Multistability of Small Zero-One Reaction Networks

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Abstract

This work addresses the challenging problem of detecting the smallest reaction networks that admit more than one nondegenerate/stable positive steady state, a property termed nondegenerate multistationarity/multistability. In particular, we are interested in the networks arising from the study of cell signaling, say zero-one networks. The main contribution of this work is to show that the smallest zero-one networks that admit nondegenerate multistationarity/multistability contain three species and five/six reactions, and they are three-dimensional. This work also gives insights on the other interesting dynamical features for the small zero-one networks such as dissipativity, degeneracy and absolute concentration robustness. Also, we provide a computational procedure to detect a multistable network, and by this method we successfully check through over sixty thousands networks.

Motivation

- Many important networks in cell signaling are zero-one, eg., cell cycle:

$$C+M^{+} \xrightarrow{\kappa_1} X+M \xleftarrow{\kappa_2} C^{+}+M, \qquad C \xrightarrow{\kappa_5} C^{+},$$
$$M^{+}+W \xleftarrow{\kappa_3} M+W \xrightarrow{\kappa_4} M+W^{+}, \qquad W^{+} \xrightarrow{\kappa_6} W.$$

- Inheritance of dynamical behaviors from large networks, eg., oscillation; multistationarity/multistability

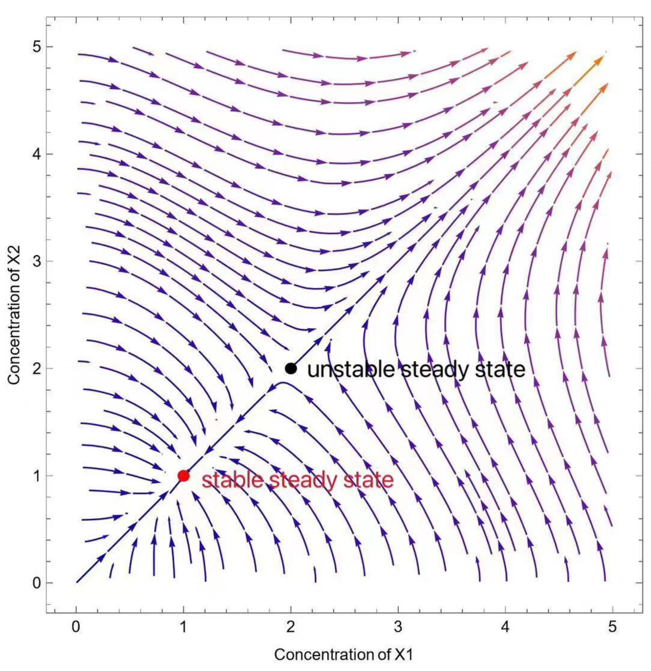
Results

The smallest zero-one networks that admit multistationarity (multistability) contain 3 species and 5 (6) reactions, and they are three-dimensional.

Example 1

A 3-species, 5-reaction zero-one network admitting multistationarity:

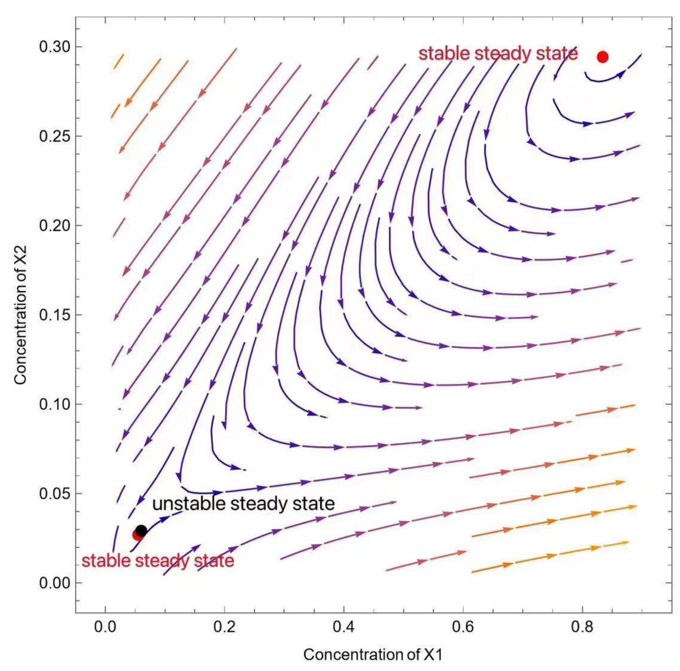
$$X_1+X_2 \xrightarrow{\kappa_1} X_3, \quad X_3 \xrightarrow{\kappa_2} 0, \quad 0 \xrightarrow{\kappa_3} X_3,$$
$$X_1+X_3 \xrightarrow{\kappa_4} X_1+X_2+X_3,$$
$$X_2+X_3 \xrightarrow{\kappa_5} X_1+X_2+X_3.$$



Example 2

A 3-species, 6-reaction zero-one network admitting multistability:

$$X_1+X_2+X_3 \xrightarrow{\kappa_1} 0, \quad 0 \xrightarrow{\kappa_2} X_3,$$
$$X_3 \xrightarrow{\kappa_3} 0, \quad X_1 \xrightarrow{\kappa_4} X_1+X_2,$$
$$X_2 \xrightarrow{\kappa_5} X_1, \quad X_1+X_2 \xrightarrow{\kappa_6} X_1+X_3.$$



Monostationarity of One-dimensional Networks

Let G be a one-dimensional zero-one network with s species. Classify the indices of the species ($\{1,\ldots,s-1\}$) by defining three sets as follows.

$$\mathcal{J}_1 := \{i \mid x_i = x_s + c_i\}, \ \mathcal{J}_2 := \{i \mid x_i = -x_s + c_i\}, \ \mathcal{J}_3 := \{i \mid x_i = c_i\}.$$

Theorem 1: Let G be a one-dimensional zero-one network with a stoichiometric matrix $\mathcal{N}$. Let $\mathcal{J}_1$, $\mathcal{J}_2$, and $\mathcal{J}_3$ be defined above.

(I) If at least one non-zero row of $\mathcal{N}$ does not change sign, then G admits no positive steady state.

(II) If all non-zero rows of $\mathcal{N}$ change sign, then for any $c \in \mathbb{R}^{s-1}$, we have the following statements.

 (i) If there exists $k \in \mathcal{J}_2 \cup \mathcal{J}_3$ such that $c_k \leq 0$ or there exists $(i,j) \in \mathcal{J}_1 \times \mathcal{J}_2$ such that $c_i \geq c_j$, then for any $\kappa \in \mathbb{R}^m_{>0}$, G has no positive steady state.

 (ii) If $c_k > 0$ for any $k \in \mathcal{J}_2 \cup \mathcal{J}_3$, and $c_i < c_j$ for any $(i,j) \in \mathcal{J}_1 \times \mathcal{J}_2$, then for any $\kappa \in \mathbb{R}^m_{>0}$, G has exactly one positive steady state, and the steady state is stable.

Note: (I) means one can determine whether the network admits positive steady states by reading off the non-zero rows of $\mathcal{N}$. (II) means all the parameters can be completely classified according to if the network indeed has a stable positive steady state.

Monostationarity of Two-dimensional Networks

Theorem 2: Any two-dimensional zero-one network with up to three species either only admits degenerate positive steady states or admits at most one nondegenerate (stable) positive steady state.

Corollary 1: Any two-dimensional zero-one network with up to three species admits no multistationarity/multistability.

Example 3

A two-dimensional 2-species zero-one network only admitting degenerate steady states:

$$0 \xrightarrow{\kappa_1} X_1, \quad 0 \xrightarrow{\kappa_2} X_2, \quad 0 \xrightarrow{\kappa_3} X_1+X_2,$$
$$X_1+X_2 \xrightarrow{\kappa_4} 0, \quad X_1+X_2 \xrightarrow{\kappa_5} X_1, \quad X_1+X_2 \xrightarrow{\kappa_6} X_2.$$

The system of ODEs is

$$f_1 = \kappa_1+\kappa_3-\kappa_4 x_1x_2-\kappa_6 x_1x_2,$$
$$f_2 = \kappa_2+\kappa_3-\kappa_4 x_1x_2-\kappa_5 x_1x_2.$$

Check that

$$det(\mathrm{Jac}_f(\kappa,x)) = 0.$$

Some Nice Properties for Two-dimensional Networks

(a) We can always get another conservation law by relabeling the species as $\bar{x}_1, \bar{x}_2, \bar{x}_3$ such that the conservation law $\bar{x}_1 = \bar{a}\bar{x}_2 + \bar{b}\bar{x}_3 + \bar{c}$ satisfies

$$(|\bar{a}|, |\bar{b}|) \in \{(1,0),(0,1),(0,0),(\tfrac{1}{2},\tfrac{1}{2}),(1,1)\}.$$

(b) We classify all maximum networks $\mathcal{G}$ into three classes,

$$\mathcal{G}_1 := \{G \mid (a,b) = (\tfrac{1}{2},\tfrac{1}{2}),\ G \in \mathcal{G}\}, \tag{1}$$
$$\mathcal{G}_2 := \{G \mid (a,b) \in \{(1,0),(0,1),(0,0)\},\ G \in \mathcal{G}\}, \tag{2}$$
$$\mathcal{G}_3 := \mathcal{G} \setminus \{\mathcal{G}_1 \cup \mathcal{G}_2\}. \tag{3}$$

(c) For the networks in $\mathcal{G}_3$, we can prove Theorem 2 by proving

 (i) the network is dissipative,

 (ii) there are no boundary steady states in $\mathcal{P}_c$, and

 (iii) $\mathrm{sign}(\det(\mathrm{Jac}_h(x^*))) = (-1)^r$, for all steady states $x^* \in \mathcal{P}_c$.

 For the networks in $\mathcal{G}_1 \cup \mathcal{G}_2$, we apply the theory of real algebraic geometry.

Similarities/Differences between One and Two-dimensional Networks

Table 1. Comparing one-dimensional and two-dimensional zero-one networks

	Multistability	ACR for full-dimension	Dissipativity	Degeneracy
one-dim	No	Yes	Yes	No
two-dim	No	Uncertain	Uncertain	Yes

Computational Procedure

Figure 1. The flow diagram of proof of main result.

Enumerate all "non-trivial" 3-species zero-one networks with 5 reactions

↓ 65440 networks

Delete the injective networks

↓ 39233 networks

Delete the networks admitting no multistationarity by using `RealRootClassification` in Maple

↓ 429 networks

Delete the networks admitting no multistability by Hurwitz criterion

↓ 0 networks

Apply a similar procedure to find a 3-species zero-one network with 6 reactions having multistability

Note: "Non-trivial": the network admits nondegenerate positive steady states.

Table 2. Computational Time (h: hours) for Running the Procedure

STEPS	TIME	# NETWORKS
Delete the injective networks	0.1h	65440
Delete the networks admitting no multistationarity	18h	39233
Delete the networks admitting no multistability	0.1h	429

Notes: (i) The column "STEP" lists the names of the blue steps in the procedure. (ii) The column "TIME" records the computational time for each step. (iii) The last column records the number of networks we dealt with.

References

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