

# School of Mathematical Sciences

## MATHEMATICAL BIOLOGY (HONOURS)

*Cell and tissue, shell and bone, leaf and flower, are so many portions of matter, and it is in obedience to the laws of physics that their particles have been moved, moulded and conformed. They are no exception to the rule that God always geometrizes. Their problems of form are in the first instance mathematical problems, their problems of growth are essentially physical problems, and the morphologist is, ipso facto, a student of physical science.*

-Sir D'Arcy Wentworth Thompson, '*On Growth and Form*' [5]

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## 1 Introduction: Basic Ideas in Mathematical Modelling

### 1.1 Mathematical modelling

The aim of mathematical modelling is to improve our understanding of some real-life problem. In areas such as physics, chemistry or engineering, mathematics has been so important in testing hypotheses and making predictions that (to the dismay of many students!) it is now impossible to study these subjects without first learning a significant amount of mathematics. This is not true to the same extent in biology, but their conspicuous success in the physical sciences has meant that there is an increasing readiness to apply mathematical techniques to biological problems. Correspondingly, the field of mathematical biology has grown rapidly in the last 20 years or so.

The general process of mathematical modelling can be summarised as follows:

1. Develop a hypothesis regarding the important mechanisms underlying the problem. This requires a detailed knowledge of the processes at work. In mathematical biology research, the input of experimental collaborators is often very important at this stage.
2. Formulate the hypothesis in mathematical terms. This often involves recasting the assumptions you have made about what is happening in the problem in the form of differential equations.
3. Analyse the resulting mathematical problem so as to understand the behaviour of the solution. (For very simple models, you may be able to write down a closed-form solution; in other cases, more complicated techniques will need to be applied to gain insights into its behaviour.)

4. Interpret the mathematical results in the context of the original problem. Is the solution consistent with what is observed in experiments? If so, are there new experiments you could devise based on your model, which would further test its validity? If not, what assumptions in your model might you need to revisit?

As mathematicians, your training up to now has probably focused mainly on stage 3; however, in many cases stage 2 can be equally if not more important. A problem which has been experimentally intractable to biologists can sometimes be solved quite straightforwardly once it has been formulated in mathematical terms. Similarly, a mathematical formula on a piece of paper is not likely to be much use to a biologist; you need to see the significance (and the limitations) of the result in the context of the problem (stage 4) if any real biological insight is to be gained. One of the aims of this course is to help you develop these additional skills.

## 1.2 Building mathematical models

One of the golden rules of mathematical modelling is: **keep it simple!** No understanding will be gained by converting an intractable biological problem into a mathematical model that is too complicated to analyse. When building a model, we must focus on the processes we think are the most important, and neglect the others, at least to begin with. (Once the basic model is fully understood, additional effects can be added to it and their effect on the solution investigated.) Knowing what to put in, and what to leave out, is something of an art, and requires experience. However, there are a couple of basic techniques that can be very helpful.

### 1.2.1 Dimensional analysis

It is obvious that in order to be physically consistent, we can only equate together quantities which have the same dimensions - *e.g.* in Newton's Second Law,  $F = ma$ , the quantities on both sides of the equation must have the dimensions of force. Measurements of quantities are taken with respect to a reference value; the particular reference value used will depend upon the system of units adopted. Physical relationships must be true irrespective of the system of units used. In defining a system of units some quantities are considered fundamental - *e.g.* mass, length and time, which we shall denote [M], [L] and [T]. Other units are derived from these - *e.g.* speed is the rate of change of distance, and so has dimensions of [L] [T]<sup>-1</sup>. Other fundamental units include electric charge, [Q], and temperature, [Θ].

#### **Example: Coulomb's law**

The force,  $F$  acting on two particles with charges  $q_1$  and  $q_2$ , separated by a distance  $r$ , is given by

$$F = k_e \frac{q_1 q_2}{r^2}$$

where  $k_e$  is a constant. What are the dimensions of  $k_e$ ?

Both sides of the equation must have the dimensions of force - *i.e.*  $[M] [L] [T]^{-2}$ . Hence

$$\frac{[M][L]}{[T]^2} = [k_e] \frac{[Q]^2}{[L]^2}, \quad \Rightarrow \quad [k_e] = \frac{[M][L]^3}{[Q]^2[T]^2}.$$

A quantity which has no units is said to be **dimensionless**. Recall that the length,  $a$ , of an arc of a circle of radius  $r$ , subtended by an angle,  $\theta$ , is given by  $a = r\theta$ . Since both  $a$  and  $r$  have dimensions of  $[L]$ ,  $[\theta] = [1]$  (*i.e.*  $\theta$  is dimensionless). Note that we can create dimensionless quantities by making appropriate combinations of dimensional quantities. For example, in the case of a simple pendulum of length,  $l$ , which oscillates with a frequency  $\omega$  in a gravitational field of strength,  $g$ , the quantity  $\frac{g}{l\omega^2}$  is dimensionless (exercise).

We can exploit dimensionless quantities to help us deduce model equations. Suppose we are considering a problem with dimensional variables  $x_1, x_2, \dots, x_n$  and dimensional parameters (constants)  $\alpha_1, \dots, \alpha_m$ , and want to determine the relationship between these quantities. Since we can only equate quantities of the same dimension, this limits the combinations of the  $x_i$  and  $\alpha_j$  which are possible. Obviously, dimensionless quantities can be equated in this way, so if the  $x_i$  and  $\alpha_j$  can be combined to create  $k$  dimensionless groups,  $\beta_1, \beta_2, \dots, \beta_k$ , the relationship between these can be written in the format

$$f(\beta_1, \beta_2, \dots, \beta_k) = 0.$$

It is frequently the case that only a small number of dimensionless groups can be created from the dimensional variables and parameters which we believe to influence the problem. This will simplify the modelling very considerably. For example, if there is only one dimensionless group, we have must have a relationship of the form  $f(\beta) = 0$ . This means  $\beta$  is a zero of the function  $f$  - *i.e.* the physical relationship between our variables can be expressed as  $\beta = \text{constant}$ .

### Example: How powerful is an atomic bomb?

In 1945, the USA test-detonated the world's first atomic bomb, a device code-named Trinity, in the New Mexico desert. Information concerning the test was highly classified by the US government at the time (in fact, the full technical report on the explosion was not published until 1976), though a series of photographs of the explosion (which included the time since detonation) were declassified in 1947. The UK government was intensely interested in the results of the US test, as they wanted to develop their own atomic weapons; in particular, they wanted to know how much energy such a device might release. They asked Sir Geoffrey Taylor (G. I. Taylor) an applied mathematician at the University of Cambridge, to work on the problem. For explosions which took place in the open, he assumed the blast wave created would be spherical in shape. He reasoned that, in the early stages of an explosion (before energy could be radiated as heat), the radius of the blast,  $R$ , could only depend on the energy of the explosion,  $E$ , the time since detonation,  $t$ , and the density of the air,  $\rho$ . By using dimensional analysis, he realised that only one dimensionless number could be created from these quantities, and so

$$\frac{Et^2}{\rho R^5} = \text{constant}.$$

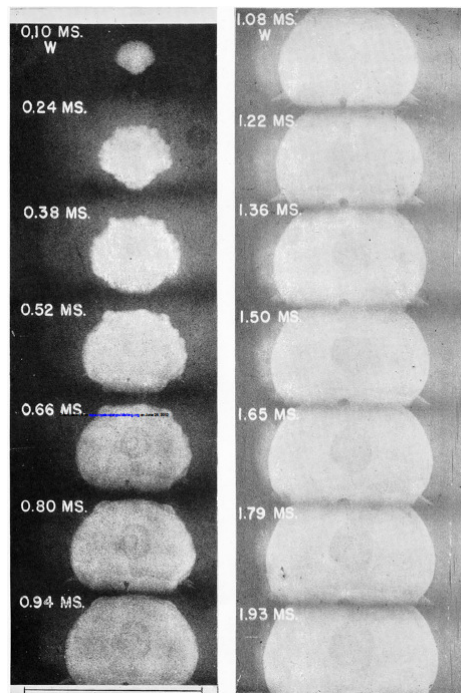


Figure 1: Photographs of the Trinity atomic bomb test used by G. I. Taylor (from [4]).

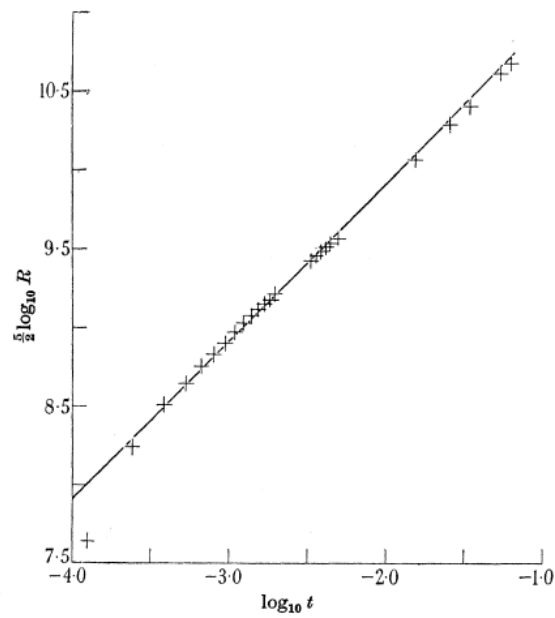


Figure 2: Graph of data from the photographs, showing clearly that  $R^5 \propto t^2$  (from [4]).

By means of other arguments, Taylor determined that the value of the constant would be approximately one.

Assuming a typical value for the density of air,  $\rho$ , and making measurements from the published photographs of the test to estimate  $R$  at each value of  $t$ , Taylor was able to obtain a value for  $E$ , the energy of the blast, of  $16.8 - 23.7$  kT (*i.e.* equivalent to 16,800-23,700 tons of TNT). The official test determined it was 20 kT. Taylor published his results in 1950 [4], two years before the first UK atomic weapons test.

### 1.2.2 Nondimensionalisation and scaling

Although dimensional analysis can sometimes help us to deduce the equations governing a process, another important reason for dealing with dimensionless quantities is that it allows us to compare the relative importance of various effects very easily. This is not really true with dimensional equations.

**Example:** Suppose for a moment, we are interested in the spread of a pollutant being released from a factory chimney into the air over a small town. The chemical will diffuse, and will also be carried on the wind. We are told the typical wind speed in the area is  $5 \text{ km h}^{-1}$ , and the diffusion coefficient of the chemical in air at  $25^\circ\text{C}$  has been measured as  $0.3 \text{ cm}^2 \text{ s}^{-1}$ . Is the pollutant transported mainly by diffusion, or on the wind?

In order to answer this question, we first need to think about how the pollutant concentration,  $c$  evolves. For simplicity, let us just consider the spread of the pollutant in one dimension, and assume that the concentration profile is steady (*i.e.* does not change with time). We let  $x$  be the distance downwind of the chimney. Then the concentration obeys

$$U \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial x^2}, \quad c = c_0 \quad \text{at } x = 0, \quad c \rightarrow 0 \quad \text{as } x \rightarrow \infty,$$

where  $U$  is the wind speed and  $D$  is the diffusion coefficient. (You can just accept this equation for now, we will derive it later in the course.) We are interested in how the pollutant spreads over a town, so a typical lengthscale (distance) we be around a kilometre; let  $L$  be the distance from the chimney to the town centre. Then we notice there are some obvious natural scales in the problem. It is convenient to specify the concentration in terms of the fraction of the value at the site of release,  $c_0$ , and similarly to measure length in terms of the fraction of the distance to the town centre. Hence we set

$$\tilde{x} = \frac{x}{L}, \quad \tilde{c} = \frac{c}{c_0},$$

where the tildes indicate dimensionless quantities. We then note that  $UL/D$  is a dimensionless quantity, which is called the Péclet number,  $\mathcal{P}$ . Hence the dimensionless concentration obeys

$$\mathcal{P} \frac{\partial \tilde{c}}{\partial \tilde{x}} = \frac{\partial^2 \tilde{c}}{\partial \tilde{x}^2}, \quad \tilde{c} = 1 \quad \text{at } \tilde{x} = 0, \quad \tilde{c} \rightarrow 0 \quad \text{as } \tilde{x} \rightarrow \infty.$$

This equation has some obvious superficial advantages over the dimensional version: there are fewer constants, so there is less chance of us making a mistake. But more

importantly, we now see that if  $\mathcal{P} \ll 1$ , diffusion is the dominant transport mechanism, whilst for  $\mathcal{P} \gg 1$ , transport on the wind is the more important factor. If  $\mathcal{P} = O(1)$ , then both mechanisms play an equal role. For our situation, we find that  $U \approx 1.4 \text{ m s}^{-1}$ ,  $D = 3 \times 10^{-5} \text{ m}^2 \text{ s}^{-1}$  and  $L = 10^3 \text{ m}$ . Hence

$$\mathcal{P} \approx \frac{1.4 \times 1000}{3 \times 10^{-5}} \approx 5 \times 10^7 \gg 1.$$

Therefore, transport by the wind is vastly more important than diffusion, so we can make our lives easier by neglecting the diffusion term in the equation.

To summarise, it is very helpful to work with dimensionless models for the following reasons:

- The equations involve fewer symbols, so we are less likely to make mistakes in calculations, and it is often easier to recognise the type of equations involved. Since the coefficients are real numbers, rather than dimensional quantities, their magnitudes can be directly compared, which is useful for determining the most important effects in the problem, and making simplifications where appropriate.
- Reducing the number of parameters means results can be investigated more quickly and presented in more compact form. Above, we reduced the number of parameters from 3 ( $c_0$ ,  $U$  and  $D$ ) to one. Hence the behaviour of the solution depends on only one parameter,  $\mathcal{P}$  - we do not have to give separate plots for different values of  $c_0$ ,  $U$  and  $D$ ). This can be particularly important when we have to solve a problem numerically - especially if the simulation takes a long time to run.
- Solutions obtained for one system can be applied to another which obeys the same equation, but with different parameter values - there is no need to recalculate the solution.
- Often the dimensionless equations can help in the design of experiments - *e.g.* we could investigate the pollutant dispersal problem experimentally by building a scale model in the lab, such that  $\mathcal{P}$  takes the same value as for the real problem.

### 1.3 Types of models

In this course, we will concentrate on models based on ordinary and partial differential equations. As these are so numerous in the literature, it might be tempting to think that they are a good way to attack any real-life problem: this is certainly not the case (we will discuss the cautionary example from [1] in class). It is useful to remind ourselves at this point that there may be other more appropriate modelling approaches for certain problems, such as:

- **Difference equations** (also known as recurrence relations, iterated maps, or just maps): The dependent variable can be discrete or continuous; time is always discrete; suitable for seasonal events; can have deterministic and stochastic difference equations.

- **Stochastic processes:** A family of random variables  $\{X(t)\}$ , indexed by a parameter  $t$ , is called a stochastic process; Markov-chain models are one class of (memory-less) stochastic model; particularly useful for small populations.
- **Cellular automata:** Fully discrete models, all independent variables and all dependent variables are discrete; analysis is mainly restricted to computer analysis and numerical simulation; can be either deterministic or stochastic, using a random number generator.

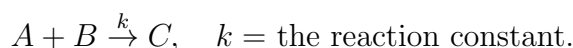
## 2 Biochemical reactions

In the next two sections, we will consider mathematical models consisting of ordinary differential equations, with which you will already be familiar. As much of the challenge in mathematical modelling is simply knowing what equations to write down, we give considerable attention to this aspect. We consider how the important variables are identified, and how we can use the processes of scaling and inspectional analysis introduced earlier to identify appropriate simplifying assumptions. Since only the simplest models can be solved analytically, we also introduce techniques which allow us to gain insight into the qualitative behaviour of the models, without actually having to solve them.

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### 2.1 Chemical reactions

Chemical reactions are important in many biological processes - *e.g.* digestion, photosynthesis, respiration. We first consider an irreversible reaction process in which reactants  $A$  and  $B$  produce  $C$  - *i.e.*



Let  $a = [A]$ ,  $b = [B]$ ,  $c = [C]$  denote the concentrations of  $A$ ,  $B$  and  $C$ , respectively. (The use of square brackets to indicate a concentration is standard in biology and chemistry, and hence appears in many papers and books. However, I think it can result in equations that look very cluttered, and so will try to avoid it in this course.) The SI units of concentration are moles  $\text{m}^{-3}$  (abbreviated to  $\text{mol m}^{-3}$ ), where a *mole* is simply a number of molecules -  $6.023 \times 10^{23}$ . Since a cubic metre is often an inconveniently large volume, moles per litre (also called *molar*,  $\text{M}$ ) is a common alternative unit.

We argue

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

which yields the ODE

$$\frac{dc}{dt} = k a b.$$

This is the **Law of Mass Action**. While called a law, it is really just a mathematical model, which is useful in many, but not all situations. Reactions which obey mass action kinetics are called *elementary reactions*. However, there are many biological reactions which proceed through complex mechanisms consisting of several elementary steps which are not known in sufficient detail for the law of mass action to be applied.

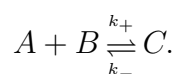
It is also worth remarking that the assumption that the reaction rate,  $k$ , is constant is strictly only true if the reaction occurs at a constant temperature. Many chemical



reactions give off, or take in, significant amounts of heat. (In modelling such a case, we would need to know the reaction rate as a function of temperature, and either measure, or have a model for, the temperature throughout the reaction. This would make the modelling much more complicated.) However, for reactions occurring under physiological conditions, the assumption of constant temperature is usually quite appropriate - *e.g.* body temperature in mammals is maintained very close to constant under a wide range of external conditions.

*Extension: What equation would we write down for a reaction involving  $m$  molecules of  $A$  and  $n$  molecules of  $B$  reacting to produce a molecule of  $C$ ?*

Next, consider a reversible reaction



Here, as for many biological processes it is necessary to follow the time evolution of more than one factor, leading to systems of ODEs. Balancing the production and consumption terms for each participating chemical species gives

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

Note that this system is reducible to just one equation, since

$$\frac{d}{dt}(c + a) = \frac{d}{dt}(c + b) = 0,$$

and given initial concentrations  $a_i, b_i, c_i$  we have  $a = c_i + a_i - c$  and  $b = c_i + b_i - c$ .

## 2.2 Enzymes

A *catalyst* is a substance that speeds up a chemical reaction without itself being consumed in the reaction. An *enzyme* is a biological catalyst: most are proteins. The increase in the rate of reaction they induce is staggering - often of the order of several million-fold. The substances on which they operate are called *substrates*.

Enzymes regulate a vast array of processes in the body, particularly those related to digestion and metabolism. For example, amylase in saliva starts to break down starch in our food into sugars, which are in turn further broken down into glucose, the body's primary source of energy. The release of energy from glucose also occurs through a chain of enzyme-mediated reactions. However, they are also important industrially. An everyday example would be the use of enzymes in laundry powder, which help to

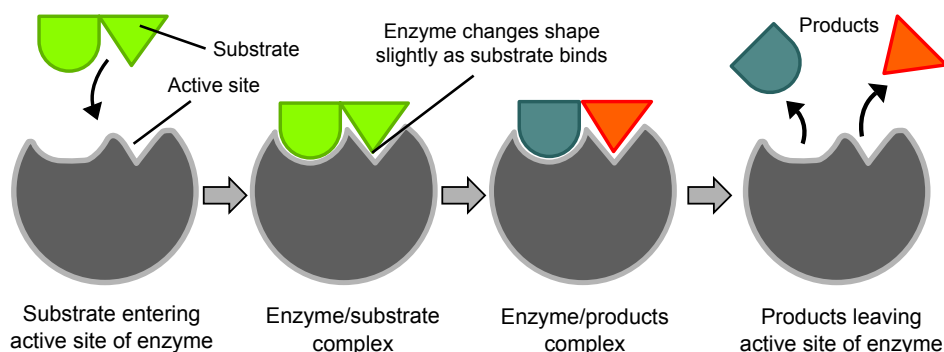


Figure 3: Schematic of the induced fit theory of enzyme action. (Diagram credit: TimVickers, Wikimedia.)

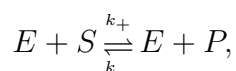
break down the fats in stains.

Each enzyme catalyses a specific reaction. This specificity is usually explained in terms of the ‘lock and key’ theory (or its slight modification- the induced fit theory, shown diagrammatically in Fig. 3). The idea is that the enzyme and its substrates both have specific, complementary shapes. The substrate must bind to the enzyme in order for the reaction to occur, and this is only possible when the two fit together like a ‘lock and key’. (The induced fit theory allows for some flexibility in the enzyme, which helps the binding become tighter.) Thus, the enzyme is unable to bond with other substrates, as they do not have the correct shape.

Since enzymes are proteins, they tend to work best within a narrow range of temperature and pH. At low temperatures, molecules have low kinetic energy, so the number of collisions is reduced, and hence the rate of reaction. At temperatures above around  $40^{\circ}\text{C}$  (or extremes of pH), proteins become *denatured*, meaning their structure is changed (*e.g.* think of what happens to egg white as it is cooked). This makes the enzyme less effective at catalysing the reaction.

## 2.3 Michaelis-Menten kinetics

Consider the enzymatic reaction



involving the reaction of a substrate  $S$  with an enzyme  $E$  to gain a product  $P$ , and the enzyme. The enzyme is a catalyst.

To allow use of the Law of Mass Action, we assume  $E$  and  $S$  form an intermediate complex  $C$  which then decays into  $P$  and  $E$ :



Letting  $s = [S]$ ,  $e = [E]$ ,  $c = [C]$ ,  $p = [P]$ , we can describe the process using ODEs:

$$\begin{aligned}\frac{ds}{dt} &= -k_1 s e + k_{-1} c, \\ \frac{de}{dt} &= -k_1 s e + k_{-1} c + k_2 c, \\ \frac{dc}{dt} &= k_1 s e - k_{-1} c - k_2 c, \\ \frac{dp}{dt} &= k_2 c.\end{aligned}$$

Note that the units of the constant  $k_1$  differ from those of  $k_{-1}$  and  $k_2$ . We take the initial conditions for the system to be

$$s(0) = s_i > 0, \quad e(0) = e_i > 0, \quad c(0) = p(0) = 0. \quad (2.1)$$

We note that by adding the second and third equations above, integrating and applying the initial conditions, we find that

$$e(t) + c(t) = e_i. \quad (2.2)$$

Hence we can eliminate  $e$  from the equations for  $s$  and  $c$ . Since  $p$  depends only on  $c$ , we need only consider the reduced system

$$\frac{ds}{dt} = -k_1 s (e_i - c) + k_{-1} c = -k_1 s e_i + (k_1 s + k_{-1}) c, \quad (2.3a)$$

$$\frac{dc}{dt} = k_1 s (e_i - c) - k_{-1} c - k_2 c = k_1 s e_i - (k_1 s + k_{-1} + k_2) c, \quad (2.3b)$$

with initial conditions  $s(0) = s_i$ ,  $c(0) = 0$ .

These have no known exact solution but approximate solutions have been obtained. The best known and most commonly used is the approximation introduced by Michaelis and Menten in 1913, which is motivated by the observation that the availability of the enzyme is often the limiting factor in the reaction. In order to develop our approximate solution, we must use the techniques of scaling and inspectional analysis we met earlier in the course.

We translate the assumption that the reaction is limited by the availability of the enzyme into the mathematical assumption that  $e_i \ll s_i$ . We let  $T$  be the timescale over which the substrate is observed to be converted into product (we will specify this in terms of the system parameters shortly). Since we start with a finite amount of substrate and no product, we must have  $0 \leq s \leq s_i$  and  $0 \leq p \leq s_i$ . From (2.2) we have  $0 \leq c \leq e_i$ , so  $c \ll s_i$ . We hence nondimensionalise our variables as follows (where tildes indicate dimensionless variables):

$$t = T\tilde{t}, \quad s = s_i\tilde{s}, \quad c = \epsilon s_i\tilde{c},$$

where we have introduced the dimensionless parameter  $\epsilon = e_i/s_i \ll 1$ . Equation (2.3a) then becomes (dropping tildes):

$$\frac{ds}{dt} = \epsilon k_1 s_i T (c s - s) + \epsilon k_{-1} T c, \quad (2.4)$$

Since, by definition,  $T$  is the timescale for  $s$  to undergo an  $O(1)$  change, we expect the parameters on the RHS of (2.4) to be  $O(1)$ . Hence we choose  $T = 1/\epsilon k_1 s_i$ , which implies that the timescale on which the substrate is converted to product is much longer than the timescale of complex formation. We also assume  $A = \epsilon k_{-1} T = k_{-1}/k_1 s_i = O(1)$ , so the rates of complex formation and dissociation are of the same order of magnitude. Hence (2.3) simplifies to

$$\frac{ds}{dt} = cs - s + Ac, \quad (2.5a)$$

$$\epsilon \frac{dc}{dt} = s - cs - (A + B)c, \quad (2.5b)$$

where  $B = k_2/k_1 s_i$  is the ratio of the rate of product formation to complex formation, and the initial conditions become  $s(0) = 1$ ,  $c(0) = 0$ .

We now expand  $s$  and  $c$  as power series in the small parameter,  $\epsilon$ , so

$$s = s_0 + \epsilon s_1 + O(\epsilon^2), \quad c = c_0 + \epsilon c_1 + O(\epsilon^2).$$

Substituting the above into (2.5), at leading order we find

$$c_0 = \frac{s_0}{K_m + s_0} \quad \text{where} \quad K_m = A + B = \frac{k_{-1} + k_2}{k_1 s_i} \quad (2.6)$$

$$\frac{ds_0}{dt} = \frac{-Bs_0}{K_m + s_0}. \quad (2.7)$$

This is the most common Michaelis-Menten function used, among other things, for rate of depletion of nutrients in biological systems.  $B$  is the maximum uptake rate;  $K_m$  is the concentration at which the uptake rate is one half of the maximum.

### Remarks:

- Note how the different timescales in the reaction have emerged naturally from the scaling analysis. In fact, it is possible to show that the approximate solution remains valid under the weaker assumption that  $\epsilon/(K_m + 1) \ll 1$  (*i.e.* either there is little enzyme compared to substrate, or the rates of complex dissociation and product formation are slow compared to the rate of complex formation). Full details are given in [3].
- Our leading order solution for  $c$ ,  $c_0$  as given in equation (2.6) does not obey the initial condition  $c(0) = 0$ . This is because, in obtaining it, we neglected the time derivative in equation (2.5b). Situations like this, where the small parameter multiplies the highest derivative in an equation are called **singular perturbation problems**, and generally give rise to a leading-order solution that does not obey one or more of the initial or boundary conditions. If, in equation (2.5b) we introduce the new, shorter timescale  $t = \epsilon \tau$ , then the time derivative term becomes  $O(1)$ . Physically, this implies that there is a short timescale in the problem on which  $c$  changes from zero to the value given in (2.6). See Chapter 6 of [2] for full details.

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