J Math Chem (2014) 52:222–230
DOI 10.1007/s10910-013-0257-1

ORIGINAL PAPER

A transformed time-dependent Michaelis–Menten enzymatic reaction model and its asymptotic stability

Kristina Mallory · Robert A. Van Gorder

Received: 23 June 2013 / Accepted: 20 August 2013 / Published online: 31 August 2013

Abstract The dynamic form of the Michaelis–Menten enzymatic reaction equations provide a time-dependent model in which a substrate S reacts with an enzyme E to form a complex C which in turn is converted into a product P and the enzyme E. In the present paper, we show that this system of four nonlinear equations can be reduced to a single nonlinear differential equation, which is simpler to solve numerically than the system of four equations. Applying the Lyapunov stability theory, we prove that the non-zero equilibrium for this equation is globally asymptotically stable, and hence that the non-zero steady-state solution for the full Michaelis–Menten enzymatic reaction model is globally asymptotically stable for all values of the model parameters. As such, the steady-state solutions considered in the literature are stable. We finally discuss properties of the numerical solutions to the dynamic Michaelis–Menten enzymatic reaction model, and show that at small and large time scales the solutions may be approximated analytically.

Keywords Dynamic Michaelis–Menten model · Nonlinear dynamics · Stability · Enzyme reactions

1 Introduction

The Michaelis–Menten model [1] is extensively used in the theoretical study of enzyme kinetic reactions. In this model, a substrate S reacts with an enzyme E to form a complex C which in turn is converted into a product P and the enzyme E; the schematic is $E + S \rightleftharpoons C \rightarrow E + P$. From the law of mass action, the dynamic form of the Michaelis–Menten enzymatic reaction model [1] reads

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K. Mallory · R. A. Van Gorder (✉)
Department of Mathematics, University of Central Florida, Orlando, FL 32816-1364, USA
e-mail: rav@knights.ucf.edu

$$\begin{aligned}
\frac{dS}{dt} &= -k_1 ES + k_{-1}C, \\
\frac{dE}{dt} &= -k_1 ES + (k_{-1} + k_2)C, \\
\frac{dC}{dt} &= k_1 ES - (k_{-1} + k_2)C, \\
\frac{dP}{dt} &= k_2 C, \qquad (1.1)
\end{aligned}$$

where $S(t)$ is the concentration of a substrate, $E(t)$ is the concentration of an enzyme, $C(t)$ is the concentration of the resulting complex, and $P(t)$ is the concentration of the resulting product. Here, $k_1 > 0$ is the rate of reaction governing the production of the complex from the substrate and the enzyme, $k_{-1} > 0$ is the rate of reaction governing decomposition of the complex to the substrate and enzyme, and $k_2 > 0$ is the rate of reaction governing the breakdown of the complex into the product and the enzyme. It is reasonable to consider initial conditions of the form $S(0) = S_0$, $E(0) = E_0$, $C(0) = 0$ and $P(0) = 0$. Here we may normalize the parameters (the k's) and the time variable so that the concentrations themselves are normalized. In this way, the system (1.1) is non-dimensional.

A common method that is often used to deal with the Michaelis–Menten nonlinear system is to consider the quasi-steady state assumption [2–5]. Golicnik [6] presented some solutions to a Michaelis–Menten model in terms of the Lambert W(x) function, and also considered the time-dependent problem [7]. Abu-Reesh [8] derived analytical equations for the optimal design of a number of membrane reactors in series performing enzyme catalyzed reactions described by Michaelis–Menten kinetics with competitive product inhibition. Most of the solutions in the literature for (1.1) are either static or quasi-static, or exist for various reductions of (1.1). Previously, the homotopy perturbation method has been applied to the study of enzyme reaction models [9,10]. In this method, perturbation is done with respect to an auxiliary parameter. However, such solutions may or may not converge (see, for instance [11,12], for examples of when the homotopy perturbation method does not converge). Some limitations were discussed in [10], and it was shown that the homotopy perturbation method solutions are good for some parameter regimes, and poor for others. On the other hand, the homotopy analysis method often can be made to converge, since it includes a type of convergence control parameter. Recently, Motsa, Shateyi, and Khan [13] considered this approach, and obtained homotopy analysis solutions which converge for the parameter regimes considered. Either way, these methods are often cumbersome, despite their usefulness when other approaches fail, and can be treated as a sort of mixed analytical-numerical routine. It is clearly desirable to have an efficient way of obtaining solutions to such nonlinear reaction models, particularly for more complicated models in which the dimension of the system is increased.

Often times in modeling physical problems, one can exploit certain symmetries or other properties of the problem, in order to reduce the dimension of the problem being solved. In the present paper, we start with the four-dimensional mathematical model (1.1). Through several manipulations, we are able to obtain a single equation which holds all of the relevant information needed to recover the solution to (1.1). We should remark that this particular form of the Michaelis–Menten enzymatic reaction model (1.1) has not previously been considered in the literature. We use this reduced form of the model to prove that the non-zero steady-state of the Michaelis–Menten model is globally asymptotically stable. One may use this reduction to obtain numerical solutions to the Michaelis–Menten model.

2 Reduction of the system (1.1) into a single equation

We shall begin by reducing the four-dimensional system (1.1) into a single equation, as this will aid in the solution process. Combining the E and C differential equations, we see that

$$\frac{d}{dt}(E+C)=0 \qquad \text{so that} \qquad C(t)=E_0-E(t). \tag{2.1}$$

Subtracting the E equation from the S equation gives

$$\frac{d}{dt}(S-E)=-k_2C=-k_2(E_0-E(t)), \tag{2.2}$$

and integrating, we find that

$$S(t)=S_0+E(t)-E_0+k_2\int_0^t(E(\tau)-E_0)d\tau. \tag{2.3}$$

Finally, using (2.1) in the P differential equation, we obtain

$$P(t)=k_2\int_0^t(E_0-E(\tau))d\tau. \tag{2.4}$$

With this, we have the functions $C(t)$, $S(t)$, and $P(t)$ uniquely determined in terms of $E(t)$. So, it will suffice to solve for $E(t)$. Placing (2.1) and (2.3) into the original E differential equation, we have

$$\frac{dE}{dt}=(k_1E+k_{-1}+k_2)(E_0-E(t))-k_1S_0E(t)+k_1k_2E(t)\int_0^t(E_0-E(\tau))d\tau. \tag{2.5}$$

If we manipulate (2.5) through differentiation to remove the integration (thereby removing non-locality from the equation) and define a new function F and time variable T by the transformations

$$E(t)=\frac{k_2}{k_1}F(T) \qquad \text{where} \qquad T=k_2t, \tag{2.6}$$

we obtain the nonlinear differential equation

$$FF'' + F^2F' + \mu_1 F' - F'^2 - \mu_2 F^2 + F^3 = 0, \tag{2.7}$$

where prime denotes differentiation with respect to T, and the constants μ_1 and μ_2 are given by

$$\mu_1 = \frac{k_1^2 E_0}{k_2^2} K_m > 0 \quad \text{and} \quad \mu_2 = \frac{k_1 E_0}{k_2} > 0, \tag{2.8}$$

where μ_1 represents a scaling of the Michaelis constant [14], $K_m = \frac{k_{-1}+k_2}{k_1}$. Note also that

$$\mu_1 = \frac{\mu_2^2}{E_0} K_m. \tag{2.9}$$

The initial condition

$$F(0) = \frac{k_1 E_0}{k_2} = \mu_2 > 0 \tag{2.10}$$

is clear from the transformation (2.6), while from (2.5) it follows that

$$\frac{dE}{dt}(0) = -k_1 S_0 E_0 \quad \text{and thus} \quad F'(0) = -\frac{k_1^2 S_0 E_0}{k_2^2} = -\frac{S_0}{E_0}\mu_2^2 < 0. \tag{2.11}$$

In order to condense (2.7), we shall make another transformation. Let $f(T) = \ln F(T)$ and note that $f(T)$ is well-defined, since $E(t) > 0$ and hence $F(T) > 0$. From Eq. (2.7), we obtain

$$f'' + \left(e^f + \mu_1 e^{-f}\right) f' + e^f = \mu_2, \tag{2.12}$$

where, again, prime denotes differentiation with respect to T. Initial conditions are then found to be given by $f(0) = \ln \mu_2$ and $f'(0) = \frac{F'(0)}{F(0)} = -\frac{S_0}{E_0}\mu_2$. We shall now be concerned with the solution to this initial value problem. Once such a solution is found, it is clear that we may invert the relevant transformations to obtain

$$E(t) = \frac{k_2}{k_1} e^{f(T)} = \frac{k_2}{k_1} \exp(f(k_2 t)). \tag{2.13}$$

The other quantities of interest may then be recovered by the formulas

$$C(t) = E_0 - \frac{k_2}{k_1} \exp(f(k_2 t)), \tag{2.14}$$

$$S(t) = S_0 + \frac{k_2}{k_1}\exp(f(k_2 t)) - E_0 + \int\limits_0^{k_2 t}\left(\frac{k_2}{k_1}\exp(f(\tau)) - E_0\right)d\tau, \tag{2.15}$$

$$P(t) = \int\limits_0^{k_2 t}\left(E_0 - \frac{k_2}{k_1}\exp(f(\tau))\right)d\tau. \tag{2.16}$$

Thus, knowledge of the solution f to the second order differential equation (2.12) gives us complete knowledge of the solution to the four-dimensional Michaelis–Menten system (1.1).

3 Asymptotic stability of the solutions

We may apply Lyapunov stability theory [15] in order to demonstrate that the non-zero equilibrium for the Michaelis–Menten system (1.1) is globally asymptotically stable. Let us first write (2.12) in system form. Defining $y_1 = f$ and $y_2 = f'$, we see that

$$\begin{aligned} y_1' &= y_2, \\ y_2' &= \mu_2 - \exp(y_1) - (\exp(y_1) + \mu_1\exp(-y_1))y_2. \end{aligned} \tag{3.1}$$

Now, consider the candidate Lyapunov function

$$V(y_1, y_2) = \frac{1}{2}y_2^2 + G(y_1), \tag{3.2}$$

where $G(y_1) = \mu_2(\ln\mu_2 - 1) - \mu_2 y_1 + \exp(y_1)$. We claim that V is a global Lyapunov function, and that the equilibrium $(y_1, y_2) = (\ln\mu_2, 0)$ is globally asymptotically stable. We must verify three things: (i) $\frac{d}{dt}V < 0$ for all $(y_1, y_2) \neq (\ln\mu_2, 0)$, (ii) $V = 0$ for $(y_1, y_2) = (\ln\mu_2, 0)$ while $V > 0$ for $(y_1, y_2) \neq (\ln\mu_2, 0)$, and (iii) V radially unbounded.

First, observe that

$$\begin{aligned} \frac{dV}{dt} &= \frac{\partial V}{\partial y_1}y_1' + \frac{\partial V}{\partial y_2}y_2' \\ &= -(\mu_2 - \exp(y_1))y_2 + y_2(\mu_2 - \exp(y_1)) - y_2^2(\exp(y_1) + \mu_1\exp(-y_1)) \\ &= -y_2^2(\exp(y_1) + \mu_1\exp(-y_1)) \\ &\leq -2\sqrt{\mu_1}y_2^2, \end{aligned} \tag{3.3}$$

hence $\frac{d}{dt}V < 0$ for all $(y_1, y_2) \neq (\ln\mu_2, 0)$. Second, by verification we have that $V(\ln\mu_2, 0) = 0$. On the other hand, note that $G'(y_1) < 0$ for $y_1 < \ln\mu_2$ yet $G'(y_1) > 0$ for $y_1 > \ln\mu_2$, so $G(y_1) > 0$ for all $y_1 \neq \ln\mu_2$. Clearly, $V > 0$ for all $(y_1, y_2) \neq (\ln\mu_2, 0)$. Finally, $G(y_1)$ is radially unbounded (again, because $G'(y_1) < 0$ for $y_1 < \ln\mu_2$ yet $G'(y_1) > 0$ for $y_1 > \ln\mu_2$), and of course so is y_2^2. Therefore, V is radially unbounded.

With this, we have shown that the candidate function V is globally positive definite, radially unbounded, and the time-derivative of the candidate function is globally negative definite. Therefore, the equilibrium $(y_1, y_2) = (\ln \mu_2, 0)$ is globally asymptotically stable. Since Eq. (2.12) was just a transformation of (1.1), it follows that the non-zero equilibrium of (1.1) is globally asymptotically stable. This is in contrast to other models, which may exhibit chaotic behaviors [16].

4 Numerical simulation of the solution f

Since a solution f for (2.12) approaches a globally asymptotically stable equilibrium $f^* = \ln \mu_2$ for $\mu_1 > 0$, we should expect any numerical simulations to satisfy this large-time behavior. While a variety of numerical methods could be applied, we use the Runge–Kutta–Fehlberg 4–5 method [17], since it is standard in many mathematics programs (Maple, MatLab, Mathematica). In Fig. 1, we provide numerical solutions to (2.12) for various values of the physical parameters. Indeed, the required behaviors discussed above are apparent in these solutions. One can then use the relations (2.13)–(2.16) to recover the numerical solutions of the system of interest (1.1). From these solutions, some observations are in order.

First, note that the numerical solution profiles can be approximated by an expression of the form

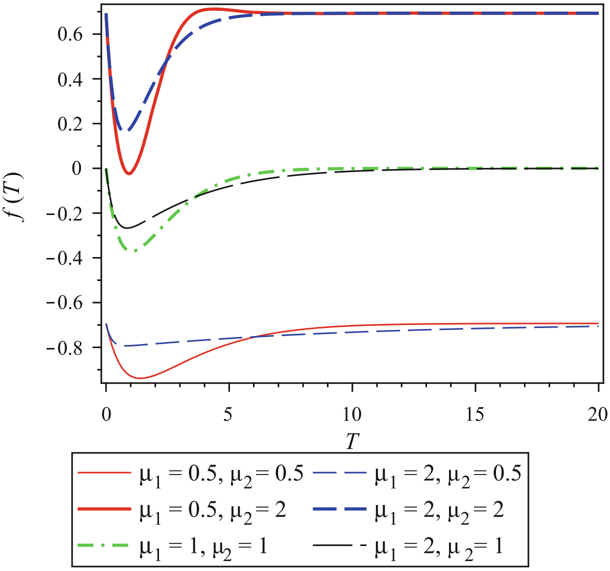
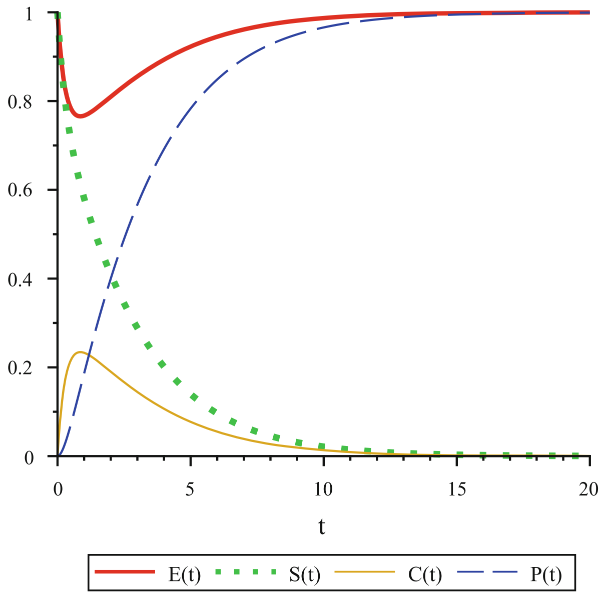


Fig. 1 Plot of the solutions f to (2.12) for various values of μ_1 and μ_2. We fix the ratio $S_0/E_0 = 1$. All solution profiles dip and then return to their initial values. As f is a transformation of the enzyme concentration, it is a measure of enzyme availability: during the reaction, the enzymes are used, while after the reaction they become free

Fig. 2 Plot of the solutions to the dynamic Michaelis–Menten enzymatic reaction model (1.1). We fix the parameter values $k_{-1} = k_1 = k_2 = 1$ and $E_0 = S_0 = 1$, yielding $K_m = 2$ and $\mu_1 = 2$, $\mu_2 = 1$. Similar plots may be obtained for other parameter values



$$\hat{f}(T) = \ln \hat{F}(T), \quad \hat{F}(T) = \mu_2 + \frac{S_0 \mu_2^2}{(\alpha - \beta) E_0} \left(\exp(-\alpha T) - \exp(-\beta T)\right), \tag{4.1}$$

where $\alpha > \beta > 0$. It can be verified that $\hat{f}(0) = \ln \mu_2$ and $\lim_{T\to\infty} \hat{f}(T) = \ln \mu_2$ as required, while the needed condition on $\hat{f}'(0)$ also holds. Here, α is a measure of the initial usage rate of the enzyme, while β is a measure of the recovery rate of the enzyme. Since $\alpha > \beta$, the solution first decays and then recovers. A variational method or regression approach can be considered for the calculation of α and β; the complete discussion of this point is beyond the scope of this paper.

Secondly, note that there is a time $T^* > 0$ at which enough of the enzyme is used to create the compound and the compound begins to decay into the product and enzyme, so that the quantity of enzyme begins to increase. This time corresponds to the minima of the graphs in Fig. 1. For the approximate solution form (4.1), note that this corresponds to $F'(T^*) = 0$, hence we find that $T^* = (\alpha - \beta)^{-1} \ln(\alpha/\beta)$.

In order to see how numerical solutions of f translate into solutions to the physical system (1.1), we plot solution profiles in Fig. 2. While we fix the model parameters in order to generate plots, this can be done for any choice of model parameters.

Let's see how our approximating expression may be used. Since there is no exact solution to (1.1), in order to determine the error of such an approximation, we need to consider residual errors. Define

$$J[F] = \int_0^\infty \left\{ F F'' + F^2 F' + \mu_1 F' - F'^2 - \mu_2 F^2 + F^3 \right\}^2 dT, \tag{4.2}$$

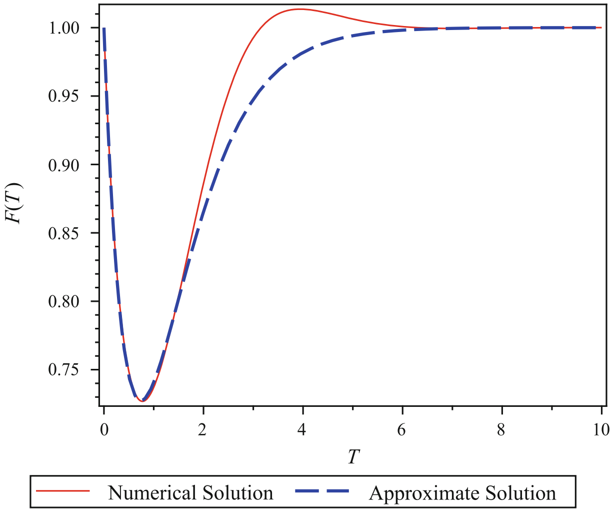


Fig. 3 Plot of the numerical and approximate solutions (using the approximate solution (4.1)) to F obtained by solving (2.7). We fix the parameter values $k_{-1} = k_1 = k_2 = 1$ and $E_0 = S_0 = 1$, yielding $K_m = 2$ and $\mu_1 = 2$, $\mu_2 = 1$. Similar plots may be obtained for other parameter values. In order to obtain the approximate solution, we minimized the functional $J[\hat{F}]$ with respect to parameters α and β, finding $\alpha = 1.4$ and $\beta = 1.3$ to give $J[\hat{F}] = 0.0126252$. This is the optimal approximation of the form (4.1). Note that the approximation is very good for both small and large values of the scaled time variable, T, so the approximation can accurately model small and asymptotic dynamics of the Michaelis–Menten system. For intermediate values, the two exponential functions cannot model the dynamics of the additional turn in the graph which occurs at about $T = 4$. Once could assume a more complicated approximation, involving an additional exponential, to more accurately model this regime. Note that this peak does not occur for all parameter values, in which case the analytical solution is more accurate. The minimal value of F occurs at $T^* = (\alpha - \beta)^{-1} \ln(\alpha/\beta) = 0.741$

which is the integral of the squared residual error over the domain. In order to determine the parameters α and β, we minimize this functional with respect to these parameters. In Fig. 3 we demonstrate the utility of this approach. We find that the analytical assumption (4.1) is useful for large and small time scales. For intermediate time scales, this approximation may break down. In such a case, a more complicated form of the approximate solution, involving more than two exponential terms, can be employed to yield more accurate results in this intermediate time regime.

5 Conclusions

In summary, we have reduced the dynamic Michaelis–Menten system (1.1) into a single time-dependent differential equation, which is easier to solve numerically than the original system. This sheds light on the features of the model which influence the solution process. We have used this equation to prove that solutions to the Michaelis–Menten system tend toward globally asymptotically stable equilibria as time gets large. Numerical solutions agree with what we qualitatively expect from the model. With this, we have completely determined the types of behaviors emergent from the dynamic Michaelis–Menten system.

Note that we have effectively reduced the fourth-order dynamic Michaelis–Menten system (1.1) into a dynamical system of second order. This reduction of phase space casts some light on the physical processes at play. Indeed, the fact that we can perform this reduction without loss of information implies that there are effectively two free quantities in the dynamic Michaelis–Menten system (1.1), while the remaining two quantities are completely controlled by the first two.

We have determined a method for obtaining an approximate solution, through a variational approach. Balancing two exponential modes, we have been able to construct an approximate solution that agrees with numerical simulations for small and large time scales. For intermediate time scales, the solutions may lose accuracy. In this case, a more complicated form of the approximate solution, using three or more exponential modes, will improve accuracy of the approximate solutions.

Acknowledgments R.A.V. supported in part by NSF Grant # 1144246.

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