

## **TWO NUMERICAL APPROACHES TO THE NON-LINEAR LEAST-SQUARES METHOD VIA PRACTICAL EXAMPLES**

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**Abstract.** Our contribution is meant to be an example of multidisciplinary approach to the teaching of numerical methods. By employing the Michaelis-Menten's model for enzyme kinetics, we show a practical application of numerical methods in biochemistry. Given the experimental data, we find a dependence of a reaction rate on a concentration of a substrate. In a preliminary section, we derive and explain The Michaelis-Menten kinetics from behaviour of biochemical reactions. In a first part, the problem is linearized and then solved by the least squares method. In a second part, we do not use linearization and solve the original problem by the Newton's method for systems of non-linear equations. We conclude our contribution with a comparison of both approaches and results. We also offer several problems for students to clarify and deepen their understanding of the linearization. Our solution is provided in a form of a thoroughly commented MATLAB Code.

**Keywords:** teaching of numerical methods, non-linear least-squares method, Newton's method for systems, linearization

*Mathematics subject classification:* Primary 97N50; Secondary 49M15, 93E24

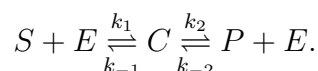
### **1 Introduction**

We put the strong accent on the theoretical aspects of engineering which allows our graduates to develop an interdisciplinary way of thinking and to be able to handle engineering problems with efficiency and bold creativity. For this purpose we have developed a collection of solved exercises where (besides other things) we show usage of numerical methods in applied sciences (see [4]). We strongly believe that the students of engineering are capable of comprehension and even appreciation of the abstract concepts of the pure mathematics. Nevertheless, the first contact should be carried out under the cover of a real tangible problem. In what follows you can taste a flavour of our blend of biochemistry, numerical mathematics and MATLAB coding.

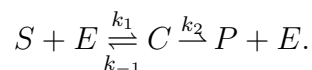
### **2 Michaelis-Menten kinetics**

In 1913, Michaelis and Menten proposed a model which is one of the best-known for enzyme kinetics ([2, p. 7]). They assumed a reaction scheme where the enzyme  $E$  converts the substrate  $S$  into the

product  $P$  through a two-step process with a complex  $C$  being an intermediate. The reaction scheme is represented by



Both reactions must be reversible but reaction rates are typically measured under conditions where  $P$  is continually removed which prevents the reverse reaction  $k_{-2}$  to happen. Hence, it is reasonable to assume no reverse reaction occurs:



Let us denote the quantities  $s = [S]$ ,  $c = [C]$ ,  $e = [E]$  and  $p = [P]$ . The *law of mass action* then gives four differential equations for the rates of change of  $s$ ,  $c$ ,  $e$  and  $p$ ,

$$\begin{aligned}\frac{ds}{dt} &= k_{-1}c - k_1se, \\ \frac{de}{dt} &= (k_{-1} + k_2)c - k_1se, \\ \frac{dc}{dt} &= k_1se - (k_2 + k_{-1})c, \\ \frac{dp}{dt} &= k_2c.\end{aligned}$$

Let us remark that  $p$  can be found by direct integration and also  $\frac{de}{dt} + \frac{dc}{dt} = 0$  which means that  $e + c$  is constant. We denote the constant by  $e_0$  and it has meaning of the total amount of available enzyme.

Michaelis and Menten made an additional assumption that the substrate  $s$  is in instantaneous equilibrium with the complex  $c$ , which means

$$k_1se = k_{-1}c.$$

Since  $e + c = e_0$ , we obtain a system of two equations, we consider  $c$  and  $e$  as unknowns and solve it for  $c$ :

$$c = \frac{k_1e_0s}{k_{-1} + k_1s} = \frac{e_0s}{\frac{k_{-1}}{k_1} + s}.$$

Finally, the velocity  $v$  of the reaction is given by

$$v = \frac{dp}{dt} = k_2c = \frac{k_2e_0s}{\frac{k_{-1}}{k_1} + s}.$$

### 3 Introducing the problem

Michaelis-Menten model takes the form of an equation

$$v(x) = \frac{a_1x}{a_2 + x},$$

relating a reaction rate  $v$  to a concentration of a substrate denoted by  $x$ . Constants  $a_1$  and  $a_2$  are unknown.

Analyze the experimental data (see Table 1) and find appropriate values of constants  $a_1$  and  $a_2$ .

$x_i [10^{-4} \text{ mol} \cdot \text{dm}^{-3}]$	2.267	2.703	3.575	4.098	4.098	3.974	4.211
$v_i [10^{-8} \text{ mol} \cdot \text{dm}^{-3} \cdot \text{s}^{-1}]$	1.220	2.451	4.897	9.780	14.688	19.576	24.483

Tab. 1. The experimental data

#### 4 Solution with linearization

The original equation

$$v = \frac{a_1 x}{a_2 + x}$$

can be rewritten into an equivalent form

$$\frac{1}{v} = \frac{a_2 + x}{a_1 x} \quad \Rightarrow \quad \frac{1}{v} = \frac{a_2}{a_1} \cdot \frac{1}{x} + \frac{1}{a_1}.$$

After substitutions  $V := \frac{1}{v}$ ,  $X := \frac{1}{x}$ ,  $A := \frac{1}{a_1}$  and  $B := \frac{a_2}{a_1}$ , it becomes

$$V = BX + A.$$

A manoeuvre we have just described is called a **linearization** (see [1, p. 201]) of a problem. Considering the new variables  $X$  and  $V$  we obtain a transformed data, see Table 2.

$X_i$	0.441	0.370	0.280	0.244	0.244	0.252	0.238
$V_i$	0.820	0.408	0.204	0.102	0.068	0.051	0.041

Tab. 2. The linearized data

To acquire reasonable values of constants  $A$  and  $B$  we employ the least square method (see [3, p. 85] or [5, p. 431]) for the modified problem. Hence, our goal is finding a minimum of the function

$$\Psi(A, B) = \sum_i [(BX_i + A) - V_i]^2.$$

First, we compute the partial derivatives of  $\Psi$  and we set both of them equal zero.

$$\frac{\partial \Psi}{\partial A} = 2 \sum_i (BX_i + A - V_i) = 0,$$

$$\frac{\partial \Psi}{\partial B} = 2 \sum_i (BX_i + A - V_i)X_i = 0.$$

After straightforward modification we get the **normal equation** in a matrix form

$$\begin{pmatrix} \sum_i 1 & \sum_i X_i \\ \sum_i X_i & \sum_i X_i^2 \end{pmatrix} \begin{pmatrix} A \\ B \end{pmatrix} = \begin{pmatrix} \sum_i V_i \\ \sum_i X_i V_i \end{pmatrix}.$$

The normal equation is easily solvable with use of MATLAB.

```

>> x = [2.267 2.703 3.575 4.098 4.098 3.974 4.211];
>> v = [1.220 2.451 4.897 9.780 14.688 19.576 24.483];
>> X = 1./x;
>> V = 1./v;
>> [7 sum(X); sum(X) sum(X.^2)] \ [sum(V); sum(X.*V)]
ans =
    -0.8054
     3.5455

```

Therefore  $A = -0.8054$  and  $B = 3.5455$ . If we go back to the original unknowns, we end up with

$$a_1 = \frac{1}{A} = -1.2416, \quad a_2 = \frac{B}{A} = -4.4022,$$

hence  $v^L(x) = \frac{-1.2416x}{-4.4022 + x}$ .

## 5 Solution without linearization

The linearization leads to a great simplification of the problem. Nevertheless, we pay a price for this simplicity as the resulting function is not necessarily the best fit in the least-squares sense. Now, we carry out a computation without the linearization trick. We are looking for a minimum of a function

$$\Psi(a_1, a_2) = \sum_i \left( \frac{a_1 x_i}{a_2 + x_i} - v_i \right)^2.$$

We compute the partial derivatives of  $\Psi$  and we set both of them equal zero.

$$\frac{\partial \Psi}{\partial a_1} = 2 \sum_i \left( \frac{a_1 x_i}{a_2 + x_i} - v_i \right) \frac{x_i}{a_2 + x_i} = 2 \sum_i \left( \frac{a_1 x_i^2}{(a_2 + x_i)^2} - \frac{x_i v_i}{a_2 + x_i} \right) = 0,$$

$$\frac{\partial \Psi}{\partial a_2} = 2 \sum_i \left( \frac{a_1 x_i}{a_2 + x_i} - v_i \right) \frac{-a_1 x_i}{(a_2 + x_i)^2} = -2 \sum_i \left( \frac{a_1^2 x_i^2}{(a_2 + x_i)^3} - \frac{a_1 x_i v_i}{(a_2 + x_i)^2} \right) = 0.$$

We adjust the equations by cancelling the constants 2 and  $-2$ . Moreover, we denote the functions by  $f_1$  and  $f_2$  and rewrite the equations as

$$f_1(a_1, a_2) = \sum_i \left( \frac{a_1 x_i^2}{(a_2 + x_i)^2} - \frac{x_i v_i}{a_2 + x_i} \right) = 0,$$

$$f_2(a_1, a_2) = \sum_i \left( \frac{a_1^2 x_i^2}{(a_2 + x_i)^3} - \frac{a_1 x_i v_i}{(a_2 + x_i)^2} \right) = 0.$$

The computation is carried out in MATLAB. We begin with definitions of vectors  $x$ ,  $v$  and functions  $f_1$ ,  $f_2$ . Take notice of a vector  $A$  as an input variable of the functions.

```
>> x = [2.267 2.703 3.575 4.098 4.098 3.974 4.211];
>> v = [1.220 2.451 4.897 9.780 14.688 19.576 24.483];
>> f1 = @(A) sum(A(1)*x.^2./(A(2)+x).^2-x.*v./(A(2)+x));
>> f2 = @(A) sum(A(1).^2*x.^2./(A(2)+x).^3-A(1)*x.*v./(A(2)+x).^2)
;
```

We have obtained a rather difficult system of equations but with the assistance of the **Newton's method** (see [3, p. 31] or [5, p. 283]) may gain at least an approximate solution. We need to find a Jacobi matrix of the mapping  $f(a_1, a_2) = (f_1(a_1, a_2), f_2(a_1, a_2))^T$  which is

$$\mathbf{J}_f(a_1, a_2) = \begin{pmatrix} \frac{\partial f_1}{\partial a_1}(a_1, a_2) & \frac{\partial f_1}{\partial a_2}(a_1, a_2) \\ \frac{\partial f_2}{\partial a_1}(a_1, a_2) & \frac{\partial f_2}{\partial a_2}(a_1, a_2) \end{pmatrix} =$$

$$= \begin{pmatrix} \sum_i \frac{x_i^2}{(a_2 + x_i)^2} & \sum_i \frac{-2a_1 x_i^2}{(a_2 + x_i)^3} + \frac{x_i v_i}{(a_2 + x_i)^2} \\ \sum_i \frac{2a_1 x_i^2}{(a_2 + x_i)^3} - \frac{x_i v_i}{(a_2 + x_i)^2} & \sum_i \frac{-3a_1^2 x_i^2}{(a_2 + x_i)^4} + \frac{2a_1 x_i v_i}{(a_2 + x_i)^3} \end{pmatrix}.$$

Assuming  $\mathbf{J}_f$  is regular at points where necessary, the Newton's method defines a sequence  $(\mathbf{a}^k)$  such that

$$\mathbf{a}^0 = (-1.2416, -4.4022)^T \quad (\text{i.e., the result of linearized problem}),$$

$$\mathbf{a}^{k+1} = \mathbf{a}^k - \mathbf{J}_f(\mathbf{a}^k)^{-1} \mathbf{f}(\mathbf{a}^k).$$

Then, we define the Jacobian matrix in MATLAB.

```
>> Jf = @(A) [sum(x.^2./(A(2)+x).^2),
sum(-2*A(1)*x.^2./(A(2)+x).^3+x.*v./(A(2)+x).^2);
sum(2*A(1)*x.^2./(A(2)+x).^3-x.*v./(A(2)+x).^2),
sum(-3*A(1)^2*x.^2./(A(2)+x).^4+2*A(1)*x.*v./(A(2)+x).^3)
];
```

We pick a result of the linearized problem as an initial approximation and accomplish the first step of the Newton's method. We also save the computed value into the variable X.

```
>> X = [-1.2416;-4.4022];
>> Xnew = X-inv(Jf(X))*[f1(X);f2(X)], X=Xnew;
Xnew =
-1.2411
-4.4224
```

We repeat the last command while the visible digits of the approximation vector  $X_{\text{new}}$  change.

```
% After several repetitions:
>> Xnew = X-inv(Jf(X))*[f1(X);f2(X)], X = Xnew;
Xnew =
    -1.6433
    -4.5168
```

We may conclude that

$$a_1 = -1.6433, \quad a_2 = -4.5168$$

is a good approximation of the problem and hence

$$v^N(x) = \frac{-1.6433 x}{-4.5168 + x}.$$

## 6 Solution by MATLAB

We may also use a non-linear least-squares solver implemented in MATLAB. It's application is simple but it uses internal numerical methods which are sensitive on a choice of initial approximation. Since we are furnished with knowledge of a very good approximation of solution, we can choose a very precise initial approximation here.

```
>> f = @(a) a(1)*x./(a(2)+x)-v;
>> a0=[-1 -5]; % the initial approximation
>> aM = lsqnonlin(f,a0)
aM =
    -1.6430    -4.5168
```

MATLAB generates a solution

$$v^M(x) = \frac{-1.6430 x}{-4.5168 + x}.$$

Notice that the parameters are almost the same as in case of the previous solution without linearization.

## 7 Comparison of results

Let us summarize our results

$$v^L(x) = \frac{-1.2416 x}{-4.4022 + x}, \quad v^N(x) = \frac{-1.6433 x}{-4.5168 + x}.$$

The linearization is a very useful tool which may help us handle problems that would be unsolvable otherwise. Nevertheless, as we observe in the Table 3 and in the Figure 1, the results obtained by linearization may be distorted in general.

$x_i$	$v_i$	$v^L(x_i)$	$v^N(x_i)$	$(v^L(x_i) - v_i)^2$	$(v^N(x_i) - v_i)^2$
2.2670	1.2200	1.3182	1.6559	0.0097	0.1900
2.7030	2.4510	1.9751	2.4489	0.2265	0.0000
3.5750	4.8970	5.3660	6.2378	0.2199	1.7979
4.0980	9.7800	16.7261	16.0799	48.2482	39.6882
4.0980	14.6880	16.7261	16.0799	4.1538	1.9373
3.9740	19.5760	11.5229	12.0311	64.8519	56.9257
4.2110	24.4830	27.3451	22.6290	8.1915	3.4375

Tab. 3. Comparison of results

Finally, let us show the sums of squares of both results which allows to measure an accuracy in sense of least squares ("the smaller the better"). Their difference is less negligible than one would probably expect

$$\sum_i (v^L(x_i) - v_i)^2 = 125.9015, \quad \sum_i (v^N(x_i) - v_i)^2 = 103.9764 .$$

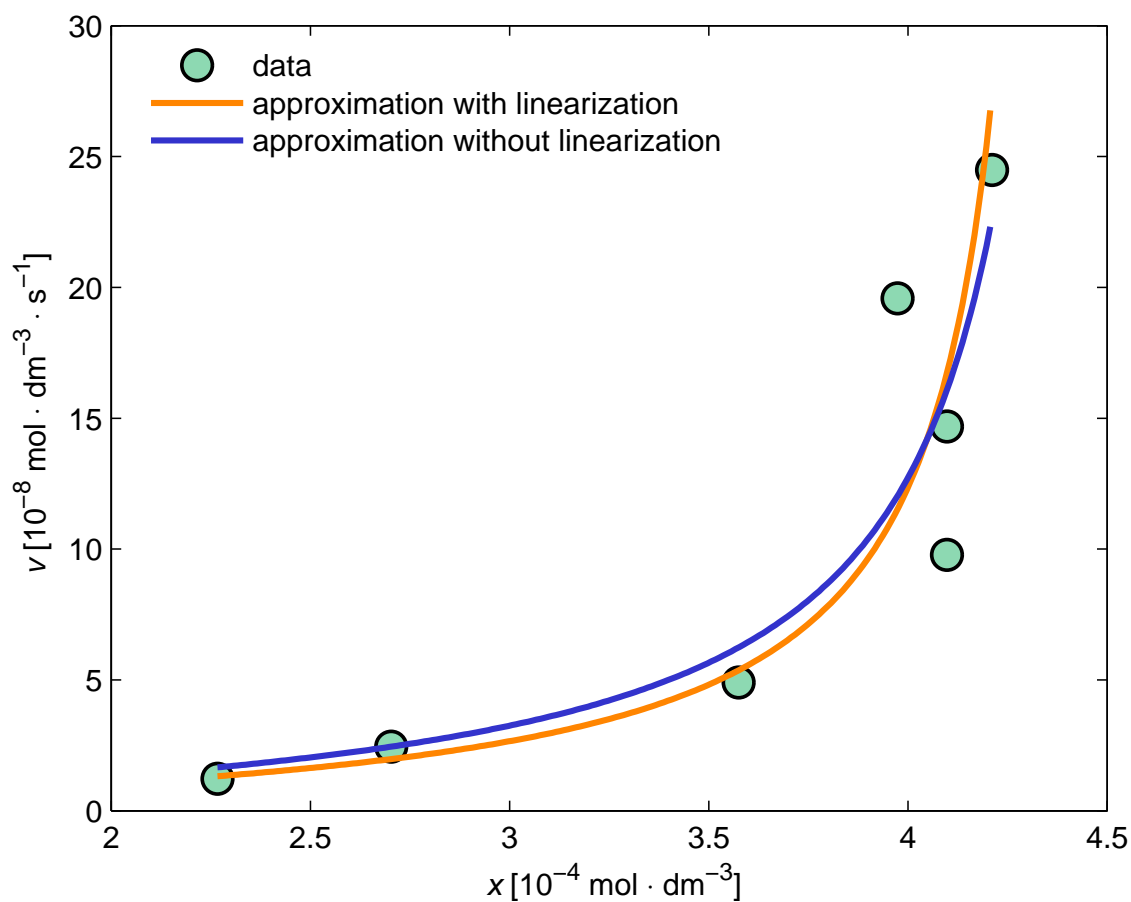


Fig. 1. Comparison of results and data

## 8 The examples of linearization

Linearization is a simple tool to transform a non-linear approximation problem to a linear one. We can apply a linear least-squares method afterwards. The quality of a resulting approximation is usually satisfying even though a routine linearization might add an error which is difficult to control. On the other hand, mathematically rigid usage of a non-linear least-squares method leads to a non-linear system of equations which is often solvable only by a numerical (and therefore only approximate) method.

We append a table of some of the most useful linearization formulas.

$v = a_1 x^{a_2}$	$V := \ln v, X := \ln x, A := \ln a_1, B := a_2$	$V = A + BX$
$v = a_1 e^{a_2 x}$	$V := \ln v, X := x, A := \ln a_1, B := a_2$	$V = A + BX$
$v = e^{a_1 + \frac{a_2}{x}}$	$V := \ln v, X := \frac{1}{x}, A := \ln a_1, B := a_2$	$V = A + BX$
$v = \ln(a_1 + a_2 x)$	$V := e^v, X := x, A := a_1, B := a_2$	$V = A + BX$
$v = a_1 x e^{a_2 x}$	$V := \ln \frac{v}{x}, X := x, A := \ln a_1, B := a_2$	$V = A + BX$
$v = a_1 + a_2 \ln x$	$V := v, X := \ln x, A := a_1, B := a_2$	$V = A + BX$

## Conclusion

We hope this exercise teaches a lesson that every problem in numerical mathematics permits many solutions. It can be very useful to use a simplified model of the situation. Nevertheless, you cannot expect to obtain the same result as if you do all the hard work.

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