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A NOTE ON THE MICHAELIS–MENTEN KINETICS FOR ENZYMATIC PROCESSES IN SOLUTIONS

JENS STRUCKMEIER*

Abstract. We derive analytical formulas in terms of elementary functions which should approximate exact solutions of the Michaelis–Menten equations on different time scales. For short times the approximation is based on an analytical solution of a Riccati differential equation with constant coefficients. An approximation which is uniformly valid in time as long as the initial free enzyme is much larger than the free substrate is obtained from a linearization around the unique equilibrium point. Moreover we apply asymptotic expansion techniques which might give uniform approximations in time and relate the present work to the quasi–steady state approximations (QSSA) given in the literature.

Key words. Michaelis–Menten kinetics, conservation relations, linearization, asymptotic expansions, quasi–steady state approximation

AMS subject classifications. 34A05, 41A60, 92C45

1. Introduction. In the present work we are concerned with the following nonlinear system of ordinary differential equations from mathematical biology given by:

$$\frac{dE}{dt} = k_{-1}\,C - k_1\,ES + k_2\,C \tag{1.1}$$

$$\frac{dS}{dt} = k_{-1}\,C - k_1\,ES \tag{1.2}$$

$$\frac{dC}{dt} = k_1\,ES - k_2\,C - k_{-1}\,C \tag{1.3}$$

$$\frac{dP}{dt} = k_2\,C \tag{1.4}$$

which describes the reaction mechanism for enzymatic processes in solution, already formulated in 1913 by Michaelis and Menten and therefore referred as the Michaelis–Menten scheme [3]. The reaction kinetics of the scheme reads

$$E + S \longleftrightarrow C \longrightarrow E + P$$

where E and C denote the free and bound enzyme, respectively, S the free substrate and P the products. We further denote by k_1 the rate constant for the formation of bound enzyme, by k_{-1} the corresponding backward reaction rate and finally by k_2 the catalysis rate constant, i.e. the rate for the reaction $C \to E + P$. Because k_1, k_{-1} and k_2 are rate constants they are assumed to be strictly positive. The system is typically closed by the initial conditions $(E(0), S(0), C(0), P(0)) = (E_T, S_T, 0, 0)$.

System (1.1)–(1.4) is somehow the prototype model of biochemistry and even the basic example for what is called the quasi–steady state approximation (QSSA), which is an usual way to simplify models based on nonlinear ordinary differential equations appearing in biology and other branches of science.

The aim of the QSSA is to derive analytical formulas as approximations for solutions of nonlinear equations, which are not integrable in closed form. The method is also applied to overcome stiffness problems in the numerical integration of the equations.

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The standard QSSA (sQSSA) for equations (1.1)–(1.4), which are integrable in closed form only for $k_2 = 0$ (i.e. $P = 0$), is derived as follows [4]: using the conservation relation $E + C = E_T$ in (1.1)–(1.4) yields the equations

$$\frac{dS}{dt} = k_{-1}\, C - k_1\, (E_T - C)S \tag{1.5}$$

$$\frac{dC}{dt} = k_1\, ((E_T - C)S - K_M\, C) \tag{1.6}$$

$$\frac{dP}{dt} = k_2\, C \tag{1.7}$$

with the standard notation

$$K_M = \frac{k_{-1} + k_2}{k_1} \tag{1.8}$$

Now one assumes that after a fast transient, the bound enzyme C reaches an equilibrium point, such that $dC/dt \approx 0$. Then the problem reduces to the single nonlinear differential equation

$$\frac{dS}{dt} = -k_2 \frac{E_T S}{K_M + S} \tag{1.9}$$

and this equation is solved using the same initial condition like for the full equations, i.e. $S(0) = S_T$. One should notice that equation (1.9) can be "integrated in closed form", but the solution is expressed in terms of the Lambert W function, defined as the real valued solution of the equation

$$W(x)e^{W(x)} = x$$

One can show that the sQSSA is valid providing that

$$E_T \ll S_T + K_M$$

see [4] and [5], but fails drastically outside the domain of validity. One reason is that there may occur initial layers in the free substrate S and the bound enzyme C, where the first one drops down significantly and the latter one reaches its maximal value. Hence solving equation (1.9) together with $S(0) = S_T$ is certainly wrong.

Modifications (and improvements) of the sQSSA are the reversed QSAA (rQSSA) [5] and the total QSSA [1],[6]. In the rQSSA one simplifies the equations assuming $dS/dt = 0$ and in [5] it is shown that the rQSSA is valid for "large" values of E_T. The tQSSA reformulates the system in terms of the new variable $\bar{S} = S - C$ and proceeds afterward with the same technique like in the sQSSA. One should notice that the tQSSA yields again a single differential equation, but the equation is not integrable in closed form. Hence, Tzafriri [6] introduced a first order tQSSA, which is defined as a single differential equation similar to (1.9). In [6] it is also shown, e.g, by numerical experiments, that the (first order) tQSSA extends the domain of validity of the standard and reverse QSSA.

In the following we derive analytical formulas in terms of elementary functions which should approximate exact solutions of (1.1)–(1.4) on different time scales. An analytical expression for the initial layer behavior based on a Riccati equation with constant coefficients is formulated in Section 2.1. The formulas may even be used to

derive a different initial condition for equation (1.6) of the sQSSA in order to improve the domain of validity.

An approximation, which is uniformly valid in time providing $S_T \ll E_T$, is obtained in Section 2.2. Here we use a linearization around the unique equilibrium point of the Michaelis–Menten equations. In Section 3 we discuss the quality of the simplified models using parameter values taken from Tzafriri [6]. An asymptotic treatment of the model is done in Section 4 and in particular we show that the Riccati equation from Section 2.1. comes out naturally when treating the equations as a singular perturbed problem solved by asymptotic matching techniques. Some conclusion on the present work are given in Section 5.

2. Simplified models for the Michaelis–Menten kinetics. The conservation relations of (1.1)-(1.4), namely

$$E + C = E_T$$
$$S + C + P = S_T$$

suggest the following transformation of variables:

$$E_T = E + C, \quad S_T = S + C + P, \quad X = C, \quad Y = P \tag{2.1}$$

Substituting (2.1) into (1.1)–(1.4) yields the equations

$$\dot{X} = k_1(E_T - X)(S_T - X - Y) - (k_2 + k_{-1})X \tag{2.2}$$
$$\dot{Y} = k_2 X \tag{2.3}$$

formulated in the unknowns $X(t)$ and $Y(t)$. Again the system is not integrable in closed form except for the case $k_2 = 0$.

In order to obtain analytical approximations to the system we will proceed as follows:

1) assuming $Y \equiv 0$ on the right hand side of (2.2) yields a system, which can be solved analytically. The corresponding equation for $X(t)$ is a Riccati equation with constant coefficients. This model may serve as an approximation of the (fast) transient behavior of (1.1)–(1.4) when looking at small time scales. Indeed we will show in Section 4, that the equation can be derived using an asymptotic expansion technique.
2) a linearization around the unique, asymptotically stable equilibrium point of (2.2), (2.3) yields a linear system, which is integrable in closed form and should be uniformly valid in time providing $S_T \ll E_T$.

2.1. Approximation for small times. Equations (2.2), (2.3) are typically closed by the initial conditions $X(0) = 0$ and $Y(0) = 0$. Hence, for small times, it makes sense to neglect the term Y on the right hand side of (2.2). The resulting system then reads

$$\dot{X} = k_1(E_T - X)(S_T - X) - (k_2 + k_{-1})X \tag{2.4}$$
$$\dot{Y} = k_2 X \tag{2.5}$$

and the main advantage is that the system can be solved analytically. Rewriting (2.4) in a more compact way yields the Riccati–equation

$$\dot{X} + AX + BX^2 = C \tag{2.6}$$

with

$$A = k_1(E_T + S_t) + k_{-1} + k_2, \quad B = -k_1, \quad C = k_1 E_T S_T$$

The exact solution of (2.6) with $X(0) = 0$ and $\omega = \sqrt{A^2 + 4CB}$ reads

$$X(t) = \frac{1}{2B}\left[-A + \omega\frac{(\omega + A)e^{\omega t} - (\omega - A)}{(\omega + A)e^{\omega t} + (\omega - A)}\right]$$

In the limit as $t \to \infty$ one has

$$X(t) \to \frac{\omega - A}{2B}$$

which indicates that the approximation can only be valid for small times. Moreover, it is easy to check that the approximation given above is strictly monotone increasing, such that the maximum of $X(t)$ is attained for $t \to \infty$. One should notice that equation (2.5) can be integrated analytically using the expression for $X(t)$.

2.2. Linearization around the equilibrium point. Let us return to the system (2.2), (2.3): the unique equilibrium point is given by $X_e = 0$ and $Y_e = S_T$ and the transformation $x = X$, $y = Y - S_T$ yields

$$\dot{x} = -k_1(E_T - x)x - (k_{-1} + k_2)x - k_1(E_T - x)y \tag{2.7}$$

$$\dot{y} = k_2 x \tag{2.8}$$

such that a linearization around (X_e, Y_e) reads

$$\dot{x} = -\alpha x - \beta y \tag{2.9}$$

$$\dot{y} = \gamma x \tag{2.10}$$

with

$$\alpha = k_1 E_T + k_2 + k_{-1}, \quad \beta = k_1 E_T, \quad \gamma = k_2$$

One should notice that equation (2.9) is independent of S_T – the dependence is hidden in the initial condition $y(0) = Y(0) - S_T$. Moreover, the eigenvalues of the linear system are

$$\lambda_{1/2} = -\frac{\alpha}{2} \pm \frac{1}{2}\left(\alpha^2 - 4\beta\gamma\right)^{1/2}$$

such that for all parameter values we get $\mathrm{Re}(\lambda_{1/2}) < 0$, which means that the equilibrium point (X_e, Y_e) is asymptotically stable. Fig. 2.1 shows the two eigenvalues $\lambda_{1/2}$ for various values of k_{-1} and k_2 keeping $k_1 E_T = 10$ fixed.

The linear system is solvable using standard techniques and one obtains with initial conditions $x(0) = 0$ and $y(0) = -S_T$ the solution

$$x(t) = \frac{\beta S_t}{\delta}\left[\exp\left(-\frac{\alpha - \delta}{2}\,t\right) - \exp\left(-\frac{\alpha + \delta}{2}\,t\right)\right]$$

$$y(t) = \frac{S_t}{2\delta}\left[(\alpha - \delta)\exp\left(-\frac{\alpha + \delta}{2}\,t\right) - (\alpha + \delta)\exp\left(-\frac{\alpha - \delta}{2}\,t\right)\right]$$

with $\delta = \sqrt{\alpha^2 - 4\beta\gamma}$.
Using the exact formulas for $x(t)$ and $y(t)$, the free enzyme and substrate, $E(t)$ and $S(t)$, respectively, are simple given by the formulas

$$E(t) = E_T - x(t)$$
$$S(t) = -x(t) - y(t)$$

A sufficient condition for the validity of the linear model – only using the initial

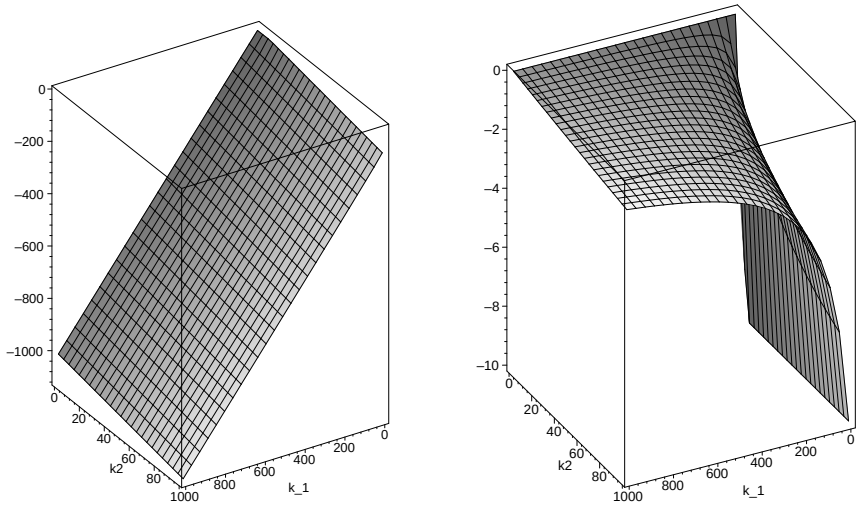

FIG. 2.1. *Dependence of the eigenvalues $\lambda_{1/2}$ of the linear system (2.9), (2.10) on k_{-1} and k_2 keeping the term $k_1 E_T = 10$ fixed.*

conditions E_T and S_T – is given by $S_T \ll E_T$, which may be motivated as follows: using the relation $S(t) = -(x(t) + y(t))$ equation (2.7) reads

$$\dot{x} = -k_1(E_T + S)x - (k_{-1} + k_2)x - k_1 E_T y$$

and to obtain (2.9) one neglects the term $-k_1 S x$. This is valid as long as

$$k_1 S \ll \alpha = k_1 E_T + k_2 + k_{-1}$$

and from the estimate $S(t) \leq S_T$ one arrives at the condition

$$S_T \ll E_T$$

The validity of this condition is confirmed in the next section.

Because the rate constants are positive, a weaker condition – including the rate constants – reads

$$S_T \ll E_T + K_M$$

with K_M defined by (1.8).

3. Discussion of the simplified models. One simple contribution of the present work is to give some new analytical formulas to approximate solutions of the nonlinear Michaelis–Menten kinetics. In the following we give some comparisons

TABLE 3.1
Parameters used for the following examples, taking from [6].

Test	k_1	k_{-1}	k_2	E_T	S_T	S_T/E_T
a)	1	1	1	10	1	1/10
b)	1	100	10	10	1	1/10
c)	1	90	10	100	100	1
d)	1	90	10	200	100	1/2

between the full equations and the approximations discussed in the previous section, where the solutions of (2.2), (2.3) are computed using a standard numerical integration routine of MAPLE.

The parameters used in the following are taken from reference [6] and summarized in Table 3.1. The initial conditions for (1.1)–(1.4) and the reduced models of the previous section are always $(E(0), S(0), C(0), P(0)) = (E_T, S_T, 0, 0)$.

Fig. 3.1 and 3.2 show the initial behavior of the free substrate S and the bound enzyme C, respectively, for the original system (1.1)–(1.4) (solid line) and the reduced model (2.4), (2.5) (boxes) of Section 2.1. according to the parameters given in Table 3.1. Equations (2.4), (2.5) work markedly well in all four cases considered

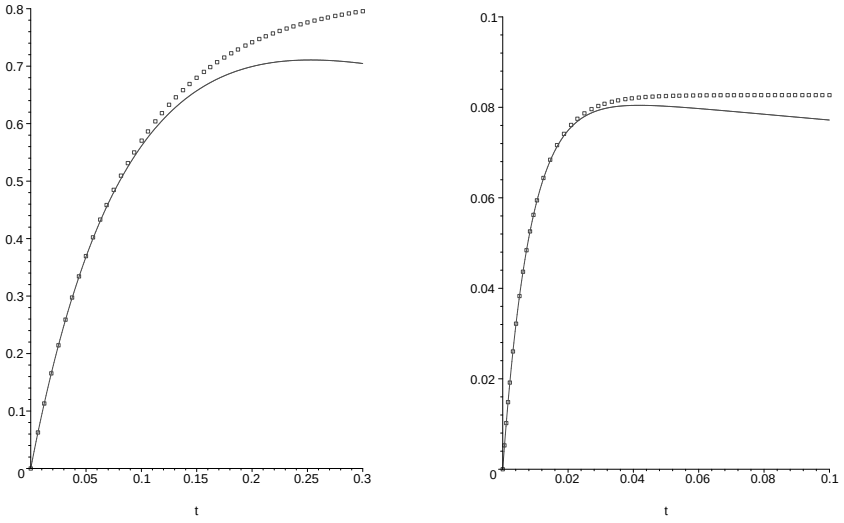

FIG. 3.1. *Bound enzyme C for case a) (left) and b) (right) of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the reduced model (2.4), (2.5) (boxes).*

here as long as we restrict the reduced model to a small initial layer. The size of the initial layer strongly depends on the value of S_T: due to (2.4) the solution $X(t)$ is a strictly increasing function such that the same holds for $Y(t)$. Hence, neglecting the term $Y(t)$ on the right hand side of (2.4) is valid for small values of $Y(t)$ and because $\lim_{t\to\infty} Y(t) = \infty$ the reduced model has to break down for larger times. A comparison between the exact solution and the linearized model for the parameters of Table 3.1 is shown in Fig. 3.3–3.6. In the first two cases *a*) and *b*) the linearized model works markedly well. There is only a small overshoot at the maximum of the bound enzyme.

A strong deviation in all three curves is detected in case *c*): the maximal value of the bound enzyme C is overestimated by about 28 %, whereas the free substrate S is

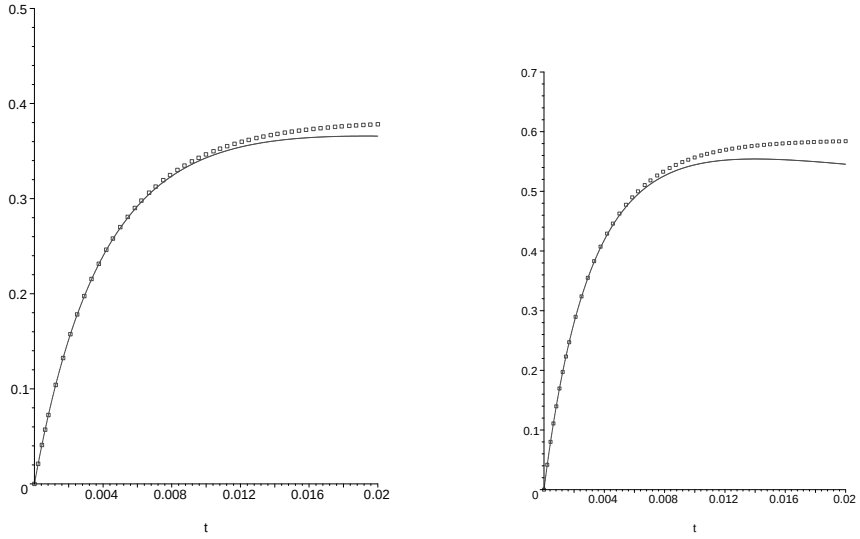

FIG. 3.2. *Bound enzyme C for case* c) *(left) and* d) *(right) of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the reduced model (2.4), (2.5) (boxes).*

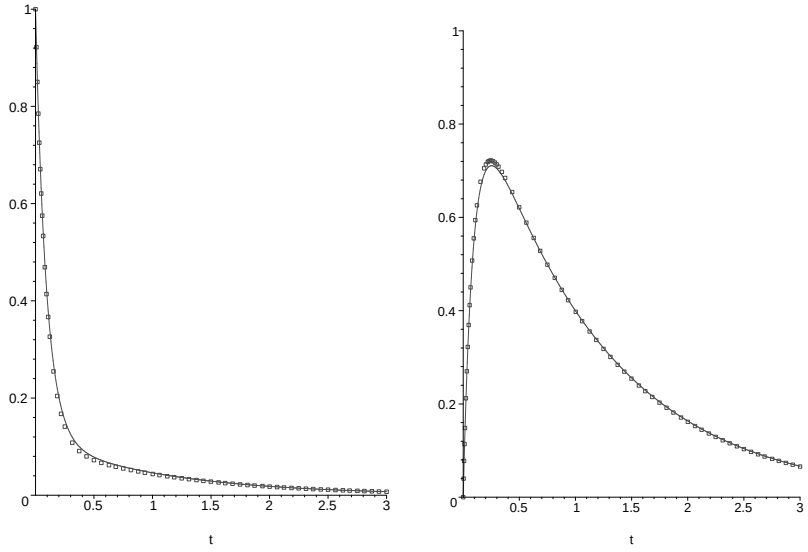

FIG. 3.3. *Free substrate S (left) and bound enzyme C (right) for test* a) *of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the linearized model (boxes).*

underestimated over the whole time interval. The same effect is observed in case c) although the differences between the exact solution and the linearized model are much smaller compared to the previous case. Let us compare our linear model of Section 2.1 with the results given by Tzafriri in [6] on the QSSA methods: in case a) our linear model seems to work better than the rQSSA and the (first order) tQSSA, because the linear model captures the transient behavior of the free substrate S and the bound enzyme C over the whole time interval $[0, 3]$ including early and late phases. For case b), where the rQSSA fails in the behavior of the free substrate S, the linear model

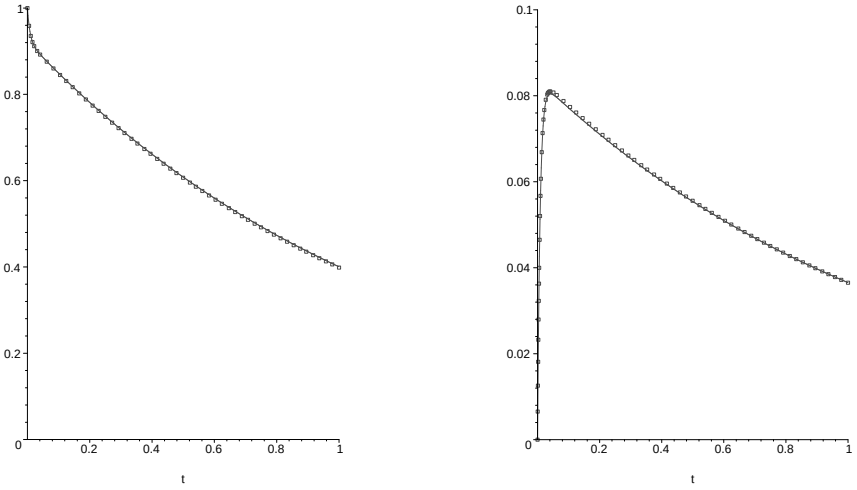

FIG. 3.4. *Free substrate S (left) and bound enzyme C (right) for test b) of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the linearized model (boxes).*

works as good as the first order tQSSA.
In case c), where Fig. 3.5 shows the largest deviations from the exact solution, the linear model works better than the rQSSA, but certainly cannot compete with the tQSSA. The quality of the approximation is comparable with that of the first order tQSSA. In the final case d) our linear model works significantly better than the rQSSA and the first order tQSSA, but again cannot compete with the tQSSA. Together with the ratio S_T/E_T of Table 3.1 the results confirm that the relation $S_T/E_T \ll 1$ derived in the previous section is a sufficient condition for the validity of the linear model (2.9), (2.10).

4. Asymptotic treatment of the Michaelis–Menten kinetics. Fig. 3.3–3.6 show that the dynamic behavior of the free substrate S and the bound enzyme C contain small initial layers, wherein the free substrate drops down significantly and the bound enzyme reaches its maximal value. In the following we will show that the behavior in these layers can be described (up to higher order corrections) by the Riccati equation formulated in 2.1.
Introducing the scaling $\bar{x} = x/S_T$ and $\bar{y} = y/S_T$ in equations (2.9), (2.10) yields (omitting the bars)

$$\dot{x} = -k_1 \left(\frac{E_T}{S_T} - x \right) S_T x - (k_{-1} + k_2)x - k_1 \left(\frac{E_T}{S_T} - x \right) S_T y$$
$$\dot{y} = k_2 x$$

With the parameters of case c) of Table 3.1, i.e. $E_T = S_T = k_{-1} + k_2 = 100$, $k_1 = 1$ and $k_2 = 10$, one may rewrite these equations in the form

$$\varepsilon \dot{x} = -(1-x)x - x - (1-x)y \tag{4.1}$$
$$\dot{y} = k_2 x \tag{4.2}$$

with $\varepsilon \ll 1$.

From asymptotic analysis it is known that the solution of (4.1) may contain a small initial layer due to the singular nature of the equation as $\varepsilon \to 0$, see, e.g., [2].

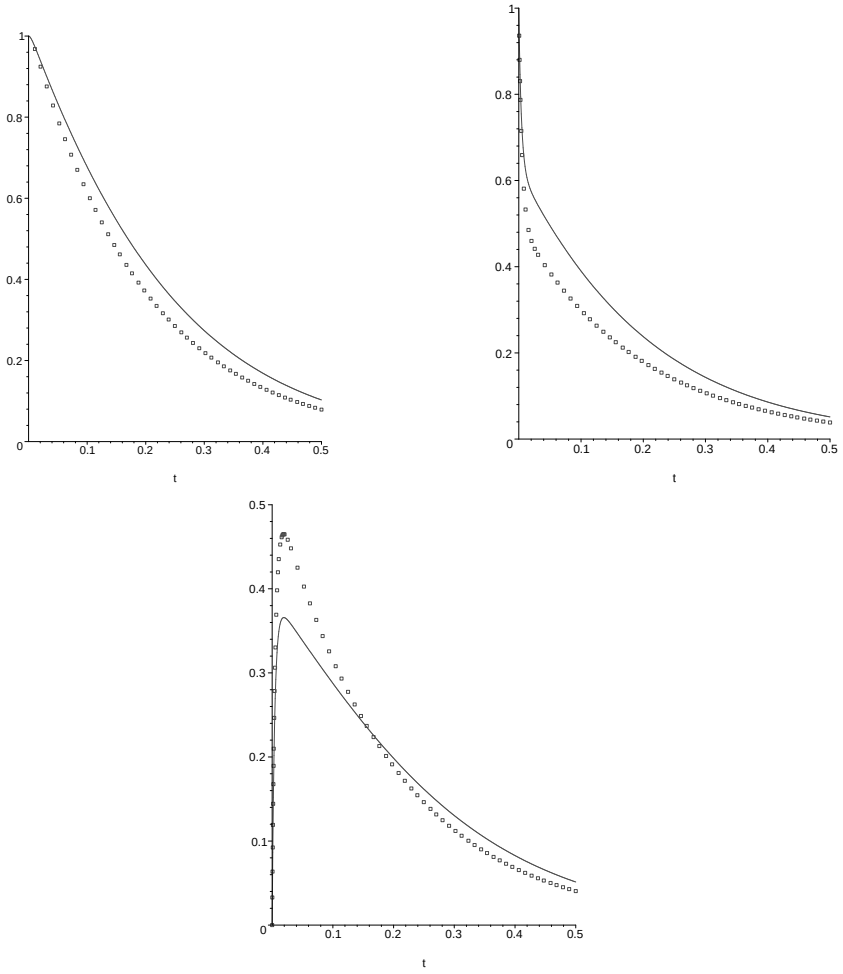

FIG. 3.5. *Free substrate and bound enzyme $S + C$ (upper left), free substrate S (upper right) and bound enzyme C (down) for test* c) *of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the linearized model (boxes).*

A general method to obtain an asymptotic solution in the initial layer is to perform a scaling in time such that equation (4.1) becomes a regular perturbed problem. Together with an asymptotic expansion in the outer region one may define a matched asymptotic expansion as long as the problems induced by an asymptotic expansion are integrable in closed form.

Let us first derive an asymptotic expansion for the initial layer: introducing the time scaling $\tau = t/\varepsilon$ yields

$$x' = -(1-x)x - x - (1-x)y \tag{4.3}$$

$$y' = \varepsilon k_2 x \tag{4.4}$$

where now both x and y are functions of τ and $'$ denotes the derivative with respect to τ. Substituting the asymptotic expansions

$$x = x_0 + \varepsilon x_1 + \ldots, \qquad y = y_0 + \varepsilon y_1 + \ldots$$

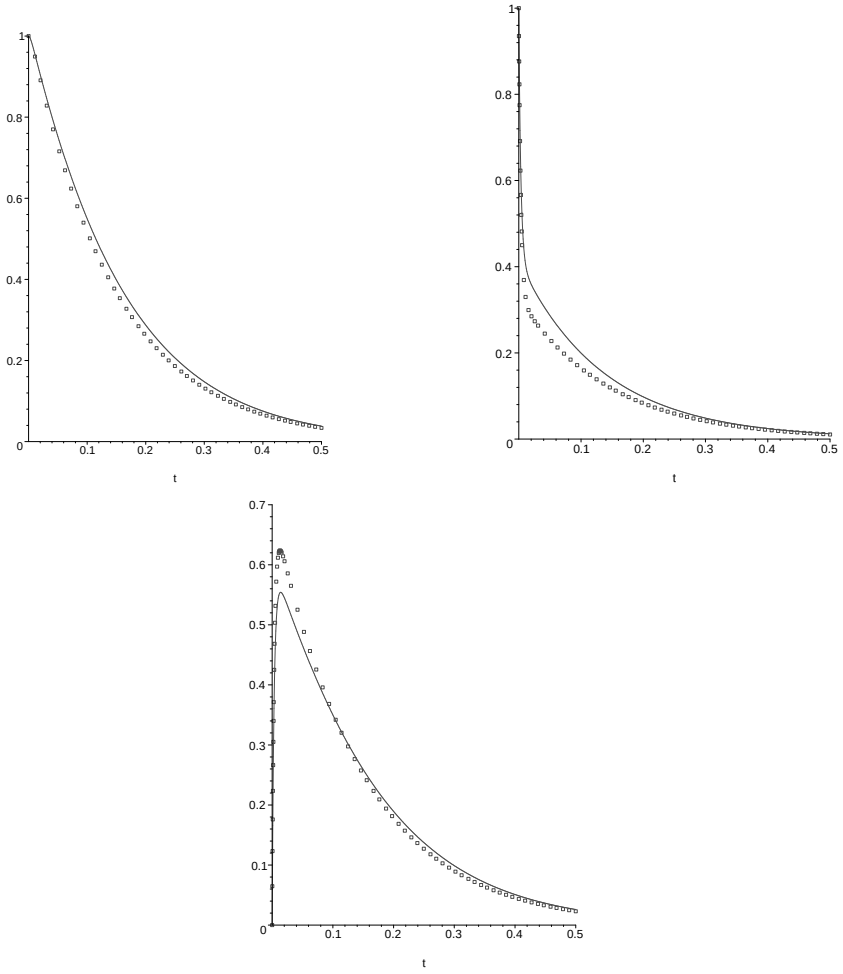

FIG. 3.6. *Free substrate and bound enzyme $S + C$ (upper left), free substrate S (upper right) and bound enzyme C (down) for test d) of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the linearized model (boxes).*

into equations (4.3), (4.4) yields the zeroth order equations

$$x_0' = -(1 - x_0)x_0 - x_0 - (1 - x_0)y_0 \tag{4.5}$$

$$y_0' = 0 \tag{4.6}$$

which are closed by the initial conditions $x_0(0) = 0$ and $y_0(0) = -1$.
From (4.6) and the initial condition we conclude $y_0(\tau) = -1$ and substituting this solution into (4.5) yields the Riccati equation

$$x_0' = -x_0 + (1 - x_0)^2 \tag{4.7}$$

It is straightforward to notice that equation (4.7) is the scaled form of the Riccati equation (2.6) of Section 2.1 and therefore the solution reads

$$x(\tau) = \frac{3}{2} - \frac{\sqrt{5}}{2}\frac{(\sqrt{5}+3)e^{\sqrt{5}\tau} - (\sqrt{5}-3)}{(\sqrt{5}+3)e^{\sqrt{5}\tau} + (\sqrt{5}-3)} \tag{4.8}$$

The next step is to compute an outer expansion, but unfortunately the zeroth order equations do not give analytical formulas: putting $\varepsilon = 0$ in (4.1) yields the differential equation

$$\dot{y}_0 = k_2 x_0 \tag{4.9}$$

together with the algebraic equation

$$x_0^2 + (y_0 - 2)x_0 - y_0 = 0 \tag{4.10}$$

where x_0 and y_0 are now again function of t. Substituting the relevant root of (4.10) into (4.9) yields the differential equation

$$\dot{y}_0 = -k_2 \left(1 - \frac{y_0}{2} - \frac{\sqrt{4 + y_0^2}}{2}\right)$$

which turns out to be not integrable in closed form.
An approximation for the outer expansion is obtained by neglecting the quadratic term in (4.10). This yields the differential equation

$$\dot{y}_0 = k_2 \frac{y_0}{y_0 - 2}$$

and the (implicit) solution reads

$$y_0(t) = -2W\left(C \exp\left(-\frac{k_2}{2}t\right)\right) \tag{4.11}$$

where W again denotes the Lambert W function, see Section 1.
One should notice that the differential equation for the outer solution should be solved without any initial condition and therefore the constant C in (4.11) denotes an integration constant. The idea of inner and outer solutions is to fix the constant afterward by a matching procedure of the inner and outer solutions, see [2].

The solution $y_0(t)$ in (4.11) is still not given in closed form and one may further simplify the expression using the asymptotic behavior $W(x) \sim x$ for $x \ll 1$. Then, the solution $y_0(t)$ becomes

$$y_0(t) = C \exp\left(-\frac{k_2}{2}t\right) \tag{4.12}$$

and the corresponding expression for $x_o(t)$ reads

$$x_0(t) = \frac{\exp\left(-\frac{k_2}{2}t\right)}{\exp\left(-\frac{k_2}{2}t\right) - C} \tag{4.13}$$

The constants in (4.12) and (4.13) may be fixed using van Dyke's matching rule [2] and this yields the following outer solutions

$$x_0(t) = \frac{(\sqrt{5} - 3)\exp\left(-\frac{k_2}{2}t\right)}{(\sqrt{5} - 3)\exp\left(-\frac{k_2}{2}t\right) - (\sqrt{5} - 1)} \tag{4.14}$$

$$y_0(t) = -\exp\left(-\frac{k_2}{2}t\right) \tag{4.15}$$

Moreover, using the inner solution (4.8) and $y_0(\tau) = -1$ as well as the outer solutions (4.14) and (4.15) gives the following composite zeroth approximations

$$X_0(t) = \frac{(\sqrt{5}-3)e^{-k_2 t/2}}{(\sqrt{5}-3)e^{-k_2 t/2} - (\sqrt{5}-1)} + \frac{(5-3\sqrt{5})}{(\sqrt{5}+3)e^{\sqrt{5}t/\varepsilon} + (\sqrt{5}-3)} \tag{4.16}$$

$$Y_0(t) = -e^{-k_2 t/2} \tag{4.17}$$

Fig. 4.1 shows a comparison between the numerical solution of equations (2.2), (2.3) (*solid line*), the linearized model of Section 2.2 (*boxes*) and the composite zeroth order approximation given by (4.16) and (4.17). One can notice that the bound enzyme C is much better approximated by the composite asymptotic expansion compared to the linear model. On the other hand the improvement for the free substrate S is only marginally. The reason for this is that the linear solution $y(t)$ given in Section 2.1 and the composite approximation $Y_0(t)$ given by (4.17) are nearly identical. Here the influence of the crude approximation of the Lambert W function becomes significant.

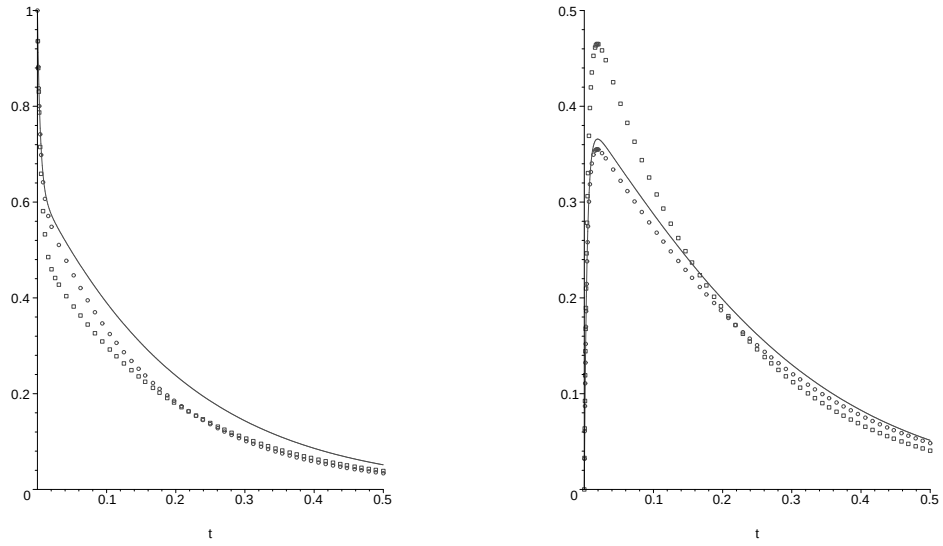

FIG. 4.1. *Free substrate S (left) and bound enzyme C (right) for test c) of Table 3.1: numerical solution of equations (2.2), (2.3) (solid line), analytical solution of the linearized model (boxes), matched asymptotic expansion (4.16), (4.17) with $\varepsilon = 0.01$ (circles).*

5. Conclusion. The Michaelis–Menten equations are an important model in biochemistry and the basic example for various quasi–steady state approximations. In the present work we try to find analytical formulas in terms of elementary functions, which approximate solutions of the model on various time scales. It was shown that the (fast) transient behavior in the initial layers of the free substrate and the bound enzyme can be sufficiently accurate described by the solution of a Riccati equation, which integrable in closed form. This equation was even derived using an asymptotic expansion technique.

A linearization around the unique equilibrium point of the Michaelis–Menten equations yields formulas with work markedly well at high enzyme concentrations.

An improved solution formula in the case when the free enzyme and substrate are of the same order of magnitude was obtained from matched asymptotic expansions. In summary, compared to the various QSSA methods, which are even not always explicitly solvable, the linear model (and the corrected formula based on matched asymptotic expansions) works sufficiently good in all parameter cases considered here.

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