STABILITY OF SWITCHED GENE REGULATORY NETWORKS MODEL

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Stability properties of the equilibrium of the model of switched gene regulatory networks is studied. The switching rule as well as the switching times are given initially and the switching rule is a piecewise constant function. The algorithm for construction of the solution is provided and the equilibrium is defined and its exponential stability is investigated. The basis of the study is the Lyapunov approach by quadratic Lyapunov functions. Several examples are provided to illustrate our theoretical results and the influence of the switching rule on the stability behavior of the equilibrium.

Keywords: stability, gene regulatory networks, nonlinear switched systems, Lyapunov functions

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1. Introduction

The process through which cells take on a specific role, termed differentiation, can be implemented by changing the accessibility of binding sites required for regulation, essentially enabling and disabling interactions in the genetic regulatory network (GRN). For biological modeling, the concept of switching networks provides a useful abstraction for capturing the processes at work as cells change type (see, for example, [20]). Switched systems composed of a class of subsystems (continuous or discrete) and a switching law that controls the subsystems, are adequate tools for modeling complex interactions in GRN. A good description and biological reasoning of switched genetic regulatory networks (SGRN) is given in [20]. Various properties of linear SGRN with different switching rules are studied, for example, in [11, 12, 15, 26]. Some SGRN modeled by fractional derivatives are defined and studied in [1, 18].

Based on biological knowledge, the stability of SGRN has received a lot of attention (see, for example [25] for SGRN with an average dwell time). Three basic problems regarding the stability and design of switched systems have been presented in [10]. The global stability of switched recurrent neural networks under arbitrary switching laws by Lyapunov functions is studied in [9], whereas GRN are studied

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in [16, 27]. Recently, some stability properties are studied in [2, 3, 4, 7, 13, 17, 19, 21, 22, 24]. Also, GRN with various types of delays are considered and the stability properties are investigated in [8, 14, 23].

Motivated by the above discussion, we study a continuous time switched system describing a complex GRN. The studied model involves a switching rule which is a piecewise constant function given initially and is different than the known results, (see, for example, [22]), and it relates to a change of the activator functions of messenger ribonucleic acid (mRNA). The equilibrium for SGRN is appropriately defined in the general case of activator functions of mRNA. Note that in the partial case of activator functions of mRNAs null-able at zero, the defined equilibrium is reduced to zero equilibrium which is applied in the literature to define and study stability of SGRN. The exponential stability of the defined equilibrium is defined. Some sufficient conditions for the exponential stability are obtained by an application of Lyapunov functions. The theoretical study as well as the influence of the switching rule on the behavior of the equilibrium is applied to several models.

The contributions in this paper can be summarized as follows:

- the dynamics is described by a family of ordinary differential subsystems;
- the switching rule reflects on the regulatory functions of mRNAs at initially given switching times;
- The activated subsystems have different activator functions of protein of mRNA and keep the rates of degradation and the translation rate constants;
- an equilibrium of the switched model is appropriately defined;
- an exponential stability of the equilibrium is defined and studied;
- several particular examples of switched gene regulatory networks models are provided and the theoretical study and influence of the switching rule on the behavior of the equilibrium are illustrated.

2. **Description of the switched gene regulatory networks model**

We study a switched gene regulatory networks model. It consists of a family of continuous-time subsystems of ordinary differential equations, initially given switching times (times at which the systems will be changed eventually from one to another) and a given switching rule. The switching rule plays an exceedingly crucial role, in determining both, the switching time of the system and the subsystem becoming active after each switching. We will consider the case when the regulatory functions of mRNA in the activated subsystems are different (see the discussions in [20]). It is different than SGRN with different rates of degradation and different translation rates (see, for example, [22]).

Let $m \leq \infty$ be a given natural number, $\mathcal{I} = \{0, 1, 2, 3, \ldots, m-1\}$ and the sequence of activator functions $\{h_j^{(k)}(.)\}_{k\in\mathcal{I}},\ j \in \mathcal{P}$ be given.

Let the points $\tau_k,\ k = 0, 1, 2, \ldots, m$, be given such that $\tau_0 = 0,\ \tau_k < \tau_{k+1}$, $k \in \mathcal{I}$ and if $m = \infty$ then $\lim_{k\to\infty} \tau_k = \infty$.

Remark 1. *If $m < \infty$ we denote $\tau_m = \infty$.*

Let the switching rule $\sigma(t) = C_k$ for $t \in [\tau_k, \tau_{k+1}),\ k \in \mathcal{I}$, where $C_k \in \mathcal{I}$.
The points $\tau_k,\ k = 1, 2, \ldots, m-1$, determine the switching time.

In this paper, we will consider a model of switched gene regulatory networks (SGRN):

$$\begin{aligned}
\zeta_i'(t) &= -d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{\sigma(t)}(\wp_j(t)) + \Theta_i, \\
\wp_i'(t) &= -b_i\wp_i(t) + c_i\zeta_i(t), \quad \text{for} \quad t > 0, \quad i \in \mathcal{P}, \\
\zeta_i(0) &= \zeta_i^0, \quad \wp_i(0) = \wp_i^0, \quad i \in \mathcal{P},
\end{aligned} \tag{1}$$

where N is the number of nodes, $\mathcal{P} = \{1, 2, \ldots, N\}$, $\zeta_j^0, \wp_j^0 \in \mathbb{R}$, $\zeta_j(t), \wp_j(t)$, $j \in \mathcal{P}$, denote the concentrations of messenger ribonucleic acid (mRNA) and protein of the j-th node at time t, respectively, d_j and b_j are degradation velocities of mRNA and protein, respectively, $c_j > 0$ is the translation rate, the functions $h_j^{\sigma(t)} \in C(\mathbb{R}, \mathbb{R})$, $j \in \mathcal{P}$, represent the activator initiates of protein of mRNA, Θ_i, $i \in \mathcal{P}$, is the basal rate, and the coupling matrix of the network $A = (a_{jm}) \in \mathbb{R}^{N\times N}$ is described by

$$a_{jm} = \begin{cases} -\gamma_{jm} & m \text{ is a repressor of gene } j \\ 0 & m \text{ does not regulate gene } j \\ \gamma_{jm} & m \text{ is a initiator of gene } j\ . \end{cases}$$

Remark 2. *Usually, the activator functions are indicated in the Hill form* $h(s) = \frac{s^\beta}{\alpha^\beta + s^\beta}$, $s \in \mathbb{R}$, *where* β *is the Hill coefficient and* $\alpha \geq 0$ *is a constant. Changing the constant* α *reflects on the behavior of the concentrations of mRNA and protein. These constants will determine the activator functions for any switching rule.*

Remark 3. *Note that if for an integer* $j : 0 \leq j \leq m-2$ *the equality* $C_j = C_{j+1}$ *holds, then the switching rule is not activated at time* τ_{j+1}. *If* $m < \infty$ *then the switching rule is activated a finite number of times and for the time greater or equal to* τ_{m-1} *the given system is a regular system without any switching.*

Therefore SGRN (1) is reduced to :

$$\begin{aligned}
\zeta_i'(t) &= -d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{(C_k)}(\wp_j(t)) + \Theta_i, \\
\wp_i'(t) &= -b_i\wp_i(t) + c_i\zeta_i(t), \\
&\qquad \text{for} \quad t \in (\tau_k, \tau_{k+1}], \quad i \in \mathcal{P}, \quad k \in \mathcal{I}, \\
\zeta_i(0) &= \zeta_i^0, \quad \wp_i(0) = \wp_i^0, \quad i \in \mathcal{P}.
\end{aligned} \tag{2}$$

We will say assumption (H) is satisfied if:

(H1). The activator functions $h_j^{(k)} \in C(\mathbb{R}, \mathbb{R})$, $j \in \mathcal{P}$, $k \in \mathcal{I}$, and there exist constants $\gamma_j^{(k)} > 0$ such that for any $u, v \in \mathbb{R}$ with $u \neq v$, the inequalities

$$|h_j^{(k)}(u) - h_j^{(k)}(v)| \leq \gamma_j^{(k)}|u - v|, \ j \in \mathcal{P}, \quad k \in \mathcal{I},$$

hold.

(H2). For any $k \in \mathcal{I}$ the system

$$\zeta_i'(t) = -d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{(k)}(\wp_j(t)) + I_i,\ \wp_i'(t) = -b_i\wp_i(t) + c_i\zeta_i(t),\ t \in (\tau, \infty),\ \ i \in \mathcal{P} \tag{3}$$

has a solution with any initial values at the time point $\tau \geq 0$.

Remark 4. *Note if (H1) holds, then the solution of* (3) *in assumption (H2) is unique.*

Remark 5. *For typical Hill function-based models, i.e.,* $h_j^{(k)}(u) = \frac{1}{1+u^{\beta_j}}$ *or* $h_j^{(k)}(u) = \frac{u^{\beta_j}}{1+u^{\beta_j}}$ *where* β_j *is the Hill coefficient, the solutions of* (3) *exist globally in time and if the initial concentrations of proteins and mRNAs are positive, they remain non-negative for all* $t \geq \tau$*, i.e. condition (H2) is satisfied (see, for example* [5]*).*

2.1. **Algorithm for construction the solution of SGRN** (2)

Assume condition (H) holds.
Let $t \in (\tau_0, \tau_1]$. Then, SGRN (2) is reduced to

$$\begin{aligned} &\zeta_i'(t) = -d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{(C_0)}(\wp_j(t)) + \Theta_i, \\ &\wp_i'(t) = -b_i\wp_i(t) + c_i\zeta_i(t), \quad \text{for} \quad t \in (0, \tau_1], \quad i \in \mathcal{P}, \\ &\zeta_i(0) = \zeta_i^0, \quad \wp_i(0) = \wp_i^0, \quad i \in \mathcal{P}, \end{aligned} \tag{4}$$

where $C_0 \in \mathcal{I}$ and the activator function $h_j^{(C_0)}(.)$ is given in condition (H1).

According to conditions (H) there exists a unique solution $(\zeta_i^{(0)}(t), \wp_i^{(0)}(t))$, $i \in \mathcal{P},\ t \in [0, \tau_1]$, of (4). Denote

$$U^{(0)}(t) = (U_1^{(0)}(t), U_2^{(0)}(t), \ldots, U_N^{(0)}(t), U_{N+1}^{(0)}(t), U_{N+2}^{(0)}(t), \ldots, U_{2N}^{(0)}(t)),$$

with $U_i^{(0)}(t) = \zeta_i^{(0)}(t)$ and $U_{N+i}^{(0)}(t) = \wp_{N+i}^{(0)}(t),\ i \in \mathcal{P},\ t \in [0, \tau_1]$.

Let $C_0 \neq C_1$. Then, at time τ_1, the switching rule ($\sigma(t) = C_1$) is activated, and the system of equations is changed, i.e., consider the IVP for the system of differential equations:

$$\begin{aligned} &\zeta_i'(t) = -d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{(C_1)}(\wp_j(t)) + \Theta_i, \\ &\wp_i'(t) = -b_i\wp_i(t) + c_i\zeta_i(t), \quad \text{for} \quad t \in (\tau_1, \tau_2], \quad i \in \mathcal{P}, \\ &\zeta_i(\tau_1) = U_i^{(0)}(\tau_1), \quad \wp_i(\tau_1) = U_{N+i}^{(0)}(\tau_1), \quad i \in \mathcal{P}, \end{aligned} \tag{5}$$

where $C_1 \in \mathcal{I}$ and the activator function $h_j^{(C_1)}(.)$ is given in condition (H1).

According to conditions (H) there exists a unique solution $(\zeta_i^{(1)}(t), \wp_i^{(1)}(t))$, $i \in \mathcal{P},\ t \in [\tau_1, \tau_2]$, of (5). Denote

$$U^{(1)}(t) = (U_1^{(1)}(t), U_2^{(1)}(t), \ldots, U_N^{(1)}(t), U_{N+1}^{(1)}(t), U_{N+2}^{(1)}(t), \ldots, U_{2N}^{(1)}(t)),\ t \in [\tau_1, \tau_2],$$

with $U_i^{(1)}(t) = \zeta_i^{(1)}(t)$ and $U_{N+i}^{(1)}(t) = \wp_{N+i}^{(1)}(t),\ i \in \mathcal{P},\ t \in [\tau_1, \tau_2]$.

Let $k:\ 2 \le k \le m$ be an integer and $C_k \ne C_{k-1}$. Then, at time τ_k, the switching rule $(\sigma(t) = C_k)$ is activated, and the system of equations is changed, i.e., consider the IVP for the system of differential equations

$$\begin{aligned} \zeta_i'(t) &= -d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{(C_k)}(\wp_j(t)) + \Theta_i, \\ \wp_i'(t) &= -b_i\wp_i(t) + c_i\zeta_i(t), \quad \text{for } \ t \in (\tau_k, \tau_{k+1}], \quad i \in \mathcal{P}, \\ \zeta_i(\tau_k) &= U_i^{(k-1)}(\tau_k), \quad \wp_i(\tau_k) = U_{N+i}^{(k-1)}(\tau_k), \quad i \in \mathcal{P}, \end{aligned} \tag{6}$$

where $C_k \in \mathcal{I}$ and the activator function $h_j^{(C_k)}(.)$ is given in condition (H1).

According to conditions (H) there exists a unique solution $(\zeta_i^{(k)}(t), \wp_i^{(k)}(t))$, $i \in \mathcal{P},\ t \in [\tau_k, \tau_{k+1}]$, of (6). Denote

$$U^{(k)}(t) = (U_1^{(k)}(t), U_2^{(k)}(t), \ldots, U_N^{(k)}(t), U_{N+1}^{(k)}(t), U_{N+2}^{(k)}(t), \ldots, U_{2N}^{(k)}(t))$$

for $\ t \in [\tau_k, \tau_{k+1}]$ with $U_i^{(k)}(t) = \zeta_i^{(k)}(t)$ and $U_{N+i}^{(k)}(t) = \wp_{N+i}^{(k)}(t),\ i \in \mathcal{P}$.

Note that $U^{(k)}(\tau_{k+1}) = U^{(k+1)}(\tau_{k+1}), \quad k \in \mathcal{I}$.

If $m = \infty$, we use the above procedure infinite times and define the solution of (2) by

$$U(t) = \begin{cases} U^{(0)}(t), & \text{for } t \in [\tau_0, \tau_1], \\ U^{(1)}(t), & \text{for } t \in (\tau_1, \tau_2] \\ U^{(2)}(t), & \text{for } t \in (\tau_2, \tau_3] \\ \ldots\ldots\ldots\ldots\ldots \end{cases}$$

If $m < \infty$ then the last eventual switching time is τ_{m-1}, and the solution of (2) is given by

$$U(t) = \begin{cases} U^{(0)}(t), & \text{for } t \in [\tau_0, \tau_1], \\ U^{(1)}(t), & \text{for } t \in (\tau_1, \tau_2] \\ U^{(2)}(t), & \text{for } t \in (\tau_2, \tau_3] \\ \ldots\ldots\ldots\ldots\ldots \\ U^{(m-1)}(t), & \text{for } t \in (\tau_{m-1}, \infty). \end{cases}$$

Remark 6. *The solution $(U(t))$ of SGRN* (2) *is continuous at any switching point* $\tau_k,\ k = 1, 2, 3, \ldots, m-1$.

2.2. **Equilibrium of the switched model** (2)

We will introduce an equilibrium of SGRN (2).

Definition 1. *An equilibrium of SGRN* (2) *on the interval* $[\tau_k, \tau_{k+1}]$ *is the constant vector* $W^{(k)} = (\frac{b_1}{c_1}P_1^{(k)}, \frac{b_2}{c_2}P_2^{(k)}, \ldots, \frac{b_N}{c_N}P_N^{(k)}, P_1^{(k)}, P_2^{(k)}, \ldots, P_N^{(k)}) \in \mathbb{R}^{2N}$ *with non-negative components satisfying the algebraic system*

$$d_i\frac{b_i}{c_i}P_i^{(k)} = \sum_{j=1}^{N} a_{ij} h_j^{(C_k)}(P_j^{(k)}) + \Theta_i, \quad i \in \mathcal{P}.$$

Remark 7. *On each interval* $[\tau_k, \tau_{k+1}]$ *the equilibrium of SGRN* (2) *is a constant vector which could be different on different intervals between two consecutive switching times.*

If for a number $k \in \mathfrak{I}$ *the activator function* $h_j^{(k)}(0) = 0$ *and* $\Theta_j = 0,\ \ j \in \mathcal{P}$, *then the equilibrium of SGRN* (2) *on the interval* $[\tau_k, \tau_{k+1}]$ *is zero.*

Definition 2. *A global equilibrium of SGRN* (2) *is the piecewise constant vector function* W *defined by*

- *if* $m < \infty$

$$W = \begin{cases} W^{(0)}, & \text{for } t \in [\tau_0, \tau_1], \\ W^{(1)}, & \text{for } t \in (\tau_1, \tau_2] \\ W^{(2)}, & \text{for } t \in (\tau_2, \tau_3] \\ \cdots\cdots\cdots\cdots \\ W^{(m-1)}, & \text{for } t \in (\tau_{m-1}, \infty), \end{cases} \tag{7}$$

- *if* $m = \infty$

$$W = \begin{cases} W^{(0)}, & \text{for } t \in [\tau_0, \tau_1], \\ W^{(1)}, & \text{for } t \in (\tau_1, \tau_2] \\ W^{(2)}, & \text{for } t \in (\tau_2, \tau_3] \\ \cdots\cdots\cdots\cdots, \end{cases}$$

where $W^{(k)} \in \mathbb{R}^{2N}$ *is the equilibrium of SGRN* (2) *on the interval* $[\tau_k, \tau_{k+1}]$, $k \in \mathfrak{I}$.

Remark 8. *If for all* $k \in \mathfrak{I}$ *the activator functions* $h_j^{(k)}(0) = 0$ *and* $\Theta_j = 0,\ \ j \in \mathcal{P}$, *then the global equilibrium of SGRN* (2) *reduces to the zero constant function. Note in the literature the stability of the zero equilibrium of SGRN is considered (see, for example,* [22]*).*

We will say assumption (A) is satisfied if:

(A1). The SGRN (2) has a global equilibrium.

(A2). There exist positive constants $\mu_i \geq 1, \mu_{N+i} \geq 1$ and $\mathcal{B}_i,\ i \in \mathcal{P}$ such that

$$-2d_i + \frac{\mu_{N+i}}{\mu_i} c_i + \sum_{j=1}^{N} |a_{ij}| \gamma_j^{(C_k)} \leq -\mathcal{B}_i,$$

$$-2b_i + c_i + \gamma_i^{(C_k)} \sum_{j=1}^{N} \frac{\mu_j}{\mu_{N+i}} |a_{ij}| \leq -\mathcal{B}_i, \quad i \in \mathcal{P}.$$

Let $u = (u_1, u_2, \ldots, u_n) \in \mathbb{R}^n$. In this paper we will use the norm $\|u\|_n = \sqrt{\sum_{i=1}^n u_i^2}$.

Definition 3. *The global equilibrium* $\mathcal{W} \in \mathbb{R}^{2N}$ *of the model* (2) *(see, Definition 1 and Definition 2) is exponentially stable if there exist constants* $M, \lambda > 0$ *such that*

$$\|X(t) - \mathcal{W}\|_{2N} \leq M \|X^0 - \mathcal{W}^{(0)}\|_{2N}\ e^{-\lambda t}, \quad t \geq 0,$$

where $X(t) = (\zeta(t), \wp(t))$ *is the solution of* (2) *with initial values* $X^0 = (\zeta^0, \wp^0)$.

3. **Exponential stability of the switched model** (2)

We will apply quadratic Lyapunov functions to obtain sufficient conditions for exponential stability of the equilibrium of (2).

Theorem 1. *Let the assumptions (H), (A1) and (A2) hold. Then, the global equilibrium of the model* (2) *is exponentially stable.*

Proof. According to condition (A1) there exists a global equilibrium (a constant vector) $\mathcal{W}$ defined by (7), where the constant vector

$$\mathcal{W}^{(k)} = (\frac{b_1}{c_1}\mathcal{A}_1^{(k)}, \frac{b_2}{c_2}\mathcal{A}_2^{(k)}, \ldots, \frac{b_N}{c_N}\mathcal{A}_N^{(k)}, \mathcal{A}_1^{(k)}, \mathcal{A}_2^{(k)}, \ldots, \mathcal{A}_N^{(k)}) \in \mathbb{R}^{2N}$$

is the equilibrium of SGRN (2) on the interval $[\tau_k, \tau_{k+1}]$ respectively.

According to condition (A2) there exist constants $\mu_k > 1,\ k \in \mathcal{P}$, and we consider the Lyapunov function $V : \mathbb{R}^{2N} \to \mathbb{R}_+$ by

$$V(u_1, u_2, \ldots, u_N, v_1, v_2, \ldots, v_N) = \sum_{k=1}^{N} \mu_k u_k^2 + \sum_{k=1}^{N} \mu_{N+k} v_k^2.$$

Let $X(t) = (\zeta(t), \wp(t)),\ t \geq 0$, be the unique solution of SGRN (2) with initial values $X^0 = (\zeta^0, \wp^0)$ (it exists according to conditions (H)).

Let $k \in \mathcal{I}$ be a given integer and consider the interval $(\tau_k, \tau_{k+1}]$. We apply the definition of a global equilibrium (see Definition 1 and Definition 2), the inequality $2ab \leq a^2 + b^2$ and we obtain for $t \in (\tau_k, \tau_{k+1}]$ the inequalities

$$\begin{aligned}
\frac{d}{dt}V(X(t) - \mathcal{W}^{(k)}) &= \sum_{i=1}^{N} \mu_i \frac{d}{dt}\left(\zeta_i(t) - \frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2 + \sum_{j=1}^{N} \mu_{N+j} \frac{d}{dt}\left(\wp_j(t) - \mathcal{A}_j^{(k)}\right)^2 \\
&= 2\sum_{i=1}^{N} \mu_i \left(\zeta_i(t) - \frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right) \frac{d}{dt}\zeta_i(t) + 2\sum_{j=1}^{N} \mu_{N+j} \left(\wp_j(t) - \mathcal{A}_j^{(k)}\right) \frac{d}{dt}\wp_j(t) \\
&= 2\sum_{i=1}^{N} \mu_i \left(\zeta_i(t) - \frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right) \left(-d_i\zeta_i(t) + \sum_{j=1}^{N} a_{ij} h_j^{(C_k)}(\wp_j(t)) + d_i\frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right. \\
&\quad \left. - \sum_{j=1}^{N} a_{ij} h_j^{(C_k)}(\mathcal{A}_j^{(k)})\right) + 2\sum_{j=1}^{N} \mu_{N+j} \left(\wp_j(t) - \mathcal{A}_j^{(k)}\right) (-b_j\wp_j(t) + c_j\zeta_j(t)) \\
&= -2\sum_{i=1}^{N} d_i\mu_i \left(\zeta_i(t) - \frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2 \\
&\quad + 2\sum_{i=1}^{N} \mu_i \left(\zeta_i(t) - \frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right) \sum_{j=1}^{N} a_{ij} \left(h_j^{(C_k)}(\wp_j(t)) - h_j^{(C_k)}(\mathcal{A}_j^{(k)})\right) \\
&\quad + 2\sum_{j=1}^{N} \mu_{N+j} \left(\wp_j(t) - \mathcal{A}_j^{(k)}\right) \left(-b_j \left(\wp_j(t) - \mathcal{A}_j^{(k)}\right) + c_j \left(\zeta_j(t) - \frac{b_j}{c_j}\mathcal{A}_j^{(k)}\right)\right) \\
&\leq -2\sum_{i=1}^{N} d_i\mu_i \left(\zeta_i(t) - \frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2 - 2\sum_{j=1}^{N} b_j\mu_{N+j} \left(\wp_j(t) - \mathcal{A}_j^{(k)}\right)^2
\end{aligned}$$

$$
\begin{aligned}
&+2\sum_{i=1}^{N}\mu_i\left(\zeta_i(t)-\frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)\sum_{j=1}^{N}|a_{ij}|\gamma_j^{(C_k)}\left(\wp_j(t)-\mathcal{A}_j^{(k)})\right)\\
&+\sum_{j=1}^{N}\mu_{N+j}c_j\left(\wp_j(t)-\mathcal{A}_j^{(k)}\right)^2+\sum_{j=1}^{N}\mu_{N+j}c_j\left(\zeta_j(t)-\frac{b_j}{c_j}\mathcal{A}_j^{(k)}\right)^2\\
\le&\sum_{i=1}^{N}(-2d_i\mu_i+\mu_{N+i}c_i)\left(\zeta_i(t)-\frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2\\
&+\sum_{j=1}^{N}(-2b_j\mu_{N+j}+\mu_{N+j}c_j)\left(\wp_j(t)-\mathcal{A}_j^{(k)}\right)^2\\
&+\sum_{i=1}^{N}\sum_{j=1}^{N}\mu_i|a_{ij}|\gamma_j^{(C_k)}\left(\zeta_i(t)-\frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2\\
&+\sum_{i=1}^{N}\sum_{j=1}^{N}\mu_i|a_{ij}|\gamma_j^{(C_k)}\left(\wp_j(t))-\mathcal{A}_j^{(k)})\right)^2. \qquad (8)
\end{aligned}
$$

Apply condition (A2) with the existing constants $\mathcal{B}_i>0$ to inequality (8) and we get

$$
\begin{aligned}
\frac{d}{dt}V(X(t)-\mathcal{W}^{(k)})\le&\sum_{i=1}^{N}\mu_i\left(-2d_i+\frac{\mu_{N+i}}{\mu_i}c_i+\sum_{j=1}^{N}|a_{ij}|\gamma_j^{(C_k)}\right)\left(\zeta_i(t)-\frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2\\
&+\sum_{i=1}^{N}\mu_{N+i}\left(-2b_i+c_i+\gamma_i^{(C_k)}\sum_{j=1}^{N}\frac{\mu_j}{\mu_{N+i}}|a_{ij}|\right)\left(\wp_i(t)-\mathcal{A}_i^{(k)}\right)^2\\
\le&-\sum_{i=1}^{N}\mu_i\mathcal{B}_i\left(\zeta_i(t)-\frac{b_i}{c_i}\mathcal{A}_i^{(k)}\right)^2-\sum_{i=1}^{N}\mu_{N+i}\mathcal{B}_i\left(\wp_i(t)-\mathcal{A}_i^{(k)}\right)^2\\
\le&-\mathcal{B}V(X(t)-\mathcal{W}^{(k)}),
\end{aligned}
$$

where $\mathcal{B}=\min_{i=1,2,\dots,N}\mathcal{B}_i$. Therefore,

$$V(X(t)-\mathcal{W}^{(k)})\le V(X(\tau_k)-\mathcal{W}^{(k)})e^{-\mathcal{B}(t-\tau_k)},\ t\in(\tau_k,\tau_{k+1}].$$

By induction we get

$$
\begin{aligned}
&V(X(t)-\mathcal{W}^{(k)})\le V(X(\tau_k)-\mathcal{W}^{(k)})e^{-\mathcal{B}(t-\tau_k)}\\
&\le V(X(\tau_{k-1})-\mathcal{W}^{(k-1)})e^{-\mathcal{B}(t-\tau_k)}e^{-\mathcal{B}(\tau_k-\tau_{k-1})}\\
&\dots\dots\dots\dots\dots\\
&\le V(X(\tau_0)-\mathcal{W}^{(0)})e^{-\mathcal{B}(t-\tau_0)}\le M||X(\tau_0)-\mathcal{W}^{(0)}||_{2N}^2e^{-\mathcal{B}(t-\tau_0)},\ t\in(\tau_k,\tau_{k+1}],
\end{aligned}
$$

where $M=\max_{i=1,2,\dots,N}\{\mu_i,\mu_{N+i}\}$ or

$$\|X(t)-\mathcal{W}^{(k)}\|_{2N}^2\le V(X(t)-\mathcal{W}^{(k)})\le\sqrt{M}\|X(\tau_0)-\mathcal{W}^{(0)}\|_{2N}e^{-0.5\mathcal{B}t},\ t\ge0. \qquad (9)$$

Inequality (9) proves the claim. □

4. **Applications**

In this section we will provide some particular models to illustrate the theoretical study.

4.1. **Application 1**

We will consider the model of several repressor-protein concentrations and their corresponding mRNA concentrations, which are defined and studied in [6]. Differently than [6] we will consider the case of presence of a switching rule $\sigma(t) = C_k$ for $t \in (\tau_k, t_{k+1}]$, $k \in \mathcal{I}$, $\tau_0 = 0$, $m \leq \infty$, which is changing the activator function $h_i^k(u) = \frac{1}{\zeta_k + u^2}$, i.e., consider the model

$$\begin{aligned} q_i'(t) &= -q_i(t) + \sum_{j=1}^{3} a_{ij} \frac{1}{(\zeta_k + p_j^2)} + \Theta \\ p_i'(t) &= -\beta(p_i(t) - q_i(t)), \quad t \in (\tau_k, \tau_{k+1}], \ i = 1, 2, 3, \ k \in \mathcal{I} \end{aligned} \tag{10}$$

where $\zeta_k > 0$ are constants and (see [6]):

- Θ is the number of protein copies per cell produced from a given promoter type during continuous growth in the presence of saturating amounts of repressor;
- β is the ratio of the protein decay rate (varies massively, from minutes to months) to the mRNA decay rate (from minutes in prokaryotes (3-8 min in E. coli, or hours in eukaryotes).

System (10) is similar to (2) with $N = 3$, $d_i = 1$, $b_i = c_i = \beta$, $I_i = \Theta$ and activator functions $h_k(u) = \frac{1}{(\zeta_k + u^2)}$.

From Remark 5 note condition (H2) is satisfied.

Consider the case of $\alpha_0 = 0$ and $\beta = 0.01$ (see [18]).

Case 1. Let $a_{ii} = 1.5$ and $a_{ik} = 0$ for $k \neq i$, $i, k = 1, 2, 3$.

Since in the model (10) the dynamics of any i-th repressor-protein concentration and their corresponding mRNA concentration do not depend on the dynamics of the $i-1$-th and $i+1$-th repressor-protein concentration and their corresponding mRNA concentration, we could study

$$\begin{aligned} q'(t) &= -q + \frac{1.5}{(\zeta_k + p^2)} \\ p'(t) &= -0.01(p - q), \quad t \in (\tau_k, \tau_{k+1}], \quad k \in \mathcal{I}. \end{aligned} \tag{11}$$

Case 1.1 (*no switching rule*). Consider the model (11) without any switching rule, i.e., $\zeta_k = 1$. The equilibrium is given as a solution of the algebraic equation $\mathcal{A} = \frac{1.5}{1+\mathcal{A}^2}$, i.e. $W = (0.861224, 0.861224)$, i.e. the condition (A1) holds.

We have

$$\begin{aligned} |h(u) - h(v)| &= \left| \frac{1}{1+u^2} - \frac{1}{1+v^2} \right| \\ &\leq |u - v| \frac{|u+v|}{(1+u^2)(1+v^2)} \leq 0.649519|u - v| \end{aligned}$$

because $\max \frac{|u+v|}{(1+u^2)(1+v^2)} = 0.649519$, i.e., $\gamma_k = 0.649519$ in assumption (H1).

Condition (A2) holds with $\mu = 100$, $\mu_3 = 1$, $\mathcal{B} = 0.000257215$ because inequalities (8) are reduced to $-2+100\cdot 0.01+1.5\cdot 0.649519 = -0.0257215$ and $-2 \cdot 0.01 + 0.01 + 0.01 \cdot 1.5 \cdot 0.649519 = -0.000257215$.

According to Theorem 1 the equilibrium is exponentially stable with constants $M = 100$ and $\lambda = 0.5\mathcal{B} = 0.0001286$. i.e.

$$||(q(t), p(t)) - W|| \leq 10||(q_0, p_0) - W||e^{-0.0001286t}.$$

We solve (11) numerically by Wolfram Mathematica for several initial values, $(q_0, p_0) = (0, 0)$, and $(q_0, p_0) = (20, 1)$, and graph the norm of the difference $||(m(t), p(t)) - W||$ (see Figure 1 and Figure 2). From both graphs we see the solution is exponentially stable.

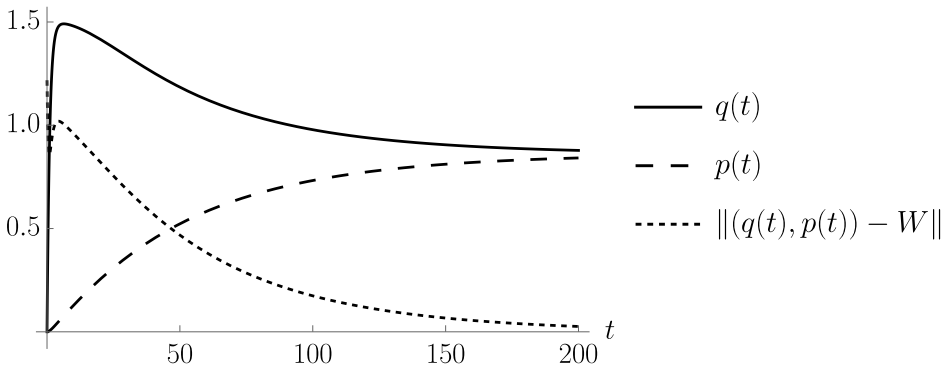

FIGURE 1. Graphs of the solution of (11) without any switching rule and zero initial values and the norm of the difference $||(q(t), p(t)) - W||$.

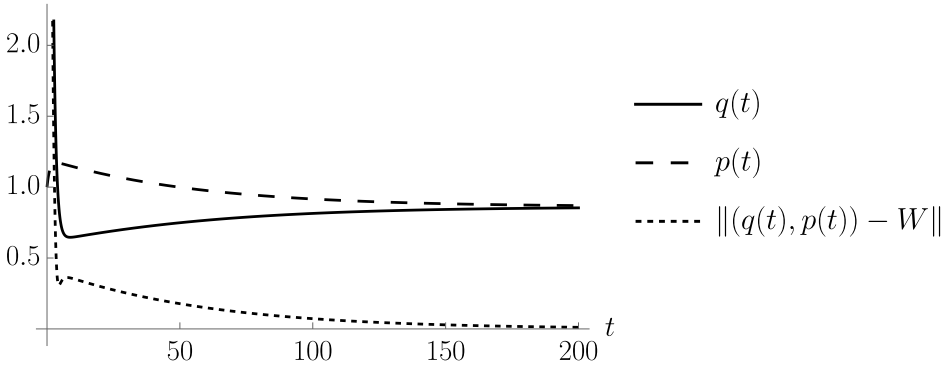

FIGURE 2. Graphs of the solutions of (11) without any switching rule and initial values $(q_0, p_0) = (20, 1)$ and the norm of the difference $||(q(t), p(t)) - W||$.

Case 1.2. (*finite sequence of switching times*) Let the switching rule be activated three times, i.e. $m = 3$ and $\tau_k = 2k$, $k = 0, 1, 2$ with a switching rule $\sigma(t) = C_k$, where $C_0 = 0, C_1 = 1, C_2 = 2$ and $h_0(u) = \frac{1}{(1+u^2)}$, $h_2(u) = \frac{1}{(8+u^2)}$, $h_2(u) = \frac{1}{(20+u^2)}$.

The equilibrium on the interval $[k, k+1]$, $k = 0, 1, 2$ is given as a solution of the system

$$\mathcal{A}^{(k)} = \frac{1.5}{C_k + \left(\mathcal{A}^{(k)}\right)^2}, \quad k = 0, 1, 2.$$

Then the global equilibrium of (11) is given by

$$\mathcal{W} = \begin{cases} (0.861224, 0.861224), & \text{for } t \in [0, 2], \\ (0.186687, 0.186687), & \text{for } t \in (2, 4], \\ (0.0749789, 0.0749789), & \text{for } t \in (4, \infty) \end{cases} \tag{12}$$

Assumption (A1) is satisfied.
Also, we have

$$\begin{aligned} |h^{\sigma(t)}(u) - h^{\sigma(t)}(v)| &= \left| \frac{1}{C_k + u^2} - \frac{1}{C_k + v^2} \right| \\ &\leq |u - v| \frac{|u + v|}{(C_k + 1 + u^2)(C_k + 1 + v^2)} \\ &\leq 0.649519|u - v| \end{aligned}$$

because $\max_{k=0,1,2} \frac{|u+v|}{(C_k+1+u^2)(C_k+1+v^2)} = 0.649519$, i.e., $\gamma_k = 0.649519$ in assumption (A1) and $\mu = 100$, $\mu_3 = 1$, $\mathcal{B} = 0.000257215$ in condition (A2).

According to Theorem 1, the global equilibrium given by (12) is exponentially stable with the following constants: $M = 10$, $\lambda = 0.5 \cdot 0.000257215 = 0.00021286$, i.e.,

$$||(q(t), p(t)) - \tilde{W}|| \leq 10||(q_0, p_0) - (0.861224, 0.861224)||e^{-0.00021286t}, \ t \geq 0.$$

We solve the model (11) by computer realization of the algorithm in Section 2.1 on Wolfram Mathematica and we graph the solutions for various initial values. Note, that, differently than Case 1.1, in Case 1.2 the norm of the difference between the global equilibrium and the solution is discontinuous at any switching time (in spite the solution is continuous at these points, see Figure 3 and Figure 4).

Also, from Figure 5 it could be seen that in both cases 1.1 and 1.2 solutions are exponentially stable but the presence of the switching rule can change the rate of approaching zero.

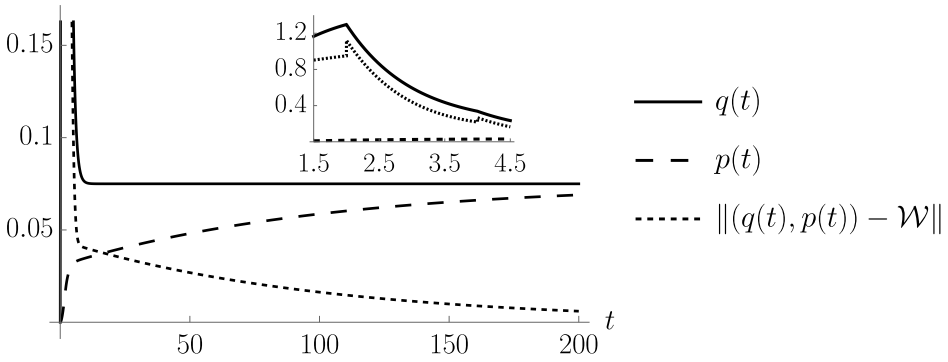

FIGURE 3. Graphs of the solution of (11) with a switching rule and zero initial values and the norm of the difference $||(q(t), p(t)) - \mathcal{W}||$.

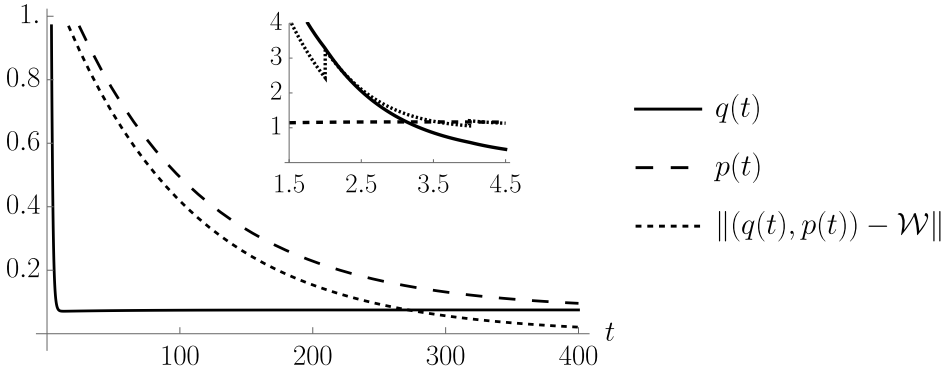

FIGURE 4. Graphs of the solution of (11) with a switching rule and initial values $(q_0, p_0) = (20, 1)$ and the norm of the difference $||(q(t), p(t)) - \mathcal{W}||$.

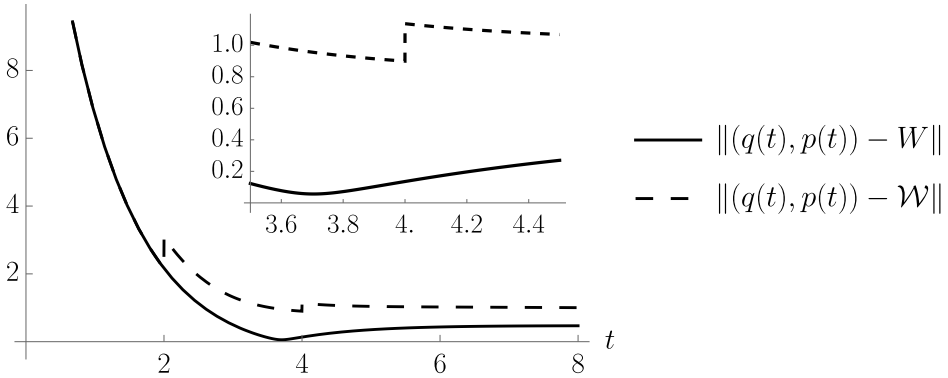

FIGURE 5. Graphs of the norm of the difference of the solutions of (11) $||(q(t), p(t)) - \mathcal{W}||$ with a switching rule and without a switching rule.

Case 1.3. (*infinite sequence of switching times*) Let the sequence of activation points is infite, i.e. $m = \infty$, and $\tau_k = 2k, k \in \mathcal{I}$.Then the global equilibrium is given by

$$W = \begin{cases} (0.861224, 0.861224), & \text{for } t \in [0, 2], \\ (0.186687, 0.186687), & \text{for } t \in (2, 4], \\ (0.0749789, 0.0749789), & \text{for } t \in (4, 6], \\ \dots\dots\dots\dots\dots\dots \\ (0, 0), & \text{for } t = \infty. \end{cases}$$

The conditions (H) and (A) are satisfied and according to Theorem 1, the global equilibrium is exponentially stable.

Case 2. Let $a_{ij} = 1.5,\ i, j = 1, 2, 3$. Let the switching rule be activated at a finite number of time points, for example, i.e., $m = 3$ and the switching times are $\tau_k = 2k,\ k = 0, 1, 2$ with $C_0 = 1, C_1 = 8, C_2 = 20$.
The equilibrium of (10) is given as a solution of the system

$$\mathcal{A}_i^{(k)} = 1.5 \sum_{i=1}^{3} \frac{1}{C_k + \left(\mathcal{A}_i^{(k)}\right)^2}, \quad k = 0, 1, 2.$$

Then the global equilibrium of (11) is given by

$$\mathcal{W} = \begin{cases} (1.45019, 1.45019, 1.45019, 1.45019, 1.45019, 1.45019), \text{for } t \in [0, 2], \\ (0.542538, 0.542538, 0.542538, 0.542538, 0.542538, 0.542538), \text{for } t \in (2, 4], \\ (0.224435, 0.224435, 0.224435, 0.224435, 0.224435, 0.224435), \text{for } t \in (4, \infty). \end{cases}$$

All conditions of Theorem 1 are satisfied and then the global equilibrium $\mathcal{W}$ of the model (10) is exponentially stable.
We solve the model (10) with zero initial values by the algorithm in Section 2.1 and we graph the norm of the difference between the global equilibrium and the solution to illustrate the exponential stability of the global equilibrium (see Figure 6).

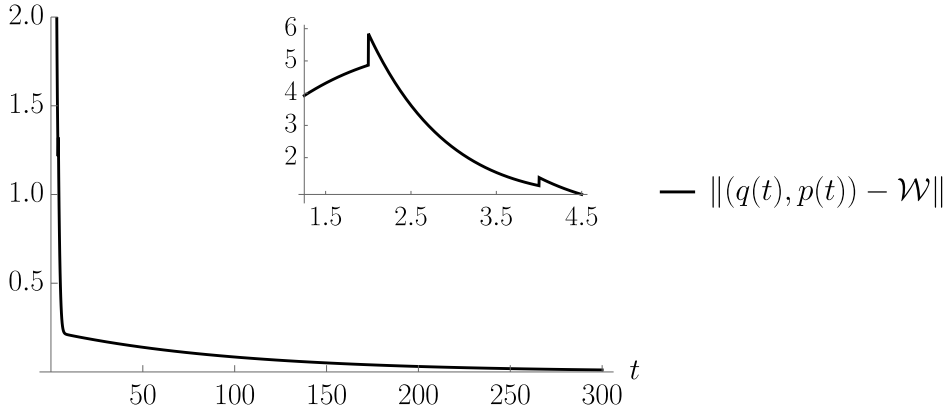

FIGURE 6. Graph of the norm of the difference $||(q(t), p(t)) - \mathcal{W}||$ of the solutions of (10) with zero initial values.

4.2. **Application 2.**

Consider model (10) with different activator functions, i.e., $h_k(s) = \frac{s^2}{\zeta_k^2+s^2}$ for $s \in \mathbb{R}$, $k \in \mathcal{J}$, i.e., consider

$$\begin{aligned} q_i'(t) &= -q_i + \sum_{j=1}^{3} a_{ij} h_{\sigma(t)}(p_j) + \alpha_0, \\ p_i'(t) &= -\beta(p_i - q_i),\ t \in (\tau_k, \tau_{k+1}],\quad i = 1, 2, \ldots, N,\ k \in \mathcal{J}. \end{aligned} \tag{13}$$

System (13) is similar to (2) with $N = 3$, $d_i = 1$, $b_i = c_i = \beta$, $\Theta_i = \alpha_0$.

Consider the case of $\alpha_0 = 0$ and $\beta = 0.01$, $a_{ii} = 2.5$ and $a_{ik} = 0$ for $k \neq i$, $k, i \in \mathcal{J}$. Let the switching rule be activated at a finite number of time points, for example, $m = 3$, $\tau_k = 2k$, $k = 0, 1, 2$, $h_0(s) = \frac{s^2}{1+s^2}$, $h_1(s) = \frac{s^2}{2^2+s^2}$, $h_2(s) = \frac{s^2}{5^2+s^2}$, $s \in \mathbb{R}$ and switching rule $\sigma(t) = C_k$ with $C_0 = 0, C_1 = 2, C_2 = 1$.

Since the activator functions $h_k(0) = 0$ for $k = 0, 1, 2$, according to Remark 8 the global equilibrium W of (13) is the zero vector. Therefore, assumption (A1) is satisfied. Also, we have

$$\begin{aligned} |h_0(u) - h_0(v)| &= |\frac{u^2}{1+u^2} - \frac{v^2}{1+v^2}| \le |u-v| \frac{|u+v|}{(1+u^2)(1+v^2)}, \\ |h_1(u) - h_1(v)| &= |\frac{u^2}{25+u^2} - \frac{v^2}{25+v^2}| \le |u-v| \frac{25|u+v|}{(25+u^2)(25+v^2)}, \\ |h_2(u) - h_2(v)| &= |\frac{u^2}{4+u^2} - \frac{v^2}{4+v^2}| \le |u-v| \frac{4|u+v|}{(4+u^2)(4+v^2)}. \end{aligned}$$

Therefore, $\gamma = 0.649519$ in assumption (H1).

From Remark 5 note condition (H2) is satisfied.

Condition (A2) holds with $\mu = 100$, $\mu_3 = 1$, $\mathcal{B} = 0.000257215$ because inequalities (8) are reduced to $-2 + 100 \cdot 0.01 + 1.5 \cdot 0.649519 = -0.0257215$ and $-2 \cdot 0.01 + 0.01 + 0.01 \cdot 1.5 \cdot 0.649519 = -0.000257215$.

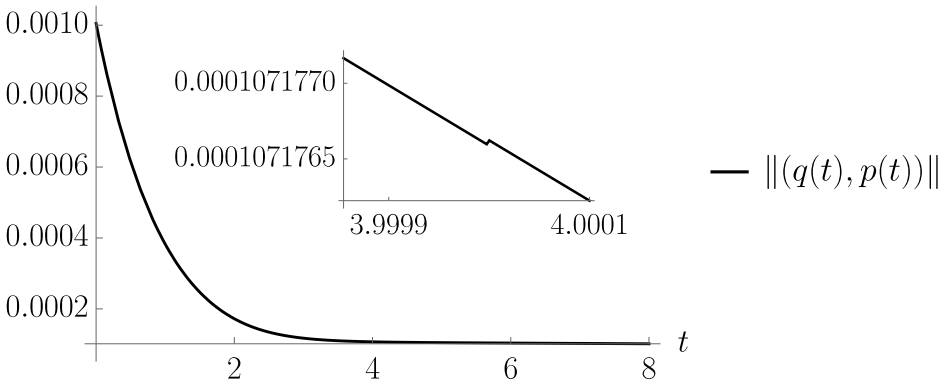

FIGURE 7. Graph of the norm of $||(q(t), p(t)) - 0||$ for (13) with initial values $(0.001, 0.0001)$.

According to Theorem 1 the zero global equilibrium is exponentially stable with constants $M = 100$ and $\lambda = 0.5\mathcal{B} = 0.0001286$, i.e.,

$$||(q(t), p(t))|| \leq 10||(q_0, p_0)||e^{-0.0001286t}.$$

We solve (13) numerically by Wolfram Mathematica for several initial values $(q_0, p_0) = (0.001, 0.0001)$ and graph the norm of $||(q(t), p(t))||$ (see Figure 7). From the graph it can be seen the solution is exponentially stable.

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