbb{R}^E_{>0}$ *belonging to a single-sign-change chamber, the system generated by G and* k *is disguised toric.*

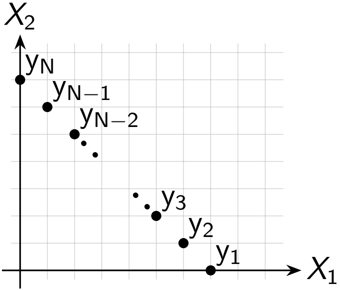
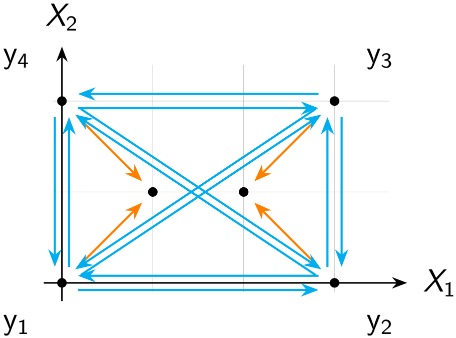


Figure: The N-gon on a line.

Single-sign-change chambers - idea of proof

Single-sign-change chambers: a procedure one might use to find sufficient semialgebraic conditions on $\mathrm{k} \in \mathbb{R}^{E}_{>0}$ for being in $\hat{K}(G)$.
Step 1: For a given $\mathrm{k} \in \mathbb{R}^{E}_{>0}$, realize the dynamical system generated by (G, k) using an E-graph $\hat{G} = (\hat{V}, \hat{E})$ where the detailed balance condition can be established.
Step 2: Pullback to $\mathrm{k} \in \mathbb{R}^{E}_{>0}$ the equations of the detailed balance condition on $\hat{\mathrm{k}} \in \mathbb{R}^{\hat{E}}_{>0}$.
The obtained semialgebraic set will be contained in $\hat{K}(G)$, since detailed balance dynamical systems are toric.

Filling an empty toric locus



Theorem (Craciun, Jin, and Yu, 2020)

The dynamical system generated by the orange E-graph above is dynamically equivalent to complex balanced iff $\frac{1}{25} \leq \frac{k_1 k_3}{k_2 k_4} \leq 25$.

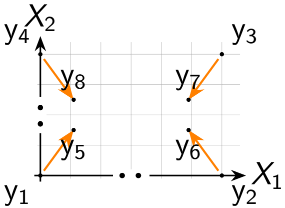


Figure: Four reactions that start at the corners of a rectangle.

$$\mathbf{y_1} \coloneqq \begin{pmatrix} 0 \\ 0 \end{pmatrix} \qquad \mathbf{y_2} \coloneqq \begin{pmatrix} \alpha \\ 0 \end{pmatrix} \qquad \mathbf{y_3} \coloneqq \begin{pmatrix} \alpha \\ \beta \end{pmatrix} \qquad \mathbf{y_4} \coloneqq \begin{pmatrix} 0 \\ \beta \end{pmatrix}$$

$$\mathbf{y_5} \coloneqq \mathbf{y_1} + \begin{pmatrix} \alpha A \\ \beta B \end{pmatrix} \qquad \mathbf{y_6} \coloneqq \mathbf{y_2} + \begin{pmatrix} -\alpha A \\ \beta B \end{pmatrix} \qquad \mathbf{y_7} \coloneqq \mathbf{y_3} + \begin{pmatrix} -\alpha A \\ -\beta B \end{pmatrix} \qquad \mathbf{y_8} \coloneqq \mathbf{y_4} + \begin{pmatrix} \alpha A \\ -\beta B \end{pmatrix}$$

Theorem 7 (Brustenga, Craciun, S., 2022)

The disguised toric locus $\hat{K}(G)$ is the set of $k_1, \ldots, k_4 > 0$ such that

$$\left(\frac{\alpha - \beta}{\alpha + \beta}\right)^2 \leq \frac{k_1 k_3}{k_2 k_4} \leq \left(\frac{\alpha + \beta}{\alpha - \beta}\right)^2.$$

Key idea of the proof:

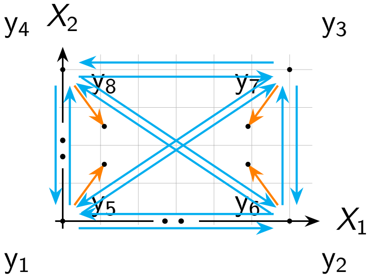


Figure: Complete graph over the sources of G: graph $\hat{G}$, rates $\hat{k}_i \geq 0$.

Theorem (Craciun, Jin, and Yu, 2020)

A mass-action system G is dynamically equivalent to some vertex-balanced mass-action system if and only if it is dynamically equivalent to a vertex-balanced mass-action system $\hat{G}$ that only uses the source vertices of G.

Algorithm 8 (Simplified version-Computing the disguised toric locus)

Input: a reaction network G.
Output: the disguised toric locus of G, or a subset of the disguised toric locus of G.

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Step 2. Choose an algebraic parametrization of $\hat{\mathrm{k}}_{\mathrm{y}}$ coordinates such that:

$$\sum_{\mathrm{y}\to\mathrm{y}'\in\hat{G}} \hat{k}_{\mathrm{y}\to\mathrm{y}'}(\mathrm{y}'-\mathrm{y}) \in C_{G,\mathrm{y}} \cap \overline{C}_{\hat{G},\mathrm{y}} \tag{7}$$

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Step 3. Impose the complex balance conditions for the graph $\hat{G}$ on the *parametrized* $\hat{\mathsf{k}}$ values, and use quantifier elimination to obtain sufficient conditions for a vector k to be contained in the disguised toric locus of G.

Example

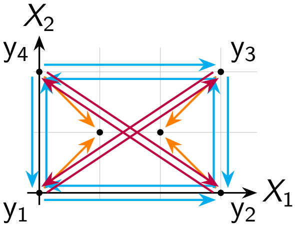

Figure: Realization using the complete bidirected graph on the rectangle.

Denote by $\hat{k}_{ij} > 0$ the rate of the reaction $y_i \to y_j$ in $\hat{G}$. We realize the dynamical system using the graph $\hat{G}$:

$$\begin{aligned}
&\hat{k}_{\mathbf{12}} = k_{\mathbf{1}}(\frac{1}{3} - a), && \hat{k}_{\mathbf{21}} = k_{\mathbf{2}}(\frac{1}{3} - b), && \hat{k}_{\mathbf{32}} = k_{\mathbf{3}}(\frac{1}{2} - c), && \hat{k}_{\mathbf{41}} = k_{\mathbf{4}}(\frac{1}{2} - d),\\
&\hat{k}_{\mathbf{14}} = k_{\mathbf{1}}(\frac{1}{2} - a), && \hat{k}_{\mathbf{23}} = k_{\mathbf{2}}(\frac{1}{2} - b), && \hat{k}_{\mathbf{34}} = k_{\mathbf{3}}(\frac{1}{3} - c), && \hat{k}_{\mathbf{43}} = k_{\mathbf{4}}(\frac{1}{3} - d),\\
&\hat{k}_{\mathbf{13}} && \hat{k}_{\mathbf{24}} = k_{\mathbf{2}}b, && \hat{k}_{\mathbf{31}} = k_{\mathbf{3}}c, && \hat{k}_{\mathbf{42}} = k_{\mathbf{4}}d.
\end{aligned} \tag{8}$$

Example

Impose the complex balanced equations for $\hat{G}, \hat{\mathrm{k}}$:

$$\begin{aligned} \hat{k}_{12} + \hat{k}_{14} + \hat{k}_{13} &= \hat{k}_{41} x_2^2 + \hat{k}_{21} x_1^3 + \hat{k}_{31} x_1^3 x_2^2; \\ \hat{k}_{21} x_1^3 + \hat{k}_{23} x_1^3 + \hat{k}_{24} x_1^3 &= \hat{k}_{12} + \hat{k}_{32} x_1^3 x_2^2 + \hat{k}_{42} x_2^2; \\ \hat{k}_{32} x_1^3 x_2^2 + \hat{k}_{34} x_1^3 x_2^2 + \hat{k}_{31} x_1^3 x_2^2 &= \hat{k}_{43} x_2^2 + \hat{k}_{23} x_1^3 + \hat{k}_{13}; \end{aligned} \tag{9}$$

We have the following inequalities:

$$\begin{aligned} k_1, k_2, k_3, k_4 > 0, \\ 0 < a, b, c, d < \frac{1}{3}. \end{aligned} \tag{10}$$

Eliminating the variables x_1, x_2 from equations (8) and (9), we obtain that there exists $\mathrm{x} := (x_1, x_2) \in \mathbb{R}^2_{>0}$ verifying the equations if and only if $k_1 k_3 (6(a+c)-5)^2 = k_2 k_4 (6(b+d)-5)^2$. By (10), we obtain the condition $\frac{1}{25} \leq \frac{k_1 k_3}{k_2 k_4} \leq 25$.

Thank you for your attention!

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