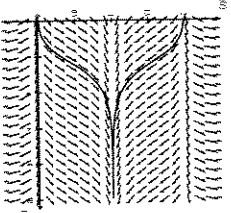


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by de Vries et al.



### Chapter 3 Ordinary Differential Equations

#### 3.1 Introduction to ODEs

We have seen in the introductory section (Section 1.2) that the recovery of infected individuals can be modeled by a differential equation (equation (1.2)). In general, differential equations are extremely useful in modeling biological processes. On the one hand, modeling with differential equations is quite transparent, even for complicated biological systems. On the other hand, there is an enormously powerful mathematical theory available, which includes explicit solutions, approximate solutions, numerical solutions, qualitative behavior, and the theory of dynamical systems. As soon as a model has been derived, it can be treated as a mathematical entity. General theorems and analytical methods can be applied to generate useful results. These results can then be interpreted in biological terms.

The possibility of abstraction is the essential advantage of mathematical modeling. For example, to understand the behavior of solutions of the equation

$$x'(t) = 2x(t),$$

it does not matter whether  $x(t)$  describes a growing fish population, a growing tumor, or the increase in infected individuals. Mathematically, it is just the equation for exponential growth which can be treated and solved without referring to the interpretation at hand. Once the results are established, they need to be understood in biological terms.

An *ordinary differential equation* (ODE) is an equation for an unknown function of one variable, say  $x(t)$ , which involves the function and some of its derivatives. For example,

$$x'(t) = 2, \quad y'(t) = 3t, \quad z'(t) = \frac{1}{z} z(t) \tag{3.1}$$

are three differential equations. A *solution* is a function which satisfies the differential equation. For the above examples, (3.1), it is easy to check that the solutions are of the form

$$x(t) = 2t + c_1, \quad y(t) = \frac{3}{2}t^2 + c_2, \quad z(t) = c_3 e^{t^2}, \tag{3.2}$$

respectively, with constants of integration  $c_1, c_2$ , and  $c_3$ . The solutions as given in (3.2) are called *general solutions*. If we specify one value for  $x, y$ , or  $z$ , then the value of  $c_1, c_2$ , or  $c_3$  is fixed and we obtain a unique solution. In many cases, we specify an *initial condition*, for example,

$$x(0) = 1, \quad y(0) = 2, \quad \text{and} \quad z(0) = 1.$$

With use of the above general solutions, we find  $c_1 = 1, c_2 = 2$ , and  $c_3 = 1$ . We say that  $x(t) \equiv 2t + 1$  solves the *initial value problem*

$$x'(t) = 2t, \quad x(0) = 1.$$

Similarly,  $y(t) \equiv \frac{1}{2}t^2 + 2$  solves the initial value problem  $y'(t) = 3t, y(0) = 2$ , and  $z(t) \equiv e^{1/t}$  solves the initial value problem  $z'(t) = \frac{1}{t^2}z(t), z(0) = 1$ .

In general, an ODE for an unknown function,  $x(t)$

$$x'(t) = f(x(t), t),$$

has the following interpretation. The left-hand side,  $x'(t)$ , describes the *rate of change* of the quantity  $x(t)$  over time. The right-hand side,  $f(x(t), t)$ , describes all sources of change in  $x(t)$ . For the recovery from a disease (equation (1.2)), the change in the amount of infected individuals,  $\frac{d}{dt}I(t)$ , is given by the recovery rate  $-\alpha I$  times the number of infected  $I(t)$ .

To solve a differential equation means to use *local information* ("What happens next?") to deduce *long-time behavior* ("What happens in the future?").

This interpretation makes ODEs useful for modeling biological processes. If we know all factors for the process at hand, and if we know the rates of change these factors invoke, then we can write down a differential equation. We analyze and solve it and find explanations and predictions for our biological question.

Before we come to modeling, we will introduce some of the wonderful analytical methods for ODEs, which can be explained using elementary calculus.

### 3.2 Scalar Equations

We first study *scalar equations of the first order*, that is, equations of the form

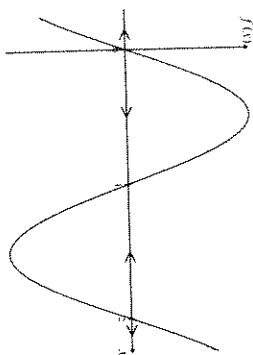
$$x'(t) = f(x(t), t),$$

where  $x(t)$  is a scalar function and the equation involves first-order derivatives. If the function  $f(x, t)$  does not depend on  $t$ , we call the equation *autonomous*. For first-order autonomous scalar ODEs,

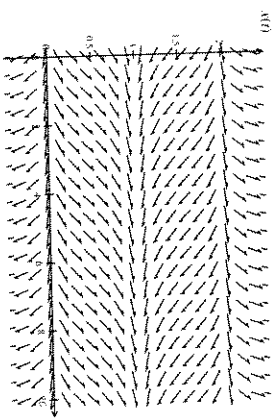
$$x' = f(x), \quad (3.3)$$

the *phase-line analysis* explains the qualitative behavior of solutions without even solving the equation. We consider  $f(x) \equiv x(1-x)(2-x)$ , for which the graph is shown in Figure 3.1. The function  $f(x)$  has zeros at 0, 1, and 2. We can easily check that  $x(t) \equiv 0, x(t) \equiv 1$ , and  $x(t) \equiv 2$  are three constant solutions to the differential equation

$$x' = x(1-x)(2-x). \quad (3.4)$$



**Figure 3.1.** Phase-line analysis of  $f(x) = x(1-x)(2-x)$ . The arrowheads indicate whether the solution of the corresponding ODE is increasing or decreasing.



**Figure 3.2.** Vector field of (3.4).

These special solutions are called *equilibria* or *steady states* of (3.4). If initially, at  $t = 0$ , a solution has value 0 (or 1 or 2), it remains so for all times  $t > 0$ . The left-hand side of (3.4) describes the change of  $x(t)$  over time: the solution  $x(t)$  is increasing whenever  $f(x) > 0$  and decreasing whenever  $f(x) < 0$ . In our example,  $x(t)$  is increasing in the intervals  $(0, 1)$  and  $(2, \infty)$ ; it is decreasing in the intervals  $(-\infty, 0)$  and  $(1, 2)$ . We indicate this behavior by adding arrowheads to the  $x$ -axis in Figure 3.1. If, for instance, the initial condition  $x(0)$  is in  $(0, 1)$ , then the solution will grow and converge to  $x = 1$  for  $t \rightarrow \infty$ .

To get an even better qualitative understanding of the behavior of the solutions of (3.4), we plot the corresponding *vector field*. For that, we evaluate the *slope* of the solution  $x(t)$  for many points  $(t, x)$  and draw a short arrow indicating the slope in the  $(t, x)$  diagram. Since  $x' = f(x)$ , the slope is given by  $f(x)$ . In Figure 3.2, we show the time interval of  $[0, 10]$  and the  $x$ -interval of  $[0, 2.5]$ . At approximately 200 points, we have slope  $x'(t)$ , the slope of the solution with a short arrow. Now, solutions  $x(t)$  must have slope  $x'(t)$ , hence solution curves are *tangential* to these short arrows. In Figure 3.3, we show two typical solutions. Note how nicely they follow the vector field. The steady states 0, 1, 2, which we discussed earlier, appear as lines with horizontal arrows, which means the slope

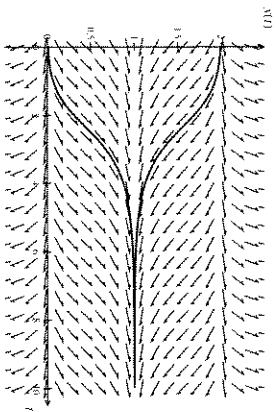


Figure 3.3. Two typical solutions in the vector field of (3.4).

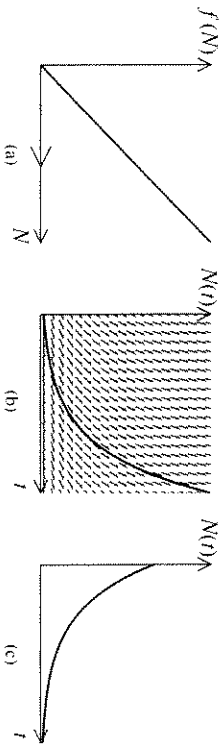


Figure 3.4. (a) Phase-line analysis for Example 3.2.1, for  $r = 2$ ; (b) vector field and typical solution for  $r = 2$ ; (c) typical solution for  $r = -2$ .

is zero ( $r'(t) = 0$ ). Solutions which do not start at 0, 1, or 2 tend to get away from the two equilibria  $x = 0$  and  $x = 2$ , while they converge to  $x = 1$ . We say that  $x = 1$  is a *stable equilibrium*, and  $x = 0$  and  $x = 2$  are *unstable equilibria*.

With the above *phase-line analysis* and *vector-field analysis* we get a very good understanding of the qualitative properties of the solutions *without solving* (3.4). Equation (3.4) can be solved explicitly as well, using separation and partial fractions (see the exercises). These classical solution techniques can be found in most introductory ODE textbooks (such as Boyce and DiPrima [25]).

**Example 3.2.1: Exponential Growth and Exponential Functions.** Solutions to the exponential growth equation,

$$N' = rN, \tag{3.5}$$

have the form  $N(t) = N_0 e^{rt}$ , where  $N_0 = N(0)$  is the initial condition. The phase line, the vector field, and a typical solution for  $r > 0$  are shown in Figures 3.4(a) and (b). Figure 3.4(c) shows a solution for  $r < 0$ . For  $r > 0$ , equation (3.5) describes exponential growth, which can be applied to population growth. In the case of  $r < 0$ , equation (3.5) describes exponential decay, which can be applied to radioactive decay or to the decay of a drug in the blood circulation.

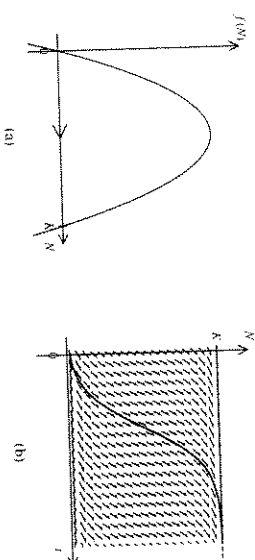


Figure 3.5. (a) Phase-line analysis for Example 3.2.1; (b) vector field and a typical solution.

**Logistic Growth**

In many cases, exponential growth is not an appropriate model. At a certain size, a growing population will reach a limit where all available resources are used to sustain the high population level, but the habitat will not support any more individuals. Hence, we alter the previous model and consider the logistic equation, also known as the Verhulst equation,

$$N' = rN \left( 1 - \frac{N}{K} \right), \tag{3.6}$$

where  $r > 0$  is the intrinsic growth rate and  $K$  is the carrying capacity. Compared to the exponential growth model (3.5), the logistic equation contains the additional term  $-(r/K)N^2$ . This term can be understood as a competition term from individuals of the same species who compete for the same resources. We use phase-line analysis in Figure 3.5 to obtain the qualitative behavior of the solution  $N(t)$ . The population grows and converges to the equilibrium solution  $N = K$  for  $t \rightarrow \infty$ . Note that it will not reach  $K$  in finite time, since solutions of ODEs do not intersect (see Theorem 3.2). In Section 10.1, we use a logistic equation to model growth of cell populations.

**3.2.1 The Picard–Lindelöf Theorem**

Let us return to the theory of differential equations. There is a general result which states that, under reasonable assumptions, solutions of differential equations do not intersect. To formulate the corresponding theorem, we need the notion of *Lipschitz-continuity*. This means that the function  $f(x)$  is continuous and, in addition, it satisfies a growth inequality,

**Definition 3.1.** A function  $f : D \rightarrow \mathbb{R}$  with domain  $D \subset \mathbb{R}$  is called Lipschitz continuous if there is a constant  $L > 0$  such that  $|f(x) - f(y)| \leq L|x - y|$  for all  $x, y \in D$ .

**Theorem 3.2 (Picard–Lindelöf).** Assume the function  $f : D \rightarrow \mathbb{R}$  is Lipschitz continuous. Let the initial condition  $x_0$  lie in  $D$ . Then there is an  $\varepsilon > 0$  such that the initial

value problem

$$\frac{d}{dt}x = f(x), \quad x(0) = x_0$$

has a unique solution  $x(t)$  for  $0 \leq t \leq \epsilon$ .

**Remark 3.2.1.**

1. Although the theorem is formulated for a small time interval  $[0, \epsilon]$ , it implies that solutions to different initial data never intersect. Why?
2. The same result holds true for systems of differential equations which can be written in vector notation as

$$\frac{d}{dt} \begin{pmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{pmatrix} = \begin{pmatrix} f_1(x_1, \dots, x_n) \\ \vdots \\ f_n(x_1, \dots, x_n) \end{pmatrix}.$$

In this case, we require that each of the functions  $f_1, \dots, f_n$  is Lipschitz continuous in all of its arguments.

3. A continuously differentiable function is always Lipschitz continuous (on a bounded domain  $D \subset \mathbb{R}^n$ ). Hence as soon as  $f_1, \dots, f_n$  are differentiable, solutions will never intersect. This includes all differential equations which are built from polynomials, exponentials, sine functions or cosine functions, etc.

### 3.3 Systems of Equations

For many biological processes, it is necessary to follow the time evolution of more than one factor or more than one species. For example, a predator–prey system needs two dependent variables: predator and prey. Similarly, an epidemic SIR model needs three variables: the susceptibles,  $S$ , the infected,  $I$ , and the recovered,  $R$ . We are automatically led to systems of differential equations. To introduce modeling with systems of ordinary differential equations, we study chemical networks, interacting populations, and the spread of an infectious disease in the following sections.

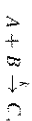
#### 3.3.1 Reaction Kinetics

In this section, we introduce the *Law of Mass Action*, and we show how to use it to model chemical reactions. This method is certainly important for the modeling of many physiological processes. It also serves as a good tool for modeling populations. In fact, as we will see shortly, the epidemic model of Figure 1.1 can be understood in terms of reaction kinetics.

### 3.3. Systems of Equations

#### The Law of Mass Action

First, we consider an irreversible reaction process in which reactants  $A$  and  $B$  produce  $C$ :



where  $k$  is the reaction constant. We are interested in the product  $C$  and we argue as follows:

$$\left[ \begin{array}{l} \text{change of} \\ \text{the product} \\ \text{over time} \end{array} \right] = \left[ \begin{array}{l} \text{number of} \\ \text{collisions of} \\ \text{molecules } A \\ \text{and } B \end{array} \right] \cdot \left[ \begin{array}{l} \text{probability that a} \\ \text{collision has enough} \\ \text{kinetic energy to} \\ \text{initiate a reaction} \end{array} \right].$$

Let  $a = [A]$ ,  $b = [B]$ , and  $c = [C]$  denote the concentrations of the reactants  $A$ ,  $B$ , and  $C$ , respectively. The product  $ria\Delta t$  is a good approximation to the number of collisions in time  $\Delta t$ . The probability that a collision has enough energy to overcome the activation energy of this reaction is denoted by a constant  $r_2$ . If we let  $\Delta C$  denote the change of the product  $C$  over time, then the above work equation can be written as

$$\Delta C = abk\Delta t,$$

where  $k = r_1r_2$ . Dividing both sides by  $\Delta t$ , we obtain

$$\frac{\Delta C}{\Delta t} \approx k \cdot a \cdot b,$$

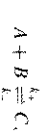
In the limit of  $\Delta t \rightarrow 0$ , we get

$$\frac{dc}{dt} \approx k \cdot a \cdot b,$$

which is called the *Law of Mass Action*. Please note that although it is called a *Law of Mass Action*, it is indeed a mathematical model. It is no longer valid if the concentration of one participating is many orders of magnitude larger than the other.

#### Reversible Reactions

For a reversible reaction,



we assume that the molecules of  $C$  break apart at a rate that is in proportion to the concentration of  $C$  molecules. If we balance all production and consumption terms for each participating chemical, then we obtain the following system of differential equations:

$$\begin{aligned} \frac{dc}{dt} &= k_+ a b - k_- c, \\ \frac{da}{dt} &= k_- c - k_+ a b, \\ \frac{db}{dt} &= k_- c - k_+ a b. \end{aligned}$$