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An Iterative Solution of the Michaelis–Menten Equations

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Abstract

A new approach is developed for the study of the Michaelis-Menten kinetic equations in all times *t*, based on their solution in the limit of large *t*. The linear terms in concentration of the substrate and the intermediate complex are more dominant than their product in this limit and the quadratic term can therefore be treaded iteratively. The proper behavior of the analytical solutions we give, in the small and large time limit, leads for the first time to a remarkable indistinguishability between the analytical and the numerical results in all times and for a large region of the parameters of the problem. Enlargement of the region of imperceptibility is found going from the zeroth to the first order iteration. The analytical description of the steady state where the concentration of the intermediate complex becomes maximum, permits the exploration of the conditions of both fast and slow transient to this region.

1.Introduction

The Michaelis-Menten mechanism [1,2] describes the transformation of a substrate *S* into the product *P* via the catalytic action of an enzyme *E*. The process passes through an intermediate state where the enzyme-substrate complex *C* is formed, and is schematically depicted as :

$$S+E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} E+P \quad . \qquad (1)$$

The forward and the reverse rate constants of the complex formation are k_1(in $M^{-1}s^{-1}$) and k_{-1} (in s^{-1}) while k_2(in s^{-1}) is the rate of product formation and the recruiting of the enzyme. If we use the same symbols to describe the concentrations of the four species the four ordinary differential equations that describe the evolution of the system, based on the mass action, are:

$$\frac{dS}{dt} = -k_1 SE + k_{-1} C \qquad (2a)$$

$$\frac{dE}{dt} = -k_1 SE + (k_{-1} + k_2)C \quad (2b)$$

$$\frac{dC}{dt} = k_1 SE - (k_{-1} + k_2)C \quad (2c)$$

$$\frac{dP}{dt} = k_2 C \quad . \quad (2d)$$

While the fourth equation can lead to the determination of the product P from C the addition of the second with the third equation yields the conservation of the sum $E+C$ of the two concentrations. With the assumption that no complex exists at the beginning of the reactions the complex concentration at $t=0$ can be taken equal to zero, leading to the relation $E=E_0-C$, where E_0 is the concentration of the enzyme at $t=0$. With the substitution of E with E_0-C the following two independent differential equations are obtained which fully describe the evolution of the system:

$$\frac{dS}{dt} = k_1 SC - k_1 SE_o + k_{-1} C \quad (3a)$$

$$\frac{dC}{dt} = -k_1 SC + k_1 SE_o - (k_{-1} + k_2)C \quad . \quad (3b)$$

Differentiation with respect to time a further reduction of Eqs. (3) to only one nonlinear differential equation of the second order is also possible [3]. Equivalently a single integro-differential equation can be obtained which has recently been used to study transient dynamics of the system [4]. After all the concentration of the substrate S_0 has been catalyzed, S which starts with a value S_0 at $t=0$ tends to zero at $t \to \infty$ decreasing in a monotonous way. The concentration of the complex C on the other hand, vanishes again in the limit of large times after the completion of the reaction, but since it starts at zero at $t=0$, it has to pass through a maximum at intermediate times. This general description is in accord with the numerical solution for all values of the initial concentrations E_0, S_0 and the rate constants k_1, k_{-1} and k_2, see the graphs of Figs. 1 and 2. However, since analytical solutions of Eqs. (3), valid for all parameters in all times have not been given yet, approximate description is very helpful in understanding the general behavior.

In the initial efforts to find the solution of Eqs. (2) and describe the behavior of the system the steady state(SS) assumption was used [2]. The concentration C of the intermediate complex has been considered to be constant after an initial time with its derivative dC/dt

equal to zero. Equating the second part of Eq.3b with zero, the concentration of the complex can be found, under the steady state assumption, equal to $C= SE_o/(S+\underline{K_M})$ with $\underline{K_M} = (k_{-1}+k_2)/k_1$ the Michaelis-Menten constant which represents the ratio of the rates of consumption of C to that of its production. Employing $C= SE_o/(S+\underline{K_M})$ in Eq.3a, a differential equation is obtained leading to a transcendental equation for S. The function $W(x)$ which obeys the transcendental equation $W(x)Exp[W(x)]=x$ has already been used in the study of the time evolution of the system [5,6]. The validity of steady state approximation is based on the existence of a substantial region where C remains constant but uncertainties attending the steady state assumption has been presented by means of computer investigation [7]. By means of perturbation theory in the small ratio E_o/S_o the SS assumption has been given as the limit of small E_o/S_o [8]. Furthermore conditions under which the SS assumption is valid have been examined and the declines have been found to be small at low ratio of E_o/S_o or $E_o/\underline{K_M}$ [9]. Further progress in the field has been achieved with the quasi-steady state approximation (QSSA) which assumes that the concentration C of the intermediate complex is almost constant in a quasi-steady state, with dC/dt approaching zero [10]. The QSSA has also been defined by means of perturbation expansion with the small parameter the ratio $E_o/\underline{K_M}$ [11]. Conditions for validity of QSSA have also been studied when $S_o>>E_o$ [12] but the QSSA condition $dC/dt \approx 0$ has been challenged at high E_o [13]. An extension of the region of validity of QSSA by changing variables has also been given [14] and based on dimensionless parameters a convergence in a perturbation expansion is observed for any combination of the parameters [15]. As far as specific time regions are concerned analytical approximations have been given for the early stage of the reaction [16] but also for both regions at small and large times [5]. The present effort comes to support further the quantitative description of the solution of MM kinetic equations. We present an analytical solution based on the fact that at large times the product of the concentration of the intermediate complex C with the substrate concentration S is small. Starting with the solution at $t \to \infty$ with proper initial condition at $t \to 0$, we can incorporate the product of the two concentrations in an iterative scheme without the necessity to use extra small perturbation parameters. The analytical solution which we give describes the whole time region including the maximum of the concentration of the complex and its neighbourhood for a large region of the parameters of the problem. By means of the analytical solution conditions of validity of QSSA are also presented.

2.The Iterative Solution

Convenient for the study of the Michaelis-Menten equations (3) are the reduced dimensionless variables $s=S/S_0$, $c=C/E_0$, and the dimensionless constants $k_\mu=(k_{-1}+k_2)/(k_1S_0) = K_M/S_0$, $k_\sigma=k_{-1}/(k_1S_0)$ and $\lambda=E_0/S_0$ where S_0 and E_0 are the initial concentrations of the substrate and enzyme respectively. By dividing Eqs. (3) with $k_1S_0E_0$ we take that

$$\frac{ds}{d\tau} = sc - s + k_\sigma c \tag{4a}$$

$$\lambda\frac{dc}{d\tau} = -sc + s - k_\mu c \quad , \tag{4b}$$

where the scaled time $\tau=k_1E_0\,t$ is a dimensionless variable. Easier to be handled are the second order differential equations (5), taken from Eqs. (4) after a differentiation with respect to τ and proper eliminations. The quadratic term $f=cs$ is a function of time and it is treated independently.

$$\frac{\lambda d^2s}{d\tau^2} + (\lambda + k_\mu)\frac{ds}{d\tau} + s(k_\mu - k_\sigma) = \lambda\frac{df}{d\tau} + f(k_\mu - k_\sigma), \quad f=cs \ , \tag{5a}$$

$$\frac{\lambda d^2c}{d\tau^2} + (\lambda + k_\mu)\frac{dc}{d\tau} + c(k_\mu - k_\sigma) = -\frac{df}{d\tau} \quad . \tag{5b}$$

Notice that only the three constants λ, k_μ, and k_σ , remain to describe the system of the two differential equations, and that the reduced dimensionless concentration variables $s=S/S_0$, and $c=C/E_0$, vary from 0 to 1. The reduction of the initial five constants S_0,E_0,k_1,k_{-1} and k_2 to only three k_μ , k_σ and λ together with the reduced variables c, s and τ permits the investigation in a large region of controlled values of the five parameters of the system. Regions of small and large values of k_μ , k_σ and λ of practical interest can properly be described.

In the limit $t\to\infty$ both s and c tend to zero so that the function $f=sc$ becomes negligible at large times compared to the linear concentration terms and can be neglected. The auxiliary algebraic equation of the remaining second order differential equations (5), is $\lambda\omega^2+(\lambda+k_\mu)\omega+k_\mu-k_\sigma=0$ with its two solutions x_p and x_m given by

$$x_p = \frac{-(\lambda + k_\mu) + \sqrt{(\lambda - k_\mu)^2 + 4\lambda k_\sigma)}}{2\lambda} \quad , \tag{6a}$$

$$x_m = \frac{-(\lambda + k_\mu) - \sqrt{(\lambda - k_\mu)^2 + 4\lambda k_\sigma)}}{2\lambda} \ . \tag{6b}$$

The quantities x_p and x_m , used also before [4], will be central quantities in what follows. In terms of x_p and x_m Eqs. (5) can be written as:

$$s''(\tau)-(x_p+x_m)s'(\tau)+x_p x_m s(\tau)=f'+x_p x_m f \qquad (7a)$$

$$c''(\tau)-(x_p+x_m)c'(\tau)+x_p x_m c(\tau)=-\lambda^{-1}f' \qquad (7b)$$

which in their right parts include the function f and its time derivative f'. The values of the variables at time τ=0 are $s(0)=1$, $c(0)=0$ while the values of their derivatives can be found from Eqs.4 and at time $\tau=0$ they are equal to $ds/d\tau(0)=-1$ and $dc/d\tau(0)=1/\lambda$ respectively. Notice that x_p and x_m with $x_p>x_m$, are both negative and lead to functions s and c of the structure $\mathrm{Exp}(-b\tau)$ with b positive constants independent of the time τ. Therefore the solutions s and c die in the large time limit, as expected. An iterative scheme can be used to explore the solution of Eqs. (7). In the limit $\tau \to \infty$ the f function and its derivative are negligible because f is the product of the two vanishing functions s and c. We thus can start considering that f is zero in the large time limit and determine in this zeroth order approximation the solution s_o and c_o of Eqs. (7). Next we obtain $f_o=s_o c_o$ and employ it in the right parts of Eqs. (7) to determine in this first iteration the substrate and complex concentrations s_1 and c_1. Subsequently, $f_1=s_1\ c_1$ can be determined and used in the right part of Eqs. (7). The concentrations s_2 and c_2 of the second iteration can then be determined from Eqs. (7) and so on. This, can be repeated to higher order iterations. Of interest is that Eqs. (7) always yield exponential functions of τ and are exactly soluble in all iterations. In the present effort the zeroth and first iterations are determined. In a comparison with numerical solution taken by means of the Mathematica program(http://www.wolfram.com/mathematica) a remarkable agreement is found in all times τ and for a large region of the parameters of the problem. These regions of perfect matching are increased with the order of iteration.

Starting with the zeroth order iteration we consider the f function and its derivative zero, at $\tau \to \infty$. In this limit Eqs. (7) read as

$$s_0''(\tau)-(x_p+x_m)s_0'(\tau)+x_p x_m s_0(\tau)=0 \qquad (8a)$$

$$c_0''(\tau)-(x_p+x_m)c_0'(\tau)+x_p x_m c_0(\tau)=0 \qquad . \qquad (8b)$$

Proper initial conditions are also necessary for the determination of $s_o(\tau)$ and $c_o(\tau)$. We use the boundary conditions at the limit of zero τ where $s_0(0)= 1$, $c_0(0)=0$ and $ds_0/d\tau(0)=-1$, $dc_0/d\tau(0)=1/\lambda$. From Eqs. (8) we obtain the solution:

$$s_0(\tau) = \frac{(x_p+1)Exp[x_m\tau]-(x_m+1)Exp[x_p\tau]}{x_p - x_m} \tag{9a}$$

$$c_0(\tau) = \frac{Exp[x_p\tau]-Exp[x_m\tau]}{\lambda(x_p - x_m)} \quad . \tag{9b}$$

These two expressions tie the approximate and numerical solutions in the two ends of the time, the beginning at $\tau \to 0$ and the infinity at $\tau \to \infty$ bringing closer the approximate solution with the exact one for all times. Even in this zeroth order iteration with the solution given in Eqs. (9) which has the right behavior in the $\tau \to \infty$ limit and the proper boundary condition at τ = 0, the whole region of time is exactly described for certain values of the parameters k_μ, k_σ and λ. In Figs. 1 and 2 we depict both c_0 of Eq. (9b) but also that from the numerical determination of c from Eqs. (4). The cases with large k_μ but also small k_μ are drawn in Figs.1a, 2a, and 1b, 2b respectively in order to show that interesting cases can be studied in both regions.

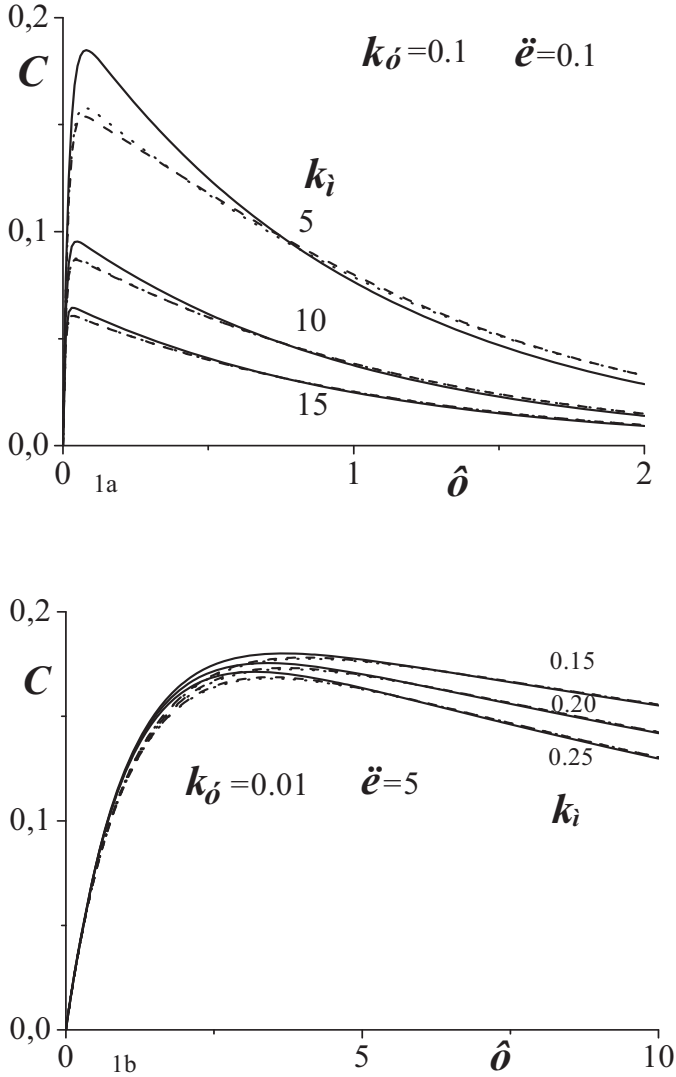

Fig.1. Plots of the concentrations c_0(Eq. (9b), solid), c_1(Eq. (18b), dash) and the numerical solution c(dot) of equations (4), as a function of the reduced time variable $\tau=k_1E_0t$ for various a)large and b)small values of $k_\mu=(k_{-1}+k_2)/(k_1S_0)$. The values of the rest constants are written in the figures. Notice the approach and the indistinguishability of the numerical c(dot) and the first iteration c_1(dash) lines in both Figs.1 and 2 for many values of the parameters.

From Fig. 1a it is clear that for larger values of k_μ the agreement of numerical results(dot lines) and those of c_0 from the expression Eq. (9b) (*solid* lines) is larger. For the values k_σ=0.1, λ=0.1 of Fig. 1a and for k_μ larger than 15 the two families of graphs become indistinguishable. This proves the appropriateness even of the zeroth iteration solution Eq. (9b) to describe the evolution of the system for a large region of the constants of the problem. Important to notice from the graphs of Fig. 1a is that larger values of k_μ give smaller times τ_m where the concentrations of the complex become maximum. Less negative gradients of the graphs for $\tau > \tau_m$, are also observed in Fig. 1a for larger k_μ and for a small value of λ. In Fig.1b smaller values of k_μ are used in order to show that the method applies to both regions of interest where K_M is larger or smaller than S_0.

In Fig. 2a we vary λ while we keep k_μ and k_σ constant. Again larger values of λ yield better agreement. For the example of Fig. 2a the graphs become indistinguishable for λ>13. It is worth to notice though, from all graphs that τ_m is a good approximation for the time where the maxima of the concentrations occur, even for the cases with different values of the maxima of the concentrations. This observation and the analytical expression of τ_m from the zeroth iteration solution , Eq. (11), permit the study of the reaction in the next first iteration stage for a wider region of the parameters. In Fig. 2b we vary k_σ and we see that though the solution is less sensitive on the variation of k_σ smaller values of k_σ give better matching in larger time extensions. The dependence of the behavior of the concentrations on the three parameters k_μ, k_σ and λ can be understood from the structure of the differential equation (5b) as well. The effect from the right part of Eq. (5b) is smaller when the value of this part is smaller than the left part of the equation. The iterative solutions will then be more successful when the left part becomes more dominant than the right one. Both k_μ and λ appear twice in the left part of Eq. (5b) and make their contribution to the left part larger when they become larger. Unlikely, k_σ appears with a negative sign that explains the opposite character to the perturbation than those of k_μ and λ. It appears though only once in the left part of the equation which makes weaker the effects of its variation. Another thing to notice from the graphs of Fig. 2b is that larger values of k_σ lead to smaller negative gradients for $\tau > \tau_m$, approaching in this way easier the steady state. Similar approaches to those of the three concentrations of the complex are observed among the substrate concentration as well.

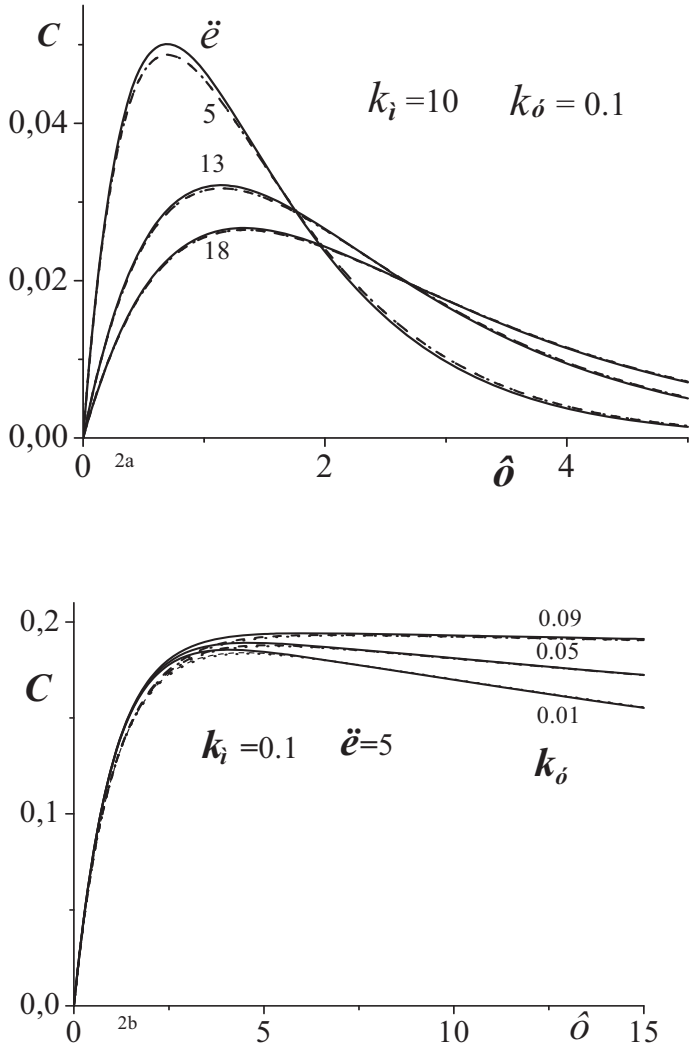

Fig.2. Plots of the concentrations c_0(Eq. (9b), solid), c_1(Eq. (18b), dash) and the numerical solution c(dot) of equations (4), as a function of the reduced time variable $\tau=k_1E_0t$ for various values of a) $\lambda=E_0/S_0$, b) $k_\sigma=(k_{-1}/(k_1S_0)$. The values of the rest constants are written in the figures. Notice the approach and in most of the cases the indistinguishability of the numerical c(dot) and the first iteration c_1(dash) lines.

3. The time τ_m of the maximum c_0 and the gradient of c_0 after τ_m. The limit of quasi steady approximation(QSSA)

From Eq. (9b) the time $\tau = \tau_m$ where the maximum of the concentration c_0 of the intermediate complex takes place can analytically be determined. The derivative

$$\frac{dc_0}{d\tau} = \frac{x_p Exp[x_p \tau] - x_m Exp[x_m \tau]}{\lambda(x_p - x_m)} \quad , \tag{10}$$

vanishes at this point and we take that

$$\tau_m = \frac{Ln[x_p / x_m]}{x_m - x_p} \quad . \tag{11}$$

The analytical expression of the derivative of c_0, Eq. (10), permits the exploration of the general behavior of the gradient in all times in various regions of the rest parameters where the overall approximation applies. The value of the derivative

$$F = dc_0/d\tau(1.1\tau_m) \quad , \tag{12}$$

at time $\tau = 1.1\tau_m$, a bit larger than the time of the maximum of c_0, reveals how close to the vanishing of F we are and whether a quasi steady state can be reached, where F tends to zero and c_0 to a constant. By means of the expressions of x_m and x_p, Eqs. (6), and the functions τ_m and F a study of the way the parameters k_μ and λ affect the approach to the steady state can be done.

We present some plots of the time τ_m of the maximum of c_0 and the gradient F at times $1.1\tau_m$ just after τ_m. In Fig. 3a we plot both quantities as a function of the parameter k_μ under constant values of λ and k_σ. Both quantities tend to zero, τ_m being always positive while the derivative F being always negative, as expected.

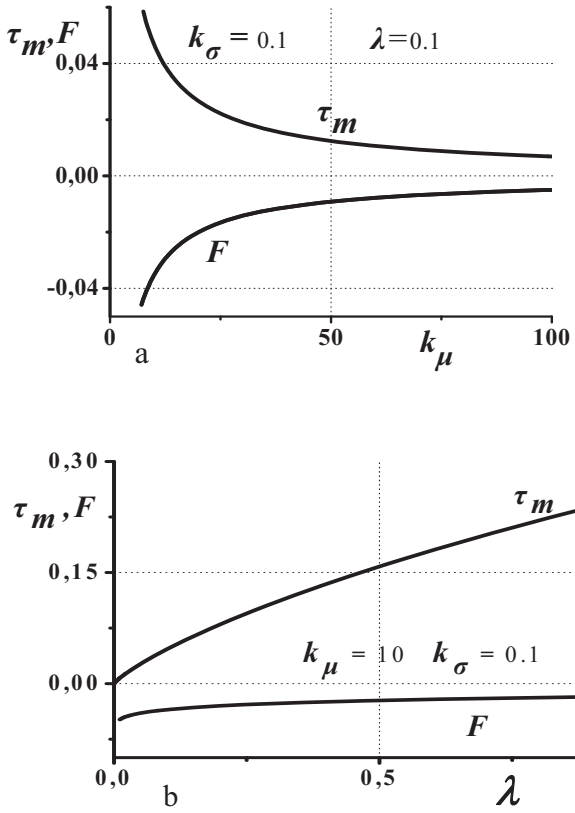

Fig.3. The dependence of the time τ_m of maximum c_0 , and the derivative F after τ_m , as a function of a) k_μ , b) λ . The constant values of the rest parameters are written in the figures.

The simultaneous vanishing of these two quantities for large k_μ reveals the approach of a quasi steady state at small times τ_m, and this is in accord with the previous assumption that faster reactions reach quickly a quasi steady like state where c_0 stays almost constant. This quasi-steady state is only an ideal limit which according to Fig. 3a takes place in the limit of k_μ tending to infinity. This limit can analytically be described by means of the expressions Eqs. (11) and (12). The relations of both τ_m and the function F, in this limit, are:

$$\tau_m = \frac{\lambda(Ln[k_\mu] - Ln[\lambda])}{k_\mu} + 0[\frac{1}{k_\mu}]^2 \quad (13)$$

$$F = -\frac{1}{k_\mu} + \frac{\lambda^{0.1}}{k_\mu^{1.1}} + 0[\frac{1}{k_\mu}]^2 \quad . \quad (14)$$

We see that both quantities reduce absolutely and tend to zero for $k_\mu \to \infty$, the one from positive and the other from negative values, as expected and in accord with the graphs of Fig. 1a. Indeed, it is seen in the graphs of c_0(solid lines) but also of the numerical solution(dot lines) that at the limit of large k_μ both τ_m and the derivative F after τ_m get absolutely smaller.

In Fig. 3b another class of a general behavior is presented. Plotting the two quantities as a function of λ we see that though τ_m reduces in the limit of small λ, the gradient F increases absolutely going to a constant value. Such behavior is also seen in the graphs of Fig. 2a and it reveals another behavior where the reach of a quasi state where F tends to zero, takes place at larger times τ_m.The exact limits of these two functions at small and large λ are given by

$$\tau_m = -\frac{\lambda Ln[\lambda]}{k_\mu} + 0[\lambda] \quad (15a)$$

$$F = -\frac{(k_\mu - k_\sigma)}{k_\mu^{\,2}} + 0[\lambda] \quad , \quad \text{for} \quad \lambda \to 0 \quad (15b)$$

$$\tau_m = Ln[\lambda] + 0[\frac{Ln[\lambda]}{\lambda}] \quad (16a)$$

$$F = -\frac{(k_\mu - k_\sigma)}{\lambda^2} + 0[\frac{1}{\lambda^{2.1}}] \quad , \quad \text{for} \quad \lambda \to \infty \quad (16b)$$

which are the quantitative expressions of the behaviors at the two limits of small and large λ. After the quantitative description of τ_m and F which reveal the fastness and the gradient of c_0 after its maximum, we proceed and study under what conditions several assumptions hold. When $E_0 << S_0$, is the approach to the steady state faster? For $E_0 << S_0$, $\lambda = E_0/S_0$ tends to zero and according to the limit (Eq. (15a)) and the graphs of Figs. 2a and 3b , τ_m tends indeed to zero which means faster reactions. However, the gradient after τ_m is not always small and only when k_μ is very large both τ_m and F get absolutely reduced. Under these circumstances,

the approach to a constant c_0 and the steady state is possible. Of interest though is that F is absolutely smaller considered as a function of $x=\lambda/(1+k_\mu)$ which is always smaller than λ, approaching faster the steady state. This is in accord with the result that the condition $E_0<<S_0$ or $\lambda<<1$ can be amended with the condition of $E_0<< S_0+k_M$ or $x<<1$ as far as the approach to the steady state is concerned [14,17,18].

4. First order iteration solution

Having found the zeroth iteration solutions c_0 and s_0, Eqs. (9), the product $f_0 = s_0\, c_0$ can be determined and following the iteration scheme explained in Section 2, we write for the first iteration differential equations the expressions:

$$s_1''(\tau)-(x_p+x_m)s_1'(\tau)+x_p x_m s_1(\tau)=f_0'(\tau)+x_p x_m f_0(\tau) \tag{17a}$$

$$c_1''(\tau)-(x_p+x_m)c_1'(\tau)+x_p x_m c_1(\tau)=-\lambda^{-1} f_0'(\tau) \tag{17b}$$

These equations with the proper boundary conditions at $\tau=0$ with $s_1(0)=1$, $c_1(0)=0$ but also those of their first derivatives $ds_1/d\tau(0)=-1, dc_1/d\tau(0)=1/\lambda$ are soluble and give the solutions Eqs. (18). Before proceeding to the study of this first iteration solution we have to notice that it is the result of not only a strong tying at the two ends but also takes care of the quadratic term $s_0\, c_0$ which is important at intermediate times. It is expected to amend the zeroth order solution. The solutions of first iteration include simple exponential functions of time and they are given in terms of x_p and x_m by:

$$\begin{aligned} s_1=\{&a_1(x_p,x_m)Exp[\tau x_p]+a_1(x_m,x_p)Exp[\tau x_m]+a_2(x_p,x_m)Exp[2\tau x_p]\\ &+a_2(x_m,x_p)Exp[2\tau x_m]+a_3(x_p,x_m)Exp[\tau x_p+\tau x_m]\}/a_4(x_p,x_m)\end{aligned} \tag{18a}$$

$$\begin{aligned} c_1=\{&b_1(x_p,x_m)Exp[\tau x_p]+b_1(x_m,x_p)Exp[\tau x_m]+b_2(x_p,x_m)Exp[2\tau x_p]\\ &+b_2(x_m,x_p)Exp[2\tau x_m]+b_3(x_p,x_m)Exp[\tau x_p+\tau x_m]\}/b_4(x_p,x_m)\end{aligned} \tag{18b}$$

$$\begin{aligned} a_1(x_p,x_m)=\lambda(&-2x_p^4x_m^2+7x_p^3x_m^3-7x_p^2x_m^4+2x_px_m^5-2x_p^4x_m+7x_p^3x_m^2-7x_p^2x_m^3+2x_px_m^4)\\ &-2x_p^4x_m-x_p^3x_m^2+5x_p^2x_m^3-2x_px_m^4-2x_p^4-5x_p^3x_m+11x_p^2x_m^2-4x_px_m^3-4x_p^3+6x_p^2x_m-2x_px_m^2\end{aligned}$$

$$a_2(x_p,x_m)=-x_p^2x_m^3-3x_p^2x_m^2-2x_p^2x_m+2x_px_m^4+6x_px_m^3+4x_px_m^2$$

$$\begin{aligned} a_3(x_p,x_m)=&2x_p^4x_m+2x_p^4-3x_p^3x_m^2+3x_p^3x_m+4x_p^3-3x_p^2x_m^3-16x_p^2x_m^2\\ &-6x_p^2x_m+2x_px_m^4+3x_px_m^3-6x_px_m^2+2x_m^4+4x_m^3=a_3(x_m,x_p)\end{aligned}$$

$$a_4(x_p,x_m)=\lambda(2x_p^5x_m-9x_p^4x_m^2+14x_p^3x_m^3-9x_p^2x_m^4+2x_px_m^5)=a_4(x_m,x_p)$$

$$b_1(x_p,x_m)=\lambda(-2x_m^4x_p+7x_m^3x_p^2-7x_m^2x_p^3+2x_mx_p^4)+2x_m^2x_p$$
$$+2x_m^3x_p-6x_mx_p^2-5x_m^2x_p^2+4x_p^3+x_mx_p^3+2x_p^4$$

$$b_2(x_p,x_m)=-4x_m^2x_p-4x_m^3x_p+2x_mx_p^2+2x_m^2x_p^2$$

$$b_3(x_p,x_m)=-4x_m^3-2x_m^4+6x_m^2x_p+x_m^3x_p+6x_mx_p^2$$
$$+6x_m^2x_p^2-4x_p^3+x_mx_p^3-2x_p^4$$

$$b_4(x_p,x_m)=\lambda^2(2x_m^5x_p-9x_m^4x_p^2+14x_m^3x_p^3-9x_m^2x_p^4+2x_mx_p^5)\ .$$

An interesting outcome of this solution is its coincidence with the numerical solution based on Mathematica. We plot c_1 in Figs. 1 and 2 (dash lines), together with the zeroth order solution c_0 (solid lines) and we observe that indeed its indistingushability from the numerical solution c(dot lines) of Eqs. (4) is extended to a larger region of the parameters of the problem. We see again that larger values of λ, k_μ and smaller values of k_σ lead to a better agreement of the first iteration solution and numerical results. This can be explained by means of Eq. (5b) where we see that larger λ and k_μ but smaller k_σ make the left terms of Eq. (5b) larger and increase the dominance over the right terms of the differential equation. Second and higher iterations are expected to increase the region of the values where the analytical and numerical results coincide.

5. Conclusions

An iterative scheme for the solution of Michaelis-Menten kinetic equations in all times t is given, based on the solution in the long time limit. Tying the time dependent expressions at the two time regions of small and large times a solution is presented which hardly differs from the numerical results at any t, in a large region of the parameters of the problem. Higher order iterations increase further this indistinguishability. Based on the zeroth iteration solution the time where the maximum of the concentration c of the intermediate complex occurs is determined and is used to find the fastness of the approach to the steady state studied also before. The gradient of the concentration of the intermediate complex at times just after the time of the maximum reveals the way the steady like state is approached which can occur at small or larger times. The first iteration solution is also found and plotted, confirming the amendments to the zeroth order iteration solution. The method and results of

the present study provide new ways to literally describe the solution of MM kinetic equations. Therefore, it can be used for the quantitative exploration of certain regularities in real problems.

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