

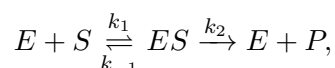
# Introduction to modelling biological systems using ordinary differential equations

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## Introduction

In biological systems certain types of proteins called enzymes act as catalysts for biochemical reactions. They facilitate reactions converting substrates into products while remaining basically unchanged once all stages of the reaction cycle are complete. Like all catalysts, enzymes work by lowering the activation energy for a reaction, thus dramatically increasing the rate of the reaction. Most enzyme reaction rates are millions of times faster than those of the uncatalyzed reactions.<sup>1</sup>

In a simple enzymatic reaction using only one substrate, the enzyme  $E$  attaches to the substrate  $S$ , and forms a complex  $ES$ . The complex formation can lead to a permanent change in the substrate so it is converted into a product  $P$  leaving the enzyme unchanged. We also assume that this step is irreversible. This can be expressed via the set of three reactions between four different species



where  $k_{-1}, k_{+1}, k_2$  represent the **rate constants of the reactions**. You should note that this is a much simplified model - there may be many steps in the arrow labelled  $k_2$ , for example. The questions we would like to address are

- **how can we model the rates of these reactions?;**
- **starting with some initial concentrations of enzyme,  $E$ , substrate,  $S$ , complex,  $ES$ , and product,  $P$ , how does the system evolve over time?**

We will eventually see how to formulate the problem as a **system of differential equations**.

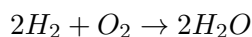
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<sup>1</sup>A good book on enzyme reactions is Enzyme Kinetics by Athel Cornish-Bowden (ISBN 3527330747).

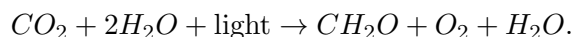
# 1 Reactions

## 1.1 Thinking in terms of reactions

A very useful way to think about modelling systems is in terms of **species** and **reactions**. We are all familiar with reactions such as the burning of hydrogen to make water

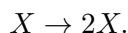


or the conversion of  $CO_2$  during photosynthesis



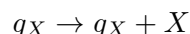
We will often be modelling chemical and biochemical reactions so the reaction formalism will obviously be applicable in these cases. However, the concept generalises much more widely to other systems including cell population and ecological systems. Therefore the techniques we will learn will apply to modelling many types of system in biology.

**Example 1: PCR amplicon** Here we have a piece of DNA (the amplicon) denoted by  $X$ . In the PCR reaction over one cycle the amplicon is replicated. For simplicity we can ignore the polymerase. In terms of reactions we can write this as



This system has one species,  $X$ , which we also refer to as a **state variable**.

**Example 2: Gene expression** Here we have a gene,  $gX$ , that produces protein  $X$ . For simplicity we will group transcription and translation together into one reaction



Note that in this system we have two state variables corresponding to  $gX$  and  $X$ .

**Example 3: Protein degradation** A protein  $X$  is broken down by a proteasome and therefore decays over time. We might model this in a number of ways. We can include the proteasome eg ClpXP in *E. coli*, denoted by  $C$

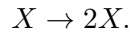


Or under some circumstances we could ignore  $C$  and write



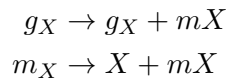
The  $\emptyset$  symbol indicates zero, which you can think of as  $X$  disappearing from the system. The differences in these kinds of modelling choices will be explored later on.

**Example 4: Bacterial growth** Here we have bacteria, the number of which we denote by  $X$ . We can imagine that every 20 minutes the bacteria double. In terms of reactions we can write this as



Note that this reaction is identical to Example 1. We will see later how this corresponds to exponential growth.

**Example 5: Transcription and translation** In Example 2 we modelled gene expression in a single reaction. Many biological processes involve multiple reactions. We can split gene expression up into transcription and translation. Here we have a gene,  $gX$ , that produces mRNA molecule  $mX$ , which is then translated into protein  $X$ .



Note that in this system we have three state variables corresponding to  $gX$ ,  $mX$  and  $X$ .

## 1.2 Modelling choices

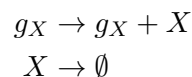
Note in the previous examples we had two different versions of reactions for gene expression. Note also that we haven't included DNA polymerase, ribosomes. In fact translation and transcription are themselves complex biochemical processes involving many different processes. We could easily add more reactions but would make the system more complex. These kinds of modelling choice depend on the task at hand, the purpose of the model and on the data available for comparison. We refer to different models of the same overall biological process as **abstractions**.

**Exercise 1:** Can you write down some reactions that model simple gene expression in a bacterial cell. Do this for two abstractions:

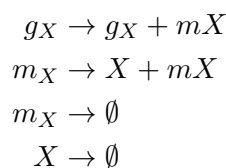
- Protein level only
- Protein and RNA level

Hint: in the first case there are two general processes: expression of the gene and decay of the protein

**Solution:** Protein level:



Protein and RNA level



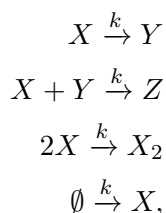
### 1.3 Reactions and rates

We have seen above how to write down reaction representations for a few different systems. Each reaction has a rate constant (say  $k$ ), that relates the concentration of the reactants to the rate of the reaction. Increasing the concentration of the reactants will increase the rate of the reaction according to  $k$ . Note:  $k$  can dependent on environmental factors, such as temperature and pressure in a chemical reaction

Before we go on to develop differential equations for these systems we must also specify how the rates of the reactions depends on the species involved. There is no hard and fast rule for assigning these and it is a modelling assumption (much like the reactions we choose to use to model a system). However, one extremely useful way to assign reaction rates in the absence of any other information is called the **law of mass action**. This arises out of chemical kinetics, but again, just as reactions can be thought of more generally, so too can this law.

#### Law of mass action: underlying assumptions

Here we are interested in modelling chemical reactions, such as



where the last reaction uses the notation  $\emptyset$  to denote  $X$  being produced from ‘thin air’. More specifically, we want to write down the **rates** of these reactions in terms of the concentrations of the reactants and products<sup>2</sup>.

To simplify things, we will assume that the reactions are taking place in **dynamic equilibrium**, which implies

- constant temperature, pressure and volume;
- the reactants and products are well mixed and there are no spatial gradients in concentration (homogeneous);
- the reactants and products are at sufficiently high concentrations such that lots of reactions are occurring per unit time.

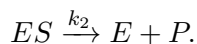
These are strong assumptions and worth bearing in mind. However as with many other modelling techniques, this approach can still provide very useful and accurate approximations even in cases where some of these assumptions are invalid.

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<sup>2</sup>Actually it turns out that the rate only depends on the concentrations of the reactants

### First order reactions

Let us consider first the reaction where the enzyme substrate-complex is converted into the enzyme plus the product



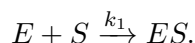
What is the rate of this reaction? We know that the reaction rate should have units of concentration per second ( $M/s = Ms^{-1}$ ). We will denote the concentration of enzyme-substrate complex as  $ES$ . We intuitively know that if  $ES$  increases we will have more of E and P produced. Thus the rate of the reaction must be proportional to  $ES$ . Mathematically we can write

$$R(ES \xrightarrow{k_2} E + P) = k_2 ES,$$

where  $k_2$ , known as the rate constant, is the constant of proportionality and  $R(.)$  is a shorthand for the rate of the reaction within the parentheses. In general the rate constant depends on the specific reaction taking place and measurements can be made to determine it. Note that here the units of  $k_2$  are  $s^{-1}$ .

### Second order reactions

Now let us consider the reaction



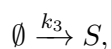
Again we can appeal to our intuition. We know that increasing/decreasing **either**  $E$  or  $S$  should increase/decrease the rate of the reaction. We can capture this mathematically as

$$R(E + S \xrightarrow{k_1} ES) = k_1 ES.$$

Again the rate constant  $k_1$  is the constant of proportionality but note that here its units are  $M^{-1}s^{-1}$ .

### Zero order reactions

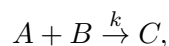
Although not included in the enzymatic system, we will also come across reactions of the type



which could correspond to pumping more substrate into the system (something that might be desirable in an industrial process). Here there are no reactants and the reaction rate is simply given by the constant  $k_3$ , which has units of  $Ms^{-1}$ .

### The law of mass action

Given a chemical reaction involving two reactants  $A$  and  $B$



the law of mass action states that the rate of the reaction  $r$  is given by

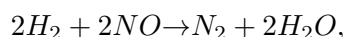
$$r = kAB,$$

where  $A$  and  $B$  denote the concentrations of the species  $A$  and  $B$  respectively, and  $k$  denotes the rate constant.

This law is *extremely* useful and allows us to construct systems of ordinary differential equations to describe the evolution of concentrations of species in a biochemical system. Note that because this law really refers to the probability of a reaction between  $A$  and  $B$  occurring it has much wider applicability to other areas of modelling such as ecology.

#### 1.4 A more complex example

We can write the reaction of hydrogen with nitric oxide to form water and nitrogen as follows



From the law of mass action we would assume that the reaction rate would be  $k[H_2]^2[NO]^2$ . However, when we measure the reaction rate we see that it is  $k[H_2][NO]^2$ . Notice that the observed rate is first order in  $H_2$  rather than the expected second order.

Our reaction model assumes that there is a single step in the reaction - hydrogen and nitric oxide reacting to form nitrogen and water. In fact, this reaction is composed of several elementary steps and our model is a simplification. Not all of these steps affect the rate of reaction; often the slowest step controls the reaction rate. For this example, a possible mechanism is



Because the second reaction is the slowest, it is the rate determining step

$$r = k_2[H_2][N_2O_2],$$

where  $k_2$  is the rate constant for the second step.

$N_2O_2$  is an intermediate which is in equilibrium, so that  $[N_2O_2] = K_1[NO]^2$ , where  $K_1$  is the equilibrium constant of the first step. Substitution into the previous equation leads to a rate in terms of the original reactants

$$r = k_2K_1[H_2][NO]^2,$$

This agrees with the form of the observed rate equation if it is assumed that  $k = k_2K_1$ . The second molecule of  $H_2$  does not appear in the rate equation because it reacts in the third step, which is a rapid step after the rate-determining step, so that it does not affect the overall reaction rate.