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A Switched Systems Approach for the Analysis and Control of Mode Transitions in Biological Networks

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Abstract— **This work present a methodology for the analysis and control of mode transitions in biological networks. The proposed approach is predicated upon the notion of orchestrating switching between the domains of attraction of the steady-states of the constituent modes. Initially, the overall network is modeled as a switched nonlinear system that consists of multiple modes, each governed by a set of continuous-time differential equations. The transitions between the continuous modes are triggered by discrete events (changes in model parameters that correspond to alterations in physiological conditions). Then, following the characterization of the steady-state behavior of each mode, Lyapunov techniques are used to characterize the domains of attraction of the steady-states. Finally, by analyzing how the domains of attraction of the various modes overlap with one other, a switching rule is derived to determine when, and if, a given mode transition at a given time results in the desired steady-state behavior. The proposed approach has implications both for understanding the outcome of naturally-occurring mode transitions and for the ability to manipulate network behavior by enforcing mode transitions. The proposed approach is demonstrated using a model of a biological network that arises in the bacteriophage λ-switch system.**

I. Introduction

In a biological cell, cellular functions, such as metabolism, DNA synthesis, movement and information processing, are implemented and controlled by vast arrays of complex networks of biochemical interactions. Understanding how these networks are integrated and regulated, and how the regulation may be influenced – possibly for therapeutic purposes – is a major goal of molecular cell biologists and bioengineers. While experimental techniques have been, and will continue to be, an indispensable tool in the quest for such an understanding, it is now clear that the sheer complexity of biological networks is such that informal biochemical intuition alone cannot reliably deduce the underlying logic of these networks. This intuition must be supplemented by precise mathematical and computational tools that can provide both qualitative and quantitative insights into the description, analysis and manipulation of biological networks underlying basic cellular function. From a practical point of view, such techniques could potentially reduce the degree of trial-and-error experimentation. More importantly, computational and theoretical approaches can lead to testable predictions regarding the current understanding of biological networks, which can serve as the basis for revising existing hypotheses. These realizations, together with recent technological advances that are increasingly enabling experimental validation of theoretical predictions, have been major driving forces behind a large and growing body of research work, in recent years, on the development and application of analytical and computational tools for the modeling, simulation, and analysis of biological networks (e.g., see the review papers [10], [19] and the references therein).

Biological networks are intrinsically dynamical systems, driving the adaptive responses of a cell in space and time. The behavior of these dynamical systems is determined by "biochemical kinetics," or rate equations, in which the variables of interest are the concentrations of individual network components (proteins, metabolites, etc.) within the cell, and the dynamics describe the rates of production and decay of these components. The dynamic models of biological networks typically consist of systems of nonlinear ordinary differential equations, permitting the modeler to apply the analytical techniques of nonlinear dynamics. These techniques have been developed considerably in recent decades, making the rate-equation approach a promising avenue for combining mathematical analysis and computational simulation.

While the resulting models are typically based on purely continuous dynamics, the dynamics of biological networks often involve switching between many qualitatively different modes of behavior. At the molecular level, for example, the fundamental process of inhibitor proteins turning off the transcription of genes by RNA polymerase reflects a switch between two continuous processes. An example of this is the classic genetic switch observed in the bacteriophage λ (e.g., see [17], [9], [18]), where two distinct behaviors, lysis and lysogeny, each with different mathematical models, are seen. Also, at the cellular level, the cell growth and division in a eukaryotic cell is usually described as a sequence of four processes, each being a continuous process that is triggered by a set of conditions or events (e.g., see [11], [15], [20]). At the inter-cellular level, cell differentiation can also be viewed as a switched system [7]. In addition to naturally occurring switches, switched dynamics can be the result of external intervention that attempts to re-engineer a given network by turning on or off, for example, certain pathways. In all of these examples, the overall behavior of the network is more appropriately viewed as

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a switched system, i.e., intervals of continuous dynamics interspersed by discrete transitions, and, therefore, a hybrid approach that combines elements of discrete and continuous dynamics is necessary, not only for the modeling, simulation and analysis (e.g., see [1]), but also for controlling and modifying the network behavior.

Hybrid system models are increasingly being used for modeling a diverse array of engineering systems, such as automotive and chemical process control systems. A hybrid system consists of a finite family of continuous dynamical subsystems (or modes), each of which is governed by a different set of differential equations, together with a set of discrete events (or logic-based switching rules) that orchestrate the transition between the constituent modes. Research on hybrid systems, both within control systems theory and computer science, has led to the development of systematic tools for the modeling (e.g., [21], [2]), simulation (e.g., [2]), optimization (e.g., [8]), stability analysis (e..g, [12], [16], [4]), and control (e.g., [3], [14], [5]) of several classes of hybrid systems. Given the similarity that many biological networks exhibit to switched systems encountered in engineering (e.g., involving feedback mechanisms and switching), it is instructive to investigate how all these tools can be applied to model, analyze and possibly modify the dynamics of biological networks.

Changes in network dynamics can result from alterations in local conditions (e.g., temperature, nutrient and energy source, light, cell density) and/or changes in the molecular environment of individual regulatory components (e.g., intra-cellular concentrations of transcription factors). Often, the network can be switched between different modes by changes in parameter values. These parameters typically include rate constants and total enzyme concentrations that are under genetic control. Changing the expression of certain genes will change the parameter values of the model and move the network across bifurcation boundaries into regions of qualitatively different behavior (e.g., transitions from limit cycles to single and multiple steady-states). Understanding and analyzing the nature of these qualitatively different modes of behavior typically involves bifurcation analysis which determines how the attractors of the vector field depend on parameter values, leading to a characterization of the regions in parameter space where the different behaviors are observed. The boundaries of these regions represent the bifurcation boundaries.

An important question, however, that is not addressed by bifurcation analysis is that of when, or where in the state space, is a transition from one mode to another feasible. For example, bifurcations can predict that a change in a certain parameter is required for the network to move from an oscillatory mode (stable limit cycle) to a multi-stable mode (multiple stable steady-states) but cannot tell us when, or which, of the new steady-states will be observed upon switching. This is an important consideration when one tries to manipulate the network behavior to achieve a certain desirable behavior or steady-state. To address this question, bifurcations must be complemented by a dynamical analysis of the transient behavior of the constituent modes of the overall network. Intuitively, one expects that the newly switched mode will exhibit the desired steady-state if, at the time of switching, the network state is in the vicinity of that steady-state. A precise concept from nonlinear dynamical systems theory that quantifies this closeness is that of the domain of attraction, which is the set of all points in the state space, starting from where the trajectories of the dynamical system converge to a given equilibrium state.

In this work, we present a methodology for the dynamic analysis and control of mode transitions in biological networks. The proposed approach is based on the notion of coupling the switching logic to the domains of attraction of the constituent modes introduced in [5]. To this end, we initially model the overall network as a switched nonlinear system that dwells in multiple modes, each governed by a set of continuous-time differential equations. The transition between the continuous modes are triggered by discrete events (changes in model parameters that correspond to alterations in physiological conditions). Then, following the characterization of the steady-state behavior of each mode, Lyapunov techniques are used to characterize the domains of attraction of the steady-states. Finally, by analyzing how the stability regions of the various modes overlap with one other, it is possible to determine when, and if, a given steady-state behavior, for a given mode transition, is feasible or not. The proposed approach is demonstrated using a model of a biological network that arises in the bacteriophage λ-switch system.

II. A Switched System Representation of Biological Networks

We consider biological networks modeled by systems of nonlinear ordinary differential equations of the general form:

$$\begin{aligned} \frac{dx(t)}{dt} &= f_{i(t)}(x(t), p_{i(t)}) \\ i(t) &\in \mathcal{I} = \{1, \cdots, N\} \end{aligned} \tag{1}$$

where $x = [x_1 \ x_2 \ \cdots \ x_n]^T \in \mathbb{R}^n$ is the vector of continuous state variables (e.g., concentrations of the various network components such as proteins, genes, metabolites, etc.), $f_i(\cdot)$ is a smooth nonlinear function, p_i is a vector of network parameters (e.g., kinetic constants, total enzyme concentrations) that are typically under genetic control, $i : [0, \infty) \to \mathcal{I}$ is the switching signal which is assumed to be a piecewise continuous (from the right) function of time, i.e., $i(t_k) = \lim_{t \to t_k^+} i(t)$ for all k, implying that only a finite number of switches occurs on any finite interval of time. N is the number of modes of the switched system, $i(t)$, which takes different values in the finite index set, $\mathcal{I}$, represents a discrete state that indexes the vector field $f(\cdot)$ which determines $\dot{x}$. For each value that i takes in $\mathcal{I}$, the temporal evolution of the continuous state is governed by a different

set of differential equations. The system of Eq.1 is therefore a switched (multi-modal) system that consists of a finite family of continuous nonlinear subsystems (modes) and a switching rule that orchestrates the transitions between them. In biological networks, mode transitions can be the result of a fundamental change in the vector field itself (e.g., different modes having different f_i's) or, more commonly, a change in network parameter values due to changes in levels of gene expression and enzyme activities (which can occur spontaneously or be induced externally).

The basic problem that we address in this work is that of determining when (or where in state-space) can a transition from one mode to another produce a certain desired behavior that exists in the target mode (e.g., a desired steady-state). From an analysis point of view, the answer to this question sheds light on why certain naturally-occurring mode transitions seem to always favor a certain steady-state behavior. From a control point of view, on the other hand, the answer provides insight into how and when the designer should enforce the transition in order to bring about a desired steady-state behavior. In the next section, we outline a methodology that addresses these questions.

III. Methodology for Analysis and Control of Mode Transitions

The methodology proposed here is based on the idea of designing the switching logic on the basis of the stability regions of the constituent modes, which was introduced in [5] in the context of constrained control of switched nonlinear systems. However, unlike the results in [5], where the presence of the stability regions was a consequence of the constraints imposed on the manipulated input of each mode, the stability regions considered here are directly linked to the intrinsic dynamic behavior of the constituent modes, which is dictated by the dependence of the attractors of the vector field on the network parameters. For example, the presence of multiple equilibrium points in a given mode gives rise to multiple stability regions, or domains of attraction, whose union covers the entire state space. Clearly, which equilibrium state is attained depends on which region contains the system state at the switching time. Below is the proposed methodology:

1) Identify the different modes of the network, where each mode is characterized either by a different set of differential equations or by the same set of equations but with different parameters.
2) Compute the steady-state(s) of each mode by solving, $0 = f_i(x_s, p_i)$, where x_s is an admissible steady-state solution. Depending on the values of p, each mode might possess a limit cycle, a single steady-state, or multiple steady-states.
3) Characterize the domain of attraction (stability region) of each steady-state in each mode. For a given steady-state, x_s, the domain of attraction, $\Omega(x_s)$, consists of the set of all states starting from where the system trajectories converge to that steady-state. Estimates of the domain of attraction can be obtained using Lyapunov techniques [13]. For example, consider the case of isolated equilibrium points and let V_i be a Lyapunov function candidate, i.e., $V_i(x_s) = 0$ and $V_i(x) > 0$ for all $x \neq x_s$. Consider also the set

$$\Pi(x_s) \quad := \quad \{x \in \mathbb{R}^n : \dot{V}_i(x) \; < \; 0\} \qquad (2)$$

Then the level set given by $\bar{\Omega}(x_s) = \{x \in \mathbb{R}^n : V_i(x) \leq c_i^{max}\}$, where $c_i^{max} > 0$ is the largest constant for which $\bar{\Omega}$ is fully contained in Π, provides an estimate of the domain of attraction of x_s. An advantage of using level-sets is that they provide a way of estimating the domain of attraction without the need to perform extensive simulations. For example, verifying whether a given point belongs to $\bar{\Omega}$ is a matter of simply checking an algebraic expression. This aspect is particularly useful when dealing with relatively high-order systems. Due to the possible conservatism of the resulting estimates, however, Lyapunov techniques are usually coupled with other methods (both computational and analytical) in order to obtain larger estimates (e.g., multiple Lyapunov functions; see Chapter 4 in [13] for further details on this issue).
4) Analyze how the stability regions of a given mode overlap with those of another mode. Suppose, for example, that the network is initialized within mode i and let T be the transition time from mode i to mode j. Also, let x_s be an admissible steady-state (among several others) of the j-th mode. Then, after switching, the x_s steady-state will be observed if and only if

$$x(T) \quad \in \quad \Omega_j(x_s) \qquad (3)$$

and no further switches take place. The switching rule of Eq.3 requires monitoring the temporal evolution of the state evolution in order to locate where the state is at the switching time, with respect to the stability regions of the mode to be activated.

In the next section, we demonstrate, through computer simulations, the application of this methodology to the analysis of mode transitions in the bacteriophage λ-switch system. We note here that the focus in the example is not on the modeling aspect, but rather on illustrating how the proposed analysis method can be applied given some available model of the network (which could come either from first-principles or from data). An application of the methodology to biological networks arising in eukaryotic cell cycle regulation can be found in the full version of this work in [6].

IV. Application to Mode Transitions in the Bacteriophage λ-Switch System

We consider an example of a biological switch observed in the bacteriophage λ. An excellent review and detailed description of the molecular regulatory mechanisms in the

bacteriophage λ-switch can be found in [17]. Bacteriophage λ is a virus capable of infecting *Escherichia coli* bacteria. The virus attaches its tail to the surface of host bacterium cell, drills a hole in the cell wall, and squirts its chromosome into the bacterium, leaving its coat behind. λ is an obligate parasite – it must inject its DNA into the bacterium to multiply. Upon infection, it can follow either one of two different pathways. First, the injected phage chromosome lysogenizes its host: all but one of the phage genes are turned off, and one phage chromosome, called prophage, becomes part of the host chromosome. As the lysogen (the bacterium bearing the prophage) grows and divides, the prophage is passively replicated and quiescently distributed to the progeny bacteria. Second, the phage chromosome enters the lytic mode: various sets of phage genes are turned on and off according to a precisely regulated program, the λ chromosome is extensively replicated, new head and tail proteins are synthesized, new phage particles are formed within bacterium, and some 45 minutes following the infection the bacterium lyses and releases about 100 progeny phage. Once the virus is in the lysogenic state, it can shift to the lysis state under certain conditions, e.g., if the bacterial culture is irradiated with ultraviolet (UV) light.

The molecular regulatory mechanism responsible for the lysogeny/lysis decision is known as the phage λ-switch. The switch to lytic growth is called induction. To understand how the switch works, we need to consider two regulatory genes (*cI* and *cro*) and the regulatory region called O_R (right operator). In a lysogen, *cI* is on and *cro* is off, and vice versa when lytic growth ensues. The operator comprises three binding sites (O_{R1}, O_{R2}, and O_{R3}) that overlap two opposing promoters. One of these, P_R, directs transcription of lytic genes and the other, P_{RM}, directs transcription of the *cI* gene.

In a lysogen, the λ repressor (the product of *cI* gene), at O_R, is bound at the two adjacent sites O_{R1} and O_{R2}. At these positions, it performs two functions: it represses rightward transcription from the promoter P_R, thereby turning off expression of *cro* and other lytic genes; simultaneously it activates transcription of its own gene from the promoter P_{RM}.

Upon induction, repressor vacates the operator and transcription from P_R commences spontaneously. The first newly made protein is *Cro*. This protein binds first to O_{R3}, apparently helping to abolish repressor synthesis. To illustrate the application of our methodology, we consider the following bacteriophage λ synthetic network model described in [9] (other more detailed models could also be used):

$$\begin{aligned} \frac{dx}{dt} &= \frac{m_x(1+x^2+\alpha\sigma_1 x^4)}{Q(x,y)} - \gamma_x x \\ \frac{dy}{dt} &= \frac{m_y\rho_y(1+y^2)}{Q(x,y)} - \gamma_y y \end{aligned} \tag{4}$$

where

$$\begin{aligned} Q(x,y) &= 1 + x^2 + \sigma_1 x^4 + \sigma_1\sigma_2 x^6 + y^2 + \beta_1\beta_3 y^6 \\ &+ (\beta_1+\beta_2)y^4 + \sigma_1\beta_4 x^4 y^2 + \beta_5 x^2 y^2 \end{aligned} \tag{5}$$

x and y represent dimensionless concentrations of the *CI* and *Cro* proteins, respectively; t represents dimensionless time; σ_1 and σ_2 are prefactors denoting the relative affinities for dimer binding to O_{R1} versus that of binding to O_{R2} and O_{R3}, respectively; $\alpha > 1$ represents degree to which transcription is enhanced by dimer occupation of O_{R2}; β_1–β_5 represent prefactors denoting binding strengths on reactions entailing the binding of *Cro* to different operator sites; the integers m_x and m_y represent the plasmid copy numbers for the two species; ρ_y represents a constant related to the scaling of y relative to x; γ_x and γ_y are directly proportional to the decay rates of *CI* and *Cro* proteins, respectively. The even polynomials in x occur due to dimerization and subsequent binding to the promoter region. The x^4 term represents the transcription when the two operator sites O_{R1} and O_{R2} are occupied (x^2x^2). The x^6 term represents the occupation of all three operator sites and arises in the denominator because dimer occupation of O_{R3} inhibits polymerase binding and shuts off transcription. The values of the model parameters in Eqs.4-5 are given by: $\rho_y = 62.92$, $\alpha = 11$, $m_x = 1$, $m_y = 1$, $\sigma_1 = 2$, $\sigma_2 = 0.08$, $\beta_1 = 0.08$, $\beta_2 = 0.08$, $\beta_3 = 0.08$, $\beta_4 = 1$, $\beta_5 = 1$. The steady-state values for different *CI* and *Cro* degradation rate are given in Table I.

TABLE I

STEADY-STATE VALUES (x_s,y_s) FOR THE LYSOGENIC, LYTIC, AND UNSTABLE STATES FOR DIFFERENT VALUES OF γ_x AND γ_y.

γ_x	γ_y	Lysogenic state	Lytic state	Unstable state
0.004	0.008	(32.39,0)	(0,16.22)	(2.79,15.27)
0.05	0.008	(13.71,0.01)	(0,16.22)	(4.89,6.38)
0.1	0.008	(10.75,0.03)	(0,16.22)	(5.37,4.10)
1	0.008	n/a	(0,16.22)	n/a
0.004	1	(32.39,0)	n/a	n/a

Bifurcation and phase-plane analysis of the above model show that, by changing the values of γ_x and γ_y, the system of Eq.4 can exhibit one of the following modes of behavior:

- A mode with a single globally asymptotically stable equilibrium point corresponding to the lysogenic steady-state (low γ_x and high γ_y).
- A mode with a single globally asymptotically stable equilibrium point corresponding to the lytic steady-state (high γ_x and low γ_y).
- A bi-stable mode where the stable lysogenic and lytic steady-states coexist together with a third unstable steady-state.

Note from Table I that for a fixed γ_y, as the degradation rate of protein *CI* is increased (larger γ_x value), the lysogenic steady-state keeps shifting to smaller concentrations until the system exhibits only the lytic steady-state (the

lysogenic steady-state vanishes). By contrast, for a fixed γ_x, when the degradation rate of protein *Cro* is increased (larger γ_y value), the lytic steady-state keeps shifting to smaller concentrations until the system exhibits only the lysogenic steady-state (the lytic steady-state vanishes).

TABLE II

LYAPUNOV FUNCTIONS USED IN ESTIMATING THE INVARIANT SET $\Omega_{lysogenic}$ FOR THE LYSOGENIC STATE.

γ_x	γ_y	Lysogenic state	c^{max}
0.004	0.008	$V=(x-x_s)^2+(y-y_s)^2$	800
0.1	0.008	$V=(x-x_s)^2+0.6(y-y_s)^4$	100

TABLE III

LYAPUNOV FUNCTIONS USED IN ESTIMATING THE INVARIANT SET Ω_{lytic} FOR THE LYTIC STATE.

γ_x	γ_y	Lytic state	c^{max}
0.004	0.008	$V=20(x-x_s)^2+(y-y_s)^2$	100
0.1	0.008	$V=0.5(x-x_s)^2+(y-y_s)^2$	150

Focusing on the bi-stable mode, we initially computed the domains of attraction of both steady-states for different values of the *CI* protein degradation rate. Due to the complex nonlinearity of the system, a combination of computational and Lyapunov-based techniques were employed. Estimates of the domains of attraction were obtained using the level sets of several Lyapunov functions (see Tables II-III). For each steady-state, we initially used the corresponding V to determine the region, Π, where $\dot{V}<0$ (see Eq.2) and then constructed an invariant set (a level set) within this region, $\Omega=\{x: V(x)\leq c_{max}\}$, where c_{max} is a positive constant for which $\bar{\Omega}$ is contained in Π. To get an idea of the possible conservatism of these estimates, we also used computer simulations to compute, for each steady-state, the entire domain of attraction (shaded regions) and verify that the corresponding level set is contained within it.

Figs.1, 2a-b show the domains of attraction for the lysogenic and lytic steady-states for: (1) a moderate *CI* degradation rate ($\gamma_x=0.05$, $\gamma_y=0.008$), (2) a relatively low *CI* degradation rate ($\gamma_x=0.004$, $\gamma_y=0.008$), and (3) a relatively high *CI* degradation rate ($\gamma_x=0.1$, $\gamma_y=0.008$), respectively. The shaded (grey) area is the domain of attraction for the lysogenic steady-state, while the unshaded (white) area is the domain of attraction for the lytic steady-state. Both steady-states are denoted by asterisks on each plot. The dotted curves in Figs.2a-b represent the boundaries of the level sets (for each level set, only the part that is contained within the given x-y range is shown). It is clear from the plots that an increase in the *CI* degradation rate results in a smaller domain of attraction for the lysogenic state (and a larger one for the lytic state) and vice versa. In the limiting case of very high degradation rates, the lysogenic state vanishes and the domain of attraction of the lytic state occupies the entire state space (single globally asymptotically stable equilibrium point). The opposite trend is observed when the *Cro* protein degradation rate is increased (results are not shown due to space limitations). In particular, increasing γ_y leads to a smaller domain of attraction for the lytic state and a larger one for the lysogenic state. For very high *Cro* degradation rates, the lytic steady-state vanishes and the domain of attraction for the lysogenic state turns into the entire state-space.

Therefore, in the bistable mode, the initial condition plays a critical role in deciding which steady-state the bacteriophage λ will attain. Also, the size of the domain of attraction for each state helps explain why the lysogenic state is more likely to be observed under a given set of conditions (e.g., [18]), while the lytic state is more likely to be seen under a different set of conditions. Fig.1 shows that starting from an initial condition of high *CI* and *Cro* concentrations, the phage ends up in the lytic state since the initial condition is within its domain of attraction (solid trajectory). Initializing the system, however, at high *CI* but low *Cro* concentrations drives the phage to the lysogenic state (dashed trajectory).

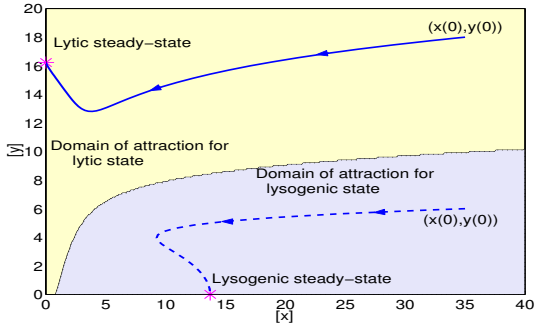

Fig. 1. A phase plot for the moderate *CI* degradation mode showing that starting within the lysogenic domain of attraction the phage converges to the lysogenic steady-state (dashed trajectory) and that starting within the lytic domain of attraction, it converges to the lytic steady-state (solid trajectory).

We now demonstrate the effect of switching in the *CI* protein degradation rate on whether the bacteriophage will exhibit the lytic or lysogenic steady-state. To this end, we initialize the system within the moderate *CI* degradation mode ($\gamma_x=0.05$, $\gamma_y=0.008$) at the initial condition $(x(0),y(0))=(35,18)$ and allow it to evolve in this mode until, at $t=20$, a mode transition is enforced (see dashed trajectories in Figs.2a-b). The results show that, for a fixed transition time, depending on which mode is being switched in, the phage takes a different path. For example, Fig.2a shows that when the system switches to the relatively low *CI* degradation mode ($\gamma_x=0.004$, $\gamma_y=0.008$) at $t=20$, the system state is within the domain of attraction of the lysogenic steady-state and, therefore, the phage ends up with lysogeny. Fig.2b, on the other hand, shows that when the relatively high *CI* degradation mode ($\gamma_x=0.1$, $\gamma_y=0.008$) is switched in at $t=20$, the system state is within the domain of attraction of the lytic steady-state and, therefore, the phage ends up with lysis.

So far in our analysis, we have fixed the transition time and showed that which mode is activated at that time

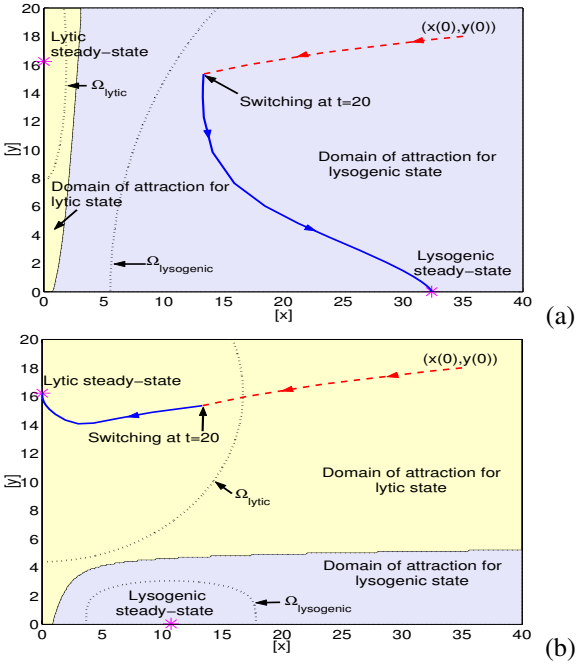

Fig. 2. A phase plot showing the system of Eq.4 being initialized using $\gamma_x = 0.05$ (dashed trajectory) and undergoing: (a) a decrease in the degradation rate of *CI* protein (to $\gamma_x = 0.004$) at $t = 20$, and (b) an increase in the degradation rate of *CI* protein (to $\gamma_x = 0.1$) at $t = 20$. In both cases, the *Cro* degradation rate is fixed at $\gamma_y = 0.008$.

determines the final state of the phage. In our last simulation run, we demonstrate the effect of varying the transition time, for a given mode transition, on the steady-state behavior of the phage. To this end, we reconsider the switching scenario presented in Fig.2a, where the system switches from the moderate ($\gamma_x = 0.05$) to the relatively low *CI* degradation mode ($\gamma_x = 0.004$). However, instead of carrying out the transition at $t = 20$ as in Fig.2a, the switch is delayed until $t = 70$. The result is depicted in Fig.3 which shows that at $t = 70$, the system state is within the domain of attraction of the lytic steady-state and, therefore, the phage ends up with lysis. By comparing Fig.2a with Fig.3, we conclude that an early transition from moderate to relatively low *CI* degradation rate favors lysogeny, while a late transition favors lysis.

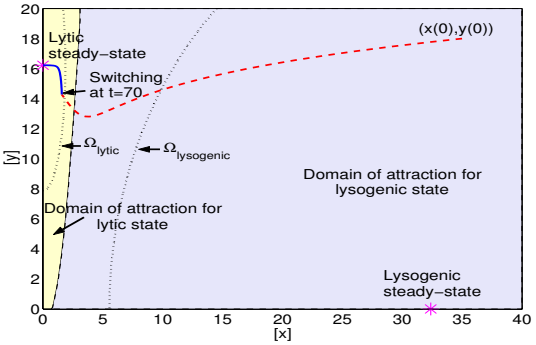

Fig. 3. A phase plot showing the system undergoing a transition from the $\gamma_x = 0.05$ mode (dashed trajectory) to the $\gamma_x = 0.004$ at $t = 70$ and converging (solid trajectory) to the lytic steady-state. The *Cro* degradation rate is fixed at $\gamma_y = 0.008$.

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