Chemical Oscillations: The Templator Model

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Abstract: Recently, Rebek has synthesized self-replicating molecules in the laboratory. Given the importance of such molecules, we are introducing a simple model of self-replicating molecules for the first time. The model mimics the experimental template mechanism and is an important new dynamical model with cubic nonlinearity. This nonlinearity is modeled after the self-replicating mechanism recently reported in the literature. Here we consider the full templator model and a minimal model, which disregard the uncatalyzed step in the mechanism. For the minimal model, we find an exact analytical expression for the locations of the bifurcation points. For the full model, however, we obtain analytical approximations for the bifurcation points that compare very well with the exact numerical solutions.

Introduction

Eighty years after Lotka's prediction of damped oscillations [1] and Bray's experimental paper [2], chemical oscillations have developed into a robust research field both theoretically and experimentally. A solid introduction to chemical oscillations, therefore, is imperative in the undergraduate curriculum [3, 4]. Moreover, the overlap with other areas, like biology, makes the study of chemical oscillations a fertile multidiciplinary field. Consequently, the need for different points of view and techniques makes the study of nonlinear chemical kinetics a welcoming field to newcomers. As a result, an accessible introduction to this field should be part of an undergraduate education in chemistry.

Currently, most texts use the Lotka–Volterra model (LVM) [1–5] to introduce some, but not all, important mathematical concepts in nonlinear chemical kinetics. Though this is common practice, the LVM is not an optimal example. Recently, we have presented a modified LVM [6] that allows us to introduce several of the fundamental concepts of nonlinear dynamics. Although this model is dynamically richer, it is not related to any chemical system. We also presented an example of chemical oscillations in enzyme kinetics [7]. This model's algebraic calculations, however, proved to be quite challenging and time consuming to most undergraduate students. A chemical-based model with accessible algebraic manipulations is, therefore, desirable.

With this purpose in mind, we introduce another model. This time, the model is based on Julius Rebeck, Jr.'s experimental work on self-replicating molecules [8–12]. In Section 2 we review Rebek's work and introduce the templator model that mimics these experiments. We proceed with a linear analysis of a simplified version of the templator in Section 3. In Section 4 we consider the full templator model and derive approximate expressions for the bifurcation points. Also we compared our analytical expressions to an exact numerical analysis. Finally, in Section 5 we discuss the use of the model in an undergraduate environment.

Self-Replicating Molecules

Periodic oscillations are characteristic of any living system [19]. Oscillations can be observed in systems spanning many orders of magnitude, from ecosystems to the human body. Although current understanding of oscillating systems is fairly limited, it is believed that without an autocatalytic step chemical oscillation will not be observed. Studying autocatalytic systems, therefore, gives us a better feeling for the factors that determine whether or not a system will display stable limit cycles. Examining the characteristics associated with living systems will deepen our understanding of those systems and may shed light on the conditions required for life to appear. A number of oscillating systems have been studied extensively. Among these are the Lotka–Volterra system and the Oregonator (or BZ reaction) [20]; other theoretical oscillating systems ignore conservation of mass. Even though such systems produce oscillation, their usefulness in studying life is diminished because the chemical models proposed are not realistic from a chemical point of view.

Our work attempts to find a reasonable self-replicating chemical model that sustains oscillations. In particular, we focus on a template model of a primitive self-replicating molecule. Self-replicating molecular systems have been synthesized in the laboratory by Rebek et al. [8–12]. Rebek's self-replicating system is represented schematically below:

$$A + B \xrightarrow{k_{\text{uncat}}} P \qquad (1)$$

$$A + B + P \xrightarrow{k_{\text{templ}}} P + P \qquad (2)$$

Molecule A can stand for adenine ribose (AR), diaminotriazine xanthene (DIX), adenine ribose-Z (ZAR), or adenine ribose-Z-N_2 (ZNAR), where Z is a blocking group like benzyloxycarbonyl. The other molecule, B, can be naphthaline imide (NI), biphenyl imide (BI), or thymine (T). We notice that these molecules are self-complementary and when bound covalently form a product that can work as a template for the formation of more product, except for DIXBI that cannot self-replicate.

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In the uncatalyzed step, molecules A and B collide in a relatively low-probability process to form 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 with the formation of P. The newly created template and the template from which it was formed can then split apart to catalyze further reactions. Because this mechanism has been observed in the laboratory, a templator model is clearly chemically meaningful.

In particular we consider the most efficient self-replicating molecule. In this case the mixture of adenine ribose and thymine yields ART. The mechanism includes an uncatalyzed formation of the self-replicating species with rate constant K_u:

$$A + B \xrightarrow{k_u} P \tag{3a}$$

$$` A + B + P \xrightarrow{k_t} P + P \tag{3b}$$

with rate constant k_t.

To prevent the system from reaching equilibrium, we pump A and B into the system from a pool A_0, B_0 at a constant rate, k_0,

$$A_0 \xrightarrow{k_0} A \tag{3c}$$

$$B_0 \xrightarrow{k_0} B \tag{3d}$$

We also assume that P is removed by an enzymatic reaction that converts it to R. Namely, we consider the following step:

$$P \xrightarrow{k_m, K_M} R \tag{3e}$$

where k_m and K_M are the constants associated with an enzymatic reaction.

The ordinary differential equations (ODEs) associated with eqs 3a–3e are

$$\frac{dA}{d\tau} = k_0 A_0 - K_u AB - k_t ABP \tag{4a}$$

$$\frac{dB}{d\tau} = k_0 B_0 - K_u AB - k_t ABP \tag{4b}$$

$$\frac{dP}{d\tau} = K_u AB + k_t ABP - \frac{k_m P}{K_M + P} \tag{4c}$$

Furthermore, using the following scaling:

$$A = a\left(\frac{k_m}{k_t}\right)^{1/3} \tag{5a}$$

$$B = b\left(\frac{k_m}{k_t}\right)^{1/3} \tag{5b}$$

$$P = c\left(\frac{k_m}{k_t}\right)^{1/3} \tag{5c}$$

$$\tau = \frac{t}{\left[k_t k_m^2\right]^{1/3}} \tag{5d}$$

we obtain a set of dimensionless differential equations,

$$\frac{da}{dt} = r_0 a_0 - k_u ab - abc \tag{6a}$$

$$\frac{db}{dt} = r_0 b_0 - k_u ab - \frac{c}{K + c} \tag{6b}$$

$$\frac{dc}{dt} = k_u ab + abc\frac{c}{K + c} \tag{6c}$$

where we have defined the following dimensionless parameters:

$$\gamma_0 = \frac{k_0}{\left[k_t k_m^2\right]^{1/3}} \tag{7a}$$

$$a_0 = A_0\left(\frac{k_t}{k_m}\right)^{1/3} \tag{7b}$$

$$k_u = \frac{K_u}{\left[k_t k_m^2\right]^{1/3}} \tag{7c}$$

$$K = K_M\left(\frac{k_t}{k_m}\right)^{1/3} \tag{7d}$$

Now, we consider the following simple definitions

$$x = \frac{a + b}{2} \tag{8a}$$

$$y = \frac{a - b}{2} \tag{8b}$$

where x stands for either the rescaled concentration of a or b, and y the numerical difference between a and b. Using these variables, we obtain the following equations:

$$\frac{dx}{dt} = r_0\frac{(a_0 + b_0)}{2} - k_u\left(x^2 - y^2\right) - \left(x^2 - y^2\right)c \tag{9a}$$

$$\frac{dy}{dt} = r_0\frac{(a_0 - b_0)}{2} \tag{9b}$$

$$\frac{dc}{dt} = k_u\left(x^2 - y^2\right) + \left(x^2 - y^2\right)c - \frac{c}{K + c} \qquad (9c)$$

Furthermore, by selecting the same pumping concentration, $a_0 = b_0$, and defining $x_0 = \frac{(a_0 + b_0)}{2}$, we obtain

$$\frac{dx}{dt} = r_0 x_0 - k_u\left(x^2 - y^2\right) - \left(x^2 - y^2\right)c \qquad (10a)$$

$$\frac{dy}{dt} = 0 \qquad (10b)$$

$$\frac{dc}{dt} = k_u\left(x^2 - y^2\right) + \left(x^2 - y^2\right)c - \frac{c}{K + c} \qquad (10c)$$

Now we can integrate eq 10b and consider that at $t = 0$ the concentrations of a and b are the same, for example, $y(0) = 0$. Using this initial condition, we trivially obtain that $y(t) = 0$. Namely, if the initial difference in concentration between a and b is zero, it is zero for any other time. With this simplification, we reduce the number of differential equations from three to two:

$$\frac{dx}{dt} = f_0 - k_u x^2 - x^2 c \equiv f_1(x,c) \qquad (11a)$$

$$\frac{dc}{dt} = k_u x^2 + x^2 c - \frac{c}{K + c} \equiv f_2(x,c) \qquad (11b)$$

where we have defined $f_0 = r_0 a_0$. Equation 11 constitutes the templator model of self-replicating molecules.

Minimal Model, $k_u = 0$

The elimination of the uncatalyzed reaction, eq 3a, defines the minimal templator model. On the one hand, this simplification allows us to carry on a linear stability analysis without the help of any symbolic algebraic algorithm. On the other hand, it introduces a fixed point at infinity when $c \to 0$. Thus in the analysis we will stay away from this fixed point.

First, we find the steady states of eqs 11,

$$\bar{x} = \sqrt{\frac{1 - f_0}{K}} \qquad (12)$$

$$\bar{c} = \frac{K f_0}{1 - f_0} \qquad (13)$$

Because the concentrations are greater than zero, the physical region in parameter space is defined by

$$f_0 < 1 \qquad (14)$$

Once these stationary state solutions are obtained, stability analysis [13–22] studies what happens to the dynamic variables, $\bar{x}$ and $\bar{c}$, when they are slightly perturbed. Namely, we want to know if the perturbations to $\bar{x}$ and $\bar{c}$ grow or die out. This information can be extracted from the relaxation matrix, **R**, which is the Jacobian associated to a set of ODEs [18]. The relaxation matrix is defined by the following equation:

$$\mathbf{R} = \begin{pmatrix} \left(\frac{\partial f_1}{\partial x}\right)_{(\bar{x},\bar{c})} & \left(\frac{\partial f_1}{\partial c}\right)_{(\bar{x},\bar{c})} \\ \left(\frac{\partial f_2}{\partial x}\right)_{(\bar{x},\bar{c})} & \left(\frac{\partial f_2}{\partial c}\right)_{(\bar{x},\bar{c})} \end{pmatrix} \qquad (15)$$

Next, we have to find the corresponding eigenvalues of **R**. The analysis of the eigenvalues will yield the dynamic properties of the steady-state solutions.

Finding the eigenvalues of **R** is equivalent to finding the solutions, λ, of the following equation:

$$\left|\mathbf{R} - \lambda\mathbf{I}\right| = 0 \qquad (16)$$

where **I** is the identity matrix, and the vertical lines stand for the determinant. For any two variable models, eq 16 reduces to the following characteristic quadratic polynomial:

$$\lambda^2 - \mathrm{tr}\mathbf{R}\lambda + \det\mathbf{R} = 0 \qquad (17)$$

where tr**R** and det**R** stand for the trace and determinant of **R**. Furthermore, the solutions of the quadratic equation are

$$\lambda_{\pm} = \frac{1}{2}\left(\mathrm{tr}\mathbf{R} \pm \sqrt{\mathrm{tr}\mathbf{R}^2 - 4\det\mathbf{R}}\right) \qquad (18)$$

From this equation, we can infer general properties for any two-variable models. First, consider the case of a negative determinant, det**R** < 0. In this case we get two real eigenvalues, one positive and one negative. These two values imply that the steady-state solution is a saddle point. Second, we consider the case of a positive determinant of **R** and 4 det**R** less than (tr**R**)^2. These two conditions imply two real eigenvalues both either positive or negative. On the one hand, if the trace is negative, then both eigenvalues are negative, and we have a stable node. On the other hand, if the trace is positive, then both eigenvalues are positive, and we have an unstable node. In the particular case where det**R** = 0, we obtain one zero eigenvalue and a second eigenvalue that is either negative or positive. Finally, we consider the case of a positive determinant and 4 det**R** > (tr**R**)^2. In this case we have two imaginary eigenvalues, and the stability of the solutions is now determined by the real part, which in this case is given by the trace of the relaxation matrix. Damped oscillations will be observed for a stable focus if the trace of **R** is negative. In contrast, so-called spiraling out will be observed for an unstable focus if the trace of **R** is positive. In the latter case, the growing oscillations most likely will settle in a stable limit cycle.

For our minimal templator, we first find the following relaxation matrix:

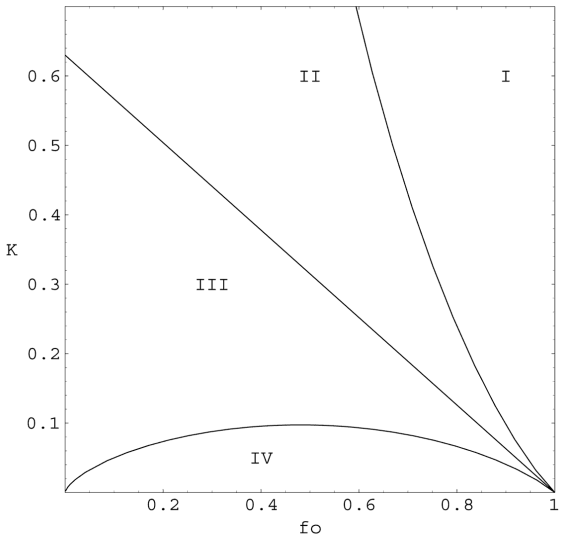


Figure 1. Parameter space diagram, K versus f_0, for the minimal templator model. The regions are divided by the curves tr**R** = 0 and discriminant = 0.

$$\mathbf{R} = \begin{pmatrix} -2\bar{x}\,\bar{c} & -\bar{x}^2 \\ 2\bar{x}\,\bar{c} & \bar{x}^4\,\bar{c} \end{pmatrix} \tag{19}$$

Second, we find the trace and the determinant of **R** calculated at the steady states:

$$\mathrm{tr}\mathbf{R} = \bar{x}\,\bar{c}\left(\bar{x}^3 - 2\right) \tag{20}$$

$$\det \mathbf{J} = 2\bar{x}^3\bar{c}\left(1 - \bar{x}^2\bar{c}\right) \tag{21}$$

The solutions to

$$\bar{x}^3 - 2 = 0 \tag{22}$$

define a curve in parameter space and determine the bifurcation points. At these points, the eigenvalues are pure imaginary because tr**R** = 0. Also, for a fixed value of f_0, we can solve eq 22,

$$\bar{x} = 2^{1/3} \tag{23}$$

If we use eq 12, we obtain an expression for the bifurcation value of K as a function of f_0,

$$K^{\mathrm{bif}} = 2^{-2/3}\left(1 - f_0\right) \tag{24}$$

This equation gives us the value of K at which the stable steady state becomes unstable. In other words, if $K < K^{\mathrm{bif}}$, the trace is positive, and thus the steady state unstable.

For completeness, we need to find the zeros for the discriminant,

$$\mathrm{dis} \equiv \left(\mathit{trace}\mathbf{J}\right)^2 - 4\det\mathbf{J} = \bar{x}^2\,\bar{c}\left[\bar{c}\left(\bar{x}^3 + 2\right)^2 - 8\bar{x}\right] = 0 \tag{25}$$

From eq 25, we find that the nontrivial zeros of the discriminant satisfy the following relation:

$$\bar{c} = \frac{8\bar{x}}{\left(\bar{x}^3 + 2\right)^2} \tag{26}$$

Equations 12–13 allow us to reduce eq 26 to

$$f_0 = \frac{8u}{\left(u + 2\right)^2} \tag{27}$$

where we have defined

$$u \equiv \left[\frac{1 - f_0}{K}\right]^{3/2} \tag{28}$$

Solving the quadratic equation satisfied by u, we get eventually two solutions for K,

$$K_{\pm} = \frac{2^{-2/3}\left(1 - f_0\right)}{\left[\left(\frac{2}{f_0} - 1\right) \pm \sqrt{\left(\frac{2}{f_0} - 1\right)^2 - 1}\right]^{2/3}} \tag{29}$$

These equations separate the parameter space into four regions. Regions I and II in Figure 1 represent stable steady-state solutions like fixed points and damped oscillations. The last two regions, III and IV, are regions where the steady states are unstable.

As an example, we have considered $f_0 = 0.30$ and $K = 0.30$. From Figure 1 we conclude that we have an unstable steady state. For this case, we integrated eqs 11a and 11b and found oscillatory solutions. We depict the oscillation of the two-variable template mechanism in Figure 2.

In summary, our two-variable and two-parameter minimal template model is capable of sustaining stable oscillatory solutions. In addition, a simple calculation yields the bifurcation curve in parameter space.

Template Model

In this section we consider the uncatalyzed step and perform an analysis similar to that in the previous section. First, we find the steady states of eq 11,

$$\bar{x} = \sqrt{\frac{f_0\left(1 - f_0\right)}{Kf_0 + k_{\mathrm{u}}\left(1 - f_0\right)}} \tag{30a}$$

$$\bar{c} = \frac{Kf_0}{1 - f_0} \tag{30b}$$

Second, we calculate the relaxation matrix, R, and find

Table 1. Dimensionless Values

Parameter	Value
k_u	0
f_0	0.30
K	0.30

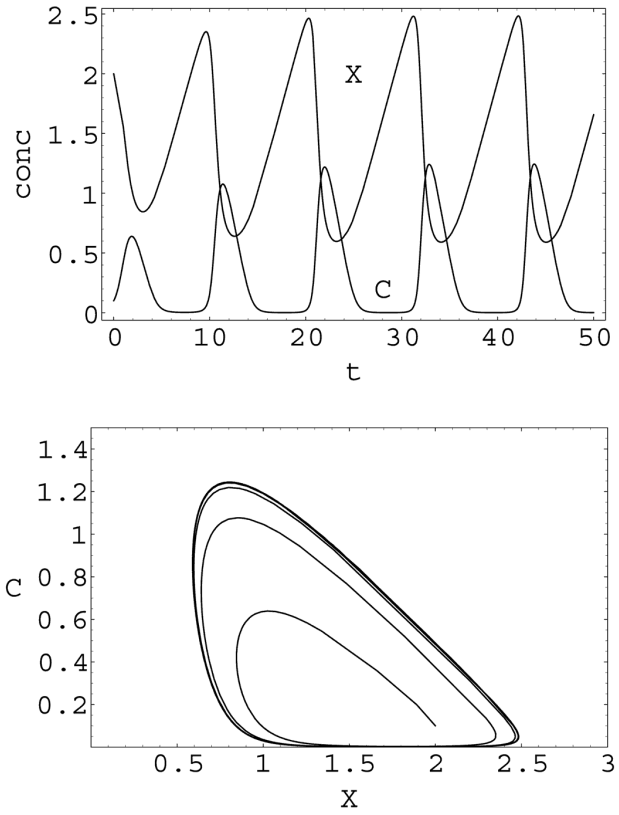


Figure 2. Time series of x and c for the minimal templator model. Parameter values are taken from Table 1.

$$\mathbf{R} = \begin{pmatrix} -2\bar{x}\ \bar{c} - 2k_u\bar{x} & -\bar{x}^2 \\ 2\bar{x}\ \bar{c} + 2k_u\bar{x} & \bar{x}^4\ \bar{c} + \dfrac{k_u\bar{x}^2}{\bar{c}}\left[\bar{x}^2\ \bar{c} - (1-f_o)\right] \end{pmatrix} \quad (31)$$

where we have used some of the relations satisfied by eq 30. Now we can consider the trace of **R**,

$$\mathrm{tr}\mathbf{R} = \bar{x}\left[\bar{c}\left(\bar{x}^3 - 2\right)\ - 2k_u + \frac{k_u\bar{x}}{\bar{c}}\left(\bar{x}^2\ \bar{c} - (1-f_0)\right)\right] \quad (32)$$

From eq 32, we find that the nontrivial zeros satisfy the following cubic equation:

$$\bar{x}^3 - \frac{k_u(1-f_0)}{\bar{c}\left(\bar{c}+k_u\right)}\bar{x} - 2 = 0 \quad (33)$$

Using eq 30, we can now express eq 33 as

$$\bar{x}^3 = \frac{2}{1 - \dfrac{k_u(1-f_0)^2}{Kf_0^2}} \quad (34)$$

From eq 34, we find the following transcendental equation:

$$K = \frac{(1-f_0)^{3/2}}{2\sqrt{f_0}} \frac{\left[Kf_0^2 - k_u(1-f_0)^2\right]}{\left[Kf_0 + k_u(1-f_0)\right]^{3/2}} \quad (35)$$

Here we have two choices. One is to numerically solve eq 35 for K as a function of f_0. Another option is to consider approximate analytical solutions for $k_u << 1$. In the former case, we used MATHEMATICA's ContourPlot function [23] to obtain the zero-trace curve. In the latter case, we can expand the right-hand side of eq 35 for small values of k_u and get a quadratic equation for K with solutions

$$K_{\pm} = \frac{2^{-2/3}(1-f_0)}{2}\left[1 \pm \sqrt{1 - \frac{4(2)^{2/3}(2+f_0)k_u}{3f_0^2}}\right] + 0\left(k_u^2\right) \quad (36)$$

Notice that there is no real solution if

$$\frac{4(2)^{2/3}(2+f_0)k_u}{3f_0^2} > 1 \quad (37)$$

This condition implies that there is a minimum value of f_0 associated with real solutions and thus to the stability of the steady states.

Finally, we could perform a final expansion of eq 36 for small values of k_u and obtain

$$K_+ = 2^{-2/3}(1-f_0) - \frac{(1-f_0)(2+f_0)k_u}{3f_0^2} + 0\left(k_u^2\right) \quad (38a)$$

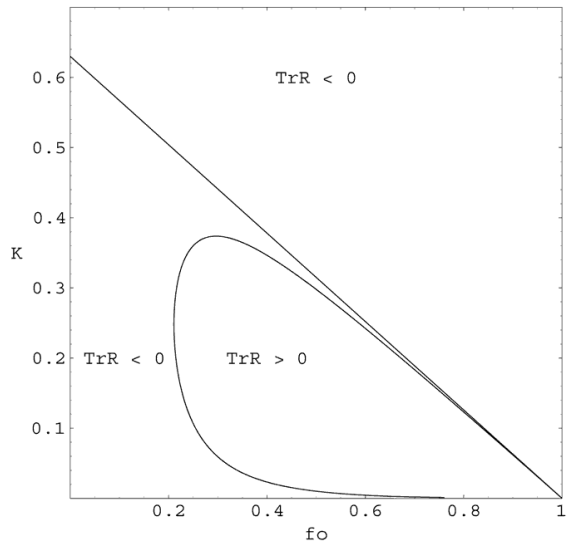
$$K_- = \frac{(1-f_0)(2+f_0)k_u}{3f_0^2} + 0\left(k_u^2\right) \quad (38b)$$

In Figure 3a, we compare the numerical solution of eq 35 and the minimal templator's region of instability in parameter space. We can observe dramatic changes in the dynamic behavior of the templator model. From this comparison, we concluded that the minimal model is, therefore, structurally unstable with respect to the uncatalyzed step. Other more sophisticated studies of the templator's dynamics have been published elsewhere [24–25].

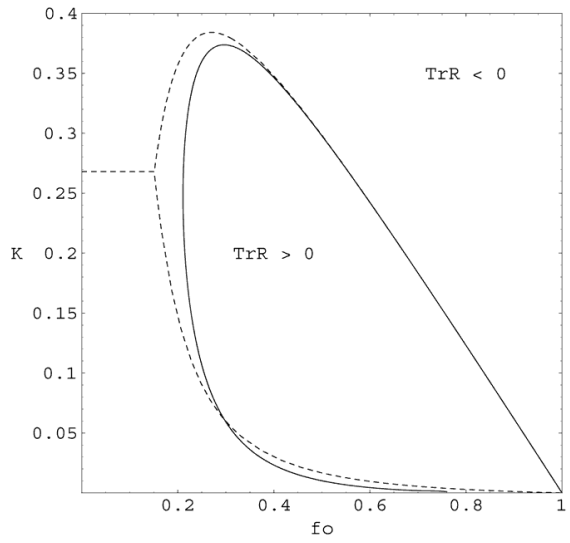
In Figure 3b we compare the numerical solution of eq 35 and the approximation given by eqs 38a and 38b. Notice the horizontal dashed line depicting the region of no solution and the point where the approximate solutions are equal. Thus, the crude approximation gives us an accurate qualitative description of the regions in parameter space. One would expect that our approximation would give us a better description for $k_u = 0.001$ than for $k_u = 0.010$, but this is left as an exercise for the reader. So, eqs 38a and 38b, even for k_u =

Table 2. Dimensionless Values

Parameter	Value
k_u	0.010
K	0.30



(a) Regions of instability for the Minimal and the Templator models.



(b) Comparison between approximate and exact solutions.

Figure 3. Parameter-space diagram, K versus f_0 for the templator model. The regions are divided by the curve tr**R** = 0. The dashed curve represents the approximate solutions and the full line the exact numerical solutions.

0.010, give us a good qualitative description of the system's stability properties.

Discussion

Typically, we first discuss the minimal templator in the classroom to introduce linear stability analysis. Second, we assign the analytical study of the full templator model as a problem set. The former model shows stable oscillations and a simple bifurcation relation. Also, all the linear stability analysis associated with this model is extremely accessible to undergraduates. Third, we study the templator numerically in a laboratory session. The numerical analysis of the parameter space can be carried out using MATHEMATICA. Also, any available ODE solver can be used to integrate the differential equations and obtain time series. Finally, a laboratory report is required, which should include several examples of the different bifurcations as well as the predictions derived from the analytical analysis. As a result, the students have a better sense of how the analytical and numerical analyses, carried out in chemical kinetics, complement each other.

As an example of a possible study, we consider different parameter values from Figure 3 and discuss the time series. First we fix K at 0.20 and vary f_0 taking values from both sides of the unstable interval. This means that as we vary f_0 the system goes through two bifurcations. In Figure 4, we depict damped oscillations for f_0 = 0.20, K = 0.30, and k_u = 0.010. Now, we increase the value of f_0. Because we change the value to f_0 = 0.30, the system goes through a bifurcation, and we observe the stable oscillations depicted in Figure 5. If we again increase the value to f_0 = 0.60, the system goes through a second bifurcation, and we recover damped oscillations, as we can see in Figure 6. Finally, we consider f_0 = 0.80 and observe the stable node in Figure 7.

Now we fix f_o at 0.30 and vary K. Again, the system goes through two bifurcations. Initially, we find the stable node at K = 0.04 depicted in Figure 8. We finally consider K = 0.4 in Figure 9 and observe damped oscillations. When we compare Figures 5, 8, and 9, we observe the transition due to the two bifurcations as we change K.

Remember that damped oscillations are associated with a negative real part and a nonvanishing imaginary part of the relaxation matrix's eigenvalue. In contrast, stable oscillations have a positive real part and a nonvanishing imaginary part. Finally, a node steady state has a negative real part and a vanishing imaginary part, as we can observe in Figures 7 and 8.

In the present work, we introduce a template mechanism of autocatalysis. This model mimics a self-replicating template mechanism observed experimentally in chemical systems in the laboratory. First we analyze a simple two-variable, two-parameter minimal model. For this minimal model, we obtain analytical expressions for the bifurcation curve in parameter space. This curve locates the bifurcation points and separates parameter space into regions where the trace of the relaxation matrix is either greater or less than zero.

For the templator model, we obtain approximate analytical expressions for the bifurcation points that are very good when compared with the exact numerical solution. In addition, we find that the templator model can go through two bifurcations when we vary either K or f_0. This last property is more physical because it has been observed experimentally that chemical systems are able to sustain oscillations for parameter values within an interval. Thus, minimum and maximum parameter values define an unstable region in parameter space.

In summary, we have introduced an autocatalytic template mechanism that is an important new dynamical model with a cubic nonlinearity. This nonlinearity is modeled after the self-replicating mechanism recently reported in the literature [8–12].

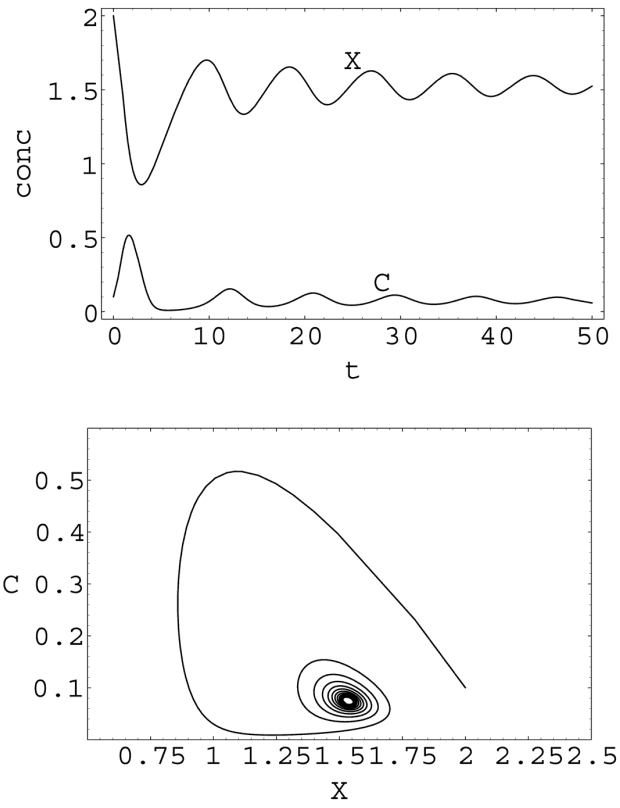


Figure 4. Time series of x and c for the templator model. In this case $f_0 = 0.20$, and the other parameters are taken from Table 2.

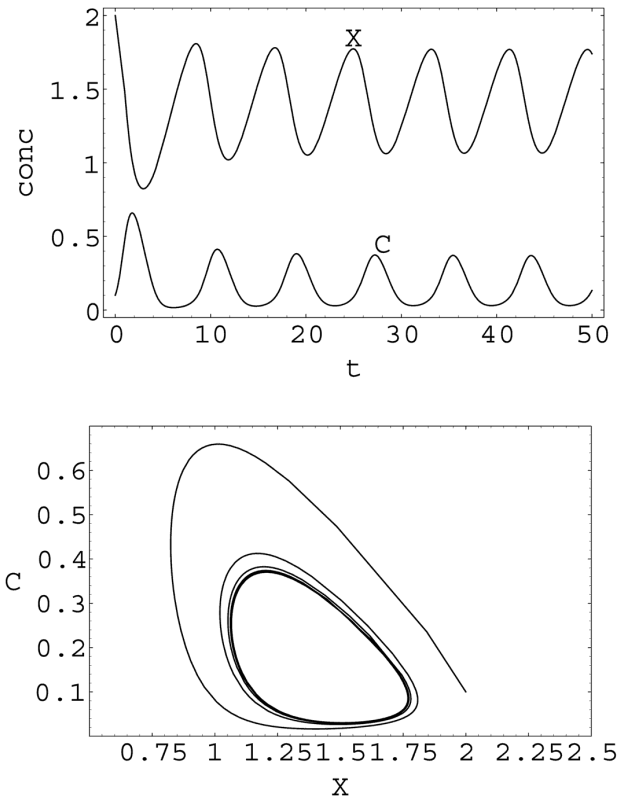


Figure 5. Time series of x and c for the templator model. In this case $f_0 = 0.30$ and the other parameters are taken from Table 2.

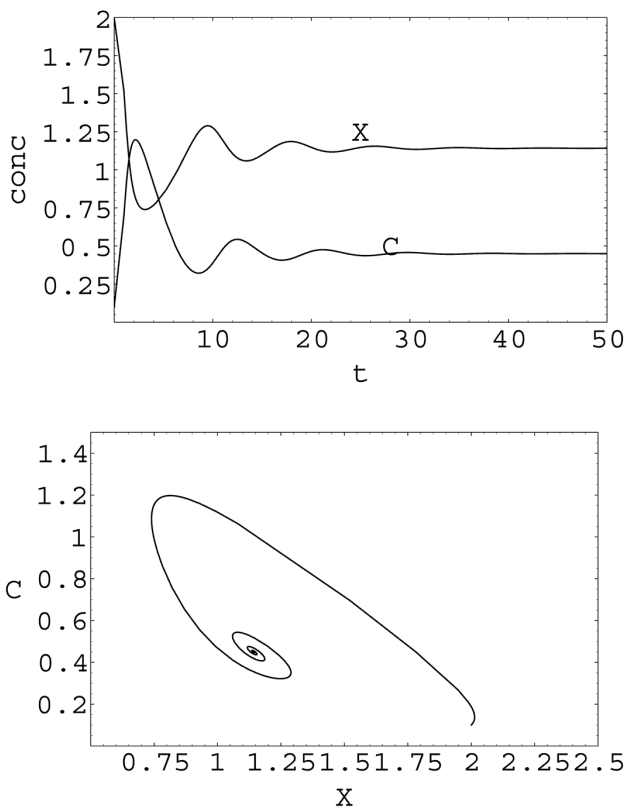


Figure 6. Time series of x and c for the templator model. In this case $f_0 = 0.60$ and the other parameters are taken from Table 2.

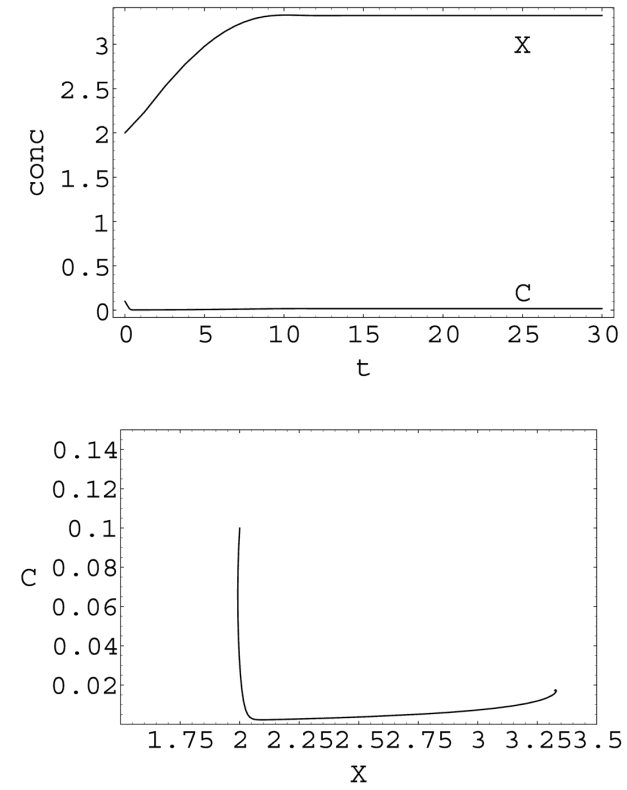


Figure 7. Time series of x and c for the templator model. In this case $f_0 = 0.80$ and the other parameters are taken from Table 2.

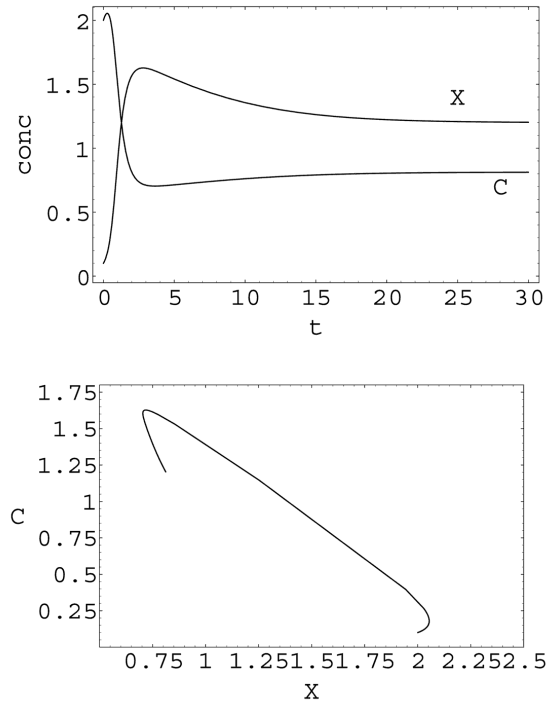


Figure 8. Time series of x and c for the templator model. In this case $K = 0.04$ and the other parameters are taken from Table 3.

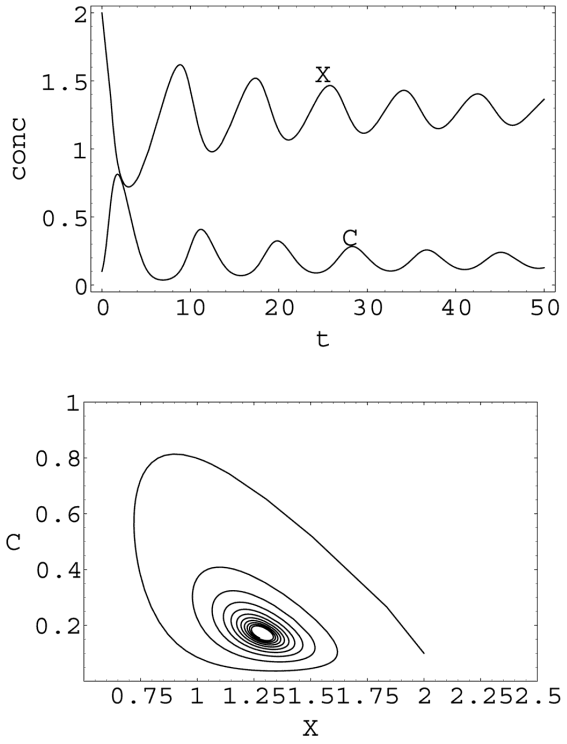


Figure 9. Time series of x and c for the templator model. In this case $K = 0.4$ and the other parameters are taken from Table 3.

Table 3. Dimensionless Values

Parameter	Value
k_u	0.010
f_0	0.30

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