CHAPTER V

ANALYTICAL EXPRESSION OF SUBSTRATE AND ENZYME CONCENTRATION IN THE HENRI-MICHAELIS-MENTEN MODEL USING HOMOTOPY ANALYSIS METHOD

5.1. INTRODUCTION

The vast majority of chemical transformations inside cells are catalyzed by enzymes. Enzymes accelerate the rate of chemical reactions (both forward and backward) without being consumed in the process and tend to be very selective, with a particular enzyme accelerating only a specific reaction. The model for enzyme action, first suggested by Brown and Henri but later established more thoroughly Michaelis and Menten, suggests the binding of free enzyme to the reactant forming an enzyme-reactant complex. This complex undergoes a transformation, releasing product and free enzyme. The free enzyme is then available for another round of binding to new reactant.

The Michaelis-Menten model was proposed in 1913 [1] and was mathematically described by Brigg and Haldane [2] and recently extended to conditions beyond the steady-state [3]. In a recent report, Bajzer and Strechler [4] discussed various aspects of the enzyme-substrate dependence of kinetic processes involving the Henri-Michaelis-Menten (HMM) model of enzyme action. These authors proposed a model of enzyme action based on a quasi-steady-state condition involving a prolonged steady-state that is achieved when the total substrate concentration is near the initial substrate concentration and higher than the initial enzyme concentration. Most of the previous investigation addressed that had generally started with the classic Michaelis-Menten equation obtained for conditions of high substrate concentration [5-7]. Bispo et.al. [8] proposed a
more complete explanation of this behavior based on a numerical simulation of the extent of reaction equations that described the above process. Even, the solution obtained with this approach is similar when compared with the previous work [3], they are generally more accurate. Then these results can be used to determine the kinetic behavior of enzyme action at any enzyme-substrate ratio based on a numerical simulation using the respective velocities of reaction.

Very recently Bispo et. al. [8], solved the non-linear equations in Michaelis – Menten kinetics using fourth order Runge-Kutta method. However to the best of my knowledge, there were no rigorous analytical expression of concentration of substrate, enzyme, enzyme-substrate complex and product have been derived. The purpose of this chapter is to derive approximate analytical expressions for concentration of substrate, enzyme, enzyme-substrate complex and product using Homotopy analysis method.

5.2. MATHEMATICAL FORMULATION OF THE PROBLEM

In Michaelis–Menten kinetics, enzyme reaction scheme is expressed by [3]

\[ S + E \xrightleftharpoons[k_1]{k_2} ES \to P + E \] (5.1)

where \( S, E, ES \) and \( P \) represent substrate, free enzyme, enzyme-substrate complex and product respectively. The time-dependence of the concentration of each species in solution, \( C(t) \), can be expressed in the following equations:

\[ C_S(t) = c_S - x_1(t) + x_{-4}(t) \] (5.2)

\[ C_E(t) = c_E - x_1(t) + x_{-4}(t) + x_2(t) \] (5.3)

\[ C_{ES}(t) = x_1(t) - x_{-4}(t) - x_2(t) \] (5.4)

\[ C_P(t) = x_2(t) \] (5.5)
where \( c \) represents the initial concentration, \( x \) the extent of reaction (mol/L) and the subscript indicates the corresponding direction of the process. The reaction rate is expressed in terms of the rate constant as follows:

\[
\frac{dx_i(t)}{dt} = k_i[c - x_i(t) + x_{-i}(t) - x_{-j}(t)]
\]  
(5.6)

\[
\frac{dx_{-i}(t)}{dt} = k_{-i}[x_i(t) - x_{-i}(t) - x_{-j}(t)]
\]  
(5.7)

\[
\frac{dx_{-j}(t)}{dt} = k_{-j}[x_i(t) - x_{-i}(t) - x_{-j}(t)]
\]  
(5.8)

The boundary conditions appropriate to the problem are

\[x_i(0) = l, \ x_{-i}(0) = m \ \text{and} \ x_{-j}(0) = n\]  
(5.9)

Eq. (5.7) and Eq. (5.8) have the following relation

\[
\frac{dx_{-i}(t)}{dt} = \frac{k_{-i}}{k_2} \frac{dx_{-j}(t)}{dt}
\]  
(5.10)

Integrating the above Eq. (5.10) on both sides, we get

\[x_{-i}(t) = \frac{k_{-i}}{k_2} x_{-j}(t) + c_1\]  
(5.11)

Where \( c_1 \) is an arbitrary constant.

Substituting Eq. (5.11) in Eq. (5.6) and Eq. (5.8) we obtain the following non-linear differential equations:

\[
\frac{dx_i(t)}{dt} = k_i \left[ c - x_i(t) + \frac{k_{-i}}{k_2} x_{-j}(t) + c_1 \right] \left[ c - x_i(t) + \frac{1}{k_2} \frac{dx_{-j}(t)}{dt} \right]
\]  
(5.12)

\[
\frac{dx_{-j}(t)}{dt} = k_{-j} \left[ x_i(t) - (1 + \frac{k_{-i}}{k_2}) x_{-j}(t) - c_1 - x_{-j}(t) \right]
\]  
(5.13)
5.3. SOLUTION OF BOUNDARY VALUE PROBLEM USING HOMOTOPY ANALYSIS METHOD.

The Homotopy analysis method is also an extremely simple method [9-12] to solve the non-linear differential equations. Furthermore, the obtained result is of high accuracy. The basic concept of Homotopy analysis method is given in Appendix A. Using this method (see Appendix B), $x_1(t)$ and $x_2(t)$ are obtained as follows:

$$x_1(t) = (A + l)e^{-k_E t} - hk_2\left\{ \frac{c_s + c_l + \frac{nk_{r,E}c_E}{k_1}e^{-k_E t} + \frac{(c_l + c_s)m}{k_1}e^{-k_E t}}{k_1(k_cE - k_2) + \frac{nk_{r,E}c_E}{k_2}e^{-k_E t}} \right\} (5.14)$$

$$x_2(t) = (B + n)e^{-k_E t} - hk_2\left\{ \frac{\ln e^{-(k_{r,E} + k_2)t} - \frac{k_E n^2}{k_2(k_cE - 2k_2)}e^{-2k_E t}}{k_2 - k_1 c_E - \frac{k_{r,E}c_E}{k_2}e^{-k_E t} - \frac{c_l}{k_2}} \right\} (5.15)$$

Using Eq. (5.11), we get

$$x_{-1}(t) = \frac{k_{-1}}{k_2}\left( (B + n)e^{-k_E t} - hk_2\left\{ \frac{\ln e^{-(k_{r,E} + k_2)t} - \frac{k_E n^2}{k_2(k_cE - 2k_2)}e^{-2k_E t}}{k_2 - k_1 c_E - \frac{k_{r,E}c_E}{k_2}e^{-k_E t} - \frac{c_l}{k_2}} \right\} \right) + c_{-1} (5.16)$$

Substituting the above equations Eq.(5.14)-(5.16) into Eq.(5.2)-(5.5), we get the concentration of substrate, enzyme, enzyme-substrate complex and product as follows:

$$C_S(t) = c_S - (A + l)e^{-k_E t} + hk_2\left\{ \frac{c_s + c_l + \frac{nk_{r,E}c_E}{k_1}e^{-k_E t} + \frac{(c_l + c_s)m}{k_1}e^{-k_E t}}{k_1(k_cE - k_2) + \frac{nk_{r,E}c_E}{k_2}e^{-k_E t}} \right\} (5.17)$$

$$+ \frac{k_{-1}}{k_2}\left( (B + n)e^{-k_E t} - hk_2\left\{ \frac{\ln e^{-(k_{r,E} + k_2)t} - \frac{k_E n^2}{k_2(k_cE - 2k_2)}e^{-2k_E t}}{k_2 - k_1 c_E - \frac{k_{r,E}c_E}{k_2}e^{-k_E t} - \frac{c_l}{k_2}} \right\} \right) + c_{-1}$$

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\[ C_E(t) = c_E - (A + l)e^{-k_2 t} + h k_1 \left\{ \sum_{k=1}^{c_1} \frac{c_S + c_1 + \frac{nk_2 e_k}{k_1} e^{-k_2 t}}{k_2 (k_c E - k_2)} e^{2k_2 t} + \frac{(c_1 + c_2)n}{k_c E - k_2} \right\} \]

\[ C_{ES}(t) = (A + l)e^{-k_2 t} - h k_2 \left\{ \sum_{k=1}^{c_1} \frac{c_S + c_1 + \frac{nk_2 e_k}{k_1} e^{-k_2 t}}{k_2 (k_c E - k_2)} e^{2k_2 t} + \frac{(c_1 + c_2)n}{k_c E - k_2} \right\} \]

\[ C_p(t) = (B + n)e^{-k_2 t} - h k_2 \left\{ \sum_{k=1}^{c_1} \frac{c_S + c_1 + \frac{nk_2 e_k}{k_2} e^{-k_2 t}}{k_2 (k_c E - k_2)} e^{2k_2 t} + \frac{(c_1 + c_2)n}{k_c E - k_2} \right\} \]

where the constant \( A, B \) and \( c_1 \) are given in the equations (5.B.11-5.B.13). Here \( h \) is the convergence control parameter. Determination of \( h \) is explained in Appendix C.

5.4. NUMERICAL SIMULATION

The HAM provides an analytical solution in terms of an infinite power series. However, there is a practical need to evaluate this solution and to obtain numerical values from the infinite power series. The consequent series truncation and the practical procedure conducted to accomplish this task, together transforms the other-wise analytical results into an exact solution, which is evaluated to a finite degree of accuracy.

In order to investigate the accuracy of the HAM solution with a finite number of terms, the system of differential equation were solved. To show the efficiency of the present method for our problem in comparison with the numerical solution (SCILAB program) we report our results graphically. The SCILAB program is also given in Appendix-C.
The Eq. (5.17)-(5.20) are also solved by numerical method. The function main4 in scilab software is used for solving the initial value problems. The obtained analytical results are compared with the numerical results for various values of parameters $k_1, k_2$ and $k_3$ in Fig. 5.1-5.8. In all cases the concentration of the species $C_S, C_E, C_{ES}$ and $C_P$ gives good agreement with the numerical results.

5.4. RESULTS AND DISCUSSION

Eq. (5.17)-Eq. (5.20) represent the new analytical expressions for the substrate, free enzyme, enzyme-substrate complex and product concentration respectively. Fig.5.1 and Fig.5.2 represent the substrate concentration versus time for various values of $c_S$ and $c_E$. From Fig.5.1 (a), it is inferred that $S$ increases when $c_S$ increases. As the time $t$ increases, $S$ decreases and reaches to zero. From Fig.5.2 (a), it is inferred that $S$ decreases when $c_E$ increases. As the time $t$ increases, $S$ decreases and reaches to zero.

Fig.5.3 and Fig.5.4 represent the enzyme concentration versus time for various values of $c_S$ and $c_E$. From Fig.5.3 (a), it is inferred that $E$ decreases when $c_S$ increases. As the time $t$ increases, $E$ decreases when $t > 0.5$, enzyme concentration slowly increases and reaches its maximum value 5 when $c_E = 5$. From Fig.5.4 (a), it is inferred that $E$ increases when $c_E$ increases. As the time $t$ increases, $E$ decreases and suddenly reaches its maximum value when $c_S = 1$.

Fig.5.5 and Fig.5.6 represent the enzyme-substrate concentration versus time for various values of $c_S$ and $c_E$. From Fig.5.5 (a), it is inferred that $ES$ increases when $c_S$ increases. As the time $t$ increases, $ES$ increases and attains its maximum value when $c_E = 5$ and slowly decreases and reaches to zero. From Fig.5.6 (a), it is inferred that $ES$
increases when \( c_E \) increases. As the time \( t \) increases, \( ES \) increases and attains its maximum value and suddenly decreases and reaches zero.

Fig.5.7 and Fig.5.8 represent the product concentration versus time for various values of \( c_s \) and \( c_E \). From Fig.5.7 (a), it is inferred that \( P \) increases when \( c_s \) increases. As the time \( t \) increases, \( P \) increases and attains its steady-state value when \( c_E = 5 \). From Fig.5.8 (a), it is inferred that \( P \) increases when \( c_E \) increases. As the time \( t \) increases, \( P \) increases and attains its maximum value 1. Figs. 5.1(b) - 5.8(b) represent the three dimensional diagram on concentration of species versus time and their initial concentration. The three dimensional figures confirms all the above discussed results.
Fig. 5.1 (a). Time dependence of substrate concentration in the HMM model. Solid line represent analytical expression (Eq. (5.17)) and ‘+’ represent numerical simulation. In this method \( k_i = 1, k_{2i} = 1.2, k_2 = 1000, c_k = 5 \) and \( c_s \) (initial substrate concentration \([S_0]\)) varied from 1 to 10 for \( h = -1 \). (b). Countour plots of the time dependence of substrate concentration at distinct \([s_0]\) values.
Fig. 5.2 (a). Time dependence of substrate concentration in the HMM model. Solid line represent analytical expression (Eq. (5.17)) and ‘+’ represent numerical simulation. In this method $k_i = 10, k_{-i} = 1, k_j = 1, c_s = 1$ and $c_r$ (initial enzyme concentration $[E_0]$) varied from 1 to 10 for $h = -1$. (b). Contour plots of the time dependence of substrate concentration at distinct $[E_0]$ values.
Fig. 5.3 (a). Time dependence of enzyme concentration in the HMM model. Solid line represent analytical expression (Eq. (5.18)) and ‘+’ represent numerical simulation. In this method $k_i = 2, k_{-i} = 1.5, k_f = 1, c_E = 5$ and $c_s$ (initial substrate concentration $[S_0]$) varied from 1 to 7. (b). Contour plots of the time dependence of free enzyme concentration at distinct $[S_0]$ values.
Fig. 5.4 (a). Time dependence of enzyme concentration in the HMM model. Solid line represent analytical expression (Eq. (5.18)) and ‘+’ represent numerical simulation. In this method $k_1 = 2, k_2 = 1.5, k_3 = 1, c_s = 1$ and $c_E$ (initial enzyme concentration $[E_0]$) varied from 1 to 7 for $h = -0.4809$. (b). Contour plots of the time dependence of free enzyme concentration at distinct $[E_0]$ values.
Fig. 5.5 (a) Time dependence of enzyme-substrate concentration in the HMM model. Solid line represents analytical expression (Eq. (5.19)) and ‘+’ represent numerical simulation. In this method $k_1 = 2, k_2 = 1.5, k_3 = 1, c_E = 5$ and $c_S$ (initial substrate concentration $[S_0]$) varied from 1 to 5. (b) Contour plots of the time dependence of complex concentration at distinct $[S_0]$ values.
Fig.5.6 (a). Time dependence of enzyme-substrate concentration in the HMM model. Solid line represent analytical expression (Eq.(5.19)) and ‘+’ represent numerical simulation. In this method \( k_1 = 2, k_2 = 1.5, k_3 = 1, c_s = 1 \) and \( c_E \) (initial enzyme concentration \([E_0]\) ) varied from 1 to 5 for \( h = -0.4805 \). (b). Contour plots of the time dependence of complex concentration at distinct \([E_0]\) values.
Fig. 5.7 (a). Time dependence of product concentration in the HMM model. Solid line represent analytical expression (Eq.(5.20) and ‘+’ represent numerical simulation. In this method \(k_1 = 10, k_2 = 1.1, k_3 = 1, c_k = 5\) and \(c_s\) (initial substrate concentration \([S_0]\) ) varied from 1 to 10. (b). Contour plots of the time dependence of product formation at distinct \([s_0]\) values.
Fig 5.8 (a). Time dependence of product concentration in the HMM model. Solid line represent analytical expression (Eq.(5.20)) and ‘+’ represent numerical simulation. In this method $k_1 = 10, k_2 = 1.1, k_3 = 1, c_S = 5$ and $c_E$ (initial enzyme concentration $[E_0]$) varied from 1 to 10 for $h = -0.3741$. (b). Contour plots of the time dependence of product formation at distinct $[E_0]$ values.
5.6. CONCLUSION

In this work, the time dependent non-linear differential equations have been solved analytically. In this chapter, the analytical expressions of the concentration of the species $C_s$, $C_E$, $C_{ES}$ and $C_p$ are derived in terms of the parameters $k_r$, $k_j$ and $k_z$ using Homotopy analysis method. All the analytical results are compared with our numerical results. A good agreement with the available numerical results is thus notified. The analytical result is a powerful tool for analyzing kinetic system. Also theoretical result derived in this chapter is useful for a better understanding and optimization of biological systems.

5.7. APPENDICES

A. BASIC CONCEPT OF HOMOTOPY ANALYSIS METHOD

Consider the following differential equation [10-12]:

$$N[u(t)] = 0 \quad (5.A.1)$$

Where $N$ is a nonlinear operator, $t$ denotes an independent variable, $u(t)$ is an unknown function. For simplicity, we ignore all boundary or initial conditions, which can be treated in the similar way. By means of generalizing the conventional Homotopy method, Liao [10] constructed the so-called zero-order deformation equation as:

$$(1 - p)L[\varphi(t; p) - u_0(t)] = phH(t)N[\varphi(t; p)] \quad (5.A.2)$$

where $p \in [0,1]$ is the embedding parameter, $h \neq 0$ is a nonzero auxiliary parameter, $H(t) \neq 0$ is an auxiliary function, $L$ an auxiliary linear operator, $u_0(t)$ is an initial guess of $u(t)$, $\varphi(t; p)$ is an unknown function. It is important, that one has great freedom to choose auxiliary unknowns in HAM. Obviously, when $p = 0$ and $p = 1$, it holds
\[ \phi(t;0) = u_0(t) \text{ and } \phi(t;1) = u(t) \]  

(5.A.3)

respectively. Thus, as \( p \) increases from 0 to 1, the solution \( \phi(t;p) \) varies from the initial guess \( u_0(t) \) to the solution \( u(t) \). Expanding \( \phi(t;p) \) in Taylor series with respect to \( p \), we have

\[ \phi(t;p) = u_0(t) + \sum_{m=1}^{\infty} u_m(t) p^m \]  

(5.A.4)

where

\[ u_m(t) = \frac{1}{m!} \left. \frac{\partial^m \phi(t;p)}{\partial p^m} \right|_{p=0} \]  

(5.A.5)

If the auxiliary linear operator, the initial guess, the auxiliary parameter \( h \), and the auxiliary function are so properly chosen, the series Eq. (5.A.4) converges at \( p=1 \) then we have

\[ u(t) = u_0(t) + \sum_{m=1}^{\infty} u_m(t) \]  

(5.A.6)

Differentiating Eq. (5.A.2) for \( m \) times with respect to the embedding parameter \( p \), and then setting \( p = 0 \) and finally dividing them by \( m! \), we will have the so-called \( m-th \) order deformation equation as:

\[ L[u_m - \mathcal{X}_m u_{m-1}] = hH(t) \mathcal{R}_m(u_{m-1}) \]  

(5.A.7)

where

\[ \mathcal{R}_m(u_{m-1}) = \frac{1}{(m-1)!} \frac{\partial^{m-1} N[\phi(t;p)]}{\partial p^{m-1}} \]  

(5.A.8)

and

\[ \mathcal{X}_m = \begin{cases} 
0, & m \leq 1, \\
1, & m > 1.
\end{cases} \]  

(5.A.9)
Applying $L^{-1}$ on both side of Eq. (5.A.7), we get

$$u_m(t) = \chi_{m}u_{m-1}(t) + hL^{-1}[H(t)\mathcal{R}_{m}(u_{m-1})]$$  \hspace{1cm} (5.A.10)

In this way, it is easily to obtain $u_m$ for $m \geq 1$, at $M^{th}$ order, we have

$$u(t) = \sum_{m=0}^{M} u_m(t)$$  \hspace{1cm} (5.A.11)

When $M \to +\infty$, we get an accurate approximation of Eq. (5.A.1). For the convergence of the above method we refer the reader to Liao [10]. If Eq. (5.A.1) admits unique solution, then this method will produce the unique solution.

**B. SOLUTION OF THE Eq. (5.12) AND Eq. (5.13) USING HAM**

We construct the Homotopy for the Eq. (5.12) and Eq. (5.13) as follows:

$$(1 - p)\left(\frac{dx_1}{dt} + k_1c_kx_1\right) = hp\left[\frac{dx_1}{dt} + k_1c_kx_1 - k_1\left[c_5 + \frac{k_{-1}}{k_2}x_2 + c_1\right]\left[c_k - \frac{1}{k_2} \frac{dx_2}{dt}\right]\right]$$ \hspace{1cm} (5.B.1)

$$(1 - p)\left(\frac{dx_2}{dt} + k_2x_2\right) = hp\left[\frac{dx_2}{dt} + k_2x_2 - k_2(x_1 - \frac{k_{-1}}{k_2}x_2 - c_1)\right]$$ \hspace{1cm} (5.B.2)

The approximate solution of Eq. (5.B.1) and Eq. (5.B.2) is

$$x_1 = x_{10} + px_{11} + p^2x_{12} + \ldots$$ \hspace{1cm} (5.B.3)

$$x_2 = x_{20} + px_{21} + p^2x_{22} + \ldots$$ \hspace{1cm} (5.B.4)

Substituting Eq. (5.B.3) and Eq. (5.B.4) into Eq. (5.B.1) and Eq. (5.B.2) respectively, and equate the terms with the identical powers of $p$, we obtain

$$p^0 : \frac{dx_{10}}{dt} + k_1c_kx_{10} = 0, \frac{dx_{20}}{dt} + k_2x_{20} = 0$$ \hspace{1cm} (5.B.5)
Solving (5.B.5) and (5.B.6) and using the initial conditions Eq. (5.9) we can obtain the following results:

\[ x_t = le^{-k_1 t} \quad (5.B.7) \]
\[ x_{20} = ne^{-k_2 t} \quad (5.B.8) \]
\[ x_j = A e^{-k_1 t} - hk_1 \left\{ \frac{c_5 + c_1 + \frac{nk_j c_E}{k_1}}{k_1 (k_j c_E - k_2)} e^{-k_1 t} + \frac{(c_1 + c_5) n}{k_2 c_E - k_2} e^{-k_2 t} + \frac{nl}{k_2} e^{-(k_1 x + k_2) t} - \frac{k_1 n^2}{k_2 (k_j c_E - k_2)} e^{-k_1 t} \right\} \quad (5.B.9) \]
\[ x_{2j} = B e^{-k_2 t} - hk_2 \left[ \frac{le^{-k_1 t} - \frac{nk_j c_E}{k_2}}{k_2 - k_j c_E} - c_1 \right] \quad (5.B.10) \]

where

\[ A = hk_1 \left\{ \frac{c_5 + c_1 + \frac{nk_j c_E}{k_1}}{k_1 (k_j c_E - k_2)} + \frac{(c_1 + c_5) n}{k_2 c_E - k_2} + \frac{ln}{k_2} - \frac{k_1 n^2}{k_2 (k_j c_E - k_2)} \right\} \quad (5.B.11) \]
\[ B = hk_2 \left[ \frac{l}{k_2 - k_j c_E} - \frac{c_1}{k_2} \right] \quad (5.B.12) \]
From Eq. (5.11), we get (by using Eq. (5.9)),

\[ c_1 = m - \frac{k_{c1}}{k_2} \]  

(5.B.13)

According to the HAM, we can conclude that

\[ x_1 = \lim_{p \to 1} x_1(t) = x_{10} + x_{11} \]  

(5.B.14)

\[ x_2 = \lim_{p \to 1} x_2(t) = x_{20} + x_{21} \]  

(5.B.15)

After putting Eq. (5.B.14) and Eq. (5.B.15) in Eq. (5.B.1) and Eq. (5.B.2) respectively, we obtain Eq. (5.14) and Eq. (5.15) in the text.

C. DETERMINING THE REGION OF \( h \) FOR VALIDITY

The analytical solution should converge. It should be noted that the auxiliary parameter \( h \) controls the convergence and accuracy of the solution series. The analytical solution represented by (5.6), (5.7) and (5.8) contains the auxiliary parameter \( h \), which gives the convergence region and rate of approximation for the homotopy analysis method. In order to define region such that the solution series is independent of \( h \), a multiple of \( h \) curves are plotted. The region where the concentration profiles \( C_S(t) \) and \( C_S'(t) \) versus \( h \) is a horizontal line known as the convergence region for the corresponding function. The common region among \( C_S(t) \) and its derivatives are known as the overall convergence region. To study the influence of \( h \) on the convergence of solution, \( h \)-curves of \( C_S(5) \) and \( C_S'(5) \) are plotted in Figs.5.9 (a) and (b) respectively for \( c_s = 1, c_E = 1.2, \ k_i = 1, \ k_j = 1.2 \ and \ k_2 = 1000 \). These figures clearly indicate that the valid region of \( h \) is about \(-1.1 < h < -0.9\). Similarly we can
find the value of the convergence control parameter $h$ for different values of the constant parameters.

**Fig. 5.9.** The h-curve for Eq. (5.17) to indicate the convergence region, for $k_1 = 1$, $k_j = 1.2$, $k_2 = 1000$ and $C_E = 5$. Here $h = -1$. (This value of $h$ is used to draw the figures (1a) and (1b)).
5.8. NOMENCLATURE

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tr>
<td>S</td>
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<td>E</td>
<td>Enzyme (mol/l)</td>
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<tr>
<td>ES</td>
<td>Enzyme Substrate (mol/l)</td>
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<td>Product (mol/l)</td>
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<tr>
<td>$k_{-1}, k_2$</td>
<td>Rate constants ($s^{-1}$)</td>
</tr>
</tbody>
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5.9. REFERENCES

1. L. Michaelis, M. L. Menten, Biochem. Z., 49 (1913), 333.
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