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Biophysical Chemistry 65 (1997) 171–178

Biophysical Chemistry

# Mixed-mode oscillations in a self-replicating dimerization mechanism

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Received 8 August 1996; revised 15 November 1996; accepted 15 November 1996

## Abstract

Recently, self-replicating molecules have been synthesized in the laboratory by Rebek. Given the importance of such molecules, we proposed a simple model of a self-replicating dimer, which works as a template for its own formation. Here we consider a three variable model. For the model, we obtain mixed-mode and chaotic oscillations. Also, we find coexistence between two periodic attractors as well as a periodic and a chaotic attractor. © 1997 Elsevier Science B.V.

*Keywords:* Mixed-mode oscillations; Self-replicating dimerization mechanism

## 1. Introduction

Oscillations in metabolite concentration are characteristic of living systems [1]. These oscillations can be observed in systems spanning many orders of magnitude in scale, from ecosystems to the human body. Current understanding of oscillating systems is fairly limited, but it is believed that without an autocatalytic step oscillation will not be observed. Studying autocatalytic systems gives us a deeper understanding of the factors determining 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); other theoretical oscillating systems ignore conservation of mass. Even though such systems produce oscillation, their usefulness in studying biochemical systems is diminished because the chemical models proposed are not realistic from the chemical point of view.

Our work attempts to find a reasonable chemical model for self-replicating molecules that sustains oscillations.In particular, we focus on a template model of a primitive self-replicating dimer. Self-replicating molecular system have been synthesized in the laboratory by Rebek et al. [2–4]. Rebek's self-replicating system is represented schematically below:

$$R + S \overset{k_{\text{uncat}}}{\rightarrow} T \qquad (1)$$

$$R + S + T \overset{k_{\text{templ}}}{\rightarrow} T + T \qquad (2)$$

where R can stand for adenine ribose (AR), diaminotriazine xanthene (DIX), adenine ribose-Z (ZAR), adenine ribose-Z-$N_2$ (ZNAR), and where Z is a blocking group like benzyloxycarbonyl. The other

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*PII* S0301-4622(96)02259-4

molecule, T, 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 products except for DIXBI that cannot self-replicate.

In the uncatalyzed step, molecules R and S collide in a relatively low probability process to form the template, T. The structure of the product T is such that once it is formed, it preferentially binds R and S in a conformation that facilitates covalent bonding with formation of T. The newly created compound and the template on which it was formed can then split apart to catalyze further reactions. Because the mechanism has been observed in the lab, the template mechanism is clearly chemically feasible.

In Section 2, we work with a modified Rebek system. We eliminate the second of the species that make up the self-replicating molecule and, instead, assume that the reacting molecules are of the same species. Thus we model a self-replicating dimer that we couple to a third variable. The particular coupling chosen has been used in other cases where chaotic oscillations have been reported [5]. Finally in Section 3, we summarize our results.

## 2. Template mechanism

In this section we consider a minimal template self-replicating dimerization mechanism. In this model the species (X) forms a dimer (Y) that can catalyze its own formation in an irreversible process. In other words, Y can bind to one molecule of X in a fast equilibrium process to form the intermediate I. When I comes into contact with an other molecule of X, the intermediate reacts quickly and irreversibly to form 2Y. To prevent the system from reaching equilibrium, we pump X into the system from a pool $X_0$ at a constant rate. We also assume that Y is removed in an enzymatic step that converts it to W. Namely, we consider the following steps:

$$\mathrm{X}_0 \xrightarrow{f_0} X \tag{3}$$

$$\mathrm{X}+\mathrm{X}+\mathrm{Y} \xrightarrow{k_t} \mathrm{Y}+\mathrm{Y} \tag{4}$$

$$\mathrm{Y} \xrightarrow{k_\mathrm{m}, K_\mathrm{M}} \mathrm{W} \tag{5}$$

where $\mathrm{X}_0$ is a pool concentration, $f_0$ and $k_t$ are rate constants and $k_\mathrm{m}$, $K_\mathrm{M}$ are the constants associated with an enzymatic step.

Next we include the uncatalyzed formation of the dimer, and we couple the first variable with a third variable, W, using a W-dependent influx of the first species [5]. In other words, we add the following steps to the template mechanism represented by Eqs. (3)–(5):

$$\mathrm{X}_0+\mathrm{W} \xrightarrow{k_c} \mathrm{X}+\mathrm{W} \tag{6}$$

$$\mathrm{X}+\mathrm{X} \xrightarrow{k_\mathrm{u}} \mathrm{Y} \tag{7}$$

where $k_c$, $k_\mathrm{u}$ are rate constants. Finally, we add a linear removal of the third species,

$$\mathrm{W} \xrightarrow{k_\mathrm{r}} \mathrm{P} \tag{8}$$

with rate constant $k_\mathrm{r}$.

The steps (3)–(8) represent a three variable model based in the two variable template mechanism (3)–(5).The coupling chosen in this work has been used by others in the analysis of the autocatalator [5]. Therefore we compare our results with the analysis of the three variable autocatalator.

Furthermore, using the following scaling:

$$\mathrm{X}=K_\mathrm{M}a \tag{9}$$

$$\mathrm{Y}=K_\mathrm{M}b \tag{10}$$

$$\tau=\frac{t}{k_t K_\mathrm{M}^2} \tag{11}$$

we obtain a set of dimensionless differential equations:

$$\frac{\mathrm{d}a}{\mathrm{d}t}=k_0a_0-2a^2b-2k_1a^2+k_2a_0c \tag{12}$$

$$\frac{\mathrm{d}b}{\mathrm{d}t}=a^2b+k_1a^2-\frac{qb}{1+b} \tag{13}$$

$$\frac{\mathrm{d}c}{\mathrm{d}t}=\frac{qb}{1+b}-k_3c \tag{14}$$

where we have defined the following dimensionless parameters:

$$k_0 = f_0/\left(k_t K_M^2\right) \tag{15}$$

$$a_0 = X_0/K_M \tag{16}$$

$$q = k_m/\left(k_t K_M^3\right) \tag{17}$$

$$k_1 = k_u/\left(k_t K_M\right) \tag{18}$$

$$k_2 = k_c/\left(k_t K_M\right) \tag{19}$$

$$k_3 = k_r/\left(k_t K_M^2\right) \tag{20}$$

Notice that the templator resembles the autocatalator since both have a cubic nonlinearity. But that is as far as the similarities go. Although both have a cubic nonlinearity, their nature is different. In the case of the templator the cubic nonlinearity is quadratic in the first variable and first order in the second. In contrast, the autocatalator's nonlinearity is first order in the first variable and quadratic in the second. Also the templator includes a factor of two due to the stoichiometry of the mechanistic steps. Another difference between the templator and the autocatalator is the uncatalyzed term. The autocatalator includes a linear uncatalyzed term while the autocatalator has a quadratic term. Finally, the templator considers an enzymatic step in the removal of the second variable. In contrast, the autocatalator considers a linear removal of the second variable.

For the parameter values in Table 1, we find mixed-mode oscillations, $L^s$, depicted in Fig. 1a–c [6–8]. These oscillations show multiple maxima with $L$ large maxima and $s$ small amplitude maxima. From Fig. 1b–c, it is clear that the system displays $1^5$ mixed-mode oscillations. Furthermore, if we consider the same parameters and changed the initial conditions, the system displays period two small amplitude oscillations as depicted in Fig. 1d–f. Thus we observe the coexistence of the $1^5$ mixed-mode occillations and a period-2 oscillation.

Table 1
Dimensionless values

| Parameter | Value |
|---|---|
| $a_0$ | 100 |
| $k_0$ | 10000 |
| $q$ | $10^6$ |
| $k_1$ | 1.0 |
| $k_2$ | 0.760000 |
| $k_3$ | 3000 |

To understand the coexistence of attractors, we obtained a bifurcation diagram constructed as a Poincaré section for the maximum value of $b$ for parameter values in Table 1 and $k_2$, the bifurcation parameter. In Fig. 2a we depict the bifurcation diagram as we vary parameter $k_2$ from 0.70 to 0.90. This figure shows the region in parameter space where we expect to find the $0^1$ oscillations and mixed-modes oscillations.

In Fig. 2b, we observe in more detailed the region of the small amplitude oscillation components of the mixed-mode oscillations. From Fig. 2a–b, we see that in this region in parameter space, the system will sustain $1^n$ mixed-mode oscillations with $n$ ranging from one to five. Furthermore, we notice a bifurcation of the $0^1$ oscillations. Therefore, in Fig. 2c, we blow-up this region, and we can clearly see a period doubling route to chaos, a chaotic region and a sharp transition to mixed-mode oscillations. Also in Fig. 2c, the thinner line represent the construction of the bifurcation diagram by increasing the value of the bifurcation diagram; the thicker line represents part of the bifurcation diagram that was constructed by backtracking the bifurcation parameter. From this figure, we confirmed our previous results that for the value $k_2 = 0.760000$, small amplitude period-2 and $1^5$ mixed-mode oscillations coexist. In other words, depending of the initial conditions, the system may display either of the periodic solutions.

Furthermore, this diagram allow us to locate other coexisting attractors.For example, for $k_2 = 0.760340$, small amplitude chaotic oscillations coexist with $1^5$ mixed-mode oscillations. For the values in Table 2 and different initial conditions, we construct the phase diagrams depicted in Fig. 3. Fig. 3 shows the $(a, b)$ and $(a, c)$ phase diagrams for the $1^5$ mixed-mode that coexist with the small amplitude chaotic attractor. Thus for the parameter values in Table 2 and as we vary $k_2$, the small amplitude attractor goes from a period-1 oscillation to a chaotic attractor via a period-doubling route, while the mixed-mode attractor coexist with these attractors.

Also we have obtained a bifurcation diagram for parameters in Table 3. Notice in Fig. 4b that small

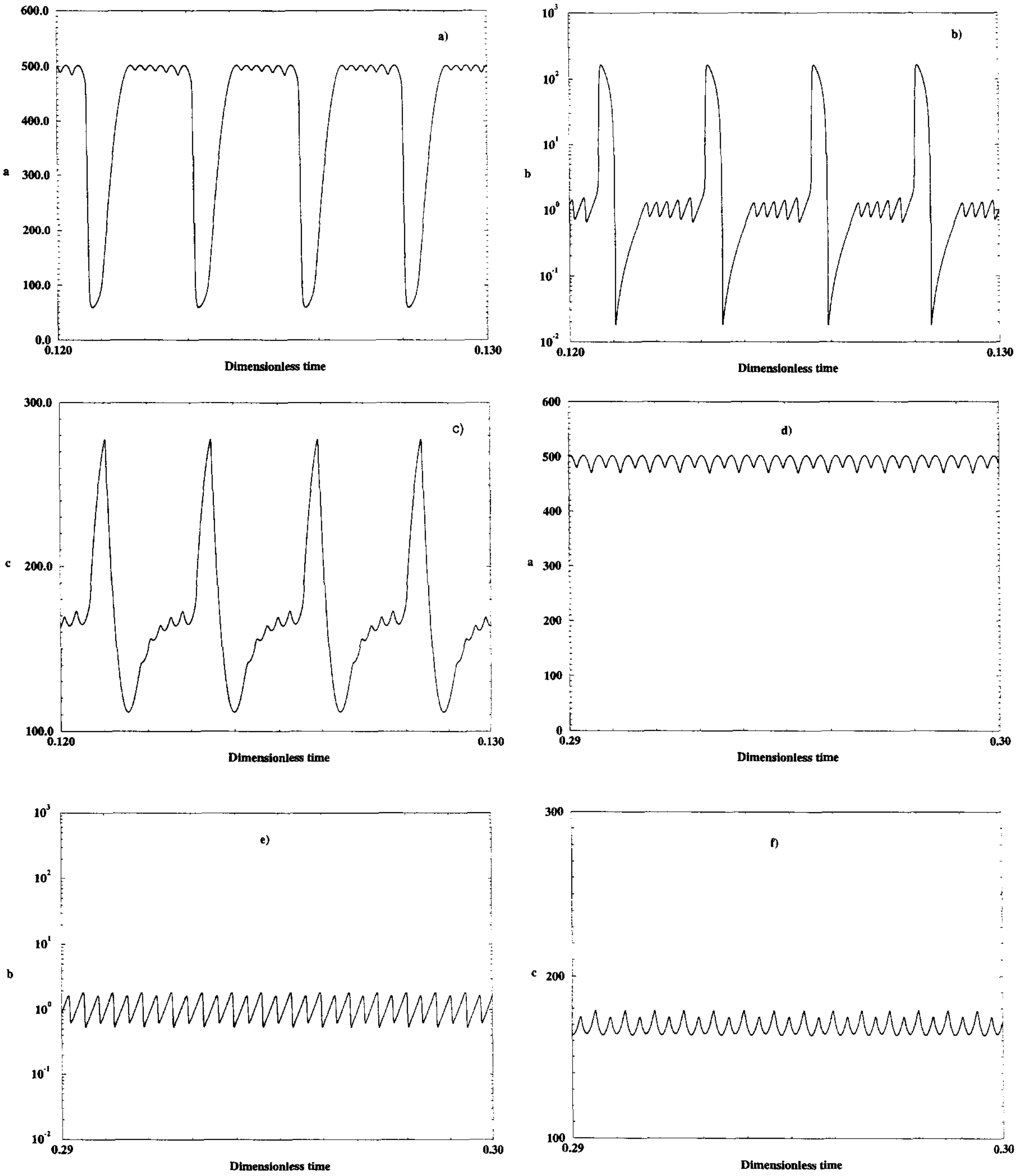

Fig. 1. Time series for the three variable dimensionless templator with values taken from Table 1. Figs. (a)–(c) differ from Figs. (d)–(f) only in the initial conditions. (a) $a$ vs. $t$, (b) $b$ vs. $y$, (c) $c$ vs. $t$, (d) $a$ vs. $t$, (e) $b$ vs. $t$, and (f) $c$ vs. $t$.

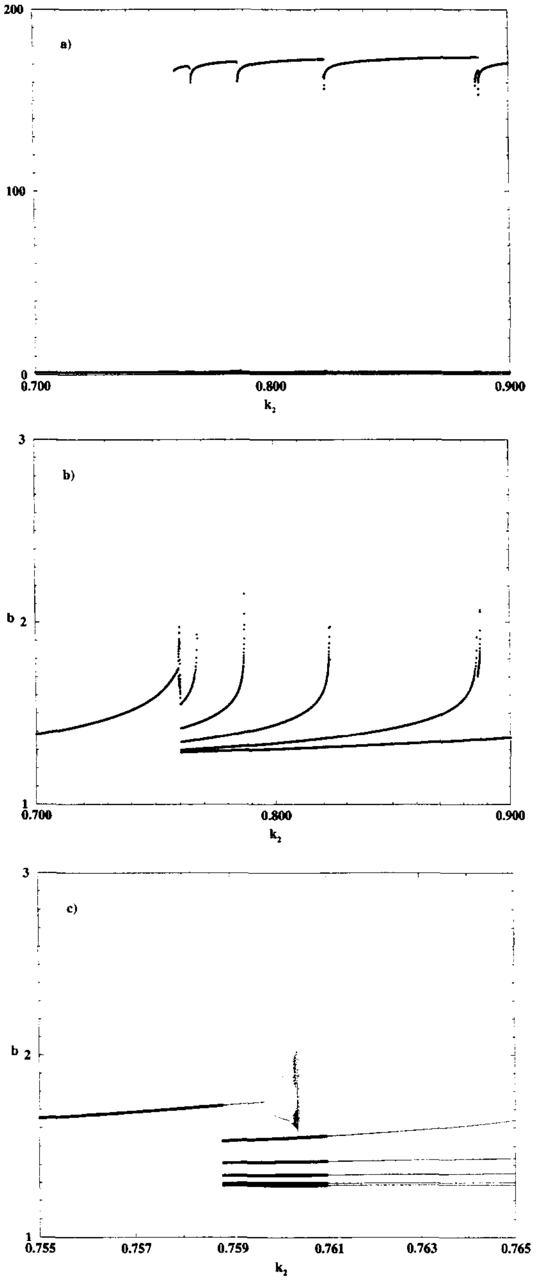

Fig. 2. Poincaré section for maximum of $b$ vs. $k_2$. Other parameters taken from Table 1.

Table 2
Dimensionless values

| Parameter | Value |
|---|---|
| $a_0$ | 100 |
| $k_0$ | 10000 |
| $q$ | $10^6$ |
| $k_1$ | 1.0 |
| $k_2$ | 0.760340 |
| $k_3$ | 3000 |

amplitude period-doubling route to chaos has been shifted to smaller value of $k_2$. For $k_2$ values near 0.761000 we notice the destabilization of the mixed-mode branches. For values less than 0.76100 we notice stable $1^5$ mixed-mode oscillations. As we increase $k_2$, we notice that one of the branches becomes unstable, giving two possible maxima in an

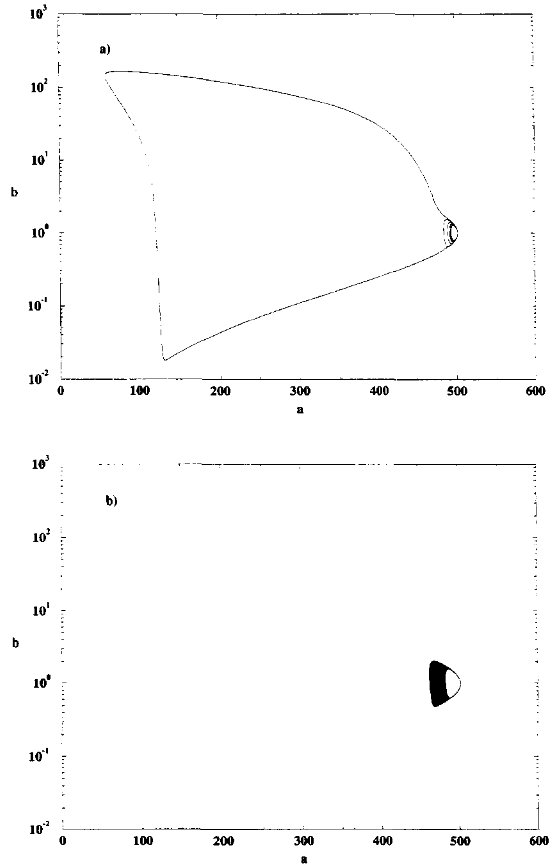

Fig. 3. Phase diagrams for the three variable dimensionless templator with values taken from Table 2. Fig. (b) differs from Fig. (a) only in the initial condition. (a) $a$ vs. $b$, (b) $a$ vs. $b$.

Table 3
Dimensionless values

| Parameter | Value |
|---|---|
| $a_0$ | 100 |
| $k_0$ | 10000 |
| $q$ | $10^6$ |
| $k_1$ | 1.0 |
| $k_2$ | 0.761000 |
| $k_3$ | 2973.85 |

unpredictable sequence. In other words, one of the branches of the $1^5$ mixed-mode yields what appears to be $1^6$ and $1^5$ mixed-mode oscillations.

From our analysis, we notice that the small amplitude attractor is sensitive to $k_2$. In contrast, the mixed-mode attractor is sensitive to the $k_3$ parameter and displays an unpredictable sequence of $1^4$, $1^5$ and $1^6$ mixed-modes with the $1^5$ branch unpredictably displaying either 5 or 6 small amplitude maxima. Furthermore, from Fig. 4c–d we notice two windows of stability. In the first, we notice from Fig. 4c six small amplitude maxima and from Fig. 4d two large amplitude maxima. In the second window we notice again six small amplitude maxima but three large amplitude maxima. In Fig. 5a we depict the behavior of the mixed-mode oscillations corresponding to the second window where $k_2 = 0.761026000$. We notice that for this window the systems displays $(1^4)^2 1^6$ mixed mode oscillations; Fig. 5b depicts the $(1^4)^3 1^6$ mixed-mode oscillation for $k_2 = 0.761030000$. Thus from Fig. 5 we can infer a transition from the $1^5$ to the $1^4$ mixed-mode through a series of $(1^4)^n 1^6$ mixed

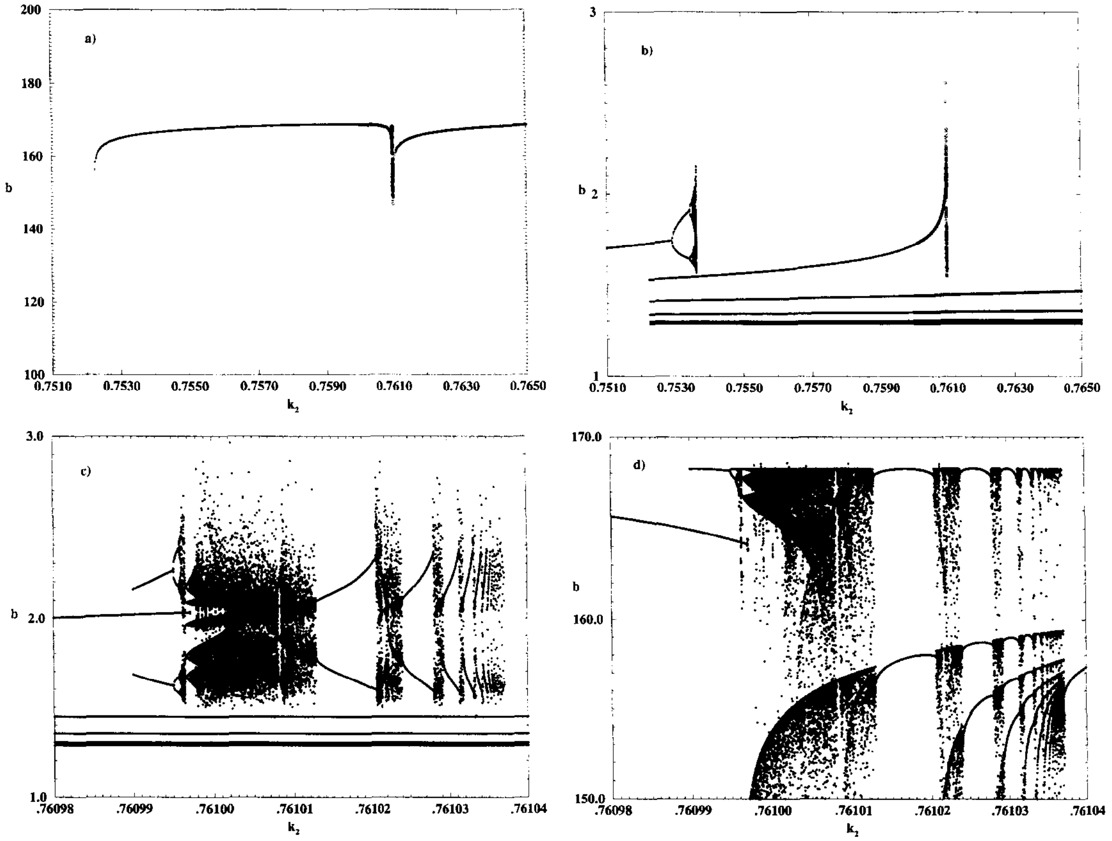

Fig. 4. Poincaré section for maximum of $b$ vs. $k_2$. Other parameters taken from Table 3.

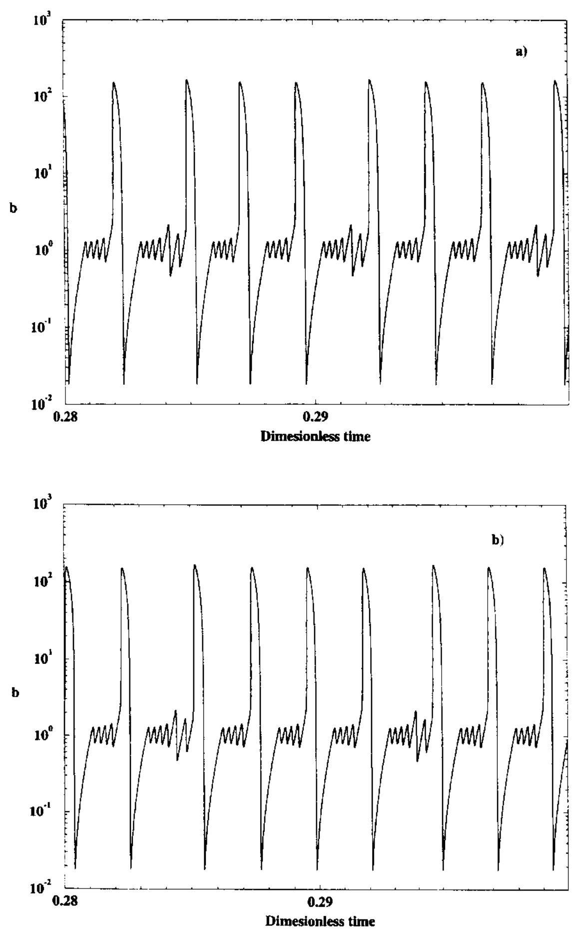

Fig. 5. Mixed-mode oscillations. (a) $(1^4)^2 1^6)$ oscillations for $k_2 = 0.761026000$ and (b) $(1^4)^3 1^6)$ oscillations for $k_2 = 0.761030000$. Other parameters from Table 3.

modes where $n$ tends to a large number until the system reaches the $1^4$ mixed-mode as we vary $k_2$.

## 3. Conclusions

In the present work, we have introduced a template mechanism of autocatalysis. This model mimics a simplified self-replicating template mechanism observed experimentally in chemical systems in the laboratory.

For template dimerization, we introduce a two variable minimal model. If we include a third variable and couple it with the influx of the first variable, we find complex oscillation as well as chaotic oscillations. Our results are consistent and similar to the work reported for the autocatalator, which is similar to the Brusselator by Petrov et al. [9], and the complementary work by Chaudry et al. [10]. For example, our bifurcation diagrams are similar to Petrov's diagrams, and our coexisting period-2 and $1^5$ mixed-oscillations are similar to Chaudry's coexisting chaotic and periodic attractors.

The major difference is in the two variable oscillator [11,12]. In our case we have an enzymatic step that is represented by a saturation term in the differential equations. In has been proven [13] that without this step the minimal template mechanism can not sustain stable limit cycles. Also the nature of the cubic nonlinearity is quite different. While in the autocatalator we find a linear term in the first variable multiplied by a quadratic term in the second, we have a quadratic term in the first variable multiplied by a linear term in the second variable. Also, the uncatalyzed term in the templator is quadratic compared with the linear uncatalyzed term of the autocatalator. Finally, the stoichiometry of the template mechanism includes a factor of two in the rate of change of the first variable and a factor of one in the rate of change of the second variable. Thus the nature of the nonlinearities of the two variable oscillator is quite different.

In summary, we have introduced a template mechanism, which represents another important dynamical model with a cubic nonlinearity. This nonlinearity is modeled after the self-replicating mechanism recently reported in the literature [2–4]. The expansion of the mechanism and coupling to a third variable yield mixed-mode oscillations and coexisting attractors. This study presents the first model of the nonlinear kinetics of simple self-replicating molecules in our attempt to understand more complex template mechanisms like RNA synthesis.

## Acknowledgements

The authors would like to thank Casey H. Londergan for helpful comments. Also, support from the National Science Foundation (CHE-9312160) is gratefully acknowledged. One of us (E. P-L) would like to thank Professor Katja Lindenberg for her hospitality during his visits to the Department of Chemistry and Biochemistry of the University of California at San Diego, where part of the work was done.

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