Abstract. We summarize some of the work on enzyme kinetics presented by J. D. Murray in his Mathematical Biology I book. We study a basic model for enzyme-substrate reaction. Through several assumptions and via nondimensionalization, we simplify the equations. Then we use a multiple timescales method to derive asymptotic solutions to the model.

Keywords: enzyme, substrate, multiple timescales

1 Introduction

An enzyme is “a protein molecule that catalyzes a biochemical reaction...” [1]. These molecules regulate many biological processes and may act as activators or inhibitors. Enzymes act on substances called substrates to create a product. An example of an enzyme is the viral enzyme reverse transcriptase. Retroviruses use this enzyme to make a copy of DNA from their RNA [2]. Our goal here is to study a mathematical model of enzyme-substrate reactions in order to better understand them.

2 Michaelis and Menten’s Model

A basic enzyme reaction model by Michaelis and Menten can be represented with the following diagram:

\[ S + E \xrightarrow{k_1} SE \xrightarrow{k_2} P + E \xrightarrow{k_{-1}} S \]  \hspace{1cm} (1)

where \( S \) is the substrate, \( E \) is the enzyme, \( SE \) is the substrate-enzyme complex, \( P \) is the product, and \( k_1, k_{-1}, \) and \( k_2 \) are constants [3]. This diagram states that one molecule of the enzyme combines with one molecule of the substrate to form a molecule of the substrate-enzyme complex. The substrate-enzyme complex could decompose back into enzyme and substrate or may give rise to one molecule of the product and one molecule of the enzyme. Let \( s = [S], e = [E], c = [SE], \)
and \( p = [P] \), where \([\ ]\) denotes the concentration of a substance. The Law of Mass Action states that “the rate of a reaction is proportional to the product of the concentration of the reactants” [3]. We use this law to derive the following equations for the enzyme reaction described above:

\[
\begin{align*}
\frac{ds}{dt} &= -k_1es + k_{-1}c, \\
\frac{de}{dt} &= -k_1es + (k_{-1} + k_2)c, \\
\frac{dc}{dt} &= k_1es - (k_{-1} + k_2)c, \\
\frac{dp}{dt} &= k_2c,
\end{align*}
\]

(2)

where \( k_{-1}, k_1, k_2, s_0, \) and \( e_0 \) are positive constants [3].

Notice that

\[
\frac{dc}{dt} + \frac{de}{dt} = 0 \Rightarrow c(t) + e(t) = e_0.
\]

Hence, we can write

\[
e(t) = e_0 - c(t).
\]

(3)

Moreover,

\[
\frac{dp}{dt} = k_2c \Rightarrow p(t) = k_2 \int_0^t c(\tau)d\tau.
\]

Thus, we only need the equations for \( s \) and \( c \). Plugging equation (3) into the first three equations of system (2) we obtain the following reduced system

\[
\begin{align*}
\frac{ds}{dt} &= -k_1e_0s + (k_1s + k_{-1})c, \\
\frac{dc}{dt} &= k_1e_0s - (k_1s + k_{-1} + k_2)c,
\end{align*}
\]

(4)

For enzyme-substrate reactions, it is usually assumed that the initial stage of enzyme-substrate complex formation occurs very fast, and subsequently the reaction goes to a quasi-equilibrium or quasi-steady state, in which the concentration of the complex barely changes \( (\frac{dc}{dt} \approx 0) \) [3]. In this case, solving the second equation of system (4) for \( c \) gives
A Mathematical Model for Enzyme Kinetics: Multiple Timescales Analysis

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\[ c(t) = \frac{k_1 e_0 s(t)}{k_1 s(t) + K_m} \]

\[ = \frac{e_0 s(t)}{s(t) + k_1 + k_2} \]

\[ = e_0 s(t) \]

where \( K_m \) denotes the Michaeli’s constant.

Plugging the above result for \( c(t) \) into the first equation in system (4) we obtain the following:

\[
\frac{ds}{dt} = -k_1 e_0 s(t) + (k_1 s(t) + k_{-1}) s(t) + K_m
\]

\[= \frac{(k_{-1} - k_1 K_m)e_0 s(t)}{s(t) + K_m} \]

\[= \frac{-k_2 e_0 s(t)}{s(t) + K_m} \]

Now, we can solve for \( s(t) \) by using separation of variables and integrating both sides of equation (6) from 0 to \( t \) to obtain

\[ s(t) = s_0 + K_m \ln(s_0) - k_2 e_0 t. \]

Notice that the solution we obtained here does not satisfy the initial conditions in system (4); for, if \( c(0) = 0 \), then either \( s_0 = s(0) = 0 \) or \( e_0 = 0 \), by equation (5). This result would imply that either there is no substrate or no enzyme (or neither) in the beginning of the process. However, this quasi-steady state solution might be “a reasonable approximation for most of the time” [3].

3 Multiple Timescales Analysis

There are two timescales in the enzyme reaction:

1. First case (transitional stage): near \( t = 0 \), where \( \frac{ds}{dt} \approx 0 \) and \( \frac{dc}{dt} \neq 0 \), under the usual assumption that the amount of enzyme present is much smaller than that of the substrate.

2. Second case: \( t \geq \delta > 0 \), for some constant \( \delta \), where the substrate’s concentration changes significantly (\( \frac{ds}{dt} \neq 0 \)) and the substrate-enzyme complex’s concentration is almost at equilibrium (\( \frac{dc}{dt} \approx 0 \)). The quasi-steady state approximation, equations (5) and (7), applies in this case [3].
3.1 Nondimensionalization

As done by Murray in [3], we use the substitutions
\[\tau = k_1 e_0 t, \quad u(\tau) = \frac{s(t)}{s_0}, \quad v(\tau) = \frac{c(t)}{c_0},\]
\[\lambda = \frac{k_2}{k_1 s_0}, \quad K = \frac{k_1 + k_2}{k_1 s_0} = \frac{K_m}{s_0}, \quad \epsilon = \frac{e_0}{s_0}\]
(8)
to rewrite system (4) in the form
\[\frac{du}{d\tau} = -u + (u + K - \lambda)v, \quad \epsilon \frac{dv}{d\tau} = u - (u + K)v\]
(9)
\[u(0) = 1, \quad v(0) = 0.\]

We will focus our discussion on this non-dimensional system. The equations in system (9) are not easy to solve analytically. In our analysis, we must keep in mind that \(\epsilon\) is a very small, positive parameter. Notice that \(\epsilon\) is multiplied by \(dv/d\tau\). As we saw before, we cannot expect to find a uniformly valid approximate solution of the system by simply setting \(\epsilon = 0\), because that would reduce the order of the equation. This is, in fact, what we did before when we derived the approximate solution given by equations (5) and (7), which do not satisfy the initial conditions in system (4). This situation is characteristic of a singular perturbation problem.

3.2 Outer and Inner Solutions

To proceed with our analysis, let us suppose that
\[u(\tau; \epsilon) = \sum_{n=0}^{\infty} \epsilon^n u_n(\tau), \quad v(\tau; \epsilon) = \sum_{n=0}^{\infty} \epsilon^n v_n(\tau).\]
(10)
We are interested in the case where \(0 < \epsilon = e_0/s_0 << 1 (\epsilon \to 0)\), since this is the usual assumption \(e_0 << s_0\), i.e., that the initial concentration of enzyme is much smaller than the initial concentration of the substrate. Substituting equations (10) into system (9) gives a sequence of differential equations for \(u_n(\tau)\) and \(v_n(\tau)\).

The \(O(1)\) equations are
\[\frac{du_0}{d\tau} = -u_0 + (u_0 + K - \lambda)v_0, \quad 0 = u_0 - (u_0 + K)v_0,\]
\[u_0(0) = 1, \quad v_0(0) = 0.\]
(11)
Solving the second equation in system (11) for \(v_0\) we get
\[v_0(\tau) = \frac{u_0(\tau)}{u_0(\tau) + K}\]
(12)
and then
\[\frac{du_0}{d\tau} = -u_0 + (u_0 + K - \lambda)\frac{u_0}{u_0 + K} = -\lambda \frac{u_0}{u_0 + K},\]
which has the same form as equation (6) and, thus, has solution

\[ u_0(\tau) + K\ln(u_0(\tau)) = u_0(0) + K\ln(u_0(0)) - \lambda\tau = 1 - \lambda\tau. \]  (13)

As before, we see that \( v_0(0) = \frac{1}{1+K} \neq 0 \), so this solution does not work for \( \tau = 0 \). In other words, the approximate solution found here is not uniformly valid for all \( \tau \geq 0 \). In our case, we say that there is a boundary layer in the immediate neighborhood of \( \tau = 0 \).

In deriving system (11) we neglected the term \( \epsilon\frac{dv}{d\tau} \). We must then include this term in our analysis, since without it the initial condition on \( v_0(\tau) \) cannot be satisfied. Put

\[ \sigma = \frac{\tau}{\epsilon}, \quad u(\tau; \epsilon) = U(\sigma; \epsilon), \quad v(\tau; \epsilon) = V(\sigma; \epsilon). \]  (14)

This transformation to a new timescale allows us to “magnify” the time neighborhood around \( \tau = 0 \), since, as \( \epsilon \) approaches 0, for any fixed value of \( \tau \) with \( 0 < \tau << 1 \), \( \sigma \) becomes much larger than 1. With the new transformation (14), system (9) becomes

\[ \frac{dU}{d\sigma} = -\epsilon U + \epsilon(U + K - \lambda)V, \quad \frac{dV}{d\sigma} = U - (U + K)V, \]

\[ U(0) = 1, \quad V(0) = 0. \]  (15)

Write

\[ U(\sigma; \epsilon) = \sum_{n=0}^{\infty} \epsilon^n U_n(\sigma), \quad V(\sigma; \epsilon) = \sum_{n=0}^{\infty} \epsilon^n V_n(\sigma). \]  (16)

Plugging equations (16) into system (15) and equating powers of \( \epsilon \) gives, for \( n = 0 \),

\[ \frac{dU_0}{d\sigma} = 0, \quad \frac{dV_0}{d\sigma} = U_0 - (U_0 + K)V_0, \]

\[ U_0(0) = 1, \quad V_0(0) = 0. \]  (17)

System (17) has solution

\[ U_0(\sigma) = 1, \quad V_0(\sigma) = \frac{1}{1 + K} \left[ 1 - \exp\left[ -(1 + K)\sigma \right] \right]. \]  (18)

This solution works for \( \sigma = 0 \) and, hence, \( \tau = 0 \), but cannot be expected to work for all \( \tau \geq 0 \). If it did, that would imply that \( u(\tau) = \frac{s(t)}{t_0} \approx 1 \) for all \( t \geq 0 \) (since the contribution from the higher order terms in the expansion for \( u(\tau) \) for small \( \epsilon \) are negligible [3]). In other words, the concentration of substrate would remain virtually constant throughout the enzyme reaction, which contradicts our assumption that the substrate’s concentration changes significantly after the transitional stage. We call (18) the inner solution for \( u \) and \( v \), which is valid for \( 0 \leq \tau << 1 \). The solution given by equations (12) and (13) is called the outer solution, which is valid for values of \( \tau \) not close to 0 [3].

We can continue this way, by using equations (9), (10), (15), and (16) to derive the \( O(\epsilon) \), \( O(\epsilon^2) \), ... equations for the outer and inner solutions. However, as stated above, since we are interested here in the case when \( 0 < \epsilon << 1 \), the \( O(1) \) equations will suffice.

The matching principle of inner and outer solutions requires that, to all orders of \( \epsilon \),

\[ \lim_{\sigma \to \infty} [U(\sigma; \epsilon), V(\sigma; \epsilon)] = \lim_{\tau \to 0} [u(\tau; \epsilon), v(\tau; \epsilon)] \]  [3].  (19)
From equations (13) and (18) we see that
\[
\lim_{\sigma \to \infty} U(\sigma) = 1 = \lim_{\tau \to 0} u_0(\tau)
\]
and
\[
\lim_{\sigma \to \infty} V(\sigma) = \lim_{\tau \to 0} v_0(\tau) = \frac{1}{1 + K}.
\]
Hence, our solution satisfies the matching principle of inner and outer solutions for the equations of $O(1)$. Thus, we obtain a uniformly valid asymptotic solution, to $O(1)$, of system (9) for $0 < \epsilon << 1$ [3].

The overall asymptotic solution, which is valid for all $\tau \geq 0$ ($t \geq 0$) can be summarized as follows:

\[
\begin{aligned}
&\begin{cases}
    u(\tau;\epsilon) = u_0(\tau) + O(\epsilon), \\
    v(\tau;\epsilon) = v_0(\tau) + O(\epsilon),
\end{cases} & \epsilon = 0.1, 0.001, s_0 = 10, c_0 = 1, k_{-1} = 1, k_1 = 2, \text{ and } k_2 = 3.
\end{aligned}
\]

Notice that the asymptotic solutions for $v$ tend to be closer to its numerical solutions in comparison to the asymptotic and numerical solutions for $u$. Even when $\epsilon = 0.1$, the asymptotic inner and outer solutions are very close to the numerical solutions for $v$. For both functions, though, as $\epsilon$ approaches zero, the asymptotic outer solutions and the numerical solutions become almost identical.
5 Summary and Conclusions

We studied a system of differential equations for enzyme-substrate reactions. We used nondimensionalizations and asymptotic expansions to find approximate solutions to the system. The approximate solutions were derived using a singular perturbation method utilizing two different timescales. The inner solution is valid in the immediate neighborhood of the initial time $\tau = 0$, corresponding to the initial stage of the enzyme reaction, when there is little change in the substrate’s concentration. The outer solution is valid for larger values of $\tau > 0$ (not in the immediate neighborhood of $\tau = 0$), when the substrate’s concentration changes significantly.
In addition to the asymptotic solutions, we also computed numerical solutions for our enzyme reaction model equations. We compared both types of solutions graphically and observed that the solutions get closer to each other as $\epsilon \to 0$. This property of the solutions suggests that the perturbation method of multiple timescales gives a very accurate approximation to the solution of our model when the general assumption that the initial concentration of enzyme is much smaller than the initial concentration of substrate.
References

