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NUMERICAL COMPARISON BETWEEN TWO ENZYME-KINETIC MODELS*

Nadejda Grigorova

Using a guaranteed numerical method we show that two familiar Michaelis-Menten models used for the same purpose generally produce substantially different solutions.

1. Introduction. The enzyme-substrate metabolic interactions can be effectively described mathematically by the following system of nonlinear differential equations further called Michaelis-Menten system, see e. g. [1, 4, 5]:

$$\begin{array}{rcl} ds/dt &=& -k_1 es + k_{-1} c \\ dc/dt &=& k_1 es - (k_{-1} + k_2)\, c \\ de/dt &=& -k_1 es + (k_{-1} + k_2)\, c \\ dp/dt &=& k_2 c, \end{array} \tag{1}$$

wherein s, e, c, p are concentrations of the substrate, enzyme, complex and product, resp., and the initial conditions are $s(0) = s_0$, $c(0) = 0$, $e(0) = e_0$, $p(0) = 0$.

Typically, the concentration of the enzyme is much smaller than those of the substrate, e. g. $e_0/s_0 \in [10^{-7}, 10^{-2}]$. This makes system (1) stiff, i.e. the substrate variable s changes near 0 much slower than the enzyme e and complex variable c change. Since p can be found by direct integration, $p(t) = k_2 \int_0^t c(t')dt'$, we concentrate on the first three equations of (1). Adding the second and the third equation of (1), we obtain $dc/dt + de/dt = 0$. Using the initial conditions for the complex and the enzyme, the above equation gives: $e + c = e_0$, resp. $e = e_0 - c$. Thus system (1) reduces to two equations for s and c, namely:

$$\begin{array}{rcl} ds/dt &=& -k_1 e_0 s + (k_1 s + k_{-1})c \\ dc/dt &=& k_1 e_0 s - (k_1 s + k_{-1} + k_2)c \end{array} \tag{2}$$

with initial conditions: $s(0) = s_0$, $c(0) = 0$. However, the reduced system (2) cannot be solved in a closed form, see [5]. On the other hand, another widely used (for the same purpose) simplified model, further referred to as Michaelis-Menten law, is given by

$$ds/dt = -V_{max} s/(s + K_M),\ s(0) = s_0, \tag{3}$$

where $K_M = (k_{-1} + k_2)/k_1$ is the Michaelis constant and $V_{max} = k_2 e_0$ is the maximum velocity.

2. Problem Formulation. Consider the Michaelis-Menten system (2) and the Michaelis-Menten law (3). Both models produce solutions for the substrate concentration

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s, and, in practice, the solution of (3) is used as an approximation of the solution s of (2). In both cases one has to use some numerical method to find these solutions, cf. [5], hence computational errors are introduced. We would like to know, are the solutions of the two models substantially different taking into account all errors introduced by the numerical treatment of the corresponding differential equations? In other words, is the difference between the two solutions of the order of the numerical error involved? To illustrate the problem, let us consider a particular case study.

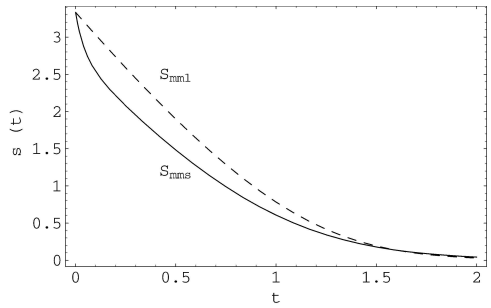

Figure 1. The solutions of s_{mms} and s_{mml} for data (4)

Numerical example. For the numerical solution of the Michaelis-Menten system and law we use an Euler method and a uniform mesh with step size $h = 0.007$. The following values for the parameters and initial data are assumed:

$$k_1 = 5,\ k_{-1} = 1,\ k_2 = 4,\ s_0 = 10/3,\ e_0 = 1. \tag{4}$$

For the data (4) the Michaelis-Menten constant is $K_M = 1$. With these data for the relative difference:

$$r = max_t \frac{s_{mml}(t) - s_{mms}(t)}{(s_{mml}(t) + s_{mms}(t))/2} \tag{5}$$

we obtain: $r \approx 0.28 = 28\%$, where s_{mms} is the substrate concentration obtained from the Michaelis-Menten system (2), and s_{mml} is the substrate concentration satisfying the Michaelis-Menten law (3).

Figure 1 presents graphically the numerical solutions $s_{mms}(t)$ and $s_{mml}(t)$ to the Michaelis-Menten system (2) and equation (3), resp. As the computed relative difference (5) between the numerical solutions is corrupted by errors coming from the numerical method and roundoff errors, the number r gives us little information about the actual difference between the two solutions. For instance, from Figure 1 we see that $s_{mml} > s_{mms}$, but this may not be true unless we know the computational error.

The use of (3) as an approximation of (2) in more complex systems of enzyme-kinetic equations, see e. g. [3], may be of considerable interest for the simplification of the corresponding models. However, this rises again the issue of a guaranteed estimation of the difference between the original model and the corresponding simplified model. Since we do not know how to treat this problem analytically, in this work we investigate the problem numerically (with verification). That is, we solve both problems (2), (3) using a numerical method with result verification taking into account all possible errors (errors from input data, truncation errors, roundoff errors).

In the sequel we shall use a guaranteed interval method, which will allow us to make a rigorous statement as regard to the comparison of the two solutions discussed above.

3. Numerical Method and Experiments. A simple interval method for the solution of the Michaelis-Menten system and the Michaelis-Menten law, producing bounds for the solution of the initial value problem for systems of ordinary differential equation [2] has been implemented in the computer algebra system MATHEMATICA. For convenience we briefly describe the method for the general IVP of ODE:

$$\frac{ds}{dt} = f(s),\ s(t_0) = s_0 \in [\underline{s}_0, \overline{s}_0]. \tag{6}$$

Assume that $s = s(t)$ is the solution of (6) on an interval $T \in [t_0, \overline{t}]$ (the method does not assume uniqueness of the solution). We shall enclose s in an interval $[\underline{s}, \overline{s}]$ on $T = [t_0, \overline{t}]$, i.e. $\underline{s}(t) \le s(t) \le \overline{s}(t)$ for any solution s of (6) and for any $t \in T$. Let $h > 0$ be a step, defining a mesh $t_k = t_0 + kh, k = 0, 1, \ldots, \overline{k},\ \overline{k}h \le \overline{t}$.
We set $\underline{s}(t_0) = \underline{s}_0, \overline{s}(t_0) = \overline{s}_0$. Assuming that $\underline{s}, \overline{s}$ are already computed at some t_k, i.e. $\underline{s}(t_k) \le s(t_k) \le \overline{s}(t_k)$ then we compute $\underline{s}, \overline{s}$ in the interval $T_k = [t_k, t_{k+1}]$ by means of the following iteration procedure:

a) for the upper bound $\overline{s}$ we compute for $r = 0, 1, 2, \ldots, \underline{r}$:

$$\begin{aligned} \overline{Z}^{(0)} &= [0, \overline{s}_0] \\ [\overline{p}^{(r)}, \overline{q}^{(r)}] &= \{f(s) \mid s \in \overline{Z}^{(r)}\} \\ \overline{Z}^{(r+1)} &= \overline{s}(t_k) \vee (\overline{s}(t_k) + \overline{p}^{(r)}h) \vee (\overline{s}(t_k) + \overline{q}^{(r)}h), \end{aligned}$$

where the notation $\alpha \vee \beta \vee \gamma = [\min\{\alpha, \beta, \gamma\}, \max\{\alpha, \beta, \gamma\}]$ has been used. Using the computed value $\overline{q}^{(\underline{r})}$ we obtain: $\overline{s}(t) = \overline{s}(t_k) + \overline{q}^{(\underline{r})}(t - t_k),\ t \in T_k$.

b) similarly, for the lower bound $\underline{s}$ we compute for $r = 0, 1, 2, \ldots, \underline{r}$:

$$\begin{aligned} \underline{Z}^{(0)} &= [0, \overline{s}_0] \\ [\underline{p}^{(r)}, \underline{q}^{(r)}] &= \{f(s) \mid s \in \underline{Z}^{(r)}\} \\ \underline{Z}^{(r+1)} &= \underline{s}(t_k) \vee (\underline{s}(t_k) + \underline{p}^{(r)}h) \vee (\underline{s}(t_k) + \underline{q}^{(r)}h), \end{aligned}$$

and subsequently, $\underline{s}(t) = \underline{s}(t_k) + \underline{p}^{(\underline{r})}(t - t_k),\ t \in T_k$.

Consider equation (3) with initial condition $s(t_0) = s_0$, and assume that the initial value s_0 of the substrate is not exact, $s_0 \in [\underline{s}_0, \overline{s}_0]$. Using that the right-hand side of the Michaelis-Menten law, $f(s) = -V_{max}s/(s + K_M)$, is a decreasing function we compute:

$$[\overline{p}^{(r)}, \overline{q}^{(r)}] = \{f(s) \mid s \in \overline{Z}^{(r)}\} = [f(\overline{Z}^{(r)}[2]), f(\overline{Z}^{(r)}[1])],$$

here and in the sequel $Z[1]$ denotes the left endpoint of the interval Z and $Z[2]$ is the right endpoint of Z.

Consider the Michaelis-Menten system (2). We seek to enclose the solution s, c of the system in bounds $[(\underline{s}, \underline{c}), (\overline{s}, \overline{c})]$ on $T = [t_0, \overline{t}]$. We set $\underline{s}(t_0) \le s_0 \le \overline{s}(t_0)$ and $\underline{c}(t_0) \le c_0 \le \overline{c}(t_0)$. The interval method requires some (rough) initial bounds for the solution; in our case we have: $0 \le s \le s_0$, $0 \le c < e_0$. Assuming that $\overline{s}$, $\overline{c}$, $\underline{s}$, $\underline{c}$ are already computed for some t_k, i.e. $\underline{s}(t_k) \le s(t_k) \le \overline{s}(t_k)$, $\underline{c}(t_k) \le c(t_k) \le \overline{c}(t_k)$, we compute the values of $\overline{s}$, $\overline{c}$, $\underline{s}$, $\underline{c}$ on the next time interval $T_k = [t_k, t_{k+1}]$, using the same algorithm as follows:

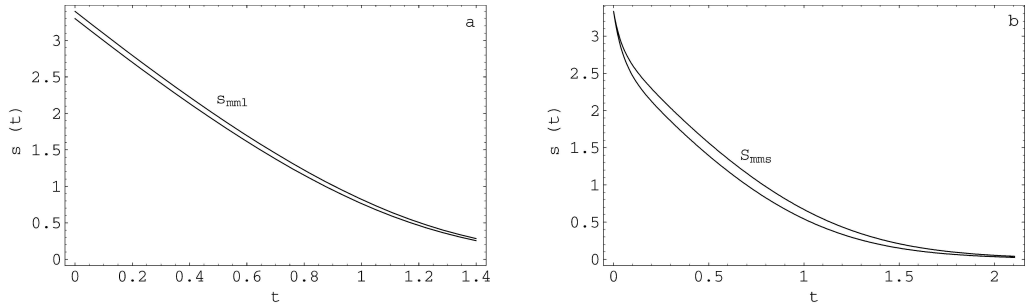

Figure 2. Bounds for a) s_{mml} b) s_{mms} for data (4).

a) for the upper bound $\overline{s}$ and $\overline{c}$ we compute for $r = 0, 1, 2, \ldots, \underline{r}$:

$$\begin{aligned}
\overline{Z}_1^{(0)} &= [0, s_0], \ \overline{Z}_2^{(0)} = [0, e_0] \\
[\overline{p}_1^{(r)}, \overline{q}_1^{(r)}] &= \{f_1(s,c) \mid s \in \overline{Z}_1^{(r)}, c \in \overline{Z}_2^{(r)}\} \\
[\overline{p}_2^{(r)}, \overline{q}_2^{(r)}] &= \{f_2(s,c) \mid s \in \overline{Z}_1^{(r)}, c \in \overline{Z}_2^{(r)}\} \\
\overline{Z}_1^{(r+1)} &= \overline{s}(t_k) \vee (\overline{s}(t_k) + \overline{p}_1^{(r)} h) \vee (\overline{s}(t_k) + \overline{q}_1^{(r)} h) \\
\overline{Z}_2^{(r+1)} &= \overline{c}(t_k) \vee (\overline{c}(t_k) + \overline{p}_2^{(r)} h) \vee (\overline{c}(t_k) + \overline{q}_2^{(r)} h) \\
\overline{s}(t) &= \overline{s}(t_k) + \overline{q}_1^{(r)}(t - t_k), \ t \in T_k \\
\overline{c}(t) &= \overline{c}(t_k) + \overline{q}_2^{(r)}(t - t_k), \ t \in T_k;
\end{aligned}$$

b) for the lower bounds $\underline{s}$ and we compute for $r = 0, 1, 2, \ldots, \underline{r}$:

$$\begin{aligned}
\underline{Z}_1^{(0)} &= [0, s_0], \ \underline{Z}_2^{(0)} = [0, e_0] \\
[\underline{p}_1^{(r)}, \underline{q}_1^{(r)}] &= \{f_1(s,c) \mid s \in \underline{Z}_1^{(r)}, c \in \underline{Z}_2^{(r)}\} \\
[\overline{p}_2^{(r)}, \overline{q}_2^{(r)}] &= \{f_2(s,c) \mid s \in \underline{Z}_1^{(r)}, c \in \underline{Z}_2^{(r)}\} \\
\underline{Z}_1^{(r+1)} &= \underline{s}(t_k) \vee (\underline{s}(t_k) + \underline{p}_1^{(r)} h) \vee (\underline{s}(t_k) + \underline{q}_1^{(r)} h) \\
\underline{Z}_2^{(r+1)} &= \underline{c}(t_k) \vee (\underline{c}(t_k) + \underline{p}_2^{(r)} h) \vee (\underline{c}(t_k) + \underline{q}_2^{(r)} h) \\
\underline{s}(t) &= \underline{s}(t_k) + \underline{p}_1^{(r)}(t - t_k), \ t \in T_k \\
\underline{c}(t) &= \underline{c}(t_k) + \underline{p}_2^{(r)}(t - t_k), \ t \in T_k.
\end{aligned}$$

The function $f_1(s,c) = -k_1 e_0 s + (k_1 s + k_{-1})c$ is a decreasing function of s (for $c \le e_0$, which is always satisfied) and increasing function of c. For the function $f_2(s,c) = k_1 e_0 s - (k_1 s + k_{-1} + k_2)c$ we have the opposite, it is a increasing function of s (since $c \le e_0$) and decreasing function of c, therefore we calculate the corresponding intervals $[p_i^{(r)}, q_i^{(r)}]$ as follows:

$$\begin{aligned}
[\overline{p}_1^{(r)}, \overline{q}_1^{(r)}] &= [f_1(\overline{Z}_1^{(r)}[2], \overline{Z}_2^{(r)}[1]), f_1(\overline{Z}_1^{(r)}[1], \overline{Z}_2^{(r)}[2])], \\
[\underline{p}_1^{(r)}, \underline{q}_1^{(r)}] &= [f_1(\underline{Z}_1^{(r)}[2], \underline{Z}_2^{(r)}[1]), f_1(\underline{Z}_1^{(r)}[1], \underline{Z}_2^{(r)}[2])], \\
[\overline{p}_2^{(r)}, \overline{q}_2^{(r)}] &= [f_2(\overline{Z}_1^{(r)}[1], \overline{Z}_2^{(r)}[2]), f_2(\overline{Z}_1^{(r)}[2], \overline{Z}_2^{(r)}[1])], \\
[\underline{p}_2^{(r)}, \underline{q}_2^{(r)}] &= [f_2(\underline{Z}_1^{(r)}[1], \underline{Z}_2^{(r)}[2]), f_2(\underline{Z}_1^{(r)}[2], \underline{Z}_2^{(r)}[1])].
\end{aligned}$$

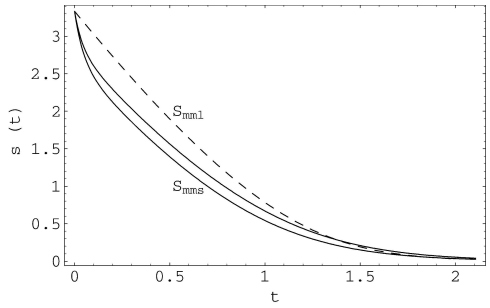

Figure 3. Comparison of the solutions s_{mml} and s_{mms}.

Figure 2a) presents the numerical solution of the Michaelis-Menten law using the above interval method for the data for the data (4); thereby the initial condition is taken to be $s_0 \in [3.3, 3.4]$. The exact solution lies between the two curves on Figure 2a).

Figure 2b) presents graphically the numerical solution of the Michaelis-Menten system for $k_1 = 5, k_{-1} = 1, k_2 = 4, s_0 = 10/3, e_0 = 1$; the following parameters of the interval method are used: step size $h = 0.007$, number of corrections $r = 5$. The (true) solutions of the Michaelis-Menten system are enclosed between the computed solutions $\underline{s}(t) \leq s(t) \leq \overline{s}(t)$, $\underline{c}(t) \leq c(t) \leq \overline{c}(t)$, $t \in T_k$, only the pair $(\underline{s}, \overline{s})$ is presented on the figures.

Figure 3 presents graphically the numerical solutions s_{mms} and s_{mml} of the Michaelis-Menten system, resp. law. Both solutions are computed using the interval method (however, the bounds for s_{mml} are too narrow to be seen on the figure). Clearly, the two solutions are substantially distinct from each other. For these examples the same values for the parameters as on Figure 2 are used.

Conclusion. An interval method for the guaranteed solution of the IVP for ODE has been implemented in MATHEMATICA. The method has been used to compare numerically the solutions of the Michaelis-Menten system (2) and the Michaelis-Menten law (3) often used as an approximation of (1). Our numerical experiments have shown that the two solutions are substantially distinct to each other. Our algorithm allows us to observe how the difference between the two solutions varies with changes in the input parameters. Thus it has been observed, that when K_M is small the difference between the two solutions is big, and when K_M increases the difference decreases. As in practice K_M is small, we should be careful when using the solution of the Michaelis-Menten law (3) as an approximation of the system (2). A quantitative measure for the relative difference between the two solution is given by the variable (5).

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Nadejda Grigorova
Bulgarian Academy of Sciences
Institute of Mathematics and Informatics
Acad. G. Bonchev Str., Bl. 8
1113 Sofia, Bulgaria
e-mail: nadejdag@iph.bio.bas.bg

ЧИСЛЕНО СРАВНЯВАНЕ НА ДВА МОДЕЛА ОТ ЕНЗИМНА КИНЕТИКА

Надежда Григорова

С помощта на гарантиран числен метод е показано, че два известни модела на Михаелис-Ментен, използвани за едни и същи цели, дават различни решения.