

A brief overview of modeling with ordinary differential equations for life scientists for the National Program of Excellence in Biomedical Computing Seminars

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1 Some Philosophy

Since this is the first of the National Program of Excellence in Biomedical Computing cross-training seminars, it seemed appropriate to take a little time to explain two of the things mathematics and computation can do for the life sciences.

The first of the two uses is a bit more grand than the second. Modeling can help us organize our knowledge. By accounting for what appear to be separate phenomena in a single model, we are often able to find a unifying approach or idea that ties several apparently distinct observations together as aspects of a single process. In this case, modeling can assist in creating an over arching intellectual framework into which a variety of experimental outcomes may be placed in context.

The second use is somewhat easier to come to and more direct. By developing models for separate phenomena, these distinct models can be used to develop more complex models of situations where the separate phenomena are occurring in a single environment. Such predictive models can point the way toward new experimental goals. Indeed, ideally, modeling and experimentation play off of each other with models being continually revised on the basis of experimental insight and experimentation driven, in part, by predictions made by models. In fact, modeling can reduce the amount of needed experimentation as follows. If a scientist has a theory of why certain results are observed in the laboratory and an accurate model can be developed of the theory, simulations can be conducted to see if the theory is plausible.

Modeling tools include ordinary and partial differential equations, difference equations, integral equations, and numerous other examples. Beyond using computational power to approximate solutions of the models and thus simulate

the phenomenon being modeled, mathematical analysis can give general insight as to what is expected in solutions to the models, including long term behavior over time.

In the end, the test of a model is in the laboratory. Does the model predict the outcome of novel experiments and account for all observations? Even when the answer is yes, the model remains tentative, always up for review in the light of new facts.

It is worth noting at this point that models often require physical or biological rates as parameters. When these rates can be computed ab initio, well and good. Unfortunately, most of the time, finding these parameters requires the use of the model in combination with experimental data. This can be a challenge and is an active area of research. If we work with models that are too complex for the stage of parameter identification, we can end up with the ability to fit any given data set, without gaining any insight. Thus our goal must always be to develop models for the simplest phenomena first, identify the relevant parameters, and then attempt to use these simple models as building blocks in our understanding of larger phenomena.

2 The derivative as a rate of change

One of the major advances calculus made as a tool for describing the natural world was its ability to describe quantities that change with respect to other quantities. Consider the following situation: Let $c(t)$ be the concentration of a chemical in a reactor at time t . We assume that the reactor is well mixed so that the concentration does not vary from point to point. For now we assume that c is measured in milligrams per milliliter and that time is measured in seconds. **(Ignoring units is a good way to mess up! It is always important to keep track of units.)**

What do we mean by the rate of change in c ? Let us assume that we take two measurements of c ; the first at a time t_0 and the second after some small amount of time, Δt . We will get two concentration measurements, $c(t_0)$ and $c(t_0 + \Delta t)$. We get the *average rate of change in c* between time t_0 and time $t_0 + \Delta t$ as

$$\frac{c(t_0 + \Delta t) - c(t_0)}{\Delta t}$$

in units of milligrams per milliliter-second or $\frac{mg}{ml \cdot s}$. If we have that the concentration is changing at a constant rate, this constant rate will be the same as the average rate of change.

Example 1 *Let us say that we have a vat with 100 ml of water in it. At time $t = 0$, we assume that the concentration of salt in the vat is $.1 \frac{mg}{ml}$. Now assume that we start to add one milligram of salt every second. Then we are increasing our concentration by $\frac{1}{100} \frac{mg}{ml} = .01 \frac{mg}{ml}$ every second. Thus, the concentration at time t is $c(t) = .1 + .01t$. Between any times t_0 and $t_0 + \Delta t$, the average rate of*

change in concentration is

$$\begin{aligned}\frac{c(t_0 + \Delta t) - c(t_0)}{\Delta t} &= \frac{.1 + .01t_0 - (.1 + .01(t_0 + \Delta t))}{\Delta t} \\ &= \frac{.01\Delta t}{\Delta t} \\ &= .01.\end{aligned}$$

When we have a constant rate of change, we always have a fixed average rate of change equal to the constant rate of change.

Now we can not always expect constant rates of change. We generalize the idea of the average rate of change with the instantaneous rate of change or **derivative**. If we wish to know at what rate the concentration c is changing at a particular time t_0 , it makes sense to expect that the rate of change in c at t_0 will be close to the average rate of change between t_0 and $t_0 + \Delta t$ for very small Δt . That is,

$$\text{the rate of change in } c \text{ at } t_0 \approx \frac{c(t_0 + \Delta t) - c(t_0)}{\Delta t} \text{ for very small } \Delta t.$$

This is not the proper place for a formal definition of the derivative. (You should read the section of a standard calculus book to refresh your memory.) Intuitively, the derivative of c at t_0 , denoted $c'(t_0)$ or $\frac{dc}{dt}(t_0)$, is the number that the average rate of change gets arbitrarily close to as Δt gets closer and closer to 0. More formally,

$$c'(t_0) = \frac{dc}{dt}(t_0) = \lim_{\Delta t \rightarrow 0} \frac{c(t_0 + \Delta t) - c(t_0)}{\Delta t},$$

which is read “the derivative of c at t_0 with respect to t is the limit as Δt approaches 0 of the average rate of change in c between t_0 and $t_0 + \Delta t$.”

Example 2 Suppose that the concentration of a contaminant is given by $c(t) = 3t^2$, where the 3 has units of $\frac{\text{mg}}{\text{ml}\cdot\text{sec}^2}$. The average rate of change is given by

$$\begin{aligned}\frac{c(t_0 + \Delta t) - c(t_0)}{\Delta t} &= \frac{3(t_0 + \Delta t)^2 - 3t_0^2}{\Delta t} \\ &= \frac{3t_0^2 + 3(\Delta t)^2 + 6t_0\Delta t - 3t_0^2}{\Delta t} \\ &= 3\Delta t + 6t_0\end{aligned}$$

Letting Δt approach 0, we obtain

$$c'(t_0) = 6t_0$$

One further point on this matter. We have discussed finding the derivative or instantaneous rate of change in a function; for us, a function representing concentration. Notice that we can define a new function so that given a function $c(t)$, the new function will return the derivative of c at each t . Thus, for the last example, the function would be $c'(t) = 6t$.

So far, we have discussed variations in concentration over time. In fact, concentration can vary over space as well. Consider a core sample with constant cross section A taken from a remediation site. Let x represent the position in the core sample that is x centimeters from the end of the sample. Then we make use of the *continuum assumption* that we can define the density of a contaminant at each point x . We assume that for each x less than the overall length of the sample, the limit of

$$\frac{\text{total mass of contaminant between } x - \Delta x \text{ and } x + \Delta x}{2\Delta x A}$$

as Δx approaches 0 exists. The limit will be $c(x)$, the density or concentration of the contaminant present at point x in milligrams per cubic centimeter.

As in the case where our concentration depended on time, we can ask about the average rate of change in the concentration over space. That is, we can ask at what rate is the concentration changing in space between a point x_0 and a point $x_0 + \Delta x$. Analogous to our approach above, we obtain

$$\frac{c(x_0 + \Delta x) - c(x_0)}{\Delta x}.$$

Letting the Δx approach 0, we obtain the instantaneous rate of change or concentration gradient $c'(x_0)$. Again, we can define a function that returns the concentration gradient at any given x , $c'(x)$.

In this note, we will only deal with quantities that depend on one variable. To model quantities that vary in several variables would bring us to the topic of partial differential equations, which is the topic of a later seminar. In fact, we will restrict our attention to quantities that vary with time. However, we will find it necessary to consider the behavior of several quantities that depend on time.

3 Two examples of linear problems: The phase line and the phase plane

(Parts of this section are lifted almost directly from [10].)

We want to use derivatives to describe physical phenomena. So we begin with a simple example that leads to a single ordinary differential equation.

Let us consider a chemical compound that is disappearing spontaneously from an aqueous solution with probability $P > 0$ in any given second. We assume we have a whole macroscopic sample with mass M grams. The mass of the sample will be proportional to the number of particles in the sample.

Let us also assume we can measure the mass at time t seconds to get the mass measurement of $M(t)$. We expect that in a given second, the rate at which the mass is decaying is given by $pM(t)$ with units gs^{-1} of where $p = Ps^{-1}$. Now we can also write the rate of change in the mass as $\frac{dM}{dt}$. Thus we end up with a differential equation

$$\frac{dM}{dt} = -pM \quad (1)$$

where the minus sign indicates disappearance.

Before attempting a solution to (1) we can get information on the process by looking at a phase line for this equation. The phase line is simply a number line provided with arrows to indicate in what direction a point will move. See figure 1:

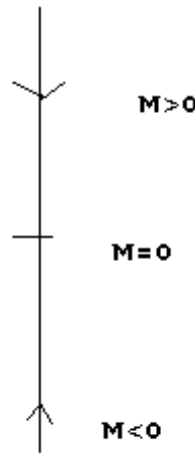


Figure 1. Phase line for equation (1)

The point $M = 0$ is called a stationary or equilibrium point. If $M = 0$, there will be no change over time. Notice that $M = 0$ is the value for M which makes $\frac{dM}{dt} = 0$. For $M > 0$, the arrow points down, because when we have a positive mass of material, the mass will decrease over time. The up arrow for $M < 0$ is a mathematical artifact because we can have no negative mass. Mathematically, it states if there were such a thing as negative mass, it would tend to become less negative over time. By mathematical artifact here, we mean a fact about the mathematical model that does not relate to the physical system we are trying to model.

Notice that all of the arrows point toward $M = 0$; this means that 0 is an attracting equilibrium point or sink.

We can approach this problem analytically and obtain

$$M(T) = M_0 e^{-pt} \quad (2)$$

where $M_0 = M(0)$. Notice that the analytic solution does exactly what the phase line diagram says it should; go to $M = 0$. If we could not find an analytic solution, we could do a numerical approximation, although we might lose our understanding of the long-term behavior of the system.

In another numerical example, let us assume we are adding mass at the rate of $a \text{ gs}^{-1}$. Our rate of change is now the loss $pM(t)$ of plus a . This gives us a differential equation of

$$\frac{dM}{dt} = -pM + a \quad (3)$$

What are our equilibrium points? We obtain these by solving the problem $\frac{dM}{dt} = 0$, or $-pM + a = 0$, or $M = \frac{a}{p}$. When $M > \frac{a}{p}$, we will get $\frac{dM}{dt} < 0$, and when $M < \frac{a}{p}$, we will get $\frac{dM}{dt} > 0$ as is reflected in the phase line. See figure 2.

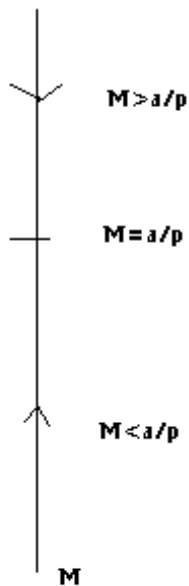


Figure 2. Phase line for equation 3.

Here we have no physical problems with $M < \frac{a}{p}$ and we see that no matter what mass of material we start with, in the long run we tend toward an equilibrium of $M = \frac{a}{p}$. We note that we can draw the phase line for the mass in

this manner because the "right hand side" of (3) does not depend explicitly on t , i.e., the equation is autonomous.

It happens that we can also find an analytic solution to the above problem using

$$M(t) = \frac{a}{p} (1 - e^{-pt}) + M_0 e^{-pt} \quad (4)$$

but we have a great deal of information using only the phase line.

It is worthwhile to consider how an experiment's data would normally be presented. For this purpose, we will take $a = 2$ and $p = 1$. In Figure 3, the graph is a plot of mass versus time with a starting mass of $M_0 = 3.5$.

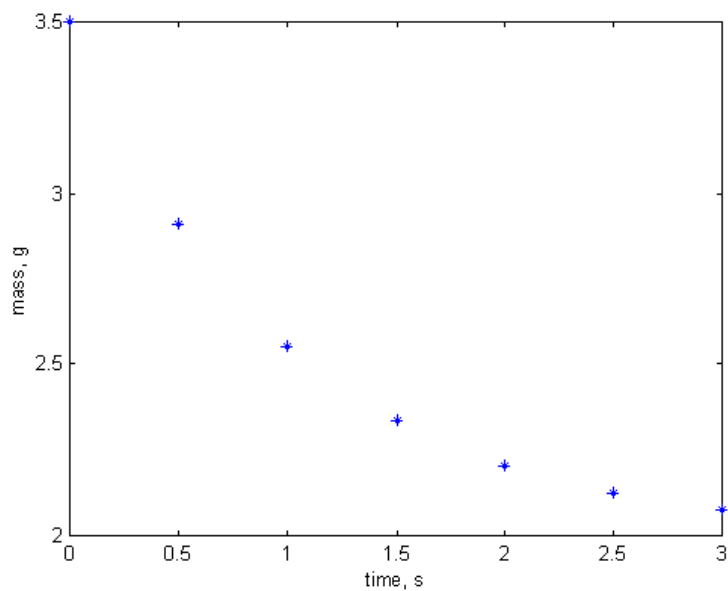


Figure 3. Equation 4, with $M_0 = 3.5$

In Figure 4, the graph is a plot of mass versus time with a starting mass of

$M_0 = 0.5$ for equation (4).

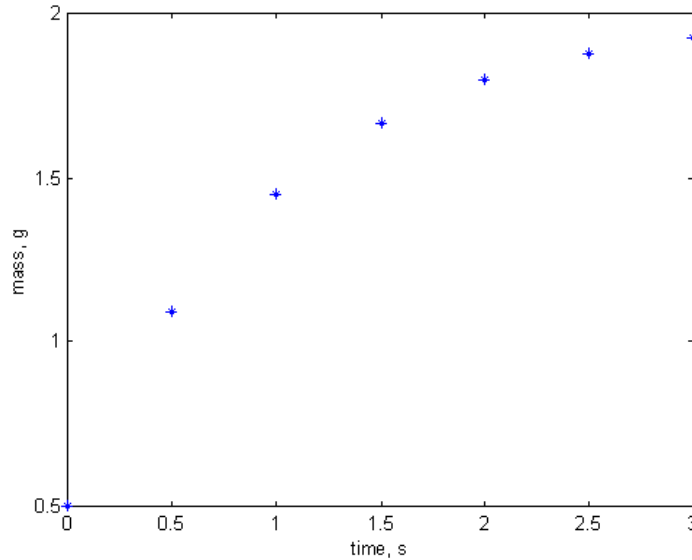


Figure 4. Equation 4 with $M_0 = .5$.

Looking at the two figures, we can see what is going on in terms of an approach to an equilibrium, but not as easily as when we use the phase line.

We wish to look at models where more than one quantity is changing with time. For instance, if we are modeling chemotherapy for cancer, we might wish to model the level of the drug in the blood stream, the mass of the tumor we are trying to kill, and the mass of the bone marrow we do not wish to kill. Our goal is to develop something like a phase line for this case. However, three dimensions are as high as we can expect to go, and beyond what we will discuss in this talk. However, we will look at the two dimensional case, the phase plane. The general (autonomous) two dimensional example, with quantities x and y is

$$\begin{aligned}\frac{dx}{dt} &= f(x, y) \\ \frac{dy}{dt} &= g(x, y) \\ x(0) &= x_0 \\ y(0) &= y_0.\end{aligned}$$

It turns out that when (x_0, y_0) is close to a stationary point, a point (\bar{x}, \bar{y}) such

that $f(\bar{x}, \bar{y}) = g(\bar{x}, \bar{y}) = 0$, we can often study the related linear problem

$$\begin{aligned}\frac{dx}{dt} &= ax + by \\ \frac{dy}{dt} &= cx + dx \\ x(0) &= x_0 - \bar{x} \\ y(0) &= y_0 - \bar{y}.\end{aligned}$$

(It is beyond the scope of this talk, but for those interested $a = \frac{\partial f}{\partial x}(\bar{x}, \bar{y})$, $b = \frac{\partial f}{\partial y}(\bar{x}, \bar{y})$, $c = \frac{\partial g}{\partial x}(\bar{x}, \bar{y})$, and $d = \frac{\partial g}{\partial y}(\bar{x}, \bar{y})$.) This can be written in matrix form as

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{X}$$

where

$$\mathbf{A} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

and

$$\mathbf{X} = \begin{bmatrix} x \\ y \end{bmatrix},$$

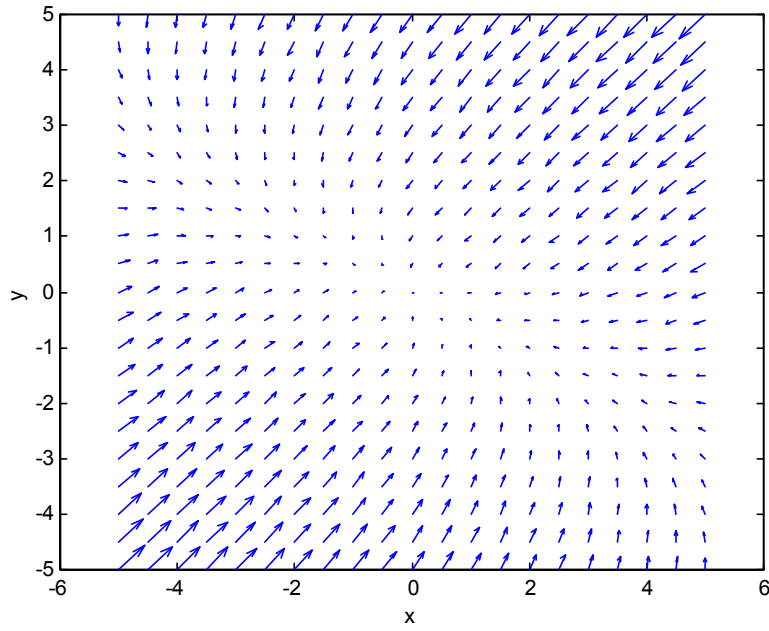
a vector differential equation. The important thing to understand is that the behavior of solutions to this problem close to $(0, 0)$ is completely determined by the eigenvalues of the matrix \mathbf{A} . (Notice that for the linear problem, $(0, 0)$ is the only stationary point.) Thus the behavior of solutions to the original problem is also completely determined by the eigenvalues of the matrix \mathbf{A} when (x_0, y_0) is close to the stationary point (\bar{x}, \bar{y}) . The interesting thing to note is that the same ideas hold true in more than two dimensions.

Here are some examples. For

$$\mathbf{A} = \begin{bmatrix} -2 & -2 \\ -1 & -3 \end{bmatrix}$$

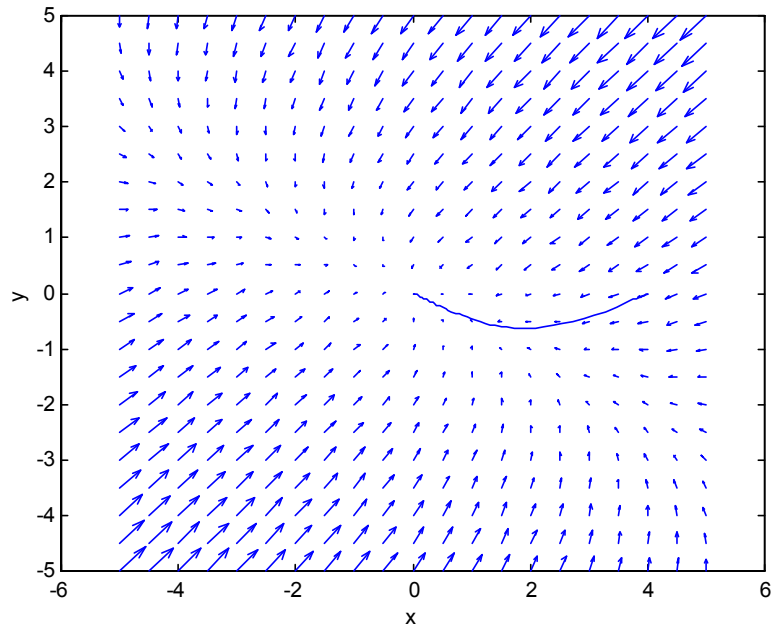
the eigenvalues are -1 and -4. As in the case of the phase line, we can plot what

direction a point would move in the xy -plane. This is called a direction field.



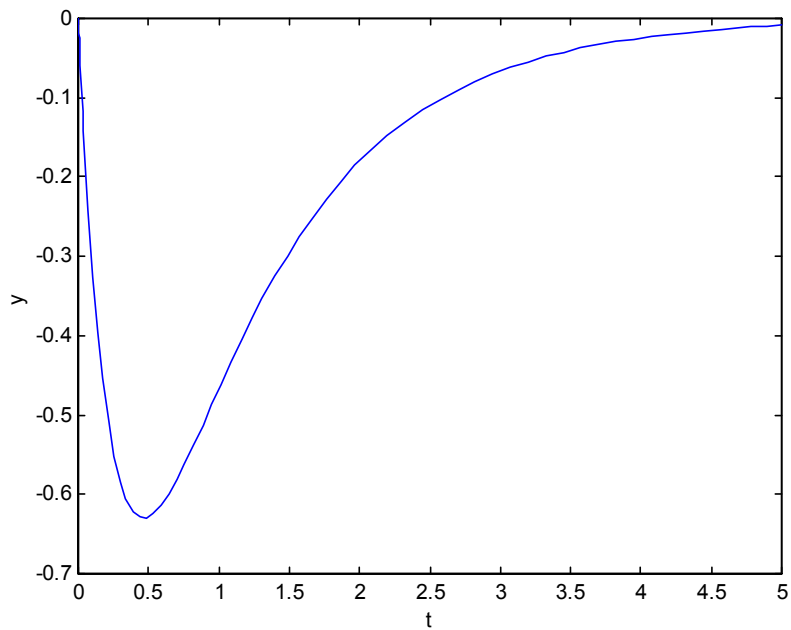
To see how this works for a specific starting value, we choose a starting point

of $(4, 0.5)$.



We see that both x and y seem to be tending towards 0. In fact, a mathematical

analysis will guarantee this. We can plot y against t to see as well.

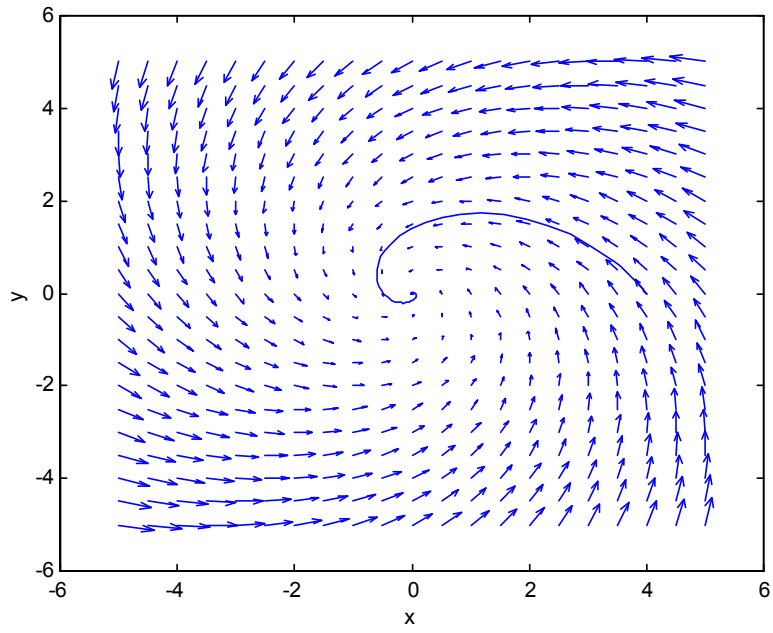


More complex behavior may be seen if the eigenvalues are complex. Here is another example. Let

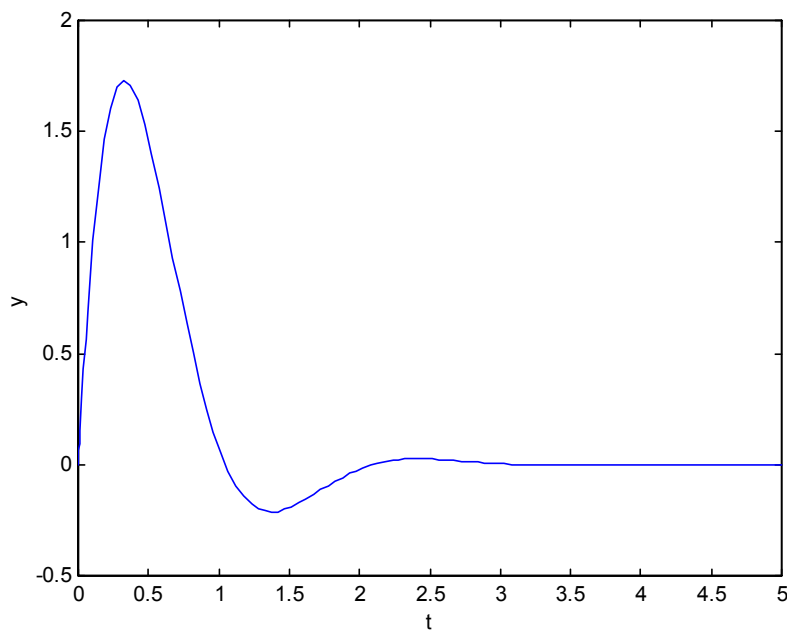
$$\mathbf{A} = \begin{bmatrix} -2 & -3 \\ 3 & -2 \end{bmatrix}.$$

This matrix has eigenvalues $-2 + 3i$ and $-2 - 3i$. The fact that the imaginary parts are nonzero indicates that we can expect to see oscillatory behavior. The fact that the real parts are all negative indicates that solutions will tend to 0 as time increases. Here is what the direction field looks like with a solution

starting at $(4, 0.5)$.



We can also plot y against time again



and see some indication of the oscillatory behavior.

Much deeper and informative analysis of ordinary differential equations models is possible. We have only skimmed some of the surface. Obviously, the problems become more interesting as the number of time varying quantities we are studying increases. Unmentioned so far is the use of computers in our work of analyzing such models. Suffice it to say that in-so-far as simulations and parameter identification go, without modern computational tools, we would be up the proverbial creek. I will note, that although exact solutions can be found for the two examples we looked at above, a numerical routine was used to approximate the solutions for the purpose of graphing them.

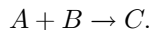
4 Examples

For the remainder of this talk, we will build and briefly discuss several ordinary differential equations models arising in biology.

4.1 Example 1: Law of mass action and chemical kinetics

We start with a model of chemical kinetics. Consider a well mixed solution in which there are two chemical species, A and B . The molarity of A will be denoted by $[A]$. Similarly, we denote the molarity of B by $[B]$. We assume

that the reaction is



That is, one molecule of A and one molecule of B join to form one molecule of a product C . The question we must ask is, at what rate, in molarity per unit time, does this reaction take place? It is reasonable to suppose that, in a given period of time, the number of reactions that takes place is proportional to the number of time a molecule of A is sufficiently close to a molecule of B . Along with this assumption, we would expect that if we hold the number of molecules of A fixed and double the number of molecules of B present, then the number of interactions between molecules of A and molecules of B would double. We expect a similar outcome if the roles of A and B are switched. Thus we would expect the rate of reaction to be proportional to both the molarity of A and the molarity of B . This gives that the rate is proportional to $[A][B]$. If we call the constant of proportionality k , we get the system of equations

$$\frac{d[A]}{dt} = -k[A][B]$$

$$\frac{d[B]}{dt} = -k[A][B]$$

$$\frac{d[C]}{dt} = k[A][B].$$

This approach to modeling the chemical kinetics is called the law of mass action. We start with it because we can show how this particular model works with real data.

Notice that as long as we are not actually interested in C we may ignore the third equation.

We have used this approach, along with a new modeling approach in studying the inhibition of cholinesterase (ChE) by organophosphorus insecticides (OP's). Using data from experiments where we used only one OP, we identified rate constants for separate OP's in two by two systems

$$\frac{d[C]}{dt} = -k_j[X_j][C]$$

$$\frac{d[X_j]}{dt} = -k_j[X_j][C]$$

where here C represents ChE and X_j represents the j^{th} OP. We can write down an explicit solution to this model. Using these separately identified rate constants, k_j , and the model, we were able to accurately predict the results of applying interactions between ChE and two different OP's. In this case the

model looks like

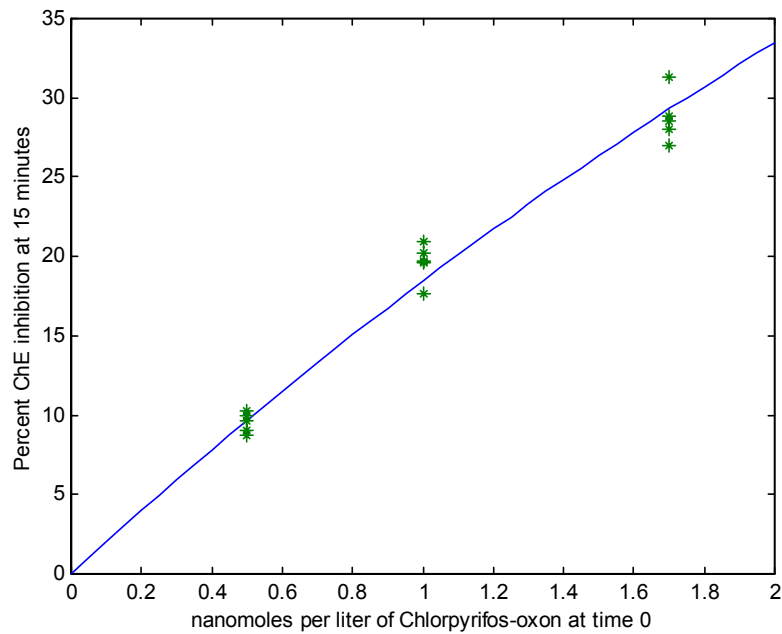
$$\frac{d[C]}{dt} = -k_j [X_j] [C] - k_i [X_i] [C]$$

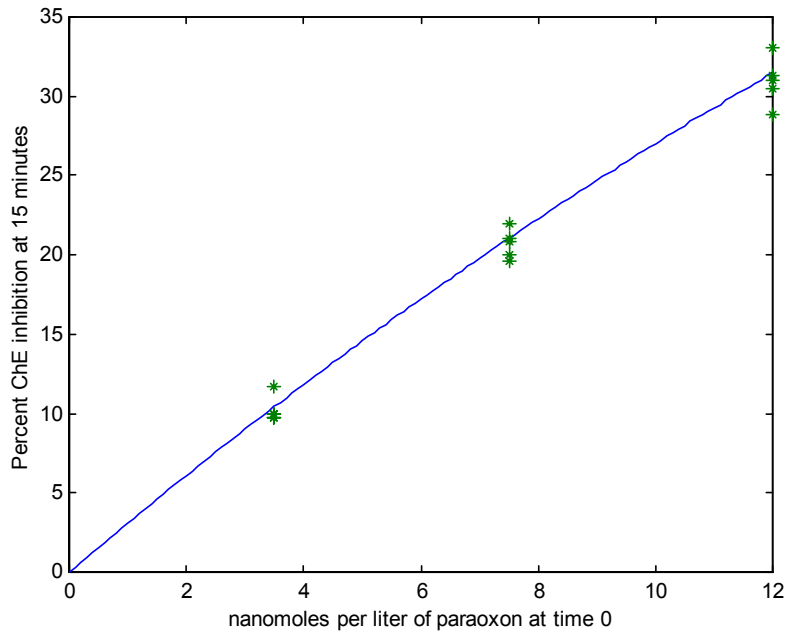
$$\frac{d[X_j]}{dt} = -k_j [X_j] [C]$$

$$\frac{d[X_i]}{dt} = -k_i [X_i] [C].$$

The identification involves using optimization routines on a computer to find the parameters that minimize a measure of error.

As an example we will consider a problem with real data from the laboratory of Jan Chambers. We will examine the values for percent inhibition of ChE after 15 minutes of separate Chlorpyrifos-oxon and of paraoxon exposure. The *'s are data points and the solid line is the predicted curve.





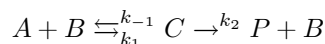
The identified parameters are $k_c = 0.0136$ and $k_p = 0.0021$. We now show what the combined model predicts using only these values.

Nanomoles of Paraoxon per liter at time 0	Nanomoles of chlorpyrifos per liter at time 0	Observed inhibition	Predicted inhibition	observed-predicted
3.5	.5	18.1	19.1	-1
3.5	1	27.7	27	0.7
3.5	1.7	36.33	36.7	-0.37
7.5	.5	27.1	28.7	-1.6
7.5	1	35	35.6	-0.6
7.5	1.7	42	44.2	-2.2
12	.5	35	38.1	-3.1
12	1	41.7	44.1	-2.4
12	1.7	49	51.6	-2.6

We see that the model works reasonably well, with errors less than those seen in the experimental data.

4.2 Example 2: An Catalyst problem

We continue with another chemical kinetics problem. We will study the problem where a chemical A interacts with a catalyst B to produce a complex C which will either break back into A and B or produce a product P and release the catalyst B . Symbolically this can be represented as



The differential equations to describe this are

$$\begin{aligned}\frac{d[A]}{dt} &= -k_1 [A] [B] + k_{-1} [C] \\ \frac{d[B]}{dt} &= -k_1 [A] [B] + k_{-1} [C] + k_2 [C] \\ \frac{d[C]}{dt} &= k_1 [A] [B] - k_{-1} [C] - k_2 [C] \\ \frac{d[P]}{dt} &= k_2 [C].\end{aligned}$$

As it stands, this is just a more complicated version of the mass action model we have already studied. But I would like to take a little time to discuss how we can simplify things. First, all of the other values are independent of P and we can start by removing the last equation and coming back to solving for P once we know C . Adding the first equation to the second yields

$$\frac{d([C] + [B])}{dt} = 0$$

In other words, $[C] + [B] = \beta$, a constant. We can therefore eliminate either equation 2 or equation 1. We shall eliminate equation 2. We now have the system

$$\begin{aligned}\frac{d[A]}{dt} &= -k_1 [A] (\beta - [C]) + k_{-1} [C] \\ \frac{d[C]}{dt} &= k_1 [A] (\beta - [C]) - k_{-1} [C] - k_2 [C]\end{aligned}$$

and we are down from four to two equations. We could now use phase plane analysis and obtain information; however we will take a different approach.

I will avoid the technicalities of nondimensionalization and perturbation methods and make a heuristic argument at this point. In most cases, the original amount of catalyst B will be much, much smaller than the amount of the chemical A . Furthermore, we can expect that the over abundance of A will be so great that, very rapidly, the vast majority of the catalyst will always be bound in the complex. Therefore, we can expect for all times except at the very beginning of the process we can make the *quasi-steady-state-assumption*

$$\frac{d[C]}{dt} \approx 0.$$

Thus we can compute

$$0 = k_1 [A] (\beta - [C]) - k_{-1} [C] - k_2 [C]$$

or

$$[C] = \frac{k_1 \beta [A]}{k_1 [A] + k_{-1} + k_2}.$$

Returning to the equation for $[A]$, we may compute

$$\begin{aligned} \frac{d[A]}{dt} &= \frac{-\beta k_1 k_2 a}{k_1 a + k_{-1} + k_2} \\ &= \frac{-\beta k_2 a}{k a + \frac{k_{-1}}{k_1} + \frac{k_2}{k_1}} \end{aligned}$$

or,

$$\frac{d[A]}{dt} = -\frac{K_{\max} c}{k + c}$$

where $K_{\max} = \beta k_2$ and $k = \frac{k_{-1}}{k_1} + \frac{k_2}{k_1}$ and we have arrived at the familiar Michaelis-Menten rate law.

4.3 Example 3: A compartment model

We will build a simple compartment model for the presence of a particular chemical in the blood stream and a given organ, say the liver. Each will be represented as a separate well-mixed compartment. We can easily adapt this to more organ systems as desired. The volume of each organ will be V_b and V_l , respectively. We will represent the concentration of the chemical in the organs by c_b and c_l respectively and recognize that each of these will be functions of time, t . We will assume that the chemical is being added to the blood stream at a rate of $r \frac{\text{mass}}{\text{time}}$ and we have two exchanges going on. The chemical is leaving the blood at a rate of $k_u c_b(t) \frac{\text{mass}}{\text{time}}$ and being eliminated from the body and the chemical is flowing from the blood to the liver at a rate of $k_{bl}(c_b(t) - c_l(t)) \frac{\text{mas}}{\text{time}}$ and the chemical is flowing from the liver to the blood at a rate of $-k_{bl}(c_b(t) - c_l(t)) \frac{\text{mas}}{\text{time}}$. We see here that the mass exchange must balance and an assumption in our modeling is conservation of mass. Notice that we are just making the exchange rate proportional to the differences in concentration. Thus we are ignoring the possibility of active transport through organ boundaries, although this can certainly be modeled. We now write out the model by requiring conservation of mass. The mass of the chemical in each organ is given by $V_b c_b(t)$ and $V_l c_l(t)$. The rate at which the mass is changing in the blood is given by

$$\frac{d(V_b c_b)}{dt} = r - k_u c_b(t) - k_{bl}(c_b(t) - c_l(t))$$

and the rate at which the mass is changing in the liver is

$$\frac{d(V_l c_l)}{dt} = k_{bl}(c_b(t) - c_l(t)).$$

We will assume that the volumes are constant over time to obtain the system

$$\begin{aligned}\frac{dc_b}{dt} &= \frac{r}{V_b} - \frac{k_a}{V_b}c_b(t) - \frac{k_{bl}}{V_b}(c_b(t) - c_l(t)) \\ \frac{dc_l}{dt} &= \frac{k_{bl}}{V_l}(c_b(t) - c_l(t)).\end{aligned}$$

This is a nonhomogeneous linear system. If r is constant or nice, we can write down an exact solution. If r is nasty or the system more complex, we can use mathematical analysis to obtain information about the behavior of solutions and numerical analysis to run detailed simulations under a wide variety of assumptions.

More importantly, this model can be used as a jumping off point. We could construct a similar model for another chemical and then add on our model of chemical kinetics we have already discussed in each organ. We can even model an organ response to the presence of the chemicals. Furthermore, if the first chemical is a toxin and the second chemical will neutralize the first chemical, we can use the model to determine optimal strategies for treatment. In fact, there is recent work [3] in which a compartment-type model was used to find optimal chemotherapy dosing strategies for cancer treatment.

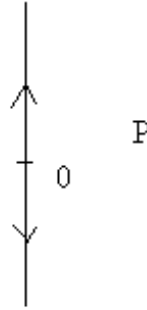
4.4 Example 4: Modeling a single population

The simplest continuous model for a population assumes that the population's death rate and birth rate are proportional to the population. That is, if $P(t)$ is the population of an organism at time t , we assume the death rate is $dP(t)$ individuals per unit time and the birth rate is $bP(t)$ individuals per unit time. If we set $r = b - d$, we get the population model

$$\frac{dP}{dt} = rP.$$

This has an explicit solution of $P(t) = P(0)e^{rt}$. We can see the similarity to the model given in equation (1) for the decay of a chemical in solution. Indeed, if $r < 0$, that is, the death rate is greater than the birth rate, then we obtain the same phase line and see that the population dies out. If we have $r > 0$, our

phase line looks like



and we expect our population to grow without bound.

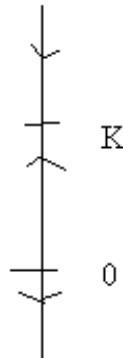
Let us build a more realistic population model. Let us assume that the population will grow close to an optimal rate, rP , when the population is small, but as the population increases, crowding pressures and competition for food eventually bring about a situation where the population is holding constant. Furthermore, if the population exceeds this population where zero growth occurs, the population will start to shrink. This critical population is called the carrying capacity of the environment. We will denote the carrying capacity by K . The simplest function that has the properties we desire for the population growth rate is

$$rP \left(1 - \frac{P}{K} \right).$$

This gives us the logistic population growth model

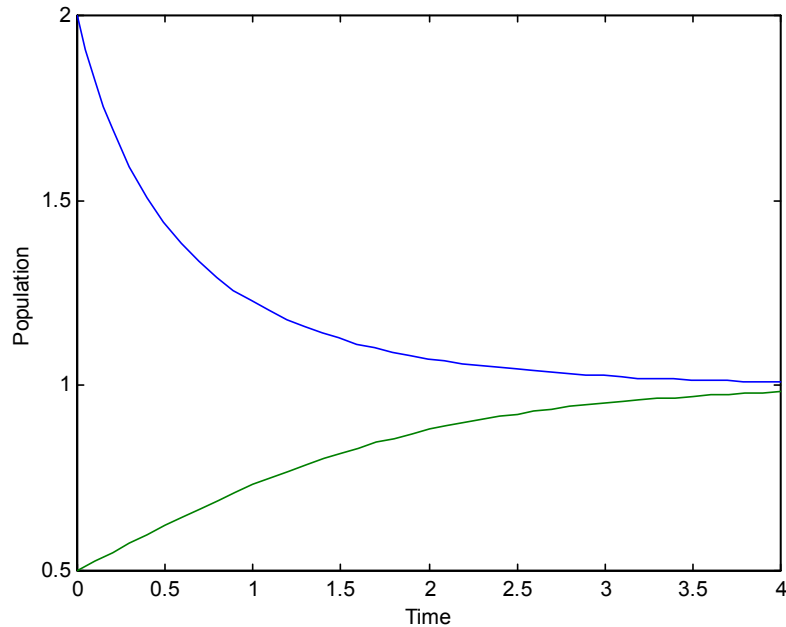
$$\frac{dP}{dt} = rP \left(1 - \frac{P}{K} \right).$$

The phase line is



There are two stationary points, $P = 0$ and $P = K$. From the phase line it is easy to see that any positive population will tend to the carrying capacity. As

an example I will set $r = 1 = K$ and plot two starting populations, 2 and 0.5, against time.



Let us consider one more single population model. We will consider a population of fish following the logistic growth law, but we shall be harvesting them at a rate of h fish per unit time. This gives the model

$$\frac{dP}{dt} = rP \left(1 - \frac{P}{K} \right) - h.$$

It is instructive to consider the stationary points and the phase line. Computing

$$0 = rP \left(1 - \frac{P}{K} \right) - h$$

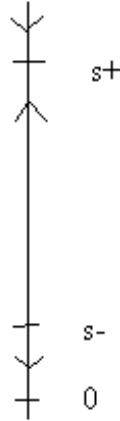
gives us two facts. If $\frac{r}{2} < h$ we have no stationary points and

$$\frac{dP}{dt} < 0$$

and we expect our fish to die out. Of course, our ability to really harvest at rate h will have already broken down before this and our model will no longer be valid. However, it is pretty clear that trying to harvest at such a large h will result in the destruction of the fishery. On the other hand, if $\frac{r}{2} > h$, we obtain two distinct stationary points

$$s_{\pm} = \frac{K}{2r} \left(r \pm \sqrt{r^2 - 4h^2} \right).$$

This gives the following phase line



We see that for any population over s_- , the population will tend to s_+ . Note that as h increases to $\frac{r}{2}$, the stationary points will move together and then disappear. We say that there is a bifurcation at $h = \frac{r}{2}$. The optimal strategy will be to set a harvesting level as close to, but below $h = \frac{r}{2}$ as possible.

This model can be generalized extensively, both by adding terms, such as age structure and stocking, and but adding spatial variation, as in the work of R. Shivaaji, and producing a partial differential equation.

4.5 Example 5: Multispecies models

We will consider a classic model of two species interaction that dates back to the early twentieth century and V. Volterra. Consider two species. A happy herbivore, say rabbits, and a predator, say coyotes. We will assume that, left alone, the rabbit population will follow the simple unbounded growth model,

$$\frac{dR}{dt} = aR,$$

where $R(t)$ is the rabbit population at time t . This model is OK as long as the rabbit population does not get out of hand. Letting $P(t)$ represent the coyote population at time t , we assume that when there are no rabbits, the coyotes will starve to death at a rate of $cP(t)$ individuals per unit time. However, we will also assume that the birth rate of the coyotes is proportional to the numbers of rabbits eaten. We assume that the number of rabbits eaten per unit time is proportional to the number of Coyote-rabbit interactions per unit time. Using the same reasoning we used when discussing the law of mass action, we assume that the number of Coyote-rabbit interactions per unit time is proportional to

the product $R(t)P(t)$. Thus, we assume there are constants of proportionality b and d so that the number of rabbits eaten per unit time is equal to $bR(t)P(t)$ and the number of coyotes born per unit time is $dR(t)P(t)$. We can now write down the system of equations

$$\begin{aligned}\frac{dR}{dt} &= aR - bRP \\ \frac{dP}{dt} &= -cP + dRP\end{aligned}$$

We will do a phase plane analysis of this model. We first find all of the stationary points, the solutions to

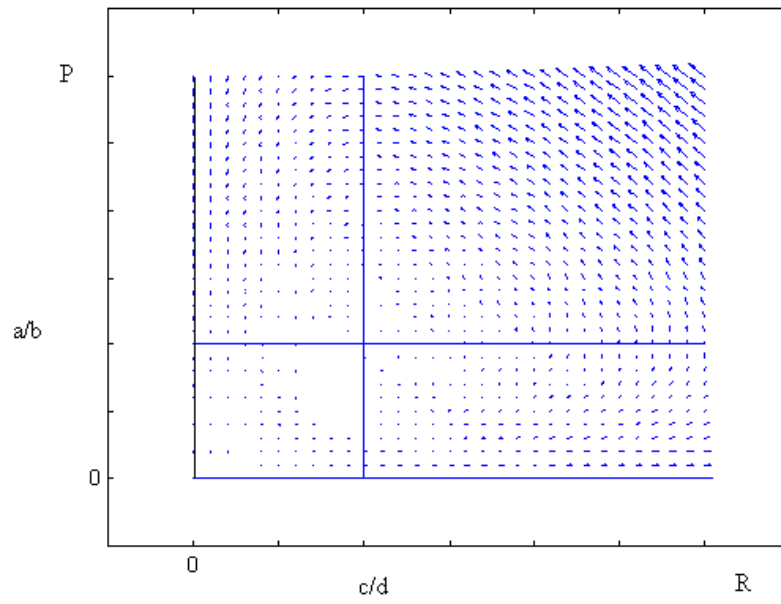
$$\begin{aligned}\frac{dR}{dt} &= 0 \\ \frac{dP}{dt} &= 0\end{aligned}$$

or

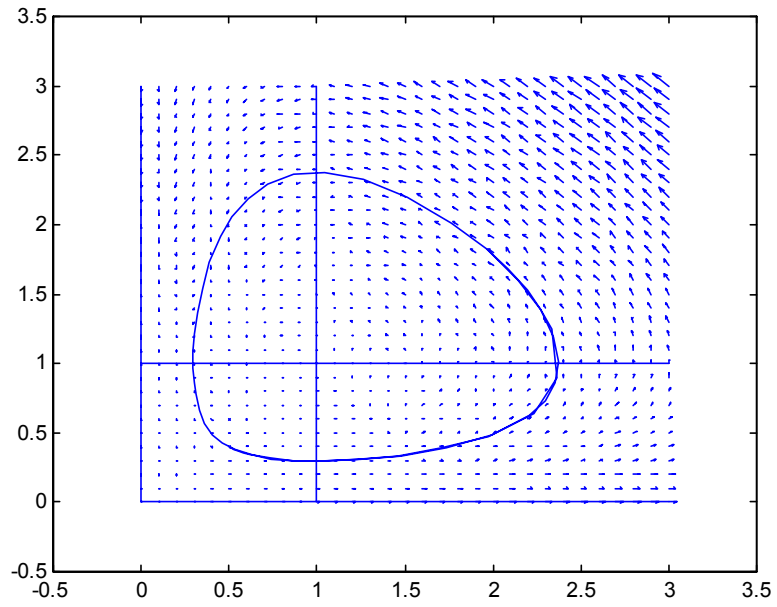
$$\begin{aligned}aR - bRP &= 0 \\ -cP + dRP &= 0.\end{aligned}$$

We have that $\frac{dR}{dt} = 0$ when $R = 0$ or $P = \frac{a}{b}$. We have $\frac{dP}{dt} = 0$ when $P = 0$ or $R = \frac{c}{d}$. The lines so defined are called nullclines. The stationary points, where both derivatives are 0, are $(0, 0)$ and $(\frac{c}{d}, \frac{a}{b})$. The phase plane below indicates

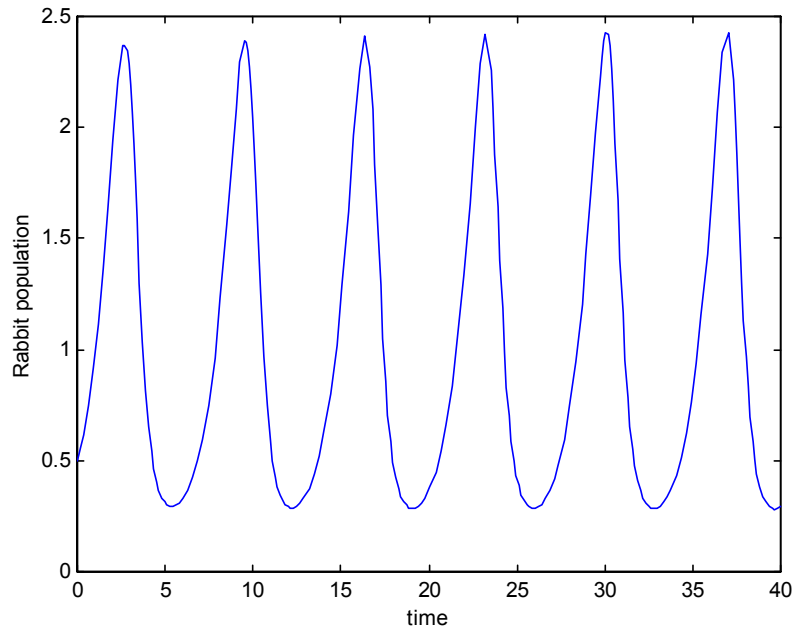
that we expect to see some kind of cyclic behavior.



In fact, if we plot a solution on the phase plane we see this:



Plotting the rabbit population against time yields



These sort of population models (and more realistic ones) can be combined with other models of disease, harvesting, and, of spatial variation. We can see how such a model can be expanded to consider disease spread by a vector.

4.6 Example 6: Epidemic models

We will describe one of the classic SIRS models of disease spread. We will assume that our population is fixed. (This can, of course, be dispensed with.) The population will consist of individuals susceptible to the disease, S , those infected with the disease, I , and those recovered from the disease (or removed), R . The rate of new infection of susceptible individuals will be taken as proportional to the number of interactions between susceptible individuals and infected individuals. Using mass action arguments, we will assume this is proportional to the product of S and I , βIS . Notice that by such strategies as quarantine, we can decrease β . The rate of recovery of infected individuals will be νI individuals per unit time. Finally, the rate at which recovered or removed (perhaps vaccinated) individuals become susceptible again is γR . This leads to a system

of 3 differential equations.

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI + \gamma R \\ \frac{dI}{dt} &= \beta SI - vI \\ \frac{dR}{dt} &= vI - \gamma R.\end{aligned}$$

We will simplify the problem and then proceed to do a phase plane analysis. Observe that our requirement that the population is fixed forces there to be a constant for the total population, N , and $S + I + R = N$. Thus we can replace R in the first two equations with $N - S - I$. We then obtain

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI + \gamma(N - S - I) \\ \frac{dI}{dt} &= \beta SI - vI\end{aligned}$$

We will start by looking for the stationary points. We obtain two possibilities. Either we have

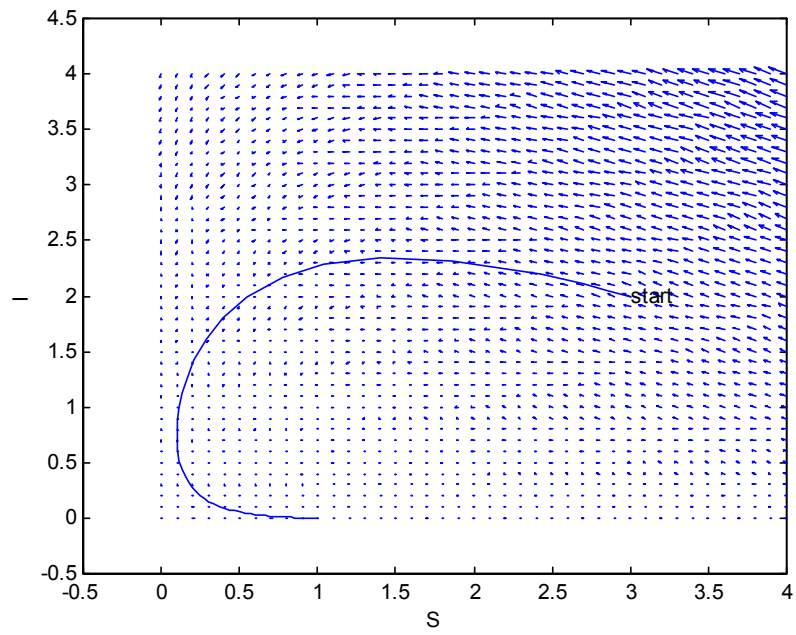
$$I = 0 \text{ and } S = N,$$

that is, there is no disease and the whole population is susceptible or

$$S = \frac{v}{\beta} \text{ and } I = \frac{\gamma}{v + \gamma} \left(N - \frac{v}{\beta} \right).$$

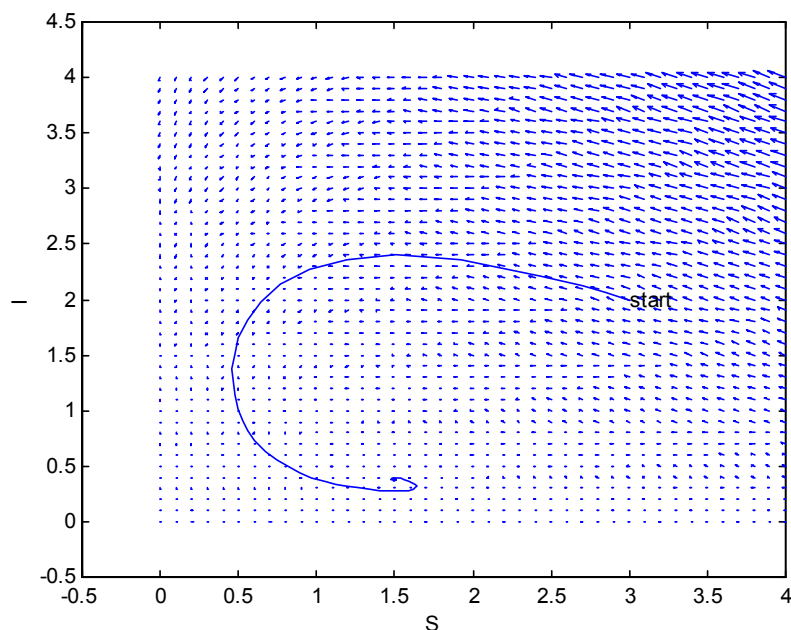
If $N > \frac{v}{\beta}$, there is a physically meaningful stationary point where part of the population is always infected, and the disease is endemic. If not, only the disease-free stationary point is physically meaningful. It is important to note that if we do the eigenvalue analysis of the case where $N > \frac{v}{\beta}$, it indicates that we will always have the disease. Furthermore, if $N < \frac{v}{\beta}$, we see can look at the

phase plane and see



that the disease tends to die out.

What does the vector field look like in the case?



Thus, if this model is accurate in its broad outline, a strategy to eliminate disease is to increase v and decrease β .

5 Conclusion

What we have looked at here is a small collection of some of the simplest ordinary differential equation models in mathematical chemistry, mathematical biology, and mathematical ecology. Similarly, we have barely scratched the surface of the techniques of analysis, both analytical and numerical, available to the modeler. When we consider that all of these models can be tied together to form systemic models, with all of the challenges of vastly different time scales, we see that there are powerful tools for the life scientist, as well as research challenges for the mathematician and the computational scientist.

Furthermore, what we have been looking at is just one flavor of "local kinetics models" that can be tied together across spatially heterogeneous environments in a variety of ways. It is hoped that some notion of what it is possible to do with mathematical modeling has been shown here, as well as an introduction to some of the ideas of continuous modeling with differential equations. Several of the books listed in the references, from which I borrowed freely, will be useful to the interested life scientist. I have also list a few research papers that might be of interest.

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