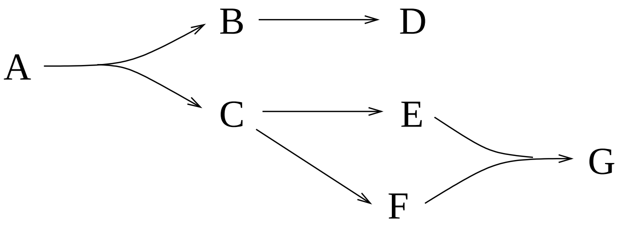
Appendix D

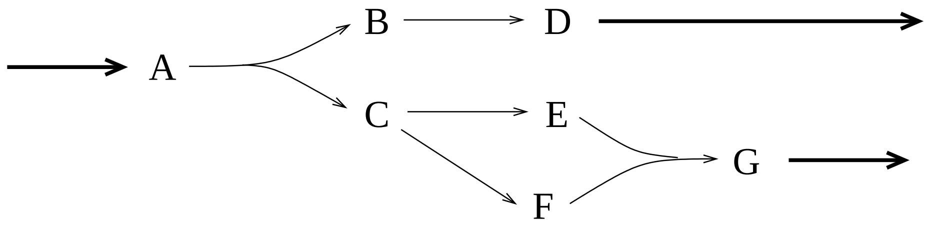
Exercise Solutions

Chapter 2

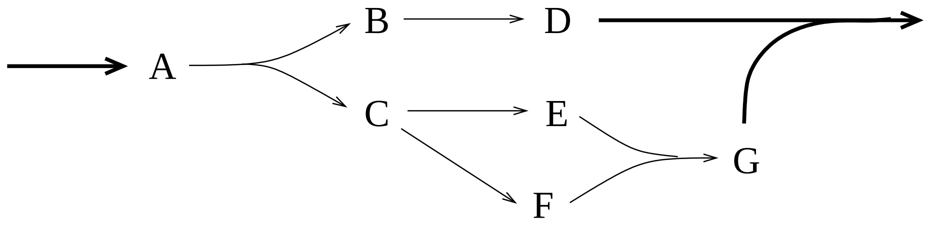
2.1.1. The reaction graph is:



2.1.2. Adding three reactions, we can write:



We can construct the following nextwork by adding two reactions to the original:



2.1.3. The rate constant k_0 has dimensions of concentration $\cdot$ time^{-1}. The rate constant k_1 has dimensions of time^{-1}. The ratio k_0/k_1 thus has dimensions of concentration.

2.1.4. With $z(t) = a(t) - a^{ss} = a(t) - \frac{k_0}{k_1}$, we have

$$\frac{d}{dt}z(t) = \frac{d}{dt}(a(t) - a^{ss}) = \frac{d}{dt}a(t) + 0 = \frac{d}{dt}a(t) = k_0 - k_1 a(t)$$

where the last equality follows from equation (2.5). Then, note that

$$k_0 - k_1 a(t) = k_1(k_0/k_1 - a(t)) = -k_1(a(t) - k_0/k_1) = -k_1 z(t).$$

Thus we have

$$\frac{d}{dt}z(t) = -k_1 z(t).$$

This has the same form as equation (2.2), and so has solution (compare with equation (2.4)):

$$z(t) = De^{-k_1 t}$$

where $D = z(0)$. Then, since $z(t) = a(t) - k_0/k_1$, we have

$$a(t) - k_0/k_1 = De^{-k_1 t}$$

so that

$$a(t) = De^{-k_1 t} + k_0/k_1.$$

2.1.5. From equation (2.6) we have $a(t) = De^{-k_1 t} + \frac{k_0}{k_1}$, so that, at time $t = 0$,

$$a(0) = De^0 + \frac{k_0}{k_1} = D + \frac{k_0}{k_1}.$$

Then $D = a(0) - \frac{k_0}{k_1}$, so equation (2.6) gives

$$a(t) \quad = \quad \left(A_0 - \frac{k_0}{k_1}\right) e^{-k_1 t} + \frac{k_0}{k_1}.$$

2.1.6. a) With $z(t) = a(t) - a^{ss} = a(t) - \frac{k_- T}{k_+ + k_-}$, we have

$$\frac{d}{dt}z(t) = \frac{d}{dt}(a(t) - a^{ss}) = \frac{d}{dt}a(t) + 0 = \frac{d}{dt}a(t) = k_- T - (k_+ + k_-)a(t)$$

where the last equality is equation (2.12). Then, note that

$$k_- T - (k_+ + k_-)a(t) = (k_+ + k_-)(\frac{k_- T}{k_+ + k_-} - a(t)) = -(k_+ + k_-)(a(t) - \frac{k_- T}{k_+ + k_-}) = -(k_+ + k_-)z(t).$$

Thus we have

$$\frac{d}{dt}z(t) = -(k_+ + k_-)z(t).$$

This has the same form as equation (2.2), and so has solution (compare with equation (2.4)):

$$z(t) = De^{-(k_+ + k_-)t}$$

where $D = z(0)$. Then, since $z(t) = a(t) - \frac{k_- T}{k_+ + k_-}$, we have

$$a(t) - \frac{k_- T}{k_+ + k_-} = De^{-(k_+ + k_-)t}$$

so that

$$a(t) = De^{-(k_+ + k_-)t} + \frac{k_- T}{k_+ + k_-}.$$

b) From $a(t) = De^{-(k_+ + k_-)t} + \frac{k_- T}{k_+ + k_-}$ we have, at time $t = 0$,

$$A_0 = a(0) = De^0 + \frac{k_- T}{k_+ + k_-} = D + \frac{k_- T}{k_+ + k_-}.$$

Then $D = a(0) - \frac{k_- T}{k_+ + k_-}$, so, with the solution (2.14), we can write

$$a(t) \quad = \quad \left(A_0 - \frac{k_- T}{k_+ + k_-}\right) e^{-(k_+ + k_-)t} + \frac{k_- T}{k_+ + k_-}.$$

2.1.7. Species A and C are not involved in any conservation: they can be exchanged directly with the external environment. Species B and D, however, only cycle back and forth: when a molecule of D is produced, a molecule of B is consumed, and vice-versa. Consequently, the total concentration $[B] + [D]$ is fixed.

2.1.8. Each time the a reaction occurs, a pair of C and D molecules are either produced or consumed. Thus all changes in the number of C and D molecules are coordinated. For example, if the numbers of C and D molecules are initially equal, they will always be equal. Likewise, if there is initially a difference between the number of C molecules and the number of D molecules, (e.g. 5 more C than D molecules), then that difference will be maintained even if the numbers of molecules changes.

2.1.9. Given $a(t) = 1/(2kt + 1/A_0))$ we begin by observing that

$$a(0) = \frac{1}{0 + 1/A_0} = A_0$$

as required. We next calculate

$$\frac{d}{dt}a(t) = -\frac{1}{(2kt + 1/A_0)^2} \cdot 2k = \frac{-2k}{(2kt + 1/A_0)^2},$$

while

$$-2k(a(t))^2 = \frac{-2k}{(2kt + 1/A_0)^2},$$

confirming that this is a solution of the differential equation.

2.1.10. The steady state concentrations satisfy the algebraic equations:

$$\begin{aligned} 0 &= 3 - 2a^{ss} - 2.5a^{ss}b^{ss} \\ 0 &= 2a^{ss} - 2.5a^{ss}b^{ss} \\ 0 &= 2.5a^{ss}b^{ss} - 3c^{ss} \\ 0 &= 2.5a^{ss}b^{ss} - 4d^{ss}. \end{aligned}$$

To solve this system of equation, we note that the second equation can be factored as

$$0 = a^{ss}(2 - 2.5b^{ss}).$$

Then, since a^{ss} cannot be zero (from the first equation), we have

$$0 = 2 - 2.5b^{ss} \qquad \text{so} \qquad b^{ss} = 4/5.$$

Substituting this into the first equation gives

$$0 = 3 - 2a^{ss} - 2.5a^{ss}(4/5) \qquad \text{so} \qquad 3 = (2+2)a^{ss}$$

giving $a^{ss} = 3/4$. Then $2.5a^{ss}b^{ss} = (5/2)(3/4)(4/5) = 3/2$, we can solve the last two equations: $c^{ss} = 1/2$, $d^{ss} = 3/8$. (Concentrations are in units of mM.)

2.2.1. The conversion reaction ($A \leftrightarrow B$) can be assumed in rapid equilibrium, because its time-scale is shorter than either decay reaction. Using $\tilde{a}$, $\tilde{b}$ for the concentrations in the reduced model, we have the equilibrium condition

$$\frac{\tilde{b}(t)}{\tilde{a}(t)} = \frac{k_1}{k_{-1}},$$

from which we can write

$$\tilde{b}(t) = \tilde{a}(t)\frac{k_1}{k_{-1}}.$$

With this condition in hand, we now turn to the dynamics of the decay processes. The rapid equilibrium assumption leads to A and B forming an equilibrated pool. The decay processes are best described by addressing the dynamics of this mixed pool. The reaction network (2.23) thus reduces to:

$$\longleftarrow (\text{pool of } A \text{ and } B) \longrightarrow$$

Let $\tilde{c}(t)$ be the total concentration in the pool of A and B (that is, $\tilde{c}(t) = \tilde{a}(t) + \tilde{b}(t)$). The relative fractions of A and B in the pool are fixed by the equilibrium ratio. This allows us to write

$$\begin{aligned} \tilde{c}(t) &= \tilde{a}(t) + \tilde{b}(t) \\ &= \tilde{a}(t) + \tilde{a}(t)\frac{k_1}{k_{-1}} \\ &= \frac{k_{-1} + k_1}{k_{-1}}\tilde{a}(t). \end{aligned}$$

Thus

$$\tilde{a}(t) = \frac{k_{-1}}{k_{-1}+k_1}\tilde{c}(t)$$

while

$$\tilde{b}(t) \quad = \quad \tilde{c}(t) - \tilde{a}(t) = \frac{k_1}{k_{-1}+k_1}\tilde{c}(t).$$

The species pool decays at rate $k_0\tilde{a}(t) + k_2\tilde{b}(t)$. Thus, the pooled concentration satisfies

$$\begin{aligned}
\frac{d}{dt}\tilde{c}(t) &= -(k_0\tilde{a}(t) + k_2\tilde{b}(t)) \\
&= -\left(k_0\frac{k_{-1}}{k_{-1}+k_1}\tilde{c}(t) + k_2\frac{k_1}{k_{-1}+k_1}\tilde{c}(t)\right) \\
&= -\frac{k_0k_{-1}+k_2k_1}{k_{-1}+k_1}\tilde{c}(t)
\end{aligned}$$

Schematically, we have reduced the model to a single degradation reaction:

$$C \xrightarrow{\frac{k_0k_{-1}+k_2k_1}{k_{-1}+k_1}}.$$

2.2.2. The model is

$$\begin{aligned}
\frac{d}{dt}a(t) &= k_0 + k_{-1}b(t) - k_1a(t) \\
\frac{d}{dt}b(t) &= k_1a(t) - (k_{-1}+k_2)b(t)
\end{aligned}$$

To determine steady state, we solve

$$\begin{aligned}
0 &= k_0 + k_{-1}b^{ss} - k_1a^{ss} \\
0 &= k_1a^{ss} - (k_{-1}+k_2)b^{ss}
\end{aligned}$$

Adding these equation together, we have

$$0 = k_0 - k_2b^{ss} \qquad \text{so} \qquad b^{ss} = \frac{k_0}{k_2}.$$

Then, substituting, we have

$$0 \quad = \quad k_1a^{ss} - (k_{-1}+k_2)\frac{k_0}{k_2} \qquad \text{so} \qquad a^{ss} = \frac{k_0(k_{-1}+k_2)}{k_1k_2}.$$

In steady state, the ratio b/a is then

$$\frac{b^{ss}}{a^{ss}} = \frac{k_1}{k_{-1}+k_2}$$

which is different from the equilibrium constant k_1/k_{-1} if $k_2 \neq 0$. When k_{-1} is large compared to k_2 (so that the time-scale separation is extreme), this concentration ratio is close to the equilibrium constant, since in that case $k_{-1} + k_2 \approx k_{-1}$.

2.2.3. From Exercise 2.2.2 we have the steady-state concentration of A in the original model as

$$a^{ss} = \frac{k_0(k_{-1}+k_2)}{k_1k_2}$$

From the reduced model (2.25), we have

$$\tilde{c}^{ss} = \frac{k_0(k_{-1}+k_1)}{k_2k_1}$$

so in this reduced model

$$\tilde{a}^{ss} = \frac{k_{-1}}{k_{-1}+k_1}\tilde{c}^{ss} = \frac{k_{-1}k_0}{k_2k_1}$$

Comparing these two descriptions of the steady-state concentration of A, we have

$$a^{ss} - \tilde{a}^{ss} = \frac{k_0(k_{-1}+k_2)}{k_1k_2} - \frac{k_{-1}k_0}{k_2k_1} = \frac{k_0}{k_1k_2}(k_{-1}+k_2-k_{-1}) = \frac{k_0}{k_1}.$$

The relative error is then

$$\frac{a^{ss}-\tilde{a}^{ss}}{a^{ss}} = \frac{\frac{k_0}{k_1}}{\frac{k_0(k_{-1}+k_2)}{k_1k_2}} = \frac{k_2}{k_{-1}+k_2}$$

which is near zero when k_{-1} is much larger than k_2.

2.2.4. With $\tilde{a}(t) = a^{qss}(t) = (k_0 + k_{-1}\tilde{b}(t))/k_1$, we have, at the initial time $t = 0$:

$$\tilde{a}(0) + \tilde{b}(0) = \frac{k_0 + k_{-1}\tilde{b}(0)}{k_1} + \tilde{b}(0) = \frac{k_0 + (k_{-1}+k_1)\tilde{b}(0)}{k_1}.$$

To ensure that the total concentration in the reduced model agrees with the original model, we set:

$$a(0) + b(0) = \tilde{a}(0) + \tilde{b}(0)$$

so that

$$\tilde{b}(0) = \frac{k_1(a(0)+b(0)) - k_0}{(k_{-1}+k_1)}.$$

For the parameter values in Figure 2.14, we have

$$\tilde{b}(0) = \frac{20(12) - 5}{(12+20)} = \frac{235}{32}.$$

2.2.5. The original model is

$$\begin{aligned}
\frac{d}{dt}a(t) &= k_{-1}b(t) - (k_0+k_1)a(t) \\
\frac{d}{dt}b(t) &= k_1a(t) - (k_{-1}+k_2)b(t).
\end{aligned}$$

If $k_0 \gg k_2$ and $k_1 + k_{-1} \gg k_2$, then A is only involved in fast reactions, and we may put $a(t)$ in quasi-steady-state with respect to $b(t)$. We set

$$0 = k_{-1}b(t) - (k_0 + k_1)a^{qss}(t) \qquad \text{so} \qquad a^{qss}(t) = \frac{k_{-1}b(t)}{k_0 + k_1}.$$

To perform a model reduction, we set $\tilde{a}(t) = a^{qss}(t)$ and substitute:

$$\frac{d}{dt}\tilde{b}(t) \quad = \quad k_1\frac{k_{-1}\tilde{b}(t)}{k_0 + k_1} - (k_{-1} + k_2)\tilde{b}(t) = -\left(\frac{k_{-1}k_0}{k_0 + k_1} + k_2\right)\tilde{b}(t).$$

Together with $\tilde{a}(t) = \frac{k_{-1}b(t)}{k_0+k_1}$, this is the reduced model.

Chapter 3

3.1.1. Applying a rapid-equilibrium assumption to the association/disocciation reaction gives

$$k_1 se(t) = \text{forward rate of reaction} = \text{backward rate of reaction} = k_{-1}c(t)$$

Making use of the moiety conservation $e_T = e + c$, we have

$$k_{-1}c(t) = k_1 s(t)(e_T - c(t)).$$

Solving gives

$$c(t) = \frac{k_1 e_T s(t)}{k_{-1} + k_1 s(t)}$$

which can be written as

$$c(t) = \frac{e_T s(t)}{\frac{k_{-1}}{k_1} + s(t)}.$$

The rate of formation of product p is then

$$\frac{dp}{dt} = k_2 c(t) = \frac{k_2 e_T s(t)}{\frac{k_{-1}}{k_1} + s(t)}.$$

Defining $V_{\text{max}} = k_2 e_T$ and $K_M = \frac{k_{-1}}{k_1}$, this rate can be written in the standard form:

$$\frac{V_{\text{max}} s(t)}{K_M + s(t)}.$$

3.1.2. a) With $v(s) = ks^n$, we find

$$\frac{s}{v}\frac{dv}{ds} = \frac{s}{ks^n}\frac{d}{ds}ks^n = \frac{s}{ks^n} \cdot kns^{n-1} = n$$

So the substrate s has kinetic order n in this reaction.

b) When s is near zero, we have $K_M + s \approx K_M$ so

$$\frac{V_{\max} s}{K_M + s} \approx \frac{V_{\max}}{K_M} s$$

The first-order behaviour of the enzyme-catalysed reaction is thus characterized by rate constant $\frac{V_{\max}}{K_M}$.

3.1.3. The equilibrium conditions for the two reactions in the reaction scheme (3.8) are:

$$sek_1 = k_{-1}c \qquad \text{and} \qquad ck_2 = k_{-2}pe$$

Solving for c, we have

$$c = sek_1/k_{-1}$$

Substituting gives

$$sek_1k_2/k_{-1} = k_{-2}pe$$

Dividing out e and re-arranging gives

$$\frac{p}{s} = \frac{k_1k_2}{k_{-1}k_{-2}}$$

3.1.4. With $c_1 = [EA]$ and $c_2 = [EAB]$, we have

$$\begin{aligned}
\frac{dc_1}{dt} &= k_1ea - k_{-1}c_1 - k_2c_1b + k_{-2}c_2 \\
\frac{dc_2}{dt} &= k_2c_1b - k_{-2}c_2 - k_3c_2
\end{aligned}$$

At quasi-steady state,

$$\begin{aligned}
0 &= k_1ea - k_{-1}c_1 - k_2c_1b + k_{-2}c_2 \\
0 &= k_2c_1b - k_{-2}c_2 - k_3c_2
\end{aligned}$$

along with the conservation $e = e_T - c_1(t) - c_2(t)$. Solving this system, we find, from the second equation

$$k_2bc_1 - (k_{-2} + k_3)c_2 = 0$$

so

$$c_1 = \frac{k_{-2} + k_3}{k_2b} c_2$$

From the first equation

$$k_1(e_T - c_1 - c_2)a - (k_{-1} + k_2b)c_1 + k_{-2}c_2 = 0$$

so

$$k_1e_Ta - (k_1a + k_{-1} + k_2b)c_1 + k_{-2}c_2 - k_1ac_2 = 0$$

Substituting for c_1,

$$k_1e_Ta - (k_1a + k_{-1} + k_2b)\frac{k_{-2} + k_3}{k_2b}c_2 + (k_{-2} - k_1a)c_2 = 0$$

so

$$k_2bk_1e_Ta - (k_1a + k_{-1} + k_2b)(k_{-2} + k_3)c_2 + (k_{-2} - k_1a)k_2bc_2 = 0$$

Solving for c_2,

$$\begin{aligned}
c_2 &= \frac{k_1k_2e_Tab}{(k_1a + k_{-1} + k_2b)(k_{-2} + k_3) - k_{-2}k_2b + k_1k_2ab} \\
&= \frac{k_1k_2e_Tab}{k_1k_{-2}a + +k_1k_3a + k_{-1}k_{-2} + k_{-1}k_3 + k_2k_{-2}b + k_2k_3b - k_{-2}k_2b + k_1k_2ab} \\
&= \frac{k_1k_2e_Tab}{k_{-1}(k_{-2} + k_3) + k_1(k_{-2} + k_3)a + k_2k_3b + k_1k_2ab} \\
&= \frac{e_Tab}{\frac{k_{-1}(k_{-2}+k_3)}{k_1k_2} + \frac{k_{-2}+k_3}{k_2}a + \frac{k_3}{k_1}b + ab}
\end{aligned}$$

The rate of formation of product is

$$k_3c_2 = \frac{k_3e_Tab}{\frac{k_{-1}(k_{-2}+k_3)}{k_1k_2} + \frac{k_{-2}+k_3}{k_2}a + \frac{k_3}{k_1}b + ab}$$

as required.

3.1.5. a) When a is large, all terms that don't involve a are negligible. In that case, rate law (3.12) reduces to

$$v = \frac{V_{\max}ab}{K_Ba + ab} = \frac{V_{\max}b}{K_B + b}$$

To verify that this is consistent with the reaction scheme, consider the reduced network

$$\begin{aligned}
EA + B &\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} EAB \\
EAB &\xrightarrow{k_3} EA + P + Q
\end{aligned}$$

Letting c denote the concentration of ternary complex EAB, and letting e be the concentration of EA, we have

$$\frac{d}{dt}c(t) = k_2e(t)b(t) - k_{-2}c(t) - k_3c(t).$$

With the conservation $e_T = e + c$, we have, in quasi-steady state:

$$0 = k_2(e_T - c^{qss}(t))b(t) - (k_{-2} + k_3)c^{qss}(t).$$

The rate of formation of P and Q is then

$$k_3 c^{qss} = \frac{k_3 e_T b}{\frac{k_{-2}+k_3}{k_2} + b}$$

as required.

b) When b is large, all terms that don't involve b are negligible. In that case, rate law (3.12) reduces to

$$v = \frac{V_{\max} ab}{K_A b + ab} = \frac{V_{\max} a}{K_A + a}$$

To verify that this is consistent with the reaction scheme, consider the reduced network

$$E + A \xrightarrow{k_1} EAB$$

$$EAB \xrightarrow{k_3} E + P + Q$$

Letting c denote the concentration of ternary complex EAB, and letting e be the concentration of E, we have

$$\frac{d}{dt}c(t) = k_1 e(t)a(t) - k_3 c(t).$$

With the conservation $e_T = e + c$, we have, in quasi-steady state:

$$0 = k_1(e_T - c^{qss}(t))a(t) - k_3 c^{qss}(t).$$

The rate of formation of P and Q is then

$$k_3 c^{qss} = \frac{k_3 e_T a}{\frac{k_3}{k_1} + a}$$

as required.

3.2.1. The concentrations of the two complexes satisfy

$$\begin{aligned}\frac{d}{dt}c(t) &= k_1 s(t)e(t) - k_{-1}c(t) - k_2 c(t)\\ \frac{d}{dt}c_I(t) &= k_3 e(t)i - k_{-3}c_I(t),\end{aligned}$$

along with the conservation $e(t) = e_T - c(t) - c_I(t)$. In quasi-steady state:

$$\begin{aligned}0 &= k_1 s(e_T - c - c_I) - (k_{-1} + k_2)c\\ 0 &= k_3 i(e_T - c - c_I) - k_{-3}c_I.\end{aligned}$$

From the second equation, we have

$$c_I = \frac{k_3 i(e_T - c)}{k_{-3} + k_3 i}$$

Substituting into the first equation gives

$$0 = k_1 s e_T - k_1 s c - \frac{k_1 s k_3 i e_T}{k_{-3} + k_3 i} + \frac{k_1 s k_3 i c}{k_{-3} + k_3 i} - (k_{-1} + k_2)c$$

which is

$$0 = k_1 s e_T (1 - \frac{k_3 i}{k_{-3} + k_3 i}) + c\left(k_1 s\left(-1 + \frac{k_3 i}{k_{-3} + k_3 i}\right) - (k_{-1} + k_2)\right)$$

so

$$\begin{aligned}
c &= \frac{k_1 s e_T (1 - \frac{k_3 i}{k_{-3}+k_3 i})}{(k_{-1} + k_2) + k_1 s (1 - \frac{k_3 i}{k_{-3}+k_3 i})} \\
&= \frac{k_1 s e_T (\frac{k_{-3}}{k_{-3}+k_3 i})}{(k_{-1} + k_2) + k_1 s \frac{k_{-3}}{k_{-3}+k_3 i}} \\
&= \frac{k_1 s e_T}{(k_{-1} + k_2)(k_{-3} + k_3 i)/k_{-3} + k_1 s} \\
&= \frac{s e_T}{(k_{-1} + k_2)(k_{-3} + k_3 i)/(k_1 k_{-3}) + s} \\
&= \frac{s e_T}{\left(\frac{k_{-1}+k_2}{k_1}\right)\left(1 + \frac{k_3}{k_{-3}} i\right) + s}
\end{aligned}$$

The reaction rate is $k_2 c$.

3.2.2. In the case of uncompetitive inhibition, the reaction scheme is

$$\begin{aligned}
E + S \; &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \; ES \; \xrightarrow{k_2} \; E + P \\
ES + I \; &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \; ESI
\end{aligned}$$

With $c = [ES]$ and $c_I = [ESI]$, we have

$$\begin{aligned}
\frac{d}{dt} c(t) &= k_1 s(t) e(t) - (k_{-1} + k_2) c(t) \\
\frac{d}{dt} c_I(t) &= k_3 i c(t) - k_{-3} c_I(t).
\end{aligned}$$

With the conservation $e = e_T - c - c_I$, we have, in quasi-steady state

$$\begin{aligned}
0 &= k_1 s(e_T - c - c_I) - (k_{-1} + k_2)c \\
0 &= k_3 i c - k_{-3} c_I.
\end{aligned}$$

This gives

$$c_I = \frac{k_3 i}{k_{-3}} c.$$

So that we arrive at

$$0 \quad = \quad k_1 s(e_T - c - \frac{k_3 i}{k_{-3}} c) - (k_{-1} + k_2)c,$$

giving

$$\begin{aligned} c \quad &= \quad \frac{k_1 s e_T}{k_1 s(1 + \frac{k_3 i}{k_{-3}}) + (k_{-1} + k_2)} \\ &= \quad \frac{s e_T}{s(1 + \frac{k_3 i}{k_{-3}}) + \frac{k_{-1}+k_2}{k_1}}. \end{aligned}$$

The reaction rate is $k_2 c$. Dividing through by $(1 + \frac{k_3 i}{k_{-3}})$ gives the required form.

3.3.1. We consider an enzyme E that has two binding sites for ligand X. We suppose that the binding sites are identical, but the binding affinity may depend on state of the protein in a cooperative manner. Take the reaction scheme as:

$$E + X \underset{k_{-1}}{\overset{2k_1}{\rightleftharpoons}} EX$$

$$EX + X \underset{2k_{-2}}{\overset{k_2}{\rightleftharpoons}} EX_2$$

The fractional saturation is given by

$$Y = \frac{2[EX_2] + [EX]}{2([EX_2] + [EX] + [E])}.$$

We find in steady state

$$[EX] = \frac{2k_1}{k_{-1}}[E][X]$$

while

$$[EX_2] = \frac{k_2}{2k_{-2}}[EX][X] = \frac{k_2}{k_{-2}}\frac{k_1}{k_{-1}}[E][X]^2.$$

Let $K_1 = \frac{k_{-1}}{k_1}$ and $K_2 = \frac{k_{-2}}{k_2}$. Then

$$\begin{aligned} Y \quad &= \quad \frac{2[EX_2] + [EX]}{2([EX_2] + [EX] + [E])} \\ &= \quad \frac{2[E][X]^2/(K_1K_2) + 2[E][X]/K_1}{2([E][X]^2/(K_1K_2) + 2[E][X]/K_1 + [E])} \\ &= \quad \frac{[X]^2/(K_1K_2) + [X]/K_1}{[X]^2/(K_1K_2) + 2[X]/K_1 + 1}, \end{aligned}$$

as required.

3.3.2. With

$$Y = \frac{x^n}{K^n + x^n}$$

we note that the limiting value of Y is one, and that it reaches half this limiting value when $x = K$. Taking the derivative of Y, we have

$$\begin{aligned} \frac{d}{dx}Y(x) &= \frac{nx^{n-1}(K^n + x^n) - x^n(nx^{n-1})}{(K^n + x^n)^2} \\ &= \frac{nx^{n-1}K^n}{(K^n + x^n)^2}. \end{aligned}$$

When $x = K$, we have

$$\left.\frac{d}{dx}Y(x)\right|_{x=K} = \frac{nK^{n-1}K^n}{(K^n + K^n)^2} = \frac{nK^{2n-1}}{(2K^n)^2} = \frac{nK^{2n-1}}{4K^{2n}} = \frac{n}{4K}$$

as required.

3.3.3. With binding scheme:

$$P + nX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PX_n,$$

the equilibrium condition is

$$k_1[P][X]^n = k_{-1}[PX_n] \qquad \text{so} \qquad [PX_n] = [P][X]^n/K_1$$

where $K_1 = k_{-1}/k_1$. The fractional saturation is

$$Y = \frac{n[PX_n]}{n([P] + [PX_n])}.$$

In steady state, we find

$$Y = \frac{n[P][X]^n/K_1}{n([P] + [P][X]^n/K_1)} = \frac{[X]^n/K_1}{1 + [X]^n/K_1}$$

Equation (3.19) is recovered by setting $K^n = K_1$.

3.3.4. The concentration c of the complex satisfies

$$\frac{d}{dt}c(t) = k_1 e(t)s^2(t) - (k_{-1} + k_2)c(t)$$

where e is the enzyme concentration and s is the substrate concentration. With the conservation $e(t) = e_T - c(t)$, we have, in quasi-steady-state:

$$0 = k_1(e_T - c^{qss}(t))s^2(t) - (k_{-1} + k_2)c(t)$$

so

$$c^{qss} = \frac{k_1 e_T s^2}{k_1 s^2 + k_{-1} + k_2}$$

The rate of production of P is then

$$2k_2 c^{qss} = \frac{2k_2 e_T s^2}{\frac{k_{-1}+k_2}{k_1} + s^2}$$

as required.

3.4.1. A two-ligand symporter follows the overall scheme:

$$A_1 + B_1 + T \rightleftharpoons TA_1B_1 \rightleftharpoons TA_2B_2 \rightleftharpoons T + A_2 + B_2$$

As in the discussion of two-substrate enzymes in Section 3.1.2, the initial reaction is unlikely to be a three-molecule collision, but rather will follow a particular reaction scheme, e.g. a compulsory order mechanism in which A binds first, or a random-order scheme. The rate of transport will be equivalent to the rate law derived in Section 3.1.2, but will be reversible.

The analysis is identical for an antiporter: this is simply a matter of renaming the species in the 'reactant' and 'product' roles, e.g.:

$$A_1 + B_2 + T \rightleftharpoons TA_1B_2 \rightleftharpoons TA_2B_1 \rightleftharpoons T + A_2 + B_1$$

3.4.2. The scheme is

$$2C_1 + T \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} TC_2 \xrightarrow{k_2} 2C_2 + T,$$

where the the transport event has been put in rapid equilibrium. This is identical to the scheme in Exercise 3.3.4; the rate law follows from putting the complex in quasi-steady state.

3.5.1. The S-system model is

$$\begin{aligned}\frac{d}{dt}s_1(t) &= \alpha_0 - \alpha_1 s_1^{g_1}\\ \frac{d}{dt}s_2(t) &= \alpha_1 s_1^{g_1} - \alpha_2 s_2^{g_2}.\end{aligned}$$

At steady state, we have

$$\begin{aligned}\alpha_0 &= \alpha_1 s_1^{g_1}\\ \alpha_1 s_1^{g_1} &= \alpha_2 s_2^{g_2}.\end{aligned}$$

Taking logarithms gives

$$\begin{aligned}\log \alpha_0 &= \log \alpha_1 + g_1 \log s_1\\ \log \alpha_1 + g_1 \log s_1 &= \log \alpha_2 + g_2 \log s_2\end{aligned}$$

Solving, we have

$$\log s_1 = \frac{\log \alpha_0 - \log \alpha_1}{g_1}$$
$$\log s_2 = \frac{\log \alpha_0 - \log \alpha_2}{g_2}.$$

Taking exponents gives the steady-state concentrations:

$$\begin{aligned} s_1 &= \exp\left(\frac{\log \alpha_0 - \log \alpha_1}{g_1}\right) \\ s_2 &= \exp\left(\frac{\log \alpha_0 - \log \alpha_2}{g_2}\right). \end{aligned}$$

Chapter 4

4.1.1. Evaluating the right-hand side of the differential equations as a vector $(dx/dt, dy/dt)$, we have

$$\begin{aligned} (x,y) = (1,0) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (0,1) \\ (x,y) = (1,1) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (-1,1) \\ (x,y) = (0,1) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (-1,0) \\ (x,y) = (-1,1) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (-1,-1) \\ (x,y) = (-1,0) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (0,-1) \\ (x,y) = (-1,-1) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (1,-1) \\ (x,y) = (0,-1) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (1,0) \\ (x,y) = (1,-1) &\Rightarrow \left(\frac{dx}{dt}, \frac{dy}{dt}\right) = (-y,x) = (1,1) \end{aligned}$$

The direction arrows, sketched in Figure D.1, show that the trajectories spiral around the origin in a counter-clockwise direction.

4.1.2. If two trajectories were to cross, the intersection point would have to produce two distinct direction arrows. Because each point generates a unique direction arrow, every point is on a unique trajectory.

4.1.3. The model is

$$\begin{aligned} \frac{d}{dt}s_1(t) &= \frac{k_1}{1 + (s_2(t)/K)^n} - k_3 s_1(t) - k_5 s_1(t) \\ \frac{d}{dt}s_2(t) &= k_2 + k_5 s_1(t) - k_4 s_2(t) \end{aligned}$$

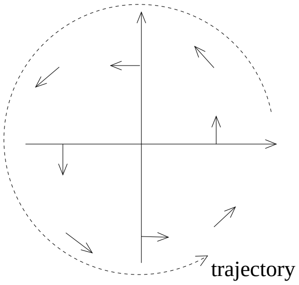


Figure D.1: Direction field for Exercise 4.1.1.

The s_1-nullcline is defined by

$$0 = \frac{k_1}{1 + (s_2/K)^n} - k_3 s_1 - k_5 s_1,$$

which can be written as

$$s_1 = \frac{k_1}{(1 + (s_2/K)^n)(k_3 + k_5)}$$

as required. The s_2-nullcline is defined by

$$0 = k_2 + k_5 s_1 - k_4 s_2$$

which we can write as

$$s_2 = \frac{k_2 + k_5 s_1}{k_4}.$$

4.2.1. a) With $v_1 = k_1 s$ and $v_2 = k_2 s^2$, steady state occurs when

$$k_1 s = k_2 s^2.$$

This is satisfied when

$$s = 0 \qquad \text{or} \qquad s = \frac{k_1}{k_2}.$$

The rate of change of s is $\frac{d}{dt}s = k_1 s - k_2 s^2 = k_1 s(1 - \frac{k_2 s}{k_1})$. When s is between 0 and k_1/k_2, we find that $\frac{d}{dt}s > 0$, so s will increase toward k_1/k_2. Alternatively, when s is greater than k_1/k_2, then $\frac{d}{dt}s < 0$, and so s decreases toward k_1/k_2. We conclude that $s = k_1/k_2$ is a stable steady state.

b) The rate of change is given by

$$\frac{d}{dt}s(t) = 6/11 + \frac{\frac{60}{11}s^2}{11 + s^2} - s$$

Substituting $s = 1$, $s = 2$ and $s = 3$ gives $\frac{d}{dt}s = 0$ in each case. Testing points on either side of each equilibrium, we find

$$s = 0.9 \Rightarrow \frac{d}{dt}s = 0.0196 > 0$$

$$\begin{aligned} s = 1.1 &\Rightarrow \frac{d}{dt}s = -0.014 < 0 \\ s = 1.9 &\Rightarrow \frac{d}{dt}s = -0.007 < 0 \\ s = 2.1 &\Rightarrow \frac{d}{dt}s = 0.0064 > 0 \\ s = 2.9 &\Rightarrow \frac{d}{dt}s = 0.009 > 0 \\ s = 3.1 &\Rightarrow \frac{d}{dt}s = -0.011 < 0 \end{aligned}$$

Thus trajectories are attracted to $s = 1$, repelled from $s = 2$, and attracted to $s = 3$. The points $s = 1$ and $s = 3$ are thus stable steady states, while $s = 2$ is an unstable steady state.

4.2.2. a) With $f(s) = \frac{V_{\max}s}{K_M+s}$, we have

$$\frac{df}{ds} = \frac{V_{\max}(K_M + s) - V_{\max}s}{(K_M + s)^2} = \frac{V_{\max}K_M}{(K_M + s)^2}.$$

Then, the linearization at $s = \bar{s}$ is

$$f(\bar{s}) + \frac{df}{ds}(\bar{s})\cdot(s - \bar{s}) = \frac{V_{\max}\bar{s}}{K_M + \bar{s}} + \frac{V_{\max}K_M}{(K_M + \bar{s})^2}\cdot(s - \bar{s}). \tag{D.1}$$

b) Substituting $\bar{s} = 0$, into (D.1), we have

$$\frac{V_{\max}\cdot 0}{K_M + \bar{s}} + \frac{V_{\max}K_M}{(K_M)^2}\cdot s = \frac{V_{\max}}{K_M}s,$$

which is a first-order mass action rate law.

c) When $\bar{s}$ is large, we have $K_M + \bar{s} \approx \bar{s}$ so the approximation (D.1) becomes

$$\frac{V_{\max}\bar{s}}{\bar{s}} + \frac{V_{\max}K_M}{(\bar{s})^2}\cdot(s - \bar{s}) = V_{\max} + \frac{V_{\max}K_M}{(\bar{s})^2}\cdot(s - \bar{s}) \approx V_{\max},$$

where the last approximation result from the fact that $K_M/\bar{s}$ is near zero if $\bar{s}$ is much larger than K_M.

4.2.3. The partial derivatives of $f(s, i)$ are:

$$\begin{aligned} \frac{\partial f}{\partial s} &= \frac{V_{\max}(K_M(1 + i/K_i) + s) - V_{\max}s}{(K_M(1 + i/K_i) + s)^2} = \frac{V_{\max}(K_M(1 + i/K_i))}{(K_M(1 + i/K_i) + s)^2} \\ \frac{\partial f}{\partial i} &= -\frac{V_{\max}s}{(K_M(1 + i/K_i) + s)^2}\frac{K_M}{K_i} \end{aligned}$$

At $(s, i) = (1, 0)$, we evaluate:

$$\begin{aligned} \frac{\partial f}{\partial s}(1, 0) &= \frac{V_{\max}K_M}{(K_M + 1)^2} \\ \frac{\partial f}{\partial i}(1, 0) &= -\frac{V_{\max}}{(K_M + 1)^2}\frac{K_M}{K_i} \end{aligned}$$

Then, since $f(1,0) = \frac{V_{\max}}{K_M+1}$, we can write the approximation (4.3) as

$$f(s,i) \approx \frac{V_{\max}}{K_M+1} + \frac{V_{\max}K_M}{(K_M+1)^2}(s-1) - \frac{V_{\max}}{(K_M+1)^2}\frac{K_M}{K_i}\,i.$$

4.2.4. If at least one of b or c is zero, then the product $bc = 0$, so the formulas in (4.7) reduce to

$$\lambda_1 = \frac{(a+d)+\sqrt{(a+d)^2-4ad}}{2}, \qquad \lambda_2 = \frac{(a+d)-\sqrt{(a+d)^2-4ad}}{2}.$$

We then note that $(a+d)^2 - 4ad = a^2 + 2ad + d^2 - 4ad = a^2 - 2ad + d^2 = (a-d)^2$. Then, since $\sqrt{(a-d)^2} = a - d$, we have

$$\lambda_1 = \frac{(a+d)+(a-d)}{2} = a, \qquad \lambda_2 = \frac{(a+d)-(a-d)}{2} = d,$$

as required.

4.2.5. The Jacobian matrix has entries $a = -5/3$, $b = 1/3$, $c = 2/3$ and $d = -4/3$. Substituting into the formula (4.7) for the eigenvalues, we find

$$\lambda_1 = \frac{-9/3 + \sqrt{(-9/3)^2 - 4(20/9 - 2/9)}}{2} = \frac{-3+\sqrt{9-4(18/9)}}{2} = \frac{-3+\sqrt{1}}{2} = -1$$

and likewise

$$\lambda_2 = \frac{-3-\sqrt{1}}{2} = -2.$$

Then, substituting these eigenvalues into the general solution formula (4.7), we know that the solutions of the system of equations (4.8) take the form

$$\begin{aligned} x_1(t) &= c_{11}e^{-t} + c_{12}e^{-2t} \\ x_2(t) &= c_{21}e^{-t} + c_{22}e^{-2t}. \end{aligned}$$

At time $t = 0$, the initial conditions gives

$$\begin{aligned} 1/3 &= c_{11} + c_{12} \\ 5/3 &= c_{21} + c_{22}. \end{aligned}$$

Next, calculating the derivative, we find

$$\begin{aligned} \frac{d}{dt}x_1(t) &= -c_{11}e^{-t} - 2c_{12}e^{-2t} \\ \frac{d}{dt}x_2(t) &= -c_{21}e^{-t} - 2c_{22}e^{-2t}. \end{aligned}$$

Substituting into the differential equation, we have

$$\begin{aligned} -\frac{5}{3}x_1(t) + \frac{1}{3}x_2(t) &= -c_{11}e^{-t} - 2c_{12}e^{-2t} \\ \frac{2}{3}x_1(t) - \frac{4}{3}x_2(t) &= -c_{21}e^{-t} - 2c_{22}e^{-2t}. \end{aligned}$$

At time $t = 0$, we have

$$\begin{aligned} -\frac{5}{3}x_1(0) + \frac{1}{3}x_2(0) &= -c_{11} - 2c_{12} \\ \frac{2}{3}x_1(0) - \frac{4}{3}x_2(0) &= -c_{21} - 2c_{22} \end{aligned}$$

With the initial conditions $(x_1(0), x_2(0)) = (\frac{1}{3}, \frac{5}{3})$ this gives

$$\begin{aligned} -\frac{5}{3}\left(\frac{1}{3}\right) + \frac{1}{3}\left(\frac{5}{3}\right) &= -\frac{5}{9} + \frac{5}{9} = 0 = -c_{11} - 2c_{12} \\ \frac{2}{3}\left(\frac{1}{3}\right) - \frac{4}{3}\left(\frac{5}{3}\right) &= \frac{2}{9} - \frac{20}{9} = -2 = -c_{21} - 2c_{22} \end{aligned}$$

All together, we have

$$\begin{aligned} 1/3 &= c_{11} + c_{12} \\ 5/3 &= c_{21} + c_{22} \\ 0 &= -c_{11} - 2c_{12} \\ -2 &= -c_{21} - 2c_{22} \end{aligned}$$

From the third equation

$$c_{11} = -2c_{12}$$

so

$$1/3 = -2c_{12} + c_{12} = -c_{12}.$$

giving $c_{12} = -1/3$, $c_{11} = 2/3$. Likewise, we find

$$c_{21} = 2 - 2c_{22}$$

so

$$5/3 = c_{21} + c_{22} = 2 - 2c_{22} + c_{22} = 6/3 - c_{22}.$$

This gives $c_{22} = 1/3$, and $c_{21} = 4/3$. The required solution is then

$$\begin{aligned} x_1(t) &= \frac{2}{3}e^{-t} - \frac{1}{3}e^{-2t} \\ x_2(t) &= \frac{4}{3}e^{-t} + \frac{1}{3}e^{-2t}. \end{aligned}$$

This solution can be confirmed by substituting $t = 0$ to recover the initial conditions, and then by taking derivatives and substituting into the system of differential equations to verify that they are satisfied, as follows. (This is not necessary—it is simply a double-check that the answer is correct.) The initial condition is:

$$\begin{aligned} x_1(0) &= \frac{2}{3} - \frac{1}{3} = \frac{1}{3} \\ x_2(0) &= \frac{4}{3} + \frac{1}{3} = \frac{5}{3}. \end{aligned}$$

as required. Taking derivatives, we find

$$\begin{aligned}
\frac{d}{dt}x_1(t) &= -\frac{2}{3}e^{-t} + \frac{2}{3}e^{-2t} \\
\frac{d}{dt}x_2(t) &= -\frac{4}{3}e^{-t} - \frac{2}{3}e^{-2t}.
\end{aligned}$$

The differential equation is satisfied if

$$\begin{aligned}
\frac{d}{dt}x_1(t) &= -\frac{5}{3}x_1(t) + \frac{1}{3}x_2(t) \\
\frac{d}{dt}x_2(t) &= \frac{2}{3}x_1(t) - \frac{4}{3}x_2(t)
\end{aligned}$$

To verify that these are equal, we calculate:

$$\begin{aligned}
-\frac{5}{3}x_1(t) + \frac{1}{3}x_2(t) &= -\frac{5}{3}(\frac{2}{3}e^{-t} - \frac{1}{3}e^{-2t}) + \frac{1}{3}(\frac{4}{3}e^{-t} + \frac{1}{3}e^{-2t}) \\
&= -\frac{10}{9}e^{-t} + \frac{5}{9}e^{-2t} + \frac{4}{9}e^{-t} + \frac{1}{9}e^{-2t} \\
&= -\frac{6}{9}e^{-t} + \frac{6}{9}e^{-2t} \\
&= -\frac{2}{3}e^{-t} + \frac{2}{3}e^{-2t}
\end{aligned}$$

which agrees with our calculation for $\frac{d}{dt}x_1(t)$ above. Likewise, we find, for $\frac{d}{dt}x_2(t)$,

$$\begin{aligned}
\frac{2}{3}x_1(t) - \frac{4}{3}x_2(t) &= \frac{2}{3}(\frac{2}{3}e^{-t} - \frac{1}{3}e^{-2t}) - \frac{4}{3}(\frac{4}{3}e^{-t} + \frac{1}{3}e^{-2t}) \\
&= \frac{4}{9}e^{-t} - \frac{2}{9}e^{-2t} - \frac{16}{9}e^{-t} - \frac{4}{9}e^{-2t} \\
&= -\frac{12}{9}e^{-t} - \frac{6}{9}e^{-2t} \\
&= -\frac{4}{3}e^{-t} - \frac{2}{3}e^{-2t}
\end{aligned}$$

as we calculated above.

4.2.6. The model is

$$\begin{aligned}
\frac{d}{dt}s_1(t) &= \frac{20}{1 + s_2^4(t)} - 5s_1(t) \\
\frac{d}{dt}s_2(t) &= \frac{20}{1 + s_1(t)} - 5s_2(t).
\end{aligned}$$

The Jacobian is

$$\mathbf{J}(s_1, s_2) = \begin{bmatrix} -5 & -\frac{20}{(1+s_2^4)^2}4s_2^3 \\ -\frac{20}{(1+s_1)^2} & -5 \end{bmatrix}.$$

Substituting the steady state $(\bar{s}_1, \bar{s}_2) = (0.0166, 3.94)$, we have

$$\mathbf{J}(0.0166, 3.94) = \begin{bmatrix} -5 & -0.0836 \\ -19.35 & -5 \end{bmatrix}.$$

The eigenvalues of this matrix are $\lambda_1 = -6.27$ and $\lambda_2 = -3.72$. We thus confirm that the steady state is stable.

4.2.7. The steady state equation is

$$\begin{aligned} 0 &= V_0 - k_1 s_1^{ss} \\ 0 &= k_1 s_1^{ss} - \frac{V_2 s_2^{ss}}{K_M + s_2^{ss}} \end{aligned}$$

from which we have

$$s_1^{ss} = \frac{V_0}{k_1} \qquad \text{and} \qquad V_0 = \frac{V_2 s_2^{ss}}{K_M + s_2^{ss}}$$

Solving gives

$$s_2^{ss} = \frac{V_0 K_M}{V_2 - V_0}.$$

The system Jacobian is

$$\mathbf{J}(s_1, s_2) = \begin{bmatrix} -k_1 & 0 \\ k_1 & -\frac{V_2 K_M}{(K_M + s_2)^2} \end{bmatrix}.$$

Because one of the off-diagonal entries of this matrix is zero, the eigenvalues are simply the diagonal entries. Regardless of the value of s_2, these two entries are negative, so the steady state is stable.

4.3.1. a) The model follows from the network and the law of mass action. Note that the third reaction proceeds at rate $k_3[X]^2[Y]$, and converts one molecule of Y to one molecule of X.
b) The steady-state equations are

$$\begin{aligned} 0 &= k_1 - k_2 x^{ss} + k_3 (x^{ss})^2 y^{ss} - k_4 x^{ss} \\ 0 &= k_2 x^{ss} - k_3 (x^{ss})^2 y^{ss}. \end{aligned}$$

On substituting, the first equation reads

$$0 = k_1 - k_4 x^{ss}$$

so $x^{ss} = \frac{k_1}{k_4}$. The second equation then gives

$$y^{ss} = \frac{k_2}{x^{ss} k_3} = \frac{k_2 k_4}{k_1 k_3}$$

c) With $k_2 = 2$ (time^{-1}), $k_3 = \frac{1}{2}$ (time$^{-1}\cdot$ concentration^{-1}) and $k_4 = 1$ (time^{-1}), we have, in steady state, $x = k_1$ and $y = \frac{4}{x} = \frac{4}{k_1}$. The system Jacobian is

$$\mathbf{J}(x, y) = \begin{bmatrix} -k_2 + 2k_3 xy - k_4 & k_3 x^2 \\ k_2 - 2k_3 xy & -k_3 x^2 \end{bmatrix},$$

so at the given parameter values

$$\mathbf{J}(k_1, 4/k_1) = \begin{bmatrix} 1 & \frac{k_1^2}{2} \\ -2 & -\frac{k_1^2}{2} \end{bmatrix}.$$

The eigenvalues of this matrix are

$$\begin{aligned}\lambda_i &= \frac{(1-\frac{k_1^2}{2}) \pm \sqrt{\left(1-\frac{k_1^2}{2}\right)^2 - 4\left(-\frac{k_1^2}{2}+k_1^2\right)}}{2} \\ &= \frac{\left(1-\frac{k_1^2}{2}\right) \pm \sqrt{\left(1-\frac{k_1^2}{2}\right)^2 - 2k_1^2}}{2}\end{aligned}$$

We note that $1-\frac{k_1^2}{2} > 0$ when $k_1 < \sqrt{2}$. If the expression under the root is negative, then the two eigenvalues have the same sign as $1-\frac{k_1^2}{2}$. If the expression is positive, it is less than $(1-\frac{k_1^2}{2})^2$, so the sign of the eigenvalues is the same as the sign of $1-\frac{k_1^2}{2}$. We conclude that both eigenvalues have positive real part when $k_1 < \sqrt{2}$. (As a rate constant, k_1 necessarily satisfies $k_1 > 0$.)

4.4.1. The steady state is $x = 0$. Consider first the case when $a < -1$. Then, for $x < 0$ we have $\frac{d}{dt}x > 0$ and for $x > 0$ we have $\frac{d}{dt}x < 0$. The steady state at $x = 0$ is thus stable, as trajectories are drawn to $x = 0$. Next, consider the case for which $a > -1$. Then, for $x < 0$ we have $\frac{d}{dt}x < 0$ and for $x > 0$ we have $\frac{d}{dt}x > 0$. The steady state at $x = 0$ is thus unstable, as trajectories are repelled from this point. (Equivalently, we note that the Jacobian is $\mathbf{J} = 1 + a$, which is its own eigenvalue. This eigenvalue is negative when $a < -1$, and positive when $a > -1$.)

4.5.1. From equation (4.11), we have

$$\frac{ds}{dK_M} = \frac{V_0}{V_{\max} - V_0}$$

The relative sensitivity coefficient is then

$$\frac{K_M}{s^{ss}}\frac{ds}{dK_M} = \frac{K_M}{V_0 K_M/(V_{\max}-V_0)}\frac{V_0}{V_{\max}-V_0} = 1.$$

4.5.2. From equation (4.12) we have

$$\begin{aligned}V_{\max} = 4 \ \Rightarrow s^{ss} &= \frac{3}{4-2} = 1.5 \\ V_{\max} = 4.2 \ \Rightarrow s^{ss} &= \frac{3}{4.2-2} = 1.3636 \\ V_{\max} = 4.04 \ \Rightarrow s^{ss} &= \frac{3}{4.04-2} = 1.4706\end{aligned}$$

Equation (4.15) then gives, with $V_{\max}$ as the parameter, and values $p_1 = 4$ and $\Delta p_1 = 0.2$,

$$\frac{ds^{ss}}{dV_{\max}} \approx \frac{s^{ss}(4.2) - s^{ss}(4)}{\Delta p_1} = \frac{1.3636 - 1.5}{0.2} = -0.682,$$

and, with $p_1 = 4$ and $\Delta p_1 = 0.04$,

$$\frac{ds^{ss}}{dV_{\max}} \approx \frac{s^{ss}(4.04) - s^{ss}(4)}{\Delta p_1} = \frac{1.4706 - 1.5}{0.04} = -0.735.$$

These are decent approximations to the true absolute sensitivity of -0.75. The approximation is better for smaller Δ.

4.5.3. Treating s as a function of k_1, i.e. $s = s(k_1)$, we differentiate the steady-state equation with respect to k_1 to find

$$0 = \frac{1}{1+s^n} - \frac{k_1}{(1+s^n)^2} n s^{n-1} \frac{ds}{dk_1} - k_2 \frac{ds}{dk_1}$$

Solving, we find

$$\frac{ds}{dk_1} = \frac{\frac{1}{1+s^n}}{\frac{k_1}{(1+s^n)^2} n s^{n-1} + k_2}.$$

All terms are positive, so this sensitivity coefficient is positive, regardless of the parameter values.

4.6.1. (i) The sum of squared errors is

$$\begin{aligned} SSE &= ([s_1^{ss}(k_1,k_2,k_3) + s_2^{ss}(k_1,k_2,k_3)] - 6)^2 + ([s_1^{ss}(k_1/10,k_2,k_3) + s_2^{ss}(k_1/10,k_2,k_3)] - 0.6)^2 \\ &= \left(\frac{k_1}{k_2} + \frac{k_1}{4} - 6\right)^2 + \left(\frac{k_1}{10k_2} + \frac{k_1}{40} - 0.6\right)^2. \end{aligned}$$

Both terms are zero if $\frac{k_1}{k_2} + \frac{k_1}{4} = 6$. This problem is thus underdetermined. The model wil fit the data provided that $k_1 = \frac{24k_2}{4+k_2}$ regardless of the (positive) value of k_2.
(ii) In this case, the error is

$$\begin{aligned} SSE &= (s_1^{ss}(k_1,k_2,k_3) + s_2^{ss}(k_1,k_2,k_3) - 6)^2 + (s_1^{ss}(k_1,k_2/10,k_3) + s_2^{ss}(k_1,k_2/10,k_3) - 0.6)^2 \\ &= \left(\frac{k_1}{k_2} + \frac{k_1}{4} - 6\right)^2 + \left(\frac{10k_1}{k_2} + \frac{k_1}{4} - 18\right)^2. \end{aligned}$$

The error is minimized (at the value zero) when

$$\frac{k_1}{k_2} + \frac{k_1}{4} = 6 \qquad \text{and} \qquad \frac{10k_1}{k_2} + \frac{k_1}{4} = 18.$$

These equations can be rewritten as

$$4k_1 + k_2k_1 = 24k_2 \qquad \text{and} \qquad 40k_1 + k_2k_1 = 72k_2$$

Substituting gives

$$40k_1 + (24k_2 - 4k_1) = 72k_2 \qquad \text{so} \qquad k_1 = \frac{4k_2}{3}.$$

Substituting again gives

$$\frac{16}{3}k_2 + \frac{4}{3}k_2^2 = 24k_2$$

Dividing through by k_2 and solving gives

$$k_2 = 14 \qquad \text{so} \qquad k_1 = \frac{56}{3}.$$

In the first case, the controlled parameter k_1 affects s_1 and s_2 equivalently, so no new information is obtained from the experimental condition. There is thus one data-point to constrain two parameters—the problem is underdetermined. In case (ii), the controlled parameter affects only one of the states, so new information is attained from the experimental measurement, resulting in a fully-determined fitting problem.

Chapter 5

5.1.1. In steady state, we have

$$\begin{aligned} 0 &= e_1([S_0] - s_1) - (e_2 + e_3)s_1 \\ 0 &= e_2 s_1 + e_4 s_3 - e_5 s_2 \\ 0 &= e_3 s_1 - e_4 s_3. \end{aligned}$$

The first equation gives

$$s_1 = \frac{e_1[S_0]}{e_1 + e_2 + e_3}$$

Substituting s_1 into the third equation gives

$$\frac{e_3 e_1[S_0]}{e_1 + e_2 + e_3} = e_4 s_3$$

so

$$s_3 = \frac{e_3 e_1[S_0]}{e_4(e_1 + e_2 + e_3)}$$

Substituting both s_1 and s_3 into the second equation, we have

$$e_5 s_2 = \frac{e_2 e_1[S_0]}{e_1 + e_2 + e_3} + \frac{e_4 e_3 e_1[S_0]}{e_4(e_1 + e_2 + e_3)} = \frac{(e_2 + e_3)e_1[S_0]}{e_1 + e_2 + e_3}.$$

Thus

$$s_2 = \frac{(e_2 + e_3)e_1[S_0]}{e_5(e_1 + e_2 + e_3)}$$

as required.

5.1.2. From the network model, we have, in steady state:

$$\begin{aligned} 0 &= v_1^{ss} - v_2^{ss} - v_3^{ss} \\ 0 &= v_2^{ss} + v_4^{ss} - v_5^{ss} \\ 0 &= v_3^{ss} - v_4^{ss}. \end{aligned}$$

Thus $J = v_1^{ss} = v_2^{ss} + v_3^{ss}$, and $J = v_5^{ss} = v_2^{ss} + v_4^{ss}$.

5.1.3. The pathway flux is equal to the rate of consumption of S_0. This rate depends on $[S_0]$, e_1, and s_1. The concentration s_1 depends, in turn, on $[S_0]$, e_1, e_2 and e_3. Because consumption of S_1 is irreversible, the downstream activity has no effect on s_1.

5.1.4. a) Taking the derivative of equation (5.3) with respect to e_1, and scaling, we find

$$\begin{aligned} C^J_{e_1} = \frac{e_1}{J}\frac{dJ}{de_1} &= \frac{e_1}{\frac{(e_2+e_3)e_1[S_0]}{(e_1+e_2+e_3)}}\frac{(e_2+e_3)[S_0](e_1+e_2+e_3)-(e_2+e_3)e_1[S_0]}{(e_1+e_2+e_3)^2} \\ &= \frac{e_1+e_2+e_3}{(e_2+e_3)[S_0]}\frac{(e_2+e_3)^2[S_0]}{(e_1+e_2+e_3)^2} \\ &= \frac{e_2+e_3}{e_1+e_2+e_3} \end{aligned}$$

Taking the derivative of equation (5.3) with respect to e_2, and scaling, we find

$$\begin{aligned} C^J_{e_2} &= \frac{e_2}{J}\frac{dJ}{de_2} = \frac{e_2}{\frac{(e_2+e_3)e_1[S_0]}{(e_1+e_2+e_3)}}\frac{e_1[S_0](e_1+e_2+e_3)-(e_2+e_3)e_1[S_0]}{(e_1+e_2+e_3)^2} \\ &= \frac{e_2(e_1+e_2+e_3)}{(e_2+e_3)e_1[S_0]}\frac{e_1^2[S_0]}{(e_1+e_2+e_3)^2} \\ &= \frac{e_1e_2}{(e_2+e_3)(e_1+e_2+e_3)} \end{aligned}$$

Noting the symmetry in e_2 and e_3 in formula (5.3), we have immediately that

$$C^J_{e_3} = \frac{e_3}{J}\frac{dJ}{de_3} = \frac{e_1e_3}{(e_2+e_3)(e_1+e_2+e_3)}.$$

b) The flux control coefficients for e_4 and e_5 are zero because the flux, given by equation (5.3), does not depend on e_4 or e_5. This is a result of the assumptions of irreversibility on the reactions consuming S_1: the pathway flux is determined only by those parameters impacting the rate of consumption of S_0.

c) We find

$$\begin{aligned} C^J_{e_1}+C^J_{e_2}+C^J_{e_3}+C^J_{e_4}+C^J_{e_5} &= \frac{e_2+e_3}{e_1+e_2+e_3}+\frac{e_1e_2}{(e_2+e_3)(e_1+e_2+e_3)} \\ &\quad +\frac{e_1e_3}{(e_2+e_3)(e_1+e_2+e_3)}+0+0 \\ &= \frac{(e_2+e_3)^2+e_1e_2+e_1e_3}{(e_2+e_3)(e_1+e_2+e_3)} \\ &= \frac{e_2^2+2e_2e_3+e_3^2+e_1e_2+e_1e_3}{e_1e_2+e_2^2+e_2e_3+e_3e_1+e_2e_3+e_3^2} \\ &= 1. \end{aligned}$$

5.1.5. From equation (5.2) for s_1^{ss}, we find

$$\begin{aligned} C^{s_1}_{e_1} &= \frac{e_1}{s_1^{ss}}\frac{ds_1^{ss}}{de_1} = \frac{e_1}{\frac{e_1[S_0]}{e_1+e_2+e_3}}\frac{[S_0](e_1+e_2+e_3)-e_1[S_0]}{(e_1+e_2+e_3)^2} \\ &= \frac{e_1+e_2+e_3}{[S_0]}\frac{[S_0](e_2+e_3)}{(e_1+e_2+e_3)^2} \\ &= \frac{e_2+e_3}{e_1+e_2+e_3}, \end{aligned}$$

and

$$\begin{aligned}
C_{e_2}^{s_1} &= \frac{e_2}{s_1^{ss}}\frac{ds_1^{ss}}{de_2} = \frac{e_2}{\frac{e_1[S_0]}{e_1+e_2+e_3}}\frac{-e_1[S_0]}{(e_1+e_2+e_3)^2} \\
&= \frac{e_2(e_1+e_2+e_3)}{e_1[S_0]}\frac{-e_1[S_0]}{(e_1+e_2+e_3)^2} \\
&= -\frac{e_2}{e_1+e_2+e_3}.
\end{aligned}$$

Symmetry of e_2 and e_3 in the formula (5.2) for s_1^{ss} gives

$$C_{e_3}^{s_1} = -\frac{e_3}{e_1+e_2+e_3}.$$

Since s_1^{ss} does not depend on e_4 or e_5, we have $C_{e_4}^{s_1} = C_{e_5}^{s_1} = 0$.

5.2.1. Differentiating and scaling, we have

$$\begin{aligned}
C_{e_1}^{J} &= \frac{e_1}{J}\frac{\partial J}{\partial e_1} = -\frac{e_1}{J}\frac{[S_0]q_1q_2q_3 - [P]}{(\frac{q_1q_2q_3}{e_1k_1}+\frac{q_2q_3}{e_2k_2}+\frac{q_3}{e_3k_3})^2}\left(\frac{-q_1q_2q_3}{(e_1k_1)^2}\right)k_1 \\
&= \frac{1}{(\frac{q_1q_2q_3}{e_1k_1}+\frac{q_2q_3}{e_2k_2}+\frac{q_3}{e_3k_3})}\left(\frac{q_1q_2q_3}{e_1k_1}\right) \\
C_{e_2}^{J} &= \frac{e_2}{J}\frac{\partial J}{\partial e_2} = -\frac{e_2}{J}\frac{[S_0]q_1q_2q_3 - [P]}{(\frac{q_1q_2q_3}{e_1k_1}+\frac{q_2q_3}{e_2k_2}+\frac{q_3}{e_3k_3})^2}\left(\frac{-q_2q_3}{(e_2k_2)^2}\right)k_2 \\
&= \frac{1}{(\frac{q_1q_2q_3}{e_1k_1}+\frac{q_2q_3}{e_2k_2}+\frac{q_3}{e_3k_3})}\left(\frac{q_2q_3}{e_2k_2}\right) \\
C_{e_3}^{J} &= \frac{e_3}{J}\frac{\partial J}{\partial e_3} = -\frac{e_3}{J}\frac{[S_0]q_1q_2q_3 - [P]}{(\frac{q_1q_2q_3}{e_1k_1}+\frac{q_2q_3}{e_2k_2}+\frac{q_3}{e_3k_3})^2}\left(\frac{-q_3}{(e_3k_3)^2}\right)k_3 \\
&= \frac{1}{(\frac{q_1q_2q_3}{e_1k_1}+\frac{q_2q_3}{e_2k_2}+\frac{q_3}{e_3k_3})}\left(\frac{q_3}{e_3k_3}\right),
\end{aligned}$$

as required.

5.2.2. Take $s = [S]$ and $i = [I]$. Taking the derivative and scaling, we find

$$\begin{aligned}
\varepsilon_S &= \frac{s}{v}\frac{\partial v}{\partial s} = \left(\frac{s}{\frac{V_{\max}}{1+i/K_i}\frac{s}{K_M+s}}\right)\frac{\partial}{\partial s}\frac{V_{\max}}{1+i/K_i}\frac{s}{K_M+s} \\
&= \frac{(K_M+s)(1+i/K_i)}{V_{\max}}\frac{V_{\max}}{1+i/K_i}\frac{K_M}{(K_M+s)^2} \\
&= \frac{K_M}{(K_M+s)}
\end{aligned}$$

and

$$\varepsilon_I = \frac{i}{v}\frac{\partial v}{\partial i} = \left(\frac{i}{\frac{V_{\max}}{1+i/K_i}\frac{s}{K_M+s}}\right)\frac{\partial}{\partial i}\frac{V_{\max}}{1+i/K_i}\frac{s}{K_M+s}$$

$$\begin{aligned}
&= \frac{i}{\frac{V_{\max}}{1+i/K_i}\frac{s}{K_M+s}}\left(-\frac{V_{\max}}{(1+i/K_i)^2}\frac{1}{K_i}\frac{s}{K_M+s}\right)\\
&= -\frac{i/K_i}{K_i+i}
\end{aligned}$$

5.2.3. The signs of the elasticities are dictated by the influence of the species S_1 and S_2 on the reactions. We note that $\varepsilon^1_{S_1} \le 0$, since S_1 is a product of the first reaction (so an increase in $[S_1]$ causes a decrease in reaction rate v_1. Likewise, $\varepsilon^2_{S_2} \le 0$. Because S_1 and S_2 are substrates for reactions two and three, respectively, we have $\varepsilon^2_{S_1} > 0$ and $\varepsilon^3_{S_2} > 0$. Finally, because S_2 can inhibit the first reaction, we have $\varepsilon^1_{S_2} \le 0$. Then $\varepsilon^2_{S_1}\varepsilon^3_{S_2} > 0$, $\varepsilon^1_{S_1}\varepsilon^3_{S_2} < 0$, $\varepsilon^1_{S_1}\varepsilon^2_{S_2} \ge 0$ and $\varepsilon^2_{S_1}\varepsilon^1_{S_2} \le 0$, as required.

5.4.1. The transpose of the stoichiometry matrix is

$$\mathbf{N}^T = \begin{bmatrix} -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 1 & 0 & -1 & 1 \end{bmatrix}.$$

Multiplying, we confirm that

$$\begin{bmatrix} -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 1 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} 0 \\ 1 \\ 1 \\ 1 \\ 0 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and

$$\begin{bmatrix} -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 1 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} 1 \\ 0 \\ 1 \\ 1 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

as required.

5.4.2. In this case, the stoichiometry matrix is

$$\mathbf{N} = \begin{bmatrix} \mathbf{N}_1 \\ \mathbf{N}_2 \\ \mathbf{N}_3 \\ \mathbf{N}_4 \\ \mathbf{N}_5 \end{bmatrix} = \begin{array}{ccccc|c} 1 & -1 & 0 & 0 & 0 & \leftarrow S \\ 0 & -1 & 0 & 1 & 0 & \leftarrow E \\ 0 & 1 & -1 & 0 & 0 & \leftarrow ES \\ 0 & 0 & 1 & -1 & 0 & \leftarrow EP \\ 0 & 0 & 0 & 1 & -1 & \leftarrow P \\ \uparrow & \uparrow & \uparrow & \uparrow & \uparrow & \\ v_0 & v_1 & v_2 & v_3 & v_4 & \end{array}$$

The rows corresponding to S and P cannot be involved in a sum that equals one. The remaining rows still sum to zero: rows $\mathbf{N}_2 + \mathbf{N}_3 + \mathbf{N}_4 = \mathbf{0}$, so $[E] + [ES] + [EP] =$ constant.

5.4.3. The stoichiometry matrix for this network is

$$\mathbf{N} = \begin{bmatrix} \mathbf{N}_1 \\ \mathbf{N}_2 \\ \mathbf{N}_3 \\ \mathbf{N}_4 \\ \mathbf{N}_5 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & -1 & 1 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 1 & 0 & -1 \end{bmatrix}$$

We note that $\mathbf{N}_3 + \mathbf{N}_4 = \mathbf{0}$, so $[S_3] + [S_4] =$ constant, and $\mathbf{N}_1 - \mathbf{N}_2 - \mathbf{N}_5 = \mathbf{0}$, so $[S_1] - [S_2] - [S_5] =$ constant. This latter conservation involves the difference between $[S_1]$ and $[S_2]$, so cannot be written as a sum.

5.4.4. For $\mathbf{w}_1$, we confirm that

$$\mathbf{N}\mathbf{w}_1 = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix} \begin{bmatrix} 2 \\ 2 \\ 1 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

We note that

$$\mathbf{w}_1 = \begin{bmatrix} 2 \\ 2 \\ 1 \\ 1 \end{bmatrix} = \alpha_1 \mathbf{v}_1 + \alpha_2 \mathbf{v}_2 = \alpha_1 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \end{bmatrix}$$

for $\alpha_1 = 1$, $\alpha_2 = 1$. The vector $\mathbf{w}_1$ corresponds to an equal split ratio at the branch point.

For $\mathbf{w}_2$, we confirm that

$$\mathbf{N}\mathbf{w}_2 = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix} \begin{bmatrix} 6 \\ 6 \\ 5 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

We note that

$$\mathbf{w}_1 = \begin{bmatrix} 6 \\ 6 \\ 5 \\ 1 \end{bmatrix} = \alpha_1 \mathbf{v}_1 + \alpha_2 \mathbf{v}_2 = \alpha_1 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \end{bmatrix}$$

for $\alpha_1 = 5$, $\alpha_2 = 1$. The vector $\mathbf{w}_2$ corresponds to an uneven split ratio: five sixths of the incoming flux passes through reaction 3.

For $\mathbf{w}_3$, we confirm that

$$\mathbf{N}\mathbf{w}_3 = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

We note that

$$\mathbf{w}_1 = \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \end{bmatrix} = \alpha_1 \mathbf{v}_1 + \alpha_2 \mathbf{v}_2 = \alpha_1 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \end{bmatrix}$$

for $\alpha_1 = -1$, $\alpha_2 = 1$. For the in flux profile $\mathbf{w}_3$ there is no flux down the 'main pathway'. Instead, material flows backwards through reaction 3 and then forward through reaction 4.

5.4.5. We find that

$$\begin{aligned}
\mathbf{w}_1 &= \begin{bmatrix} 2 \\ 2 \\ 1 \\ 1 \end{bmatrix} = \alpha_1 \hat{\mathbf{v}}_1 + \alpha_2 \hat{\mathbf{v}}_2 = \alpha_1 \begin{bmatrix} -2 \\ -2 \\ -2 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ -1 \\ 2 \end{bmatrix} \quad \text{for } \alpha_1 = -\tfrac{3}{4},\ \alpha_2 = \tfrac{1}{2} \\
\mathbf{w}_2 &= \begin{bmatrix} 6 \\ 6 \\ 5 \\ 1 \end{bmatrix} = \alpha_1 \hat{\mathbf{v}}_1 + \alpha_2 \hat{\mathbf{v}}_2 = \alpha_1 \begin{bmatrix} -2 \\ -2 \\ -2 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ -1 \\ 2 \end{bmatrix} \quad \text{for } \alpha_1 = -\tfrac{11}{4},\ \alpha_2 = \tfrac{1}{2} \\
\mathbf{w}_3 &= \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \end{bmatrix} = \alpha_1 \hat{\mathbf{v}}_1 + \alpha_2 \hat{\mathbf{v}}_2 = \alpha_1 \begin{bmatrix} -2 \\ -2 \\ -2 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ -1 \\ 2 \end{bmatrix} \quad \text{for } \alpha_1 = \tfrac{1}{4},\ \alpha_2 = \tfrac{1}{2}.
\end{aligned}$$

5.4.6. The given vector $\mathbf{v}$ satisfies the balance equation, as follows:

$$\mathbf{N}\mathbf{v} = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix} \begin{bmatrix} 2 \\ 2 \\ 3 \\ -1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

However, we see that $\mathbf{v}$ cannot be written in the form $\alpha_1 \mathbf{v}_1 + \alpha_2 \mathbf{v}_2$:

$$\mathbf{v} = \begin{bmatrix} 2 \\ 2 \\ 3 \\ -1 \end{bmatrix} = \alpha_1 \mathbf{v}_1 + \alpha_2 \mathbf{v}_2 = \alpha_1 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \end{bmatrix} + \alpha_2 \begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \end{bmatrix}$$

unless $\alpha_2 = -1$. (In which case $\alpha_1 = 3$.)

5.4.7. a) The flux profile $\mathbf{v}$ corresponds to flux of 1 through the chain consisting of reactions 1, 2, and 3, and flux of one around the loop consisting of reactions 2, 4 and 5. This is a valid steady state flux profile, and does not violate the irreversibility constraints on reactions 1 and 3. To verify that the balance equation is satisfied, we can construct the stoichiometry matrix $\mathbf{N}$ and verify that

$$\mathbf{N}\mathbf{v} = \begin{bmatrix} 1 & -1 & 0 & 0 & -1 \\ 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} 1 \\ 2 \\ 1 \\ -1 \\ -1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

This flux mode is not elementary because it can be written as the sum of two other flux modes:

$$\mathbf{w}_1 = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 0 \\ 0 \end{bmatrix} \qquad \text{and} \qquad \mathbf{w}_2 = \begin{bmatrix} 0 \\ 1 \\ 0 \\ -1 \\ -1 \end{bmatrix}$$

b) Along with $\mathbf{w}_1$ and $\mathbf{w}_2$, the third elementary flux mode is

$$\mathbf{w}_3 = \begin{bmatrix} 0 \\ -1 \\ 0 \\ 1 \\ 1 \end{bmatrix}$$

which represents flow around the loop in the opposite direction.

5.4.8. a) When reaction 1 is reversible, the profile

$$\mathbf{v_7} = \begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}$$

is an elementary flux mode. Material can only flow into the network through reactions 1 and 2, so this is the only additional mode.
b) When reaction 3 is reversible, the profile

$$\mathbf{v_7} = \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 1 \end{bmatrix}$$

is an elementary flux mode. This is the only new behaviour that is feasible: material that flows into the system through reaction 3 (reversed), has to flow through reaction 10, and hence out through reaction 4. Reaction 7 balances reaction 10.

c) Reaction 5 could only achieve a negative steady-state flow if reaction 6 had a negative steady-state flow. As long as reaction 6 is irreversible, no new steady-state behaviours result from relaxing the irreversibility of reaction 5.

5.4.9. Referring to Figure 5.18, we note that the steady-state conditions for each species give:

$$\begin{aligned}
S_1 :&\quad v_1 + v_8 = v_5 + v_9 \\
S_2 :&\quad v_2 + v_7 = v_6 + v_8 + v_{10} \\
S_3 :&\quad v_9 = v_3 + v_{10} \\
S_4 :&\quad v_{10} = v_4 \\
S_5 :&\quad v_5 = v_6 \\
S_6 :&\quad v_6 + v_{10} = v_7
\end{aligned}$$

Then if v_1, v_2, v_3 and v_4 are all known, we find

$$\begin{aligned}
v_{10} &= v_4 \\
v_9 &= v_3 + v_{10} = v_3 + v_4 \\
v_8 &= v_2 + v_7 - v_6 - v_{10} = v_2 + (v_7 - v_6 - v_{10}) = v_2 \\
v_5 &= v_1 + v_8 - v_9 = v_1 + v_2 - (v_3 + v_4) \\
v_6 &= v_1 + v_2 - (v_3 + v_4) \\
v_7 &= v_6 + v_{10} = v_1 + v_2 - (v_3 + v_4) + v_4 = v_1 + v_2 - v_3.
\end{aligned}$$

5.4.10. The steady-state balance conditions are (as in Exercise 5.4.9):

$$\begin{aligned}
S_1 :&\quad v_1 + v_8 = v_5 + v_9 \\
S_2 :&\quad v_2 + v_7 = v_6 + v_8 + v_{10} \\
S_3 :&\quad v_9 = v_3 + v_{10} \\
S_4 :&\quad v_{10} = v_4 \\
S_5 :&\quad v_5 = v_6 \\
S_6 :&\quad v_6 + v_{10} = v_7
\end{aligned}$$

If v_3 and v_4 are known, then we have $v_{10} = v_4$ and $v_9 = v_3 + v_4$. The other reaction rates are not constrained to particular values.

5.4.11. a) Flux into the network is constrained to less than 2. Flux out (through v_3 and v_4) will be likewise constrained. Flux $v_3 = 2$ can be achieved with $v_1 = v_2 = v_8 = 1$, $v_9 = v_3 = 2$. Flux $v_4 = 2$ can be achieved with $v_1 = v_2 = v_8 = 1$, $v_9 = v_{10} = v_4 = v_7 = 2$.
b) Flux $v_3 = 2$ can be achieved as in part (a). With $v_7 \leq 1$, we have $v_{10} \leq$ (to maintain balance of S_6. Then, balance at S_4 demands that $v_4 \leq 1$. The maximal flux through reaction 4 will then be $v_4 = 1$, achieved with $v_1 = v_9 = v_{10} = v_7 = v_4 = 1$.
c) With $v_8 = 0$, flux through reaction 2 cannot feed flux through reactions 3 or 4. The maximal flux through reactions 3 and 4 are then both equal to one (the upper limit on v_1). These can be achieved by $v_1 = v_9 = v_3 = 1$ and $v_1 = v_9 = v_{10} = v_7 = v_4 = 1$, respectively.

Chapter 6

6.1.1. Taking the ligand concentration $[L]$ as a fixed input, the model is

$$\begin{aligned}
\frac{d}{dt}[R](t) &= -k_{RL}[R](t)\cdot[L] + k_{RLm}[RL](t) \\
\frac{d}{dt}[RL](t) &= k_{RL}[R](t)\cdot[L] - k_{RLm}[RL](t) \\
\frac{d}{dt}[G](t) &= -k_{Ga}[G](t)\cdot[RL](t) + k_{G1}[Gd](t)\cdot[Gbg](t) \\
\frac{d}{dt}[Ga](t) &= k_{Ga}[G](t)\cdot[RL](t) - k_{Gd0}[Ga](t) \\
\frac{d}{dt}[Gd](t) &= k_{Gd0}[Ga](t) - k_{G1}[Gd](t)\cdot[Gbg](t) \\
\frac{d}{dt}[Gbg](t) &= k_{Ga}[G](t)\cdot[RL](t) - k_{G1}[Gd](t)\cdot[Gbg](t)
\end{aligned}$$

There are three conservations: $[R]+[RL] = R_T$, $[G]+[Ga]+[Gd] = Ga_T$, and $[G]+[Gbg] = Gbg_T$. These conservations could be used to back-substitute for R, Gd and Gbg, leaving three differential equations for RL, G and Ga.

6.2.1. With response

$$R = \frac{Vs}{K+s},$$

we note that the response is $x\%$ of full activation when $R = xV/100$. This occurs when

$$\frac{xV}{100} = \frac{Vs}{K+s},$$

which gives

$$\frac{(K+s)x}{100} = s.$$

Solving for s gives

$$s = \frac{xK/100}{1-x/100} = \frac{xK}{100-x}.$$

Ten-percent activation and ninety-precent activation are thus achieved at

$$s_{10} = \frac{10K}{90} \qquad \text{and} \qquad s_{90} = \frac{90K}{10}.$$

The ratio of these two concentrations is

$$s_{90}/s_{10} = \frac{90K}{10}\frac{90}{10K} = 81,$$

as required.

Alternatively, with

$$R = \frac{Vs^4}{K+s^4}$$

we find $x\%$ activation when

$$\frac{xV}{100} = \frac{Vs^4}{K+s^4},$$

which gives

$$\frac{(K+s^4)x}{100} = s^4.$$

Solving for s gives

$$s = \sqrt[4]{\frac{Kx/100}{1-x/100}} = \sqrt[4]{\frac{Kx}{100-x}}.$$

Then ten- and ninety-percent activation occur at

$$s_{10} = \sqrt[4]{\frac{10K}{90}} \qquad \text{and} \qquad s_{90} = \sqrt[4]{\frac{90K}{10}}$$

The ratio of these two doses is

$$s_{90}/s_{10} = \sqrt[4]{\frac{90K}{10}\frac{90}{10K}} = \sqrt[4]{81} = 3,$$

as required.

6.2.2. Equation 6.2 reads:

$$\frac{k_1 E_{1T}}{k_2 E_{2T}} = \frac{w^*(w+K_1)}{w(w^*+K_2)}.$$

When the system is at 10% activation, we have $w^* = 0.1$ and $w = 0.9$. The corresponding input E_{1T}^{10} thus satisfies

$$\frac{k_1 E_{1T}^{10}}{k_2 E_{2T}} = \frac{0.1(0.9+K_1)}{0.9(0.1+K_2)}.$$

Likewise, the input E_{1T}^{90} that gives a 90% response satisfies

$$\frac{k_1 E_{1T}^{90}}{k_2 E_{2T}} = \frac{0.9(0.1+K_1)}{0.1(0.9+K_2)}$$

The ratio is then

$$\frac{E_{1T}^{90}}{E_{1T}^{10}} = \frac{0.9(0.1+K_1)}{0.1(0.9+K_2)}\frac{0.9(0.1+K_2)}{0.1(0.9+K_1)} = \frac{81(0.1+K_1)(0.1+K_2)}{(0.9+K_1)(0.9+K_2)}$$

as required. When K_1 and K_2 are large, this ratio tends to $81\frac{K_1K_2}{K_1K_2} = 81$. When K_1 and K_2 are near zero, this ratio tends to $\frac{81(0.1)(0.1)}{(0.9)(0.9)} = 1$.

6.2.3. We can measure steepness by considering the slope given by the derivative. Applying the chain rule, we find

$$\frac{d}{dx}f_3(f_2(f_1(x))) = \frac{df_3}{dx}\frac{df_2}{dx}\frac{df_1}{dx}.$$

Thus the steepness (slope) of the pathway's dose-response is the product of the steepness (slope) of the dose-responses of the individual steps.

6.3.1. CheA induces tumbling (by activating CheY), so a CheA knockout will be constantly running. CheB demethylates the receptor. In the absence of CheB activity, receptors will be fully methylated. Methylation enhances CheA activity, so in this case, CheA activity will be high, so active CheY levels will be high, and the cell will be constantly tumbling.

6.3.2. From the model, we have, if $k_2 = 0$,

$$\frac{d}{dt}([Am] + [AmL]) = (k_{-1} + k_{-2})[R] - \frac{k_1[B\text{-}P]\cdot[Am](t)}{k_{M1} + [Am](t)}$$

Then, in steady state, we have

$$0 = (k_{-1} + k_{-2})[R] - \frac{k_1[B\text{-}P]\cdot[Am]^{ss}}{k_{M1} + [Am]^{ss}}$$

This can be solved to yield an explicit formula for $[Am]^{ss}$. Because $[L]$ does not appear in this equation, the steady state activity level $[Am]^{ss}$ is independent of $[L]$, meaning that the model exhibits perfect adaptation.

6.4.1. IAP binds active caspase-3, removing it from the pathway. By enhancing degradation of IAP, active caspase-3 increases its own concentration. This enhances the self-sustaining positive feedback that makes caspase activation irreversible.

6.6.1. With

$$f_1(x_1, x_2, u) = u + x_1 - 2x_1^2 \qquad \text{and} \qquad f_2(x_1, x_2, u) = -x_1 - 3x_2$$

The Jacobian is

$$\mathbf{J}(x_1, x_2) = \begin{bmatrix} \frac{\partial f_1}{x_1} & \frac{\partial f_1}{x_2} \\ \frac{\partial f_2}{x_1} & \frac{\partial f_2}{x_2} \end{bmatrix} \begin{bmatrix} 1 - 4x_1 & 0 \\ -1 & -3 \end{bmatrix},$$

which has the desired form for $\mathbf{A}$ at $(x_1, x_2) = (0, 0)$, $u = 0$. We find

$$\mathbf{B} = \begin{bmatrix} \frac{\partial f_1}{u} \\ \frac{\partial f_2}{u} \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \end{bmatrix},$$

for any values of x_1, x_2, u. Taking derivatives of the output map $y = h(x_1, x_2, u) = x_2$ we find

$$C = \begin{bmatrix} \frac{\partial h}{\partial x_1} & \frac{\partial h}{\partial x_2} \end{bmatrix} = [0 \;\; 1] \qquad \text{and} \qquad D = \begin{bmatrix} \frac{\partial h}{\partial u} \end{bmatrix} = 0,$$

as required.

6.6.2. With

$$\frac{d}{dt}s(t) = V(t) - \frac{V_m s(t)}{K + s(t)},$$

the steady state for $V = V_0$ satisfies

$$0 = V_0 - \frac{V_m s^{ss}}{K + s^{ss}} \qquad \text{so} \qquad s^{ss} = \frac{V_0 K}{V_m - V_0}.$$

To determine the linearization, we take the derivative

$$\begin{aligned} \frac{\partial}{\partial x}\left(V(t) - \frac{V_m s(t)}{K + s(t)}\right) &= \frac{\partial}{\partial s}\left(V(t) - \frac{V_m s(t)}{K + s(t)}\right) \\ &= -\frac{V_m(K+s) - V_m s}{(K+s)^2} \\ &= -\frac{V_m K}{(K+s)^2}. \end{aligned}$$

At the steady state, this evaluates to

$$A = -\frac{V_m K}{(K + s^{ss})^2} = -\frac{V_m K}{\left(K + \frac{V_0 K}{V_m - V_0}\right)^2} = -\frac{V_m K}{\left(\frac{V_m K}{V_m - V_0}\right)^2} = -\frac{(V_m - V_0)^2}{V_m K}.$$

Taking the derivative with respect to the input u, we find

$$B = \frac{\partial}{\partial u}\left(V(t) - \frac{V_m s(t)}{K + s(t)}\right) = \frac{\partial}{\partial V}\left(V(t) - \frac{V_m s(t)}{K + s(t)}\right) = 1.$$

Since the output is $y = h(x, u) = x$, we have $C = \frac{\partial h}{\partial x} = 1$ and $D = \frac{\partial h}{\partial u} = 0$.

6.6.3. a) Here we have $B = C = 1$ and $D = 0$. Because a is a scalar, the formula (6.6) gives

$$H(\omega) = \frac{1}{i\omega - a}.$$

b) To determine the magnitude of H, we find

$$H(\omega) = \frac{1}{i\omega - a}\left(\frac{i\omega + a}{i\omega + a}\right) = \frac{i\omega + a}{-\omega^2 - a^2} = -\frac{a}{\omega^2 + a^2} - i\frac{\omega}{\omega^2 + a^2}.$$

Then, the gain is

$$\sqrt{\left(-\frac{a}{\omega^2 + a^2}\right)^2 + \left(-\frac{\omega}{\omega^2 + a^2}\right)^2} = \frac{1}{\omega^2 + a^2}\sqrt{a^2 + \omega^2} = \frac{1}{\sqrt{\omega^2 + a^2}},$$

as required.

Chapter 7

7.1.1. In steady state, we find

$$[OA] = [O][A]/K_A, \qquad [OB] = [O][B]/K_B, \qquad [OAB] = [A][OB]/K_A = [A][B][O]/(K_A K_B).$$

Then, the fraction of operators with both A and B bound is

$$\frac{[OAB]}{[O_{total}]} = \frac{[OAB]}{[O]+[OA]+[OB]+[OAB]} = \frac{\frac{[A][B]}{K_A K_B}}{1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A][B]}{K_A K_B}}$$

as required. Replacing $[OAB]$ in the numerator with $[O]$, $[OA]$, and $[OB]$ in the numerator gives the remaining formulas in equations (7.6).

7.1.2. If B completely blocks the promoter, then no expression occurs from states OB or OAB. Since no expression occurs when A is unbound, the only state that leads to expression is OA. The transcription rate is then

$$\alpha \frac{\frac{[A]}{K_A}}{1+\frac{[A]}{K_A}+\frac{[B]}{K_B}+\frac{[A][B]}{K_A K_B}}.$$

7.1.3. a) In steady state, we have

$$0 = \alpha \frac{p/K}{1+p/K} - \delta_p p = \alpha \frac{p}{K+p} - \delta_p p$$

So

$$0 = \alpha p - \delta_p K p - \delta_p p^2$$

Then, either $p = 0$, or we can divide by p and solve:

$$p = \frac{\alpha - \delta_p K}{\delta_p}.$$

This expression is positive when $\alpha > \delta_p K$; otherwise this expression is negative, and so does not represent a steady-state concentration.

To determine stability, we find the Jacobian as

$$\mathbf{J}(p) = \alpha \frac{(K+p)-p}{(K+p)^2} - \delta_p = \alpha \frac{K}{(K+p)^2} - \delta_p.$$

For the zero steady state, we have

$$\mathbf{J}(0) = \alpha \frac{K}{(K)^2} - \delta_p = \frac{\alpha}{K} - \delta_p$$

which is positive when $\alpha > \delta_p K$, in which case the zero steady state is unstable. For the positive steady state, we find

$$\mathbf{J}\left(\frac{\alpha-\delta_p K}{\delta_p}\right) = \alpha \frac{K}{\left(K+\frac{\alpha-\delta_p K}{\delta_p}\right)^2} - \delta_p = \alpha \frac{K}{\left(\frac{\delta_p K+\alpha-\delta_p K}{\delta_p}\right)^2} - \delta_p = \alpha \frac{K\delta_p^2}{\alpha^2} - \delta_p = \delta_P \left(\frac{K\delta_P}{\alpha} - 1\right)$$

which is negative when $\alpha > \delta_p K$, in which case this steady state is stable.

7.1.4. The steady-state condition is

$$0 = \alpha \frac{p^2}{K^2 + p^2} - \delta_p p$$

which gives

$$0 = \alpha p^2 - \delta_p p (K^2 + p^2)$$

There is one steady state at $p = 0$. Dividing through by p, we find that any other steady states must satisfy:

$$0 = \alpha p - \delta_p (K^2 + p^2) = \alpha p - \delta_p K^2 - \delta_p p^2.$$

Applying the quadratic formula gives

$$p = \frac{\alpha \pm \sqrt{\alpha^2 - 4\delta_p^2 K^2}}{2\delta_p}$$

The discriminant $\alpha^2 - 4\delta_p^2 K^2$ is non-negative when $\alpha > 2\delta_p K$. In this case $\sqrt{\alpha^2 - 4\delta_p^2 K^2} < \alpha$, so both roots are positive, and thus represent steady states of the system.

7.2.1. If dilution is negligible, in quasi-steady state, we have

$$0 = \frac{k_g b(t) L(t)}{K_{Mg} + L(t)} - \frac{k_g b(t) A^{qss}}{K_{Mg} + A^{qss}},$$

which has solution $A^{qss}(t) = L(t)$ as required.

7.2.2. IPTG mimics allolactose in inducing expression, but does not undergo metabolism. With the intracellular IPTG concentration fixed, we find that the fraction of unbound repressor monomers (equation (7.16)) is given by

$$\frac{K_2}{K_2 + A(t) + [IPTG]}$$

The concentration of active repressor tetramers (equation (7.17)) is then

$$r(t) = R_T \left(\frac{K_2}{K_2 + A(t) + [IPTG]} \right)^4.$$

7.2.3. In steady state, each binding reaction is in equilibrium:

$$\begin{aligned}
[\mathrm{O(cI_2)_2}] &= K_1[\mathrm{O}][\mathrm{cI_2}]^2 \\
[\mathrm{O(cI_2)_3}] &= K_2[\mathrm{O(cI_2)_2}][\mathrm{cI_2}] = K_2 K_1 [\mathrm{O}][\mathrm{cI_2}]^3 \\
[\mathrm{O(cro_2)}] &= K_3[\mathrm{O}][\mathrm{cro_2}] \\
[\mathrm{O(cro_2)_{2+}}] &= K_4[\mathrm{O(cro_2)}][\mathrm{cro_2}] = K_4 K_3 [\mathrm{O}][\mathrm{cro_2}]^2
\end{aligned}$$

The fraction of operators in the unbound state is then

$$\begin{aligned}\frac{[\mathrm{O}]}{O_T} &= \frac{[\mathrm{O}]}{[\mathrm{O}]+[\mathrm{O}(\mathrm{cI}_2)_2]+[\mathrm{O}(\mathrm{cI}_2)_3]+[\mathrm{O}(\mathrm{cro}_2)]+[\mathrm{O}(\mathrm{cro}_2)_{2+}]}\\ &= \frac{[\mathrm{O}]}{[\mathrm{O}]+K_1[\mathrm{O}][\mathrm{cI}_2]^2+K_2K_1[\mathrm{O}][\mathrm{cI}_2]^3+K_3[\mathrm{O}][\mathrm{cro}_2]+K_4K_3[\mathrm{O}][\mathrm{cro}_2]^2}\\ &= \frac{1}{1+K_1[\mathrm{cI}_2]^2+K_2K_1[\mathrm{cI}_2]^3+K_3[\mathrm{cro}_2]+K_4K_3[\mathrm{cro}_2]^2}\\ &= \frac{1}{1+K_1(r/2)^2+K_2K_1(r/2)^3+K_3(c/2)+K_4K_3(c/2)^2}\end{aligned}$$

The fraction of operators in state $\mathrm{O}(\mathrm{cI}_2)_2$ is likewise

$$\frac{[\mathrm{O}(\mathrm{cI}_2)_2]}{O_T}\frac{K_1(r/2)^2}{1+K_1(r/2)^2+K_2K_1(r/2)^3+K_3(c/2)+K_4K_3(c/2)^2}$$

while the fraction of operators in state $\mathrm{O}(\mathrm{cro}_2)$ is

$$\frac{[\mathrm{O}(\mathrm{cro}_2)]}{O_T}\frac{K_3(c/2)}{1+K_1(r/2)^2+K_2K_1(r/2)^3+K_3(c/2)+K_4K_3(c/2)^2}$$

Adding terms with coefficients as in the table gives the formulas in equation (7.19).

7.2.4. For concreteness suppose that the model

$$\frac{d}{dt}p(t)=\frac{\alpha}{K+p(t)}-\delta p(t).$$

is specified in terms of minutes (t) and nM (p). Then K has units of nM, and is equal to 1 in units of K·nM. We then write the species concentration as $\tilde{p}=p/K$, where $\tilde{p}$ is measured in units of K· nM. Likewise, δ has units of 1/min and is equal to 1 in units of δ/min. We thus measure time $\tau=t/\delta$ in units of δ·min to arrive at a decay rate of $\tilde{p}$. The maximal expression rate α, which has units of nM/min, must then be rescaled to $\tilde{\alpha}=\alpha/(K\delta)$, with units of $K\delta$ nM/min.

7.2.5. When $\beta=\gamma=1$, and $\alpha_1=\alpha_2=\alpha$, steady-state condition is

$$\frac{\alpha}{1+p_2}-p_1=0, \qquad \frac{\alpha}{1+p_1}-p_2=0.$$

These give

$$\alpha=p_2(1+p_1)=p_2\left(1+\frac{\alpha}{1+p_2}\right)=p_2\left(\frac{1+p_2+\alpha}{1+p_2}\right),$$

so

$$\alpha+\alpha p_2=p_2+p_2^2+\alpha p_2.$$

This reduces to

$$p_2^2+p_2-\alpha=0,$$

which is solved by

$$p_2 = \frac{-1 \pm \sqrt{1+4\alpha}}{2}.$$

Only one of these roots is non-negative, so there is a single steady state.

7.3.1. The original formulation is valid if consumption of the metabolite Z is a first-order processes, as opposed having a hyperbolic (Michaelis-Menten) dependence on $[Z]$.
a) The interpretation: X is nuclear mRNA, Y is cytoplasmic mRNA, Z is protein product, is valid if (i) mRNA export is irreversible and first order, (ii) $b = \alpha$ or $b > \alpha$ and the difference accounts for degradation of X.
b) The interpretation: X is mRNA, Y is inactive protein product, Z is active protein product, is valid if (i) the activation process is first order, and (ii) $\beta = \gamma$ or $\beta > \gamma$ and the difference accounts for degradation of Y.
In every case, transport into the nucleus must be considered fast.

7.3.2. The repressor binds the unoccupied operator with strong cooperativity, so we can approximate the binding events as:

$$O + 4Y \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} OY_4$$

So in steady state $[OY_4] = [O][Y]^4(k_1/k_{-1})$. We choose units of concentration scale Y so that k_1/k_{-1} is scaled to 1. The activator als binds cooperatively. The binding events are

$$O + 2X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} OX_2 \qquad\qquad OX_2 + 2X \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} OX_4$$

$$OY_4 + 2X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} OY_4X_2 \qquad\qquad OY_4X_2 + 2X \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} OY_4X_4.$$

At steady state

$$\begin{aligned}
[OX_2] &= [O][X]^2(k_2/k_{-2}) \\
[OY_4X_2] &= [OY_4][X]^2(k_2/k_{-2}) = [O][Y^4][X]^2(k_2/k_{-2}) \\
[OX_4] &= [OX_2][X]^2(k_3/k_{-3}) = [O][X]^4(k_2/k_{-2})(k_3/k_{-3}) \\
[OY_4X_4] &= [OY_4X_2][X]^2(k_3/k_{-3}) = [O][Y]^4[X]^4(k_2/k_{-2})(k_3/k_{-3})
\end{aligned}$$

We choose the concentration scale for X so that k_2/k_{-2} is scaled to 1. We set $k_3/k_{-3} = \sigma$. The fraction of operators in the unbound state is then

$$\begin{aligned}
\frac{[O]}{O_T} &= \frac{[O]}{[O]+[OY_4]+[OX_2]+[OY_4X_2]+[OX_4]+[OY_4X_4]} \\
&= \frac{[O]}{[O](1+[Y]^4+[X]^2+[Y]^4[X]^2+\sigma[X]^4+\sigma[Y]^4[X]^4} \\
&= \frac{1}{(1+[Y]^4)(1+[X]^2+\sigma[X]^4)}.
\end{aligned}$$

Scaling time so that the rate of activator expression from the states O and OX_2 is equal to one, and letting α be the rate of expression from state OX_4, we have the activator expression rate

$$\frac{1+[X]^2+\alpha\sigma[X]^4}{(1+[Y]^4)(1+[X]^2+\sigma[X]^4)}.$$

The rest of the model follows by defining a_y as the basal expression rate of repressor, and γ_x and γ_y as the degradation/dilution rates of X and Y respectively.

7.4.1. The dependence of LuxR production on AHL introduces an additional positive feedback on AHL production, and so will make the response even steeper than shown in Figure 7.25

7.4.2. The behaviour of the receiver cells in Figure 7.26 can be described by:

$$\begin{aligned}
\frac{d}{dt}A(t) &= -n(A(t)-A_{\text{out}})-2k_1(A(t))^2(R_T-2R^*(t))^2+2k_2R^*(t)\\
\frac{d}{dt}R^*(t) &= k_1(A(t))^2(R_T-2R^*(t))^2-k_2R^*(t)\\
\frac{d}{dt}G(t) &= \frac{a_0R^*}{K_M+R^*(t)}-bG(t),
\end{aligned}$$

where A is the AHL concentration, R^* is the concentration of active LuxR-AHl complexes, G is the GFP concentration, and the extracellular AHL concentration A_{out} is taken as a constant parameter.

7.4.3. There are four operator sites: unbound (O), activator-bound (OR), repressor-bound (OC_2) and fully-bound (ORC_2). Putting the binding events in steady state, we have

$$[OR]=[O][R]/K_R \qquad [OC_2]=[O][C]^2/K_C^2 \qquad [ORC_2]=[O][R][C]^2/(K_RK_C^2),$$

where K_R and K_C^2 are dissociation constants. The fraction of operators in state OR is then

$$\begin{aligned}
\frac{[OR]}{O_T} &= \frac{[O][R]/K_R}{[O]+[OR]+[OC_2]+[ORC_2]}\\
&= \frac{[O][R]/K_R}{[O](1+[R]/K_R+[C]^2/K_C^2+[R][C]^2/(K_RK_C^2))}\\
&= \frac{[R]/K_R}{1+[R]/K_R+([C]/K_C)^2+([R]/K_R)([C]/K_C)^2}
\end{aligned}$$

as in the model.

7.5.1. The NOR truth table is

NOR		
inputs		output
A	B	
0	0	1
1	0	0
0	1	0
1	1	0

The output is the inverse of the OR gate output, so an OR gate followed by an inverter yields a NOR logic.

The NAND truth table is

NAND		
inputs		output
A	B	
0	0	1
1	0	1
0	1	1
1	1	0

The output is the inverse of the AND gate output, so an AND gate followed by an inverter yields a NAND logic.

7.5.2. For the *lac* operon, let A be the allolactose input and R the repressor input. The truth table for operon activity is then

IMPLIES		
inputs		output
A	R	
0	0	1
1	0	1
0	1	0
1	1	1

where $R = 0$ means the repressor is absent. This same behavior results from inverting the repressor signal and then applying an OR logic to this inverted signal and the allolactose signal: A OR (NOT R).

7.6.1. When the system is in state $\mathbf{N} = (N_A, N_B)$, it can transition out of that state via (i) reaction 1, with propensity k_1; (ii) reaction 2, with propensity k_2; or (iii) reaction 3, with propensity $k_3 N_A N_B$. Transitions into state $\mathbf{N} = (N_A, N_B)$ can occur (i) from state $(N_A - 1, N_B)$, via reaction 1, with propensity k_1; (ii) from state $(N_A, N_B - 1)$, via reaction 2, with propensity k_2; or (iii) from state $(N_A + 1, N_B + 1)$, via reaction 3, with propensity $k_3(N_A + 1)(N_B + 1)$. Constructing the probability balance as in equation (7.27) gives

$$\begin{aligned} P((N_A, N_B), t + dt) &= P((N_A, N_B), t)\,[1 - (k_1 + k_2 + k_3 N_A N_B)dt] \\ &\quad + P((N_A - 1, N_B), t) \cdot k_1 dt + P((N_A, N_B - 1), t) \cdot k_2 dt \\ &\quad + P((N_A + 1, N_B + 1), t) \cdot (N_A + 1)(N_B + 1) k_3 dt, \end{aligned}$$

as required.

7.6.2. Considering the probability balance in Exercise 7.6.1, we have

$$\begin{aligned} \frac{d}{dt} P((N_A, N_B), t) &= -P((N_A, N_B), t)\,(k_1 + k_2 + k_3 N_A N_B) \\ &\quad + P((N_A - 1, N_B), t)\, k_1 + P((N_A, N_B - 1), t)\, k_2 \\ &\quad + P((N_A + 1, N_B + 1), t)\, (N_A + 1) N_B + 1) k_3. \end{aligned}$$

7.6.3. Let $P_0 = P^{ss}(0,2)$, $P_1 = P^{ss}(1,1)$ and $P_2 = P^{ss}(2,0)$. Then, we have

$$\begin{aligned} 0 &= -2k_1P_2 + k_2P_1 \\ 0 &= -k_2P_1 - k_1P_1 + 2k_1P_2 + 2k_2P_0 \\ 0 &= -2k_2P_0 + k_1P_1. \end{aligned}$$

From the first equation,

$$P_2 = \frac{k_2}{2k_1}P_1$$

Conservation then gives $P_0 = 1 - P_1 - P_2 = 1 - (1 + \frac{k_2}{2k_1})P_1$. Substituting into the last equation gives

$$\begin{aligned} 0 &= -2k_2\left(1 - \left(1 + \frac{k_2}{2k_1}\right)P_1\right) + k_1P_1 \\ &= -2k_2 + \left(k_1 + 2k_2 - \frac{k_2^2}{k_1}\right)P_1 \end{aligned}$$

so

$$P_1 = P^{ss}(1,1) = \frac{2k_2}{k_1 + 2k_2 + k_2^2/k_1} = \frac{2k_1k_2}{k_1^2 + 2k_1k_2 + k_2^2} = \frac{2k_1k_2}{(k_1+k_2)^2}.$$

Then

$$P_2 = P^{ss}(2,0) = \frac{k_2}{2k_1}P_1 = \frac{k_2^2}{(k_1+k_2)^2},$$

and, from the thrid equation,

$$P_0 = P^{ss}(0,2) = \frac{k_1}{2k_2}P_1 = \frac{k_1^2}{(k_1+k_2)^2}.$$

In the case illustrated in Figure 7.40, when $k_1 = 3$, $k_2 = 1$, we have $P^{ss}(2,0) = 1/16$, $P^{ss}(1,1) = 6/16$, and $P^{ss}(0,2) = 9/16$, which correspond to the probabilities shown for $t = 1$, so steady state has been reached.

7.6.4. The mass action-based model has steady state concentrations a and b characterized by

$$k_1a = k_2b,$$

where conservation gives $a + b = T$. The steady state concentrations are then

$$a = \frac{k_2T}{k_1+k_2} \qquad \text{and} \qquad b = \frac{k_1T}{k_1+k_2}.$$

The expected (mean) abundance of A in the probability distribution (7.31) is

$$\begin{aligned} E(N_A) &= 2\left(\frac{k_2^2}{(k_1+k_2)^2}\right) + 1\left(\frac{2k_1k_2}{(k_1+k_2)^2}\right) + 0\left(\frac{k_1^2}{(k_1+k_2)^2}\right) \\ &= \frac{2k_2^2 + 2k_1k_2}{(k_1+k_2)^2} = \frac{2k_2(k_2+k_1)}{(k_1+k_2)^2} = \frac{2k_2}{(k_1+k_2)}. \end{aligned}$$

Likewise

$$\begin{aligned} E(N_B) &= 0\left(\frac{k_2^2}{(k_1+k_2)^2}\right) + 1\left(\frac{2k_1k_2}{(k_1+k_2)^2}\right) + 2\left(\frac{k_1^2}{(k_1+k_2)^2}\right) \\ &= \frac{2k_1}{(k_1+k_2)}. \end{aligned}$$

With molecule count $T = 2$, these expected values correspond to the deterministic description.

Chapter 8

8.1.1. Using the formula for the Nernst potential (equation (8.1)), we have, with $\frac{RT}{F} = 26.7 \times 10^{-3}$ J/C,

$$\begin{aligned} E_{\text{Na}} &= \frac{26.7}{1} \ln\left(\frac{145}{12}\right) \text{ mV} = 66.5 \text{ mV} \\ E_{\text{K}} &= \frac{26.7}{1} \ln\left(\frac{4}{155}\right) \text{ mV} = -97.6 \text{ mV} \\ E_{\text{Ca}} &= \frac{26.7}{2} \ln\left(\frac{1.5}{0.0001}\right) \text{ mV} = 128.4 \text{ mV} \end{aligned}$$

8.1.2. The resting potential is the weighted average (equation (8.2)):

$$V^{ss} = \frac{E_{\text{Na}}g_{\text{Na}} + E_{\text{K}}g_{\text{K}} + E_{\text{Cl}}g_{\text{Cl}}}{g_{\text{Na}} + g_{\text{K}} + g_{\text{Cl}}}.$$

Substituting the Nernst potentials, and writing $g_{\text{K}} = 25g_{\text{Na}}$ and $g_{\text{Cl}} = 12.5g_{\text{Na}}$, we have

$$V^{ss} = \frac{54g_{\text{Na}} - 75(25g_{\text{Na}}) - 59(12.5g_{\text{Na}})}{g_{\text{Na}} + 25g_{\text{Na}} + 12.5g_{\text{Na}}} \text{ mV} = \frac{54 - 1875 - 737.5}{1 + 25 + 12.5} \text{ mV} = -66.5 \text{ mV}.$$

8.1.3. With

$$V(t) = E - e^{-(g/C)t}(E - V_0),$$

we have $V(0) = E - (E - V_0) = V_0$ as required. Differentiating, we find

$$\frac{d}{dt}V(t) = \frac{g}{C}e^{-(g/C)t}(E - V_0) = \frac{g}{C}(E - (E - e^{-(g/C)t}(E - V_0))) = \frac{g}{C}(E - V(t)),$$

as required to satisfy equation (8.5).

8.1.4. a) The steady state of equation (8.8) satisfies

$$0 = \frac{1}{C}\Big(g_{\text{Na}}\cdot(E_{\text{Na}} - V^{ss}) + g_{\text{K}}\cdot(E_{\text{K}} - V^{ss}) + g_{\text{Cl}}\cdot(E_{\text{Cl}} - V^{ss})\Big),$$

giving

$$V^{ss} = \frac{E_{\text{Na}}g_{\text{Na}} + E_{\text{K}}g_{\text{K}} + E_{\text{Cl}}g_{\text{Cl}}}{g_{\text{Na}} + g_{\text{K}} + g_{\text{Cl}}},$$

which corresponds to equation (8.2).
b) Equation (8.8) can be written as

$$\begin{aligned}\frac{d}{dt}V(t) &= \frac{1}{C}\Big(g_{\mathrm{Na}}\cdot E_{\mathrm{Na}} \ + g_{\mathrm{K}}\cdot E_{\mathrm{K}} + g_{\mathrm{Cl}}\cdot E_{\mathrm{Cl}} - (g_{\mathrm{Na}} + g_{\mathrm{K}} + g_{\mathrm{Cl}})\cdot V(t)\Big)\\ &= \frac{g_T}{C}\Big(\frac{g_{\mathrm{Na}}\cdot E_{\mathrm{Na}} \ + g_{\mathrm{K}}\cdot E_{\mathrm{K}} + g_{\mathrm{Cl}}\cdot E_{\mathrm{Cl}}}{g_T} - V(t)\Big),\end{aligned}$$

where $g_T = g_{\mathrm{Na}} + g_{\mathrm{K}} + g_{\mathrm{Cl}}$. This has the same form as equation (8.5), so, as in Exercise 8.1.3, the solution relaxes exponentially to steady state, with rate $e^{-(g_T/C)t}$.

8.2.1. a) At steady state, $w^{ss} = w_\infty$, which lies between zero and one. The steady state for V satisfies:

$$V^{ss} = \frac{\bar{g}_{\mathrm{Ca}} m^{ss} E_{\mathrm{Ca}} + g_{\mathrm{leak}} E_{\mathrm{leak}} + \bar{g}_{\mathrm{K}} w^{ss} E_{\mathrm{K}} + I_{\mathrm{applied}}}{\bar{g}_{\mathrm{leak}} + \bar{g}_{\mathrm{K}} w^{ss} + g_{\mathrm{Ca}} m^{ss}}.$$

Provided that $E_K < 0$, the contribution of E_K reduces the steady-state voltage. With $E_{Ca} > 0$, the contribution of E_{Ca} is maximized when all calcium channels are open. An upper bound is thus reached when $w^{ss} = 0$ and $m^{ss} = 1$, i.e.

$$V^{ss} < \frac{\bar{g}_{\mathrm{Ca}} E_{\mathrm{Ca}} + g_{\mathrm{leak}} E_{\mathrm{leak}} + I_{\mathrm{applied}}}{\bar{g}_{\mathrm{leak}} + g_{\mathrm{Ca}}}.$$

Alternatively, a lower bound is reached with potassium channels fully open and calcium channels closed: $w^{ss} = 1$ and $m^{ss} = 0$,

$$V^{ss} > \frac{g_{\mathrm{leak}} E_{\mathrm{leak}} + \bar{g}_{\mathrm{K}} E_{\mathrm{K}} + I_{\mathrm{applied}}}{\bar{g}_{\mathrm{leak}} + \bar{g}_{\mathrm{K}}}.$$

b) A one-dimensional model can only display monotonic behaviour, since each point on the phase-line has a specific direction. The voltage thus would not be able to rise and fall as needed for an action potential.

Appendix B

B.1.1. a) i) Applying the addition rule and the power rule, we have

$$\frac{d}{dx}(2x + x^5) = \frac{d}{dx}(2x) + \frac{d}{dx}(x^5) = 2 + 5x^4.$$

ii) The quotient rule gives

$$\frac{d}{ds}\left(\frac{2s}{s+4}\right) = \frac{2(s+4) - 2s(1)}{(s+4)^2} = \frac{8}{(s+4)^2}.$$

iii) The product rule gives

$$\frac{d}{dx}x^3 e^x = 3x^2 e^x + x^3 e^x = (3x^2 + x^3)e^x.$$

iv) Applying the quotient rule, we have

$$\frac{d}{ds}\left(\frac{3s^2}{0.5 + s^4}\right) = \frac{6s(0.5 + s^4) - 3s^2(4s^3)}{(0.5 + s^4)^2} = \frac{3s - 6s^5}{(0.5 + s^4)^2}.$$

b) i) The derivative is

$$\frac{d}{ds}(s^2+s^3) = 2s+3s^2.$$

At $s = 2$ the derivative evaluates to

$$2(2)+3(2)^2 = 16.$$

ii) The derivative is

$$\frac{d}{dx}\left(\frac{x}{x+1}\right) = \frac{1(x+1)-x(1)}{(x+1)^2} = \frac{1}{(x+1)^2}.$$

At $x = 0$, the derivative evaluates to

$$\frac{1}{(0+1)^2} = 1.$$

iii) The derivative is

$$\frac{d}{ds}\left(\frac{s^2}{1+s^2}\right) = \frac{2s(1+s^2)-s^2(2s)}{(1+s^2)^2} = \frac{2s}{(1+s^2)^2}.$$

At $s = 1$, the derivative evaluates to

$$\frac{2}{(1+1^2)^2} = 1/2.$$

iv) The derivative is

$$\frac{d}{dx}\left(\frac{e^x}{1+x+x^2}\right) = \frac{e^x(1+x+x^2)-e^x(1+2x)}{(1+x+x^2)^2} = \frac{e^x(x^2-x)}{(1+x+x^2)^2}.$$

At $x = 2$, the derivative evaluates to

$$\frac{e^2(4-2)}{(1+2+4)^2} = \frac{2e^2}{49} = 0.302.$$

B.1.2. i) Differentiating both sides of the equation:

$$\frac{d}{dx}\left(\frac{x}{y^2(x)+1}\right) = \frac{d}{dx}x^3,$$

gives

$$\frac{y^2(x)+1-x(2y(x)\frac{dy}{dx})}{(y^2(x)+1)^2} = 3x^2.$$

Solving for $\frac{dy}{dx}$ we have

$$\frac{dy}{dx} = \frac{-3x^2(y^2(x)+1)^2+(y^2(x)+1)}{2xy(x)} = \frac{(y^2(x)+1)(1-3x^2(y^2(x)+1))}{2xy(x)}.$$

B.1.3. i) The partial derivatives are:

$$\begin{aligned}\frac{\partial}{\partial s_1}\left(\frac{3s_1-s_2}{1+s_1/2+s_2/4}\right) &= \frac{3(1+s_1/2+s_2/4)-(3s_1-s_2)\frac{1}{2}}{(1+s_1/2+s_2/4)^2}=\frac{3+5s_2/4}{(1+s_1/2+s_2/4)^2}.\\ \frac{\partial}{\partial s_2}\left(\frac{3s_1-s_2}{1+s_1/2+s_2/4}\right) &= \frac{-(1+s_1/2+s_2/4)-(3s_1-s_2)\frac{1}{4}}{(1+s_1/2+s_2/4)^2}=\frac{-1-5s_1/4}{(1+s_1/2+s_2/4)^2}.\end{aligned}$$

ii) The partial derivatives are:

$$\begin{aligned}\frac{\partial}{\partial s}\left(\frac{2s^2}{i+3s^2}\right) &= \frac{4s(i+3s^2)-2s^2(6s)}{(i+3s^2)^2}=\frac{4si}{(i+3s^2)^2}.\\ \frac{\partial}{\partial i}\left(\frac{2s^2}{i+3s^2}\right) &= \frac{-2s^2}{(i+3s^2)^2}.\end{aligned}$$

B.2.1. a) i)

$$[1\ 2\ 4]\cdot\begin{bmatrix}3\\2\\-1\end{bmatrix}=(1)(3)+(2)(2)+(4)(-1)=3.$$

ii)

$$[1\ 1]\cdot\begin{bmatrix}-2\\2\end{bmatrix}=(1)(-2)+(1)(2)=0.$$

b) i)

$$\begin{bmatrix}1&0&1\\1&2&3\\-1&-2&0\end{bmatrix}\cdot\begin{bmatrix}-2\\-1\\0\end{bmatrix}=\begin{bmatrix}(1)(-2)+(0)(-1)+(1)(0)\\(1)(-2)+(2)(-1)+(3)(0)\\(-1)(-2)+(-2)(-1)+(0)(0)\end{bmatrix}=\begin{bmatrix}-2\\-1\\4\end{bmatrix}.$$

ii)

$$\begin{bmatrix}-1&0&-2&3\\-2&2&3&3\end{bmatrix}\cdot\begin{bmatrix}1\\-2\\1\\1\end{bmatrix}=\begin{bmatrix}(-1)(1)+(0)(-2)+(-2)(1)+(3)(1)\\(-2)(1)+(2)(-2)+(3)(1)+(3)(1)\end{bmatrix}=\begin{bmatrix}0\\0\end{bmatrix}.$$

c) i)

$$\begin{bmatrix}1&1&1&3\\-2&0&1&-1\end{bmatrix}\cdot\begin{bmatrix}2&2\\-1&-1\\1&4\\0&5\end{bmatrix}$$

$$=\begin{bmatrix}(1)(2)+(1)(-1)+(1)(1)+(3)(0)&(1)(2)+(1)(-1)+(1)(4)+(3)(5)\\(-2)(2)+(0)(-1)+(1)(1)+(-1)(0)&(-2)(2)+(0)(-1)+(1)(4)+(-1)(5)\end{bmatrix}=\begin{bmatrix}2&20\\-3&-5\end{bmatrix}.$$

ii)

$$\mathbf{M}\cdot\mathbf{N} = \begin{bmatrix} 1 & 0 & 1 \\ 2 & 2 & 3 \\ 2 & -4 & 1 \end{bmatrix} \cdot \begin{bmatrix} 2 & 2 & 2 \\ -1 & -1 & 0 \\ 1 & 4 & 5 \end{bmatrix}$$

$$= \begin{bmatrix} (1)(2)+(0)(-1)+(1)(1) & (1)(2)+(0)(-1)+(1)(4) & (1)(2)+(0)(0)+(1)(5) \\ (2)(2)+(2)(-1)+(3)(1) & (2)(2)+(2)(-1)+(3)(4) & (2)(2)+(2)(0)+(3)(5) \\ (2)(2)+(-4)(-1)+(1)(1) & (2)(2)+(-4)(-1)+(1)(4) & (2)(2)+(-4)(0)+(1)(5) \end{bmatrix}$$

$$= \begin{bmatrix} 3 & 6 & 7 \\ 5 & 14 & 19 \\ 9 & 12 & 9 \end{bmatrix}.$$

d) We find

$$\mathbf{N}\cdot\mathbf{M} = \begin{bmatrix} 2 & 2 & 2 \\ -1 & -1 & 0 \\ 1 & 4 & 5 \end{bmatrix} \cdot \begin{bmatrix} 1 & 0 & 1 \\ 2 & 2 & 3 \\ 2 & -4 & 1 \end{bmatrix}$$

$$= \begin{bmatrix} (2)(1)+(2)(2)+(2)(2) & (2)(0)+(2)(2)+(2)(-4) & (2)(1)+(2)(3)+(2)(1) \\ (-1)(1)+(-1)(2)+(0)(2) & (-1)(0)+(-1)(2)+(0)(-4) & (-1)(1)+(-1)(3)+(0)(1) \\ (1)(1)+(4)(2)+(5)(2) & (1)(0)+(4)(2)+(5)(-4) & (1)(1)+(4)(3)+(5)(1) \end{bmatrix}$$

$$= \begin{bmatrix} 10 & -4 & 10 \\ -3 & -2 & -4 \\ 19 & -12 & 18 \end{bmatrix}.$$

B.2.2. We find

$$\mathbf{M}\cdot\mathbf{I}_3 = \begin{bmatrix} 2 & -1 & 3 \\ 1 & 1 & 4 \\ -1 & -2 & 2 \end{bmatrix} \cdot \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

$$= \begin{bmatrix} (2)(1)+(-1)(0)+(3)(0) & (2)(0)+(-1)(1)+(3)(0) & (2)(0)+(-1)(0)+(3)(1) \\ (1)(1)+(1)(0)+(4)(0) & (1)(0)+(1)(1)+(4)(0) & (1)(0)+(1)(0)+(4)(1) \\ (-1)(1)+(-2)(0)+(2)(0) & (-1)(0)+(-2)(1)+(2)(0) & (-1)(0)+(-2)(0)+(2)(1) \end{bmatrix}$$

$$= \begin{bmatrix} 2 & -1 & 3 \\ 1 & 1 & 4 \\ -1 & -2 & 2 \end{bmatrix} = \mathbf{M}$$

Likewise

$$\mathbf{I}_3\cdot\mathbf{M} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} 2 & -1 & 3 \\ 1 & 1 & 4 \\ -1 & -2 & 2 \end{bmatrix}$$

$$= \begin{bmatrix} (1)(2)+(0)(1)+(0)(-1) & (1)(-1)+(0)(1)+(0)(2) & (1)(3)+(0)(4)+(0)(2) \\ (0)(2)+(1)(1)+(0)(-1) & (0)(-1)+(1)(1)+(0)(2) & (0)(3)+(1)(4)+(0)(2) \\ (0)(2)+(0)(1)+(1)(-1) & (0)(-1)+(0)(1)+(1)(2) & (0)(3)+(0)(4)+(1)(2) \end{bmatrix}$$

$$= \begin{bmatrix} 2 & -1 & 3 \\ 1 & 1 & 4 \\ -1 & -2 & 2 \end{bmatrix} = \mathbf{M}.$$

B.2.3. a) We find

$$\mathbf{M}\cdot\mathbf{M}^{-1} = \begin{bmatrix} 1 & 0 \\ 2 & 2 \end{bmatrix} \cdot \begin{bmatrix} 1 & 0 \\ -1 & \frac{1}{2} \end{bmatrix} = \begin{bmatrix} (1)(1)+(0)(-1) & (1)(0)+(0)(1/2) \\ (2)(1)+(2)(-1) & (2)(0)+(2)(1/2) \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} = \mathbf{I}_2.$$

and

$$\mathbf{M}^{-1}\cdot\mathbf{M} = \begin{bmatrix} 1 & 0 \\ -1 & \frac{1}{2} \end{bmatrix} \cdot \begin{bmatrix} 1 & 0 \\ 2 & 2 \end{bmatrix} = \begin{bmatrix} (1)(1)+(0)(2) & (1)(0)+(0)(2) \\ (-1)(1)+(1/2)(2) & (-1)(0)+(1/2)(2) \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} = \mathbf{I}_2.$$

b) i) We note that for any matrix $\mathbf{N}$, the bottom row of the product $\mathbf{M}_1\cdot\mathbf{N}$ will be zero, beacuse it is a sum of products each involving a term in the bottom row of $\mathbf{M}_1$ (all of which are zero). Such a product cannot be the identity matrix, so $\mathbf{M}_1$ has no inverse.
ii) We find the general product

$$\begin{aligned} \mathbf{M}_2\cdot\mathbf{M} &= \begin{bmatrix} 2 & 2 \\ -1 & -1 \end{bmatrix} \cdot \begin{bmatrix} m_1 & m_2 \\ m_3 & m_4 \end{bmatrix} \\ &= \begin{bmatrix} (2)(m_1)+(2)(m_3) & (2)(m_2)+(2)(m_4) \\ (-1)(m_1)+(-1)(m_3) & (-1)(m_2)+(-1)(m_4) \end{bmatrix} = \begin{bmatrix} 2(m_1+m_3) & 2(m_2+m_4) \\ -(m_1+m_3) & -(m_2+m_4) \end{bmatrix}. \end{aligned}$$

This product can never take the form of the identity matrix, since the second row is a multiple of the first.

B.2.4. We find

$$\mathbf{M}\cdot\mathbf{v} = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & -1 & 2 & -1 \end{bmatrix} \begin{bmatrix} 2 \\ 2 \\ 1 \\ 0 \end{bmatrix} = \begin{bmatrix} (1)(2)+(-1)(2)+(0)(1)+(0)(0) \\ (0)(2)+(-1)(2)+(2)(1)+(-1)(0) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix},$$

and

$$\mathbf{M}\cdot\mathbf{w} = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & -1 & 2 & -1 \end{bmatrix} \begin{bmatrix} 1 \\ 1 \\ 0 \\ -1 \end{bmatrix} = \begin{bmatrix} (1)(1)+(-1)(1)+(0)(0)+(0)(-1) \\ (0)(1)+(-1)(1)+(2)(0)+(-1)(-1) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

B.3.1. The probability distribution is

$$\begin{aligned} P(X=2) &= P((H,H)) = \frac{1}{9} \\ P(X=4) &= P((H,T)) + P((T,H)) = \frac{4}{9} \\ P(X=6) &= P((T,T)) = \frac{4}{9} \end{aligned}$$

The cumulative distribution function is

$$F(b) = P(X \le b) = \begin{cases} 0 & \text{for } b < 2 & \text{(since } X \text{ is never less than 2)} \\ 1/9 & \text{for } 2 \le b < 4 & \text{(since } X < 4 \text{ only for (H,H))} \\ 5/9 & \text{for } 4 \le b < 6 & \text{(since } X < 6 \text{ for (H,H), (H,T) or (T,H))} \\ 1 & \text{for } 6 \le b & \text{(since } X \text{ is always less than or equal to 6)} \end{cases}$$

The expected value is

$$E[X] = \sum_{X_i=2,4,6} X_i \cdot P(X_i) = 2 \cdot \frac{1}{9} + 4 \cdot \frac{4}{9} + 6 \cdot \frac{4}{9} = \frac{14}{3}.$$