Introduction to modelling biological systems using ordinary differential equations

Chris P Barnes

3 Interconnected systems

3.1 Input-output models and bathtubs

Before we move on to model the full enzymatic system let's think about an analogy of the system. Figure 1 depicts a scenario where four bathtubs at different heights are connected to each other. This is a very common modelling scenario, known as a **compartment model** and can be applied to many areas including drugs inside difference tissue or proteins in different forms. In particular, each bathtub, y_1 flows into the bathtub directly below. The amount of water in each bathtub are denoted by y_1, y_2, y_3, y_4. Each equation tells us about the rate of change of the amount of water in each tub. For example the first equation

$$\frac{dy_1}{dt} = -\text{rate}_1$$

tells us that water flows out of the first bathtub at some rate, rate$_1$. This water cannot go anywhere but flow into bathtub 2, so the rate of water entering bathtub 2 must equal the rate of water flowing out of bathtub 1. The equation of bathtub 2 therefore given by

$$\frac{dy_2}{dt} = +\text{rate}_1 - \text{rate}_2,$$

where $-\text{rate}_2$ is the flow rate of water *out* of bathtub 2. Repeatedly applying this logic gives us the four equations in Figure 1. This is known as an input-output model and is a very common way of deriving differential equation models. Because each equation is linked to each other (via the rates of input and output) this is known as a **system of differential equations**. Generally there is no way to solve these analytically and we must use a computer to numerically integrate them and to get the amounts asa function of time. We will use the input-output approach to model the enzymatic system.

3.2 The enzymatic system

Now let's apply what we have learned so far to model the enzymatic system described at the start

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P,$$
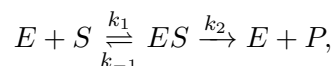
where k_{-1}, k_{+1}, k_2 represent the rate constants of the reactions. There are a number of ways in which this can be done, we will first adopt the input-output modelling approach.
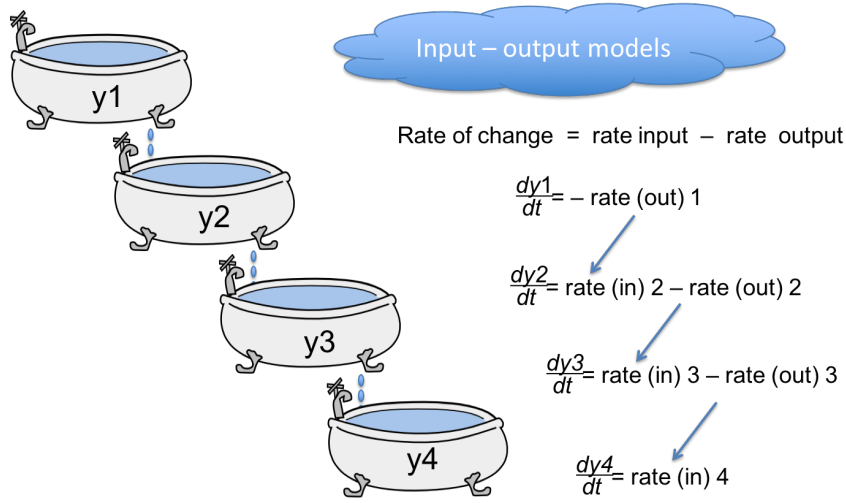
Figure 1: A model of connected bathtubs

The input-output model approach

In Figure 2, we view the enzymatic system as a system of four bathtubs where water can be pumped between them. The analogy is not quite as nice in this case, but it will help you to visualise the system. The differential equations for each species are obtained by writing the inputs and outputs of each bathtub. For example, the equation of ES has one input term, $k_1 E.S$, and two output terms, $k_{-1}ES$ and k_2ES. Therefore we can write this differential equation as

$$\frac{dES}{dt} = +k_1 E.S - k_{-1}ES - k_2ES$$

Similarly for S we have

$$\frac{dS}{dt} = +k_{-1}ES - k_1 E.S$$

Repeating this for all bathtubs gives us a system of differential equations that govern the **dynamics** of the reaction system

$$\begin{aligned}
\frac{dS}{dt} &= -k_1 E.S + k_{-1}ES \\
\frac{dE}{dt} &= -k_1 E.S + k_{-1}ES + k_2ES \\
\frac{dES}{dt} &= +k_1 E.S - k_{-1}ES - k_2ES \\
\frac{dP}{dt} &= +k_2ES.
\end{aligned}$$

$$(1)$$

We now have a set of differential equations relating rates of changes of concentrations to concentrations. What we wish to obtain are the solutions $E(t), S(t), ES(t), P(t)$. In general, systems of
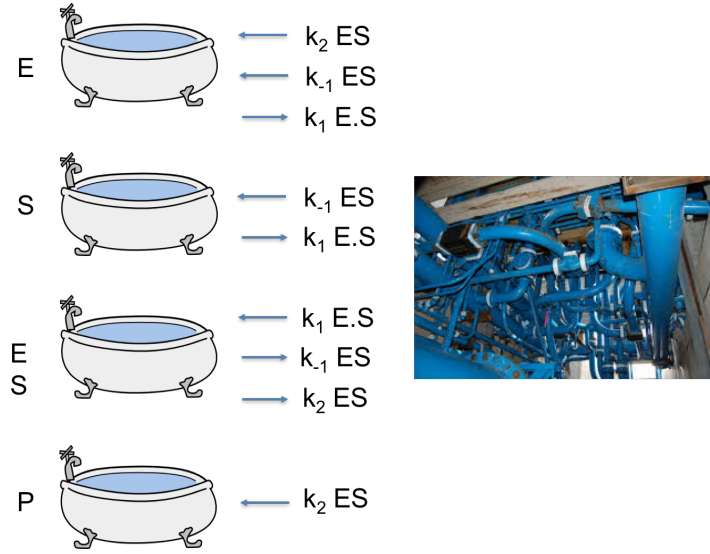
Figure 2: The enzymatic system as a model of connected bathtubs

nonlinear differential equations cannot be solved analytically (exactly) and we must use software to get a numerical approximation.

Figure 3 shows the dynamics of the system, obtained by using a differential equation numerical integration function in Python. We have to assume some values for the rate constants k_1, k_{-1}, k_2. In this context we refer to these as the **parameters** of the system. We must also assume some starting values for the four species and these are known as the **initial conditions**[1]. Note that the x axis represents time and the y axis, the concentrations of the species. Another thing to notice is that the behaviour of the system cannot easily be seen from the structure of the equations.

An alternative approach to the derivation

The input-output approach is an intuitive way to derive systems of differential equations but can become cumbersome for larger systems. In this alternative approach we write down all the individual differential equations corresponding to each reaction. Consider the reaction $ES \xrightarrow{k_2} E + P$. First of all, by inspection of the reaction, we can see that this single reaction affects the rates of change of three species, ES, E and P, so we are looking for three separate expressions. Also, note that there is only one reaction rate, so it must apply to all three species. The only question is whether the reaction increases or decreases the concentrations. The correct

---

[1]Solving a system of differential equations given some initial conditions and parameters is known in mathematics as the **initial value problem**.
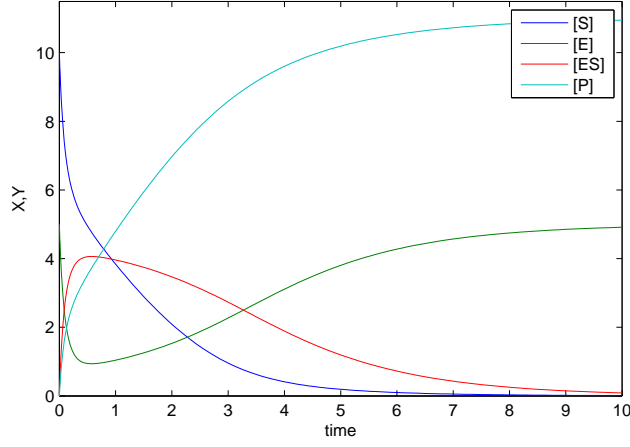
3

Figure 3: The dynamics of the enzymatic reaction for fixed values of $k_1 = 1, k_{-1} = 0.5$ and $k_2 = 0.6$ and initial conditions $S_0 = 10, E_0 = 5, ES_0 = P_0 = 0$.

expressions are

$$\frac{dES}{dt} = -k_2 ES,$$
$$\frac{dE}{dt} = +k_2 ES,$$
$$\frac{dP}{dt} = +k_2 ES.$$

The first equation includes a negative sign on the rate since this particular reaction **decreases** the amount of ES. In the second and third equations the reaction **increases** the concentrations of E and P so the rates are positive.

We can do the same for the reaction $E + S \xrightarrow{k_1} ES$

$$\frac{dE}{dt} = -k_1 E.S,$$
$$\frac{dS}{dt} = -k_1 E.S,$$
$$\frac{dES}{dt} = +k_1 E.S,$$

and the reverse reaction $ES \xrightarrow{k_{-1}} E + S$,

$$\frac{dES}{dt} = -k_{-1} ES,$$
$$\frac{dE}{dt} = +k_{-1} ES,$$
$$\frac{dS}{dt} = +k_{-1} ES.$$

4

Now we need to combine the individual expressions for the time derivatives of the species under each of the three reactions. The table below summarises the different reactions, their rates and their contributions to the rates of change of the four different species.

| reaction	rate	ΔS	ΔE	ΔES	ΔP
$E + S \rightarrow ES$	$k_1 E.S$	$-$	$-$	$+$	0
$ES \rightarrow E + S$	$k_{-1} ES$	$+$	$+$	$-$	0
$ES \rightarrow E + P$	$k_2 ES$	0	$+$	$-$	$+$

For example, by looking down the column labelled ΔS we can add up the contributions to the rate of change of S due to the different reactions. For example, the equation for dS/dt is given by

$$\frac{dS}{dt} = -1 \times k_1 ES + 1 \times k_{-1} ES + 0 \times k_2 ES.$$

By considering the rates of change of all species we arrive at the same system of differential equations. This approach uses the stoichiometry matrix, which we will examine in the next section.

3.3   Stoichiometry matrices

Another example that is instructive to consider is the case of **cooperative reactions** where multiple substrate molecules bind to the enzyme. The familiar enzymatic system become modified as follows

$$E + nS \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES_n \overset{k_2}{\longrightarrow} E + P,$$
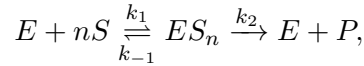
where n is called the **stoichiometry** of bound substrate molecules. We now have to take account of changes in the numbers of molecules when different reactions occur. We can follow exactly the same procedure as in the previous section; namely writing the rates assuming mass action kinetic for each reaction and collecting together the terms. Our table now becomes

reaction	rate	ΔS	ΔE	ΔES	ΔP
$E + nS \rightarrow ES_n$	$k_1 E.S^n$	$-n$	-1	$+1$	0
$ES_n \rightarrow E + nS$	$k_{-1} ES_n$	$+n$	$+1$	-1	0
$ES_n \rightarrow E + P$	$k_2 ES$	0	$+1$	-1	$+1$

Following the same arguments the system of differential equations for the species in the system is given by

$$\frac{dS}{dt} = -nk_1 E.S^n + nk_{-1} ES_n$$

$$\frac{dE}{dt} = -k_1 E.S^n + k_{-1} ES_n + k_2 ES_n$$

$$\frac{dES_n}{dt} = +k_1 E.S^n - k_{-1} ES_n - k_2 ES_n$$

$$\frac{dP}{dt} = +k_2 ES_n.$$

5

This system of equations now accounts for the stoichiometry of the first reaction.

More generally the matrix defined by

$$\mathbf{A} = \begin{pmatrix} -n & -1 & +1 & 0 \\ +n & +1 & -1 & 0 \\ 0 & +1 & -1 & +1 \end{pmatrix},$$

is called the **stoichiometry matrix** and accounts for how each species changes with each reaction. A more useful representation is the transpose of this matrix

$$\mathbf{S} = \mathbf{A}^T = \begin{pmatrix} -n & +n & 0 \\ -1 & +1 & +1 \\ +1 & -1 & -1 \\ 0 & 0 & +1 \end{pmatrix}.$$

Written in this form the structure of the system of differential equations can be written in the form of a matrix multiplication

$$\frac{d\mathbf{x}}{dt} = \mathbf{Sr},$$

where column vectors $\mathbf{x} = (S, E, ES_n, P)^T$ represents the species and $\mathbf{r} = (k_1 E.S^n, k_{-1} ES_n, k_2 ES)^T$ represents the rates. (Note that these are column vectors but for ease of reading them we wrote them as row vectors with a transpose.)

3.4 The Michaelis-Menten approximation

Here we are going to derive the Michaelis-Menten equation that model the rate of product formation in the enzymatic reaction

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P,$$

where E, S, ES and P are enzyme, substrate, enzyme-substrate complex and product respectively and k_{-1}, k_1, k_2 represent the rates of the reactions. Using the law of mass action we can write a system of differential equations for the species in the system

$$\dot{S} = -k_1 E.S + k_{-1} ES$$
$$\dot{E} = -k_1 E.S + k_{-1} ES + k_2 ES$$
$$\dot{ES} = +k_1 E.S - k_{-1} ES - k_2 ES$$
$$\dot{P} = +k_2 ES,$$

where we have used the shorthand notation $\dot{X} \equiv dX/dt$.

From looking at the equations we can immediately see that $\dot{E} + \dot{ES} = 0$, so we can write this as a **conservation law**

$$E + ES = E_0, \tag{2}$$

where we have denoted the initial concentration of the enzyme E as E_0. We now make an assumption that is commonly used, known as the **quasi-steady state assumption**, which is related to a technique in physics known as **time scale separation**. We assume that the enzyme binding and dissociation happens fast enough that the process is in equilibrium, that is the concentration of complex, ES, is approximately constant. Under this assumption the reactions of complex formation balance complex consumption, and this gives the following relationship

$$\text{rate of formation of } ES = \text{rate of consumption of } ES$$
$$k_1 E.S = k_{-1} ES + k_2 ES. \tag{3}$$

Combining Equations (2) and (3) one can obtain the expression (after some algebra)

$$ES = \frac{E_0 S}{K_m + S},$$

where K_m is the Michaelis constant $K_m = (k_{-1} + k_2)/k_1$. This then gives the familiar Michaelis-Menten equation

$$\dot{P} = k_2 \frac{E_0 S}{K_m + S} = \frac{V_{max} S}{K_m + S}$$

where $V_{max} = k_2 E_0$.

Now, an obvious question to ask is when is the quasi-steady state approximation valid? Despite the wide-spread use of this approximation, there are a number of analyses of this question (see the resources eg Schell (2013)), but an important case is where $S \gg E$, which occurs in many natural and experimental situations.