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Switching in Mass Action Networks Based on Linear Inequalities*

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Abstract. Many biochemical processes can successfully be described by dynamical systems allowing some form of switching when, depending on their initial conditions, solutions of the dynamical system end up in different regions of state space (associated with different biochemical functions). Switching is often realized by a bistable system (i.e., a dynamical system allowing two stable steady state solutions) and, in the majority of cases, bistability is established numerically. In our view, this approach is too restrictive. On the one hand, due to predominant parameter uncertainty, numerical methods are generally difficult to apply to realistic models originating in systems biology. On the other hand, switching already arises with the occurrence of a saddle-type steady state (characterized by a Jacobian where exactly one eigenvalue is positive and the remaining eigenvalues have negative real part). Consequently we derive conditions based on linear inequalities that allow the analytic computation of states and parameters where the Jacobian derived from a mass action network has a defective zero eigenvalue so that—under certain genericity conditions—a saddle-node bifurcation occurs. Our conditions are applicable to general mass action networks involving at least one conservation relation; however, they are only sufficient (as infeasibility of linear inequalities does not exclude defective zero eigenvalues).

Key words. switching, bistability, saddle-node bifurcation, qualitative matrix theory, L^+-matrix

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1. Introduction.

Many biochemical processes can successfully be described by dynamical systems allowing some form of switching, where, depending on, for example, initial conditions, solutions of the dynamical system end up in different regions of state space (associated with different biochemical functions). Often dynamical systems admitting bistability (i.e., the existence of two stable steady states) are used for this purpose. There is a long tradition of establishing bistability, both experimentally and computationally, in areas ranging from signal transduction (see, e.g., [2]) to the cell cycle (see, e.g., [6]).

From our point of view, however, bistability is too strong a requirement, as already a saddle-type steady state with just one algebraically simple positive eigenvalue and all other eigenvalues having negative real part gives rise to the desired switching behavior (with the global stable manifold of the saddle as a switching surface; see [19, Remark 3.2]). The approach presented here tries to directly establish such points and is hence capable of establishing switching that is not necessarily associated with bistability. Therefore we expect this approach to be of particular interest for researchers working in systems biology and other areas of quantitative biology.

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In many applications, bistability of a dynamical system has been established numerically using bifurcation analysis or simulations that can become arduous tasks even for relatively small systems. Moreover, parameter uncertainty is a predominant issue in systems biology: the dynamical systems consist of a large number of states and parameters, while measurement data are often very noisy, and data points and repetitions are usually few. Hence techniques allowing the direct analytic computation of parameter vectors at which a given system exhibits switching are desirable.

In developing these techniques we identified two promising approaches: (i) establishing multiple steady states as a mechanism for possible switching and bistability [9, 11, 12, 19] and (ii) establishing points where the dynamical system undergoes a saddle-node bifurcation so that the global stable manifold of the saddle is acting as a switching surface. The first approach is motivated by the so-called chemical reaction network theory developed by Feinberg and coworkers (see [16, 17, 18] and [12, 19, 20]). The second approach is based on the structure of the Jacobian of a mass action network [10]. This approach was successful for a double-phosphorylation mechanism where the nullspace of the Jacobian admits a very special representation (cf. [10]).

Here we extend these ideas to mass action networks in general (involving at least one conservation relation) by making use of a property that is frequently observed in dynamical systems originating in systems biology: one often faces dynamical systems that involve so-called *conservation relations* confining trajectories to affine linear subspaces of state space.

Thus, the Jacobian of such a system evaluated at an arbitrary point in state space has at least as many zero eigenvalues as there are conservation relations. Consequently, for a saddle-node to occur at a particular point in state space, the Jacobian has to have an *additional* zero eigenvalue at that point. Generically, mass action systems undergo a bifurcation at that point—one can state conditions guaranteeing a saddle-node bifurcation (cf. Appendix A or [10]). One can expect that such sufficient conditions for a saddle-node bifurcation can be established for mass action networks originating in systems biology since there are many parameters which can be chosen as continuation parameters. Hence, such an additional zero eigenvalue frequently entails a saddle-node bifurcation and thus switching in a mass action network.

The main result of our paper offers sufficient conditions guaranteeing such an additional zero eigenvalue, which take the form of linear inequality systems and are thus easy to check. Moreover, our result is constructive in the sense that the solutions to one of the inequality systems determine a state and parameter vector where the Jacobian has an additional zero eigenvalue and thus fulfills the necessary degeneracy condition for a saddle-node. Infeasibility of all inequality systems does not exclude additional zero eigenvalues; hence feasibility of at least one inequality system is a sufficient, but not a necessary, condition for an additional zero eigenvalue. In case the remaining eigenvalues of the linearization have negative real parts such feasibility is generically sufficient for a saddle-node and the associated bifurcation into a saddle and a node. We verify this splitting in our case studies by computing bifurcation diagrams.

Finally we'd like to point out that our results are in a certain sense complementary to those obtained in [27], [13, 14, 15], [29], [3, 4, 5]: all these references present sufficient conditions for the global injectivity of a dynamical system defined by a biochemical reaction network

(not necessarily restricted to mass action systems). In particular, these conditions exclude switching. More along the lines of our work is the approach of Mincheva and coworkers [24, 25]. There the tight connection between the characteristic polynomial of the Jacobian and the cycles of certain graphs associated with the Jacobian are exploited to derive conditions for certain instabilities (e.g., saddle-node or Hopf bifurcations). The major difference between our work and theirs is that we are not working with the characteristic polynomial but rather exploit the fact (reported in [10]) that Jordan blocks of size ≥ 2 imply additional zero eigenvalues (and thus candidates for, for example, saddle-node bifurcations).

In the following we briefly describe the organization of the paper and at the same time offer conclusions that can be drawn. In section 2 we describe dynamical systems defined by mass action networks, recall some results from [10], and *characterize* positive state vectors where the Jacobian has such an additional and thus defective zero eigenvalue (Lemma 2.1, Theorem 2.4). Those state vectors arise from elements of a semialgebraic set that contains only polynomials of degree two or less—regardless of the exponents in the polynomial ODE system defined by a mass action network. In section 3, based on a result from qualitative matrix theory ensuring the existence of positive null vectors, we present a sufficient condition allowing the computation of elements of that semialgebraic set that takes the form of linear inequality systems. The solvability of these inequality systems is then sufficient for the existence of an additional zero eigenvalue (Theorem 3.2). In section 4, finally, we demonstrate the applicability of the results presented here by analyzing as a proof of principle two competing mass action networks describing the G1/S transition in the cell cycle of budding yeast. These networks were originally presented in [12] and [19] where the investigation was based on subnetwork analysis. Both networks are not accessible using the results of [10].

For the convenience of the reader we provide some additional information in four appendices. In Appendix A we recall some remarks concerning saddle-node bifurcations in mass action networks that were made earlier in [10]; in Appendices B and C we collect the relevant structural information of the G1/S transition networks discussed in section 4. The final Appendix D, using basic linear algebra, discusses some of the assumptions and results in the present work.

2. Dynamical systems defined by mass action systems. To introduce our notation, we use the network depicted in (2.1) below. This network is analyzed in [16], where multiple steady states are established.

$$
\begin{aligned}
&A + 2\,S \underset{\mathbf{k_2}}{\overset{\mathbf{k_1}}{\rightleftharpoons}} A\,S_2\\
&B + S \underset{\mathbf{k_4}}{\overset{\mathbf{k_3}}{\rightleftharpoons}} B\,S\\
&A\,S_2 + B\,S \xrightarrow{\mathbf{k_5}} C + 3\,S\\
&A \underset{\mathbf{k_7}}{\overset{\mathbf{k_6}}{\rightleftharpoons}} 0 \underset{\mathbf{k_9}}{\overset{\mathbf{k_8}}{\rightleftharpoons}} B\\
&\qquad\quad \mathbf{k_{10}}\uparrow\\
&\qquad\quad C
\end{aligned}
\tag{2.1}
$$

Network (2.1) consists of n *species* ($n = 6$), and with each species we associate a variable x_i representing its concentration and the corresponding unit vector e_i of $\mathbb{R}^6$: x_1 and e_1 with A, x_2 and e_2 with B, x_3 and e_3 with S, x_4 and e_4 with $A\,S_2$, x_5 and e_5 with $B\,S$, and x_6 and e_6 with C.

The nodes of the network graph are called *complexes*, and with each complex we associate the sum of its constituent species. The above network contains m complexes ($m = 10$). The complex 0 will be denoted by the zero vector $0 \in \mathbb{R}^6$ and is used to encode that the system is open with respect to A, B, and C: A and B can enter and leave the system, while C can only leave the system. As a complex, A is associated with $e_1 \in \mathbb{R}^6$, B with e_2, C with e_6, $A + 2\,S$ with $e_1 + 2\,e_3$, $A\,S_2$ with e_4, $B + S$ with $e_2 + e_3$, $B\,S$ with e_5, $A\,S_2 + B\,S$ with $e_4 + e_5$, and $C + 3\,S$ with $e_6 + 3\,e_3$.

The network consists of r reactions ($r = 10$), e.g., $A + 2\,S \to A\,S_2$, where the complex at the tail of the arrow is called the *educt complex* and the complex at the tip of the arrow is called the *product complex*. With each reaction is associated a *reaction rate* $v_i(k, x)$. For mass action systems $v_i(k, x)$ is proportional to the product of (powers of) concentrations of the species forming the educt complexes: let y_i be an educt complex vector; then one has $v_i(k, x) = k_i\, x^{y_i}$ (where $x^p = \prod_j x_j^{p_j}$ for n-vectors x and p). For the above network one obtains

$$v(k, x) = (\, k_1 x_1 x_3^2,\, k_2 x_4,\, k_3 x_2 x_3,\, k_4 x_5,\, k_5 x_4 x_5,\, k_6 x_1,\, k_7,\, k_8,\, k_9 x_2,\, k_{10} x_6\,)^T\,.$$

We collect the exponents y_i of the monomials contained in $v_i(k, x)$ in the *rate-exponent matrix* $\mathcal{Y}$. For the above network one obtains the $(n \times r)$-matrix

$$\begin{aligned}\mathcal{Y} &= [y_1, \ldots, y_{10}] \\ &= \left[e_1 + 2\,e_3,\, e_4,\, e_2 + e_3,\, e_5,\, e_4 + e_5,\, e_1,\, 0,\, 0,\, e_2,\, e_6\right]\,.\end{aligned}$$

The reactions are encoded in the *stoichiometric matrix* S, where each column corresponds to one reaction and is defined as the difference between product and educt complex. For example, for the reaction $A + 2\,S \to A\,S_2$ one obtains $r_1 = -(e_1 + 2\,e_3) + e_4$. The stoichiometric matrix for the above network is

$$S = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 & 0 & 0 & 1 & -1 & 0 \\ -2 & 2 & -1 & 1 & 3 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & -1 \end{bmatrix}.$$

A reaction network then defines a dynamical system

$$\dot{x} = S\, v(k, x), \tag{2.2}$$

which in case of the above network translates to

$$\begin{aligned}
\dot{x}_1 &= \quad k_7 - k_6x_1 - k_1x_1x_3^2 + k_2x_4\,,\\
\dot{x}_2 &= \quad k_8 - k_9x_2 - k_3x_2x_3 + k_4x_5\,,\\
\dot{x}_3 &= -k_3x_2x_3 - 2k_1x_1x_3^2 + 2k_2x_4 + k_4x_5 + 3k_5x_4x_5\,,\\
\dot{x}_4 &= \quad k_1x_1x_3^2 - k_2x_4 - k_5x_4x_5\,,\\
\dot{x}_5 &= \quad k_3x_2x_3 - k_4x_5 - k_5x_4x_5\,,\\
\dot{x}_6 &= \quad k_5x_4x_5 - k_{10}x_6\,.
\end{aligned}$$

In general we consider a mass action network with n species, m complexes, and r reactions. Any such system defines a dynamical system in the form given in (2.2). Note that $v(k,x) \in \mathbb{R}^r$ is a *monomial, vector-valued* function of the form

$$v(k,x) = \operatorname{diag}(k)\,\phi(x),$$

where $\operatorname{diag}(k)$ is a $(r\times r)$ diagonal matrix with the k_i on the diagonal and $\phi(x) = (x^{y_i})_{i=1,\dots,r} \in \mathbb{R}^r$ is a vector of monomials in x. Note that the rate-exponent matrix $\mathcal{Y}$ defined above contains the exponent vectors of the monomials contained in $\phi(x)$. In what follows, we speak of steady states (k,x) of (2.2) when $S\,v(k,x)$ vanishes for positive (k,x).

For many realistic systems in systems biology the matrix $S \in \mathbb{R}^{n\times r}$ does not have full row rank $s := \operatorname{rank}(S)$ (i.e., $s < n$). This gives rise to $n - s$ conservation relations: let Z be any matrix whose columns form a basis of $\ker(S^T)$, the left kernel of S. Solutions $x(t)$ to (2.2) then satisfy

$$Z^T x(t) = Z^T x(0) =: c\,; \tag{2.3a}$$

that is, these solutions lie in invariant domains $x(0) + \operatorname{im}(S)$ that are parallel translates of $\operatorname{im}(S)$. For the above example (2.1) one obtains

$$x_3 + 2x_4 + x_5 = c\,. \tag{2.3b}$$

2.1. The Jacobian associated with a mass action network. In the remainder of this contribution we will use the following notation to denote positivity/nonnegativity of vectors $v \in \mathbb{R}^n$: $v > 0$ and $v \geq 0$ are interpreted componentwise; that is, $v > 0$ is understood as $v_i > 0$, $i = 1,\dots,n$, while $v \geq 0$ is understood as $v_i \geq 0$, $i = 1,\dots,n$. We also use $\mathbb{R}^n_{>0}$ to denote the interior of the nonnegative orthant $\mathbb{R}^n_{\geq 0}$.

At positive (k,x) the Jacobian of a mass action network (by this we mean the Jacobian of a dynamical system defined by a mass action network) is given by

$$Jac(k,x) = S\,\operatorname{diag}\left(v(k,x)\right)\,\mathcal{Y}^T\,\operatorname{diag}\left(x^{-1}\right), \tag{2.4}$$

with stoichiometric matrix S and rate-exponent matrix $\mathcal{Y}$.

Observe that a positive pair (k,x) is a steady state of (2.2) if and only if $v(k,x) \in \ker(S) \cap \mathbb{R}^r_{>0}$. For computational purposes we resort to the pointed polyhedral cone $\ker(S) \cap \mathbb{R}^r_{\geq 0}$ that is generated by a finite set of unique (up to scalar multiplication) extreme rays [26]. (The

calculation of these rays is in general computationally hard; however, there exist a variety of algorithms and software tools, for example [22, 30].) Let p be the number of extreme rays, and let E be a matrix whose columns are generators of $\ker(S) \cap \mathbb{R}^r_{\geq 0}$. Then (k, x) is a positive steady state if and only if there exists a ν with

$$v(k,x) = E\,\nu > 0, \quad \nu \in \mathbb{R}^p_{\geq 0}\,. \tag{2.5a}$$

So we ask for all components of $E\,\nu$ to be (strictly) positive. We collect all such ν in the set

$$\mathcal{V} := \left\{ \nu \in \mathbb{R}^p_{\geq 0} | E\,\nu > 0 \right\}. \tag{2.5b}$$

Since E is a nonnegative matrix, $\mathcal{V}$ consists of the positive orthant $\mathbb{R}^p_{>0}$, i.e., the interior of $\mathbb{R}^p_{\geq 0}$, and potentially certain faces of $\mathbb{R}^p_{\geq 0}$ (i.e., elements $\nu \in \mathcal{V}$ are either positive or nonnegative with predefined sign pattern).

As we are interested in the Jacobian $Jac(k, x)$ evaluated at a positive steady state, we use (2.5a) in (2.4) to obtain

$$Jac(k,x) \equiv J(\nu,x) = N(\nu)\ \mathrm{diag}\left(x^{-1}\right), \quad (\nu,x) \in \mathcal{V} \times \mathbb{R}^n_{>0}\,, \tag{2.5c}$$

with the ν-linear

$$N(\nu) := S\ \mathrm{diag}\,(E\,\nu)\ \mathcal{Y}^T \in \mathbb{R}^{n\times n}, \quad (\nu,x) \in \mathcal{V} \times \mathbb{R}^n_{>0}\,. \tag{2.5d}$$

We'd like to emphasize that points $(\nu, x) \in \mathcal{V} \times \mathbb{R}^n_{>0}$ define points $(k, x) \in \mathbb{R}^r_{>0} \times \mathbb{R}^n_{>0}$ via

$$k = \mathrm{diag}\left(\phi\left(x^{-1}\right)\right)\ E\,\nu\,. \tag{2.6}$$

Hence finding points (ν, x) where $J(\nu, x)$ is singular is equivalent to finding points (k, x) where the Jacobian $Jac(k, x)$ is singular. Null vectors of $Jac(k, x) = J(\nu, x)$ of the form $\mathrm{diag}\,(x)\,z$ will be obtained from the identity

$$J(\nu,x)\,\mathrm{diag}(x)\,z \;=\; N(\nu)\,z \;=\; H(z)\,\nu = 0\,, \quad \nu \in \mathcal{V}\,, \tag{2.7a}$$

with the z-linear

$$H(z) \;:=\; S\,\mathrm{diag}\left(\mathcal{Y}^T z\right) E \;\in\; \mathbb{R}^{n\times p}\,. \tag{2.7b}$$

Our goal in (2.7a) is to use a condition from qualitative matrix theory that entails the existence of a positive null vector ν for the matrix $H(z)$ (cf. Theorem 3.2).

Example 1 ($J(\nu, x)$ derived from network (2.1)). *The generator matrix of* $\ker(S) \cap \mathbb{R}^r_{\geq 0}$ *is given by*

$$E = \begin{bmatrix} 1 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \tag{2.8a}$$

and hence satisfies

$$E\,\nu > 0 \Leftrightarrow \nu > 0 \quad \textit{and thus } \mathcal{V} \equiv \mathbb{R}^5_{>0}. \tag{2.8b}$$

The matrix $J(\nu, x)$ *is given by*

$$J(\nu,x) = \begin{bmatrix} -\frac{\nu_1+\nu_3+\nu_5}{x_1} & 0 & -\frac{2(\nu_1+\nu_5)}{x_3} & \frac{\nu_1}{x_4} & 0 & 0 \\ 0 & -\frac{\nu_2+\nu_4+\nu_5}{x_2} & -\frac{\nu_2+\nu_5}{x_3} & 0 & \frac{\nu_2}{x_5} & 0 \\ -\frac{2(\nu_1+\nu_5)}{x_1} & -\frac{\nu_2+\nu_5}{x_2} & -\frac{4\nu_1+\nu_2+5\nu_5}{x_3} & \frac{2\nu_1+3\nu_5}{x_4} & \frac{\nu_2+3\nu_5}{x_5} & 0 \\ \frac{\nu_1+\nu_5}{x_1} & 0 & \frac{2(\nu_1+\nu_5)}{x_3} & -\frac{\nu_1+\nu_5}{x_4} & -\frac{\nu_5}{x_5} & 0 \\ 0 & \frac{\nu_2+\nu_5}{x_2} & \frac{\nu_2+\nu_5}{x_3} & -\frac{\nu_5}{x_4} & -\frac{\nu_2+\nu_5}{x_5} & 0 \\ 0 & 0 & 0 & \frac{\nu_5}{x_4} & \frac{\nu_5}{x_5} & -\frac{\nu_5}{x_6} \end{bmatrix}.$$

2.2. Zero eigenvalues of the Jacobian of a mass action system. We assume $s = \operatorname{rank}(S) < n$ so that the Jacobian always has $n - s$ zero eigenvalues. In addition we assume

$$\operatorname{im}(S) \;=\; \operatorname{im}(J(\nu,x))\,. \tag{2.9}$$

In other terms, we assume that the columns of the matrix Z from (2.3a) form a basis for $\ker\left(J^T(\nu,x)\right)$ so that $J(\nu,x)$ does not possess more conservation laws than S. In the end, we will have to validate this condition (2.9) (cf. Appendices D.1 and D.3).

In looking for bifurcations, we reduce the system to the affine subspaces $x(0) + \operatorname{im}(S)$. To this end let U, W be orthonormal bases of $\operatorname{im}(S)$, $\operatorname{im}(S)^\perp$, respectively, and introduce

$$\xi = U^T x, \quad \eta = W^T x, \quad \text{and} \quad x(\xi,\eta) = U\,\xi + W\,\eta \tag{2.10a}$$

to obtain the reduced system

$$\dot{\xi} = U^T S\, v\,(k, x(\xi,\eta)) =: g\,(\xi,\eta,k)\,, \tag{2.10b}$$

$$\dot{\eta} = 0. \tag{2.10c}$$

Then the upper left block of the Jacobian of this mass action network is given by

$$D_\xi\, g(\xi,\eta,k) = U^T\, Jac(k, x(\xi,\eta))\, U$$

and at $(\nu, x) \in \mathcal{V} \times \mathbb{R}^n_{>0}$ by

$$G(\xi,\eta,\nu) = U^T\, J(\nu, x(\xi,\eta))\, U \;\in \mathbb{R}^{s\times s}\,, \tag{2.11}$$

where we recall the relation (2.6) between k, ν, and x. In [10] we presented a method that links zero eigenvalues of $G(\xi,\eta,\nu)$ to zero eigenvalues of $J(\nu, x(\xi,\eta))$. Lemma 2.1 below is required for Theorem 2.4, the main result of this section. We state it here without proof; for a proof, see [10].

We start with some notation and, as in [31], call an eigenvalue λ of a matrix $A \in \mathbb{R}^{n\times n}$ *defective* if its *algebraic multiplicity* $m_{alg}(\lambda)$ is greater than its *geometric multiplicity* $m_{geo}(\lambda)$, that is, if the multiplicity of λ as a root of the characteristic polynomial is greater than the

number of linear independent eigenvectors corresponding to λ. Hence, $\lambda_0 = 0$ is a defective eigenvalue of A if and only if $\dim(\ker(A)+\mathrm{im}(A))$ is less n. This can be stated in the following way.

Fact 1. *$\lambda_0 = 0$ is a defective eigenvalue of a matrix $A \in \mathbb{R}^{n\times n}$ if and only if there exists an $x \neq 0$ with $x \in \mathrm{im}\,(A) \cap \ker\,(A)$.*

Remark 1. *An alternative argument for Fact 1 is based on the Jordan canonical form of a matrix A (cf., for example, [31]). Assume an $n \times n$ matrix A with eigenvalue $\lambda_0 = 0$ and $m_{alg}(\lambda_0) > m_{geo}(\lambda_0)$ in Jordan canonical form. Then the $m_{alg} \times m_{alg}$ block matrix corresponding to λ_0 is not the zero-matrix, implying the existence of nontrivial $u_1 \neq u_2$ with $A\,u_1 = 0$ and $A\,u_2 = u_1$ and hence $u_1 \in \ker(A) \cap \mathrm{im}(A)$.*

We recall another fact from Lemma 1 in [10], as follows.

Lemma 2.1. *Let $A \in \mathbb{R}^{n\times n}$ be a matrix of rank $s < n$, and let U be an orthonormal basis for $\mathrm{im}\,(A)$. Then $\lambda_0 = 0$ is a defective eigenvalue of A if and only if $\lambda_0 = 0$ is an eigenvalue of $B_1 := U^T\,A\,U \in \mathbb{R}^{s\times s}$.*

Based on Fact 1 and Lemma 2.1, one is led to the following observation.

Lemma 2.2. *Let Z_0 be a basis of $\mathrm{im}\,(S)^\perp$. Then the Jacobian $G(\xi,\eta,\nu)$ of the reduced system, evaluated at $\nu \in \mathcal{V}$ and $x = U\,\xi + W\,\eta \in \mathbb{R}^n_{>0}$ (cf. (2.11) and (2.10a)), has a zero eigenvalue if and only if there exist a nontrivial vector $z \in \mathbb{R}^n$, a vector $x \in \mathbb{R}^n_{>0}$, and a vector $\nu \in \mathcal{V}$ with*

$$H(z)\,\nu = 0, \tag{2.12a}$$

$$Z_0^T\ \mathrm{diag}(x)\,z = 0. \tag{2.12b}$$

In what follows, we take for Z_0 the matrix Z describing the conservation laws (cf. (2.3a)).

Proof. From Lemma 2.1 it follows that $G(\xi,\eta,\nu)$ has $\lambda_0 = 0$ as an eigenvalue if and only if $J(\nu,x)$ has $\lambda_0 = 0$ as a defective eigenvalue. From Fact 1 it follows that $J(\nu,x)$ has a defective eigenvalue if and only if there is a nontrivial vector $\tilde{z} \in \ker\,(S) \cap \mathrm{im}\,(S)$. That is, $\tilde{z}$ must satisfy $N(\nu)\ \mathrm{diag}\left(\frac{1}{x}\right)\ \tilde{z} = 0$ and $Z^T\,\tilde{z} = 0$ (cf. (2.5c) and (2.9)). Let $\tilde{z} = \mathrm{diag}\,(x)\ z$; then (2.12a) and (2.12b) follow. ∎

First we consider condition (2.12b) and establish necessary and sufficient conditions for the existence of solutions $(x,\,z) \in \mathbb{R}^n_{>0} \times \mathbb{R}^n$, where we assume that z is given.

Lemma 2.3. *Let $M \in R^{q_1\times q_2}$ be any matrix, and let $z \in \mathbb{R}^{q_1}$ be given. Then there exists a positive vector $x \in \mathbb{R}^{q_1}_{>0}$ such that*

$$M^T\ \mathrm{diag}(x)\,z = 0$$

if and only if

$$\exists \omega \in \ker\left(M^T\right) \quad \textit{with } \mathrm{sign}(\omega) = \mathrm{sign}(z). \tag{2.13}$$

In this case $x = (x)_{i=1,\ldots,q_1}$ is given by

$$x_i = \begin{cases} \frac{\omega_i}{z_i} & \textit{if } z_i \neq 0, \\ \bar{x}_i > 0 \textit{ arbitrary} & \textit{if } z_i = 0. \end{cases} \tag{2.14}$$

Proof. Assume that $M^T \operatorname{diag}(x)\, z = 0$ holds for positive x and some z. Then $\omega := \operatorname{diag}(x)\, z \in \ker(M^T)$ and $\operatorname{sign}(\omega) = \operatorname{sign}(z)$ follows from positivity of x. Conversely, let $z \in \mathbb{R}$ and $\omega \in \ker(M^T)$ with $\operatorname{sign}(\omega) = \operatorname{sign}(z)$ be given. Let x be as in (2.14). Then $\operatorname{sign}(\omega) = \operatorname{sign}(z)$ implies positivity of x, and one has $\operatorname{diag}(x)\, z = \omega \in \ker(M^T)$. ∎

Remark 2. *Observe that, given a vector z, the condition* (2.13) *takes the form of linear inequalities: one has to establish feasibility of the system*

$$M^T \omega = 0, \quad \operatorname{sign}(z_i)\, \omega_i > 0 \text{ if } z_i \neq 0, \quad \text{and} \quad \omega_i = 0 \text{ if } z_i = 0.$$

Remark 3 (connection to [10]). *The condition* (2.12a) *requires the* symbolic computation *of* $\ker(H(\nu))$. *This can be of forbidding complexity, especially for large networks, even though it is in principle possible.*

So far, the only application of the simple fact in Lemma 2.1 that we are aware of was in [10]. *There we analyzed a mass action network describing the double phosphorylation of a protein. For this network we obtained a symbolic representation of* $\ker(N(\nu))$ *that could be brought into a ν-independent form. In general, the previous approach requires positive solutions to some well-defined polynomial equations in ν and is thus limited to certain classes of systems (cf.* [9]*).*

In what follows, we employ the structure of $H(z)$, given by (2.7b), when discussing $H(z)\,\nu = 0$. Let the columns of $S_0 \in \mathbb{R}^{r\times(r-s)}$ be a basis of $\ker(S)$, and let $S_\# \in \mathbb{R}^{r\times r}$ be a matrix such that $S_\# S_0 = \left[\begin{smallmatrix} I_{r-s} \\ \mathbf{0}_{s\times(r-s)} \end{smallmatrix}\right]$. If we let the columns of S_c be a basis for $\operatorname{im}(S^T)$ and if we denote the Moore–Penrose inverse $(S_0^T S_0)^{-1} S_0^T$ by $S_0^\#$, we will consider a particular such $S_\#$ by setting $S_\#^{part} = \left[\begin{smallmatrix} S_0^\# \\ S_c^T \end{smallmatrix}\right]$.

Equation (2.12a) is now equivalent to

$$S_0\, \alpha \;=\; \operatorname{diag}\left(\mathcal{Y}^T z\right)\, E\, \nu \tag{2.15}$$

for some vector $\alpha \in \mathbb{R}^{r-s}$ and, by left multiplication with $S_\#^{part}$, to

$$\begin{bmatrix} \alpha \\ 0 \end{bmatrix} = \begin{bmatrix} P(z) \\ Q(z) \end{bmatrix} \nu \quad \text{with} \quad \begin{bmatrix} P(z) \\ Q(z) \end{bmatrix} := S_\#^{part} \operatorname{diag}\left(\mathcal{Y}^T z\right) E\,. \tag{2.16}$$

Observe that z and ν satisfy $H(z)\,\nu = 0$ (cf. (2.7a) and (2.7b)) if and only if one has

$$Q(z)\,\nu = 0, \quad \nu \in \mathcal{V}\,. \tag{2.17}$$

The corresponding α will be given by $P(z)\nu$. We note that the elements of the matrices $P(z)$ and $Q(z)$ are linear forms in z. Appendix D.2 shows that the condition (2.17) is independent from the chosen bases for $\ker(S)$ and $\operatorname{im}(S^T)$.

Theorem 2.4. *The Jacobian $G(\xi,\eta,\nu)$ of the reduced system, evaluated at ξ and η with $x = x(\xi,\eta) \in \mathbb{R}^n_{>0}$ as in* (2.10a) *and $\nu \in \mathcal{V}$, has zero as an eigenvalue with algebraic multiplicity ≥ 1 if and only if there exist $z \in \mathbb{R}^n$, $\omega \in \mathbb{R}^n$, and $\mu \in \mathbb{R}^p_{\geq 0}$ with*

$$Q(z)\mu = 0, \quad E\mu > 0, \quad Z^T\omega = 0, \quad \operatorname{sign}(\omega) = \operatorname{sign}(z)\,. \tag{2.18}$$

Proof. With the settings $\omega = \mathrm{diag}(x)z$ as in (2.14), $x = U\xi + W\eta$ as in (2.10a), and $\nu = \mu$, Theorem 2.4 follows immediately from the Lemmas 2.2 and 2.3 and the equivalence of $H(z)\nu = 0$ with (2.17). ∎

Remark 4 (open condition (2.16)). *Observe that $Q(z)\,\mu = 0$ in (2.18) can also be written in the form $\tilde{Q}(\mu)\,z = 0$ since $N(\mu)z = H(z)\mu$ (cf. (2.7a) with (2.5d) and (2.7b)) implies the equivalence of (2.16) and*

$$\text{(2.19)} \qquad \begin{bmatrix} \alpha \\ 0 \end{bmatrix} = \begin{bmatrix} \tilde{P}(\mu) \\ \tilde{Q}(\mu) \end{bmatrix} z \quad \textit{with} \quad \begin{bmatrix} \tilde{P}(\mu) \\ \tilde{Q}(\mu) \end{bmatrix} := S_{\#}^{part}\,\mathrm{diag}\,(E\,\mu)\,\mathcal{Y}^T.$$

This reformulation reveals that (2.16) is an open condition: Given a particular solution $(\tilde{z}, \tilde{\omega}, \tilde{\mu})$, there will exist a solution (z, ω, μ) for all μ's that are sufficiently close to $\tilde{\mu}$. So, there is some freedom in the choice of μ; cf. Appendix D.3.

Note that the semialgebraic set given by (2.18) is always defined by polynomials of degree two or less, independent of the exponents in the polynomial ODEs. Any element gives rise to a defective eigenvalue 0 of the Jacobian $Jac(k, x)$. For the computation of elements of that set we will later on employ the following observation: in case the vector μ in (2.18) can be chosen as a positive null vector of $Q(z)$, the condition $E\mu > 0$ is automatically satisfied. Thus we arrive at a sufficient condition for a defective eigenvalue 0 of the Jacobian $Jac(k, x)$ by imposing conditions on the matrix $Q(z)$ that imply the existence of a positive null vector μ and conditions on the vector z ensuring the sign-compatibility of z with $\ker(Z^T)$.

Since the elements of $Q(z)$ derived from a mass action network are always linear forms in z, one can determine all sign patterns that $\mathrm{sign}\,(Q(z))$ can admit by analyzing the corresponding inequality systems. The idea is to look for sign patterns guaranteeing that *every matrix* with that sign pattern has a *positive* kernel vector. To this end we resort in subsection 3.2 to *qualitative matrix theory* [7] and to *L^+-matrices* in particular [23]. We first exemplify our approach by examining (2.18) for network (2.1) and turn to the general case in section 3.2.

3. Conditions for a singular reduced Jacobian G.

3.1. System (2.18) for network (2.1). Note that for network (2.1) the matrix E of (2.8a) is also a basis for $\ker(S)$ (in general this need not be the case). Using this E, we obtain for (2.16) (where gray indicates rows belonging to $Q(z)$)

$$\begin{bmatrix} z_4 & 0 & 0 & 0 & 0 \\ 0 & z_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -z_6 \\ 0 & 0 & 0 & z_2 & 0 \\ 0 & 0 & 0 & 0 & z_6 \\ \hline z_1 + 2z_3 - z_4 & 0 & 0 & 0 & z_1 + 2z_3 - z_6 \\ 0 & z_2 + z_3 - z_5 & 0 & 0 & z_2 + z_3 - z_6 \\ 0 & 0 & 0 & 0 & z_4 + z_5 - z_6 \\ 0 & 0 & z_1 & 0 & z_6 \\ 0 & 0 & 0 & -z_2 & -z_6 \end{bmatrix} \nu = \begin{bmatrix} \alpha_1 \\ \vdots \\ \alpha_5 \\ \hline 0 \\ \vdots \\ 0 \end{bmatrix}.$$

Table 1
Vectors $\tilde{z}$, $\tilde{\omega}$, and x.

	1	2	3	4	5	6
$\tilde{z}$	4	1	-5	-8	3	-5
$\tilde{\omega}$	1	1	-3	-1	5	-1
x	$\frac{1}{4}$	1	$\frac{3}{5}$	$\frac{1}{8}$	$\frac{5}{3}$	$\frac{1}{5}$

One has $s = 5$ and $r = 10$; hence the matrix $Q(z)$ is defined by rows 6–10. However, it is easy to see that $v \in \mathcal{V}$ (and hence positive ν by (2.8b)) exist only if $z_6 = z_4 + z_5$. Hence $Q(z)$ consists only of the rows 6, 7, 9, and 10, as row 8 evaluated at $z_6 = z_4 + z_5$ is identically zero. One obtains

$$Q(z) = \begin{bmatrix} z_1 + 2z_3 - z_4 & 0 & 0 & 0 & z_1 + 2z_3 - z_4 - z_5 \\ 0 & z_2 + z_3 - z_5 & 0 & 0 & z_2 + z_3 - z_4 - z_5 \\ 0 & 0 & z_1 & 0 & z_4 + z_5 \\ 0 & 0 & 0 & -z_2 & -z_4 - z_5 \end{bmatrix}.$$

For this $Q(z)$ one has positive ν if and only if the following pairs of linear forms are either of opposite sign or both equal to zero:

$$\begin{aligned} \ell_1(z) &:= z_1 + 2z_3 - z_4 \quad \text{and} \quad \ell_2(z) := z_1 + 2z_3 - z_4 - z_5, \\ \ell_3(z) &:= z_2 + z_3 - z_5 \quad \text{and} \quad \ell_4(z) := z_2 + z_3 - z_4 - z_5, \\ \ell_5(z) &:= z_1 \quad \text{and} \quad \ell_6(z) := z_4 + z_5, \\ \ell_7(z) &:= -z_2 \quad \text{and} \quad \ell_8(z) := -z_4 - z_5. \end{aligned} \tag{3.1}$$

These conditions can be expressed as *linear inequality systems*, for example,

$$\begin{aligned} z_1 + 2z_3 - z_4 > 0,\ z_1 + 2z_3 - z_4 - z_5 < 0, \\ z_2 + z_3 - z_5 < 0,\ z_2 + z_3 - z_4 - z_5 > 0, \\ z_1 > 0,\ z_4 + z_5 < 0, \\ -z_2 < 0,\ -z_4 - z_5 > 0. \end{aligned} \tag{3.2a}$$

This system is feasible; pick any $\tilde{z} \in \mathbb{R}^5$ satisfying (3.2a) and let $\tilde{z}_6 = \tilde{z}_4 + \tilde{z}_5$. Then $Q(z)$ evaluated at that $\tilde{z}$ has a positive kernel vector ν (cf. Table 1 and (3.3)). We apply Lemma 2.3 with $M^T = Z^T = (0, 0, 1, 2, 1, 0)$ from (2.3b) and need to find a vector $\tilde{\omega} \in \ker\left(Z^T\right)$ with $\operatorname{sign}(\tilde{\omega}) = \operatorname{sign}(\tilde{z})$. For the choice of $\tilde{\omega}$ with $\tilde{\omega}_3 < 0$, $\tilde{\omega}_4 < 0$, and $\tilde{\omega}_5 > 0$ we consequently add

$$\tilde{z}_3 < 0, \quad \tilde{z}_4 < 0, \quad \tilde{z}_5 > 0 \tag{3.2b}$$

to the inequality system. The overall system (3.2a) and (3.2b) is feasible, and one solution $\tilde{z}$ is given in Table 1. Table 1 also contains a vector $\tilde{\omega} \in \ker\left(Z^T\right)$ with $\operatorname{sign}(\tilde{z}) = \operatorname{sign}(\tilde{\omega})$ and the vector $x = \frac{\tilde{\omega}}{\tilde{z}}$ (cf. Lemma 2.3, equation (2.14)). Evaluating $Q(z)$ at $\tilde{z}$ from Table 1, one has the matrix

$$Q(\tilde{z}) = \begin{bmatrix} 2 & 0 & 0 & 0 & -1 \\ 0 & -7 & 0 & 0 & 1 \\ 0 & 0 & 4 & 0 & -5 \\ 0 & 0 & 0 & -1 & 5 \end{bmatrix},$$

which has the positive kernel vector

$$\nu = (14,\ 4,\ 35,\ 140,\ 28)^T . \tag{3.3}$$

Vector x from Table 1 and the above ν define a vector of rate constants:

$$k = \left(\frac{1400}{3},\ 112,\ \frac{160}{3},\ \frac{12}{5},\ \frac{672}{5},\ 140,\ 63,\ 168,\ 140,\ 140\right)^T .$$

Evaluation of $Jac\,(k, x)$ at this k and x from Table 1 confirms $\lambda = 0$ as a defective eigenvalue.

All in all, there are 81 different inequality systems where the pairs from (3.1) are of different sign or both zero. There are also 13 inequality systems like (3.2b) that constrain z such that there is a $\omega \in \ker\,(Z^T)$ with $\text{sign}\,(\omega) = \text{sign}\,(z)$. Of these $13 \times 81 = 1053$ inequality systems only the following four are feasible:

$$(P_1^+)\qquad \begin{array}{c} z_3 < 0,\ z_4 < 0,\ z_5 > 0, \\ \ell_1(z) > 0,\ \ell_2(z) < 0, \\ \ell_3(z) < 0,\ \ell_4(z) > 0, \\ \ell_5(z) > 0,\ \ell_6(z) < 0, \\ \ell_7(z) < 0,\ \ell_8(z) > 0, \end{array} \qquad (P_2^+)\qquad \begin{array}{c} z_3 < 0,\ z_4 > 0,\ z_5 < 0, \\ \ell_1(z) < 0,\ \ell_2(z) > 0, \\ \ell_3(z) > 0,\ \ell_4(z) < 0, \\ \ell_5(z) > 0,\ \ell_6(z) < 0, \\ \ell_7(z) < 0,\ \ell_8(z) > 0, \end{array}$$

and

$$(P_1^-)\qquad \begin{array}{c} z_3 > 0,\ z_4 > 0,\ z_5 < 0, \\ \ell_1(z) < 0,\ \ell_2(z) > 0, \\ \ell_3(z) > 0,\ \ell_4(z) < 0, \\ \ell_5(z) < 0,\ \ell_6(z) > 0, \\ \ell_7(z) > 0,\ \ell_8(z) < 0, \end{array} \qquad (P_2^-)\qquad \begin{array}{c} z_3 > 0,\ z_4 < 0,\ z_5 > 0, \\ \ell_1(z) > 0,\ \ell_2(z) < 0, \\ \ell_3(z) < 0,\ \ell_4(z) > 0, \\ \ell_5(z) < 0,\ \ell_6(z) > 0, \\ \ell_7(z) > 0,\ \ell_8(z) < 0. \end{array}$$

Because of the definitions of ℓ_5, ℓ_6, and ℓ_7 in (3.1), feasible z's do not have vanishing components. All in all, we have established the following necessary and sufficient condition for a defective eigenvalue of $J(\nu, x)$ of (2.1).

Fact 2. *The Jacobian $J(\nu, x)$ of (2.1) evaluated at $(\nu, x) \in \mathcal{V} \times \mathbb{R}^6_{>0}$ (and hence $Jac(k, x)$ evaluated at positive (k, x) via (2.6)) has $\lambda_0 = 0$ as a defective eigenvalue if and only if ν and x satisfy the following:*

1. *The vector x can be written as $x = \frac{\omega}{z}$ with* (i) *$z \in \mathbb{R}^6$ satisfying one of the inequality systems $(P_1^\pm)$, $(P_2^\pm)$ and $z_6 = z_4 + z_5$ (implying $z_i \neq 0$ for $i = 1, \ldots, 6$),* (ii) *$\omega \in \ker\left(Z^T\right)$, and* (iii) *$\text{sign}\,(z) = \text{sign}\,(\omega)$.*
2. *The above z and the vector $\nu > 0$ are such that $Q(z)\,\nu = 0$.*

Note that, if $z \in \mathbb{R}^6$ with $z_6 = z_4 + z_5$ satisfies one of the systems $(P_1^\pm)$ and $(P_2^\pm)$, then the sign pattern $\text{sign}\,(Q(z))$ is one of the following:

- If z satisfies $(P_1^{\pm})$, then

$$\operatorname{sign}(Q(z)) = \pm \begin{bmatrix} 1 & 0 & 0 & 0 & -1 \\ 0 & -1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix}.$$

- If z satisfies $(P_2^{\pm})$, then

$$\operatorname{sign}(Q(z)) = \pm \begin{bmatrix} -1 & 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix}.$$

3.2. A sufficient condition. For the example of network (2.1) we obtained necessary and sufficient conditions in form of linear inequalities in z guaranteeing a *positive* kernel vector ν of $Q(z)$. The idea is to look for sign patterns $\operatorname{sign}(Q(z))$ guaranteeing that *every matrix* with that sign pattern has a *positive* kernel vector (as was the case with the sign patterns of the previous section). To this end we try to establish that a sign pattern $\operatorname{sign}(Q(z))$ is what is called an L^+*-matrix* in *qualitative matrix theory* [7] (see in particular [23]).

Formally, given a sign pattern Σ and matrices A realizing this sign pattern (i.e., $\operatorname{sign}(A) = \Sigma$), the sign pattern Σ is called an L^+-matrix if and only if the following implication holds for *all matrices* A satisfying $\operatorname{sign}(A) = \Sigma$ (cf. [23]):

$$y^T A \geq 0 \Rightarrow y = 0.$$

Concerning sign patterns with this property one has the following theorem that, having our application in mind, can be summarized in the following way: if a sign pattern $\operatorname{sign}(Q(z))$ is an L^+-matrix, then every matrix with the same sign pattern has a positive kernel vector.

Theorem 3.1 (cf. [23, Theorem 2.4, p. 6]). *For an* $(m \times n)$ *sign pattern* A*, the following are equivalent:*

(i) A *is an* L^+*-matrix.*

(ii) *Every matrix with the sign pattern* A *has a* positive null vector*, and* A *has no zero row.*

(iii) *For each nonzero vector* $\sigma \in \{-1, 0, 1\}^m$*, some column of* $\operatorname{diag}(\sigma)\, A$ *is nonzero and nonnegative.*

(iv) *For each nonzero vector* $\sigma \in \{-1, 0, 1\}^m$*, some column of* $\operatorname{diag}(\sigma)\, A$ *is nonzero and nonpositive.*

Note that Theorem 3.1 already contains—by the parts (iii) or (iv)—a primitive algorithm for determining whether or not a given sign pattern is an L^+-matrix. So by Theorem 3.1 one can decide whether or not a particular sign pattern is an L^+-matrix.

With respect to the z-linear matrix $Q(z) = Q_{ij}(z) \in \mathbb{R}^{s \times p}$ from (2.17) we propose the following: we first stack the columns of Q and consider the column vector

$$(Q_{11}, \ldots, Q_{s1}, \ldots\ldots, Q_{1p}, \ldots, Q_{sp})^T.$$

Then we omit the components that are trivial linear forms to obtain a bijective mapping of the form

$$\psi : \; Q(z) \in \mathbb{R}^{s\times p} \;\mapsto\; L\,z = (\ell_1 z, \ldots, \ell_\gamma z)^T \in \mathbb{R}^\gamma \tag{3.4}$$

with nontrivial n-dimensional row-vectors $\ell_1, \ldots, \ell_\gamma$, $\gamma \le sp$. So, the $(\gamma \times n)$-matrix

$$L = (\ell_i)_{i=1,\ldots,\gamma} \tag{3.5}$$

just corresponds to the nontrivial linear forms in $Q(z)$. Since we look for a $\nu \in \mathcal{V}$ with $Q(z)\nu = 0$, we are interested in the sign patterns that Lz can assume. So we define the set $\mathcal{L}^+$ of all *sign pattern matrices* $\Sigma \in \{-1,0,1\}^{s\times p}$ that are L^+*-matrices* and that are realized by $Q(z)$ for some z. Since the mapping (3.4) associates a *signature vector* $\sigma = \psi(\Sigma) \in \{-1,0,1\}^\gamma$ with $\Sigma \in \{-1,0,1\}^{s\times p}$, one arrives at

$$\begin{aligned}\mathcal{L}^+ := \Big\{ \Sigma \in \{-1,0,1\}^{s\times p} \;\Big|\; & \Sigma \text{ is an } L^+\text{-matrix}, \\ & \exists z \in \mathbb{R}^n \text{ with } \sigma_i\,(Lz)_i > 0 \text{ if } \sigma_i \neq 0 \text{ and } (L\,z)_i = 0 \text{ if } \sigma_i = 0 \Big\}.\end{aligned} \tag{3.6}$$

Fact 3. *Assume that $\mathcal{L}^+$ is nonempty, and let $\Sigma \in \mathcal{L}^+$ and $\sigma = \psi(\Sigma)$. Then there exists a vector $z \in \mathbb{R}^n$ with*

$$\sigma_i\,(L\,z)_i > 0 \text{ if } \sigma_i \neq 0, \quad (L\,z)_i = 0 \text{ if } \sigma_i = 0$$

so that $\sigma = \operatorname{sign}(L\,z)$. Moreover, for each such $z \in \mathbb{R}^n$ there exists a positive $\nu = \nu(z)$ with $Q(z)\,\nu = 0$ by Theorem 3.1. By the discussion of (2.17), this implies that the pair $(z,\,\nu)$ satisfies $H(\nu)\,z = 0$.

Theorem 3.2. *Consider a dynamical system defined by a mass action network as described in section 2. Recall the matrix $Q(z)$ defined in (2.16), the matrix L defined in (3.4) and (3.5), and the set $\mathcal{L}^+$ defined in (3.6). If there exist an element $\Sigma = \operatorname{sign}(Q(z)) \in \mathcal{L}^+$ and an element $\omega \in \ker\left(Z^T\right)$ with*

$$\operatorname{sign}(\omega) = \operatorname{sign}(z), \tag{3.7}$$

then there exists a solution $\nu \in \mathbb{R}^p_{>0}$ to $Q(z)\,\nu = 0$, and the Jacobian $G(\xi,\eta,\nu)$ of the reduced system has zero as an eigenvalue with algebraic multiplicity ≥ 1. The corresponding steady state in original $(k,\,x)$-coordinates is given by

$$x = (x_i)_{i=1,\ldots,n}\,, \tag{3.8a}$$

$$x_i = \begin{cases} \frac{\omega_i}{z_i} & \text{if } z_i \neq 0, \\ \bar{x}_i > 0 \text{ arbitrary} & \text{if } z_i = 0, \end{cases} \tag{3.8b}$$

$$k = \operatorname{diag}\left(\phi\left(x^{-1}\right)\right) E\,\nu. \tag{3.8c}$$

The corresponding (ξ,η)-coordinates in $G(\xi,\eta,\nu)$ are then given by (2.10a).

Proof. The statements follow directly from Lemma 2.3 and Fact 3. ∎

The condition (3.7) can be tested by examining the following linear inequality systems defined by orthants of R^n. To establish these we identify each orthant by its sign pattern $\delta \in \{-1,0,1\}^n$: let $x \in \mathbb{R}^n$; then the sign pattern of x is defined as $\delta := \operatorname{sign}(x)$, and the orthant containing x is given by $\mathbb{R}^n_\delta := \{x \in \mathbb{R}^n | \operatorname{sign}(x) = \delta\}$. To find z and ω satisfying (3.7) for a given signature $\sigma = \psi(\Sigma)$ for an L^+-matrix Σ then amounts to finding an orthant $\mathbb{R}^n_\delta$ such that

$$\sigma_i\,(Lz)_i > 0 \ \text{ if } \sigma_i \neq 0, \qquad (Lz)_i = 0 \ \text{ if } \sigma_i = 0, \tag{3.9a}$$

$$Z^T\omega = 0, \ \text{ with } \delta_i\,\omega_i > 0,\ \delta_i\,z_i > 0 \ \text{ if } \delta_i \neq 0 \quad \text{and} \quad \omega_i = 0,\ z_i = 0 \ \text{ if } \delta_i = 0. \tag{3.9b}$$

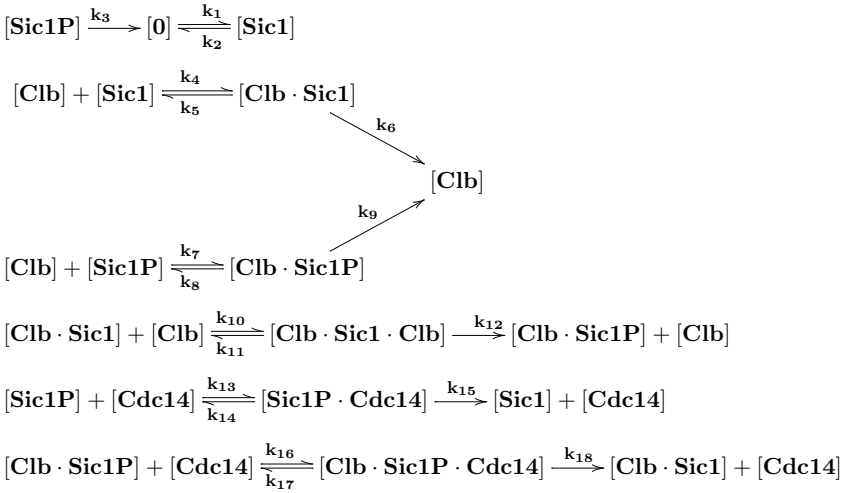
Corollary 3.3. *If there exist a signature $\Sigma \in \mathcal{L}^+$ and an orthant $\mathbb{R}^n_\delta$ such that the linear inequality system (3.9a), (3.9b) is feasible, then the reduced Jacobian $G(\xi,\eta,\nu)$ has zero as an eigenvalue with algebraic multiplicity ≥ 1.*

Remark 5. *In the previous discussion we have only considered positive kernel vectors of $Q(z)$. However, the set $\mathcal{V}$ can contain nonnegative vectors ν. Thus, suppose ν contains the facet of $\mathbb{R}^p_{\geq 0}$ given by $\{\nu \in \mathbb{R}^p_{\geq 0} | \nu_i = 0,\ \nu_j > 0,\ i \neq j = 1,\dots,p\}$. Then one may fix $\nu_i = 0$, replace $Q(z)$ in the discussion above by the submatrix $\tilde{Q}(z)$ obtained by deleting the ith column (and possibly occurring zero rows), and obtain the remaining ν_i by asking for positive kernel vectors of $\tilde{Q}(z)$ (i.e., by establishing the L^+-property for $\tilde{Q}(z)$).*

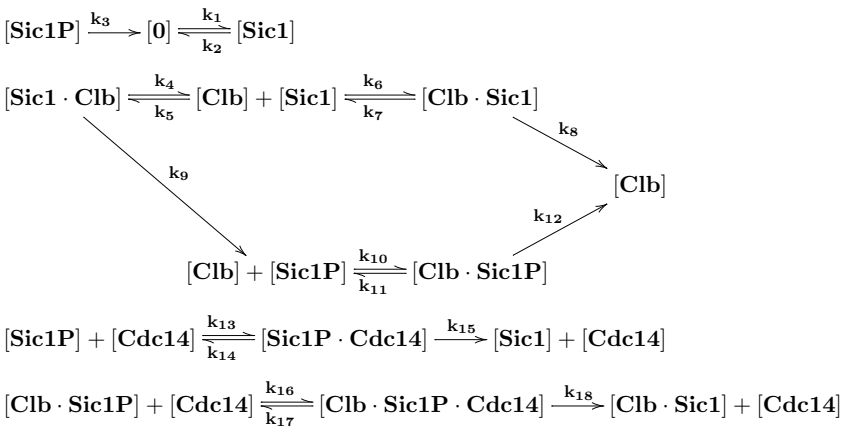
Remark 6. *The condition (3.9a) tests whether the given L^+-matrix Σ belongs to $\mathcal{L}^+$. By the definition of the matrix L this requires the labeling of the hyperplane arrangement given by Lz, which is computationally expensive (for an algorithm, see [1, 28]). We have shown that all z's satisfying (3.9a) lead to a positive null vector of $Q(z)$. The condition (3.9b) then stands for the compatibility with the kernel of Z^T: it tests whether there is a z in the solution set of (3.9a) that possesses a signature that is compatible with $\ker(Z^T)$. Since one has to decide whether or not one of the systems (3.9a), (3.9b) is feasible, the overall procedure can be computationally demanding, even though the individual steps involve only simple matrix computations.*

4. Saddle-node bifurcations for the G1/S transition in budding yeast. The networks displayed in (4.1) and (4.2) below are competing hypotheses describing the G1/S transition in budding yeast. Both networks are biologically plausible and hard to distinguish experimentally [12].

(4.1)



(4.2)



Switching is a desired property of models describing the G1/S transition: depending on its past, a trajectory should move to different regions of state space, associated with the G1 and S phases of cell cycle. Classically this has been realized by choosing rate constants and total concentrations, such that the ODE system shows bistability and hence hysteretic behavior [6, 21]. For example, in [12], multistationarity has been established for both models, indicating that both may be valid models. Here we demonstrate the applicability of our results by confirming switching for both networks. We show that both models satisfy the conditions of Theorem 3.2 and compute states and rate constants where the Jacobian has a defective eigenvalue. We verify by numerical continuation that the system undergoes a saddle-node bifurcation, as generically expected, so that the codimension-1 stable manifold of the saddle-node and—after bifurcation—that of the saddle represent a switching surface.

For the network given in (4.1) one obtains, using the stoichiometric matrix S given in Appendix B,

$$Q(z) = \begin{bmatrix} -z_1 & 0 & 0 & 0 & 0 & 0 & -z_9 & -z_4 & -z_9 & z_7 - z_9 & z_8 - z_9 \\ 0 & 0 & 0 & 0 & 0 & 0 & z_2 - z_9 & 0 & z_5 - z_9 & z_7 - z_9 & z_8 - z_9 \\ 0 & z_1 + z_3 - z_4 & 0 & 0 & 0 & 0 & z_1 + z_3 - z_9 & z_1 + z_3 - z_4 & z_1 + z_3 - z_9 & z_1 + z_3 - z_9 & z_8 - z_9 \\ 0 & 0 & z_2 + z_3 - z_5 & 0 & 0 & 0 & -z_5 + z_9 & 0 & -z_5 + z_9 & -z_5 + z_9 & -z_8 + z_9 \\ 0 & 0 & 0 & z_3 + z_4 - z_9 & 0 & 0 & z_3 + z_4 - z_9 & 0 & z_3 + z_4 - z_9 & z_3 + z_4 - z_9 & z_3 + z_4 - z_9 \\ 0 & 0 & 0 & 0 & z_2 + z_6 - z_7 & 0 & 0 & 0 & 0 & z_2 + z_6 - z_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & z_5 + z_6 - z_8 & 0 & 0 & 0 & 0 & z_5 + z_6 - z_8 \end{bmatrix}.$$

From the last three rows of $Q(z)$ one has that positive ν's with $Q(z)\,\nu = 0$ exist only if

$$z_3 + z_4 - z_9 = 0, \quad z_2 + z_6 - z_7 = 0, \quad z_5 + z_6 - z_8 = 0 \tag{4.3}$$

and hence, for example,

$$z_2 = -z_6 + z_7, \quad z_3 = -z_4 + z_9, \quad z_5 = -z_6 + z_8.$$

In this case columns 4, 5, and 6 will be the zero column, indicating that ν_4, ν_5, $\nu_6 > 0$ are unconstrained. Thus we need consider only the matrix

$$Q_s(z) = \begin{bmatrix} -\pi_8\, z & 0 & 0 & -\pi_{10}\, z & -\pi_9\, z & -\pi_{10}\, z & \pi_6\, z & \pi_5\, z \\ 0 & 0 & 0 & \pi_2\, z & 0 & -\pi_4\, z & \pi_6\, z & \pi_5\, z \\ 0 & \pi_3\, z & 0 & \pi_7\, z & \pi_3\, z & \pi_7\, z & \pi_7\, z & \pi_5\, z \\ 0 & 0 & \pi_1\, z & \pi_4\, z & 0 & \pi_4\, z & \pi_4\, z & -\pi_5\, z \end{bmatrix}$$

with

$$\begin{aligned}
\pi_1 z &:= -z_4 + z_7 - z_8 + z_9, & \pi_2 z &:= z_5 + z_7 - z_8 - z_9,\\
\pi_3 z &:= z_1 - 2z_4 + z_9, & \pi_4 z &:= -z_5 + z_9,\\
\pi_5 z &:= z_8 - z_9, & \pi_6 z &:= z_7 - z_9,\\
\pi_7 z &:= z_1 - z_4, & \pi_8 z &:= z_1,\\
\pi_9 z &:= z_4, & \pi_{10} z &:= z_9.
\end{aligned}$$

For example, the system

$$\begin{aligned}
\pi_1 z < 0,\ \pi_2 z > 0,\ \pi_3 z < 0,\ \pi_4 z > 0,\ \pi_5 z < 0,\\
\pi_6 z > 0,\ \pi_7 z > 0,\ \pi_8 z > 0,\ \pi_9 z > 0,\ \pi_{10} z < 0,\\
z_1 > 0,\ z_2 > 0,\ z_3 < 0,\ z_4 > 0,\ z_5 < 0,\ z_6 > 0,\ z_7 > 0,\ z_8 < 0,\ z_9 < 0,\\
\omega_1 > 0,\ \omega_2 > 0,\ \omega_3 < 0,\ \omega_4 > 0,\ \omega_5 < 0,\ \omega_6 > 0,\ \omega_7 > 0,\ \omega_8 < 0,\ \omega_9 < 0
\end{aligned} \tag{4.4}$$

is feasible. Let $z \in \mathbb{R}^9$ such that (4.3) and (4.4) hold. Then

$$\operatorname{sign}(Q_s(z)) = \begin{bmatrix} -1 & 0 & 0 & 1 & -1 & 1 & 1 & -1 \\ 0 & 0 & 0 & 1 & 0 & -1 & 1 & -1 \\ 0 & -1 & 0 & 1 & -1 & 1 & 1 & -1 \\ 0 & 0 & -1 & 1 & 0 & 1 & 1 & 1 \end{bmatrix}$$

is an L^+-matrix (cf. Theorem 3.1(iii) and (iv)). One obtains, for example, the feasible points

$$\tilde{z} = (13,\ 2,\ -10,\ 8,\ -6,\ 2,\ 4,\ -4,\ -2)^T, \qquad \tilde{\omega} = (1,\ 1,\ -1,\ 6,\ -1,\ 1,\ 1,\ -2,\ -1)^T.$$

Vectors $\tilde{z}$ and $\tilde{\omega}$ yield the state vector

$$\tilde{x} = \frac{\tilde{\omega}}{\tilde{z}} = \left(\frac{1}{13},\ \frac{1}{2},\ \frac{1}{10},\ \frac{3}{4},\ \frac{1}{6},\ \frac{1}{2},\ \frac{1}{4},\ \frac{1}{2},\ \frac{1}{2}\right)^T. \tag{4.5}$$

For the matrix $Q(z)$ evaluated at $\tilde{z}$ one has

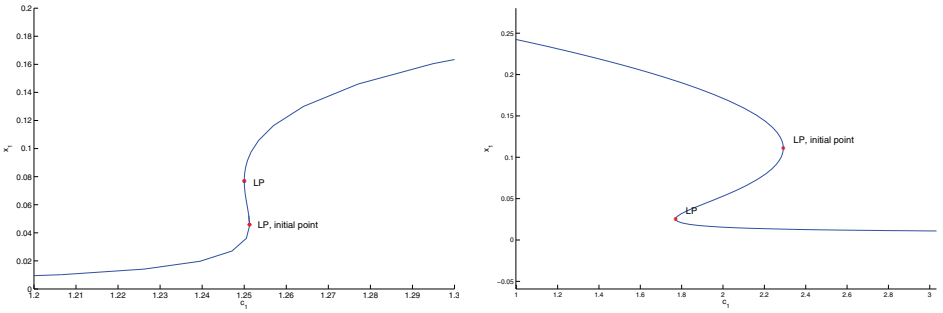
$$Q(\tilde{z}) = \begin{bmatrix} -13 & 0 & 0 & 0 & 0 & 0 & 2 & -8 & 2 & 6 & -2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 4 & 0 & -4 & 6 & -2 \\ 0 & -5 & 0 & 0 & 0 & 0 & 5 & -5 & 5 & 5 & -2 \\ 0 & 0 & -2 & 0 & 0 & 0 & 4 & 0 & 4 & 4 & 2 \end{bmatrix}.$$

The kernel of $Q(\tilde{z})$ contains the following positive vector:

$$\tilde{\nu} = \left(18,\ 1,\ 2000,\ 1,\ 1,\ 1,\ 1,\ \frac{246}{35},\ \frac{5114}{105},\ \frac{1996}{5},\ \frac{23146}{21}\right)^T.$$

Vectors $\tilde{x}$ and $\tilde{\nu}$ yield the rate constants

$$\begin{aligned}
\tilde{k} = \Bigg(&\frac{1121}{15},\ 234,\ 2,\ \frac{178204}{3},\ \frac{4}{3},\ \frac{328}{35},\ 40000,\ \frac{72006}{5},\ \frac{10228}{35},\ \frac{1303760}{63},\\
&2,\ \frac{65146}{21},\ \frac{8004}{5},\ 4,\ \frac{7984}{5},\ \frac{92668}{7},\ 2,\ \frac{46292}{21}\Bigg)^T.
\end{aligned} \tag{4.6}$$



(a) Continuation for network (4.1). (b) Continuation for network (4.2).

Figure 1. *Numerical continuation for the networks* (4.1) *and* (4.2) *using rate constants* $\tilde{k}$ *and initial condition* $\tilde{x}$ *given in* (4.5), (4.6) *for network* (4.1) *and in* (4.9), (4.10) *for network* (4.2). *In both cases the upper and lower branches correspond to exponentially stable steady states. The total concentration* c_1 *is used as a bifurcation parameter.*

A numerical continuation with this $\tilde{k}$ and initial condition $\tilde{x}$ verifies that the dynamical system undergoes a saddle-node bifurcation at $(\tilde{k}, \tilde{x})$; cf. Figure 1(a).

For the network given in (4.2) one obtains, using the stoichiometric matrix S as given in Appendix C,

$$Q(z) = \begin{bmatrix} -z_1 & 0 & 0 & 0 & 0 & 0 & -z_4 & -z_9 & z_7 - z_9 & -z_9 & -z_4 + z_8 - z_9 & z_8 - z_9 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & z_2 - z_9 & z_7 - z_9 & z_5 - z_9 & z_8 - z_9 & z_8 - z_9 \\ 0 & -z_1 - z_3 + z_9 & 0 & 0 & 0 & 0 & 0 & -z_1 - z_3 + z_9 & -z_1 - z_3 + z_9 & -z_1 - z_3 + z_9 & -z_1 - z_3 + z_9 & -z_1 - z_3 + z_9 \\ 0 & 0 & z_1 + z_3 - z_4 & 0 & 0 & 0 & z_1 + z_3 - z_4 & 0 & 0 & 0 & -z_4 + z_8 & -z_4 + z_8 \\ 0 & 0 & 0 & z_2 + z_3 - z_5 & 0 & 0 & 0 & 0 & 0 & z_2 + z_3 - z_5 & z_2 + z_3 - z_8 & z_2 + z_3 - z_8 \\ 0 & 0 & 0 & 0 & z_2 + z_6 - z_7 & 0 & 0 & 0 & z_2 + z_6 - z_7 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & z_5 + z_6 - z_8 & 0 & 0 & 0 & 0 & z_5 + z_6 - z_8 & z_5 + z_6 - z_8 \end{bmatrix}.$$

From rows 3, 6, and 7 of $Q(z)$ one has that positive ν's with $Q(z)\,\nu = 0$ exist only if

$$-z_1 - z_3 + z_9 = 0, \quad z_5 + z_6 - z_8 = 0, \quad z_2 + z_6 - z_7 = 0 \tag{4.7}$$

and hence, for example,

$$z_1 = -z_3 + z_9, \quad z_2 = z_5 - z_8 + z_7, \quad z_6 = -z_5 + z_8.$$

In this case columns 2, 5, and 6 will be the zero column, indicating that ν_2, ν_5, $\nu_6 > 0$ are unconstrained. Thus we need consider only the matrix

$$Q_s(z) = \begin{bmatrix} \pi_{10}\, z & 0 & 0 & -\pi_{11}\, z & -\pi_{12}\, z & \pi_7\, z & -\pi_{12}\, z & \pi_4\, z & \pi_9\, z \\ 0 & 0 & 0 & 0 & \pi_3\, z & \pi_7\, z & \pi_8\, z & \pi_9\, z & \pi_9\, z \\ 0 & \pi_5\, z & 0 & \pi_5\, z & 0 & 0 & 0 & \pi_6\, z & \pi_6\, z \\ 0 & 0 & \pi_2\, z & 0 & 0 & 0 & \pi_2\, z & \pi_1\, z & \pi_1\, z \end{bmatrix}$$

with

$$\begin{aligned}
\pi_1 z &= z_3 + z_5 + z_7 - 2z_8, & \pi_2 z &= z_3 + z_7 - z_8,\\
\pi_3 z &= z_5 + z_7 - z_8 - z_9, & \pi_4 z &= -z_4 + z_8 - z_9,\\
\pi_5 z &= -z_4 + z_9, & \pi_6 z &= -z_4 + z_8,\\
\pi_7 z &= z_7 - z_9, & \pi_8 z &= z_5 - z_9,\\
\pi_9 z &= z_8 - z_9, & \pi_{10} z &= z_3 - z_9,\\
\pi_{11} z &= z_4, & \pi_{12} z &= z_9.
\end{aligned}$$

One obtains the feasible inequality system

$$\begin{aligned}
&\pi_1 z > 0,\ \pi_2 z < 0,\ \pi_3 z > 0,\ \pi_4 z = 0,\ \pi_5 z > 0,\ \pi_6 z < 0,\ \pi_7 z > 0,\\
&\pi_8 z > 0,\ \pi_9 z < 0,\ \pi_{10} z < 0,\ \pi_{11} z < 0,\ \pi_{12} z < 0,\\
&z_1 > 0,\ z_2 > 0,\ z_3 < 0,\ z_4 < 0,\ z_5 > 0,\ z_6 < 0,\ z_7 > 0,\ z_8 < 0,\ z_9 < 0,\\
&\omega_1 > 0,\ \omega_2 > 0,\ \omega_3 < 0,\ \omega_4 < 0,\ \omega_5 > 0,\ \omega_6 < 0,\ \omega_7 > 0,\ \omega_8 < 0,\ \omega_9 < 0,
\end{aligned} \tag{4.8}$$

where $Q(z)$ is an L^+-matrix. For example, the feasible points

$$\tilde{z} = (9,\ 9,\ -11,\ -4,\ 2,\ -8,\ 1,\ -6,\ -2)^T, \qquad \tilde{\omega} = (1,\ 1,\ -1,\ -1,\ 4,\ -1,\ 2,\ -1,\ -1)^T$$

define the state vector

$$\tilde{x} = \left(\frac{1}{9},\ \frac{1}{9},\ \frac{1}{11},\ \frac{1}{4},\ 2,\ \frac{1}{8},\ 2,\ \frac{1}{6},\ \frac{1}{2}\right)^T. \tag{4.9}$$

For the matrix $Q(z)$ evaluated at $\tilde{z}$ one obtains

$$Q(\tilde{z}) = \begin{bmatrix}
-9 & 0 & 0 & 0 & 0 & 0 & 4 & 2 & 3 & 2 & 0 & -4\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 11 & 3 & 4 & -4 & -4\\
0 & 0 & 2 & 0 & 0 & 0 & 2 & 0 & 0 & 0 & -2 & -2\\
0 & 0 & 0 & -4 & 0 & 0 & 0 & 0 & 0 & -4 & 4 & 4
\end{bmatrix},$$

with the positive kernel vector

$$\tilde{\nu} = (297,\ 11,\ 22,\ 11,\ 11,\ 11,\ 440,\ 1,\ 11,\ 451,\ 456,\ 6)^T.$$

Finally, one obtains for the rate constants

$$\begin{aligned}
\tilde{k} = \Bigg(&1645,\ 2673,\ 9,\ 22,\ 92664,\ 45738,\ 112,\ 3584,\ 1850,\ 91476,\\
&\frac{11}{2},\ \frac{451}{2},\ 1584,\ \frac{11}{2},\ \frac{11}{2},\ 1892,\ 66,\ 2772\Bigg)^T.
\end{aligned} \tag{4.10}$$

Again, numerical continuation shows a saddle-node bifurcation at $(\tilde{k},\ \tilde{x})$; cf. Figure 1(b).

Appendix A. Saddle-node bifurcations in mass action networks. This subsection is a recollection of some remarks concerning saddle-node bifurcations in mass action systems that were originally made in [10]. We repeat them here to demonstrate the tight connection between zero eigenvalues of $G(\xi,\eta,\lambda)$ obtained via (2.12a) and (2.12b) and saddle-node bifurcations.

The following well-known theorem gives necessary and sufficient conditions for a saddle-node bifurcation of the system $\dot{\xi} = g(\xi,\eta,k)$ as defined in (2.10b). Let μ be the component of the parameter vector $\nu = (\eta,k)$ that will be used as bifurcation parameter.

Theorem A.1 (see, e.g., [8, p. 497]). *Suppose that (ξ_0,ν_0) is a zero of g, and suppose that the $s\times s$ matrix $G(\xi_0,\nu_0) = D_\xi\, g(\xi_0,\nu_0)$ has an algebraically simple eigenvalue 0 with right eigenvector b and left eigenvector β^T. Furthermore suppose that the following conditions are satisfied:*

$$\beta^T D_\mu\, g(\xi_0,\nu_0) \neq 0, \quad \beta^T \left[D^2_\xi\, g(\xi_0,\nu_0)(b,b)\right] \neq 0. \tag{A.1}$$

Then there is a smooth curve of zeros of g passing through (ξ_0,ν_0). Depending on the signs of the expressions in (A.1), there are no or two zeros near ξ_0 for $\mu \neq \mu_0$ when the other components of ν_0 remain fixed.

In the remainder of this section we examine, in terms of the Jacobian $J(\nu,x)$, when the conditions (A.1) are satisfied for the reduced system (2.10b). We recall the relations (2.5a), (2.6), and (2.10b). First observe that Fact 2.2 states conditions guaranteeing that $G(\xi,\eta,\lambda)$ has zero as an eigenvalue. For general mass action networks its algebraic multiplicity is expected to be 1.

Now, if $G(\xi_0,\eta_0,\nu_0)$ has an algebraically simple eigenvalue 0, we add two comments regarding (A.1) (cf. [10]):

(N1) Recall the monomial function $\phi(x)$; cf. section 2. If μ is any rate constant k_i, then we have

$$D_\mu\, g(\xi_0,\mu_0) = U^T\, S\, \mathrm{diag}\,(\phi(x_0))\; e_i$$

and therefore

$$\beta^T D_\mu\, g(\xi_0,\mu_0) = \phi_i\,(x_0)\, \beta^T\, U^T\, S\, e_i \neq 0$$

for at least one i (as $\phi_i(x_0) > 0$ and $[U] = \mathrm{im}\,(S)$).

(N2) From the above Lemma 2.1 we deduce

$$\begin{aligned} &\beta^T \left[D^2_\xi\, g(\xi_0,\eta_0,k_0)(b,b)\right] \neq 0 \Leftrightarrow \\ &\alpha^T \left[D^2_x\, f(x(\xi_0,\eta_0),k_0)(A\,a, A\,a)\right] \neq 0 \end{aligned} \tag{A.2}$$

with $A := J(\lambda,x)$ and with left and right principal vectors α^T and a of $J(\lambda,x)$.

As a consequence of this discussion, in particular of the comment (N1), we obtained in [10] the following remark concerning the originally given system (2.2), (2.3a).

Remark 7. *The system (2.2), (2.3a) has a saddle-node bifurcation at (k_0,x_0) (within the plane $Z^T x = Z^T x_0 =: c$) if the following conditions are satisfied:*

(i) *0 is a defective eigenvalue of $J(\lambda_0,x_0)$ with $m_{alg} = m_{geo} + 1$, and the remaining eigenvalues have negative real parts.*

(ii) *$\alpha^T \left[D^2_x\, f(x_0,k_0)(Aa,Aa)\right] \neq 0$ is satisfied for left and right principal vectors w_0^T and v_0 of $J(\lambda_0,x_0)$.*

Appendix B. The data for network (4.1).

B.1. Species and complexes of network (4.1).

Species	x_i	Complex	y_i
$Sic1$	x_1	0	y_1
$Sic1P$	x_2	$Sic1$	y_2
Clb	x_3	$Sic1P$	y_3
$Clb \cdot Sic1$	x_4	$Clb + Sic1$	y_4
$Clb \cdot Sic1P$	x_5	$Clb \cdot Sic1$	y_5
$Cdc14$	x_6	Clb	y_6
$Sic1P \cdot Cdc14$	x_7	$Clb + Sic1P$	y_7
$Clb \cdot Sic1P \cdot Cdc14$	x_8	$Clb \cdot Sic1P$	y_8
$Clb \cdot Sic1 \cdot Clb$	x_9	$Clb \cdot Sic1 + Clb$	y_9
		$Clb \cdot Sic1 \cdot Clb$	y_{10}
		$Clb \cdot Sic1P + Clb$	y_{11}
		$Sic1P + Cdc14$	y_{12}
		$Sic1P \cdot Cdc14$	y_{13}
		$Sic1 + Cdc14$	y_{14}
		$Clb \cdot Sic1P + Cdc14$	y_{15}
		$Clb \cdot Sic1P \cdot Cdc14$	y_{16}
		$Clb \cdot Sic1 + Cdc14$	y_{17}

B.2. Ordinary differential equations.

$$
\begin{aligned}
\dot{x}_1 &= k_1 - k_2\,x_1 - k_4\,x_1\,x_3 + k_5\,x_4 + k_{15}\,x_7,\\
\dot{x}_2 &= -k_3\,x_2 - k_7\,x_2\,x_3 + k_8\,x_5 - k_{13}\,x_2\,x_6 + k_{14}\,x_7,\\
\dot{x}_3 &= -k_4\,x_1\,x_3 + k_5\,x_4 + k_6\,x_4 - k_7\,x_2\,x_3 + k_8\,x_5\\
&\qquad + k_9\,x_5 - k_{10}\,x_3\,x_4 + k_{11}\,x_9 + k_{12}\,x_9,\\
\dot{x}_4 &= k_4\,x_1\,x_3 - k_5\,x_4 - k_6\,x_4 - k_{10}\,x_3\,x_4 + k_{11}\,x_9 + k_{18}\,x_8,\\
\dot{x}_5 &= k_7\,x_2\,x_3 - k_8\,x_5 - k_9\,x_5 + k_{12}\,x_9 - k_{16}\,x_5\,x_6 + k_{17}\,x_8,\\
\dot{x}_6 &= -k_{13}\,x_2\,x_6 + k_{14}\,x_7 + k_{15}\,x_7 - k_{16}\,x_5\,x_6 + k_{17}\,x_8 + k_{18}\,x_8,\\
\dot{x}_7 &= k_{13}\,x_2\,x_6 - k_{14}\,x_7 - k_{15}\,x_7,\\
\dot{x}_8 &= k_{16}\,x_5\,x_6 - k_{17}\,x_8 - k_{18}\,x_8,\\
\dot{x}_9 &= k_{10}\,x_3\,x_4 - k_{11}\,x_9 - k_{12}\,x_9.
\end{aligned}
$$

B.3. Conservation relations.

$$
\begin{aligned}
Z_1^T x &= x_6 + x_7 + x_8 = c_1,\\
Z_2^T x &= x_3 + x_4 + x_5 + x_8 + 2\,x_9 = c_2.
\end{aligned}
$$

B.4. The stoichiometric matrix.

$$
S = \begin{bmatrix}
1 & -1 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0\\
0 & 0 & -1 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & -1 & 1 & 1 & -1 & 1 & 1 & -1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1\\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 1 & 0 & 0 & 0 & -1 & 1 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 1 & -1 & 1 & 1\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}
$$

B.5. The vector of reaction rates.

$$v(k,x) = \big(k_1,\ k_2x_1,\ k_3x_2,\ k_4x_1x_3,\ k_5x_4,\ k_6x_4,\ k_7x_2x_3,\ k_8x_5,\ k_9x_5,\ k_{10}x_3x_4,$$
$$k_{11}x_9,\ k_{12}x_9,\ k_{13}x_2x_6,\ k_{14}x_7,\ k_{15}x_7,\ k_{16}x_5x_6,\ k_{17}x_8,\ k_{18}x_8\big)^T.$$

Appendix C. The data for network (4.2).

C.1. Species and complexes of network (4.2).

Species	x_i	Complex	y_i
$Sic1$	x_1	0	y_1
$Sic1P$	x_2	$Sic1$	y_2
Clb	x_3	$Sic1P$	y_3
$Clb \cdot Sic1$	x_4	$Sic1 \cdot Clb$	y_4
$Clb \cdot Sic1P$	x_5	$Clb + Sic1$	y_5
$Cdc14$	x_6	$Clb \cdot Sic1$	y_6
$Sic1P \cdot Cdc14$	x_7	Clb	y_7
$Clb \cdot Sic1P \cdot Cdc14$	x_8	$Clb + Sic1P$	y_8
$Sic1 \cdot Clb$	x_9	$Clb \cdot Sic1P$	y_9
		$Sic1P + Cdc14$	y_{10}
		$Sic1P \cdot Cdc14$	y_{11}
		$Sic1 + Cdc14$	y_{12}
		$Clb \cdot Sic1P + Cdc14$	y_{13}
		$Clb \cdot Sic1P \cdot Cdc14$	y_{14}
		$Clb \cdot Sic1 + Cdc14$	y_{15}

C.2. Ordinary differential equations.

$$\begin{aligned}
\dot{x}_1 &= k_1 - k_2\,x_1 + k_4\,x_9 - k_5\,x_1\,x_3 - k_6\,x_1\,x_3 + k_7\,x_4 + k_{15}\,x_7,\\
\dot{x}_2 &= -k_3\,x_2 + k_9\,x_9 - k_{10}\,x_2\,x_3 + k_{11}\,x_5 - k_{13}\,x_2\,x_6 + k_{14}\,x_7,\\
\dot{x}_3 &= k_4\,x_9 - k_5\,x_1\,x_3 - k_6\,x_1\,x_3 + k_7\,x_4 + k_8\,x_4\\
&\qquad + k_9\,x_9 - k_{10}\,x_2\,x_3 + k_{11}\,x_5 + k_{12}\,x_5,\\
\dot{x}_4 &= k_6\,x_1\,x_3 - k_7\,x_4 - k_8\,x_4 + k_{18}\,x_8,\\
\dot{x}_5 &= k_{10}\,x_2\,x_3 - k_{11}\,x_5 - k_{12}\,x_5 - k_{16}\,x_5\,x_6 + k_{17}\,x_8,\\
\dot{x}_6 &= -k_{13}\,x_2\,x_6 + k_{14}\,x_7 + k_{15}\,x_7 - k_{16}\,x_5\,x_6 + k_{17}\,x_8 + k_{18}\,x_8,\\
\dot{x}_7 &= k_{13}\,x_2\,x_6 - k_{14}\,x_7 - k_{15}\,x_7,\\
\dot{x}_8 &= k_{16}\,x_5\,x_6 - k_{17}\,x_8 - k_{18}\,x_8,\\
\dot{x}_9 &= -k_4\,x_9 + k_5\,x_1\,x_3 - k_9\,x_9.
\end{aligned}$$

C.3. Conservation relations.

$$\begin{aligned}
Z_1^T x &= x_6 + x_7 + x_8 = c_1,\\
Z_2^T x &= x_3 + x_4 + x_5 + x_8 + x_9 = c_2.
\end{aligned}$$

C.4. The stoichiometric matrix.

$$S = \begin{bmatrix} 1 & -1 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 1 & 0 & -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 & 1 & 1 & 1 & -1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 1 & -1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 \\ 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

C.5. The vector of reaction rates.

$$v(k,x) = \big(k_1,\, k_2x_1,\, k_3x_2,\, k_4x_9,\, k_5x_1x_3,\, k_6x_1x_3,\, k_7x_4,\, k_8x_4,\, k_9x_9,\, k_{10}x_2x_3,\\ k_{11}x_5,\, k_{12}x_5,\, k_{13}x_2x_6,\, k_{14}x_7,\, k_{15}x_7,\, k_{16}x_5x_6,\, k_{17}x_8,\, k_{18}x_8\big)^T.$$

Appendix D. Some linear algebra.

D.1. The hypothesis $\mathrm{im}(S) = \mathrm{im}(J(\nu,x))$ in (2.9). We consider the factorization $J = S\,[\mathcal{Y}V]^T \operatorname{diag}(x^{-1})$ from (2.5c) and (2.5d), where $V = \operatorname{diag}(E\nu)$ and $\operatorname{diag}(x^{-1})$ are diagonal matrices with positive entries. The equality $\mathrm{im}(S) = \mathrm{im}(J)$ is thus equivalent to $\mathrm{im}(S) = \mathrm{im}(S[\mathcal{Y}V]^T)$ since the invertible factor $\operatorname{diag}(x^{-1})$ can be discarded.

Given such $(n\times r)$-matrices S and $B = \mathcal{Y}V$ of $\operatorname{rank}(S) = s$ and $\operatorname{rank}(B) = \operatorname{rank}(Y) =: \beta$, respectively, one always has $\operatorname{im}(S) \supset \operatorname{im}(SB^T)$ and $s \geq \operatorname{rank}(SB^T)$. We discuss the equality

$$S(\mathbb{R}^r) = \operatorname{im}(S) = \operatorname{im}(SB^T) = S(\operatorname{im} B^T), \tag{D.1a}$$

which is obviously equivalent to $s = \operatorname{rank}(SB^T) = \operatorname{rank}(BS^T)$ and to

$$\dim\big(\ker(SB^T)\big) = n - s = \dim\big(\ker(BS^T)\big). \tag{D.1b}$$

Obviously, (D.1a) necessitates $\beta \geq s$. Moreover, one has $\operatorname{im}(S) \subset \operatorname{im}(SB^T)$ if and only if $[\operatorname{im}(S)]^\perp = \ker(S^T) \supset \ker(B^TS) = [\operatorname{im}(SB^T)]^\perp$ and thus if and only if

$$BS^T\xi = 0 \;\Rightarrow\; S^T\xi = 0. \tag{D.1c}$$

The elements ξ of the $(n-s)$-dimensional subspace $\ker(S^T)$ satisfy (D.1c). Therefore, $\operatorname{rank}(S) = \operatorname{rank}(SB^T)$ is equivalent to $B\,|_{\operatorname{im}(S^T)}$ being an injective map. This can be reformulated in terms of matrices S_c and B_c, whose columns form a basis of $\operatorname{im}(S^T)$ and $\operatorname{im}(B^T)$, respectively: $\operatorname{rank}(S) = \operatorname{rank}(SB^T)$ is equivalent to $B_c^TS_c \in \mathbb{R}^{r\times s}$ being of full column rank s. Finally, this fact leads with the help of matrices S_c and $\mathcal{Y}_c$, whose columns form a basis of $\operatorname{im}(S^T)$ and $\operatorname{im}(\mathcal{Y}^T)$, respectively, to the following characterization:

$$\operatorname{im}(S) = \operatorname{im}(J(\nu,x)) \;\Leftrightarrow\; \mathcal{Y}_c^T \operatorname{diag}(E\nu)\, S_c \in \mathbb{R}^{r\times s} \text{ has full column rank } s. \tag{D.1d}$$

D.2. The reduced system $Q(z)\nu = 0$ in (2.17). When discussing $H(z)\,\nu = 0$ with $H(z)$ given by (2.7b), we have introduced matrices S_0 and S_c such that the columns of S_0 and S_c form a basis of $\ker(S)$ and $\mathrm{im}(S^T)$, respectively. Furthermore, we have chosen the Moore–Penrose inverse $S_0^{\#}$ and a particular matrix $S_{\#}$ with $S_{\#}\,S_0 = \left[\begin{smallmatrix} I_{r-s} \\ \mathbf{0}_{s\times(r-s)} \end{smallmatrix}\right]$, namely, $S_{\#}^{part} = \left[\begin{smallmatrix} S_0^{\#} \\ S_c^T \end{smallmatrix}\right]$. These choices have led to the equivalence of $H(z)\,\nu = 0$ and $Q(z)\nu = 0$, with the corresponding α given by $P(z)\nu$ (cf. the set-up for (2.15), (2.16), and (2.17)).

When considering a different basis representation $\tilde{S}_0 = S_0 R_0$ of $\ker(S)$ for a regular matrix $R_0 \in \mathbb{R}^{(r-s)\times(r-s)}$ and when working with the general form of $S_{\#}$ given by

$$S_{\#}^{gen} = \begin{bmatrix} \tilde{S}_0^{\#} + \Lambda S_c^T \\ R_c^T S_c^T \end{bmatrix} = \begin{bmatrix} R_0^{-1} & \Lambda \\ 0 & R_c^T \end{bmatrix} \begin{bmatrix} S_0^{\#} \\ S_c^T \end{bmatrix} \tag{D.2a}$$

for regular matrices $R_c \in \mathbb{R}^{s\times s}$ and arbitrary matrices $\Lambda \in \mathbb{R}^{(r-s)\times s}$, one arrives at the equivalence of $\tilde{S}_0\,\tilde{\alpha} = \mathrm{diag}\left(\mathcal{Y}^T z\right) E\,\nu$ (cf. (2.15)) to

$$\begin{bmatrix} R_0^{-1} & \Lambda \\ 0 & R_c^T \end{bmatrix} \begin{bmatrix} P(z)\,\nu \\ Q(z)\,\nu \end{bmatrix} = \begin{bmatrix} \tilde{\alpha} \\ 0 \end{bmatrix} \tag{D.2b}$$

for some matrix Λ of suitable dimensions. Hence, for general $S_{\#}^{gen}$ one obtains (in analogy to (2.17)) the condition

$$R_c^T\,Q(z)\,\nu = 0. \tag{D.2c}$$

As R_c is regular, one has that any pair $(z,\,\nu) \in \mathbb{R}^n \times \mathcal{V}$ satisfying (D.2c) also satisfies (2.17) and vice versa. Hence we conclude that (2.17) is independent from the chosen bases for $\ker(S)$ and $\mathrm{im}(S^T)$. The corresponding $\tilde{\alpha}$ depends on the choice of R_0 and Λ, as (D.2b) shows.

D.3. Ad Remark 4. By Appendix D.1 one has $\mathrm{im}\,(S) = \mathrm{im}\,(J)$ if and only if one of the $(s \times s)$-minors of $\mathcal{Y}_c^T\,\mathrm{diag}\,(E\nu)S_c$ is nonzero for the chosen ν from the kernel of $Q(z)$. We want to add that these minors are polynomials in the components of $E\nu$ of order not greater than s. By Remark 4 following Theorem 2.4, the ν's might be varied locally. Such a variation might be employed to establish (D.1d).

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