Compartment models

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Chapter 1

Compartment models

Background: It is important to master the ability to develop models. Modeling of dynamical systems plays a very important role in applied science, and compartment models are among the most important tools used for analyzing dynamical systems.

Aim: The aim with this chapter is to learn more about development of compartment models.

1.1   Introduction

Compartment models are often used to describe transport of material in biological systems. A compartment model contains a number of compartments, each containing well mixed material. Compartments exchange material with each other following certain rules. Figure 1.1 shows a sketch of such a system. In this figure, compartments are represented by boxes and the connections between the compartments are represented by arrows. Every compartment (that is every box) has a number of connections leading to the box (inflows) and a number of arrows leading from the box (outflows). Material can either flow from one compartment to another, it can be added from the outside through a source, or it can be removed through a drain or a sink. Think of a bathtub, where water (the well-mixed material) is added through the faucet and leaves through the drain. In the example above, the material was water, but it can be used in a more abstract way. Generally, the material represents the amount of something that we wish to account for. To account for the material the model must fulfill some conservation law. In the bathtub example, we could develop a model based on conservation of mass. Most compartment models (as the one shown in Figure 1.1) have more than one compartment and equations for such a model are obtained by describing a conservation law for each compartment. Conservation laws
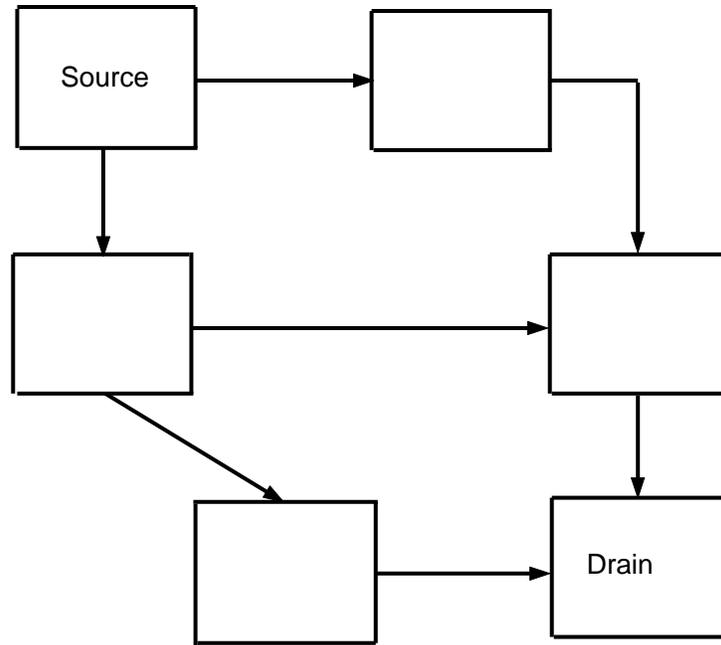
Figure 1.1: Sketch of a compartment model. Material can be stored in the boxes and transported between boxes following arrows.

state that the difference between what flows in and what flows out amounts to how much will be stored in the compartment.

A compartment model could also represent an ecological system where the material could be energy, the compartments could represent different species of animals and plants, and the flow between compartments could account for uptake and loss of food (or energy). In this case we would base the equations on laws describing conservation of energy. Compartment models also arise in physiology, where the material could be oxygen that is transported with the blood between different organs (compartments) in the body.

It should be emphasized, that one cannot think of compartments and the flows in and out of compartments as individual components where each part can be described independently of each other. Both the in- and the outflow from any compartment may depend on the volume inside the compartment. Similarly, the inflow into a compartment may dependent on the outflow from another compartment. In other words, it is important to think of the system as a whole, where the parameter representing the material in the compartment (the state-variable) can dependent on what flows in and what flows out. In addition, since what flows into one compartment typically flows out of another compartment, the state-variables depend on each other and on the state of the system as a whole. The important point to remember is, that it is the person modeling the system who chooses how the
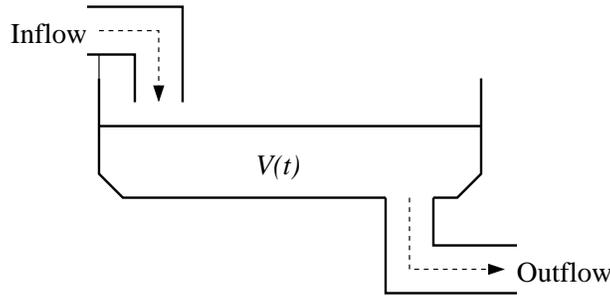
Figure 1.2: A bathtub with an external source (the faucet) and sink (the drain).

model parameters and variables, in a consistent way, depend on each other.

Before we start with a more detailed description of compartment models and their abilities and limits, we will discuss a few examples and demonstrate how conservation of mass can be used.

1.1.1 Example 1: A Bathtub

Figure 1.2 shows a bathtub, that at the start of the investigation (at $t = 0$) contains $V_0 = 100$ l (liter) of water. When the faucet is opened water flows into the bathtub with a velocity of 5 l/min. If the drain is opened, an additional 4 l/min will flow out of the bathtub. Now, let us derive an equation that can be used to describe the volume $V(t)$ l of water in the bathtub as a function of time. The material that is transported in and out of the bathtub is water, and it is our job to determine how the volume of water changes with time, i.e. we want to determine the function $V(t)$.

The function $V(t)$ can be determined using simple calculations, however, we will use this example to establish a more general method, that also works for more complicated examples, such as example 2 discussed in the next section. It is our aim to develop an equation, that describes how the volume changes during a small period of time (from t to $t + \Delta t$). The change in volume during the time increment Δt is given by $V(t + \Delta t) - V(t)$ (this can be both positive and negative). Since water is an incompressible fluid, conservation of mass states that the change in volume equals the difference between what flows in and what flows out from the bathtub. Assume that both the faucet and the drain are open. Then, the flow into the bathtub is 5 l/min and the flow out of the bathtub is 4 l/min. In other words

$$\begin{aligned} V(t + \Delta t) - V(t) &= 5 \text{ l/min } \cdot \Delta t \text{ min } - 4 \text{ l/min } \cdot \Delta t \text{ min} \\ &= 1 \text{ l/min } \cdot \Delta t \text{ min}. \end{aligned}$$

If both sides of the equation are divided by Δt we get the following difference equation:

$$\frac{(V(t) + \Delta t) - V(t)}{\Delta t} = 1 \text{ l/min.}$$

If we let $\Delta t \to 0$ we recover the derivative of $V(t)$

$$V'(t) = 1 \text{ l/min.}$$

From this equation it becomes clear, that our method does not provide a direct way for determining the volume $V(t)$, but instead we get the derivative $V(t)$. However, using integration we can solve this equation for $V(t)$. For any constant C, the solution is given by

$$V(t) = 1 \text{ l/min } \cdot t \text{ min } + C \text{ l.} \tag{1.1}$$

All functions of the above type are candidates for the complete solution. To find the exact solution we need to have one more piece of information. For, example, if we know that $V(0) = 100$ l we can find C as

$$V(0) = 100 \text{ l } = 1 \text{ l/min } \cdot 0 \text{ min } + C \text{ l} \quad \Leftrightarrow \quad C = 100 \text{ l.}$$

Inserting this value for C into the general solution (1.1) we can find the specific form of $V(t)$. For this example, the specific solution is given by

$$V(t) = 1 \text{ l/min } \cdot t \text{ min } + 100 \text{ l.}$$

If both the inlet and the outlet are open, and we start with 100 l of water, then every 1 min we add 1 l of water to the bathtub.

In this example, we could have gotten to the same conclusion without introducing this complex notation, but in the next example, we will see that our notation is necessary to solve the problem. Before we move on to the next example, let us reflect upon what we have learned so far. We have illustrated our results using the diagram shown in Figure 1.3. We have used a compartment with the volume of water representing the state variable $V(t)$. Water flows into the bathtub at a rate of 5 l/min (this is represented by an arrow pointed into the compartment, V_{inflow}) and water is flowing out of the bathtub with a rate of 4 l/min (this is represented by an arrow pointing away from the compartment, $V_{outflow}$). Note, that the arrows indicate what way the water is flowing.

1.2   Example 2: Salt Dissolved in Water

The second example describes water flowing through a tank. Our focus will not be on the water, but on how much salt (NaCl) that is dissolved in the water. At the start of our
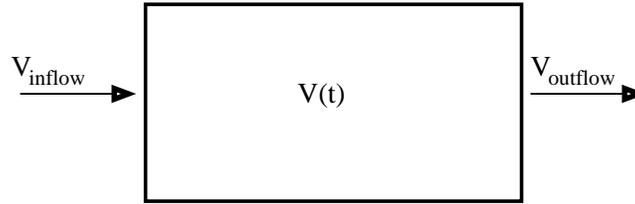
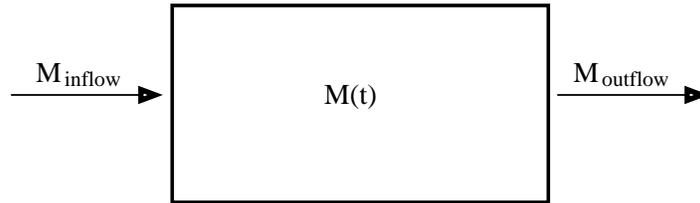Figure 1.3: Compartment illustrating in- and outflow of water.

Figure 1.4: Compartment illustrating in- and outflow of salt-water. Note, in this example the compartment illustrate the amount of salt stored.

investigation (at $t = 0$) our tank has 0.8 kg of salt which is dissolved in $V_0 = 300$ l of water. We now add salt-water to the tank at a velocity of 5 l/min. This water contains 0.006 kg of salt per liter of water. The well-mixed salt-water is drained from the tank with the same velocity of 5 l/min, i.e. the volume of water in the tank does not change. Our goal is to calculate the amount of salt $M(t)$ (mass in kg) in the tank at time t. To do so, we choose the amount of salt to be the quantity that we want to keep track of. Hence, the compartment will no longer represent the amount of water, but an abstraction, the amount of salt in the water. What flows in and out of the compartment is an amount of salt per unit of time M_{inflow} and $M_{outflow}$, this is illustrated in Figure 1.4.

Again, the first step towards determining $M(t)$ is to derive an equation for mass conservation during a period of time (from t to $t + \Delta t$). During this period of time the amount of salt flowing into the compartment can be computed as

$$M_{inflow} = 5 \text{ l/min } \cdot \Delta t \text{ min } \cdot 0.006 \text{ kg/l } = 0.03 \text{ kg/min } \cdot \Delta t \text{ min.}$$

At time t, the water flowing out has a salt concentration of $M(t)/V_0$ (remember the volume in the container remains constant, since water flows in and out with the same velocity). Hence, the amount of salt flowing out can be computed by

$$M_{outflow} = 5 \text{ l/min } \cdot \Delta t \text{ min } \cdot \frac{M(t)}{V_0} \text{ kg/l.}$$

The difference equation, obtained by computing the difference between what flows in and

what flows out, divided by Δt is given by

$$\frac{M(t + \Delta t) - M(t)}{\Delta t} = 0.03 \text{ kg/min} - \frac{5M(t)}{V_0} \text{ kg/min}$$

$$= 0.03 \text{ kg/min} - \frac{M(t)}{60} \text{ kg/min}.$$

The latter is obtained by using that the volume $V_0 = 300$ l. The derivative $M'(t)$ can be obtained by letting $\Delta t \to 0$

$$M'(t) = 0.03 \text{ kg/min} - \frac{M(t)}{60} \text{ kg/min}. \qquad (1.2)$$

This is a linear differential equation, where $M'(t)$ is a function of $M(t)$. A function $M(t)$ that fulfills the above equation is the solution of the differential equation. This differential equation can be solved using separation of variables. The solution is given by

$$M(t) = 1.8 \text{ kg} + C \text{ kg } e^{-t/60}.$$

To prove that this solution fulfills the above differential equation, we differentiate M(t) and compare the derivative with the right hand side of (1.2). To determine the constant C we need to know an initial value for $M(t)$. Let $M(0) = 0.8$ kg., then

$$M(0) = 0.8 \text{ kg} = 1.8 \text{ kg} + C \text{ kg } e^{-0/60} \quad \Leftrightarrow \quad C = -1.0 \text{ kg}.$$

Hence,

$$M(t) = \left(1.8 - e^{-t/60}\right) \text{ kg}. \qquad (1.3)$$

Differentiating the solution gives:

$$M'(t) = \frac{1 \text{ kg}}{60 \text{ min}} e^{-t/60}$$

Inserting the above derivative into the differential equation (1.2) gives:

$$M'(t) = 0.03 \text{ kg/min} - \frac{1.8 \text{ kg } e^{-t/60}}{60 \text{ min}} = \frac{e^{-t/60}}{60} \text{ kg/min}.$$

The result (1.3) can be interpreted as follows: Water is poured into the tank with a concentration of 0.006 kg/l. Hence, with time the water in the tank will obtain exactly that concentration. Since the tank contains 300 l of water, we will have 300 l $\times$ 0.006 kg/l = 1.8 kg salt. This works well with the solution in (1.3) because if we let $t \to \infty$ the exponential term will go towards 0, written formally we get $\lim_{t \to \infty} e^{-t/60} = 0$. The solution for $M(t)$ is shown in Figure 1.5.
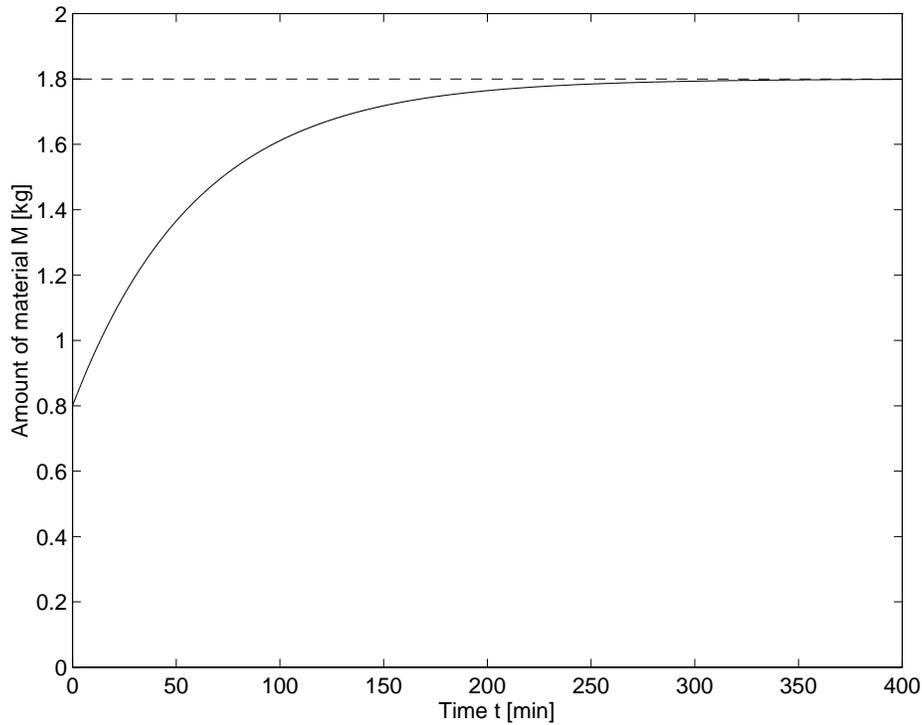
Figure 1.5: Graph representing the solution $M(t)$ to the differential equation in (1.6).

1.3   General Terms

Based on the two examples discussed above we can introduce some general concepts used to formulate a compartment model. Note that even though both models discussed above only had one compartment, a general compartment model will have multiple compartments. Since the material in each compartment must fulfil a conservaton law, the general concepts arising from compartments can all be described by studying a single compartment. Models with more compartments will be discussed in Chapter 2.

We will use a model with one compartment to develop a number of general terms. The transport in and out of the compartment is characterized by the **velocity** of the inflow and the outflow, respectively. Velocity is measured in an amount of material per unit of time. Consider a compartment that is empty at $t = 0$. If the flow into the empty compartment is I [kg/min] and the flow out of the compartment is O [kg/min], then it will take $T = M/I$ [kg]/[kg/min] = [min] time units to fill the compartment (if $O = 0$) , where M is the amount of material that can be stored in the full compartment. Similarly, if we consider a full compartment, it will take $T = M/O$ [kg] / [kg/min] = [min] time units to empty the compartment (if $I = 0$). If we consider a compartment with constant in- and outflow, then $M/I = M/O$. The time $T = M/I(= M/O)$ is often called the **turn-over time**, while the

velocity of the material flowing into the compartment is called the **turn-over rate**.

In the salt-water example discussed above, we computed the amount of salt in the compartment. A closer study of this model reveals that the outflow can be described by

$$O = aM$$

where a is a real constant. Computing outflow as described above is very common, both for examples as the one described above, but more generally in situations where every particle leaves the compartment with a given probability, independent of how long the particle has been stored inside the compartment. For example, if the compartment contains living animals, and we expect that the animals die with a given probability, then the rate of what flows out from the compartment have the form listed above. The factor of proportionality a is called a **rate**. In this example, this factor is the death-rate. The rate a has an interesting interpretation: In the stationary situation, i.e. if the inflow I equals the outflow O, then $a = O/M$. Hence, $a = I/M$ or using previous information we get $a = 1/T$.

In general, the change of mass in a compartment during a time interval Δt can be written as

$$M(t + \Delta t) - M(t) = I\Delta t - O\Delta t$$

where I is the velocity of the incoming fluid and O is the velocity of the fluid that is leaving. as before, a differential equation is obtained if we divide by Δt and take the limit as $\Delta t \to 0$, we get:

$$M'(t) = I - O$$

This equation states that the change of material with time is given by the difference between the inflow and the outflow. In the following we use this approach to calculate concentration of salt in a compartment. It should be noted that this approach only works if the velocities for the in- and out-flowing material are known. We use these velocities to determine the growth of the concentration in the compartment.

In the following section, we will discuss how a number of situations can be included into this compartment strategy. Both sections discuss **linear compartment models**, i.e. models where the rates are constant. However, in later sections we discuss models were the rates are dependent of the amount of material in the various compartments.

1.4   Balance of Concentrations

In this example we will use a compartment model to determine the balance between concentrations (this is similar to the mass-balances, however, instead of balancing masses we balance concentrations).

Again, we depart from the salt-water model model. Denote the amount of salt (in kg) that is dissolved in a volume V_0 of water by M. In the example above, we showed that the change of the amount of salt in the compartment can be computed as

$$M'(t) = 0.030 \text{ kg/min} - \frac{1}{60 \text{ min}} M(t)$$

(this was shown in equation (1.2)). In example 2, the differential equation for the mass $M'(t)$ was determined based on an inflow $I = 5$ (l/min) and the concentration of salt in the inflow $c_i = 0.006$ (kg/l) . Using the symbols I and c_i, equation (1.2) can be written as

$$M'(t) = Ic_i - \frac{O}{V_0} M \tag{1.4}$$

Note, in the example discussed above $I = O$ and the equation can be rewritten as

$$M'(t) = Ic_i - \frac{I}{V_0} M \tag{1.5}$$

From this notation, it becomes clear that we can find the mass $M(t)$ by solving a linear first order differential equation. In the previous section we showed, that the solution to the salt-water equation is given by

$$M(t) = 1.8 \text{ kg} - 1.0 \text{ kg } e^{-t/60}$$

In this example we are interested in determining the concentration of salt, not the mass. To do so, we need to establish a fundamental law for the concentration. By definition concentration can be computed as mass divided by the volume, i.e. $c_i = M(t)/V_0$. Since the volume V_0 is constant differentiation yield $c_i'(t) = M'(t)/V_0$. Inserting (1.4) for $M'(t)$ gives:

$$c'(t) = \frac{I}{V_0} c_i - \frac{I}{V_0} c$$

If we let the quantity $a = I/V_0$ this equation can be rewritten as

$$c'(t) = a(c_i - c)$$

This is again a linear differential equation of first order. Studying the equation in terms of changes in concentration seems realistic. If the concentration in the water flowing into the compartment is bigger than the concentration of the material inside the compartment, then the concentration grows, i.e. $c_i > c$ and $c'(t) > 0$. If instead $c_i < c$ then the concentration of salt in the compartment will fall.
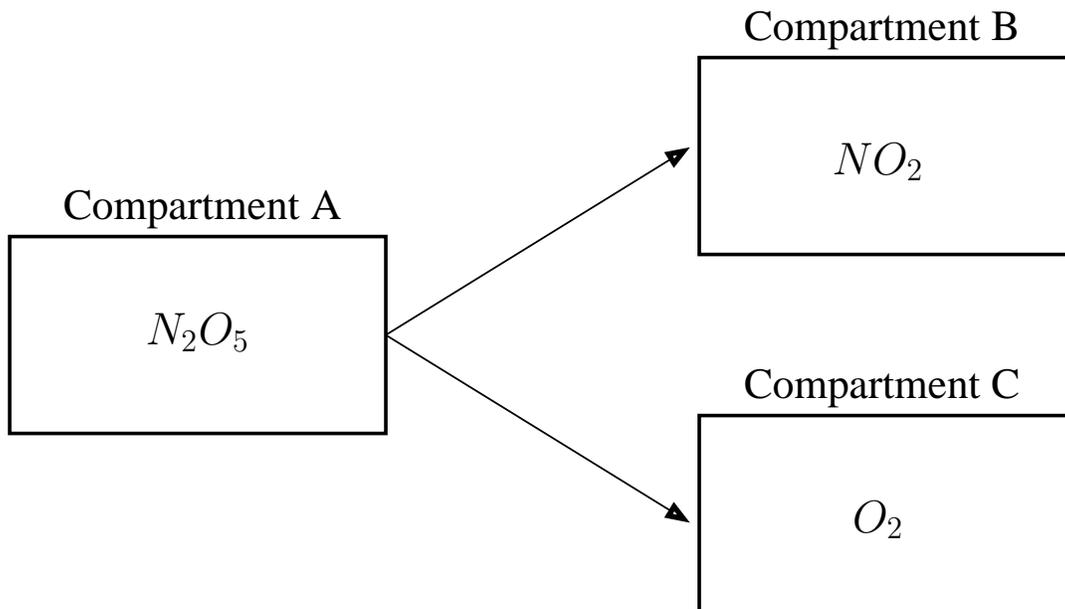
Figure 1.6: Compartments in reaction.

1.5   Chemical Reactions

Compartment models are often used to describe the outcome of chemical reactions. Where conservation of mass is one of the fundamental principles. For example, let us study the following reaction in a solution with volume V_0:

$$2N_2O_5 \rightarrow 4NO_2 + O_2 \tag{1.6}$$

If we focus on oxygen, we can think of this system as one consisting of three components: A, components on the form N_2O_5, B, components on the form NO_2, and C, components on the form O_2. The connection between the three components (each included in a separate compartment) is shown in Figure 1.6.

The amount of material (in this case the number of oxygen molecules) in compartment A is given by $M_A = V_0[N_2O_5]$ where the brackets indicate the concentration of the material in question, for example in moles/l, the number "5" indicates that one atom of N_2O_5 contain 5 oxygen molecules. The amount of material in the other compartments can be computed similarly.

The velocity of the reaction in (1.6), i.e. the velocity with which one molecule of N_2O_5 is transformed into NO_2 and O_2, is proportional to the amount of N_2O_5:

$$\frac{d}{dt}(V_0[N_2O_5]) = -kV_0[N_2O_5] \tag{1.7}$$

where the factor of proportionality is given by k^1. The number of oxygen molecules can be found by converting the equation above to an equation for the number of oxygen molecules in compartment A (M_A):

$$\frac{d}{dt}M_A = -kM_A. \tag{1.8}$$

In other words, the oxygen that leaves compartment A flows into compartments B and C. The reaction tells us that 4/5 of the oxygen molecules flow into B as NO_2, while 1/5 of the oxygen molecules flow into C. For the two other compartments, the following equations are obtained:

$$\frac{d}{dt}M_B = \frac{4}{5}kM_A \tag{1.9}$$

$$\frac{d}{dt}M_C = \frac{1}{5}kM_A \tag{1.10}$$

Since we focused on the concentration of oxygen on the form N_2O_5 (compartment A), the solution to the differential equation in (1.8) is given by

$$M_A(t) = M_0e^{-kt}$$

where M_0 is the amount of oxygen on the form N_2O_5 at the start of the reaction. If we insert this solution into equations (1.9) and (1.10) we get:

$$\frac{d}{dt}M_B = \frac{4}{5}kM_0e^{-kt}$$

$$\frac{d}{dt}M_C = \frac{1}{5}kM_0e^{-kt}$$

Both M_A and M_B can be determined using simple integration on the right hand side of the equation.

While all chemical reactions in principle can be described by compartment models, we will not necessarily get differential equations on the form shown in (1.7). For example if the reaction is given by

$$A + B \rightarrow AB,$$
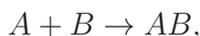
then the velocity of the concentration will depend on the product of the two concentrations, as

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

where v is the constant of proportionality, which depend on the incoming chemical reactants. Reactions like the one shown above, where the velocity v of the reaction, depends on the incoming material is called second order reactions. Similarly, reactions where v is proportional to the concentration is called first order reactions.

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[1]In chemistry it is common to calculate concentrations such as $[N_2O_5]$. The definition of a reaction velocity appears by dividing both sides of the differential equation by the volume V_0

1.6 Limitations of Compartment Models

The basic idea with compartment models is to describe a system as a number of compartments and to derive equations of mass-balance for each of these compartments. In itself writing equations for mass balance is a very healthy technique, which assures that the model has a fundamental background, and that it is possible to judge the validity of the model. However, there is no guarantee that a good compartment model will appear from this exercise.

1.6.1 Is the system closed

The equation for conservation of mass is only correct, if all the material that is added to or removed from the system is described in the model. That is, if the system is closed in some sense. In other words the compartments may not include un-accounted for sources or sinks. Normally, a closed system is obtained by assuming that the total amount of material is constant. Our definition of closed is less strict, since we allow to study systems were material is continuously added or removed. However, in such systems it is crucial to describe how material is added and/or removed.

1.6.2 Is homogeneity a reasonable assumption?

When we use compartment models we assume that all material in the compartment is homogeneous. This assumption can not directly be seen from the equations. Equations only include information about the total amount of material in the compartment, i.e. we cannot include more detailed description of the system. An example could be a compartment model of the blood in the circulatory system. We can describe arteries, veins and the heart, by compartments. These compartments would include blood, for example, it would not be possible to distinguish between plasma, red, and white blood-cells.

It is not always possible to assume homogeneity, for example let us try to use a one-compartment model to describe the concentration of phosphor in a lake. Following this strategy, we assume that the lake has an inflow, an outflow, and a compartment representing the concentration of phosphor. This implies that we assume that all material in the lake is uniformly mixed, and that the amount of phosphor leaving the lake is constant. This is not correct. For example in deep lakes (deeper than 5-10 meter), it is normal to see partition into several layers with different concentration of phosphor. This has to do with the fact that the temperature in the water changes with depth. Often, most of the water flowing into the lake stays at the surface and flow through the lake without exchange with

water in the deeper layers. Hence, we can not calculate the amount of phosphor using a one-compartment model. One way to solve this problem is to let the lake consist of several layers each having a different concentration, and a different amount of phosphor transported between the layers. The disadvantage with splitting the lake into several compartments is that more information is needed to describe the system. For example if the water in the lake is split into two compartments we need to know the concentration of phosphor in the water flowing into and out of the deep layer. This could be very difficult to measure. Even if it is not possible to determine all parameters analytically, it may be advantageous to split the model into smaller subsystem. It is possible using optimization to estimate some unknown parameters, but care must be taken, that enough data exist to obtain realistic parameter values.

1.6.3 Is the balance equation accurate enough?

When the equation of mass balance is derived it is important that all essential transports are known. In real biological systems this is typically not the case. In a realistic system, some of the mass-balances are known but others are not. Before a model can be completed all parameters must be estimated either based on experiments, or calculated based on values found in the literature.

1.6.4 Is the balance of mass relevant?

This last question can seem rather surprising? However, it is not all systems that can be described in terms of mass-balance. This question is easier to understand by discussing a counter example.

In 1950 a compartment model was used to mark rabbits as the biggest thread for survival of the grass-land in Australia. The model was based on observations, that rabbits could eat all grass on an entire field. These observations overestimated the number of rabbits and the amount of damage they could make. The reason for this was that all grass-land was lumped into one compartment independent of their location. As a result the Australian state started to poison rabbits by exposing them to the deadly virus myxomatois, which killed 90% of all rabbits. Today, rabbits are no thread to Australia, and the original study has been criticized for being too crude.

1.6.5 Sensitivity analysis

When a compartment model is derived not all models and initial conditions are known precisely. In addition, the solution to the model will change depending on the model
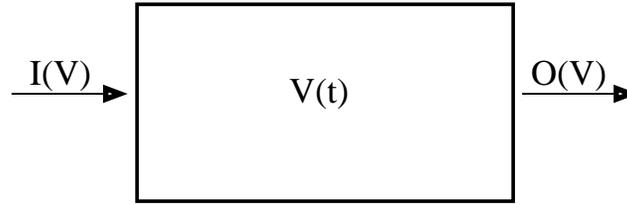
Figure 1.7: Compartment illustrating the volume of fluid in the human body.

parameters and initial conditions. Therefore, it is important to investigate the sensitivity of parameters and initial conditions. This can be done by varying each parameter and record the change in the results.

1.7   Equilibrium Points

In this section we will discuss the qualitative behavior of solutions to compartment model, i.e. we will discuss solutions without computing them quantitatively. We will limit our discussion to solutions that are close to **equilibrium points**.

Assume that we have a compartment with a volume $V(t)$ that varies as a function of time. The compartment has an inflow I and an outflow O (see Figure 1.7). Assume that the both the inflow I and the outflow O depend on V. As an example we consider the balance of fluid in the body. Let $V(t)$ describe the amount of fluid that a given person has at time t. Using a simple model we assume that the intake of fluid I depends on how much fluid is already in the body (i.e. we would not feel thirst, unless the amount of fluid in the body is low). In other words we assume that $I = I(V)$ and that I is a decreasing function of V (as V increases I decreases). Similarly, we assume that the amount of fluid leaving the body (by respiration, transpiration, and urination) also depend on the amount of fluid in the body $O = O(V)$. The flow out of the body will be an increasing function of V (as the fluid volume increases, so does the outflow). This behavior of I and O is illustrated in Figure 1.8. From the compartment in Figure 1.7 we can derive the following differential equation describing the balance of fluid in the body

$$\frac{dV}{dt} = I - O$$

If a solution $V(t)$ to the differential equation exist, that does not depend on t, i.e. $V(t) = V_0$ is constant, then this solution is called the **equilibrium solution**. In other words,if $V(t)$ is in equilibrium, then the in- and outflow is in equilibrium, and as a result the amount of fluid in the body does not change. If the solution is in equilibrium, then the derivative $dV/dt = 0$ and $V(t) = V_0$. Since both I and O depend on V this must imply that $I(V_0) = O(V_0)$.
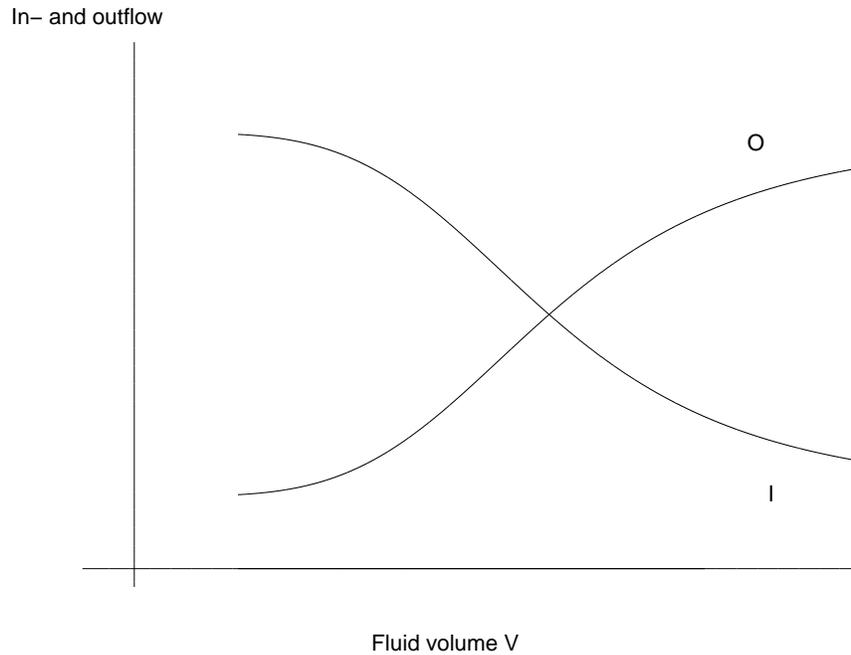
In– and outflow

Fluid volume V

Figure 1.8: Graphs representing inflow I and outflow O.

Since V is monotonically increasing and I is monotonically decreasing only one point can fulfill this condition. This point will be the volume where the two solutions cross each other. In this example only one such point can exist, however, depending on the form of I and O several such points may exist.

Consider the equality point $V(t) = V_0$. If the system is perturbed a small amount ϵ to the right $V(t) = V_0 + \epsilon$ then Figure 1.8 shows that the outflow is increased, i.e. $O(V_0 + \epsilon) > O(V_0)$ and that the inflow is decreased, i.e. $I(V_0 + \epsilon) < I(V_0)$. As a result $I - O$ becomes negative and hence dV/dt becomes negative resulting in a decrease of V. This happens for any small epsilon bigger than zero. As a result V will decrease and get back to V_0. Similarly, if the system is perturbed to the left, i.e. $V = V_0 - \epsilon$. In this case the outflow is decreased $O(V_0 - \epsilon) < O(V_0)$ and the inflow is increased $I(V_0 - \epsilon) > I(V_0)$. Consequently, $dV/dt > 0$ and the volume will be increased and the equilibrium point V_0 will be reached again. Generally, if an equilibrium point exist and if any perturbation of the system makes the solution go back towards the equilibrium point, then the equilibrium point is said to be **stable**. This is marked on Figure 1.9 with arrows on the x-axis. If the opposite happens, that a perturbation of the solution does not make the solution go back to the equilibrium point, then the point is said to be **unstable**.
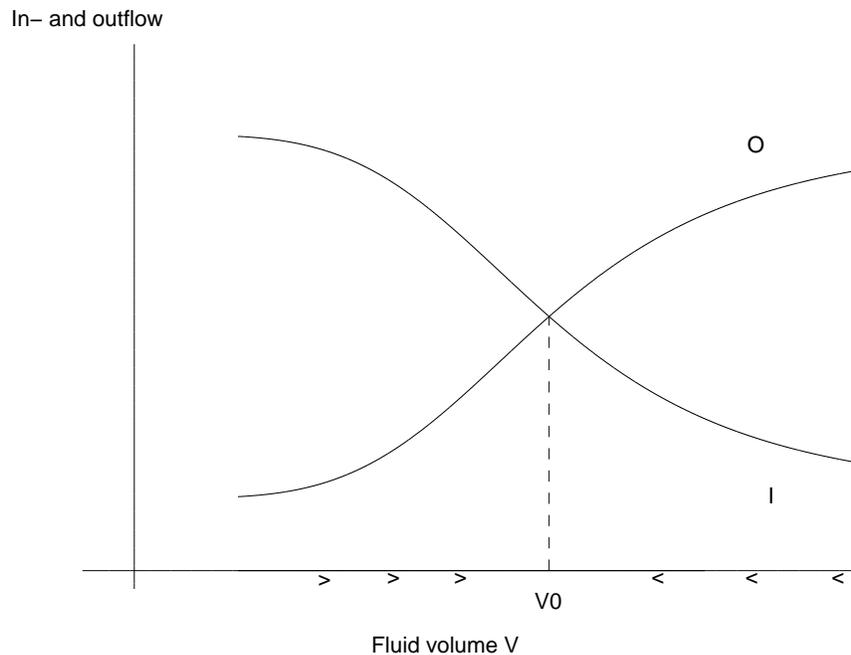
Figure 1.9: Graphs representing inflow I and outflow V. The arrows on the x-axis illustrates stability of the system.

1.8   Exercises

1. Assume that $I = I(V)$ and $O = O(V)$ given in the example above are switched, i.e. that I is increasing function and that O is a decreasing function. Determine possible equilibrium points if any, and determine their stability.

2. Set up a compartment model for a lake with inflow from a creek and from rain and outflow into a sewage system and into another creek. Setup all equations and determine realistic parameters for inflow and outflow.

3. A container has at the start of an experiment 200 ml of fluid. 5 ml of fluid is added to the container with a velocity of 5 ml/min, at the same time, fluid is flowing out from the container at a rate of 8 ml/min.

   (a) Write up an expression for the volume of the fluid $V(t)$.

   (b) At some point in time the volume becomes negative, what is wrong?

4. An amount of sodium chloride NaCl is poured into a bucket with clean water. In this solution sodium chloride is transfered to Na^+ and Cl^- with a rate k_1. At the same time Na^+ reacts with Cl^- to form NaCl with a rate k_2. Set up a compartment model that describes this situation.

5. Derive a compartment model for a system that you find.

Chapter 2

Differential Equations

Background: Mathematical modeling of dynamical phenomena often gives rise to differential equations. As a result it is essential for the modeler to understand basic concepts of differential equations. The modeler should be able to identify differential equations as well as have knowledge of various constructs for solving differential equations.

Aim: The aim with this chapter is to learn to derive differential equations for a given problem and to be aware of principles for analysis and solution of differential equations.

2.1   A mink farm

In this example we will study the dynamics of the population of mink in a farm. To study the dynamics we let $N(t)$ denote the size of the mink population at any time t. To derive our model we need to identify the factors that can change the size of the mink population. We include three factors: birth, death, and sale. We assume that both the birth and the death rates are constant. Assume that B% minks are born every week and that D% die. We assume that to make money the farmer has to sell P minks every week. This scenario is illustrated in Figure 2.1, where $b = B/100$ and $d = D/100$. Using the conservation principles for compartment models discussed in Chapter 1 we can set up the following differential equation:

$$N'(t) = bN(t) - dN(t) - P = (b - d)N(t) - P$$

This is a linear inhomogeneous first order differential equation. To solve this equation we first solve the particular equation and then superimpose this solution with the solution to
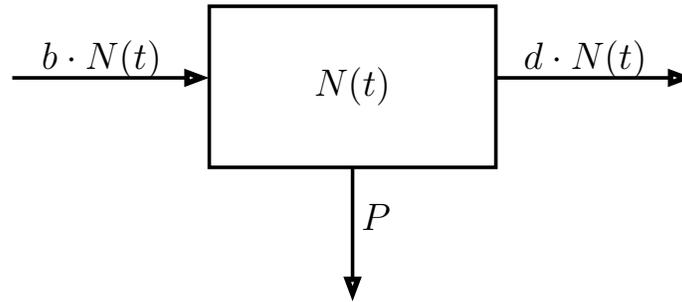
Figure 2.1: Compartment model for the mink farm

the homogeneous differential equation. The particular solution can be found by solving the equilibrium equation

$$N'(t) = (b - d)N(t) = 0 \quad \Rightarrow \quad N(t) = \frac{P}{b - d}$$

If we let the birth rate $b = 4\%$, the death rate $d = 1.5\%$, and $P = 150$, then we get the equilibrium solution $N(t) = 6000$. In other words, to keep a constant population the farmer needs 6000 minks.

The solution to the homogeneous differential equation

$$N'(t) = (b - d)N(t)$$

is given by $N(t) = Ce^{(b-d)t}$ where C is an arbitrary constant that can be found by applying the initial condition. Superimposing the two solution gives the following complete solution

$$N(t) = 6000 + Ce^{0.025t}$$

For $C = 0$ we get the equilibrium solution. Using an initial condition $N(0) = 5000$ (smaller than the equilibrium solution) we get that $C = -1000$. A graph of this situation is shown in Figure 2.2. This solution indicates that with an initial population of 5000 the population decreases with time. If instead $N(0) = 7000$ (larger than the equilibrium solution) we get that $C = 1000$. A graph of this solution is also shown in Figure 2.2. Note that an initial population larger than the equilibrium population makes the population grow while an initial population smaller than the equilibrium population makes the population decrease in size. In other word this differential equation is unstable. To the farmer, this means that it is very important that he monitors the size of the population and tries to keep it at 6000. In real biological setting, the birth and death rates are not constant they could vary around the given numbers with a certain error. However, if the farmer keeps track of the birth and death rates for any given week he can use this model to compute how many minks he can sell to obtain a stable population. Another way for the farmer to use this
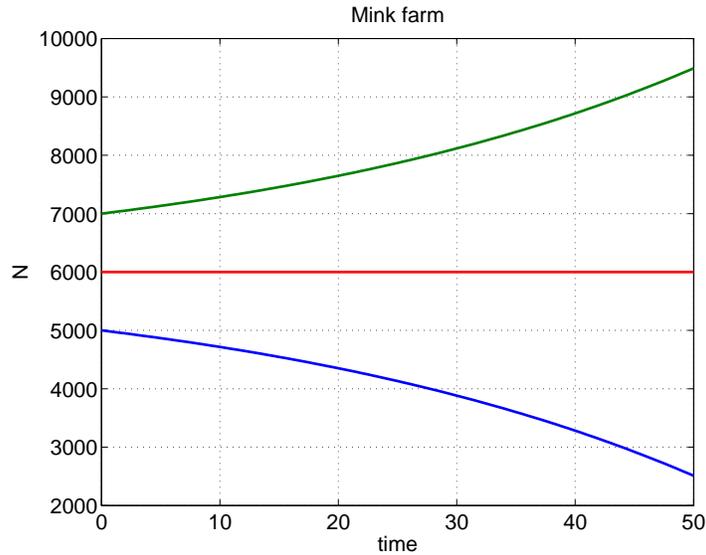
Figure 2.2: Solutions to the differential equation describing the dynamics of a mink population.

model is to calculate how many mink he can sell with a given population. For example, let us assume that the birth and death rates are always approximately 4% and 1.5%. In addition assume that farmer A has room for 15,000 minks while farmer B has room for 12,000 mink. Based on these numbers we can compute how many minks these two farmers are able to sell to keep a constant population.

2.2 Numerical solution of differential equations

The problems we have seen so far could all be solved using analytical solution methods, while this is very nice, it is far from reality. Most mathematical models that we set up for biological systems can not be solved using such methods. The first method we will discuss is called Euler's method after the Swiss mathematician Leonhard Euler (1707-1783). The method can be used to solve first order initial value problems on the form $y' = F(t, y)$ with the initial condition (t_0, y_0) where $y_0 = y(t_0)$. The method starts by evaluating the function $F(t_0, y_0)$ and uses this on the right-hand-side of the differential equation $y'(t_0) = F(t_0, y_0)$; this equation gives us the slope of y at the point (t_0, y_0). Euler's way of solving this system is based on evaluating the derivative using "finite differences". In calculus we learned that

$$y'(t_0) = \lim_{\Delta t_0 \to 0} \frac{y(t_0 + \Delta t) - y(t_0)}{\Delta t} \tag{2.1}$$

What Euler discovered was that if we choose a finite (but small) value for Δt and use that we can solve the differential equation. Let $y(t_0 + \Delta t) = y_1$. Euler's method can be obtained by discretizing the differential equation using a fixed Δt in (2.1) and evaluating the right-hand-side at $F(t_0, y_0)$:

$$\frac{y_1 - y_0}{\Delta t} = F(t_0, y_0) \quad \Leftrightarrow \quad y_1 = y_0 + F(t_0, y_0)\Delta t$$

This expression finds the solution y_1 at $t = t_1 = t_0 + \Delta t$ based on the solution at $t = t_0$ (we advanced the solution by one time-step Δt). The result of this action is illustrated in Figure 2.3. In this figure we are analyzing the differential equation $y' = y(1 - y)$ with the initial value (0,0.1). The exact solution to this differential equation is given by

$$y(t) = \frac{1}{1 + 9e^{-t}}$$

In the figure the exact solution is plotted together with Euler's approximated solution. In this example we get:

$$t_1 = \Delta t = 0.5; \quad y_1 = 0.1(1 - 0.1)0.5 = 0.1450$$

but the exact solution is given by

$$y(0.5) = \frac{1}{1 + 9e^{-0.5}} \approx 0.1548$$

The straight line (dashed) is the solution approximated by Euler's scheme and the exponentially increasing line (solid) is obtained by the exact solution. Notice, for $t = t_0$ (the initial value) the approximated solution equals the exact solution. The approximated solution is obtained by calculating the tangent line in this point and the solution y_1 at $t_1 = t_0 + \Delta t$ is obtained by taking the value of y at $t = t_0 + \Delta t$ along the tangent line. The difference between this approximated value of y_1 and the exact solution is called the error. In the example discussed above, the error during the first time-step is

$$E_1 = 0.1548 - 0.1450 = 0.0098$$

From the graph shown in Figure 2.3 it becomes clear that if the step-size is decreased, the approximation becomes more correct. However, since these values are found on the computer it is easy to see that in practice it would not be possible to take the limit of Δt going to 0, because it would take infinitely long time to compute the result.

Above, we only talked about finding the solution at y_1. To compute the solution for any value of t we have to advance the solution further. Notice that $t = t_2 = t_0 + 2\Delta t = t_1 + \Delta t$ can be found following the exact same recipe.
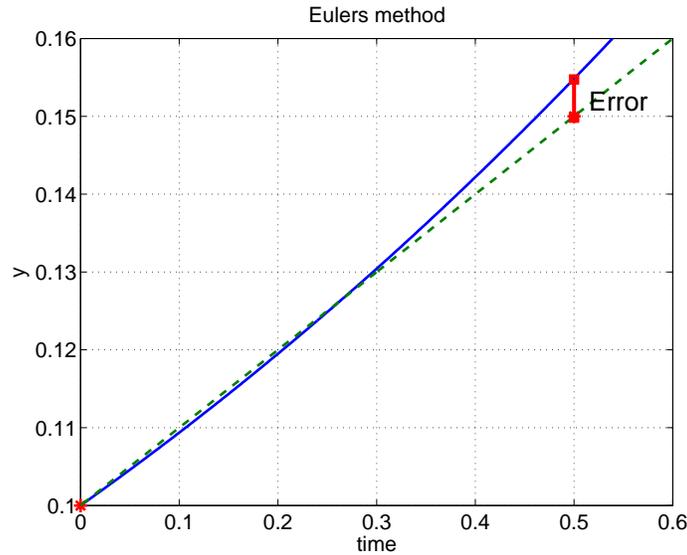
$$y_2 = y_1 + F(t_1, y_1)\Delta t$$

Figure 2.3: The exact (solid line) and approximated (dashed line) solutions. The difference between the exact solution and the approximated solution is the error (marked by the vertical solid line).

In general, the solution y_{n+1} at $t_{n+1} = t_0 + (n+1)\Delta t$ can be found by iteration from the the values obtained at (t_n, y_n) using the iteration scheme

$$y_{n+1} = y_n + F(t_n, y_n)\Delta t$$

The iteration is best understood by studying the graph in Figure 2.4. When calculating the first step we have the exact value at the initial time and then we approximate the value y_1. When calculating the second value we start with the solution at y_1 and calculate y_2 based on the value of $F(t_1, y_1)$ (the right hand side of the equation). The figure shows the exact solution (solid line) and the approximated solution (marked by stars), the tangent lines used to evaluate the approximated solutions are marked by dashed lines. Notice, since we re-iterate the solution for each point, different slopes are obtained depending on what approximated solution is used as a starting point. In other words to calculate y_1 we use t_0, y_0 as initial values, and to calculate y_2 we use t_1, y_1 as initial values etc. The solid line represent the exact solution of the differential equation and the dashed line represent the solution approximated by Euler's method.

Using this iteration formula we can find higher values of y_i for the example discussed above. We already computed that for $t_1 = 0.5$, then $y_1 = 0.1450$. Using these values to compute $F(t_1, y_1) = 0.1450(1 - 0.1450) = 0.1240$. Inserting this into the iteration scheme gives:

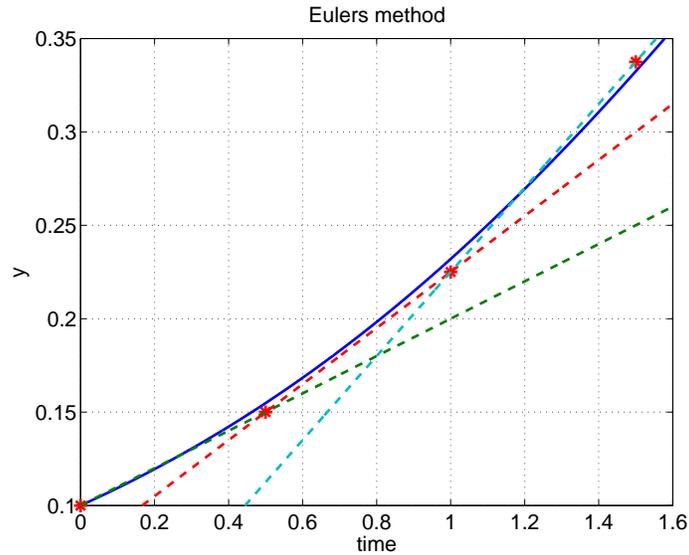$$t_2 = 1; \quad y_2 = 0.1450 + 0.1240 \cdot 0.5 = 0.2070$$

Figure 2.4: The figure shows the exact solution (solid line) and the approximated solution (stars). The tangent lines used to calculate (iterate) the approximated solutions are marked by dashed lines.)

In Table 2.1 we have given both the exact solution and the approximate solution to the differential equation for $t \in [0:5]$. As we discussed earlier, more exact solutions can be obtained if we let Δt be smaller. Whereas the values in Table 2.1 can easily be computed with pencil and paper and a calculator, it becomes harder to keep track of the numbers the more numbers we need to compute. A nice way to solve this problem on a computer is to use the mathematical programming language Matlab. In the following we have inserted a Matlab program that can solve the differential equation and compare the approximated solution with the exact solution.

Matlab-code for Euler's method

```
% This program uses Euler's method to solve the initial value problem
% y' = y (1 - y) for the initial value (0,0.1). In this example the
% differential equation is solved for t between 0 and 5.
%
tstart = 0;  % Start time
tend   = 5;  % End time

% Solving equation for dt = 0.5
dt1   = 0.5;            % delta t
```

t	y	$y'(t,y)$	f(t)
0.0	0.1000	0.0900	0.1000
0.5	0.1450	0.1240	0.1548
1.0	0.2070	0.1641	0.2320
1.5	0.2891	0.2055	0.3324
2.0	0.3918	0.2383	0.4509
2.5	0.5110	0.2499	0.5751
3.0	0.6359	0.2315	0.6906
3.5	0.7517	0.1867	0.7863
4.0	0.8450	0.1310	0.8585
4.5	0.9105	0.0815	0.9091
5.0	0.9512	0.0464	0.9428

Table 2.1: Numerical solution of the initial value problem $y' = y(1 - y)$ with initial value $(0, 0.01)$. The first column is time, the second column the approximated value of y, the third column is the right-hand-side $y(1 - y)$, and the last column gives the exact solution evaluated at the times given in the left column.

```
n1    = tend/dt1;      % number of points that the solution is computed in
t1    = zeros(1,n1+1); % create table to store t-values
y1    = zeros(1,n1+1); % create table to store y-values
t1(1) = tstart;        % insert start time in table
y1(1) = 0.1;           % insert initial condition in table

for i = 2:n1+1         % Euler's iteration scheme
   y1(i) = y1(i-1) + y1(i-1)*(1-y1(i-1))*dt1; % update y
   t1(i) = t1(i-1)+dt1; % update time
end;

% Solving equation for dt = 0.25, the code below is an exact copy of
% the code above. The only change is that dt = 0.25.
dt2 = 0.25;
n2  = tend/dt2;
t2 = zeros(1,n2+1);
y2 = zeros(1,n2+1);
t2(1) = tstart;
y2(1) = 0.1;

for i = 2:n2+1
   y2(i) = y2(i-1) + y2(i-1)*(1-y2(i-1))*dt2;
```

```
    t2(i) = t2(i-1)+dt2;
end;

% Solving equation for dt = 0.125.
dt3 = 0.125;
n3  = tend/dt3;
t3 = zeros(1,n3+1);
y3 = zeros(1,n3+1);
t3(1) = tstart;
y3(1) = 0.1;

for i = 2:n3+1
   y3(i) = y3(i-1) + y3(i-1)*(1-y3(i-1))*dt3;
   t3(i) = t3(i-1)+dt3;
end;

% The exact solution, computed on vector form using the t-values for
% dt=0.125.
f = 1./(1+9*exp(-t3));

% Display solutions
figure(1);
h=plot(t3,f,t3,y3,'.',t2,y2,'-.',t1,y1,'--'); % plot lines indicators
% '.', '-.', and '--' indicate the type of line, dotted, dash-dotted, and
% dashed.
set(h,'LineWidth',2);    % set the width of the line
set(gca,'Fontsize',16); % set fontsize to 16
xlabel('time');          % x-label
ylabel('y');             % y-label
title('Eulers Method'); % title
legend('exact','dt=0.125','dt=0.25','dt=0.5',4); % draw legends on the graph
                         % in the bottom right corner.
grid on;                 % add grid-lines to graph
print -depsc2 Euler_comp.eps % save graph as a eps color file.
```

2.2.1   A second-order Runge-Kutta method

Euler's method is first order accurate, this means that the error between the exact solution
and the computed solution is smaller than a constant time Δt (in mathematical terms this
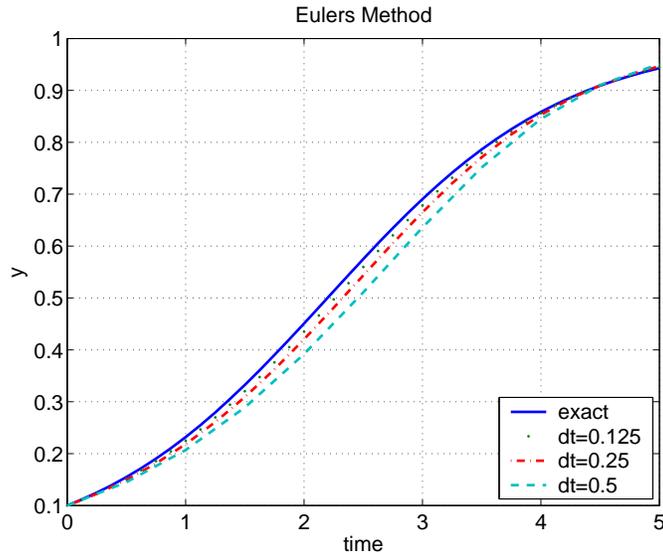
Figure 2.5: Numerical solution of the initial value problem using Euler's method. Solutions are computed using the exact function, and three values of Δt (0.5, 0.25, 0.125).

can be written as $\mathcal{O}(\Delta t))$. In general, the order of the method can be computed by comparing the magnitude of the error to the time-step to some power k. For example, the error for a second order method is $\mathcal{O}\left((\Delta t)^2\right)$ and the error for a third order method is $\mathcal{O}\left((\Delta t)^3\right)$. A first order method is not particularly accurate, but there exist numerical methods that are a lot more precise. An example is the second order Runge-Kutta method which has an error bounded by $\mathcal{O}\left((\Delta t)^2\right)$. Several Runge-Kutta methods exist, common for these methods is that they calculate the derivative of y using a weighted method. Runge-Kutta methods are finite-difference methods and they can be derived by discretizing the differential equation by averaging the sum of two slopes as we will illustrate below.

Generally, higher order finite-difference methods are obtained by discretizing the equation using a combination of forward differences, backward differences, and central differences. The Euler method is a so-called a backward difference method (we evaluated the right-hand-side of the equation at the previous time-step). In a forward difference scheme the right-hand-side at the new time-step, e.g.

$$\frac{y(t + \Delta t) - y(t)}{\Delta t} = F(t + \Delta t, y(t + \Delta t))$$

Methods based on forward differences result in systems of equations that needs to be solved. These systems arise because we have $y(t+\Delta t)$ on both the left and the right-hand-side of the equation. Such discretization schemes are often known as implicit differentiation schemes, whereas schemes that predict y_{n+1} explicitly as a function of y_n are known as explicit

differentiation schemes. In a central difference scheme, the weight of both the derivative and the right-hand-side has to be balanced, i.e. we could discretize the derivative by:

$$y'(t) \approx \frac{y(t + \Delta t) + 2y(t) - y(t - \Delta t)}{\Delta t}$$

In other words, differential equations can be discretized (written so that can be solved on a computer) using a number of different ways. To solve models it is not necessary to understand the details of all of these methods, but it is important to know that different methods exist and what are their limitations. Matlab includes a number of library routines that can be used to solve differential equations and in the following we'll discuss these in more detail.

The departure for the second order Runge-Kutta methods is the same as for Euler's method, namely an initial value differential equation of first order, i.e. $y'(t) = F(t, y)$ with the initial value $(t_0, y(t_0))$. To predict t_{n+1}, y_{n+1} using the second order Runge-Kutta method, we start by evaluating the right hand side using the previous step (t_n, y_n), we compute $k_1 = F(t_n, y_n)$. Then coordinates for the next time-step is computed using Euler's method, we find

$$(t_n + \Delta t, y_n + k_1 \Delta t)$$

These coordinates are then inserted into the differential equation and a second slope $k_2 = F(t_n + \Delta t, y_n + k_1 \Delta t)$ is calculated. It is the average of these two slopes k_1 and k_2 that is used to advance the solution one time-step,

$$(t_{n+1}, y_{n+1}) = \left(t_n + \Delta t, y_n + \frac{1}{2}(k_1 + k_2)\Delta t \right)$$

where $k_1 = F(t_n, y_n)$ and $k_2 = F(t_n + \Delta t, y_n + k_1 \Delta t)$.

A very popular Runge-Kutta method is the fourth' order method, which is similar to the above, except it advances the solution by combining four different slopes.

2.2.2   The "ode" solvers in Matlab

As mentioned above Matlab has a range of differential equation solvers for initial value problems. Some of these include ode23, ode113, ode15s, ode23s, ode23t, ode23tb. These differ in the way the problem is discretized and how the time is advanced. Common for the solvers that can be used to solve initial value problems is that they are all prefixed with the letters "ode" abbreviated from "ordinary differential equations". Some of these methods are designed for special types of differential equations (see further description below). In the following we will discuss ode23 and ode45 and give an overview of the other functions.

Ode23 solves initial value problem using Runge-Kutta methods of 2-3'rd order, i.e. the error obtained by computing the solution is smaller than some constant multiplied by $(\Delta t)^k$ where k is either 2 or 3. Similarly, ode45 uses Runge-Kutta methods of 4-5'th order.

These methods are developed as described above, the only difference is that they use even more points to advance the solution from t to $t+\Delta t$, in addition the methods are developed such that they can adjust the length of the step-size to obtain the most accurate solution. Especially they make the step-size very small if the graphs are very steep or if they change direction fast. The syntax for using both these functions are similar and will (together with the other methods) be discussed in the sections to follow. Common for all the ode-routines is that the function on the right-hand-side of the differential equation has to be entered into a Matlab function. For the first order differential that we discussed in the previous section $y' = y(1 - y)$ the Matlab function will look as follows:

```
function ydot = f(t,y)
  ydot = y*(1-y)
```

The first line defines a function that returns the variable `ydot` and requires an input with two arguments t and y. The second line computes the right-hand-side of the differential equation $y(1 - y)$ using the input variable y. This particular example does not use t, however, we have chosen to include t such that this Matlab function can easily be used to solve other problems.This function can either be put into a separate Matlab file called f.m (the same name as the name of the function) or it can be placed in the main program.

The solve this differential equation for $t \in [0 : 5]$ (as we did in the previous example) the following Matlab program can be used:

Matlab program

The following program solves the differential equation $y' = y(1 - y)$ for $t \in [0 : 5]$ with the initial condition $y(0) = 0.1$. The program computes the solution first using 'ode23' and then using 'ode45', then the exact solution is computed from $f = 1/(1+9e^{-t})$. The result of this computation is shown in Figure 2.6A. This graph show that it is almost impossible to distinguish the exact solution from the numerical ones. This is much better than the result we computed using Euler's method. Only a very detailed zoom (see Figure 2.6B) shows a slight difference between the numerically computed solutions and the exact solution. It should be noted the the two numerically computed solutions cannot be distinguished.

```
% Matlab program solving the differential equation y' = y (1-y) with
% initial condition t=0, y=0.1. The differential equation is solved
```
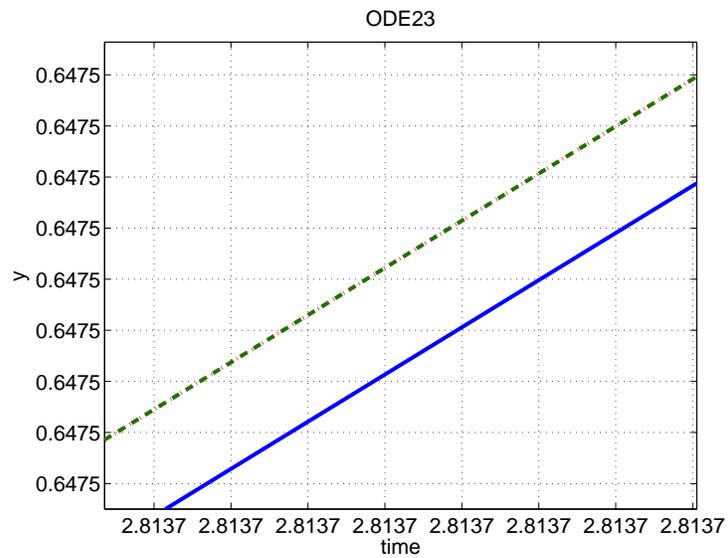
A
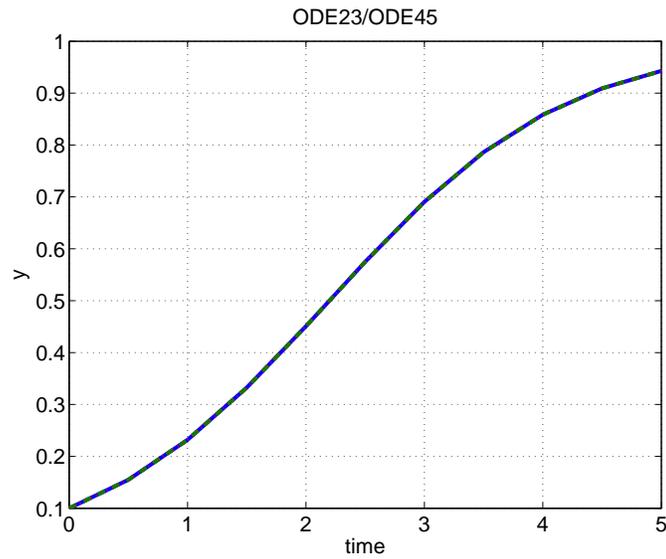
B

Figure 2.6: Solution of the logistic equation using ode23 and ode45. Results presented together with the exact solution. Figure A shows results for $t \in [0 : 5]$ and figure B showed a zoom to display the differences between the numerical and exact solution.

```
% using ode23

% Set options for the ode-solver, a list of all possible options can be
% obtained by typing ''help odeset'' on the Matlab command line.
% The two options set are two different error-estimates.
% From Matlabs help: RelTol - Relative error tolerance  [ positive
% scalar {1e-3} ]. This scalar applies to all components of the solution
% vector, and defaults to 1e-3 (0.1% accuracy) in all solvers. The estimated
% error in each integration step satisfies
% e(i) <= max(RelTol*abs(y(i)),AbsTol(i)).
% AbsTol - Absolute error tolerance  [ positive scalar or vector {1e-6} ].
% A scalar tolerance applies to all components of the solution vector.
% Elements of a vector of tolerances apply to corresponding components of
% the solution vector. AbsTol defaults to 1e-6 in all solvers. See RelTol.
options = odeset('RelTol',1e-4,'AbsTol',1e-4);

% solve the differential equation using the function defined in 'f.m'.
% the second argument provides start and end time for the solution. If a
% vector is provided, e.g. [0, 0.25, 0.5, 0.75, 1.0 ...] the returned solution
% will only be computed for these values (even though the solver internally
% computes the solution for more values). The third argument is the initial
% condition, the fourth argument is options (see above). After options it is
% possible to pass other parameters to the function f.m (see later discussion).
% the solution is returned in the object soli. soli.x (i-1,2) includes time
% and sol.y includes the corresponding $y$ values.
sol1 = ode45(@f,[0 5], 0.1, options);
sol2 = ode45(@f,[0 5], 0.1, options);

% Move times at which solution is calculated into the vector ti.
t1 = sol1.x;
t2 = sol2.x;

% Move the solution from soli.y into the vector yi.
y1 = sol1.y;
y2 = sol2.y;

% Compute the exact solution for the time-steps provided in t1.
fe = 1./(1+9*exp(-t1));

% Plot the results, this plotting rutine is similar to the one disccused
% earlier.
```

```
figure(1);clf;
h=plot(t1,fe,t1,y1,'--',t2,y2,':');
set(h,'LineWidth',3);
set(gca,'Fontsize',16);
xlabel('time');
ylabel('y');
title('ODE23/ODE45');
grid on;


print -depsc2 solOde23.eps
```

A summary of the other methods for solving ordinary differential equations are given in Table 2.2. The is taken directly from Matlab's help file. More detailed explanation can be found in the on-line documentation.

Short description of the various ode-solvers

ode45 is based on an explicit Runge-Kutta (4,5) formula, the Dormand-Prince pair. It is a one-step solver - in computing $y(t_n)$, i.e. it needs only the solution at the immediately preceding time point, $y(t_n - 1)$. In general, ode45 is the best function to apply as a "first try" for most problems (Dormand 1980).

ode23 is an implementation of an explicit Runge-Kutta (2,3) pair of Bogacki and Shampine. It may be more efficient than ode45 at crude tolerances and in the presence of moderate stiffness. Like ode45, ode23 is a one-step solver (Bogacki 1989).

ode113 is a variable order Adams-Bashforth-Moulton PECE solver. It may be more efficient than ode45 at stringent tolerances and when the ODE file function is particularly expensive to evaluate. ode113 is a multistep solver - it normally needs the solutions at several preceding time points to compute the current solution (Shampine 1975). The above algorithms are intended to solve non-stiff systems. If they appear to be unduly slow, try using one of the stiff solvers below.

ode15s is a variable order solver based on the numerical differentiation formulas (NDFs). Optionally, it uses the backward differentiation formulas (BDFs, also known as Gear's method) that are usually less efficient. Like ode113, ode15s is a multistep solver. Try ode15s when ode45 fails, or is very inefficient, and you suspect that the problem is stiff, or when solving a differential-algebraic problem (Shampine 1997, 1999).

ode23s is based on a modified Rosenbrock formula of order 2. Because it is a one-step solver, it may be more efficient than ode15s at crude tolerances. It can solve some kinds of stiff problems for which ode15s is not effective (Shampine 1997).

Solver	Problem Type	Method	Accuracy	When to use
ode45	Non-stiff	Runge-Kutta	Medium	Most of the time. This should be the first solver to try.
ode23	Non-stiff	Runge-Kutta	Low	If using crude error tolerances or solving moderately stiff problems
ode113	Non-stiff	Adams	Low-High	If using stringent error tolerances or solving a computationally intensive ODE file.
ode15s	Stiff & DAEs[a]	NDFs[b]	Low-Medium	If ode45 is slow because the problem is stiff.
ode23s	Stiff	Rosenbrock	Low	If using crude error tolerances to solve stiff and the mass matrix is constant.
ode23t	Moderately stiff and DAEs	Trapezoidal	Low	If the problem is only moderately stiff and you need a solution without numerical damping.
ode23tb	Stiff	TR-BDF2	Low	If using crude error tolerance to solve stiff systems.

Table 2.2: The ode-solvers included in Matlab. These solvers are described in more detail in the Matlab documentation.

[a]Differential Algebraic Equations

[b]Numerical differentiation formulas

ode23t is an implementation of the trapezoidal rule using a "free" interpolant. Use this solver if the problem is only moderately stiff and you need a solution without numerical damping. ode23t can solve DAEs (Shampine 1999).

ode23tb is an implementation of TR-BDF2, an implicit Runge-Kutta formula with a first stage that is a trapezoidal rule step and a second stage that is a backward differentiation formula of order two. By construction, the same iteration matrix is used in evaluating both stages. Like ode23s, this solver may be more efficient than ode15s at crude tolerances (Shampine 1997, Bank 1985).

Above mentioned references can be found in the Matlab on-line help file.

A lot of new terms was introduced in the previous description, the basic term appearing again and again is the notion of a stiff problem. A stiff differential equation is one in which both small and large values exist making it difficult for the solver to predict the numerical solution at a high level of accuracy. Biological problems will often be stiff, since we often need to compare changes that occur over a short time-scale or of small quantities with changes occurring over long time-scales or of large quantities.

In the example discussed so far, we only investigated the solution of one differential equation with one variable. Most real systems will give rise to a number of differential equations that are coupled. All of the above methods can also be used for systems of differential equations, and in the following we will discuss such systems.

2.3   Exercises

1. Write a Matlab code for Euler's method and solve the differential equation $y' = y(1 - y)$ for $\Delta t = 0.5, 0.25, 0.125$. Use the initial condition $t = 0$ $y(0) = 0.1$. Compare this solution (e.g. by writing up a table) with the solution exact solution.

2. Use the forward Euler method $y_{n+1} = y_n + \Delta t f(t_{n+1}, y_{n+1})$ to solve the equation $y' = y(1 - y)$ with $y(0) = 0.1$. Use the same values for Δt as in question 1, and compare the two methods.

3. For the mink-farm compute the equilibrium solution (i.e. how many mink the farmer can sell) if he has room for 12,000 or 15,000 mink.

4. Use Euler's method to solve the initial value problem $y' = t^3 - y^3$, with the initial condition $y(0) = 0$.

5. Show that Euler's method is exact if the solution to the differential equation is a straight line.

Chapter 3

Systems of differential equations

Prerequisites: Knowledge of first order differential equations, modeling using compartments, and numerical solutions of first order differential equations.

Background: Modeling of dynamical phenomena often involves more than one variable, and typically the variables depend on each other. When modeled, such phenomena gives rise to systems of coupled differential equations. To solve real problems it is necessary to obtain knowledge of the basic principles for systems of coupled equations including solution and analysis methods.

Aim: The aim with this chapter is to obtain an understanding of systems of differential equations, and to teach some of the basic techniques needed to solve systems of coupled first order differential equations.

Hardware: Pen, paper, and a computer.

3.1 Concentrations of salt - a two-compartment model

This example extends the model, discussed in Chapter 1, that describes the concentration of salt in a compartment. The extended model has two tanks, tank one includes $x(t)$ kg of salt dissolved in 200 l of water, while tank two has $y(t)$ kg of salt dissolved in 300 l of water. Salt-water flows between tank one and tank two with rates shown in Figure 3.1. In addition, water flows into tank one (from the exterior) at a rate of 10 l/min and water flows out of tank two with a rate of 10 l/min. Let's first study the balance of volume in the two tanks. For tank one we notice that
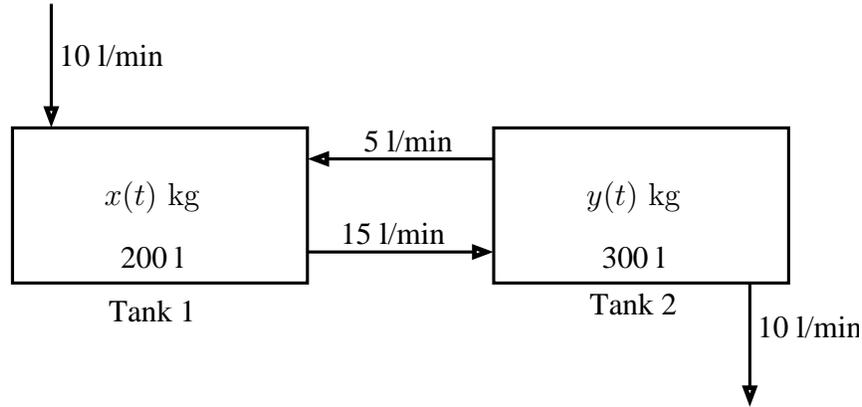
Figure 3.1: Compartments illustrating the flows in and out of the two tanks.

$$
\begin{aligned}
V_1(t + \Delta t) - V_1(t) &= \text{``water in'' (l/min) } \Delta t - \text{``water out'' (l/min) } \Delta t \\
&= 10 \text{ (l/min) } + 5 \text{ (l/min) } - 15 \text{ (l/min)} \\
&= (15 - 15) \text{ (l/min) } \Delta t = 0.
\end{aligned}
$$

The net volume in tank one stays the same. Similarly, the volume in tank two is conserved, since

$$
\begin{aligned}
V_2(t + \Delta t) - V_2(t) &= \text{``water in'' (l/min) } \Delta t - \text{``water out'' (l/min) } \Delta t \\
&= 15 \text{ (l/min) } - 5 \text{ (l/min) } - 10 \text{ (l/min)} \\
&= (15 - 15) \text{ (l/min) } \Delta t = 0.
\end{aligned}
$$

However, as in Chapter 1, if we want to describe the changes in the amount of salt, we get a different set of equations. The amount of salt in tank one is $x(t)$ and the amount of salt in tank two is $y(t)$. The goal is to study the dynamics of the amount of salt transported between the compartments. To compute this lets start by studying the dynamics of compartment one. Assume that the water flowing into compartment one does not contain any salt, hence this inflow can be ignored when studying the dynamics of the salt. Therefore, all salt flowing into compartment one comes from compartment two. The salt flows in at a rage of 5 l/min. This water comes from tank two which at any given time has $y(t)$ kg of salt. Assuming that the salt water in tank two is perfectly mixed this water will have amount of salt flowing into tank one is 5 l/min $\times y(t)/300$ kg/l $= y(t)/60$ kg/min. In addition, salt-water flows out of tank one at a rate of 15 l/min. The concentration of salt in tank one is $x(t)/200$ kg per liter, so the rate at which salt out of tank one is 15 (l/min) $\times x(t)/200$ kg/l $= 3x(t)/40$ kg/min. The dynamics for tank two can be derived similarly (see equations below). The compartment model in Figure 3.1 shows all inflows and outflows, a similar diagram can be developed to show salt transport (see Figure 3.2). From this diagram it is easy to derive the system of equations describing
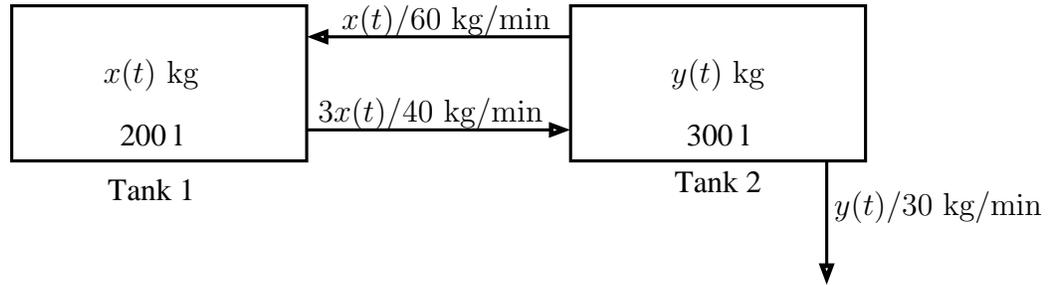
Figure 3.2: Compartments illustrating the transport of salt between the two tanks.

the dynamics of the salt:

$$
\begin{aligned}
x'(t) &= \frac{y(t)}{60}\ \text{kg/min} \ -\ \frac{3x(t)}{40}\ \text{kg/min} \\
y'(t) &= \frac{3x(t)}{40}\ \text{kg/min} \ -\ \left(\frac{y(t)}{60} + \frac{y(t)}{30} \right)\text{kg/min}
\end{aligned}
$$

Note both outflows from compartment two needs to be taken into account.

Matlab code to solve the two-compartment salt model

The following Matlab program uses ode45 to solve the system of differential equations describing the flow of salt between two compartments. Since we have two differential equations, two initial conditions are needed. For this problem we choose to let $x(0) = 1$ kg of salt and $y(0) = 0$. The solution of this problem is shown in Figure 3.3. The figure shows, that first salt moves into tank two, where the amount of salt is build up. After having reached a local maximum the amount of salt declines to zero in both tanks. That is to be expected, since clean water flows in to tank one and salt water flows out of tank two.

```
%%%%%%%%%%%% salt_sys.m %%%%%%%%%%%%%
%
% Matlab program solving differential equations describing the
% dynamics of salt-transport between two compartments.
%
V1  = 200;  % Volume in tank 1 200 l
V2  = 300;  % Volume in tank 2 300 l
F12 = 15;   % Flow from tank 1 to tank 2 15 l/min
F21 = 5;    % Flow from tank 2 to tank 1 5 l/min
F2o = 5;    % Flow leaving tank 2 10 l/min
```

```
par = [V1 V2 F12 F21 F2o]; % Vector with model paramters.

options = odeset('RelTol',1.0e-6,'AbsTol',1.0e-6); % Options for ode45 solver
% Initial conditions for the system of equations are x(0) = 1 and
% y(0) - 0. The equations are solved for t = 0 to t = 250.
sol = ode45(@fsalt,[0 250],[1 0],options,par);     % Notice, we pass the parameters
                                                   % par to the function fsalt as the l
                                                   % argument.


t = sol.x;      % Save times at which problem is solved in the vector t
x = sol.y(1,:); % The first row in sol.y contains the solution for tank one
y = sol.y(2,:); % The second row in sol.y contains the solution for tank two

% Plot results in figure 1
figure(1);clf;
h=plot(t,x,t,y,'--');
set(h,'LineWidth',3);
set(h,'MarkerSize',10);
set(gca,'Fontsize',16);
xlabel('time');
ylabel('solution');
legend('x','y');
title('ODE45');
grid on;
print -depsc2 salt_sys.eps


%%%%%%%%%%%% fsalt.m %%%%%%%%%%%%
function ydot = fsalt(t,y,par);
%
% Function calculating the right hand side of the system of
% differential equations.
%
V1  = par(1);  % Volume in tank 1 200 l
V2  = par(2);  % Volume in tank 2 300 l
F12 = par(3);  % Flow from tank 1 to tank 2 15 l/min
F21 = par(4);  % Flow from tank 2 to tank 1 5 l/min
F2o = par(5);  % Flow leaving tank 2 10 l/min
```
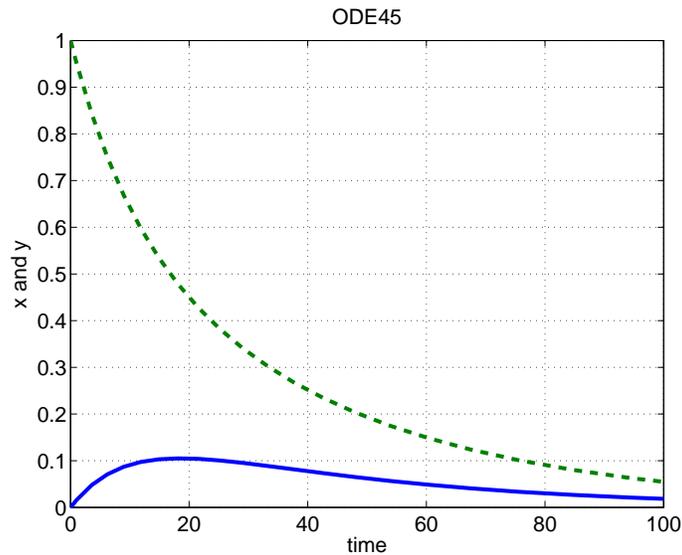
Figure 3.3: Solution to the two-compartment model predicting the dynamics of salt transport between the compartments.

```
ydot = [F21*y(2)/V2 - F12*y(1)/V1; ...
        F12*y(1)/V1 - (F21+F2o)*y(2)/V2;];
```

3.2   A physiological two-compartment model

The second example is based on physiology. It is difficult to describe physiology exactly, but insight can often be obtained from analysis performed using compartment models. When deriving compartment models for physiological systems, the compartments will always contain some physical quantity.

In the current example we want to describe the dynamics of cholesterol in the body. The amount of cholesterol in the body at a given time originates partly from the food we eat and partly by synthesis. Cholesterol leaves the body through the liver where it is broken down. This system can be described using a two-compartment model [1], where some of the tissue (primarily the liver, which is the main organ playing a role in the dynamics of the cholesterol levels) and the blood exchange cholesterol with the blood. This exchange is performed at a high velocity, hence we assume that the exchange occurs instantaneously and lump the blood and the liver together into our first compartment.

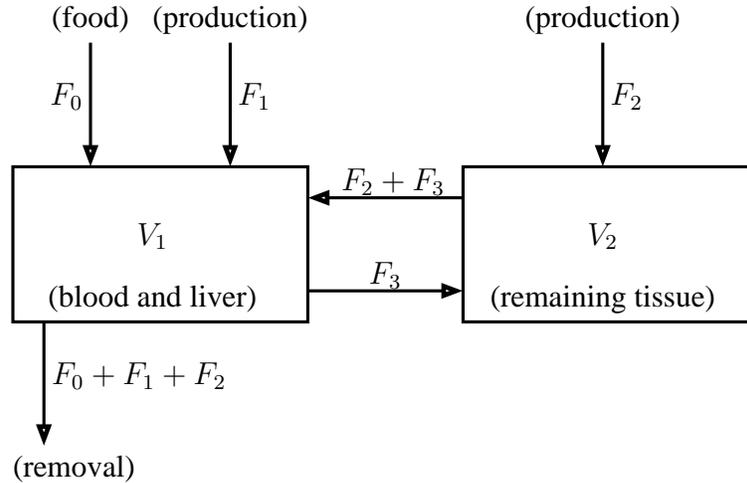[1]This example is based on work by Goodman and Noble, 1968

Figure 3.4: Compartment model describing the dynamics of cholesterol.

Slower exchange occurs between the first compartment (blood and liver) and other organs and tissues in the body. Hence, the remaining tissue and organs are lumped together in a separate compartment. In other words, we use one compartment to describe the amount of cholesterol in the blood and the liver and another compartment to describe the amount of cholesterol in all other tissues and organs. The dynamics of this model is shown in Figure 3.4. In this figure we describe the amount of material in each compartment by V (in units of gram), while the flow in and out of each compartment is described by F (grams of cholesterol per unit of time). Assume that $V_1 = 30$ g and $V_2 = 20$ g. In addition assume that $F_1 = 0.3$ g/day, $F_2 = 0.5$ g/day. The exchange rate between the two compartments is assumed to be $F_3 = 0.2$ g/day. Finally, the intake via food is $F_0 = 2$ g/day. The dynamics of cholesterol can be monitored by injecting a small amount of C^{14} into the venous blood stream. Let $Q_1(t)$ and $Q_2(t)$ describe the amount of radioactive cholesterol in the two compartments. The concentration of radioactive cholesterol in the two compartments can be computed by $Q_1(t)/V_1$ and $Q_2(t)/V_2$. This example is similar to the previous example. We have flow into the compartment, but aim to monitor the dynamics of the radioactive cholesterol. Similar to the previous example the total amount of cholesterol V_1 and V_2 are constant and we can derive a compartment model for the circulation of radioactive cholesterol. As before we start by analyzing compartment one. The cholesterol flowing into compartment via food and from production is not radioactive, and as a result this inflow can be ignored. Hence, the only inflow into compartment one comes from compartment two. The total flow of cholesterol into compartment two is $F_2 + F_3$ g of cholesterol / day and amount of radioactive cholesterol per grams of cholesterol is given by $Q_2(t)/V_2$, Hence, the the amount of radioactive cholesterol flowing into compartment one is given by $(F_2 + F_3)Q_2(t)/V_2$. Similarly, the amount of radioactive cholesterol flowing out of compartment one into compartment two is given by $F_3 Q_1(t)/V_1$. In addition, the amount

of radioactive cholesterol extracted to the surroundings is given by $(F_0 + F_1 + F_2)Q_1(t)/V_1$. From these balances we are able to derive our system of differential equations:

$$
\begin{aligned}
Q_1'(t) &= \frac{F_2 + F_3}{V_2}Q_2(t) - \frac{F_0 + F_1 + F_2 + F_3}{V_1}Q_1(t) \\
Q_2'(t) &= \frac{F_3}{V_1}Q_1(t) - \frac{F_2 + F_3}{V_2}Q_2(t)
\end{aligned}
$$

Both these examples show how two compartments can interact with each other. An analytical solution of this system would provide a set of functions (e.g. $x(t)$ and $y(t)$) that can fulfill both differential equations. In general problems as we will see later real models often include more than two compartments. The nice thing about models with two compartments is that we can analyze the system dynamics as we will discuss later. But first, we will use this general idea to develop and solve a system with multiple compartments.

Matlab code to solve the two-compartment cholesterol model

The Matlab code used to solve this problem is very similar to the one we used for the salt model. It is shown, together with the solution (which also look similar) below (see Figure 3.5).

```
%%%%%%%% cholesterol.m %%%%%%%%
V1  = 30;  % Volume in tank 1 30 l
V2  = 20;  % Volume in tank 2 20 l
F0  = 2;   % Flow into tank 1 from food 2 g/day
F1  = 0.3; % Flow into tank 1 from synthesis 0.3 g/day
F2  = 0.5; % Flow into tank 2 from synthesis 0.5 g/day
F3  = 0.2; % Flow from tank 1 to tank 2 0.2 g/day

par = [V1 V2 F0 F1 F2 F3];

options = odeset('RelTol',1.0e-6,'AbsTol',1.0e-6);
sol = ode45(@fsalt,[0 250],[1 0],options,par);
t = sol.x;
x = sol.y(1,:);
y = sol.y(2,:);

figure(1);clf;
h=plot(t,x,t,y,'--');
set(h,'LineWidth',3);
```
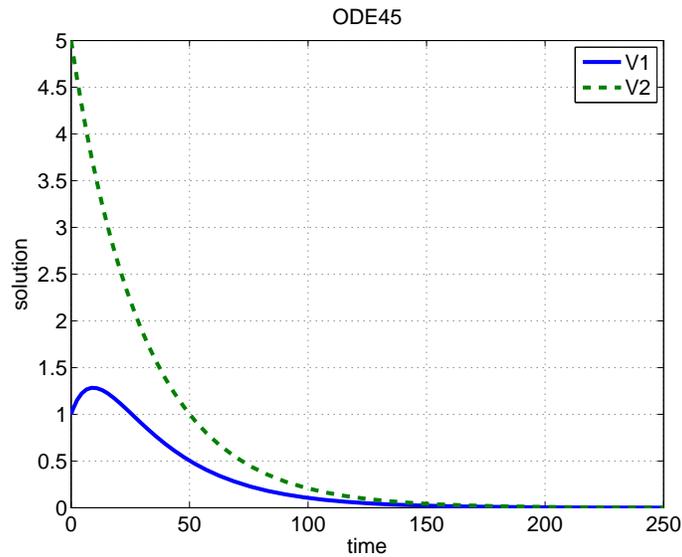
Figure 3.5: Solution to the two-compartment model predicting the dynamics of radioactive cholesterol transport between the compartments.

```
set(h,'MarkerSize',10);
set(gca,'Fontsize',16);
xlabel('time');
ylabel('solution');
legend('x','y');
title('ODE45');
print -depsc2 chol_sys.eps

%%%%%%%%% fchol.m %%%%%%%%%
function ydot = fchol(t,y,par);

V1  = par(1);
V2  = par(2);
F0  = par(3);
F1  = par(4);
F2  = par(5);
F3  = par(6);

ydot = [(F2+F3)/V2*y(2) - (F0+F1+F2_F3)/V1*y(1); ...
        F3/V1*y(1) - (F2+F3)/V2*y(2);];
```

Both this and the previous model gave rise to a system of two coupled differential equations derived from analysis of the interaction between the two compartments and the environment. These equations both had constant coefficient and could be solved analytically using methods describedin most books on differential equations. Note that typically, real models would typically include significantly more compartments, and in general, the resulting equations would be more complicated, and would not necessarily be solvable using analytical methods.

3.3 Notes on compartment models

When setting up a compartment model it is essential that one first describes (e.g. using a diagram) the states of the model (depicted by compartments). To determine what are reasonable states it could be essential to also think about what quantities flow to and from the compartments. An essential thing to keep in mind, is that this phase of the modeling often gives rise to the most simplificatons of the system. For example, in the cholesterol model, we lumped blood and liver into one compartment while keeping everyting else in the other compartment. Alternative formulations could have included e.g. three compartments blood, liver, and remaining tissues, or much more complicated systems. The most important thing to keep in mind is to start simple, and then expand the model as more details are required.

3.4 Qualitative graphical analysis

So far we have set up differential equations and solved them using the ode-solvers in matlab. However, additional analysis can be performed without actually solving the equations. While we discussed how the equations can be solved numerically, some systems of equations can be solved analytically and some can be analyzed "graphically" without actually solving the equations. In this section we will discuss how systems of differential equations can be analyzed without solving the equations.

To do so we first introduce slope-fields. A slope-field can be obtained by by plotting the slope of the differential equation at any time t. As an example we study the differential equation

$$y' = 0.1ty \qquad (3.1)$$

This equation is satisfied by a function $y(t)$ that at any point (t, y) is 0.1 times the product of the coordinates of the point. For example, the point (1,1) the curve representing the solution of the equation has the slope $0.1 \cdot 1 \cdot 1 = 0.1$, in the point (2,2) the solution has
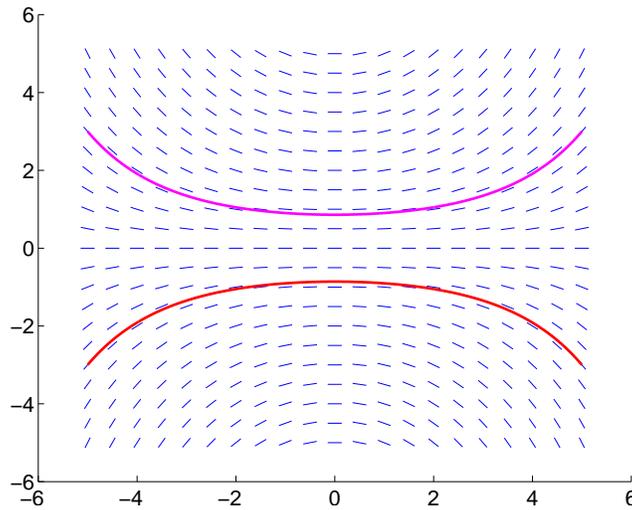
Figure 3.6: Slope-field for the differential equation $y' = 0.1ty$. The two lines indicate solutions through the points (-5,3) and (-5,3).

the slope is $0.2 \cdot 2 \cdot 2 = 0.4$, and in the point (10,8) the slope is 8, etc. To get an overview of how the slope of the solution changes with t and y it is advantageous to plot the slopes of the solution for consequtive collection of points. This is done in a slope-field. A slope-field for a differential equation shows how the value of y', represented by a short line-segment (a slope-element) in a lettuce of chosen points, changes with t and y. Figure 3.6 shows the slope-field for the differential equation (3.1) for $t \in [-5:5]$ and $y \in [-5:5]$. It is easy to sketch a solution curve starting at a given point in the slopefield. You set the pen in any point draw a line following the small line-segments, such that the curve continues to be tangential to the small line-segments. In Figure 3.6, we have sketched two solution curves for the differential equation (3.1) through the points (-5,-3) and (-5,3).

From the slope-field it is possible to obtain information about the behaviour of the solution. For example, if the slope-field is horizontal axis at any location along the two axis, which corresponds to the fact that $y' = 0$ for one of the two dependent variables. In this case, it can be seen that $y(t) = 0$ is a solution to the differential equation. Such a solution is an equilibrium solution, because the state of the system does not change. In conclusion, equilibrium solutions in a slope-field always can be displayed by horizontal slope-elements.

Existence and uniqueness of solutions to initial value problems imply, that through each point of a slope-field passes only one solution curve. Solution curves can be determined uniquely from an initial point, and the solution curves will not intersect at any point. As soon as the penn has been at any point in the slope-field, the path of the cure will be uniquely determined at any following point. In addition, the path for the curve to the left of the initial point will also be termined uniquely. In this way, all points have a unique

story. In other words there is only one solution curve curve, that can provoked the system to be in a givn state. From the slope-field, one can get some informaion of how close the solotion curves lie. For the current example, the curves. In the current example one can see that the family of solution curves are parallel tot he fifrst axis. Notice, that the curves do not appear from a simple vertical paralel to the x-axis.