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A graph-theoretic method for detecting potential Turing bifurcations

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The conditions for diffusion-driven (Turing) instabilities in systems with two reactive species are well known. General methods for detecting potential Turing bifurcations in larger reaction schemes are, on the other hand, not well developed. We prove a theorem for a graph-theoretic condition originally given by Volpert and Ivanova [*Mathematical Modeling* (Nauka, Moscow, 1987) (in Russian), p. 57] for Turing instabilities in a mass-action reaction-diffusion system involving n substances. The method is based on the representation of a reaction mechanism as a bipartite graph with two types of nodes representing chemical species and reactions, respectively. The condition for diffusion-driven instability is related to the existence of a structure in the graph known as a critical fragment. The technique is illustrated using a substrate-inhibited bifunctional enzyme mechanism which involves seven chemical species. © 2006 American Institute of Physics.

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I. INTRODUCTION

The aim of this work is to provide graph-theoretic conditions for detecting possible diffusion-driven (Turing) instabilities in biochemical or chemical reaction networks and locating the corresponding Turing bifurcation.¹ Finding the Turing instabilities in biochemical models involves the analysis of a system of reaction-diffusion equations. Most studies on diffusion-driven instabilities consider systems of two equations only² with a few exceptions of three or more.^{3–5} In most cases, e.g., the Brusselator⁶ and Belousov-Zhabotinsky reactions,^{7,8} autocatalysis implies a Turing instability. However, many biochemical reactions involve a large number of substances (genes, proteins, metabolites, signaling molecules) and reactions creating large biochemical (genetic, metabolic, signaling) networks.⁹ This requires generalization of the autocatalysis rule.

Several prior studies^{2,4,10} have concentrated on obtaining algebraic conditions for diffusion-driven instability that relate to matrix stability theory.^{11,12} Recently, however, a large amount of research has been devoted to complex biochemical networks.^{1,13–15} One difficulty which has stimulated work on network properties is the absence of kinetic parameters necessary for a differential equation model¹⁶ and thus for techniques such as numerical bifurcation analysis. Therefore it is essential to develop graphical conditions for analyzing properties of biochemical networks.

A major topic in systems biology is the connection between smaller recurring network modules and specific biological functions.^{14,17} Some modules are known to be responsible for oscillations or multistability.^{18–20} However, the

repertoire of modules which may cause such behaviors is no doubt much larger than is known at present. Moreover, even the known modules may be difficult to recognize when embedded in a large metabolic network. Therefore, methods that can be used to identify such modules are particularly valuable. Moreover only the network itself, i.e., the graph of relationships between molecular species, is available for many signaling pathways,¹⁶ making graph-theoretic analysis one of the few possible approaches.²¹

Biochemical networks are often represented by various types of graphs.^{15,22–24} Here we study mass-action kinetics reaction networks and will represent them as bipartite graphs.²⁵ The convenience of bipartite graph representation, especially for biochemical networks, has been emphasized elsewhere.^{16,26,27}

We will follow Volpert and Ivanova²⁸ closely and will review some of their results. However, they do not provide proofs for their propositions in Ref. 28, a gap which we fill in here. To our knowledge, Ref. 28 contains the first general condition for diffusion-driven instability applicable to a reaction-diffusion system. This condition generalizes the concept of indirect catalysis.²⁹

The ordinary differential equation counterpart to this problem has been studied elsewhere^{23,28} and many of the results therein are essential for understanding the theory in this paper.

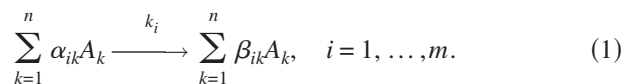
In Sec. II some preliminaries about the ordinary differential equation model relevant to the corresponding reaction-diffusion system are explained. In Sec. III the main ideas of the graph-theoretic analysis are introduced. In Sec. IV the reaction-diffusion system and the graph-theoretic condition for diffusion-driven instability are given. An example of a Turing instability in a model for the function of a bifunctional enzyme is studied using these new methods in Sec. IV.

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II. PRELIMINARIES

We study chemical mechanisms of n chemical substances A_k , $k=1, \dots, n$, and m chemical reactions with rate constants $k_i > 0$, $i=1, \dots, m$. Symbolically, the mechanism can be represented as



In a fully detailed mechanism the constants α_{ik} and β_{ik} are non-negative integers, called stoichiometric coefficients.

Let the concentration of A_k be denoted by u_k , $k=1, \dots, n$. If the law of mass action is used then the rate of the i th reaction in (1) is

$$w_i(\mathbf{u}) = k_i u_1^{\alpha_{i1}} \cdots u_n^{\alpha_{in}}, \quad i = 1, \dots, m, \quad (2)$$

where it is understood that $u_k^0 = 1$ for $u_k \geq 0$. In biochemistry it is typical that several elementary reactions are combined into one with an overall rate. The extension of the theory presented in this paper to models with non-mass-action rates is an open problem. In the case in which the rates are monotone functions of the reactant concentrations, we suspect that this extension should be straightforward although we have made no attempt to study this case.

Let $\gamma_{ik} = \beta_{ik} - \alpha_{ik}$ for $i=1, \dots, m$ and $k=1, \dots, n$. Then a solution of the initial value problem

$$\frac{du_k}{dt} = \sum_{i=1}^m \gamma_{ik} w_i(\mathbf{u}), \quad k = 1, \dots, n, \quad (3a)$$

$$u_k(0) = u_k^{(0)} \geq 0 \quad (3b)$$

gives the time evolution of the concentrations u_k .

A vector in \mathbb{R}^n will be denoted by \mathbf{u} , i.e., $\mathbf{u} = [u_1, \dots, u_n]^T$. If $u_k \geq 0$ for all $k=1, \dots, n$, we write $\mathbf{u} \geq \mathbf{0}$. Similarly, if $u_k > 0$ for all k then $\mathbf{u} > \mathbf{0}$.

The system (3a) can be written in a vector form as $d\mathbf{u}/dt = \Gamma^T \mathbf{w}(\mathbf{u})$, where $\Gamma^T = [\gamma_{ik}]^T$ is the $n \times m$ stoichiometric matrix.

If the rank of Γ^T is $r \leq n$ then there are $(n-r)$ conservation relations.^{30,31} Let $\boldsymbol{\sigma} \in \mathbb{R}^n$ be such that $\sum_{k=1}^n \gamma_{ik} \sigma_k = 0$ for all $i=1, \dots, m$. It follows that $\sum_{k=1}^n \sigma_k u_k(t) = C$, where C is a constant which depends on the initial reactant concentrations (3b). The set of all conservation relations

$$\sum_{k=1}^n \sigma_k^l u_k = a_l, \quad l = 1, \dots, n-r \quad (4)$$

forms an invariant plane.²⁵ That is, if $\mathbf{u}(t)$ belongs to (4) for $t=0$ then $\mathbf{u}(t)$ stays in it for all $t > 0$.

The system (3a) is linearly asymptotically stable if and only if the Jacobian matrix

$$J_{ik} = \sum_{j=1}^m \gamma_{ji} \alpha_{jk} \frac{w_j(\mathbf{u})}{u_k} = \sum_{j=1}^m (\beta_{ji} - \alpha_{ji}) \alpha_{jk} \frac{w_j(\mathbf{u})}{u_k} \quad (5)$$

evaluated at a positive equilibrium has only eigenvalues $\lambda_1, \dots, \lambda_n$ with negative real parts. If non-mass-action kinetics is used then the term $\alpha_{jk} w_j(\mathbf{u})/u_k$ in (5) is replaced by $\partial w_j / \partial u_k$.

The matrix J can be parametrized by the so called ‘‘convex’’ parameters $h_k = u_k^{-1} > 0$, $k=1, \dots, n$, and $w_{p_j} \geq 0$, $j=1, \dots, s$, selected as independent variables from the rate function vector \mathbf{w} .³² The vector \mathbf{w} can be written as $\mathbf{w} = \sum_{j=1}^s w_{p_j} \mathbf{E}_j$, where the vectors $\mathbf{E}_j \geq \mathbf{0}$ are solutions to $\Gamma^T \mathbf{w} = \mathbf{0}$, subject to $\mathbf{w} \geq \mathbf{0}$. The vectors \mathbf{E}_j are referred to as extreme currents and in general may be linearly dependent.³³ Here $s = m - r$, where r is the rank of Γ^T and $\{\mathbf{E}_j\}$ are linearly independent. We will denote the set of independent rate functions as \mathbf{w}_{ind} and the rest as \mathbf{w}_{dep} . The convex parameters are more convenient to work with than the original rate constants and initial conditions in the sense that computation of a positive equilibrium solution to (3a) is not required. The algebraic relations between rate constants and initial conditions and convex parameters are stated in Ref. 34.

III. GRAPH-THEORETIC APPROACH TO STABILITY ANALYSIS

If the matrix J has only eigenvalues with negative real parts then J is said to be stable. If J has at least one eigenvalue with a positive real part then J is unstable. It is convenient to study the stability of J in terms of the coefficients of its characteristic polynomial

$$\det(\lambda I - J) = \lambda^n + a_1 \lambda^{n-1} + \cdots + a_n = 0. \quad (6)$$

The coefficients a_k , $k=1, \dots, n$, are sums of all possible principal minors of order k , denoted by $M(-J)(i_1, \dots, i_k)$, where $1 \leq i_1 < \cdots < i_k \leq n$.¹² For systems with mass-action kinetics the rank of J equals the rank of the stoichiometric matrix Γ^T , implying $n=r$ in (6).

A necessary condition for all roots of (6) to have negative real parts is $a_k > 0$ for all $k=1, \dots, r$.¹¹ The sufficient condition requires that all Hurwitz determinants $H_i(J)$, $i=1, \dots, r$, be positive.¹¹ The Liénard-Chipart stability criterion¹¹ is easier to apply, since it requires the computation of about half of the Hurwitz determinants up to the $(r-1)$ st one.

Bifurcations in mathematical models are associated with phenomena such as oscillations and multistability, often generically referred to as instabilities. For a bifurcation to occur it is necessary that the real part of an eigenvalue of J crosses through zero as parameters change values. A single real eigenvalue changing sign implies a possible saddle-node bifurcation. A change in sign of the real part of a single pair of complex eigenvalues implies a possible Hopf bifurcation. By the necessary condition given in the previous paragraph, if a_r changes sign then a real root can change its sign as parameters vary, and if a_k changes sign for some $k \neq r$ then the real part of a pair of complex roots can change its sign.²³

The connection of the bipartite graph G of the chemical mechanism (1) with instabilities in spatially homogeneous mass-action kinetics models has been studied elsewhere.^{23,28} The bipartite graph can be constructed directly from the chemical mechanism (1). It allows for multiple paths between the same substances (unlike, e.g., the digraph²³) which makes it suitable to represent more complex reactions. Next we give the definition of a bipartite graph.

The use of the bipartite graph G associated with (1) has been developed by Volpert and Hudyaev²⁵ and Volpert and Ivanova.²⁸ The vertices of G are divided into two sets: one for the chemical substances $V_1=\{A_1, A_2, \dots, A_n\}$ and one for the reactions $V_2=\{B_1, B_2, \dots, B_m\}$. If $\alpha_{jk} > 0$ in (1) then A_k participates in reaction j and (A_k, B_j) is an arc of G . Similarly if $\beta_{ji} > 0$ in (1) then A_i is produced in reaction j and (B_j, A_i) is an arc of G . The set of arcs $E(G)$ consists of directed edges (A_k, B_j) and (B_j, A_i) with one end in V_1 and the other in V_2 . Thus $G=\{V, E(G)\}$, where $V=\{V_1, V_2\}$, is a directed bipartite graph implied by the chemical mechanism (1).²⁵

The connection between the structure of a graph implied by a chemical mechanism (1) and the stability of the corresponding model system (3a) has been studied extensively.^{22,28,32,35-42} In the context of linear stability analysis, a graph-theoretic formula for the determinant of a matrix can be derived, where there is a one-to-one correspondence between the nonzero terms in the determinant and all subgraphs of the bipartite graph.^{23,28} See also Ref. 43 for a graph-theoretic formula of a matrix determinant using the digraph of the matrix. The subgraphs corresponding to negative terms in a coefficient of the characteristic polynomial imply the structure in the graph responsible for the potential instability.

Next we introduce the graph-theoretic formula for a coefficient a_k of (6). First though we need definitions of some key characteristics of the bipartite graph. These definitions of review material were presented elsewhere.^{23,28}

The element $[A_k, B_j]$ is an edge of G if $\alpha_{jk} > 0$. If $\alpha_{jk}\beta_{ji} > 0$ then the arcs (A_k, B_j) and (B_j, A_i) form a positive path, denoted $[A_k, B_j, A_i]$, that corresponds to the production of A_i from A_k in a reaction j . If $\alpha_{jk}\alpha_{ji} > 0$ the arcs (A_k, B_j) and (A_i, B_j) form a negative path, $[A_k, B_j, A_i]$, that corresponds to A_k and A_i both being reactants in a reaction j . The negative paths $[A_k, B_j, A_i]$ and $[A_i, B_j, A_k]$ are considered to be different since they start at a different V_1 vertex.

A cycle C of G is a sequence of distinct paths with the last V_1 vertex of each path being the same as the first of the next path $(A_{i_1}, B_{j_1}, A_{i_2}), (A_{i_2}, B_{j_2}, A_{i_3}), \dots, (A_{i_{k-1}}, B_{j_{k-1}}, A_{i_k}), (A_{i_k}, B_{j_k}, A_{i_1})$. A cycle will be denoted by

$$C = \left(\begin{array}{c} A_{i_1}, A_{i_2}, \dots, A_{i_k} \\ B_{j_1}, B_{j_2}, \dots, B_{j_k} \end{array} \right),$$

where the number of V_1 vertices defines its order. A cycle is positive if it contains an even number of negative paths and negative if it contains an odd number of negative paths.

A subgraph $g=\{C_1, C_2, \dots, C_s\}$ of G consists of edges $C_i=E_i$ or cycles C_i , where each V_1 vertex is the beginning of only one edge or path. The number of V_1 vertices in a subgraph is defined to be its order.

The set of all subgraphs g of order k with the same vertex sets $\bar{V}_1=\{A_{i_1}, \dots, A_{i_k}\}$ and $\bar{V}_2=\{B_{j_1}, \dots, B_{j_k}\}$ is called a fragment of order k and is denoted by

$$S_k \left(\begin{array}{c} i_1, \dots, i_k \\ j_1, \dots, j_k \end{array} \right).$$

The reader may refer to Ref. 23 for more details and some examples of the graph structures.

The following is the graph-theoretic formula for a coefficient of the characteristic polynomial (6):

$$a_k = \sum_{S_k \left(\begin{array}{c} i_1, \dots, i_k \\ j_1, \dots, j_k \end{array} \right)} K_{S_k} w_{j_1} \cdots w_{j_k} h_{i_1} \cdots h_{i_k}, \quad (7)$$

where $K_{S_k} = \sum_{g \in S_k} K_g$. Each

$$K_g = (-1)^{t_g} \prod_{[A_k, B_j] \in g} \alpha_{jk}^2 \prod_{C \in g} K_C, \quad (8)$$

where t_g is the number of cycles C in g and

$$K_C = \prod_{[A_k, B_j, A_i] \in C} (-\alpha_{jk}\alpha_{ji}) \prod_{[A_k, B_j, A_i] \in C} \alpha_{jk}\beta_{ji}. \quad (9)$$

The formula (7) is stated in Ref. 28 and proved in Ref. 23. A fragment S_k such that $K_{S_k} = \sum_{g \in S_k} K_g < 0$ is called a critical fragment. A critical fragment contains at least one subgraph with an odd number of positive cycles, i.e., $K_g < 0$ in (8) and $K_C > 0$ in (9), respectively. A positive cycle corresponds to indirect catalysis²⁹ and therefore critical fragments generalize classical conditions for instability.

It is clear that if G contains a critical fragment it is possible that a_k can change sign as the parameters (\mathbf{h}, \mathbf{w}) vary, leading to instabilities. The following theorem, which was first formulated by Volpert and Ivanova²⁸ and proved by Mincheva and Roussel,²³ implies a necessary graph-theoretic condition for instabilities.

Theorem 1: *If G does not have a critical fragment of order $k \in \{1, 2, \dots, r\}$, where $r = \text{rank}(\Gamma^T)$, then $a_k > 0$ for all values of the parameters $h_1, \dots, h_n, w_1, \dots, w_m$.*

We note that since some of the rate functions w_j may be linearly dependent, \mathbf{w}_{ind} should be substituted into the coefficients a_k to verify that the negative terms in a_k do not all cancel out.

IV. GRAPH-THEORETIC CONDITIONS FOR DIFFUSION-DRIVEN INSTABILITY

In this section we show how the theory from Sec. III can be applied to the corresponding reaction-diffusion system of (1). We are particularly interested in graph-theoretic conditions for diffusion-driven instability arising from the inclusion of diffusion in the model.

If the concentrations u_k are spatially nonhomogeneous functions, the corresponding reaction-diffusion system to (3a) with initial condition and no-flux boundary condition is

$$\frac{\partial u_k}{\partial t} = d_k \Delta u_k + \sum_{i=1}^m \gamma_{ik} w_i, \quad \mathbf{x} \in \Omega, \quad 0 < t < T, \quad (10a)$$

$$u_k(\mathbf{x}, 0) = u_k^{(0)}(\mathbf{x}), \quad \mathbf{x} \in \Omega, \quad (10b)$$

$$\frac{\partial u_k}{\partial \nu}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in \partial\Omega, \quad 0 < t < T, \quad (10c)$$

for $k=1, \dots, n$. The diffusion coefficients d_k are positive constants and Δ denotes the Laplacian in (10a). The directional derivative normal to the boundary $\partial\Omega$ is denoted by $\partial/\partial\nu$ in (10c). Since only local existence of $\mathbf{u}(\mathbf{x}, t)$ is guaranteed, $t \in (0, T)$ for some $T > 0$. The set $\Omega \in \mathbb{R}^s$ is bounded, open,

and connected with twice continuously differentiable boundary $\partial\Omega$. The initial functions satisfy $u_k^{(0)}(\mathbf{x}) \geq 0$ for all $k=1, \dots, n$ and $\mathbf{x} \in \Omega$, since they represent concentrations.

The no-flux boundary condition (10c) is considered standard for systems studied for Turing instabilities.² In fact, to observe a Turing pattern in a chemical system, it is necessary for the system to be open to mass flow. In a typical arrangement, a thin layer of gel in which the reactions occur is fed from below.⁴⁴ Because the gel layer is thin, it can be treated as a two-dimensional domain with zero-flux boundary condition along its one-dimensional perimeter.

The system (10a)–(10c) can be written compactly in vector form as

$$\frac{\partial \mathbf{u}}{\partial t} = D\Delta \mathbf{u} + \Gamma^T \mathbf{w}(\mathbf{u}), \quad \mathbf{x} \in \Omega, \quad 0 < t < T, \quad (11a)$$

$$\mathbf{u}(\mathbf{x}, 0) = \mathbf{u}^{(0)}(\mathbf{x}), \quad \mathbf{x} \in \Omega, \quad (11b)$$

$$\frac{\partial \mathbf{u}}{\partial \nu}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in \partial\Omega, \quad 0 < t < T, \quad (11c)$$

where $D = \text{diag}(d_1, \dots, d_n)$ is the diagonal matrix of diffusion coefficients.

A Turing instability occurs in the system (11a) with no-flux boundary condition (11c) if a spatially homogeneous equilibrium $\bar{\mathbf{u}} > \mathbf{0}$ is linearly asymptotically stable as a solution to the ordinary differential equation (ODE) system (3a) and unstable as a solution to the reaction-diffusion system.⁴⁵

The linearization of (11a) and (11c) gives

$$\frac{\partial \mathbf{z}}{\partial t} = D\Delta \mathbf{z} + J\mathbf{z}, \quad \mathbf{x} \in \Omega, \quad t > 0, \quad (12a)$$

$$\frac{\partial \mathbf{z}}{\partial \nu} = \mathbf{0}, \quad \mathbf{x} \in \partial\Omega, \quad t > 0, \quad (12b)$$

where $\mathbf{z}(\mathbf{x}, t) = \mathbf{u}(\mathbf{x}, t) - \bar{\mathbf{u}}$. Let each of the functions ψ_j be a solution to the eigenvalue problem

$$\Delta \psi_j + \mu_j \psi_j = 0, \quad \frac{\partial \psi_j}{\partial \nu} = 0, \quad (13)$$

where $\mu_j \geq 0$ denotes the corresponding eigenvalue of the negative Laplacian. The eigenvalues μ_j satisfy $0 = \mu_0 \leq \mu_1 \leq \dots \leq \mu_r \leq \dots$. In general, the eigenvalues μ_j depend on the set Ω and cannot be computed analytically for arbitrary sets, although solutions exist for simple domains, such as intervals and rectangles.² Let $e^{(J-\mu_j D)t}$ be the matrix solution to $d\mathbf{y}_j(t)/dt = (J-\mu_j D)\mathbf{y}_j$ for each j with initial condition equal to the $n \times n$ identity matrix. Then the solution to the linearized system (12a) can be written as

$$\mathbf{z}(\mathbf{x}, t) = \sum_{j=0}^{\infty} \psi_j(\mathbf{x}) e^{(J-\mu_j D)t} \mathbf{z}_{0j}, \quad (14)$$

where $\mathbf{z}_{0j} = \int_{\Omega} \mathbf{z}(\mathbf{x}, 0) \psi_j(\mathbf{x}) d\mathbf{x}$.

Therefore the problem of diffusion-driven instability is reduced to the problem of stability of the matrix $J-\mu D$ with $\mu \geq 0$, where μ will be treated as a continuous variable. If for $\mu=0$, the matrix $J-\mu D$ is stable and for some eigenvalue

$\mu = \mu_j > 0$, the matrix $J-\mu D$ is unstable then diffusion-driven instability can occur. Notice that for large $\mu \gg 0$, assuming all the parameters are kept fixed, the matrix $J-\mu D$ has only eigenvalues with negative real parts by Geršgorin's theorem.¹²

Similar conditions for bifurcations associated with multistability and oscillations hold in the reaction-diffusion case as in the homogeneous case.⁴⁶ If a single eigenvalue of $J-\mu D$ goes through zero then there can be an appearance of a spatially nonhomogeneous solution associated with a saddle-node bifurcation. If a single pair of complex eigenvalues of $J-\mu D$ goes through the imaginary axis then there can be an appearance of periodic solutions associated with a Hopf bifurcation. Here we will associate diffusion-driven instability and, in particular, the corresponding graph-theoretic condition with the appearance of a new nonhomogeneous solution.

The assumed stability of J implies that the coefficients of the characteristic polynomial (6) are all positive, i.e., that $a_k > 0$ for $k=1, \dots, r$, where r is the rank of Γ^T , and for the Hurwitz determinants $H_i(J) > 0$ for $i=1, \dots, r$.¹¹

Diffusion-driven instability can occur if the characteristic polynomial of $J-\mu D$,

$$P(\kappa) = \det(\kappa I - J + \mu D) = \kappa^n + b_1 \kappa^{n-1} + \dots + b_n, \quad (15)$$

has a coefficient $b_k=0$ for some values of the parameters. Each b_k is a polynomial of k th degree in μ and its coefficients are functions of the convex parameters (\mathbf{h}, \mathbf{w}) and the diffusion coefficients d_l , $l=1, \dots, n$.

We are interested in the bifurcation of a spatially nonhomogeneous solution and therefore we study the possibility for a zero eigenvalue of $J-\mu D$ for $\mu > 0$. The characteristic polynomial (15) has a zero root if and only if $b_n = \det(\mu D - J) = 0$ for some $\mu > 0$. Since all $d_k > 0$, $b_n = 0$ if and only if $\det(\mu I - JD^{-1}) = 0$ or in other words if JD^{-1} has a positive eigenvalue μ . The matrix JD^{-1} is the Jacobian (5) with the k th column J_k multiplied by d_k^{-1} for $k=1, \dots, n$. Therefore the graph-theoretic formula for the coefficients of the characteristic polynomial of JD^{-1} ,

$$\tilde{p}(\mu) = \det(\mu I - JD^{-1}) = \mu^n + \tilde{a}_1 \mu^{n-1} + \dots + \tilde{a}_n = 0, \quad (16)$$

can be derived easily from (7),

$$\tilde{a}_k = \sum_{S_k(i_1, \dots, i_k)} K_{S_k} w_{j_1} \dots w_{j_k} \frac{h_{i_1} \dots h_{i_k}}{d_{i_1} \dots d_{i_k}}, \quad k=1, \dots, n. \quad (17)$$

If the rank of Γ^T equals r for some $r < n$, then $\tilde{a}_{r+1} = \dots = \tilde{a}_n = 0$.

If all of the diffusion coefficients are equal, i.e., if $d_k = d > 0 \forall k$, then $d^k \tilde{a}_k = a_k > 0 \forall k$, where a_k is a coefficient of (6). This implies that $\tilde{p}(\mu) > 0$ for all $\mu > 0$. Therefore different diffusion coefficients are a necessary condition for diffusion-driven instability. This condition is of course well known for $n=2$ chemical species.

We require at least one $\tilde{a}_k < 0$ for some $k \in \{1, \dots, r\}$ and for some values of the diffusion coefficients d_k , $k=1, \dots, n$, otherwise $\tilde{p}(\mu) > 0$ for $\mu > 0$. This means that there is a negative term in one of the \tilde{a}_k 's corresponding to a critical

fragment S_k in the graph G . Therefore a critical fragment S_k of order $k \in \{1, \dots, r\}$ in G is a necessary condition for diffusion-driven instability.

The necessary condition for diffusion-driven instability is similar to the condition for instability in the ordinary differential equation case.^{23,28} This follows because the same bipartite graph G can be used for both models since it is associated with the same chemical mechanism (1). However, the weight functions, corresponding to the negative or positive paths (A_k, B_j, A_i) , are different in the reaction-diffusion case, since they are associated with the matrix JD^{-1} instead of J . For example, the path $[A_k, B_j, A_i]$ has a weight function²³ $\alpha_{jk}\beta_{ji}w_j/(d_k u_k)$ in the reaction-diffusion case.

If $a_r = M(-J)(i_1, \dots, i_r) > 0$ then $\tilde{a}_r = a_r/(d_{i_1} \cdots d_{i_r}) > 0$ in (16). However, if $a_r > 0$ is the sum of several principal minors of order r where at least one can be negative then it is possible that $a_r > 0$ and $\tilde{a}_r < 0$ for some values of the parameters.^{4,47} In most cases diffusion-driven instability occurs when $a_r > 0$ for all values of $(\mathbf{h}, \mathbf{w}_{\text{ind}})$ and $\tilde{a}_k < 0$ for some $k \neq r$, for some values of the diffusion coefficients. This is similar to the two-species models² where an algebraic condition for oscillations for zero diffusion leads to an algebraic condition for diffusion-driven instability.

If $\tilde{a}_k < 0$ for some particular $k \neq r$ with all other $\tilde{a}_{i \neq k} > 0$, then the polynomial (16) can have either zero or two positive roots $\tilde{\mu}_1 < \tilde{\mu}_2$ by Descartes' rule.¹¹ If there is an eigenvalue μ_j of the negative Laplacian such that $\tilde{\mu}_1 = \mu_j$ or $\tilde{\mu}_2 = \mu_j$ then $b_n = \det(\mu_j D - J) = 0$. The values of $\tilde{\mu}_1$ and $\tilde{\mu}_2$ can be varied by varying the parameters of the system. Similarly if $\tilde{a}_r < 0$, $b_n(\mu) = 0$ has one positive root $\tilde{\mu}$ and it should equal μ_j for some $j > 0$ for a Turing instability to occur.

Recall that a Turing bifurcation occurs when, at fixed rate constants in a system of the form (10a)–(10c), the steady state is stable when all the diffusion coefficients d_k are zero, and the spatially homogeneous steady state becomes unstable with respect to a spatially inhomogeneous pattern at some positive values of the diffusion coefficients. It may not be possible to obtain a Turing bifurcation at all values of the rate constants. The following theorem, which is a slightly modified version of one originally stated by Volpert and Ivanova,²⁸ gives a necessary condition for a Turing bifurcation, which may not, however, be sufficient due to the foregoing considerations.

Theorem 2: *In order for a Turing instability to occur at some values of the diffusion constants $\{d_1, d_2, \dots, d_n\}$, it is necessary that a critical fragment S_k of G of order $1 \leq k \leq r$ exists, where $r = \text{rank}(\Gamma^T)$.*

Note that a critical fragment

$$S_k \begin{pmatrix} i_1, \dots, i_k \\ j_1, \dots, j_k \end{pmatrix}$$

with $K_{S_k} < 0$ corresponds to a negative term in a_k (6) and \tilde{a}_k (16). For diffusion-driven instability $a_k > 0$ for some choice of the parameters (\mathbf{h}, \mathbf{w}) and $\tilde{a}_k < 0$ for the same parameters and with some choice of the diffusion coefficients $\{d_i\}$. More precisely, a principal minor $M(i_1, \dots, i_k)(-J)$ should be negative with $a_k > 0$ so that $M(i_1, \dots, i_k)(-JD^{-1}) < 0$ can make $\tilde{a}_k < 0$ for some choice of the diffusion coefficients.⁴⁷ It fol-

lows from (17) that the product $d_{i_1} d_{i_2} \cdots d_{i_k}$ corresponding to $K_{S_k} < 0$ should be chosen small and the remaining diffusion coefficients large in order for $\tilde{a}_k < 0$. This condition is another generalization of the usual condition that the ratio of diffusion coefficients should be much larger than unity for two-species systems.

The instabilities we have studied here are associated with the coefficients of the characteristic polynomial and the necessary condition for linear stability. If all $b_k > 0$ in (15) for all values of the parameters but there is a Hurwitz determinant $H_i(J - \mu D) < 0$ for some $i \in \{1, 2, \dots, n\}$, then $J - \mu D$ is unstable by the Routh-Hurwitz criterion.¹¹

In Theorem 3.2 in Ref. 47, it is shown that for a stable matrix A of order 3 or less with $-A$ having only non-negative principal minors, i.e., A satisfies the minors condition, the matrix $A - D$ is stable for all choices of diffusion matrices $D \geq 0$. However, in Ref. 10, an example is provided of a matrix A of order 4 that is stable and satisfies the minors condition, but $A - D$ is unstable for some $D \geq 0$. All coefficients of the characteristic polynomial of $A - D$ are positive; however, the Hurwitz determinants $H_3(A - D) < 0$ and $H_4(A - D) < 0$. In fact, the matrix $A - D$ has a pair of complex eigenvalues with a positive real part.

As an example, we study here a seven-variable variant of a model for the kinetics of the bifunctional enzyme phosphofructo-2-kinase:fructose-2,6-bis-phosphatase which is involved in the glycolysis/gluconeogenesis switch.^{48,49} Substrate inhibition mechanisms are often associated with oscillations in spatially homogeneous models.^{50,51} We show here that the corresponding reaction-diffusion model displays a Turing bifurcation based on the graph-theoretic condition from Theorem 2.

We use the same numbering as in Ref. 48 for the reactants, but renumber the reactions for convenience:



The last reaction was added to the original model in order to avoid a runaway condition which occurs when the concentration of fructose-2,6-bisphosphate (A_4) is large: under these conditions, inhibition of the cyclic adenosine monophosphate

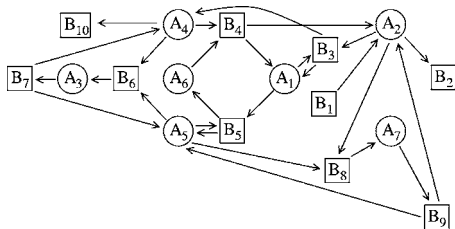


FIG. 1. Bipartite graph of the substrate-inhibited bifunctional enzyme reaction (18). The chemical species names A_i are circled. The boxed symbols B_i represent reactions. An arrow from a chemical species to a reaction box indicates that the species is a reactant, while an arrow from a reaction box to a chemical species indicates that the latter is a product of the reaction.

(cAMP)-dependent protein kinase A_5 leads to accumulation of the bifunctional enzyme in its kinase form A_1 . Since the phosphatase A_6 provides the only means of eliminating A_4 , any phosphosugar added to the system through reaction (18a) eventually accumulates at A_4 , so that the concentration $u_4 \rightarrow \infty$, which of course is physically wrong. Although it was not noted there, Fig. 3 of the original paper⁴⁸ actually shows the beginning of a runaway solution. Adding reaction (18j) to the model retains all the original behavior while preventing this runaway condition from occurring. In a brief numerical survey of the resulting homogeneous mass-action model, we have also observed a period-doubling bifurcation sequence leading to chaos. However, since the behavior of the homogeneous model is not our primary concern here, we set this issue aside.

The bipartite graph for this reaction is shown in Fig. 1. The corresponding mass-action kinetics reaction-diffusion system with non-negative initial condition and no-flux boundary condition is

$$\frac{\partial u_1}{\partial t} = d_1 \Delta u_1 + k_4 u_4 u_6 - k_5 u_1 u_5, \quad (19a)$$

$$\begin{aligned} \frac{\partial u_2}{\partial t} &= d_2 \Delta u_2 + k_1 - k_2 u_2 - k_3 u_1 u_2 + k_4 u_4 u_6 - k_8 u_2 u_5 \\ &+ k_9 u_7, \end{aligned} \quad (19b)$$

$$\frac{\partial u_3}{\partial t} = d_3 \Delta u_3 + k_6 u_4 u_5 - k_7 u_3, \quad (19c)$$

$$\frac{\partial u_4}{\partial t} = d_4 \Delta u_4 + k_3 u_1 u_2 - k_4 u_4 u_6 - k_6 u_4 u_5 + k_7 u_3 - k_{10} u_4, \quad (19d)$$

$$\frac{\partial u_5}{\partial t} = d_5 \Delta u_5 - k_6 u_4 u_5 + k_7 u_3 - k_8 u_2 u_5 + k_9 u_7, \quad (19e)$$

$$\frac{\partial u_6}{\partial t} = d_6 \Delta u_6 - k_4 u_4 u_6 + k_5 u_1 u_5, \quad (19f)$$

$$\frac{\partial u_7}{\partial t} = d_7 \Delta u_7 + k_8 u_2 u_5 - k_9 u_7. \quad (19g)$$

The system with zero diffusion has two conservation relations:

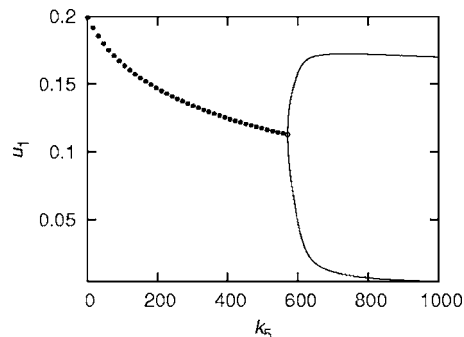


FIG. 2. Bifurcation diagram for the homogeneous Goldstein and Maevsky model with parameters $k_1=0.001$, $k_2=5 \times 10^{-5}$, $k_3=5$, $k_4=10$, $k_6=10$, $k_7=1$, $k_8=0.5$, $k_9=0.05$, $k_{10}=0.001$, $C_1=0.2$, and $C_2=0.31$. The solid dots represent stable steady states, the open circle is the Hopf bifurcation point, and the solid lines track the minima and maxima of u_1 on the limit cycle as a function of the control parameter k_5 . All parameters are in arbitrary units.

$$u_1 + u_6 = C_1, \quad (20a)$$

$$u_3 + u_5 + u_7 = C_2. \quad (20b)$$

Therefore the rank of the Jacobian matrix J equals 5. At equilibrium the following relations exist among the reaction rates: $w_1=w_2+w_{10}$, $w_3=w_4+w_{10}$, $w_5=w_4$, $w_7=w_6$, and $w_9=w_8$, and therefore $\mathbf{w}_{\text{ind}}=(w_2, w_4, w_6, w_8, w_{10})$.

The homogeneous model can have multiple steady states. Solving the steady-state conditions, we find one non-negative steady state at $\{\bar{u}_1=\bar{u}_3=\bar{u}_4=0, \bar{u}_2=k_1/k_2, \bar{u}_5=k_2 k_9 C_2 / (k_1 k_8 + k_2 k_9), \bar{u}_6=C_1, \bar{u}_7=k_1 k_8 C_2 / (k_1 k_8 + k_2 k_9)\}$. A Turing bifurcation cannot arise from this steady state since spatially oscillatory solutions about this steady state would imply negative concentrations. There may be up to two additional steady states (possibly both positive depending on the parameters) satisfying

$$\begin{aligned} k_4 [k_3 C_1 (k_1 - k_{10} \bar{u}_4) - k_2 k_{10} \bar{u}_4] [k_7 k_8 (k_1 - k_{10} \bar{u}_4) \\ + k_2 k_9 (k_6 \bar{u}_4 + k_7)] - k_2^2 k_5 k_7 k_9 C_2 (k_4 C_1 + k_{10}) = 0, \end{aligned} \quad (21a)$$

$$\bar{u}_2 = (k_1 - k_{10} \bar{u}_4) / k_2, \quad (21b)$$

$$\bar{u}_1 = \frac{\bar{u}_4 (k_4 C_1 + k_{10})}{k_3 \bar{u}_2 + k_4 \bar{u}_4}, \quad (21c)$$

$$\bar{u}_6 = C_1 - \bar{u}_1, \quad (21d)$$

$$\bar{u}_5 = k_4 \bar{u}_4 \bar{u}_6 / (k_5 \bar{u}_1), \quad (21e)$$

$$\bar{u}_3 = k_3 \bar{u}_4 \bar{u}_5 / k_7, \quad (21f)$$

$$\bar{u}_7 = C_2 - \bar{u}_3 - \bar{u}_5. \quad (21g)$$

Turing bifurcations are possible for these nontrivial steady states when the parameters are chosen so one or both of them are physically realizable. Figure 2 shows a bifurcation diagram of one of these nontrivial steady states computed using XPPAUT (Ref. 52) for a set of parameters inspired by those used by Goldstein and Maevsky.⁴⁸ (For these parameters, the other nontrivial steady state lies outside the physically real-

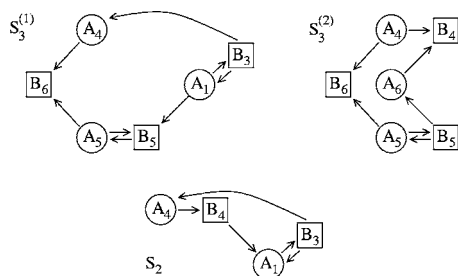


FIG. 3. Critical fragments of the substrate-inhibited bifunctional enzyme reaction.

izable region of phase space.) There is a Hopf bifurcation at $k_5=571.0=k_5^{\text{HB}}$. Thus, this steady state is stable for $k_5 < k_5^{\text{HB}}$.

The most important critical fragments, shown in Fig. 3, are

$$S_2 = \begin{pmatrix} 1, 4 \\ 3, 4 \end{pmatrix},$$

$$S_3^{(1)} = \begin{pmatrix} 1, 4, 5 \\ 3, 6, 5 \end{pmatrix},$$

and

$$S_3^{(2)} = \begin{pmatrix} 4, 5, 6 \\ 6, 5, 4 \end{pmatrix}.$$

Any other critical fragment of higher order consists of S_2 , $S_3^{(1)}$, or $S_3^{(2)}$ and some additional edges. Interesting and perhaps not surprising is the fact that all of these critical fragments contain the positive path and the edge through the vertices A_1 , B_3 or A_5 , B_5 . The positive path, in particular, increases the possibility that a fragment with a subgraph containing it will be critical. For example, the critical fragment $S_3^{(2)}$ contains a positive cycle subgraph

$$g_1 = \begin{pmatrix} A_4, A_5, A_6 \\ B_6, B_5, B_4 \end{pmatrix},$$

the subgraph of two edges and a positive cycle $g_2 = \{[A_4, B_6], [A_6, B_4], [A_5, B_5, A_5]\}$, and the subgraph of three edges $g_3 = \{[A_4, B_6], [A_6, B_4], [A_5, B_5]\}$. Therefore $K_{S_3^{(2)}} = K_{g_1} + K_{g_2} + K_{g_3} = -1 - 1 + 1 = -1 < 0$; without the positive cycle $[A_5, B_5, A_5]$ the fragment $S_3^{(2)}$ would not be critical.

For linear stability with zero diffusion $a_i > 0$ for $i=1, \dots, 5$ in (6) is required, as well as positive Hurwitz determinants $H_i(J) > 0$, $i=1, \dots, 4$, by the Routh-Hurwitz theorem.¹¹ On the other hand a necessary condition for $\tilde{a}_3 < 0$ (17) and $b_5=0$ (15) is that at least one of the principal minors $M(-J)(1, 2, 4)$, $M(-J)(1, 3, 4)$, $M(-J)(1, 4, 5)$, $M(-J)(1, 4, 7)$, or $M(-J)(4, 5, 6)$ is negative. For example,

$$M(-J(4, 5, 6)) = h_4 h_5 h_6 w_4 [w_{10}(w_6 + w_8) + w_6(w_8 - w_4)] < 0, \quad (22)$$

if w_4 is sufficiently large. If $M(-J(4, 5, 6)) < 0$ with $a_3 > 0$, it follows from Eq. (17) that \tilde{a}_3 can be negative if the product $d_4 d_5 d_6$ is sufficiently small.

Now suppose that we set the parameters as in Fig. 2 with $k_5=500$ using initial conditions which are compatible with

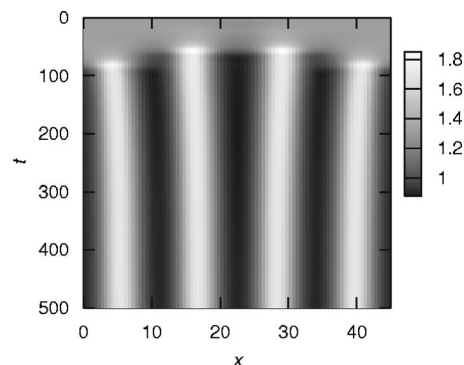


FIG. 4. Development of a Turing pattern in one dimension in the Goldstein-Maevsky model for the same parameters as in Fig. 2 with $d_1=d_2=d_3=d_7=1$, $d_5=d_6=0.1$, and $d_4=0.5$. This space-time plot displays the values of u_2 . The initial conditions are chosen to place the system near its homogeneous steady state, viz., $u_1^{(0)}=0.1173$, $u_2^{(0)}=1.319$, $u_3^{(0)}=0.1231$, $u_4^{(0)}=0.9340$, $u_5^{(0)}=0.0131$, $u_6^{(0)}=0.0827$, and $u_7^{(0)}=0.1738$, except in the range $21.5 \leq x \leq 23.5$, where $u_2^{(0)}=1.4$. Note that these initial conditions are consistent with the values of C_1 and C_2 used in Fig. 2. The simulation was carried out using a simple three-point finite-difference scheme. We have verified that the results are not very sensitive to the spatial mesh size.

the values of C_1 and C_2 used in the figure. This places the system in the regime where the steady state of the homogeneous model is stable. The steady-state concentrations are $\bar{u}_1=0.1173$, $\bar{u}_2=1.319$, $\bar{u}_3=0.1231$, $\bar{u}_4=0.9340$, $\bar{u}_5=0.01317$, $\bar{u}_6=0.08271$, and $\bar{u}_7=0.1738$, from which we can calculate that $M(-J(4, 5, 6))=-71.26$. All the a_i 's are positive, as of course they must be since the steady state is stable at these parameter values. In particular, $a_3=10.6121$. If we choose $d_1=d_2=d_3=d_7=1$, $d_5=d_6=0.1$, and $d_4=0.5$ (for instance), then all the \tilde{a}_i 's are positive except $\tilde{a}_3=-7711$. Thus the system should have gone through a Turing bifurcation relative to, say, the case where all the d_i 's are equal. Figure 4 shows the formation of a Turing pattern at these parameter values from a small initial disturbance, confirming our analysis.

V. DISCUSSION

The complexity of biochemical models is increasing with the inclusion of diffusion, delays, stochasticity, and sometimes even combinations of such effects. Since patterns occur often in nature, Turing instabilities are being studied extensively in connection with reaction-diffusion models in biochemistry. The autocatalysis condition for pattern formation is generalized to a critical fragment condition by Volpert and Ivanova.²⁸ We have filled in the proofs missing from this earlier work and presented an example in a seven-variable model. This is one of the larger models in which a Turing bifurcation analysis has been carried out, and we were led directly to an appropriate parameter range by our analysis. Searching for parameters which permitted the observation of a Turing pattern without the aid of our graphical method would have been extraordinarily tedious.

The classification of schemes that have the potential for Turing instabilities is based on the condition of a critical fragment in the bipartite graph of the chemical mechanism. Such a classification can help in understanding the subnetworks of a mechanism associated with the Turing instabili-

ties and even suggests ways of constructing more complicated schemes displaying diffusion-driven instabilities.

The existence of a critical fragment is only a necessary condition and the parameter values, equilibrium concentrations, reaction rates at equilibrium, and diffusion coefficients will further determine if the system will undergo a Turing bifurcation. Once a critical fragment has been identified, we can formulate conditions for the Turing instability by inspection of the corresponding principal minor as we did in our example. As a general rule, one of the requirements for a Turing instability is that the product of diffusion coefficients corresponding to the critical fragment which appears in Eq. (17) be sufficiently small.

Here we have discussed Turing instabilities associated with positive cycles, or as they are often referred to, with positive feedback. Instabilities associated with negative cycles are still to be classified both in the case of zero diffusion and positive diffusion.

The graph-theoretic methods presented here are suitable for computerization and can thus in principle be applied to very large network models. The development of efficient algorithms for finding critical fragments will be necessary.

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- ¹S. H. Strogatz, *Nature* (London) **410**, 268 (2001).
- ²J. D. Murray, *Mathematical Biology*, 2nd ed. (Springer-Verlag, New York, 1993).
- ³H. Qian and J. D. Murray, *Appl. Math. Lett.* **14**, 405 (2001).
- ⁴R. A. Satnoianu, M. Menzinger, and P. K. Maini, *J. Math. Biol.* **41**, 493 (2000).
- ⁵K. A. J. White and C. A. Gilligan, *Philos. Trans. R. Soc. London, Ser. B* **353**, 543 (1998).
- ⁶I. Prigogine and R. Lefever, *J. Chem. Phys.* **48**, 1695 (1968).
- ⁷B. P. Belousov, *Collection of Short Papers on Radiation Medicine* (Medical, Moscow, 1959), p. 145.
- ⁸A. M. Zhabotinsky, *Biofizika* **9**, 306 (1964).
- ⁹R. Thomas, D. Thieffry, and M. Kaufman, *Bull. Math. Biol.* **57**, 247 (1995).
- ¹⁰R. A. Satnoianu and P. van den Driessche, *Linear Algebr. Appl.* **398**, 69 (2005).
- ¹¹F. R. Gantmakher, *Applications of the Theory of Matrices* (Interscience, New York, 1959).
- ¹²P. Lancaster and M. Tismenetsky, *The Theory of Matrices* (Academic, Orlando, 1985).
- ¹³U. S. Bhalla and R. Iyengar, *Science* **283**, 381 (1999).
- ¹⁴R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii, and U. Alon, *Science* **298**, 824 (2002).
- ¹⁵E. de Silva and M. P. H. Stumpf, *J. R. Soc., Interface* **2**, 419 (2005).
- ¹⁶I. Zevedei-Oancea and S. Schuster, *Comput. Chem. Eng.* **29**, 597 (2005).
- ¹⁷H. Kitano, *Science* **295**, 1662 (2002).
- ¹⁸A. Goldbeter, *Biochemical Oscillations and Cellular Rhythms: The Molecular Basis of Periodic and Chaotic Behaviour* (Cambridge University Press, Cambridge, 1996).
- ¹⁹P. Smolen, D. A. Baxter, and J. H. Byrne, *Bull. Math. Biol.* **62**, 247 (2000).
- ²⁰J. J. Tyson, K. C. Chen, and B. Novak, *Curr. Opin. Cell Biol.* **15**, 221 (2003).
- ²¹H. de Jong, *J. Comput. Biol.* **9**, 67 (2002).
- ²²M. Feinberg, *Arch. Ration. Mech. Anal.* **49**, 187 (1972).
- ²³M. Mincheva and M. R. Roussel, *J. Math. Biol.* (submitted).
- ²⁴K. Gatermann, *Contemp. Math.* **286**, 53 (2001).
- ²⁵A. Volpert and S. Hudyaev, *Analyses in Classes of Discontinuous Functions and Equations of Mathematical Physics* (Martinus Nijhoff, Dordrecht, 1985), Chap. 12.
- ²⁶J. W. Pinney, D. R. Westhead, and G. A. McConkey, *Biochem. Soc. Trans.* **31**, 1513 (2003).
- ²⁷A. V. Zeigarnik and O. N. Temkin, *Kinet. Katal.* **35**, 647 (1994).
- ²⁸A. Volpert and A. Ivanova, *Mathematical Modeling* (Nauka, Moscow, 1987), (in Russian) p. 57.
- ²⁹J. J. Tyson, *J. Chem. Phys.* **62**, 1010 (1975).
- ³⁰A. Cornish-Bowden and J.-H. S. Hofmeyr, *J. Theor. Biol.* **216**, 179 (2002).
- ³¹S. Schuster and T. Höfer, *J. Chem. Soc., Faraday Trans.* **87**, 2561 (1991).
- ³²B. L. Clarke, *Adv. Chem. Phys.* **43**, 1 (1980).
- ³³R. T. Rockafellar, *Convex Analysis* (Princeton University Press, Princeton, 1970).
- ³⁴B. L. Clarke, *Cell Biophys.* **12**, 237 (1988).
- ³⁵G. Craciun and M. Feinberg, *SIAM J. Appl. Math.* **66**, 1321 (2006).
- ³⁶M. Eiswirth, A. Freund, and J. Ross, *Adv. Chem. Phys.* **80**, 127 (1991).
- ³⁷B. N. Goldstein and E. L. Shevelev, *J. Theor. Biol.* **112**, 493 (1985).
- ³⁸A. N. Ivanova, *Kinet. Katal.* **20**, 1019 (1979).
- ³⁹A. N. Ivanova and B. L. Tarnopolskii, *Kinet. Katal.* **20**, 1541 (1979).
- ⁴⁰C. Soulé, *ComplexUs* **1**, 123 (2003).
- ⁴¹R. Thomas and M. Kaufman, *Chaos* **11**, 170 (2001).
- ⁴²V. Vasilev, A. Volpert, and S. Hudyaev, *Zh. Vychisl. Mat. Mat. Fiz.* **13**, 683 (1973).
- ⁴³J. Maybee, D. Olesky, P. van den Driessche, and G. Wiener, *SIAM J. Matrix Anal. Appl.* **10**, 500 (1989).
- ⁴⁴W. Y. Tam, W. Horsthemke, Z. Noszticzius, and H. L. Swinney, *J. Chem. Phys.* **88**, 3395 (1988).
- ⁴⁵E. Conway, in *Partial Differential Equations and Dynamical Systems*, edited by W. E. Fitzgibbon (Pitman, Boston, 1984), p. 85.
- ⁴⁶Y. A. Kuznetsov, *Elements of Applied Bifurcation Theory*, 2nd ed. (Springer, New York, 1998).
- ⁴⁷L. Wang and M. Y. Li, *J. Math. Anal. Appl.* **254**, 138 (2001).
- ⁴⁸B. N. Goldstein and A. A. Maevsky, *FEBS Lett.* **532**, 295 (2002).
- ⁴⁹B. N. Goldstein and A. N. Ivanova, *FEBS Lett.* **217**, 212 (1987).
- ⁵⁰P. Shen and R. Larter, *Biophys. J.* **67**, 1414 (1994).
- ⁵¹M. G. Slin'ko and M. M. Slin'ko, *Catal. Rev. - Sci. Eng.* **17**, 119 (1978).
- ⁵²B. Ermentrout, *Simulating, Analyzing, and Animating Dynamical Systems* (SIAM, Philadelphia, 2002).