Chapter

Complex Dynamics of Competitive First Order Chemical Self-Replication

Anuj K. Shah and Enrique Peacock-López

Abstract

In most experimental conditions, the initial concentrations of a chemical system are at stoichiometric proportions, allowing us to eliminate at least one variable from the mathematical analysis. Under different initial conditions, we need to consider other manifolds defined by stoichiometry and the principle of conservation of mass. Therefore, a given set of initial conditions defines a dynamic manifold and the system, a tall times, has to satisfy a particular relation of its concentrations. To illustrate the relevance of the initial conditions in a dynamic analysis, we consider a chemical system consisting of two first-order self-replicating peptides competing for a common nucleophile in a semi-batch reactor. For the symmetric case, we find different complex oscillations for a given set of parameter values but different initial conditions.

Keywords: chemical self-replication, limiting reagent, coexistence

1. Introduction

Chemical self-replication is how an individual molecule can duplicate itself. In a first-order process, a product molecule directs in own synthesis by facilitating the binding of two or more component molecules to form a new product molecule. The product molecule acts as an auto-catalytic template to position the components for a ligation reaction. There are two critical steps in chemical self-replication. First, the product molecules must bind available components to facilitate the ligation and formation of the product molecules. Second, once this ligation is completed, the product-template complex (duplex) must readily dissociate so that the newly formed product molecule may join the other product molecules. In an efficient self-replicating system, as soon as the new product molecule is formed after ligation, it should readily dissociate from the template molecule and begin to act as a template by binding component molecules. Since product molecules can participate in multiple replication cycles as a template, the product concentration's growth rate is directly proportional to its concentration. This relationship characterizes autocatalysis, and it yields an exponential growth rate for the concentration of the product molecule. This process of sustained exponential growth is known as autocatalytic self-replication.

In reality, however, it is not easy to achieve the delicate balance between a strong binding of the component molecules to facilitate the formation of a new product

molecule and an easy dissociation of the duplex, which is required for autocatalytic self-replication. The most significant challenge is the difficulty of dissociating the product-template intermediate to yield a new product molecule and the original template. When product-template molecules remain together, the number of template molecules is reduced, and thus the growth rate is less than exponential.

Over the past 25 years, the interest in understanding chemical self-replication has grown. Researchers have developed several experimental systems in aqueous solutions using peptides [1–10], oligonucleotides [11–15], modified ribozymes [16–18], and DNA [19–24]. In particular, we have considered Joyce's [16–18], Ashzkenazy's [25–34], and Rebek's [35–40] experimental systems and have proposed simple model [41] to analyze their experiments.

In most reported cases, researchers start with an initial set of concentrations and monitor over time the concentrations of the reactants, product, and, on some occasions, the intermediate. Under these so-called batch conditions, researchers have found exponential growth and, therefore, self-replication. Using Joyce's experiments, we have proposed a minimal Templator Mode [41] and determined parameter values for our model, and we have extended our analyses to open conditions to characterize probable dynamic behaviors [41–51].

However, most of our early work has only emphasized auto-catalysis mediated by a single template, and, lately, we have considered a generalization of the first model to include the so-called parabolic growth and the association of multiple product/template molecules to form an active auto-catalytic template multimer [45, 46]. We have also considered cross-catalysis, where a system of four component molecules and two templates can cross-replicate [47]. In other words, one template catalyzes the formation of the other template and vis versa.

Another critical aspect of chemical self-replication is its implications for understanding life's origins [52–55]. Although chemical self-replication is necessary to develop models of the origins of life, competition between chemical systems must also be included in the discussion. To consider competition in our analysis of chemical self-replication, we study a two-template system competing for one common reagent. In the next section, we discuss an extension of our previous work to include the three different reactants and two self-replicating templates. Section 3 presents and discusses our dynamic analysis in cases where the templates are similar, but one is a better replicator than the other. Finally, section 4 summarizes the dynamic behavior of a simple competing system of self-replicating templates.

2. General model

In previous work [41–51], we have considered Rebek's and Joyce's self-replicating systems and modeled ideal self-replication using a self-complementary template mechanism. For this experimental design, we used a reasonable chemical model consistent with the laboratory work on self-replication. In particular, we consider a simple self-replicating mechanism characterized by a cubic nonlinearity, and in general, chemical self-replication can be represented schematically by the following mechanistic steps

$$A + B \xrightarrow{k_{u1}} P, \tag{1}$$

$$A + B + P \xrightarrow{k_{templ}} P + P, \tag{2}$$

where P represents the self-replicating molecule, and A and B are the component fragments. In the uncatalyzed step, components A and B interact with a relatively low probability of forming the template, P. The structure of the product P is such that once it is formed, it preferentially binds A and B in a conformation that facilitates covalent bonding between the A and B molecules to form another P molecule. The newly created template and the original template molecules then split apart and independently catalyze further reactions.

While considering first-order self-replication, we can couple the autocatalytic process with an enzymatic formation of a regulatory product, Q,

$$P \xrightarrow{E} Q \tag{3}$$

where the rate shows saturation at high concentrations of P.

Following Joyce's ribozyme systems and Ashkenazy's peptide systems, where the components are RNA strands or electrophilic or nucleophilic peptide fragments, we build a competitive Templator model by first considering the uncatalyzed formation of the template P from strands A and B. Likewise, we include the uncatalyzed formation of the template R from strands A and C,

$$A + B \xrightarrow{k_{u1}} P \ , \tag{4}$$

$$A + C \xrightarrow{k_{u2}} R, \tag{5}$$

In Eqs. (4) and (5), k_{u1} and k_{u2} represent the rate constants of the uncatalyzed reactions, respectively. These equations imply that strands B and C compete for the common component A to form their respective templates. The competitive Templator model also incorporates the catalyzed formation of templates P and R, where the covalent bonding of strands A, B, and C to either P or R templates is included,

$$A + B + P \xrightarrow{k_{t1}} P + P, \tag{6}$$

$$A + C + R \xrightarrow{k_{t2}} R + R, \tag{7}$$

Here, k_{t1} and k_{t2} represent the rate constants for each self-catalyzed reaction, and we have contracted the bimolecular process to yield Eqs. (6) and (7).

As in most of our previous work, we have considered a simple constant volume ideal open conditions that assume a continuous inflow of reactants to the system. Therefore, to prevent the chemical system from reaching equilibrium, we pump A, B, and C into the system from pools A_o, B_o, and C_o at a constant rate, k_o:

$$A_o \xrightarrow{k_o} A, \tag{8}$$

$$B_o \xrightarrow{k_o} B, \tag{9}$$

$$C_o \xrightarrow{k_o} C, \tag{10}$$

Finally, we must incorporate the removal of each template from the system through an enzymatic reaction that converts them to another compound, S_1 and S_2:

$$P \xrightarrow{q_1, K_{M1}} S_1 \ , \tag{11}$$

$$R \xrightarrow{q_2, K_{M2}} S_2, \tag{12}$$

where q_1, q_2, K_{M1}, and K_{M2} are rate constants associated with the enzymatic reactions.

Based on Eqs. (4) and (5), we can consider a competitive two-template system with the following ODEs:

$$\frac{d\,A}{d\,t} = \ k_o A_o - k_{u1} AB - k_{u2} AC - k_{t1} ABP - k_{t2} ACR, \tag{13}$$

$$\frac{d\,B}{d\,t} = k_o B_o - k_{u1} AB - k_{t1} ABP, \tag{14}$$

$$\frac{d\,C}{d\,t} = k_o C_o - k_{u2} AC - k_{t2} ACR, \tag{15}$$

$$\frac{d\,P}{d\,t} = k_{u1} AB + k_{t1} ABP - \frac{q_1\,P}{K_{M1} + P}, \tag{16}$$

$$\frac{d\,R}{d\,t} = k_{u2} AC + k_{t2} ACR - \frac{q_2\,R}{K_{M2} + R}, \tag{17}$$

For details on dimensionless systems, see references [41, 43].

However, before analyzing the dynamic behavior of these five ODEs, we must understand the behavior of the chemical system in the absence of one of the competing templates, the role of the external fluxes, and the initial conditions on the dynamics. Therefore, if we ignore the competing template, R, our system reduces from five to three ordinary differential equations for components A and B, and product P,

$$\frac{d\,A}{d\,t} = \ k_o A_o - k_{u1} AB - k_{t1} ABP, \tag{18}$$

$$\frac{d\,B}{d\,t} = k_o B_o - k_{u1} AB - k_{t1} ABP, \tag{19}$$

$$\frac{d\,P}{d\,t} = k_{u1} AB + k_{t1} ABP - \frac{q_1\,P}{K_{M1} + P}, \tag{20}$$

Since the overall reaction shows that A and B are in a one-to-one relation, we next employ the following simple definitions:

$$X(t) = \ \frac{A(t) + B(t)}{2}, \tag{21}$$

$$Y(t) = \frac{A(t) - B(t)}{2}, \tag{22}$$

Where X(t) stands for the total concentration of A and B, and Y(t) represents the difference in concentration between A and B, both at a given time t. From Eqs. (21) and (22), we determine the new ODEs,

$$\frac{d\,X}{d\,t} = k_o X_o - k_{u1}\left(X^2 - Y^2\right) - k_{t1}\left(X^2 - Y^2\right)P, \tag{23}$$

$$\frac{d\,Y}{d\,t} = k_o Y_o, \tag{24}$$

$$\frac{d\,P}{d\,t} = k_{u1}\left(X^2 - Y^2\right) + k_{t1}\left(X^2 - Y^2\right)P - \frac{q_1\,P}{K_{M1} + P}, \tag{25}$$

where

$$X_o = \frac{A_o + B_o}{2}, \tag{26}$$

$$Y_o = \frac{A_o - B_o}{2}, \tag{27}$$

Notice that in self-replicating chemical systems, the uncatalyzed process occurs with a very low probability, so $k_u << k_t$, and Y_o needs to be zero; otherwise, the system accumulates one of the reactants, and it blows up. In other words, we need to pump the reagents accordingly to their stoichiometric proportions; for details, see references [41, 43].

In previous work, we have analyzed at length the case of no-limiting reagent, $Y(t) = Y(0) = 0$, where $A(t) = B(t)$ [41–51]. But here we relax the no-limiting reagent condition and notice, since $Y_o = 0$, that the variable Y has a simple solution, $Y(t) = Y(0)$. Consequently, the solution $Y(0)$ appears as a pseudo-parameter in the other two ODEs associated with X and P. The presence of $Y(0)$ has a net effect on the amplitude of the limit cycles because the initial difference between A and B has to be preserved,

$$Y(t) = Y(0) = \frac{A(t) - B(t)}{2}, \tag{28}$$

or

$$A(t) = X(t) + Y(0), \tag{29}$$

$$B(t) = X(t) - Y(0), \tag{30}$$

In other words, the difference in initial concentrations introduces a mass constraint on the dynamic behavior of the concentrations.

Regardless of initial conditions, we find a linear relationship (with a slope m equal to 1) between the change in concentrations of A and B, $A(t) = B(t) + 2Y(0)$. However, each initial difference in concentrations produces a unique basin of attraction defined by a simple manifold, $A(0) = B(0) + Y(0)$. This dependence on $Y(0)$ implies, in principle, an infinite number of limit cycles. This infinite number of possible types of behavior is unusual for chemical systems, but in this case, we impose a chemical restriction required to achieve a steady state.

In **Figure 1**, we consider the following dimensionless parameter values: $k_o = 0.6$, $A_o = B_o = 1.0$, $k_{u1} = 0.01$, $k_{t1} = 1.0$, $q_1 = 1.0$, $K_{M1} = 0.05$, and different initial concentrations. Notice that in the symmetric case, $Y(0) = 0$ yields the largest amplitude, and as the absolute value of $Y(0)$ increases, the amplitude decreases. But it is important to note that once we choose the initial difference in concentration, $Y(0)$, the system is *not* dependent on specific initial values for the concentrations of A and B, as long as they belong to the same manifold. For example, if two different initial

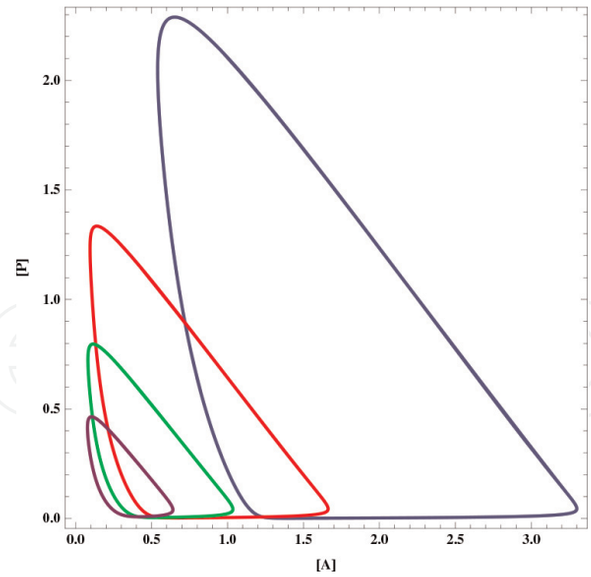

Figure 1.
For the phase plot above, we consider the following differences in initial concentrations of A and B: $Y(0) = 0$ *(*$A = 20$*,* $B = 20$*; blue),* $Y(0) = -5$ *(*$A = 15$*,* $B = 20$*; red),* $Y(0) = -10$ *(*$A = 10$*,* $B = 20$*; green), and* $Y(0) = -18$ *(*$A = 2$*,* $B = 20$*; purple).*

conditions have the same $Y(0)$, they belong to the same basin of attraction, and each reaches the same attractor. Additionally, switching the initial values for the concentrations of A and B does not change the characteristics of the attractor. However, two cases with different values of $Y(0)$ reach a limit cycle of varying amplitude.

As in the three-variable system, in competitive scenarios, stoichiometric pumping is necessary for the existence of a steady state. It is straightforward to prove that a steady state exists if the pumping pools satisfy the stoichiometric condition $A_o = B_o + C_o$. Otherwise, accumulation dominates the system, increasing one of the concentrations without a bound. Under a balanced pumping restriction, we find that $Y(t) = A(t) - B(t) - C(t)$ is a constant equal to $Y(0) \equiv Y_i$, which determines the basin of attraction for each attractor characterized by Y_i. In other words, for a given set of parameters, the set of initial concentrations $A(0) = B(0) + C(0) + Y$ reaches the same attractor Y_i. Notice that in this case, we can solve for $A(t)$, use the relation $A(t) = B(t) + C(t) + Y_i$, and reduce the system of ODEs to a four variables system, but with a pseudo-parameter, Y_i. We reemphasize that this behavior is a consequence of the balanced pumping and the limiting reagent constraint. Consequently, since not all experiments satisfy the no-limiting reagent condition, we pay attention to the initial conditions of the five species evolving in time and characterize the dynamic behavior by the limiting reagent constraint.

3. Dynamic characterization of the symmetric case

In this section, we examine the symmetric case in which both templates exhibit the same replicative efficiency for their catalyzed and uncatalyzed formation. Although we may think the symmetric case is not that interesting, an initial limiting reagent condition can give us interesting dynamic behaviors. In **Figure 2**, we plot the time Series [56] for R, and P, and its phase plot for a symmetric case, and $Y_i = 0$, and it serves as a reference for other values of Y_i. For simplicity, in our analysis of the full

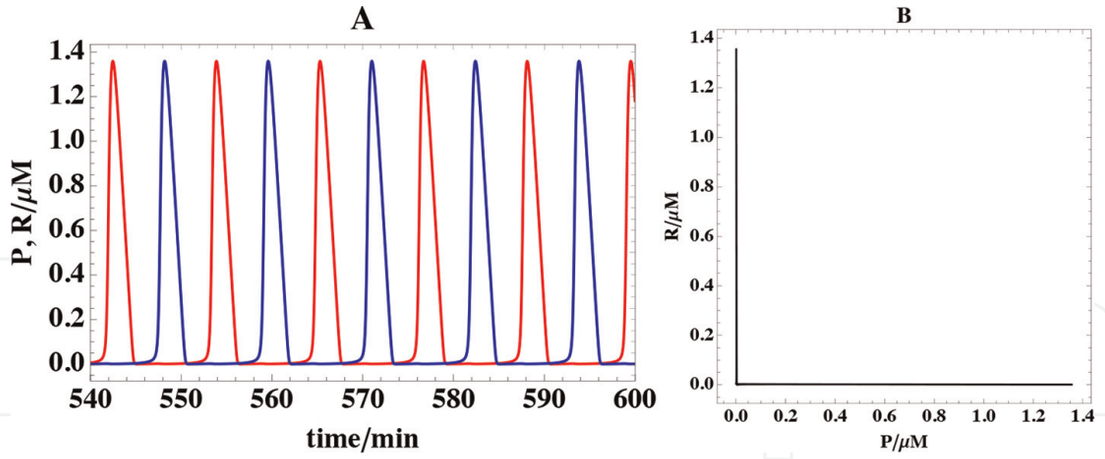

Figure 2.
Symmetric attractor Y = 0: $k_o = 0.6, A_o = 1.0, B_o = C_o = 0.5, k_{u1} = k_{u2} = 0.01, q_1 = q_2 = 1.0, K_{M1} = K_{M2} = 0.05$, $k_{t1} = k_{t2} = 2, A(0) = 40, B(0) = 20, C(0) = 20$. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).

competitive self-replicator model, we set P(0) and R(0) equal to zero for all cases. For $Y = 0 = A(0) - B(0) - C(0)$, we observe similar oscillations of period-one, (P1), which is not surprising. But the oscillations are out of phase, where P and R alternate maxima. One may expect similar synchronized oscillations since all the parameters for both templates are the same. In contrast, for $Y = 10$, we observe synchronized oscillations in **Figure 3**, and we would only expect these two attractors, but in the synchronized case, notice that the amplitude of the oscillation is smaller than in the out of phase case. So it makes sense that in the synchronized case, both templates compete simultaneously, while in the out-of-phase case, only one is actively replicating.

For example, in **Figure 4**, we hold A(0) at 40 and C(0) at 20 while increasing B(0) to 45 (Y = −25), and, in this case, we find period two, (P2), out of phase oscillations with larger amplitude that in **Figure 3**. At this point, we have changed $B(0)$ from 20 to 45 and observe a change from P1 to P2. But notice that if we change $B(0) = 46$, the system shows chaotic dynamics, as shown in **Figure 5**. Furthermore, when we change $B(0) = 57$, we observe complex oscillation, as shown in **Figure 6**. Notice that in all cases, both self-replicating templates, P and R, show the same complex oscillation but are out of phase.

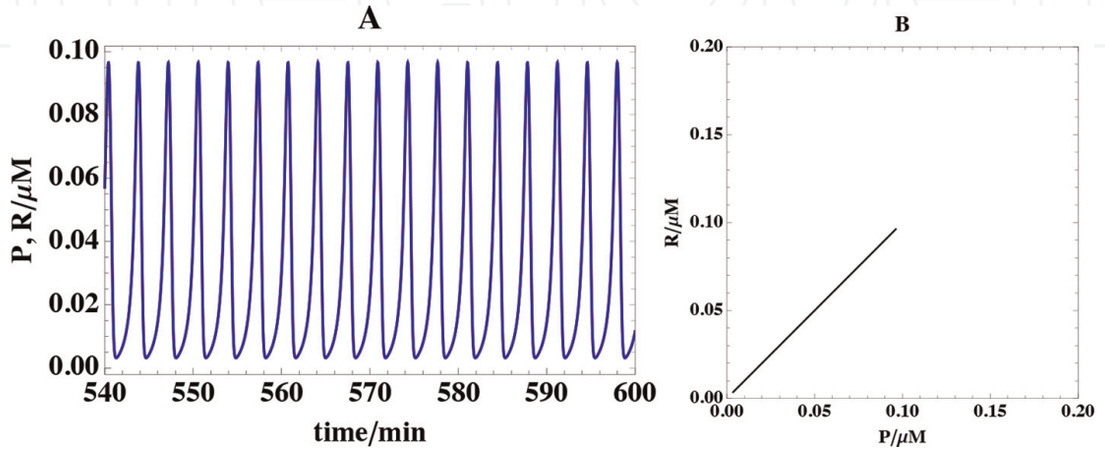

Figure 3.
*Symmetric attractor Y = 10: parameters same as in **Figure 2**, $A(0) = 50, B(0) = 20, C(0) = 20$. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).*

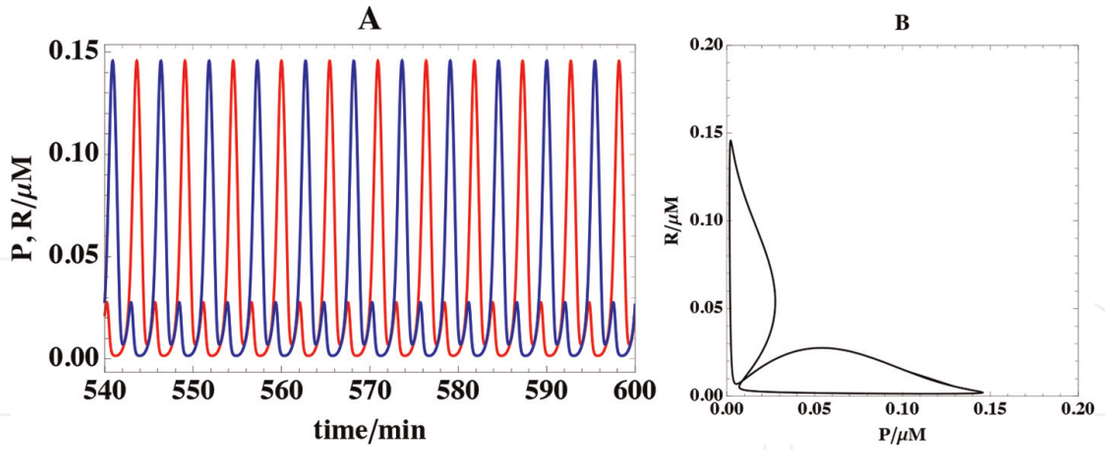

Figure 4.
Symmetric attractor Y = −25: parameters same as in ***Figure 2****,* $A(0) = 40, B(0) = 45, C(0) = 20$*. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).*

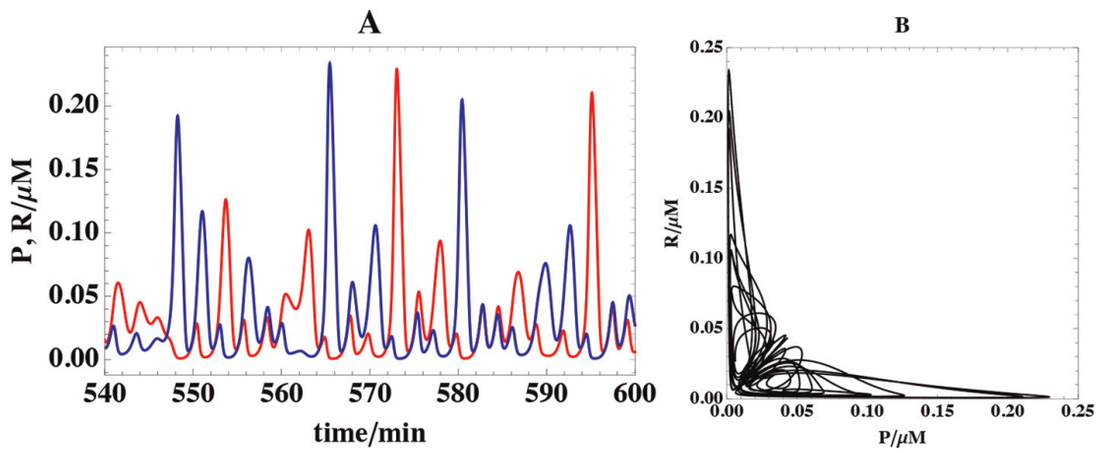

Figure 5.
Symmetric attractor Y = −26: parameters same as in ***Figure 2****,* $A(0) = 40, B(0) = 46, C(0) = 20$*. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).*

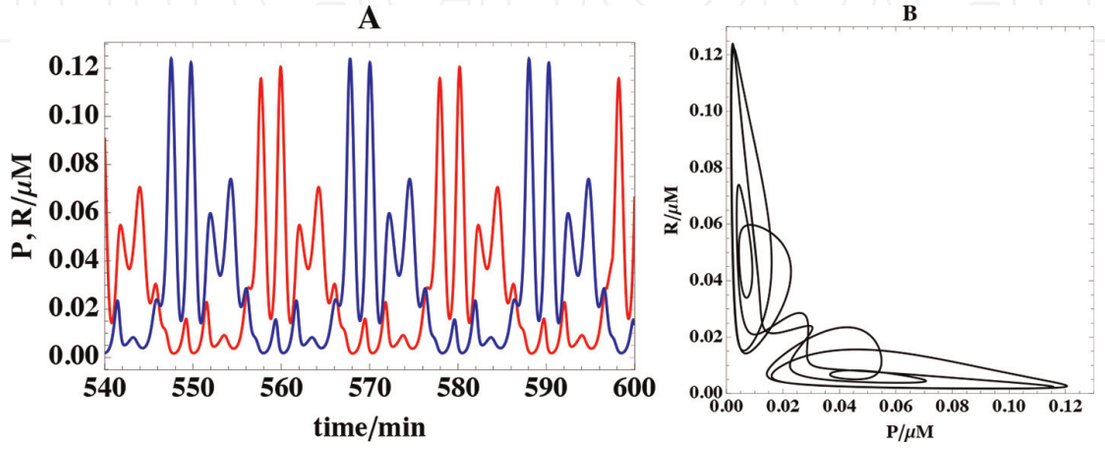

Figure 6.
Symmetric attractor Y = −37: parameters same as in ***Figure 2****,* $A(0) = 40, B(0) = 57, C(0) = 20$*. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).*

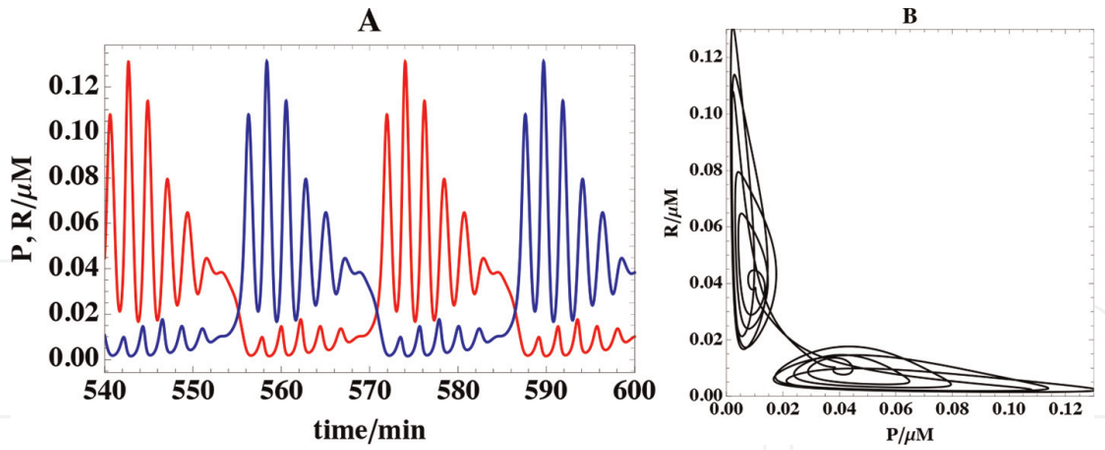

Figure 7.
Symmetric attractor Y = −40: parameters same as in ***Figure 2****,* $A(0) = 40, B(0) = 60, C(0) = 20$*. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).*

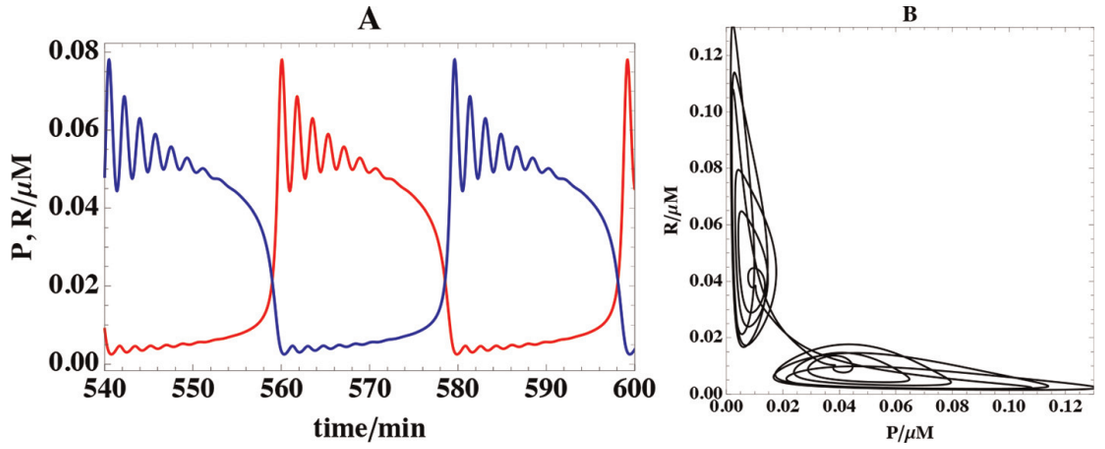

Figure 8.
Symmetric attractor Y = −57: parameters same as in ***Figure 2****,* $A(0) = 20, B(0) = 57, C(0) = 20$*. A) Time series for P[t], in red, and R[t] in blue. B) Phase plot of P(t) vs. R(t).*

Upon further increase of the initial concentration of B to 25 while holding A(0) and C(0) at the same values (Y = −5), the chemical system returns to simple alternating oscillations, with template R exhibiting greater amplitude (**Figure 3**). Inspection of the case in which A(0) = B(0) = C(0) = 20 (Y = −20) indicates that the system exhibits the same behavior, though the amplitude values of the templates are approximately the same (**Figure 4**). We again see this simple oscillatory behavior when Y = −25 (**Figure 5**), but when Y = −26, the system transitions to chaotic behavior (**Figure 6**). We find another transition in behavior in the competitive model when Y is equal to −37 at higher values of B(0) as it begins to exhibit complex rather than chaotic oscillations (**Figure 7**). At more extreme values of B(0) (Y = −50), we continue to see complex behavior in this system (**Figure 8**).

4. Discussion

We can emphasize the synchronized and unsynchronized oscillations in figures for the symmetric case (2,3). The synchronized oscillations have a smaller amplitude than

the case of unsynchronized oscillations. But, in general, the oscillations tend to be unsynchronized, as shown in **Figures 4–8**, and, in the cases of the plots in phase space (P, R), where the symmetry is easy to observe. In the previous section, we have shown simple P1 and P2 oscillations and complex oscillations. The symmetric case serves as a benchmark as we continue our analysis.

At first glance, we may inquire why the initial conditions influence the observed attractor. We emphasize that one needs to satisfy the condition $A_o = B_o + C_o$; otherwise, one ends with an accumulation of a reagent. In mathematical terms, the concentration of one reagent grows to infinity. By pumping the reagents at a stoichiometric proportion, one avoids such accumulation of a reagent. In other words, if we define $Z(t) = (A(t) - B(t) - C(t))/2$ we get from Eqs. (3)–(17). the following relation:

$$\frac{dZ}{dt} = ko\, Z_o \tag{31}$$

$$Z_o = \frac{A_o - B_o - C_o}{2}, \tag{32}$$

where A_o, B_o, C_o are the concentrations of the external stock solutions, being pumped with a rate k_o. It is clear that $Z(t) = Z(0) + k_o Z_o t$ and grows unbound for $Z_o \neq 0$, and $Z(t) = A(t) - B(t) - C(t) = Z(0) = A(0) - B(0) - C(0)$. Therefore $Z(0)$ defines a manifold associated with an attractor.

The restriction due to the mass conservation expressed in the reaction's stoichiometry is not particular to the assumed system's conditions. The mass constraint manifests through the initial concentrations for our ideal open system. But in the case of a continuous stirred tank reactor (CSTR), the mass constraint manifests through the stock concentrations and in this case $Z(t) = A(t) - B(t) - C(t) \rightarrow Z_o = A_o - B_o - C_o$. In other words, due to the mass conservation and stoichiometry, $A(t) - B(t) - C(t) = constant$, and the constant defines a manifold of concentrations associated with an attractor. To consider our approach to model biological systems, one may need to assume that the inflow should be regulated by membrane proteins translocating the reagents, and the system volume should be kept constant. These conditions may or may not be easy to satisfy.

In most model reductions, one assumes stoichiometrically balanced inputs and initial conditions, simplifying the ODEs. But experimentally, it may not be the case, and one may have a limiting reagent and mathematically have an additional parameter in the ODEs. In this case, the mass constraint enters as a parameter, as seen in Eqs. (23)–(25), and all the initial conditions are related by the constraint belonging to the same manifold. In summary, under experimental conditions, one may need to pay attention to the stock solutions and the initial concentrations and include them in the ODEs associated with a particular mechanism.

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Author contributions

Anuj K Shah: Formal analysis(lead);Methodology (equal);Writing-original draft (equal). Enrique Peacock-López: Funding acquisition; Writing -review, and editing (equal).

Conflict of interest

The authors have no conflicts to disclose.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Author details

Anuj K. Shah and Enrique Peacock-López*
Department of Chemistry, Williams College, Williamstown, MA, USA

*Address all correspondence to: epeacock@williams.edu

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