Uncovering Oscillations, Complexity, and Chaos in Chemical Kinetics Using *Mathematica*

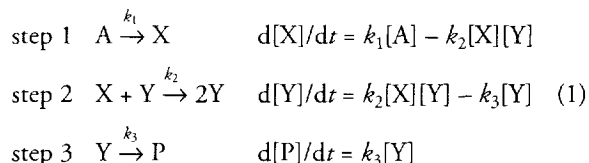**M. M. C. Ferreira,**[*][†] **W. C. Ferreira Jr.,**[‡] **A. C. S. Lino,**[†] **and M. E. G. Porto**[†]
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In recent textbooks and educational literature, a strong emphasis is given to the use of computers as tool for teaching undergraduate courses (1–5). However, to turn a computer into a useful tool for scientific computation, the appropriate mathematical models and tools and their applications must be introduced (2, 6–8).

In the past few years, theoretical and practical interest in oscillatory reactions has increased enormously. Unlike common reactions with no peculiar temporal behavior, these reactions contain reagents, intermediates, or products whose concentrations can rise and fall spontaneously in a cyclic or disorganized fashion. This article reports the use of *Mathematica* software (9) for a theoretical study of some kinetic mechanisms exhibiting oscillating and chaotic behaviors. The use of a high-level[1] computational environment is extremely convenient in this context owing to the availability of efficient built-in routines that can be used to analyze and numerically solve the differential equations describing the chemical reactions. Also, the visual and graphical capabilities of these computational environments allow the use of many powerful geometrical tools from modern nonlinear dynamics (2), which can make the treatment qualitatively richer and much more appealing to students.

The Lotka Reaction

In 1925, Alfred Lotka designed a very simple pedagogic example of a reaction exhibiting a temporal behavior characterized by damped oscillations. The reaction converges in an oscillatory manner to a stationary stable state. Lotka's kinetic mechanism and rate equations for this three-step reaction are:

step 1 $A \xrightarrow{k_1} X$ $d[X]/dt = k_1[A] - k_2[X][Y]$

step 2 $X + Y \xrightarrow{k_2} 2Y$ $d[Y]/dt = k_2[X][Y] - k_3[Y]$ (1)

step 3 $Y \xrightarrow{k_3} P$ $d[P]/dt = k_3[Y]$

where the reagent A is maintained at a fixed concentration equal to 1.0. In order to keep [A] constant in the reaction process, a flow of reagent A at rate $k_1[A]$ must be provided into the system (i. e., the reaction system is open). Step 2 is autocatalytic; X is being formed in step 1 and consumed in the following step. The concentration of Y increases steadily, since it is produced in double. That in turn causes a decrease in the concentration of X, and the velocity of reaction in step 2 and the concentration of Y develop toward the equilibrium since Y is being consumed in step 3. To simplify the mathematical notation, lowercase letters a, x, y, p will be used to represent the concentrations of the chemical substances denoted by uppercase letters A, X, Y and P instead of the usual

chemical notation [A], [X], [Y], and [P]. Observe that the first two kinetic equations are not uncoupled to the third and can be treated separately.

The first step in analyzing the reaction will be to determine the stationary states specified by the condition that all the rates of change should vanish simultaneously,

$$dx/dt = k_1 a - k_2 xy = 0$$

$$dy/dt = k_2 xy - k_3 y = 0$$

which gives only one solution: $(x_1, y_1) = (k_3/k_2, ak_1/k_3)$.

A very illuminating approach to the reaction kinetic mechanism can be obtained by interpreting the pair of concentrations (x, y) as a *state* of the reaction and geometrically representing it by a point in the Cartesian plane. The evolution of the reaction with time can then be visualized as a trajectory of a point $R(t) = (x(t), y(t))$ in what is called a *phase plane* in dynamical system theory (2, 6). The dynamics of this point at each time is described by its vector velocity

$$\frac{dR}{dt} = \left(\frac{dx}{dt}, \frac{dy}{dt} \right)$$

On the other hand, the kinetic rate equations (1) constrain the velocity vector of the point R as a function of its coordinates; that is,

$$\frac{dR}{dt} = \left(\frac{dx}{dt}, \frac{dy}{dt} \right) = \left(k_1 a - k_2 xy, k_2 xy - k_3 y \right)$$

The main advantage of this representation is that one can then interpret the right-hand term of the equation as a *vector field* in the plane independently of the solutions of the differential equations. That is, to each point (x, y) in the plane, an arrow vector $V(x, y) = (k_1 a - k_2 xy, k_2 xy - k_3 y)$ is attached, giving the velocity of a trajectory when, if ever, it passes through that point. The modern theory of ordinary differential equations is largely based on that geometrical interpretation (2, 6).

The points (x, y) where $V(x, y) = 0$ are called *stationary states*. They give the states where the reaction can theoretically be maintained at constant equilibrium. The interest here is restricted to the first quadrant of the plane $(x \geq 0, y \geq 0)$, although mathematically the whole plane can be explored. The length of the arrow at a point gives the rate change of the system at that corresponding state, the first component referring to the reaction rate of X and the second to the reaction rate of Y.

With this point of view, one can build a global qualitative picture of all possible trajectories without solving the differential equations, by simply drawing a number of sample arrows in the plane. Figure 1 shows some examples for $V(x, y)$ such as $V(0, y)$, $V(x, 0)$, and $V(1, 1)$. Note that in the Lotka reaction, the component parallel to the x axis always has a constant

value $(k_1 a)$. Starting with an initial point $R_o = (x_o, y_o)$ at instant $t = 0$, the resulting trajectory, "powered" by the established vector field $V(x, y)$, is simply the geometrical interpretation of a chemical reaction that begins with concentrations x_o and y_o. Figure 2 (top) shows the vector field representation for the Lotka reaction mechanism characterized by $k_1 = 0.3$, $k_2 = 0.6$, and $k_3 = 0.8$ and $[A] = a = 1.0$. From this it is easily guessed that, regardless of the initial concentrations of X and Y, the trajectories end up at (x_1, y_1). This plot can be very quickly done in Mathematica with a single command

```
<<Graphics'PlotField'
PlotVectorField[{k1 a-k2 xy, k2 x y-k3 y},{x,xmin,xmax},{y,ymin,ymax}]
```

However, the geometrical picture gives only a qualitative description of the Lotka reaction determined by a set of parameters (k_1, k_2, k_3, a). To describe one (or any) experiment, the initial conditions, $x_o = x(0)$ and $y_o = y(0)$, must be given. After the initial condition is set, the differential equations have to be numerically solved to obtain an exact description of this particular trajectory. The numerical integration of the differential equations (1) can be obtained by using built-in routines of *Mathematica* through the command "NDSolve":

```
sol=NDSolve[{x'[t]==k1 a - k2 x[t] y[t],
    y'[t]==k2 x[t] y[t] - k3 y[t],
    p'[t]==k3 y[t]
    x[0]==0.2,p[0]==0.0,y[0]==.1},
    {x,y,p},{t,0,totaltime},MaxSteps->Infinity]
```

where "totaltime" is a given time interval of interest. Another way to represent the evolution of this particular reaction is to plot the concentrations $x(t)$ and $y(t)$ with respect to time. These are given by the numerical solution of the reaction rate equations. This can be easily done using a "Plot" command. A particular experiment starting with initial concentrations $x(0) = 0.2$, $y(0) = 0.1$, and $p(0) = 0.0$ can be followed in Figure 2 (middle) through the graphs of $x(t) = [X](t)$ and $y(t) = [Y](t)$.

```
Plot[Evaluate[{x[t],y[t]}/.sol],{t,0,totaltime},PlotRange->All]
```

The plane trajectory which geometrically represents the evolution of the reaction in the phase plane, $(x(t), y(t))$, can be obtained with the ParametricPlot command (see Figure 2, bottom).

```
ParametricPlot[Evaluate[{x[t],b[t]}/.sol],{t,0,totaltime},PlotRange->All]
```

The ideas and techniques introduced in this section are straightforward and easily followed by students. The diagrams generated capture the students' geometrical intuition and illustrate well the techniques in a modern way. Computational experiments with different sets of parameters (rate constants) and different initial concentrations can be easily done and will help students acquire familiarity with the basic concepts of nonlinear dynamics in a concrete and simple setting.

The Lotka–Volterra Reaction

Another example of oscillatory reaction with a very simple mechanism is the Lotka–Volterra reaction. About the time of Lotka's work (1925), an Italian mathematician, V. Volterra, independently proposed (1926) a model for population dynamics of interacting organisms (predator–prey), which can also be interpreted as a reaction mechanism whose solutions are steady oscillations without damping. The kinetic mechanism and rate equations are also represented in three
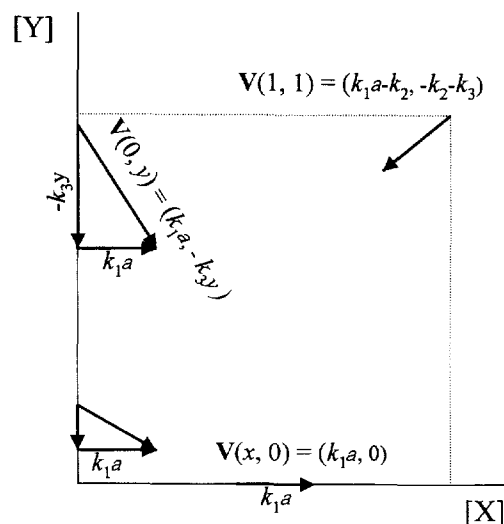

Figure 1. Some samples of the vector field in the phase plane.
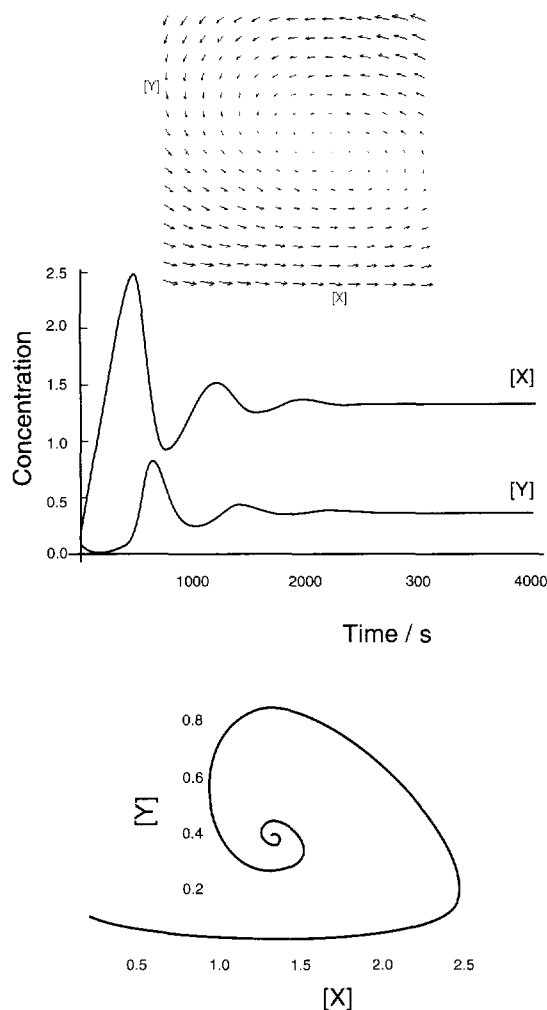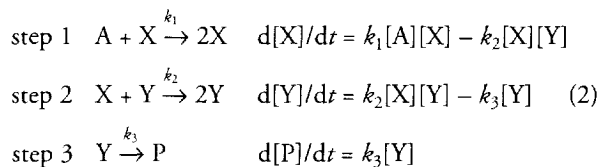

Figure 2. The Lotka reaction (see text for set of rate constants being used). Top: The Lotka vector field sketch in the phase plane. Middle: Damped oscillations of intermediates X and Y as a function of time. Bottom: A trajectory of $(x(t), y(t))$ in the phase plane starting with $(x_0 = 0.2, y_0 = 0.1)$.

steps, the most important difference between this and the former reaction being that in the present case there are two autocatalytic steps (step 1 and step 2) instead of only one.

step 1 $\quad A + X \xrightarrow{k_1} 2X \quad d[X]/dt = k_1[A][X] - k_2[X][Y]$

step 2 $\quad X + Y \xrightarrow{k_2} 2Y \quad d[Y]/dt = k_2[X][Y] - k_3[Y]$ $\quad$ (2)

step 3 $\quad Y \xrightarrow{k_3} P \quad\quad\quad d[P]/dt = k_3[Y]$

[A] = a is set constant and equal to 1.0 as in the previous example. Observe that, when [Y] $\cong$ 0, then dx/dt $\cong$ $k_1 a$ and $x(t) \cong x(0)e^{k_1 at}$, and so the concentration of X increases exponentially at the beginning. But then, from step 2, the con-

centration of Y also increases exponentially, consuming the intermediate X and producing more Y than is consumed. As [Y] increases, the product P starts being formed (step 3). So with the decreasing of [X], step 2 slows down and [Y] also falls. This causes [X] to start increasing again in step 1, and the cycle starts again. Of course this verbal description only suggests but does not prove that the process will be periodic, since it might restart in a different state. The vector field representation indicates even more clearly the presence of closed circuits (cycles), although it still does not prove it.

The numerical integration of eq 2 will again be obtained through the command NDSolve, using the rate constants k_1 = 0.3, k_2 = 0.6, and k_3 = 0.4.

```
sol=NDSolve[{x'[t]==k1 x[t] a - k2 x[t] y[t],
         y'[t]==k2 x[t] y[t] - k3 y[t],
         p'[t]==k3 y[t]},
         {x,y,p},{t,0,totaltime}, MaxSteps->6000]
```

In Figure 3 (top) are shown both the vector field and two *orbits* (closed trajectories) obtained by numerical solution of the differential equations, starting with initial concentrations $x(0)$ = 0.8, $y(0)$ = 0.8, and $p(0)$ = 0.0, and then a second orbit beginning with $x(0)$ = 0.8, $y(0)$ = 1.0, and $p(0)$ = 0.0. Figure 3 (middle) shows the temporal evolution of the intermediates X and Y, starting with the initial concentrations $x(0)$ = 2.0, $y(0)$ = 0.1, and $p(0)$ = 0.0.

Oscillatory behavior can also be conveniently analyzed from a different point of view by applying a Fourier decomposition to the numerical solution of the rate equations (*10–11*). The main idea behind the Fourier analysis is the decomposition of a function with respect to standard oscillations, the so-called *normal modes*, given by trigonometric functions: in complex notation, $e^{2i\pi nt}$ = cos $2\pi nt$ + i sin $2\pi nt$, where n is any integer.

Now, if a function of time $f(t)$ is Fourier decomposed as

$$f(t) = \sum_{-\infty}^{\infty} a_n e^{2i\pi nt}$$

then each a_n can be thought of as the contribution of frequency n to the construction of $f(t)$. The function of n, $a(n)$ = a_n, is called the Fourier transform of the function $f(t)$. It shows which oscillations are the most important for the behavior of $f(t)$, something very difficult to visualize directly from the temporal graph of $f(t)$.

The Fourier decomposition of the above kinetics in normal modes of oscillation is characterized by the relative weight $|a_n|^2$ with respect to the frequency n, also called the *power spectrum* of $f(t)$. This feature can be easily visualized through the ListPlot command:

```
a=Transpose[Table[Evaluate[x[t]/.sol],{t,0,totaltime}]];
freqdata=Abs[Fourier[a[[1]]]];
ListPlot[freqdata,PlotJoined->True]
```

Note that Fourier analysis is an approach complementary to the qualitative phase plane representation, since it gives temporal quantitative information that is absent from the latter.

The power spectrum for $x(t)$ obtained from the third numerical experiment above is shown in Figure 3 (bottom) for totaltime = 1000 and n ranging from zero to 300. The characteristic frequency of oscillation ω = $2n\pi$/totaltime is 0.28 s^{-1}. Note that besides this main amplitude contribution to the expansion, there are other prominent contributions,
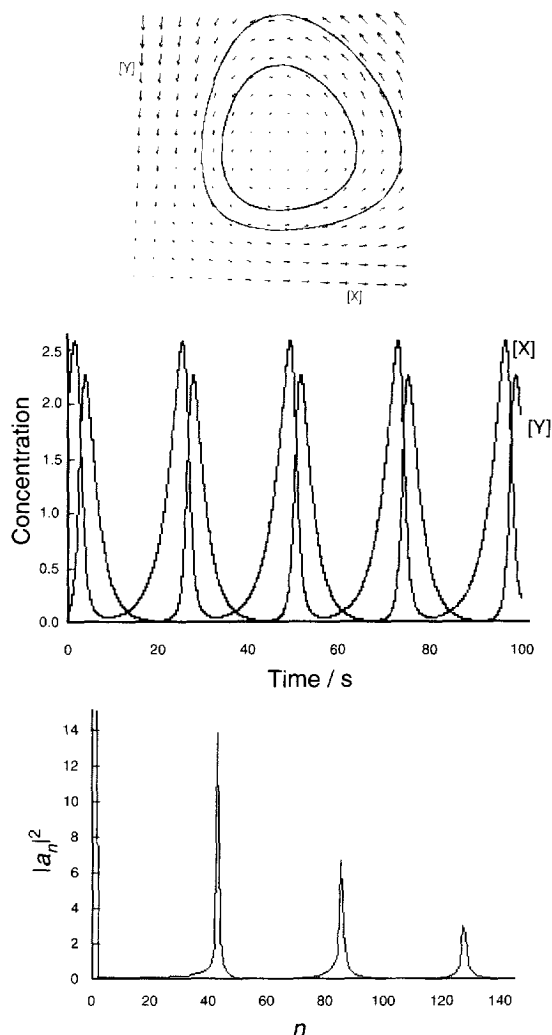

Figure 3. The Lotka–Volterra reaction (see text for the set of rate constants being used). Top: The Lotka–Volterra vector field sketch and one of its orbit in the phase plane. Middle: Periodic oscillations of intermediates X and Y as a function of time. Bottom: Power spectrum, showing the characteristic frequency of one oscillation. The initial concentrations are x_0 = 2.0 and y_0 = 0.1.

equally spaced, which is characteristic of a very definite periodic behavior (11). A nice exercise would be to explore how this frequency varies with respect to the initial concentration of X.

A very annoying and unrealistic aspect of this reaction model is that any small perturbation (which always exists, all the time) to a mathematical cycle will change its "orbit". Therefore no definite periodic solution will be chosen by the system, and consequently, no definite period of oscillation is experimentally obtainable.

A more realistic reaction mechanism, which provides a very definite periodic oscillation, is exemplified by equations with *limit cycles*, called *stable* or *attractor orbits*. In those cases, any small deviation from the cycle regime is self-corrected by an internal damping mechanism. The most famous example of a limit cycle is provided by the following model equations describing an electrical oscillator characterized by the vector field $V(x,y) = (y, -x + y(1 - x^2 - y^2))$. As can be seen from its phase plane representation (Fig. 4), there is a very definite limit cycle and any deviation from it is promptly self-corrected by the system (2). Thus its dynamical behavior is very much like that of a clock pendulum. As in the spectral theory of quantum mechanics, for those reaction models, a very definite number (i.e., the period of oscillation for the limit cycle) is determined. Since any initial conditions will produce a trajectory that quickly approaches the same limit cycle, an oscillatory regime will be experimentally observed after a short transitory accommodation. One real chemical reaction that exhibits such periodic oscillation is the famous (and not so simple) Belousov–Zhabotinsky reaction in which malonic acid is oxidized by BrO_3^- in an acidic medium (H_2SO_4) with or without a catalyst (usually Ce^{III}). In biochemical reactions, those cycles can frequently be related to the rhythms of life (12).

In the next example, a model for a class of biochemical reactions that can exhibit limit cycles and also a more complex behavior called chaos will be analyzed.

Glycolytic Reaction

There has recently been an explosion of research on complex dynamical behavior phenomena generated by relatively simple equations (6, 7, 12) consisting of limit cycles and chaotic behavior. A chaotic behavior is not easily defined except to say that it is very complicated. A simple way to better characterize this kind of behavior in a first approximation is obtained through its Fourier analysis, which shows no definite prominence of any finite number of periodic oscillations. However, it must be stressed that chaos is quite different from noise, since it is deterministic and not stochastic.

This section shows how a relatively simple model of enzymatic reactions can be useful for understanding complex behavior of many important metabolic mechanisms. Among common biochemical examples exhibiting complex periodic oscillations and chaos are the glycolytic oscillations in muscle, yeast glycolysis, and the periodic synthesis of cyclic AMP (13).

A few of the many types of behaviors that can result from the interaction between two instability mechanisms will be described using a model for enzymatic reactions proposed by Decroly and Goldbeter (8, 13–15). It can be viewed as a simple prototype for the interplay between two instability-generating mechanisms. In addition to simple periodic oscillations, this system can give rise to the phenomenon of birhythmicity;
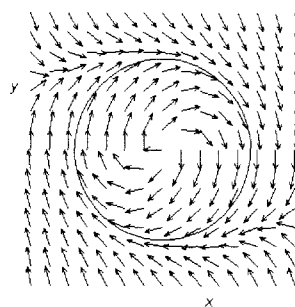

Figure 4. The vector field sketch in the phase plane showing a definite periodic cycle and the oscillations given by an electrical oscillator.
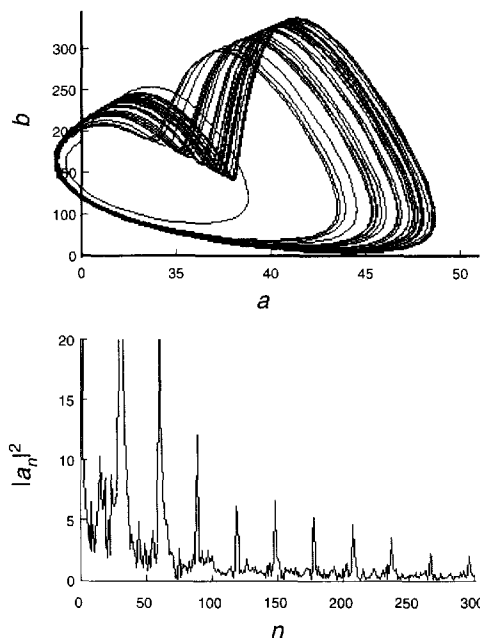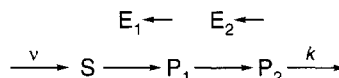

Figure 5. The glycolytic reaction for $k = 4.422$ (see text for other parameters characterizing the reaction). Top: Projection of a three-dimensional phase space trajectory associated with the chaotic regime into the plane (a, b). Bottom: Power spectrum of the function $a(t)$, showing the disorganized feature of this chaotic regime starting with initial concentrations $a_0 = 30.0$, $b_0 = 188.8$, $c_0 = 0.3367$.

that is, the simultaneous existence of two attracting cycles, one of them "chosen" by the system depending on the initial concentrations, and chaos.

The sequence of reactions can be represented as

$$\begin{array}{ccc} & E_1 \leftarrow & E_2 \leftarrow \\ \xrightarrow{v} S \longrightarrow P_1 \longrightarrow P_2 \xrightarrow{k} \end{array}$$

where the substrate S is synthesized or injected into the system at a constant rate denoted by v and its transformation into P_1 is catalyzed by an allosteric enzyme E_1. The product P_1 activates E_1. The second enzyme E_2 uses P_1 as substrate to produce P_2 and is activated by its own product P_2; k is the
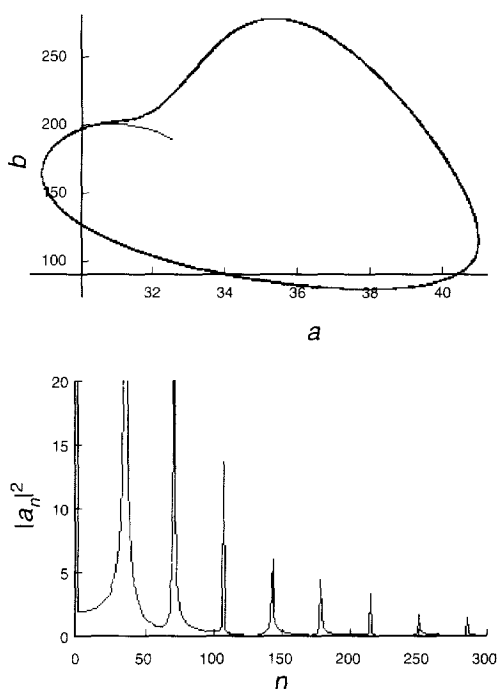
Figure 6. The glycolytic reaction for $k = 4.422$ (see text for other parameters characterizing the reaction). Top: Projection of a three-dimensional phase space trajectory associated with the limit cycle into the plane (a,b). Bottom: Power spectrum of the function $a(t)$, showing the characteristic frequency of oscillation starting with initial concentrations $a_0 = 32.5$, $b_0 = 188.8$, $c_0 = 0.3367$.

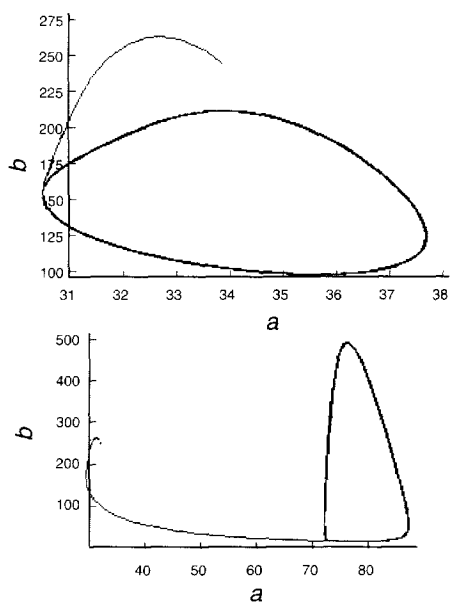

Figure 7. The glycolytic reaction showing the projection of two trajectories approaching different limit cycles for $k = 4.0$ Top: starting with initial conditions $a_0 = 33.9$, $b_0 = 250.0$, $c_0 = 0.25$. Bottom: starting with initial conditions $a_0 = 32.0144$, $b_0 = 250.0$, $c_0 = 0.25$.

rate constant for removing P_2. This model is an extension of the glycolytic oscillation models proposed by Monod–Wyman–Changeux (16); it has only one positive feedback and evolves to a stable stationary state (damped oscillation) or to a mono-periodic stable regime (a limit cycle). The time evolution of the metabolite's concentrations is governed by three ordinary differential equations:

$$da/dt = (v/K_{m_1}) - \sigma_1\Phi$$
$$db/dt = q_1\sigma_1\Phi - \sigma_2\eta \qquad (3)$$
$$dc/dt = q_2\sigma_2\eta - kc$$

where
$$\Phi = \frac{a(1+a)(1+b)^2}{\left[L_1 + \left((1+a)^2(1+b)^2\right)\right]}$$

and
$$\eta = \frac{b(1+db)(1+c)^2}{\left[L_2 + \left((1+db)^2(1+c)^2\right)\right]}$$

and where, a, b, and c denote the normalized (dimensionless) concentrations of substrate S and the intermediates P_1 and P_2 (i.e., $a = S/K_{m_1}$, $b = P_1/k_{p_1}$, and $c = P_2/k_{p_2}$. The constants σ_1 and σ_2 are the maximum activities of enzymes E_1 and E_2 divided by K_{m_1} and K_{m_2}, the Michaelis constants for E_1 and E_2, respectively. L_1 and L_2 are allosteric constants; $q_1 = K_{m_1}/k_{p_1}$ and $q_2 = K_{m_2}/k_{p_2}$.

The detailed biochemical reactions that give rise to these kinetic equations are rather complicated and will not be described further here; the reader is referred to the literature (13–15).

Observe that in this case, the geometrical representation of the vector field should be displayed in a three-dimensional space, which has much more room than the plane, and although it is not quite as helpful it still is an important conceptual tool. The values of the parameters that will be used are experimentally (i.e., computationally) obtained in order to yield the interesting behaviors that are intended. Because that involves a lot of computational work, the values suggested in ref 8 are used here. Students and the instructor may further explore the system behavior by using sets of parameters close to but different from those given here.

A basic routine for solving the glycolytic reaction shown in eq 3 is given by

```
sol=NDSolve[
   {a'[t] == nu/km1 - sigma1 (a[t] (1+a[t]) ((1+b[t])^2))/
      (L1 +((1+a[t])^2) ((1+b[t])^2)),
   b'[t] == q1 sigma1 (a[t] (1+a[t]) ((1+b[t])^2))/(L1 +
      ((1+a[t])^2) ((1+b[t])^2)) - sigma2 (b[t] (1+d b[t])
      ((1+c[t])^2))/(L2 + ((1+d b[t])^2) ((1+c[t])^2)),
   c'[t] == q2 sigma2 (b[t] (1+d b[t]) ((1+c[t])^2))/(L2 +
      ((1+d b[t])^2) ((1+c[t])^2)) - k c[t],
   },{a,b,c},{t,0,totaltime},MaxSteps->Infinity]
```

where (nu/km1), sigma1, and sigma2 represent v/K_{m_1}, σ_1, and σ_2, respectively.

If into the above routine are set the values nu/km1 = 1.0, sigma1 = sigma2 = 22.2222, q1 = 50, q2 = 0.02, L1 = 5×10^8, L2 = 100, d = 0.0, totaltime = 1500, k = 4.422 and initial concentrations $a(0) = 30.0$, $b(0) = 188.8$ and $c(0) = 0.3367$, the

system shows a chaotic behavior. The trajectory described by the system is attracted by a set of points in a three-dimensional space (a, b, c) with an extremely irregular structure, possibly a fractal, called a *strange attractor* (*2*). This can be visualized by using the command "ParametricPlot" (see Fig. 5, top). For k in the range between 4.422 and 4.520, the system shows a chaotic behavior for some initial set of concentrations. Note that the range of values for which chaos occurs is very small.

It is also observed that in this same range of k, chaos coexists with a stable oscillatory regime. Figure 6 (top) shows an example where the initial set of concentrations $a(0) = 32.5$, $b(0) = 188.8$, and $c(0) = 0.3367$ evolves to a limit cycle for the same set of parameters as before.

Some other very interesting features of this set of reactions can be obtained by setting the parameter k in the range between 3.52 and 4.04. The system exhibits two limit cycles, which means that for the same value of k, depending only on the initial concentration of a, the system converges to one of the two periodic regimes after some adaptation time (transient regime). The trajectories for these two limit cycles can be seen in Figure 7 for $k = 4.0$. In one case (Fig. 7, top), the initial concentrations are $a(0) = 33.9$, $b(0) = 250.0$, and $c(0) = 0.25$; in the other (Fig. 7, bottom), $a(0)$ is slightly changed to $a(0) = 32.0144$, $b(0)$ and $c(0)$ being kept the same. This bistability between two oscillatory states (i.e., the existence of two attracting cycles) is called birhythmicity.

These behaviors can also be analyzed from a Fourier point of view. The power spectrum of the solution shown in Figure 6 (bottom) has a high-amplitude component at $n = 43$, which shows a well-determined frequency of $\omega = 0.05$ s^{-1}. The figure shows the power spectrum for up to $n = 300$. The small contributions are superharmonics. On the other hand, the power spectrum graphic for the chaotic regime shows a disorganized feature as can be seen in Figure 5 (bottom). The higher amplitudes in some way resemble the results obtained for the limit cycle, which is understandable since the chaotic behavior occurs when the parameters are given values close to those that previously resulted in a limit cycle behavior. Observe that for a whole range of frequencies the Fourier components are far from zero, with no repetitive pattern.

These experiments reflect only a small sample of the many possible behaviors for this complex and rich system. Students should explore other sets of parameters or initial concentrations and get acquainted with the many interesting aspects of these fascinating phenomena (*13–15*). These computational experiments will be conceptually helpful to students when they meet complex dynamic behavior in the

future, as they almost certainly will (*2, 6, 13*). If they are not prepared to look for an interpretation of a complex phenomenon, it is almost sure that important information will be discarded without proper appraisal.

Acknowledgments

Note

1. "High level" in this computational context means that routines for common but complicated calculations (like polynomial and matrix calculus, numerical solution of systems of linear equations or differential equations, or plotting) are available as simple commands.

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