Mathematical Modeling and Chemical Kinetics

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1 Introduction

What is the role of mathematics in the life sciences? By now you should have begun to form your own answer to this question. Part of the mission of the MLS program is to show you why mathematics is important in science. Perhaps you will become a scientist and use mathematics to help discover something new.

You have seen how probability theory is used to explain results of the bacterial fluctuation experiment on Lamarckian versus Darwinian evolution and how the calculus of exponential growth proves Beer's law, which was used to make some of the measurements employed in this experiment. You also saw how the concept of scaling can help to explain some of what we see in nature. Most recently, you have seen some of the formulas that arise in the underlying chemistry that produces oscillating reactions. All of these uses of mathematics are aspects of what is called mathematical modeling, which we are going to discuss. We should also be reminded that statistical analysis and statistical modeling is another very important use of mathematics in experimental science. Counting the outcomes of experimental trials and using statistical analysis to determine the significance of these results is an essential part of modern (life) science. While you might imagine that science could progress without the introduction of mathematical models, it is not

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possible for experimental science to operate without statistics. We will certainly discuss the use (and misuse) of statistics more fully at another time. Mathematical modeling is the subject for today.

What is a mathematical model anyway? What are they good for?

Let us start with a mathematical model you know well: The height x above the ground of a particle of mass m in free fall at time t is given by

$$x = x_0 + v_0 t - \frac{1}{2} g t^2,$$

where t is the time measured in seconds, x_0 is the initial height (that is, the height at time $t = 0$) measured in meters, v_0 is the initial velocity measured in meters/second, and g is equal to 9.8 meters/second/second (the acceleration due to the gravitational field of Earth). We have a mathematical equation that is supposed to *agree with physical reality.*

Note that the mass of the falling object is not mentioned in the model; thus, according to the model, every two objects fall in exactly the same manner. This is an amazing *prediction* that is counter-intuitive. A related quantitative prediction is that every object falling from rest at height x_0 reaches the ground when

$$t_{\text{to ground}} = \sqrt{2x_0/g}.$$

We *use mathematics to make this prediction*; indeed, we must solve the quadratic equation

$$0 = x_0 - \frac{1}{2} g t^2.$$

Our prediction could be tested by experiment. For example, we could drop some object from a known height and measure how long it takes for it to reach the ground. An object dropped from a height of 3 meters is predicted to reach the ground approximately 0.782461 seconds later. Perhaps you did this experiment in a high school physics class. The model, which is due to Galileo Galilei, was obtained by working backward from experiments. He dropped lots of balls[1] and measured how fast they fell before discovering his law of falling bodies, which in mathematical language is exactly the model equation we are discussing.

[1]Actually, he rolled balls down inclined planes to slow the rate of fall so that more accurate measurements could be made. Electronic stop watches were not available in the year 1603.

Does Galileo's model agree with physical reality? The answer depends on what is meant by the word "agree." Our prediction will agree with experiments in case we drop heavy objects and do not measure time too accurately. Why do heavy objects give better experimental results? You may already be thinking of the reason: *the model does not take into account all of the physical reality.* It models the force due to gravity only. You may have fun thinking of a good reason why the forces on the object due to the presence of the atmosphere are less important for massive falling objects. At least, we should learn an important fact: *mathematical models always leave out some aspects of physical reality.*

We have seen one reason why mathematical models are important: they can be used to make predictions. For instance, we may change the height of an object or its initial velocity as we please and predict where it will be at some later time *without doing an experiment.* Moreover, because we can make predictions, we might hope to design strategies based on this mathematics to *control* physical processes. The belief that mathematically correct predictions from mathematical models (based on physical laws) will be verified by experiments is part of the bedrock of science. Indeed, if it ever happens that a mathematical prediction from a physical model is not validated by an experiment, we do not discard the mathematics; we discard the physical theory on which the model is based.

While Galileo's model is very close to being a correct description of the motion of particles in free fall near the surface of the earth, it does not explain *why* objects fall. To do so, requires a fancy mathematical language and a more fundamental theory of gravity (called the General Theory of Relativity). But this is much too long a story for us to pursue at this time.

We are going to discuss a mathematical model for an oscillating chemical reaction similar to the reaction responsible for the experiments you performed. Why should we care about making a mathematical model? We made the reaction and it worked! What else matters? In fact, the brilliant people who discovered oscillating chemical reactions did not rely on mathematics; they used chemistry.

Going back to gravity for a moment, let us recall the next step after Galileo in the development of gravitational theory: the contribution of Isaac Newton. He made two monumental contributions: he proposed a law of motion—the rate of change of momentum of a particle is equal to the sum of the forces acting on the particle (mass×acceleration=force), and he proposed a law of universal gravitation—the gravitational attraction between

two bodies is directly proportional to the product of their masses and inversely proportional to the square of the distance between them:

$$\text{gravitational force} = GMm/\text{distance}^2.$$

Using the law of motion (Newton's 2nd law), the law of universal gravitation and some mathematics, we can obtain Galileo's law as a prediction of Newton's theory. Of course, the combination of the 2nd law and the law of universal gravitation is much more powerful; for example, we can use it to determine the motion of the planets. A practical use of this capability is the planning of space missions. We do not have the luxury of doing experiments to see what will happen when we wish to land on Mars. Rather, we use Newton's model along with some sophisticated mathematics and intensive computation to predict a strategy for our proposed space mission. If the spacecraft performs as it should, the predictions derived from Newton's model fly us to the Moon, Mars, and beyond!

The LIGO (Laser Interferometer Gravitational Wave Observatory), which is perhaps a less familiar example, was constructed at a cost of over 360 million dollars and is currently being used to perform experiments. The fundamental motivation for building this observatory is based on the mathematical prediction, made from Einstein's theory of universal gravitation, that gravitational waves exist. According to this prediction, an exploding star (or the motion of every massive object) causes a wave of distortion to move at the speed of light through spacetime that affects the gravitational field as it passes your observation point. No gravitational waves have been observed. But, since we are so confident of the validity of mathematical predictions from mathematical models, our society is willing to make a large financial investment to build an observatory based on this prediction. Of course, if gravitational waves exist, this mathematical prediction will introduce a new type of astronomy: gravitational wave astronomy, which would open a new window to the cosmos. On the other hand, if gravitational waves do not exist, Einstein's theory will have to be modified or replaced.

There are many other examples where mathematical predictions from mathematical models have led to major scientific progress: radio communications (prediction of waves from Maxwell's equations), existence of elementary particles (predictions from the equations of quantum mechanics), etc.

The examples mentioned so far come from physics. This is no accident. Modeling the fundamental forces of nature, especially gravity (general relativity) and electromagnetism (Maxwell's Equations), have proved to be so

precise that every mathematical prediction from these models that has been tested by experiment has proved to be physically correct. Exactly why mathematics works so well is a deep philosophical question. A famous essay on this subject "The unreasonable effectiveness of mathematics in the natural sciences" by Eugene Wigner is highly recommended (see [W]). Wigner points out that making predictions from mathematical models—our subject for today—is not the most important role of mathematics in physics; the "sovereign role" of mathematics in physics is its use in expressing the laws of physics:

> The miracle of the appropriateness of the language of mathematics for the formulation of the laws of physics is a wonderful gift which we neither understand nor deserve. We should be grateful for it and hope that it will remain valid in future research and that it will extend, for better or for worse, to our pleasure, even though perhaps also to our bafflement, to wide branches of learning.

What about the role of mathematics in the life sciences? We might go to a biology department at a university and ask the professors we find there if mathematics plays an essential role in their research. In the year 2009, the likely answer would be "no." On the other hand, we could find some professors in some biology departments who would answer in the affirmative. There is a definite trend toward more mathematical thinking in the life sciences. Prestigious agencies like the National Science Foundation are investing substantial amounts of money to educate bright young university students about this trend with the hope that they will participate in the life science of the 21st century. The 20th century was the century of mechanics; it seems that the 21st century will be the century of life science.

The great success of mathematics in physics suggests that more mathematics might be good for the life sciences. At present, it seems fair to say that much applied mathematics in life science is based on application of physics to the life sciences. Some aspects of the understanding of "soft matter" are not different in principle from what is already understood in physics: electromagnetic waves interact with molecules in living tissue the same way they do in condensed matter; the theory of elasticity can be applied to muscle fibers as well as to carbon fibers; chemical kinetics can be used to model reactions in living systems as well as in a stirred tank reactor, fluid dynamics can be used to model blood flow as well as water flowing through a pipe, etc. All

of these applications are based at a fundamental level on the laws of physics that are already known to be true. There is much to be discovered using these tools. Research in this direction is exciting and is just beginning to blossom.

Mathematics might eventually play a sovereign role in life science that is totally unexpected. There is certainly mathematics that has not yet been invented which will prove useful in life sciences. We might wonder if one or two of those bright young scholars supported by the NSF—perhaps after they learn much more mathematics and life science—will discover some laws that put life into mathematical models. How do we couple life and physics into mathematical laws? That is the question!

Students of science are invited to study mathematics to understand the language of mathematical modeling and acquire the tools to derive predictions from these models. But, mathematical thinking sometimes takes students well beyond these goals.

2 A prediction from a mathematical model in chemical kinetics

You have now become familiar with two oscillating chemical reactions: the Belousov-Zhabotinsky reaction (which did not work so well in our lab) and the Briggs-Rauscher reaction (which gave a spectacular result). The mathematical models of these reactions are amenable to mathematical analysis; but, the models are complicated. A simpler reaction is the Lengyel-Epstein reaction for chlorine dioxide ClO_2, iodine I_2, and (our friend) malonic acid MA. The reactions are believed to be

$$MA + I_2 \rightarrow IMA + I^- + H^+, \tag{1}$$

$$ClO_2 + I^- \rightarrow ClO_2^- + \tfrac{1}{2}\, I_2, \tag{2}$$

$$ClO_2^- + 4I^- + 4H^+ \rightarrow Cl^- + 2I_2 + 2H_2O. \tag{3}$$

We will discuss a mathematical model for two state variables x and y that correspond to the iodide concentration I^- and the chlorite concentration ClO_2^-. This model consists of two differential equations (that is, equations involving these concentrations and their rates of change). The rates of change of the concentrations have to be determined by experiments; there is no simple translation of reactions into differential equations. The proposed rate

equations, where X is the concentration of iodide and Y the concentration of chlorite, are given by

$$\frac{dX}{dt} = k_1\frac{[\mathrm{MA}][\mathrm{I_2}]}{k_2+[\mathrm{I_2}]} - k_4[\mathrm{ClO_2}]X - 4(k_5[\mathrm{H^+}]XY + k_6[\mathrm{I_2}]\frac{XY}{\alpha+X^2}), \quad (4)$$

$$\frac{dY}{dt} = k_4[\mathrm{ClO_2}]X - (k_5[\mathrm{H^+}]XY + k_6[\mathrm{I_2}]\frac{XY}{\alpha+X^2}), \quad (5)$$

where the square brackets denote concentrations, the k_i are rate constants and α is a constant with units of (mass/volume)^2. There are rate equations for all of the molecules and ions involved in the process. But, it has been determined by experiment that the concentrations of iodide and chlorite change must faster than the concentrations of the other molecules. Thus, it is reasonable to assume for simplicity that the concentrations of the other molecules remain constant during the reaction. We are not forced to make this assumption; but, as in all mathematical modeling, we must choose to go toward realism (which leads to complicated models) or simplicity (which might leave out important effects). Having made the choice of direction toward simplicity, we will also ignore the k_5 term as did Lengyel and Epstein for no obvious reason except perhaps because the concentration of the hydrogen ion $\mathrm{H^+}$, the lightest nucleus, is certain to be very small. These assumptions lead to the differential equations

$$\frac{dX}{dt} = A - BX - 4C\frac{XY}{\alpha+X^2}, \quad (6)$$

$$\frac{dY}{dt} = CX - C\frac{XY}{\alpha+X^2}, \quad (7)$$

where A, B, and C are positive parameters.

Good practice in mathematical modeling requires mathematical models to be made dimensionless. This is accomplished here by the change of variables

$$X = \sqrt{\alpha}\,x, \quad Y = \frac{\alpha B}{C}y, \quad t = \frac{\tau}{B}$$

and the definition of two lumped (dimensionless) parameters

$$a := \frac{A}{B}, \qquad b := \frac{C}{B\sqrt{\alpha}}.$$

After some manipulation, the dimensionless Lengyel-Epstein model is

$$\frac{dx}{d\tau} = a - x - 4\frac{xy}{1+x^2}, \qquad \frac{dy}{d\tau} = bx(1 - \frac{y}{1+x^2}) \quad (8)$$

(see [LRE, EKL, EP]). There are at least three important reasons why dimensionless models are useful: they are elegant, the important combinations of the parameters are obtained, and the relative sizes of these dimensionless combinations is determined.

We have considered differential equations before, for example, the ubiquitous equation

$$\frac{dx}{dt} = ax, \tag{9}$$

which we know has the solution $x(t) = x(0)e^{at}$. Let us recall the meaning of the derivative dx/dt. Perhaps it helps to view the differential equation in the form

$$\frac{dx(t)}{dt} = ax(t)$$

so that it is clear we are solving for the unknown function x whose independent variable is called t.

Recall that the derivative is given by a limit process (which is the hallmark of Calculus). In fact,

$$\frac{dx(t)}{dt} := \lim_{h\to 0} \frac{x(t+h) - x(t)}{h}, \tag{10}$$

which is just the rate of change of x with respect to t.

One way to *approximate* the differential equation (9) is to replace the limit in display (10) by a difference quotient for some fixed value of h:

$$\frac{x(t+h) - x(t)}{h} \approx ax(t),$$

which we may write in the more suggestive form

$$x(t+h) \approx x(t) + hax(t). \tag{11}$$

In other words, if we already know the value of the desired solution x at some value of t, we may approximate the value of x at the new time $t+h$ using equation (11).

We have to start somewhere, so let us assume we have fixed the *time-step size* h and we know the value of the unknown solution x of our differential equation at time $t = 0$; that is, $x(0) = x_0$ for some number x_0. The approximation of x at time $t+h$ is

$$x(h) \approx x_0 + hax_0.$$

Using the slightly different notation $x_1 := x_0 + hax_0$ and $t_1 := t_0 + h$ (where in this example $t_0 = 0$), we have that

$$x_1 = x_0 + hax_0, \qquad t_1 = h.$$

More generally, we simply repeat the process to obtain

$$x_n = x_{n-1} + hax_{n-1} = (1 + ha)x_{n-1}, \qquad t_n = t_{n-1} + h.$$

In other words, $t_n = t_{n-1} + h$ is the time at the nth step and we may take the exact solution x to be approximated by $x(t_n) \approx x_n$.

This idea for approximating solutions of differential equations was introduced by Leonhard Euler (1707–1783), one of history's greatest mathematicians. While this method has been superseded by much more sophisticated approximation methods, it remains the prototypical method for numerical integration of differential equations; and, as we will see, it still gives useful results for many differential equations.

To make a concrete example, let us take $a = 1$, $x_0 = 1$ and $t_0 = 0$, and approximate the value of the solution of the differential equation (9) at $t = 1$. A natural choice for the time-step is $h = 1/N$ (for a positive integer N); because, after N steps, the time will be exactly $t = 1$. The Euler approximations x_0, x_1, x_2,..., x_N at each corresponding time-step 0, $1/N$, $2/N$, $3/N$, ..., N/N are easily computed to be

$$1, (1 + \frac{1}{N}), (1 + \frac{1}{N})^2, (1 + \frac{1}{N})^3, \ldots, (1 + \frac{1}{N})^N.$$

In particular, the approximation of $x(1) = x(0)e^1 = e$ is given by

$$e \approx (1 + \frac{1}{N})^N.$$

How accurately have we approximated the solution of our differential equation? The value of the desired solution at $t = 1$ is known (by pencil and paper mathematics) to be

$$e \approx 2.718281828.$$

The Euler approximations of e at $t = 1$, for different step sizes h from $h = 1$ to $h = 1/80$, are given by

2.0, 2.25, 2.37037, 2.44141, 2.48832, 2.52163, 2.5465, 2.56578,
2.58117, 2.59374, 2.6042, 2.61304, 2.6206, 2.62715, 2.63288, 2.63793,
2.64241, 2.64643, 2.65003, 2.6533, 2.65626, 2.65897, 2.66145,
2.66373, 2.66584, 2.66778, 2.66959, 2.67128, 2.67285, 2.67432,
2.6757, 2.67699, 2.67821, 2.67936, 2.68044, 2.68146, 2.68244,
2.68336, 2.68423, 2.68506, 2.68586, 2.68661, 2.68733, 2.68802,
2.68868, 2.68931, 2.68992, 2.6905, 2.69105, 2.69159, 2.6921, 2.6926,
2.69307, 2.69353, 2.69398, 2.6944, 2.69481, 2.69521, 2.6956, 2.69597,
2.69633, 2.69668, 2.69702, 2.69734, 2.69766, 2.69797, 2.69827,
2.69856, 2.69884, 2.69912, 2.69938, 2.69964, 2.69989, 2.70014,
2.70038, 2.70061, 2.70084, 2.70106, 2.70127, 2.70148.
The last approximation (which corresponds to $h = 1/80$) has a relative error of

$$\frac{2.70148 - 2.718281828}{2.718281828} \approx 0.6\%.$$

What do you suppose will happen as N increases toward infinity?

We may apply Euler's method to approximate the solution of the Lengyel-Epstein model (8). To do so, we must choose values of the parameters a and b (positive real numbers), a value of the (scaled) time-step h, and a starting point (x_0, y_0), which we assume to be given (scaled) concentrations at $\tau = 0$. The approximate value after n steps (that is, at $\tau = nh$) is obtained by iteration of the equations

$$\begin{aligned} x_{n+1} &= x_n + h(a - x_n - 4\frac{x_n y_n}{1 + x_n^2}), \\ y_{n+1} &= y_n + hbx_n(1 - \frac{y_n}{1 + x_n^2}), \end{aligned} \tag{12}$$

which is usually done using a computer.[2] [3] Each step of Euler's method produces a pair of numbers

$$(x_0, y_0), \quad (x_1, y_1), \quad (x_2, y_2), \quad \ldots$$

and a corresponding time t_0, t_1, t_2, ...

[2] An Excel spreadsheet is available to implement Euler's method for the Lengyel-Epstein model.

[3] Differential equations were routinely approximated by people, who were called computers, working with pencil and paper until approximately 1880 when they switched to mechanical adding machines. Electronic computers were introduced during the Second World War.

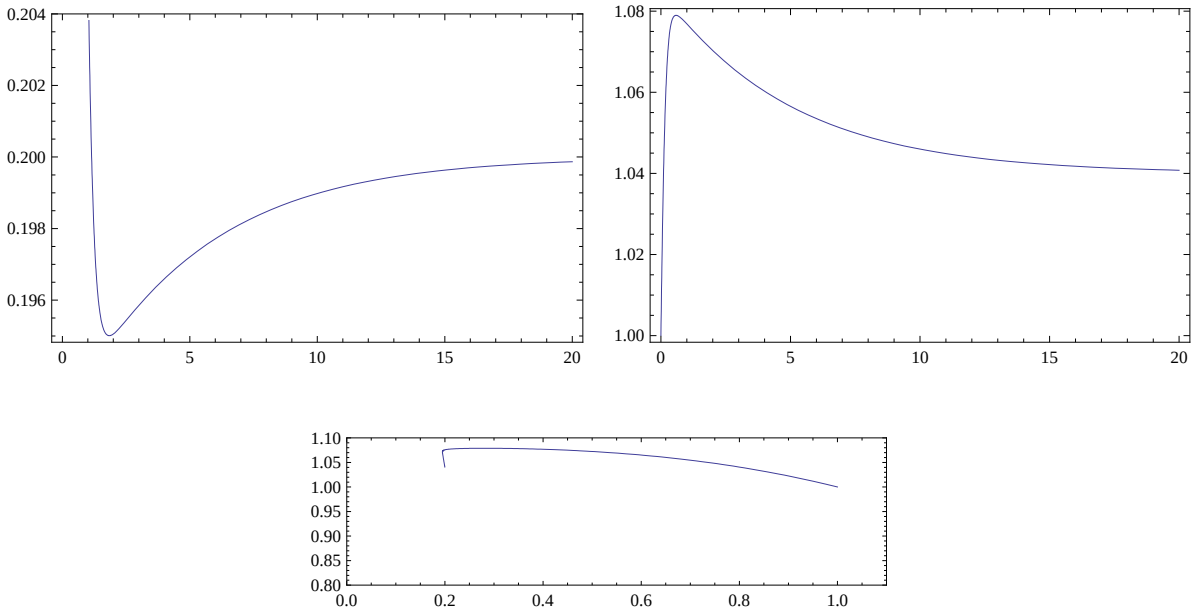

Figure 1: Approximations of x versus t, y versus t, and y versus x for the Lengyel-Epstein model (8) with $a = 1$, $b = 12$, $(x(0), y(0)) = (1, 1)$.

The solution of the Lengyel-Epstein model (8) is a pair of functions (x, y). Perhaps the best way to observe the qualitative behavior of these functions is to graph x versus τ, y versus τ, or y versus x. These graphs can be approximated by graphing x_n versus n, y_n versus n, and y_n versus x_n, where we may fill in between the dots with continuous curves if we wish. The results of some computer calculations using Euler's method are depicted in Fig. 1 for the case $a = 1$ and $b = 20$. Note that the model predicts that the concentrations for these parameter values do not oscillate; rather they go toward a *steady state* (that is, a state (x_∞, y_∞) which does not change with time). The exact value of this steady state for this choice of parameters is $(x_\infty, y_\infty) = (0.2, 1.04)$. The system behaves in the desired manner (that is, the approximate concentrations oscillate) for the case $a = 20$ and $b = 8$ (see Fig. 2).

Since there seem to be at least two possible behaviors predicted from the Lengyel-Epstein model, it seems a natural question to ask if it is possible to determine exactly which choices of the parameters correspond to oscillations. It turns out that some pencil and paper mathematics can be used to show

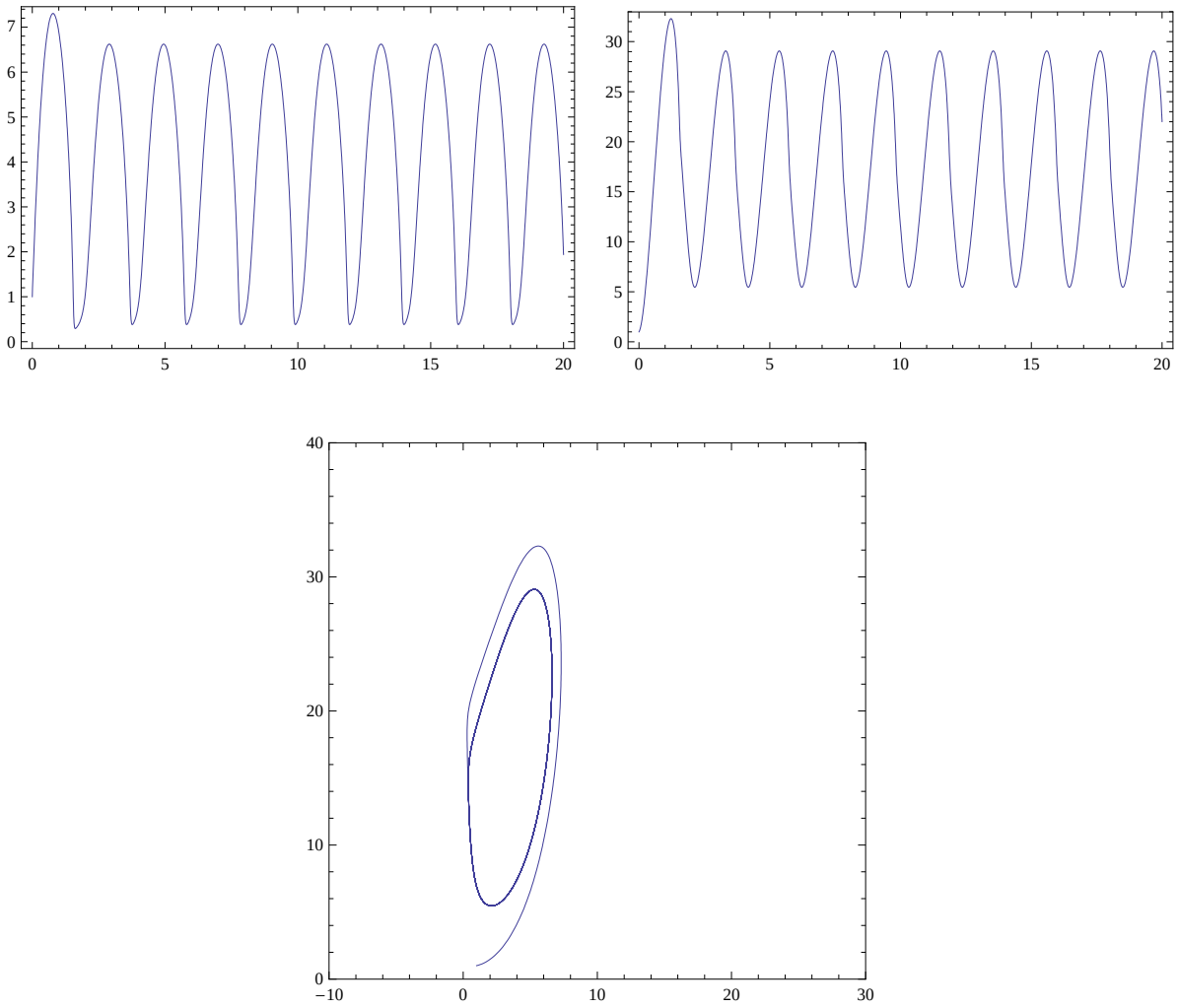

Figure 2: Approximations of x versus t, y versus t, and y versus x for the Lengyel-Epstein model (8) with $a = 20$, $b = 8$, $(x(0), y(0)) = (1, 1)$.

that this set of values can be determined exactly. In fact, the change in qualitative behavior (called a Hopf bifurcation) occurs at the curve in the parameter space given by

$$b = \frac{3a}{5} - \frac{25}{a}.$$

If $b > 3a/5 - 25/a$, then the concentrations will go toward a steady state. On the other hand, if $b < 3a/5 - 25/a$, then the concentrations will go toward a solution that oscillates for all time.

How can we predict the steady state? Think about it. By our definition of a steady state, the concentrations do not change with time. This is just another way to say that the rates of change of the concentrations vanish. For the Lengyel-Epstein model, the state (x, y) is a steady state if (and only if)

$$0 = a - x - 4\frac{xy}{1+x^2}, \qquad 0 = bx(1 - \frac{y}{1+x^2}). \tag{13}$$

There is exactly one solution:

$$x = \frac{a}{5}, \qquad y = 1 + \frac{a^2}{25}.$$

Note that the steady state exists for every choice of the parameter vector (a, b). Thus, the existence of a steady state does not imply that other solutions of the differential equation will approach the steady state as time increases. This observation is the key to understanding the Hopf bifurcation. For $b > 3a/5 - 25/a$, the steady state attracts all other solutions and for $b < 3a/5 - 25/a$ it repels all other solutions. These statements can be proved. In the latter case, all solutions except the steady state are attracted to a periodic solution (as in Fig. 2), which is also sometimes called a steady state. A periodic steady state changes with time—which is a weird use (or perhaps an abuse) of language.

Mathematically sophisticated readers may check that as b decreases through the value $3a/5 - 25/a$ a pair of complex conjugate eigenvalues of the system matrix for the linearized system at the steady state pass through the imaginary axis, which is the signature of the Hopf bifurcation. The appropriate non-degeneracy conditions are satisfied, so a (supercritical) Hopf bifurcation occurs; that is, a limit cycle emerges from the steady state as b decreases. A stronger result can be proved as an application of the Poincaré-Bendixson theorem. Indeed, the instability of the steady state along with the existence of a positively invariant rectangle containing it supplies a trapping region

that contains no rest points. By the Poincaré-Bendixson theorem, the ω-limit set of every orbit in this region is a limit cycle (see [S]). The uniqueness of this periodic solution is another story.

How reliable are the predictions from the Lengyel-Epstein model? Since we made several simplifying assumptions, we cannot expect our prediction to be precise. We assumed that certain chemical concentrations do not change over time. This assumption is not true over long time-intervals unless these reactants are continuously replenished. Thus, we cannot expect oscillations to be maintained forever. Perhaps a more realistic prediction is that the oscillations we seek are more likely to occur if a is much larger than b. To make more accurate predictions, more of the reactions would have to be incorporated into our model. Of course, since our model does sustain oscillations, it also serves to point out the main reactions responsible for the oscillations (the Chlorite-Iodide interaction).

While perhaps the main reason for constructing models is to make predictions, they also lead to scientific understanding and physical insight. Sometimes they also lead to beautiful mathematics, which can be its own reward.

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