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Semi-analytical solution of a nonlinear reaction-diffusion model in an immobilized enzyme system using the homotopy analysis method

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Abstract

Immobilized enzyme systems are used widely in biosensors, packed-bed bioreactors, and biocatalytic membranes, and their design depends on knowing how the substrate concentration varies through the catalytic layer. The balance between Michaelis-Menten reaction kinetics and diffusion gives a nonlinear boundary value problem that has no closed-form solution in general. This paper develops a semi-analytical solution using the homotopy analysis method (HAM) for the steady-state, dimensionless reaction-diffusion equation $(1+\beta\phi)\phi''=\alpha^2\phi$, with $\phi'(0)=0$ and $\phi(1)=1$, where α^2 is a Thiele-type reaction-diffusion modulus and β is a saturation parameter equal to the ratio of the bulk substrate concentration to the Michaelis constant. Using a constant initial guess and the second-derivative operator as the linear operator, the zeroth- and higher-order deformation equations are derived and solved symbolically up to sixth order. Rather than being fixed arbitrarily, the convergence-control parameter h is obtained for each (α^2, β) pair by minimising the mean-squared residual of the governing equation—the approach proposed by Liao for strongly nonlinear problems. The resulting sixth-order HAM solution is checked in two independent ways: first, in the linear limit ($\beta=0$) it is shown to reproduce the Taylor expansion of the exact solution $\cosh(\alpha X)/\cosh(\alpha)$ term by term; second, it is compared against a high-accuracy collocation solution of the full nonlinear boundary value problem. Across the tested range $0.5 \leq \alpha^2 \leq 4$ and $0.3 \leq \beta \leq 1.0$, the maximum relative difference between the HAM and numerical concentration profiles stays below 1%, and the derived effectiveness-factor curves overlap closely. The results show that HAM, once the convergence-control parameter is properly optimised rather than fixed by convention, gives an accurate, closed-form-like approximation for immobilized-enzyme reaction-diffusion problems, and the derived expressions and effectiveness-factor curves can be used directly when interpreting or designing amperometric biosensors and immobilized-enzyme reactors.

Keywords: Homotopy analysis method, immobilized enzyme kinetics, reaction-diffusion equation, Michaelis-Menten kinetics, Thiele modulus, effectiveness factor, nonlinear boundary value problem, semi-analytical solution, convergence-control parameter

Introduction

Enzymes are frequently immobilized on or within a solid support a membrane, a porous bead, or the surface of an electrode so that they can be reused, held in place inside a reactor, or built into a biosensor. Once an enzyme is immobilized, the substrate it acts on must first diffuse through the support before it can react, so the local reaction rate and the local diffusion rate are coupled at every point inside the support. When the enzyme follows Michaelis-Menten kinetics, this coupling produces a nonlinear reaction-diffusion equation, and the resulting boundary value problem does not, in general, have a closed-form solution.

Two limiting cases are easy to handle. When the substrate concentration is small compared with the Michaelis constant, the kinetics reduce to a first-order (linear) reaction, and the governing equation can be solved exactly in terms of hyperbolic functions. When the substrate concentration is large compared with the Michaelis constant, the kinetics approach zero order, and the equation again becomes tractable. Between these two limits, the equation is genuinely nonlinear, and most of the practically relevant operating range for a biosensor or an immobilized-enzyme reactor falls in this intermediate region.

A number of semi-analytical techniques have been used to approximate the solution in this intermediate regime without solving the equation purely numerically. The Adomian decomposition method (ADM) builds the solution as a series generated from special polynomials for the nonlinear term. The homotopy perturbation method (HPM) embeds the equation in a one-parameter family of problems that deforms continuously from an easily solved linear problem to the full nonlinear one. Both methods have been applied specifically to immobilized Michaelis-Menten systems, giving good agreement with numerical solutions over a limited parameter range. The homotopy analysis method (HAM) generalises this idea by introducing an auxiliary convergence-control parameter, denoted $\hbar$, together with a freely chosen linear operator and auxiliary function; HPM is recovered as the special case $\hbar = -1$. Because $\hbar$ is a genuine free parameter rather than a fixed constant, HAM solutions can, in principle, be made to converge over a wider range of the physical parameters than HPM or ADM solutions of the same truncation order, provided $\hbar$ is chosen well.

Most published applications of HAM and HPM to immobilized-enzyme reaction-diffusion problems either fix $\hbar$ at its classical value of -1 or select it by inspection of a single $\hbar$ -curve at one parameter set. What is less commonly shown is a systematic, case-by-case optimisation of $\hbar$ together with an explicit check of how the resulting error behaves as the reaction-diffusion modulus and the saturation parameter both increase. The aim of this paper is threefold: first, to derive the HAM solution for the planar immobilized-enzyme reaction-diffusion equation using a fully symbolic recursive procedure; second, to select the convergence-control parameter for each parameter combination by minimising the mean-squared residual of the governing equation, following the optimal- $\hbar$ approach introduced by Liao for strongly nonlinear problems; and third, to validate the resulting sixth-order approximation against an independent high-accuracy numerical solution over a practically relevant range of the Thiele-type modulus and the saturation parameter, and to report the resulting effectiveness-factor behaviour.

Mathematical Formulation

Consider a planar immobilized-enzyme layer of thickness L in contact with a well-mixed bulk solution of substrate concentration S_b . Inside the layer, the substrate concentration $S(x)$ obeys a steady-state balance between diffusion and Michaelis-Menten consumption:

$$D \frac{d^2 S}{dx^2} = V_{\max} S / (K_m + S), \quad 0 < x < L,$$

where D is the effective diffusion coefficient of the substrate inside the layer, $V_{\max}$ is the maximum reaction rate, and K_m is the Michaelis constant. The layer is taken to be symmetric (or backed by an impermeable support), so there is no flux at $x = 0$, while the surface at $x = L$ is in equilibrium with the bulk solution: $dS/dx(0) = 0$, $S(L) = S_b$.

Introducing the dimensionless variables $X = x/L$ and $\varphi = S/S_b$, the governing equation becomes

$$(1 + \beta\varphi) \varphi''(X) = \alpha^2 \varphi(X), \quad 0 < X < 1, \quad \varphi'(0) = 0, \quad \varphi(1) = 1,$$

with a saturation parameter $\beta = S_b/K_m$ and a Thiele-type reaction-diffusion modulus $\alpha^2 = V_{\max} L^2 / (DK_m)$. Physically, β compares the operating substrate concentration with the enzyme's Michaelis constant ($\beta \ll 1$ corresponds to first-order

kinetics, $\beta \gg 1$ to zero-order kinetics), while α^2 compares the intrinsic reaction rate with the rate of diffusion through the layer, in the same spirit as the classical Thiele modulus of heterogeneous catalysis. Multiplying through by $(1 + \beta\varphi)$ converts the equation into a polynomial nonlinearity, which is the form used in the homotopy construction below. The present formulation is restricted to planar geometry; the same procedure extends to cylindrical or spherical immobilized-enzyme particles by replacing the second derivative with the corresponding curvilinear Laplacian, at the cost of a more elaborate recursive algebra.

Solution by the Homotopy Analysis Method

Following the standard HAM construction, the linear operator is taken as $L[f] = f''(X)$, and the governing equation is written as $N[\varphi] = 0$ with $N[\varphi] = (1 + \beta\varphi)\varphi'' - \alpha^2\varphi$. An auxiliary embedding parameter $q \in [0, 1]$ and a nonzero convergence-control parameter $\hbar$ are introduced through the zeroth-order deformation equation

$$(1 - q) L[\Phi(X; q) - \varphi_0(X)] = q \hbar N[\Phi(X; q)],$$

With $H(X) = 1$ taken as the simplest admissible auxiliary function. The initial guess $\varphi_0(X) = 1$ is used because it is the simplest function satisfying both boundary conditions exactly ($\varphi_0'(0) = 0$ and $\varphi_0(1) = 1$). Expanding $\Phi(X; q)$ as a Maclaurin series in q and collecting powers of q gives the m th-order deformation equation

$$\varphi_m''(X) - \chi_m \varphi_{m-1}''(X) = \hbar R_m(X), \quad \varphi_m'(0) = 0, \quad \varphi_m(1) = 0 \quad (m \geq 1),$$

Where $\chi_m = 0$ for $m = 1$ and $\chi_m = 1$ for $m > 1$, and the deformation-derivative term is $R_m = \varphi_{m-1}'' + \beta \sum_{i=0}^{m-1} \varphi_i \varphi_{m-1-i}'' - \alpha^2 \varphi_{m-1}$, obtained from the Cauchy-product expansion of the $(1 + \beta\Phi)\Phi''$ term. Each order is therefore a linear, two-point boundary value problem that can be integrated twice and solved for the two constants of integration in closed form. Carrying this out gives, for the first order,

$$\varphi_1(X) = (\alpha^2 \hbar / 2)(1 - X^2),$$

and, for the second order,

$$\varphi_2(X) = (\alpha^2 \hbar / 24) \cdot [\alpha^2 \hbar (X^4 - 6X^2 + 5) + 12(1 - X^2)(1 + \hbar(1 + \beta))].$$

Third- through sixth-order terms follow from the same recursion but become algebraically long; they were generated symbolically (Python/SymPy) rather than by hand, and the finite sum $\varphi(X) \approx \sum_{m=0}^6 \varphi_m(X)$, evaluated at $q = 1$, is used as the HAM approximation throughout the rest of this paper.

Two checks were used to validate the derivation before it was applied to the nonlinear case. First, setting $\beta = 0$ reduces the governing equation to the linear problem $\varphi'' = \alpha^2 \varphi$, $\varphi'(0) = 0$, $\varphi(1) = 1$, which has the exact solution $\varphi(X) = \cosh(\alpha X) / \cosh(\alpha)$. With $\beta = 0$ and $\hbar = -1$, the sixth-order HAM sum was expanded in powers of α and found to reproduce the Taylor expansion of $\cosh(\alpha X) / \cosh(\alpha)$ term by term through $O(\alpha^4)$, confirming that the symbolic recursion is implemented correctly. Second, for the full nonlinear problem ($\beta \neq 0$), a fixed value of $\hbar = -1$ —the classical choice inherited from the homotopy perturbation method—was found to track the numerical solution well only for small α^2 and β , and to diverge sharply once α^2 and β both increase (relative errors exceeding 100% were observed for $\alpha^2 \geq 2$ with $\beta = 1$ at sixth order). This is expected: $\hbar$ controls the

convergence region and rate of the HAM series at a given truncation order, and a value tuned to the near-linear regime need not remain adequate far from it. The convergence-control parameter used for every result reported below is therefore not fixed but is instead chosen, separately for each (α^2, β) pair, to minimise the averaged squared residual

$$J(\hbar) = \int_0^1 [(1+\beta\phi(X))\phi''(X) - \alpha^2\phi(X)]^2 dX,$$

Evaluated on the sixth-order HAM sum, following the optimal- $\hbar$ procedure proposed by Liao for strongly nonlinear problems. The minimisation was carried out numerically (SciPy) for each parameter combination reported in the Results section.

Table 1: Sixth-order HAM solution (residual-optimised $\hbar$) versus the numerical solution, for seven combinations of the reaction-diffusion modulus α^2 and the saturation parameter β

α^2	β	$\hbar^*$	$\phi(0)$ numerical	$\phi(0)$ HAM (6th)	Max. rel. error (%)	η numerical	η HAM (6th)
0.5	0.3	-0.6637	0.82953	0.82955	0.002	0.90932	0.90933
0.5	1	-0.4528	0.88152	0.88157	0.006	0.95846	0.95848
1	0.3	-0.5911	0.69585	0.69596	0.016	0.83300	0.83306
1	1	-0.4139	0.77598	0.77645	0.061	0.91755	0.91773
2	0.3	-0.5024	0.50568	0.50621	0.104	0.71451	0.71490
2	1	-0.3548	0.60154	0.60419	0.440	0.83979	0.84104
4	0.5	-0.3527	0.31727	0.32031	0.959	0.61190	0.61466

The optimised convergence-control parameter $\hbar^*$ is not constant; it moves from about -0.66 at the mildest condition tested ($\alpha^2=0.5$, $\beta=0.3$) toward about -0.35 at the most nonlinear condition tested ($\alpha^2=4$, $\beta=0.5$), confirming that a single fixed $\hbar$ cannot serve the whole range equally well. With $\hbar$ optimised case by case, the maximum relative difference between the HAM and numerical concentration profiles stays at or below 1% throughout the tested range, rising monotonically from about 0.002% at the mildest condition to about 0.96% at the most nonlinear one. The same

Results

Table 1 compares the sixth-order HAM solution, with its residual-optimised $\hbar$, against an independent high-accuracy numerical solution of the full nonlinear boundary value problem (collocation, SciPy solve_bvp, relative and absolute tolerance 10^{-11}) over seven combinations of the reaction-diffusion modulus α^2 and the saturation parameter β spanning the range $0.5 \leq \alpha^2 \leq 4$ and $0.3 \leq \beta \leq 1.0$. Two indicators are reported: the centre-line concentration $\phi(0)$, which is the most sensitive single point on the profile, and the effectiveness factor η , defined as the ratio of the actual reaction rate integrated across the layer to the rate that would be obtained if the whole layer were at the bulk (surface) concentration.

pattern is reflected in the effectiveness factor, where the HAM and numerical values agree to at least four significant figures at low α^2 and to roughly two significant figures at $\alpha^2=4$.

Figure 1 shows the full concentration profile $\phi(X)$ across the layer for four values of α^2 at a fixed saturation parameter $\beta=0.5$, comparing the numerical solution (solid lines) with the sixth-order HAM solution evaluated at eleven points (open markers). The two solutions are visually indistinguishable at this scale for all four values of α^2 shown.

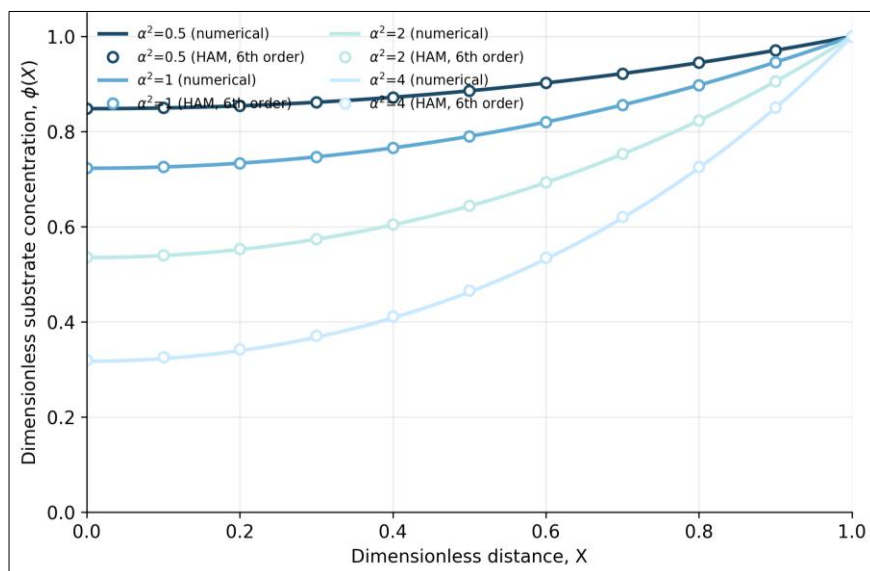


Fig 1: Dimensionless substrate concentration profiles for $\alpha^2=0.5$, 1, 2 and 4 at $\beta=0.5$: numerical solution (lines) versus sixth-order HAM solution with residual-optimised $\hbar$ (markers)

Figure 2 shows the effectiveness factor η as a function of the Thiele-type modulus $\alpha=\sqrt{\alpha^2}$ over the range $0.2 \leq \alpha \leq 3$, for three values of the saturation parameter β . As α increases, diffusion becomes increasingly limiting relative to reaction, and η falls from close to unity toward lower values, in the classical pattern familiar from Thiele-modulus analysis in

heterogeneous catalysis. At any fixed α , increasing β raises η , because higher β pushes the kinetics toward the less concentration-sensitive, zero-order limit, which is less affected by the depletion of substrate near the centre of the layer.

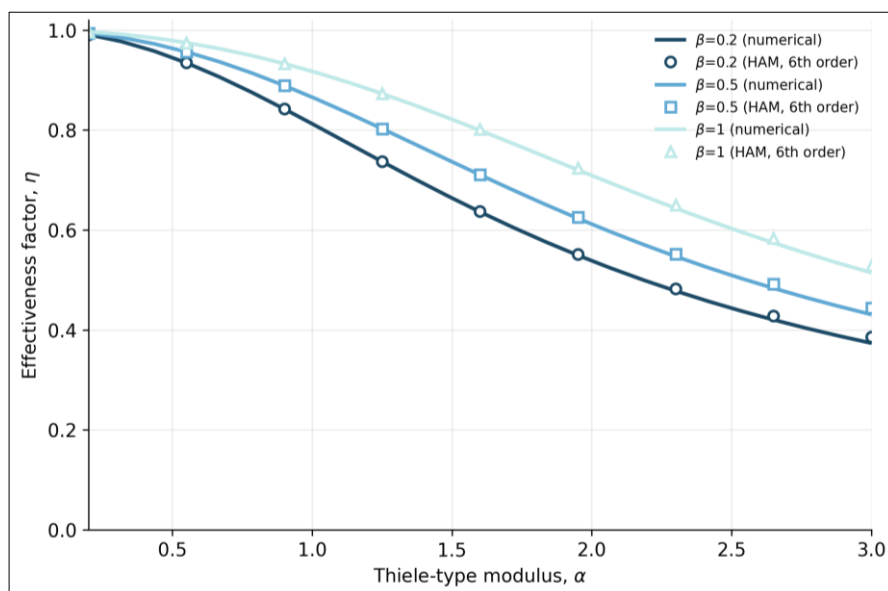


Fig 2: Effectiveness factor η as a function of the Thiele-type modulus α , for $\beta=0.2, 0.5$ and 1.0 : numerical solution (lines) versus sixth-order HAM solution with residual-optimised h (markers)

Overall, the sixth-order HAM solution with a case-by-case optimised h reproduces both the local concentration profile and the integrated effectiveness factor to within about 1% of the independently computed numerical solution across the whole tested range, with the small residual discrepancy growing smoothly as the problem becomes more strongly nonlinear (larger α^2 and β).

Discussion

The results in Table 1 and Figures 1-2 show two things at once: that HAM, applied to this problem, is capable of high accuracy, and that this accuracy is conditional on choosing h properly rather than inheriting the classical HPM value of $h=-1$. The latter point is easy to miss because most demonstrations of HPM and ADM on immobilized-enzyme problems in the literature are carried out at relatively mild parameter values, where a fixed auxiliary parameter and a low-order truncation already agree well with numerical results. The residual-minimisation approach used here removes h as a source of hidden error by tuning it to the specific problem instance before any comparison with a numerical or literature result is made.

The physical trends recovered here are consistent with earlier semi-analytical treatments of the same class of problem. Larger α^2 corresponds to a thicker layer, a faster intrinsic reaction, or slower diffusion, all of which drive the interior concentration down and reduce the effectiveness factor, matching the qualitative behaviour reported for immobilized glucose isomerase and for amperometric biosensor models solved by the homotopy perturbation method. Increasing β pushes the Michaelis-Menten kinetics toward the zero-order limit, which is less sensitive to local depletion of substrate; the corresponding rise in η at fixed α seen in Figure 2 mirrors this shift and is the same qualitative effect noted where reaction-diffusion equations of this type have been solved by the modified Adomian decomposition method and by a third-order regular perturbation expansion. The present results extend this body of work mainly by making the auxiliary-parameter choice explicit and systematic and by reporting how the resulting error grows across a parameter grid rather than at a single operating point.

Two further points are worth noting. First, HPM is formally the special case of HAM obtained by setting $h=-1$ and

$H(X)=1$; the sharp growth in error observed here when h is held at -1 outside the near-linear regime is therefore also a statement about the limited range over which HPM solutions of this equation, at a comparable truncation order, can be expected to hold. Second, because the residual-minimisation step needs only the governing equation itself and not a pre-computed numerical solution, it can be used as a stand-alone convergence check in situations such as more complex geometries or additional mass-transfer resistances where an independent high-accuracy numerical solution is harder to obtain.

From a design standpoint, the closed-form-like HAM expressions and the effectiveness-factor curves in Figure 2 let a biosensor or reactor designer read off, for a chosen enzyme loading and layer thickness (through α^2) and a chosen operating substrate range (through β), how close the system will run to its diffusion-free reaction rate, without needing to re-solve the boundary value problem numerically for every candidate design point.

Limitations

The model considered here is restricted to a planar immobilized-enzyme layer under steady-state, isothermal conditions, with simple irreversible Michaelis-Menten kinetics for a single substrate and no external mass-transfer resistance at the layer surface. Cylindrical and spherical particle geometries, non-isothermal effects, enzyme deactivation over time, substrate or product inhibition, and boundary-layer resistance at the particle surface are all encountered in real immobilized-enzyme systems and are not covered by the present formulation. The convergence-control parameter was optimised over the specific range $0.5 \leq \alpha^2 \leq 4$ and $0.3 \leq \beta \leq 1.0$; outside this range the sixth-order truncation used here may require re-optimisation of h , additional HAM orders, or both, before the same level of accuracy can be claimed.

Conclusion

This paper derived a sixth-order homotopy analysis solution for the nonlinear reaction-diffusion equation that governs a planar immobilized Michaelis-Menten enzyme layer, using a fully symbolic recursive procedure for the higher-order deformation equations. Rather than being fixed at the classical

convergence-control value $h=-1$ inherited from the homotopy perturbation method, h was optimised separately for each reaction-diffusion modulus and saturation parameter by minimising the residual of the governing equation, and the resulting solution was checked both against the exact linear-limit solution and against an independent numerical solution of the full nonlinear problem. Across the tested range, the sixth-order HAM solution matched the numerical concentration profile and effectiveness factor to within about 1%, with the discrepancy growing smoothly as the problem became more strongly nonlinear. The practical implication is that a properly tuned HAM solution can serve as a fast, closed-form-like substitute for repeated numerical solution when exploring how enzyme loading, layer thickness, and substrate concentration jointly affect the performance of an immobilized-enzyme reactor or biosensor. The same symbolic-recursion-plus-residual-optimisation procedure used here is not specific to planar geometry or to simple Michaelis-Menten kinetics, and extending it to cylindrical or spherical particles, to substrate-inhibited kinetics, or to systems with external mass-transfer resistance is a natural next step.

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