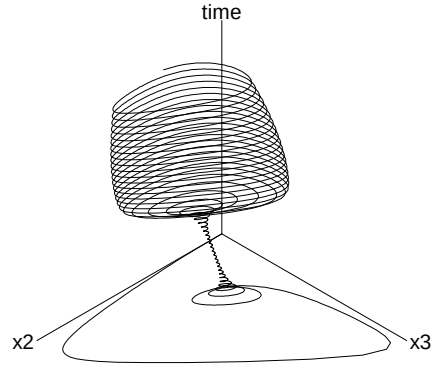
CHAPTER 8

Compartment Models



Oscillating chemical reactions on a wineglass?

Overview A salt solution is pumped through a series of tanks. We'll use the *balance law* to model the rate of change of the amount of salt in each tank:

$$\left\{\begin{matrix}\text{Net rate of change of}\\ \text{amount of salt in tank}\end{matrix}\right\} = \left\{\begin{matrix}\text{Rate into}\\ \text{tank}\end{matrix}\right\} - \left\{\begin{matrix}\text{Rate out of}\\ \text{tank}\end{matrix}\right\}$$

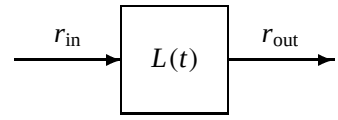
If we know the initial amount of salt and the inflow and outflow rates of the solution in each tank, then we can set up an IVP that models the physical system. We'll use this "balance law" approach to model the pollution level in a lake; the flow of a medication; the movement of lead among the blood, tissues, and bones of a body; and an autocatalytic chemical reaction.

Key words Compartment model; balance law; lake pollution; pharmacokinetics; chemical reactions; chemical law of mass action; autocatalysis; Hopf bifurcation

See also Chapter 9 for more compartment models, and Chapter 6 for linear systems and flow through interconnected tanks.

◆ Lake Pollution

Modeling how pollutants move through an environment is important in the prediction of harmful effects, as well as the formulation of environmental policies and regulations. The simplest situation has a single source of pollution that contaminates a well-defined habitat, such as a lake. To build a model of this system, we picture the lake as a *compartment*; pollutants in the water flow into and out of the compartment. The rates of flow determine the amount of build-up or dissipation of pollutants. It is useful to represent this conceptual model with a *compartment diagram*, where a box represents a compartment and an arrow represents a flow rate. Here is a compartment diagram for a simple model of lake pollution:



The amount of pollutant in the lake at time t is $L(t)$, while r_{in} is the rate of flow of pollutant into the lake and r_{out} is the rate of flow of pollutant out of the lake. To obtain the equation for the rate of change of the amount of pollutant in the lake, we apply the *balance law*: the net rate of change of the amount of a substance in a compartment is the difference between the rate of flow into the compartment and the rate of flow out of the compartment:

$$\frac{dL}{dt} = r_{\text{in}} - r_{\text{out}}$$

This ODE is sufficient when we know the rates r_{in} and r_{out}, but these rates are usually not constant: they depend on the rate of flow of water into the lake, the rate of flow of water out of the lake, and the pollutant concentration in the inflowing water. Let s_{in} and s_{out} represent the volume rates of flow of water into and out of the lake, V the volume of water in the lake, and p_{in} the concentration of pollutant in the incoming water. Now we can calculate the rates shown in the compartment diagram:

☞ You can get the volume $V(t)$ of water in the lake by solving the IVP $V' = s_{in} - s_{out}$, $V(0) = V_0$.

$$r_{\text{in}} = p_{\text{in}} s_{\text{in}}, \quad r_{\text{out}} = \frac{L}{V} s_{\text{out}}$$

The ODE for the amount of pollutant in the lake is now

$$\frac{dL}{dt} = p_{\text{in}} s_{\text{in}} - \frac{L}{V} s_{\text{out}} \tag{1}$$

☞ So we need to know $V(0)$, $L(0)$, p_{in}, s_{in}, and s_{out} in order to determine $L(t)$ and $V(t)$.

To obtain an IVP, we need to specify $L(0)$, the initial amount of pollutant in the lake. The solution to this IVP will reveal how the level of pollution varies in time. Figure 8.1 shows a solution to the ODE (1) for the pollution level in the lake if the inflow is contaminated for the first six months of every year and is clean for the last six months (so $p_{in}(t)$ is a square wave function).

☞ Take a look as Screen 1.4 in Module 8 for on-off inflow concentrations.

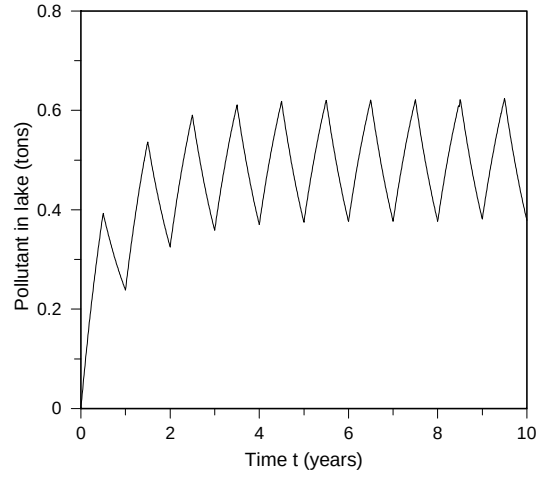


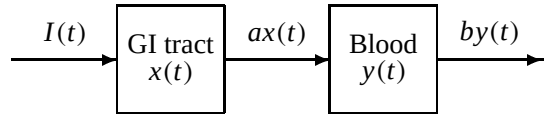
Figure 8.1: Pollutant level in a lake (on-off inflow rates).

✓ "Check" your understanding by finding the volume $V(t)$ of water in the lake at time t if $V(0) = 10$, $s_{in} = 3$, and $s_{out} = 1$, 3, or 5 (all quantities in suitable units). Does the lake dry up, overflow, or stay at a constant volume?

◆ Allergy Relief

Medications that relieve the symptoms of hay fever often contain an antihistamine and a decongestant bundled into a single capsule. The capsule dissolves in the gastrointestinal (or GI) tract and the contents move through the intestinal walls and into the bloodstream at rates proportional to the amounts of each medication in the tract. The kidneys clear medications from the bloodstream at rates proportional to the amounts in the blood.

Here is a compartment diagram for this system:



The symbols in this diagram have the following meanings:

- $I(t)$: The rate at which the dissolving capsule releases a medication (for example, a decongestant) into the GI tract
- $x(t)$: The amount of medication in the GI tract at time t
- $ax(t)$: The clearance rate of the medication from the GI tract, which equals the entrance rate into the blood (a is a positive rate constant)
- $y(t)$: The amount of medication in the blood at time t
- $by(t)$: The clearance rate of the medication from the blood (b is a positive rate constant)

Applying the balance law to each compartment, we have a system of first-order linear ODEs:

$$\begin{aligned} x' &= I - ax \\ y' &= ax - by \end{aligned} \tag{2}$$

If you know $I(t)$, the rate constants a and b, and the initial amounts $x(0)$ and $y(0)$ of medication in the GI tract and the bloodstream, you can use ODE Architect to track the flow of the medication through the body. From a pharmacological point of view, the goal is to get the medication levels in the blood into the effective (but safe) zone as quickly as possible and then to keep them there until the patient recovers.

☞ Medication levels in the blood (easily measured) indicate the levels in the tissues (hard to measure), where the medication does its good work.

There are two kinds of medication-release mechanisms: continuous and on-off. In the first kind, the medication is released continuously at an approximately constant rate, so $I(t)$ is a positive constant. In the on-off case, each capsule releases the medication at a constant rate over a brief span of time and then the process repeats when the next capsule is taken. In this case we model $I(t)$ by a square wave:

$$I(t) = A\ \text{SqWave}(t, T_{per}, T_{on})$$

☞ Screen 2.4 in Module 8 shows what happens if $a = 0.6931\ \text{hr}^{-1}$, $T_{on} = 1$ hr, and b and A are adjustable parameters.

which has amplitude A, period T_{per}, and "on" time T_{on}. For example, if the capsule releases 6 units of medication over a half hour and the dosage is one capsule every six hours, then

$$I(t) = 12\ \text{SqWave}(t, 6, 0.5) \tag{3}$$

Note that 12 (units/hr)$\times$0.5 (hr) = 6 units.

Compartment models described by equations such as (2) are called *cascades*. They can be solved explicitly, one equation at a time, by solving the first ODE, inserting the solution into the second ODE, solving it, and so on down the cascade. Although this approach theoretically yields explicit solution formulas, in practice the formulas farther along in the cascade of solutions get so complicated that they are difficult to interpret. That's one reason why it pays to use a numerical solver, like the ODE Architect. Figure 8.2 shows how the amounts of decongestant in the body change when administered by the on-off method [equation (3)].

☞ ODE Architect to the rescue!

✓ By inspecting Figure 8.2 decide which of the clearance coefficients a or b is larger.

References

Borrelli, R.L., and Coleman, C.S., *Differential Equations: A Modeling Perspective*, (1998: John Wiley & Sons, Inc.)

Spitznagel, E., "Two-Compartment Phamacokinetic Models" in C·ODE·E, Fall, 1992, pp. 2–4, http://www.math.hmc.edu/codee

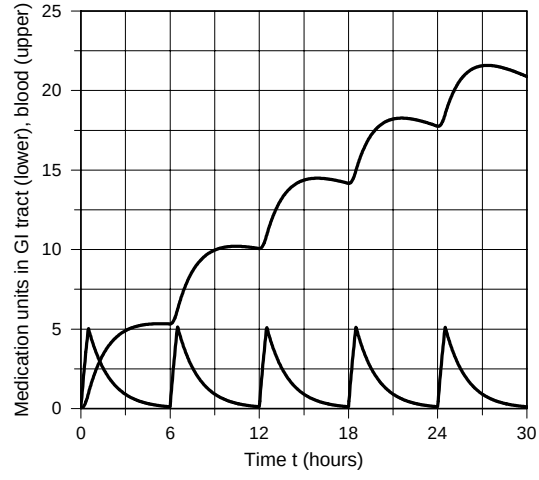
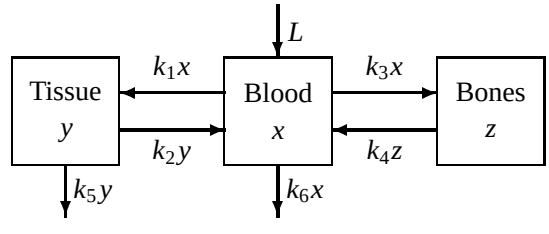


Figure 8.2: Decongestant levels in the GI tract and in the blood.

◆ Lead in the Body

☞ In ancient times lead was used to sweeten wine.

Lead gets into the digestive and respiratory systems of the body via contaminated food, air, and water, as well as lead-based paint, glaze, and crystalware. Lead moves into the bloodstream, which then distributes it to the tissues and bones. From those two body compartments it leaks back into the blood. Lead does the most damage to the brain and nervous system (treated here as tissues). Hair, nails, and perspiration help to clear lead from the tissues, and the kidneys clear lead from the blood. The rate at which lead leaves one compartment and enters another has been experimentally observed to be proportional to the amount that leaves the first compartment. Here is the compartment diagram that illustrates the flow of lead through the body.



In the diagram, L is the inflow rate of lead into the bloodstream (from the lungs and GI tract), x, y, and z are the respective amounts of lead in the blood, tissues, and bones, and $k_1, \ldots, k_6$ are experimentally determined positive rate constants. The amount of lead is measured in micrograms (1 microgram $= 10^{-6}$ gram), and time (t) is measured in days.

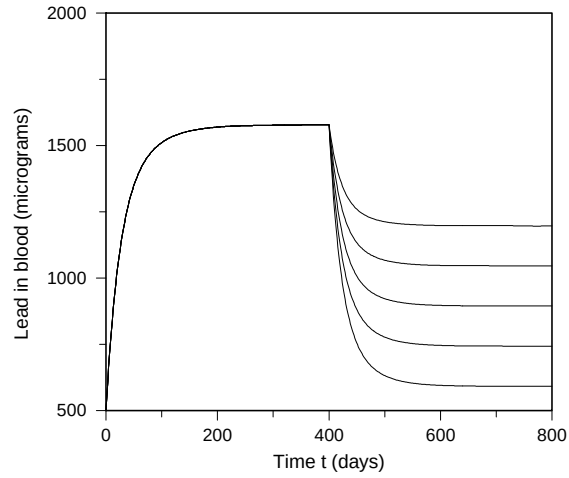


Figure 8.3: Five environmental clean-up scenarios for $t > 400$ days result in five different steady-state lead levels in the blood.

Applying the balance law to each compartment, we have the linear system of ODEs that models the flow of lead through the body compartments:

☞ System (4) is a driven linear system with constant coefficients, so eigenvalue/eigenvector techniques can be used to find solution formulas if L is a constant (see Chapter 6).

$$\begin{aligned} x' &= (L + k_2 y + k_4 z) - (k_1 + k_3 + k_6)x \\ y' &= k_1 x - (k_2 + k_5)y \\ z' &= k_3 x - k_4 z \end{aligned} \tag{4}$$

Unlike the allergy relief system (2), system (4) is not a cascade. Lead moves back and forth between compartments, so the system cannot be solved one ODE at a time. ODE Architect can be used to find $x(t)$, $y(t)$, and $z(t)$ if $x(0)$, $y(0)$, $z(0)$, $L(t)$, and $k_1, \ldots, k_6$ are known.

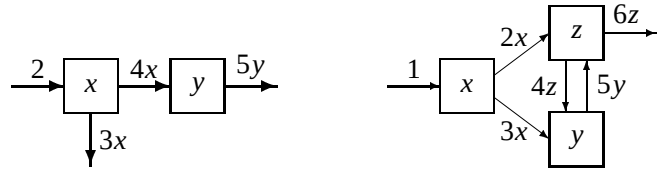
If the goal is to reduce the amount of lead in the blood (and therefore in the tissues and bones), we can clean up the environment (which reduces the inflow rate) or administer a medication that increases the clearance coefficient k_6. However, such medication carries its own risks, so most efforts today are aimed at removing lead from the environment. A major step in this direction was made in the 1970s and '80s when oil companies stopped adding lead to gasoline and paint manufacturers began to use other spreading agents in place of lead. Figure 8.3 shows the effects of changing the lead intake rate L.

☞ It was in the 1970's and '80s that most of the environmental protection laws were enacted.

The Food and Drug Administration and the National Institutes of Health have led the fight against lead pollution in the environment. They base their efforts on data acquired from several controlled studies of lead flow, where the study groups were made up of human volunteers in urban areas. The numbers we use in Submodule 3 of Module 8 and in this chapter come from one of those studies. Some references on the lead problem are listed below.

☞ See Screen 3.3 in Module 8 for the rate constants and the inflow rate L.

✓ Write down the systems of ODEs for the two compartment diagrams:



(a) (b)

References

Batschelet, E., Brand, L., and Steiner, A., "On the kinetics of lead in the human body," *J. Math. Bio.*, **8** (1979), pp. 15–23

Kessel, I., and O'Conner, J., *Getting the Lead Out* (1997: Plenum)

Rabinowitz, M., Wetherill, G., and Kopple, J., "Lead metabolism in the normal human: Stable isotope studies," *Science*, **182** (1973), pp. 725–727.

◆ Equilibrium

In many compartment models, if the inflow rates from outside the system are constant, then the substance levels in each compartment tend to an equilibrium value as time goes on. Mathematically, we can find the equilibrium values by setting each rate equal to zero and solving the resulting system of equations simultaneously. For example, the equilibrium for the system

$$\begin{aligned} x' &= 1 - 2x \\ y' &= 2x - 3y \end{aligned} \tag{5}$$

is $x = 1/2$, $y = 1/3$, which is the solution to the algebraic system $1 - 2x = 0$ and $2x - 3y = 0$. If the system is complicated, you can use ODE Architect to find the equilibrium values. Just use the Equilibrium tabs in the lower left quadrant and in one of the right quadrants, and you will get approximate values for the equilibrium levels.

☞ The Equilibrium tabs in ODE Architect work for systems such as (5), where the rate functions don't depend explicitly on time (i.e., the systems are autonomous).

✓ Go to Things-to-Think-About 2 on Screen 3.5 of Module 8 for the lead flow model with constant values for L and the coefficients k_j. Use the Equilibrium tabs in the tool screen to estimate the equilibrium lead levels in the blood, tissues, and bones for the given data.

☞ You need to know about matrices to tackle this one.

✓ Suppose that x is a column vector with n entries, b is a column vector of n constants, and A is an $n \times n$ invertible matrix of real constants. Can you explain why the linear system $x' = Ax - b$ has a constant equilibrium x^*? Find a formula for x^* in terms of A^{-1} and b.

◆ The Autocatalator and a Hopf Bifurcation

So far the compartments in our models have represented physical spaces through which substances move. However, there are other ways to think about compartments. For example, they can represent substances that transform into one another, such as uranium 238 and all of its seventeen radioactive decay products, ending with stable lead 206. Or think of a chemical reactor in which chemicals react with one another and produce other chemicals. The *autocatalator* is a mathematical model for one of these chemical reactions.

In an *autocatalytic reaction*, a chemical promotes its own production. For example, suppose that one unit of chemical X reacts with two units of chemical Y to produce three units of Y, a net gain of one unit of Y:

$$X + 2Y \xrightarrow{k} 3Y$$

where k is a positive rate constant. This is an example of *autocatalysis*. We'll come back to autocatalysis, but first we need to make a quick survey of how chemical reactions are modeled by ODEs.

Most chemical reactions are *first-order* in the sense that the rate of decay of each chemical in the reaction is directly proportional to its own concentration:

$$\frac{dz}{dt} = -kz \tag{6}$$

where $z(t)$ is the concentration of chemical Z at time t in the reactor and k is a positive rate constant.

While a first-order reaction is modeled by a *linear* ODE, such as (6), autocatalytic reactions are higher-order and the corresponding rate equations are *nonlinear*. In order to build models of higher-order chemical reactions, we will use a basic principle called the *Chemical Law of Mass Action*:

The Chemical Law of Mass Action. If molecules $X_1, \ldots, X_n$ react to produce molecules $Y_1, \ldots, Y_m$ in one step of the chemical reaction

$$X_1 + \cdots + X_n \xrightarrow{k} Y_1 + \cdots + Y_m$$

that occurs with rate constant k, then

$$x_i' = -kx_1x_2\cdots x_n,\ 1 \le i \le n$$
$$y_j' = kx_1x_2\cdots x_n,\ 1 \le j \le m$$

where x_i and y_j are, respectively, the concentrations of X_i and Y_j. The chemical species $X_1, \ldots, X_n, Y_1, \ldots, Y_m$ need not be distinct from each other: more than one molecule of a given type may be involved in the reaction.

For example, the chemical law of mass action applied to the reaction

$$X + Y \xrightarrow{k} Z$$

gives

$$x' = -kxy, \quad y' = -kxy, \quad \text{and} \quad z' = kxy$$

where k is a positive rate constant and $x,\ y,\ z$ denote the respective concentrations of the chemicals $X,\ Y,\ Z$ in the reactor. The autocatalytic reaction

$$X + 2Y \xrightarrow{k} 3Y$$

is modeled by

$$\begin{aligned} x' &= -kxy^2 \\ y' &= -2kxy^2 + 3kxy^2 = kxy^2 \end{aligned}$$

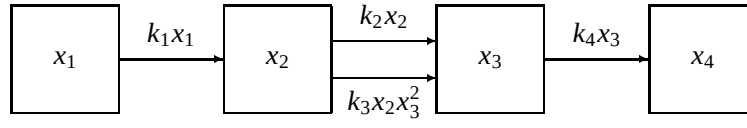
because the rate of decrease of the reactant concentration x is kxy^2 (think of $X + 2Y$ as $X + Y + Y$), the rate of decrease of the reactant concentration y is $2kxy^2$ (because two units of Y are involved), and the rate of increase in the product concentration y is $3kxy^2$ (think of $3Y$ as $Y + Y + Y$).

✓ If you want to speed up the reaction should you increase the rate constant k, or lower it? Any guesses about what would happen if you heat up the reactor? Put the reactor on ice?

With this background, we can model a sequence of reactions that has been studied in recent years:

$$X_1 \xrightarrow{k_1} X_2, \qquad X_2 \xrightarrow{k_2} X_3, \qquad X_2 + 2X_3 \xrightarrow{k_3} 3X_3, \qquad X_3 \xrightarrow{k_4} X_4$$

Note the nonlinear autocatalytic step in the midst of the first-order reactions. A compartment diagram for this reaction is



where x_1, x_2, x_3, and x_4 denote the respective concentrations of the chemicals X_1, X_2, X_3, and X_4. The corresponding ODEs are:

$$\begin{aligned} x_1' &= -k_1x_1 \\ x_2' &= k_1x_1 - (k_2x_2 + k_3x_2x_3^2) \\ x_3' &= (k_2x_2 + k_3x_2x_3^2) - k_4x_3 \\ x_4' &= k_4x_3 \end{aligned} \tag{7}$$

☞ The term $k_3x_2x_3^2$ makes this system nonlinear.

In a reaction like this, we call X_1 the reactant, X_2 and X_3 intermediates, and X_4 the final product of the reaction. For certain ranges of values for the rate constants $k_1,\ k_2,\ k_3,\ k_4$ and for the inital reactant concentration $x_1(0)$, the

☞ See Screen 4.3 of Module 8 for values of the rate constants.

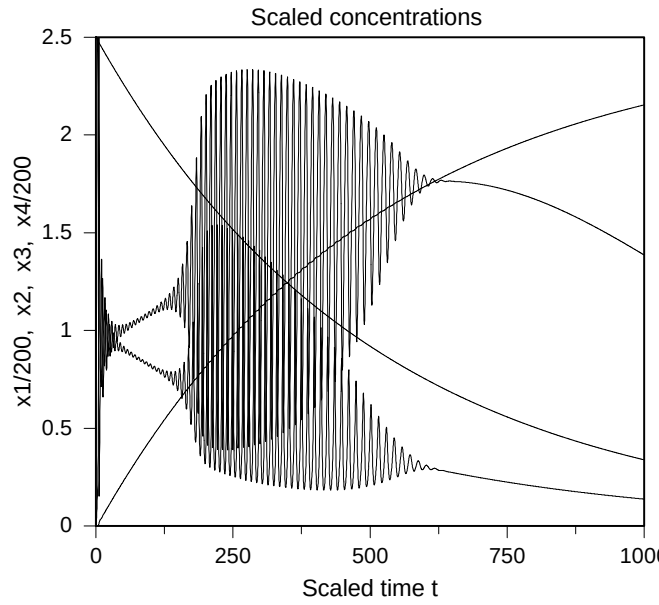


Figure 8.4: As the reactant falls into the Hopf bifurcation zone, the oscillations of the intermediates turn on as the product rises. Later the oscillations turn off and the reaction approaches completion.

☞ The chapter cover figure shows how the intermediate concentrations $x_2(t)$ and $x_3(t)$ play off against each other as time increases.

intermediate concentrations $x_2(t)$ and $x_3(t)$ will suddenly begin to oscillate. These oscillations eventually stop and the intermediates decay into the final reaction product. See Figure 8.4.

The onset of these oscillations is a kind of a *Hopf bifurcation* for $x_2(t)$ and $x_3(t)$. In this context, if we keep the value of x_1 fixed at, say x_1^*, the rate term $k_1 x_1^*$ in system (7) can be viewed as a parameter c. Then the middle two rate equations can be decoupled from the other two:

$$\begin{aligned} x_2' &= c - k_2 x_2 - k_3 x_2 x_3^2 \\ x_3' &= k_2 x_2 + k_3 x_2 x_3^2 - k_4 x_3 \end{aligned} \tag{8}$$

Now let's fix k_2, k_3, and k_4 and use the parameter c to turn the oscillations in $x_2(t)$ and $x_3(t)$ on and off. This is the setting for a *Hopf bifurcation*, so let's take a detour and explain what that is.

As a parameter transits a bifurcation value the behavior of the state variables suddenly changes. A Hopf bifurcation is a particular example of this kind of behavioral change. Suppose that we have a system that involves a parameter c,

$$\begin{aligned} x' &= f(x, y, c) \\ y' &= g(x, y, c) \end{aligned} \tag{9}$$

and that has an equilibrium point P at $x = a$, $y = b$ [so that $f(a, b, c) = 0$

and $g(a, b, c) = 0$]. Suppose that the matrix of partial derivatives

☞ This is the Jacobian matrix of system (9). See Chapter 6.

$$J = \begin{bmatrix} \dfrac{\partial f}{\partial x} & \dfrac{\partial f}{\partial y} \\ \dfrac{\partial g}{\partial x} & \dfrac{\partial g}{\partial y} \end{bmatrix}_{x=a, y=b}$$

has the complex conjugate eigenvalues $\alpha(c) \pm i\,\beta(c)$. The Dutch mathematician Eberhard Hopf showed that *if*:

☞ The Hopf conditions.

(a) the functions f and g are twice differentiable,
(b) P is a stable, attracting sink for some value c_0 of the parameter c,
(c) $\alpha(c_0) = 0$,
(d) $[d\alpha/dc]_{c=c_0} \neq 0$,
(e) $\beta(c_0) \neq 0$,

☞ Since $\alpha'(c_0) \neq 0$, $\alpha(c)$ changes sign as c goes through c_0; this means that P goes from a sink to a source, or the other way around.

then as the parameter c varies through the bifurcation value c_0, the attracting equilibrium point P destabilizes and an attracting limit cycle appears (i.e., an attracting periodic orbit in the xy-phase plane) that grows in amplitude as c changes beyond the value c_0.

It isn't always a simple matter to check the conditions for a Hopf bifurcation (especially condition (b)). It is often easier just to apply the Architect to the system and watch what happens to solution curves and trajectories when a parameter is swept over a range of values. For instance, for system (8) with values $k_2 = 0.08$ and $k_3 = k_4 = 1$ for the rate constants, we can sweep the parameter c and observe the results. In particular, we want to find values of c for which an attracting limit cycle is either spawned by P, or absorbed by P. At and near the special c values we can use the Equilibrium feature of the ODE Architect tool to locate the equilibrium point, calculate the Jacobian matrix, and find its eigenvalues. We expect the eigenvalues to be complex conjugates and the real part to change sign at the bifurcation value of c.

Figure 8.5 shows a sweep of twenty-one trajectories of system (8) with c sweeping down from 1.1 to 0.1 and the values of k_1, k_2, and k_3 as indicated in the figure. See also Problem 3, Exploration 8.4.

✓ (This is the first part of Problem 3 of Exploration 8.4.) Use ODE Architect to duplicate Figure 8.5. Animate (the right icon under Tools on the top menu bar) so that you can see how the trajectories change as c moves downward from 1.1. Then use the Explore feature to determine which values of c spawn or absorb a limit cycle. For what range of values of c does an attracting limit cycle exist?

This behavior of the system (8) carries over to the autocatalator system (7). Notice that the first equation in (7) is $x_1' = -k_1 x_1$, which is easily solved to give $x_1(t) = x_1(0)e^{-k_1 t}$. If k_1 is very small, say $k_1 = 0.002$, the exponential decay of x_1 is very slow, so that if $x_1(0) = 500$, the term $k_1 x_1(t)$,

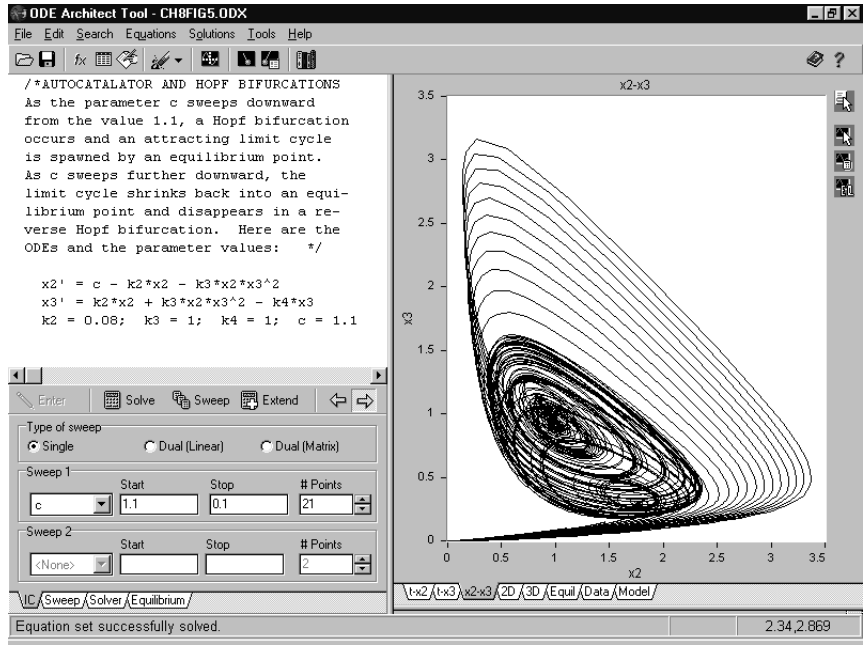


Figure 8.5: Twenty-one trajectories of system (8) for twenty-one values of c; initial data is $x_2(0) = x_3(0) = 0$, time interval is 100 with 1000 points.

though not constant, has values between 1 and 0.01 for a long time interval. The behavior of the autocatalator will be similar to that of system (8).

The section "Bifurcations to a Limit Cycle" in Chapter 7 gives another instance of a Hopf bifurcation. For more on bifurcations, see the references.

References

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Hubbard, J.H., and West, B.H., *Differential Equations: A Dynamical Systems Approach, Part II: Higher Dimensional Systems*, (1995: Springer-Verlag)

Scott, S.K., *Chemical Chaos* (1991: Oxford Univ. Press)

Answer questions in the space provided, or on attached sheets with carefully labeled graphs. A notepad report using the Architect is OK, too.

Name/Date _____

Course/Section _____

Exploration 8.1. Tracking Pollution in a Lake

1. Suppose that the water flow rates into and out of a lake are $s_{\text{in}} = s_{\text{out}} = 10^9$ m^3/yr. The (constant) lake volume is $V = 10^{10}$ m^3, and the concentration of pollutant in the water flowing into the lake is $p_{\text{in}} = 0.0003$ lb/m^3. Solve the IVP with $L(0) = 0$ (no initial pollution) and describe in words how pollution builds up in the lake. Estimate the steady-state amount of pollution, and estimate the amount of time for the pollution level to increase to half of the asymptotic level.

2. Suppose that the lake in Problem 1 reaches its steady-state level of pollution, and then the source of pollution is removed. Build a new IVP for this situation, and estimate how much time it will take for the lake to clear out 50% of the pollution. How does this time compare to the time you estimated in Problem 1 for the build-up of pollutant?

3. What would be more effective in controlling pollution in the lake: (**i**) reducing the concentration of pollutant in the inflow stream by 50%, (**ii**) reducing the rate of flow of polluted water into the lake by 50%, or (**iii**) increasing the outflow rate from the lake by 50%?

Answer questions in the space provided, or on attached sheets with carefully labeled graphs. A notepad report using the Architect is OK, too.

Name/Date _____

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Exploration 8.2. What Happens When You Take a Medication?

1. Go to the Library in ODE Architect and check out the file "Cold Pills I: A Model for the Flow of a Single Dose of Medication in the Body" in the folder "Biological Models." This model tracks a unit dose of medication as it moves from the GI tract into the blood and is then cleared from the blood. Read the file and carry out the explorations suggested there. Record your results below.

2. Go to the Library in ODE Architect and check out "Cold Pills II: A Model for the Flow of Medication with Periodic Dosage" in the folder "Biological Models." Carry out the suggested explorations.

3. Suppose you take a decongestant pill every four hours to relieve the symptoms of a cold. Each pill dissolves slowly and completely over the four-hour period between doses, releasing 16 units of decongestant at a constant rate. The decongestant diffuses from the GI tract into the bloodstream at a rate proportional to the amount in the GI tract (rate constant is $a = 0.5/$ hr) and is cleared from the bloodstream at a rate proportional to the amount in the blood (rate constant is $b = 0.1/$ hr). Assume that initially there is no decongestant in the body. Write a report in which you address the following points. Be sure to attach graphs.

(a) Write out ODEs for the amounts $x(t)$ and $y(t)$ in the GI tract and the blood, respectively, at time t.

(b) Find explicit formulas for $x(t)$ and $y(t)$ in terms of $x(0)$ and $y(0)$.

(c) Use ODE Architect to plot $x(t)$ and $y(t)$ for $0 \leq t \leq 100$ hr. What are the equilibrium levels of decongestant in the GI tract and in the blood (assuming that you continue to follow the same dosage regimen)?

(d) Graph $x(t)$ and $y(t)$ as given by the formulas you found in part (b) and overlay these graphs on those produced by ODE Architect. What are the differences?

(e) Imagine that you are an experimental pharmacologist for Get Well Pharmaceuticals. Set lower and upper bounds for decongestant in the bloodstream, bounds that will assure both effectiveness and safety. How long does it take from the time a patient starts taking the medication before the decongestant is effective? How long if you double the initial dosage (the "loading dose")? How about a triple loading dose?

(f) For the old or the chronically ill, the clearance rate constant from the blood may be much lower than the average rate for a random sample of people (because the kidneys don't function as well). Explore this situation and make a recommendation about lowering the dosage.

4. Repeat all of Problem 3 but assume the capsule is rapidly dissolving: it delivers the decongestant at a constant rate to the GI tract in just half an hour, then the dosage is repeated four hours later.

Answer questions in the space provided, or on attached sheets with carefully labeled graphs. A notepad report using the Architect is OK, too.

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Exploration 8.3. Get the Lead Out

1. Check out the ODE Architect Library file "A Model for Lead in the Body" in the "Biological Models" folder and carry out the explorations suggested there. (The notation for the rate constants in the library file differs from the notation used in this chapter.)

2. Use the following rate constants: $k_1 = 0.0039,\ k_2 = 0.0111,\ k_3 = 0.0124,\ k_4 = 0.0162,\ k_5 = 0.000035,\ k_6 = 0.0211$, and put $L = 49.3\ \mu$g/day in the lead system (4). These values were derived directly from experiments with volunteer human subjects living in Los Angeles in the early 1970s. Using the data for the lead flow model, describe what happens if the lead inflow rate L is doubled, halved, or multiplied by a constant α. Illustrate your conclusions by using the ODE Architect to graph the lead levels in each of the three body compartments as functions of t. Do the long-term lead levels (i.e., the equilibrium levels) depend on the initial values? On L? Find the equilibrium levels for each of your values of L using ODE Architect. Find the eigenvalues of the Jacobian matrix for each of your values of L. With the names given in Chapter 6 to equilibrium points in mind, would you call the equilibrium lead levels sinks or sources? Nodes, spirals, centers, or saddles?

3. The bones act as a lead storage system, as you can see from the graphs in Submodule 3 of Module 8. What happens if the exit rate constant k_4 from the bones back into the blood is increased from 0.000035 to 0.00035? To 0.0035? Why might an increase in k_4 be harmful? See Problem 2 for the values of L and the rate constants k_i.

4. The medication now in use for acute lead poisoning works by improving the efficiency of the kidneys in clearing lead from the blood (i.e., it increases the value of the rate constant k_6). What if a medication were developed that increased the clearance coefficient k_5 from the tissues? Explore this possibility. See Problem 2 for the values of L and the rate constants k_i.

5. In the 1970s and '80s, special efforts were made to decrease the amount of lead in the environment because of newly enacted laws. Do you think this was a good decision, or do you think it would have been better to direct the efforts toward the development of a better antilead medication for cases of lead poisoning? Why? What factors are involved in making such a decision?

Answer questions in the space provided, or on attached sheets with carefully labeled graphs. A notepad report using the Architect is OK, too.

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Exploration 8.4. Chemical Reactions: the Autocatalator

1. Check out "The Autocatalator Reaction" in the "Chemical Models" folder in the ODE Architect Library and graph the concentrations suggested. Describe how the concentrations of the various chemical species change in time.

2. Here are schematics for chemical reactions. Draw a compartment diagram for each reaction. Then write out the corresponding sets of ODEs for the individual chemical concentrations. [Use lower case letters for the concentrations (e.g., $x(t)$ for the concentration of chemical X at time t).]

(a) $X + Y \xrightarrow{k} Z$

(b) $X + Y \xrightarrow{k_1} Z \xrightarrow{k_2} W$

(c) $X + 2Y \xrightarrow{k} Z$

(d) $X + 2Y \xrightarrow{k} 3Y + Z$

3. Explore the behavior of $x_2(t)$ and $x_3(t)$ as governed by system (8). Start with $c = 1.1$, $k_2 = 0.08$, $k_3 = k_4 = 1$, and $x(0) = y(0) = 0$. Then sweep c from 1.1 down to 0.1 and describe what happens to orbits in the x_2x_3-plane. Find the range of values of c between 1.1 and 0.1 for which attracting limit cycles are visible. These are Hopf cycles. Fix c at a value that you think is interesting and sweep one the parameters k_2, k_3, or k_4. Describe what you observe. [*Suggestion:* Take a look at Figure 8.5, use the Animate feature of ODE Architect to scroll through the sweep trajectories. Then use the Explore option to get a data table with information about any of the trajectories you have selected.]

4. Look at the autocatalator system (7) with $x_1(0) = 500$, $x_2(0) = x_3(0) = x_4(0) = 0$ and $k_1 = 0.002$, $k_2 = 0.08$, $k_3 = k_4 = 1$. Graph $x_2(t)$ and $x_3(t)$ over various time ranges and estimate the times when sustained oscillations begin and when they finally stop. What are the time intervals between successive maxima of the oscillations in x_2? Plot a 3D tx_2x_3-graph over various time intervals ranging from $t = 100$ to $t = 1000$. Describe what you see. [*Suggestion:* Look at the chapter cover figure and Figure 8.4.]

☞ Use the Explore feature to estimate the starting and stopping times of the oscillator.

Now sweep the values of $x_1(0)$ downward from 500. What is the minimal value that generates sustained oscillations? Then fix $x_1(0)$ at 500 and try to turn the oscillations off by changing one or more of the rate constants k_1, k_2, k_3, k_4—this corresponds to heating or chilling the reactor. Describe your results.