

Dynamical Analysis of Michaelis-Menten Enzyme Reactions

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Abstract: In this paper Michaelis-Menten type enzyme reactions are studied. With an output of this kind one could consider the following set of equations $\frac{dx}{d\tau} = a - bx - x^p y^q$, $\frac{dy}{d\tau} = x^p y^q - \frac{cy}{y+1}$. Taking some particular values of the parameters a, b, p, q a detailed analysis of the system is taken up. The system is analysed by studying the associated differential equations, phase plane analysis and bifurcation analysis.

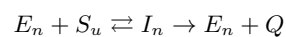
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1. Introduction: Michaelis-Menten Enzyme Reaction

Enzymes are biological catalysts that alter the rates of reactions in cells without being, changed themselves during the course of a reaction. A biochemical reaction almost invariably has an output which is not necessarily linear. Such nonlinear phenomena involving enzymes have been explained by several people, amongst them Michaelis and Menten are worth mentioning. Following the law of mass action [17], there are many mathematical models with a Michaelis-Menten type output. Michaelis and Menten in [1, 2] studied a simple enzyme reaction. If an enzyme E_n combines with another reactant S_u and gives rise to an intermediate substance I_n and this intermediate splits into two substances one of which is the original enzyme E_n again and some other substance Q . The reaction can be written as



Michaelis Menten Equation is

$$V = \frac{V_{\max} [S]}{K_m + [S]} \quad (1)$$

where V is the velocity of the reaction, $V_{\max}$ is the maximum velocity of the reaction, $[S]$ is the concentration of the substrate S , K_m is the Michaelis constant.

Michaelis Menten Plot:

Some enzyme reactions like Michaelis-Menten reaction are studied by L.S. Dai in [3–5]. In [6–8] D. Erle and others and C. Escher study some enzyme catalyzed reactions where they show the existence of oscillations, limit cycles and the conditions

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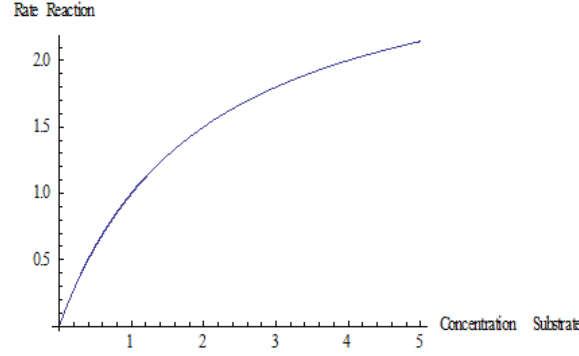
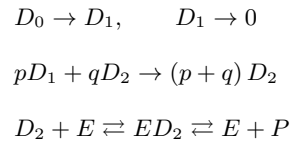


Figure 1. Plot of equation (1) taking $V_{max} = 3$ and $K_m = 2$

required for the associated biochemical reactions. The mathematical model corresponding to this simple reaction can be derived, considering a general enzyme reaction, as follows [16]:



The differential equation corresponding to this enzyme reaction, can be written as

$$\begin{aligned} \frac{d}{dt} [D_1] &= [D_0] - k_1 [D_1] - k_2 [D_1]^p [D_2]^q \\ \frac{d}{dt} [D_2] &= k_2 [D_1]^p [D_2]^q - \frac{V[D_2]}{k + [D_2]} \end{aligned} \quad (2)$$

where V represents the velocity of the enzyme reaction, k is some constant. After adjusting the constants the equations become

$$\begin{aligned} \frac{dx}{d\tau} &= a - bx - x^p y^q \\ \frac{dy}{d\tau} &= x^p y^q - \frac{cy}{y+1} \end{aligned} \quad (3)$$

where $a = [D_0] k_2^{-1} k^{-(p+q)}$, $b = k_1 k_2^{-1} k^{-(p+q)}$ and $c = V k_2^{-1} k^{-(p+q)}$. The second term in the equation (3) namely $\frac{cy}{y+1}$, when considered from a prey-predator point of view, represents the type II functional response of Holling.

2. A Generalised Enzyme Equation with a Michaelis-Menten Functional Response Term

C.S.Holling studied the factors involved in the utilization of resources by predators. He described the changes in the feeding rate of organisms as “the functional response term”. He showed that there were three categories of functional response [9].

Type 1. Refers to animals which consume food proportional to the rate of their encounter with food items.

Type 2. Where the organisms take some time to eat and to capture their prey.

Type 3. In this category the organism will not consume the prey if it is below a certain threshold density.

There is a remarkable parallel between enzyme reactions and the predator-prey Holling functional response. The Michaelis-Menten enzyme reaction follows a type 2 functional response. Keeping this type of functional response in mind the following

model is proposed and analysed.

$$\begin{aligned}\frac{dx}{dt} &= a - bx - x^p y^q \\ \frac{dy}{dt} &= x^p y^q - \frac{cxy}{y+1}\end{aligned}\quad (4)$$

For the purpose of understanding and analysis, $b = 0$, $p = 2$, $q = 1$ are taken. Equations (4) reduce to

$$\begin{aligned}\frac{dx}{dt} &= a - x^2 y \\ \frac{dy}{dt} &= x^2 y - \frac{cxy}{y+1}\end{aligned}\quad (5)$$

The equilibrium points of equations (5) are

$$\left(\frac{1}{2} \left[c - \sqrt{c^2 - 4a} \right], \frac{-2a + c^2 + c\sqrt{c^2 - 4a}}{2a} \right)$$

and

$$\left(\frac{1}{2} \left[c + \sqrt{c^2 - 4a} \right], \frac{-2a + c^2 - c\sqrt{c^2 - 4a}}{2a} \right)$$

Linearising the system (5) about its equilibrium point, the Jacobean matrix is

$$M = \begin{bmatrix} -2x_0 y_0 & -x_0^2 \\ 2x_0 y_0 - \frac{c y_0}{1+y_0} & x_0^2 + \frac{c x_0 y_0}{(1+y_0)^2} - \frac{c x_0}{1+y_0} \end{bmatrix}$$

where the elements in the linearised matrix are to be treated as the functions of the parameter c . The characteristic equation of this matrix has the form $\lambda^2 - S\lambda + D = 0$ where

$$S(c) = \text{the trace of } M = -2x_0 y_0 + x_0^2 + \frac{c x_0 y_0}{(1+y_0)^2} - \frac{c x_0}{1+y_0}$$

and

$$D = \text{determinant of } M = -\frac{2c x_0^2 y_0^2}{(1+y_0)^2} + \frac{c x_0^2 y_0}{1+y_0}$$

The two eigenvalues of this matrix λ_1 and λ_2 are function of c

$$\lambda_1, \lambda_2 = \frac{1}{2} \left[S(c) \pm \sqrt{S^2(c) - 4D(c)} \right]$$

A Hopf bifurcation occurs when the real part of the eigenvalues is equal to zero and the imaginary part is nonzero. Solving for the parameter c after setting the trace to zero

$$(1). -2x_0 y_0 + x_0^2 + \frac{c x_0 y_0}{(1+y_0)^2} - \frac{c x_0}{1+y_0} = 0 \Rightarrow c = (x_0 - 2y_0)(1+y_0)^2$$

$$(2). \frac{d}{dc}(\text{Trace}) = \frac{x_0 y_0}{(1+y_0)^2} - \frac{c x_0}{1+y_0} \neq 0.$$

(1) is the non-hyperbolicity condition and (2) is the transversality condition. Thus showing the existence of a Hopf bifurcation for the parameter c . A simulation of the limit cycle is shown in Figure 2.



Figure 2. A limit cycle of equations (5) for the values of the parameter $a = 1.8$; $c = 1$; $p = 2$; $q = 1$.

3. Qualitative Analysis of Trimolecular Reaction

From the chemical reactions the dynamical equations corresponding to Belousov's reaction [9, 10] can be represented as

$$\begin{aligned}\frac{d[B]}{dt} &= [A] - K_1 [B] - K_2 [B]^p [C]^q \\ \frac{d[C]}{dt} &= K_2 [B]^p [C]^q - K_3 [C]\end{aligned}$$

where the square brackets denote the concentration of the substance. K_1, K_2, K_3 are the reaction rates, p and q represent the number of molecules of the chemical B and C . After readjusting the constants and relabeling the concentrations, this equation can be written as

$$\begin{aligned}\frac{dx}{dt} &= 1 - ax - x^p y^q \\ \frac{dy}{dt} &= b(x^p y^q - y)\end{aligned}\tag{6}$$

where $x, y \geq 0$, integers $p, q \geq 0$ and parameters $a \geq 0, b \geq 0$. A particular case of trimolecular equations i.e. $p + q = 3$ is discussed. Let $p = 1, q = 2$. The following result given in [8] is used.

Theorem 3.1 ([8]). Suppose that $p, q \in N, q > 1$,

$$\begin{aligned}a &> 0, b > \frac{aq}{q-1} \\ a &< a_0 = \left(\frac{p^p (q-1)^{q-1}}{(p+q-1)^{p+q-1}} \right)^{\frac{1}{p}} \text{ and} \\ \sigma &= \left(\frac{p}{a(p-1) + b(q-1)} \right)^p \left(\frac{b(q-1) - a}{a(p-1) + b(q-1)} \right)^{q-1} = 1\end{aligned}$$

(i). If $b \neq \frac{a(p+2q-1)}{q-1}$ then at most one limit cycle arises from a Hopf bifurcation. The cycle is stable when $b > \frac{a(p+2q-1)}{q-1}$ and unstable when

$$\frac{aq}{q-1} < b < \frac{a(p+2q-1)}{q-1}$$

(ii). If $b = \frac{a(p+2q-1)}{q-1}$ then at most two limits cycles arises from Hopf bifurcation.

To satisfy the conditions of this theorem, the values of the parameters are taken as $p = 1, q = 2, b > 2a$

$$a > a_0 = \left(\frac{1^1 \cdot 1^1}{2^2} \right) = \frac{1}{4}$$

Let us take $\frac{1}{5} = 0.2$, $b > \frac{2}{5} = 0.4$

$$\sigma = \left(\frac{1}{b}\right) \left(\frac{b-a}{b}\right) = 1$$

Therefore $b^2 - b + a = 0 \Rightarrow b = 0.7236$ or 0.2764 . Take $b = 0.7236$ ($b > 2a$). Thus $p = 1$, $q = 2$, $a = 0.2$, $b = 0.7236$. The plot corresponding to these values is shown in Figure 3.

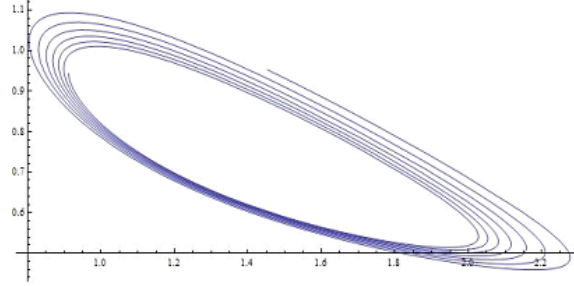


Figure 3. Unstable limit cycle in system (6) with $a = 0.2$, $b = 0.7236$.

The system is

$$\begin{aligned} \frac{dx}{dt} &= \dot{x} = 1 - 0.2x - xy^2, \\ \frac{dy}{dt} &= \dot{y} = 0.7236(xy^2 - y). \end{aligned}$$

For Case (ii) of the theorem, if $a = 0.16$ then

$$b = \frac{a(p + 2q - 1)}{q - 1} = \frac{(0.16)(1 + 4 - 1)}{1} = 0.64$$

Therefore take $p = 1$, $q = 2$, $a = 0.16$, $b = 0.64$. The system (6) is

$$\begin{aligned} \frac{dx}{dt} &= \dot{x} = 1 - 0.16x - xy^2 \\ \frac{dy}{dt} &= \dot{y} = 0.64(xy^2 - y) \end{aligned} \tag{7}$$

A limit cycle arises which can be seen in Figure (4).

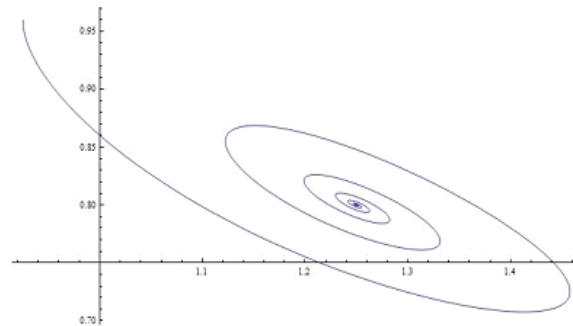


Figure 4. Phase plane of system (6) with parameter values $p = 1$, $q = 2$, $a = 0.16$, $b = 0.64$.

The system is $\dot{x} = 1 - 0.16x - xy^2$, $\dot{y} = 0.649(xy^2 - y)$. Further, let $b = 0.8$,

$$\sigma = \left(\frac{1}{b}\right) \left(\frac{b-a}{b}\right) = 1$$

$$\therefore b^2 - b + a = 0$$

$$a = b - b^2 = 0.8 - 0.64 = 0.16$$

Therefore take $p = 1$, $q = 2$, $a = 0.16$, $b = 0.8$. The system (6) is

$$\dot{x} = 1 - 0.16x - xy^2$$

$$\dot{y} = 0.8(xy^2 - y)$$

A stable limit cycle arises since $\left(b > \frac{a(p+2q-1)}{q-1}\right)$ which can be seen in Figure 5.

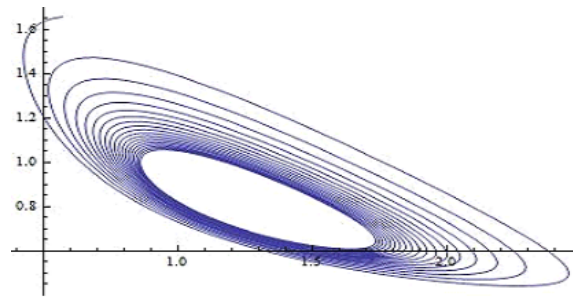


Figure 5. Stable limit cycle in system (6) with parameter values $p = 1$, $q = 2$, $a = 0.16$, $b = 0.8$.

The system is $\dot{x} = 1 - 0.16x - x^2y$, $\dot{y} = 0.8(xy^2 - y)$.

4. Conclusions

- Starting with a simple enzyme reaction a dynamical system is derived.
- The similarity between Michaelis-Menten enzyme reaction and the Holling Type 2 predation term is shown.
- A dynamical analysis of the generalized enzyme reaction is performed.
- The criteria for the existence of limit cycles and Hopf Bifurcation is studied.
- Using different values of the parameters the phase portraits are plotted.

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