Gene regulatory networks with incorporated delay

ARCADY PONOSOV
Norwegian Univ. of Life Sciences
Dept. of Math. Sc. and Technology
N-1430 Ås
NORWAY

ANDREI SHINDIAPIN
Eduardo Mondlane Univ.
Dept. of Math. and Informatics
C.P. 257 Maputo
MOZAMBIQUE

JOSE JOAO MIGUEL
Eduardo Mondlane Univ.
Dept. of Math. and Informatics
C.P. 257 Maputo
MOZAMBIQUE

Abstract: A method to study asymptotic properties of solutions to systems of differential equations with distributed time-delays and Boolean-type nonlinearities (step functions) is offered. Such systems arise in many applications, but this paper deals with specific examples of such systems coming from genetic regulatory networks. A challenge is to analyze stable stationary points which belong to the discontinuity set of the system (thresholds). The paper describes an algorithm of localizing stationary points in the presence of delays as well as stability analysis around such points. The basic technical tool consists in replacing step functions by the so-called "logoid functions" and investigating the smooth systems thus obtained.

Key–Words: Gene regulation, delay equations, stability

1 Introduction

We study asymptotically stable steady states (stationary points) of the system

$$\begin{array}{l} \dot{x_i} = F_i(Z_1, ..., Z_n) - G_i(Z_1, ..., Z_n)x_i, \\ Z_i = Z_i(y_i), \\ y_1(t) = (\Re x_1)(t) \quad (t \geq 0), \\ y_i = x_i \quad (i = 2, ..., n) \end{array} \tag{1}$$

This system describes a specific gene regulatory network with autoregulation [**?**], [**?**], where changes in one of the genes happen slower than in the others, which courses delay effects in one of the variables.

The functions F_i, G_i, which are affine in each Z_i and satisfy

$$F_i(Z_1, ..., Z_n) \geq 0, \;\; G_i(Z_1, ..., Z_n) > 0$$

($0 \leq Z_i \leq 1$, $i = 1, ..., n$) stand for the production rate and the relative degradation rate of the product of gene i respectively, and x_i denoting the gene product concentration. The input variables y_i endow System (**??**) with feedbacks which, in general, are described by nonlinear Volterra ("delay") operators depending on the gene concentrations $x_i(t)$. The delay effects in the model arise from the time required to complete transcription, translation and diffusion to the place of action of a protein [**?**].

Below we assume that $\Re$ is the integral operator given by

$$(\Re x)(t) = c_0 x(t) + \int_{-\infty}^{t} K(t-s)x(s)ds, \; t \geq 0, \tag{2}$$

where $K(u) = \sum_{\nu=1}^{p} c_\nu K^\nu(u)$, $c_\nu \geq 0$ ($\nu = 0, 1, ..., p$), $c_0 + \sum_{\nu=1}^{p} c_\nu = 1$, and

$$K^\nu(u) = \frac{\alpha^\nu u^{\nu-1}}{(\nu-1)!} e^{-\alpha u}. \tag{3}$$

For instance,

$$K^1(u) = \alpha e^{-\alpha u}, \; \alpha > 0, \tag{4}$$

$$K^2(u) = \alpha^2 u e^{-\alpha u}, \; \alpha > 0, \tag{5}$$

which are called "the weak generic delay kernel" and "the strong generic delay kernel", respectively.

The functions K^ν have the following properties:

$$\begin{array}{c} K^\nu(\infty) = 0, \\ K^\nu(0) = 0, \quad (\nu \geq 2.) \\ K^1(0) = \alpha\,. \end{array} \tag{6}$$

It is also straightforward to show that

$$\begin{array}{c} \frac{d}{du} K^\nu(u) = \alpha K^{\nu-1}(u) - \alpha K^\nu(u) \quad (\nu \geq 2) \\ \frac{d}{du} K^\nu(u) = -\alpha K^\nu(u) \quad (\nu = 1). \end{array} \tag{7}$$

The *"the response functions"* Z_i express the effect of the different transcription factors regulating the expression of the gene. Each Z_i is *a steep sigmoid function* depending on the input variable y_i, i.e. $Z_i(y_i) = \Sigma(y_i, \theta_i, q_i)$. In the vicinity of the threshold value θ_i the response function Z_i switches from 0 to 1. Thus, in the limit the response function is close to the step function having the unit jump at $y_i = \theta_i$. There are many ways to model response functions. In this paper we adopt the one introduced in [**?**] and based on the so-called *"logoids"* (see the next section). This concept simplifies significantly the stability analysis of the steady states around thresholds (singular stationary points - SSP) in the non-delay model [**?**].

The simplest way, however, to model genetic regulatory networks is to study the response functions which are either "on": $Z_i = 1$, or "off": $Z_i = 0$. In such a case System (**??**) splits into two affine scalar delay systems, and it is usually an easy exercise (see Section 2) to find all their solutions explicitly. However, coupled together these simple systems can produce some rather strange effects, especially when a trajectory approaches the switching domains ("the walls"), i.e. the hyperplanes $y_i = \theta_i$, where a switching from one affine system to an other occurs. Particularly sensitive is the stability analysis of the stationary points which belong to these switching domains. This may require the use of smooth approximations $Z_i(y_i) = \Sigma(y_i, \theta_i, q_i)$ ($q_i > 0$) of the involved response functions. The presence of delays may course additional troubles.

The aim of this paper is to examine stability properties of SSP when a critical variable is subject to a delay. The main method we use is a sort of localization procedure for SSP presented in [**?**] for rather general genetic regulatory networks with delay.

2 Response functions

In this section we describe the properties of general logoid functions and introduce some examples as well. These will serve as response functions in the model given by (**??**).

Let $Z = \Sigma(y, \theta, q)$ be any function defined for $y \in \mathbf{R}$, $\theta > 0$, $0 < q < q^0$. The following assumptions describe the response functions:

Assumption 2.1: *$\Sigma(y, \theta, q)$ is continuous in $(y, q) \in \mathbf{R} \times (0, q^0)$ for all $\theta > 0$, continuously differentiable w.r.t. $y \in \mathbf{R}$ for all $\theta > 0, 0 < q < q^0$, and $\frac{\partial}{\partial y}\Sigma(y, \theta, q) > 0$ on the set $\{y \in \mathbf{R} : 0 < \Sigma(y, \theta, q) < 1\}$.*

Assumption 2.2: *$\Sigma(y, \theta, q)$ satisfies*

$$\Sigma(\theta, \theta, q) = 0.5, \;\; \Sigma(0, \theta, q) = 0, \;\; \Sigma(+\infty, \theta, q) = 1$$

for all $\theta > 0$, $0 < q < q^0$.

Clearly, **2.1-2.2** imply that $Z = \Sigma(y, \theta, q)$ is nondecreasing in $y \in \mathbf{R}$ and strictly increasing in y on the set $\{y \in \mathbf{R} : 0 < \Sigma(y, \theta, q) < 1\}$. The inverse function $y = \Sigma^{-1}(Z, \theta, q)$ is defined for $Z \in (0, 1)$, $\theta > 0$, $0 < q < q^0$, where it is strictly increasing in Z and continuously differentiable w.r.t. Z.

Assumption 2.3: *For all $\theta > 0$, $\frac{\partial}{\partial Z}\Sigma^{-1}(Z, \theta, q) \to 0$ ($q \to 0$) uniformly on compact subsets of the interval $Z \in (0, 1)$, and $\Sigma^{-1}(Z, \theta, q) \to \theta$ ($q \to 0$) pointwise for all $Z \in (0, 1)$ and $\theta > 0$.*

Assumption 2.4: *For all $\theta > 0$, the length of the interval $[y_1(q), y_2(q)]$, where $y_1(q) := \inf\{y \in \mathbf{R} : \Sigma(y, \theta, q) = 0\}$ and $y_2(q) := \sup\{y \in \mathbf{R} : \Sigma(y, \theta, q) = 1\}$, tends to 0 as $q \to 0$).*

The following simple proposition was proved in [**?**]

Proposition 1 *If **Assumptions 2.1-2.3** are satisfied, then the function $Z = \Sigma(y, \theta, q)$ has the following properties [**?**]:*

1. *If $q \to 0$, then $\Sigma^{-1}(Z, \theta, q) \to \theta$ uniformly on all compact subsets of the interval $Z \in (0, 1)$ and every $\theta > 0$;*
2. *if $q \to 0$, then $\Sigma(y, \theta, q)$ tends pointwise to 1 (if $y > \theta$), to 0 (if $y < \theta$), and to 0.5 (if $y = \theta$) for all $\theta > 0$;*
3. *$\frac{\partial\Sigma}{\partial y}(y, \theta, q) \to +\infty$, whenever $q \to 0$, $\Sigma(y, \theta, q) \to Z^*$ for some $0 < Z^* < 1$.*

Here is an example of a function satisfying **Assumptions 2.1-2.3**.

Example 2 *Let $\theta > 0, q > 0$. The Hill function is given by*

$$\Sigma(y, \theta, q) := \begin{cases} 0 & \textit{if} \;\; y < 0 \\ \frac{y^{1/q}}{y^{1/q} + \theta^{1/q}} & \textit{if} \;\; y \geq 0. \end{cases}$$

However, the Hill function does not satisfy **Assumption 2.4**, as it e. g. never reaches the value $Z = 1$. This assumption is fulfilled for the following function:

Example 3 *[**?**] Let*

$$\Sigma(y, \theta, q) := L\left(0.5 + \frac{y - \theta}{2\delta(q)}, \; \frac{1}{q}\right),$$

where

$$L(u, p) = \begin{cases} 0 & \textit{if} \;\; u < 0 \\ 1 & \textit{if} \;\; u > 1 \\ \frac{u^p}{u^p + (1-u)^p} & \textit{if} \;\; 0 \leq u \leq 1, \end{cases}$$

and $\delta(q) \to +0$ if $q \to +0$.

The last function assumes the value $Z = 1$ for all $y \geq \theta + (2q)^{-1}$ and the value $Z = 1$ for all $y \leq \theta - (2q)^{-1}$.

The following trivial proposition will be used in this paper.

Proposition 4 *If **Assumption 2.4** is satisfied, then the function $\Sigma(y, \theta, q)$ has the following properties:*

1. *If $y \neq \theta$, then $\Sigma(y, \theta, q) = 0$ or 1 for sufficiently small $q > 0$ and any $\theta > 0$;*
2. *If $y \neq \theta$, then $\frac{\partial \Sigma}{\partial y}(y, \theta, q) = 0$ for sufficiently small $q > 0$ and any $\theta > 0$.*

Property 2 from Proposition **??** justifies the following notation for the step function with threshold θ:

Example 5

$$Z = \Sigma(y, \theta, 0) := \begin{cases} 0 & \text{if } y < \theta \\ 0.5 & \text{if } y = \theta \\ 1 & \text{if } y > \theta. \end{cases}$$

Remark 6 *The function $Z = \Sigma(y, \theta, 0)$ is slightly different from the standard step (Heaviside) function, as $\Sigma(\theta, \theta, 0) = 0.5$. However, putting $Z_i = \Sigma(y_i, \theta_i, 0)$ into System (**??**) we can disregard this difference, as the solutions do not depend on the value of Z_i at $y_i = \theta_i$.*

In what follows we only use the logoids, i.e. functions satisfying **Assumptions 2.1-2.4**. However, some results are valid for more general sigmoids satisfying **Assumptions 2.1-2.3**. We refer the reader to the paper [**?**] where this problem is addressed in more detail.

3 Obtaining a system of ordinary differential equations

A method to study System (**??**) is well-known in the literature, and it is usually called ”the linear chain trick” (see e.g. [**?**]). However, a direct application of this ”trick” in its standard form is not suitable for our purposes, because we want Z_1, as in (**??**), to depend on a single variable, i.e. on y_1. Modifying the linear chain trick we can remove this drawback of the method. In [**?**] it was done for the general system (**??**). Here we only provide the final formulae for the case of one delay operator (**??**), which is sufficient for our purposes. The formulae follow from the general results proved in [**?**], but they can also be checked by a straightforward calculation.

For the sake of notational simplicity we will replace System (**??**) with the following scalar differential equation depending on a single response function:

$$\begin{aligned} \dot{x}(t) &= F(Z) - G(Z)x(t) \\ Z &= Z(y) \\ y(t) &= (\Re x)(t) \quad (t \geq 0), \end{aligned} \tag{8}$$

where we assume that $y = y_1,\ q = q_1, \theta = \theta_1\ Z_1 = Z = \Sigma(y, \theta, q)$.

Let us put

$$w_\nu(t) = \int_{-\infty}^{t} K^\nu(t-s)x(s)ds, \tag{9}$$

where $t \geq 0$.

It is easy to see that $\dot{w}_1 = -\alpha w_1 + \alpha x$ and $\dot{w}_\nu = \alpha w_{\nu-1} - \alpha w_\nu$ ($\nu \geq 2$).

In what follows, we will use the following variables:

$$\begin{aligned} y &= c_0 x + \textstyle\sum_{\nu=1}^{p} c_p w_p, \\ v_\nu &= \textstyle\sum_{j=1}^{p-\nu+1} c_{j+\nu-1} w_j, \end{aligned} \tag{10}$$

where $\nu = 2, ..., p$.

In particular, $v_p = c_p w_1$. Then

$$\begin{aligned} \dot{x}(t) &= F(Z) - G(Z)x(t) \\ \dot{\mathbf{v}}(t) &= A\mathbf{v}(t) + \Pi(x(t)), \quad t > 0 \\ Z &= \Sigma(y, \theta, q), \quad y = v_1, \end{aligned} \tag{11}$$

where

$$A = \begin{pmatrix} -\alpha & \alpha & 0 & \dots & 0 \\ 0 & -\alpha & \alpha & \dots & 0 \\ 0 & 0 & -\alpha & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 0 & -\alpha \end{pmatrix},$$

$$\mathbf{v} = \begin{pmatrix} v_1 \\ v_2 \\ \vdots \\ v_p \end{pmatrix},$$

and

$$\mathbf{\Pi}(x) := \alpha x \pi + c_0 \mathbf{f}(Z, x)$$

with

$$\pi = \begin{pmatrix} c_0 + c_1 \\ c_2 \\ \vdots \\ c_p \end{pmatrix},$$

$$\mathbf{f}(Z, x) = \begin{pmatrix} F(Z) - G(Z)x \\ 0 \\ \vdots \\ 0 \end{pmatrix}.$$

For $p = 1$ we put

$$\mathbf{v} = y, \tag{12}$$

which yields the following system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= F(Z) - G(Z)x \\ \dot{y} &= c_0(F(Z) - G(Z)x) + \alpha x - \alpha y, \end{aligned} \tag{13}$$

where $Z = \Sigma(y, \theta, q)$.

Recall that $c_0 + c_1 = 1$ for $p = 1$.

For $p = 2$ we have that $c_0 + c_1 + c_2 = 1$. Putting

$$\mathbf{v} = \begin{pmatrix} y \\ u \end{pmatrix} \tag{14}$$

yields the following system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= F(Z) - G(Z)x \\ \dot{y} &= c_0(F(Z) - G(Z)x) + \alpha x(c_0 + c_1) - \alpha y + \alpha u \\ \dot{u} &= \alpha c_2 x - \alpha u \end{aligned}$$

where $Z = \Sigma(y, \theta, q)$.

Finally, for $p = 3$ we put

$$\mathbf{v} = \begin{pmatrix} y \\ u \\ v \end{pmatrix}, \tag{15}$$

which yields the following system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= F(Z) - G(Z)x \\ \dot{y} &= c_0(F(Z) - G(Z)x) + \alpha x(c_0 + c_1) - \alpha y + \alpha u \\ \dot{u} &= \alpha c_2 x - \alpha u + \alpha v \\ \dot{v} &= \alpha c_3 x - \alpha v, \end{aligned} \tag{16}$$

where $Z = \Sigma(y, \theta, q)$.

In this case, $c_0 + c_1 + c_2 + c_3 = 1$.

These systems are all equivalent to (**??**).

4 Stationary points

We are studying the delay system (**??**), which is now replaced by the equivalent system of ordinary differential equation (**??**).

It is easy to localize stationary points for this system if $Z_i = \Sigma(y_i, \theta_i, q_i)$ are all smooth ($q_i > 0$). However, in this case the stability analysis and computer simulations may be cumbersome and time consuming. To simplify the model, one uses the step functions $Z_i = \Sigma(y_i, \theta_i, 0)$. The system becomes discontinuous within switching domains, thus making it necessary to give precise definitions of stable and unstable stationary points. To do it, we replace the step functions $Z_i = \Sigma(y_i, \theta_i, 0))$ with a smooth logoid $Z_i = \Sigma(y_i, \theta_i, q_i)$ ($q_i > 0$), which leads to the following natural definition:

Definition 7 *A point P^0 is called a stationary point for System (**??**) with $Z_i = \Sigma(y_i, \theta_i, 0)$ ($i = 1, ..., n$) if there exist a number $\varepsilon > 0$ and points P^q, $q = (q_1, ..., q_n)$, $q_i \in (0, \varepsilon)$ ($i = 1, ..., n$) such that*

- *P^q is a stationary point for System (**??**) with $Z_i = \Sigma(y_i, \theta_i, q_i)$ ($i = 1, ..., n$);*
- *$P^q \to P^0$ as $q \to 0$.*

It is evident that if the limit point P^0 does not belong to the discontinuity set of System(**??**) with $Z_i = \Sigma(y_i, \theta_i, 0)$, i.e. if $x_i \neq \theta_i$ ($i = 1, ..., n$), then P^0 is just a usual stationary point for this system. Clearly, neither the delay operator $\Re$, nor the logoids $Z_i = \Sigma(y_i, \theta_i, 0)$ ($i = 1, ..., n$, $q > 0$), satisfying **Assumptions 2.1-2.4** from Section 2, influence the position of the stationary point.

Thus obtained P^0 is called *regular stationary point*.

The case where some of the coordinates coincide with the respective thresholds is more involved. Below we provide a sufficient condition for P^0 to be *singular stationary point*. The proof of the result can be found in [**?**].

Proposition 8 *Let $\mathbf{B} := (B_i)$ ($i = 2, ...n$) be a finite sequence consisting of 0 or 1. Assume then that*

$$\bar{J} := \frac{\partial}{\partial Z_1} F_1(Z_1, \mathbf{B}) - \frac{\partial}{\partial Z_1} G_1(Z_1, \mathbf{B})\theta_1 \tag{17}$$

is non-zero (the derivative does not depend on Z_1) and that the system

$$\begin{aligned} &F_1(Z_1, \mathbf{B}) - G_1(Z_1, \mathbf{B})\theta_1 = 0 \\ &F_i(Z_1, \mathbf{B}) - G_i(Z_1, \mathbf{B})x_i = 0 \quad (i \geq 2) \end{aligned} \tag{18}$$

with the constraints

$$\begin{aligned} &0 < Z_1 < 1 \\ &\Sigma(x_i, \theta_1, 0) = B_i \quad (i \geq 2) \end{aligned} \tag{19}$$

has a solution Z_1^0, x_i^0 ($i \geq 2$).

*Then there exists a unique p-vector $\mathbf{v}^0$) such that the point $P^0 = (x_1^0, ..., x_n^0, \mathbf{v}^0)$ is SSP for System (**??**) with $Z_i = \Sigma(y_i, \theta_i, 0)$ ($i = 1, ..., n$). This point is independent of the choice of the operator $\Re$ and the logoids $Z_i = \Sigma(y_i, \theta_i, q_i)$ ($q_i > 0$, $i = 1, ..., n$), satisfying* **Assumptions 2.1-2.4** *from Section 2.*

In a similar way, we define the notion of a stable stationary point (see e.g. [**?**]).

Definition 9 *A stationary point $P^0 = (x_1^0, ..., x_n^0, \mathbf{v}^0)$ for System (**??**) with $Z_i = \Sigma(y_i, \theta_i, 0)$ $(i = 1, ..., n)$ is called asymptotically stable if for any set of approximating stationary points $P^q \to P^0$ $(q \to 0)$ for System (**??**) with $Z_i = \Sigma(y_i, \theta_i, q_i)$ $(q_i > 0, i = 1, ..., n)$, there exist a number $\varepsilon > 0$ such that P^q are asymptotically stable for $q_i \in (0, \varepsilon)$ $(i = 1, ..., n)$.*

5 Stability results for $p = 1$ and $p = 2$

In the non-delay case any regular stationary point is always asymptotically stable as soon as it exists. This is due to the assumptions $G_i > 0$, while the condition $\bar{J} < 0$ (see (**??**)) gives asymptotic stability of singular stationary points.

Including delays leads to more complicated stability conditions. We start with the case $p = 1$.

Proposition 10 *Let $p = 1$ and let the equation*

$$F(Z) - G(Z)\theta = 0 \tag{20}$$

have a solution Z^0 satisfying $0 < Z^0 < 1$.

Then the point $P^0(x^0, y^0)$, where $x^0 = y^0 = \theta$, will be asymptotically stable if $J < 0$, and unstable if $J > 0$, where

$$J = F'(Z) - G'(Z)\theta \tag{21}$$

is independent of Z (as both F and G are affine).

Proof: According to Definition **??**, we have to look at the Jacobi matrix $M(q)$ of the smooth system (**??**) with $Z = \Sigma(y, \theta, q)$, $q > 0$, evaluated at the stationary point P^q. Evidently,

$$M(q) := \begin{pmatrix} -g(q) & J(q)d(q) \\ \alpha - c_0 g(q) & -\alpha + c_0 J(q)d(q) \end{pmatrix}. \tag{22}$$

where we, to simplify the notation, put

$$g(q) := G(Z^q) \quad J(q) := F'(Z^q) - G'(Z^q)x^q,$$
$$d(q) := \frac{\partial \Sigma}{\partial y}(y^q, \theta, q).$$

To study spectral properties of the matrix $M(q)$ as $q \to 0$, we should remember the following:

$$x^q \to \theta, \;\; y^q \to \theta, \;\; Z^q \to Z^0 \;\; (0 < Z^0 < 1) \tag{23}$$

as $q \to +0$ (see (**??**)). Therefore,

$$g(q) \to g(Z^0) > 0, \quad J(q) \to J \neq 0 \quad d(q) \to +\infty \tag{24}$$

as $q \to +0$. This is due to (**??**) and Proposition **??**, part 3.

Calculating the trace and the determinant of the matrix $M(q)$ gives

$$\operatorname{tr} M(q) = -\alpha - g(q) + c_0 J(q)d(q),$$
$$\det M(q) = \alpha g(q) - \alpha J(q)d(q).$$

As $J(q)d(q) \to \infty$ when $q \to 0$, we observe that $J > 0$ implies $\operatorname{tr} M(q) > 0$ for sufficiently small $q > 0$ and, thus, instability of the matrix **??**. On the other hand, if $J < 0$, then $\operatorname{tr} M(q) < 0$ and $\det M(q) > 0$ for sufficiently small $q > 0$ for sufficiently small $q > 0$. By this, the matrix **??** is stable. □

Proposition 11 *Let $p = 2$ and let the equation (**??**) have a solution Z^0 satisfying $0 < Z^0 < 1$.*

A. *Assume that $c_0 > 0$ in (**??**). Then the point $P^0(x^0, y^0, v^0)$, where $x^0 = y^0 = \theta$, $v_0 = c_2\theta$, will be asymptotically stable if $J < 0$, and unstable if $J > 0$. Moreover, assuming $J < 0$ there exists $\varepsilon > 0$ such that*

1. *if $c_1^2 < 4c_0c_2$, then the stationary points P^q are stable spiral points for all $0 < q < \varepsilon$;*
2. *if $c_1^2 > 4c_0c_2$, then the stationary points P^q are stable nodes for all $0 < q < \varepsilon$.*

B. *Assume that $c_0 = 0$ in (**??**). Then the point $P^0(x^0, y^0, v^0)$, where $x^0 = y^0 = \theta$, $v_0 = c_2\theta$, has the following properties*

1. *If $J > 0$, then P^0 is unstable.*
2. *If $J < 0$, $c_1 = 0$, then P^0 is unstable.*
3. *If $J < 0$, $c_1 \neq 0$ and $G(Z^0) < \alpha {c_1}^{-1}(1 - 2c_1)$, then P^0 is unstable.*
4. *If $J < 0$, $c_1 \neq 0$ and $G(Z^0) > \alpha {c_1}^{-1}(1 - 2c_1)$, then P^0 is asymptotically stable (in fact, the stationary points P^q are stable spiral points for small $q > 0$).*

*Here J is again given by (**??**).*

Proof: As before, we keep fixed an arbitrary logoid function $Z = \Sigma(y, \theta, q)$, $q > 0$, satisfying **Assumptions 2.1-2.4**. Let $P^q(x^q, y^q, v^q)$ be the corresponding approximating stationary points from Definition **??**, which converge to P^0 as $q \to 0$. Then

$$Z^q := \Sigma(y^q, \theta, q) \to \Sigma(y^0, \theta, 0) := \bar{Z}$$

due to **Assumption 2.1**. As P^q is a stationary point for the 3×3-system in Section 3 with $Z = \Sigma(y, \theta, q)$ for sufficiently small $q > 0$, we have $F(Z^q) -$

$G(Z^q)x^q = 0$. Letting $q \to +0$ we obtain the equality $F(\bar{Z}) - G(\bar{Z})\theta = 0$. From the assumptions of the theorem it follows, however, that $F(Z^0) - G(Z^0)\theta = 0$. As the functions $F(Z)$ and $G(Z)$ are affine in Z, the function $F(Z) - G(Z)\theta$ is affine as well and, moreover, it is not constant because $J \neq 0$. This implies that $\bar{Z} = Z^0$. In particular,

$$Z^q = \Sigma(y^q, \theta, q) \to Z^0 \ \ (q \to 0). \qquad (25)$$

According to Definition **??**, we have to look at the Jacobi matrix $M(q)$ of the smooth system with $Z = \Sigma(y, \theta, q)$, $q > 0$, evaluated at the stationary point P^q. Put

$$\kappa_1 := \alpha(c_0 + c_1) - c_0 g(q) \qquad (26)$$

$$\kappa_2 := -\alpha + c_0 J(q) d(q). \qquad (27)$$

Evidently,

$$M(q) := \begin{pmatrix} -g(q) & J(q)d(q) & 0 \\ \kappa_1 & \kappa_2 & \alpha \\ \alpha c_2 & 0 & -\alpha \end{pmatrix}.$$

where we again put

$$g(q) := G(Z^q) \quad J(q) := F'(Z^q) - G'(Z^q)x^q,$$
$$d(q) := \frac{\partial \Sigma}{\partial y}(y^q, \theta, q).$$

The rest of the analysis is omitted because of the lack of the space. □

6 The case $p = 3$

The Jacobi matrix in this case reads

$$M(q) := \begin{pmatrix} -g(q) & J(q)d(q) & 0 & 0 \\ \kappa_1 & \kappa_2 & \alpha & 0 \\ \alpha c_2 & 0 & -\alpha & \alpha \\ \alpha c_3 & 0 & 0 & -\alpha \end{pmatrix},$$

where

$$g(q) := G(Z^q) \quad J(q) := F'(Z^q) - G'(Z^q)x^q,$$
$$d(q) := \frac{\partial \Sigma}{\partial y}(y^q, \theta, q)$$

and κ_1 and κ_2 are given by (**??**) and (**??**), respectively.

The challenge is to study spectral properties of the matrix $M(q)$ as $q \to 0$. To be able to do it, we should remember that

$$x^q \to \theta, \ \ y^q \to \theta, \ \ Z^q \to Z^0 \ \ (0 < Z^0 < 1) \qquad (28)$$

as $q \to +0$ (see (**??**)). Therefore,

$$g(q) \to g(Z^0) > 0, \quad J(q) \to J \neq 0, \quad d(q) \to +\infty$$

as $q \to +0$. This is due to (**??**) and Proposition **??**, part 3.

Stability analysis in this case has been performed with the help of Mathematica.

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