

SIMULATION OF TIME-DEPENDENT ENZYME KINETICS BY MULTISTAGE PICARD ITERATIVE METHOD

(Simulasi Kinetik Enzim Bergantung Masa Menggunakan Kaedah Iteratif Picard Berperingkat)

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ABSTRACT

The time-dependent behaviour of reactant concentrations in a basic enzyme–substrate system is analysed using a modified formulation of the Picard Iterative Method (PIM). In this approach, the classical PIM is reformulated into a multistage framework, where the solution is approximated over successive time subintervals, resulting in a hybrid numerical–analytical scheme known as the Multistage Picard Iterative Method (MPIM). Numerical comparisons show that the standard PIM suffers from increasing error accumulation and reduced accuracy as time progresses, while the Padé-enhanced PIM improves convergence only within a limited time range. In contrast, the MPIM maintains excellent agreement with the classical fourth-order Runge–Kutta (RK4) method throughout the entire simulation interval, producing significantly smaller absolute errors and enhanced numerical stability. These results confirm that the multistage reformulation effectively suppresses error propagation and provides a reliable and accurate approach for modelling enzyme–substrate dynamics and solving nonlinear biochemical systems over extended time domains.

Keywords: Multistage Picard Iterative Method; nonlinear ODEs; biochemical reaction

ABSTRAK

Tingkah laku kebergantungan masa bagi kepekatan reaktan dalam sistem asas enzim–substrat dianalisis menggunakan suatu pengubahsuaian Kaedah Iteratif Picard (KIP). Dalam pendekatan ini, KIP klasik dirumus semula ke dalam kerangka berbilang peringkat, di mana penyelesaian dihipotesis secara berperingkat merentasi subselang masa berturutan, lalu menghasilkan satu skim hibrid numerik–analitik yang dikenali sebagai Kaedah Iteratif Picard Berperingkat (KIPB). Perbandingan berangka menunjukkan bahawa KIP konvensional mengalami pengumpulan ralat yang semakin meningkat serta kehilangan ketepatan apabila masa bertambah, manakala KIP yang digabungkan dengan penghampiran Padé hanya memperbaiki penumpuan dalam julat masa yang terhad. Sebaliknya, KIPB mengekalkan kesepadanan yang sangat baik dengan kaedah Runge–Kutta tertib keempat (RK4) sepanjang keseluruhan selang simulasi, dengan menghasilkan ralat mutlak yang jauh lebih kecil serta kestabilan berangka yang lebih tinggi. Dapatan ini mengesahkan bahawa perumusan berbilang peringkat berupaya mengekang perambatan ralat secara berkesan dan seterusnya menyediakan suatu pendekatan yang boleh dipercayai serta tepat bagi pemodelan dinamik enzim–substrat dan penyelesaian sistem biokimia tak linear dalam domain masa yang panjang.

Kata kunci: Kaedah Iteratif Picard Berperingkat; persamaan pembezaan bukan linear; tindak balas biokimia

1. Introduction

Biochemical systems are commonly expressed through nonlinear ordinary differential equations (ODEs) that describe the dynamic interaction among substrates, enzymes, intermediates and final products. These equations form the mathematical backbone of modern biochemical

kinetics, enabling researchers to understand the mechanisms underlying enzyme-catalysed reactions (Khader 2013). However, the strong nonlinearity and interdependence among these variables often make the derivation of exact analytical solutions extremely difficult, especially when the system involves multiple reactions or feedback mechanisms (Burke 2019). As a result, the study of enzyme kinetics has progressively evolved from relying solely on experimental observations towards the use of mathematical modelling and computational simulation (Jurich *et al.* 2025; Puniya *et al.* 2024). Through these approaches, researchers can analyse the sensitivity of reactions to parameter changes, predict system behaviour under different biochemical conditions, and develop new strategies for improving reaction efficiency in biochemical engineering and pharmacology. Thus, mathematical modelling not only complements experimental work but also serves as a predictive tool for exploring the complex dynamics of living systems (Banga & Villaverde 2025).

According to the law of mass action, the rate of a biochemical reaction is directly proportional to the product of the concentrations of the reactants involved (Chan *et al.* 2025; Li *et al.* 2023). This fundamental concept provides a bridge between physical chemistry and mathematical analysis, allowing the time-dependent behaviour of enzyme–substrate interactions to be represented as a system of coupled nonlinear ODEs (Waluga *et al.* 2025; Rajaraman 2025). The resulting mathematical formulations describe how concentrations evolve over time, forming the basis for dynamic enzyme kinetics models. Despite this clear theoretical framework, finding closed-form analytical solutions for such nonlinear systems remains a major challenge due to their intrinsic complexity (Szabó & Lente 2025). This difficulty increases further when additional kinetic effects, such as substrate inhibition, cooperative binding or multiple enzyme pathways, are introduced (Baronas 2025; Rajaraman 2025). Therefore, the focus has shifted towards efficient computational algorithms that can approximate the solution with high precision while maintaining numerical stability (Bilal *et al.* 2025). The development of such algorithms is crucial for understanding biochemical reactions across a wide range of conditions and timescales.

Over the years, numerous analytical and semi-analytical methods have been developed to solve nonlinear differential equations in biochemical modelling (Hussain *et al.* 2024). Recent studies have also demonstrated that semi-analytical and numerical iterative techniques can be effectively applied to solve differential, integral and optimisation-related problems (Eshkuvatov *et al.* 2022; Alhawarat *et al.* 2024). Classical approaches such as perturbation techniques, decomposition methods, Taylor series expansions and transform methods have provided useful approximations but often require simplifying assumptions such as small parameters, weak nonlinearity or linearisation of terms (Liu *et al.* 2024; Chauhan & Khirsariya 2023). These restrictions limit their applicability to real biochemical processes that are inherently nonlinear and time-dependent (Bakshi *et al.* 2025; Rajaraman 2025). To overcome these limitations, iterative algorithms have emerged as powerful alternatives for constructing successive approximations of the true solution without the need for such assumptions (Waluga *et al.* 2025; Chethan *et al.* 2024).

Among these, the PIM stands out as one of the most fundamental and elegant iterative schemes (Talitskii & Peet 2024; Schmidt *et al.* 2024). It is based on the concept of successive approximations, where the next estimate of the solution is obtained by integrating the previous one through the original differential equation in its integral form (Ansari & Akrami 2024). This iterative formulation allows the solution to evolve naturally with each iteration, refining the approximation at every step. The PIM possesses several advantages; it is conceptually simple, analytically consistent, and does not depend on perturbation parameters or discretisation grids (Mohammad & Mohammed Al-Rozbayani 2024). Moreover, when the method converges, it does so rapidly and yields a smooth, continuous approximation that closely resembles the analytical solution (Pollock *et al.* 2025).

Nevertheless, while the classical PIM performs remarkably well for short-term dynamics and weakly nonlinear systems, it often exhibits local convergence limitations when applied to large time domains or strongly nonlinear models (Khairuddin *et al.* 2025). The accumula-

tion of local truncation errors or divergence of the iterative series may lead to inaccuracies in long-term simulations (Li 2025). To overcome this constraint, the MPIM is introduced as an improved extension of the standard PIM procedure. In the MPIM framework, the total simulation interval is partitioned into several smaller subintervals, and the PIM is executed sequentially within each stage. The final approximation from one interval serves as the initial condition for the next, effectively creating a time-marching process that improves convergence, accuracy and computational robustness. This modification transforms the traditional PIM into a hybrid numerical–analytical algorithm, maintaining the analytical elegance of the PIM while extending its applicability to more complex and longer-duration problems.

Despite the widespread use of the Michaelis–Menten equation in enzyme kinetics, obtaining accurate analytical or semi-analytical solutions remains challenging due to its nonlinear coupled nature. Conventional numerical methods such as the fourth-order Runge–Kutta (RK4) method often require small step sizes to maintain stability, while classical iterative techniques such as the PIM may lose accuracy over extended time domains. To address these limitations, this study aims to derive reliable approximate solutions for the substrate concentration $x(t)$ and enzyme–substrate complex $y(t)$ using three approaches: the PIM, the Picard–Padé approximation, and the proposed MPIM. The novelty of this work lies in introducing a multistage modification to the traditional PIM, transforming it into a hybrid analytical–numerical algorithm capable of preserving analytical accuracy while improving convergence across longer time intervals. Comparative analyses with the RK4 benchmark further validate the enhanced precision, stability and computational efficiency of the proposed MPIM in modelling nonlinear biochemical systems governed by the Michaelis–Menten mechanism.

2. Mathematical Preliminaries

This section provides a detailed description of the biochemical reaction model, specifically the Michaelis–Menten equation, which characterises the catalytic interaction between an enzyme and its substrate in enzyme kinetics.

2.1. The Model Problem

The biochemical process considered in this study is the *Michaelis–Menten enzyme–substrate reaction*, one of the most fundamental mechanisms used to describe catalytic biochemical systems (Michaelis & Menten 1913; Schnell & Maini 2002; Schnell *et al.* 2006). The classical Michaelis–Menten scheme is represented by the following reaction sequence:



where E denotes the free enzyme, A is the substrate, Y represents the enzyme–substrate complex, and X is the product.

According to the law of mass action, each term in Equation (1) contributes to the rate of change of the corresponding species. Consequently, the system can be modelled by the following coupled nonlinear ODEs (Sen 1988):

$$\frac{dA}{dt} = -k_1 EA + k_2 Y, \quad (2)$$

$$\frac{dE}{dt} = -k_1 EA + (k_2 + k_3) Y, \quad (3)$$

$$\frac{dY}{dt} = k_1 EA - (k_2 + k_3) Y, \quad (4)$$

$$\frac{dX}{dt} = k_3 Y, \quad (5)$$

subject to the initial conditions

$$A(0) = A_0, \quad E(0) = E_0, \quad Y(0) = 0, \quad X(0) = 0. \quad (6)$$

To simplify the analysis and reduce the number of governing parameters, the dimensional variables A and Y are rescaled into nondimensional variables x and y , respectively. This nondimensionalisation leads to the reduced system of equations given in (7) and (8). The parameters k_1 , k_2 and k_3 are positive rate constants for each reaction. The system of Equations (2)–(5) can be simplified to two governing equations involving the substrate A and the enzyme–substrate complex Y . In the dimensionless form, the corresponding concentrations of the substrate and the intermediate complex are denoted by x and y , respectively (Schnell *et al.* 2006; Sen 1988).

$$\frac{dx}{dt} = -x + (\beta - \alpha)y + xy, \quad (7)$$

$$\frac{dy}{dt} = \frac{1}{\varepsilon}[x - \beta y - xy], \quad (8)$$

subject to the initial conditions

$$x(0) = 1, \quad y(0) = 0. \quad (9)$$

The parameters $\alpha = 0.375$, $\beta = 1$ and $\varepsilon = 0.1$ are adopted from the study by Hashim and Selamat (2008), where α denotes the dimensionless rate constant associated with enzyme activity, β represents the dimensionless rate constant corresponding to substrate conversion, and ε is defined as the dimensionless scaling parameter for time or reaction rate.

3. Solution Method

The system of nonlinear ODEs representing the dimensionless Michaelis–Menten mechanism, as expressed in Equations (7)–(8), exhibits a highly nonlinear and coupled structure. Analytical solutions to such systems are generally intractable through direct integration. Therefore, this study employs three closely related yet distinct semi-analytical approaches, namely the PIM, the Picard–Padé method, and the MPIM, to obtain effective approximate solutions. In addition, this section also presents the convergence analysis of the proposed methods to evaluate their accuracy and stability.

3.1. Picard Iterative Method (PIM)

The PIM, originally introduced by Picard (1893), is an iterative analytical technique designed to construct an approximate solution to an initial value problem through a successively refined sequence of functions. The method is based on the integral form of a first-order differential equation, expressed as

$$\frac{du}{dt} = f(t, u), \quad u(t_0) = u_0. \quad (10)$$

By integrating Equation (10) with respect to t from t_0 to t , its equivalent integral form can be obtained as

$$u(t) = u_0 + \int_{t_0}^t f(s, u(s)) ds. \quad (11)$$

The PIM defines a sequence of approximations $u_0, u_1, u_2, \dots$ by successively substituting

the previous estimate into the integral expression of Equation (11), yielding

$$u_{n+1}(t) = u_0 + \int_{t_0}^t f(s, u_n(s)) ds, \quad n = 0, 1, 2, \dots \quad (12)$$

This recursive process gradually converges to the exact solution, provided that the function $f(t, u)$ satisfies the Lipschitz condition, ensuring convergence within a given interval (Oludoun *et al.* 2019).

Applying this procedure to the Michaelis–Menten system in (7) and (8), with the initial conditions in (9), the PIM is initialised by setting $x_0(t) = 1$ and $y_0(t) = 0$. Subsequent approximations are obtained by integrating iteratively:

$$x_{n+1}(t) = 1 + \int_0^t [-x_n(s) + (0.625)y_n(s) + x_n(s)y_n(s)] ds, \quad (13)$$

$$y_{n+1}(t) = \int_0^t \frac{1}{0.1} [x_n(s) - (1)y_n(s) - x_n(s)y_n(s)] ds. \quad (14)$$

Each iteration provides a higher-order approximation of the substrate and enzyme–substrate complex concentrations. The convergence speed depends on the nonlinearity strength and the chosen parameters $(\alpha, \beta, \varepsilon)$.

The PIM is first applied to the Michaelis–Menten kinetic system to generate approximate analytical solutions for $x(t)$ and $y(t)$. Starting from the initial conditions in (9), the iterative procedure constructs higher-order corrections at each iteration level n . Symbolic computations were performed using Maple software to ensure both analytical accuracy and computational efficiency. For brevity, only the final iteration ($n = 4$) is presented here, as the preceding iterations ($n = 0$ – $n = 3$) follow the same recursive structure and are omitted for conciseness. The resulting analytical approximations of $x(t)$ and $y(t)$ are given by

$$\begin{aligned} x_5(t) = & 1 - 1.0000 t + 15.1737 t^2 - 132.3237 t^3 + 792.0621 t^4 - 4287.4300 t^5 \\ & + 13084.8294 t^6 - 66944.2126 t^7 + 2.8660 \times 10^5 t^8 - 1.0403 \times 10^6 t^9 \\ & + 3.2763 \times 10^6 t^{10} - 1.1176 \times 10^7 t^{11} + 3.2833 \times 10^7 t^{12} - 8.3897 \times 10^7 t^{13} \\ & + 2.1829 \times 10^8 t^{14} - 4.8736 \times 10^8 t^{15} + \dots - 23907.0624 t^{31}, \end{aligned} \quad (15)$$

$$\begin{aligned} y_5(t) = & 25.6392 t - 475.8614 t^2 + 4119.6629 t^3 - 24271.9080 t^4 + 1.2844 \times 10^5 t^5 \\ & - 3.6101 \times 10^5 t^6 + 1.8087 \times 10^6 t^7 - 7.5963 \times 10^6 t^8 + 2.7044 \times 10^7 t^9 \\ & - 8.4774 \times 10^7 t^{10} + 2.8731 \times 10^8 t^{11} - 8.4267 \times 10^8 t^{12} + 2.1516 \times 10^9 t^{13} \\ & - 5.5969 \times 10^9 t^{14} + 1.2496 \times 10^{10} t^{15} + \dots + 6.1296 \times 10^5 t^{31}. \end{aligned} \quad (16)$$

The above expressions represent the fully converged analytical approximation obtained after four Picard iterations.

3.2. Picard Iterative Method with Padé Approximation

The French mathematician Henri Padé developed the Padé approximation, a mathematical method for estimating functions, in 1892. A rational function approximation of a given function, represented as the ratio of two polynomials, is known as the Padé approximation. In comparison with conventional Taylor series expansions, it offers an efficient way to approximate functions, particularly in terms of increasing precision and convergence.

Although the standard PIM generates an analytical power series solution, its convergence

radius is often limited, especially for large values of time t . To extend the validity of the obtained series and enhance the global accuracy of the approximation, the Padé approximation is introduced (Padé 1892).

Padé (1892) states that the Padé approximation can be written as follows:

$$P_{[m/n]}(t) = \frac{a_0 + a_1t + a_2t^2 + \cdots + a_mt^m}{1 + b_1t + b_2t^2 + \cdots + b_nt^n}, \quad (17)$$

where m and n are the degrees of the numerator and denominator polynomials, respectively. By matching the Taylor expansion of $P_{[m/n]}(t)$ to the PIM series expansion of the solution, the Padé form captures more global features of the solution with improved convergence behaviour.

In this study, after obtaining the PIM series for $x(t)$ and $y(t)$ up to a finite number of terms, each series is transformed into its corresponding Padé form $P_{[L/M]}(t)$ to improve convergence behaviour and extend the applicability of the analytical solution. This hybrid Picard–Padé approach provides a more stable and accurate approximation, capable of simulating enzyme kinetics beyond the transient regime where the standard PIM solution tends to diverge. Specifically, the final expressions of $x(t)$ and $y(t)$ obtained from Equations (15) and (16) are substituted into the Padé approximation formula given in Equation (17), which converts the truncated power series into rational functions represented by $P_{[m/n]}$. This transformation enhances both the accuracy and stability of the approximations, particularly for larger values of t , while maintaining the analytical structure of the original solution. In this study, the Padé approximation of order $P_{[4/4]}$ is employed, as it offers an optimal balance between computational simplicity and approximation precision, ensuring sufficient numerator–denominator symmetry to capture the nonlinear characteristics of the Michaelis–Menten dynamics without introducing numerical instability from higher-order formulations. The resulting rational representations of $x(t)$ and $y(t)$ are expressed as follows:

$$x(t) = \frac{1.0 + 15.4890t - 41.1004t^2 - 1107.4467t^3 - 5887.3835t^4}{1.0 + 16.4890t - 39.7851t^2 - 1265.1066t^3 - 5158.9846t^4}, \quad (18)$$

$$y(t) = \frac{25.6392t + 209.7226t^2 - 10237.0059t^3 + 62255.2614t^4}{0.99910 + 26.7397t - 63.6632t^2 - 2103.2784t^3 - 8502.9934t^4}. \quad (19)$$

Equations (18) and (19) are subsequently solved using Maple computational software to obtain the corresponding Padé approximations. The advantage of this combination lies in its ability to maintain the analytical structure while compensating for the limited convergence of the PIM series. It is especially useful when modelling biochemical reactions with longer time spans or strongly nonlinear interactions.

3.3. Multistage Picard Iterative Method (MPIM)

The development of the MPIM is inspired by previous studies that introduced multistage approaches, such as the Adomian Decomposition Method and the Variational Iteration Method, to solve both linear and nonlinear differential equations. The present multistage framework follows a similar principle to the successive approximation technique proposed by Mungkasi (2020). In this formulation, the overall time domain $I = [t_0, T]$ is divided into a finite number of equal subintervals $I_j = [t_{j-1}, t_j]$, $j = 1, 2, 3, \dots, J$, where each subinterval is assigned a constant step size $h = t_j - t_{j-1}$. The function $u_{n,j}(t)$ denotes the approximate solution of $u(t)$ at the n -th iteration of the Picard scheme on the j -th subdomain, while m represents the total number of Picard iterations executed in the MPIM. For $j = 1, 2, 3, \dots, J$, the Picard iteration is sequentially performed within each subinterval, and for $n = 0, 1, 2, \dots, m - 1$, the iterative

relation can be expressed as

$$x_{n+1,j}(t) = x_{m,j-1}(t_{j-1}) + \int_{t_{j-1}}^t f(s, x_{n,j}(s)) ds, \quad t \in [t_{j-1}, t_j]. \quad (20)$$

To solve Equations (7) and (8) using the MPIM, the iterative scheme in (20) is constructed as follows:

$$x_{n+1,j}(t) = x_{m,j-1}(t_{j-1}) + \int_{t_{j-1}}^t [-x_{n,j}(s) + (\beta - \alpha)y_{n,j}(s) + x_{n,j}(s)y_{n,j}(s)] ds, \quad (21)$$

$$y_{n+1,j}(t) = y_{m,j-1}(t_{j-1}) + \int_{t_{j-1}}^t \frac{1}{\varepsilon} [x_{n,j}(s) - \beta y_{n,j}(s) - x_{n,j}(s)y_{n,j}(s)] ds. \quad (22)$$

This sequential propagation ensures that the solution remains stable and accurate over longer simulation periods. Essentially, the MPIM converts the PIM into a time-marching analytical algorithm, where each interval solution serves as the initial condition for the next. The method maintains the analytical integrity of the PIM process while achieving a convergence performance comparable to that of numerical solvers such as the RK4 method.

Based on the above multistage formulation, the MPIM is applied by performing the Picard iteration locally on each subinterval, where the terminal value of one stage is used as the initial condition for the subsequent stage. This staged formulation effectively minimises the accumulated truncation error and improves the global accuracy of the solution. By substituting the initial conditions given in (9) into Equations (21) and (22), the MPIM is implemented to iteratively compute the approximate analytical solutions of $x(t)$ and $y(t)$ for successive stages. For brevity, only the final-stage result is presented here, corresponding to $j = 200$ with five iterations ($n = 4$). The obtained analytical approximations for $x(t)$ and $y(t)$ at the last stage are expressed as follows:

$$\begin{aligned} x_{5,200}(t) = & 0.9914 - 0.6921t + 3.6636t^2 - 14.3924t^3 + 33.2073t^4 - 48.7105t^5 \\ & + 66.9884t^6 - 113.1831t^7 + 142.7257t^8 - 134.1187t^9 + 113.9675t^{10} \\ & - 96.4068t^{11} + 64.4865t^{12} - 36.8161t^{13} + 21.0034t^{14} - 9.8896t^{15} \\ & + \dots - 1.9075 \times 10^{-17}t^{31}, \end{aligned} \quad (23)$$

$$\begin{aligned} y_{5,200}(t) = & 0.1055 + 6.2382t - 44.6610 \times 10^6 t^2 + 174.4047t^3 - 394.2651t^4 \\ & + 547.8636t^5 - 693.3573t^6 + 1152.4239t^7 - 1439.5908t^8 \\ & + 1344.2325t^9 - 1140.5345t^{10} + 964.1972t^{11} - 644.8841t^{12} \\ & + 368.1631t^{13} + 210.0345t^{14} - 98.8963t^{15} + \dots + 1.9075 \times 10^{-16}t^{31}. \end{aligned} \quad (24)$$

3.4. Convergence of the Method

The convergence properties of the proposed MPIM are established for the nonlinear enzyme kinetic model described in the previous section. Consider the integral representation of the method written as

$$u_{n+1}(t) = u_0(t) + \int_{t_0}^t K(t, s, u_n(s)) ds, \quad (25)$$

where $K(t, s, u)$ denotes the integral kernel constructed from the governing differential equation of the enzyme kinetics system. Let $\mathcal{T}$ be the Picard operator defined by

$$(\mathcal{T}u)(t) = u_0(t) + \int_{t_0}^t K(t, s, u(s)) ds.$$

Assume that the kernel $K(t, s, u)$ satisfies the Lipschitz condition with respect to its third argument,

$$|K(t, s, u_1) - K(t, s, u_2)| \leq L|u_1 - u_2|, \quad L > 0, \quad (26)$$

and that $K(t, s, u)$ is continuous on $[t_0, T] \times [t_0, T] \times \mathbb{R}$. Then, for any two successive iterates u_{n+1} and u_n generated by (25), we obtain

$$\begin{aligned} |u_{n+1}(t) - u_n(t)| &= \left| \int_{t_0}^t [K(t, s, u_n(s)) - K(t, s, u_{n-1}(s))] ds \right| \\ &\leq L \int_{t_0}^t |u_n(s) - u_{n-1}(s)| ds. \end{aligned} \quad (27)$$

Applying the inequality recursively yields

$$|u_{n+1}(t) - u_n(t)| \leq \frac{(L(t - t_0))^n}{n!} \|u_1 - u_0\|_\infty, \quad (28)$$

which demonstrates that the sequence $\{u_n(t)\}$ is Cauchy in $C([t_0, T])$. Therefore, it converges uniformly to a unique fixed point $u(t)$ satisfying

$$u(t) = u_0(t) + \int_{t_0}^t K(t, s, u(s)) ds.$$

Consequently, the MPIM converges to the exact solution of the enzyme kinetic model, provided that $L(T - t_0) < 1$. This ensures that the operator $\mathcal{T}$ is a contraction on $C([t_0, T])$.

4. Results and Discussion

This section presents the convergence analysis of the proposed methods. The results obtained from the PIM, the Picard–Padé method and the MPIM are evaluated within the dimensionless time interval $0 \leq t \leq 6$. The performance of each semi-analytical scheme is compared with the numerical benchmark solution obtained using the RK4 method. The PIM, Picard–Padé and MPIM algorithms are implemented in the computer algebra system Maple, with the environment variable `Digits` set to 16 for all computations to ensure high-precision numerical accuracy. The absolute error for each semi-analytical method is computed with respect to the RK4 results to assess the convergence behaviour, accuracy and numerical stability of the proposed MPIM relative to the conventional PIM and Picard–Padé approaches.

4.1. Convergence Analysis for the Michaelis–Menten Equation

The following criterion was used to evaluate the convergence of the iterative method, where the successive difference between two consecutive approximations serves as an a posteriori error indicator (Rao *et al.* 2018):

$$\varepsilon = |x_{(n+1)}(t) - x_{(n)}(t)|.$$

This expression quantifies the change between iterations, and convergence is assumed when the variation becomes sufficiently small, indicating that the solution has stabilised within a desired tolerance. For this evaluation, $t = 0.01$ is used, since smaller step sizes generally improve accuracy (Arefin *et al.* 2021). The iterative process was stopped when $\varepsilon \leq 10^{-2}$.

Table 1 presents the convergence behaviour of the PIM and the MPIM across successive iterations when applied to the Michaelis–Menten enzyme kinetics model. As shown, both methods exhibit a monotonic decrease in the convergence values, indicating progressive improvement in the accuracy of the approximate solutions. For the PIM, the convergence value begins at 0.1 during the first iteration and gradually decreases to 0.002345 by the fifth iteration. This steady reduction signifies that the PIM effectively refines the approximate solution at each stage, leading to a consistent improvement towards the true analytical behaviour of the nonlinear system.

Table 1: Convergence behaviour across iterative computations

Number of Iterations	PIM	MPIM
1	0.100000	0.010000
2	0.082917	0.000859
3	0.055371	0.000059
4	0.039003	0.306×10^{-5}
5	0.002345	1.270×10^{-7}

In contrast, the MPIM demonstrates a significantly faster rate of convergence. Starting with a convergence value of 0.01 at the first iteration, the error reduces sharply to 1.270×10^{-7} by the fifth iteration, which is several orders of magnitude smaller than that achieved by the standard PIM. This rapid decay in error reflects the improved stability and accuracy achieved through the multistage correction mechanism integrated within the MPIM framework. The inclusion of intermediate stages within each iteration enhances the method's ability to capture the nonlinear coupling between substrate and enzyme concentrations, resulting in superior numerical precision.

Overall, the comparison highlights that while the standard PIM achieves satisfactory convergence within five iterations, the MPIM attains a much higher level of accuracy under the same iteration limit. This improvement verifies that the multistage modification significantly accelerates convergence and minimises residual errors without increasing computational complexity. Hence, the MPIM can be regarded as a more robust and efficient alternative for solving nonlinear biochemical models such as the Michaelis–Menten mechanism, particularly in scenarios requiring rapid and high-accuracy computations. To further validate these findings, the following figures illustrate the temporal evolution of the substrate concentration $x(t)$ and enzyme–substrate complex $y(t)$, along with their respective absolute error profiles.

4.2. Substrate Concentration, $x(t)$

Figure 1 illustrates the solutions of $x(t)$ obtained using the 5-iteration PIM, 5-iteration Picard–Padé [4/4] method and 5-iteration MPIM with time step $\Delta t = 0.001$, compared with the RK4 method with time step $\Delta t = 0.001$. The RK4 solution is used as a reference benchmark due to its well-established numerical accuracy.

As shown in Figure 1, the results obtained using the 5-iteration PIM indicate that the method performs reasonably well at the early stage of the simulation, where the predicted substrate concentration $x(t)$ remains close to the RK4 reference solution. However, as time increases, the PIM solution begins to deviate noticeably, producing a faster decline in substrate concentration than expected. This behaviour is primarily due to the accumulation of truncation errors associated with the finite Picard series and the limited convergence radius when applied to non-

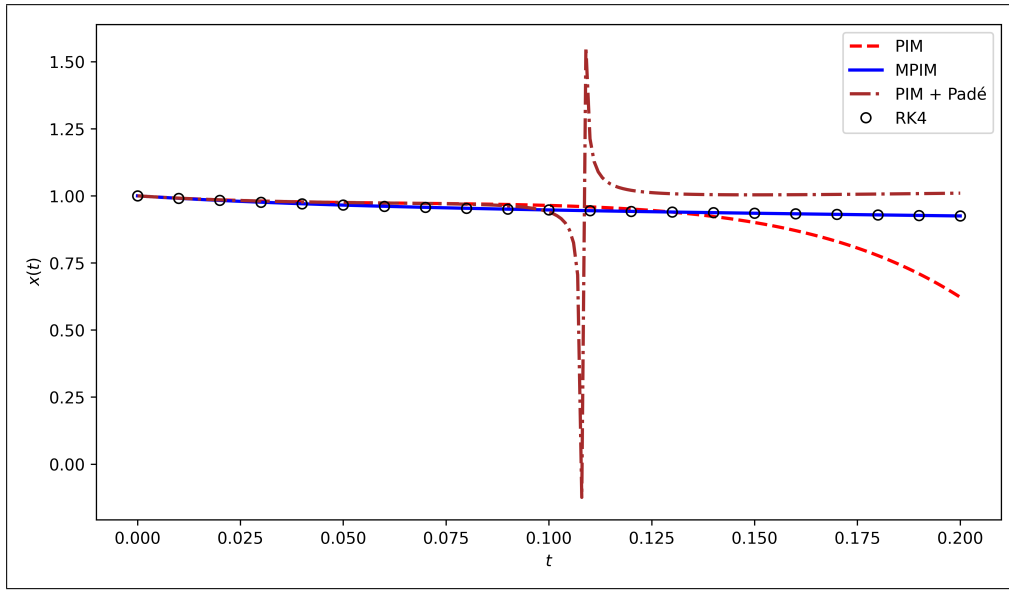


Figure 1: Solutions of $x(t)$ using the 5-iteration PIM, 5-iteration Picard–Padé [4/4] method and 5-iteration MPIM with time step $\Delta t = 0.001$, compared with the RK4 method with time step $\Delta t = 0.001$

linear systems. Consequently, the classical PIM demonstrates reduced reliability in capturing the long-term dynamics of the Michaelis–Menten substrate depletion process.

The application of the 5-iteration Picard–Padé [4/4] approach leads to a markedly different numerical behaviour compared to the other methods. Despite its theoretical advantage in extending series convergence, the Padé approximation introduces a singularity at approximately $t \approx 0.11$, resulting in a sudden divergence of the substrate concentration. This instability originates from the presence of poles in the rational approximation, which produce nonphysical values that contradict the smooth kinetic behaviour expected in enzyme–substrate reactions. These results suggest that the Picard–Padé method, without additional stabilisation or domain control, may be unsuitable for nonlinear biochemical models.

In contrast, the 5-iteration MPIM demonstrates consistently accurate behaviour across the entire time interval, closely matching the RK4 benchmark solution. The method successfully captures the smooth and gradual decay of the substrate concentration without exhibiting divergence or oscillatory artefacts. This enhanced performance is attributed to the multistage strategy, where the Picard iteration is restarted at each subinterval with updated initial conditions. By effectively limiting error accumulation and improving convergence, the MPIM provides a stable and reliable numerical approximation for nonlinear kinetic equations.

In summary, the comparative study highlights the superiority of the MPIM in terms of numerical stability and accuracy for modelling substrate concentration dynamics. While the classical PIM is constrained by convergence limitations and the Picard–Padé method suffers from severe numerical instability due to singularities, the MPIM consistently produces physically meaningful results that closely align with the RK4 solution. These findings confirm that the multistage formulation of the MPIM is well suited for solving nonlinear enzyme–substrate systems such as the Michaelis–Menten model.

4.3. Absolute Error Analysis for $x(t)$

In addition to the graphical comparisons, the accuracy of the proposed methods was also evaluated quantitatively through the computation of absolute errors with respect to the numerical benchmark RK4 method. Table 2 shows the comparison of absolute errors between analytical

Table 2: Absolute error comparison for $x(t)$ between analytical approaches and RK4

Time	RK4 – PIM	RK4 – Picard Padé	RK4 – MPIM
0.01	0.000589591	0.00058959	9.80405×10^{-12}
0.05	0.009648841	0.009634035	2.07946×10^{-11}
0.10	0.016803451	0.007677011	1.46442×10^{-11}
0.15	0.034476641	0.06862314	7.81641×10^{-12}
0.20	0.302819608	0.084935652	3.66662×10^{-12}

approaches and RK4 for the substrate concentration $x(t)$ at selected time points.

From Table 2, at the early time level $t = 0.01$, both PIM and Picard–Padé exhibit comparable absolute errors on the order of 10^{-4} , indicating similar initial accuracy. In contrast, MPIM achieves a significantly smaller error of order 10^{-11} , demonstrating superior precision even at the initial stage of computation.

As time increases to $t = 0.05$ and $t = 0.10$, the absolute errors associated with PIM continue to grow steadily, reflecting the accumulation of truncation errors inherent in the classical Picard iteration. Although the Picard–Padé method initially shows a modest improvement over PIM at $t = 0.10$, this advantage is not sustained. Meanwhile, MPIM consistently maintains extremely small error magnitudes, remaining within the range of 10^{-11} , which confirms its robustness and numerical stability over extended time intervals.

A more pronounced divergence is observed at $t = 0.15$ and $t = 0.20$, where the absolute error of PIM increases rapidly, reaching 0.302819608 at $t = 0.20$. This sharp rise indicates a significant loss of accuracy and highlights the limited convergence domain of the classical Picard method when applied to nonlinear kinetic equations. The Picard–Padé method also exhibits increasing errors at later times, with values approaching 10^{-1} , suggesting that the rational approximation introduces instability that degrades solution accuracy as time progresses.

Overall, the error analysis clearly demonstrates the superiority of the MPIM in approximating the substrate concentration $x(t)$. Across all evaluated time levels, the MPIM produces errors several orders of magnitude smaller than those of the PIM and Picard–Padé, maintaining near-machine precision accuracy. These results validate the effectiveness of the multistage strategy in the MPIM for suppressing error accumulation and ensuring stable convergence, making it a reliable numerical approach for solving nonlinear biochemical models such as the Michaelis–Menten system.

4.4. Enzyme–Substrate Complex Concentration, $y(t)$

Figure 2 presents the solutions of $y(t)$ obtained using the 5-iteration PIM, 5-iteration Picard–Padé [4/4] method and 5-iteration MPIM with time step $\Delta t = 0.001$, compared with the RK4 method with time step $\Delta t = 0.001$. The RK4 results once again serve as the numerical reference to assess the accuracy and stability of the semi-analytical methods.

From Figure 2, the numerical solution obtained using the 5-iteration PIM exhibits an increasing trend in the enzyme–substrate complex concentration $y(t)$. However, noticeable deviations from the RK4 reference solution are observed from the early stage of the simulation. The PIM solution consistently overestimates the formation of the enzyme–substrate complex, indicating that the method fails to accurately capture the nonlinear reaction dynamics even at small time values. As time progresses, this discrepancy becomes more pronounced, leading to an unbounded growth in $y(t)$. This behaviour highlights the inherent limitations of the classical Picard approach, where accumulated truncation errors and a restricted convergence region result in nonphysical solutions for nonlinear biochemical systems.

The 5-iteration Picard–Padé [4/4] approximation initially follows a similar increasing trend, but rapidly develops severe numerical instability near $t \approx 0.10$. The emergence of a vertical

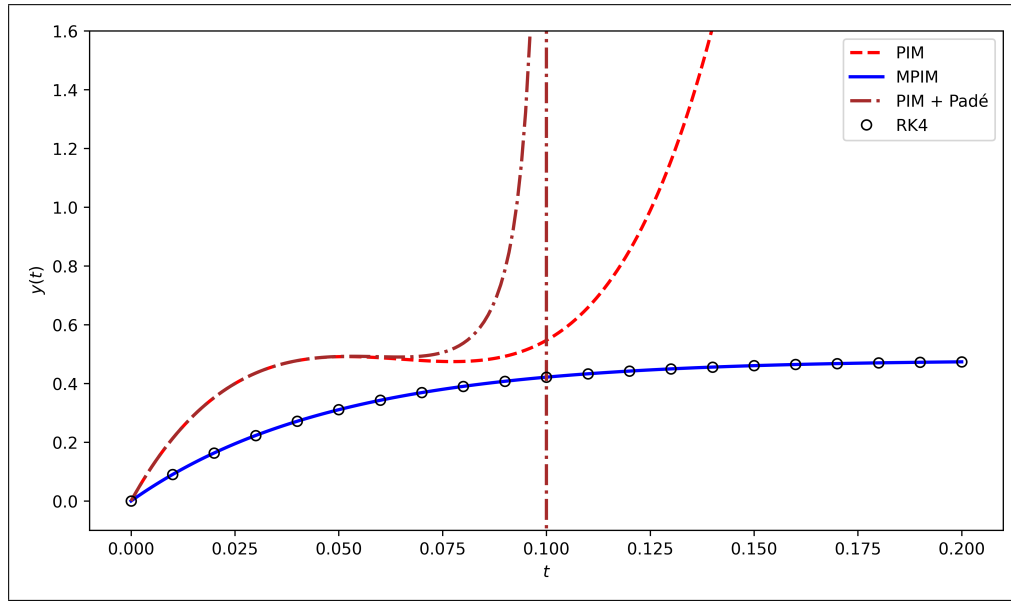


Figure 2: Solutions of $y(t)$ using the 5-iteration PIM, 5-iteration Picard–Padé [4/4] method and 5-iteration MPIM with time step $\Delta t = 0.001$, compared with the RK4 method with time step $\Delta t = 0.001$

asymptotic behaviour indicates the presence of a singularity introduced by the rational Padé approximation. This behaviour produces unrealistic values for the enzyme–substrate complex concentration, contradicting the bounded and saturating nature of biochemical reaction kinetics. Although Padé approximants are often employed to enhance convergence, these results demonstrate that, for nonlinear enzyme–substrate dynamics, the method may introduce artificial poles that compromise solution reliability.

The 5-iteration MPIM provides a stable and accurate approximation of $y(t)$ across the entire time interval considered. The MPIM solution closely matches the RK4 benchmark, capturing the gradual increase and eventual saturation of the enzyme–substrate complex concentration. This consistent behaviour is attributed to the multistage formulation, where the Picard iteration is repeatedly reinitialised over small time subintervals. By reducing error propagation and extending the effective convergence domain, the MPIM successfully maintains numerical stability and preserves the physical characteristics of the underlying kinetic process.

In conclusion, the comparative analysis for the enzyme–substrate complex concentration confirms the superiority of the MPIM over the conventional PIM and Picard–Padé approaches. While the PIM suffers from divergence due to convergence limitations and Picard–Padé exhibits catastrophic instability caused by singularities, the MPIM consistently yields bounded and physically meaningful solutions that align with the RK4 reference. These findings further emphasise the robustness of the multistage Picard framework in modelling nonlinear biochemical reaction systems governed by Michaelis–Menten kinetics.

4.5. Absolute Error Analysis for $y(t)$

To further evaluate the accuracy of the three methods, the absolute error between each analytical approach and the numerical benchmark RK4 was computed for the enzyme–substrate complex $y(t)$ at different time levels. Table 3 presents the comparison of absolute errors between the RK4 method with time step $\Delta t = 0.001$, the 5-iteration PIM, the 5-iteration Picard–Padé [4/4] method and the 5-iteration MPIM with time step $\Delta t = 0.001$.

From Table 3, at the initial time level $t = 0.01$, both PIM and Picard–Padé exhibit relatively large absolute errors of approximately 0.122475147, indicating that neither method accurately

Table 3: Absolute error comparison for $y(t)$ between analytical approaches and RK4

Time	RK4 – PIM	RK4 – Picard Padé	RK4 – MPIM
0.01	0.122475147	0.122475147	1.21723×10^{-10}
0.05	0.180469843	0.181110219	2.59512×10^{-10}
0.10	0.125282227	7.33459804	1.84625×10^{-10}
0.15	1.798761719	1.167590498	1.00387×10^{-10}
0.20	10.17304132	1.646378318	4.90844×10^{-11}

captures the early-stage dynamics of complex formation. In contrast, MPIM produces an error on the order of 10^{-10} , demonstrating a substantial improvement in accuracy from the outset.

As the simulation progresses to $t = 0.05$ and $t = 0.10$, the errors associated with PIM remain significant, fluctuating around 10^{-1} , while the Picard–Padé method shows erratic behaviour, with a sudden escalation of error to 7.33459804 at $t = 0.10$. This sharp increase reflects severe numerical instability, consistent with the presence of singularities observed in the corresponding solution profiles. Meanwhile, MPIM maintains consistently small error magnitudes, remaining below 2×10^{-10} , which confirms its robustness in handling the nonlinear dynamics of the enzyme–substrate interaction.

At later time levels $t = 0.15$ and $t = 0.20$, the deficiencies of the conventional methods become more pronounced. The PIM error increases dramatically, reaching values exceeding 10^0 and ultimately rising above 10 at $t = 0.20$, indicating a complete loss of numerical accuracy. The Picard–Padé method also exhibits large errors, remaining on the order of unity, further demonstrating its instability for prolonged simulations. In contrast, MPIM continues to deliver highly accurate approximations, with errors decreasing to the order of 10^{-11} , highlighting its ability to suppress error accumulation effectively.

Overall, the absolute error analysis clearly demonstrates that MPIM significantly outperforms both PIM and Picard–Padé in approximating the enzyme–substrate complex concentration $y(t)$. The multistage formulation enables MPIM to maintain near-machine precision accuracy throughout the entire time interval, while the other methods suffer from divergence and instability. These findings further validate MPIM as a reliable and efficient numerical scheme for solving nonlinear biochemical reaction models governed by Michaelis–Menten kinetics.

4.6. Discussion

Overall, the comparison among the three analytical schemes demonstrates a clear improvement in solution stability and accuracy as the method progresses from standard PIM to Picard–Padé and finally to MPIM. The classical PIM provides a basic analytical approximation but suffers from divergence in strongly nonlinear regions. The introduction of the Padé approximation enhances global convergence, while the multistage formulation of MPIM further strengthens the accuracy by combining local iteration with stepwise integration.

From the graphical results, both $x(t)$ and $y(t)$ obtained using MPIM match almost perfectly with RK4 within the tested time interval, confirming the efficiency of the multistage approach. Moreover, MPIM achieves this accuracy with fewer computational steps compared to RK4, as it operates on analytical expressions instead of discrete numerical evaluations.

Hence, MPIM can be considered a reliable and efficient hybrid numerical–analytical technique for solving nonlinear biochemical systems, particularly those with stiff or rapidly varying components. The findings presented here suggest that MPIM can be extended to more complex enzyme kinetic models or other nonlinear reaction mechanisms in future work.

5. Conclusions

In this paper, the time-dependent behaviour of the enzyme–substrate reaction governed by the Michaelis–Menten mechanism has been simulated using three analytical and semi-analytical approaches, namely the PIM, the PIM enhanced with Padé approximation, also known as Picard–Padé, and the MPIM. The study aimed to evaluate the efficiency, convergence and stability of these iterative schemes when applied to nonlinear biochemical models.

The results demonstrate that while the classical PIM provides an initial analytical approximation, it exhibits limited convergence and fails to maintain accuracy beyond a short time interval. This limitation is effectively addressed by introducing the Padé approximation, which improves the global convergence of the PIM series by representing the solution in a rational polynomial form. The hybrid Picard–Padé formulation successfully extends the valid range of simulation and produces results that remain consistent with the numerical benchmark, RK4, for longer time periods.

The most significant improvement is achieved through the MPIM, which integrates the PIM within a time-partitioned framework. By dividing the simulation domain into smaller subintervals and reinitialising the iteration at each stage, MPIM minimises the accumulation of numerical errors and preserves convergence throughout the entire time span. The MPIM results show excellent agreement with the RK4 method for both substrate concentration $x(t)$ and enzyme–substrate complex concentration $y(t)$, confirming its accuracy and stability. Moreover, MPIM offers the advantage of maintaining an explicit semi-analytical structure, which facilitates theoretical interpretation and parameter sensitivity analysis compared to fully numerical schemes.

In summary, the findings confirm that MPIM serves as an efficient and reliable hybrid numerical–analytical algorithm for solving nonlinear biochemical systems. It combines the simplicity and analytical transparency of the PIM with the robustness of stepwise integration. Given its demonstrated performance, MPIM can be effectively extended to other classes of nonlinear differential equations, including complex reaction networks, diffusion–reaction systems and higher-order biochemical kinetics, where conventional analytical or numerical methods face limitations. Future studies may focus on the application of MPIM to stiff systems or chaotic biochemical models to further assess its potential as a general-purpose solver in computational biology and applied mathematics.

Acknowledgement

The authors wish to express their sincere gratitude to Universiti Teknologi MARA (UiTM) for the continuous support and research facilities provided throughout this study.

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Received: 3 November 2025

Accepted: 28 January 2026

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