Carryover of a saddle-node bifurcation after transformation of a parameter into a variable

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Abstract

Abstract goes here.

Consider a dynamical system, which we denote *original system*,

$$\dot{z} = f(z; \mu_1, \mu_2), \tag{1}$$

where $z \in \mathbb{R}^n$ and one of the parameters $\mu_1, \mu_2 \in \mathbb{R}$ drives a saddle-node bifurcation as it crosses a critical value. Using continuation, we can determine the set of points in the parameter space (μ_1, μ_2) where the bifurcation occurs. Now, transforming one of the parameters, for example, μ_1, into a variable, we define the *extended system*

$$\begin{aligned} \dot{z} &= f(z, \mu_1; \mu_2), \\ \dot{\mu}_1 &= g(\mu_1; \mu_2), \end{aligned} \tag{2}$$

where $(z, \mu_1) \in \mathbb{R}^{n+1}$ and $g(\mu_1; \mu_2)$ is the vector field of the new variable μ_1. We are interested in finding conditions for which a saddle-node bifurcation occurs as μ_2 varies. If the bifurcation point in the extended system corresponds to a bifurcation point in the original system, then we say that the bifurcation point of the former is the *carryover* of the latter.

Saddle-node bifurcations in mathematical models of biological systems are associated with biologically meaningful properties such as biological switches and hysteresis. When adding more complexity to the model of a biological system exhibiting a saddle-node bifurcation, it might be important to preserve the existence of the bifurcation. In particular, if a set of differential equations describing a biological system (original system) exhibits a saddle-node bifurcation driven by a parameter, it might be relevant to add more complexity to the system by transforming the bifurcation parameter into a dynamical variable and obtain a system with one additional dimension (extended system). Note that in the extended system, a saddle-node bifurcation might still be present but with respect to another parameter. If this is the case, we call this property the carryover of a saddle-node bifurcation.

The main objective of this work is to find conditions that guarantee the carryover of a saddle-node bifurcation. Moreover, we would like to unfold the relationship, if any, between the saddle-node bifurcation in the original system and the saddle-node bifurcation of the extended system.

In order to motivate our work, we introduce the following two applications, which will be fully analyzed in Section 4. First, consider the dimensionless model for the activation of gene x by a biochemical signal substance s given by

$$\dot{x} = s - rx + \frac{x^2}{1+x^2}, \tag{3}$$

where $r > 0$ is the degradation rate, and $s \geq 0$ [Strogatz, 1994, Lewis et al., 1977]. This model is characterized by an irreversible switch-like activation (critical transition) of gene x given by a saddle-node bifurcation as s increases from zero above a threshold s^*. This means that the biochemical signal needs to be high enough to increase the activity of the gene from low to high (see Section 4 for more details). Suppose that we include the dynamics of the substance s in an extended system by adding a differential equation for s in the original system (3). In such a case, we would be interested in finding the conditions that guarantee the carryover of the saddle-node bifurcation for the extended system with respect to the parameter r. In other words, we would like to know if the activation or inactivation of the gene x could be driven now by the degradation rate r.

As a second example, we consider the regulatory network for the cell cycle involving the mutual antagonism of Cyclin B and APC (Anaphase Promoting Complex) that regulates the beginning and the end of the cell cycle. The beginning of the cell cycle, during the G1 phase, is characterized by low levels of Cyclin B caused by the action of active APC. Cell growth promotes APC inactivation, which in turn allows for Cyclin B synthesis in a critical transition, known as the *start* of the cell cycle. During the S-G2-M phase, Cyclin B activity is high which promotes activity of Cdc20, an activating subunit of APC. At the end of the S-G2-M phase, active APC lowers the level of Cyclin B, thus closing the cycle and defining the *finish* of the cell cycle. In this regulatory network, the cell mass acts as a parameter that drives the critical transition towards the beginning of the cell cycle through a saddle-node bifurcation in which the activity of Cyclin B increases quickly as the cell mass increases. The system describing the cell cycle is modelled by the following system of differential equations

$$\begin{aligned} \frac{dY}{dt} &= k_1 - (k_{2p} + k_{2pp}P)Y, \\ \frac{dP}{dt} &= \frac{(k_{3p} + k_{3pp}A)(1-P)}{J_3 + (1-P)} - k_4 m \frac{YP}{J_4 + P}, \\ \frac{dA}{dt} &= k_{5p} + k_{5pp}\frac{(mY/J_5)^n}{1+(mY/J_5)^n} - k_6 A, \end{aligned} \tag{4}$$

where Y is the concentration of Cyclin B, P is the concentration of active APC (given by subunit Cdh1), A is the concentration of active of Cdc20, m is the cell mass, k parameters are production and decay rates, and J parameters are saturation constants, and n is the Hill coefficient [Segel and Edelstein-Keshet, 2013, Tyson and Novák, 2001]. This basic model for the cell cycle accounts for the G1 (or start) checkpoint, identified with an equilibrium where the concentration of Cyclin B is low, and the irreversible transition to S-G2-M phase, identified with a saddle-node bifurcation where the low level equilibrium of Cyclin B is lost (see Section 4 for more details).

This model can be extended by including more elements of the cell cycle, such as other Cyclin proteins and checkpoints [Tyson et al., 2002, 2003], or by considering the mass, m, as a variable. In this latter case, we would have an extended system where the beginning of the cell cycle occurs dynamically and the G1 checkpoint, described by the saddle-node bifurcation with respect to the parameter m in system (4), is lost. This leads to the question of whether or not there exists another parameter that drives the G1 checkpoint in the extended system through a saddle-node bifurcation. In other words, our interest would be to find the conditions that guarantee the carryover of the saddle-node bifurcation for the extended system with respect to a new parameter.

Note that in both examples, we are transforming the parameter that drives a saddle-node bifurcation into a variable, and aiming to find the conditions for the extended system that guarantee the carryover of the saddle-node bifurcation so that the particular biological characteristics of the original system are preserved in the extended system.

In this paper we provide sufficient conditions to guarantee the carryover of the saddle-node bifurcation. For this purpose, we review the basic concepts of a saddle-node bifurcation in Section 1, state the main results for the carryover of a saddle-node bifurcation for the one-dimensional case in Section 2, and extend the results to the n-dimensional case in Section 3. We provide a practical graphical approach that can be used to guarantee the carryover of a saddle-node bifurcation. In Section 4, we will apply the results to the above-mentioned examples. Finally, in Section 5, we discuss the limitations of our results and future work.

1 Mathematical Background

Saddle-node bifurcations in $\mathbb{R}^n$ are characterized by three conditions: singularity, nondegeneracy, and transversality conditions. They guarantee the creation (or destruction) of two equilibria as one parameter crosses the bifurcation value. This is summarized in the following results taken from Meiss [2007, Ch. 8].

Theorem 1 (saddle node)**.** *Let $f \in C^2(\mathbb{R}^n \times \mathbb{R}^k, \mathbb{R}^n)$, and suppose that $f(z;\mu)$ satisfies*

$$f(0;0) = 0, \quad \operatorname{spec}(D_z f(0;0)) = \{0, \lambda_2, \lambda_3, \ldots, \lambda_n : \lambda_k \neq 0, k \neq 1\}. \tag{5}$$

Choose coordinates so that $D_z f(0;0)$ is diagonal in the zero eigenvalue and set $z = (x, y)$ where $x \in \mathbb{R}^1$ corresponds to the zero eigenvalue and $y \in \mathbb{R}^{n-1}$ are the remaining coordinates. Then

$$\begin{aligned} \dot{x} &= f_1(x, y; \mu), \\ \dot{y} &= My + f_2(x, y; \mu), \end{aligned} \tag{6}$$

where $f_1(0,0;0) = 0$, $f_2(0,0;0) = 0$, $D_z f_1(0,0;0) = 0$, $D_z f_2(0,0;0) = 0$, and M is an invertible matrix. Suppose that

$$D_{xx} f_1(0,0;0) = c \neq 0. \tag{7}$$

Then there exists an interval $I(\mu)$ containing 0, functions $y = \eta(x;\mu)$ and extremal value $m(\mu) = \operatorname{Ext}_{x \in I(\mu)}[f_1(x; \eta(\mu); \mu)]$, and a neighborhood of $\mu = 0$ such that if $m(\mu)c > 0$ there are no equilibria and if $m(\mu)c < 0$ there are two. Suppose that M has a u-dimensional *unstable space and an $(n-u-1)$-dimensional stable space. Then, when there are two equilibria, one has a u-dimensional unstable manifold and an $(n-u)$-dimensional stable manifold and the other has a $(u+1)$-dimensional unstable manifold and an $(n-u-1)$-dimensional stable manifold.*

Equations (5) and (7) are the singularity and nondegeneracy conditions, respectively. They are necessary conditions for the function f_1 to be zero up to the zero- and first-order approximations about the bifurcation point, but nonzero in the second-order approximation. The function $y = \eta(x;\mu)$ allows us to reduce the dynamics in a neighborhood of the bifurcation point to one-dimension, i.e.,

$$\dot{x} = f_1(x, \eta(x;\mu);\mu).$$

The extremal value function $m(\mu)$ determines a single condition on the parameters, $m(\mu) = 0$, along which two equilibria are created (or destroyed). Having one condition on the parameters means that the bifurcation that takes place has codimension-one. In order to be a saddle-node bifurcation, the equilibria need to be created as some combination of the parameters crosses the bifurcation point. This can be guaranteed with a simple condition.

Corollary 1. *If μ_1 is a single parameter such that*

$$D_{\mu_1} f_1(0,0;0) \neq 0, \tag{8}$$

then a saddle-node bifurcation takes place when μ_1 crosses zero.

Equation (8) is known as the transversality condition because, geometrically, $m(\mu) = 0$ is crossed transversally as μ_1 crosses zero. Note that μ_1 is an arbitrary parameter, and that the transversality condition can hold for several parameters at the same time. We only consider saddle-node bifurcations that take place as a single parameter crosses the bifurcation point.

In the context of this paper, we only consider two parameters for the sake of simplicity, i.e., $\mu = (\mu_1, \mu_2) \in \mathbb{R}^2$. We show that as long as a saddle-node bifurcation takes place in system (1) for at least one of the parameters, the extended system (2) also has a saddle-node bifurcation for the other parameter (i.e., the extended variable does not need to be a bifurcation parameter in the original system) under some singularity and transversality conditions.

The Implicit Function Theorem is an essential tool in the study of saddle-node bifurcations in general. For example, the function $y = \eta(x;\mu)$ in Theorem 1 is consequence of this theorem. The following form of the Implicit Function Theorem is taken from Meiss [2007, Ch. 8].

Theorem 2 (implicit function)**.** *Let U be an open set in $\mathbb{R}^n \times \mathbb{R}^k$ and $F \in C^r(U, \mathbb{R}^n)$ with $r \geq 1$. Suppose there is a point $(x_0, \mu_0) \in U$ such that $F(x_0;\mu_0) = c$ and $D_x F(x_0;\mu_0)$ is a nonsingular matrix. Then there are open sets $V \subset \mathbb{R}^n$ and $W \subset \mathbb{R}^k$ and a unique C^r function $\xi(\mu) : W \mapsto V$ for which $x_0 = \xi(\mu_0)$ and $F(\xi(\mu);\mu) = c$.*

2 One-dimensional case

In this section, we focus on the case where the variable z in the system (1) is one-dimensional, i.e., we consider the system

$$\dot{x} = f(x; \mu_1, \mu_2), \tag{9}$$

where $x \in \mathbb{R}$, $\mu_1, \mu_2 \in \mathbb{R}$, and f is a sufficiently smooth function on (x, μ_1, μ_2). This system is extended by transforming one of the parameters, for example, μ_1, into a variable to define the extended system

$$\begin{aligned} \dot{x} &= f(x, \mu_1; \mu_2), \\ \dot{\mu}_1 &= g(\mu_1; \mu_2), \end{aligned} \tag{10}$$

where $g(\mu_1; \mu_2)$ is the sufficiently smooth vector field of the new variable μ_1. We want to find conditions for the carryover of a saddle-node bifurcation in the original system (9) to the extended system (10).

Suppose, without loss of generality, that the saddle-node bifurcation for (9) occurs at the origin as one parameter, μ_1, crosses zero. That is, f at $(x, \mu_1, \mu_2) = (0, 0, 0)$ satisfies the singularity conditions

$$\begin{cases} f(x; \mu_1, \mu_2) = 0, \\ D_x f(x; \mu_{1,\mu_2}) = 0, \end{cases} \tag{11}$$

and the nondegeneracy and transversality conditions

$$\begin{cases} D_{xx} f(x; \mu_1, \mu_2) \neq 0, \\ D_{\mu_1} f(x; \mu_1, \mu_2) \neq 0. \end{cases} \tag{12}$$

Note that system (11) has two equations in $\mathbb{R}^3$ with coordinates (x, μ_1, μ_2) and Jacobian

$$J = \begin{pmatrix} D_x f & D_{\mu_1} f & D_{\mu_2} f \\ D_{xx} f & D_{x\mu_1} f & D_{x\mu_2} f \end{pmatrix} = \begin{pmatrix} 0 & D_{\mu_1} f & D_{\mu_2} f \\ D_{xx} f & D_{x\mu_1} f & D_{x\mu_2} f \end{pmatrix}.$$

This matrix has full rank since

$$\det \begin{pmatrix} D_x f & D_{\mu_1} f \\ D_{xx} f & D_{x\mu_i} f \end{pmatrix} = \det \begin{pmatrix} 0 & D_{\mu_1} f \\ D_{xx} f & D_{x\mu_1} f \end{pmatrix} = -D_{\mu_1} f D_{xx} f \neq 0,$$

by conditions (11) and (12). The Implicit Function Theorem 2 guarantees the existence of an interval I and unique functions

$$\begin{aligned} x &= \mathcal{X}(\mu_2), \\ \mu_1 &= \mathcal{M}(\mu_2), \end{aligned} \tag{13}$$

for $\mu_2 \in I$, such that

$$\mathcal{X}(0) = 0, \quad \mathcal{M}(0) = 0,$$

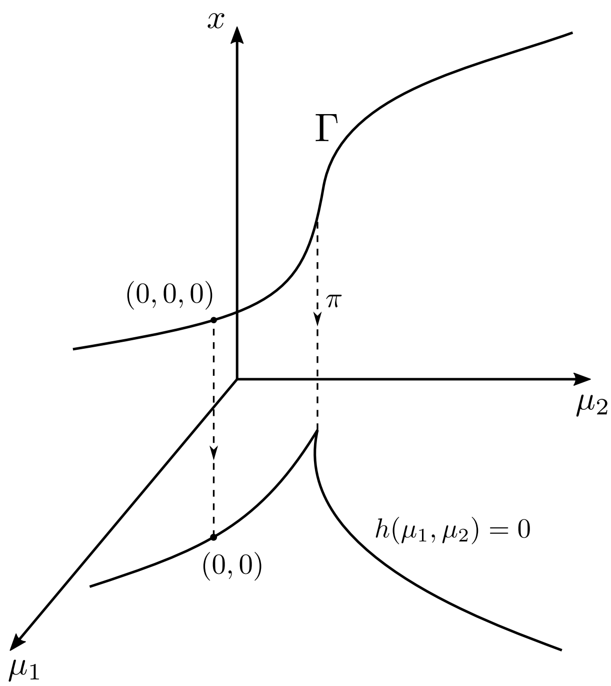

Figure 1: A bifurcation curve Γ and its corresponding bifurcation boundary $h(\mu_1, \mu_2) = 0$ (projection onto the (μ_1, μ_2)-plane). Modified from Figure 8.1 in Kuznetsov [2004].

and the singularity conditions (11) are satisfied in I. This defines a smooth one-dimensional curve Γ that follows the bifurcation point $(x, \mu_1, \mu_2) = (0, 0, 0)$, and is parameterized by μ_2, i.e.,

$$\Gamma = \{(x, \mu_1, \mu_2) \colon x = \mathcal{X}(\mu_2), \mu_1 = \mathcal{M}(\mu_2), \mu_2 \in I\}, \tag{14}$$

and satisfies (11).

By continuity, we can start from $(x, \mu_1, \mu_2) = (0, 0, 0)$ and follow the points that satisfy the singularity conditions (11) and the nondegeneracy and transversality conditions (12) to extend Γ. If the transversality condition is violated at some point, $D_{\mu_1} f = 0$, but the same condition is satisfied for the other parameter, $D_{\mu_2} f \neq 0$, we apply similar arguments to parameterize Γ by μ_1 in that section. Hence, we can extend Γ from the bifurcation point $(x, \mu_1, \mu_2) = (0, 0, 0)$ beyond the interval I as long as the transversality condition is satisfied for at least one of the parameters (see Figure 1). The projection of the extended Γ onto the (μ_1, μ_2)-plane, given by $\pi : (x, \mu_1, \mu_2) \mapsto (\mu_1, \mu_2)$, defines an implicit function

$$h(\mu_1, \mu_2) = 0,$$

known as *bifurcation boundary*, commonly found numerically using continuation (for example, using `PyDSTool`, `XPPAUT`, or `MatCont`). Note that although Γ is a smooth curve, $h(\mu_1, \mu_2) = 0$ is not necessarily smooth at every point. For more details on birfucation curves and two-parameter bifurcations see Kuznetsov [2004].

If the extended system (10) has a saddle-node bifurcation that is the carryover of the saddle-node bifurcation of interest in the original system (9), then this bifurcation must take place on Γ as it is the set of points satisfying the conditions for a saddle-node bifurcation.

Proposition 1. *Consider the system* (9)*. Suppose* $f(x;\mu_1,\mu_2) \in C^2(\mathbb{R}\times\mathbb{R}^2,\mathbb{R})$ *with a nonhyperbolic equilibrium at the origin,* $f(0;0,0) = 0$*,* $D_x f(0;0,0) = 0$*, and satisfying the nondegeneracy condition*

$$D_{xx} f(0;0,0) \neq 0,$$

and transversality condition for either μ_1 *or* μ_2

$$D_{\mu_1} f(0;0,0) \neq 0 \quad \text{or} \quad D_{\mu_2} f(0;0,0) \neq 0,$$

i.e., the system (9) *has a saddle-node bifurcation where either* μ_1 *or* μ_2 *is the bifurcation parameter. This defines a one-dimensional smooth curve* $\Gamma \subset \mathbb{R}^3$ *in a neighbourhood of* $(x,\mu_1,\mu_2) = (0,0,0)$ *in which* f *satisfies the singularity and nondegeneracy conditions.*

Consider the extended system (10) *by transforming parameter* μ_1 *into a variable, where* $f \in C^2(\mathbb{R}^2\times\mathbb{R},\mathbb{R})$ *and* $g \in C^2(\mathbb{R}\times\mathbb{R},\mathbb{R})$*. If there is a point* $(x,\mu_1,\mu_2) = (x^*,\mu_1^*,\mu_2^*) \in \Gamma$ *such that* $g(\mu_1;\mu_2)$ *satisfies the singularity conditions*

$$g(\mu_1^*;\mu_2^*) = 0, \quad D_{\mu_1} g(\mu_1^*;\mu_2^*) = b \neq 0, \tag{15}$$

and the transversality condition

$$\det\begin{pmatrix} D_{\mu_1} f & D_{\mu_1} g \\ D_{\mu_2} f & D_{\mu_2} g \end{pmatrix} = D_{\mu_1} f D_{\mu_2} g - D_{\mu_1} g D_{\mu_2} f \neq 0, \tag{16}$$

at $(x,\mu_1,\mu_2) = (x^*,\mu_1^*,\mu_2^*)$*, then the extended system* (10) *has a saddle-node bifurcation at* $(x,\mu_1) = (x^*,\mu_1^*)$ *as* μ_2 *crosses* μ_2^**.*

Moreover, there exists a unique function $\mu_1 = \nu(\mu_2)$ *such that* $\mu_1^* = \nu(\mu_2^*)$*, and the extended system is reduced to one dimension around* (x^*,μ_1^*)

$$\dot{\xi} = f(\xi + \tfrac{a}{b}(\nu(\mu_2) - \mu_1^*) + x^*, \nu(\mu_2);\mu_2) - \tfrac{a}{b} g(\nu(\mu_2);\mu_2),$$

where $\xi = x - x^* - \frac{a}{b}(\mu_1 - \mu_1^*)$ *and* $a = D_{\mu_1} f(x^*,\mu_1^*;\mu_2^*)$*.*

Proof. Let $z = (x,\mu_1)^T$ and $F(z;\mu_2) = F(x,\mu_1;\mu_2) = (f(x,\mu_1;\mu_2), g(\mu_1;\mu_2))^T$. By definition of Γ, the singularity conditions ($f = 0$ and $D_x f = 0$), the nondegeneracy condition ($D_{xx} f \neq 0$), and one of the transversality conditions ($D_{\mu_1} f \neq 0$ or $D_{\mu_2} f \neq 0$) are satisfied at the point $(z^*,\mu_2^*) = (x^*,\mu_1^*,\mu_2^*) \in \Gamma$. Since $g(\mu_1^*;\mu_2^*) = 0$, we also have $F(x^*,\mu_1^*;\mu_2^*) = 0$ (first singularity condition for F). The Jacobian of F evaluated at z^* is

$$A = D_z F(x^*,\mu_1^*;\mu_2^*) = \begin{pmatrix} D_x f & D_{\mu_1} f \\ D_x g & D_{\mu_1} g \end{pmatrix}\Bigg|_{z=z^*} = \begin{pmatrix} 0 & a \\ 0 & b \end{pmatrix},$$

where $a = D_{\mu_1} f(x^*,\mu_1^*;\mu_2^*)$ and $b = D_{\mu_1} g(\mu_1^*;\mu_2^*) \neq 0$, by assumption (15). Since $\det(A) = 0$ and $\mathrm{tr}(A) = b \neq 0$, the eigenvalues of A are $\lambda_1 = 0$ and $\lambda_2 = b \neq 0$ with corresponding eigenvectors

$$v_{\lambda_1} = \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \quad v_{\lambda_2} = \begin{pmatrix} a \\ b \end{pmatrix}.$$

Note that condition $D_{\mu_1} g \neq 0$ is needed to guarantee only one zero eigenvalue. Thus, $D_z F$ is singular with only one zero eigenvalue (second singularity condition for F).

The diagonalization matrix P and its inverse are given by

$$P = \begin{pmatrix} 1 & a \\ 0 & b \end{pmatrix}, \quad P^{-1} = \frac{1}{b} \begin{pmatrix} b & -a \\ 0 & 1 \end{pmatrix}.$$

Let the new shifted coordinates be defined by

$$\begin{pmatrix} \xi \\ \upsilon \end{pmatrix} = P^{-1} \begin{pmatrix} x - x^* \\ \mu_1 - \mu_1^* \end{pmatrix} = \begin{pmatrix} x - x^* - \frac{a}{b}(\mu_1 - \mu_1^*) \\ \frac{1}{b}(\mu_1 - \mu_1^*) \end{pmatrix}.$$

Then the corresponding extended system is given by

$$\begin{aligned} \dot{\xi} &= f(\xi + a\upsilon + x^*, b\upsilon + \mu_1^*; \mu_2) - \tfrac{a}{b} g(b\upsilon + \mu_1^*; \mu_2^*), \\ \dot{\upsilon} &= \tfrac{1}{b} g(b\upsilon + \mu_1^*; \mu_2^*). \end{aligned}$$

Define

$$f_1(\xi, \upsilon; \mu_2) = f(\xi + a\upsilon + x^*, b\upsilon + \mu_1^*; \mu_2) - \tfrac{a}{b} g(b\upsilon + \mu_1^*; \mu_2^*), \tag{17}$$

and define $f_2(\upsilon; \mu_2)$ such that

$$\tfrac{1}{b} g(b\upsilon + \mu_1^*; \mu_2^*) = b\upsilon + f_2(\upsilon; \mu_2).$$

Then,

$$\begin{aligned} \dot{\xi} &= f_1(\xi, \upsilon; \mu_2), \\ \dot{\upsilon} &= b\upsilon + f_2(\upsilon; \mu_2). \end{aligned} \tag{18}$$

Note that the singularity conditions are satisfied by construction,

$$\begin{aligned} & f_1(0, 0; \mu_2^*) = f_2(0; \mu_2^*) = 0, \\ & D_\xi f_1(0, 0; \mu_2^*) = D_\upsilon f_1(0, 0; \mu_2^*) = D_\xi f_2(0; \mu_2^*) = D_\upsilon f_2(0; \mu_2^*) = 0. \end{aligned} \tag{19}$$

The nondegeneracy condition for f_1 is satisfied since

$$D_{\xi\xi} f_1(0, 0; \mu_2^*) = D_{xx} f(x^*, \mu_1^*; \mu_2^*)) \neq 0.$$

The transversality condition for f_1 follows from dividing the determinant in (16) by $-b \neq 0$ and the definition of f_1 (17)

$$\begin{aligned} & (\cancelto{a}{D_{\mu_1} f(x^*, \mu_1^*; \mu_2^*)} D_{\mu_2} g(\mu_1^*; \mu_2^*) - \cancelto{b}{D_{\mu_1} g(\mu_1^*; \mu_2)} D_{\mu_2} f(x^*, \mu_1^*; \mu_2^*)) \neq 0, \\ \implies & D_{\mu_2} f(x^*, \mu_1^*; \mu_2^*) - \tfrac{a}{b} D_{\mu_2} g(\mu_1^*; \mu_2^*) = D_{\mu_2} f_1(0, 0; \mu_2^*) \neq 0. \end{aligned}$$

Then, by Theorem 1 and Corollary 1, the transformed system (18) has a saddle-node bifurcation point at $(0, 0)$ as μ_2 crosses μ_2^*.

Transforming back to the variable z, we have that the extended system (10) has a saddle-node bifurcation point at (x^*, μ_1^*) as μ_2 crosses μ_2^*.

Now, denote

$$F_2(\upsilon; \mu_2) = b\upsilon + f_2(\upsilon; \mu_2) = 0.$$

Note that $D_\upsilon F_2(0; \mu_2^*) = b \neq 0$, by equation (19). By the Implicit Function Theorem 2, there is a neighbourhood of $\mu_2 = \mu_2^*$ where there exists a unique function $\upsilon = \hat{\nu}(\mu_2)$ such that $\hat{\nu}(\mu_2^*) = 0$ and $F_2(\eta(\mu_2), \mu_2) = 0$. Then, equation (18) reduces to

$$\dot{\xi} = f_1(\xi, \hat{\nu}(\mu_2); \mu_2).$$

Changing back to μ_1, we have

$$\begin{aligned} \upsilon &= \tfrac{1}{b}(\mu_1 - \mu_1^*) \\ \implies \mu_1 &= b\upsilon + \mu_1^* = b\hat{\nu}(\mu_2) + \mu_1^*. \end{aligned}$$

Define $\mu_1 = \nu(\mu_2) = b\hat{\nu}(\mu_2) + \mu_1^*$, then $\nu(\mu_2^*) = b\hat{\nu}(\mu_2^*) + \mu_1^* = \mu_1^*$. Finally, using the definition of $f_1(\xi, \nu, \mu_2)$, we have

$$\begin{aligned} \dot{\xi} &= f_1(\xi, \nu(\mu_2); \mu_2) \\ &= f_1(\xi, \tfrac{1}{b}(\nu(\mu_2) - \mu_1^*); \mu_2) \\ &= f(\xi + \tfrac{a}{b}(\nu(\mu_2) - \mu_1^*) + x^*, \nu(\mu_2); \mu_2) - \tfrac{a}{b} g(\nu(\mu_2); \mu_2) \\ &= f(\xi + \tfrac{a}{b}(\nu(\mu_2) - \mu_1^*) + x^*, \nu(\mu_2); \mu_2) - \tfrac{a}{b} g(\nu(\mu_2); \mu_2). \end{aligned}$$

□

This theorem provides a way to extend the scalar system (9) where a saddle-node occurs by transforming any parameter, μ_1 for convenience, into a variable to obtain the extended system (2) where a saddle-node bifurcation now occurs as the other parameter, μ_2, passes through some bifurcation value μ_2^*. Note that the transformed parameter, μ_1, does not need to be the original bifurcation parameter. Thus, we say that the saddle-node bifurcation in the extended system is the carryover of the saddle-node bifurcation in the original system. Also note that Proposition 1 requires that $g(\mu_1; \mu_2)$ does not depend explicitly on x. This makes the conditions of this proposition easy to verify with graphical and numerical tools.

Proposition 2. *Under the conditions of Proposition* (1), *let* $h(\mu_1, \mu_2) = 0$ *be the projection of* Γ *onto the* (μ_1, μ_2)*-plane. If* $h(\mu_1, \mu_2)$ *is differentiable at* (μ_1^*, μ_2^*)*, then conditions* (16) *and* (15) *are equivalent to*

1. $g(\mu_1; \mu_2) = 0$ *intersects* $h(\mu_1, \mu_2) = 0$ *transversally at a point* (μ_1^*, μ_2^*)*, and*

2. *the tangent line to* $g(\mu_1; \mu_2) = 0$ *at* (μ_1^*, μ_2^*) *is not parallel to the* μ_1*-axis,*

respectively.

This proposition says that in order to find the saddle-node bifurcation points for the extended system, we plot the two-parameter bifurcation diagram of the original system, superimpose the nullclines of the new equation in the extended system, and look for transverse intersections between the saddle-node bifurcation curve and the nullclines. This is enough to verify the singularity and transversality conditions in the extended system.

Proof of Proposition 2. Note that (μ_1^*, μ_2^*) satisfies $g = 0$. Now, two vectors $u, v \in \mathbb{R}^2$ are transverse (parallel) if and only if the determinant of the matrix formed by them is non-zero (is zero), i.e.,

$$det(u, v) = u_1 v_2 - v_1 u_2 = |u||v| \sin(\theta) \neq 0 \iff \theta \neq 0, \pi.$$

Recall that $h(\mu_1, \mu_2) = 0$ is defined by the projection of Γ onto the (μ_1, μ_2)-plane, given by $(x, \mu_1, \mu_2,) \mapsto (\mu_1, \mu_2)$. Since at least one of $D_{\mu_1} f$ or $D_{\mu_2} f$ is non-zero, points on Γ have a unique correspondence to points on $h(\mu_1, \mu_2) = 0$. Thus, a point (μ_1^*, μ_2^*) at which $g = 0$ and $h = 0$ intersect has a unique corresponding point $(z^*, \mu_2^*) = (x^*, \mu_1^*, \mu_2^*) \in \Gamma$.

Assume $D_{\mu_1} f \neq 0$ at $(z^*; \mu_2^*)$. Then, by the Implicit Function Theorem 2, we can parameterize Γ by μ_2 with functions $x = \mathcal{X}(\mu_2)$ and $\mu_1 = \mathcal{M}(\mu_2)$ such that $x^* = \mathcal{X}(\mu_2^*)$ and $\mu_1^* = \mathcal{M}(\mu_2^*)$ (see equation (13)). Implicit differentiation of $f(x, \mu_1; \mu_2) = 0$ with respect to μ_2 gives

$$D_x f \mathcal{X}' + D_{\mu_1} f \mathcal{M}' + D_{\mu_2} f = 0.$$

At z^*, $D_x f = 0$ and we have

$$\mathcal{M}' = -\frac{D_{\mu_2} f}{D_{\mu_1} f}.$$

Implicit differentiation of $h(\mu_1, \mu_2) = 0$ with respect to μ_2 gives

$$D_{\mu_1} h \mathcal{M}' + D_{\mu_2} h = 0.$$

Evaluating at z^*, substituting the $\mathcal{M}'$ and multiplying by $-D_{\mu_1} f$, we obtain

$$D_{\mu_1} h D_{\mu_2} f - D_{\mu_2} h D_{\mu_1} f = 0.$$

This means that vectors $(D_{\mu_1} f, D_{\mu_2} f)^T$ and $(D_{\mu_1} h, D_{\mu_2} h)^T$ are multiple of each other at z^*. Note that this is also true if $D_{\mu_1} f = 0$ since we must have $D_{\mu_2} f \neq 0$ and similar arguments follow. Thus, $(D_{\mu_1} h, D_{\mu_2} h)^T$ and $(D_{\mu_1} g, D_{\mu_2} g)^T$ are transverse if and only if $(D_{\mu_1} f, D_{\mu_2} f)^T$ and $(D_{\mu_1} g, D_{\mu_2} g)^T$ are transverse, which is equivalent to saying that the transversality condition (16) holds.

Finally, the condition that the tangent line of $g(\mu_1; \mu_2) = 0$ at (μ_1^*, μ_2^*) is not parallel to the μ_1-axis is clearly equivalent to $D_{\mu_1} g(\mu_1^*, \mu_2^*) \neq 0$. $\square$

In the previous propositions, it is possible to generalize the arguments of the new scalar field, $g(\mu_1; \mu_2)$, to include dependence on x, i.e., $g(x, \mu_1; \mu_2)$, provided Γ and $g = 0$ intersect in the (x, μ_1, μ_2)-space. However, in the case of $g(\mu_1; \mu_2)$, the conditions of Proposition 1 are easy to verify with graphical and numerical tools.

In order to illustrate the application of Propositions 1 and 2, we introduce the following examples, where we consider a one-dimensional system with two parameters, a and b,

$$\dot{x} = f(x; a, b),$$

and transform the parameter a into a variable to obtain the extended system

$$\begin{aligned}\dot{x} &= f(x, a; b),\\ \dot{a} &= g(a; b).\end{aligned}$$

Example 1. *Consider $f(x; a, b) = -a - b - x^2$. Since $D_x f = -2x = 0$ at $x = 0$, $D_{xx} f = -2 \neq 0$, and $D_a f = -1 \neq 0$, there is a saddle-node bifurcation at $x = 0$ as a crosses zero and $b = 0$. Furthermore, since $D_b f = -1 \neq 0$, b could be also taken as bifurcation parameter when $a = 0$. The bifurcation boundary is given by $h(a, b) = -a - b = 0$. Figure 2a shows the two-parameter bifurcation diagram along with the following three choices for $g(a; b)$.*

1. *If $g(a; b) = a + b$, then $g = 0$ overlaps $h = 0$ and they are never transverse. Indeed, the extended system does not have a saddle-node bifurcation since it always has a unique steady state at $(x, a) = (0, -b)$, for all values of b.*

2. *If $g(a; b) = -a + b$, then $g = 0$ intersects $h = 0$ transversally at $(a, b) = (0, 0)$. According to Proposition 2, the extended system has a saddle-node bifurcation at $(x, a) = (0, 0)$ as b crosses $b = 0$. Indeed, there are two steady states, $(x, a) = (\pm\sqrt{-2b}, b)$ when $b < 0$, and they collide and disappear as b becomes positive. Figure 2b shows the bifurcation diagram for the extended system.*

3. *If $g(a; b) = a^2 - b$, then $g = 0$ intersects $h = 0$ transversally at $(a, b) = (0, 0)$ and $(a, b) = (-1, 1)$, but the tangent line of $g(a; b) = 0$ at $(a, b) = (0, 0)$ is parallel to the a-axis. Proposition 2 guarantees the saddle-node bifurcation at $(x, a, b) = (0, -1, 1)$, but not at $(x, a, b) = (0, 0, 0)$. In fact, at $(x, a, b) = (0, 0, 0)$, there is a Bogdanov-Takens (double-zero) bifurcation (see Section 8.4 in Kuznetsov [2004]), since $D_a g = 0$ implies that there are two zero eigenvalues. When $b = 0$, there is a single steady state at $(x, a) = (0, 0)$. When $0 < b < 1$, two steady states emerge from the origin, a stable node $(x, a) = (\sqrt{\sqrt{b} - b}, -\sqrt{b})$, and saddle $(x, a) = (-\sqrt{\sqrt{b} - b}, -\sqrt{b})$. When $b = 1$ there is a saddle-node bifurcation at $(x, a) = (0, -1)$ as the two steady states collide and $D_a g \neq 0$. Figure 2c shows the bifurcation diagram for the extended system.*

Example 2. *Consider $f(x; a, b) = b^2 + 1 - a - x^2$. Since $D_x f = -2x = 0$ at $x = 0$, $D_{xx} f = -1 \neq 0$, and $D_a f = -1 \neq 0$, there is a saddle-node bifurcation at $x = 0$ as a crosses 1 and $b = 0$. However, since $D_b f = 2b = 0$ at $b = 0$, there is no saddle-node bifurcation at $(x, a, b) = (0, 1, 0)$ if b is taken as bifurcation parameter. The bifurcation boundary is given by $h(a, b) = b^2 + 1 - a = 0$. Figure 3a shows the two-parameter bifurcation diagram along with the following three choices for $g(b; a)$. Moreover, there is a saddle-node bifurcation at $x = 0$ as a crosses $b^2 + 1$, for fixed b.*

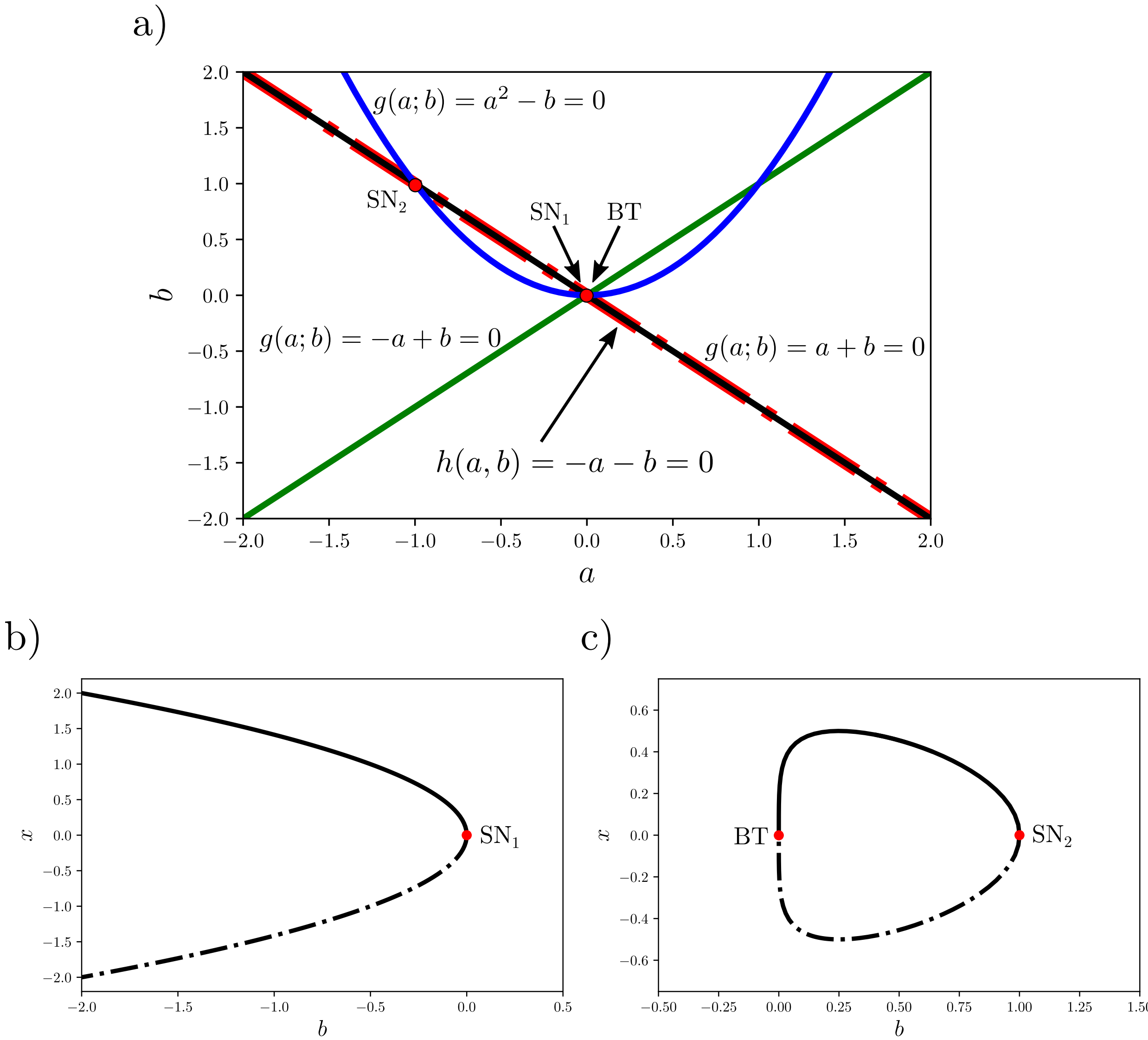

Figure 2: Bifurcation diagrams for Example 1 where $f(x;a,b) = -a - b - x^2$. a) Two-parameter bifurcation boundary (red dash-dotted line) for f with a and b as bifurcation parameters, and nullclines for three choices of $g(a;b)$: $g(a;b) = a + b$ (black) nullcline is never transverse; $g(a;b) = -a + b$ (green) nullcline is transverse at $(a,b) = (0,0)$; and $g(a;b) = a^2 + b$ (blue) nullcline is transverse at $(a,b) = (-1,1)$ and $(a,b) = (0,0)$ but $D_a g(0;0) = 0$. b) Bifurcation diagram when $g(a;b) = -a + b$. A saddle-node bifurcation (SN_1) occurs at $(x,a,b) = (0,0,0)$. c) Bifurcation diagram when $g(a;b) = a^2 - b$. A saddle-node bifurcation (SN_2) occurs at $(x,a,b) = (0,1,1)$ and a Bogdanov-Takens (double-zero) bifurcation (BT) occurs at $(x,a,b) = (0,0,0)$.

1. *If $g(a;b) = -a + 2$, then $g = 0$ intersects $h = 0$ transversally twice, at $(a, b) = (2, \pm 1)$. Thus, by Proposition 2, the extended system undergoes two saddle-node bifurcations at $(x, a) = (0, 2)$, one as b crosses $b = -1$ from the left where the two steady states, $(x, a) = (\pm\sqrt{b^2 - 1}, 2)$, collide and disappear, and one as b crosses $b = 1$ from the left where the two steady states, $(x, a) = (\pm\sqrt{b^2 - 1}, 2)$, emerge. Figure 3b shows the bifurcation diagram for the extended system.*

2. *If $g(a;b) = -a + 1$, then $g = 0$ is tangential to $h = 0$ at $(a, b) = (1, 0)$. No saddle-node bifurcation occurs since the two steady states $(x, a) = (\pm\sqrt{b^2}, 1) = (\pm|b|, 1)$ collide and bounce back, as seen in Figure 3c. In fact, at $(x, a, b) = (0, 1, 0)$, the extended system satisfies the singularity conditions ($\lambda = 0, -1$) and nondegeneracy condition ($D_{xx}f = -2 \neq 0$), but not the transversality condition ($D_a f D_b g - D_a g D_b f = -2b|_{b=0} = 0$). Note that this is not a transcritical bifurcation since the steady states $(|b|, 1)$ and $(-|b|, 1)$ are a stable node (two negative eigenvalues) and a saddle point (eigenvalues with opposite sign), respectively, for all b. In other words, they do not exchange stability when they collide, instead they touch and bounce back preserving their stability.*

3. *If $g(a;b) = b - a + 1$, then $g(a;b) = 0$ is transverse at $(a, b) = (1, 0)$ and $(a, b) = (2, 1)$. Moreover, the tangent line to $g(a, b) = 0$ at $(1, 0)$ and $(2, 1)$ is not parallel to the a-axis since $D_a g(a;b) = -1$. Thus, as in the first case ($g(a;b) = -a + 2$), two saddle-node bifurcations occur, one as b crosses $b = 0$ from the left where two steady states $(x, a) = (\pm\sqrt{b(b-1)}, b + 1)$ collide and disappear, and one as b crosses $b = 1$ where two steady states $(x, a) = (\pm\sqrt{b(b-1)}, b + 1)$ emerge. Figure 3d shows the bifurcation diagram for the extended system. This case is interesting because at $(a, b) = (1, 0)$, the transversality condition is not satisfied for the original system with respect to b, i.e., $D_b f(0; 1, 0) = 0$. In other words, even if b is not a bifurcation parameter in the original system at (x^*, μ^*), b becomes a bifurcation parameter in the extended system at the same point.*

4. *If we extend the parameter b instead using $\dot{b} = g(b;a) = b - a + 1$, it follows from the previous case that two saddle-node bifurcations occur at $(x, a, b) = (0, 1, 0)$ and $(x, a, b) = (0, 2, 1)$, as seen in Figure 3e. However, note that b is not a bifurcation parameter in the original system at $(x, a, b) = (0, 1, 0)$ yet transforming b into a variable there is a carryover of the saddle-node bifurcation that occurs in the original system with a as bifurcation parameter.*

Propositions 1 and 2 will be used in Section 4 in the analysis of the first biological application, namely the gene activation model (3).

3 n-dimensional case

In the previous section, we showed the carryover of a saddle-node bifurcation in the one-dimensional case. In this section, we show that this result also holds in the n-dimensional case. In short, this is true because the saddle-node bifurcations can be reduced to one-dimension around the bifurcation point.

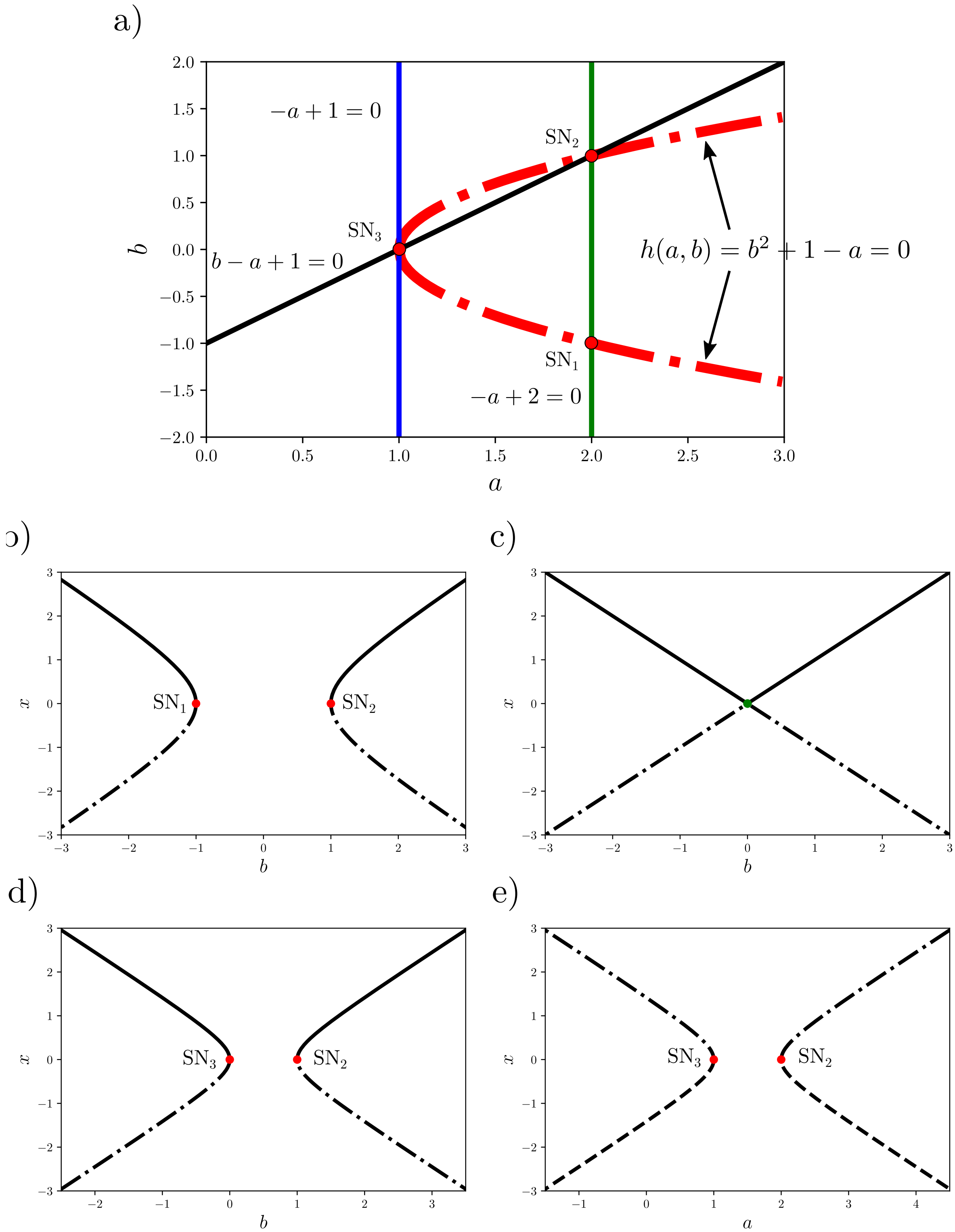

Figure 3: Bifurcation diagrams for Example 2 where $f(x;a,b) = b^2 + 1 - a - x^2$. a) Two-parameter bifurcation boundary (red dash-dotted curve) for f with a and b as

(continued)

Figure 3: bifurcation parameters, and nullclines for three choices of $g(a;b)$: $g(a;b) = -a+2$ (green) nullcline is transverse at $(a,b) = (2,-1)$ and $(a,b) = (2,1)$; $g(a;b) = -a+1$ (blue) is tangential at $(a,b) = (1,0)$; and $g(a;b) = b-a+1$ (black) nullcline is transverse at $(a,b) = (1,0)$ and $(a,b) = (2,1)$. b) Bifurcation diagram when $g(a;b) = -a+2$. Two saddle-node bifurcations occur at $(x,a,b) = (0,2,\pm 1)$. c) Bifurcation diagram when $g(a;b) = -a+1$. No bifurcation occurs because the steady states collide but do not disappear. d) Bifurcation diagram when $g(a;b) = b-a+1$. Two saddle-node bifurcations occur at $(x,a,b) = (0,1,0)$ and $(x,a,b) = (0,1,1)$. e) Bifurcation diagram when $\dot{b} = g(a;b) = b-a+1$. Two saddle-node bifurcations occur at $(x,a,b) = (0,1,0)$ and $(x,a,b) = (0,2,1)$.

Suppose that f in the original system (1) satisfies the conditions of Theorem 1. Then we can reduce the system to one-dimensional form

$$\dot{x} = f_1(x, \eta(x;\mu_1,\mu_2);\mu_1,\mu_2),$$

where functions $f_1(x,y;\mu_1,\mu_2)$ and $y = \eta(x;\mu_1,\mu_2)$ are given by the theorem, in a neighbourhood of $(x,y,\mu) = (0,0,0)$ in regards to the saddle-node bifurcation. Now, suppose that f_1 satisfies the transversality condition of Corollary 1 for either μ_1 or μ_2. Then, in a similar fashion as in the one-dimensional case, the Implicit Function Theorem 2 guarantees the existence of an interval I and unique functions $\mathcal{X}$ and $\mathcal{M}$ such x and μ_1 can be parameterized in terms of μ_2 (for example), i.e.,

$$x = \mathcal{X}(\mu_2), \mu_1 = \mathcal{M}(\mu_2), \mu_2 \in I, \quad \text{and} \quad \mathcal{X}(0) = 0, \mathcal{M}(0) = 0.$$

This defines the smooth one-dimensional bifurcation curve

$$\Gamma = \{(z,\mu_1,\mu_2)\colon z = (x,y) = (\mathcal{X}(\mu_2), \eta(\mathcal{X}(\mu_2);\mathcal{M}(\mu_2),\mu_2)), \\ \mu_1 = \mathcal{M}(\mu_2), \mu_2 \in I\}. \quad (20)$$

To extend Γ in this case, we take a point in Γ, different from $(x,y,\mu) = (0,0,0)$, and apply again Theorem 1 (after some appropriate translation) followed by the Implicit Function Theorem 2 as shown above. Note that functions f_1, $\mathcal{X}$, and $\mathcal{M}$ do not need to be the same as before. By continuity we can apply this process repetitive times and further extend Γ as long as the transversality condition holds for either μ_1 and μ_2 at each step. Finally, the bifurcation boundary, $h(\mu_1,\mu_2) = 0$, is defined by the projection of extended Γ onto the (μ_1,μ_2)-plane, given by $\pi(z,\mu_1,\mu_2) \mapsto (\mu_1,\mu_2)$. Thus, the definition of Γ and $h(\mu_1,\mu_2) = 0$ is similar to the one-dimensional case.

Proposition 3. *Let $f(z;\mu_1,\mu_2) \in C^2(\mathbb{R}^n \times \mathbb{R}^2, \mathbb{R}^n)$ and suppose that the hypotheses of Theorem 1 are satisfied at $(z,\mu_1,\mu_2) = (0,0,0)$. Suppose also that the transversality condition in Corollary 1 is satisfied for either μ_1 or μ_2. Let $m(\mu_1,\mu_2)$ be the extremal value defined in Theorem 1. This defines a one-dimensional smooth curve $\Gamma \subset \mathbb{R}^{n+2}$ in a neighbourhood of (z,μ_1,μ_2) that satisfies the singularity and nondegeneracy conditions.*

Consider the extended system (2) by transforming parameter μ_1 into a variable, where $f \in C^2(\mathbb{R}^{n+1} \times \mathbb{R}, \mathbb{R}^n)$ and $g \in C^2(\mathbb{R} \times \mathbb{R}, \mathbb{R})$. If there is a point $(z, \mu_1, \mu_2) = (z^*, \mu_1^*, \mu_2^*) \in \Gamma$ such that $g(\mu_1; \mu_2)$ satisfies

$$g(\mu_1^*; \mu_2^*) = 0, \quad b = D_{\mu_1} g(\mu_1^*; \mu_2^*) \neq 0, \tag{21}$$

and the transversality condition

$$\det \begin{pmatrix} D_{\mu_1} m & D_{\mu_1} g \\ D_{\mu_2} m & D_{\mu_2} g \end{pmatrix} = D_{\mu_1} h D_{\mu_2} g - D_{\mu_1} g D_{\mu_2} h \neq 0, \tag{22}$$

is satisfied at $(z, \mu_1, \mu_2) = (z^*, \mu_1^*, \mu_2^*)$, then (2) has a saddle-node bifurcation at $(z, \mu_1) = (z^*, \mu_1^*)$ as μ_2 crosses μ_2^*.

Proof. First, we translate the point z^* to the origin using a new variable $\zeta = z - z^*$ to obtain the translated system

$$\dot{\zeta} = f(\zeta + z^*; \mu_1, \mu_2),$$

that satisfies all the conditions of Theorem 1 at $\zeta = 0$. By Theorem 1, we choose new translated coordinates $x \in \mathbb{R}$ and $y \in \mathbb{R}^{n-1}$ such that

$$\begin{aligned} \dot{x} &= f_1(x, y; \mu_1, \mu_2), \\ \dot{y} &= My + f_2(x, y; \mu_1, \mu_2), \end{aligned}$$

where $f_1 = 0$, $f_2 = 0$, $D_x f_1 = 0$, $D_x f_2 = 0$, $D_y f_1 = 0$, $D_y f_2 = 0$, and $D_{xx} f_1 \neq 0$ at $(x, y; \mu_1, \mu_2) = (0, 0; \mu_1^*, \mu_2^*)$, and M is invertible. Moreover, there is an interval $I(\mu_1, \mu_2)$ of 0 and function $y = \eta(x; \mu_1, \mu_2)$ where the extremal value

$$m(\mu_1, \mu_2) = \mathrm{Ext}_{x \in I(\mu_1, \mu_2)} [f_1(x, \eta(x; \mu_1, \mu_2); \mu_1, \mu_2)]$$

is defined. Therefore, the system is reduced to one equation

$$\dot{x} = f_3(x; \mu_1, \mu_2) = f_1(x, \eta(x; \mu_1, \mu_2); \mu_1, \mu_2)$$

in a neighborhood of $(\zeta, \mu_1, \mu_2) = (0, \mu_1^*, \mu_2^*)$ where the singularity and nondegeneracy conditions are satisfied. Then, the extended system (2) can be reduced to

$$\begin{aligned} \dot{x} &= f_3(x, \mu_1; \mu_2) = f_1(x, \eta(x; \mu_1, \mu_2); \mu_1, \mu_2), \\ \dot{\mu}_1 &= g(\mu_1; \mu_2), \end{aligned}$$

in a neighborhood of $(\zeta, \mu_1, \mu_2) = (0, \mu_1^*, \mu_2^*)$. By assumption, the transversality condition, $D_{\mu_i} f_1 \neq 0$, is satisfied for either μ_1 or μ_2. Then, by Proposition 1, this system has a saddle-node bifurcation at $(x, \mu_1) = (0, \mu_1^*)$ as μ_2 crosses μ_2^*. It follows that the extended system (2) has a saddle-node bifurcation at $(z, \mu_1) = (0, \mu_1^*)$ as μ_2 crosses μ_2^*. $\square$

As we might expect, Proposition 2 also applies to the n-dimensional case. The proof follows similar arguments to the one-dimensional case.

Proposition 4. *Under the conditions of Proposition 3, let* $h(\mu_1, \mu_2) = 0$ *be the projection of* Γ *onto the* (μ_1, μ_2)*-plane. If* $h(\mu_1, \mu_2)$ *is differentiable at* (μ_1^*, μ_2^*)*, then conditions* (22) *and* (21) *are equivalent to:*

1. $g(\mu_1; \hat{\mu}, \nu) = 0$ *intersects* $h(\mu_1, \mu_2) = 0$ *transversally at a point* (μ_1^*, μ_2^*)*, and*
2. *the tangent line to* $g(\mu_1; \mu_2) = 0$ *at* (μ_1^*, μ_2^*) *is not parallel to the* μ_1*-axis,*

respectively.

Example 3. *Consider the system*

$$\begin{aligned} \dot{x} &= \mu - x^2 + xy - xy^2, \\ \dot{y} &= \lambda - y - x^2 + x^2 y, \end{aligned}$$

taken from Meiss [2007, p. 292]. There is a saddle-node bifurcation at the origin as μ *crosses zero. The two-parameter bifurcation diagram starting from this bifurcation point is shown in Figure 4a. Now, consider the extended system*

$$\begin{aligned} \dot{x} &= \mu - x^2 + xy - xy^2, \\ \dot{y} &= \lambda - y - x^2 + x^2 y, \\ \dot{\mu} &= g(\mu; \lambda) = \mu - \tfrac{1}{2}. \end{aligned}$$

The μ*-nullcline is transverse to the two-parameter bifurcation diagram in two points near* $\lambda = 0.5$ *and* $\lambda = 1.1$ *(see Figure 4a). Since the tangent line of* $g(\mu; \lambda)$ *is not parallel to the* μ*-axis at neither intersection, two saddle-node bifurcations are inherited with* λ *as bifurcation parameter. Indeed, the bifurcation diagrams for* x *and* y *are shown in Figures 4b and 4c, respectively. The corresponding bifurcation points are found to be*

$$\begin{aligned} (x, u, \mu; \lambda) &\approx (-0.6792, 0.0604, 0.5; 0.4940), \\ (x, u, \mu; \lambda) &\approx (-0.8429, 1.2069, 0.5; 1.0599). \end{aligned}$$

4 Applications

In this section we apply Propositions 1 and 2 to the the gene activation model (3), and Proposition 4 to the cell cycle regulatory model (4).

4.1 Gen activation

Consider the gene activation model (3), where

$$f(x; r, s) = s - rx + \frac{x^2}{1 + x^2}.$$

This model is characterized by the existence of a switch activation of the gene via saddle-node bifurcation as s increases from zero for $r < \frac{1}{2}$ (see Figures 5a–b). With initial condition $x(0) = 0$, increasing s would drive a critical transition that brings the activity of gene x to

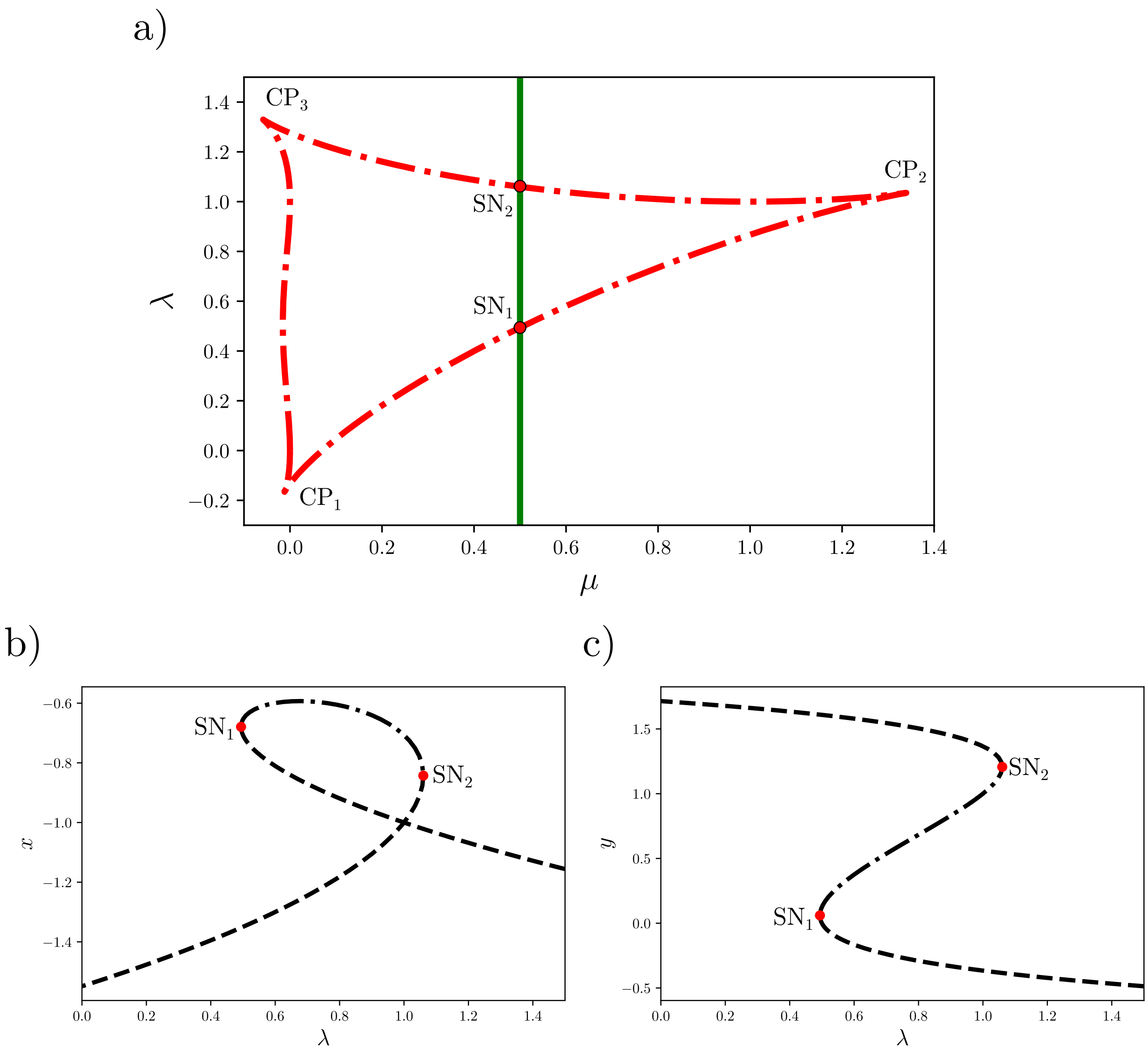

Figure 4: Bifurcation diagrams for Example 3. a) Two-parameter bifurcation boundary (red dashed-dotted curve) and nullcline for $g(\mu; \lambda) = \mu - \frac{1}{2}$ (green). Two saddle-node bifurcations (SN_1 and SN_2) occur at the transverse intersection between the g-nullcline and the bifurcation boundary. Note that there are cups bifurcations (CP_1, CP_2, and CP_3) associated with the system at the intersection of two saddle-node bifurcations. b-c) Bifurcation diagrams for the extended system with λ as bifurcation parameter and variables x and y in the ordinate, respectively. The dashed lines indicate the unstable node with associated three-dimensional unstable manifold, while the dot-dashed lines indicate the saddle-node with associated one-dimensional stable manifold and two-dimensional unstable manifold.

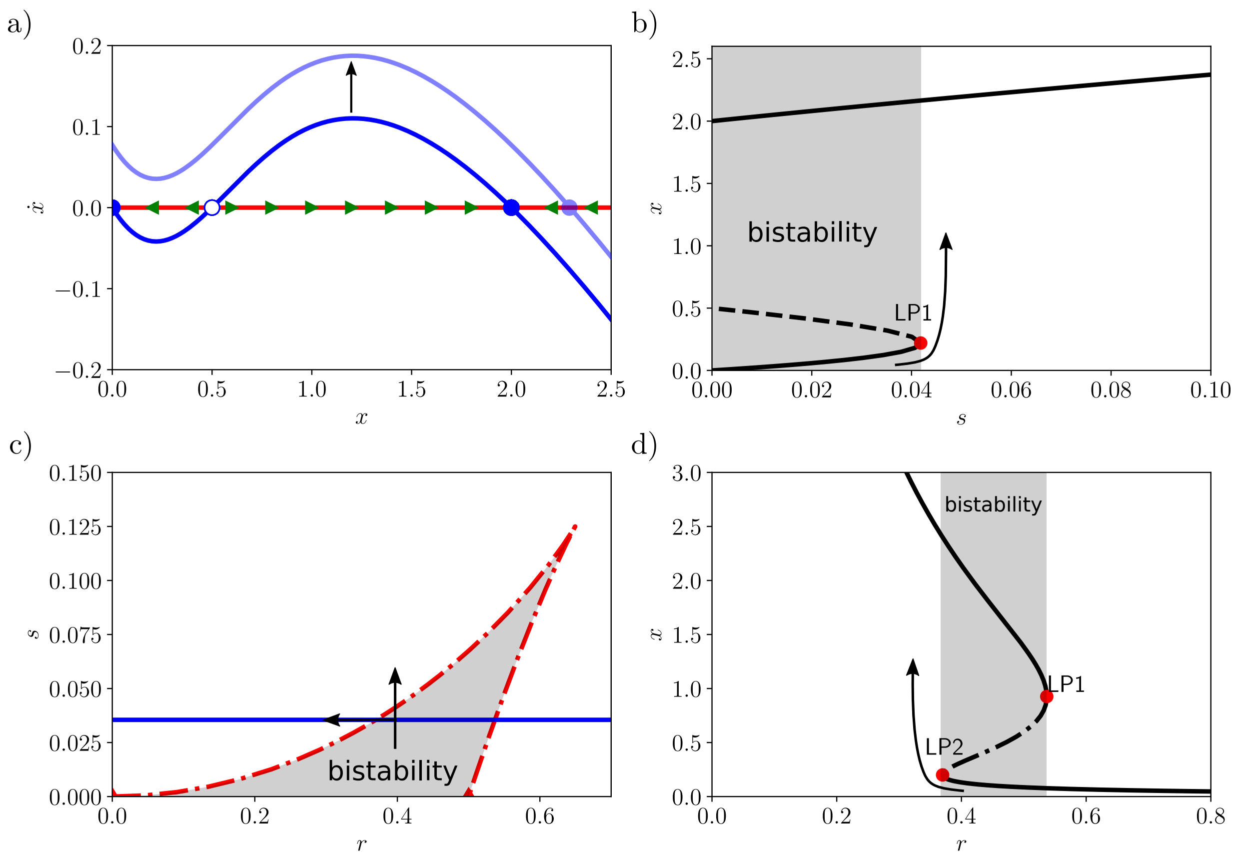

Figure 5: a) Phase plot of (3) for $r = 0.4$ and $s = 0$ (solid) and $s = 0.06$ (transparent). The critical transition occurs when s increases and the left and middle equilibria collide and disappear at $s^* \approx 0.0418$, forcing gene activity to the remaining (stable) equilibria to the right. b) Bifurcation diagram of the original system (3) for s. The arrow indicates gen activation and the bifurcation point is labeled as LP1. c) Two-parameter bifurcation diagram of (3) with r and s ans bifurcation parameters. A vertical cross section at $r = 0.4$ corresponds to b) and the vertical arrow matches that in b). The bifurcation boundary (red curve) is the continuation of the point LP1 in b) projected onto the rs-plane. The point in the upper right corner corresponds to $x = \sqrt{3}/3$ (nondegeneracy condition not met) where a cusp bifurcation occurs. The blue horizontal line is the nullcline $g = 0$ of the extended system, which intersects transversally the bifurcation boundary and Proposition 2 applies. d) Bifurcation diagram for the extended system (3) and (24). Switch gene activation is possible if r is decreased below the bifurcation value and the corresponding bifurcation point is labeled as LP2. The arrow matches the horizontal arrow in Figure c).

a high value, thus activating the gene. However, if the value of s is decreased, the activity of the gene remains in the active mode. For $r = 0.4$ the bifurcation occurs at $s^* \approx 0.0418$.

For this simple application, we can compute all conditions satisfying Theorem 1 and Corollary 1. From the singularity conditions, $f = 0$ and $D_x f = 0$, we obtain a parametrization of r and s in terms of $0 < x \leq 1$,

$$r = \frac{2x}{(1+x^2)^2}, \quad s = \frac{x^2(1-x^2)}{(1+x^2)^2}.$$

The nondegeneracy condition requires

$$D_{xx}f = \frac{2(1-3x^2)}{(1+x^2)^3} \neq 0 \implies x \neq \frac{\sqrt{3}}{3},$$

but the transversality conditions, $D_s f = 1 \neq$ and $D_r f = -x \neq 0$, do not impose extra conditions. Thus, the bifurcation curve is given by

$$\Gamma = \left\{ (x, r, s) : r = \frac{2x}{(1+x^2)^2}, s = \frac{x^2(1-x^2)}{(1+x^2)^2}, x \in (0, 1] \right\}, \tag{23}$$

and there is a saddle-node bifurcation at any $(x, a, b) \in \Gamma$ except for $x \neq \frac{\sqrt{3}}{3}$. In Figure 5c, we show the projection of Γ (bifurcation boundary) onto the rs-plane. Here we see that the bifurcation boundary separates the parameter space into three regions which differ on the number and position of equilibria, and that the switch activation of the gene via s corresponds to crossing the upper bifurcation boundary from below.

Now consider transforming s into a variable with linear synthesis and degradation terms

$$\dot{s} = g(s; r) = a - bs. \tag{24}$$

where $a, b > 0$. Note that the signal s goes to a stable equilibrium $s = c = \frac{a}{b}$. If $c = \frac{6}{169} \approx 0.0355 < s^* \approx 0.0418$, starting from $x(0) = 0$ and $s(0) = 0$ initial conditions the gene would not become active since the trajectory always remains within the bistability region (see Figure 5c). Would it be possible to activate the gene by varying the inactivation rate r? Note that the point $(x, s, r) = (\frac{1}{5}, \frac{6}{169}, \frac{125}{338})$ belongs to Γ and satisfies the singularity conditions (15), $g = 0$ and $D_r g = -b \neq 0$; and transversality condition (16),

$$\det \begin{pmatrix} D_r f & D_r g \\ D_s f & D_s g \end{pmatrix} = \begin{pmatrix} -x & -a \\ 1 & 0 \end{pmatrix} = a \neq 0.$$

Thus, by Proposition 1, there is a saddle node-bifurcation at $r^* = \frac{125}{338} \approx 0.3698$ as r decreases from 0.4. In fact, this point was found by substituting $x = 0.2$ into (23).

We can also apply Proposition 2 to the two-parameter bifurcation Figure 5c, where we observe that the nullcline $g = 0$ crosses transversally the bifurcation boundary and the nullcline is not tangential to the s-axis at the intersection. Note that in this figure it is clear that the switch activation occurs in both the original and the extended systems as the corresponding bifurcation parameter crosses the upper bifurcation boundary from the bistability region. This can be verified from the bifurcation diagram of the extended system as shown in Figure 5d. Therefore, the saddle-node bifurcation associated with the switch gene activation driven by r in the extended system is the carryover of the saddle-node bifurcation associated with the switch gene activation driven by s in the original system.

4.2 Cell cycle start

Consider the cell cycle model (4) where $z = (Y, P, A)$. This basic model is characterized by a saddle-node bifurcation driven by m and associated with the start of start of the cell cycle, as illustrated in Figure 6a. The lower stable equilibrium is associated with the G1 phase since the concentration of Y is low. If m remains lower that approximately $m^* \approx 0.8$, the cell remains in G1 checkpoint as the concentration of Y need to increase for cell cycle progression. As m increases beyond the bifurcation value $m*$, the lower equilibrium is lost, allowing for the concentration of Y to increase abruptly and the start of the cell cycle. It can be shown that this bifurcation is in fact a saddle-node loop bifurcation and the details of this can be found in Segel and Edelstein-Keshet [2013], but for the purpose of this paper we focus on the local saddle-node bifurcation.

We now consider including the dynamics of the slow parameter m by transforming it into a variable following logistic growth

$$\frac{dm}{dt} = \mu m \left(1 - \frac{m}{K}\right), \tag{25}$$

where μ is the growth rate, and K is the carrying capacity. If K is larger than the bifurcation value ($m^* \approx 0.8$), then the start of the cell cycle occurs naturally as m increases dynamically beyond m^*. We are interested in G1 checkpoint activation driven by k_{5p} as it is known that Polo-like kinase 1 (Plk1) plays a role in Cdc20 activation and has potential in cancer treatment [Hansen et al., 2004, Liu et al., 2017]. That is, we are interested in the carryover of the saddle-node bifurcation to the extended system with k_{5p} as the bifurcation parameter. Note that, as opposed to the previous application, computing the bifurcation the curve Γ in this example is considerably more complicated, therefore we study the potential carryover of saddle-node bifurcation graphically by Proposition 4.

The two-parameter bifurcation diagram (using m and k_{5p} as bifurcation parameters) for the original system (4) is shown in Figure 6b. The start of the cell cycle is seen here as crossing the lower portion of the bifurcation boundary from the G1 region to the right. With the addition of equation (25), the nullcline $g = 0$ appears at $m = K$. If $K = 2$, for example, there is a saddle-node bifurcation for $k_{5p} \approx 0.025$ as the intersection between the nullcline and the bifurcation boundary is tangential and not parallel to the m-axis, and Proposition 4 applies. Thus, we can increase k_{5p} beyond the intersection value (possibly with Plk1 treatment) to enter the G1 region and activate the G1 checkpoint, and allow it to drop down (possibly by natural degradation) in order to resume the cell cycle. However, if $K = 3$, G1 checkpoint activation would not be possible by modifying k_{5p} as the saddle-node bifurcation is lost beyond $m \approx 2.6$ in a cusp bifurcation. The bifurcations diagram of the extended system with respect to k_{5p} is shown in Figure 6c showing the appearance of a stable equilibria associated with the G1 checkpoint where the concentration of Y is low.

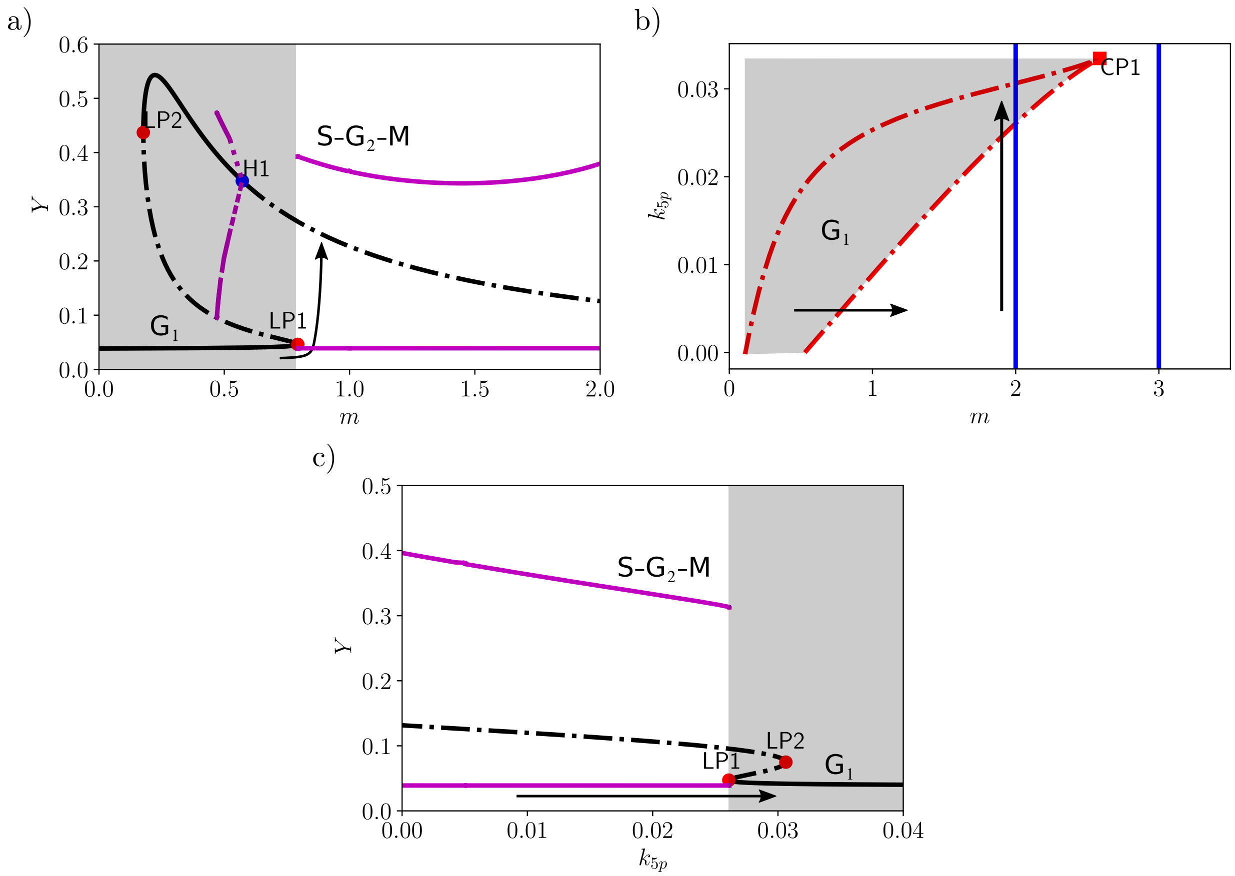

Figure 6: a) Bifurcation diagram for the original system (4) with m as bifurcation parameter. The arrow indicates the transition from G1 to S-G2-M at the *start* of the cell cycle when the cell mass increases and the stable equilibria of low Y concentration disappears via a saddle-node bifurcation (labeled LP1). In the S-G2-M region, a limit cycle appears (globally, LP1 is a saddle-node loop bifurcation), indicated in pink by maximum and minimum concentration of Y, in which the concentration of Y increases and decreases (the decrease in Y concentration defines the *finish* of the cell cycle). b) Two-parameter bifurcation diagram for original system (4) with m and k_{5p} as bifurcation parameters. The horizontal arrow matches that in a) indicating the start of the cell cycle, and the red curve is the continuation of the saddle-node loop bifurcation (LP1 in a)) which collides with the other saddle-node bifurcation (LP2 in a)) in a cusp bifurcation (labeled CP1). The nullcline $m = K$ of (25), indicated in blue for $K = 2$ and $K = 3$, crosses transversally the bifurcation curve and Proposition 4 applies. c) Bifurcation diagram for extended system (4) and (25) with k_{5p} as bifurcation parameter. The arrow indicating G1 checkpoint activation matches the vertical arrow in b).

5 Discussion

Here we studied the carryover of a saddle-node bifurcation, which consists on preserving the existence of a saddle-node bifurcation present in a original system to an extended system with one extra equation obtained by transforming a bifurcation parameter into a variable. Our focus was restricted to the case where there are two parameters of interest and the vector field of the new equation does not depend on the variables already present in the original system. We showed that additional singularity and transversality conditions in the extended system are sufficient for the carryover of a saddle-node bifurcation on top of the necessary singularity, non-degeneracy, and transversality conditions in the original system. We provided a graphical approach to verify such conditions using numerical continuation software, such as *AUTO*, *XPP*, *MatCont*, and *PyDSTool*.

We provided a proof of our statement first for the one dimensional case in Proposition 1, which was later used to proof the n-dimensional case in Proposition 3. Our proofs are based on the application of the Implicit Function Theorem 2 to follow the bifurcation curve, and the Saddle Node Bifurcation Theorem 1 to either verify the conditions for a saddle-node bifurcation in the one dimensional case or to reduce the system to one dimension at the saddle-node bifurcation for the n-dimensional case. Equivalent graphical results for the one-dimensional and n-dimensional cases are given in Propositions 2 and 4, respectively. These graphical results provide a practical numerical tool to study all the points where a carryover is possible based on a two-parameter bifurcation diagram and the nullclines of the new vector field.

It is irrelevant which of the two parameters (or both) satisfies the transversality condition for the original system, we only need to start from a saddle-node bifurcation point and follow the bifurcation along the bifurcation curve. In fact, the bifurcation curve can be continued as long as the transversality condition is satisfied for at least one of the parameters. Interestingly, a carryover can happen at a point where either the transformed variable or the remaining parameter is a bifurcation parameter in the original system. These cases were illustrated with examples in the text. It is still left to show that a carryover can happen at a point where the bifurcation happens as both μ_1 and μ_2 change simultaneously (but not individually) or when k parameters change simultaneously.

The case where the new differential equation depends on the other variables, i.e., $\dot{\mu}_1 = g(z, \mu_1; \mu_2)$ in equation (2), is not covered here. Assuming the bifurcation curve and the μ_1-nullcline intersect in $\mathbb{R}^{n+2}$, an extra condition (or conditions) would be required to guarantee that the matrix A, as defined within the proof of Proposition (1), is invertible. We leave this case open for future research. We also leave open the interesting exploration of the carryover of other types of bifurcation (transcritical, pitchfork, Hopf, etc).

We complemented this paper with two applications in mathematical biology in which the carryover of a saddle-node bifurcation is of interest. The first application is the one-dimensional gene activation model, in which we are able to show the carryover of a saddle-node bifurcation both theoretically and numerically. The second application is a model for the cell cycle progression, in which we are only able to show the carryover numerically. In practice, the study of bifurcations in limited to numerical software, thus our graphical approach becomes a powerful tool to study the carryover of a saddle-node bifurcation in applications.

The problem of the carryover of a saddle-node bifurcation was motivated by our results in Chapter 2, where we found an interesting, yet unclear, relationship between the $\text{SNIC}_{\text{Mass}}$ bifurcation and the $\text{SNIC}_{V_{c2}}$ bifurcation. In fact, studying Figure (Figure in Chapter 2) motivated us to conjecture Proposition 4, which indeed applies to conclude that the $\text{SNIC}_{V_{c2}}$ (locally, saddle-node) bifurcation is the carryover of the $\text{SNIC}_{\text{Mass}}$ (locally, saddle-node) bifurcation after transforming $Mass$ into a variable. Inaddition to clarifying the true origin of the SNICV_{c2} bifurcation, our results from this chapter are used in the next chapter. For instance, in Contreras [2020, Chapter 5], the author apply the carryover of a saddle-node bifurcation (globally a saddle-node on a invariant circle (SNIC) bifurcation in that application) to show that the G2 checkpoint of the cell cycle can be activated by ionizing radiation. G2 checkpoint activation by radiation was identified, but not fully understood, in Contreras et al. [2019], and is now explained by the carryover conceptualization.

The carryover of bifurcations is a novel concept that contributes to the analysis, building, and development of models. The main idea is to guarantee that a bifurcation that exists in a model still exists after we include more dynamics into the model and extend it. We chose the word *carryover* to express the fact that the bifurcation can also be transferred to a new parameter that was not originally the bifurcation parameter, but other choices include *persistence*, *extension* and *continuation*.

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