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Explicit Solutions for Real-time Reversible Inhibition Kinetics using Lambert *W* Function: Towards Progress Curve Analysis

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Abstract

Accurate estimation of kinetic parameters is challenging due to the dynamics and mathematical nature of the chemical systems. This paper presents simple, yet efficient closed-form solutions for the enzymatic conversion of the substrate to the product in real-time derived using the Lambert *W* function. The real values of the Lambert *W* function were calculated from the Lambert package as implemented in MATLAB. The expressions exhibit remarkable robustness in estimating the parameters for randomized data at 1% to 4% variation in noise levels. Furthermore, unlike the initial rates method, the expressions estimate chemical kinetic parameters utilizing a full range of experimental data, thus minimizing the risk of missing information that would be detected at an extended time-span. Thus, the implementation of closed-form solutions presented in this paper for the estimation of kinetic parameters eliminates common pitfalls imposed by the initial rates and double reciprocal methods.

Keywords: Enzyme, Lambert *W* function, Reversible inhibition, Closed-form solutions.

Introduction

The Michaelis-Menten kinetics has been the foundation on which most quantitative analyses involving enzymatic reactions are built today (Liu et al. 2022, Blomhøj and Niss 2021, Abedanzadeh et al. 2022, Cho and Lim 2018). Michaelis-Menten kinetics has been a tool for the description of biochemical reactions, such as those found in drug metabolism (Rubin and Tozer 1986, Kim and Tyson 2020, Seibert and Tracy 2021); non-linear pharmacokinetics (Emanuelsson et al. 1987, Ludden 1991, Singh et al. 2021, Wilson and Gerber 2021), alcoholic fermentation (Gee and Ramirez 1988, Gee and Ramirez 1994), protein binding (Kim and Tyson 2020) and cell density distribution (Magliaro et al. 2019).

However, the determination of kinetic parameters is becoming difficult nowadays following the increased complexity of chemical reactions, for example, estimating kinetic parameters in a chemical system involving multi-step reactions. Therefore, simplified means for data analysis of such complex systems are often thought. For example, the determination of kinetic parameters such as Michaelis-Menten constant K_m and maximum reaction velocity V_{max} usually are performed through a double reciprocal plot which Lineweaver and Burk first developed in their original article (Lineweaver and Burk 1934). However, accurate estimation parameters through this technique requires a large amount of data and substrate concentration higher than K_m values (Bäuerle et al. 2017). Furthermore, a linearized Lineweaver-Burk plot involves data transformation that can result in severe drawbacks such as distortion error which may lead to biased parameter estimates (Zavrel et al. 2010).

In contrast, a non-linear fit of the initial reaction rates to the Michaelis-Menten expression has been a popular method whose popularity is supported by the initial linear region on the reaction progress curve. This linearity holds only at the assumption that only 10% of substrate concentration is converted into product. Nevertheless, the initial rate method has limitations, such as being sensitive to noise and becoming laborious to measure. Additionally, the method cannot be used to determine the phenomenon occurring at longer time intervals (Zavrel et al. 2010). Aside from those drawbacks, Cornish-Bowden questioned the linear fitting of data to the expression, claiming that only a 1% conversion is acceptable for defining initial rates. To elaborate, the author asserted that while the reaction progress curve may appear linear in the given range, an imperceptible non-linearity that is invisible to the human eye may occur, influencing the quality of the estimated parameters (Cornish-Bowden 2013, González et al. 2017).

To address challenges observed by Cornish-Bowden, it has been recommended that the reaction progress curve be divided into approximate linear portions where gradients are evaluated for each linear piece, eventually extrapolating the varying slope to zero time (Baici 2015). The first- derivative with respect to time, set at time zero, can be used to compute the initial reaction rate for each best-fit non-linear model curve. However, rather than considering the presumed linear region, it is recommended that a more precise technique could be contemplating a non-linear fit for the entire reaction progress curve to all experimental data and extracting kinetic parameters of interest. The adoption of numerical schemes such as bi-section and Newton-Raphson methods to numerically integrated differential equations representing the dynamics of substrate depletion and product generation is the ideal instrument for achieving the suggested strategy. On the other hand, inadequate programming skills and individuals' mathematical backgrounds obstruct the implementation. Therefore, searching for a simple yet efficient and user-friendly approach to minimize the limitations mentioned is paramount to bridging the gap. Thus, this work aims to present and demonstrate an efficient approach based on the Lambert W function for determining kinetic parameters. The paper presents a brief yet precise description of the derivation of explicit solutions of substrate concentrations on kinetic reactions analogous to the Michaelis-Menten based on the Lambert W function. Briefly, the remaining vignettes demonstrate the determination of the kinetic parameters and illustrate with examples the use of the derived expressions using the MATLAB package.

Methods

Theoretical framework

We have considered a reversible inhibition when the inhibitor binds to both the free enzyme and the enzyme-substrate complex with varying affinities. Therefore, the inhibitor free mixed inhibition, competitive inhibition, noncompetitive inhibition and uncompetitive inhibition reaction models have been used to derive the time-dependent explicit solution of substrate conversion.

Lambert W function

The Lambert W function is a mathematical expression popular in many fields and known for its high accuracy in parameter estimation. However, the literature's description of Lambert W function to reversible inhibition kinetics is limited, especially in estimating kinetic parameters (Kesisoglou et al. 2021). Therefore, deriving expressions that describe substrate depletion and product accumulation over time can help achieve better-estimated parameters rather than the techniques based on initial velocity and other methods to estimate kinetic parameters, as discussed earlier in the introduction section. The general form of the Lambert W function is defined as the inverse function satisfying the transcendental Equation 1 (Goličnik 2012):

$$x = ye^{y} \qquad (1)$$

and the solution to Equation 1 is expressed by the Lambert *W* function as:

$$y = W(x) \qquad (2)$$

where *W* is the Lambert *W* function and x the argument of *W*. In particular, if x is real, $W(x)$ is double-valued in the range $(-e^{-1}, 0)$. Then if we consider $W \geq -1$ and $W \leq -1$, the two are well-defined functions. Thus, the Lambert *W* function has two branches of the solution, namely W_0 and W_{-1}. The branch satisfying $W(x) \geq -1$ is known as the principal branch, denoted by W_0, while the one satisfying $W(x) \leq -1$ is known as the lower branch, represented by W_{-1}. The two branches are demonstrated in Figure 1.

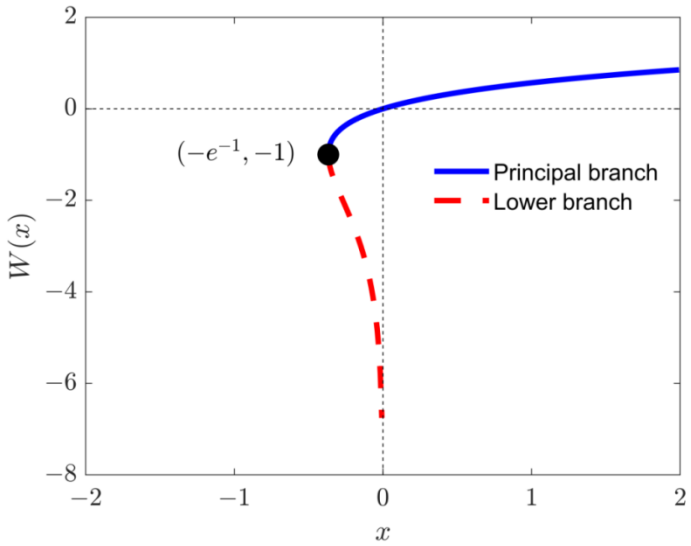

Figure 1: The plot of principal branch W_0 and the lower branch W_{-1} of Lambert *W* function.

For simplicity, we shall write W_0 simply as *W*. The branch *W* has real values in the range $(-e^{-1}, \infty)$. The following are special values for the Lambert *W* function:

$$\begin{cases} W(-e^{-1}) = -1 \\ W(0) = 0 \\ W(1) \approx 0.56714329 \end{cases} \qquad (3)$$

Lambert *W* function has self-decomposable property, which is the consequence of the ordinary differential equation (Pakes 2018):

$$\frac{dW(x)}{dx} = \frac{W(x)}{x(1+W(x))} \qquad (4)$$

The integrated form of Equation 4 *is* as follows:

$$\int W(x)\mathrm{d}x = x\left(W(x) - 1 + \frac{1}{W(x)}\right) + C \qquad (5)$$

where *C* is the constant of integration. Equations 4 and 5 are valid for $W(x) \neq -1$ and $W(x) \neq 0$, that is $x \neq -e^{-1}$ and $x \neq 0$, respectively (Consigli et al. 2017).

Results

Michaelis-Menten model: Inhibition free

The initial rate of metabolism by an enzyme following classical Michaelis-Menten enzyme kinetics is proportional to the concentration of the enzyme-substrate complex (Ring et al. 2014). The ordinary differential equation used to describe the dynamics of substrate concentration depletion is presented by Equation 6.

$$v = -\frac{d[S]_t}{dt} = \frac{d[P]_t}{dt} = \frac{V_{\max}[S]_t}{K_m + [S]_t} \qquad (6)$$

The integral form of Michaelis-Menten for first-order differential Equation 6 is as shown in Equation 7.

$$V_{\max} t = K_m \ln\left(\frac{[S]_0}{[S]_t}\right) + [S]_0 - [S]_t \qquad (7)$$

where v is the rate of reaction; $[S]_t$ is the concentration of substrate; $[P]_t$ is the concentration of the product; $V_{\max}$ is the maximal enzyme activity and K_m is the Michaelis-Menten half saturation constant. Following a systematic derivation through

Equations 8-11, Equation 12 is the explicit solution for substrate concentration as a function of time for free inhibitor model.

$$[S]_t = [S]_0 \exp\left(\frac{[S]_0 - [S]_t - tV_{\max}}{K_m}\right) \quad (8)$$

$$[S]_t \exp\left(\frac{[S]_t}{K_m}\right) = [S]_0 \exp\left(\frac{[S]_0 - tV_{\max}}{K_m}\right) \quad (9)$$

$$\frac{[S]_t}{K_m} = W\left[\frac{[S]_t}{K_m} \exp\left(\frac{[S]_t}{K_m}\right)\right] \quad (10)$$

$$= W\left[\frac{[S]_0}{K_m} \exp\left(\frac{[S]_0 - tV_{\max}}{K_m}\right)\right] \quad (11)$$

$$[S]_t = K_m W\left[\frac{[S]_0}{K_m} \exp\left(\frac{[S]_0 - tV_{\max}}{K_m}\right)\right] \quad (12)$$

Mixed inhibition

Mixed-type inhibitors bind to both enzyme-substrate complex and free enzymes. They affect both substrate binding and the catalyzed reaction rate, leading to the variations of both K_m and V_{max}. This effect decreases the value of V_{max} while decreasing or increasing K_m value. These interactions result in the rate Equation 13:

$$v = -\frac{d[S]_t}{dt} = \frac{d[P]_t}{dt} = \frac{V_{\max}[S]_t}{K_m\left(1+\frac{[I]}{K_{ic}}\right)+[S]_t\left(1+\frac{[I]}{K_{iu}}\right)} \quad (13)$$

where [I], inhibitor concentration; K_{ic}, inhibitor dissociation constant of enzyme-inhibitor complex and K_{iu}, inhibitor dissociation constant of enzyme-substrate-inhibitor complex. The simplification of mixed type of inhibition model gives rise to other inhibition models with fewer constants namely, competitive, noncompetitive, uncompetitive and inhibition-free (Ring et al. 2014). Let,

$$\mathcal{X} = \left(\frac{[I]}{K_{ic}}\right)$$

$$\xi = 1 + \frac{[I]}{K_{iu}}$$

The integrated form of Equation 13 is:

$$V_{\max} t = \mathcal{X} K_m \ln\frac{[S]_0}{[S]_t} + ([S]_0 - [S]_t)\xi \quad (14)$$

Equation 14 is implicit with respect to the substrate concentration. To obtain the explicit form, Equation (14) is rearranged as follows:

$$[S]_t = [S]_0 \exp\left(\frac{\xi([S]_0 - [S]_t - tV_{\max})}{K_m \mathcal{X}}\right) \quad (15)$$

$$[S]_t \exp\left(\frac{\xi[S]_t}{K_m \mathcal{X}}\right) = [S]_0 \exp\left(\frac{\xi([S]_0 - [S]_t - tV_{\max})}{K_m \mathcal{X}}\right) \quad (16)$$

Multiply through to (16) by the factor $\xi/K_m\mathcal{X}$ yields:

$$\frac{\xi[S]_t}{K_m \mathcal{X}} \exp\left(\frac{\xi[S]_t}{K_m \mathcal{X}}\right) = \frac{\xi[S]_0}{K_m \mathcal{X}} \exp\left(\frac{\xi[S]_0 - tV_{\max}}{K_m \mathcal{X}}\right) \quad (17)$$

$$\frac{\xi[S]_t}{K_m \mathcal{X}} = W\left[\frac{\xi[S]_0}{K_m \mathcal{X}} \exp\left(\frac{\xi[S]_0 - tV_{\max}}{K_m \mathcal{X}}\right)\right] \quad (18)$$

$$[S]_t = \frac{K_m \mathcal{X}}{\xi} W\left[\frac{\xi[S]_0}{K_m \mathcal{X}} \exp\left(\frac{\xi[S]_0 - tV_{\max}}{K_m \mathcal{X}}\right)\right] \quad (19)$$

Equation (19) presents real-time substrate concentration depletion.

Competitive inhibition

In this case, the inhibitor competes with substrates for the active sites on the enzyme. The reaction rate is obtained by considering $K_{iu} \to \infty$, and thus $[I]/K_{iu} \to 0$ in (13).

$$v = -\frac{d[S]_t}{dt} = \frac{d[P]_t}{dt} = \frac{V_{\max}[S]_t}{K_m\left(1+\frac{[I]}{K_{ic}}\right)+[S]_t} \quad (20)$$

The integral form of Equation (20) is as follows:

$$V_{\max} t = K_m \mathcal{X} \ln\left(\frac{[S]_0}{[S]_t}\right) + ([S]_0 - [S]_t) \quad (21)$$

The implicit Equation (21) is rearranged to obtain the expression in explicit solution in terms of substrate concentration as:

$$[S]_t = [S]_0 \exp\left(\frac{[S]_0 - [S]_t - tV_{\max}}{K_m \mathcal{X}}\right) \quad (22)$$

$$[S]_t \exp\left(\frac{[S]_t}{K_m \mathcal{X}}\right) = [S]_0 \exp\left(\frac{([S]_0 - tV_{\max})}{K_m \mathcal{X}}\right) \quad (23)$$

Multiplying Equation (23) by the factor $(K_m\mathcal{X})^{-1}$ and rearranging the resultant equation gives:

$$\frac{[S]_t}{K_m \mathcal{X}} \exp\left(\frac{[S]_t}{K_m \mathcal{X}}\right) = \frac{[S]_0}{K_m \mathcal{X}} \exp\left(\frac{[S]_0 - tV_{\max}}{K_m \mathcal{X}}\right) \quad (24)$$

Employing Lambert W function to Equation 24 leads to the following:

$$\frac{[S]_t}{K_m \mathcal{X}} = W\left[\frac{[S]_t}{K_m \mathcal{X}} \exp\left(\frac{[S]_t}{K_m \mathcal{X}}\right)\right] \quad (25)$$

$$= W\left[\frac{[S]_0}{K_m \mathcal{X}} \exp\left(\frac{[S]_0 - tV_{\max}}{K_m \mathcal{X}}\right)\right] \quad (26)$$

$$[S]_t = K_m \mathcal{X} W\left[\frac{[S]_0}{K_m \mathcal{X}} \exp\left(\frac{[S]_0 - tV_{\max}}{K_m \mathcal{X}}\right)\right] \quad (27)$$

Equation 27 presents an explicit solution governing time-dependent substrate depletion in the competitive type of inhibition.

Noncompetitive inhibition

Unlike competitive inhibition, where an inhibitor binds to the active site, in this type of inhibition, the inhibitor does not affect substrate binding; instead, entering the active site attaches itself to some other parts of the enzyme molecule. Noncompetitive inhibitors

can either bind to the enzyme alone or enzyme-substrate complex causing the V_{max} to decrease, while the K_m remains unaffected. In general, noncompetitive inhibition decreases the amount of enzyme capable of mobilizing the substrate. The rate of the reaction is given by:

$$v = -\frac{d[S]_t}{dt} = \frac{d[P]_t}{dt} = \frac{V_{\max}[S]_t}{(K_m+[S]_t)\left(1+\frac{[I]}{K_{ic}}\right)} \quad (28)$$

The integral form for noncompetitive inhibition first order differential Equation 28 is as follows:

$$V_{\max}t = \mathcal{X}\left[K_m \ln\left(\frac{[S]_0}{S}\right) + [S]_0 - [S]_t\right] \quad (29)$$

The implicit Equation 29 is rearranged to an explicit form solution in terms of substrate concentration through the following steps:

$$[S]_t = [S]_0 \exp\left(\frac{[S]_0-[S]_t}{K_m} - \frac{tV_{\max}}{K_m\mathcal{X}}\right) \quad (30)$$

$$[S]_t \exp\left(\frac{[S]_t}{K_m}\right) = [S]_0 \exp\left(\frac{[S]_0}{K_m} - \frac{tV_{\max}}{K_m\mathcal{X}}\right) \quad (31)$$

Multiply through to Equation 31 by the term K_m^{-1} results into:

$$\frac{[S]_t}{K_m}\exp\left(\frac{[S]_t}{K_m}\right) = \frac{[S]_0}{K_m}\exp\left(\frac{[S]_0}{K_m} - \frac{tV_{\max}}{K_m\mathcal{X}}\right) \quad (32)$$

Introducing Lambert *W* function to the left-hand side of Equation 32, we obtain the following:

$$\frac{[S]_t}{K_m} = W\left[\frac{[S]_t}{K_m}\exp\left(\frac{[S]_t}{K_m}\right)\right]$$
$$= W\left[\frac{[S]_0}{K_m}\exp\left(\frac{[S]_0}{K_m} - \frac{tV_{\max}}{K_m\mathcal{X}}\right)\right]$$

The explicit solution for the time-dependent substrate for a noncompetitive inhibition regime is:

$$[S]_t = K_m W\left[\frac{[S]_0}{K_m}\exp\left(\frac{[S]_0}{K_m} - \frac{tV_{\max}}{K_m\mathcal{X}}\right)\right] \quad (33)$$

Uncompetitive inhibition

For uncompetitive inhibition, the inhibitor has no affinity for the free enzyme. Thus, it binds to the enzyme-substrate complex and reduces V_{max} and K_m values. It means that as $K_{ic} \to \infty$, the term $[I]/K_{ic} \to 0$ in Equation 13. The ordinary differential Equation 34 is the rate equation for uncompetitive inhibition:

$$v = -\frac{d[S]_t}{dt} = \frac{d[P]_t}{dt} = \frac{V_{\max}[S]_t}{K_m+[S]_t\left(1+\frac{[I]}{K_{iu}}\right)} \quad (34)$$

Equation 35 represents enzyme kinetic time course information through the integrated form of uncompetitive type of inhibition.

$$V_{\max}t = K_m \ln\left(\frac{[S]_0}{[S]_t}\right) + ([S]_0 - [S]_t)\xi \quad (35)$$

An explicit solution can be obtained by rearranging Equation 36 into a few steps:

$$[S]_t = [S]_0 \exp\left(\frac{\xi[S]_0-[S]_t-tV_{\max}}{K_m}\right) \quad (36)$$

$$[S]_t \exp\left(\frac{\xi[S]_t}{K_m}\right) = [S]_0 \exp\left(\frac{\xi[S]_0-tV_{\max}}{K_m}\right) \quad (37)$$

Multiplying ξ/K_m to Equation 37 yields Equation 38:

$$\frac{\xi[S]_t}{K_m}\exp\left(\frac{\xi[S]_t}{K_m}\right) = \frac{\xi[S]_0}{K_m}\exp\left(\frac{\xi[S]_0-tV_{\max}}{K_m}\right) \quad (38)$$

Introducing Lambert *W* function techniques, we have:

$$\frac{\xi[S]_t}{K_m} = W\left[\frac{\xi[S]_0}{K_m}\exp\left(\frac{\xi[S]_0-tV_{\max}}{K_m}\right)\right] \quad (39)$$

$$[S]_t = \frac{K_m}{\xi}W\left[\frac{\xi[S]_0}{K_m}\exp\left(\frac{\xi[S]_0-tV_{\max}}{K_m}\right)\right] \quad (40)$$

Following a systematic derivation, Equations 12, 19, 27, 33 and 40 represent the closed-form solutions for the progress of the substrate concentration, $[S]_t$ for the enzyme kinetics at any time, *t* relative to initial concentration $[S]_0$, described using the Lambert *W* function. The concentration of the product at any time is obtained by applying the following expression:

$$[P]_t = [S]_0 - [S]_t \quad (41)$$

for the inhibitor-free; where for the case of the presence of inhibition, the real-time concentration of product is governed by the following expression:

$$[P]_t = [P]_0 + [S]_0 - [S]_t \quad (42)$$

where $[P]_0$ is the initial product concentration. Equations 41 and 42 help predict the time a reaction takes to yield a certain amount of product and vice versa, depending on the information available. The expressions can fit the real-time experimental data, thus making it possible to estimate all kinetic parameters by utilizing codes implemented in MATLAB and R packages. The estimation of kinetic parameters involves the minimization of the residual sum of square errors (RSSE) between the observed and calculated values

$$\text{RSSE} = \sum_{i=0}^{N-1}\left[S_i^{\exp}(t) - S_i^{\text{calc}}(t)\right]^2 \quad (43)$$

where $S_i^{\exp}(t)$ is the i^{th} observed experimental concentration of substrate at time *t*, $S_i^{\text{calc}}(t)$ represents i^{th} calculated values for substrate at time *t* in a total of N observations. The process of estimating parameters involves finding an optimal fit; the parameters in question are varied to find

the function that mimics the time course of the reaction. The small value of RSSE indicates a tight fit of the model to experimental data. Eventually, parameters are derived directly via a complex function.

Discussion

The demonstration of the explicit solutions 12, 19, 27, 33 and 40 for applicability on the estimation of kinetic parameters was performed. Experimental uncertainties were simulated by adding noise to substrate concentration using a pseudo-random number generator at the mean of zero and standard deviation (SD) values ranging from 1% to 4%. The ideal values for the kinetic parameters K_m, V_{max}, K_{ic} and K_{iu} were fixed to 1.000 µM. Figure 2 demonstrates the progress curve analysis for the simulated data fitted with the derived equations for an initial concentration of 10 µM.

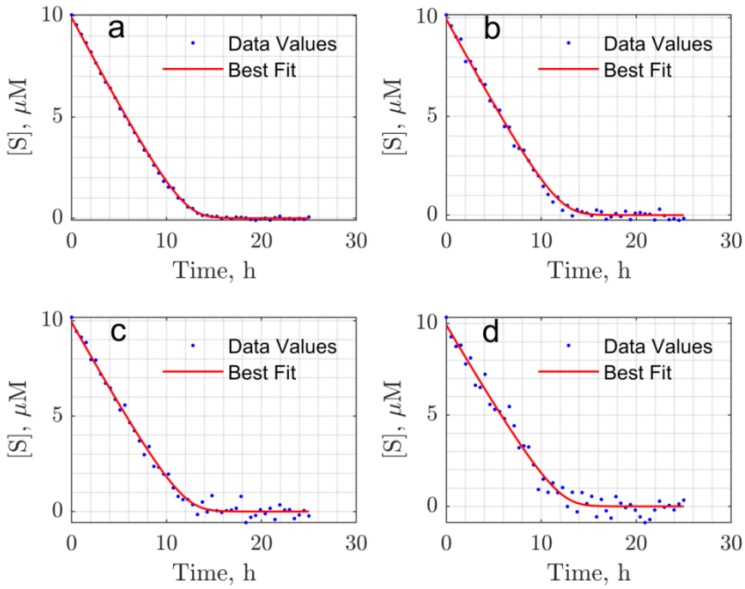

Figure 2: Progress curve analysis with model predictions (solid red lines) fitted to simulated substrate depletion data points (blue dots).

The estimated kinetic parameters for mixed, competitive, noncompetitive and uncompetitive are presented in Table 1 to Table 4, respectively. The results show that, even at a higher noise level of up to 4%, the estimated values are closer to the ideal values despite the relatively large error component. It is important to point out that we used the Lambert *W* function as implemented in MATLAB to solve a least-squares problem instead of nonlinearFit. One would anticipate Lambert *W* function to be faster than nonlinearfit for this purpose.

Table 1: Mixed inhibition

SD, µM	K_m, µM	V_{max}, µM h^{-1}	K_{iu}, µM	K_{ic}, µM	RSSE
0.01	1.006	1.006	1.001	0.988	0.001
0.02	0.976	0.978	0.999	1.049	0.023
0.03	0.985	0.990	1.009	1.025	0.030
0.04	1.103	1.143	1.002	0.768	0.070

Table 2: Competitive inhibition

SD, µM	K_m, µM	V_{max}, µM h^{-1}	K_{ic}, µM	RSSE
0.01	1.000	1.000	1.000	0.003
0.02	0.997	0.997	0.997	0.051
0.03	0.997	0.996	0.997	0.084
0.04	1.000	1.001	1.000	0.141

Table 3: Noncompetitive inhibition

SD, µM	K_m, µM	V_{max}, µM h^{-1}	K_{ic}, µM	RSSE
0.01	1.000	1.003	1.000	0.001
0.02	1.008	1.022	1.008	0.042
0.03	1.000	1.000	1.000	0.083
0.04	1.000	1.016	1.000	0.179

Table 4: Uncompetitive inhibition

SD, µM	K_m, µM	V_{max}, µM h^{-1}	K_{iu}, µM	RSSE
0.01	0.996	0.995	1.010	0.000
0.02	0.999	0.999	1.002	0.050
0.03	0.967	0.968	1.069	0.089
0.04	1.003	1.003	0.994	0.164

We also present in Figure 3 the residual sum of squares error (RSSE) that illustrates the errors during model fitting. The RSSE quantifies the degree of the accuracy of the method. At low standard deviation, the model fits well to the simulated values resulting in lowest RSSE values.

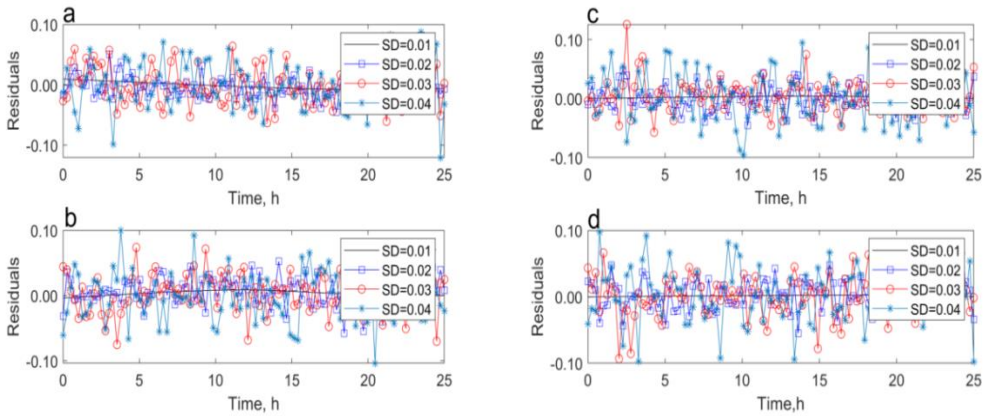

Figure 3: The plots for the residual sum of squares error (RSSE) (a) mixed (b) competitive (c) noncompetitive and (d) uncompetitive inhibition.

The RSSE increase with increase in SD values, higher amplitude of fluctuation in RSSE can be noted at a 4% SD value. Residuals in all types of inhibition appear randomly distributed below and above the predicted curve. The observation strongly indicates the absence of systematic errors and further confirms that the derived expressions describe well the simulated data. Statistical fit of the derived expressions to the simulated values upon randomization results in a maximum RSSE < 0.2.

Unlike other methods such as non-linear fit and double reciprocal, the derived expressions fits to entire set of experimental measurements considering substrate depletion or product formation as function of time, thus minimizing errors on estimated kinetic

parameters. For example, Figure 4 (a) shows a non-linear fitting to the experimental data (Michaelis and Menten 1913) resulting in V_{max} = 3.9109 and K_m = 0.0179 in their respective units, while for Lineweaver-Burk plot Figure 4 (b) we obtain V_{max} = 3.9509 and K_m = 0.0184 estimated in their respective units.

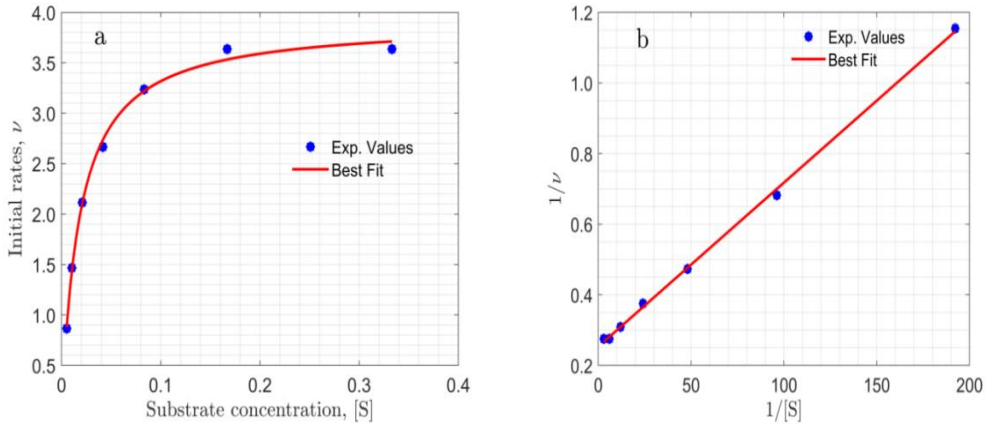

Figure 4: (a) Non-linear fitting and (b) Lineweaver-Burk fitting to the experimental data (Michaelis and Menten 1913).

Through least-square fit to initial rates vs [S], the K_m value differs to that through the reciprocal plot by 5×10^{-4}, whereas the V_{max} difference is 4×10^{-2}. The differences may be attributed to the manipulation (transformation) of the original data to be analyzed, thus, using derived expressions 12, 19, 27, 33 and 40 will eliminate such errors.

We compared results obtained using our derived expressions (to be specific we used Equation 12) with those reported in the literature as presented in Table 5. In both cases, the ideal values were set to a unit. The obtained results for both K_m and V_{max} are comparable to those in Goudar et al. (2004).

Table 5: The influence of standard deviation (SD) on the parameter estimated

SD	K_m	K_m (Goudar et al. 2004)	V_{max}	V_{max} (Goudar et al. 2004)
0.01	1.001	1.022	1.000	1.005
0.02	0.996	0.997	0.998	1.002
0.03	0.989	1.032	0.998	0.999
0.04	0.954	1.038	0.987	1.017

The errors for both V_{max} and K_m were observed to increase with the increasing noise level; this observation signifies that proper data handling is vital during experiments to minimize errors for accurate kinetic parameters. Therefore, the model can adequately handle experimental data and provide precise parameter estimates. Contrary to traditional approaches, such as reciprocal velocity where only a few data points are usually considered; the presented method ensures global regression. The software used in this work is easy to learn for scientists, we have also included source codes for implementation; also there are alternative tools for evaluation Lambert *W* function values such as excel spreadsheet add-in which can be found at https://github.com/mdscheuerell/Lambert-W-in-Excel, and for those using Fortran, C, C++ may use free library TOMS743 (Evaluation of Lambert's *W* function) developed by researchers based at Florida State University.

Conclusions

In this work, we have presented closed form solution for various chemical kinetics models, the derived expressions are based the Lambert *W* function in obtaining explicit solutions for the differential equation describing the dynamics of substrate consumption and product formation. Furthermore, the study demonstrated that the obtained expressions can be applied in parameter estimation problems for the models analogous to Michaelis-Menten. The technique revealed significant robustness in estimated parameters; even at a higher noise level of up to 4%, results with accuracy of more than 90% could be obtained. The study recommends real-time recording of concentrations (substrate or product) as it is essential that measurements are taken over the entire duration of the reaction and not only for the initial phase. We propose that the recording should be taken at short time intervals since the accuracy is improved with the high number of data points. The derived expressions hold for both lower and higher substrate concentrations. Furthermore, the study showed that the derived explicit solution can be easily implemented in MATLAB, thus, eliminating some of the technical challenges typically faced when other numerical approaches are used. This justification emphasizes that the Lambert *W* function is easier to apply and may be extended to more complex models with several inhibitors, where, all parameters inherent in the model can be obtained in a single fit. Application of Lambert *W* function is therefore a tool and novel approach to resolve challenges associated with both dynamics and mathematical nature of the chemical systems.

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Conflict of interest

There is no conflict of interest to declare.

References

Abedanzadeh S, Karimi B, Moosavi-Movahedi Z, Pourshiani O, Badiei A and Moosavi-Movahedi AA 2022 Artificial metalloenzyme with peroxidase-like activity based on periodic mesoporous organosilica with ionic-liquid framework. *Micropor. Mesopor. Mater*. 348: 112384.

Baici A 2015 Kinetics of enzyme-modifier interactions: Selected Topics in the Theory and Diagnosis of Inhibition and Activation Mechanisms. Springer.

Bäuerle F, Zotter A and Schreiber G 2017 Direct determination of enzyme kinetic parameters from single reactions using a new progress curve analysis tool. *Protein Eng. Design Select.* 30: 151-158.

Blomhøj M and Niss M 2021 Decoding, understanding, and evaluating extant mathematical models: what does that take? *Quadrante* 30: 9-36.

Cho YS and Lim HS 2018 Comparison of various estimation methods for the parameters of Michaelis-Menten equation based on in vitro elimination kinetic simulation data. *Translat. Clin. Pharmacol.* 26: 39.

Consigli G, Stefani S and Zambruno G 2017 Handbook of Recent Advances in Commodity and Financial Modeling: Quantitative Methods in Banking, Finance, Insurance, Energy and Commodity Markets. Springer.

Cornish-Bowden A 2013 Fundamentals of Enzyme Kinetics. John Wiley and Sons.

Emanuelsson BM, Beermann B and Paalzow L 1987 Non-linear elimination and protein binding of probenecid. *Eur. J. Clin. Pharmacol.* 32: 395-401.

Gee DA and Ramirez WF 1988 Optimal temperature control for batch beer fermentation. *Biotechnol. Bioeng.* 31: 224-234.

Gee DA and Ramirez WF 1994 A flavour model for beer fermentation. *J. Inst. Brewing*. 100: 321-329.

Goličnik M 2012 On the Lambert W function and its utility in biochemical kinetics. *Biochem. Eng. J.* 63: 116-123.

González MLR, CornelL-Kennon S, Schaefer E and Kuzmič P 2017 An algebraic model

to determine substrate kinetic parameters by global nonlinear fit of progress curves. *Anal. Biochem.* 518: 16-24.

Goudar CT, Harris SK, Mcinerney MJ and Suflita JM 2004 Progress curve analysis for enzyme and microbial kinetic reactions using explicit solutions based on the Lambert W function. *J. Microbiol. Methods.* 59: 317-326.

Kesisoglou I, Singh G and Nikolaou m 2021 The Lambert function should be in the engineering mathematical toolbox. *Comput. Chem. Eng.* 148: 107259.

Kim JK and Tyson JJ 2020 Misuse of the Michaelis–Menten rate law for protein interaction networks and its remedy. *PLoS Comput. Biol.* 16(10): e1008258.

Lineweaver H and Burk D 1934 The determination of enzyme dissociation constants. *J. Am. Chem. Soc.* 56: 658-666.

Liu F, Shang T, Han L, He N and Liu X 2022 Electrochemical investigation on kinetics of xanthine metabolism and inhibition effect of febuxostat on xanthine oxidase activity. *Electroanalysis*.

Ludden TM 1991 Nonlinear pharmacokinetics. *Clin. Pharmacokinet.* 20: 429-446.

Magliaro C, Mattei G, Iacoangeli F, Corti A, Piemonte V and Ahluwalia A 2019 Oxygen consumption characteristics in 3D constructs depend on cell density. *Front. Bioeng.Biotechnol.* 7: 251.

Michaelis L and Menten ML 1913 Die kinetik der invertinwirkung. *Biochem.* 49: 352.

Pakes AG 2018 The Lambert W function, Nuttall's integral, and the Lambert law. *Stat. Probab. Lett.* 139: 53-60.

Ring B, Wrighton SA and Mohutsky M 2014 Reversible mechanisms of enzyme inhibition and resulting clinical significance. *Enzyme Kinet. Drug Metabolism* 1113: 37-56.

Rubin GM and Tozer TN 1986 Hepatic binding and Michaelis-Menten metabolism of drugs. *J. Pharmaceutic. Sci.* 75: 660-663.

Seibert E and Tracy TS 2021 Fundamentals of Enzyme Kinetics: Michaelis-Menten and Non-Michaelis–Type (Atypical) Enzyme Kinetics. *Enzyme Kinet. Drug Metabol.* Springer.

Singh R, Moreno M and Stanimirovic D 2021 Comparison of various approaches to translate non-linear pharmacokinetics of monoclonal antibodies from cynomolgus monkey to human. *Eur. J. Drug Metabol. Pharmacokinet.* 46: 555-567.

Wilson CH and Gerber S 2021 Theoretical insights from upscaling Michaelis–Menten microbial dynamics in biogeochemical models: a dimensionless approach. *Biogeosci.* 18: 5669-5679.

ZavreL M, Kochanowski K and Spiess AC 2010 Comparison of different approaches and computer programs for progress curve analysis of enzyme kinetics. *Eng. Life Sci.* 10: 191-200.

Appendix: Supplementary Material

Sample MATLAB CODES

```
  ebar = -1/exp(1)
% Primary branch
s0 = 10;
vmax = 1;
km = 1;
n = 50
t = [linspace(0,25,n)]';
x = s0./km.*exp((s0-vmax.*t)./km)
  sl = km.*Lambert_W(x,0);
a = [0.01 0.02 0.03 0.04]
b = 0; % Mean
for i = 1:length(a)
y(:,i) = a(i).*randn(n,1) + b;
end
s1 = sl +y(:,1);
s2 = sl +y(:,2);
s3 = sl +y(:,3);
s4 = sl +y(:,4);
z = [t sl s1 s2 s3 s4];
constant = lsqcurvefit(@fw,[5;10], t, s1);
VMAX1 = constant(1);
KM1 = constant(2);
constant = lsqcurvefit(@fw,[5;10], t, s2);
VMAX2 = constant(1);
KM2 = constant(2);
constant = lsqcurvefit(@fw,[5;10], t, s3);
VMAX3 = constant(1);
KM3 = constant(2);
constant = lsqcurvefit(@fw,[5;10], t, s4);
VMAX4 = constant(1);
KM4 = constant(2);
xfit = t;
yfit = fw(constant,xfit)
R1 = [sl yfit];
DS1 = (R1(:,1)-R1(:,2)).^2;
RSSE1 = 0;
for i = 1:length(DS1)
   RSSE1 = RSSE1+DS1(i);
end
SEE1 = sqrt(RSSE1/(length(DS1(:,1))-2));
R2 = [s2 yfit];
DS2 = (R2(:,1)-R2(:,2)).^2;
RSSE2 = 0
for i = 1:length(DS2)
   RSSE2 = RSSE2+DS2(i);
end
SEE2 = sqrt(RSSE2/(length(DS2(:,1))-2));
R3 = [s3 yfit];
DS3 = (R3(:,1)-R3(:,2)).^2;
RSSE3 = 0;
for i = 1:length(DS3)
   RSSE3 = RSSE3+DS3(i);
end
SEE3 = sqrt(RSSE3/(length(DS3(:,1))-2));
R4 = [s4 yfit];
DS4 = (R4(:,1)-R4(:,2)).^2;
RSSE4 = 0;
for i = 1:length(DS4)
   RSSE4 = RSSE4+DS4(i);
end
SEE4 = sqrt(RSSE4/(length(DS4(:,1))-2));
```