

Introduction to modelling biological systems using ordinary differential equations (L2)

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2 Dynamics

2.1 Deriving differential equations for reaction systems

Rates are also derivatives...

Now that we have written down a model for the rates of our reactions can we go further and try to relate them to each other. We know that this should be possible. Let's think about what a rate represents. If you were to go and measure the rate of a reaction that produced species Y , then you would probably go and take an initial measurement of Y , denoted by Y_s . You would then wait some time, Δt , and take another measurement denoted by Y_f . The rate would be calculated as

$$\text{rate} \approx \frac{Y_f - Y_s}{\Delta t},$$

which we can write as

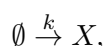
$$\text{rate} \approx \frac{\Delta Y}{\Delta t},$$

where we have used ΔY to represent the *change in the concentration of Y* . Therefore we can think of the rate as the change in concentration over the change in time. If the reaction occurs at a constant rate then this might be a good estimate, however reactions don't necessarily proceed at constant rates. If the rate is not constant we have to make Δt smaller and smaller in order to make our estimate more and more accurate. In calculus we can take the limit as Δt goes to zero and we obtain the **derivative**¹ of Y with respect to t

$$\frac{\Delta Y}{\Delta t} \rightarrow \frac{dY}{dt}.$$

Example: Ions entering a cell through a channel

Consider the following reaction system



¹The derivative is formally defined as $\frac{df(x)}{dx} = f'(x) = \lim_{x \rightarrow x_0} \frac{f(x) - f(x_0)}{x - x_0}$.

which models the concentration of ions passing through a membrane channel in a mammalian cell. This is a zero order reaction and in this case we know the rate of this reaction is equal to the rate constant k . Therefore we can equate this rate to the time derivative of X to obtain

$$\frac{dX}{dt} = k.$$

This defines the system behaviour. However, this is an equation for dX/dt , which is the rate of change of concentration of X , and what we want is an equation for $X(t)$, which is shorthand for *concentration of X as a function of time, t* . To obtain this from the derivatives we need to perform the operation of **integration** to solve for the concentrations as a function of time. By integrating explicitly (you can also try this in MATLAB or SymPy), we can see that this is the equation of a straight line

$$X(t) = X_0 + k(t - t_0),$$

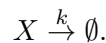
where X_0 and t_0 are the initial conditions. Dropping the explicit time dependence notation (t), and assuming that there are no ions present at $t=0$, we can write

$$X = X_0 + kt.$$

This is known as an **analytical solution** because we can derive the explicit function $X(t)$.

Example: Ions leaving a cell through a channel

Consider the following reaction system, which models the number of ions leaving a cell through an (open) ion channel



We know that this is a first-order reaction and that therefore the rate of this reaction is equal to kX assuming the law of mass action. We can equate this to the time derivative of X to obtain

$$\frac{dX}{dt} = -kX,$$

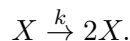
where we have included a negative term because the reaction *reduces* the concentration of X . By inspection, or by integrating explicitly using separation of variables, we can see that this is the equation of **exponential decay**

$$X(t) = X_0 \exp -k(t - t_0),$$

where X_0 and t_0 are the initial conditions.

Example: Bacterial growth

Consider the following reaction system, which we introduced earlier



Again, this is a first-order reaction and, assuming mass-action, we know that the rate of this reaction is equal to kX , and we can equate this to the time derivative of X to obtain

$$\frac{dX}{dt} = kX,$$

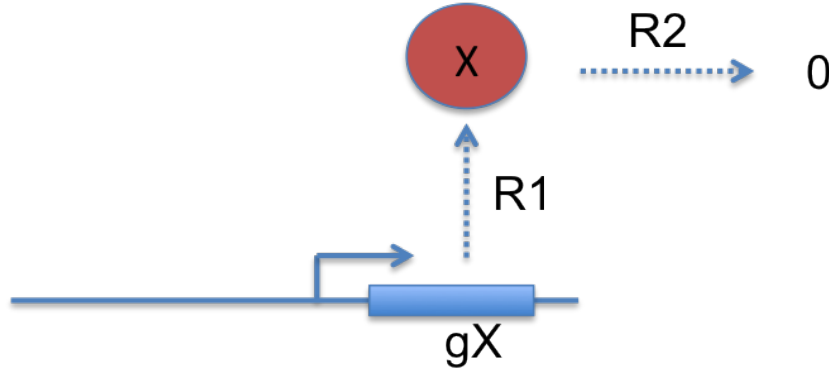


Figure 1: The simple gene expression model.

where we have included a positive term because the reaction *increases* the concentration of X . By inspection, or by integrating explicitly using separation of variables, we can see that this is the equation of **exponential growth**

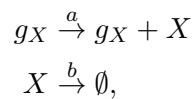
$$X(t) = X_0 \exp k(t - t_0),$$

where X_0 and t_0 are the initial conditions.

2.2 Worked example: Simple gene expression model

Here we are going to model the expression of a single gene, g_X , and we denote the concentration of the protein it encodes by X . We are going to consider transcription and translation as a single process, a common simplification and represented in Figure 1.

Let us further assume that the protein can also degrade (or is diluted due to cell growth). We can write the following reaction system down for this process



where a and b are the rate constants for expression and decay respectively. Assuming the law of mass action we can write down the rates for this process

$$\begin{aligned} R(g_X \xrightarrow{a} g_X + X) &= ag_X \\ R(X \xrightarrow{b} \emptyset) &= bX \end{aligned}$$

Now we use the **input-output principle** to derive the differential equation. This simple principle states that

$$\text{accumulation} = \text{input} - \text{output}$$

If we think in terms of accumulation rate then we can argue that the rate of accumulation is equal to the rate of production minus the rate of degradation (later we will argue this thinking

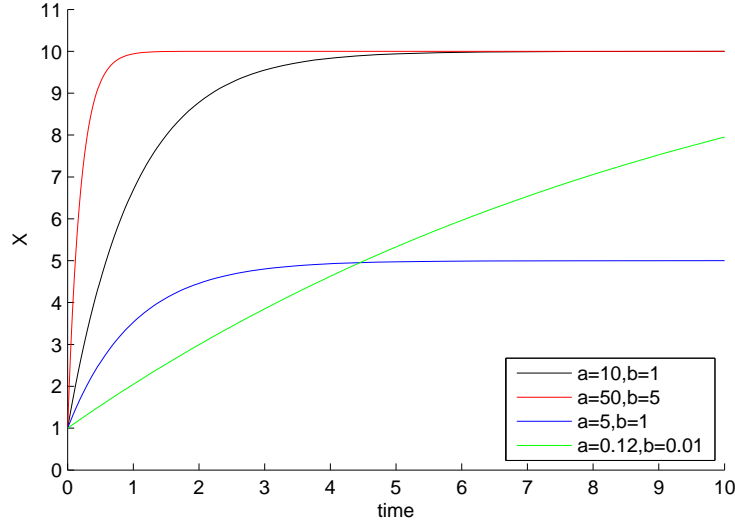


Figure 2: Simple model of gene expression. Concentration of expressed protein X as a function of time for $X_0 = 1$ and different levels of production and degradation.

in terms of filling a bathtub with a hole in it). This allows us to write the rate of accumulation dX/dt in terms of the expression and decay rates

$$\frac{dX}{dt} = ag_X - bX. \quad (1)$$

For simplicity we can further assume that the copy of the gene, $g_X = 1$, and the system reduces to the simple differential equation

$$\frac{dX}{dt} = a - bX. \quad (2)$$

Upon examination of Equation 2 we can see that if we include only the first term we have a linear growth of the protein X ($dX/dt = \text{const}$) and if we have only the second term we have an exponential decay of X ($dX/dt = -bX$). We can use Python to plot the solutions for different values of a and b and these are shown in Figure 2.

Analytical solution

In this case we can perform the integration to obtain $X = X(t)$ explicitly, that is in terms of mathematical functions rather than a numerical approximation (note that we may still use a computer algebra package to do the analytical integration). The solution to equation 1 can be obtained in this way and is given by

$$X(t) = \frac{a}{b} - \frac{\exp(-bt)(a - X_0b)}{b}.$$

What we notice is that the solutions reach a constant value after some time (which seems to depend on the parameters a and b). Once this constant value is reached there is no further change to the system. This is known as a **steady state**.

2.3 Steady states

The steady state, or fixed point, of a system is defined as the solution to

$$\frac{dX}{dt} = 0.$$

Let's find the steady state for the simple gene expression system as follows

$$\begin{aligned} a - bX &= 0 \\ X &= a/b. \end{aligned}$$

We find that the value of X at the steady state is a/b which is verified from Figure 2. Steady states are very important for understanding behaviour of a system because they tell us about the long term behaviour. For example consider increasing t to very large values, what happens to the solution $X(t)$? We write this mathematically as

$$\lim_{t \rightarrow +\infty} \frac{a}{b} - \frac{\exp(-bt)(a - X_0b)}{b}.$$

Since $\exp(-bt) \rightarrow 0$ as $t \rightarrow +\infty$ we see that the solution goes to a/b . The fact that the steady states tell us about the long term behaviour of the system is very important because sometimes this is all the information we require. Note also that in general obtaining the steady states of a system is a much simpler task than trying to determine the full time dependence.