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Introduction to Mathematical Biology

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Chapter 1
Introduction

The progress in the biological sciences over the last several decades has been revolutionary, and it is reasonable to expect that this pace of progress, facilitated by huge advances in technology, will continue in the following decades. Mathematics has historically contributed to, as well as benefited from, progress in the natural sciences, and it can play the same role in the biological sciences. For this reason we believe that it is important to introduce students very early, already at the freshman or sophomore level, with just basic knowledge in Calculus of one variable, to the interdisciplinary field of mathematical biology. A typical case study in mathematical biology consists of several steps. The initial step is a description of a biological process which gives rise to several biological questions where mathematics could be helpful in providing answers. The second step is to develop a mathematical model that represents the relevant biological process. The next step is to use mathematical theories and computational methods in order to derive mathematical predictions from the model. The final step is to check that the mathematical predictions provide answers to the biological question. One can then further explore related biological questions by using the mathematical model.

This book is based on one semester course that we have been teaching for several years. We chose two sets of case studies. The first set includes chemostat models, predator-prey interaction, competition among species, the spread of infectious diseases, and oscillations arising from bifurcations. In developing these topics we also introduced the students to the basic theory of ordinary differential equation, and taught them how to work and program with MATLAB without any prior programming experience. The students also learned how to use codes to test biological hypotheses,

The second set of case studies were cases adapted from recent and current research papers to the level of the students. We selected topics that are of great public health interest. These include the risk of atherosclerosis associated with high cholesterol level, cancer and immune interactions, cancer therapy, and tuberculosis. Throughout these case studies the student will experience how mathematical models and their numerical simulations can provide explanations that may actually guide biological and biomedical research. Toward this goal we have also include

in our course "projects" for the students. We divide the students into small groups, and each group is assigned a research paper which they are to present to the entire class at the end of the course. Another special feature of this book is that in addition to teach students how to use MATLAB to solve differential equations, we also introduce some very basic numerical methods to familiarize the students with some numerical techniques. That will greatly help their understanding in using different MATLAB functions, and can further help them when they try to use other computer languages in the future. Overall, our book is different from traditional mathematical biology textbooks in many aspects.

We hope the book will help demonstrate to undergraduate students, even those with little mathematical background and no biological background, that mathematics can be a powerful tool in furthering biological understanding, and that there are both challenge and excitement in the interface of mathematics and biology.

This book is the undergraduate companion to the more advanced book "Mathematical Modeling of Biological Process" by A. Friedman and C.-Y. Kao (Springer, 2014), and there is some overlap with Chapters 1, 4-6 of that book. We would like to thank Chiu-Yen Kao who taught the very first version of this undergraduate course.

Chapter 2
Bacterial Growth in Chemostat

A chemostat, or bioreactor, is a continuous stirred-tank reactor (CSTR) used for continuous production of microbial biomass. It consists of a fresh water and nutrient reservoir connected to a growth chamber (or reactor), with microorganism. The mixture of fresh water and nutrient is pumped continuously from the reservoir to the reactor chamber, providing feed to the microorganism, and the mixture of culture and fluid in the growth chamber is continuously pumped out and collected. The medium culture is continuously stirred. Stirring ensures that the contents of the chamber is well mixed so that the culture production is uniform and steady. If the steering speed is too high, it would damage the cells in culture, but if it is too low it could prevent the reactor from reaching steady state operation. Figure 2 is a conceptual diagram of a chemostat.

Chemostats are used to grow, harvest, and maintain desired cells in a controlled manner. The cells grow and replicate in the presence of suitable environment with medium supplying the essential nutrient growth. Cells grown in this manner are collected and used for many different applications.

These application include:

Pharmaceutical: for example in analyzing how bacteria respond to different antibiotics, or in production of insulin (by the bacteria) for diabetics.

Food industry: for production of fermented food such as cheese.

Manufacturing: for fermenting sugar to produce ethanol.

A question which arises in operating the chemostat is how to adjust the effluent rate, that is, the rate of pumping out the mixture. In order to operate the chemostat efficiently, the effluent rate should not be too small. But if this rate is too large, then the bacteria in the growth chamber may wash out. In order to determine the optimal rate of pumping out the mixture we need to use mathematics. In this chapter, we develop a simple mathematical model in order to determine the optimal effluent rate. A more comprehensive model will be developed in Chapter 8.

We first need to develop a mathematical model describing the growth of bacteria. The density x of bacteria is defined as the number of bacteria per unit volume. If the bacteria grow at a fixed rate r, then

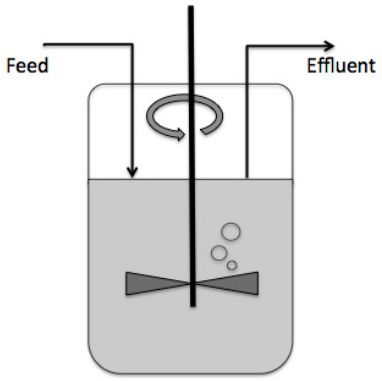


Fig. 2.1 Stirred bioreactor operated as a chemostat, with a continuous inflow (the feed) and outflow (the effluent). The rate of medium flow is controlled to keep the culture volume constant.

$$x(t+\Delta t) - x(t) = rx(t)\Delta t,$$

or

$$\frac{x(t+\Delta t) - x(t)}{\Delta t} = rx(t),$$

and, taking $\Delta t \to 0$, we get

$$\frac{dx}{dt} = rx. \tag{2.1}$$

The explicit formula for the growth of x is then

$$x(t) = x(0)\, e^{rt}.$$

The **doubling time** T is defined by $x(T) = 2x(0)$, and it is given by

$$2 = e^{rT}, \quad \text{or} \quad T = \ln 2 / r.$$

If a colony of bacteria, or other microoganism, is dying at rate s, then its density x satisfies

$$\frac{dx}{dt} = -sx, \tag{2.2}$$

and

$$x(t) = x(0)e^{-st}.$$

The population density is halved at time $\bar{T}$, called the **half-life**, given by

$$\bar{T} = \frac{\ln 2}{s}.$$

When bacteria are confined to a bounded chamber, they cannot grow exponentially forever, according to (2.1). There is going to be a **carrying capacity** B of the medium which the bacterial density cannot exceed. This is modeled by replacing

the exponential growth (2.1) by the **logistic growth**

$$\frac{dx}{dt} = rx(1 - \frac{x}{B}). \tag{2.3}$$

The solution of (2.3) with an initial condition

$$x(0) = x_0$$

is given by

$$x(t) = \frac{B}{1 + (\frac{B}{x_0} - 1)e^{-rt}}. \tag{2.4}$$

Indeed, to derive (2.3), we rewrite (2.1) in the form

$$\frac{dx}{x(1 - \frac{x}{B})} = rdt,$$

or

$$(\frac{1}{x} + \frac{1}{B}\frac{1}{1 - \frac{x}{B}})dx = rdt,$$

and integrate to obtain

$$\ln x - \ln \frac{1}{1 - \frac{x}{B}} = rt + const.$$

Then

$$\frac{x}{1 - \frac{x}{B}} = Ce^{rt},$$

yielding

$$x(t) = \frac{Ce^{rt}}{1 + \frac{C}{B}e^{rt}} = \frac{B}{1 + \frac{B}{C}e^{-rt}}.$$

Substituting $t = 0, x(0) = x_0$, we get

$$1 + \frac{B}{C} = \frac{B}{x_0}, \text{ or } C = \frac{x_0}{1 - \frac{x_0}{B}}.$$

Equation (2.1) is a special differential equation. Later on we shall encounter other differential equations that model biological processes.

Consider a general differential equation

$$\frac{dx}{dt} = f(x) \tag{2.5}$$

where $f(x)$ is a continuous function together with its first derivative. We wish to solve (2.5) with an initial condition

$$x(0) = x_{0.} \tag{2.6}$$

Theorem 2.1. *There exists a unique solution of (2.5), (2.6) for some interval* $0 \leq t \leq t_1$.

The soution can actually be continued for all $t > 0$ as long as $f(x(t))$ remains bounded. Similarly, the solution can be continued to all $t < 0$ as long as $x(t)$ remains bounded. One often refers to a solution of (2.5), $x(t)$ for $0 \leq t < \infty$, as a **trajectory**.

If x_0 is a point such that $f(x_0) = 0$, then the unique solution of (2.5), (2.6) is clearly $x(t) \equiv x_0$. Such a point x_0 is called an **equilibrium point**, a **steady state** or a **stationary point**. By Taylor's formula,

$$f(x) = f(x_0) + f'(x_0)(x - x_0) + (x - x_0)\varepsilon(x - x_0)$$

where $\varepsilon(x - x_0) \to 0$ if $x \to x_0$.

Suppose x_0 is an equilibrium point such that $f'(x_0) < 0$. Setting $y = x - x_0$, we then have

$$\frac{dy}{dt} = f'(x_0)y + y\varepsilon(y).$$

If $|y|$ is small enough so that $|\varepsilon(y)| < |\frac{1}{2}f'(x_0)|$, then, for $y > 0$,

$$\frac{dy}{dx} < f'(x_0)y + \frac{1}{2}|f'(x_0)|y = f'(x_0)y - \frac{1}{2}f'(x_0)y = \frac{1}{2}f'(x_0)y,$$

so that

$$\frac{dy}{dt} < 0 \quad \text{if} \quad y > 0.$$

Hence $y = y(t)$ is decreasing toward $y = 0$. Similarly

$$\frac{dy}{dt} > 0 \quad \text{if} \quad y < 0,$$

so that $y = y(t)$ is increasing toward $y = 0$.

Hence the solution $x(t)$, starting near x_0, moves toward x_0 as t increases; in fact, $x(t) \to x_0$ as $t \to \infty$. We therefore call x_0 a **stable equilibrium** (or more precisely **asymptotically stable equilibrium**). Similarly, if

$$f'(x_0) > 0$$

then solutions initiating near x_0 move away from x_0, as long as they are within a small distance from x_0. We call such a point x_0 an **unstable** equilibrium.

In the logistic growth equation (2.3), $x = B$ is a stable equilibrium. From (2.4), we see that $x = B$ is actually a **globally (asymptotically) stable** stable point of (2.3) in the sense that no matter what x_0 is, $x(t) \to B$ as $t \to \infty$.

Modeling the chemostat

Figure 2 shows a schematics of a chemostat with a stock of nutrient C_0 pumped into the chamber of the bacterial culture. We assume that the chemostat chamber is well stirred so that the nutrient concentration is constant at each time t. We then model the bacterial growth by the logistic equation (2.3), where r depends on the constant nutrient concentration C_0. If we denote by s the rate of the bacterial outflow from the chamber, then the balance between growth and outflow is given by

$$\frac{dx}{dt} = rx(1-\frac{x}{B}) - sx. \tag{2.7}$$

We shall denote by $[X]$ the dimension of any quantity X. For example,

$$[x] = \frac{\text{number}}{\text{volume}}, \quad [B] = \frac{\text{number}}{\text{volume}},$$

$$[r] = \frac{1}{\text{time}}, \quad [s] = \frac{1}{\text{time}}.$$

There are two equilibrium points to (2.7), namely, $x = 0$, and $x = (1-\frac{s}{r})B$. Note that if $s < r$, then $x = 0$ is an unstable equilibrium, whereas $x = (1-\frac{s}{r})B$ is a stable equilibrium. If $s > r$, then $x = 0$ is a stable equilibrium, whereas the equilibrium point $x = (1-\frac{s}{r})B$ is not biologically relevant since it is negative.

Consider the case $s < r$ and $x(0) < (1-\frac{s}{r})B$. Since $(1-\frac{s}{r})B$ is a stable equilibrium, if $x(0)$ is near $(1-\frac{s}{r})B$, it will remain smaller than $(1-\frac{s}{r})B$ and will converge to it as $t \to \infty$. We can actually solve $x(t)$ explicitly: writing

$$\frac{1}{rx(1-\frac{x}{B}) - sx} = \frac{1}{r-s}(\frac{1}{x} + \frac{r/B}{(r-s) - rx/B})$$

we have

$$\frac{1}{r-s}\left[\frac{dx}{x} + \frac{r/B}{(r-s) - rx/B}dx\right] = dt.$$

By integration

$$\frac{1}{r-s}[\ln x - \ln((r-s) - rx/B)] = t + const,$$

or

$$\frac{x}{(r-s) - rx/B} = ce^{(r-s)t} \quad (c \text{ is constant}).$$

Hence

$$(\frac{1}{c}e^{-(r-s)t} + \frac{r}{B})x = r - s,$$

or

$$x(t) = \frac{r-s}{\frac{r}{B} + \frac{1}{c}e^{-(r-s)t}}. \tag{2.8}$$

We see that $x(t) \to (1-\frac{s}{r})B$ as $t \to \infty$, whenever $x(0) < (1-\frac{s}{r})B$. Note that the formula (2.8) is valid also when $x(0) > (1-\frac{s}{r})B$ and that c is determined by

$$x(0) = \frac{r-s}{\frac{r}{B}+\frac{1}{c}}, \quad \text{or} \quad \frac{1}{c} = \frac{r-s}{x(0)} - \frac{r}{B}.$$

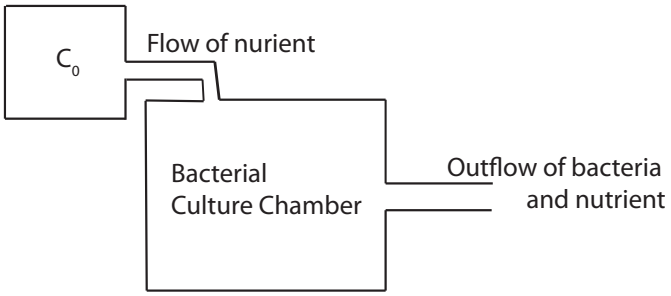


Fig. 2.2 The chemostat device.

The chemostat operator would like to adjust the outflow rate s so as to get the largest output of bacteria. The mathematical model we developed can determine the optimal rate. Indeed, at steady state the outflow rate s is to be multiplied by the steady state of the bacteria, which is, $x = (1-\frac{s}{r})B$. The function $s(1-\frac{s}{r})B$ takes its maximum at $s = \frac{r}{2}$, and with this outflow rate the maximum outflow per unit time is $\frac{1}{2}rB$.

Summary. The chemostat operates most efficiently when $s = \frac{r}{2}$, that is, when the outflow rate is half the inflow rate.

Problem 2.1. Find the general solution of the differential equation

$$\frac{dx}{dt} = ax + b$$

where a, b are constants.

Problem 2.2. Prove the following statements:
(i) If $\frac{dx}{dt} \le b - \mu x$ $(b > 0, \mu > 0)$ for all $t > 0$, then, for any $\varepsilon > 0$,

$$x(t) \le \frac{b}{\mu} + \varepsilon \quad \text{if } t \text{ is large enough;}$$

(ii) If $\frac{dx}{dt} \ge b - \mu x$ $(b > 0, \mu > 0)$ for all $t > 0$, then, for any $\varepsilon > 0$,

$$x(t) \ge \frac{b}{\mu} - \varepsilon \quad \text{if } t \text{ is large enough.}$$

[Hint: Rewrite the inequality in (i) in the form $\frac{d}{dt}(xe^{\mu t}) = (\frac{dx}{dt} + \mu x)e^{\mu t} \le be^{\mu t}$.]

Problem 2.3. Consider the equation

$$\frac{dx}{dt} = x(x-a)(x-2), \quad 0 < a < 2.$$

It has three steady points, $x = 0$, $x = 2$ and $x = a$. Determine which of them are stable points.

Problem 2.4. Consider the equation

$$\frac{dx}{dt} = x^{\alpha}, \quad x(0) = 1$$

where $0 < \alpha < \infty$. Show that (i) if $\alpha > 1$ then the solution exists for $0 < t < \frac{1}{\alpha-1}$ and $x(t) \to \infty$ as $t \to \frac{1}{\alpha-1}$. (ii) if $\alpha < 1$ then the solution exists for all $t > 0$ and $x(t) \to \infty$ as $t \to \infty$.

Problem 2.5. Consider the equation

$$\frac{dx}{dt} = (x-a)(2-x) \qquad x(0) < a,$$

where $a < 2$. Find the solution explicitly in either the form $t = t(x)$, or $x = x(t)$, and use it to prove the following:
(i) If $x(0) > a$ then the solution exists for all $t > 0$ and $x(t) \to 2$ as $t \to \infty$;
(ii) If $x(0) < a$ then the solution exists for $t < T$, where $T = \frac{1}{2-a} \ln |\frac{a-x(0)}{2-x(0)}|$, and $x(t) \to -\infty$ as $t \to T$.

2.1 Numerical Simulations – Introduction to MATLAB

MATLAB is a software developed by MathWorks, and it is widely used in science and engineering. MATLAB is a high-level language and interactive environment for numerical computation, symbolic calculation and visualization. It is also known for its easy handling of matrices and vectors. To access this software, in many universities, students can install licensed MATLAB software (you can request from the schools' IT department), and individual licenses can also be purchased through MathWorks website.

We will refer the readers to MathWorks' website for details of installation and launching of the software. In this chapter, we will introduce some basics of MATLAB and prompt to solving an ODE problem with MATLAB. The codes and explanations about MATLAB is based on the version MATLAB R2014b.

The introduction here is elementary and not comprehensive, but it will give the readers the basic idea of how MATLAB operates and how to use this software to solve our models.

2.1.1 Scalar calculations

Once we launch MATLAB, the default window will have several compartments: a panel with function buttons, and main columns "Current folder", "Command Window" and "Workspace". We can change to the directory that we would like to work in, and the corresponding folders and subfolders will show in the "Current Folder" part. The "Command Window" is for us to enter commands and do some calculations, and the "Workspace" will save the variables that have been used in our calculations.

MATLAB can do basic calculations as in regular calculators. MATLAB recognizes the usual arithmetic operation: + (addition), - (subtraction), * (multiplication), / (division), ^ (power). In the Command Window, we will see the prompt sign (>>), and we can type after prompt sign and press enter.

For example, `>> (5*2+3.5) / 5`

```
ans =
2.7000
```

If we do not want to see the the display of the answer, we can add a semicolon to suppress the display. We can also store the result into a variable that the user assigns, for example:

```
>> x = (5*2+3.5) / 5
x =
2.7000
```

If we check the Workspace column, you will see x is stored and the value is also shown in that column. If we didn't not specify the name of the variable, the result will be store in `ans` in the Workspace. It is worth noting that a valid variable name starts with a letter, followed by letters, digits, or underscores. MATLAB is case sensitive, so B and b are not the same variable. We should avoid creating variable names that conflict with function names (functions will be introduced later).

MATLAB recognizes different types of numbers: (1) Integer (example: 112, -2185); (2) real number (example: 2.452, -100.448); (3) complex (example: $-0.11+4.4i$, $i=\sqrt{-1}$); (4) Inf (infinity); (5) NaN (not a number).

All the calculation in MATLAB are done in double precision, which means that the numbers are accurate up to 15 significant figures. However, we may not see that many digits on the display window, and that is because the default output format is to display 4 decimal places. If you type `format long`, you will see the full display of all the digits. To know about more format, type `help format`. This `help` command is very useful when we would like to know how to use a command or a function; we simply type `help xx`, in which `xx` is the command of interest.

MATLAB has some built-in trigonometric function and elementary functions. We choose some commonly used ones to list in Table 2.1.

It is convenient and important to make comments in the codes, for future reference. In MATLAB, we use the percentage sign (%), and MATLAB will take all the characters after (%) as comments and those will not be executed, for example: `>> x = (5*2+3.5) / 5^2 % store the result in variable z, and show the result on the screen.`

MATLAB build-in functions	descriptions
abs(x)	absolute value of x
sqrt(x)	square root of x
sin(x)	sine of x in radians
sind(x)	sine of x in degrees
cos(x)	cosine of x in radians
cosd(x)	cosine of x in degrees
tan(x)	tangent of x in radians
cot(x)	cotangent of x in radians
sec(x)	secant of x in radians
csc(x)	cosecant of x in radians
asin(x)	inverse sine of x in radians
acos(x)	inverse cosine of x in radians
atan(x)	inverse tangent of x in radians
sinh(x)	hyperbolic sine of x in radians
cosh(x)	hyperbolic cosine of x in radians
exp(x)	exponential of x
log(x)	natural logarithm of x
log2(x)	base 2 logarithm of x
log10(x)	base 10 logarithm of x
ceil(x)	round x toward infinity
floor(x)	round x toward minus infinity
round(x)	round x to the nearest integer

Table 2.1 Commonly used MATLAB built-in functions.

If the operation is too long, one can use (...) to extend the command to the next line, for example:

```
>> z = 10*sin(pi/3)*...
>> sin(pi^2/4)
```

2.1.2 Vector and matrix operations

In previous examples, we have discussed how to use MATLAB to do the usual scalar calculations. In fact, MATLAB is very powerful when it comes to calculations of vectors and matrices, and it is a vector oriented program. For this reason, we should maximize the use of vector-matrix operations in design of our codes.

In the previous section, variables are used to store scalars. Here we show that they can also be used to store vectors. The following is an example to assign vectors in a variable:

```
>> s = [1 3 5 2]; % note the use of [], and the spaces
between the numbers; one can also use comma (,) to separate
the numbers
>> t = 2*s + 1 % 1 will be added to all the entries of
2*s
```

```
t =
3 7 11 5
```

In the above example, MATLAB uses [] to establish a row vector [1 3 5 2] and stores it in the variable *s*, and does operation on it to make a new row vector [3 7 11 5] and stores it in the variable *t*. To extract one element from the vector or part of the vector to do operations, we type:

```
>> t(3) % display third entry of vector t
ans =
 11
>> t(3) = 2 % assign another value to the third entry of
vector t
t =
 3 7 2 5
>> 2*t - 5*s
ans =
 1 -1 -21 0
```

As we learn in linear algebra, in order to add or subtract, two vectors need to have the same length.

```
>> a = [1 2 3]; b = [5 6];
>> a + b
Error using +
Matrix dimensions must agree.
```

When we see the above message, that means we have inconsistent matrix or vector dimensions, so we need to go back to check the dimensions of our matrices or vectors. Although we cannot add or subtract `a` and `b`, we can put them together in a vector, such as

```
>> cd = [-b, 3*a]
cd =
 -5 -6 3 6 9
```

Sometimes, we need vectors whose entries are part of an arithmetic sequence, a convenient way to define it is to use the colon notation:

```
>> 1:2:6 % this will generate a row vector, starting at
1, ending at 6, with increment 2
ans =
 1 3 5
>> 3:10 % without specifying the increment, it will be
set as 1
ans =
 3 4 5 6 7 8 9 10
```

Knowing this shortcut, we can easily extract sections in a vector, and do operations:

```
>> t(2:4) - 1 % this will be the same as typing t([2 3
4])-1
ans =
 6 1 4
```

We have learned how to define and use row vectors, and the operations are similar for column vectors. The only difference is that the entries of a column vector are separated by semicolon (;) or making a new line.

```
>> cv = [-1; pi; exp(2)]
cv =
 1.0000
 3.1416
 7.3891
>> cv2 = [1
2
3]
cv2 =
 1
 2
 3
```

The row and column vectors can be transposed to become column and row vectors, respectively.

```
>> cv', t'
ans =
 1.0000 3.1416 7.3891
ans =
 3
 7
 2
 5
```

Similarly to making vectors, users can make a $m \times n$ matrix, by adding a semicolon ; after the end of each row. Next we define matrices. Similar to row and column vectors, entries in a row are separated by spaces or commas, while different rows are made by using semicolon or a new line. For example:

```
>> A = [1 2 3 4; 5 6 7 8; 9 10 11 12]
A =
  1 2  3  4
  5 6  7  8
  9 10 11 12
```

We can extract or change any single entry in the matrix

```
>> A(2,3) = 5; % change the (2,3) entry of A to 5
```

or extract part of the matrix

```
>> B = A(2,1:3) % take the second row, the first to third
column, store as a new matrix B
>> B =
>> 5 6 7
```

We can combine matrices, as long as the dimensions are consistent. `>> A =[A B'] % transpose B, make it as the last column vector and merge with A`

```
A =
```

```
 1  2  3  4  5
 5  6  7  8  6
 9 10 11 12  7
```

We can extract the whole row or colon by using semicolon

```
>> A(:,3)
A =
  3
  7
 11
>> A(1,:)
A =
 1 2 3 4 5
```

Then we can redefine or delete a row or a column:

```
>> A(:,2) = [] % delete the second row of A (: represents
all the rows, [] is an empty vector
>> A = [A; 4 3 2 1; 0 -1 -2 -3]; % adding the fourth and
fifth row in the matrix A
```

To obtain the size of a matrix, we use the command "size".

```
>> size(A')
 ans =
 4 5
```

To obtain the length of a vector, we use "length".

```
>>length(A(1,:))
 ans =
 4
```

There are some built-in special matrices,

```
>> ones(2,3) % this generates a 2x3 matrix with ones
>> zeros(4,4) % this generates a 4x4 matrix with zeros
>> eye(5) % this generates a 5x5 identity matrix
>> diag([1 3 5]) % this generates a matrix with 1 3 5 on
its diagonal
```

Next, let us about matrix-matrix or matrix-vector multiplication. When we use * in the matrix operations, it will operates as the matrix multiplication, what we learned in linear algebra. For example,

```
>> X = [1 2 3; 0 2 4]; Y = [5 2; 1 1; 10 7]; W = X*Y
 W =
 37 25
 42 30
```

If we try

```
>> X*X
```

then we will see an error message about the matrix dimension, because an $m \times n$ matrix can only by multiplied by an $n \times k$ matrix. Sometime we do not perform component-by-component operations, but not matrix-matrix multiplications, for that purpose we need to use .* instead of *. The following commands will give different result:

```
>> W.* W % component by component operation
```

```
>> W* W % matrix-matrix multiplication
```

and we will find that `X.*X` works because it is component-by-component operation.

2.1.3 Numerical algorithms of solving ODE

Most of the time, the solution of an ODE problem does not have a closed-form solution. In this case, one looks for numerical solutions that approximate the real solution. Since numerical solutions are just approximations, it is important to understand the accuracy of the numerical method and robustness of it.

Suppose a scalar ODE is

$$\frac{dy}{dt} = f(y,t) \quad y(0) = y_0, t \geq 0.$$

Let t_0 be some time point with $t_0 \geq 0$, then by integrating the ODE, one gets

$$y(t) = y(t_0) + \int_{t_0}^{t} f(x,\tau)d\tau \approx y(t_0) + (t-t_0)f(y(t_0),t_0).$$

As long as t is sufficiently close to t_0, this provides a good approximation. Define h as the step size, we then define the numerical solution by

$$Y_{n+1} = Y_n + hf(Y(t_n),t_n).$$

This is call **forward Euler Method**, named after Leonhard Euler (1707-1783). The error of this scheme is $O(h)$, which can be formally derived from Taylor expansion. Generally, a numerical scheme is called kth order accurate if the error is $O(h^k)$, where h is the discretization size. Therefore, Euler method is first order accurate. Nowadays, there are many high order accurate schemes to solve ODE, but Euler method is still a classical one as one first learn numerical methods. We will revisit the details about Euler methods in Chapter 6. In MATLAB, we have some options of using Runge-Kutta methods to solve ODE systems, which will be introduced in the following.

Using MATLAB to solve ODE

When solving ODE with MATLAB, we need to represent $f(y,t)$ as a "FUNCTION" in MATLAB, with the input t and y, and output dy. If we call teh FUNCTION file as "odefile.m", the format of ODE is as follows: `[t,y]=solver('odefile',[t0,t1],y0)`, where $[t_0,t_1]$ is the time interval of interest, and y_0 is the initial conditions. The options for the solver can be found be look up "help" in MATLAB. For example:

```
>>[t,y]=ode45('odefile',[1,3],2)
```

The above solves ODE with the prescibed $f(y,t)$ in odefile.m, within the time range $[0,1]$ and initial data $y(1) = 2$. Let us find out what is in that file:

```
>> type odefile.m
function dy = odefile(t,y)
dy = y^2 + t;
```

Problem 2.6. Try the following command to generate a vector **x**.

```
>> x = 0:0.01:2
```

What is x , explain what you see in MATLAB. Then use the command

```
>> y = sin(x)
```

to generate another vector **y**, what is **y**?

Using the above commands to plot the figure of $f(x) = 2\sin x^2$ for $0 \le x \le 3$, with x incremented by 0.05 in the discretization.

Problem 2.7. Write a code to solve the ODE

$$\frac{dN}{dt} = N\left(1 - \frac{N}{2}\right), \quad 0 \le t \le 5,$$

with initial condition $N(0) = 0.5$. Plot the numerical solution and the exact solution on the same figure with different markers and different colors (refer to the numerical section of Chapter 3 for plotting).

Problem 2.8. Solve the equation in Problem 2.5 with $a = 1$ numerically in the form $x = x(t)$ when (i) $x(0) = \frac{1}{2}$, (ii) $x(0) = \frac{3}{2}$.

Chapter 3
Linear Differential Equations

In order to use mathematics to answer biological questions we need to develop further the theory of differential equations. In this chapter we introduce linear differential equations of the second order, and a system of two first-order differential equations.

Consider a second order differential equation

$$a\frac{d^2x}{dt^2}+b\frac{dx}{dt}+cx=0 \tag{3.1}$$

where $a,\ b,\ c$ are real constants and $a\neq 0$. The general solution is

$$x(t)=c_1e^{\lambda_1 t}+c_2e^{\lambda_2 t}, \qquad c_1,c_2 \text{ are constants,} \tag{3.2}$$

where λ_1,λ_2 are the solutions of the quadratic equation

$$a\lambda^2+b\lambda+c=0,$$

namely,

$$\lambda_{1,2}=\frac{1}{2a}(-b\pm\sqrt{b^2-4ac}) \tag{3.3}$$

provided $\lambda_1\neq\lambda_2$. If $\lambda_1=\lambda_2=-\frac{b}{2a}$, then $te^{\lambda_1 t}$ is another solution of (3.1), and the general solution of (3.1) is

$$x(t)=c_1e^{\lambda_1 t}+c_2te^{\lambda_1 t}. \tag{3.4}$$

We can use the general solution to solve Eq. (3.1) subject to initial conditions

$$x(0)=\alpha, \quad x'(0)=\beta. \tag{3.5}$$

Problem 3.1. Consider the equation (3.1) with initial conditions (3.5). Prove that there is a unique solution of the form (3.2) if $\lambda_1\neq\lambda_2$, and of the form (3.4) if $\lambda_1=\lambda_2$.

If b^2-4ac is negative, then λ_1 and λ_2 are complex numbers,

$$\lambda_{1,2}=\frac{1}{2a}(-b\pm i\sqrt{4ac-b^2})=\mu\pm i\nu \tag{3.6}$$

and

$$e^{\lambda_{1,2}t}=e^{\mu t}(\cos\nu t\pm i\sin\nu t).$$

Then the general solution can be written in the form

$$x(t)=c_1e^{\mu t}\cos\nu t+c_2e^{\mu t}\sin\nu t.$$

Consider next a 2×2 linear system

$$\begin{array}{l}\frac{dx_1}{dt}=a_{11}x_1+a_{12}x_2\\ \frac{dx_2}{dt}=a_{21}x_1+a_{22}x_2\end{array} \tag{3.7}$$

We try to solve it in the form

$$x_1=v_1e^{\lambda t},\quad x_2=v_2e^{\lambda t}.$$

Then

$$\begin{aligned}a_{11}v_1+a_{12}v_2&=v_1\lambda\\ a_{21}v_1+a_{22}v_2&=v_2\lambda.\end{aligned}$$

We can rewrite this system in matrix form

$$\begin{pmatrix}a_{11}-\lambda & a_{12}\\ a_{21} & a_{22}-\lambda\end{pmatrix}\begin{pmatrix}v_1\\ v_2\end{pmatrix}=\begin{pmatrix}0\\ 0\end{pmatrix}, \tag{3.8}$$

or $(A-\lambda I)\mathbf{v}=0$ where

$$A=\begin{pmatrix}a_{11}\ a_{12}\\ a_{21}\ a_{22}\end{pmatrix},\quad I=\begin{pmatrix}1\ 0\\ 0\ 1\end{pmatrix},\quad \mathbf{v}=\begin{pmatrix}v_1\\ v_2\end{pmatrix}.$$

A nonzero solution $\mathbf{v}$ exists if and only if λ satisfies the **characteristic equation**

$$\det(A-\lambda I)=0. \tag{3.9}$$

A solution λ of (3.9) is called an **eigenvalue** of A and a corresponding $\mathbf{v}$ is called **eigenvector**. Eq. (3.9) can be written explicitly as

$$\lambda^2-\lambda(a_{11}+a_{22})+(a_{11}a_{22}-a_{12}a_{21})=0. \tag{3.10}$$

If the two eigenvalues λ_1,λ_2 are different, then the general solution of Eq. (3.7) is

$$\mathbf{x}(t)=c_1\mathbf{w}_1e^{\lambda_1t}+c_2\mathbf{w}_2e^{\lambda_2t}, \tag{3.11}$$

where $\mathbf{w}_1$ and $\mathbf{w}_2$ are the eigenvectors corresponding to λ_1 and λ_2, respectively. More precisely,

Theorem 3.1. *If $\lambda_1 \neq \lambda_2$ then for any initial values*

$$\mathbf{x}(0) = \mathbf{b} \quad \textit{where } \mathbf{b} = \begin{pmatrix} b_1 \\ b_2 \end{pmatrix}, \tag{3.12}$$

there is a unique solution of (3.7), (3.12) in the form (3.11).

Proof. We first claim that $\mathbf{w}_1, \mathbf{w}_2$ are linearly independent, that is,

$$\text{if } \alpha_1 \mathbf{w}_1 + \alpha_2 \mathbf{w}_2 = 0, \text{then } \alpha_1 = \alpha_2 = 0.$$

Indeed this relation implies that

$$\alpha_1 \lambda_1 \mathbf{w}_1 + \alpha_2 \lambda_2 \mathbf{w}_2 = \alpha_1 A \mathbf{w}_1 + \alpha_2 A \mathbf{w}_2 = A(\alpha_1 \mathbf{w}_1 + \alpha_2 \mathbf{w}_2) = 0.$$

Since also $\alpha_1 \mathbf{w}_1 + \alpha_2 \mathbf{w}_2 = 0$, we get, by subtraction,

$$\alpha_2 \lambda_2 \mathbf{w}_2 - \lambda_1 \alpha_2 \mathbf{w}_2 = 0, \quad \text{or } (\lambda_2 - \lambda_1)\alpha_2 \mathbf{w}_2 = 0.$$

If follows that $\alpha_2 = 0$, and then also $\alpha_1 = 0$.

Setting

$$\mathbf{w}_1 = \begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix}, \quad \mathbf{w}_2 = \begin{pmatrix} v_{21} \\ v_{22} \end{pmatrix}$$

we conclude that

$$\text{if } \sum_{i=1}^{2} v_{ij} \alpha_i = 0 \text{ for } j = 1, 2, \text{ then } \alpha_1 = \alpha_2 = 0.$$

Hence, $det(v_{ij}) = 0$. But then, by linear algebra, for any (b_1, b_2) there is a unique solution (c_1, c_2) of the system

$$\sum_{i=1}^{2} v_{ij} c_i = b_i \quad (j = 1, 2),$$

and the function $\mathbf{x}(t)$ in (3.11) is the solution asserted in the theorem.

Consider now the case where λ_1 is a complex number, $\lambda_1 = \mu + i\nu$. Then the components of the eigenvector $\mathbf{w}_1$ are also complex numbers. But we are interested only in real-valued solutions. So in order to construct real-valued solutions we write

$$\mathbf{w}_1 e^{\lambda_1 t} = \begin{pmatrix} v_{11} + iv_{12} \\ v_{21} + iv_{22} \end{pmatrix} e^{\mu t} (\cos \nu t + i \sin \nu t) \tag{3.13}$$

where v_{ij} are real numbers. We note that the complex conjugate of $\mathbf{w}_1 e^{\lambda_1 t}$ is also a solution of (3.7) and, hence, so are the real and imaginary parts of (3.13). It follows

that

$$e^{\mu t}\begin{pmatrix} v_{11}\cos \nu t - v_{12}\sin \nu t \\ v_{21}\cos \nu t - v_{22}\sin \nu t \end{pmatrix} \quad \text{and} \quad e^{\mu t}\begin{pmatrix} v_{11}\sin \nu t + v_{12}\cos \nu t \\ v_{21}\sin \nu t + v_{22}\cos \nu t \end{pmatrix} \tag{3.14}$$

are two solutions.

Problem 3.2. Prove that the two solutions in (3.14) are linearly independent.

From Problem 3.2 it follows, as in the proof of Theorem 3.1, that any solution of (3.7) is a linear combination of the two solutions in (3.14).

By writing the roots λ_1, λ_2 of (3.10) in the form (3.3) or (3.6), we see that $Re\lambda_1 < 0$ and $Re\lambda_2 < 0$ if and only if

$$\begin{array}{c} \text{trace of } A \equiv a_{11} + a_{22} < 0, \\ \text{determinant of } A \equiv a_{11}a_{22} - a_{12}a_{21} > 0. \end{array} \tag{3.15}$$

If $\lambda_1 = \lambda_2$, then in addition to a solution $\mathbf{w}_1 e^{\lambda_1 t}$ of Eq. (3.7) where $\mathbf{w}_1$ is an eigenvector of (3.8) there is another solution of the form $\mathbf{w}_1 t e^{\lambda t} + \hat{\mathbf{w}}_2 e^{\lambda t}$ where $\hat{\mathbf{w}}_2$ is an appropriate vector. Setting $\mathbf{w}_2 = \mathbf{w}_1 + \hat{\mathbf{w}}_2$, the general solution of Eq. (3.7) is

$$\mathbf{x}(t) = c_1 \mathbf{w}_2 e^{\lambda_1 t} + c_2 \mathbf{w}_1 t e^{\lambda_1 t}.$$

Set $\mathbf{x} = (x_1, x_2)$. The proint $\mathbf{x} = \mathbf{0}$ is called an **equilibrium** point of (3.7), since the solution $\mathbf{x}(t)$ with $\mathbf{x}(0) = \mathbf{0}$ is $\mathbf{x}(t) \equiv \mathbf{0}$. We define the **phase space** for Eqs. (3.7) as the (x_1, x_2)-space, and we want to draw the portrait of the trajectories in this space near $\mathbf{x} = \mathbf{0}$, at least qualitatively. This can be done with the aid of the form (3.11) of the general solution. The protrait will depend on the eigenvalues λ_1, λ_2 as follows.

Figures 3.1(B) and 3.1(E) show that when both eigenvalues have negative real parts, all the trajectories converge to $\mathbf{x} = \mathbf{0}$; we say that $\mathbf{x} = \mathbf{0}$ is a **stable** equilibrium (or more precisely, **asymptotically stable** equilibrium). On the other hand, when at least one of the eigenvalues has positive real part, there are always trajectories that go away from $\mathbf{x} = \mathbf{0}$ even if they start initially near $\mathbf{x} = \mathbf{0}$; we say that $\mathbf{x} = \mathbf{0}$ is an **unstable** equilibrium.

In order to solve an inhomogeneous linear equation

$$a\frac{d^2x}{dt^2} + b\frac{dx}{dt} + cx = f(t) \tag{3.16}$$

with a given function $f(t)$, we first find a special solution $\tilde{x}(t)$ and, then, the general solution is a sum of $\tilde{x}(t)$ and the general solution of the homogeneous equation. The same procedure applies to inhomogeneous linear systems.

Problem 3.3. Find the general solution of $x'' + x' - x = t^2$.

Problem 3.4. Find the solution of $x'' - 4x' + 3x = e^{-t}$ with $x(0) = \frac{1}{8}, x'(0) = \frac{1}{4}$.

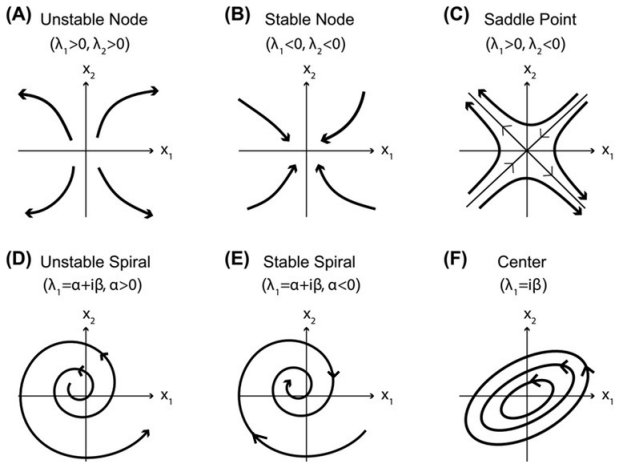


Fig. 3.1 Phase portrait

Problem 3.5. Find the general solution of

$$\frac{dx_1}{dt} = -2x_1 + 7x_2$$
$$\frac{dx_2}{dt} = 2x_1 + 3x_2.$$

Problem 3.6. Find the general solution of

$$\frac{dx_1}{dt} = x_1 - 2x_2$$
$$\frac{dx_2}{dt} = 2x_1 + x_2.$$

3.1 Numerical Simulations

3.1.1 Solving a second order ODE

In previous chapters, we have simulated scalar first order ODEs with MATLAB. A natural question is that whether we need additional MATLAB functions to simulate

higher oder equations? The answer is no. What we need to do is to convert higher order equations into systems of ODEs, and then we will simulate the ODE systems. Let's take a second order ODE as an example:

$$u''(t) + 16u'(t) + 192u(t) = 0$$

can be converted to

$$\begin{cases} x_1' = & x_2 \\ x_2' = -16x_2 - 192x_1 \end{cases}$$

by letting $x_1 = u$ and $x_2 = u'$. In general, a system of two first order ordinary differential equations has the form

$$\begin{cases} x_1' = F_1(x_1, x_2, t) \\ x_2' = F_2(x_1, x_2, t) \end{cases} \tag{3.17}$$

For example, given an ODE system

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 1 & 2 \\ 2 & 3 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} 0 \\ t^2 \end{pmatrix}, \quad 0 \le t \le 1,$$

with initial condition $\begin{pmatrix} x_1(0) \\ x_2(0) \end{pmatrix} = \begin{pmatrix} 2 \\ 3 \end{pmatrix}$, we can solve with MATLAB as follows. First, we create the main script file, named main.m, in which we type

```
x_ini = [2,3]';
[t,x] = ode45('odefile', [0,1], x_ini);
```

This file is the file we execute in MATLAB, which may call other functions. Now we have defined the initial condition, and we need to define $F_1(x_1, x_2, t)$ and $F_2(x_1, x_2, t)$. To do that, we create another script file called define.m, which is a function file that will be called while MATLAB is running ode45. In odefile.m, we type

```
function dx = odefile(t,x)
A = [1,2; 2,3];
dx = A*x + [0, t^2]';
```

By running main.m, we end up with MATALB variables t and x, which are column vectors. Variable t has components as the discrete time that MATLAB uses to in the simulation, and the components of x are approximated values for the corresponding component in t.

3.1.2 Plotting figures

Suppose $x = [x_1, x_2, x_3, \cdots, x_n]$ is a vector representing sampling points on $x-$axis and $y = [y_1, y_2, y_3, \cdots, y_n]$ represents the corresponding function values of components of x (note that x and y must be of the same length), then to plot x versus y, one uses

```
>> plot(x,y)
```

To label the axis, we can use

```
>> xlabel('x'), ylabel('y')
```

One can also specify the color and marker by addtng an option in the "plot" function

```
>> plot(x,y,'r o') % this marks those point values by red circles
```

If we would like to overlay two curves, x versus y and x versus z, where $z = [z_1, z_2, z_3, \cdots, z_n]$, we can use

```
>> plot(x,y,'r',x,z,'b') % mark the first y(x) function in red and the second z(x) in blue.
```

or

```
>> plot(x,y,'r'), hold on
>> plot(x,z,'b')
```

The "hold on" command holds the first figure data and the second will be plotted on top of the first one. Without this command, the previous data in the figure will be overwritten.

Problem 3.7. (a) Rewrite Problem 3.4 into first order systems. (b) Take the initial condition to be $x(0) = 1, x'(0) = 0$, and the time interval $0 \le t \le 3$. Use MATLAB to solve the system you get in (a), and plot the two variables on the same figure.

Problem 3.8. Solve $y'' - 5y' = 0$, $y(0) = 1$, $y'(0) = 2$, first explicitly, and then numerically. Compare the two graphs of $y(t)$ for $0 \le t \le 3$.

Problem 3.9. Solve

$$\frac{dx_1}{dt} = x_1 - x_2$$
$$\frac{dx_2}{dt} = x_1 + x_2$$

with $x_1(0) = 1, x_2(0) = 5$, first explicitly and then numerically and compute the two graphs of $x_1(t)$ for $0 \le t \le 2$.

Chapter 4
Systems of two differential equations

The system (3.7) is linear. In this chapter we study general systems of two differential equations has the form

$$\frac{dx_1}{dt} = f_1(x_1,x_2), \quad \frac{dx_2}{dt} = f_2(x_1,x_2), \tag{4.1}$$

where $f_1(x_1,x_2), f_2(x_1,x_2)$ are any given functions, not necessarily linear. A point (a,b) such that

$$f_1(a,b) = 0, \quad f_2(a,b) = 0$$

is called an **equilibrium** point, a **stationary** point or a **steady** point of the system (4.1). The x_1-**nullcline** of (4.1) is the curve consisting of points satisfying the equation

$$f_1(x_1,x_2) = 0.$$

Similarly, the x_2-**nullcline** is the curve defined by

$$f_2(x_1,x_2) = 0.$$

The equilibrium points of the system (4.1) are the points where the two nullclines intersect. To get an idea how trajectories behave near a stationary point (a,b), we **linearize** the system.

We set

$$X_1 = x_1 - a, \quad X_2 = x_2 - b.$$

Then, by Taylor's formula,

$$f_i(x_1,x_2) = f_i(a+X_1,b+X_2) = f_i(a,b) + \frac{\partial f_i}{\partial x_1}X_1 + \frac{\partial f_i}{\partial x_2}X_2 + \text{small terms},$$

where

$$\frac{\partial f_i}{\partial x_1} = \frac{\partial f_i}{\partial x_1}(a,b), \quad \frac{\partial f_i}{\partial x_2} = \frac{\partial f_i}{\partial x_2}(a,b).$$

If we define

$$a_{ij} = \frac{\partial f_i}{\partial x_j}(a,b)$$

then the system (4.1) near (a,b) has the form

$$\frac{dX_i}{dt} = a_{i1}X_1 + a_{i2}X_2 + \text{small terms} \quad (i = 1,2)$$

when X_1, X_2 are near 0. Hence the trajectories of (4.1) are expected to behave approximately like the trajectories of

$$\frac{dX_i}{dt} = a_{i1}X_1 + a_{i2}X_2, \quad i = 1,2. \tag{4.2}$$

Accordingly, the equilibriun point (a,b) of (4.1) is said to be **stable** if the equilibrium point $\mathbf{x} = \mathbf{0}$ of (4.2) is stable, that is, if the real parts of eigenvalues of the matrix $A = (a_{ij})$ are negative.

We conclude that the equilibrium point (a,b) of the system (4.1) is stable if and only if the following inequalities hold at (a,b):

$$\begin{array}{c} \frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} < 0, \\ \frac{\partial f_1}{\partial x_1}\frac{\partial f_2}{\partial x_2} - \frac{\partial f_1}{\partial x_2}\frac{\partial f_2}{\partial x_1} > 0. \end{array} \tag{4.3}$$

i.e., trace of $\left(\frac{\partial f_i}{\partial x_j}\right) < 0$ and determinant of $\left(\frac{\partial f_i}{\partial x_j}\right) > 0$. The matrix $(\frac{\partial f_i}{\partial x_j}(a,b))$ is called the **Jacobian matrix** at the equilibrium point (a,b).

Problem 4.1. The system

$$\begin{aligned} \frac{dx}{dt} &= x^2 - y^2 \\ \frac{dy}{dt} &= x(1-y) \end{aligned}$$

has two nonzero equilibrium points $(1,1), (-1,1)$. Find the eigenvalues of the Jacobian matrix for each of these points, and determine the behavior of the trajectories in terms of the classification described in the graphs in Fig. 3.1.

Problem 4.2. Do the same for the system

$$\frac{dx}{dt} = x - xy^2, \quad \frac{dy}{dt} = y + xy^2 + 1$$

with its steady points $(0,-1), (-2,1)$.

4.1 Numerical Simulations

As mentioned in the previous chapter. In general, a system of two first order ordinary differential equations has the form

$$\begin{cases} x_1' = F_1(x_1, x_2, t) \\ x_2' = F_2(x_1, x_2, t) \end{cases} \tag{4.4}$$

If it is a linear system, the general form can be written as

$$\begin{cases} x_1' = a_{11}(t)x_1 + a_{12}(t)x_2 + b_1(t) \\ x_2' = a_{21}(t)x_1 + a_{22}(t)x_2 + b_2(t), \end{cases} \tag{4.5}$$

which can be written concisely as

$$x' = A(t)x + b(t)$$

where

$$x = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix}, b(t) = \begin{pmatrix} b_1(t) \\ b_2(t) \end{pmatrix}, A(t) = \begin{pmatrix} a_{11}(t) & a_{12}(t) \\ a_{21}(t) & a_{22}(t) \end{pmatrix}$$

When A is a constant matrix and $b = 0$, the solution can be easily carried out via eigenvalue and eigenfunction computation.

Example 1:

$$x' = \begin{pmatrix} 1 & 1 \\ 4 & 1 \end{pmatrix} x \tag{4.6}$$

$$x = c_1 \begin{pmatrix} 1 \\ 2 \end{pmatrix} e^{3t} + c_2 \begin{pmatrix} 1 \\ -2 \end{pmatrix} e^{-t}$$

The origin is a saddle point and is unstable (Figure 4.1).

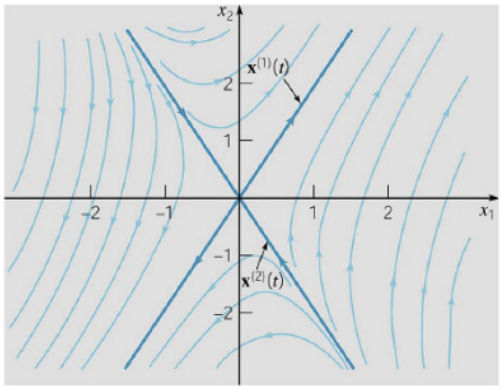


Fig. 4.1 Unstable saddle point.

In MATLAB, this is a simple one-line command to compute eigenvalue and eigenvector.

```
>> A=[1 1;4 1];
>> [V,D]=eig(A)
V =
0.4472 -0.4472
0.8944 0.8944
D =
3.0000 0 0 -1.0000
```

Example 2:

$$x' = \begin{pmatrix} -3 & \sqrt{2} \\ \sqrt{2} & -2 \end{pmatrix} x$$

$$x = c_1 \begin{pmatrix} 1 \\ \sqrt{2} \end{pmatrix} e^{-t} + c_2 \begin{pmatrix} -\sqrt{2} \\ 1 \end{pmatrix} e^{-4t}$$

The original is a stable node (Figure 4.2). (Figure 4.1).

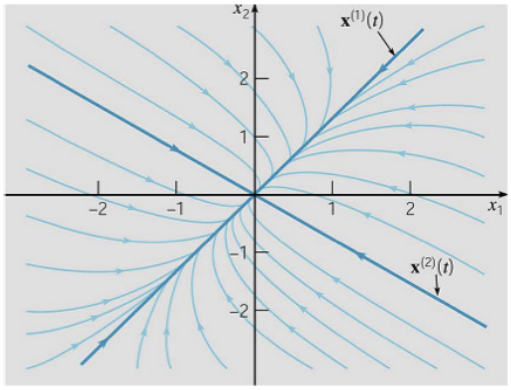


Fig. 4.2 Stable saddle point.

Example 3:

$$x' = \begin{pmatrix} -\frac{1}{2} & 1 \\ -1 & -\frac{1}{2} \end{pmatrix} x$$

$$x = c_1 \begin{pmatrix} \cos(t) \\ -\sin(t) \end{pmatrix} e^{-t/2} + c_2 \begin{pmatrix} \sin(t) \\ \cos(t) \end{pmatrix} e^{-t/2}$$

The origin is a spiral point and is asymptotically stable (Figure 4.3).

Example 4:

$$x' = \begin{pmatrix} 1 & -1 \\ 1 & 3 \end{pmatrix} x$$

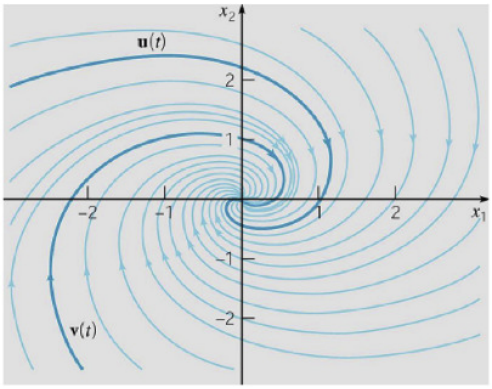


Fig. 4.3 Stable spiral.

$$x = c_1 \begin{pmatrix} 1 \\ -1 \end{pmatrix} e^{2t} + c_2 \left[\begin{pmatrix} 1 \\ -1 \end{pmatrix} t e^{2t} + \begin{pmatrix} 0 \\ -1 \end{pmatrix} e^{2t} \right]$$

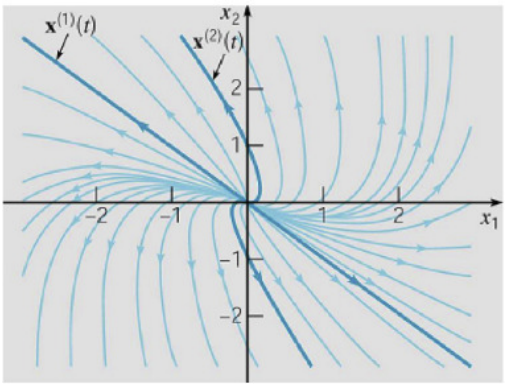


Fig. 4.4 Unstable steady state.

The origin is an improper mode, and is unstable (Figure 4.4).

Problem 4.3. Give a 2 by 2 linear system that the origin is (a) unstable node, real eigenvalues and $\lambda_1 > 0$, $\lambda_2 > 0$ (b) stable node, real eigenvalues and $\lambda_1 < 0$, $\lambda_2 < 0$ (c) saddle point, real eigenvalues and $\lambda_1 \lambda_2 < 0$ (d) unstable spiral, complex eigenvalues $\lambda = \alpha + i\beta$ and $\alpha > 0$ (e) stable spiral, complex eigenvalues $\lambda = \alpha + i\beta$ and $\alpha < 0$ (f) center, $\lambda = \alpha + i\beta$ and $\alpha = 0$. For all the above systems, plot the directional fields for $-3 \leq x \leq 3, -3 \leq y \leq 3$.

Problem 4.4. Solve numerically

$$\dot{x} = xy - y, \quad \dot{y} = xy + x$$

with $x(0) = 1,\ y(0) = 1$, for $0 \le t \le 3$.

Problem 4.5. Solve numerically

$$\dot{x} = x - xy^2, \quad \dot{y} = y + xy^2 + 1$$

with $x(0) = 1,\ y(0) = 1$, for $0 \le t \le 3$.

Problem 4.6. 3.6. Solve numerically

$$\dot{x} = -xy, \quad \dot{y} = (1 - x)(1 + y)$$

with $x(0) = 2,\ y(0) = 0$, for $0 \le t \le 4$.

Chapter 5
Predator-Prey Models

A predator is an organism that eats another organism. A prey is an organism that a predator eats. In ecology, a **predation** is a biological interaction where a predator feeds on a prey. Predation occurs in a wide variety of scenarios, for instance in wild life interactions (lions hunting zebras, foxes hunting rabbits), in herbivore-plant interactions (cows grazing), and in parasite-host interactions.

If the predator is to survive over many generations, it must ensure that it consumes sufficient amount of prey, otherwise its population will decrease over time and will eventually disappear. At the same time the predator must not over-consume the prey, for if the prey population will decrease and disappear, then also the predators will die out, from starvation.

Thus the question arises: what is the best strategy of the predator that will ensure its survival. This question is very important to ecologists who are concerned with biodiversity. But it is also an important question in the food industry; for example, in the context of fishing, what is the sustainable amount of fish harvesting?

In this chapter we use mathematics to provide answers to these questions.

We begin with a simple predator-prey example.

We denote by x the density of a prey, that is, the number of prey animals per unit area on land (or volume in sea) and by y the density of predators. We denote by a the net growth rate in x (birth minus natrual death), and by c the net death rate of predators. The growth of predators is assumed to depend only on the prey as food. Predation occurs when predator comes into close contact with prey, and we take this encounter to occur at an average rate b. Hence

$$\frac{dx}{dt} = ax - bxy. \tag{5.1}$$

The growth of predators is proportional to bxy, so that

$$\frac{dy}{dt} = dxy - cy. \tag{5.2}$$

In terms of dimensions,

$$[a] = \frac{1}{\text{time}}, \quad [b] = \frac{1}{\text{density of predator}} \frac{1}{\text{time}},$$

and

$$[c] = \frac{1}{\text{time}}, \quad [d] = \frac{1}{\text{density of prey}} \frac{1}{\text{time}}.$$

The system (5.1), (5.2) has two equilibrium points. The first one is $(0,0)$; this corresponds to a situation where both species die. This equilibrium point is unstable. Indeed the Jacobian matrix at $(0,0)$ is

$$\begin{pmatrix} a & 0 \\ 0 & -c \end{pmatrix}$$

and one of the eigenvalues, namely a, is positive.

The second equilibrium point is $(\frac{c}{d}, \frac{a}{b})$ and the Jacobian matrix at this point is

$$\begin{pmatrix} 0 & \frac{-bc}{d} \\ \frac{ad}{b} & 0 \end{pmatrix}$$

The corresponding eigenvalues are $\lambda = \pm i\sqrt{ac}$. According to Fig. 3.1 the phase portrait is a circle. We conclude: The predator and prey can both survive forever, and their population will undergo periodic (seasonal) oscillations.

Eqs. (5.1), (5.2) are examples of what is known as **Lotka-Volterra** equations. One can introduce various variants into these equations. For example, if the prey population is quite conjested, we may want to use the logistic growth, and write

$$\frac{dx}{dt} = ax(1 - \frac{x}{B}) - bxy. \tag{5.3}$$

More general models of predator-prey are written in the form

$$\frac{dx}{dt} = xf(x,y), \quad \frac{dy}{dt} = yg(x,y)$$

where x is the prey and y is the predator, $\partial f/\partial y < 0, \partial g/\partial x > 0$, and $\partial f/\partial x < 0$ for large x, $\partial g/\partial y < 0$ for large y. The first two inequalities mean that the prey population is depleted by the predator and the predator population is increased by feeding on the prey. The last two inequalities represent natural death due to the logistic growth model.

We next consider a plant-herbivore model. The herbivore N feeds on plant P. We take the consumption rate of the plant to be

$$\frac{\sigma P}{1+P} N;$$

this means that, at small amount of P, N consumes P at a linear rate σP, but the rate of consumption by N is limited and cannot exceed σN. Thus,

$$\frac{dP}{dt} = rP - \sigma \frac{P}{1+P} N. \tag{5.4}$$

The equation for the herbivore is

$$\frac{dN}{dt} = \lambda \sigma \frac{P}{1+P} N - dN. \tag{5.5}$$

Here d is the death rate of N, and λ is the **yield constant**, that is,

$$\lambda = \frac{\text{mass of herbivore formed}}{\text{mass of plant used}};$$

naturally $\lambda < 1$. Note that if $\lambda\sigma < d$ then $\frac{dN}{dt} < 0$ and the herbivore will die out.

Problem 5.1. Show that in the model (5.2), (5.3), if $B > \frac{c}{d}$ then the point $(x,y) = (\frac{c}{d}, \frac{a}{b}(1 - \frac{c}{Bd}))$ is a stable equilibrium point.

In both models (5.1), (5.2) and (5.3), (5.2), the consumption rate of the prey by the predator is proportional to the density of the prey. In both models the predator and prey co-exist, either as stable steady state for model (5.3), (5.2) and as periodic solution for model (5.1), (5.2). The situation is quite different for the model model (5.4), (5.5), since the herbivore consumption is not proportional to the density of the plant, but is rather limited by the parameter σ. In this case, since $(0,0)$ is unstable equilibrium, we expect herbivore and plant to co-exist but their dynamics is quite complicated.

We conclude that if the prey undergoes logistic growth then the populations of predator and prey will survive and stabilize at fixed levels, rather than survive with seasonal oscillation (as was the case in the model (5.1), (5.2)).

Factorization rule

Consider a system (4.1) where the f_i can be factored as follows:

$$f_1(x_1,x_2) = x_1 g_1(x_1,x_2), \quad f_2(x_1,x_2) = x_2 g_2(x_1,x_2),$$

so that

$$\frac{dx_1}{dt} = x_1 g_1(x_1,x_2), \quad \frac{dx_2}{dt} = x_2 g_2(x_1,x_2)$$

In this case there are equilibrium points $P_1 = (0,0), P_2 = (0,\bar{x}_2)$ if $g_2(0,\bar{x}_2) = 0$, $P_3 = (\bar{x}_1,0)$ if $g_1(\bar{x}_1,0) = 0$, and $P_4(\tilde{x}_1,\tilde{x}_2)$ if $g_1(\tilde{x}_1,\tilde{x}_2) = 0$, $g_2(\tilde{x}_1,\tilde{x}_2) = 0$. We can then quickly compute the Jacobian matrix $J(P_i)$ at each point P_i. For example, to compute $J(P_4)$ when $\tilde{x}_1 > 0, \tilde{x}_2 > 0$, we notice that since $g_1 = g_2 = 0$ at P_4,

$$J(P_4) = \begin{pmatrix} x_1 \frac{\partial g_1}{\partial x_1} & x_1 \frac{\partial g_1}{\partial x_2} \\ x_2 \frac{\partial g_2}{\partial x_1} & x_2 \frac{\partial g_1}{\partial x_2} \end{pmatrix}_{(\tilde{x}_1,\tilde{x}_2)}.$$

Similarly,

$$J(P_1) = \begin{pmatrix} g_1(0,0) & 0 \\ 0 & g_2(0,0) \end{pmatrix},$$

$$J(P_2) = \begin{pmatrix} g_1 & 0 \\ x_2 \frac{\partial g_2}{\partial x_1} & x_2 \frac{\partial g_1}{\partial x_2} \end{pmatrix}_{(0,\bar{x}_2)}$$

and

$$J(P_3) = \begin{pmatrix} x_1 \frac{\partial g_1}{\partial x_1} & x_1 \frac{\partial g_1}{\partial x_2} \\ 0 & g_2 \end{pmatrix}_{(\tilde{x}_1,0)} \quad \text{where } \tilde{x}_1 > 0.$$

We shall refer to these shortcuts in the computation of the Jacobian matrix as the **factorization rule**.

Use the factorization rule to solve Problems 5.2, 6.3.

Problem 5.2. Show that in the plant-herbivore model (5.4)-(5.5), the equilibrium point $(0,0)$ is unstable.

Problem 5.3. Assume that in the model (5.4)-(5.5), $\lambda\sigma > d$. Prove that there is a second equilibrium point (P_2, N_2) where

$$P_2 = \frac{d}{\lambda\sigma - d}, \quad N_2 = \frac{\lambda r}{\lambda\sigma - d}, \tag{5.6}$$

and that it is unstable.

The **Allee** effect refers to the biological fact that increased fitness correlates positively with higher population, or that "undercrowding" decreases fitness. More specifically, if the size of a population is below a threshold then it is destined for extinction. Endangered species are often subject to the Allee effect.

Consider a predator-prey model where the prey is subject to the Allee effect,

$$\frac{dx}{dt} = rx(x-\alpha)(1-x) - \sigma xy, \quad (0 < \alpha < 1), \tag{5.7}$$

that is, if the population $x(t)$ decreases below the threshold $x = \alpha$, then $x(t)$ will decrease to zero as $t \to \infty$. The predator y satisfies the equation

$$\frac{dy}{dt} = \lambda\sigma xy - \sigma y \tag{5.8}$$

where λ is the yield constant. The point $(0,0)$ is an equilibrium point of the system (6.14)-(6.15).

Problem 5.4. Show that if $\alpha < \frac{\delta}{\lambda\sigma} < 1$, then the system (6.14)-(6.15) has a second equilibrium point $(\bar{x}, \bar{y}) = (\frac{\delta}{\lambda\sigma}, r(\frac{\delta}{\lambda\sigma} - \alpha)(1 - \frac{\delta}{\lambda\sigma}))$, and it is stable if

$$\frac{\delta}{\lambda\sigma} > \frac{1+\alpha}{2}.$$

This result shows that for the predator to survive, the prey must be allowed to survive, and the predator must adjust its maximum eating rate, σ, so that

$$\frac{\delta}{\lambda} < \sigma < \frac{\delta}{\lambda}\frac{2}{1+\alpha}.$$

If the Allee threshold, α, deteriorates and approaches 1, the predator must then decrease its rate of consumption of the prey and bring it closer to δ/λ, otherwise it will become extinct.

5.1 Numerical Simulations

The following algorithms code (5.1)-(5.2). These codes also demonstrate how to implement nonlinear systems (see fun_predator_prey.m). Also note that in model_predator_prey.m, when we plot both x and y variables, we use "subplot" command. The "subplot" allows one to plot more than one subfigures in one plot. Its argument (m,n,k) stands for total number of rows, total number column and the place of the subfigurem respectively. You can type

```
>> help subplot
```

to see how to use it.

Algorithm 1 model_predator_prey.m

```
% This code simulates model (5.1)-(5.2).
close all,
clear all,
% define global parameters
global a b c d
% starting and final time
t0 = 0; tfinal = 5;
% paramters
a = 5; b = 2; c = 9; d = 1;
% initial conditions
v0 = [10,5];
[t,v] = ode45('fun_predator_prey',[t0,tfinal],v0);
subplot(1,2,1)
plot(t,v(:,1)) % plot the evolution of x
xlabel t, ylabel x
subplot(1,2,2)
plot(t,v(:,2)) % plot the evolution of y
xlabel t, ylabel y
```

Problem 5.5. Plot the time evolution of model of equations (5.1)-(5.2) with $a = 5, b = 2, c = 9, d = 1$ starting from $(10,5)$, for time from 0 to 5.

Algorithm 2 fun_predator_prey.m

```
% This is the function file called by model_predator_prey.m
function dy = ffun_predator_prey(t,v)
global a b c d
dy = zeros(2,1);
dy(1) = a*v(1) - b*v(1)*v(2);
dy(2) = -c*v(2) + d*v(1)*v(2);
```

Problem 5.6. Draw the phase portrait for (5.1), (5.2) with $a = 5, b = 2, c = 9, d = 1$ starting from several points near $(9, 5/2)$.

Problem 5.7. The only nonzero steady point of (5.2), (5.3) is $(\frac{c}{d}, \frac{a}{b} - \frac{ac}{bdB})$; it is biologically meaningful only if $1 - \frac{c}{dB} > 0$, and it is a stable spiral. Draw several trajectories when $a = b = c = d, B = 2$.

Problem 5.8. Draw the phase diagram for (5.2), (5.3) in case $a = b = c = d, B = \frac{1}{2}$.

Problem 5.9. Change the codes (adding one more global parameter B, and change dy(1) in fun_predator_prey.m) to implement (5.2)-(5.3). Plot the time evolutionwith $a = 5, b = 5, c = 5, d = 5, B = 0.5$ starting from $(2, 3)$, for time from 0 to 5.

Chapter 6
Two competing populations

Competition is an interaction between organisms, or species, sharing resources that are in limited supply. This is an important topic in ecology. The 'competitive exclusion principle' asserts that species less suited to compete will either adapt or die out. In aggressive competition one species may attempt to kill the other. This situation occurs, for example, among some species of ants, and some species or yeast. When enough data is known about the history of a specific competition between two species, mathematics can then be used to predict whether both species will survive and co-exist or whether one of them will die out.

In this chapter we consider some examples of competing populations and determine, using mathematics, whether one or both species will survive. We begin with the following model:

$$\frac{dx}{dt} = r_1 x(1 - \frac{x}{k_1}) - b_1 xy, \tag{6.1}$$

$$\frac{dy}{dt} = r_2 x(1 - \frac{y}{k_2}) - b_2 xy, \tag{6.2}$$

In Eq. (6.1), r_2 is the growth rate of species x, k_1 is the carrying capacity which limits its growth, and b_1 is the rate by which the competitor y kills x. Eq. (6.2) has similar interpretation.

The system (6.1)-(6.2) has equilibrium points

$$(0,0), \quad (k_1,0), \quad (0,k_2). \tag{6.3}$$

Note that the equilibrium point $(k_1,0)$ means that the second population becomes extinct. Similarly, $(0,k_2)$ corresponds to a situation where the first population becomes extinct.

In order to determine whether there exist additional equilibrium points, we must solve the equations

$$r_1(1-\frac{x}{k_1})-b_1y=0,$$
$$r_2(1-\frac{y}{k_2})-b_2x=0.$$

The solution is given by

$$(\frac{\beta_1k_2-k_1}{\beta_1\beta_2-1},\frac{\beta_2k_1-k_2}{\beta_1\beta_2-1}) \quad \text{where } \beta_i=\frac{k_ib_i}{r_i}, \quad (i=1,2). \tag{6.4}$$

This steady point is of biological relevance only if the two components are positive, which occurs only when either

$$k_1>\frac{r_2}{b_2}, \quad k_2>\frac{r_1}{b_1}$$

or

$$k_1<\frac{r_2}{b_2}, \quad k_2<\frac{r_1}{b_1}.$$

Problem 6.1. Determine whether the equilibrium points in (6.3) are stable.

Problem 6.2. Show that the steady point defined in (6.4) is the unique equilibrium point (x,y) of (6.1) with $x\neq 0, y\neq 0$, and show that it is stable if $k_1<\frac{r_2}{b_2}$ and $k_2<\frac{r_1}{b_1}$.

The result means that both species will co-exist provided that rate of killing by b_j is less than the rate r_i/k_i of growth rate divided by the carrying capacity, for $j=1,i=2$ and for $j=2,i=1$.

In the next example two species are competing for space. Consider for example grass (x) and weed (y) growing in the same field. They share some resources, e.g., nutrients from the ground. But they also receive resources independently from each other, e.g., sunshine and rain. Thus they only partially infringe upon each other in terms of the medium carrying capacity which supports their growth. We can model their dynamics as follows:

$$\frac{dx}{dt}=r_1x(1-\frac{x+\alpha y}{K})-\mu_1x, \tag{6.5}$$
$$\frac{dy}{dt}=r_2y(1-\frac{\beta x+y}{K})-\mu_2y, \tag{6.6}$$

where $0<\alpha<1, 0<\beta<1$. Assuming that $r_1=r_2=r$, $\mu_1=\mu_2=\mu$ and $r>\mu$, there is a steady state, $(\bar{x},\bar{y})$, where they co-exist:

$$r(1-\frac{\bar{x}+\alpha\bar{y}}{K})-\mu=0,$$
$$r(1-\frac{\beta\bar{x}+\bar{y}}{K})-\mu=0.$$

Problem 6.3. Show that the steady state of co-existence is given by

$$(\frac{K(1-\frac{\mu}{r})(1-\alpha)}{1-\alpha\beta}, \frac{K(1-\frac{\mu}{r})(1-\beta)}{1-\alpha\beta}).$$

and that this steady point is stable.

Problem 6.4. The model (6.5), (6.6) with $\alpha > 1, \beta > 1$ represents the growth of two species under fierce competition for resources. In this case, the steady point of co-existence is given by the same expression as in Problem 6.3. Show that this steady state is unstable.

The results of Problems 6.3 and 6.4 show that when two species are using the same resources, they both will stably co-exist if they do not infringe significantly upon each other, but they cannot stably co-exist if the competition is too aggressive.

Cancer model

Recall that logistic growth for a population with density x was modeled by

$$\frac{dx}{dt} = rx(1-\frac{x}{K}) - \mu x$$

where r is the growth rate, μ is the death rate, and K is the medium carrying capacity which is determined by the resources available to support the population. If $\mu > r$ then $\frac{dx}{dt} + (\mu - r)x \leq 0$ so that

$$x(t) \leq x(i)e^{-(\mu-r)t} \to 0, \text{ as } t \to \infty.$$

We are interested in cases where populations persist, so we shall take $\mu < r$.

If two populations x and y co-exist in the same medium and follow a logistic growth, then

$$\frac{dx}{dt} = r_1 x(1-\frac{x+y}{K}) - \mu_1 x,$$
$$\frac{dy}{dt} = r_2 y(1-\frac{x+y}{K}) - \mu_2 y.$$

where r_1 and r_2 are the growth rates of the populations x and y, respectively, and μ_1 and μ_2 are their respective death rates. Note that the two population share the medium, hence the term $(x+y)/K$ represents the load of the total population $x+y$ on the medium carrying capacity K. We shall apply this model to cancer in a human tissue, where x represents the density of normal healthy cells and y represents the density of cancer cells in the same tissue. Since cancer cells proliferate faster than normal healthy cells, we take

$$r_2 > r_1$$

. For simplicity we assume that $\mu_1 = \mu_2 = \mu$. Writing

$$\frac{dx}{dt} = x[r_1(1-\frac{x+y}{K})-\mu], \tag{6.7}$$

$$\frac{dy}{dt} = y[r_2(1-\frac{x+y}{K})-\mu], \tag{6.8}$$

we observe that there cannot be a steady point $(\bar{x},\bar{y})$ with $\bar{x}>0,\bar{y}>0$. On the other hand there are steady points

$$((1-\frac{\mu}{r_1})K,0), \quad (0,(1-\frac{\mu}{r_2})K).$$

Problem 6.5. Prove that $(0,(1-\frac{\mu}{r_2})K)$ is stable, and $((1-\frac{\mu}{r_1})K,0)$ is unstable.

This result means that cancer-free state is unstable whereas the steady state where all cells are cancer cells is stable.

It is interesting to explore the dynamics of the system (6.16), (6.8). We have

$$\frac{d}{dt}\ln\frac{y}{x} = \frac{1}{y}\frac{dy}{dt} - \frac{1}{x}\frac{dx}{dt} = (r_2-r_1)(1-\frac{x+y}{K}). \tag{6.9}$$

To make use of this formula we first show that if $x(0)+y(0)<K$ then for any sufficiently small $\varepsilon>0$ with $x(0)+y(0)+\varepsilon<K$, there holds:

$$x(t)+y(t)<K-\varepsilon \quad \text{for all } t>0. \tag{6.10}$$

Indeed, suppose this claim is not true, then there is a smallest $\bar{t}$ such that (6.10) holds for all $t<\bar{t}$ but

$$x(\bar{t})+y(\bar{t}) = K-\varepsilon. \tag{6.11}$$

It follows that

$$\frac{d}{dt}(x(t)+y(t))_{t=\bar{t}} \geq 0. \tag{6.12}$$

However, form Eqs. (6.16), (6.8) and (6.11), we get

$$\begin{aligned}\frac{d}{dt}(x(t)+y(t))_{t=\bar{t}} &\leq (K-\varepsilon)r_1(1-\frac{K-\varepsilon}{K})-\mu x(\bar{t})\\ &\quad +(K-\varepsilon)r_2(1-\frac{K-\varepsilon}{K})-\mu y(\bar{t})\\ &< K(r_1+r_2)\frac{\varepsilon}{K}-\mu(K-\varepsilon)<0\end{aligned}$$

if ε is sufficiently small, which is a contradiction to (6.12). Hence the assertion (6.10) is valid.

Substituting (6.10) into (6.9) we get

$$\frac{d}{dt}\ln\frac{y}{x} \geq (r_2-r_1)(1-\frac{K-\varepsilon}{K}) = \frac{(r_2-r_1)\varepsilon}{K} \equiv \delta.$$

It follows that

$$\ln \frac{y(t)}{x(t)} \geq \ln \frac{y(0)}{x(0)} + \delta t$$

if $y(0) > 0, x(0) > 0$, so that, with $C = y(0)/x(0)$,

$$\frac{y(t)}{x(t)} \geq Ce^{\delta t}.$$

But since, by (6.10), $y(t) < K$ for all $t > 0$, we conclude that

$$x(t) \leq \frac{K}{C} e^{-\delta t} \to 0, \quad \text{as } t \to \infty. \tag{6.13}$$

From (6.8) and (6.13) we deduce that if $y(t) > (1 - \frac{\mu}{r_2})K$ and t is large, then $\frac{dy(t)}{dt} < 0$, whereas if $y(t) < (1 - \frac{\mu}{r_2})K$ and t is large then $\frac{dy(t)}{dt} > 0$. Hence $y(t) \to (1 - \frac{\mu}{r_2})K$ as $t \to \infty$.

We have thus proved:

Theorem 6.1. *The steady cancer-only state* $(0, (1 - \frac{\mu}{r_2})K)$ *is globally asymptotically stable.*

Thus, the model (6.16), (6.8) predicts that, without treatment, the cancer cells will fill the entire tissue.

6.1 Numerical Simulations

6.1.1 Revisiting Euler method for solving ODE – consistency and convergence

Suppose the system of ODEs we would like to solve is

$$\frac{dx}{dt} = f(x,t), \quad t \geq t_0, \quad x(t_0) = x_0 \tag{6.14}$$

where f is a Lipschitz function in x and t and the initial condition x_0 is a given value in R. Note that even now we consider a single equation where x is a scalar, the discussion in the following can be easily generalized to systems in which x and f represent vectors. There are various ways to derive Euler method, here we give one derivation based on linear interpolation.

Integrating Eq. (6.14) from t_1 to $t_1 + h$, with $t_1 > t_0$, one abtains

$$x(t_1 + h) = x(t_1) + \int_{t_1}^{t_1+h} f(x(\tau), \tau) d\tau.$$

If we approximate the integral by $hf(x(t_1), t_1)$, which would be a good approximation given h sufficiently small, then

$$x(t_1+h) \approx x(t_1) + hf(x(t_1), t_1).$$

Thus, we have the forward Euler method by denoting X_j as the numerical solution at time t_n, $j = 1, \cdots, N$, where t_n are equi-distanced grid points with $t_0 < t_1 < \cdots < t_N$ and $h = t_{n+1} - t_n$,

$$X_{n+1} = X_n + hf(X_n, t_n). \tag{6.15}$$

This type of scheme is call **explicit scheme** because the solution X_{n+1} is explicitly defined in function of X_n. In other words, knowing X_n, one can explicitly compute X_{n+1}. Furthermore, it is called a **single step** method because it requires only solution at one time step in order to compute the solution at the following time step.

In order to understand how good the numerical solution is, we define **local truncation error** to measure how closely the difference operator approximates the differential operator, for Euler method:

$$d_n = \frac{x(t_{n+1}) - x(t_n)}{h} - f(x(t_n), t_n) = \frac{h}{2} x''(\bar{t}_n) + O(h^2).$$

where $\bar{t}_n$ is some point in the interval $[t_n, t_{n+1}]$. If a method has the local truncation error $O(h^p)$, we say that the method is pth order accurate.

However, the real goal is not consistency but **convergence**. Assume Nh is bounded independent of N. The method is said to be **convergent of order** p if the **global** error e_n, where $e_n = X_n - x(t_n)$, $e_0 = 0$, satisfies

$$e_n = O(h^p), \quad n = 1, 2, \cdots, N.$$

Problem 6.6. Consider the scalar problem

$$y' = -5ty^2 + \frac{5}{t} - \frac{1}{t^2}, \quad y(1) = 1.$$

(a) Verify that $y(t) = \frac{1}{t}$ is a solution to the problem. (b) Use forward Euler method until $t = 10$. Compute the error between the numerical solution and exact solution using $h = 0.002, 0.004, 0.008, 0.016$. From the errors, what can you say about the order of the scheme?

6.1.2 Backward Euler Method

While forward Euler method allows one to compute the numerical solution explicitly, backward Euler method is an implicit method in which one may have to solve a system of nonlinear equations. Given the equation

$$\frac{dx}{dt} = f(x,t), \quad t \geq t_0, \quad x(t_0) = x_0,$$

if we denote X_j as the numerical solution at time t_n, $j = 1, \cdots, N$, where t_n are equidistanced grid points with $t_0 < t_1 < \cdots < t_N$ and $h = t_{n+1} - t_n$, the backward Euler Method is

$$X_{n+1} = X_n + hf(X_{n+1}, t_{n+1}). \tag{6.16}$$

Note that the difference between forward Euler and backward Euler is that we are using unknown X_{n+1} in function f of Eq. (6.16). To solve Eq. (6.16), one needs to solve

$$X_{n+1} - hf(X_{n+1}, t_{n+1}) = X_n,$$

which may require a nonlinear solver to solve this system. Recall that in the forward Euler method, X_{n+1} is directly computed from the right-hand-side using X_n.

Why would we want to use an implicit method which involves time consuming nonlinear solvers? The reason is "stability". Consider the test equation $y' = \lambda y$, the backward Euler for that equation is

$$X_{n+1} = X_n + h\lambda X_{n+1},$$

therefore

$$(1 - h\lambda)X_{n+1} = X_n,$$

and

$$X_{n+1} = \frac{X_n}{1 - h\lambda}.$$

Because we assume $\lambda < 0$, we have $|X_{n+1}| < |X_n|$ regardless of the choice of h. In other word, this scheme is stable for every h! We call this scheme "unconditionally stable". This scheme is very useful if one requires a very small time step h to obtain a stable numerical solution with explicit scheme. In that case, solving nonlinear systems will pay off by gaining stability.

Problem 6.7. Consider

$$\frac{dy}{dt} = -10y, \quad y(0) = 1, \quad 0 \le t \le 3.$$

(i) Impliment backward Euler method, use $h = 0.01, 0.05, 0.1, 0.2$. Compare those solutions with the exact solution. (ii) Use $h = 0.21$ in forward Euler and backward Euler methods, and compare both numerical solutions with exact solutions in one figure. (iii) Use $h = 0.3$ in forward Euler and backward Euler methods, what do you see. Plot your numerical solutions if possible.

Problem 6.8. Implement the backward Euler method for

$$\frac{dy}{dt} = -y + t, \quad y(0) = 1, \quad 0 \le t \le 1.$$

Compare your numerical solution with the exact solution (you need to derive yourself).

In MATLAB, there are also implicit methods that would efficiently and robustly calculate stiff problems. The widely used function is called “ode15s”. Consider a stiff problem

$$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} -1 & -1 \\ 1 & -5000 \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \tag{6.17}$$

with initial conditions

$$\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}.$$

Problem 6.9. (a) Solve (6.8) with the initial condition with “ode45” in matlab. Compute the CPU time with “tic” and “toc”. (b) Repeat (a) with “ode15s”.

Chapter 7
General systems of differential equations

In this chapter, we develop a theory for a system of differential equations that will be used to study models with many species. We write the system either as

$$\frac{dx_i}{dt} = f_i(x_1, x_2, \cdots, x_n), \quad i = 1, 2, \cdots, n \tag{7.1}$$

or, in vector notation,

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) \tag{7.2}$$

where $\mathbf{x} = (x_1, \cdots, x_n), \mathbf{f} = (f_1, \cdots, f_n)$.

A point $\mathbf{x_0} = (x_{01}, \cdots, x_{0n})$ such that $\mathbf{f}(\mathbf{x_0}) = \mathbf{0}$ is called an **equilibrium point**, a **stationary point** or a **steady point**, of the system (7.1). The unique trajectory $\mathbf{x}(t)$ with $\mathbf{x}(0) = \mathbf{x_0}$ is then $\mathbf{x}(t) \equiv \mathbf{x_0}$, for all $t \geq 0$.

Writing

$$\mathbf{f}_i(\mathbf{x}) = \mathbf{f}_i(\mathbf{x}_0) + \sum_{j=1}^{n} (\mathbf{x}_j - \mathbf{x}_{j0}) \left[\frac{\partial f_i}{\partial x_j} + \varepsilon_j(|\mathbf{x} - \mathbf{x}_0|) \right]$$

where $\varepsilon_j(s) \to 0$ if $s \to 0$, we see that the linear system of differential equations

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} a_{ij}(x_j - x_{j0}), \quad (a_{ij} = \frac{\partial f_i(\mathbf{x_0})}{\partial x_j}) \tag{7.3}$$

is a good approximation to (7.1) near $\mathbf{x} = \mathbf{x_0}$. As in the analysis in Chapters 2 and 3, we wish to determine under what conditions all solutions of (7.3) converge to $\mathbf{x_0}$ as $t \to \infty$, and in this case we call $\mathbf{x_0}$ a **stable** equilibrium point, or, more **precisely**, **asymptotically** stable equilibrium point.

We try to find solutions of (7.3) in the form $\mathbf{v}e^{\lambda t}$ where $\mathbf{v} = (v_1, v_{2,} \cdots, v_n)$. Then λ and $\mathbf{v}$ must satisfy the equations

$$\sum_{j=1}^{n} (a_{ij} - \lambda \delta_{ij}) v_j = 0, \quad j = 1, \cdots, n \tag{7.4}$$

or, in matrix form,

$$(J - \lambda I)\mathbf{v} = \mathbf{0} \tag{7.5}$$

where I is the unit matrix, with elements $\delta_{ij} = 0$ if $i \neq j$, $\delta_{ii} = 1$, and the matrix J is given by

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & & & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}$$

where $\frac{\partial f_i}{\partial x_j}$ is computed at $\mathbf{x}_0$; we also write $J = (\frac{\partial f_i}{\partial x_j})$. The matrix J is called the **Jacobian matrix** at $\mathbf{x}_0$.

The system (7.4) has a solution $\mathbf{v} \neq \mathbf{0}$ if and only if λ satisfies the equation

$$\det(a_{ij} - \lambda \delta_{ij}) = 0. \tag{7.6}$$

This polynomial equation is called the **characteristic equation**, and the solutions λ are called **eigenvalues**. A solution $\mathbf{v}$ of (7.5) is called an **eigenvector** corresponding to λ.

Equation (7.6) is a polynomial equation of order n,

$$\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n = 0. \tag{7.7}$$

It is well known that such an equation has n solutions, which may be real or imaginary. If all the eigenvalues $\lambda_1, \lambda_2, \cdots, \lambda_n$ are different from one another, then the general solution of the linear system (7.3) is

$$\mathbf{x}(t) = \sum_{j=1}^{n} c_j \mathbf{v}_j e^{\lambda_j t},$$

where $\mathbf{v}_j$ are eigenvectors corresponding to λ_j, and the c_j are arbitrary constants.

If $\lambda_1 = \lambda_2$ then we need to replace $c_2\mathbf{v}_2 e^{\lambda_2 t}$ by $c_2(t\mathbf{v}_1 + \hat{\mathbf{v}}_2)e^{\lambda_1 t}$ where $\hat{\mathbf{v}}_2$ is an appropriate vector; if $\lambda_1 = \lambda_2 = \lambda_3$, then we replace $c_3\mathbf{v}_3$ by $c_3(t^2\mathbf{v}_1 + t\hat{\mathbf{v}}_3 + \hat{\hat{\mathbf{v}}}_3)$, where $\hat{\mathbf{v}}_3$ and $\hat{\hat{\mathbf{v}}}_3$ are appropriate vectors, etc.

We conclude that if the real parts of all the eigenvalues are negative, then $\mathbf{x}(t) \to 0$ as $t \to \infty$. Since the linear system is a good approximation to the full system (7.1) near the point $\mathbf{x}_0$, we have the following result:

Theorem 7.1. *If $Re\lambda_j < 0$ for each eigenvalue of the Jacobian matrix at $\mathbf{x}_0$, then the point $\mathbf{x}_0$ is an asymptotically stable (or, briefly, a stable) equilibrium point for (7.1).*

That means that any trajectory $\mathbf{x}(t)$, with $\mathbf{x}(0)$ near $\mathbf{x}_0$, converges to $\mathbf{x}_0$ as $t \to \infty$.

The next question is under what conditions on the coefficients $a_1, a_2, \cdots, a_n$ is it true that $Re\lambda_j < 0$ for all j. The answer is provided by the well known criteria of Routh-Hurwitz, In the sequel we shall need to use the Routh-Hurwitz criteria only in case $n = 3$:

Theorem 7.2. *All the roots of a polynomial*

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

have negative real parts if and only if $a_1 > 0, a_3 > 0, a_1a_2 > a_3$.

This theorem will be used in the following example.

Problem 7.1. Consider the model of one predator x and two prey species y and z:

$$\begin{aligned}\frac{dx}{dt} &= \beta_1 xy + \beta_2 xz - \mu x\\ \frac{dy}{dt} &= r_1 y - \gamma_1 xy\\ \frac{dz}{dt} &= r_2 z(1-z) - \gamma_2 xz.\end{aligned}$$

Check that the only steady point $(\bar{x},\bar{y},\bar{z})$ with $\bar{x} > 0, \bar{y} > 0, \bar{z} > 0$ is given by

$$\bar{x} = \frac{r_1}{\gamma_1}, \quad \bar{z} = 1 - \frac{\gamma_2}{r_2}\bar{x}, \quad \beta_1\bar{y} = \lambda - \beta_2\bar{z}$$

provided $\gamma_2\bar{x} < r_2$ and $\beta_2\bar{z} < \mu$. Use the Routh-Hurwitz theorem to prove that $(\bar{x},\bar{y},\bar{z})$ is stable.

Consider a model of two predators, x and y, and one prey, z:

$$\begin{aligned}\frac{dx}{dt} &= r_1 x(1 - \frac{x}{k_1}) + \beta_1 xz,\\ \frac{dy}{dt} &= r_2 y(1 - \frac{y}{k_2}) + \beta_2 yz,\\ \frac{dz}{dt} &= \alpha z(1 - \frac{z}{B}) - r_1 xz - r_2 yz.\end{aligned} \tag{7.8}$$

Note that in this model each of the predators, x and y, can actually survive on its own, even if they do not feed on z.

Problem 7.2. Show that the system (7.8) has a unique steady point $(\bar{x},\bar{y},\bar{z})$ with $\bar{x} > 0, \bar{y} > 0, \bar{z} > 0$, and that this point is stable.

Problem 7.3. Consider a model of one prey (x) and two predators (y_i):

$$\begin{aligned}\frac{dx}{dt} &= ax(1 - \frac{x}{A}) - \sum_{j=1}^{2} bxy_j\\ \frac{dy_i}{dt} &= -c_i y_i + d_i xy_i, \quad i = 1,2.\end{aligned}$$

where $\frac{c_1}{d_1} < \frac{c_2}{d_2} < A$. There are four equilibrium points:

$$(0,0,0), \quad (A,0,0), \quad (\frac{c_1}{d_1}, \frac{a}{b}(1-\frac{c_1}{Ad_1}),0), \quad (\frac{c_2}{d_2},0,\frac{a}{b}(1-\frac{c_2}{Ad_2})).$$

Determine which of these points are stable.

7.1 Numerical Simulations

A system of first order ordinary differential equation has the general form

$$\begin{cases} x_1^{'} = F_1(x_1,x_2,...,x_n,t) \\ x_2^{'} = F_2(x_1,x_2,...,x_n,t) \\ \quad \vdots \\ x_n^{'} = F_n(t,x_1,x_2,...,x_n) \end{cases} \tag{7.9}$$

As shown in Chapter 3, higher order equations can be converted to system of first order equations, so once we know how to solve first order systems, we can solve all the ODEs.

In particular, if it is a linear system, the general form can be written as

$$\begin{cases} x_1^{'} = a_{11}(t)x_1 + a_{12}(t)x_2 + ... + a_{1n}(t)x_n + b_1(t) \\ x_2^{'} = a_{21}(t)x_1 + a_{22}(t)x_2 + ... + a_{2n}(t)x_n + b_2(t) \\ \quad \vdots \\ x_n^{'} = a_{n1}(t)x_1 + a_{n2}(t)x_2 + ... + a_{nn}(t)x_n + b_n(t) \end{cases} \tag{7.10}$$

The system can be written as

$$x' = A(t)x + b(t).$$

The code to solve a general ODE system is similar to that in Chapter 3 and 4. The readers can practice to expand the code in problem with the following problem.

Problem 7.4. Solve the system

$$\begin{aligned} x_1^{'} &= 2x_1 - x_2^2 + \sin(t) \\ x_2^{'} &= \sqrt{x_1} + x_2 - 5x_3 - t \\ x_3^{'} &= 3x_1 + x_3 \end{aligned}$$

with initial conditions $(x_1(0),x_2(0),x_3(0)) = (1,1,1)$ for $0 \le t \le 1$.

Chapter 8
The chemostat model revisited

In Chapter 2 we considered the chemostat model and used mathematics to answer the question: How should we choose the outflow rate in order to harvest the maximum amount of bacteria. Our model however was incomplete because we assumed that the nutrient concentration in the growth chamber is constant in time, and hence our answer is questionable. In the present chapter we want to correct the answer, by basing it on a more complete mathematical model of the chemostat.

We begin by introducing the following notation:

$$\begin{aligned} V &= \text{volume of the bacterial chamber,} \\ C(t) &= \text{concentration of nutrients in the chamber,} \\ r &= \text{rate of inflow and outflow,} \\ x &= \text{concentration of the bacteria in the chamber.} \end{aligned}$$

We assume that

$$\frac{\text{mass of the bacteria formed}}{\text{mass of the nutrients used}} = const. = \gamma;$$

γ is the *yield constant*. By conservation of nutrient mass

$$\text{rate of change=input-washout-consumption.}$$

Based on experimental evidence we take the rate of bacterial growth to be

$$\frac{m_0 C}{a+C}x,$$

which m_0 and a are constants, and the rate of nutrient consumption to be

$$\frac{m_0 C}{a+C}\frac{x}{\gamma},$$

since mass $1/\gamma$ of the bacteria is formed from consumption of mass 1 of nutrients. Then

$$(VC)'(t) = C_0 r - C(t)r - \frac{m_0 C}{a+C}\frac{x}{\gamma}.$$

Dividing both sides by V and setting $D = r/V$ (the **dilution rate**), we get

$$C' = (C_0 - C)D - \frac{mC}{a+C}\frac{x}{\gamma} \tag{8.1}$$

where $m = m_0/V$. The bacterial growth is given by

$$x' = x\left(\frac{mC}{a+C} - D\right). \tag{8.2}$$

Note that the units of C_0, C, a, x are mass/volume (e.g. gm/cm^3), and the units of m and D are $1/$time (e.g. $1/$sec); γ is a dimensionless parameter.

By scaling

$$\bar{C} = \frac{C}{C_0}, \quad \bar{x} = \frac{x}{\gamma C_0}, \quad \bar{t} = Dt$$

we can simplify the system (8.1) and (8.2). After dropping the bars over C and x, we then obtain (with new constants $\bar{m} = \frac{m}{D}$, $\bar{a} = \frac{a}{C_0}$):

$$\begin{aligned} C' &= 1 - C - \tfrac{\bar{m}Cx}{\bar{a}+C} \\ x' &= x\left(\tfrac{\bar{m}C}{\bar{a}+C} - 1\right) \end{aligned} \tag{8.3}$$

Problem 8.1. The steady states of (8.3) are $(C_1, x_1) = (1, 0)$ and $(C_2, x_2) = (\lambda, 1-\lambda)$ where $\lambda = \frac{\bar{a}}{\bar{m}-1}$, provided $\bar{m} > 1$, $\lambda < 1$. Prove

(i) (C_1, x_1) is stable if $\frac{\bar{m}}{\bar{a}+1} < 1$.

(ii) (C_2, x_2) is stable.

To biologically interpret the mathematical results of Problem 4.1 we return to the original parameters, and consider for example the role of the dilution D. Setting

$$D_0 = \frac{m_0/V}{a/C_0 + 1}.$$

We have

$$\frac{\bar{m}}{\bar{a}+1} = \frac{(m_0/V)/D}{a/C_0+1} = \frac{D_0}{D}.$$

If $D > D_0$ then $\bar{m}/(\bar{a}+1) < 1$, so that $(C_1, x_1) = (1, 0)$ is stable, and in steady state the chemostat does not produce any bacteria, that is, if $D > D_0$ then there is a washout. On the other hand, if $D < D_0$ then $\bar{m}/(\bar{a}+1) > 1$, so that $\bar{m} > 1$ and $\lambda < 1$; hence, in steady state the chemostat yields bacteria at the (scaled) amount $1 - \lambda$, and one can adjust the parameter D, or other parameters of the model, to obtain the desired amount of bacteria per nutrient.

Since $\bar{t} = Dt$, the outflow speed per unit time is D, so that the actual bacterial yield per unit time (when $D < D_0$) is

$$\frac{dx}{dt} = \frac{dx}{d\bar{t}}\frac{d\bar{t}}{dt} = D\frac{dx}{d\bar{t}}$$

for the effluent x. Hence in steady state when the bacterial yields is $1-\lambda$ in unit time $\bar{t}$, the actual bacterial yield per unit time (when $D < D_0$) is

$$D(1-\lambda) = D\left(1 - \frac{\bar{a}}{\bar{m}-1}\right) = D\left(1 - \frac{aVD}{C_0(m_0 - VD)}\right) \equiv f(D).$$

To maximize the bacterial harvest one should take the dilution rate to be such that it maximizes $f(D)$ in the interval $0 < D < D_0$.

Problem 8.2. Prove that the maximum of $f(D)$ is attained at the smaller of the two positive solutions of the quadratic equation

$$\alpha D^2 + \beta D + m_0^2 = 0,$$

where $\alpha = V^2(1+\frac{a}{C_0}), \beta = -2m_0V(1+a/C_0)$.
[**Hint:** Verify that

$$f'(D) = \frac{\alpha D^2 + \beta D + m_0^2}{(m_0 - VD)^2}.$$

The polynomial $g(D) = \alpha D^2 + \beta D + m_0^2$ has two positive roots, $D_1 < D_2$ and $g(D) > 0$ if $D < D_1$ or $D > D_2$, $g(0) < 0$ if $D_1 < D < D_2$. Hence $f''(D_1) < 0, f''(D_2) > 0$. Finally verify that $g(D_0) < 0$ so that $0 < D_1 < D_0$.]

Problem 8.3. Consider another model of a chemostat, given by

$$\begin{aligned} \frac{dx}{dt} &= Cx - x, \\ \frac{dC}{dt} &= -Cx - C + \beta, \qquad (\beta > 1). \end{aligned}$$

There are two equilibrium points: $(0,\beta)$ and $(\beta-1,1)$. Show that $(0,\beta)$ is unstable and $(\beta-1,1)$ is stable.

8.1 Numerical Simulations

In previous chapters, we discussed how to solve an ordinary differential equations

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x})$$

by using Euler's method or using subroutine ode45 in MATLAB. We also introduced how to plot phase diagram near steady states. Here, we will introduce how to solve for the stationary solution of the ODE, i.e., the solution of the steady state equation

$$\mathbf{f}(\mathbf{x}) = \mathbf{0}.$$

If $\mathbf{f}(\mathbf{x})$ is linear or is of a simple function form, it may be solved analytically; however, if it is nonlinear or if the system is large, solving by hand is not feasible, and thus one needs to use **root-finding algorithms**. Two of the best known root finding algorithms are the *bisection method* and *Newton's method*, name after the eminent 18th century mathematician and scientist Issac Newton. The bisection method is a "gradient free" approach and usually takes longer to converge but it is more robust. Newton method uses gradient (slope in one dimension) information and is more efficient.; however, it may fail when the initial estimate is too far away from the root. To explain the basic ideas, we will use scalar equation $f(x) = 0$, but the generalization to $\mathbf{f}(\mathbf{x}) = \mathbf{0}$ is straightforward.

8.1.1 Bisection Method

The idea of the bisection method comes from the intermediate value theorem: continuous function f must have at least one root in the interval (a,b) if $f(a)$ and $f(b)$ have opposite signs. The method repeatly bisects an interval then selects, for further processing, a subinterval in which a root must lie. Suppose that we have two initial points $a_0 = a$ and $b_0 = b$ such that $f(a)f(b) < 0$. The method divides the interval into two by computing the midpoint $c = \frac{a+b}{2}$ of the interval. If c is a root, then the algorithm terminates. Otherwise, the algorithm checks whether $f(a)f(c)$ or $f(c)f(b)$ is negative. If $f(a)f(c) < 0$, the root must lie in the interval (a,c) and the method sets a as a_1 and c as b_1. Repeating this process, we can construct a sequence of intervals $[a_n, b_n]$ such that

$$|b_n - a_n| = \frac{|b_0 - a_0|}{2^n}.$$

Since the root must lie in these subintervals, the best estimate for the location of the root is the midpoint of the smallest subinterval found. In that case, the absolute error after n steps is at most

$$\frac{|b-a|}{2^{n+1}}. \tag{8.4}$$

If either endpoint of the interval is used, then the maximum absolute error is

$$\frac{|b-a|}{2^n}. \tag{8.5}$$

If we use (8.5) to determine the number of step such that the error is smaller than the given tolerance ε, the number of iterations needs to satisfy

$$n > \log_2 \frac{|b-a|}{\varepsilon}.$$

8.1.2 Newton's Method

Instead of using only the value of the function f, Newton's method uses also the derivative of the function. Given the initial guess x_0, Newton's method generates a sequence of approximations of the root by

$$x_{n+1} = x_n - \frac{f(x_n)}{f'(x_n)}. \tag{8.6}$$

until a sufficiently accurate value is reached. This idea originates from the linear approximation near the root,

$$f(x_{n+1}) \approx f(x_n) + (x_{n+1} - x_n) f'(x_n) \approx 0.$$

If the function f is continuously differentiable and its derivative does not vanish at the root α and if f has a second derivative in some interval containing α, then the convergence is quadratic. To prove this, we use the Taylor expansion near α,

$$0 = f(\alpha) = f(x_n) + f'(x_n)(\alpha - x_n) + R_1$$

where

$$R_1 = \frac{1}{2} f''(\xi_n)(\alpha - x_n)^2$$

and ξ_n is in between x_n and α. Thus

$$\alpha = x_n - \frac{f(x_n)}{f'(x_n)} - \frac{f''(\xi_n)}{2f'(x_n)}(\alpha - x_n)^2. \tag{8.7}$$

Setting $e_n = \alpha - x_n$, and subtracting (8.6) from (8.7), we have

$$e_{n+1} = -\frac{f''(\xi_n)}{2f'(x_n)} e_n^2.$$

Taking absolute value of both sides gives

$$|e_{n+1}| = \frac{f''(\xi_n)}{2|f'(x_n)|} e_n^2.$$

Set

$$M = \sup_{x \in I} \frac{1}{2} \left| \frac{f''(\xi_n)}{f'(x_n)} \right|, \quad I = [\alpha - r, \alpha + r] \text{ for some} r > 0.$$

The necessary condition of convergence for the initial point x_0 is $M|e| < 1$. Thus the rate of convergence is quadratic if $f'(x) \neq 0$ for $x \in I$, $f''(x)$ is bounded for $x \in I$, and x_0 sufficiently close to the root α, so that $|x_0 - \alpha| < r$. This requirement does not explicitly tell us how to choose x_0 since we do not know the root α before the computation.

Newton's method can be easily extended to solve the general nonlinear systems. Instead of dividing in (8.6) by $f'(x_n)$, one has to left multiply by the inverse of $n \times n$ Jacobian matrix $J_{\mathbf{f}}(x_n)$, i.e.,

$$X_{n+1} = X_n - \left[\mathbf{f}'(X_n)\right]^{-1} \mathbf{f}(X_n). \tag{8.8}$$

For numerical purposes it is more common to rewrite (8.8) in the form

$$\mathbf{f}'(X_n)\,(X_{n+1} - X_n) = \mathbf{f}(X_n).$$

One can first solve the linear system

$$\mathbf{f}'(X_n)\left(\tilde{X}\right) = \mathbf{f}(X_n)$$

for $\tilde{X}$ and then the approximation at next step is obtained by

$$X_{n+1} = \tilde{X} + X_n.$$

Problem 8.4. Implement Newton's method to solve $x^5 = 213$. Use initial guess 2. What is the root you find? How many iterations do you need to reach the tolerance 10^{-12}. Plot the convergence history.

Chapter 9
Spread of Disease

Epidemiology is the study of patterns, causes, and effects of health and disease conditions in a population. It provides critical support for public health by identifying risk factors for disease and targets for preventive medicine. Epidemiology has helped develop methodology used in clinical research and public health studies. Major areas of epidemiological study include disease etiology, disease break, disease surveillance, and comparison of treatment effects such as in clinical trials.

Epidemiologists used gather data and a broad range of biomedical and psychosocial theories to generate theory, test hypotheses, and make educated, informed assertions as to which relationships are causal and in which way. For example, many epidemiological studies are aimed at revealing unbiased relationships between exposure to smoking, biological agents, stress, or chemicals to mortality and morbidity. In the identification of causal relationship between these exposures and outcome epidemiologists use statistical and mathematical tools.

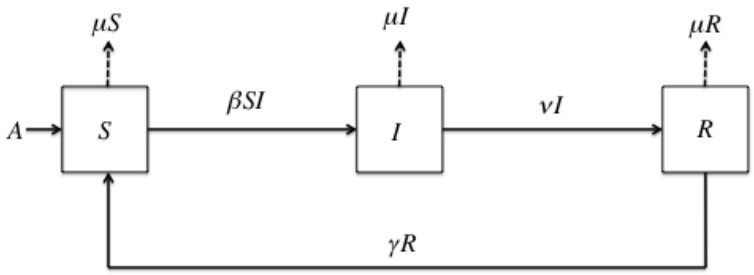
In this chapter we focus on epidemiology of infectious diseases. The adjectives **epidemic** and **endemic** are used to distinguish between a disease spread by an infective agent (epidemic) and a disease which resides in a population (endemic). For example, there are occasional spreads of the **cholera** epidemic in some countries, while **malaria** in endemic is Southern Africa. In this chapter we shall use mathematics in order to determine which epidemic will die out and which will become endemic.

In what follows we shall develop several different mathematical models for infectious diseases.

We begin with a simple model of a disease in a population of size N. We divide the population into three classes: susceptible S, infected I, and recovered R. Let

$$\begin{aligned}
\beta &= \text{infection rate,}\\
\mu &= \text{death rate, the same for all individuals,}\\
\nu &= \text{recovery rate,}\\
\gamma &= \text{rate by which recovered individuals have lost}\\
&\quad\ \text{their immunity and became susceptible to the disease.}
\end{aligned}$$

Then we have the following diagram:



where A is the growth of susceptible. If all newborns are healthy, then, not only S and R, but also I contribute to the growth term A. We view each of the populations S, I, R, N as representing a number of individuals (or a number density, that is, the number of individuals per unit area). The dimension of γ, μ, ν is $1/\text{time}$, the dimension of β is $1/(\text{individual}\cdot\text{time})$, and the dimension of A is individual/time. Based on the above diagram, we set up the following system of differential equations:

$$\begin{aligned}\frac{dS}{dt} &= A-\beta SI+\gamma R-\mu S\\ \frac{dI}{dt} &= \beta SI-\nu I-\mu I\\ \frac{dR}{dt} &= \nu I-\gamma R-\mu R\end{aligned} \tag{9.1}$$

To examine more carefully the meaning of A, we introduce a differential equation for $N(t)$, which is abtained by adding all the equations in (9.1),

$$\frac{dN}{dt} = A-\mu N.$$

Given initial population density N_0, we find that

$$N(t) = N_0e^{-\mu t}+\frac{A}{\mu}(1-e^{-\mu t}).$$

Hence $N(t)\to A/\mu$ as $t\to\infty$. Thus A/μ is equal to the asymptotic density of the population (as $t\to\infty$).

The system (9.1) is called the **SIR model**. The SIR model has an equilibrium point which is disease free, namely

$$(S_0,I_0,R_0) = (\frac{A}{\mu},0,0);$$

we call it the **disease free equilibrium** (DFE). The Jacobian matrix at the DFE is

$$\begin{pmatrix} -\mu & -\beta\frac{A}{\mu} & \gamma \\ 0 & \beta\frac{A}{\mu}-(\nu+\mu) & 0 \\ 0 & \nu & -\mu-\gamma \end{pmatrix}.$$

The characteristic polynomial is

$$(\mu+\lambda)(\beta\frac{A}{\mu}-(\nu+\mu)-\lambda)(\mu+\gamma+\lambda).$$

and the eigenvalues are $\lambda_1=-\mu, \lambda_2=-\mu-\gamma, \lambda_3=\beta\frac{A}{\mu}-(\nu+\mu)$. Hence the DFE is stable if

$$\beta\frac{A}{\mu}<\nu+\mu. \tag{9.2}$$

When (9.2) holds, any new small infection will die out with time. On the other hand if

$$\beta\frac{A}{\mu}>\nu+\mu, \tag{9.3}$$

the DFE is unstable; there are arbitrarily small infections that will not disappear in the population. Furthermore, there is an equilibrium point $(\bar{S},\bar{I},\bar{R})$ with $\bar{I}>0$, namely

$$\beta\bar{S}=\nu+\mu, \quad \bar{R}=\frac{\nu}{\gamma+\mu}\bar{I}, \quad \frac{\beta}{\mu}\bar{I}=\frac{(\beta\frac{A}{\mu}-(\nu+\mu))}{\nu+\mu-\frac{\gamma\nu}{\gamma+\mu}}. \tag{9.4}$$

Problem 9.1. Prove that if (9.3) holds then the equilibrium point $(\bar{S},\bar{I},\bar{R})$ is stable. [Hint: You need to use the Routh-Hurwitz theorem.]

An important concept in epidemiology is the **basic reproduction number**:

In a healthy population introduce one infection and compute the expected infection among the susceptibles caused by this single infection We call it the **expected secondary infection**, or **basic reproduction number**, and denote it by R_0.Then intuitively it is clear that DFE is stable if $R_0<1$ (the secondary infection will be smaller than the initial infection) whereas if $R_0>1$ then the DFE will be unstable.

Consider, for example, the SIR model (9.1). The DFE is $(A/\mu,0,0)$. One infection evolves according to

$$\frac{dI}{dt}=-\nu I-\mu I, \quad I(0)=1,$$

so that $I(t)=e^{-(\nu+\mu)t}$ at time t, with total life-time infection

$$\int_0^\infty I(t)dt=\frac{1}{\nu+\mu}.$$

The secondary infection is then

$$R_0=\beta\frac{A}{\mu}\cdot\frac{1}{\nu+\mu}.$$

As already computed in (9.2), (9.3), the DFE is stable if $R_0 < 1$ and unstable if $R_0 > 1$.

A stable equilibrium point with $I > 0$ is call **endemic**; it represents a disease that will never disappear.

When a susceptible is exposed to an infected individual, he/she may or may not become immediately sick. With this in mind, we may extend the SIR model by introducing a new class E, of exposed individuals. The new model, called the **SEIR model**, consists of the following equations:

$$\begin{aligned} \frac{dS}{dt} &= A - \beta SI + \gamma R - \mu S, \\ \frac{dE}{dt} &= \beta SI - \kappa E - \mu E, \\ \frac{dI}{dt} &= \kappa E - \nu I - \mu I, \\ \frac{dR}{dt} &= \nu I - \gamma R - \mu R. \end{aligned} \tag{9.5}$$

Here κ is the rate by which the exposed become infected, and β is the rate of infection of susceptibles by infected individuals. The DFE for the SEIR model is $(\frac{A}{\mu}, 0, 0, 0)$.

Problem 9.2. Show that the DFE of (9.5) is stable if

$$\beta \frac{A}{\mu} < \frac{(\nu+\mu)(\kappa+\mu)}{\kappa}.$$

Problem 9.3. Prove that if the DFE is not stable, then there exists another equilibrium point.

In the SIR model we have taken the infection term to be βSI, that is, it depends on the **density** of the infected individuals. Another possibility is to take the infection term to be $\frac{\beta SI}{N}$, where $\frac{I}{N}$ is the relative proportion of the infected individuals, namely, the **frequency** or **prevalence** of the infection.

Problem 9.4. Show that when βSI is replaced by $\frac{\beta SI}{N}$ in (9.1), where $N = S + I + R$, the DFE $(\frac{A}{\mu}, 0, 0)$ is stable if $\beta < \nu + \mu$.

Problem 9.5. If in the previous problem (9.2) is replaced by $\beta > \nu + \mu$, then the DFE is not stable, and there exists another equilibrium point.

HIV

In humans infected with HIV, the HIV virus enters the $CD4^+$ T cells and hijack the machinery of the cells in order to multiply within these cells. As an infected T cell

dies, an increased number of virus emerge to invade and infect new CD4$^+$ T cells. This process eventually lead to significant depletion of the CD4$^+$ T cells, from over 700 in cm^3 of blood to 200 in cm^3. This state of the disease is characterized as AIDS; the immune system is too weak to sustain life for too long. In order to determine whether an initial infection with HIV will develop into AIDS we introduce a simple model which includes the CD4$^+$ T cells, denoted by T, the infected CD4$^+$ T cells, denoted by T^*, and the HIV virus outside the T cells, denoted by V. Their number densities satisfy the following system of equations:

$$\begin{array}{l} \frac{dT}{dt} = A - \beta TV - \mu T, \\ \frac{dT^*}{dt} = \beta TV - \mu^* T^*, \\ \frac{dV}{dt} = \gamma \mu^* T^* - \kappa V. \end{array} \tag{9.6}$$

Here β is the infection rate of healthy T cells by external virus, μ and $\mu^*$are the death rates of T and T^*, respectively, and γ is the number of virus particle that emerge upon death of infected one CD4$^+$ T cell.

Problem 9.6. In the model (9.6), the DFE is $(\frac{A}{\mu},0,0)$. Prove that the DFE is stable if

$$\frac{\beta A}{\mu} < \frac{\kappa}{\gamma},$$

and is unstable if this inequality is reversed.

We can compute the basic reproduction number R_0 for the modle (9.6) as follows:

One virion has the life time of $\frac{1}{\lambda}$ (since $\frac{dV}{dt} = -\lambda V, V(t) = e^{-\lambda t}$, $\int_0^\infty V(t)dt = \frac{1}{\lambda}$) and it infects A/μ T cells at rate β, which each infected T^* with life time $1/\mu^*$ gives rise to γ virus particles. Hence

$$R_0 = \frac{1}{\lambda}\beta\frac{A}{\mu}\frac{1}{\mu^*}\gamma = \frac{\beta A\gamma}{\lambda\mu\mu^*}.$$

From Problem 9.6 we see that the DFE is stable if $R_0 < 1$ and is unstable if $R_0 > 1$.

9.1 Numerical Simulations

Finding the roots using MATLAB

In the previous chapter, we have introduced basic schemes to calculate a root of an equation or system. Here we introduce how this is solved in MATLAB. There are several built-in functions in MATLAB that can be used to solve $\mathbf{f}(\mathbf{x}) = \mathbf{0}$:

```
>> x = fzero(fun,x0)
```

which attempts to find a zero of fun near x_0, if x_0 is a scalar and fun is a function handle. For example,

```
>> x = fzero(@cos,[1 2])
x = 1.5708
```

Another matlab function is

```
>> x = fsolve(fun,x0)
```

starts at x_0 and tries to solve the equations described in fun. For example, solve

$$2x_1 - x_2 = e^{-x_1},$$
$$-x_1 + 2x_2 = e^{-x_2},$$

with the initial guess $[x_1, x_2] = [-5, -5]$. First, write a file that computes F, the values of the equations at x.

```
function F = myfun(x)
F = [2*x(1) - x(2) - exp(-x(1)); -x(1) + 2*x(2) - exp(-x(2))];
```

Save this function file as myfun.m somewhere on your MATLAB path. Next, set up the initial point and options and call fsolve:

```
x0 = [-5; -5]; % Make a starting guess at the solution

options=optimset('Display','iter'); % Option to display
output
[x,fval] = fsolve(@myfun,x0,options) % Call solver
```

After several iterations, fsolve finds an answer as shown in Table (9.1).

Iteration	Func-count	f(x)	Norm of step	First-order optimality	Trust-region radius
0	3	47071.2		2.29e+04	1
1	6	12003.4	1	5.75e+03	1
2	9	3147.02	1	1.47e+03	1
3	12	854.452	1	388	1
4	15	239.527	1	107	1
5	18	67.0412	1	30.8	1
6	21	16.7042	1	9.05	1
7	24	2.42788	1	2.26	1
8	27	0.032658	0.759511	0.206	2.5
9	30	7.03149e-06	0.111927	0.00294	2.5
10	33	3.29525e-13	0.00169132	6.36e-07	2.5

Table 9.1 output for fsolve

fsolve completed because the vector of function values is near zero as measured by the default value of the function tolerance, and the problem appears regular as measured by the gradient.

```
x =
0.5671
0.5671
fval =
1.0e-006 *
-0.4059
-0.4059.
```

Another two MATLAB functions which are useful to study the phase protraits are "contour" and "quiver". For example, the contour plot of the function

$$z = xe^{(-x^2-y^2)}$$

over the range $-2 \le x \le 2, -2 \le y \le 3$ can be done by

```
[X,Y] = meshgrid(-2:.2:2,-2:.2:3);
Z = X.*exp(-X.^2-Y.^2);
[C,h] = contour(X,Y,Z,[-1:0.1:1]); clabel(C,h)
```

Now we can add the vector field plot by using quiver

```
[DX,DY] = gradient(Z,.2,.2);
hold on; quiver(X,Y,DX,DY)
```

From the vector field, we can easier tell the stability properties of a steady state.

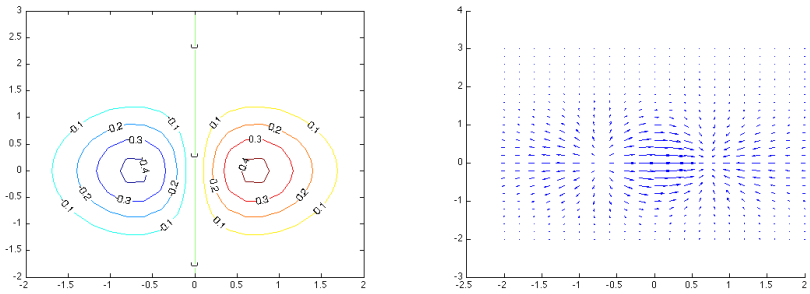


Fig. 9.1 (a) contour plot (b) vector field plot

Problem 9.7. 8.6. Use "fsolve" to solve

$$x_1^3 + x_2 = 1,$$
$$x_2^3 - x_1 = -1.$$

Indicate your initial condition and how many steps it requires to reach the tolerance of error to be within 10^{-6}.

Problem 9.8. 8.7 Plot the nullclines and directional field of

$$z = e^{(-2x^2-y^2)} \sin x$$

in the range of $-2 \le x \le 2, -2 \le y \le 3$.

Chapter 10
Enzyme Dynamics

Cells are the basic units of life. A cell consists of a concentrated aqueous solution of molecules contained in a membrane, called **plasma membrane**. A cell is capable of replicating itself by growing and dividing. Cells that have a nucleus are called **eukaryotes**, and cells that do not have a nucleus are call **prokaryotes**. Bacteria are prokaryotes, while yeast and amoebas, as well as most cells in our body, are eukaryotes. The **Deoxyribonucleic acid** (**DNA**) are very long polymeric molecules, consisting of two strands of chains, having double helix configuration, with repeated nucleotide units A, C, G, and T. The DNA is packed in chromosomes, within the nucleus in eukaryotes. In humans, the number of chromosomes is 46, except in sperm and egg cells where the number is 23.

The DNA is the genetic code of the cell; it codes for proteins. Proteins lie mostly in the cytoplasm of the cells, that is, outside the nucleus; some proteins are attached to the plasma membrane, while some can be found in the nucleus. Proteins are polymers of amino acids whose number typically ranges from hundreds to thousands; there are 20 different amino acids from which all proteins are made. Each protein assumes 3-dimensional configuration, called **conformation**. Proteins perform specific tasks by changing their conformation.

Two proteins, A and B, may combine to form a new protein C. We express this process by writing

$$A + B \to C.$$

Biological processes within a cell involves many such reactions. Some of these reactions are very slow, other are very fast, and in some cases the reaction rate may start slow, then speed up until it reaches a maximal level. In this chapter we consider the question: How to determine the speed of biochemical reactions among proteins. In order to address this question we shall develop some mathematical models.

We begin with a simple case. Suppose we have two proteins, A and B, or more generally, two molecules A and B. We assume that A and B, when coming in contact, undergo a reaction, at some rate k_1, that make them form a new molecule C. We express this reaction by writing

$$A + B \xrightarrow{k_1} C;$$

k_1 is called the **rate coefficient**. The respective concentrations of three molecules are denoted by $[A]$, $[B]$, and $[C]$. The **law of mass action** states that the reaction rate $\frac{d[C]}{dt}$, or v_1, of the above reaction is given by

$$v_1 = k_1[A][B],$$

that is,

$$\frac{d[C]}{dt} = k_1[A][B] \tag{10.1}$$

Note that the above reaction implies that

$$\frac{d[A]}{at} = -k_1[A][B], \quad \frac{d[B]}{at} = -k_1[A][B].$$

If the reaction is reversible with rate coefficient k_{-1}, then

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

and

$$\frac{d[C]}{dt} = k_1[A][B] - k_{-1}[C],$$

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k_1[A][B] + k_{-1}[C].$$

Metabolism in a cell is the sum of physical and chemical processes by which material substances are produced, maintained or destroyed, and by which energy is made available. **Enzymes** are proteins that act as catalysts in speeding up chemical reactions within a cell. They play critical roles in many metabolic processes within the cell. An enzyme, say E, can take a molecule S and convert it to a molecule P in one millionth of a second. The original molecule S is referred to as the **substrate**, and P is called the **product**. The enzyme-catalyzed conversion of a substrate S into a product P is written in the form

$$S \xrightarrow{E} P. \tag{10.2}$$

Figure 10.1 illustrate how an enzyme can convert substrate S into a product P.

The profile $[S] \to [P]$ can take different forms, depending on the underlying biology. Two typical profiles are shown in Figure 10.2.

Figures 10.2(A) and 10.2(B) have been shown to hold in different experiments, but it would be useful to derive them by mathematical analysis based on known properties of enzymes. Indeed such a derivation will give us a precise mathematical formula for the profiles displayed in Figure 10.2. We begin with the derivation of a formula that yields the profile of Figure 10.2(A).

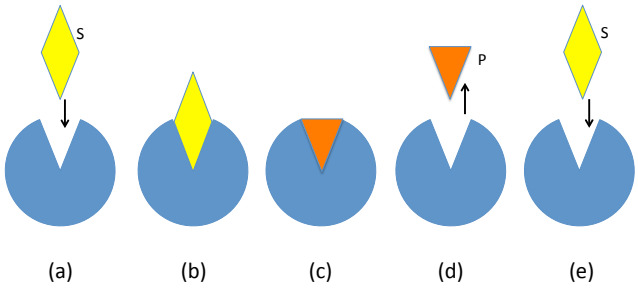


Fig. 10.1 (a) Enzyme attracts S; (b) S is inside E; (c) Enzymatic process converts S into P; (d) P is released; (e) Enzyme is ready to attract another S.

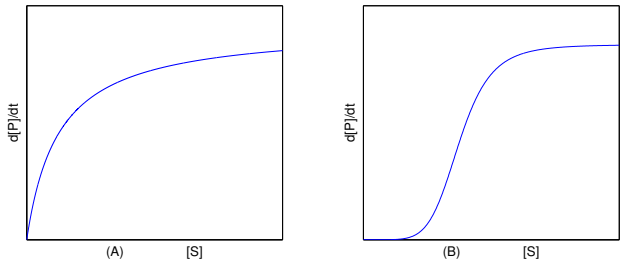


Fig. 10.2 Two different profiles of the enzymatic conversion of $S \to P$.

In what follows we show how such a profile can be derived from the law of mass action. We write, schematically,

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

where C is the complex SE,

$$C \xrightarrow{k_2} E + P.$$

By the law of mass action

$$\frac{d[C]}{dt} = k_1[S][E] - (k_{-1} + k_2)[C], \tag{10.3}$$

$$\frac{d[E]}{dt} = -k_1[S][E] + (k_{-1} + k_2)[C], \tag{10.4}$$

$$\frac{d[S]}{dt} = -k_1[S][E] + k_{-1}[C], \tag{10.5}$$

$$\frac{d[P]}{dt} = k_2[C]. \tag{10.6}$$

Notice that

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

so that $[E]+[C]=const=e_0$; e_0 is the total concentration of the enzyme in both E and the complex C. Note that $\frac{d[C]}{dt}+\frac{d[S]}{dt}+\frac{d[P]}{dt}=0$, so equation (10.5) depends on equations (10.4) and (10.6) and may therefore be dropped.

We focus on equation (10.3) and note that in the enzymatic process the complex C changes very fast. Hence $d[C]/dt$ is approximately zero, so that

$$k_1[S][E]-(k_{-1}+k_2)[C]=0.$$

Substituting $[E]=e_0-[C]$ we get

$$k_1[S](e_0-[C])=(k_{-1}+k_2)[C]$$

or

$$[C]=\frac{k_1e_0[S]}{(k_{-1}+k_2)+k_1[S]}=\frac{e_0[S]}{k_M+[S]}$$

where $K_M=\frac{k_{-1}+k_2}{k_1}$.

Then

$$\frac{d[P]}{dt}=k_2[C]=k_2e_0c=\frac{V_{max}[S]}{K_M+[S]} \tag{10.7}$$

where $V_{max}=k_2e_0$.

we have thus derived the **Michaelis-Menten formula**

$$\frac{d[P]}{dt}=\frac{V_{max}[S]}{K_M+[S]} \tag{10.8}$$

where V_{max} and K_M are constants; note that

$$\frac{d[P]}{dt}\to V_{max} \quad \text{as} \quad [S]\to\infty.$$

The assumption we made in the derivation of (10.8) that $d[C]/dt$ is very small is quite reasonable and, indeed, the Michaelis-Menten formula is widely used in describing enzymatic processes.

But what about Figure 10.2(B)? Such a profile is based on a different enzymatic process, for example when an enzyme E can bound first with one substrate S and then with another substrate S. Furthermore, in such a case, as is well established experimentally, the speed by which the enzyme bounds with the second substrate is much faster, as illustrated in Figure 10.3.

We model such processes as follows:

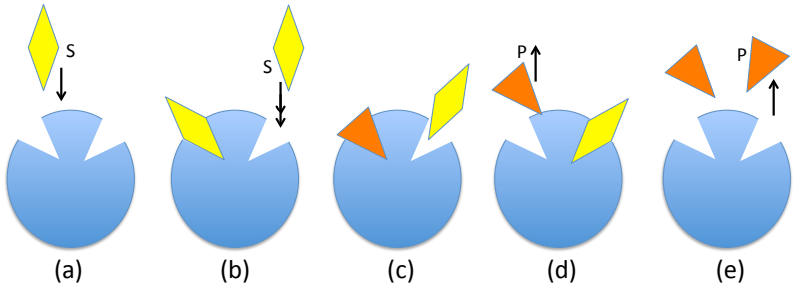


Fig. 10.3 Enzyme with two sites for absorbing and converting substrate S to product P; the conversion of the second substrate is faster than the conversion of the first substrate.

$$\begin{array}{lll} S+E & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & C_1, \qquad (C_1 = SE) \\ C_1 & \overset{k_2}{\rightarrow} & E+P \\ S+C_1 & \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} & C_2 \quad (C_2 = SC_1 = S^2E) \\ C_2 & \overset{k_4}{\rightarrow} & C_1+P \end{array} \tag{10.9}$$

so that

$$\frac{d[P]}{dt} = k_2[C_1] + k_4[C_2].$$

Note that $[E]+[C_1]+[C_2] = const. = e_0$. Assuming the steady state approximations

$$\frac{d[C_1]}{dt} = \frac{d[C_2]}{dt} = 0$$

one can show that

$$\frac{d[P]}{dt} = \frac{(k_2K_2 + k_4[S])e_0[S]}{K_1K_2 + K_2[S] + [S]^2}, \tag{10.10}$$

where

$$K_1 = \frac{k_{-1}+k_2}{k_1}, \quad K_2 = \frac{k_{-3}+k_4}{k_3}.$$

Steps 1 and 3 in equations (10.9) represent sequential binding of two substrate molecules to the enzyme. We assume that previously enzyme-bound substrate molecule significantly increases the rate of binding of a second substrate molecule, so that $k_3 >> k_1$. In the extreme case of $k_1 \to 0$, $k_3 \to \infty$, with k_1k_3 a finite positive constant, we get $K_1 \to \infty$, $K_2 \to 0$, $K_1K_2 \to K_H > 0$, so that

$$\frac{d[P]}{dt} = \frac{V_{max}[S]^2}{K_H + [S]^2} \tag{10.11}$$

where V_{max} and K_H are constants. Formula (10.11) is called the **Hill kinetics**; it displays a profile similar to Figure 10.2(B).

Some enzymes can bound with three or more substrates. In this case it is often the case that when enzyme has already bounded with m substrates S, it has a greater affinity to bound with the next substrate S. Under this biological assumption, one can derive the Hill kinetics of order n,

$$\frac{d[P]}{dt} = \frac{V_{max}[S]^n}{K_H + [S]^n}. \tag{10.12}$$

The Michaelis-Menten formula is used also in other biological processes. For example, when macrophages M ingest bacteria B they become infected macrophages M_i. The resulting growth in M_i is described by the Michaelis-Menten formula

$$\frac{d[M_i]}{dt} = \lambda [M] \frac{[B]}{K + [B]}.$$

Notice that for small $[B]$, this is approximately the mass conservation law

$$M + B \to M_i.$$

However the capacity of macrophages to ingest bacteria is limited by the following fact: After receptor proteins on the macrophage membrane have been engaged in the ingestion process, they need to take time off for recycling. Hence there is a limit, λ, on how fast macrophages can ingest the bacteria.

Problem 10.1. Consider the chemical reactions

$$A + B \xrightarrow{k} C, \quad B + C \xrightarrow{k} A$$

with $[A] + [C] = 3$ at time $t = 0$. Show that $y = [B]$ satisfies $y(t) = y_0 e^{-3kt}$.

Problem 10.2. The law of mass action can be extended to interaction among three or more molecules. Consider for example three species X_1, X_2, X_3 that interact to form a species Y:

$$X_1 + X_2 + X_3 \xrightarrow{k} Y$$

where k is the reaction rate. Then the law of mass action states that

$$\frac{d[X_i]}{dt} = -k[X_1][X_2][X_3] \text{ for i=1,2,3.}$$

In particular, if $X_1 = A$, $X_2 = X_3 = B$, $Y = C$, then

$$A + 2B \xrightarrow{k} C$$

and

$$\frac{d[A]}{dt} = -k[A][B]^2,$$
$$\frac{d[B]}{dt} = -2k[A][B]^2.$$

Assuming that $2[A(0)] + [B(0)] = 1$, show that $y(t) = [B(t)]$ satisfies the equation

$$y' = -ky^2(1-y), \quad 0 < y(t) < 1$$

if $0 < y(0) < 1$, that the solution of the above equation is given by

$$\frac{1}{y} + \ln\frac{1-y}{y} = kt + C, \quad \text{C constant},$$

and that $y(t) \to 0$ as $t \to \infty$

Problem 10.3. Derive Equation (10.10) under the steady state approximations $d[C_1]/dt = 0$, $d[C_2]/dt = 0$.

10.1 Numerical Simulations

Problem 10.4. Suppose

$$A + B \xrightarrow{k} C, \quad C \xrightarrow{3} A + B$$

Set $x = [A]$, $y = [B]$, $z = [C]$ and take $x(0) = y(0) = 1$, $z(0) = 8$. Derive a system of differential equations for $x(t), y(t), z(t)$, and compute $x(0)$ as a function of k, for $1 \le k \le 5$.

Problem 10.5.

$$A + B \xrightarrow{k} C, \quad C \xrightarrow{3} A + 2B$$

Set $x = [A]$, $y = [B]$, $z = [C]$ and take $x(0) = y(0) = 1$, $z(0) = 8$. Derive a system of differential equations for $x(t), y(t), z(t)$, and compute $x(0)$ as a function of k, for $1 \le k \le 5$.

Chapter 11
Bifurcation Theory

Consider two populations, x and y, that are interacting either by competition, or as predator and prey. They may end up near a stable steady state, or possibly in seasonally varied states; this depends on their proliferation rates, death rates, available resources, climate change, etc. In this chapter we wish to explore theses varied possibilities using mathematics. To do that we begin by a short introduction the theory of bifurcations. The change that occurs at $p = p_c$ typically involves two or more branches of solutions which depend on the parameter p; the nature of these 'bifurcation' branches changes radically at $p = p_c$. **Bifurcation theory** is concerned with the question of how the behavior of a system which depends on a parameter p changes with the parameter. It focuses on any critical value, $p = p_{cr}$, where the behavior of the system undergoes radical change; such values are called **bifurcation points**. We shall consider bifurcation phenomena for a system of differential equations with parameter p,

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}, p). \tag{11.1}$$

Bifurcation points can arise in different ways. For example, suppose a steady state of Equation (11.1), which depends on p, is stable for $p < p_c$ but loses stability at p_c. Then a qualitative change has occurred in the phase portrait of the system (11.1), and $p = p_c$ is a bifurcation point. It sometimes happens that as p increases from $p < p_c$ to $p > p_c$ the differential system will begin to have periodic solutions, a well recognized biological phenomena. Thus we would like to determine, mathematically, when such a situation takes place.

Problem 11.1-11.3 are simple but typical examples of bifurcations that frequently occur in biology.

Problem 11.1. Consider the equation

$$\frac{dx}{dt} = p + x^2.$$

It has two steady states $x = \pm\sqrt{-p}$ if $p < 0$ and no steady states if $p > 0$. Prove that $x = -\sqrt{-p}$ is stable and $x = +\sqrt{-p}$ is unstable. The point $p = 0$ is called a **saddle-point** bifurcation.

Problem 11.2. Consider the equation

$$\frac{dx}{dt} = px - x^2.$$

It has steady points $x = 0$ and $x = p$. Prove that $x = 0$ is stable if $p < 0$ and unstable if $p > 0$, and $x = p$ is unstable if $p < 0$ and stable if $p > 0$. Such a point $p = 0$, where there is an exchange of stability in the branches of the steady points, is called a **transcritical** bifurcation.

Problem 11.3. Consider the equation

$$\frac{dx}{dt} = px - x^3.$$

Show that $x = 0$ and $x = \pm\sqrt{p}$ (for $p > 0$) are the steady states of this equation, and determine their stability. The point $p = 0$ is called a **pitchfork** bifurcation.

Figure 11 illustrates the last three examples.

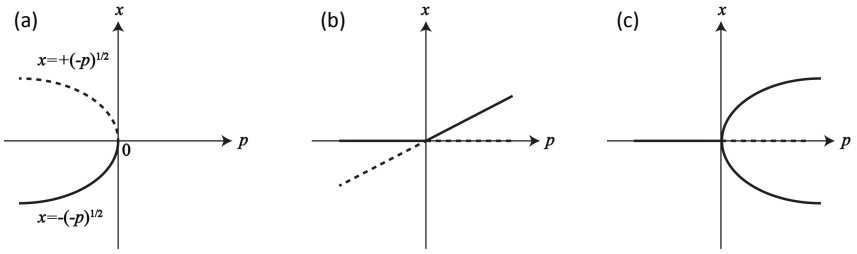


Fig. 11.1 (a) Saddle-point bifurcation diagram; (b) transcritical bifurcation diagram. (c) Pitchfork bifurcation. Solid curves represent stable steady states, while dotted curves are unstable steady states.

Consider a species x with logistic growth whose death rate is a parameter p,

$$\frac{dx}{dt} = rx(1 - \frac{x}{K}) - px.$$

It has two steady states: $x = 0$ and $x = K(1 - \frac{p}{r})$, but the last one is biologically feasible only if $x > 0$, that is, if $p < r$. The two branches of steady points intersect at $p = r$ where exchange of stability occurs: $x = 0$ is stable if $p > r$ and unstable if $p < r$, whereas $x = K(1 - \frac{p}{r})$ is stable if $p < r$ and unstable if $p > r$. Thus transcritical bifurcation occurs at $p = r$.

When the density of species x is very small (say $0 < x < 1$) mating becomes difficult: The probability of a male from x to meet and mate with a female from x is proportional to x^2. Hence instead of growth rates

$$\frac{dx}{dt} = rx, \text{ or } \frac{dx}{dt} = rx(1 - \frac{x}{K})$$

we have growth rates

$$\frac{dx}{dt} = rx^2, \text{ or } \frac{dx}{dt} = rx^2(1 - \frac{x}{K}).$$

Consider species x with dynamics

$$\frac{dx}{dt} = rx^2(1 - \frac{x}{K}) - px.$$

It has three branches of steady points given by $x = 0$ and

$$rx(1 - \frac{x}{K}) - p = 0, \text{ or } x = \frac{K}{2} \pm \sqrt{\frac{K^2}{4} - \frac{p}{r}}.$$

In this example pitchfork bifurcation occurs at $p = \frac{r}{4}K^2$. We next consider a different type of bifurcation whereby steady points bifurcate into periodic solutions; this of course must involve a dynamical system with at least two equations.

Consider the following system of two equations, with bifurcation parameter p:

$$\frac{dx_1}{dt} = px_1 - \mu x_2 - ax_1(x_1^2 + x_2^2), \tag{11.2}$$

$$\frac{dx_2}{dt} = \mu x_1 + px_2 - ax_2(x_1^2 + x_2^2), \tag{11.3}$$

where μ, a are positive constants. It is easily seen that the point $x = 0$ is a steady point, stable if $p < 0$ and unstable if $p > 0$. But for $p > 0$ there also exists a periodic solution,

$$x_1(t) = \sqrt{\frac{p}{a}} \cos \mu t, \quad x_2(t) = \sqrt{\frac{p}{a}} \sin \mu t$$

which traces the circle $x_1^2 + x_2^2 = \frac{p}{a}$ as t varies.

This type of bifurcation, which gives rise to periodic solutions, is called **Hopf bifurcation**. Note that the Jacobian matrix J at the $(0,0)$, where the bifurcation occurs, is given by

$$J = \begin{pmatrix} p & -\mu \\ \mu & p \end{pmatrix},$$

and the characteristic equation is

$$(p - \lambda)^2 + \mu^2 = 0,$$

so that the eigenvalues are

$$\lambda = p \pm i\mu.$$

As p crosses from $p < 0$ to $p > 0$, the two eigenvalues, at $p = 0$, become pure imaginary numbers. It is this behavior of the eigenvalues of the Jacobian matrix that gives rise to the periodic solutions. In fact, the bifurcation behavior in the example of the system (11.2)-(11.3) is a special case of the following theorem.

Theorem 11.1. ***(Hopf Bifurcation)*** *Consider the system*

$$\frac{dx}{dt} = f(x,y,p), \quad \frac{dy}{dt} = g(x,y,p). \tag{11.4}$$

Assume that for all p in some interval there exists a steady state $(x^s(p), y^s(p))$, and that the two eigenvalues of the Jacobian matrix (evaluated at the steady state) are complex numbers $\lambda_1(p) = \alpha(p) + i\beta(p)$ and $\lambda_2(p) = \alpha(p) - i\beta(p)$. Assume also that

$$\alpha(p_0) = 0, \quad \beta(p_0) \neq 0 \quad \textit{and} \ \frac{d\alpha}{dp}(p_0) \neq 0.$$

Then one of the three cases must occur:

1. *there is an interval $p_0 < p < c_1$ such that for any p in this interval there exists a unique periodic orbit containing $(x^s(p_0), y^s(p_0))$ in its interior and having a diameter proportional to $|p - p_0|^{1/2}$;*
2. *there is an interval $c_2 < p < p_0$ such that for any p in this interval there exists a unique periodic orbit as in case (1);*
3. *for $p = p_0$ there exist infinitely many orbits surrounding $(x^s(p_0), y^s(p_0))$ with diameters decreasing to zero.*

In the special case of (11.2)-(11.3), $p_0 = 0$, $(x^s(p_0), y^s(p_0)) = (0,0)$, $\alpha(p) = p$, $\beta(p) = \mu$, and both cases (1) and (3) occur; case (3) is illustrated in Fig. 3.1(F).

As first example of Hopf bifurcation we consider a model of herbivore-plant interaction. The plant P has logistic growth with capacity K, and the herbivore N has eating capacity σ, which is the bifurcation parameter.

Problem 11.4. Consider a herbivore-plant model

$$\begin{aligned} \frac{dP}{dt} &= rP(1 - \frac{P}{K}) - \sigma \frac{P}{1+P} N, \\ \frac{dN}{dt} &= \gamma\sigma \frac{P}{1+P} N - \mu N, \end{aligned}$$

where γ is the yield constant and μ is the death rate of the herbivore. Prove that if $\gamma = 2\mu$, $K = 10$ then Hopf bifurcation occurs at $\sigma = 5 + \sqrt{25 - 11/2}$. [Hint: The steady state for each σ is

$$P = \frac{\mu}{\gamma\sigma - \mu}, \quad N = \frac{r}{\sigma}(1+P)(1 - \frac{P}{K}) = \frac{r\gamma}{\gamma\sigma - \mu}(1 - \frac{\mu}{K(\gamma\sigma - \mu)}).$$

The Jacobian matrix is

$$J = \begin{pmatrix} P(-\frac{r}{K} + \frac{\sigma N}{(1+P)^2}) & -\sigma \frac{P}{1+P} \\ \frac{\gamma\sigma N}{(1+P)^2} & 0 \end{pmatrix}.$$

Write the eigenvalue equation in the form $\lambda^2 + a\lambda + b = 0$, and show that $a = 0$, $b > 0$, $\frac{da}{d\sigma} < 0$ at $\sigma = 5 + \sqrt{25 - 11/2}$.]

Setting $\sigma^* = 5 + \sqrt{25 - 11/2}$ we conclude that, as σ increases and crosses σ^*, the stable steady equilibrium (P,N) becomes unstable and instead the dynamics of the herbivore-plant model develops periodic solutions with diameters which increase with σ. Thus both plant and herbivore will coexist, and their populations will vary "seasonally".

Neuronal oscillations are periodic electrical oscillations along the axon of the neurons, and some simplified models represent them in the form

$$\frac{dv}{dt} = f(v) - w + I,$$
$$\frac{dw}{dt} = \varepsilon(\gamma v - w)$$

where I is the applied current, arriving from dendrites, which triggers the oscillations. The function $f(v)$ is a cubic polynomial and ε is a small parameter. The diameter of the periodic oscillations depends on f but is independent of the parameter I. Motivated by this model we consider here the case where f is a *quadratic* polynomial, and show that this case gives rise to Hopf bifurcation, that is, to periodic oscillations which begin with small diameter as I crosses a bifurcation parameter I_0, and then increase with I proportionally to $(I - I_0)^{1/2}$. For simplicity we take $f(v) = v^2$.

Problem 11.5. Consider a system

$$\frac{dv}{dt} = v^2 - w + I,$$
$$\frac{dw}{dt} = 2\gamma v - w,$$

where $\gamma > \frac{1}{4}$ and $0 < I < \gamma^2$. Show that the only steady state $(\bar{v}, \bar{w})$ is given by $\bar{v} = \gamma - \sqrt{\gamma^2 - I}$, $\bar{w} = 2\gamma\bar{v}$, that it is stable if $I < \gamma - \frac{1}{4}$, and that Hopf bifurcation occurs at $I = \gamma - \frac{1}{4}$.

11.1 Endangered Species

Species with very small density v is endangered as a result of endemic incurable disease caused by a parasite with density w. If the population of v is spread over a large territory then mating between a male from v and female from v is proportional to $v \times v = v^2$. Hence

$$\frac{dv}{dt} = rv^2 - \alpha vw$$

where α is the rate by which the parasite w depletes v. On the other hand, the growth of the parasite is proportional to v, so that

$$\frac{dw}{dt} = \gamma v - \beta w$$

where β is the death rate of w. If $r\beta - \alpha\gamma \neq 0$ then the only steady point is $(\bar{v}, \bar{w}) = (0,0)$. In order to save the endangered species v from extinction, new population of the species are introduced into the territory, at density rate I, so that

$$\frac{dv}{dt} = rv^2 - \alpha vw + I.$$

This results in steady point $(\bar{v}, \bar{w})$ where $\bar{v} > 0$, $\bar{w} > 0$, and the question arises: are these points $(\bar{v}(I), \bar{w}(I))$ stable for all I?

To address this question we take, for simplicity, $r = \alpha = \beta = 1$, and $1 < \gamma < 2$. Then

$$\frac{dv}{dt} = v^2 - wv + I,$$
$$\frac{dw}{dt} = \gamma v - w.$$

The only steady point is $\bar{w} = \gamma\bar{v}$, $\bar{v} = (\frac{I}{\gamma - 1})^{1/2}$, and the Jacobian matrix about $(\bar{v}, \bar{w})$ is

$$I = \begin{pmatrix} (2-\gamma)\bar{v} & -\bar{v} \\ \gamma & -1 \end{pmatrix}.$$

Hence $\det J = 2(\gamma - 1) > 0$ and

$$\text{trace } J = (2-\gamma)(\frac{I}{\gamma - 1})^{1/2} - 1 \equiv A(I)$$

where $A(I) < 0$ if $I < I_0$, $A(I) > 0$ if $I > I_0$, and

$$I_0 = \frac{\gamma - 1}{(2-\gamma)^2}.$$

The eigenvalues of J are

$$\lambda = \sigma \pm i\tau$$

where $\sigma = \frac{1}{2}A(I)$, $\tau = [(\frac{1}{2}A(I))^2 - 2(\gamma-1)]^{1/2}$, and $\frac{d\sigma}{dI} > 0$ at $I = I_0$. Hence $(\bar{v}, \bar{w})$ is a stable steady point if $I < I_0$, and Hopf bifurcation occurs at $I = I_0$. We conclude that as I is increased the population $\bar{v}$, in the steady state, will increase and remain stable as long as $I < I_0$; thereafter the steady point will become unstable, and the populations of v and w will oscillate periodically.

Problem 11.6. Consider the following predator-prey model with sparse prey population, x,

$$\frac{dx}{dt} = x^2(1-x) - xy$$
$$\frac{dy}{dt} = 4xy - 4\alpha y$$

where $\alpha > 0$. It has an equilibrium point $(\alpha, \alpha(1-\alpha))$ for any $0 < \alpha < 1$. Prove that Hopf bifurcation occurs at $\alpha = \frac{1}{2}$.

The biological interpretation is that if the predator death rate is smaller than 2 then both predator and prey coexist in steady state, but if the predator death rate exceeds 2 then both predator and prey still coexist but their densities vary periodically, or "seasonally".

11.2 Numerical Simulations

To plot the bifurcation diagram, one needs to scan through the parameter space and solve the ODEs for those parameters. If we would like to plot the bifurcation diagram for

$$\frac{dx}{dt} = f(x, p),$$

the first step is to plot the the nullcline on the x-p plane ($f(x, p) = 0$), which correponds to the steady states x_s under different p. On the nullcline, part of the curve corresponds to stable steady state, and part of that corresponds to unstable steady state (of course, it is possible that only one of them exist). Let us consider the example

$$\frac{dx}{dt} = x^2 + p.$$

First we would like to plot the curve of $x^2 + p = 0$ on x-p plane. In MATLAB, define the right-hand-side function in a script file:

```
function y = saddlefun(p,x)
y = p + x.^2;
```

Note that p and x could be matrices (so is y) in order to accomodate the discretized mesh grid matrix of x-p space. To plot the bifurcation diagram, we create bifur.m, a function file (see Algorithm 1)., with inputs the name of the function (e.g. 'saddlefun') and the range of x and p to plot. In bifru.m, we first discretize x-p plane

in 101 by 101 mesh grid (use the command 'meshgird'). Then we try to fplot the zeros of $x^2 + p$ by using the 'contour command, as shown in Fig. Next, for each p, we need to start with an initial condition x_0 which is NOT a steady state and see at what steady state it ends up. To achieve that, we avoid the nullclines (by using $|f(x_i, p_j)| > 0.1 \times mean|f(x_i, p_j)|$), use the rest of the points as intial conditions and solve the ODE. The solution will get away from the unstable steady state (branch) and be attracted to stable steady state (branch) (Fig.).

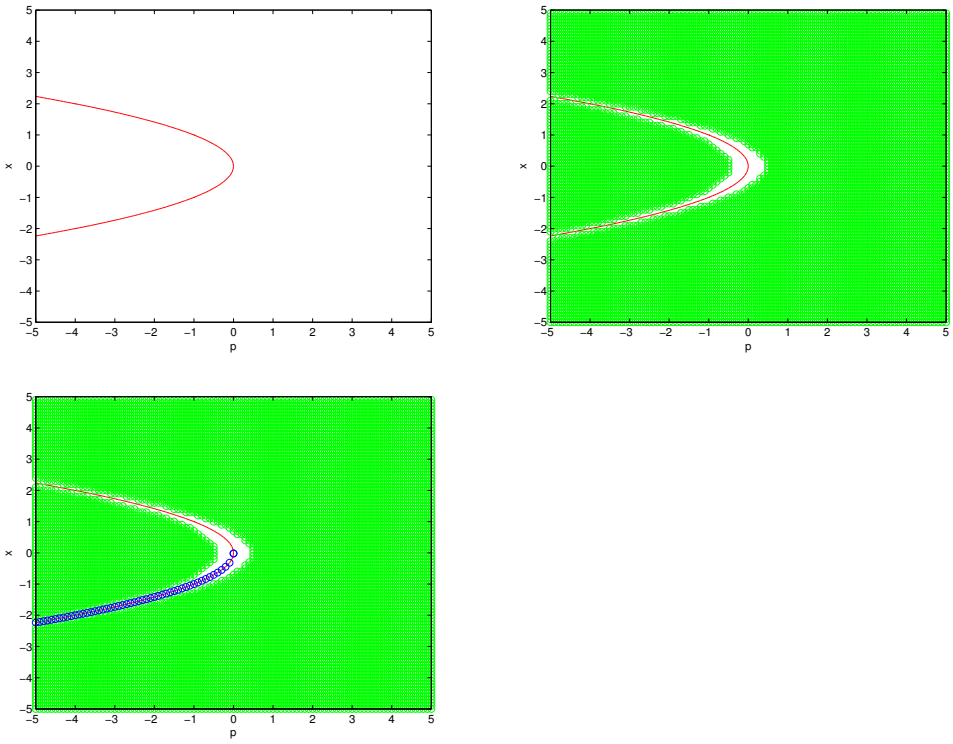


Fig. 11.2 Bifurcation diagram for saddle point bifurcation. (a) Red curves are the steady states; (b) green circles are non-steady-state points; (c) solutions converge to stable steady states (blue circles).

Problem 11.7. Plot the bifrcation diagram for

$$\frac{dx}{dt} = px - x^3.$$

with range $-5 \leq p \leq 5, -5 \leq x \leq 5$.

Algorithm 3 bifur.m

```
% BIFUR Draws bifurcation diagrams
% BIFUR(FCN,XRANGE,PRANGE) draws the
% bifurcation diagram % for the function FCN over the specified x and p ranges.
% FCN is a handle to a user-defined function that takes as
% arguments a variable x and a parameter p. XRANGE is a
% row vector of the form [XMIN XMAX]. PRANGE is a row vector % of the form [PMIN
PMAX].
%
% Example:
% bifur(@saddlefun,[-5 5],[-5 5]);
%
% where saddlefun is a user-defined function of the form
%
% function y=saddlefun(x,p)
% y=p+x.^2;
%
function bifur(fcn,xrange,prange)
nn = 100; % number of points plotted in each range
p1 = [prange(1):(prange(2)-prange(1))/nn:prange(2)]; % sample points in p
x1 = [xrange(1):(xrange(2)-xrange(1))/nn:xrange(2)]; % sample points in x
[p,x] = meshgrid(p1,x1); % generate grid points in [p,x]
fval = feval(fcn,x,p); % evaluate the points value
figure(1);[c,h] = contour(p,x,fval,[0,0],'r'); % plot the zero contour line
xlabel('p'), ylabel('x') x = x(:); p = p(:);
ind = find(abs(fval)¿0.05*mean(abs(fval(:))));
x = x(ind); p = p(ind);
if 1
figure(1); hold on; plot(p,x,'go') % draw the initial points
end
for iter = 1:1000
x = x + 0.05*feval(fcn,x,p); % solve ode
end hold on; plot(p(:),x(:),'bo')
```

Chapter 12
Atherosclerosis: the risk of high cholesterol

Arteries are blood vessels that carry oxygen-rich blood to the heart, brain and other parts of the body. Atherosclerosis is a disease in which a plaque builds up inside arteries. The plaque consists of cholesterol, calcium, cells from the blood, and cells from the arterial wall. Over time the plaque grows, hardens, and narrows the artery. This reduces the flow of oxygen-rich blood, and also make it more likely to cause a blood clot, or thrombus, that will block the blood flow. A blockage formed in the coronary arteries may trigger a heart attack. A blockage formed in the carotid artery (located on each side of the neck, feeding oxygen to the brain) may cause a stroke. Atheroselerosis is the leading cause of death in the United States and worldwide, with annual deaths of 900,000 in the United States and 13 millions worldwide.

The exact cause of atheroselerosis is unknown, and in many cases there are no symptoms until an episode of heart attack or stroke occurs. There are however risk factors which contribute to the disease, namely, high cholesterol, heavy smoking, and hypertension. In this chapter we focus on the risk associated with high cholesterol, and use mathematics to quantify this risk.

Cholesterol is a protein that each cell in our body needs, But cholesterol does not dissolve in blood, and must therefore be transported in the blood stream. It is transported by carrier called lipoprotein, made of fat (lipid) and protein. There are two types of lipoproteins that carry the cholesterol to and from cells. They are called: low-density lipoproteins, LDL, and high-density lipoproteins, HDL. The LDL are "bad" cholesterols, and the HDL are "good" cholesterols. The LDL contributes to plaque growth and the HDL reduce the plaque by removing the LDL from the plaque.

The level of cholesterol in the blood is measured in units of $10^{-5} gm/cm^3$. The American Heart Association established guidelines regarding the atherosclerosis risk associated with the levels of LDL and HDL in the blood. For example,

LDL=190, HDL=40 is high risk,

LDL=110, HDL=50 is risk free.

In this chapter, we develop a mathematical model of plaque growth and use it to predict the risk associated with any pair of values (LDL, HDL). We introduce the notation

$$L_0 = \text{Concentration of LDL in blood,}$$
$$H_0 = \text{Concentration of HDL in blood,}$$

and wish to determine, based on (L_0, H_0), whether a plaque will grow or shrink. To do that we need to understand how a plaque is formed.

Under the pressure of the bloodstream, a small lesion may occur in the inner surface of the arterial wall, enabling cholesterol to invade into the inner layer, called intima. Free radicals are molecules or ions that have umpaired valence electrons, and are therefore highly reactive in many chemical processes in our body; they play useful role in metabolic processes. **Macrophages** are cells of the immune system that travel around the body and engulf and digest foreign particles, cellular debris, and invading microorganisms. When LDL enters the intima, they immediately become oxidized by radicals. Macrophages from the blood then move into the intima and engulf the oxidized LDL. The fat-laden macrophages saturated with oxidized LDL, are called **foam cells**. Figure 12.1 shows a cross section of a plaque in the artery.

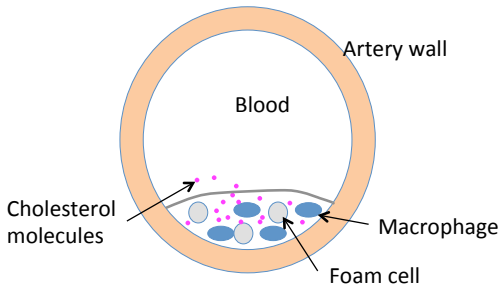


Fig. 12.1 Cross section of a plaque in an artery.

In our mathematical model we assume that the plaque consists mainly of macrophages and foam cells. This is a simplification, since also other cells are involved, such as smooth muscle cells which move from the middle layer of the arterial wall into the intima.

Our model will include the following variables:

- Macrophage density, M,
- Foam cell density, F,
- "Bad" cholesterol concentration, LDL or L,
- "Good" cholesterol concentration, HDL or H.

We shall not distinguish between LDL and oxidized LDL. The equation for LDL is the following:

$$\frac{dL}{dt} = L_0 - k_1 M \frac{L}{K_1 + L} - r_1 L. \tag{12.1}$$

The first term on the right-hand side, L_0, is the LDL concentration in the blood. The second term represents the ingestion of LDL by macrophages, which is described by the Michaelis-Menten formula. The last term is the degradation of LDL.

In a similar way we write the equation for HDL:

$$\frac{dH}{dt} = H_0 - k_2 H \frac{F}{K_2 + F} - r_2 H. \tag{12.2}$$

Here the second term on the right-hand side is interpreted as follows: HDL is being absorbed by a foam cell (more precisely, it forms a complex with a membrane protein of a foam cell) and this initiates a process that empties out the oxidized LDL from the foam cell. The foam cells returns to become a macrophage, while the emptied-out oxidized LDL is removed from the plaque and is transported back (by the blood) to the liver for recycling. We note that when H forms a complex with a receptor protein on F, it takes some time for the receptor to again become free. Thus the receptor "recycling" limits the ability of F to react to H, and this explains why we used $k_2 HF/(K_2 + F)$ instead of $k_2 HF$ in Eq. (12.2).

The equations for macrophages and foam cells are

$$\frac{dM}{dt} = -k_1 M \frac{L}{K_1 + L} + k_2 H \frac{F}{K_2 + F} + \lambda \frac{ML}{\delta + H} - \mu_1 M, \tag{12.3}$$

$$\frac{dF}{dt} = k_1 M \frac{L}{K_1 + L} - k_2 H \frac{F}{K_2 + F} - \mu_2 F. \tag{12.4}$$

The first two terms or the right-hand sides of Eqs. (12.3)-(12.4), account for the exchanges between macrophages and foam cells, as already explained above. The terms $\mu_1 M$, $\mu_2 F$ represent the natural deaths of macrophages and foam cells. The remaining term that needs explanation is $\lambda ML/(\delta + H)$. The oxidized LDL in the plaque triggers infiltration of macrophages from the blood into the plaque, and this is accounted by the factor λML. On the other hand, the HDL are oxidized by radicals (as the LDL are) and this reduces the amount of radicals available to oxidize LDL. In this sense H acts as inhibitor, which restricts the effect of λML by a factor $1/(\delta + H)$, for some $\delta > 0$.

We wish to solve the system of equations (12.1)-(12.4) and compute the weight of the plaque

$$w(t) = M(t) + F(t)$$

at time t; the weight of the cholesterol is negligible. We take initial values

$$L = 0, H = 0, F = 0, M = M_0 = 5 \times 10^{-4} g/cm^3.$$

We set

$$R(t) = \frac{w(t)}{w(0)} = \frac{w(t)}{M_0}$$

so that $R(0) = 1$.

Given cholesterol level (L_0, H_0), we wish to determine whether $R(t)$ will increase, indicating risk of atherosclerosis, or decrease which means risk-free of atherosclerosis.

The following problems show that if L_0 is sufficiently small then $R(t) \to 0$ as $t \to \infty$, that is: if the level of "bad" cholesterol is low then there is no risk of a plaque to form.

Problem 12.1. Show that for any small $\varepsilon > 0$, $L(t) < \frac{L_0}{r_1} + \varepsilon$ if t is sufficiently large.

Problem 12.2. Assume that $\mu_1 = \mu_2 = \mu$ and prove that if

$$L_0 < \frac{r_1 \delta \mu}{\lambda}$$

then $R(t) \to 0$ if $t \to \infty$.

12.1 Numerical Simulations

We wish to compute $R(t)$ for $0 < t < T$, say $T = 300$ days.

We say that (L_0, H_0) is in the **risk zone** if $R(T) > 1$, and in the **risk-free zone** if $R(T) < 1$. In the following simulations we use the parameters taken from the model developed in []: $k_1 = 144/day$, $k_2 = 10/day$, $K_1 = 10^{-2} g/cm^3$, $K_2 = 0.5\ g/cm^3$, $\mu_1 = 0.015/day$, $\mu_2 = 0.03/day$, $r_1 = 2.4 \times 10^{-5}/day$, $r_2 = 5.5 \times 10^{-7}/day$, $\lambda = 2.57 \times 10^{-3}/day$, $\delta = -2.54\ g/cm^3$.

Problem 12.3. Compute $R(300)$ (300 days) for the 25 pairs (L_0, H_0), where $L_0 = 100, 120, 140, 160, 180$ and $H_0 = 40, 45, 50, 55, 60$.

Problem 12.4. Verify that in each of these cases $R(300) > 1$ if $L_0 > \frac{\mu_1}{\lambda}(\delta + H_0)$, and $R(300) < 1$ if $L_0 < \frac{\mu_1}{\lambda}(\delta + H_0)$.

We may thus conclude that, roughly, (L_0, H_0) is in the risk zone if

$$L_0 > \frac{\mu_1}{\lambda}(\delta + H_0),$$

and in the no-risk zone if

$$L_0 < \frac{\mu_1}{\lambda}(\delta + H_0).$$

The borderline between the two zones is the linear $L_0 = aH + b$ where $a = \frac{\mu_1}{\lambda}, b = \frac{\mu_1}{\lambda}\delta$.

Chapter 13
Cancer-immune Interaction

An abnormally new growth of tissue with cells that grow more rapidly than normal cells and has no physiological function is called a neoplasm or a tumor. The abnormally rapidly growing cells compete with normal cells for space and nutrients. When the new growth is localized, it is called a benign tumor. When a tumor in tissue has reaches a size of several millimeters it requires a large supply of nutrients, for otherwise it can no longer grow. Such a tumor is called **avascular**. Avascular tumors try to induce the formation of new blood vessels (**angiogenesis**) and direct their movement toward them. They do so by secreting **tumor endothelial growth factor** (VEGF) and, if successful, the tumors become **vascular**. A vascular tumor continues to grow and some of its cells may break away and travel to other parts of the body through the bloodstream or the lymph system. **Metastatic cancer** is a tumor that spread from the original location where it started to other parts of the body. Metastatic cancer is also called **malignant cancer**, or, briefly, **cancer**, although people often use the words tumor and cancer interchangeably. Most cancer deaths are due to metastasized cancer.

Cancer is a disease of tissue growth failure, and it is the result of normal cells transforming into cancer cells because of mutations in genes that regulate cell growth and differentiation. In the context of cancer, these genes are classified either as **oncogenes** or **tumor suppressor genes**. Oncogenes are genes which promote cell growth and reproduction. Tumor suppressor genes are genes which inhibit cell division and survival. Malignant transformation occurs when oncogenes become overexpressed compared to normal oncogenes, or when tumor suppressor genes become underexpressed, or disabled. Typically a transformation of a normal cell to a tumor cell occurs after not one but several gene mutations.

It is commonly believed that most mutations leading to cancer are due to external conditions, such as smoking, dietary factors, environmental pollutants, exposure to radiation, and certain infections. But some mutations are hereditary.

There are more than one hundred known types of human cancer, broadly categorized according to the tissue of origin. **Carcinomas** begin with epithelial cells; **sarcomas** arise from connective tissues, muscles and vasculature; **leukemias** and **lymphomas** are cancers of the hematopoietic (blood) and immune system, respectively;

gliomas are cancers of the central nervous system, including the brain; **retinoblastomas** are cancers of the eyes.

The most common cause of cancer-related death in the United States are lung, colorectal, breast (for women) and prostate (for men), and pancreatic cancers. Malignancy typically induces moderate cellular immune response. But cancer cells try to evade the immune response by inducing favorable changes in phenotype of immune cells. The interaction between cancer cells and the immune system is complex, and it affects the efficacy of chemotherapeutic drugs. In order to determine this efficacy, we need to develop a mathematical model of cancer-immune interaction and then use it to evaluate the efficacy of various drugs; this is the aim of the present chapter.

We begin with a few facts that are needed in order to build the mathematical model. An important class of immune cells that confront a tumor are T cells. Another type of cells are macrophage, which we already met in Chapter 11. Here we distinguish between two phenotypes: pro-inflammatory macrophages M_1, and anti-inflammatory macrophages M_2. M_1 Macrophages produce inflammatory cytokine, interleukin IL-12, and M_2 macrophages produce anti-inflammatory cytokine, interleukin IL-10. IL-12 activates T cells, whereas IL-10 inhibits this activation. Activated T cells kill tumor cells. In order to evade the immune system, cancer cells produce transforming growth factor β (TGF-β) that attaches to the membrane of M_1 macrophages and starts a process that changes their phenotype to M_2 macrophages, resulting in reduced killing of cancer cells by T cells. Figure. 13.1 is a schematics of the cancer-immune interaction described above.

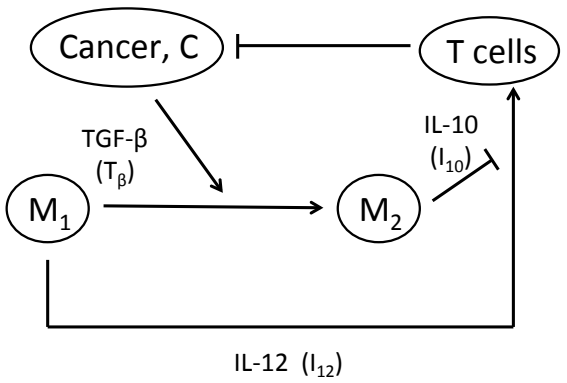


Fig. 13.1 Tumor-immune interaction. Arrow means production or activation; blocked arrow-head means inhibition or killing.

Based on Fig. 13.1 we can write down the following equations for the cells:

$$\frac{dC}{dt} = \lambda_c C(1-\frac{C}{C_0}) - \mu_c TC, \tag{13.1}$$

$$\frac{dM_1}{dt} = k_1 - \tilde{\gamma} M_1 \frac{T_\beta}{\tilde{k}_1 + T_\beta} - \mu M_1, \tag{13.2}$$

$$\frac{dM_2}{dt} = \tilde{\gamma} M_1 \frac{T_\beta}{\tilde{k}_1 + T_\beta} - \mu M_2, \tag{13.3}$$

$$\frac{dT}{dt} = \tilde{k}_T \frac{I_{12}}{\tilde{k}_2 + I_{10}} - \mu_T T. \tag{13.4}$$

We also have the following equations for the cytokines:

$$\frac{dI_{12}}{dt} = \lambda_{12} M_1 - \mu_{12} I_{12}, \tag{13.5}$$

$$\frac{dI_{10}}{dt} = \lambda_{10} M_2 - \mu_{10} I_{10}, \tag{13.6}$$

$$\frac{dT_\beta}{dt} = \lambda_\beta C - \mu_\beta I_\beta. \tag{13.7}$$

In Eq. (13.1) we assume a logistic growth for cancer cells, and that T cells kill cancer cells at rate μ_c. In Eq. (13.2) we assume constant production rate k_1 and death rate μ_1 of M_1 macrophage. T_β changes the phenotype of M_1 to M_2, and this is accounted by the term $\tilde{\gamma} M_1 \frac{T_\beta}{\tilde{k}_1 + T_\beta}$. In Eq. (13.4) the first term represents the activation of T cells by I_{12}, a process inhibited by I_{10} which appears in the factor $1/(\tilde{k}_2 + I_{10})$.

We simplify the model (13.1)-(13.6) by noting that the cytokines dynamics is much faster than the cells dynamics. Hence we may assume steady state in the equations of (13.5)-(13.7). Thus $I_{12} = const\ M_1$, $I_{10} = const\ M_2$ and $T_\beta = const\ C$. Using these relations in Eqs. (13.2)-(13.4), the system (13.1)-(13.7) reduces to the following system of four equations:

$$\frac{dC}{dt} = \lambda_c C(1-\frac{C}{C_0}) - \mu_c TC, \tag{13.8}$$

$$\frac{dM_1}{dt} = k_1 - \gamma M_1 \frac{C}{K_1 + C} - \mu M_1, \tag{13.9}$$

$$\frac{dM_2}{dt} = \gamma M_1 \frac{C}{K_1 + C} - \mu M_2, \tag{13.10}$$

$$\frac{dT}{dt} = k_T \frac{M_1}{K_2 + M_2} - \mu_T T. \tag{13.11}$$

with coefficients γ, k_T and K_1, K_2.

A common chemotherapeutic drug is TGF-β inhibitor. The effect of this drug is to increase μ_β and hence to reduce γ.

Problem 13.1. Use Eq. (13.5) to deduce that for any small $\varepsilon > 0$,

$$M_1(t) \leq \frac{k_1}{\mu} + \varepsilon$$

if t is large enough.

Problem 13.2. Use Eq. (13.9) to deduce that for any small $\varepsilon > 0$,

$$M_1(t) \geq \frac{k_1}{\mu + \gamma} - \varepsilon$$

if t is large enough.

Problem 13.3. Use Eq. (13.10) to deduce that for any small $\varepsilon > 0$,

$$M_2(t) \leq \frac{\gamma k_1}{\mu^2} + \varepsilon$$

if t is large enough.

Problem 13.4. Use Eq. (13.11) to deduce that for any small $\varepsilon > 0$,

$$T(t) \geq \frac{k_T}{\alpha(\gamma)} - \varepsilon$$

if t is large enough, where

$$\alpha(\gamma) = \frac{\mu_T}{k_1}(\mu + \gamma)(k_2 + \gamma k_1/\mu^2).$$

Problem 13.5. Use Eq. (13.8) and Problem 13.4 to conclude that if

$$k_T \mu_C > \lambda_c \alpha(\gamma). \tag{13.12}$$

then $\lim_{t\to\infty} C(t) = 0$.

The coefficients k_T and μ_C depend on the immune system, i.e., on the response of the T cells to cancer. The aggressiveness of the cancer depends on TGF-β, that is, on the parameter γ, which may be decreased by TGF-β inhibitor. Problem 13.5 asserts that is the immune system is strong enough relative to the aggresiveness of the cancer then the cancer will disappear.

13.1 Numerical Simulations

We would like to investigate how effective the drug is for various "strengths" μ_c of the T-cells killing rate. So we shall determine how $C(t)$, say for $0 \leq t \leq 60$ days, depends on the drug and on the immune strength (μ_c). All other parameters are given as follows: $k_c = 10^{-2}/day$, $\mu_c = 10^{-7}/cell/day$, $C_0 = 10^6\ cell/cm^3$, $\mu = 0.3/day$,

$k_1 = 3000\ cell/cm^3/day$, $\gamma = 1.1\mu\ /day$, $k_T = 2\mu_T\ /cell/day$, $K_1 = 0.5C_0$, $K_2 = 10^5\ cell/cm^3$, $\mu_T = 0.2/day$.

Problem 13.6. Solve the model (13.6)-(13.11) under the initial conditions $C(0) = 10^2\ cell/cm^3$, $M_1(0) = 5 \times 10^4\ cells/cm^3$, $M_2(0) = 0$, $T(0) = 0$, for $0 \leq t \leq 60$ days.

Problem 13.7. Repeat the calculation with γ replaces by γ/A, $A = 2, 5, 10$ and draw the 3 profiles of $C(t)$, $0 \leq t \leq 60$.

Problem 13.8. Repeat Problem 11.2 with

1. μ_c replaced by $\frac{\mu_c}{10}$.
2. μ_c replaced by $10\mu_c$.

Draw conclusions on how the efficacy of TGF-β inhibitor on the strength of the immune system parameter μ_c.

Chapter 14
Cancer Therapy

There are many drugs that are used in the treatment of cancer; some drug kill cancer cells directly while others change the cancer microenviroment to make it resistant to cancer cells growth. In Chapter 11, we considered the drug TGF-β inhibitor, which changes the macrophage phenotype, thereby enabling the immune system to kill cancer cells more effectively.

In this chapter we consider two entirely different kinds of anti-cancer drugs. The first one blocks the activity of VEGF, and the second one uses virus to kill tumor cells.

14.0.1 VEGF receptor inhibitor

In order to continue to grow abnormally, the tumor requires increasing amounts of oxygen from the blood. So the tumor secrets VEGF which attracts endothelial cells that from the inner lining of the blood vessels wall, thereby leading to the formation of new blood vessels (**angiogenesis**) that deliver oxygen to the tumor. To model this process we introduce the following variables:

$$\begin{aligned} c &= \text{ density of tumor cells,} \\ e &= \text{ density of endothelial cells,} \\ h &= \text{ concentration of VEGF,} \\ w &= \text{ concentration of oxygen,} \end{aligned}$$

We assume logistic growth

$$\tilde{\lambda}_1 c(1-\frac{c}{K})$$

of the tumor, where K is the **carrying capacity** and $\tilde{\lambda}_1$ is the growth rate. We assume that $\tilde{\lambda}_1$ is proportional to w, $\tilde{\lambda}_1 = 0$ if $w = 0$, and that

$$w = Be \quad (\text{B a positive constant}). \tag{14.1}$$

Hence,

$$\frac{dc}{dt} = \lambda_1 ec(1 - \frac{c}{K}) - \mu_1 c, \quad c(0) < K. \tag{14.2}$$

Here λ_1 is a positive constant and μ_1 is the death rate of cancer cells.

Next we model the equation for VEGF by

$$\frac{dh}{dt} = \lambda_2 c - \mu_2 h, \tag{14.3}$$

where λ_2 is the production rate of VEGF by tumor cells, and μ_2 is the degradation rate.

Endothelial cells proliferation is assumed to be proportional to h,

$$\frac{de}{dt} = \lambda_3 h.$$

But we need to take into account that e is proportional to w (by Eq. (14.1)) whereas oxygen is decreased by consumption by cancer cells as well by dissipation in the tissue, that is,

$$\frac{dw}{dt} = -\tilde{\mu}_3 cw - \tilde{\mu}_4 w.$$

Hence the complete equation for e has the form

$$\frac{de}{dt} = \lambda_3 h - \mu_3 ce - \mu_4 e, \tag{14.4}$$

where all the parameters are positive constants.

Avastin is a drug that inhibits VEGF receptor (VEGFR) and thus does not allow the activation of VEGF. We can model the effect of Avastin by replacing λ_2 in Eq. (14.3) by $\lambda_2/(1+A)$ where A is proportional to the amount of the delivered drug. Then Eq. (14.3) becomes

$$\frac{dh}{dt} = \frac{\lambda_2 c}{1+A} - \mu_2 h. \tag{14.5}$$

The following problems show that if A is large enough then the tumor will decrease to zero as $t \to \infty$.

Problem 14.1. Observe that $c(t) < K$ for all $t > 0$, and use Eq. (14.5) to show that, for any $\varepsilon > 0$,

$$h(t) \le \frac{\lambda_2 K}{\mu_2(1+A)} + \varepsilon \quad \text{if } t \text{ is large enough.}$$

Problem 14.2. Use Eq. (14.4) and Problem 14.1 to show that, for any $\varepsilon > 0$,

$$e(t) \le \frac{\lambda_2 \lambda_3 K}{\mu_2 \mu_4(1+A)} + \varepsilon \quad \text{if } t \text{ is large enough.}$$

Problem 14.3. Use Eq. (14.2) and Problem 14.2 to show that if

$$1+A > \frac{\lambda_1\lambda_2\lambda_3 K}{\mu_1\mu_2\mu_4}$$

then $c(t) \to 0$ as $t \to \infty$.

We concluded that if Avastin is administered in large enough amount then the tumor will shrink to zero. We note however that Avastin has negative side effects, including damage to the liver, and thus can only be administered in limited amounts.

We next introduce a completely different model for anti-tumor treatment by blocking VEGF. We begin with a model of cancer cells suggested by **Gumpertz**. It includes cancer cells x and growth factor γ which act, like VEGF, to provide nutrients to the cancer:

$$\begin{array}{rl} \frac{dx}{dt} = & \gamma x, \\ \frac{d\gamma}{dt} = & -\alpha\gamma. \end{array} \tag{14.6}$$

Problem 14.4. Prove that the solution of (14.6) satisfies the **Gompertz equation**

$$\frac{dx}{dt} = -\alpha x \ln\frac{x}{K}, \quad (0 < x < K) \tag{14.7}$$

where K is given by

$$\ln\frac{x(0)}{K} = -\frac{\gamma(0)}{\alpha}.$$

We view K as the carrying capacity and α as the growth rate. The constant K depends on the density of the blood vessels which provides nutrients to the tumor. We can refine the model (14.7) by taking K to be a function of the concentration of the blood capillaries, which we shall denote by y. We take $K = y$ so that

$$\frac{dx}{dt} = \alpha x \ln\frac{x}{y}, \tag{14.8}$$

and model the concentration y by the equation

$$\frac{dy}{dt} = A - 2\mu y + \delta xy. \tag{14.9}$$

Here $A - 2\mu y$ represents that natural growth and degradation of capillaries, and δxy represents the formation of new capillaries from existing capillaries, induced by growth factors secreted by the tumor cells.

Problem 14.5. The system (14.8)-(14.9) has steady states

$$x = y = Z_\pm \quad \text{where } Z_\pm = \frac{1}{\delta}\{\mu \pm \sqrt{\mu^2 - \delta A}\},$$

provided $\delta A < \mu^2$. Prove that the steady state $x = y = Z_-$ is stable, and that the steady state $x = y = Z_+$ is unstable.

The biological interpretation is that (i) if $\delta A > \mu^2$, then the tumor receives sufficient nutrients so it grows indefinitely (no steady states); (ii) if $\delta A < \mu^2$, there will be a steady state (benign tumor).

We recall that tumor secrets VEGF that increase angiogenesis, and hence A. A drug that blocks VEGF such as soluble VEGFR-1 (e.g. Avastin), reduces A. If the drug decreases A so that $\delta A < \mu^2$, then the tumor will not grow indefinitely. Furthermore, the drug will also decrease the size of the benign tumor, in the sense that it decreases the stable steady point with $x = y = \frac{1}{\delta}(\mu - \sqrt{\mu^2 - \delta A})$.

14.0.2 Virotherapy

We next consider anti-cancer drug which employs virus particles to kill cancer cells; such a treatment is called **virotherapy**. The virus particles are genetically modified so that they can infect cancer cells but not normal healthy cells. Such viruses are called **oncolytic viruses**. The viruses are injected directly into the tumor.

After entering a cancer cell, a virus begins to quickly replicate, and when the cancer cell dies, a large number of virus particles burst out and proceed to infect other cancer cells.

To model this process we introduce the following variables:

$x =$ number density of cancer cells,

$y =$ number density of infected cancer cells,

$n =$ number density of dead cells,

$v =$ number density of virus particles which are not contained in cancer cells,

Virotherapy is modeled by the following system of equations:

$$\begin{array}{l} \frac{dx}{dt} = \lambda x - \beta x v, \\ \frac{dy}{dt} = \beta x v - \delta y, \\ \frac{dn}{dt} = \delta y - \mu n, \\ \frac{dv}{dt} = b\delta y - \gamma v. \end{array} \tag{14.10}$$

where

$\lambda =$ proliferation rate of cancer cells,

$\beta =$ rate of infection of cancer cells by viruses,

$\delta =$ death rate of infected cancer cells,

$\mu =$ removal rate of debris of dead cells,

and, finally, b is the replication number of a virus at the time of death of the infected cancer cell. Adding Eqs. (14.10), we get

$$\frac{d}{dt}(x+y+n) = \lambda x - \mu n. \tag{14.11}$$

We assume that the tumor is spherical with radius $R(t)$ and that the cells are continuously moving around in a way that keeps their distribution constant within the sphere. Hence

$$x(t)+y(t)+n(t)=\theta(t) \tag{14.12}$$

where $\theta(t)$ is the total cell density. By (14.11), the increase in the number of cells in the growing sphere is given by

$$\frac{d}{dt}(\frac{4\pi}{3}R^3(t)\theta(t))=(\lambda x(t)-\mu n(t))\frac{4\pi}{3}R^3(t).$$

We assume that $\theta(t)$ is approximately a constant θ_0. Then, after using also (14.12) we get

$$\theta_0\frac{3}{R}\frac{dR}{dt}=(\lambda+\mu)x+\mu y-\mu\theta_0 \tag{14.13}$$

where x and y satisfy the first two equations of (14.10) and v satisfies the last equation of (14.10).

In experiments, viral therapy as described above was not initially successful because it failed to address the effect of the immune system. Immune cells recognize the infected cancer cells and destroy them before the virus particles get a chance to replicate to their full potential. To make virotherapy more effective the immune system must therefore be suppressed. In Problem 14.8 we extend the model (14.10)-(14.13) to include the density of the immune cells, z, and the chemotherapy P which suppresses the immune system.

Problem 14.6. Show that the system for (x,y,v) in (14.10) has a steady point $(\bar{x},\bar{y},\bar{v})$ with $\bar{x}>0$, and determine whether it is asymptotically stable.

14.1 Numerical Simulations

To simulate the model (14.10)-(14.13), we provide the following codes which uses 'ode45' to solve the ODEs.

Problem 14.7. Take $\lambda=2\times10^{-2}$/h, $\delta=(1/18)$/h, $\mu=(1/48)$/h, $\theta_0=10^6$ cells/mm^3, $\beta=7\times10^{-8}$ mm^3/(h·virus), $\gamma=2.5\times10^{-2}$/h. Compute $R(t)$ for $0\le t\le 20$h, with initial conditions $x_0=8\times10^5$ cells/mm^3, $y_0=10^5$ cells/mm^3, $v_0=10^9$ virus/mm^3, $R(0)=2$ mm when $b=50,100,200,500$.

Problem 14.8. Consider the system

$$\frac{dx}{dt}=\lambda x-\beta xv,\quad \frac{dy}{dt}=\beta xv-kyz-\delta y,$$

$$\frac{dn}{dt}=kyz+\delta y-\mu n,\quad \frac{dz}{dt}=syz-\omega z^2-P(t)z,\quad \frac{dv}{dt}=b\delta y-k_0vz-\gamma v,$$

Algorithm 4 model_cancer.m

```
% This code simulates model (14.10)-(14.13).
close all,
clear all,
% define global parameters
global lambda delta mu theta_0 beta gamma b
% starting and final time
t0 = 0; tfinal = 20;
% paramters
lambda = 2 * 10^-2; delta = 1/18; mu = 1/48; theta_0 = 10^6; beta = 7 * 10^-8; gamma = 2.5 *
10^-2;
b = 100;
% initial conditions
v0 = [8*10^5, 10^5, theta_0-8*10^5-10^5, 10^9, 2];
[t,v] = ode45('fun_cancer',[t0,tfinal],v0);
plot(t,v(:,5)) % Plot the evolution of the radius of tumor
```

Algorithm 5 fun_cancer.m

```
% This is the function file called by model_cancer.m
function dy = fun_cancer(t,v)
global lambda delta mu theta_0 beta gamma b
dy(1) = lambda*v(1) - beta*v(1)*v(4);
dy(2) = beta*v(1)*v(4) - delta*v(2);
dy(3) = delta*v(2) - mu*v(3);
dy(4) = b*delta*v(2) - gamma*v(4);
dy(5) = v(5)/(3*theta_0)*((lambda+mu)*v(1)+mu*v(2)-mu*theta_0);
dy = [dy(1);dy(2);dy(3);dy(4);dy(5)];
```

where $z =$ number density of immunity cells, $P(t) =$ immune suppressor drug, $x + y + n + z = \theta_0$, k = rate of immune cell killing infected cell, k_0 = take-up rate of virus by immune cells, s = stimulation rate of immune cells by infected cells, ω = clearing rate of immune cells. We take $P(t) = 8 \times 10^{-2}$/h, $k = 2 \times 10^{-8}$ mm^3/(h·immune cell), $k_0 = 10^{-8}$ mm^3/(h·immune cell), $s = 5.6 \times 10^{-7}$ mm^3/(h·infected cell), $\omega = 2 \times 10^{-7}$ mm^3/(h·immune cell) and all other parameters as in Problem 14.7, $z_0 = 6 \times 10^4$ cells/mm^3, and all other initial conditions as in Problem 14.7. (i) Compute $R(t)$ for $0 \leq t \leq 20$h, when $b = 50, 100, 200, 500$ and compare the results with those of Problem 14.7. (ii) Do the same when the chemotherapy dose is increased to $P(t) = 16 \times 10^{-2}$/h.

Chapter 15
Turberculosis

Tuberculosis (TB) is an infective disease caused by Mycobacterium tuberculosis (Mtb). The bacteria is spread through the air when people who have active TB infection cough or sneeze. The bacteria attack the lungs, primarily, but can also spread and attack other parts of the body. The most common symptom of active TB infection is chronic cough with blood-tinged sputum. It is estimated that one-third of the world's population have been infected with Mtb, although only 13 million chronic cases were active globally in 2013, and 1.5 million associated death occurred. Treatment of TB uses antibiotics to kill the bacteria, but the treatment is not entirely effective. Vaccination, in children decreases significantly the risk of infection.

TB infection in the lungs begins when inhaled mycrobacteria tuberculosis reach the pulmonary alveoli and invade into, or are ingested by, alveoli macrophages; alveoli are tiny air sacs within the lungs where exchange of oxygen and carbon dioxide takes place. It is clearly important to determine whether infection by inhaled Mtb will develop into chronic TB. This cannot be determined directly by measurement, so we shall use mathematics to address this question. In what follows we develop a mathematical model and use it to determine the threshold of initial infection that will develop into active TB.

We introduce the following variables:

$M =$ number of alveolar macrophages in cm^3;
$M_i =$ number of infected alveolar macrophages in cm^3;
$B_e =$ number of extracellular bacteria (residing in tissue, outside macrophages) in cm^3;
$B_i =$ number of intracellular bacteria (residing inside macrophages) in cm^3;

M satisfies the differential equation

$$\frac{dM}{dt} = \mu_M - \lambda_1 M \frac{B_e}{K + B_e} - d_M M. \tag{15.1}$$

Here μ_M is the production rate of M and d_M is the death rate when there is not infection; in steady state, $\mu_M = d_M M_0$ where M_0 is the number of macrophages in cm^3 in

healthy lungs. The second term on the right-hand side of Eq. (15.1) represents the ingestion of bacteria by macrophages, modeled by the Michaelis-Menten formula, which turns M into M_i.

The infected macrophages satisfy the equation

$$\frac{dM_i}{dt} = \lambda_1 M \frac{B_e}{K+B_e} - \lambda_2 M_i \frac{B_i^2}{B_i^2 + (NM_i)^2} - d_{M_i} M_i. \tag{15.2}$$

The first term on the right-hand side comes from macrophages ingesting extracellular bacteria, and d_{M_i} is the death rate of M_i macrophages. The second term on the right-hand side of Eq. (15.2) accounts for the burst of M_i under bacterial load. The probability for macrophage burst increase to 50% when the number of internal bacteria reaches N, that is, when $B_i = NM_i$, the burst rate is $\lambda_2/2$. Note that we have assumed here that the transition from non-bursting state to bursting-state is sharp, as in Fig. 10.2(B) rather than Fig. 10.2(A), and so we used the Hill kinetics rather than the Michaelis-Menten law.

We next write a differential equation for the extracellular bacteria:

$$\frac{dB_e}{dt} = N\lambda_2 M_i \frac{B_i^2}{B_i^2 + (NM_i)^2} - \lambda_1 M \frac{B_e}{K+B_e}. \tag{15.3}$$

The first term on the right-hand side accounts for the number of bacteria released at burst of infected macrophages, and the second term represents the loss of B_e due to ingestion by macrophages.

The equation for intracellular bacteria B_i is

$$\frac{dB_i}{dt} = \gamma B_i + \lambda_1 M \frac{B_c}{K+B_c} - N\lambda_2 M_i \frac{B_i^2}{B_i^2 + (NM_i)^2}. \tag{15.4}$$

The bacteria grow within macrophages at rate γ. The last two terms in Eq. (15.4) have already been explained above.

The question then arises: How does it happen that most infections with *Mtb* do not lead to chronic active TB? The answer is that the adaptive immune system (located in the lymph nodes) receives stress signals from the M_i, and then inflammatory macrophages (in contrast to non-inflammatory alveolar macrophages) and T cells migrate into the lung and kill bacteria. For simplicity we consider only the T cells. Their number per cm^3, satisfies the equation

$$\frac{dT}{dt} = \alpha M_i - d_T T, \tag{15.5}$$

where d_T, and α is the rate by which T cells are activated by the (signaling sent by the) M_i. The killing of bacteria means that we have to replace Eqs. (15.3)-(15.4) by the following equations:

$$\frac{dB_e}{dt} = N\lambda_2 M_i \frac{B_i^2}{B_i^2 + (NM_i)^2} - \lambda_1 M \frac{B_e}{K + B_e} - \delta_1 T B_e, \tag{15.6}$$

$$\frac{dB_i}{dt} = \gamma B_i + \lambda_1 M \frac{B_e}{K + B_e} - N\lambda_2 M_i \frac{B_i^2}{B_i^2 + (NM_i)^2} - \delta_2 T B_i, \tag{15.7}$$

For simplicity we take $\delta_1 = \delta_2 = \delta$. The parameters α, δ determine the course of the *Mtb* infection.

The question of susceptibility to TB can be framed as follows: how many ingested bacteria it takes to cause an initial infection to develop into chronic TB? We shall address this question with the following simple model which involves only extracellular bacteria B and uninfected macrophages M:

$$\frac{dM}{dt} = M_0 - \mu_1 \frac{MB}{B + K} - \alpha M, \tag{15.8}$$

$$\frac{dB}{dt} = \lambda B - \mu_2 \frac{MB}{B + K}. \tag{15.9}$$

Here M_0 is a baseline supply of new macrophages, α is the natural death rate of macrophages, μ_1 is the rate by which macrophages ingest bacteria, a process that depletes the bacteria at rate μ_2, and λ is the ingestion process (or endocytosis) modeled by the Michaelis-Menten law because the uptake of bacteria by a macrophage is time-limited. In steady state of healthy individuals $M_0 - \alpha M = 0$.

The model (15.8)-(15.9) is very simple since, as we know from the more detailed model (15.1)-(15.7), λ is a function of B_i, M_i and T. Nevertheless, already the present simple model sheds some light on the consideration of susceptibility to TB, as we see from the following problems.

Problem 15.1. We may view the system (15.8)-(15.9) as a model of an infections disease with DFE

$$(M, B) = (\frac{M_0}{\alpha}, 0).$$

Setting

$$b = \frac{\mu_2 M_0}{\alpha} - \lambda K,$$

show that the DFE is stable if $b > 0$ and unstable if $b < 0$.

We next study the behavior of solutions of Eqs. (15.8)-(15.9) when the initial values are not necessarily near the DFE.

Problem 15.2. Show that if $M(0) \leq \frac{M_0}{\alpha}$ then $M(t) \leq \frac{M_0}{\alpha}$ for all $t > 0$, and deduce that

$$\frac{dB}{dt} \geq B \frac{\lambda B - b}{B + K}.$$

Problem 15.3. Deduce from Problem 15.2 that if initially $M_0 \leq \frac{M_0}{\alpha}$ and $B(0) > b/\lambda$ then $B(t) \to \infty$ as $t \to \infty$, which means that TB will develop; note that if $b < 0$ we only need to assume that $M(0) \leq \frac{M_0}{\alpha}$ and $B(0) > 0$.

We next show that if $M(0) > \frac{M_0}{\alpha}$ and $b > 0$ then small infection with Mycobacteria tuberculosis does not result in TB. Let ε be so small that if

$$\beta = \alpha + \frac{\mu_1 \varepsilon}{\varepsilon + K}$$

then

$$M(0) > \frac{M_0}{B} \text{ and (since } b > 0) \ \lambda < \frac{\mu_2 M_0}{\beta(\varepsilon + K)}. \tag{15.10}$$

We shall prove that if $B(0) < \varepsilon$ the $B(t) < \varepsilon$ for all $t > 0$. Indeed, otherwise there is a first time t_0 such that

$$B(t) < \varepsilon \text{ if } t < t_0, \text{ and } B(t_0) = \varepsilon.$$

It follow that

$$\frac{dB}{dt}(t_0) \geq 0 \tag{15.11}$$

and

$$\frac{B(t)}{B(t) + K} < \frac{\varepsilon}{\varepsilon + K} \text{ if } t < t_0.$$

Hence, by (15.8),

$$\frac{dM}{dt} > M_0 - \mu_1 M \frac{\varepsilon}{\varepsilon + K} - \alpha M = M_0 - \beta M. \tag{15.12}$$

Rewriting (15.12) in the form

$$\frac{d}{dt}(Me^{\beta t}) > M_0 e^{\beta t}$$

we obtain, by integration,

$$M(t) > M(0)e^{-\beta t} + \frac{M_0}{\beta} - \frac{M_0}{\beta} e^{-\beta t} > \frac{M_0}{\beta} \text{ for } 0 < t \leq t_0$$

where we used the inequality $M(0) > \frac{M_0}{\beta}$ from (15.10). We now use Eq. (15.9) to deduce that

$$\frac{dB}{dt}(t_0) = (\lambda - \frac{\mu_2 M}{B + K})B|_{t=t_0} < (\lambda - \frac{\mu_2 M}{B + K})\varepsilon < 0$$

by the second inequality in (15.10), and this is a contradiction to (15.11).

Problem 15.4. Use the last result and Problem 15.2 to show that if $M(0) > \frac{M_0}{\alpha}$, $b > 0$ and $B(0)$ is sufficiently small then $(M(t), B(t)) \to (\frac{M_0}{\alpha}, 0)$ as $t \to \infty$. [Hint: show that that $M(t) - \frac{M_0}{\alpha} < C\varepsilon$ if t is large, where C is a constant.]

15.1 Numerical Simulations

In the following problems the parameters of the system (15.1)-(15.4) are given as follows: $\lambda_1 = 14/day$, $\lambda_2 = 0.05/day$, $d_M = 8\times 10^{-3}/day$, $M_0 = 1.5\times 10^6\ cell/cm^3$, so that $\mu_M = d_M M_0 = 1.2\times 10^4\ cell/day$, $d_{M_i} = 5\times 10^{-2}/day$, $K = 10^5 B_e/cm^3$, $\gamma = 0.8\ day$. At the beginning of infection with Mtb we have: $M = M_0, M_i = 0, B_i = 0$ and B_e is the number of inhaled bacteria per cm^3. We also take $d_T = 0.3/day$, $\alpha = 2.5/day$ and $T(0) = 0$.

Problem 15.5. Simulate the model (15.1)-(15.5) for $0 < t < 30$ days with $B_e(0) = 1$. You should find that the functions $B_e(t), B_i(t)$ are monotonically increasing.

Problem 15.6. Take $\delta = 0.1$ and $B_e(0) = 2, 5, 10$. In each of these three cases, compute $B_e(30)$ and $B_i(30)$.

Problem 15.7. Repeat the calculations of Problem 15.6 with $\delta = 1$ and with $\delta = 5$.