The Transcritical Bifurcation in Absolutely Stable Feedback Systems

Matthias A. Müller, Steffen Waldherr* and Frank Allgöwer

***Abstract*— The paper gives new conditions for the occurrence of a transcritical bifurcation in a non-negative passive system under non-linear static feedback. In biological systems, this provides a mechanism for defining activation thresholds in positive feedback systems. We apply the results to a simple gene regulation system to compute an activation threshold in the feedback regulation strength.**

I. INTRODUCTION

Passive systems subject to a static non-linear feedback connection appear in several physical applications and have therefore been studied extensively in systems theory. Recently, passivity based approaches have also been applied to the stability and bifurcation analysis of biochemical reaction networks [1]. In particular, it is well known that if the feedback non-linearity satisfies a sector condition, the closed loop system is globally stable irrespective of the specific form of the feedback function. This property is referred to as absolute stability in the literature [2].

If the sector condition is violated, the closed loop system may become unstable. An interesting special case occurs if the static non-linearity is of the form

$$\Phi_k(y) = -ky + \Phi(y)$$

where k is an adjustable parameter, and Φ satisfies a sector condition. This setup was shown to give rise to the Hopf or the pitchfork bifurcation in the closed loop system under some additional assumptions [3].

In this paper, we consider specifically systems with non-negative state variables and non-negative outputs. Then, $\Phi(y)$ may satisfy a sector condition even if its second-order terms do not vanish. A block-diagram for the considered setup is shown in Figure 1. It will turn out that this may give rise to a transcritical bifurcation in the closed loop system. In this bifurcation, the equilibrium branch at the origin looses global stability at a critical value k^*, and a second equilibrium branch emerges that is almost globally stable for values of k slightly larger than k^*. This case is of particular interest in biological applications, which typically contain non-negative state variables, and where symmetries that would provide for a vanishing second order term in $\Phi(y)$ are often not present. In these applications, the transcritical bifurcation may correspond to some threshold value in the feedback strength k. Crossing this threshold would correspond to activation of a particular gene regulation system or biochemical signalling pathway.

The authors are with the Institute of Systems Theory and Automatic Control, Universität Stuttgart, Stuttgart, Germany.

* Corresponding author, waldherr@ist.uni-stuttgart.de

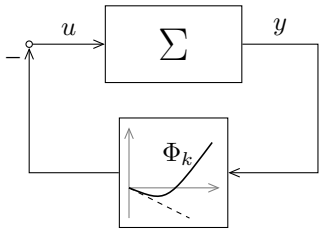

Fig. 1. Passive system Σ under static non-linear feedback Φ_k

The paper is structured as follows. In Section II, first the notation and preliminary results that we need are introduced. Second, we provide a theorem stating conditions for occurrence of a transcritical bifurcation in the prescribed class of systems. In Section III, we apply our results to a simple gene regulation system with positive feedback regulation, where we can thus conclude to a transcritical bifurcation corresponding to some activation threshold value in the regulation strength.

A. Notation

We denote by $\mathbb{R}_{0+}$ the non-negative real numbers. The relation $k \gtrsim k^*$ is used to denote a value of k near the value k^*, i.e. $k \in (k^*, \overline{k}]$ for some $\overline{k} > k^*$.

II. CONDITIONS FOR THE TRANSCRITICAL BIFURCATION

A. Preliminaries

Consider the negative feedback interconnection of a non-linear, input affine SISO system Σ and a static non-linearity Φ_k, as shown in Figure 1. The system Σ has the following state space description:

$$\Sigma : \begin{aligned} \dot{x} &= f(x) + g(x)u \\ y &= h(x), \end{aligned} \tag{1}$$

where $x \in \mathbb{R}^n_{0+}$, $u \in \mathbb{R}$ and $y \in \mathbb{R}_{0+}$. Assume that $f(0) = 0$, $h(0) = 0$, $h(x) = \mathcal{O}(x)$ for $x \to 0$ and $g(0) \neq 0$. In the following, we denote by $G(s)$ the transfer function of the linearization of Σ at the origin.

The static nonlinearity in the feedback path is given by

$$\Phi_k(y) = -ky + \Phi(y) \tag{2}$$

where $\Phi : \mathbb{R}_{0+} \to \mathbb{R}_{0+}$ is a smooth function satisfying

$$\begin{aligned} \Phi(0) = 0 \quad \Phi''(0) = \eta > 0 \\ \Phi'(0) = 0 \quad \Phi(y) > 0,\ y > 0. \end{aligned} \tag{3}$$

Since Φ is positive and takes only non-negative arguments, it can be seen as a sector non-linearity in the sector $(0, \infty)$.

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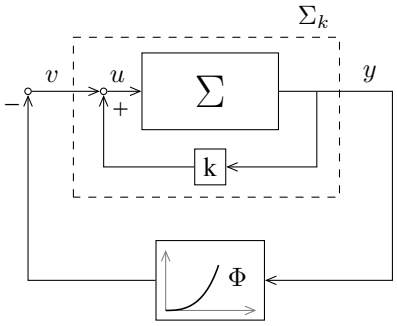

Fig. 2. Feedback interconnection of Σ_k and Φ

The negative feedback interconnection of Σ and Φ_k is equivalent to the negative feedback interconnection of Σ_k and the nonlinearity Φ (Figure 2), where Σ_k is given by

$$\Sigma_k : \begin{aligned} \dot{x} &= f(x) + kg(x)h(x) + g(x)v \\ y &= h(x). \end{aligned} \tag{4}$$

The transfer function of the linearization of Σ_k at the origin is denoted by $G_k(s)$. The closed loop system is described by the state space equation

$$\dot{x} = f(x) + kg(x)h(x) - g(x)\Phi(h(x)). \tag{5}$$

We assume that $\mathbb{R}^n_{0+}$ is positively invariant under (5), i.e. $x(t_0) \in \mathbb{R}^n_{0+}$ implies that $x(t) \in \mathbb{R}^n_{0+}$ for all $t \geq t_0$. Note that for the described setup, there is always an equilibrium point at the origin.

We use the following definition for strong passivity [3], which is slightly stronger than what is usually used in the literature.

Definition 1: The system Σ (1) is said to be *strongly passive* if there exists a continuously differentiable positive semidefinite storage function $V(x)$ such that

$$\forall x \in \mathbb{R}^n_{0+}, u \in \mathbb{R}: \quad uy \geq \frac{\partial V}{\partial x}(f(x) + g(x)u) \tag{6}$$

and the storage function $V(x)$ satisfies

1) $V(x)$ is positive definite and radially unbounded, i.e. $V(x) \to \infty$ as $\|x\| \to \infty$.
2) $V(x)$ is twice continuously differentiable in a neighbourhood of the origin and the Hessian evaluated at zero, $\frac{\partial^2 V}{\partial x^2}(0)$, is a positive definite matrix.

Before coming to the main result, we provide a Lemma which will be useful in showing that the second equilibrium point emerging from the transcritical bifurcation is actually non-negative. Consider the system

$$\dot{x} = F(x), \tag{7}$$

where $x \in \mathbb{R}^n$ and $F(0) = 0$. Assume that the Jacobian $\frac{\partial F}{\partial x}$ has a single eigenvalue at the origin and all other eigenvalues have negative real parts. The center manifold theorem [4] asserts that the system possesses a one-dimensional center manifold locally at the origin. Assume furthermore that there is a neighbourhood $\mathcal{U}$ of the origin such that $x(0) \in \mathbb{R}^n_{0+} \cap \mathcal{U}$ implies that $x(t) \to 0$ as $t \to \infty$.

Lemma 1: If $\mathbb{R}^n_{0+}$ is positively invariant for the flow of (7), then the center manifold admits a parametrisation $\mathcal{M}_c = \{x_c \in \mathbb{R}^n \mid x_c = m_c(\xi),\ \xi \in \mathbb{R}\}$ such that $\xi \gtrsim 0$ corresponds to $x_c \in \mathbb{R}^n_{0+}$.

Equivalently, we can say that the center manifold has a branch that extends into the non-negative orthant from the origin.

Proof: The proof is by contradiction and is based on the idea that trajectories of the system with initial condition not on the stable manifold first converge to the center manifold before converging to the origin.

By the reduction principle, system (7) is locally topologically equivalent to the system

$$\begin{aligned} \dot{\xi} &= \alpha(\xi) \\ \dot{\zeta} &= -\zeta, \end{aligned} \tag{8}$$

where $\xi \in \mathbb{R}$, $\zeta \in \mathbb{R}^{n-1}$ and $\alpha(\xi) = \mathcal{O}(\xi^2)$ [4]. Denote the corresponding coordinate transformation by $x = \Psi(\xi, \zeta)$.

Now assume that the center manifold does not admit a parametrisation as suggested, i.e. it does not have a branch that extends into the non-negative orthant. Let $\mathcal{U}$ be a suitable open neighbourhood of the origin. Then define a set

$$\mathcal{C} = \Psi(\{(\xi, \zeta) \mid \xi \neq 0,\ \frac{\|\zeta\|}{|\xi|^k} < \varepsilon\}) \cap \mathcal{U}$$

with $k \geq 1$ and $\varepsilon > 0$ such that $\mathcal{C} \cap \mathbb{R}^n_{0+} = \emptyset$. Consider a trajectory of the system with initial condition (ξ_0, ζ_0) with $\xi_0 \neq 0$ such that $x_0 = \Psi(\xi_0, \zeta_0) \in \mathbb{R}^n_{0+} \cap \mathcal{U}$. By assumption, $\lim_{t\to\infty} \xi(t) = 0$ and $\lim_{t\to\infty} \zeta(t) = 0$. We also have $\xi(t) \neq 0$ for all $t > 0$. Since $\zeta(t)$ converges exponentially and $\xi(t)$ only algebraically, $\lim_{t\to\infty} \frac{\zeta(t)}{\xi(t)^k} = 0$ for any $k \geq 1$, which can also be established by using L'Hôpital's rule. Thus for any $\varepsilon > 0$ and $k \geq 1$ there exists $T > 0$ such that $\frac{\|\zeta(T)\|}{|\xi(T)|^k} < \varepsilon$, i.e. $x(T) \in \mathcal{C}$. This contradicts the assumption that $\mathbb{R}^n_{0+}$ is positively invariant. ■

B. Main result

We are now in a position to state the main result of the paper. Consider the negative feedback interconnection of the system Σ (1) and the static nonlinearity Φ_k (2), where Φ_k satisfies the additional properties (3). We make the following assumptions.

- (A1) The system Σ is strongly passive.
- (A2) Both Σ and its linearization are detectable.
- (A3) The closed loop system (5) is ultimately bounded, i.e. there exists a compact set Ω and $T > 0$ such that $x(t) \in \Omega$ for all $t > T$.

Note that Σ being passive implies that it has relative degree 1, and a root locus consideration of Σ_k shows that the origin becomes unstable for increasing k. Thus there is a critical value of k for which we have a pole on the imaginary axis.

Theorem 1: Assume (A1-3) hold. Let $k^* \geq 0$ be the minimum value for which the transfer function $G_k(s)$ has a pole on the imaginary axis, and assume that this pole is unique.

If Σ_{k^*} is strongly passive, the closed loop system (5) undergoes a transcritial bifurcation at the origin: for $k \gtrsim k^*$,

the origin is unstable and there is a second, almost globally asymptotically stable equilibrium x_{02} which is non-negative and different from 0.

Proof: In [3], a passivity approach for Hopf and pitchfork bifurcations is stated. Thus the proof of Theorem 1 is similar to a proof which can be found in [3, pp.813-814] and it consists of a local and a global argument. The local argument will show the existence of a transcritical bifurcation at $\beta = k - k^* = 0$. This implies that there exists a constant $\beta_1 > 0$ and a neighbourhood U of the origin $x = 0$, such that for each $\beta \in (0, \beta_1]$, all solutions x with initial condition in U either converge to the origin or to the second stable equilibrium point x_{02}. The global argument will show that eventually we can apply the local argument to each solution, i.e. there exists a constant $\beta_2 \leq \beta_1$ such that for each $\beta \in (0, \beta_2]$, all solutions enter the set U in finite time.

We start proving the global argument. As the feedback system is ultimately bounded, we know that for each $\beta \in (0, \beta_3]$, all solutions enter an invariant compact set $\Omega = \Omega(\beta)$. As Σ_{k^*} is strongly passive and (zero-state) detectable the origin is globally asymptotically stable for $\beta = 0$. The robustness of global asymptotic stability at $\beta = 0$ implies semi-global practical asymptotic stability of the solution $x = 0$ [5, Theorem 2.25, p.28], which means that we can find a constant $\beta_2 \leq \beta_3$ such that for each $\beta \in (0, \beta_2]$, all solutions with initial condition in Ω enter the set U in finite time.

Let us now consider the local argument. At $\beta = 0$, i.e. $k = k^*$, the system possesses a center manifold which is one-dimensional as $G_{k^*}(s)$ has a unique pole on the imaginary axis. If $x(t_0)$ is sufficiently small then the solution $x(t)$ of (1) converges to the center manifold exponentially fast [4]. In normal form coordinates, the center manifold dynamics write [6]:

$$\dot{\xi} = a_2\xi^2 + \mathcal{O}(\xi^3), \qquad \xi \in \mathbb{R} \tag{9}$$

As Σ_{k^*} is strongly passive, inequality (6) is satisfied with a locally quadratic storage function $V(x)$. Thus the restriction of V to the center manifold is (up to a positive scaling factor) $V = \frac{1}{2}\xi^2 + \mathcal{O}(\xi^3)$ and the following inequality is satisfied:

$$\begin{aligned} \dot{V} &= a_2\xi^3 + \mathcal{O}(\xi^4) \\ &\leq -y\Phi(y) = -\eta y^3 + \mathcal{O}(y^4) = -\eta y^3 + \mathcal{O}(\xi^4) \end{aligned} \tag{10}$$

Detectability of the linearized system implies observability of the linearized center manifold dynamics, i.e. $\dot{V} = 0$ implies $\xi = 0$.

Let the center manifold coordinate ξ be chosen such that $\xi \gtrsim 0$ corresponds to $x \in \mathbb{R}^n_{0+} \setminus \{0\}$. By Lemma 1, this is possible, because we assume $\mathbb{R}^n_{0+}$ to be positively invariant, and strong passivity of Σ_{k^*} guarantees convergence of trajectories to the origin. Thus from the above inequality $\dot{V} = a_2\xi^3 + \mathcal{O}(\xi^4) \leq -\eta y^3 + \mathcal{O}(\xi^4)$ for $\xi > 0$ we conclude that $a_2 < 0$.

We therefore obtain a transcritical bifurcation at the origin for $\beta = 0$, where for $\beta > 0$ the origin becomes unstable and a second equilibrium emerges that is non-negative, different from 0 and asymptotically stable. This can be seen if we consider an extended system where β is an additional state variable with $\dot{\beta} = 0$. The dynamics on the center manifold then write

$$\dot{\xi} = a_1\beta\xi + a_2\xi^2 + \xi\mathcal{O}(\|(\xi, \beta)\|^2) =: l(\xi, \beta) \tag{11}$$

With $\beta = 0$ we get equation (9). As the origin is globally asymptotically stable for $\beta \leq 0$, we have $a_1 > 0$. Thus for $k \gtrsim k^*$, i.e. $\beta \gtrsim 0$, the second equilibrium point is $\xi_{02}(\beta) = -\frac{a_1\beta}{a_2} + \mathcal{O}(\beta^2) > 0$, which can be calculated out of (11) by using the implicit function theorem and solving the equation

$$0 = a_1\beta + a_2\xi + \mathcal{O}(\|(\xi, \beta)\|^2)$$

for $\xi = \xi(\beta)$. Asymptotic stability of the equilibrium point $\xi_{02}(\beta)$ follows from the fact that for $\beta \gtrsim 0$, the first order term of the center manifold dynamics at ξ_{02} is negative:

$$\frac{\partial}{\partial\xi} l(\xi_{02}, \beta) = -a_1\beta + \mathcal{O}(\beta^2) < 0$$

Finally, $\xi_{02}(\beta) > 0$ implies that $x_{02}(\beta)$ is non-negative and different from zero for $\beta \gtrsim 0$. ■

III. APPLICATION TO A BIOLOGICAL POSITIVE FEEDBACK SYSTEM

In this section, we consider a gene regulation system, where the protein acts as a positive regulator for its own synthesis. It will turn out that the results obtained in the previous section allow to characterise a transcritical bifurcation in the system. In this way, we obtain a threshold that the regulation strength needs to pass in order for the protein to be present in the system at all.

A. Dynamical model of a gene regulatory feedback loop

We study a simple dynamical model of gene regulation, where a protein *P* is produced by action of the mRNA polymerase *MP*. The model includes a positive feedback, because the protein acts as a transcription factor for its own expression, i.e. the mRNA polymerase needs to bind the protein to form the complex *P-MP* in order to induce gene expression.

The setup that we study here appears quite frequently in gene regulation systems over a wide variety of biological systems. An example is the regulation of stress response in bacteria [7]. Also mammalian cells make extensive use of positive feedback loops in gene regulation, although those tend to act via more intermediate steps than we have assumed here [8]. The same setup has also been used in the construction of synthetic gene regulation systems [9].

The model is constructed as a biochemical reaction network. It includes the basic processes of transcription, i.e. the production of an mRNA molecule according to a specific sequence in the cell's DNA, and of translation, i.e. the production of a specific protein according to the mRNA sequence [10]. Also degradation of both the mRNA molecule and the protein are included in the model. Transcription of

1)	*P-MP* $\rightarrow$ *P-MP* + *mRNA*	$v_1 = b$[*P-MP*]
2)	*mRNA* $\rightarrow \emptyset$	$v_2 = a$[*mRNA*]
3)	*mRNA* $\rightarrow$ *mRNA* + *P*	$v_3 = d$[*mRNA*]
4)	*P* $\rightarrow \emptyset$	$v_4 = c[P]$
5)	*MP* + *P* $\leftrightarrow$ *P-MP*	$v_5 = \frac{k_1}{\varepsilon}[P][MP] - \frac{k_2}{\varepsilon}$[*P-MP*]

TABLE I

BIOCHEMICAL REACTION NETWORK OF AUTOREGULATORY GENE EXPRESSION WITH POSITIVE FEEDBACK

the mRNA molecule is catalyzed by the complex formed of protein (acting as transcription factor) and the mRNA polymerase. The formation of this complex is accounted for by an additional reaction in the model. We make the reasonable assumption that the formation of this complex is fast compared to transcription and translation. The reactions in the model and the corresponding reaction rates are given in Table I, where a, b, c, d, k_1, k_2 and ε are positive parameters. ε is small and is used to describe the time scale differences between the formation of the protein/mRNA polymerase complex and the other processes.

Introducing the state variables $x_1 = [mRNA]$, $\overline{x}_2 = [P]$ and $z = [P\text{-}MP]$ and considering the conservation relation $[MP]+[P\text{-}MP] = m$ yields the following differential equation model for the considered biochemical reaction network:

$$\begin{aligned} \dot{x}_1 &= -ax_1 + bz \\ \dot{\overline{x}}_2 &= dx_1 - c\overline{x}_2 - \frac{k_1}{\varepsilon}\overline{x}_2(m-z) + \frac{k_2}{\varepsilon}z \\ \dot{z} &= \frac{k_1}{\varepsilon}\overline{x}_2(m-z) - \frac{k_2}{\varepsilon}z \end{aligned}$$

with $x_1, \overline{x}_2, z \geq 0$.

In the following, we want to simplify this differential equation model by using singular perturbation [2]. Therefore, in order to get a right hand side of the differential equation for x_2 which is continuously differentiable in ε, we transform the state variables by setting $x_2 = \overline{x}_2 + z = [P] + [P\text{-}MP]$. Biochemically, this represents the total amount of protein *P* in the system, both free protein and protein bound to the mRNA polymerase. The transformed model writes

$$\dot{x}_1 = -ax_1 + bz \quad (12)$$

$$\dot{x}_2 = dx_1 - cx_2 + cz \quad (13)$$

$$\varepsilon\dot{z} = k_1(x_2 - z)(m - z) - k_2 z \quad (14)$$

with $x_1, x_2, z \geq 0$.

The singular perturbation corresponds to letting ε tend to zero. From (14), we get the equation

$$k_1(x_2 - z)(m - z) - k_2 z = 0, \quad (15)$$

which we solve for x_2 to obtain

$$\begin{aligned} z = h(x_2) = \frac{1}{2}(x_2 + m + \frac{k_2}{k_1}) \\ - \sqrt{\frac{1}{4}(x_2 + m + \frac{k_2}{k_1})^2 - mx_2}. \end{aligned} \quad (16)$$

Note that $h(x_2)$ is real for all $x_2 \geq 0$.

Substituting (16) into the slow subsystem, i.e. the first two equations of the original model, we obtain

$$\dot{x}_1 = -ax_1 + bh(x_2) \quad (17)$$

$$\dot{x}_2 = dx_1 - cx_2 + ch(x_2). \quad (18)$$

B. The transcritical bifurcation in the gene regulatory feedback loop

In this section, we apply the theory developed in Section II to the gene regulatory feedback loop modelled by (17) - (18). It will turn out that the linear feedback gain as described by the parameter k in the theoretical setup is a function of the parameters m, k_1 and k_2 in the model. These parameters represent the amount of mRNA polymerase and its interactions with the protein, respectively, and as such the feedback gain can also be interpreted as regulation strength from a biochemical perspective. Moreover, we will show that the gene expression process as modelled by reactions 1–4 in Table I is passive, if a certain condition on the parameters a, b, c and d is satisfied. Thus the theory developed in Section II allows us to characterise a transcritical bifurcation in the autoregulatory feedback loop.

In a first step, we rewrite the reduced model (17) - (18) into

$$\begin{aligned} \Sigma: \quad \dot{x} &= \begin{bmatrix} -a & 0 \\ d & -c \end{bmatrix} x + \begin{bmatrix} b \\ c \end{bmatrix} u \\ y &= x_2 \\ u &= h(y) \end{aligned} \quad (19)$$

where $x_1, x_2, y \geq 0$. In the perturbed system, $h(x_2)$ represents the non-linearity in the feedback path as introduced in Section II by the relation

$$h(y) = -\Phi_k(y). \quad (20)$$

Clearly, $h(0) = 0$, as required by (3). Next, we compute the parameter k for the linear part and check that the second derivative is positive. Indeed, we get

$$\begin{aligned} k &= \frac{\partial h}{\partial x_2}(0) = \frac{m}{m + \frac{k_2}{k_1}} > 0 \\ \eta &= -\frac{\partial^2 h(0)}{\partial x_2^2} = 2m\frac{k_2}{k_1}\frac{1}{(m + \frac{k_2}{k_1})^3} > 0. \end{aligned}$$

Thus we have $\Phi(y) = \eta y^2 + \mathcal{O}(y^3)$. In order to satisfy the properties (3), it remains to show that $\Phi(y) > 0$ for all $y > 0$. This can be done by noting that $\frac{\partial^2 h(y)}{\partial y^2} < 0$ for all $y \geq 0$, and thus we have

$$-\Phi_k(y) = ky - \Phi(y) = h(y) < \frac{\partial h}{\partial y}(0)y = ky$$

which implies that $\Phi(y) > 0$ for all $y > 0$.

The transfer function of Σ is given by

$$G(s) = \frac{cs + ac + bd}{(s + a)(s + c)}.$$

The system Σ_k is then given by

$$\Sigma_k : \begin{array}{l} \dot{x} = \begin{bmatrix} -a & bk \\ d & -c(1-k) \end{bmatrix} x + \begin{bmatrix} b \\ c \end{bmatrix} v \\ y = x_2 \end{array} \quad (21)$$

and the non-linear feedback by

$$v = h(y) = -\Phi(y). \quad (22)$$

For the transfer function of Σ_k we obtain

$$\begin{aligned} G_k(s) &= \frac{G(s)}{1 - kG(s)} \\ &= \frac{cs + ac + bd}{s^2 + (a + c - kc)s + (1-k)ac - kbd}. \end{aligned}$$

The critical value k^* at which $G_k(s)$ has a pole at the origin is computed by solving $1 - kG(0) = 0$. We obtain the critical value

$$k^* = \frac{ac}{ac + bd}. \quad (23)$$

In order to show that $\mathbb{R}^2_{0+}$ is positively invariant under (17) - (18) it is sufficient to show that $x_1 = 0 \Rightarrow \dot{x}_1 \geq 0$ and $x_2 = 0 \Rightarrow \dot{x}_2 \geq 0$, i.e. that on the boundaries of $\mathbb{R}^2_{0+}$, the vectorfield of the system (17) - (18) doesn't point away from $\mathbb{R}^2_{0+}$ [11]. Out of (17) we obtain that $x_1 = 0 \Rightarrow \dot{x}_1 = bh(x_2) \geq 0$ as $h(x_2) \geq 0$ for all $x_2 \geq 0$. Similarly, (18) yields $x_2 = 0 \Rightarrow \dot{x}_2 = dx_1 \geq 0$ for all $x_1 \geq 0$. Thus $\mathbb{R}^2_{0+}$ is positively invariant under (17) - (18).

In the following, we will verify that the conditions of Theorem 1 are satisfied. It can be easily checked, that the (linear) system Σ is observable. Thus (A2) is satisfied.

As described in [2], for passivity of linear systems it is sufficient to examine whether their transfer functions are positive real. It turns out that both $G(s)$ as well as $G_k(s)$ are positive real if

$$c^2 \geq ac + bd$$

and thus both Σ and Σ_k are strongly passive if this condition on the parameters is satisfied.

Last, we have to show that condition (A3) is satisfied, i.e. that the closed loop system (5) is ultimately bounded. This can be done by taking the radially unbounded Lyapunov function $W(x) = \frac{1}{2}(x_1^2 + x_2^2)$ and observing that the derivative of W along the trajectories of the closed loop system (5) is negative for $\|x\|$ large enough.

As all the conditions of Theorem 1 are satisfied, we conclude that a transcritical bifurcation occurs at $k = k^* = \frac{ac}{ac+bd}$. For $k \gtrsim k^*$, the origin becomes unstable and a second equilibrium emerges that is non-negative, different from 0 and almost globally asymptotically stable. The resulting stationary protein amounts for different binding affinities $\frac{k_1}{k_2}$ are shown in the bifurcation diagram in Figure 3.

The obtained result can be biologically interpreted in the following way: The feedback gain k is interpreted as the regulation strength of the autoregulatory loop, and it depends on the amount of mRNA polymerase m in the cell and on the binding kinetics k_1 and k_2 of the protein and the mRNA polymerase. Below a certain threshold k^*, which depends on the production and degradation rates c and d of the protein P, and a and b of the mRNA, the protein P is not present in the system at all, as the only equilibrium point is the origin. In order to express the protein, the regulation strength has to exceed this threshold value, which can be achieved by either increasing the amount of mRNA polymerase or by increasing the affinity of mRNA polymerase and the protein. In fact, transcription usually involves several factors which in a system as studied here may be used to alter this affinity [10].

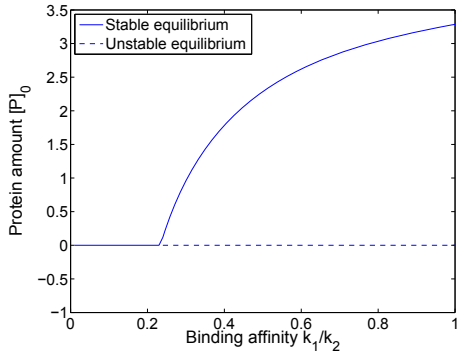

Fig. 3. Bifurcation diagram of the autoregulatory gene expression system. Parameter values where chosen as $a = 0.7$, $b = 0.1$, $c = 1$, $d = 0.3$, $m = 100$, $k_2 = 1$ and $k_1 \in [0, 1]$.

C. Remarks on passivity of gene expression systems

The example studied in the previous section uses a very simplistic model of cellular gene expression. It is clearly of interest, though beyond the scope of this paper, to check whether the results also apply to more complex models of gene expression. Because the feedback non-linearity we consider here is quite general, the main question will be whether the open loop system is passive.

In particular, passivity requires the open loop system to have a relative degree of one. On first sight, this might seem quite restrictive for gene expression systems, which usually involve many intermediate steps from transcription factor activity to the final protein output. However, if one models the actual mechanism of the regulation carefully, as we did in the example model via singular perturbation, one can in fact expect to obtain a relative degree one system. This can be understood by considering the typical molecular mechanism by which feedback is implemented. In order to act on the molecule that constitutes the input, the "output molecule" has to bind to the "input molecule". Since this binding obviously affects the output directly, and its rate depends on the input, we see that such a system will typically be of relative degree one, no matter how many steps might lay in between.

IV. SUMMARY

The paper proves a new result on occurrence of the transcritical bifurcation in a feedback interconnection of a passive system with a static non-linearity. The results are particularly suited for biochemical systems, which are typically non-negative and where symmetries that would favor a pitchfork

bifurcation are not present. The analysis is based on an input–output consideration in the form of passivity conditions, and thus does in general not require a detailed state-space model of the forward path, if passivity can be established by other means.

The biological interpretation of the proposed mechanism is that of an activation threshold in the feedback characteristics, which has to be crossed in order for the system to become activated in a biological sense.

To make this interpretation clear, we have worked out an example where the theoretical result is applied to a simple model of a gene expression system with positive autoregulation. It was shown that under certain conditions on the properties of the system, our theorem can be used to show existence of a threshold value in the regulation strength which has to be exceeded in order to express the considered protein. The regulation strength is characterised from a systems-theoretic perspective as the slope of the feedback non-linearity, and from a biochemical perspective as a function of the mRNA polymerase concentration and the affinity of binding to the protein.

REFERENCES

[1] M. Arcak and E. D. Sontag, "A passivity-based stability criterion for a class of interconnected systems and applications to biochemical reaction networks," in *Proc. of the 46th IEEE Conf. on Dec. and Control, New Orleans, USA*, 2007, pp. 4477–4482, arXiv:0705.3188v1 [q-bio.QM].

[2] H. K. Khalil, *Nonlinear Systems*. Prentice Hall, 2002.

[3] R. Sepulchre and G.-B. Stan, "Feedback mechanisms for global oscillations in Lure systems," *Syst. Contr. Lett.*, vol. 54, pp. 809–818, Aug. 2005.

[4] Y. A. Kuznetsov, *Elements of Applied Bifurcation Theory*. Springer-Verlag New York, 1995.

[5] G.-B. Stan, "Global analysis and synthesis of oscillations: a dissipativity approach," Ph.D. dissertation, University of Liège, 2005.

[6] S. Wiggins, *Introduction to Applied Nonlinear Dynamical Systems and Chaos*. Springer-Verlag Berlin, 1990.

[7] G. M. Sel, J. Garcia-Ojalvo, L. M. Liberman, and M. B. Elowitz, "An excitable gene regulatory circuit induces transient cellular differentiation." *Nature*, vol. 440, pp. 545–550, Mar 2006.

[8] S. L. Harris and A. J. Levine, "The p53 pathway: positive and negative feedback loops." *Oncogene*, vol. 24, pp. 2899–2908, Apr 2005.

[9] N. J. Guido, X. Wang, D. Adalsteinsson, *et al.*, "A bottom-up approach to gene regulation." *Nature*, vol. 439, pp. 856–860, Feb 2006.

[10] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, *Molecular Biology of the Cell*, 4th ed. Garland Science, 2002.

[11] F. Blanchini, "Set invariance in control," *Automatica*, vol. 35, pp. 1747–1767, Nov. 1999.