Application of a quasi-linear technique to a class of mathematical models satisfying conservation properties

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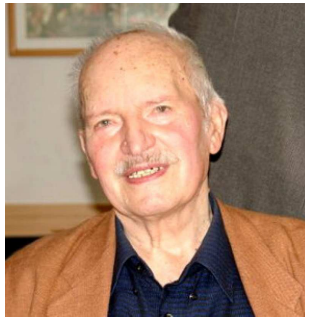
Outline

Inspiration and motivation

Erich Bohl (1936–2016) and Ivo Marek (1933–2017)



1. Draw attention to a special class of nonlinear mathematical models with conservation properties.
2. Explanation of the formulation *"How nonlinear systems become quasi-linear"*.
3. How the **M-matrix** (negativ, singular) appears in ODEs.
4. Show the benefits of using *quasi-linear formulation*.
5. Bohl and Marek used the quasi-linear formulation in their papers for theoretical purposes (*existence, uniqueness of the solution, ...*).

[Bohl, Marek, 2005]

Outline

Nonlinear formulation

In the real world, there is a substantial class of special biological and chemical processes that are described by nonlinear ordinary differential equations. The most general form:

$$x'(t,p) = L(p)x(t,p) + n(t,x(t,p),p) + c(t,p)$$

where

- derivation is according to time
- matrix $L(p) \in \mathcal{R}^{n_x \times n_x}$ represents a linear part
- vector $n(t,x(t,p),p) \in \mathcal{R}^{n_x}$ represents a nonlinear part
- vector $c(t,p) \in \mathcal{R}^{n_x}$ represents a constant part
- vector $x(t,p) \in \mathcal{R}^{n_x}$ are state variables (concentrations)
- t is time, $t \in [0,T]$
- $p \in \mathcal{R}^{n_p}$ represents the set of parameters occurring in the system
- in addition, we can have a set of (experimental) data $d \in \mathcal{R}^{n_d}$ representing the values of (usually one) state variable

Model parameters

There are two classes of model parameters $p \in \mathcal{R}^{n_p}$:

- Known – their values can be obtained from the literature or from direct experimental measurements.
- Unknown – their values must be obtained by estimation and subsequent fitting using experimental data $d \in \mathcal{R}^{n_d}$.

Parameter estimation is an integral part of the modelling process itself.

Fitting is an optimization problem (usually the sum of squares minimization) with simple bounds:

- the desired parameters should be positive and
- should lie within a physically meaningful interval.

The model must be called repeatedly during the parameter estimation process! – an example why to use a quasi-linear formulation

Quasi-linear formulation

Many processes are special in that they can be described (reformulated) by linear evolutions

$$x^{(k)\prime}(t,p) = L^{(k)}(p)\, x^{(k)}(t,p), \quad k = 1,\ldots,r,$$

where $x^{(k)}(t,p) \in \mathcal{R}^{n_k}$ are sets (subvectors) of partially overlapping state variables $x(t,p)$ and the extended vector

$$\tilde{x}(t,p) = \left[x^{(1)}(t,p)^T,\ldots,x^{(r)}(t,p)^T\right]^T$$

contains all state variables $x(t,p)$ (some components multiple times).

Matrices $L^{(k)}(p)$ are negative singular M-matrices, whose elements do not depend on $x^{(k)}(t,p)$, but may depend on other variables occurring in the system. Thus the matrices $L^{(k)}(p)$ are in fact quasi-linear.

Through this dependence the whole system is nonlinear and the matrix of the whole system is a block diagonal negative singular M-matrix:

$$\tilde{x}'(t,p) = \tilde{L}(\tilde{x}(t,p),p)\,\tilde{x}(t,p),$$

where $\tilde{L}(\tilde{x}(t,p),p) = \mathrm{diag}\left\{L^{(1)}(p),\ldots,L^{(r)}(p)\right\}$.

Conservation property

The theory of these subsystems (for each k) is well developed. In particular, the conservation property holds for all of them.

Conservation property

Models have the property that the amount of different chemicals changes over time, but the total amount remains constant. Thus, if $x^{(k)}(t,p) \in \mathcal{R}^{n_k}$, then

$$\sum_{i=1}^{n_k} x_i^{(k)}(t,p) = const. \quad \forall t \in [0,T], \quad k = 1,\ldots,r.$$

Negative singular M-matrix

Matrix $A = (a_{ij}) \in \mathcal{R}^{n\times n}$ is a negative singular M-matrix, if

$$a_{ij} \geq 0, \quad i,j = 1,\ldots,n, \quad i \neq j; \qquad a_{ji} = -\sum_{k=1,k\neq i}^{n} a_{ki}, \quad i = 1,\ldots,n.$$

[Fiedler, 2013].

Advantages of the quasi-linear formulation

1. The quasi-linear form is introduced to facilitate proofs of the existence, uniqueness and stability of the respective systems of ODEs.
2. The fact that submatrices are negative M-matrices leads to memory and/or computational time savings.
3. It is possible to formulate an algorithm that is less complicated and computationally less demanding than the algorithm for general nonlinear ODEs.
4. When solving a system of ODEs with nonlinear terms, e.g. by the Euler method, we must additionally consider the Newton method as an extra inner iteration cycle.
5. In cases where it is not possible to directly obtain a quasi-linear formulation, it may be possible to introduce dummy state variables to artificially create such a situation.

Outline

Model

It is the simplest case of enzyme kinetics, applied to enzyme-catalysed reactions of one substrate and one product. The model describes the conversion of the substrate S into the product P (e.g. a metabolite) by the enzyme E.

Biochemical process	**Chemical notation**	**Parameters**
Substrate dosing (external input)	$\emptyset \rightarrow S_{ext}$	
Substrate enters the cell, e.g. by permeation	$S_{ext} \rightleftharpoons S_{int}$ reversible reaction	k_{up}, k_{up}
Enzyme E associates (binds) to substrate S and forms the complex C	$S_{int} + E \rightleftharpoons C$ reversible reaction	k_{ass}, k_{diss}
Complex C falls apart in product P and E	$C \rightarrow P + E$	k_{cat}

Denote the state variables for substance concentrations as

$$\begin{aligned} x(t) &= [x_1(t),\ x_2(t),\ x_3(t),\ x_4(t),\ x_5(t)]^T \\ &= [S_{ext}(t),\ S_{int}(t),\ E(t),\ C(t),\ P(t)]^T, \end{aligned}$$

for more details see [Papáček et al., 2023].

Corresponding ODE – full system

Corresponding nonlinear (full) system of ODE has the form

$$\begin{aligned}
x_1'(t) &= -k_{up}\, x_1(t) + k_{up}\, x_2(t) \\
x_2'(t) &= k_{up}\, x_1(t) - k_{up}\, x_2(t) + k_{diss}\, x_4(t) - k_{ass}\, x_2(t)\, x_3(t) \\
x_3'(t) &= (k_{diss} + k_{cat})\, x_4(t) - k_{ass}\, x_2(t)\, x_3(t) \\
x_4'(t) &= -(k_{diss} + k_{cat})\, x_4(t) + k_{ass}\, x_2(t)\, x_3(t) \\
x_5'(t) &= k_{cat}\, x_4(t)
\end{aligned}$$

or

$$x'(t) = Lx(t) + n(t, x(t)), \tag{1}$$

where

$$L = \begin{pmatrix}
-k_{up} & k_{up} & 0 & 0 & 0 \\
k_{up} & -k_{up} & 0 & k_{diss} & 0 \\
0 & 0 & 0 & k_{diss} + k_{cat} & 0 \\
0 & 0 & 0 & -k_{diss} - k_{cat} & 0 \\
0 & 0 & 0 & k_{cat} & 0
\end{pmatrix}, \quad n(t, x(t)) = \begin{pmatrix}
0 \\
-k_{ass}\, x_2(t)\, x_3(t) \\
-k_{ass}\, x_2(t)\, x_3(t) \\
k_{ass}\, x_2(t)\, x_3(t) \\
0
\end{pmatrix}$$

with initial conditions

$$x(0) = [S_0,\ 0,\ E_0,\ 0,\ 0]^T.$$

Conservation properties

The enzyme-substrate transport network has two subsets of substances whose total concentration remains constant:

$$x_3'(t) + x_4'(t) = 0, \tag{2}$$

$$x_1'(t) + x_2'(t) + x_4'(t) + x_5'(t) = 0. \tag{3}$$

Hence the conservation properties are:

$$x_3(t) + x_4(t) = E_0, \tag{4}$$

$$x_1(t) + x_2(t) + x_4(t) + x_5(t) = S_0. \tag{5}$$

Simplified formulation

Due to (4)-(5), system (1) can be simplified. Since

$$x_3(t) = E_0 - x_4(t),$$

the variable $x_3(t)$ can be replaced in all equations and the corresponding equation for $x_3'(t)$ can be omitted.

In addition, only three equations can be considered because the last variable $x_5(t)$ can be computed as

$$x_5(t) = S_0 - x_1(t) - x_2(t) - x_4(t).$$

Corresponding ODE – simplified system

The full system (1) can be equivalently reformulated using only three variables $\bar{x}(t) = [x_1(t), x_2(t), x_4(t)]^T$ as

$$\begin{aligned}
x_1'(t) &= -k_{up}\, x_1(t) + k_{up}\, x_2(t) \\
x_2'(t) &= k_{up}\, x_1(t) - (k_{up} + E_0\, k_{ass})\, x_2(t) + k_{diss}\, x_4(t) - k_{ass}\, x_2(t)\, x_4(t) \\
x_4'(t) &= E_0\, k_{ass}\, x_2(t) - (k_{diss} + k_{cat})\, x_4(t) - k_{ass}\, x_2(t)\, x_4(t)
\end{aligned}$$

or

$$\bar{x}'(t) = \bar{L}\,\bar{x}(t) + \bar{n}(t, \bar{x}(t)), \tag{6}$$

where

$$\bar{L} = \begin{pmatrix} -k_{up} & k_{up} & 0 \\ k_{up} & -(k_{up} + E_0\, k_{ass}) & k_{diss} \\ 0 & E_0\, k_{ass} & -(k_{diss} + k_{cat}) \end{pmatrix}, \quad \bar{n}(t, \bar{x}(t)) = \begin{pmatrix} 0 \\ k_{ass}\, x_2(t)\, x_4(t) \\ -k_{ass}\, x_2(t)\, x_4(t) \end{pmatrix}$$

with initial conditions

$$\bar{x}(0) = [S_0,\ 0,\ 0]^T .$$

Two subnetworks

The variables involved in conservation properties (4)-(5) define two conservative subnetworks and two sets of partially overlapping state variables (i.e., $r = 2$)

$$x^{(1)}(t) = [x_3(t),\ x_4(t)]^T,$$

$$x^{(2)}(t) = [x_1(t),\ x_2(t),\ x_4(t),\ x_5(t)]^T,$$

We can formulate a quasi-linear system for the extended state vector

$$\begin{aligned} \tilde{x}(t) &= \left[x^{(1)}(t)^T,\ x^{(2)}(t)^T\right]^T \\ &= [x_3(t),\ x_4(t),\ x_1(t),\ x_2(t),\ x_4(t),\ x_5(t)]^T. \end{aligned}$$

The overlapping state variable is $x_4(t) = \tilde{x}_2(t) = \tilde{x}_5(t)$:

- For $x_4(t)$ we can take $x_4(t) = \tilde{x}_2(t)$ or $x_4(t) = \tilde{x}_5(t)$ or average.
- We will also be interested in the difference between $\tilde{x}_2(t)$ and $\tilde{x}_5(t)$, expecting that

$$\tilde{x}_2(t) \cong \tilde{x}_5(t)\ \forall t.$$

Corresponding ODE – quasi-linear formulation

The quasi-linear formulation has the form

$$
\begin{aligned}
x_3'(t) &= -k_{ass}\, x_2(t)\, x_3(t) + (k_{diss} + k_{cat})\, x_4(t) \\
x_4'(t) &= k_{ass}\, x_2(t)\, x_3(t) - (k_{diss} + k_{cat})\, x_4(t) \\
x_1'(t) &= -k_{up}\, x_1(t) + k_{up}\, x_2(t) \\
x_2'(t) &= k_{up}\, x_1(t) - (k_{up} + k_{ass}\, x_3(t))\, x_2(t) + k_{diss}\, x_4(t) \\
x_4'(t) &= k_{ass}\, x_3(t)\, x_2(t) - (k_{diss} + k_{cat})\, x_4(t) \\
x_5'(t) &= k_{cat}\, x_4(t)
\end{aligned}
$$

or

$$
\tilde{x}'(t) = \tilde{L}\tilde{x}(t), \tag{7}
$$

where

$$
\tilde{L} = \begin{pmatrix}
-k_{ass}\, x_2(t) & k_{diss} + k_{cat} & 0 & 0 & 0 & 0 \\
k_{ass}\, x_2(t) & -k_{diss} - k_{cat} & 0 & 0 & 0 & 0 \\
0 & 0 & -k_{up} & k_{up} & 0 & 0 \\
0 & 0 & k_{up} & -k_{up} - k_{ass}\, x_3(t) & k_{diss} & 0 \\
0 & 0 & 0 & k_{ass}\, x_3(t) & -k_{diss} - k_{cat} & 0 \\
0 & 0 & 0 & 0 & k_{cat} & 0
\end{pmatrix}
$$

with initial conditions

$$
\tilde{x}(0) = [E_0,\ 0,\ S_0,\ 0,\ 0,\ 0]^T.
$$

Outline

Three models and parameters

Numerical comparison of three models:

1. Full nonlinear system (1) – **5 equations**. At least one inner Newton iteration must be performed.
2. Simplified nonlinear system (6) – **3 equations** for x_1, x_2, x_4; remaining variables x_3, x_5 are computed using conservation properties (4)-(5). At least one inner Newton iteration must be performed.
3. Quasi-linear system (7) – **6 equations**. No inner Newton iteration is performed.

Parameters (corresponding to a practical situation):

$$k_{up} = 10^{-1}, \quad k_{ass} = 10^{6}, \quad k_{diss} = 10^{-4}, \quad k_{cat} = 10^{-1},$$

$$S_0 = 5 \cdot 10^{-7}, \quad E_0 = 2 \cdot 10^{-7}.$$

The Euler method:

$$t \in [0, T], \ T = 120, \quad \text{step } \tau = 10^{-3}, \quad M = T/\tau.$$

Comparison of models using the Euler method

Model	NWT	Time	Speedup
(NS) Nonlinear system (1)	0	28.09	1.00
(SS) Simplified system (6)	0	18.96	0.68
(QS) Quasi-linear system (7)	-	5.82	0.21

Model	Choice of x_4	$\|\tilde{x}_2 - \tilde{x}_5\|$	Error
(SS) Simplified system (6)	-	-	6.27E-5
(QS) Quasi-linear system (7)	$\tilde{x}_2$	1.60E-14	6.49E-5
(QS) Quasi-linear system (7)	$\tilde{x}_5$	1.60E-14	3.42E-5
(QS) Quasi-linear system (7)	$(\tilde{x}_2 + \tilde{x}_5)/2$	1.60E-14	4.39E-5

$$\|\tilde{x}_2 - \tilde{x}_5\| = \frac{1}{M}\sqrt{\sum_{j=0}^{M}[\tilde{x}_2(t_j) - \tilde{x}_5(t_j)]^2},$$

$$\textbf{Error} = \frac{1}{n}\sum_{i=1}^{n}\sqrt{\frac{1}{M}\sum_{j=0}^{M}\left[\frac{x_i^{NS}(t_j) - x_i^{model}(t_j)}{x_i^{NS}(t_j)}\right]^2}, \quad model \in \{SS, QS\}$$

Data for fitting

Now assume that k_{ass} and k_{cat} are unknown parameters. Using their exact values we compute the values $x_5(t_j)$ for some time instants t_j which will serve as data d_j for fitting.
Note that $x_5(t)$ corresponds to a concentration that can be measured experimentally in practice (product P).

j	t_j	d_j
1	5	0.106644E-07
2	10	0.465241E-07
3	15	0.942874E-07
4	20	0.144851E-06

There is usually very little experimental data available in practice, thus here $j = 4$.

Minimization

The goal:

- Choose initial values k_{ass}^{init} and k_{cat}^{init}.
- Set appropriate lower bounds k_{ass}^{LB} and k_{cat}^{LB}.
- Find a solution k_{ass}^{*} and k_{cat}^{*} for which the computed values $x_5(t_j)$ fit the data d_j as best as possible (the smallest deviation).

This leads to the minimization of the function

$$F(k) = \sum_{j=1}^{m_d} \left[\frac{x_5(t_j) - d_j}{d_j} \right]^2 \quad \rightarrow \quad \min_k,$$

where $k = [k_{ass}, k_{cat}]^T \in \mathcal{R}^2$ and $m_d = 4$.

Optimization software used: UFO [Lukšan et al., 2017];
Optimization methods used:

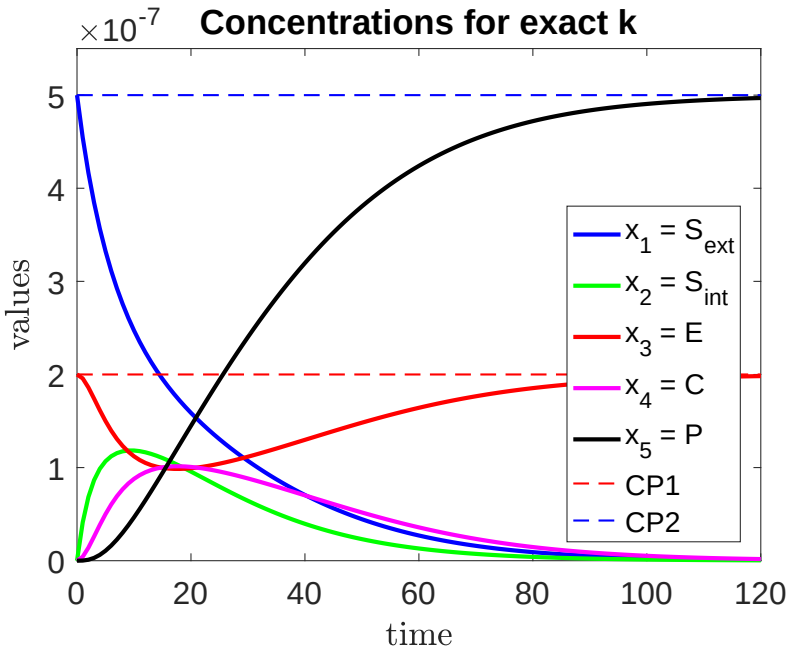
- trust region method (TR)
- variable metric method (VM)

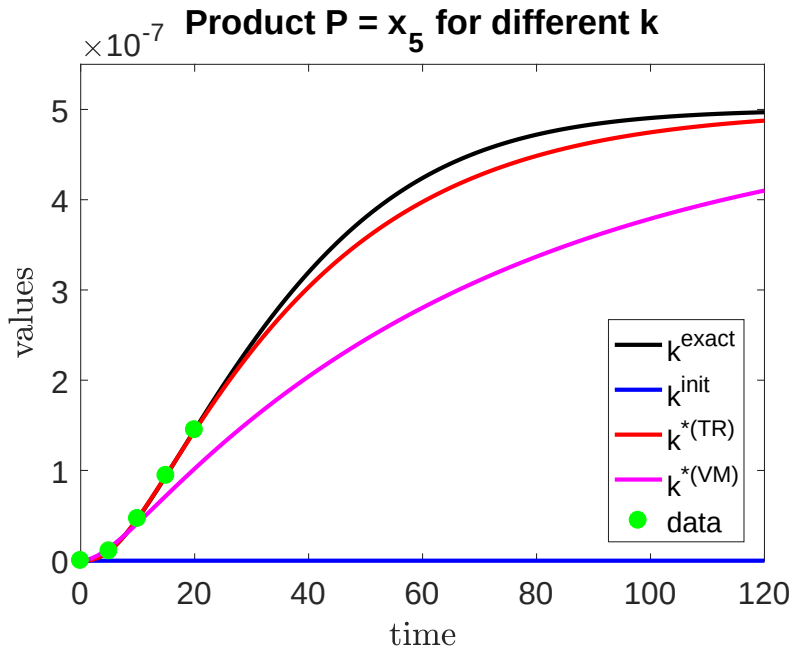
Comparison of the methods

TR / Model	**NS** (1)	**SS** (6)	**QS** (7)
k^*_{ass}	4.68E+5	4.68E+5	4.68E+5
k^*_{cat}	2.06E-1	2.06E-1	2.06E-1
$F(k^*)$	1.69E-4	1.69E-4	1.69E-4
NIT	505	542	508
NFV	4 075	4 373	4 110
time	108.46	120.75	24.25

VM / Model	**NS** (1)	**SS** (6)	**QS** (7)
k^*_{ass}	1.62E+5	1.62E+5	1.62E+5
k^*_{cat}	1.98E+6	1.98E+6	1.98E+6
$F(k^*)$	2.61E-1	2.61E-1	2.61E-1
NIT	2 160	2 161	2 162
NFV	8 634	8 642	8 636
time	221.45	228.81	51.09

Graphs





Left: Concentrations $x_1(t), \ldots, x_5(t)$ for exact $k_{ass} = 10^6$ and $k_{cat} = 10^{-1}$;

$$\text{CP1} = x_3 + x_4, \quad \text{CP2} = x_1 + x_2 + x_4 + x_5;$$

Right: Concentration of product $x_5(t)$ for different k_{ass} and k_{cat}: exact, initial for fitting, computed using TR and VM methods.

Outline

Summary

- To cope with nonlinearities arising in real processes, we have described a special reformulation of the original nonlinear system into an apparently linear but in fact quasi-linear system.
- The solution of the original “large” nonlinear system is using a quasi-linear formulation split into the solution of several “small” linear systems.
- Nonlinear formulation and quasi-linear formulation are mathematically equivalent.
- On a simple example which simulates a biological situation with a given choice of parameters it is shown a significant speedup of numerical computations without loosing accuracy.
- If it is necessary to do parameter estimation through curve fitting, the models must be called repeatedly in iteration process and the computational speedup is yet more significant.

For more details see [Duintjer Tebbens et al., 2024].

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Thank you for your attention.