SOLUTION OF THE MICHAELIS-MENTEN EQUATION USING THE DECOMPOSITION METHOD

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ABSTRACT. We present a low-order recursive solution to the Michaelis-Menten equation using the decomposition method. This solution is algebraic in nature and provides a simpler alternative to numerical approaches such as differential equation evaluation and root-solving techniques that are currently used to compute substrate concentration in the Michaelis-Menten equation. A detailed characterization of the errors in substrate concentrations computed from decomposition, Runge-Kutta, and bisection methods over a wide range of s_0:K_m values was made by comparing them with highly accurate solutions obtained using the Lambert W function. Our results indicated that solutions obtained from the decomposition method were usually more accurate than those from the corresponding classical Runge-Kutta methods. Moreover, these solutions required significantly fewer computations than the root-solving method. Specifically, when the stepsize was 0.1% of the total time interval, the computed substrate concentrations using the decomposition method were characterized by accuracies on the order of 10^{-8} or better. The algebraic nature of the decomposition solution and its relatively high accuracy make this approach an attractive candidate for computing substrate concentration in the Michaelis-Menten equation.

1. **Introduction.** The Michaelis-Menten equation [15] has been widely used to describe the kinetics of enzyme-catalyzed reactions. Evoking the pseudo-steady state approximation, this expression reduces to a single first-order nonlinear ordinary differential equation which describes the rate of depletion of the substrate of interest [8]. While this equation can be readily integrated, the resulting expression is implicit in the substrate concentration. As a result, root-solving techniques such as the bisection and Newton-Raphson methods have often been used to compute the substrate concentration in the integrated Michaelis-Menten equation [9]. Alternatively, substrate concentration can be estimated by numerically integrating the

differential form of the Michaelis-Menten equation as shown in several studies [10, 11, 24].

An explicit closed-form solution to the Michaelis-Menten equation has been proposed only recently [17]. This solution is based on the Lambert W function [7], and the accuracy of this solution was independently verified to be on the order of 10^{-15} [13]. Moreover, this solution is valid for all values of substrate concentration and kinetic parameters, unlike solutions from perturbation methods, which rely on a parameter being large or small.

Having an accurate closed-form solution to the Michaelis-Menten equation opens up the possibility of examining the utility of other non-conventional solution techniques to solve the Michaelis-Menten equation. In the present study, we present a solution to the Michaelis-Menten equation based on the decomposition method [1]. This approach has been used in the past to obtain solutions to the Michaelis-Menten equation under pseudo-steady state conditions [5] and also under transient conditions [18-20]. However, a rigorous analysis of the errors associated with the solution in both cases was not made, as a closed-form solution to the Michaelis-Menten equation was not available. Moreover, the transient solution [18-20] was accurate only in the neighborhood of the reference point and significant errors were seen at points away from the reference point. While error was reduced through the use of convergence acceleration techniques such as Padé approximants and Shanks transformation, the narrow range over which this solution is valid precludes its use for characterizing the complete profile of the substrate concentration as a function of time.

In this study, we use the Lambert W function solution for the Michaelis-Menten equation [13, 17] to present a systematic analysis of the error associated with the solution from the decomposition method. Based on the results of this analysis, we present an approach that provides a decomposition solution of any desired accuracy for the Michaelis-Menten equation. A similar error analysis was also performed for other commonly used solution methods including the Runge-Kutta and root-solving methods. Our results indicate that solutions obtained through the decomposition method were generally superior to those from the corresponding classical Runge-Kutta methods. Moreover, these solutions required significantly fewer computations than the root-solving method.

2. **Theory.** The Michaelis-Menten equation can be used to describe the dynamics of substrate depletion in the differential form as

$$\frac{ds}{dt} = -\frac{V_m s}{K_m + s}, \tag{1}$$

where s is the substrate concentration, t is time, and V_m and K_m are the limiting rate and Michaelis constant, respectively. All solutions with positive initial datum remain non-negative for all times > 0 and decay monotonically to zero as $t \to \infty$. Equation (1) can be readily integrated to obtain the integral form of the Michaelis-Menten equation

$$K_m \ln\left(\frac{s_0}{s}\right) + s_0 - s = V_m t \tag{2}$$

where s_0 is the initial substrate concentration. Equation (2) is nonlinear and clearly implicit with respect to the substrate concentration which explains the need for numerical approaches such as the bisection and Newton-Raphson methods for its

solution. However, as shown recently [13,17], Equation (2) may be written in a form that is explicit in the substrate concentration

$$s = K_m W \left\{ \frac{s_0}{K_m} \exp \left[\frac{s_0 - V_m t}{K_m} \right] \right\} \tag{3}$$

where W is the Lambert omega function as described in [7]. Details of the derivation of Equation (3) have been presented elsewhere [13]. In the following section, we will illustrate the use of the decomposition method for solution of Equation (1). The result is a simple algebraic expression that is explicit with respect to the substrate concentration.

2.1. Decomposition method solution for the Michaelis-Menten equation.
The solution to the Michaelis-Menten equation (Equation 1) will be presented in three sections. The first section introduces the decomposition method for a general ordinary differential equation. The second section deals with application of the decomposition method to the Michaelis-Menten equation while the last section deals with error estimates for this approach.

2.1.1. *Decomposition method applied to a general ordinary differential equation.* We will follow Adomian's [1] development for the general one-dimensional (1-D) differential equation. Consider a 1-D differential equation

$$(F) s(t) = g(t), \tag{4}$$

where F is a 1-D differential operator. This general operator may be expressed as the sum of a linear invertible operator L, a residual linear operator R, and a nonlinear operator N. The operator F may thus be replaced by the three operators as

$$(L + R + N) s = g, \tag{5}$$

which can be rewritten as

$$(L)s = g - (R)s - (N)s, \tag{6}$$

where the time dependence of s and g have not been shown explicitly. Since L is an invertible linear operator, it has an inverse L^{-1}. For concreteness, if L is an mth order differential operator, then L^{-1} is an m-fold integration operator. Solutions that differ by an arbitrary polynomial of degree m-1 cannot be distinguished and are determined from the initial or boundary conditions. All of these terms may be represented by a function, ψ. The application of the inverse operator L^{-1} to Equation (6) results in

$$\left(L^{-1} \right) \{ (L)s \} = (L^{-1})g - \left(L^{-1} \right) \{ (R)s \} - \left(L^{-1} \right) \{ (N)s \} \tag{7}$$

or

$$s = \psi + (L^{-1})g - \left(L^{-1} \right) \{ (R)s \} - \left(L^{-1} \right) \{ (N)s \} . \tag{8}$$

The function ψ along with $(L^{-1})g$, which together provide a priori information, are usually grouped into a term s_0, and the above equation reduces to

$$s = s_0 - \left(L^{-1} \right) \{ (R)s \} - \left(L^{-1} \right) \{ (N)s \} . \tag{9}$$

Two key steps in the decomposition method consist of expressing the nonlinear operation $(N)s$ as a sum of polynomials, commonly referred to as Adomian polynomials A_k

$$(N)s = \sum_{k=0}^{\infty} A_k \tag{10}$$

and recursively generating higher-order terms of the solution. This recursive solution is based on a series solution for s, where a given order term is derived from the lower-order terms, namely,

$$s = s_0 + \sum_{k=1}^{\infty} s_k = s_0 - \left(L^{-1}\right)\left\{(R)\sum_{k=0}^{\infty} s_k\right\} - \left(L^{-1}\right)\left\{\sum_{k=0}^{\infty} A_k\right\} \tag{11}$$

or for any $k \geq 0$, the recursive relationship is given by

$$s_{k+1} = \left(L^{-1}\right)\left\{(R)s_k\right\} - \left(L^{-1}\right)A_k. \tag{12}$$

It should be noted that A_k is a function of $s_0, s_1, \ldots s_k$ only. Hence the higher-order terms are obtained recursively from the lower-order terms. The solution is obtained as a partial sum, and for practical utility it is essential that the partial sums of s_k converge rapidly to a solution of acceptable accuracy.

2.1.2. *Decomposition method applied to the Michaelis-Menten equation.* The linear operator $L = d/dt$ in Equation (1) is easily invertible; hence there is no residual linear operator R. Equation (1) can thus be expressed as

$$(L)s = -(N)s = -f\left(s\left(t\right)\right) = -\frac{V_m s}{K_m + s}. \tag{13}$$

The inverse operator L^{-1}, is given by

$$(L^{-1})s = \int_0^t s\left(x\right) dx. \tag{14}$$

The initial condition is specified as $s(0) = s_0$. There is no $g(t)$ term and the recursion reduces to

$$s_{k+1} = -(L^{-1})A_k; \ for \ all \ k \geq 0. \tag{15}$$

The problem of finding the higher-order solution terms reduces to finding A_k and integrating them. The Adomian polynomials, A_k are defined as the terms of a Taylor series of $f(s(t))$ about $t = 0$, $s = s_0$. The function $f(s(t))$ is a composite function, and its derivatives with respect to t can be expressed as a sum of the product of the derivatives of f with respect to s and derivatives of s with respect to t. Adomian [1] has shown that the polynomial A_k depends only on the derivatives of $f(s(t))$ with respect to s to an order k and the previously determined values of $s, s_0, s_1, \ldots s_k$.

Each term of the solution corresponds to a correction of a given order, and the solution itself is a partial sum. As an illustration, let us look at the first four order derived terms

$$s_1 = -tf\left(s_0\right) \tag{16}$$

$$s_2 = -\left(\frac{t}{2}\right) f^{(1)} s_1 \tag{17}$$

$$s_3 = -\left(\frac{t}{3}\right)\left(\frac{f^{(2)} s_1^2}{2} + f^{(1)} s_2\right) \tag{18}$$

$$s_4 = -\left(\frac{t}{4}\right)\left(\frac{1}{3!} f^{(3)} s_1^3 + f^{(2)} s_1 s_2 + f^{(1)} s_3\right), \tag{19}$$

where $f^{(n)}$ is the nth derivative of $f(s)$. For any $n > 0$, it is given by

$$f^{(n)} = -\left(V_m K_m\right)(n!)\left(-\frac{1}{K_m + s_0}\right)^{(n+1)}. \tag{20}$$

2.1.3. *Error computation for the decomposition solution.* For a Taylor series, the error from a partial sum is well established [6]. For a stepsize of h and a partial sum of order n, it is given by

$$Q = -\frac{h^{n+1}}{(n+1)!} \frac{d^{(n+1)} s}{dt^{(n+1)}}(x)\,; 0 < x < h. \tag{21}$$

The decomposition method, like the Runge-Kutta method which is also based on Taylor series approximation, exhibits the same order of accuracy. From an implementation point of view, the choice of a stepsize and order of approximation arise just as in the Runge-Kutta approach. The dependence of error on the stepsize and order of approximation is analyzed in later sections.

3. Materials and methods.

3.1. **Computational methods.** For solutions to the Michaelis-Menten equation based on the Lambert W function, W was evaluated using the approach described in [7]. For the differential form of the Michaelis-Menten equation, substrate concentrations were estimated using the classical second-, third-, and fourth-order Runge-Kutta solutions with a fixed stepsize [6, 16]. For the integral form of the Michaelis-Menten equation, substrate concentrations were determined using a root-solving algorithm that was based on golden section search and parabolic interpolation, details of which have been described by [12].

Although Equation (21) provides an error estimate for the decomposition solution, the time interval over which the decomposition method yields an acceptable solution is not known. While the decomposition method provides highly accurate estimates of substrate concentration in regions close to the reference point, the accuracy decreases with increased distance from the reference point. Figure 1 shows degradation of the solution as the computation point is moved away from the reference point ($s_0 = 10$ mg/L in this case). Consequently, we divide the time interval into several equally spaced subintervals, and the solution obtained at the end of these subintervals serves as the starting solution for the next subinterval. This approach is identical to the stepsize concept used in the Runge-Kutta method and also allows for a direct comparison of the performance between these two solution methods.
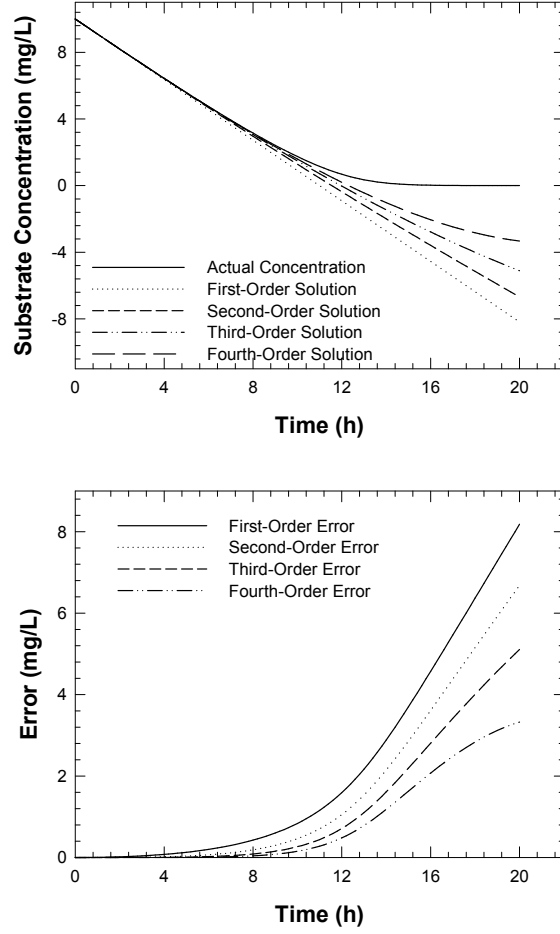
FIGURE 1. Calculation of substrate concentration in the Michaelis-Menten equation using first-, second-, third-, and fourth-order decomposition solutions (Equations 16-19). The reference point for all substrate concentration calculations is s_0. (s_0=10 mg/L, V_m=1.0 mg/L h and K_m=1.0 mg/L).

3.2. **Performance comparison of the various solution approaches.** In order to verify the accuracies of the solution methods described above, substrate depletion curves were computed using the various algorithms from Equations (1)/(2) using the initial conditions and kinetic parameters described in Table 1. Specifically, the K_m value was varied such that solutions were obtained for $s_0 : K_m$ values ranging from 0.1 to 100. The Lambert W function solution, which was accurate to double precision [13], was used as the basis for determining accuracies of the other solution methods. Comparisons were made between the W function solution and those from

the decomposition, Runge-Kutta, and root-solving methods resulting in estimates of the relative accuracies of these solution approaches.

TABLE 1. Initial conditions and kinetic parameters used for simulating substrate concentration data in the Michaelis-Menten equation

Parameter	Value
s_0	10 mg/L
V_m	1.0 mg/L h
K_m	0.1, 1, 10 and 100 mg/L

3.3. **Generation of synthetic substrate depletion data.** In order to illustrate applicability of the decomposition method solution for estimating V_m and K_m through progress curve analysis, synthetic substrate concentration data were generated from Equation (3) using the initial concentrations and kinetic parameters presented in Table 1. For the resulting error-free substrate depletion data to be representative of experimental observations, noise of known type and magnitude was introduced in the error-free substrate concentration data set. Normally distributed error with a mean of zero and standard deviations ranging from 0.25 to 1% of the magnitude of the initial substrate concentration (10 mg/L) was generated using a pseudo-random number generator. This noise was added to the error-free substrate concentration data obtained from Equation (3) and the resulting data set was used for estimating V_m and K_m using nonlinear least squares analysis.

3.4. **Kinetic parameter estimation.** The kinetic parameters V_m and K_m were estimated by minimizing the residual sum of squares error (RSSE) between synthetic and calculated substrate concentration data

$$Minimize\ RSSE = \sum_{i=1}^{n} \left\{ (s_{syn})_i - (s_{cal})_i \right\}, \tag{22}$$

where $(s_{syn})_i$ is the ith synthetic substrate concentration and $(s_{cal})_i$ is the ith calculated substrate concentration in a total of i observations. In the decomposition approach, parameter estimation was initiated by computing substrate concentrations from Equations (16)-(19) with appropriate initial estimates of the kinetic parameters V_m and K_m. In the differential equation solution approach, Equation (1) was numerically integrated using the fourth-order Runge-Kutta method, while Equation (2) along with appropriate initial V_m and K_m estimates was used to compute substrate concentrations in the root-solving approach. Subsequently, for all three approaches a comparison was made between synthetic and calculated substrate concentrations, and the RSSE was computed from Equation (22). The kinetic parameters were systematically updated using the Levenberg-Marquardt method [14] until the RSSE in Equation (22) was minimized.

4. Results.

4.1. Accuracy of the decomposition, Runge-Kutta, and root-solving methods.

Substrate concentrations in the Michaelis-Menten equation were generated
from the decomposition, Runge-Kutta, and root-solving approaches using the initial conditions and kinetic parameters from Table 1. Four sets of substrate depletion
profiles were generated using K_m values of 0.1, 1, 10, and 100 mg/L, which corresponded to $s_0 : K_m$ ratios of 100, 10, 1, and 0.1, respectively. The initial substrate
concentration, s_0, and V_m values were held constant at 10 mg/L and 1.0 mg/L
h, respectively, for all four cases. As the accuracy of both the decomposition and
Runge-Kutta methods strongly depends on the stepsize over which they are applied,
three different time stepsizes corresponding to 10, 1, and 0.1% of the entire time
interval were chosen for investigation.

In order to evaluate the influence of higher-order terms on the decomposition
solution, three separate solution sets were generated where the highest-order terms
in the series solution were second-, third-, and fourth-order, respectively. For each
of these cases, a corresponding solution was obtained using the classical second-
, third-, and fourth-order Runge-Kutta method. A comparison was then made
between solutions from the decomposition and Runge-Kutta methods with those
from the W function solution, which helped determine the error associated with
the decomposition and Runge-Kutta solutions. The magnitude of this error was
subsequently used as the termination point for solutions obtained from the root-
solving technique. It is important to note that while the decomposition and Runge-
Kutta methods are characterized by an order of approximation, the root-solving
approach requires an external specification of the desired error level.

TABLE 2. Comparison of errors in second-order decomposition,
second-order Runge-Kutta, and root-solving approaches for calculating substrate concentration in the Michaelis-Menten equation

$s_0 : K_m$	Solution	Maximum of Absolute Error		
		$h = 10\%$	$h = 1\%$	$h = 0.1\%$
	DM-2	–	2.30×10^{-3}	2.22×10^{-5}
$s_0 : K_m = 100$	RK-2	–	3.20×10^{-3}	2.00×10^{-5}
	Root	–	3.70×10^{-3}	0.38×10^{-5}
	DM-2	6.54×10^{-2}	5.95×10^{-4}	5.92×10^{-6}
$s_0 : K_m = 10$	RK-2	1.31×10^{-1}	5.76×10^{-4}	5.36×10^{-6}
	Root	3.71×10^{-2}	2.95×10^{-4}	9.92×10^{-7}
	DM-2	4.71×10^{-2}	3.68×10^{-4}	3.59×10^{-6}
$s_0 : K_m = 1$	RK-2	8.66×10^{-2}	6.64×10^{-4}	6.47×10^{-6}
	Root	2.29×10^{-2}	8.60×10^{-4}	9.97×10^{-6}
	DM-2	1.48×10^{-1}	1.13×10^{-3}	1.10×10^{-5}
$s_0 : K_m = 0.1$	RK-2	1.66×10^{-1}	1.24×10^{-3}	1.21×10^{-5}
	Root	3.72×10^{-1}	4.79×10^{-3}	1.00×10^{-5}

Table 2 shows a comparison of errors in the second-order decomposition, second-
order Runge-Kutta method, and the root-solving methods. For each value of the

$s_0 : K_m$ ratio, three different stepsizes that corresponded to 10%, 1%, and 0.1% of the time interval were used to obtain substrate concentration estimates. Based on the magnitudes of errors from these solutions, termination criteria were specified in the root-solving approach and the resulting errors from the root-solving method are also shown in Table 2.

TABLE 3. Comparison of errors in fourth-order decomposition, fourth-order Runge-Kutta, and root-solving approaches for calculating substrate concentration in the Michaelis-Menten equation

$s_0 : K_m$	Solution	Maximum of Absolute Error		
		$h = 10\%$	$h = 1\%$	$h = 0.1\%$
	DM-2	–	7.66 x 10^{-5}	6.20 x 10^{-9}
$s_0 : K_m = 100$	RK-2	–	2.14 x 10^{-4}	1.26 x 10^{-8}
	Root	–	9.90 x 10^{-6}	9.97 x 10^{-9}
	DM-2	8.54 x 10^{-3}	4.85 x 10^{-7}	4.73 x 10^{-11}
$s_0 : K_m = 10$	RK-2	2.90 x 10^{-2}	1.02 x 10^{-6}	9.19 x 10^{-11}
	Root	7.77 x 10^{-3}	2.17 x 10^{-6}	6.67 x 10^{-11}
	DM-2	7.42 x 10^{-4}	5.99 x 10^{-8}	5.88 x 10^{-12}
$s_0 : K_m = 1$	RK-2	2.00 x 10^{-3}	1.39 x 10^{-7}	1.34 x 10^{-11}
	Root	4.29 x 10^{-3}	9.05 x 10^{-7}	5.12 x 10^{-11}
	DM-2	6.09 x 10^{-4}	3.45 x 10^{-8}	3.24 x 10^{-12}
$s_0 : K_m = 0.1$	RK-2	2.08 x 10^{-3}	1.51 x 10^{-7}	1.46 x 10^{-11}
	Root	8.71 x 10^{-4}	8.38 x 10^{-8}	1.36 x 10^{-13}

Similar results are shown in Table 3 for the fourth-order solution. For the $s_0 : K_m$ ratio of 100 and a stepsize of 10%, both the decomposition and Runge-Kutta solutions grossly misrepresented substrate concentrations at low values of s. Thus error values for these cases are not presented in Tables 2 and 3. This is primarily because of the rapid switching of the substrate depletion curve from a zero-order curve to that of a first-order curve at low values of s. This rapid change in s values could not be accurately predicted by either the decomposition or the Runge-Kutta solutions over a stepsize that was 10% of the time interval. However, when the stepsize was lowered to 1% and 0.1%, accurate predictions of the substrate concentrations were possible using these methods. Several unifying themes emerge from the results shown in Tables 2 and 3 and are presented below.

4.1.1. *Comparison of error between decomposition and Runge-Kutta solutions at a fixed stepsize and solution order.* At a given $s_0 : K_m$ ratio and stepsize (h) value, the errors in the decomposition and Runge-Kutta methods are usually of the same order of magnitude for all the solution orders examined in this study. This is evident from the data presented in Tables 2 and 3 for the second- and fourth-order solutions, respectively.

4.1.2. *Dependence of decomposition and Runge-Kutta solution error on stepsize.* Another common observation from Tables 2 and 3 is the significant reduction in error with decreasing stepsize for both the decomposition and Runge-Kutta solutions.

For example, at a $s_0 : K_m$ ratio of 10, the maximum values of the absolute error decreases from 6.54 x 10^{-2} at $h = 10\%$ to 5.95 x 10^{-4} at $h = 1\%$ and to 5.92 x 10^{-6} at $h = 0.1\%$ (Table 2). Similar decreases in error were seen for the second-order Runge-Kutta solutions also (Table 2). This trend is also seen in Table 3 for the fourth-order decomposition and Runge-Kutta methods.

4.1.3. *Dependence of decomposition and Runge-Kutta solution error on solution order.* The data in Tables 2 and 3 also suggest that higher-order solutions are significantly more accurate than lower-order solutions under similar conditions of $s_0 : K_m$ ratio and stepsize. For instance, when $s_0 : K_m = 10$ and $h = 1\%$, the maximum errors from the second- and fourth-order decomposition solutions are 5.95 x 10^{-4} and 4.85 x 10^{-7}, respectively, a trend that is also reflected in the respective Runge-Kutta solutions.

4.1.4. *Dependence of decomposition and Runge-Kutta solution error on the number of computations.* A comparison of the floating point operations revealed that both the decomposition and Runge-Kutta solutions were characterized by a very similar number of computations for almost all values of $s_0 : K_m$ and at all stepsizes (data not shown). However, when the root-solving technique was used to obtain estimates of substrate concentrations that had errors comparable to those obtained from the decomposition and Runge-Kutta methods, a significantly higher number of computations were needed. Specifically, the number of floating operations was an order of magnitude higher for the root-solving approach.

5. **Discussion.** It follows from the data in the previous section that the decomposition method provides estimates of substrate concentration in the Michaelis-Menten equation that are in most cases more accurate than those obtained from the corresponding classical Runge-Kutta methods while requiring a similar number of computations to arrive at the solution. However, the primary advantage of the decomposition method over both the Runge-Kutta and root-solving methods is that it provides an algebraic expression as the solution of the Michaelis-Menten equation (Eqs. 16-19). This makes it very easy to implement the solution on a wide variety of computing platforms including the spreadsheet computing environment, the preferred method of many experimentalists.

5.1. **Application of convergence acceleration techniques.** The decomposition method produces a sequence of approximations that converge to the solution. An obvious improvement to the approximation is through the use of convergence acceleration transformations that can enhance convergence to the solution. A certain degree of success has been reported in the literature for the Michaelis–Menten equation when applied to an expansion about a reference [18-20]. Decreased computation times were observed when the Shanks transformation was applied to the fourth-order decomposition solution [5]. These improvements appear to be applicable to selected cases with one large step or a few of them.

In order to test the efficacy of convergence acceleration techniques, we evaluated solution accuracies for small stepsizes over a range of parameters. Three commonly used convergence acceleration transformations, namely- Aitken's iterated delta squared process [2], Wynn's epsilon algorithm [22,23] and Brezenski's theta algorithm [4], were applied to the five terms of a fourth-order decomposition solution. Over the range of parameters studied, no consistent increase in solution accuracy, was observed (Table 4) for any of the four algorithms. The only case

TABLE 4. Comparison of errors in the fourth-order decomposition solution with those from the application of various convergence acceleration algorithms

$s_0 : K_m$	Solution	Maximum of Absolute Error		
		$h = 10\%$	$h = 1\%$	$h = 0.1\%$
	DM-4	–	7.66 x 10^{-5}	6.20 x 10^{-9}
	Aitken	–	1.94 x 10^{-4}	3.47 x 10^{-8}
$s_0 : K_m = 100$	Iterated Aitken	–	2.14 x 10^{-4}	3.69 x 10^{-8}
	Epsilon	–	9.50 x 10^{-5}	1.00 x 10^{-8}
	Theta	–	8.30 x 10^{-4}	8.72 x 10^{-8}
	DM-4	8.54 x 10^{-3}	4.85 x 10^{-7}	4.73 x 10^{-11}
	Aitken	1.59 x 10^{-2}	2.00 x 10^{-6}	2.29 x 10^{-9}
$s_0 : K_m = 10$	Iterated Aitken	1.76 x 10^{-2}	2.17 x 10^{-6}	2.34 x 10^{-9}
	Epsilon	8.43 x 10^{-3}	7.70 x 10^{-7}	7.75 x 10^{-11}
	Theta	1.96 x 10^{-2}	1.31 x 10^{-6}	1.02 x 10^{-9}
	DM-4	7.42 x 10^{-4}	5.99 x 10^{-8}	5.88 x 10^{-12}
	Aitken	3.03 x 10^{-2}	6.38 x 10^{-7}	6.21 x 10^{-11}
$s_0 : K_m = 1$	Iterated Aitken	1.46 x 10^{-2}	6.61 x 10^{-7}	6.48 x 10^{-11}
	Epsilon	1.02 x 10^{-3}	1.05 x 10^{-7}	1.05 x 10^{-11}
	Theta	1.23 x 10^{-2}	8.44 x 10^{-7}	3.80 x 10^{-10}
	DM-4	6.09 x 10^{-4}	3.45 x 10^{-8}	3.24 x 10^{-12}
	Aitken	8.86 x 10^{-4}	6.76 x 10^{-8}	6.60 x 10^{-12}
$s_0 : K_m = 0.1$	Iterated Aitken	8.14 x 10^{-5}	7.05 x 10^{-9}	7.00 x 10^{-13}
	Epsilon	3.84 x 10^{-4}	3.68 x 10^{-8}	3.66 x 10^{-12}
	Theta	4.82 x 10^{-4}	2.86 x 10^{-8}	2.69 x 10^{-12}

where convergence acceleration seems to have made a predictable difference is the $s_0 : K_m = 0.1$ case. Both the iterated Aitken and theta algorithms increased solution accuracy for the three stepsizes used in this study. This improvement is in agreement with the conclusions reached by [21]. Both the iterated Aitken and theta algorithm perform better than other acceleration techniques like the epsilon algorithm when sequence convergence is slower than linear.

The other complicating factor here arises from progression in time with errors in starting values at each step. The original decomposition solution typically shows a sinusoidal error behavior (Fig. 3), suggestive of error compensation. When this is combined with the error introduced by the acceleration algorithms, the compound error appears to be unpredictable. These relationships for various convergence acceleration techniques will be presented in a separate manuscript. For the stepsizes considered in this study, we conclude that commonly used convergence acceleration techniques should be avoided as they do not provide consistent improvements in the accuracy of the solutions.

5.2. **Implications for practical implementation of the decomposition solution.** The decomposition solution presented in this study can be used both for
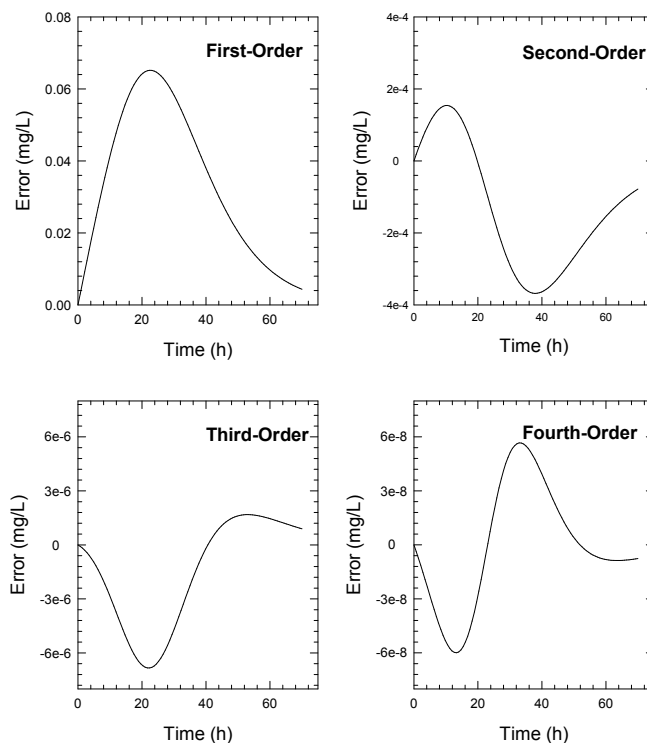
FIGURE 2. Time course of error estimates for the first-, second-, third-, and fourth-order decomposition method solutions ($s_0 = 10$ mg/L, $V_m = 1.0$ mg/L h, and $K_m = 10$ mg/L; $h = 1\%$). Mean and maximum values of absolute error are shown in Table 5.

simulation as well as for estimating the kinetic parameters V_m and K_m from experimental substrate depletion versus time data. Depending on the desired accuracy in substrate concentrations, the decomposition method can be applied in several ways to arrive at the solution. Our data clearly indicate that increased accuracies can be obtained either by using higher-order solutions or by decreasing the stepsize. The impact of higher-order terms on solution accuracy is presented in Figure 2 where error profiles for first, second, third, and fourth-order decomposition solutions are shown for $s_0 : K_m = 1$. Significant decreases in error are seen with increasing order and the mean and maximum values of the absolute errors at varying solution orders are shown in Table 5. There is approximately two orders of magnitude decrease in the mean value of the errors for an increase in the order of the solution. This reduction in the error by increasing the solution order comes at a price. The number of terms required for computation of the solution grows very rapidly with increasing order in accordance with the Hardy-Ramanujam-Rademacher formula [3]. In addition, the elegance and simplicity of a low-order solution are lost as we move to higher orders. Increasing accuracies can also be obtained by decreasing stepsizes as shown in Figure 3 for $s_0 : K_m = 1$. Reduction in stepsize from 10% to 1% and subsequently to 0.1% resulted in maximum absolute error values of 7.42 x10^{-4}, 5.99 x 10^{-8}, and 5.88 x 10^{-12}, respectively. This is in agreement with the error estimate provided by Equation (21).
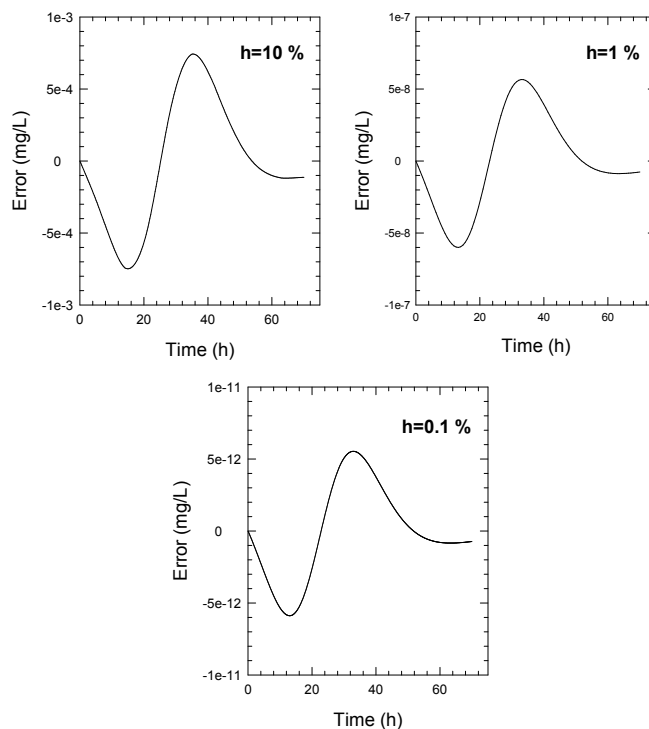
FIGURE 3. Time course of error estimates for the fourth-order decomposition solutions at $s_0 : K_m = 1$ and stepsizes of 10%, 1%, and 0.1%.

TABLE 5. Mean and maximum errors for different order decomposition solutions

No. of Terms	Absolute Mean Error	Absolute Maximum Error
2	3.37×10^{-2}	6.52×10^{-2}
3	1.91×10^{-4}	3.68×10^{-4}
4	2.62×10^{-6}	6.84×10^{-6}
5	2.68×10^{-8}	5.99×10^{-8}

For all practical purposes, accuracies on the order of 10^{-5} are sufficient as experimental data are often characterized by significantly higher inaccuracies. If one desires to use the second-order decomposition solution, a stepsize of 0.1% or lower must be used to obtain the desired accuracy (Table 2), while a fourth-order solution with a stepsize of 1% will result in solutions that have accuracies on the order of 10^{-6} or higher (Table 3). It is our recommendation that the fourth-order decomposition solution with a stepsize of 0.1% be used for solving the Michaelis-Menten equation at all $s_0 : K_m$ ratios as it results in substrate concentration errors that are less than 10^{-8}.

5.3. **Application of the decomposition solution for estimation of V_m and K_m from progress curve data.** The applicability of the decomposition solution
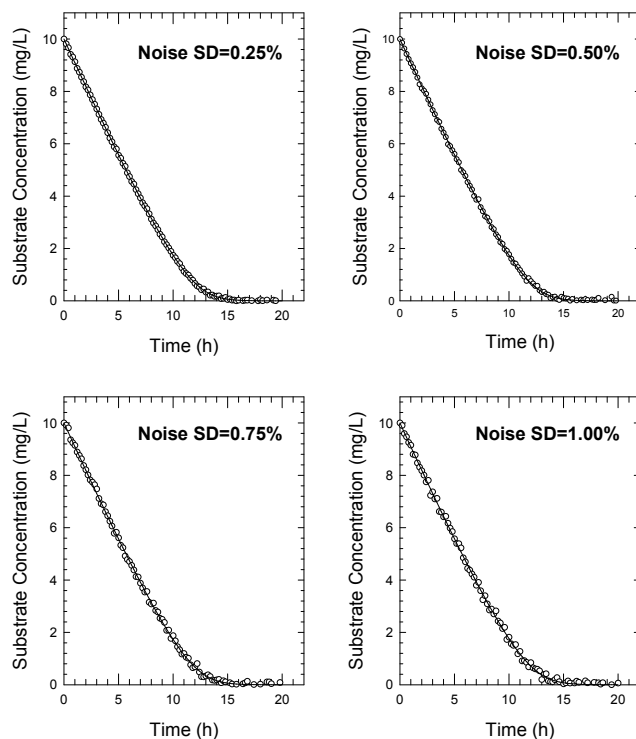
FIGURE 4. Synthetic substrate concentration data (points) along with calculated values (solid lines) from the fourth-order decomposition solution and the best fit kinetic parameters in Table 6. Synthetic substrate concentration data were characterized by normally distributed noise with a mean value of zero and standard deviations of 0.25, 0.5, 0.75, and 1.0% of the initial substrate concentration of 10 mg/L.

for nonlinear kinetic parameter estimation from progress curve data was verified using synthetic substrate depletion data obtained from Equation (3) and $s_0 = 10$ mg/L, $V_m = 1$ mg/L h, and $K_m = 1.0$ mg/L. This resulting error-free substrate depletion data set was superimposed with normally distributed noise of varying magnitude to be representative of experimental data. Figure 4 shows synthetic substrate concentration data along with calculated values from the fourth-order decomposition solution ($h = 0.1\%$) corresponding to the best fit kinetic parameters shown in Table 6. For the substrate concentration data sets characterized by 0.25% and 0.5% noise, final estimates of V_m and K_m were very close to the actual values of 1.0 mg/L h and 1.0 mg/L, respectively. Higher deviation from actual values was seen with increasing noise, especially for K_m that had a final estimate of 1.065 ± 0.064 mg/L at a noise level of 1%. Standard errors for both V_m and K_m increased with increasing noise levels, and the off-diagonal element of the parameter correlation matrix was greater than 0.96 for all cases indicating some parameter correlation. Identical kinetic parameter estimates were obtained when the above substrate concentration data was analyzed using the differential equation

solution and root-solving approaches (data not shown). This is to be expected as the fourth-order decomposition solution with $h = 0.1\%$ approximates the substrate concentration with an accuracy on the order of 10^{-8} (Table 3), while the synthetic substrate depletion data were characterized by accuracies on the order of 10^{-3}.

TABLE 6. Final kinetic parameter estimates obtained through non-linear parameter estimation from synthetic substrate concentration data

Error (% of s_0)	V_m (mg/L h)	K_m (mg/L)	RMS Error	Correlation
0.25%	0.999 ± 0.003	1.003 ± 0.016	0.7 x 10^{-3}	0.968
0.50%	1.003 ± 0.006	1.011 ± 0.034	2.9 x 10^{-3}	0.968
0.75%	1.003 ± 0.008	1.007 ± 0.050	6.4 x 10^{-3}	0.968
1.00%	1.008 ± 0.011	1.065 ± 0.064	0.1 x 10^{-3}	0.968

It should be noted that the above nonlinear parameter estimation exercise for the Michaelis-Menten equation can be readily performed using the Lambert W function as shown in [13]. However, application of the decomposition method to the Michaelis-Menten equation provides a "proof of concept," as the results can be easily compared with the practically exact Lambert W solution. This allows for a clear quantification of errors associated with the decomposition solution, something which was not addressed in earlier studies of the same solution [5, 18-20]. For most other kinetic expressions that do not reduce to a form analogous to the Michaelis-Menten equation, closed-form solutions that are explicit in the substrate concentration are not available. Simulation of substrate concentrations in these kinetic expressions and nonlinear parameter estimation from experimental data will greatly benefit from algebraic solutions such as those which can be obtained from the decomposition method. This is currently being investigated and will be presented in subsequent manuscripts.

6. **Conclusions.** We have presented a low-order recursive solution to the Michaelis-Menten equation based on the decomposition method. The error characteristics of this solution have been described in detail, and this solution is slightly more accurate than a solution obtained from the corresponding fixed stepsize Runge-Kutta methods. Perhaps the most important feature of this decomposition solution is it replaces numerical solutions of the integral and differential forms of the Michaelis-Menten equation with the evaluation of a simple algebraic expression, a task that can be readily accomplished on a spreadsheet. While results of any desired accuracy can be obtained from the decomposition solution through an appropriate selection of solution order and stepsize, we recommend using the fourth-order solution (Equations 16-19) with a stepsize corresponding to 0.1% of the time interval. This will result in estimates of substrate concentration that are characterized by accuracies on the order of 10^{-8} or better, which should be adequate for most simulation and nonlinear kinetic parameter estimation applications. This new solution, which is algebraic in nature, simplifies computation of substrate concentration in the Michaelis-Menten equation and should make progress curve analysis more attractive for estimating V_m and K_m through the nonlinear least squares approach.

REFERENCES

[1] G. Adomian, "Solving Frontier Problems in Physics: The Decomposition Method," Kluwer Academic Publishers, Dordrecht, 1994.

[2] A. C. Aitken, *On Bernoulli's numerical solution of algebraic equations*, Proceedings of the Royal Society, Edinburgh, **46** (1926), 289–305.

[3] G. E. Andrews, "The Theory of Partitions," Vol. 2, Addison-Wesley, Reading, Massachusetts, 1976.

[4] C. Brezinski, *Accélération de suites à convergence logarithmique*, C. R. Acad. Sci. Paris, **273** (1971), 727–730.

[5] B. T. Bullman and P. W. Kuchel, *Comparison of biochemical simulations using integrators derived from "Adomian" decomposition with traditional methods*, Biomedica Biochimica Acta, **8/9** (1990), 661–670.

[6] S. C. Chapra and R. P. Canale, "Numerical Methods for Engineers: With Programming and Software Applications," McGraw-Hill, New York, 1998.

[7] R. M. Corless, G. H. Gonnet, D. E. Hare, D. J. Jeffrey and D. E. Knuth, *On the Lambert W function*, Advances in Computational Mathematics, **5** (1996), 329–359.

[8] A. Cornish-Bowden, "Fundamentals of Enzyme Kinetics," Portland Press Ltd., London, 1995.

[9] R. G. Duggleby, *Analysis of enzyme progress curves by non-linear regression*, Methods in Enzymology, **249** (1995), 61–90.

[10] R. G. Duggleby, *Analysis of progress curves for enzyme-catalyzed reactions: Application to unstable enzymes, coupled reactions and transient-state kinetics*, Biochimica et Biophysica Acta, **1205** (1994), 268–274.

[11] R. G. Duggleby, *Quantitative analysis of the time course of enzyme catalyzed reactions*, Methods, **24** (2001), 168–174.

[12] G. E. Forsythe, M. A. Malcolm and C .B. Moler, "Computer Methods for Mathematical Computations," Prentice-Hall, Englewood Cliffs, NJ, 1976.

[13] C. T. Goudar, J. R. Sonnad and R. G. Duggleby, *Parameter estimation using a direct solution of the integrated Michaelis-Menten equation,* Biochimica et Biophysica Acta, **1429** (1999), 377–383.

[14] D. W. Marquardt, *An algorithm for least squares estimation of nonlinear parameters*, Journal of the Society for Industrial and Applied Mathematics, **11** (1963), 431–441.

[15] L. Michaelis and M. L. Menten, *Die kinetik der invertinwirkung*, Biochemistry Z, **49** (1913), 333–369.

[16] W. H. Press, S. A. Teukolsky, W. T. Vettering and B. B. Flannery, "Numerical Recipies in FORTRAN: The art of scientific computing," Cambridge University Press, New York, 1992.

[17] S. Schnell and C. Mendoza, *Closed form solution for time-dependent enzyme kinetics*, Journal of Theoretical Biology, **187** (1997), 207–212.

[18] A. Sen, *An application of the Adomian decomposition method to the transient behavior of a model biochemical reaction*, Journal of Mathematical Analysis and Applications, **131** (1988), 232–245.

[19] A. Sen, *An approximate solution for the transient behavior of enzyme-catalyzed reactions: The irreversible Michaelis-Menten kinetics*, Mathematical Biosciences, **85** (1987), 141–151.

[20] A. Sen, *On the time course of the reversible Michaelis-Menten reaction*, Journal of Theoretical Biology, **135** (1988), 483–493.

[21] E. J. Weniger, *Prediction properties of Aitken's iterated Δ^2 process, of Wynn's epsilon algorithm and of Brezinski's iterated theta algorithm*, Journal of Computational and Applied Mathematics, **122** (2000), 329–356.

[22] P. Wynn, *On a device for computing the $e_m(S_n)$ transformation*, Mathematical Tables Aids Computation, **10** (1956), 91–96.

[23] P. Wynn, *On the convergence and the stability of the epsilon algorithm*, SIAM Journal of Numerical Analysis, **3** (1966), 91–122.

[24] C. T. Zimmerle and C. Frieden, *Analysis of progress curves by simulations generated by numerical integration*, Biochemical Journal, **258** (1989), 381–387.

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