M^3_4A21: Chemical Reaction Kinetics – Michaelis-Menten theory

Biochemical reactions take place all the time in living organisms. Most of these reactions involve proteins called **enzymes**, E, which are not themselves used up in the reaction, but act as catalysts. They act selectively on certain compounds called **substrates**, S. For example, haemoglobin acts as an enzyme on the substrate oxygen, as the latter is absorbed into the blood stream. In a simple enzyme reaction, E and S combine to form an intermediate **complex**, C, which eventually decomposes to produce a product, P. This reaction process is written schematically as

$$E + S \underset{k_-}{\overset{k_1}{\rightleftarrows}} C \qquad C \overset{k_2}{\longrightarrow} E + P \ . \tag{4.1}$$

The symbol $\overset{k_2}{\longrightarrow}$ indicates that the reaction takes place in one direction only, at a rate k_2. In contrast, the first reaction is reversible. Molecules of E and S combine at a rate k_1 to form C, but simultaneously molecules of C decompose back into E and S at a rate k_-.

The **Law of Mass Action** states that the rate at which a reaction proceeds is proportional to the product of the concentrations of all the reactants. Thus, denoting by e, s, c and p the (time-dependent) concentrations of E, S, C and P, the following equations can be deduced:

$$\left.\begin{aligned} \frac{ds}{dt} &= -k_1 es + k_- c & \qquad \frac{de}{dt} &= -k_1 es + k_- c + k_2 c \\ \frac{dp}{dt} &= k_2 c & \qquad \frac{dc}{dt} &= k_1 es - k_- c - k_2 c \end{aligned}\right\} \tag{4.2}$$

The problem is completed by the initital conditions $c = p = 0$, $s = s_0$, $e = e_0$ at $t = 0$.

We note from (4.2) that $\frac{de}{dt} + \frac{dc}{dt} = 0$, so that $e(t) + c(t) = e_0$. The enzyme is conserved, possibly hidden in the complex C. Also, p only appears in one equation of (4.2), so that if we find $c(t)$ then $p(t)$ is determined. Substituting $e = e_0 - c$, we find

$$\frac{ds}{dt} = -k_1 s(e_0 - c) + k_- c \qquad \frac{dc}{dt} = k_1 s(e_0 - c) - (k_2 + k_-)c \ .$$

Non-dimensionalising by writing

$$\tau = k_1 e_0 t \ , \qquad u(\tau) = \frac{s(t)}{s_0} \ , \qquad v(\tau) = \frac{c(t)}{e_0} \ ,$$

we obtain

$$\frac{du}{d\tau} = -u + uv + \left(\frac{k_-}{k_1 s_0}\right) v \qquad \frac{e_0}{s_0}\frac{dv}{d\tau} = u - uv - \left(\frac{k_2 + k_-}{k_1 s_0}\right) v \ .$$

So introducing the three positive constants

$$\frac{e_0}{s_0} = \varepsilon \ , \qquad K = \frac{k_2 + k_-}{k_1 s_0} \ , \qquad \lambda = \frac{k_2}{k_1 s_0} \ ,$$

we obtain the simplified system, where $'$ denotes $d/d\tau$,

$$\left.\begin{aligned} u' &= -u + (u + K - \lambda)v & \qquad u(0) &= 1 \\ \varepsilon v' &= u - (u + K)v & \qquad v(0) &= 0 \end{aligned}\right\} . \tag{4.3}$$

We see from (4.3) that initially u decreases and v increases. When $v > u/(u+K)$, however, v decreases. The only steady state is $u = 0$, $v = 0$, which is a stable node. Ultimately, as is clear from the physics, the reaction continues until all the substrate, u, is used up.

Solution for $0 < \varepsilon \ll 1$: Frequently only a small amount of enzyme is present initially compared to the amount of substrate, so that $\varepsilon = e_0/s_0$ is small. In that case we can seek an asymptotic solution to (4.3) as $\varepsilon \to 0$. However, in this limit we have a *singular perturbation problem.* We cannot set $\varepsilon = 0$ in (4.3) without violating the initial conditions. We infer that for small values of τ, $v' \sim 1/\varepsilon$, while $u' = O(1)$. That is, for small times the value of v changes rapidly, until $u - (u + K)v \simeq 0$. The assumption that $v = u/(u + K)$ is known as the *Michaelis-Menten steady state hypothesis.* Essentially, the idea is that one of the two processes proceeds more rapidly than the other, so that it can be considered to have reached equilibrium before considering the other.

For $O(1)$ values of τ, the problem reduces to

$$v \simeq \frac{u}{u+K} , \qquad u' \simeq \frac{-\lambda u}{u+K} , \qquad u(0) = 1 , \tag{4.4}$$

which can be integrated to find $u(\tau)$ implicitly

$$-\lambda\tau + O(\varepsilon) = \int_1^u \left(\frac{u+K}{u}\right) du = u - 1 + K \ln u . \tag{4.5}$$

To understand what happens initially, we introduce a **fast time-scale** $T = \tau/\varepsilon$, so that $T = O(1)$ when $\tau \sim \varepsilon$. Writing $U(T) = u(\tau)$ and $V(T) = v(\tau)$, then $u'(\tau) = (1/\varepsilon)dU/dT$ and (4.3) becomes

$$\frac{dU}{dT} = -\varepsilon U + \varepsilon(U + K - \lambda)V , \quad \frac{dV}{dT} = U - (U + K)V , \quad U(0) = 1 , \quad V(0) = 0 . \tag{4.6}$$

Thus, to leading order in ε, U is a constant and so $U = 1 + O(\varepsilon)$. Then V satisfies

$$\frac{dV}{dT} = 1 - (K + 1)V + O(\varepsilon) , \qquad V(0) = 0$$

and solving this problem gives

$$V = \frac{1}{K+1}\left(1 - e^{-(K+1)T}\right) + O(\varepsilon) . \tag{4.7}$$

We have thus found the solution to (4.3) for short times (4.7) and for longer times (4.5). Combining these, we obtain an implicit solution for $u(\tau)$ and $v(\tau)$, uniformly valid as $\varepsilon \to 0$,

$$\begin{aligned} u + K \ln u &= 1 - \lambda\tau + O(\varepsilon) \\ v &= \frac{u}{u+K}\left(1 - e^{-(K+1)\tau/\varepsilon}\right) + O(\varepsilon) \end{aligned} . \tag{4.8}$$