Persistence and Permanence in Biological Interaction Networks

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Introduction

Determining qualitative properties of solutions of dynamical systems arising from nonlinear interactions is generally a daunting task. A relevant mathematical theory that pertains to biochemical interactions obeying mass-action kinetics has been developed over the last 40 years, starting with work of Horn, Jackson and Feinberg [4, 5]. Generally termed "Chemical Reaction Network Theory", this theory establishes qualitative results that describe the surprisingly stable dynamic behavior of large classes of mass-action systems, *independently of the values of the reaction rate parameters* [4]. This fact is especially useful since the exact values of the system parameters are usually unknown.

Here we focus on the properties of *persistence and permanence* for mass-action systems, and the more general power-law systems. A dynamical system on $\mathbb{R}^n_{>0}$ is called persistent if no trajectory that starts inside $\mathbb{R}^n_{>0}$ approaches the boundary of $\mathbb{R}^n_{>0}$ arbitrarily close and is called permanent if all trajectories that start inside $\mathbb{R}^n_{>0}$ eventually enter a compact subset of $\mathbb{R}^n_{>0}$. Persistence and permanence are important in understanding properties of biochemical networks (e.g., will each chemical species be available indefinitely in the future), and also in ecology (e.g., will a species become extinct in an ecosystem) and in the dynamics of infectious diseases (e.g., will an infection die off, or will it infect the whole population).

The class of *weakly reversible* [4] biochemical networks is very important in chemical reaction network theory. One of the most important open questions in this field is the following:

Persistence Conjecture. *Any weakly reversible mass-action system is persistent.*

We prove the Persistence Conjecture for the case of networks *with two-dimensional stoichiometric subspace*. In fact, we show a more general statement: *any endotactic two-species κ-variable mass action systems is permanent*. All these notions are explained in the subsequent sections of this poster.

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References

[1] D.F. Anderson, A. Shiu, *The dynamics of weakly reversible population processes near facets,* to appear in SIAM J. Appl. Math,

[2] G. Craciun, A. Dickenstein, A. Shiu, B. Sturmfels, *Toric Dynamical Systems,* J. Symb. Comp., 44:11, 1551–1565, 2009.

[3] G. Craciun and C. Pantea, *Persistence and permanence of mass-action and power-law dynamical systems,* submitted

[4] M. Feinberg, *Lectures on chemical reaction networks.* Notes of lectures given at the Mathematics Re- search Center of the University of Wisconsin in 1979, ∼

[5] F. Horn, R. Jackson, *General mass action kinetics,* Archive for Rational Mechanics and Analysis, 47, 81–116, 1972.

[6] J.D. Murray, *Mathematical Biology: I. An Introduction,* Third edition, Springer, 2002.

[7] M.A. Savageau, *Biochemical systems analysis. I. Some mathematical properties of the rate law for the component enzymatic reactions,* Journal of Theoretical Biology 25(3), 365–369, 1969.

[8] Eduardo Sontag, *Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction,* IEEE Trans. Automat. Control, 46, 1028–1047, 2001.

Chemical reaction networks and systems

If I is a finite set we denote by $\mathbb{R}^I_{\geq 0}$ the set of formal sums $\sum_{i\in I} \alpha_i i$ for all $\alpha_i \in \mathbb{R}_{\geq 0}$. If $u = \sum_{i\in I} u_i i$ and $v = \sum_{i\in I} v_i i$ are in $\mathbb{R}^I_{\geq 0}$, we let $u^v = \prod_{s\in\mathcal{S}} (u_s)^{v_s}$, setting $0^0 = 1$.

Chemical reaction networks

Definition. A *CRN* is a triple $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, where
$\mathcal{S}$ is the set of chemical *species*
$\mathcal{C} \subseteq \mathbb{R}^{\mathcal{S}}_{\geq 0}$ is the set of *complexes*
$\mathcal{R} = \{P \to P', \text{for } P, P' \in \mathcal{C}\}$ is the set of *reactions.*

The complexes of a reaction networks can be viewed as vectors in a basis given by the set of species.

Definition. The *stoichiometric subspace* of $\mathcal{R}$ is

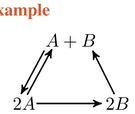
$$S = span\{P' - P \mid P \to P' \in \mathcal{R}\}.$$

As illustrated in the next example, a reaction network can be viewed as a directed graph with vertices given by $\mathcal{C}$ and edges given by $\mathcal{R}$.

Definition. A reaction network is called *weakly reversible* if its reaction graph has strongly connected components.

A weakly reversible example

$\mathcal{S} = \{A, B\}$
$\mathcal{C} = \{2A, A + B, 2B\}$
$\mathcal{R} = \{A+B \rightleftharpoons 2A,\ 2A \to 2B,$
$2B \to A + B\}$



κ-variable mass-action systems

Definition.
A *κ-variable mass-action system* is a quadruple $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ where $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is a reaction network and $\kappa : \mathbb{R}_{\geq 0} \to (\eta, 1/\eta)^{\mathcal{R}}$ for some $\eta < 1$ is a piecewise differentiable function called the rate constants function. Given the initial condition $c^0 \in \mathbb{R}^d_{\geq 0}$, the concentration vector is the solution of the of the κ-variable mass-action ODE system

$$\dot{c}(t) = \sum_{P\to P'} \kappa_{P\to P'}(t) c(t)^P (P' - P) \qquad (1)$$

where $c(0) = c^0$.

The κ-variable mass-action kinetics is a natural generalization of *mass-action kinetics*, where the rate constant functions $\kappa(\cdot)$ are simply positive constants.

Note that the solution of (1) with initial condition c^0 is confined to the affine space $c^0 + S$, where S is the stoichiometric sunspace of $\mathcal{R}$.

ODEs corresponding to our example

$$\begin{bmatrix}\dot{c}_A\\ \dot{c}_B\end{bmatrix} = k_{2A\to A+B}c^{2A}\begin{bmatrix}-1\\1\end{bmatrix} + k_{A+B\to 2A}c^{A+B}\begin{bmatrix}1\\-1\end{bmatrix} + k_{2A\to 2B}c^{2A}\begin{bmatrix}-2\\2\end{bmatrix} + k_{2B\to A+B}c^{2B}\begin{bmatrix}1\\-1\end{bmatrix}$$
$$= \begin{bmatrix}-k_{2A\to A+B}c_A^2 + k_{A+B\to 2A}c_Ac_B - 2k_{2A\to 2B}c_A^2 + k_{2B\to A+B}c_B^2\\ k_{2A\to A+B}c_A^2 - k_{A+B\to 2A}c_Ac_B + 2k_{2A\to 2B}c_A^2 - k_{2B\to A+B}c_B^2\end{bmatrix}.$$

Endotactic networks

Our results are applicable to endotactic networks, which is a large class of reaction networks characterized by a simple geometric property. The class of endotactic networks is larger than the class of weakly reversible networks.

We illustrate the notion of endotactic networks for the case of two species A and B. Let

$$\mathcal{SC}(\mathcal{R}) = \{(m, n) \in \mathbb{Z}^2_{\geq 0} \text{ such that } mX + nY \in \mathcal{C} \text{ is a source complex}\}$$

be the set of source complexes of a reaction network $\mathcal{R}$, represented as a set of lattice points. We depict lattice points corresponding to source complexes using blue dots. For example, the reaction network

$$\mathcal{R} = \{A \to B,\ B \to 2A,\ B \rightleftharpoons A + B\}$$

is illustrated in Figure 1.

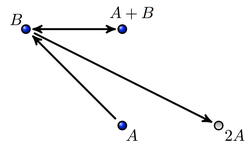


Figure 1. Lattice points corresponding to $\mathcal{R}$.

The "parallel sweep" test

Definition. A network is endotactic if and only if it passes the "parallel sweep test" for any nonzero vector $\mathbf{v}$: sweep the lattice plane with a line L orthogonal to $\mathbf{v}$, going in the direction of $\mathbf{v}$, and stop when L encounters a source complex corresponding to a reaction which is not parallel to L. Now check that no reactions with source on L points towards the swept region.

For example, the reaction network in Figure 1 is endotactic. More examples are presented in Figure 2.

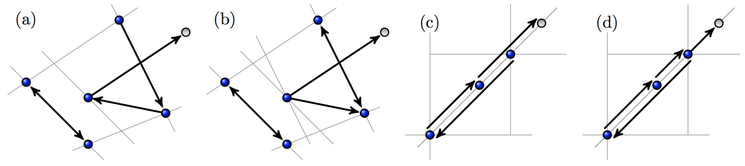


Figure 2. Examples of endotactic networks – (a) and (c), and non-endotactic networks – (b) and (d).

Two theorems

Theorem 1. [Craciun, Nazarov, Pantea]. *Any endotactic κ-variable mass-action system with two species is permanent.*

Theorem 2. [Craciun, Pantea]. *Any endotactic κ-variable mass-action system with two-dimensional stoichiometric subspace and bounded trajectories is persistent.*

In particular, the Persistence Conjecture is true for two-species systems and for systems with two-dimensional stoichiometric subspace and with bounded trajectories.

We prove the theorems above by constructing polygons $\mathcal{P}$ that are forward-invariant for the κ-variable mass-action dynamics. This construction relies on pairwise comparisons of monomials $c(t)^P$ appearing in the expression of $\dot{c}(t)$ in the κ-variable mass-action kinetics (1), which give rise to curves of the form $y = Cx^\sigma$. Starting from the geometric configuration of these curves, we construct the polygon $\mathcal{P}$.

This construction is illustrated in Figure 3 for the case of a small reversible network. In this case (and for any reversible network) we may construct an invariant polygon for each reversible reaction ((a),(b) and (c) in Figure 3) and combine these polygons to obtain an invariant polygon for the whole network ((d) in Figure 3).

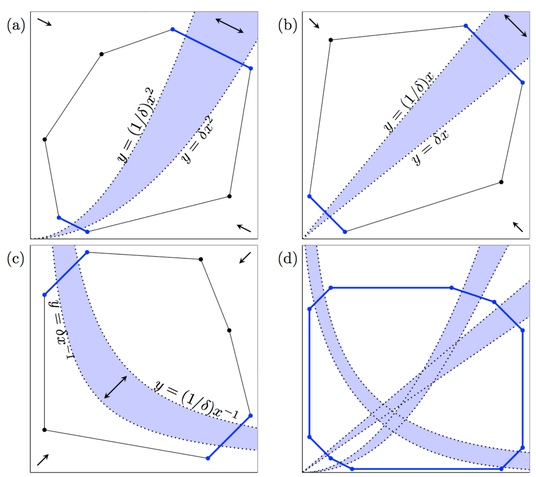


Figure 3. Construction of an invariant polygon for the system $2X \rightleftharpoons Y,\ X \rightleftharpoons Y,\ X \rightleftharpoons 2Y + Y$.

Examples

The Thomas mechanism

The Thomas mechanism ([6, ch. 6]) is a substrate inhibition model for a specific reaction involving oxygen and uric acid in the presence of the enzyme uricase. After nondimensionalization the ODEs for oxygen (v) and uric acid (u) become

$$\frac{du}{dt} = a - u - \frac{\rho uv}{1 + u + Ku^2} \qquad (2)$$
$$\frac{dv}{dt} = \alpha(b - v) - \frac{\rho uv}{1 + u + Ku^2}.$$

This dynamical system can be written as a κ-variable mass-action system with reactions given in Figure 4, where the reaction rates are specified on the reaction arrows and $T(t) = \rho(1 + u + Ku^2)^{-1}$. This network is endotactic and Theorem 1 implies that (2) is permanent.

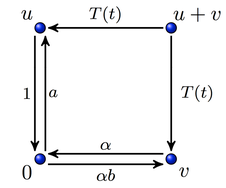


Figure 4. Reaction network for the Thomas model

Power-law systems

Theorems 1 and 2 may be applied to more general power-law dynamical systems which are not necessarily polynomial.

An important example of power-law system is the class of *S-systems* ([7]), where each component of the flow consists of a difference of two "generalized monomials" (i.e., monomials with real exponents). S-systems are common in the modeling of metabolic and genetic networks. For example, consider the following S-system:

$$\frac{dx}{dt} = 2x^{-1}y^{1.5} - y^{0.8} \qquad (3)$$
$$\frac{dy}{dt} = y^{-2} - \sqrt{5}x^{-1}y^{1.5}$$

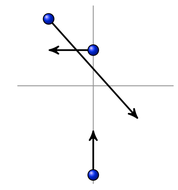


Figure 5. Network for the power-law example

Note that it is not obvious that trajectories of (3) cannot reach the boundary of $\mathbb{R}^2_{>0}$ in finite time. However, using Theorem 2 we can easily see that (3) is in fact permanent. Indeed, the generalized monomials in (3), i.e. the points $(-1, 1.5), (0, 0.8)$ and $(0, -2)$, as well as the corresponding "reaction vectors" $(2, -\sqrt{5}), (-1, 0)$ and $(0, 1)$ are illustrated in Figure 5. This configuration is endotactic.

Lotka-Volterra systems

The classical two-species predator-prey model $A \to 2A \quad A + B \to 2B \quad B \to 0$ is not endotactic, as one can see in Figure 7.

Since, *for fixed parameters*, the trajectories of the corresponding dynamical system are either constant or closed orbits, the system is not permanent. On the other hand, for fixed parameters, the system has bounded trajectories and *is persistent.* However, in general, the *κ-variable* Lotka-Volterra system is *not* persistent. This fact is illustrated in Figure 6, where a trajectory of a fixed-parameter Lotka-Volterra system is depicted in black, and the trajectory of a κ-variable Lotka-Volterra system with the same initial condition is depicted using color.

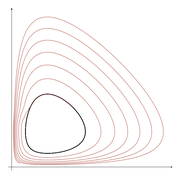


Figure 6. Trajectories of Lotka-Volterra systems for fixed and variables parameters

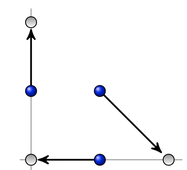


Figure 7. The Lotka-Volterra network is not endotactic

The Global Attractor Conjecture

The Global Attractor Conjecture is the central open problem in Chemical Reaction Network Theory. It is concerned with the global asymptotic stability of positive equilibria for the class of "complex-balanced" [5, 4] mass-action systems. It is known that such systems admit a unique positive equilibrium c_Σ within each affine invariant subset Σ. Moreover, each such equilibrium admits a strict Lyapunov function and therefore c_Σ is locally asymptotically stable with respect to Σ [4, 5]. However, the existence of this Lyapunov function does not guarantee that c_Σ is a global attractor, which is the object of the

Global Attractor Conjecture. *Given a complex-balanced mass-action system and any of its stoichiometric compatibility classes Σ, the positive equilibrium point c_Σ is a global attractor on $int(\Sigma)$.*

It has been shown in [1] that the Global Attractor Conjecture is true for systems with two-dimensional stoichiometric subspace. Using Theorem 2 we have extended this result to dimension three:

Theorem 3. *The Global Attractor Conjecture holds for systems with three-dimensional stoichiometric subspace.*

For the proof we use Theorem 2 to construct a hypersurface that separates a given trajectory from the boundary of $\mathbb{R}^n$, as illustrated in Figure 8.

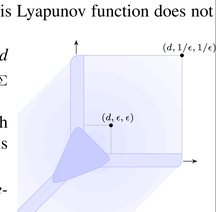


Figure 8. Idea of proof for Theorem 3.