

Chapter 2

Modelling Chemical Reaction Networks

It behoves us always to remember that in physics it has taken great [minds] to discover simple things. They are very great names indeed which we couple with the explanation of the path of a stone, the droop of a chain, the tints of a bubble, the shadows in a cup. It is but the slightest adumbration of a dynamical morphology that we can hope to have until the physicist and the mathematician shall have made these problems of ours their own...

—D’Arcy Thompson, On Growth and Form

Models of cellular phenomena often take the form of schematic interaction diagrams, as in Figure 1.1. For biochemical and genetic networks, the components in these diagrams are *molecular species*, which could be ions, small molecules, macromolecules, or molecular complexes. An interaction diagram depicts the species in a system and indicates how they interact with one another. The interactions (arrows) in the diagram can represent a range of processes, such as chemical binding or unbinding, reaction catalysis, or regulation of activity. In each case, the rate of the process depends on the abundance of certain molecular species within the network. These processes, in turn, result in the production, interconversion, transport, or consumption of the species within the network. Over time, the abundance of each species changes, leading to corresponding changes in the rates of the processes. For simple systems, we can understand the resulting behaviour intuitively. However, for more complex networks—especially those involving feedback—the interaction diagram leaves ambiguity with respect to time-varying behaviours. In these cases, an accurate description of system behaviour is only possible if we describe the interactions more precisely—in quantitative terms.

These quantitative descriptions can be used to construct dynamic mathematical models. In this chapter we will address the construction of models that describe chemical reaction networks. The next chapter will introduce quantitative descriptions of biochemical processes. Together, these chapters lay a foundation for dynamic modelling of cellular behaviour.

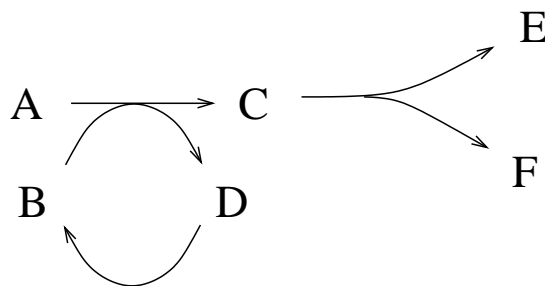
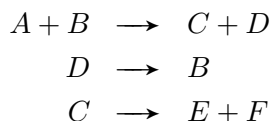


Figure 2.1: Closed reaction network.

2.1 Chemical Reaction Networks

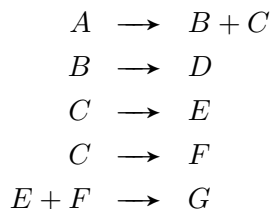
Consider a group of chemical species (i.e. chemically distinct molecules) that can undergo the following reactions:



These reactions are assumed to be *irreversible*—they only proceed in the direction indicated. (The assumption of irreversibility is necessarily an approximation. The laws of thermodynamics dictate that all chemical reactions are reversible. Nevertheless, it is often reasonable to describe a reaction as irreversible under conditions in which the reverse reaction proceeds at a negligible rate.)

A set of reactions constitutes a **chemical reaction network**. The manner in which the species interact is referred to as the network *topology* (or *architecture*). The organization of the network is apparent if we re-arrange the reactions in the form of an *interaction graph*.^{*} This network's interaction graph is shown in Figure 2.1.

Exercise 2.1.1 Draw the interaction graph for the following reaction network:



□

2.1.1 Closed and open networks

The reaction network considered above is **closed**, meaning that there are no reactions whose products or reactants lie outside of the network. The steady-state behaviour of such networks is *thermal equilibrium*, a state in which all net reaction rates are zero.

^{*}The use of the term ‘graph’ here is, unfortunately, different from its use in the visualization of a function or a data set. In mathematical graph theory, a graph consists of a set of objects (called *nodes*) that are connected to one another by links (called *edges*). Here, the nodes are the chemical species; the edges are the reactions.

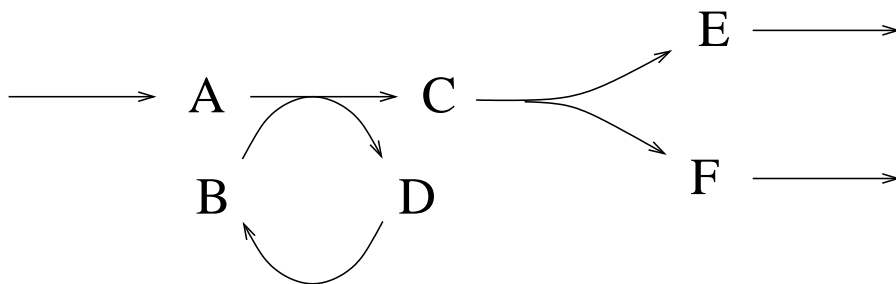
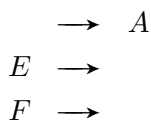


Figure 2.2: Open reaction network.

In contrast, most biochemical networks are **open** systems—they exchange material with the outside environment and reach a steady state that involves a steady flow through the network. Such a state is called a *dynamic equilibrium*. (A familiar example of a dynamic equilibrium is a steady jet of water flowing from a waterfall or faucet. Although this might appear to be an unmoving object, it is a steadily active process.) The network above could be made into an open network by adding the reactions



resulting in the network in Figure 2.2. These additional reactions indicate that material is being exchanged with the ‘world outside the network,’ and are referred to as *exchange reactions*.

Exercise 2.1.2 Add three exchange reactions to the reaction network in Exercise 2.1.1 so that the system can support steady flow through all of the species in the network. Can this be achieved by adding just two exchange reactions? \square

2.1.2 Dynamic behaviour of reaction networks

Imagine an experiment in which the reactions in a network proceed in a fixed volume; suppose the species are initially present at specified concentrations. To predict the time-varying changes in species concentrations, we need to know the rates at which the reactions occur. The rate of a reaction depends on the concentrations of the reactants and the physico-chemical conditions (e.g. temperature, pH). We will presume that the physico-chemical environment is fixed, so rate laws can be described solely in terms of reactant concentrations.

Reaction rates are usually described under two assumptions:

Assumption 1: The reaction volume is well-stirred. This means that the reactants are equally distributed throughout the volume. Consequently, the rate of each reaction is independent of position in space. This allows us to refer unambiguously to *the* reaction rate in the volume (rather than having to specify different rates at different locations).

Assumption 2: There are a great many molecules of each species present, so we can describe molecular abundance by a concentration that varies continuously (as opposed to an integer-valued molecule count).

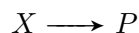
The first of these assumptions—referred to as *spatial homogeneity*—typically holds in stirred laboratory reaction vessels. It can be a good approximation in the cell, as diffusion acts quickly to mix the molecular components of this tiny ‘reaction vessel’. However, there is a great deal of spatial structure within the cell, so that in many cases the assumption of spatial homogeneity does not hold.

The second assumption—that there are a great many reactant molecules—is referred to as the *continuum hypothesis*; it allows discrete changes in molecule number to be approximated by continuous changes in concentration: individual reaction events cause infinitesimal changes in abundance. This assumption is perfectly valid when Molar quantities of reactants are involved (recall, Avogadro’s number is 6.02×10^{23}), and is appropriate for cellular species with molecule counts of thousands or more. However, some cellular processes are governed by populations of molecules numbering dozens or less. In those cases, changes in molecule abundance should be treated as discrete steps in population size.

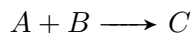
We will build our modelling framework under the assumptions of spatial homogeneity and continuously-varying concentrations. The resulting models yield accurate descriptions of a wide range of biological phenomena. Modelling frameworks for addressing spatial variation and small molecule counts will be introduced in Sections 8.4 and 7.6, respectively.

The law of mass action

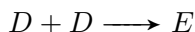
In a fixed volume, under the well-stirred assumption and the continuum hypothesis, a simple description of reaction rates is provided by the **law of mass action**: *the rate of a chemical reaction is proportional to the product of the concentrations of the reactants*. Using $[\cdot]$ to denote concentration, the rate of the reaction



is $k_1[X]$ (because there is a single reactant), while the rate of



is $k_2[A][B]$ (two reactants), and the rate of

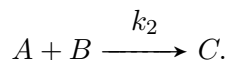


is $k_3[D]^2$ (two identical reactants). Here k_1 , k_2 , and k_3 are constants of proportionality.

Some notes on mass action

- 1) The law of mass action has an intuitive basis: it states that the probability of a reaction occurring is proportional to the probability of the reactants colliding with one another.
- 2) The exponent to which each reactant appears in the rate law is called the *kinetic order* of the reactant in the reaction. For example, reactant A has kinetic order 1 in the second reaction listed above, while D has order 2 in the third reaction. If a reaction describes uptake from the outside environment, it can be written with no explicit reactant (e.g. $\longrightarrow A$). The rate of such a reaction is constant. Because these reactions satisfy a rate law with a reactant concentration raised to the power zero ($k[S]^0 = k$), they are called *zero-order* reactions.

3) The constant of proportionality in a mass action rate law is called the **(mass action) rate constant** and can be indicated in the reaction formula:



The dimensions of the rate constant depend on the number of reactants. The rate constant for a single-reactant reaction has dimensions of time^{-1} . If a reaction has two reactants, the rate constant has dimensions of $\text{concentration}^{-1} \cdot \text{time}^{-1}$. For a zero-order reaction, the reaction rate is equal to the rate constant, which has dimensions of $\text{concentration} \cdot \text{time}^{-1}$.

4) In cases where the environment is not constant, the rate constant can be replaced by an *effective rate constant* that depends on factors that affect the reaction rate. In a biochemical context, effective rate constants may depend on the concentration of enzyme catalysts.

In the following sections we will use the law of mass action to construct dynamic mathematical models of chemical reaction networks. These models will take the form of *ordinary differential equations* (ODEs).[†] We will make use of this differential equation-based framework throughout the rest of the book.

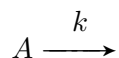
In the chapters to follow, models investigations will be carried out via computational software. However, in the remainder of this chapter, we will address elementary networks for which pen-and-paper calculations yield explicit formulas describing the time-varying species concentrations. Such formulas are called *analytic solutions* of the differential equation. The analysis of these simple cases will provide valuable insight into the more complex models to follow.

2.1.3 Simple network examples

Some readers may find it useful to review the brief summary of calculus in Appendix B before proceeding.

Example I: decay

As a first example, consider a trivial open reaction system consisting of a single species decaying at a steady rate:



The rate of the reaction is $k[A]$. To understand how the concentration of A behaves in time, we need to consider the rate of change of the concentration. Since the reaction consumes A , we have

$$\text{rate of change of } [A] = -(\text{rate of reaction}) \quad (2.1)$$

Let

$$a(t) = \text{concentration } [A] \text{ at time } t$$

[†]The modifier *ordinary* is used to distinguish these from *partial* differential equations (PDEs). PDE-based modelling, which addresses spatially varying behaviour, is introduced briefly in Section 8.4.

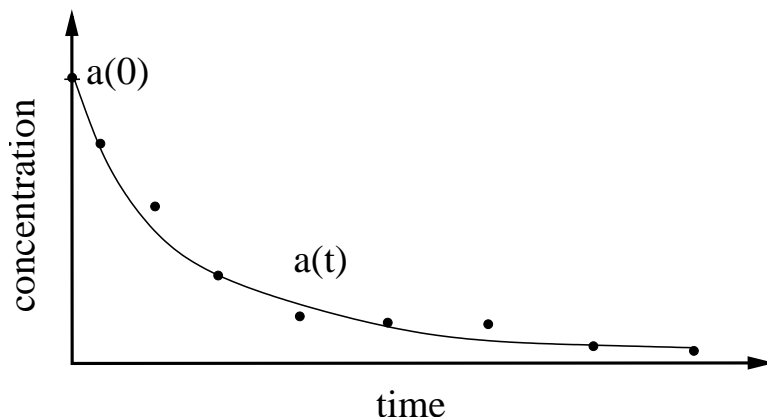


Figure 2.3: Model behaviour. The points represent a hypothetical experimental time series. The curve is the corresponding model-based prediction. Discrepancies between model prediction and data may be attributed to experimental error or to inaccuracy in the model formulation.

Then, recalling that the derivative of a function describes its rate of change, we can rewrite statement (2.1) as

$$\underbrace{\frac{d}{dt}a(t)}_{\text{rate of change of } [A] \text{ at time } t} = \underbrace{-ka(t)}_{\text{rate of reaction at time } t} \quad (2.2)$$

This is a **differential equation** whose solution is the function $a(t)$.

Imagine this reaction has been set up in a laboratory test-tube. As the reaction proceeds, the concentration of A will decrease over time. Experimentally, we might observe a time-series of concentrations as in Figure 2.3. If our mathematical model is accurate, then the solution $a(t)$ of the differential equation should describe the behaviour of the system over time. That is, it should agree with the experimental measurements (Figure 2.3).

To use the model to make a prediction about a particular experiment, we need to supplement the differential equation with knowledge of the concentration $[A]$ at some time. We typically know the concentration at the beginning of the experiment, at time $t = 0$. This known concentration, $a(0)$, is referred to as the **initial condition**.

There are standard solution methods for simple classes of differential equations. Because the models of biological phenomena addressed in this text are not amenable to such solution techniques, they will not be addressed here. Nevertheless, it will prove insightful to derive an explicit solution formula for this simple differential equation. To do so, we will take a direct (and rather unsatisfactory) route to the solution: we guess.

Well, it's not quite guessing. We'll begin by considering a special case of the differential equation in which $k = -1$. We do not have a chemical interpretation of the equation in this case, since rate constants are never negative. However, it will be useful to momentarily consider the resulting differential equation:

$$\frac{d}{dt}a(t) = a(t) \quad (2.3)$$

A solution $a(t)$ of this differential equation has the property that its derivative has the same value as the function itself at each time point t . That is, the function $a(t)$ is its own derivative. You

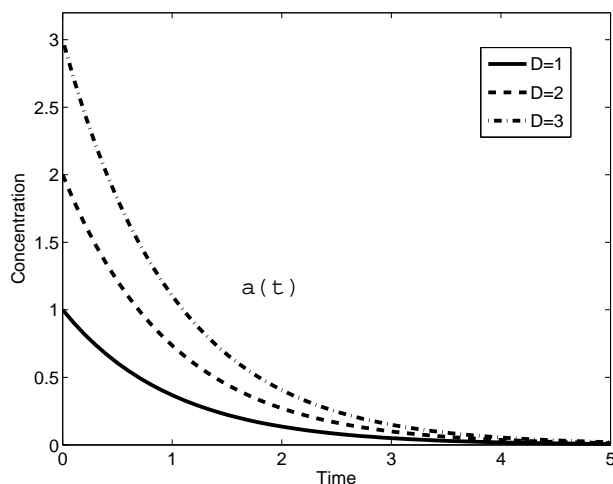


Figure 2.4: Exponentially decaying concentration profiles (equation (2.4)). Parameter values are $k = 1$, $D = 1$, $D = 2$, $D = 3$.

may recall that the exponential function $a(t) = e^t$ has this property, as does any constant multiple of this function. Thus any function of the form $a(t) = De^t$, for a given constant D , satisfies the differential equation (2.3).

A more relevant case occurs if we take $k = 1$, which leads to:

$$\frac{d}{dt}a(t) = -a(t).$$

Invoking the chain rule leads to the correct guess in this case: $a(t) = De^{-t}$. (By the chain rule: $\frac{d}{dt}e^{-t} = e^{-t} \left(\frac{d}{dt}(-t) \right) = e^{-t}(-1) = -e^{-t}$.)

Finally, consider the general case:

$$\frac{d}{dt}a(t) = -ka(t)$$

Appealing to the chain rule again, we arrive at the solution $a(t) = De^{-kt}$. How should the constant D be chosen so that this function will agree with experimental observations? Recall that we are presuming we know the initial concentration: $a(0)$. Let's call that A_0 , so $a(0) = A_0$. Substituting time $t = 0$ into the solution $a(t) = De^{-kt}$ we find

$$a(0) = De^{-k \cdot 0} = De^0 = D.$$

Since we have $a(0) = A_0$, we conclude that $D = A_0$. That is, the constant D is equal to the initial concentration of A . The species concentration can then be written as a function of time:

$$a(t) = A_0 e^{-kt}. \quad (2.4)$$

This behaviour is referred to as *exponential decay*.

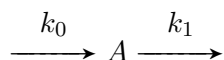
The time-varying behaviour of this family of solutions is shown in Figure 2.4. The curves all approach zero as time passes. We say they *decay* to zero, or they *relax* to zero, or that their

asymptotic value is zero. Moreover, the curves in the figure all decay at the same characteristic rate. This decay rate is characterized by the **time constant** of the process, defined, in this case, as $\tau = \frac{1}{k}$. (The *half-life* $\tau_{1/2}$ is closely related to the time constant: $\tau_{1/2} = \frac{\ln 2}{k} = \tau \ln 2$.)

The time constant provides a useful scale for addressing the dynamics of the reaction. For example, if $\tau = 1$ second, then it is appropriate to plot system behaviour on a scale of seconds. Alternatively, if $\tau = 100$ seconds, then a time-scale of minutes is more appropriate. The time-scale of a process determines the time interval over which model simulations should be run, and is also used in the design of time-series experiments. For example, if the time-scale of the dynamics is minutes, then useful data will be collected on that time-scale. Data separated by longer periods (e.g. hours) may miss crucial aspects of the behaviour; conversely, a strategy of observation at a greater frequency (say, every second) will be wasteful, as the data will be highly redundant.

Example II: production and decay

We next consider an open network involving two reactions, production and decay:



The first reaction is zero-order; the reaction rate is equal to k_0 . (Zero-order reactions are used when the concentration of the reactant is considered constant. This occurs when the reactant pool is large—so that depletion of the reactant is negligible—or when the concentration of the reactant pool is buffered by some unmodelled process. These reactions are written with the reactant absent (as above), or with a reactant whose concentration is a fixed model parameter (e.g. $X \rightarrow A$, $[X]$ fixed).)

Again letting $a(t)$ denote the concentration of A at time t , the reaction dynamics are described by

$$\text{rate of change of } [A] = \text{rate of production of } A - \text{rate of decay of } A$$

which leads to the model

$$\underbrace{\frac{d}{dt}a(t)}_{\text{rate of change of } [A] \text{ at time } t} = \underbrace{k_0}_{\text{rate of production}} - \underbrace{k_1 a(t)}_{\text{rate of decay}} \quad (2.5)$$

Before addressing the time-varying behaviour of $a(t)$, we first consider the concentration that A will reach in steady state. We note that the concentration of A will remain fixed when the rate of decay is equal to the rate of production. Mathematically, this means that the steady state concentration a^{ss} satisfies

$$\text{rate of change of } [A] = k_0 - k_1 a^{ss} = 0.$$

This yields

$$a^{ss} = \frac{k_0}{k_1}.$$

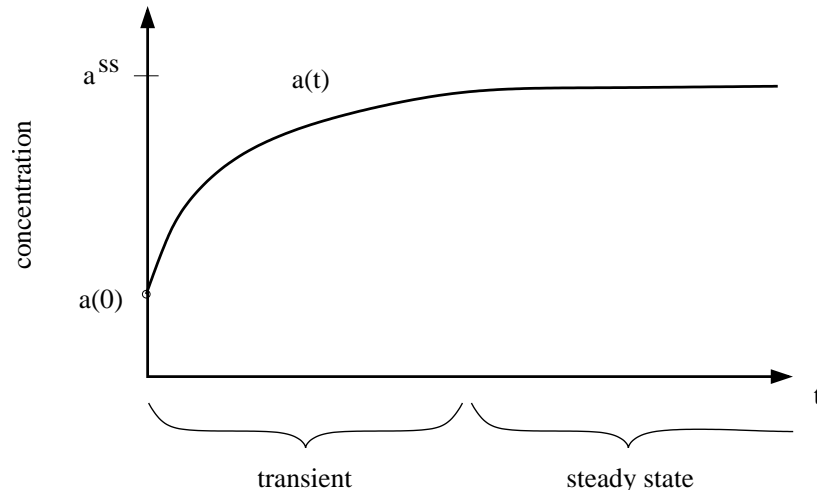


Figure 2.5: Transient and steady-state behaviour. The transient occurs while the concentration relaxes to its steady-state value.

Exercise 2.1.3 Verify that the ratio $\frac{k_0}{k_1}$ has dimensions of concentration. \square

We will regularly use this procedure to find steady states without solving the corresponding differential equation. Note that in steady state there is a non-zero flux through this network; the steady-state rate of both reactions is k_0 .

Turning now to the time-varying behaviour of $[A]$, we expect to observe the concentration transitioning from its initial value to the steady-state concentration, as in Figure 2.5. The time-course leading to the steady state is called the **transient**.

To derive an explicit description of the time-varying concentration, we will solve the differential equation (2.5) by employing another ‘guess’: we expect the solution $a(t)$ to approach the steady state value exponentially. If this is the case, the displacement from steady state ($a(t) - a^{ss}$) will decay exponentially to zero, and so it will satisfy a differential equation similar to our earlier model of exponential decay in equation (2.2). This insight leads to a solution of the form (details in Exercise 2.1.4):

$$a(t) = De^{-k_1 t} + \frac{k_0}{k_1}. \quad (2.6)$$

As before, the constant D depends on the initial concentration.

The concentration of A relaxes exponentially to the steady state value of $a^{ss} = \frac{k_0}{k_1}$. The relaxation rate k_1 is independent of the production rate k_0 . This illustrates a general principle: the time-scale on which the concentration of a species varies is typically determined by its decay rate rather than by its production rate.

Exercise 2.1.4 Determine the solution to equation (2.5) as follows. Let z denote the displacement of the concentration a from its steady state: $z(t) = a(t) - a^{ss} = a(t) - \frac{k_0}{k_1}$. Next use equation (2.5) to verify that $z(t)$ satisfies the differential equation

$$\frac{d}{dt}z(t) = -k_1 z(t). \quad (2.7)$$

Hint: Verify that $\frac{d}{dt}z(t) = \frac{d}{dt}a(t) = k_0 - k_1a(t)$ and that $k_0 - k_1a(t) = -k_1z(t)$. Finally, recall that the solution of equation (2.7) is

$$z(t) = De^{-k_1t},$$

so that from the definition of $z(t)$, we have equation (2.6). □

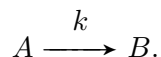
Exercise 2.1.5 Verify from equation (2.6) that $D = A_0 - \frac{k_0}{k_1}$, where $A_0 = a(0)$. Confirm that the concentration of A can be written as

$$a(t) = \left(A_0 - \frac{k_0}{k_1}\right)e^{-k_1t} + \frac{k_0}{k_1}.$$

□

Example III: irreversible conversion

Next we consider a closed system involving a single reaction:



This reaction is irreversible; molecules of B cannot be converted back to A . Because no material is exchanged with the external environment, the system is closed.

The rate of the reaction is $k[A]$. (Species B has no influence on the reaction rate.) Each reaction event consumes a molecule of A and produces a molecule of B , so we have

$$\begin{aligned}\text{rate of change of } [A] &= -(\text{rate of reaction}) \\ \text{rate of change of } [B] &= \text{rate of reaction}.\end{aligned}$$

Let

$$\begin{aligned}a(t) &= \text{concentration } [A] \text{ at time } t \\ b(t) &= \text{concentration } [B] \text{ at time } t.\end{aligned}$$

The reaction system can then be modelled by

$$\begin{aligned}\underbrace{\frac{d}{dt}a(t)}_{\text{rate of change of } [A] \text{ at time } t} &= \underbrace{-ka(t)}_{\text{rate of reaction at time } t} \\ \underbrace{\frac{d}{dt}b(t)}_{\text{rate of change of } [B] \text{ at time } t} &= \underbrace{ka(t)}_{\text{rate of reaction at time } t}\end{aligned}$$

This is a **system of differential equations**: two equations involve the two unknowns $a(t)$ and $b(t)$. Typically, it is much more difficult to solve systems of differential equations than to solve individual differential equations. However, in this case the system can be reduced to a single equation, as follows.

Since the behaviour of $a(t)$ is identical to the decay reaction of Example I, we know that $a(t) = A_0 e^{-kt}$, where $A_0 = a(0)$ is the initial concentration of A . To determine the concentration $b(t)$, we observe that the total concentration of A and B is conserved—every time a molecule of B is produced, a molecule of A is consumed.

Conservation is a general feature of closed systems. In this case it says that $a(t) + b(t) = T$ (constant) for all time t . If $a(0) = A_0$ and $b(0) = B_0$, then $T = A_0 + B_0$, and we can write

$$b(t) = B_0 + A_0 - a(t).$$

As time passes, $[A]$ decays to zero, and $[B]$ tends to $B_0 + A_0$; eventually all of the molecules of species A are converted to B .

We derived this conservation from inspection of the reaction system. Conservations can also be derived from differential equation models; they appear as balances in the rates of change. In this case, the conservation $a(t) + b(t) = T$ follows from the symmetry in the rates of change for A and B . We can write

$$\begin{aligned} \frac{d}{dt}(a(t) + b(t)) &= \frac{d}{dt}a(t) + \frac{d}{dt}b(t) \\ &= -ka(t) + ka(t) \\ &= 0, \end{aligned}$$

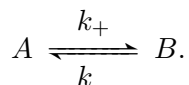
confirming that the total concentration $a(t) + b(t)$ does not change with time.

Example IV: reversible conversion

Our final example is a closed system consisting of a single reversible reaction:



or more concisely



Applying the law of mass action we find that

The rate of $A \rightarrow B$ is $k_+[A]$.

The rate of $B \rightarrow A$ is $k_-[B]$.

Letting, as before, a and b denote the concentrations of A and B , we have

$$\begin{aligned} \text{rate of change of } [A] &= (\text{rate of production of } A) - (\text{rate of consumption of } A) \\ &= (\text{rate of } B \rightarrow A) - (\text{rate of } A \rightarrow B). \end{aligned}$$

This can be written as

$$\underbrace{\frac{d}{dt}a(t)}_{\text{rate of change of } [A] \text{ at time } t} = \underbrace{k_-b(t)}_{\text{rate of production}} - \underbrace{k_+a(t)}_{\text{rate of consumption}} \quad (2.8)$$

Likewise

$$\underbrace{\frac{d}{dt}b(t)}_{\text{rate of change of [B] at time } t} = \underbrace{k_+a(t)}_{\text{rate of production}} - \underbrace{k_-b(t)}_{\text{rate of consumption}} \quad (2.9)$$

To begin our analysis, consider the steady-state condition, in which the rates of change of both $[A]$ and $[B]$ are zero. (This does not mean that both reactions have zero rates, but rather that the *net* flux between A and B is zero.) A steady state concentration profile $[A] = a^{ss}$, $[B] = b^{ss}$ must satisfy

$$\begin{aligned} 0 &= k_-b^{ss} - k_+a^{ss} \\ 0 &= k_+a^{ss} - k_-b^{ss}. \end{aligned}$$

Solving these equations (they are equivalent) we find

$$\frac{b^{ss}}{a^{ss}} = \frac{k_+}{k_-}. \quad (2.10)$$

The number $K_{eq} = \frac{k_+}{k_-}$ is called the *equilibrium constant* for the reaction. It is the ratio of the concentrations of the two reactants at steady state ($[B]/[A]$).

The concentrations can be derived by writing (from the conservation),

$$b(t) = T - a(t) \quad (2.11)$$

where $T = a(0) + b(0) = A_0 + B_0$ is the total concentration. Equation (2.8) can then be re-written as:

$$\begin{aligned} \frac{d}{dt}a(t) &= k_-b(t) - k_+a(t) \\ &= k_-(T - a(t)) - k_+a(t) \\ &= k_-T - (k_+ + k_-)a(t). \end{aligned} \quad (2.12)$$

The steady-state concentration satisfies

$$0 = k_-T - (k_+ + k_-)a^{ss}.$$

Solving gives

$$a^{ss} = \frac{k_-T}{k_+ + k_-} \quad \text{and so} \quad b^{ss} = \frac{k_+}{k_-}a^{ss} = \frac{k_+T}{k_+ + k_-}. \quad (2.13)$$

This system relaxes exponentially to its steady state. We can verify this by solving the differential equations (2.8-2.9) to yield (Exercise 2.1.6):

$$a(t) = De^{-(k_+ + k_-)t} + \frac{k_-T}{k_+ + k_-}, \quad (2.14)$$

for constant D .

The time constant for this reversible reaction, $\tau = \frac{1}{k_+ + k_-}$, involves two rate constants, in contrast with Example II (in which decay and production were uncoupled).

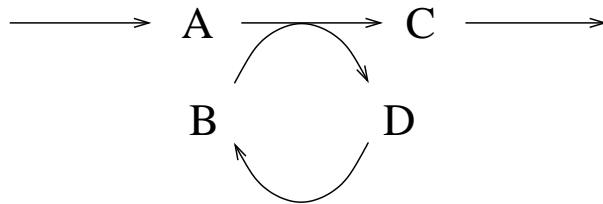


Figure 2.6: Open reaction network for Exercise 2.1.7.

Exercise 2.1.6 a) Verify that the solution (2.14) can be derived from equation (2.12) following the procedure outlined in Exercise 2.1.4.

b) Verify that the constant D in solution (2.14) is given by $D = A_0 - \frac{k_- T}{k_+ + k_-}$, where $A_0 = a(0)$, so we can write

$$a(t) = \left(A_0 - \frac{k_- T}{k_+ + k_-} \right) e^{-(k_+ + k_-)t} + \frac{k_- T}{k_+ + k_-}. \quad (2.15)$$

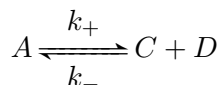
□

A remark on conservations. In Examples III and IV the total concentration of A and B was conserved throughout the reaction dynamics. This is a conservation of concentration (equivalently, of molecule count); it may or may not reflect a conservation of mass. The term **moiety** is used to describe a group of atoms that form part of a molecule, and so chemical conservation is often referred to as *moiety conservation*. More generally, chemical conservations are referred to as *structural conservations*.

Exercise 2.1.7 Identify the moiety conservation in the open system in Figure 2.6.

□

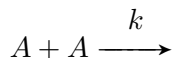
Exercise 2.1.8 The system



satisfies the structural conservation that the *difference* between the concentrations of C and D is constant for all time. Explain why.

□

Exercise 2.1.9 The examples in this section may have given the reader the mistaken impression that all chemical systems relax exponentially to steady state. As an example of non-exponential dynamics, consider the bimolecular decay reaction:



The rate of the reaction is $k[A]^2$. The differential equation model is

$$\frac{d}{dt}a(t) = -2k(a(t))^2.$$

(The stoichiometric factor 2 appears because each reaction event consumes two molecules of A .) Verify, by substituting into both sides of the differential equation, that

$$a(t) = \frac{1}{2kt + \frac{1}{A_0}}$$

is the solution of the differential equation that satisfies the initial condition $a(0) = A_0$. □

2.1.4 Numerical simulation of differential equations

The exponential relaxation exhibited by the examples in the previous section is characteristic of *linear* systems. Nonlinear models exhibit a wide range of behaviours, and do not typically admit explicit solutions such as the concentration formulas derived above. Differential equation models of biochemical and genetic systems are invariably nonlinear. We will resort to **numerical simulation** to investigate the behaviour of these system.

Constructing Simulations

We will use computational software packages to simulate differential equation models. In this section, we give a brief introduction to the algorithms used by that software.

Numerical simulations do not generate continuous curves. They produce approximate values of the solution at a specified collection of time-points (analogous to an experimental time-series). The first step in constructing a numerical simulation is to select this mesh of time-points. The solution will be constructed by stepping from one time-point to the next using an update formula. The simplest procedure for generating solutions in this manner is *Euler's method*, which is based on the following approximation. Given a differential equation of the form

$$\frac{d}{dt}a(t) = f(a(t)),$$

the derivative $\frac{d}{dt}a(t)$ can be approximated by a difference quotient:

$$\frac{d}{dt}a(t) \approx \frac{a(t+h) - a(t)}{h}, \quad \text{for } h \text{ small.}$$

(Recall, the derivative is *defined* as the limit of this quotient as h shrinks to zero.) Substituting this approximation into the differential equation gives

$$\frac{a(t+h) - a(t)}{h} \approx f(a(t)).$$

Treating this as an equality yields an update formula that can be used to determine the (approximate) value of $a(t+h)$ given the value $a(t)$:

$$a(t+h) = a(t) + hf(a(t)). \tag{2.16}$$

Euler's method consists of applying this update formula repeatedly.

To implement Euler's method, we choose a step-size h . This yields a mesh of time-points $t = 0, h, 2h, 3h, \dots, nh$, for some fixed number of steps n . Given the initial value of $a(0)$, we

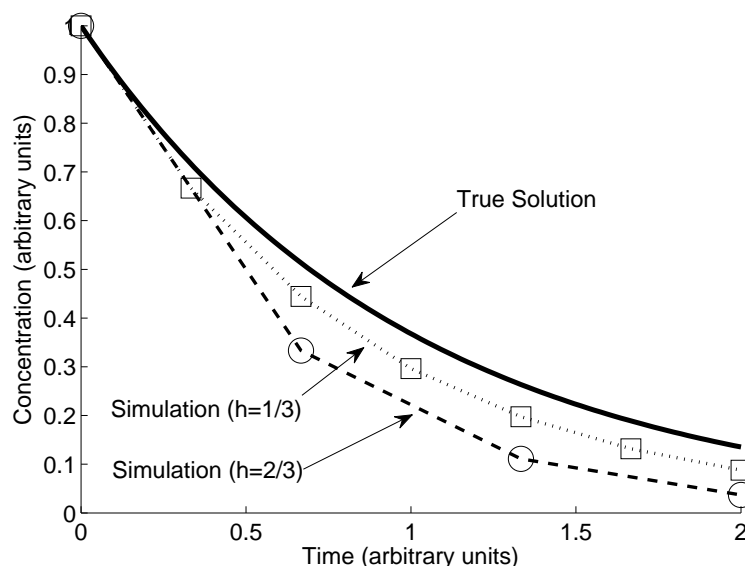


Figure 2.7: Numerical simulation of the model $\frac{d}{dt}a(t) = -a(t)$. The initial condition is $a(0) = 1$. For $h = 2/3$, the algorithm provides approximations of $a(2/3)$, $a(4/3)$ and $a(2)$ (open circles). The points are connected by straight lines for illustration. For $h = 1/3$, twice as many points are calculated (open squares), giving an improved approximation of the true solution.

then use formula (2.16) to approximate the value of $a(h)$. Repeated application of (2.16) provides approximate values at the other points on the grid:

$$\begin{aligned}
 a(0) &= a(0) && \text{(given)} \\
 a(h) &= a(0) + hf(a(0)) \\
 a(2h) &= a(h) + hf(a(h)) \\
 a(3h) &= a(2h) + hf(a(2h)) \\
 &\vdots \\
 a(nh) &= a((n-1)h) + hf(a((n-1)h))
 \end{aligned}$$

Because a computer can carry out these repeated calculations rapidly, the step-size h is often chosen so small that the set of points generated by this algorithm appears as a continuous curve. Figure 2.7 illustrates a case where the step-size was deliberately chosen to be large so that the discrete steps in the simulation are identifiable. The figure shows simulations generated for two different step-sizes. The simulation is more accurate—closer to the true solution—when the step-size h is chosen to be smaller (at the cost of more iterations to cover the same time interval).

Computational software packages that implement numerical simulation make use of sophisticated algorithms that improve on Euler's method. These details are hidden from the user, who simply passes the model to the simulation function and receives the output data. Appendix C introduces numerical simulation in the computational software packages MATLAB and XPPAUT.[‡]

[‡]MATLAB: www.mathworks.com/products/matlab, XPPAUT: www.math.pitt.edu/~bard/xpp/xpp.html.

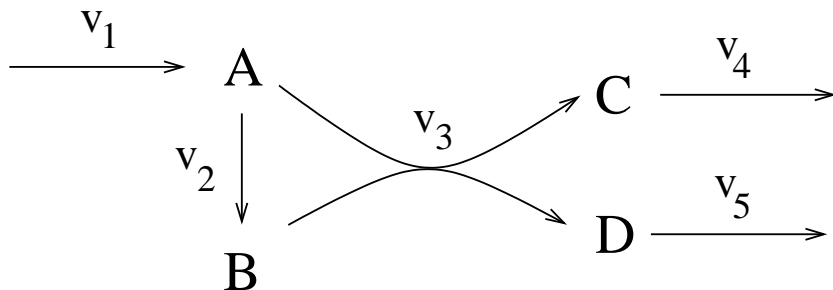


Figure 2.8: Open reaction network. The reaction rates are labelled v_i as indicated. (The v_i are not mass action rate constants.)

Numerical simulations of differential equation models are not as useful as analytic solution formulas, for two reasons. Firstly, an analytic formula is valid for all initial conditions. In contrast, each numerical simulation must be generated from a particular initial condition. Secondly, the dependence on the model parameters can be easily discovered from an analytic solution formula (e.g. the time constants discussed above). No such insights are granted by the numerical simulation, in which the parameter values must be fixed. (Computational exploration of different parameter values demands running multiple simulations.)

Nevertheless, in what follows we will rarely encounter differential equation models for which analytic solutions can be derived, and so numerical simulation will be an invaluable tool for model investigation.

Network example

To illustrate simulations of reaction network models, consider the reaction scheme in Figure 2.8. The rate of each reaction is labelled v_i . (Reaction rates are commonly referred to as *velocities*.) We will follow the convention of using v_i to label reaction rates in network graphs.

Suppose the reaction rates are given by mass action, as follows:

$$v_1 = k_1 \quad v_2 = k_2[A] \quad v_3 = k_3[A][B] \quad v_4 = k_4[C] \quad v_5 = k_5[D].$$

Let a , b , c , and d denote the concentrations of the corresponding species. Taking rate constants of $k_1 = 3$ mM/sec, $k_2 = 2$ /sec, $k_3 = 2.5$ /mM/sec, $k_4 = 3$ /sec and $k_5 = 4$ /sec, the species concentrations satisfy the following set of differential equations, expressed in mM/sec:

$$\begin{aligned} \frac{d}{dt}a(t) &= 3 - 2a(t) - 2.5a(t)b(t) \\ \frac{d}{dt}b(t) &= 2a(t) - 2.5a(t)b(t) \\ \frac{d}{dt}c(t) &= 2.5a(t)b(t) - 3c(t) \\ \frac{d}{dt}d(t) &= 2.5a(t)b(t) - 4d(t). \end{aligned} \tag{2.17}$$

Note, because rate v_3 depends on the product $a(t)b(t)$, this system of equations is nonlinear. Once an initial concentration profile has been specified, numerical simulation can be used to generate the resulting concentration time-courses. One such *in silico* experiment is shown in Figure 2.9. In

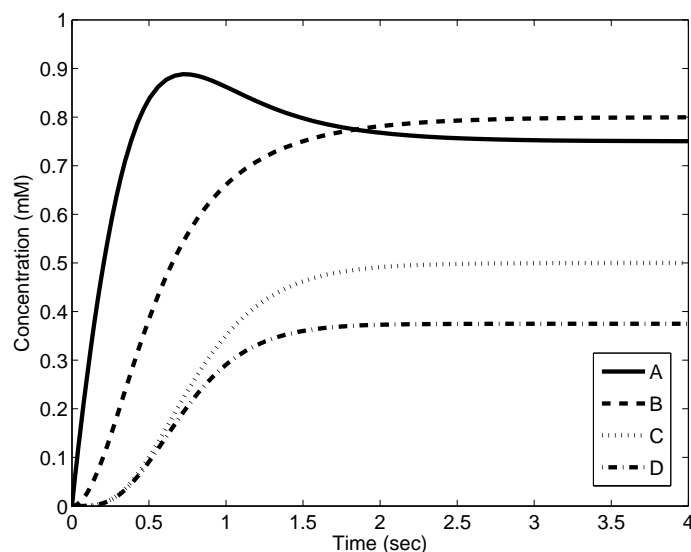


Figure 2.9: Numerical simulation of the network in Figure 2.8. All species start with initial concentration of zero at time $t = 0$.

this case the initial concentrations of all species were zero. The curves show the concentrations growing as the species pools ‘fill up’ to their steady-state values. The concentration of A overshoots its steady state because the formation of C and D proceeds slowly until a pool of B has accumulated.

Exercise 2.1.10 Determine the steady-state concentrations for the species in model (2.17). \square

2.2 Separation of Time-Scales and Model Reduction

When constructing a dynamic model, one must decide which time-scale to address. This choice is typically dictated by the time-scale of the relevant reactions and processes. For the simple examples considered above, the time-scales (time constants) could be deduced from the reaction system. For nonlinear processes, characteristic time-scales are not so neatly defined.

Biological processes take place over a wide range of time-scales. Consider, for example, a genetic network that generates a circadian rhythm. (Such networks will be taken up in Section 7.3.2.) A model of this network will describe oscillatory behaviour with a period of roughly 24 hours, and so will incorporate processes acting on the time-scale of hours. However, the network is based on gene expression, which involves the binding of proteins to DNA—these chemical processes happen on the scale of seconds. Moreover, the circadian oscillator is entrained to seasonal changes in the light-dark cycle—changes that occur on the order of months. It would not be possible to resolve all of these time-scales in a single model.

The same issue is faced in plotting the time-trace of a process that varies on multiple time scales. Consider Figure 2.10, which shows behaviour on three distinct time-scales. On the short time scale, a fast rise occurs. This leads to the steady oscillatory behaviour that dominates the middle time scale. On the long time scale, a slower process leads to a decreasing trend. If the differences in

time-scales were more extreme, a graph that focuses on the middle time scale would not reflect the other two: the fast behaviour would not be properly resolved, and the slow behaviour would not be captured.

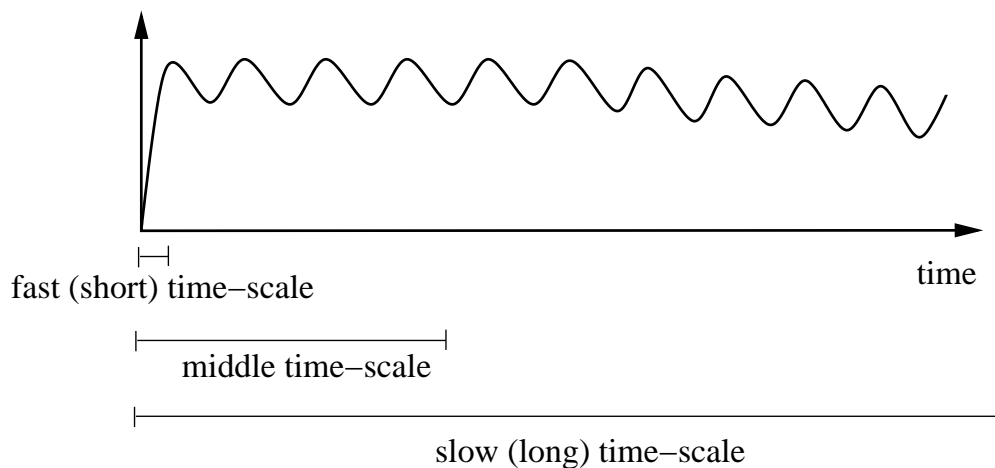


Figure 2.10: Behaviour on multiple time-scales. On the fast time scale, the process shows a rapid rise. This leads to an oscillatory behaviour on a middle time scale. The height of the oscillations declines slowly over a longer time-scale.

To model a system that involves processes acting on different time-scales, a primary time-scale must be chosen. Other time-scales are then treated as follows:

- processes occurring on slower time-scales are approximated as frozen in time;
- processes occurring on faster time-scales are presumed to occur instantaneously.

In most cases, these time-scale separations are made during model construction; they often motivate the decisions as to which species and processes should be included in the model and which will be neglected. In other cases, existing models that incorporate distinct time-scales can be simplified. This **model reduction** process approximates the original model by a model of reduced complexity.

Recall that for each of the closed reaction systems analysed in the previous section, we used conservation to replace the differential equation for the concentration of B (i.e. the equation for $\frac{d}{dt}b(t)$) with a much simpler algebraic description ($b(t) = T - a(t)$). We thus *reduced* a model involving two differential equations to a model involving one differential equation and one algebraic equation.

Model reduction by time-scale separation leads to a similar result—a differential equation describing a state variable is replaced by an algebraic equation. However, while reduction via conservation does not change the model, time-scale separation leads to an approximate version of the original model. Consequently, model reduction by time-scale separation should only be carried out in cases where the approximation will be accurate. A useful rule of thumb is that a difference in time scales of at least an order of magnitude (i.e. at least a factor of ten) can be used for model reduction.

We next present techniques for model reduction by separation of time-scales. Elimination of slow variables is straightforward—we simply assign a constant value to each slow variable and treat

it as fixed parameter, rather than as a state variable. The treatment of fast variables requires more care. We will consider two approaches that allow processes to be treated as instantaneous: the *rapid equilibrium assumption* and the *quasi-steady state assumption*.

2.2.1 Separation of time-scales: the rapid equilibrium assumption

Consider the open network



With mass action rate constants as indicated, the concentrations $a(t)$ and $b(t)$ satisfy

$$\begin{aligned} \frac{d}{dt}a(t) &= -k_1a(t) + k_{-1}b(t) \\ \frac{d}{dt}b(t) &= k_1a(t) - k_{-1}b(t) - k_2b(t). \end{aligned} \quad (2.19)$$

There are two processes acting here: the reversible conversion $A \leftrightarrow B$ and the decay $B \rightarrow \cdot$. As derived in Section 2.1.3, the time constants of these two processes are $\frac{1}{k_1+k_{-1}}$ and $\frac{1}{k_2}$, respectively. If the conversion has a much smaller time constant than the decay (that is, $k_1 + k_{-1} \gg k_2$), then the conversion reaches equilibrium quickly, compared to the time-scale of the decay process. This case is illustrated by Figure 2.11, in which the separation of time-scales reveals itself in the concentration time-courses. On a short time-scale, A and B molecules interconvert until they quickly reach an equilibrium ratio; little decay occurs over this time-period. On the longer time-scale, the equilibrated pool of A and B molecules slowly decays.

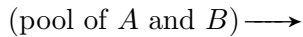
Once the equilibrium ratio of A and B is reached, this ratio is maintained throughout the decay process. This observation suggests a strategy for model reduction: if we choose to neglect the fast time-scale, we can make use of the fact that the equilibrium is maintained to relate the two concentrations. This is the **rapid equilibrium assumption**. By assuming that the conversion reaction is in equilibrium at all times, we simplify our dynamic description of the network because one concentration is now easily described in terms of the other, via the equilibrium condition. To emphasize that the model reduction leads to an approximate model that is different from the original, we introduce the notation $\tilde{a}(t)$ and $\tilde{b}(t)$ for the concentrations in the reduced model. For network (2.18), the equilibrium condition states that

$$\frac{\tilde{b}(t)}{\tilde{a}(t)} = \frac{k_1}{k_{-1}},$$

from which we have

$$\tilde{b}(t) = \tilde{a}(t) \frac{k_1}{k_{-1}}.$$

With this condition in hand, we now turn to the dynamics of the decay process, which is best described by addressing the dynamics of the equilibrated pool. The reaction network (2.18) thus reduces to:



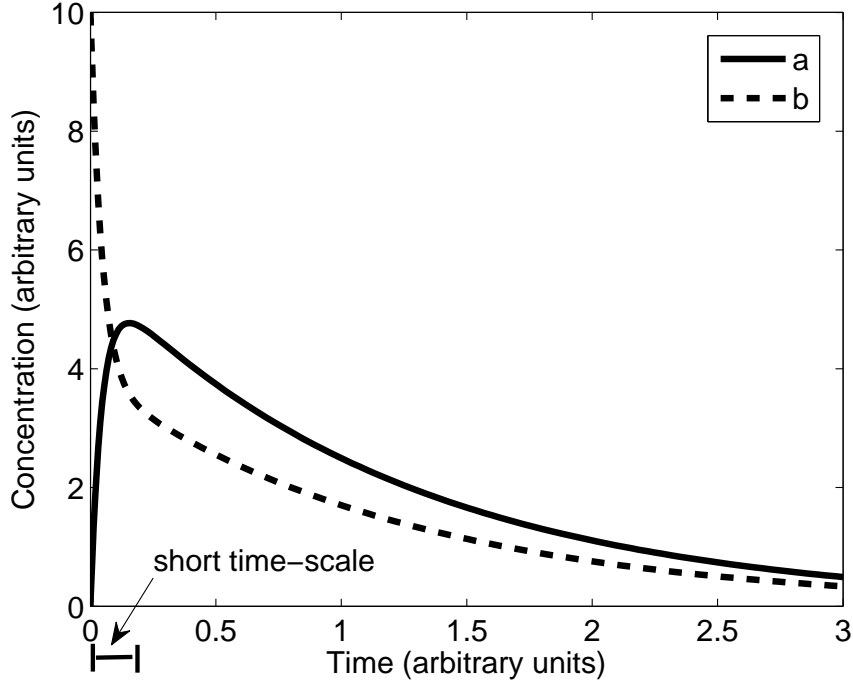


Figure 2.11: Simulation of network (2.18) with parameter values (in time^{-1}) $k_1 = 9$, $k_{-1} = 12$, and $k_2 = 2$. The time constant for the conversion is $1/21$; the decay process has a time constant of $1/2$. On the short time-scale, the conversion comes rapidly to equilibrium (in which $[B]/[A] \approx 3/4$). On the longer time-scale, the equilibrated pool of A and B molecules decays. The initial conditions are $a(0) = 0$, $b(0) = 10$.

Let $\tilde{c}(t)$ be the total concentration in the pool of A and B (that is, $\tilde{c}(t) = \tilde{a}(t) + \tilde{b}(t)$). The relative fractions of A and B in the pool are fixed by the equilibrium ratio. This allows us to write

$$\begin{aligned}\tilde{c}(t) &= \tilde{a}(t) + \tilde{b}(t) \\ &= \tilde{a}(t) + \tilde{a}(t) \frac{k_1}{k_{-1}} \\ &= \frac{k_{-1} + k_1}{k_{-1}} \tilde{a}(t).\end{aligned}$$

Thus

$$\tilde{a}(t) = \frac{k_{-1}}{k_{-1} + k_1} \tilde{c}(t) \quad (2.20)$$

while

$$\tilde{b}(t) = \tilde{c}(t) - \tilde{a}(t) = \frac{k_1}{k_{-1} + k_1} \tilde{c}(t). \quad (2.21)$$

The pool decays at rate $k_2 \tilde{b}(t)$. Thus, the pooled concentration satisfies

$$\begin{aligned}\frac{d}{dt} \tilde{c}(t) &= -k_2 \tilde{b}(t) \\ &= -k_2 \frac{k_1}{k_{-1} + k_1} \tilde{c}(t)\end{aligned} \quad (2.22)$$

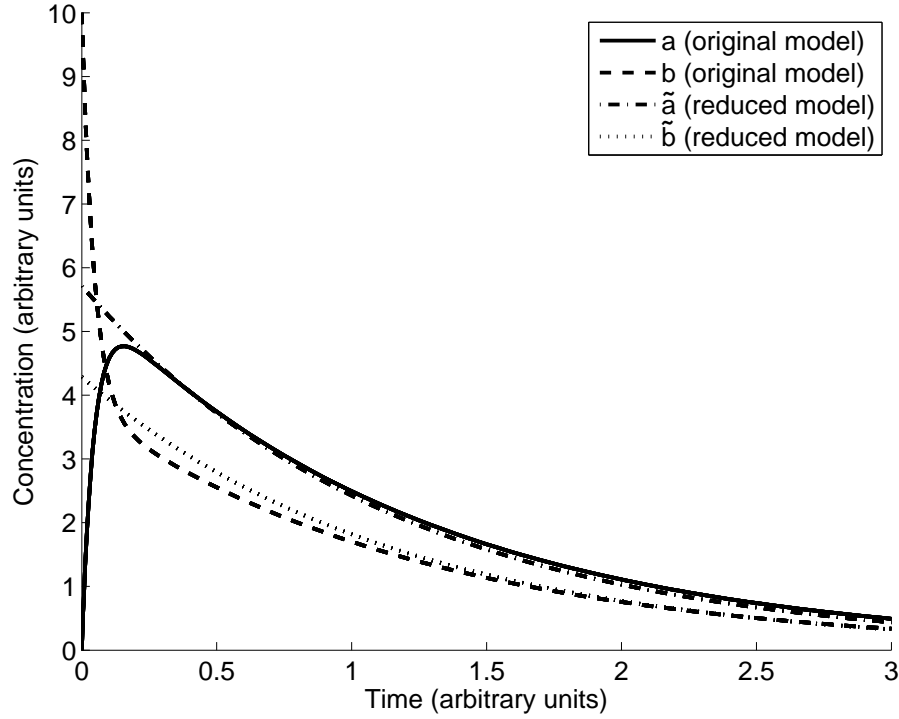
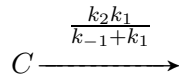


Figure 2.12: Rapid equilibrium approximation for network (2.18). The original model (2.19) was simulated with parameter values (in time^{-1}) $k_1 = 9$, $k_{-1} = 12$ and $k_2 = 2$ (as in Figure 2.11). The approximate model (2.22) was simulated from initial value $\tilde{c}(0) = a(0) + b(0)$; the corresponding approximate concentrations $\tilde{a}(t)$ and $\tilde{b}(t)$ were calculated from equations (2.20) and (2.21). Initial conditions are $a(0) = 0$, $b(0) = 10$ for the original model.

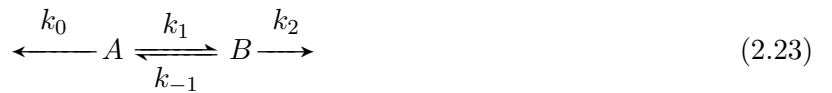
Schematically, we have reduced the model to a single decay reaction:



which is the **rapid equilibrium approximation** of the original model. To predict the concentration time-courses, we simulate the dynamics of the pooled concentration $\tilde{c}(t)$ in equation (2.22) and then use equations (2.20) and (2.21) to determine the corresponding concentrations $\tilde{a}(t)$ and $\tilde{b}(t)$ at each time point.

Figure 2.12 shows the behaviour of the reduced model in comparison with the original model. Except for the initial fast dynamics, the reduced model provides a good approximation.

Exercise 2.2.1 Use the rapid equilibrium approximation to construct a reduced model for the network

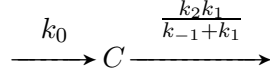


under the conditions that $k_1 + k_{-1} \gg k_2$ and $k_1 + k_{-1} \gg k_0$. \square

To further explore the rapid equilibrium approximation, consider the network



This network is similar to (2.18). The zero-order reaction ($\rightarrow A$) does not affect the time-scale on which the concentrations of A and B relax to their steady-state values, so, as in the previous case, a rapid equilibrium assumption is valid if $k_1 + k_{-1} \gg k_2$. In that case, the pool concentration $\tilde{c}(t) = \tilde{a}(t) + \tilde{b}(t)$ can be used to describe a reduced network



with dynamics

$$\frac{d}{dt}\tilde{c}(t) = k_0 - \frac{k_2 k_1}{k_{-1} + k_1}\tilde{c}(t) \quad (2.25)$$

This approximation is illustrated in Figure 2.13. The approximation is good, but exhibits a persistent error in the concentration of A . This is a consequence of the fact that the original model comes to a dynamic steady state in which the conversion reaction ($A \leftrightarrow B$) is not in equilibrium.

In the next section, we will consider a model-reduction method that is guaranteed to be accurate at steady state.

Exercise 2.2.2 Develop a model for network (2.24) and determine the steady-state concentrations. Compare the steady state ratio $[B]/[A]$ to the equilibrium constant for the conversion reaction (which was used for model reduction). Verify that the steady-state concentration ratio is not equal to the equilibrium constant k_{-1}/k_1 , but the difference is small when k_{-1} is much larger than k_2 . \square

Exercise 2.2.3 The accuracy of the rapid equilibrium approximation improves as the separation of time-scales becomes more significant. Derive a formula for the steady state concentration of A in both model (2.25) and the full model for network (2.24). Consider the relative steady-state error, defined as

$$\left| \frac{[A]_{\text{full}}^{ss} - [A]_{\text{reduced}}^{ss}}{[A]_{\text{full}}^{ss}} \right|$$

Verify that the relative steady-state error in $[A]$ is small when k_{-1} is much larger than k_2 . \square

2.2.2 Separation of time-scales: the quasi-steady-state assumption

The rapid equilibrium approximation is reached by treating individual *reaction processes* as instantaneous. We now consider an alternative model-reduction method that focuses on individual *species*. Consider again the network



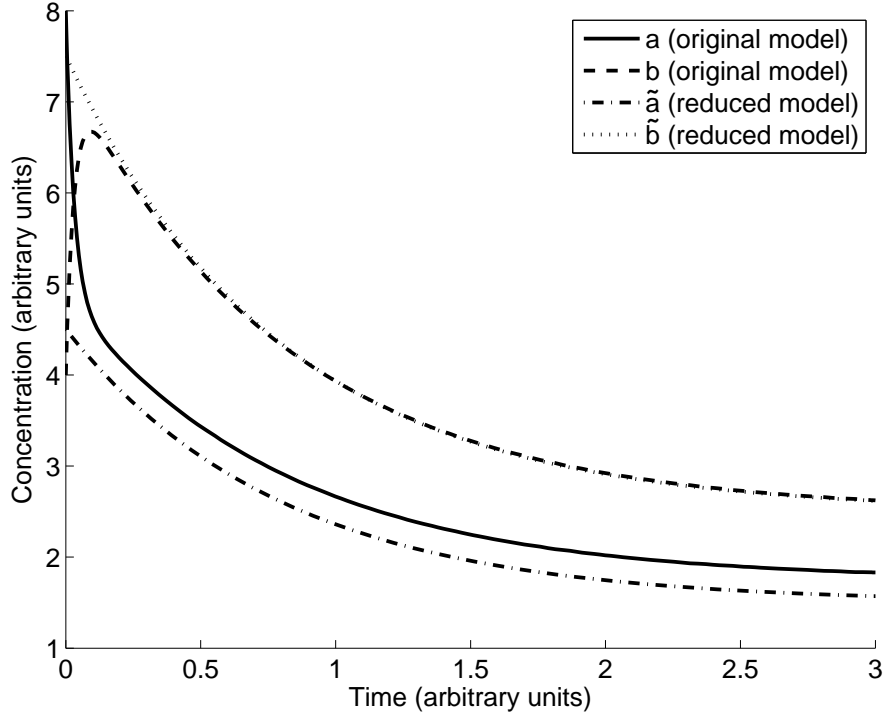


Figure 2.13: Rapid equilibrium approximation for network (2.24). Model (2.25) is used to approximate the full model for network (2.24). Parameter values (in time^{-1}) are $k_0 = 5$, $k_1 = 20$, $k_{-1} = 12$, and $k_2 = 2$. There is a persistent error in the approximation for $[A]$, caused by the fact that the conversion reaction does not settle to equilibrium in steady state. Initial conditions are $a(0) = 8$, $b(0) = 4$ (and so $\tilde{c}(0) = 12$).

and again suppose $k_1 + k_{-1} \gg k_2$. Instead of focusing on the conversion reaction, we observe that all dynamic reactions involving species A occur on the fast time-scale, so that, compared to the dynamics of B , species A comes rapidly to its steady-state concentration.

Following this idea, we replace our original differential equation-based description of the behaviour of $[A]$ (that is, $\frac{d}{dt}a(t) = k_0 + k_{-1}b(t) - k_1a(t)$) with an algebraic description indicating that concentration $a(t)$ is in steady state *with respect to the other variables* in the model (in this case, $b(t)$). We introduce a *quasi-steady state* for $[A]$ in our approximate model: $\tilde{a}(t) = a^{qss}(t)$, and specify that a^{qss} ‘keeps up’ with the transitions in any slower variables. For each time instant t , the quasi-steady state $a^{qss}(t)$ satisfies

$$0 = k_0 + k_{-1}b(t) - k_1a^{qss}(t)$$

or equivalently

$$a^{qss}(t) = \frac{k_0 + k_{-1}b(t)}{k_1}. \quad (2.27)$$

This procedure is sometimes summarized as “set $\frac{d}{dt}a^{qss}(t)$ to zero”. However, this is a problematic statement because it suggests that we are setting $a^{qss}(t)$ to a constant value, which is not the case.

Instead, we are replacing the differential description of $a(t)$ with an algebraic description that says $[A]$ instantaneously reaches the steady state it would attain if all other variables were constant. Because it equilibrates rapidly, the other variables are essentially constant ‘from A ’s point of view,’ i.e. on its fast time-scale. (A mathematically rigorous treatment of this procedure consists of a *singular perturbation* of the original model. A careful treatment of this technique provides explicit bounds on the error made in the approximation. See (Segel and Slemrod, 1989) for details.)

The reduced model, called the **quasi-steady-state approximation** (QSSA), follows by replacing $a(t)$ with $a^{qss}(t)$ in the original model. Again, using the alternative notation \tilde{b} for the reduced model:

$$\begin{aligned}\frac{d}{dt}\tilde{b}(t) &= k_1 a^{qss}(t) - (k_{-1} + k_2)\tilde{b}(t) \\ &= k_1 \frac{k_0 + k_{-1}\tilde{b}(t)}{k_1} - (k_{-1} + k_2)\tilde{b}(t) \\ &= k_0 + k_{-1}\tilde{b}(t) - (k_{-1} + k_2)\tilde{b}(t) \\ &= k_0 - k_2\tilde{b}(t)\end{aligned}\tag{2.28}$$

The quasi-steady state approximation is illustrated in Figure 2.14. A significant error occurs during the transient, but diminishes as the steady state is approached (in contrast with the rapid equilibrium approximation in Figure 2.13). This is a general feature of the QSSA: when the system is at steady state, the quasi-steady-state description $a^{qss}(t)$ is equal to the true value of $a(t)$ (because the quasi-steady-state condition is satisfied).

In the subsequent chapters, we will use both the rapid equilibrium and the quasi-steady-state approximations for model reduction. The rapid equilibrium approximation can be easier to apply, because it addresses individual reaction processes; the quasi-steady-state approximation is sometimes more difficult to justify, because it typically involves multiple processes. However, the QSSA is simpler to implement mathematically, and leads to better approximations over long times; for those reasons, it is often favored over the rapid equilibrium approximation.

Exercise 2.2.4 In applying the reduced model (2.28) to approximate the behaviour of network (2.26), the initial condition must be chosen carefully. Suppose a simulation involves initial concentrations $a(0)$ and $b(0)$. The reduced model cannot retain the same initial concentration of B (i.e. $\tilde{b}(0) = b(0)$), because, together with the corresponding quasi-steady state for A (i.e. $\tilde{a}(0) = \frac{k_0 + k_{-1}\tilde{b}(0)}{k_1}$), the total initial concentration would not be in agreement with the original simulation. An improved approach maintains the total concentration ($\tilde{a}(0) + \tilde{b}(0) = a(0) + b(0)$), while respecting the concentration *ratio* dictated by the quasi-steady-state condition.

Given initial conditions $a(0)$ and $b(0)$, determine an appropriate initial condition $\tilde{b}(0)$ in the reduced model (2.28). You can check your answer by confirming the initial condition $\tilde{b}(0)$ used in Figure 2.14.

□

Exercise 2.2.5 Consider a model for network (2.23). Suppose that $k_0 \gg k_2$ and $k_1 + k_{-1} \gg k_2$. Apply an appropriate quasi-steady-state approximation to reduce the model by eliminating one of the differential equations.

□

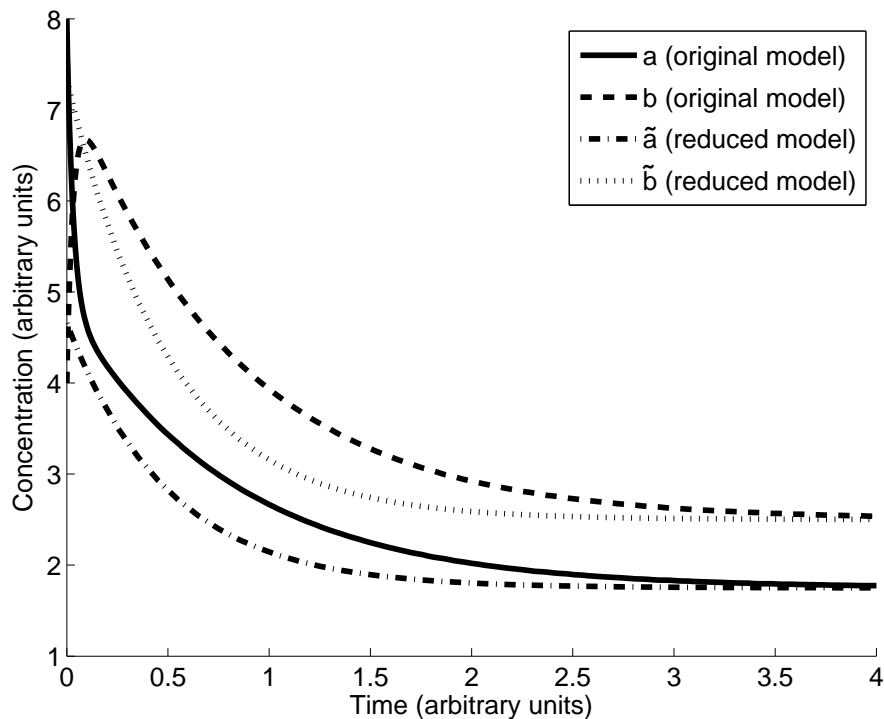


Figure 2.14: Quasi-steady-state approximation. Network (2.26) is approximated by model (2.28) and equation (2.27). Parameter values are (in time^{-1}) $k_0 = 5$, $k_1 = 20$, $k_{-1} = 12$, and $k_2 = 2$ (as in Figure 2.13). The approximation exhibits an error over the transient, but converges to the original model in steady state. Initial conditions are $a(0) = 8$, $b(0) = 4$, and $\tilde{b}(0) = 235/32$ (see Exercise 2.2.4).

2.3 Suggestions for Further Reading

- **Calculus:** There are many introductory texts covering differential calculus, some of which focus specifically on life science applications. The book *Modeling the Dynamics of Life: Calculus and Probability for Life Scientists* (Adler, 2004) is especially well-suited to the study of dynamic biological models.
- **Differential Equations:** A general introduction to differential equations, including treatment of numerical simulation, can be found in *Elementary Differential Equations and Boundary Value Problems* (Boyce and DiPrima, 2008). An introduction to the theory in the context of biological applications is presented in *Differential Equations and Mathematical Biology* (Jones *et al.*, 2009).
- **Chemical Reaction Network Theory:** There is a rich literature on the dynamic behaviour of chemical reaction networks. An introduction is provided by *Mathematical Models of Chemical Reactions: Theory and Applications of Deterministic and Stochastic Models* (Erdi and Tóth, 1989).

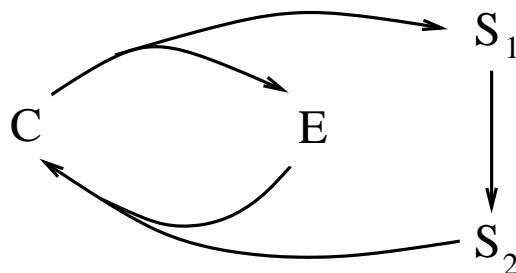
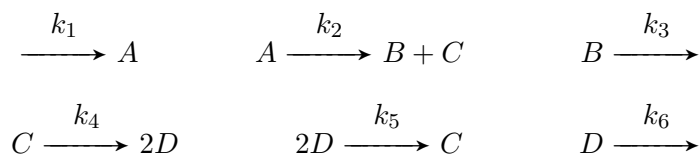


Figure 2.15: Closed reaction network for Problem 2.4.3.

2.4 Problem Set

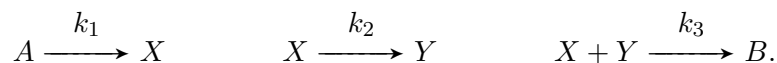
2.4.1 Open reaction network. Suppose a reaction network is composed of the following reactions



with mass-action rate constants as indicated.

- Construct a differential equation model of the network.
- Determine the steady-state concentrations of all species as functions of the mass-action constants.

2.4.2 Open reaction network: buffered species. Consider the reaction network:



where the concentrations of A and B are buffered (i.e. $[A]$ and $[B]$ are fixed model parameters).

- Construct a differential equation model for the dynamics of $[X]$ and $[Y]$. (The rate of the first reaction is constant: $k_1[A]$.)
- Determine the steady-state concentrations of X and Y as functions of $[A]$ and the rate constants. Verify that the steady-state concentration of Y is independent of $[A]$. Can you explain this independence intuitively?

2.4.3 Moiety Conservations. Consider the reaction scheme in Figure 2.15.

- Identify two moiety conservations in the network.
- Consider an experiment in which the initial concentrations are (in mM) $s_1(0) = 3.5$, $s_2(0) = 1$, $e(0) = 3$ and $c(0) = 0$. Suppose that the steady-state concentrations of S_1 and S_2 have been measured as $s_1^{ss} = 2$ mM and $s_2^{ss} = 1.5$ mM. Determine the steady-state concentrations of E and C . (Note: there is no need to consider the reaction rates or network dynamics. The conclusion follows directly from the moiety conservations.)

2.4.4 Steady-state production rate. Consider the reaction network



Suppose that the species S and P are held at fixed concentrations (i.e. $[S]$ and $[P]$ are fixed model parameters). Suppose that the reaction rates are given by mass action, with reaction rates as indicated. If the initial concentrations of $[A]$ and $[B]$ are both 1 mM, determine the rate of production of P at steady state (as a function of k_1 , k_2 , and $[S]$).

2.4.5 Linear system of differential equations. Consider the coupled system of differential equations

$$\frac{d}{dt}x(t) = x(t) + 2y(t) \qquad \frac{d}{dt}y(t) = x(t).$$

a) Verify that for any choice of constants c_1 and c_2 , the functions

$$x(t) = c_1 e^{-t} + 2c_2 e^{2t} \qquad y(t) = -c_1 e^{-t} + c_2 e^{2t}$$

are solutions to these equations. (This can be verified by differentiating $x(t)$ and $y(t)$ and comparing the two sides of the differential equations.)

b) The constants c_1 and c_2 in part (a) are determined by the initial conditions for x and y . Determine the values of c_1 and c_2 that correspond to the initial conditions $x(0) = 0$, $y(0) = 1$. What is the asymptotic (long-term) behaviour of the resulting solutions $x(t)$ and $y(t)$?

c) Find a set of (non-zero) initial conditions $x(0)$, $y(0)$ for which the solution $(x(t), y(t))$ converges to $(0, 0)$.

2.4.6 Numerical simulation. Use a software package (e.g. XPPAUT or MATLAB—introduced in Appendix C) to simulate solutions to the equation

$$\frac{d}{dt}c(t) = -c(t) + 1$$

with initial conditions $c(0) = 0$, $c(0) = 1$, and $c(0) = 3$. Repeat for the system

$$\frac{d}{dt}c(t) = 5(-c(t) + 1).$$

Explain the difference in behaviour between the two systems.

2.4.7 Network Modelling.

a) Consider the closed reaction network in Figure 2.16 with reaction rates v_i as indicated. Suppose that the reaction rates are given by mass action as $v_1 = k_1[A][B]$, $v_2 = k_2[D]$ and $v_3 = k_3[C]$.

i) Construct a differential equation model for the network. Use moiety conservations to reduce your model to three differential equations and three algebraic equations.

ii) Solve for the steady-state concentrations as functions of the rate constants and the initial concentrations. (Note, because the system is closed, some of the steady-state concentrations are zero.)

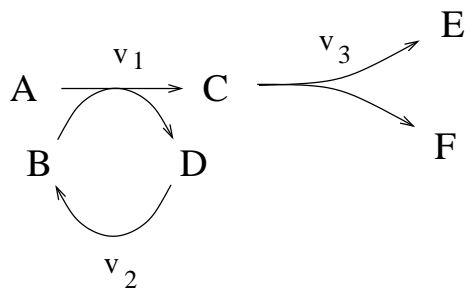


Figure 2.16: Closed reaction network for Problem 2.4.7(a).

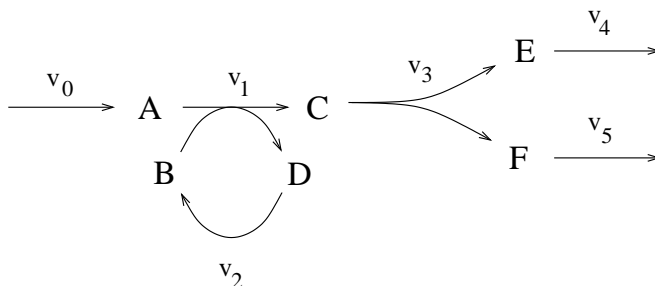


Figure 2.17: Open reaction network for Problem 2.4.7(b).

iii) Verify your result in part (ii) by running a simulation of the system from initial conditions (in mM) of $([A], [B], [C], [D], [E], [F]) = (1, 1, \frac{1}{2}, 0, 0, 0)$. Take rate constants $k_1 = 3/\text{mM}/\text{sec}$, $k_2 = 1/\text{sec}$, $k_3 = 4/\text{sec}$.

b) Next consider the open system in Figure 2.17 with reaction rates v_i as indicated. Suppose that the reaction rates are given by mass action as $v_0 = k_0$, $v_1 = k_1[A][B]$, $v_2 = k_2[D]$, $v_3 = k_3[C]$, $v_4 = k_4[E]$, and $v_5 = k_5[F]$.

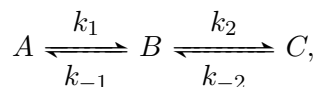
i) Construct a differential equation model for the network. Identify any moiety conservations in the network.

ii) Solve for the steady state as a function of the rate constants and the initial concentrations.

iii) Verify your result in (ii) by running a simulation of the system from initial conditions (in mM) of $([A], [B], [C], [D], [E], [F]) = (1, 1, \frac{1}{2}, 0, 0, 0)$. Take rate constants $k_0 = 0.5 \text{ mM}/\text{sec}$, $k_1 = 3/\text{mM}/\text{sec}$, $k_2 = 1/\text{sec}$, $k_3 = 4/\text{sec}$, $k_4 = 1/\text{sec}$, $k_5 = 5/\text{sec}$.

iv) Given the initial conditions and rate constants in part (iii), why would there be no steady state if we take $k_0 = 5 \text{ mM}/\text{sec}$?

2.4.8 Rapid equilibrium approximation. Consider the closed system:



with mass-action rate constants as shown. Suppose the rate constants are (in min^{-1}) $k_1 = 0.05$, $k_2 = 0.7$, $k_{-1} = 0.005$, and $k_{-2} = 0.4$.

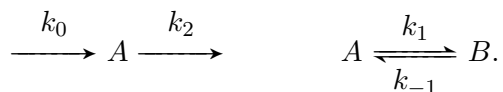
a) Construct a differential equation model of the system. Simulate your model with initial conditions (in mM) of $A(0) = 1.5$, $B(0) = 3$, $C(0) = 2$. Plot the transient and steady-state behaviour of the

system. You may need to make two plots to capture all of the dynamics (i.e. two different window sizes).

b) It should be clear from your simulation in part (a) that the system dynamics occur on two different time-scales. This is also apparent in the widely separated rate constants. Use a rapid equilibrium assumption to reduce your description of the system to two differential equations (describing one of the original species and one combined species pool) and two algebraic equations (describing the contents of the combined pool).

c) Run a simulation of your reduced model in part (b) to compare with the simulation in part (a). Verify that the simulation of the reduced system is in good agreement with the original, except for a short initial transient. (Note, you will have to select initial conditions for the reduced system so that the initial total concentration is in agreement with part (a), and the rapid equilibrium condition is satisfied at time $t = 0$.)

2.4.9 Quasi-steady-state approximation. Consider the reaction network:



Suppose the mass-action rate constants are (in min^{-1}) $k_0 = 1$, $k_1 = 11$, $k_{-1} = 8$, and $k_2 = 0.2$.

a) Construct a differential equation model of the system. Simulate your model with initial conditions $A(0) = 6 \text{ mM}$, $B(0) = 0 \text{ mM}$. Plot the transient and steady-state behaviour of the system. You may need to make two plots to capture all of the dynamics (i.e. two different window sizes).

b) It should be clear from your simulation in part (a) that the system dynamics occur on two different time-scales. This is also apparent in the widely separated rate constants. Use a quasi-steady-state assumption to reduce your description of the system by replacing a differential equation with an algebraic equation.

c) Run a simulation of your reduced model in part (b) to compare with the simulation in part (a). Verify that the simulation of the reduced system is a good approximation to the original at steady state, but not over the initial transient. (Note, you will have to select initial conditions for the reduced system so that the total concentration is in agreement with part (a), and the quasi-steady state condition is satisfied at time $t = 0$, as in Exercise 2.2.4.)