# Enzyme Kinetics: Using slow manifold and perturbation analysis

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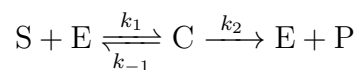## Mathematical Considerations

Question:

- Can we place the Michaelis-Menton approximation on a solid mathematical footing?

Answer:

- Of course! via:

    - slow manifold analysis

    - perturbation analysis.

Consider the chemical reaction:

$$\text{S} + \text{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{C} \xrightarrow{k_2} \text{E} + \text{P}$$

Let the concentration of each substrate be denoted with the corresponding lower case letter. We apply the Law of Mass Action and eliminate the equation for $E$ via $e + c = r$. Since the enzyme is conserved in this reaction, $r$ is constant. Also, initially $c(0) \approx 0$, so $e(0) = r$. We arrive at the following set of ODEs for S and C. Note that the equation for P is decoupled, so we leave it out.

$$\frac{ds}{dt} = -k_1 rs + k_{-1}c + k_1 sc$$

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

Introducing the following dimensionless variables and parameters

$$u = \frac{s}{s_0} \qquad v = \frac{c}{r} \qquad\qquad \tau = k_1 rt$$

$$\alpha = \frac{k_{-1}}{k_1 s_0} \qquad \kappa = \frac{k_{-1} + k_2}{k_1 s_0} = \frac{K_n}{s_o} \qquad \epsilon = \frac{r}{s_0}$$

leads to

$$\frac{du}{d\tau} = -u + uv + \alpha v \tag{0.1}$$

$$\frac{dv}{d\tau} = \frac{1}{\epsilon}(u - uv - \kappa v). \tag{0.2}$$

subject to $u(0) = 1$, $v(0) = 0$. Its reasonable to assume $0 < \epsilon \ll 1$, as we should expect less enzyme than reactant, initially.

Now, rewriting (0.2) as:

$$\epsilon \frac{dv}{d\tau} = u - uv - \kappa v \tag{0.3}$$

We can apply the quasi-steady-state assumption and set

$$\epsilon \frac{dv}{dt} = 0.$$

This leads to

$$v = \frac{u}{\kappa + u}.$$

Now we aim to work through the slow manifold analysis and perturbation analysis of the full 2-D model for $u$ and $v$.

# 1   Slow Manifold Analysis

The $\frac{1}{\epsilon}$ in (0.2) implies that v is a fast variable. This means that if $v$ is not near the set $u - uv - \kappa v = 0$ in phase space, then $v$ will be changing fast.

The curve, or set $u - uv - \kappa v = 0$ (or $v = \frac{u}{\kappa+u}$) is called the **slow manifold.**
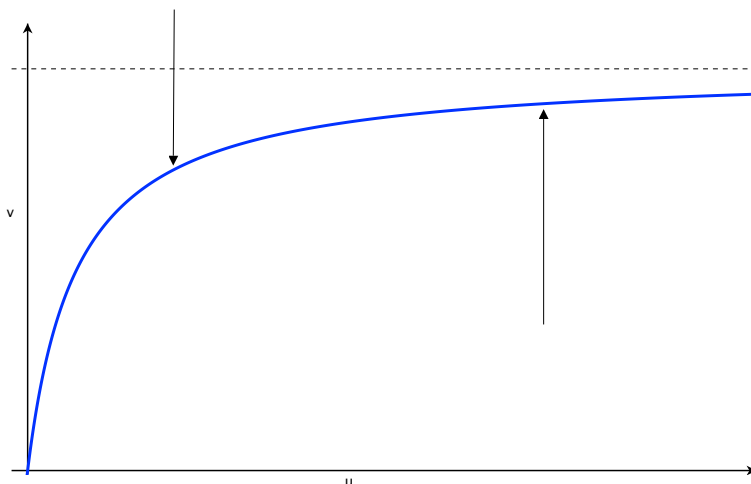
**Figure 1:** *blue curve is the slow manifold, $v = \frac{u}{\kappa+u}$. If the solution starts away from the slow manifold, then $\frac{dv}{dt}$ is large initially, and moves rapidly to the vicinity of the slow manifold.*

Question:

- What is the direction of movement near/on the slow manifold?

Well, intuitively we can argue the movement is towards the origin. Why is this? thinking about the chemical equation.

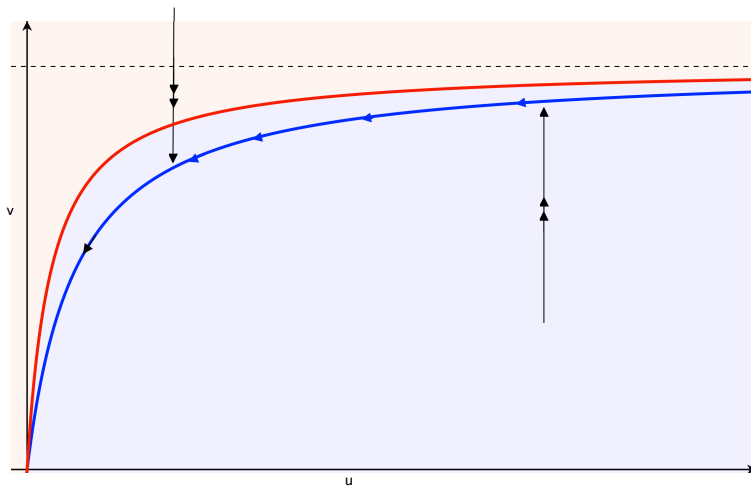Alternatively, we can consider the sign of $\frac{du}{d\tau}$.



**Figure 2:** *The red curve is $\dfrac{du}{d\tau} = 0$. The red and blue shaded region show where the derivative is positive and negative respectfully.*

The slow manifold lies below the $u$ nullcline implying $\dfrac{du}{d\tau} < 0$. Thus we can conclude that the direction near or on the slow manifold is to the left, towards the origin.

# 2 Perturbation analysis

Start again with the non-dimensional system:

$$\frac{du}{d\tau} = -u + uv + \alpha v \tag{2.1}$$

$$\epsilon \frac{dv}{d\tau} = u - uv - \kappa v. \tag{2.2}$$

$$u(0) = 1 \quad v(0) = 0 \tag{2.3}$$

This is a singular perturbation problem. Why?[1]

We can construct an outer and inner solution. These terms come from boundary layer problems and the inner solution refers to the dynamics near the boundary, or for small time in this case. The outer solution refers to the dynamics significantly far enough away from the boundary, or for larger enough time.

We start by looking for the outer solution. We apply an asymptotic expansion of the form[2]:

$$u(\tau) = u_0(\tau) + \epsilon u_1(\tau) + \epsilon^2 u_2(\tau) + \cdots \tag{2.4}$$

$$v(\tau) = v_0(\tau) + \epsilon v_1(\tau) + \epsilon^2 v_2(\tau) + \cdots \tag{2.5}$$

We substitute the expansions into the system, collect like terms and simplify. The leading order problem, for the outer solution, is given by[3];

$$\mathcal{O}(1): \quad \frac{du_0}{d\tau} = -u_0 + u_0 v_0 + \alpha v_0$$

$$0 = u_0 - u_0 v_0 - \kappa v_0.$$

$$u_0(0) = 1 \quad v_0(0) = 0.$$

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[1]Its clear that is $\epsilon$ is set to zero the order of the system is reduced to a differential algebraic system.

[2]The expansion can have functional coefficients of epsilon, but must still be of increasing orders.

[3]This is the problem we solved earlier when we made the quasi-steady-state assumption.

The second equation is algebraic and we can solve for $v_0(\tau)$:

$$v_0(\tau) = \frac{u_0(\tau)}{\kappa + u_0(\tau)}, \tag{2.6}$$

which allows us to write the first equation as:

$$\frac{du_0}{d\tau} = \frac{-(\kappa - \alpha)u_0}{\kappa + u_0}, \tag{2.7}$$

which furthermore can be solved;

$$u_0(\tau) + \kappa \ln u_0(\tau) = A - (\kappa - \alpha)\tau, \tag{2.8}$$

Where $A$ is a constant of integration, that upon imposing the initial condition $u_0(0) = 1$ gives $A = 1$.

**Remark 2.1.** A note about the initial conditions of the outer solution. The initial conditions for the full model may not always be satisfied by the outer solution. Can you say why this might be? For example, the initial condition $v(0) = 0$ can not be satisfied by $v_0(\tau)$. We will see later that this is of no issue, because technically the initial conditions only need to be satisfied by the inner solution and later matched to the outer solution.

So our outer solution is given by

$$u_0(\tau) + \kappa \ln u_0(\tau) = 1 - (\kappa - \alpha)\tau \tag{2.9}$$

$$v_0(\tau) = \frac{u_0(\tau)}{\kappa + u_0(\tau)} \tag{2.10}$$

Where we solved for $A$ a posteriori.

Question:

- What assumptions were made when constructing the outer problem?

We neglect the $\epsilon \frac{dv}{d\tau}$ term, which in essence implies that:

$$\epsilon \frac{dv}{d\tau} = \mathcal{O}(\epsilon).$$

This is true when

$$\frac{dv}{d\tau} = \mathcal{O}(1),$$

or when the reaction is well underway. But at the start of the reaction, for $\tau \ll 1$, $\frac{dv}{d\tau} \gg 1$.

Question:

- How do we handle what happens for $\tau \ll 1$?

We introduce a new timescale, one that lets us take a closer look at the neighbourhood near $\tau = 0$.

Let the new timescale be $\sigma = \delta(\epsilon)\tau$, were $\delta(\epsilon)$ is to be determined. We want $\sigma$ to be $\mathcal{O}(1)$ when $\tau = \mathcal{O}(\epsilon)^4$.

We introduce the fast, or inner, variables;

$$u(\tau; \epsilon) = U(\sigma; \epsilon) \quad v(\tau; \epsilon) = V(\sigma; \epsilon) \tag{2.11}$$

subject to initial conditions $U(0) = 1$, $V(0) = 0$. Then by chain rule,

$$\frac{dv}{d\tau} = \delta(\epsilon)\frac{dV}{d\sigma} \tag{2.12}$$

We furthermore apply the asymptotic expansion;

$$U(\sigma; \epsilon) = U_0 + \epsilon U_1 + \epsilon^2 U_2 + \cdots \tag{2.13}$$

$$V(\sigma; \epsilon) = V_0 + \epsilon V_1 + \epsilon^2 V_2 + \cdots \tag{2.14}$$

Then our system becomes;

$$\frac{dU}{d\sigma} = \frac{1}{\delta(\epsilon)}(-U + (U + \alpha)V) \tag{2.15}$$

$$\delta(\epsilon)\epsilon\frac{dV}{d\sigma} = U - (U + \kappa)V \tag{2.16}$$

We chose $\delta(\epsilon) = \frac{1}{\epsilon}$ so that we retain the $\frac{dV}{d\sigma}$ term at leading order. In other words, we force a regular perturbation.

The leading order problem for the inner solution is now given by:

$$\mathcal{O}(1): \quad \frac{dU_0}{d\sigma} = 0 \tag{2.17}$$

$$\frac{dV_0}{d\sigma} = U_0 - (U_0 + \kappa)V_0 \tag{2.18}$$

$$U_0(0) = 1 \quad V_0(0) = 0 \tag{2.19}$$

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[4]We only want this because of the way we assumed our asymptotic expansion to be.

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Solving we get:

$$U_0(\sigma) = 1 \tag{2.20}$$

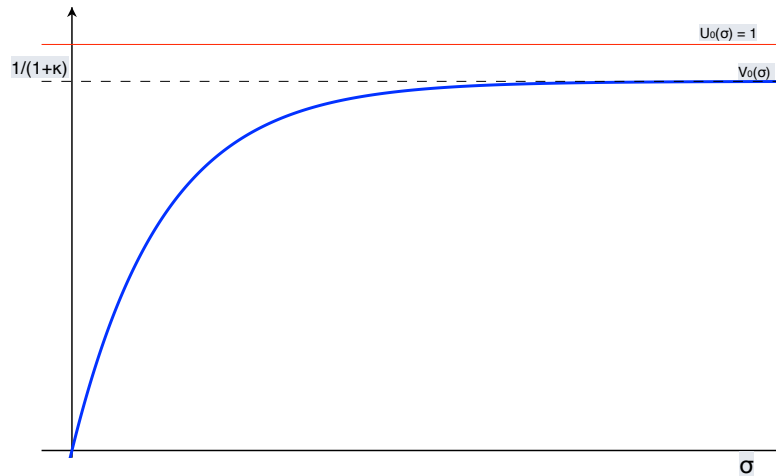$$V_0(\sigma) = \frac{1}{1+\kappa}(1 - e^{-(1+\kappa)\sigma}) \tag{2.21}$$



**Figure 3:** *The red curve describes $U_0$ as given in $(2.20)$ and the blue curve shows $V_0$ given in $(2.20)$.*

Here, the inner solution can satisfy the initial conditions, however for large values of $\sigma$ a contradiction arises. That is, the complex and substrate both should tend to zero in the reaction. Conveniently, the outer solution tends to zero.

Question:

- How to we link the inner and outer solutions?

We use the asymptotic matching condition. We essentially glue the solutions together to come up with a uniform (for all time) solution, still of the first order.
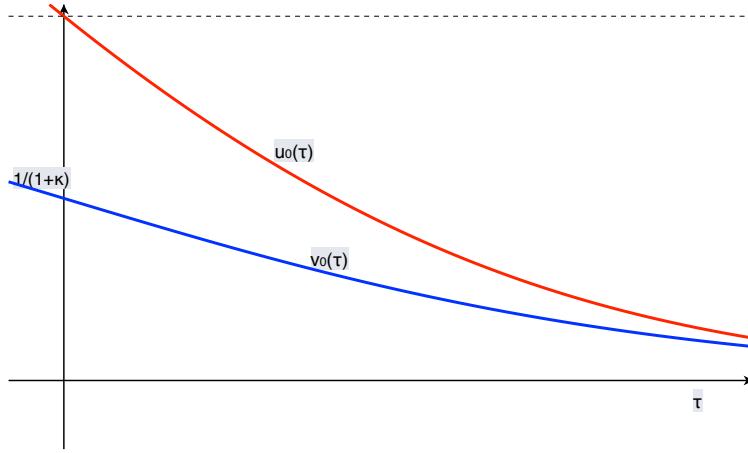
**Figure 4:** *The outer solutions. $u_0(\tau)$ in red, $v_0(\tau)$ in blue.*

We need to "match" these solutions. The matching process is as follows:

- We start on the inner solution

- Eventually, the inner solution will not make sense,

- But the outer solution will become valid.

- they must meet at some transition layer.

That is, for the matching we require;

$$\lim_{\sigma \to \inf} U_0(\sigma) = \lim_{\tau \to 0} u_0(\sigma) = u_{m0} \tag{2.22}$$

$$\lim_{\sigma \to \inf} V_0(\sigma) = \lim_{\tau \to 0} v_0(\sigma) = v_{m0} \tag{2.23}$$

In our example, this condition is satisfied naturally, and

$$\lim_{\sigma \to \inf} U_0(\sigma) = \lim_{\tau \to 0} u_0(\sigma) = u_{m0} = 1, \tag{2.24}$$

$$\lim_{\sigma \to \inf} V_0(\sigma) = \lim_{\tau \to 0} v_0(\sigma) = v_{m0} = \frac{1}{\kappa + 1}. \tag{2.25}$$

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We can finally construct an uniform first order approximation given by;

$$u_0^u(\tau) = u_0(\tau) + U_0(\tau/\epsilon) - u_{m0}$$

$$v_0^u(\tau) = v_0(\tau) + V_0(\tau/\epsilon) - v_{m0}$$

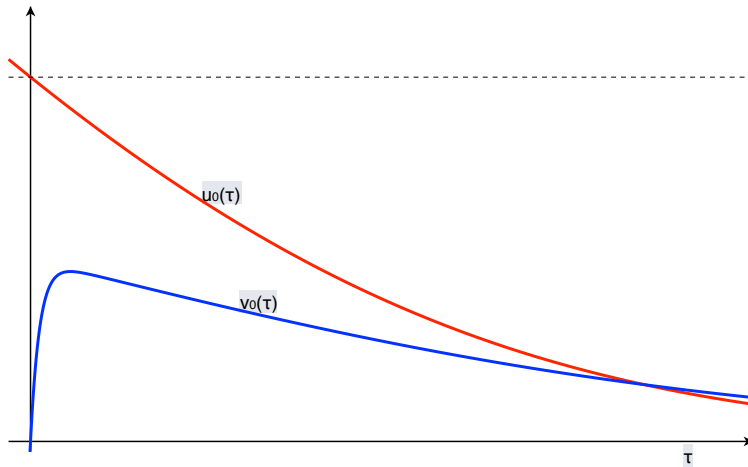Unfortunately this uniform approximation is only given implicitly.



**Figure 5:** *Uniform approximation*