Self-regulation in a minimal model of chemical self-replication

Sylvia J. Lou · Enrique Peacock-López

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Abstract In biological systems, regulation plays an important role in keeping metabolite concentrations within physiological ranges. To study the dynamical implications of self-regulation, we consider a functional form used in genetic networks and couple it to a mechanism associated with chemical self-replication. For the two-variable minimal model, we find that activation can yield chemical toggles similar to those reported for gene repression in *E. coli* as well as more complex dynamics.

Keywords Chemical self-replication · Genetic regulation · Bistability

1 Introduction

At the microscopic level, biological systems are composed of coupled networks of biochemical reactions. To control metabolite concentrations, the networks or some key reactions are regulated at the genetic or metabolic level. Mechanistic studies of metabolic regulation have been performed for systems where relevant enzymes are regulated by phosphorylation and/or dephosphorylation or by gene expression [1–4]. Other types of regulation concern the coupling of biochemical networks, where metabolite transport may show activation or repression [5, 6]. In general, repression, characterized by a negative feedback, is more common in biological systems because of its tendency to stabilize the concentration of relevant metabolites [7, 8]. Nevertheless, activation characterized by a positive feedback is

S. J. Lou · E. Peacock-López (✉)
Department of Chemistry, Williams College, Williamstown, MA 01267, USA
e-mail: epeacock@williams.edu

E. Peacock-López
Department of Chemistry, University of Cape Town, Rondebosch, 7701 Cape Town, South Africa

also observed in biological systems [9–13], and it is considered necessary for multistability [8–14].

In particular, regulated gene expression more often shows repression rather than activation mechanisms. Typically, researchers have considered that a repressor can block gene transcription of a relevant network protein and that the repressor is the product of the biochemical network. More than 40 years ago, Goodwin [15] considered a simple model of genetic regulation of enzyme synthesis. Although the model was simple, it still showed oscillations for unphysical parameters. Goodwin's work was revised by Tyson [16–18], who considered variations of the Goodwin model, including more biochemically appropriate features. The latter model showed oscillatory behavior for plausible physical parameters and gave us an understanding of periodic enzyme synthesis.

More recently in *Escherichia coli*, Collins et al. [19] designed a bistable gene-regulated network of a pair of repressible promoters arranged to mutually repress each other. Concurrently, Elowitz and Leibler [20] constructed a network of three transcriptional repressors in *E. coli* known as the “Repressilator.” In this case, the periods of the observed oscillations were of the order of hours beyond the cell-division cycle. In both cases, however, the modeling considered repression linked to simple protein and messenger RNA degradation reactions, with no further participation in any biochemical reactions. These contemporary examples of relatively simple experimental artificial gene networks were modeled using functional regulatory forms first discussed by Goodwin [15]. More recently, these functional forms have been referred as Hill's functions, which have been used to model genetic transcription. So considering the same functional forms used in different models of genetic networks and enzyme kinetics, we study regulated reactant sources, where the reactants participate in a series of chemical reactions, and the final products have a negative or positive regulatory effect on the reactant source.

In this paper, we consider reactant source regulation, where the regulatory functional form resembles those used in artificial genetic networks. In contrast to other studies [19, 20], we link the initial reactants to a set of biochemical reactions associated with chemical self-replication, resulting in a final product that either represses or activates the reactant source. In particular, we consider not only repression, which tends to stabilize the system, but also activation, which may be a source of complex dynamics. Furthermore, we use our model of chemical self-replication, or the so-called Templator model (TM), which we have characterized for a constant input, as the set of chemical reactions linked to the regulated reactant. Thus, we can compare the effect of the regulatory mechanism on the dynamics of the TM. The essence of this work is to look at the effects of different regulatory functions on the dynamics of a chemical system characterized in the absence of positive or negative regulatory feedback.

In Section 2, we briefly discuss the Templator model under reactant regulation and we first consider the steady states. In Section 3, we study the dynamic changes of the system as we vary the parameters associated with reactant regulation, using bifurcation diagrams for the case of repression, as well as for the case of activation. Finally, in Section 4, we discuss our results.

2 General model

In this section, we first consider the model of chemical self-replication [21] that we have studied in the past [22–30]. After we describe the model, we include a particular regulatory

mechanism, which has been considered by others to model genetic regulation [15–19]. Therefore, we start by showing the following mechanism of self-replication [21]:

In this mechanism, the first step is a regulated source of A and C followed by an uncatalyzed reaction yielding B . The third step is the autocatalytic replication of B . Finally, B is degraded by an enzyme E . For the last step, we use the steady-state approximation for the enzymatic species.

Since in the experimental systems one observes that there are no limiting reagents, we consider the addition and difference of the concentrations of the reagents A , and C as dynamical variables, $a = ([A] + [C])/2$, and $c = ([A] - [C])$, where $[A]$, and $[C]$ represent the reagent concentrations. Therefore, under the assumption of no limiting reagents, we find that c is zero as a function of time, leaving us with only two dynamical variables, a and $b = [B]$. For more details, see references [24, 25]. Thus, using the mass action laws, we obtain the following ordinary differential equations (ODEs):

$$\frac{da}{dt} = R(b) - k_1 a^2 - k_t a^2 b \quad (8)$$

$$\frac{db}{dt} = k_1 a^2 + k_t a^2 b - \frac{V_c b}{K_c + b}, \quad (9)$$

where a and b represent the concentrations, and $R(b)$ is a source that depends on the concentration of B . In previous work, we have considered a constant source, also known as the chemical pool approximation, where the reactant precursor concentration is much greater than the concentrations of the reactants and products [24, 31].

In the case of biochemical systems, the chemical pool approximation may not accurately describe plausible experimental and biological systems. Therefore, we consider the possibility of a regulated source of reactant of the type used in the description of genetic networks. We consider the Collins [19] and Elowitz [20] models of regulated gene expression, where the product of the chemical reactions regulates transcription, and translation is proportional

to the amount of messenger RNA (mRNA). This simplified model is represented as follows:

$$\frac{dmR}{dt} = r_o + \frac{\alpha b^m}{K_r + \beta b^n} - \gamma mR \quad (10)$$

$$\frac{da}{dt} = \kappa mR - k_u a^2 - k_t a^2 b \quad (11)$$

$$\frac{db}{dt} = k_u a^2 + k_t a^2 b - \frac{V_c b}{K_c + b}, \quad (12)$$

where mR represents the concentration of mRNA, r_o is the so-called leak transcription rate, γ is the rate constant of mRNA degradation, and κ is the rate constant of mRNA translation. For a more detailed discussion of the mean field rate equations used in the analysis of genetic networks, we refer our readers to some general references in the literature [32–37].

Like others, i.e., [12, 19] and [38, 39], we consider a simple functional form to model either repression or activation of gene transcription characterized by the values (m, n) . Since genetic repression is more often observed in biochemical systems, the repression case $(0, 2)$ has been widely studied in the literature [40–45], while the activation case has been seldom used [9–13]. Although repression tends to stabilize a dynamical system, activation coupled with degradation can show oscillatory behavior or even complex oscillations. Thus activation is an appropriate and important mechanism of complex dynamics.

In contrast to the Elowitz modeling approach in which mRNA is a dynamic species, Collins uses the steady-state approximation for the mRNA concentration under the assumption that protein half-lives are much longer than mRNA's half-lives. Within this approximation, we find an expression for the concentration of the mRNA,

$$mR = \frac{1}{\gamma} \left[r_o + \frac{\alpha b^m}{K_r + \beta b^n} \right]. \quad (13)$$

We now substitute in (10) to obtain a two-variable system of dimensional differential equations representing the coupling between the genetic regulated protein production and a chemical mechanism of self-replication,

$$\frac{da}{dt} = \left[r_1 + \frac{\alpha_1 b^m}{K_r + \beta b^n} \right] - k_u a^2 - k_t a^2 b \quad (14)$$

$$\frac{db}{dt} = k_u a^2 + k_t a^2 b - \frac{V_c b}{K_c + b} \quad (15)$$

where we have defined the following parameters:

$$r_1 = \frac{\kappa}{\gamma} r_o \quad (16)$$

$$\alpha_1 = \frac{\kappa}{\gamma} \alpha. \quad (17)$$

Consequently, from (14), we can now define the source term $R(b)$ as

$$R(b) = \left[r_1 + \frac{\alpha_1 b^m}{K_r + \beta b^n} \right], \quad (18)$$

and in Fig. 1 we illustrate the repression (0,2) and the activation with saturation (2,2) cases. The parameter values related to the regulatory mechanism are taken from Elowitz and Leibler's experimental and theoretical work on an artificial genetic network [20] designed in *E. coli*.

Given the dimensional ODEs in (14), we now rescale the concentrations and time to obtain a set of dimensionless ODEs [24]. First we define the following concentration and time scalings:

$$X = \left(\frac{k_t}{V_c} \right)^{1/3} a \quad (19)$$

$$X = \left(\frac{k_t}{V_c} \right)^{1/3} b \quad (20)$$

$$\tau = (k_t V_c^2)^{1/3} \quad (21)$$

which yield the following dimensionless ODEs:

$$\frac{dX}{d\tau} = \left[r + \frac{k_2 Y^m}{K_2 + \beta Y^n} \right] - k_u X^2 - X^2 Y \quad (22)$$

$$\frac{dY}{d\tau} = k_u X^2 + X^2 Y - \frac{Y}{K + Y}. \quad (23)$$

Fig. 1 Regulated source $R(b)$ with $r_1 = 0$, $\alpha_1 = 0.20$, $K_r = 0.20$, and $\beta = 1$ for the pure repression case, ($m = 0$, $n = 2$), and the activation with saturation case (2,2)

Finally, in (22) we have defined the following five dimensionless parameters as follows:

$$r = \left(\frac{1}{V_c} \right) r_1 \quad (24)$$

$$k_2 = \left(\frac{V_c}{k_t} \right)^{\frac{m-n}{3}} \left(\frac{1}{V_c} \right) \alpha_1 \quad (25)$$

$$K_2 = \left(\frac{k_t}{V_c} \right)^{1/3} K_r \quad (26)$$

$$k_u = \left(\frac{1}{k_t^2 V_c} \right)^{1/3} k_1 \quad (27)$$

$$K = \left(\frac{k_t}{V_c} \right)^{1/3} K_c. \quad (28)$$

In the next section, we consider dimensionless parameter values for k_u , and K that we have used in other studies [23–30]. Our parameter selection is based on our analysis of chemical self-replication, where parameters are determined by fitting experimental data published by Paul and Joyce [46] and Lincoln and Joyce [47] for self-replicating ribozymes. In the case of genetic regulation, we consider parameter values previously determined by several experimental groups [15, 19, 20, 32, 33, 44]. In particular, we follow Widder's [32] parameter selection.

3 Steady states

Before we consider the steady states, we recall the physical relevance of the parameters m and n . As is well known, these parameters are associated with the number of transcription factors required for repression or activation and represent the cooperativity associated with the genes. In our case, m and n represent the number of particles X and/or Y necessary for repression or activation of the source of X particles. Therefore their values range between zero and at the most five. Larger values may not have a physical interpretation. Moreover, the number of steady states depends on the values of m and n , which may define bistable or multistable systems. Bistability is necessary for chemical switches similar to genetic toggles. So we consider different possible values of the m and n parameters and their implications for multistability, before we consider the stability of the steady states.

First, from the model's ODEs, we consider the steady states, $(\bar{X}, \bar{Y})$, of (22) for any values of m and n . Thus from (22), we get the following algebraic equation, which yields the $\bar{Y}$ steady state:

$$\beta [1 - r] \bar{Y}^{n+1} - k_2 \bar{Y}^{m+1} - \beta r K \bar{Y}^n - k_2 K \bar{Y}^m + K_2 [1 - r] \bar{Y} - r K K_2 = 0 \quad (29)$$

where there is no dependence on k_u . Notice that the equation's order depends on m and n , and that a positive real solution cannot be obtained for $r \geq 1$. The latter observation is consistent with our previous analysis [22–30], and it means that the influx of reagents is greater than the outflux, leading to a divergence at $r = 1$, and complex or negative real solutions for $r > 1$.

Second, we consider some of the possible cases of repressed or activated regulation by considering values of m , n , and β . These choices of values reflect the common regulatory

functions found in the literature [15–19]. In the case of pure repression, the values that most closely mirror experimental observations are $m = 0$, $n = 2$, and $\beta = 1$. For these values, we get a cubic algebraic equation,

$$[1 - r] \bar{Y}^3 - r K \bar{Y}^2 + [K_2(1 - r) - k_2] K_2 \bar{Y} - K(r K_2 + k_2) = 0. \quad (30)$$

Notice that if

$$k_2 < K_2(1 - r) \quad (31)$$

We can obtain up to three positive real roots or only one. Therefore, the number of roots could be a function of k_2 , the maximum translation rate. In principle, it is possible to obtain analytical general conditions for three positive real roots of (30), but such expressions are quite cumbersome, and we do not include them in this study.

In Fig. 2 we depict the behavior of the steady-state (Y) for typical dimensionless parameter values. In general for this case and within the physical parameter space, we obtain only one real positive root. Consequently, for our model, pure repression favors only one root avoiding the bistable case, which requires three real positive roots of (30).

For the case of activation with saturation, we set $m = n = 2$ and $\beta = 1$, and for this choice, we again get a cubic algebraic equation,

$$[(1 - r) - k_2] \bar{Y}^3 - K [r + k_2] \bar{Y}^2 + K_2 [1 - r] \bar{Y} - r K K_2 = 0. \quad (32)$$

As in the previous case, we check the possible sign changes and find that for

$$k_2 < 1 - r \quad (33)$$

we could have either one or three positive real roots. However, if

$$1 - r < k_2 \quad (34)$$

we could obtain either two or no positive real roots. In the latter case, the system collapses since the source adds more reactants to the system than the system can eliminate, causing the product concentration to blow up. In Fig. 3, we show the behavior of the steady state,

Fig. 2 Steady-state solutions for pure repression as a function of k_2 , with $m = 0$, $n = 2$, $r = 0.10$, $k_u = 0.01$, and $\beta = 1$. **a** $K_2 = 0.30$ and $K = 0.10$; **b** $K_2 = 0.05$, and $K = 0.20$

Fig. 3 Steady-state solutions for activation with saturation as a function of k_2 with $m = n = 2$, $r = 0.10$, $K_2 = 0.05$, $K = 0.20$, $k_u = 0.01$, and $\beta = 1$. The figure on the *right* is an enlargement of the *left-hand* figure, showing the three-root region of (29)

where we notice a singularity for $k_2 = 1 - r$ that reduces the cubic to a quadratic equation. We also emphasize the region of three real positive roots, which is characteristic of bistable systems. Therefore in this model, the over-expression of genes clearly pushes the system to more complex dynamics as the value of k_2 increases.

In a third case, considered elsewhere [23], we set $\beta = 0$ and $m = 1$, which implies a linear feedback. For this case, the steady-state Y satisfies a quadratic equation,

$$k_2 \bar{Y}^2 - [K_2(1 - r) - k_2 K] \bar{Y} + r K K_2 = 0. \quad (35)$$

As before, we check possible sign changes and find that for

$$k_2 < \frac{K_2(1 - r)}{K} \quad (36)$$

we have two or no positive real roots. For larger values of k_2 , there are no positive real roots, which implies that the system blows up since over-expression overwhelms the enzymatic sink.

4 Bifurcation diagrams

Following common procedures [48–51], we consider the stability analysis of the steady states using the XPP software package [52]. We start by considering the case of pure repression, $m = 0$, $n = 2$, and $\beta = 1$. First, we depict in Fig. 4 the reference bifurcation diagram for $k_2 = 0$.

Basal gene transcription (r) and regulated transcription (k_2) are affected by both environmental as well as genetic factors. A detail discussion can be found in the literature [10, 32, 33, 35, 53]. In the case of the enzymatic degradation (K), the dynamic enzymatic response can be modified by the increase in concentration of environmental factors, as well as reflect transcription defects that yield a faulty enzyme, as has been addressed by Portle et al. [53].

Fig. 4 Bifurcation diagrams for $k_2 = 0$ and $m = 0$, $n = 2$, $K_2 = 0.05$, $k_u = 0.01$, and $\beta = 1$. *Thick dark line* encloses the region of oscillations, *thin dark line* shows stable steady states, and *thin light line*, inside the oscillatory region, shows unstable steady states. **a** One parameter, r , diagram with $K = 0.20$, and **b** Two parameter diagram, (r, K)

The diagram in Fig. 4 had been studied at length elsewhere [22–30], and corresponds to the case of the chemical pool approximation. As usual, the thin light line represents unstable steady states and the darker line represents stable solutions. The thick dark line in Fig. 4a represents the amplitude of the system oscillations and the initial and final supercritical Poincaré–Adronov–Hopf (PAH) bifurcations [54–56]. In Fig. 4b, we depict the two-parameter (r, K) bifurcation diagram, where oscillations are stable inside the loop and steady states are stable outside the loop.

Any changes to the diagram in Fig. 4 are due to the regulated feedback. For example, in Fig. 5 we consider a k_2 value of 0.10 and find that the system, in comparison with $k_2 = 0$ in Fig. 4, has a larger range of r values associated with stable steady states. Or, in other words, the parameter space region of oscillatory behavior is dramatically reduced. Notice that in Fig. 5a the left-hand side PAH bifurcation collapses such that oscillations are present in the case of no leak transcription, e.g., $r = 0$. It is believed in general that pure repression favors steady states and simpler dynamics, but that over-transcription can overwhelm the system. Therefore, we will not consider further the case $\beta = 0$, where the source adds reactant

Fig. 5 Bifurcation diagrams for $k_2 = 0.10$ and $m = 0$, $n = 2$, $K_2 = 0.05$, and $k_u = 0.01$. For meaning of the line types, see Fig. 4. **a** One parameter, r , diagram with $K = 0.20$, and **b** two parameter diagram, (r, K)

Fig. 6 Bistability for $m = n = 2$, $r = 0.10$, $k_2 = 0.80$, $K_2 = 0.05$, $K = 0.20$, $k_u = 0.01$, and $\beta = 1$. The blue dots show the three steady states and the black lines show the trajectories of four different initial conditions. Two of the initial conditions are close to the separatrix

proportionally with the concentration of the product. This positive feedback will tend to blow up the system, so it is not representative of biological systems.

Next, we consider the case of activation with saturation that reflects experimental behavior. In this case, we set $m = n = 2$ and $\beta = 1$, where, for low values of the product, the source is activated. As the product concentration increases, the source increases its rate of formation, but this increase is limited by a maximum value, as we can see from Fig. 1. In this case, the steady states can show multistability. From Fig. 2, we pick parameter values to study bistability, and in Fig. 6 we illustrate the bistable behavior. Because one of the steady-state values is small ($Y \approx 0$), the system behaves like a toggle, like that reported by Collins et al. [19]. Thus, the system can be on at a value $Y \approx 1.5$ or off at a value $Y \approx 0$. Moreover, fluctuations in the concentrations can turn the system on or off depending on the magnitude of the changes and the proximity to the separatrix that defines the basin of attraction. Usually, toggles are associated with repression, but here we show that activation can also yield chemical toggle behavior.

Fig. 7 Bifurcation diagram for activation with saturation and leak transcription, where r is the bifurcation parameter with $m = n = 2$, $K_2 = 0.10$, $K = 0.20$, $k_u = 0.01$, and $\beta = 1$. **a** $k_2 = 0.20$, and **b** $k_2 = 0.40$. For interpretation of the lines, see Fig. 4

Fig. 8 Bifurcation diagram for activation with saturation and leak transcription, where r is the bifurcation parameter with $m = n = 2$, $K_2 = 0.10$, $K = 0.20$, $k_u = 0.01$, and $\beta = 1$. **a** $k_2 = 0.50$, and **b** $k_2 = 0.60$. For interpretation of the lines, see Fig. 4

Besides bistability, our model shows other more interesting behavior related to the interaction of the saddle-node and the PAH bifurcations. To explore this interaction, we choose parameter values $K_2 = 0.10$ and $K = 0.20$, and consider r as our bifurcation parameter for different values of k_2 . For small values of k_2 we find no saddle-node bifurcation, but as we increase k_2 the stable steady state branch squeezes the PAH bifurcation. We illustrate this behavior in Fig. 7.

In the final case, we increase the value of k_2 such that the saddle-node (SN) bifurcation is able to interact with the PAH bifurcation. In Fig. 8 we clearly show this type of interaction, where the SN bifurcation breaks the original “bubble” formed by the PAH bifurcation in Fig. 7. Moreover, in Fig. 9, we blow up the region where an abrupt change from oscillations to steady state occurs if we increase the value of the leak expression. In this case, large amplitude oscillations collapse to a stable steady state once the bifurcation parameter, r , crosses the critical value. This is an example of dynamical behaviors due to the presence and interaction of a saddle-node and a PAH bifurcation.

Fig. 9 Bifurcation diagram for activation with saturation and leak transcription, where r is the bifurcation parameter. **a** $m = n = 2$, $K_2 = 0.10$, $K = 0.20$, $\beta = 1$, $k_u = 0.01$, and $k_2 = 0.50$, and **b** amplification of the figure near the saddle-node. For interpretation of the lines, see Fig. 4

5 Discussion

In biochemical networks, repression and activation regulation play a key role in maintaining metabolite concentrations within physiological ranges. In this paper, we consider the Templator model of chemical self-replication, where the product regulates the reactant source. This feedback can take different functional forms depending on the nature of the regulation. In some cases, enzymes are activated or inhibited by phosphorylation or by other metabolites. In our analysis, we consider a functional form that has been used by others [19, 20] to model regulated gene expression in *E. coli* in order to explain experimental data. In the Collins model, for example, a pair of mutual repressors yields a biochemical toggle, and in the Elowitz model, three consecutive repressors yield oscillations in the concentration of the protein associated with the genes.

As an extension of the experimental papers, we explore the dynamical consequences of a possible genetic regulation. In our analysis, the gene products are part of a biochemical mechanism in which the final product is either a gene repressor or activator. In the case of pure repression, we find that the parameter space regions, where the Templator model shows oscillations, shrinks considerably. Therefore, as expected, repression has a stabilizing effect on the chemical mechanism. In contrast, positive feedback represented by an activated gene expression shows more dynamical behaviors. In particular, the cubic equation associated with the steady states can have one, three, two, or no real positive solutions. In contrast, the cubic equation for repression only shows one real positive solution.

The presence of three real positive solutions is related to a saddle-node bifurcation in the transition from one steady state to three steady state concentrations. This saddle-node bifurcation is capable of interacting with the PAH bifurcation that characterizes the Templator's oscillatory behavior. Among the relevant results is the bistable behavior of the Templator that behaves like a toggle, as in the Collins case. Biochemical toggles have been associated with repression, but in our case we have a chemical toggle associated with activation.

Furthermore, activation can yield drastic dynamical changes. For example, the transition from three steady-state solutions to two steady states occurs through a singularity associated with the coefficient of the cubic term. Since the coefficient depends on the leak expression parameter, r , as we vary r the coefficient reaches a zero value. Therefore, the system goes from a cubic to a quadratic equation. The changes in the r value can be related to changes in the chemical equilibrium binding constant between the genes and the activators, which may be prone to change its value.

Also, as we vary parameter values within the physical parameter space, the saddle-node bifurcation can destroy one of the supercritical PAH bifurcations, yielding a sudden change from oscillatory behavior to steady state (Fig. 9). This behavior can be due to changes in the nature of the enzymatic sink through K , or the transcription parameters, k_2 or K_2 , as well as the leak expression (Fig. 10). For completeness, we include a two-parameter bifurcation diagram in Fig. 11, where we show the regions of single steady states (SS), the oscillatory region, and the two branches of the saddle-node bifurcation (SN in parameter space). From Fig. 11, we notice the relevance of the “leak transcription” (r) in generating complex dynamics. The “regulated transcription”, characterized by k_2 , also has a very important role. For example, for values less than $1/2$, we find only two PAH bifurcations and only one steady state as we vary r . Bistability is present when k_2 is greater than $1/2$, with the presence of two SN bifurcations. Interesting dynamics occur for $k_2 \gg 1/2$ and $r \approx 0.27$, where the PAH and the SN bifurcation interact near the Bogdanov–Takens (BT) bifurcation. A BT bifurcation occurs when the Jacobian has a double-zero eigenvalue, while

Fig. 10 Bifurcation diagram for activation with saturation and leak transcription, where r is the bifurcation parameter. **a** $m = n = 2$, $K_2 = 0.05$, $K = 0.20$, $\beta = 1$, $k_u = 0.01$, and $k_2 = 0.50$. **b** Amplification of the figure near the saddle-node. For interpretation of the lines, see Fig. 4. Notice the region of coexistence between stable limit cycles and stable steady states, which could be a source of hysteresis

the remaining eigenvalues are not purely imaginary [57]. In other words, the PHA and SN curves both terminate on a saddle node branch at the BT point.

Finally, we notice that the system can show the coexistence of stable steady states and limit cycles, as depicted in Fig. 10. In this figure we observe a supercritical and a subcritical PAH bifurcation. In the latter case, the limit cycle is unstable and defines the separatrix between the steady state and the stable limit cycle, resulting in a fold of periodic bifurcation. Consequently, we could potentially observe a hysteresis loop if we change the value of the bifurcation parameter, r . For example, the system could oscillate as we increase the value of the bifurcation parameter, but the oscillatory behavior would collapse into a steady state once we reach a critical bifurcation. If now we decrease the bifurcation parameter value, the system could show a steady-state value until the parameter reaches the saddle-node bifurcation, where the system would suddenly change to an oscillatory mode. This particular cycle is likely to yield bursting oscillations if the bifurcation parameter is also a slow dynamic variable.

Fig. 11 **a** Two-parameter bifurcation diagram for activation with saturation and leak transcription, where r and k_2 are the bifurcation parameters. Other parameters are: $m = n = 2$, $K_2 = 0.05$, $K = 0.20$, $\beta = 1$, and $k_u = 0.01$. **b** Amplification of the figure near the saddle node (SN) bifurcations showing the PAH bifurcation

Although our model is not representative of a particular biological system, it consists of two observed dynamical biological systems. The biological implications of our findings can be separated into two categories. The first is genetic regulation, which has been manipulated in simple artificial genetic networks, where the gene product is not involved in any chemical network. This case is simplistic in the sense that in biological systems of interest the gene product is most likely to participate in a biochemical network, where the final product can either repress or activate the gene. The second category considers chemical self-replication reactions that have been characterized in vitro as models of plausible biological processes. Thus, our work considers possible dynamic consequences of gene regulation coupled with a biochemical mechanism, in which the final product is the regulatory metabolite. A biological example is clearly observed in the regulation of the heat-shock (HS) response [58–61], where the HS protein (HSP) participates in a series of biochemical reactions that phosphorylate and polymerize HSP yielding a relevant transcriptional factor. We can also suggest an in vitro experiment where one could regulate the reagent inputs in a continuous stirred tank reactor (CSTR). One candidate for the self-replicating system could be the R3C RNA enzyme designed by Lincoln and Joyce. The R3C enzyme self-replicates by binding two RNA molecules [46, 47, 62, 63], but most recently, it has been modified to replicate via cross-catalytic pathway [47]. Previous experiments have been done in batch reactions. Therefore, by considering CSTR conditions, the regulatory mechanism can be externally controlled to mimic the regulatory function used in our analysis.

In summary, we considered two well-characterized biochemical mechanisms and couple them using a feedback loop. In contrast with most studies of artificial gene networks, we consider that the gene products are part of a chemical mechanism, where the end product has regulatory effects on the reactant source. In general, our results show that negative feedback can yield simpler dynamical behaviors when coupled with a biochemical mechanism, and that positive feedback can have drastic dynamical effects on simple oscillatory behavior. From the previous discussion, it seems that the type of regulation considered in our analysis may be related to so-called gene bursting [64–66].

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