

Dynamics of the Irreversible Michaelis–Menten Kinetic Mechanism

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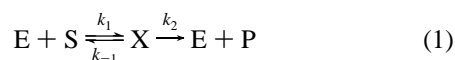
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Solutions using Abel's method are developed for the irreversible Michaelis–Menten mechanism that governs enzyme action. From these phase plane solutions, an approximate solution is derived that permits a study of the time course of substrate and complex. Performance of the solutions in the phase plane and in temporal evolution is assessed in comparison to numerical solutions, the quasi-equilibrium and pseudo-steady-state approximations, and the iterative solution obtained by Fraser and co-workers. Both the complete and approximate solutions perform well, especially in parameter regions of most practical interest.

1. Introduction

The description of the transients of enzyme-catalyzed reactions has evolved since the first measurements by Chance¹ quantified the intermediate complex. Using the difference in light absorbance of enzyme, substrate, and complex in reactions of horseradish peroxidase and catalase enzyme with rapid mixing and flow techniques, the existence of the complex was experimentally confirmed. Until then, the simplest two-step mechanism of enzyme action, proposed by Henri² and given in eq 1, was treated using the approaches of Michaelis and Menten³



and Briggs and Haldane.⁴ While many systems do not follow such a simple model, eq 1 is useful as a first step in describing more complex reaction networks. Further, most networks are usually governed by the steps in eq 1 as the subsequent steps are much faster.

In eq 1, S represents substrate, E is enzyme, X is the intermediate or complex, and the k 's denote rate constants. We note that eq 1 is used under "closed" system conditions, where steps connecting the reaction mechanism to the outside environment are not important. For open systems such steps, described by input and output fluxes, are important. Michaelis and Menten³ demonstrated that the kinetic description of eq 1 was possible using only two parameters by assuming that the binding step was at equilibrium, unperturbed by product formation. This has become known as the quasi-equilibrium assumption (MM in text). Briggs and Haldane⁴ removed this assumption of equilibrium, but assumed that the rate of change of the complex was negligible. This is known as the pseudo-steady-state hypothesis (PSS in text). For several systems, especially in vitro, the profiles were essentially in the decay regimes. This is especially true when the value of μ (defined as the ratio of initial enzyme to initial substrate) was very small. μ was around 10^{-3} – 10^{-6} for the majority of reactions they considered; therefore, the PSS worked very well. However the PSS fails over significant regions of the time profile, whenever μ is high.⁵ Such conditions are realistic in attempting to use enzymes as

industrial catalysts. Chance's work motivated several analyses aimed at improving the PSS.^{6–11} Heineken et al.¹² and, more recently, Li et al.¹³ and Fraser and co-workers^{14,15} are notable attempts to achieve a complete solution.

In this work we will find solutions to describe the substrate and complex concentrations both in the phase plane and with time. To do this we first describe (section 2) a special type of differential equation, the Abel¹⁶ form, which can be obtained from the above mechanism. Solutions of these types of differential equations are found as roots of nonlinear equations in the phase plane. Section 3 presents comparisons of the exact, numerical solution with the phase plane solutions for several sets of enzyme reactions. These parameters include many of those discussed in previous presentations of solutions to the dynamics of eq 1 involving perturbation theory^{12,13} or functional equation^{14,15} methods. The phase plane solution is not readily decoupled to generate time profiles. An approximation is proposed that permits the time variation of substrate and complex to be calculated in the slow decay regime. The solution is compared with the pseudo-steady-state approximation and other solutions in the slow decay regime. Errors are tabulated for a comparison of all solutions (both the complete phase plane and in the slow decay regime) over a wide range of the key parameters of the system.

2. Basic Equations

Following the law of mass action, we can write four differential equations for eq 1

$$dS/dt = -k_1SE + k_{-1}X \quad (2)$$

$$dX/dt = k_1SE - k_{-1}X - k_2X \quad (3)$$

$$dE/dt = -k_1SE + k_{-1}X - k_2X \quad (4)$$

$$dP/dt = k_2X \quad (5)$$

with the initial conditions $S(t=0) = S_0$, $E(t=0) = E_{\text{tot}}$, and $X(t=0) = P(t=0) = 0$. Here E_{tot} is the total enzyme concentration. The two mass conservation equations for a closed system are $E_{\text{tot}} = E + X$ and $S_0 = S + X + P$ with no

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enzyme deactivation with the initial conditions $S(0) = S_0$ and $X(0) = 0$. Following ref 13, $\sigma = S/S_0$, $\kappa = X/E_{\text{tot}}$ are defined so that σ and κ are the dimensionless substrate and complex concentrations. The time variable is scaled according to $\tau = k_1 E_{\text{tot}} t$ and dimensionless parameters are defined as $\mu = E_{\text{tot}}/S_0$, $\nu = E_{\text{tot}}/K_M$, $\omega = k_2/(k_{-1} + k_2)$, $K_M = (k_{-1} + k_2)/k_1$, $\chi = K_M/S_0$, and $\lambda = k_2/k_1 S_0$. Here $\mu = \nu\chi$ and $\lambda = \omega\chi$. Equations 2–5 are rewritten as

$$d\sigma/d\tau = -\sigma + (\sigma + \chi - \lambda)\kappa \quad (6)$$

$$\mu(d\kappa/d\tau) = \sigma - (\sigma + \chi)\kappa \quad (7)$$

Equations 6 and 7 may be combined in two ways

$$\frac{d\sigma}{d\kappa} = \frac{\frac{\mu(\chi - \lambda)}{1 - \kappa}\kappa - \mu\sigma}{\frac{-\chi\kappa}{1 - \kappa} + \sigma} \quad (8)$$

$$\frac{d\kappa}{d\sigma} = \frac{\frac{\sigma}{\mu(\sigma + \chi - \lambda)} - \frac{(\sigma + \chi)}{\mu(\sigma + \chi - \lambda)}\kappa}{\frac{-\sigma}{\sigma + \chi - \lambda} + \kappa} \quad (9)$$

Equations 8 and 9 are in the σ, κ -plane or what will be referred to henceforth as the phase plane. They are special types of the Abel differential equation¹⁶ of the form

$$\frac{dy}{dx} = \frac{p_0 + p_1 y}{q_0 + q_1 y} \quad (10)$$

We can identify the functions $p_0(x)$, $p_1(x)$, $q_0(x)$, and $q_1(x)$ for either eq 8 or 9. According to Haentzschel¹⁶ the unconstrained solution to eq 10 takes the form

$$(y + \alpha_1)^{h_1}(y + \alpha_2)^{h_2} = C \quad (11)$$

where α_1 and α_2 are functions of x and h_1, h_2 , and C are constants. The form of the functions α_1 and α_2 has to be determined. To do this the following recipe¹⁶ is used

$$q_1 = 1 = h_1 + h_2 \quad (12)$$

$$p_0 = -h_1\alpha_1'\alpha_2 - h_2\alpha_2'\alpha_1 \quad (13)$$

$$p_1 = -h_1\alpha_1' - h_2\alpha_2' \quad (14)$$

$$q_0 = h_1\alpha_2 + h_2\alpha_1 \quad (15)$$

where the primes denote derivatives (e.g. $d\alpha_2/dx$) and the p 's and q 's are specified by the particular problem at hand. Given the definitions in eqs 12–15 and taking the derivative of the logarithm of eq 11, we can show that eq 11 is the form of solution for eq 10. To make this solution practical, we must find the unknowns $\alpha_1, \alpha_2, h_1, h_2$, and C using eqs 12–15. Eliminating α_1' and α_1 from eqs 13–15 we obtain

$$\alpha_2' = \frac{p_0 - p_1\alpha_2}{-q_0 + \alpha_2} \quad (16)$$

One could use the functional equation method^{14,15} to solve this equation approximately, use eq 15 to find α_1 , and then find solutions in the phase plane as roots of eq 11. This did not

give meaningful roots for eq 11 so we use another, simplified approach that leads to tractable expressions, which are significant improvements on the PSS and MM expressions. Equation 16 is in the same form as eq 10, with a change in the sign of the off-diagonal terms. To simplify the problem we write the differential of eq 15 as

$$q_0' = h_1\alpha_2' + h_2\alpha_1' \quad (17)$$

Using eqs 13, 15, and 17 to eliminate α_1' and α_1

$$\alpha_2' = \frac{h_1 q_0' + h_2 p_1}{h_1 - h_2} \quad (18)$$

Now, equating eqs 16 and 18 the expression for α_2 is

$$\alpha_2 = q_0 \left(1 + \frac{(p_0/q_0) - p_1}{q_0' + p_1} \frac{(h_1 - h_2)}{h_1} \right) \quad (19)$$

Substituting α_2 into eq 14

$$\alpha_1 = \frac{-\int p_1 dx + C_1}{h_1} - \frac{h_2\alpha_2}{h_1} \quad (20)$$

Alternately, substituting eq 19 into eq 15 we obtain the same form as in eq 19, but with the terms h_1 and h_2 interchanged. The form of α_1 in eq 20 will be used in the rest of the analysis. The three constants h_2, C_1 , and C must be evaluated. h_1 is then found from eq 12. For the p 's and q 's of eq 9, α_1 and α_2 can be determined as

$$\alpha_2 = \frac{-\sigma}{\sigma + \chi - \lambda} \left[1 - \frac{\frac{\lambda}{\mu}(1-P)}{\frac{\chi - \lambda}{\sigma + \chi - \lambda} + \frac{\sigma + \chi}{\mu}} \right] \quad (21)$$

$$\alpha_1 = \frac{\sigma}{\mu h_1} + \frac{\lambda}{\mu h_1} \ln[\sigma + \chi - \lambda] + C_1 - P\alpha_2 \quad (22)$$

In eqs 21 and 22, $P = h_2/h_1$ and the solution to eq 9 takes the form

$$(\kappa + \alpha_1)^{h_1}(\kappa + \alpha_2)^{h_2} = C \quad (23)$$

The constant C is found using the initial point $[\sigma = 1, \kappa = 0]$, giving

$$(\alpha_{1i})^{h_1}(\alpha_{2i})^{h_2} = C \quad (24)$$

The final point $[\sigma = 0, \kappa = 0]$ can be used to determine C_1 . Since α_2 and κ are both zero this creates a singularity in eq 23. This singularity can be avoided if we prescribe that $h_2 < 0$, so that $\alpha_1 = 0$ and therefore C_1 is found from eq 22 with $\sigma = 0$ as

$$C_1 = \frac{-\lambda}{\mu h_1} \ln(\chi - \lambda) \quad (25)$$

The constant h_2 remains to be found and can be evaluated from the initial slope which is found from eq 9 to be $-1/\mu$. The derivative of eq 23 at the initial point results in a quartic equation in P , with two real roots, one of which is $h_2 = -1$, which is inapplicable, and two complex roots. The desired real root for h_2 can be calculated using a conventional nonlinear equation

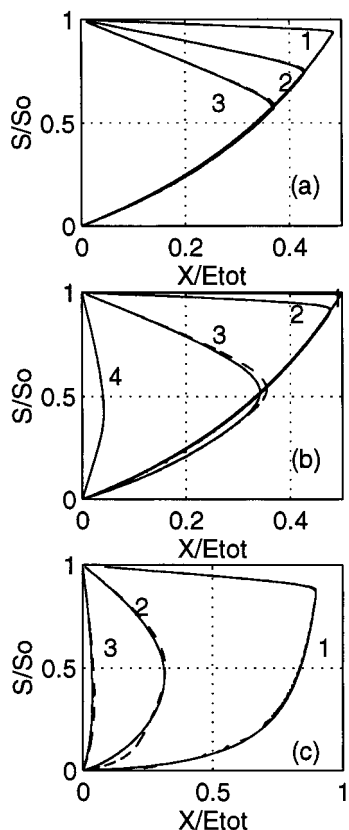


Figure 1. Solutions in phase plane for systems of (a) ref 5, (b) ref 12, and (c) large ω (0.889). Lines are numerical solutions and dashed lines are solutions from eq 23. Parameters for part a, curve 1: $\mu = 0.1$, $\nu = 0.1$, $\omega = 0.1$, $h_2 = -0.00229$. Curve 2: $\mu = 0.5$, $\nu = 0.5$, $\omega = 0.1$, $h_2 = -0.00895$. Curve 3: $\mu = 1.0$, $\nu = 1.0$, $\omega = 0.1$, $h_2 = -0.0136$. Parameters for part b, curve 1: $\mu = 0.01$, $\nu = 0.01$, $\omega = 0.375$, $h_2 = -0.000845$. Curve 2: $\mu = 0.1$, $\nu = 1.0$, $\omega = 0.375$, $h_2 = -0.0080795$. Curve 3: $\mu = 1.0$, $\nu = 1.0$, $\omega = 0.375$, $h_2 = -0.05426$. Curve 4: $\mu = 10.0$, $\nu = 1.0$, $\omega = 0.375$, $h_2 = -0.1235$. Parameters for part c, curve 1: $\mu = 0.1$, $\nu = 1.0$, $\omega = 0.889$, $h_2 = -0.00533$. Curve 2: $\mu = 1.0$, $\nu = 1.0$, $\omega = 0.889$, $h_2 = -0.098$. Curve 3: $\mu = 10.0$, $\nu = 1.0$, $\omega = 0.889$, $h_2 = -0.839$.

solver such as those available in the International Mathematical Software Library (IMSL). The package DNEQNF was used here.

3. Enzyme Reaction Examples and Comparisons in Phase Plane

We considered several different enzyme reactions: (Figure 1a) the system of Lim⁵ for chymotrypsin and acetyl-L-phenyl alanine ester, (Figure 1b) the values used by Heineken et al.¹² for the system trypsin and benzoyl-L-arginine ester, and (Figure 1c) a set with very high $\omega = 0.889$. The last set may not be realistic, yet it explores the limitations of eq 23. ω expresses the degree of reversibility of the complex formation step. It is defined solely by the reaction rate constants and, when large, suggests that the Michaelis–Menten quasi-equilibrium assumption is not reliable. In Figure 1, the parameter sets and the calculated value of h_2 are given in the captions. The Abel solution eq 23, with the constants defined in eqs 24 and 25 and the value of h_2 calculated from the initial slope, was used to study the parameter combinations. These solutions are compared to simultaneous solutions of eqs 6 and 7 from an ordinary differential equation solver, LSODE. Since eq 23 is a nonlinear equation in one variable κ , it was solved using DNEQNF with fixed values of σ . The initial guess for κ was chosen as an

arbitrary, small number, which may sometimes produce poor solutions in a narrow range. This is an artifact of the convergence of the nonlinear root finder. The solution is improved on using a better initial guess for the root finder, such as the value of κ from the simultaneous, numerical solution itself.

Since our aim here is to show that solutions in the phase plane possess the form of eq 23, we do not use any other choice of initial guesses. Figure 1 shows that the solution of the Abel type equation maps the initial and decay regimes of the mechanism in eq 1. For several combinations the solution (dashed lines) is indistinguishable from the numerical solution, even though the initial guess to the root finder is considerably distant from the numerical solution. Curve 3 of Figure 1b and curve 2 of Figure 1c, however, indicate that the root of eq 23 differs from the numerically calculated solution in the phase plane when μ or ν are close to 1. When ω is large this discrepancy exists even when μ or ν are not close to 1.

On the basis of Table 1 and figures such as Figure 1, an error less than 1.0×10^{-7} is deemed acceptable for the complete solution. Then the poorest match of eq 23 and the numerical solution is obtained when ω is large and $\mu = \nu > 1$. There is only small numerical error in finding the roots of eq 23 for the particular value of h_2 being used. Since the numerical solution is accepted as accurate, it is possible that the use of eq 17, introduced to generate a solution for α_2 , places constraints on the solution space. When h_2 is very small, the complete solution matches the numerical solution very well. Curve 3 of Figure 1b shows that the error is comparable to solutions from singular perturbation¹² for the same data. The situation with small μ or $\nu \{ < 0.1 \}$ can be created by manipulating the initial levels of substrate and enzyme. These levels are, however, still large enough so that the PSS will still be in error¹⁷ whereas the fast asymptote is described well by the roots of eq 23 for any ω . When $\nu > 1$ errors from eq 23 show a maximum as μ approaches 1 at fixed ω . Since the value of h_2 is generally not integral, eq 23, which relates κ and σ , is not decoupled easily. To investigate the possibility of a simpler, useful solution, h_2 was set at zero. With $h_2 = 0$ only the individual factors on the left-hand side of eq 23 can be used. These solutions cannot pass through the initial point. Recognizing this, $\sigma = \alpha_2(\kappa)$ or $\kappa = \alpha_2(\sigma)$ were used as approximate solutions. Equation 19 with $h_2 = 0$ gives the solutions for eqs 8 and 9 as

$$\sigma = \frac{\chi\kappa}{1-\kappa} \left\{ 1 - \frac{\omega\nu}{\nu + \frac{1}{(\kappa-1)^2}} \right\} \quad (26)$$

$$\kappa = \frac{\sigma}{\sigma + \chi - \lambda} \left\{ 1 - \frac{\lambda(\sigma + \chi - \lambda)}{(\sigma + \chi - \lambda)(\sigma + \chi) + \mu(\chi - \lambda)} \right\} \quad (27)$$

Terms outside the brackets in eqs 26 and 27 are the PSS and MM kinetic limits. Reference 10 arrived at expansions with similar forms as eqs 26 and 27. The performance of eqs 26 and 27 was compared with the iterated solutions of Fraser and co-workers for the same mechanism.^{14,15} This solution relies on writing the phase plane equation as a functional equation, then performing iteration to refine the solution. Figure 2a,b shows that the iterative solution, even with only the third iterate, is quite powerful. Table 1 confirms this over the slow manifold portion for a range of parameters. We note here that over the slow asymptote there are rigorously only two independent parameters, since S_0 is essentially eliminated.^{14,15} Since Table 1 shows errors for the complete solution as well, all three parameters are shown; however, calculated error magnitudes

TABLE 1: Errors from Complete Solution and Solutions in Slow Asymptote

parameters			complete solution			slow asymptote solutions			
μ	ν	ω	h_2	eq 23	no. of pts	ref 14 error ^b	eq 26	eq 27	no. of pts
0.1	0.1	0.1	-0.0023	6.95e-7 ^a	400	9.4e-16	9.37e-4	1.08e-4	350
1	0.1	0.1	-0.0071	9.95e-9	400	1.1e-15	1.37e-3	1.06e-5	350
10	0.1	0.1	-0.0083	4.2e-12	400	2.5e-16	1.4e-3	1.43e-7	350
0.1	1	0.1	-7.4e-3	4.86e-8	250	8.9e-16	1.53e-3	6.12e-5	200
1	1	0.1	-0.0136	2.04e-6	250	2.2e-12	4.0e-3	8.1e-4	200
10	1	0.1	-0.0255	6.5e-10	250	1.9e-13	4.2e-3	3.8e-5	200
0.1	10	0.1	-8.8e-5	8.3e-11	300	0.0	2.58e-7	3.8e-11	250
1	10	0.1	-0.004	1.6e-5	300	1.1e-14	1e-3	6.9e-4	250
10	10	0.1	-0.0128	4.9e-8	300	3.0e-14	5.4e-4	2.91e-4	250
0.1	0.1	0.5	-0.0103	1.57e-6	400	1.4e-11	9.27e-3	1.4e-3	350
1	0.1	0.5	-0.0372	1.84e-8	400	1.79e-9	0.0117	1.08e-4	350 ^c
1	0.1	0.5	-0.0372	1.84e-8	400	1.7e-12	0.0137	1.2e-4	300 ^c
10	0.1	0.5	-0.0461	1.3e-10	400	9.5e-14	0.014	1.77e-6	300
0.1	1	0.5	-0.0035	1.75e-6	200	1.98e-9	6.9e-4	7.3e-4	150
1	1	0.5	-0.0729	2.18e-5	200	2.73e-8	1.47e-2	3.3e-2	150
10	1	0.5	-0.1918	2.85e-8	200	2.3e-9	1.5e-2	2.67e-4	150
0.1	10	0.5	-4.3e-4	5.35e-8	200	0.0	7.9e-2	1.45e-4	150
1	10	0.5	-0.0198	2.6e-4	200	3.4e-6	1.78e-2	1.28e-2	150
10	10	0.5	-0.1029	3.08e-5	200	2.75e-9	1.3e-2	9.16e-3	150

^a Read as 6.95×10^{-7} . ^b Third iterate of Fraser and co-workers.^{14,15} ^c Uses fewer points along slow asymptote for error computation; error = average of the square of the deviations from the numerical solution.

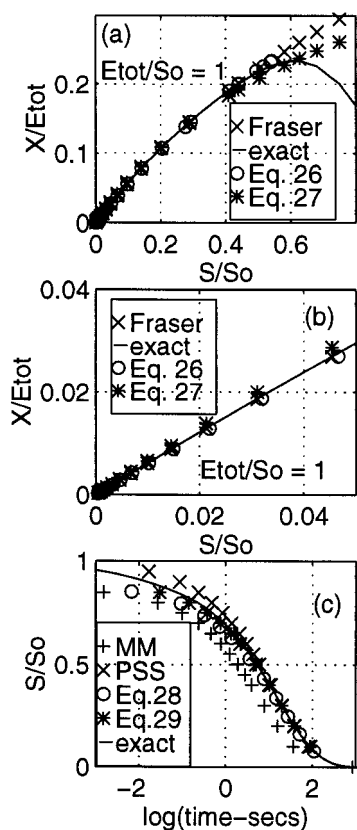


Figure 2. Solutions in phase plane for $\mu = 1$, $\nu = 0.5$, $\omega = 0.5$: a, shorter time; b, longer times. Crosses refer to third iterate of Fraser¹⁴ solution. (c) Time evolution of σ for $\mu = 0.5$, $\nu = 0.125$, $\omega = 0.375$.

are unaffected. To calculate errors we used a large number of points for the complete solution and reduced the number for the slow asymptote since these solutions do not approach the initial point. The match with the numerical solution of the third iterate over the slow asymptote is extremely good even where substrate and enzyme initial concentrations are equal. The iterative solution can also be refined to any degree desired. A similar functional equation can be written for velocity. Other,

complicated mechanisms have been treated by the same method^{14,15} as well. For two-dimensional problems this method is equivalent to ordinary perturbation expansion. However for three or more concentrations this equivalence breaks down.¹⁸ This simple yet powerful solution is the proper standard against which to compare eqs 26 and 27, which can be shown to be superior to the PSS or MM approximations using the error measure of Crooke et al.¹¹ Figure 2a shows the case for parameters from ref 14 which translate to $\mu = 1$, $\nu = 0.5$, and $\omega = 0.5$. Figure 2b applies to longer times. The solution on the scale of the figures is quite good for the approximations. In the slow asymptote, errors less than $1.0 \times 10^{-4} - 1.0 \times 10^{-5}$ are acceptable although neither eq 26 nor 27 are as accurate as the third iterate solution. All the solutions are superior to the PSS or MM approximations. The quantitative measures given in Table 1 show that eqs 26 and 27 are greatly improved if $\mu = 0.1$ or 10 for larger values of $\nu (>0.5)$. In extracting rate constants velocity profiles are needed. The simplified form of eqs 26 and 27 are useful, provided suitable values of μ or ν far from unity are chosen. Time profiles require the calculation of a positioning constant since the solutions in eqs 26 and 27 do not start at $t = 0$. The point of intersection of the initial slope line with the solutions from eqs 26 and 27 in the phase plane was used to assign the zero-time position. DIR refers to eq 26 and INV to eq 27. Substitute eq 26 in eq 7 and integrate to obtain

$$\tau_{\text{DIR}} = \frac{\ln(1 - \kappa) - (\nu + 1) \ln(\kappa) - \frac{1}{1 - \kappa}}{\omega} + \frac{k_2 \nu}{\omega} C_{\text{DIR}} \quad (28)$$

Equation 27 in eq 6 gives

$$\tau_{\text{INV}} = \frac{\mu \ln(\sigma + \chi - \lambda) - (\chi + \mu) \ln(\sigma) - \sigma}{\omega \chi} + \frac{k_2 \mu}{\omega \chi} C_{\text{INV}} \quad (29)$$

MM and PSS solutions are

$$\tau_{\text{MM}} = \frac{\mu \ln(\sigma + \chi - \lambda) - (\chi + \mu) \ln(\sigma) - \sigma}{\omega\chi} + \ln(\sigma) + \frac{k_2\mu}{\omega\chi} C_{\text{MM}} \quad (30)$$

$$\tau_{\text{PSS}} = \frac{1 - \sigma - \chi \ln(\sigma)}{\omega\chi} \quad (31)$$

These integrations are a direct result of being able to decouple eqs 6 and 7 so that they are written only in terms of a single variable for the two-dimensional system of eq 1. Figure 2c shows the extracted profiles for a region where PSS and MM solutions fail, yet where eqs 28 and 29 perform well. Exact solution of eqs 6 and 7 was found numerically using LSODE.

4. Summary

The governing kinetic equations for the irreversible, Michaelis–Menten enzyme-catalyzed reaction, which is also significant in other chemical processes, are shown to be special types of the Abel differential equation. Several works^{9,11,19} have pointed out the intractability of formulating the problem in this manner. However, on the basis of Haentzschel's¹⁶ suggestions, a solution was derived and uses the Abel differential equation written in the form of eq 10. This particular form is commonly observed in the course of kinetic analysis of general plane autonomous systems. The solution accurately describes initial transients and the decay regime for a large range of parameters, provided μ and ν are small. These values, however, are such that the conventional steady-state approximations are still invalid. Initial transients were maintained in the analysis through the initial substrate concentration which appears in the balances.^{12,13} If only a description of the invariant manifold^{14,15,20} is sought, such initial information is eliminated since the system is assumed to be in the slow decay phase.

The parameter h_2 was calculated from the initial slope and is a negative number. When h_2 is very small (yet negative and non-zero) this solution in the phase plane is indistinguishable from the exact solution, even during the initial transients. However, the complete phase plane solution for the two-dimensional mechanism of eq 1 is not easily reduced to a time profile. For this purpose an approximation ($h_2 = 0$) was made that leads to two forms of asymptotic solutions, eqs 26 and 27. These bracket the exact solution in the slow asymptote yet with

far lower error than the PSS and MM expressions. These approximations and the resulting time profiles compare favorably with the rigorous iterative solution for the slow decay regime based on a functional equation approach. The positioning technique developed is applicable even when the quasi-equilibrium assumption is invalid.

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