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Supercritical Hopf Bifurcations in Two Biochemical Reaction Systems

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Abstract

The characteristics of models representing biochemical phenomena exhibit complicated steady states and numerous state transitions that remain interesting in applications. Examining these states by combining the effective methods of bifurcation theory and computational algebra is profoundly appreciable to obtain bifurcation points near which the qualitative behavior of the model varies and parameter ranges that promote particular behavior. This study reveals several essential characteristics of two biochemical reaction models that have not been detected before. Utilizing the Lyapunov function, we compute the general form of the first Lyapunov coefficient to determine Hopf bifurcation for the Brusselator model. Then, for the smallest 3D biochemical reaction model, we obtain a center manifold up to third-degree to study Hopf bifurcation in this system. We demonstrate all results by numerical simulation.

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1 Introduction

Biochemical processes are the life-long operations of the chemical substances that appear in the habits of plants, animals, the human body, and microorganisms involving biomolecules. Biomolecules are organic compounds containing carbon, hydrogen, nitrogen, and oxygen, or macromolecules such as crude protein, polysaccharide, and nucleic acids. Biomolecules include polymers (proteins, peptides, cellulose, hemoglobin, nucleic acids, and polysaccharides) or monomers, which are the basic building blocks of polymers (alcohol, amino acids, nucleotides, carbohydrates, hormones, vitamins, acrylics, epoxides, and monosaccharides). The biochemical research results based on empirical evidence have significant applications in medicine, such as finding the causes of diseases and developing novel treatments, nutrition, such as determining the effects of nutrition on health, and agriculture, such as increasing crop quality and pest control. Through dynamical modeling of these processes by systems of ordinary differential equations employing the relative proportional changes in the state variables and dynamical analysis, it is possible to unravel the effects of exterior forces on living organisms [1]. In this way, biochemical models can describe chemical processes involving organic building compounds such as protein, carbohydrate, lipid, and nucleic acids, vitamins, and hormones, which are of great importance in vital biochemical reactions [2, 3]. We can classify biochemical models into three categories as structural biological models, enzyme models, and metabolic models. Moreover, we can perform the structural and qualitative analysis of the biochemical models by using the theory of dynamical systems and the novel methods of computational algebra to explain the life processes in living organisms such as protein synthesis, the conversion of nutrients into energy, and the transmission of hereditary characteristics by chemical mechanisms.

In 1960 Michael Savageau and Eberhard Voit introduced the idea of biochemical systems motivated by employing dynamical systems to investigate chemical processes involving biomolecules [4–7]. Thenceforth, studies on biochemical processes have elucidated the complications in the models, caused by the complex mechanisms underlying biochemical processes, by submitting some simplifications [8, 9]. Due to the complex nonlinear structure of biochemical reaction models, Hopf bifurcations have been studied mostly numerically for randomly chosen parameter values, and the investigation of limit cycles are limited to these numerical Hopf bifurcation studies except for some recently proposed

computational algebra approaches [10–15].

This paper utilizes an approach depending on Lyapunov functions and center manifold theory to study Hopf bifurcation in two biochemical systems. We obtain general parameter conditions for which the systems change qualitative behavior. In Sec. 2, we analyze the limit cycles of the Brusselator model, a prototype of the autocatalytic oscillatory reaction model with an approach by using the Lyapunov functions for two-dimensional systems to determine Hopf bifurcation. We show that under given parameter conditions, the Brusselator model undergoes a supercritical Hopf bifurcation, and there is no possibility for a subcritical Hopf bifurcation. In Sec. 3, we investigate the dynamics of the three-dimensional smallest biochemical model with Hopf bifurcation with the help of the approach for finding limit cycles using Lyapunov functions similar to Sec. 2. We obtain a center manifold of the three-dimensional system up to degree three and investigate the limit cycle bifurcations on the center manifold with an approach for analytic or smooth systems depending on parameters.

First, we give some general introduction about stability analysis and Hopf bifurcation and the theory related to the methods used in the paper.

Remark 1 . *It is well-known that for any system*

$$\begin{aligned} \dot{x} &= -y + P(x,y) = P_1(x,y) \\ \dot{y} &= x + Q(x,y) = Q_1(x,y), \end{aligned} \tag{1}$$

it is always possible to find a function $\Phi(x,y)$ *of the form [16]*

$$\Phi(x,y) = x^2 + y^2 + \sum_{j+k=3} \phi_{jk} x^j y^k, \tag{2}$$

such that

$$\frac{\partial \Phi}{\partial x} \cdot P_1(x,y) + \frac{\partial \Phi}{\partial y} \cdot Q_1(x,y) = g_1 \left(x^2+y^2\right)^2 + g_2 \left(x^2+y^2\right)^3 + \dots. \tag{3}$$

Notice that Φ *is a Lyapunov function for* (1)*, hence by the Lyapunov Theorem on asymptotic stability [17], the origin is a stable (unstable) focus if the first nonzero Lyapunov coefficient* g_i *on the right-hand side of* (3) *is negative (positive).*

When we transform system

$$\begin{aligned} \dot{x} &= ax + by + P'(x,y) = P_2(x,y) \\ \dot{y} &= cx - ay + Q'(x,y) = Q_2(x,y), \end{aligned} \tag{4}$$

which is a system where the trace of the linear approximation matrix is zero, to the form (1)*, we obtain expressions involving radicals. To avoid working with radicals, we look for a positive-definite Lyapunov function* Ψ *of the form*

$$\Psi(x,y) = \alpha x^2 + \beta xy + \gamma y^2 + \sum_{j+k=3} \psi_{jk} x^j y^k, \tag{5}$$

satisfying (3) *for system* (4)*. Computations explicate that the equality* (3) *can take place if we set*

$$\alpha = -\frac{c\beta}{2a}, \ \gamma = \frac{b\beta}{2a} \tag{6}$$

for system (4)*. As it is known the quadratic form*

$$\alpha x^2 + \beta xy + \gamma y^2 \tag{7}$$

is positive-definite, if $\alpha > 0$ *and* $4\alpha\gamma - \beta^2 > 0$*. In view of* (6)*,* $4\alpha\gamma - \beta^2 = -\beta^2\left(1 + \frac{bc}{a^2}\right)$*. Hence, when the origin of system* (4) *is a center or a focus, quadratic form* (7) *is positive-definite [11].*

We now present the Local Center Manifold Theorem, which shows that in some cases, the qualitative behavior in a neighborhood of a singular point x_0 of the system

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \tag{8}$$

with $\mathbf{x} \in \mathbf{R}^n$ is determined by its behavior on the center manifold near $\mathbf{x_0}$ [18]. Since the center manifold is generally of smaller dimension than system (8), this simplifies the problem of determining the stability and qualitative behavior of the flow near the singular points of system (8). We only present the theory for our purpose when there are no eigenvalues with positive real parts.

Theorem 1 (The Local Center Manifold Theorem) *[18]. Let* $\mathbf{f} \in \mathbf{C^r}(E)$*, where* E *is an open subset of* $\mathbf{R}^n$ *containing the origin and* $r \geq 1$*. Suppose that* $\mathbf{f}(\mathbf{0}) = \mathbf{0}$ *and the matrix of the linear part of* $\mathbf{f}$ *has* c *eigenvalues with zero real parts and* s *eigenvalues with negative real parts, where* $c + s = n$*. Then, system* (8) *can be written in the form*

$$\begin{aligned} \dot{\mathbf{x}} &= C\mathbf{x} + \mathbf{F}(\mathbf{x},\mathbf{y}) \\ \dot{\mathbf{y}} &= P\mathbf{y} + \mathbf{G}(\mathbf{x},\mathbf{y}), \end{aligned} \tag{9}$$

where $(\mathbf{x},\mathbf{y}) \in \mathbf{R^c} \times \mathbf{R^s}$*,* C *is a square matrix with* c *eigenvalues having zero real parts,* P *is a square matrix with* s *eigenvalues with negative real parts, and* $\mathbf{F}(0) = \mathbf{G}(0) = 0$*,*

$D\mathbf{F}(0) = D\mathbf{G}(0) = 0$; furthermore, there exists a $\delta > 0$ and a function $\mathbf{h}$ that defines the local center manifold

$$W^c(\mathbf{0}) = \{(\mathbf{x}, \mathbf{y}) \in \mathbf{R^c} \times \mathbf{R^s} | \mathbf{y} = \mathbf{h}(\mathbf{x}) for |\mathbf{x}| < \delta\}, \tag{10}$$

and satisfies

$$D\mathbf{h}(\mathbf{x})[C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{h}(\mathbf{x}))] - P\mathbf{h}(\mathbf{x}) - \mathbf{G}(\mathbf{x}, \mathbf{h}(\mathbf{x})) = 0 \tag{11}$$

for $|\mathbf{x}| < \delta$; and the flow on the center manifold $W^c(\mathbf{0})$ is defined by the system of differential equations

$$\dot{\mathbf{x}} = C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{y}) \tag{12}$$

for all $\mathbf{x} \in \mathbf{R}^c$ with $|\mathbf{x}| < \delta$.

Although equation (11) is a quasilinear partial differential equation for the components of $\mathbf{h}(\mathbf{x})$, which can be challenging to solve for $\mathbf{h}(\mathbf{x})$, it still gives us a method to compute $\mathbf{h}(\mathbf{x})$ to any degree that we wish, provided that the integer r in Theorem 1 is sufficiently large. This is accomplished by substituting the series expansion for the components of $\mathbf{h}(\mathbf{x})$ into equation (11).

Note that one of the important applications of center manifolds (called the Pliss reduction principle [19]) is that the reduction of the study of the stability of the original high-dimensional system to studying the stability of a lower dimensional system.

Now, we consider a three-dimensional system of the form

$$\dot{\mathbf{x}} = A\mathbf{x} + \mathbf{F}(\mathbf{x}) = \tilde{\mathbf{F}}(\mathbf{x}), \tag{13}$$

where $\mathbf{x} = (x, y, z)$, the matrix A has a pair of pure imaginary eigenvalues $\lambda_{1,2}$ and a real eigenvalue $\lambda_3 < 0$. $\mathbf{F}$ is an analytic vector-function in a neighborhood of the origin such that its series expansion starts from quadratic or higher terms, and $\tilde{\mathbf{F}}(\mathbf{x}) = (\tilde{F}_1(x), \tilde{F}_2(x), \tilde{F}_3(x))^T$.

After a linear transformation and rescaling of time, system (13) can be written in the form

$$\begin{aligned} \dot{u} &= \quad -v + P(u, v, w) = \widetilde{P}(u, v, w) \\ \dot{v} &= \quad u + Q(u, v, w) = \widetilde{Q}(u, v, s) \\ \dot{w} &= -\lambda w + R(u, v, w) = \widetilde{R}(u, v, w), \end{aligned} \tag{14}$$

where λ is a positive real number and P, Q, R are polynomials without constant or linear terms. By Theorem 1, system (14) has a center manifold $w = f(u, v)$ [20]. Hence, the

trajectories in a small neighborhood of the origin tend to the trajectories of the center manifold as time increases. The phase portrait of system (14) in a neighborhood of the origin on W^c can be either a center or a focus depending on the added nonlinear terms P, Q, and R. Since system (14) is analytic, for every $r \in \mathbb{N}$ there exists in a sufficiently small neighborhood of the origin a $\mathbf{C^r}$ invariant manifold W^c, the local center manifold, that is tangent to the (u, v)-plane at the origin and which contains all the recurrent behavior of system (14) in a neighborhood of the origin in $\mathbb{R}^{\mathbf{3}}$. To investigate the behavior of trajectories on the center manifold of system (14), we can find an initial string of the Taylor expansion of the manifold looking for it in the form $w = a_1 u + a_2 v + \ldots$, plug the expansion into the first two equations of system (14), and then study the dynamics of the resulting two-dimensional system.

For the proof of the following theorem, see [21].

Theorem 2 (Lyapunov Center Theorem) *[21]. For system* (14) *with the corresponding vector field*

$$\mathfrak{X} := \widetilde{P}\tfrac{\partial}{\partial u} + \widetilde{Q}\tfrac{\partial}{\partial v} + \widetilde{R}\tfrac{\partial}{\partial w},$$

the origin is a center for $\mathfrak{X}|W^c$ *if and only if* $\mathfrak{X}$ *admits a real analytic local first integral of the form*

$$\Phi(u, v, w) = u^2 + v^2 + \sum_{j+k+l \geq 3} \phi_{jkl} u^j v^k w^l \tag{15}$$

in a neighborhood of the origin in $\mathbb{R}^{\mathbf{3}}$*. Moreover, when there exists a center, the local center manifold* W^c *is unique and is analytic.*

For system (14), we can find a function $\Phi(u, v, w)$ of the form (15) such that

$$\mathfrak{X}\Phi(u, v, w) = \sum_{k=1}^{\infty} g_k \left(u^2 + v^2\right)^{k+1}. \tag{16}$$

Functions g_k and ϕ_{jkl} depend on the parameters of the system, if on the right-hand sides of (14) are functions depending on parameters. If all g_k vanish for some parameter values, system (14) has a center at the origin. If all g_k do not vanish for some parameter values, by the Lyapunov stability theorem [16], the singular point at the origin is a stable focus (unstable focus), if the first nonzero g_k is negative (positive). If the first nonzero coefficient in (16) is g_K, by perturbing the system such that $|g_{i-1}| \ll |g_i|$ and the signs of g_k alternate, we obtain $K - 1$ limit cycles bifurcated from the origin of the system [11, 22]. The following theorem shows that a similar approach can be applied to

study bifurcations of limit cycles on the center manifold of system (13). Although it is possible to transform system (13) to system (14), such transformation usually involves expressions containing radicals which will also appear in the coefficients of system (14). By this approach, we study system (13) for which we assume that function $\tilde{\mathbf{F}}$ depends on parameters $\mathbf{a} = (a_1, a_2, \ldots, a_s)$ to bypass radical expressions. For the proof of the next theorem, see [11].

Theorem 3 *[11]. Assume that for system* (13)*, there exists a polynomial*

$$\Psi(x, y, z) = \sum_{i+j+k=2}^{\infty} \psi_{ijk} x^i y^j z^k, \tag{17}$$

such that

$$\begin{aligned} \mathfrak{X}\Psi &= \frac{\partial \Psi}{\partial x} \cdot \tilde{F}_1 + \frac{\partial \Psi}{\partial y} \cdot \tilde{F}_2 + \frac{\partial \Psi}{\partial z} \cdot \tilde{F}_3 \\ &= g_1 \left(x^2 + y^2\right)^2 + g_2 \left(x^2 + y^2\right)^3 + \ldots + g_{n-1} \left(x^2 + y^2\right)^n + O\left(\|(x, y, z)\|^{2n+1}\right). \end{aligned} \tag{18}$$

Let

$$z = f(x, y, \boldsymbol{a}^*) \tag{19}$$

be the center manifold of system (13) *corresponding to the value* $\boldsymbol{a}^*$ *of parameters of the system, and*

$$p_2(x, y, z, \boldsymbol{a}^*) = \sum_{i+j+k=2} \psi_{ijk} x^i y^j z^k \tag{20}$$

be the quadratic part of (17)*. Let* $\tilde{p}_2(x, y, \boldsymbol{a}^*)$ *be* $p_2(x, y, z, \boldsymbol{a}^*)$ *evaluated on* (19)*. Assume that* $\tilde{p}_2(x, y, \boldsymbol{a}^*)$ *is a positive-definite quadratic form and*

$$g_1(\boldsymbol{a}^*) = g_2(\boldsymbol{a}^*) = \ldots = g_\ell(\boldsymbol{a}^*) = 0, \quad g_{\ell+1}(\boldsymbol{a}^*) \neq 0, \tag{21}$$

where $\ell < n - 1$*. Then,*

i) *if* $g_{\ell+1}(\boldsymbol{a}^*) < 0$ *(*$g_{\ell+1}(\boldsymbol{a}^*) > 0$*), system* (13) *has a stable (unstable) focus at the origin on the center manifold,*

ii) *if it is possible to choose perturbations of the parameters* $\boldsymbol{a}$ *in system* (13) *such that*

$$|g_1(\boldsymbol{a}^{(\ell,*)})| \ll |g_2(\boldsymbol{a}^{(\ell-1,*)})| \ll \ldots \ll |g_\ell(\boldsymbol{a}^{(1,*)})| \ll |g_{\ell+1}(\boldsymbol{a}^*)|, \tag{22}$$

$\boldsymbol{a}^{(i+1,*)}$ *is arbitrarily close to* $\boldsymbol{a}^{(i,*)}$*, and the signs of* $g_s(\boldsymbol{a}^{(m,*)})$ *in* (22) *alternate, then system* (13) *corresponding to the parameter* $\boldsymbol{a}^{(\ell,*)}$ *has at least* ℓ *limit cycles on the center manifold.*

By using the Lyapunov functions and Theorem 3, we look for function (17) satisfying (18) and use Theorem 4 to eliminate x, y, z from the system. We describe the following computational procedure to find the first m polynomials g_i below.

1. Write down the initial string of (17) up to order $2m$,

$$\Psi_{2m}(x, y, z) = \sum_{i+j+k=2}^{2m} \psi_{ijk} x^i y^j z^k.$$

2. Equalize the coefficients of the terms of order ℓ in the expression

$$\frac{\partial \Psi_{2m}}{\partial x} \cdot \tilde{F}_1 + \frac{\partial \Psi_{2m}}{\partial y} \cdot \tilde{F}_2 + \frac{\partial \Psi_{2m}}{\partial z} \cdot \tilde{F}_3 - g_1(x^2+y^2)^2 - \cdots - g_{m-1}(x^2+y^2)^m = 0 \quad (23)$$

to zero for each $\ell = 2, \ldots, 2m$ to obtain $2m-1$ linear systems with unknown variables ψ_{ijk} and $g_1, \ldots, g_m$.

3. Look for solutions of all linear systems beginning from $\ell = 2$. Note that, the linear systems that correspond to odd $\ell = 2\ell_0 - 1$ always have unique solutions. Then substitute the resulting ψ_{ijk} values in the linear systems that correspond to $\ell > 2\ell_0 - 1$. For systems that correspond to even $\ell = 2i_0$, consider the linear system with unknowns ψ_{ijk} and g_{ℓ_0}. In this case, one of the ψ_{ijk} values can be chosen arbitrarily. After solving the system, if $\ell_0 = 2$, assign 1 to the undefined ψ_{ijk}, and if $\ell_0 > 2$ assign 0 to undefined ψ_{ijk}. Then, substitute the resulting ϕ_{ijk} to the linear systems that correspond to $\ell > 2\ell_0$.

4. Evaluate (23) with the resulting ϕ_{ijk} $(i + j + k \leq 2i_0)$ to find the coefficient of $x^{i_0} y^{j_0} z^{k_0}$ which is denoted by $g_{\ell_0 - 1}$.

By the Pliss reduction principle, the stability of the origin of system (14) is the same as the stability of the singular point at the origin on the center manifold. Therefore, if condition (21) holds, the origin of system (14) is asymptotically stable if $g_{k+1}(\mathbf{a}^*) < 0$, and it is unstable if $g_{k+1}(\mathbf{a}^*) > 0$ [19].

Now, we recall some theory about elimination ideals, which we will use later.

Consider a system of polynomials with coefficients in some field k,

$$f_1(x_1, \ldots, x_n) = \cdots = f_k(x_1, \ldots, x_n) = 0, \quad (24)$$

and the corresponding ideal $I = \langle f_1, \ldots, f_k \rangle \subset k[x_1, \ldots, x_n]$.

Definition 1 *[16]. Let I be an ideal in $k[x_1, \ldots, x_n]$ with the implicit ordering of the variables $x_1 > x_2 > \cdots > x_n$, and fix $\ell \in \{0, 1, \ldots, n-1\}$. The ℓth* elimination ideal *of I is the ideal $I_\ell = I \cap k[x_{\ell+1}, \ldots, x_n]$.*

Theorem 4 (Elimination Theorem) *[16]. Let us fix the lexicographic term order on the ring $k[x_1, \ldots, x_n]$ with $x_1 > x_2 > \cdots > x_n$ and let G be a Gröbner basis for an ideal I of $k[x_1, \ldots, x_n]$ with respect to this order. Then for every ℓ, $0 \leq \ell \leq n-1$, the set*

$$G_\ell := G \cap k[x_{\ell+1}, \ldots, x_n]$$

is a Gröbner basis for the ℓth elimination ideal I_ℓ.

We apply this theory by examining the first Lyapunov coefficients to study the Brusselator model in Sec. 2 and the smallest biochemical model with Hopf bifurcation in Sec. 3.

2 The Brusselator model

In 1971, Ilya Prigogine introduced a prototype of the autocatalytic oscillatory reaction model, called the Brusselator model, concerning the reaction schemes [23]

$$A \xrightarrow{\tilde{k}_1} X$$

$$B + X \xrightarrow{\tilde{k}_2} Y + D$$

$$2X + Y \xrightarrow{\tilde{k}_3} 3X$$

$$X \xrightarrow{\tilde{k}_4} E,$$

where A and B are initial reactants, D and E are reaction products and X and Y are the autocatalytic reactants, $\tilde{k}_1, \tilde{k}_2, \tilde{k}_3$, and $\tilde{k}_4$ are values of the reaction rate coefficients for each component reaction. Acknowledging the law of mass action in these schemes, we obtain the system

$$\begin{aligned} \dot{x} &= k_1 - (k_2 + k_4)x + k_3 x^2 y \\ \dot{y} &= k_2 x - k_3 x^2 y, \end{aligned} \tag{25}$$

under the transformation $k_1 = A_0 \tilde{k}_1$ and $k_2 = B_0 \tilde{k}_2$, where A and B are assumed to be constant, and A_0 and B_0 are their initial values. Here, $\dot{x}$ and $\dot{y}$ denote the change in the concentrations of the two variables with respect to time.

Similar to various autocatalytic models, the Brusselator model possesses numerous steady-states and periodic orbits [24]. Llibre et al. examined the first integrals of the Brusselator model in function of its parameters in 2012 [13], and its dynamics by analyzing the flow of it in the Poincaré disc in 2020 [14]. The existence of Hopf bifurcation for

the generic models of Brusselator type subject to the homogeneous Neumann boundary condition is presented by Li, by adapting useful notations of diffusion-driven instability [25]. Nevertheless, there is no comprehensive study on the general case of Hopf bifurcation analysis in the original Brusselator model. In this section, we determine the existence and the stability of Hopf bifurcation for the diffusion-free Brusselator model by utilizing Lyapunov functions.

System (25) has a unique singular point at $E = (\frac{k_1}{k_4}, \frac{k_2 k_4}{k_1 k_3})$ which is positive for chemically relevant parameters $k_1 > 0$, $k_2 > 0$, $k_3 > 0$ and $k_4 > 0$. Replacing (x, y) with E, the characteristic equation of system (25) is

$$\lambda^2 + \left(\frac{k_1^2 k_3}{k_4^2} - k_2 + k_4\right)\lambda + \frac{k_1^2 k_3}{k_4} = 0 \ . \tag{26}$$

To have a pair of pure imaginary roots

$$\lambda^2 + w^2 = 0, \tag{27}$$

the characteristic polynomial must satisfy

$$k_2 > k_4, k_3 = \frac{k_4^2}{k_1^2}(k_2 - k_4). \tag{28}$$

To verify the transversality conditions at E [11]

$$\frac{d}{dk_3} Re(\lambda_{1,2}^+) > 0, \frac{d}{dk_3} Re(\lambda_{1,2}^-) < 0, \tag{29}$$

we differentiate characteristic equation (26) with respect to k_3 and we get

$$\frac{d\lambda}{dk_3}\left(2\lambda + \frac{k_1^2 k_3}{k_4^2} - k_2 + k_4\right) + \frac{k_1^2}{k_4^2}\lambda + \frac{k_1^2}{k_4} = 0, (k_4 \neq 0) \tag{30}$$

from which follows

$$\left(\frac{d\lambda}{dk_3}\right)^{-1} = \frac{2\lambda + \frac{k_1^2 k_3}{k_4^2} - k_2 + k_4}{-\frac{k_1^2}{k_4^2}\lambda - \frac{k_1^2}{k_4}}. \tag{31}$$

Thus,

$$\begin{aligned} sign\left\{\frac{d}{dk_3}(Re\lambda_{1,2})\right\}_{k_3^+} &= sign\left\{Re(\frac{d\lambda_{1,2}}{dk_3})_{k_3^+}^{-1}\right\} \\ &= sign\left\{Re\left(\frac{2\lambda + \frac{k_1^2 k_3^+}{k_4^2} - k_2 + k_4}{-\frac{k_1^2}{k_4^2}\lambda - \frac{k_1^2}{k_4}}\right)\right\} \\ &= sign\left\{\frac{\frac{k_1^2 k_3^+}{k_4^2} - k_2 + k_4}{-\frac{k_1^2}{k_4^2}}\right\} = 1(k_2 > k_4) \end{aligned} \tag{32}$$

Similarly,

$$\begin{aligned} sign\left\{\frac{d}{dk_3}(Re\lambda_{1,2})\right\}_{k_3^-} &= sign\left\{Re\left(\frac{d\lambda_{1,2}}{dk_3}\right)^{-1}_{k_3^-}\right\} \\ &= sign\left\{\frac{\frac{k_1^2k_3^-}{k_4^2}-k_2+k_4}{-\frac{k_1^2}{k_4^2}}\right\} = -1(k_2<k_4)\ . \end{aligned} \tag{33}$$

Thus, (29) holds. The eigenvalues of the Jacobian of system (25) at E are

$$\lambda_{1,2} = \frac{(k_2-k_4)k_4^2-k_1^2k_3 \pm \sqrt{((k_2-k_4)k_4^2-k_1^2k_3)^2-4k_1^2k_3k_4^3}}{2k_4^2}\ . \tag{34}$$

If $(k_1^2k_3+k_4^2(k_4-k_2))^2-4k_1^2k_3k_4^3<0$, the eigenvalues of the Jacobian matrix of system (25) are complex conjugates. Additionally, when $(k_2-k_4)k_4^2-k_1^2k_3\neq 0$, all trajectories are spirals in the neighborhood of the singular point E and the singular point is a focus. Moreover, when $(k_2-k_4)k_4^2-k_1^2k_3<0$, all near trajectories move towards E, and when $(k_2-k_4)k_4^2-k_1^2k_3>0$, all near trajectories move away from E [26]. When $(k_2-k_4)k_4^2-k_1^2k_3=0$, the singular point E is either a center where all trajectories are elliptical, or a focus, known as the center-focus problem which is a challenging task to study [16].

To determine the Hopf bifurcation of system (25), we first move the singular point $E(\frac{k_1}{k_4},\frac{k_2k_4}{k_1k_3})$ to the origin by performing the linear transformation

$$x \to X+\frac{k_1}{k_4},\quad y\to Y+\frac{k_2k_4}{k_1k_3},$$

which after rewriting X as x and Y as y, yields the following system.

$$\begin{aligned} \dot{x} &= \frac{k_4^2x(k_1(k_2-k_4)+k_2k_4x)+k_1k_3(k_1+k_4x)^2y}{k_1k_4^2} = F(x,y) \\ \dot{y} &= -\frac{(k_1+k_4x)(k_2k_4^2x+k_1k_3(k_1+k_4x)y)}{k_1k_4^2} = G(x,y)\ . \end{aligned} \tag{35}$$

A common approach to determine Hopf bifurcations is the computation of normal forms [27]. Considering that the computation of the normal form is a highly laborious procedure, we propose a diverse approach based on Lyapunov functions, for which the computations are comparatively more manageable for chemical systems.

Theorem 5 . *If in system* (35) *(or* (25)*) parameters satisfy conditions* (28)*, then the singular point is a stable focus.*

Proof 1 . *The eigenvalues of the linearized system are*

$$\mu_{1,2} = \pm\sqrt{k_4(k_4-k_2)}\ .$$

The expression under the radical is always negative since $k_2 > k_4$, therefore the singular point at the origin of (35) *is either a center or a focus (the same conclusion holds for the point E of system* (25)*). For system* (35) *we look for a function of the form*

$$\Psi_8(x,y) = \sum_{k+s=2}^{8} \psi_{ks} x^k y^s \tag{36}$$

satisfying

$$\frac{\partial \Psi_8}{\partial x} \cdot F(x,y) + \frac{\partial \Psi_8}{\partial y} \cdot G(x,y) = g_1(x^2+y^2)^2 + g_2(x^2+y^2)^3 + g_3(x^2+y^2)^4. \tag{37}$$

For $k+s=2$, the left-hand side of equation (37) *is*

$$\begin{aligned}
&\frac{\partial(\alpha x^2+\beta xy+\gamma y^2)}{\partial x} \cdot F(x,y) + \frac{\partial(\alpha x^2+\beta xy+\gamma y^2)}{\partial y} \cdot G(x,y) \\
&= (2\alpha x+\beta y)\frac{k_4^2 x(k_1(k_2-k_4)+k_2k_4x)+k_1k_3(k_1+k_4x)^2 y}{k_1k_4^2} \\
&- (\beta x+2\gamma y)\frac{(k_1+k_4x)(k_2k_4^2x+k_1k_3(k_1+k_4x)y)}{k_1k_4^2} \\
&= (2\alpha(k_2-k_4)-\beta k_2)x^2 + \left(-2\gamma k_2+\beta(k_2-\frac{k_1^2k_3}{k_4^2}-k_4)+\frac{2\alpha k_1^2k_3}{k_4^2}\right)xy \\
&+ (\beta-2\gamma)\frac{k_1^2k_3}{k_4^2}y^2 + h.o.t. = 0,
\end{aligned} \tag{38}$$

from which we obtain

$$\alpha = \frac{\beta k_2}{2(k_2-k_4)}, \quad \gamma = \frac{\beta}{2} \tag{39}$$

by equalizing the coefficients in front of each quadratic term to zero. Note that

$$\begin{aligned}
\frac{\partial F(x,y)}{\partial x}\Big|_{y=0} &= k_2-k_4, \frac{\partial F(x,y)}{\partial y}\Big|_{x=0} = \frac{k_1^2k_3}{k_4^2}, \frac{\partial G(x,y)}{\partial x}\Big|_{y=0} \\
&= -k_2, \frac{\partial G(x,y)}{\partial y}\Big|_{x=0} = -\frac{k_1^2k_3}{k_4^2},
\end{aligned} \tag{40}$$

hence,

$$\frac{\partial F(x,y)}{\partial x}\Big|_{y=0} + \frac{\partial G(x,y)}{\partial y}\Big|_{x=0} = k_2-k_4-\frac{k_1^2k_3}{k_4^2} = 0 \tag{41}$$

gives (28). *Continuing by this manner and equalizing the coefficients in front of the same monomials $x^k y^s$ on both sides of equation* (37), *we obtain all coefficients up to degree 8. We choose $\beta = 2$ without loss of generality, so that the quadratic form* (7) *of* (36) *is positive-definite, since $4\alpha\gamma - \beta^2 = \frac{4k_4}{k_2-k_4} > 0 (k_2 > k_4)$. Since the quadratic form* (7) *is positive-definite, $\Psi_8(x,y)$ given in* (36) *is a positive-definite Lyapunov function*

in a sufficiently small neighborhood of the origin for system (35). *Performing further computations, we obtain the first Lyapunov coefficient*

$$g_1 = -\frac{2k_4^3(k_2-k_4)(k_2+k_4)}{k_1^2(12k_2^2-16k_2k_4+7k_4^2)} \ . \tag{42}$$

The semi-algebraic system

$$g_1 \geq 0 \ \wedge \ k_1 > 0 \ \wedge \ k_2 > k_4 \ \wedge \ k_4 > 0 \ \wedge \ k_3 = \frac{k_4^2}{k_1^2}(k_2-k_4) \tag{43}$$

has no solution; therefore, g_1 *is always negative. Since* $g_1 < 0$*, the derivative with respect to the vector field is negative-definite considering* (37). *Consequently, system* (35) *undergoes supercritical Hopf bifurcation near* E.

Example 1 . *We have shown that system* (25) *undergoes Hopf bifurcation under condition* (28). *In particular, for* $(k_1, k_2, k_4) = (1, 2.6, 1.8)$*, and* $k_3 = \frac{k_4^2}{k_1^2}(k_2 - k_4) = 2.592$*, system* (25) *becomes*

$$\dot{x} = 1 - 4.4x + 2.592x^2y \, , \quad \dot{y} = 2.6x - 2.592x^2y \ . \tag{44}$$

The eigenvalues of the Jacobian matrix of system (44) *at singular point* $E = (0.55, 1.805)$ *are* $\pm 1.2i$*. Since* $g_1 = -1.41968 < 0$*, singular point* E *is a stable focus of system* (44) *as shown in Fig. 1* (*a*)*. Near trajectories moving towards* E *from initial point* $(0.54, 2.1)$ *is illustrated. When parameter* k_3 *changes to the slightly smaller value* 2.55*, the focus at* E *becomes unstable leading to a supercritical Hopf bifurcation for system* (25) *as shown in Fig. 1* (*b*)*. The trajectories emerging from initial point* $(0.54, 1.79)$ *move away from* E *and the trajectories emerging from initial point* $(0.42, 1.78)$ *move towards* E.

3 The smallest biochemical model

In 1995, Wilhelm et al. presented the smallest biochemical system based on a sufficient condition for a Hopf bifurcation in three-dimensional systems with the reaction scheme [28, 29]

$$A + X \xrightarrow{\tilde{k}} 2X$$

$$X + Y \xrightarrow{\tilde{k}_2} A + Y$$

$$Y \xrightarrow{\tilde{k}_3} A$$

$$X \xrightarrow{\tilde{k}_4} Z$$

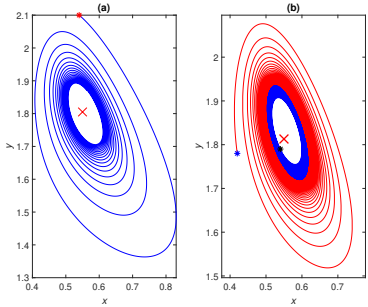

Figure 1. In (a), $\times$ and $\star$ denote the singular point and initial point for system (44) respectively. In (b), red $\times$ denotes singular point, blue $\star$ and black $\star$ denote initial points.

$$Z \xrightarrow{\tilde{k}_5} Y$$

where A denotes outer reactants representing at least two different substances for thermodynamical reasons, and X, Y and Z are the autocatalytic reactants, $\tilde{k}, \tilde{k}_2, \tilde{k}_3$, $\tilde{k}_4$, and $\tilde{k}_5$ values are the reaction rate coefficients for each component reaction. By considering the mass action law, the system dynamics are governed by the system of differential equations

$$\begin{aligned} \dot{x} &= kx - k_2xy \\ \dot{y} &= -k_3y + k_5z \\ \dot{z} &= k_4x - k_5z, \end{aligned} \tag{45}$$

where the parameters k, k_2, k_3, k_4 and k_5 are positive real numbers. In 2009, Wilhelm discussed the roles of the reactions concerning the necessary conditions for the bistability of system (45) [30]. Smith presented the global behavior of solutions for system (45) that exhibits a Hopf bifurcation, a competitive system with a monotone cyclic feedback, with the help of the Poincaré-Bendixson theory by ruling out periodic orbits with a Bendixson criterion in 2012 [31]. This section describes an approach to studying limit cycle bifurcations of system (45) using a Lyapunov function on the center manifold.

System (45) has two singularities, $E_0 = (0, 0, 0)$ and

$$E_1 = \left(\frac{kk_3}{k_2k_4}, \frac{k}{k_2}, \frac{kk_3}{k_2k_5} \right). \tag{46}$$

We consider E_1 when all parameters are positive real numbers in order for the system to have a chemical meaning. The Jacobian of the matrix of the linear approximation of

system (45) at singular point E_1 is

$$A = \begin{pmatrix} 0 & -\frac{kk_3}{k_4} & 0 \\ 0 & -k_3 & k_5 \\ k_4 & 0 & -k_5 \end{pmatrix}.$$

The eigenvalues of A are roots of a cubic polynomial and have rather complicated expression. To simplify calculations, we use the following approach [32] based on the elimination theory [16, 33]. The characteristic polynomial of matrix A is

$$p(\lambda) = kk_3k_5 - k_3k_5\lambda - k_3\lambda^2 - k_5\lambda^2 - \lambda^3.$$

By equalizing the coefficients of the same terms on both sides of the equation

$$p(\lambda) = -(\lambda^2 + w^2)(\lambda + b), \tag{47}$$

we obtain the system

$$-kk_3k_5 + bw^2 = 0, -k_3k_5 + w^2 = 0, b - k_3 - k_5 = 0. \tag{48}$$

Computation of the second elimination ideal of the ideal $I = \langle -kk_3k_5 + bw^2, -k_3k_5 + w^2, b - k_3 - k_5\rangle$ with respect to the ordering $\{w, b\} > \{k, k_2, k_3, k_4, k_5\}$ to eliminate the variables w and b from system (48), yields the ideal $\langle k - k_3 + k_5\rangle$, which gives the condition

$$k = k_3 + k_5. \tag{49}$$

Hence, system (45) has a pair of pure imaginary eigenvalues if (49) is satisfied. In this case, system (45) becomes

$$\begin{aligned} \dot{x} &= (k_3 + k_5)x - k_2xy \\ \dot{y} &= -k_3y + k_5z \\ \dot{z} &= k_4x - k_5z, \end{aligned} \tag{50}$$

which for positive values k_i, $(i = 2, 3, 4, 5)$ has a pair of pure imaginary eigenvalues $\lambda_{1,2} = \pm i\sqrt{k_3k_5}$ and a negative eigenvalue $\lambda_3 = -k_3 - k_5$. Moving E_1 to the origin by the linear transformation under (49)

$$X = x - \frac{k_3(k_3 + k_5)}{k_2k_4}, \quad Y = y - \frac{k_3 + k_5}{k_2}, \quad Z = z - \frac{k_3(k_3 + k_5)}{k_2k_5}$$

and rewriting X as x and Y as y, yields the system

$$\begin{aligned} \dot{x} &= -\frac{k_3^2 + k_3k_5}{k_4}y - k_2xy \\ \dot{y} &= -k_3y + k_5z \\ \dot{z} &= k_4x - k_5y. \end{aligned} \tag{51}$$

Theorem 6 . *If in system* (51) *(or* (50)*) parameters satisfy conditions* (49)*, then the singular point is a stable focus.*

Proof 2 . *For system* (51) *we look for a function of the form* (36) *satisfying* (**??**)*. The calculations using the procedure described in the Introduction applied similarly to system* (25) *leads*

$$\begin{aligned} g_1 = &-\frac{4k_5^2(k_2^2k_3^3k_4^2+k_2^2k_3^2k_4^2k_5)}{k_3^2+6k_3k_5+k_5^2}\left(3k_3^6+12k_3^5k_5+2k_3^3k_4^2k_5+18k_3^4k_5^2+4k_3^2k_4^2k_5^2\right.\\ &\left.+3k_4^4k_5^2+12k_3^3k_5^3+2k_3k_4^2k_5^3+3k_3^2k_5^4\right)\ , \end{aligned} \tag{52}$$

for system (51)*, which is negative.*

Now, we look for a center manifold of system (51) *of the form* $z = h(x, y)$*. Substituting the series expansion for the components of* $h(x, y)$ *into*

$$\dot{z} = \frac{\partial h}{\partial x}\dot{x} + \frac{\partial h}{\partial y}\dot{y},$$

we determine the center manifold $h(x, y)$ *up to degree three:*

$$\begin{aligned} h(x,y) = &\frac{k_4}{k_3+k_5}x+\frac{k_3}{k_5}y-\frac{k_2k_4^2k_5}{(k_3+k_5)^2(k_3^2+6k_3k_5+k_5^2)}x^2\\ &+\frac{k_2k_4}{k_3^2+6k_3k_5+k_5^2}xy+\frac{k_2k_3}{k_3^2+6k_3k_5+k_5^2}y^2\\ &+\frac{6k_2^2k_4^3k_5^2(k_3^4+8k_3^3k_5+19k_3^2k_5^2+8k_3k_5^3+k_5^4)}{(k_3+k_5)^3(k_3^2+6k_3k_5+k_5^2)^2(k_3^4+14k_3^3k_5+35k_3^2k_5^2+14k_3k_5^3+k_5^4)}x^3\\ &+\frac{k_2^2k_4(k_3^6+4k_3^5k_5+10k_3^4k_5^2+32k_3^3k_5^3+10k_3^2k_5^4+4k_3k_5^5+k_5^6)}{(k_3+k_5)(k_3^2+6k_3k_5+k_5^2)^2(k_3^4+14k_3^3k_5+35k_3^2k_5^2+14k_3k_5^3+k_5^4)}xy^2\\ &+\frac{k_2^2k_4^2k_5(5k_3^4+34k_3^3k_5+79k_3^2k_5^2+34k_3k_5^3+5k_5^4)}{(k_3+k_5)(k_3^2+6k_3k_5+k_5^2)^2(k_3^4+14k_3^3k_5+35k_3^2k_5^2+14k_3k_5^3+k_5^4)}x^2y\\ &+\frac{k_2^2k_3(k_3+k_5)(k_3^4-19k_3^2k_5^2+k_5^4)}{(k_3^2+6k_3k_5+k_5^2)^2(k_3^4+14k_3^3k_5+35k_3^2k_5^2+14k_3k_5^3+k_5^4)}y^3+\dots. \end{aligned} \tag{53}$$

For system (51)*, the quadratic part of function* (17) *is*

$$p_2(x,y,z) = k_4^2x^2 - 2k_3k_4xy + k_3^2y^2 + k_3k_5y^2 + 2k_3k_5yz + k_3k_5z^2\ . \tag{54}$$

We substitute the linear terms of the center manifold, $z = h(x, y) = \frac{k_4}{k_3+k_5}x + \frac{k_3}{k_5}y$*, into* (54)*, and obtain*

$$\tilde{p}_2(x,y) = \frac{k_4^2(k_3^2+3k_3k_5+k_5^2)}{(k_3+k_5)^2}x^2 + \frac{k_3(k_3^2+3k_3k_5+k_5^2)}{k_5}y^2$$

which is a positive-definite quadratic form. Hence, supercritical Hopf bifurcation occurs for the flow of system (45) *restricted to the center manifold.*

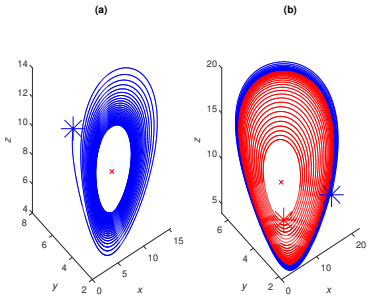

Figure 2. In (a) and (b), red $\times$ represents the singular point E and red and blue $*$ represent initial points.

Example 2 . *When* $(k, k_2, k_3, k_4, k_5) = (3.5, 1, 2.5, 1.3, 1)$, *system* (45) *has the singular point* $E = (6.73077,\ 3.5,\ 8.75)$ *with the eigenvalues* $\lambda_{1,2} = \pm 1.58114i$ *and* $\lambda_3 = -3.5$. *In Fig. 2* (*a*), *we see that the singular point* E *is a stable focus. When* $k = 3.85$, *the stable limit cycle is observed as given in Fig. 2* (*b*) *with the first Lyapunov coefficient* $g_1 = -0.000501049$. *The eigenvalue spectrum of system* (45) *at the singular point where supercritical Hopf bifurcation occurs is given in Fig. 3.*

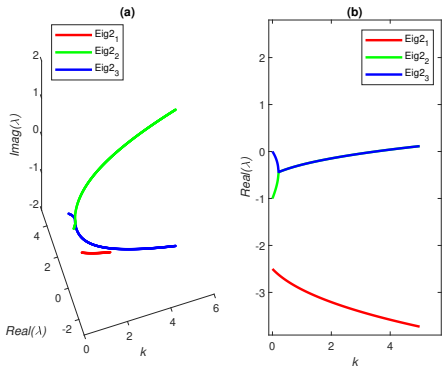

Figure 3. Eigenvalue spectrum of the singular point E for system (45).

4 Conclusion

In this paper, we have studied the existence and the stability of Hopf bifurcation for a two-dimensional and a three-dimensional biochemical reactor models by using Lyapunov

functions and center manifold theory. This approach can help study steady-state solutions and bifurcations of more realistic biochemical models for which analytical solutions can not be obtained. The biochemical systems which have no analytical solutions, allow the investigations to be carried on with this computational algebraic method.

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