國 立 交 通 大 學

應用數學系

碩　士　論　文

多維度的細胞分化在數學上的研究

Mathematical Studies on Multi-dimensional Cellular Differentiation　Models

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指導老師：石至文　教授

中 華 民 國 九 十 七 年 十 二 月

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摘　　　　要

我們分析並總結在文獻裡提到的三個細胞分化模型的數學特性。這些數學模型描述細胞分化過程中一些相關蛋白質與基因表現控制網路中多重開關之動態。這些系統是可由多個對抗性分部所組成，在基因控制中，每一分部各以全有或無之方式引導細胞分化成特定之形式。

Mathematical Studies on Multi-dimensional Cellular Differentiation Models

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December 2008

Abstract

We summarize mathematical properties for three cellular differentiation models proposed in the literatures. These mathematical models are used to describe basic multi-switching dynamics in generic master regulatory networks. These systems consist of arbitrary number of antagonistic components which direct differentiation in an all-or-none fashion to a specific cell-type chosen in gene regulation.

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1 Introduction

Cellular differentiation is the process by which a less specialized cell becomes a more specialized cell type. Differentiation occurs numerous times during the development of a multicellular organism as the organism changes from a single zygote to a complex system of tissues and cell types. How the differentiation proceeds is the context of gene regulation and is rather complex. Several mathematical models have been proposed to depict and analyze the process. There were some reports on bistable switches for systems with two variables, for example, in [3], [7]. From experimental evidence, switching involving more than two variables and outcomes also deserves investigations.

In this report, we study three models proposed by Olivier and Demongeot [4]. The model consists of arbitrary number of components. Each of them represents the intracellular concentration of a differentiation factor, called switch element. Each of these components promotes itself and represses all others. Each of these variables can be regarded as a protein which corresponds to an antagonistic factor in the cell differentiation, for example, in hematopoiesis. These models aim at characterizing multi-dimensional switches in the cellular differentiation. In particular, the phases of co-expressed components and some up-regulating, some down-regulating are desired dynamic features in the models.

In the following, we discuss the properties of these models. The presentation is organized as follow. Section 2 addresses the model with mutual inhibition and autocatalysis. Each switch element is supposed to undergo non-regulated degradation (modelled as exponential decay, with an arbitrary speed 1), and transcription/translation with a relative speed σ. Each element positively auto-regulates itself, and represses expression of others, with a cooperativity c. Calling x_i the concentration of each switch element, the corresponding equations are

$$\dot{x}_i = -x_i + \frac{\sigma x_i^c}{1 + \sum_{j=1}^n x_j^c}, \; 1 \le i \le n.$$

Section 3 addresses the model with mutual inhibition, autocatalysis and leak. The model is the same as previously, except that each element has a "leaky" expression, modelled as a constant production term α. The equations become

$$\dot{x}_i = -x_i + \frac{\sigma x_i^c}{1 + \sum_{j=1}^n x_j^c} + \alpha, \; 1 \le i \le n.$$

Section 4 addresses a model for bHLH proteins. Each switch bHLH protein is supposed to bind to a common activator according to the law of mass action, with a binding constant K_c, and a total quantity of activator a_t.

$$\dot{x_i} = -x_i + \frac{\sigma(\frac{a_t x_i}{1+\sum_{j=1}^{n} x_j})^c}{K_c + (\frac{a_t x_i}{1+\sum_{j=1}^{n} x_j})^c},\ 1 \leq i \leq n.$$

Throughout the presentation, we consider the system on the cone

$$\{(x_1, x_2, \cdots, x_n) : x_j \geq 0, j = 1, 2, \cdots, n\},$$

and we consider the following five kinds of equilibria for the three model systems:
(i) the origin

$$(0, 0, \cdots, 0) \in \mathbb{R}^n; \tag{1.1}$$

(ii) One switch on and $(n-1)$ off, i.e., the equilibrium $(\bar{x}_1, \bar{x}_2, \cdots, \bar{x}_n)$ with $\bar{x}_i = a \neq 0$ for some $i \in \{1, 2, \cdots, n\}$ and $\bar{x}_j = 0$ for all others j. Without loss of generality, we set it as

$$(a, 0, 0, \cdots, 0) \in \mathbb{R}^n; \tag{1.2}$$

(iii) k switches on with identical components $(k > 1)$, and $(n-k)$ off (zero), i.e., the equilibrium $(\bar{x}_1, \bar{x}_2, \cdots, \bar{x}_n)$ with k's $i \in \{1, 2, \cdots, n\}$ such that $\bar{x}_i = a \neq 0$ and $\bar{x}_j = 0$ for all others j. Without loss of generality, we set it as

$$(a, a, \cdots, a, 0, 0, \cdots, 0) \in \mathbb{R}^n; \tag{1.3}$$

(iv) all switches on with identical components, i.e., the equilibrium $(\bar{x}_1, \bar{x}_2, \cdots, \bar{x}_n)$ with $\bar{x}_i = a \neq 0$ for all $i \in \{1, 2, \cdots, n\}$,

$$(a, a, \cdots, a) \in \mathbb{R}^n; \tag{1.4}$$

(v) k switches on with identical components, and $(n-k)$ off with identical components, i.e., the equilibrium $(\bar{x}_1, \bar{x}_2, \cdots, \bar{x}_n)$ with k's $\bar{x}_i = a \neq 0$, and $(n-k)$'s $\bar{x}_j = b \neq 0$ for $i, j \in \{1, 2, \cdots, n\}$ where $k > 1$ and $(n-k) > 1$ and $a > b$. Without loss of generality, we set it as

$$(a, a, \cdots, a, b, b, \cdots, b) \in \mathbb{R}^n. \tag{1.5}$$

We shall analyze the existence of those equilibria. In addition, we study the stability of these equilibria through linearization at these equilibria; namely, if all eigenvalues have negative real parts, then the equilibrium is stable; if one of the eigenvalues has positive real part, then the equilibrium is unstable. As the first two models are gradient systems, we also justify that the global convergence for these systems.

In this report, propositions 2.1, 3.1, 3.2, 3.4, and 3.5 are completed in this study, while the others are recasted from [4], with more details.

2 Model with mutual inhibition and autocatalysis

In the section, we consider the equations

$$\dot{x_i} = -x_i + \frac{\sigma x_i^c}{1 + \sum_{j=1}^{n} x_j^c}, \quad 1 \le i \le n \tag{2.1}$$

where $x_i \geqslant 0$ is the concentration of each switch element, $\sigma > 1$ is transcription/ translation with a relative speed, and c is cooperativity. Clearly, the origin is an equilibrium for every $c > 0$. In addition, if $c \geq 1$, then the i-component of an equilibrium is either zero or satisfies

$$\frac{\sigma x_i^{c-1}}{1+\sum_{j=1}^{n} x_j^c} = 1$$

$$\Leftrightarrow \quad 1 + \sum_{j=1}^{n} x_j^c = \sigma x_i^{c-1}.$$

Next, we consider three cases for c, i.e. $c = 0$, $c = 1$, and $c > 1$. If $c = 0$, then (2.1) becomes

$$\dot{x_i} = -x_i + \frac{\sigma}{1+n}, \ 1 \le i \le n.$$

Let the right hand side of (2.1) be f_i, $J_{ij} = \partial f_i / \partial x_j$. Then

$$J_{i,i} = -1 + \frac{(1 + \sum_{j \neq i}^{n} x_j^c)(\sigma c x_i^{c-1})}{(1 + \sum_{j=1}^{n} x_j^c)^2}, \tag{2.2}$$

$$J_{i,j} = \frac{-\sigma c x_i^c x_j^{c-1}}{(1 + \sum_{j=1}^{n} x_j^c)^2} \text{ for } j \neq i.$$

Proposition 2.1. For $c = 0$, there exists a stable equilibrium with all switches on, whose components are identically $\sigma/(1+n)$.

Proof: Consider the existence of the equilibrium with all switches on, whose components are identical. We have $(\sigma/(1+n), \sigma/(1+n), \cdots, \sigma/(1+n)) \in \mathbb{R}^n$ is an equilibrium. Next, consider the local stability of the equilibrium. Note that the linearization at $(\sigma/(1+n), \sigma/(1+n), \cdots, \sigma/(1+n))$ is

$$\begin{pmatrix} -1 & 0 & \cdots & 0 \\ 0 & -1 & \vdots & \vdots \\ \vdots & \cdots & \ddots & 0 \\ 0 & \cdots & 0 & -1 \end{pmatrix}.$$

We have all eigenvalues are negative. Thus, the equilibrium is stable. The assertion follows.

Example 2.1: In proposition 2.1, if $n = 2$ and $\sigma = 2$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{2}{1+2} \\ \dot{x_2} = -x_2 + \frac{2}{1+2} \end{cases},$$

then $(2/3, 2/3)$ is a stable equilibrium for the above system (see figure 1).

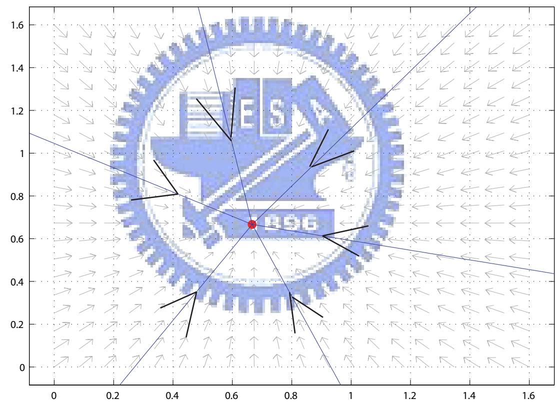


Figure 1: $(2/3, 2/3)$ is a stable equilibrium (in example 2.1).

Next, consider $c = 1$ (no cooperativity), then (2.1) becomes

$$\dot{x}_i = -x_i + \frac{\sigma x_i}{1 + \sum_{j=1}^{n} x_j}, \quad 1 \le i \le n.$$

Suppose $\sigma > 1$. If $x_i \neq 0$ for some i, then $1 + \sum_{j=1}^{n} x_j = \sigma$. Note that the set

$$\{(x_1, x_2, \cdots, x_n) | 1 + \sum_{j=1}^{n} x_j = \sigma\} \tag{2.3}$$

is a hyperplane of equilibria. In addition, (2.2) becomes

$$J_{i,i} = -1 + \frac{\sigma(1 + \sum_{j\neq i}^{n} x_j)}{(1 + \sum_{j=1}^{n} x_j)^2}, \tag{2.4}$$
$$J_{i,j} = \frac{-\sigma x_i}{(1 + \sum_{j=1}^{n} x_j)^2} \text{ for } j \neq i.$$

The result of proposition 2.2. is only stated in [4]. We provide a detailed proof herein.

Proposition 2.2. ([4]) For $c = 1$ and $\sigma > 1$, the hyperplane of equilibria (2.3) is stable and the origin is an unstable equilibrium.

Proof: With (2.4), the origin is unstable since $-1 + \sigma > 0$ is the only eigenvalue. Consider the distance from the point $(x_1(t), x_2(t), \cdots, x_n(t))$ to the hyperplane

$$y_1 + y_2 + \cdots + y_n = \sigma - 1.$$

Set the square of distance of a point $(x_1, x_2, \cdots, x_n)$ to the plane as

$$D(x_1, x_2, \cdots, x_n) = \frac{(x_1 + x_2 + \cdots + x_n - \sigma + 1)^2}{n}.$$

Then

$$\begin{aligned} \dot{D}(\mathbf{x}) &= \frac{dD}{dt}(x_1(t), x_2(t), \cdots, x_n(t)) \\ &= \frac{\partial D}{\partial x_1}\dot{x_1}(t) + \frac{\partial D}{\partial x_2}\dot{x_2}(t) + \cdots + \frac{\partial D}{\partial x_n}\dot{x_n}(t) \\ &= -\frac{2}{n}\frac{s \cdot (s - \sigma + 1)^2}{1 + s} \\ &\leq 0, \end{aligned}$$

where $s = x_1 + x_2 + \cdots + x_n$. Therefore, D is a Lyapunov function. Moreover, $\dot{D}(\mathbf{x}) = 0$ if and only if $s = \sigma - 1$ or $s = 0$, i.e., the hyperplane of equilibria or the origin. Thus, the manifold of equilibria are stable. So, the assertion follows.

Example 2.2 : In proposition 2.2, if $n = 2$ and $\sigma = 2$, i.e, the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{2x_1}{1+x_1+x_2} \\ \dot{x_2} = -x_2 + \frac{2x_2}{1+x_1+x_2} \end{cases},$$

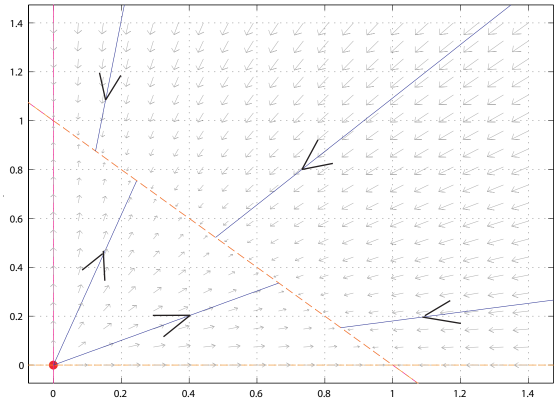


Figure 2: $(0,0)$ is unstable and and $\{(x_1, x_2)|x_1 + x_2 = 1\}$ are stable manifold of equilibria (in example 2.2).

then $(0,0)$ is unstable equilibrium and $\{(x_1, x_2)|x_1 + x_2 = 1\}$ are stable manifold of equilibria (see Figure 2).

We need the following lemma in the subsequent propositions.

Lemma 2.1: The eigenvalues of $n \times n$ matrix

$$A = \begin{pmatrix} a & b & \cdots & b \\ b & a & \vdots & \vdots \\ \vdots & \cdots & \ddots & b \\ b & \cdots & b & a \end{pmatrix},$$

are $(a - b)$ and $a + (n - 1)b$. In addition, the number of $(a - b)$ is $(n - 1)$.

Proof. Clearly, $a - b$ is an eigenvalue of A. We have

$$A - (a-b)I = \begin{pmatrix} b & b & \cdots & b \\ b & b & \vdots & \vdots \\ \vdots & \cdots & \ddots & b \\ b & \cdots & b & b \end{pmatrix},$$

$rank(A - (a - b)I) = 1$, and $dimKer(A - (a - b)I) = n - 1$. By the dimension theorem [6], $(n - 1)(a - b) + \lambda = na \Leftrightarrow \lambda = a + (n - 1)b$. So, the result follows.

These results of proposition 2.3 are sketched in [4]. We recast them with more details.

Proposition 2.3. ([4]) Let $c > 1$.

(i) If $(\sigma/c)^c((c-1)/k)^{c-1} \geq 1$, then there exist equilibria with k switches on with identical components, and $(n-k)$ off (zero), for $1 \leq k \leq n$. In addition, the equilibrium with one switch-on $(k = 1)$, and $n-1$ off (zero) exists if $\sigma \geq 2$.

(ii) The equilibrium with one switch-on of value a and $(n-1)$ off (zero) is stable, if $a > (c/\sigma)^{\frac{1}{c-1}}$, and unstable if $a < (c/\sigma)^{\frac{1}{c-1}}$.

(iii) The above equilibria with k switch-on for $1 < k \leq n$ are unstable.

Proof: (i) A steady state solution of the form $(a, a, \cdots, a, 0, 0, \cdots, 0)$ satisfies

$$-a + \frac{\sigma a^c}{1 + ka^c} = 0 \text{ or } 1 + ka^c = \sigma a^{c-1} \text{ if } a \neq 0. \tag{2.5}$$

Set $g(\xi) = k\xi^c - \sigma\xi^{c-1}$, then $g'(\xi) = kc\xi^{c-1} - \sigma(c-1)\xi^{c-2} = 0$. Thus $\xi = \sigma(c-1)/kc$ is a critical point of g, and $g(\sigma(c-1)/kc) = -(\sigma/c)^c((c-1)/k)^{c-1}$. Since $g(\xi) \to \infty$ as $\xi \to \infty$, and $g(\xi)$ passes point $(0, 0)$, g attains its minimum at $-(\sigma/c)^c((c-1)/k)^{c-1}$. If $-(\sigma/c)^c((c-1)/k)^{c-1} \leq -1$, then there exists solution of (2.5). In addition, when $k = 1$, the above equation becomes

$$\sigma^c > c(\frac{c}{c-1})^{c-1} \Leftrightarrow \ln \sigma > \frac{\ln c + \ln(\frac{c}{c-1})^{c-1}}{c}. \tag{2.6}$$

Let

$$h(c) = \frac{\ln c + \ln(\frac{c}{c-1})^{c-1}}{c}.$$

We compute

$$h'(c) = \frac{-\ln(c-1)}{c^2} = 0 \Leftrightarrow c = 2.$$

In addition, $\ln(c-1) < 0$ if $1 < c < 2$ and $\ln(c-1) > 0$ if $c > 2$. Hence, the right-hand side of (2.6) has a maximum for $c = 2$, matched by $\sigma = 2$. So, $\sigma \geq 2$, there exist solutions of (2.5).

(ii) From (2.2), the linearization at $(a, 0, \cdots, 0)$ is

$$J = \begin{pmatrix} -1 + \frac{c}{\sigma a^{c-1}} & 0 & \cdots & 0 \\ 0 & -1 & \vdots & \vdots \\ \vdots & \cdots & \ddots & 0 \\ 0 & \cdots & 0 & -1 \end{pmatrix}.$$

Thus, -1 and $-1+c/\sigma a^{c-1}$ are the eigenvalues of J. If

$$-1+\frac{c}{\sigma a^{c-1}}<0 \Leftrightarrow a>(c/\sigma)^{\frac{1}{c-1}},$$

then the equilibrium is stable. In addition, it is unstable if $a<(c/\sigma)^{\frac{1}{c-1}}$.
(iii) When $1<k<n$, the linearization at $(a,a,\cdots,a,0,0,\cdots,0)$ is

$$\left(\begin{array}{ccc|ccc} -1+\frac{\sigma c(1+(k-1)a^c)a^{c-1}}{(1+ka^c)^2} & & -\frac{\sigma c a^{2c-1}}{(1+ka^c)^2} & & & \\ & \ddots & & & \mathbf{0} & \\ -\frac{\sigma c a^{2c-1}}{(1+ka^c)^2} & & -1+\frac{\sigma c(1+(k-1)a^c)a^{c-1}}{(1+ka^c)^2} & & & \\ \hline & & & -1 & & \mathbf{0} \\ & \mathbf{0} & & & \ddots & \\ & & & \mathbf{0} & & -1 \end{array}\right)$$

By Lemma 1, the eigenvalues are -1, and

$$\begin{aligned} \lambda_1 &= -1+\frac{\sigma c(1+(k-1)a^c)a^{c-1}}{(1+ka^c)^2}+\frac{\sigma c a^{2c-1}}{(1+ka^c)^2}, \text{ and} \\ \lambda_2 &= -1+\frac{\sigma c(1+(k-1)a^c)a^{c-1}}{(1+ka^c)^2}-\frac{(k-1)\sigma c a^{2c-1}}{(1+ka^c)^2}<\lambda_1. \end{aligned} \tag{2.7}$$

Note that $\lambda_1>0$ if and only if $c>1$. Indeed,

$$\begin{aligned} & -(1+ka^c)^2+\sigma c(1+(k-1)a^c)a^{c-1}+\sigma c a^{2c-1}\leq 0 \\ \Leftrightarrow\ & \sigma c(1+(k-1)a^c)+\sigma c a^c\leq \sigma^2 a^{c-1} \\ \Leftrightarrow\ & 1+ka^c\leq \frac{\sigma}{c}a^{c-1} \\ \Leftrightarrow\ & c\leq 1. \end{aligned}$$

Thus, the equilibrium unstable.

In addition, when $k=n$, then the linearization at $(a,a,\cdots,a)$ is

$$\begin{pmatrix} -1+\frac{\sigma c(1+(n-1)a^c)a^{c-1}}{(1+na^c)^2} & -\frac{\sigma c a^{2c-1}}{(1+na^c)^2} & \cdots & -\frac{\sigma c a^{2c-1}}{(1+na^c)^2} \\ -\frac{\sigma c a^{2c-1}}{(1+na^c)^2} & -1+\frac{\sigma c(1+(n-1)a^c)a^{c-1}}{(1+na^c)^2} & \vdots & \vdots \\ \vdots & \cdots & \ddots & -\frac{\sigma c a^{2c-1}}{(1+na^c)^2} \\ -\frac{\sigma c a^{2c-1}}{(1+na^c)^2} & \cdots & -\frac{\sigma c a^{2c-1}}{(1+na^c)^2} & -1+\frac{\sigma c(1+(n-1)a^c)a^{c-1}}{(1+na^c)^2} \end{pmatrix}.$$

The analysis of eigenvalues is as the case $1<k<n$. The assertion then follows.

The result of proposition 2.4 is sketched in [4]. We recast it with more details.

Proposition 2.4.([4]) : For $c \geq 1/2$, every solution of systems (2.1) tends to an equilibrium as time tends to infinity.

Proof: Let $y_i = \sqrt{x_i}$. Then $\dot{y_i} = \dot{x}_i/2y_i$, i.e.,

$$\begin{aligned} \dot{y_i} &= \frac{-x_i + \frac{\sigma x_i^c}{1+\sum_{j=1}^n x_j^c}}{2y_i} = \frac{-y_i^2 + \frac{\sigma y_i^{2c}}{1+\sum_{j=1}^n y_j^{2c}}}{2y_i} \\ &= \frac{1}{2}(-y_i + \frac{\sigma y_i^{2c-1}}{1+\sum_{j=1}^n y_j^{2c}}) \\ &= -\frac{\partial V}{\partial y_i}, \end{aligned}$$

where

$$V(\mathbf{y}) = \frac{1}{4}\sum_{j=1}^n y_j^2 - \frac{\sigma}{4c}\log(1+\sum_{j=1}^n y_j^{2c}).$$

Thus $\dot{y_i} = \dot{x}_i/2y_i$ is a gradient system. Moreover,

$$-2\frac{\partial V}{\partial y_i} = y_i - \frac{\sigma y_i^{2c-1}}{1+\sum_{j=1}^n y_j^{2c}} = 0 \Leftrightarrow 1 = \frac{\sigma y_i^{2c-2}}{1+\sum_{j=1}^n y_j^{2c}},$$

i.e.,

$$1 + \sum_{j=1}^n x_j^c = \sigma x_i^{c-1}.$$

By the Lasalle's invariant principle [1], thus, every solution of the system converges to one of the equilibria as time tends to infinity. The assertion follows.

Example 2.3 : In proposition 2.3, first consider $n = 2$, $c = 2$ and $\sigma = 2$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{2x_1^2}{1+x_1^2+x_2^2} \\ \dot{x_2} = -x_2 + \frac{2x_2^2}{1+x_1^2+x_2^2} \end{cases},$$

then $(0,0)$ is stable equilibrium and $(1,0)$, $(0,1)$ are saddle points since $1 = (c/\sigma)^{\frac{1}{c-1}}$.

Next, consider $n = 2$, $c = 2$ and $\sigma = 3$. i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{3x_1^2}{1+x_1^2+x_2^2} \\ \dot{x_2} = -x_2 + \frac{3x_2^2}{1+x_1^2+x_2^2} \end{cases}, \tag{2.8}$$

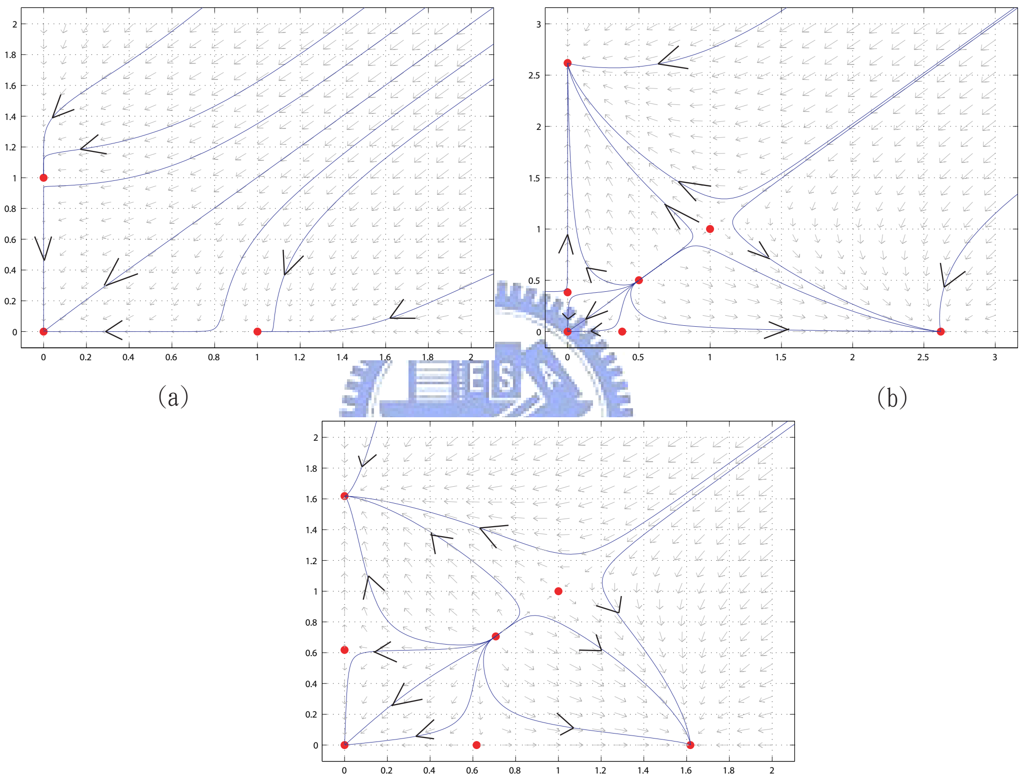
then there exist seven equilibria: three stable equilibria are $(0,0)$, $(2.618,0)$, $(0,2.618)$, since it satisfies $(3+\sqrt{5})/2 \approx 2.618 > (c/\sigma)^{\frac{1}{c-1}} = \frac{2}{3}$, and four unstable equilibria are $(1,1)$, $(0.5,0.5)$, $(0.382,0)$, $(0,0.382)$. The reasons are first two satisfy

$(\sigma/c)^c((c-1)/2)^{c-1} = 9/8 > 1$ and the last two satisfy $(3-\sqrt{5})/2 \approx 0.382 < (c/\sigma)^{\frac{1}{c-1}} = 2/3$.

If consider $y_i = \sqrt{x_i}$, then the above system become

$$\begin{cases} \dot{y_1} = \frac{1}{2}(-y_1 + \frac{3y_1^3}{1+y_1^4+y_2^4}) \\ \dot{y_2} = \frac{1}{2}(-y_2 + \frac{3y_2^3}{1+y_1^4+y_2^4}) \end{cases}, \tag{2.9}$$

then there exist seven equilibria: three stable equilibria are $(0,0)$, $(1.618,0)$, $(0,1.618)$, and four unstable equilibria are $(1,1)$, $(0.707,0.707)$, $(0.618,0)$, $(0,0.618)$. We see that same dynamical behavior in systems (2.8) and (2.9) (see figure 3).



(a) (b)

(c)

Figure 3: In figure (a), $(0,0)$ is stable equilibrium and $(1,0)$, $(0,1)$ are saddle points. (b) is for $\dot{x}_i(t)$ system, it has seven equilibria: three stable equilibria are $(0,0)$, $(2.168,0)$, $(0,2.168)$, and four unstable equilibria are $(1,1)$, $(0.5,0.5)$, $(0.382,0)$, $(0,0.382)$. (c) is for $\dot{y}_i(t)$ system, ut has seven equilibria: three stable equilibria are $(0,0)$, $(1.618,0)$, $(0,1.618)$, and four unstable equilibria are $(1,1)$, $(0.707,0.707)$, $(0.618,0)$, $(0,0.618)$ (in example 2.3).

In this section, for $c = 0$, there exists a stable equilibrium with all switches on, whose components are identically $\sigma/(1+n)$. For $c = 1$ and $\sigma > 1$, the manifold of equilibria (2.3) is stable and the origin is an unstable equilibrium.

Let $c > 1$.

(i) If $(\sigma/c)^c((c-1)/k)^{c-1} \geq 1$, then there exist equilibria with k switches on with identical components, and $(n-k)$ off (zero), for $1 \leq k \leq n$. In addition, the equilibrium with one switch-on ($k = 1$), and $n-1$ off (zero) exists if $\sigma \geq 2$.

(ii) The equilibrium with one switch-on of value a and $(n-1)$ off (zero) is stable, if $a > (c/\sigma)^{\frac{1}{c-1}}$, and unstable if $a < (c/\sigma)^{\frac{1}{c-1}}$.

(iii) The above equilibria with k switch-on for $1 < k \leq n$ are unstable.

Finally, the model is a gradient system, we also justify that for $c \geq 1/2$, every solution of systems (2.1) tends to an equilibrium as time tends to infinity. .

3 Model with mutual inhibition, autocatalysis, and leak

In this section, we add leak $\alpha > 0$ to the equations (2.1), i.e.,

$$\dot{x}_i = -x_i + \frac{\sigma x_i^c}{1 + \sum_{j=1}^n x_j^c} + \alpha, \ 1 \leq i \leq n. \tag{3.1}$$

If one component of the equilibrium is zero, then it contradicts the assumption $\alpha > 0$. Thus, $(0, 0, \cdots, 0)$, $(a, 0, 0, \cdots, 0)$, $(a, a, \cdots, a, 0, 0, \cdots, 0)$ can not satisfy the above equations. We have the origin, one switch on and $(n-1)$ off, k switches on with identical components ($k > 1$) and $(n-k)$ off (zero) are not equilibria.

By the numerical illustrations, we guess that if the leak is small, then it does not have a major effect on the systems, except when the cooperativity is close to 1. To give an instance: when $n = 2$, $c = 2$, $\sigma = 3$, $\alpha = 0.01$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{3x_1^2}{1+x_1^2+x_2^2} + 0.01 \\ \dot{x_2} = -x_2 + \frac{3x_2^2}{1+x_1^2+x_2^2} + 0.01 \end{cases},$$

then there exist seven equilibria (0,2.631), (2.631,0), (0.010,0.010), (0,0.368), (0.368,0), (0.471,0.471), (1.029,1.029). The first three are stable; the last four are unstable. The dynamical behavior in figure 4 is similar to (b) in figure 3.

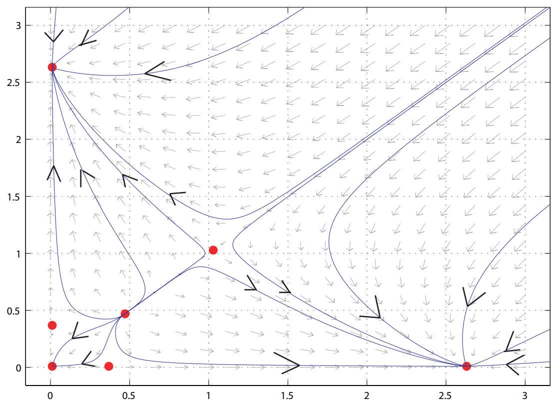


Figure 4: If the leak is small, it does not have a major effect on the system. In addition, it has seven equilibria.

Moreover, we compare the system

$$\begin{cases} \dot{x_1} = -x_1 + \frac{3x_1^{1.1}}{1+x_1^{1.1}+x_2^{1.1}} \\ \dot{x_2} = -x_2 + \frac{3x_2^{1.1}}{1+x_1^{1.1}+x_2^{1.1}} \end{cases} \tag{3.2}$$

with

$$\begin{cases} \dot{x_1} = -x_1 + \frac{3x_1^{1.1}}{1+x_1^{1.1}+x_2^{1.1}} + 0.01 \\ \dot{x_2} = -x_2 + \frac{3x_2^{1.1}}{1+x_1^{1.1}+x_2^{1.1}} + 0.01 \end{cases}. \tag{3.3}$$

In system (3.2), it has seven equilibria: (0,0), (0,2.070) and (2.070,0) are stable; (1,1), (0.00002,0.00002), (0,0.00002) and (0.00002,0) are unstable. In system (3.3), it has three equilibria: (0,2.085) and (2.085,0) are stable; (1.016,1.016) is unstable. The numbers of equilibria is clearly different. Thus, when the leak is small and the cooperativity is close to 1, it has a substantial effect on the systems (see figure 5).

Next, we consider three cases for c, i.e. $c = 0$, $c = 1$, and $c > 1$. If $c = 0$, then (3.1) becomes

$$\dot{x_i} = -x_i + \frac{\sigma}{1+n} + \alpha,\ 1 \le i \le n.$$

Proposition 3.1 : For $c = 0$, there exists a stable equilibrium with all switches on, whose components are identically $\alpha + \sigma/(1+n)$.

Proof: Consider the existence of the equilibrium with all switches on, whose components are identical. Then $(\alpha+\sigma/(1+n), \alpha+\sigma/(1+n), \cdots, \alpha+\sigma/(1+n)) \in \mathbb{R}^n$ is an equilibrium. Next, consider the local stability of the equilibrium. Since α is

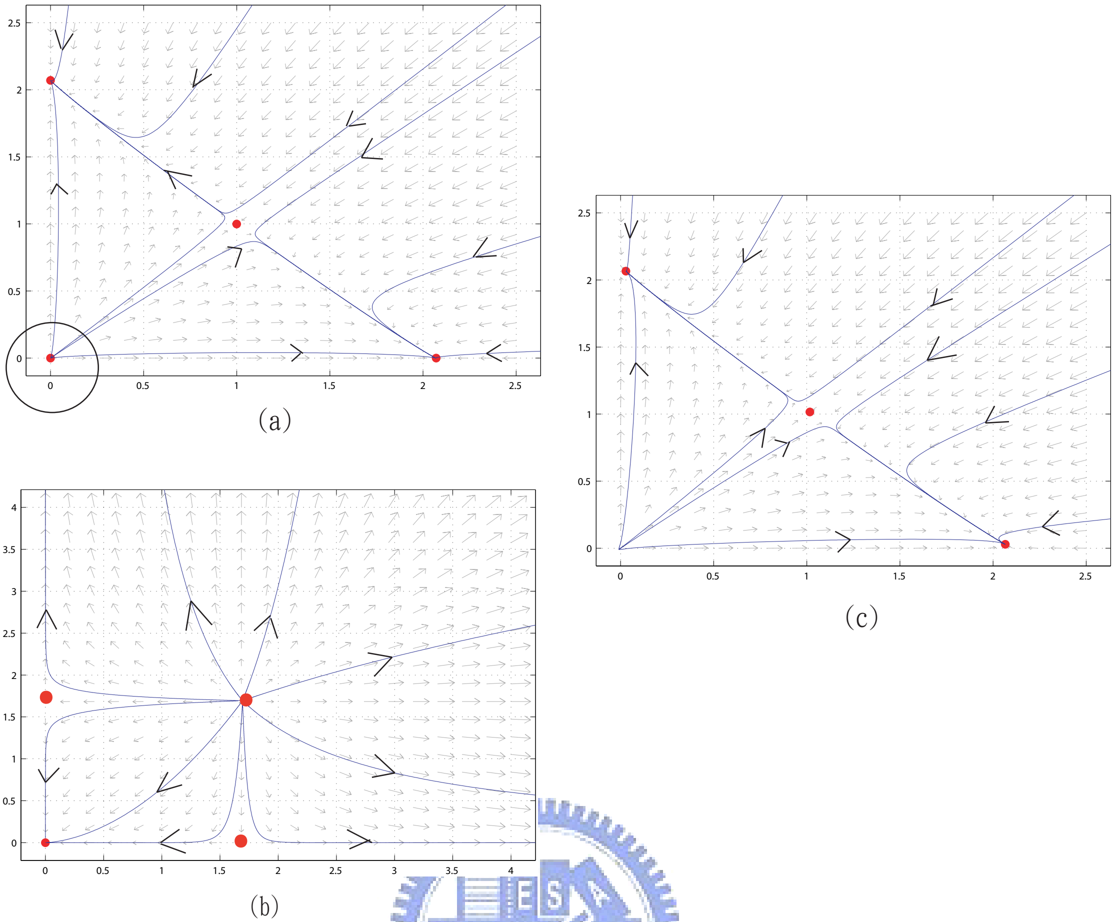


Figure 5: The leak is small and the cooperativity is close to 1, it has a substantial effect on the system. Figure (a) depicts the dynamics of system (3.2). (b) is a zoom-in of (a) near the origin by scale 10^5. (c) is for system (3.3).

constant, it does not affect the linearization at the equilibrium. The result is similar to proposition 2.1. Hence, the equilibrium is stable. The assertion follows.

Next, consider $c = 1$, then (3.1) become

$$\frac{dx_i}{dt} = -x_i + \frac{\sigma x_i}{1 + \sum_{j=1}^{n} x_j} + \alpha,\ 1 \le i \le n.$$

Proposition 3.2 : For $c = 1$, there exists a stable equilibrium with all switches on, whose components are identically $[-1 + n\alpha + \sigma + \sqrt{(1 - n\alpha - \sigma)^2 + 4n\alpha}]/2n$.

Proof: A steady state solution of the form $(a, a, \cdots, a)$ satisfies

$$-a + \frac{\sigma a}{1+na} + \alpha = 0 \text{ or } na^2 + (1 - n\alpha - \sigma)a - \alpha = 0,$$

and the solution of above equation is $[-1 + n\alpha + \sigma + \sqrt{(1 - n\alpha - \sigma)^2 + 4n\alpha}]/2n$. Since α is constant, it does not affect the linearization at the equilibrium. From (2.2), the linearation at $(a, a, \cdots, a)$ is

$$\begin{pmatrix} -1 + \frac{\sigma(1+(n-1)a)}{(1+na)^2} & \frac{-\sigma a}{(1+na)^2} & \cdots & \frac{-\sigma a}{(1+na)^2} \\ \frac{-\sigma a}{(1+na)^2} & -1 + \frac{\sigma(1+(n-1)a)}{(1+na)^2} & \vdots & \vdots \\ \vdots & \cdots & \ddots & \frac{-\sigma a}{(1+na)^2} \\ \frac{-\sigma a}{(1+na)^2} & \cdots & \frac{-\sigma a}{(1+na)^2} & -1 + \frac{\sigma(1+(n-1)a)}{(1+na)^2} \end{pmatrix}.$$

The eigenvalues for this matrix are

$$\lambda_1 = -1 + \frac{\sigma(1+(n-1)a)}{(1+na)^2} + \frac{\sigma a}{(1+na)^2},$$
$$\lambda_2 = -1 + \frac{\sigma(1+(n-1)a)}{(1+na)^2} - \frac{(n-1)\sigma a}{(1+na)^2}.$$

Note that

$$\lambda_1 < 0 \Leftrightarrow \sigma(1+na) < (1+na)^2 \Leftrightarrow \sigma < 1 + na. \tag{3.4}$$

From the steady state equation, then $1 + na = \sigma a/(a - \alpha)$. With it to substitute for the inequality (3.4). We have $\sigma < 1 + na = \sigma a/(a - \alpha)$, i.e., $\sigma\alpha > 0$. Hence, for $c = 1$, in any condition (since $\sigma > 0$ and $\alpha > 0$), then $(a, a, \cdots, a)$ is stable. Thus, the assertion follows.

Example 3.1 : In proposition 3.2, if $n = 2$, $\sigma = 2$, and $\alpha = 1$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{2x_1}{1+x_1+x_2} + 1 \\ \dot{x_2} = -x_2 + \frac{2x_2}{1+x_1+x_2} + 1 \end{cases},$$

then (1.781,1.781) is a stable equilibrium since $\sigma\alpha = 2 > 0$ (see figure 6).

We consider $c > 1$ in the following discussions . There exist two kinds of stable equilibria. In proposition 3.3, we discuss the equilibrium with all switches on, whose components are identically less than $c\alpha/(c-1)$. The other one is that the components consists of two different values. In proposition 3.4, we restrict to the

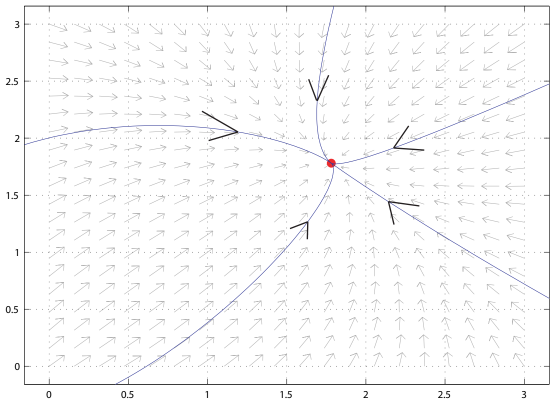


Figure 6: (1.781,1.781) is a stable equilibrium (in example 3.1).

case with dimension $n = 2, 3$; in proposition 3.5, we consider the case for dimension $n \geq 4$.

The result of proposition 3.3 is sketched in [4]. We recast it with more details.

Proposition 3.3 : For $c > 1$, there exist stable equilibrium with all switches on, whose components are identically a with $a < c\alpha/(c-1)$.

Proof: A steady state solution of the form $(a, a, \cdots, a)$ satisfies

$$-a + \frac{\sigma a^c}{1 + na^c} + \alpha = 0$$

or $na^{c+1} - (\sigma + n\alpha)a^c + a = \alpha$. Set $h(\zeta) = n\zeta^{c+1} - (\sigma + n\alpha)\zeta^c + \zeta$. We compute that

$$h'(\zeta) = n(c+1)\zeta^c - c(\sigma + n\alpha)\zeta^{c-1} + 1$$
$$h''(\zeta) = nc(c+1)\zeta^{c-1} - c(\sigma + n\alpha)(c-1)\zeta^{c-2}.$$

Therefore, $\zeta = (\sigma + n\alpha)(c-1)/n(c+1)$ is the reflection point. And $h(\zeta) \to \infty$ as $\zeta \to \infty$, and $h(\zeta)$ passes point $(0, 0)$, We have the curve of the function $h(\zeta)$ is down in the left side of the reflective point and is upper in the other. Further, there is intersection of $h(\zeta)$ and horizontal line α. Thus, it there is one solution.

Next, consider the local stability of $(a, a, \cdots, a)$. Since α is constant, it does not affect the linearization at the equilibrium. From (2.7), we have the greatest eigenvalue is $-1+\sigma ca^{c-1}/(1+na^c)$. And with the above steady state equation, then $1+na^c = \sigma a^c/(a-\alpha)$. If the greatest eigenvalue is negative, then $\sigma ca^{c-1} < 1+na^c$. We substitute $1+na^c$ for $\sigma a^c/(a-\alpha)$ in the above inequality. Thus, $(a, a, \cdots, a)$ is stable if $a < c\alpha/(c-1)$. The assertion follows.

We consider $n = 2$ and there exists an equilibrium (a, b) where $a > b$. Then (a, b) satisfies

$$\begin{cases} a^{c+1} - (\alpha+\sigma)a^c + (1+b^c)a - \alpha(1+b^c) = 0 \\ b^{c+1} - (\alpha+\sigma)b^c + (1+a^c)b - \alpha(1+a^c) = 0 \end{cases},$$

and $n = 3$ and there exists equilibrium (a, a, b) where $a > b$. Then (a, a, b) satisfies

$$\begin{cases} 2a^{c+1} - (2\alpha+\sigma)a^c + (1+b^c)a - \alpha(1+b^c) = 0 \\ b^{c+1} - (\alpha+\sigma)b^c + (1+2a^c)b - \alpha(1+2a^c) = 0 \end{cases},$$

Proposition 3.4 : Let $c > 1$.

(i) If $n = 2$ and the equilibrium (a, b) exists. Then it is stable if $\sigma^2c^2a^{2c-1}b^{2c-1} < (-(1+a^c+b^c)^2 + \sigma c(1+b^c)a^{c-1})(-(1+a^c+b^c)^2 + \sigma c(1+a^c)b^{c-1})$, with one switch-on with value a, and one off with value b.

(ii) If $n = 3$, $\sigma ca^{c-1} < 1 + 2a^c + b^c$ and the equilibrium (a, a, b) exists. Then it is stable if $2\sigma^2c^2a^{2c-1}b^{2c-1} < (-(1+2a^c+b^c)^2 + \sigma c(1+2a^c)b^{c-1})(-(1+2a^c+b^c)^2 + \sigma c(1+b^c)a^{c-1})$, with two switches-on with value a identically, and one off with value b. In addition, if a change for b, then we have the condition of the stability for the equilibrium with one switch-on with value a, and two off with value b identically.

Proof: We analysis the stability for these equilibria.
(i) From (2.2), the linearization at (a, b) is

$$\begin{pmatrix} -1 + \frac{\sigma c(1+pb^c)a^{c-1}}{(1+a^c+b^c)^2} & \frac{-\sigma ca^cb^{c-1}}{(1+a^c+b^c)^2} \\ \frac{-\sigma ca^{c-1}b^c}{(1+a^c+b^c)^2} & -1 + \frac{\sigma c(1+ka^c)b^{c-1}}{(1+a^c+b^c)^2} \end{pmatrix} \overset{\text{let}}{=} \begin{pmatrix} d & u \\ v & m \end{pmatrix}.$$

We have two eigenvalues are $[d+m+\sqrt{(d-m)^2+4uv}]/2$ and $[d+m-\sqrt{(d-m)^2+4uv}]/2$. If the larger is negative, i.e.,

$$\sigma^2c^2a^{2c-1}b^{2c-1} < (-(1+a^c+b^c)^2 + \sigma c(1+b^c)a^{c-1})(-(1+a^c+b^c)^2 + \sigma c(1+a^c)b^{c-1}),$$

then all eigenvalues are negative, i.e., (a, b) and (b, a) are stable.
(ii) From (2.2), the linearization at (a, a, b) is

$$\begin{pmatrix} -1 + \frac{\sigma c(1+a^c+b^c)a^{c-1}}{(1+2a^c+b^c)^2} & \frac{-\sigma ca^{2c-1}}{(1+2a^c+b^c)^2} & \frac{-\sigma ca^cb^{c-1}}{(1+2a^c+b^c)^2} \\ \frac{-\sigma ca^{2c-1}}{(1+2a^c+b^c)^2} & -1 + \frac{\sigma c(1+a^c+b^c)a^{c-1}}{(1+2a^c+b^c)^2} & \frac{-\sigma ca^cb^{c-1}}{(1+2a^c+b^c)^2} \\ \frac{-\sigma cb^ca^{c-1}}{(1+2a^c+b^c)^2} & \frac{-\sigma cb^ca^{c-1}}{(1+2a^c+b^c)^2} & -1 + \frac{\sigma c(1+2a^c)b^{c-1}}{(1+2a^c+b^c)^2} \end{pmatrix} \overset{\text{let}}{=} \begin{pmatrix} d & r & u \\ r & d & u \\ v & v & m \end{pmatrix}.$$

We have three eigenvalues are $d-r$, $[d+r+m+\sqrt{(d+r-m)^2+8uv}]/2$ and $[d+r+m-\sqrt{(d+r-m)^2+8uv}]/2$. If $d-r<0$ and $2uv<m(d+r)$, i.e., $\sigma c a^{c-1}<1+2a^c+b^c$ and
$2\sigma^2c^2a^{2c-1}b^{2c-1}<(-(1+2a^c+b^c)^2+\sigma c(1+2a^c)b^{c-1})(-(1+2a^c+b^c)^2+\sigma c(1+b^c)a^{c-1})$, then all eigenvalues are negative. Thus, (a,a,b), (a,b,a) and (b,a,a) are stable. In addition, if a change for b, then we have the condition of the stability for the equilibrium with one switch-on with value a, and two off with value b identically. Thus, the assertion follows.

Let $p=n-k$. The steady state solution of the form $(a,a,\cdots,a,b,b,\cdots,b)$ with $k's$ a and $p's$ b satisfies

$$\begin{cases} ka^{c+1}-(\alpha k+\sigma)a^c+(1+pb^c)a-\alpha(1+pb^c)=0 \\ pb^{c+1}-(\alpha p+\sigma)b^c+(1+ka^c)b-\alpha(1+ka^c)=0 \end{cases},$$

We assume such equilibrium exist.

The following characteristic polynomial has been mentioned in [4] without computing eigenvalues for system (3.5). We provide linear stability analysis for these equilibrium in the following proposition 3.5.

Proposition 3.5 :For $c>1$, $n\geq 4$, $k>1$, and the equilibrium $(a,a,\cdots,a,b,b,\cdots,b)$ with $k's$ a and $p's$ b exists. Then it is stable if $\sigma c a^{c-1}<1+ka^c+(n-k)b^c$ with k switches-on with value a identically, and $(n-k)$ off with value b identically.

Proof: From(2.2), the linearization at $(a,a,\cdots,a,b,b,\cdots,b)$ is

$$\begin{pmatrix} d & r & \cdots & r & u & \cdots & \cdots & u \\ r & d & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \cdots & \ddots & r & \vdots & \vdots & \vdots & \vdots \\ r & \cdots & r & d & u & \cdots & \cdots & u \\ v & \cdots & \cdots & v & m & s & \cdots & s \\ \vdots & \vdots & \vdots & \vdots & s & m & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \cdots & \ddots & s \\ v & \cdots & \cdots & v & s & \cdots & s & m \end{pmatrix} \tag{3.5}$$

where

$$
\begin{aligned}
d &= -1 + \frac{\sigma c(1+(k-1)a^c + pb^c)a^{c-1}}{(1+ka^c+pb^c)^2}, \\
m &= -1 + \frac{\sigma c(1+ka^c + (p-1)b^c)b^{c-1}}{(1+ka^c+pb^c)^2}, \\
r &= \frac{-\sigma c a^{2c-1}}{(1+ka^c+pb^c)^2}, \\
s &= \frac{-\sigma c b^{2c-1}}{(1+ka^c+pb^c)^2}, \\
u &= \frac{-\sigma c a^c b^{c-1}}{(1+ka^c+pb^c)^2}, \\
v &= \frac{-\sigma c a^{c-1} b^c}{(1+ka^c+pb^c)^2}.
\end{aligned}
$$

We do row operations and column operations.

$$
\begin{pmatrix}
d & r & \cdots & r & u & 0 & \cdots & 0 \\
r & d & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\vdots & \cdots & \ddots & r & \vdots & \vdots & \vdots & \vdots \\
r & \cdots & r & d & u & 0 & \cdots & 0 \\
v & \cdots & \cdots & v & m & s-m & \cdots & s-m \\
\vdots & \vdots & \vdots & \vdots & s & m-s & & \mathbf{0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & & \ddots & \\
v & \cdots & \cdots & v & s & \mathbf{0} & & m-s
\end{pmatrix} \rightarrow
$$

$$
\begin{pmatrix}
d-r & & \mathbf{0} & r-d & 0 & 0 & \cdots & 0 \\
 & \ddots & & \vdots & \vdots & \vdots & \vdots & \vdots \\
\mathbf{0} & & d-r & r-d & 0 & \vdots & \vdots & \vdots \\
r & \cdots & r & d & u & 0 & \cdots & 0 \\
v & \cdots & \cdots & v & m & s-m & \cdots & s-m \\
\vdots & \vdots & \vdots & \vdots & s & m-s & & \mathbf{0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & & \ddots & \\
v & \cdots & \cdots & v & s & \mathbf{0} & & m-s
\end{pmatrix} \rightarrow
$$

$$
\begin{pmatrix}
d-r & & \mathbf{0} & r-d & 0 & 0 & \cdots & 0 \\
 & \ddots & & \vdots & \vdots & \vdots & \vdots & \vdots \\
\mathbf{0} & & d-r & r-d & 0 & \vdots & \vdots & \vdots \\
r & \cdots & r & d & u & 0 & \cdots & 0 \\
pv & \cdots & \cdots & pv & m+(p-1)s & 0 & \cdots & 0 \\
v & \cdots & \cdots & v & s & m-s & & \mathbf{0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & & \ddots & \\
v & \cdots & \cdots & v & s & \mathbf{0} & & m-s
\end{pmatrix} \rightarrow
$$

$$
\begin{pmatrix}
d-r & & \mathbf{0} & 0 & 0 & 0 & \cdots & 0 \\
 & \ddots & & \vdots & \vdots & \vdots & \vdots & \vdots \\
\mathbf{0} & & d-r & 0 & 0 & \vdots & \vdots & \vdots \\
r & \cdots & r & d+(k-1)r & u & 0 & \cdots & 0 \\
pv & \cdots & pv & kpv & m+(p-1)s & 0 & \cdots & 0 \\
v & \cdots & v & kv & s & m-s & & \mathbf{0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & & \ddots & \\
v & \cdots & v & kv & s & \mathbf{0} & & m-s
\end{pmatrix}.
$$

The characteristic polynomial of the matrix is
$(m-s-x)^{p-1}(d-r-x)^{k-1}((d+(k-1)r-x)(m+(p-1)s-x)-kpuv) = (m-s-x)^{p-1}(d-r-x)^{k-1}(x^2-(d+m+(k-1)r+(p-1)s)x+dm+(p-1)sd+(k-1)mr+(k-1)(p-1)rs-kpuv)$.
We have two eigenvalues are

$$
d-r = -1+\frac{\sigma c a^{c-1}}{1+ka^c+pb^c},
$$

$$
m-s = -1+\frac{\sigma c b^{c-1}}{1+ka^c+pb^c}.
$$

If the larger is negative, then $\sigma c a^{c-1} < 1+ka^c+pb^c$. The others satisfy

$$
\begin{aligned}
\lambda_1+\lambda_2 &= d+m+(k-1)r+(p-1)s \\
&= (d-r)+(m-s)+kr+ps < 0, \text{ and} \\
\lambda_1\lambda_2 &= (p-1)sd+(k-1)mr+(k-1)(p-1)rs+dm-kpuv \\
&= ps(d-r)+kr(m-s)+(s-m)(r-d) > 0.
\end{aligned}
$$

So, if $\sigma c a^{c-1} < 1+ka^c+pb^c$, then all eigenvalues are negative, i.e., the equilibrium is stable. The assertion follows.

In proposition 3.6, the main result is proposed from [4], but we recast it with more details.

Proposition 3.6. ([4]) : For $c \geq 1/2$, every solution of systems (2.1) tends to an equilibrium as time tends to infinity.

Proof: Let $y_i = \sqrt{x_i}$. Then $\dot{y_i} = \dot{x_i}/2y_i$, i.e.,

$$\begin{aligned}\dot{y_i} &= \frac{-x_i + \frac{\sigma x_i^c}{1+\sum_{j=1}^n x_j^c} + \alpha}{2y_i} = \frac{-y_i^2 + \frac{\sigma y_i^{2c}}{1+\sum_{j=1}^n y_j^{2c}} + \alpha}{2y_i} \\ &= \frac{1}{2}(-y_i + \frac{\sigma y_i^{2c-1}}{1+\sum_{j=1}^n y_j^{2c}} + \frac{\alpha}{y_i}) \\ &= -\frac{\partial V}{\partial y_i},\end{aligned}$$

where

$$V(y_i) = \frac{1}{4}\sum_{j=1}^n y_j^2 - \frac{\sigma}{4c}\log(1+\sum_{j=1}^n y_j^{2c}) - \frac{1}{2}\log(\prod_{j=1}^n y_j^{\alpha}).$$

Thus $\dot{y_i} = \dot{x_i}/2y_i$ is a gradient system. Moreover

$$-y_i + \frac{\sigma y_i^{2c-1}}{1+\sum_{j=1}^n y_j^{2c}} + \frac{\alpha}{y_i} = 0 \Leftrightarrow -x_i + \frac{\sigma x_i^c}{1+\sum_{j=1}^n x_j^c} + \alpha = 0.$$

By the Lasalle's invariant principle [1], thus, every solution of the system converges to one of the equilibria as time tends to infinity. The assertion follows.

Example 3.2 : In proposition 3.3 and 3.4, if $n = 2$, $c = 2$, $\sigma = 2$ and $\alpha = 0.1$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{2x_1^2}{1+x_1^2+x_2^2} + 0.1 \\ \dot{x_2} = -x_2 + \frac{2x_2^2}{1+x_1^2+x_2^2} + 0.1 \end{cases}. \tag{3.6}$$

First, consider (a, a) is an equilibrium, we have

$$-a + \frac{2a^2}{1+2a^2} + 0.1 = 0,$$

or $20a^3 - 22a^2 + 10a - 1 = 0$, it only exists a real root. Thus, (0.135, 0.135) is a stable equilibrium since $a = 0.135 < 0.2 = c\alpha/(c-1)$. Next, consider (a, b), and (b, a) are equilibria, we have

$$\begin{cases} -a + \frac{2a^2}{1+a^2+b^2} + 0.1 = 0 \\ -b + \frac{2b^2}{1+a^2+b^2} + 0.1 = 0 \end{cases}.$$

By calculating, we have $100b^4 - 22b^3 + 121b^2 - 20b + 2 = 0$, the solutions only have two real roots. Thus, there exist four equilibria: (0.107, 1.458), (1.458, 0.107), (0.122, 0.557), and (0.557, 0.122). The first two are stable and the last two are unstable since they satisfy the condition in proposition 3.4.

If consider $y_i = \sqrt{x_i}$, then the above system become

$$\begin{cases} \dot{y_1} = \frac{1}{2}(-y_1 + \frac{2y_1^3}{1+y_1^4+y_2^4} + \frac{0.1}{y_1}) \\ \dot{y_2} = \frac{1}{2}(-y_2 + \frac{3y_2^3}{1+y_1^4+y_2^4} + \frac{0.1}{y_2}) \end{cases}. \tag{3.7}$$

We see that the two systems (3.6) and (3.7) have same dynamical behavior (see figure 7).

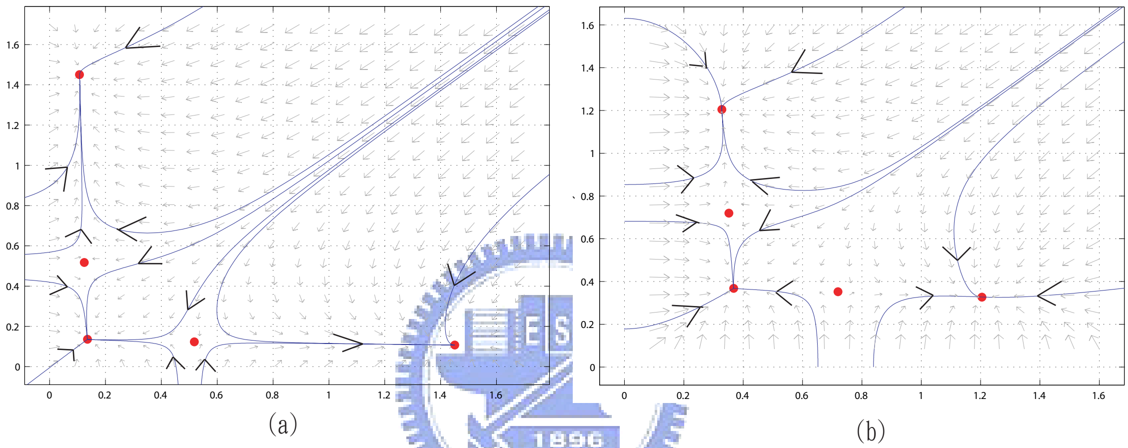


Figure 7: (a) is for $\dot{x}_i(t)$ system and (b) is for $\dot{y}_i(t)$. They have same dynamical behavior.

In this section, for any c, the origin, one switch on and $(n-1)$ off, k switches on with identical components $k > 1$ and $(n-k)$ off (zero) are not equilibria. The result is different to section 2. For $c = 0$, there exists a stable equilibrium with all switches on, whose components are identically $\alpha + \sigma/(1+n)$.

For $c = 1$, there exists a stable equilibrium with all switches on, whose components are identically $[-1 + n\alpha + \sigma + \sqrt{(1 - n\alpha - \sigma)^2 + 4n\alpha}]/2n$.

For $c > 1$, there exist stable equilibrium with all switches on, whose components are identically lower than $c\alpha/(c-1)$. It is also different to proposition 2.3. Moreover,

(i) If $n = 2$ and the equilibrium (a, b) exists. Then it is stable if $\sigma^2 c^2 a^{2c-1} b^{2c-1} < (-(1 + a^c + b^c)^2 + \sigma c(1 + b^c)a^{c-1})(-(1 + a^c + b^c)^2 + \sigma c(1 + a^c)b^{c-1})$, with one switch-on with value a, and one off with value b.

(ii) If $n = 3$, $\sigma c a^{c-1} < 1 + 2a^c + b^c$ and the equilibrium (a, a, b) exists. Then it is stable if $2\sigma^2 c^2 a^{2c-1} b^{2c-1} < (-(1 + 2a^c + b^c)^2 + \sigma c(1 + 2a^c)b^{c-1})(-(1 + 2a^c + b^c)^2 + \sigma c(1 + b^c)a^{c-1})$, with two switches-on with value a identically, and one off with value b. In addition, if a change for b, then we have the condition of the stability for the equilibrium with one switch-on with value a, and two off with value b identically.

Finally, the model is a gradient system, we also justify that the global convergence for the system.

4 A model for bHLH proteins

In this section, consider the bHLH proteins model

$$\dot{x}_i = -x_i + \frac{\sigma(\frac{a_t x_i}{1+\sum_{j=1}^n x_j})^c}{K_c + (\frac{a_t x_i}{1+\sum_{j=1}^n x_j})^c}, \ 1 \le i \le n$$

where $K_c = \alpha a_t^c$ is binding constant and a_t is a total quantity of activator. Set $D = 1 + \sum_{j=1}^n x_j$, the above equations become

$$\dot{x}_i = -x_i + \frac{\sigma x_i^c}{\alpha D^c + x_i^c}, \ 1 \le i \le n \tag{4.1}$$

where $\alpha = \frac{K_c}{a_t^c} \in \mathbb{R}^+$ is a measure of the harshness of the competition between switches. In the following, consider two cases for c, i.e. $c = 1$ and $c = 2$. When $c = 1$, then (4.1) become

$$\dot{x}_i = x_i(-1 + \frac{\sigma}{\alpha(1 + \sum_{j=1}^n x_j) + x_i}), \ 1 \le i \le n. \tag{4.2}$$

Note that the Jacobian matrix of the vector field is $J = [J_{ij}]$ with

$$J_{i,i} = -1 + \frac{\sigma\alpha(1 + \sum_{j\ne i}^n x_j)}{(\alpha(1 + \sum_{j=1}^n x_j) + x_i)^2}, \tag{4.3}$$
$$J_{i,j} = \frac{-\sigma\alpha x_i}{(\alpha(1 + \sum_{j=1}^n x_j) + x_i)^2} \text{ for } j \ne i.$$

In proposition 4.1, the result of (i) is new. In addition, the results of (ii) and (iii) are stated in [4], but we recast them with more details.

Proposition 4.1 : Let $c = 1$.

(i) If $\sigma < \alpha$, then the origin is stable.

(ii) If $\sigma > \alpha$ and $1 \leq k < n$, then there exist unstable equilibria with k switches on, whose components are identically $(\sigma - \alpha)/(\alpha k + 1)$, and $(n - k)$ off (zero).

(iii) There exists a stable equilibrium with all switches on, whose components are identically $(\sigma - \alpha)/(\alpha n + 1)$.

Proof: (i) The linearizaation at the origin is

$$\begin{pmatrix} -1+\frac{\sigma}{\alpha} & 0 & \cdots & 0 \\ 0 & -1+\frac{\sigma}{\alpha} & \vdots & \vdots \\ \vdots & \cdots & \ddots & 0 \\ 0 & \cdots & 0 & -1+\frac{\sigma}{\alpha} \end{pmatrix}.$$

If $-1 + \frac{\sigma}{\alpha} < 0$ or $\sigma < \alpha$, then the origin is stable. The result follows.

(ii) The steady state equation for the $(a, a, \cdots, a, 0, 0, \cdots, 0)$, $a \neq 0$ is an equilibrium if and only if

$$-a + \frac{\sigma a}{\alpha(1 + ka) + a} = 0,$$

i.e. $a = (\sigma - \alpha)/(\alpha k + 1) > 0$. Thus, $\sigma > \alpha$ is the condition of existence. From (4.3), the linearization at $(a, a, \cdots, a, 0, 0, \cdots, 0)$ is

$$\left(\begin{array}{ccc|ccc} -1+\frac{\sigma\alpha(1+(k-1)a)}{(\alpha(1+ka)+a)^2} & & \frac{-\sigma\alpha a}{(\alpha(1+ka)+a)^2} & & & \\ & \ddots & & & \frac{-\sigma\alpha a}{(\alpha(1+ka)+a)^2} & \\ \frac{-\sigma\alpha a}{(\alpha(1+ka)+a)^2} & & -1+\frac{\sigma\alpha(1+(k-1)a)}{(\alpha(1+ka)+a)^2} & & & \\ \hline & & & -1+\frac{\sigma}{\alpha(1+ka)} & & \mathbf{0} \\ & \mathbf{0} & & & \ddots & \\ & & & \mathbf{0} & & -1+\frac{\sigma}{\alpha(1+ka)} \end{array}\right).$$

So, $-1 + \sigma/\alpha(1 + ka)$ is a eigenvalue. To substitute a for $(\sigma - \alpha)/(\alpha k + 1)$. Thus, the above eigenvalue becomes $-1 + (\sigma\alpha k + \sigma)/(\sigma\alpha k + \alpha)$. It always positive. Moreover, when $k = 1$, the above result also holds. Thus, $(a, 0, 0, \cdots, 0)$ and $(a, a, \cdots, a, 0, 0, \cdots, 0)$ are unstable equilibria. The result follows.

(iii) The steady state equation for the $(a, a, \cdots, a)$, $a \neq 0$ is an equilibrium if and only if

$$-a + \frac{\sigma a}{\alpha(1+na)+a} = 0,$$

i.e., $a = (\sigma - \alpha)/(\alpha n + 1) > 0$. Thus, $\sigma > \alpha$ is the condition of existence. From (4.3), the linearization at $(a, a, \cdots, a)$ is

$$\begin{pmatrix} -1+\frac{\sigma\alpha(1+(n-1)a)}{(\alpha(1+na)+a)^2} & \frac{-\sigma\alpha a}{(\alpha(1+na)+a)^2} & \cdots & \frac{-\sigma\alpha a}{(\alpha(1+na)+a)^2} \\ \frac{-\sigma\alpha a}{(\alpha(1+na)+a)^2} & -1+\frac{\sigma\alpha(1+(n-1)a)}{(\alpha(1+na)+a)^2} & \vdots & \vdots \\ \vdots & \cdots & \ddots & \frac{-\sigma\alpha a}{(\alpha(1+na)+a)^2} \\ \frac{-\sigma\alpha a}{(\alpha(1+na)+a)^2} & \cdots & \frac{-\sigma\alpha a}{(\alpha(1+na)+a)^2} & -1+\frac{\sigma\alpha(1+(n-1)a)}{(\alpha(1+na)+a)^2} \end{pmatrix}.$$

By Lemma 2.1, the eigenvalues are

$$\lambda_1 = -1 + \frac{\sigma\alpha(1+na)}{(\alpha(1+na)+a)^2}, \text{ and}$$
$$\lambda_2 = -1 + \frac{\sigma\alpha}{(\alpha(1+na)+a)^2} < \lambda_1.$$

If λ_1 is negative, then

$$\sigma\alpha(1+na) < (\alpha(1+na)+a)^2.$$

To substitute $a(\alpha n+1)$ for $(\sigma-\alpha)$, the above inequality becomes $\sigma\alpha(1+na) < \sigma^2$. i.e., $a < (\sigma-\alpha)/\alpha n$. It always holds since $a = (\sigma-\alpha)/(\alpha n+1)$. Hence, we have $(a, a, \cdots, a)$ is stable. The assertion follows.

Example 4.1 : In proposition 4.1, if $n = 2$, $\sigma = 2$ and $\alpha = 3$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{2x_1}{3(1+x_1+x_2)+x_1} \\ \dot{x_2} = -x_2 + \frac{2x_2}{3(1+x_1+x_2)+x_2} \end{cases},$$

then $(0, 0)$ is stable equilibrium, since it satisfies $\sigma < \alpha$.

Next, if $n = 2$, $\sigma = 3$ and $\alpha = 2$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{3x_1}{2(1+x_1+x_2)+x_1} \\ \dot{x_2} = -x_2 + \frac{3x_2}{2(1+x_1+x_2)+x_2} \end{cases},$$

then there exist four equilibria: $(0.2, 0.2)$ is stable; moreover, $(0, 0)$, $(1/3, 0)$, $(0, 1/3)$ are unstable (see figure 8).

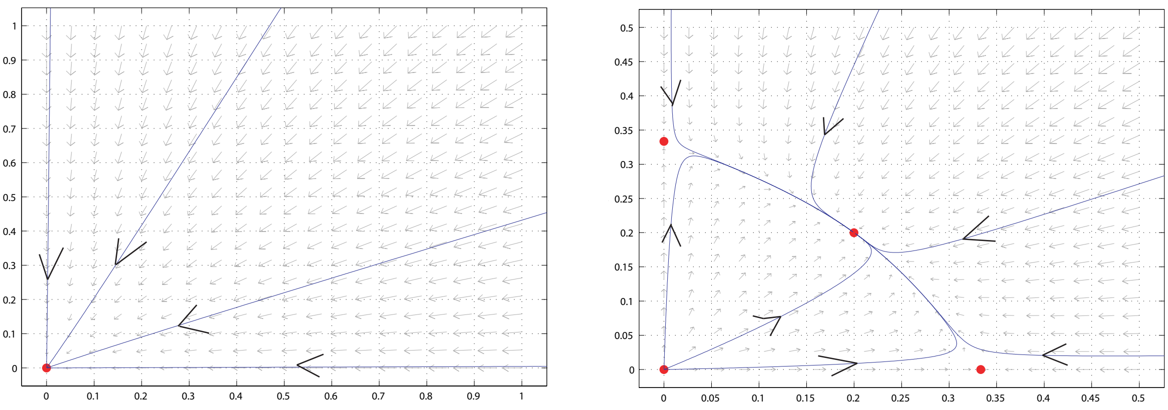


Figure 8: In figure (a), $(0,0)$ is stable. In (b), $(0.2,0.2)$ is stable; moreover, $(0,0)$, $(1/3,0)$, $(0,1/3)$ are unstable (Example 4.1).

In the following, it is assumed that transcriptional activation occurs with cooperativity $c=2$. The systems (4.1) become

$$\dot{x}_i = -x_i + \frac{\sigma x_i^2}{\alpha D^2 + x_i^2} \tag{4.4}$$

where $D = 1 + \sum_{j=1}^{n} x_j$, and $\alpha = \frac{K_2}{a_i^2}$. The steady state equation is

$$x_i = \frac{\sigma x_i^2}{\alpha D^2 + x_i^2}$$

or $\alpha D^2 + x_i^2 = \sigma x_i$ if $x_i \neq 0$. Note that

$$J_{i,i} = -1 + 2\sigma\alpha x_i \frac{D(D-x_i)}{(\alpha D^2 + x_i^2)^2} = 1 - \frac{2}{\sigma}(x_i + \alpha D) \text{ if } x_i \neq 0, \tag{4.5}$$

$$J_{i,j} = \frac{-2\alpha D \sigma x_i^2}{(\alpha D^2 + x_i^2)^2} = \frac{-2\alpha D}{\sigma} \text{ if } x_i \neq 0 \text{ for all } j \neq i.$$

Clearly, the origin is a stable equilibrium, since the linearization at the origin is

$$\begin{pmatrix} -1 & 0 & \cdots & 0 \\ 0 & -1 & \vdots & \vdots \\ \vdots & \cdots & \ddots & 0 \\ 0 & \cdots & 0 & -1 \end{pmatrix}.$$

Thus, all eigenvalues are -1.

In proposition 4.2, the results are stated in [4]. We provide detailed proof herein.

Proposition 4.2. ([4]) Let $c = 2$, and $1 \le k \le n$.

(i) If $4\alpha(k\sigma+1)/\sigma^2 \le 1$, then there exist equilibria with k switches on, whose components are identically $[\sigma - 2\alpha k + \sqrt{\sigma^2 - 4\alpha(k\sigma+1)}]/2(1+\alpha k^2)$ or $[\sigma - 2\alpha k - \sqrt{\sigma^2 - 4\alpha(k\sigma+1)}]/2(1+\alpha k^2)$, and $(n-k)$ off (zero). In short, the condition of existence is $\alpha < 1/k^2$.

(ii) When $k = 1$, if the non-zero components are larger than $(\sigma - 2\alpha)/2(1+\alpha)$, then the above equilibria are stable.

(iii) When $1 < k \le n$, if the non-zero components are larger than $\alpha/2$, then the above equilibria are stable. In short, the condition of stability is $\sigma > 2\sqrt{\alpha}/(1-k\sqrt{\alpha})$.

Proof: (i) The steady state equation for $(a, a, \cdots, a, 0, 0, \cdots, 0)$, $a \ne 0$ is an equilibrium if and only if

$$-a + \frac{\sigma a^2}{\alpha(1+ka)^2 + a^2} = 0$$

i.e.,

$$a^2(1+\alpha k^2) + a(2\alpha k - \sigma) + \alpha = 0 \text{ if } a \ne 0.$$

The solutions are

$$a = \frac{\sigma - 2\alpha k \pm \sqrt{\sigma^2 - 4\alpha(k\sigma+1)}}{2(1+\alpha k^2)}.$$

A sufficient and necessary condition for the existence is $4\alpha(k\sigma+1)/\sigma^2 \le 1$. However, from (4.4), we have

$$a^2 - \sigma a + \alpha D^2 = 0.$$

The only solution is $a = (\sigma + \sqrt{\sigma^2 - 4\alpha D^2})/2$, where $D \le \sigma/2\sqrt{\alpha}$. Note that

$$D - 1 = n(\frac{\sigma + \sqrt{\sigma^2 - 4\alpha D^2}}{2}),$$

it can rearranged to

$$2 + n\sigma + n\sqrt{\sigma^2 - 4\alpha D^2} \le \frac{\sigma}{\sqrt{\alpha}}.$$

It follows that $n\sigma < \sigma/\sqrt{\alpha}$, or $\alpha < 1/n^2$. Since $\alpha < 1/n^2 < 1/k^2$. In short, the condition of existence is $\alpha < 1/k^2$.

(ii) From (4.5), the linearization at $(a, 0, 0, \cdots, 0)$ is

$$\left(\begin{array}{c|cc} 1-\frac{2}{\sigma}(a+\alpha(1+a)) & -\frac{2\alpha(1+a)}{\sigma} & \\ \hline & -1 & 0 \\ 0 & & \ddots \\ & 0 & -1 \end{array}\right).$$

If $1 - 2(a + \alpha(1 + a))/\sigma$ is negative, then all eigenvalues are negative. Thus, if $a > (\sigma - 2\alpha)/2(1 + \alpha)$, then this equilibrium is stable.

(iii) First, consider $k = n$, from (4.5), the linearization at $(a, a, \cdots, a)$ is

$$\begin{pmatrix} 1-\frac{2}{\sigma}(a+\alpha(1+na)) & \frac{-2\alpha(1+na)}{\sigma} & \cdots & \frac{-2\alpha(1+na)}{\sigma} \\ \frac{-2\alpha(1+na)}{\sigma} & 1-\frac{2}{\sigma}(a+\alpha(1+na)) & \vdots & \vdots \\ \vdots & \cdots & \ddots & \frac{-2\alpha(1+na)}{\sigma} \\ \frac{-2\alpha(1+na)}{\sigma} & \cdots & \frac{-2\alpha(1+na)}{\sigma} & \frac{2}{\sigma}(a+\alpha(1+na)) \end{pmatrix}.$$

By Lemma 2.1, the eigenvalues are

$$\lambda_1 = 1 - \frac{2a}{\sigma}, \text{ and}$$
$$\lambda_2 = 1 - \frac{2a + 2\alpha n(1 + na)}{\sigma} < \lambda_1.$$

If $\lambda_1 < 0$, i.e., $a > \sigma/2$, then $(a, a, \cdots, a)$ is stable. To replace with the solution, we have

$$\sigma - 2\alpha n + \sqrt{\sigma^2 - 4\alpha(n\sigma + 1)} > \sigma + n^2\alpha\sigma.$$

The solution of the equation

$$(1 - n^4\alpha^2)\sigma^2 - (4\alpha n + 4n^3\alpha^2)\sigma - 4\alpha - 4n^2\alpha^2 > 0$$

are $\sigma > 2\sqrt{\alpha}/(1 - n\sqrt{\alpha})$.

Next, consider $1 < k < n$, the linearization at $(a, a, \cdots, a, 0, 0, \cdots 0)$ is

$$\left(\begin{array}{ccc|cc} 1-\frac{2(a+\alpha(1+ka))}{\sigma} & & \frac{-2\alpha(1+ka)}{\sigma} & & \\ & \ddots & & \frac{-2\alpha(1+ka)}{\sigma} & \\ \frac{-2\alpha(1+ka)}{\sigma} & & 1-\frac{2(a+\alpha(1+ka))}{\sigma} & & \\ \hline & & & -1 & 0 \\ & 0 & & & \ddots \\ & & & 0 & -1 \end{array}\right)$$

Since $\sigma > 2\sqrt{\alpha}/(1-n\sqrt{\alpha}) > 2\sqrt{\alpha}/(1-k\sqrt{\alpha})$, then $(a, a, \cdots, a, 0, 0, \cdots 0)$ is also stable. The assertion follows.

In proposition 4.3, the results are stated in [4]. We provide detailed proof herein.

Proposition 4.3. ([4]) For $c = 2$, $n \geq 4$, and $k > 1$, there exist unstable equilibria with k switches on with value a identically, and $(n-k)$ off with value b identically.

Proof: Without loss of generality, assume $a > b$. By the steady state equation,

$$a^2 - \sigma a = b^2 - \sigma b$$

or $(a-b)(a+b-\sigma) = 0$, we have $a + b = \sigma$. Let $p = n - k$, from (4.5), the linearization at $(a, a, \cdots, a, b, b, \cdots, b)$ is

$$\left(\begin{array}{ccc|ccc}
\frac{\sigma-2(a+\alpha(1+ka+pb))}{\sigma} & & \frac{-2\alpha(1+ka+pb)}{\sigma} & & & \\
 & \ddots & & & \frac{-2\alpha(1+ka+pb)}{\sigma} & \\
\frac{-2\alpha(1+ka+pb)}{\sigma} & & \frac{\sigma-2(a+\alpha(1+ka+pb))}{\sigma} & & & \\
\hline
 & & & \frac{\sigma-2(b+\alpha(1+ka+pb))}{\sigma} & & \frac{-2\alpha(1+ka+pb)}{\sigma} \\
 & \frac{-2\alpha(1+ka+pb)}{\sigma} & & & \ddots & \\
 & & & \frac{-2\alpha(1+ka+pb)}{\sigma} & & \frac{\sigma-2(b+\alpha(1+ka+pb))}{\sigma}
\end{array}\right)$$

By Lemma 2.1, we have $1 - 2b/\sigma$ is a eigenvalue. If it is negative, then $b > \sigma/2$ which contradicts the assumption. Thus, the assertion follows.

Example 4.2 : In proposition 4.2 and 4.3, if $n = 2$, $\sigma = 3$ and $\alpha = 0.1$, i.e., the system is

$$\begin{cases} \dot{x_1} = -x_1 + \frac{3x_1^2}{0.1(1+x_1+x_2)^2+x_1^2} \\ \dot{x_2} = -x_2 + \frac{3x_2^2}{0.1(1+x_1+x_2)^2+x_2^2} \end{cases},$$

then there exist nine equilibria: four equilibria are stable and five are unstable. We have $(0, 0)$ is stable. $(2.509, 0)$ and $(0, 2.509)$ are stable since $(14+\sqrt{185})/11 \approx 2.509 > (\sigma - 2\alpha)/2(1+\alpha) \approx 1.727$. $(1.853, 1.853)$ is also stable since it satisfies $\sigma = 3 > 2\alpha/(1-\sqrt{\alpha}) \approx 1.721$. These equilibria $(2.475, 0.525)$, $(0.525, 2.475)$, $(0.652, 0.652)$, $(0.036, 0)$, $(0, 0.036)$ are unstable (see figure 9).

In this section, for $c = 1$.

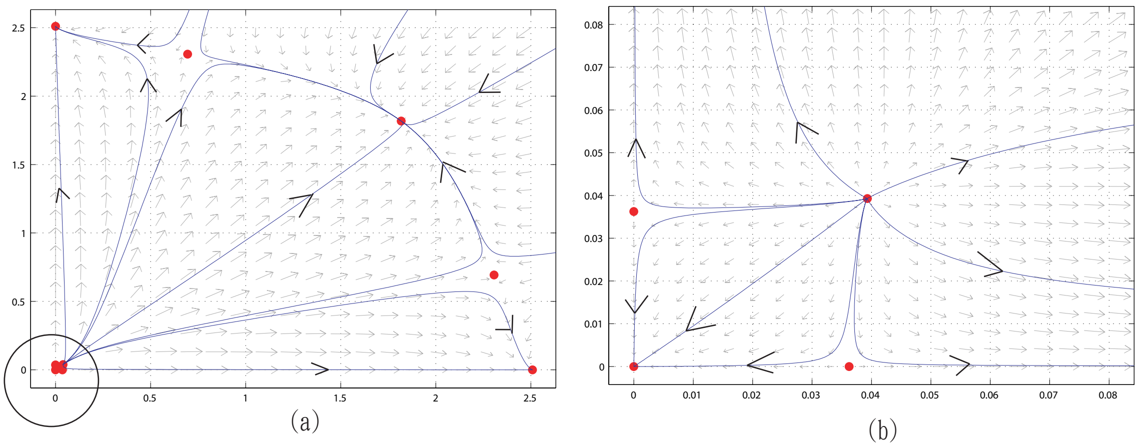


Figure 9: Figure (b) is a zoom-in of (a) near the origin. There exist nine equilibria: four equilibria are stable and five are unstable. We have $(0,0)$, $(2.509,0)$, $(0,2.509)$ and $(1.853,1.853)$ are stable. These equilibria $(2.475,0.525)$, $(0.525,2.475)$, $(0.652,0.652)$, $(0.036,0)$, $(0,0.036)$ are unstable.

(i) If $\sigma < \alpha$, then the origin is stable.

(ii) If $\sigma > \alpha$ and $1 \leq k < n$, then there exist unstable equilibria with k switches on, whose components are identically $(\sigma-\alpha)/(\alpha k+1)$, and $(n-k)$ off (zero).

(iii) There exists a stable equilibrium with all switches on, whose components are identically $(\sigma-\alpha)/(\alpha n+1)$.

For $c = 2$, and $1 \leq k \leq n$.

(i) If $4\alpha(k\sigma+1)/\sigma^2 \leq 1$, then there exist equilibria with k switches on, whose components are identically $[\sigma - 2\alpha k + \sqrt{\sigma^2 - 4\alpha(k\sigma+1)}]/2(1+\alpha k^2)$ or $[\sigma - 2\alpha k - \sqrt{\sigma^2 - 4\alpha(k\sigma+1)}]/2(1+\alpha k^2)$, and $(n-k)$ off (zero). In short, the condition of existence is $\alpha < 1/k^2$.

(ii) When $k = 1$, if the non-zero components are larger than $(\sigma - 2\alpha)/2(1+\alpha)$, then the above equilibria are stable.

(iii) When $1 < k \leq n$, if the non-zero components are larger than $\alpha/2$, then the above equilibria are stable. In short, the condition of stability is $\sigma > 2\sqrt{\alpha}/(1-k\sqrt{\alpha})$.

In addition, when $c = 2$, $n \geq 4$, and $k > 1$, there exist unstable equilibria with k switches on with value a identically, and $(n-k)$ off with value b identically.

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