5. Enzyme-Substrate Kinetics

(J.D. Murray, Volume 1, Chapter 6, Sections 6.1 - 6.3).

5.1 Michaelis-Menten (1913)

Consider the case of a substrate, S, combining with an enzyme, E, to produce a complex, SE, which then gives back the enzyme, together with the product, P.

Here, k_1, k_{-1}, k_2 are *rate constants*.

$$\underset{\text{substrate}}{S} + \underset{\text{enzyme}}{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{complex}}{SE}$$

$$SE \xrightarrow{k_2} \underset{\text{pdt.}}{P} + \underset{\text{enzyme}}{E}$$

Law of mass action: The rate of a reaction is proportional to the product of the (active) concentrations of the reactants.

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SE$$

substrate enzyme complex

$$SE \xrightarrow{k_2} P + E$$

pdt. enzyme

Let $s = [S]$, $e = [E]$, $c = [SE]$, $p = [P]$

$$\therefore \quad \frac{ds}{dt} = -k_{+1} se + k_{-1} c$$

$$\frac{de}{dt} = -k_1 se + k_{-1} c + k_2 c$$

$$\frac{dc}{dt} = k_1 se - k_{-1} c - k_2 c$$

$$\frac{dp}{dt} = k_2 c \quad \leftarrow \text{uncoupled.}$$

N.B. $\frac{de}{dt} + \frac{dc}{dt} = 0 \Rightarrow e(t) + c(t) = e_0 \Rightarrow e(t) = e_0 - c(t)$

Conservation law – enzyme is conserved

I.C. $s(0) = s_0$, $e(0) = e_0$, $c(0) = 0$, $p(0) = 0$

$$\Rightarrow \quad \frac{ds}{dt} = -k_1 e_0 s + (k_1 s + k_{-1}) c$$

$$\frac{dc}{dt} = k_1 e_0 s - (k_1 s + k_{-1} + k_2) c$$

Nondimensionalise: $\tau = k_1 e_0 t$, $u(\tau) = \frac{s(t)}{s_0}$, $v(\tau) = \frac{c(t)}{e_0}$, $\lambda = \frac{k_2}{k_1 s_0}$,

$$k = \frac{k_{-1} + k_2}{k_1 s_0}, \quad \varepsilon = \frac{e_0}{s_0}$$

$$\Rightarrow \quad \begin{aligned} u' &= -u + (u + k - \lambda) v \qquad & u(0) &= 1 \\ \varepsilon v' &= u - (u + k) v \qquad & v(0) &= 0 \end{aligned}$$

Coupled system of two ODEs

- Do phase planes and linear stability analysis etc?
- Exercise

$\lambda > 0,\ k > 0 \quad \left[k - \lambda = \frac{k_{-1}}{k_1 s_0} > 0\right]$

$$u' = -u + (u + k - \lambda)v \qquad u(0) = 1$$

$$\varepsilon v' = u - (u + k)v \qquad v(0) = 0$$

$\therefore$ Put $\varepsilon = 0 \quad \therefore \quad v = \dfrac{u}{u+k}$

$$\therefore \quad u' = -u + \frac{(u + k - \lambda)u}{u+k} = \frac{-\lambda u}{u+k}$$

$$\Rightarrow \quad u = u(\tau)$$

N.B. $v(0) = 0$, $u(0) = 1$

$\therefore \quad 0 = \dfrac{1}{1+k} \quad \cancel{\div}$!!

This is a singular perturbation problem.

Summary

- Derived Michaelis-Menten Model.
- This is a singular perturbation problem.

5.2 Singular Perturbation and the Quasi-Steady State Approximation (QSSA) or Pseudo-Steady State Hypothesis (PSSH)

$u' = -u + (u+k-\lambda)v \qquad u(0)=1$

$\varepsilon v' = u - (u+k)v \qquad v(0)=0$

Note, initially $u' \approx -1$ $\therefore$ u decreasing

$v' \approx \frac{1}{\varepsilon}$ $\therefore$ v increases rapidly

$\therefore$ "expand" time near $\tau=0$ ie. set $\sigma = \tau/\varepsilon$ Let $u(\tau,\varepsilon) = \hat{u}(\sigma,\varepsilon)$

$$\therefore \frac{d}{d\tau} = \frac{d}{d\sigma}\frac{1}{\varepsilon}$$

$$\frac{d\hat{u}}{d\sigma} = \epsilon\left(-\hat{u} + (\hat{u}+k-\lambda)\hat{v}\right)$$

$$\frac{d\hat{v}}{d\sigma} = \hat{u} - (\hat{u}+k)\tilde{v}$$

Note that putting $\varepsilon = 0$ in the original equations turned the 2nd order system into a 1st order system. However, in this transformed system, we can put $\varepsilon = 0$ without changing the order of the system!

$$\tilde{u} = \hat{u}_0 + \varepsilon \hat{u}_1 + \cdots \qquad \hat{u}_i = \hat{u}(\sigma)$$
$$\tilde{v} = \hat{v}_0 + \varepsilon \hat{v}_1 + \cdots \qquad \hat{v}_i = \hat{v}_i(\sigma)$$

$$\frac{d\hat{u}}{d\sigma} = \epsilon\left(-\hat{u} + (\hat{u}+k-\lambda)\hat{v}\right)$$
$$\frac{d\hat{v}}{d\sigma} = \hat{u} - (\hat{u}+k)\hat{v}$$

$$O(1): \quad \frac{d\hat{u}_0}{d\sigma} = 0$$
$$\frac{d\hat{v}}{d\sigma} = \hat{u}_0 - (\hat{u}_0+k)\tilde{v}_0$$

$$\hat{u}(0) = 1, \quad \hat{v}(0) = 0$$

$$\left.\begin{aligned} \Rightarrow \tilde{u}_0(\sigma) = 1, \quad \hat{v}_0(\sigma) &= \frac{1}{1+k}\left[1 - e^{-(1+k)\sigma}\right] \\ &= \frac{1}{1+k}\left[1 - e^{-(1+k)\tau/\varepsilon}\right] \end{aligned}\right\} \text{inner sol}^{n.}$$

Back to the original equations

- Let us assume that after the initial period of time in which v changes rapidly we can go back to the original system.

Outer sol^{n}. : $u(\tau) = u_0 + \varepsilon u_1 + \cdots$

$v(\tau) = v_0 + \varepsilon v_1 + \cdots$

$$\frac{du}{d\tau} = -u + (u + k - \lambda)v$$

$$\varepsilon \frac{dv}{d\tau} = u - (u+k)v$$

$O(1)$: $$\frac{du_0}{d\tau} = -u_0 + (u_0 + k - \lambda)v_0$$

$$0 = u_0 - (u_0 + k)v_0$$

QSSA or PSSH

$$\Rightarrow v_0 = \frac{u_0}{u_0 + k}$$

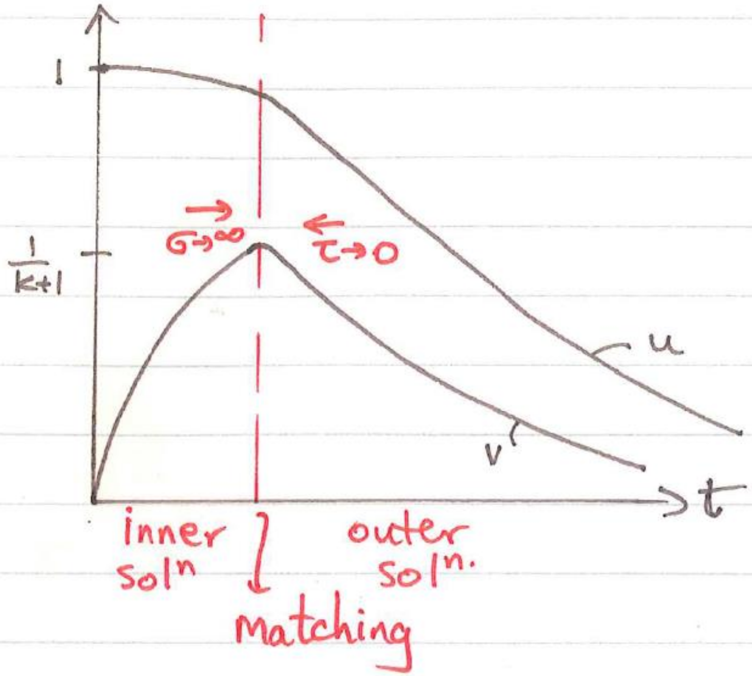
$$\Rightarrow u_0(\tau) + k\ln u_0(\tau) = A - \lambda\tau$$

$$u_0(0) = 1 \Rightarrow 1 = A$$

$$\tilde{v}_0(\sigma) = \frac{1}{1+k}\left[1 - e^{-(1+k)\sigma}\right]$$

$$= \frac{1}{1+k}\left[1 - e^{-(1+k)\tau/\varepsilon}\right]$$

$$\left.\begin{aligned} \therefore\ & u_0(\tau) + K\ln u_0(\tau) = 1 - \lambda\tau \\ & v_0(\tau) = \frac{u_0(\tau)}{K + u_0(\tau)} \end{aligned}\right\}\ \text{outer sol}^{n}.$$



Usually the inner sol^n is not seen ∴ we consider the outer sol^n which, to 1st order, is given by

$$\frac{du}{dt} = -\frac{\lambda u}{u+K}$$ Michaelis-Menten uptake.

Defn. $r(u)$ is called the velocity of reaction if

$$\frac{du}{d\tau} = -r(u).$$ $\frac{du}{d\tau}$ is called the uptake function.

- So, now we have equations for the substrate and the complex.
- We can then integrate the equation for the product to find it.
- We can use the conservation law to find the enzyme concentration.

In general biochemical reactions occur due to several enzyme catalysts $\therefore$ the rate eqns. have the form:

$$\frac{du_1}{d\tau} = f(u_1, u_2, - u_n)$$

$$\varepsilon_i \frac{du_i}{d\tau} = f_i(u_1, — u_n) \quad , i = 2, 3, \ldots, n \qquad \varepsilon_i \ll 1 \ \forall i$$

The PSSH assumes $f_i(u_1, — u_n) = 0 \quad i = 2, 3, — n$

$$\Rightarrow u_i = u_i(u_1) \quad i = 2, 3, — n$$

$$\Rightarrow \frac{du_1}{d\tau} = f(u_1, h(u_1)) \quad \text{etc.}$$