2

Stoichiometric Networks

2.1 Stoichiometry

A chemical reaction is usually depicted in the form of a chemical equation which describes the transformation of one or more **reactants** into one or more **products**. The reactants appear on the left of the equation and the products on the right. Both sides are separated by an arrow indicating the positive direction of the transformation. The simplest possible reaction is the conversion of a single reactant, A, into a single product, B, as depicted in the following way:

$$A \rightarrow B$$

Such a reaction can be studied by observing the change in concentration of A and/or B in time. Experimentally there are a variety of ways to do this, for example by observing the emission or absorption of light at a specific wavelength, the change in pH, or the incorporation of a radioactive or heavy isotope into the product. An example of an actual biochemical

reaction is the familiar interconversion of the adenine nucleotides:

$$2\ \text{ADP} \rightarrow \text{ATP} + \text{AMP}$$

This describes two molecules of ADP being transformed into one molecule of ATP and one molecule of AMP. Sometimes a double arrow is used to explicitly indicate that a reaction is reversible, as in:

$$2\ \text{ADP} \rightleftharpoons \text{ATP} + \text{AMP}$$

If a reaction is reversible (as almost all reactions are to some extent), then the reaction rate can be positive or negative. By convention, a positive rate means that the reaction progresses from left to right, whereas a negative rate indicates a right to left reaction.

Example 2.1

What does the following reaction notation mean:

$$3A + 4B \rightarrow 3C + D$$

This notation means that during a reaction event, 3 molecules of A and 4 molecules of B react to form 3 molecules of C and one molecule of D.

We now need to define a number of terms: the stoichiometric amount, rate of change, stoichiometric coefficient, and reaction rate.

Stoichiometry refers to the molar proportions of reactants and products in a chemical reaction. We will first distinguish two related measures of stoichiometry, stoichiometric amounts and stoichiometric coefficients.

2.1.1 Stoichiometric Amounts

The **stoichiometric amount** is defined as the number of molecules of a particular reactant or product taking part in a reaction. Stoichiometric amounts will always be **positive** numbers. For example, in the reaction:

$$2\ \text{ADP} \rightleftharpoons \text{ATP} + \text{AMP}$$

ADP has a stoichiometric amount of two, ATP a stoichiometric amount of one, and AMP also with a stoichiometric amount of one. If the same species occurs on the reactant and product side of a reaction then it must be treated separately. For example, in the reaction:

$$2A + B + C \rightarrow 3A + D + 2B$$

The stoichiometric amounts on the reactant side include: A with two, B with one and C with one. On the product side the stoichiometric amounts include: A with three, D with one and B with two.

The **stoichiometric amount** is the number of molecules of a particular reactant or product taking part in a reaction.

Example 2.2

List the stoichiometric amounts in the following reaction:

$$2A + B \rightarrow A + C$$

On the reactant side the stoichiometric amount for A is two and for B is one. On the product side, the stoichiometric amount for A is one and for C one.

2.1.2 Stoichiometric Coefficients

Stoichiometry deals with static information about the amounts of substances involved in a chemical transformation, whereas kinetics relates rates of change that occur in these amounts. To paraphrase a statement made by Aris [3], stoichiometry provides the framework within which chemical change takes place irrespective of the forces that bring them about, and by kinetics the speed of chemical change. Aris then went on to state, "Just as the latter can only be built on a proper understanding of the kinematics, so the analysis of stoichiometry must precede that of kinetics". We will do the same here.

The stoichiometry coefficient refers to the **relative** amount of substance that is consumed and/or produced by a reaction. Given a reaction such as:

$$2A \longrightarrow B$$

the stoichiometric amount of A is 2 and for B, 1. The species stoichiometry or **stoichiometric coefficient** however, is the difference between the stoichiometric amounts of a given species on the product side and the stoichiometric amount of the same species on the reactant side. The definition below summarizes this more clearly.

The **stoichiometric coefficient**, c_i, for a molecular species A_i, is the difference between the stoichiometric amount of the species on the product side and the stoichiometric amount of the same species on the reactant side, that is:

$$\begin{aligned} c_i = &\text{ Stoichiometric Amount of Product, } A_i \\ &- \text{Stoichiometric Amount of Reactant, } A_i \end{aligned}$$

In the reaction, $2A \longrightarrow B$, the stoichiometric amount of A on the product side is **zero** while on the reactant size it is two. Therefore the stoichiometric coefficient of A is given by $0 - 2 = -2$. In many cases a particular species will only occur on the reactant or product side and it is relatively uncommon to find situations where a species occurs simultaneously as a product and a reactant. As a result, reactant stoichiometric coefficients tend to be **negative** and product stoichiometric coefficients tend to be **positive**. To illustrate this further consider the more complex reaction:

$$3A + 4B \longrightarrow 2C + D$$

Since A only appears on the reactant side, its stoichiometric coefficient will be -3, similarly for B which will have a stoichiometric coefficient of -4. Species C only occurs on the product side, therefore its stoichiometric coefficient is $+2$, and similarly for D which will have a stoichiometric coefficient of $+1$. In these cases the stoichiometric amounts and the stoichiometric coefficients are the same except for the sign difference on the reactant stoichiometric coefficients.

Finally consider the following reaction where a species occurs on both the reactant and product side:

$$2A + B \longrightarrow A + C$$

The stoichiometric coefficient of A must take into account the fact that A appears both as a reactant and a product. The overall stoichiometric coefficient of A is therefore $+1 - 2$ which gives -1.

The last example highlights how information can be lost when computing stoichiometric coefficients. It is not possible to recreate the original reaction equation from the stoichiometric coefficients alone, and therefore underscores the danger of just supplying stoichiometric coefficients when communicating information on reaction equations to other researches. One option is to store the stoichiometric amounts together with the associated reactant or product. Computer exchange formats, such as the Systems Biology Markup Language (SBML) [37] are specifically designed to preserve complete reaction equation information for this very reason.

Example 2.3

Write down the stoichiometric coefficients for the following reactions:

a) $A + A \rightarrow A + B$

The stoichiometric amount of A on the reactant side is 2 and on the product side, 1. Therefore the stoichiometric coefficient for A is $1 - 2 = -1$. The stoichiometric amount of B on the product side is 1 and on the reactant side, 0, therefore the stoichiometric coefficient for B is $1 - 0 = 1$.

b) $A \rightarrow B + \frac{1}{2}A$

The stoichiometric amount of A on the reactant side is 1 and on the product side $\frac{1}{2}$, therefore the stoichiometric coefficient for A is $1/2 - 1 = -1/2$. The stoichiometric amount of B on the reactant side is 0 and on the product side, 1, therefore the stoichiometric coefficient for B is $1 - 0 = 1$.

Example 2.3 (b) highlights another fact about stoichiometric coefficients. The coefficients can be fractional amounts, often represented as rational fractions.

2.2 Reaction Kinetics

Reaction kinetics is the study of how fast chemical reactions take place, what factors influence the rate of reaction and what mechanisms are responsible. Many variables can affect the reaction rate including temperature, pressure and composition. In this chapter we will review a number of topics related to reaction kinetics that have a significant bearing on the development of mathematical models of cellular networks.

2.2.1 Rates of Change

The rate of change can be defined as the rate of change in concentration or amount (depending on units) of a designated species. If S is the species then the rate of change is given by:

$$\text{Rate} = \frac{\Delta S}{\Delta t}$$

Because rates change as reactants are consumed and products made, the rate of change is better defined as the instantaneous change in concentration, or a derivative:

$$\text{Rate} = \frac{dS}{dt}$$

If we were to plot the rate of product formation as a function of time, the rate of reaction would be given by the slope of the curve (Fig. 2.1). If concentrations are measured in moles per liter (L) and time in seconds (sec), then the rate of reaction is expressed in mol L^{-1} sec^{-1}.

Figure 2.1: Progress curve for a simple irreversible reaction, $A \rightarrow B$. Initial reactant concentration, A, is set at 5 units. The plot shows the accumulation of product, B, as the reaction proceeds. The rate of change of product is given by the slope of the curve which changes over the course of the reaction.

When reporting a rate of change, it is important to give the name of the species that was used to make the measurement. For example, in the re-

action $2A \rightarrow B$, the rate of change of A is twice the rate of change of B. In addition, the rate of change of A is negative because it is consumed, whereas the rate of change of B is positive because it is being made.

2.2.2 Reaction Rates

In this section we will introduce the concept of a **reaction rate**, denoted by v. The standard unit for the reaction rate is amount per volume per time. This is an intensive property, which does not depend on the amount of substance, for example mol L^{-1} sec^{-1}. In a previous section we introduced the rate of change. In practice it is the rate of change that we measure experimentally. We also briefly mentioned that in the reaction $2A \rightarrow B$, A is consumed twice as fast as the production of product, B. This means that the sign and magnitude of the rates of change will vary depending on which species we choose to measure.

A simple way to avoid these differences is to divide each rate of change by the species **stoichiometric coefficient**. In this case the stoichiometric coefficient of A is -2 and for B is $+1$. If we do this we obtain:

$$\frac{1}{-2}\frac{dA}{dt} = \frac{1}{1}\frac{dB}{dt} = v$$

In general, for a reaction of the form

$$n_1 A + n_2 B + \ldots \longrightarrow m_1 P + m_2 Q + \ldots$$

where $n_1, n_2, \ldots$ and $m_1, m_2, \ldots$ represent the stoichiometric coefficients, the reaction rate is given by:

$$\text{Rate} = v \equiv -\frac{1}{n_1}\frac{dA}{dt} = -\frac{1}{n_2}\frac{dB}{dt} \ldots = \frac{1}{m_1}\frac{dP}{dt} = \frac{1}{m_2}\frac{dQ}{dt} \ldots \qquad (2.1)$$

Defined this way, a reaction rate is independent of the species used to measure it. The same applies if a given species appears on both sides of a reaction. For example, in the reaction $A \rightarrow 2A$, the stoichiometric coefficient is $+1$ so that the reaction rate, v, is:

$$v = \frac{1}{+1}\frac{dA}{dt}$$

To make the definition of the reaction rate more formal, let us introduce the **extent of reaction**, indicated by the symbol, ξ. We define a change from ξ to $\xi + d\xi$ in time dt to mean that $c_1\, d\xi$ moles of A_1, $c_2\, d\xi$ moles of A_2 etc, react to form $c_n\, d\xi$ moles of A_n etc. By this definition we can state that for any component i, the following is true for the time interval dt:

$$dn_i = c_i\, d\xi \tag{2.2}$$

or

$$\frac{dn_i}{dt} = c_i\, \frac{d\xi}{dt}$$

where n_i equals the amount in moles of species i. From this relation we **define** the **extensive rate of reaction**, v_E, to be:

$$v_E \equiv \frac{d\xi}{dt}$$

In other words

$$\frac{dn_i}{dt} = c_i v_E \tag{2.3}$$

For the moment we will use v_E and v_I to distinguish the extensive and intensive reaction rates. Note that ξ has units of **amount** and v_E has units of **amount per unit time** and is therefore an **extensive property**, being dependent on the size of the system. The advantage of introducing the extent of reaction is that it allows us to formally define the rate of reaction independently of the species we use to measure the rate. This convenient property can be expressed as:

$$v_E \equiv \frac{d\xi}{dt} = -\frac{1}{c_1}\frac{dn_1}{dt} = -\frac{1}{c_2}\frac{dn_2}{dt} \cdots = \frac{1}{c_n}\frac{dn_n}{dt} = \frac{1}{c_{n+1}}\frac{dn_{n+1}}{dt} \cdots$$

Example 2.4

Express the rate of reaction and the rates of change for the following biochemical reaction: 2 ADP $\rightarrow$ ATP + AMP The rate of reaction is given by

$$v = \frac{d\xi}{dt} = \frac{dn(\text{ATP})}{dt} = \frac{dn(\text{AMP})}{dt}$$
$$= -\frac{1}{2}\frac{dn(\text{ADP})}{dt}$$

If the volume, V, of the system is constant we can also express the rate in terms of concentration, $C_i = n_i / V$.

We can therefore rewrite the rate of reaction in the form:

$$\frac{v_E}{V} = -\frac{1}{c_1}\frac{dC_1}{dt} = \ldots$$

where v_E has units of amount per unit time (mol s^{-1}). The relation v_E / V is the intensive version of the rate, v_I, with units of concentration per unit time (mol L^{-1} s^{-1}) and is the most commonly used form in biochemistry.

$$v_I = \frac{v_E}{V} = \frac{1}{c_i}\frac{dC_i}{dt}$$

or

$$\frac{dC_i}{dt} = c_i v_I \tag{2.4}$$

where C_i is the concentration of species i and v_I is the **intensive rate of reaction**. For constant volume, single compartment systems, this is a commonly encountered equation in models of cellular networks. The above equation may also be expressed as:

$$\frac{1}{V}\frac{dn_i}{dt} = c_i v_I \tag{2.5}$$

to emphasize the change in mass that accompanies a reaction. Recall that v_I is expressed as mol L^{-1} s^{-1}. If a E or I subscript is not used on v then the specific form should be clear from the context. In this book, where we use v, we will generally mean v_I, the intensive form.

In situations involving multiple compartments of different volumes or where there are specific mass conservation laws at work, the intensive rate is not appropriate. This is because the intensive version is unable to keep track of the total number of moles undergoing transformation. In these situations it is necessary to deal explicitly with the extensive rate of reaction, in other words:

$$\frac{dn_i}{dt} = V\ c_i v_I$$

A Word on Notation

In many texts, the concentration (molarity) of a substance, X, is denoted using square brackets, as in [X]. To avoid unnecessary clutter in the current text, the use of square brackets to indicate molarity will be relaxed.

2.3 Mass-Balance Equations

In the last chapter we briefly considered the various ways in which biochemical networks can be depicted. Ultimately there is the desire to convert a visual map of a biochemical network into a mathematical representation. An increasingly common need is to create quantitative models where one can either describe the distribution of flows in a network or investigate how the concentration of different species change in time. A quantitative model can be used to study different perturbations, such as knockouts, on the network's phenotype. In order to create such mathematical models we must consider a fundamental principle in biochemical networks which is **mass conservation**.

Consider a simple network comprising two reactions, v_1 and v_2, with a common species, S. We assume that the first reaction, v_1 produces S and

the second reaction, v_2, consumes S (Figure 2.2).

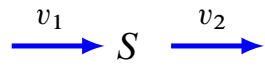
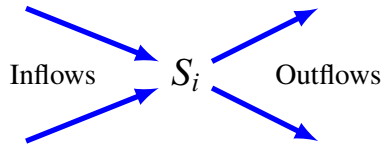


Figure 2.2: Simple Two Step Pathway.

According to the law of conservation of mass, any observed change in the amount of species, S must be due to the difference between the inward rate, v_1 and outward rate, v_2. That is the change in concentration of S is given by the differential equation:

$$\frac{dS}{dt} = v_1 - v_2$$

The above equation is called a **mass-balance equation**. In general for more complex systems such as the one shown in Figure 2.3 where there are multiple inflows and outflows, the mass-balance equation is given by:



$$dS_i/dt = \sum \text{Inflow} - \sum \text{Outflows}$$

Figure 2.3: Mass Balance: The rate of change in species S_i is equal to the difference between the sum of the inflows and the sum of the outflows

$$\frac{dS_i}{dt} = \sum Inflows - \sum Outflows \tag{2.6}$$

For an even more general representation, we can write the mass-balance equations using the stoichiometric coefficients. The rate at which a given

reaction, v_j contributes to change in a species, S_i is given by the stoichiometric coefficient of the species, S_i with respect to the reaction, c_{ij}, multiplied by the reaction rate, v_j. That is, a reaction j contributes, $c_{ij}\,v_j$ rate to changes in species S_i. For a species, S_i with multiple reactions producing and consuming S_i, the mass-balance equation (assuming constant volume conditions) is given by:

$$\frac{dS_i}{dt} = \sum_j c_{ij}\,v_j \tag{2.7}$$

where c_{ij} is the stoichiometric coefficient for species i with respect to reaction, j. For reactions that consume a species, the stoichiometric coefficient is often negative. (See "Enzyme Kinetics for Systems Biology", [77]) . In considering the simple example in Figure 2.2, the stoichiometric coefficient for S with respect to v_1 is $+1$ and for v_2 is -1. That is

$$\frac{dS}{dt} = (+1)v_1 + (-1)v_2 = v_1 - v_2$$

The way in which the construction of the mass-balance equation is described may seem overly formal, however the formality allows software to be written that can automatically convert network diagrams into mass-balance differential equations.

Example 2.5

Consider a more complex linear chain of reactants from S_1 to S_5 shown in Figure 2.4. Write out the mass-balance equations for this simple system.

$$S_1 \xrightarrow{v_1} S_2 \xrightarrow{v_2} S_3 \xrightarrow{v_3} S_4 \xrightarrow{v_4} S_5$$

Figure 2.4: Simple Straight Chain Pathway.

$$\frac{dS_1}{dt} = -v_1 \qquad \frac{dS_2}{dt} = v_1 - v_2$$
$$\frac{dS_3}{dt} = v_2 - v_3 \qquad \frac{dS_4}{dt} = v_3 - v_4$$
$$\frac{dS_5}{dt} = v_4 \tag{2.8}$$

Each species in the network is assigned a mass-balance equation which accounts for the flows into and out of the species pool.

For a branched system such as the following:

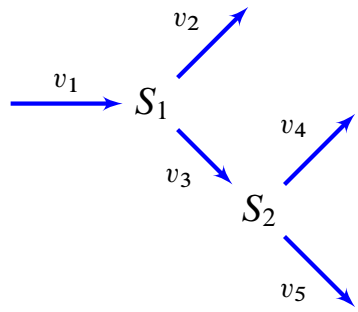


Figure 2.5: Multi-Branched Pathway.

the mass-balance equations are given by:

$$\frac{dS_1}{dt} = v_1 - v_2 - v_3$$
$$\frac{dS_2}{dt} = v_3 - v_4 - v_5$$

Example 2.6

Write out the mass-balance equation for the more complex pathway:

$$\begin{aligned} A + X &\xrightarrow{v_1} 2X \\ X + Y &\xrightarrow{v_2} Z \\ Z &\xrightarrow{v_3} Y + B \end{aligned}$$

This example is more subtle because we must be careful to take into account the stoichiometry change between the reactant and product side in the first reaction (v_1). In reaction v_1, the overall stoichiometry for X is $+1$ because two X molecules are made for every one consumed. Taking this into account the rate of change of species X can be written as:

$$\frac{dX}{dt} = -v_1 + 2v_1 - v_2$$

or more simply as $v_1 - v_2$. The full set of mass-balance equations can therefore be written as:

$$\frac{dA}{dt} = -v_1 \qquad \frac{dX}{dt} = v_1 - v_2$$

$$\frac{dY}{dt} = v_3 - v_2 \qquad \frac{dZ}{dt} = v_2 - v_3$$

$$\frac{dB}{dt} = v_3$$

Example 2.7

Write out the mass-balance equation for pathway:

$$\begin{aligned} S_1 + S_3 &\xrightarrow{v_1} S_2 \\ 2S_2 &\xrightarrow{v_2} S_3 \\ S_3 &\xrightarrow{v_3} 3S_4 \end{aligned}$$

In this example we have non-unity stoichiometries in the second and third reaction steps. The mass-balance equations are given by:

$$\frac{dS_1}{dt} = -v_1 \qquad \frac{dS_2}{dt} = v_1 - 2v_2$$
$$\frac{dS_3}{dt} = v_2 - v_3 \qquad \frac{dS_4}{dt} = 3v_3$$

It is therefore fairly straight forward to derive the balance equations from a visual inspection of the network. Many software tools exist that will assist in this effort by converting network diagrams, either represented visually on a computer screen (for example, JDesigner) or provide a text file listing the reactions in the network (for example via Jarnac).

2.4 Stoichiometry Matrix

When describing multiple reactions in a network, it is convenient to represent the stoichiometries in a compact form called the **stoichiometry matrix**, traditionally denoted by $\mathbf{N}$. The symbol $\mathbf{N}$ refers to number, although some recent researchers use the symbol $\mathbf{S}$. The stoichiometry matrix is a m row by n column matrix where m is the number of species and n the number of reactions:

$$\mathbf{N} = m \times n \text{ matrix}$$

The columns of the stoichiometry matrix correspond to the individual chemical reactions in the network, the rows to the molecular species, one row per species. Thus the intersection of a row and column in the matrix indicates whether a certain species takes part in a particular reaction or not, and, according to the sign of the element, whether there is a net loss or gain of substance, and by the magnitude, the relative quantity of substance that takes part in that reaction. That is the elements of the stoichiometry matrix do not concern themselves with the rate of reaction.

In general the stoichiometry matrix has the form:

$$\mathbf{N} = \begin{array}{c} \\ S_i \end{array} \begin{array}{c} \overset{\longleftarrow \quad v_j \quad \longrightarrow}{\begin{bmatrix} c_{ij} & \cdots & \cdots \\ \vdots & & \\ \vdots & & \end{bmatrix}} \end{array}$$

where c_{ij} is the stoichiometry coefficient for the i^{th} species and j^{th} reaction.

Example 2.8

Write out the stoichiometry matrix for the simple chain of reactions which has five molecular species and four reactions as shown below. The four reactions are labeled, v_1 to v_4.

$$S_1 \xrightarrow{v_1} S_2 \xrightarrow{v_2} S_3 \xrightarrow{v_3} S_4 \xrightarrow{v_4} S_5$$

The stoichiometry matrix for this simple system is given by:

$$\mathbf{N} = \begin{array}{c} \begin{matrix} v_1 & v_2 & v_3 & v_4 \end{matrix} \\ \begin{bmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{array} \begin{array}{l} S_1 \\ S_2 \\ S_3 \\ S_4 \\ S_5 \end{array}$$

Example 2.9

Write out the stoichiometry matrix for the multibranched pathway shown in Figure 2.5

$$\mathbf{N} = \begin{array}{c} \begin{matrix} v_1 & v_2 & v_3 & v_4 & v_5 \end{matrix} \\ \begin{bmatrix} 1 & -1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 \end{bmatrix} \end{array} \begin{array}{l} S_1 \\ S_2 \end{array}$$

To illustrate that the stoichiometry matrix can be applied to other kinds of networks, let us look at a simple signaling network and two simple gene regulatory networks.

Signaling Networks

Figure 2.6 illustrates a simple protein signaling network, comprising two double phosphorylation cycles coupled by inhibition by protein C on the lower double cycle (D, E and F). In this model, all species are proteins and we can assume that protein A and D are unphosphorylated, B and E singly phosphorylated and C and F doubly phosphorylated. C acts as a kinase and phosphorylates D and E. The reverse reactions, v_2, v_4, v_7 and v_8 are assumed to be catalyzed by phosphatases.

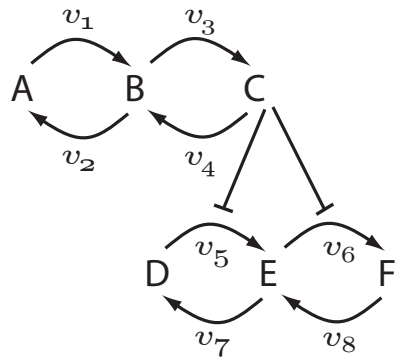


Figure 2.6: Simple Signaling Network. Protein C inhibits the activity of reactions v_5 and v_6.

There is no specified stoichiometric mechanism for the inhibition on v_5 and v_6. Therefore the stoichiometric matrix will contain no information on this. The stoichiometric matrix for this system will look like:

$$\mathbf{N} = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array} \begin{array}{c} \begin{array}{cccccccc} v_1 & v_2 & v_3 & v_4 & v_5 & v_6 & v_7 & v_8 \end{array} \\ \left[\begin{array}{cccccccc} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & -1 \end{array}\right] \end{array} \tag{2.9}$$

The stoichiometric matrix can be seen to be composed of two separate blocks corresponding to the two cycle layers. It is important to note that whenever there are regulatory interactions in a pathway diagram, these do not appear in the stoichiometry matrix. Instead, such information will reside in the rate law that describes the regulation. If however the mechanism for the regulation is made explicit then details of the regulation will appear in the stoichiometry matrix. Figure 2.7 will shows an simple example of an inhibitor I regulating a reaction, S to P. On the left is displayed the implicit regulatory interaction. All we see is a blunt ended arrow indicating inhibition. In this case, details of the regulation will be found in the rate law governing the conversion of S to P. On the right is displayed an explicit mechanism, a simple competitive inhibition. In this case all details of the mechanism will find its way into the stoichiometry matrix. Figure 2.8 shows a comparison of the implicit and explicit models in terms of the stoichiometry matrix.

Gene Regulatory Networks

Consider a transcription factor P_1 that regulates v_3 by repressing the rate of gene expression (Figure 2.9). In this model we have production of P_1 from reaction v_1 and degradation of P_1 via v_2. The construction of the stoichiometry matrix will depend on how we represent the regulated step, v_3. If regulation is implied, i.e. there is no explicit kinetic mechanism, then the regulation will not appear in the stoichiometry matrix. For the network

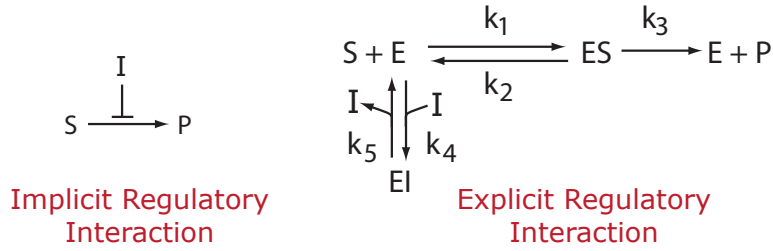


Figure 2.7: Example of implicit and explicit depiction of a regulatory interaction. The left-hand mechanism involving inhibitor I will not appear in the stoichiometry matrix where as the explicit mechanism will.

on the left in Figure 2.9, the stoichiometry matrix is given below:

$$\mathbf{N} = \begin{matrix} \\ P_1 \end{matrix} \begin{matrix} \begin{matrix} v_1 & v_2 \end{matrix} \\ \begin{bmatrix} 1 & -1 \end{bmatrix} \end{matrix} \tag{2.10}$$

The stoichiometry matrix has only one row indicating that there is only one species in the model, P_1 and there is no hint in the stoichiometry matrix that there is regulation.

Consider now that the interaction between P_1 and v_3 is made mechanistically explicit. The right hand network in Figure 2.9 shows one possible way in which to represent the interaction of the transcription factor, P_1 with gene v_3. In the explicit model, the transcription factor, P_1 is assumed to bind to a repressor site preventing gene expression. In the explicit model there are two new species, designated active gene and inactive gene. The stoichiometry matrix will therefore include two additional rows corresponding to these two species. The stoichiometry matrix for the explicit model is shown below:

$$\mathbf{N} = \begin{matrix} \\ P_1 \\ P_1(\text{Active}) \\ P_1(\text{InActive}) \end{matrix} \begin{matrix} \begin{matrix} v_1 & v_2 & v_{4r} & v_{4f} \end{matrix} \\ \begin{bmatrix} 1 & -1 & -1 & 1 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix} \end{matrix} \tag{2.11}$$

$$\mathbf{N} = \begin{array}{c} \\ S \\ P \\ I \end{array} \begin{array}{c} v_1 \\ \left[\begin{array}{r} -1 \\ 1 \\ 0 \end{array}\right. \end{array} \qquad \mathbf{N} = \begin{array}{c} \\ S \\ P \\ I \\ ES \\ EI \end{array} \begin{array}{c} \begin{array}{ccccc} v_1 & v_2 & v_3 & v_4 & v_5 \end{array} \\ \left[\begin{array}{rrrrr} -1 & 1 & 0 & -1 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 \\ 1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{array}\right. \end{array}$$

Implicit Explicit

Figure 2.8: Stoichiometry matrices corresponding to the two models in Figure 2.7

2.5 The System Equation

Equation 2.7, which describes the mass balance equation, can be reexpressed in terms of the stoichiometry matrix to form the **system equation**.

$$\frac{d\mathbf{s}}{dt} = \mathbf{N}\boldsymbol{v} \tag{2.12}$$

where $\mathbf{N}$ is the $m \times n$ stoichiometry matrix and $\boldsymbol{v}$ is the n dimensional rate vector, whose ith component gives the rate of reaction i as a function of the species concentrations. $\mathbf{s}$ is the mm vector of species.

Looking again at the simple chain of reactions in Figure 2.4, the system equation can be written down as:

$$\frac{d\mathbf{s}}{dt} = \mathbf{N}\boldsymbol{v} = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{bmatrix} \tag{2.13}$$

If stoichiometry matrix is multiplied into the rate vector, the mass-balance equations show earlier (2.8) are recovered.

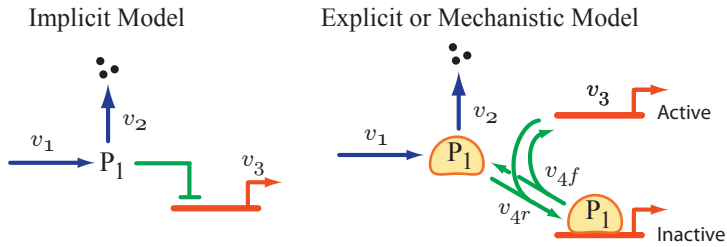


Figure 2.9: Two simple gene regulatory networks involving gene repression. On the left side is the implicit model where P_1 represses v_3, on the right side is the explicit model showing a more detailed mechanism for the regulation.

All stoichiometric interactions are placed in the stoichiometry matrix. The example shown in Figure 2.6 and Figure 2.9 illustrated non-stoichiometric interactions, namely two inhibition interactions from C to reactions v_5 and v_6 and repression on v_3 by P_1. As was noted, these interactions do no occur in the stoichiometry matrix. Instead they will be found in the rate vector, $\boldsymbol{v}$ in the form of a particular rate law.

The stoichiometry matrix represents the mass transfer connectivity of the network and contains information on the network's structural characteristics. These characteristics fall into two groups, relationships among the species and relationships among the reaction rates. These relationships will be considered in a later chapter.

Further Reading

1. Sauro HM (2011) Enzyme Kinetics for Systems Biology. ISBN: 978-0982477311

Exercises

1. Explain the difference between the terms: Stoichiometric amount, Stoichiometric coefficient, rate of change (dX/dt) and reaction rate (v_i).

2. Determine the stoichiometric amount and stoichiometric coefficient for each species in the following reactions:

$$\begin{aligned} A &\longrightarrow B \\ A + B &\longrightarrow C \\ A &\longrightarrow B + C \\ 2A &\longrightarrow B \\ 3A + 4B &\longrightarrow 2C + D \\ A + B &\longrightarrow A + C \\ A + 2B &\longrightarrow 3B + C \end{aligned}$$

3. Derive the set of differential equations for the following model in terms of the rate of reaction, v_1, v_2 and v_3:

$$\begin{aligned} A &\xrightarrow{v_1} 2B \\ B &\xrightarrow{v_2} 2C \\ C &\xrightarrow{v_3} \end{aligned}$$

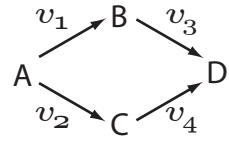
4. Derive the set of differential equations for the following model in terms of the rate of reaction, v_1, v_2 and v_3:

$$\begin{aligned} A &\xrightarrow{v_1} B \\ 2B + C &\xrightarrow{v_2} B + D \\ D &\xrightarrow{v_3} C + A \end{aligned}$$

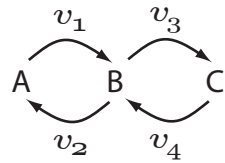
5. Write out the stoichiometry matrix for the networks in question 3 and 4

6. Derive the stoichiometry matrix for each of the following networks. In addition write out the mass-balance equations in each case.

(a)



(b)



(c)

$$A + X \xrightarrow{v_1} B + Y \qquad B + X \xrightarrow{v_2} Y$$

$$B \xrightarrow{v_3} C \qquad C + X \xrightarrow{v_4} D + Y$$

$$D + Y \xrightarrow{v_5} X \qquad X \xrightarrow{v_6} Y$$

$$X + W \xrightarrow{v_7} 2Y \qquad 2Y \xrightarrow{v_8} X + W$$

7. A gene G_1 expresses a protein p_1 at a rate v_1. p_1 forms a tetramer (4 subunits), called p_1^4 at a rate v_2. The tetramer negatively regulates

a gene G_2. p_1 degrades at a rate v_3. G_2 expresses a protein, p_2 at a rate v_9. p_2 is cleaved by an enzyme at a rate v_4 to form two protein domains, p_2^1 and p_2^2. p_2^1 degrades at a rate v_5. Gene G_3 expresses a protein, p_3 at a rate v_6. p_3 binds to p_2^2 forming an active complex, p_4 at a rate v_{10}, which can bind to gene G_1 and activate G_1. p_4 degrades at a rate v_7. Finally, p_2^1 can form a dead-end complex, p_5, with p_4 at a rate v_8.

8. (a) Draw the network represented in the description given above.

(b) Write out the differential equation for each protein species in the network in terms of $v_1, v_2, \ldots$.

(c) Write out the stoichiometric matrix for the network.

9. Write out the differential equations for the system depicted in equation 2.13.