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Multistability of genetic regulatory networks

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Multistability is found to be an important recurring theme in synthesis biology. In this article, the multistability analysis problem is investigated by applying control theory and mathematical tools. Both the modelling and analysis issues are discussed. Specifically, the genetic regulatory networks (GRNs) with multistability are modelled as switched systems with interval time-varying delays and parameter uncertainties, where the piecewise-affine models are used to approximate the inherent non-linearities existing in the GRNs. Then, by using a novel Lyapunov functional approach and linear matrix inequality (LMI) techniques, a few delay-dependent criteria for the multistability of such genetic regulatory networks are established in the form of LMIs, which can be readily verified by using standard numerical software. A three-component network and a genetic toggle switch with bistability are employed to illustrate the applicability and usefulness of the developed theoretical results.

Keywords: multistability; genetic regulatory networks; linear matrix inequality; switched system; robust stability; interval time-varying delay

1. Introduction

Pioneering theoretical work on genetic regulatory networks (GRNs) has anticipated the emergence of postgenomic research and provided a mathematical framework for the current description and analysis of complex regulatory mechanisms (Glass and Kauffman 1973; Savageau 1974). In biochemical networks, the rates of reaction of substrates, enzymes, factors or products have attracted considerable attention in correspondence with changes in concentrations. The dynamical behaviours of genes, proteins and metabolites can be modelled by a series of non-linear differential equations (Smolen, Baxter and Byrne 2000; de Jong 2002), in which the detailed understanding of different non-linear behaviours exhibited by a genetic regulatory network could be explored. One method to construct the equations is the Michaelis–Menten model which has been developed to describe the reaction relationship of metabolites in non-linear differential equations in terms of their concentrations (McAdams and Arkin 1998). Another approach is the *S*-system, one of whose hallmarks is that, although it is highly non-linear, its steady states are characterised by linear equations (see Voit (2000) and references therein). Recently, piecewise-affine models have been proposed in Ghosh and Tomlin (2004) and Batt, Yordanov, Weiss and Belta (2007) to approximate the non-linearities existing in GRNs. Therefore, one could not only explain but also predict the gene functions by means of mathematical models that can be obtained through dynamics analysis of many underlying regulation mechanisms.

The genetic regulatory network diagrams that resemble complex electrical circuits are generated by the connectivity of genes and proteins. Similar to electrical circuits, mathematical and computational tools are utilised in developing circuits and systems with biotechnological design principles of synthetic genetic regulatory networks and new kinds of integrated circuits like neurochips learnt from biological neural networks (Elowitz and Leibler 2000; Hasty, McMillen and Collins 2002; Yokobayashi, Weiss and Arnold 2002). Construction of electrical circuits benefits from a large collection of well-characterised parts and modules, including resistors, capacitors and inductors, which can be connected to generate a complex circuit with useful functions. Since capacitors and inductors are dynamic components, one can describe an electrical circuit by differential equations even when non-linear components are included. A basic theme for electrical circuits design is the feedback. The notion of feedback is also a central recurring theme in genetic regulatory circuits. In fact, feedback is so prevalent in biological systems that it can be found at all levels of organisation, from the molecular and cellular levels, to the organism and

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ecological levels (Wiener 1961). It is impossible to overstate the importance of feedback as a strategy for the maintenance and evolution of life. Since feedback is the central topic in control theory, it is reasonable to expect that ideas from control theory will lead to new understanding of the underlying biological processes (Tomlin 2005). Applying control theory to study biology is fast becoming an interesting and exciting idea, although there exist large differences in culture, approach and the tools used in these two fields.

Similar to other dynamic systems, genetic regulatory networks have the stability as their key property. In Becskei and Serrano (2000), Li, Chen and Aihara (2006) and Wang, Gao, Cao and Liu (2008), the stability has been discussed for different genetic regulatory networks models. The term 'stability' mentioned here aims at the unique equilibrium point while the term 'multistability' is concerned with the coexistence of multiple steady states in response to a single set of external inputs. Multistability, the capacity to achieve multiple internal states in response to a single set of external inputs, plays an important role in gene circuit design in synthetic biological systems, because it satisfies the minimal requirement for the networks to possess memory where the state of the networks stores information about its past. When forced by a transient stimulus into one state or the other, such a system remains in that state after the transient stimulus has been removed. Multistability has certain unique properties which are not shared by other mechanisms of integrative control and it almost certainly plays an essential role in the dynamics of living cells and organisms (Ferrell and Machleder 1998; Laurent and Kellershohn 1999; Pomerening, Sontag and Ferrell 2003). Bistability, the property of having two stable fixed points, is a special case of multistability. It is becoming increasingly clear that bistability is an important recurring theme in cell signalling. Bistability is of particular relevance to biological systems that switch between discrete states, generate oscillatory responses, or 'remember' transient stimulus. Mutual inhibition, which is an alternative to the positive feedback networks in generating bistability, bears an analogy with the Reset–Set latch circuit design in engineering. Co-repressive switches in the well-known lac operon in the bacteria *Escherichia coli* have long been proposed as a common regulatory theme (Monod and Jacob 1961), and the synthetic toggle switch (Gardner, Cantor and Collins 2000; Ozbudak, Thattai, Lim, Shraiman and van Oudenaarden 2004) serves as a model system in which the multistability or bistability is the defining character to study such networks. Applying control theory to investigate the multistability of genetic networks will be of great significance in both control engineering and biological science. Recently, it draws great attention on the modelling and stability analysis of GRNs (Wei, Wang, Shu, Fraser and Liu 2007; Wang, Lam, Wei, Fraser and Liu 2008; Wang, Yang, Ho, Swift, Tucker and Liu 2008).

Theoretical results obtained for the multistability of a genetic regulatory network have been scattered in the literature. The biological system with multistability and hysteresis has been modelled as monotone dynamic systems in Angeli and Sontag (2004), where the rich and elegant theory of monotone dynamical system has provided an efficient mathematical tool for analysis (see Angeli and Sontag (2003) and references therein). Especially, in the biological systems with bistability, each stable mode of operation is associated with an appropriate invariant set in the state space, and stability with respect to each set has been studied in terms of a local notion of input-to-state stability with respect to compact sets in Chaves, Eissing and Allgower (2008). A general method for studying multistability in a large class of biological systems has been provided in Angeli, Ferrell and Sontag (2004). Meanwhile, a piecewise power-law approximation has been proposed to approach bistability in (Savageau 2001; Savageau 2002) where the *S*-system models have been applied.

It should be pointed out that, although the multistability of GRNs has received some initial research attention, there are still many open problems left for further investigation. For example, the time-delay and parameter uncertainty issues will need to be considered in the context of multistability. On the one hand, it has been recognised that the slow processes of transcription, translation and translocation inevitably cause time delays, which should be taken into account in the biological systems or artificial genetic networks in order to have more accurate models. Time delays can be easily detected in the synthetic toggle switch (Gardner et al. 2000) shown in Figure 2. On the other hand, an accurate model can hardly be obtained when we model a dynamical system from the systems point of view. In other words, there is always some error between the mathematical model and the physical system, which can be represented in the form of external perturbations, parameter fluctuations and unstructured dynamics (Zhou, Doyle and Glover 1996). This also applies to the modelling of a genetic regulatory network, and the analysis results without taking into account modelling uncertainties may not be as useful as expected in real-time applications. Therefore, it is essential and important to investigate the *robust* multistability of *delayed* genetic regulatory networks with *parameter uncertainties*. To the best of the authors' knowledge, up to now, very little effort

has been made towards this challenging problem, which then motivates the present study.

In this article, we are concerned with two research issues. One is the modelling of time-delayed genetic regulatory networks with multistability and parameter uncertainties, and the other is the robust multistability analysis of a genetic regulatory network with time-varying delays and parameter uncertainties. The delayed uncertain genetic regulatory networks are modelled as switched systems with interval time-varying delays and parameter uncertainties, which share the similarity with Reset–Set latch and relay in electrical engineering. Methods in switched systems are applied (Branicky 1998; Daafouz, Riedinger and Iung 2002). An important feature of the model proposed here is that this model can describe a genetic regulatory network with multiple steady states (multistability) rather than only two steady states (bistability). Another feature lies in that this model serves as a more practical description of the physical system by introducing time delays and parameter uncertainties. Additionally, in many practical cases, the delay may typically exist in an interval ($0 < h_1 \le d(t) \le h_2$), that is, the range of delay varies in an interval for which the lower bound is not restricted to 0. For this purpose, we decompose the interval time-varying delay $d(t)$ as two parts: the constant part h_1 and the time-varying part $h(t)$, that is,

$$d(t) = h_1 + h(t), \tag{1}$$

$$0 \le h(t) \le h_2 - h_1. \tag{2}$$

Then, we introduce a novel Lyapunov–Krasovskii functional by utilising the most updated techniques for achieving delay dependence and guarantee less conservatism. A new condition is then proposed for the multistability of a genetic regulatory network with time-varying delays and parameter uncertainties, in the form of linear matrix inequalities (LMIs), which can be readily verified by using standard numerical software (such as Matlab) (Boyd, El Ghaoui, Feron and Balakrishnan 1994). An important feature with the results to be reported is that all the stability conditions are dependent on the upper and lower bounds of the delays, which is made possible by utilising the up-to-date techniques to achieve delay dependence and by proposing a novel Lyapunov functional dependent on the uncertain parameters to guarantee the robustness of the genetic regulatory network. A three-component network and a genetic toggle switch with bistability are employed to illustrate the applicability and usefulness of the developed theoretical results.

Notation: The notation used throughout the article is standard. The superscript T indicates matrix transposition; $\mathbb{R}^n$ denotes the n-dimensional Euclidean space and $\mathbb{R}^{n\times m}$ is the set of all $n \times m$ real matrices. I and $\mathbf{0}$ denote identity matrix and zero matrix respectively, the notation $P > 0$ means that P is symmetric and positive definite and the symbol $*$ indicates symmetric blocks in the LMIs. In addition, diag$\{\ldots\}$ stands for a block-diagonal matrix and for a matrix A.

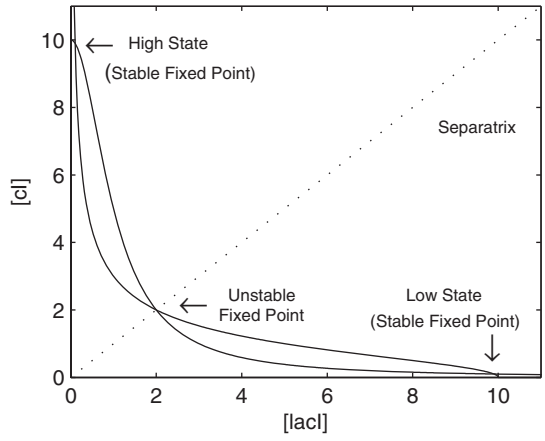

Figure 1. Phase-plane diagram of the toggle switch. Analysis of a bistable toggle network with equal promoter strengths driving the expression of lacI and cI proteins. The plots show the presence of three steady states: two stable steady states (low lacI, high cI (High State) and high lacI, low cI (Low State)) and one unstable steady state.

2. Model and preliminaries

The genetic toggle switch (Gardner et al. 2000) is shown in Figure 1. Each of the two proteins negatively regulates the synthesis of the other in such a genetic regulatory network. Intuitively, one might anticipate that there could be two possible stable steady states in this system. Because lacI production is repressed by the cI protein, an initial high concentration of cI would be self-sustaining and leads to a state with high cI and low lac repressor concentrations. Conversely, because cI production is repressed by the lac repressor, if the lac repressor is initially present in high concentrations, a second stable state would entail high lac and low cI concentrations. It is important to applying mathematical and computational tools in deducing the criteria for a robust toggle switch. The feasibility of a toggle switch is manifest in the existence of two stable fixed points; any initial state above the dividing line in Figure 1 will evolve to the fixed point that is characterised by a high cI (low lac repressor) concentration, whereas initial states below the dividing line will evolve to a high lac repressor (low cI) concentration. The design of an operating toggle depends on

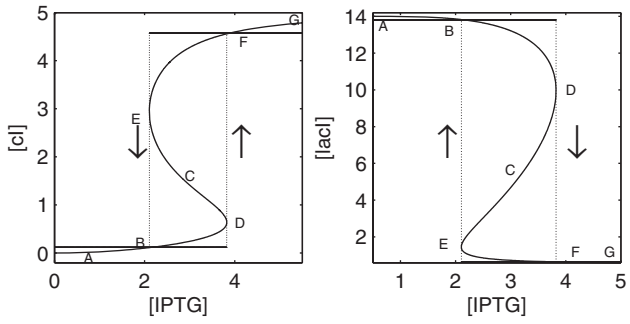

Figure 2. Bistability property.

parameter choices that lead to bistability. These criteria include the use of strong and balanced constitutive promoters, effective transcriptional repression, the formation of protein multimers and similar protein degradation rates. The reliable toggling between states is induced experimentally through the transient introduction of either a chemical or a thermal stimulus. Specifically, isopropyl-β-D-thiogalactopyranoside (IPTG), which binds to lac repressor tetramers, is used to render the lac repressor unable to repress its promoter.

As extracellular concentration of stimulus (IPTG) or environment condition (temperature, pH value) changes slightly or abruptly, the intracellular concentration of steady states changes. At one stable fixed point, the biological system that is described by non-linear differential equations could be linearised. The concentration of stimulus at the jump/switch point is treated as a threshold value. Between these two threshold values, three steady state points coexist with two stable and one unstable. By noticing Figure 2, D and E are threshold values. From low stimulus to high stimulus, the system comes across the bistable district at B, and the mode does not switch abruptly. With the concentration of stimulus rising consecutively to C, the switch occurs. From high stimulus to low stimulus, the occasion is similar. Therefore, we take B and F as threshold value points. It indicates that the history of the system is remembered: the change direction of stimulus plays the role of signal. Within the bistable district, the steady state point does not run far beyond its former state in the mono-stable district, which means that D shares neighbourhood with B and so does E with F. This property is shown in Figure 2.

Consider the non-linear differential equation that describes Michaelis–Menten model with Hill sigmoid function:

$$\dot{z}(t) = f(t, z(t)).$$

Nearing a steady-state point (e.g. when gene expression does not change substantially over time), the above non-linear system may be approximated as the first-order linear system explaining the rate of accumulation of each network species:

$$\dot{z}(t) = A(t)z(t) + u,$$

where $z(t) \in \mathbb{R}^n$ are the concentrations of RNAs, proteins and metabolites in the network; $\dot{z}(t)$ represents the rate of accumulation of the species in $z(t)$, and the system matrix $A(t)$ describes the network model. A reverse-engineering method is used to map an unknown network using only RNA expression changes that result from the steady state transcriptional perturbations to get the system matrix A (Gardner, di Bernardo, Lorenz and Collins 2003).

To facilitate the readers, we introduce the commonly used genetic regulatory network models in this section. A genetic regulatory network can be described by the following differential equation for $m = 1, 2, \ldots, n$:

$$\dot{z}_m(t) = -a_m z_m(t) + f_m(t, z(t)), \tag{3}$$

where $z_1, \ldots, z_n$ are metabolites, such as genes, proteins, activators, repressors, enzymes, factors or products of a biochemical network, and $z(\cdot) = [z_1(\cdot), z_2(\cdot), \ldots, z_n(\cdot)]^T \in \mathbb{R}^n$ is the metabolite state vector. Their rates of degradation are denoted by $a_m \in R^+$. $\dot{z}_m$, the rate of change in z_m, represents concentration change of a variable due to production or degradation. $f_m(\cdot)$ represents the feedback regulation function on the m-th metabolite, which is generally a non-linear or linear function of the variables $[z_1(\cdot), z_2(\cdot), \ldots, z_n(\cdot)]$, but has a form of monotonicity with each variable. Regulation function is used to capture the combined effect of several regulatory proteins on the control of gene expression or protein degradation and it describes the connection and topology structure of metabolites.

In this article, the function $f_m(t, z(t))$ is taken as $f_m(t, z(t)) = \sum_{j=1}^{n} f_{mj}(t, z_j(t))$, which is called SUM logic, because each metabolite acts additively to regulate the m-th metabolite. If $f_{mj}(t, z_j(t)) > 0$, x_j is an activator of z_m; if $f_{mj}(t, z_j(t)) = 0$, x_j has no link with x_m; if $f_{mj}(t, z_j(t)) < 0$, x_j is a repressor of z_m. Note that the regulation functions are generally expressed in a sigmoid form in Elowitz and Leibler (2000) and Gardner et al. (2000).

Now, we assume that the system (3) has N stable steady states. Let $z_i^* = (z_{i1}^*, z_{i2}^*, \ldots, z_{in}^*)^T$ be the i-th equilibrium point, $i = 1, 2, \ldots, N$. We linearise this non-linear differential equation at each equilibrium point and obtain

$$\dot{x}(t) = \sum_{i=1}^{N} \xi_{i_k}(A_i + B_i)x(t), \tag{4}$$

with

$$\xi_{i_k} = \begin{cases} 1, & \text{when the } i\text{-th subsystem is ON} \\ 0, & \text{otherwise} \end{cases}, \quad (i = 1, \ldots, N),$$

where

$$A_i = \text{diag}\{-a_1, \ldots, -a_n\},$$
$$B_i = [b_{mj}]_{n\times n},\ b_{mj} = \left.\frac{\partial f_{mj}(t, z_j(t))}{\partial x_j(t)}\right|_{z_j = z^*_{mj}}.$$

Then, the genetic regulatory network with multistability can be modelled as a switched system to be discussed in more detail later.

As mentioned in the Introduction, time delay often occurs in the regulation term and parameter uncertainties result from both the linearisation procedure and the external disturbances. Therefore, we generalise the model (4) as follows to reflect the time-varying delay and parameter uncertainties:

$$\begin{aligned} \dot{x}(t) = \sum_{i=1}^{N} \xi_{i_k}[&(A_i + \triangle A_i(t))x(t) \\ &+ (B_i + \triangle B_i(t))x(t - d_i(t))], \end{aligned} \tag{5}$$

with

$$\xi_{i_k} = \begin{cases} 1, & \text{when the } i\text{-th subsystem is ON at the } k\text{-th time} \\ 0, & \text{otherwise} \end{cases},$$
$$(i = 1, \ldots, N;\ k = 1, \ldots, M),$$

when $\xi_{i_k} = 1$, $x(t) \in \mathbb{R}^n$ are the concentrations of mRNA and protein deviated from the i-th equilibrium point, we certainly know the system is stable when $\lim_{t\to\infty} x(t) = 0$. The rates of degradation are denoted by the matrices $A_i \in \mathbb{R}^{n\times n}$. $A_i = \text{diag}\{a_{i1}, a_{i2}, \ldots, a_{in}\} < 0$ is a negative diagonal matrix. The matrices B_i represents the delayed feedback regulation weight coefficients of the protein on transcription. The matrices A_i and B_i are known. $\triangle A_i(t)$ and $\triangle B_i(t)$ are unknown matrices representing the uncertainties of the system, which are assumed to be of the form:

$$\triangle A_i(t) = M_{i0}F_{i0}(t)N_{i0}, \quad \triangle B_i(t) = M_{i1}F_{i1}(t)N_{i1},$$

where M_{i0}, N_{i0}, M_{i1} and N_{i1} are known real constant matrices, $F_{ij}(t) \in \mathbb{R}^{n\times n}$, $j = 0, 1$, are unknown time-varying matrices, satisfying

$$F_{ij}^T(t)F_{ij}(t) \le I, \quad j = 0, 1.$$

The time delay $d_i(t)$ is a time-varying differentiable function that satisfies

$$0 < h_{i1} \le d_i(t) \le h_{i2},$$
$$\dot{d}_i(t) \le \mu_i,$$

where h_{i2}, h_{i1} and μ_i are constants.

For convenience, set

$$f_i(t) = (A_i + \triangle A_i(t))x(t) + (B_i + \triangle B_i(t))x(t - d_i(t)).$$

Then system (5) becomes

$$\dot{x}(t) = \sum_{i=1}^{N} \xi_{i_k} f_i(t). \tag{6}$$

To be more specific, we point out that i represents the i-th subsystem, k represents the switching moment counter which goes as $0, 1, \ldots, M$, while a certain subsystem is ON, i_p may or may not equal to i_q, $p, q \in Z^+$. Throughout this article, we assume that the switching sequence is minimal in the sense that $i_k \ne i_{k+1}$, $k \in Z^+$.

We are now ready to deal with systems that switch among differential equations over time and regions of state space. One can associate such a system with the following switching sequence, indexed by an initial state,

$$x_0 : Q = x_0; \quad (i_0, t_0), (i_1, t_1), \ldots, (i_n, t_n), \ldots, \tag{7}$$

The sequence may or may not be infinite. In the finite case, we may take $t_{n+1} = \infty$, with all further definitions and results holding. However, we present in the sequel only in the infinite case to simplify notation. The switching sequence, along with (6), completely describes the trajectory of the system according to the following rule: (i_k, t_k) means that the system evolves according to $\dot{x}(t) = f_i(t)$ for $t_k \le t < t_{k+1}$. We denote this trajectory by $x_Q(\cdot)$.

Define the sequence of indexes:

$$Q_i = x_0; \quad i_0, i_1, \ldots, i_n, \ldots, \tag{8}$$

and the sequence of switching time:

$$Q_t = x_0; \quad t_0, t_1, \ldots, t_n, \ldots, \tag{9}$$

respectively. Suppose Q is a switching sequence as in (7). We denote by $Q|i$ the endpoints of the times that the i-th subsystem is active in the continuous-time cases. The interval completion $\Lambda(T)$ of a strictly increasing sequence of time $T = t_0, t_1, \ldots, t_n, \ldots$ is the set:

$$\bigcup_{k\in Z^+} [t_k, t_{k+1}], \tag{10}$$

Hence, $\Lambda(Q|i_k)$ is the set of times that the i-th subsystem is active.

Remark 1: The parameter uncertainties are inevitable during the linearisation process, and therefore we are actually dealing with the analysis problem for the *robust* multistability of (5). That is, how to establish sufficient conditions under which the system (5) with unknown-but-bounded parameters remains

asymptotically stable for all admissible parameter uncertainties and make sure that such conditions are as less conservative as possible.

Remark 2: Time delays are frequently encountered in biological networks. Time delays of biochemical reactions are the main causes of hysteresis property of a genetic regulatory network with bistability mentioned above. In many practical engineering systems, such as communication, electronics and chemical systems, time delays have gained considerable research interests and a large amount of results have appeared in the literature. Time delay may cause instability and poor performance of the control system. Most of the existing results related to time-varying delayed systems are based on the assumption $0<d(t)\le h_2$. However, it is common in practice that the delay typical exists in an interval $(0<h_1\le d(t)\le h_2)$, that is, the range of delay varies in an interval for which the lower bound is not restricted to 0. The aforementioned stability criteria for a genetic regulatory network with the assumption $0<d(t)\le h_2$ (Li et al. 2006), when applied to such cases, may be inevitably conservative due to their ignorance of the lower delay bound h_1. Therefore, it is of great significance to investigate the stability of systems with interval time-varying delay.

Remark 3: A switched system with different subsystems is analogous to a genetic regulatory network with multistability for both are running in different modes as the external inputs change. This way, the multistability analysis of a genetic regulatory network has been transformed into the stability analysis of a switched system. A switched system with time delays is referred to as a switched delay system, which is a brand new type of system and can find many applications. Roughly speaking, a switched delay system appears if switching and time delay coexist in either system modelling or signal transmission. Due to the interaction between continuous dynamics and discrete dynamics and because of the impact of time delays, the behaviour of switched delay systems is usually much more complicated than that of a switched system or a delay system. To date, there are a few correspondences on such systems (Kim, Campbell and Liu 2006; Sun, Wang, Liu and Zhao 2008).

3. Robust multistability of genetic networks

In this section, we present our new interval delay-dependent robust multistability condition for a genetic regulatory network with time-varying delays described in the above section.

Lemma 1 (Wang, Xie and de Souza 1992)**:** *Let $\mathcal{A}$, $\mathcal{D}$, $\mathcal{S}$, $\mathcal{W}$ and $\mathcal{F}$ be real matrices of appropriate dimensions such that $\mathcal{W}>0$ and $\mathcal{F}^T\mathcal{F}\le I$. Then, we have the following*:

(1) *For any scalar $\varepsilon>0$ and any vectors $x,y\in\mathbb{R}^n$, matrix $P>0$,*

$$2x^T\mathcal{D}\mathcal{F}\mathcal{S}y\le\varepsilon^{-1}x^T\mathcal{D}\mathcal{D}^Tx+\varepsilon y^T\mathcal{S}^T\mathcal{S}y, \tag{11}$$

$$2x^Ty\le x^TP^{-1}x+y^TPy; \tag{12}$$

(2) *For any scalar $\varepsilon>0$ such that $\mathcal{W}-\varepsilon\mathcal{D}\mathcal{D}^T>0$,*

$$(\mathcal{A}+\mathcal{D}\mathcal{F}\mathcal{S})^T\mathcal{W}^{-1}(\mathcal{A}+\mathcal{D}\mathcal{F}\mathcal{S})\le\mathcal{A}^T\left(\mathcal{W}-\varepsilon\mathcal{D}\mathcal{D}^T\right)^{-1}\mathcal{A}+\varepsilon^{-1}\mathcal{S}^T\mathcal{S}. \tag{13}$$

In this article, the delay we consider exists in an interval $(0<h_{i1}\le h_i(t)\le h_{i2},\ i=1,\dots,N)$, that is, the range of delay varies in an interval for which the lower bound is not restricted to 0. The main idea to solve this problem is to represent the time delay $d_i(t)$ as two parts: the constant part h_{i1} and the time-varying part $h_i(t)$,

$$d_i(t)=h_{i1}+h_i(t),\quad 0\le h_i(t)\le h_{i2}-h_{i1}.$$

Then, we introduce a novel Lyapunov–Krasovskii functional as follows:

$$V(x(t))=\sum_{i=1}^{N}\xi_{i_k}V_i(x(t)),$$

with

$$\xi_{i_k}=\begin{cases}1, & \text{when the } i\text{-th subsystem is ON at the } k\text{-th time}\\ 0, & \text{otherwise}\end{cases},$$
$$(i=1,\dots,N;\ k=1,\dots,M),$$

where

$$\begin{aligned}V_i(x(t))&=V_{i1}(x(t))+V_{i2}(x(t))+V_{i3}(x(t)),\\ V_{i1}(x(t))&=x^T(t)P_ix(t),\\ V_{i2}(x(t))&=\int_{t-h_{i1}}^{t}x^T(\alpha)Q_{i1}x(\alpha)\mathrm{d}\alpha\\ &\quad+\int_{t-d_i(t)}^{t-h_{i1}}x^T(\alpha)Q_{i2}x(\alpha)\mathrm{d}\alpha,\\ V_{i3}(x(t))&=\int_{-h_{i1}}^{0}\int_{t+\beta}^{t}\dot{x}^T(\alpha)Z_{i1}\dot{x}(\alpha)\mathrm{d}\alpha\mathrm{d}\beta\\ &\quad+\int_{-h_{i2}}^{-h_{i1}}\int_{t+\beta}^{t}\dot{x}^T(\alpha)Z_{i2}\dot{x}(\alpha)\mathrm{d}\alpha\mathrm{d}\beta.\end{aligned} \tag{14}$$

By utilising the most updated techniques for achieving delay dependence, a new condition is proposed for the asymptotic stability of switched system with time-varying delays in the form of LMIs.

Definition 1: A genetic regulatory network is said to possess *multistability* if it has more than one stable equilibrium point. Especially, the network has bistability if it has two stable equilibrium points, and the network has N-stability if it has N ($N>2$) stable equilibrium points (in this case, the network is called n-stable).

Theorem 1: *The system in* (5) *is asymptotically N-stable if there exist scalars* $\varepsilon_i>0$, $\delta_{i1}>0$, $\delta_{i2}>0$, *and positive definite matrices* $P_i>0$, $Q_{ij}>0$, $Z_{ij}>0$, $i=1,\ldots,N$ ($N>1$), $j=1,2$, *such that the following LMIs hold*:

$$\begin{bmatrix} \Theta_i & h_{i1}M_{iS}^T\mathcal{A}_i^TZ_{i1} & 0 & (h_{i2}-h_{i1})M_{iS}^T\mathcal{A}_i^TZ_{i2} & 0 & M_{ix}^TP_i\mathcal{M}_i \\ * & -h_{i1}Z_{i1} & h_{i1}Z_{i1}\mathcal{M}_i & 0 & 0 & 0 \\ * & * & -\delta_{i1}I & 0 & 0 & 0 \\ * & * & * & -(h_{i2}-h_{i1})Z_{i2} & (h_{i2}-h_{i1})Z_{i2}\mathcal{M}_i & 0 \\ * & * & * & * & -\delta_{i2}I & 0 \\ * & * & * & * & * & -\varepsilon_iI \end{bmatrix}<0, \tag{15}$$

where

$$\Theta_i = W_{iP}^T\bar{P}_iW_{iP}+W_{iQ}^T\bar{Q}_iW_{iQ}+W_{iZ}^T\bar{Z}_iW_{iZ} +(\varepsilon_i+\delta_{i1}+\delta_{i2})M_{iS}^T\mathcal{N}_i^T\mathcal{N}_iM_{iS},$$

$$\bar{Q}_i=\mathrm{diag}\{Q_{i1},-Q_{i1},Q_{i2},-Q_{i2}\},$$

$$\bar{Z}=\mathrm{diag}\{-Z_{i1},-Z_{i2}\},$$

$$\bar{P}_i=\begin{bmatrix}0 & P_i\\ P_i & 0\end{bmatrix},\quad W_{iP}=\begin{bmatrix}A_i & 0_n & B_i\\ I_n & 0_n & 0_n\end{bmatrix},$$

$$M_{iS}=\begin{bmatrix}I_n & 0_n & 0_n\\ 0_n & 0_n & I_n\end{bmatrix},\quad W_{iQ}=\begin{bmatrix}I_n & 0_n & 0_n\\ 0_n & I_n & 0_n\\ 0_n & I_n & 0_n\\ 0_n & 0_n & \sqrt{1-\mu_i}I_n\end{bmatrix},$$

$$W_{iZ}=\begin{bmatrix}\sqrt{1/h_{i1}}I_n & -\sqrt{1/h_{i1}}I_n & 0_n\\ 0_n & \sqrt{1/(h_{i2}-h_{i1})}I_n & -\sqrt{1/(h_{i2}-h_{i1})}I_n\end{bmatrix},$$

$$M_{ix}=\begin{bmatrix}I_n & 0_n & 0_n\end{bmatrix},\quad \mathcal{N}_i=\begin{bmatrix}N_{i0} & 0\\ 0 & N_{i1}\end{bmatrix},$$

$$\mathcal{A}_i=\begin{bmatrix}A_i & B_i\end{bmatrix},\quad \mathcal{M}_i=\begin{bmatrix}M_{i0} & M_{i1}\end{bmatrix}.$$

Proof: For convenience, set

$$\bar{A}_i(t)=A_i+\triangle A_i(t),\quad \bar{B}_i(t)=B_i+\triangle B_i(t).$$

Then the system becomes

$$\dot{x}(t)=\sum_{i=1}^{N}\xi_{i_k}[\bar{A}_i(t)x(t)+\bar{B}_i(t)x(t-d_i(t))], \tag{16}$$

with

$$\xi_{i_k}=\begin{cases}1, & \text{When the } i\text{-th subsystem}\\ & \text{is ON at the } k\text{-th time},\\ 0, & \text{otherwise}\end{cases}$$
$$(i=1,\ldots,N;\ k=1,\ldots,M).$$

The Lyapunov–Krasovskii functional is defined in (14). The derivatives of $V_{ij}(x(t))$, $j=1,2,3$, are given by

$$\begin{aligned}\dot{V}_{i1}(x(t))&=2x^T(t)P_i\dot{x}(t),\\ \dot{V}_{i2}(x(t))&=x^T(t)Q_{i1}x(t)-x^T(t-h_{i1})Q_{i1}x(t-h_{i1})\\ &\quad+x^T(t-h_{i1})Q_{i2}x(t-h_{i1})\\ &\quad-(1-\dot{d}_i(t))x^T(t-d_i(t))Q_{i2}x(t-d_i(t)),\\ \dot{V}_{i3}(x(t))&=\dot{x}^T(t)(h_{i1}Z_{i1}+(h_{i2}-h_{i1})Z_{i2})\dot{x}(t)\\ &\quad-\int_{t-h_{i1}}^{t}\dot{x}^T(\alpha)Z_{i1}\dot{x}(\alpha)\mathrm{d}\alpha\\ &\quad-\int_{t-h_{i2}}^{t-h_{i1}}\dot{x}^T(\alpha)Z_{i2}\dot{x}(\alpha)\mathrm{d}\alpha.\end{aligned} \tag{17}$$

From Jensen's inequality, we can easily get

$$\begin{aligned}&-\int_{t-h_{i1}}^{t}\dot{x}^T(\alpha)Z_{i1}\dot{x}(\alpha)\mathrm{d}\alpha\\ &\le-\frac{1}{h_{i1}}\left(\int_{t-h_{i1}}^{t}\dot{x}(\alpha)\mathrm{d}\alpha\right)^TZ_{i1}\left(\int_{t-h_{i1}}^{t}\dot{x}(\alpha)\mathrm{d}\alpha\right)\\ &=-\frac{1}{h_{i1}}(x(t)-x(t-h_{i1}))^TZ_{i1}(x(t)-x(t-h_{i1})),\end{aligned} \tag{18}$$

$$-\int_{t-h_{i2}}^{t-h_{i1}}\dot{x}^T(\alpha)Z_{i2}\dot{x}(\alpha)\mathrm{d}\alpha \le -\int_{t-d_i(t)}^{t-h_{i1}}\dot{x}^T(\alpha)Z_{i2}\dot{x}(\alpha)\mathrm{d}\alpha$$
$$\le -\frac{1}{h_{i2}-h_{i1}}\left(\int_{t-d_i(t)}^{t-h_{i1}}\dot{x}(\alpha)\mathrm{d}\alpha\right)^T Z_{i2}\left(\int_{t-d_i(t)}^{t-h_{i1}}\dot{x}(\alpha)\mathrm{d}\alpha\right)$$
$$\le -\frac{1}{h_{i2}-h_{i1}}(x(t-h_{i1})-x(t-d_i(t)))^T Z_{i2} \times (x(t-h_{i1})-x(t-d_i(t))). \quad (19)$$

Using (18) and (19), we have

$$\begin{aligned}\dot{V}_i(x(t)) \le{}& 2x^T(t)P_i(A_ix(t)+B_ix(t-d_i(t)))+\varepsilon_i^{-1}x^T(t)P_i\\ &\times\left(M_{i0}M_{i0}^T+M_{i1}M_{i1}^T\right)P_ix(t)\\ &+\varepsilon_i\big(x^T(t)N_{i0}^TN_{i0}x(t)+x^T(t-d_i(t))\\ &\times N_{i1}^TN_{i1}x(t-d_i(t))\big)\\ &+x^T(t)Q_{i1}x(t)-x^T(t-h_{i1})Q_{i1}x(t-h_{i1})\\ &+x^T(t-h_{i1})Q_{i2}x(t-h_{i1})\\ &-(1-\mu_i)x^T(t-d_i(t))Q_{i2}x(t-d_i(t))\\ &+\left(\bar{A}_i(t)+\bar{B}_ix(t-d_i(t))\right)^T\\ &\times(h_{i1}Z_{i1}+(h_{i2}-h_{i1})Z_{i2})\\ &\times\left(\bar{A}_i(t)+\bar{B}_ix(t-d_i(t))\right)\\ &-\frac{1}{h_{i1}}(x(t)-x(t-h_{i1}))^TZ_{i1}(x(t)-x(t-h_{i1}))\\ &-\frac{1}{h_{i2}-h_{i1}}(x(t-h_{i1})-x(t-d_i(t)))^T\\ &\times Z_{i2}(x(t-h_{i1})-x(t-d_i(t)))\end{aligned}$$

By (15), it is easy to see that

$$h_{i1}Z_{i1}-\delta_{i1}^{-1}(h_{i1})^2Z_{i1}\mathcal{M}_i\mathcal{M}_i^TZ_{i1}>0,$$
$$(h_{i2}-h_{i1})Z_{i2}-\delta_{i2}^{-1}(h_{i2}-h_{i1})^2Z_{i2}\mathcal{M}_i\mathcal{M}_i^TZ_{i2}>0.$$

Then, from (13) in Lemma 1, we have

$$\begin{aligned}&\left(\bar{A}_ix(t)+\bar{B}_ix(t-d_i(t))\right)^Th_{i1}Z_{i1}\left(\bar{A}_i(t)+\bar{B}_ix(t-d_i(t))\right)\\ &=\zeta^T(t)M_{iS}^T[\mathcal{A}_i+\mathcal{M}_i\mathcal{F}_i(t)\mathcal{N}_i]^Th_{i1}Z_{i1}\\ &\quad\times[\mathcal{A}_i+\mathcal{M}_i\mathcal{F}_i(t)\mathcal{N}_i]M_{iS}\zeta(t)\\ &\le\zeta^T(t)\Big(\Psi_{i1}+\delta_{i1}M_{iS}^T\mathcal{N}_i^T\mathcal{N}_iM_{iS}\Big)\zeta(t),\\ &\left(\bar{A}_i(t)+\bar{B}_ix(t-d_i(t))\right)^T(h_{i2}-h_{i1})Z_{i2}\\ &\quad\times\left(\bar{A}_i(t)+\bar{B}_ix(t-d_i(t))\right)\\ &=\zeta^T(t)M_{iS}^T[\mathcal{A}_i+\mathcal{M}_i\mathcal{F}_i(t)\mathcal{N}_i]^T(h_{i2}-h_{i1})Z_{i2}\\ &\quad\times[\mathcal{A}_i+\mathcal{M}_i\mathcal{F}_i(t)\mathcal{N}_i]M_{iS}\zeta(t)\\ &\le\zeta^T(t)\Big(\Psi_{i2}+\delta_{i2}M_{iS}^T\mathcal{N}_i^T\mathcal{N}_iM_{iS}\Big)\zeta(t),\end{aligned}$$

where

$$\zeta(t)=\begin{bmatrix}x(t)\\ x(t-h_{i1})\\ x(t-d_i(t))\end{bmatrix},$$

and

$$\mathcal{F}_i(t)=\begin{bmatrix}F_{i0}(t) & 0\\ 0 & F_{i1}(t)\end{bmatrix},$$

$$\begin{aligned}\Psi_{i1}={}&M_{iS}^T\mathcal{A}_i^Th_{i1}Z_{i1}\left(h_{i1}Z_{i1}-\delta_{i1}^{-1}h_{i1}^2Z_{i1}\mathcal{M}_i\mathcal{M}_i^TZ_{i1}\right)^{-1}\\ &\times h_{i1}Z_{i1}\mathcal{A}_iM_{iS},\\ \Psi_{i2}={}&M_{iS}^T\mathcal{A}_i^T(h_{i2}-h_{i1})Z_{i2}\big((h_{i2}-h_{i1})Z_{i2}\\ &-\delta_{i2}^{-1}(h_{i2}-h_{i1})^2Z_{i2}\mathcal{M}_i\mathcal{M}_i^TZ_{i2}\big)^{-1}h_{i1}Z_{i2}\mathcal{A}_iM_{iS}.\end{aligned}$$

Therefore,

$$\dot{V}_i(t)\le\zeta^T(t)\Xi_i\zeta(t),$$

where

$$\Xi_i=\Theta_i+\Phi_i+\Psi_{i1}+\Psi_{i2},$$
$$\Phi_i=\varepsilon_i^{-1}M_{ix}^TP_i\mathcal{M}_i\mathcal{M}_i^TP_iM_{ix}.$$

Applying the Schur complement formula to (15), we have

$$\Xi_i<0. \quad (20)$$

Thus, if (20) holds, we have $\dot{V}_i(x(t))<-\epsilon_i\|x(t)\|^2$ for a sufficiently small $\epsilon_i>0$ and $x(t)\neq0$, then

$$\begin{aligned}\dot{V}(x(t))&=\sum_{i=1}^N\xi_{i_k}\dot{V}_i(x(t),\\ &<-\min\epsilon_i\|x(t)\|^2\end{aligned}$$

with

$$\xi_{i_k}=\begin{cases}1, & \text{When the } i\text{-th subsystem}\\ & \quad\text{is ON at the } k\text{-th time},\\ 0, & \text{otherwise}\end{cases}$$
$$(i=1,\ldots,N;\ k=1,\ldots,M).$$

and the asymptotic multistability is established. □

Let us now consider a special case where there are no parameter uncertainties. In such a case, the genetic regulatory network (5) *becomes*

$$\dot{x}(t)=\sum_{i=1}^N\xi_{i_k}[A_ix(t)+B_ix(t-d_i(t))]. \quad (21)$$

Based on the proof of Theorem 1, we will have the following corollary readily.

Corollary 1: *The system in* (21) *is asymptotically N-stable, if there exist scalars* $\varepsilon_i>0$, $\delta_{i1}>0$, $\delta_{i2}>0$, *and positive definite matrices* $P_i>0$, $Q_{ij}>0$, $Z_{ij}>0$, $i=1,\ldots,N$, $j=1,2$, *such that the following LMIs hold*:

$$\Theta_i = W_{iP}^T \bar{P}_i W_{iP} + W_{iQ}^T \bar{Q}_i W_{iQ} + W_{iZ}^T \bar{Z}_i W_{iZ} < 0, \quad (22)$$

where

$$\bar{Q}_i = \mathrm{diag}\{Q_{i1}, -Q_{i1}, Q_{i2}, -Q_{i2}\},$$
$$\bar{Z}_i = \mathrm{diag}\{Z_{i1}, Z_{i2}, -Z_{i1}, -Z_{i2}\},$$
$$\bar{P}_i = \begin{bmatrix} 0 & P_i \\ P_i & 0 \end{bmatrix}, \quad W_{iP} = \begin{bmatrix} A_i & 0_n & B_i \\ I_n & 0_n & 0_n \end{bmatrix},$$
$$W_{iQ} = \begin{bmatrix} I_n & 0_n & 0_n \\ 0_n & I_n & 0_n \\ 0_n & I_n & 0_n \\ 0_n & 0_n & \sqrt{1-\mu_i} I_n \end{bmatrix},$$
$$W_{iZ} = \begin{bmatrix} \sqrt{h_{i1}} A_i & 0_n & \sqrt{h_{i1}} B_i \\ \sqrt{h_{i2}-h_{i1}} A_i & 0_n & \sqrt{h_{i2}-h_{i1}} B_i \\ \sqrt{1/h_{i1}} I_n & -\sqrt{1/h_{i1}} I_n & 0_n \\ 0_n & \sqrt{1/(h_{i2}-h_{i1})} I_n & -\sqrt{1/(h_{i2}-h_{i1})} I_n \end{bmatrix}.$$

Remark 4: The stability conditions given in both Theorem 1 and Corollary 1 are linear matrix inequalities over the decision variables to be determined, which can be easily verified using some standard numerical software. Moreover, the form simplified as $W_1^T X W_1 + W_2^T Y W_2 < 0$ is more laconic since it expresses the LMI in several parts, each of which has a symmetric structure with the matrix variable to be determined in centre.

4. Illustrative examples

Example 1: We consider a three-component network as follows:

$$\begin{aligned} \dot{z}_1(t) &= -z_1(t) - 2f(z_3(t-d(t))) + 0.5, \\ \dot{z}_2(t) &= -z_2(t) + f(z_3(t-d(t))) - 1, \\ \dot{z}_3(t) &= -0.5z_3(t) - 3f(z_1(t-d(t))) \\ &\quad - 0.5f(z_2(t-d(t))) - 0.2, \end{aligned} \quad (23)$$

where $f(s)=\tanh(s)$ and therefore the regulation function has a sigmoid form, and $\dot{f}(s) = 1 - \tanh^2(s)$. The topology of this genetic regulatory network is shown in Figure 3.

We denote $e_i = [x_1^*, x_2^*, x_3^*]$ as the i-th equilibrium point of the network. We can easily get three equilibrium points of the network: $e_1 = [2.4698,\ -1.9849,\ -2.4400]^T$, $e_2 = [-1.1453,\ -0.1773,\ 1.1650]^T$ and $e_3 = [-0.3023,\ -0.5989,\ 0.4250]^T$. We choose e_1 and e_2. After linearisation, we get

$$\dot{x}(t) = \sum_{i=1}^{3} \xi_{i_k} [(A_i x(t) + B_i x(t - d_i(t))],$$

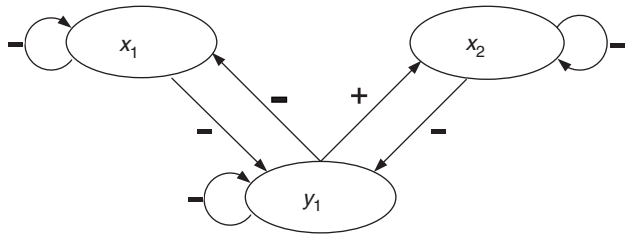

Figure 3. Topology of genetic network (23) (+: positive regulation; −: negative regulation).

with

$$\xi_{i_k} = \begin{cases} 1, & \text{when the } i\text{-th subsystem is ON} \\ 0, & \text{otherwise} \end{cases}, \quad (i = 1, 2,\ k \in Z^+),$$

where

$$A_1 = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -0.5 \end{bmatrix},$$
$$B_1 = \begin{bmatrix} 0 & 0 & -0.6465 \\ 0 & 0 & 0.3232 \\ -1.0015 & -0.4846 & 0 \end{bmatrix},$$
$$A_2 = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -0.5 \end{bmatrix},$$
$$B_2 = \begin{bmatrix} 0 & 0 & -0.0599 \\ 0 & 0 & 0.0299 \\ -0.0847 & -0.0364 & 0 \end{bmatrix}.$$

The time delays are assumed to be

$$d(t) = 0.02 + 0.01 \sin t,$$

and therefore we can have the parameters as follows:

$$h_1 = 0.01, \quad h_2 = 0.03, \quad \mu = 0.03.$$

By solving the conditions in Theorem 1 using the LMI toolbox in Matlab, we can obtain a feasible solution with the following obtained matrix variables (for space consideration, here we only list the matrix variables P_1 and P_2),

$$P_1 = \begin{bmatrix} 13.4864 & 3.3045 & 6.8045 \\ 3.3045 & 18.0211 & -4.1629 \\ 6.8045 & -4.1629 & 6.7032 \end{bmatrix},$$
$$P_2 = \begin{bmatrix} 0.9415 & 0.0014 & -0.0256 \\ 0.0014 & 0.9416 & -0.0055 \\ -0.0256 & -0.0055 & 1.2998 \end{bmatrix}.$$

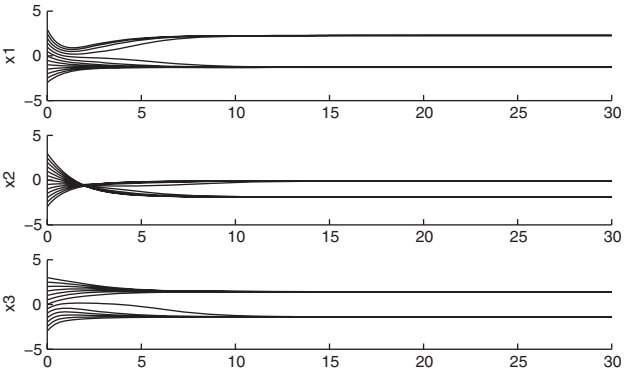

Figure 4. Dynamics of system (23).

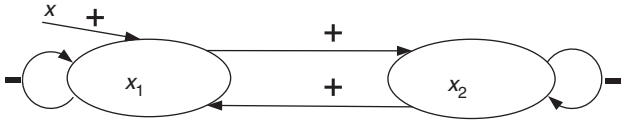

Figure 5. Topology of genetic network (23) (−, +: same as Figure 3).

For other combinations of these equilibrium points, the solutions are found to be infeasible. We conclude that the network is bistable, which is the same as the dynamics shown in Figure 4.

Example 2: We consider a genetic toggle switch with bistability (Gardner 2000):

$$\dot{z}_1(t) = \frac{\alpha_1}{1 + z_2^{\theta}(t)} - \beta_1 z_1(t),$$
$$\dot{z}_2(t) = \frac{\alpha_2 X^{\eta}}{X^{\eta} + 1 + z_1^{\gamma}(t)} - \beta_2 z_2(t), \tag{24}$$

where z_1, z_2 are the concentrations of lacI and cI respectively, X is the concentration of IPTG, and β_1, β_2 denote the ratio of the decay rate. We select a set of biologically plausible parameters as $\alpha_1 = 14$, $\alpha_2 = 5$, $\beta_1 = \beta_1 = 1$, $\theta = \eta = \gamma = 2$. From Figures 1 and 2, it is easy to know that bistability exists with this set of parameters. We linearise such non-linear differential equations at these two stable steady points and obtain the subsystem matrices A_1, A_2 respectively. The topology of this genetic regulatory network is shown in Figure 5.

We denote high (low) state when lacI concentration is high (low) and cI concentration is (high). When $X = 3.8244$, high state is switched to low state; when $X = 2.1060$, low state is switched to high state. Without considering time delay, we get

$$\dot{x}(t) = \sum_{i=1}^{2} \xi_{i_k}(A_i + B_i)x(t), \tag{25}$$

with

$$\xi_{i_k} = \begin{cases} 1, & \text{when the } i\text{-th subsystem is ON} \\ 0, & \text{otherwise} \end{cases}, \quad (i = 1, 2,\ k \in Z^+),$$

where

$$A_1 = \begin{bmatrix} -1 & 0 \\ 0 & -1 \end{bmatrix}, \quad B_1 = \begin{bmatrix} 0 & -0.2688 \\ -0.3653 & 0 \end{bmatrix},$$
$$A_2 = \begin{bmatrix} -1 & 0 \\ 0 & -1 \end{bmatrix}, \quad B_2 = \begin{bmatrix} 0 & -3.0795 \\ -0.0159 & 0 \end{bmatrix}.$$

We now introduce the time delay in the regulation terms and parameter uncertainties, then we have the model of the form (5):

$$\dot{x}(t) = \sum_{i=1}^{2} \xi_i(t)[(A_i + \triangle A_i(t))x(t) + (B_i + \triangle B_i(t))x(t - d_i(t))].$$

The time delays are assumed to be

$$d_1(t) = (1 + 0.3\sin 4t)/2,$$
$$d_2(t) = (1 + 0.5\cos 2t)/2,$$

and therefore we can get the parameters as follows:

$$h_{11} = 0.35, \quad h_{12} = 0.65, \quad \mu_1 = 0.6,$$
$$h_{21} = 0.25, \quad h_{22} = 0.75, \quad \mu_2 = 0.5.$$

We choose

$$\hat{M}_{10} = \begin{bmatrix} 0.2 & 0.3 \\ 0.6 & 0.4 \end{bmatrix}, \quad \hat{M}_{11} = \begin{bmatrix} 0.1 & 0.2 \\ 0.5 & 0.1 \end{bmatrix},$$
$$\hat{N}_{10} = \begin{bmatrix} 0.1256 & 0 \\ 0 & 0.1256 \end{bmatrix}, \quad \hat{N}_{11} = \begin{bmatrix} 0.1886 & 0 \\ 0 & 0.1886 \end{bmatrix},$$
$$\hat{M}_{20} = \begin{bmatrix} 0.4 & 0.1 \\ 0.1 & 0.4 \end{bmatrix}, \quad \hat{M}_{21} = \begin{bmatrix} 0.4 & 0.3 \\ 0.5 & 0.4 \end{bmatrix},$$
$$\hat{N}_{20} = \begin{bmatrix} 0.2112 & 0 \\ 0 & 0.2112 \end{bmatrix}, \quad \hat{N}_{21} = \begin{bmatrix} 0.1222 & 0 \\ 0 & 0.1222 \end{bmatrix}.$$

By solving the conditions in Theorem 1 using the LMI toolbox in Matlab, we can obtain a feasible solution with the following obtained matrix variables (for space consideration, here we only list the matrix variables P_1 and P_2),

$$P_1 = \begin{bmatrix} 0.7488 & -0.0807 \\ -0.0807 & 0.6077 \end{bmatrix},$$
$$P_2 = \begin{bmatrix} 12.5594 & -0.7919 \\ -0.7919 & 196.2415 \end{bmatrix}.$$

This shows the robust bistability of this kind of genetic network.

5. Conclusion

We have made an effort to show the possibility of applying control theory to investigate the multistability of a genetic network, therefore having potential applications in synthetic biology. In this article, a method has been presented for the analysis of multistability of a genetic regulatory network with interval time-varying delays and parameter uncertainties. The motivation for considering an uncertain switched system with time-delays is twofold. First, the model can describe a genetic regulatory network with multiple stable steady states (multistability) rather than only two stable steady states (bistability). Second, the model lies in the more practical description of the physical system by introducing time delays and parameter uncertainties. By using a Lyapunov functional approach and LMI techniques, the multistability criteria for a genetic regulatory network with time-varying delays and parameter uncertainties have been established in the form of LMIs, which can be readily verified by using standard numerical software. An important feature of the results reported here is that all the stability conditions are dependent on the upper and lower bounds of the delays, which is made possible by utilising the most updated techniques for achieving delay dependence. Also, a novel Lyapunov functional dependent on the uncertain parameters has been utilised to guarantee the robustness of the genetic regulatory network. To the best of our knowledge, the approach presented here is the first computational approach developed specifically for multistability of a genetic regulatory network. A three-component network and a genetic toggle switch with bistability have been employed to illustrate the applicability and usefulness of the developed theoretical results.

In the future, many results in control theory can be extended to GRNs. One important issue is to reduce the conservativeness by allowing large time delays. The idea of delay fractioning in Mou, Gao, Lam and Qiang (2008) will be useful. Another important issue is to study stochastic GRNs with mixed time-delays by referring to the results in Wang, Liu, Fraser and Liu (2006), Wang, Liu, Li and Liu (2006), Wang, Liu, Yu and Liu (2006) and Wang, Shu, Fang and Liu (2006). It is believed that control theory will be a powerful tool in biology.

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