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**Nath, Sarang S.**

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# Minimal model for oscillatory dynamics of a nonlinear chemical reaction network

Sarang S. Nath

The Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2800 Lyngby, Denmark



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## ABSTRACT

Since Bray's pioneering discovery exactly 100 years ago of the first oscillating reaction, more than 25 families of nonlinear oscillating reaction networks have been identified. The B–Z reaction network has been expanded, and complex models considering a score of chemical reactions and species have been developed. Here we look at the inverse problem and ask how the complexity of the models can be reduced. We quantify the dynamics of a minimal model by linear stability techniques and direct integration of the set of ODEs, and show that essential oscillatory and excitability features are satisfactorily captured. Reasons for the success of the minimal model are explained. Extensions of the model to fundamental chemical and biological processes are discussed, and application of the chemical reaction network to mathematically model nerve conduction is illustrated.

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## 1. Introduction

The principles of chemical kinetics have been applied to a variety of reaction networks, leading to a system of differential equations for the concentrations of the reactive species [1–4]. Nonlinear reaction networks maintained far from equilibrium reveal several dynamical properties and bifurcations such as periodic oscillations of the reaction intermediates [1,4,5]. The first chemical reaction that exhibited temporal oscillations was discovered by Bray exactly a hundred years ago [5]. Various attempts have been made to model their dynamics. For instance, the autocatalytic kinetic scheme  $A \xrightarrow{k_1} X, 2X + Y \xrightarrow{k_2} 3X, B + X \xrightarrow{k_3} Y + D, X \xrightarrow{k_4} E$  for the overall reaction  $A + B \rightarrow D + E$  has been previously proposed to explain limit cycle behavior and account for the observed complex spatial and temporal patterns [6]. However, the kinetic scheme is unlikely in that its second reaction is third-order in the concentration of the intermediates. Besides, the scheme was only a mathematical construct [6], and no real network of the kind has been found.

Subsequent experimental work has however discovered a number of interesting, real systems of chemical oscillators, [7–9], and today over 25 classes of B–Z type networks are known [9,10]. The first detailed mechanism of such nonlinear reaction networks involved 11 principal reactions and 12 species [11], which was subsequently expanded to include 20 reactions among 18

chemical species [12]. The large system of ODEs was numerically integrated to solve for the dynamics, but the mechanism was too complicated to fully comprehend [12]. Attempts have been made to reduce the complexity; however, the solution of the dynamics has generally been approached using intuitive *a priori* or semi-quantitative nullcline methods of dynamical systems theory [13–15].

A more elegant and exact approach to nonlinear dynamics using stability analysis is readily available [4,16,17] and can be invoked for a more detailed analysis. However, this requires that a core set of reactions of the B–Z network be identified for analysis, and the analytical results can subsequently be checked by actual numerical simulation. In other words, rather than expanding of the set of reactions and chemical species [11,12], a minimal model of the nonlinear B–Z system is constructed that is sufficient to elucidate the chief dynamical features of the network, and reproduce the temporal patterns and configurations. Further reduction of the minimal model of the real reaction network is inadequate to capture the network dynamics.

In this work, such a minimal approach has been used. The minimal model, the simplest model of the B–Z network currently available, has been shown to contain the essential nonlinear term responsible for temporal oscillations of the network, and the model has been analyzed by analytical and numerical approaches. The time period of the oscillations has been computed and shown to be in excellent agreement with the period obtained experimentally for the chemical oscillator. The reasons for the success of the minimal model and its many advantages have been

E-mail addresses: [sasuna@biosustain.dtu.dk](mailto:sasuna@biosustain.dtu.dk), [nathsarang@gmail.com](mailto:nathsarang@gmail.com).

outlined. The underlying mathematical structure of the minimal model has been found to be identical to that of the Hodgkin–Huxley equations for nerve and excitable systems and hence the work may have applications to fundamental biological processes also [18–20].

The above approach has been applied recently in the literature to other interesting problems in chemical reaction dynamics [2, 4, 17].

## 2. Minimal model

As explained in Section 1, in contrast to expansion of the B–Z reaction to include 20 reactions and 18 chemical species [12], the reaction mechanism has been previously reduced to five irreversible steps containing three reaction intermediates [13–15]. The sequence of elementary reactions is given by the scheme [14]



In the above reaction scheme,  $A = \text{BrO}_3^-$ ,  $B =$  the organic species, typically malonic acid or its derivatives,  $P = \text{HOBr}$ ,  $X = \text{HBrO}_2$ ,  $Y = \text{Br}^-$ , and  $Z =$  the oxidized form of the cerium catalyst, i.e.  $\text{Ce}^{4+}$ .  $f$  is a stoichiometric coefficient in the reaction (Eq. (5)) and acts as an adjustable parameter. The concentrations of the major reactants  $A$  and  $B$  are kept constant; the total cerium concentration,  $C$  (typically measuring  $\sim 1$  mM) and the hydrogen ion concentration is taken as constant under the highly acidic conditions of the reactions. The kinetic rate equations for the intermediates are

$$\frac{d[X]}{dt^*} = k_3[A][Y] - k_2[X][Y] + k_5[A][X] - 2k_4X^2 \quad (6)$$

$$\frac{d[Y]}{dt^*} = -k_3[A][Y] - k_2[X][Y] + \frac{1}{2}fk_c[B][Z] \quad (7)$$

$$\frac{d[Z]}{dt^*} = 2k_5[A][X] - k_c[B][Z] \quad (8)$$

Eqs. (6)–(8) can be converted into a dimensionless form by defining

$$x = \frac{2k_4[X]}{k_5[A]}, y = \frac{k_2[Y]}{k_5[A]}, z = \frac{k_4k_c[B][Z]}{(k_5[A])^2}, t = k_c[B]t^* \quad (9)$$

This leads to a simpler form of the kinetic rate equations:

$$\varepsilon \frac{dx}{dt} = qy - xy + x(1 - x) \quad (10)$$

$$\varepsilon' \frac{dy}{dt} = -qy - xy + fz \quad (11)$$

$$\frac{dz}{dt} = x - z \quad (12)$$

Eqs. (10)–(12) have been analyzed previously in a semi-quantitative way based on nullcline methods [13–15]. However, an even simpler form or minimal model that captures the essential oscillatory features of the B–Z class of reactions is possible. We notice that the parameters  $\varepsilon = \frac{k_5[A]}{2k_4[C]}$ ,  $\varepsilon' = \frac{k_5[A]}{k_2[C]}$ , and  $q = \frac{2k_3k_4}{k_2k_5}$  are small. The timescale constants  $\varepsilon$  and  $\varepsilon'$  are small ( $\ll 1$ ) because the values of the kinetic parameters  $k_4, k_2 \gg k_5$  for the reaction and greatly override the effects of the  $[A]/[C]$  ratio. Typically, the range of values of  $\varepsilon$  and  $q$

are 0.01 – 1.0 and 0.001 – 0.1 respectively, while  $\varepsilon'$  typically measures  $1 \times 10^{-5}$ . The parameter  $\varepsilon'$ , related to the timescale of evolution of the  $[\text{Br}^-]$  species, is the smallest and can be taken as zero, i.e. the concentration of  $[\text{Br}^-]$  can be replaced by its steady state dimensionless concentration given by

$$y = \frac{fz}{(q + x)} \quad (13)$$

Substituting Eq. (13) into Eq. (10) gives us the simplest model comprising of a set of two coupled ODEs for the evolution of the dimensionless bromous acid  $[\text{HBrO}_2]$  concentration,  $x$  and the dimensionless oxidized form of the cerium catalyst concentration,  $z$  (Eqs. (14), (15)):

$$\frac{dx}{dt} = \frac{x(1-x)}{\varepsilon} + \frac{f}{\varepsilon} \left( \frac{q-x}{q+x} \right) z \quad (14)$$

$$\frac{dz}{dt} = x - z \quad (15)$$

The above minimal model contains the essential nonlinear term of the chemical reaction network given by  $x(1-x)$ . It also contains an autocatalytic activating species,  $x$  and an inhibiting or consuming species,  $z$ . It thus has the form of activator–inhibitor models, as typified by the Lotka–Volterra system of equations and in general by equations governing predator–prey interactions.

## 3. Results and discussion

### 3.1. Qualitative analysis of the minimal model by the method of nullclines

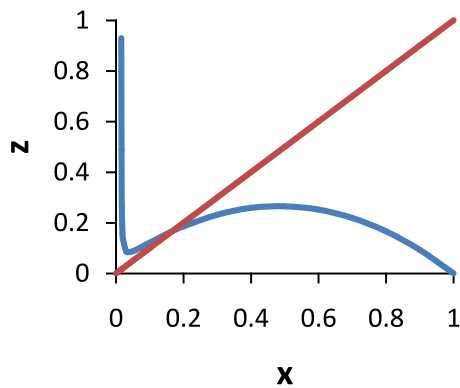
Trajectories in phase space traversed by the set of variables of a system of differential equations offer important qualitative information of system dynamics. The nullclines are an especially important special set of curves in phase space that record the succession of states of the system as it evolves in time [16]. In our case, nullclines represent  $(x, z)$  pairs with  $dx/dt = 0$  (the  $x$ -nullcline) and  $dz/dt = 0$  (the  $z$ -nullcline). The intersection of the nullcline curves correspond to the steady state/s of the system. Nullclines of the system of Eqs. (14), (15) that determine the  $x, z$  pairs of zero slope are plotted in Fig. 1. The stability of the steady state is qualitatively determined by these nullclines that separate the phase plane into four distinct regions with different combinations of signs of the derivatives of  $x$  and  $z$  (Fig. 1). If a steady state is located on the left or right branch, it is stable, while a steady state located on the middle branch of the  $x$ -nullcline is unstable. In the latter situation, there is no possibility for the perturbed system to regain its steady state, and the system gets trapped in a limit cycle, which is a characteristic of the oscillatory regime of the reaction.

The  $x$ -nullcline of the system has a local maxima at  $(x, z) = \left( 0.5, \frac{0.25}{fg} \right)$ , where  $g = \left( \frac{0.5-q}{0.5+q} \right)$ . It also shows a local minima at  $(x, z) = \left( \left[ 1 + 2^{1/2} \right] q, \left[ 3 + 2^{3/2} \right] \frac{q}{f} \right)$ .

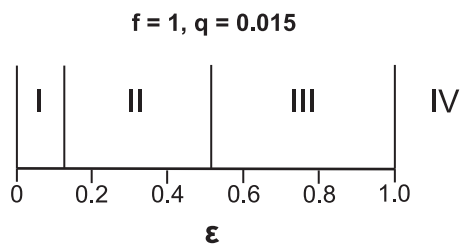
The stability and dynamical properties of the system are further analyzed quantitatively in Sections 3.2–3.4.

### 3.2. Quantitative analysis of the minimal model by linear stability techniques

The method of nullclines permits a qualitative and pictorial representation of the onset of oscillations in the reduced two-variable minimal model. A more elegant and quantitative analysis of the local dynamical characteristics of the system is possible by use of linear stability techniques upon small perturbations of the stationary steady state/fixed point of the system [4, 16, 17]. The system of Eqs. (14), (15) can be solved for the stationary



**Fig. 1.** Representation of  $x$ - and  $z$ -nullclines in phase space for the minimal model (Eqs. (14), (15)) of a real nonlinear chemical reaction network for the parameter values  $f = 1$ ,  $q = 0.015$ . The nullclines divide the  $x$ - $z$  phase space into four regions:  $\frac{dz}{dt} < 0$  and  $\frac{dx}{dt} > 0$  to the left and right of the straight line  $x = z$  (red) respectively, and  $\frac{dz}{dt} < 0$  and  $\frac{dx}{dt} > 0$  above and below the convex curve (blue) respectively.



**Fig. 2.** Various regimes of the minimal network model upon perturbation of the steady state  $x_{ss} = z_{ss} = 0.166$  as a function of the parameter  $\varepsilon$  for  $f = 1$ ,  $q = 0.015$ . The critical point of a Hopf bifurcation where the eigenvalues of the characteristic equation are purely imaginary occurs at  $\varepsilon = 0.516$  and separate stable and unstable foci oscillations (regions III and II respectively) about the steady state. The system exhibits excitable instability without oscillation for  $\varepsilon < 0.125$  (region I). Monotonic relaxation back to the steady state occurs in region IV for high, non-physical values of  $\varepsilon \gg 1$ .

steady state obtained upon fixing their LHS to zero. This gives, after discarding the trivial solution  $x_s = 0$ ,  $z_s = 0$ ,

$$x_s = z_s = -\frac{1}{2}(q + f - 1) \pm \frac{1}{2}\sqrt{(q + f - 1)^2 + 4q(1 + f)} \quad (16)$$

Evaluation of the Jacobian matrix at  $(x_s, z_s)$  yields

$$\mathbf{J}_s = \begin{bmatrix} \frac{1 - 2x_s}{\varepsilon} - \frac{2qfz_s}{\varepsilon(q + x_s)^2} & \frac{f}{\varepsilon} \left( \frac{q - x_s}{q + x_s} \right) \\ 1 & -1 \end{bmatrix} \quad (17)$$

Therefore, if  $\lambda$  represents the eigenvalues,

$$\det \begin{bmatrix} \frac{1 - 2x_s}{\varepsilon} - \frac{2qfz_s}{\varepsilon(q + x_s)^2} - \lambda & \frac{f}{\varepsilon} \left( \frac{q - x_s}{q + x_s} \right) \\ 1 & -1 - \lambda \end{bmatrix} = 0 \quad (18)$$

which has the characteristic equation

$$\lambda^2 + \left( 1 - \frac{(1 - 2x_s)}{\varepsilon} + \frac{2qfz_s}{\varepsilon(q + x_s)^2} \right) \lambda + \left\{ \frac{2qfz_s}{\varepsilon(q + x_s)^2} - \frac{(1 - 2x_s)}{\varepsilon} - \frac{f}{\varepsilon} \left( \frac{q - x_s}{q + x_s} \right) \right\} = 0 \quad (19)$$

The dynamical behavior of the model is determined by the trace and discriminant of  $\mathbf{J}_s$ . Based on these values, a phase diagram of the various regimes along with their critical bifurcation points are depicted in Fig. 2.

### 3.3. Dynamical behavior by numerical integration of the set of ODEs of the minimal model

The set of Eqs. (14), (15) were numerically integrated for various parameter values shown in Fig. 2, and the dynamics of the system was studied. Fig. 3(a) – (d) show plots of the evolution of the concentrations of  $x$  and  $z$  at fixed values of the parameters  $q$  and  $f$  and different values of  $\varepsilon$ . The results are shown as temporal plots of  $x$  and  $z$ , and as  $x - z$  phase plane plots. The set of parameters is representative of two key classes of dynamical behavior. In the first one, for the given fixed values of the other parameters, there exists a critical point at  $\varepsilon = 0.516$  where  $\text{tr}(\mathbf{J}_s) = 0$ , and the system exhibits a limit cycle (Fig. 3(a), (b)). This oscillatory pattern arises because at this bifurcation point, as shown by the linear stability methods [4,16,17] in Section 3.2 and analysis by means of Eq. (19), the eigenvalues are purely imaginary. The frequency of the oscillations,  $\nu$  is given by the expression

$$\nu = \frac{\sqrt{\det \mathbf{J}_s}}{2\pi} \quad (20)$$

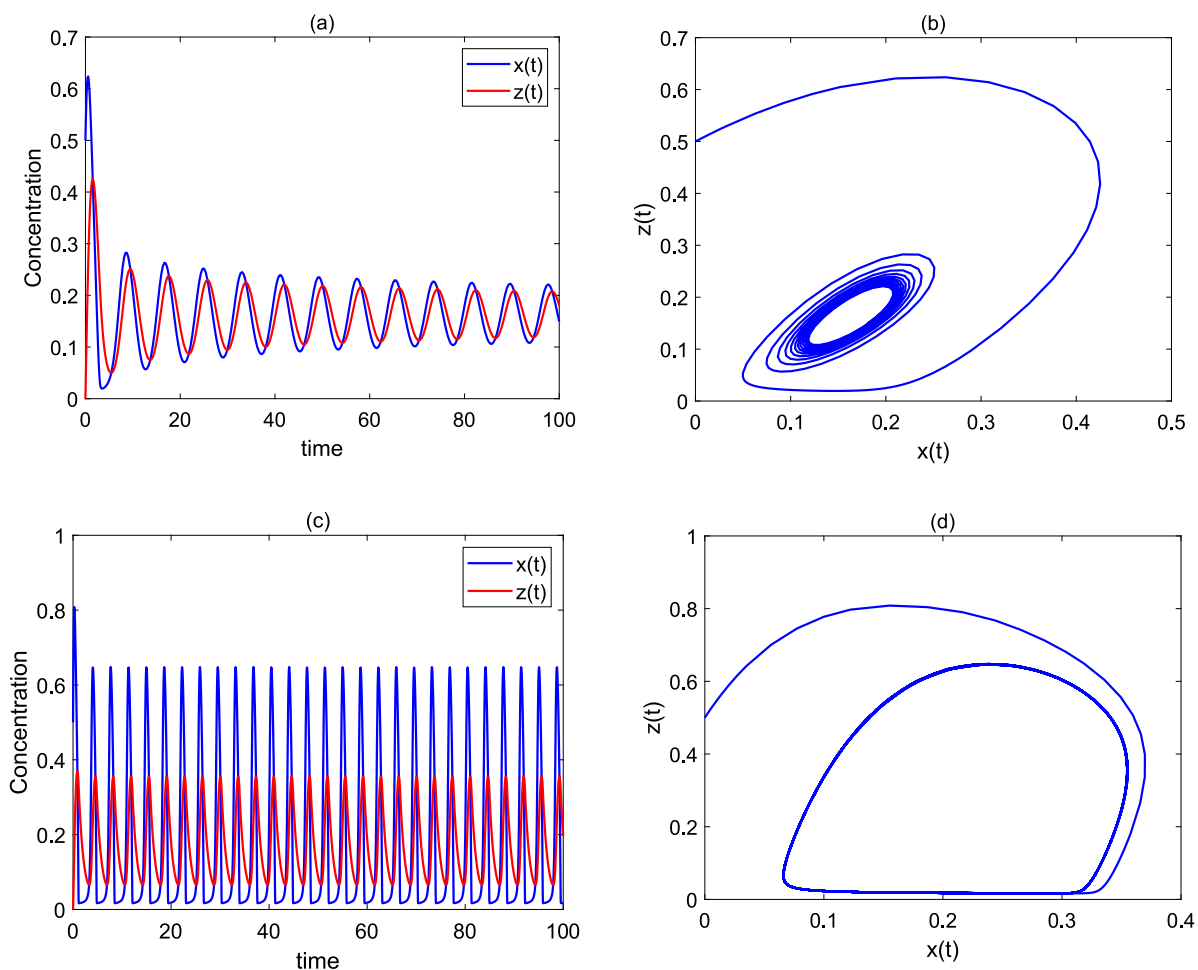
The theoretically determined frequency of oscillation using Eq. (20) gives a value of  $\nu = 0.125 \text{ s}^{-1}$  at the bifurcation point, which is in agreement with experimental data. From Fig. 1 of Ref. [11], a value of  $\sim 100 \text{ s}$  is determined for the time period of oscillation. Evaluation of Eq. (20) at the critical point yields a time period of  $0.125 \times 2k_4C / (k_5aHA)^2 \text{ s}$  using the notation and scaling of Ref. [15]. This leads to a value of the period of oscillation of  $(1/8) \times 2 \times 4 \times 10^7 \times 1 \times 10^{-3} / (2 \times 10^2 \times 5 \times 10^{-2})^2 = (1/8) \times 800 = 100 \text{ s}$ , which compares very favorably with the experimental observations on oscillations in B-Z reaction networks [15].

A different type of regime in which excitability as opposed to oscillations is found is shown by the time evolution and phase plane plots of Fig. 3(c), (d) for  $\varepsilon = 0.1$ , with all other parameters at their base-case constant values. For this case, the resting state is unstable, and the system makes a large excursion in phase space (Fig. 3(d)). This may therefore be termed as an excitable regime.

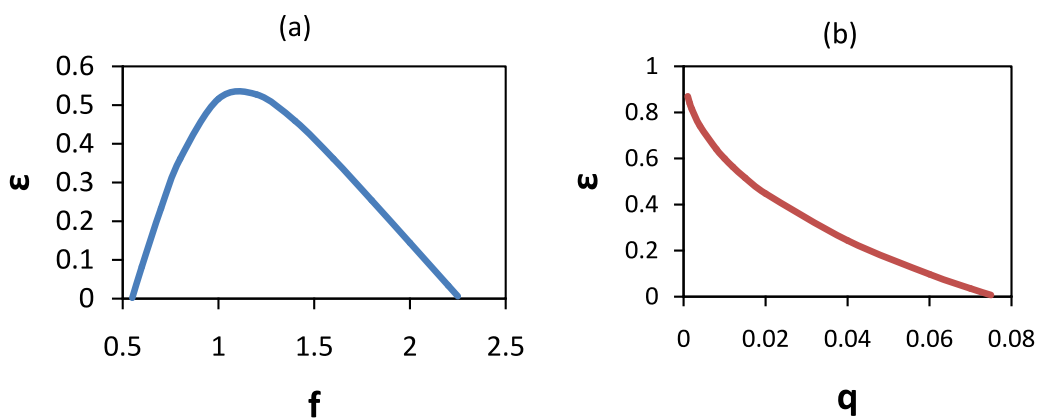
### 3.4. Locus of Hopf bifurcation points in parameter space

The locus of Hopf bifurcation points of the system given by Eqs. (14), (15) is evaluated next for  $q = 0.015$ . The value of the parameter  $f$  is progressively varied and the value of  $\varepsilon$  that leads to limit cycle oscillations is plotted in Fig. 4a in the  $f - \varepsilon$  parameter plane. Similarly, keeping  $f$  constant at its base-case value of  $f = 1.0$ , the value of  $q$  is varied and the values of  $\varepsilon$  that delimit the oscillatory region are plotted in Fig. 4b in  $q - \varepsilon$  space. Hence the regimes of the critical points can be quantified and represented diagrammatically in parameter space (Fig. 4).

The system of Eqs. (14), (15) provides the simplest model in our hands that successfully accounts for the oscillatory behavior of nonlinear B-Z type reaction networks. Some chief reasons for the success of the minimal model are given in the last paragraph of Section 2. In addition, the minimal model works really well because it considers only the core chemical reactions of a complex reaction network that are central to generation of the oscillatory and excitability properties of the network. There is further the key attribute of the separation of timescales, discussed in the literature on multiple time-scale analysis of nonlinear systems [16]. Thus, chemical reactions that are faster than the core reactions are subsumed by a quasi-steady-state approximation, while reactions that are slower than the core reactions are not included in the minimal model. The minimum number of interacting reactants/reactions needed to generate oscillatory



**Fig. 3.** Dynamics of the system for  $f = 1$ ,  $q = 0.015$ , and  $\varepsilon = 0.516$ : (a)  $x$ ,  $z$  as a function of time; (b)  $x$ - $z$  phase plane plot. Evolution of chemical species for the parameters  $f = 1$ ,  $q = 0.015$ , and  $\varepsilon = 0.1$ : (c) Temporal plot of  $x$ ,  $z$ ; (d) Phase diagram in  $x$ - $z$  coordinates.



**Fig. 4.** (a) Locus of Hopf bifurcation points in the  $f - \varepsilon$  plane for the system of Eqs. (14), (15) for  $q = 0.015$ . (b) Locus of the points that bifurcate the oscillatory region in the  $q - \varepsilon$  plane for the parameter value  $f = 1$ .

behavior is two. The nonlinear term of the form  $x(1 - kx)$  in Eq. (14) for the autocatalytic species was found to be required for oscillation. Further reduction in the number of species/reactions, or removal of the autocatalytic contribution exemplified by the mathematical term  $x(1 - kx)$  led to elimination of the interesting dynamical properties of the system seen in Fig. 3.

#### 4. Advantages of the minimal model and its importance for future work

The minimal activator-inhibitor model for oscillations and excitability is applicable to batch and well-stirred systems; however, since it pertains to a simplified model of a *real* reaction



network, it can be extended to address a host of interesting dynamical issues, with major advantages and applications for contemporary chemical research. It can be easily modified and used to study the effect of catalyst confinement on the reaction dynamics by including a new parameter  $\varepsilon''$  in Eq. (14), for example as  $(\varepsilon''f)$  that serves as a fractional multiplier of  $f$ . The minimal model can be readily extended to include diffusion coefficients, and the effect of spatial gradients on spatiotemporal dynamics of the reaction–diffusion equations can be studied. Specifically, the activator–inhibitor system of reaction equations (e.g. Eqs. (14), (15)) can be expanded by addition of a  $D \frac{d^2c}{dx^2}$  term, where  $D$  is the diffusion coefficient of the activator or inhibitor, and  $C$  its concentration over the one-dimensional space,  $x$  and Turing-like structures can be mathematically modeled; such spatial patterns do not arise in the standard treatment of the B–Z reaction. The important effects of an added convective flow  $v \frac{dc}{dx}$  – for instance by immobilizing the inhibitor species in a reactor and flowing the second, activating species at a specified flow rate or relative velocity  $v$  – has not been adequately studied to date, and this could lead to novel findings and applications. The linear stability of the reaction–diffusion or reaction–convection system is carried out in the *same* way as in Section 3.2, except that now an additional diffusion or convective term is also included in the mathematical analysis. Since these effects can be added one at a time, their contributions to the changes in the dynamics can be qualitatively grasped and quantitatively modeled.

The reaction–diffusion/convection effects mentioned above can be further elaborated to model wave propagation in space, as shown by mathematical work on wave trains [10,18]. This could lead to an improved understanding of the generation and propagation of spiral waves, accelerating waves, and so on, not only in reactors, but in a more extended setting of ocean or atmospheric systems in chemistry.

The work has a special significance for biological phenomena. Eqs. (14), (15) of the model show a striking resemblance in underlying mathematical structure to the Hodgkin–Huxley equations of nerve excitability, and this similarity can be profitably explored (Section 5). We found fairly complex models, and debates on the value of such models in mathematical and biological work [18–20]. An aim of this work is to point out that a more complete understanding may not be reached by adding all the complexity in a single sweep. However, systematic, sequential addition and modification of the minimal model appears both feasible and capable of leading to novel biological insights. In particular, it is applicable to Hammerstein–Wiener and Lur'e type nonlinear dynamical systems that are separable into linear and nonlinear blocks. Hence the model can act as a reliable guide for future interdisciplinary and biological research. This is illustrated in Section 5 by exploring the application of the chemical reaction network to biology, specifically to the problem of nerve conduction.

## 5. Application to nerve conduction

We now consider the following reduction of the system of reaction equations (Eqs. (10)–(12)) with  $w = 0$  to show the analogy with the Hodgkin–Huxley equations of neural excitation:

$$\frac{dx}{dt} = \varepsilon(y - xy + x - qx^2) \quad (21)$$

$$\frac{dy}{dt} = \frac{1}{\varepsilon}(-y - xy + fz) \quad (22)$$

where  $z \in (1, 1/q)$  is kept constant and held at its steady state value  $z = x_{ss}(f)$ .

The steady state solutions of the system of reaction equations are obtained by setting the left hand sides of Eqs. (21), (22) to zero, i.e. by solving the cubic equation

$$x^3 + \frac{(q-1)x^2}{q} + \frac{(fz-1)x}{q} - \frac{fz}{q} = 0 \quad (23)$$

Following the principles laid out by Murray in his works [21,22], we find that Eq. (23) possesses three distinct real roots,  $\alpha, \beta, \gamma$  such that  $1 < \alpha(f, z) < \beta(f, z) < \gamma(f, z) < 1/q$ . Thus for our reduced set of equations (Eqs. (21), (22)) with  $z = z_{ss}(f) = x_{ss}(f)$  we have the three steady state solutions

$$\alpha(f, x_{ss}(f)) < \beta(f, x_{ss}(f)) < \gamma(f, x_{ss}(f)) \quad (24)$$

Analogously, the Hodgkin–Huxley equations can also be shown to possess a corresponding set of three steady state solutions. The Hodgkin–Huxley equations for the potential difference  $V$  across the nerve cell membrane in terms of the  $n, m, h$  systems selected by the investigators to fit their experimental data are given by [23]

$$\frac{\partial^2 V}{\partial x^2} = \frac{\partial V}{\partial t} + f(V, n, m, h) \quad (25)$$

$$\frac{\partial n}{\partial t} = \gamma_n(V) [n_{ss}(V) - n] \quad (26)$$

$$\frac{\partial m}{\partial t} = \gamma_m(V) [m_{ss}(V) - m] \quad (27)$$

$$\frac{\partial h}{\partial t} = \gamma_h(V) [h_{ss}(V) - h] \quad (28)$$

For a space-clamped nerve system in which an electrode is inserted along the fiber length,  $\frac{\partial^2 V}{\partial x^2} = 0$ . Hence the Eq. (25) for the neural system reduces to

$$\frac{\partial V}{\partial t} = -f(V, n, m, h) \quad (29)$$

The  $n$  and  $h$  system of particles change only slowly relative to the  $m$  system—we know from molecular research today that the  $m$  system is related to the ultrafast sodium channel, i.e.  $\gamma_n \ll \gamma_m$  and  $\gamma_h \ll \gamma_m$ . Hence the  $n$  and  $h$  systems can be clamped at their resting steady state values  $n_{ss}(0)$  and  $h_{ss}(0)$ , similar to the approximation used for the chemical reaction system  $z = z_{ss}(f)$  above. This gives us the analogous reduced form of the two-dimensional nerve conduction equations, i.e.

$$\frac{\partial V}{\partial t} = -f(V, n_{ss}(0), m, h_{ss}(0)) \quad (30)$$

$$\frac{\partial m}{\partial t} = \gamma_m(V) [m_{ss}(V) - m] \quad (31)$$

The system of neural equations, Eqs. (30), (31) has the set of three steady state solutions  $(V_{ss}, m_{ss})$  given by

$$(0, m_{ss}(0)), (\alpha, m_{ss}(\alpha)), (\beta, m_{ss}(\beta)) \text{ with } 0 < \alpha < \beta \quad (32)$$

This is analogous to the three steady states determined in Eq. (24) for the two-dimensional reaction system given by Eqs. (21), (22). This results from an *underlying* mathematical similarity of the reduced system of equations of both the reaction and the nerve conduction models.

The analogy also extends to the dynamical behavior of the two reduced systems upon perturbation of the resting steady state. It is well known that if the  $n, m, h$  systems are clamped at their resting steady state values  $n_{ss}(0), m_{ss}(0), h_{ss}(0)$ , and the resting state voltage  $V(0)$  exceeds a critical threshold value,  $V^*$ , then an impulse phenomenon is generated in the neural system [22,23]. Similarly, in the reaction system, there exists a value  $y^* =$

$y^*(f, \varepsilon)$  such that for  $x(0) = z(0) = x_{ss}(f)$  and  $y^* > y(0)$  a large excursion in both the variables  $x$  and  $y$  occurs before their return to the steady state. On the other hand, for  $y^* < y(0)$ , the solution monotonically decays to the steady state without any excursion. In other words, for  $y^* > y(0)$ , a spike occurs before the return of  $y(t)$  to its steady state value  $y_{ss}(f)$ , while an impulse phenomenon does not take place if  $y^* < y(0)$  and a mere decay  $y(t) \rightarrow y_{ss}(f)$  occurs. These analogies between the two model systems are ripe for further mathematical analysis and computational evaluation.

The present work has only analyzed reduced models of (i) the B–Z reactions, and (ii) the nerve impulse. The author's aim in this limited attempt was not to analyze oscillating reactions in general. The most comprehensive tome with this aim in the author's knowledge is by Albert Goldbeter [24], which the interested reader may consult. However, Goldbeter did not cover oscillatory phenomena in the B–Z reactions or in nerve conduction in his large monograph [24], a testimony to the vast nature of the subject.

## 6. Conclusions

Minimal models for simulating the oscillatory and excitability characteristics of real nonlinear chemical reaction networks out of equilibrium have been examined. It has been found that a two-variable, autocatalytic activator–inhibitor type of model exhibits the required dynamical properties, and that it is the simplest model of an extant B–Z-type experimental system that is successfully able to do so. Attempts to further reduce the minimal model did not reproduce the main features of the experimentally observed nonlinear dynamics. Analysis by means of nullcline plots has been shown to reveal qualitatively the overall behavior of the network. Analysis based on linear stability techniques and numerical simulation of the coupled ODEs has been shown to offer more quantitative insights into parametric regions of stability, instability, and the type of dynamics. By comparison with actual experimental data on the complex reactions, it has been shown that the minimal model accurately predicts the time period of oscillations of the various intermediates of the network, which is a principal result of this work. Reasons for the predictive success of the minimal model have been analyzed. The essential autocatalytic contribution and the nonlinear mathematical term in the equations of the chemical reaction network that gives rise to oscillatory behavior has been identified. Various extensions of the minimal model to include spatiotemporal phenomena such as in the presence of diffusive and convective instabilities, and catalyst confinement have been discussed, and point to the importance of the minimalist approach, given that the effect of each element of added complexity can be readily evaluated, especially for Hammerstein–Wiener and Lur'e type nonlinear systems that can be decomposed into linear and nonlinear blocks. Applications to fundamental biological processes have been foreseen. Application to the phenomenon of nerve conduction as modeled by the Hodgkin–Huxley equations has been singled out as being particularly important, since the underlying mathematical structure of these equations is identical to that of the minimal chemical reaction network model, and a mathematical analysis has been carried out to illustrate the analogy.

## CRedit authorship contribution statement

**Sarang S. Nath:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- [1] J.H. Espenson, *Chemical Kinetics and Reaction Mechanisms*, second ed., McGraw–Hill, New York, 1995.
- [2] T.A. Bak, P. Salamon, B. Andresen, Optimal behavior of consecutive chemical reactions, *J. Phys. Chem. A* 106 (2002) 10961–10964.
- [3] A.E. Beezer, L.D. Hansen, Determination of rate constants and enthalpy changes, *J. Phys. Chem. B* 116 (2012) 6356–6360.
- [4] A. Pellissier-Tanon, G. Morgado, L. Jullien, A. Lemarchand, Quasi-steady-state and partial-equilibrium approximations in chemical kinetics: one stage beyond the elimination of a fast variable, *ChemRxiv* (2021) <http://dx.doi.org/10.26434/chemrxiv.14198768.v2>.
- [5] W.C. Bray, A periodic reaction in homogeneous solution and its relation to catalysis, *J. Am. Chem. Soc.* 43 (1921) 1262–1267.
- [6] P. Glansdorff, I. Prigogine, *Thermodynamic Theory of Structure, Stability and Fluctuations*, Wiley, New York, 1971.
- [7] Belousov B.P., A periodic reaction and its mechanism, *Sb. Ref. Radiat. Med. Medgiz Mosc.* (1959) 145, (Abstract in Russian).
- [8] A.M. Zhabotinskii, Periodic process of the oxidation of malonic acid in solution (study of the kinetics of Belousov's reaction), *Biofizika* 9 (1964) 306–311. (Article in Russian).
- [9] G.A. Frerichs, T.M. Mlnarik, R.J. Grun, R.C. Thompson, A new pH oscillator: The chlorite–sulfite–sulphuric acid system in a CSTR, *J. Phys. Chem. A* 105 (2001) 829–837.
- [10] A.T. Winfree, *The Geometry of Biological Time*, second ed., Springer, New York, 2001.
- [11] R.J. Field, E. Körös, R.M. Noyes, Oscillations in chemical systems, II. Thorough analysis of temporal oscillation in the bromate–cerium–malonic acid system, *J. Am. Chem. Soc.* 94 (1972) 8649–8664.
- [12] D. Edelson, et al., Mechanistic details of the Belousov–Zhabotinskii oscillations, *Int. J. Chem. Kinet.* 7 (1975) 417–432.
- [13] J.J. Tyson, P. Fife, Target patterns in a realistic model of the of the Belousov–Zhabotinskii reaction, *J. Chem. Phys.* 73 (1980) 2224–2237.
- [14] R.J. Field, R.M. Noyes, Oscillations in chemical systems, *J. Chem. Phys.* 60 (1974) 1877–1884.
- [15] J.J. Tyson, Scaling and reducing the mechanism of the B–Z reaction, *J. Phys. Chem.* 86 (1982) 3006–3012.
- [16] S.H. Strogatz, *Nonlinear Dynamics and Chaos with Applications in Physics, Biology, Chemistry, and Engineering*, second ed., CRC Press, Boca Raton, Florida, USA, 2018.
- [17] R. Chouket, T. Le Saux, L.L. Jullien, et al., Extra kinetic dimensions for label discrimination, *Nat. Commun.* 13 (2022) 1482, <http://dx.doi.org/10.1038/s41467-022-29172-0>.
- [18] M. Iannelli (Ed.), *Mathematics of Biology*, Springer, Berlin, 2010.
- [19] T. Heimburg, A.D. Jackson, On soliton propagation in biomembranes and nerve, *Proc. Natl. Acad. Sci. USA* 102 (2005) 9790–9795.
- [20] M. Peyrard, How is information transmitted in a nerve?, *J. Biol. Phys.* 46 (2020) 327–341.
- [21] J.D. Murray, *Mathematical Biology*, Volume I: An Introduction, third ed., Springer, New York, 2002.
- [22] J.D. Murray, *Mathematical Biology*, Volume II: Spatial Models and Biomedical Applications, third ed., Springer, New York, 2003.
- [23] A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, *J. Physiol.* 117 (1952) 500–544.
- [24] A. Goldbeter, *Biochemical Oscillations and Cellular Rhythms: The Molecular Bases of Periodic and Chaotic Behaviour*, Cambridge University Press, Cambridge, 1997.